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## Incidence, Etiology, and Severity of Acute Gastroenteritis Among Prospectively Enrolled Patients in 4 Veterans Affairs Hospitals and Outpatient Centers, 2016–2018

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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## Abstract

**Background.**—Acute gastroenteritis (AGE) burden, etiology, and severity in adults is not well characterized. We implemented a multisite AGE surveillance platform in 4 Veterans Affairs Medical Centers (Atlanta, Georgia; Bronx, New York; Houston, Texas; and Los Angeles, California), collectively serving >320 000 patients annually.

**Methods.**—From 1 July 2016 to 30 June 2018, we actively identified inpatient AGE case patients and non-AGE inpatient controls through prospective screening of admitted patients and passively identified outpatients with AGE through stool samples submitted for clinical diagnostics. We abstracted medical charts and tested stool samples for 22 pathogens by means of multiplex gastrointestinal polymerase chain reaction panel followed by genotyping of norovirus- and rotavirus-positive samples. We determined pathogen-specific prevalence, incidence, and modified Vesikari severity scores.

**Results.**—We enrolled 724 inpatients with AGE, 394 non-AGE inpatient controls, and 506 outpatients with AGE. *Clostridioides difficile* and norovirus were most frequently detected among inpatients (for AGE case patients vs controls: *C. difficile*, 18.8% vs 8.4%; norovirus, 5.1% vs 1.5%;  $P < .01$  for both) and outpatients (norovirus, 10.7%; *C. difficile*, 10.5%). The incidence per 100 000 population was highest among outpatients (AGE, 2715; *C. difficile*, 285; norovirus, 291) and inpatients 65 years old (AGE, 459; *C. difficile*, 91; norovirus, 26). Clinical severity scores were highest for inpatient norovirus, rotavirus, and *Shigella*/enteroinvasive *Escherichia coli* cases. Overall, 12% of inpatients with AGE had intensive care unit stays, and 2% died; 3 deaths were associated with *C. difficile* and 1 with norovirus. *C. difficile* and norovirus were detected year-round with a fall/winter predominance.

**Conclusions.**—*C. difficile* and norovirus were leading AGE pathogens in outpatient and hospitalized US veterans, resulting in severe disease. Clinicians should remain vigilant for bacterial and viral causes of AGE year-round.

Acute gastroenteritis (AGE), characterized by diarrhea, vomiting, fever, and abdominal pain, causes 1.3 million deaths globally every year [1]. In the United States, AGE causes 179 million cases and 1 million hospitalizations annually [2, 3]. Historically, AGE prevention and control efforts have focused on children, but adults experience a substantial proportion of illness; most US deaths are in older adults [3, 4]. Both viral and bacterial pathogens play important roles in AGE across all age groups, and norovirus and *Clostridioides difficile* are important emerging infectious causes of AGE among US adults, including AGE-associated deaths [4]. In the United States, norovirus causes 20 million AGE illnesses and about 800 deaths every year [5]. *C. difficile*, increasingly observed in community and acute care settings, caused an estimated 453 000 infections with 29 000 associated deaths in 2011 [6]. Other pathogens, such as rotavirus, contribute to AGE in children [7], but the adult burden is largely unknown.

Despite accumulating evidence on the importance of specific pathogens for AGE, population-based studies of the endemic burden of all-cause AGE in adults are rare. Although some data are available on bacterial pathogens [8], lack of population-based data on viral pathogens hinders estimations of pathogen-specific prevalence and incidence to inform clinical management and interventions, such as vaccines. Past viral AGE burden studies used indirect methods, such as billing codes without laboratory confirmation of disease; relied on clinician-ordered diagnostic testing results, which can bias detection away from viral pathogens; or focused on groups or populations that limit generalizability [3, 7, 9–11]. Moreover, traditional surveillance methods have been limited by infrequent diagnostic testing, except in severe AGE cases or outbreak settings [12]. With norovirus and *C. difficile* vaccines in clinical trials among all age groups [13, 14], robust pathogen-specific burden estimates are needed for baseline data that can serve as benchmarks for future impact evaluations.

To address these gaps, SUPERNOVA (Surveillance Platform for Enteric and Respiratory Infectious Organisms in the Veterans Affairs population) was established as a multisite outpatient and inpatient surveillance platform in VA medical centers (VAMCs) in Atlanta, Georgia; Bronx, New York; Houston, Texas; and Los Angeles, California. The project was initially designed to estimate the norovirus burden through passive surveillance [15, 16]; in 2015, an active surveillance pilot was launched at 1 site to characterize the AGE etiologic burden [17]. Subsequently, SUPERNOVA expanded to include active and passive AGE surveillance at all 4 sites, as well as testing for 22 gastrointestinal pathogens.

In the current article, we describe findings from the first 2 years of prospective, inpatient and outpatient multisite surveillance for AGE, with standardized methods and laboratory testing. We sought to estimate prevalence and incidence of outpatient encounters and inpatient hospitalizations for AGE due to norovirus, in the context of other viral, bacterial, and parasitic pathogens. Secondary objectives included describing the severity of illness among hospitalized patients with AGE caused by specific pathogens. Findings will inform clinical AGE management in adults and future treatment and control interventions for AGE pathogens.

## METHODS

### Participants and Case Definitions

SUPERNOVA sites served 322 468 unique veterans in outpatient and inpatient settings in fiscal year 2018 (24 485 in the Bronx, 83 477 in Los Angeles, 104 926 in Houston, and 109 580 in Atlanta). For inpatient active surveillance, veterans ≥18 years of age admitted to a participating VAMC were screened for eligibility during 2 surveillance years (from 1 July 2016 to 30 June 2017 and from 1 July 2017 to 30 June 2018). Active cases were defined as the occurrence of ≥3 loose stools, ≥2 episodes of vomiting, or ≥1 episode of both loose stool and vomiting in a 24-hour period and illness ≥10 days in duration. Patients were excluded if symptoms were present for >10 days or attributed to a noninfectious cause; if they were transferred from another hospital after admission of >48 hours; or if they were enrolled within the previous month. Controls were patients without AGE symptoms for ≥2 weeks, and were frequency matched to case patients by age

bracket (<65 or ≥65 years) and admission date (±1 week). All inpatients meeting inclusion criteria during core surveillance hours were invited to participate (Supplementary Methods). For outpatient passive surveillance, patients with stool specimens collected for clinician-requested diagnostic testing in each site's catchment area that met the case definition—acute onset of AGE symptoms recorded in the medical chart—were included in outpatient surveillance.

### Laboratory Testing

Whole stool specimens were tested at each VAMC using the BioFire FilmArray Gastrointestinal Panel (bioMérieux), a polymerase chain reaction (PCR)-based multidagnostic assay with targets for 22 viral, bacterial, and parasitic pathogens (<https://www.biomerieux-diagnostics.com/filmarray-gi-panel>). Stool samples with norovirus or rotavirus detected using this panel were shipped to the Centers for Disease Control and Prevention for real-time reverse-transcription quantitative PCR testing and genotyped by sequencing [18–21].

### Statistical Analysis

The final analysis included the Houston VAMC from 1 July 2016 through 30 November 2016, and all 4 sites after the Atlanta, Bronx, and Los Angeles VAMCs began surveillance from 1 December 2016 through 30 June 2018. We calculated the prevalence of each pathogen among case patients and controls; examined the severity of illness, including duration of illness, hospital stay, modified Vesikari score (Supplementary Table 1), and intensive care unit (ICU) stay; and identified deaths by follow-up interview for inpatients, stratified by pathogens. We generated confidence intervals by bootstrapping or by assuming Poisson and conducted comparisons with Mann-Whitney,  $\chi^2$ , and Fisher exact tests in SAS 9.4 software (SAS Institute). We report in-depth results for case patients where pathogen prevalence significantly differed between case patients and controls.

The incidence per 100 000 person-years among a VA patient population was calculated based on previously published methods [15, 17]. To identify only incident episodes of AGE, we counted encounters within 30 days as a single episode. Inpatient incidence estimates were stratified as community onset (illness onset before admission or on the day of or the day after admission) or hospital onset (illness onset ≥2 days after admission).

## RESULTS

### Enrollment, Demographics, and Risk Factors for AGE Case Patients

Over the 2-year surveillance period, 793 inpatients were enrolled (53% of eligible patients), and 724 (91%) completed all baseline study procedures (Figure 1). For outpatients, 544 stool specimens were available from clinician-ordered diagnostic testing; 506 (93%) met eligibility criteria and were included in analyses (Figure 1). Stool specimens were collected a median of 3 days after symptom onset for inpatients, and 4 days after onset for outpatients.

Most participants were male, reflective of the veteran population. Their median ages were 64 years for inpatients with AGE and 63 years for controls ( $P = .5$ ) (Table 1). Inpatients with

AGE were more likely than controls to have human immunodeficiency virus (HIV) (8.4% vs 2.4%;  $P = .003$ ), severe renal disease (18.1% vs 4.9%;  $P < .001$ ), or household contact with a patient with AGE (5.2% vs 2.3%;  $P = .02$ ) or to be transplant recipients (2.8% vs 0%;  $P = .01$ ).

### Pathogen Prevalence, Seasonality, and Laboratory Testing

Among inpatients, prevalence of 6 pathogens differed significantly between case patients and controls: *C. difficile* (18.8% vs 8.4%;  $P < .001$ ), norovirus (5.1% vs 1.5%;  $P = .003$ ), *Campylobacter* (3.9% vs 0.5%;  $P < .001$ ), *Shigella*/enteroinvasive *Escherichia coli* (EIEC) (2.2% vs 0%;  $P = .003$ ), *Salmonella* (1.8% vs 0.3%;  $P = .03$ ), and rotavirus (1.5% vs 0%;  $P = .01$ ) (Figure 2A). In the outpatient setting, norovirus (10.7%) and *C. difficile* (10.5%) were leading pathogens (Figure 2B). Among both inpatients and outpatients, most patients with *C. difficile* or norovirus (inpatients, 84% and 70%, respectively; outpatients, 75% and 80%) had only a single pathogen detected with FilmArray; the most common codetection was *C. difficile* and norovirus (in 8 inpatients and 2 outpatients). The highest norovirus prevalence was in adults aged 18–64 years (13%–36% by setting; Supplementary Table 2).

Most AGE cases in inpatients were community onset (80%) rather than hospital onset (20%); 78% of *C. difficile* cases, and 95% of norovirus cases were community onset (Supplementary Tables 2 and 3). The prevalence of *C. difficile* in community-onset cases did not differ from that in hospital-onset cases (18% vs 21%, respectively;  $P = .4$ ), and the prevalence of norovirus was higher in community-onset cases (6% vs 1%;  $P = .03$ ).

AGE cases were identified year-round (Figure 3A and 3B). Norovirus was detected every month, most commonly in November–January, reaching a peak prevalence of 16% in December. Rotavirus showed a distinct peak in April. Among bacterial pathogens, *C. difficile* was also detected year-round and reached a peak prevalence of 23% in October.

Norovirus-positive samples were typed into 7 GI and 12 GII types; GII.4 Sydney[P16] (56%) viruses were most common, followed by GII.2[P16] (11%) (Figure 4). The most common rotavirus genotypes were G12P[8] (79%) and G2P[4] (11%). For inpatient AGE cases with clinician-ordered testing data, 83% of *C. difficile* cases (55 of 66) positive by BioFire assay were also tested with PCR in the respective institution's clinical laboratory (Cepheid Xpert *C. difficile* or Xpert *C. difficile*/Epi; Cepheid); of these cases, 87% (48 of 55) were also positive for *C. difficile* by clinical laboratory test. Clinical symptoms were similar among *C. difficile*-positive cases tested by both methods (data not shown).

### Incidence Estimates

The incidence of AGE hospitalizations was higher in adults ≥65 years old (459 per 100 000 population) than in those <65 years old (315 per 100 000) (Table 2). For outpatients, the reverse pattern was observed, with a slightly higher incidence in those aged <65 years (3100 vs 2247 per 100 000 in those aged ≥65 years). These age group and setting trends were also observed for norovirus, *Campylobacter*, and rotavirus. Of note, *C. difficile* and *Salmonella* had higher rates in adults ≥65 years of age for both inpatients and outpatients.

*C. difficile* and norovirus had the highest inpatient and outpatient incidence rates (*C. difficile*, 71.3 and 285 per 100 000, respectively; norovirus, 19.4 and 291 per 100 000). The hospital-onset rate for *C. difficile* (114 per 100 000) was notably higher than that of other pathogens, and higher than the *C. difficile* community-onset rate (55.6 per 100 000). For norovirus, the community-onset rate (18.3 per 100 000) was more than twice the hospital-onset rate (7.6 per 100 000). Norovirus incidence was twice as high in winter (November–April) as in summer (May–October), among both outpatients (542 vs 253 per 100 000) and inpatients (29 vs 12.5 per 100 000).

### Clinical Symptoms and Severity of Illness Among Inpatients

Almost all inpatients with AGE had diarrhea (94%), and half had vomiting; the median duration of illness at follow-up was 7 days (Table 3). By modified Vesikari clinical severity scores, inpatient AGE cases were largely classified as moderate (42%) or severe (52%). Among all pathogens, norovirus, rotavirus, and *Shigella*/EIEC had higher median severity scores, and the largest proportions of severe scores (73%, 73%, and 80%, respectively).

Overall, 12% of AGE case patients had ICU stays. By pathogen, *Shigella*/EIEC and *C. difficile* case patients had the highest proportion of ICU stays (20% and 17%, respectively) (Table 3). By exposure, patients with hospital-onset AGE were twice as likely to have an ICU stay, and their median hospital stay was almost 4 times that of patients with community-onset AGE (22% vs 10% and 15 vs 4 days, respectively; both  $P < .01$ ). Among the medical conditions examined (HIV, cancer, transplants, immunosuppressive therapy, and renal disease), only severe renal disease or renal failure was associated with more severe disease in patients with AGE; those with renal disease had a longer median hospital stay and a higher death rate than those without renal disease (7 vs 5 days [ $P = .005$ ] and 8% vs 2% [ $P = .01$ ], respectively).

Seventeen deaths (2%) were captured among inpatients with AGE. These included 1 norovirus-associated and 3 *C. difficile*-associated deaths. There was 1 other enteric detection among the deaths (enteroaggregative *E. coli*), but based on the clinical course of illness and detailed record review, this pathogen was not believed to be a contributing factor. In the remaining 12 deaths, no pathogens were detected.

## DISCUSSION

SUPERNOVA is a novel multisite AGE surveillance platform in the United States using prospective, active and passive, population-based surveillance with standardized case definitions and laboratory confirmation in a medically attended veteran population. We captured mild to severe AGE illness, including hospitalized cases, ICU stays, and deaths, and identified higher risk groups for AGE, including patients with certain medical conditions (HIV, transplants, and renal disease), and older adults. Testing for a wide range of AGE pathogens in a standardized fashion allowed us to identify *C. difficile* and norovirus as leading AGE pathogens, detected in inpatient and outpatient settings every month of the year, with a fall and winter predominance. These data will aid clinicians in clinical diagnosis and management for adults with AGE seeking medical care.



Norovirus was the leading viral pathogen in inpatients and outpatients with AGE. In our multisite surveillance, it is the second leading pathogen after *C. difficile* in inpatients with AGE, and the first in outpatients with AGE. Previous single-setting burden estimates for norovirus in US adults suggested that outpatient visits account for a greater proportion of cases than inpatient hospitalizations [3, 9, 15, 17]. Our findings build on these studies, demonstrating higher norovirus prevalence in outpatients (10.7%) and inpatients with community-onset AGE (6%) than in those with hospital-onset AGE (1%), and norovirus incidence estimates >1 order of magnitude greater in outpatient (291 per 100 000) than in inpatient (19.4 per 100 000) and hospital-onset settings (7.6 per 100 000).

We also demonstrate that sporadic cases of norovirus were more common in the fall and winter months, from October through January, reaching peak prevalence of 1 in 6 AGE cases in December, and genotype GII.4 Sydney[P16] was detected in just more than half of norovirus positives. Although the genotypes are consistent with national outbreak surveillance [22], our outpatient and hospital surveillance detected an increase in norovirus cases approximately 2 months earlier in the fall. Earlier detection in the norovirus winter season can alert public health professionals to increase prevention and control efforts, and provide clinicians with timely data to inform appropriate testing and clinical decision making. We also demonstrate the heightened risk of older adults infected with norovirus. Every year in the United States, adults ≥65 years old account for almost half of norovirus hospitalizations and are at high risk for severe norovirus disease, including longer duration of symptoms and death [23]. In our study, norovirus prevalence was significantly higher in adults ≥85 years old, and the incidence of hospitalizations was almost twice as high in adults ≥65 years old as in younger adults.

*C. difficile* was the leading pathogen among inpatients; hospital-onset incidence was >10 times higher than any other pathogen, and twice the *C. difficile* community-onset incidence. Substantial *C. difficile* burden among veterans has been recognized [24, 25], and a national longitudinal study of veterans in 2003–2014 found increasing rates for initial and recurrent *C. difficile* episodes over time [25]. However, retrospective studies relying on ICD codes and laboratory test results are influenced by changing diagnostics, including increased use of nucleic acid amplification tests, which are more sensitive than toxin assays. More recent data from Centers for Disease Control and Prevention demonstrate that although community-associated *C. difficile* cases have increased, healthcare-associated cases are decreasing [26, 27]. In addition, there is increased recognition that many hospitalized patients with toxigenic *C. difficile* in their stool, identified either by toxigenic culture or nucleic acid amplification test (as in our surveillance), may be only colonized. This is reflected in clinical practice guidelines that highlight the importance of testing only patients with a high pretest likelihood for *C. difficile* and using more specific tests when this cannot be reasonably assured, as well as consideration of a multistep algorithm for testing [28]. Together with the high detection rate of *C. difficile* in non-AGE controls, this suggests that our *C. difficile* attributable fraction estimates, which indicate a 40% lower inpatient incidence rate, may provide more realistic estimates. From a clinical standpoint, these findings suggest that clinicians may consider the colonization rate in controls before starting antibiotic treatment in the setting of a positive result. Nonetheless, even with these lower adjusted estimates, *C. difficile* remained the leading inpatient pathogen, and adults ≥65 years of age with *C.*

*difficile* had higher incidences than younger adults in both inpatients and outpatients, an important finding because older adults have higher morbidity and mortality rates related to *C. difficile* infection [29].

Our platform was also unique in its capture of adult rotavirus AGE cases, which demonstrated a distinct winterspring peak and higher incidence in the first surveillance year. Rotavirus is a well-known cause of diarrhea in children, yet the epidemiology and burden of rotavirus in adult populations is not well understood, particularly in the postvaccination era. Indeed, we identified only 1 other study in the United States reporting rotavirus incidence rates in adults in the ambulatory setting, using an insurance claim database in the prevaccine era in outpatient and emergency rooms [9]. The reported incidence in the outpatient setting (8–19 per 100 000) was much lower than in our study (overall, 81 per 100 000; winter peak, 142 per 100 000); this difference could be due in part to infrequent stool diagnostic testing for rotavirus in adults, and it demonstrates the strength of our surveillance. Adult rotavirus prevalence estimates are similarly sparse. Interestingly, our rotavirus prevalence estimates (inpatients, 1.5%; outpatients, 3%) were similar to that reported from a hospital that retrospectively tested adult stool specimens collected for bacterial stool culture February to May each year from 2006 to 2011 (2.8%), as well as outpatient adult stool specimens submitted to a managed care organization in 2012–2013 (1%–3%) [30, 31]. Widespread rotavirus vaccination in children has altered the US rotavirus seasonal pattern to biennial peaks from January to April [32], and G12P[8] has been the predominant strain detected since 2012 [21]; both the seasonality and genotyping in children are consistent with our findings in the current adult population.

The severity of disease for several pathogens was notable. *Shigella*/EIEC, norovirus, and rotavirus cases had the highest proportion of severe disease as measured by modified Vesikari score, whereas *Shigella*/EIEC and *C. difficile* cases had the highest proportion of ICU stays. Case patients with *C. difficile* had the longest median hospital stay, and those with norovirus the longest median ICU stay. Among AGE case patients who died, *C. difficile* and norovirus were the only pathogens detected that were believed to contribute to death. These patients had significant medical histories in addition to AGE, including cardiac, pulmonary, and renal disease that contributed to their hospitalization course and deaths.

In addition to specific pathogens, our case definition and data collection among all AGE case patients allowed for identification of subpopulations with AGE that may be at higher risk for more severe disease. First, inpatients ≥ 65 years old with AGE had higher disease incidence and longer median hospital stays than younger adults. Second, patients with AGE were more likely than controls to have HIV, be transplant recipients, or have severe or end-stage renal disease. In particular, AGE case patients with severe renal disease or renal failure had a longer median hospital stay and a death rate that was 4 times higher than AGE case patients without renal disease. Although diarrhea is common in patients with end-stage renal disease, its etiology can be challenging to determine and may include both infectious and noninfectious causes [33]; as such, this finding merits additional investigation as our surveillance continues. A third group of patients, with hospital-onset AGE, while representing only 1 in 5 AGE hospitalizations, were twice as likely to have an ICU stay and were notable for their higher AGE incidence compared with community-onset case patients.



Patients with hospital-onset AGE had longer stays, almost 4 times longer than in patients with community-onset AGE.

Our findings are subject to limitations. First, it was challenging to obtain consent and enroll ICU patients with AGE, and some patients with AGE died before enrollment; therefore, our surveillance may underestimate AGE severity. As previously noted, PCR-based assays are sensitive, and bacterial pathogens were not independently confirmed by culture or toxin assay; detection may not indicate causation. However, the significantly higher case detection rates compared with controls, high single-pathogen detection among *C. difficile* and norovirus cases, and clinical symptoms and severity consistent with expected presentations for these pathogens gives us confidence in our interpretation. Finally, veterans are predominantly male, and results may not be representative of all US adults.

In conclusion, we offer robust assessment of the burden of AGE and specific AGE pathogens, including norovirus and *C. difficile*, in an adult population before vaccine introduction for these pathogens. Ongoing surveillance will allow further characterization of AGE pathogens, genotyping, burden, and risk factors in adults. Clinicians can use these data to inform clinical diagnosis and management for adults seeking medical care for AGE.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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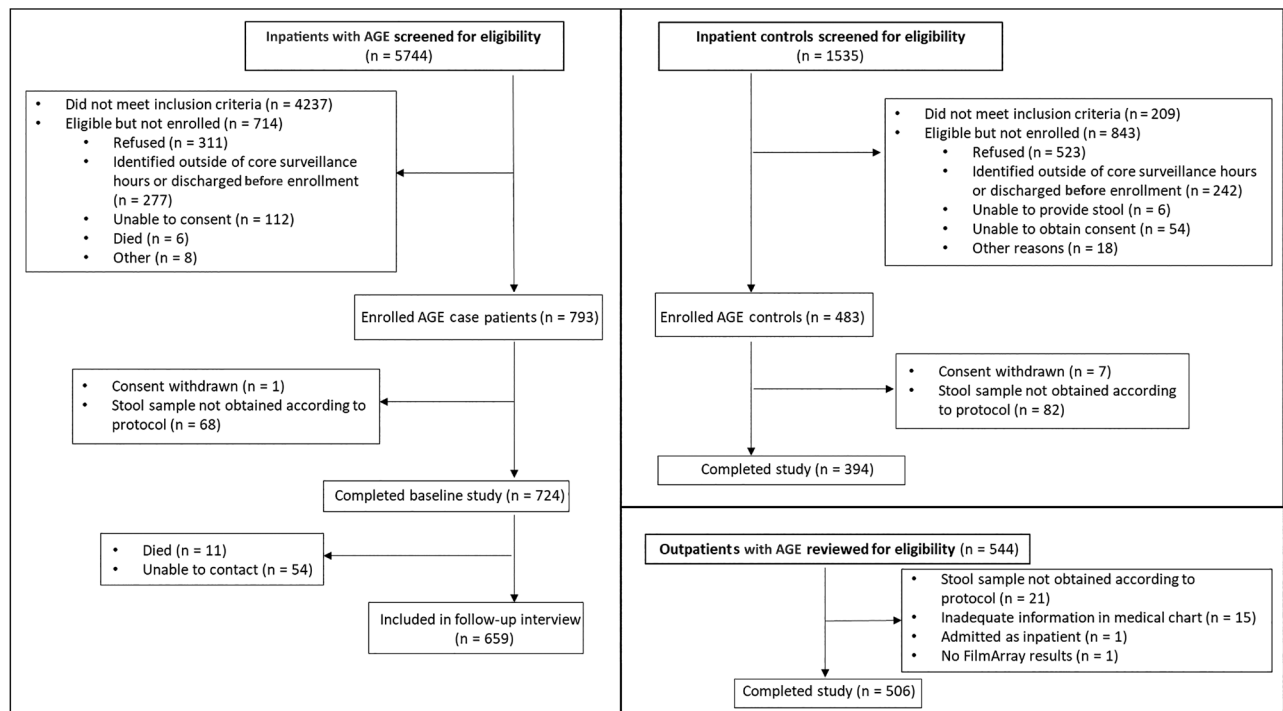
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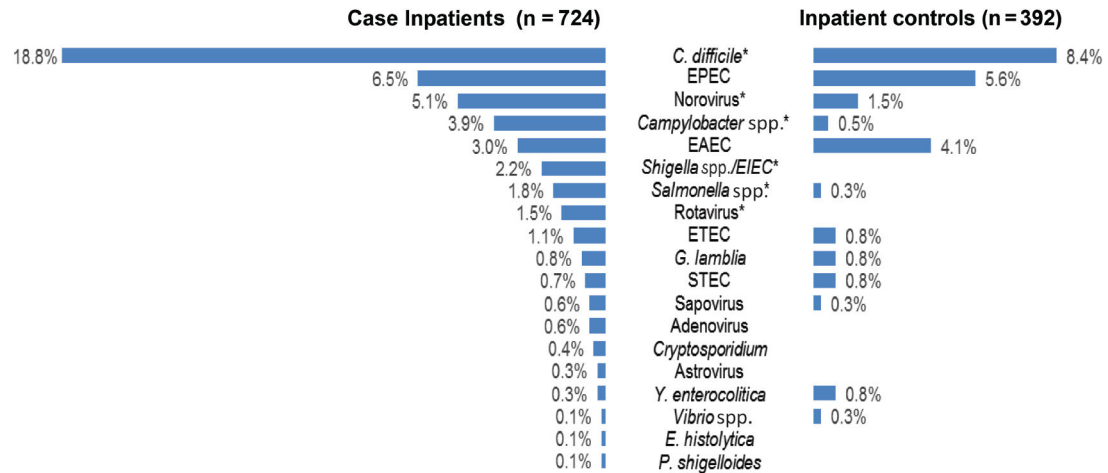
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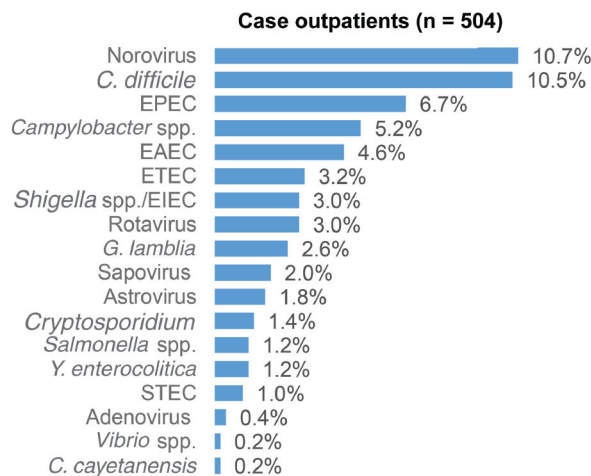


**Figure 1.** Screening, enrollment and study completion for inpatients with acute gastroenteritis (AGE), inpatient controls, and outpatients with AGE, from July 2016 to June 2018.

### a. Inpatient AGE case and non-AGE controls



### b. Outpatient AGE cases



**Figure 2.**

Prevalence of pathogens detected by means of the BioFire FilmArray Gastrointestinal Panel, from July 2016 to June 2018. A, Inpatients with acute gastroenteritis (AGE) and non-AGE inpatient controls. \*Significant difference ( $P < .05$ ;  $\chi^2$  test) in prevalence between case patients and controls for the following pathogens: *Clostridioides difficile* ( $P < .001$ ), norovirus ( $P = .003$ ), *Campylobacter* spp. ( $P < .001$ ), *Shigella*/enteroinvasive *Escherichia coli* (EIEC) ( $P = .003$ ), *Salmonella* ( $P = .03$ ), and rotavirus ( $P = .01$ ). The following pathogens are on the FilmArray panel but are not included because there were no positive detections: *Vibrio cholerae*, *Escherichia coli* O157, *Aeromonas*, and *Cyclospora cayetanensis*. Two stool specimens from inpatient controls were excluded owing to inconclusive results. B, Outpatients with AGE. The following pathogens on the FilmArray panel are not included because there were no positive detections: *Entamoeba histolytica*, *Plesiomonas shigelloides*, *V. cholerae*, *E. coli* O157, and *Aeromonas*. Two outpatient stool specimens were excluded owing to inconclusive results. Abbreviations: EAEC, enteroaggregative *Escherichia coli*; EPEC, enteropathogenic *Escherichia coli*; ETEC,

enterotoxigenic *Escherichia coli*; *G. lamblia*, *Giardia lamblia*; STEC, Shiga-like toxin-producing *Escherichia coli*; *Y. enterocolitica*, *Yersinia enterocolitica*.

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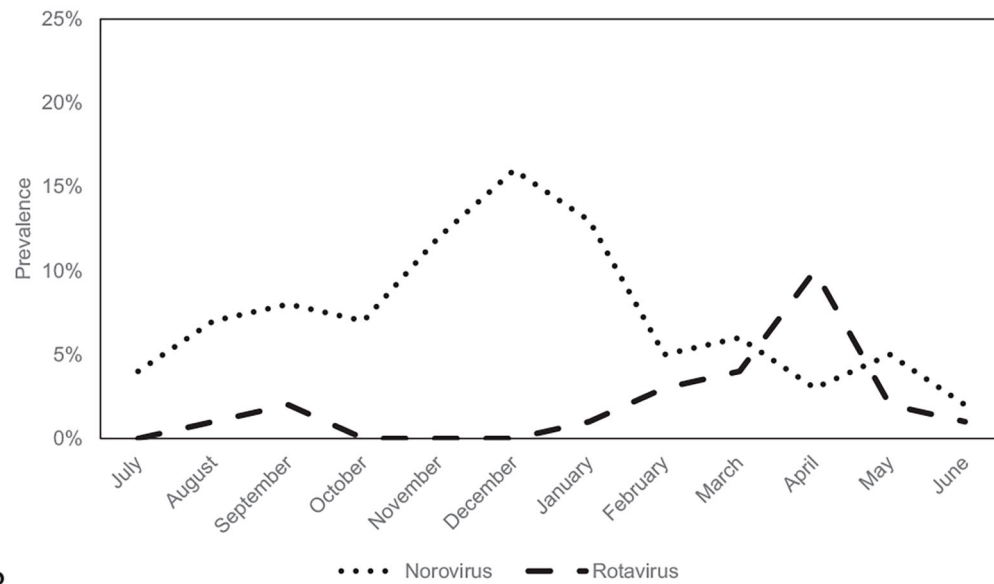
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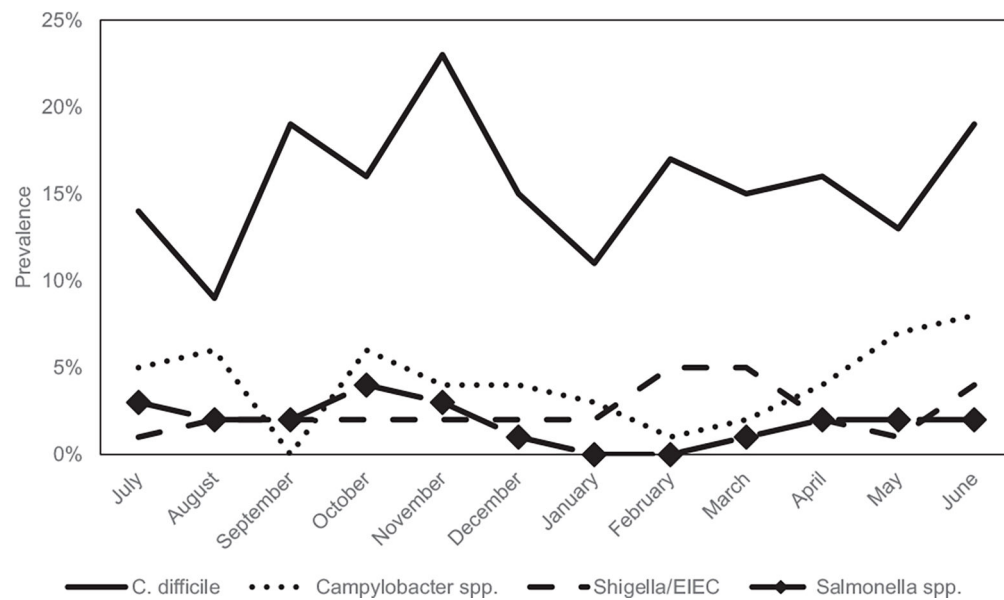
A

## Viral pathogens:

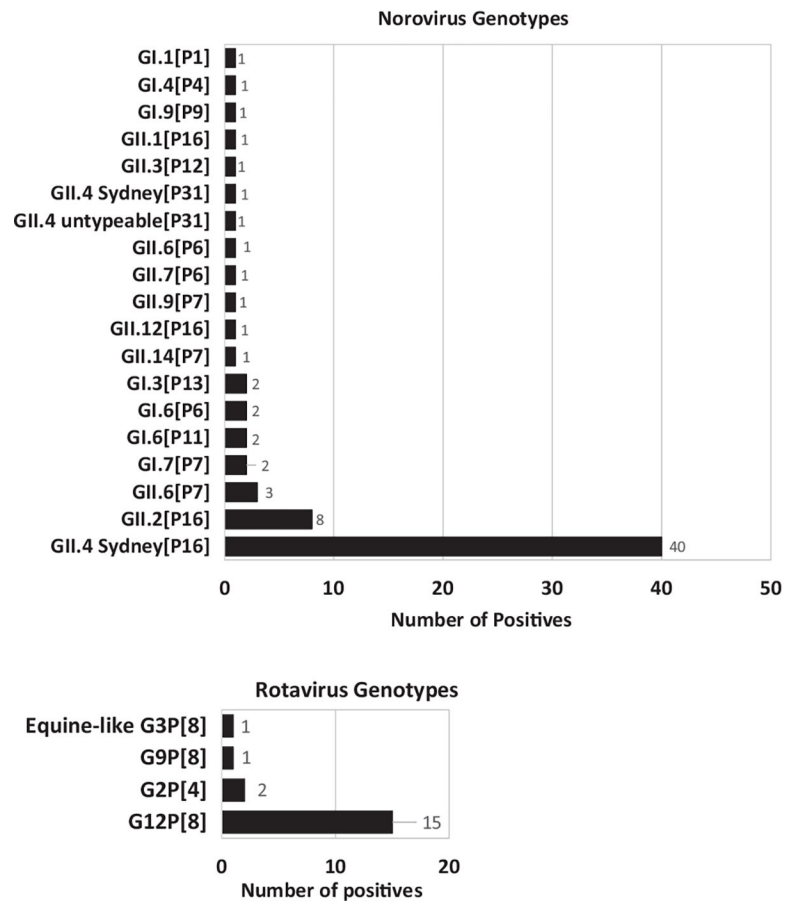


B

## Bacterial pathogens

**Figure 3.**

Seasonality of viral and bacterial pathogens among inpatient and outpatient cases, from July 2016 to June 2018. *A*, Viral pathogens. *B*, Bacterial pathogens. Abbreviations: *C. difficile*, *Clostridioides difficile*; EIEC, enteroinvasive *Escherichia coli*.



**Figure 4.**  
Genotypes for norovirus (n = 71) and rotavirus (n = 19).

Table 1.

Demographic Characteristics and Risk Factors for Inpatients with Acute Gastroenteritis (AGE), Inpatient Controls, and Outpatients With AGE, July 2016 to June 2018

Characteristic or Factor	Inpatients With AGE, No. (%) <sup>a</sup> (n = 724)	Inpatient Controls, No. (%) <sup>a</sup> (n = 394)	P Value <sup>b</sup>	Outpatients With AGE, No. (%) <sup>a</sup> (n = 506)
Age, median (range; IQR), y	64 (25–96; 55–70)	63 (23–94; 56–69)	.48	58 (23–95; 44–68)
Male sex	673 (93.0)	366 (92.9)	.97	454 (89.7)
Race				
White	343 (49.0)	182 (48.4)	<.001	253 (50)
Black	329 (47.0)	169 (45.0)		209 (41.3)
Asian	0 (0)	9 (2.4)		5 (1)
Other <sup>c</sup>	28 (4.0)	16 (4.3)		14 (2.8)
Hispanic ethnicity	102 (14.1)	43 (11.1)	.15	83 (16.7)
Study site				
Atlanta, GA	130 (18)	100 (25.4)	<.001	130 (25.7)
Bronx, NY	65 (9)	46 (11.7)		50 (9.9)
Houston, TX	375 (51.8)	98 (24.9)		184 (36.4)
Los Angeles, CA	154 (21.3)	150 (38.1)		142 (28.1)
Usual source of primary care				NA
VA primary care clinic	619 (86.1)	355 (91.7)	.006	...
Non-VA source of care <sup>d</sup>	100 (13.9)	32 (8.3)		...
Residence in 2 wk before admission				NA
Private residence (apartment/house)	270 (82.6)	179 (87.7)	.23	...
Long-term care/skilled nursing facility	11 (3.4)	5 (2.5)		...
Hotel	2 (0.6)	1 (0.5)		...
Anywhere outside (eg, street, vehicle, abandoned building)	4 (1.2)	2 (1)		...
Homeless shelter/emergency or temporary housing	3 (0.9)	4 (2)		...
Other	13 (4)	1 (0.5)		...
Multiple residences	24 (73)	12 (5.9)		...
Medical conditions <sup>e</sup>				NA

Characteristic or Factor	Inpatients With AGE, No. (%) <sup>a</sup> (n = 724)	Inpatient Controls, No. (%) <sup>a</sup> (n = 394)	P Value <sup>b</sup>	Outpatients With AGE, No. (%) <sup>a</sup> (n = 506)
HIV	56 (8.4)	5 (2.4)	.003	...
Cancer	87 (13)	26 (12.6)	.87	...
Transplant	19 (2.8)	0 (0)	.01	...
Immunosuppressive therapy	23 (3.4)	4 (1.9)	.28	...
Severe renal disease	60 (18.1)	10 (4.9)	<.001	...
Other AGE risk factors				NA
Prior hospitalization within 30 d	33 (10)	16 (79)	.44	...
Recent travel history	6 (0.8)	2 (0.5)	.72	...
Antibiotic use in 2 wk before illness onset	91 (13.2)	46 (11.9)	.55	...
Animal contact	248 (34.3)	162 (41.2)	.02	...
Household contact with AGE case patient	37 (5.2)	9 (2.3)	.02	...

Abbreviations: AGE, acute gastroenteritis; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; VA, Veterans Affairs.

<sup>a</sup>Data represent no. (%) of patients and controls unless otherwise specified. Some data were missing for race, ethnicity, residence before admission, previous hospitalization, prior antibiotic use, and household contact, representing <5% for each variable.

<sup>b</sup>P-values based on  $\chi^2$ , Fisher exact, or Wilcoxon rank-sum tests used to compare inpatients with AGE and controls.

<sup>c</sup>“Other” includes American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, multiple races, or other race.

<sup>d</sup>Non-VA sources of care included a physician's office, non-VA emergency room, urgent care center, or other non-VA site.

<sup>e</sup>Data were available for HIV/AIDS, cancer, transplants, and immunosuppressive therapy for case patients (n = 667) from October 2016 to June 2018 and for controls (n = 206) from October 2017 to June 2018. Sensitivity analysis of data from only October 2017 to June 2018 resulted in similar proportions and levels of significance. For severe renal disease (severe kidney disease or kidney failure (stage 4 [glomerular filtration rate 15–29] or 5 [glomerular filtration rate <15, or requirement for dialysis]) and prior hospitalization within 30 days, data were available for case patients (n = 331) and controls (n = 206) from October 2017 to June 2018.

Incidence Rate Estimates Among Acute Gastroenteritis Case Patients (Inpatients and Outpatients), by Pathogen and Overall, July 2016 to June 2018

Table 2.

Setting	AGE	Rate per 100 000 Population (95% CI) <sup>a</sup>					
		<i>Clostridioides difficile</i>	Norovirus	<i>Campylobacter</i>	<i>Shigella/EIEC</i>	<i>Saimoneia</i>	Rotavirus
Inpatients							
Overall	380 (363–396)	71.3 (61.3–82.3)	19.4 (13.9–26.2)	14.7 (9.4–20.4)	8.4 (4.7–12.6)	6.8 (3.7–10.5)	5.8 (2.6–9.4)
Attributable Fraction (AF) <sup>b</sup>	...	43 (41.5–44.7)	13.8 (10.7–14.8)	12.8 (0–15.8)	8.4 (4.7–12.6)	5.9 (0–76)	5.8 (2.6–9.4)
Age group							
<65 y	315 (293–334)	56.2 (44.5–68.8)	14.3 (76–21.8)	10.1 (5–15.9)	10.1 (5–15.9)	5.9 (1.7–10.1)	5.0 (1.7–9.2)
65 y	459 (433–484)	90.6 (70.9–110)	26.3 (15.8–38.1)	21 (11.8–32.8)	5.3 (1.3–11.8)	79 (2.6–14.4)	6.6 (1.3–11.8)
Exposure setting							
Community onset	218 (207–230)	55.6 (45.6–64)	18.3 (12.3–23.9)	13.6 (8.9–18.3)	79 (4.2–11.5)	6.8 (3.1–11)	5.8 (2.6–9.4)
Hospital onset	388 (347–430)	114 (79.6–145)	76 (0–19)	76 (0–19)	3.8 (0–11.4)	0 (0–0)	0 (0–0)
Season							
Winter (November–April)	504 (474–532)	84.8 (67.3–101)	29 (18.6–39.5)	12.8 (5.8–19.7)	10.4 (4.2–16.6)	5.8 (1.2–11.6)	11.6 (5.8–19.7)
Summer (May–October)	375 (351–402)	65.4 (50.9–80.0)	12.5 (6.2–19.7)	177 (9.3–26)	7 (2.3–12.8)	8.3 (3.1–14.5)	1.0 (0–3.1)
Surveillance year							
July 2016 to June 2017	268 (249–288)	46 (34.0–58.1)	15 (8–23)	10 (4.6–16.4)	6.4 (1.8–11.8)	4.6 (9–9.1)	8.0 (3.0–14)
July 2017 to June 2018	479 (453–503)	94.6 (76.7–111)	23.1 (14.7–32.6)	16.3 (9.6–24.9)	8.6 (3.8–15.3)	76 (2.9–13.4)	3.2 (0–74)
Outpatients							
Overall	2715 (2674–2755)	285 (207–361)	291 (226–366)	140 (91.6–194)	80.8 (43.1–121)	32.3 (10.8–59.2)	80.8 (48.5–119)
Age group							
<65 y	3100 (3041–3158)	272 (188–371)	329 (225–441)	169 (93.9–254)	112.7 (56.4–178)	28.2 (0–65.7)	103 (47–159)
65 y	2247 (2192–2302)	310 (207–426)	245 (155–349)	103 (38.7–181)	38.7 (0–775)	38.7 (0–90.4)	51.7 (12.9–103)
Season							
Winter (November–April)	3369 (3321–3417)	455 (313–611)	542 (381–703)	147 (73.2–234)	128 (56.9–213)	28.4 (0–71.1)	142 (56.9–227)
Summer (May–October)	2854 (2810–2899)	225 (139–321)	253 (149–372)	238 (133–357)	64.1 (21.4–117)	42.8 (5.3–85.5)	53.5 (10.7–102)
Surveillance year							
July 2016 to June 2017	2517 (2460–2574)	306 (178–428)	242 (129–354)	113 (48.4–202)	48.4 (0–112)	16.1 (0–48.4)	145 (56.5–242)
July 2017 to June 2018	2892 (2835–2950)	283 (200–374)	324 (233–420)	158 (91.4–224)	99.7 (49.9–157)	41.6 (8.3–83.1)	49.9 (16.6–91.4)

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Abbreviations: AGE, acute gastroenteritis; CI, confidence interval; EIEC, enteroinvasive *Escherichia coli*.

<sup>d</sup> CIs for AGE outpatient estimates and inpatient community and hospital-onset inpatient estimates were calculated assuming Poisson distribution. Remaining estimates including pathogen-specific CIs calculated using bootstrapping.

<sup>e</sup> The attributable fraction (AF) was calculated for inpatient pathogens based on the odds ratio (OR) of that pathogen's prevalence among case patients and controls, using the following formula:  $(OR - 1) / OR$ . The AF is an estimate of the percentage of AGE cases that can be attributed to infection with the pathogen of interest. (The AF was not calculated for other inpatient variables, owing to the small sample size for controls after stratification.)



Table 3.

Clinical Symptoms and Severity of Illness for Inpatient AGE cases, Overall and by Single and Multiple Pathogens<sup>a</sup>

	AGE (n = 724)	<i>C. difficile</i> (n = 120)	Norovirus (n = 27)	<i>Campylobacter</i> spp. (n = 22)	<i>Shigella/EIEC</i> (n = 10)	<i>Salmonella</i> spp. (n = 10)	Rotavirus (n = 11)	Multiple co-pathogens (n = 20)
Frequency of clinical symptoms, n (%)								
Fever	164/718 (23)	19/118 (16)	4/27 (15)	6/22 (27)	5/10 (50)	2/10 (20)	3/11 (27)	5/20 (25)
Diarrhea <sup>d</sup>	680/723 (94)	118/120 (98)	27/27 (100)	22/22 (100)	10/10 (100)	10/10 (100)	11/11 (100)	19/19 (100)
Vomiting	378/724 (52)	56/120 (47)	23/27 (85)	7/22 (32)	5/10 (50)	1/10 (10)	8/11 (73)	12/20 (60)
Only diarrhea	346/723 (48)	64/120 (53)	4/27 (15)	15/22 (68)	5/10 (50)	9/10 (90)	3/11 (27)	8/19 (42)
Only vomiting	43/723 (6)	2/120 (2)	0	0	0	0	0	0
Duration of clinical symptoms in days, median (range; IQR)								
Fever at enrollment	2 (1-10; 1-4)	3 (1-8; 2-4)	1 (1-1; 1-1)	3 (3-5; 3-3)	2 (1-4; 2-2)	2 (1-2; 1-2)	1 (1-1; 1-1)	2 (1-8; 1-4)
Diarrhea in 24 hours, episodes	5 (1-48; 4-8)	5 (1-30; 3-7)	5 (2-40; 4-15)	8 (3-30; 5-20)	7 (4-20; 4-10)	13 (4-30; 8-20)	10 (4-20; 5-15)	5 (2-20; 4-10)
Vomiting in 24 hours, episodes	3 (1-118; 2-6)	3 (1-118; 2-6)	4 (1-20; 2-11)	2 (1-7; 1-3)	3 (1-4; 1-3)	4 (4-4; 4-4)	3 (1-15; 2-12)	2 (1-11; 2-5)
Illness at enrollment	4 (1-10; 3-6)	4 (1-10; 3-7)	3 (1-10; 2-5)	4 (1-10; 4-6)	5 (2-9; 4-7)	5 (3-10; 4-5)	4 (2-7; 4-5)	4 (2-10; 3-5)
Illness at follow-up	7 (1-15; 4-9)	7 (1-14; 4-9)	6 (1-12; 3-7)	8 (1-15; 6-9)	7 (2-11; 4-10)	7 (3-10; 7-10)	7 (2-12; 6-9)	5 (2-15; 4-7)
Diarrhea at enrollment	4 (1-10; 2-5)	4 (1-10; 2-6)	2 (1-10; 2-5)	4 (1-10; 3-6)	5 (2-9; 3-6)	5 (3-10; 4-5)	4 (1-7; 2-5)	3 (1-10; 2-5)
Diarrhea at follow-up	6 (1-15; 4-8)	6 (1-14; 4-8)	4 (1-10; 2-7)	7 (1-15; 6-9)	6 (2-11; 4-9)	7 (3-10; 7-10)	7 (1-12; 6-8)	5 (1-15; 3-6)
Vomiting at enrollment	2 (1-10; 1-4)	2 (1-9; 1-4)	1 (1-6; 1-3)	1 (1-7; 1-2)	2 (1-4; 2-4)	4 (4-4; 4-4)	3 (1-3; 2-3)	2 (1-6; 2-3)
Vomiting at follow-up	3 (1-13; 2-5)	3 (1-10; 2-6)	2 (1-10; 1-5)	3 (1-7; 2-4)	4 (1-6; 2-4)	6 (6-6; 6-6)	3 (3-6; 3-4)	3 (1-8; 2-4)
Severity of illness								
Modified Vesikari Score (MVS), median (range) <sup>b</sup>	11 (4-19)	10 (4-18)	13 (8-17)	11 (7-17)	12 (10-16)	11 (8-17)	12 (9-18)	12 (7-16)
Mild MVS, n (%)	38 (6)	4 (4)	0	0	0	0	0	0
Moderate MVS, n (%)	293 (42)	56 (49)	7 (27)	8 (36)	2 (20)	5 (50)	3 (27)	9 (47)
Severe MVS, n (%)	362 (52)	54 (47)	19 (73)	14 (63)	8 (80)	5 (50)	8 (73)	10 (53)

	AGE (n = 724)	<i>C. difficile</i> (n = 120)	Norovirus (n = 27)	<i>Campylobacter</i> spp. (n = 22)	<i>Shigella/EIEC</i> (n = 10)	<i>Salmonella</i> spp. (n = 10)	Rotavirus (n = 11)	Multiple co-pathogens (n = 20)
ICU stay, n (%)	89/724 (12)	20/120 (17)	2/27 (7)	1/22 (5)	2/10 (20)	0	1/11 (9)	3/20 (15)
Duration of ICU stay in days, median (range; IQR)	3 (1–38; 2–6)	2 (1–11; 2–6)	11 (10–12; 10–12)	2 (2–2; 2–2)	3 (1–4; 1–4)	0	2 (2–2; 2–2)	3 (3–4; 3–4)
Duration of hospital stay in days, median (range; IQR)	5 (1–196; 3–10)	6 (2–72; 3–16)	4 (1–66; 2–8)	4 (2–26; 3–7)	3 (1–26; 3–5)	4 (2–8; 3–6)	4 (2–38; 2–6)	5 (1–28; 3–8)
Duration of hospital stay for community-onset cases	4 (1–95; 3–7)	5 (2–72; 3–8)	3 (1–13; 2–7)	4 (2–8; 3–6)	3 (1–26; 3–5)	4 (2–8; 3–6)	4 (2–38; 2–6)	5 (1–20; 3–7)
Duration of hospital stay for hospital-onset cases	15 (1–196; 9–24)	20 (5–51; 11–24)	36 (6–66; 6–66)	26 (26–26; 26–26)	0	0	0	18 (8–28; 8–28)
23 hour stay, n (%)	86/724 (12)	12/120 (10)	6/27 (22)	2/22 (9)	1/10 (10)	0	1/11 (9)	3/20 (15)
Death, n (%) <sup>c</sup>	17/723 (2)	3/120 (3)	1/27 (4)	0	0	0	0	0

<sup>a</sup>Pathogen-specific columns include AGE cases with single pathogen detections, independent of the other 5 pathogens in the table. Any co-detection ( 2) between the six pathogens are included in the multiple co-pathogens column.

<sup>b</sup>If cases were missing data for certain measurements, a Vesikari score was not assigned, pathogen (% missing): AGE (4%), Norovirus (3%), *C. difficile* (6%), *Salmonella* (8%), Modified Vesikari scoring was defined as follows: Mild (0–6), Moderate (7–10), Severe ( 11). See supplementary appendix for scoring components.

<sup>c</sup>Among these deaths, 14 occurred while hospitalized. Three deaths occurred within 1–12 days following discharge; one died in inpatient hospice, one died within 24 hours of transferring to inpatient palliative care, and one died after discharge. Deaths following discharge were ascertained when attempting the follow-up interview at 3–5 weeks post-enrollment.

*Campylobacter* spp. includes *jejuni*, *coli*, and *upsaliensis*. EIEC=*Enteroinvasive E. coli*

<sup>d</sup>Diarrhea was defined as 3 or more loose stools within a 24 hour period