

Countries race to contain resistance to key antimalarial

Resistance to an antimalarial has developed on the Thai/Cambodia border, with potential for global spread. But a huge effort is underway to contain the problem. Udani Samarasekera reports.

Pailin, a green lush province in western Cambodia, on the border with Thailand, one of the Khmer Rouge's last strongholds, was once famed for its rich gemstones and dense forests. Now it is gaining notoriety for a different reason: malaria.

But it is not a high prevalence of the disease that has made Pailin noteworthy. Rates of malaria have actually been in steady decline in the province over the past decade. What has put Pailin on the malaria map is its *Plasmodium falciparum* parasites, which, since the 1970s, have been the first in the world to successively develop resistance to key antimalarial drugs—chloroquine and sulfadoxine-pyrimethamine. These resistant parasites have not only spread throughout Cambodia but also across Asia and sub-Saharan Africa, rendering important weapons in the fight against falciparum malaria ineffective. And now, while Pailin's best gems and thick forests have long gone, the problem with antimalarial resistance has resurfaced. Scientists in and around Pailin are beginning to confirm that parasites in the region are also developing resistance to another class of antimalarial drugs—artemisinin derivatives—with potentially devastating consequences for the treatment of malaria globally.

The news is worrying health experts because WHO recommends artemisinin-based combination therapy (ACT) in the frontline treatment of uncomplicated and severe falciparum malaria. Artemisinins, which are derived from a Chinese herb, are extremely effective, fast-acting drugs with few side-effects. And, although this is still the case, some patients being treated with artesunate (the artemisinin used in Cambodia) are taking 3–5 days to clear their parasites instead of the usual 2 days—a sign that

the parasites are becoming tolerant to the drug. If these parasites develop full-blown resistance to artemisinin derivatives, it could be a global health disaster, warn experts, because there will be nothing in the malaria drug pipeline to replace these compounds for 5 years, or possibly more.

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Widespread resistance would not only be a setback for Cambodia, which has managed to substantially reduce its malaria caseload over the past decade (from 175 000 cases in 1997 to 62 000 cases in 2008), countries in sub-Saharan Africa could see their gains in combating child mortality curtailed. “Chloroquine was lost over a period of 20 years” and “child mortality in Africa increased because of an increase in malaria”, says Arjen Dondorp of the Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme, based in Bangkok, who is assessing resistance to artemisinin in clinical trials in Pailin.

But work is underway to try to stop history repeating itself. The Cambodian and Thai Governments, with the help of WHO and non-governmental agencies, and funding from the Bill & Melinda Gates Foundation, are ramping up their efforts to control malaria along their respective borders, with the aim of containing artemisinin-resistant parasites and ultimately eliminating malaria.

This is the first time the international community has tried to stop resistance clones from spreading globally. But the novelty of the containment

concept is not the only concern for observers. Containing resistance will be no mean feat. It is a huge challenge that stretches beyond the health sector and will require cross-border and cross-sector cooperation, political will, as well as substantial financial commitments and human resources. Such an endeavour is a big task for Cambodia, a country still scarred by the effects of a brutal conflict and genocide, which ranks 136 of 179 in the UN's Human Development Index.

Resistance timeline

Pascal Ringwald, medical officer at WHO, who is leading the containment project, says that doubts about the efficacy of artemisinins really came to the fore in 2005, when WHO published a global report on drug resistance. “WHO's report clearly said that there are data that are worrying from the national malaria control programme. The ACT monitoring system showed an increased treatment failure rate.” But many experts thought that this was because parasites were developing resistance to the drug that artesunate is paired with in Cambodia—mefloquine,

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Resistance to malaria drugs has emerged in Pailin and spread globally in the past



Drug shop in Pailin; around 70% of Cambodians buy drugs from the private sector

which was used as a monotherapy in the country long before ACTs were introduced. "Many scientists didn't agree", says Ringwald.

Then, in 2006, the Armed Forces Research Institute of Medical Sciences (AFRIMS)—a US army research institute attached to Walter Reed—reported two cases of artesunate resistance in Pailin's neighbouring province, Battambang. When that data came out, WHO convened an expert meeting to discuss the problem in January, 2007, involving officials from Cambodia and Thailand, as well as scientists from leading international research institutes. Soon after that meeting, the agency got funding to launch a multicentre project to try to confirm the real existence of resistance in in-vivo pharmacokinetic studies.

These trials are now beginning to report their results and they are indeed confirming what many had suspected: artemisinin resistance on the Thai/Cambodia border.

One of these studies is based at Pailin's Referral Hospital. Inside a clean, sparsely furnished ward, where a few weary looking patients are lying on thin mattresses on metal frame beds, Debasish Das, a research physician with of the Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme, explains the team's findings. In a trial of 40 patients

with uncomplicated malaria, Das and his colleagues found that 10% of patients had prolonged parasite clearance times after treatment with artesunate plus mefloquine and 30% had early treatment failure (defined as fever and parasitaemia after 3 days) after receiving artesunate. These percentages are much higher than the results of a comparison study done at a site on the Thai/Burma border, Das told *The Lancet*. In Pailin, the median time that it took artesunate to clear a patient's parasites was 84 h but in the Thai/Burma comparison it was 48 h, so the clearance time was substantially prolonged in Pailin. "This delayed response to treatment doesn't happen anywhere else in the world", says Das.

"At the beginning we talked about tolerance to artemisinin but after the Pailin study, resistance was confirmed—the 1973 definition of resistance had been met", says Ringwald.

A 2 h drive away from Pailin's Referral Hospital, along dirt tracks, past several fields of corn and cassava, another study of resistance is taking place at AFRIMS in Tasahn, Battambang. In a small, unassuming building next to Tasahn's health centre, researcher Delia Bethell says that in the AFRIMS trial, which is under the same umbrella as the Pailin study, they are also finding a delayed response to treatment with artesunate, with some parasites lingering in patients' blood for 4 or 5 days after therapy.

Both AFRIMS and the Mahidol University group in Pailin are now assessing whether patients who have a high number of parasites in their blood after 3 days of treatment respond to a large dose of artesunate. Although the studies are in progress, early findings suggest that there is no real benefit to be gained from a high dose; the drug is still taking a long time to clear patients' parasites.

The rise of resistance

So why is the Thai/Cambodia border proving to be an epicentre for the emergence of resistance? Bethell

says that several factors could be responsible. "There may be parasite factors that we do not know about. People are also self-medicating with a huge cocktail of drugs." Bethell illustrates the problem by opening up a file which has several small clear packets of pills stuck onto it, all different colours, shapes, and sizes. She explains that this is what they use at the centre to try to identify which drugs patients have taken when they come in.

The AFRIMS drug chart is necessary in a country like Cambodia because even though malaria treatment is free in the public health sector, the public health system is weak, so around 70% of people in Cambodia go to the private sector for medication. "The private sector, which is anything from pharmacies to drug shops and clinics, is huge in Cambodia", says Eva-Maria Christophel, medical officer at WHO's Western Pacific Regional Office.

Private sector drug purchases are a problem because the quality of products can vary enormously from genuine ACTs, to monotherapies, to fake drugs with only small traces of artemisinin or sometimes none at all. Between 10–30% of medicines in developing countries may be counterfeit and studies have shown that south east Asia in particular has a huge problem with fake antimalarials. Monotherapies or counterfeit drugs with traces of artemisinin are problematic because they kill off parasites that are still sensitive to the drug, leaving resistant mutants to multiply.

A couple of steps away from the AFRIMS research building, at the Tasahn health centre, the challenges facing health workers are brought into sharper focus. In a bed placed just outside the doors of the clinic for coolness, a woman who is 7 months pregnant is being treated for malaria. 33-year-old Sam Pov has signs of drug-resistant malaria—parasites have remained in her blood after 3 days of treatment. She was on her fourth day of treatment when *The Lancet* visited the centre. Her story is a familiar one

in Cambodia. She has three children, including a boy of 9 years who has had repeated malaria. She paid 10 000 riels (US\$3) for his treatment, which she bought at the local market, but she does not know what the drugs were. Either way, they did not cure her son's malaria. Sam Pov says that she is very concerned about her son.

The problems with private sector drug purchases become even more apparent at Pailin's bustling market, which sells everything from catfish to mangos to malaria drugs. Standing in front of a small drug shop, Sophal Uth from the Malaria Consortium—a non-governmental organisation involved in the containment project—explains that the government requires pharmacies, clinics, and shops to have a licence to sell medicines but the law is easily bypassed. To get a licence you need qualifications and there are many forms to fill in, says Uth. But many shops do not bother going through this process because pharmaceutical companies will provide a drug supply to them with or without a licence. This means that there are “unlicensed health practitioners who can sell drugs but they don't know how to give the drug properly”, says Uth. Furthermore, “some shops just sell whatever the customer wants”.

Although Cambodia has recently banned artemisinin monotherapy, when *The Lancet* visited some of Pailin's drug shops many had monotherapy for sale; law enforcement remains a major issue. Even when ACTs are sold, things can still go awry. People may fail to finish a course of treatment when they start to feel better or they may throw the mefloquine part of the drug treatment away because it makes them feel nauseous, so effectively they end up taking artesunate monotherapy.

Containment project

Controlling the sale of malaria drugs in the private sector is a large part of the project to contain resistance. “Cambodia is working on its private sector strategy to try to develop a

contract with private providers so that they are trained to use diagnosis and the right drugs”, says Christophel. “We want to be able to bring them on board—and find an agreement where it is a win-win situation. We don't want to drag them out of business but we need to make sure they provide an adequate amount of drugs—the issue here is underdosing.”

Duong Socheat, director of Cambodia's national centre for malaria control, told *The Lancet* that his team is informing the private sector about the monotherapy ban through workshops and television broadcasts. Around 200 justice police have also been deployed to enforce the law. Those working on the containment project hope that these measures will help to reduce what they call the drug pressure on the parasites. “Under this idea, the parasite mutated, but if you take the drug away, you reduce the drug pressure and then they revert to wildtype”, says Christophel.

Meanwhile, in areas where resistance is suspected, which includes four provinces in Cambodia and two in Thailand, the government is trying to take treatment out of the hands of drug shop owners and into the hands of village malaria workers. These villagers are being armed with rapid diagnostic tests, so they can detect whether locals with a fever actually have malaria and, if they do, they can ensure they get the right treatment. “Cambodia has a long experience with using village malaria workers in the east of the country where there is a high prevalence of malaria”, says Christophel. “We now need to expand those to villages in the west where there is not such a high malaria prevalence.” But Christophel admits that attempts to scale-up will be “logistically challenging”.

Logistics aside, village malaria workers face another problem: asymptomatic cases. Some locals have built up an immunity to malaria and it can be hard to identify whether they have the disease because they have



Long-lasting insecticide-treated bednets are being distributed to villagers in Pailin

low levels of parasitaemia and no fever, or mild symptoms, as a result. But, even so, they can still transmit resistant parasites. Cambodia is therefore planning to detect and treat asymptomatic cases via mass screening and treatment campaigns in villages with suspected resistance to artemisinin. Large teams will be trained to do rapid diagnostic tests and to treat patients with directly observed therapy in these programmes.

Health workers also aim to improve coverage of long-lasting insecticide-treated bednets (LLINs) in key target areas. At a malaria outpost near Pichkiri village, Pailin province, around 200 people have gathered opposite a school to receive LLINs from Family Health International—a non-governmental organisation that is helping Cambodia with its malaria control efforts. Around 600 nets are being distributed—one net for every two people in a family.



Migrants working on Pailin's road to Phnom Penh might spread resistant parasites

Using a microphone and loudspeaker tied to a tree, health workers first tell the audience how to use the nets. Then, names are called out as if on a school register, and in an orderly fashion, each family representative comes up to collect their nets, walking quickly back into the crowd or onto an awaiting bicycle or motorbike to whisk their new prized possession away.

Migrants on the move

Distributing bednets to locals such as the villagers of Pichkiri, at least during Cambodia's dry season, is a fairly easy task. One of the biggest challenges that the containment project faces is the provision of bednets to Pailin's highly mobile migrant population, who might inadvertently spread resistant parasites to other parts of the country or abroad.

"The population movement is amazing in the area—after the Khmer Rouge there was still land available, so people came to cut the forest and do farming", says Christophel. Now, there are newer economic migrants, victims of the global financial crisis, people like 21-year-old Samnang, who has come to work on the road linking Pailin with Cambodia's capital, Phnom Penh. Standing by his charge—a blue, battered looking cement mixer—he told *The Lancet* that he came here 2 months ago after the Phnom Penh garment factory that he worked in closed, one of 30 such closures in the capital. His wife

is also working on the road. But she is currently off sick and is resting in their home further up the road—a plastic shelter between some trees, where four other families are also staying. Samnang says that his wife has had a fever and chills for 3 days now and she has taken paracetamol for relief but her fever keeps coming back. He says that they had never heard of malaria until they came to work in Pailin.

Yok Sovann, deputy director of Pailin's health department and malaria coordinator for the province, says that like Samnang "many new migrants don't know about malaria. They come from areas of Cambodia with low or no transmission of malaria, so even

"We need long-term thinking with the current situation. We need to take a look at the past and what happened with chloroquine."

if people are provided with bednets they still sleep outside. They also don't know the symptoms of malaria and suspect flu, so they don't go to hospital and their disease becomes severe."

The containment project is trying to achieve 100% coverage with LLINs in the key zones that could be affected by resistance along the Thai/Cambodia border—which means providing migrants like Samnang and his wife with bednets and information about malaria. "But it's a huge population to be covered", says Christophel. Around 70 000 people live in Pailin alone. "And the population is fluctuating, so it's difficult to know the numbers." A study has already found that the containment project has underestimated the population that need bednets, "so we are trying to procure more", says Christophel.

Addressing migration—cross border and in country—will not be an easy task for the containment project. "There are all sorts of issues playing into this—politics, police, everything. It's a very big challenge and health has a very small say in some of these issues",

says Christophel. "Commitment is needed from government at very high level, so that all sectors can be a part of the containment strategy."

Next steps

But there is a possibility that it might be too late. "Resistance used to move west to Burma but now people travel from Bangkok to Nairobi", says Mark Fukuda, who is leading the clinical trials on resistance at the AFRIMS centre in Tasahn. He plans to work with the military to do a wider geographical study on resistance in Latin America and Africa. "We need to expand our global surveillance", he says.

But even if resistance to artesunate has spread, it is not clear yet whether other artemisinin derivatives will also be affected. As Fukuda says, "if there's resistance to one artemisinin, do you lose the whole class?" His team is "testing blinded compounds, different artemisinin derivatives" on resistant parasites grown in the laboratory. "So it tells us if we need to get out of the class and we won't waste time doing tests in man." He adds that, "there are some preclinical leads in the non-artemisinin class. But most companies are working on artemisinin synthetics because it is not definite that the class has failed yet."

For Duong Socheat, director of Cambodia's national centre for malaria control, the containment project's success is dependent on two things: time and money. "The country only has support for 2 years", he says. "But 6 months have already gone to procure drugs and bednets."

Mahidol University's Arjen Dondorp agrees that funding is an issue. "To get rid of resistance is very expensive. The government needs to get rid of malaria in western Cambodia to take out resistant parasites."

"We need long-term thinking with the current situation. We need to take a look at the past and what happened with chloroquine", he says.

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