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Noroviruses as a Cause of Diarrhea in Travelers to Guatemala, India, and Mexico▽

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Noroviruses (NoVs) are increasingly being recognized as an important enteric pathogen of gastroenteritis worldwide. The prevalence of NoVs as a cause of diarrhea acquired by travelers in developing countries is not well known. We examined the prevalence and importance of NoV infection in three international traveler cohorts with diarrhea acquired in three developing regions of the world, Mexico, Guatemala, and India. We also characterized the demographics and symptoms associated with NoV diarrhea in these travelers. Stool samples from 571 international travelers with diarrhea were evaluated for traditional enteropathogens. NoVs were identified using reverse transcription-PCR and probe hybridization. NoVs were identified in 10.2% of cases of travelers' diarrhea and, overall, was the second most common pathogen, following diarrheagenic *Escherichia coli*. The detection of NoV diarrhea significantly varied over the three study time periods in Guadalajara, Mexico, ranging from 3 of 98 (3.0%) diarrheal stools to 12 of 100 (12.0%) fecal specimens ($P = 0.03$). The frequency of NoV diarrhea was also dependent upon the geographic region, with 17 of 100 (17.0%) travelers to Guatemala, 23 of 194 (11.9%) travelers to India, and 3 of 79 (3.8%) travelers to Mexico testing positive for NoVs from 2002 to 2003 ($P = 0.02$). NoVs are important pathogens of travelers' diarrhea in multiple regions of the world. Significant variation in the prevalence of NoV diarrhea and in the predominant genogroup infecting travelers was demonstrated, dependent upon the specific geographic location and over time.

Travelers' diarrhea (TD) is the most common illness experienced by travelers from industrialized nations to high-risk developing regions (24, 28). Bacterial enteropathogens, such as enterotoxigenic *Escherichia coli* (ETEC) and enteroaggregative *Escherichia coli* (EAEC), are responsible for the majority of TD cases (1, 27). However, up to 40% of TD cases never have any specific etiologic agent identified. These undiagnosed diarrheal illnesses are likely caused by undetected bacterial and nonbacterial enteropathogens (10–12, 27).

Noroviruses (NoVs) are important pathogens of gastroenteritis and are the most common cause of epidemic nonbacterial gastroenteritis outbreaks worldwide. NoVs are highly communicable with a low infectious dose and infect persons of all ages through fecal-oral transmission (4). NoVs are classified into five genogroups on the basis of phylogenetic analysis of the major capsid protein, with genogroup I (GI) and genogroup II (GII) strains being most commonly associated with human infections (3). GII NoV strains are the predominant circulating genogroup worldwide (6).

The prevalence of NoV infection in travelers is not well known, with only two previous studies evaluating the frequency of NoV infection in travelers with diarrhea. The two reports demonstrated significant but variable prevalence rates of NoV diarrhea of 17% and 65% in persons visiting Mexico or Mexico and Guatemala, respectively. Interestingly, both studies identified GI NoVs as the genogroup most frequently detected (7, 16). The present study was designed to compare patterns of prevalence of NoV infection in international travelers with diarrhea acquired in Mexico over several time periods and in different developing regions of the world, including Mexico, Guatemala, and India, and to characterize the symptoms associated with NoV diarrhea.

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MATERIALS AND METHODS

Study populations. Three cohorts of travelers from industrialized nations with diarrhea acquired in developing regions of the world were evaluated for the prevalence of NoVs as a cause of TD. The first cohort consisted of 98 U.S. travelers to Guadalajara, Mexico, enrolled from 1 June 2007 to 30 September 2007. The second group of subjects included 100 U.S. travelers with diarrhea acquired in Guadalajara, Mexico, enrolled from 15 June 2006 to 15 August 2006. A third cohort comprised 373 U.S. and European adults with diarrhea acquired in Guadalajara, Mexico; Antigua, Guatemala; or Kolkata or Goa, India from 10 July 2002 to 14 May 2003. Subjects from the third cohort were participants of a clinical trial evaluating therapy for TD (27). The third cohort was retrospectively evaluated as a comparison group, to determine if NoV diarrhea prevalence varied over time and in different geographic regions of the world. All subjects

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TABLE 1. Primer and probe sequences for RT-PCR and Southern blotting

NoV genogroup	Name	Use	Sequence (5′ to 3′)[a]	Sense
I	MON 434	Primer	GAASCGCATCCARCGGAACAT	Reverse
	MON 432	Primer	TGGACICCYGGICCYAAYCA	Forward
II	MON 433	Primer	AAYCTCATCCAYCTGAAYCAT	Reverse
	MON 431	Primer	TGGACIAGRGGICCYAAYCA	Forward
I	MON 458	Probe	ATGTATGTRCCACGATGGCARGCC	Forward
II	MON 459	Probe	ATGGATTTTTACGTGCCCAGGCAA	Forward

[a] I, inosine; R, purine (A/G); Y, pyrimidine (C/T); S, Strong (C/G).

provided an illness stool specimen confirmed as unformed by team members if they developed TD. TD was defined as the passage of at least three unformed stools within a 24-hour period associated with at least one symptom of abdominal pain or cramps, excessive gas/flatulence, nausea, vomiting, fever (≥100°F or ≥37.8°C), fecal urgency, blood and/or mucus in the stool, or tenesmus. Exclusion criteria for all cohort groups included duration of diarrhea for more than 72 h, moderate or severe dehydration, clinically important underlying illness other than diarrhea, and for women, being pregnant or breast feeding. In addition, patients were excluded if they had taken any antimicrobial or antidiarrheal agent active against diarrheal pathogens. All patients provided written, informed consent. The Committee for the Protection of Human Subjects at the University of Texas—Houston Health Science Center approved the study protocol.

Microbiology. Stool samples were screened for enteric bacterial and parasitic pathogens by previously published methods (14). Five *E. coli*-like colonies were isolated from each stool specimen, transferred to peptone stabs for storage, and transported to the Houston laboratory. *E. coli* bacteria were tested by the probe hybridization technique for ETEC (14) and by the HEp-2 cell adherence assay for EAEC (1). Samples were kept at −80°C prior to use.

RNA extraction. A total of 100 μg of stool was weighed, diluted 1:10 in 0.01 M phosphate-buffered saline (PBS), and vortexed for 30 s. Samples were clarified by centrifugation at 4,200 × *g* for 10 min at room temperature. Viral RNA was extracted from 140 μl of the supernatant with the QIAamp viral RNA kit (Qiagen) according to the column centrifugation procedure described by the manufacturer. The RNA extracts were kept at −80°C prior to use.

RT-PCR. A two-step multiplex reverse transcription-PCR (RT-PCR) was performed for every sample, using a set of previously described degenerate region B primers (Table 1) designed to amplify NoV RNA with an expected PCR product size of 213 bp (2). The RT reaction was performed by adding 5 μl of extracted RNA to a reaction mixture consisting of 3 μl of GeneAmp 10× PCR buffer (Applied Biosystems), 10 units of Optizyme RNase inhibitor (Fisher BioReagents), 2 μl of a 10 mM mix of deoxynucleoside triphosphates, 200 nanomoles of each reverse primer (MON 433, MON 434), 5 units of avian myeloblastosis virus (AMV) RT (Life Sciences Inc.), and 18.5 μl of diethyl pyrocarbonate (DEPC)-treated, DNase- and RNase-free, deionized water (MP Biomedicals). Samples were incubated for 60 min at 43°C followed by 5 min at 94°C. After completion, samples were immediately quenched in ice water, and 70 μl of PCR mix was added. The PCR mix included 200 nanomoles of each forward primer (MON 431, MON 432), 7 μl GeneAmp 10× PCR buffer (Applied Biosystems), 5 units of AmpliTaq DNA polymerase (Applied Biosystems), and 60 μl of DEPC-treated, DNase- and RNase-free, deionized water (MP Biomedicals). cDNA was amplified under the following conditions: initial denaturation for 2 min at 94°C; 40 cycles consisting of template denaturation for 15 s at 92°C, primer annealing for 30 s at 50°C, and primer extension for 30 s at 72°C; and a final extension for 7 min at 72°C. PCR amplicons were analyzed on a 1.5% agarose gel.

Southern blotting. All NoV-positive samples were confirmed by hybridization at 55°C with digoxigenin-labeled oligoprobes (MON 458, MON 459) (Table 1) by use of the Genius detection kit (Boehringer Mannheim) as described previously (5).

Statistical analysis. Significant differences between proportions of NoV diarrhea were evaluated with Fisher's exact test. All analyses were conducted using STATA (version 9.2) software.

RESULTS

The overall prevalence of NoV infection in travelers with diarrhea was 10.2%. NoVs were identified in diarrheal stool samples from 3 of 98 (3.0%) travelers to Mexico in the summer of 2007, with 66.7% of NoV strains belonging to GI (Table 2). During the summer of 2006, NoVs were recovered from 12 of 100 (12.0%) travelers who acquired diarrhea in Mexico, with 83.3% of NoVs detected belonging to GII. From 2002 to 2003, 3 of 79 (3.8%) travelers to Mexico experienced NoV diarrhea, with 66.7% of NoV strains identified as GII. The difference in proportions of NoV diarrhea acquired in Guadalajara, Mexico, over the three time periods was statistically significant ($P = 0.03$). NoV diarrhea was detected in 17 of 100 (17.0%) travelers to Guatemala, with 52.9% of NoV strains belonging to GI. Twenty-three of 194 (11.9%) travelers to India were positive for NoV, with 69.6% of NoVs identified as GII strains. The frequency of NoV diarrhea in the three developing countries was significantly different during the 2002-to-2003 study period ($P = 0.02$).

The majority of NoV diarrhea cases presented as mixed infections with other enteric pathogens (Table 3). However, 21 of 58 (36.2%) of NoV diarrheal stool samples were infected with NoV alone. The most frequent copathogens identified were ETEC (23/58 [39.7%]), EAEC (17/58 [29.3%]), *Cryptosporidium* spp.

TABLE 2. Prevalence of NoV diarrhea in international travelers, by genogroup and geographic location

Location	No. of travelers (%) with:			
	NoV diarrhea	GI strain	GII strain	Genogroup indeterminate strain
Guatemala	17/100 (17.0)	9/17 (52.9)	8/17 (47.1)	0
India	23/194 (11.9)	7/23 (30.4)	16/23 (69.6)	0
Mexico (2002–2003)	3/79 (3.8)	1/3 (33.3)[a]	2/3 (66.7)[a]	1/3 (33.3)
Mexico (2006)	12/100 (12.0)	1/12 (8.3)	10/12 (83.3)	1/12 (8.3)
Mexico (2007)	3/98 (3.0)	2/3 (66.7)	1/3 (33.3)	0

[a] One specimen tested positive for both genogroups.

TABLE 3. Copathogens of NoV infection

Copathogen(s)	No. of travelers (%) with coinfection
NoV alone	21/58 (36.2)
ETEC	23/58 (39.7)
EAEC	17/58 (29.3)
Cryptosporidium spp.	3/58 (5.2)
Salmonella spp.	3/58 (5.2)
Giardia lamblia	2/58 (3.4)
Shigella sonnei	2/58 (3.4)
Aeromonas spp.	1/58 (1.7)
Plesiomonas shigelloides	1/58 (1.7)
Multiple (≥3) pathogens	13/58 (22.4)

TABLE 4. Demographic and clinical characteristics of international travelers with NoV diarrhea (excluding travelers with copathogens)

Characteristic	Value[a]
Age (mean yr ± SD)	28.8 ± 12.1
Male	84.2
No. of unformed stools (mean ± SD)[b]	5.7 ± 2.3
Abdominal cramping	94.7
Nausea	73.7
Fecal urgency	63.2
Flatulence	36.8
Fever	21.1
Vomiting	21.1
Tenesmus	10.5
Presence of blood/mucus	10.5

[a] $n = 21$. Data are percentages of subjects, unless otherwise indicated. Data are missing for one patient from Guatemala and India.
[b] Within 24 h prior to enrollment.

(3/58 [5.2%]), *Salmonella* spp. (3/58 [5.2%]), *Giardia lamblia* (2/58 [3.4%]), and *Shigella sonnei* (2/58 [3.4%]). Multiple (≥3) enteric pathogens were found in 13/58 (22.4%) NoV diarrheal specimens, with ETEC and EAEC being most commonly identified as copathogens in these infections.

To better characterize diarrheal disease attributable only to NoVs in travelers, we chose to examine travelers with NoVs as the sole enteric pathogen identified as the cause of their diarrhea ($n = 21$) rather than potential copathogens. We evaluated the demographic and clinical characteristics associated with NoV diarrhea (Table 4). There was a predominance of males (84.2%) infected with NoV. The mean number (± standard deviation [SD]) of unformed stools passed by travelers with NoV diarrhea within the 24 h prior to enrollment was 5.7 (±2.3). The most common symptoms associated with NoV diarrhea were abdominal cramping (94.7%), nausea (73.7%), flatulence (63.2%), and fecal urgency (36.8%). Fever (21.1%), vomiting (21.1%), tenesmus (10.5%), and presence of blood or mucus in stools (10.5%) were less commonly reported.

DISCUSSION

This study demonstrates that NoVs are an important pathogen of TD in multiple regions of the world. The overall prevalence of NoV diarrhea in travelers was 10.2%. NoVs were the second most common enteropathogen identified in travelers, following diarrheagenic *E. coli* (52.9%).

There was a distinct variation in the prevalence of NoV diarrhea and in the predominant genogroup infecting travelers, dependent upon the specific geographic location and over time, despite consistency in detection methods. In this study, the majority of NoV strains were identified as GII, except for the Guatemala cohort, which had nearly equal numbers of NoV GI and GII strains. Travelers who acquired diarrhea in Mexico in 2007 had more NoV GI than GII strains identified, although there were relatively few NoV diarrhea cases in Mexico during this time period. Similarly, in a previous surveillance study performed by our group in Mexico during the summer of 2004, 81% of NoVs detected were NoV GI strains (16). In the present study, 66.7% and 83.3% of NoVs identified in travelers to Mexico in 2002 to 2003 and 2006, respectively, were GII strains. Future studies are needed to investigate the potential underlying determinants of variation in NoV diarrhea frequency, including the prevalence of NoV infections in the indigenous communities, variable climate conditions, such as increased rainfall leading to more fecal contamination of the water supply, and host genetic and immunologic susceptibility patterns among the indigenous populations and travelers.

Travelers likely acquire NoV infections from local resident populations in developing regions of the world, where sanitation and hygienic standards may be inadequate, facilitating fecal-oral transmission of enteric pathogens. Unfortunately, the current lack of defined molecular epidemiology of NoV infections in developing nations, such as Guatemala, India, and Mexico, hinders correlation between the prevalence of NoV strains endemic in indigenous populations and NoV diarrhea in travelers. Limited epidemiologic surveillance has been conducted in these high-risk regions for TD and primarily evaluate NoV diarrhea in pediatric populations. In a rural Guatemalan community, 72% of screened children ($n = 522$) between the ages of 6 and 36 months were shown to have been previously exposed to Norwalk viruses by enzyme-linked immunosorbent assay (ELISA), using antibody to recombinant expressed Norwalk capsid proteins. No evaluation for GII NoVs was performed in this study (25). Multiple epidemiologic investigations have been performed in eastern, western, and southern India (8, 9, 15, 19, 21–23). The majority of these studies examined outpatient or hospitalized children with acute gastroenteritis for NoV infection by RT-PCR. Overall, the prevalence of NoV diarrhea in these Indian children ranged from 10.9% to 18.9%, with a predominance of GII strains (90% to 100%). One surveillance study of southern India detected a greater percentage of GI NoVs (25%), but a potentially less specific ELISA was used for detection (15). The prevalence of NoV diarrhea in our cohort of travelers to India (11.9%) was similar to the detection of NoV diarrhea in these local pediatric populations, but the relative proportion of GII NoV strains identified in travelers (69.6%) was lower than rates reported in these studies. In Mexico, children <5 years of age hospitalized for acute gastroenteritis have been evaluated for NoVs. GII NoVs were detected in 4.7% of stools tested, while no GI NoV strains were recognized (13). In our study, the prevalence of NoV diarrhea in travelers to Mexico varied from 3.0% to 12.0%, with a fluctuating predominant NoV genogroup. In the future, we plan to characterize NoV strains infecting Mexican children with diarrhea to determine whether they may serve as a reservoir for NoV strains infecting travelers to Mexico.

Mixed infections with other enteric pathogens were commonly found in travelers with NoV diarrhea. The most commonly isolated copathogens in the NoV diarrheal stool samples were ETEC and EAEC. The distribution of the rates of detection of these copathogens is not surprising because it is similar to the frequency with which these enteric pathogens cause TD (1).

Travelers with NoV diarrhea in the present study passed an average of six unformed stools within 24 h, which may be considered moderate to severe diarrheal illness (18, 20). The most common symptoms associated with NoV diarrhea were abdominal cramping, nausea, flatulence, and fecal urgency. Interestingly, vomiting was less commonly noted by travelers, although infection with NoVs is classically described as a "winter vomiting" disease (17). However, since diarrhea was an inclusion criterion for participation in this study, travelers with NoV infection manifesting only as vomiting may have been

excluded, leading to decreased reports of vomiting associated with NoV diarrhea in this study.

Limitations of this study include the possible exclusion of travelers with NoV infection who may not have manifested diarrhea as part of their clinical illness. It is possible that NoV RNA degradation in stool specimens may have contributed to decreased rates of NoV detection. However, we feel that it is unlikely that significant RNA degradation led to lower NoV detection in fecal specimens from travelers who went to Mexico in 2002 to 2003, since the highest NoV diarrhea frequency was identified in travelers to Guatemala during this time period. Subsequent testing of more recent stool specimens from travelers to Mexico in 2007 confirmed a variable pattern of NoV detection with relatively lower frequency. Finally, tests for other viral pathogens were not performed; however, previous studies have shown that other enteric viruses play a much less significant role in the pathogenesis of TD (14, 28).

NoVs are an important cause of TD endemic in at least two regions of Latin America and one Asian country. It is likely that this enteric pathogen has long been underestimated as a cause of TD due to limitations of detection methods. We believe that future studies of TD will demonstrate that NoVs are an important cause of diarrhea in travelers to other high-risk developing regions across the world. Future studies will be important to characterize the genetic diversity of the circulating NoV strains, which may impact future therapeutic and preventative strategies targeting NoV infection. More studies are necessary to help us to better understand the human immunological response to NoVs, which may help in vaccine development. International travelers to developing regions of the world may represent one of the few populations with relatively high rates of NoV endemicity, making them valuable for evaluation of NoV vaccines in the pipeline for development (26).

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