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INCIDENCE, ETIOLOGY, AND IMPACT OF DIARRHEA AMONG LONG-TERM TRAVELERS (US MILITARY AND SIMILAR POPULATIONS): A SYSTEMATIC REVIEW

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Abstract. To determine regional estimates of pathogen-specific prevalence and incidence, as well as, describe morbidity associated with diarrhea among deployed US military and similar populations, a systematic review was conducted for publications between January 1990 to June 2005. Point estimates and confidence intervals of pathogen prevalence and travelers' diarrhea incidence were combined in a random effects model and assessed for heterogeneity. In total, 262 studies were identified for potential inclusion, of which 52 fulfilled inclusion criteria. Overall, 38% were from the Middle East, 29% from Southeast Asia, 27% from Latin America/Caribbean, and 6% from sub-Saharan Africa. Median duration of travel was 1.5 months (interquartile range, 1–3 months). Enterotoxigenic *Escherichia coli* (ETEC), *Campylobacter*, and Shigella were identified as causing 38–45% of diarrhea, with regional and population differences. Incidence based on self-report was higher than studies using passive surveillance or clinic-based methods (29 versus 7 versus 6 episodes per 100 person-months, respectively) without regional differences.

INTRODUCTION

Infectious diarrhea continues to be one of the most common problems facing travelers abroad. A distinction is sometimes made in risk and/or pathogen distribution between short-term (< 2 weeks) travelers and populations living overseas for extended periods, such as military personnel, expatriates, students, and Peace Corps volunteers.[1–4] Epidemiologic studies of infectious diarrhea in deployed military account for a majority of the published experience given the well-recognized continued threat.[5–7] Studies evaluating disease and non-battle injury rates in recent peacetime and combat operational settings have consistently identified infectious gastrointestinal illness in the top five reasons for clinic visits.[8–14] Because the increasingly global economy has led to both an increase in short-term travelers and an increase in populations from developed countries moving to and residing for lengthier stays in developing countries, it is important to determine whether there are differences in the epidemiology of diarrhea in these groups.

Black[15] summarized pathogen etiology and attack rates by select geographic regions. This review was not limited to military and similar long-term traveler populations, nor did it report on disease morbidity. Furthermore, due to the date of the review, diagnostic sensitivities now available with the development of PCR and other molecular diagnostic techniques for enteric pathogen identification were lacking.[15,16] Furthermore, no studies have attempted to use a systematic methodology to combine estimates of disease incidence, morbidity, and treatment outcomes to summarize and quantify pathogen-specific disease burden in selected geographic regions. The primary objectives of this study were to determine updated regional estimates of diarrheal disease incidence and pathogen-specific prevalence and describe morbidity and treatment outcomes among long-term travelers, including US military and similar populations, through the use of a systematic review of the scientific literature.

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MATERIALS AND METHODS

The study design is a systematic review of the scientific literature based on accepted principles of good methodological design.[17,18] The systematic review included eligibility criteria for available evidence, standardized data abstraction, critical appraisal of the quality of the evidence, and standard methods of data analysis. Further description of these methodological components is as follows.

Search strategy and study selection. A comprehensive retrieval of information was conducted using a stepwise procedure of searching personal files, perform searches on electronic bibliographic databases (including MEDLINE, EMBASE, CINAHL, and the Cochrane Library), and handsearching bibliographies of retrieved articles, technical reports (including Defense Technical Information Center, National Technical Information Service), and doctoral dissertations. All searches were conducted starting with the term travelers' diarrhea or diarrhea and then followed by the addition of the following terms: epidemiology, etiology, military, peace corps, expatriate, incidence, burden, morbidity, and treatment. In addition, MEDLINE searches were conducted using major MeSH headings (medical subject headings) determined from articles known to be eligible. All publications and reports published between January 1, 1990 and June 30, 2005 were screened by a single reviewer to determine if they met the eligibility criteria. Those deemed to be irrelevant were excluded, and reasons for exclusion were noted. When the information provided by the titles and/or abstracts was inadequate to decide on eligibility, the full-text article was retrieved and evaluated. Review articles were obtained for the purpose of screening reference lists.

Based on the goal and specific aims of this systematic review original research in the form of observational cohorts, surveys, database analyses, or clinical trials published in English and conducted on long-term travelers (including US military or other similar traveler populations) were considered for inclusion. Similar traveler populations were defined as expatriates of a developed country living abroad in an under-developed country, as well as any traveler in country for a month or longer. All studies involving US military, regardless of travel duration, were eligible. Studies involving tourists and short-term business travelers were excluded. Jus-

tification for the criteria of study selection for these eligible populations was based on the primary interests of developing stable estimates of disease incidence among long-term traveler populations finding (e.g., living conditions, risk profile). Studies were categorized to geographic regions of sub-Saharan Africa, Latin America and the Caribbean, Southeast Asia, and the Middle East based on logical geographic regions and the convention of previous reviews. Only studies detailing information for variables of interest were included.

Data abstraction/validation. Data from obtained articles and reports were abstracted using a pre-tested, standard data abstraction form. Bibliographic information, study design description, study years, geographic location, population characteristics, primary outcome measures, and other study characteristics (e.g., follow-up period, case definition used) necessary to answer the key questions and to evaluate heterogeneity were included in the data abstraction form. Pathogen prevalence was abstracted as a percent of total cases along with the study denominator that was used to compute the prevalence. For consistency, pathogen prevalence was abstracted based on tables or text reporting the number of diarrheic samples in which a particular pathogen was isolated. Because it is difficult to determine the exact etiology when more than one pathogen is found, prevalence was reported as number of cases infected with a particular agent inclusive of cases with multiple pathogens. In studies that were clinical trials involving antimicrobial prophylaxis, the placebo control arm was used to estimate pathogen prevalence. Prevalence of multiple pathogens was also abstracted when available. Incidence was abstracted as an event number and person-time as the denominator when available. The source of the event number was also recorded as either based on self-report, clinic-based case series, or disease and non-battle injury (DNBI). For studies conducted over a period of more than 1 year, the mid-point of the study period was used for analysis.

To evaluate how the validity of study design may affect interpretation of the results, each article was scored for quality by two reviewers using a standardized grading criteria that was specifically developed for prevalence and incidence systematic reviews.[19] These grading criteria placed primary emphasis on domains of study design and sampling method, sample size, standardization and unbiased collection of outcome measures, adequate response rate, appropriate analysis, and applicability of the study population. For each validity domain, an ordinal score of 0, 1, or 2 depending on whether the criteria was "not met," "partially met," or "fully met" was assigned. All domains were assumed to be of equal importance to the validity of the study and were summed to create an overall quality score. Inter-rater reliability between scorers where assessed using a quadratic weighted κ statistic. Abstraction and quality scoring were not blinded. Accuracy of data abstraction was reviewed and validated for all articles and abstraction forms by duplicate review. Data was entered into a database, and a 100% check for accuracy of entry was performed by visual confirmation of each abstraction form.

Analysis. The analysis of pathogen prevalence and incidence was stratified by region as geographic differences have been previously described.[8,15] A primary goal of this study was to define point estimates and confidence intervals for pathogen prevalence and incidence to be used later in an economic analysis. Furthermore, because of known variations in study design, methodologies, population characteristics, and other factors, heterogeneity of prevalence and incidence estimates across studies was expected and assessed graphically through the use of Forest plots and statistically through the use of heterogeneity statistics and non-parametric methods. For purpose of summary, point estimates and standard 95% confidence intervals were combined using a random effects model with methodology developed by DerSimonian and Laird[20] and reporting point estimates with 99% confidence intervals. This method is considered more conservative compared with a fixed effects model and weights studies by both sample size and between-study variance. The use of 99% confidence intervals also assures a more robust estimate of any given prevalence or incidence.

Heterogeneity was tested using a χ^2 heterogeneity statistic, and potential sources of heterogeneity were assessed graphically by Forest plots and using non-parametric methods (e.g., Kruskal-Wallis, Mann-Whitney *U* test) to compare differences in prevalence or incidence between two or more groups of a given population or study characteristic. In the case of parameters where only a few studies were found (e.g., probabilities and outcomes associated diarrhea and treatment), a median and range of estimates are reported. As a principle purpose of this systematic review was to summarize studies reporting pathogen prevalence and diarrhea incidence (not an evaluation of intervention effectiveness), publication bias was not assessed, because the concern for non-published findings caused by negative studies or disappointing results was considered to be minimal.

All analyses were conducted using Stata V9 (College Station, TX).

RESULTS

In total, 262 studies were identified as eligible, of which 49 articles fulfilled all criteria and were suitable for inclusion in the analysis, abstracted, and scored for quality. The study selection process is further detailed in Figure 1. One study

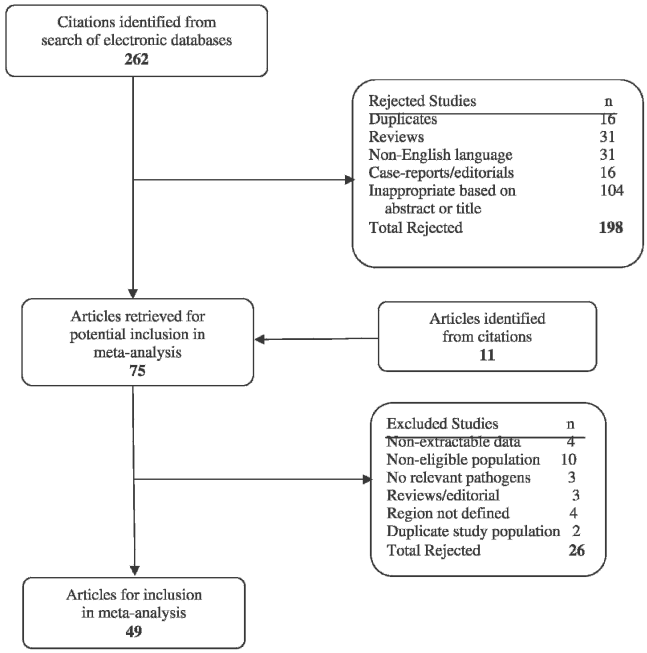

FIGURE 1. Flow diagram of study selection for inclusion in the systematic review.

TABLE 1
Characteristics of included studies

Reference	First author	Year	Year(s) of study	Study design	*N*	*n*	Country	Dur. travel	Population	Setting	Quality total (problem areas)
					Sub-Saharan Africa						
16	Bourgeois	1993	1985–1987	Descriptive	740	47	Multiple		US Military	RD	8.5 (G)
39	Sharp	1995	1992–1993	Descriptive	1,225	113	Somalia	2	US Military	HA&P	14.5
56	Sharp	1995	1992–1993	Descriptive	138		Somalia		EE&NGO		4 (ACF)
					Latin America/Carribean						
29	Adachi	2003	1999–2001	Clinical Trial		217	Mexico	3	Student		8 (A)
16	Bourgeois	1993	1985–1987	Descriptive	1,625	242	Multiple		US Military	RD	8.5 (G)
30	Dupont	1992	1998–1990	Clinical Trial		191	Mexico		Student		5.5 (ABF)
21	Dupont	1998	1996	Clinical Trial		72	Mexico		Student		4 (AC)
57	Dupont	2005	2003	Clinical Trial		54	Mexico		Student		10
22	Ericsson	2001	1994–1995	Clinical Trial		88	Mexico		Student		4.5 (ACFG)
58	Heck	1993		Clinical Trial		30	Multiple	0.5	EE&NGO		8.5 (G)
1	Herwaldt	2000	1991–1993	Cohort	36		Guatemala	26	Peace Corps		11 (C)
59	Jiang	2000	1992–1997	Descriptive		928	Mexico	1.25	Student		8 (F)
60	Miser	1995	1989–1990	Descriptive	471		Panama	0.75	US Military	Combat	8.5 (DG)
61	Pazzaglia	1991	1984–1989	Descriptive		655	Peru	21	EE&NGO		4.5 (ABF)
23	Salam	1994	1993	Clinical Trial	180		Belize	2	For. Military	RD	4 (DEFG)
8	Sanchez	1998	1981–1984	Mixed Design	538*		Multiple	0.75	US Military	RD	10.5
24	Thornton	1992	1986–1987	Clinical Trial		142	Multiple		US Military	RD	8.5 (G)
					Middle East						
55	Cohen	1992	1987	Cohort	423	77	Israel	2.5	For. Military	RD	7 (G)
34	Cohen	2001	1993–1997	Cohort	6,426	2,197	Israel		For. Military	RD	12.5
62	Haberberger	1991	1987	Cohort	4,500	183	Egypt	1.3	US Military	EX	5 (FG)
33	Haberberger	1994	1988	Descriptive	5,000	118	Egypt	0.25	US Military	RD	9.5
63	Haberberger	1994	1985–1987	Descriptive		126	Egypt		EE&NGO		10 (FG)
7	Hyams	1991	1990	Descriptive	2,022	432	S. Arabia	2	US Military	Combat	9 (A)
64	Hyams	1993	1990–1991	Cohort		304	Kuwait	5	US Military	Combat	9.5
65	Hyams	1995	1990	Descriptive	830		Multiple	4.3	US Military	Combat	9 (G)
25	Johnson	1992	1990	Case-Control		73	Egypt	6.5	US Military	Combat	4.5 (BG)
66	Oyofo	1995	1993	Descriptive	3,284	36	Egypt	0.75	US Military	EX	6 (CFG)
67	Oyofo	1997	1995	Descriptive	1,200	19	Egypt	1	US Military	EX	7 (FG)
35	Paparello	1993	1990–1991	Descriptive	722		Persian Gulf		US Military	Combat	12.5 (E)
68	Rudland	1996	1991	Descriptive	108		Iraq	1.25	For. Military	Combat	7.5 (CD)
8	Sanchez	1998	1981–1989	Mixed Design	528*		Multiple	1	US Military	RD	10.5
32	Sanders	2005	2000	Mixed Design	3,725	129	Egypt	2	US Military	EX	10.5
69	Scott	1990	1988	Clinical Trial		17	Egypt	0.25	US Military	RD	10 (F)
26	Taylor	1991	1989	Clinical Trial	162	104	Egypt	0.75	US Military	EX	8 (CG)
70	Taylor	1997	1990–1991	Descriptive	204		Kuwait	7.5	US Military	Combat	8 (FG)
44	Thornton	2005	2003	Descriptive		129	Iraq		US Military	Combat	6 (DEF)
71	Willshaw	1995	1990–1991	Descriptive		181	S. Arabia		For. Military	Combat	4.5 (AEFG)
					Southeast Asia						
72	Adkins	1990	1985	Cohort	1,914	100	Multiple	1.75	US Military	RD	6 (BG)
73	Arthur	1990	1988	Clinical Trial	993	296	Thailand	1.25	US Military	EX	10 (F)
37	Beecham	1997	1996	Descriptive	170	16	Thailand	0.75	US Military	EX	9
10	Buma	1999	1992–1993	Cohort	2,283		Cambodia	5.1	For. Military	HA&P	8 (DEF)
36	Echeverria	1993	1993	Cohort	333	24	Thailand	1	US Military	EX	10 (F)
2	Hoge	1996	1992–1993	Case-Control	70	69	Nepal	9	EE&NGO		7.5 (A)
27	Kuschner	1995	1993	Clinical Trial		72	Thailand	1	US Military	EX	7 (C)
74	Lesho	1994	1992	Descriptive	1,159		Thailand	1.5	US Military	EX	4.5 (DG)
75	Murphy	1996	1994	Descriptive		104	Thailand	1	US Military	EX	7.5 (CF)
76	Oyofo	1999	1996	Descriptive	721	49	Multiple	3	US Military	RD	9.5 (CF)
28	Petruccelli	1992	1990	Mixed Design	169	137	Thailand	1	US Military	EX	10 (G)
8	Sanchez	1998	1981–1990	Mixed Design	836*		Thailand	1	US Military	RD	10.5
31	Sanders	2002	1998	Descriptive		143	Thailand	3	US Military	EX	10
77	Shlim	1999	1994–1995	Cohort	77	158	Nepal	11	EE&NGO		9.5 (F)
38	Walz	2001	1995	Mixed Design	369	170	Thailand	1	US Military	EX	9.5

* Median value of deployed population denominator.
N, population denominator used for incident estimation; *n*, population denominator used for pathogen etiology prevalence or other parameter estimation; Dur. Travel, duration of travel in months.
Setting: RD, routine deployment; EX, exercise; HA&F, humanitarian assistance and peacekeeping.
Quality findings: A, sampling design/method; B, sampling frame; C, sample size; D, standard outcomes; E, unbiased outcomes; F, response rate; G, analysis; H, applicability.

reported incidence estimates and treatment probabilities stratified by three regions and one study reported pathogen prevalence distributions stratified by two regions. These studies were abstracted separately for each region and included as if they were individual studies in the analysis. Table 1 provides descriptive details of the 52 included studies.

Study characteristics. Overall, there were 20 studies (38%) from the Middle East, 15 (29%) from Southeast Asia, 14 (27%) from Latin America and the Caribbean, and 3 (6%)

from sub-Saharan Africa. A majority of the studies were conducted among US military populations ($N = 33$, 63%), with foreign military, expatriate (including non-government organizations (NGOs) and Embassy populations), and student populations each consisting of about 12% of the included studies. Of the 41 (79%) studies reporting duration of travel, median duration of travel for these populations was 1.5 months (interquartile range [IQR], 1–3 months; range, 1 week to 26 months). Twenty-four of the studies (46%) were defined as descriptive surveys, 12 (23%) were clinical trials, 9 (17%) were cohort studies, 5 were mixed design (usually including an observational study with an added survey component, and 2 were case-control. A standard definition for diarrhea (at least three loose stools in a 24-hour period or at least two loose stools in a 24-hour period with associated symptoms) was used in 36 (69%) of included studies. Median study population size was 235 (IQR, 128–883); however, studies reporting pathogen prevalence ($N = 36$) were generally much smaller (median, 116; IQR, 62–182). Some study characteristics were not extractable on a majority of studies, including sex proportion and mean or median age. While the eligible period for published studies was between 1990 and 2005, the median year of the studies actually being conducted was 1992.

Study quality. Agreement of quality scores assigned by two observers were compared using a quadratic weighted κ and was found to be good ($\kappa = 0.73$), with scores ranging from a low of 3 to a maximum of 14 (of 16), with a median of 8 (IQR, 6–10) for both reviewers. Quality scores were averaged between observers for the remaining analysis. Quality domains that consistently scored well across studies (median values > 1) were the use of standard outcome measures and applicability of study population, whereas the analysis quality domain was lower across all studies (median values < 1). Overall study quality scores were found to be associated with factors related to study design and study population. Studies using a mixed design ($N = 5$) had a better overall median scores (11; IQR, 10–11) compared with other study designs (8; IQR, 6–9.5; Mann-Whitney U, $P = 0.01$). Studies conducted among US military populations had higher median total quality scores compared with non--US military studies (median, 9 versus 7.5; Mann-Whitney U, $P = 0.007$). There were no differences in overall quality score by geographic region or year of publication.

Pathogen prevalence. Summary estimates of pathogen prevalence by region are detailed in Table 2. Overall, we found regional differences in pathogen distributions of ETEC ($P = 0.02$), *Campylobacter* ($P = 0.001$), and *Salmonella* (Kruskal-Wallis, $P = 0.001$). The differences seem to be because of Southeast Asia having a relatively lower prevalence of ETEC and a higher prevalence of *Campylobacter* and *Salmonella* compared with other regions. ETEC was the most common pathogen identified in Latin America and the Caribbean and the Middle East, accounting for 29% and 28% of cases, respectively. Whereas *Campylobacter* accounted for nearly one quarter of all cases in Southeast Asia, ETEC was also quite common, accounting for nearly one of every six cases. The two studies from sub-Saharan Africa describe ETEC and *Shigella* as important pathogens, accounting for approximately 16% and 9% of pathogens, respectively. *Salmonella* was reported in a majority of studies in each of the regions and was highest in Southeast Asia (11%) compared with regions of the Middle East (1%) and Latin America and the Caribbean (3%). Other bacterial and viral pathogens were inconsistently reported across studies within regions; however, pooled summary estimates of prevalence for EAEC was 8–19%, norovirus was 4–13%, and rotavirus was 2–6%. Multiple pathogens were also common and higher in Southeast Asia, accounting for 16%, compared with a frequency of 7–9% in the other regions (excluding sub-Saharan Africa, which reported 4% and 13% in two studies), although this difference was not statistically significant.

There was marked heterogeneity among studies estimating prevalence for individual pathogens in all regions (χ^2 heterogeneity statistic, $P < 0.001$ in all models). Attempts to explain this heterogeneity by non-parametric testing for most variables (e.g., study design, study setting, population type, military branch) was limited because of the small number of studies in subgroups of the independent variable. However, there were differences in prevalence of individual pathogens when stratifying by whether the population was US military or other. US military populations experienced a lower prevalence of *Shigella* compared with other populations (median, 2% versus 7%; Mann-Whitney U, $P = 0.02$) and had a higher prevalence of any identified pathogen compared with other populations (median, 52% versus 42%; $P = 0.04$). Increasing overall study quality (as measured by increasing tertiles) was

TABLE 2
Summary pathogen prevalence and diarrhea incidence among US military and similar populations by region and overall

	Geographic region				
	Sub-Saharan Africa*	Latin America and Caribbean	Middle East and N. Africa	Southeast Asia	Summary estimate (99% CI)
Pathogen prevalence (%)/number of studies	$n = 2$	$n = 7$	$n = 13$	$n = 12$	
ETEC	16, 17	29.1	28.3	13.3	22.2 (16.9–27.5)
EAEC	4	6.0	16.8	12.4	13.3 (7.7–18.9)
Campylobacter	0, 2	2.6	1.2	23.9	9.9 (5.4–14.5)
Norovirus	13	9.0	7.1	9.2	8.4 (4.0–12.8)
Shigella	9, 33	6.2	7.1	3.8	6.6 (3.4–9.7)
Salmonella	1, 9	3.0	1.4	11.1	5.0 (3.1–6.9)
Rotavirus	1, 36	5.6	1.5	3.4	3.9 (1.6–6.2)
Multiple pathogens	4, 13	7.0	9.3	15.9	11.2 (7.4–15.1)
No pathogens identif.	48, 50	52.9	46.3	40.2	45.6 (38.6–52.5)
Incidence (95% CI)/number of studies	$n = 2$	$n = 5$	$n = 13$	$n = 12$	
Active surveillance†	–	29.9 (6.7–53.1)	24.3 (7.3–41.2)	37.3 (18.7–55.8)	28.9 (16.2–41.5)
Passive surveillance	3.0, 8.0	10.8 (2.5–19.1)	5.3 (3.6–7.1)	6.2 (4.7–7.8)	6.2 (4.9–7.4)

* Pathogen prevalence (if tested) and incidence for each of two studies reported (unpooled).
† Cohort study and self-report surveys.

also associated with increasing prevalence of pathogen recovery across studies (nonparametric trend, $P = 0.047$). While not statistically significant, the probability of recovering a pathogen showed an increasing trend by year of study activity as well ($r = 0.29$, $P = 0.11$). In assessing confounding between these variables, there was an association between year of publication and population type with a median study year of 1990 for US military studies compared with 1993 for non-military studies (Mann-Whitney U, $P = 0.08$). However, if year of study was confounding the association found with population type, one would expect the median year of study to be higher in US military studies. As previously described, there was an association between study quality and study population, with US military studies showing higher quality. Small numbers limited further evaluation of heterogeneity because of these variables. Multiple pathogen prevalence was not associated with any of the independent variables abstracted.

Incidence. Incidence estimates were extracted for 32 studies. As with pathogen prevalence, there was considerable heterogeneity between studies used to estimate diarrhea incidence (χ^2 heterogeneity statistic, $P < 0.001$). Table 2 describes the summary incidence estimates stratified by passive (clinic-based studies, DNBI) and active (cohort studies, self-report) surveillance ascertainment methodology by region, for which there did not seem to be any association between incidences graphically or statistically (data not shown). There was a higher incidence based on how the incidence measurements were ascertained, with pooled summary incidence estimates among studies that based incident events on self-report (e.g., post-deployment/travel questionnaires and cohort studies) being higher (29 cases per 100 person-months) compared with DNBI-based (7 cases per 100 person-months) and case-surveillance study estimates (6 cases per 100 person-months; Kruskal-Wallis test, $P = 0.001$).

Additionally, an association was noted with higher incidence in populations that were not in the military compared with other foreign and US military populations (Kruskal-Wallis, $P = 0.04$). However, this association may be confounded because more non-military population studies ascertained incidence estimates based on designs using self-report. No association of differential incidence with other variables such as study design, quality, use of standard definition, or duration of travel were identified.

Twelve studies reported data to estimate the probability that an individual might seek treatment if they became ill with diarrhea (Table 3). Eight of these included estimates of self-reported incidence and clinic-based incidence (visits to a medical treatment facility). Overall, it seemed that a median of 23% (IQR, 12–29%) of individuals who became ill with diarrhea sought treatment at a medical treatment facility. No differences in the probability of seeking treatment could be explained.

Morbidity. Seventeen studies had extractable information that described the probabilities associated with disease and treatment outcomes (Table 4). Eight studies (seven clinical trials and one case-control study) reported no adverse events to antibiotic treatment in 1,045 clinical visits (binomial exact 95% confidence interval [CI], 0–0.0035).[21–28] Six studies reported on the probability of treatment failure with a median estimate of 5% (range, 3–9%).[27–32] While case definitions for treatment failure varied, they generally involved either worsening of symptoms after 24 hours, no improvement of symptoms after 72–96 hours, or relapse. Nine studies reported a median probability of 27% (range, 3–56%) that a person with diarrhea would be placed sick-in-quarters (SIQ) or be incapacitated because of the illness.[7,31–38] Four studies reported the probability of requiring intravenous hydration ranging from 0% to 18%.[31,37–39] Two studies (from the same reference) reported provider estimates of the probability of hospitalization caused by diarrhea among those seeking treatment to be between 10% and 13%.[8]

Twenty studies had extractable information related to outcomes of treated and untreated diarrheal disease, of which 12 found pre-treatment duration of symptoms to be about 1.3 days (IQR, 1.1–1.5 days). Post-treatment duration ranged from less than 1 day to just more than 2 days, and there was a trend toward a shorter post-treatment duration in studies where an antibiotic regimen was adjuvanted with an anti-motility agent such as loperamide ($N = 2$) compared with studies that did not adjuvant ($N = 5$; median, 1.1 versus 1.7 days; Mann-Whitney U, $P = 0.12$). Relatively few studies described pathogen-specific differences associated with disease probabilities and outcomes. Those that did provide this information are summarized in Table 5.

DISCUSSION

In this review, pathogens were identified in a majority of specimens, with an overall pooled estimate of 55% and five

TABLE 3
Probability of seeking treatment for diarrhea

Reference	Author	Region	Size	Clinical incidence	Self-report incidence	Probability seek treatment
72	Adkins	SE Asia	1,914	3	50	.06
73	Arthur	SE Asia	253	6	39	.15
37	Beecham	SE Asia	170	16	53	.30
33	Haberberger	Middle East	155	12	85	.14
62	Haberberger	Middle East	4,500	4	34	.12
7	Hyams	Middle East	2,022	–	–	.22
35	Paparello	Middle East	722	–	–	.08
8	Sanchez	Middle East	528	–	–	.32
8	Sanchez	SE Asia	836	6	24	.25
8	Sanchez	Latin Am/Carribean	538	–	–	.29
32	Sanders	Middle East	3,725	–	–	.29
38	Walz	SE Asia	369	8	35	.23
	Median			6	39	0.225

Incidence, events per 100 person-months.

TABLE 4
Disease outcomes associated with treated and untreated disease

Outcome duration (days)	No. of studies	Mean (value)	Median	IQR	Min, max	Reference
Pre-treatment symptoms	13	1.4	1.5	1.3–1.5	0.3, 4.1	7, 21, 22, 24–27, 29, 31, 32, 34, 36, 39
Post-treatment symptoms	8	1.4	1.4	1.0–1.8	0.6, 2.2	21, 24, 25, 27, 28, 30, 32, 39
Regimen w/loperamide	2	1.1	1.1	NA	0.7, 1.4	24, 28
Regimen w/o loperamide	6	1.7	1.7	1.5–1.8	1.3, 2.2	21, 24, 27, 30, 32, 39
TLUS (no loperamide)	3	0.6	0.5	NA	0.5, 0.9	22, 23, 29
Lost to SIQ or incapacitation	1	(1.4)	NA	NA	NA	33
Lost to hospital admission	1	(2.5)	NA	NA	NA	39
Symptom duration in non-treatment seeking individuals	9	3.1	3	2.6–3.5	2.1, 4.3	23, 25, 30, 32, 33, 37, 39, 68, 77

NA, not applicable; TLUS, time to last unformed stool.

studies showing rates of 80% or more. This finding compares favorably to the 1990 review by Black,[15] where a pooled estimate of pathogen recovery of 45% was reported (*t* test, $t = 1.935$, $P = 0.06$, data not shown). It is possible that better techniques and recovery methods were factors in this trend toward improvement, although approximately one fourth of studies were conducted during before 1990. While this review did not specifically look at the pathogen identification techniques used, we did find that there was a trend toward an increase in pathogen recovery rate of approximately 1% per year of study between 1985 and 2003 ($P = 0.11$). In addition to quality of study, we found that studies conducted among US military populations were associated with higher pathogen recovery rates. This finding might be explained by differences in how military studies are generally conducted compared with non-military studies. Particularly, military studies are most often conducted by establishing advanced laboratories in the field environment, where collected samples are immediately processed and cultured, and pathogens are isolated, whereas non–US military studies often rely on storage and transport of specimens to a laboratory that is at a distant location. Because of the different specimen processing and testing in these two settings, there may be differences in pathogen recovery rates. Confounding between these to potential predictors could not be further evaluated because of the small numbers of studies.

An additional important finding was that studies conducted in the Southeast Asia region showed a trend toward having higher pathogen recovery rates compared with the other regions (61% versus 50%, $P > 0.05$). This finding could be explained by factors involving the characteristics of studies in this region or other factors inherent to the region. There were no differences between study design or quality by region, but there were more US military studies conducted in the Southeast Asia region compared with other regions (80% versus 56%, $P = 0.19$), and this may confound the trend toward finding an association of higher pathogen recovery rates in Southeast Asia compared with other regions. This suggestive regional association might also be explained by regional differences in pathogen etiologies. *Campylobacter* is known to cause more severe disease than most other common diarrheal pathogens.[31,36,40,41] Therefore, it could be hypothesized in regions where there is a predominance of *Campylobacter* infections (or more severe diarrhea), more patients may be presenting for treatment, and subsequently, a pathogen, particularly *Campylobacter*, is more often identified. Extractable data on severity of diarrheal disease were not available for all studies; thus, an assessment for severity of disease could not be evaluated for association with prevalence of pathogen identified.

While there were regional differences in pathogen prevalence, no differences in diarrhea incidence by region was found. We did find that method of case ascertainment was associated with differential estimates of incidence. Not unexpectedly, incidence based on self-report was much higher than incidence based on studies using passive surveillance data (DNBI) or clinic-based case series (29 versus 7 versus 6 episodes per 100 person-months, respectively). This finding is corroborated by studies that reported both self-report and clinic-based estimates of incidence. From these studies, it seems that less than one quarter of all episodes of diarrhea that occur among deployed US military personnel and similar traveler populations are seen by a health care provider.

The self-reported incidence in the long-term traveler population that we describe is comparatively lower to estimates reported from business/leisure travelers and the previously reported review.[15] Compared with the review of Black, which reported a summary incidence rate of 60 cases/100 person-months (95% CI: 47–73 cases/100 person-months), our finding of 29 cases/100 person-months (among cohort and self-

TABLE 5
Pathogen-specific illness probability or outcome

Probability (*P*) or outcome	Reference	Region	*Campylobacter*	ETEC	*Shigella*	Other
(*P*) of SIQ/incapacitation	34	Middle East	–	–	0.56	0.27
(*P*) of SIQ/incapacitation	7	Middle East	–	0.21	0.64	–
(*P*) of SIQ/incapacitation	38	SE Asia	–	–	0.92	0.46
Post-RX duration, days*	27	SE Asia	1.6	–	–	1
Post-RX duration, days*	39	sub-Saharan Africa	–	2.2	2.9	1.9
Total duration of symptoms	31	SE Asia	3.3	–	–	1.6
Total duration of symptoms	34	Middle East	–	–	7.1	5.1

* No loperamide.

reported incidence data) is much lower (Kruskall-Wallis, $P < 0.0001$, data not shown). Possible factors that could explain this difference are differences in populations between the two studies and/or changes risk behavior of travelers' over time. Our current review consists of studies with relatively more US military, no tourists, and longer travel durations compared with the study of Black. Given these differences, high attack rates among populations with shorter travel durations may explain the differences in the incidence estimates. Also, military populations, with their often controlled food and water distribution systems, may account for the lower incidence compared with other travelers. Changes in risk behavior over time because of increased traveler education with the advent of pre-travel counseling and recognition of travel medicine as an independent discipline may also help to explain a decrease in incidence over time. In fact, when studies from the article of Black and this study are combined, we find an inverse association between year of study (published) and incidence (Spearman $\rho = -0.61$, $P < 0.001$)—a trend that persists with the exclusion of US military studies (Spearman $\rho = -0.33$, $P = 0.07$; data not shown).

Specific to the US military, there are a number of possible reasons to suggest why a person with diarrhea may not seek care at a treatment facility, including lack of access to care, less severe disease, self-treatment, or a belief that there is nothing to be done to treat the condition. None of the studies reported reasons why individuals chose not to seek care. However, Hyams et al.,[7] in their report of US military troops in the first Gulf War, found that, of those that did not seek treatment, 20% used antibiotics, suggesting self-treatment may play a role. In our review, nine studies described the self-reported total duration of illness among those individuals not seeking care to be about 3 days (IQR, 2.6–3.5 days). Travelers' diarrhea is generally thought to have a median illness duration of 3–4 days; thus, it does not seem that the diarrhea illness experienced by those not seeking treatment is any less severe, although further studies defining these disease episodes (e.g., etiology and impact) that are not encountered in medical treatment facilities are warranted.[42]

ETEC, *Campylobacter,* and *Shigella* continue to be identified as important pathogens, causing anywhere from 38% to 45% of diarrhea cases among US military and similar traveler populations. However, this review also highlights the importance of other pathogens, including norovirus, rotavirus, and enteroaggregative *Escherichia coli* (EAEC), which were responsible for ~20% of identified pathogens recovered. Furthermore, because the case definition of most studies focused on illness with diarrhea or vomiting, but not vomiting alone, this review may have underestimated the burden of acute enteric infectious disease caused by norovirus, rotavirus, and other enteric viruses that often cause a vomiting predominant illness. This burden of these enteric viruses is beginning to be understood, but more surveillance is likely needed to further describe the incidence and morbidity of disease associated with these agents in comparison to travelers' diarrhea (TD) and other infectious diseases of military importance.[43–46]

While only a few studies reported on outcomes of disease and treatment, important findings regarding the clinical significance of diarrhea disease are noted. The finding that one quarter of individuals seeking treatment are reported to be incapacitated because of this illness is significant. The estimates of 10% requiring hospitalization are alarming and need to be further evaluated. Admittedly, this estimate seems to be quite high based on the experience of a number of the study authors who have experience in treatment of diarrhea in field settings. These estimates could be overstated because of the limited number of studies that reported this finding ($N = 2$) and the fact that these estimates were based on provider estimates and not population-based hospitalization data. A 0–15% probability of requiring intravenous fluids for treatment of disease is consistent with practice patterns of military treatment of diarrhea and aggressive rehydration therapy that is often instituted to assure timely recovery of those that become ill. Too few studies were available to review for estimation of the pathogen-specific disease outcomes, probabilities, and treatment response caused by ETEC, *Campylobacter,* and *Shigella*. The increased severity and duration of illness caused by *Campylobacter* and *Shigella* compared with other pathogens were noted in only a few studies and need further description to assess their importance in these traveler populations, although it is consistent with what has been described in other studies on the epidemiology of these potentially invasive enteric pathogens.[31,36,40,41,47]

This review includes a comprehensive literature search, prospective inclusion and exclusion criteria, standardized data abstraction, quality scoring, and current analytic methods, all of which reduce the potential bias in the resultant population of studies used for analysis. Limitations of this review include the significant heterogeneity in the prevalence and incidence estimates among many different study designs, populations, and across regions, and sparseness in some data, particularly pathogen-specific disease probabilities and outcome. While a number of independent variables were found to explain some of the heterogeneity, small study numbers precluded further assessment of what factors may be associated with differential pathogen prevalence and incidence. Caution should be taken in generalizing the estimates to an entire region, because many of the articles came from serial studies of the same populations in same countries of a particular region (e.g., Bright Star Exercises in Egypt, Cobra Gold Exercises in Thailand, student populations in Mexico). Furthermore, the exclusion of leisure and business travelers' should be considered in generalizing the results to these populations. However, a review of excluded studies based on population non-eligibility does not find appreciable differences in estimates than what are described herein.[48–52] In addition, as this review shows, the collapsing of US military with other similar populations describing the epidemiology of diarrhea among long-term travelers presents a challenge. Also, clearly there is a gap of epidemiologic data from important regions of India, China, Oceana, and sub-Saharan Africa.

Additionally, this systematic review focused primarily on endemic (sporadic) diarrheal disease that occurs in these populations. While these are important and contribute to a large burden of disease, pathogens that have the potential to cause epidemic disease also need to be considered, particularly for military populations. Bacterial and viral agents having the potential to cause explosive and debilitating outbreaks may be as important, from a military perspective, because these agents cause the heavy burden of endemic disease.[43,53,54] In this respect, a study conducted among Israeli Defense Force troops during a routine deployment period found that, while sporadic cases of disease were caused by a

number of different pathogens, most outbreaks were associated with *Shigella*, norovirus, and *Salmonella.*[55] Furthermore, impact of these agents with epidemic potential have been anecdotally described in a number of studies, including a study among United States Air Force personnel in this review that reported that onset of diarrheal illness in 5 of 222 airmen on 1 day had an adverse affect on operations,[36] and another study reported a flight mission was aborted mid-flight because of sudden onset of gastrointestinal illness in the pilot.[37] Last, more epidemiologic studies in sub-Saharan Africa need to be conducted to better describe the regional incidence and pathogen prevalence in these geographic regions.

CONCLUSION

This review of studies on diarrhea in long-term travelers (US military and similar populations) provides some certain conclusions. First, diarrhea is frequent, and a large burden of disease is not seen by a health care provider. It remains to be known whether this illness is milder illness or is illness that is being successfully self-treated. Second, ETEC, *Campylobacter*, and *Shigella* bacteria are significant pathogens globally, and the latter two seem to also be associated with more severe symptoms with often longer duration. Third, a number of other bacterial, viral, and parasitic pathogens, including EAEC, *Salmonella*, norovirus, and rotavirus, should continue to be considered as important pathogens causing disease in these populations. Last, the combination of disease incidence requiring treatment, disease incidence among individuals who do not seek treatment, and incapacitation caused by these illnesses should be considered an important health threat and be addressed with further studies evaluating timely and effective management, as well as other strategies including the evaluation of vaccines to prevent these infections.

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