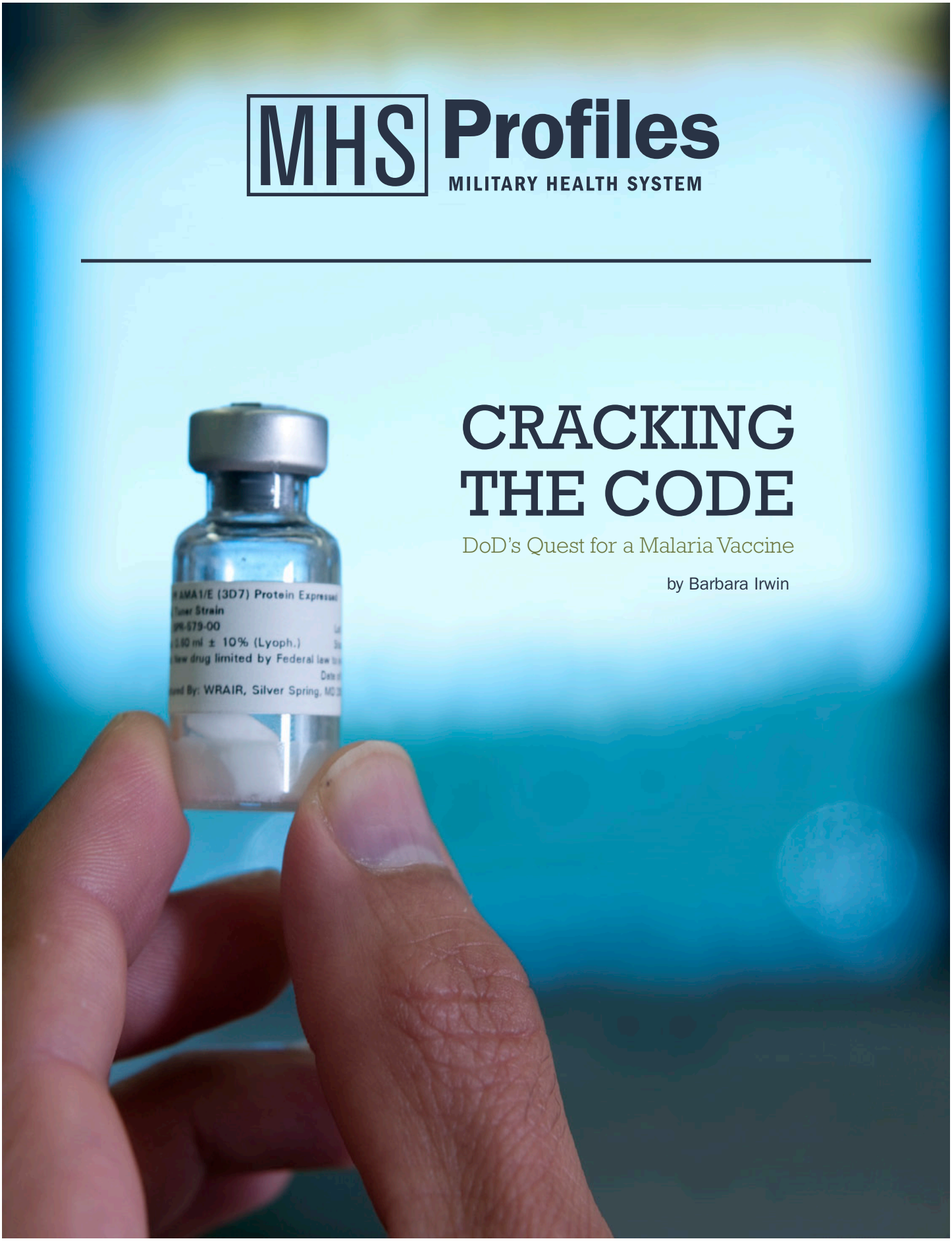
MHS Profiles
MILITARY HEALTH SYSTEM



CRACKING THE CODE

DoD's Quest for a Malaria Vaccine

by Barbara Irwin

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In the bottle: *The United States Military Malaria Vaccine Program hopes to unravel the major complexities of the malaria parasite to develop a vaccine that will control, and someday eradicate, malaria. (Photo by Caroline Deutermann)*

> "We are thrust into scientifically new territory, trying to do something that's never been done before."

Situated in sleepy Silver Spring, Md., the Walter Reed Army Institute of Research (WRAIR) and the Naval Medical Research Center (NMRC) unite to form the United States Military Malaria Vaccine Program (USMMVP). The program's inconspicuous home belies the daily battle being waged within its walls against a deadly foe. USMMVP, a combined Army-Navy research and development initiative that represents the continuation of more than 20 years of research by the Army and the Navy, is focused on a single goal: to create vaccines, drugs and diagnostics that will eradicate, or at least more effectively control, the vicious malaria parasite.

Army Col. Christian Ockenhouse, M.D., Ph.D., overall scientific director of USMMVP, and Capt. Thomas Richie, M.D., Ph.D, director of the program's Navy component, have helped foster a thriving program, in part due to USMMVP's unique organization and structure. The program incorporates several layers of oversight, including military activities that provide a defined goal for mission-driven research and a civilian Scientific Advisory Board that reviews and recommends optimal directions for research. "There is zero perception that two co-located military branches result in separate tasks or approaches," says Ockenhouse. The two components' synchronicity and synergy create optimal efficiency. "We identify gaps in achieving our goal and we use the strengths of military, government service and contracted personnel who can do the best job of filling those gaps," says Richie. "This combined, complementary approach allows us to share a number of resources, yet avoid any duplication of efforts."

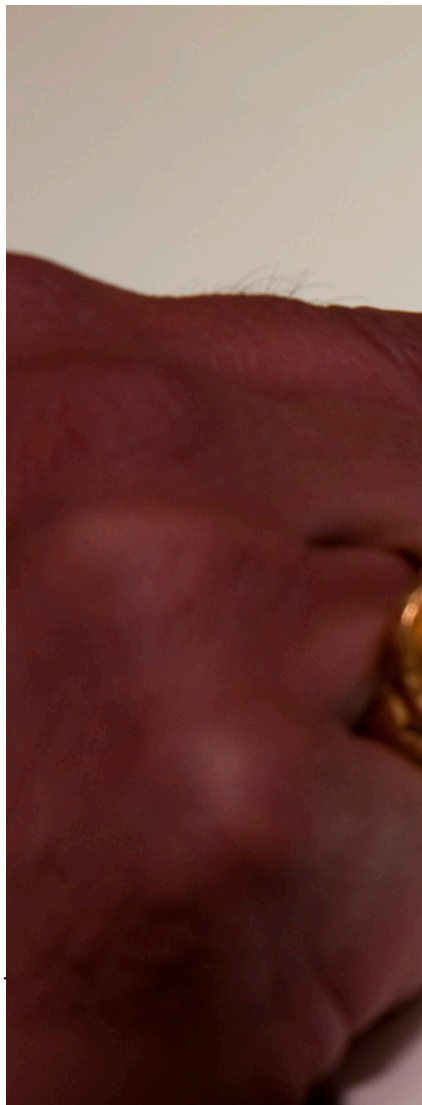
The cross-collaboration of innovative research and world-class clinical vaccine testing has enabled USMMVP to establish global relationships in its fight against malaria. Dr. Sheetij Dutta personifies this global reach. A native of the culturally diverse city of Lucknow, India, the clinical research management scientist at USMMVP is mindful that malaria kills nearly 900,000 people each year, most of whom are children from sub-Saharan Africa. From an early age, Dutta was aware that India's children are a part of that statistic, and he hopes

that USMMVP will soon achieve the global goal of licensing a highly effective malaria vaccine.

A Microscopic Battlefield

Most people believe malaria is a disease of the past, but the United States has battled the parasite in virtually every military campaign. In fact, during military engagements in tropical regions, there have been more person-days lost among U.S. military personnel due to malaria than to bullets. Just last December a Navy Seabee lost his life

> "The malaria mosquito and the parasites it transmits to humans have proven to be elusive targets, even after many years of intense scientific research."



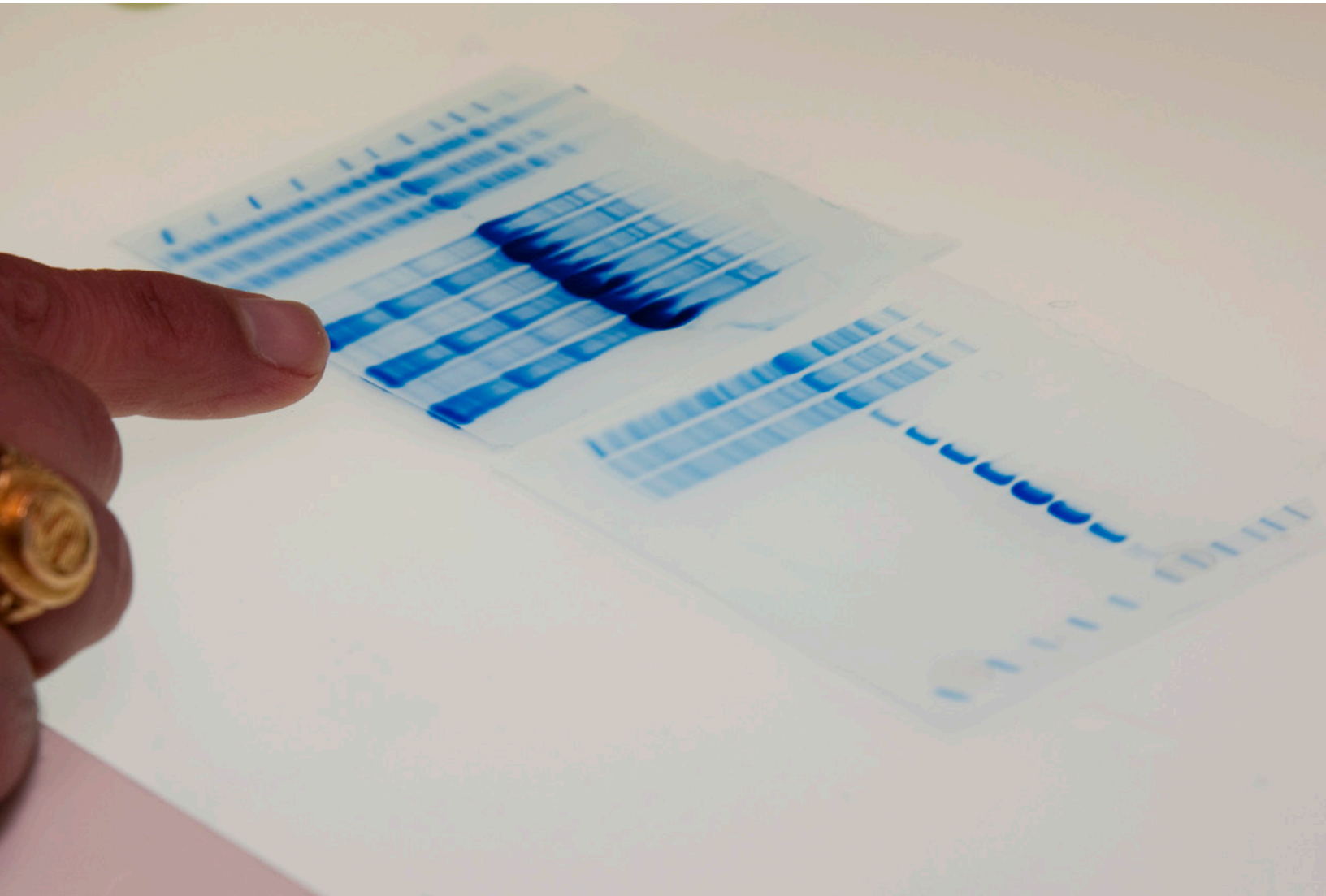
to malaria, and in 2003, 43 marines infected with malaria had to be evacuated from Liberia. Malaria is also a major threat to non-military travelers and people with low or compromised immune systems, particularly children under five years of age living in high-endemic regions. Today, this parasitic disease requires deployed service members to adhere to the conventional weapons of infection control: insect repellant, bed nets, uniforms treated with insecticide, and strict anti-malarial drug regimes that minimize the severity of infection.

Papers, files, books and journals stacked throughout Ockenhouse's office represent an imposing warehouse of scientific and statistical data he must consider in USMMVP's battle against malaria. Ever since he was a young boy reading countless books about African explorers, Ockenhouse knew that many adventurers contracted malaria and died from the disease. "I was always curious and loved science and medicine," he says. "I became obsessed about this parasite; I thought it was fascinating."

His obsession with microscopic evils yielded major benefits:

Waiting: *A boy waits to receive his malaria lab results at a dispensary in Tanga, Tanzania, in 2008, during a medical civic action project conducted by U.S. Soldiers and Sailors assigned to Camp Lemonier, Djibouti. (DoD photo by Mass Communication Specialist 2nd Class Johansen Laurel, U.S. Navy/ Released)*

Cracking the Code: *The malaria protein is purified using chromatography until only a single vaccine specific protein band is visible (right gel). USMMVP scientists will develop this one, pure protein into a malaria vaccine candidate. (Photo by Caroline Deutermann)*



By the Numbers

- **1 trillion** – Number of parasites that circulate in the blood stream over the course of one to two weeks after rupturing from the red blood cells
- **1.5 billion** – Number of dollars the Bill and Melinda Gates Foundation has devoted to the development and licensure of a malaria vaccine
- **900,000** – Number of people who die from malaria every year
- **30,000 – 40,000** – Number of progeny parasites produced from the replication of one plasmodium parasite while in the liver over the course of five days
- **16,000** – Number of infants and children enrolled in the first-ever Phase III RTS,S malaria vaccine candidate trial from 11 sites in seven African countries
- **5,000** – Number of different genes in one malaria parasite
- **3,000** – Number of children, ages 5 and under, who die from malaria every day in sub-Saharan Africa
- **48** – Number of hours it takes one plasmodium parasite to produce eight to 24 copies of itself within a red blood cell

Source: GlaxoSmithKline Biologicals, PATH

Feeding Frenzy: *USMMVP scientists allow female mosquitoes to ingest malaria parasite infected blood. A female mosquito carries the parasite in her salivary glands, transmitting it to the human host, causing malaria infection. (Photo by Caroline Deutermann)*

The Department of Defense awarded him the opportunity to attend medical school through the US Army Health Professions Scholarship Program, which pays for medical education in exchange for service as a commissioned medical department officer. "I could never have gone to medical school without it," he says. Ockenhouse studied medicine and infectious disease at Walter Reed Army Medical Center, and during a tour of duty in Korea he saw occasional cases of malaria when he cared for soldiers and their families. Now holding a Ph.D. in immunology and parasitology, Ockenhouse is proud to be among the elite scientists performing cutting-edge research at WRAIR.

Ockenhouse's passion for malaria vaccine development and anti-malarial drug improvement is, well, infectious. He is happy to

discuss at length the science of the malaria parasite and USMMVP's challenges, methods and successes. "We have three areas of focus in our fight against malaria: improved diagnostics that allow earlier detection and treatment; vaccine development to prevent infection and interrupt the parasite's destructive life cycle during the early liver stages of infection, before the damaging blood stages begin; and an anti-malarial drug program to prevent infection but also to treat those who are infected and suffer from disease severity," he says. His energetic pride is most evident, however, when referring to the USMMVP's dedicated staff and diagnostic research and vaccine development laboratories.

"C'mon, I'll show you!" he says, opening a door that reveals a narrow, humid room. "This is the insectory where we house the non-malarial mosquitoes," he explains. Long pans of warm water provide the ideal environment for larva-stage mosquitoes to grow to adulthood. Once mature, they emerge as flying insects and are moved to small plastic buckets, where they are ready to receive the malaria parasite. "The malaria parasite is transmitted through the female's bite, but these buckets contain both male and female mosquitoes, so next we separate them," he explains. On a nearby table just outside

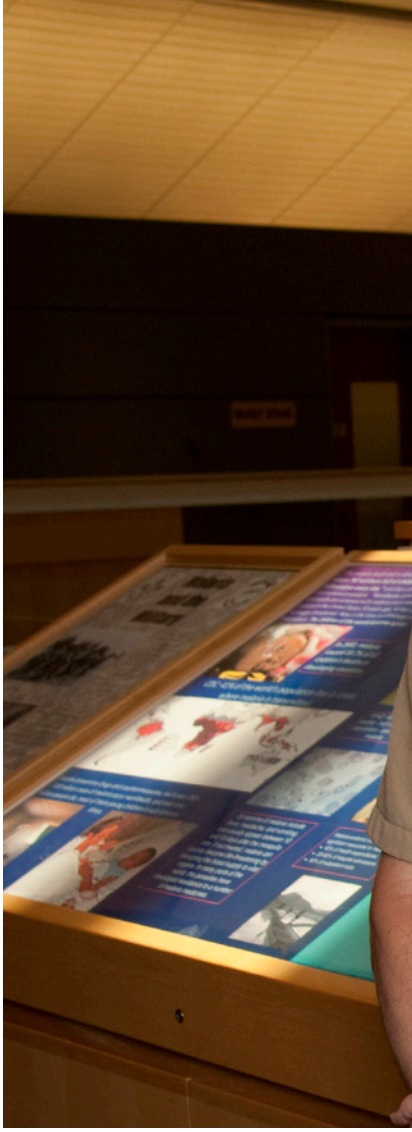
> "Understanding the burden of disease is critical in formulating the appropriate disease response."

the insectory, a plastic bucket full of mature mosquitoes sits next to a small heater. "Do you see how about half the mosquitoes have migrated to the side of the bucket closest to the heater? These are the females, and now that we have separated them from the males, we can feed them malarial-infected blood. Once we confirm that the females are now parasite carriers, we can use them in a challenge model trial."

Ockenhouse dashes from the insectory room to the laboratory where the mosquitoes are fed parasite-infected blood. "A very big challenge is that we must find a target on the malaria parasite that we can aim our drugs and vaccines against and attack it at vulnerable points in its life cycle," he says. "The solution lies in developing a vaccine that kills the parasite during its first few days of development in the liver, before it breaks out into the blood, multiplies and then attacks and kills red blood cells."

An Elusive Enemy Meets a Formidable Force

The malaria mosquito and the devastating Plasmodium falciparum (P. falciparum) and Plasmodium vivax (P. vivax) parasites it transmits to humans have proven to be elusive targets, even after many years of intense scientific research. Other infectious diseases such as chicken pox, measles, mumps, rubella



A Team Effort: *Standing left to right: Capt. Tom Richie, Col. Chris Ockenhouse, Ms. Susan Cicatelli, Cdr. Ilin Chuang, Maj. Jitta Murphy, and Lt. Col. Mike O'Neil. Col. Mark Polhemus is seated. (Photo courtesy of Capt. Tom Richie)*

A Fighter for Good: *Capt. Tom Richie is hopeful that USMMVP will develop a malaria vaccine that will protect America's soldiers and end the suffering of children in high-endemic regions. (Photo by Caroline Deutermann)*

and the mosquito-transmitted yellow fever have been successfully controlled through the use of childhood vaccines against these pathogens, meaning they no longer pose a significant global health concern. Smallpox, another viral killer, has been eradicated from the human population; unlike when a virus is "eliminated," an "eradicated" virus is wiped out forever and so will never again recur. But an effective vaccine against malaria continues to escape even the best scientists.

Navy Capt. Tom Richie would love to develop a "fire and forget it" vaccine that would free those who are non-immune or who already have the disease from the bothersome and sometimes painful anti-malarial drug regimes. "I was in Indonesia when a little girl died of malaria," he recalls. "Three weeks later, her mother died. It was devastating to the family, and I could empathize. I wanted to help this family deal with the grief of losing a child. It was frustrating to me as a physician who knows that no one should die from malaria."

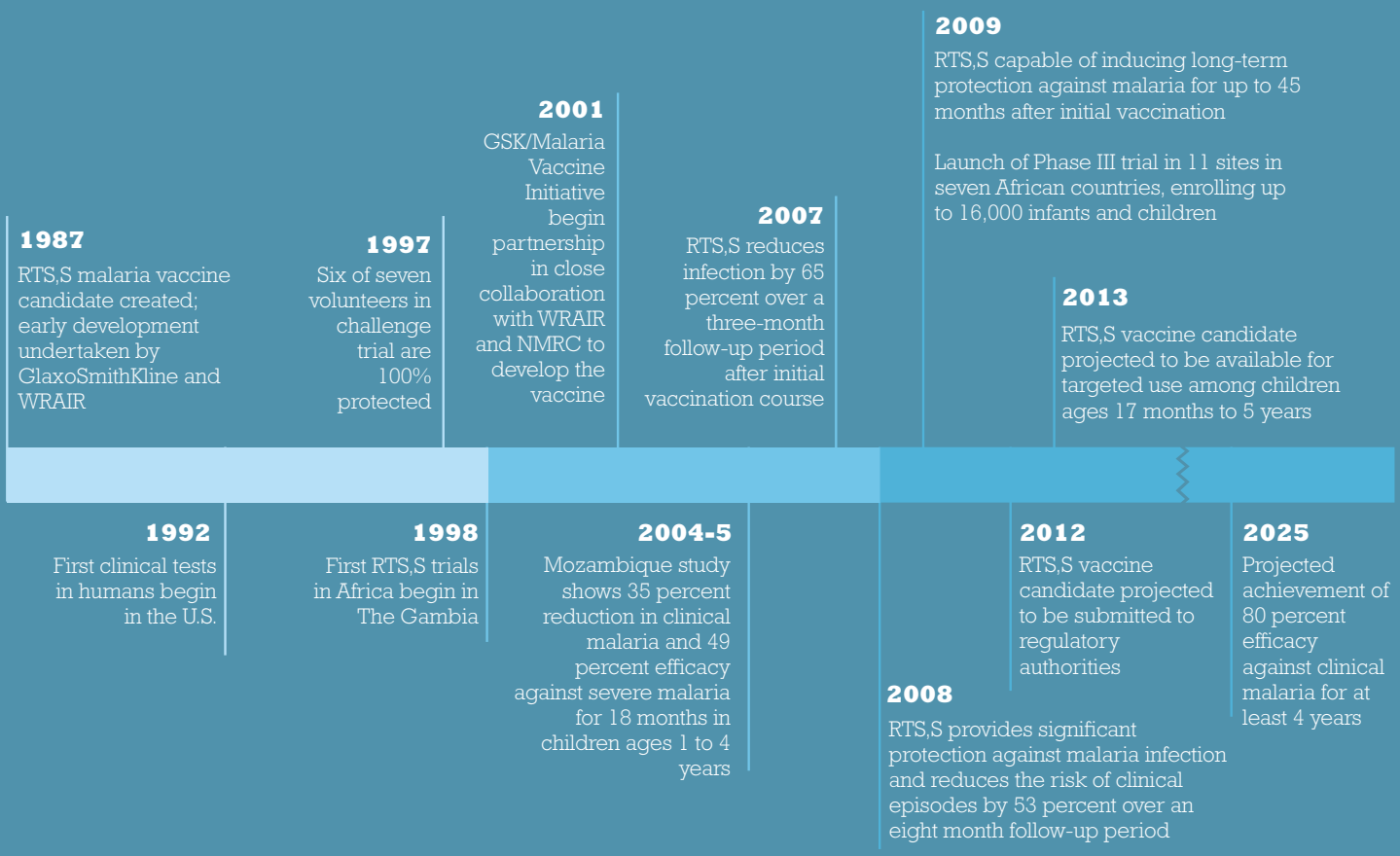
Essentially, vaccines give the body a preview of the invading agent, allowing it to learn how to defend itself. An ideal malaria vaccine would prevent all infection by priming the immune system to destroy all malaria parasites, whether multiplying in the liver, swimming freely in the blood, or "hidden" inside red blood cells.

Richie believes that the greatest scientific challenge in

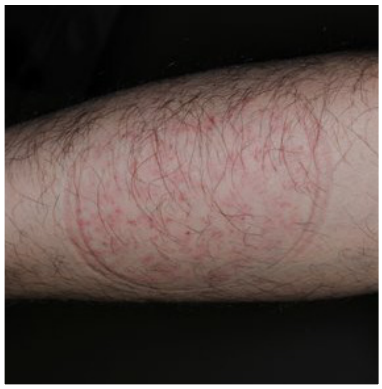
fighting malaria is developing a vaccine proven to be effective and durable against a chronic infectious disease. "We are thrust into scientifically new territory, trying to do something that's never been done before," he says. This includes employing a wide variety of recombinant and attenuated approaches—which entail genetic engineering and triggering the immune response—in developing vaccine candidates. "Having more than one approach provides us with valuable risk mitigation," he notes. "Should one approach stall or even fail, we have others that we can rely on to continue our research and development."

The malaria vaccine candidate known as "RTS,S" has given USMMVP its greatest success to date. In 1987, USMMVP created the recombinant RTS,S, which remains the most clinically advanced malaria vaccine candidate in the world. GlaxoSmithKline, the research-based pharmaceutical company, worked closely with WRAIR throughout the early development stages of RTS,S. In May 2009, RTS,S became the first malaria vaccine candidate to ever reach a large-scale Phase III clinical trial, the last stage of development before regulatory file submission. (Definitions of the clinical trial phases are provided on the next spread.) RTS,S has demonstrated an unprecedented 53 percent efficacy rate, giving much-

RTS,S Malaria Vaccine Candidate Timeline



Source: GlaxoSmithKline Biologicals, PATH



> During military engagements in tropical regions there have been more person-days lost among U.S. military personnel due to malaria than to bullets.

needed hope to the global health community. “The malaria vaccine candidate RTS,S has been a superior return on investment for the Defense Department,” Richie says. The Phase III trial currently involves 16,000 infants and children at 11 sites in seven sub-Saharan African countries. “Once approved, it will be the first vaccine for humans against any parasite,” says Richie.

As Ockenhouse continues the tour of USMMVP, he opens a door to one of its research and development labs, where Dr. Sheetij Dutta is working. The Indian scientist with newly acquired U.S. citizenship is busy developing a malaria vaccine that will meet the stringent 80 percent efficacy rate standard for U.S. military use. At an early age, Dutta was inspired by his father, who worked all his life on malaria

Defining Moments: *Scientist Dr. Sheetij Dutta oversees a lab in USMMVP’s Division of Malaria Vaccine Development. Dutta was inspired by his father and WRAIR scientists Col. Wilbur Milhous and Dr. David E. Lanar. (Photo by Caroline Deutermann)*

Snapshots: *The two photos above center show a mosquito blood feed and the forearm of a newly-infected volunteer of a test.*

drugs at India's Central Drug Research Institute. Dutta recalls evenings when his father would bring CDRI's top researchers to their home for dinner. It was then that young Sheetij Dutta met Col. Wilbur Milhous, an experimental therapeutics scientist from WRAIR. Later, during his doctoral studies in biotechnology, Dutta had another formative encounter. "I was delivering a presentation in Hyderabad, India, on the vaccine candidate AMA-1 when a man approached me and asked if I would be interested in working at WRAIR, specifically in the process phase of malaria vaccine," recalls Dutta. "I came to discover that this individual was Dr. David E. Lanar, WRAIR's chief of molecular engineering in the Division of Malaria Vaccine."

Jump forward 12 years and Dr. Dutta now oversees his own lab in USMMVP's Division of Malaria Vaccine Development. His job, located in the guts of the operation, is to isolate and examine a single malaria parasite that is made up of more than 5,000 different genes with proteins that are 300 times more diverse than other, more common viruses. Dutta's lab is tasked with the immense challenge of unraveling the major complexities of the malaria parasite and "bottling it" so that it is ready for field testing in accordance with military health requirements.

Dutta and his staff have had success with a malaria vaccine candidate known as FMP 2.1. In preclinical testing at USMMVP, FMP 2.1 induced antibodies that inhibited parasite invasion and multiplication in blood stage infection, and its safety and tolerability profile moved it to a Phase II clinical trial. From May 2007 to June 2009, FMP 2.1 was tested in 400 Malian children in West Africa. Results have not yet been published, but Dutta remains hopeful that even if the current FMP 2.1 does not advance to Phase III clinical trials, he and his staff will be able to improve the candidate for additional testing and possible future licensing.

Once a malaria vaccine candidate is ready for clinical testing, USMMVP scientists employ WRAIR's Human Challenge Model, of which Ockenhouse is especially proud. Developed at WRAIR nearly 20 years ago, the Human Challenge Model is one of the most important advances in military medical research and development. "The model is unique in that it allows for numerous testing of several drugs and vaccines, all in a short period of time," says Ockenhouse. Under this model, community and military

Phases for Clinical Testing of Viruses

USMMVP has a three-pronged approach to control, eliminate and eradicate malaria. This involves using diagnostics to better detect the malaria parasite, developing vaccines to prevent infection and clinical malaria, and working with WRAIR's Division of Experimental Therapeutics, improving existing anti-malarial drugs to not only prevent infection but to also treat those who are suffering from severe disease. USMMVP researchers on malaria vaccine development use the following universal standards for clinical testing:

- **Research and Preclinical Development:** Identify useful antigens and create vaccine concept, evaluate in animals and validate product manufacturing process
- **Phase 1 Clinical Trials:** Establish a safe dosage, observe how the product affects the human body and measure immune response
- **Phase 2 Clinical Trials:** Monitor safety and potential side effects: measure immune response, measure preliminary efficacy against infection and determine optimum dosage and schedule
- **Phase 3 Clinical Trials:** Continue to monitor safety, potential side effects and efficacy
  - Licensure: Obtain regulatory approval for distribution
  - Introduction: Begin vaccine use
- **Phase 4 Clinical Trials:** Perform follow-up safety monitoring; measure duration of protection and assess public acceptance

volunteers are vaccinated with the malaria vaccine candidate, after which they are exposed to bites from five female malaria-infected mosquitoes. Two weeks later the volunteers are dispatched to individual hotel rooms. Challenge Model volunteers are able to come and go as they please, but they are checked daily for the presence of malaria parasites.

"Our goal is to not find any malaria parasites; if we don't, we know the vaccine candidate is working," explains Ockenhouse. If malaria parasites are present, volunteers are promptly treated and go about their lives, just as healthy as they were before the initial vaccination and subsequent mosquito bites. The data gathered from the Human Challenge Model leads to what Ockenhouse refers to as the "use it, lose it, or improve it" decision. "If a vaccine candidate shows rates of efficacy that meet or exceed expected standards, we will use it in the next phase of clinical trials. Vaccine candidates that show some efficacy will be sent back to

Human Challenge Model: *Scientific director Col. Chris Ockenhouse demonstrates the Human Challenge Model for allowing infected mosquitoes to feed on human volunteers. Cloth is draped over the arm to simulate nocturnal conditions since mosquitoes from the genus Anopheles prefer to bite between the hours of dusk and dawn. (Photo by Caroline Deutermann)*

the labs for improvement, while other candidates will be abandoned altogether."

USMMVP Global Advancements

On June 21 of this year, the World Health Organization announced that USMMVP's Human Challenge Model would become the world standard for detecting and diagnosing P. falciparum, the deadliest of the four malaria virus strains. "Our military's position on the global health stage is through USMMVP's great capacity to engage in medical research and development," says Ockenhouse. "We have labs in Kenya, Thailand, Tanzania, Mali, Ghana and Peru. We are there at the request of U.S. Embassies and foreign partners. We are ambassadors in the countries where we work and we are there to lend assistance to their public health initiatives, all the while winning the hearts and minds of people by bringing them health solutions."

The U.S. Military Malaria Vaccine Program works closely with GlaxoSmithKline, the U.S. Agency for International Development, the Bill and Melinda Gates Foundation, and PATH (via its Malaria Vaccine Initiative) to ensure that anti-malarial efforts move forward effectively. Industry, pharmaceutical and research lab personnel pass their work along a horizontal chain and can lose track of the vaccine candidate's development status. In contrast, USMMVP practices a vertical collaboration in which every researcher, scientist and doctor involved remains fully aware of a particular malaria vaccine candidate's progress and status. "The industry's structure results in a very lengthy, very costly process," explains Richie. "We have a process that is much faster and that has a dramatically lower cost."

Like Ockenhouse and Richie, Dutta has great pride in—and dedication to—USMMVP's work. In 2008, Dr. Dutta received a job offer that would have taken him back

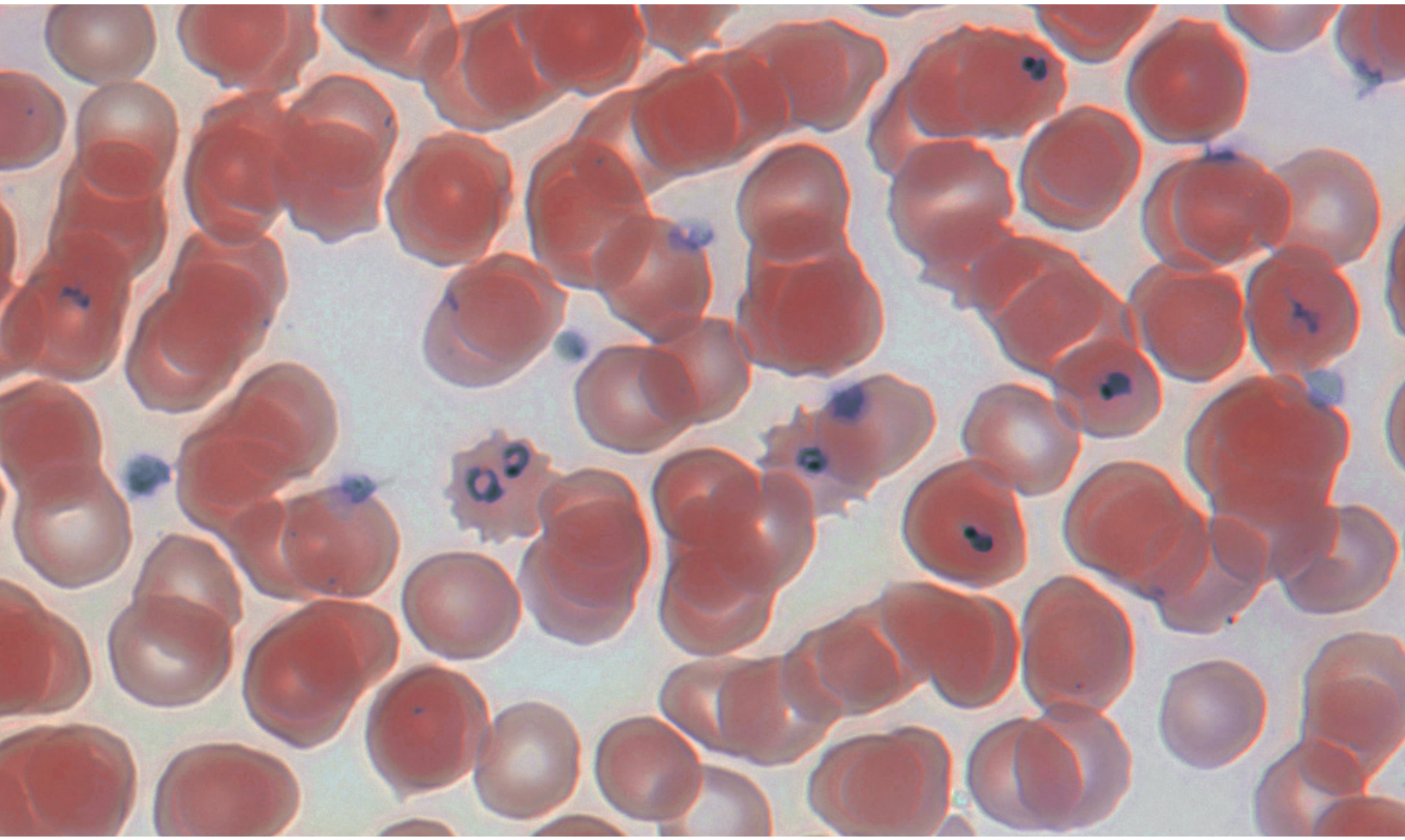
to India. “It was the toughest decision of my life. Going back meant following in my father’s footsteps, something I would be very proud to do.” But Dutta chose to stay on at WRAIR. He is devoted to improving WRAIR’s two malaria vaccine candidates that, by global health standards, are “in the bottle” and ready for field testing.

Despite the sizeable obstacles and occasional setbacks in USMMVP’s malaria work, Richie perseveres in the hope of one day extinguishing a virus that has inflamed places like Indonesia, where he spent nearly seven years of his Navy career, and wrought so much suffering that he knows can be prevented.

“Personally, I sometimes wonder if I make a difference in the world,” he says. “But I still get up every day, and I love coming to work. At the end of the day I know I’ve done my best at a job that’s worth fighting for. We may not win this battle during our individual careers, but we are true to our principles. I’d like to think that through this work, we are making a contribution to countries suffering from malaria. But really it is these countries that are making the contribution to us, by giving us this great mission.” ■

Protein Development:
Before a vaccine candidate can be developed, the malaria vaccine and bacteria proteins must be separated in the lab using a chromatographic system that removes bacterial impurities from the vaccine candidate. (Photo by Caroline Deutermann)

Deadly Intruder:
The deadly P. falciparum, shown here as “ring forms” inside red blood cells, will make eight to 12 copies of itself, erupt from its host blood cell and reenter the blood stream to invade another red blood cell and repeat the multiplying process. (Photo public domain courtesy of Wikipedia)



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coming next...

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