RECORD VERSION

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ON THE US CONTRIBUTION TO THE FIGHT AGAINST MALARIA

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Chairman Smith, Ranking Member Bass, and distinguished members of the subcommittee, thank you for the opportunity to appear before you to discuss the Army's medical research initiatives to improve Soldier readiness and global health, and highlight the incredible work of the military medical research community, the Walter Reed Army Institute of Research, and the US Army Medical Research and Materiel Command. On behalf of the over 150,000 dedicated Soldiers and civilians that make up Army Medicine, I extend our appreciation to Congress for the support to military medicine faithfully given, which provides the resources we need to deliver leading edge health services, and diligently continue innovative research.

The Global Threat of Malaria

Malaria is a global ancient scourge that has haunted mankind for much of our history, and yet it still impacts our lives and our society today. Conservative estimates suggest that over 3.3 billion people remain at risk for the disease worldwide; over 200 million cases of the disease appear every year along with over 650,000 deaths. Among the most vulnerable are young children, who account for over 85 percent of the malaria-related mortality globally. A preventable disease transmitted by the *Anopheles* mosquito, malaria is a leading cause of death in children under five years old in Sub-Saharan Africa.

Despite plans in the 1950s to eradicate malaria worldwide with powerful tools like chloroquine (a powerful drug for treatment) and DDT (dichlorodiphenyltrichloroethane, a remarkably effective mosquito control compound), the emergence of widespread chloroquine-resistant malaria parasites, along with concern regarding the environmental effects of DDT, resulted in the declaration of the eradication effort's failure and eventual demise in 1972.

Not to be defeated, Roll Back Malaria (RBM) was launched in 1998 with a goal to halve the number of malaria cases by 2010, and eliminate malaria in 8 to 10 countries by the year 2015. As progress continues around the globe, in Africa, where the majority of the malaria mortality burden is borne, we have seen malaria death cut by one-third in the last decade alone. Outside of Africa, of the over 50 countries affected by malaria, total numbers of cases have been reduced by fifty percent in the last decade. This progress, due in part to large distributions of insecticide-treated mosquito bed nets, vector control interventions, and to the wide-spread use of artemisinin-combination therapies, has been so dramatic that in 2008, malaria eradication, which was not thought possible thirty-five years earlier, was considered an attainable goal once again.

Malaria has existed for centuries as four recognized species of parasite, all with minor variations on the cycle, hosts, vectors, and sensitivity to treatments available. Some of the species are harder to treat or need longer periods of time to eliminate the disease burden from a population, taking as long as twenty years in some instances. Maintaining vigilance for that length of time, and the public health efforts needed for actual elimination are challenges that require extraordinary dedication and political will. Even if elimination on a global scale is achieved, medicine cannot overlook the possibility that there will be identification of additional malaria species and vectors entering into the human population, as science advances. The

identification of a fifth human malaria species in 2008, originally identified from a monkey source, brings to light the possibility of identifying an additional threat from an old adversary.

Military Relevance of Malaria

The U.S. military has felt the threat of malarial disease as far back as 1775, when George Washington had to expend his very limited monetary resources to purchase quinine for the treatment of malaria in the Revolutionary Army. In the 1860s, the Civil War saw 50 percent of Caucasian troops and a staggering 80 percent of Black troops contracting malaria annually. The military impact continued during World War II, Vietnam, and even recently in Afghanistan, where we still see approximately 100 cases annually, despite the resources we have to protect our troops. While the days of massive debilitating impact on military operations are behind us, we only have to look back to 2003, when a military peacekeeping operation in Liberia failed after only a few weeks due to 80 cases of malaria in 225 Marines, 44 requiring medical evacuation, in order to appreciate the potential impact on military readiness.

This is an enduring mission. The U.S. military is engaged in malaria research for several key reasons: to preserve the fighting strength of our men and women in uniform; to protect our Nation's citizens who encounter these threats world-wide; to impact the global health and stability of our Allies. It was less than a generation ago that malaria was present in the United States. Just as we have seen the spread of other vector-borne diseases such as West Nile Virus, there is a real potential, given the global nature of our population and the simple nature of the disease host, for malaria to be reintroduced into the U.S.

Global Health Impact

The destabilizing effects that diseases such as HIV and malaria have on the critical infrastructure of developing nations is compelling evidence that global health is a means to global security. These diseases undermine education and health systems, economic growth, micro enterprises, policing and military capabilities, political legitimacy, family structures, and overall social cohesion. They undermine the stability of already weakened states and add to their vulnerability to extremists/terrorists who will seek to corrupt or coerce. Our response through medical engagement needs to be comprehensive, fought at many levels, and on many fronts, to provide for global stability and our own Nation's security.

Partnerships and Progress

Assigned to the newly opened Army Medical School in 1893, Army Major Walter Reed was instrumental in defining the concept of mosquitoes transmitting disease. In the case of Yellow Fever, it was Major Reed's hypothesis on disease transmission that opened the door for

William C. Gorgas to abate the spread of Yellow Fever and malaria in the construction of the Panama Canal.

The first synthetic anti-malarial medication, Atabrine, was developed through the coordinated activities of the Allied medical forces, setting the stage for the involvement of the Walter Reed Army Institute of Research (WRAIR) in anti-malarial drug development. The Experimental Therapeutics branch of the WRAIR remains the only sustained drug development program in the Department of Defense, holding the distinction of initiating or being involved in virtually every anti-malarial drug development available for fighting malaria since WWII.

Developing a vaccine against malaria is a complex science, requiring an immune response differs from what is seen with natural infection. The best potential for a way forward is through several strategies at immune stimulation. The Malaria Vaccine Branch of WRAIR and the Malaria Department of the Naval Medical Research Center (NMRC) work cooperatively as the US Military Malaria Vaccine Program (USMMVP) on a joint mission to develop vaccines against the two types of malaria that cause the most serious disease in humans.

The WRAIR Malaria Vaccine Program, along with a pharmaceutical company, has developed what is currently the world's leading malaria vaccine candidate. Known as RTS,S/AS01, it is the first candidate malaria vaccine able to demonstrate reduction in the number of episodes (by 50 percent) or clinical severity of malaria infections, particularly in infants age five to seventeen months old. This product is currently in phase 3 clinical trials in Africa at our overseas operations, demonstrating a key step towards prevention.

The NMRC Malaria Department currently has two main vaccine research efforts, one in partnership with a commercial biotech company on a DNA prime/adenovirus boost vaccine, NMRC-M3V-D/Ad-PfCA, which has shown low level protection (27 %) in early stage clinical trials. Additionally, NMRC is partnering with a commercial pharmaceutical company and the National Institute of Allergy and Infectious Diseases Vaccine Research Center, of the National Institutes of Health, on a novel purified, radiation-attenuated, cryopreserved, whole sporozoite vaccine that is in an early stage clinical trial.

The Entomology branch of WRAIR has worked diligently on personal protective measures such as treated bed nets, new insecticides, and permethrin-treated clothing to prevent not only malaria, but several other insect-borne diseases.

The WRAIR has a trusted partnership in several countries that has been established for decades. Long term relationships have been built with host countries as well as health organizations, allowing both personnel and logistical support to establish larger work. We have been in partnership with the Royal Thai Army for over 50 years, where we use Thailand as a base of operations to work with malaria and other infectious diseases throughout the region. Our relationship with the Kenya Medical Research Institute is over 40 years old and serves as our touchstone in the African continent. There, as in Thailand, we have established robust relationships that have allowed the important work of Army medicine's research, as well as the important work of the President's Emergency Plan for AIDS Relief (PEPFAR) and the President's Malaria Initiative (PMI). The US military's exceptional science, logistic, and

regulatory expertise allows for testing of new products to the best standards of care for the local population as well as the delivery of critical life-saving HIV and malaria interventions.

Military medicine also serves as a partner in the critical platform of disease surveillance. Both the Army and Navy conduct overseas disease surveillance operations that not only keep a watchful eye on malaria patterns and malaria resistance throughout the world, but also survey for other infectious disease threats. Much of this work is accomplished through funding from the Global Emerging Infections Surveillance and Response System (GEIS) at the Armed Forces Health Surveillance Center (AFHSC). These overseas operations are a part of a complex ecosystem that provides not only surveillance, but also a platform for testing new products, medical engagement with many countries worldwide, and outreach for the execution of the PEPFAR and PMI missions and programs.

Military Medical Research Funding

Funding for malaria research and development in the military has been suffering since Vietnam. The US military is able to best utilize governmental funding for malaria research through research partnerships around the globe for malaria programs and projects, sustaining us to date despite the diminishing budget. The FY12 budget for all malaria effects in the DoD (approximately $20 million) was increased to $60 to $100 million through matched funds achieved by leveraging partnerships with other governmental agencies, private industry, and academic partners.

The military malaria research budget is approximately equal between drug and vaccine research and development (drug budget approximately $8.9 million and vaccine budget approximately $10.2 million in FY13 and FY14). The malaria drug effort feeds the entire range of pharmaceutical research, from looking at new chemical entities all the way through clinical trials for anti-malarial drugs getting licensed. The vaccine research effort of the joint Army/Navy program is exploring multiple different candidate vaccines and looking at what strategy will work the best.

Despite all of this exceptional work, which not only benefits the military but also those impacted by malaria worldwide, there is still much to be done. While we optimistically consider eradication, new threats emerge through resistance to current therapy and current insecticides. Despite being effective today, current medications for prophylaxis and treatment are being used to treat organisms that have consistently found a way to defeat most every one of our older drugs; these organisms will likely find a way to defeat any new medications discovered for malaria treatment. Resistance is a fact of drug development and even with the most cautious use of drugs, the organisms we are fighting will always find a way to defeat our treatments. The best we can do is through prudent use of these agents to extend the life of these drugs until new ones are found. While our vaccines show promise, it will likely be years, if not decades, before we have anything that can really make a global difference.

Like most tropical parasitic diseases, malaria is a disease that is tied to poverty and social disruption. Global medicine has reached a critical tipping point in terms of the technology used in medical research. Advances in genetics (such as with pyrosequencing) have helped us better understand the pathogens and organisms we are dealing with, providing the tools to make significant progress as we stay on course and effectively utilize what these new platforms have taught us.

Closing

In closing, I am proud of global impact that military medical research has had throughout history, and the continued diligence being done to combat one of the oldest infectious threats man has known. In partnership with the Department of Defense, my colleagues here at the panel today, our global partnerships, and the Congress, we will be prepared for tomorrow's challenges. The Army Medicine team is serving to heal -- and honored to serve.