MAJOR ARTICLE







Active Surveillance for Norovirus in a US Veterans Affairs Patient Population, Houston, Texas, 2015–2016

Anita K. Kambhampati, ^{1,2} Blanca Vargas, ^{3,4} Mahwish Mushtaq, ^{3,4} Hannah Browne, ^{1,5} Scott Grytdal, ¹ Robert L. Atmar, ⁴ Jan Vinjé, ¹ Umesh D. Parashar, ¹ Benjamin Lopman, ^{1,6} Aron J. Hall, ¹ Maria C. Rodriguez-Barradas, ^{3,4} and Cristina V. Cardemil

¹National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; ²IHRC, Inc., Atlanta, Georgia; ³Infectious Diseases Section, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; ⁴Infectious Diseases Section, Baylor College of Medicine, Houston, Texas; ⁵Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee; ⁶Rollins School of Public Health, Emory University, Atlanta, Georgia

Background. Norovirus is a leading cause of acute gastroenteritis (AGE); however, few data exist on endemic norovirus disease burden among adults. Candidate norovirus vaccines are currently in development for all ages, and robust estimates of norovirus incidence among adults are needed to provide baseline data.

Methods. We conducted active surveillance for AGE among inpatients at a Veterans Affairs (VA) hospital in Houston, Texas. Patients with AGE (≥3 loose stools, ≥2 vomiting episodes, or ≥1 episode of both loose stool and vomiting, within 24 hours) within 10 days of enrollment and non-AGE control patients were enrolled. Demographic data and clinical characteristics were collected. Stool samples were tested using the FilmArray gastrointestinal panel; virus-positives were confirmed by real-time reverse transcription polymerase chain reaction and genotyped by sequencing.

Results. From November 2, 2015 through November 30, 2016, 147 case patients and 19 control patients were enrolled and provided a stool specimen. Among case patients, 139 (95%) were male and 70 (48%) were aged \geq 65 years. Norovirus was the leading viral pathogen detected (in 16 of 20 virus-positive case patients) and accounted for 11% of all AGE cases. No viral pathogens were detected among control patients. Incidence of norovirus-associated hospitalization was 20.3 cases/100 000 person-years and was similar among those aged \leq 65 and \geq 65 years.

Conclusions. This active surveillance platform employed screening and enrollment of hospitalized VA patients meeting a standardized AGE case definition, as well as non-AGE control patients. Data from this study highlight the burden of norovirus in a VA inpatient population and will be useful in policy considerations of a norovirus vaccine.

Keywords. acute gastroenteritis; burden; norovirus; veterans.

With approximately 19–21 million cases each year, norovirus is a leading cause of acute gastroenteritis (AGE) in the United States [1]. Following the introduction of rotavirus vaccines in the United States, pediatric hospitalizations due to all-cause AGE have decreased [2]. This reduction has been driven by a marked decline in rotavirus, resulting in the increased relative importance of norovirus as a cause of severe pediatric AGE in the United States and other countries [3–5]. Further, AGE hospitalizations have increased among adults, with norovirus estimated to cause approximately 6%–13% of cause-unspecified gastroenteritis discharges among adults aged ≥18 years [6]. Still, few data are available on the burden of laboratory-confirmed norovirus infections among adults in the United States. Until recently, laboratory diagnostics for norovirus

have not been widely available, so incidence estimates have largely been based on indirect modeling methods [1, 6–9]. Recent estimates have included laboratory-confirmed cases; however, these were based on passive sampling methods [10, 11]. Other estimates have focused on pediatric populations or have generated community-based or outpatient estimates for all age groups [3, 12].

The clinical presentation of norovirus infection can vary widely. Norovirus disease is generally mild and self-limiting, and ~20%–30% of norovirus infections are asymptomatic [13, 14]. However, although rates of norovirus disease and associated medical care are highest in children <5 years of age, severe outcomes, such as hospitalization and death, are more common among older adults (ie, ≥65 years of age) [1, 15]. Additionally, older adults and immunocompromised individuals are at increased risk of prolonged illness and other complications [16, 17].

With 2 candidate norovirus vaccines in clinical trials, and several others in preclinical stages, there is a need to determine the age-specific endemic burden of norovirus [18, 19]. Robust estimates of sporadic disease burden and severity among various age groups, including adults, are crucial for assessing the potential public health value of these vaccines. We aimed to

Received 2 January 2019; editorial decision 27 February 2019; accepted 1 March 2019. Correspondence: A. K. Kambhampati, MPH, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS H24-5, Atlanta, GA 30329 (wyc4@cdc.gov).

Open Forum Infectious Diseases®

Published by Oxford University Press on behalf of Infectious Diseases Society of America 2019. This work is written by (a) US Government employee(s) and is in the public domain in the US.

DOI: 10.1093/ofid/ofz115

estimate the incidence of norovirus using an active surveillance platform in a US Veterans Affairs hospital.

METHODS

Active surveillance for AGE was conducted at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) daily from November 2, 2015 through November 30, 2016. MEDVAMC, located in Houston, Texas, is one of >1700 Department of Veterans Affairs (VA) facilities offering health care to eligible veterans of the US military [20]. Beginning in 2011, MEDVAMC, along with 3 other VA medical centers in Georgia, California, and New York, conducted surveillance for AGE using passive sampling methods [11]. In 2015, passive surveillance activities ceased at the other VA medical centers, and MEDVAMC transitioned to an active enrollment strategy. Although active surveillance was conducted among patients who presented to the primary care clinic (outpatients) and those who were admitted to the hospital or held for observation (inpatients), only surveillance in the inpatient setting will be described herein.

All registered members of the VA who were admitted to MEDVAMC were eligible for inclusion. Acute gastroenteritis (AGE) was defined as ≥ 3 loose stools, ≥ 2 episodes of vomiting, or ≥1 episode of both loose stool and vomiting, in a 24-hour period, as previously used for norovirus AGE [18, 21]. Patients who developed AGE either before or during hospitalization were eligible for enrollment as a case if illness onset occurred within 10 days of enrollment. Patients were not considered eligible for case enrollment if their symptoms had been present for >10 days or could be attributed to a noninfectious cause (eg, pregnancy or drug ingestion), or if they were transferred from another hospital after an admission of >48 hours, to minimize the potential of detecting a hospital-acquired infection acquired elsewhere. Additionally, patients could not be enrolled in surveillance more than once per month. To assess rates of asymptomatic infection, patients without symptoms of either AGE or acute respiratory illness on the day of enrollment or in the preceding 14 days were enrolled as controls.

To identify potentially eligible patients, study staff reviewed admission logs for patients who were admitted with symptoms of AGE and clinical laboratory logs for patients whose stools were submitted for clinician-requested diagnostic testing. Additionally, study staff received referrals of patients from hospital clinical staff and conducted daily walkthroughs of hospital wards. Study staff then reviewed the medical charts for all patients identified through any of the above means (ie, "screened") and approached these patients for confirmation of eligibility and subsequent enrollment.

After consent, a standardized interview was conducted for all enrolled participants (case and control patients) to collect demographic data, exposure history, and clinical characteristics.

Additional data about the AGE illness and hospitalization were obtained for case patients through a medical chart abstraction, and a follow-up interview was conducted approximately 2-3 weeks after enrollment to assess post-enrollment symptoms. A stool specimen was collected from all participants within 10 days of AGE symptom onset for case patients or within 5 days of enrollment for control patients. Participants who did not provide a stool specimen within the required time frame were considered study noncompleters and were excluded from analyses. Stool specimens were tested using the FilmArray Gastrointestinal Panel (BioFire Diagnostics, Salt Lake City, UT), a multiplex platform for the molecular detection of 22 gastrointestinal pathogens. Specimens positive for any of the 5 viruses detectable by FilmArray (adenovirus F type 40 or 41, astrovirus, norovirus genogroups I or II, rotavirus A, sapovirus genogroups I, II, IV, or IV) were confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) and genotyped by sequencing [22, 23]. Pathogen-specific prevalence (eg, norovirus prevalence) was defined as the proportion of study-completing participants who tested positive for a pathogen, among all study-completing participants. As norovirus was our primary pathogen of interest, our analyses focused on norovirus prevalence and incidence, including the prevalence of asymptomatic norovirus detected among control patients and comparisons with AGE case patients who were norovirus-negative.

Incidence calculations were based on previously published methods from Grytdal et al. [11] and were adapted to account for active surveillance procedures. The number of unique patients served at MEDVAMC during fiscal year (FY) 2016, which spanned from October 1, 2015 through September 30, 2016, was used as the denominator for incidence calculations, except for incidence calculation of hospital-acquired infections, for which the total number of inpatient discharges was used. Veterans who are eligible for VA services must enroll in the VA health care system to utilize services. The number of unique patients served represents enrolled veterans who utilized the facility for inpatient or outpatient health care services during FY 2016 and excludes those who only utilized the VA for pharmacy, laboratory, or telephone triage services, or who did not use any VA services, in order to more accurately estimate the population under surveillance.

Norovirus incidence per 100 000 person-years was calculated using the following equation:

$$\frac{10^5 \times E \times p(noro)}{N \times t}$$

where E = number of eligible inpatients during the study period, p(noro) = norovirus prevalence among enrolled inpatients, N = number of unique patients served during FY 2016 (ie, $104\,504$ unique patients), and t = time in years spent conducting

surveillance (ie, 13 months or 1.08 years). Incidence was calculated for norovirus cases overall, then stratified by cases <65 and ≥65 years of age.

Incidence estimates were also stratified by community-acquired norovirus, defined as those with illness onset before admission, on the day of admission, or on the first day after admission, or hospital-acquired norovirus, defined as those with illness onset 2 or more days after the admission date. Similar to the method used by Grytdal et al., the proportion of enrolled inpatients with community- or hospital-acquired gastroenteritis was also applied to the number of eligible inpatients during the study period to estimate the number of eligible inpatients for the community- and hospital-acquired norovirus estimates [11]. Thus, community-acquired norovirus incidence was calculated using the following equation:

$$\frac{10^{5} \times [E \times p \, (comm)] \times p (noro)_{comm}}{N \times t}$$

where E = number of eligible inpatients during the study period, p(comm) = the proportion of enrolled inpatients with community-acquired gastroenteritis, $p(noro)_{comm}$ = norovirus prevalence among enrolled inpatients with community-acquired gastroenteritis, N = number of unique patients served during FY 2016, and t = time in years spent conducting surveillance.

Hospital-acquired norovirus incidence was calculated using the following equation:

$$\frac{10^{5} \times \left[E \times p \, (hosp)\right] \times p (noro)_{hosp}}{D \times t}$$

where E = number of eligible inpatients during the study period, p(hosp) = the proportion of enrolled inpatients with hospital-acquired gastroenteritis, $p(noro)_{hosp} =$ norovirus prevalence among enrolled inpatients with hospital-acquired gastroenteritis, D = number of inpatient discharges during FY 2016 (ie, 12 199 discharges), and t = time in years spent conducting surveillance.

Confidence intervals were generated using bootstrap analysis. Comparisons between cases and controls and norovirus-positive and -negative cases were conducted using the Mann-Whitney, chi-square, and Fisher exact tests. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Enrollment and Demographics

In total, 212 inpatients were eligible for inclusion as cases, of whom 158 (74%) were enrolled; of those, 147 (93%) provided a stool specimen within the required time frame (Figure 1). Additionally, of 40 screened inpatients who were eligible controls, 21 (53%) were enrolled, of whom 19 (90%) provided a stool specimen within the required time frame. Among case patients who provided a stool specimen within the required time frame, the median time between AGE symptom onset and stool collection (range) was 3 (0–10) days. Among control patients who provided stool within the required time frame, the median time between enrollment and stool collection (range) was 1 (0–3) days.

Demographic characteristics of participants are described in Table 1. Sex, ethnicity, and race were similar between case and

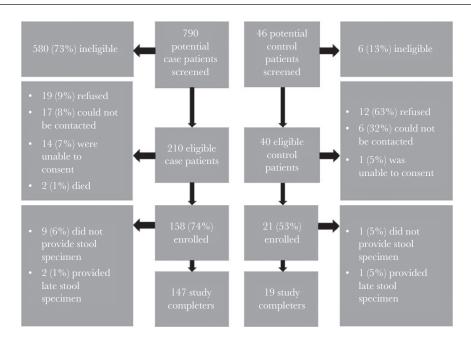


Figure 1. Screening and enrollment of acute gastroenteritis (AGE) case patients and non-AGE control patients identified through active surveillance of hospitalized veteran patients, Houston, Texas, 2015–2016.

Table 1. Demographic Characteristics of AGE Case Patients and Non-AGE Control Patients Enrolled in Active Surveillance of Hospitalized Veteran Patients, Houston, Texas, 2015–2016

	Case Patients (n = 147), No. (%)	Control Patients (n = 19), No. (%)	P Value
Age			.047
<65 y	77 (52)	15 (79)	
≥65 y	70 (48)	4 (21)	
Sex			.32
Male	139 (95)	17 (89)	
Female	8 (5)	2 (11)	
Ethnicity			.36
Hispanic/Latino	26 (18)	5 (26)	
Race			.61
Black	51 (35)	8 (42)	
White	96 (65)	11 (58)	

Abbreviation: AGE, acute gastroenteritis.

control populations; similar to the distribution of the veteran population, males comprised the majority of participants. Case and control patients differed with respect to age group; 79% of control patients were <65 years of age, compared with 52% of case patients (P < .05).

Pathogen Prevalence and Norovirus Incidence

At least 1 of the 5 viral pathogens detectable by the FilmArray Gastrointestinal Panel was detected among 20 (14%) of the 147 case patients. Norovirus was the most frequently identified viral pathogen; 16 (11%) cases were identified. Among 15 norovirus case patients with stool specimens confirmed by real-time RT-PCR, genogroup (G) II noroviruses were detected in all but 1 case (Table 2). Half of those specimens positive for GII norovirus were genotyped as GII.4 Sydney. Adenovirus F type 41 was identified in 2

Table 2. Prevalence and Genotypes of Viral Pathogens Detected Through Active Surveillance of Hospitalized Veteran Patients, Houston, Texas, 2015–2016

Pathogen	Genotype	Frequency (n = 147), No. (%)
Norovirus ^a		16 (11)
	GI.Pd-GI.3	1 (7)
	GII.P16-GII.4 Sydney	4 (29)
	GII.Pe-GII.4 Sydney	2 (14)
	GII.P16-GII.2	2 (14)
	GII.P7-GII.14	2 (14)
	GII.P17-GII.17	2 (14)
	GII.P4 New Orleans-GII.4 Sydney	1 (7)
Adenovirus	F type 41	2 (1)
Astrovirus	Type 1	1 (<1)
Sapovirus	GIV	1 (<1)

^aOne norovirus-positive case detected by FilmArray was real-time reverse transcription polymerase chain reaction (RT-PCR)–negative; a second specimen was RT-PCR-positive for norovirus genogroup II but could not be sequenced. Percentages of norovirus genotypes are therefore based on the 14 specimens that were sequenced.

(1%) case patients, and astrovirus type 1 and sapovirus GIV were each identified in 1 (<1%) case patient. No viral pathogens, including norovirus, were detected among control patients.

Norovirus cases were identified during 10 of the 13 months of surveillance, with the majority of cases experiencing illness onset during December 2015–January 2016 or October–November 2016 (Figure 2). The overall estimated norovirus incidence was 20.3 hospitalized cases/100 000 person-years (95% confidence interval [CI], 11.4–30.4 cases/100 000 person-years) (Table 3). The estimated incidence was similar when stratified by age group: 21.9/100 000 among persons aged \geq 65 years and 18.6/100 000 among persons aged \leq 65 years (P = .78). Almost all (94%) norovirus-positive cases had community-acquired gastroenteritis, resulting in a community-acquired norovirus incidence of 19.0/100 000 person-years (95% CI, 11.4–29.1 cases/100 000 person-years). Among inpatients with hospital-acquired AGE, norovirus incidence was 10.8/100 000 person-years (95% CI, 0.0–32.5 cases/100 000 person-years).

Clinical Characteristics

Overall, 143 (97%) AGE case patients reported experiencing diarrhea; 79 (54%) case patients reported experiencing only diarrhea (Table 4). Vomiting was reported by 67 (46%) case patients, and 20 case patients (14%) reported a fever (defined as ≥100.4°F) upon enrollment. Of 80 case patients who provided information regarding the full duration of illness upon follow-up interview, norovirus-positive case patients experienced illness for a significantly shorter duration, with a median (range) of 1.5 (1-5) days, whereas norovirus-negative case patients were ill for a median (range) of 5 (1–13) days (P < .01) (Table 4). The maximum number of vomiting episodes in a 24-hour period was significantly greater among norovirus-positive case patients (median [range], 6 [1-16] episodes) compared with norovirus-negative case patients (median [range], 3 [1–20] episodes; P < .01). There were no significant differences in reported fever or diarrhea between norovirus-positive and -negative case patients.

Exposures before illness onset and enrollment, including animal contact, travel, and antibiotic use, were generally similar between norovirus-positive and -negative case patients (Table 4). More norovirus-positive case patients (n = 4, 25%) than norovirus-negative case patients (n = 2, 2%; P < .01) reported contact with an individual inside their own household who had experienced vomiting or diarrhea in the week before their illness onset.

Outcomes among all case patients, both norovirus-positive and -negative, were also similar (Table 4). Although few cases took oral rehydration fluids of any type before arriving at the hospital, a majority of case patients, including all norovirus-positive case patients, reported at enrollment that they had received intravenous (IV) fluids for their illness during their hospitalization. Of 4 deaths that occurred among case patients, none were recorded among norovirus- or other virus-positive case patients.

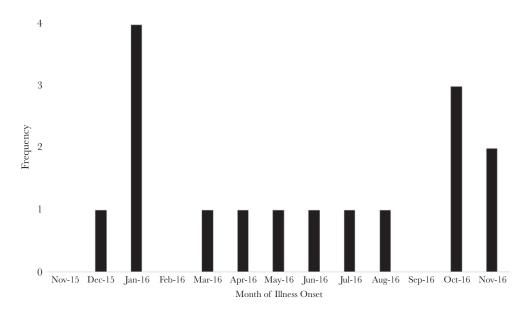


Figure 2. Norovirus cases identified through active surveillance of hospitalized veteran patients, by month of illness onset, Houston, Texas, 2015–2016 (n = 16).

DISCUSSION

This study employed active surveillance and robust screening methods to enroll patients meeting a standardized AGE case definition as well as a non-AGE control group to assess rates of asymptomatic infection. Surveillance was conducted among veterans enrolled in the VA health care system, allowing for calculation of incidence of norovirus-associated hospitalizations among patients who utilized VA health care services over approximately 1 year. Confirming previous findings among laboratory-confirmed acute gastroenteritis cases across the age spectrum, norovirus was the most commonly detected viral pathogen in this population. Norovirus was detected in 11% of case patients, almost all of whom had community-acquired infections, resulting in an estimated overall incidence of 20.3 cases/100 000 person-years (95% CI, 11.4–30.4 cases/100 000 person-years), with similar estimates for those under and over 65 years of age.

The prevalence of norovirus detected among case patients in this surveillance platform is higher than the prevalence rates of previously reported studies using laboratory-confirmed infections, which ranged from approximately 4% to 6% of adult specimens tested overall [11, 12, 15]. These other studies utilized passive surveillance methods and tested specimens that were submitted for routine clinical testing (eg, bacterial culture), which may have included specimens from individuals with chronic gastroenteritis and other varying clinical presentations, which could potentially underestimate norovirus prevalence. In contrast, our platform actively enrolled patients within 10 days of symptom onset and utilized a standardized case definition for eligibility that required a minimum number of vomiting and/or diarrheal episodes in a 24-hour period. This may have restricted the number of patients who were eligible for inclusion but may have increased the potential for identification of norovirus-associated AGE cases, leading to more accurate estimates of norovirus prevalence.

The estimates of norovirus incidence reported in this study, however, are generally consistent with those previously published for adults in the inpatient setting. Lopman et al. used an indirect statistical method to estimate norovirus-associated hospital discharges from 1996 to 2007; this method resulted in estimates between 10 discharges/100 000 patients and 185 discharges/100 000 patients in patients aged 18–64 years through

Table 3. Norovirus Prevalence and Incidence Among Hospitalized Veteran Patients Enrolled in Active Surveillance, Houston, Texas, 2015–2016

	Total Patients ^a	Eligible Inpatients, <i>No</i> .	Enrolled Inpatients With Specimen Submitted, No.	Norovirus Positive, <i>No.</i>	Norovirus Prevalence, %	Norovirus Incidence per 100 000 Person-Years (95% CI)
Overall	104 504	210	147	16	10.9	20.3 (11.4–30.4)
<65 y	57 550	99	77	9	11.7	18.6 (8.3–31.0)
≥65 y	46 954	111	70	7	10.0	21.9 (9.4–37.5)
Community-acquired	104 504	156	109	15	13.8	19.0 (11.4–29.1)
Hospital-acquired	12 199	54	38	1	2.6	10.8 (0.0–32.5)

Abbreviation: CI, confidence interval.

^aUnique patients served was used as the denominator for all calculations except hospital-acquired incidence, for which total inpatient discharges was used. Community-acquired and hospital-acquired incidence estimates are both less than the overall incidence estimate due to these differences in denominators.

Table 4. Characteristics of AGE Case Patients and Comparisons Between Norovirus-Positive and -Negative AGE Case Patients Identified Through Active Surveillance of Hospitalized Veteran Patients, Houston, Texas, 2015–2016

	No. of Case Patients With Information (n = 147)	All AGE Case Patients	Norovirus-Positive Case Patients (n = 16)	Norovirus- Negative Case Patients (n = 131)	<i>P</i> Value ^a
Symptoms reported by patient upon enrollment					
Diarrhea	n = 147	143 (97)	16 (100)	127 (97)	1.00
Maximum no. of episodes in a 24-h period	n = 137	5 (1–30)	6 (2–20)	5 (1–30)	.90
Diarrhea only	n = 147	79 (54)	5 (31)	74 (56)	.07
Vomiting	n = 146	67 (46)	11 (69)	56 (43)	.06
Maximum no. of episodes in a 24-h period	n = 62	4 (1-20)	6 (1–16)	3 (1–20)	<.01
Vomiting only	n = 147	4 (3)	0 (0)	4 (3)	1.00
Fever (100.4°F or greater)	n = 140	20 (14)	4 (27)	16 (13)	.23
Highest temperature reported at enrollment, °F	n = 20	102 (101–107)	102 (102-103)	102 (101–107)	.99
Total duration of AGE illness (vomiting and/or diarrhea), b d	n = 80	5 (1–13)	1.5 (1–5)	5 (1–13)	<.01
Exposure history					
Animal contact in the 7 d before enrollment	n = 147	61 (42)	6 (38)	55 (42)	.79
Travel in the 7 d before enrollment	n = 147	2 (1)	0 (0)	2 (1)	1.00
Received antibiotics in the 2 wk before illness onset	n = 146	7 (5)	0 (0)	7 (5)	1.00
Community-acquired AGE (vs hospital-acquired)	n = 147	109 (74)	15 (94)	94 (72)	.07
Contact with someone inside the household with diarrhea or vomiting, in the wk before illness onset	n = 146	6 (4)	4 (25)	2 (2)	<.01
Contact with someone outside the household with diarrhea or vomiting, in the wk before illness onset	n = 139	3 (2)	1 (7)	2 (2)	.29
Outcomes					
Consulted a doctor for illness before admission	n = 147	7 (5)	1 (6)	6 (5)	.56
Took oral rehydration fluids for illness	n = 147	25 (17)	4 (25)	21 (16)	.48
Received antibiotics for illness	n = 144	41 (28)	2 (13)	39 (30)	.24
Received intravenous fluids for illness	n = 144	119 (83)	16 (100)	103 (80)	.07
Deceased	n = 147	4 (3)	0 (0)	4 (3)	1.00

Data are presented as No. (%) or median (range).

Abbreviation: AGE, acute gastroenteritis.

patients aged 85 years or older, respectively [6]. Additionally, from 2011 to 2012, Grytdal et al. tested specimens that were previously submitted for clinician-requested diagnostics at 4 VA medical centers, including MEDVAMC [11]. Through this passive surveillance approach, the authors estimated a community-acquired inpatient norovirus incidence of 11/100 000 patients per year, and a hospital-acquired inpatient norovirus incidence of 54/100 000 patients per year in the inpatient setting [11]. Notably, although our community-acquired inpatient norovirus estimate was slightly higher than that reported by Grytdal et al., our hospital-acquired inpatient norovirus estimate was considerably lower. This was likely due to a hospital outbreak of norovirus that occurred at 1 site during Grytdal et al's study period, which affected the overall incidence estimate. No outbreaks in the hospital were reported to our study team during this study period, and thus our estimates likely reflect the incidence of sporadic illness.

The exposure history, symptoms, and outcomes reported by norovirus-positive case patients in this study are consistent with previous descriptions of the clinical characteristics and epidemiology of norovirus. More norovirus-positive case patients than norovirus-negative case patients reported contact with

someone inside their home who had AGE symptoms the week before illness, which is in line with the high level of infectiousness of the virus and predominantly person-to-person route of transmission [24–26]. Norovirus-positive case patients in our study also reported a shorter duration of illness and more episodes of vomiting than norovirus-negative case patients, consistent with the clinical characteristics of norovirus [27, 28].

Our study was conducted over a 13-month time frame, from early November 2015 through the end of November 2016. Norovirus incidence tends to exhibit a seasonal pattern, with peak activity occurring during the winter months (December-February) [29]. Changes in the predominantly circulating genotype can lead to differences in the magnitude and timing of peak norovirus activity, including, as previously indicated, outbreaks in both community and hospital settings [30, 31]. However, sporadic illness can occur throughout the year, and conducting year-round surveillance allows for capture of such sporadic cases, as seen in this surveillance platform.

The results of this study are subject to some limitations. Our study population was predominantly male, and participants were generally older in age. This is representative of the overall

^aComparisons between norovirus-positive and -negative AGE case patients

^bAs reported upon follow-up.

population that uses VA services; in 2016, female veterans comprised only 9% of all veterans using VA services [32]. However, this is not representative of the broader US population, and therefore results may not be generalizable across other populations. Second, although all inpatients were screened for eligibility and enrolled when possible, there is potential for underascertainment of illness. The number of unique patients served in FY 2016, which was used as the denominator for the incidence estimates, includes any patient enrolled in the VA health care System who utilized services (as described) at least once at MEDVAMC over that year, regardless of their location of residence. VA patients who were hospitalized with AGE outside of MEDVAMC would not have been captured in surveillance, potentially resulting in underestimation of the incidence of illness among these patients. Additionally, due to a strict control definition that did not allow for any symptoms of acute gastroenteritis or acute respiratory illness in the 2 weeks before enrollment, few non-AGE control patients were enrolled. This limited our ability to assess the prevalence and incidence of asymptomatic viral infection among inpatients.

This study provides laboratory-confirmed estimates of norovirus prevalence and incidence among US veterans hospitalized at MEDVAMC. We report a higher prevalence of norovirus among hospitalized adults than previously demonstrated, with norovirus as the most commonly detected viral pathogen and incidence estimates that are comparable to previous studies. Additional data collected from surveillance of adult populations utilizing laboratory-confirmed diagnoses are essential for determining target populations for candidate norovirus vaccines and calculating robust estimates of sporadic illness.

Acknowledgments

Financial support. This work was supported in part by an appointment (of H.B.) to the Research Participation Program at the Centers for Disease Control and Prevention administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and CDC.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- Hall AJ, Lopman BA, Payne DC, et al. Norovirus disease in the United States. Emerg Infect Dis 2013; 19:1198–205.
- Curns AT, Steiner CA, Barrett M, et al. Reduction in acute gastroenteritis hospitalizations among US children after introduction of rotavirus vaccine: analysis of hospital discharge data from 18 US states. J Infect Dis 2010; 201:1617–24.
- Payne DC, Vinjé J, Szilagyi PG, et al. Norovirus and medically attended gastroenteritis in U.S. children. N Engl J Med 2013; 368:1121–30.
- Bucardo F, Reyes Y, Svensson L, Nordgren J. Predominance of norovirus and sapovirus in Nicaragua after implementation of universal rotavirus vaccination. PLoS One 2014; 9:e98201.
- Hemming M, Räsänen S, Huhti L, et al. Major reduction of rotavirus, but not norovirus, gastroenteritis in children seen in hospital after the introduction of RotaTeq vaccine into the National Immunization Programme in Finland. Eur J Pediatr 2013; 172:739–46.

- Lopman BA, Hall AJ, Curns AT, Parashar UD. Increasing rates of gastroenteritis hospital discharges in US adults and the contribution of norovirus, 1996-2007. Clin Infect Dis 2011; 52:466-74.
- Vinjé J. Advances in laboratory methods for detection and typing of norovirus. J Clin Microbiol 2015; 53:373–81.
- Rha B, Lopman BA, Alcala AN, et al. Incidence of norovirus-associated medical encounters among active duty United States military personnel and their dependents. PLoS One 2016; 11:e0148505.
- Gastañaduy PA, Hall AJ, Curns AT, et al. Burden of norovirus gastroenteritis in the ambulatory setting–United States, 2001-2009. J Infect Dis 2013; 207: 1058–65
- Rha B, Burrer S, Park S, et al. Emergency department visit data for rapid detection and monitoring of norovirus activity, United States. Emerg Infect Dis 2013; 19:1214–21.
- Grytdal SP, Rimland D, Shirley SH, et al. Incidence of medically-attended norovirus-associated acute gastroenteritis in four Veteran's Affairs medical center populations in the United States, 2011-2012. PLoS One 2015; 10:e0126733.
- Hall AJ, Rosenthal M, Gregoricus N, et al. Incidence of acute gastroenteritis and role of norovirus, Georgia, USA, 2004-2005. Emerg Infect Dis 2011; 17: 1381-8.
- Phillips G, Tam CC, Rodrigues LC, Lopman B. Prevalence and characteristics of asymptomatic norovirus infection in the community in England. Epidemiol Infect 2010: 138:1454–8.
- Graham DY, Jiang X, Tanaka T, et al. Norwalk virus infection of volunteers: new insights based on improved assays. J Infect Dis 1994; 170:34–43.
- Grytdal SP, DeBess E, Lee LE, et al. Incidence of norovirus and other viral pathogens that cause acute gastroenteritis (AGE) among Kaiser Permanente member populations in the United States, 2012-2013. PLoS One 2016; 11:e0148395.
- Cardemil CV, Parashar UD, Hall AJ. Norovirus infection in older adults: epidemiology, risk factors, and opportunities for prevention and control. Infect Dis Clin North Am 2017; 31:839–70.
- 17. Lopman BA, Reacher MH, Vipond IB, et al. Clinical manifestation of norovirus gastroenteritis in health care settings. Clin Infect Dis **2004**; 39:318–24.
- Bernstein DI, Atmar RL, Lyon GM, et al. Norovirus vaccine against experimental human GII.4 virus illness: a challenge study in healthy adults. J Infect Dis 2015; 211:870-8
- Cortes-Penfield NW, Ramani S, Estes MK, Atmar RL. Prospects and challenges in the development of a norovirus vaccine. Clin Ther 2017; 39:1537–49.
- US Department of Veterans Affairs. Vetarans Health Administration. 2018. https://www.va.gov/health. Accessed January 2018.
- Atmar RL, Opekun AR, Gilger MA, et al. Norwalk virus shedding after experimental human infection. Emerg Infect Dis 2008; 14:1553–7.
- Cannon JL, Barclay L, Collins NR, et al. Genetic and epidemiologic trends of norovirus outbreaks in the US demonstrated emergence of novel GII. 4 recombinant viruses, 2013–2016. J Clin Microbiol 2017; 55:2208–21.
- Chhabra P, Payne DC, Szilagyi PG, et al. Etiology of viral gastroenteritis in children <5 years of age in the United States, 2008-2009. J Infect Dis 2013; 208-790-800
- Phillips G, Tam CC, Rodrigues LC, Lopman B. Risk factors for symptomatic and asymptomatic norovirus infection in the community. Epidemiol Infect 2011; 139:1676–86.
- de Wit MA, Koopmans MP, van Duynhoven YT. Risk factors for norovirus, Sapporo-like virus, and group A rotavirus gastroenteritis. Emerg Infect Dis 2003; 9:1563-70.
- Wikswo ME, Kambhampati A, Shioda K, et al; Centers for Disease Control and Prevention (CDC). Outbreaks of acute gastroenteritis transmitted by person-to-person contact, environmental contamination, and unknown modes of transmission–United States, 2009-2013. MMWR Surveill Summ 2015; 64:1–16.
- Rockx B, De Wit M, Vennema H, et al. Natural history of human calicivirus infection: a prospective cohort study. Clin Infect Dis 2002; 35:246–53.
- Kaplan JE, Feldman R, Campbell DS, et al. The frequency of a Norwalk-like pattern of illness in outbreaks of acute gastroenteritis. Am J Public Health 1982; 72:1329–32.
- Ahmed SM, Lopman BA, Levy K. A systematic review and meta-analysis of the global seasonality of norovirus. PLoS One 2013; 8:e75922.
- Zheng DP, Widdowson MA, Glass RI, Vinjé J. Molecular epidemiology of genogroup II-genotype 4 noroviruses in the United States between 1994 and 2006. J Clin Microbiol 2010: 48:168–77.
- Yen C, Wikswo ME, Lopman BA, et al. Impact of an emergent norovirus variant in 2009 on norovirus outbreak activity in the United States. Clin Infect Dis 2011; 53:568–71.
- US Department of Veterans Affairs. VA utilization profile, FY 2016. November
 https://www.va.gov/vetdata/docs/Quickfacts/VA_Utilization_Profile.pdf.
 Accessed January 2018