DEFEATING MALARIA EDITION

WRAIR Walter Reed Army Institute of Research

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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PROMOTED HASHTAGS

#WRAIR #WRAIRProtectsYourSix
#DefeatMalaria #WorldHealth
#PreventMalaria #SoldierHealth
#DODGHE #GHSAgenda

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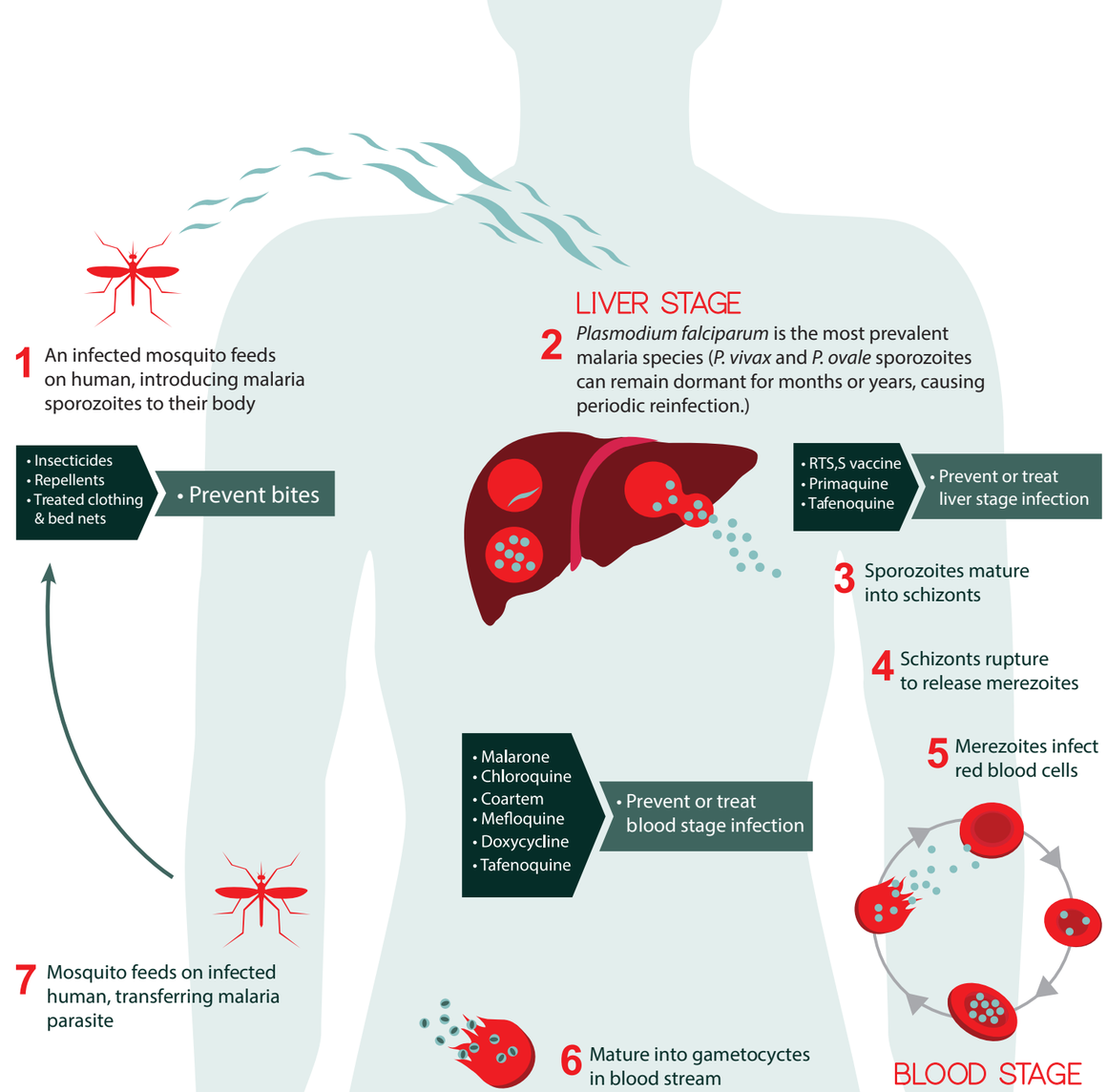
DEFEATING MALARIA AT EVERY STAGE

WRAIR has contributed to the discovery and development of 100% of all Food and Drug Administration-approved malaria prevention drugs as well as the world's most advanced malaria vaccine candidates, to include RTS,S.



"It's going to be a very long war if for every division I have facing the enemy, I have one sick in hospital and another recovering from this dreadful disease."

- Gen. Douglas MacArthur

WRAIR'S GAME-CHANGING SUCCESSES IN COMBATING MALARIA

- **All FDA-approved malaria prophylaxis drugs, including all five available today**
- **Global leader in the discovery and development of multiple vaccine candidates to protect from malaria, to include the most clinically validated malaria vaccine, RTS,S.**

World's Deadliest Animals

Due to their ability to carry and spread diseases, mosquitoes are one of the deadliest animals in the world. Disease, not combat injuries, is the leading health threat on the battlefield.

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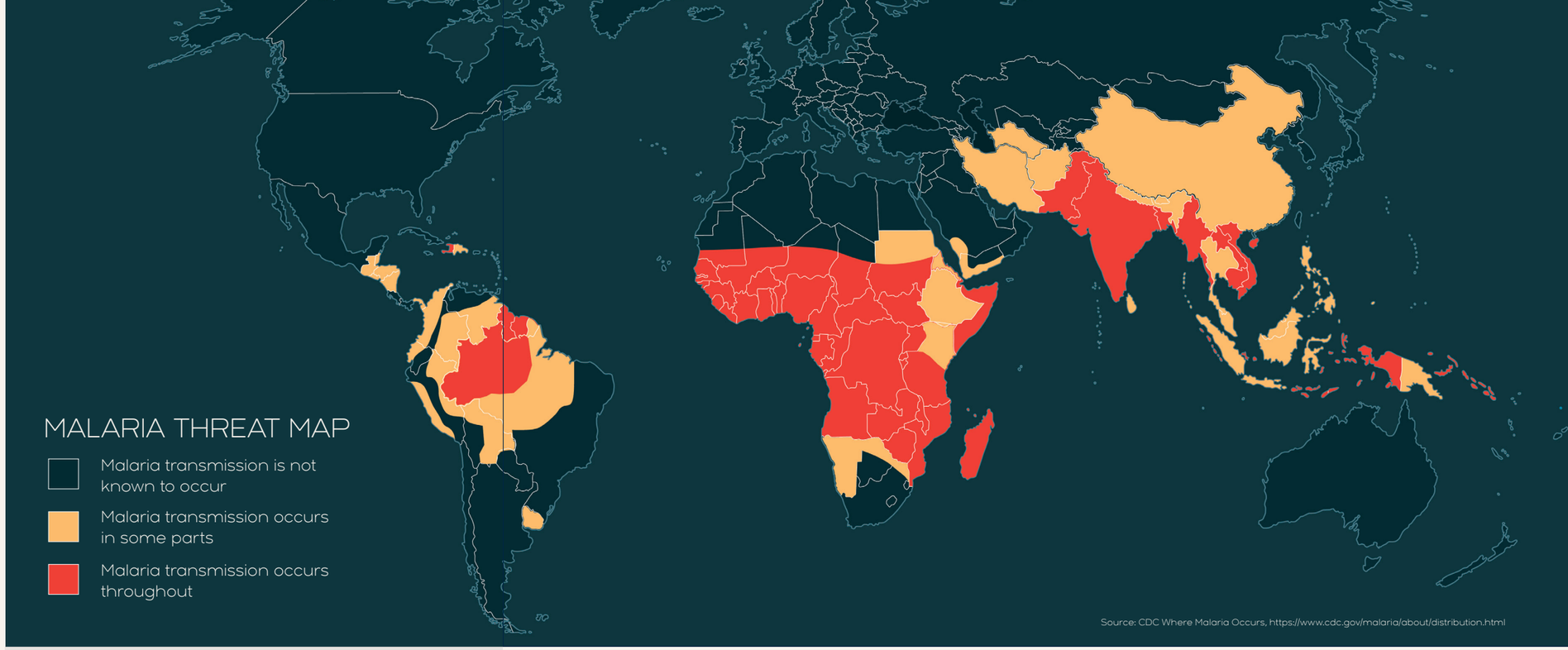
Risk. Resurgence. Resistance

Challenges

- Warfighters deploy to areas of responsibility and interest, under austere conditions, where malaria causes human illness and global health efforts often fail.
- In multi-domain operations, Soldiers need to maintain their supply of medication in the face of disrupted medical logistics channels requiring durable solutions such as vaccines or medications that can be taken weekly or monthly.
- Malaria has developed drug resistance against currently available antimalarial drugs such as: chloroquine, pyrimethamine, quinine, piperaquine, atovaquone (a component of Malarone), mefloquine, and artemisinin.

- Resistance to artemisinin-based combination therapy, a stalwart treatment for drug-resistant malaria, is spreading across Southeast Asia and has the potential to be spread to Africa via travel.
- The U.S. military currently relies on Malarone as its preferred malaria medication. Historically, malaria develops resistance to malaria drugs making them ineffective. Therefore, the pipeline for new antimalarial treatments should remain active to protect against emerging malaria drug resistance.
- Tafenoquine and primaquine are the only two drugs approved to treat relapsing malaria. However, these drugs are contraindicated for glucose-6-phosphate dehydrogenase deficient (G6PDd) individuals due to hemolytic toxicity. This limits choices in treating relapsing malaria in G6PDd individuals.



MALARIA, AN ENDURING THREAT

1942: Allied Base at Milne Bay, Papua

At the Allied base at Milne Bay, Papua, located in a malaria "hot spot" with particularly high infection rates, every Soldier was infected on average four times per year. This equated to a loss of around 12,000 man-days per month due to malaria illness.

1942: Rabaul, New Britain

A large Japanese force pursued an Allied contingent of 250-soldiers. After running out of antimalarial medication, over a period of five weeks, all of the Allied soldiers are heavily infested by malaria infection and one in five soldiers die of deadly cerebral malaria.

1955 to 1975: Vietnam War

In 1965, the number of Soldiers evacuated from Vietnam for malaria equaled the number evacuated for combat wounds. The military was underprepared for the presence of chloroquine-resistant malaria. Malaria was the single most common cause of medical (non-surgical) mortality in hospitalized Service Members in Vietnam. Since Vietnam represented our first true "jet travel" war, malaria also produced substantial problems back on the home front, as Service Members with relapsing *P. vivax* infections returned to the U.S. to unprepared medical systems.

PROPHYLAXIS WORKS

Directly observed therapy (DOT) for prophylactic drugs has been effective, particularly for focused deployment missions such as Liberia 2014-2015. Because of the Ebola threat during this particular deployment, increased compliance was observed as a result of a combination of intensive deployment training, command emphasis, DOT, and daily fever checks.

WHAT WE'RE DOING ABOUT IT

THE TRIAZINES EFFORT:

Prior to 2018, the WRAIR Experimental Therapeutics (ET) division's primary strategy was finding alternate weekly chemoprophylactic drugs to replace weekly options no longer in widespread use (chloroquine and mefloquine). As a result, the triazines, a new class of blood stage-active compounds, were pursued as a potential materiel solution. In July 2018, tafenoquine (TQ) was approved by the U.S. FDA for single dose treatment of relapsing malaria in adults, and in August 2018, for weekly chemoprophylaxis of all forms of malaria. As a result ET reassessed the malaria prophylaxis landscape, particularly in the context of the Army's new modernization targets for MDO in 2028-2035. The key remaining gap in this future fight is a broad spectrum weekly prophylaxis drug. In this context the triazines no longer met Warfighter needs, and ET pivoted in response. ET's rapid response to evolving chemoprophylactic gaps and modernization priorities highlights WRAIR's agility in preserving Soldier lethality and Warfighter medical readiness objectives.

ITERATIVE IMPROVEMENT FOR TQ:

Though TQ remains a powerful chemoprophylactic drug, it cannot be used in all populations at present due to its contraindication for G6PDd individuals. WRAIR is currently assessing combinations of TQ with new partner drugs that could mitigate the risks previously observed in G6PDd patients while still preserving TQ's efficacy against all life-cycle stages of the parasite in all geographic combatant commands.

TOOLS: EXPERIMENTAL THERAPEUTICS

ET established the first-in-the-world high-throughput Plasmodium cynomolgi in vitro assay capable of assessing liver-stage malaria parasites. This bench-top assay allows scientists to prioritize candidate compounds with the greatest chance of success, enabling better stewardship of critical taxpayer resources previously needed for traditional non-human primate assessments. In addition, ET established an *in vitro* eryptosis assay which monitors red blood cell death (hemolysis) following administration of test compounds. These new capabilities allow ET to quickly identify and transition compounds, with prophylactic and anti-relapse activity, and without G6PD contraindication, from discovery to advanced development.

TOOLS: MALARIA BIOLOGICS

From raising malaria-infected mosquitoes, to evaluating safety and efficacy in human clinical trials, WRAIR is one of the few places in the world that is able to evaluate the efficacy of malaria vaccines, biologics, and drugs in the WRAIR controlled human malaria infection model.

FORGING THE FUTURE

WRAIR is exploring the use of alternate drug delivery mechanisms (such as implantables and injectables), vaccines, and biologics (such as antibodies) to extend protective coverage to multiple months without the need to carry pill supply or exercise DOT while in MDO. This will give Soldiers a "fire and forget" solution for malaria prevention.

MALARIA PREVENTION

TOPLINE MESSAGES

Bite prevention and malaria drugs (chemoprophylaxis) protect the individual from malaria.	Mosquito surveillance, vector control, repellent systems, a properly-worn uniform, and a risk assessment are the first-line of defense to prevent an infectious bite.	Chemoprophylaxis is an individual's only line of defense after being bitten by an infected mosquito.	The WRAIR is researching vaccines, biologics, and new drugs to improve protection against malaria.

PREVENTING DISEASE: ONGOING RESEARCH FOR THE WARFIGHTER

PROTECT THE WARFIGHTER

REDUCE THE SOURCE

Environmental Traps
Allow scientists to detect and understand the malaria threat of a region

Spatial Repellents
are in development to drive away mosquitos

Insecticide Application
is fatal to mosquitos but safe for humans to eliminate the malaria vector

FIGHT THE THREAT

Repellants and insecticides prevent mosquito bites

Drug prophylaxis prevents illness

A highly effective malaria vaccine could prevent illness for long periods of time. WRAIR completed the world's largest malaria candidate vaccine human challenge study in 2019.

WHAT WE'RE DOING ABOUT IT

IMPROVING COMPLIANCE

- Developing next-generation delivery systems to improve Soldier-use of DEET and picardin repellents
- Evaluating non-DEET, natural compounds that Soldiers may view as "safer than DEET" to improve wear of repellents
- Developing spatial repellents, deployed within a small room or tent, to overcome limited use of personal repellents

VECTOR SURVEILLANCE

- Monitor suitable habitats for mosquitoes to breed and target control activities to prevent population growth
- Surveillance of potential insect vectors among displaced or migrating populations to track disease threat spread

VECTOR CONTROL

- Developing enhanced traps to attract mosquitoes and kill on contact, reducing local population near camp
- Exploring offensive control strategies that use a range of methods to target the pathogen within the mosquito before it ever infects a person

NOVEL PROPHYLAXIS

- New tafenoquine combinations in development for rapid transition to clinical trials and advanced development
- WRAIR actively maintains a robust pipeline of advanced drug candidates to meet and defeat the future malaria threat

NEWEST TOOLS

- Tafenoquine, now FDA-approved, kills all parasite stages and relapsing infections
- Protect Soldiers from other vector-borne diseases without a treatment. The DOD Insect Repellent System protects against the vectors that are associated with Zika, dengue, and Mayaro virus, and emerging known and unknown threats

ENABLING IMMUNITY

- Key partner in the development of the leading malaria vaccine candidate (RTS,S) and other next-generation malaria vaccines
- Creating and testing next-generation malaria vaccines and new biologics, such as injectable antibodies, in order to protect Soldiers from malaria infection for extended periods of time, anywhere in the world, even in settings with poor resupply

FORGING THE FUTURE

- Leadership advocacy and buy-in to the DOD Insect Repellent System for personal protection and spatial controls will reduce the stigma of DEET used in your ranks
- Use year-round education, command emphasis, daily checks, and the buddy system to improve daily use of chemoprophylaxis and PPE countermeasures
- Support fielding of tafenoquine with USAMMDA and training/ education campaigns on implementation of this new weekly prophylaxis measure
- Advocate for ongoing efforts to develop a durable, efficacious vaccine as the long term solution - "fire and forget"

LEVERAGING PARTNERS AND CAPABILITIES TO DEFEAT MALARIA

EMPLOY MULTI-DOMAIN FORMATIONS

WRAIR employs a global enterprise through research, diplomacy, and continued disease surveillance at 26 foreign satellite facilities in areas where malaria exists.

CALIBRATE FORCE POSTURE

WRAIR employs next-generation and high-throughput scientific capabilities to defeat malaria in multi-domain operations around the globe.

CONVERGE CAPABILITIES

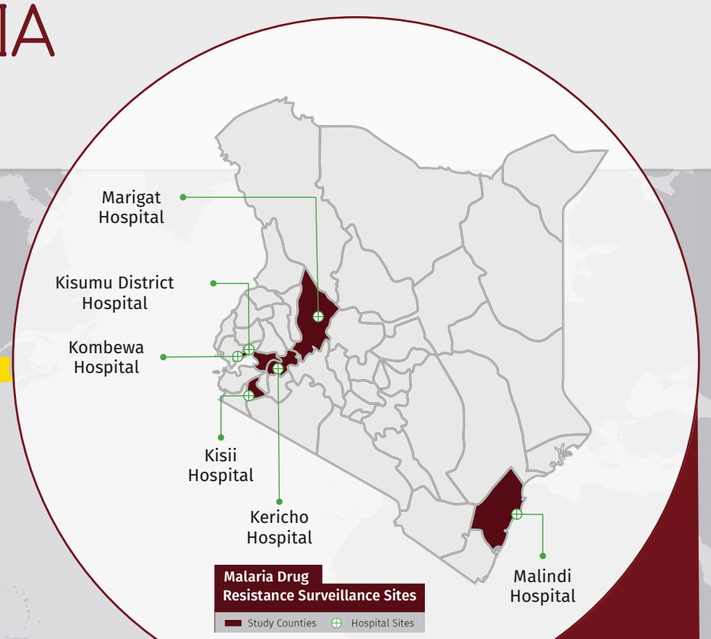
WRAIR can take part in every step of malaria countermeasure development.

MALARIA AFFECTS ALL COMBATANT COMMANDS

In 2018, 58 military members, a 65.7% increase from 2017, were diagnosed with malaria from all geographical combatant commands (Armed Forces Health Surveillance Branch, 2019). These cases occurred despite mandated use of chemoprophylaxis and other countermeasures. This emphasizes that even in optimal modern conditions, the malaria threat persists globally. Future near-peer conflicts in affected areas which create an environment of instability, have suboptimal medical resupply, and delayed evacuation can expect to suffer significant malarial illness.

COST OF MALARIA PER YEAR

Up to $5.6 million per year spent treating and evacuating Warfighters with malaria.



WRAIR

- Capable of rearing over 20,000 *Aedes* and *Anopheles* mosquitoes a week
- Supports preclinical and challenge model studies
- Develops or tests bite protection products like uniforms, repellents or insecticides

USAMRD-AFRICA

- Only DOD entomology research department in Africa
- Rears mosquitoes and sand flies
- Extensive surveillance sites across Kenya to track vectors and their diseases
- Develops and test novel pest management mitigation strategies to include insecticide resistance

AFRIMS

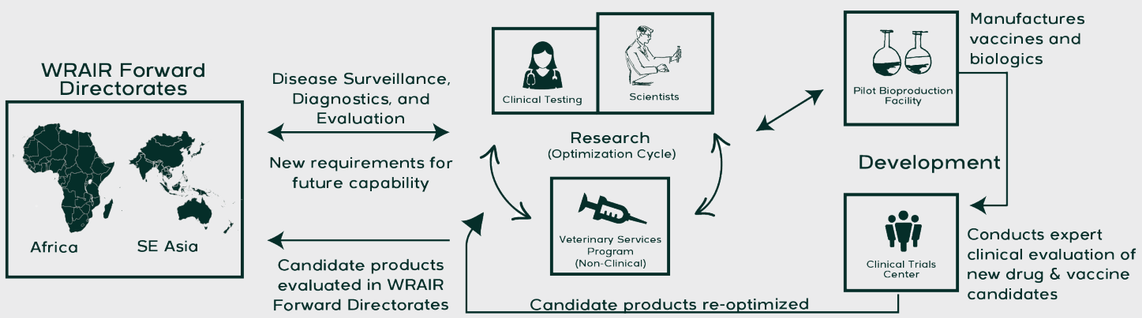
- Hub of vector surveillance across Southeast Asia
- Rears sand flies, all major Southeast Asian malaria vectors and the only scrub typhus-infected chigger colonies in the world
- One of two DOD labs capable of producing *P. vivax* (relapsing malaria)-infected mosquitoes
- Develops or tests bite protection products like uniforms, repellents or insecticides

MEDICAL DIPLOMACY AND RESEARCH

- Developing and executing Defense Malaria Assistance Program (DMAP), a mil-mil operation, to defeat malaria as an operational threat to DOD and allied forces
- Enhancing DOD research relevance in anticipation of future research priorities
- DMAP spans the knowledge gap between what works in theory (efficacy) vs what works in practice (operational effectiveness)
- DMAP enhances Force Health Protection by optimizing the mix of personnel protective measures in areas where malaria is a high risk
- DMAP evaluates approved malaria solutions in the unique operational endemic environment

WRAIR'S VACCINE & BIOLOGICS DEVELOPMENT CAPABILITIES

WRAIR has established a large portfolio of malaria detection capabilities, malaria animal models, malaria immune assays, and live malaria collections to help evaluate and develop effective vaccines, biologicals, and drugs against malaria.



MEDICINAL CHEMISTRY AND WORLD'S LARGEST ANTIPARASITIC COMPOUND LIBRARY

- WRAIR scientists and clinicians have a rapid, cost-effective, "bench-to-bedside" in-house testing strategy for new drugs, spanning early discovery to clinical development, based on iterative medicinal chemistry and data-driven design to optimize drug efficacy, safety, and drug-like properties.
- WRAIR's decades of experience in product development for malaria have established a global platform, including medicinal and analytical chemistry and a global clinical trial network, that can be leveraged for any military relevant therapeutic area.

PILOT BIO PRODUCTION FACILITY (PBF)

- Manufactures vaccines and biologics for early human test and evaluation.
- Produces malaria parasites for use in controlled human malaria infection challenge model to evaluate efficacy of candidates quickly and inexpensively.
- Provides at-the-ready pilot-scale manufacturing at a fraction of the cost and effort over external sources.
- Continuously plan and develops technology transfer and ramp-up from bench-to-pilot scale to minimize schedule and cost.

CLINICAL TRIALS CENTER

Conducts expert clinical evaluation of new drug and vaccine candidates to rapidly and cost- efficiently obtain human safety and efficacy data needed to make go/no-go project decisions.

INSECTARY

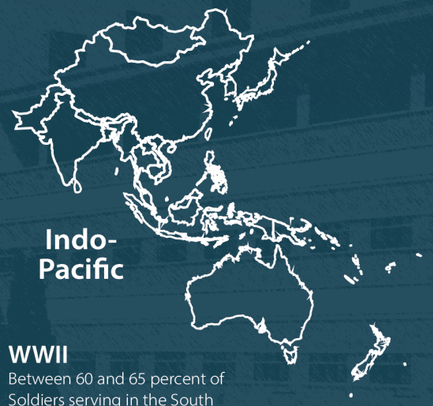
Mosquito rearing to support malaria human infection model and to study diseases, the effectiveness of personal protective measures, and vector control methods.

TAFENOQUINE

History and Antimalarial Drug Development at WRAIR

"Doctor, this will be a long war if for every division I have facing the enemy I must count on a second division in hospital with malaria and a third division convalescing from this debilitating disease!"

– General Douglas MacArthur

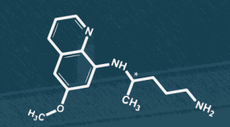


WWII

Between 60 and 65 percent of Soldiers serving in the South Pacific reported having malaria at some point.

Korean War

3,000 U.S. troops returned home from the Korean War with relapsing malaria.



Primaquine

Primaquine, developed by a collaborative funded by the Army, became the anti-relapse drug of choice in the U.S. However, due to safety concerns never went into widespread use for malaria prophylaxis.

WRAIR Experimental Therapeutics (ET)

Since the Korean War, ET, a branch in WRAIR's Center for Infectious Disease Research has played a role **in every** FDA - approved malaria prophylaxis drug.

Malarone

Approved in 2000, this combination of atovaquone and proguanil has become one of two first-line prophylaxis options for U.S. Warfighters and travelers, and has an outstanding safety and tolerability profile.

Tafenoquine

1970 ET and the Armed Forces Institute of Medical Sciences in Thailand (U.S. - AFRIMS) screened about 4000 new anti-relapse drugs and from these screenings, tafenoquine emerged.

1988 WRAIR transitioned tafenoquine to U.S. Army Medical Materiel Development Activity for Advanced Development.

1991 Army submits tafenoquine's investigational new drug application to the U.S. FDA.

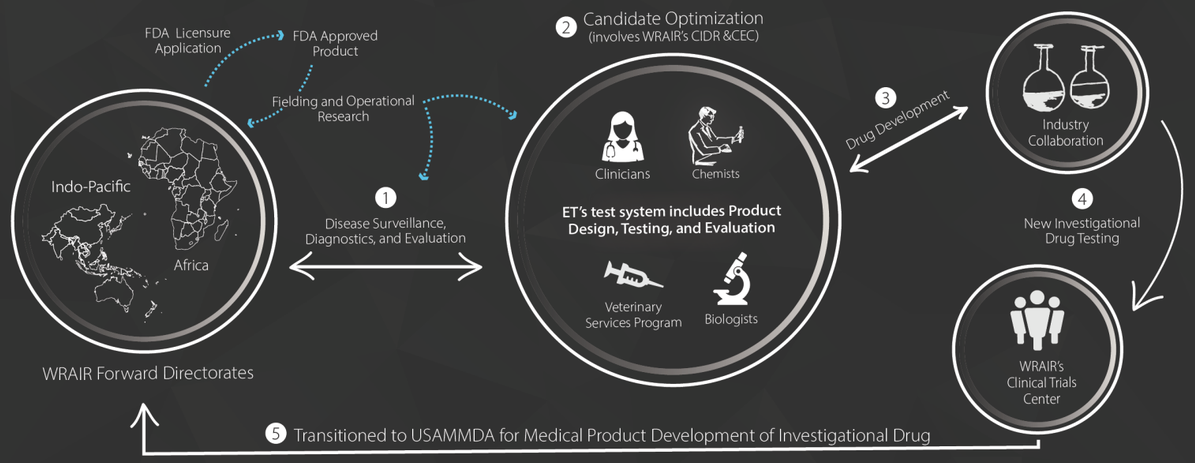
1992 USAMMDA and ET starts first-in-human study in Florida followed by a Controlled Human Malaria Infection challenge study at WRAIR.

1996 to 1997 USAMMDA and ET conducts field treatment and prophylaxis trials at U.S. - AFRIMS and MRD - Africa

2000 to 2018 The program continued through Advanced Development in 2000, and ultimately to FDA approval. New research for the next generation of anti-malarials is ongoing.

WRAIR's Drug Development Capabilities

Every FDA-approved malaria prophylaxis drug has come from or through WRAIR's Experimental Therapeutics test systems.



Daily vs Weekly Malaria Drugs

Tafenoquine and Doxycycline

Malaria Life Cycle & Parasites

The Malaria Lifecycle:

mosquito to liver to blood and back again

Five Species of *Plasmodium* Parasites can Cause Disease in Humans

Tafenoquine

- Active against relapsing and transmitted forms
- Kills blood and liver stage parasites

Doxycycline

- No activity against relapsing or transmitted forms
- Kills blood stage parasites
- Only mild liver stage activity

Tafenoquine and Doxycycline

Both tafenoquine and Doxycycline are active against all five malaria parasites that infect humans

Medication Needed for a Six Month Deployment

Tafenoquine: 56 pills

- Take it once a week at any time during the day
- Only one dose upon return
- Approved for six months of continuous use

Doxycycline: 226 pills

- Must take everyday at the same time to be effective
- Requires 14 doses upon return

The Science on Adherence

Deployment	Year	% Adherence, weekly drug	% Adherence, daily drug
Operation Restore Hope (Somalia; Sanchez et al 1993)	1992 to 1993	98%	81%
OEF (Afghanistan; Saunders et al. 2015)	2006 to 2007	80%	60%

From the 2018 CDC Yellow Book:

"...drugs with longer half-lives, which are taken weekly, offer the advantage of a wider margin of error if the traveler is late with a dose."

Weekly Prophylaxis = Increased Protection = Increased Soldier Readiness

GLOBAL IMPACT OF WRAIR'S MALARIA RESEARCH

›3,000

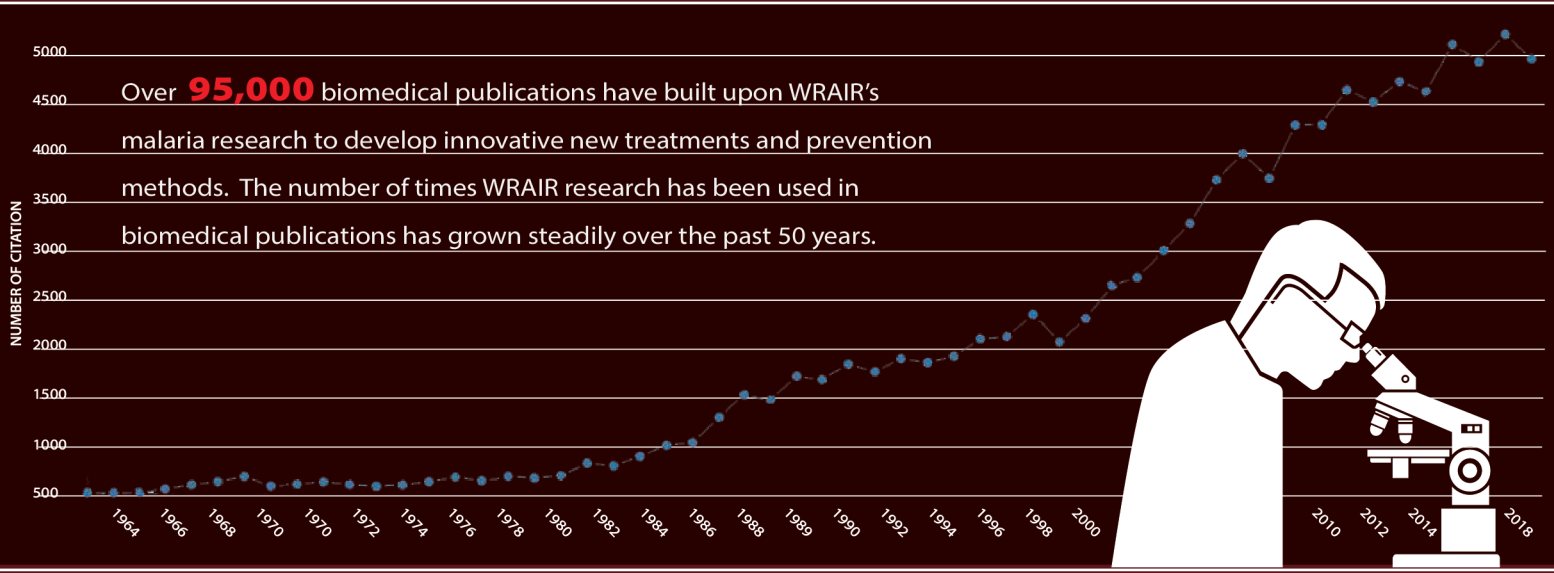
malaria research biomedical publications generated by WRAIR

TOP 4

contributors of published biomedical malaria research in the US, behind only the University of California System, the National Institutes of Health, and the Centers for Disease Control and Prevention.

TOP 10

Institution Publishing About Malaria Worldwide



Over **95,000** biomedical publications have built upon WRAIR's malaria 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 50 years.

WRAIR'S Global Malaria Partners

TOP FIVE TYPES OF PARTNERS

- ACADEMIA/HOSPITAL (113)
- INDUSTRY (9)
- RESEARCH INSTITUTE (32)
- OTHER (8)
- MILITARY/GOVERNMENT (27)

MOST FREQUENT PARTNERS

- NATIONAL INSTITUTE OF HEALTH
- KENYA MEDICAL RESEARCH INSTITUTE
- JOHNS HOPKINS UNIVERSITY
- MAHIDOL UNIVERSITY
- GLAXOSMITHKLINE
- UNIFORMED SERVICES UNIVERSITY
- UNITED STATES NAVY
- UNIVERSITY OF OXFORD
- LONDON SCHOOL OF MEDICINE
- UNIV. OF WASHINGTON SEATTLE
- CENTER FOR GLOBAL INFECTIOUS DISEASE RESEARCH