Journal of Travel Medicine

International Society of Travel Medicine
Established 1991
Promoting healthy travel worldwide

Journal of Travel Medicine, 2022, 1–8
https://doi.org/10.1093/jtm/taab139
Advance Access Publication Date: 6 September 2021
Original Article

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A disease severity scale for the evaluation of vaccine and other preventive or therapeutic interventions for travellers' diarrhoea

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Submitted 22 July 2021; Revised 9 August 2021; Editorial Decision 16 August 2021; Accepted 16 August 2021

Abstract

Background: Travellers' diarrhoea (TD) is the most common travel-related illness with an estimated 10 million people afflicted annually. Outcome measures to assess the efficacy of primary and secondary TD interventions were historically based on diarrhoea frequency with ≥1 associated gastrointestinal symptom. Furthermore, efficacy determination is often made on the presence or absence of TD, rather than on TD illness severity. Current severity classifications are based on subjective consideration of impact of illness on activity. We sought to develop a standardized scoring system to characterize TD severity to potentially apply as a secondary outcome in future field studies.

Methods: Data on multiple signs and symptoms were obtained from a previously published multisite TD treatment trial conducted by the US Department of Defense (TrEAT TD). Correlation, regression and multiple correspondence analyses were performed to assess impact on activity and a TD severity score was established.

Results: Numerous signs and symptoms were associated with impaired function, with malaise and nausea most strongly associated [odds ratio (OR) 5.9–44.3, $P < 0.0001$ and OR 2.8–37.1, $P < 0.0001$, respectively). Based on co-varying symptomatology, a TD severity score accounting for diarrhoea frequency in addition to several signs and symptoms was a better predictor of negative impact on function than any single sign/symptom ($X^2 = 127.16$, $P < 0.001$). Additionally, there was a significant difference ($P < 0.0001$) in the mean TD severity score between those with acute watery diarrhoea (3.9 ± 1.9) and those with dysentery or acute febrile illness (6.2 ± 2.0).

Conclusions: The newly developed disease severity score better predicted a negative impact on activity due to TD than did any single sign or symptom. Incorporating multiple parameters into the TD severity score better captures illness severity and moves the field towards current recommendations for TD management by considering symptoms with high functional impact. Further validation of this score is needed in non-military travellers and other settings.

Key words: Functional impact, illness, score, nausea, vomiting, dysentery

Introduction

Travellers' diarrhoea (TD) is the most common travel-related illness, with an estimated 10 million people afflicted annually and a reported attack rate of 30–70% depending on destination and season.[1–3] TD also significantly affects deployed military personnel, with an estimated attack rate of 30 cases per 100-person months.[4–6]

Travel medicine is an evolving field that is increasingly important in this era of globalization. The global travel vaccines market was forecasted to reach a value of US$2.94 billion in 2020, with the number of global tourists increasing from 1.0 billion in 2012 to 1.4 billion in 2018, a significant proportion of those travellers journeying from developed countries to areas with endemic diseases.[7] With travel projections anticipated to increase, the demand for vaccines will also increase. Moreover, many regulatory authorities strongly recommend or mandate travellers to be vaccinated prior to travelling to disease-prone regions,[8] often making vaccines a requirement for travelling internationally. As such, vaccines against TD remain a goal of pivotal importance.

TD vaccines have traditionally focused on the prevention outcome of moderate-to-severe diarrhoea caused by the target pathogen.[9–11] However, the definitions of moderate-to-severe diarrhoea have varied across studies. While most, if not all, have based severity on the number of unformed stools in a 24-h period, some have incorporated additional gastrointestinal symptoms.[12,13] Table 1 summarizes the clinical endpoints used for field trials testing TD vaccine candidates. These endpoints are critical in interpreting vaccine efficacy as estimates may vary significantly depending on the endpoint utilized. Furthermore, for the traveller, the effect of the illness on function accounting for stool output and other outcomes may be a more informative endpoint than just frequency of loose stools given that functional impairment may impede travel and/or business plans.[14,15]

Numerous scoring systems have been developed and validated to address this issue in pediatric studies of diarrhoeal disease.[16–24] Furthermore, Porter and colleagues have sought to standardize clinical endpoints and establish disease scoring systems for use in controlled human infection models for enterotoxigenic *Escherichia coli* (ETEC)[25] and *Shigella*.[26] There is no comparable, standardized disease severity score for TD, limiting the interpretation of results within and across studies. A standardized disease severity scoring system optimized for TD is needed to ensure consistency and inform efficacy estimates of interventions targeting prevention and treatment. Therefore, we examined the clinical attributes of TD and, based on the distribution and overlap of those parameters, propose a disease severity score for future validation and utilization.

Methods

Data were obtained from a previously published multisite TD treatment trial (TrEAT TD).[27] Eligibility included active-duty US or UK military personnel or beneficiaries, aged ≥18 years of age, deployed to one of five countries (Kenya, Djibouti, Afghanistan, Honduras or Thailand) who presented with TD (≥3 loose stools in 24 h or ≥2 loose stools in 24 h with associated symptoms) of ≤ 96-h duration who were ambulatory at the time of enrollment. Only subjects enrolled in the TrEAT TD study who had complete TD symptom data available were included in this analysis.

In addition to demographic information, site location, disease classification (presenting with acute-watery diarrhoea or febrile or dysentery illness), impact of illness on activity level (normal, decreased ≤50%, decreased >50%, completely unable to function) as well as detailed clinical information on the signs and symptoms of disease were obtained. Symptom severity was based on the maximum observed severity of the TD episode from disease onset to enrollment into TrEAT TD. The following subjective symptoms were documented as not present, mild (present, but not serious or intense); moderate (caused some amount of distress but was manageable); severe (extreme, caused a great deal of discomfort or distress): nausea, tenesmus, malaise/fatigue, faecal incontinence, abdominal cramps and excessive gas/flatulence. Fever severity was based on maximum measured temperature and diarrhoea output based on the maximum number of loose stools in a 24-h period from disease onset to enrollment. The number of loose/liquid stools in the 8 h prior to enrollment and the total number of loose/liquid stools since symptom onset were also analysed. Episodes of vomiting were documented and classified as follows: none (0 episodes in 24 h), mild (1 episode in 24 h), moderate (2 episodes in 24 h), severe (≥3 episodes in 24 h).

Spearman correlations of sign and symptom severity were estimated. Univariable linear regression was utilized to describe the strength of the association between stool output and other TD-attributable signs and symptoms. Separate cumulative odds ordinal logistic regression models with proportional odds were developed to estimate the association between individual clinical signs and TD symptoms as well as metrics of stool output on activity impact. A Classification and Regression Tree (CART) analysis was conducted to determine optimal cut points of the maximum number of loose stools in 24 h for this analysis and inclusion in the scoring system.[28] A Multiple Correspondence Analysis (MCA) was performed to graphically illustrate clustering of TD symptom severity. Parameters were assigned a value from 0 to 3 in the final TD score based on grouping within the MCA. The pattern of these outcome groupings were compared with the overlap in symptom severity from the regression analyses, as well as how strongly each symptom correlated with the other, to further inform how each should be weighted within the final scoring algorithm. Based on this iterative process to maximize our ability to differentiate symptoms and predictability on impact on activity to more appropriately characterize the TD illness profile, a TD severity score was developed similar to what has been utilized for ETEC- and *Shigella*-specific severity scores.[25,26] Logistic regression models were utilized to assess the severity score's ability to predict impact of illness on an individual's activity.

This research was approved by the Uniformed Services University Institutional Review Board and the Ministry of Defence Research Ethics Committee in compliance with all applicable Federal regulations governing the protection of human subjects.

Results

Data were utilized from 363 subjects (Supplementary Table 1). The mean age was 29.3 years, with a majority being male

Table 1. Clinical endpoints in TD-vaccine field studies

Publication	Vaccine candidate	Study population (*n*)	Primary endpoint definition	Vaccine efficacy (VE)
Scerpella *et al*., 1995[29]	Killed whole-cell *Vibrio cholerae* O1 with a recombinant B-subunit of cholera toxin (WC/rBS)	Student travellers to Mexico ($n=502$)	≥4 loose stools in 24 h (or 3 in 8 h) plus an additional symptom	VE against ETEC = 50% (95% CI, 14–71%) beginning 7 days after the second dose. However, no efficacy was demonstrated within 7 days of the second vaccination when 74% of ETEC cases occurred
Wiedermann *et al*., 2000[30]	Inactivated whole-cell ETEC and cholera vaccines plus recombinant B-subunit of cholera toxin (rCTB)	Austrian travellers to tropical or subtropical destinations (44 different countries in Africa, Asia, Latin-America) ($n=250$)	≥3 liquid stools and ETEC-only pathogen detected in stool	ETEC vaccine VE = 79% ($P=0.119$) Cholera vaccine VE = 82% ($P=0.0496$)
Leyten *et al*., 2005[31]	Live-attenuated oral cholera vaccine strain CVD 103-HgR	Travellers to Indonesia, India, Thailand and West Africa ($n=134$)	≥3 loose stools in 24 h, or 2 loose stools plus additional symptoms	Study terminated early as the primary endpoint ≥50% VE not achieved at point of interim analysis
Sack *et al*., 2007[32]	Inactivated whole-cell ETEC vaccine plus recombinant B-subunit of cholera toxin (rCTB)	Travellers to Mexico and Guatemala ($n=672$)	Primary vaccine preventable outcome (VPO): ≥3 loose stools in 24 h plus ≥1 gastrointestinal symptom caused by homologous ETEC vaccine strain	VE = 24% (n.s.)
Bourgeois *et al*., 2007[33]	Inactivated whole-cell ETEC vaccine plus recombinant B-subunit of cholera toxin (rCTB)	Travellers to Mexico and Guatemala ($n=1406$)	VPO-ETEC TD: ≥5 unformed or liquid stools in 24 h plus ≥1 gastrointestinal symptom and homologous ETEC vaccine strain isolated within 24 h of episode	VE = −59 (95% CI, −384, 48)
Frech *et al*, 2008[47]	Heat-labile toxin LT-patch	Travellers to Mexico and Guatemala ($n=170$)	Mild TD: 3 loose stools in 24 h Moderate TD: 4–5 loose stools in 24 h and ETEC LT, LT/ST or ST positive Severe TD: ≥6 loose stools in 24 h and ETEC LT, LT/ST or ST positive	VE against moderate-to-severe TD = 75% ($P=0.007$) VE against severe TD = 84% ($P=0.0332$)
Steffen *et al*., 2013[34]	Heat-labile toxin LT-patch	Travellers to India ($n=723$)	Mild TD: 3 loose stools in 24 h	VE near zero ($P=1.000$)
Behrens *et al*., 2014[35]	Heat-labile toxin LT-patch	Travellers to Mexico and Guatemala ($n=1644$)	Moderate TD: 4–5 loose stools in 24 h and ETEC LT, LT/ST or ST positive Severe TD: ≥6 loose stools in 24 h and ETEC LT, LT/ST or ST positive	VE against moderate-to-severe TD = 34.6% (95% CI, −2.2, 58.9)

Note: Table adapted from various vaccine field trials[29–35,47] and 2018 VASE Workshop Presentation[11]

(93.4%) and white (83.2%). Most subjects presented with acute watery diarrhoea (87.3%) with only 46 (12.7%) presenting with acute dysentery or febrile illness. Most subjects ($n=284$, 77.4%) reported some negative impact on activity due to illness, with 45.2% ($n=166$) reporting a decrease in activity ≤50%, 26.2% ($n=96$) reporting a decrease in activity of >50% and 6% ($n=22$) reporting illness that precluded their ability to function.

The frequency of common signs and symptoms and maximum 24-h loose stool output are shown in Supplementary Table 2 and Supplementary Figure 1, respectively. The most common subjective symptoms were abdominal cramps (75.4%) and malaise (64.3%), followed by nausea reported in approximately half the subjects (52.5%), gas (38.9%), tenesmus (29.1%) and faecal incontinence (14.3%). In contrast, the more objective signs of vomiting and fever were less frequently observed (20.4% and 15.8%, respectively). Stooling was not normaly distributed, with the highest proportion of subjects ($n=214$; 58.9%) producing between ≥3 and ≤6 loose/liquid stools/24 h with a median of 6 loose stools (interquartile range: 4, 8).

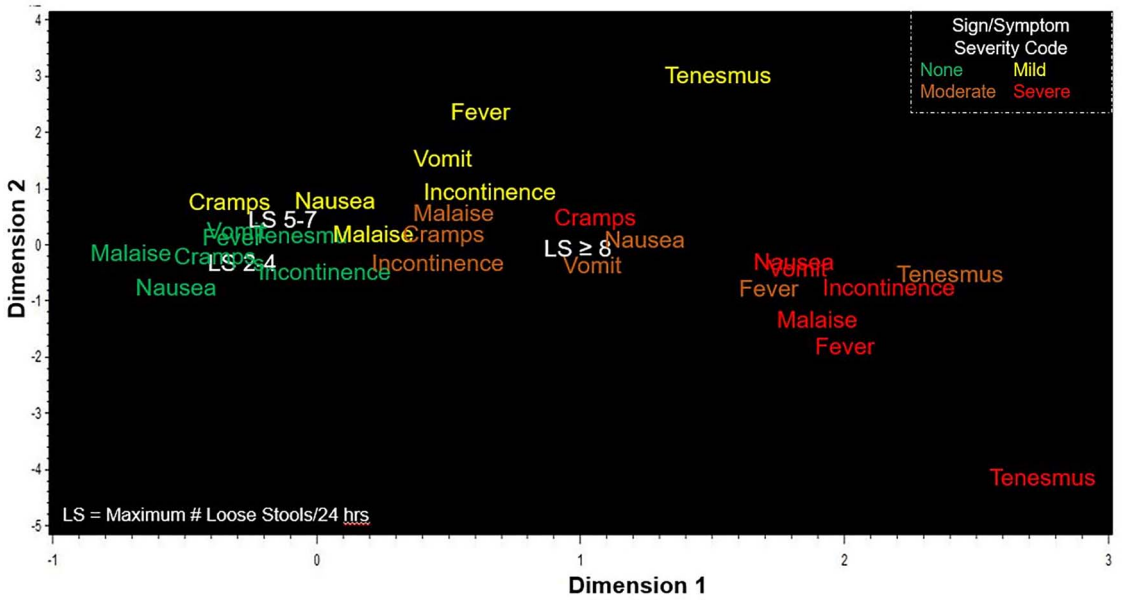

Figure 1. MCA of signs and symptoms of TD (TrEAT TD Dataset)

Statistically significant correlations were observed between various signs and symptoms of TD-attributable illness. Among those signs and symptoms that were significantly correlated, the strength of correlation varied (Supplementary Table 3). The strongest correlation observed was between nausea and vomiting ($\rho = 0.49$; $P < 0.001$), although only 20.4% of participants reported vomiting. Malaise was positively correlated with all signs and symptoms, with the strongest correlation with nausea ($\rho = 0.43$; $P < 0.001$), vomiting ($\rho = 0.34$; $P < 0.001$), fever ($\rho = 0.30$; $P < 0.001$) and abdominal cramps ($\rho = 0.31$; $P < 0.001$). Similarly, abdominal cramps were positively correlated with all analysed signs and symptoms, with smaller correlations observed between nausea ($\rho = 0.25$; $P < 0.001$) loose stools ($\rho = 0.21$; $P < 0.001$) and tenesmus ($\rho = 0.21$; $P < 0.001$). Gas was only significantly correlated with malaise ($\rho = 0.13$; $P = 0.01$) and faecal incontinence was only significantly correlated with loose stools ($\rho = 0.20$; $P = 0.01$), malaise ($\rho = 0.13$; $P = 0.01$), nausea ($\rho = 0.11$; $P = 0.03$) and abdominal cramps ($\rho = 0.14$; $P = 0.007$). Tenesmus showed small, statistically significant correlations with all signs and symptoms except fever and faecal incontinence.

Numerous signs and symptoms were associated with impaired function; however, severe malaise and nausea were most strongly associated [odds ratio (OR) 44.3, $P < 0.0001$ and OR 37.1, $P < 0.0001$, respectively] (Supplementary Table 4). MCA showed co-variability in multiple signs and symptoms with severity being the most common factor associated with similar dimensions in a 2D space (Figure 1). Mild fever, vomiting, faecal incontinence, nausea and malaise clustered tightly with moderate abdominal cramps and faecal incontinence; whereas moderate nausea and vomiting clustered with more severe abdominal cramps and ≥8 loose stools/24 h. As expected, most severe signs and symptoms (with the exception of abdominal cramps and ≥8 loose stools/24 h) tended to cluster together, with moderate fever and tenesmus also included in this grouping, the latter two parameters receiving a maximum of '3' in the final disease severity score. Categories of maximum 24-h stool output were included with the two lowest categories of output (0–1 loose stools/24 h and 2–4 loose stools/24 h) clustering with absence of concurrent signs and symptoms. The highest category of loose stool output (≥8 loose stools/24 h) was most proximal to mild and moderate symptoms.

Based on the grouping of clinical outcomes in the MCA and results of the correlation, univariate logistic regression analyses, a three-component disease score was developed utilizing objective signs, subjective symptoms and stool frequency yielding a score ranging from 0 (no disease) to 9 (most severe disease) (Table 2). To mitigate the unequal distribution of stool output as a measure of TD disease severity, we tried to establish new stool frequency/volume cut-points based on existing data, as was done in the development of scoring systems for ETEC and *Shigella*.[25,26] Stool categories in the scoring system were primarily based on the resulting CART analysis, whereas other signs and symptoms were assigned a value from 0 to 3 in the scoring system based on their clustering pattern in the MCA. For example, mild tenesmus grouped with moderate-to-severe symptoms, resulting in its elevated scoring of '2' in the final disease severity score, representing a subjective symptom weighted according to its placement in the MCA.

There were significant differences in TD score across all classifications of functional impact (Figure 2). As TD score increased, so did the odds of reporting a negative impact on activity (Table 3), with a slight exception between those with a TD score of 6 vs 7. There was significant incremental increase in effect at each level of score with the primary outcome of impact from TD Score = 1 to TD Score = 9. Even subjects with a disease score of 2 had 6.5 times higher odds of reporting a negative impact on activity [OR = 6.5, 95% confidence interval (CI) 1.8–23.9] compared with those with a score of 1. No subjects had a TD Score of 0, as enrollment required diarrhoeal illness of some severity.

There was a significant difference ($P < 0.0001$) in the mean TD Score between those with acute watery diarrhoea (3.9 ± 1.9) and those with dysentery or acute febrile illness

Table 2. TD disease complex score

Parameter	Outcome	Score
Objective signs	Severe: ≥3 episodes vomiting OR	3
	Moderate-to-severe fever	3
	Two episodes vomiting	2
	One episode vomiting OR Mild fever	1
	No objective symptoms	0
Subjective symptoms	Severe: tenesmus, malaise, nausea, faecal incontinence OR	3
	Moderate tenesmus	3
	Severe abdominal cramps OR	2
	Moderate nausea OR	2
	Mild tenesmus	2
	Moderate: abdominal cramps, faecal incontinence, malaise OR	1
	Mild: abdominal cramps, nausea, malaise, faecal incontinence	1
	No subjective symptoms	0
Loose stool output (max. 24 h freq)	≥8 loose stools/24 h	3
	5–7 loose stools/24 h	2
	2–4 loose stools/24 h	1
	0–1 loose stools/24 h	0

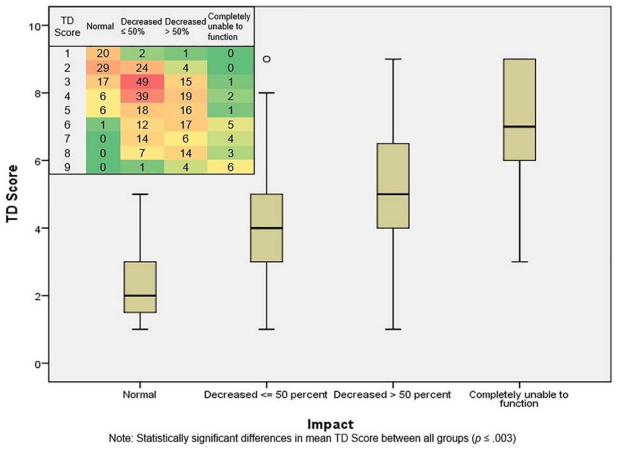

Figure 2. TD Disease Score and impact on activity (TrEAT TD dataset). Note statistically significant differences in mean TD Score between all groups ($P \leq 0.003$). Numbers in heat diagram represent number of participants within each category

(6.2 ± 2.0) (Supplementary Table 5; Supplementary Figure 2). Additionally, disease severity varied significantly across study sites (Supplementary Table 5; Supplementary Figure 2), with Thailand yielding the highest mean score [M = 6.4, standard deviation (SD) = 1.4], compared with Honduras (M = 4.5, SD = 2.2, $P = 0.02$), Kenya (M = 3.6, SD = 2.1, $P = 0.001$) and Djibouti (M = 4.0, SD = 1.7, $P = 0.05$). There was also a statistically significant increase in mean TD Score for Afghanistan (M = 5.3, SD = 2.0) compared with Kenya and Djibouti ($P < 0.001$). There were no statistically significant differences in mean TD Scores between Kenya, Honduras and Djibouti.

Discussion

Since research on TD and related vaccines, prophylaxis or treatments began, primary efficacy endpoints have varied.[27,29–34] Some studies have attempted to characterize TD symptom severity in the context of interference with daily activities,[32,33] whereas others have used stool-based endpoints.[34,35] Uniformly consistent in these studies is the focus on diarrhoea frequency as a key metric in primary endpoints. However, loose stool frequency alone may not be an inadequate predictor of disease severity, and other symptoms may more strongly predict traveller disability.[11] This was the first attempt to integrate stool frequency and associated symptoms into a comprehensive TD severity score based on functional impact outcome assessment. In our score derivation, while an increase in diarrhoea frequency was significantly associated with a greater likelihood to report a negative impact on activity, it remained a poor predictor of impact on activity compared with other symptoms. For example, the odds of reporting a negative impact on activity while having ≥8 loose stools/24 h (OR = 8.51) was not as great as when afflicted with severe incontinence (OR 10.8), nausea (OR 116.7) or malaise (OR 44.29). Additionally, the likelihood of reporting a negative impact on activity with a TD Score of '2' or '3' was only slightly lower (OR 6.53) and approximately three times higher (OR 24.53), respectively, compared with the sole outcome of maximum stool output (Supplementary Figure 3). This indicates that stool frequency alone may not be a useful predictive measure of serious disease and indicates that symptoms beyond diarrhoea frequency contribute as much, if not more, to a severe illness profile impacting a traveller's function.

Reported symptomology within the TrEAT TD dataset reflected trends similar to previous TD studies,[12,32,33,36] especially regarding abdominal cramps, nausea, vomiting and fever. Malaise, tenesmus, gas and faecal incontinence have not been as consistently reported across TD studies, yet ~64%, 29%, 39% and 14% of TrEAT TD participants reported those symptoms, respectively. Tenesmus is a common symptom of infectious gastroenteritis often associated with pathogens that cause dysentery and inflammatory enteritis.[38–40] Given the pathogen distribution in TrEAT TD, with ETEC and EAEC infections isolated as a sole pathogen in 24.6% and 38.6% of subjects, respectively, the high frequency of reported tenesmus is surprising. Additional efforts are needed to more completely

Table 3. Ordinal logistic regression analysis of the relationship between TD disease score and impact on activity (TrEAT TD dataset; $N = 363$)

Variable	β	Standard error	Adjusted OR	95% CI for OR	*P*-value
Impact on activity (ref: completely unable to function)					
Normal	1.87	0.61	6.41	1.94–21.17	0.002
Decreased ≤ 50%	4.63	0.64	102.67	29.20–360-98	<0.0001
Decreased ≥ 50%	7.12	0.69	1241.16	322.77–4772-69	<0.0001
TD Score (ref.: TD Score 1)					
TD Score 2	1.88	0.66	6.53	1.78–23.86	0.005
TD Score 3	3.20	0.65	24.53	6.77–88.56	<0.0001
TD Score 4	3.93	0.67	50.84	13.64–189.55	<0.0001
TD Score 5	4.09	0.70	59.95	15.27–235.38	<0.0001
TD Score 6	5.12	0.72	167.54	40.97–685.19	<0.0001
TD Score 7	4.84	0.74	126.00	29.66–535.23	<0.0001
TD Score 8	5.42	0.76	225.17	51.04–993.39	<0.0001
TD Score 9	7.26	0.90	1422.84	244.69–8273.63	<0.0001

validate data collection instruments used to obtain self-collected symptomology. Tenesmus is more commonly associated with pathogens that cause dysentery and inflammatory enteritis. Self-reporting of tenesmus may be subject to bias is a symptom that is easily misunderstood by study participants and therefore often inaccurately reported. It could be there was not enough rigor on assuring participants truly understood how to report this accurately, thus potentially contributing disproportionately to the disease severity score and should be further confirmed in prospective studies.

Each sign and symptom (except gas and tenesmus) was significantly associated with the maximum 24-h stool output as measured by frequency. The lack of significant association between gas and stool frequency was consistent with its negligible effect on activity and, given its lack of correlation with all other signs and symptoms except malaise, it was subsequently excluded as a parameter in the TD disease complex score. In contrast, while tenesmus was prevalent in TrEAT TD and significantly associated with a negative impact on activity, it was not significantly associated with stool output. Because of the prevalence of tenesmus in the TrEAT TD, its significant association with subject activity and its significant clustering with more severe symptoms in the MCA, tenesmus was an important clinical parameter to include in the TD complex score. Despite not being significantly associated with stool output but shown in correlation, various regression and multiple correspondence analyses to be a meaningful clinical parameter, tenesmus is an excellent example of how other symptoms, independent of stool frequency, might play an important role in TD severity. Application of this score in future studies would need to provide guidance to those collecting these same symptom parameters, and application retrospectively to datasets where there may have been symptom misclassification would need to be done cautiously. Based on these results, using stool frequency as the sole parameter to define TD illness is likely suboptimal. While this score proposes new stool frequency cut-points for the TD score, it was on a single dataset and would benefit from further study to see if these cut-points are consistent. It is important to emphasize that a relatively high proportion of subjects reported for care within 24 h of illness onset. Therefore, diarrhoea frequency may be lower than what would be observed if subjects waited longer to report illness.

The proportion of TrEAT TD subjects who experienced acute dysentery or febrile illness compared with acute watery diarrhoea remains consistent with data reported in other studies, with ~10% of TD cases being dysenteric across most travel destinations.[41] There was a statistically significant difference in the mean TD score between the two illness profiles, due to inclusion of fever, and more severe tenesmus and abdominal pain reported in the acute dysentery or febrile illness group. While more subjects in the acute watery diarrhoea group experienced higher maximum 24-h stool frequency, the presence of more severe objective signs and subjective symptoms were not observed and lowered the overall mean TD score in this group. The higher mean TD score of the acute dysentery or febrile illness group is reflective of a recent expert panel of recommended standard TD definitions, in which severe TD includes all dysenteric cases.[1,27]

TD score differences across TrEAT TD sites were in large part driven by the TD syndrome distribution, with Thailand yielding the highest mean score due to enrollment being restricted to those presenting with acute dysentery or febrile diarrhea (ADF). Nevertheless, mean TD scores across TrEAT TD sites aligns with the geographic differences in distribution of pathogens and manifestation of clinical illness. For example, *Salmonella* and *Campylobacter* are the most commonly isolated TD pathogens in Southeast Asia,[42,43] both of which are associated more with dysenteric cases or illness with fever.[44] The rate of multipathogen recovery is also highest in Southeast Asia (~16%).[42] ETEC is the most commonly isolated pathogen in the Middle East, followed by ETEC and EAEC in Africa,[42] which correlate to the slightly milder disease profile observed in participants enrolled in Afghanistan and Kenya as those etiologies are more associated with acute watery diarrhoea. Norovirus features heavily into the etiology of TD in Latin and South America, and with a clinical manifestation of increased vomiting, perhaps that is what contributed to a mean TD Score of 4.52 in Honduras, the third highest among the six study sites. The regional variability in TD score and etiology were aligned and potentially provides another metric to help guide more targeted treatment or eventual vaccination efforts.

This analysis was conducted using data from a predominantly active-duty military population potentially limiting its external validity. As Mary Roach stated in her 2016 *New York Times*

magazine article describing the TrEAT TD study, 'For every person who shows up at the morning sick call, four tough it out'.[45] As a result, it should be considered that it may differ from the routine travel population.

TrEAT TD utilized diary cards to collect symptoms from subjects while ill and prior to enrollment, thus limiting the risk of recall bias. However, it is possible that response bias persisted in reporting of symptoms. For example, a participant who experienced a severe symptom might have been more likely to report other signs and symptoms as he/she was more focused on what might have been making him/her feel unwell. In contrast, a participant who experienced mild symptoms with little impact on activity might have been less focused on feeling unwell and recorded fewer symptoms. While reporting bias may be a potential limitation, previous studies with military participants report a moderate rate of care-seeking behaviour for their TD.[37,42] Furthermore, a recent review revealed an increase in care-seeking behaviour for the treatment of TD among both military and long-term travel populations.[42]

Conclusion

This TD disease severity score aims to advance beyond historical measures focused solely on loose stool frequency. In addition to more accurately predicting functional impact of TD, this holistic approach begins to address recommendations that disease severity should be based on an individual's assessment that his/her illness is tolerable, distressing or incapacitating.[14] Our assessment of the role of multiple TD-attributable signs and symptoms on functional impairment assists in understanding TD as a complex syndrome and advances the field beyond solely stool output-based endpoints.[14] Furthermore, an ordinal score increases statistical power to differentiate treatment effects in interventional trials.[26,46] This research reinforces recently published workshop-derived conclusions regarding the need for disease scoring algorithms for vaccine efficacy trials.[11] Future research is needed to further develop and validate this score in other traveller populations and settings, and application and refinement of the score could be considered for evaluation of other TD preventive and treatment measures.

Supplementary data

Supplementary data are available at *JTM* online.

Disclaimer

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Author contributions

C.K.P., M.S.R., R.G., J.F., P.C. and D.R.T. were involved in primary data collection. N.M., C.K.P. and M.S.R. planned the analysis. N.M. performed all statistical analysis. N.M. and C.K.P. wrote the manuscript. All other authors contributed to the interpretation of results and critical review and revision of the manuscript and have approved the final version.

Funding

This work (IDCRP-065) was conducted by the Infectious Disease Clinical Research Program (IDCRP), a Department of Defense (DoD) program executed by the Uniformed Services University of the Health Sciences (USU) through a cooperative agreement with The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF). This project has been supported with federal funds from the Bureau of Medicine and Surgery, Uniformed Services University of the Health Sciences (USU grant agreement HU0001-11-1-0022, USU project G187V2) and the National Institute of Allergy and Infectious Diseases, National Institutes of Health (interagency agreement Y1-AI-5072).

Conflict of interest: None declared.

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