WRAIR'S INVESTIGATOR'S DISPATCH

DIARRHEAL DISEASE COUNTERMEASURES

INTERMEDIATE RISK
HIGH RISK

WRAIR PROTECTS YOUR SIX

Protecting your brain - the most important six inches on the battlefield

CENTER FOR MILITARY PSYCHIATRY AND NEUROSCIENCE

- Blast Induced Neurotrauma and Neuroprotection
- Sleep & Resilience
- Team Performance and Mental Fitness
- Military Psychiatry

Protecting the most important six microns between you and the threat of disease

CENTER FOR INFECTIOUS DISEASE RESEARCH

- Vaccines & Entomology
- Viral & Bacterial Diseases
- Military HIV Research Program
- Experimental Therapeutics & Emerging Infectious Diseases

WHETHER YOU'RE AT HOME STATION OR SIX THOUSAND MILES AWAY

WALTER REED ARMY INSTITUTE OF RESEARCH'S MISSION

Discover, design, and develop solutions for military relevant infectious disease and brain health threats through innovative research protecting and optimizing warfighter lethality.

LIKE AND FOLLOW WRAIR

- WRAIROfficial
- @WRAIR
- https://www.wrair.army.mil
- WalterReedArmyInstituteOfResearch

PROMOTED HASHTAGS

#SoldierHealthWorldHealth

#ForgeTheFuture #TravelersDiarrhea

#BacterialDysentary #MilitaryDiarrhea

#PreventTheDiarrhealThreat

WALTER REED ARMY INSTITUTE OF RESEARCH IS A SUBORDINATE COMMAND OF MRDC

The opinions or assertions contained herein are the private views of the author and are not to be construed as official.

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SUMMARY POINTS PAGE

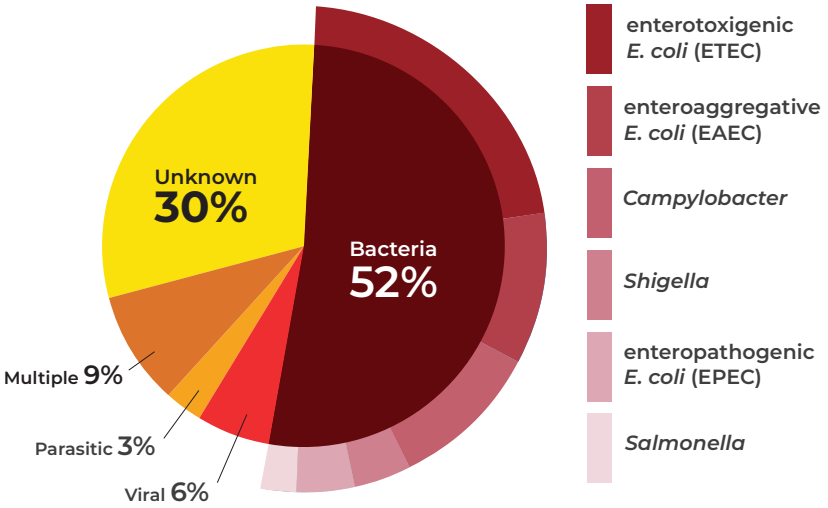
IMPACT & CAUSES OF DIARRHEA

Diarrhea ranks #1 of the infectious disease threats for the military based on its impact on readiness.

Bacterial pathogens are the predominant risk to readiness, thought to account for the majority of traveler's diarrhea.

76% of Soldiers in OIF and OEF experienced traveler's diarrhea early in their deployment.

The threat of diarrhea will only grow as the effectiveness of antibiotics continues to diminish.



Olson et al. "Tropical Diseases, Travel Medicine and Vaccines, 2019, 5:1-15 Page 3

HOW DIARRHEA SPREADS IN A MILITARY SETTING

Diarrhea occurring in military operational settings closely resembles "traveler's diarrhea" commonly diagnosed in civilian populations.

Traveler's diarrhea is an intestinal infection that occurs most often as a result of eating or drinking contaminated food or water.

The Five F's of Traveler's Diarrhea Transmission

Fluids | Food | Feces | Fingers | Fomites*

Studies show that even if you "boil it, cook it, peel it or forget it" you can still get traveler's diarrhea.

https://wwwnc.cdc.gov/travel/yellowbook/2018/the-pre-travel-consultation/travelers-diarrhea

* Fomites are objects or materials which are likely to carry infection, such as clothes, utensils, and furniture.

'I expect that our imaginations cannot fathom the problems...from the absolute urgency for relief from explosive...diarrhea when experienced within an armored vehicle under fire and at ambient temperature of >40°C.'

D.O. Matson
Infectious Diseases Section, Center for Pediatric Research, Norfolk, VA. Clin Infect Dis (editorial) 2005;40:526-7.

DIARRHEAL DISEASE TOPLINE MESSAGES

TOPLINE MESSAGES

- Diarrhea commonly takes Soldiers out of the fight and degrades Soldier lethality.
- The risks for developing traveler's diarrhea are similar for military personnel and long-term travelers.
- Diarrhea can result in a loss of duty/work days per incident and can have large outbreaks across a military unit.
- Diarrheal cases average **two days** of lost duty and **four days** of limited duty per incident resulting in **six total days** of impacted readiness.[1]
- Diarrhea incidence among U.S. troops deployed during OIF and OEF outpaced respiratory illiness and injury.[2]
- WRAIR conducts worldwide surveillance for diarrhea-causing bacterial prevalence and antibiotic resistance.
- WRAIR develops medical countermeasures to prevent or treat acute diarrhea.
- WRAIR improves clinical practice and personal and environmental hygiene guidelines in austere environments where access to prevention or treatment options is limited.

1. J R Army Med Corps. 2013 Sep;159(3):229-36. doi: 10.1136/jramc-2013-000084. Epub 2013 May 27.
2. Am J Trop Med Hyg. 2005 Oct;73(4):713-9. https://doi.org/10.4269/ajtmh.2005.73.713

TABLE OF CONTENTS

HISTORY AND IMPACT OF DIARRHEA IN WAR

Vietnam War

- Diarrhea was the most burdensome disease
- Diarrhea exceeded malaria 4 to 1 in number of cases

Desert Shield/Storm

- 57% of Soldiers developed diarrhea
- 20% of Soldiers were unable to perform duties

Operation Enduring Freedom

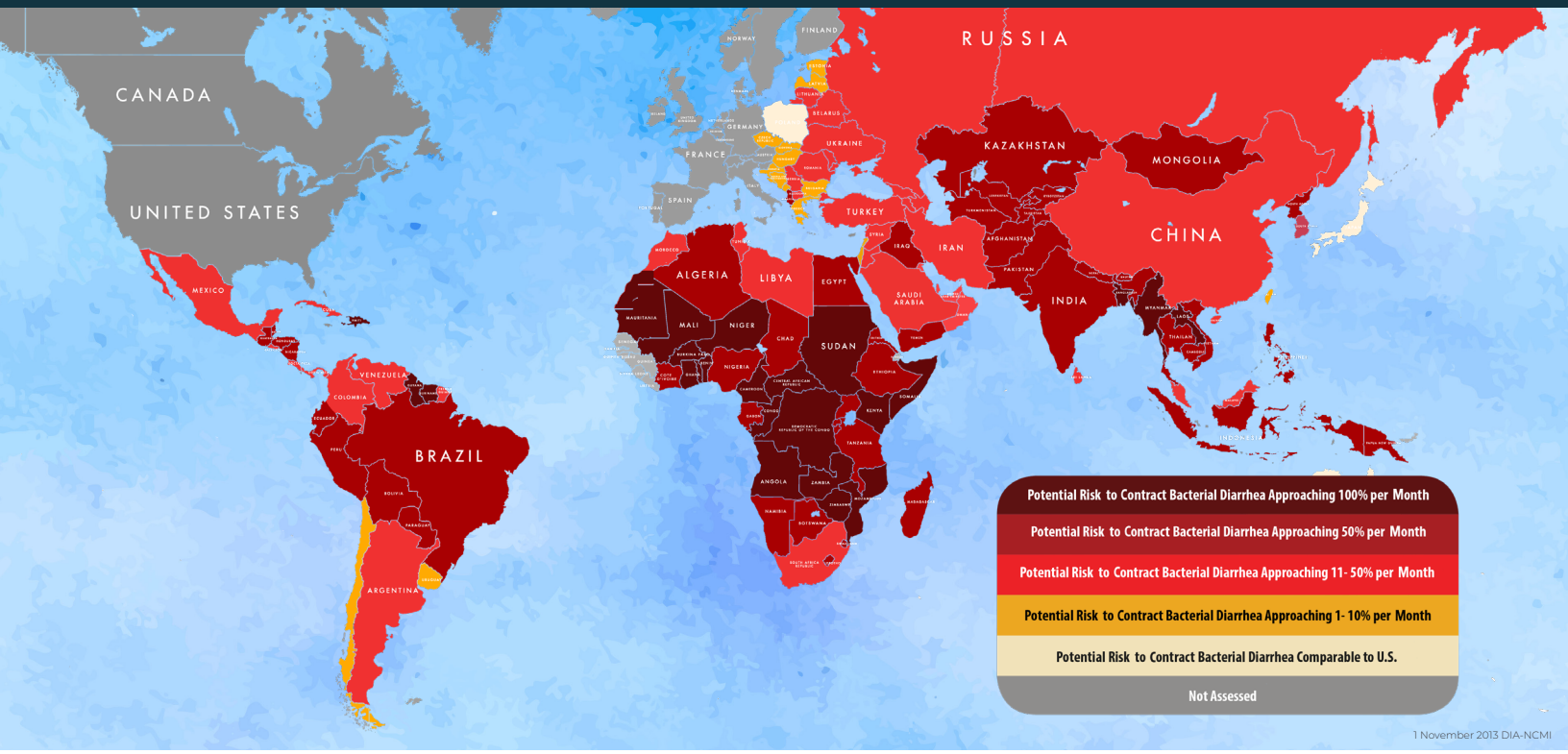
- 54.4% of Soldiers self-reported at least one episode in 2003 – 2004
- 2009: 40% attack rate with 43,000 man-days lost in six-month period

Operation Iraqi Freedom

- 76.8% of Soldiers developed symptoms

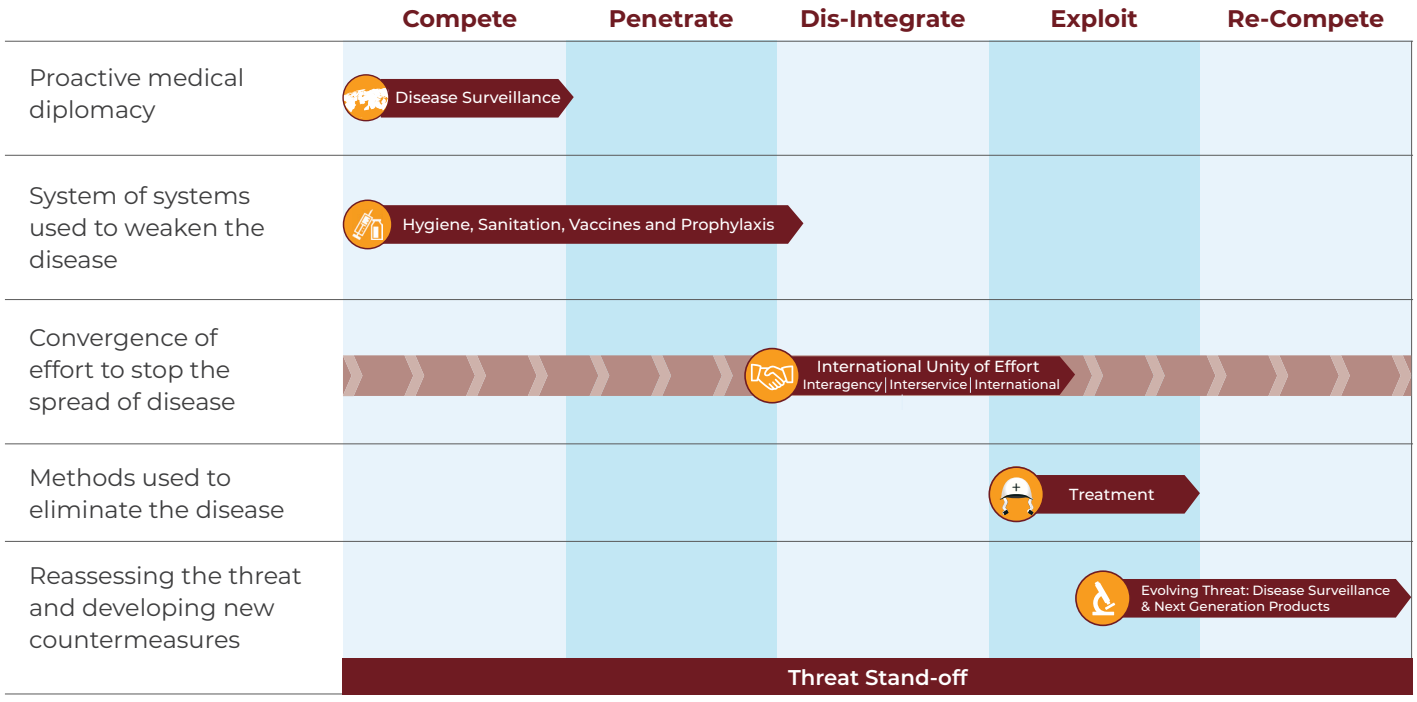
1. Olsen S et al. Trop Dis Travel Med Vaccines. 2019 Jan 15;5:1. doi: 10.1186/s40794-018-0077-1. eCollection 2019
2. Porter C, Mil Med. 2017 Sep;182(S2):4-10. doi: 10.7205/MILMED-D-17-00064
3. Riddle, M Am J Trop Med Hyg. 2006 May;74(5):891-900

WORLDWIDE RISK TO U.S. FORCES



1 November 2013 DIA-NCMI

COMBATING THE ENTERIC DISEASE THREAT ACROSS THE PHASES OF MDO



CALIBRATE FORCE POSTURE

WRAIR has 26 strategically placed forward areas of operation overseas in areas of endemic disease threats to the U.S. military.

CONVERGE CAPABILITIES

WRAIR optimizes its unique capabilities through collaboration with other U.S. military services, foreign militaries and civilian partnerships to ensure overmatch against endemic infectious disease threats.

EMPLOY MULTI-DOMAIN FORMATIONS

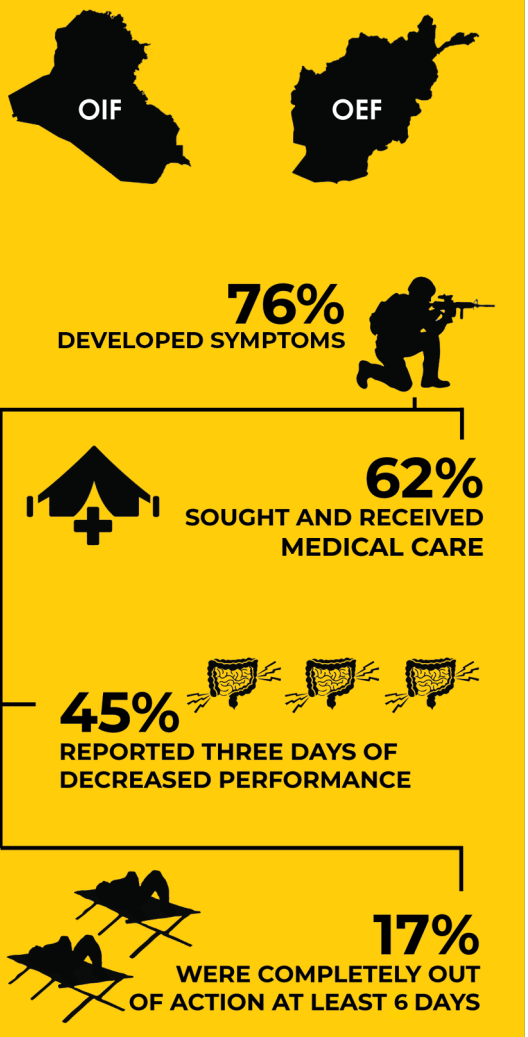
WRAIR utilizes personnel, facilities and advanced technologies within areas of operations that maximize its human potential through research and development to fight across multiple domains.

IMPACT OF DIARRHEA ON OPERATIONAL READINESS

CHALLENGES

- U.S. military personnel must be ready to deploy to austere environments where the risk of exposure to diarrhea-causing pathogen threats may be significant and treatment options may not be adequately available.
- In these environments, routine preventive health efforts are often either impractical or inadequate and diarrhea can rapidly spread through units.
- Infectious diarrhea results in lost work days, increased health care utilization and compromised operational readiness and effectiveness.

IMPACT OF DIARRHEAL DISEASES DURING OIF & OEF



Current Opinion in Gastroenterology 2005, 21:9–14

WHAT THIS MEANS FOR SOLDIERS

Data from Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) shows traveler's diarrhea as the most common non-combat disease among deployed U.S. personnel, **with incidence as high as 45 cases per month per 100 deployed U.S. personnel.**

Chad K. Poter, PhD, MPH; Nadia Thura; CDR Mark S. Riddle, MC USN

Short Term Impact For a Force of 4,400

22% reduction in combat effectiveness

(956 cases out of a force of 4,400) for an infantry brigade combat team deployed to a highly endemic region without effective countermeasures.

- **20% (191 of 956) of these cases would result in severe diarrhea (>6 stools/day)**
- **80% of the cases** would require antibiotics, intravenous fluids, or other medical assistance from field medics.

Trop Dis Travel Med Vaccines. 2019 Jan 15;5:1. doi: 10.1186/s40794-018-0077-1. eCollection 2019.

Long-Term Impact

- Diarrhea-causing bacteria can produce chronic disease long after infection such as:
  - Reactive Arthritis
  - Irritable Bowel Syndrome
  - Guillain-Barré Syndrome

Chad k. Poter, PhD, MPH; Nadia Thura; CDR Mark S. Riddle, MC USN

IMPACT OF DIARRHEA ON OPERATIONAL READINESS

WRAIR DELIVERS

Vaccines In Development*

Shigella

In partnership with National Institutes of Health (NIH) and industry, WRAIR is developing the WRSs2 and Invaplex vaccines for *Shigella*.

Enterotoxigenic *E.coli* & *Campylobacter*

Naval Medical Reseach Center (NMRC) and WRAIR are working towards vaccines for:

- ETEC: CfaEB (CFA/I), CssBA (CS6)
- *Campylobacter jejuni*: CjCV2

* All vaccine efforts are fully funded through other government, NGO, and industry partner funding.

Development & Production

WRAIR is developing and producing critical reagents and assays for enteropathogen countermeasure development and rapid point-of-care diagnostics.

Disease Surveillance

WRAIR conducts disease surveillance around the globe in military-relevant populations and travelers with funding from the Global Emerging Infections Surveillance (GEIS).

FORGING THE FUTURE

Clinical Trials

Currently, WRSs2 is being tested at Cincinnati Children's Hospital Medical Center (funded by NIH).

The ongoing clinical Shigella vaccine trial (funded by LimmaTech Biologics) is currently being conducted in Kericho, Kenya.

The clinical trials for two additional Shigella vaccines developed by GSK and Pasteur Institute respectively are set to begin in Kericho in Fall 2020.

Bacteria Resistance Surveillance

WRAIR is conducting worldwide surveillance to assess emerging resistance to common antibiotics used for acute diarrhea, particularly for *Campylobacter*, ETEC and *Shigella*.

ONGOING BACTERIAL RESISTANCE THREAT

CHALLENGES

» Among Soldiers, treatment adherence and improper self-medication are common concerns. Worldwide indiscriminate use of antibiotics, as well as the use of counterfeit antibiotics are contributing to resistance.

» Standard antibiotics in use today are becoming increasingly less effective.

» Antimicrobial resistance in pathogens causing traveler's diarrhea is a growing significant threat in Southeast Asia and Africa.

» Overseas travelers who are being treated with antibiotics can still actively shed the pathogen which can spread to others while they travel or return home.

WHAT THIS MEANS FOR SOLDIERS

» More emphasis on preventive measures for diarrhea

» Prolonged disease duration and severity, keeping Soldiers out of the fight

» Increased risk of disease transmission between infected and non-infected Soldiers

» Increased recovery time for return to normal duty

WHAT WE'RE DOING ABOUT IT

» WRAIR is identifying the genes and mechanisms responsible for enabling the spread of antibiotic resistance.

» As a result of the multi-institutional and multi-site TrEAT TD Study conducted by IDCRP, WRAIR, NMRC and the British Army, clinical practice guidelines for the management of deployment-related traveler's diarrhea were published in 2017 in *Military Medicine*. *

* References:
Trial Evaluating Ambulatory Therapy of Travelers' Diarrhea (TrEAT TD) Study: A Randomized Controlled Trial Comparing 3 Single-Dose Antibiotic Regimens With Loperamide.
Riddle MS, Connor P, Fraser J, Porter CK, Swierczewski B, Hutley EJ, Danboise B, Simons MP, Hulseberg C, Lalani T, Gutierrez RL, Tribble DR; TrEAT TD Study Team. Clin Infect Dis. 2017 Nov 29;65(12):2008-2017. doi: 10.1093/cid/cix693.

Management of Acute Diarrheal Illness During Deployment: A Deployment Health Guideline and Expert Panel Report
Travelers' Diarrhea Deployment Health Guideline Expert Panel Author Notes
Military Medicine, Volume 182, Issue suppl_2, 1 September 2017, Pages 34–52, https://doi.org/10.7205/MILMED-D-17-00077

PARTNERSHIPS

Defense Health Agency, Global Emerging Infections Surveillance (GEIS), Naval Medical Research Unit Six, Naval Medical Research Center and Infectious Diseases Clinical Research Program (IDCRP), Uniformed Services Health University

FORGING THE FUTURE

Disease Surveillance

Continue surveilling emerging antibiotic resistance at WRAIR forward sites:

USAMRD-Africa
Seven surveillance sites located in Kenya

USAMRD-Georgia
Two surveillance sites located in Tbilisi and Gori

AFRIMS
Six surveillance sites located in Nepal, Thailand, Cambodia, and the Philippines

PREVENTING THE DIARRHEAL THREAT

CHALLENGES

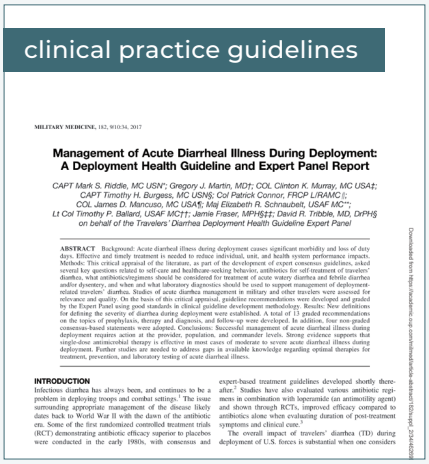
- Lack of lab diagnostic capabilities in forward locations makes it difficult to identify the cause of diarrhea and limits effectiveness of treatment.
- While care-seeking behaviors have been improving over the last ten years, most diarrheal disease cases are not brought to medical attention.

WRAIR DELIVERS

TrEAT Traveler's Diarrhea Clinical Trials

- Conducted among U.S. and UK military personnel deployed to Afghanistan, Djibouti, Kenya, Thailand and Honduras in collaboration with Naval Medical Research Center, Infectious Diseases Clinical Research Program (IDCRP).
- Improves current treatment and prevention of acute diarrhea by comparing three other single-dose therapies to determine the best regimen for deployed personnel.
- Resulted in new clinical practice guidelines for the treatment of acute diarrhea which were published in *Military Medicine* in October 2017.

clinical practice guidelines



MILITARY MEDICINE, 182, 9/10:34, 2017

Management of Acute Diarrheal Illness During Deployment: A Deployment Health Guideline and Expert Panel Report

*CAPT Mark S. Riddle, MC USN†; Gregory J. Martin, MD†; COL Clinton K. Murray, MC USA‡; CAPT Timothy H. Burgess, MC USN§; Col Patrick Connor, FRCP L/RAMC‖; COL James D. Mancuso, MC USA¶; Maj Elizabeth R. Schnaubelt, USAF MC**; Lt Col Timothy P. Ballard, USAF MC††; Jamie Fraser, MPH‡‡; David R. Tribble, MD, DrPH§ on behalf of the Travelers' Diarrhea Deployment Health Guideline Expert Panel*

ABSTRACT Background: Acute diarrheal illness during deployment causes significant morbidity and loss of duty days. Effective and timely treatment is needed to reduce individual, unit, and health system performance impacts. Methods: This critical appraisal of the literature, as part of the development of expert consensus guidelines, asked several key questions related to self-care and healthcare-seeking behavior, antibiotics for self-treatment of travelers' diarrhea, what antibiotics/regimens should be considered for treatment of acute watery diarrhea and febrile diarrhea and/or dysentery, and where and what laboratory diagnostics should be used to support management of deployment-related travelers' diarrhea. Studies of acute diarrhea management in military and other travelers were assessed for relevance and quality. On the basis of this critical appraisal, guideline recommendations were developed and graded by the Expert Panel using good standards in clinical guideline development methodology. Results: New definitions for defining the severity of diarrhea during deployment were established. A total of 13 graded recommendations on the topics of prophylaxis, therapy and diagnosis, and follow-up were developed. In addition, four non-graded consensus-based statements were adopted. Conclusions: Successful management of acute diarrheal illness during deployment requires action at the provider, population, and commander levels. Strong evidence supports that single-dose antimicrobial therapy is effective in most cases of moderate to severe acute diarrheal illness during deployment. Further studies are needed to address gaps in available knowledge regarding optimal therapies for treatment, prevention, and laboratory testing of acute diarrheal illness.

INTRODUCTION

Infectious diarrhea has always been, and continues to be a problem in deploying troops and combat settings.[1] The issue surrounding appropriate management of the disease likely dates back to World War II with the dawn of the antibiotic era. Some of the first randomized controlled treatment trials (RCT) demonstrating antibiotic efficacy superior to placebos were conducted in the early 1980s, with consensus and expert-based treatment guidelines developed shortly thereafter.[2] Studies have also evaluated various antibiotic regimens in combination with loperamide (an antimotility agent) and shown through RCTs, improved efficacy compared to antibiotics alone when evaluating duration of post-treatment symptoms and clinical cure.[3]

The overall impact of travelers' diarrhea (TD) during deployment of U.S. forces is substantial when one considers

FORGING THE FUTURE

- A follow-on study, TrEAT Traveler's Diarrhea 2.0, will focus on the U.S. and UK military personnel deployed to Honduras and Kenya in which different dosages of one antibiotic, rifaximin, will be tested.

WHAT WE'RE DOING OCONUS

USAMRD-GEORGIA, TBILISI, GEORGIA

- Conducts bacterial diarrhea surveillance studies via Global Emerging Infections Surveillance (GEIS) funding and enrolls traveling U.S. government personnel as its target population.
- Establishes sites for diarrheal surveillance and product development and evaluation in travel clinics located in Tbilisi and potentially in Gori.
- Provides laboratory support within EUCOM and participates in the NATO Force Health Protection Working Group.

DEFEATING TRAVELER'S DIARRHEA AT USAMRD-AFRIMS

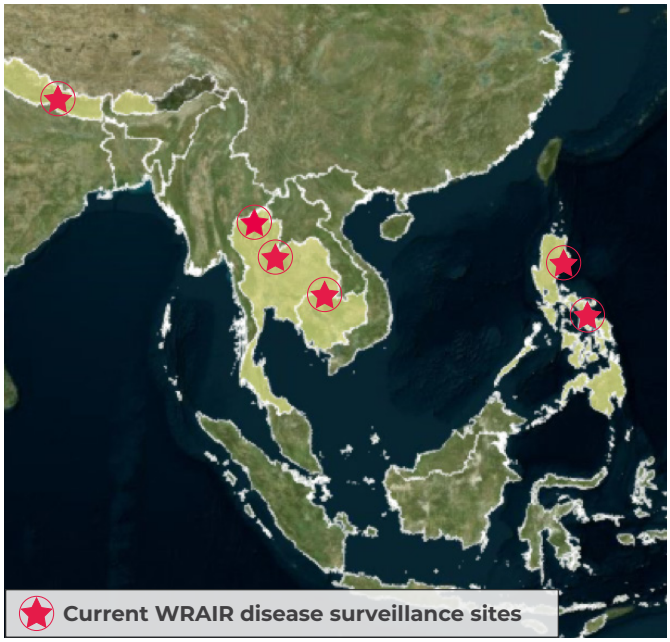
ARMED FORCES RESEARCH INSTITUTE OF MEDICAL SCIENCES, BANGKOK, THAILAND

- Provides laboratory support to Service Members deployed to Thailand as part of successive Cobra Gold exercises, which has resulted in no reported cases of diarrheal disease.
- Named one of three centers of excellence for *Campylobacter* research in Thailand by the Thai Ministry of Health.
- Conducts disease surveillance via GEIS funding in Thailand, Cambodia, Nepal and Vietnam for deployed U.S. military personnel and travelers in Southeast Asia.
- Provides INDOPACOM with relevant data on diarrheal pathogen incidence and antibiotic resistance to guide preventive medicine measures and treatment.
- Partners with the World Health Organization.

AFRIMS TESTS

Travelan®

- Travelan is a product marketed for the prevention of traveler's diarrhea that won't cause antimicrobial resistance.
- WRAIR, AFRIMS and NMRC partnered with Immuron to test Travelan against *Shigella*, ETEC, *Vibrio cholerae* and *Campylobacter jejuni* isolates.
- In a recent preclinical study, Travelan prevented the development of Shigellosis in 75% of animals receiving therapy.



Current WRAIR disease surveillance sites

PARTNERSHIPS

WRAIR partners with Johns Hopkins University, University of Maryland, University of Alabama-Birmingham, University of Virginia, Mahidol University and Wellcome Trust.

AFRIMS was also one of the partnering institutions in the Bill and Melinda Gates Foundation sponsored MAL-ED Study. An international network of partners conducted research at eight geographically distinct sites (AFRIMS being Bhaktapur, Nepal) within populations known to have high rates of enteric infections and malnutrition early in life.

DEFEATING TRAVELER'S DIARRHEA AT USAMRD-AFRICA

USAMRD-AFRICA, MICROBIOLOGY HUB
KERICHO, KENYA

- Partners with industry to test their vaccine candidates in regions with disease.
- Accredited by the College of American Pathologists since 2012.
- Over 9000 sq ft of lab space for bacteriology, parasitology, virology, immunology and molecular sections.
- Provides technical support to U.S. AFRICOM and works closely with the Kenya Medical Research Institute (KEMRI).
- Conducting upcoming *Shigella* vaccine trials (funded by LimmaTech Biologics, GSK and Pasteur Institute).

CHALLENGES

In Western Kenya, *Shigella spp.* represent between 7%-12% of pathogens detected in acute diarrheal stool. Decreased susceptibility to a range of antibiotics has been observed over the past decade, which has complicated treatment for shigellosis.

PARTNERSHIPS

PATH

gsk GlaxoSmithKline

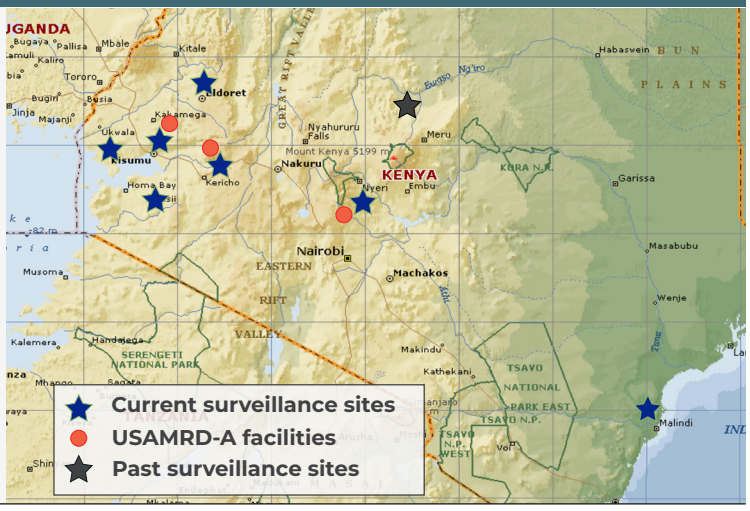
LimmaTech Biologics

Institut Pasteur

USAMRD-AFRICA DELIVERS

Disease Surveillance

Using funding from Global Emerging Infections Surveillance, the Microbiology Hub in Kericho (MHK) began sample collection and analysis for enteric pathogens in Sept 2009. Presently, MHK has seven active sites.



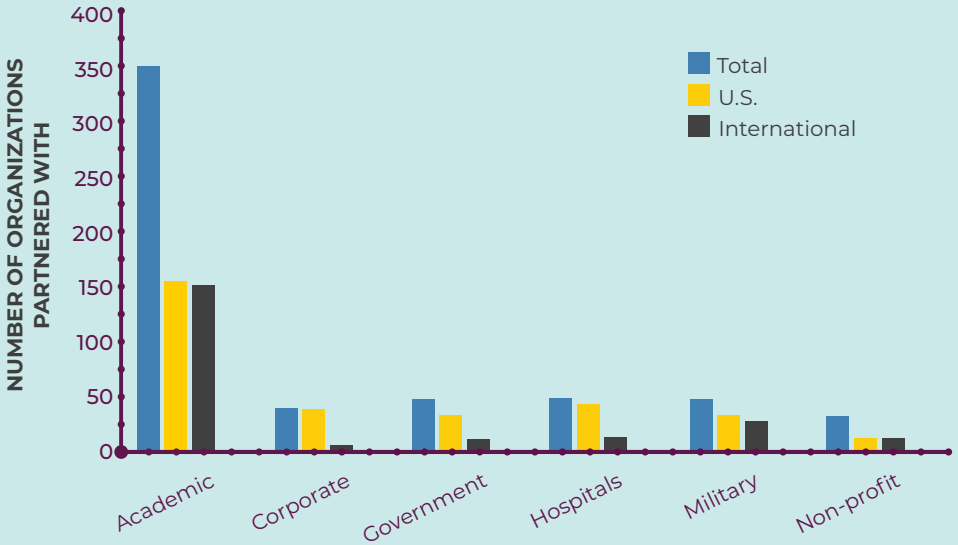
FORGING THE FUTURE

Through industry partnership two *Shigella* vaccine Phase 2B studies will commence in Fall 2020. Due to the severity of shigellosis, the disease caused by *Shigella*, and increasing antibiotic resistance, a vaccine is of paramount importance to the global community.

GLOBAL IMPACT OF WRAIR'S TRAVELER'S DIARRHEA RESEARCH

WRAIR'S RESEARCH ON DIARRHEA IN OPERATIONAL SETTINGS HAS GENERATED OVER **1,700** BIOMEDICAL PUBLICATIONS.

TYPES OF ORGANIZATIONS WE'VE PARTNERED WITH

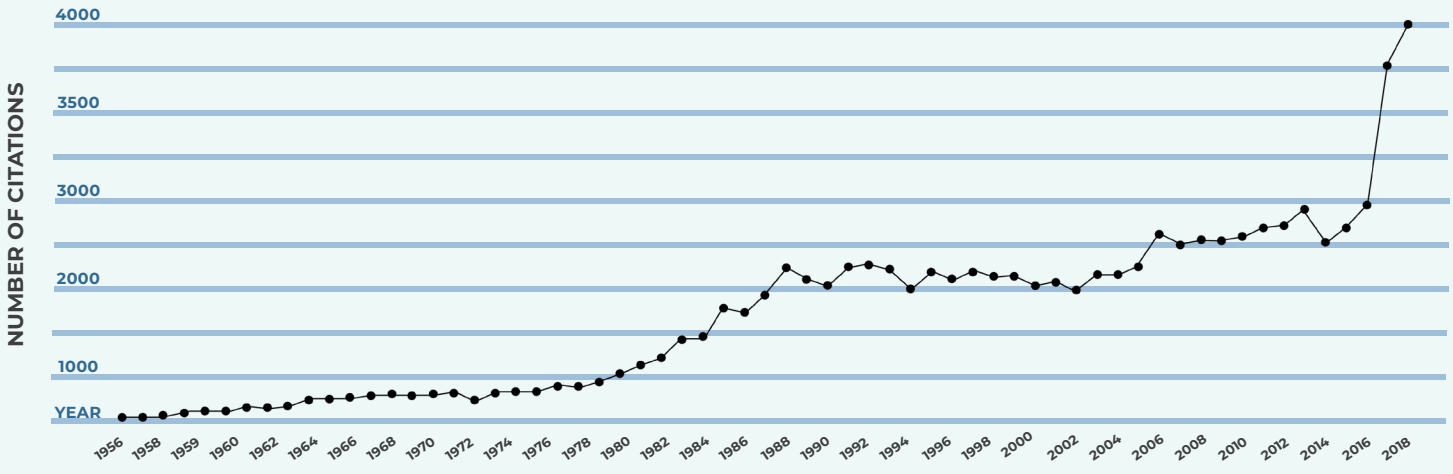


MOST FREQUENT PARTNERS

1. Naval Medical Research Center
2. National Institutes of Health
3. Uniformed Services University of the Health Sciences
4. University of Maryland School of Medicine
5. Johns Hopkins University School of Medicine
6. University of Virginia
7. International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh
8. Johns Hopkins Bloomberg School of Public Health
9. Food and Drug Administration
10. Henry M. Jackson Foundation
11. Mahidol University, Bangkok, Thailand

SUM OF TIMES CITED PER YEAR

Over **65,000** biomedical publications have built upon WRAIR's traveler's diarrhea research to develop innovative new treatments and prevention methods. The number of times WRAIR research has been cited in biomedical publications has grown steadily over the past 60 years.



Source: Web of Science