NETWORKing MALARIA

Scientists with UF's Emerging Pathogens Institute are trying to help governments eliminate one of the world's most deadly diseases

By DeLene Beeland

As a teen, Dawit Woldu and some friends had to walk 25 miles from their village in the east African country of Eritrea to take a high school entrance exam, their excitement tempered by fear about contracting deadly malaria.

"Growing up, you just knew not to go to this area," Woldu recalls. "But it was the only way to get into high school. This was the only testing site in the whole province."

The test took several days, and the boys slept in the school, swatting mosquitoes throughout the hot summer nights. Five days later, Woldu and his friends returned home, anxious about whether they'd passed the test. They were hungry for an education, a better life.

Within a week, Woldu fell ill. He'd had milder forms of malaria throughout his childhood, but this time it was much worse. Woldu grew so sick with fever that the skin on his lips burned. Tell-tale white spots remain today.

"My family thought I was dying," Woldu says. He was hospitalized and, though he eventually improved, Woldu missed almost two months of the high school education he so eagerly sought because he'd contracted malaria. Woldu was lucky. Two of his friends died.

Ray Carson

Two decades later, Woldu is pursuing a doctorate in medical anthropology at the University of Florida. His research seeks correlations between cultural, geographic, socio-economic and genetic factors that seem to protect certain human populations against the parasites that cause malaria.

Woldu's story is all too familiar for many Africans, where a child dies from malaria every 30 seconds, according to the World Health Organization. It's a statistic African parents live daily, but the illness remains a foreign malady to many Americans. For us, the threat looms elsewhere. But it was not always so.

INVISIBLE ANCHOR

Until World War II, the southeastern United States was as prone as any developing country to the ravages of malaria.

As the war effort ramped up and soldiers at southern bases began to get sick, the federal government initiated the National Malaria Eradication Program. Long before scientists knew the widespread effects DDT had on wildlife, they bombarded mosquito breeding grounds with the chemical. And it worked. By 1951 malaria had been eliminated in the United States and a new federal agency, the Centers for Disease Control and Prevention, had emerged. The agency's southern origins explain why the CDC headquarters is in Atlanta and not Washington.

Even though it no longer threatens Americans, around the world malaria sickens between 350 and 500 million people per year, and claims more than a million lives, according to the WHO. Most victims are African children living south of the Sahara Desert.

Just one glance at a map of where malaria is most prevalent makes obvious the disproportionate effect it has upon developing nations. Malaria is like an invisible anchor dragging down human potential, drowning education and economic growth. It is both a cause and an effect of poverty worldwide.

The illness is caused by protozoan parasites in the genus Plasmodium. Some species are more virulent than others. The parasites enter the bloodstream through the bite of an infected Anopheles mosquito, and they enter the mosquito when it bites an infected person.

Each time a doctor treats an infected person with anti-malarial medicines, some of the parasites survive. They pass their resistant genes on to their offspring and in time an entire population of parasites can evolve to be drug-resistant.

After Sir Donald Ross discovered that malaria was transmitted by mosquitoes in 1897, several classes of anti-malarial drugs were used extensively as world powers like Britain, France and the United States colonized tropical regions around the globe. But by the 1950s many of these drugs had begun to fail as the parasites evolved resistance.

Now the same is happening with newer drugs.

For the past eight years, the WHO has recommended using artemisinin-based combination therapies, or ACTs, in areas where resistance to older drugs has emerged. Artemisinin drugs — which are formulated from extracts of an Asian herb used for thousands of years to treat fever — trigger chemical reactions that damage the parasites.

But if ACTs are to remain effective, they need to be used strategically, says Dave Smith, associate director for disease ecology at UF's Emerging Pathogens Institute and an expert in malaria modeling studies.

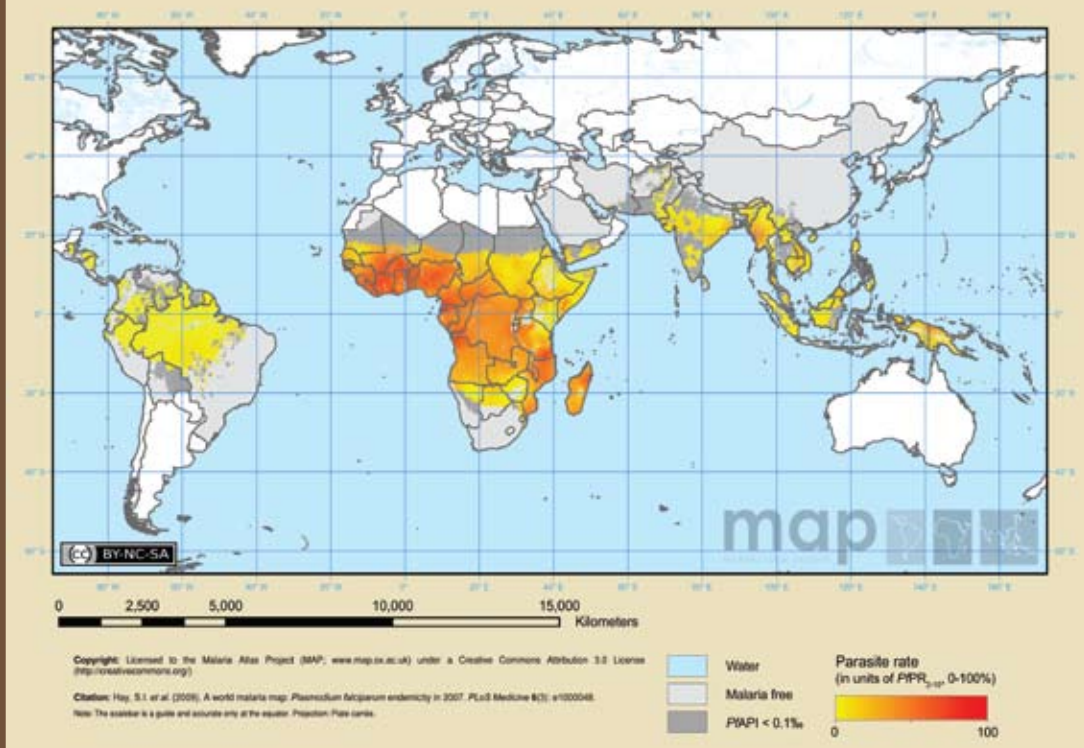
In a study published in the *Proceedings of the National Academy of Sciences* in 2008, Smith and several colleagues modeled rates at which Plasmodium parasites evolve resistance to first-, second- and third-line malaria drugs. Their statistical model predicted the effectiveness and clinical outcomes of using single or multiple first-line drug therapies to treat malaria within a population over a 20-year period.

His team's results show that when clinicians prescribe a combination of ACTs to patients it reduces the total clinical cases and number of failed treatments.

"Artemisinins have been combined with other drugs to make them last longer," Smith says, "but using two or more artemisinin combination therapies — a combination of combinations — works better than drug cycling."

These combination therapies slow the rate at which drug-resistant genes spread within the Plasmodium parasites, whereas using individual drugs in succession accelerates the

WORLDWIDE RISK OF *P. FALCIPARUM* MALARIA



While people living in the white and gray areas indicated on this map have little risk of contracting malaria, the risk increases as colors warm from yellow to red.

rate at which resistance evolves, according to Smith's models. In fact, prescribing drugs in succession leads to a decline in their efficacy in as little as three and a half years, Smith says. But when several anti-malarial drugs are combined in equal proportion within a population, a decline in efficacy does not occur for nearly a decade.

The implications of these findings to policymakers and doctors are significant. Most countries currently use one or two drugs to treat patients with malaria, and when those drugs lose their efficacy, they switch to a new drug.

Smith hopes the model will illustrate the importance of combining drug therapies in order to tilt the evolutionary clock in our favor.

"We don't have anything in the pipeline after ACTs, and it's basically just a matter of time until drug resistance evolves and artemisinin also fails," Smith says. "So the question becomes how do we keep ACTs in our arsenal for as long as effectively possible?"

Simon Levin, a Princeton University professor of theoretical ecology and the National Academy of Sciences member who edited Smith's *PNAS* paper, believes the study's recommendations deserve serious consideration.

"Their demonstration that multiple first-line therapies produce the best results is an important conclusion that should influence practice," Levin says.

But to eradicate malaria completely from a region or country, combination drug therapies need to occur in conjunction with other efforts during the narrow window of time

Malaria is like an invisible anchor dragging down human potential, drowning education and economic growth. It is both a cause and an effect of poverty worldwide.

Prescribing drugs in succession leads to a decline in their efficacy in as little as three and a half years. But when several anti-malarial drugs are combined in equal proportion within a population, a decline in efficacy does not occur for nearly a decade.

— Dave Smith

MALARIA QUICK FACTS

- Malaria is primarily caused by four species of parasites in the genus Plasmodium: *P. falciparum*, *P. vivax*, *P. ovae* and *P. malariae*.
- *P. falciparum* causes the most deadly form of malaria.
- *P. vivax* causes most repeat-cases of malaria.
- Wiping out mosquitoes is not necessary to eliminate or eradicate malaria, but disrupting the parasite's life cycle is crucial.
- Insect-treated bed nets are a useful control measure in regions where mosquitoes bite at night; insecticide spraying of breeding sites is a useful control measure in regions where mosquitoes bite during the day.

"Malaria kills nearly 1 million children per year, but companies and governments have invested very little in new drugs and vaccines because the disease has been eliminated from rich countries."
— Bill Gates

Gates Foundation

when the drug's efficacy is still strong — because while medications are one piece of the puzzle, malaria is a complicated, multi-faceted disease.

COORDINATION PROBLEM

The fight against malaria is not relegated to medicine and clinics alone. Politics, money, community perseverance, a responsive health-care system and a well-planned control strategy are also necessary.

"Eliminating malaria is not a drug problem," Smith says. "Eliminating malaria is a coordination problem, because there are so many inter-connected factors."

In late 2007, the Bill and Melinda Gates Foundation announced an initiative to eliminate malaria from large swaths of the globe.

"Malaria kills nearly 1 million children per year, but companies and governments have invested very little in new drugs and vaccines because the disease has been eliminated from rich countries," Bill Gates wrote in his 2009 foundation letter.

In 1945, only nine countries had eradicated malaria. Today, that number has reached 108, including the United States. The Malaria Atlas Project — a multi-national effort to map malaria — estimates that eliminating malaria is feasible for another 39 countries that are home to nearly 2.2 billion people. Both Smith and colleague Andy Tatem, a geographer with UF's Emerging Pathogens Institute, have collaborated with MAP.

"One level of the mapping project is describing where malaria is and where it isn't," Smith says. "The other level is describing malaria transmission intensity within the ranges where it is. We are slowly shrinking the malaria map, but there is still a long way to go."

Identifying which countries should be targeted for elimination first is the focus of a second project, led by Smith and funded at $1.5 million by the Bill and Melinda Gates Foundation. For this project, Smith and Tatem are using their collective modeling and mapping expertise to devise a new set of tools to help policymakers in these "elimination" countries decide whether to "go the extra mile" and eliminate malaria within their borders.

Smith also collaborates with the Malaria Elimination Group, which released demographic data in June 2009 about the 39 elimination countries. All lay at the margins of zones where malaria is endemic, which means they likely have a steady flow of infected people and mosquitoes crossing their borders.

But, all of these countries also have significant areas without malaria. And 28 of the 39 are wealthy enough that they should be able to fund their own elimination efforts. These factors, and many more, led the MEG researchers to assert that these countries were excellent candidates for elimination.

The lingering question for, say, a health minister in Costa Rica or the Solomon Islands is, "How?"

Jeff Gage

Dave Smith (left) and Andy Tatem are using their collective modeling and mapping expertise to devise a new set of tools to help policymakers in these "elimination" countries decide whether to "go the extra mile" and eliminate malaria within their borders.

"The aim of the Gates grant is basically to try to bring together all the little individual models out there and make a broader one that can then convert data from the field into predictions of what will happen in the future," Tatem says.

Smith and Tatem began the project by identifying a country to use as a case study.

Most malaria models today rely on data from the prevalence of parasites in humans within a population (the parasite rate) and the rate at which people are infected within a population (the transmission rate). But what Smith and Tatem are setting out to do is much more comprehensive.

"The ultimate aim will be to produce a more user-friendly, online interface where people can input numbers for their region and visualize what they can expect to happen if they were to spend a bit more money on control in certain areas," Tatem says.

Government officials could log onto a Web site and tweak a host of variables until they find an optimal strategy with a reasonable time table that they can sustainably fund.

But to create this interface, Smith and Tatem need to distill a lot of math and a lot of maps, scouring and adapting existing data sets and coming up with a few new ones.

They have begun their modeling in Zanzibar, a group of islands off the east African coast of Tanzania.

By mining nearly 21 million cell phone records from 700,000 individuals (nearly 75 percent of the islands' population) along with air and ferry passenger data, they are creating a model of human movement into and out of Zanzibar, which they can then combine with parasite rate and entomological data to model Zanzibar's expected rates of malaria coming onto the islands from the mainland.

They are also building models of outbreak rates, which capture the risk of an imported case being transmitted to someone else, given the local control measures in place. Devising the importation rates and outbreak rates is something entirely new, and will add several powerful layers to existing measures.

"Zanzibar is a good place for us to start because they had about a 50-percent *P. falciparum* parasite rate about 15 years ago," Tatem says. "But an uptick in monetary resources from tourism, and political will, allowed them to lower their infection rate to nearly 1 percent. A strong control program and socio-economic changes drove the downward trend. When we get the model for Zanzibar, we will widen it to explain and predict countries in Central America and the Pacific Islands."

Creating models is an iterative process of testing reality against what you think you know, Smith says.

"But when it comes down to it, modeling is a true science," Smith says. "To come up with a model that accurately describes reality and has predictive power is a very scientific process."

Their model's success hinges not only on accurately identifying all the parameters but also on the commitment of local authorities and funding availability for elimination measures. Levin, the Princeton University professor, says that if these two elements are in place then he sees no obstacles to the team creating a useful model. But it wouldn't be easy.

"Elimination of malaria from any country is a massive undertaking, and the bigger and less insular the country, the harder the challenge," Levin says. "Given the number of deaths we experience each year from malaria, we have no alternative but to try, however."

In his own childhood, Woldu also had no alternative but to try. And despite his brush with death due to malaria — or perhaps because of it — he is pursuing an educational path that he hopes will contribute to a solution.

"I feel emotionally attached to the cause of malaria eradication," he says. "I am a malaria survivor."

Dave Smith
Associate Professor, Department of Biology
(352) 392-0090
davesmith@ufl.edu

Andy Tatem
Assistant Professor, Department of Geography
(352) 392-0494
atatem@ufl.edu