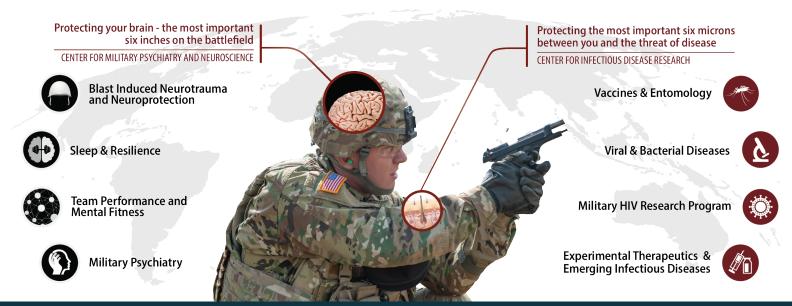
WRAIR'S INVESTIGATOR'S DISPATCH



WRAIR PROTECTS YOUR SIX



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

- **f** WRAIROfficial
- **e** @WRAIR
- https://www.wrair.army.mil
- **▶** WalterReedArmyInstituteOfResearch

PROMOTED HASHTAGS

#WRAIRProtectsYourSix

#DefeatInfections #WorldHealth

#OptimizeHumanPotential

#ForgeTheFuture #SoldierHealth



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.

MILITARY MEDICINE'S

CONTRIBUTION TO THE DEVELOPMENT OF

DISEASE COUNTERMEASURES

- 1 WRAIR and its global research sites played a role in developing nearly half of the vaccines.
- One key aspect of WRAIR's vaccine program is partnership and collaboration across U.S.

 Army Medical Research and Development Command, U.S.

 Army Medical Materiel

 Development Activity, and our nearly 400 academic and industry partners.
- WRAIR's contributions to countermeasure development include disease surveillance, discovery, small batch vaccine production, phase I-III clinical trials, and phase IV post-licensure clinical trials.

YELLOW FEVER

Demonstrated that the etiologic agent was a filterable virus transmitted by *Aedes aegypti* mosquitoes, leading to disease control through vector eradication and, eventually, vaccination.

PNEUMOCOCCUS

Tested first multivalent polysaccharide vaccine at the Sioux Falls Army Air Base, S.D., which reduced incidence of pneumonia and the pneumococcal carrier state.

INFLUENZA

Described how the influenza virus evolved from year to year and developed a vaccine minimizing the impact of a major pandemic in the United States.

RUBELLA

First isolation of rubella virus; identification led to development of a safe and effective vaccine.

ADENOVIRUS

Isolated the causative agent, described the epidemiology and clinical spectrum, and developed a vaccine to prevent adenovirus infection. Subsequent manufacturing concerns led to the development of a new vaccine in the 1970s.

TYPHOID

Developed the first American typhoid vaccine at WRAIR's predecessor, the Army Medical School.

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MENINGOCOCCAL DISEASE

Described the immune response to meningococcal disease, developed the first polysaccharide immunogen against it and proved the preventive's efficacy in clinical trials.

HEPATITIS A

Investigated safety and immunogenicity of inactivated vaccines and directed a pivotal efficacy study among 40,000 Thai children.

CHOLERA

Developed a live oral cholera vaccine candidate derived from C6709, a Peruvian strain of V. cholerae O1, biotype El Tor.

ANTHRAX

Evaluated a new vaccine delivery route from subcutaneous to intramuscular that decreased dosing.

DENGUE

Evaluated the safety and immunogenicity of three different formulations of

EBOLA

Conducted six Ebola vaccine studies testing three candidates; current Ebola vaccine being used in the DRC has been shown to be 97% effective, conducting a Marburg vaccine study (VRC) and another Ebola Sudan vaccine trial in Uganda.

ADENOVIRUS

Ad4 and Ad7 vaccines were approved by the U.S. FDA and vaccination resumed in 2011 at all military recruiting centers.

JAPANESE ENCEPHALITIS

Contributed technology, preclinical studies, pilot-scale manufacturing, clinical studies, and additional field studies for final FDA approval of a vaccine against Japanese encephalitis.

HEPATITIS B

Demonstrated antibodies from individuals infected with hepatitis B are protective, allowing for an immunoglobulin preventive.

MERS COV

Completed the first-in-human, and still only, phase I trial of a MERS vaccine candidate intended for use in humans.

RTS, S/MALARIA

WRAIR's Controlled Human Malaria Infection model showed safety and efficacy of this malaria vaccine in humans. Currently being used by WHO in three countries in Africa to decrease childhood deaths.

ZIKA

Moved from an initial concept of a Zika vaccine to clinical studies within nine months.

Dis-integrating Deployment Related Infectious Diseases

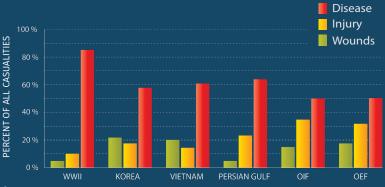
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Disease Priorities & Partnerships

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Disease Causes More Casualities Than Enemy Action



- soutice.

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 2. Hauret KG, Pacha L, Taylor BJ, Jones BH. Surveillance of Disease and Nonbattle Injuries During US Army
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PROLONGED FIELD CARE IMPLICATIONS FOR INFECTIOUS DISEASES



CHALLENGE

- During near-peer competition, air superiority diminishes, limiting availability to evacuate Soldiers from the point of injury limiting Warfighter sanitation, treatment and resupply capabilities.
- During the penetrate, dis-integrate, and exploit phases of MDO, when casualty rates are elevated and MEDEVAC is limited, there will be a corresponding rise in wound infection rates; complicated by growing resistance to existing antibiotics, wound infection is an increasingly devastating source of mortality.
- During OIF and OEF, when we had the benefit of the Golden Hour, 10-30% of casualties experienced a serious wound infection.
- When we are in a near-peer competition, wound infections could be the signature wound of MDO.
- The most lethal Soldiers on the MDO battlefield will be the ones durably protected against infectious diseases by countermeasures delivered prior to entry into theater that are not dependent upon a battlefield medical logistics system, which is highly vulnerable to enemy interdiction.



52,352





On average 45 - 90 minutes from injury to field hospital



of those wounded had bacteria in their wounds

combat casualties develop infections during their initial hospitalization





deep infection rate for type III open tibia fractures



How many infections will we have when we extend to the Golden Day+?

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WHAT WE'RE DOING ABOUT IT

WRAIR is investigating new far-forward therapeutic interventions to extend the Golden Hour to the Golden Day, which is required to sustain a lethal and responsive force during high-intensity combat.

Advances in Wound Infection Therapeutic Development

Due to the unique nature of combat injuries, wound contamination frequently results in bacterial infection by multidrug-resistant (MDR) organisms. WRAIR is developing novel solutions through:

- Small and large preclinical infection models with clinically relevant multidrug-resistant bacteria
- · Preclinical models of bacteriophage therapy leading to human proof-of-concept studies
- · Monoclonal antibody therapeutic development
- Home to the Army's only structual biology center for drug discovery and vaccine development

I Maximizing Joint Force Generation

- · Immunize for vaccine preventable disease
- Disease surveillance information from OCONUS labs inform disease risk to guide preventive countermeasures (vectors/pathogens)

Safer Blood Supply

The need to develop a safe, effective, rapidly-acting, and durable product that minimizes or eliminates the ongoing issues with non-compliance, medication side effects, and host genetics restriction remain a critical goal—a "fire and forget" solution.

Fielded Solutions

BinaxNow

Point of care testing for rapid diagnosis and treatment of malaria infection.



Future Solutions

Topical Paromomycin

Showed efficacy as treatment for ulcerative cutaneous leishmaniasis in FDA regulated study



FORGING THE FUTURE

- WRAIR, in partnership with other MRDC and DOD organizations, are creating new far-forward therapeutic interventions to prevent and treat bacterial wound infections and extend the Golden Hour to the Golden Day+.
- WRAIR is investigating novel, small molecule antibiotics, monoclonal antibodies and bacteriophage solutions to overmatch this threat.

INFECTIOUS DISEASES IN DENSE URBAN AND SUBTERRANEAN ENVIRONMENTS Challenge In dense urban environments, diseases spread by human contact will increase. War will disrupt infrastructure in urban environments (sewage, water) presenting additional risks capable of defeating the most lethal and combat effective troops.

- Environmental and infectious disease threats not routinely seen in the U.S present health risks to Warfighters.
- Large troop movements introduce threats due to diarrheal disease and airborne pathogens.
- MRDC has taken a global lead to develop the next generation of infectious disease countermeasures against diseases of military relevance.

SUCCESS STORY

ADENOVIRUS (AD)





in the military between 2000-2011 when vaccine was unavailable.



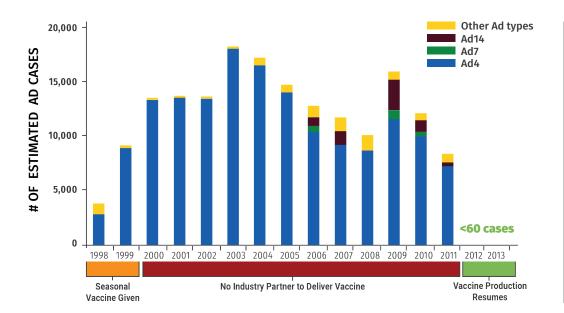
Adenovirus types 4&7

infections affect up to 8 of 10 Service Members during basic training.



to 60 cases per year

since reintroduction of the vaccine which WRAIR led with USAMMDA and industry partners.



"Infectious disease threats have the potential to endanger lives and disrupt economies, travel, trade, and the food supply. Outbreaks do not respect national boundaries and can spread rapidly jeopardizing the health, security, and prosperity of the United States. It is in the national security interest of the United States to strengthen global health security and manage the risk of infectious disease outbreaks."

 United States's Government Global Health Security Strategy, 2019

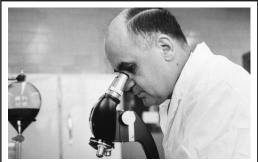
INFLUENZA, AN ENDURING THREAT



More than 43,000 U.S. sailors and soldiers died of flu and pneumonia in 1918.



1945 WRAIR helped develop first influenza vaccine.



1957 Maurice Hilleman at WRAIR isolated new strain of flu that led to improved vaccines.

"U.S. Army's Medical Research and Development Command (MRDC) product development mission and research platforms serve to protect DOD personnel from infectious disease threats, by supporting the National Defense Strategy, the National Military Strategy and is nested in the President's National Security Strategy. It achieves this by operating a global research network to detect and mitigate outbreaks to contain the spread of disease."

WRAIR CONTINUES TO

In partnership with Global Emerging Infectious Surveillance (GEIS), WRAIR informs annual flu vaccine development through global surveillance.

Evaluate human and environmental factors that can be used to predict and prevent influenza transmission in closequarter settings.

Model and study the risk of vaccine failure in highly vaccinated DOD populations.

NOROVIRUS, OPERATIONAL IMPACT OF COMMUNICABLE DISEASE

is the leading cause of acute gastrointestinal illness outbreaks in military settings.

is spread by infected:



Beverages



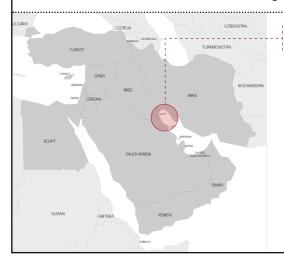
Fomites







Symptoms begin within 12-48 hours of exposure and include vomiting, nausea and diarrhea.



Camp Arifjan, Kuwait

- There were approximately 14,000 Service Members at Camp Arifjan, 3,000-4,100 were in transit and 10,000 were permanently assigned there.
- A Soldier with symptoms of nausea, vomiting, and diarrhea was treated and released to his unit.
- Over 14 days, more than 90 Soldiers experienced symptoms of nausea, vomiting, and diarrhea, resulting in the shutdown of Camp Arifjan for about 10 days.

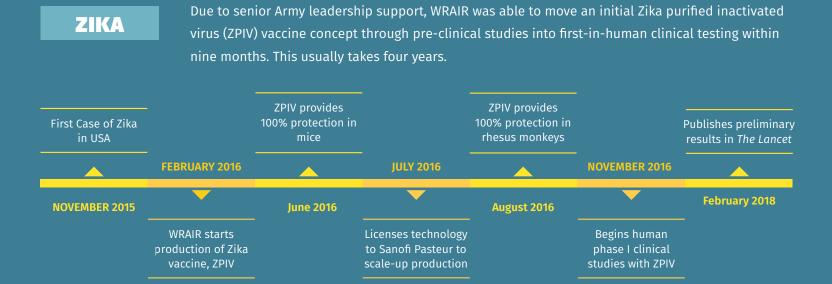
EMERGING INFECTIOUS DISEASES DEGRADING COMBAT EFFECTIVENESS

CHALLENGE

Emerging infectious disease threats have the potential to overwhelm U.S. and partner capacity; this can significantly threaten political and economic stability, supporting an environment conducive to transnational crime and violent extremism. Emerging infectious disease disrupts strategic goals in the compete phase of MDO and limits the ability to consolidate gains during the re-compete phase of MDO.

WHAT WE'RE DOING ABOUT IT

WRAIR's extensive international research infrastructure and capabilities allow its scientists to anticipate and develop countermeasures against emerging infectious disease (EID) threats. The Institute's longstanding capabilities, which include subject matter expertise, in-house manufacturing, a broad network of international sites and public-private partnerships, enable the Emerging Infectious Diseases Branch (EIDB) to respond rapidly to outbreaks, through an accelerated cycle of countermeasure development: from conception to human clinical trials.



MILITARY RELEVANCE

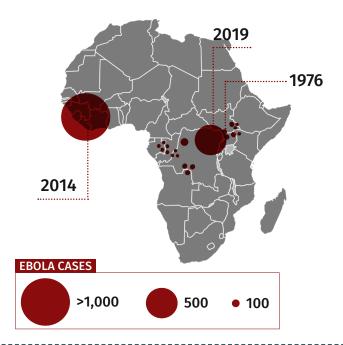




the most Zika cases.

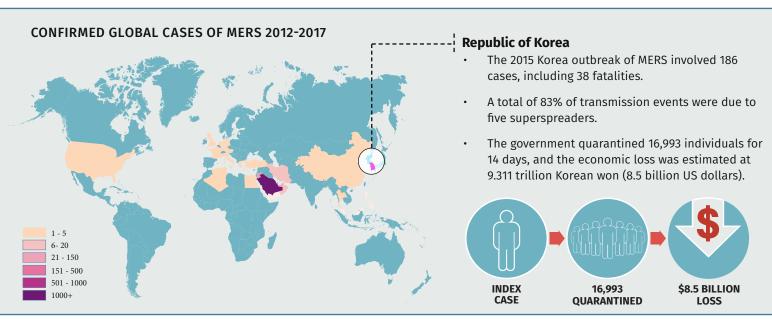
EBOLA OUTBREAK

- Leveraging partners and clinical trial capabilities,
 WRAIR pivoted to advance an Ebola Zaire vaccine candidate during the 2014 West Africa outbreak into first-in-human clinical trials in just 11 weeks.
- The vaccine showed efficacy when used less than a year later during an outbreak later in Guinea.
- The Ebola Zaire vaccine efficacy is estimated at 97% based on a WHO meta analysis of its use in the current Ebola outbreak in the Democratic Republic of Congo.
- To date, WRAIR has conducted six Ebola vaccine studies testing three candidates; is conducting a Marburg vaccine clinical trial at WRAIR currently and another Ebola Sudan vaccine trial in Uganda.



MIDDLE EAST RESPIRATORY SYNDROME (MERS)





MILITARY RELEVANCE

- MERS is a growing global concern due to its high fatality rate of nearly 40%.
- Given deployments to the Middle East and South Korea—where large outbreaks have occurred coupled with close living quarters in those situations, military personnel are at increased risk for exposure to MERS.
- There are currently no approved countermeasures for MERS.

FORGING THE FUTURE

- WRAIR initiated and now has completed the first-in human, and still only, phase I trial of a MERS vaccine candidate intended for use in humans.
- The study, conducted at the WRAIR Clinical Trials Center, evaluated a candidate DNA vaccine codeveloped with industry.
- The promising results from this study, published in, July, 2019, in *The Lancet Infectious Diseases*, have prompted advancement to a second phase I/IIa trial in South Korea and a phase II study in the Middle East.

DIS-INTEGRATING DEPLOYMENT RELATED INFECTIOUS DISEASES

Challenge

- Each year we send Soldiers to 140 countries where they not only face the threat of the enemy but the threat of diseases.
- Historically, disease non-battle injury (DNBI) has resulted in greater loss of combat strength and combat efficacy than the enemy. Attrition from DNBI disrupts the ability of the Army to penetrate, dis-integrate, and exploit the MDO battlefield.
- Although emerging technologies like artificial intelligence, hypersonics, machine learning, nanotechnology, and robotics are driving a fundamental change in the character of war, the nature of war remains a human endeavor. The Soldier remains the most essential weapon system to ensure success in MDO.
- In conflicts occurring on battlefields in the enemy's backyard. U.S. forces could find themselves more susceptible to endemic diseases than our opponents because of protection stemming from previous exposure.
- These pathogens are often highly contagious, they may spread within a unit of Warfighters and not just decrease the efficacy of the individual but remove entire combat units from the battlefield.
- Just as the joint force must dis-integrate the enemy's antiaccess and area denial systems, countermeasures created by MRDC and WRAIR must provide a convergence of effort to stop the spread of disease; thus providing a foundation for combat effectiveness.

WHAT MILITARY MEDICINE IS DOING ABOUT IT

CONTROL THE THREAT

- Picaridan and IR3535 are proven, effective repellents
- Treated bed nets
- Permethrin-treated uniform



WRAIR evaluated in partnership with the Armed Forces Pest Management Board and USAMMDA

COUNTERMEASURE DEVOLOPMENT

In 2019, FDA approved
Dengvaxia in dengue endemic
areas (restricted for use of
local populations)



WRAIR'S CURRENT TARGETS

- Dengue
- Malaria
- Chikungunya
- Leptospirosis
- Acute Respiratory, Viral
- Diarrhea
- Multidrug-Resistant Organisms



SUCCESS STORY HEPATITIS A VIRUS (HepA)

A liver infection that is highly contagious



is spread by infected:







Feces



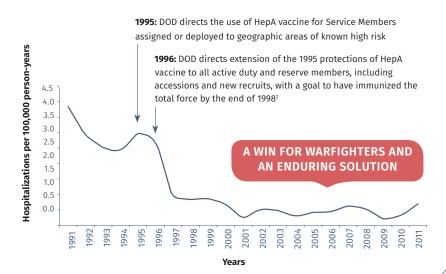




HepA VACCINE MILITARY RELEVANCE

- Biologic solution that maintains combat effectiveness
- HepA is highly contagious and a concern of the U.S. military as outbreaks can spread quickly through a unit and sideline a Soldier for a few weeks to several months
- The youngest age group of Service Members are most at risk for HepA exposure
- HepA vaccine provides life-long immunity; only 237 incidents of acute HepA were reported between 2007-2016

TREND OF INCIDENT HOSPITALIZATIONS FOR HEPATITIS A, **ACTIVE COMPONENT, U.S. ARMED FORCES, 1991-2011**



SUCCESS STORY JAPANESE ENCEPHALITIS VIRUS (JEV)

is spread by infected:



JEV virus is transmitted to humans through bites from infected Culex mosquitoes.

JEV is the most common cause of encephalitis in Asia.



20% to 30%

reported case fatality rate, with 30-50% of the survivors having longterm medical issues that often lead to an early death.

IEV MILITARY RELEVANCE

- Based on our innovation, the Republic of Korea implemented mandatory childhood vaccination (1967), which reduced incidences from 2500 cases (695 deaths) in 1966 to 0-7 cases 1984-2007.
- JEV vaccine reduces exposure risk to U.S. Service Members deployed to the Republic of Korea.
- The continued presence of JEV in the Republic of Korea poses a potential threat to over 29,000 U.S. personnel and greater than 13,000 beneficiaries.
- INDOPACOM implemented JEV vaccine in force protection policy for TDY/PCS to endemic area of >30 days.

WRAIR'S INFECTIOUS DISEASE TARGETS

ACUTE
RESPIRATORY,
VIRAL

CHIKUNGUNYA

DENGUE

DIARRHEA,
BACTERIAL

DIARRHEA,
VIRAL

INFLUENZA

LEPTOSPIROSIS

MALARIA

MULTDRUGRESISTANT
ORGANISMS



KEY PARTNERSHIPS

• BURNET INST.

ISGLOBAL

Our robust partnerships, especially our MIL-MIL partnerships, provide a competitive advantage and help build strategic depth during all phases of MDO. Partnerships with biotech and pharmaceutical companies in the development of drugs and vaccines, allows for cost sharing, sped up timelines and takes advantage of robust development platforms in the civilian sector.

	• DHA-AFHSC	• CDC	• FDA	• NMRC	• USAMMDA
U.S. GOVERNMENT	• AFPMB	• DARPA	• MIDRP	• OGAC	• USMMVP
& DEPARTMENT OF	• CCCRP	 DEPARTMENT OF STATE 	• MOMRP	• PVC	• USUHS
DEFENSE	• CHAMP	• DHA	 NIH (NIAD, NCI, NCATS, 	• USAID	
	• CBER/FDA	• DTRA	NIDDK, VRC)	• USDA	
	ARKANSAS STATE UNIV.	EMORY UNIV.	• MIT	UNIV. OF ALABAMA	UNIV. OF NOTRE DAME
	BETH ISRAEL DEACONESS	HARVARD UNIV.	 NORTHEASTERN UNIV. 	 UNIV. OF BUFFALO 	 UNIV. OF PENN.
	BROAD INSTITUTE	 JOHN HOPKINS UNIV. 	OREGON HEALTH AND SCI.	UNIV. OF COLORADO	UNIV. OF SOUTH FL
	CALVIN COLLEGE	KAROLINSKA INSTITUTET	UNIV.	UNIV. OF ESSEN	UNIV. OF VIRGINIA
ACADEMIA	CASE WESTERN RESERVE	• LEIDEN UNIV. MED. CENTER	OXFORD UNIV.	UNIV. OF HAWAII	UNIV. OF WASHINGTON
	UNIV.	LONDON SCHOOL OF MED.	PORTLAND STATE UNIV.	UNIV. OF IOWA	UNIV. SOUTHERN FL
	CHULALONGKORN UNIV.	MAKERERE UNIV.	RAGON INST.	UNIV. OF MARYLAND	UNIV. TEXAS MED. BRANCH
	COLUMBIA UNIV.	MAHIDOL UNIV.	SOUTHWEST RES. INST.	UNIV. OF MIAMI	VIRGINIA MILITARY INST.
	DUKE UNIV.	MASSACHUSETTS GEN. HOS	SP. • OHIO STATE UNIV.	• UNIV. OF MISSISSIPPI	VANDERBILT UNIV.
	• 60 DEGREES	• CRUCELL	• GSK	• MICROBIOTIX	SANOFI PASTEUR
	PHARMACEUTICALS	DAFRA PHARMA	• INOVIO PHARMACEUTICALS	MILTENYI BIOTEC	• TAKEDA
	ABBOTT LABORATORIES	EMERGENT BIOSOLUTIONS	• IOGENETICS	• NOVARTIS	TITAN PHARMACEUTICALS
INDUSTRY	 ACUITAS THERAPEUTICS 	ENTASIS THERAPEUTICS	• JANSSEN, J&J	NOVADIGM	• THEMIS
	ALPHA-O-PEPTIDE	FRAUNHOFER BIOLOGICALS	LYNDRA THERAPEUTICS	• PFIZER	VLP THERAPEUTICS
	ANTIGEN DISCOVERY	FREQUENCY THERAPEUTICS	MESO SCALE DIAGNOSTICS	PRECISION BIOSERVICES	
	BECTON DICKINSON	GENEONE LIFE SCIENCE	• MERCK	• SANARIA	
	ARMED FORCES OF LIBERIA	BUNDESWEHR	JORDAN MINISTRY OF HEALT	TH HEALTH MOZAMBIQUE	TANZANIA MIN OF HEALTH
FOREIGN	 ARMED FORCES OF THE 	BRAZIL MINISTRY OF HEALTH	H • KENYA MEDICAL RESEARCH	NIGERIAN ARMED FORCES	AND SOCIAL WELFARE
GOVERNMENT	PHILIPPINES	GHANA ARMED FORCES	INSTITUTE	 ROYAL CAMBODIAN ARMED 	
& MILITARY	AUSTRALIAN DEFENCE	ISRAEL DEFENSE FORCES	KENYA DEFENCE FORCES	FORCES	FORCE
	FORCE	JORDANIAN ARMED FORCES	NATIONAL INSTITUTE OF	ROYAL THAI ARMY	THAI RED CROSS SOCIETY
NONPROFIT &	• ASTMH	DISEASE INITIATIVE	• JENNER INST.	• SRI INT.	
NON-GOVERNMENTAL	BILL & MELINDA GATES	• HJF	MEDICINES FOR MALARIA	TEXAS BIOMED	THIS IS A SUBSET OF
NUN-GUVEKNMEN IAL	FOUNDATION	INTERNATIONAL VACCINE	VENTURE	TRUDEAU INSTITUTE	WRAIR'S MORE THAN

POISON CONTROL CENTER

ORGANIZATION