The Unrelenting Specter of Drug-Resistant Malaria

Every time scientists think they've controlled malaria, drug resistance pops up in Southeast Asia. What will it take to stop a deadly global comeback of the disease?

A view of the Thai-Myanmar border. Hidden in the trees in the distance is the Moei river marking the official boundary between Thailand and Myanmar (formerly known as Burma). Photographs by Ian Teh

For the last seventy years, malaria could have starred in *Groundhog Day*. Despite scientists' best efforts to fight the ancient disease—which today kills over 400,000 people a year—the parasite has remained irritatingly defiant, acting in some places like a recurring villain.

After World War 2 ended, malaria was prevalent throughout the world, its spread no doubt aided by the war. At the time, the recently developed medicine chloroquine was hailed as a key to getting rid of it for good. Together with DDT to kill parasite-carrying mosquitos, the World Health Organization was convinced they had the tools to see the end of the disease.

In some places, the WHO's plan worked. The United States was declared malaria-free in 1951, and much of Europe soon after that.

The same was not true in Southeast Asia. In 1957, there were reports that chloroquine stopped working in villages on the Thai-Cambodia border; a few parasites had somehow grown resistant to the drug. The resistant strain grew more widespread, and by the 1970s, it had hopped over the Indian Ocean and Arabian Sea to coastal areas in eastern Africa. Chloroquine resistance then moved inland in Africa, where it claimed millions of lives. (Separately, a resistant strain originated in South America, which caused its own harm half a planet away.)

Luckily, scientists had been developing other drugs to cure malaria, notably mefloquine, and they began treating patients with that instead. But within a few years, the same thing happened. There were reports from Southeast Asia of mefloquine resistance, and within a few years, resistant strains traveled through India and ended up in Africa.

"Mefloquine was introduced, and we lost that in a few years," said Arjen Dondorp, Deputy Director of the Mahidol-Oxford Research Unit (MORU), where he leads malaria research in Bangkok. "We were saved by this new group of drugs, the artemisinins. These are wonderful drugs—they're very potent and kill all stages of parasites."

But today, the specter of drug resistance has appeared once again. A few years ago, there were reports that artemisinin was no longer effective in some parts of the Greater Mekong Subregion (an economic area that comprises Cambodia, Laos, Myanmar, Thailand, Vietnam, and two Chinese provinces).

> *The strange thing is that, with the exception of Myanmar—formerly known as Burma—malaria isn't very widespread*

in that region anymore. Last year, there were only a few hundred cases reported from Southeast Asia.

By contrast, people in countries like Burundi and Zambia are significantly more likely to contract malaria. But ironically, there's a lower likelihood of drug resistance developing in sub-Saharan Africa, where over 90 percent of today's malaria cases are found.

"Resistance always starts in low transmission areas like [the Greater Mekong]," said Dondorp. There are a few theories for this—counterfeit or substandard drugs, lack of acquired immunity, poor drug adherence—but no definitive reason why.

In response, scientists and health workers have stepped up their game. They're no longer looking to control malaria in Southeast Asia, but stop it in its tracks. They want to eliminate the deadliest malaria strain, *P. falciparum*, in its "cradle of resistance" by 2030—ideally, before drug resistance to artemisinin reaches Africa at all, where it could wreak havoc once again.

Francois Nosten and SMRU staff on a tractor returning back to Thailand after a visit to the survey center in Htee Kaw Taw Village in Myanmar. These centers are part of SMRU's strategy to fight against the Malaria parasite's growing resistance to artemisinin. The plan is named the Targeted Malaria Elimination Project.

"**Our concern now is that history** is repeating itself," said Francois Nosten, Director of the Shoklo Malaria Research Unit in Thailand (which is a sister unit of MORU). "When I started 30 years ago, malaria was the number one cause of mortality and morbidity. We are eight years in and literally nothing has been done [to stop the new wave of malaria resistance in the Greater Mekong]. That story tells me that we, meaning the scientific community, have failed."

A big reason for the failure, according to Nosten and other malaria experts, is that it's not seen as an emergency in the region. In fact, malaria is considered to be eliminated in most of Thailand, Singapore, and Vietnam—which are now pouring resources into addressing growing health threats like diabetes and road traffic accidents.

Malaria is spread through female *Anopheles* mosquitos, which must first bite a person who has the parasite in their blood. (As a note, it's possible for someone to harbor the malaria parasite but not be actively sick). About a week later, the mosquito is "infective"—meaning it is primed to infect someone else.

Around the world, there are variations on how this story plays out. In the Greater Mekong, infective mosquitos prefer to live in the trees, as opposed to cities, and they typically infect people after the sun goes down. The places in Thailand where malaria remains a threat run along the borders of Myanmar, Cambodia, and Laos. In addition to being heavily forested, these are places that see a lot of migration, where national health services and politics sometimes collide, and where health providers can't always reach everyone at risk.

> *Importantly, the malaria "risk" in Southeast Asia is qualitatively different from global health emergencies like Zika or Ebola. In some Burmese villages, for example, it might mean that a few dozen people are infected with a hard-to-treat form of a familiar parasite.*

The low perceived risk of malaria has real implications on the fight against it. "We proposed additional budget from the government, because malaria elimination is in our strategy," said Nakorn Premsri, a director at the Department of Disease Control in the Thailand Ministry of Public Health. "The major hurdle is with the Ministry of Finance. We need to defend our activity to them."

To eliminate malaria throughout the Greater Mekong, Arjen Dondorp estimates that it would cost between three and four billion dollars over the next decade. Premsri's team has been lobbying for his Thai team to spend between $15–20 million a year, or 0.1% of the country's overall healthcare spending. But since malaria has been eliminated in Bangkok, and only exists in faraway border towns, government officials may have more reason to discount the threat.

This attitude, Dondorp believes, is echoed throughout the global health and pharmaceutical community. "Novartis has a philanthropic unit in Singapore that's working on this," he said, "but in general, Big Pharma isn't interested in malaria."

To Nosten, the fault lies equally with multilateral agencies like the World Health Organization. “With Ebola, people got scared, so the WHO woke up,” he said. “With malaria, it’s different. People aren’t worried. Malaria is resisting and progressing below the radar screen. Few people are sick. Those who are sick, we treat. And parasites are evolving.”

“We are in a race against the parasite,” he continued. “There are new drugs in the pipeline, but they won’t be ready for 5–6 years. We need to eliminate malaria before this window is shut down.”

> *Therein lies the rub. How do you get people in one part of the world to feel urgency about resistance to a disease that barely affects them today, and tomorrow might have stronger consequences elsewhere?*

“The devastation we saw with chloroquine resistance in Africa—we’re trying to avoid that again,” said Jimee Hwang, a medical epidemiologist in the malaria branch of the U.S. Centers for Disease Control and Prevention. “If we could prevent that in the future, it would be one of the biggest achievements. I honestly don’t know if we can eradicate malaria [worldwide], especially with our current tools, but if we could get it done in the Mekong, it would be a huge contribution in the overall fight.”

Thai staff working at the microbiology lab at the SMRU headquarters.

As with many things, the more effective responses to malaria are slow, plodding, and surprisingly simple.

In the western Thai city of Mae Sot, two researchers huddle over a large, color-coded map of eastern Myanmar. Every colored section contains dozens of dots, each of which represents an isolated village that rarely receives government services. Many dots signify ethnically Karen areas, which usually means Burmese government intervention would explicitly be unwelcome.

Map of villages along the Thai-Myanmar border. Photo courtesy of Suphak Nosten, SMRU.

These researchers are part of Francois Nosten's team at Shoklo Medical Research Unit (SMRU), one of many players working to eliminate malaria in Southeast Asia.

If not for SMRU, these villages wouldn't exist on a map at all; in 2009, the research unit realized it couldn't serve the region without understanding its physical boundaries, so it set off to make a map. Some villages are only accessible by long treks through a dense forest, and reaching others requires small fishing boats.

"In some of these places the government wasn't even allowed to do a census," recalled Daniel Parker, a postdoctoral geographer at SMRU. "If we said we were doing a census, it would make the government angry and villagers suspicious. We did it specifically under the impetus to build malaria services —and we didn't get very detailed information. If we stuck around and asked tough questions, they would get suspicious."

Over the last three decades, he added, the organization has worked extensively with the ethnic minorities in the region, and has made sure to hire people from the communities in which they work.

After mapping more than 1,200 villages on the Thai-Myanmar border, Parker's team set up "malaria posts" in 800 of them. A trusted person in the community is picked as a malaria post worker, which means that he/she tests villagers for malaria and treats them immediately. After an introductory training, the worker is given equipment for testing malaria, medicines, a few forms, and a smartphone to transmit data back to SMRU's office in Mae Sot. SMRU officers travel to the villages every few weeks to pick up blood samples, which they test for drug resistance.

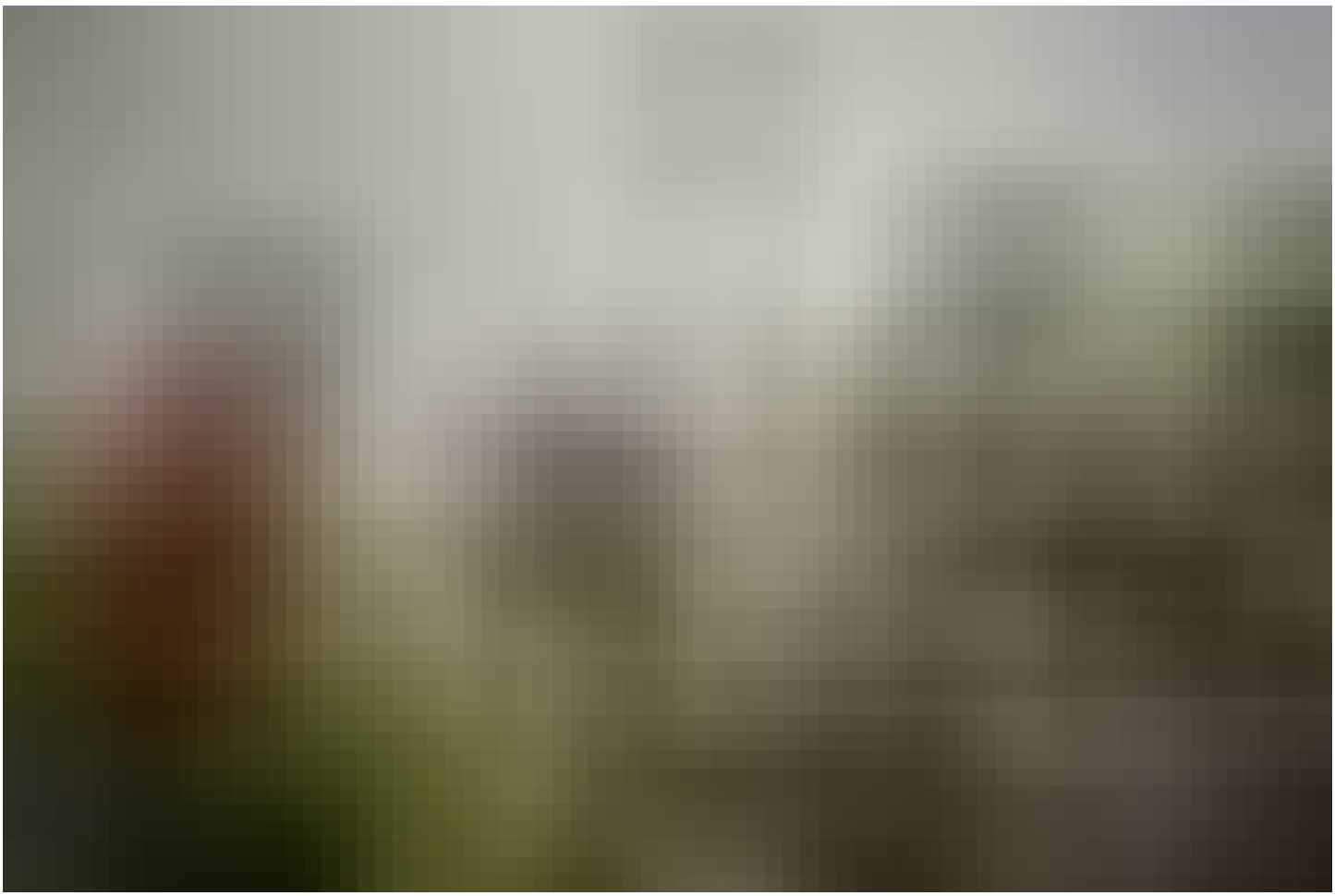
"We see a huge impact from [patients] being able to get treated in the first day," said Parker. "That alone cuts down the malaria problem."

> *To SMRU, painstaking surveillance through low-cost malaria posts is the way to ultimately win. If every person in every isolated community could get randomly tested and immediately treated—and if this close monitoring could continue for years—perhaps we could beat malaria.*

There have been countless instances, Nosten said, of places that thought they were rid of malaria and thus stopped putting resources into it, only to have it return with a vengeance.

"I've learned this from Francois [Nosten]—it's so simple that it works," said Parker. "If it's complicated and sophisticated, it'll break down. The malaria posts aren't easy to mess up, and if it does mess up, we can fix it. There are

just three basic things: a way to test people, a way to treat people, and proper staffing. The simplicity is the key."



Farm workers returning home after a days work at the border between Thailand and Myanmar.

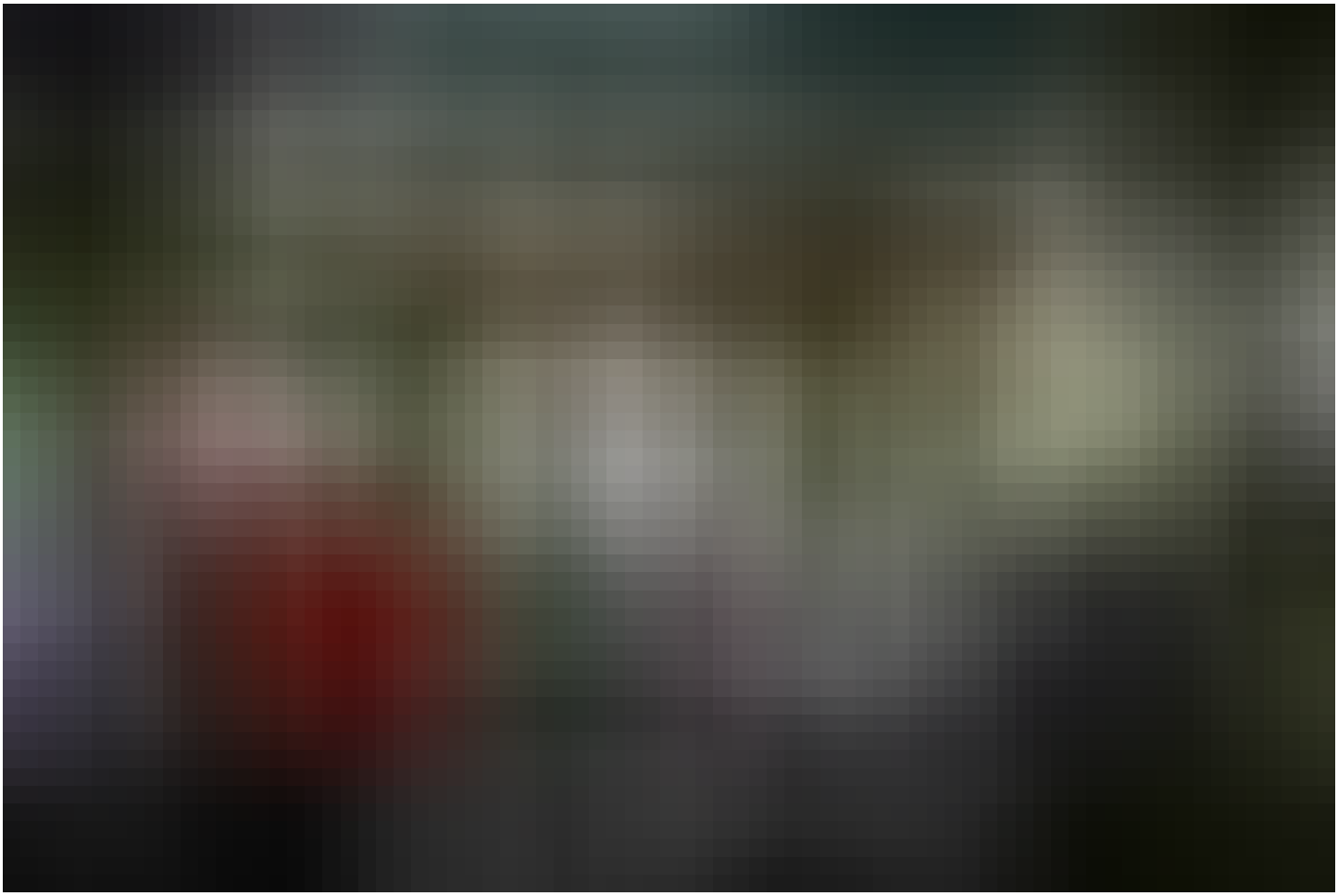
Given the near impossibility of complete surveillance, the SMRU team has another strategy for quick—albeit shorter-lived—wins. To kill "reservoirs" of drug resistance, they've been trying mass drug administration in select communities. This means they treat a full population for malaria, whether they have the disease or not.

For many public health experts, mass drug administration (MDA) is an essential tool to kill malaria in highly endemic areas. "There's a very long history with the use of MDA, from when they were using quinine in Italy," said Hwang. "They were giving massive doses to eliminate it from the country. There aren't a lot of tools that tackle parasites or mosquitos rapidly, and this is one of the few that does."

"But time and time again," she added, "things come very quickly back to baseline." It's hard to get a full population to agree to treatment—especially healthy people who don't trust the researchers.

Even if you manage to treat everyone, new people may immigrate there a few months later. This is part of the reason why island nations like Sri Lanka have been able to eliminate malaria, and conversely, why it stubbornly persists among migratory populations in the Greater Mekong.

There's also the ethical dilemma of treating healthy individuals for a disease they don't have. "It's a really difficult thing to weigh the risks potentially faced by someone who is uninfected or asymptomatic to the potential community-level benefit," said Hwang. "There have been a lot of discussion recently about this with vaccines. Everything we do, even vaccinations, carries a risk, but there is that societal benefit you're taking on. The community really needs to mobilize—they would hopefully understand the benefit of never experiencing malaria again."



A Burmese doctor from Yangon teaches SMRU staff.

After weighing the costs and benefits, SMRU decided to pilot MDA in select communities. The map and malaria posts have helped; they are able to quickly pinpoint where resistance is springing up, and where MDA might make the biggest difference. Researchers look for villages where at least 40 percent of the population is suspected to harbor the parasite, knowing that some of them won't exhibit symptoms of malaria. Once the village is identified, SMRU's "community engagement" team gets to work.

The community engagement process usually starts with someone of the same ethnicity speaking to a village leader about the importance of MDA. "It's important for people to understand the concept, that you are not sick but have to take the drugs," said Ladda Kajeechiwa, who leads community engagement efforts at SMRU. "If community doesn't understand, the communication will collapse."

Suphak Nosten, the organization's communication personnel, said her team often appeals to moral and religious sentiments.

> *"Most are Buddhist," she said. "We explain that they're saving the life of another, that they're investing for the next generation. We explain they are doing something that has merit for people they don't even know."*

While this reasoning can be effective, it's not foolproof. Hwang told me that in one Burmese village, half the village was controlled by one warlord and the other half by another. If one warlord endorsed a practice like MDA, the other half would refuse to comply on principle.

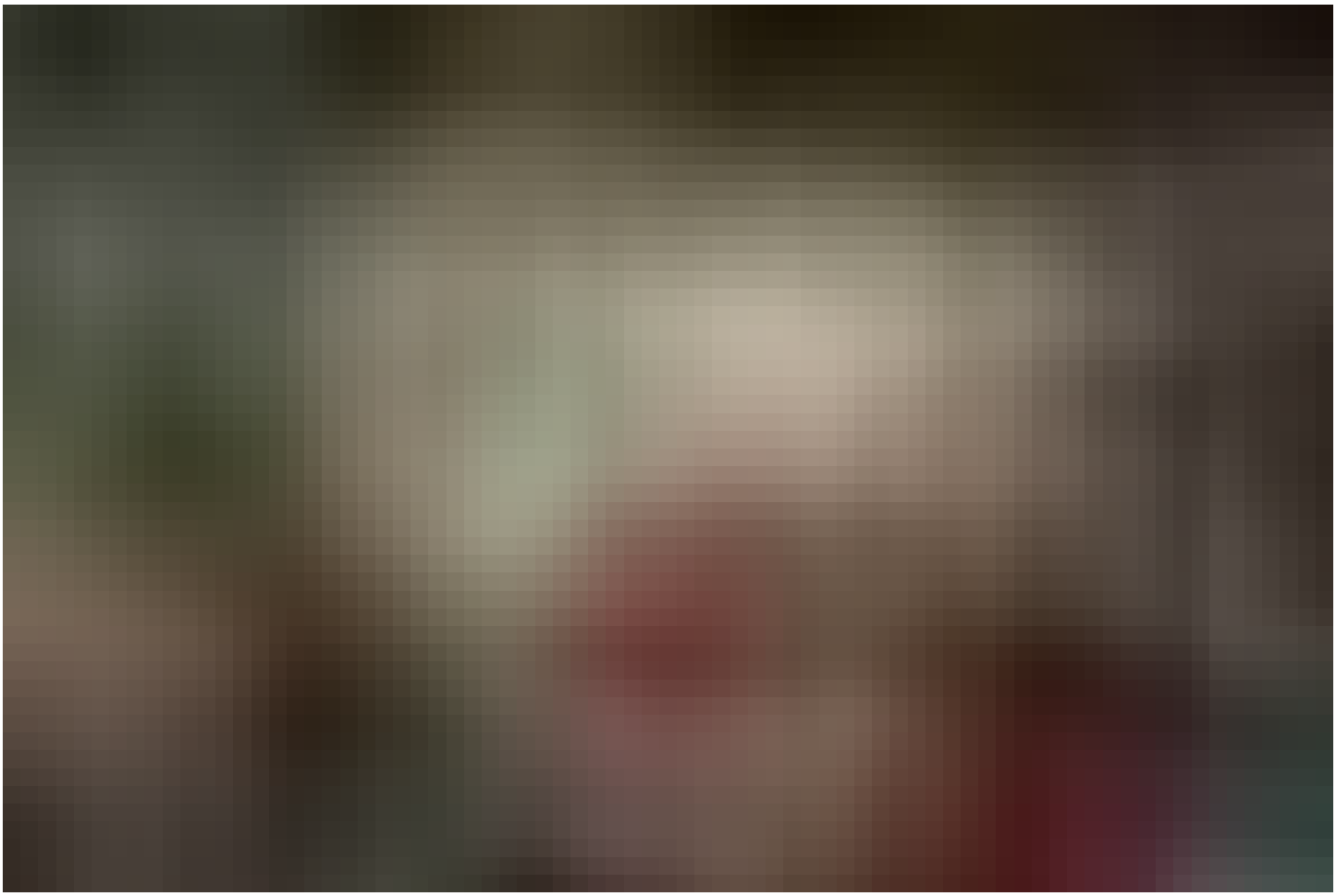
Assuming it's a village without competing warlords, SMRU's community engagement team spends about two weeks explaining to villagers the importance of taking the drugs, even if they're healthy. Then, when the time comes to administer MDA, they must get villagers to take the treatment regimen for three days in a row. This includes making sure all laborers take medicine before they hitch a ride to find work for the day.

Ironing out the logistics of this is crucial; if someone skips a day of treatment, the parasites have the opportunity to evolve into being resistant, multiply, and infect others.

> *But if MDA works, it could possibly wipe malaria out of a community where the disease had been taking a strong toll.*

Across the board, researchers emphasized that MDA is only a piece of a larger strategy to eliminate malaria in the Greater Mekong. "At the end of the day, the systems issues will be much more important," said Hwang. "Doing a one-off MDA might not be that effective, but if you went in and built the systems for that village, the benefits [of MDA] would be longer lasting. You're biasing your system to be more successful."

Parker agreed—but acknowledged the challenges inherent in setting up a fully functional surveillance system. "If we got health services to all communities, that would almost do the trick by itself," he said. "I don't know why it's so difficult. Rural health services aren't always at the top of the list."



Patients waiting for medical attention at the SMRU Wang Pha clinic in Mae Sot, Thailand. The center provides general medical services in addition to treating and eradicating malaria. Most of the patients tend to be Karen or Burmese, and a small percentage are Thai.

Until malaria is eliminated from the region, the fear of drug resistance will remain.

One recent afternoon in the town of Ponhea Kraek, Cambodia, 700 miles southeast of Mae Sot, a 50-year-old doctor named Rung Bunkok prepared to draw a few drops of blood from a younger man sitting in front of him. (Technically, Bunkok holds a secondary nursing degree, but his patients regard him as a doctor.)

Po Taeam, 29, arrived to the clinic on the back of his brother's motorcycle. Taeam was feeling feverish, with occasional chills and goosebumps. He had done a blood test elsewhere in mid-October, he told Bunkok, which was positive for malaria. "After I took my medicine [last time] I felt better, so I stopped taking them," he told the doctor. "It was only yesterday I realized I was sick again."

For work, Taeam works at a logging company in Cambodia's Stung Treng province, which Bunkok said is known to be more malaria-endemic.

As they chatted, Bunkok drew two drops of blood. He put one under his microscope, and the other on a "rapid diagnostic test" for malaria. (Both instruments were given to him by Population Services International, a nonprofit.) Within minutes, Bunkok confirmed that Taeam had falciparum malaria.

Since Taeam had stopped his previous drug regimen early, Bunkok wasn't sure if the parasites in his blood had evolved to be resistant—but decided ultimately that an artemisinin-led combination of drugs was the right course for his patient.

"You are in severe fever," Bunkok told Taeam. "You might get dizzy but you will be cured. Take all of these pills at the same time, 2pm, for all days of the treatment. Tomorrow you have to come here again to take the pills. Take a lot of coconut juice."

Taeam, who was visibly ill, appeared to take the instructions seriously. He thanked the doctor, paid him $9 for the malaria test and medication (about a day's wages), and went on his way.

Not everyone in the Greater Mekong has the good fortune to see a doctor, much less one with malaria testing equipment on hand and knowledge of drug resistance. If they did, perhaps we could finally see the end of the disease.

Sarika Bansal reported from Thailand and Cambodia on a fellowship from the International Center for Journalists (ICFJ) and Malaria No More.

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