

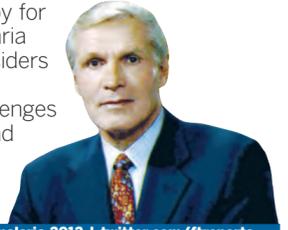
# FT HEALTH

## Combating Malaria

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### Online

The UN secretary-general's special envoy for malaria considers the challenges ahead



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# Fears over finances cast shadow

Optimism grows but funding worries and drug-resistant strains threaten any advances, writes **Andrew Jack**

A new spirit of cautious optimism is taking hold across Africa as a decade of investment in tackling malaria begins to pay off.

There has been a sharp decline in the human tragedy of deaths and illness caused by the disease, as well as the accompanying economic brake it has put on development.

New funding, political commitment and enhanced tools to treat and prevent the disease have emerged. But these are offset by worries about donor support and the looming threat of resistance to drugs and insecticides, serving as reminders that advances could swiftly be reversed without sustained investment.

Rob Newman, head of the malaria programme at the World Health Organisation (WHO), says: "We continue to make good progress against a formidable foe. There has been greater access and evidence of impact."

Academic debates have raged in recent months on the precise burden of malaria, as fresh analysis of healthcare data prepared by a group at the Institute of Health Metrics in Seattle suggested that adult deaths in Africa were higher than previously thought. The finding contradicted the WHO's figures of 665,000 deaths a year.

However, whatever the precise figures, they are at the same time disturbingly high and



promisingly in decline. The different analyses agreed there was a downward trend, driven in large part by the funding and delivery of three potent tools: artemisinin-combination therapy; long-lasting insecticide-treated bed nets; and rapid diagnostic tests.

Between them, these interventions offer techniques for prevention, diagnosis and treatment that were unimaginable a

few years earlier, and remain far more effective than the equivalents for many other diseases, including infections such as tuberculosis and HIV.

They have been supported by an explosion in funding from donors, from \$200m a year a decade ago to more than \$1.6bn today. And there has been accompanying political support too, notably from the African Leaders' Malaria Alliance

(Alma), chaired by Ellen Johnson Sirleaf, the president of Liberia.

"Ultimately, this fight will be won in Africa by Africans," she says. Alma's scorecard to measure progress has spurred competition among the heads of states by providing "a level of transparency and accountability that just wasn't there before".

She is now pushing for the promised regional funding from

African governments to be delivered.

Positive developments in recent months include studies pointing to the efficacy of intermittent use of drug sulfadoxine-pyrimethamine in pregnant women in low doses in countries with periodic malaria outbreaks.

And enhanced implementation has had an impact, such as Ghana's "hang-up" campaigns to ensure bed nets are used

rather than neglected, sold or given away.

Meanwhile, late-stage clinical trials continue on RTSS, a malaria vaccine developed by GlaxoSmithKline, which offers promise in prevention, though discussion continues on the role it could eventually play given questions over its efficacy, duration and cost.

Continued on Page 2

### Inside this issue



**Myanmar-Thai border**  
Drug resistance is on the increase **Page 2**

**Country profile** Ghana does more to fight the disease than hand out bed nets **Page 2**

**Regulatory code** Generic bed net makers face less rigorous standards **Page 3**

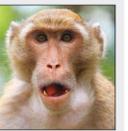
**Uniform protection** New uses are proposed for military clothes **Page 4**

**Chinese donations** Difficulties mar well-meaning aid efforts **Page 4**

**Text messaging** Keeping track of drug stocks **Page 4**

### Knowlesi malaria

Deforestation is aiding the spread of a south-east Asian variant **Page 5**



**Disease control** Mosquitoes are the target in efforts to beat the scourge **Page 5**

**Travel** Migrants going home are more at risk than tourists **Page 6**

**Drug development** Treatments need refinement **Page 7**



**History lessons** Sierra Leone looks to its pioneering past **Page 8**



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## WHO Global Malaria Programme

Tracking worldwide progress against malaria

The WHO Global Malaria Programme keeps independent score of global progress in the fight against malaria. Our flagship annual publication, the *World Malaria Report*, contains the latest available data on the impact of malaria interventions around the world.

The Programme also sets evidence-based norms, standards, policies and guidelines to support 99 malaria-affected countries as they scale up their prevention, control and elimination efforts. Our aim is to ensure that no-one dies from malaria for lack of a 5 dollar bed net, 50 cent diagnostic test, and a 1 dollar antimalarial drug.

[www.who.int/malaria](http://www.who.int/malaria)



What investment would generate \$80 billion for Africa over the next five years and help Ayodele realise his dreams?

## Malaria control



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When I grow up I want to be an engineer.  
Ayodele, age 8

Invest in malaria · Invest in development  
[www.rollbackmalaria.org](http://www.rollbackmalaria.org)



# Combating Malaria



Thomas Sandow, his wife Alice and children Henry and Irene demonstrate the benefits of fitting bed nets properly

Malaria No More UK

## Ghana goes beyond handouts to improve healthy outcomes

### Country profile

The country is doing more than doling out bed nets, says Andrew Jack

In a small hamlet up a rugged dirt road from Yawkwei in Ghana's Ashanti region, Emmanuel Appiah pays a morning visit to Felicia Donkor, ducking swiftly from the makeshift shop on her porch into her tiny living quarters.

It is three days since he passed by to hand her a blue plastic mosquito net. Now he wants to check it has been installed correctly and is being used to protect her and her children from malaria as they sleep.

"I'm very happy with it," she says, pointing to the net dangled over their single shared bed as she describes how her family has suffered from the disease in the past.

Mr Appiah, along with a dozen other volunteers recruited by a local pastor in recent weeks, had to get up before dawn for several days – arriving before sun-up, when the farmers leave for their fields – to distribute 700 bed nets paid for by international donors and

the government's own malaria programme. For most, they were the first received by the local community, which clubs together to offer small gifts or food to the distributors.

In many ways the work mirrors that being undertaken by others across Africa, as public health officials seek to implement pledges for universal coverage of bed nets, a practice that already appears to be having a significant effect in reducing cases of malaria.

However, there is one important difference in Ghana. In some countries, the emphasis has been primarily on distribution, ensuring that bed nets are delivered to the country, the village, or perhaps to individuals.

But in Ghana there has been greater focus in recent months on improved outcomes, for example, ensuring the nets are correctly installed and their users are educated through a "hang-up" campaign.

There are plenty of apocryphal stories about nets being misused for fishing, bridal veils or fences. There are sensitivities about the cultural associations of different coloured nets. And there are certainly frustrations about the hotter,

stiffer material of some nets and the greater difficulties of hanging rectangular than conical ones.

But the very practical aspects of hanging up the nets, now being closely studied and replicated elsewhere in Africa, include removing the plastic outer wrapping, helping install them and educating recipients as to their use.

This reduces the temptation to resell them, tuck them away to use as a gift

'We don't have rapid diagnostic tests. Over 30 per cent of paediatric outpatients have malaria'

or store them for the future.

Foreign donations have supported Ghana's strong local efforts, including assistance from the UK's Department for International Development and the US President's Malaria Initiative, as well as non-profit organisations such as Malaria No More.

The country's relative economic prosperity, physical safety and political stability – compared with many of its west Africa

neighbours – has helped to foster significant innovation, ranging from the introduction of a national health insurance scheme to the non-profit mPedigree system, which uses mobile phones to verify if medicines are counterfeit.

Accra, the capital, has gained a mosquito research centre funded by Vestergaard Frandsen, the bed net manufacturer, which it moved from neighbouring Ivory Coast after concerns about security.

The country hosts a pilot of the Affordable Medicines Facility – Malaria, which is subsidising artemisinin combination therapies to make them accessible to patients buying drugs in the private sector, although some local medicine manufacturers express frustration at being excluded pending international audits of their quality.

Paul Lartey, manager at US company LaGray Chemical's Ghana office, says: "Our government should support people like us. Reliance on donors is unsustainable."

Ghana also has two clinical research sites for GlaxoSmithKline's experimental RTS,S malaria vaccine, being tested across Africa.

Samuel Adjei, clinical co-ordinator for the vaccine

site at the Presbyterian Hospital in Agogo, sees signs of improvement while stressing the need for fresh approaches.

"Artemisinin combination therapy has made a huge difference," he says. "But we still rely on microscopy and don't have rapid diagnostic tests. More than 30 per cent of paediatric outpatients have malaria."

One concern is a fresh push for pesticides to kill mosquito larvae, pushed notably by Cuba in Ghana and much of Africa. While the approach has been successfully applied in limited areas in some countries, the latest advice from the World Health Organisation is that its current potential on the continent is modest.

Widespread use risks not only proving ineffective but is also wasteful of increasingly scarce resources.

The most significant threat noticed in Ghana is reduced donor funding, which could cause recent developments to falter and be lost.

Michael Steen Lunde, Vestergaard Frandsen's regional manager, says: "We need to find fresh mechanisms for financing. Malaria may be becoming less sexy, but it carries on and will come back to bite with a vengeance."

## Spectre of 'untreatable' variant rears its head

### Myanmar border

Greater drug resistance is being found in the region, reports Gwen Robinson

The Myanmar-Thai border zone has become a front line in the war on malaria, where the most deadly species of parasite, *Plasmodium falciparum*, is developing drug resistance. Not only has it shown signs of resistance to the most effective anti-malaria drug, say researchers, but the parasite could spread, first to India and China, raising what some term the "spectre of untreatable malaria".

Because of fears of a possible rise in resistance, artemisinin, the standard treatment, has been used mostly in conjunction with other drugs in artemisinin-combination therapies (ACTs). However, two papers have highlighted the increase of the falciparum parasite on the Thai-Myanmar border, one published in *The Lancet* and the other in the *Journal of Clinical Investigation*.

Nick White, professor of tropical medicine at Mahidol University in Thailand, who worked on the studies in both journals, says malaria sufferers in the Thai-Myanmar border region have been responding much more slowly to the ACT treatment than in other areas over the past few years.

The same phenomenon was seen in western Cambodia, where the ACT-resistant parasite appeared about eight years ago.

ACTs gained the World Health Organisation's endorsement in 2004 as the first-line treatment for uncomplicated falciparum malaria in endemic nations.

Prof White says: "There are early stage signs of resistance in the parasite – it's not as bad as it was in western Cambodia. While it's still small, we know that small things evolve rapidly, and if the parasite spreads to India and China, it could cause mayhem and spread to the west."

According to Prof White and Frank Smithuis, director of Medical Action Myanmar, a Yangon-based non-government organisation, Myanmar is the "likely conduit for [malaria's] spread west".

Because of its location, between the Andaman Sea and the Himalayas,



Treatment in Myanmar

Myanmar is in a unique geographic position to halt the spread of resistance to India and Africa.

Yet politically the country has little capacity to deal with the threat thanks to decades of diplomatic isolation and 15 years of western sanctions.

Although Myanmar's government, with the WHO and other partners, has developed a plan to contain artemisinin resistance, there is little external financial support for the plans, researchers noted.

One reason for the parasite's spread is the increasing availability of counterfeit and substandard ACT drugs, as well as the use of artemisinin alone as a "monotherapy" treatment. "The use of such substandard drugs, which contain very low levels of ACTs, is a huge problem in both Cambodia and Myanmar," says Prof White. "It has been possible in parts of south-east Asia for more than 20 years to buy counterfeit pills. To compound the problem, people will take a few pills, until they feel better and not finish the course."

While ACT treatment is still working "very well" in most endemic areas, and "relatively well" in the threat area along the Thai-Myanmar border, action should be taken now, says Prof White.

There are an estimated 140,000 refugees from Myanmar, mostly ethnic Karen, housed in border camps that are often equipped with health centres dispensing ACTs.

François Nosten, who runs a malaria research operation in Mae Sot on the Thai side of the border, says there is "virtually no transmission" of malaria at refugee camps.

However, beyond the camps there is growing resistance to ACTs. Tests cited in *The Lancet* and elsewhere show half-life clearance times of ACT-resistant parasites from the

bloodstreams of malaria patients had gone up in the past 10 years.

In Myanmar, there are about 5m to 10m cases of malaria a year. The real problem, says Prof White, is that once the ACT-resistant parasite spreads throughout Myanmar, it stands at the gateway to the west.

He says: "Malaria control in Myanmar is much weaker than in the rest of the region. It is going to be more difficult to contain it – we're talking about letting it loose in a huge field compared to the small garden that is western Cambodia."

There are only several thousand malaria cases a year in the western Cambodia region, where the ACT-resistant parasite appeared, he says.

The vital weapon to fight the parasite, he noted, was "more and better intelligence – on its spread, on how to treat it. We need a single, cohesive, co-ordinated group that can acquire information."

The problem, Prof White and others believe, is the view malaria is a threat only in certain parts of the world. "If this were bird flu, the west would be mobilising all its forces," he says. "Yet, malaria has killed millions of children in Africa. It continues to kill 2,000 people a day, mainly children. And here we have it again. We urgently need to scale up. It is going to require an international effort."

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**"Net coverage in Makoda, Nigeria reduced malaria parasite prevalence in children under 5 from 43% to 17% in just one year" \***

**Evidence should drive good investment**

[www.malariaconsortium.org](http://www.malariaconsortium.org)

Monitoring Area Survey Results 2011, SuNMaP, Malaria Consortium

malaria consortium  
disease control, better health

Malaria Consortium is the world's leading organisation dedicated to the comprehensive control of malaria. We work with governments, the private sector and directly with the people most affected, helping to bring an end to deaths from malaria and other communicable diseases.

Photo: Bennett Carpenter

## Fears over continued financing cast a shadow

Continued from Page 1

Such innovations are desperately needed. As Ray Chambers, the UN secretary-general's special envoy for malaria, says: "There is growing evidence that both the parasite and the mosquito are evolving in ways that could diminish the effectiveness of our most powerful tools for preventing and treating the disease."

"Millions of lives hang in the balance – and time is not on our side."

Studies in south-east Asia have confirmed that artemisinin drug resistance is spreading, fuelled by use of inappropriate medicines and the complexities of migration and labour practices. History – notably of the old drug chloroquine – suggests what begins there soon spreads elsewhere.

In parts of Africa some evidence of resistance to insecticides is also emerging, including to those released through the fabric in bed nets. That means nets may last for shorter periods than expected, with their efficacy diminished.

Scientists are aware of the problems, but face considerable hurdles. A number of drug companies, academic groups and non-profit organisations are working on new medicines, including the nirvana of a one-pill cure.

Yet progress so far has been painfully slow, including on a combination of dihydroartemisinin with piperazine, only just approved by European regulators, which could have helped stem the use of poor-



Ellen Johnson Sirleaf: 'Ultimately this fight will be won in Africa by Africans'

AP

quality drugs in south-east Asia several years ago – a process that has boosted resistance.

Promising insecticides are being researched, but net manufacturers warn that the existing advisory system operated by the WHO opens a door too rapidly to generic manufacturers, providing scant incentives to developers of the technologies to repay their investment in innovation.

All of these issues come at a time of a squeeze on donor support, driven by the global economic slowdown and the sometimes faddish nature of international aid.

"The single biggest chal-

lenge is financial rather than biological," says Mr Newman. "The thing we most need is to make sure the money keeps coming."

No blow was greater than the cancellation of the most recent round of fundraising planned by the Global Fund to Fight Aids, TB and Malaria, a mainstay of support for fighting the disease.

It has been hit by governance concerns against a backdrop of financial austerity among the donors who channel support through the organisation.

Stephen O'Brien, a minister in the UK's department for international development, says: "After a very

thorough review to assess what had the greatest developmental impact for the poor, malaria came out as our number one priority." The UK is one of the few countries to maintain its commitment.

However, Mr O'Brien is a rare voice among richer countries. Ms Sirleaf Johnson says African member states should tap greater World Bank support. Many eyes will be on the leadership of Jim Kim, the organisation's new Korean-born US-nominated head, a doctor and former WHO official with extensive experience in infectious diseases.

There is no doubt that countries with the greatest

burden of malaria will have to provide greater domestic leadership and funding if recent progress is to be sustained.

Value for money will dominate the debate. That requires measures such as tougher disease surveillance and better use of diagnostics to ensure expensive malaria drugs are not misused.

It will mean more sophisticated investment in logistics – such as through expanding existing mobile phone pilot programmes – to avoid drug shortages that are costing lives.

Ironically, at a time when western donors' support is wavering, China and Cuba are both vying to offer help while enhancing their influence. The problem is that these efforts risk diverting ever scarcer resources.

China's malaria health centres in Africa have lacked sufficient technical support and training, while Cuba's promotion of killing off mosquito larvae is viewed as a diversion from more effective measures.

Meanwhile, for all its problems, many say the antimalaria community could work more closely with those fighting other diseases that have received less funding.

Thus bed nets could play a greater role in tackling lymphatic filariasis, or elephantiasis, caused by nematode worms. In an age of austerity, co-operation and co-ordination will be more important than ever.

Read Stephen O'Brien on the UK's efforts at [ft.com/reports/malaria-2012](http://ft.com/reports/malaria-2012)

# Makers call for overhaul of regime for bed net sales

## Regulatory code

Manufacturers of generic copies face less rigorous standards on the way to market, reports **Andrew Jack**

It took Vestergaard Frandsen, the Lausanne-based bed net developer, five years and several million dollars to produce and win approval for its most recent model of long-lasting insecticide-treated net. But within a year of launch a Chinese rival was on the market with a copy of its design.

Helen Pates Jamet, head of entomology at the company, which had this experience with its PermaNet2 model, says: "It's impossible to get a return when you have generics launching so quickly. If the current policy carries on, some companies with large banks of insecticides may pull out of vector control."

There is increasing evidence of a trend of rising resistance by mosquitoes to existing insecticides in the most widely used bed nets, which are threatening the effectiveness of nets in preventing the disease. But there is far less agreement over what needs to be done to ensure better replacements are developed.

To several leading manufacturers, the current fragile system of innovation – essential in order to tackle resistance – is being threatened by low entry hurdles that allow cheap generic rivals to swiftly

follow their lead without the need to invest in research. Another difficulty is caused by a poor system of promoting newer designs of bed nets in regions where resistance to older versions has been identified.

Adam Flynn, UK sales manager for global vector control at Sumitomo of Japan, which has committed substantial philanthropic resources to its Olyset net programme, calls for the approach to be overhauled. He wants a two-tier system that incentivises innovation by endorsing higher-performance nets specifically for areas where they are needed.

"With growing resistance, we need to move away from the 'one size fits all' approach," he says. "But despite calls from manufacturers, the regulatory ecosystem hasn't evolved at all. Sumitomo has a real political commitment to malaria. But, strategically, for others it doesn't make a lot of sense."

Innovative manufacturers such as Sumitomo and Vestergaard Frandsen point an accusatory finger at the World Health Organisation's pesticide evaluation scheme (Whopes), which, they say, has ignored calls for reform over the past two years while the problem has become ever more pressing.

Whopes assesses the safety and efficacy of products, including bed nets, using guidelines developed with national malaria programmes, academics and industry.

Its administrators say its recommendations "are intended to facilitate registration and use of pesticides by member states" and do not "imply approval".

Ms Pates Jamet, however,



Net benefits: a woman cradles her seven-month-old daughter in her arms behind a protective covering at a hospital in Mogadishu in Somalia

Getty

argues that Whopes does act as a de facto regulator, as its advice is widely adopted by countries and its credibility provides the endorsement required for funders to authorise purchases of different varieties of bed nets.

With most insecticides already off-patent, or with intellectual property unenforceable in the countries where most sales take place, she says manufacturers' fates are closely linked to the scheme, which she claims provides too much information

and too low a bar of entry for

"me too" producers. Generic companies can gain access rapidly to the technical specifications of an innovative product and the data concerning its testing, while only having to provide for test a few samples of their own product to prove "equivalence".

If the original innovator subsequently wants to tighten any specifications to improve performance it has to seek its generic rivals' consent for the change.

By contrast AgroChem, a Chinese producer, has argued in consultations in recent months

that Whopes guards some technical information as "commercial in confidence", limiting its ability to gain the full access required to produce equivalent nets. Like other generic companies, it argues swift competition has helped cut prices sharply.

However, while Vestergaard Frandsen ran extensive tests in the laboratory and the field for PermaNet2, Yorkool of China was able to submit just four of its equivalent nets for preliminary examination and 10 for intermediate tests as the

precondition for authorisation for sale. This allowed its version to be swiftly approved, though the Swiss company says tests it subsequently funded on Yorkool samples showed they failed to meet the same performance standard.

This finding could reflect differences not only in the insecticide but the way it is formulated and mixed into the fabric, and the way the nets are sewn.

The surge in generic competition in bed nets in the past few years has helped cut

prices and stretched funding further to save lives. But some object that tenders won on the lowest price have not always translated into the quality expected, let alone to delivery on time or in the quantities promised. That has reduced the ability to save lives, offsetting the benefit of nominal cost cuts.

At a time when fresh innovation is clearly needed to sustain recent reductions in malaria incidence, many believe it is time for a fresh look at rebalancing the incentives required.

## The Novartis Malaria Initiative Innovating to help eliminate malaria

# For over a decade, Novartis has been a pioneer in the fight against malaria\*

Since 2001, Novartis has delivered **500 million antimalarial treatments** to malaria-endemic countries, impacting more than 1 million lives.<sup>1</sup>

We believe that no one should die of malaria today. Together with our partners, and with our continued patient-centric approach, we are committed to the common goal of malaria elimination.

Resting on four key pillars, the Novartis Malaria Initiative is tailored to best meet patient needs.

- 1 Treatment – starting with the patient**
  - Novartis artemether-lumefantrine (AL) was the first fixed-dose artemisinin-based combination therapy (ACT) prequalified by the WHO for its efficacy, safety and quality.<sup>2</sup>
  - Novartis, in collaboration with Medicines for Malaria Venture, developed the first dispersible AL treatment, tailored to the needs of infants and children.<sup>3</sup>
- 2 Research & Development – leading the path to malaria elimination**
  - In an effort to contribute to the decrease in malaria transmission, Novartis is conducting a study in Burkina Faso<sup>4</sup> to evaluate the effect of mass screening followed by targeted treatment of asymptomatic patients. If effective, this could become a stepping stone toward malaria elimination.<sup>5</sup>
  - In 2011, Novartis started Phase II clinical trials for an antimalarial with a novel mechanism of action.<sup>6</sup> The same year, we announced the discovery of a second new compound that acts on both blood and liver infections.<sup>7</sup>
- 3 Access – improving affordability and availability of medicines**
  - In 2009, Novartis led "SMS for Life," an innovative Roll Back Malaria public-private project. Using SMS technology, the project provides visibility of antimalarial stock levels to improve access to essential malaria medicines in rural areas.<sup>8</sup> SMS for Life has now been rolled out across Tanzania and pilots have started in Ghana and Kenya. Further, the portfolio has been expanded to include bed nets, RDTs, additional medicines, health products and data.
  - Today, the Novartis Malaria Initiative is engaged in more than 20 public-private partnerships, from R&D, sourcing, production, and access, through to distribution and impact assessment.
- 4 Capacity building – empowering patients and healthcare professionals**
  - Novartis has developed innovative packaging for its AL treatment, to enhance adherence for not yet fully literate populations through the use of pictograms.
  - We continuously foster best practice exchange between public health officials responsible for malaria control on topics such as the role of rapid diagnostic tests, home-based management of malaria, healthcare worker training, stock management and health impact measurement.

"I fear that my child can die because of this disease malaria. This medicine is good because the child can swallow fast and does not have any side effects such as rashes. The fever also goes down very fast. Now she can speak and play and truly I have seen a big difference."

Rose Aluoch, mother, Kenya.

 NOVARTIS

### References

- Data on file at Novartis Malaria Initiative. Most recently published statistic on this can be found in the Novartis Annual Report 2011.
- WHO Prequalified Medicines List.
- Abdulla S, Sagara I, Bornmann S, et al. *Lancet* 2008; 372:1819-1827.
- ClinicalTrials.gov identifier: NCT01256658.

5. Ogutu B, et al. *Malar J* 2010; 9:30.

6. Rottmann M, et al. *Science* 2010; 329:1175-1180.

7. Imaging of Plasmodium liver stages to drive next generation antimalarial drug discovery. *Science Express*, Nov 17, 2011.

8. Barrington J, et al. *Malar J* 2010; 9:298.

\* Uncomplicated *Plasmodium falciparum* malaria

# Combating Malaria



Spray-on protection: US army personnel treat uniforms with permethrin to ward off insects, including malaria-carrying mosquitoes

Walter Reed Institute

## A uniform idea for protection

### Military clothing

New uses are proposed for outfits designed to protect soldiers, says Sarah Murray

The military is often responsible for innovations and this has certainly been the case with antimalarial clothing impregnated with the insecticide permethrin. However, as the battle against malaria extends into new areas and the spectre of drug-resistant looms, non-military uses for such clothing are being explored.

Clothing treated with insecticide can repel insects, prevent biting and kill insects. Treating clothing involves similar processes to those used for impregnated bed nets, with fibres coated during the manufacturing process.

"The big benefit of permethrin clothing is that it stops mosquitoes surviving to transmit disease," says Abraham Mnzava, co-ordinator for malaria vector control at the World Health Organization's global malaria programme.

Reducing non-combat deaths has long been a challenge. In the first world war, there were almost 17,000 cases of malaria among US soldiers. In February, the Army Times reported cases of malaria among US troops in Afghanistan had reached their highest level in nine years.

Permethrin, which was pioneered by the US army in the 1970s, became widely used for treating clothing, particularly for military uniforms and camping apparel.

In 2010 the US military started issuing all deploying soldiers with flame-resistant uniforms treated with permethrin and providing protection from insect bites for up to 50 launderings (the estimated life of a combat uniform).

Organisations engaged in the global battle to eradicate malaria have now begun looking at the potential of impregnated clothing as a preventive tool.

With a grant from the Bill & Melinda Gates' Grand Challenges Explorations programme, which funds innovation in global health research, the UK-based Malaria Consortium is conducting field research into the potential of insecticide-impregnated clothing.

Several factors are driving interest in this intervention. First, evidence of the spread along the Thai-Myanmar border of a malaria strain that is resistant to artemisinin – the most effective drug treatment – has been the catalyst for research into alternative prevention methods.

"There's a need to intensify efforts to interrupt transmission – and that has its challenges," says Sylvia Meek, technical director at the Malaria Consortium.

'The big benefit of permethrin clothing is that it stops mosquitoes surviving to transmit disease'

sorium. "But this also offers some new areas for testing of insecticide-treated clothing."

Second, the interest in impregnated clothing is part of efforts to take the battle against malaria further, particularly as evidence emerges of the fact that mosquitoes are increasingly biting outdoors.

Vulnerable groups include victims

of emergencies, disasters or wars forced to live in temporary shelters. Also at risk are workers such as fishermen, forest labourers and rubber tappers, who work outside.

"They're sleeping in makeshift accommodation," says Dr Meek. "And there are only limited things they can do to protect themselves, such as attach a burning mosquito coil to their hats."

However, while many see impregnated clothing as having potential to protect these groups, experts point out that is not a single solution.

"To enhance the protection of clothing people tend to apply topical repellent, because there will be places that are still exposed," says Dr Mnzava.

Moreover, while protecting soldiers with impregnated clothing is relatively simple – since they all wear the same garments – researchers have to take cultural factors into account when it comes to civilian wear.

In Cambodia, for example, the Malaria Consortium has examined the possibility of impregnating the traditional Khmer checked scarf – called a *krama* – with insecticide.

"A lot of it involves looking at people's behaviour and what's acceptable to them," says Dr Meek.

### Text messaging SMS keeps track of vital stocks

The global effort to combat malaria frequently breaks down at the final stage in the supply chain, when the local dispensary runs out of the necessary medicines.

Yet maintaining regular deliveries to remote villages is vital because, to be fully effective, anti-malarial treatment must be started within 18-24 hours of the symptoms becoming apparent.

Fortunately for health campaigners, the widespread use of mobile phones throughout the developing world has provided an essential tool for managing that delivery chain.

A combination of mobiles, short messaging service (SMS) and electronic mapping technology is being applied in a growing number of countries in Africa to track weekly stock levels of antimalarial medicines at remote locations.

Real-time technology is replacing paper-based systems that require multiple entry of the data and are often up to 18 months out of date.

SMS for Life was launched in Tanzania in 2009 as a pilot programme by Roll Back Malaria, a global co-ordinating partnership; Novartis, a drug company; Vodafone, a mobile phone group; and IBM, an information technology company. It has since been extended across the country by the Ministry for Health.

At the start of the project 26 per cent of health facilities had no malaria medicines of any dose type. By the end of the pilot this had been reduced to just 0.8 per cent.

Once a week the SMS for Life system sends an automatic text message to the nominated healthcare worker at each health centre asking for the current stock of medicines.

A reply is sent back using a free short code number, at no cost to the healthcare worker. This means the mobile does not have to be in credit for a reply to be sent. A standard message format is used to indicate stock levels.

Regional and district medical officers and their staff have access to the data and can authorise the transfer of drugs between health facilities in response to any identified shortages.

Statistical analysis of the data collected can be used to provide early warning of malaria outbreaks by, for example, highlighting a sharp rise in demand for medicines in a number of closely located health centres.

"Ours is a sustainable business model," says Jim Barrington, director of SMS for Life and a former chief information officer at Novartis. "It is commercially based, is designed to be affordable by developing countries,

and does not depend on donations as some other projects do. Most importantly, it is designed and built to be scalable, without limits, to any number of health facilities and countries. This is critical if it is to be effective in reducing the more than 2,000 deaths a day from malaria alone."

The Tanzania service is offered on a commercial basis by Vodafone, says Mr Barrington. Total annual costs for a typical district are less than \$5,000. Pilots are now being extended to Ghana, Kenya and the Democratic Republic of Congo.

Despite the rise of mobile phone use throughout Africa the technology is not without its problems.

"We needed to make sure we could send and receive SMS across all the available networks in a country," says Andrew Wyborn, managing director of Greenmesh, a supplier of health-related telecoms programmes and SMS for Life's partner in Ghana and Kenya.

He says: "It can be quite tricky engaging with local network service providers. You need to find a local partner, a local telecoms software company that can provide a gateway."

Local climate conditions, including high winds and high levels of humidity, can interfere with signals, while on one occasion a ship dragged its anchor, cutting an undersea cable and so bringing down an internet connection off east Africa.

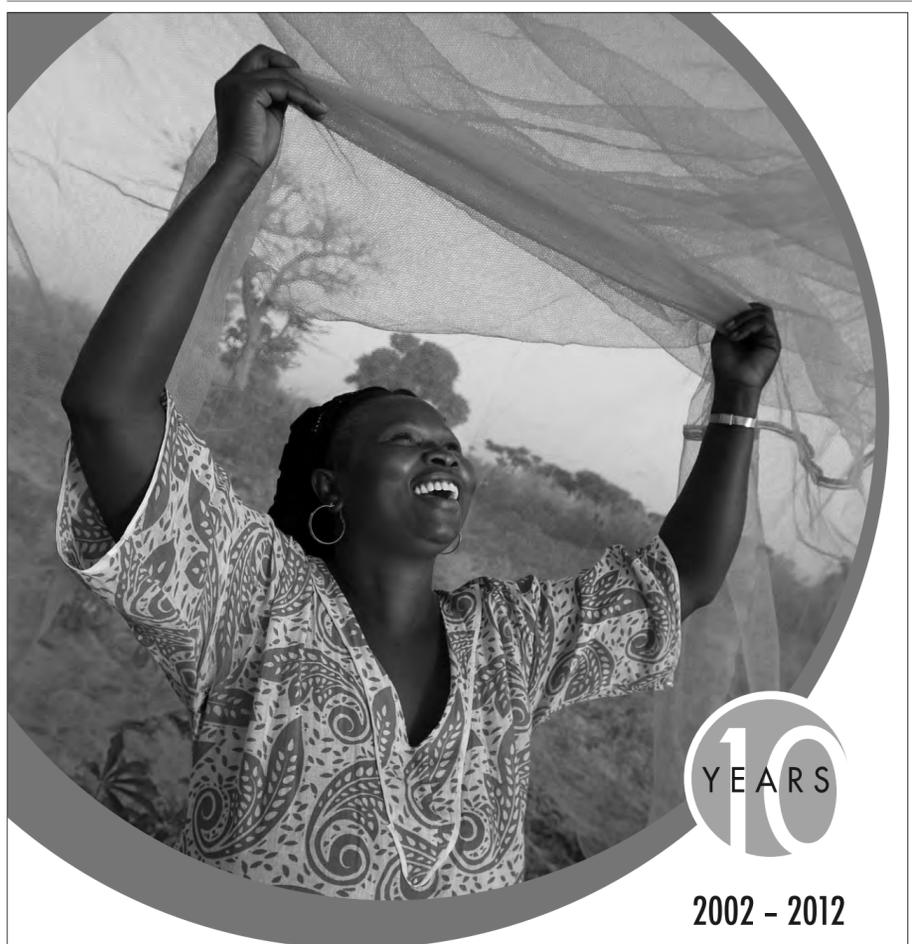
Network providers can also be unpredictable in switching services on and off.

But pharmaceutical companies are showing a growing interest in the opportunities provided by SMS technology. Pfizer, the US drugs group, ran a pilot initiative, SMS for Health, in Gambia and has now handed this to the ministry of health.

In Gambia, dispensary assistants, nurses and store managers were trained to use a simple coding system to text stock levels and expiry dates for 20 medicines and the rate for 10 specified diseases to a central database. There the information is analysed on a weekly basis and compiled into web-based reports.

These efforts helped plug information gaps that had hampered government efforts to improve public health, says Pfizer. It also allowed the development of a more connected network of healthcare providers and suppliers with the potential to improve access to medicines and increase positive health outcomes.

Charles Batchelor



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## Tale of frustration that lies behind health aid to Africa

### Chinese donations

Difficulties hamper well-meant efforts to help, writes Beibei Yin

In the best-equipped laboratory in Amana hospital, one of the largest in Tanzania, Focus Mbawala still diagnoses malaria with a simple microscope, despite the cutting-edge equipment that surrounds him.

A donated computer, freezer and a PCR (Polymerase Chain Reaction) machine for amplifying DNA all remain untouched since the Chinese-funded malaria centre opened in November 2010.

"We were given very little instruction on how to operate them," says Mr Mbawala, who runs the malaria centre in the hospital in the Ilala district of Dar es Salaam. In 2009, he was given a five-day crash course led by doctors from China, but it was hardly useful as their English was very limited.

Picking up a pack of disposable medical gloves, he says: "I cannot read the Chinese written on the package, I even feel a bit afraid of them."

Nearby, 10,000 treatments of donated Arco Chinese malaria medicines have been sitting in a corner and collecting dust for almost two years. Still sealed, they are within a few months of their expiry date.

Meshack Shimela, the hospital's chief medical officer, says: "Arco was introduced to Tanzania quite recently. It is effective, but no tests have been made to prove it is safe to use on young children." The centre only treats patients aged under five.

Since 2007, China has set up 30 malaria centres across Africa, with facilities and medicines donated by Chinese companies through a government scheme, each estimated to have cost about \$500,000.

Yanzhong Huang, director of the Centre for Global Health Studies at

Seton Hall University in the US, says China's health aid focuses on rebranding the Chinese healthcare service and promoting the export of Chinese medical products.

"In the words of a ministry of health official, China's health aid should 'not only serve China's foreign policy, but also act as a broker for economic development in China and recipient countries'," he says.

Chinese drug companies that participated in state schemes are also frustrated. "Supplying to the government donation scheme is never commercially incentivised," says Zhou Yong, general manager at Holley Tanzania.

Holley-Cotec, its parent company, contributes a third of China's overseas malaria drug donations.

Mr Zhou says purchases by the government are all but compulsory, and the orders are usually placed at a price that only just covers costs. "We normally make the donation

'Supplying to the government donation scheme is never commercially incentivised'

Zhou Yong  
General manager,  
Holley Tanzania

to gain better brand recognition overseas."

While donated Chinese drugs are left untouched in Tanzania, doctors instead prescribe Coartem, sold by Novartis.

"Coartem was discovered by Chinese scientists," says Claude Faruq, a consultant at Holley-Cotec who says promotion abroad has become a political project of the state. "They lacked the ability to exploit its commercial value overseas, so sold it to Novartis in 1994."

He adds: "The Chinese are now eager to demonstrate their research and innovation capacity in the pharmaceutical sector and the field of malaria drugs is where they are most likely to achieve a breakthrough."

Africa is the single biggest market for world's malaria drug makers. But, having arrived late in Africa, Chinese malaria drug businesses have so far struggled to catch up.

Hamisi Malebo, research scientist at the National Institute of Medical Research in Tanzania, says: "Western companies have invested a lot in clinical trials in Africa, and we lack the data from the Chinese companies to compare their products."

The greatest barrier for two of the biggest Chinese producers, Holley-Cotec and Kunming, which produces Arcom, is that they cannot supply to the public sector in Africa. International donors strictly limit procurement to products that have passed international standards, including pre-qualification by the World Health Organisation.

Between 2007 and 2009, Holley Pharma spent \$10m seeking international approval for its drug Duo-Cotecxin. This burden drove the company to spin off its pharmaceutical unit in 2010. This leaves Mr Zhou, in Holley's Tanzanian subsidiary, concentrating on winning a fifth of private sector sales with his so-far unendorsed drug.



Yanzhong Huang,  
director of the  
Centre for Global  
Health Studies  
at Seton Hall  
University

# Mosquitoes are target in battle to beat the scourge

## Disease control

The carriers are at the centre of initiatives to tackle the illness, reports **Clive Cookson**

The scientific battle against malaria is being fought on three fronts. We need better drugs to kill the plasmodium parasites; better vaccines to prime the human immune system to resist infection in the first place; and better ways to control the anopheles mosquitoes that transmit the disease.

The third front – against the insects – has been relatively neglected as a research topic in recent years compared with drug and vaccine development.

“Part of the problem is there is a relative shortage of very good people in entomology and insect biology,” says Sir Mark Walport, director of the Wellcome Trust, an important funder of malaria research. “There has been less work in general on the development of insecticides.”

But there are now signs of a renaissance in “vector control”, as the field is known, with projects to attack mosquitoes not only with new chemicals but also using biological and genetic approaches.

The biggest issue with today’s insecticides is the same as that facing anti-malarial drugs: resistance.

Just as medical experts are alarmed by the emergence of parasites that do not respond to artemisinin drugs, the vector control community faces a rapid increase in the number of mosquitoes that survive pyrethroid insecticides. These are favoured for mosquito control because they are environmentally less harmful and less dangerous to non-insect life than persistent chemicals such as DDT.

A study by Senegal’s Institute of Research for Development found the proportion of anopheles gambiae mosquitoes with the genetic mutation that confers resistance to pyrethroid insecticides – organic-based compounds that break down easily in the atmosphere – rose from 8 per cent in 2007 to 48 per cent in 2010.

“These findings are of great concern, since they support the idea that insecticide resistance might not permit a substantial decrease in malaria morbidity in many parts of Africa,” the authors wrote in the *Lancet Infectious Diseases* journal.

Alternatives to pyrethroids are in existence. Even the notorious DDT is still sprayed occasionally. Bendiocarb – withdrawn from the US pesticide market because of safety concerns – is still approved by the World Health Organisation for indoor spraying to combat malaria.

A study in Benin, published in the *American Journal of Tropical Medicine and Hygiene*, showed a large decrease in malaria transmission as a result of bendiocarb spraying.

“Our results should provide reassurance that, despite the rise in pyrethroid resistance, indoor spraying can continue to play a vital role in reducing the burden of malaria across Africa,” says Gil Germain Padonou, a co-author of the paper. But, he adds, researchers are already seeing early evidence of bendiocarb resistance in neighbouring Burkina Faso, demonstrating the need for multiple alternatives to pyrethroids.

“We need to intensify support for efforts to develop and test insecticides and seek better strategies for using them, such as rotating among several compounds that make it harder for mosquitoes to become resistant,” said Peter Hotez, president of the American Society of Tropical Medicine and Hygiene.

An alternative insecticide is expected to reach the public health market this year in the form of chlorfenapyr. BASF, the German chemical manufacturer that has been selling chlorfenapyr since 1995 as an agricultural pesticide, has reformulated it for use against malarial mosquitoes, both as a long-lasting insecticidal net and as an indoor spray for walls.

Chlorfenapyr disrupts the energy-producing mitochondria in insect cells, whereas pyrethroids attack insects’ nervous systems.

A different approach, still in the early stages of research, is to modify mosquitoes genetically to prevent them transmitting the parasites. Scientists at Johns Hopkins Malaria



A municipal worker fumigating a residential area in Mumbai during an anti-malarial drive in the city in August 2010

Getty

Research Institute in Baltimore have genetically engineered the immune system of anopheles mosquitoes to produce high levels of a protein called Rel2 when they feed on blood. This induces an immune attack on plasmodium parasites inside the insects.

The Johns Hopkins researchers showed that the GM insects lived as long and laid as many eggs as wild-type mosquitoes, suggesting the modification had not impaired their fitness.

Meanwhile, scientists at Imperial College London have demonstrated a way to accelerate the introduction of genetic changes into a mosquito population. They bred a large number of mosquitoes carrying a green fluorescent gene – a classic marker in genetics experiments – and allowed them to mingle and mate with a small number of mosquitoes genetically engineered in a different way. The latter made an enzyme that permanently switches off

the fluorescent gene. In an experiment that started with 99 per cent of mosquitoes glowing green in ultraviolet light, more than half the insects had lost this marker gene within 12 generations.

The trick was to use a homing endonuclease gene, a “selfish gene” that not only produces the disruptive enzyme but also makes an extra copy of itself in the mosquitoes’ sperm cells. This means that, when they mate, almost all the offspring receive

the gene, which spreads rapidly through the population. The next research step will be to disrupt a gene that the mosquito needs either to reproduce or to transmit malaria.

Preparing anti-malarial genetically modified mosquitoes for release into the wild will require five years or more research. Then, there will have to be a public-relations campaign to persuade people to overcome any qualms about the genetically modified insects for the sake of global health.

‘Part of the problem is the relative shortage of very good people in entomology and insect biology’

Reaching further  
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## Emergent strain poses threat to global containment efforts

### Knowlesi malaria

Deforestation is aiding a south-east Asian variant, says **Katherine Rowland**

A malaria parasite emerging in south-east Asia could pose a setback to global elimination goals.

Since 2004, plasmodium knowlesi malaria, long known to affect macaque monkeys, has been identified in hundreds of people in Malaysia. There have also been scattered cases in Thailand, Cambodia, Vietnam and the Philippines.

While knowlesi is unlikely to reach pandemic proportions, health authorities are concerned it could harm eradication initiatives. Kevin Palmer, former director of the western Pacific regional office of the World Health Organisation, says health systems are ill-prepared to respond to a zoonotic form of malaria, a strain of the disease that transmits from animals to humans.

A big problem is that knowlesi malaria is often misdiagnosed. Under microscopy, the most common diagnostic tool, it is indistinguishable from a benign strain, malariae malaria. Even though knowlesi responds to the artemisinin-based therapies used to cure most malarias, treatments are infrequently administered. “Clinicians don’t really know what they’re dealing with,” says Dr Palmer.

The consequences of not receiving proper care can be severe, says Janet Cox-Singh of the St George’s University of London Centre for Infection. Routine misdiagnosis has resulted in prolonged sickness, treat-



Macaques have been blamed for spreading malaria

Dreamstime

ment complications, fatalities and at least one instance in which a patient was operated on for the wrong condition.

Researchers think the spread of knowlesi in humans is being fuelled by deforestation. In Malaysian Borneo, where the first cases appeared, the combination of population growth and forest loss has brought record numbers of people into jungle tracts. As a result, humans, monkeys and mosquitoes have come into close contact.

Unlike the malaria strains common to South America and Africa, knowlesi is transmitted from monkeys to humans by a particular mosquito that is confined to the forest.

However, John Barnwell, chief of the Malaria Branch Laboratory at the US Centers for Disease Control and Prevention, says: “If other types of mosquito acquire the parasite, knowlesi malaria could become a much wider problem.”

Dr Cox-Singh, who is also a senior fellow at the

Malaria Research Centre in Malaysia Sarawak, says that vivax malaria – the second most common type in humans – emerged from the same monkey population some 30,000 to 40,000 years ago.

“The question is whether we’re creating environmental conditions for knowlesi malaria to do the same. Is it going to make the switch from animals to humans?”

Anu Kantele, of the Helsinki University Central Hospital, who was the first clinician to diagnose knowlesi in a western traveller, says the growing numbers of cases indicate the disease is beginning to make the switch.

But other researchers are uncertain whether humans will become a reservoir for the parasite.

Dr Palmer says deforestation will outpace the ability of the disease to survive. “We’ll see a decrease in incidence as forest losses deplete the habitats for the monkeys carrying the disease.”

In February 2011, the WHO convened a meeting with south-east Asian regional experts to discuss the public health threat of zoonotic malaria. The group recommended dedicated diagnostic labs, clinician awareness campaigns and studies to assess the true scope of the disease, which is assumed to be vastly under-reported.

A lack of resources presents a barrier to implementing surveillance or treatment plans.

“There’s no funding for knowlesi,” says Dr Barnwell. “The problem isn’t just misdiagnosis. People who don’t receive proper treatment get really sick. This has the potential to be much more severe.”

“It’s something we have to keep an eye on.”

‘The problem isn’t just misdiagnosis. Without proper treatment, people get really sick’



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## Combating Malaria

# Returning migrants at more risk than tourists

### Travel

Emigrants visiting home are more likely to be infected, writes Katherine Rowland

Reported cases of malaria in western travellers are increasing, despite declines in global prevalence. Although infections have decreased among tourists, emigrants from areas where malaria is endemic face significant risk of acquiring the disease when visiting their countries of origin.

Compared with business and leisure travellers, emigrant groups returning to their home countries are eight times more likely to become infected. Of the 1,500 to 2,000 cases diagnosed annually in the UK, more than half acquired the illness in Ghana and Nigeria. In central European countries, emigrants who had travelled to endemic areas account for as much as 70 per cent of all imported cases.

Malaria affects between 20,000 and 30,000 travellers annually, though official data are believed vastly to underestimate levels of incidence, capturing less than 60 per cent of actual cases.

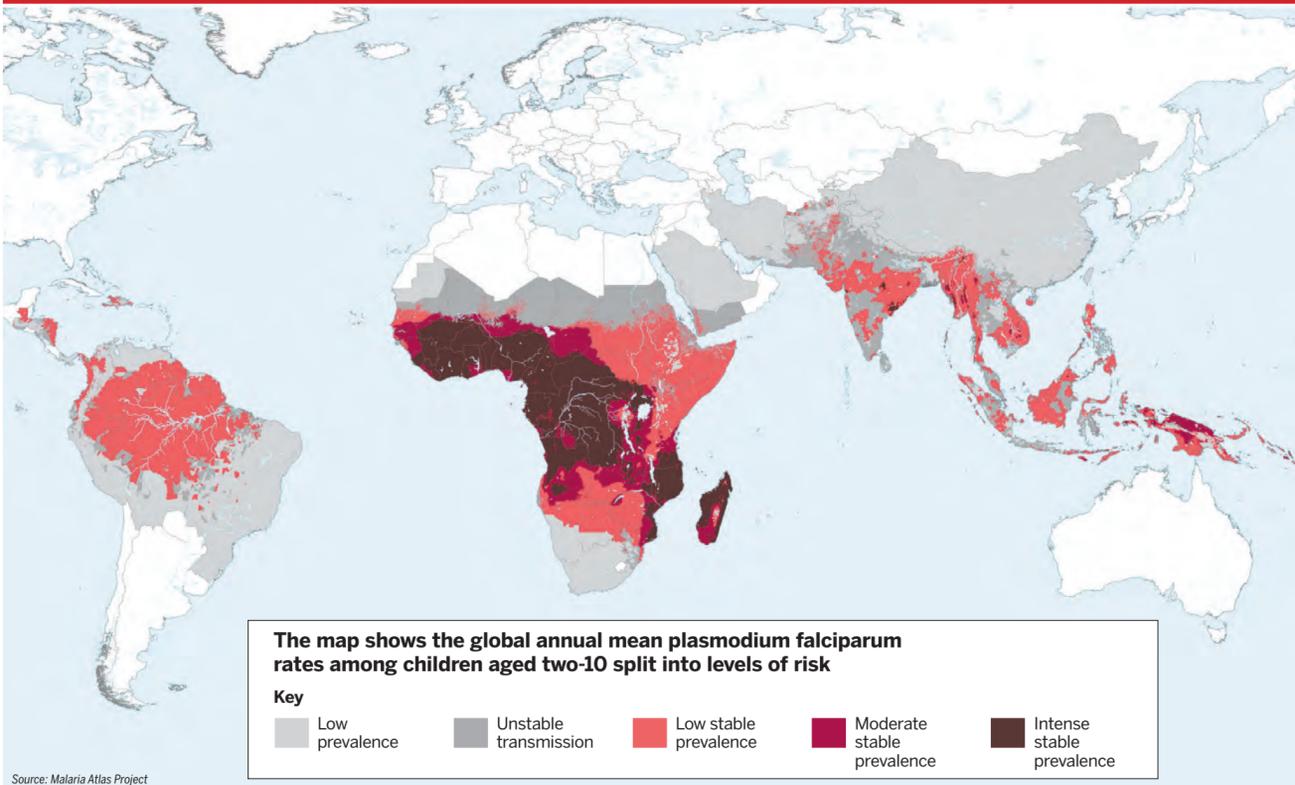
Adding to the challenge of accurate surveillance is the fact that malaria is rare in western nations and physicians are not always trained to identify it.

Additionally, when travellers visit multiple countries, the site where they acquire the disease may differ from that where they receive a diagnosis, leading to inaccurate records of transmission.

In the UK, recorded cases of travellers' malaria increased 30 per cent between 2008 and 2010, according to the Health Protection Agency (HPA).

However, official data reveal little about underlying trends in international travel and migration. The HPA figures are misleading says Ron Behrens, a travel medicine specialist at the London School of Medicine and Tropical Hygiene. While the number of Britons diagnosed with malaria appears to have grown by nearly a third, the fig-

### Infected world Global picture of malaria hotspots



ures do not account for the 200 per cent increase in travel to endemic countries over the past decade.

"Just because malaria is present does not mean it's a threat to all visitors," says Dr Behrens.

A review of data collected by 11 industrial countries over 10 years identified important differences between general tourists and groups visiting friends and relatives in Africa. While a child of tourists travelling to Namibia carries a 0.4 in 10,000 risk of catching malaria, the child of emigrants visiting the Democratic Republic of Congo faces a 778 in 10,000 chance.

'Professionals have a duty to get the message out and engage with at-risk groups'

Returning migrants are more likely to visit high-risk areas and remain for long periods. While populations living in endemic zones tend to acquire some immunity to the disease during early or middle childhood, this protective factor wanes within months of moving to a non-malarial area, making returning migrants especially vulnerable.

Healthcare, access to medications and prevention information also play a crucial part in driving this disparity. Among emigrant groups there is a common misperception of continued immunity, says Patricia Schlegelhauf of the University of

Zurich Centre for Travel Medicine. She suggests that groups may think they run a low risk or that, having been exposed to it in childhood, they are no longer susceptible.

Malaria is almost entirely preventable. Even in the absence of a vaccine, preventive drugs and mosquito avoidance strategies afford near-comprehensive protection. Among travellers, some 80 per cent of cases occur among people who have not taken preventive treatments.

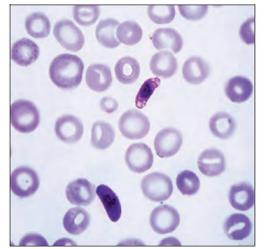
But emigrant communities often fall outside the reach of travel medicine specialists.

"It can be quite a challenge to access hard-to-reach populations

and overcome health beliefs," says Peter Chiodini, director of the HPA Malaria Reference Laboratory. However, he says: "Healthcare professionals have a duty to get the message out in a more direct form and engage with at-risk groups."

Not only is travellers' malaria increasing, but the type of disease showing up in western health clinics has changed. A decade ago, roughly half of recorded cases were infections with vivax, a less-virulent strain of the malaria parasite common to India and south-east Asia.

Today, observes Dr Chiodini, 70 per cent of reported cases are plasmodium falciparum, a more



Cause of harm: the plasmodium falciparum parasite

deadly form of the disease endemic to western Africa.

Although medicines provide protection, public health authorities are increasingly conservative in recommending their use.

Anti-malarial drugs come with severe side effects, whose risks may outweigh the benefits when the possibility of transmission is low. In the past few years Germany, Austria and Switzerland have revised their policies, and now recommend preventive treatments only for travellers who have a high risk of exposure.

The new measures have not affected incidence among travellers from these countries.

Given their adverse side effects, such drugs are likely to lose their place at the front line of disease prevention, says Dr Chiodini.

However, in order for medical authorities to advance new guidelines, more robust surveillance of travellers' malaria is needed to map the distribution of risk. Although the World Health Organisation tracks reported cases, the data focuses on endemic malaria and often misses incidents diagnosed outside endemic regions.

What is most needed, says David Smith of the Johns Hopkins Malaria Research Institute, is better scientific evidence.

However, Dr Smith points out that as a disease that disproportionately affects developing countries, malaria rarely ranks as a research or funding priority for western governments and institutions.

For more maps giving details of global malaria infection rates, go to: [www.map.ox.ac.uk](http://www.map.ox.ac.uk)

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# Treatments need constant refinement

## Drug development

Pharmaceuticals groups continue trying to improve existing remedies, reports Andrew Jack

More than a decade after Novartis of Switzerland – with more than a little help from the Chinese – won approval for Coartem (a combination of lumefantrine with the artemisinin-derived artemether), it is still hoping to develop a wide range of improvements.

There are many diseases with no cures, or ones for which drugs offer only modest benefits and extreme side effects, but malaria is not one of them. Coartem and similar generic versions of the artemisinin combination drugs are the standard of care, saving millions of lives a year. The drug has become the single largest product for Novartis at 100m packs a year.

Yet the nature of the parasite – along with human nature and market constraints – mean there is still demand for significant further innovation. Mark Fishman, head of research and development at Novartis, says: "Resistance is developing in the Thai-Cambodian border zone. And it spreads very quickly."

He supports a series of research projects spearheaded by special Novartis units in Singapore and San Diego, led by a drug codenamed 609, which tackles a parasite protein not targeted by other malaria drugs, offering a possible lead, as artemisinin's power is threatened by increased resistance.

Novartis is not alone. David Reddy, head of the Medicines for Malaria Venture (MMV), a Switzerland-based public-private partnership that helps co-ordinate research in the field, says: "There is a lot of promise now, with

some projects undertaken by pharmaceutical companies and others by academia."

A number of experimental drugs are in the clinic, being tested in human volunteers, including projects by Pfizer, Sanofi and GlaxoSmithKline as well as Novartis. Others have been undertaken by generic drug companies, including Ranbaxy in India and Shin Poong in South Korea.

Since Coartem's launch, a number of modifications have been made to provide incremental improvement, demonstrating the weak spots even of a highly successful drug.

One such alteration, with MMV's support, was a soluble cherry-flavoured version designed for children, those most affected by malaria but who often found the original drug difficult to swallow.

Artesunate, a derivative of artemisinin, has also been approved in injected form for treatment of severe malaria, and has won increasing acceptance in developed as well as developing countries.

Sigma Tau, a drugmaker, recently used a special approval process for developing countries established by the European Medicines Agency to win authorisation for a combination of dihydroartemisinin with piperazine, offering another tool to combat resistance in regions including south-east Asia.

Not all therapy progress has involved new drugs. Recent studies have demonstrated that low dose use of the existing sulfadoxine-pyrimethamine in pregnant women in countries with intermittent malaria very substantially reduces the risk of infection.

Cipla of India this month won regulatory approval in Malaysia for a fixed-dose combination of artesunate with mefloquine, a way to boost efficacy and fend off resistance, as patients otherwise tend to take only the artesunate.

One important focus for the future is studying ways to reduce the cost and improve supplies of artemisinin,



Room for improvement: Novartis, which sells Coartem, hopes to develop the next generation of malaria drugs

Corbis

'Resistance is developing in the Thai-Cambodian border zone. And it spreads very quickly'

which is still largely purchased from farmers cultivating the sweet wormwood plant from which it was first derived. New semi and fully synthetic versions are under development.

Mr Fishman stresses the importance of developing new drugs to tackle plasmodium vivax. And he believes that the work by Novartis on treatment of malaria during its stage in the human liver offers promise, including as a preventive treatment.

Mr Reddy says: "We need drugs that are better and easier to take."

The nirvana is a single-dose cure that dispenses with the need to take drugs over several days. Repeated doses risk fostering incomplete cures and accelerated drug resistance,

because patients cannot always afford a full course of treatment or see no further need to take pills once their symptoms disappear.

Mr Reddy and others acknowledge that the challenges do not end with the science – and uncertainties – of drug development.

One of the biggest issues is access to treatment. Even with international donor support, public clinics are often thinly spread and periodic "stock outs" leave the best malaria drugs unavailable to patients.

That means increasing efforts to address both supplies through the private sector – where counterfeit, substandard and unapproved drugs are often available – and the high prices

that exclude many of the poorest patients.

This has led to a continuing debate over the expanded role of the Affordable Medicines Facility – Malaria subsidy, designed to lower the retail price of the best artemisinin combination therapies.

Another discussion concerns the bundling of drugs with diagnostics, so that pharmacists do not sell malaria drugs if diagnostics show that patients have another disease instead.

Opinions remain divided and evaluations are still under way. But in the fight to improve treatment, medical science needs to be ever more integrated with social science.



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# Combating Malaria



A disease of the poor: the sewage and rubbish-strewn Crocodile River – a breeding ground for malaria-spreading mosquitoes – in Freetown's Kroo Bay slum area

PA

## Sierra Leone returns to pioneer's methods

### Historic overview

After more than a century, the country is again trying to eliminate the carriers, writes **Katrina Manson**

The scientists who discovered, after years of effort, that malaria came not from bad air – as the name (from the Italian *mal' aria*) suggests – but from mosquitoes, have acquired the reputation of being far bolder thinkers than their modern counterparts when it came to solutions.

No sooner had Sir Ronald Ross, scientist and wannabe wordsmith, decried the “unseen, small, but million-murdering cause” in one of his starchy poems than he set his sights on exterminating them altogether.

At the tail-end of 1899, the Nobel Prize winner who determined the bite of the anopheles mosquito spread malaria sent hit squads into Sierra Leone's capital Freetown to attack the fetid water pools that doubled as breeding grounds for the insects.

Sierra Leone was the perfect place to try this, and it still is. The lush green lands are home to a large natural harbour; the territory is filled with torpid swamps and rain deluges the country every year.

Malaria produced so many fatalities that the country – and west Africa in general – became known as the White Man's Grave, leading the British imperial authorities to forbid it as a convict destination, lest death mete out too harsh a punishment.

Sir Ronald convinced his supervisor, Sir Patrick Manson, of the need for extreme action, raised funds privately and set to work.

A 50-strong team collected broken

bottles, empty cans and buckets that held stagnant water, drained pools, smoothed roads to eradicate puddles and straightened rivers to eliminate festering corners. Documenting the work in his 1902 book *Mosquito Brigades and How To Organise Them*, he says they cleared 10 cartloads of empty tins and broken bottles by the day, poisoned water with creosote and within two months had cleared 6,500 houses.

It worked – for a while. Incidence declined, but the onslaught of the rainy season meant the work would be needed year after year. No one was prepared to fund it.

More than 110 years later, the picture in Sierra Leone is painfully similar. Among the world's 10 least developed countries, malaria accounts for more than 40 per cent of outpatient mortality and is the top killer of children under five.

“The disease is a cause and a conse-

quence of poverty,” reports the country's 2011-15 Malaria Control Strategic Plan, which says each bout puts people out of action for about 7-12 days.

It has always been a disease of the poor. When it first became clear that Sierra Leone's swamplands were

out of the malodorous bad air they thought spread malaria. Solutions many deem to be more timid than those put forward under “Mosquito Manson” have concentrated on less ambitious approaches.

Prevention focuses on protecting people rather than halting mosquitoes: bed nets and drug systems prevail.

Now the authorities want to return to eradication, hoping to reduce mosquito numbers and transmission long-term. The new strategy plumps for indoor spraying and killing mosquito larvae in their swampy breeding grounds, in a hope of boosting the number of people benefiting from at least one form of prevention from 25.9 per cent to 80 per cent by 2015.

Indoor spraying pilots in four districts show success so far, says Samuel Smith, manager of Sierra Leone's malaria control programme. He says that late last year, for the first time,

acute respiratory illnesses overtook malaria in these areas as the top killers of children under five.

“We are trying to get better strategies. A combination of spraying and bed nets has a better impact,” says Dr Smith.

As in 1899, cash is scarce. Although the government spends 13.1 per cent of gross domestic product on health, triple the amount on education, the four-year plan envisages a donor-assisted \$231m budget to fight malaria. Indoor residual spraying is the most expensive and unproven approach: it will cost \$114m, nearly 10 times as the amount needed for bed nets, 3m of which have been distributed since the strategy was published.

“Such measures as these have one great defect,” said Sir Ronald of his own experiment. “They protect only those who could afford them.”

His words appear to be as true in 2012 as they were in 1899.

Prevention focuses on protecting people rather than halting mosquitoes. The authorities want to return to eradication

responsible for the disease, expatriates were shifted out of their picturesque seaside residences – now slums with detritus for foundations – and a £30,000 railway line was built to relocate them up the hill.

Gracious houses on stilts kept them



Our mandate is to contribute to the improvement of the health of populations internationally, nationally, and locally through excellence in research, services, and teaching and training.

Our vision is to achieve significant improvement of human health and well-being through a better understanding of disease- and health-systems and acting on this knowledge.

Academic and professional **TEACHING & TRAINING** in epidemiology, public health, and malaria control/elimination.

**Sustaining the gain – save lives** through innovation, validation and application.

### RESEARCH

- R&D of vaccines, drugs, and diagnostics
- Vector control
- Health systems effectiveness

**SERVICE** provision at local, national, and international level through health system strengthening, and scaling up control.

[www.swisstph.ch](http://www.swisstph.ch)

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Institut Tropical et de Santé Publique Suisse

Associated Institute of the University of Basel

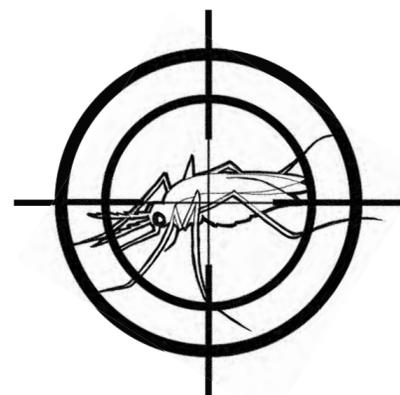
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Swiss TPH, since 1943 a center of excellence in research, training, and services.

— INSECTICIDE RESISTANCE —

**TO FIGHT IT,  
YOU HAVE  
TO FIND IT**



Public health actors have made impressive gains in the fight against malaria: Over 700,000 lives have been saved in the past decade, largely due to distribution of over 300 million insecticidal bed nets throughout Africa. But the dramatic spread of insecticide resistance in malaria-carrying mosquitoes threatens these advances.

Vestergaard Frandsen has led the response to this threat by developing **PermaNet 3.0**, the first-ever bed net to combine chemical compounds for increased efficacy. Proven killing power even in the face of insecticide resistance means that

PermaNet 3.0 is the net of choice in many areas burdened with malaria.

But even the best tools must be used in the right place at the right time. That's why we've partnered with academic and public and private sector actors to develop **IR Mapper**, a new mapping platform free to all users that consolidates fresh data on resistance to show areas of concern.

Knowledge, as they say, is power—and malaria control managers and researchers can rely on Vestergaard Frandsen to help them stay abreast of the latest intelligence on insecticide resistance.

[WWW.IRMAPPER.COM](http://WWW.IRMAPPER.COM)

**VESTERGAARD FRANDSEN**  
DISEASE CONTROL TEXTILES