

Diarrhoea during military deployment: current concepts and future directions

Patrick Connor^a, Chad K. Porter^b, Brett Swierczewski^c, and Mark S. Riddle^b

Purpose of review

Diarrhoea among military travellers deployed globally in conflict and peacekeeping activities remains one of the most important health threats. Here we review recent advances in our understanding of the epidemiology, laboratory identification, treatment and chronic health consequences of this multi-cause infection, and consider the implications for public health management and future research.

Recent findings

The incidence of diarrhoea among deployed military personnel from industrialized countries to lesser developed countries is approximately 30% per month overall, with clinical incidence between 5 and 7% per 100 person-months. The risk appears to be higher early during deployment and is associated with poor hygienic conditions and contaminated food sources. Gaps remain in our understanding of the cause, given the lack of laboratory capability in austere conditions of deployment; however, recent advances in molecular methods of characterization hold promise in improving our detection capabilities. While there have been improvements in understanding of best treatments, more work needs to be done in transforming this knowledge into action and optimizing single-dose antibiotic treatment regimens. Finally, the underrecognized burden of chronic consequences of these infections is gaining awareness and reinforces the need to find effective preventive strategies.

Summary

Our understanding of the epidemiology of diarrhoea is improving but further research is needed to fully account for acute operational-focused health impacts as well as the chronic enduring disease impacts. Improved field diagnostics would be of great value to support these efforts.

Keywords

diagnostics, epidemiology, irritable bowel syndrome, military, travellers' diarrhoea

INTRODUCTION

Historically, diarrhoea has been the scourge of almost all identifiable military campaigns. References attest to its importance in force generation and preservation and can be found as far back as the first crusades. In the 19th century, conflicts in the Crimea, the China Wars and the Boer wars were significant in raising both public and military awareness of the role diarrhoea plays in expeditionary warfare, as well as how armies managed what was starting to be recognized as a preventable attrition [1]. In more modern times, both world wars, the Korean war, the war in Vietnam and the current conflicts in Iraq and Afghanistan have exemplified the persistent nature of the problem despite significant advances in both environmental protection measures, understanding as to the microbiological causes of the disease itself and advances in management [2-4].

Military diarrhoea is, in its essence, travellers' diarrhoea. They are both illnesses suffered by individuals travelling from a developed to an underdeveloped area of the world, and attributed to being exposed to enteric pathogens previously not encountered or to which no protective immunity has been acquired. What separates military diarrhoea from travellers' diarrhoea is its population

^aEnteric Diseases Research Group, Royal Centre for Defence Medicine, Birmingham, UK, ^bEnteric Diseases Department, Naval Medical Research Center, Silver Spring, Maryland, USA and ^cUS Army Research Unit – Kenya, Nairobi, Kenya

Correspondence to Col Patrick Connor, FRCP, AGAF L/RAMC, Military Enteric Disease Group, Department of Military Medicine, Royal Centre for Defence Medicine, Birmingham B15 2SQ, UK. Tel: +44 121 415 8860; e-mail: pconnor@doctors.org.uk

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KEY POINTS

- Diarrhoea among military deployments remains an important cause of morbidity in terms of acute and chronic health effects.
- Diagnostic methods are improving and hold promise to provide improved epidemiological understanding, as well as provide real-time information with public health and clinical management implications.
- Effective treatment regimens for travellers' diarrhoea exist, although improvements in utilization are needed.
- Our understanding of the chronic health problems associated with these acute infections in unique stressful environments is evolving, and draws important attention to the importance of primary prevention.

dynamics, the context for treatment and the impact. Military populations are typically large, move en masse and may stay in an area for a long period of time. The impact of this is typically recurrent episodes and the potential for mini-epidemics, causing significant morbidity. Viral causes are of secondary importance compared to bacterial causes, though are important early on during deployment and are a frequent cause of outbreaks [5,6]. The importance of military diarrhoea as a health problem is exemplified by the growing number of scientific publications on this subject matter (Fig. 1), and would suggest that this problem will remain given the geopolitical instabilities and the perpetual need to use military forces for both combat and peace-time operations. Thus, this review provides an update of recent research efforts in the areas of epidemiology, field diagnostics and chronic health consequences.

UPDATE IN EPIDEMIOLOGY

The incidence and cause of diarrhoea among military and similar populations (e.g. expatriates, long-term travellers) were recently reviewed by a study by Riddle et al. [7], in which a total of 52 studies published from 1999 to 2005 were included. US military populations (63%) made up a majority of study populations, with foreign military, expatriate (including non-governmental organizations and embassy populations) and student populations accounting for the rest. The geographic distribution from which these studies were conducted included 37% from the Middle East, 31% from south-east Asia, 24% from Latin America/Caribbean and 6% from sub-Saharan Africa, revealing a current gap in our understanding. Similar to short-term traveller studies, enterotoxigenic Escherichia coli (ETEC), Campylobacter and Shigella were identified as causing 38–45% of diarrhoea, with regional and population differences (Fig. 2) [8]. Furthermore, it was described in this review that among military populations in recent times, incidence based on self-report is higher than incidence based on studies using passive surveillance or clinical-based methods (29 versus 7 versus 6 episodes per 100 person-months, respectively) without regional differences [7].

Recent studies have provided much needed data from the African region, as well as corroborated the current estimates of incidence among militaries

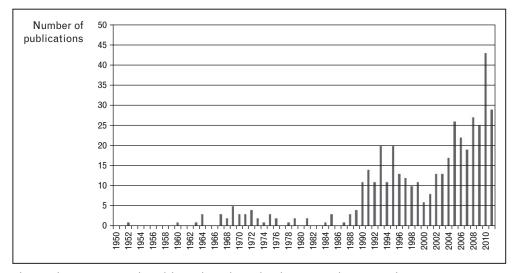


FIGURE 1. Yearly trends in papers indexed by PubMed on diarrhoea in military populations, 1950–2011. Medline trend: automated yearly statistics of PubMed results for any query, 2004. Web resource at URL: HTTP://DAN.CORLAN.NET/MEDLINE-TREND.HTML. Accessed 14 February 2012. (Archived by WebCite at HTTP://WWW.WEBCITATION.ORG/65RKD48SV). Search terms: *military* AND *diarr**. Source: Alexandru Dan Corlan.

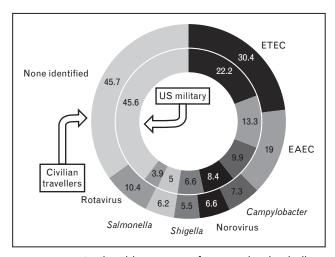


FIGURE 2. Attributable causes of acute diarrheal illness based on systematic reviews of travellers' diarrhoea and military diarrhea. Sources: (1) Military population [7]; (2) Traveller population [8]. EAEC, enteroaggregative *E. coli*; ETEC, enerotoxigenic *E. coli*.

during deployment. A pair of studies describes the epidemiology based on the experience of the French military in N'Djamena, Chad. A prospective study was conducted using clinic-based surveillance for diarrhoea during a 5-month French military deployment using standard travellers' diarrhoea case definitions, collection of stool samples and survey [9]. In this study a total of 240 cases of diarrhoea were clinically identified, with an estimated incidence rate of 4.9 cases per 100 personmonths. Among 196 samples collected from the 240 cases, pathogens were identified in 40% of samples, with enteric viruses being the most common (28.1%). It is important to note that evaluation for diarrhoeagenic E. coli was not performed. Risk factors identified included a four-fold increased risk if the individual had sick contacts, and a decreased risk among those who stated they always took meals from the military food establishment. Data on selfreporting of travellers' diarrhoea in this population were further provided, indicating that the incidence was three-fold higher, and only 42% of the troops reported seeking medical care, mainly for the first episode [10]. These data would appear to be in line with previously reported incidence estimates from the Riddle et al. [7] systematic review, and highlight the fact that only a proportion of cases with diarrhoea who are ill seek care.

Additional studies from recent deployments among US troops deployed to the Sinai region of Egypt and British troops in Afghanistan are also notable. A report from a prospective cohort study of travellers' diarrhoea conducted between May 2004 and January 2005 among US troops at the Multinational Force and Observers (MFO) camp in

the southern Sinai followed 211 volunteers during their 5-month deployment with baseline entry questionnaire, stool specimen at study entry and when acutely ill, and routinely whether ill or not every 6 weeks [11]. Of the 211 volunteers, 145 (68.7%) completed one or more follow-up visits and an overall incidence of 25.2 episodes per 100 personmonths [95% confidence interval (CI) 21.2–30.0] was noted. Among 72 of 77 diarrhoea-associated clinic visits stools were collected and bacterial pathogens most commonly isolated including ETEC in 42% samples and *Campylobacter jejuni* in 10%.

Finally, a medical record review of 1903 cases (mean of 10.3 new cases per day) from the front lines of Afghanistan at a British Army Regimental Aid Post between April and October 2009 describes the impact of diarrhea [12*]. In this study, there were 117 cases of diarrhoea and/or vomiting and a further 16 cases of dysentery, representing approximately 7% of acute care visits during this period. These enteric illnesses were second to dermatological conditions (23.5%, mostly dry skin and heat rash) as a leading cause of disease and nonbattle injury. Of important notice was that a change from an open pit latrine (with burning twice a day) to a buried system of stool sanitation appeared to decrease the incidence.

Beyond 'the numbers' we are, however, learning the important impacts that military diarrhoea has on personnel and mission effectiveness. The following descriptions are extracted from sources with recent experience in Afghanistan and demonstrate the unique nature of this problem.

During OPERATION HERRICK 8 (April–Oct 2008, Afghanistan), 200 British paratroopers were deployed to Forward Operating Base (FOB) Inkerman in Helmand province. Living conditions were basic and toilet facilities were deep-trench latrines – holes dug into the ground, which are then filled in when full. Further latrines are then dug elsewhere on the base. Within a few weeks of arrival, diarrhoea caused significant degradation to individuals and the unit's ability to perform its role. Each soldier was lost for at least 8 days with each episode, and at one time, 50% of the fighting force was unfit for duty due to diarrhoea [13].

Questionnaires completed during this period suggested that over a 2-month period, 98% of soldiers in the FOB had at least one episode of diarrhoea, 33% complained of continuous diarrhoea for the prior 2 months and weight measurements indicated an average weight loss of 6 kg in the same time period. Repeated environmental assessments of the FOB showed no remediable risks, but analysis of the questionnaires for risk factors showed that patrolling through open water or ditches was the only independent factor associated with

diarrhoea (P. Connor, personal communication). Irrigation ditches in this part of Afghanistan are an integral part of life, and during this period of the conflict they provided a much needed safe haven during a fire-fight as they allowed soldiers to take cover below line of sight.

Such descriptions provide some of the clearest insight into the challenges that acute diarrhoeal illness poses during current (and future) operations. Incapacitation occurs with each attack, and repeated attacks cause significant, and cumulative, physical degradation. Mitigation of risk through improved food, water and sanitation is critical, but an understanding that not all risk can be avoided is important.

DEVELOPMENTS AND NEEDS IN THE AREA OF FIELD DIAGNOSTICS AND ADVANCED CHARACTERIZATION

Diarrhoea can be caused by a variety of microbial pathogens which can create a significant diagnostic problem due to the difficulty in providing sensitive and accurate identification of pathogen cause [14]. It is common in diarrhoeal disease surveillance studies to find that a large percentage of diarrhoea cases have an unknown cause, which can be attributed to poor sample collection/storage, an incomplete repertoire of skills or a lack of modern technology with a broad range of identification capabilities. Approaches for the identification of diarrhoeal pathogens comprise traditional microbiology, microscopy and antigen detection. Although microscopy for ova and parasite identification is fairly inexpensive, it can be time- and labour-intensive, and diagnosis usually depends on the microscopist's level of expertise [15,16]. Traditional culture methods for enteric bacteria can often times yield low results if antibiotic use is not controlled, and certain preservation medium is used which can decrease the recovery of some bacteria such as Shigella [17,18]. Antigen detection kits have emerged as a highly sensitive alternative method for identification to traditional microbiology, but these assays can be expensive and are limited to a small number of enteric viruses and protozoan parasites [19]. Furthermore, in an austere forward deployed environment, logistical barriers may commonly prevent the availability of laboratory equipment and reagents and transport of quality specimens shipped out of theatre for analysis by current traditional methods of diagnosis.

Recent advances in other technologies focused on nucleic acid and protein detection have been shown to provide more timely and accurate identification of diarrhoeal pathogens as opposed to traditional methods and may be better suited for laboratories in forward deployed areas. Multiple studies have shown PCR assays to be significantly superior to traditional methods for identification of enteropathogens in terms of sensitivity and time [20,21]. More recently, multiplex PCR assays have been developed and validated to identify multiple enteropathogens in a single reaction [22-24]. Liu et al. [25] using a Luminex bead multiplex PCR assay reported sensitivity and specificity ranging from 89 to 97% for the detection of Campylobacter, Salmonella, Shigella and Vibrio, respectively. This assay has also been adapted for the identification of soil-transmitted helminths and parasitic protozoa to include E. histolytica, Cryptosporidium and Giardia lamblia [26]. A recent study by Velasco et al. [27**] used singleplex PCR to detect enteric bacteria from frozen stool samples collected from US Navy and Marine personnel participating in a joint exercise in the Republic of the Philippines. In forward deployed areas, storage for frozen stool samples may not be available and an alternative method for the collection and storage of stool samples that does not require processing and freezing would be beneficial for surveillance studies in these deployed personnel. A previous study showed that ETEC and enteroaggregative E. coli were detected significantly more often by multiplex PCR using DNA extracted from stool smeared on occult blood cards than from traditional laboratory methods [28]. Molecular diagnostics could be more advantageous in military populations due to the high degree of detection of enteric pathogens compared to traditional methods. Furthermore, additional studies aimed to identify better methods of stool collection and storage that do not require refrigeration would also benefit military microbiology laboratories in forward deployed areas.

MANAGEMENT OF TRAVELLERS' DIARRHOEA

The most cost-effective response to this threat to military readiness is to prevent the exposure leading to diarrhoea. There are currently two strategies for primary prevention: exposure avoidance, and prophylactic measures [including chemoprophylaxis, immunoprophylaxis (active and passive), immunomodulators/bowel flora competitors (such as probiotics)]. The first strategy is to prevent exposure to potential pathogens focusing on environmental measures, with the provision of clean food and water and appropriate disposal of waste. Although this strategy is reasonably effective when it is possible to develop the proper infrastructure, it can break down during rapid deployments and in small forward deployed outposts. Even in large-scale deployments conducted under strict security measures that prohibit routine exposure to indigenous food and water, diarrhoea remains a serious problem. For example, during the joint multinational military exercise conducted in Egypt (Operation Bright Star '01), which was conducted entirely under a strict security environment which limited on- and off-base access, 9% of personnel reported developing diarrhoea [29]. Controlling the base area infrastructure may be possible, but patrolling patterns in high-risk areas often involves uncontrollable exposure to local pathogens. Pretravel education and counselling of individuals on reducing risk behaviours (e.g. avoid ice/tap water, undercooked meat, and unwashed/ unpeeled fruits/vegetables) is also common practice; however, although this intuitively makes sense, multiple studies have failed to show any consistent evidence that a reduction in these types of risky behaviour results in reduction of disease incidence [30]. Antibiotic chemoprophylaxis represents a second available strategy, and efforts are underway to evaluate the effectiveness and practicality of newer antimicrobials (rifaximin) as a chemoprophylaxis option, although additional data are needed to evaluate the effectiveness in regions other than Central America and for pathogens other than diarrhoeagenic E. coli. Although such a strategy could be considered in some military settings (e.g. short-term critical missions, port visits, initial periods of deployment), it may be impracticable in many deployments given the extensive durations of exposure and the lack of safety and efficacy information on long-term use for this indication [31].

A third strategy to mitigate the impact of travellers' diarrhoea using secondary prevention is through timely and effective treatment. The UK military have guidelines published in their 'Clinical Guidelines for Operations' series, which consider not just the management of the individual with diarrhoea, but also the effect on the unit, and the prevention of developing epidemics. The US Military has guidance for treatment of travellers' diarrhoea in the region of current deployment including Iraq and Afghanistan, but not other regions [32]. Furthermore, there are published guidelines on the general approach to treatment of travellers' diarrhoea which provide evidencebased recommendations for treatment in nonmilitary travellers [17,33]. However, such guidelines may not consider military-specific factors including issue of adherence, lack of individual-level provision of antibiotics and different treatment thresholds to minimize operational impact events and risk for dehydration and heat-related illness. Two recent review articles have been published which provide evidence with military considerations on the management of nondysentery travellers' diarrhoea, as well as chronic diarrhoea in the returning traveller, and thus will not be reviewed here [34,35]. Figure 3 outlines the management approach reproduced from Gutiérrez *et al.* [35].

For dysentery or febrile diarrhoea, the use of adjunct loperamide is controversial. Concern has been raised that the use of loperamide and antibiotics in dysentery infections can precipitate shock and enterocolitis [36,37], and may not be as effective as multidose/multiday regimens since fevers or dysentery often imply invasive disease and is often caused by Shigella, Salmonella or Campylobacter, and more rarely enterohaemorrhagic *E. coli* (EHEC) or an invasive parasite such as Entamoeba histolytica. Campylobacter and Shigella may typically require more than a single dose of antibiotics, although this has not been definitively shown. These concerns have led to the current recommendations for avoiding the use of loperamide or other antimotility agents and using an antibiotic alone [38–41]. However, the data substantiating the primary safety concerns in a healthy adult traveller population are lacking, and evidence running counter to both safety and efficacy assumptions exists [42–46], suggesting that loperamide-adjuncted antibiotic regimens may offer additional benefit to patients with inflammatory diarrhoea. Further study is warranted.

Despite all the available evidence, reports emerging from the past decade consistently find that the medical care provided for acute diarrhoea in these deployment settings is heterogeneous, is not in accordance with available guidelines and is substandard in some cases [47,48]. The most recent study by Hayat et al. [49"] reports the results of a survey conducted among a convenience sample of 117 US military clinical providers with a broad range of training and operational experience. Although most were aware of the standard definition of travellers' diarrhoea (77%), knowledge about the epidemiology was lower, with less than 24% correctly answering questions on cause of diarrhoea, and 31% believing that a viral pathogen (not bacterial) was the primary cause of watery diarrhoea during deployment. For management of a clinical scenario of moderate travellers' diarrhoea it was reported that approximately two-thirds would not use antibiotics to treat, and one of the five providers felt that severe inflammatory diarrhoea was best treated with hydration only. Better management practice patterns were reported for those with a Doctor of Medicine or Doctor of Osteopathy degree, greater knowledge of travellers' diarrhoea epidemiology and more favourable attitudes towards antimotility or antibiotic therapy. However, even among these sub-groups there was relatively poor adherence to current best evidence [49]. The reason for these inadequacies may include the lack of

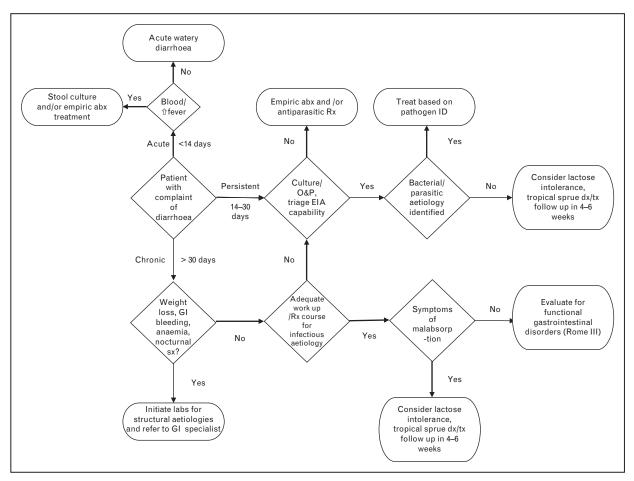


FIGURE 3. Diagnostic and treatment algorithm for acute and chronic diarrhoea among military travellers. abx, antibiotic; dx/tx, diagnosis and treatment; EIA, enzyme immunoassay; GI, gastrointestinal; ID, identification; O&P, ova and parasites; Rx, treatment; sx, symptom.

institutionalization of clear guidelines and training that may be disseminated and used among deployed personnel. Also, single-dose regimens, adjuncted with loperamide, have shown promise in small trials and pose an attractive option for the combat setting as they are simple, inexpensive and may, therefore, be associated with decreased costs in terms of healthcare utilization and duty-days lost [50–54]. A large multisite randomized controlled trial evaluating single-dose loperamide-adjuncted regimens for treatment of acute watery diarrhoea and dysentery is underway and will provide the necessary evidence to develop global treatment guidelines for the forces (ClinicalTrials.gov Identifier: NCT01618591). The dissemination and translation of such evidence into practice will be an important challenge.

POST-INFECTIOUS SEQUELAE: THE LINGERING EFFECT OF DIARRHOEA DURING DEPLOYMENT

The pathogens associated with travellers' diarrhoea and military diarrhoea have been linked to several

chronic health sequelae affecting multiple organ systems. Perhaps the most well described from a mechanistic perspective is the link between *Campylobacter* infection and Guillain–Barré syndrome [55]. Similarly, incident rheumatological manifestations following gastrointestinal infection with several invasive bacteria have been reported, although the disease mechanisms are less well understood [56]. Although these sequelae are important, their relative low incidence makes them a difficult outcome of study in travel populations. In contrast, functional gastrointestinal disorders (FGDs) following acute enteric infection appear to occur at rates amenable to studying the effect of travellers' diarrhoea and military diarrhoea on disease risk.

Systematic reviews of postinfectious irritable bowel syndrome (IBS) risk have reported just over a seven-fold increase in incident IBS following acute enteric infection [57,58]. These studies have focused on a variety of exposures from specific pathogens to general infectious gastroenteritis; additionally, reports of travel-related exposures and postinfectious IBS risk are increasing (Table 1) [59–64].

Utilizing a prospective cohort study, Pitzurra *et al.* [64] reported in the past year that among European travellers to developing world countries, those reporting at least a single episode of diarrhoea experienced more than a five-fold increase in IBS risk compared to travellers without travellers' diarrhoea. This effect was even higher (six-fold) in those experiencing multiple travellers' diarrhoea episodes.

Whereas these data support an increased IBS risk among travellers with travellers' diarrhoea, deployed military populations represent a specific sub-population of travellers with unique demographics and exposures, and recent reports have expanded our understanding in this area. A study by Trivedi et al. [63] found associations between FGD among 121 US military travellers returning from routine deployment (>6 month follow-up) to the Middle East where it was reported that there was an over five-fold increase in incident IBS among those who experienced an episode of travellers' diarrhoea during travel compared to those who did not (17.2 versus 3.7%; P = 0.12). Importantly, this study also showed significant impacts of these incident disorders on health-related quality of life. In addition, through use of US Department of Defense medical encounter databases linked to postdeployment health surveys, it was reported that incident IBS risk among military personnel following deployment to Iraq or Afghanistan showed a similar increased risk [adjusted odds ratio (OR) 6.26; 95% confidence interval (CI) 2.5, 15.4] of IBS among those self-reporting gastroenteritis during deployment compared to those with no self-reported gastroenteritis, with an apparent higher risk in persons with more severe acute illness [65]. Importantly, an increased risk of other FGDs, namely functional constipation and functional dyspepsia, was also observed furthering prior reports on the risk of these FGDs following enteric infection [66–70]. In total, these data support a 2010 Institute of Medicine report linking Gulf War deployment with

gastrointestinal symptoms consistent with FGDs [71], and further evidence suggests that increased psychological stressors such as war trauma may increase visceral sensitivity and, concurrent with an acute infection that may result in dysmotility, mucosal inflammation and increased intestinal permeability may be contributory [72].

Whereas data on rheumatological outcomes among travellers' diarrhoea cases are limited, an increased risk of reactive arthritidies and arthropathies following infection with *Campylobacter*, *Shigella*, *Yersinia* and nontyphoidal *Salmonella* is well established [56]. Given the proportion of travellers' diarrhoea caused by these pathogens, it is fair to assume an increased risk among deployed military populations. This is supported by Curry *et al.* [73] who not only showed an increased risk of reactive arthritis diagnoses following acute enteric infection, but also reported a two-fold increased risk subsequent to deployment to regions with high travellers' diarrhoea rates.

CONCLUSION

In summary, evidence for the impact of acute infectious diarrhoea on military deployments accumulates and is multiplied by the emerging evidence finding chronic health consequences as important causes of increased direct medical costs and disability among those returning from deployment and leaving the military. Additional data are needed to understand the acute effects of travellers' diarrhoea, including the impact of these infections on the individual performance (physical and cognitive) of those deployed. With respect to chronic health consequences, areas of research include further investigation on pathogen-specific mechanisms in human and animal models which may explore the interactions between genomics, microbiome and immune mechanisms behind infection and chronic health consequences, and evaluation of early

Table 1. Studies of postinfectious irritable bowe	syndrome among military	and other traveller populations
(alphabetical order)		

Study	Year	Study size	Follow-up (months)	Origin of traveller	IBS diagnosis	Study type	IBS risk in exposed/ unexposed (%)	Effect estimate (P value)
Ilnyckyj et al. [62]	2003	110	3	Canada	Rome I	Cohort	4.2/1.6	RR 2.5 (0.41)
Okhuysen <i>et al.</i> [61]	2004	101	6	US	Rome II	Cohort	12.7/2.6	OR 5.5 (0.09)
Pitzurra et al. [64]	2011	2476	6	Switzerland	Rome III	Cohort	3.1/0.7	OR 3.0 (<0.05)
Porter et al. [60]	2011	527	NA	US	ICD-9	Case-control	17.4/3.6	OR 6.3 (<0.001)
Stermer et al. [59]	2006	405	6	Israel	Rome II	Cohort	13.6/2.4	RR 5.2 (<0.0001)
Trivedi et al. [63]	2011	120	6	US	Rome II	Cohort	17.2/3.7	OR 5.4 (0.12)

ICD-9, International Classification of Disease; NA, not applicable; NOS, not otherwise specified; OR, odds ratio; RR, relative risk.

treatment on the effectiveness of acute morbidity reduction and long-term disease outcome prevention [74].

The value of sensitive and specific assays to determine the cause of travellers' diarrhoea may have important implications for understanding the epidemiology surrounding these infections, not least of which is to support the assessment and value of novel enteric vaccines on the horizon (e.g. ETEC, Campylobacter, Shigella and norovirus) [75]. Furthermore, the identification of outbreak-associated causes in a field deployment setting would significantly help public health efforts on the ground, as well as clinical management strategies. This critical need for field-deployable diagnostics cannot be over emphasized.

Finally, mitigative strategies of primary and secondary prevention of both the acute and chronic consequences of travellers' diarrhoea in deployed settings are known and need to be rapidly deployed. A randomized controlled trial evaluating the effectiveness of antimicrobial or probiotic chemoprophylaxis for prevention of acute travellers' diarrhoea and the chronic consequences is quite feasible given the known high attack rates of travellers' diarrhoea and associated risk of sequelae. Military service members of all nations have and will continue to deploy to austere areas in support of combat and humanitarian assistance and disasterrelief missions. The maintenance of effectiveness of these forces is critical to achieve the mission, and the reduction of disease impact (both acute and chronic) is also important given the fiscal impact and global economic constraints.

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None.

Conflicts of interest

Disclaimer: The opinions and assertions herein should not be construed as official or representing the views of the UK Ministry of Defence, the UK Defence Medical Services, the US Department of the Navy, the US Department of Defense or the US Government. This is a collaborative work by members of the UK and US Governments, and as such there are no restrictions on its use. There were no financial conflicts of interests among any of the authors.

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military service member or employee of the US Government as part of that person's official duties.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 601).

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