Postinfectious Gastrointestinal Disorders Following Norovirus Outbreaks

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Background. The US Centers for Disease Control and Prevention estimates 20.9 million norovirus infections annually in the United States. Although the acute disease burden is sizeable, emerging data suggest norovirus may be associated with chronic gastrointestinal problems. We identified known outbreaks in US military recruits and used the Defense Medical Encounter Database (DMED) to identify the risk of new onset functional gastrointestinal disorders (FGD) and gastroesophageal reflux disease (GERD).

Methods. Subjects reporting for care of acute gastroenteritis (AGE) at a military treatment clinic during 3 known norovirus outbreaks were identified. Each AGE subject was matched with up to 4 subjects with unrelated medical encounters. Medical encounter data were analyzed for the duration of military service time (or a minimum of 1 year) to assess for incident FGD or GERD. Relative risks were calculated using regression models.

Results. We identified 1718 subjects from 3 outbreaks. After controlling for important demographic covariates, the incidence of constipation, dyspepsia, and GERD was approximately 1.5-old higher ($P < .01$) in AGE-exposed subjects than matched subjects. We also noted variability in outcome incidence across outbreaks.

Conclusions. It appears that the risk of dyspepsia, constipation, and GERD are higher among those who have AGE during a confirmed norovirus outbreak. Although these findings need confirmation, they suggest that dysmotility may result subsequent to these infections. If confirmed, the costs and morbidity associated with the chronic consequences of norovirus should be considered.

Norovirus is the major cause of epidemic gastroenteritis and is spread by the fecal-oral and vomitus-oral routes [1]. Symptomatic cases generally present with a vomiting predominant and/or watery diarrhea gastroenteritis with symptoms commonly lasting 2–3 days and are self-limiting in the young and healthy; however, excess mortality has been described in elderly populations [2].

Epidemiological evidence linking infectious gastroenteritis (IGE), of which norovirus is one cause, and functional gastrointestinal disorders (FGD) has accumulated in recent years [3]. The archetypal FGD studied to date has been irritable bowel syndrome (IBS), and prospective studies have shown that 3%–36% of all enteric infections lead to an incidence IBS diagnosis [4]. Although the majority of studies have identified pathogenic bacteria as an etiologic agent in postinfectious (PI)-IBS, recent data point to an association with other pathogens, including viruses and parasites [4]. A recent prospective study of IBS following an outbreak of norovirus-attributed severe gastroenteritis reported that 3 months postoutbreak, IBS was significantly higher in subjects with acute gastroenteritis than in control subjects [5]. Other FGD such as gastroesophageal reflux disease (GERD), dyspepsia, and constipation have shown variable association with antecedent IGE [6, 7].

In addition to outbreaks in civilian populations, norovirus is recognized as an important cause of acute gastroenteritis in active duty military populations [8–11]. Norovirus-like illness outbreaks are frequently reported and can cause transient shortages of personnel and impact military operations [12]. As has been seen with chronic sequelae after bacterial causes

Received 16 February 2012; accepted 30 May 2012; electronically published 19 June 2012.

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Clinical Infectious Diseases 2012;55(7):915–22
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2012.
DOI: 10.1093/cid/cis576

Table 1. Presumed Norovirus Outbreaks of Interest

Site of Outbreak	Outbreak Dates	Genotype	No. Ill	Reference
San Diego MCRD	1/12/04–2/8/04	Unknown	615	[30]
San Diego MCRD	12/19/04–4/14/05	GII	2301	Faix D., personal communication, 2011
Parris Island MCRD	1/16/07–2/16/07	GII	300	[31]

Abbreviation: MRCD, Marine Corps Recruit Depot.

of IGE, potential associations between norovirus and long-term PI sequelae may shed new light on the full burden of these infections and inform policy makers of previously unappreciated disability and medical costs for which mitigation strategies are needed.

MATERIALS AND METHODS

This retrospective cohort study (2004–2011) assessed the risk of PI sequelae in active duty US military personnel with acute gastroenteritis during a known norovirus outbreak. Medical data were obtained from ambulatory and inpatient claims data for care obtained within the Military Health Services databases [13]. Demographic information was obtained from personnel records, and deployment data were derived from deployment rosters and postdeployment health assessments.

The primary exposure of interest was acute IGE attributed to norovirus. Personnel reporting for care of acute gastroenteritis during a confirmed norovirus outbreak were identified using ICD9-CM and catchment-specific military treatment facility (MTF) codes. Norovirus outbreaks were identified by local public health authorities as unexpected increases in IGE illnesses that were epidemiologically linked and identified to have norovirus identified in one or more stool samples. Norovirus was identified in each of the outbreaks by local civilian or military public health laboratories using an enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR) based on standardized protocols. Start and stop times for the norovirus-associated outbreaks were based on outbreak investigations and epidemiological curves, and all first visits of patients presenting to the clinic with an IGE-associated ICD9-CM were considered to be norovirus-associated. The outbreaks considered for this exposure are shown in Table 1 and Figure 1.

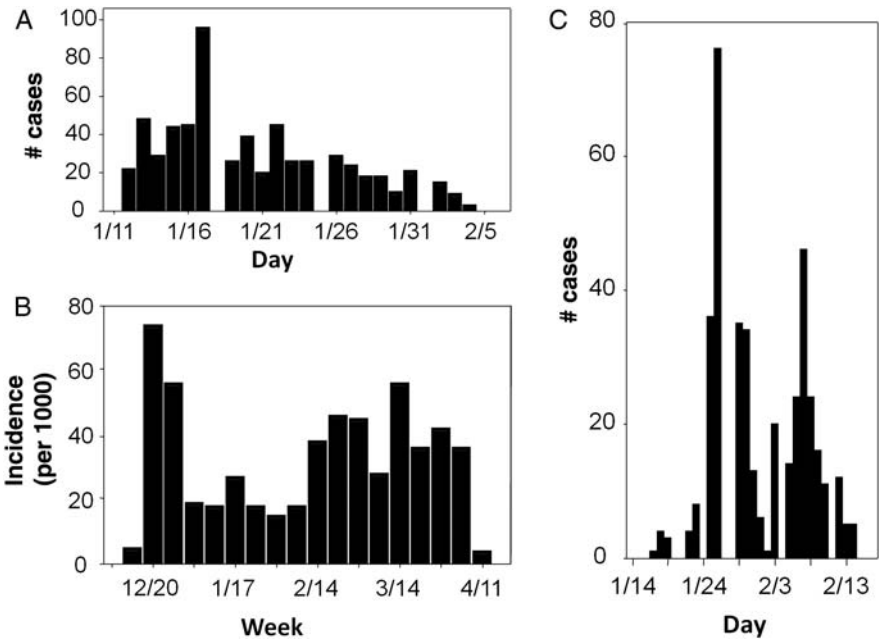

Figure 1. Incidence curves for select norovirus outbreaks at Marine Corps Recruit Depots (MCRD) in San Diego and Parris Island. *A*, Outbreak at the MCRD–San Diego between 12 January 2004 and 8 February 2004. *B*, Outbreak at the MCRD–San Diego between 19 December 2004 and 14 April 2005. *C*, Outbreak at the MCRD–Parris Island between 16 January 2007 and 16 February 2007. Data on subjects reporting for emergency care outside of traditional "sick call" (eg, Sundays) are not available. Those subjects were excluded from this study.

The ICD-9 codes used to identify infectious gastroenteritis were as follows: 009.0, 009.1, 009.2, 009.3, 008.6 (all subgroups), 008.8 (all subgroups). Each norovirus-exposed subject (using above ICD-9 codes during the outbreak period) was matched with up to 4 subjects with an unrelated medical encounter. Two were selected from personnel reporting for care at the same MTF within 45 days of the identified exposed subject, whereas an additional 2 were selected from the same MTF between May and September (outside of the outbreak window) within 1 calendar year of the outbreak of interest. Both sets of matched subjects were from the same clinical setting (inpatient/outpatient) as the identified exposed subject. Matched subjects were of the same branch of service and similar military rank.

All subjects had to have a minimum of 1 year of documented follow-up within the Defense Medical Surveillance System (DMSS) to be included in this study. In addition to norovirus exposure, other covariates analyzed included age, sex, marital status, deployments and antecedent or concurrent psychological comorbidities.

The primary outcomes were select functional gastrointestinal disorders (FGD) based on ICD9-CM first medical encounters including functional constipation (564.0; all subgroups), nonulcer dyspepsia (536.8), irritable bowel syndrome (IBS, 564.1), and gastroesophogeal reflux disease (GERD, 530.81). No preexisting medical history data were available as subjects were new accessions into the Marine Corps. Recruit medical screening is standardized in this population and generally identifies recruits without any baseline medical problems, although undiagnosed preexisting FGD conditions cannot be ruled out. Incidence rates were calculated using the number of new onset episodes of PI sequelae, total observed person-time and were adjusted to a standard reference (per 100 000 person-years). Ninety-five percent confidence intervals (95% CI) for incidence were calculated using a Poisson distribution.

Prior to providing the data to the investigators, personnel at the Armed Forces Health Surveillance Center (AFHSC) linked all available information on selected subjects using the defined ICD9-CM codes and requested fields into a single database. Identifiable information was removed from the dataset prior to being provided to the study investigators.

Associations were initially explored by univariate methods. Continuous variables were analyzed using a Student t test (when assumptions were met) and categorical variables by Cochran χ^2 test. Modified Poisson regression models were used to evaluate the relationship between norovirus-associated infections and PI sequelae [14]. Using a backward elimination approach, all variables were initially added to the models. The variable with the largest insignificant P value was removed, and the models were refit. This process continued iteratively until all variables retained in the models were significant at $\alpha = 0.25$. Statistical analyses were performed using SAS v. 8.2 for Windows (SAS Institute, Cary, North Carolina). Two-tailed statistical significance was evaluated using an α of 0.05.

The study protocol was approved as exempt human subjects research by the Naval Medical Research Center Institutional Review Board in compliance with all applicable federal regulations governing the protection of human subjects.

RESULTS

A total of 1718 subjects with documented IGE during a confirmed norovirus outbreak were included and were predominately male (99.4%) and white (74.0%; Table 2). Because the outbreaks were mostly isolated to Marine Corps recruit training facilities, exposed subjects were predominately of lower enlisted rank (99.1%), were in the Marines (99.7%), and were fairly young (mean age, 20.3 years). Unexposed subjects were similar demographically, with some differences including a slightly higher proportion of African-Americans as well as other races (32.1% and 26.0%, respectively; $P < .001$) and a higher proportion of females (1.7% and 0.6%, respectively; $P = .002$). There were no differences in the demographic characteristics or outcome incidence in the 2 unexposed (proximal and distal to the outbreak) populations (data not shown) and for analysis these 2 subgroups were combined. The mean duration of follow-up of the study population was 4.5 (standard deviation, 1.38) years.

Table 3 outlines the number of diagnoses made during the follow-up period. The overall incidence of IBS was 126 per 100 000 person-years (95% CI: 96–168) with no significant difference between subjects with antecedent viral gastroenteritis and the unexposed referent population (adjusted relative risk [RR]: 0.68; 95% CI: 0.30–1.52). There were no cases of IBS in norovirus-exposed subjects associated with either the first or the third outbreak and only 7 IBS cases associated with the second outbreak (115 per 100 000 person-years).

A total of 69 cases of dyspepsia were diagnosed, 18 of which followed a norovirus outbreak. The incidence of dyspepsia was higher among those with antecedent norovirus-associated illness than in the unexposed population (adjusted RR: 1.44); however, this difference was not statistically significant ($P = .18$). Importantly, the rate of dyspepsia was higher in subjects associated with the second norovirus outbreak (279 per 100 000 person-years) than following either the first or third outbreaks (0 and 170 per 100 000 person-years, respectively) and 1.7 times higher than the incidence of dyspepsia in the unexposed population ($P = .06$).

Constipation was diagnosed more often in subjects with antecedent norovirus-associated IGE compared to the referent population (adjusted RR: 1.32, $P = .08$). Similar to dyspepsia, constipation was more readily diagnosed following a specific outbreak, Outbreak 3 (1358 per 100 000 person-years), than in

Table 2. Demographic Characteristics of Study Population

Outbreak Demographics	Norovirus Outbreak Exposure			No Norovirus Exposure Not Applicable
	1/12/04–2/8/04	12/19/04–3/14/05	1/16/07–2/16/07	
Designation	Outbreak 1	Outbreak 2	Outbreak 3	Referent
No.	203	1360	155	6875
Mean (SD) age, years	20.3 (1.7)	20.2 (2.1)	20.7 (2.0)	20.0 (2.3)
Race[a]				
Black	3 (1.5)	42 (3.1)	17 (11.0)	319 (4.6)
White	157 (77.3)	988 (72.7)	126 (81.3)	4666 (67.9)
Other	43 (21.2)	330 (24.3)	12 (7.7)	1890 (27.5)
Sex[a]				
Male	203 (100)	1359 (99.9)	145 (93.6)	6760 (98.3)
Female	0 (0.0)	1 (0.1)	10 (6.4)	115 (1.7)
Marital status[a]				
Single	194 (95.6)	1300 (95.6)	147 (94.8)	6562 (95.5)
Married	6 (3.0)	56 (4.1)	8 (5.2)	284 (4.1)
Other	3 (1.5)	4 (0.3)	0 (0.0)	29 (0.4)
Branch of service[a]				
Marines	203 (100)	1356 (99.7)	154 (99.4)	6855 (99.7)
Navy	0 (0.0)	2 (0.2)	1 (0.7)	12 (0.2)
Coast Guard	0 (0.0)	2 (0.2)	0 (0.0)	8 (0.1)
Rank[a]				
E1 to E4	202 (99.5)	1347 (99.0)	153 (98.7)	6811 (99.1)
E5 to E9	1 (0.5)	13 (1.0)	2 (1.3)	64 (0.9)
≤High school education[a]	195 (96.1)	1306 (96.0)	150 (96.8)	6567 (95.5)
Age, years[b]	20.3 (1.7)	20.2 (2.1)	20.7 (2.0)	20.0 (2.3)
Duration of follow-up, years[b]	4.7 (1.9)	4.5 (1.3)	3.8 (0.7)	4.5 (1.4)

Abbreviation: SD, standard deviation.

[a] Presented as No. (%).

[b] Presented as mean (standard deviation).

either Outbreak 1 or 2 (522 and 624 per 100 000 person-years, respectively) or in the referent population (545 per 100 000 person-years). As shown in Figure 2, the rate of diagnoses was consistent over the duration of follow-up for these 2 study populations with a clear separation between the 2 curves after approximately 6 months of follow-up.

Table 3. Incidence and Relative Risk of Long-term Sequelae Among Those Seeking Care for Acute Viral Gastroenteritis Compared to an Unexposed Referent Population

Outcome	Study Population	No.[a]	Incidence[b]	Crude RR	Adjusted[c] RR
IBS	Outbreak	7	92	0.68 (0.30, 1.51)	0.68 (0.30, 1.52)
	Unexposed	42	135	…	…
Dyspepsia	Outbreak	18	236	1.44 (0.84, 2.46)	1.44 (0.84, 2.47)
	Unexposed	51	164	…	…
Constipation	Outbreak	51	668	1.23 (0.90, 1.68)	1.32 (0.96, 1.81)
	Unexposed	169	545	…	…
GERD	Outbreak	74	969	1.37 (1.05, 1.78)	1.39 (1.07, 1.81)
	Unexposed	220	709	…	…

Abbreviations: GERD,gastroesophageal reflux disease; IBS, irritable bowel syndrome; RR, risk ratio.

[a] No. with outcome.

[b] Per 100 000 person-years.

[c] Adjusted for the following variables (IBS: branch of service, sex; dyspepsia: military rank; constipation: sex, ethnicity; GERD: military rank, sex).

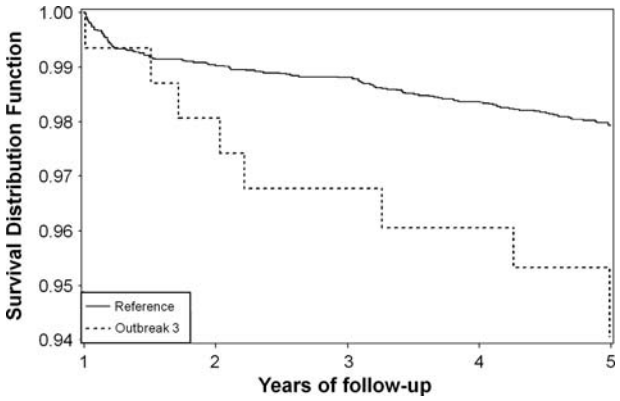

Figure 2. Survival curve of constipation diagnoses following a specific norovirus outbreak (Outbreak 3) compared to a reference population.

GERD was the most commonly diagnosed outcome during the follow-up period with a total of 294 cases for an overall incidence of 761 cases per 100 000 person-years and was significantly higher among those with antecedent norovirus-associated gastroenteritis than in the referent cohort (adjusted RR: 1.39, $P = .02$). As shown in Figure 3, the increased incidence of GERD among norovirus exposed subjects seemed to be isolated to subjects associated with Outbreaks 2 and 3 at 1018 and 1188 cases per 100 000 person-years, respectively, compared to Outbreak (522 per 100 000 person-years). Of the 294 GERD cases, 3.4% were also diagnosed with IBS, 6.8% with dyspepsia, and 8.5% with constipation.

DISCUSSION

We present the results from a large epidemiologic study of multiple postinfective gastrointestinal sequelae following illness attributed to norovirus outbreaks in a young healthy population. We found a borderline significant increase in the incidence of constipation ($P = .05$) and dyspepsia ($P = .08$) and a significant increase in the incidence of GERD ($P = .02$) in subjects with outbreak-associated norovirus IGE after controlling for important covariates. Several studies to date have reported an increased risk of constipation and dyspepsia following infectious gastroenteritis. Ford et al and Mearin et al have separately reported an increased risk of dyspepsia among those ill with acute gastroenteritis during outbreaks associated with bacterial pathogens compared to a reference population [6, 15]. Similarly, we reported an increase in diagnoses of dyspepsia and constipation among subjects with documented episodes of IGE, to include viral etiologies [7, 16]. Studies on the PI risk of GERD are lacking. Functional dyspepsia is a diagnosis given to subjects whose dyspepsia has no identifiable cause. However, the most common cause of dyspeptic symptoms is GERD, which can be attributed to pathogenic mechanisms including lower esophageal sphincter abnormalities, hiatal hernias, abnormal esophageal contractions, and slow or prolonged emptying of the stomach. GERD can be diagnosed by a variety of modalities including therapeutic trial, endoscopy, esophageal acid and motility testing, and gastric emptying studies. Our outcome assessment based on medical encounter ICD9-CM did not allow for verification of cases based on diagnostic criteria for GERD or functional dyspepsia. Interestingly, in this study the effect estimates of functional dyspepsia and GERD are similar overall and among outbreaks, suggesting diagnostic misclassification of upper gastrointestinal dysfunction, or perhaps similar pathoetiological mechanisms resulting in these gastroduodenal disorders. Confirmatory studies using better defined diagnostic criteria or database case-validation methods are needed.

In addition to reliance on ICD-9 CM diagnostic codes, the inability to rule out baseline gastrointestinal disorders may have resulted in bias favoring association if subjects were taking proton pump inhibitors or H2 receptor antagonists for undiagnosed dyspepsia or GERD that increased their susceptibility to enteric norovirus infection. It would be unlikely that an individual recruit requiring these medications would be accessioned into the Marine Corps; however, future studies with detailed preexisting health status determination, as well as concomitant medication usage would be useful. Additional detail on predominant clinical features of the functional disorders and GERD would have facilitated evaluation of predominant clinical disease subtypes.

Exposure ascertainment was also limited. As such, it is possible that included subjects had nonnorovirus infectious gastroenteritis, which may have biased effect estimates in either direction. However, in the context of well-defined outbreaks, such misclassification is likely limited. Furthermore, we lacked data on other important covariates that may have contributed

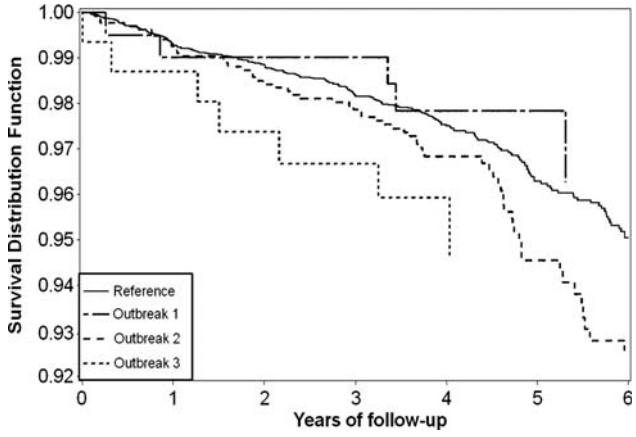

Figure 3. Survival curve of gastroesophageal reflux disease diagnoses following norovirus outbreaks compared to a reference population.

to the observed associations. Future prospective studies should be designed to capture all potentially relevant covariates. Additionally, the US military represents a unique study population that differs from the general US population in demographic makeup and likely in healthcare seeking behavior. Extrapolation of results to the general population should be performed with caution.

Nonetheless, exploration of potential pathoetiological mechanisms of observed associations is warranted. Studies of PI functional dyspepsia have identified dysfunction in gastric accommodation and delayed gastric emptying [17, 18]. Compared to idiopathic FD or health controls, PI-FD has been associated with histopathological findings of focal T-cell aggregates, decreased $CD4^+$ cells, and increased macrophage and eosinophil counts in duodenal biopsies that correlate with disease symptoms. Fugami et al reported that subjects with PI-FD had no delay in gastric emptying, although histological duodenitis was identified and the degree of inflammation correlated with patient symptoms of epigastric burning [19]. In summary, current evidence would suggest an aberrant chronic immune system processes resulting from an inciting transient infection which may have a potential role in the sensorymotor dysfunction seen in PI-FD. Although no studies have been published on PI GERD, disease mechanisms identified in PI-FD including delayed gastric accommodation, delayed gastric emptying, and mucosal hypersensitivity are consistent with the factors thought to lead to GERD, though other mechanism may also be of origin. Investigative efforts to further delineate pathological changes explaining the various symptoms of PI functional dyspepsia and GERD that include genetic, immunologic, and microbiologic assays in varied patient populations with well-characterized gastrointestinal infectious exposures and disease outcomes are needed.

Molecular and cellular changes during acute disease afford several potential hypotheses for the observed associations. Norovirus infections have been characterized by intact intestinal mucosa with distinct histological changes of the duodenum and jejunum, including broadened, blunted, and shortened microvilli, enlargement of the mitochondria, increased cytoplasmic vacuolization, and intercellular edema [20]. Additionally, studies in mice and pigs have identified enterocyte apoptosis [20], as well as a reduction in tight junction protein expression, and intestinal barrier and transport dysfunction [21, 22].

Our current understanding is that clinical disease in immunocompetent adults is limited to a few days though the virus may be shed for up to a few weeks [21, 22]. How acute norovirus infection may trigger chronic gastrointestinal sequelae has not been studied in human or animal models. However, it is conceivable that disruption of epithelia barrier and immune activation associated with acute disease in the duodenal and jejunal regions may trigger chronic immune activation through a bystander effect toward nonpathogen luminal antigens or lead to chronic immune stimulation, or alteration of gastric motor function.

Interestingly, we observed variability in FGD risk among different norovirus outbreaks. Epidemiologic studies have demonstrated clear variability in the populations effected by various norovirus genetic clusters. Specifically, strains identified as GII.4 are more likely to impact populations living in close proximity such as nursing homes and cruise ships than are other GII or GI strains [23]. Furthermore, Huhti et al reported on variability in disease severity across different norovirus geontypes with GII.4 causing more severe disease in children and elderly than other norovirus genotypes [24, 25]. Additionally, variable disease severity of a specific genotype, GII.4, has been reported across years [24]. Unfortunately, we were unable to genotype all strains associated with the outbreaks reported here. As with acute disease, it is possible that variations in structural and nonstructural proteins associated with different norovirus genotypes could have differential effects on the risk of chronic gastrointestinal sequelae in susceptible individuals. A recent study of norovirus-mediated inflammatory bowel disease in a genetically susceptible mouse model would suggest that host genetic factors may also play a role in the aberrant immune response associated with chronic inflammation of norovirus-triggered immune mediated chronic disorders [26].

We found no association between norovirus-associated IGE and an increased risk of IBS and a trend toward an association with constipation. The lack of an IBS association contrasts with a study by Marshall et al in which the prevalence of IBS 3 months following an outbreak was approximately 7-fold higher among subjects with norovirus-attributed gastroenteritis than in controls [5]. Possible explanations for this apparent discrepancy may lie in the variability of study designs (cohort vs case–control), sex (predominately male vs predominately female), age (middle age vs young adult), or a nonnorovirus outbreak. Additionally, it is possible that outbreak strain variability may play an important role in these discrepant data given the variability in associations among outbreaks with constipation, dyspepsia, and GERD outcomes. The trend toward an association with constipation in one of the 3 outbreaks is interesting and should be confirmed in future studies exploring chronic consequences of norovirus infection.

Recently, the Centers for Disease Control and Prevention (CDC) highlighted the importance of norovirus as the principal cause of foodborne-related illness in the United States with the acute illness resulting in over 56 000 hospitalizations annually. Although the acute illness associated with infection are significant, the long-term morbidity and related direct and indirect costs associated with potential chronic health sequelae may further highlight the need for improved primary

prevention. Given the incidence of norovirus-attributable illness globally, even a small increase in the relative risk of these sequelae results in a significant number of new onset cases. For example, we observed an approximate 1.4-fold increase in the risk of GERD following norovirus-attributed gastroenteritis. Given the estimated 20.9 million cases of norovirus annually in the United States [27], one would anticipate that norovirus contributes to approximately 1.7% of the incident GERD cases annually. A recent systematic review estimated 500 new GERD cases per 100 000 person-years in the United States, for an approximate 1.5 million cases annually [28]. If our estimates are correct, norovirus may account for approximately 25 000 cases of GERD annually in the United States. Given an estimated increase in direct healthcare related costs of $3355 per case per year [29], the implications of these findings are significant.

Norovirus is by far the most predominant cause of infectious gastroenteritis in the United States, with just fewer than 21 million cases annually [27]. Although the acute disease is significant, the long-term effects of these infections may also be very important. Studies evaluating the etiological mechanisms behind postnorovirus-associated GERD and dyspepsia are needed. Future challenge trials with a human norovirus should consider evaluating long-term consequences, and vaccine studies when reaching the field should consider the prevention of these outcomes as secondary endpoints.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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.

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