

# 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.

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WalterReedArmyInstituteOfResearch

#### PROMOTED HASHTAGS

#SoldierHealthWorldHealth  
#ForgeTheFuture #TravelersDiarrhea  
#BacterialDysentery #MilitaryDiarrhea  
#PreventTheDiarrhealThreat

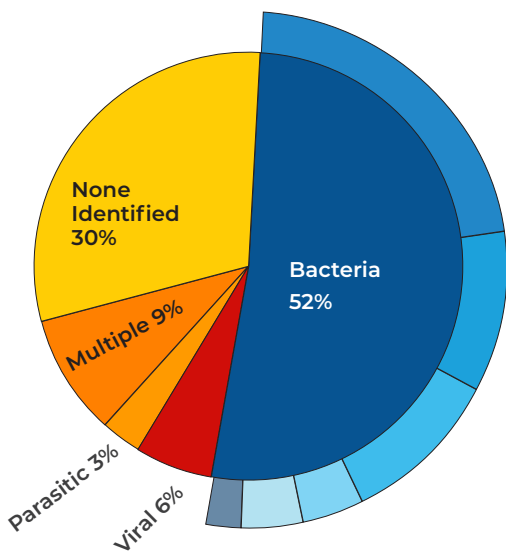


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COMMAND OF MRDC

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# SUMMARY POINTS PAGE

## CAUSES & IMPACT OF DIARRHEA



Listed In Order

- enterotoxigenic *E. coli* (ETEC)
- enteroaggregative *E. coli* (EAEC)
- Campylobacter*
- Shigella*
- enteropathogenic *E. coli* (EPEC)
- Salmonella*



### Diarrhea ranked 1<sup>st</sup> among 57

infectious disease threats by the 2019 Military Infectious Disease Research Program's Infectious Disease Threat Prioritization Panel based on its impact to readiness.

Bacterial pathogens are the predominant risk, 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

### Traveler's Diarrhea:

Defined as three or more loose, watery or bloody stools in less than 24 hours and can be associated with vomiting, fever, anorexia, nausea and electrolyte loss.

### The Five F's of Traveler's Diarrhea Transmission



Fluids



Food



Feces



Fingers



Fomites

- » Consumption of local food and water is the largest contributor to traveler's diarrhea.
- » 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.



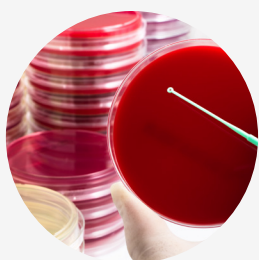
# DIARRHEAL DISEASE TOPLINE MESSAGES

## TOPLINE MESSAGES

- » Diarrhea 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, which can result in:
  - a loss of duty/work days per incident
  - 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.<sup>1</sup>
- » Diarrhea incidence among U.S. troops deployed during OIF and OEF outpaced respiratory illness and injury.<sup>2</sup>
- » 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 is limited to prevention or treatment options.

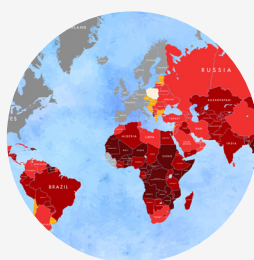
1. J R Army Med Corps. 2013 Sep;159(3):229-36. doi: 10.1136/jramc-2013-000084. Epub 2013 May 27.  
2. Am J Trop Med Hyg. 2005 Oct;73(4):713-9.

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# HISTORY AND IMPACT OF DIARRHEA IN WAR



## ● Vietnam War

- » Diarrhea was the most burdensome disease
- » Diarrhea exceeded Malaria 4 to 1

## ● Desert Shield/ Storm

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

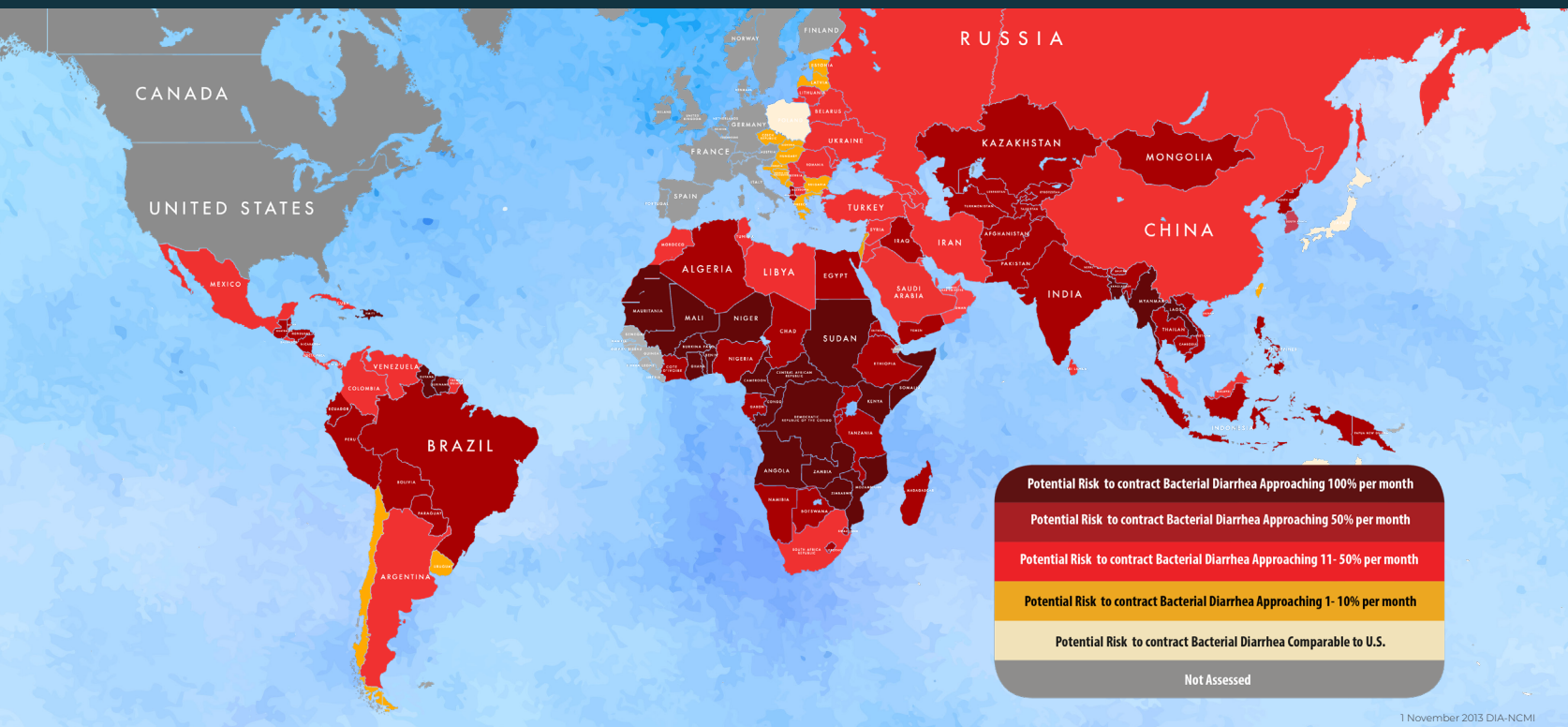
## ● Operation Enduring Freedom

- » 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

# WORLDWIDE RISK TO U.S. FORCES



## COMBATING THE ENTERIC DISEASE THREAT ACROSS THE PHASES OF MDO

	Compete	Penetrate	Dis-Integrate	Exploit	Re-Compete
Proactive medical diplomacy	Disease Surveillance				
Systems of systems used to weaken the disease	Hygiene, Sanitation, Vaccines and Prophylaxis				
Convergence of effort to stop the spread of disease	International Unity of Effort Interagency   Interservice   International				
Methods used to eliminate the disease				Treatment	
Reassessing the threat and developing new countermeasures				Evolving Threat: Disease Surveillance & Next Generation Products	
Threat Stand-off					

### 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

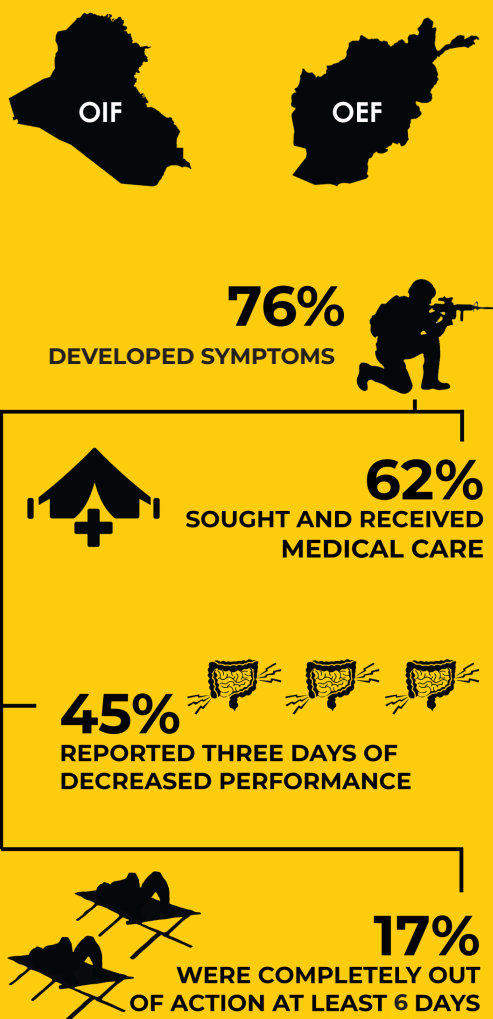
WRAIR utilizes personnel, facilities and advanced technologies within areas of operations that maximize its human potential through research and development to fight across multiple domains.

# 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.
- » Diarrhea infections result 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. Potter, 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;51. 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 Barre Syndrome

Chad K. Potter, 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 NIH and industry, WRAIR is developing the WRSs2 and Invaplex vaccine for *Shigella*

#### **Enterotoxigenic *E.coli* & *Campylobacter***

Naval Medical Research Center(NMRC) and WRAIR work towards vaccines for:

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

### Development & Production

Development and production of critical reagents and assays for enteric 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).

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



## FORGING THE FUTURE



### Clinical Trials

A Phase 2B clinical trial to determine the efficacy of the *Shigella sonnei* vaccine, WRSs2, is scheduled to commence in November 2019 at Cincinnati Children's Hospital Medical Center and in seven other sites in Kenya in 2020 (funded by NIH and industry partners).



### Bacteria Resistance Surveillance

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

**To protect personnel overseas and keep Soldiers in the fight, WRAIR's Bacterial Diseases branch aims to develop a safe and effective vaccine against multiple *Shigella* strains, a notable diarrheal disease.**

[WWW.WRAIR.ARMY.MIL](http://WWW.WRAIR.ARMY.MIL)

# ONGOING BACTERIAL RESISTANCE THREAT

## CHALLENGES

- » Among Soldiers, treatment adherence and improper self-medication are common concerns. Worldwide indiscriminate use of and counterfeit antibiotics are contributing to emerging antibiotic resistance.
- » Standard antibiotics in use today are becoming increasingly less effective.



- » Antimicrobial resistance in pathogens causing traveler's diarrhea is a growing threat in Southeast Asia and Africa.
- » Overseas travelers, who treat their diarrhea with antibiotics, still have the pathogens present in their colon, which can spread to others while they travel or return home.

### WHAT THIS MEANS FOR SOLDIERS

- » More emphasis on preventive medicine 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.
- » Through the TrEAT Traveler's Diarrhea Study, WRAIR, Infectious Diseases Clinical Research Program (IDCRP) and NMRC will be able to determine a single-dose regimen that will assist Soldiers quicker, lessening the possibility of spread and resistance.

## 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

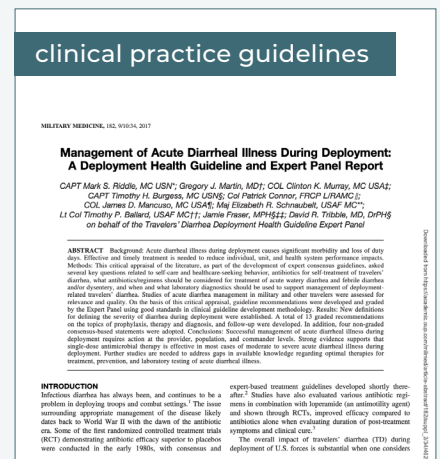
## CHALLENGES

- » 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.



## 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.

### AFRIMS TESTS

**Travelan<sup>®</sup>**

- » Travelan is a natural product marketed for the prevention of traveler's diarrhea and 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 those receiving therapy.



### 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

### CHALLENGES

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

### PARTNERSHIPS

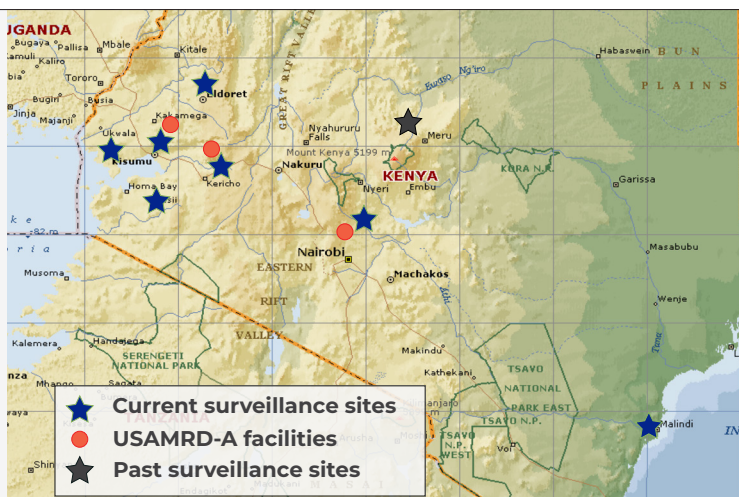


### USAMRD-AFRICA DELIVERS



#### 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 studies.



### FORGING THE FUTURE

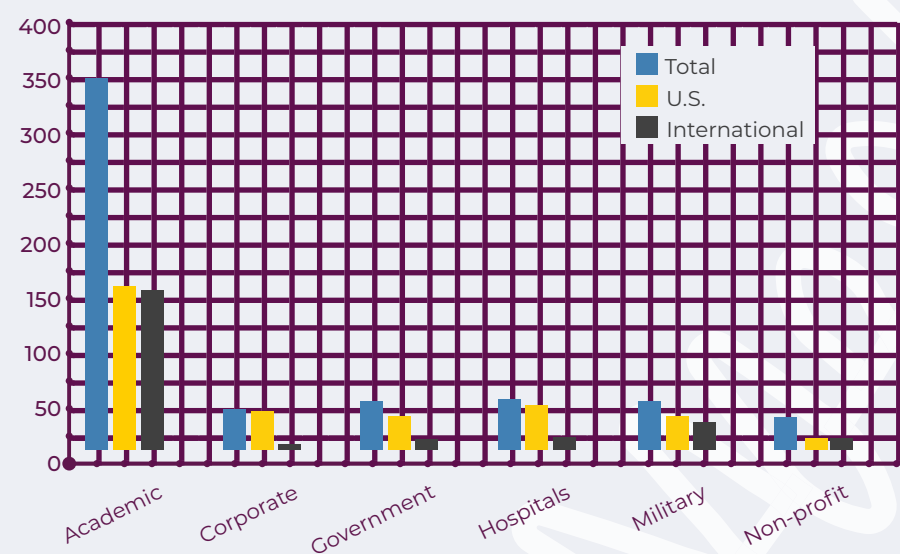
Through industry partnership two *Shigella* vaccine Phase 2B studies will commence in Summer 2020. Due to the severity of shigellosis, the disease caused by *Shigella*, and increasing antibiotic resistance, a vaccine is of paramount importance to the global community.



# GLOBAL IMPACT OF WRAIR'S TRAVELER'S DIARRHEA RESEARCH

WRAIR'S RESEARCH ON DIARRHEA IN OPERATIONAL SETTINGS HAS GENERATED AROUND **1,800** BIOMEDICAL PUBLICATIONS.

## TYPES OF ORGANIZATIONS WE'VE PARTNERED WITH

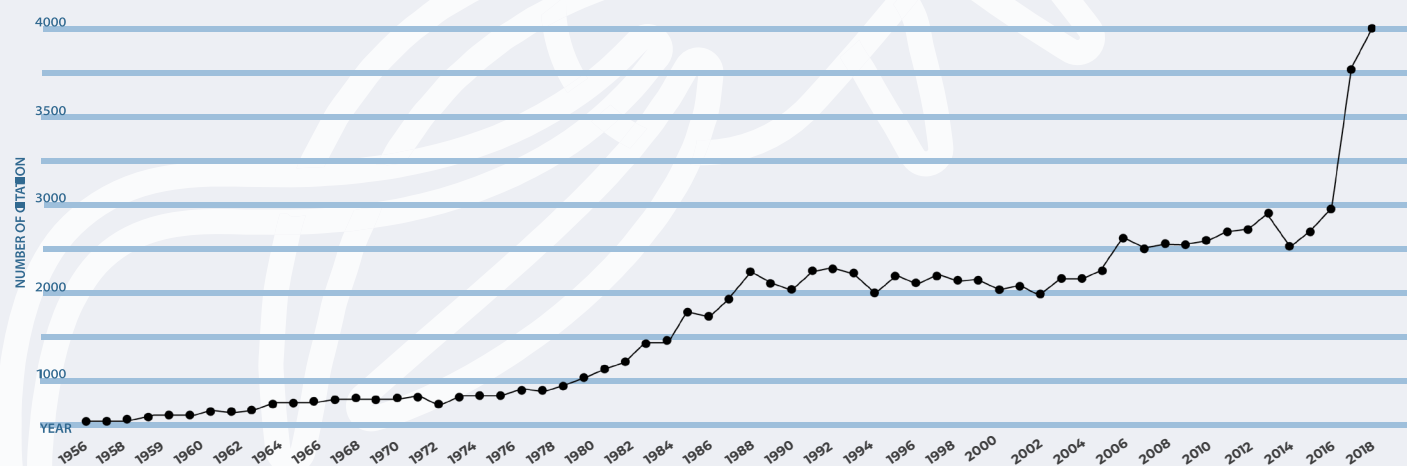


## MOST FREQUENT PARTNERS

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 used in biomedical publications has grown steadily over the past 60 years.



Source: Web of Science