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U.S. Department of Defense Contributions to Malaria Elimination in the Era of Artemisinin Resistance

Mark Fukuda and Tom Cullison¹

In the Greater Mekong Subregion (GMS), militaries remain essential to any effort to control and eliminate artemisinin-resistant malaria. Stretching back to World War II and the Vietnam War, the U.S. Department of Defense (DoD) has a long and distinguished history researching and developing new tools for malaria control, in partnership with both military and civilian host government experts. Since the mid-1990s, DoD has significantly expanded its global surveillance, training, and capacity-building investments. As Southeast Asian countries have mobilized in recent years against artemisinin-resistance with the ultimate aim of malaria elimination, DoD and regional militaries have actively joined the effort, initiating promising pilot approaches in Southeast Asia. To strengthen DoD's contribution, it is proposed that the United States launch a Defense Malaria Elimination Program that will significantly enhance partner militaries' capacities, advance the goal of elimination, including the threat of resistance, and accelerate the development of drugs and vaccines.

The Urgency of Malaria Elimination in the Era of Artemisinin Resistance

Experts widely agree that *P. falciparum* artemisinin resistance is a potential public health disaster. To prevent this threat from becoming reality, the World Health Organization (WHO) and the global malaria community have reacted swiftly, initiating the Global Plan for Artemisinin Resistance Containment (GPARC) in 2011.² The GPARC's two stated goals were to "contain or eliminate artemisinin resistance where it already exists, and to "prevent artemisinin resistance where it has not yet appeared." Two years later, international development partners, in collaboration with WHO, conducted a joint assessment of the response to artemisinin resistance in the

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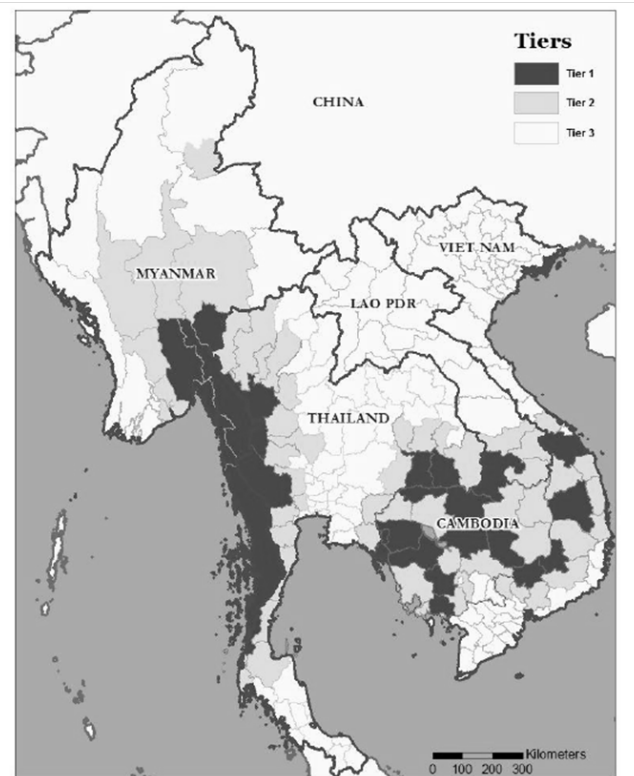
² World Health Organization (WHO), *Global Plan for Artemisinin Resistance Containment* (Geneva: WHO, January 2011), <http://www.who.int/malaria/publications/atoz/9789241500838/en/>.

GMS, stating, “it is impossible to avoid the conclusion that not enough is yet being done, with enough intensity, coverage and quality, to respond to a problem that could not only slow future progress but also undo the gains already made in malaria control worldwide.”³

WHO subsequently released its Emergency Response to Artemisinin Resistance (ERAR) framework in April 2013. The ERAR reaffirmed the value of previous containment efforts, but placed greater priority on “the eventual elimination of artemisinin-resistant parasites as part of a subnational, national, and regional elimination effort.” Later that year, the Board of the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) approved \$100 million over three years to the “regional artemisinin initiative (RAI),” intended to take a region-wide approach to artemisinin resistance. The RAI includes a specific “inter-country” component to target mobile-migrant populations (MMPs). This emphasis is repeated in the Roll Back Malaria Global Malaria Action Plan, which states that “entire populations, including migrants, and citizens of neighboring countries should have access to timely . . . diagnosis and treatment.”⁴ The mobility of such populations and their uneven access to malaria treatment and prevention services underscores their potential as a malaria reservoir capable of perpetuating and spreading resistant strains.

In the Mekong region, highly mobile populations transit and seek employment in areas where antimalarial drug resistance has been confirmed near national road networks and international borders. Indeed, most of the WHO ERAR designated “Tier 1” areas (those with credible evidence of artemisinin resistance) are located along international borders⁵ where there are dynamic population movements, sparsely developed health infrastructure, and deployment of military personnel. This array of malaria risk factors is reflected in a recent WHO technical report focusing on MMPs that argues that “advocacy should be continued, and the involvement of non-health stakeholders, especially the private sector **and military**, should be increased”⁶ [emphasis added]. The WHO draft strategy for

Figure 1: “Tier 1” areas of artemisinin resistance in dark gray (WHO 2014)²



³ WHO, *Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion: Regional Framework for Action, 2013–2015* (Geneva: WHO, April 2013), <http://www.who.int/malaria/publications/atoz/9789241505321/en/>.

⁴ Roll Back Malaria, *Global Malaria Action Plan for a Malaria Free World* (Geneva: WHO, 2008), <http://www.rbm.who.int/gmap/gmap.pdf>.

⁵ WHO, “Update on artemisinin resistance,” September 2014, <http://www.who.int/malaria/publications/atoz/update-artemisinin-resistance-sep2014/en/>.

⁶ WHO, “Technical Consultation on Improving Access to Malaria Control Services for Migrants and Mobile Populations in the Context of the Emergency Response to Artemisinin Resistance in the Greater Mekong

elimination of *P. falciparum* malaria in the GMS states that “special efforts are needed to assure that all security forces have adequate protection and access to malaria diagnosis and treatment,” but that military health services “may be under-funded.”⁷ These pointed references to “military” affirm that militaries should be directly engaged in malaria elimination efforts as key partners.

U.S. Department of Defense Historical Contributions to Malaria Control

DoD’s long history of combating malaria is inextricably tied to the large numbers of U.S. military forces deployed in twentieth-century conflicts. Malaria’s toll in both World War II and Vietnam was of sufficient concern to focus military public health authorities on the immediate need to control malaria in areas of high troop concentration in order to preserve operational capabilities. Gen. Douglas MacArthur famously lamented during World War II, “This will be a long war, if for every division I have facing the enemy, I must count on a second division in the hospital with malaria, and a third division convalescing from this debilitating disease.”⁸

In fact, much of twentieth-century malaria control evolved through the experience of military public health authorities who brought a level of rigor and intensity to reducing the operational impact of malaria on a scale not commonly seen. Over the decades, as malaria remained a disease of high operational concern, DoD developed successful research and development programs to combat infectious diseases of military threat, focusing on the development of diagnostics, drugs, and vaccines to mitigate their impact. Malaria has consistently ranked as the highest priority of these disease threats.

DoD’s malaria research programs have traditionally been executed by the Walter Reed Army Institute of Research (WRAIR) and the Naval Medical Research Center (NMRC), and their affiliated overseas research laboratories. Two of these laboratories are located in the GMS—the U.S. Army/Royal Thai Army Armed Forces Research Institute of Medical Sciences (AFRIMS), located in Bangkok, and the U.S. Navy Medical Research Center–Asia (NMRC-A) currently headquartered in Singapore with satellite laboratories throughout the region. Both are closely allied with host nation Ministries of Health and Defense in order to advance common public health goals in the realm of surveillance, operations research, and product development.

Both research organizations have produced landmark research and clinical products to combat malaria. NMRC and WRAIR were early pioneers in the development of vaccines, including the most advanced malaria vaccine candidate in development. This vaccine, targeted for licensure by the European Medicines Agency, could aid in elimination efforts, particularly in MMP populations not covered by traditional

Subregion,” September 2014, http://www.who.int/malaria/areas/greater_mekong/access-migrants-mobile-populations/en/.

⁷ WHO, “Strategy for Elimination of Falciparum Malaria from the Greater Mekong Subregion” (paper presented at Workshop to plan for Elimination of Falciparum Malaria in the Greater Mekong Subregion in the Context of Artemisinin Resistance, Phnom Penh, Cambodia, November 20–21, 2014).

⁸ P. Russell, *Communicable Diseases: Malaria*, vol. VI of *Preventive Medicine in World War II*, ed. J. B. Coates Jr. (Washington, DC: Office of the Surgeon General, Department of the Army, 1963), <http://history.amedd.army.mil/booksdocs/wwii/Malaria/DEFAULT.htm>.

prevention measures. A second vaccine candidate significantly showed complete protection in a proof of concept study.

Drug development efforts by WRAIR and the U.S. Army Medical Materiel Development Agency have resulted in the availability of an investigational artemisinin formulation for severe and life-threatening malaria, with superior safety and efficacy than the current FDA-licensed treatment.⁹ In fact, WRAIR has directly contributed to the development and licensure of nearly every malaria drug in widespread use today¹⁰ and continues to invest in the development of new leads in an attempt to forestall the impact of resistance.

In 1996, Presidential Decision Directive NSTC-7 formally created the DoD Global Emerging Infections Surveillance and Response System (DoD-GEIS) to further advance DoD's global surveillance, training, and capacity-building efforts to respond to emerging infectious diseases.¹¹ The expanded emphasis on global surveillance and response generates important epidemiological data to support product development while also providing partner nation public health officials with evidence to inform public health policy. In the realm of DoD malaria surveillance, DoD-GEIS provided support to AFRIMS for a clinical surveillance study that ultimately characterized the first case report of artemisinin-resistant malaria in 2008.¹² In 2009, NRMCA completed a similar *P. falciparum* efficacy study demonstrating that resistance extended beyond the initially suspected areas along the Thailand-Cambodia border. These studies were instrumental in defining the geographic map of artemisinin resistance to guide WHO's GPARC and ERAR efforts.¹³ Beyond its initial focus in Southeast Asia, DoD is expanding efforts to characterize artemisinin resistance worldwide. A major effort involves the coordinated execution of multicenter clinical trials to assess parasite clearance in three DoD laboratories in Peru, Kenya, and Thailand. This is the first effort to expand artemisinin-resistance surveillance into the Americas using this approach.¹⁴

⁹ U.S. Army Medical Materiel Development Activity (USAMMDA), "Pharmaceutical Systems Project Management Office (PSPMO)," March 18, 2013, <http://www.usammda.army.mil/documents/brochures/Pharm-Brochure.pdf>.

¹⁰ James B. Peake et al., *The Defense Department's Enduring Contributions to Global Health: The Future of the U.S. Army and Navy Overseas Medical Research Laboratories* (Washington, DC: CSIS, June 2011), http://csis.org/files/publication/110615_Peake_DoDOverseasLabs_Web_0.pdf.

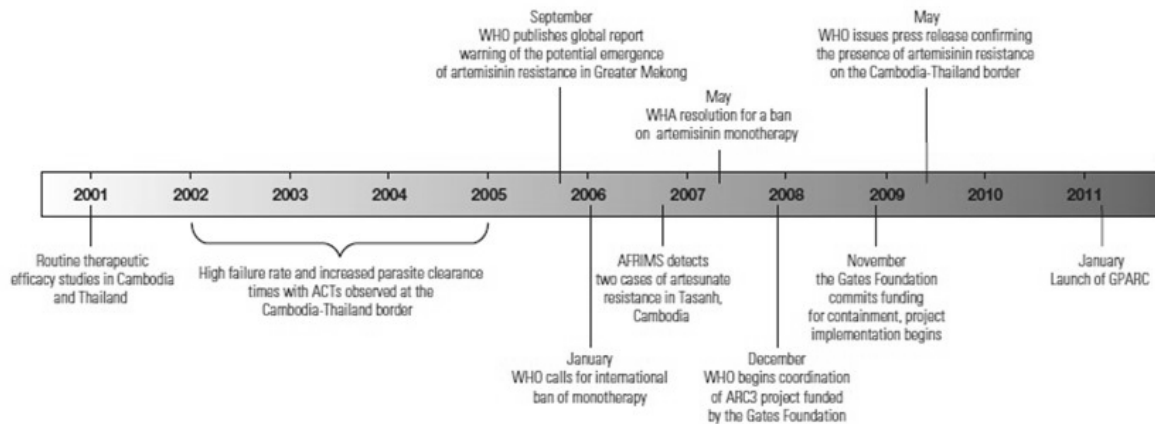
¹¹ The White House, "Presidential Decision Directive NSTC-7: Emerging Infectious Diseases," 1996, <http://fas.org/irp/offdocs/pdd/pdd-nstc-7.pdf>.

¹² H. Noedl et al., "Evidence of Artemisinin-Resistant Malaria in Western Cambodia," *New England Journal of Medicine* 359, no. 24 (2008): 2619–20.

¹³ WHO, *Global Report on Antimalarial Drug Efficacy and Drug Resistance: 2000-2010* (Geneva: WHO, 2010), 54, http://whqlibdoc.who.int/publications/2010/9789241500470_eng.pdf.

¹⁴ D. Saunders et al., "US Department of Defense contributions to malaria surveillance," *Lancet Infectious Diseases* 13, no. 4 (April 2013): 293–94, <http://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2813%2970065-3/fulltext>.

Figure 2: Sequence of events depicting global health response to artemisinin resistance (WHO 2010)¹⁵



In the midst of initial reports of artemisinin resistance, DoD pursued simultaneous efforts to identify optimal dosing of artemisinin regimens to support its investigational artemisinin treatment *and* determine if the public health impact of resistance can be overcome, concluding that resistant malaria strains cannot be safely and reliably cured by simply increasing dosing. This information, relevant for both DoD-led FDA new drug applications and global health authorities considering alternate artemisinin based treatments, exemplifies the complementarity of the DoD product development and public health missions.

U.S. DoD's Pilot Programs in Malaria Control and Elimination

The NMRC in 2013 instituted a program in partnership with Vietnam's national malaria control and the University of California-San Francisco Global Health Group to pilot approaches for malaria elimination in Vietnam. Vietnam is an ideal setting for this pilot due to its strong military and civilian public health systems and the country's high-level political support for malaria elimination. The NMRC-A's program seeks to characterize specific epidemiological characteristics of malaria risk and evaluate specific intervention packages and their impact on malaria burden. In 2015, NMRC-A intends to expand its elimination program to encompass military-to-military elimination projects with the Vietnam People's Army Military Institute of Preventive Medicine to characterize the malaria cases diagnosed and treated in the military health system. This project will help to establish a malaria burden baseline in populations—both military and civilian—typically not well represented in global or regional malaria control efforts.¹⁵

In addition, AFRIMS is collaborating with the Cambodian armed forces and the national civilian malaria control program to evaluate potential approaches to malaria elimination in Cambodia. The primary outcome will be a practical, achievable, evidence-based approach to malaria elimination that can be scaled to a nationwide program. A pilot research study will be used to devise an analytical framework for

¹⁵ C. Ohrt, personal communication, November 11, 2014.

malaria elimination, developing malaria information systems and data-sharing agreements, comparing diagnostic and treatment approaches, assessing the effectiveness of vector control approaches, and building capacity within the Cambodian armed forces for treatment and prevention within military and surrounding populations.¹⁶

Current Status of Malaria Dialogue among the Global Fund to Fight AIDS, Tuberculosis and Malaria; WHO; and the Department of Defense

In light of increased awareness of the significance of malaria in military populations, two recent meetings brought together key stakeholders from Mekong nations' Ministries of Defense (MoD) and Ministries of Health (MoH). The first was sponsored by the regional steering committee of the Global Fund's Regional Artemisinin Initiative (RAI). The U.S. Pacific Command (USPACOM) and DoD GEIS followed this with a similar meeting in which the USPACOM surgeon strongly endorsed working as part of "one U.S. government approach" to support regional militaries in their elimination efforts.

The outputs from these meetings, intended to enhance collaboration between military and civilian malaria-control officials to tackle malaria elimination as part of a unified national approach, identified several critical areas in which militaries can substantially augment civilian health systems or in which militaries possess unique needs. Specific conclusions are:

- Malaria elimination requires adherence to prevention and control practices that extend beyond the scope of military medical departments. Advocacy is needed at the MoD level to convey a fundamental shift in thinking to military line commanders underscoring the necessity of malaria elimination. The threshold for acceptable malaria morbidity cannot simply be based on preserving operational capability.
- Advocacy is needed at the MoD level to convey the need for adequate MoD malaria resources to support the elimination mission.
- Military malaria-control programs vary widely between regional militaries in terms of surveillance, availability of prevention, diagnosis and treatment capacities, case reporting, and logistics management. For this reason, country-specific rather than regional approaches should be formulated.
- Many military health facilities, positioned in border areas to provide services in areas with active-duty personnel, also provide services to civilian populations for which they may not be adequately resourced. These civilian beneficiaries may be family members of active-duty personnel, or may seek care in military facilities simply due to geographic proximity.

¹⁶ D. Saunders, personal communication, November 12, 2014.

- Many regional military medical departments enjoy close working relationships with their civilian national malaria-control program counterparts, though the extent of data sharing between MoD and MoH health systems varies widely.
- Military logistics and health systems are operated under the command and control of military authorities, posing challenges in harmonizing treatments, training curricula, and prevention measures between civilian and military health systems.
- Areas of highest need include capacity building in regional militaries, specifically in surveillance systems, and training for military medical personnel in malaria prevention, diagnosis, and treatment.
- Regional militaries share unique occupational risk factors in common with other MMPs and are ideally poised to pilot novel prevention approaches such as use of targeted chemoprophylaxis, insecticide-treated uniforms, and novel repellents. These approaches, if successful, are of potential benefit to all MMPs.

Additionally, the GFATM and USPACOM meetings developed a prioritized framework specifically targeting interventions in military health systems. This framework was presented to the GFATM RAI's regional steering committee, consisting of representatives from the five Mekong country GFATM coordinating mechanisms, national malaria-control programs, civil society, the private sector, the Association of Southeast Asian Nations (ASEAN), the Asian Development Bank, WHO, academia, and other development partners. The steering committee voted to support specific capacity-building efforts in militaries—a further affirmation of the work across sectors for the sake of advancing elimination goals.

The DoD HIV/AIDS Prevention Program: A Precedent for a DoD Malaria Elimination Program

The relationship between the President's Emergency Plan for AIDS Relief (PEPFAR) and the Defense HIV/AIDS Prevention Program (DHAPP) provides a useful framework for expanding malaria assistance to foreign militaries in concert with the President's Malaria Initiative (PMI) and other civilian efforts.

In FY 2001, Congress appropriated \$10 million for DoD to begin a program of targeted assistance to 35 nations, including several in the Mekong Region, to develop and implement focused, military-specific HIV/AIDS prevention, care, and treatment capabilities in their respective armed forces to protect foreign militaries from HIV/AIDS. DHAPP espouses the need to “minimize the pain and suffering caused by HIV/AIDS,” its “devastating impact” on families, focusing on training, prevention, and education, as well as equipping HIV testing centers in foreign militaries. In addition, the DHAPP supports the U.S. DoD's Military HIV Research Program's efforts similarly curtail impact through development of an HIV/AIDS vaccine.¹⁷

¹⁷ Naval Health Research Center, “DoD HIV/AIDS Prevention Program: Background Info,” <http://www.med.navy.mil/sites/nhrc/dhapp/background/Pages/BackgroundInfo.aspx>.

The urgency of malaria elimination and the attendant need to address all risk populations now presents a similar opportunity for DoD's collective malaria expertise. This is not to propose that DoD needs to, or should, pursue the execution of a fully comprehensive malaria control along military-military sectoral lines. The fundamental operating principle of the regional control strategies is to target malaria interventions in the public and private sectors and at the community level under the leadership of the MoH. Similarly, DoD should operate within the context of a "one U.S. government" approach to malaria elimination, in which DoD integrates its traditional technical and organizational strengths within the construct of the partner-country national malaria strategy.

The creation of a Defense Malaria Prevention Program could capitalize on existing DoD malaria expertise while responding to the call to enhance malaria control and elimination in the military sector. This program must be fully resourced to ensure that existing DoD malaria programs are not jeopardized while ensuring successful implementation. The formal creation of a Defense Malaria Prevention Program would build upon the existing NMRC-A and AFRIMS pilot initiatives and enable the strategic implementation of true military partner malaria programs in the following ways:

- Build capacity in military health departments to monitor active-duty troop health during deployment to malaria endemic areas, whether domestically or overseas.
- Provide programmatic support for continued malaria capacity-building initiatives, specifically to develop partner military medical capacity to prevent, diagnose, and treat malaria at the lowest possible level within the military health system.
- Along with other U.S. government malaria stakeholders, advocate with partner Ministries of Defense to adequately resource and prioritize malaria-elimination activities, both within their medical departments and in higher-level military authorities.
- Assist foreign militaries by developing policies, treatment guidelines, training documents to codify best malaria practices.
- Apply experience and expertise garnered as part of DoD's mandate to perform regulated clinical trials in the realm of monitoring and evaluation of malaria interventions.
- Support and maintain DoD malaria expertise and drug- and vaccine-development efforts through training and capacity building in research, surveillance, and evaluation of malaria specific interventions in partner military medical departments.

The urgency that artemisinin resistance imposes on targeting global malaria elimination on all risk populations and sectors has taken on a new significance in the context of the recent catastrophic Ebola epidemic. Malaria, with its propensity to affect those at the poorly resourced areas, presents a unique health systems strengthening challenge in this regard, particularly in the need to report timely

surveillance data, provision malaria resources at the lowest possible level, and protect military personnel while engaged in operational settings. Investments in malaria infrastructure can pay dividends across disease lines, positioning militaries to better respond to inevitable future outbreaks. The urgency presented by both the Ebola and malaria elimination mandates requires full attention to the strengthening of all health systems.

The United States and the nations of the GMS have a shared interest in eliminating artemisinin-resistant malaria, and a shared need to make optimal, systematic use of both civilian and military capacities. In the past few years, high-level political attention has focused on the problem of bringing new resources and a promising mobilization of coordinated international efforts. Through implementation of an adequately resourced Defense Malaria Prevention Program, the United States can strengthen DoD's contributions to this effort and increase the likelihood of eliminating malaria altogether.



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