



INCIDENCE AND RISK FACTORS ASSOCIATED WITH TRAVELERS' DIARRHEA IN INTERNATIONAL TRAVELERS

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ABSTRACT

Despite knowledge on the causes and prevention strategies for travelers' diarrhea (TD), TD continues to be one of the most common illnesses experienced by international travelers in the US. However, studies of risk factors associated with TD among US travelers are limited. In this study, we aimed to explore the frequency and nature of TD among international travelers who sought pre-travel counseling at two travel clinics in Salt Lake City, Utah, and the risk factors associated with TD. In this cross-sectional study, we collected and analyzed data from anonymous post-travel questionnaires submitted by international travelers seen at the University of Utah and Salt Lake County travel clinics. Questionnaires administered from October 2016 to March 2020 collected information on demographics and health-related behaviors during travel.

To analyze the 22 potential risk factors, we fit bivariate logistic regression models adjusted for a priori selected confounders, and present the odds ratio (OR) and 95% confidence intervals (95% CI) of travelers' diarrhea. Out of 570 completed post-travel surveys, 489 (85.8%) answered the TD question, of which 114 (23.3 %) had TD. Risk factors associated with increased odds of travelers' diarrhea included travel to Southeast Asia (OR=2.08; 95% CI:1.34-3.23), visiting an urban destination (OR=2.82; 95% CI:1.32-6.98), taking medications/supplements to prevent TD (OR=2.73; 95% CI:1.78-4.22), and inadequate hand hygiene behaviors (OR=2.84; 95% CI:1.04-7.64). Travelers' diarrhea continues to be common in international travelers from the US. Our findings provide insights regarding traveler's behaviors, and shows the need for additional research into prevention strategies for travelers' diarrhea.

INTRODUCTION

Despite current knowledge on the causes and prevention strategies for diarrhea among travelers, the burden of traveler's diarrhea (TD) remains high.^{1,5} Traveler's diarrhea is defined as ≥ 3 unformed bowel movements in 24 hours along with at least one associated symptom such as fever, nausea, vomiting, abdominal cramping, tenesmus, or fecal urgency after arriving at their travel destination.¹ Travelers' diarrhea continues to be one of the most common medical concerns experienced by international travelers in the US, with 10%-40% of travelers reporting TD over a two-week trip depending on the travel destination and other characteristics.¹ Amongst travelers visiting high-risk regions, the likelihood of developing diarrhea is 30%-70%,⁶ despite knowledge of risk factors gained from prior research, and traveler education programs addressing such.^{1,2,5} Among the one billion international tourists globally,⁷ US travelers completed over 99 million international trips in 2019.⁸ Although often self-limited, TD can lead to business/travel disruptions, lost productivity, and healthcare costs resulting in economic burden.^{5,9,10} Wang et al. estimated that illness in returning travelers costs the US approximately \$300 million in

healthcare costs and \$650 million due to lost productivity. Recent studies among travelers have worked to improve our understanding of TD through enlarging sample sizes, increasing destination diversity, investigating new diagnostics or treatment strategies, and/or improving generalizability.^{3,4,11-16} Still, questions remain regarding optimal identification of TD etiology, improving our approach to empiric treatment given varying patterns of regional disease, understanding host susceptibility and response, and the identification of new pathogens or disease mechanisms.^{1,11,17} More representative research in US travelers has the potential to clarify risk factors and support the development of additional prevention and control strategies.

The purpose of this study is to determine the incidence and risk factors associated with travelers' diarrhea. To do this, we analyzed data from anonymous post-travel questionnaires submitted by international travelers seen at the University of Utah or Salt Lake County Health Department travel clinics. The primary characteristics examined were travel destination (WHO region), geographic type of destination (urban, rural/countryside, and/or high altitude), age, and travel-related activities. The results from this study can ultimately be used in pursuit of improving health education efforts to reduce risk of travelers' diarrhea by contributing information on American travelers who present for pre-travel healthcare.

MATERIALS and METHODS

Participants We aimed to study health-related practices among prospective international travelers seen at the University of Utah and the Salt Lake County travel clinics from October 2016 to March 2020. Potential participants provided their consent, email address, and anticipated return date from international travel on a recruitment form during their pre-travel healthcare visit. A week following their return date, they received a link to the anonymous post-travel questionnaire (Supplemental materials) using the survey tool REDCap. All data were recorded in the REDCap database. The post-travel survey asked participants questions regarding

demographics, health-related activities before, during, and after travel, symptoms they experienced, and any treatment strategies they used. Ethical oversight and approval was provided by the Institutional Review Board (IRB) of the University of Utah.

Outcomes We defined travelers' diarrhea as 3 or more loose stools per day during a participant's trip. Using the questionnaire, traveler's bowel movements were further characterized as follows: daily TD frequency (3-6 times, 7-9, 10-12, and more than 12); TD description (watery, bloody, and accompanied by fever); TD duration (a few hours, one day, 2-4 days, 5-7 days, and more than one week); and TD symptom interference with planned activities (no, somewhat, and completely).

Variables A total of 22 independent variables were examined, including patient demographics, travel behaviors and factors influencing travelers' diarrhea incidence, and TD characteristics. The following variables were collected after a participant's return from travel using structured questionnaires: age (analyzed as continuous); gender (female, male, and prefer not to answer); self-reported education (advanced degree, bachelor's degree, associate degree, high school diploma/GED or less); WHO-designated region(s) visited (South East Asia, Eastern Mediterranean, Western Pacific, Europe, and the Americas); reason(s) for travel (recreation/sightseeing/pleasure, work-related business, visiting friends or family, research/education, and religious/humanitarian/or other service work); geographic type(s) of destination (urban, rural/countryside, and high altitude); trip duration; trip accommodation(s) (hotel/hostel/guesthouse/or other enclosed structure, car/RV/caravanning, or camping/tent); use of TD prevention medication/supplements and type used (over-the-counter medication, probiotics, and other); TD hydration method if applicable (nothing, oral rehydration source, sports drinks, water only, and other); street food consumption; handwashing practice(s) (soap

and water, water only, alcohol-based hand sanitizer, other, and none); and an alternate handwashing practice variable (includes soap/water or alcohol-based hand sanitizer).

Statistical Analysis The association between travelers' diarrhea and potential risk factors was assessed using bivariate logistic regression, adjusted for a *priori* selected confounders (age), and odds ratio (OR) and 95% confidence intervals (95% CI) are presented. Multivariable regression analysis was explored, but not included in the final results due to potentially confounding factors. All data analysis was completed using R version 3.2.2.

RESULTS

570 travelers were enrolled in the study from October 2016 to March 2020 and completed a post-travel survey. Of these, 81 respondents were excluded based on no response to the travelers' diarrhea survey question. In total, 489 (85.8%) travelers were eligible for analysis, and of these, 114 (23.3%) had travelers' diarrhea (TD). Most travelers who experienced TD had 3-6 bowel movements a day (98, 86.0%), and the majority (89.5%) of TD cases had a reported duration of 7 days or less, with 78.1% (46 travelers) lasting 4 days or less. For most travelers, the TD did not interfere with planned activities (66, 57.9%), and very few experienced watery or bloody diarrhea, or accompanying fever (Table 1).

The characteristics and results of our survey respondents are reported in Table 2. Overall, participants ranged in age from 18 to 81 years, and 286 (58.5%) of the participants self-identified as female. Most of the population had at least a bachelor's degree (188, 38.4% bachelor's degree, 193 (39.5%) advanced degree), 44 (9.0%) had an associate degree, and 64 (13.1%) had a high school diploma/GED, primary school education, or no formal education. The most frequently visited WHO region was South East Asia, with 152 (31.1%) of participants reporting travel there, followed by, 135 (27.6%) to Africa, 132 (27.0%) to the Americas, 75 (15.3%) to the Western Pacific, 40 (8.2%) to Europe, and 24 (4.9%) to the Eastern Mediterranean, and

participants reported visiting 117 countries in total. The vast majority of participants went to urban (419, 85.7%) or rural/countryside (387, 79.1%) regions, and 85 (17.4%) visited a high-altitude region. Most were traveling for recreating/sightseeing/pleasure (364 74.4%), with 72 (14.7%) for religious/humanitarian/or other service work, 71 (14.5%) for work-related business, 50 (10.2%) for visiting family or friends, and 31 (6.3%) for research/education. Median trip duration for all travelers was 14 days (interquartile range 9 days). Most international travelers did not report consuming street food (322, 65.8%). Travelers reported using a variety of non-mutually exclusive (could report multiple behaviors) hand cleaning practices before eating. Most travelers reported using soap and water (452, 92.4%) or alcohol-based hand sanitizer (357, 73.0%) to wash their hands, though 41 (8.4%) reported they had only used water to clean their hands before eating, and 17 (3.5%) reported using no hand washing method. About a third (180, 36.8%) of all participants reported using some form of medication/supplement(s) for prevention of TD - 161 used over-the-counter medication, 37 used probiotics, and 10 reported using some other preventative medication/supplement.

Associations between each risk factor and TD were explored using logistic regression adjusted for age, and four factors were identified and associated with higher odds of travelers' diarrhea. These included visiting Southeast Asia (OR=2.08; 95% CI:1.34-3.23), visiting an urban destination (OR=2.82; 95% CI:1.32-6.98), taking medications/supplements to prevent TD (OR=2.73; 95% CI:1.78-4.22), and not using a hand hygiene method (OR=2.84; 95% CI:1.04-7.64). The remaining risk factors were not statistically significantly associated with TD.

DISCUSSION

This single-center cross-sectional study of 489 travelers returning from 117 countries, we aimed to better understand travel behaviors and other potential risk factors of TD. Of the 489 travelers, almost a quarter (23.3%) reported diarrhea during their trip, though this diarrhea tended

not to interfere with planned activities and generally resolved within a week. We found that visiting Southeast Asia, visiting an urban destination, taking medications/supplements to prevent TD, and inadequate hand hygiene behaviors were associated with increased risk of travelers' diarrhea.

We observed a TD attack rate (23%) towards the lower end of the reported range among international travelers. TD review articles cite attack rates affecting 10%-70% of travelers with risk affected by travel destination and activity^{1, 2, 6, 11, 18-20}. Studies focusing on American travelers have found TD to represent the most common post-travel health complication^{3, 4, 10, 12, 21}. Amongst travelers returning to Europe from Mombasa, Kenya, nearly half (49.3%) of tourists reported having more diarrhea in East African than at home²². A recent review found that over 60% of travelers to areas with high TD incidence rates experience TD⁸.

In our study, we found that travelers to Southeast Asia had the highest odds of TD. Previous studies using data from the GeoSentinel network of travel clinics emphasize the relationship between travel location and diarrheal risk^{11, 20}, and a multisite network assessment positively associated travel to Southeast Asia with contracting TD²³. Likewise, a systematic review and meta-analysis of 5 studies examining long-term travelers and military personnel reported the highest incidence of TD in Southeast Asia (41 cases per 100 person-months, 5 studies) compared to other regions examined²⁴. In comparison, analysis of >17,000 travelers found an association between travel to South Central Asia and acute diarrhea, whereas travel to Southeast Asia was associated with increased rates of systemic febrile illness¹¹. Similarly, Greenwood et al. found that country-specific reporting rate ratios (RRR) for gastrointestinal infections were highest for travel to South Asia, South America, and sub-Saharan African; they noted only moderate RRRs for travel to Southeast Asia²⁰. Differences between our findings and other reported studies may be attributable to underrepresentation of certain travel destinations.

Consistent with prior studies, we identified inadequate hand hygiene and high transmission environments as risk factors for TD. We found that travel to urban areas was significantly associated with TD, which is consistent with an Ecuadorian case-control study that found travelers visiting urban regions had a higher risk of diarrhea and diarrheagenic *Escherichia coli* (DEC) infections compared to travelers visiting rural regions.²⁵ We also found that inadequate hand hygiene behaviors were associated with higher odds of TD, which is consistent with a recent systematic review and meta-analysis showing that handwashing with soap reduces the risk of diarrheal disease by 40%; of note, this estimated effect decreased to 23% when adjusting for unblinded studies²⁶. Similarly, a study of adult travelers in Thailand found eating street food and not washing hands after using the toilet to be associated with increased incidence of TD.²⁷

A higher proportion of females than males reported TD in our study, but this association was not statistically significant (OR: 0.75; 95% CI: 0.48-1.17). This is concordant with prior studies, which on the whole suggest no differences in risk of TD between genders. According to a systematic review and meta-analysis, incidence rates are generally equal between men and women.¹

We briefly explored seasonality of TD by examining the prevalence of TD among travelers by month and season of return, and found no obvious patterns (data not shown). Prior studies have described an association between seasons and diarrheal pathogens; however, we cannot comment on the possible effect of seasonality as we did not investigate diarrheal etiology among our patients. Our study population is based on international travelers seeking pre-travel advice, and is therefore not generalizable to travelers who do not visit pre-travel clinics. Personal behavior can have a large influence on TD risk, and education about these behaviors is often obtained at pre-travel clinics²⁸. While we found a positive association between preventative

medications/supplements and TD, we suspect this is due to reverse causation, whereby those traveling to areas of high TD risk are more likely to adhere to preventative recommendations. A Scottish retrospective study examining pre-travel health consultation effectiveness in reducing diarrhea incidence determined that pre-travel medical advice was not associated with reducing the likelihood of experiencing diarrhea while abroad, but that pre-travel advice may be more effective to help travelers in managing their illness²⁹. Furthermore, travelers visiting high-risk destinations who sought pre-travel advice were less likely to need medical help while abroad or on their return²⁹. This suggests that while pre-travel advice may not prevent TD, it may play a role in reducing the morbidity of TD. Indeed, in our study, most reported TD did not interfere with planned activities, diarrhea occurred 6 or fewer times a day and resolved within a week, and few people experienced watery or bloody diarrhea, or accompanying fever. Despite pre-travel clinics often providing useful information, less than half of travelers visiting low-income regions seek pre-travel health advice²⁸. This behavior is especially concerning considering that morbidity rates can range between 64%-70% for visitors traveling to developing regions²⁸. It is likely that ability/willingness to visit a pre-travel clinic and ability/willingness to follow safer travel behaviors are related in complex ways that are outside the scope of this study.

Our study has several limitations. First, only adults at least 18 years old were eligible for our survey, meaning we were unable to examine the incidence and risk factors of TD in children. Second, we limited our survey to those with travel duration of <1 year, so our results do not generalize to long-term travelers such as missionaries and Peace Corps volunteers. Third, participation was voluntary and questionnaires were completed after travel, possibly leading to sampling bias (e.g. those who experienced TD more likely to complete survey). Fourth, while we asked about hand cleaning behavior before eating, we did not collect information on frequency of each of those behaviors. Finally, our study enrolled from two specific clinics in a single urban

area, which in turn led to fewer respondents traveling to certain destinations. In our sample, the largest region visited was Southeast Asia with 152 total responses recorded, whereas only 24 people total reported visiting the Eastern Mediterranean. Because of this underrepresentation in certain travel destinations, we weren't able to explore the role of destination on TD incidence. Ultimately having a larger and more diverse sample size can provide more informative results.

Altogether, the results from this study are consistent with previous relevant literature showing that a high proportion (23% in our study) of international travelers have TD, and we shown the association of TD with travel destination, medications taken, and inadequate hand hygiene behaviors. This study also contributes to the current literature and expands our understanding of travel behaviors for international travelers seeking pre-travel advice using recent data. Moreover, this can be used to improve health education efforts for this preventable illness from travelers living in a high-income country. Ultimately, updating data, establishing trends, and improving education/safe travel behaviors can improve outcomes for international travelers.

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Table 1. Characteristics of those reporting travelers' diarrhea (TD) among study participants.

Variables	TD N= 114
Daily TD frequency	
3-6 times	98 (86.0%)
7-9	9 (7.9%)
10-12	3 (2.6%)
More than 12	4 (3.5%)
No response or did not answer	0 (0.0%)

TD description*	
Watery	9 (7.9%)
Bloody	3 (2.6%)
Accompanied by fever	6 (5.3)
TD duration	
A few hours	13 (11.4%)
One day	30 (26.3)
2-4 days	46 (40.4%)
5-7 days	13 (11.4%)
More than a week	9 (7.9%)
No response or did not answer	3 (2.6%)
TD interference with planned activities	
No	66 (57.9%)
Somewhat	41 (36.0%)
Completely	4 (3.5%)
No response or did not answer	3 (2.6%)

* TD descriptors asked presence/absence of each, therefore not mutually exclusive, do not sum to 100%

Table 2. Characteristics of international traveler's seeking pre-travel consultation at University of Utah and Salt Lake County travel clinics from October 2016 to March 2020 (n=489).

Variables	Total N= 489 (100%)	TD N= 114 (23.3%)	OR** (95% CI)
Sex			
Female	286	74 (64.9%)	Ref.
Male	(58.5%)	40 (35.1%)	0.75 (0.48,
Missing	201	0 (0%)	1.17)
	(41.1%)		
	2 (0.4%)		
Age			
Median (IQR)	46.0 (30)	41.5 (30)	0.99 (0.97, 1.00)
Highest education level			
≤High school/GED	64 (13.1%)	15 (13.2%)	Ref.
Associate degree	44 (9.0%)	4 (3.5%)	0.36 (0.10,
Bachelor's degree	188	53 (46.5%)	1.08)
Advanced degree	(38.4%)	42 (36.8%)	1.37 (0.72, 2.74)
	193		1.1 (0.55, 2.27)
	(39.5%)		
WHO-designated region(s) visited*			
South East Asia	152	51 (44.7%)	2.08 (1.34,
African	(31.1%)	30 (26.3%)	3.23)
Eastern Mediterranean	135	5 (4.4%)	0.97 (0.59,
Western Pacific	(27.6%)	22 (19.3%)	1.55)
The Americas	24 (4.9%)	23 (20.2%)	0.9 (0.29,
European	75 (15.3%)	13 (11.4%)	2.31)
Total number of regions visited			

	132 (27.0%) 40 (8.2%)		1.38 (0.78, 2.37) 0.63 (0.37, 1.03) 1.67 (0.81, 3.31) 1.87 (1.23, 2.92)
Reason(s) for travel*			
Recreation, sightseeing, pleasure, etc.	364 (74.4%)	82 (71.9%)	0.93 (0.58, 1.51)
Work-related business	71 (14.5%)	21 (18.4%)	1.39 (0.78, 2.42)
Visiting family or friends	50 (10.2%)	12 (10.5%)	1.39 (0.78, 2.42)
Research/education	31 (6.3%)	9 (7.9%)	0.99 (0.48, 1.92)
Religious, humanitarian, or other service work	72 (14.7%)	20 (17.5%)	0.99 (0.48, 1.92)
Total number of reasons for travel			1.11 (0.46, 2.48) 1.23 (0.68, 2.15) 1.29 (0.84, 1.93)
Region type(s) visited*			
Urban	419 (85.7%)	107 (93.9%)	2.82 (1.32, 6.98)
Rural/countryside	387 (79.1%)	96 (84.2%)	1.63 (0.95, 2.95)
High Altitude	85 (17.4%)	22 (19.3%)	1.17 (0.67, 1.99)
Total number of types visited			1.56 (1.13, 2.16)
Travel group size			
Median (IQR)	3.00 (2)	3.0 (2)	1.04 (0.83, 1.30)
Missing	2 (0.4%)	0 (0%)	
Trip duration			
Median (IQR)	14.0 (9)	16 (10)	1.01 (1.00, 1.01)
Missing	3 (0.6%)	1 (0.9%)	
Used TD prevention medication/supplement			
No	309 (63.2%)	51 (44.7%)	2.73 (1.78, 4.22)
Yes	180 (36.8%)	63 (55.3%)	
Type(s) of TD prevention medication/ supplement**			
Over the counter medication	161 (32.9%)	54 (47.4%)	2.22 (1.44, 3.43)
Probiotics	37 (7.6%)	16 (14.0%)	3.04 (1.50, 6.11)
Other	10 (2.0%)	4 (3.5%)	
Total number of meds/supplements used			

			2.42 (0.60, 8.72) 2.06 (1.49, 2.85)
Hand-cleaning practice(s) during trip before eating*			
Washed with soap and water	452 (92.4%)	103 (90.4%)	0.74 (0.36, 1.62)
Washed with water only	41 (8.4%)	16 (14.0%)	2.12 (1.06, 4.12)
Alcohol-based hand sanitizer	357 (73.0%)	86 (75.4%)	1.18 (0.73, 1.94)
None	17 (3.5%)	8 (7.0%)	2.84 (1.04, 7.64)
Any hand sanitizing practice (soap/water or alcohol-based hand sanitizer)	472 (96.5%)	109 (95.6%)	0.80 (0.29, 2.59)
Trip accommodation			
Hotel, hostel, guesthouse, other enclosed structure	475 (97.1%)	112 (98.2%)	1.67 (0.44, 10.90)
Car, RV, caravanning, etc.	23 (4.7%)	6 (5.3%)	1.06 (0.37, 2.64)
Camping/tent	61 (12.5%)	16 (14.0%)	1.23 (0.65, 2.25)
Raw food consumed			
No	377 (77.1%)	82 (71.9%)	1.41 (0.86, 2.27)
Yes	111 (22.7%)	31 (27.2%)	
Missing	1 (0.2%)	1 (0.9%)	
Street food consumed			
No	322 (65.8%)	64 (56.1%)	1.57 (0.99, 2.48)
Yes	166 (33.9%)	50 (43.9%)	
Missing	1 (0.2%)	0 (0%)	

*Respondents could select more than one option; therefore, numbers sum to more than total sample size, and odds ratios compare yes/no for each sub-category.

**Adjusted for a priori selected confounders (age)

Abbreviations: IQR=interquartile range

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