FT Health Combating Malaria

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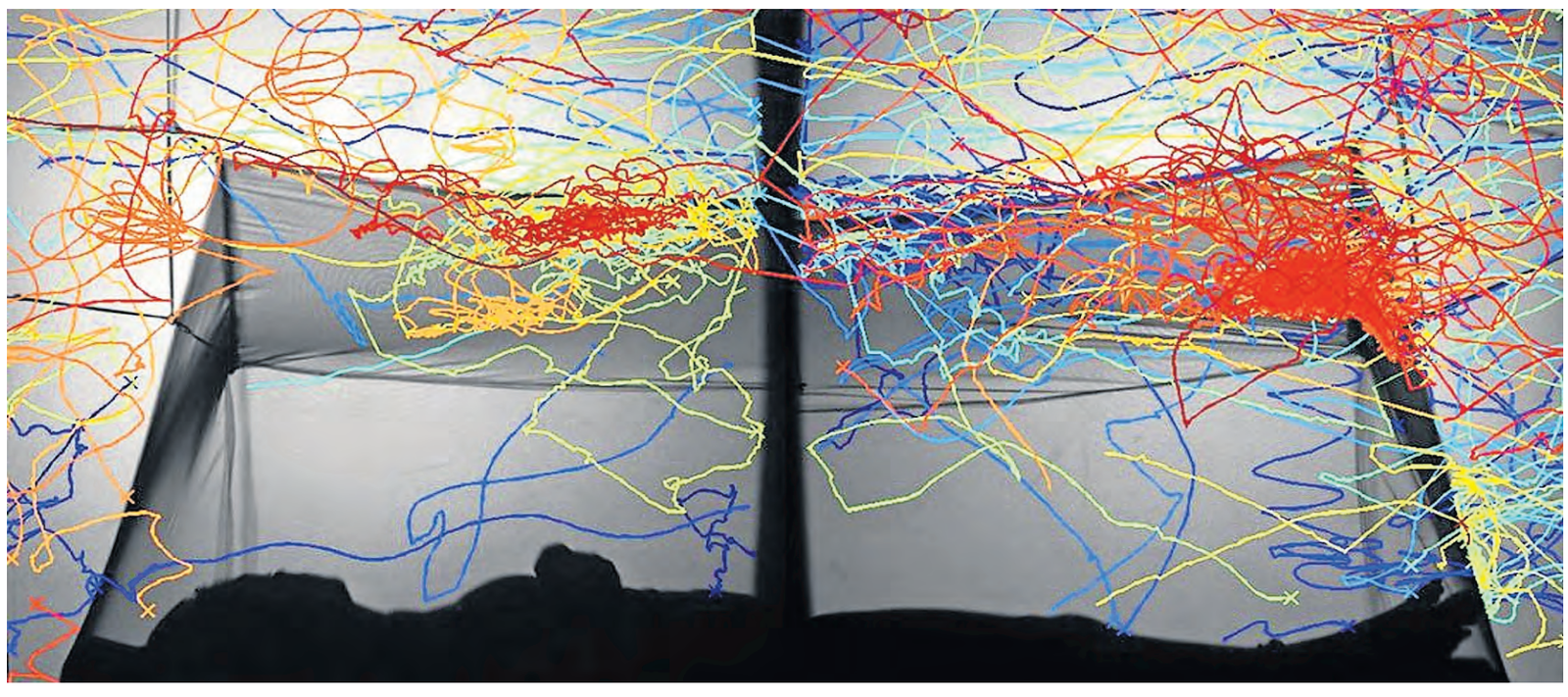
Fight intensifies against a killer disease

Despite progress, existing treatments and pesticides are losing their effectiveness, says *Andrew Jack*



Challenge: infrared tracking of multiple mosquitoes attempting to reach a human volunteer
Liverpool School of Tropical Medicine/University of Warwick

This will be a decisive year for malaria. From the jungles of the Greater Mekong or the urban shanties of Haiti, new tools and tactics are being used to counter the spread of the disease and to alleviate its huge economic and human costs.

It still infects 200m people each year and kills nearly 600,000, yet enormous progress has been made since the start of the millennium — the death rate has halved and an estimated 4.3m lives have been saved but there are concerns over funding and biological resistance.

Pedro Alonso, director of the World Health Organisation's global malaria programme, says: "Malaria has been a success story. The progress made is really unprecedented. But we are at a tipping point. We are worried about losing the gains achieved over the past decade."

Meanwhile, 19 countries are moving towards elimination. Argentina is set to be declared malaria-free this year, while other nations including Sri Lanka and Saudi Arabia are close.

Leaders of countries where malaria is endemic have stepped up their cross-border commitments spearheaded by organisations such as the African Leaders' Malaria Alliance and the Elimination Eight of southern African countries as well as the Asia Pacific Leaders Malaria Alliance. Some prominent business people have also increased support, such as Aliko Dangote in Nigeria.

Increased funding to disseminate existing tools — including indoor residual spraying and insecticide treated bed nets, rapid diagnostic tests for accurate confirmation of malaria and artemisinin-combination drug therapy for treatment — has helped strengthen the fight against the disease. New experimental approaches are also advancing. The Medicines for Malaria Venture and its academic and pharmaceutical industry partners report progress towards a single-dose malaria treatment.

GlaxoSmithKline's RTS,S, a vaccine it is developing against the parasite, is being scrutinised regulators. Meanwhile, Oxitec is developing genetically modified sterile mosquitoes to eradicate the insects that transmit the infection.

There is fresh momentum on yet more ambitious goals. The Bill & Melinda Gates Foundation is reviving a decades-old discussion about eradication. "The great debate now is a malaria-free world," says Alan Magill, in charge of work on the disease at the Seattle-based organisation. "Do we just accept the status quo or start to chart paths towards a new vision?"

Already the World Health Organisation is set to seek approval next month from ministers of health at the World Health Assembly in Geneva of a bolder plan for 2016-2030 that envisages elimination of malaria in at least 35 more countries, with a 90 per cent reduction in death and infection.

> 'We are at a tipping point. We are worried about losing the gains achieved over the past decade'

In the Greater Mekong, a growing number of studies have shown that the parasite has become resistant to artemisinin and the other drugs with which it is combined on the Thai-Cambodia border. There are plans for a rapid shift towards elimination of the disease using techniques including mass drug administration to the entire population.

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Inside

War on Anopheles mosquitoes heats up

Research Scientists are learning more about how the insects target humans, writes *Clive Cookson*

Malaria depends on a complex triangle of biological relationships between the Plasmodium parasite and its two hosts: humans and mosquitoes. Although most scientific attention in recent years has focused on attacking the parasite itself through drugs and vaccines, the war on the Anopheles mosquitoes, which spread Plasmodium to people, is gathering pace.

But progress is threatened by the evolution of resistance against pyrethroids, the main class of insecticides used for bed nets and indoor spraying.

Genetic mutations can produce three different types of resistance: metabolic resistance leads to enzymes that break down insecticides more efficiently; penetration resistance hardens the insects' outer cuticle so they absorb less chemical; and target-site resistance reduces the ability of the insecticide to target the mosquito's immune system.

In January, researchers from the University of California, Davis, reported in Proceedings of the National Academy of Sciences the emergence of a "super-mosquito" in Mali as a result of interbreeding between Anopheles gambiae, the most important malaria carrier, and a related mosquito, A. coluzzii.

"It is 'super' with respect to its ability to survive exposure to the insecticides on treated bed nets," says Gregory Lanzaro, who led the research team. The study "provides convincing evidence indicating that a man-made change in the environment — the introduction of insecticides — has altered the evolutionary relationship between two species, in this case a breakdown in the reproductive isolation that separates them."

Such evidence is driving the growing effort to develop entirely new insecticides, with the Innovative Vector Control Consortium leading the way.

Meanwhile, more fundamental research into mosquito biology proceeds apace. Recent work is uncovering unsuspected relationships between mosquitoes' DNA and behaviour. In November, the journal Science published two papers comparing the genomes of 16 Anopheles species that live in different parts of the world with differing abilities to transmit malaria.

The comparison shows that Anopheles mosquitoes evolve very fast by insect standards. Genes involved in reproduction change particularly rapidly.

"These dynamic changes may offer clues to understanding the diversification of Anopheles mosquitoes: why some breed in salty water while others need temporary or permanent pools of fresh water, or why some are attracted to livestock while others will only feed on humans," says Daniel Neafsey who leads the Malaria Genome Sequencing and Analysis Group at the Broad Institute in Massachusetts.

Follow-up research, which Science published online in February, focused more closely on the evolution of Anopheles' reproductive traits. The findings suggest that understanding the insects' sexual biology may produce new targets for malaria control. For example, the ability of Anopheles species to transmit malaria to humans is related to the amount of a steroid hormone called 20-hydroxyecdysone produced by male mosquitoes. Blocking the hormone could prevent transmission.

Mosquito larvae: some breed in salty water, while others need fresh water — Alamy

Research has been published this year on the chemical cues that prompt mosquitoes to bite people. "Understanding the molecular basis of mosquito attraction and host choice is important for figuring out how you might prevent people from getting bitten in the first place," says Audrey Odom of Washington University in St Louis.

She is senior author of a paper published last month in the journal mBio that shows how Plasmodium enhances its transmission. It entices mosquitoes to take blood meals from infected people by emitting molecules called terpenes. The discovery could lead to new diagnostic tests for malaria, if the terpenes can be detected in patients' sweat or breath.

Another study, published in January in the Journal of Chemical Ecology, showed carbon dioxide, the gas produced by respiration, plays a central role in mosquito biting. The insects do not respond to human skin odours unless some additional CO2 is present, too.

Ring Cardé, entomology professor at the University of California, Riverside, whose lab carried out the research, suggests mosquitoes use human smells to locate the presence of people — and in particular the houses where they live.

"We already know that mosquitoes will readily fly upwind towards human skin odour. But landing, the final stage of host location which typically takes place indoors, does not happen unless a fluctuating concentration of carbon dioxide indicates that a human host is present," he says.

Lethal gene relies on laws of attraction

Genetics

Impressive results as biological warfare is deployed to combat insects, reports *Clive Cookson*

Chemical insecticides are the main weapons used against mosquitoes today, but future campaigns could focus on biological warfare waged with genetically modified insects.

Oxitec, a company spun out of Oxford university in 2002, is the advance guard of this approach, using technology that inserts a "dominant lethal gene" into mosquitoes. It produces lusty but infertile males that mate with all available females; the resulting larvae die before hatching.

The strategy, tested over the past five years in field trials in Malaysia, the Cayman Islands, Panama and Brazil, is to release enough of these sterile males to swamp the natives. That means releasing many millions of insects — the number must be 10 or more times higher than the wild population.

Oxitec is focusing its research and development efforts on Aedes aegypti, the mosquito that transmits both dengue fever and the chikungunya virus that is spreading rapidly around the warmer parts of the world.

Hadyn Parry, chief executive of Oxitec, says the company's scientists have shown that the same technology can be applied to the Anopheles mosquitoes that transmit malaria, though considerable investment would be needed to adapt it to their life cycle. "We know that it is feasible . . . but we are a small company and we don't have the funding or resources," he says.

The four field trials carried out so far with Oxitec's modified Aedes aegypti mosquitoes, known as strain OX513A, reduced the number of disease-carrying mosquitoes by between 93 and 96 per cent in six months, Mr Parry adds.

OX513A contains two added genes. One is a fluorescent marker gene that enables scientists to identify any progeny from the released mosquitoes, estimate population sizes and monitor population suppression.

The other gene is designed to kill their larvae. But there has to be a way to override it so that the mosquitoes can be bred for release. The chosen antidote is the common antibiotic tetracycline, which switches off the lethal gene.

This use of tetracycline is one of several aspects of the technology on which Oxitec's opponents have seized. GeneWatch UK says mass production of GM insects in breeding factories could spread antibiotic resistance into the environment.

But according to the company, the amount of tetracycline required to breed OX513A mosquitoes is "insignificant" compared with the quantities used for veterinary, agricultural and medical purposes.

Mr Parry concedes that the technology is controversial. "There will always be people opposing us who are anti-GM in principle," he says.

Hadyn Parry: 'There will always be people opposing us who are anti-GM in principle'

The company has made most progress in Brazil, where it has received national technical approval for commercial release of OX513A from the national biosafety committee.

It also hopes to break into the US market with a field trial in Florida. The Food and Drug Administration is currently considering that application.

Mr Parry insists that the Oxitec approach is far preferable from the safety and environmental point of view to controlling mosquitoes with toxic pesticides. "It is highly targeted to the one insect species that causes harm to humans. Other insect life is untouched," he says. "Once the release of the Oxitec mosquitoes is stopped, the modification disappears from the gene pool and the environment."

Time has come to cast net wider as pesticide resistance grows

Prevention

As bed nets begin to lose their effectiveness, researchers are coming up with new approaches, writes *Sarah Murray*

The humble lightbulb is not often counted among the tools used to fight infectious disease. But, as questions hang over the efficacy of the insecticide-treated mosquito net, some argue that additional measures — from innovative indoor lighting to land reuse — will be needed to halt the disease's spread.

Most agree that the distribution of bed nets has been a success and accounted for a large proportion of the 4.3m lives saved between 2001 and 2013 through all interventions monitored by the WHO.

The nets have two functions. They provide a protective barrier that shields people from the insects. And when treated with pyrethroid-based insecticides — which are less harmful to the environment and humans than other products — they kill mosquitoes on contact, shrinking their numbers.

Yet, despite their success, it is becoming clear that nets cannot be the sole solution to arresting the spread of malaria.

First, a growing number of mosquitoes are developing resistance to the insecticides. Alternatives are being developed but getting them to market will take time.

Others worry about the nets' environmental impact. On the shores of Lake Tanganyika, for example, one recent study found free bed nets being used for fishing in 87 per cent of the shoreline households studied by the Lake Tanganyika Floating Health Clinic, a non-governmental organisation.

The problem is that the finely meshed nets catch far more fish than traditional nets, threatening fish stocks and damaging the lake's ecosystem. Concerns have also been raised about the potential water pollution the insecticide chemicals can cause when the nets are used for fishing.

Moreover, even where nets are widely distributed and being used for their intended purpose, there is evidence that malaria rates are rising.

One surveillance study found this to be the case in rural areas of Uganda. In spite of the fact that bed nets were given to all children under 10, malaria incidence remained high and increased over the two-year study period.

"We think Uganda is representative of a lot of sub-Saharan Africa, where we still have a long way to go," says Philip Rosenthal, a professor in the School of Medicine at the University of California, San Francisco, which studies malaria in Africa.

Such evidence, along with insecticide resistance and environmental worries, is prompting some to suggest that additional measures must be used in conjunction with bed nets.

For the lightbulb, it is early days. But researchers at the University of Southern California believe that using indoor lighting that is less attractive to insects means fewer mosquitoes would be drawn to the light.

'You shouldn't be replacing a yellow light with a blue-ish light'

The difference is in the light's colour temperature, as measured through the Kelvin scale. The researchers have found that if lighting gives off a blue colour wavelength, it is more attractive to certain insect species, including mosquitoes.

Using this knowledge, the team worked with Philips, the conglomerate that makes lightbulbs, to develop lamps with a colour wavelength that attracted about 20 per cent fewer insects than off-the-shelf LED bulbs.

"This could be an additional tool to minimise their abundance in areas where you don't have screens and glass windows but you need an inside light," says Travis Longcore, associate professor at the university's Spatial Sciences Institute. By the same token, he says, the current push to replace kerosene lamps with standard LEDs could increase the spread of malaria in some developing countries if those lights give off cooler wavelengths. "In those situations, you shouldn't be replacing a yellow light with a blue-ish light as it will attract more insects."

Fighting the blues: on a warmer wavelength

In addition to lighting, some argue that improved housing must be part of the strategy to combat malaria. While large-scale trials of the effectiveness of housing measures have yet to be conducted, experience suggests that mosquito-proofing homes by installing window and door screens can be effective.

Between 1925 and 1927, for example, the British army reduced the incidence of malaria in its barracks in Lahore, Pakistan, from 569 cases per 1,000 people to 45 after the barracks were mosquito-proofed with screens.

In a report citing this and many other early studies, Habitat for Humanity, the housing non-profit organisation, calls for further exploration of the link between housing improvement and malaria reduction.

Others point to the benefits of land use changes.

Reclaiming swamps and planting crops on the land would reduce breeding sites, says William Jobin, a public health engineer who worked on large irrigation and drainage systems in central Sudan.

"Malaria dropped to barely measurable levels," he says. "So the technique works."

Of course, not all these measures are free of controversy. Draining swamps has implications for ecosystems and biodiversity. Malaria-proofing houses with screens can be logistically tricky and unaffordable for some people. But while bed nets will play an important role in reducing the spread of malaria, it is becoming clear that a broader package of solutions is needed.

"It's not that things have got worse, but things are not obviously getting better," says Prof Rosenthal. "And that tells us we need more interventions."

Human trials speed up delivery of vaccines

R&D Australian drug trial research on healthy volunteers is attracting international donors, writes *Jamie Smyth*

Imagine volunteering to be infected with a disease that kills nearly 600,000 people a year. That is what Celeste Farmer, a psychology student at the University of Queensland in Australia, agreed to do in order to help researchers develop drugs to treat malaria.

"I'm healthy, but there are plenty of people out there who are not," she says. "It is important for people to donate their bodies like this to help others."

Ms Farmer is one of 230 volunteers who have taken part in trials using the "challenge model", in which healthy human subjects are infected with low doses of malaria to test the efficacy of new drug treatments.

Advocates say the trials, undertaken by the QIMR Berghofer Medical Research Institute and other global institutes, are speeding up the delivery of new anti-malaria drugs, saving pharmaceutical companies millions of dollars in R&D costs and providing hope for the development of more effective vaccines.

"While many new drugs and vaccines are being developed, it is difficult to determine which are the best to take to areas where malaria is a life-threatening disease," says James McCarthy, a professor at QIMR. "Malaria is becoming more resistant to existing treatments, which makes the speedy development of new drugs vital. These trials are helping to achieve this," he says.

The World Health Organisation reports that there were about 198m cases in 2013, mostly in Africa, Asia and South America which led to an estimated 584,000 deaths.

Under QIMR's challenge model, participants in the trials are injected with a sample of malaria that is much less than the amount that reaches the blood when a human catches the disease from a mosquito bite.

Volunteers are closely monitored using tests that measure the DNA of malaria parasites in the blood. This enables researchers to treat the volunteers before they become ill. They can administer trial drugs to monitor their effectiveness at tackling the disease and capture valuable information that can help develop treatments.

Challenge model: James McCarthy with one of the drug-test volunteers

The critical component of any human-challenge model is that an existing drug has to work 100 per cent to rescue the volunteer who has been infected. This is one of the reasons that the model works well in the case of malaria.

"This method reduces costs, increases the speed of drug testing and provides a valid path to develop new malaria drugs," says Prof McCarthy. "By using this method, we have [ruled out] three trial drugs at an earlier stage than would normally be possible. The data we collect also enable us to guide the dosage applied in larger field studies."

> 'It saved us a year at least, which is important, knowing we need new treatments'
> **Chief scientific officer, MMV**

None of the participants in the trials, which have continued for several years, have become ill, say the researchers — a positive outcome which they attribute to intensive monitoring and the timely deployment of proven drugs to kill the malaria parasites in the blood before they become a risk.

"I did have a headache at one stage but that may just have been the hospital environment," says Ms Farmer. "I had complete trust in the medical people."

The challenge-model research has attracted support from Medicines for Malaria Venture (MMV), a Switzerland-based non-profit agency. A big international donor will shortly be announced by the institute.

Tim Wells, chief scientific officer at MMV, says: "QIMR learns lots about the basic immunology of malaria — it's a valuable resource, and . . . James's [Prof McCarthy's] team has learnt a lot about how the human body deals with low levels of infection."

MMV and pharmaceutical company partners provide the new drug compounds, which are tested by QIMR. It now has three molecules moving into full clinical development — and MMV picked the dose to be applied for two of the drugs based on data provided by the QIMR team.

"It saved us a year at least, which is important knowing that we urgently need new treatments," says Mr Wells. "We know really early on in a project if it works. That gives us the confidence to move quickly into the big clinical studies in Africa, which are expensive and also complicated."

The "silver bullet" for researchers is the development of a 90-100 per cent effective vaccine for malaria. The current vaccine in phase III trials is expected to be only 30-50 per cent protective. Groups working on vaccines are making progress and the data provided by the challenge model are building knowledge on how one should work.

"Too often people prefer to fund big "pivotal" clinical trials based on not enough science," says Mr Wells. "But what is important is that we understand the human biology of the vaccines before we start doing big clinical trials."

Fight intensifies against a killer disease

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The aim is a $4bn decade-long effort to wipe out the parasite in the region where resistance to drugs has emerged in the past and further resistance risks spreading around the world today. The danger is malaria's ability to adapt — there are well documented past failures of widespread elimination programmes that ultimately only spurred resistance. Migrant and often clandestine workers on contested borders in the region will add to the complications.

Still more troubling, notably in Africa, is a growing pattern of resistance to existing insecticides used to spray indoors and to impregnate bed nets. Manufacturers and academic teams are working on alternatives, but are concerned at slow progress

Luke Lucas, in charge of global vector control at Sumitomo Chemical, says: "It's like we are steaming on the Titanic towards the iceberg but having to wait until we sink and large numbers of people die before there is a willingness to change." He and others raise the alarm about counterfeit, substandard and inappropriate insecticides, bed nets and drugs that accelerate resistance. Despite international guidelines against the use of "monotherapy" artemisinin drugs, for instance, eight countries still authorise their use and two dozen Indian companies manufacture them.

$2.5bn
The amount spent globally every year fighting malaria

$6.5bn
The annual amount WHO estimates will needed by 2020

In the absence of stronger public health systems, there are also continued worries about the role of the private medical sector.

But if tougher controls and incentives for appropriate use of newer technologies are important, so are more targeted approaches to stretch existing resources further. Nigeria and the Democratic Republic of Congo alone account for 40 per cent of total global malaria deaths each year, yet progress has been slow.

In Haiti, older chloroquine drugs remain effective while bed nets are less useful than elsewhere, given that mosquitoes in Haiti tend to bite earlier in the evening. That suggests the need for different approaches to malaria in different locations.

Increased funding will be fundamental to continued progress.

The WHO's own plan envisages that annual spending on malaria needs to rise from $2.5bn currently to $6.5bn by 2020 and $9bn by 2030.

In September, the UN general assembly is set to adopt Sustainable Development Goals to replace the Millennium Development Goals (MDGs) that expire at the end of 2015. The fear is that the new objectives will distract attention from health in general and malaria in particular.

Ray Chambers, the businessman and UN secretary-general's special envoy for financing the health MDGs and the fight against malaria, says: "We've been working hard to retain quantifiable and measurable outcomes. We're a bit concerned about the number of additional draft goals and how to keep the focus."

Whatever the outcomes, there are growing calls for fast-growing emerging economies with a significant malaria burden to pay more themselves.

To complicate matters, there is debate about the explanations for reduced malaria cases in recent years, and hence how best to respond in the future. Case numbers in parts of Africa began falling before the big upsurge in funding from the early 2000s. That implies other factors than health programmes — such as infrastructure and broader economic and social development — were at least partly responsible for the decline in cases.

"We need to think more about joining forces with other sectors," says Fatoumata Nafo-Traoré, head of the Roll Back Malaria partnership. "Construction and small-scale irrigation create breeding sites for mosquitoes. Improving housing, education and tackling malaria through tourism ministries are all important."

In the fight against malaria, health responses alone will not be enough.

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Haiti revives eradication aim

Case study
Recent experience and limited funding point to the need for a more targeted approach, writes *Andrew Jack*

Fumigation: a Haitian government worker sprays pesticide to kill mosquitoes in Port-au-Prince — Hector Retamal/Getty

Half a century ago, the Dominican Republic and Haiti combined forces in a bold but ultimately unsuccessful initiative: to eliminate malaria from the island of Hispaniola. Now, despite continuing political tensions, they are uniting again for a fresh attempt.

"There is longstanding interest in Hispaniola to make it a malaria-free region," says Patrick Kachur, chief of the US Centers for Disease Control and Prevention, which is working on the programme. "Both countries are interested and, politically, there is the will."

Yet the experience of recent years — and the limited resources available — highlight the need for a more targeted approach.

Malaria and the mosquitoes that carry it were probably brought to the Caribbean by slaves in the late 15th century. Plantation agriculture helped its spread by creating stagnant pools of water allowing mosquitoes to breed.

Today, the island of Hispaniola is the last place in the region where the disease is endemic, and its continued presence has periodically led to cases spreading to nearby countries such as Jamaica. There are an estimated 15,000-30,000 cases a year in Haiti, and fewer than 50 deaths.

In the 20th century, malaria in much of the Caribbean and Central America was tackled by a mixture of extensive spraying with the pesticide DDT to kill mosquitoes, combined with swamp drainage. Then, US funding for such programmes diminished in the 1960s, slowing the momentum. Widespread use of DDT also went out of fashion, reflecting environmental concerns.

While the Dominican Republic had cut annual infections to just 21 by 1968, Haiti — already falling behind its neighbour economically and politically — struggled to keep pace, in turn providing a way for malaria to spread back across the border.

Since 2009, a fresh effort has been launched in conjunction with the two countries' ministries of health and the Carter Center, a charity founded by former US president Jimmy Carter.

Its International Task Force for Disease Eradication concluded that elimination was technically feasible, medically desirable and economically beneficial. The aim, with estimated total funding requirements of $194m, is to end malaria on Hispaniola by 2020.

Jean Frantz Lemoine, head of Haiti's malaria control programme, says he believes the elimination objective is worth pursuing, but he remains cautious about whether the scale of additional funding required is achievable.

According to the World Malaria Report 2014, support dropped from a recent peak of $8m in 2004 to almost zero in 2010, rising again since, but still to less than $4m in 2013. The good news is that in Haiti the parasite remains sensitive to chloroquine — a cheap and widely available medicine — as opposed to many other parts of the world where it is ineffective.

Furthermore, the introduction in recent years of rapid diagnostic tests has shown that malaria may in fact be less common in Haiti than was thought. But it has also demonstrated the poor quality of reporting. That highlights the need for more accurate compilation of test results to focus efforts where they are needed, using tools such as text messaging and geospatial mapping.

"Haiti offers a chance to use current tools with new strategies rather than current tools with the current strategy," says Alan Magill from the Bill & Melinda Gates Foundation, which has helped fund the new programmes. "A simple redirection to target where the disease is will make a huge difference."

There are other particularities of malaria in the region.

According to the CDC, in Africa mosquitoes typically bite overnight and indoors, while people are sleeping. In Haiti, by contrast, they tend to bite earlier in the evening, between 5.30pm and 9pm. They also typically do so largely outdoors, or fly outdoors after biting inside, rather than lingering on internal walls or ceilings.

That means insecticide-treated bed nets — despite being widely funded and distributed by donors in the country — are not particularly effective either in protecting people from being bitten or in killing mosquitoes. Indoor residual spraying with insecticide may also prove less effective than elsewhere.

Instead, specialists are examining how to provide "mass drug administration", the idea being pre-emptively to provide drugs to populations at high risk of infection, in an effort to eliminate the parasite and stop it circulating.

Tests get cheaper and more sensitive

Technology

Rapid diagnosis could help detect victims with low-grade infections who are unwittingly spreading the disease, says *Sarah Murray*

Next-generation technologies are about to transform the diagnostics landscape, with far-reaching implications for malaria reduction.

Rapid diagnostic tests (RDTs) have already brought quick results to many more people, but new variants offer greater accuracy, which could be critical in the fight against malaria. They will not only help prevent indiscriminate use of antimalarial drugs but could uncover more victims with very mild infections who are unwittingly helping to spread the disease.

RDTs have played a critical role. Carried out cheaply, they do not require clinics with sophisticated equipment.

"The biggest achievement of the past couple of years has been the increase in the use of rapid diagnostic tests," says Iveth González, head of the malaria programme at the Foundation for Innovative New Diagnostics (Find). But she says that the accuracy of the tests needs to be improved. "The current rapid test is not sensitive enough to detect very low levels of infection," she explains.

Factors ranging from low-quality manufacturing or exposure to high temperatures during transport and storage mean the tests often vary in quality. To address this, Find has been working with the World Health Organisation and others on a programme to improve the quality of the tests.

Now, a number of researchers and start-ups are using next-generation technologies to develop alternative tests that are cheap and fast but also able to detect low levels of infection.

At Path, the Seattle-based non-profit organisation, the Diagnostics for Malaria Elimination Toward Eradication (Diameter) project is seeking to identify sensitive tests that could be commercialised at low cost. US-based Disease Diagnostic Group, a medical device company, is developing a reusable test that aims to detect malaria with 94 per cent accuracy in less than a minute. At a projected cost of $0.25, the test can make a diagnosis before symptoms appear.

The test relies on a magnet and a laser pointer in a handheld device that detects the hemozoin crystals released by parasites to assess infection levels.

Magnets are also the tool for researchers at MIT and Singapore's National Research Foundation, where they have found a way to use magnetic resonance relaxometry to detect hemozoin.

Meanwhile, Nanobiosym, a start-up based in Cambridge, Massachusetts, has developed what it calls Gene-RADAR technology to detect any disease in a matter of minutes by decoding DNA and RNA genetic information from a blood sample on a nano-chip inserted into a mobile device.

"You hit the button and the machine analyses the blood at DNA and RNA level, depending on what virus you are looking for. It tells you if it is present and how much of it there is," explains Anita Goel, chairman and chief executive of Nanobiosym. "And quantification is the gold standard."

RDT: community health workers are already using mobile phones to help with testing and data collection

Start-ups and researchers are not alone in seeking new malaria diagnostics. GE is working with Global Good — a collaboration between Bill Gates and Intellectual Ventures, a privately held invention capital company — to develop an affordable testing kit to detect the presence of low levels of malaria in people without symptoms.

"The most important thing is finding people who have not been properly treated because they can carry for many months," says David Bell, who leads Intellectual Ventures' work on global health technology.

The plight of victims and losses to the economy have been a call to action

GUEST COLUMN

Aliko Dangote

Bed-nets: their use has reduced rates of infection — William Daniels/Malaria Consortium

Little Ahmed was restless and febrile as he sweated profusely in his wooden bed. His temperature soared despite his mother Amina rubbing him down with a towel soaked in water. "It is malaria," she said, pressing on his chin to help him swallow a syrup from a local medicine store.

Such is the plight of the average poor family with no access to insecticide-treated bed nets and decent living conditions. To ease their suffering and bring attention to their plight is why this week we mark World Malaria Day.

The day has been set aside for health advocates and individuals around the world to raise awareness of malaria as a disease that is preventable and treatable, and to mobilise action to end its ravages.

This year, the burning question is what more can we do collectively and what specifically is the role of the private sector, of which I am a part, to help eliminate the disease?

I have chosen to be a part of this global effort because in the past 20 years I have witnessed scores of children afflicted by the scourge of malaria. Studies show that Nigeria has a quarter of the world's disease burden and reports more deaths from the disease than any other country.

In Nigeria, each year malaria is responsible for killing an estimated 300,000 children and contributes to more than 4,000 maternal deaths. It is also the leading cause of absenteeism, resulting in loss of productivity at work and school.

An estimated 97 per cent of Nigerians are at risk from malaria, and half of adults suffer at least one infection every year. Malaria accounts for 60 per cent of outpatient visits and 30 per cent of hospitalisations.

The Nigerian economy loses some $2.4bn annually from malaria-related absenteeism and treatment costs. In addition to the direct costs to business and the economy, it inflicts indirect damage through the deterioration of human capital, the loss of savings, investments and tax revenues. This is clearly too high a price.

Because malaria is so prevalent and many people can easily seek an over-the-counter cure, many people have become desensitised to the debilitating effects of the disease.

What works for prevention is the use of insecticide-treated bed nets and spraying affected areas. We also know the value of systematic testing with rapid diagnostic tests to ensure only people with malaria are given anti-malaria drugs; and that artemisinin-combination drugs cure the disease.

Over the past 10 years, the government of Nigeria and its partners have committed huge amounts of money to bring malaria under control. Although these efforts have reduced prevalence by more than 8 per cent, much more needs to be done.

As the founding patron and funder of the Private Sector Health Alliance of Nigeria (PSHAN), I have focused on

> 97 per cent of Nigerians are at risk from malaria, and half of adults suffer at least one infection every year

mobilising business leaders in Nigeria to leverage their capabilities, advocacy, innovation and resources to support the government in scaling up coverage of simple cost-effective, life-saving interventions across the value chain, including financing, manufacturing and distributing life-saving commodities.

Through my foundation, I have and continue to contribute funds to support the government-led National Malaria Elimination Programme, and other non-governmental organisations including the Clinton Health Access Initiative to which we gave $500,000 to test seasonal malaria chemoprevention (with antimalarials) in the north of Nigeria, which has proven successful.

This effort should now be replicated and scaled up with support from others. The Dangote Foundation will continue to advocate increased awareness and commitment as the best approach to eliminate malaria entirely from Nigeria.

As the malaria ambassador for Nigeria, I will continue to use my voice to attract attention to the fight against the disease. I will be a part of the global campaign using social media, television, newspapers and radio to raise awareness of malaria and its prevention.

As we come together on World Malaria Day, I urge every individual, group, conglomerate and community not just to join the fight but to sustain the battle against malaria by taking practical steps to prevent the health problems it causes and to safeguard our collective future.

Aliko Dangote is president and chief executive of Dangote Group. He is malaria ambassador for Nigeria, presides over the Dangote Foundation and is founding patron of the Private Sector Health Alliance of Nigeria.

Researchers hope vaccines can work on several fronts

Progress The first malaria vaccine will be a milestone but not a magic bullet, explains *Andrew Ward*

For years, researchers have been hunting for a vaccine to protect people against malaria. But what about a vaccine that could stop mosquitoes from transmitting the disease?

That is one of the approaches being worked on by the Malaria Vaccine Initiative, an offshoot of the Seattle-based Path health charity and backed by the Bill & Melinda Gates Foundation.

Ashley Birkett, director of the initiative, says such "transmission-blocking" vaccines could become a powerful weapon against malaria by disabling the parasites that cause the disease.

This approach would not prevent a vaccinated person from contracting malaria. But it would trigger antibodies in the parasite that would stop it being passed on to other people by mosquitoes.

This would be especially useful in reducing the many instances of asymptomatic malaria carriers, who spread the disease without knowing they have it. "Many people do not feel sick but are infecting mosquitoes all day long," Mr Birkett says. "Transmission-blocking vaccines would break that cycle."

Vaccines of this kind have shown promise in early trials but remain years away from production for sale. The fact that Mr Birkett and other leading malaria researchers are placing so much hope in them reflects the limitations of other approaches tried so far.

This assessment may sound unduly negative considering that the world's first malaria vaccine is on the cusp of approval. GlaxoSmithKline, the UK-based drugmaker, is hoping for a green light this year from the European Medicines Agency for the vaccine, known as RTS,S.

Mr Birkett, whose organisation helped GSK develop the product, says RTS,S is an "important first milestone" but it "was never going to be a magic bullet".

In clinical trials, the vaccine cut infections by almost half in children aged between five months and 17 months and by about a quarter in younger babies.

Some in the global health community have expressed disappointment that these prevention rates were not higher after 30 years of work on the vaccine. Mr Birkett says such sentiments are misplaced.

"We all want 99 per cent efficacy but we have to be realistic. These are going to be incremental steps. If we can reduce incidence by 50 per during the first five years of life when children are most vulnerable that would be a big step forward."

If approved by European regulators, the next step would be a recommendation from the World Health Organisation for its use. It would then be up to countries in Africa and other malaria-prone regions to decide whether to adopt the vaccine.

GSK has made clear that it sees RTS,S as a primarily humanitarian rather than commercial product. It says the price will cover the cost of manufacturing plus a profit of about 5 per cent to be reinvested in research and development for further vaccines against malaria and other neglected tropical diseases.

Mr Birkett says RTS,S must be the beginning not the end of the story. "We're taking a portfolio approach rather than putting all our eggs in one basket," he adds.

Other organisations are also entering the race. One of the most promising and advanced alternatives to RTS,S is being developed by a Maryland-based biotech company called Sanaria. Its vaccine, known as PfSPZ, successfully completed early-stage clinical trials last year.

Only three of 15 participants who received a high dose of the vaccine developed malaria after being exposed to infected mosquitoes.

Mr Birkett says the speed with which potential Ebola vaccines have been rushed into clinical trials from a standing start shows what can be achieved when the global community commits funding and attention to a health challenge.

He would like to see a similar push against malaria — a disease that kills more people around the world in a week than Ebola has killed in the past year.

"We need to build a whole suite of innovations including better diagnostics and better vector control, but the key missing ingredient has been a vaccine," says Mr Birkett. "We can battle the parasite with drugs and bed nets but eventually the parasite catches up. We believe the long-term solution has to be vaccination and eradication."

High hopes: a baby is injected as part of a malaria vaccine trial — Joseph Okanga/Reuters

Drugs New treatment could be ready by 2018

Artemisinin has been used to treat malaria since at least 1596, when Li Shizhen, a Chinese medical scholar, recommended that the plant extract should be given to infected patients in the form of a tea.

Four centuries later, artemisinin, derived from the sweet wormwood plant, remains the key ingredient in one of the most commonly used malaria treatments.

Modern artemisinin-based medicines were developed by the Chinese military in the 1960s to help protect North Vietnamese soldiers from the disease during their jungle battles with US-backed South Vietnam. The drug was commercialised by Novartis of Switzerland in the 1990s and artemisinin-based combination therapies (ACTs) have since become a main line of defence against malaria. About 260m courses are distributed each year.

However, like other treatments before it, ACTs are being gradually blunted as drug-resistant strains of malaria spread through parts of Southeast Asia. If these were to reach Africa, where the bulk of global cases are concentrated, the big gains made against the disease in recent decades could be quickly lost.

This explains the mounting urgency behind efforts to develop a new generation of malaria medicines. "New treatments must be developed that attack the malaria parasites in novel ways in case resistance against current treatments spreads," says Roger Waltzman, who is leading the development of an experimental Novartis drug called KAE609.

In a study among 21 patients in Thailand published last year, researchers saw "rapid parasite clearance" after the medicine was taken. This included some people with the ACT-resistant strain.

Nick White, professor of tropical medicine at Mahidol University in Thailand and lead author of the study findings, said KAE609 was "the first new antimalarial drug candidate with a completely novel mechanism of action to reach phase II clinical development in 20 years".

Novartis has predicted that, if further trials prove successful, KAE609 could be ready for market by 2018.

The drug is one of two experimental antimalarials under development by Novartis in collaboration with the Medicines for Malaria Venture (MMV), a Swiss non-profit group. Sanofi of France, GlaxoSmithKline of the UK and Takeda of Japan are among others working with the public-private partnership. They were joined this month by Merck Serono, the pharmaceuticals arm of Germany's Merck group, when it agreed to work with MMV on an experimental drug discovered at the University of Dundee in Scotland. Timothy Wells, chief scientific officer at MMV, said the compound "holds great promise".

While new drugs may be on the way, artemisinin-based treatments will continue to play an important role for years to come. Sanofi last year launched an ACT using semi-synthetic artemisinin to reduce dependence on volatile supplies of the sweet wormwood plant. The French company said it had capacity to produce 50-60 tonnes a year of the ingredient using genetically modified yeast, enough to meet a third of annual global need.

AW

Nick White: reports 'rapid parasite clearance' from a new treatment

Race against time to kill resistant mosquitoes

Insecticides Scientists and manufacturers must innovate to avoid a catastrophe in the decades to come, says *Andrew Bounds*

At the turn of the millennium, health experts hit on a way to reduce the scourge of malaria in the developing world. Distribute cheap bed nets impregnated with pyrethroid insecticides to as many households as possible, and spray homes regularly.

It worked well. Human death rates have almost halved while mosquitoes were killed in untold numbers: except for the tiny numbers immune to pyrethroids.

Those mosquitoes survived and became more prevalent. That growing resistance has left scientists and manufacturers in a race to develop new insecticides.

The World Health Organisation estimates that without new approaches, an extra 120,000 people will die each year.

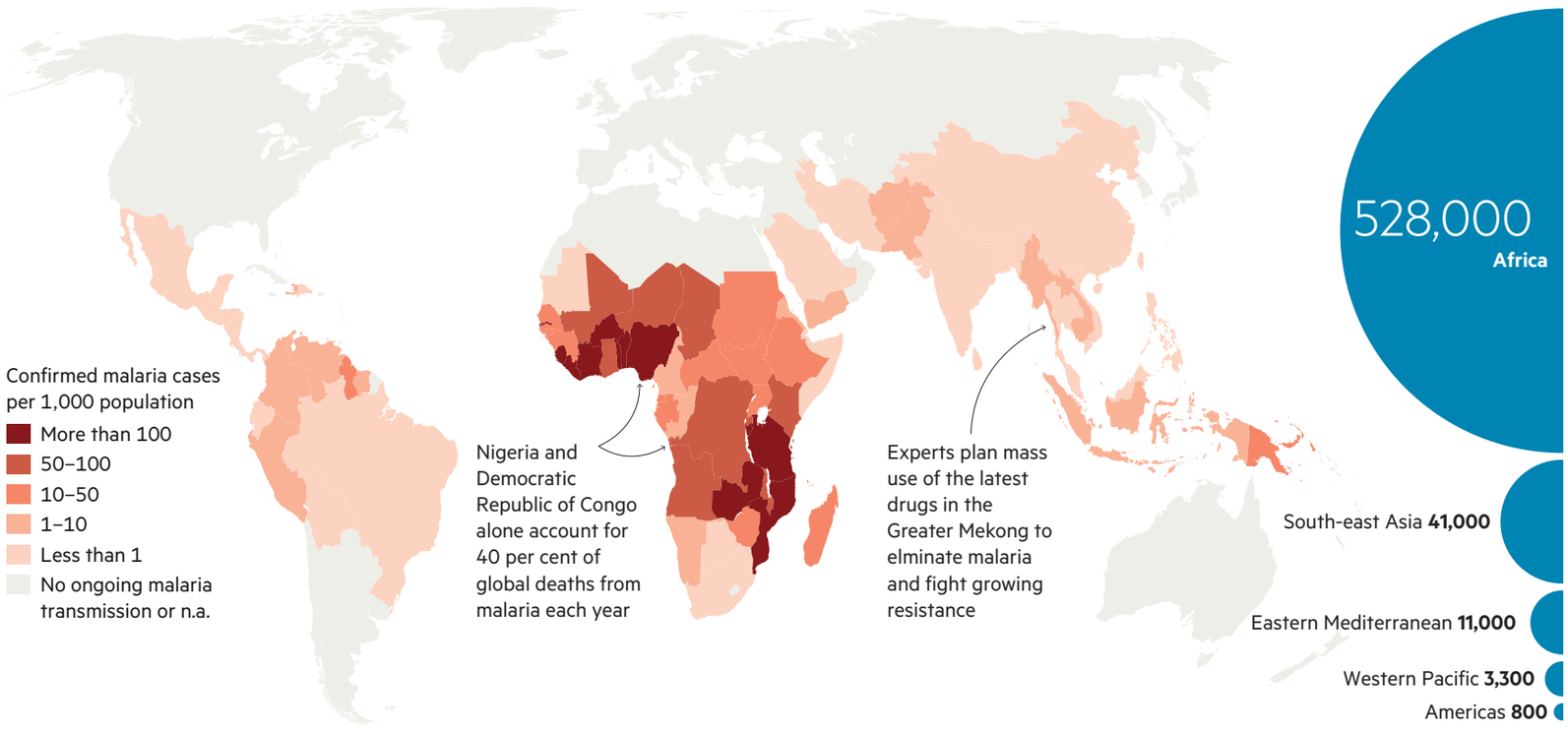
The Innovative Vector Control Consortium (IVCC), a disease research centre, says: "Resistance can occur at a low frequency for many years until a tipping point is reached, when resistance rises extremely rapidly, which can result in catastrophic failure of an intervention. We are almost at that point in many countries in sub-Saharan Africa."

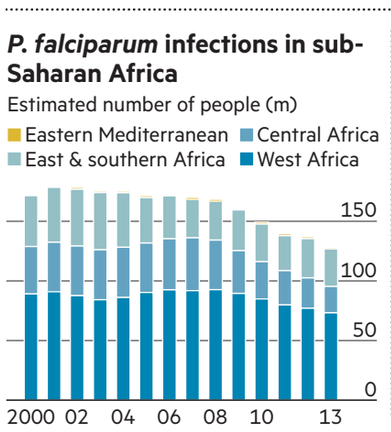
The IVCC, based at the Liverpool School of Tropical Medicine in the UK, is a not-for-profit organisation that works with companies such as Syngenta, Bayer, BASF, Sumitomo, Dow and DuPont to develop products that can help control diseases such as malaria.

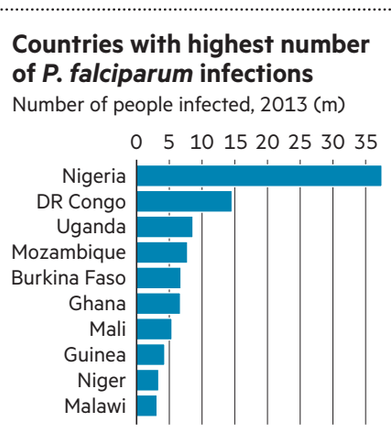
Professor Janet Hemingway, director of the of the School and an expert on mosquito behaviour, presides over some of the most advanced research anywhere into malaria and its carriers.

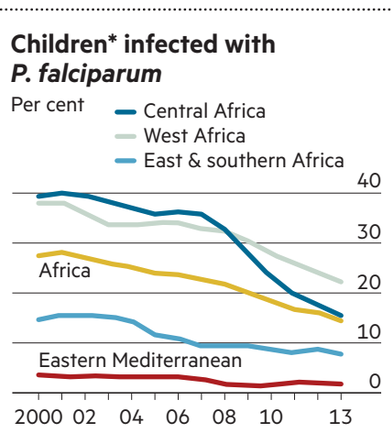
"Everyone is confident we will produce new insecticides in five to 10 years' time. The problem is we do not have very much beyond pyrethroids until then," she says.

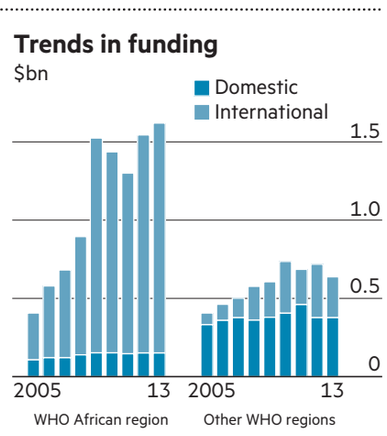
Malaria in numbers











FT graphic Source: World Malaria Report 2014

* Aged 2-10 years

Syngenta and the IVCC last year won WHO approval for Actellic 300CS, a spray for houses that is an organophosphate rather than a pyrethroid. It requires only one treatment per season but is between five and 10 times more expensive than a pyrethroid.

The WHO is trialling nets with a combination of insecticides, hoping they will work on resistant mosquitoes. Another new design has insecticide impregnated into yarn before the net is woven rather than sprayed after it is made, increasing efficacy. But costs could mount.

"There is nothing as cheap as pyrethroids," says Prof Hemingway. "It is going to be more expensive and people will have to factor that into their [donor] programmes."

Sumitomo Chemical has already warned of increased costs. Luke Lucas, business development manager for its malaria programme, says that different insecticides should be rotated.

The company's latest product, Olyset Plus, includes a pyrethroid but also piperonyl butoxide that can kill resistant insects.

"We see Olyset Plus as an interim solution," says Mr Lucas. "Of course, with all the research and development that goes into it, the net will cost more.

"Where resistance levels are seen to start to rise it's incumbent on those people to put pressure locally to say 'What other solutions have we?'" He adds that options could include larvicides, space sprays and residual indoor sprays.

Another priority is to reduce the use by farmers of pyrethroids to kill other pests, says Kobie Hyacinthe Toé, a PhD student who has been testing another Sumitomo product, the Olyset Duo, in Burkina Faso.

Farmers use the same insecticide to protect their rice and cotton crops. The rice and cotton fields are where mosquito larvae are found, increasing the likelihood of the adult insects becoming resistant. "We need the ministry of health and [the ministry of] agriculture to work together," he says.

Olyset Duo uses a pyrethroid insecticide and a chemical that prevents mosquitoes laying eggs, which will stop new resistant ones from hatching.

The trial is in its first year, with more than 60,000 nets distributed. Early signs are encouraging, says Mr Toé. However, he says malaria deaths in the country are increasing.

> 'There is nothing as cheap as pyrethroids . . . it is going to be more expensive'

"Because the number of mosquitoes is not very high, people sometimes go without the bed net."

Phil McCall, of the Liverpool School, believes products can save money by being smarter. He has been studying mosquito behaviour, rigging a hut in Africa with motion-sensitive cameras that allow researchers to record the flight pattern of a mosquito heading for a victim. Early findings could help net design by concentrating insecticide on those areas the insects visit most frequently.

Prof Hemingway says donors are investing in resistance-free alternatives. "The message is getting through."

A Tribute to Dr. Joel Jones

A Malaria Hero To Inspire Us All

Dr. Joel J. Jones, former manager of Liberia's National Malaria Control Program (NMCP), died suddenly on March 19, 2015. Dr. Jones was a physician and surgeon with a Masters in Public Health from the Institute of Tropical Medicine in Belgium. His education, coupled with his deep experience managing his network of private laboratories, FEW Diagnostics, which he founded and named in honor of his mother, Frances Estella Woods, served him well as the NMCP program manager.

Dr. Jones led national malaria control efforts in Liberia for more than ten years as a dynamic, capable, and effective, yet humble, manager. He was a strong leader with a kind heart and an amazing sense of humor that he skillfully used to bring levity to even the most serious situations, softening everyone's mood with his candid remarks and deep, honest, heartfelt laughter. Amicable and approachable he seamlessly coupled his technical knowledge on malaria control with his passion and vision for reducing malaria and saving lives of the most vulnerable in Liberia. Dr. Jones often wore traditional African clothes while presenting at international conferences, a way to show his pride in and confidence in Liberia's path to achieve this goal.

The malaria community would like to express its heartfelt condolences to Dr. Jones' family for their loss. He will be missed by his vast network of friends, colleagues, students, patients and his extended family in the USA, who fondly remember his longing for Liberian food while visiting. Colleagues and friends from all corners of the earth have reached out to share their condolences and good memories, noting that Dr. Jones was a natural and charismatic leader who touched and transformed so many lives through his generosity, kindness, hard work, and entrepreneurship. Dr. Jones' reach was boundless, always organizing, teaching and mentoring colleagues. He was generous with his time, energy, intellect and financial support, all provided with humor and love. He has touched all of us by his dedication to malaria control, yes, but primarily through his personal warmth.

Dr. Jones you will be missed – the malaria world has lost a good friend and an important advocate for what is possible with the right leadership and vision. May you rest in perfect peace.

— A Message from the "Friends of Dr. Joel Jones"