

Breaking the Cycle

The U.S. Army and its partners have been trying to develop a malaria vaccine for decades. But given a disease that has thwarted man for centuries and gets scant attention from the West, is this a battle they can win?

By Michael Leahy
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TO REACH THE SPECIAL MOSQUITOES, an Army researcher like Gray Heppner must walk through seven heavy doors off a corridor at Walter Reed Army Institute of Research in Silver Spring. The mosquitoes, called *Anopheles gambiae*, are behind that last door, in meshed cartons. They don't fly much in their confined space and appear quite benign in this room where everything feels unremarkable, even the high heat and humidity, which are meant to mimic the sweltering environs in which the anopheles thrives.

Only the unusual routines of the area, known as the insectary, belie the air of ordinariness. No two doors out of these seven are ever to be opened at the same time -- this to guard against the escape of any mosquitoes, which have been infected with malaria parasites by Army lab technicians. Just in case, small plastic bags, illuminated by an icy-blue light, hang between all the doors -- mosquito traps guarding against the remote chance that an anopheles gets loose. If a fugitive mosquito ever made it beyond all seven doors, it would be an unprecedented event, an entomological feat akin to an escape from Alcatraz.

By conservative estimates, malaria claims more than 1 million lives globally each year, 90 percent of them in sub-Saharan Africa, the vast majority children. Young survivors are frequently left with cognitive damage that can cause them to fail at school and work. African adults, while having lived long enough to gain some immunity against malaria's worst effects, often lose weeks of work while recovering from the disease. Western economists estimate that malaria results in an economic loss of \$12 billion annually in Africa, the continent least able to foot the bill for fighting the disease.

But in the consciousness of the average Westerner or in the official discourse of a governmental body such as the U.S. Congress, the scourge hardly registers -- a relic, like polio. Although affecting regions that make up about 40 percent of the planet, malaria is overshadowed by diseases that directly touch the West, such as AIDS, and worries about possible pandemics, such as bird flu. With U.S. government funds scarce, Heppner is vying with rival malaria vaccine researchers -- and rival approaches to fighting the disease -- for public attention and private research dollars, most of which come from philanthropic organizations with deep pockets, such as the Bill and Melinda Gates Foundation. As a colonel and the chief of Walter Reed's department of immunology and its malaria vaccine research program, Heppner's ultimate ambition is simple: Create a vaccine that will prevent infection and eradicate malaria in the way that Jonas Salk's vaccine wiped out polio in most places.

But malaria vaccine research must always compete for funding against more conventional methods for battling the disease, such as antimalarial drugs and insecticide-treated bed nets, as well as methods still in development -- including dreams of sterilizing mosquitoes and of making a vaccine to stop the transmission of parasites from an infected human to a healthy mosquito, thereby breaking the cycle of disease.

This particular summer day marks the launch of what Heppner estimates to be the 30th clinical trial of a malaria vaccine since the Walter Reed program began in 1983. There have been a lot of colossal failures. In the early '90s, not long after he accepted a position in the malaria program, an eager Heppner volunteered to take a shot of a prospective vaccine and allow himself to be bitten by an infected mosquito, as part of a clinical trial. The vaccine failed, and Heppner contracted malaria, after which an antimalarial drug treatment left him disoriented and suffering from nightmares for a couple of days.

But vaccine makers, like oil men and gold diggers, never stop dreaming. Sixteen years after he started at Walter Reed, Heppner's hopes are higher than ever in the wake of promising test results from a vaccine called RTS,S, which Walter Reed helped develop with a prominent pharmaceutical company, [GlaxoSmithKline](#) Biologicals.

In this latest clinical trial, Heppner and other Walter Reed researchers will evaluate another vaccine candidate, different from RTS,S and not yet publicly identified. Its potency in mice has fueled confidence at Walter Reed and brought 28 visitors to the insectary. They are the clinical trial's volunteers, drawn in some cases by newspaper advertisements. Others were recruited by Walter Reed personnel or heard about the trial from friends. According to Walter Reed staff members, 22 of the 28 participants have already received two doses of the vaccine.

The vaccine's inventor, David Lanar, is an Army researcher who has worked for years with others at Walter Reed to make the vaccine ready for clinical trials. Their efforts have cost several million dollars, in a field where government funding is hard to come by; one contributor, the Department of Defense, annually allocates \$8 million (about .002 percent of the Defense budget) for malaria vaccine research, equally divided between Heppner's Army unit and a similar Navy group. The stakes of this trial feel high to Lanar. "There are only so many chances that [a researcher] will get in a career to make a vaccine," he says.

He has been in this position before. In the early '90s, he created another vaccine, NYVAC-7, whose possibilities thrilled Heppner and others during early testing. Lanar fleetingly pondered the possibility that he might become famous: The Man Who Cured Malaria. "I could see myself on the cover of Science [magazine]," Lanar remembers, smiling. But then the vaccine failed. "It was pretty devastating."

Now waiting on the test of his new vaccine, Lanar is no less daunted by the challenge. "The parasites have learned how to withstand desperate attempts to eradicate them for thousands of years," he says. "They've survived the attempts of the body's [immune system] to wipe them out for millions of years."

Nearly all the volunteers know that human beings can be infected by four species of malaria parasites, the most dangerous of which, the one responsible for virtually all malaria deaths around the world, *Plasmodium falciparum*, is the parasite carried by the mosquitoes behind door seven. The volunteers understand that if the vaccine doesn't work, even those treated quickly are likely to experience a few days of nasty flu-like symptoms that could include screaming headaches, high fever, chills and vomiting fits. Some admit to feeling spooked ever since they volunteered to be bitten by an infected anopheles.

The six visitors who didn't get the vaccine are referred to as "control" subjects, aware that they are certain to get malaria if all is working right. But the group of vaccinated volunteers has the more jittery participants. Seated at a table, a woman is waving a hand in front of her hot eyes, trying to fight off tears. A paper cup has been brought out from behind door seven and placed on the table in front of her. Five infected anopheles are in the cup, which is covered with a tight mesh so the mosquitoes can't escape. They fly around the cup and press up against the mesh, bumping it repeatedly. The Army researchers theorize that the excited mosquitoes have smelled the carbon dioxide from the woman's exhalations. The scent of carbon dioxide is like a dinner bell. The woman is now supposed to put her arm over the mesh, enabling the mosquitoes to bite her from the other side. "Oh, gosh," she groans in a quavering voice. "Oh."

Gray Heppner says softly: "It's okay if you're having second thoughts. We have plenty of volunteers."

But a fellow volunteer, a blond nursing student at Montgomery College named Samantha Nolte, urges the woman not to quit. She has put her own arm over a cup and allowed the mosquitoes to start biting. "Just don't think about it," Nolte tells her. "Just do it."

At the researchers' request, Nolte has placed a blue dish towel over her arm. Mosquitoes like to feed when the sun goes down, and the towel will create the illusion that it's dark -- and time to eat. Nolte laughs. "I can feel them," she says to the other woman. "It's no big deal."

"God, *I gotta get to work*, I gotta get to work," the other woman barks. She lowers her arm onto the cup. "Just bite me, and let's get this over with," she says, trembling.

Nolte grins. The mosquitoes are still feasting on her. "They just feel like little scratches, like tiny needles," she says, an apt description, because a mosquito "bite" is merely a euphemism. The mosquitoes have actually pierced her skin with their needle-like stylets, a sting, just before injecting mosquito saliva into Nolte to thin her blood and make it easier to consume. In the process, the mosquitoes' salivary glands have released malaria parasites that have been in the glands since shortly after the mosquitoes themselves were infected from biting an infected host.

No mosquito is a born carrier of a malaria parasite. Across an ocean from the lab, the infected carrier that bedevils the anopheles is not another insect but a bitten African or

Asian person carrying the malaria parasite. Here, in Silver Spring, the host infecting the mosquitoes was an artificial membrane filled with blood purposely tainted by the researchers with malaria parasites. But whether in a Maryland lab or in Africa, the transmission of the parasite is a perfect circle in which a mosquito infects a human, who infects the next mosquito and so on, the cycle never ending. Only female mosquitoes bite people, needing the protein from human blood to lay eggs (male mosquitoes live off such things as the sap of trees). When a female anopheles gets malaria, she generally lays fewer eggs and flies more erratically than her uninfected sisters.

But there is one thing an infected mosquito does superbly: transmit the parasite to humans. In this moment, Samantha Nolte has probably been infected with from one to about 100 parasites from each of the five mosquitoes that has bitten her. To make certain that the insects in her cup are carriers, researchers lop off the heads of each mosquito with tweezers, examining the salivary glands under microscopes. In a few minutes, they pass the news on to Nolte: Yes, they've found parasites.

"That wasn't bad at all," Nolte says. "I feel great."

If she does contract malaria, the symptoms won't appear for at least a week. But already the parasites are active inside her, single-cell organisms fighting to stay alive.

Nolte, whose fiance has joined her as a participant, has been moved by stories she heard about the suffering caused by malaria from fellow nursing students, many of whom have emigrated from Africa. "I think it would be great to be part of history, part of something that stopped a disease that has killed so many people," Nolte says. And it doesn't hurt, she adds, that the trial will be paying her \$100 daily for as long as the nurses draw her blood each morning and it shows no parasites.

Matt Randall, a doctoral student in comparative politics at Georgetown University, likes the money, too, though he says he is principally motivated by intellectual curiosity. "How many people get to say they're involved in something that could produce a breakthrough of this magnitude?" he asks.

And there is Brian Kiragu, who grew up in Kenya. Most of Kenya has high malaria rates, but Kiragu's family lived in Nairobi, whose high elevation and relatively mild temperatures have made life inhospitable for mosquitoes. Feeling lucky that he never contracted the disease, Kiragu would like to help his countrymen and other Africans. "If this vaccine we received doesn't work, it will at least get the doctors a step closer; they'll be able to rule out this approach," he says. "But what if it does work?" He chuckles at the boldness of the thought. "It would change everything."

THE QUEST TO DEFEAT MALARIA IS AN OLD ONE. Modern scientists started laying the groundwork a century ago. Optimism peaked in 1955, when the World Health Organization launched a malaria eradication campaign using insecticides such as DDT. Supported by foreign aid from governments and international organizations, the campaign largely overlooked Africa in favor of concentrating resources in Asia's more

temperate subtropics, where mosquitoes were regarded as more vulnerable. Malaria rates quickly fell in targeted areas. But the malaria campaign waned, soon to be abandoned, when it became clear that the disease could not be altogether annihilated.

Malaria rates immediately rose again in Asia. In Africa, which had experienced some success in combating the disease on its own with pesticides and drugs, the death toll rose again in the 1980s, when the use of DDT in many countries was suspended under pressure from Westerners concerned about its impact on the food supply and environment. (WHO reversed its 30-year-old policy last month, declaring support for indoor spraying of DDT in malaria-prone regions.) Then the malaria parasite became increasingly resistant to antimalarial drugs that were once effective in treating the disease on the continent, and the death rate there spiked yet again. "It was more apparent than ever to people in [malaria] research that we needed something other than drugs," Heppner says. "A vaccine has always been the most cost-effective and permanent solution to these kinds of challenges."

Not everyone shares that view. Heppner's critics say that vaccine researchers have sometimes squandered government and philanthropic funding on a quixotic dream, when money could be put to better use on more established interventions for reducing malaria, such as drug treatments and insecticide-treated bed nets. But results from a trial of the vaccine RTS,S -- which was tested on more than 2,000 children in Mozambique after the Army helped to develop it with GlaxoSmithKline -- has generated cautious optimism that "a vaccine with reasonable rates of protection against infection and disease is close," as Heppner says.

"Reasonable rates" does not mean anything approaching 100 percent, as a polio vaccine offers, or even the 80 percent and upward that is Heppner's long-term goal. Throughout the 18-month Mozambique trial, the RTS,S vaccine protected about 49 percent of its 1-to-4-year-old subjects against severe disease and about 35 percent against malaria infection. Even those modest rates of protection are unprecedented in clinical trials, with the potential to cut Africa's annual death rate by malaria in half if the vaccine were widely distributed. That is reason for everyone involved to believe that the vaccine will be ready for mass pediatric use by 2011, after the last stages of trials are complete. For now, in those vast parts of Africa untouched by clinical trials, the outlook for the stricken is as grim as ever.

ON A SATURDAY MORNING IN AUGUST, Heppner is in Kenya. He has come to a town in the western part of the country called Kisumu, where Walter Reed has a facility for conducting malaria research and clinical trials of prospective vaccines and drugs. He stays at the Imperial Hotel, a place that Westerners like in no small part because of its in-room amenities, which include a light pesticide spraying around the walls and mosquito nets for the beds. Opposite him at breakfast that morning are two monied tourists, one American, the other Canadian, both of them serene because they are on a highly effective antimalarial drug called Malarone. That's the prudent move, Heppner tells them, because there is no area in the world with a higher rate of malaria transmission than western Kenya, especially balmy Kisumu, much of which sits on the beautiful and hippo-

populated Lake Victoria, a mosquito haven. Heppner doesn't take an antimalarial. He figures if he contracts the disease, the symptoms won't hit him until he gets home, where he can be treated at Walter Reed.

Still, watching Westerners here who have the good drugs always reminds him of the capriciousness of health care in a sub-Saharan country such as Kenya, where 30,000 children die annually from malaria. Somebody can afford a good antimalarial pill and lives; somebody else can't and maybe dies. Today, he's traveling with a group to Siaya, a town and governmental district, where about 22 percent of children perish from disease before they reach age 5. Siaya District has 510,000 residents, and last year more than one-third of them were stricken by malaria, according to district health statistics. Siaya is about a 90-minute drive northwest of Kisumu, toward the Ugandan border, on a paved two-lane, rural highway that has a colloquial name that sounds like something out of a Bogart film -- The Road to Busia.

Along the shoulder of the road on the way to Siaya, there are small boys herding goats and cows, which obediently lumber single file up the road. Young men try to repair the caved tin roof and gaping holes of another mud-and-thatch abode, which is home to human and mosquito alike. Women with strong, straight backs lug babies and traverse uphill with huge loads balanced atop their heads. Public transport in the way of small buses is often beyond the walkers' economic reach. In some spots, the nearest hospital is 30 kilometers away.

The vehicle bearing Heppner and a group of others from the Walter Reed Kenyan unit stops at Siaya District Hospital. Heppner and his colleagues have come to receive an update on the care burden posed in Siaya by malaria. It is an informal briefing, some of it delivered in an office, the rest in a hospital yard, where a rooster is crowing nearby and a doctor is having a \$47 water pump installed -- "The most important \$47 we're going to spend all day here," the doctor tells Heppner -- to get rid of standing water attracting mosquitoes.

A light rain has stopped, replaced by a faint rainbow, a blue sky the color of a robin's egg and a tropical breeze carrying a fragrance that smells like jasmine. The glory of the African morning makes what is happening on the other side of the walls only more incongruous. The doctors report that malaria now accounts for more than 70 percent of their patients. Ten to 20 malaria cases require hospitalization daily there, and, as is the case across the Siaya District and all of Africa, the disease is the biggest killer of children at the hospital: 15 die there of malaria in an average month. There are days with so many malaria-stricken children in the emergency section that the tiny victims must be placed six at a time across an examination table meant for one.

Segueing to a more hopeful subject, the Siaya doctors mention a district project just completed: the distribution of free insecticide-treated bed nets to families with young children. "We think this intervention could be very promising," a doctor says.

Heppner smiles neutrally. He sees all kinds of complications with bed nets: Sometimes they're not hung correctly; sometimes there are holes in roofs that make them useless; and they can't protect children who are playing outside at dusk, when mosquitoes start feeding. "Well, you're doing great work," Heppner says.

In the last half-hour, as the doctors have been talking, another child has died. Her name was Anne Achieng. She was 4 months old and had lived about five miles away, in a village called Obambo. She arrived at the hospital last night with severe anemia brought on by malaria, according to the medical report. There was also evidence that, before arriving at the hospital, someone had tried treating her illness with useless herbs, a common folk medicine of sorts that is often used in lieu of a real anti-malarial for one reason: People can afford nothing else. Anne Achieng had enough herbs in her that she was also suffering from herbal intoxication.

The next day, Heppner is back in Kisumu. With so many young malaria victims in the hospital wards of western Kenya, there is little time for doctors to dwell on names. The medical staff of Kisumu District Hospital tends to refer to each of the young patients as "this one" -- as in, "This one here is in some trouble." This one, the 14-month-old girl lying on the pillow in bed 18, the one with a couple of flies dancing on her face, arrived at the hospital the other day in a coma, suffering from critical malaria. Her name is Bibianca Anyango. A Kenyan doctor named Bernhards Ogutu hovers over her bed. Ogutu leans down, stares at the closed-eyed and motionless Bibianca and presses the center of the girl's tiny chest with his index and middle fingers. Hard. Then harder still. He wants her to feel a spasm of pain, hopeful of eliciting a reaction that might signal that her coma is ebbing.

No reaction.

What has happened to Bibianca is what always happens in severe malaria cases. Days ago, after she was bitten by a mosquito, the falciparum parasites swiftly made their way into her liver, with each parasite ensconcing itself in an individual liver cell, where it was protected against her body's immunological defenses. The parasites developed and multiplied, bursting in about six days from Bibianca's liver into her bloodstream, where each parasite invaded a red blood cell. Unchecked, the parasites multiplied yet again, bursting from those cells into new red blood cells in about two days. That triggered the release of toxins that brought on the early symptoms of her malaria, including fever and chills. In this oft-repeated 48-hour cycle of breakout and invasion, the disease soon had produced hundreds of billions of parasites in Bibianca. The parasites destroyed her blood cells and fed off her hemoglobin, which, in a healthy person, carries oxygen to the body's tissues and organs. By the time Bibianca arrived at the hospital, death was a possibility.

Parasites had clogged her oxygen-starved blood cells and blocked blood vessels, leading to her coma and likely beginning the stages of organ damage.

Bibianca's mother, a stately woman named Benta Okoth who sits on the edge of the bed in a long dirt-stained white skirt and a blue sweater over a ragged brown T-shirt that says

VERSACE on it, has been stolid. But something in the renewed urgency with which Ogutu is pressing on the child's chest dissolves her. She jerks her head away. She stares out a window screen, shielding her bloodshot eyes with a long hand. Ogutu keeps poking Bibianca's chest. Finally, in a noise that sounds like something from an inanimate doll, a moan escapes from the little girl's shut lips. Her eyes stay closed. Ogutu looks at Heppner and smiles wanly.

"No movement, still comatose with severe malaria, but the moan means a little improvement," Ogutu says, shrugging.

"A little."

"A little" is mixed news. A little means, on the one hand, that Bibianca will probably come out of her coma and survive -- which in itself will be no small feat. But escaping death might mean trading horrors. "She still has a significant chance of brain damage in a case like this," Ogutu says, touching Bibianca's forehead, feeling her fever. "It will be harder for her to learn if that happens. She might have problems with mobility or with one or more limbs. She could have behavioral problems that will be mistaken for [disobedience]."

He looks over at Heppner and, talking in medical shorthand, describes the symptoms and prognosis, his shrug reflecting the limits of what either man can do here. "Her coma could have been avoided," says Ogutu, the principal clinical investigator for the U.S. Army's malaria field trials in Kenya. "But that's the way it is with a lot of malaria cases. This is a case where, if they had had the right things in other [health facilities], this girl would never have arrived here in a coma. You ask yourself, What happened?"

It is a question he also poses to Okoth, to whom he speaks softly in Luo, their tribal language. Okoth's explanation for what happened to her daughter over the past week has a familiar ring to Ogutu, a story illustrative of the maladies of a typically poor and inefficient African health system. Five days earlier, while at home in the western Kenya sugar plantation village of Chemilil, Okoth had become alarmed when a touch of her listless daughter's skin seemed to indicate a fever.

In Kenya, the most reliable antimalarial drugs cost about \$6, or about four days' earnings for the average Kenyan. The drugs are generally unavailable in shops. Accessible antimalarials in Kenya generally mean cheap antimalarials -- usually ranging from 10 to 30 Kenyan shillings, or roughly 15 to 40 cents -- but they are also the least effective treatments, as the disease has become wholly resistant to many of these drugs once famously effective.

Okoth did not have even the cheap anti-malarials. She carried Bibianca, as she tells the story, to a nearby government dispensary, which had no effective antimalarials on hand and whose attendants could tell Okoth nothing more than that Bibianca appeared to have malaria. They referred her daughter to another government health facility, where Okoth paid 20 shillings as a registration fee and was told that Bibianca, who by then was lapsing

into a coma, needed a blood transfusion. But the facility didn't have the equipment or blood to do the procedure. Okoth was referred yet again, this time to a health facility up the chain of Kenya's medical bureaucracy, Kisumu District Hospital, 30 kilometers away and reachable only by a public bus that would cost Okoth a considerable sum, about 100 shillings.

She needed to go home for the money, but by that time it was too late to catch a bus to Kisumu. When Okoth arrived at the hospital the next afternoon, her daughter had already been in an untreated coma for a full day. Unable to breathe, Bibianca was given oxygen for two days. Now, as Ogutu and Heppner study the girl, she is breathing on her own, and her vital signs look stable. She is receiving an intravenous quinine drip to fight the parasites, but her coma has shown no signs of breaking, and both Ogutu and Heppner worry about what they cannot see in Bibianca. "There's just no way of knowing," a frustrated Ogutu says. "Not here."

Heppner sighs, shakes his head.

"They don't have the right tools here to measure the glucose [in her blood]," Ogutu says softly to Heppner, alarmed because a low glucose level can itself cause a coma. "There's no glucose meter."

"I think I'd be giving her glucose every eight hours," Heppner says. "But there's a danger in giving someone too much glucose. You need that meter."

"Yes," Ogutu says, touching Bibianca's forehead. "You ask, Why isn't there a meter?"

Part of the reason that Heppner sees a vaccine-based solution as a medical and moral imperative is that he views the health-care infrastructure of African countries as woefully inadequate to the task of treating malaria. And Bibianca's case is just one more reminder. Heppner and Ogutu say that the technical equipment used at the Kisumu hospital to look for microscopic parasites is substandard, meaning that some malaria cases will be missed. And there are no first-line antimalarial drugs yet at the hospital; they are caught up in a Kenyan bureaucratic tangle that has them sitting in a distant warehouse.

"What good are treatments for malaria if they're not in a hospital?" Heppner says. "That's why you need something like a vaccine that reduces the need for treatments. But look: Obviously, you still need equipment, you still need drugs -- people are getting sick. I think it's just not possible to [address] malaria without looking at all of it -- poverty, infrastructure, lack of hospitals, bad [health care] delivery. And there will be challenges, too, for anyone who develops a vaccine. If we have a vaccine, we'll need to get it to people, and so you need to start thinking about all that now."

From the corner of the bed, Benta Okoth clears her throat. She rubs at her eyes; she jerks her head away from the window and mumbles something in Luo.

"She is saying that she won't be able to sleep, really, until her daughter comes out of the coma," Ogutu whispers. "Too nervous."

Okoth is still mumbling. Ogutu leans closer.

"It makes her very scared," Ogutu adds. "It has happened before, she says."

Happened to Bibianca?

Okoth morosely shakes her head. No. For a while, she can't speak. Then her words come in a torrent. Her head drops. Ogutu takes a deep breath: "She says she's already lost two children. One at age 10 to a heart condition. Another at age 7 to malaria or typhoid fever or meningitis. It is that way with malaria quite often. No one around is sure what it is. No doctor was present for the second child, it seems. The child just died."

Okoth turns back to the window. Ogutu whispers to her that he will return, assuring her that he thinks her daughter is improving. But all those hours her comatose brain was without treatment -- almost no one recovers from that kind of malaria without paying a severe price, he will say later. "It can't be good," he mutters in English. He walks on to the next bed, where another mother, bending over another closed-eyed child, tells him her story.

DONALD GRAY HEPPNER JR. DOES NOT GIVE UP EASILY ON A DREAM.

Raised in Lynchburg, Va., and inspired by the intellect and stature of physicians in his town, he set his sights on becoming a doctor, only to be rejected by every medical school to which he applied. Rather than surrender, he started knocking on doors at the University of Virginia, where he had graduated with an undergraduate degree. He got a job there as a technician in an endocrinologist's research laboratory, hoping to impress his superiors enough that their recommendations would help him gain entry to U-Va.'s medical school.

Admitted into the medical program a year later, he became intrigued by the work of faculty members who had a passion for infectious diseases -- "the dominant tribe" of the med school, he says. He was particularly fascinated by their work with the deadly, resilient malaria parasite.

After graduating from medical school, he did his internship and a residency at the University of Minnesota, where, in the late '80s, he went looking in his spare time for another lab to advance himself, offering his services for free. He assisted a malaria researcher who, among other things, was growing falciparum parasites. While in Minnesota, he joined the Army Reserves after hearing from an involved Army doctor about the armed forces' work in tropical disease research. But Heppner didn't sign on for active duty in the Army until 1990, when he accepted a position as an infectious disease officer in Walter Reed's malaria program, which had first tested a malaria vaccine in 1986.

Most researchers in the program, wanting to assist their colleagues in the study of promising vaccines, volunteered to serve as subjects in at least one clinical trial. Heppner volunteered for the trial of a vaccine called RLF, which was a complete bust, just one in a long series of failures during the '90s. Heppner spent four years in Thailand, running a lengthy clinical trial of a greatly anticipated vaccine invented by a prominent Colombian researcher. That one flopped, too, but by then Heppner was convinced that the research community was on the right path. And besides, it was Heppner's nature. "I'm not a morose guy," he says. "Every time we had a disappointment, I saw a benefit."

David Lanar has admired Heppner's resolve and optimism. "He's very supportive, and a [researcher] always appreciates support in a [field] so . . ." -- Lanar pauses, searching for the tactful word -- "uncertain." Heppner became chief of the Walter Reed malaria program in 1999. Many members of the department had more glittering academic backgrounds than Heppner's. But, at 50, Heppner is about nothing so much as tenacity. His license plate spells MALARIA. A few weeks after his trip to Kenya, he will head to Paris to speak about RTS,S to a symposium of immunologists. He says his speech will note that the development of RTS,S has been "a study of perseverance."

THE ARMY'S PURSUIT OF A VACCINE, any vaccine, is never rooted in altruism. Other scientists in the malaria research community might be chiefly focused on saving foreign children, but the Defense Department has its own agenda. "The Army's goal above all else is to protect American soldiers," Heppner says.

To keep soldiers alive and fit for duty, the Army has been attacking cruel diseases in its ranks for three centuries. Its immunization efforts flourished as early as the Revolutionary War, when Gen. George Washington, responding to a lethal smallpox outbreak among his troops, agreed to recommendations from his medical corps that soldiers be inoculated with an application of live smallpox virus to the skin, a painful procedure that nonetheless protected against the disease.

During World War II, the Army recorded more than a half-million cases of malaria among its troops in the Pacific theater. "This will be a long war," Gen. Douglas MacArthur reportedly said, "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."

Intravenous quinine helped to treat the disease by neutralizing the parasites in the infected. It got soldiers back on their feet, though in many cases recoveries took weeks. In 1965, while fighting in Vietnam, more than 10 percent of American troops contracted malaria, the beginning of a six-year wave that resulted in 80,000 cases of the disease among GIs there, according to an Army study. In some Army units deployed to Vietnamese jungles, malaria rates were as high as 60 percent. Only effective drugs kept deaths from the disease low (less than one in every 500 troops who fought in Vietnam).

Regulations prohibit Heppner from lobbying Congress for funding, and his discussions with military brass have had at best a negligible impact in recent years: The funding that

his program receives from the Defense Department has increased little. Heppner and his Army colleagues remain serious players in the vaccine research field only because of the largess of other groups. His department received \$2.7 million last year from the U.S. Agency for International Development and \$1 million from its vaccine collaborator GlaxoSmithKline. But his most critical source of funding in recent years has been the private nonprofit Malaria Vaccine Initiative, created with a grant from the Gates Foundation in 1999.

Worldwide funding for malaria, last calculated by the research group Malaria R&D in 2004, stood at \$323.4 million. Columbia University economist Jeffrey Sachs estimates it would take \$3 billion to vaccinate every African child who needs it.

Last year, the White House announced a five-year plan and pledged \$1.2 billion to fight the disease with drugs, bed nets and pesticides. Publicly, the pledge has drawn praise from malaria activists. But, privately, several of the same activists observe that the commitment is less than one-tenth of the funding in the White House's AIDS initiative -- and assert that much of the money is merely making up for the Bush administration's previous cuts to malaria programs. And they note that what's missing is specific funding for malaria vaccine research. Administration spokesmen, noting that the president plans to convene a malaria "summit" in December, say that Bush's plan to fight the disease reflects a preference for spending any new money on techniques already yielding benefits.

IN ANY WAR, AS HEPPNER KNOWS, the longer a man chases a resilient enemy, the more likely he will acquire a grudging respect for it. "The parasite has survived everything meant to eradicate it to this point," Heppner says. "You can't say that about many things under attack this long. It's been a battle."

A few drugs have had an upper hand temporarily against the parasite, most notably an antimalarial called chloroquine, which was developed in 1934 and proved effective in Africa, off and on, for several decades. But by the 1970s, adaptive parasites began showing signs of resistance to chloroquine. By the late '80s, resistance to the drug was fierce, as evidenced by increasing deaths among children who used it. Africa's new front-line antimalarial became sulfadoxine-pyrimethamine, commonly called SP. But the parasites' resistance to SP took a frightening leap within five years, and by 2004, the drug's rate of protection was so low, and so many kids were dying, that the Kenyan Ministry of Health concluded that SP ought to be phased out, too.

That hasn't stopped African parents from buying SP for their ill children. The drug costs just pennies. Nowadays, a new antimalarial in Kenya receiving international subsidies is Coartem, a so-called combination therapy. There are high hopes for Coartem, not least because it contains several components, which means the parasite will need to become resistant not to only one element in the drug but several. Still, Heppner sees the same fate awaiting Coartem as every other drug: obsolescence and failure.

But Heppner and his allies at GlaxoSmithKline face their own stiff challenge: Never has anyone created a successful vaccine against a parasitic disease affecting a human being. Their chief weapon for the moment is RTS,S, whose goal is to destroy the parasite before it leaves the liver and enters the blood. The vaccine contains a part of the same protein present on the surface of the parasite as it attempts to invade the liver. Researchers believe that the protein will be recognized by the body as a foreign invader, triggering the body's immune system to attack the proteins wherever it can find them, including the proteins of incoming malaria parasites.

Heppner knows that, scientifically speaking, this is a bold combat plan, complicated by the number of invading parasites that accompany a bite from an infected mosquito, sometimes as many as 100. Heppner uses a combat metaphor: "The idea is that RTS,S will work like a Patriot missile system," he says. "All these parasites will be coming in like missiles, and RTS,S will be shooting them down. And even if a couple of the parasites get through sometimes, the vaccine will have been successful -- because it will have already significantly reduced the number of missiles that we have to get [later]."

RTS,S he says, "takes aim at the parasite twice. It tries to get the parasite with antibodies before it enters the liver, and then it will surveil the liver with special white blood cells that will attack the [parasites that make it in] . . . If we have a combination vaccine made up of several vaccines, RTS,S will be the first attacker. The other vaccines will get the remaining parasites at the next stages."

At the time of the Silver Spring trials, the plan was to test David Lanar's vaccine in the bodies of those 22 volunteers. The goal was to train the body's immune system to recognize a protein on the parasite that protects it inside the liver, at its most vulnerable developmental stage.

Just as some skeptics don't believe an antimissile system can be foolproof, there are those who see serious flaws to the Walter Reed-GlaxoSmithKline approach. One of Heppner's rivals, Louis Miller of the National Institute of Allergy and Infectious Diseases, questions the idea of trying to fight off malaria infection altogether. Miller has devoted himself to creating a vaccine whose principal aim is simply to slash the number of parasites, so as to reduce the severity of the disease. Something like RTS,S hasn't yet shown in clinical trials that it can stop most or all parasites, Miller says. "And an important thing to remember is that malaria isn't like measles or mumps; it isn't something that people, young or old, necessarily get just once in their lives and it never comes back. This is more like flu; many people are likely to get malaria several times in a lifetime . . . So how long is the [RTS,S] vaccine or any other vaccine going to protect people? How often will they need to be [re-vaccinated] if the [goal] is to stop all the parasites?"

With his vaccine, Miller aims to keep children alive long enough for their bodies to build immunity against severe disease. But that alone isn't enough for Heppner, who needs to keep soldiers and Western travelers from falling ill at all.

Heppner says that the Army and GlaxoSmithKline can't be sure how long protection will last beyond the duration of the RTS,S clinical trials. Like the critics, he wonders whether the parasite might one day mutate in the face of a vaccine and render it less effective, if not impotent. "What we're doing here -- trying to stop the parasite altogether and prevent infection -- may be more complicated," Heppner says. "But that doesn't mean it's not the best way."

ON A SATURDAY MORNING, the 10th day after being bitten by the infected mosquitoes, a small group of volunteers in the clinical trial of Lanar's vaccine say they feel great. The nursing student Samantha Nolte and her fiance, John Davis, tease each other over who between them will be safe from malaria the longest, knowing the longer that parasites don't show up in their blood draws, the more money they'll take home.

Meanwhile, the volunteers feel as if they are on a mini-vacation, though most are still going to their jobs. Walter Reed has put them all up at the Courtyard by Marriott in Silver Spring, where they eat breakfast and then go about their normal routines. The doctors, researchers and support staff also have rooms at the hotel, where they study the volunteers' blood, looking for parasites. "If anyone does get sick, we'll know it right away, and we can quickly treat them right here," Heppner says. "All they'll have to do afterward is walk down a hallway, go into their room and rest."

Nolte goes shopping at a mall with Davis. At about 1:30 that afternoon, her cellphone rings; she receives news from a Walter Reed nurse: Parasites have been detected in her blood; the vaccine has failed to protect her. Nolte is stunned. She feels great, she tells herself. Well, maybe not exactly great. Actually, she's feeling a tad lethargic, listless. But for now she still can't quite believe this news.

In the next hour, Nolte is back at the hotel. A researcher pulls out a glass slide with the thinnest smear of Nolte's blood, sticks it under a microscope and shows a parasite to Nolte. It looks like a round dot with a crescent moon surrounding it. While the nursing student in her understands the ruinous wonder of this thing, another part of her is still grappling with a question: How can anything this tiny make you so sick?

The 57-year-old Lanar has reminded himself that one positive test will not amount to failure. If most of the volunteers are protected by his vaccine, it will be dubbed a success. If, say, 18 of the 22 are protected, it will be declared a stunning achievement, with profound implications for malaria and vaccines. He might still make it onto the cover of Science.

But over the weekend, many more of the trial subjects test positive, including all six volunteers who did not receive the vaccine. Several of the inoculated volunteers have gotten sick, experiencing the first wave of malaria and receiving treatment that will cure them within a couple of days. John Davis tests positive the next day, and within a day he is racked by fever and the shakes. Brian Kiragu is positive, too.

However, the Georgetown grad student Matt Randall continues to show no parasites. "I'm feeling good," he says. "I've still got some confidence in the vaccine because nothing has happened to me."

The next day, Lanar comes to the hotel to receive disappointing numbers: More than half of the volunteers have tested positive. While he digests that information, the numbers are updated to include more positive tests.

"Well, sometimes something works, and sometimes it doesn't," he says, then reminisces about the vaccine's high moments, when it tested so well in mice. "This is a [vaccine] that the worldwide vaccine community wanted to evaluate for many years, and now we have done that. Sure, I'd like to have been the inventor of the malaria vaccine. But people who get awards must stand on the shoulders of those before them."

A few seconds later, a strange sound comes from the suite's bathroom. Lanar walks over to investigate. A woman in sweats, a trial subject, is bent over a toilet, vomiting.

"Are you all right?" Lanar asks.

She retches again.

"Obviously not," he says.

"Ohhhh," the woman groans, face down in that toilet bowl.

"Oh, no," Lanar says. "Do you want to see a doctor?"

It takes a while for her to get the next words out. "I just saw one."

She finishes vomiting and trudges out of the room. Lanar turns back and falls into his chair. It has been a long day.

"Yeah," he says, allowing himself a little smile, "that could have gone better."

IN WASHINGTON, THE TRIAL SUBJECT MATT RANDALL, whose confidence in the vaccine has remained unshakable, receives a call early in the afternoon on the 12th day of the trial. Parasites have been found in his latest blood test.

He rides the Metro back to the hotel in Silver Spring. Within a few minutes, he is experiencing terrible chills and is huddled up on a back seat, with a scorching headache. He has a fever, too, which will peak at 102.5 degrees that night.

Now all 22 trial subjects who took the vaccine have tested positive for the parasite. The vaccine is a failure. Lanar would like to figure out, if possible, where it went wrong. "Either immunity was not developed with the way we designed the vaccine, or our basic idea was off the wall," he says. "But am I fatalistic now about vaccines? No, not at all."

We will still have a malaria vaccine someday. It's bigger than me; it's bigger than any of us."

Heppner is also resolute. He says he has a promising vaccine to be tested in the fall and that Lanar is helping to develop a new one, too. And he is more confident than ever in RTS,S, whose latest clinical trial appeared to protect against severe malaria for 18 months in about half the children tested. "There have never been numbers like that in the history of malaria research," he says. "We are getting closer all the time to what we all want . . . But I don't have a date, a year, for anybody. I don't think anyone honestly does. We've never faced anything like the parasite."

Michael Leahy is a staff writer for the Magazine. He will be fielding questions and comments about this article Monday at noon at washingtonpost.com/liveonline.