

Suck it and see: Zambian researchers capture the mosquitoes that prey on them.

THE BIG PUSH

Zambia, with help from partners around the world, is stepping up its battle against malaria.

Michael Hopkin reports from the rural front line.

It's not long after dark on a starry night, and three SUVs are bumping along a dirt track in a remote corner of southern Zambia. Inside the vehicles is a troop of more than a dozen men, most dressed in green overalls that bear more than a passing resemblance to army fatigues. Their mission is mundane, even boring: they will spend the entire night sitting still — up to 12 straight hours punctuated only by the odd insect bite. They say that the boredom really begins to kick in at around 02:00.

But for all the tedium, the mosquito-hunters' mission is vitally important. The insects they catch will provide information about exactly when and where people receive bites that transmit the malaria parasite and help researchers to compile a genetic catalogue of the local mosquito population. This is the front line of the battle with malaria.

Zambia sees nearly four million cases of malaria diagnosed each year, and some 50,000 deaths, mostly among children. Two years ago, its Ministry of Health embarked on an ambitious plan to cut the incidence of malaria by 75%. As a result, the country is now a destination for a significant fraction of the estimated US\$3.6 billion

pledged to fight malaria worldwide by a host of sources, including the World Bank, the Global Fund to Fight AIDS, Tuberculosis and Malaria and the Bill & Melinda Gates Foundation. Bill Gates has described the Zambian initiative as an “inspiring example of a nationally coordinated effort”.

Last October, Gates and his wife called for the malaria parasite to be sent the same way as the smallpox virus, which remains the only pathogen that humans have ever successfully removed from the natural world. Few have dared to suggest that malaria, which still kills a million people every year, could be totally wiped out — most efforts focus on control rather than eradication. But although the Gates admit that the goal will take “multiple decades” to reach, they believe it can be done. And Zambia is seen by many as one of the places where the winning formula might be devised.

It is a long way from the world of megabucks philanthropy to the grassroots work that will make inroads against the disease (see page 1051). And people do not always agree on how best to fight the battle. Some researchers in Zambia share the Gates's absolutist attitude;

others argue that it needs to be tempered with a little more pragmatism and a lot more data.

As the mosquito-catchers at their nightly vigil will testify, collecting malaria data is tedious work. The researchers, from the Malaria Institute at Macha (MIAM), some four hours' drive from the Zambian capital Lusaka, spend hours catching mosquitoes because it's the best way to learn about how malaria spreads.

Captive audience

The technique is called ‘human landing capture’, and involves sitting with sleeves and trouser-legs rolled up, waiting for a mosquito to bite. The researchers work in pairs — as one is bitten, his partner uses a plastic tube to suck up the mosquito and collect it for study. They do their fieldwork in real dwellings, one pair sitting inside and another outside, to sample both indoor and outdoor biters. The team is currently calibrating a set of mosquito-attracting light traps that will eventually do the same job with less manpower.

Researchers at MIAM are also preparing a bid to wipe out malaria from a 1,000-square-kilometre swath of countryside around Macha, as

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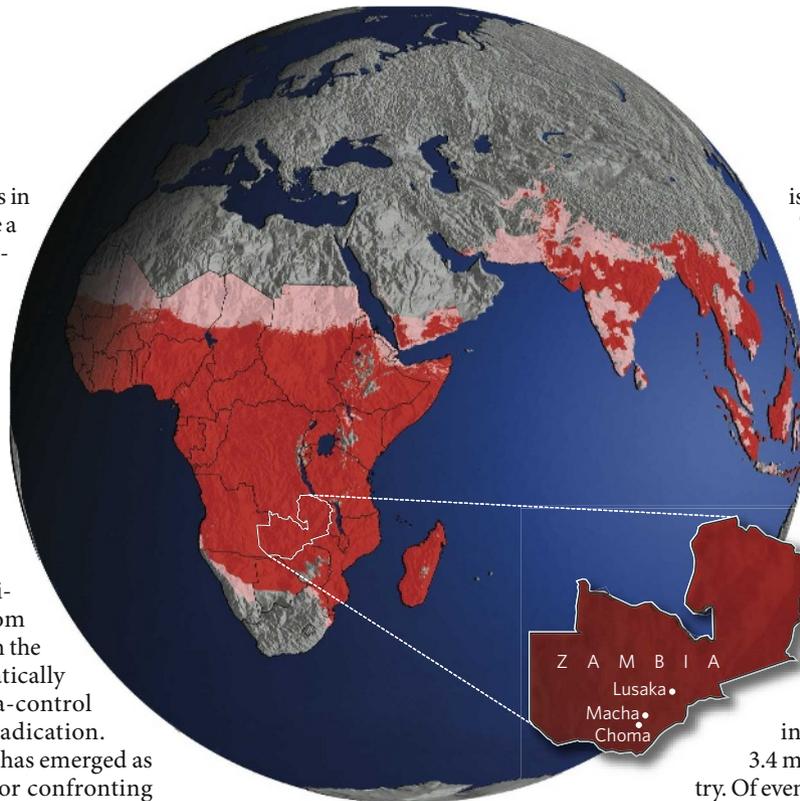
a proof of principle. The plan is in its infancy, but will probably be a 'shock-and-awe' campaign consisting of several interventions. "We'll be using techniques we know work — we'll throw everything at it," says Sungano Mharakurwa, MIAM's scientific director. "If it works in that area, we would want to go for the district and then the national level. On ethical grounds, people won't want to wait."

The methodology they envision is not that different from the nationwide plan, although the government is more pragmatically focusing on a set of malaria-control targets, rather than total eradication. The national strategy, which has emerged as the favoured combination for confronting malaria in Africa, focuses on four key interventions, each of which has a coverage target: getting insecticide-treated bed nets to 80% of the population; treating 80% of acute malaria cases with a new generation of drugs called artemisinin-based combination therapies (ACTs) within 24 hours; the routine provision of an alternative malaria drug combination, sulphadoxine and pyrimethamine, to pregnant women to protect unborn children; and indoor spraying of pesticide in 85% of households in 15 urban districts. The global community has set itself a goal of halving the number of malaria deaths by 2010 using similar interventions.

Slow but sure

So far, Zambia's progress has been slower than it had hoped. The initial time-frame for cutting malaria by 75% set a 2008 deadline, but this has been put back to 2011. To date, the Zambian government claims that the number of people dying from malaria has dropped by 10% since its project began in earnest in 2006. Yet a preliminary report¹ for four African countries compiled by the World Health Organization (WHO) offers hope of greater progress to come. Clinical data for Zambia collected between November and December 2007 show that, since 2000, malaria incidence in children under five — the agegroup at greatest risk — has declined by 29%; mortality has fallen by 33%.

Two other countries covered by the WHO report, Ethiopia and Rwanda, achieved even greater reductions in childhood deaths from malaria, at 51% and 66%, respectively. Unlike Zambia, these two countries have high-altitude terrain that limits mosquito breeding, but they managed to achieve these cuts even though



In areas where malaria affects fewer than 1 person per 10,000 per year (pink, population 1 billion), the disease is more amenable to control than in areas where transmission rates are higher (red, population 1.4 billion), such as Zambia.

they had not met their coverage targets for any of the interventions.

The WHO data, based on hospital admissions, are the first nationwide update on Zambia's malaria situation since a 2006 government survey² of some 3,000 of the nation's more than 2 million households. Mark Grabowsky, who helped to compile the WHO figures, says that Zambia and its partner organizations need to spend more resources on monitoring the progress of its programme — getting up-to-date information on incidence and mortality to decide which interventions should receive the most effort. "There is no surveillance system in place that allows these decisions to be made." He says that most big health projects, such as the international drive to stamp out polio, have conventionally put aside at least 10% of their funds for surveillance.

John Miller, a monitoring and evaluation specialist with the Malaria Control and Evaluation Partnership in Africa (MACEPA), admits that although there is fairly strong evidence of a downward trend in malaria, the exact figures are hard to compile, not least because some of its symptoms can also be caused by other diseases. "Malaria is a difficult disease to measure well — it is a disease of poverty, it is a rural disease. Understanding how much

is there is difficult," Miller says. The Gates foundation is planning another survey for this year, and aims to do one every two years to monitor progress, says David Brandling-Bennett, a US-based senior programme officer with the foundation.

The 2006 survey revealed some useful information on interventions that has guided MACEPA's activities. For example, the report showed that only 50% of the population owned any sort of bed net, and barely 20% of children slept under an insecticide-treated net. So

in 2007, the project handed out 3.4 million bed nets across the country. Of even greater concern is the shortfall in speedy access to ACTs. The survey showed that only 13% of children with acute malaria received the drugs within 24 hours. But Miller says that "not all interventions can be scaled up at the same pace. Delivery of antimalarial treatments through the public-health sector by its very nature requires many broader health systems to function well." Zambia is still ahead of many other countries in providing such drugs and infrastructure. "A lot has happened since 2006," says Miller.

Death traps

Back in Macha, MIAM's mosquito-trappers are collecting the sort of valuable information that could help to delay the emergence of resistance to malaria drugs — something that is essential if malaria control or eradication efforts are to succeed. Earlier attempts at malaria eradication in the 1960s failed because the effectiveness of the best available drugs, such as chloroquine, was severely hampered by the emergence of resistant strains of malaria. Today, chloroquine is almost useless in sub-Saharan Africa.

Mharakurwa believes that detailed monitoring of the malaria parasite in the field is key to preserving the effectiveness of newer drugs. "Drugs are getting more and more expensive, so we want to get it right," he says. And his field data, although only preliminary, illustrate how the complex biology of the malaria parasite can affect the emergence of resistance.

The researchers who study the emergence of resistance in Zambia's main malaria parasite, *Plasmodium falciparum*, have only a limited

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— John Miller

understanding of how resistance spreads. Based on his research at Macha, Mharakurwa thinks that spraying buildings with long-lasting pesticides to help keep mosquitoes at bay helps reduce drug resistance. Samples of the parasite taken from local infected people showed that almost all were resistant to sulphadoxine–pyrimethamine, which is a drug combination still widely used. But the *P. falciparum* population living in mosquitoes was different: in areas where houses were sprayed, only 10% were resistant to the drug.

Furthermore, Mharakurwa thinks that spraying reduces resistance through subtle effects linked to the complex life cycle of *P. falciparum*. His data suggest that although drug-resistant parasites have a competitive edge when living in humans, this advantage may come at a cost of poorer performance inside the mosquito's body. And this population effect could be narrowed still further by spraying, which reduces mosquito numbers and so increases the competition among the parasites.

Spraying is a key component of the government's malaria plan, but it has not been rolled out nationwide. Unlike drug distribution, which can piggyback on existing health infrastructure, spraying requires additional government coordination and training of personnel to scale up effectively. As a rural area, Macha is not currently included in the spraying programme, which focuses on the one-third of the population in the most urbanized districts. But Mharakurwa is keen to introduce it there.

After years of controversy over the side effects of the pesticides used, the WHO finally endorsed spraying as an effective way to fight malaria in September 2006. But some still see drug use or bed nets as the dominant strategies to be pursued. And the latest WHO data from Ethiopia and Rwanda could support this view. Both countries achieved dramatic drops in malaria deaths by relying on mass distribution of bed nets and ACTs with little if any documented spraying. Nevertheless, Mharakurwa insists that spraying is a proven weapon and that “we should attack malaria with all the weapons that we have to hand”. “It depends where you are and what goals are feasible,” he says, “one size does not fit all. However, if we want to eventually eliminate the problem of malaria, which many believe is realistic in southern Africa, then spraying is one tool that we know works.”

If his bid to eradicate malaria in the 1,000-square kilometre patch works, it will earn

Macha a reputation as a test bed for dealing with malaria in remote rural areas, where the poorest, and hardest hit by malaria, live. As with the national plans, MIAM will need to collect careful data on malaria prevention, treatment, cases and deaths to bolster their case.

“It's not easy,” says James Phiri, Macha's environmental-health technician, a vocal advocate of spraying and the man in charge of handing out bed nets to the local community. “Right now I estimate that we have 4,000 nets, against a population of 20,000.” Popular stories about bed nets being used for fishing or even as wedding dresses suggest that some people at a local level are yet to be fully convinced of the benefits of malaria programmes.

Double jeopardy

Next door to MIAM is the local hospital, which despite being two hours' drive from the nearest paved road not only deals with malaria but also offers a twice-weekly HIV clinic — a reminder that no health problem, no matter how pressing, can ever be viewed in

clinical officer Onaty Hanyuma. Another problem is that, in the absence of nationally coordinated health records (Macha's hospital still uses cards to record patients' details), it can be difficult to keep track of case numbers at all. Hanyuma is reserving judgement on figures for

2008 until after the peak malaria months of April and May, by which time several months of rains will have bolstered the mosquito population. During those times, Hanyuma says, he typically sees around 30 new cases of acute malaria a day. He thinks that cases “have gone down a bit” since the government programme got under way,

but he cannot provide more details than that.

The experts at MACEPA are fervently hoping that the lessons learned in Zambia can be transferred to other parts of sub-Saharan Africa. But critics point out that Zambia is at the southern end of malaria's distribution, and the problem is more entrenched elsewhere. They also suggest that strategies against *Anopheles arabiensis*, the main mosquito carrier in Zambia, may not work in more northerly regions, where the disease is transmitted by other mosquitoes.

In the meantime, donors are determined to press ahead with a continent-wide boost in the scale of malaria programmes. A branch of MACEPA called the Learning Community, based in Lusaka, is aiming to spread Zambia's expertise to several countries, including Ethiopia, Tanzania, Malawi and Zimbabwe. And household assessments are planned by the governments of more than 40 countries in Africa. “We are confident that these are the same strategies that will work in a Tanzania or a Zimbabwe, for example,” says Judith Robb-McCord, who runs the Learning Community. “They may have a different spin in terms of their adaptation in particular countries, but we're relying on the theory that practices that work here will work in other countries.”

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1. WHO Global Malaria Program Surveillance, Monitoring and Evaluation Unit. *Impact of Long-Lasting insecticidal-treated nets (LLINs) and artemisinin-based combination therapies (ACTs) measured using surveillance data, in four African countries* (WHO, Geneva, 2008).
2. MACEPA Technical Brief 1. *Zambia 2006 National Malaria Indicator Survey* (MACEPA, 2007).

See Editorial, page 1030, and online at www.nature.com/news/specials/malaria/index.html.

“We should attack malaria with all the weapons that we have to hand.”
— Sungano Mharakurwa



Spraying homes with pesticides could help tackle the problem of malaria drug resistance.

isolation in Africa. The facility also illustrates the often-fragmented nature of healthcare in the developing world. The hospital pharmacy has a healthy stock of ACTs, including Coartem (artemether and lumefantrine), the Novartis-owned drug currently viewed as the best available treatment. But logistics are a constant headache — the only transport link is a bumpy, waterlogged dirt road to Choma, the district's main town.

“Last year, we ran out of Coartem and saw a real, real increase [in illness],” says the hospital's