

MALARIA WARS

Can malaria be eliminated from the Mekong region before multiple-drug resistance makes it untreatable?

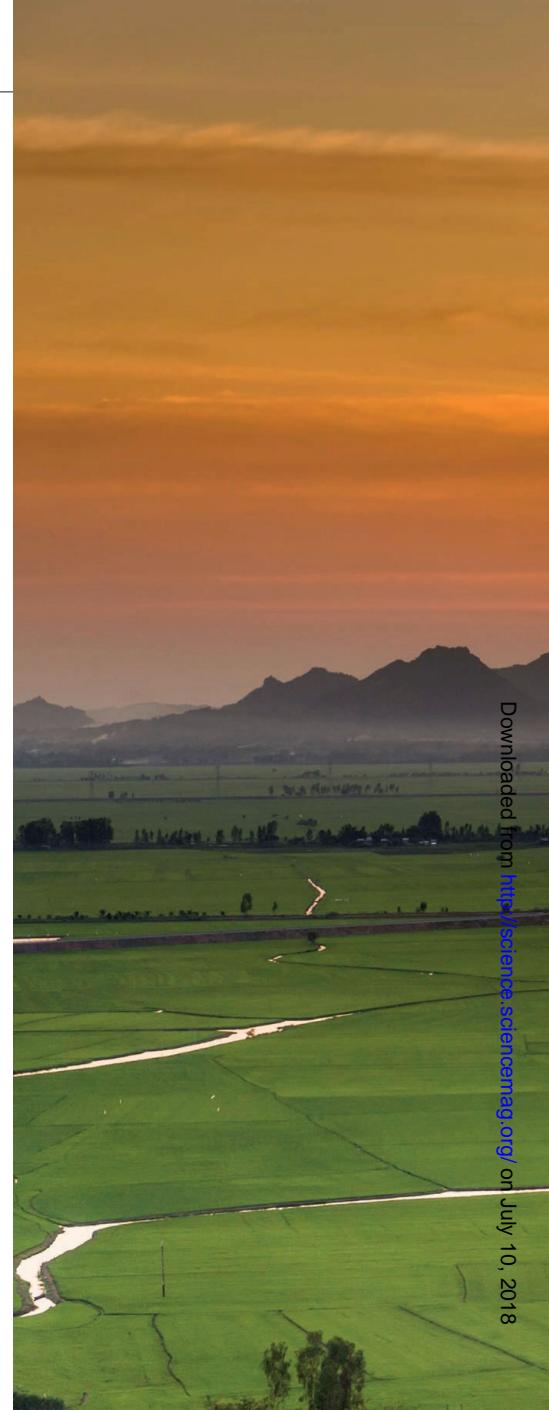
By Leslie Roberts, in Pailin, Cambodia



No one knows exactly why resistance to malaria drugs always emerges first in this remote western province of Cambodia, nestled in the Cardamom Mountains. “The reasons are as much social as biological,” says malariologist Tom Peto, who is here in this dusty, unremarkable-looking town battling the latest threat to global malaria control: multiple drug-resistant (MDR) malaria.

Rubies certainly play a role. For decades, the gems and the once-lush stands of teak have lured people here, along the Thai border, where the forests and jungle are thick with mosquitoes that transmit the malaria

parasite. Then there’s Pailin’s tragic history as the last stronghold of the Khmer Rouge, which left the population shattered, isolated, uneducated, suspicious, and devastatingly poor. Health care is abysmal; there is a surfeit of fake or lousy drugs—and a long-standing practice of not taking them all. Paradoxically, the low malaria transmission contributes, and there is something about the parasite circulating here, maybe its genetics, that helps it mutate fast and ensures that the hardiest, most resistant survive. Or maybe, says Peto, who is part of the Mahidol Oxford Tropical Medicine Research Unit, better known as MORU, in Bangkok, “it’s because we look here first.”



Whatever the reason, this is where it starts. Resistance to chloroquine surfaced here in the 1950s before sweeping through the wider Mekong region and then into India and Africa, causing millions of deaths. Sulfadoxine-pyrimethamine went next, in the 1960s. Mefloquine failed in the 1970s.

Then in late 2008 and 2009 came reports that rocked the malaria world: Artemisinin, the so-called wonder drug that has sent malaria deaths plummeting across the globe over the past decade, was losing its effectiveness here. That sparked global alarm and prompted an ultimately futile emergency plan to contain resistance in Cambodia before the last, best drug was lost.



The Mekong delta at Chau Doc, Vietnam, one of six countries in the region threatened by drug-resistant malaria. A Khmer family in Cambodia (left) being screened soon after artemisinin-resistant malaria was first discovered.

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Now, Pailin is the epicenter of what some say is the greatest threat yet to malaria control: the deadliest malaria parasite, *Plasmodium falciparum*, has become resistant not only to artemisinin, but to a key partner drug, piperaquine, or PPQ, that is used in combination with artemisinin and is critical to its success. The emergence of this MDR parasite is raising the specter of untreatable malaria in the Mekong region and perhaps beyond.

PPQ resistance is a “disaster,” says Peto’s boss, Arjen Dondorp, who is the head of malaria research at MORU. It’s now confined to Cambodia, but “I’m afraid it is just a matter of time until it will reach the other countries in the region,” he says. That’s

the “nightmare scenario,” adds François Nosten, who runs the Mahidol group’s Shoklo Malaria Research Unit (SMRU) in Mae Sot, Thailand, along the border with Myanmar. “If that happens,” he says, “that’s it, we are done, and malaria will come back.”

The only way to avert that crisis, says a growing chorus of malaria researchers, international agencies, and donors, is to wipe out all malaria from the entire Greater Mekong subregion—five countries and a southwestern spit of China bound together by the world’s 12th longest river. The World Health Organization (WHO), the Global Fund, and other international agencies and donors are rallying around an ambitious

plan to do just that by 2030. The aim is to ensure that every last parasite is gone from the region, focusing first on *P. falciparum* because of the urgent threat of multiple-drug resistance. The Bill & Melinda Gates Foundation (BMGF) is lobbying hard, and the five countries, some better known for their corruption than their cooperation, are on board, on paper at least.

But it is not at all clear they can pull it off, or whether it is already too late. Malaria has been eliminated before, in the “easy” places such as the southern United States, Europe, and Turkey, and similar efforts are underway elsewhere. But no one has ever eliminated the disease in a place as socially and

epidemiologically complex as the Mekong.

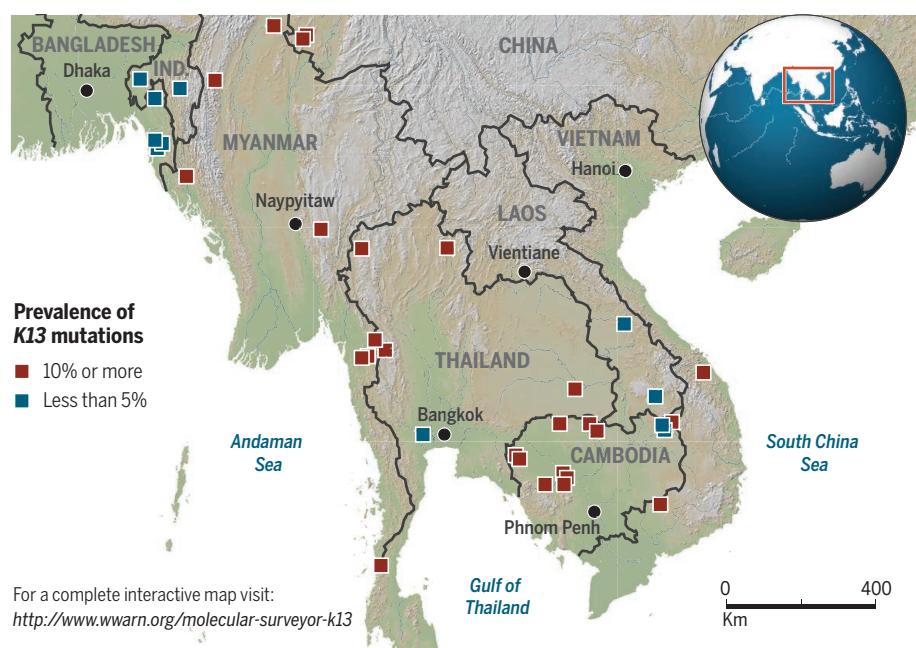
The science is uncertain, the data imperfect, the tools far too crude. Researchers here, many with outsized personalities and egos to match, argue over everything from the strength of the evidence to the ethics of clinical trials—even to the magnitude of the MDR malaria disaster: Is it a category 4 or category 5? Is there enough time for careful studies to see what really works, or is the situation so dire that you must throw largely untested strategies at it, whatever the risks, and hope something sticks?

All the while they face one disquieting conundrum: how to eliminate a disease when there's no vaccine, the very drugs you need are failing, and the parasite is evolving faster than people can keep up.

MALARIA IS A DIFFERENT BEAST in the Mekong than it is in Africa, where it kills roughly 500,000 children a year. The main vector across Africa, *Anopheles gambiae*, is so ubiquitous that people can be exposed to thousands of infectious bites a year, and transmission is the highest in the world.

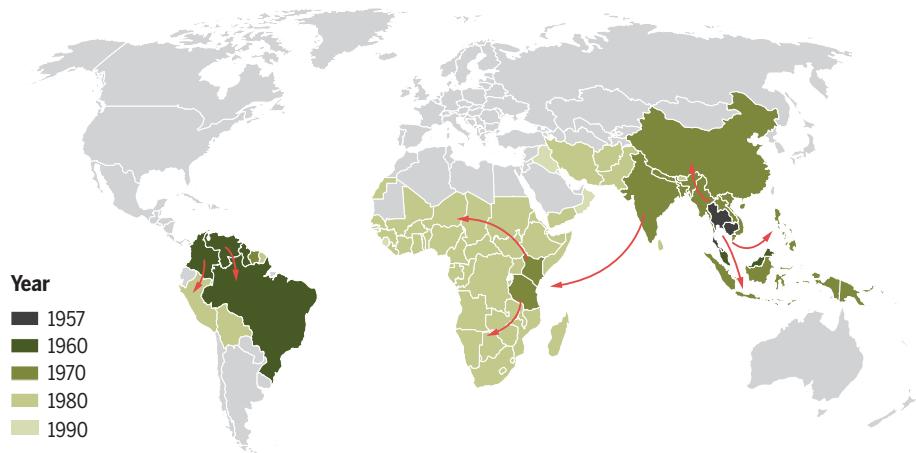
A growing threat

Artemisinin-resistant parasites are now widespread in the Mekong. Resistance has been linked to mutations in the parasites' *K13* gene; this map shows the percentage of samples with *K13* mutations reported since 2010.



The path of chloroquine resistance

Malaria parasites resistant to chloroquine swept out of the Mekong region and spread around the world. So far, artemisinin resistance hasn't followed that path, and researchers are debating the likelihood it will.



In the Mekong, by contrast, malaria is a disease of the edges, and there are fewer than 200 deaths a year. The expansive lowlands are largely malaria-free, but as the rice paddies give way to hills and then mountains, the risk rises, and malaria holds sway in the shrinking forest fringe where the mosquito vectors thrive. Its victims, too, are literally off the map: people who work in the forest—largely poor, itinerant loggers, miners, or migrant workers, and marginalized ethnic minorities who live along the messy international borders. The majority of cases occur in adult men, most in Myanmar, which bears the greatest malaria burden of any country in the Greater Mekong.

It's not the sheer toll of malaria here, but the uncanny ability of the parasite population to mutate and acquire resistance to any drug thrown at it, that has put the Mekong front and center in the global fight against malaria.

The roots of the problem go back decades and are mired in the misuse of malaria drugs. Many of those who streamed into the forests decades ago in search of riches, or were forced from the cities to the countryside by the Khmer Rouge, came from areas without malaria, so they had no natural immunity and were especially vulnerable. When they got sick, people often treated themselves with whatever drugs they could get by the bagful from the local shopkeeper, which, if they were lucky, might contain an antimalarial at some unspecified dose. Or people would take a few tablets of chloroquine for protection before entering the forest and then pocket the rest. Either way, taking antimalarials at low doses, for a short period, is a surefire way to generate resistance.

Artemisinin was especially easy to misuse. The drug was available here as a monotherapy, not a combination, long before the rest of the region, thanks to the Khmer Rouge's close ties to China, where the drug was developed. (The Chinese scientists who rediscovered the remarkable malaria-fighting properties of this ancient herbal remedy won the Nobel Prize in Medicine last year.) What sets artemisinin apart is its speed of action—it can clear almost all malaria parasites from the bloodstream in just 48 hours, so fast that people often don't finish the course, enabling the parasite to evolve under low drug pressure.

"Artemisinin is quite simply the best drug we've ever had," says Nicholas White, a U.K. malariologist who presides over MORU's far-flung enterprise from Bangkok and who seems to have mentored just about everyone who works in malaria in Southeast Asia.

Invariably called "brilliant" and usually "hard-headed," White helped bring artemis-



inin out of obscurity in the 1990s. His group did pivotal clinical trials of artemisinin and its derivatives, paired with a partner drug that mops up residual parasites. These so-called artemisinin combination therapies (ACTs)—there are six combinations—are designed to stave off resistance, in much the same way that combinations curb HIV's ability to develop resistance to any single drug. Then White and his colleagues began a bruising, decadelong battle to get WHO to endorse ACTs as the first-line therapy for malaria worldwide.

THE FIRST SIGNS OF TROUBLE appeared around 2007. Dondorp's MORU group was working here when it found artemisinin took twice as long to clear parasites from the bloodstream of malaria patients there as it did in Wang Pha, Thailand, where the drug had only recently been introduced. A group from the Armed Forces Research Institute of Medical Science (AFRIMS) in Bangkok, working nearby, found similar, disturbing indications. Dondorp, Nosten, White, and a who's who of malaria researchers from across the region sounded the alarm in a 2009 paper in *The New England Journal of Medicine*. Without immediate action, they said, artemisinin resistance would fol-

low the arc of chloroquine resistance, race westward through Myanmar into Bangladesh and India, and ultimately into Africa, destroying all the gains of the past decade.

From the outset, a few scientists questioned whether what the group described was really drug resistance or should instead be called "slow clearance" of the parasite—and some even accused the Mahidol group of crying wolf (see box, p. 403). After all, unlike chloroquine, which fails to kill resistant parasites, artemisinin still worked, just more slowly.

Still, it was a significant threat, and in 2011 WHO and the Roll Back Malaria Partnership launched what became an "emergency response" to artemisinin resistance in the Mekong. The strategy was containment: Build a firewall around areas of drug resistance by ramping up control measures, such as bednets, rapid diagnostic tests, and ACTs.

Despite the plan, artemisinin resistance spread. It has yet to sweep into Africa, as feared, and there is some debate over whether it will. But it has now been found in five countries in the Mekong. Some blame a bumbling global response and corrupt and inefficient governments ill-equipped to handle the bolus of money that came their way; others point to new

Migrant workers, like these in Cambodia, are hard to reach in a major effort to wipe out malaria in the Greater Mekong subregion.

genetic evidence that shows that, in addition to spreading, artemisinin resistance is popping up independently in multiple spots across the region, dooming any attempt to build a firewall.

It was simply too late, adds Didier Ménard, who directs the malaria molecular epidemiology unit at the Pasteur Institute in Phnom Penh. Last year, his group found the hotly sought molecular marker of artemisinin resistance, the Kelch 13 or *K13* gene, enabling researchers to map its extent and spread in exquisite detail. Those retrospective analyses suggest that as early as 2001–2002, 50% of the parasites here were already resistant to artemisinin—there's no way they could be stuffed back into the bottle.

Whatever the reason, the failure to rein in artemisinin resistance set the stage for the current crisis: MDR malaria.

NO ONE SHOULD HAVE been surprised when resistance to the partner drug exploded in Cambodia. "We predicted it," says Dondorp, who is known as the calm, measured voice of the MORU group but

who is clearly exasperated. When the artemisinin component of an ACT doesn't clear the parasite quickly, Dondorp explains, the weaker and slower-acting companion drug must carry an extra load. It's essentially like monotherapy.

The first hints again came from around Pailin, where the ACT of choice is a combination of dihydroartemisinin, an artemisinin derivative, and PPQ, known as DHA-PPQ. Scattered reports started coming in that people on DHA-PPQ were not being cured. "You treat the sick, and 3 weeks later they are sick again, and they keep getting sick," Ménard says. This was not just the slow clearance seen so far with artemisinin resistance—it was actual treatment failure.

Two teams nailed the connection, one led by Ménard, the other by David Saunders of AFRIMS. Both groups confirmed in genetic, cell, and clinical studies that, for the first time, the parasite had developed resistance to both drugs used in an ACT. (Rick Fairhurst's group at the U.S. National Institutes of Health in Bethesda, Maryland, provided even more evidence in January of this year.)

The MDR parasites are spreading at a frightening rate. "Overall in Cambodia, the DHA-PPQ failure rate is 50%," Ménard says. "In Pailin, it is 70%, probably higher." And it bodes poorly for other ACTs, Nosten says. "If we lose one partner drug, any partner drug, they are all going to fall like dominoes very quickly."

There are a few stopgap measures—if countries can be nimble. After years on the shelf, mefloquine is effective again in Cambodia, and WHO has recommended that the country switch to a combination of artesunate and mefloquine. But it's a short-term fix: "Mefloquine will fail in 6 months," Ménard predicts. "It is like a race. The problem here is the parasite is working fast, so we have to also work fast." MORU is testing triple ACTs—a combination of three instead of two drugs—to see whether they can outwit resistance, but the results aren't in yet.

"I think it is one of our few choices to go for elimination," Dondorp says. "The longer we wait, or the longer we are not successful, the more difficult it will get to treat malaria—and thus to eliminate it."

At its September 2014 meeting, the influential Malaria Policy Advisory Committee at WHO endorsed an aggressive plan for

malaria elimination in the Mekong, and the World Health Assembly signed off on it in May 2015. The goal is to rid the region of *P. falciparum* by 2025 and its milder relative *P. vivax* by 2030, for an estimated cost of \$3 billion. For Cambodia, the birthplace of drug-resistant malaria, the target date for *P. falciparum* is even sooner—less than 4 years away.

As Frank Smithuis, an irrepressible Dutch malariologist who works with MORU and runs his own nongovernmental organization out of one of Yangon, Myanmar's crumbling buildings, puts it: "Then we had better hurry."

ELIMINATION IS MALARIA CONTROL on steroids. "In malaria control, what we are trying to do is detect people with malaria and treat them, prevent people from dying

ers tend to spend several nights at a time in the forest, where transmission occurs, sleeping outside in hammocks. Many don't know that mosquitoes transmit malaria, and even if they do, it is too hot and muggy to don long-sleeved shirts and pants. The main vectors, *A. dirus* and *A. minimus*, bite outdoors, so in contrast to Africa, bednets are of limited use. "How do you deal with a vector that doesn't fit the paradigm of *Anopheles*?" asks Tom Kanyok, BMGF's point person for malaria elimination in the Mekong.

The biggest challenge to elimination in the Mekong, however, is the "asymptomatic reservoir"—people who carry the parasite without any symptoms but are, to some unknown extent, still involved in disease transmission. Confounding matters, they



Multiple drug-resistant malaria was first discovered in this poor, remote region of Pailin, Cambodia.

and being sick," Nosten explains. "In elimination we are doing that plus eliminating the parasite. We are going after the malaria parasite everywhere we can."

But in the Mekong, the parasite is very hard to find. "The people you most want to reach in malaria are the most difficult to reach," Peto says. They live in isolated villages days from any town on foot, or hours away by jeep or motorbike, down rutted dirt roads that become impassable in the monsoon rains. Some are in rebel-held areas off-limits to government health workers or too dangerous for aid groups to enter. No maps show the routes migrant workers take, and those who are working illegally don't want to be found.

Rubber plantation workers and oth-

er harbor parasites at such low levels they can be detected only with the highly sensitive polymerase chain reaction (PCR); rapid diagnostic tests, and even microscopy, will miss them.

In Africa, where transmission is high, the phenomenon is well-known—many people have built up enough immunity that they can carry the parasite without getting sick. But the common wisdom in the Mekong and other low-transmission areas has been that "people here get bitten by an infected mosquito, they get sick, end of story," Nosten explains. "We saw the extent of it and said, 'Wow,'" Dondorp recalls.

Everyone agrees the asymptomatic reservoir must be drained to have any chance of

eliminating malaria. But consensus crumbles on how to do that, and things can get downright nasty.

"In malaria science, a lot of people are religiously for or against things, and I think religion and science don't mix very well," Smithuis says.

In the malaria world, religion is often code for mass drug administration, or MDA, which involves giving everyone in a region antimalarial drugs, whether or not they are sick. And its high priests, according to the critics, are Nosten, White, *et al.* They are accused of dogmatically pushing a risky strategy with little evidence it works. (MDA has long been used for lymphatic filariasis and other parasitic diseases but has a checkered history with malaria.)

For the past couple of years, Nosten has been conducting a pilot study of MDA in four remote villages along the Thai/Myanmar border, where he has worked with refugees from Myanmar's beleaguered Karen ethnic minority for the past 30 years. With support from the Wellcome Trust, the Global Fund, and BMGF, the team identifies villages that are "hot spots" of transmission and then gives everyone the standard 3-day course of DHA-PPQ and one dose of primaquine, a drug that targets another stage of the parasite's life cycle, each month for 3 months.

Nosten's team is still analyzing the data, but their first impression is that MDA is safe, well-tolerated, largely acceptable—and sometimes remarkably successful. "I can tell you after one-and-a-half years of trying very hard, we are eliminating malaria, and

it's going down very fast," Nosten says. But, he concedes, MDA is extremely time- and labor-intensive, especially because it entails convincing healthy people to take drugs and have their blood drawn repeatedly (see p. 407). The SMRU group is now scaling up and has "mapped" the parasite loads in 1200 villages in Karen state and conducted MDAs in 34.

WHO has just given MDA its blessing in some circumstances in the Mekong, but the strategy remains highly controversial.

You treat the sick, and 3 weeks later they are sick again, and they keep getting sick.

Didier Ménard, Pasteur Institute

Ménard says there is a very real risk MDA could backfire. "Are we sure we will kill all the parasites and not select resistant ones? If you want to select drug-resistant parasites, maybe this is the best strategy," he says. MDR malaria "is an emergency, and we need to act, but I am not sure we need MDA. I am not against it, but we need to conduct studies, and with the results we will make decisions." Malariaologist Chris Plowe, who heads the Institute for Global Health at the University of Maryland School of Medicine in Baltimore, says his own work in Myanmar suggests that the size of the

asymptomatic reservoir varies enormously, even in close-by villages, and that means a very targeted approach is in order. "There is no 'cookie-cutter approach,'" he contends.

Often, it is not so much Nosten and White's message that riles people, but the stridency with which they push it. "François has a big mouth," his close colleague Dondorp says. "But he also has a big heart."

For now, Ménard thinks a better strategy is to develop tools that approach the sensitivity of PCR but can be deployed in the field. With those in hand, it would be possible to test everyone for asymptomatic infection and then treat just those who are infected. Such work is already well underway in his lab and others. Plowe's group, for instance, is experimenting with collecting blood spots on filter paper with a simple finger stick and then analyzing those with ultrasensitive PCR in the lab. BMGF is funding research to develop more sensitive rapid diagnostic tests. And the race is on to find a molecular marker for PPQ resistance, the equivalent of the *K13* gene. "This is the beginning of the story," says Ménard, who believes the science is moving so fast that there is time to get it right.

"We have wasted so much time we don't have more time to waste," Nosten moans in response. "We still have to learn about the submicroscopic infection, but we don't want to wait until we understand everything about it before eliminating it. It's a catch-22 thing. People are saying there is no evidence. But if you don't do this [MDA] on a large scale to see what it does, then you don't get the evidence."



Rubber workers on the front lines

To tap a rubber tree, you have to cut the bark just so, at an angle, running halfway around the tree, and not too deep or you will kill it. Immediately the viscous, white liquid begins to ooze, collecting slowly in a small wooden bowl tied to the tree that looks like a coconut shell.

Srey Kheng, the manager of Try Pheap plantation in Kampong Thom province, right in the middle of Cambodia, is demonstrating with his special,

Tha Sitheth was 13 years old when he got malaria while working on a rubber plantation.

ebony-handled chisel—the actual tapping is done late at night with far cruder implements.

The young men who perform this task have some of the highest rates of malaria in the country—and they and their counterparts throughout the Greater Mekong subregion are one of the greatest challenges to the new plan to eliminate malaria there (see main story, p. 398). Plantation workers are some of the hardest people to reach, moving frequently to follow jobs and living in remote areas in squalid conditions. They work and sleep outside with no protection

Besides, White asks, what else is on the table? "The only other option I've heard is to do nothing." Except, of course, have more meetings "with heartfelt pleas for how hard this is and all that bureaucratic language to do with strengthening and capacity building and transformative and god knows what else—a lot of stupid buzzwords. The Belgians call it fried air."

Even if the researchers could agree on the best way forward, the plan could still be hobbled by bureaucratic inertia and corruption. More than 2 years after WHO recommended Cambodia switch from DHA-PPQ to an artesunate-mefloquine combination, the drugs are just arriving.

Transparency International ranks Cambodia and Myanmar among the most corrupt countries in the world. Recently, the Global Fund froze millions of dollars intended to pay malaria workers while it investigated travel expenses and other irregularities in the Cambodian national malaria control program. (The dispute was finally resolved and money released in December 2015.)

"It is too crazy for words," Smithuis says. "If you are a malaria parasite and you want to stay ahead of drugs and you are looking at all this you think, 'Yo, this is exactly what I need. I need a bunch of people falling all over each other with so much envy and bickering and so little action.' The parasite must be laughing." ■

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PHOTO: OPEN SOCIETY FOUNDATION

from the abundant mosquitoes that transmit the disease. Repeatedly infected, they often forgo treatment or take substandard drugs or monotherapies, which fuel resistance to malaria drugs. Private plantation owners, sometimes engaged in illegal logging, are loath to let in outsiders, even to treat or prevent malaria.

But Try Pheap is taking part in a program run by Population Services Khmer (PSK), part of the non-governmental organization (NGO) Population Services International (PSI), to bring rapid malaria diagnosis and early treatment to the plantations. "NGOs just don't waltz in," explains Abigail Pratt,

a technical adviser to PSI's malaria and child survival program in Phnom Penh. Persuading the owners "is a delicate dance," she says, assuring them that PSI is interested only in improving health and will not report any violations such as illegal logging or underage workers.

The community on the plantation has elected a local malaria worker—in this case, the manager, Kheng, who is supplied with free drugs and trained to treat only those with confirmed cases of malaria. When a tapper or family member develops a fever, Kheng uses a rapid diagnostic test that shows whether someone is infected with one of the two

malaria parasites circulating here, *Plasmodium vivax* or *P. falciparum*, or both. Almost a third of the fevers tested on this plantation are malaria, Pratt says. There were five cases of *P. vivax*, the milder form of the disease, in the past 8 months.

One worker recently had malaria three times, showing up sick again 2 months after treatment. It could be drug-resistant malaria or new infections, but most likely, he felt better after a couple days and didn't finish his medicine.

As we talk, the workers, who look considerably younger than the legal age of 20, are running and punching each other and peeking out at the

foreigners from behind the dizzyingly straight rows of trees. They finally come out to pose for a photograph.

At first PSK offered just malaria services, but few people came for a fever alone, says Mak Sarath, who directs the malaria program in Phnom Penh. Now, PSK is moving into integrated health care, offering diarrhea treatment kits, condoms, and deworming tablets. Supplies are an issue, however. Right now Kheng is out of diarrhea kits and has just three courses of malaria drugs left.

Since 2013, PSK has signed up 118 plantations in Cambodia. They have about 500 to go. —Leslie Roberts

THE UNLIKELY DIPLOMAT

Myaing Myaing Nyunt fled Myanmar in 1988; now she is back, forging alliances against malaria

By Leslie Roberts

On a blistering hot October day last year, the air thick with impending rain, Myaing Myaing Nyunt and I lurch in a wooden oxcart toward Sa-ka-pin, a small village in the rich agricultural lowlands about 20 kilometers northeast of Mandalay, Myanmar. We grip the splintery sides of the cart as the animals plunge chest deep in the muck; when they swish their tails, mud splatters everywhere. It's 1 month before Myanmar's historic election, and with us in the back is a young doctor with "NLD," the initials of Aung San Suu Kyi's opposition party, the National League for Democracy, shaved into



Myaing Myaing Nyunt

his close-cropped hair. A second cart carrying township medical officers follows close behind. We stop at a wide, shallow river, where a man in a dugout canoe ferries us across. Two more carts are waiting for us.

Nyunt, a malariologist at the University of Maryland School of Medicine (UMD) in Baltimore, is visiting Sa-ka-pin to assess the

extent of one of the biggest problems facing an ambitious campaign to wipe out malaria from the Mekong region (see main story, p. 398): the number of people infected with malaria who have no symptoms. It's part of a unique collaboration led by Nyunt and her husband, molecular epidemiologist and malariologist Chris Plowe, who heads the Institute for Global Health

Science

Malaria wars

Leslie Roberts

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