FT Health Combating Malaria

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Dose of reality hits hopes for vaccine

The World Health Organisation is positive but wants to see more evidence of benefits, writes *Andrew Ward*

No pain, no gain: the WHO has ordered up to five pilot programmes to take place in sub-Saharan Africa — AP Photo/Karel Prinsloo

It should be a time for optimism among those engaged in the fight against malaria. Incidence of the disease fell 37 per cent globally between 2000 and 2015, and mortality by 60 per cent, saving over 6m lives, according to the most recent World Malaria Report.

Malaria still kills more than 400,000 people a year, most of them children in Africa. But new weapons are arriving to aid the fight against it, most notably a vaccine that could eventually protect millions from infection.

So why, with so much good news, is the mood not more celebratory? For decades, a malaria vaccine was seen as the holy grail of tropical medicine. Yet, now one has arrived, it is causing fraught debate.

After 30 years of development by GlaxoSmithKline and its predecessor companies, the Mosquirix vaccine — also known as RTS, S — was endorsed last year by the European drugs regulator and the World Health Organisation.

On the face of it, the rulings were a vindication of the hundreds of millions of dollars invested in the project by GSK and donors led by the Bill & Melinda Gates Foundation.

The recommendations came with strong caveats and conditions, however, because the clinical data in favour of the vaccine were far from overwhelming. Malaria cases were reduced by between a third and a half in children aged 5-17 months — much lower than most vaccines. Moreover, the WHO concluded that four separate doses were required to provide enduring protection.

Médecins Sans Frontières, the health charity, said the benefits did not justify the investment needed to administer multiple doses in countries with weak health systems. MSF said resources would be "better placed on scaling up existing malaria treatment and prevention activities".

The WHO was more positive, highlighting the vaccine's potential to prevent up to 700 deaths per 100,000 vaccinations, amounting to "a significant public health impact" and "a high-level of cost-effectiveness" at an expected price of about $5 per dose.

It said more evidence was needed, however, to prove that the benefits shown in the controlled environment of a clinical trial could be replicated in more haphazard "real world" settings. To test this, the WHO has ordered up to five pilot programmes to take place in sub-Saharan Africa. Only if those prove successful will a wider go-ahead be given.

This has left advocates of the vaccine on the defensive. "It's the first vaccine for a parasitic infection. That's a big deal," says Jeremy Farrar, director of the Wellcome Trust, the London-based medical charity. "So I'm in the glass-half-full camp. You never expect first generation vaccines to be perfect."

Thomas Breuer, chief medical officer at GSK's vaccines unit, says the group is talking to the WHO "on a weekly basis" about the pilot programmes, which are expected to begin next year. GSK has promised to price the vaccine at "cost plus 5 per cent", with the profit put back into further malaria research.

GSK's main collaborator is the Malaria Vaccine Initiative, an offshoot of the Seattle-based Path health charity backed by the Gates Foundation. MVI's director, Ashley Birkett, says researchers are working on an improved, second-generation version of RTS, S, while also exploring other approaches. One of the most promising is a so-called transmission-blocking vaccine that creates antibodies in the blood which, when imbibed by a mosquito, disables the insect's ability to pass on the parasite to other people.

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Inside

Conditions conspire against DRC control effort

Raised threat Stability may have returned to the country but so have more mosquitoes, *Andrew Jack* reports

Overwhelmed: three or four patients have to share a bed at an MSF-supported hospital in Baraka, eastern DRC
MSF/Eddy Van Wessel

Floribe Sefu, the chief of Kimeso, a remote and dusty village in the Bandundu province of the Democratic Republic of Congo, does not hesitate as he reels off from memory the long list of prices of different medical treatments when his people fall ill. One stands out in particular. "It costs us 30,000 [Congolese francs, some $32] for a blood transfusion for malaria," he says.

The fact that he and other poor villagers have to pay for medical services at all might be seen as burdensome enough. Such payments consume a significant share of local farmers' incomes and act as deterrent to people seeking medical help when it is required.

That Mr Sefu highlights the price tag for a malaria treatment reflects the continued heavy toll taken by the disease in the country. Its effects have persisted despite a decade of rising global donor assistance providing new bed nets, diagnostics and drugs that have helped sharply to reduce malaria's impact across most of Africa.

The village head's account also suggests one of two troubling scenarios — either there is significant incidence of severe malaria with anaemia, which in extreme cases can justify blood transfusions, or perverse financial incentives are encouraging the costly and risky overuse of such transfusions.

Pete Zacharias from the Safe Blood for Africa Foundation, a South African charity supporting improved services, doubts there is overuse of transfusions but warns of a lack of funding and data in the DRC. "There is not sufficient attention being paid to blood safety," he says.

Such issues are very important not only for the DRC. It and Nigeria account for more than a third of the annual estimated 438,000 deaths in the world from malaria, according to the World Health Organisation's malaria report for 2015. Without marked improvements, the absolute numbers will remain high and a deadly threat to the quality of life in the DRC and beyond.

Dr Hamidou Ouattara from Médecins Sans Frontières, the medical charity, says he is bracing himself for a renewed surge in malaria cases in the DRC. His expectation is the result of a pattern that MSF has observed in the past few years, notably in the country's eastern provinces. "The explosion in cases is high," he says. "Medical structures are overflowing. It's a problem."

In the past, political instability undermined medical services and created severe difficulties in treating malaria. While uncertainty could return, for now the relative peace and resettlement of people in areas previously hit by conflictbrings a different type of threat. Farmers returning to their fields are growing rice and digging ponds to cultivate fish. Both encourage stagnant water, a breeding ground for malaria-carrying mosquitoes.

> 'The explosion in cases is high. Medical structures are overflowing'

In MSF-supported clinics in the east, Dr Ouattara sees blood transfusions as a barometer of the heavy continued burden of the disease: "10 per cent of our patients were transfused — because it's a problem linked to serious malaria. Malaria is the main cause of hospitalisation for children."

Michael Humes, who oversees the DRC for the US government's President's Malaria Initiative, says substantial investment in the fight against malaria in the past few years has meant a drop in child mortality in the country from all causes, though much of it is likely through a fall in the burden of malaria. He says the most recent surveys suggest 70 per cent of families now have a bed net to protect against mosquitoes, and over half of children sleep under them regularly.

"We are at an interesting time," says Mr Humes, "with a real emphasis on scaling up" the use of bed nets across the country. In this, he stresses the role played by strong local leadership from government officials responsible for malaria. Also of great importance has been investment in an internet-based district health information system, which is beginning to increase understanding of malaria and how to respond.

Yet the DRC, with its sprawling landmass, fragmented transport and communications network and weak funding for government health structures, has difficulties with widespread and consistent application of techniques to tackle malaria. Best estimates suggest the DRC had 16m-26m cases in 2014 and 33,000-72,000 deaths. In the absence of reliable reporting systems, the figures amount to guesswork.

In the village of Nsele, in the eastern environs of the DRC's capital Kinshasa, it takes villagers over an hour to walk to the nearest clinic. In the predominantly rural district's own rudimentary pharmacy, the only drug available to treat malaria is sulfadoxine-pyrimethamine (SP).

The medicine is cheap and can help prevent infections in mothers with young children but SP is no longer recommended as the first line of therapy for people who have already been infected.

In larger pharmacies in Kinshasa and elsewhere, different drugs are available, although not only artemisinin-combination therapy (ACT), which is the recommended treatment in Africa.

For now, there are few indications that malaria in the country is proving resistant to ACTs, although a study by MSF in 2013 suggested some patients were not taking the medicine as prescribed, therefore limiting the effectiveness of the treatment.

There are also some signs of rising resistance by mosquitoes to insecticide-treated bed nets.

At the same time, efforts to fight malaria encounter more basic problems — a limited awareness of the disease and its consequences is sometimes among them.

In Loma, in the coastal province of Bas Congo to the west of Kinshasa, for example, local resident Nana Tekabanza lives in a cramped adobe hut. Inside her home, she points to a mosquito net recently given to her by her five children. The net lies unused and still in its wrapper. "It is too hot to sleep under," Ms Tekabanza says.

Impact measurement set to play innovative role in fundraising

Financing

While charitable giving is still vital, bonds open way to some intriguing possibilities, writes *Sarah Murray*

In January, the UK government and the Bill & Melinda Gates Foundation announced funding of £3bn over the next five years for the battle against malaria. Such donor support will remain crucial, yet other and quite innovative forms of funding projects could also come to play a vital role.

One is the so-called development impact bond, or DIB. The idea of issuing a DIB to raise money to fund the fight against malaria was born a few years ago. At that time, the Roll Back Malaria campaign engaged Dalberg, a global development consultancy, to structure a malaria bond and study its feasibility.

"We got the endorsement from Roll Back Malaria that this was an interesting model to test so we looked at how to pilot that in Mozambique," says Barbara Kong, a senior investment principal at D. Capital Partners, the Dalberg subsidiary that has structured the bond.

The first malaria bond has yet to be issued but, with a goal of raising $3.5m, so far the bond has secured a commitment from Nandos, the restaurant chain, which has pledged funding of $1.5m.

As with social impact bonds, DIBs raise funds from private investors. The bonds rely on "outcome funders" — governments, international donors, companies — who commit to paying returns to investors when a programme's goals have been reached. "Outcome funders only pay for the result once it's achieved," says Ms Kong.

The results might take the form of fewer incidences of people going into hospital and lower demand for medicine. Also, incomes rise when people are no longer falling ill, which means they also have more disposable income to spend on consumer goods — outcomes that could also be tracked, explains Sherwin Charles, co-founder and chief executive of Goodbye Malaria, a public-private consortium established to help launch the malaria bond.

While DIBs are in their infancy, those behind them believe the model lends itself to combating malaria. In order to trigger returns to investors, goals must be met that require assessment of the impact of measures.

"Funders are starting to become more aware of using data," says Aunnie Patton of the University of Cape Town. She leads the innovative finance programme at the university's Bertha Centre for Social Innovation and Entrepreneurship.

While traditional funding is often directed towards individual programmes — from drug research to the provision of mosquito bed nets — the DIB allows for holistic approaches to eradication that might include several forms of intervention.

$3.5m Figure that first malaria bond aims to raise

$1.5m Sum pledged by restaurant chain Nandos

Although it was corporate funding rather than a bond that financed it, Dalberg's three-year pilot programme that concluded last year in several small districts in Mozambique demonstrated that this co-ordinated approach reduced the prevalence of malaria by 70 per cent, approximately in line with global targets. It is this approach that the Goodbye Malaria consortium intends to scale up once funding is raised through a DIB.

Mr Charles argues that malaria bonds could provide funding for the elimination of malaria in places where the disease is lower on the list of government or donor priorities.

Investors are expressing interest, says Ms Patton: "Being able to eradicate malaria and get a financial return is incredibly attractive."

However, Mr Charles reports that the Goodbye Malaria consortium faces problems given the difficulties that confront some potential investors. "A lot of mining companies are in malaria areas," says Mr Charles. "[But] because of the downturn in their business, they don't have the money to invest as an outcome funder."

Ms Kong says while it may take time to secure outcome funders, and DIBs will not remove the need for donor funding, the underlying rationale for the financing model is strong.

"It can help mobilise new sources of funding from the private sector," she says. "The focus on outcomes brings in more efficiency."

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Scientists zero in on mosquito DNA to repel transmission

Biology Genetic modification may prove to be vital tool in reduction of outbreaks, writes *Clive Cookson*

Big buzz: Anthony James (above) of the University of California regards developments so far as 'significant'—Steven Zylius

Researchers are waging war against malaria on two broad fronts. One is development of drugs and vaccines against *Plasmodium*, the protozoan parasite that directly causes the disease. The other uses new technology to attack the mosquitoes that transmit the parasite between people.

Long before the 19th century discovery of the role mosquitoes play in transmitting malaria, people recognised that the disease was most prevalent in marshland. They blamed the bad air (*mal'aria* in old Italian) associated with swamps and, as they drained the land, health improved because mosquitoes no longer had stagnant water in which to breed.

This ancient and inadvertent method of mosquito control was extended during the 20th century with chemical warfare, which was waged with insecticides and insect repellents.

The 21st century promises to bring biology to the forefront of the battle. This is through releasing genetically modified (GM) mosquitoes that either suppress the wild population of disease-transmitting insects or replace it with a GM strain that does not carry the parasite.

GM insect technology is not yet in commercial use anywhere in the world and some environmental campaigners oppose its introduction, saying it poses an unacceptable ecological risk. Nonetheless, research is increasing rapidly.

There are two main reasons for the current urgency in the battle against mosquitoes. The most immediate is a new epidemic of Zika, a mosquito-borne disease, in Latin America.

Although the *Aedes* mosquitoes that transmit Zika — and other diseases including dengue, chikungunya and yellow fever — are a different genus to the *Anopheles* carriers of malaria, much of the research is likely to be applicable to both types.

The second accelerator of GM insect research is the emergence over the past three years or so of new "gene editing" technology. In particular, this involves a technique called Crispr — pronounced "crisper" — and which is short for "clustered regularly interspaced short palindromic repeats". The method enables researchers to manipulate specific genes — adding, subtracting or changing DNA — far quicker and more precisely than previous techniques of genetic engineering.

Crispr has a guidance molecule that can be targeted to any stretch of DNA. Then a companion enzyme cuts the DNA in exactly the right place, allowing scientists to snip out unwanted DNA, add new DNA or regulate genetic activity, before joining up the cut ends.

Several labs have reported successful mosquito-modifying experiments using Crispr, which include the "gene drive" technique. This process overrides the normal constraints of evolution and ensures that when a GM mosquito mates with an unmodified wild mosquito almost all of the offspring receive the edited gene, rather than half, as would otherwise be the case. As a result it can spread very fast through an insect population.

Last November, for example, scientists at the University of California inserted a gene for anti-malaria antibodies with a gene drive system into *Anopheles* mosquitoes. The research is at an early stage and further lab tests are needed to show how effectively the antibodies prevent malaria infection.

> 'It will be at least 10 more years before "gene drive" malaria mosquitoes could be a working intervention'

"This is a significant first step," says Anthony James of the University of California, Irvine, the project leader. "We know the gene works. The mosquitoes we created are not the final brand but we know this technology allows us efficiently to create large populations."

Scientists at Imperial College London have created a different type of gene drive, which disrupts egg production in female *Anopheles gambiae*, the most important carrier of malaria in Africa. This infertility would quickly reduce wild mosquito populations — and therefore the malaria transmission to humans — to very low levels.

African ecosystems should not be affected significantly by suppressing just one of the continent's 800 mosquito species, researchers say, while the benefits to human health could be enormous.

"As with any new technology, there are many more steps we will go through to test and ensure the safety of the approach we are pursuing," says Professor Austin Burt of Imperial College. "It will be at least 10 more years before gene drive malaria mosquitoes could be a working intervention."

One approach, based on older GM technology, however, is much closer to commercialisation. The "sterile insect technology" produced by Oxitec, a UK company spun out of Oxford university in 2002, inserts a "dominant lethal gene" that enables males to mate with females but kills their offspring while young. A sufficient number of these GM males are bred in the laboratory to be released and swamp their wild counterparts. They mate with all available females, which then fail to reproduce. The effect is to suppress the pest population greatly.

The strategy, tested over the past five years in field trials in several tropical countries, means releasing many millions of insects — 10 times more at least than the wild population.

Oxitec is focusing its research and development efforts on *Aedes* mosquitoes but Hadyn Parry, chief executive, says the company's scientists have shown that the same technology can be applied to the *Anopheles* mosquitoes that transmit malaria.

Dose of reality greets high hopes for vaccine

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Mr Birkett cautions against expecting any vaccine to provide a "silver bullet" against the disease. "Every tool against malaria is imperfect. The vaccine is a supplemental tool on top of what we already have."

BT Slingsby, chief executive of the Global Health Innovative Technology Fund, the Japanese public-private partnership which has invested $21m in antimalarial initiatives, says improved diagnostic technology should be another priority. His fund is helping develop a test that can be used in the field to diagnose malaria in 10 minutes.

"Diagnostics can be a game-changer by ensuring that the right people get the right treatment quickly," says Mr Slingsby. "They can also help tackle drug resistance by reducing unnecessary courses of treatment."

Thomas Breuer, GSK's chief medical officer, says the group speaks to the WHO 'on a weekly basis'

Resistance to existing drugs and insecticides is an ever-present threat to progress against malaria, as the Plasmodium parasites responsible for the disease gradually find ways to evade them. Artemisinin-based therapies — the dominant treatment for malaria — is encountering pockets of resistance in Southeast Asia. Should these strains spread to Africa it could put the gains of the past 15 years into reverse.

"Progress is still fragile," says Dr Farrar. "Back in the 1960s we had a surge of resistance and that could happen again. We have to come up with new drugs but in the end we will always be in a race with the evolution of the parasite.

"Some people fall into the trap of saying it's all about vaccines, or it's all about drugs or bed nets. We need to get out of our silos and find the best way of using them together."

Pharmaceuticals Disease-carrying mosquitoes are overcoming ancient remedy, reports *Andrew Ward*

Hunt is on for ways to fight raised insect resistance

China's first Nobel Prize for physiology or medicine was 419 years in the making. Tu Youyou, an 85 year-old chemist, won last year's prize for her work in the 1970s developing artemisinin as a malaria treatment.

She had been alerted to the potential of artemisinin — an extract from the sweet wormwood plant — after scouring Chinese literature in search of traditional herbal remedies for the disease.

Records of sweet wormwood, or *Artemisia annua*, being used against malaria date back to at least 1596, when Li Shizhen, a Chinese medical scholar, suggested that it be given to patients as a tea.

It is still one of the main weapons in the world's armoury against the disease. Treatment courses of artemisinin-based combination therapies increased from 11m in 2005 to 392m in 2013 as global health authorities put the drug at the centre of their fight against the mosquito-borne scourge.

Concern is growing, however, that four centuries after artemisinin's first use, the parasites responsible for malaria may be starting to get the better of its ancient powers. Artemisinin-resistant strains were first detected eight years ago in western Cambodia. Cases have since been detected in Myanmar, Thailand, Vietnam and Laos.

For global health leaders, the pattern is alarmingly similar to the way resistance to chloroquine, another malaria treatment, emerged in Southeast Asia in the 1950s and spread to Africa — where the large majority of cases occur.

"We see a little bit of history repeating itself," says Thierry Diagana, head of the Novartis Institute for Tropical Diseases. "Artemisinin resistance has spread as far as the western border of Thailand and Cambodia. If it crosses into India it will become a much bigger challenge."

Novartis, the Swiss pharmaceuticals group, commercialised artemisinin combination therapy in the 1990s. The group is among the leaders in the hunt for new drugs to replace artemisinin as its efficacy fades.

In 2014, the Novartis unit led by Dr Diagana demonstrated the first clinical proof-of-concept — a clinical trial showing that a drug works — for a new malaria treatment. The compound, codenamed KAE 609, works by interfering with the sodium concentration in both of the two parasites that cause the majority of cases. *Plasmodium vivax* is common in Asia and South America, while the more virulent *Plasmodium falciparum* is most prevalent in Africa. Importantly, KAE 609 also worked in people with artemisinin-resistant strains in Southeast Asia.

Prize find: Nobel laureate Tu Youyou scoured Chinese literature in search of traditional herbal medicines — Jin Liwang/Xinhua/AP

'Artemisinin resistance has spread [and] if it crosses into India it will become a much bigger challenge'

Proof-of-concept data are expected soon on a second Novartis compound, known as KAF 156. It has shown promise against drug-resistant strains of both parasites as well as a further unique advantage. Unlike artemisinin-based therapies, KAF 156 acts against the parasites while still in the asymptomatic "liver stage" of the disease, before it has spread into the blood stream.

This would enable it not only to treat sufferers at malaria's earliest stage — the disease can remain dormant in the liver for months after infection — but also prevent them passing on the parasite to mosquitoes for further transmission.

The positive early data must be replicated in larger studies if KAE 609 and KAF 156 are to satisfy regulators. Dr Diagana says Novartis aims to have at least one of them on the market by 2021.

The Novartis compounds are among the most promising of over 50 antimalarial products being developed in partnership with the Medicines for Malaria Venture (MMV). Donors including the Bill & Melinda Gates Foundation, the UK Department for International Development and the Wellcome Trust have pledged $865m to the non-profit organisation since it was set up in 1999.

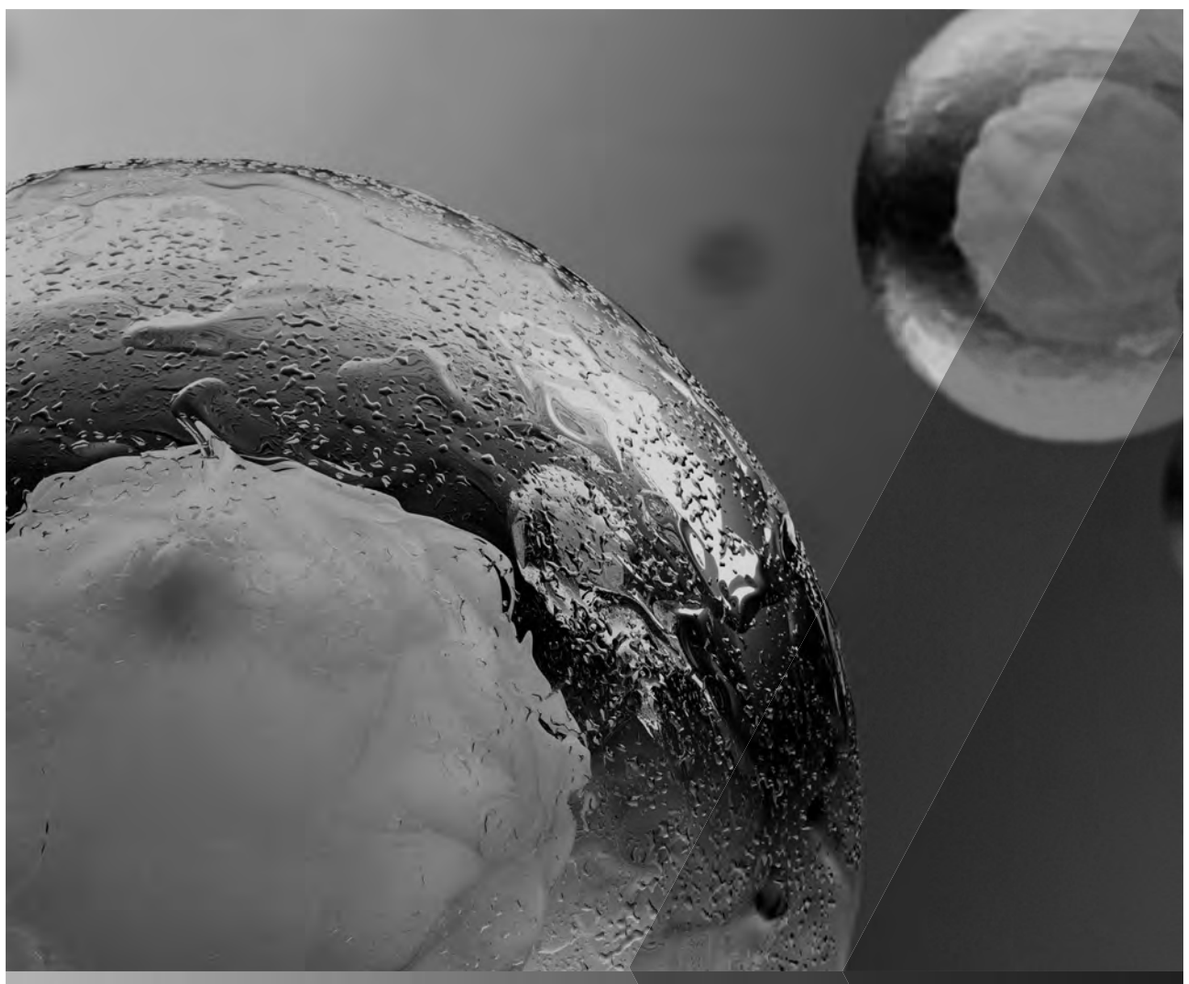
However, that is small compared with the billions of dollars invested by the pharmaceuticals industry in more commercially attractive disease areas such as cancer, and progress is slow. It typically takes about 10 years to get a new drug from early stage development to market and less than 10 per cent of candidates make it all the way.

The MMV is not relying solely on big pharmaceuticals groups. It has also awarded research grants for academics to pursue assets from its so-called Malaria Box of compounds that have shown potential against the disease but have lacked funding for development.

Back in China, last year's Nobel Prize for Ms Tu — she is neither a doctor nor professor — has stirred pride but also surprise that she received little previous recognition in her own country. The official Xinhua news agency said that the four-decade gap between her discovery and the award showed that "science is never about instant success."

The spread of artemisinin-resistant malaria is adding urgency to the search for a fresh generation of drugs. In her Nobel lecture in Stockholm in December, Ms Tu issued a "severe warning" over the looming threat to the drug she helped discover.

Dr Diagana says that Novartis and its partners are moving as fast as possible. "It's a good time for malaria drug discovery," he says. "But we need to make progress quickly so we can avoid another global failure like we had with chloroquine."



Mobile phone data help contain the human spread of infections

Surveillance

Understanding how people carry malaria parasites is essential to eliminating the disease, reports *Fergus Ryan*

Namibia is one of the driest places on earth, with large tracts of its often desert landscape having less than 50mm of rain a year. Nonetheless, it has suffered the effects of malaria and, up until 2004, as many as 600,000 new cases were reported each year.

Cases have since fallen about 98 per cent to 14,400 a year. While this is a remarkable feat for any health service, the Namibian government is resolved to push on. From 2007, it has been signatory to the Elimination 8, or E8, initiative, which aims to stamp out malaria in eight southern African countries.

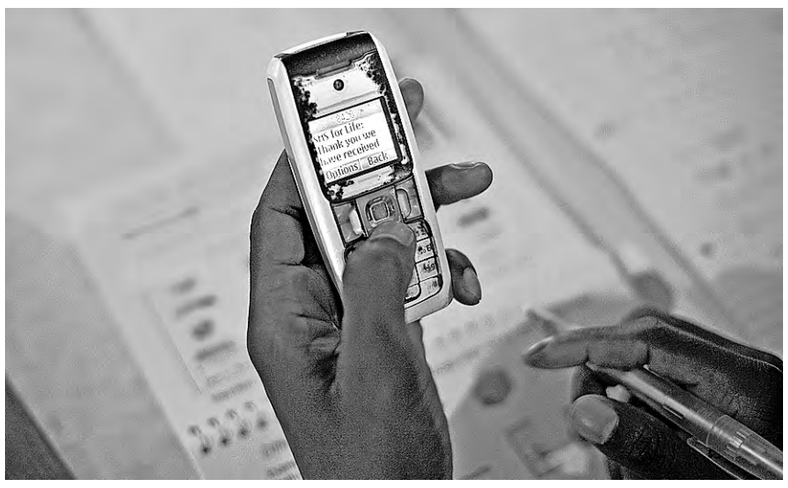
Namibia's health and social services ministry aims to reduce malaria infections to fewer than one in 1,000 in every district of the country's 824,000 sq km by 2017. Understanding the distribution of the changing malaria transmission, it says, "is essential in guiding and defining the elimination strategy". To achieve this, it is vital to have highly sophisticated data.

Across the continent, lying off Africa's east coast, is Zanzibar, a semi-autonomous part of Tanzania. Zanzibar's regional government aims to rid its land of malaria and has called in experts, including Andy Tatem, a professor at the University of Southampton and director of the WorldPop project focused on population distributions and dynamics. "Malaria is typically not spread over large distances by mosquitoes. Mosquitoes fly short distances and only live for a few days. It's humans who carry the disease across and between countries," says Prof Tatem.

Understanding how humans move and carry malaria parasites between areas is essential to eliminating the disease from a region, he says.

Prof Tatem is also co-director of the Flowminder Foundation, a non-profit organisation based in Stockholm. Its mission "is to improve public health and welfare" in developing countries.

To achieve this, the foundation "collects, aggregates, integrates and analyses anonymous mobile operator data, satellite and household survey data".



On the record: phonecalls aided creation of detailed map of transmission

When the Zanzibar study began in 2008 there was little information on how people moved between its islands and the mainland, so Prof Tatem and his team turned to mobile phone records provided by telecoms operator Zantel to track population movement.

The anonymous phone records were used in conjunction with malaria maps from across the Tanzanian mainland, where travellers from Zanzibar were exposed to higher infection risks.

Prof Tatem and his colleagues used the phone records and risk maps in a mathematical model to produce the first malaria importation rate estimates for Zanzibar. The model highlighted that strategies to eliminate the disease were costly in the short term compared with maintaining control efforts, such as indoor spraying and using insecticide-treated bed nets. It also found that reducing transmission in mainland Tanzania would be effective.

The study was to pave the way for the use of mobile data for a host of development initiatives across the world.

'We've made a good start [but] we still have some way to go before we can consign malaria to history'

The financial and human cost of malaria is staggering. The African Leaders Malaria Alliance estimates that 40 per cent of healthcare spending in endemic countries is spent on dealing with malaria, costing the continent about $12bn a year. According to the UK's Department for International Development (DfID), as many as three out of 10 hospital beds in endemic countries are occupied by malaria patients.

DfID estimates that up to 39 per cent of total health expenditure in Tanzania is directed to malaria prevention and care, costing the country 3.4 per cent of its gross domestic product.

Malaria also reduces foreign direct investment, trade and tourism. For Namibia, and indeed many African countries, tourists are a vital source of foreign currency and employment. The significant reduction in malaria cases is a boon for international tourism. The disease, however, has still not gone away completely.

In Namibia, Prof Tatem and the National Vector Borne Disease Control Programme worked with Mobile Telecommunications, the country's largest mobile operator. Satellite images and case data were used to map the environment in which mosquitoes thrived. Those images and the anonymous mobile phone records helped create a detailed map of malaria transmission.

Before the map, it was estimated that 1.2m people were at high risk, requiring substantial costs and effort to reach everyone with control methods. The new map, however, highlighted that only 80,000 people were at high risk in the malaria transmission cycle. With that information, the Namibian health department was better equipped to intervene, by such as indoor spraying of insecticide to disrupt transmission.

"We've made a good start," says Prof Tatem, "[but] we still have some way to go before we can consign malaria to history."

Net makers afforded scant protective cover

Africa Global market can make life tough for local manufacturers, reports *John Aglionby*

Logic would suggest that A to Z Textile Mills is a company in the right place at the right time. This family-owned enterprise on the western outskirts of Arusha in northern Tanzania is one of the largest makers of long-lasting insecticidal bed nets in Africa, where 90 per cent of such nets are found.

Yet, despite being nearer to the main market than most of its competitors and a buoyant demand, Kalpesh Shah, one of the directors, says the company in the past year had to lay off almost 600 of the 4,500 staff who make the nets. This is thanks to fierce competition with companies manufacturing elsewhere in the world, particularly east Asia.

The majority of the world's mosquito net business is funded by donors such as western aid agencies. But most offer tenders based on the price at the point of dispatch from the factory without taking into account delivery costs, which are borne by manufacturers. Mr Shah says A to Z would "have some sort of parity" if donors considered overall costs. "We have to import all of our raw materials and so we're always going to be expensive [at the point of dispatch]."

The Global Fund to fight Aids, Tuberculosis and Malaria does have a tender process that "uses delivery to market prices", it says. "This is more effective and cost-efficient for the Global Fund and the people who will receive the nets. Procuring nets close to where they will be used means we save money on shipping costs and delivery is much faster."

Since the Global Fund introduced market delivery tenders in 2012, A to Z has won "the largest portion of the tenders for the Global Fund for bed nets worldwide", it says. But, despite this, the company says it is still losing out.

Mr Shah says A to Z, which claims to have started with a single sewing machine five decades ago, made almost 25m nets in the past year, about a sixth of the demand in sub-Saharan Africa. Most were delivered to east and southern Africa, places where, because of the factory's location, it is competitive on an overall cost basis. The cost of doing business in Africa, however, means manufacturers such as A to Z cannot compete entirely equally. "Distribution costs to west Africa are higher from Tanzania than Vietnam," he says of the south-east Asian nation, which is also one of the world's leading producers. "This demonstrates the challenges of doing business in Africa and why more manufacturers are not based here."

Up in the air: Africa would not be 'an accountant's first choice' — Charles Ommanney/Getty

A steadily more crowded marketplace is making life tougher. Since 2010 the number of manufacturers of World Health Organisation-approved nets has risen significantly, to the extent that annual global output capacity is more than 300m. Aid agency tenders — which comprise the majority of demand — total about 60 per cent of that.

Indeed, A to Z, which also makes agricultural bags, garments and plastic products, only started manufacturing bed nets thanks to a corporate social responsibility partnership with Sumitomo Chemical. It began with a transfer of technology pilot project in 2003. Five years later this progressed into a manufacturing joint venture, even though both companies conduct marketing operations individually and sometimes compete for tenders.

Adam Flynn, a Sumitomo strategic communications and marketing manager, admits: "African manufacturing wouldn't be an accountant's first choice.

"But, with our corporate and social responsibility ethos, we're taking a long-term view," he says. "We think we have a moral duty to Africa and it has the skills and a rich textile heritage."

In addition to the nets made by A to Z, Mr Flynn hails the social, economic and indirect health benefits that accrue from manufacturing in Africa. For example, he cites the jobs that have been created at A to Z — most filled by women — as another way of helping to fight diseases such as malaria.

"Look at the millennium development goals and the sustainable development goals," he says. "They talk about [lack of] development being a big part of why global health epidemics survive."

While most manufacturers do not have factories in Africa, they do have research facilities on the continent. Swiss-based Vestergaard, one of the world's biggest producers, says it is not economically viable to manufacture nets in Africa but has a laboratory at the University of Ghana.

Helen Pates Jamet, head of entomology at the company, says it is "crucial to maintain a strong presence on the ground, both by being able to access the right mosquitoes and building capacity in Africa to address capacity gaps".

She says products developed at the laboratory are tested and used by staff and their extended families.

The good news for manufacturers such as A to Z is that, although more countries are moving towards elimination and eradication of malaria, demand for nets is not likely to abate soon.

"In order to cement the progress that has been made nets are going to continue to be necessary for many years," Ms Pates Jamet says. "And even if there wasn't malaria, people still like to sleep under a net to keep mosquitoes away."

Doctors focus on role of disease in maternal deaths

India

Experts in deprived tribal areas say pregnant women need better treatment and testing, writes *Amy Kazmin*

India's vast tribal belt, which ranges across its central heartland and up its eastern flank, is home to indigenous and animist communities, whose disparate mother tongues traditionally had no written form. Isolated and undeveloped, these regions have some of India's highest incidence of malaria, as mosquitoes thrive in its dense forests. The tribal belt also has some of India's highest rates of women dying during or after pregnancy and childbirth.

India's public health establishment has not identified malaria as a contributory factor in the country's estimated 44,000 maternal deaths each year. Nor does India have specific policies for routine testing and treatment of malaria in pregnant women, unless they report to doctors exhibiting classic malaria symptoms.

Public health professionals working in the tribal regions are convinced, however, that the disease is an underlying factor in a significant number of the maternal deaths they see. They believe India needs new approaches to identifying and treating pregnant women infected with the parasites in order to protect them and their unborn children.

"We usually find there are 20 to 30 per cent more maternal deaths in districts that have malaria compared with those that don't," says Prabir Chatterjee, a doctor at the state health resource centre in Chattisgarh, a tribal belt state. "My interpretation is that the 20 to 30 per cent may be due to malaria."

In many African countries with a high incidence of malaria, pregnant women are routinely screened for malaria or given preventive treatment. In India, malaria has never been treated as a big problem for pregnant women, as the national incidence is relatively low.

Doctors working in the tribal areas say India needs different protocols for malaria hotspots. Specifically, they advocate that pregnant women be tested routinely for malaria during their prenatal check-ups using low-cost rapid diagnostic kits. Women found to be infected could receive treatment to ensure they do not develop a full-blown case of the disease. Many private hospitals follow such practices.

'Is malaria in pregnancy an issue? Yes. How big? Nobody knows'

"Is malaria in pregnancy an issue? Yes," says John Oommen, a doctor at Christian Hospital in the remote Bissamcuttak district of Orissa, another state in the tribal belt. "How big? Nobody knows. Are some things being done? Yes. Can we do more? Yes."

Researchers from the London School of Hygiene and Tropical Medicine are conducting a long-term study in Jharkhand state, also in the tribal belt, to assess whether routine malaria screening would improve maternal health. The results are expected to tilt the debate on whether the cost of such an intervention would be worth it for India's cash-strapped public health system. "We are at a crossroads," says Suranjeen Pallipamula, a maternal mortality expert in Jharkhand. "We can't really say it should be done. We are still waiting for evidence to see if it's effective or efficient."

Doubts: critics contest official data

Chattisgarh officials decided last year to require such testing as part of antenatal care in high-malaria districts. The scheme has yet to be implemented fully. In Jharkhand, some urge such screening on a pilot basis in areas with the highest burden of malaria. "We believe the malaria programme is definitely improving every day," says Dr Pallipamula. "But unless you focus on pregnant women, you are not going to impact malaria in pregnancy."

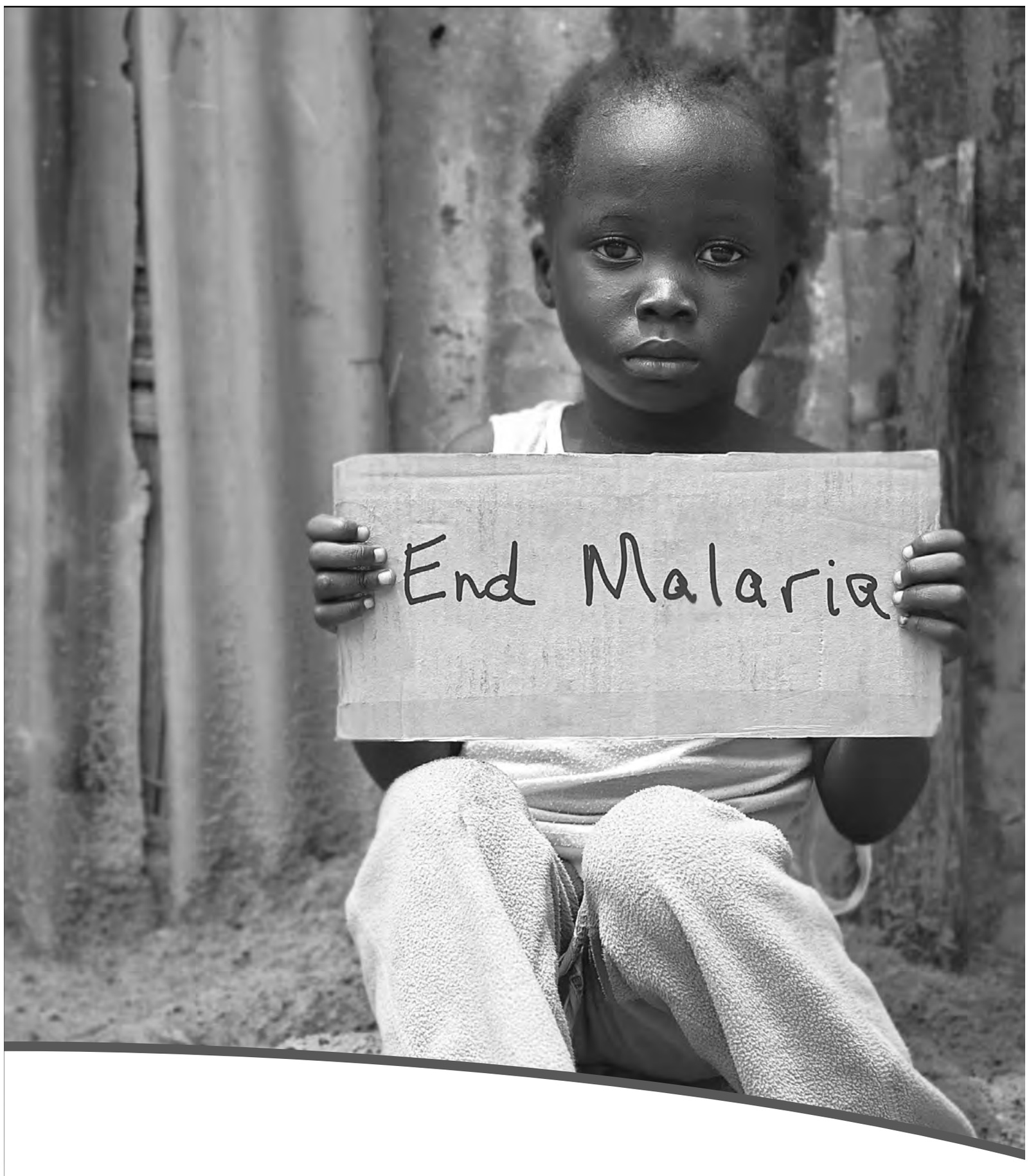
India's malaria burden is debated hotly between the government and independent researchers. New Delhi estimates it has some 1m cases and a few hundred fatalities a year. Researchers who have studied mortality patterns say 125,000 to 277,000 malaria fatalities a year is a more "plausible range".

India's policy is only to count a malaria case or death if the disease is confirmed by blood-test at a government hospital. Critics believe this severely underestimates the true burden, as many ailing Indians seek private treatment, or never see a doctor.

What is clear is that malaria is disproportionately concentrated in the tribal belt and its poorly-educated indigenous communities which have limited public healthcare provision.

An analysis in the Indian Journal of Medical Research last year observed that districts with a tribal population of 30 per cent or more account for just 8 per cent of India's total population. Yet these districts account for 46 per cent of India's total malaria cases and malaria deaths.

For pregnant women and their unborn babies, malaria can have severe consequences ranging from low birth weight to miscarriage. It can leave women severely anaemic, raising risk of complications during labour and delivery, particularly the risk of severe, possibly lethal, post-partum bleeding.



Industry wants WHO to accelerate testing regime

Public health New products delayed as arguments about efficacy continue, reports *Andrew Jack*

Hilary Ranson is concerned about data that defy the longstanding trend in Africa that the use of insecticide-treated bed nets to kill mosquitoes substantially reduces malaria deaths.

In Burkina Faso, Uganda and some regions in a growing number of other countries, mosquito resistance to pyrethroids, the only insecticide approved for bed nets since the 1980s, is rising.

Yet, despite efforts to launch new products that will keep killing mosquitoes, their introduction has been tardy. "I have been shocked," says Prof Ranson, head of the department of vector biology at the Liverpool School of Tropical Medicine. "There is pretty effective bed net coverage but malaria cases are going up. I really feel this is the tip of the iceberg for Africa."

Work is under way by companies and academics, including those at Prof Ranson's university, to replace pyrethroids with new chemical compounds, but she predicts none will be available until at least 2020.

Several companies have developed alternatives that could be a stopgap, but they have yet to be deployed. Studies show that adding the compound piperonyl butoxide (PBO) neutralises mosquitoes' ability to resist pyrethroids. These include Sumitomo's Olyset Plus and Vestergaard's PermaNet 3.0.

Mikkel Vestergaard, chief executive of Vestergaard, is frustrated by the slow progress of his new nets, which include both a pyrethroid and PBO. Approval of them by a varied and evolving constellation of expert groups convened by the World Health Organisation (WHO) has been pending since 2007. Without a green light, donors and malaria-endemic countries are reluctant to buy and distribute the nets.

"WHO has lost sight of its own guidelines and processes," Mr Vestergaard says. "We're seeing resistance in 78 countries and we ought to have a new model. If you see clear evidence for a new tool, it should be used. But if it takes 10 years to fail to approve a net — three years more than to approve a cancer drug — clearly something is wrong."

An editorial in The Lancet medical journal this year warned: "With no new insecticide class to replace the pyrethroids expected for a decade, the threat of resistance derailing malaria control has become an issue of urgency that can no longer be ignored without risking a global public health catastrophe."

Pedro Alonso, director of the global malaria programme at the WHO, says the evidence for PBO nets is unclear. They have been shown in some tests to be more effective in killing pyrethroid-resistant mosquitoes but questions remain about their efficacy in reducing the incidence of malaria.

"The subject is complex and some of our colleagues from industry may not have been as reasonable as one would expect," Dr Alonso says.

"There is insufficient information on the potential public health impact these products would have. The WHO frankly has followed its processes and has been very reasonable."

He adds: "The innovators wanted an outright recommendation of worldwide application of these tools. I'm sorry to say the evidence does not sustain that. We have to be responsible. This is public health and we have to do what is best for the public."

Egon Weinmueller, business management head in the global public health division of German chemicals multinational BASF, which is also developing new insecticides, is not convinced by this argument. "Academia wants to continue their testing forever. Their business is testing and having enough money to keep on testing. We have already been testing for 10 years."

He wants a more pragmatic approach that ensures any new insecticide is safe but permits small-scale comparative trials in different African districts to demonstrate efficacy. "That way we could see what actually happens," he says. "We're not putting anyone in danger. We would have small-scale feedback, which would be very practical, provide data and speed up the process."

Prof Ranson agrees. "There is enough evidence out there. Now is the time to get it out. I share industry's frustration. The goalposts keep changing. The big problem for the WHO is they have got themselves into a corner. They have argued strongly for universal coverage of nets but the newer ones are more expensive. They don't want to say nets are failing — they are worried about donors walking away."

> 'Academia wants to continue their testing forever. We have already been testing for 10 years'

Mr Vestergaard says the price of existing bed nets has fallen sharply, in part because of the drop in the oil price from which the net material is derived, from $5 to nearer $2. At scale, he says his new PBO nets would cost about $3.

He warns that without more streamlining of WHO processes, the ability to keep up with malaria's rising resistance risks being jeopardised. "Whether or not companies are speaking openly about this, it's clear that all of them are questioning the value of investing in malaria prevention."

Hard fought gains: a Thai medic carries out a blood test on a child at a clinic in Kanchanaburi near the border with Myanmar — Pornchai Kittiwongsakul/AFP/Getty Images

Eradication campaign Teams 'race against time' in the 'Mekong Five' countries

Malaria deaths have declined worldwide but a big fight is on in Southeast Asia to stop the disease making a comeback. The UN-backed Global Fund is sinking $100m into an multi-agency regional programme to quell the rising resistance in mosquitoes to artemisinin, the main drug used to fight the disease.

The eradication campaign is in what Professor François Nosten, a malaria researcher and regional expert, calls a "tight race against time" to halt resistance before it spreads west to India and onward to Africa. "It is hard work but seems to be working," Prof Nosten says of the effort, which is concentrated on countries clustered around the Mekong river.

Artemisinin resistance has been recorded in the past eight years in the "Mekong Five" of Vietnam, Thailand, Myanmar, Cambodia and Laos, even as the region has reported a sharp fall in malaria deaths. Mark Dybul, the Global Fund's executive director, says the increase of resistance in mosquitoes "threatens to undo hard-fought gains" in the region and worldwide.

The Global Fund's programme focuses on eradication among the people seen as most likely to spread the disease, among them itinerant farmers and other seasonal workers. Those involved in the effort range from scientific researchers to nurses and volunteers equipped with test kits and drugs deployed in resistant mosquito hotspots such as the Thai-Myanmar border.

The Fund says a pilot mass drug administration programme appears to have been a success. Now the scaled-up campaign needs to achieve similar results — and quickly.

Michael Peel