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Epidemiology and Self-Treatment of Travelers' Diarrhea in a Large, Prospective Cohort of Department of Defense Beneficiaries

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Background. Infectious diarrhea is a common problem among travelers. Expert guidelines recommend the prompt use of antibiotics for self-treatment of moderate or severe travelers' diarrhea (TD). There is limited data on whether travelers follow these self-treatment guidelines. We evaluated the risk factors associated with TD, the use of TD self-treatment, and the risk of irritable bowel syndrome (IBS) during travel.

Methods. Department of Defense beneficiaries traveling outside the United States for ≤6.5 months were enrolled in a prospective cohort study. Participants received pre- and post-travel surveys, and could opt into a travel illness diary and follow-up surveys for symptoms of IBS. Standard definitions were used to assess for TD and IBS. Suboptimal self-treatment was defined as the use of antibiotics (with or without antidiarrheal agents) for mild TD, or the use of antidiarrheals alone or no self-treatment in cases of moderate or severe TD.

Results. Twenty-four percent of participants (270/1,120) met the criteria for TD. The highest incidence was recorded in Africa [8.6 cases/100 person-weeks, 95% confidence interval (CI): 6.7–10.5]. Two hundred and twelve participants with TD provided information regarding severity and self-treatment: 89 (42%) had mild TD and 123 (58%) had moderate or severe TD. Moderate or severe TD was independently associated with suboptimal self-treatment [OR 10.4 (95% CI: 4.92–22.0)]. Time to last unformed stool did not differ between optimal and suboptimal self-treatment. IBS occurred in 4.5% (7/154) of TD cases and in 3.1% (16/516) of cases without TD ($p = 0.39$). Among TD cases, a lower incidence of IBS was noted in participants who took antibiotics [4.8% (5/105) vs 2.2% (1/46)] in those who did not, but the difference did not reach statistical significance ($p = 0.60$).

Conclusions. Our results suggest the underutilization of antibiotics in travelers with moderate or severe TD. Further studies are needed to systematically evaluate pre-travel instruction and traveler adherence to self-treatment guidelines, and the impact of suboptimal self-treatment on outcomes.

Travelers' diarrhea (TD) is a common cause of incapacitation in travelers and deployed military personnel, resulting in disruption of planned activities and impacting mission readiness. Randomized trials have established the efficacy of combination therapy with antibiotics and loperamide in limiting the duration of TD symptoms.[1–3] Expert guidelines recommend rehydration with or without loperamide for self-treatment of mild watery diarrhea that does not interfere with daily activities, and a combination of antibiotics (eg,

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quinolones, azithromycin, or rifaximin) and loperamide for moderate or severe symptoms.[4–6] However, there are limited prospective data on how travelers use these medications for self-treatment, and their effectiveness in shortening the duration of symptoms and preventing long-term sequelae.[7,8]

The TravMil study [Deployment and Travel Related Infectious Disease Risk Assessment, Outcomes, and Prevention Strategies Among Department of Defense (DoD) Beneficiaries] prospectively evaluates infectious disease risks, and the effectiveness of prevention and treatment strategies, in DoD beneficiaries traveling outside the continental United States.[9] We utilized data from the TravMil cohort to assess (1) the incidence and risk factors for TD; (2) the risk factors for suboptimal self-treatment and their impact on outcomes; and (3) the risk of irritable bowel syndrome (IBS) following TD.

Methods

Study Design

TravMil is a prospective, observational cohort of DoD beneficiaries traveling outside the continental United States for ≤6.5 months. Adult and pediatric travelers enrolled pre-travel from three military travel clinics (Naval Medical Center, Portsmouth, VA; Naval Medical Center, San Diego, CA; and Walter Reed National Military Medical Center, Bethesda, MD) between January 2010 and July 2013 were included. Itineraries limited to Western or Northern Europe, Canada, or New Zealand were excluded. Travel medicine physicians counseled travelers on prevention and self-treatment of diarrhea, and provided relevant prescriptions. No standardization of counseling for TD self-treatment was performed as part of this study. The study was approved by the Uniformed Services University Infectious Disease Institutional Review Board.

Participant demographics, travel itinerary, medical history, and prescriptions were obtained during the pre-travel visit. Participants received two surveys. A pre-travel survey evaluated demographic data, previous travel to developing countries, and symptoms of IBS. A post-travel survey, completed up to 8 weeks after return, collected information regarding dietary habits during travel, diarrheal episodes, associated symptoms, perceived severity and incapacitation, and the use of self-treatment.

Participants were invited to opt into the following procedures at the pre-travel visit:

- Travel illness diary: daily record of the number of unformed stools per 6-hour period during a diarrheal episode along with associated symptoms, severity, level of incapacitation, timing of self-treatment, and associated side effects.
- Follow-up survey: sent at 3, 6, 9, and 12 months post-travel to evaluate for symptoms of IBS.

Definitions

Travel destinations were divided into five regions, modified from the GeoSentinel model[10]: (1) Southeast Asia, North Asia, and Oceania; (2) South, Central, and West Asia; (3) South America, Central America, and the Caribbean; (4) Africa; and (5) Eastern Europe. Travel to >1 region was classified as "multiple destinations," except where travel was limited to Eastern Europe and one other destination. In this instance, participants were classified as traveling to the destination other than Eastern Europe, since the incidence of TD is higher elsewhere. For the multivariate analyses regarding TD risk factors and suboptimal treatment, we dichotomized travel regions into "Africa" and "regions other than Africa" (since travel to Africa was associated with the highest TD attack rates).

Trip purpose was categorized as follows: visiting friends and relatives (VFR), vacation, business, military travel, and other (teaching/study, providing medical support, missionary/humanitarian work, adventure travel/ecotour, adoption, and other). For the multivariate analyses, we combined VFR and vacation travel into a single "vacation" category (because of the small number of VFR travelers in our cohort and no significant difference in the rate or severity of diarrhea) and all other trip purposes into a single "non-vacation" category.

TD was defined as ≥3 unformed stools, or 2 unformed stools with at least one accompanying symptom (nausea, vomiting, abdominal pain, fever, blood in stool) within 24 hours. Participants with unformed stool that did not meet these criteria were classified as having loose stools. Participants with TD were categorized into the following hierarchy: (1) mild TD, defined as acute watery diarrhea (AWD) (ie, diarrhea without fever or blood in stool) of mild severity (ie, allowing for normal level of activity) and (ii) moderate or severe TD, defined as AWD with moderate or severe symptoms (ie, decreased level or complete inability to participate in daily activities), dysentery (visible blood in stool), or acute febrile watery diarrhea (AFWD) (diarrhea associated with subjective fever). Multiple episodes of TD were defined as having a diarrhea-free interval of ≥72 hours.

We evaluated optimal use of self-treatment in participants with TD. Suboptimal self-treatment was defined as the use of antibiotics for mild TD, or the use of an antidiarrheal agent alone or no self-treatment for moderate or severe TD. Conversely, no self-treatment or the use of antidiarrheals alone was considered optimal self-treatment for mild TD, as was the use of antibiotics alone or in combination with antidiarrheals for moderate or severe TD.

Participants with TD who completed a travel illness diary were included in the effectiveness analysis. The primary measure was time to last unformed stool (TLUS), defined as the time from treatment initiation to passage of the last unformed stool. Clinical cure was defined as passage of no unformed stools

and resolution of all associated symptoms after initiation of self-treatment. The modified Rome III criteria were used to classify participants with IBS in the pre-travel and follow-up surveys.[11] Participants with IBS pre-travel and those who did not complete any follow-up surveys were excluded from the IBS analysis.

Statistical Analysis

Data analysis was performed using SAS statistical software, version 9.3 (SAS Institute, Cary, NC, USA). TD incidence rates were calculated as the number of cases/100 person-weeks of travel. The median time to first episode of TD between geographic regions was compared using hazard ratios computed by a univariate Cox proportional hazards model. A multivariable logistic regression model with backward selection was used to determine risk factors for TD and suboptimal self-treatment. A Mann–Whitney–Wilcoxon test for continuous variables and the Fisher's exact test for categorical variables were used to compare median TLUS, clinical cure rates, and risk factors for IBS. TLUS was compared between optimal and suboptimal self-treatment by a Kaplan-Meier analysis with a log-rank test. A left-truncation was performed on the cohort that received no self-treatment using the median time from start of symptoms to treatment in participants in the self-treatment cohort. Participants could be included in the analysis multiple times if they took multiple trips, but only the first episode of diarrhea that met the criteria for TD per trip was used in the treatment analysis.

Results

A total of 1,215 patients were enrolled in the study—79 patients enrolled for multiple trips, for a total of 1,323 enrollments. Of these, 1,120 (85%) completed a post-travel survey and/or a travel illness diary (Figure S1, Supporting Information). The median trip duration was 17 days (interquartile range, IQR: 12–29 days) and the median duration between trip return and completion of the post-travel survey was 21 days (IQR: 10–34 days). Seven hundred and eighty four (70%) participants had no diarrhea during travel, 66 (6%) experienced loose stool, and 270 (24%) developed TD [incidence rate of 5.3 cases/100 person-weeks (95% CI: 4.7–6.0 cases/100 person-weeks)]. TD was associated with a maximum (median) of 4 (IQR: 2–4) stools per day and lasted for a median of 1 day (IQR: 1–2 days). There were 208 cases of AWD, 52 cases of AFWD, and 10 cases of dysentery. Patients with mild TD reported a maximum (median) of 3 stools per day (IQR: 2–4) lasting for 1 day (IQR: 1–2), while moderate or severe TD was associated with 4 stools per day (IQR: 3–6) for 2 days (IQR: 1–3).

The highest incidence rates for TD were recorded in Africa (8.6 cases/100 person-weeks, 95% CI: 6.7–10.5) and South, Central, and West Asia (6.1 cases/100 person-weeks, 95% CI: 3.4–8.7). Information regarding timing of symptoms was obtained from 164 participants with TD and the median time from start of travel to development of TD was 9 days (IQR: 6–16 days). Figure 1 represents the time to first TD episode, and the TD hazard ratio at 9 days for the highest risk regions. A longer median interval to symptom onset was observed for Asia [11 days (IQR: 7–20); $n = 54$] as compared to Africa [8 days (IQR: 5–14); $n = 47$; Africa vs Asia $p = 0.02$] and Central and South America [7 days; (IQR: 4–13); $n = 53$; Central and South America vs Asia $p = 0.01$]. Participants who traveled to Asia were more likely to be vacationing or VFR and to consume meals prepared by street vendors as compared to those who traveled to Africa and the Americas ($p < 0.05$).

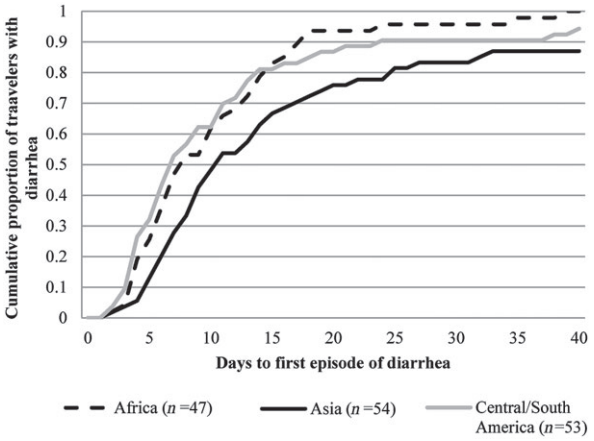

Figure 1 Time from trip start date to first episode of travelers' diarrhea (TD) stratified by travel destination for participants who met criteria for TD, completed a travel diary, and traveled to regions with high risk for TD ($n = 154$). Unadjusted Cox proportional hazards model used to calculate hazard ratio for TD within 9 days of travel (9 days was the median time to development of TD for the overall cohort); log-rank p-value = 0.0541. Hazard ratio for TD within 9 days of travel (95% CI): Asia: Reference; South/Central America: 1.85 (1.09–3.16), $p = 0.03$; Africa: 1.46 (0.83–2.58), $p = 0.19$.

Risk factors independently associated with TD were female gender [risk ratio: 1.33 (1.03–1.71)] and travel to Africa either for vacation/VFR [risk ratio: 1.88 (1.26–2.80)] or for business [risk ratio: 1.73 (1.18–2.57)]. Dietary indiscretion (consumption of poorly cooked meat, unsafe drinking water, the use of ice in beverages, and eating meals prepared by street vendors) during travel was not associated with TD (Table 1). We performed a separate univariate analysis of incidence of TD within the first 14 days of travel among short-term (ie, ≤ 2 weeks) versus long-term (>2 weeks) travelers, for patients who provided information regarding timing of diarrheal episodes. Short-term travelers were significantly more likely to develop TD in the first 2 weeks compared to longer-term travelers [risk ratio: 2.97 (2.15–4.09)].

Table 1 Risk factors for travelers' diarrhea (TD) ($n = 1,120$)*

Variable	Number of participants who met criteria for TD	Person-time (days)	Rate (cases/100 person-weeks)	Univariate rate ratio (95% CI)	Multivariate rate ratio (95% CI)
Age					
>55 years	104	12,210	5.96	Ref.	Ref.
26–55 years	116	15,668	5.18	0.87 (0.67–1.13)	1.11 (0.81–1.52)
≤25 years	50	7,723	4.53	0.76 (0.54–1.07)	1.01 (0.67–1.51)
Gender					
Male	120	18,643	4.51	Ref.	Ref.
Female	150	16,958	6.19	1.37 (1.08–1.75)	1.32 (1.03–1.71)
Trip purpose and destination					
Non-vacation excluding Africa	96	17,924	3.75	Ref.	Ref.
Vacation excluding Africa	96	11,268	5.96	1.59 (1.20–2.11)	1.36 (0.98–1.89)
Africa for non-vacation travel	37	2,973	8.71	2.32 (1.59–3.40)	1.74 (1.18–2.57)
Africa for vacation travel	41	3,362	8.54	2.28 (1.58–3.28)	1.88 (1.26–2.80)
Meals prepared by street vendors†					
No	186	24,412	5.33	Ref.	
Yes	70	9,147	5.36	1.00 (0.76–1.32)	
Consumption of poorly cooked meat (pork, beef, or seafood)†					
No	200	26,580	5.27	Ref.	
Yes	32	4,786	4.68	0.89 (0.61–1.29)	
Consumption of unsafe drinking water†					
No	200	26,092	5.30	Ref.	
Yes	56	6,924	5.47	1.03 (0.77–1.39)	
Ice in beverages†					
No	104	10,968	6.64	Ref.	
Yes	145	21,332	4.76	0.72 (0.56–0.92)	
History of H2 blockers/PPI use					
No	222	29,672	5.24	Ref.	
Yes	48	5,885	5.71	1.09 (0.80–1.49)	

CI, confidence interval; PPI, proton pump inhibitors.

*TD defined as report of ≥3 loose stools in a 24-hour period or 2 unformed stools with at least one accompanying symptom (nausea, vomiting, abdominal pain, fever, blood in stool).

†Subjects with missing information: meals prepared by street vendors = 14 subjects; consumption of poorly cooked meat = 38 subjects; consumption of unsafe drinking water = 14 subjects; ice in beverages = 21 subjects.

Two hundred and twelve TD cases (79%) were included in the analysis for suboptimal self-treatment (Figure S1). A moderate or severe diarrheal illness was the only independent predictor for suboptimal self-treatment (OR: 10.4; 95% CI: 4.92–22.0) (Table 2). Eighty-eight percent (77/88) of mild TD patients took optimal self-treatment. However, only 42% of moderate or severe TD patients took optimal self-treatment [moderate or severe AWD: 30/81 (37%), AFWD 17/35 (49%), dysentery 4/8 (50%)]. The most commonly used antibiotic was ciprofloxacin (68%), followed by azithromycin (32%), with 5% reporting the use of both.

One hundred and twenty-four TD cases (46%) were included in the effectiveness analysis (Figure S1). TLUS and 48-hour cure rate was compared between suboptimal and optimal self-treatment, stratified by severity of diarrhea. No significant difference in the TLUS (log-rank p-value >0.05) or 48-hour cure rates was observed [mild TD: suboptimal treatment: 100% (7/7); optimal self-treatment: 85% (28/33); $p = 0.36$; moderate or severe TD: suboptimal treatment: 77% (36/47); optimal self-treatment: 73% (27/37); $p = 0.70$] (Table 3). Poor compliance with the travel diary and the lack of antibiotic use for moderate or severe diarrhea significantly limited the sample size for analysis.

The overall incidence of IBS was 3.4% (23/670). Of the 23 patients, eight (35%) developed new IBS symptoms within 3 months after their return date—seven (30%) first developed symptoms 6 months after returning, three (13%) first developed symptoms 9 months after returning, and five (22%) first developed symptoms on the last survey 12 months after returning. Thirty percent (7/23) displayed symptoms over multiple time points. Participants with TD had a numerically higher incidence of IBS versus those without TD (4.5% vs 3.1%; $p = 0.39$) (Figure 2 and Table 4). Among the 154 participants with TD, 5 of 105 (4.8%) who received no treatment or antidiarrheal alone developed post-travel IBS versus 1 of the 46 participants (2.2%) who took antibiotics alone or in combination with an antidiarrheal ($p = 0.67$).

Discussion

We utilized a large, prospective cohort of DoD beneficiaries traveling to intermediate and high-risk TD

Table 2 Factors associated with suboptimal self-treatment in participants with travelers' diarrhea (TD)*†

Variable	Optimal self-treatment ($n = 129$)	Suboptimal self-treatment ($n = 83$)	Univariate odds ratio—suboptimal self-treatment (95% CI)	Multivariate odds ratio—suboptimal self-treatment (95% CI)
Age				
>55 years	48 (38)	30 (36)	Ref.	Ref.
26–55 years	55 (43)	38 (46)	1.10 (0.60–2.05)	1.07 (0.53–2.17)
≤25 years	25 (19)	15 (18)	1.02 (0.46–2.25)	1.36 (0.54–3.43)
Gender				
Male	61 (47)	33 (40	Ref.	Ref.
Female	68 (53)	50 (60)	1.36 (0.78–2.38)	1.11 (0.57–2.15)
Severity of diarrhea				
Mild	78 (60)	11 (13)	Ref.	Ref.
Moderate or severe	51 (40)	72 (87)	10.0 (4.84–20.7)	10.4 (4.95–22.0)
Race				
White	102 (79)	68 (82)	Ref.	
Non-White	27 (21)	15 (18)	0.83 (0.41–1.68)	
Trip duration				
≤2 weeks	40 (31)	31 (37)	1.32 (0.74–2.37)	
>2 weeks	89 (69)	52 (63)	Ref.	
Trip purpose				
Non-vacation/VFR	46 (36)	23 (28)	Ref.	
Vacation or VFR	83 (64)	60 (72)	1.44 (0.79–2.64)	
Region of travel				
Travel to Africa	88 (68)	67 (81)	Ref.	
Travel to regions other than Africa	41 (32)	16 (19)	0.51 (0.27–0.99)	
High-risk behavior for TD‡				
No	30 (25)	18 (22)	Ref.	
Yes	89 (75)	62 (78)	1.16 (0.60–2.27)	

CI, confidence interval; VFR, visiting friends and relatives.

*TD defined as report of ≥3 loose stools in a 24-hour period or 2 unformed stools with at least one accompanying symptoms(nausea, vomiting, abdominal pain, fever, blood in stool). 212 participants with TD provided information regarding the severity of diarrhea and the use of self-treatment and were included in the analysis.

†Suboptimal self-treatment is defined as the use of antibiotic therapy for mild acute watery diarrhea (AWD), or the use of antidiarrheal medication alone, or no treatment for moderate or severe AWD, dysentery and acute febrile watery diarrhea (AFWD). Conversely, no self-treatment or the use of antidiarrheals alone was considered optimal self-treatment for mild TD, as was the use of antibiotics alone or in combination with antidiarrheals for moderate or severe TD.

‡Defined as consumption of meals prepared by street vendors, poorly cooked meat, unsafe drinking water or the use of ice in beverages during travel. Risk behavior was unknown for 13 participants.

regions to describe the incidence and characteristics of TD, the use and effectiveness of self-treatment, and the incidence of IBS. Approximately one-quarter of participants developed TD, with a regional attack rate of between 22 and 26% for all regions of travel except Eastern Europe. Our incidence rate was substantially lower than the historic rates of >50% reported for high-risk destinations,[12–14] and slightly lower than the 28% to 34% attack rates reported in recent observational cohorts.[7,8,15–17] This may be attributable to the pooling of intermediate- and high-risk destinations, and could also indicate a general trend toward better food hygiene in those parts of the developing world frequented by travelers.

Several interesting associations with TD incidence were observed. Travelers with trip durations of ≤2 weeks had a three times greater TD incidence rate in the first 2 weeks of travel than longer-term travelers, possibly because of altered dietary behaviors (eg, cooking at home) in long-term travelers that allowed them to remain well. A slightly longer median interval to TD onset was noted in travelers to Asia (11 days vs 8 days for Africa and 7 days for the Americas), possibly reflecting the longer incubation periods of pathogens such as *Campylobacter* spp. and *Salmonella* spp. found more commonly in Asia. Despite receiving pre-travel advice on avoidance measures, only 14% were fully compliant with the dietary precautions, and no association between dietary indiscretion and TD was observed, highlighting the limitations of education on avoidance behaviors in mitigating the risk of TD.[7,18,19]

TD cases were relatively mild, lasting a median of 8.5 hours, with a maximum (median) of 3 to 5 stools/day, but had a significant impact on travel plans: 52% reported partial or complete incapacitation for a day, 23% had febrile diarrhea or dysentery, and 10% sought medical care or hospitalization. This disruption in daily activities may be especially important in business travelers or deployed personnel, where the tolerance for any short-term illnesses is low. It is these subsets of short-term travelers that may be good candidates for chemo- or immunoprophylaxis.

Table 3 Outcomes associated with travelers' diarrhea (TD) self-treatment*

Mild diarrhea ($n = 40$)			
Outcome characteristics	Optimal self-treatment (no treatment or antidiarrheals) ($n = 33$)	Suboptimal self-treatment (antibiotics ± antidiarrheals) ($n = 7$)	p-Value
TLUS, median h (IQR)†	8.5 (3.5–25.0)	14.0 (7.3–27.3)	0.22
Clinical cure at 24 hours, *n* (%)	23 (70)	4 (57)	0.66
Clinical cure at 48 hours, *n* (%)	28 (85)	7 (100)	0.36
Post-treatment side effects			
Nausea, *n* (%)	0 (0)‡	1 (14)	0.35
Vomiting, *n* (%)	1 (8)‡	0 (0)	1.0
Moderate or severe diarrhea ($n = 84$)			
Outcome	Optimal self-treatment (antibiotics ± antidiarrheals) ($n = 37$)	Suboptimal self-treatment (no treatment or antidiarrheals) ($n = 47$)	p-Value
TLUS, median h (IQR)†	7 (2–62)	8.5 (2.5–38.5)	0.97
Clinical cure at 24 hours, *n* (%)	24 (65)	30 (64)	0.92
Clinical cure at 48 hours, *n* (%)	27 (73)	36 (77)	0.70
Post-treatment side effects			
Nausea, *n* (%)	11 (30)‡	0 (0)‡	0.005
Vomiting, *n* (%)	5 (14)‡	0 (0)‡	0.15

TLUS, time to last unformed stool; IQR, interquartile range.
*Participants who met the criteria for TD and completed a diary noting the timing of diarrheal episodes and the use of self-treatment ($n = 124$).
†Median time to beginning of therapy for the treatment group was 3.5 hours. For patients who took no self-treatment [$n = 47$ (20 mild diarrhea, 27 moderate or severe diarrhea)], TLUS was calculated as the mean number of unformed stools by 3.5 hours after start of episode. Six subjects' symptoms had resolved before this time.
‡Reported only for patients who took antidiarrheals.

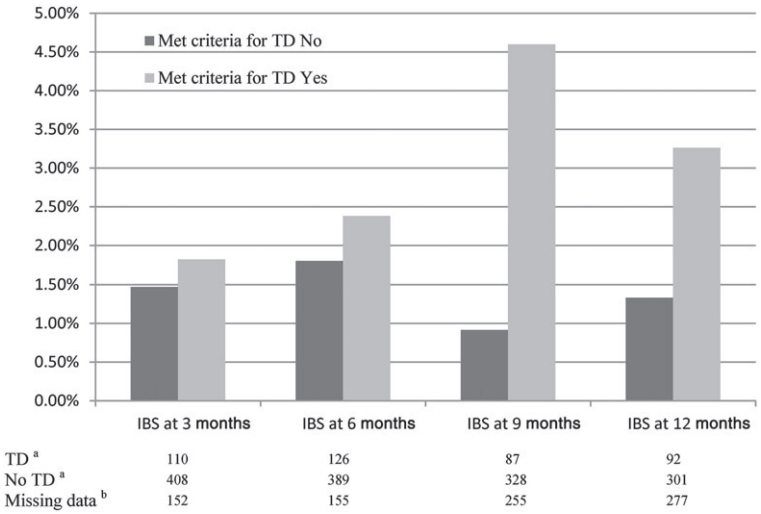

Figure 2 Frequency of irritable bowel syndrome (IBS) among travelers' diarrhea (TD) cases and those without TD. [a]Total number of participants who met criteria or did not meet criteria for TD, and completed an extended follow-up survey at the specified time point. Participants counted at multiple time points. [b]Number of participants who did not fill out an extended follow-up survey at the specified time point.

Expert guidelines and efficacy trials support prompt treatment with antibiotics and loperamide for moderate or severe TD.[1–6] We observed that participants with moderate or severe TD were ten times more likely to use suboptimal self-treatment compared to participants with mild diarrhea. Only 32% of participants with moderate or severe diarrhea took an antibiotic despite receiving pre-travel counseling and an antibiotic prescription for self-treatment. Underutilization of antibiotics for self-treatment has been reported in other observational cohorts, with rates ranging from 7% to 45%, although these studies did not stratify by severity of TD.[7,8,16] Most patients with moderate or severe TD in our cohort experienced mild, self-limited diarrhea

Table 4 Comparison of travelers who developed irritable bowel syndrome (IBS) post-travel and those who did not*

Variable	No IBS reported post-travel ($n=647$)	IBS reported post-travel ($n=23$)	p-Value
Age			
>55 years	326 (50)	15 (65)	
26–55 years	252 (39)	8 (35)	0.41
≤25 years	69 (11)	0 (0)	0.96
Male gender	322 (97)	9 (3)	0.32
Active duty (enlisted or officer)	118 (18)	4 (17)	0.92
Trip duration			
≥2 weeks	400 (62)	9 (39)	
<2 weeks	247 (38)	14 (61)	0.03
Trip purpose			
Non-vacation or VFR	170 (26)	7 (30)	
Vacation/VFR	474 (74)	16 (70)	0.67
Region of travel			
Southeast Asia, North Asia, and Oceania	155 (24)	5 (22)	
South Asia, Central Asia, and West Asia	51 (8)	5 (22)	0.09
South America, Central America, and the Caribbean	193 (30)	6 (26)	0.95
Africa	185 (28)	3 (13)	0.35
Eastern Europe	16 (2)	1 (4)	0.56
Multiple destinations	47 (7)	3 (13)	0.36
Travelers' diarrhea (TD)			
No diarrhea	500 (77)	16 (70)	
Mild TD	69 (11)	1 (4)	0.45
Moderate or severe TD	78 (12)	6 (26)	0.08
Duration of TD			
No TD	500 (77)	16 (70)	
≤1 day	65 (10)	1 (4)	0.48
>1 day	82 (13)	6 (26)	0.09
Multiple episodes of TD†	19 (20)	2 (40)	0.28
TD self-treatment‡			
No treatment/antidiarrheal only	100 (69)	5 (83)	
Antibiotic	45 (31)	1 (17)	0.67
Unknown	2	1	

VFR, visiting friends and relatives.
*Only participants who did not report symptoms of IBS pre-travel and completed at least 1 extended follow-up survey at 3, 6, 9, or 12 months post-travel were included in the analysis.
†Participants who completed a diary and had multiple episodes that met the criteria for TD.
‡Participants who completed a diary or post-travel survey and met the criteria for TD.

(4 stools/day lasting 1–2 days), which could explain why they were inclined to defer self-treatment or use loperamide alone. We did not observe a benefit associated with taking antibiotics for moderate or severe diarrhea, likely because of the self-limited TD episodes in our cohort along with the poor compliance with the travel illness diaries and underutilization of antibiotics for self-treatment, which limited the sample size for determining the impact of self-treatment on outcome. Further studies are needed to systematically evaluate pre-travel counseling regarding the use and timing of self-treatment, traveler adherence, and impact of non-compliance on outcomes.

IBS occurred in 3.4% of the overall cohort, similar to rates reported in previous studies.[20–23] TD was not associated with increased risk of IBS as reported in prior studies, which could be related to the nature of TD in our cohort and the infrequency of IBS.[24] In participants with TD, rates of PI-IBS were higher with moderate or severe diarrhea (7% vs 1.4% for mild diarrhea) and diarrhea lasting >1 day (7% vs 2% for ≤1 day), although these findings did not reach statistical significance. In addition, TD patients who did not take an antibiotic developed PI-IBS more often than antibiotic-treated patients (4.8% vs 2.2%). Experimental evidence suggests that PI-IBS may result from uncontrolled chronic inflammation following infectious diarrhea, and similar associations between duration and severity of infectious diarrhea and PI-IBS have been reported previously.[25–29] Further studies are needed to identify travelers that are at high risk for development of PI-IBS and to design prospective studies to evaluate the use of prophylactic and therapeutic strategies.

Research in travel medicine poses unique methodological challenges including the heterogeneity of the population, travel itineraries, utilization of pre-travel

health care, and recall bias on post-travel surveys. Selection bias may have influenced our results because participants were enrolled at travel clinics, and represented a different risk profile compared to individuals who do not seek pre-travel health care or see non-specialist providers. Poor compliance with completion of travel illness diaries limited our analyses for effectiveness of self-treatment and risk of IBS.

In conclusion, our results indicate suboptimal use of self-treatment in patients with moderate or severe TD. Additional studies are needed to systematically evaluate the possible causes including the knowledge, attitudes, and practice patterns of providers, adherence to counseling by travelers, and the impact of suboptimal TD self-treatment on outcomes.

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Declaration of Interests

The authors state that they have no financial conflicts or disclosures to report.

Supporting Information

Supporting Information may be found in the online version of this article:

Fig. S1. Flow diagram of participants included in the travelers' diarrhea (TD) and irritable bowel syndrome (IBS) analyses.

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