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A Prospective Study of Acute Diarrhea in a Cohort of United States Military Personnel on Deployment to the Multinational Force and Observers, Sinai, Egypt

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Abstract. To better understand the epidemiology of diarrhea in deployed personnel to the Middle East, a prospective cohort study of travelers' diarrhea (TD) was conducted between May 2004 and January 2005 at the Multinational Force and Observers (MFO) camp in the southern Sinai. A baseline entry questionnaire and stool specimen was provided on study entry, and volunteers were followed every 6 weeks. Of 211 volunteers, 145 (68.7%) completed one or more follow-up visits. In total, 416 follow-up surveys were completed, which described an overall incidence of 25.2 episodes per 100 person months (95% confidence interval = 21.2–30.0). Additionally, stools were collected in 72 of 77 diarrhea-associated clinic visits, with bacterial pathogens most commonly isolated (enterotoxigenic *Escherichia coli* in 30 [42%] samples and *Campylobacter jejuni* in 7 [10%] samples) Despite modern preventive methods, diarrhea is still a common problem for deployed US military personnel in Egypt, frequently resulting in diminished ability to work.

INTRODUCTION

Travelers' diarrhea (TD) is one of the most common medical problems for military troops deployed abroad.[1,2] Often, the disorder leads to increased healthcare service use, loss of man-hours, and transient critical shortages in the deployed force.[3] Although most causes of TD are bacterial in etiology,[4] viruses, particularly norovirus, are now being recognized as significant pathogens among troops, with the potential to cause explosive epidemics.[5,6] This has led to a call for a better understanding of the current microbiological and clinical epidemiology of gastrointestinal disorders and the development of safe, efficacious enteric vaccines. A prospective cohort study was undertaken at the Multinational Force and Observers (MFO) camp, located in the Sinai Desert of Egypt, to explore three objectives: (1) define regional incidence and pathogen distribution of agents associated with gastroenteritis in a US military population, (2) measure and define pathogen-specific correlates of immunity, and (3) describe the impact of enteric diseases on this population relative to acute respiratory illness (ARI) and injury.

METHODS

Study site. The study was conducted in the South Sinai Peninsula of Egypt at an MFO camp, a camp created by an independent (non-United Nations) peacekeeping mission as a result of the 1978 Camp David Accords. Approximately 500 US troops are stationed at the camp for a 6-month duty assignment. From this base camp, soldiers are sent periodically for 1-month stays at outlying posts. At the main camp, soldiers live in fixed barracks, with each barrack containing communal showers and toilets. Dining occurs at a common cafeteria for all base personnel. When personnel rotate to an outpost, they are housed in small Quonset hut barracks, have a common kitchen, and share a field latrine. Every outpost is assigned a field medic who serves as a first responder and liaison to the primary clinic at the main camp. All observations in the current study were performed at the main camp, because many of the outposts were inaccessible to the research personnel.

Study population. Any individual at least 18 years of age living at the main camp for at least 2 months and able to comply with the study procedures was eligible for participation. In an attempt to minimize confounding variables, individuals were excluded from study participation if they had been diagnosed previously with irritable bowel syndrome or other functional gastrointestinal disorder or had two or more episodes of diarrhea during the 2 months before arrival at the camp. Only participants who enrolled and completed at least one follow-up visit were included in the final analysis.

Enrollment and follow-up procedures. On arrival at the camp, individuals were provided information about the study and asked if they would like to enroll. Interested individuals were explained the study in detail and after given an opportunity to ask questions about participation, provided written informed consent was given if they elected to join the study. Individuals then provided a stool sample and completed a structured, pre-tested questionnaire designed to evaluate past travel, prior episodes of TD, diarrhea/vomiting history since arrival, risk behavior attitudes, health behaviors, and other pertinent medical health history. Subjects were asked to return 21 (±3) days later to provide another stool sample and complete a second questionnaire asking about changes in duty status and/or health status, including recent injuries, respiratory and diarrheal illnesses, and changes in medication. Subjects also were asked to return to the clinic if, at any time during the study period, they developed vomiting or diarrhea. Participants returning to clinic for a sick visit were evaluated by the study clinician; a questionnaire was completed, and the person was asked to submit a stool specimen. Volunteers who developed vomiting or diarrhea while at an outpost were instructed to report this event during routine study follow-up visits at the main camp.

Before completion of their duty at the MFO, a final stool sample was collected, and participants completed a study questionnaire querying overall impact of illnesses and injuries during their deployment and their impression of participating in the study.

Specimen processing and testing. After collection, the stool was split into eight aliquots, with one placed in a tube containing Cary–Blair (CB) transport media, a second placed in a tube

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14. ABSTRACT

To better understand the epidemiology of diarrhea in deployed personnel to the Middle East, a prospective cohort study of travelers? diarrhea (TD) was conducted between May 2004 and January 2005 at the Multinational Force and Observers (MFO) camp in the southern Sinai. A baseline entry questionnaire and stool specimen was provided on study entry, and volunteers were followed every 6 weeks. Of 211 volunteers, 145 (68.7%) completed one or more followup visits. In total, 416 follow-up surveys were completed, which described an overall incidence of 25.2 episodes per 100 person months (95% confidence interval = 21.2?30.0). Additionally, stools were collected in 72 of 77 diarrhea-associated clinic visits, with bacterial pathogens most commonly isolated (enterotoxigenic Escherichia coli in 30 [42%] samples and Campylobacter jejuni in 7 [10%] samples) Despite modern preventive methods, diarrhea is still a common problem for deployed US military personnel in Egypt, frequently resulting in diminished ability to work.

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of Campy Thio Broth (CTB) transport media, a third placed into 10% formalin, and the remaining five placed into empty cryovials. The samples in media were immediately refrigerated at 4°C, and the remaining cryovials were stored at −70°C. Within 3 days of collection, all the samples were transported to Naval Medical Research Unit, No. 3 (NAMRU-3) in Cairo, Egypt, an approximately 6-hour drive from the study site. On arrival at NAMRU-3, the stool in CB and CTB was streaked onto MacConkey, *Shigella-Salmonella*, Skirrow's, and thio citrate agar plates. Bacterial pathogens were cultured using standard microbial techniques, and antibiotic susceptibility testing was performed using the disk-diffusion method. Bacterial speciation was performed using available commercial antisera. In addition, five individual lactose-fermenting colonies with typical *Escherichia coli* morphology were collected from each stool culture and stored at at −70°C in trypticase soy broth with 15% glycerol until toxin testing was performed using a GM1 enzyme-linked immunosorbent assay (ELISA).[7] Toxin-producing *E. coli* (ETEC) was further tested for expression of a panel of colonization factor antigens (CFAs).[8] Detection of *Cryptosporium parvum* oocyst antigen in fecal specimens was done using a commercially available ELISA kit (TECHLAB, Blacksburg, VA) according to manufacturer's instruction. Detection of rotavirus by a commercially available kit (Premier Rotaclone, Meridian Bioscience Inc., Cincinnati, OH) and norovirus using baculovirus-expressed human calicivirus capsid proteins in fecal specimens were done by ELISA.[9]

Study definitions. Diarrhea was defined as three or more loose stools in a 24-hour period or two loose stools in a 24-hour period associated with other infectious gastrointestinal symptoms, such as nausea, vomiting, abdominal cramps, tenesmus, bloody stools, or fever, which was defined as an oral temperature ≥ 38°C. The case definition of gastroenteritis (GE) was two episodes of vomiting in a 24-hour period or one episode of vomiting with one additional gastrointestinal symptom (diarrhea, nausea, fever, abdominal cramps, abdominal pain, blood in stool, or mucus in stool). GE associated with excessive alcohol consumption in the previous 24-hour period was excluded based on the clinical history elicited by the study physician. A pathogen-specific episode of diarrhea or GE was defined as an episode where a pathogen was directly identified from the stool specimen submitted.

Data management. To ensure confidentiality while allowing for the linking of subjects to their study samples, each participant was assigned a unique identification number (ID). The ID was included on all of the questionnaires, clinical forms, samples, and laboratory forms. All data were entered manually and checked for accuracy by double data entry. Logic checks were performed on all important outcome and predictor variables.

Statistical analysis. Enrollees who completed at least one follow-up visit were compared with those who enrolled but did not complete any follow-up. Both self-reported incidence and clinic visit incidence were calculated using episodes of diarrhea that met the case definition over the person-time contribution of the individual minus the days of symptom duration. Clinic visit incidence of GE was calculated in the same manner. Differences in incidence because of demographic and risk factor covariates were assessed as an incidence rate ratio (IRR) using Poisson regression (requirements for Poisson regression were met). Dimensional variables were included as continuous in the model if they met the linearity assumption. Otherwise, they were categorized into groups based on the risk distributional profile. A multivariate model was constructed, adjusting for age and other covariates that were significant at the $P < 0.20$ level in the univariate analysis. A nested case-control analysis was performed comparing the differences in rates of pathogen-specific identification in diarrheal samples of symptomatic cases with asymptomatic stool collected during routine follow-up visits. Only cases and controls where a solo pathogen was identified were included. All data analysis was done using Stata Version 9 (StataCorp, College Station, TX), and statistical significance was set at $P < 0.05$.

RESULTS

Two hundred eleven people enrolled in the study, and 145 (68.7%) completed at least one follow-up visit and/or clinic visit. Of these, 101 (70.6%) were temporary duty personnel, and the remainder were permanent party. This represents approximately 20% of all temporary duty personnel deployed for a 6-month rotation. Those that did not complete at least one follow-up visit were younger and more likely to have an occupation reported as infantry (Table 1). The remaining cohort enrollees completed 416 routine follow-up visits, and 70 (33.2%) of the enrollees reported to the clinic for 77 acute visits, provided a stool specimen, and completed a clinical assessment. Median length of follow-up was 3.8 months (Interquartile range [IQR] = 2.1–5.3), and median time in Egypt at the end of study was 5.7 months (IQR = 4.3–6.0).

The self-reported incidence of diarrhea was 25.2 episodes per 100 person months (95% confidence interval [CI] = 21.2–30.0), whereas the clinical incidence was 10.7 episodes per 100 person-months (95% CI = 8.1–13.8). When stratified by time of year, disease incidence was highest during May through July (Table 2). The clinical incidence of GE was 1.9 (95% CI = 0.9–3.4) episodes per 100 person-months. In univariate and multivariate models, factors associated with an increased risk of diarrhea included being an officer, being Caucasian, having significant prior travel, and having a previous episode of diarrhea during the current deployment (Table 3).

TABLE 1

Demographic characteristics comparing individuals that did and did not follow-up

	No follow-up [66 (31%)]*	Follow-up [145 (69%)]*	Total (211)*	*P* value
Median age (IQR)	27 (22–33)	33 (27–40)	31 (25–40)	< 0.0001
Age, *n* (%)				0.002
20–27 years	34 (54)	42 (30)	76 (37)	
28–33 years	16 (25)	32 (23)	48 (24)	
34–40 years	8 (13)	33 (24)	41 (20)	
41–56 years	5 (8)	33 (24)	38 (19)	
Rank				NS
Enlisted	61 (95)	130 (91)	191 (92)	
Officer	3 (5)	13 (9)	16 (8)	
Race				NS
African American	6 (12)	23 (18)	29 (16)	
Caucasian	38 (73)	85 (66)	123 (68)	
Other	8 (15)	20 (16)	28 (16)	
Occupation				0.0009
Infantry	48 (74)	71 (49)	119 (57)	
Medical	2 (3)	27 (19)	29 (14)	
Other	15 (23)	47 (32)	62 (29)	

*Distribution across demographic variable may not add up to 100% because of missing values. IQR = interquartile range.

TABLE 2
Incidence of diarrheal illnesses by month and pathogen type

	Incidence*	95% CI
Overall incidence (N = 145)	25.2	21.2–30.0
Clinical incidence (N = 145)	10.7	8.1–13.8
Clinical incidence by month (N = 145)		
May	23.9	6.5–61.2
June	40.8	21.1–71.2
July	51.4	29.9–82.2
August	8.2	3.3–16.8
September	6.3	2.3–13.8
October	3.1	0.6–9.1
November	2.4	0.3–8.7
December	1.4	0.04–7.8
January	21.0	6.8–49.0
Clinical incidence by pathogen (N = 70)		
Campylobacter	1.7	0.8–3.2
Cryptosporidium	1.1	0.4–2.5
ETEC	18.4	14.9–22.5
Norovirus	0.4	0.05–1.4
Rotavirus	3.4	2.0–5.4
Shigella	0.2	0.005–1.1

*Episodes per 100 person-months.

For those reporting diarrhea at routine follow-up visits, the median duration of the episode was 3 days (IQR = 2–4). The most common associated symptoms were abdominal pain (82%), nausea (45%), and headache (40%). Most individuals chose to self-treat (61%); however, 22% sought treatment at the clinic, and one individual (2%) required after-hours emergent care for his symptoms. Lost work days were estimated at 1.3 (95% CI = 0.5–2.7) days per 100 person-months. In terms of military impact, 51% of cohort subjects agreed that diarrhea adversely impacted job performance, whereas 45% agreed that their overall unit's readiness was affected by diarrhea.

TABLE 3
Incidence rate ratio (IRR) for predictors associated with the risk of diarrhea in univariate and multivariate models

	Univariate IRR	95% CI	Multivariate IRR	95% CI
Age				
20–27 years	1.00		1.00	
28–33 years	1.13	0.67–1.89	1.35	0.75–2.44
34–40 years	1.47	0.91–2.36	1.64	0.98–2.73
41–56 years	1.28	0.79–2.07	1.36	0.80–2.30
Rank				
Enlisted	1.00		1.00	
Officer	1.95	1.23–3.11	1.99	1.22–3.26
Race				
African American	1.00		1.00	
Caucasian	2.12	1.19–3.79	1.85	1.22–2.82
Other*	1.39	0.68–2.87		
Occupation*				
Medical	1.00			
Infantry	1.44	0.89–2.34		
Other	1.14	0.67–1.93		
Diarrhea before current assignment while outside the United States*				
No	1.00			
Yes	1.62	1.10–2.37		
Diarrhea during prior assignment during travel outside the United States				
No	1.00		1.00	
Yes	1.96	1.27–3.01	1.59	1.00–2.52
Episode of diarrhea during this assignment				
No	1.00		1.00	
Yes	1.66	1.18–2.34	1.54	1.06–2.25
Eating off base but no ice*				
Agree	1.00			
Disagree	0.95	0.57–1.59		
Eating off base but no raw vegetables*				
Agree	1.00			
Disagree	0.60	0.29–1.24		
I eat off base*				
Rarely or never	1.00			
Sometimes or frequently	1.07	0.75–1.52		

*Variable not included in final model.

To compare the impact of diarrhea on the mission, data were collected on the number of clinic visits for acute respiratory infections and non-combat injuries, both known to occur frequently during deployment. The self-reported incidence for injuries sustained during deployment was 3.5 (95% CI = 2.1–5.5), with approximately 1.3 (95% CI = 0.5–2.7) days of work lost per 100 person-months. The self-reported incidence for respiratory illnesses sustained during deployment was 4.1 (95% CI = 2.6–6.2) per 100 person-months, with approximately 0.9 (95% CI = 0.3–2.2) days of work lost per 100 person-months. Neither non-combat injuries nor respiratory infections seemed to significantly impact the job performance or the unit's operational readiness, although the number of reported injuries (N = 19) and respiratory infections (N = 22) were minimal.

Microbiology. Stools were collected in 72 of 77 symptomatic visits, and one or more pathogens were isolated from 44 samples (61%). ETEC was the most common bacterial pathogen, isolated in 30 (42%) samples, followed by *Campylobacter jejuni* in 7 (10%) samples. Pathogenic parasites and virus were infrequently isolated, with *Cryptosporidium* (N = 3), rotavirus (N = 4), and norovirus (N = 1) recovered in case patients. Mixed infections occurred in seven samples (9.7%), with ETEC and *Campylobacter* coinfection being most common (N = 5). Microscopic examination of formalin-fixed stool revealed that non-pathogenic protozoa were detected in 23% of volunteers. The most common were *Blastocystis hominis* (63%) followed by *Entamoeba coli* (20%) and *Endolimax nana* (17%). Among the 10 *Campylobacter jejuni* isolated in symptomatic and asymptomatic stool samples, all were resistant to tetracycline, 9 of 10 were resistant to ciprofloxacin and naladixic acid, and one-half were resistant to streptomycin and ampicillin; however, all remained susceptible to erythromycin. Among ETEC recovered from 111 cases and asymptomatic stools, toxin testing resulted in 36 isolates positive for heat labile toxin (LT) toxin, 64 positive for heat stabile toxin (ST), and 11 positive for LTST. ETEC CFA analysis showed that CS6 was the predominant CFA identified (14.4%); however, only 43.3% of ETEC colonies had an identifiable CFA. Table 2 details pathogen-specific incidence, with ETEC being the most predominant organism associated with 18.4 (95% CI = 14.9–22.5) episodes per 100 person-months. To further evaluate pathogenicity of recovered organisms, a nested case-control study comparing relative pathogen recovery rates from symptomatic and asymptomatic visits was performed. Analysis was limited to those cases where a sole potential pathogen was isolated from the stool, which showed that both ETEC and *Campylobacter* were significantly more likely to be identified in symptomatic individuals compared with asymptomatic controls (Table 4).

DISCUSSION

To our knowledge, this is the first prospective cohort study conducted among a US military population with the primary objective of studying diarrheal disease incidence. Our finding

TABLE 4

Pathogen recovery rates in symptomatic and asymptomatic (routine) visits among cohort participants limited to cases where only a single pathogen was isolated

Pathogen	Symptomatic visits ($N = 66$)	Asymptomatic visits ($N = 574$)	RR	95% CI
Campylobacter	2 (3)	2 (0.3)	8.8	1.3–61.6
Cryptosporidium	1 (2)	2 (0.3)	4.4	0.4–48.0
ETEC	26 (39)	77 (13)	3.0	2.1–4.3
Rotavirus	1 (2)	12 (2)	0.7	0.1–5.6
Norovirus	1 (2)	1 (0.2)	8.8	0.6–139.5
Shigella	0 (0)	1 (0.2)	–	–
No pathogen identified	34 (52)	480 (84)	–	–

RR = relative risk.

of an overall incidence of diarrhea of 25.2 episodes per 100 person-months (33.0 episodes/person per year) is in close comparison with a recent systematic review of 13 studies from the Middle East and North Africa region, which estimated incidence at 24.3 episodes per 100 person-months.[4] Both figures are lower than estimates among non-military long-term traveler populations of Peace Corps volunteers in Guatemala (4.7 episodes/person per year) and expatriates in Nepal (5.9 episodes/person per year), likely because of a number of factors, including a higher public health infrastructure in the military population.[10,11]

This study confirmed our previous finding that officers were nearly two times as likely to develop diarrhea compared with the enlisted ranks (IRR = 1.99, 95% CI = 1.22–3.26).[12,13] Although the exact reason for the increased risk is uncertain, it is likely related to an increased consumption of non-military–provided food. However, a general attitude survey question assessing frequency of eating off-base showed no significant difference between officers and enlisted personnel. We also noted that increase risk was associated with increased age (independent of rank), which is consistent with previous military studies.[13,14] Interestingly, the age effect direction among military populations is different to what has been traditionally found in previous non-military cohort studies or among general travelers, where increased risk is associated with younger age and more adventurous travel (i.e., increased risk-taking behavior).[10,15] Prior history of diarrhea was also found to be a risk factor for developing diarrhea during the study. Plausible explanations could include differences in susceptibilities of individuals or risk behaviors. The finding of increased diarrhea risk among Caucasian troops compared with their non-white counterparts is interesting and has not been extensively addressed in previous studies. One previous study found an association among US troops between higher levels of pre-deployment serum antibodies against *Shigella* anti-lipopolysaccharide (LPS) and non-white race and ethnicity, and it was hypothesized that these persons may have lived in areas with higher levels of transmission of *Shigella* spp. and possibly other enterobacteriaceae with cross-reacting antigens.[16] A possible extrapolation to the current study could be that the non-white populations were at lower risk because of pre-existing immunity, a potential avenue of further study.

Although incidence estimates and risk seemed to be consistent with published data among US military populations, there were differences in pathogen etiology in this study, with a finding of higher recovery of ETEC and *Campylobacter*, than has been previously described in the region.[17] This could be because of real increases in prevalence of these particular pathogens or better methods of detection in the current study relative to previous studies in the region. However, the finding of no pathogen detected in 53% of cases is on par with previous studies among similar populations and settings.[4] The finding of nearly one of four participants with evidence of protozoa (pathogen and non-pathogenic) suggests that the relatively poor hygienic conditions and fecal oral exposure continues to occur, despite efforts to improve hygiene in the deployed setting. In addition, the 90% fluoroquinolone resistance to *Campylobacter* spp. is alarming and supports a continued trend to increasing resistance, which has been recently described among *Campylobacter* recovered in Egypt over recent years.[15]

Self-reported diarrhea incidence was seven times more common than self-reported injury estimates and six times more common than acute respiratory illnesses, two of the most commonly reported health problems in the troops. Days lost were similar for diarrhea and non-combat injury (1.3 days per 100 person-months) and higher compared with respiratory illness (0.9 days per 100 person-months). The similarity in days lost between diarrhea and non-combat injury, despite differential incidence estimates, is likely to be explained by the prompt and effective treatment of diarrhea (with antibiotics and anti-motility agents) that mitigated the numbers of days lost because of diarrheal illness and the considerable morbidity that non-combat injuries can have during deployments.[1]

Although this study has the strength of prospective cohort design, it is not without limitations. Among the initial enrollees, there were differences in demographic features among those who completed at least one follow-up visit and those that did not, which may result in selection bias. Those who followed up were older and were more likely to be in the medical profession. The effect of this selection bias (for age and profession) is uncertain. Similar to this study, previous studies in the military have found increasing age to be associated with an increased risk of TD, which may represent more freedom to obtain exposure to local food sources.[13,14] Although not studied in the military, it could be assumed that, compared with other occupations, those in the medical field are likely to have lower risk of infectious diarrhea (i.e., more familiar/adherent to precautions). Therefore, the selection bias in this study is uncertain; the older age of participants might bias to increased risk, whereas the preponderance of personnel in the medical occupations might bias to decreased risk. Furthermore, we only enrolled approximately 20% of the temporary duty population, which may also limit our ability to generalize these results. For these reasons, caution must be exercised in generalizing these findings, although the results seem to be consistent with the current knowledge of diarrhea epidemiology in deployed US military.

Another limitation included our ability to obtain stool specimens only while troops were at the main camp (number of episodes versus clinic episodes). Although it is assumed that the pathogen distribution between cases that occurred while on an outpost was similar to that in the main camp, this could not be tested. Our microbiological assessment was limited and did not include testing of enteroaggregative *E. coli* (EAEC); instead, it relied on phenotypic identification of ETEC, which may have underestimated our detection of diarrheagenic *E. coli*.[18–20] Furthermore, our methods of detection for viral gastroenteritidis relied on ELISA-based assays, which are known to be less sensitive than genotypic methods.[21] In addition, study subjects often enrolled in the study after they had

been deployed an average of 2 months, and therefore, subjects could have missed the period of highest risk for developing diarrhea. If there was differential diarrhea risk during deployment times, this might bias our estimates. However, our study included participants who were enrolled throughout the deployment cycle and thus, should have captured the risk. Lastly, our incidence estimate did not include any observation time during the months of February to April, a period, from our experience, that generally has been associated with lower risk of infectious diarrhea, and this may have resulted in a bias to a higher summary incidence.

Population-based studies on TD, specifically in military populations, are rare. These studies are difficult to perform, particularly in the situation of a military operation in foreign countries. However, to estimate disease risk and provide a platform for primary preventive interventions (e.g., prophylaxis or vaccines), trials and cohort studies need to be conducted. Although this study had limitations, the estimates derived are consistent with our understanding of TD among military populations in this region and provide further evidence that diarrhea among a deployed US military population in Egypt continues to be a common problem, with ETEC being the most frequently identified cause. Illness is reported to affect the ability to work and is seen as an impediment to readiness. Because treatment may not always be practically provided in a timely manner, continued efforts need to be pursued to prevent diarrheal incidence in deployed military settings.

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