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Abstract

An Economic Evaluation of a Vaccine Acquisition Strategy to Mitigate Acute Diarrheal Illness Among Deployed US Military Forces

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Background. To this day acute diarrheal illness continues to be a significant health threat for deployed military personnel, resulting not only in significant numbers of lost days, but also increased health care utilization, and compromise in mission capability and effectiveness. Despite the advances in environmental health interventions and effective empiric treatment regimens, the high incidence and disease burden associated with enteric infections continues unabated. Vaccines have been proposed as a cost-effective method of primary prevention in operational settings where the risk of exposure is high. However, infectious diarrhea is but one of many threats to deployed service members, and in the face of limited resources, a decision to pursue a vaccine acquisition strategy should be based on sound epidemiological evidence that weighs the costs and benefits of such a strategy compared to alternatives. Therefore, my study was conducted to characterize and quantify the pathogen-specific burden of travelers' diarrhea (TD) among deployed US military personnel using best available evidence in order to evaluate the cost-effectiveness of a vaccine acquisition strategy against three primary causes of TD compared with current clinical management in a deployed setting.

Methods. Based on a theoretical framework for the economic model, estimates for all cause diarrhea and pathogen-specific parameters for incidence and morbidity were

obtained from a systematic review of the literature. The focus was on enterotoxigenic *Escherichia coli* (ETEC)-, *Campylobacter*- and *Shigella*-associated diarrheal disease among US military and other similar traveler populations in high risk geographic regions (Latin America and the Caribbean, the Middle East and SE Asia). Because of information gaps, particularly related to vaccine development costs, development time frames, and vaccine efficacy, a formal Delphi survey was undertaken to obtain estimates of model parameters from a panel of subject matter experts. Data gathered from the systematic review, the Delphi survey, and addition sources, including expert opinion, were used to build an economic model from a deployment health perspective to estimate the average cost to avert either a duty day lost due to diarrhea, or a day of diarrheal illness for a vaccine acquisition strategy compared to current treatment. Secondary analyses were conducted for two scenarios: immediate availability of a vaccine and specific pathogen-region combinations.

Results. Over the past two decades, diarrhea attack rates among troops deployed to high risk regions have averaged about 29% per month. Globally, ETEC, *Campylobacter* and *Shigella* infection account for 26 to 52% of these infections, with notable regional differences. Only 23% of troops who develop diarrhea during deployment seek care from a healthcare provider, and in a third of these case, the care provided is considered to be sub-optimal (no antibiotics). Among those not seeking care, about one-third attempt self-treatment, without apparent differences in disease severity compared with those seeking care. These current practice patterns amount to a significant burden of illness which could potential be reduced by changes in current management as well as an effective vaccine. Illness caused by these infections result in

operationally relevant outcomes, such as lost duty days, and direct medical costs associated with seeking care, being ill with diarrhea, being confined to bed-rest, and hospitalization.

It is estimated that a vaccine against each of these major pathogens will be developed in the next 10 years at a direct cost to the DOD of approximately $376 Million. Over a 30 year time horizon, development and acquisition of a multiplex vaccine against three primary causes of travelers' diarrhea would potentially prevent 265,451 lost duty days annually among a cohort of 147,000 troops deployed for 3.5 months. At a cost of $48.98 per vaccine dose, the present value of a vaccination program was estimated at $256,145,050 for a three-dose series, and the present value of the cost of care averted by the vaccine acquisition strategy was estimated at $16,266,784. Based on this model, the cost-effectiveness ratio was estimated to be $2,102 per duty day lost averted. If this vaccine were available for use today, the estimate would be $907 (IQR $575 - $1463) per duty day lost averted. A vaccine against *Campylobacter* and ETEC appeared to be more favorable than a vaccine for *Shigella*, and a Campylobacter vaccine with targeted use in SE Asia the was most cost-effective at $170 per duty day lost averted. Deployment time, time horizon, disease incidence, discount rate, number of doses, vaccine preventable pathogen prevalence, cost per dose, effectiveness outcomes associated with illness running its course, vaccine efficacy, and deployment size were the most influential parameters in the model.

Discussion. While the cost to avert a lost duty day by implementing a TD vaccine acquisition strategy was estimated, the monetary value of a lost duty day could not be determined. Therefore, it was not possible to base a decision on whether or not a

TD vaccine should be developed by the DOD on the results of this analysis. However, the model was able to demonstrate the relative cost-effectiveness of pathogen-specific vaccines, and provides an evidence-based decision tool, which could be used to prioritize and support decision-making when making comparisons with other countermeasures against deployment health threats. Furthermore, a review of the literature identified critical deficiencies in current management of diarrhea, which should be addressed through education and appropriate policy changes to provide a more immediate solution in mitigating the burden of diarrhea. Future studies should focus on refining estimates for model parameters, and the model should be expanded to consider a broader societal perspective and also include an assessment of important, vaccine-preventable post-infectious sequelae.

Conclusion. Much remains to be done to reduce the burden of diarrhea in deployed military personnel and similar traveler populations. It is recommended that cost-effectiveness models consider operationally-relevant outcomes for the targeted population, as was done in this study, to optimize its usefulness to decision-makers. It appears reasonable to prioritize a vaccination strategy that targets high risk combinations of specific diarrheal pathogens and particular geographic regions to maximize cost-effectiveness. The answers to important questions related to vaccine acquisition strategies or other countermeasures for health threats should be based on a systematic assessment of best available evidence in order to best protect those put in harms way while conserving limited resources.

An Economic Evaluation of a Vaccine Acquisition Strategy to Mitigate Acute Diarrheal Illness Among Deployed US Military Forces.

By

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LCDR MC USN

A DISSERTATION

SUBMITTED TO THE FACULTY OF THE DEPARTMENT OF PREVENTIVE MEDICINE AND BIOMETRICS OF THE UNIFORMED SERVICES UNIVERSITY IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PUBLIC HEALTH

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This dissertation reflects the results of my research only. All quotes from published works used here are fully cited and gratefully acknowledged with the understanding that there was no deliberate intention to infringe on copyrights. References to drugs, vaccines, or other proprietary products do not constitute a recommendation or endorsement by the US Department of Defense. All opinions

expressed are mine alone and do not represent those of the Department of Defense or the US Navy. This research was not supported by any internal Department of Defense or external funding.

Dedication

I would like to dedicate this dissertation to my mother and father who have cultivated in me drive, motivation and the belief in myself that I can accomplish any endeavor which I put myself to.

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List of Acronyms

BSS	Bismuth subsalicylate
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CER	Cost-effectiveness Ratio
CI	Confidence interval
CM	Current management
CY	Calendar year
DDL	Duty days lost
DID	Diarrhea illness days
DNBI	Disease non-battle injury
DOD	Department of Defense
EAEC	Enteroaggregative-*Escherichia coli*
ETEC	Enterotoxigenic-*Escherichia coli*
FDA	Food and Drug Administration
IOM	Institute of Medicine
IQR	Interquartile range
IV	Intravenous
M2	MHS Management Analysis and Reporting Tool
ME	Middle East
MEPRS-EAS IV	Medical Expense & Performance Reporting System and Expense Assignment System IV
MHS	Military Health System
MIDRP	Military Infectious Diseases Research Program
NV	Norovirus
PI-IBS	Post-infectious irritable bowel syndrome
QALY	Quality-adjusted life year
RV	Rotavirus
SE	Southeast
SIQ	Sick in quarters
TD	Travelers' diarrhea
TLUS	Time to last unformed stool
TMA	TRICARE Management Activity
US	United States
USAMRMC	US Army Medical Research and Materiel Command
VAS	Vaccine acquisition strategy

Definitions

Travelers' diarrhea:	An acute illness that results from infections acquired while traveling to another country and is characterized by 3 or more loose/liquid stools (bowel movements) in a 24 hour period, or at least two loose/liquid stools with one associated symptom (e.g. nausea, vomiting, cramps, fever, prostration or tenesmus). A typical episode of travelers' diarrhea lasts 2 – 5 days.
Severe diarrhea:	An episode of diarrhea which is characterized by 6 or more loose/liquid stools in any given 24 hour period.
Dysentery:	Any diarrhea which is associated with visible blood in the stool contents and is most often attributed to enteric infection by invasive bacterial pathogens including *Campylobacter* spp., *Shigella* spp. and *Salmonella* spp.
Acute gastroenteritis:	A general term referring to inflammation or infection of the gastrointestinal tract and often used with the word viral as a qualifier to denote vomiting as a prominent feature of illness caused by these infectious agents.
Vaccination:	The strategy of presenting a foreign antigen to the immune system in order to evoke a protective immune response.
Passive immunization:	The transfer of active immunity to an individual in the form of ready-made antibodies derived from humans or animals previously exposed to a particular pathogen.

Chapter 1: Introduction

Travelers' diarrhea in the military

Diarrheal disease has played a significant role in the outcomes of many military campaigns throughout history [1, 2] and continues to be a significant problem for deployed military personnel. [3-31] Presently, enteric infectious diseases, commonly referred to as travelers' diarrhea (TD), is one of the most common medical problems, with average cumulative attack rates of 36% per deployment and exceeding 70% during deployments in high-risk areas such as Southeast Asia. [5, 8, 18, 19, 23, 25, 26, 29] TD is a common clinical illness, which occurs in 20 – 50% of people who travel from developed world countries to developing world countries and is defined as the passage of 3 or more loose or liquid stools per day alone or more than 2 loose stools per day with associated symptoms such as nausea, vomiting, abdominal cramps, fever or fecal urgency. [32] The clinical course of acute TD is usually benign and resolves in 2 to 5 days among healthy travelers. While travel can be associated with stress, changes in diet, eating habits, activity levels, sleep or use of travel-related medications (e.g., sleep aids, anti-anxiety medications, chemoprophylaxis), which might contribute to alternations in bowel habits, the majority of TD cases which meet the case definition are due to the colonization of the travelers' bowels with an infectious enteropathogenic microorganism.

Furthermore, the burden of enteric infectious disease (including TD and acute gastroenteritis) relative to other disease and non-battle injury (DNBI) in US deployed forces has been described in a number of published reports [26, 30, 33-37] and are

Table 1.1 Studies reporting initial visits for DNBI among deployed military personnel

Study	Publication Year	Region	Mission Type	Relative Proportion of Total DNBI Visits (rank order)[1]		
				Enteric infectious disease	Acute respiratory illness	Non-battle injury
Sanchez et al. [26]	1990	Thailand	Joint exercise	19(1)	13(4)	16(3)
Wasserman et al. [33]	1990-1	SW Asia	Gulf War[2]	13(2)	9(3)	26(1)
Buma et al. [34]	1992-3	Cambodia	Humanitarian	20(2)	12(3)	24(1)
Sanchez et al. [35]	1992-3	Somalia	Humanitarian	8(4)	10(3)	25(1)
Gambel et al. [36]	1995	Haiti	Peacekeeping	7(4)	16(3)	17(1)
Sanchez et al. [35]	1995-6	E. Europe	Peacekeeping	6(4)	26(2)	27(1)
McKee et al. [37]	1997-8	E. Europe	Peacekeeping	6(5)	26(2)	27(1)
Taylor et al. [30]	2000	S. America	Peacekeeping	7(4)	43(1)	26(2)

[1] Category visit/total DNBI visits × 100. Excludes category of other medical/surgical from ranking.
[2] Surveillance data from squadron aid stations, 3rd Armored Cavalry Regiment, during Operation Desert Shield

summarized in Table 1.1. While there appears to be variation based on geographic region, enteric infectious disease is often in the top three DNBI categories of clinical visits among US military in deployed settings. Not all studies described morbidity measures, although Sanchez et al. examined lost work days among troops deployed for a month long exercise in Thailand.[26] They found that while diarrheal and respiratory illness were comparable with regard to frequency of health care visits (13.0% versus 13.4% respectively), diarrheal illness accounted for more than 10 times the number of lost work days due to "sick in quarters" or hospitalization compared to respiratory illness. Gambel et al. reported that enteric infectious disease was the second most frequent cause of hospitalization (15% of all hospital admissions) among persons deployed for a 1995 peacekeeping mission in Haiti. [36] Non-battle injury and acute respiratory illness accounted for 10% and 3% of hospital admissions, respectively. An additional study by Sanchez et al. found that while enteric infectious disease ranked fourth among total outpatient DNBI visits, it was the number one cause for hospital admission among troops deployed to Operation Restore Hope in Somalia from 1992 to 1993. [35] These data suggest that not only is enteric infectious disease incidence high relative to other DNBI categories, but the morbidity associated with these infections is clinically significant as well.

Intervention strategies for travelers' diarrhea

There are multiple intervention strategies; both treatment and prevention oriented, available to reduce the burden of illness due to TD in deployed US military populations.

Potential prevention strategies include risk behavior modification, environmental modification, chemoprophylaxis, and immunoprophylaxis. Currently there is no licensed vaccine against any of these infectious agents available in the US. However, intensive effort by the Department of Defense (DOD), academic, and private industry in vaccine research and development is ongoing.

Many of these intervention strategies are used routinely in deployed military populations, such as environmental modification (assuring safe food and water) and risk behavior modification, including frequent pre-deployment and intra-deployment safety briefings. Of the other possible preventive intervention strategies that could be considered, prophylaxis with bismuth subsalicylate (BSS) or probiotics are not recommended as they do not result in adequate protection.[38] On the other hand, antibiotic prophylaxis, while effective, is generally not recommended because of potential adverse reactions and increasing concern for the association between prolonged and/or widespread antibiotic use and the development of antimicrobial resistance.[39] Furthermore, in many military operations, long deployment durations would require prophylaxis beyond the recommended two-week time period.[38]

There are numerous antimicrobial treatment strategies including combinations of drug/dosing regimens (e.g. single dose, multi-dose) and stand-by therapy (self-treatment).[40-45] The current treatment standard for mild-moderate watery TD (afebrile, non-dysentery) is a 3-day course of fluoroquinolone antibiotic (e.g. ciprofloxacin or levafloxacin) with an anti-motility agent (loperamide).[46, 47] If the traveler presents with fever, dysentery or severe diarrhea, antibiotics are recommend without the use of an anti-motility agent. The newer generation macrolide,

Azithromycin, is the antibiotic of choice for empiric treatment of TD in Southeast Asia and other areas of the world, where the prevalence of fluoroquinolone-resistant *Campylobacter* is high.[48-50]

However, preventive interventions and empiric treatment are often insufficient to overcome the high incidence and burden associated with enteric infections in the deployed setting. Hyams et al. in their 1991 report of diarrheal disease during Operation Desert Shield stated:

> "Preventing infectious diseases was a priority for all branches of the US military during Operation Desert Shield. Nevertheless, *despite extensive efforts to secure a safe supply of food and water and a high level of sanitation, there were epidemics of infectious diarrhea,* as there have been throughout history when large numbers of soldiers are deployed. Because epidemic diarrhea may potentially compromise the capabilities of the US military during critical periods, *effective vaccines are needed to prevent the disease.*" [19]

This suggests that public health interventions are often not enough to reduce the burden of diarrhea among deployed US military personnel in austere environments. As long as future military operations require putting military personnel on the ground to live and work in high risk regions, diarrhea will undoubtedly continue to be a problem. In fact, in the current military operations in Iraq, diarrhea has continued to be a significant cause of disease and non-battle injury among the deployed troops.[51, 52]

Vaccine acquisition in the DOD

Protecting the health of our military service members is essential to our national security. US troops must be prepared to be deployed anywhere in the world, often on very short notice, whether it is for combat operations, for a training exercise, or to serve

as peacekeepers. Given the current political instability in many parts of the world, US warfighters must be ready to operate in environments where the risk of exposure to infectious diseases may be high and where usual or routine preventive efforts are often impractical. Today's military deployments can be characterized as smaller, faster, more diverse, distributive, and more frequent than those of earlier decades. Vaccines have been proposed as the most cost-effective way to protect individuals from infectious diseases in these and other possible future operational settings.[53] However, decision makers must consider many factors before committing to a vaccine acquisition policy. Decision makers often have to rely on imprecise estimates of potential operational, health and economic impact of infectious disease threats. In addition, they need to consider the threat of emerging antimicrobial resistance and region-specific important illnesses for which epidemiologic information may be incomplete and for which proven vaccines or medical countermeasures do not exist. Decisions often have to be made under conditions of considerable uncertainty and complexity.

The establishment of a vaccine acquisition policy is a complex process. In 2003, the Institute of Medicine (IOM) issued a report produced by the Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Disease of Military Importance, with recommendations on both technical and policy aspects of the DOD's strategy to combat infectious diseases. [53] They defined vaccine acquisition as,

> "A process [representing] a continuum extending from the first recognition of need, to the setting of priorities, to the maintenance of a technology base permitting internally conducted or externally contracted product oriented research, advanced product development, and clinical studies leading to licensure (whether or not DOD is in partnership with an industrial entity), as well as the establishment and maintenance of effective manufacturing facilities and, ultimately, the procurement

(purchase) and stockpiling of vaccine for use by DOD for protection of members of the US armed forces."

Within the DOD, research priorities evolve through multiple channels, including the office of the Assistant Secretary of Defense for Health Affairs, United States Army Medical Research and Materiel Command (USAMRMC), Army Medical Department Center and School, Military Infectious Disease Research Program (MIDRP), Armed Forces Epidemiological Board, Armed Forces Medical Intelligence Center, to name a few. The US Congress has designated the USAMRMC as the lead agent for DOD infectious diseases research, citing a 1999 Executive Order that refers specifically to "diseases endemic to an area of operations" and stating that "it is the policy of the United States Government to provide our military personnel with safe and effective vaccines, antidotes, and treatments that will negate or minimize the effects of these health threats." [54] Officially, a military product is initially conceived as a perceived need, which is first formalized as Future Operational Capabilities by USAMRMC. The MIDRP then drafts product-related objectives for review and modification by the Integrated Product Team and subsequently recommends draft objectives to USAMRMC. USAMRMC, with input from other sources, develops research plans that reflect the goals outlined in Future Operational Capabilities. The Assistant Secretary of the Army for Acquisition, Logistics, and Technology provides funds to support technology base-related research efforts.

Table 1.2 outlines the DOD infectious disease research priorities, with a vaccine for infectious diarrhea being third on the list, following research and development of a vaccine and new drugs for malaria. While these priorities appear reasonable based on

Table 1.2 DOD infectious diseases research and development priorities

MIDRP FY 2001 Program Priorities	FY 2000 Investment in Exploratory Research (millions of $)	JTCG-2 FY 2001 Priority Ranking
Malaria vaccines	5.8	1
Malaria drug discovery program	4.8	2
Diarrheal vaccines	4.4	3
Flavivirus vaccines	2.9	4
Common diagnostic systems	0.5	5
Malaria genome project	1.4	6
Identification and control of insect vectors	1.6	7
Hepatitis E virus vaccine	0.9	8
Polyvalent meningococcal vaccine	0.5	9
Hemorrhagic fever and tick-borne encephalitis virus	0.8	10
Hantavirus vaccine	0.7	10
Rickettsial diseases	0.7	11

MIDRP = Military Infectious Diseases Research Program
JTCG-2 = Joint Technology Coordinating Group-2
Table adapted from IOM report [53]

historical disease threats faced by the US military, the 2003 IOM report noted that the entire DOD vaccine acquisition process "suffers because it falters at an important first step: the setting of priorities" and, furthermore, cited that the manner in which the DOD prioritizes disease threats and research goals is unclear. [53] This deficiency was specifically addressed in one of the nine recommendations by the IOM: "Actively encourage the development, distribution, and use of a well-defined and validated research priority-setting mechanism, which could involve prioritized, weighted lists of infectious disease threats and formal scenario-planning exercises. To do so requires infectious disease surveillance and the collection and synthesis of epidemiologic information." [53]

The IOM report also noted that in the current climate of fiscal restraint, the prioritization of research efforts is an even more important component to optimizing research and development policy. This strategy will provide the DOD with a systematic,

evidence-based approach to decision making not only for the development of a vaccine for TD, but also for the evaluation of other military infectious disease threats.

Current research activities directed at protecting military personnel and travelers against the most common types of infectious diarrheal diseases by the use of vaccines target three bacterial agents: *Campylobacter* spp., enterotoxigenic *Escherichia coli* (ETEC), and *Shigella* spp. Several candidate vaccines are in various phases of basic research and development, but no vaccines directed at these three pathogens have been licensed in the US. Despite efforts to sustain a high quality research program, military investigators face many challenges, including the antigen variability of these causative organisms, the lack of protective mucosal immune response, and the lack of adequate resources for an optimal vaccine acquisition program.

Economic analyses of travelers' diarrhea and in military populations

In 1999, the IOM Committee to Study Priorities for Vaccine Development, commissioned by the National Institute of Allergy and Infectious Diseases, published the report entitled *Vaccines for the 21st Century: a tool for decision making*.[55] This report described a quantitative model that could be used by decision makers to prioritize the development of vaccines against a select number of infectious diseases considered to be significant domestic public health threats. Potential vaccines considered of domestic public health concern included vaccines against acute and chronic infectious diseases, autoimmune diseases, and cancers. Based on a societal perspective, the committee used a cost-effectiveness model to examine the trade-offs among various options using quality-

adjusted life years (QALYs) as the measure of utility in the prioritization of vaccine acquisition. Expert opinion and the published literature were used to develop estimates of model parameters. The committee categorized the results of their analysis of different vaccine strategies based on cost per QALY added:

Most Favorable	Saves money and QALYs
More Favorable	Costs <$10K per QALY saved
Favorable	Costs $10K - 100K per QALY saved
Less Favorable	Costs > $100K per QALY saved

A vaccine to prevent HIV/AIDS was excluded from the analysis due to the incontrovertable importance of this preventive intervention.

Of the 26 vaccines the committee considered, vaccines for ETEC and *Shigella* were included in a model of the cost-effectiveness of a vaccine to prevent diarrheal disease, specifically in a (non-military) traveler population. Both diarrhea models assumed 30% vaccine utilization in an adult traveler population, a vaccine efficacy of 75% over 3-5 years duration, 50% traveler susceptibility, no deaths due to disease, a purchase cost per dose of $50, a time to licensure of 7 years, and development costs of $240 million dollars per vaccine. Additional pathogen-specific assumptions for the model are outlined in Table 1.3.

While the IOM analysis found that vaccine acquisition policy for ETEC and *Shigella* in a traveler population was less favourable, based on *a priori* defined categories, caution should be exercised in applying these results to all traveler populations. The former US Surgeon General, Dr. David Satcher, made the following statement:

Table 1.3 Assumptions for economic analyses of a travelers' diarrhea vaccine acquisition policy

Pathogen	Incidence (per 100,000 person-years)	% of cases	Illness Duration (days)	Health Utility Index	Physician Visit	Re-hydration	Medication	Outcome Category
ETEC	225	90	4	0.75	15%	15%	100%	Less Favorable
	25	10	8	0.75	15%	15%	100%	
Shigella	11	100	6	0.47	75%	25%	75%	Less Favorable

Health Utility Index = relative measure of morbidity
Table adapted from [55]

> "The model determines cost effectiveness only from a societal perspective. While reasons to have done so are many, this approach has some unfortunate consequences. For example, priorities are often based upon cost effectiveness from the particular perspective of the organization making the investment, rather than for society as a whole. Further, the needs of specific components of society may be overlooked in such an analysis (e.g. the military and the need for a traveler's diarrhea vaccine)." [56]

Additionally, the use of QALYs as the standard outcome measure allowing comparisons across a heterogeneous group of diseases and potential vaccine candidates, is not necessarily the most appropriate measure for a specific disease in a specific population.[57] Furthermore, based on the health utility index used to assign values of morbidity, diseases that are acute and severe but without sequelae, tend to be undervalued.[57] In a military operational setting, days of work lost or days of decreased work performance may be more relevant outcome measures and have been traditionally reported. Additionally, the assumptions for the IOM's economic model related to disease risk and vaccine utilization are lower than what might be expected in a military population. Finally, a multiplex vaccine (ETEC, *Campylobacter*, and *Shigella*) acquisition strategy was not evaluated. Despite the limitations in the direct applicability of the IOM model to a deployed US military population, the methodology is rigorous and systematic and was, therefore, selected as a basis for the development of US military-specific economic analysis.

While no economic analyses of TD vaccine or treatment interventions have been conducted in deployed US military populations, several studies have investigated intervention strategies to prevent diarrheal disease in other vulnerable populations.[58-66] The majority focused on pediatric populations and other vulnerable populations in

developing countries. Two studies examined the cost-benefit of various intervention strategies for diarrhea in traveler populations. [59, 62] Reeves et al. evaluated strategies of chemoprophylaxis and antimicrobial therapy against the alternative strategy of no treatment among business travelers on three-, seven- and fourteen-day trips. Cost estimates for antimicrobial agents, medical expenses due to TD complications, adverse drug effects, and the inconvenience of a day of diarrheal illness, were estimated using the Delphi method of expert consensus. The cost of a day of incapacitation included unrecoverable daily expenses and airfare and was found to be the most important contributor to the mean cost of TD. Study investigators concluded that prophylaxis of TD ought to be considered as an option in individual situations and recommended further studies of its costs and benefits.

Thompson and Booth [62] conducted a similar cost-benefit analysis but used the published literature as a source for cost estimates, an improvement from the previous study. Furthermore, they compared three different prophylactic regimens and five treatment regimens. The cost of incapacitation due to TD during the period of travel was not quantified. In their discussion, the authors point out that the financial cost of an intervention may not be the most important consideration, since the intrinsic value of successful travel may be the overriding concern. The investigators recommended against prophylaxis, except in selected high-risk groups. They also favored only limited self-treatment with antibiotics, given the self-limiting nature and short duration of TD, as well as the potential for increased antimicrobial resistance with widespread use. These two studies were primarily conducted to compare chemoprophylaxis with appropriate, timely antimicrobial treatment.

While not comparing the cost-effectiveness of a specific intervention, a study by Steffen et al. reported the economic impact among 30,369 travelers returning from short-term trips (mean duration, 7.7 days) to Jamaica.[64] Based on an attack rate of 23.6%, the estimated average cost per trip for medication, medical treatment, and unrecoverable trip-related costs and missed opportunities was $116.50 per patient illness or $27.50 (range, $12.90 to $44.30) per traveler. While these economic studies specific to travelers' diarrhea do not evaluate a potential vaccine, they illustrate that primary prevention (chemoprophylaxis) may be beneficial in certain high risk groups. These results suggest that other primary prevention (immunization) strategies may also be cost-effective in high risk groups of travelers, warranting further evaluation.

A number of economic analyses of vaccine intervention strategies for diseases of importance to active duty military populations have been published [67-73] and are listed in Table 1.4. These studies used various methods for the estimation of model parameters, including secondary data analysis, the published literature, and expert opinion. In general, the results were sensitive to the outcome measure selected, as well as estimates of disease incidence. Costs for treatment and hospitalization were generally obtained from military-specific sources.

Table 1.4 Economic analyses of vaccine interventions in military populations

First Author Publ. Year	Disease	Military population	Vaccination policies compared	Findings
Howell 1998 [84]	Adenovirus	US Army recruits	1) Year-round vaccination 2) Seasonal vaccination, 3) No vaccination	Vaccination of recruits by any schedule cost-effective; seasonal immunization provided greatest cost savings
Hyer 2000 [85]	Adenovirus	US Navy recruits	1) Vaccination 2) Seasonal vaccination, 3) No vaccination	Seasonal or year-round vaccination cost-effective
Buma 1998 [82]	Hepatitis A	Dutch Marines	1) Passive immunization 2) Vaccination with screening 3) Vaccination without screening	Passive immunization most cost-effective for single 6-month deployment; vaccination without screening optimal for more frequent deployments
Jefferson 1994 [86]	Hepatitis A	British Army	1)Passive immunization 2) Vaccination	Active vaccination optimum, particularly when considering likelihood of multiple deployments
Gillis 2000 [83]	Hepatitis A	Israeli Defense Force	1) Passive immunization 2) Vaccination	Vaccination for deploying army soldiers; passive immunization for other groups.
Vold 2000 [87]	Strep. pneumonia	US Navy and Marine Corps	1) Vaccination 2) No vaccination	Vaccination cost-effective, but sensitive to side effects rate, disease incidence, and vaccine efficacy
Warren 1996 [88]	Typhoid fever in endemic region	US military	1) No vaccination 2) Vaccination pre-deployment 3) Vaccination among currently deployed	Vaccination not cost-effective unless deployment imminent or currently deployed

Statement of the problem

TD is clearly a common medical problem for military personnel deployed to developing regions of the world. The short-term morbidity associated with TD leads to increased health care utilization and lost days of work or travel. While there are some effective preventive interventions (e.g., environmental modification, sanitation, safe food and water, personal alimentary hygiene) and good clinical response with timely and appropriate antimicrobial therapy, the burden of disease remains high in these populations. There is growing concern about antimicrobial resistance and subsequent failures with empiric antimicrobial therapy.[74] Because of these concerns, the DOD, as well as other private industry and academic institutions have made it a priority to develop a vaccine to prevent travelers' diarrhea. However, the policy decision to pursue a vaccine acquisition strategy has not been based on sound epidemiological evidence and a thorough review of the costs and benefits of such a strategy compared with the current strategy of empiric antimicrobial therapy. This study is based on such an evidence-based approach.

Purpose of the study

As previously discussed, the current scientific literature on economic analyses of travelers' diarrhea and/or a vaccine acquisition strategy pertaining to a deployed US military population is lacking. Furthermore, the IOM recognized the need for evidence to

guide a systematic prioritization of research and development of vaccines by the DOD.[53] Based on a decision analysis model with a perspective specific to the US military, this study is designed to evaluate the cost-effectiveness of acquiring a vaccine against three pathogens identified by the DOD as primary candidates for vaccine research and development (i.e. ETEC, *Campylobacter* and *Shigella*).

In addition, this study will identify gaps in the knowledge base pertaining to pathogen-specific disease incidence, morbidity, and treatment outcomes associated with vaccine preventable TD in deployed US military populations and other similar high risk traveler populations in high risk regions to characterize and quantify the overall burden of TD.

Additionally, it outlines a method which may prove useful in prioritizing research and product development for other conditions of particular importance to the DOD.

Research goals and specific aims

Goals

- Characterize and quantify the pathogen-specific burden of travelers' diarrhea among deployed US military personnel and other similar traveler populations

- Evaluate the cost-effectiveness of a vaccine acquisition strategy against three primary causes of TD compared to current disease management in deployed US military personnel

- Develop a methodology that could be applied in the prioritization of other countermeasures for deployment health threats

Specific aims

1) Conduct a systematic review to develop best-estimates of pathogen-specific incidence and morbidity of travelers' diarrhea in deployed troops

2) Assemble an expert consensus panel and use the Delphi method to ascertain best estimates of important model parameters for which published literature is lacking and/or considerable uncertainty exists

3) Develop and evaluate an economic model determining the cost-effectiveness of a vaccine acquisition strategy compared with current clinical management approach

4) Using the economic model, determine relative cost-effectiveness of each individual pathogen-specific vaccine currently under development

General methods and organization of study

Based on a theoretical framework for the problem, estimates for various pathogen parameters were obtained from a systematic review of the literature and described in Chapter 2. These estimates included, pathogen-specific incidence (diarrheal episodes / person-time at risk) of ETEC-, *Campylobacter*- and *Shigella*-associated diarrheal disease

in US military and other similar traveler populations traveling to Latin America and the Caribbean, the Middle East and SE Asia; pathogen-specific morbidity (days of work lost/decreased performance, clinic visits, hospitalizations) associated with travelers' diarrhea in these populations and geographic regions; and pathogen-specific treatment outcomes (proportion of illness treated, post-treatment illness duration, antimicrobial failure, side-effects) in these populations and geographic regions. It was anticipated that for a number of parameters, particularly those related to vaccine development costs, development time frames and vaccine efficacy would be lacking from the available literature review. Therefore, a formal Delphi survey was undertaken with the aim of obtaining informed estimates from a panel of subject matter experts, of which the results are presented in Chapter 3. Based on a theoretic framework of the problem, data gathered from the systematic review, the Delphi survey, and addition sources, Chapter 4 describes the economic analyses using best available estimates of pathogen-specific travelers' diarrhea incidence, morbidity and treatment outcomes, as well as costs (related to research and development and health care), disease- and vaccine-related probabilities, development time-frames, and other important parameters specific to a deployed US military population.

Duty days lost and diarrhea illness days averted were the primary effectiveness endpoints used in the model. The average cost-effectiveness ratio (i.e. cost per unit adverse outcome averted) for a vaccine acquisition strategy was compared with current management of diarrhea during deployment. Secondary analyses were conducted for two scenarios: immediate availability of a vaccine and specific pathogen-region combinations. The influence of variables such as pathogen-specific disease incidence,

disease morbidity, treatment outcome, vaccine protective efficacy and duration, geographic region, length of deployment, and intervention side-effects were evaluated. Furthermore, subgroup analyses to determine if any subgroup of the population or pathogen-specific vaccine components might have a more advantageous cost-effectiveness profile were performed. Multi-way sensitivity analyses were used to evaluate how altering the parameter estimates within a reasonable range of values might affect the robustness of the model's conclusion.

Finally, Chapter 5 summarizes the study findings and provides conclusions, implications and recommendations for policy and decision-making, as well as for future research.

Chapter 2: Systematic Review of The Literature

Introduction

Infectious diarrhea continues to be one of the most common problems facing travelers abroad. A distinction is sometimes made in disease risk and/or pathogen distribution for short-term (< 2 weeks) travelers and populations living overseas for extended periods, such as military personnel, expatriates, students, and Peace Corps volunteers [75-78]. Epidemiologic investigations of infectious diarrhea in deployed military account for a majority of the published experience given the well-recognized continued threat.[1, 2, 19] Studies evaluating disease and non-battle injury rates in recent peacetime and combat operational settings have consistently identified infectious gastrointestinal illness among the top five reasons for clinic visits.[26, 30, 33-37] Since 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 et al. summarized pathogen etiology and attack rates by select geographic regions.[79] Their review was not limited to military and similar long-term traveler populations, did not include disease morbidity, and was completed before the advent of polymerase chain reaction (PCR) and other molecular diagnostic techniques for enteric pathogen identification.[7, 79] Furthermore, no previous studies have used a systematic methodology to combine estimates of disease incidence, morbidity, and treatment

outcomes in order to quantify a summary measure of pathogen-specific disease burden in selected geographic regions.

The primary objectives of this study were to obtain updated regional estimates of diarrheal disease incidence and pathogen-specific prevalence, as well as to describe morbidity and treatment outcomes among long-term travelers, including US military and similar populations, through a systematic review of the scientific literature.

Methods

This systematic review of the scientific literature was based on accepted principles of good methodological design and included criteria for eligibility, standardized data abstraction, critical appraisal of the quality of the evidence, and standard methods of data analysis.[80, 81]

Search strategy & study selection. A comprehensive retrieval of information was conducted using a stepwise procedure of searching personal files, performing searches in electronic bibliographic databases for published articles (including MEDLINE, EMBASE, CINAHL, and the Cochrane Library), hand-searching bibliographies of retrieved articles, searching databases containing technical reports (Defense Technical Information Center, National Technical Information Service), and electronic doctoral dissertations. All searches were initially performed using the term travelers' diarrhea or diarrhea, subsequently adding the following terms: epidemiology, etiology, military, peace corps, expatriate, incidence, burden, morbidity, and treatment. In addition,

MEDLINE searches were conducted using MeSH (Medical subject headings) terms from articles known to be eligible. The titles and abstracts of all articles published between January 1, 1990, and June 30, 2005, were screened by a single reviewer to determine if they met the eligibility criteria (box below). Those deemed to be irrelevant were excluded, and reasons for exclusion were noted. Eligibility decisions were reviewed with a second reviewer. When the information provided by the titles and/or abstracts was inadequate to determine eligibility, the full-text article was retrieved and evaluated. Review articles were obtained for the purpose of reviewing the reference lists.

Based on the goal and specific aims of this systematic review the following were used for eligibility criteria of included studies:

Inclusion criteria:

- Original research in the form of observational cohorts, surveys, database analyses or clinical trials
- Published in English language peer-reviewed medical journal between January 1990 and June 2005
- Conducted on military or similar traveler population
    - Any military, US or foreign (regardless of travel duration)
    - Similar traveler population defined as traveler population living abroad in an under-developed country, as well as any traveler in country for 1 month or longer

Exclusion criteria:

- Studies involving short-term tourists or business travelers' (< 1 month)
- Studies for which primary data could not be extracted

Study selection was based on the primary aim of developing stable estimates of disease incidence among long-term traveler populations with comparable risk profiles and environmental conditions. Studies were grouped by the following geographic regions: sub-Saharan Africa, Latin America and the Caribbean, SE Asia, and the Middle East.

Data abstraction & validation. Data from retrieved articles and reports were abstracted using a pre-tested, standard data abstraction form. Bibliographic information, study design, study years, geographic location, population characteristics, primary outcome measures, and other study characteristics (e.g., follow-up period, case definition) necessary to answer the key questions and to evaluate heterogeneity were included in the data abstraction form. Pathogen prevalence was recorded as a percent of total cases along with the denominator used to compute the prevalence. For consistency, pathogen prevalence was abstracted based on tables or text reporting the number of diarrheal samples in which a particular pathogen was isolated. As it was difficult to determine the exact etiology when more than one pathogen was identified, prevalence was reported as number of cases involving a particular agent, including cases with multiple pathogens. In clinical trials involving antimicrobial prophylaxis, the placebo control arm was used to estimate pathogen prevalence. Data on the prevalence of multiple pathogens was also abstracted when available. Incidence was preferentially abstracted or sometimes calculated as number of events with person-time as the denominator when available. The source of the number of events was also recorded as self-report, clinic-based, case series, or DNBI data. For studies conducted over a period of more than one year, the mid-point of the study period was recorded as the year of study.

To evaluate whether the validity of study design affected interpretation of the results, each article was scored for quality by two reviewers using standardized grading criteria specifically developed for prevalence and incidence systematic reviews.[82]

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 was assigned depending on whether the criteria was "not met", "partially met" or "fully met." All domains were assumed to be of equal importance to the validity of the study, and the scores were summed to create an overall quality score. Inter-rater reliability was assessed using a quadratic weighted kappa statistic. Abstraction and quality scoring was not blinded. Accuracy of data abstraction was reviewed and validated for all articles and abstraction forms by duplicate review. Data were entered into a database, and all entries were checked for accuracy by confirming the data in each abstraction form.

Analysis. The analysis of pathogen prevalence and incidence was stratified by region based on previously described geographic differences.[26, 79] A primary goal of this study was to define point estimates and confidence intervals for pathogen prevalence and incidence to be subsequently used 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. Heterogeneity was assessed graphically through the use of Peto plots, and statistically through the use of heterogeneity statistics and non-parametric methods. Point estimates and 95 percent confidence intervals were combined from various studies using a random-effects model developed by DerSimonian & Laird [83] and reported as a summary measure using point estimates with 99% confidence intervals. This method is considered

more conservative compared to a fixed effects model and uses weights for both intra- and inter-study variance. We chose to use 99% confidence intervals to assure a more inclusive estimate for any given prevalence or incidence.

Heterogeneity was assessed statistically using a χ^2 test for heterogeneity, and potential sources of heterogeneity were assessed graphically by Peto 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 were reported. Since a principal purpose of this systematic review was to summarize the results of studies reporting pathogen prevalence and diarrhea incidence, rather than an evaluation of intervention effectiveness, publication bias was not assessed. There was little concern for non-published findings due to negative studies or disappointing results.

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

Results

In total, 262 studies were identified as eligible, of which 49 articles fulfilled all criteria and were considered suitable for inclusion in the analysis. These were abstracted and scored for quality. The study selection process is detailed in Figure 2.1. One study reported incidence estimates and treatment probabilities stratified by three regions and

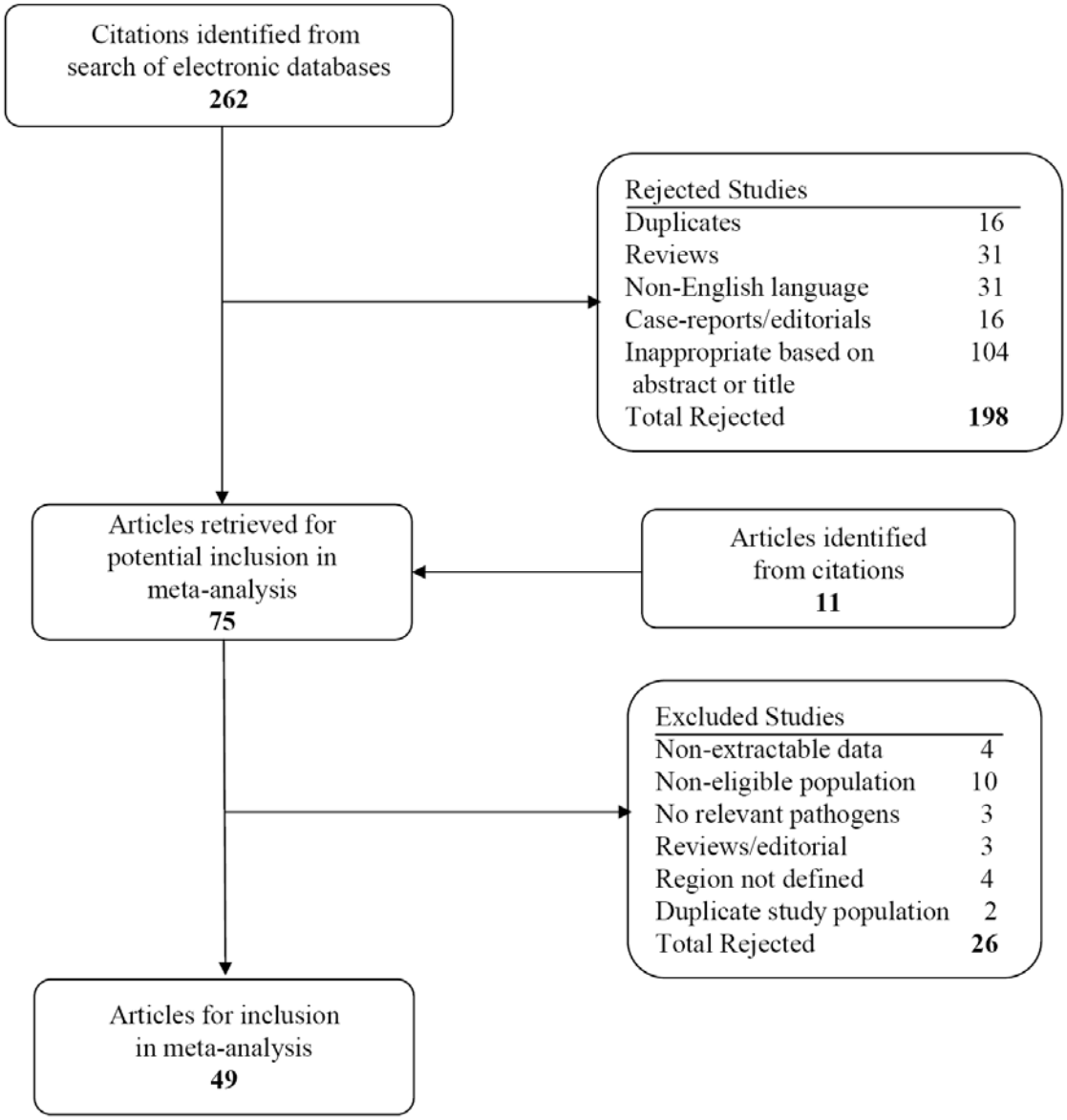

Figure 2.1 Flow diagram of study selection for inclusion in the systematic review

another study reported pathogen prevalence distributions stratified by two regions. These studies were abstracted separately by region and treated as individual studies in the analysis. Table 2.1 provides descriptive details of the 52 included studies.

Table 2.1 Characteristics of studies included in the systematic review of travelers' diarrhea

Ref. No.	*First Author*	*Publ. Year*	*Year(s) of Study*	*Study Design*	*N*	*n*	*Country*	*Duration Travel*	*Ppopulation*	*Setting*	*Quality Total (areas)*
R E G I O N											
Sub-Saharan Africa											
[7]	Bourgeois	1993	1985-1987	Descriptive	740	47	Multiple		US Military	RD	8.5 (G)
[29]	Sharp	1995	1992-1993	Descriptive	1225	113	Somalia	2	US Military	HA&P	14.5
[84]	Sharp	1995	1992-1993	Descriptive	138		Somalia		EE&NGO		4 (ACF)
Latin America / Carribean											
[85]	Adachi	2003	1999-2001	Clinical Trial		217	Mexico	3	Student		8 (A)
[7]	Bourgeois	1993	1985-1987	Descriptive	1625	242	Multiple		US Military	RD	8.5 (G)
[86]	Dupont	1992	1998-1990	Clinical Trial		191	Mexico		Student		5.5 (ABF)
[87]	Dupont	1998	1996	Clinical Trial		72	Mexico		Student		4 (AC)
[88]	Dupont	2005	2003	Clinical Trial		54	Mexico		Student		10
[89]	Ericsson	2001	1994-1995	Clinical Trial		88	Mexico		Student		4.5 (ACFG)
[90]	Heck	1993	.	Clinical Trial		30	Multiple	0.5	EE&NGO		8.5 (G)
[75]	Herwaldt	2000	1991-1993	Cohort	36		Guatemala	26	Peace Corps		11 (C)
[91]	Jiang	2000	1992-1997	Descriptive		928	Mexico	1.25	Student		8 (F)
[92]	Miser	1995	1989-1990	Descriptive	471		Panama	0.75	Military	Combat	8.5 (DG)
[93]	Pazzaglia	1991	1984-1989	Descriptive		655	Peru	21	EE&NGO		4.5 (ABF)
[94]	Salam	1994	1993	Clinical Trial	180		Belize	2	For. Military	RD	4 (DEFG)
[26]	Sanchez	1998	1981-1984	Mixed Design	538*		Multiple	0.75	US Military	RD	10.5
[43]	Thornton	1992	1986-1987	Clinical Trial		142	Multiple		US Military	RD	8.5 (G)
Middle East											
[95]	Cohen	1992	1987	Cohort	423	77	Israel	2.5	For. Military	RD	7 (G)
[96]	Cohen	2001	1993-1997	Cohort	6426	2197	Israel		For. Military	RD	12.5
[17]	Haberberger	1991	1987	Cohort	4500	183	Egypt	1.3	US Military	EX	5 (FG)
[18]	Haberberger	1994	1988	Descriptive	5000	118	Egypt	0.25	Military	RD	9.5
[97]	Haberberger	1994	1985-1987	Descriptive		126	Egypt		EE&NGO		10 (FG)
[19]	Hyams	1991	1990	Descriptive	2022	432	S. Arabia	2	US Military	Combat	9 (A)
[98]	Hyams	1993	1990-1991	Cohort		304	Kuwait	5	US Military	Combat	9.5
[99]	Hyams	1995	1990	Descriptive	830		Multiple	4.3	US Military	Combat	9 (G)
[100]	Johnson	1992	1990	Case-Control		73	Egypt	6.5	US Military	Combat	4.5 (BG)
[20]	Oyofo	1995	1993	Descriptive	3284	36	Egypt	0.75	US Military	EX	6 (CFG)
[21]	Oyofo	1997	1995	Descriptive	1200	19	Egypt	1	US Military	EX	7 (FG)
[23]	Paparello	1993	1990-1991	Descriptive	722		Persian Gulf		US Military	Combat	12.5 (E)
[25]	Rudland	1996	1991	Descriptive	108		Iraq	1.25	For. Military	Combat	7.5 (CD)
[26]	Sanchez	1998	1981-1989	Mixed Design	528*		Multiple	1	US Military	RD	10.5
[101]	Sanders	2005	2000	Mixed Design	3725	129	Egypt	2	US Military	EX	10.5

Table 2.1 (continued)

Ref. No.	*First Author*	*Publ. Year*	*Year(s) of Study*	*Study Design*	*N*	*n*	*Country*	*Duation Travel (months)*	*Population*	*Setting*	*Quality Total (problem areas)*
Middle East (continued)											
[102]	Scott	1990	1988	Clinical Trial		17	Egypt	0.25	US Military	RD	10 (F)
[45]	Taylor	1991	1989	Clinical Trial	162	104	Egypt	0.75	US Military	EX	8 (CG)
[103]	Taylor	1997	1990-1991	Descriptive	204		Kuwait	7.5	US Military	Combat	8 (FG)
[104]	Thornton	2005	2003	Descriptive		129	Iraq		US Military	Combat	6 (DEF)
[105]	Willshaw	1995	1990-1991	Descriptive		181	S. Arabia		For. Military	Combat	4.5 (AEFG)
Southeast Asia											
[4]	Adkins	1990	1985	Cohort	1914	100	Multiple	1.75	US Military	RD	6 (BG)
[106]	Arthur	1990	1988	Clinical Trial	993	296	Thailand	1.25	US Military	EX	10 (F)
[5]	Beecham	1997	1996	Descriptive	170	16	Thailand	0.75	US Military	EX	9
[34]	Buma	1999	1992-1993	Cohort	2283		Cambodia	5.1	For. Military	HA&P	8 (DEF)
[12]	Echeverria	1993	1993	Cohort	333	24	Thailand	1	US Military	EX	10 (F)
[76]	Hoge	1996	1992-1993	Case-Control	70	69	Nepal	9	EE&NGO		7.5 (A)
[41]	Kuschner	1995	1993	Clinical Trial		72	Thailand	1	US Military	EX	7 (C)
[107]	Lesho	1994	1992	Descriptive	1159		Thailand	1.5	US Military	EX	4.5 (DG)
[50]	Murphy	1996	1994	Descriptive		104	Thailand	1	US Military	EX	7.5 (CF)
[22]	Oyofo	1999	1996	Descriptive	721	49	Multiple	3	US Military	RD	9.5 (G)
[44]	Petruccelli	1992	1990	Mixed Design	169	137	Thailand	1	US Military	EX	10 (G)
[26]	Sanchez	1998	1981-1990	Mixed Design	836*		Thailand	1	US Military	RD	10.5
[108]	Sanders	2002	1998	Descriptive		143	Thailand	3	US Military	EX	10
[109]	Shlim	1999	1994-1995	Cohort	77	158	Nepal	11	EE&NGO		9.5 (F)
[110]	Walz	2001	1995	Mixed Design	369	170	Thailand	1	US Military	EX	9.5

N = population denominator used for incidence estimation
n = population denominator used for pathogen etiology prevalence or other parameter estimation.
Duration travel in months
Setting: RD = Routine Deployment, EX = Exercise, HA&P = Humanitarian Assistance & 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
* = Median value of deployed population denominator

Study characteristics. Overall, there were 20 studies (38%) from the Middle East, 15 (29%) from SE Asia, 14 (27%) from Latin America and the Caribbean, and four (8%) from sub-Saharan Africa. A majority of the studies were conducted among US military populations (n = 33, 63%) with foreign military, expatriate (including non-governmental organizations and Embassy populations), and student populations each comprising approximately 12% of the included studies. Median duration of travel for these populations was 1.5 months with an interquartile range (IQR) of 1 – 3 months (range 1 week – 26 months), among the 41 (79%) studies providing this information. Twenty-four of the studies (46%) were descriptive surveys, 12 (23%) were clinical trials, nine (17%) were cohort studies, five were mixed designs (usually an observational study with an added survey component), and two were case-control. A standard definition for diarrhea ($\geq$ 3 loose stools in a 24 hour period OR $\geq$ 2 loose stools in a 24-hour period with associated symptoms) was used in 36 (69%) of included studies. The 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 available in a majority of studies, including gender and age. While the eligible period for year of publication was between 1990 and 2005, the median year that the studies were actually conducted was 1992.

Study quality. There was good agreement of quality ratings between the two observers (K = 0.73) with scores ranging from 3 to 14 (out 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) included the use of standard outcome measures and applicability of study population, whereas the domain for analysis quality 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 better overall median scores (11, IQR 10-11) compared to 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 to non-US military studies (median 9 vs. 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 2.2. 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 appear to be due to SE Asia having relatively lower prevalence of ETEC and a higher prevalence of *Campylobacter* and *Salmonella* compared to other regions. ETEC was the most common pathogen identified in Latin America and the Caribbean, as well as in the Middle East, accounting for 27% and 29% of cases, respectively. While *Campylobacter* accounted for nearly a quarter of all cases in SE Asia, ETEC was also common, accounting for nearly 1 out of every 6 cases. The two studies from sub-Saharan Africa describe ETEC and *Shigella* as important pathogens accounting for approximately 16% and 6% of pathogens, respectively. *Salmonella* was reported in a majority of studies in each of the regions and was highest in SE Asia (11%), compared to regions of the

Table 2.2 Summary of pathogen prevalence and diarrhea incidence among US military and similar populations overall and by region

	Geographic Region				Summary Estimate (99% CI)
	Sub-Saharan Africa*	Latin America & Caribbean	Middle East & N. Africa	Southeast Asia	
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 identified	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

Middle East (2%) 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 6% - 22%, norovirus 5% - 16%, and rotavirus 2% - 6%. Multiple pathogens were also common and higher in SE Asia, accounting for 15% of cases. Other regions had a lower frequency of multiple pathogens of 7% - 9% (with the exception of sub-Saharan Africa, which reported 4% and 13% in two studies).

There was marked heterogeneity among studies estimating prevalence for individual pathogens in all regions (χ^2 test for heterogeneity, $p<0.001$ 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 due to the small

number of studies in subgroups of the independent variable. However, there were differences in prevalence of individual pathogens when stratified by type of population, with the US military experiencing a lower prevalence of *Shigella* (median 2% vs. 7%, Mann-Whitney U, p=0.02), and higher prevalence of any identified pathogen compared to other populations (median 52% vs. 42%, p=0.04). Higher study quality (measured by increasing tertiles) was associated with increasing prevalence of pathogen recovery across studies (nonparametric trend, p=0.047). While not statistically significant, the probability of recovering a pathogen demonstrated an increasing trend by year of study activity (r=0.29, p=0.11). As previously described, there was an association between study quality and study population, with US military studies demonstrating higher quality. In assessing confounding, there was an association between year of publication and population type, with a median study year of 1990 for US military studies compared to 1993 for non-military studies (Mann-Whitney U, p=0.08). However, if year of study was confounding the association between overall quality and population type, one would expect the median year of study to be higher in US military populations. Small numbers limited further evaluation of heterogeneity due to 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 among studies used to estimate diarrhea incidence (χ^2 test for heterogeneity, p<0.001). Table 2.2 describes the summary incidence estimates by region stratified by method of data collection: passive (clinic-based studies, DNBI data) and active (cohort studies, surveys). There did not appear to

be any association between regional specific-incidence graphically or statistically (data not shown). The incidence rate changed, according to the method of measurement, with studies based on self-report (e.g. post-deployment/travel questionnaires and cohort studies) being higher (29 cases per 100 person-months) compared to 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, higher incidence was noted in non-military populations compared to both foreign and US military populations (Kruskal-Wallis, p=0.04). However, this association may be confounded by method of estimating incidence through self-reported events, which was higher in non-military studies. No association between incidence and other variables such as study design, quality, use of standard definition, or duration of travel was identified.

Table 2.3 Probability of seeking treatment for diarrhea

Ref	Author	Region	Size	Clinical Encounter Incidence	Self-reported Incidence	Probability of Seeking Treatment
[4]	Adkins	SE Asia	1914	3	50	0.06
[106]	Arthur	SE Asia	253	6	39	0.15
[5]	Beecham	SE Asia	170	16	53	0.30
[18]	Haberberger	Middle East	155	12	85	0.14
[17]	Haberberger	Middle East	4500	4	34	0.12
[19]	Hyams	Middle East	2022	.	.	0.22
[23]	Paparello	Middle East	722	.	.	0.08
[26]	Sanchez	Middle East	528	.	.	0.32
[26]	Sanchez	SE Asia	836	6	24	0.25
[26]	Sanchez	Lat Am & Carrib.	538	.	.	0.29
[101]	Sanders	Middle East	3725	.	.	0.25
[110]	Walz	SE Asia	369	8	35	0.23
	Median			**6**	**39**	**0.225**

Incidence = events per 100 person-months; SE = Southeast

Twelve studies reported data that allowed the estimation of the probability that an individual might seek treatment if they became ill with diarrhea (Table 2.3). Eight of these included estimates of self-reported incidence and clinic-based incidence (visits to a medical treatment facility). Overall a median of 23% (IQR 12 - 29%) of individuals who became ill with diarrhea sought treatment at a medical treatment facility. The variability in the probability of seeking treatment could be explained.

Table 2.4 Disease outcomes associated with treated and untreated diarrheal disease

Outcomes duration (days)	No. of Studies	Mean (value)	Median	IQR	Min, Max
Pre-treatment symptoms	13	1.4	1.5	1.3-1.5	0.3, 4.1
Post-treatment symptoms	8	1.4	1.4	1.0-1.8	0.6, 2.2
Regimen w/ loperamide	2	1.1	1.1	na	0.7, 1.4
Regimen w/o loperamide	6	1.7	1.7	1.5-1.8	1.3, 2.2
TLUS (no loperamide)	3	0.6	0.5	na	0.5, 0.9
SIQ or incapacitation	1	(1.4)	na	na	na
Hospital admission	1	(2.5)	na	na	na
Symptom duration in non-treatment seeking individuals	9	3.1	3	2.6-3.5	2.1, 4.3

na = not applicable; TLUS = time to last unformed stool; IQR = interquartile range; SIQ = sick in quarters

Morbidity. Seventeen studies had extractable information providing probability estimates of outcomes associated with disease and treatment (Table 2.4). Eight studies (7 clinical trials, 1 case-control study) reported no adverse events with antibiotic treatment in 1,045 clinical visits (Binomial exact 95% CI: 0 - 0.0035).[41, 43-45, 87, 89, 94, 100] A median probability of treatment failure of 5% (Range, 3 – 9%) was found among six trials providing this data.[41, 44, 85, 86, 101, 108] 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 symptom 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 incapacitated due to the illness.[5, 12, 18, 19, 23, 96, 101, 108, 110] Four studies reported the probability of requiring intravenous hydration (IV) ranging from 0 to 18%.[5, 29, 108, 110] Two studies (from the same reference) reported provider estimates of the probability of hospitalization due to diarrhea among those seeking treatment to be 10% and 13%.[26]

Twenty studies had extractable information on the course of diarrhea, with twelve finding that the pre-treatment duration of symptoms was 1.3 days (IQR 1.1 – 1.5 days). Post-treatment duration ranged from less than one day to just over two days, and there was a trend towards a shorter post-treatment duration in studies where an antibiotic regimen included an anti-motility agent such as loperamide (n=2) compared to studies with antibiotics alone (n=5) (median 1.1 vs. 1.7 days, respectively, 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 2.5.

Table 2.5 Pathogen-specific diarrheal illness probability or outcomes

			Pathogens			
Probability (P) or Outcome	**Ref.**	**Region**	***Campy***	**ETEC**	***Shig***	**Other**
(P) SIQ/incapacitation	[96]	Middle East	.		0.56	0.27
(P) SIQ/incapacitation	[19]	Middle East	.	0.21	0.64	.
(P) SIQ/incapacitation	[110]	SE Asia	.	.	0.92	0.46
Post-RX duration duration of symptoms, days*	[41]	SE Asia	1.6	.	.	1
Post-RX duration of symptoms, days*	[29]	sub-Saharan Africa	.	2.2	2.9	1.9
Total duration of symptoms, days	[108]	SE Asia	3.3	.	.	1.6
Total duration of symptoms, days	[96]	Middle East	.	.	7.1	5.1

*no loperamide; RX = treatment; Campy = *Campylobacter*; Shig = *Shigella*

Discussion

In this review, pathogens were identified in a majority of specimens with an overall pooled estimate of 55%, and five studies demonstrated identification rates of 80% or more. This finding compares favorably to the 1990 review by Black et al.[79] that reported a pooled estimate of pathogen recovery of 45% (t-test, p=0.06, data not shown). It is possible that better techniques and recovery methods were factors in the observed improvement, although approximately one-fourth of studies were conducted prior to 1990. While this review did not specifically look at the pathogen identification techniques utilized, a trend was found towards an increased pathogen recovery rate over time of ~1% per year for studies conducted between 1985 and 2003 (p=0.11). In addition to quality of study, studies conducted among US military populations were associated with higher pathogen recovery rates. This was probably because military usually established advanced laboratories in the field environment, where collected samples are immediately processed and cultured, and pathogens are isolated. In contrast, non-US military studies often relied on storage and transport of specimens to a distant laboratory location. Additional assessment of confounding between these factors could not be accomplished due to small numbers of studies.

An additional important finding was that studies conducted in the SE Asia region tended to have higher pathogen recovery rates compared to other regions (χ^2 test, 61% vs. 50%, p = 0.1). Possible explanations include factors involving the characteristics of studies conducted in this region or other possible factors inherent to the region. While there were no differences in study design or quality by region, there were more US

military studies conducted in the SE Asia region (χ^2 test, 80% vs. 56%, p = 0.2). Another possible explanation includes regional differences in pathogen etiologies. *Campylobacter* is known to cause more severe disease than most other common diarrheal pathogens.[12, 108, 111, 112] Therefore, regions with a predominance of *Campylobacter* infections (or more severe diarrhea), may result in more patients presenting for treatment, thus higher rates of pathogen identification. Extractable data on severity of diarrheal disease was not available for all studies, and thus, the relationship between severity of disease and pathogen identification could not be assessed.

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

The self-reported incidence of diarrheal disease in the long-term traveler population which we describe is relatively low, compared to estimates reported from business/leisure travelers. [79] Compared to the Black et al. review which reported a summary incidence rate of 60 cases per 100 person-months (95% CI: 47 - 73 cases per100 person-months), our finding of 29 cases per100 person-months (among cohort and self-reported incidence data) is much lower (Kruskal-Wallis $p < 0.0001$, data not shown).

Possible explanations include differences in populations and/or changes in risk behavior of travelers over time. Our current review consists of studies with relatively more US military populations, no tourists, and longer travel durations compared to the Black et al. study. Given these distinctions, high attack rates among populations with shorter travel durations may explain the differences in the incidence estimates. Also, deployed military populations, with controlled food and water distribution systems, may account for the lower incidence of diarrheal disease compared to other travelers. Secular trends in risk behavior perhaps due to the advent of pre-travel counseling and emergence of travel medicine as an independent discipline may also help to explain a decrease in incidence over time. In fact, when studies from the Black et al. article and the present study are combined, we find an inverse association between year of study (published) and incidence (Spearman's Rho = -0.6, $p < 0.001$), a trend which persists with the exclusion of US military studies (Spearman's Rho = -0.33, $p=0.07$) (data not shown).

Specific to the US military, there are a number of possible reasons 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 nothing would be done to treat the condition. None of the studies reported reasons why individuals chose not to seek care. However, the study by Hyams on US military troops in the first Gulf War reported that of those that not seeking treatment for diarrhea, 20% used antibiotics, suggesting self-treatment may have played a prominent role.[19] 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). Travelers' diarrhea is generally thought to have a median illness duration of 3 to 4 days. Thus it does not appear that the diarrhea illness

experienced by those not seeking treatment is any less severe, although further studies defining these disease episodes not encountered by medical providers are warranted.[113]

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 systematic review also highlights the importance of other pathogens including norovirus, rotavirus, and EAEC, which constituted approximately 20% of identified pathogens recovered. Furthermore, because the case definition of most studies focused on illness with diarrhea and vomiting, but not vomiting alone, this review may have underestimated the burden of acute enteric infectious disease due to norovirus, rotavirus and other enteric viruses that often cause an illness with vomiting as the predominant symptom. The overall burden of these enteric viruses is beginning to be understood, but more surveillance is needed to further characterize the incidence and morbidity of diseases associated with these agents compared to TD and other infectious diseases of military importance.[104, 114-116]

While only a few studies reported on outcomes of disease and treatment, a number of findings important for medical decision modeling emerged. First, one-quarter of individuals seeking treatment are reported to be incapacitated due to illness. Among these, 10% required hospitalization. Admittedly, this estimate seems high based on the field experiences of a number of the study authors. These estimates could be overstated due to 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 IV 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. There were too few studies available to obtain estimates for pathogen-specific disease outcomes and treatment responses due to ETEC, *Campylobacter* and *Shigella*. The increased severity and duration of illness due to *Campylobacter* and *Shigella* compared to other pathogens were noted in only a few studies and need further investigation to assess their importance in these traveler populations. However, these findings are consistent with previous studies on the epidemiology of these potentially invasive enteric pathogens.[12, 108, 111, 112, 117]

The present review is based on a systematic and comprehensive literature search, including explicit inclusion and exclusion criteria, a standardized data abstraction form, quality scoring, and appropriate analytic methods, all of which reduced potential bias in the selection of studies used for analysis. Limitations of this review include the significant heterogeneity among studies with respect to study design, population and study location or setting. These and other factors resulted in large variability in prevalence and incidence estimates across studies. In addition, sparseness of data in some studies, particularly related to pathogen-specific disease probabilities and outcomes, was also a limitation. While a number of independent variables were found to explain some of the heterogeneity, small numbers precluded further sub-group analyses to explain differential pathogen prevalence and incidence. Caution should be exercised in generalizing these estimates to an entire geographic region, as many of the articles came from serial studies of the same populations in a particular country (e.g., Bright Star Exercises in Egypt, Cobra Gold Exercises in Thailand, student populations in Mexico). Furthermore, the exclusion of leisure and business travelers from these analyses should

be considered in generalizing the results to all travelers. However, a review of studies excluded on the basis of population non-eligibility did not find appreciable differences in estimates than what we described.[118-122] In addition, as this review demonstrates, collapsing US military populations with other similar long-term traveler populations presents a challenge. Furthermore, there is clearly a gap in epidemiologic data from important regions of India, China, Oceana and Sub-Saharan Africa. In particular, more epidemiologic studies in sub-Saharan Africa need to be conducted to better describe the regional incidence and pathogen prevalence in this important geographic region.

Finally, this systematic review focused primarily on endemic or sporadic diarrheal disease that occurs in the populations of interest. While these are important and contribute to a large burden of disease, pathogens which have the potential to cause epidemic disease also needs to be considered, particularly for military populations. Bacterial and viral agents having the potential to cause explosive and debilitating outbreaks may be just as important, from a military perspective, as the agents that cause a heavy burden of endemic disease [114, 123, 124]. In this respect, a study conducted among Israeli Defense Forces during routine deployment found that while sporadic cases of diarrheal disease were caused by a number of different pathogens, most outbreaks were associated with *Shigella*, norovirus or *Salmonella* [95]. The impact of these agents with epidemic potential has been described anecdotally in a number of studies. One study included in this review was conducted among US Air Force personnel and reported that the onset of diarrheal illness in five of 222 airmen during a single day had an adverse operational impact. [12] Another study reported that a flight mission was aborted mid-flight due to sudden onset of gastrointestinal illness in the pilot [5].

Conclusion

This systematic review of studies related to diarrhea in long-term travelers, including US military and similar populations, leads to some certain conclusions. First, diarrhea is a frequent occurrence, and a large number of cases are not seen by a health care provider where effective antibiotic therapy is available to be administered. It remains to be determined whether this unencountered illness represents milder illness or illness that is being successfully self-treated. Second, ETEC, *Campylobacter*, and *Shigella* bacteria are significant global pathogens, and the latter two also appear to be associated with more severe symptoms, often of longer duration. Third, a number of other bacterial, viral, and parasitic pathogens, including EAEC, *Salmonella*, norovirus, and rotavirus, should continue receiving attention as important diarrheal pathogens in these populations. Further assessment of infections with multiple pathogens is needed. Lastly, conditions leading to high disease incidence requiring treatment, disease incidence among individuals who do not initially seek treatment, and incapacitation due to illness, should be considered potentially important public health threats and addressed with further studies. Future studies need to focus on timely and effective clinical management, as well as other strategies, such as vaccines to prevent these infections.

Chapter 3: Delphi Survey

Introduction

The DOD, as well as other private industry and academic institutions have made it a priority to develop a vaccine to prevent travelers' diarrhea. However, the policy decision to pursue a vaccine acquisition strategy should be based on decision making principals, which include sound epidemiological evidence and a thorough review of the costs and benefits of such a strategy compared with current empiric antimicrobial therapy.[53, 56] Formal decision making methods allows a careful elaboration of the treatment options, potential outcomes, both good and bad, and provides a tool to make the decision after careful analyses. While there is a wealth of published epidemiologic literature on the incidence, etiology, and health outcomes for diarrhea among deployed troops,[19, 26, 50, 101, 108, 125-128] there are important gaps in the knowledge required to construct formal decision analysis models. Specific areas of inadequate information include health care seeking behavior, management practices, as well as vaccine development time horizons. Therefore, the primary objective of this study was to obtain parameter estimates and ranges of uncertainty related to clinical epidemiology and vaccine development for TD that are required to inform a decision-analytic model. Specific areas included treatment norms and anticipated outcomes associated with diarrhea in deployed military populations, vaccine development time frames, and acceptable vaccine performance attributes. Additional questions were designed to ascertain estimates of parameters related to vaccine product development targets,

including effectiveness, safety, and of practical applicability, number of doses, and dosing time frame.

Methods

Overview. This study used the Delphi survey technique with the following modifications made based on study requirements [129, 130]. In collaboration with the co-author of the manuscript (DT), the structured questionnaire for subject matter experts was developed *a priori*. After an initial solicitation for participation, a series of 3 rounds were conducted using the same questions with the range of parameter estimates changing based on response of the group. During the first two rounds, panelists were asked to select from a range of estimates, while the 3rd round only asked for their opinion on whether they agreed or disagreed with the final consensus estimate.

Expert panel solicitation and selection. For the purposes of this study an expert was defined as someone who has a known or stated interest in diarrheal disease among deployed US military and/or vaccine development for travelers' diarrhea. Nominations of subject matter experts were solicited from colleagues and others in the academic community. Invited expert panelists were informed of how they were nominated in a letter of introduction. The panelist's primary qualification was their subject matter expertise in the required areas of knowledge. Forty-three experts in the following areas were invited to participate in the Delphi survey including: Vaccine Industry (n = 5)**,** Academic/Military Diarrhea Vaccine Development (n = 15)**,** Military Product

Acquisition (n = 7)**,** Military Preventive Medicine (n = 6)**,** Tropical/Travel Medicine (n = 6)**,** and Military Clinical Infectious Disease (n = 4).

Though panelists were identified based on their current occupation, it was anticipated that many would also have direct experience in one or more of the other related categories. Potential panel members were informed of the study goals and objectives as well as the amount of time and effort that would be expected.

Preparation and distribution of the initial survey instrument. An initial survey instrument (Appendix A) was developed and pilot tested to obtain quantitative estimates for the identified parameters. For each question, the panelist was asked to provide a response to a question based on their knowledge and expertise and to also rate the degree of uncertainty placed on their estimate by qualifying there response to a three level question ranging from "not at all certain" to "very certain." Individuals were not required to answer every question if they felt unqualified to make an estimate. Questions were asked regarding current occupation, years of experience, and prior experience in the six areas of knowledge. This survey instrument was distributed to panelists via e-mail and a web-based platform called Surveyz™ (Qualtrics, Provo, UT). A mailed survey was also made available upon request. The panelist's responses were kept anonymous.

Questions related to a select list of enteric vaccines currently under development by the DOD (*Campylobacter*, ETEC, *Shigella*) were chosen. In addition, vaccines for three pathogens were included as comparators. Enteroaggregative-E. coli [EAEC] was selected, as it has gained prominence as an enteric pathogen causing diarrhea, but there were no published pre-clinical studies evaluating potential vaccine candidates. Norovirus

(NV) was included as a known pathogen of military importance, though the DOD currently lacks a vaccine development program. And finally, though not a major pathogen of concern to the military, rotavirus (RV) vaccine was selected for purposes of comparison as the vaccine was pending Food and Drug Administration (FDA) approval and licensure in the US.

Survey rounds. Participants were initially given two weeks to return their responses for each survey round. Two reminders were sent during the two weeks to complete the survey. If after two weeks a minimum response rate of 75% was not achieved, a 1-week extension was provided. For the first survey round, data from all panelists who answered the particular question were analyzed. Based on the frequency distribution of answers, a refined (narrower) estimate range based on at least a two-thirds majority was developed for each question. A second survey round was similarly conducted. Responses from the second round were analyzed by frequency distribution. Because of the diverse background and experience of the panelists, ranges of the estimates were further refined by limiting responses to those panelists with a minimum of 5 or more years of experience (current and previous) in a particular content area. (e.g., responses to clinical management-related questions were limited to panelists with experience in travel/tropical medicine or military infectious diseases). Based on this analysis, a range of estimates for each question, which incorporated at least 75% of the panelist's responses, were developed and asked in a final third survey round, and responses of agreement or disagreement were recorded. The results of the study were compiled and provided to all panelists.

This study was reviewed and approved as an exempt study by the Institutional Review Board at Uniformed Services University of the Health sciences. Informed consent was implied by participation in the study.

Results

Among the 43 invited panel experts, 25 (58%) chose to participate in the survey, three declined participation and 15 did not respond. Participating panelists included the following areas of expertise: Vaccine Industry (n = 3)**,** Academic/Military Diarrhea Vaccine Development (n = 6)**,** Military Product Acquisition (n = 5)**,** Military Preventive Medicine (n = 5)**,** Tropical/Travel Medicine (n = 2)**,** and Military Clinical Infectious Disease (n = 4). Figure 3.1 is a graphical representation of the Delphi study methodology.

Twenty-three of twenty-five (92%) expert panelists completed the Delphi round one survey. Seventeen of twenty-three reported having ten or more years of experience in their current profession, and all reported more than five years in one or more of the other related areas of expertise. Seventy percent reported having worked directly in support of deployed US troops. Table 3.1 describes the consensus panel ranges and relative level of uncertainty for parameter estimates related to management of diarrhea in the deployed setting among those who seek treatment and those who self-treat. Anti-motility agents, loperamide or bismuth subsalycilate (BSS), alone or in combination with an antibiotic were considered to be the most common treatment options provided to

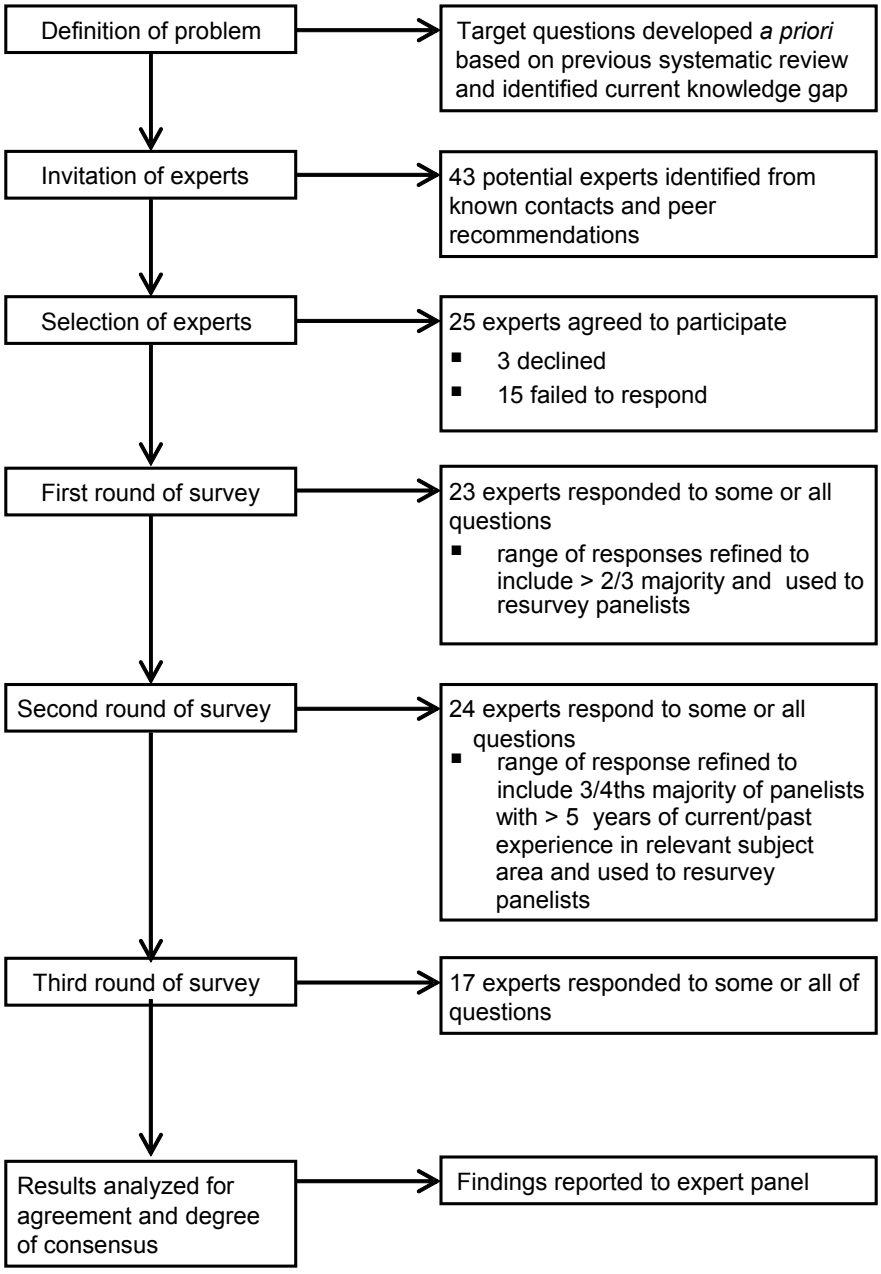

Figure 3.1 Flow diagram of modified Delphi survey to develop consensus estimates in the area of epidemiology, clinical management and vaccine development of diarrheal disease in deployed US troops

Table 3.1 Consensus estimates of first and final Delphi rounds for uncertain parameters related to disease management

Parameter Estimate	First Round (n=23)		Third Round (n=17)	
	Response Range (% panelists in range)*	% Not at all certain	Consensus Estimate (range)	% Agree
Typical management amog those who seek care for diarrhea when deployed (%)				
Loperamide or bismuth salycilate ALONE	10 - 50 (68)	47	20 (10 - 30)	77
Antibiotics ALONE	0 - 25 (85)	47	18 (11 - 25)	71
Antibiotics PLUS anti-motility agent	10 - 50 (74)	47	30 (10 - 50)	77
NONE	0 - 25 (69)	47	15 (6 -25)	77
Typical self-treatment (%)				
Loperamide or bismuth salycilate ALONE	0 - 50 (84)	53	20 (5 - 35)	94
Antibiotics ALONE	0 - 10 (68)	53	3 (0 - 5)	77
Antibiotics PLUS anti-motility agent	0 - 25 (95)	58	5 (0 - 10)	82
NONE	10 - 90 (90)	58	60 (30 - 90)	94
Self-treatment outcomes (%)				
Continued morbidity after 3 days	10 - 25 (70)	40	15 (10 - 20)	82
Among those with continued morbidity, additional treatment will be needed	10 - 75 (75)	30	25 (10 - 40)	71

*may not add to 100% due to rounding

those who sought care (response for each option ranged from 10% to 50%). For those who self-treat, no treatment (10% – 90%) or loperamide or BSS alone (0% – 50%) were regarded as the most common strategies. Ranges of estimates were extended to include a two-thirds majority of panelists' responses. There was relatively higher uncertainty surrounding estimates for self-treatment compared to clinical management by health care providers. Respondents to the first round thought that 10% – 25% of persons who self-treated would have continued morbidity due to diarrhea after 3 days and that 10% – 75% would require further treatment.

Table 3.2 Results of round 1Delphi survey: vaccine strategy most likely to be successful by pathogen

Vaccine Strategy	Killed whole-cell, n (%)*	Subunit, n (%)*	Conjugate, n (%)*	Live attenuated, n (%)*	DNA-based, n (%)*	% Not at all certain
ETEC	6 (32)	9 (47)	2 (11)	2 (11)	0	55
Campylobacter	8 (44)	4 (22)	5 (28)	1 (6)	0	75
Shigella	3 (16)	2 (11)	5 (26)	9 (47)	0	70
Norovirus	4 (21)	8 (42)	0	4 (21)	3 (16)	80
Rotavirus	3 (16)	1 (5)	2 (11)	12 (63)	1 (5)	60
Enteroaggregative E. coli	5 (26)	9 (47)	2 (11)	3 (16)	0	90

*may not add to 100% due to rounding

Table 3.2 details the vaccine design strategy selected by the panelists as the most promising among those under development. With respect to vaccine development, a majority of panelists indicated that vaccines for ETEC, *Campylobacter*, *Shigella,* and norovirus were 9 – 14 years away from licensure in the US, but a vaccine for EAEC was 10 – 15 years or more away from licensure. (Table 3.3) Uncertainty about this target time frame was highest for EAEC and *Campylobacter*. Additional questions regarding failure rates for general vaccine development candidates and acceptable performance targets were asked in this first round. Nearly two-thirds of panelists thought that 5 - 10 years were required to develop a vaccine from concept to a Good Manufacturing Process (GMP) product, and that 50% – 90% of vaccines would not advance from concept to phase I testing. Subsequent drop out rates for more advanced vaccine testing seemed to improve only slightly. Dropout rates between phase 1 and phase 2 were estimated to be 10-75%, with similar rates between phase 2 and phase 3, although there appeared to be relatively higher uncertainty in these probability estimates compared to the concept to phase 1 transition. Nearly half (48%) of respondents thought that an acceptable vaccine protective efficacy for diarrheal disease should be between 71% - 80%, and one-fourth of panelists thought 61% – 70% protective efficacy was acceptable. Though the number of respondents in each professional category was small there appeared to be an expectation for a higher minimum protective efficacy among Military Clinical Infectious Diseases and Preventive Medicine experts (median efficacy estimate 71% – 80%, n=10) compared to Military Vaccine Development and Vaccine industry panelists (median efficacy estimate 61% – 70%, n=8) (Wilcoxon rank-sum, p=0.02). Seventy-four percent of respondents thought that a 5% – 20% mild adverse event (no activity limitation) rate was

acceptable, whereas 59% thought that acceptable moderate adverse events (mild activity limitation) must be less than 2%. No participants thought that moderate adverse event rates should exceed 5%. A maximum of a 3 dose series over 2 – 6 weeks seemed to be an acceptable vaccination schedule to most expert panelists (70% and 87% respectively).

Twenty-four panelists (96%) responded to the second survey round, which had refined ranges for answers based on a two-thirds majority of responses in the first round. Seventeen out of 24 respondents self-reported having more than 5 years of current or past experience in military clinical infectious disease and/or traveler/tropical medicine practice. Based on a three-fourths majority of responses from this subset of experts, final point estimates and uncertainty ranges for parameters related to management of diarrhea in deployed troops were derived for use in a third and final round. Similarly, responses from fifteen out 24 respondents who reported having 5 or more years of current/past experience in vaccine development (industry or military) were analyzed as a subset of responses to develop refined estimates related to pathogen-specific vaccine development time frames, again for use in the final round. All responses from the 24 panelists related to minimum target efficacy and maximum vaccine series length were used to derive a final consensus point estimate and uncertainty interval.

The third and final round of the Delphi survey achieved a relatively lower response rate of 17 panelists (68%), compared to the previous two survey rounds. The final round participants included three Vaccine Industry, five Academic/Military Diarrheal Vaccine Development, five Military Preventive Medicine, three Military Clinical Infectious Diseases and one Tropical/Travel medicine expert. No panelists from the military product acquisition area responded to this final round. Twelve out of the 17

Table 3.3 Consensus estimates from first and third round of Delphi survey relating to vaccine development targets

Parameter Estimate	First Round (n=23)		Third Round (n=17)	
	Response Range (% panelists in range)*	**% Not at all certain**	**Consensus Estimate (range)**	**% Agree**
Estimated time until vaccine licensure for the following pathogens (years)				
ETEC	5 - 14 (72)	48	9 (5 - 14)	88
Campylobacter	5 - 14 (81)	62	11 (8 - 14)	88
Shigella	5 - 14 (76)	52	9 (5 - 14)	94
Norovirus	5 - 14 (86)	57	10 (8 - 14)	82
Rotavirus	0 - 9 (86)	29	2 (1 - 3)	82
Enteroaggregative E. coli	10 - 15+ (84)	67	14 (10 - 18)	94
	Panelist response, n (%)*	**% Not at all Certain**	**Consensus Estimate (range)**	**% Agree**
MINIMUM Protective Efficacy Target		17		
50 - 60%	3 (13)			
61 - 70%	6 (26)			
71 - 80%	11 (47)		60 - 80%	94
81 - 90%	3 (13)			
> 90%	0			
MAXIMUM allowable frequency of MILD, MODERATE adverse event		17, 14		
< 2%	0, 13 (59)			
2 - 5%	4 (17), 9(41)			
5 - 9%	13 (57), 0		not asked	
10 - 20%	4 (17), 0			
> 20%	2 (9), 0			
MAXIMUM number of doses allowable in primary series		17		
2 doses	5 (22)			
3 doses	16 (70)		not asked	
4 doses	2 (9)			
MAXIMUM time from start of series to protective immunity		23		
2 - 3 weeks	9 (39)			
4 - 6 weeks	11 (48)		3 - 4	94
6 -12 weeks	2 (9)			
> 3 months	1 (4)			

*may not add to 100% due to rounding

respondents reported having more than 10 years in their current occupation, and fourteen reported having worked directly in support of military troops. Final point estimates and uncertainty ranges, as well as overall agreement among panelists are described in Tables 3.1 and 3.3. In the area of treatment provided among those who seek care for diarrhea, the consensus was that about 30% of patients received antibiotics plus an anti-motility agent, while approximately 20% received either antibiotics alone or non-antibiotic therapy. Fifteen percent were thought to receive no treatment when presenting with diarrhea.

With respect to self-treatment, 94% of panelists agreed that 60% (range 30% – 90%) of deployed troops who develop diarrhea do not initiate self treatment; whereas, 20% used anti-motility or BSS therapy alone, and 5% used an antibiotic combined with an anti-motility agent. Panelist agreement rates for outcomes associated with self-treatment were higher in general (77% – 94%) compared to responses regarding treatment received when presenting for medical care (71% – 77%). Panelists agreed that approximately 15% of individuals who self-treated for diarrhea would continue to have morbidity 3 days after treatment, and one-fourth of these individuals would require further medical evaluation and treatment. The range of uncertainty was wider and agreement was relatively less for the latter estimate.

Final estimates for licensure time frames for ETEC, *Campylobacter*, *Shigella,* and norovirus vaccines were fairly similar at 9 – 11 years, whereas licensure for a vaccine against EAEC was thought to be about 14 years off. Ninety-four percent of third round respondents agreed that minimum target efficacy should be between 70% - 80%, and

maximum time from start of vaccination series and protective efficacy should be between 3 and 4 weeks.

Discussion

While the primary purpose of this study was to provide estimates for parameters lacking a solid basis in published literature, it is useful to compare the consensus estimates that were derived from this study with what may be reported in the published literature, albeit in a limited manner. In the area of travelers' diarrhea management in deployed settings, we report consensus estimates of 30% (10% – 50%) of troops receiving antibiotics plus an anti-motility agent, 20% (10% – 30%) receiving an anti-motility agent or BSS alone, 18% (11% - 25%) receiving antibiotics only, and 15% (6% – 25%) receiving no treatment. A recently published study conducted among troops deployed to Iraq and Afghanistan found that approximately 80% of troops sought care for their diarrhea, usually from their medic. [131] While the authors did not distinguish between specific treatment modalities provided by the medic or during a clinic visit staffed by physician or physican's assistant, it was reported that patients more often recieved some kind of medicine from a medic (~60%) compared to a clinic visit (48%). Reported management approaches included antibiotics in 27%, loperamide in 37%, BSS in 13%, and treatment with oral rehydration only in 15%. The percent of patients receiving combination therapy with antibiotics and loperamide was not reported. Estimates from expert consensus appear to be concordant with this survey, particularly the estimate of no therapy provided in 15%. One other survey conducted predominately

among Army physician assistants, assessed travelers' diarrhea management practices and found that for moderate diarrhea. loperamide or BSS was utilized in 36% of patients, oral rehydration alone in 27%, combination antibiotic/loperamide therapy in 25%, and antibiotic alone in 11%. [128] The reported prescribing of antibiotics (alone or in combination with loperamide) was higher (18% and 45%, respectively) in patients with severe diarrhea. These data are also consistent with the estimates of the consensus panel and further identify the practice gap in appropriate management practice for travelers' diarrhea among deployed US troops.

Similarly, consensus estimates for self-treatment management modalities was 20% for troops using loperamide or BSS alone for self-treatment, 8% for troops using antibiotics alone or in combination with loperamide, and 60% for troops not utilizing any self-treatment modality. A consensus estimate of 15% (10% – 20%) for continued morbidity after self treatment was derived from the Delphi survey. The recent publication by Putnam et al. found that 12% of troops brought medications with them to treat diarrhea and an additional 20% either bought or borrowed some during deployment. [131] Roughly, 31% of troops brought either loperamide or BSS and 8% brought antibiotics. While not described, 80% of the troops reported that their self-treatment led to cure (personal communication). Notably, the findings from this survey were published after the Delphi survey was completed and supports the expert consensus panel's estimates.

Predicting the time frame for development of a vaccine which is in the early phases of preclinical, phase 1 or phase 2 testing is difficult. Factors that might shorten this time frame include the existence of an appropriate animal model predictive of

outcomes in humans, the availability of clinically relevant measures of correlate immunity, and successful proof of concept challenge studies. The relative amount of funding available for each vaccine would also need to be considered.

Given these challenges, our expert consensus panel nonetheless provided estimates of the time frame for vaccine development that ranged from 9 to 11 years for ETEC, *Campylobacter*, *Shigella* and norovirus (uncertainty range 5 – 14 years). Rotavirus vaccine, known to be pending licensure at the time of the survey, was estimated at 2 years. A recent review of enteric vaccine development describes the current state of the science and challenges that lie ahead [132, 133] Despite the similar time horizons reported by experts, it appears that each of these vaccines are in different stages of development. The most advanced among them is an ETEC vaccine, for which a number of phase 2 and 3 trials have been completed or are currently underway utilizing a vaccine containing the cholera toxin B subunit protein combined with 4 formalin-killed ETEC strains. [132, 134] In addition to this vaccine construct, additional studies have been completed with vaccines based on colonization factor (with or without adjuvant) [135-137]. However, while some vaccines demonstrate promise based on correlates of immunity and passive protection, the development feasiblity of candidate vaccines based on colonization factor is challenging because there are more than 20 colonization factors and the fact that between between 40% - 80% of ETEC don't display a detectable colonization factor.[119, 138, 139] These challenges are likely to place the development and licensure of a broadly effective ETEC vaccine further into the future.

Shigella and *Campylobacter* vaccine candidates are both in phase 1 and 2 testing and consist of killed whole-cell and recombinant sub-unit strategies.[140-147]

Furthermore, a live attenuated vaccine for *Shigella* is under development using a number of different strains, but these efforts have been challenged by the need to balance the immunogenicity and reactogenicity of attenuated strains. [148-151] *Campylobacter* vaccine development is challenged by the paucity of applicable animal models for vaccine efficacy and the lack of a correlate of protective immunity. On the other hand, for *Shigella*, there does appear to be a good correlate of immunity [152, 153], as well as animal models that relate well to human challenge studies. [154, 155] While no recent human challenge studies have been conducted, the necessary components appear to be in place for successful development of this vaccine.

Our Delphi survey panelists considered a norovirus vaccine to be licensed in a similar time frame to ETEC, *Campylobacter,* and *Shigella* vaccines despite only three published studies testing a norovirus vaccine in humans, which relied on a single strategy of recombinant virus-like particle.[156-158] While an animal model is lacking and correlates of immunity have not been established, a human challenge model exists [159, 160], and it is possible that the increasing awareness of burden and anticipated increased research effort may have factored into the experts' consensus of an 8 – 14 year time to licensure. There is uncertainty with respect to any vaccines being developed for EAEC, and a consensus estimate of 10 – 18 years was reported.

Despite these differences in established animal models, correlates of protective immunity, and current clinical trials experience for each of the candidate vaccines, expert consensus for vaccine development time frames were homogeneous across vaccines. This finding should most likely be interpreted as a reflection of the degree of uncertainty

that surrounds predictions of this nature in the face of incremental and breakthrough advances. Future studies could validate predictions such as these.

In general, there was higher consensus for estimates regarding general vaccine safety and the potential for application of vaccines for TD with respect to vaccine target efficacy. A 60% – 80% efficacy target was a bit lower than the range for most routine immunizations and travel-related vaccines [161] but probably represents an achievable target. Given the high incidence of travelers' diarrhea in deployed troops, even a modest vaccine efficacy could have profound effects. Sub-group analysis of our expert panel showed that clinicians and preventive medicine professionals were similar in their estimates and expected a higher efficacy relative to their colleagues in vaccine development and acquisition. A recognition of the practical challenges better known to enteric vaccine developers might result in a more "achievable" efficacy targets. Furthermore, considering the burden of disease from a population perspective and taking into account herd immunity might result in a lower target efficacy compared to estimates among clinicians concerned with the protective effects on individuals.

Fifty-nine percent of panelists agreed that the maximum allowable rate for a moderate adverse event, defined by some activity limitation, should be less than 2%; 74% of panelists thought that mild adverse events (not involving activity limitiation) should not exceed 5% – 20%. Post-marketing adverse event reporting rates associated with some travel vaccines are generally higher than the level described by this Delphi panel. [162-166] Travelers' diarrhea is an extremely common, self-limited and easily treatable health risk to deployed troops. Given this consideration, a vaccine with a relatively lower reactogencity (safer) might be considered more acceptable.

The Delphi surveying technique is designed to turn individual opinion into consensus through serial questionnaires. Responses from subject mater experts are initially collated into broad range estimates.[129, 167] These estimates are then presented to the respondents in an iterative fashion for further consideration and comment. The Delphi method and other consensus-gaining techniques have previously been used in conjunction with cost-effectiveness analyses to develop parameter estimates when scientific literature is lacking, or continued uncertainty exists.[168-171] There are limitations in using the Delphi methodology, including reliability and validity of the data, and interpretation of the results. This study had strengths of expert diversity, representativeness, and high response rates (except for the final round). However, the 'effective' expert panel may have been diluted due to the focused subject area expertise required for different knowledge areas (e.g. travelers' diarrhea management, vaccine development time frames and strategies). However, many of the participants of the survey reported overlapping areas of expertise and were, therefore, qualified to answer a wide range of questions. In addition, concordance between expert panelists' consensus estimates and, where available, published literature with respect to management practices provide support for the study's validity.

In summary, making informed decisions on travelers' diarrhea vaccine acquisition for the US military or the traveling public in general necessitates a thorough understanding of the factors associated with disease incidence and outcomes, as well as vaccine development time frames, costs, safety, efficacy, and other performance characteristics [53, 55]. While the former can often be obtained from the published literature and public health surveillance data, the latter often presents challenges. The

consensus vaccine performance characteristics reported herein appear to be on the conservative side. We would do well to heed Voltaire's pragmatic advice of not letting perfection be the "enemy of the good."[172]

Though not without limitations, this study represented an important step in providing information to vaccine development researchers, policy makers and institutional officials involved with enteric vaccine development, with a focus on travelers' diarrhea. This study also called attention to the continued gap in best-practices for management of diarrhea in a deployed setting, as well as provided important estimates to be used to conduct further economic analyses on vaccine development to determine priorities for research and preventive intervention strategies within the DOD.

Chapter 4: Economic Analysis

Framework

The question of which vaccines, or other countermeasures, to use as a strategy for reducing the burden from infectious diseases for deployed troops is a difficult decision for policy makers. The US Military Infectious Diseases Research Program (MIDRP) alone spends approximately $74 million dollars per year on the research and development of vaccines, drugs, diagnostics and other products against various infectious disease threats.[173] In 2003, the Institute of Medicine (IOM) issued a report produced by the Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance, with technical and policy recommendations regarding the DOD strategy to combat infectious diseases.[53] In this report it was noted that a vaccine for infectious diarrhea was among the top three highest priorities, following research and development of a vaccine and new drugs for malaria. While these priorities appear quite reasonable based on the historical disease threats faced by the US military, the IOM committee noted that the entire DOD vaccine acquisition process "suffers because it falters at an important first step: the setting of priorities" and, furthermore, cited that the manner in which the DOD prioritizes disease threats and research goals is unclear.[53]

Processes related to the objective prioritization of new vaccine development, including vaccines against causes of infectious diarrhea, are not novel. In 1999, the IOM published a report entitled *Vaccines for the 21st Century: A tool for decision making*.[55] In their decision modeling, they found that the vaccine acquisition policy for ETEC and

Shigella, specifically in a non-military traveler population, was less favorable compared to other candidate vaccines. It used a societal perspective, which may not be appropriate for the DOD, in which each service member may play an integral part of a unit's mission and the loss of even a short amount of time can be critical. Additionally, the use of Quality Adjusted Life Year (QALY) as the measure of utility of various health outcomes in a decision analysis, is not necessarily the most appropriate outcome measure for a specific disease in a specific population. particularly for travelers' diarrhea, which is usually a self-limited disease with no sequelae.[57]

From a DOD perspective, while a policy of vaccine product acquisition may not realize costs and benefits for many years (research and development costs / time horizons), the potential benefits are many, including reduction in person-days of lost productivity, lower expenditures for antimicrobial treatment, and removal of the need for the development and clinical evaluation of empiric antibiotic treatments to keep pace with evolving antimicrobial resistance. The need for a vaccine strategy may become obsolete if military personnel are no longer at high risk for reasons such as advancement in developing world sanitation and infrastructure or changes in military deployments, although this does not appear likely in the near future. Given limited resources and opportunity costs in deciding among various infectious diseases for which vaccine or other counter-measures could be developed, the use of an objective method to prioritize vaccine acquisition strategies based on best available epidemiological data and from a military perspective is essential.

The DOD currently has three parallel vaccine development programs for *Campylobacter*, ETEC, and *Shigella*, with the goal of eventually producing a multiplex

vaccine that would protect deployed troops against the three most common bacterial pathogens.[173] In this chapter, an economic analysis was conducted to evaluate the overall cost-effectiveness of a strategy to develop and acquire a multiplex vaccine against these three primary causes of TD, as well as the relative cost-effectiveness of each component vaccine, compared to the current baseline standard of care for TD in deployed US military personnel, which involves treatment with antimicrobial agents. This study was framed from the DOD medical health system and operational deployment perspectives, using militarily-relevant outcomes of duty days lost due to diarrhea and days of diarrheal illness in forecasted annual deployment to high risk geographic regions over a 30-year time horizon. The primary goal of this economic analysis was not to evaluate the choice between empiric therapy and vaccine development to mitigate the burden of infectious diarrhea, but rather to evaluate the overall cost-effectiveness of a multiplex vaccine and the relative cost-effectiveness of pathogen-specific vaccines compared with empiric therapy, based on current, best available evidence and outcomes of military relevance. In addition, and most importantly, this analytic model was designed to provide policy and product acquisition decision makers with an evidenced-based decision making tool with potential applicability to a broad range of military-specific deployment health issues.

Data and methods

Model overview. A military-relevant economic model was developed to evaluate the cost-effectiveness of a vaccine acquisition strategy for three leading bacterial

etiologies of infectious diarrhea compared with the current disease management in a deployed environment, including treatment provided by the military health system, self-treatment, and no-treatment. (Figure 4.1) For the vaccine acquisition strategy (VAS), the following assumptions were made. After a period of vaccine development, troops would receive pathogen(s)-specific vaccine against travelers' diarrhea based on current pre-deployment vaccine coverage rates. Disease associated with these three pathogens was considered to be sporadic, occurring through water or food contamination—person-to-person spread and the potential effect of herd immunity was not considered. Once vaccinated, individuals either acquired protective immunity against diarrhea caused by the pathogen(s) or remained susceptible. For vaccinated troops not acquiring immunity or unvaccinated susceptibles, the possible outcomes are illness associated with the specific pathogen(s) or no illness. When an individual becomes ill with diarrhea, the potential behaviors include seeking treatment from a military health care provider, not seeking treatment, or rarely, requiring medical evacuation. Even though medical evacuation would always occur after a medical health care provider encounter, the event is rare and only reported as a population-based measure, so it is included as an individual branch in the model. Those who do not seek health care from a military provider either successfully self-treat, fail self-treatment, or do nothing and let the disease run its course. At the point of a medical health care provider encounter, there are four possible, mutually exclusive management pathways in the model, with probabilities based on available data from current practice patterns. The different management pathways included optimal outpatient management (antibiotic with or without anti-motility agent), sub-optimal

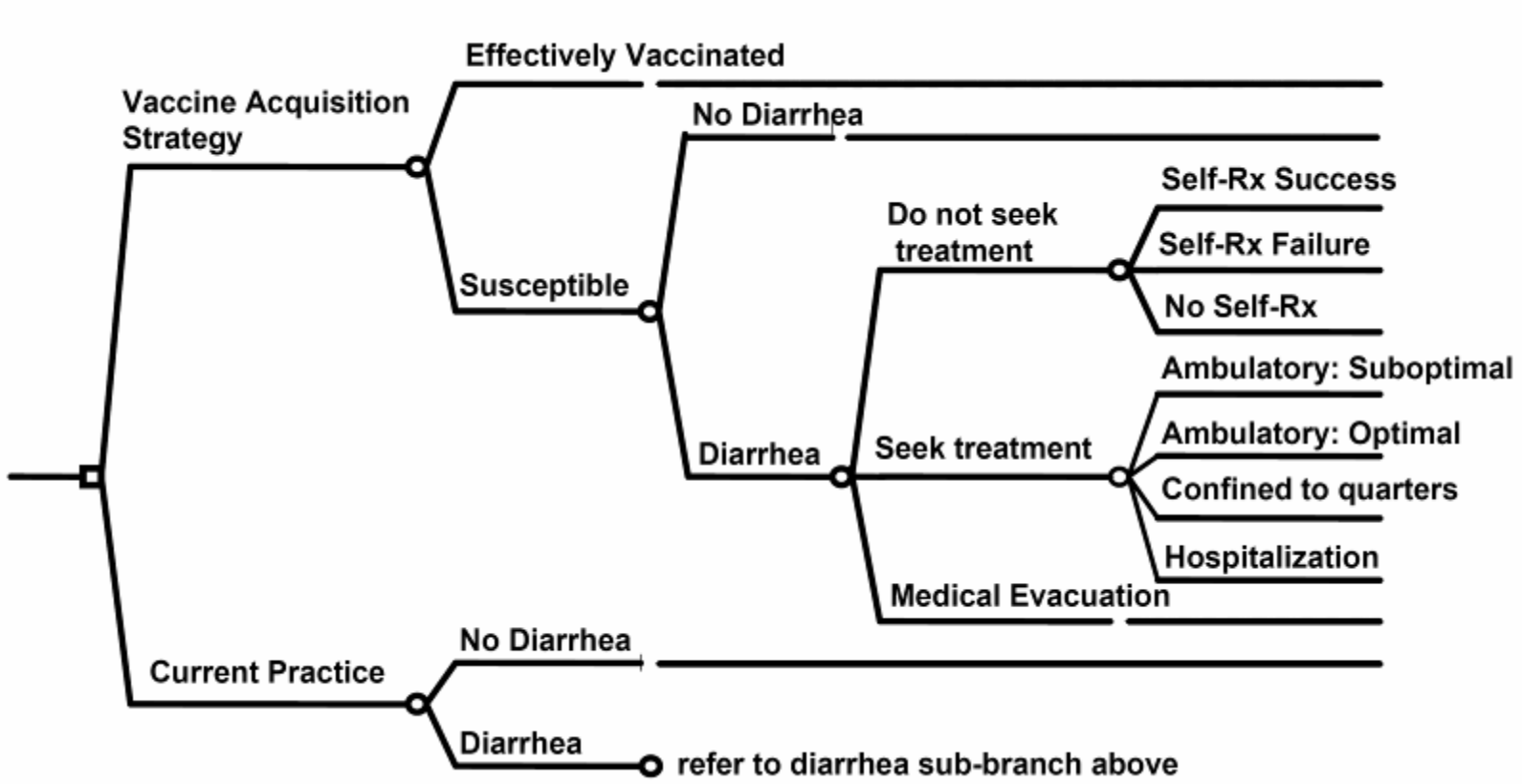

Figure 4.1 Conceptual diagram of an economic model evaluating the cost-effectiveness of a vaccine acquisitions strategy by the DOD

outpatient management (anti-motility agents alone or fluid rehydration only), medical management with confinement to bed rest, or hospitalization for treatment. With the first two pathways, based on outpatient treatment, the individual was returned to duty, while the latter two pathways resulted in lost duty days due to being sent home or being hospitalized. While the events resulting from a medical health care provider encounter could be considered as a decision point in our model, they were treated instead as probability-based events using the available literature detailing actual disease management patterns and outcomes in military deployment settings. The model explicitly assumes that sub-optimal treatment is sometimes provided, a management choice which theoretically should not occur or could be changed. However, despite several clinical trials, systematic reviews, and practice guidelines devoted to describing best treatment practices for travelers' diarrhea, variability in practice patterns, some of which are not evidence-based, appears established among military providers.[39, 45, 102, 174-176] Severe adverse events associated with antimicrobial treatment or other provided therapies that would have resulted in additional duty time lost or medical utilization were considered very rare based on treatment trial data in military settings and, thus, not considered in the model.[125] The comparator of the current approach to disease management in deployed settings mirrors the VAS sub-tree at the point of the probability node of developing a pathogen-specific diarrheal illness.

Analytic horizon. With respect to the current management of diarrhea in deployed settings, costs are ongoing, including direct treatment costs and clinical trials, and benefits accrue concurrently. However, with the VAS, the time and costs of research

and development are considerable during the initial phases, and once a vaccine is licensed and procured, costs related to a routine deployment vaccination program continue. Because vaccination is a preventive intervention, with the potential to eliminate the overall burden of illness and not just decrease the morbidity, the benefits could be enormous but might take time to accrue. Therefore, a prolonged analytic horizon was required to fully evaluate the outcomes of such a strategy. However, the need for a long analytic horizon may be obviated by other factors that reduce or eliminate the need for a vaccine against infectious diarrhea during deployment such as geopolitical isolation, increased development of smart weapons and/or robots which would prevent the need to deploy individuals—theoretically possible, but not very likely to occur. For the purpose of the base-case analysis, an analytic horizon of 30 years was selected, with a range of 20 to 50 years evaluated. While this time horizon is longer than industry time-frames for drug and vaccine development, the DOD has been in the business of developing counter measures against infectious disease threats since the late 1940s with a determined goal of developing products to protect the troops abroad, and acquisition targets are unlikely to change.[177, 178]

Annual deployment population. Forecasting annual military deployments to areas at high risk for infectious diarrhea over a 30 year analytic horizon is challenging. Following the end of the Cold War, the military has undergone a transformation in the past two decades which has involved a reduction in end strength forces from approximately 2.1 million to 1.4 million personnel, where it has remained constant throughout the past decade.[179] In addition to the Global War On Terror, the US

national security posture continues to require a capacity for large- and small-scale contingency operations, including peace enforcement/peace keeping, humanitarian assistance, disaster relief, drug interdiction, show of force, peacetime operational training, nation building, and joint exercises to strengthen relations with strategic partners.[180] The current force structure and end strength has been designed to "[articulate] a vision for the transformed force fully consistent with the demands of the anticipated security environment in 2025." [180] Given the current geopolitical environment, a conservative assumption would be that current end strength levels would not decrease over the next 30 years, but may in fact increase. This assumption formed the basis for our projections of yearly forces deployed during the analytic time horizon. Our model does not depend on end-strength *per se*, but rather on an estimate of the number of persons deployed and time period of deployment each year to operations where there is a high risk of travelers diarrhea. A recent study published by RAND, evaluating the effect of long or hostile deployments on reenlistment, provided estimates of service-specific deployment rates. [181] The authors of the study used military pay and accounting data to identify deployment periods where service members were either deployed for more than 30 days or deployed to areas where they qualified for hazardous duty or imminent danger pay, which was considered a reasonably valid basis for estimating numbers of personnel deployed to geographic areas of high risk for travelers' diarrhea. Between the periods of 1993 and 1995, rates of deployment were approximately 9% (range 6% – 14%) in the Army, 6% (range 5% – 8%) in the Air Force, 13% (range 10% – 16%) in the Navy, and 18% (range 16% – 20%) in the Marine Corps. Applying these rates to the average (and forecasted) end strength for each of the services

from 1996 to 2002, we calculated a baseline estimate of 147,000 troops deployed annually (range 114,000–194,000) to areas at high risk for acute infectious diarrhea.[179] These estimates did not include those who are permanently stationed overseas in high risk areas, and although these numbers were relatively small compared with the large troop contingents currently deployed to Iraq and Afghanistan, the base-case estimate should be considered to be conservative.

Deployment time. The RAND report also described the median time of deployment across services as lasting three to four months, with the exception of Navy with average time of deployment of six to seven months. [181] Three-and-a-half months was selected as the base-case estimate of deployment duration. This estimate was more than twice as long as the median duration of deployment (1.5 months) reported in a systematic review of diarrheal disease in military populations, [125] but well short of the one year length of deployments associated with operations in Afghanistan and Iraq. These served as the low and high estimates, respectively.

Vaccination program. The model assumed a naïve cohort of deployed travelers each year based on the following rationale. For an individual, a vaccine to prevent diarrhea is likely to have a potential protective benefit for one to two years based on current studies of naturally-acquired immunity to enteric pathogens, as well as studies of cholera and typhoid fever vaccines.[182, 183] This assumption does not take into account the potential 'boosting' that may occur when vaccinated individuals with partial immunity to a specific pathogen are subsequently exposed to this organism in a natural

infection.[184] Additional studies of naturally-acquired immunity to diarrheal illness among expatriates without prior immunity and children in endemic settings suggest that it may take up to two years to acquire protective immunity to endemic pathogens.[75, 185, 186] From a military operational perspective, force structure and unit rotations are planned so that deployments are less than 6 months in duration and occur every two to three years. [180] Based on these assumptions, in addition to expected turnover of personnel (separation and retirement from military service), it was assumed that immunity acquired from vaccination or natural infection associated with prior deployments would have minimal effect. In fact, no studies to date have found a protective effect from the occurrence of diarrhea during a prior deployment against diarrheal illness in a current deployment.[27, 51, 101, 108, 187] Therefore, the model assumes that individuals would receive the vaccine against infectious diarrhea prior to every deployment. Furthermore, the base-case estimate assumed the multiplex vaccine to be 80% effective (range 60% – 90%) against the three specified pathogens based on current programmatic targets and given in a three-dose series (range 2 – 6 doses) over a four week period.

Vaccine development costs. In addition to population deployment parameters, the economic model required an estimate of projected vaccine development costs to the DOD and time-frames for development, as well as the necessary DOD clinical research investment for ongoing antimicrobial treatment trials. Development cost estimates were obtained from a 2000 report published by an independent committee of experts, chaired by Franklin Top (Top Report), that was convened to make recommendations on

improving the DOD acquisition process for vaccines.[188] While the primary task of the committee was to examine the feasibility of vaccine production for defense against biological agents, the estimates are also relevant to other infectious diseases. Including costs for preclinical vaccine development, production, and clinical trials testing to develop a vaccine from concept through production and licensure, the committee estimated that for any given vaccine it would cost between $300 and $400 million (CY 2000 dollars). The total cost estimates of the Top Report are compatible with other reports from private industry, which estimate a cost of $300 million, 70% of which is projected for the late development or clinical trials phase.[189] Given the nature and strategic plan of the DOD acquisition process, it is expected that industry sponsors would likely incur the bulk of the costs (70%) in the late development phase, as well as some of the early development costs. Therefore, based on the assumptions of the economic model, the DOD's contribution to the total development cost of a single vaccine was estimated to be approximately 30% of total vaccine development costs--$108 million to $143 million (2006 US dollars). The midpoint of this range was used for the base-case scenario. Furthermore, for the multiplex TD vaccine model, it was assumed that each pathogen-specific vaccine component would be developed independently and either administered separately or formulated together at the end. Thus, development costs were considered to be additive.

Vaccine development timeframes. The average time required for new vaccine development was estimated overall and for each particular pathogen-specific vaccine, based on current scientific knowledge. The primary source for these estimates was

obtained from a Delphi survey (Chapter 3) conducted among subject matter experts in the vaccine industry, academic/military diarrheal vaccine development community, and military product acquisition activity.[190] Consensus estimates for target time frames for vaccine licensure for ETEC, *Campylobacter*, and *Shigella* were reported to be between 9 and 11 years (with some minor differences in the confidence intervals). These estimates were consistent with a previously published study, [191] which estimated a 10 year time-frame for development and that we used as the base-case estimate for the multiplex vaccine in our model. High and low vaccine development timeframes were selected based on the Delphi survey.[190]

Immunization program costs. The purchase price for a single pathogen vaccine was based on data obtained from current vaccine price lists published by the DOD Military Vaccine Agency. [192] A median vaccine purchase price based on a list of 24 travel vaccines was estimated at $24.74 with an interquartile range (IQR) of $17.08 – $47.23 (range $2.02 – $195.38) and was considered the minimum cost of a multiplex vaccine. A maximum cost was considered to be up to three times this cost ($74.22), and the base-case estimate was an average of the minimum and maximum values ($49.48). Because of the robustness of the current deployment vaccine program in the DOD, additional administrative costs (e.g., for storage, logistics, delivery, monitoring) associated with an additional vaccination were considered to be minimal. It was estimated to be between $0.05 and $5.06 (updated to 2006 US dollars) per dose from previously conducted economic analyses of vaccination in military populations.[70, 72] Probability estimates for a vaccine adverse event requiring further treatment and its

associated costs are presented in Table 4.1. Because any lost duty-days associated with a vaccine adverse event would occur prior to deployment, these were not included in the model.

Ongoing empiric antibiotic treatment trial costs. Because of the evolving nature of global antimicrobial resistance and changing empirical treatment regimens for travelers' diarrhea over the past three decades,[193] it was assumed that continued clinical trials to test the efficacy of new treatment regimens in military populations would be required over the entire time horizon for standard practice of care and until vaccine licensure. Based on historical funding patterns for these trials and epidemiologic studies tracking emergence of antimicrobial resistance within the DOD over the past 10 years, a baseline estimate of $250,000 per year (range $200,000–$300,000) was used. (Stephen Savarino, personal communication)

Outcome measures. From the military deployment perspective two operationally-relevant effectiveness outcomes were chosen: duty-days lost due to diarrhea (DDL) and diarrhea illness days (DID). These outcomes were not mutually exclusive as the DDL is a subcomponent of DID. That is to say, that one can be ill with diarrhea symptoms for several days; however, the actual time lost from duty (work) is a fraction of the total illness time. Based on these health-related outcomes, a cost-effectiveness analysis (CEA) model was employed. To evaluate the overall efficiency of the multiplex vaccine, and the relative cost-effectiveness of each of the

Table 4.1 Parameter estimates for multiplex vaccine model

Parameter Estimate	Multiplex Vaccine Scenario			Probability Distribution	Source
	Baseline	Low	High		
Travelers' Diarrhea					
MONTHLY incidence (as percent)	28.90%	16.20%	41.50%	Normal	[125]
Vaccine Covered Pathogen Prevalence	38.70%	25.70%	51.70%	Normal	[125]
Vaccine Acquisition Program					
Time to vaccine licensure (years)	10	5	14	Triangular	[190], [191]
Vaccine Coverage	75.00%	52.00%	98.00%	Triangular	a, [194]
Vaccine Efficacy	80.00%	60.00%	90.00%	Triangular	b, [190]
[P] of adverse event needing treatment	0.0125%	0.0050%	2.0000%	Triangular	c, [190]
Cost of vaccine administration	$2.56	$0.05	$5.07	Uniform	[72], [70]
Cost per dose of vaccine	$48.98	$24.74	$74.22	Triangular	[192]
Number of doses needed	3	2	6	Triangular	b
Cost per adverse event treated	$104	$89	$119	Triangular	e, [72]
DOD investment for research (in millions)	$418.9	$358.2	$477.6	Triangular	[188]
Current Disease Management Approach					
[P] of treatment by MHS Provider given illness	22.50%	13%	32%	Triangular	[125]
[P] of no treatment by MHS provider given illness	77.47%	68%	87%	Triangular	[125]
[P] aeromedical evacuation	0.0329%	0.0229%	0.0429%	Triangular	e, g
[P] no self-treatment (run its course)	60%	30%	90%	Triangular	[131], [190]
[P] self-treatment success	32%	16%	48%	Triangular	[190], [131], [195]
[P] self-treatment failure	8%	4%	12%	Triangular	[131], [190]
MHS Treatment Type Provided					
[P] suboptimal (outpatient)	33.5%	16%	51%	Triangular	[190], [126], [131], [128]
[P] optimal (outpatient)	42%	27%	57%	Triangular	[190],[128]
[P] confinement to bed rest (bed rest)	22.5%	13%	27%	Triangular	[96], [108], [96], [19, 131, 187]
[P] hospitalization	2.0%	1%	8%	Triangular	[125], [131]
Cost of Treatment Type					
Aeromedical evacuation	$13,917	$13,027	$14,806	Triangular	g, e
Hospitalization (deployed)	$2,336	$1,868	$2,803	Triangular	d
Confinement to bed rest	$84	$67	$100	Triangular	d
Suboptimal (outpatient)	$60	$48	$72	Triangular	d
Optimal (outpatient)	$72	$57	$86	Triangular	d
Self-treatment failure	$22	$18	$26	Triangular	d
Annual Investment on Treatment Trials	$250,000	$200,000	$300,000	Triangular	h

Table 4.1. Legend

[P] = Probability of X; MHS = Military Health System; confinement to bed rest
a. Defense Medical Surveillance System (unpublished data)
b. Baseline vaccine performance assumption
c. J Grabenstein (former MILVAX director), personal communication
d. TRICARE Management Activity, Uniform Business Office
e. Unpublished data (Iraq surveillance)
f. DOD US TRANSCOM Regulating and Command & Control Evacuation System (TRACES)
g. DOD airlift rates
h. SJ Savarino (MIDRP Diarrhea Disease Program Director), personal communication

component vaccines, a cost-effectiveness ratio (CER) was computed using a Microsoft Excel spreadsheet program (Microsoft Inc., Redmond, WA). The numerator of the CER (net cost) was calculated as the sum of the costs of vaccine development and the costs of administering the vaccine to the target population, minus the expected costs of care averted by vaccination. The denominator of the CER was computed as the DDL or DID averted (net outcome) by administering the vaccine. (See Appendix B for formulae)

Probability estimates for a multiplex vaccine. The economic model was based on probabilities associated with pathogen-specific travelers' diarrhea incidence, seeking health care, disease management, and vaccine program-related parameters (doses, adverse event rate), as well as costs attributed to the processes and health outcomes for each of the terminal branches.(Figure 4.1 & Table 4.1) A literature review was performed in PubMed, EMBASE, and Cochrane databases to identify base-case estimates and ranges for each parameter, with emphasis placed on estimates from studies conducted among deployed military populations. Clinical trials and/or observational studies pertaining to each of the probabilities and outcomes were reviewed. Probability

estimates not available from the published literature were obtained from a Delphi survey (Chapter 3), unpublished data, or personal communication with subject matter experts.[190] Several parameter estimates such as diarrhea incidence and pathogen prevalence, as well as probabilities associated with treatment by a military health care provider and hospitalization due to diarrhea, were derived from a systematic review of diarrheal disease in US military and similar populations that included 52 studies published in the last 15 years.[125]

Probability estimates for pathogen-specific vaccines. Yearly deployment size, deployment duration, time horizon, discount rate, diarrhea incidence, vaccine efficacy, and probability of seeking care were held constant across all pathogen-specific models. In order to achieve comparability to the overall model, one-third of the annual costs of clinical trials were used as the base-case estimate for pathogen-specific vaccine scenarios. Individual pathogen prevalence was obtained from the systematic review and vaccine development time frame from the Delphi survey.[125, 190] For each pathogen-specific vaccine, a two dose series was assumed (range 1 – 4) with a cost of $24.74 (range $17.08 – $47.23) per dose.

For the ETEC pathogen-specific scenario, the multiplex estimates for treatment seeking probabilities were used, as well as management and efficacy outcomes based on the knowledge that ETEC is the most common pathogen causing diarrhea. For *Campylobacter* and *Shigella,* studies were identified in which a predominate invasive pathogen was found or where a significant number of pathogen-associated cases could be used for comparison.(Table 4.2) Diarrheal illness outcomes among those who sought

treatment were estimated based on studies in military populations reporting confinement to bed rest or incapacitation for specific pathogens. Among troops seeking care for their illness, *Shigella* is estimated to have the highest probability of incapacitation at 64% [19], followed by *Campylobacter* at 47% [108], and ETEC at 22%.[19, 108] No studies reported pathogen-specific probability of hospitalization; however, these were considered

Table 4.2 Select pathogen specific parameter estimates

Parameter estimate (95% CI) or [low - high]	***Campylobacter***	**ETEC**	***Shigella***
Pathogen Prevalence	9.9% (6.4 - 13.4%)	22.2% (18.2 - 26.2%)	6.6% (4.2 - 9.0%)
Time to vaccine licensure, years	11[8 - 14]	9 [5 - 14]	9 [5 - 14]
[P] no self-treatment	60% [30 - 90%]	60% [30 - 90%]	60% [30 - 90%]
[P] self-treatment success	8% [0 - 15%]	32% [16 - 48%]	8% [0 - 15%]
[P] self-treatment failure	32 % [16 - 48%]	8% [4 - 12%]	32% [16 - 48%]
Treatment Type Provided			
[P] Outpatient: suboptimal	22% [11 - 33%]	33% [17 - 50%]	13% [7 - 20%]
[P] Outpatient: optimal	27% [14 - 41%]	42% [21 - 63%]	16% [8 - 24%]
[P] Confined to bed rest	47% [24 - 71%]	23% [12 - 35%]	64% [32 - 96%]
[P] Hospitalization	4% [2 - 6%]	2% [1 - 3%]	7% [4 - 11%]

[P] = probability

to be proportional to the differential pathogen-specific probabilities of confinement to bed rest or incapacitation and resulted in probability estimates of 7%, 4% and 2% for *Shigella*, *Campylobacter* and ETEC, respectively. The remaining probabilities associated with either optimal (antibiotic) or sub-optimal (no antibiotic) treatment for each of the pathogens were calculated among those seeking care as 55% for optimal care or 45% for sub-optimal care times one minus the sum of the probabilities of confinement to bed rest and hospitalization. While sensitivity ranges for treatment probabilities existed from published reports for the overall model, no such ranges were available for pathogen-

specific probabilities. Therefore, based on ranges of estimates for the multiplex model, widths that were 50% of the point estimates were used.

To estimate the pathogen-specific probabilities and outcomes related to self-treatment, it was assumed that for *Campylobacter* and *Shigella* infections, an antibiotic was required for treatment success and that the probability of no self-treatment would not differ between pathogen-specific infections. A recent epidemiologic study among military populations deployed to Iraq and Afghanistan found that among individuals who self-treat, 7.6% use antibiotics which they borrowed or brought from home.[131] A Delphi survey [190] reported a consensus estimate of 8% (range 0% – 15%) for individuals self-treating with antibiotics (alone or in combination with loperamide), consistent with the aforementioned study. For ETEC infections, it was assumed that antibiotics or loperamide (alone or in combination) would lead to successful self-treatment in more than 80% of cases.

Cost estimates for the military health system. Variable costs associated with managing illness in the field and treatment of adverse vaccine events were obtained from a variety of sources, including published US government documents, previous economic studies among DOD populations, as well as unpublished estimates based on DOD medical accounting systems (Table 4.1). Variable cost estimates were not directly available for deployed operational care settings and were, therefore, developed using data from two DOD health system information sources: The Medical Expense & Performance Reporting System and Expense Assignment System IV (MEPRS-EAS IV) and the Military Health System (MHS) Management Analysis and Reporting Tool (M2). The

MEPRS-EAS IV defines military treatment facilities (MTFs) in terms of the functions they perform (work centers) and then collects, aggregates and reports uniform MTF manpower, expense, and workload data to characterize those functions. For this study, costs and aggregate workload measures for selected MEPRS Functional Cost Codes (i.e., MTF work centers) were used for one estimate of variable supply costs (http://www.tricare.mil/ebc/rm_home/meprs/). A second system, the M2 uses expense data from MEPRS-EAS IV in conjunction with a set of TRICARE Management Activity (TMA)-approved formulas to calculate variable cost measures for individual inpatient cases and outpatient encounters which are reported in the M2 system, but which are not available in MEPRS EAS-IV (https://eids.ha.osd.mil/index.cfm/FuseAction/Products).

With the assistance of staff from the Uniform Business Office of the TMA, Management Control & Financial Studies Division, queries were made using the M2 system to identify the volume of patient activity and the MEPRS work centers where care was provided for both inpatient and outpatient encounters during FY2005 for cases with select primary International Classification of Diseases, Clinical Modification (ICD-9-CM) codes related to infectious diarrheal illnesses (ICD-9-CM codes 003.0, 003.9, 004.9, 008.43, 008.5, 009.1, 009.2, 009.3). Pediatrics work centers were excluded from the analysis because of our interest in capturing cost of care provided in operational settings. Once the MEPRS work centers of interest were identified, the MEPRS EAS-IV tool was used to query expenditure estimates for categories of medical, pharmaceutical, and other consumable supplies (including radiological supplies). Average supply costs were derived by dividing the supply costs by the total inpatient and outpatient encounters across MEPRS work centers. Those average supply costs were then applied to the 7,716

outpatient visits and 73 inpatient dispositions related to diarrheal illness on the basis of the ICD-9-CM codes used in this study. Average cost per outpatient visit was estimated at $58.03 (CY2006 $59.90) with 48%, 45% and 8% allocated to medical, pharmaceutical, and other supply categories, respectively. Average hospitalization cost was estimated at $2,461.23 (CY2006 $2,540.62) with 43%, 50% and 7% allocated to medical, pharmaceutical, and other supply categories, respectively.

An alternate method of estimating variable costs was developed using the MHS M2 Variable Cost measures calculated for inpatient and outpatient cases based on our selected ICD-9-CM codes. The specific M2 Variable Cost measures used included the cost categories of pharmacy, laboratory, radiology, and ancillary supplies. This alternate approach yielded an estimated average variable cost of $81.04 (CY 2006 $83.65) from 4,799 Active Duty visits. Similarly, MHS M2 data from 24 Active Duty hospitalizations yielded an estimate of $2,063.99 (CY 2006 $2,130.57) from cost categories of ICU, pharmacy, radiology, ancillary and other support. No ranges of cost estimates were available.

Based on estimates from these two systems, the base-case cost of hospitalization was assigned the value of $2,335.60, the average of the two estimates. For outpatient costs, stratification based on the categories of management in our model (optimal, sub-optimal, and confined to bed rest) was not available. It was assumed that sub-optimal treatment would cost lest than optimal treatment since this management pathway would likely utilize less pharmaceutical costs. Management that included confinement to bed rest was assumed to incur the highest cost because more severe disease would likely result in increased utilization of laboratory, radiology, pharmacy supplies and services.

Therefore, base-case cost estimates of $59.90, $71.78 and $83.65 for sub-optimal, optimal, and confined to bed rest outcomes were respectively assigned. To evaluate the uncertainty surrounding cost estimates, sensitivity analyses were conducted by adding and subtracting 20% of the point estimate values for each management outcome (Table 4.1).

Sources for all other MHS costs are described in Table 4.1, and all costs were modeled in 2006 US dollars. Costs obtained prior to 2006 were appreciated to CY2006 costs using the Consumer Price Index for inflation (http://www.bls.gov/cpi/). A 3% real discount rate was used to adjust future costs to present 2006 values. No adjustment was made for future inflation. Sensitivity analysis of the discount rate from 0% – 10% was conducted.

Effectiveness estimates. Estimates for DDL and DID for each terminal branch of the decision tree were estimated based on review of the literature and expert opinion (Table 4.3). The study investigators (MS Riddle and DR Tribble) have a combined 20 years of experience in the clinical treatment of acute diarrhea in operational deployment settings. This expertise combined with assumptions related to the clinical manifestations of diarrhea (stool frequency and illness duration), provided the basis for estimates of each of these outcome measures. With regard to DDL, a typical diarrheal illness was assumed to involve about five loose or liquid stools (bowel movements) per day for a duration of three to four days if left untreated.[111, 195] This was assumed to result in at least a quarter of one day lost from duty due to time spent traveling to and from the latrine. However, if an individual seeks treatment for the illness early enough, the duration of

Table 4.3 Efficacy estimates for multiplex and pathogen-specific models

Parameter Estimate (95% CI) or [low – high]	Vaccine Type			Source
	Multiplex/ETEC	*Campylobacter*	*Shigella*	
Duty days lost (DDL)				
Outpatient: Suboptimal	0.5 (0.3, 0.7)	1.1 (0.7 -1.5)	1 (0.6,1.4)	a
Outpatient: Optimal	0.25 (0.15, 0.35)	0.55 (0.33 -.077)	0.5 (0.3, 0.7)	a
Confined to bed rest	1 [1 – 2]	**	**	
Hospitalization	1.5 [1 – 3]	2 [1 – 3]	2 [1 – 3]	[126]
Aeromedical evacuation	7 [3 – 10]	**	**	a
Run its course	0.25 (0.15, 0.35)	0.55 (0.44, 0.66)	0.5 (0.3, 0.7)	a
Self-treatment success	0.125 (0.08, 0.17)	0.28 (0.22, 0.33)	0.25 (0.15, 0.35)	a, [86, 196-198]
Self-treatment failure	0.33 (0.20, 0.45)	0.72 (0.44, 1.00)	0.65 (0.4, 0.9)	a, [190]
Diarrhea illness days (DID)				
Outpatient: Suboptimal	3.6 (2.0, 5.2)	8.0 (4.9, 11.1)	7.1 (4.3, 9.9)	
Outpatient: Optimal	2.5 (1.5, 3.5)	4.0 (2.4, 5.6)	2.7 (1.6, 3.8)	[41, 108, 199]
Confined to bed rest	3.5 [2.5 – 4.5]	**	**	a
Hospitalization	4.5 [3.0 – 6.0]	**	**	a
Aeromedical evacuation	8.5 [4.5 – 11.5]	**	**	a
Run its course	3.6 (2.0, 5.2)	8.0 (4.9, 11.1)	7.1 (4.3, 9.9)	[111, 195],[200]
Self-treatment success	1.5 (0.9, 2.1)	3.0 (1.8, 4.2)	1.7 (1.0, 2.4)	[86, 196-198]
Self-treatment failure	3.6 (2.0, 5.2)	8.0 (4.9, 11.1)	7.1 (4.3, 9.9)	a, [111, 195], [200]

ETEC = Enterotoxigenic *E. coli;*
**same as baseline
a. subject matter expert opinion

illness could be shortened to less than 24 hours following treatment onset,[85, 201] although seeking treatment also incurs a time loss of approximately one to three hours in a deployment setting. Based on the previously described systematic review of diarrheal disease in military populations, the average duration of symptoms until treatment was sought during deployment was about 1.5 days.[125] This pre-treatment duration was assumed to be the same for all management outcomes associated with seeking treatment from the military health system. Therefore, whether an individual sought treatment and was provided optimal therapy, sought treatment and was provided sub-optimal therapy,

or allowed the disease to run its course, a minimum of 0.25 day lost (6 hours) per episode was estimated. Alternatively, if an individual self-treated successfully, treatment was assumed to be initiated in a timely manner (within 12 hours), and post-treatment duration of symptoms would continue for 24 hours (mean duration of illness 1.5 days), roughly equivalent to 0.125 DDL.[86, 196-198] However, if an individual failed self-treatment, it was estimated that in most cases the disease would run its natural course over 3.6 days, as discussed below, but in 30% of cases, the individual would end up seeking care for continuing illness, resulting in an average time lost of 0.325 days (time lost seeking care + time lost due to illness before and after seeking care) per self-treatment failure case.[190] In the absence of any basis for high and low estimates for our DDL parameter estimates, a normal distribution with a standard deviation equal to 20% of the point estimate was assumed. DDL associated with medical evacuation was estimated to be 7 (range 3 – 10) days, and estimates for confinement to bed rest and hospitalization were based on published literature.[19, 51, 125, 131]

DID were similarly obtained through use of the published literature and expert judgment. Acute infectious diarrhea (not pathogen-specific) lasts on average 3.6 days (SD 0.8) [200], but timely and effective treatment can reduce the duration of illness to less than 24 hours after treatment onset.[85, 201] Therefore, DID was estimated to be 3.6 days (95% CI 2.0 – 5.2) for sub-optimal treatment, self-treatment failure, and when the disease was allowed to run its course. Based on treatment trials and epidemiological studies, it was assumed that with appropriate antimicrobial therapy, duration of illness following the first dose of antibiotics would be approximately 24 hours.[41, 85, 88, 101, 201, 202] Furthermore, total duration of illness for individuals hospitalized or confined

to bed rest was estimated to be only slightly longer due to illness severity, given best available care. Based on these assumptions DID for those hospitalized was estimated to be 3.5 days (range 2.5 – 4.5) and for those confined to bed rest 4.5 days (range 3.0 – 6.0).

Pathogen-specific effectiveness estimates (DDL and DID) were similarly obtained from epidemiologic studies and clinical trials for both treated and untreated disease in military populations, as well as expert opinion. Multiplex vaccine estimates were used for ETEC, given that this pathogen is the most common cause of all diarrhea from which the multiplex estimates were derived. *Campylobacter* illness duration post-treatment, based on clinical trials and observational studies conducted in Thailand, were between 1.7 days and 3.3 days [41, 108, 199]; and assuming a 1.5 day pre-treatment duration of symptoms, total duration of symptoms in those who sought care and received optimal treatment was estimated to be between 3.2 and 4.8 days. A midpoint of 4.0 days was used as the point estimate and assumed to be normally distributed with a 95% CI of 2.4 to 5.6 days. Only one treatment trial has been reported with stratified results specific to *Shigella*, and a post-treatment duration of 1.2 days was reported, providing an estimate of 2.7 days (95% CI 1.6 – 3.8). DDL was estimated by applying the overall proportion of illness duration representing DDL to the total duration of illness for each specific pathogen. For example, mean duration of illness is 3.6 days for an average episode of acute diarrhea and results in a DDL of 0.25 days, or 7% of total duration of illness. This proportion was applied to pathogen-specific estimates of diarrhea illness duration, resulting in estimates of 0.5 and 0.55 DDL per episode left untreated for *Shigella* and *Campylobacter*, respectively. Other DDL outcome parameters were similarly estimated and described in Table 4.3. As with the multiplex/ETEC model, standard errors of 20%

of parameter values were calculated for each *Campylobacter*- and *Shigella*-associated DDL per episode.

To validate our initial assumptions, two additional subject matter experts (JW Sanders, DN Taylor), who also have extensive experience in the treatment of diarrhea in deployed settings, were consulted. Based on their assessment and discussions, final revised parameter estimates were selected.

Sensitivity analyses. To evaluate the robustness of the multiplex and pathogen-specific vaccine models, CERs were estimated using probabilistic sensitivity analysis (Monte Carlo simulation), in which input variables on probability, cost, and effectiveness were varied within the ranges described. The cost and effectiveness input variables were assumed to follow uniform, triangular, or normal continuous probability distributions based on the relative certainty of estimates in the model. If only range information was known for a variable, a uniform distribution was assigned along the range to allow for maximum uncertainty surrounding the true value. For parameters where a point of central tendency was known, but ranges were not symmetrical or were uncertain, a triangular distribution was used. Where data on the mean value and confidence intervals were available, or the variable was represented by data for which normality was assumed, a continuous normal distribution was constructed. For each simulation iteration, parameter values for each input variable were chosen at random from the defined probability distributions. Table 4.1 details the distributions for listed parameters. Effectiveness outcomes (DDL and DID) were assumed to be normally distributed with the exception of confinement to bed rest and hospitalization, which were assigned a

triangular distribution, and medical evacuation, which was assigned a uniform distribution.

The CERs were recorded as the outputs for each of 3,000 iterations, and the output variables were collated as probability distributions. The mean and range, encompassing 75% of estimates, were calculated and represented in summary form. The simulation assumed that all input parameters varied independently of each other, unless they were explicitly linked in the model. For probabilities associated with sub-branches beginning with "diarrhea", "seek treatment" and "do not seek treatment", estimates were normalized to unity based on the random probabilities assigned for each iteration. For example, when an individual seeks treatment, there are four mutually exclusive pathways that could occur, and the branch probabilities must sum to unity. However, the summation of randomly selected estimates from the individual probability distributions during a single simulation run could exceed or fall below a probability of 1.0 (100%). Therefore, in iterations where unity was not achieved, adjustments of individual probabilities were made to sum to unity based on their proportional distribution for that iteration.

To determine what variables most influenced the CER outcome during the 3,000 simulation iterations, each input variable was compared to the CER outcome variable by rank order and compared by calculating a Pearson correlation coefficient. A contribution to variance percentage was then estimated by summing the squared correlation coefficents for each input variable, and dividing each squared correlation coefficient by this sum to compute normalized values. These normalized values were converted to percentages to indicate which input variables were most important in explaining the

variation in the CER, and whether the inputs were positively or negatively correlated with the CER. Probabilistic sensitivity analyses were conducted using Crystal Ball Version 7.2.2 (Decisioneering, Inc., Denver, CO) Excel add-in program.

Secondary analyses. Separate analyses were conducted to evaluate the relative efficiency of pathogen-specific vaccines, assuming immediate availability of vaccines for troops ready to deploy (no development costs or time delay). For these analyses, a one year time-horizon was selected and costs associated with vaccine development and ongoing clinical and epidemiological studies were not included. All other parameter estimates and uncertainty ranges were utilized as in the primary pathogen-specific analyses, except as follows. The first sub-analysis assumed the same global deployment estimates (average 147,000 per year), incidence estimates, and pathogen prevalence. This analysis was aimed at evaluating the relative cost-effectiveness of each vaccine from a broad geographic perspective. The second sub-analysis focused on region-specific pathogen combinations and assumed a deployment size of 30,000 troops to simulate the deployment of an Army or Marine division in a typical operational setting. Region-specific pathogen combination scenarios evaluated were *Campylobacter* in SE Asia, ETEC in the Middle East, and *Shigella* in Latin America and sub-Saharan Africa. Probability estimates derived from the previously published systematic review of infectious diarrhea in military populations were used.[125] Because no region-specific incidence estimate for sub-Saharan Africa was available, the overall base-case estimate of 28.9 (SD 4.93) episodes per 100 person-months was used for this region.

Results

Base-case analysis. Over a 30 year time horizon, development and acquisition of a multiplex vaccine against three primary causes of travelers' diarrhea would potentially prevent 57,543 cases of diarrhea annually, reduce the number of duty days lost from 16,591 pre-vaccine licensure, to 5,973 post-licensure, and diarrhea illness days from 171,253 to 61,651 annually among a cohort of 147,000 troops deploying for 3.5 months. Reductions in other medical utilization and morbidity metrics pre- and post-licensure are described in Table 4.4. At a vaccine cost of $48.98 per dose, the present value of a vaccination program is estimated at $256,145,050 for a 3-dose series using base-case model assumptions of a 30-year time horizon with a 10-year vaccine development time frame. The present value of the cost of care averted by the vaccine acquisition strategy is estimated at $16,266,784. Over the 30-year time horizon, 265,451 lost duty days would be averted. Based on this model, the cost-effectiveness ratio for duty days lost (CER_{DDL}), or the cost per DDL averted, was estimated to be $2,102. Similarly, the cost per diarrhea illness days averted (CER_{DID}) was estimated to be $204. (Table 4.4).

Compared to a multiplex vaccine, base-case estimates of pathogen-specific vaccines resulted in CER_{DDL} estimates of $1,243, $1,188, and $1,860 for *Campylobacter*, ETEC and *Shigella* vaccines, respectively. Pathogen-specific vaccine CER_{DID} estimates were $119, $115 and $195 per DID averted for *Campylobacter*, ETEC and *Shigella* vaccines, respectively.

Table 4.4 Base-case results for estimates of total costs and effectiveness measures, and incremental cost effectiveness ratios for multiplex and pathogen-specific primary analyses

	Multiplex	***Campylobacter***	**ETEC**	***Shigella***
Annual vaccine-preventable illness events	57,543	14,720	33,009	9,814
Annual cost of immunizing target population	$17,215,538	$6,019,650	$6,019,650	$6,019,650
Annual number of events (pre:post licensure)				
Outpatient – suboptimal	4,337 : 651	728 : 109	2,451 : 368	287 : 43
Outpatient – optimal	5,438 : 816	893 : 134	3,119 : 468	353 : 53
Confined to bed rest	2,913 : 437	1555 : 233	1,708 : 256	1,413 : 212
Hospitalization	259 : 39	136 : 20	149 : 22	155 : 23
Medical evacuation	19 : 3	5 : 1	11 : 2	3 : 0
Run its course	26,747 : 4012	6,842 : 1026	15,343 : 2302	4,562 : 684
Self-treatment success	14,265 : 2140	912 : 137	8,183 : 1227	608 : 91
Self-treatment failure	3,566 : 535	3,649 : 547	2,046 : 307	2,433 : 365
Total cost of care for VAS	$19,806,296	$8,007,154	$10,670,211	$6,262,898
Total cost of care for current management	$36,073,081	$13,765,555	$20,710,372	$12,155,987
Annualized cost of care averted by VAS	$542,226	$191,947	$334,672	$196,436
DDL				
Total DDL VAS	232,270	144,947	125,871	82,138
Total DDL current management	497,720	293,812	286,071	186,676
Annualized DDL averted due to VAS	8,848	4,962	5,340	3,485
CER ($USD/DDL averted)	**$2,102**	**$1,243**	**$1,188**	**$1,860**
DID				
Total DID VAS	2,397,536	1,511,936	1,296,692	783,462
Total DID current management	5,137,578	3,064,736	2,947,026	1,780,595
Annualized DID averted due to VAS	91,335	51,760	55,011	33,238
CER ($USD/DID averted)	**$204**	**$119**	**$115**	**$195**

DID = Diarrhea illness days; DDL = Duty days lost; VAS = Vaccine acquisition strategy

Compared to the model with a 3% discount rate, the undiscounted cost of immunizing the target population was estimated at $344,339,415 (vs. $256,245,050) and the undiscounted cost of care averted by the vaccine acquisition strategy was estimated at $31,287,172 (vs. $16,266,784). Undiscounted estimates of CER_{DDL} for a multiplex, *Campylobacter*, ETEC, and *Shigella* vaccine were $2,577, $1,542, $1,443 and $2,286 per duty day lost averted, respectively. Similarly, undiscounted CER_{DID} estimates were computed as $250, $146, $140, and $240 per diarrhea illness day averted for multiplex, *Campylobacter*, ETEC and *Shigella* models, respectively.

Secondary analyses. Results of secondary analyses are reported in Table 4.5. Assuming a vaccine was immediately available for use without the added costs of research and development or clinical/epidemiologic studies, a multiplex vaccine utilized annually in a deployed military cohort would result in a CER_{DDL} of $1,177, which is 56% of the CER_{DDL} for the base-case analysis ($2,102). Similarly, each CER_{DDL} for pathogen-specific vaccines was also reduced compared with the base-case analysis when it was assumed that vaccine was immediately available. The CER_{DDL} was estimated at $693, $672, and $1,104 for *Campylobacter*, ETEC and *Shigella* vaccines, respectively. CER_{DID} is similarly described in Table 4.5.

Analyses were also conducted for scenarios in which a single pathogen-specific vaccine was administered to a smaller cohort of 30,000 troops deploying to a particular high-risk geographic region, simulating a peacekeeping mission or large exercise. *Campylobacter* vaccine administered to troops deploying to SE Asia was found to have the lowest CER_{DDL} at $170, which was four to six times lower than the other pathogen-

Table 4.5 Base-case estimates for secondary analyses, assuming immediate availability of vaccine and y pathogen-region categories

	Vaccine Immediately Available				Pathogen-region Categories			
	Multiplex	Campy	ETEC	Shigella	Campy--SE Asia	ETEC--Middle East	Shigella-sub-Sah. Africa	Shigella--Lat. Amer. & Carib.
Annual Deployment Size	147,000	147,000	147,000	147,000	30,000	30,000	30,000	30,000
MONTHLY incidence (as percent)	28.90%	28.90%	28.90%	28.90%	37.30%	24.30%	28.90%	29.90%
Pathogen prevalence	38.70%	9.90%	22.20%	6.60%	23.90%	22.20%	9.00%	6.20%
DDL								
Total DDL VAS	3,325	1,959	1,907	1,245	1,246	327	346	247
Total DDL current management	16,623	9,794	9,536	6,223	6,228	1,636	1,732	1,234
Annualized DDL averted due to VAS	13,298	7,835	7,629	4,978	4,982	1,309	1,385	987
CER ($USD/DDL averted)	**$1,177**	**$692**	**$672**	**$1,104**	**$170**	**$821**	**$781**	**$1,139**
DID								
Total DID VAS	34,249	20,432	19,647	11,871	12,992	3,371	3,304	2,355
Total DID current management	171,246	102,158	98,234	59,353	64,961	16,857	16,518	11,773
Annualized DID averted due to VAS	136,997	81,726	78,587	47,483	51,968	13,485	13,214	9,418
CER ($USD/DID averted)	**$114**	**$66**	**$65**	**$116**	**$16**	**$80**	**$82**	**$119**

DID = Diarrhea illness days; DDL = Duty days lost; VAS = Vaccine acquisition strategy

specific vaccine-region combinations (Table 4.5). A *Shigella* vaccine for troops deploying to Latin America and the Carribean had the highest CER_{DDL} at $1,139.

Sensitivity analyses. The results of the multivariable probabilistic sensitivity analysis (Monte Carlo simulation) of cost-effectiveness outcomes for the base-case analysis, vaccine immediately available scenario, and pathogen-specific vaccine-region-scenarios are graphically presented in Figures 2 and 3. The median value of the simulation CER_{DDL} for the multiplex vaccine was estimated at $1,279 (IQR $828 – $1,995). Seventy-five percent of simulation outcomes fell between $623 and $2,708. If a multiplex vaccine were immediately available, we estimated a CER_{DDL} of $907 (IQR $575 - $1463). With respect to individual pathogen vaccines, *Campylobacter* and ETEC were similar and had CER_{DDL} lower than the multiplex vaccine in the primary and vaccine immediately available models. In contrast, *Shigella* vaccine estimates were higher (Figure 4.2). In pathogen-specific vaccine-region combinations, *Campylobacter* vaccine used for troops deploying to SE Asia was the most cost-effective with a median CER_{DDL} of $156 (IQR $70 – $313). Similar to the probabilistic sensitivity analysis estimates for DDL, DID estimates were lower than base-case estimates for each of the model scenarios. Median CER_{DID} were estimated at $118, $86, $84, and $134 for multiplex, *Campylobacter*, ETEC, and *Shigella* models, respectively. Median CER_{DID} and IQR estimates for each scenario are presented in Figure 4.3.

In the multiplex vaccine model, deployment time was found to be the most influential input parameter, inversely rated to the CER_{DDL} (i.e. as deployment time goes up, CER goes down) and explaining 49.8% of the variance in the (48.7% in the CER_{DID}

model). The remaining top ten influential parameters in the multiplex vaccine model included time horizon, disease incidence, discount rate, number of doses, vaccine preventable pathogen prevalence, cost per dose, effectiveness outcomes associated with disease running its course, vaccine efficacy and deployment size. (Figure 4.4a & 4.4b) These influential parameters (including deployment time) explained approximately 80% of the variance in the CER_{DDL} and CER_{DID} models.

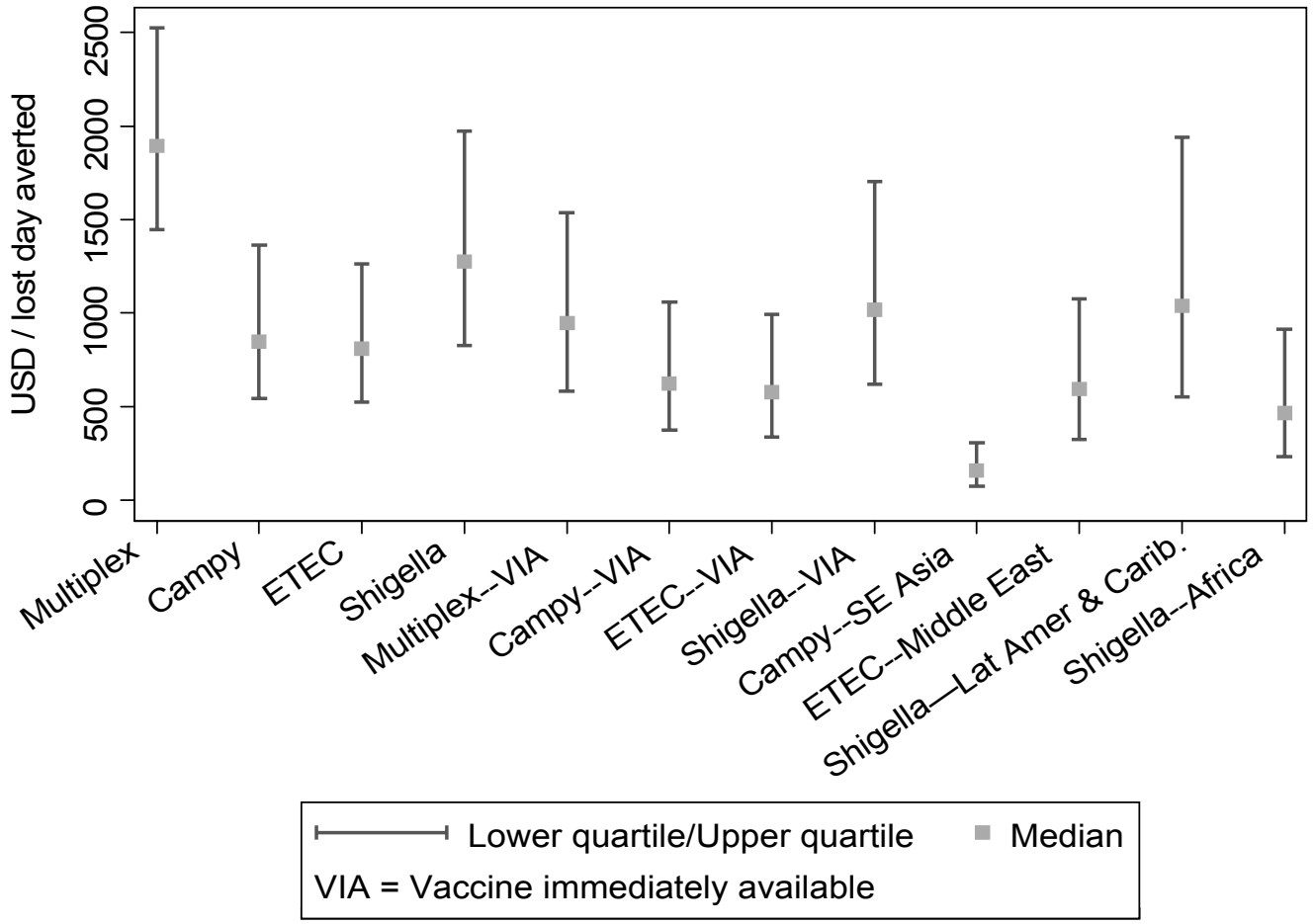

Figure 4.2 Probabalistic sensitivity analysis (Monte Carlo simulation, 3000 runs) evaluating cost per dlost duy day averted by vaccines against infectious diarrhea agents and by pathogen region categories

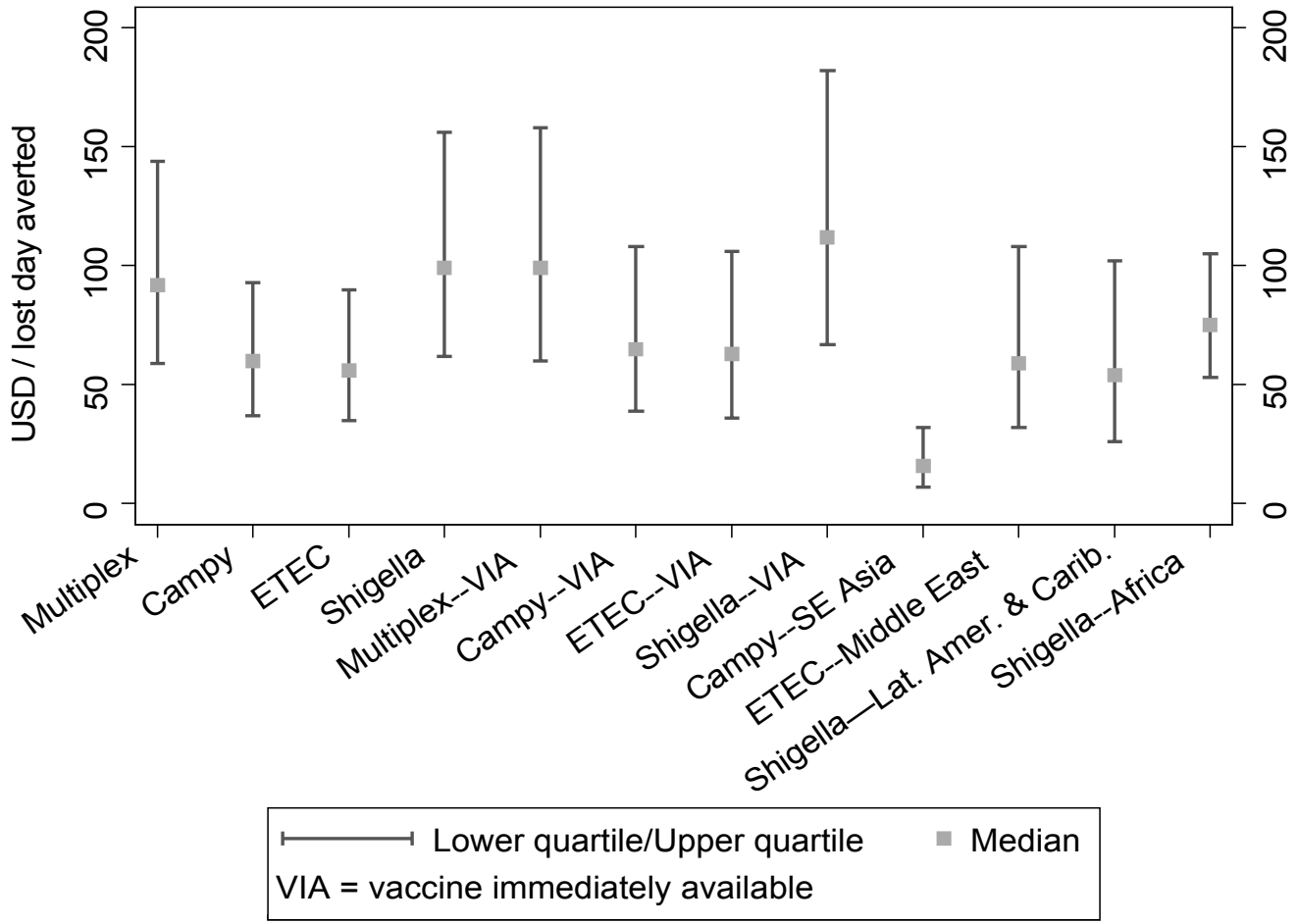

Figure 4.3 Probabalistic sensitivity analysis (Monte Carlo simulation, 3000 runs) evaluating cost per diarrhea illness day averted against infectious diarrhea agents and by pathogen-region categories.

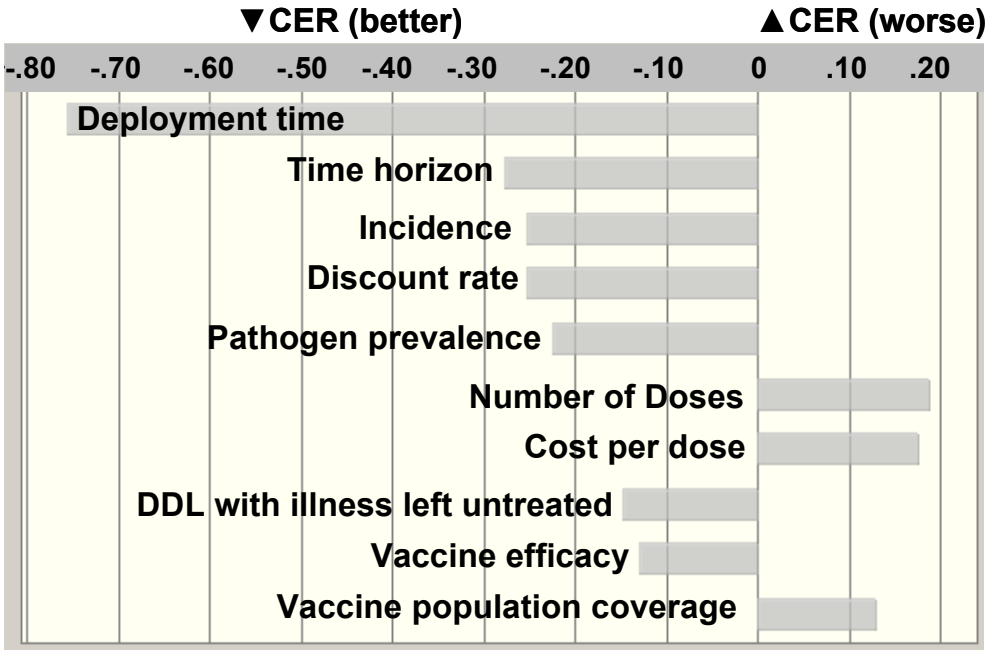

Figure 4.4a Pearson correlation coefficients for top 10 parameters most correlated to duty day lost (DDL) cost effectiveness ratio (CER) estimate.

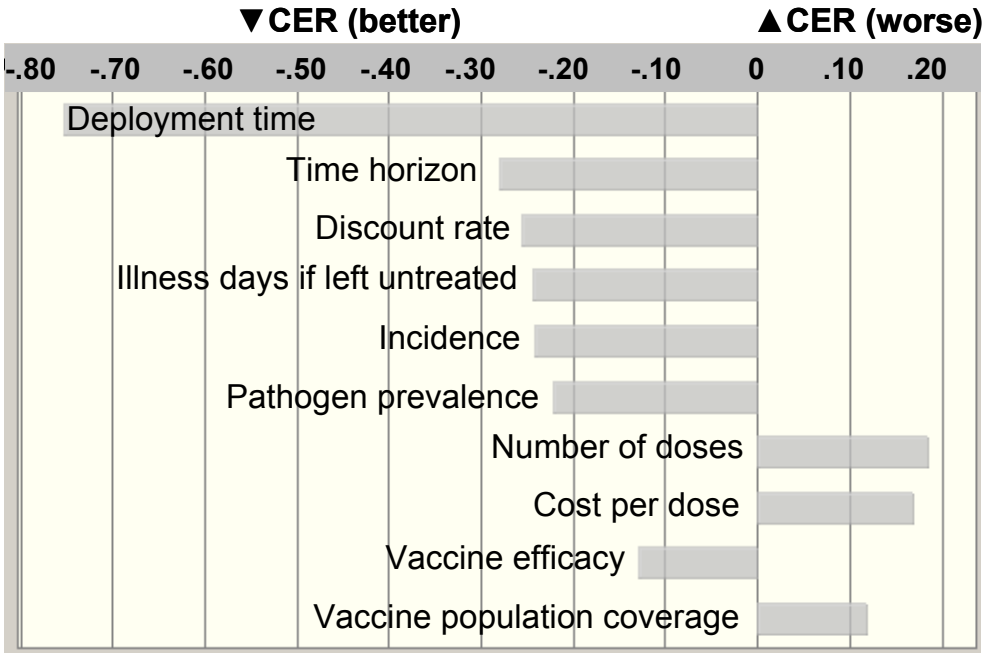

Figure 4.4b Pearson correlation coefficients for top 10 parameters most correlated to diarrhea illness day(DID) cost effectiveness ratio (CER) estimate

Discussion

Using the base-case (best estimate) parameters in the model, the cost of development, acquisition and use of a multiplex vaccine against three common bacterial pathogens (*Campylobacter*, ETEC and *Shigella*) among deployed US troops over the next 30 years would be approximately $2,100 to avert a single lost duty day. If a multiplex vaccine were available for use today, the estimated CER_{DDL} would be $907 (IQR $575 - $1463). The meaning of the absolute value of these CER_{DDL} estimates is unclear as no similar estimates exist for other medical or non-medical threat countermeasures currently being developed or already in use. A recent Congressional Budget Office (CBO) report on the monthly deployment cost in Iraq estimated it to be between $18,700-19,500 (2004 US dollars) per Soldier or Marine, including training reservists and providing backfill for deployed active-component personnel.[203] These CBO estimates equate to a daily cost of $656-685 per day (2006 US dollars) per soldier, which is closely approximated by the range of values we obtained from sensitivity analysis for current use of the multiplex vaccine. Pathogen and region-specific scenarios were even closer to this benchmark. Therefore, from a strict monetary (cost-benefit) perspective, the summary estimates for the development of a vaccine may represent a fair trade-off. The analytic approach, however, was a cost-effectiveness analysis, as it was felt that the most appropriate outcome from the perspective of the operational commander and medical health system in a deployment setting was DDL or DID averted, rather than placing a dollar value on these categories of days lost.

Using CERs, comparisons among the relevant pathogen-specific vaccines were made. A vaccine against *Campylobacter* and ETEC appeared to be more favorable than a vaccine for *Shigella*. Particularly for pathogen-specific vaccine-region scenarios, a *Campylobacter* vaccine utilized in SE Asia appears quite favorable. While all regions are considered high risk for infectious diarrhea, the systematic review of the literature to derive regional disease incidence estimates in military populations demonstrated that SE Asia had a 29% higher incidence of diarrhea compared with global rates (37 vs. 29 episodes per 100 person-months). Furthermore, *Campylobacter*, an invasive enteric disease with relatively higher morbidity, is the predominant pathogen in SE Asia, indicating a higher vaccine-preventable burden of illness for this pathogen-region combination. Thus, a vaccine against *Campylobacter*, if available today, would be relatively more cost-effective. Unfortunately, good estimates on the incidence of diarrhea in sub-Saharan Africa in military populations are lacking (only 3 studies exist). However, it is believed that *Shigella*, also an invasive pathogen associated with higher morbidity, may represent the predominate pathogen in this region.

In general, CER base-case estimates for DID averted mirrored estimates for DDL but at lower ranges of values ($16 to $204) for all scenarios. The lower range of values reflects the clinical features of diarrheal illness, which is generally characterized by mild-to-moderate symptoms lasting longer than time lost from work due to illness. As with DID, the interpretation of the absolute CER value is difficult in the absence of an appropriate external model for comparison. Although it might be reasonable to conclude that $16 is worth preventing a day of diarrheal illness, particularly if one has ever experienced a *Campylobacter*-associated illness. Indeed, it is difficult to place a cost on

the avoidance of an acute illness in a combat scenario as David O. Matson put most eloquently when he said, "I expect that our imaginations cannot fathom the problems attendant from the absolute urgency for relief from explosive vomiting and diarrhea when experienced within an armored vehicle under fire and at ambient temperature of 40°C."[204]

Sensitivity analyses. Based on the multi-way probabilistic sensitivity analysis, the following parameters were found to be the most influential variables in the model: deployment time, time horizon, disease incidence, discount rate, number of doses, vaccine preventable pathogen prevalence, cost per dose, effectiveness outcomes associated with illness running its course, vaccine efficacy, and deployment size. These findings were not unexpected and further demonstrate the face validity of the model.

Base-case CERs were greater than the probabilistic sensitivity analysis CER estimates. The parameter of deployment time was found to correlate strongly with the outcome measure, explaining approximately 50% of the outcome variance. Furthermore, deployment time was directly related to disease incidence, and its distribution represented a broad range of values (between 1 and 12 months). Therefore, when repeatedly sampled, the median value of this parameter is much higher than the base-case estimate of 3.5 months, resulting in a lower CER (e.g., more cost-effective) for any given scenario.

Implications of model assumptions. The assumptions relating to the model's perspective, scope, and structure have definite implications for interpretation, application, and generalization. The focus of this study was on a subgroup within the military, i.e.,

deployed personnel, and leaves out a number of other military populations that might benefit from a vaccine if it were available. The perspective of this study does not include Reserve or National Guard deployments, active duty who are permanently stationed overseas in countries of moderate- and high-risk for infectious diarrhea, nor military beneficiaries (family members) who accompany the active duty members to these overseas locations. All travelers who receive their care within the military health system (including active duty, beneficiaries, and retirees) would be likely to benefit from a vaccine to prevent diarrheal illness. Beyond these military beneficiaries, other traveler populations were not considered. These include leisure travelers, as well as large numbers of business travelers, who either travel frequently or relocate overseas for more permanent work assignments. DOD research is funded with public funds, so these other perspectives should be considered. Finally, there is the global burden of diarrheal disease, which is enormous. In the developing world, enteric pathogens cause the death of millions of children each year, and these affected populations would most definitely benefit from a safe, effective, and affordable vaccine (e.g. rotavirus). Some would say that any vaccine that reduces mortality and morbidity on a broad scale in the developing world would not only be considered just, but may also contribute to regional political and economic stability and reduce the need to deploy US troops. [205]

This economic analysis focused on the variable costs incurred in the acute management of diarrhea while in a field setting (except for treating rare adverse events associated with vaccine prior to deployment), and this has important implications. First, fixed costs related to staffing, supplying, and operating the military health system infrastructure during deployment were not considered. However, current medical

platform and staffing models are based on estimates of trauma-associated care and capacity, with the expectation that disease and non-battle injury are to be treated during periods of combat quiescence. Therefore, exclusion of these fixed costs was reasonable within the context of the model, since a decrease in diarrhea incidence would not likely lead to fewer beds or medical personnel, although it could be argued that a diarrhea vaccine might result in lower requirements for latrine capacity and supplies. Additionally, the opportunity cost of time spent by corpsman, medic, nurse, physician assistant or doctor treating a case of diarrhea was not addressed.

The focus on medical costs of acute treatment in the field also ignores the medical costs associated with the treatment of chronic sequelae, which may result from infection with these pathogens. The incidence of Guillian Barre syndrome has been estimated at 30.4 per 100,000 cases of *Campylobacter* infection [206], and reactive arthritis is known to be a sequelae of *Shigella* and *Campylobacter* infection.[207-209] Inflamatory bowel disease is also found to occur more frequently following enteric infection, especially those due to invasive pathogens.[210] These sequelae can result in severe morbidity, as well as increased health care costs for diagnosis and treatment. In addition, post-infectious irritable bowel syndrome (PI-IBS), a chronic functional bowel disorder, is now considered to be an important sequelae of infectious diarrhea, occurring in approximately 10% of people who report an episode of acute enteric infection.[211] Usually manifesting within six months of the acute infection and lasting several years, this illness is characterized by abdominal pain and diarrhea, resulting in decreased quality of life, lost work productivity, and increased healthcare expenses related to diagnosis and management.[212-219] This economic model focused on the consequences and costs of

acute diarrhea from the perspective of the military commander in the deployment setting. However, it is recommended that future models address these additional important aspects of infectious diarrheal diseases, specifically the sequelae of TD and the variable costs associated with their diagnosis and management.

Finally, it is important to note that the model assumed that current management practices and health-seeking behaviors will remain constant for both self-treatment and management by military providers over the analytic horizon (30 years). Furthermore, it was assumed that individuals do not self-treat effectively and that sub-optimal treatment could be provided when individuals do seek care. Probability estimates for these possible pathways were based on published data for both health-care providers and troops in deployed settings. Policy changes could result in system-wide training and guidelines for the management of diarrheal illness in the field. These changes could include the provision of antibiotics to non-licensed providers (corpsmen/medic) or even to the individual soldier for standby self-treatment. Even though variability in the model outcomes was dominated by deployment time and the treatment-related factors of duty days lost and days of illness associated with letting the disease run its course with no treatment, the probabilities associated with seeking care, self-treatment success, and receiving optimal care were all influential factors. Further study should explore the association between current practice patterns and disease morbidity, independent of vaccine development, to guide military leaders in best clinical practices to mitigate the effects of diarrhea today.

Limitations. This model represents a simplification of a complex array of chance events and outcomes for alternate pathways or strategies for a real life problem. However, it is arguably a fair representation of reality, capturing key elements based on best available data and focusing on a perspective of interest and importance to the US military, a population with a high disease burden. Although the focus on deployed US military populations does not readily allow for generalization to other populations, within or outside the DOD, the measures of effectiveness selected were considered to be the most relevant and meaningful to decision makers. Certainly, the cost to avert a lost duty day resonates with military commanders in the field, as well as with those policy and decision makers evaluating infectious disease counter measures. However, the model does not address the epidemic potential of particular pathogens. While two different pathogens could have equivalent monthly attack rates, a pathogen that incapacitates 30% of the soldiers of a particular unit within the first week (e.g. norovirus or *Shigella*) has very different operational consequences than a 30% attack rate spread over the course of the entire month. Given the transformation of force structure into smaller operational units, with soldiers performing multiple functions, and contingency operations in more remote locations without medical support, epidemic diarrhea affecting large numbers in a short amount of time could seriously degrade mission capability.

Estimates for influential parameters, such as disease incidence and pathogen prevalence, were based on the best available data in a systematic review of the literature.[125] However, these estimates were derived from data representing a limited number of studies covering only a partial list of countries in each region. Therefore, these data may poorly approximate the global risk of diarrheal disease to which deployed

troops could be exposed in the future. Particularly, the lack of data for disease incidence and pathogen prevalence in the important region of sub-Saharan Africa represents an important knowledge gap and contributes to uncertainty surrounding the outcome estimates for *Shigella* vaccine models. Future studies should focus on incidence and prevalence of enteric pathogens in this region.

For any given parameter, one could argue about the individual number used. However, on whole these parameter estimates were assigned using best available published literature and other technical reports, and are relatively correct across the multiple pathogens and regional scenarios. However, in addition to the lack of data related to pathogen prevalence in particular geographic regions, additional gaps in the current knowledge base, particularly in the area of efficacy outcomes, were uncovered. Estimates for these parameters required the alternate approach of utilizing expert judgment, and base-case estimates for probabilities and outcome measures were based on a Delphi survey. The results of the Delphi survey represents an unbiased qualitative synthesis of data from a panel of subject matter experts using rigorous and accepted methodology. Additionally, a consistent approach was used for parameter estimates specific to each pathogen. Furthermore, the Monte Carlo sensitivity analysis, utilizing probabilistic techniques, allowed assessment of the robustness of the model's conclusions, with the uncertainty in the data inputs. Future studies should be conducted to obtain more precise estimates for parameters that currently lack such information. In particular, data on efficacy outcomes (in the case of field studies) associated with various management pathways, as well as actually costs of treating diarrhea in the field, are needed.

Third, decision models are only as valid as the models themselves. A number of internal and external model validation steps were included. First, the TD vaccine acquisition model was an adaptation of an established model developed by the IOM for evaluating vaccine development priorities.[55] Whereas the IOM model took a societal perspective and focused on a broad spectrum of disease, this model adopted a military-specific perspective and focused only on a vaccine against infectious diarrhea, more specifically, for three important bacterial causes of diarrhea. Descriptive validity of the model was achieved through extensive discussions with subject matter experts in the areas of diarrheal diseases in military populations and health economics. As detailed in the methodology, this model was based on rational assumptions and a comprehensive review of population-specific literature, with an attempt to achieve balance between over-simplification of the model and complex reality.

Secondly, the technical validity of this economic model was established through independent verification of program formulas, data entry, and evaluation for logic inconsistencies (S Perez-Cachafiero). In addition, extreme values of input variables were used, with comparison of the model's actual output to expected outcomes. Zero values of hospitalization and medical evacuation rates yielded no events for these categories. Similarly, when assuming zero vaccine efficacy or zero coverage rates, the model calculated the same effectiveness outcomes for the current management strategy arm as would be expected. Face validity of this model was discussed further in the sensitivity analysis results. External validity of this model could not be evaluated as there were no independent models available to corroborate our results or conclusions.

A final important limitation is that this economic model assumed a hypothetical scenario in many ways. One, which is of considerable importance, was that in the arena of vaccine development for infectious diarrhea, fiscal constraints are current reality. The model assumed a cost of $376 million (based on DOD estimates) over the next 10 years for successful vaccine development, while in reality current DOD spending is approximately $6 million per year(8% of the Military Infectious Disease Research Program budget) on vaccine(s) against infectious diarrhea. As previously described, the IOM identified under-funding as an issue, along with failure to set priorities, in their 2003 report on the Improving Vaccine Acquisition and Availability in the US Military. [53]

Summary. Protecting the health of our Armed Forces is essential to national security. US troops must be prepared to be deployed anywhere in the world, often on very short notice, whether it is for combat operations, for a training exercise or disaster relief mission, or to serve as peacekeepers. Today's troop deployments can be characterized as smaller, more mobile, more diverse, and entailing multiple, more frequent deployments compared with earlier decades. With this transformation in contingency operations, the readiness and effectiveness of every individual soldier becomes of critical importance. Vaccines have almost always demonstrated their value as one of the best preventive interventions to mitigate the threat of acute infectious disease. The important question of which vaccines or other countermeasures the military should invest in should be answered in a systematic way in order to best protect those put in harms way.

Chapter 5: Conclusion

"Science can only ascertain what is, but not what should be, and outside of its domain value judgments of all kinds remain necessary."

--Albert Einstein

Summary of findings

Based on systematic search for the best data available to assign quantitative estimates for various parameters in the economic model, a multiplex vaccine to prevent lost duty days due to acute diarrhea illness would not be cost saving compared to current clinical management strategies. However, the cost-effectiveness ratio of pathogen-specific vaccines for ETEC and *Campylobacter*, in terms of cost per lost duty days averted, appears favorable when compared with the estimated cost of losing a soldier for a day in an operational setting. It should be recognized that the decision on implementing a preventive intervention does not always rely on the adage of an "ounce of prevention worth a pound of cure." Many instituted public health interventions are not cost saving. A recent review which focused on published cost-utility analyses of infectious disease interventions (prevention and treatment) published between 1976 and 2001 found that median cost-utility ratios varied by type of intervention and ranged from $13,500/QALY for immunizations to $810,000/QALY for blood safety.[220] Furthermore, while there is no universally recognized benchmark, it appears that <$50,000/QALY is an accepted target based on Medicare's decision to cover dialysis for patients with chronic renal failure at this threshold.[221] It would be interesting to explore the cost-effectiveness of current pre-deployment vaccines or other preventive interventions using this deployment model to identify cost-effective benchmarks. However, some vaccines may be difficult to evaluate, including yellow fever or anthrax vaccines, due to the degree of uncertainty in the risk of these diseases.

It should be noted that the utility of the decision tool is the ability to evaluate relative differences between alternative interventions, rather than the absolute values generated by the economic analysis. In this study, the ETEC vaccine, due to the ubiquitous nature of this pathogen, and the *Campylobacter* vaccine, due to the severity of illness which the bacteria causes, were shown to be relatively more cost-effective compared to the *Shigella* vaccine. The results do not advocate pursuing one vaccine over another, but they do allow a comparison of vaccines for different pathogens based on a common metric (e.g., cost per DDL averted or DID averted), and emphasize that the burden of disease is not the same for these three pathogens. It is unknown how other infectious disease vaccines that the DOD is developing would compare to a vaccine for travelers' diarrhea using this prioritization system. A primary aim of this study was to develop a model which could be applied to countermeasures against other deployment health threats. This model could serve as a tool for policy and decision makers to assist in the prioritization of product acquisition targets in the area of infectious diseases.

Implications for public health policy and decision-making

This analysis does not solve the problem of what vaccines the DOD should develop, and that was not the intent. The purpose was to provide insight into the development of a model that incorporates important and influential factors affecting measures of cost-effectiveness. The overall goal was the use of the model to inform DOD policy and decision makers in evaluating countermeasures to deployment health threats. The economics of vaccine acquisition is but one piece of information utilized in

a complex array of factors involving multiple stakeholders and trade-offs that influence the best option from among alternative strategies. Perhaps this concept is best referred to as the decision environment. (Figure 5.1)

Figure adapted from RL Keeny (1982) [222]

Figure 5.1 The decision environment

The concept of the decision environment has been utilized in political and business management realms to explain how multiple factors intertwine to increase the complexity of a particular decision.[223-225] One of the first descriptions of this concept as it relates to public health was put forth by Keeney in an introduction to medical decision analysis.[222] Several of these factors relate to the decision environment for the acquisition of infectious disease countermeasures within the DOD. Paramount is the

issue of more than one decision maker and its impact on the decision environment, as most clearly stated by the IOM:

> "Early in the committee's deliberations, one DOD representative attempted to clarify the DOD process for setting vaccine research and development priorities with an illustrative slide…[which] clearly conveys the complex gauntlet awaiting the potential acquisition of a new vaccine from the time of the first conception of its need through the late stages of development. [It] also vividly demonstrates the absence of a single organizational locus of authority and responsibility for that process. Not only is no individual in charge, but too many individuals and entities are responsible for other, unrelated activities in addition to their responsibilities for vaccines and the development of effective countermeasures against infectious disease threats."[53]

This diffuse and complex organizational structure lacking a single "locus of authority," likely has the effect of reduced responsiveness to critical needs and perpetuation of the status quo through indecision. A second important component to highlight in the decision environment for DOD vaccine acquisition is the issue of "interdisciplinary substance." Countermeasure acquisition is not only in the realm of research and development, but also requires important input from combat commanders, medical providers, production personnel, and military purchasing and logistics personnel. The cost-effectiveness of a countermeasure is but one metric representing one perspective in the decision process. Moreover, the sequential nature of decision making has an important impact on the overall decision environment. Yesterday's choices affect tomorrow's alternatives, and the desirability or value placed on those alternatives. The critical mass of research capacity, support personnel, and technical expertise cannot easily be shifted without significant opportunity costs. Related to this notion it appears that Newton's first law of physics would apply in that countermeasure targets already

started down the development pipeline will continue to be developed, whereas those that have yet to be initiated will remain on the shelf. These and other factors in this decision environment, including consideration of those countermeasures under development by non-military/industry groups to avoid duplication of effort, represent the complexity of the decision problem and the challenge of finding the best solution.

Underlying this complex decision environment is the immutable fact that resources are limited and allocation must be based on best available evidence and relevant health outcomes from a perspective that makes sense. This is where the utility of economic analyses enters the picture. Historically, funding of research and development priorities have not always been correlated with disease burden. Certainly, existing development priorities for malaria, diarrhea, and Dengue fever vaccines could be justified by prior military experience. But what about antibiotic resistant wound infections, which are causing large amounts of morbidity and health care utilization, or norovirus, which has been associated with numerous mission-compromising outbreaks? These are real problems among today's troops. Development priorities may not parallel disease burden; a New England Journal of Medicine article evaluated the correlation between the burden of a given disease in the US and National Institutes of Health (NIH) basic science funding in support of that disease.[226] There was no relation between the amount of NIH funding and the incidence, prevalence, or number of hospital days attributed to the 29 diseases or conditions they evaluated, although disability adjusted life-years and funding were strongly correlated. Interestingly, some diseases were better funded than would be expected (e.g., acquired immunodeficiency syndrome, breast cancer, diabetes mellitus, and dementia), whereas other diseases with higher burden were not as well

funded (e.g., chronic obstructive pulmonary disease, perinatal conditions, and peptic ulcer disease). Funding agencies like the NIH and MIDRP should periodically evaluate their program priorities in order to best match the limited resources with the most cost-effective research effort.

Directions for future research

In addition to further research to refine estimates for which there is a high degree of uncertainty, encompassing a broader perspective (e.g., entire MHS) or the addition of other sequelae associated with TD (e.g., PI-IBS, reactive arthritis, Guillain-Barre syndrome), and would allow other strategies to be considered to mitigate the burden of TD. Specifically, it would be informative to look at chemoprophylaxis in both small and large deployments of short duration.

Based on the literature review and development of the model, it is clear that a significant burden of TD illness could be prevented among troops deploying overseas. Estimates from the systematic review of literature, Delphi study and the model have enabled the development of a diarrhea burden pyramid from which a number of conclusions can be made. (Figure 5.2) First, between one out of four to one out of five illnesses result in a service member seeking care for diarrhea. Based on currently available data, it does not appear that illness among those not seeking treatment is any less severe. In addition, 60% of troops who do not seek care also do not attempt self-treatment and let the disease run its course. This results in a significant burden of completely untreated disease. Second, the current literature finds that sub-optimal

treatment is provided about a third of the time, with treatment consisting of fluids only in about 15% of cases. Thus, the current management (or suboptimal-management)

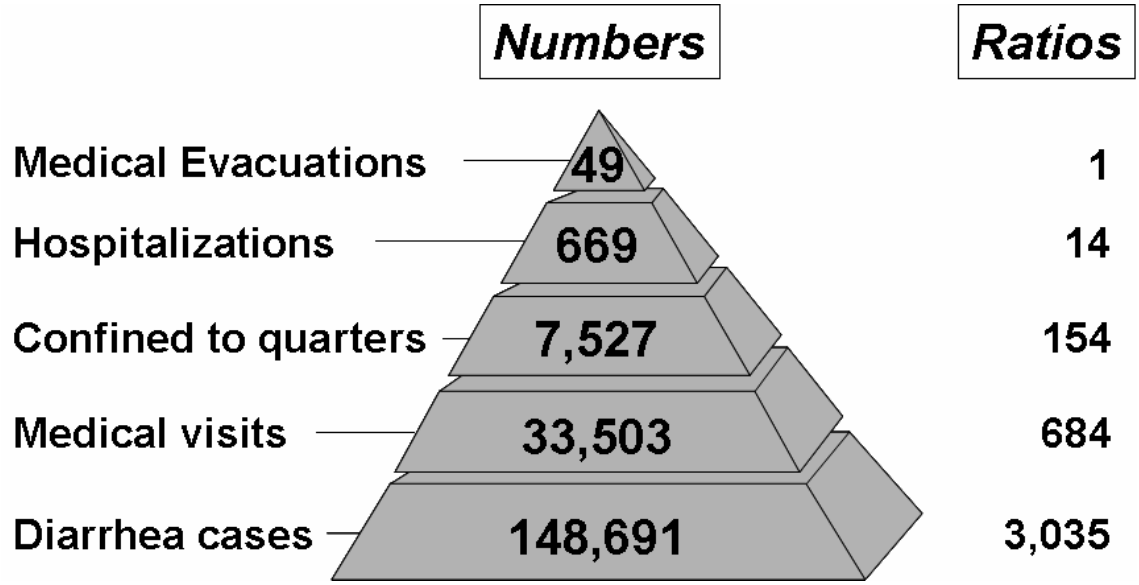

Figure 5.2 Diarrhea burden of disease pyramid in deployment

environment related to travelers' diarrhea accounts for an important added burden of disease, which could potentially be mitigated.

This variability in management and observed health outcomes needs to be further evaluated and addressed where possible. Policy changes could result in system-wide training and best practices guidelines for the management of diarrheal illness in the field. Changes in current management strategies could also include the provision of antibiotics to non-licensed providers, such as corpsmen and medics or even to the individual soldier for standby self-treatment. Finally, the individual soldier needs to understand that suffering through diarrhea is not necessary. Further study should explore the association

between current practice patterns and disease morbidity, independent of vaccine development, to guide military leaders in current best clinical practices to mitigate the effects of diarrhea.

Protecting the health of our Armed Forces is essential to national security. US troops must be prepared to be deployed anywhere in the world, often on very short notice, whether it is for combat operations, for a training exercise or disaster relief mission, or to serve as peacekeepers. Today's troop deployments can be characterized as smaller, more mobile, more diverse, and entailing multiple, more frequent deployments compared with earlier decades. With this transformation in contingency operations, the readiness and effectiveness of every individual soldier becomes of critical importance. Vaccines have almost always demonstrated their value as one of the best preventive interventions to mitigate the threat of acute infectious disease. Which vaccines or other countermeasures in which the military should invest is an important question that needs to be answered in a systematic way in order to best protect those put in harms' way. And what can be done to mitigate the burden of travelers' diarrhea today may be an even more important question.

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Appendices

Appendix A. Delphi Survey Instrument

Items Marked with * are required.

DELPHI STUDY ROUND 1

Estimation of Uncertain Parameters Regarding Travelers' Diarrhea Epidemiology, Management and Vaccine Development for Deployed U.S. Military Forces

Please check the button that best describes the CURRENT category of work you are doing.
Please choose ONE of the following *

- ☐ Vaccine Industry
- ☐ Academic/Military Diarrheal Vaccine Development
- ☐ Military Product Acquisition
- ☐ Military Preventive Medicine
- ☐ Tropical/Travel Medicine
- ☐ Military Clinical Infectious Disease

How many years of experience do you have in this area of work? *

- ☐ Less than 5 years
- ☐ 5 - 10 years
- ☐ More than 10 years

In addition to your current area of work, what is your PAST EXPERIENCE in each of the following fields?

	None	Less than 5 years	5 - 10 years	More than 10 years
Vaccine Industry	☐	☐	☐	☐
Academic or Military Diarrheal Vaccine Development	☐	☐	☐	☐
Military Product Acquisition	☐	☐	☐	☐
Tropical or Travel Medicine	☐	☐	☐	☐
Military Clinical Infectious Disease	☐	☐	☐	☐

Have you worked directly in support of Military troops? *

-- Select --

The following section asks questions regarding treatment of travelers diarrhea in deployed US military and similar populations.

Please choose the best answer.

Based on your understanding of treatment of diarrhea in the Military, please mark the following button regarding the particular treatment which is typically used for THOSE WHO SEEK CARE for diarrhea when deployed.

How certain are you about your answer?

	<10%	10-25%	26-50%	51-75%	76-90%	>90%	Not at all certain	Certain	Very certain
Loperamide or bismuth salycilate ALONE	☐	☐	☐	☐	☐	☐	☐	☐	☐
Antibiotics ALONE	☐	☐	☐	☐	☐	☐	☐	☐	☐
Antibiotics PLUS an anti-motility agent	☐	☐	☐	☐	☐	☐	☐	☐	☐
NONE	☐	☐	☐	☐	☐	☐	☐	☐	☐

Based on your understanding of SELF TREATMENT OF DIARRHEA IN THE MILITARY, please mark the following button regarding the particular treatment which is typically used for SELF TREATMENT of diarrhea when deployed.

How certain are you about your answer?

	<10%	10-25%	26-50%	51-75%	76-90%	>90%	Not at all certain	Certain	Very certain
Loperamide or bismuth salycilate ALONE	☐	☐	☐	☐	☐	☐	☐	☐	☐
Antibiotics ALONE	☐	☐	☐	☐	☐	☐	☐	☐	☐
Antibiotics PLUS an anti-motility agent	☐	☐	☐	☐	☐	☐	☐	☐	☐
NONE	☐	☐	☐	☐	☐	☐	☐	☐	☐

Based on your understanding, please mark the following button regarding the probability of continued morbidity after 3 days of SELF-TREATMENT.

How certain are you about your answer?

	<10%	10-25%	26-50%	51-75%	76-90%	>90%	Not at all Certain	Certain	Very Certain
Probability of continued morbidity	☐	☐	☐	☐	☐	☐	☐	☐	☐

Of these who have continued morbidity after 3 days, what is the probability that additional treatment would be required.

How certain are you about your answer?

Probability of additional needed treatment						How certain are you about your answer?		
<10%	10-25%	26-50%	51-75%	76-90%	>90%	Not at all certain	Certain	Very certain
☐	☐	☐	☐	☐	☐	☐	☐	☐

The following section will ask questions regarding characteristics of vaccine acquisition for vaccines against important military enteric pathogens.

Given the current state of scientific development, please provide an estimate for how long you think it would take to license a vaccine for each of the following pathogens in the United States.

How certain are you about your answer?

	<5 years	5-9 years	10-14 years	>15 years	Not at all certain	Certain	Very Certain
ETEC	☐	☐	☐	☐	☐	☐	☐
Campylobacter	☐	☐	☐	☐	☐	☐	☐
Shigella	☐	☐	☐	☐	☐	☐	☐
Norovirus	☐	☐	☐	☐	☐	☐	☐
Rotavirus	☐	☐	☐	☐	☐	☐	☐
Enteroaggregative E. coli	☐	☐	☐	☐	☐	☐	☐

Given the current state of vaccine science, in your opinion what is the best design approach to an effective vaccine for each of the following pathogens.

How certain are you about your answer?

	Killed whole-cell	Subunit	Conjugate	Live attenuated	DNA-based	Not at all certain	Certain	Very Certain
ETEC	☐	☐	☐	☐	☐	☐	☐	☐
Campylobacter	☐	☐	☐	☐	☐	☐	☐	☐
Shigella	☐	☐	☐	☐	☐	☐	☐	☐
Norovirus	☐	☐	☐	☐	☐	☐	☐	☐
Rotavirus	☐	☐	☐	☐	☐	☐	☐	☐
Enteroaggregative E. coli	☐	☐	☐	☐	☐	☐	☐	☐

In the area of enteric vaccine development, how long on average does it take from the time of a vaccine concept to development of a GMP manufactured vaccine product ready for phase 1 testing.

How certain are you about your answer?

	<5 years	5-10 years	11-15 years	16-20 years	>20 years	Not at all certain	Certain	Very Certain
Time of development from concept to GMP manufactured vaccine	☐	☐	☐	☐	☐	☐	☐	☐

Based on your understanding, please mark the following button regarding the probablity that a concept vaccine will drop out before phase 1 clinical testing?

How certain are you about your answer?

	<10%	10-25%	26-50%	51-75%	76-90%	>90%	Not at all certain	Certain	Very Certain
Probability of drop-out: concept to phase 1	☐	☐	☐	☐	☐	☐	☐	☐	☐

Based on your understanding, please mark the following button regarding the probability that a candidate vaccine will drop out between phase 1 and phase 2 testing.

How certain are you about your answer?

	<10%	10-25%	26-50%	51-75%	76-90%	>90%	Not at all Certain	Certain	Very Certain
Probability of drop-out Phase 1 --> Phase 2	☐	☐	☐	☐	☐	☐	☐	☐	☐

Based on your understanding, please mark the following button regarding the probability that a candidate vaccine will drop out between phase 2 and phase 3 testing.

How certain are you about your answer?

	<10%	10-25%	26-50%	51-75%	76-90%	>90%	Not at all Certain	Certain	Very Certain
Probability of drop-out Phase 2 --> Phase 3	☐	☐	☐	☐	☐	☐	☐	☐	☐

The following questions asks your opinion regarding technical and functional requirements for a vaccine against travelers' diarrhea to be used in the US military and similar traveler populations.

In designing a vaccine to prevent travelers' diarrhea, what should be the minimum target for protective efficacy?

How certain are you about your answer?

	50 - 60%	61 - 70%	71 - 80%	81 - 90%	> 90%	Not at all certain	Certain	Very Certain
Minimum protective efficacy target	☐	☐	☐	☐	☐	☐	☐	☐

In designing a vaccine to prevent travelers' diarrhea, what should be the maximum allowable frequency of adverse events?

How certain are you about your answer?

	< 2%	2 - 5%	5 - 9%	10 - 20%	> 20%	Not at all certain	Certain	Very Certain
Mild events (no activity limitation)	☐	☐	☐	☐	☐	☐	☐	☐
Moderate events (some activity limitation)	☐	☐	☐	☐	☐	☐	☐	☐

In designing a vaccine, what should be the MAXIMUM number of doses acceptable for a primary series?

How certain are you about your answer?

	1	2	3	4	5 or more	Not at all certain	Certain	Very Certain
MAXIMUM number of doses in primary series	☐	☐	☐	☐	☐	☐	☐	☐

In designing a vaccine, what should be the MAXIMUM time from start of vaccination series to protective immunity?

How certain are you about your answer?

	< 1 week	2 - 3 weeks	4 - 6 weeks	6 - 12 weeks	> 3 months	Not at all certain	Certain	Very Certain
MAXIMUM time from start of series to protective immunity	☐	☐	☐	☐	☐	☐	☐	☐

Thank you for taking the time to complete this survey. Please feel free to comment.

Please feel free to write in any comments here:

Please contact markriddlemd@hotmail.com if you have any questions regarding this survey.

Appendix B. Formulae and Equations

$$CER_{DDL} = (C_D + C_I - C_C) / Q$$

CER_{DDL} = cost effectiveness ratio for Duty Days Lost Averted
C_D = vaccine development costs
C_I = annual cost immunizing the target population
C_C = annualized costs of care averted by use of vaccine
Q = annual. health benefit (DDL averted) from use of vaccine

$$C_I = (d + a) \bullet Dose \bullet Pop$$

C_I = annual cost of immunizing target population
d = cost per dose of vaccine
a = cost of administering dose of vaccine
$Dose$ = number of doses each person must receive
Pop = size of the target population

$$C_C = C_{current\ management} - C_{vaccine\ intervention}$$

$$c_{ci} = (u_{ci} \bullet p_{ci} \bullet N_i \bullet t_{horiz}) - (u_{ci} \bullet p_{ci} \bullet N_i \bullet t_{acqu}) - [u_{ci} \bullet p_{ci} (N_i (1 - (V_{eff} \bullet V_{cov})) \bullet (t_{horiz} - t_{acqu})]$$

$$[C_C = (\sum c_{ci}) \div t_{horiz}]$$

i = management outcome resulting from disease
c_{ci} = cost of care averted for management outcome
u_c = unit cost of i form of management outcome care
p_{ci} = percent of patients receiving this management outcome
N_i = total number of patients with illness
t_{horiz} = time horizon
t_{acqu} = time vaccine research and development (acquisition)
V_{eff} = vaccine efficacy
V_{cov} = vaccine coverage

$$Q_S = (Q_{current\ management} - Q_{vaccine\ intervention}) \div t_{horiz}$$

$$q_j = [\sum_j (q_j \bullet P_j)] \bullet N_i$$

Q_s = total lost duty days averted due to illness for all subpopulations of given scenario
q_j = individual duty days lost in management outcome j
P_j = proportion of cases of illness experiencing outcome j
N_i = total number of cases of illness

Appendix C. Published Manuscripts

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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

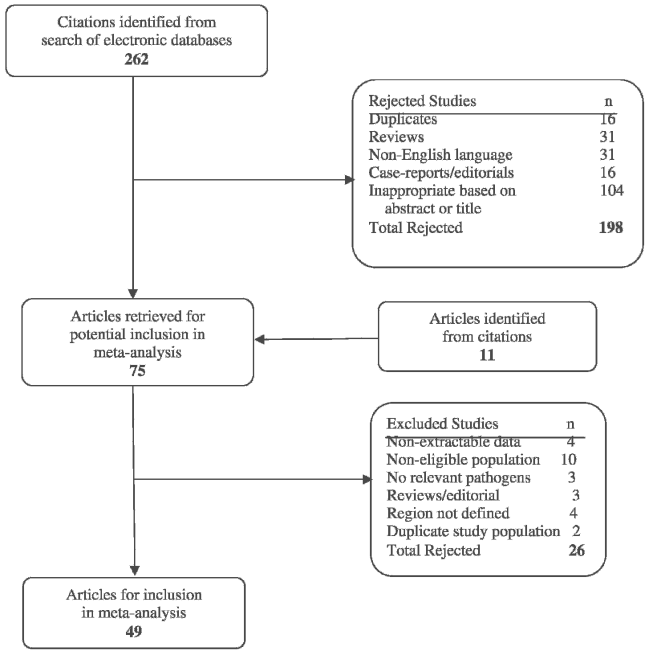

FIGURE 1. Flow diagram of study selection for inclusion in the systematic review.

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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Reaching a consensus on management practices and vaccine development targets for mitigation of infectious diarrhoea among deployed US military forces

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Abstract

Rationale, aims and objectives This study is part of a research effort to identify and quantify factors related to the cost-effectiveness of a vaccine acquisition strategy to reduce the burden of infectious diarrhoea on US military personnel deployed overseas. Where evidence is lacking in the scientific literature, or considerable uncertainty exists, it is often necessary to develop best estimates with ranges of certainty. To this end, a modified 'Delphi' survey technique to obtain the best estimates for uncertain parameters including clinical care-seeking behaviour for acute diarrhoea, routine diarrhoea management in a deployed setting, and vaccine development time frames and costs were developed from a diverse panel of experts.

Methods The study was conducted in three survey iterations. During each iteration, participants were contacted and given 2–3 weeks to complete a web-based survey designed to ascertain estimates, ranges of variability, and level of certainty for these estimates.

Results In all, 25 of 43 solicited experts agreed to participate in the study. These included three (12%) experts who identified themselves primarily as being currently involved in Vaccine Industry, six (24%) Academic/Military Diarrheal Vaccine Development, five (20%) Military Product Acquisition, five (20%) Military Preventive Medicine, two (8%) Tropical/Travel Medicine and four (16%) Military Clinical Infectious Disease. Management practices in deployed military populations (for both provider and self-treatment) were consistent with recently published literature. Similar target time frames for vaccine licensure were established for Enterotoxigenic *E. coli*, *Campylobacter*, *Shigella* and Norovirus of around 9–11 years. Targets for vaccine efficacy appear to be lower than currently licensed travel vaccines (60–80%), and there was consensus on more conservative adverse event rates.

Conclusions These data should prove useful to researchers and policy makers working in the area of vaccine acquisition for the US military and provide continued information on the gap in optimal travellers' diarrhoea management practices in a deployed setting.

Background

Travellers' diarrhoea (TD) is a common medical problem for military personnel deployed to developing countries [1,2]. The short-term morbidity associated with TD leads to increased health care utilization and lost days of work or travel [3,4]. While there are effective preventive interventions (e.g. environmental modification, safe food/water, alimentary hygiene) and good clinical response with timely and appropriate antimicrobial therapy, the burden of disease remains high in these populations and there is growing concern about antimicrobial resistance and subsequent failures with empiric antimicrobial therapy [5]. Because of these concerns, the Department of Defense (DoD), as well as other private industry and academic institutions have made it a priority to develop a vaccine to prevent TD. However, the policy decision to pursue a vaccine acquisition strategy should be based on sound epidemiological evidence and a thorough review of the costs and benefits of such a strategy compared with the current strategy of empiric antimicrobial therapy [6,7]. There is a wealth of published epidemiological literature on the incidence, aetiology and disease outcomes for diarrhoea among deployed troops [1,3,8–14]. However, there is a lack of adequate information about several areas including health care seeking probabilities, management practices, as well as vaccine development horizons. Therefore, the primary

objective of this study was to obtain estimates and ranges of uncertain parameters related to clinical epidemiology and vaccine development that are required to inform a decision-analytic model. Specific areas included treatment norms and anticipated outcomes associated with diarrhoea in deployed military populations, vaccine development time frames and acceptable vaccine performance attributes. In addition to the primary objective, questions were asked to obtain estimates of parameters related to vaccine product development targets, including targets of effectiveness, safety and practical applicability (number of doses, dosing time frame).

Methods

Overview

This study used the Delphi survey technique with the following modifications made based on the requirements of this study [15,16]. The structured questions to be answered by the experts were developed *a priori* by the authors. After an initial solicitation for participation, a series of three rounds were conducted using the same questions with the range of parameter estimates changing based on the response of the group. During the first two rounds, panellists were asked to select from a range of estimates, while the third round only asked for their opinion on whether they agreed or disagreed with the final developed consensus estimate.

Expert panel solicitation and selection

For the purposes of this study, an expert was defined as someone who has a known or stated interest in diarrhoea among deployed US military and/or vaccine development for TD. Nominations were solicited from colleagues and others in the academic community who knew persons with relevant subject matter expertise and might be willing to participate in the study. Solicited expert panellists were informed of how they were nominated in an introduction letter. The panellist's primary qualification was their subject matter expertise in the required areas of knowledge. Based on knowledge of the topic and recommendations from experts in the field, 43 experts in the following areas were solicited for participation: Vaccine Industry ($n = 5$), Academic/Military Diarrhea Vaccine Development ($n = 15$), Military Product Acquisition ($n = 7$), Military Preventive Medicine ($n = 6$), Tropical/Travel Medicine ($n = 6$) and Military Clinical Infectious Disease ($n = 4$).

Though panellists were identified based on their current occupation, it was anticipated that many would also have direct experience in one or more of the other categories. Potential panel members were informed of the study goals and objectives as well as the amount of time and effort that would be expected. Response to the invitation to participate was considered to fulfil the inclusion criteria, and implied consent to participate in the study.

Preparation and distribution of the initial survey instrument

An initial survey instrument (Appendix I), using broadly answerable questions related to the quantitative estimates of the identified parameters, was developed and pilot tested. For each question, each panellist was asked to provide a response to a question based on their understanding and rate the degree of uncertainty placed on their estimate by 'not at all certain' to 'very certain'. Individuals were not required to answer every question if they felt that their area of experience did not qualify them to make an estimate. Questions were asked regarding the current occupation, years of experience, and prior experience in the six knowledge fields of study. This survey instrument was distributed to panellists via email and a web-based platform called Surveyz™ (Qualtrics, Provo, UT, USA). If requested, a mailed survey was also made available. The recorded panellist's results were anonymous.

A select list of enteric vaccines were chosen to evaluate consensus estimates based on those which are currently under development by the DoD [*Campylobacter*, Enterotoxigenic *E. coli* (ETEC), *Shigella*]. In addition, three comparison vaccines were included. Enteroaggregative *E. coli* (EAEC) was selected as it has gained consideration as a predominate pathogen causing diarrhoea, but there were no published pre-clinical studies evaluating potential vaccine candidates. Norovirus was included as it is known to be a pathogen of military importance, but the DoD currently lacks a product development programme for a vaccine. And finally, though not a major pathogen of concern to the military, Rotavirus vaccine was selected to provide comparison and validity given that at the time of the survey the vaccine was pending FDA approval and licensure in the United States.

Survey rounds

Participants were initially given 2 weeks to return their responses to each survey round. Panellists were provided reminders during the 2 weeks to complete the survey. If after 2 weeks a minimum response rate of 75% was not achieved, a 1-week extension was provided. For the first survey round, data from responses of all panellists who answered the particular question were analysed for distribution. Based on the frequency distribution of answers, a refined (narrower) estimate range based on at least a two-thirds majority for each question was developed. A second survey round was similarly conducted. Responses from the second round were analysed by frequency distribution. Because of the diversity of the panellists and the subject matter focus of individual questions, the estimate ranges for each question were further refined based on the distribution responses limited to those panellists with a minimum of five or more years of experience (current and previous) in an appropriate content area of expertise (e.g. clinical management-related questions were limited to panellists with experience in Travel/Tropical Medicine or Military Infectious Diseases). Based on this analysis, a single estimate range for each question was developed which incorporated at least 75% of the panellist's responses. A final third round based on these refined single estimate ranges for each question was distributed to all panellists and responses of agreement or disagreement were recorded. The results of the study were compiled and provided to all panellists.

This study was determined to meet exempt status from IRB review and approval.

Results

Of the 43 solicited panel experts, 25 (58%) affirmative responses for participation in the survey were received, three declined participation and no response was received from 15. Participating panel-

lists included the following areas of expertise: Vaccine Industry ($n = 3$), Academic/Military Diarrhea Vaccine Development ($n = 6$), Military Product Acquisition ($n = 5$), Military Preventive Medicine ($n = 5$), Tropical/Travel Medicine ($n = 2$), and Military Clinical Infectious Disease ($n = 4$). Figure 1 outlines the flow of the study from panel selection to final round completion.

Twenty-three of 25 (92%) expert panellists completed the survey round one. Seventeen out of 23 reported to have 10 or more years of experience in their current profession, and all reported more than 5 years in one or more of the other subject areas of expertise. Seventy per cent responded to have worked directly in support of deployed US troops. Table 1 describes the consensus panel ranges and relative level of uncertainty for parameters related to management of diarrhoea in the deployed setting (among those who seek treatment and those who self-treat). Loperamide or bismuth subsalycilate (BSS) alone or a regimen of an antibiotic plus an antimotility agent were considered to be the most common treatment options provided to those who sought care (each 10–50%), whereas no treatment (10–90%) or loperamide or BSS alone (0–50%) were viewed to be the most common among those who self-treated. Ranges which included a two-thirds majority of panellists' responses were extended and there was relatively higher uncertainty about self-treatment compared with management among those who sought care. Respondents to the

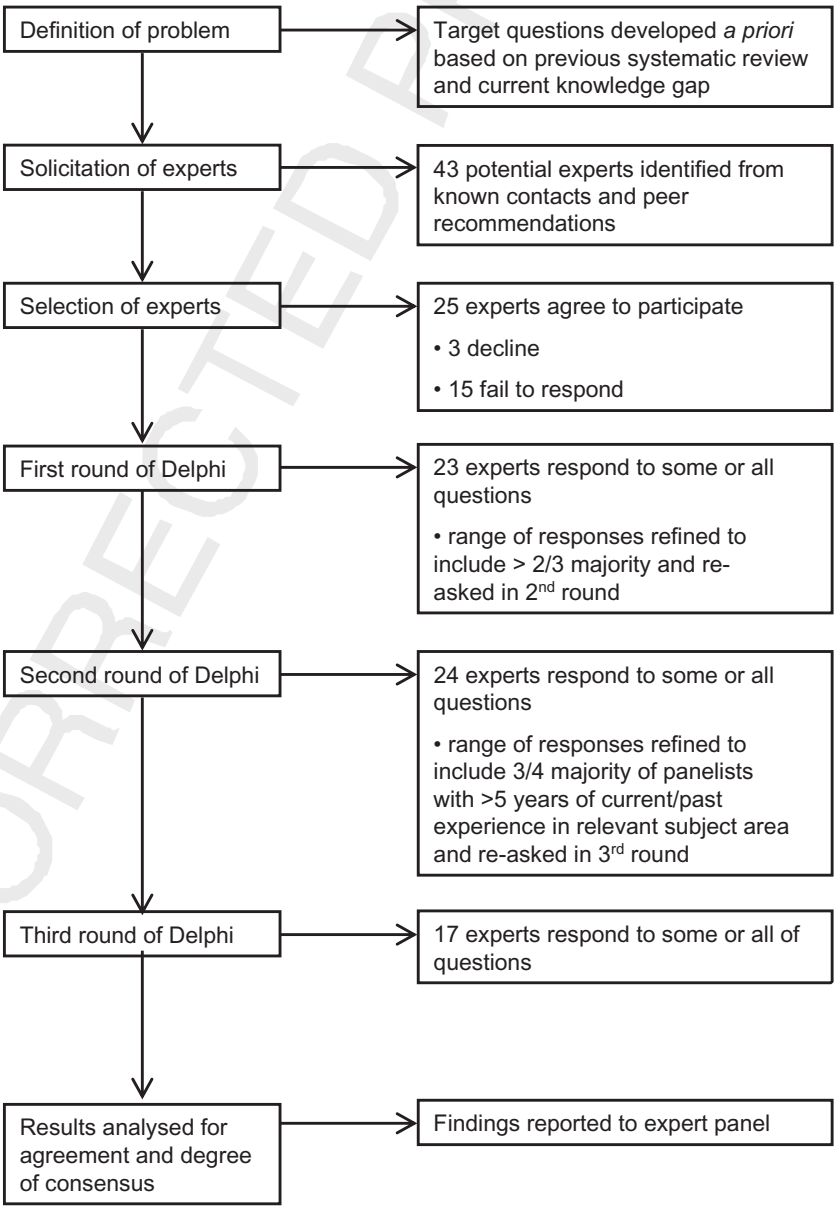

Figure 1 Flow diagram of modified Delphi survey to develop consensus estimates in the area of epidemiology, management and vaccine development of diarrhoea in deployed US troops.

Table 1 Consensus estimates of first and final Delphi rounds for uncertain parameters related to disease management

	First round ($n = 23$)		Third round ($n = 17$)	
Parameter estimate	Response range (% panellists in range)*	% Not at all certain	Consensus estimate (range)	% Agree
Typical management for those who seek care for diarrhoea when deployed (%)				
Loperamide or bismuth salycilate alo ne	10–50 (68)	47	20 (10–30)	77
Antibiotics alone	0–25 (85)	47	18 (11–25)	71
Antibiotics plus antimotility agent	10–50 (74)	47	30 (10–50)	77
None	0–25 (69)	47	15 (6–25)	77
Typical management use for self-treatment (%)				
Loperamide or bismuth salycilate alone	0–50 (84)	53	20 (5–35)	94
Antibiotics alone	0–10 (68)	53	3 (0–5)	77
Antibiotics plus antimotility agent	0–25 (95)	58	5 (0–10)	82
None	10–90 (90)	58	60 (30–90)	94
Self-treatment outcomes (%)				
Continued morbidity after 3 days	10–25 (70)	40	15 (10–20)	82
Among those with continued morbidity, additional treatment will be needed	10–75 (75)	30	25 (10–40)	71

*May not add to 100% due to rounding.

Table 2 Delphi study round one results: prevalence of vaccine strategy most likely to be successful by pathogen

Vaccine strategy	Killed whole-cell *n* (%)*	Subunit *n* (%)*	Conjugate *n* (%)*	Live attenuated *n* (%)*	DNA-based *n* (%)*	% Not at all certain
Enterotoxigenic *E. coli*	6 (32)	9 (47)	2 (11)	2 (11)	0	55
Campylobacter	8 (44)	4 (22)	5 (28)	1 (6)	0	75
Shigella	3 (16)	2 (11)	5 (26)	9 (47)	0	70
Norovirus	4 (21)	8 (42)	0	4 (21)	3 (16)	80
Rotavirus	3 (16)	1 (5)	2 (11)	12 (63)	1 (5)	60
Enteroaggregative *E. coli*	5 (26)	9 (47)	2 (11)	3 (16)	0	90

*May not add to 100% due to rounding.

first round thought that 10–25% of persons who self-treated would have continued morbidity due to diarrhoea after 3 days, and that 10–75% of these would require further treatment.

Table 2 details the most likely vaccine design strategy that panellists thought would prove successful for each of the vaccines under development. With respect to vaccine development, a majority of panellists indicated that vaccines for ETEC, *Campylobacter*, *Shigella* and Norovirus were 9–14 years away from licensure in the United States, but a vaccine for EAEC was 10–15 years or more away from licensure (Table 3). Uncertainty about this target time frame was highest for EAEC and *Campylobacter*. Additional questions regarding general vaccine development candidate failure rates and acceptable targets of performance were asked in this first round. Nearly two-thirds of panellists thought that 5–10 years were required to develop a vaccine from concept to GMP manufactured product, and 50–90% of vaccines would not advance from concept to phase I testing. Subsequent dropout rates for more advanced testing seemed to improve only slightly with 10–75% dropout rates between phase I and phase II, and phase II and phase III, though there appeared to be relatively higher uncertainty in these probabilities compared with concept to phase I transition. Nearly half (48%) of respondents thought that an acceptable vaccine protective efficacy for a diarrhoeal vaccine should be 71–80%, and one-fourth of panellists thought protective efficacy of 61–70% was acceptable. Although the number of respondents in each profession category was small, there appeared to be an expectation of a higher minimum protective efficacy among Military Clinical Infectious Diseases and Preventive Medicine experts (median efficacy choice 71–80%, $n = 10$) compared with Military Vaccine Development and Vaccine industry panellists (median efficacy choice 61–70%, $n = 8$) (Wilcoxon rank-sum, $P = 0.02$). Seventy-four per cent of respondents thought that a 5–20% mild adverse event (no activity limitation) rate was acceptable, whereas 59% thought that moderate adverse event (mild activity limitation) rates must be less than 2%. No participants thought that moderate adverse event rates should exceed 5%. A maximum of a three-dose series over 2–6 weeks seemed to be an acceptable vaccination schedule to most expert panellists (70% and 87%, respectively).

Twenty-four panellists (96%) responded to the second survey round which had refined ranges for answers based on a two-thirds majority of responses in the first round. Seventeen out of 24 respondents self-described as having more than 5 years of current or past experience in military clinical infectious disease and/or traveller/tropical medicine practice. Based on a three-fourths

Table 3 Consensus estimates from first and third round relating to vaccine development targets

	First round (n = 23)		Third round (n = 17)	
Parameter estimate	Response range (% panellists in range)*	% Not at all certain	Consensus estimate (range)	% Agree
Estimated time until vaccine licensure for the following pathogens (years)				
Enterotoxigenic *E. coli*	5–14 (72)	48	9 (5–14)	88
Campylobacter	5–14 (81)	62	11 (8–14)	88
Shigella	5–14 (76)	52	9 (5–14)	94
Norovirus	5–14 (86)	57	10 (8–14)	82
Rotavirus	0–9 (86)	29	2 (1–3)	82
Enteroaggregative *E. coli*	10–15+ (84)	67	14 (10–18)	94
	Panellist response, n (%)*	% Not at all Certain	Consensus estimate (range)	% Agree
Minimum protective efficacy target		17		
50–60%	3 (13)			
61–70%	6 (26)			
71–80%	11 (47)		60–80%	94
81–90%	3 (13)			
>90%	0			
Maximum allowable frequency of mild, moderate adverse event		17, 14		
<2%	0, 13 (56)			
2–5%	4 (17), 9 (41)			
5–9%	13, 0		Not asked	
10–20%	4 (17), 0			
>20%	2 (9), 0			
Maximum number of doses allowable in primary series		17		
2 doses	5 (22)			
3 doses	16 (70)		Not asked	
4 doses	2 (9)			
Maximum time from start of series to protective immunity		23		
2–3 weeks	9 (39)			
4–6 weeks	11 (48)		3–4	94
6–12 weeks	2 (9)			
>3 months	1 (4)			

*May not add to 100% due to rounding.

majority of responses from this expert panellist subset, final point estimates and uncertainty ranges for parameters related to management of diarrhoea in deployed troops were derived and sent out to all panellists in a final third round. Likewise, responses from 15 out of 24 respondents self-described as having five or more years of current/past experience in vaccine development (industry or military) were analysed to develop refined estimates related to pathogen-specific vaccine development time frames and sent out to all panellists in the final third round. All responses from the 24 panellists related to minimum target efficacy and maximum series length were used to derive a final consensus point estimate and uncertainty interval.

The third and final round of survey achieved a relatively lower response rate of 17 panellists (68%) compared with the previous two surveys with three Vaccine Industry, five Academic/Military Diarrheal Vaccine Development, five Military Preventive Medicine, three Military Clinical Infectious Diseases and one Tropical/Travel Medicine expert. No panellists from the military product acquisition area responded to this final round. Twelve out of the 17 respondents reported to have had more than 10 years in their current occupation, and 14 reported to have worked directly in support of military troops. Final point estimates and uncertainty ranges, as well as overall agreement among panellists are described in Tables 1 and 3. In the area of treatment provided among those who seek care for diarrhoea, consensus was that about 30% of patients received antibiotics plus an antimotility agent, while approximately 20% each received antibiotics alone or non-antibiotic therapy. Fifteen per cent were thought to receive no treatment when presenting with diarrhoea.

With respect to self-treatment, 94% of panellists agreed that 60% (range 30–90%) of deployed troops who develop diarrhoea do not initiate self-treatment, whereas 20% used antimotility or BSS therapy alone, and 5% used an antiobiotic combined with an antimotility agent. Panellist agreement rates for outcomes associ-

ated with self-treatment were higher in general (77–94%) compared with responses regarding treatment received when presenting for medical care (71–77%). Panellists agreed that approximately 15% of individuals who self-treated for diarrhoea would continue to have morbidity 3 days after treatment, and one-fourth of these individuals with continued morbidity would require further medical evaluation and treatment. Though the uncertainty range was wider and agreement was relatively less for the latter estimate.

Final estimates for licensure time frames for ETEC, *Campylobacter*, *Shigella* and Norovirus vaccines were fairly similar between 9 and 11 years, whereas licensure for a vaccine against EAEC was thought to be about 14 years off. Ninety-four per cent of third-round respondents agreed that minimum target efficacy should be 70–80%, and maximum time from start of vaccination series and protective efficacy should be 3–4 weeks.

Discussion

While the primary purpose of this study was to provide estimates to parameters for which there was uncertainty (e.g. lack of published literature), it is useful to compare the consensus estimates that were derived from this study with what is known from the literature. In the area of TD management in deployed settings, we report consensus estimates of 30% (10–50%) of troops receiving antibiotics plus an antimotility agent, 20% (10–30%) receiving an antimotility agent or BSS alone, 18% (11–25%) receiving antibiotics only, and 15% (6–25%) receiving no treatment. A recently published study conducted among troops deployed to Iraq and Afghanistan found that approximately 80% of troops sought care for their diarrhoea, usually from their 'medic' [17]. While the authors did not distinguish between specific treatment modalities provided by the 'medic' or during a clinic visit (staffed by doctor or doctor's assistant), it was reported that medics more often provided some kind of medicine (around 60%) compared with a clinic visit (48%). Reported management approaches included antibiotics in 27%, loperamide in 37%, BSS in 13%, and treatment with oral rehydration only in 15%. The percentage of patients receiving combination therapy with antibiotics and loperamide was not reported. Estimates from expert consensus appear to be concordant with this survey, particularly the estimate of no therapy provided in 15%. One other survey conducted predominately in Army doctors' assistants assessing for TD management practices, found that for clinical scenarios of moderate diarrhoea loperamide or BSS was utilized in 36% of patients, oral rehydration alone in 27% of patients, combination antibiotic/loperamide therapy in 25%, and antibiotic alone in 11% [10]. The reported use of antibiotics (alone or in combination with loperamide) was higher (18% and 45%, respectively) in patient scenarios of severe diarrhoea. These data are also consistent with the estimates of the consensus panel and further identify the gap in appropriate management practice for TD among deployed US troops.

Similarly, consensus for self-treatment management modalities and outcomes was notable for an estimated 20% of troops using loperamide or BSS alone for self-treatment, 8% using antibiotics alone or in combination with loperamide, and 60% of troops not utilizing any self-treatment modality. A consensus estimate of 15% (10–20%) of continued morbidity after self-treatment was found. The recent publication by Putnam *et al*. found that 12% of troops brought medications with them to treat diarrhoea and a further 20% either bought or borrowed some during deployment [17]. Roughly 31% of troops brought either loperamide or BSS and 8% brought antibiotics. While not described, 80% of the troops reported that their self-treatment led to cure. Surprisingly, this survey supports the expert consensus panel's estimates despite this report being published after the expert panel survey was completed.

Predicting the time frame to development of a vaccine which is in early phases of development (preclinical or phase I/II testing) is without question a difficult practice. Factors that should be considered favourable to a shorter time frame of development would be an appropriate animal model predictive of outcomes in humans, availability of clinically relevant measure for correlate immunity, and successful proof of concept challenge studies. Also under consideration would be the relative amount of funding available for each vaccine.

In light of these considerations, expert consensus estimates for ETEC, *Campylobacter*, *Shigella* and Norovirus were all around 9–11 years (uncertainty range 5–14 years) until time to licensure. Rotavirus vaccine, known to be pending licensure at the time of the survey, was given an estimate of 2 years. A recent review of enteric vaccine development describes the current state of science and challenges that lie ahead [18,19]. Despite similar time horizons reported by experts, it appears that each of these vaccines is in different stage of development. The most advanced in development ETEC under which a number of phase II and III trials have been completed or are currently underway utilizing a vaccine containing the cholera toxin B subunit protein combined with four formalin killed ETEC strains [18,20]. In addition to this vaccine construct, additional studies have been completed with colonization factor-based vaccines (with or without adjuvant) [21–23]. However, while demonstrating promise (correlate of immunity and passive protection), the efficacy of current colonization factor-based vaccine candidates is challenged because of the fact that there are more than 20 colonization factors and 40–80% of ETEC infections do not display detectable colonization factor [24–26]. These challenges place the development and licensure of a broadly effective ETEC vaccine further into the future.

Shigella and *Campylobacter* vaccine candidates are in both phase I and II testings and consist of killed whole-cell and recombinant subunit strategies [27–34]. Furthermore, a live attenuated vaccine for *Shigella* is under development using a number of different strains but has been challenged by balancing the immunogenicity and reactogenicity of attenuated strains [35–38]. *Campylobacter* vaccine development is challenged by the paucity of applicable models for vaccine efficacy determination and a correlate of immunity for protection. Whereas for *Shigella*, there does appear to be a good correlate to immunity (IgG to LPS) [39,40], as well as animal models that relate well to human challenge studies [41,42]. While no recent human challenge studies have been conducted, the necessary components appear to be in place for development of this vaccine.

The expert panellists considered Norovirus to be licensed in a similar time frame to ETEC, *Campylobacter* and *Shigella* vaccines despite only three published studies testing a Norovirus vaccine in humans relying on a single strategy of recombinant virus-like particle [43–45]. While an animal model is lacking and correlates of immunity have not been established, a human challenge model

exists [46,47], and it is possible that the increasing awareness of burden and anticipated increased research effort may have factored into the experts' consensus of an 8–14 year period to licensure. We are not aware of any vaccines being developed for EAEC, and a consensus estimate of 10–18 years is reported.

Despite these differences in established animal models, correlates of protection and current clinical trials experience for each of the candidate vaccines, expert consensus for development time frames were homogeneous. This finding should most likely be interpreted as a reflection of the uncertain nature of predicting a complex estimate in the face of incremental and breakthrough advances. Future retrospective studies may be considered to evaluate predictions such as these.

In general, there was higher consensus and certainty in estimates regarding general vaccine safety and the potential for application of travel vaccines. A 60–80% target efficacy is a bit lower than the range of most routine immunizations and travel-related vaccines [48], but probably represents an achievable target. Particularly, given the high incidence of TD in deployed troops, even a modest vaccine efficacy could have profound effects. Subgroup analysis of our expert panel found that clinicians and preventive medicine professionals were similar and expected a higher efficacy relative to their vaccine development and acquisition counter parts. This divide may be due to the differences in vaccine purpose between these two communities, or a recognition of the practical challenges known to enteric vaccine developers which might result in a more 'achievable' efficacy target. If one were to consider the burden of disease on an entire population with the potential for impacts of herd immunity, then one might accept a lower efficacy rate compared with the individual clinician concerned more about the protective efficacy for an individual.

Fifty-nine per cent of panellists agreed that the maximum allowable rate for a moderate adverse event (as defined by some activity limitation) should be less than 2%, and 74% of panellists thought that mild adverse events should not exceed 5–20%. Post-marketing adverse event report rates associated with some travel vaccines are generally higher than the level described by this panel [49–53]. However, given that TD is a extremely common, self-limited and easily treatable health risk to deployed troops, a relatively lower reactogencity might be expected.

The Delphi surveying technique is designed to turn opinion into consensus via asking content experts questions which are then coded into broad range of estimates [15,54]. These estimates are then presented to the respondents in an iterative fashion for further consideration and comment. Delphi and other consensus-gaining techniques have previously been used in conjunction with cost-effectiveness analyses to develop parameter estimates in situations lacking scientific literature, or persistent uncertainty [55–58]. There are obviously limitations in using this type of methodology and limitations in interpretation of the results, particularly with reliability and validity. Our study had strengths of expert diversity, representativeness and high response rates (except for the final round). However, our 'effective' expert panel may have been diluted because of the focused subject area expertise required for different knowledge areas (e.g. TD management, vaccine development time frames and strategies). However, many of the participants of the survey reported professional careers in multiple areas of expertise and therefore were appropriate to answer a wide range of questions relating to TD management and vaccine development. In addition, concordance between expert panellists' consensus estimates and available published literature with respect to management practices provide support for the study's validity.

In summary, making informed decisions on TD vaccine(s) acquisition for the US military or the travelling public in general necessitates a thorough understanding of the factors associated not only with disease incidence and outcomes but also with vaccine development time frames, costs, efficacy and other performance characteristics [Lemon, 2003 #2878; Stratton, 1999 #2879]. While the former can often be obtained from the published literature and public health surveillance data, the latter often presents an unknown. While the consensus performance characteristics reported herein appear to be on the conservative side, we would do well to heed the Voltaire's pragmatic advice of 'not letting perfection be the enemy of the good'.

Though not without challenge and limitations, this study represents an important step in providing information to vaccine development researchers, policy makers and institutional officials who are working in the area of enteric vaccine development, with particular focus on TD. This study also calls attention to the continued gap in best-practices in management of diarrhoea in a deployed setting, and provides important estimates to be used to conduct further vaccine economic analyses to determine research priorities within the DoD.

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