COMBATING MALARIA

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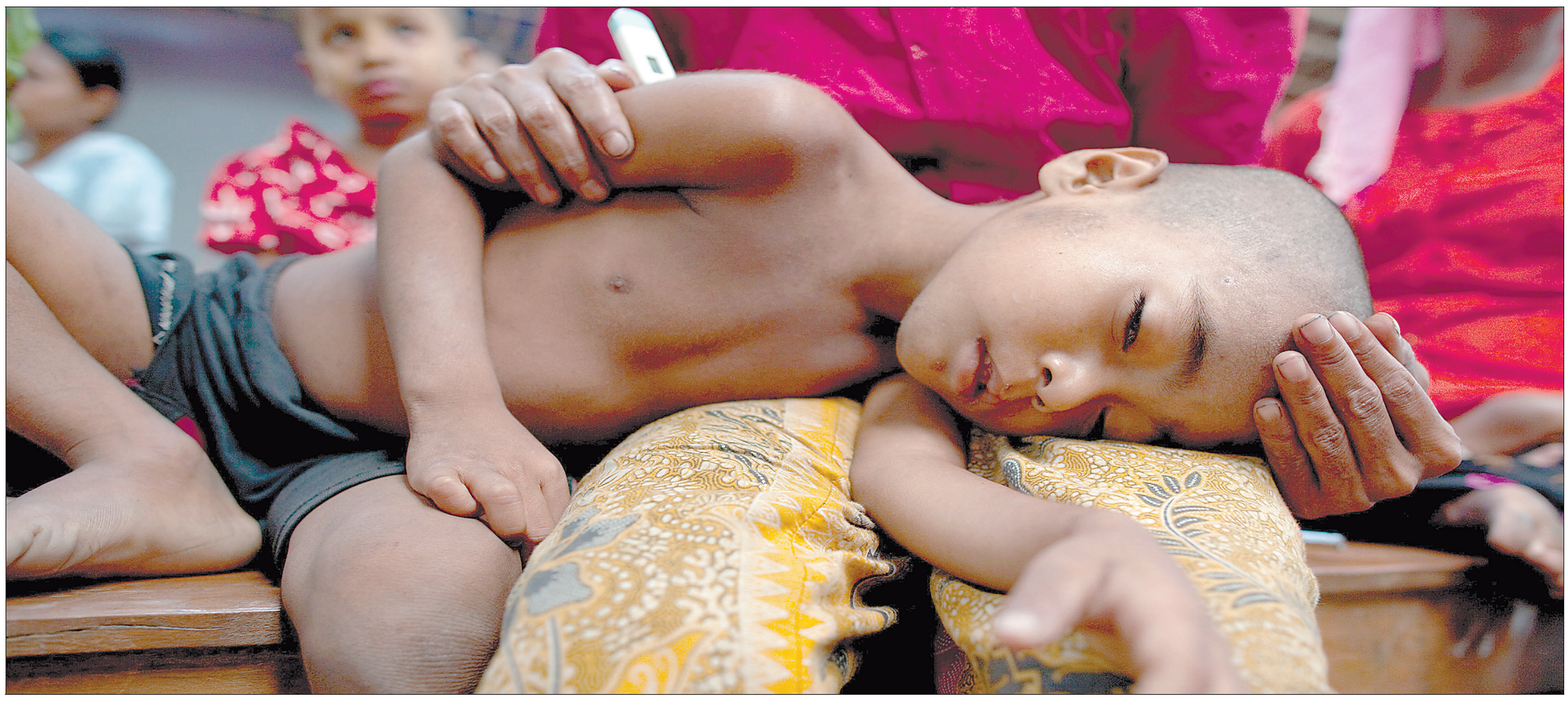
Optimism grows as target is in sight

Andrew Jack explains why there is a feeling that 2010 will mark the most hopeful World Malaria Day to date



A boy with malaria waits at a special clinic in Sittwe, Burma. Between 2000 and 2008, the level of cases there increased and activists worry about tolerant strains spreading Getty

With just eight months to meet his goal of distributing hundreds of millions of mosquito nets around the world to people at high risk of contracting malaria, Ray Chambers is feeling confident.

The UN special envoy on malaria believes efforts are on track for completion of deliveries during 2010, supporting broader plans to reduce greatly, within five years, the huge burden of illness and death from this leading killer disease.

"This is the most optimistic World Malaria Day to date," he says. "Today, we know we can achieve the goal of universal coverage of nets by the end of this year and near zero deaths from the disease by 2015."

His optimism is shared by other top officials who have observed a recent resurgence in efforts to tackle the disease, which the latest estimates suggest infects 250m people and kills more than 850,000 a year.

Imaginative advocacy has helped raise awareness, in turn stoking an upsurge in funding from $60m a year at the start of the millennium to nearer $2bn annually today.

Some far more effective tools for prevention and treatment have become available and the pipeline of technologies is growing to include more potent and easier-to-take medicines, and even possible vaccines.

There is growing management innovation, from "SMS for Life" messages to monitor drug stocks in rural Tanzania, to the Affordable Medicines Facility for Malaria, to be launched in up to nine countries next month, where it will subsidise the best drugs sold in the private sector to make them more affordable.

Respected personalities – from Senegalese musician Youssou N'Dour to football players in the United Against Malaria campaign of the World Cup in South Africa this summer – are stoking debate and spreading the message to those most affected that they can and must help tackle malaria themselves.

Community volunteers and religious organisations – Christian, Muslim and Jewish alike, sometimes working together – are filling gaps in often weak public health systems.

Tony Blair, the British former prime minister, has become involved through his inter-faith foundation, adding to a growing list of corporate chief executives and public figures who bring clout, profile and funding.

Perhaps most important, the creation last autumn of the African Leaders Malaria Alliance suggests the continent's own politicians are beginning to take a necessary fresh look at their pivotal responsibility in improving their citizens' health.

Awa Coll-Seck, head of the Roll Back Malaria partnership of public, private and non-governmental groups, says: "Things have moved really very quickly over the past three years, and you can see the results."

Her organisation has helped track progress in a dozen malaria-endemic African countries, and points to significant improvements in several. Ethiopia, Ghana, Rwanda, Zambia and Zanzibar have cut death and disease by up to 70 per cent in recent years, for instance.

But others – including some with the greatest burden such as Nigeria and the Democratic Republic of Congo – have performed much less well. Still more countries have such poor-quality data that attempting to measure progress is difficult.

In the tiny Kyekumbra clinic just two hours' drive from the Ugandan capital of Kampala, nurse Winfred Namudde says half her patients are still presenting with malaria. "But we just had three months without drugs," she says, leaving her with none of the recommended medicines to offer them.

Her experience highlights how much more needs to be done despite the positive momentum. The big challenges ahead are three-fold: deepening, broadening and sustaining the response.

The first aspect is to deepen existing approaches, which have until now focused on large-scale, efforts to bring control and treatment tools to countries in need.

That has meant a vast exercise to fund, procure and deliver drugs and bed nets,

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- **Suzanne Hill** and **George Jagoe** of the WHO and Medicines for Malaria Venture
- **Ray Chambers**, UN special envoy for malaria
- **Youssou N'Dour**, musician, Unicef and Roll Back Malaria ambassador and board member for Malaria No More

Optimism grows as target is in sight

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supplemented by insecticides and diagnostics.

Yet in the rush to meet universal coverage targets for these goods, such programmes have often taken scant account of local variations.

They have also incurred higher costs than necessary and resulted in less speed in delivering fast-expiring drugs "the final mile" to patients. More effort to ease distribution and effective use is required.

The focus on freighting in bed nets has left many sitting in warehouses, misused or simply unused in individuals' houses.

Without more culturally sensitive projects to train people in net use, as well as insecticide re-treatment and replacement plans, scarce resources are being poorly deployed and creating a large future environmental burden.

There is a need for closer scrutiny of progress, managerial fine-tuning, and monitoring better to understand local variations: how malaria transmission may vary over time and between places and, given this, the need to vary local approaches.

That issue points to a second challenge for the malaria community: to broaden its approach. Heavy top-down pressure to tackle the disease, backed by international funding has often undermined the policies, staff and systems of fragile national governments. So have the manifold well-intentioned but duplicative and, in some cases, counter-productive private and charitable initiatives.

Rob Newman, director of the World Health Organization malaria programme, says: "The issue of under-treatment may not be as catastrophic as it is made out to be." He argues that malaria should be a wedge to push for broader "horizontal" programmes.

As diagnosis and treatment becomes more reliable, other diseases, previously wrongly diagnosed as malaria, are identified and require different approaches. That calls for better trained, motivated and managed healthcare workers.

Even within the malaria field, there is a need to expand thinking and research on elimination; the use of intermittent treatment in pregnant women as a prophylaxis; alternative approaches to insecticides such as wall hangings or treated clothing; and approaches to dealing with less lethal but highly burdensome strains such as *plasmodium vivax*.

The final challenge is sustainability. History has proven the extraordinary versatility of the parasite in defying elimination. Resistance to the latest drugs – already identified in south-east Asia – risks undermining the best drugs available. If mosquitoes adapt to bite outside humans' sleeping hours, nets will be rendered less effective.

Any effort to reduce, and maintain at low levels, the burden of malaria will require large sums over many years. Yet even current needs are significantly under-funded. The financial crisis and "donor fatigue" risk diverting support further. Steven Phillips, medical director for global issues at ExxonMobil, says: "Once you get even a 10-30 per cent decrease in malaria, how do you persuade people to spend more when the problem appears to be going away?"

Recent progress is impressive, but World Malaria Day will be marked long into the 21st century.

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Funding and stamina required for the long haul

Corporate projects

Control programmes take great preparation but the results impress, says **Charles Batchelor**

When AngloGold Ashanti began spraying anti-malarial chemicals in the homes of workers at its Obuasi mine in Ghana, a large crowd of people gathered.

"There must have been about 1,000 people standing around when we sprayed the first house," recalls Steve Knowles, director of the malaria control programme at the Johannesburg-based gold-mining group.

"The lady of the house gets free pest control because, along with the mosquitoes, the chemicals kill cockroaches and ants."

Companies can benefit enormously from reducing the impact of malaria while burnishing their image with employees and increasingly demanding customers, lobbyists and governments. What they bring to the fight is their expertise in project management, their ability to train and motivate staff and a focus on results.

But with malaria, they face an enormous challenge. The disease is very resistant to efforts to control it and will recolonise treated areas from untreated regions. Successful programmes sometimes make local people think they no longer need to take precautions and the disease can return. Sufficient funding and stamina for a long haul are required.

Programmes such as AngloGold Ashanti's take a lot of preparation. There are many myths about malaria and it may not seem obvious to local people that draining patches of stagnant water and clearing blocked drains can help reduce the incidence of the disease.

"There was a six-month build-up to the launch of the programme that involved walking around and shaking hands with people," Mr Knowles explains. "You have to build credibility with the local community and you have to have motivated, trained staff to do the work. We call our community volunteer activists our John the Baptists."

AngloGold Ashanti itself had a strong motivation. It had identified malaria as the most significant public health threat to its operations in Ghana, Mali, Guinea and Tanzania.

A map of the globe shows many of its mines dotted across the malaria belt stretching from South America, through Africa and the Indian subcontinent to south-east Asia.

The company's Obuasi mine in southern Ghana lost an average of 6,983 man days a month because of malaria in 2005, with an average of 238 employees affected each month.

The cost of treating these people at the company's hospital was $22,000 a month, rising to $55,000 when family members were included. To counter the impact of malaria, staffing levels at the mine increased by 20 per cent.

The control programme, launched in 2006, involved spraying the insides of buildings, providing nets and repellents, spraying water surfaces with chemicals to control the growth of larvae and providing drugs to malaria sufferers.

Its impact has been impressive. Lost days per month fell to 273 in 2009, with some 38 employees affected. Medication costs fell to $2,000 for employees and $8,900 including their families. Eighty per cent of new cases involve people who have contracted the disease outside the control zone.

The AngloGold Ashanti anti-malaria spraying programme at its Obuasi mine in Ghana

AngloGold Ashanti is not the only company with significant activities in Africa that are threatened by malaria. Marathon Oil's regional gas processing hub on Bioko Island, in Equatorial Guinea, was affected by the disease.

Apart from the cost of treatment and the impact on production, expatriates are reluctant to work in Africa because they fear for the health of their families. Because of the disease, local employees are difficult to integrate into the company's structures and key growth sectors such as manufacturing and tourism will not develop.

Marathon launched a five-year, $15.8m programme with partners to combat malaria in 2003. It reported the results last year in terms of the impact on children below the age of five. There was a 64 per cent reduction in deaths, a 57 per cent fall in malarial infections in two-to-five year olds and an 86 per cent drop in anaemia in this age group. In 2006, the programme was extended to the mainland.

Companies with large production centres in malaria zones take little persuading that fighting the disease is a priority. But others can need some encouragement.

United Against Malaria, a partnership of public and private organisations that seeks to use football, and the 2010 World Cup in South Africa, to promote the fight against malaria, encountered early resistance.

"When I started talking to companies, they said it was not an issue in Africa," says Christina Vilupti Barrineau, director of African operations. When companies did have malaria programmes they were often very localised, involving, for example, support for a hospital.

Since starting the campaign, Ms Barrineau says she has received enthusiastic support from Nando's, a privately owned South African restaurant chain active in more than 25 countries, and from MTN, a listed mobile telephone company based in Johannesburg.

Companies with wide distribution networks – real or virtual – can use them to reach their customers, suppliers and staff with information, fund-raising campaigns and help with distributing medicines and bed nets.

Clinical intervention: a child is vaccinated as part of a trial in Kisumu-West District Hospital in Kenya Benjamin Moldenhauer

Hopeful results lead to first large-scale trial

Vaccine development

Clive Cookson assesses progress and explains methods

Over the past year, 9,000 babies and young children in seven African countries have received a shot of the first malaria vaccine to undergo a large-scale clinical trial. Eventually as many as 16,000 children will receive the so-called RTS,S vaccine.

"We are very happy with the way enrolment is going," says Joe Cohen of GlaxoSmithKline Biologicals in Belgium, who has been working on RTS,S for more than 20 years.

The vaccine originated with research at the Walter Reed Army Institute of Research in the US in the mid 1980s. After GSK had taken up RTS,S, tests in adult volunteers started in the US in 1992 and Africa in 1998.

A public-private partnership between GSK and the Path Malaria Vaccine Initiative (MVI) began in 2001 to put RTS,S through more extensive "Phase 2" trials with African children. Their encouraging results – showing an efficacy for the vaccine of about 50 per cent – led to the current much larger-scale "Phase 3" trial.

Altogether, GSK has already invested $300m in RTS,S and expects to invest at least $100m more before the project is finished. MVI has spent $200m, provided mainly by the Bill & Melinda Gates Foundation.

The long and expensive history of RTS,S illustrates the patience needed to develop malaria vaccines. And the story is far from at an end because, while a vaccine that provides 50 per cent protection would reduce significantly the toll of 800,000 African children under five who die every year from malaria, MVI aims to have a vaccine with 80 per cent efficacy available by 2025.

However Christian Loucq, MVI director, says future vaccines can be developed more quickly and at somewhat lower cost than RTS,S. Phase 3 vaccine trials require thousands of participants but the number becomes smaller as the vaccine becomes more effective, as greater effectiveness shows up more quickly. And the African infrastructure set up for the RTS,S trial could be used again.

Dozens of potentially more effective candidate vaccines are in earlier stages of development in academic and industry labs around the world. For maximum effectiveness they are likely to be used in combination rather than individually.

A partnership announced earlier this month between GSK and Crucell, the Dutch biotechnology company, is a pointer to the way things will go.

The two companies will carry out clinical trials with a combination of RTS,S with Crucell's Ad35-CS vaccine candidate. Animal tests have already shown a significant enhancement when the two are used together.

The immune-stimulating antigen in both vaccines is a surface protein from the so-called sporozoite stage of the malaria parasite's complex life cycle – the stage at which it enters the human bloodstream after a mosquito bite, and heads toward the liver where it will mature and multiply. But the antigen is packaged in different ways.

In RTS,S the antigen protein is administered with an "adjuvant" that boosts the immune response. In Ad35-CS the antigen is inserted into an adenovirus, a type of virus associated with mild respiratory infections, which delivers it to the immune system (adenoviruses are also used as vectors for gene therapy).

At an earlier stage of research – and using a very different antigen – is a "transmission-blocking vaccine" or TBV being developed by Johns Hopkins Bloomberg School of Public Health and the Sabin Vaccine Institute with support from MVI. This approach aims to stop the malaria parasite developing in the mosquito, so it cannot pass the infection on to humans.

The TBV uses a mosquito antigen called AnANP1, which plays an important role in the parasite's establishment within the insect. Field research shows that AnANP1 induces mosquito antibodies that prevent the parasite invading the insect's gut, and the idea is that vaccinated humans would pass enhanced levels of the antigen on to the mosquitoes that bite them.

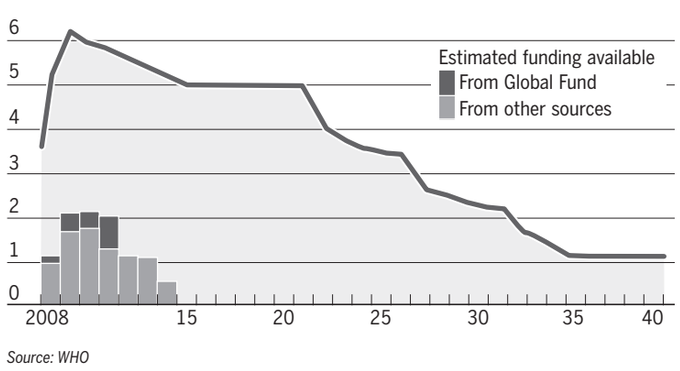
While a TBV would offer no immediate protection against malaria to the vaccinated individual, the benefits would accumulate over time as the number of infections declines with time in the community.

Another potentially fruitful field of research focuses on preventing malaria in pregnancy. Women are particularly vulnerable to infection while pregnant, because their immune defences are lowered and because the parasites accumulate in the placenta. Maternal malaria kills 10,000 women and 100,000 to 200,000 babies every year.

Researchers at the University of Copenhagen are developing a potential vaccine based on the VAR2CSA antigen which should elicit antibodies that stop the parasite binding to the placenta.

The Danish scientists have the elegant idea of attaching VAR2CSA to the human papilloma virus (HPV) vaccines that have recently been introduced to prevent cervical cancer. If HPV can indeed act as a carrier for the placental malaria vaccine, then it would be possible to protect girls in Africa against both placental malaria and cervical cancer with a single shot.

Estimated global resource requirements for malaria control
$ billion



Source: WHO

Focus on nets 'seductive but short-sighted'

Prevention

Andrew Jack says other approaches need just as much support

When Susan Lassen travelled to one southern African country recently on behalf of the JC Flowers Foundation, which distributes bed nets through Christian groups to help combat malaria, she was disturbed by what she found.

Sacks containing 90,000 nets paid for by donors had been gathering dust in a warehouse for a year, as the government struggled to find ways to distribute them "the final mile" to people in need.

Her experience highlights the flipside of the prominence given to mosquito nets, which have become the focus of a campaign to achieve "universal coverage" by the end of this year, turning net manufacture, sale and distribution into a big business.

Reduced malaria deaths and infection rates in countries where bed net use is widespread, show their importance. They are a low-cost and effective "tool" that also offers a powerful way to raise money and awareness.

Peter Chernin, the former head of News International, says: "You run into a challenge: in the US, where there is zero constituency," he says. "No one is calling their congressman to say 'Gee, what are you doing about malaria?'"

He used his influence to help launch malaria-related initiatives, for example through a US television fundraising event, Idol Gives Back, endorsements by well-known footballers and The Sun newspaper's alliance with Comic Relief in the UK.

"We have never been focused solely on nets, but it's a remarkably effective tool as a first line of defence," he says. "The big upside is that we have enormous results that can help keep people engaged."

The problem is that some of the high profile non-profit initiatives that have emerged – such as Nothing But Nets – downplay the importance of other approaches that require just as much support, including drugs, insecticide spraying and diagnostics.

Many organisations employ a powerful but somewhat oversimplified formula that equates a small donation to a tangible result.

The American Red Cross says: "One bed net, five dollars, save a life". The Foundation of the US government's Centers for Disease Control and Prevention, says: "$5 can save a child's life".

In fact, analysis suggests that it takes closer to 20 properly used nets (costing closer to $10 each, including all necessary overheads) to save a life and there is much debate about net reliability and how long they remain effective.

"We have done a terrible thing by putting a price tag on this," says Ms Lassen. "It was very seductive but also very short-sighted. In five years' time, people will say 'But I already gave my $5. Why isn't this solved?'"

There is little doubt that larger-scale, more consistent procurement of standardised nets by countries and international organisations could undoubtedly help save substantial sums.

Adam Flynn from Sumitomo Chemical, a partner of Africa's largest manufacturer of nets, says: "We are producing 25-30 per cent less than we could be because of retooling for different markets."

Another danger with some fundraisers is an over-emphasis on efficiency. The Against Malaria Foundation argues that every penny it raises goes to the purchase of nets. But that leaves others to find the resources to ensure that nets are delivered to those who need them, and then used consistently and effectively.

Susan Mukasa is head in Uganda of the non-profit group, Population Services International.

The organisation is involved in distribution campaigns, which are currently being scaled up, as large numbers of nets arrive in the country. She points out: "Getting the nets to the right people is challenging."

While she dismisses as "anecdotal" the stories of bed nets being misused by people for fishing or as wedding veils, she worries that during an election period, politics may influence their distribution to different regions.

Just as important, she says only about 32-40 per cent of nets that are successfully distributed are used consistently all night by their recipients.

> 'The problem with bed nets is that they have been designed by entomologists. I'd love consumer products companies to become involved'

People can be put off by the smell, the heat, or the inconvenience, for instance. Her organisation has launched "hang your net" campaigns designed to "make it fun and not like policing".

Janet Hemingway, head of the Liverpool School of Tropical Medicine, points out: "The problem with bed nets is that they have been developed and designed by entomologists and we have tried to force people to use them. I'd love consumer products companies to become involved."

"Baseline" data against which to measure the overall reduction in the disease is sparse in many malaria-endemic countries, and controlled studies to judge the relative impact of nets compared with other approaches is scant.

Organisations instead have rushed to deliver something that seems effective.

Sarah Staedke, a researcher from the London School of Hygiene and Tropical Medicine, says some funders now consider it unethical to conduct malaria control research that does not include net distribution as a "standard of care".

While nets play an important role, failure to keep studying how they should best be designed, distributed and used risks not taking full advantage of their value.

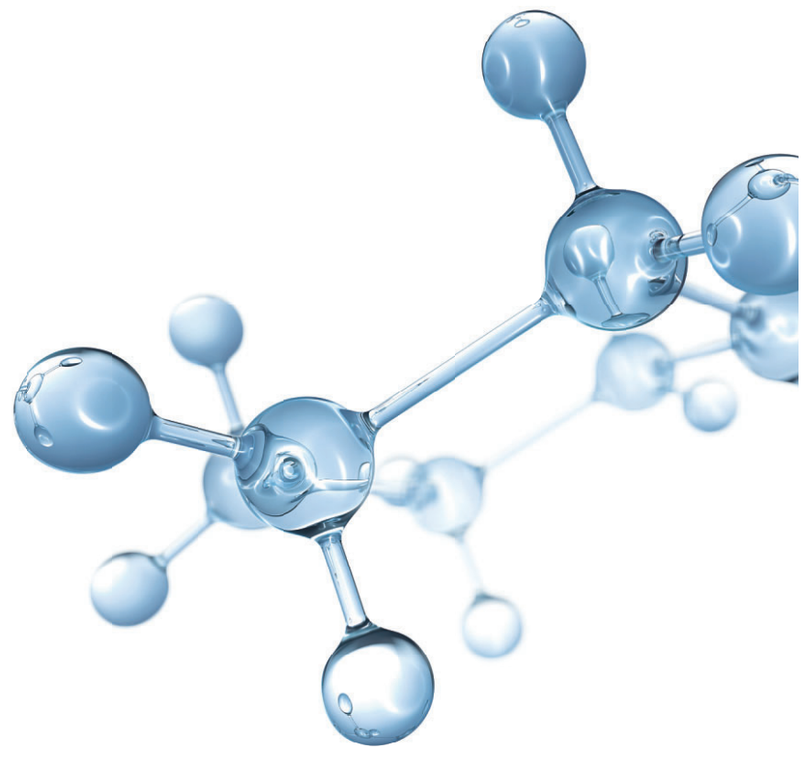
The current focus on their use also needs to be balanced with a search for sustainable, reliable and affordable alternatives.

World Malaria Day. A day we'd all like to eradicate.

Every 30 seconds malaria kills an African child. In just one year, malaria takes more than one million lives in Africa, the world's most afflicted region, and leaves poverty and devastation in its wake. Babies and young children are particularly susceptible. World Malaria Day—April 25—provides an opportunity to increase awareness and resources to combat this terrible but preventable and treatable disease.

ExxonMobil is committed to this fight. We're on the front lines, supporting new drug development and helping distribute insecticide-treated nets to places where they are desperately needed. Many companies and nations have already joined in this effort. It's essential we all work together. Present and future generations are counting on us.

To learn more about our efforts against malaria, visit exxonmobil.com/malaria.
And for what others in the global community are doing, visit rollbackmalaria.org.



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Supplies increase but distribution stalls

Procurement

The system is plagued by poor management and unreliable delivery, says **Andrew Jack**

Sarah Byasi shakes her head as she runs her finger down the stock page. She is in charge of drug supplies at the Kibogo hospital in Uganda and points to blanks showing there were no modern malaria drugs for adults for the 3 months until January; and none for children are currently available.

"We give paracetamol if there are no ACTs [artemisinin combination therapy – the current preferred treatment for malaria]," she says – a solution that provides only palliative support to patients suffering the disease's symptoms of fevers and aches.

Others in local clinics turn to quinine – a "salvage" drug. But its misuse, like that of ACTs, increases the risks of drug resistance that will render treatments still less effective.

Such "stock-outs" highlight how the development of even potent drugs such as ACTs are only the first step to ensure that treatments reach patients. Funding and medical supplies are increasing, yet they are still not saving as many lives as they should.

The frustration is compounded by scenes such as that across the road from Kibogo hospital, where a private pharmacy has no such supply problems. It offers wealthier patients a large range of ACTs – as well as many unauthorised malaria therapies that are ineffective or risk triggering resistance.

"Uganda loses 300 lives a day to malaria," says Hans Rietveld, head of global marketing and access for Coartem, the leading ACT, at Novartis. "We have seen mothers harassing healthcare workers when after walking two hours to a clinic they find there are no drugs. Perversely, compared with one year ago, there are more suppliers, but the availability is worse than before."

One issue is poor management of funds to buy ACTs, which remain relatively expensive compared with older – albeit less effective – malaria drugs. The Global Fund to Fight HIV, TB and Malaria, which channels multilateral donor support, earmarked large sums for Uganda for the drugs. Then it suspended grants after concern over the country's inability to account for how funds were spent.

In March this year, three of the principal officials managing the government's malaria programme were arrested, albeit in an investigation that some observers suggest was politically or commercially motivated and for which the civil servants are scapegoats.

Whatever the specific facts, Uganda has allowed foreign donors to take full responsibility for its malaria programme, leaving it exposed and unable to make its own drug purchases when external money dries up. It has been forced to seek help from the US President's Malaria Initiative to meet the shortfall.

That has sparked internal debates about whether such a poor country with a high disease burden ever should have switched to expensive modern drugs like ACTs; and if so, whether it should help provide domestic funding by charging patients for other essential but non life-saving drugs such as painkillers and antibiotics.

> Patients contribute to a vicious spiral, feigning malaria so they can horde for future infections

A second explanation for Uganda's stock-outs is its procurement processes. As in other countries, tenders do not always go to the lowest bidder, and deliveries from the winning bidder are not always met. Novartis has lost out in several recent tenders, and then been asked in extremis by governments to fill gaps in commitments from the winning company.

"We are an autonomous body without autonomy in procurement," says Moses Kamabare, general manager of the country's National Medical Stores, who says the process can take many months. "There has been more corruption than before. There are so many technical reasons to remove an offer. You can structure it to knock out all but the most expensive."

Even when funds are available and drugs make it into the country, they are not always effectively distributed. Mr Kamabare blames Uganda's health districts, which he says do not place orders on time or authorise the necessary payments.

Local clinics retort that they often receive incomplete orders of the wrong drugs, sometimes close to their expiry dates, long after they have been requested. Patients contribute to a vicious spiral, feigning malaria when fresh supplies arrive so they can horde for future infections. "When we have stock-outs, they have stock-ins," jokes Ms Byasi.

One response set to launch next month in nine countries is the Affordable Medicines Facility for Malaria, which uses donor funds to subsidise the ACTs sold by private distributors to ensure effective drugs are sold more affordably.

Other efforts try to improve management in the public health system. In Uganda, the medical charity Amref is helping introduce computerised information systems to monitor disease levels. In Tanzania, groups are experimenting with text messages to disseminate information on stock levels.

But, as Mr Rietveld puts it, for such initiatives to work: "We need more political accountability, with non-governmental organisations defending patients' rights."

New strain develops ways round immunity

Disease development

Clive Cookson looks at worrying mutations in the *vivax* species of the malarial parasite

Most malaria research and writing focuses on *plasmodium falciparum*, the most deadly of the four species of parasite that cause human malaria.

But the other three have a big impact on public health too, particularly *plasmodium vivax*, which is the species most widely distributed around the world.

According to the US Army Center for Health Promotion and Preventive Medicine, *p. vivax* accounts for 70m-80m cases of disease a year – about 20 per cent of all malaria.

P. vivax, unlike *p. falciparum*, is rarely fatal, but it does cause significant long-term illness. Symptoms are similar to other types of malaria, including cycles of fever and chills, headache, weakness, vomiting and diarrhoea.

Relapses can occur months or years after treatment, if the parasites become dormant in the liver. The most common complication is enlargement of the spleen, according to the Malaria Vaccine Initiative (MVI).

Like the other *plasmodium* species, *vivax* is spread by *anopheles* mosquitoes. But there are several differences from *falciparum*. It preferentially infects younger, smaller red blood cells and it can hibernate in the human liver for up to five years.

While *falciparum* is concentrated in sub-Saharan Africa, *vivax* occurs widely across Asia, the Americas, the Middle East, north Africa and the South Pacific. It can tolerate cooler conditions than the heat-loving *falciparum*.

Most cases of malaria found in travellers returning to Europe and North America are *vivax* infections. Those who fear a return of malaria to temperate regions where it has been eradicated, as a result of climate change and increased international travel, are particularly concerned about *vivax*.

Vivax is the only form of malaria endemic to the Korean peninsula. Although the World Health Organisation officially declared South Korea to be malaria-free in 1979, it reappeared there in the early 1990s and now causes what the US Army Center for Health Promotion and Preventive Medicine calls "sporadic epidemics", as its carrier, the local *anopheles sinensis* mosquito, breeds in water in rice paddies.

The country worst affected by *vivax* is India, where the species causes up to 65 per cent of malaria cases. As a result, India is a leading centre of research into *vivax* malaria.

The main reason why Africa has few cases of *vivax* malaria is that Africans are usually genetically resistant to infection by the parasite. *P. vivax*, unlike the other *plasmodium* species, enters red blood cells through the so-called Duffy receptor – which is missing in most black African populations.

But worrying research, published last month in the Proceedings of the National Academy of Sciences, suggests that *vivax* is evolving new strains that can infect previously immune people with "Duffy-negative" blood groups.

Anopheles gambiae mosquito: one of the primary vectors of malaria in sub-Saharan Africa Science Photo Library

A study in Madagascar found that 10 per cent of clinical malaria cases were occurring in Duffy-negative patients infected with *p. vivax*.

"These findings will have a major impact on efforts to eliminate malaria worldwide, particularly in large regions of Duffy-negative west, central and southern Africa," says Peter Zimmerman of Case Western Reserve University, senior author of the study.

> 'Researchers believe the new strains evolved in Madagascar because of population mixing there'

"It will be imperative for the global health community to find ways to prevent the spread of these new strains of *p. vivax* to the continent of Africa."

The researchers believe the new strains evolved in Madagascar because of population mixing there, between people with Duffy-negative African ancestors and Duffy-positive Asian ancestors. This gave *p. vivax* many opportunities to attempt infection of Duffy-negative blood cells, which eventually succeeded through mutation into a new strain.

P. vivax has traditionally been treated successfully with the long-standing antimalarial drugs, chloroquine and primaquine. The latter acts particularly against the liver stage of the parasite, reducing the risk of relapse.

But *vivax*, like *p. falciparum,* is becoming resistant to chloroquine and primaquine.

Vaccine development understandably concentrates on *p. falciparum* because it is the main malarial killer, though an Asian research network is looking for *vivax* vaccine candidates.

But the MVI says the long-term aim is to create a combined vaccine that can prevent both types of malaria – or at least reduce the severity of symptoms.

Meanwhile, its *vivax* efforts are focused on projects with the US Walter Reed Army Institute of Research and with the International Centre for Genetic Engineering and Biotechnology in India and its industrial partner Bharat Biotech.

"We know less about *p. vivax* than *falciparum*, and we are still looking for more data to understand *vivax* and the severity of the disease it causes," says Christian Loucq, MVI director.

Faith can help heal bodies as well as souls

Guest Column
TONY BLAIR

Two months ago I joined Nigerian ex-President Olusegun Obasanjo and a number of the country's religious leaders in Kuje, a township outside Abuja to promote a multi-faith programme to train 300,000 Nigerian religious leaders in malaria prevention.

The idea is simple but potentially very effective. Most communities in Africa do not have hospitals or clinics, but all have a church or mosque.

The programme uses this massive infrastructure with its imams and priests to distribute bed nets and medicines and facilitate access to trained health workers to combat malaria in Nigeria.

This has been given the backing of the Sultan of Sukoto, the leading Muslim in the country, and the Catholic Archbishop of Abuja, John Oneiyekan. There is a full-time, centrally organised team to co-ordinate the programme. If it succeeds, the impact will be enormous.

My Faith Foundation is supporting this work. The purpose of the foundation is to promote interfaith understanding.

Involving religious communities is a sensible pragmatic response to the scourge of malaria and the health challenges of the Millennium Development Goals.

For the simple truth is that, while accurate statistics are hard to come by, the World Health Organization (WHO) estimates that in sub-Saharan Africa countries, on average, faith communities supply 40 per cent of health care.

Faith communities reach into rural areas where governments find it difficult to implement national plans, for lack of infrastructure.

Embedded in local communities, religious leaders are trusted and, if trained, can give authoritative health messages. They have privileged access to dynamic and committed women, motivated by their faith, who are so important for health care. They and their communities are still there when the donors go home.

So why are very few mosque and church communities in sub-Saharan Africa fully involved in the drive to halt and reverse the spread of malaria?

Several of the most important reasons are: lack of resources and information, a degree of mistrust and, sometimes, because governments are understandably anxious about proselytism and the divisive potential of religion; and most religious leaders are overworked and lack resources.

Religious leaders generally lack understanding of how government ministries work, are almost never involved in upstream health planning, and receive less than 5 per cent of the money available for health care, although they undertake a large amount of the work. So there are obstacles to overcome.

But the process of dismantling some of these is under way. Christian Health Associations, drawing in a range of churches nationally, have signed memoranda of understanding with governments.

The Kenyan agreement to work together on health is going well. A multi-faith initiative in Mozambique, Together Against Malaria, has trained hundreds of religious leaders who are trying to share their newly acquired health education with their communities.

Pastor Rick Warren's church is doing good work in Rwanda in primary health care. The Nigerian Interfaith Action Association (NIFAA) has established itself as a "one-stop-shop" for government to make it easier to collaborate on health initiatives with faith communities. The Ministry of Health, with World Bank aid, is supporting it to the tune of $1m a year.

The Faith Foundation helps co-ordinate dialogue between public health officials and faith leaders.

We also promote research into the role of faith communities in health care. The key is to train religious leaders in health and public health officials in a deeper understanding of how the various faith communities work, their "health worlds" and their potential.

But the campaigning role of faith communities in the developed world is also significant.

> Most communities do not have clinics but they all have a church or a mosque that can be used as a health centre

The goal of the Foundation's "Faiths Act Fellows", 15 interfaith pairs of young adults in Canada, the US and the UK, is to mobilise the potential of religious communities in halting and reversing the spread of malaria.

We have volunteers in 75 countries contributing to an international campaign against what one of the bishops in Abuja dubbed "the number one terrorist in Nigeria", the mosquito vector.

An encouraging sign is that the "malaria sector" is now sometimes oddly described as "overpopulated". But this is something I welcome.

Religious leaders, transnational businesses, government development agencies, academics, and multilateral donors are all required to create the critical mass that has started the process of eradicating malaria from the African continent – just as it was eradicated from Europe.

The Rt Hon Tony Blair is founder and patron of the Tony Blair Faith Foundation.

Vagaries of weather and the market hamper deliveries

Artemisinin

Anna Wang says securing a stable supply of the plant extract is difficult

Artemisia annua, a weed found in the foothills of south-west China, is now the most effective weapon in killing the malaria parasite. However, securing a stable supply of its potent extract, artemisinin, is proving a big challenge.

Relying on the forces of supply and demand does not seem to be a solution.

The price of a kilo of artemisinin, the key ingredient in the current preferred malaria treatment, Artemisinin Combination Therapy (ACT), ranged from $1,200 in 2006 to $150 in 2008. Today, the price is hovering at $400, which is expected to increase with concerns over a shortage, because of poor weather and lack of cultivation in 2009.

When the price was at its lowest, the panic was over potential shortages of the drug because farmers were leaving the market for more lucrative crops. When prices were high, drug manufacturers could not afford to purchase the raw material and the global health community worried over the increase in prices of the drugs for patients.

According to Charles Lu, president of HolleyPharm of China, the largest supplier of artemisinin, there will very likely be a shortage in 2010 because of the severe drought in four main provinces of China where it is grown. "My fear is that last year's drought has hurt the farmers. It's not easy for them to recover their losses and their confidence," says Mr Lu.

Most Artemisia crops come from relatively small farms. In addition to the weather, public influences such as donor funding, supply chain management and drug policies, have a big impact on the market.

ACTs are a relatively new class of drug, so farmers, extractors and manufacturers are still getting to know the business. Aside from industry giants, Novartis and Sanofi-Aventis, the majority of manufacturers are generic drug companies without experience of producing drugs with a plant extract as a key ingredient.

Malcolm Cutler, an expert in the artemisinin supply chain, says: "Generic manufactures are used to picking up the phone and ordering chemicals. They are not used to planning ahead, which is what you have to do, since it takes 14 months from seed to extraction.

"We have to cut down on this boom-and-bust scenario. Long-term contracts are the key to the stability of the market."

Novartis, which supplied 84m ACT treatments in 2009, has three-year contracts with extractors. It is one of the reasons the company is able to deliver orders on time, while others have had problems meeting delivery dates.

Attracted by the success of ACTs in treating malaria and various initiatives to ensure more patients have access to the drugs, more people are getting involved, from farmers and extractors to drug manufacturers.

"Actually, the last thing we need is new players at the artemisinin extraction level. We have more than enough capacity to meet the current demand," says Patrick Henfrey, chief executive of Botanical Extracts EPZ in Kenya, one of the two main artemisinin producers in Africa.

> 'Long-term contracts are the key to the stability of the market'

"The international community is involved in ACT supply; it is necessary to include the raw material into the plan," says Mr Lu.

"I would like to see maybe six or 10 qualified suppliers who have the capacity and can meet quality standards. Then, there should be financial support, such as loans, because this is a cash business and it can create a high burden."

At the average price of $1 per treatment for the public sector, ACTs are still too expensive without donor support, as hundreds of millions of treatments are needed each year.

One solution to bring down the price is to increase crop yield. In the UK, the University of York has been researching ways to create more robust varieties of Artemisia and increase yields of artemisinin, without genetically modifying the plant.

Ian Graham, director of the Artemisia research project at York, says: "Unlike GM, we have not introduced new DNA. Instead, we have selected the most productive DNA for breeding. Our aim is to double the artemisinin yield, which would have a huge impact on the price."

Efforts to improve yield, stabilise the market, and increase access face a serious problem – drug resistance.

Resistance has been confirmed on the border of Thailand and Cambodia, the same location where chloroquine-resistant strains of malaria surfaced and later spread throughout the world. There is now an aggressive attempt to contain the resistant strain.

Ultimately, the best way to counter resistance and curb the volatile artemisinin market is a completely new class of drug that does not rely on a plant. The non-profit Medicines for Malaria Venture (MMV) has been working on the next generation of drugs for the past 10 years.

MMV aims to register two new artemisinin combinations by early 2011. The most awaited drug, however, is a non-artemisinin synthetic compound that mimics the fast-acting mechanism of artemisinin but does not require the plant. One formulation, known as OZ439, has begun trials in patients. MMV hopes it can be offered as a single dose cure.

Tim Wells, chief scientific officer of MMV, says: "We are quietly hopeful that we can have this non-artemisinin drug ready by 2015."

Better tests bring challenges

Diagnostics

Sarah Murray finds more accurate diagnosis of all causes of fever is required

As the health community continues to make progress in reducing the global incidence of malaria, the need for accurate and affordable diagnostics is gaining attention, with the World Health Organisation (WHO), which sees testing as a critical tool in the battle against the disease, advocating universal testing of all suspected cases.

Fortunately, microscopy is no longer the only diagnostic technology available. The recent development of rapid diagnostic tests (RDTs), which use a simple dipstick and a drop of blood, means testing can done on a large scale.

Yet developing RDTs for malaria has not been easy. While the tests can now be produced very cheaply, the challenge is that they need to remain stable in places where temperature and humidity levels are high. At the same time, they need to be sensitive enough to detect low densities of the parasite in blood samples, without producing false positives.

Companies may use the same reagent but the production of accurate, heat-stable tests can be more of an art than a science, says Neil Mehta, president and chief executive of Premier Medical Corporation, which has developed point-of-care rapid tests for malaria.

"You can give the same cookbook to everybody, but the food all comes out differently," he says.

This was the finding of the WHO, after it conducted the first major review of RDTs in April last year. In independent, laboratory-based evaluations of more than 40 commercially available RDTs, it found some could detect malaria in blood samples where parasite densities were low while others could only detect the parasite at high densities.

It also found test performance varied between batches, and recommended testing batches after they are purchased and before they are used.

Publishing these results has served a number of purposes. For a start, the performance evaluation will be conducted on an annual basis – with the next version publishing this month – providing a benchmark for the companies developing the tests.

Rapid response: a malaria test is performed on a blood sample at a hospital in Cambodia Bloomberg

"Once people know that there's a routine system for assessing these products, it will drive the quality of the market overall," says Robert Newman, director of the global malaria programme at the WHO.

Moreover, the data are helping health ministries and others select from the many RDTs on the market the test most suited to their local conditions.

"It makes it possible to do something that's not possible for many things sold into developing countries," says Mark Perkins, chief scientific officer at the Foundation for Innovative New Diagnostics (Find), one of the organisations behind the WHO's evaluation study.

"And that is to allow ministries of health who don't have the staff or the capabilities to do this kind of analysis to decide what to buy."

Meanwhile, new malaria guidelines published by the WHO in March stress the importance of using diagnostic testing where it is available, rather than delivering treatment based on symptoms alone.

By helping inform procurement decision-makers, the WHO data and guidelines will prove important tools in the next phase of the battle against the disease – and not just for malaria sufferers.

When the disease was rampant, health workers could, with reasonable justification, assume that anyone with signs of fever had malaria. However, as prevalence drops and the proportion of people whose fever is attributable to malaria falls, health experts stress the need to rule it out, so people can be treated for the real cause of their fever.

"The time for presumptive treatment has passed," says Dr Newman. "We do no one a service by giving them an ACT [artemisinin-based combination therapy – the current preferred treatment] when they have something other than malaria."

Health experts also point to the dangers of overusing malaria treatments. "Indiscriminate use of anti-malarial drugs fosters resistant strains and lessens the impact of the limited number of drugs we have to fight the disease," says Daniel Carucci, vice-president for global health at the United Nations Foundation, a charity and advocate for the UN.

Of course, the ability to distinguish people who have malaria from those with fevers caused by other illnesses brings a fresh challenge – the need for better diagnosis of all conditions.

"This pushes the envelope in terms of what is required of healthcare workers," says Dr Perkins. "We must recognise the real limitations of the system and the capacity for them to react to diagnostics. But it is a sea change we must face."

At the same time, universal testing remains some way off. "This isn't going to roll out everywhere and no one should be sent away without treatment because a test wasn't available," says Dr Newman. "But the bottom line is we've raised the bar."

Football fever Spreading word about public health

Malaria may wreak greatest damage among the poor and the young but it is an undiscriminating disease. Even some of Africa's most successful professionals – its highly-paid football stars who have made their names in the European leagues – have suffered.

So it is perhaps not surprising that anti-malaria campaigners have seized on the occasion of Africa's first ever World Cup, due to begin in South Africa in June, as an opportunity to get their health care message across to larger numbers of people. Nor that footballers have been willing campaigners.

As he juggles a ball for the cameras of the United Against Malaria (UAM) campaign, Kolo Touré, the Manchester City and Ivory Coast centre half, delivers a simple message. "In the 90 minutes it takes to play a football match, 180 children die from malaria. Yet a simple net prevents malaria." says Mr Touré, who was hospitalised by the disease two years ago.

The measures advocated by UAM, formed by groups including Comic Relief, the Roll Back Malaria Partnership and the UN Foundation, are straightforward: more emphasis on effective primary health care.

That means making sure programmes, which are sometimes seen as the poor relations of Aids or tuberculosis efforts, are given a high enough priority by African governments. Mosquito nets are crucial: lobbying for public funding is a priority and to advertise the effort, UAM has produced an anti-malaria bracelet, sales from which are directed towards their purchase.

It means making sure people understand how they can avoid contracting the disease and know what they need to do if they become ill.

The innovative thing about UAM is the way that it is using football fever to spread the word.

"African footballers are the new stars of world football and are the perfect messengers to individuals in Africa, and are also highly influential in getting businesses and government on board," explains Pru Smith of UAM.

"If a group of kids are watching TV and their favourite player tells them to sleep under a net they will listen," she says. "Everybody likes football. It is a way to take the message to the remotest village."

As well as global stars such as Mr Touré, local football associations from Ghana, Tanzania and several other countries have come on board, with administrators arguing that the prevalence of malaria – especially among young people – is undermining the game's potential in Africa.

Ms Smith says that the popularity of football has made it easier to get public health ministers and officials to back public education efforts.

Above all the commercial reach of the World Cup has also made it attractive for companies to dedicate some of their social responsibility budget to the campaign.

In South Africa, Standard Bank, MTN – the telecommunications group that is a big sponsor of the World Cup tournament – and Nando's, a fast food chain, have signed up.

Other heavyweights backing the campaign include cable channels ESPN and Fox, the Japanese bank, Sumitomo and the pharmaceutical companies Pfizer and Novartis.

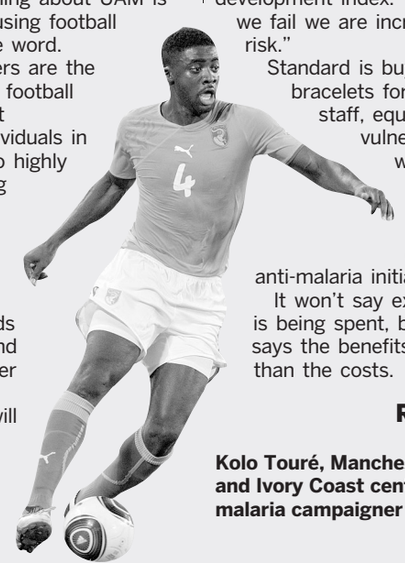
For all these groups, fighting malaria makes commercial sense. Standard employees are potentially vulnerable to the disease both in a couple of provinces of South Africa and in many of the African countries where the group has set up operations, so there is a broader risk, explains Sim Tshabalala, the deputy chief executive.

Last year, days lost through malaria cost the bank R450m. Mr Tshabalala, however, says that underestimates the real impact. Endemic diseases undermine social cohesion and in the long run represent political risk and mean companies have to pay more for their capital. "South Africa ranks among the world's biggest 30 economies but is 129th in the human development index. To the extent that we fail we are increasing country risk."

Standard is buying the publicity bracelets for all its 45,000 staff, equipping any vulnerable employee with a mosquito net and working alongside NGOs in a number of country-specific anti-malaria initiatives.

It won't say exactly how much is being spent, but Mr Tshabalala says the benefits are much greater than the costs.

Richard Lapper



Kolo Touré, Manchester City and Ivory Coast centre half and malaria campaigner

Illegal, immoral and liable to increase drug resistance

Fake medicines

Joseph Milton looks at moves to counter the trade

Few trades are as callous as the manufacture and distribution of counterfeit medicines for curable but life-threatening diseases such as malaria.

Reliable statistics about the scale of the problem are unavailable, but counterfeit drugs are thought by the World Health Organisation (WHO) to constitute between 25 and 50 per cent of the medicine supply in less developed countries.

The global trade in bogus pharmaceuticals will be worth some £45bn ($75bn) in 2010, according to the US-based Center for Medicine in the Public Interest (CMPI), an industry-backed think tank.

Fake antimalarial drugs are a particular problem, as the 500m cases of malaria worldwide every year make it a large, lucrative market.

Thirty per cent of WHO member states have ineffective or nonexistent drug regulation, so the manufacture and sale of fake antimalarials is relatively risk-free in many countries.

Paul Newton, head of the Wellcome Trust-Mahosot University Oxford Tropical Medicine Research Programme, based in Vientiane, Laos, says the human cost of the trade is almost impossible to estimate.

However, a significant proportion of the 1m deaths from malaria annually may be attributable to counterfeit drugs.

In response to the increasing sophistication and global scope of counterfeiting operations, the WHO and Interpol – the international police organisation – formed the International Medical Products Anti-Counterfeiting Taskforce (Impact) in 2006.

Aline Plançon, an Interpol officer at Impact, says: "The idea was to put together multidisciplinary groups and encourage co-ordinated enforcement."

In January, Interpol went a step further, creating the dedicated Medical Products Counterfeiting and Pharmaceutical Crime (MPCPC) unit, headed by Ms Plançon. Several successful operations have led to arrests and seizures.

Operation Mamba II, which took place throughout August 2009, involved raids across Uganda, Tanzania and Kenya. The operation resulted in 83 police cases and some convictions – often hard to achieve.

South-east Asia was targeted in Operation Storm II, which concluded in January. Impact seized about 20m pills and made more than 30 arrests.

However, it is difficult to track counterfeit drugs to their origins. Chemical testing of tablets and analysis of pollen grains found in the pills and packaging have been used to trace the location of manufacturers.

"We know there are criminal connections between Africa and Asia, and are working to identify exact source sites, but there is more work to be done," says Ms Plançon. Dr Newton thinks the majority of fakes originate in Asia and are shipped to Africa for sale.

Seized counterfeit antimalarials range from benign tablets composed entirely of flour to dangerous mixtures of toxic substances.

Some samples actually contain the correct active ingredients, probably in an attempt to evade detection. They are, however, often present in very low quantities. This not only undermines treatment, but could contribute to the development of resistance, rendering the medicines useless.

> If ACTs become cheap and readily available, fakers may be put out of business

Malaria is now frequently treated with derivatives of artemisinin, a chemical from wormwood plants. Artesunate, a semi-synthetic artemisinin derivative, was the first such drug, developed in the 1970s in China.

The WHO now recommends administering artesunate in combination with other antimalarials, known as artemisinin-based combination therapy (ACT).

These drugs have become a target for criminals, as demand is high, and they are relatively expensive. In 2008, counterfeit ACTs were estimated to account for between 33 and 53 per cent of samples in mainland south-east Asia.

Although south-east Asia is likely to be the main manufacturing base for fake antimalarials, the problem is global. Counterfeiting operations have become big business in Africa, India and Latin America.

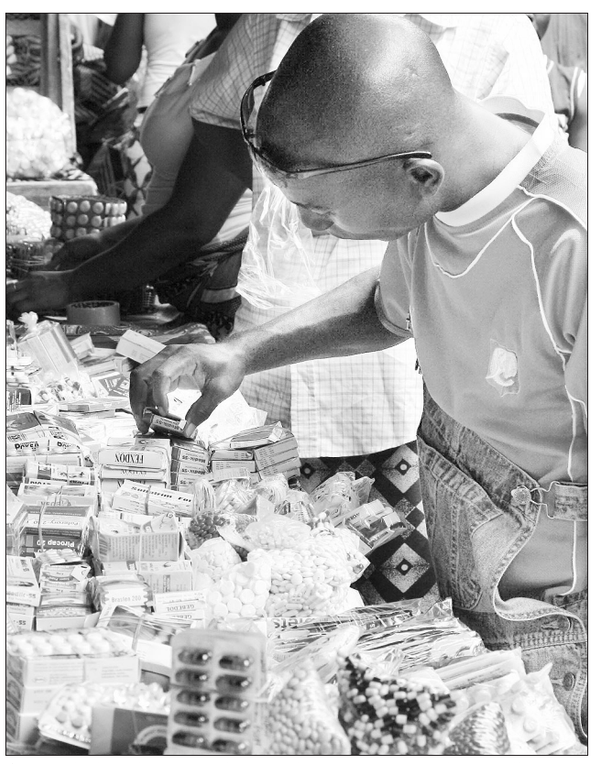
Large shipments of counterfeited ACTs were seized recently in six African countries. "Everywhere we looked, we found counterfeit medicines," says Ms Plançon.

Despite Impact's successful operations and ongoing efforts to tackle the trade, George Jagoe, of the Medicines for Malaria Venture – a not-for-profit public-private partnership aiming to tackle the disease – says the dearth of reliable data makes it impossible to judge whether the situation is improving.

Dr Newton agrees, describing the available statistical evidence as "meagre".

Mr Jagoe suggests that the problem could be tackled by introducing more sophisticated tracking of legitimate drugs, increasing public awareness of the problem and reducing the costs of medicines.

There is hope: the ACT Consortium, funded by the Bill & Melinda Gates Foundation, is working to improve access to ACTs for all those suffering from malaria in less developed countries. If ACTs become cheap and readily available, the counterfeiters may find themselves out of business.



Smuggled and counterfeit medicines on a market stall AFP

Systemic problems threaten progress

Country profile
Angola

Richard Lapper cites lack of education, bureaucracy and demotivated staff

Patient waiting: locals queue at the Ndala-Mulemba clinic in Angola Fatima Carvalho

It has been another busy morning at the health post in Ndala-Mulemba, an hour outside Angola's capital, Luanda, and the woman in charge, Fineza Amualdo, already sounds as if she has had quite enough work for one day.

"We have had six malaria cases already and another five are waiting," says the 32-year-old Ms Amualdo, as a long line of women and children takes shelter from the sun under the canopy outside her office.

"We are always telling them to use the nets but sometimes they don't. The number of cases is always high."

Angola may be on the road to recovery from a devastating three-decade civil war, with the economy growing and social spending rising, but the healthcare situation in slum areas such as Ndala-Mulemba is precarious.

Despite efforts to fight it, malaria remains the number-one killer disease, wreaking particular havoc among young children.

Considering that the local authorities – with the support of the United Nations Children's Fund (Unicef) – have radically stepped up primary health efforts over the past three years, this continuing prevalence highlights the difficulties in fighting the disease.

Since 2007, the town of Cacuaco has built the health post at Ndala-Mulemba and benefited from a Cuban health mission, which has increased the number of public sector doctors in the town of 800,000 from three to seven.

Private sector clinics have been persuaded to make some services available to their public sector counterparts and the municipality has contracted 1,000 volunteer community health agents.

The agents, who work in their spare time, receive $50 a month to cover their costs and distribute mosquito nets and chemicals to clean water. They persuade families to register births and vaccinate their children and dispense simple advice.

The effort is paying dividends in some areas. Last year, for example, 200,000 children were vaccinated against polio and whooping cough, an increase of about 20 per cent compared with two years ago.

But progress has been slow. Part of the reason is that it has been difficult to improve health standards among a badly educated population that is new to urban living.

Joanna Silva, a doctor and municipal health official who has been orchestrating the effort, says about half the population of Ndala-Mulemba are first-generation rural migrants. Many are illiterate.

"The population grows day by day," she says, which makes it difficult to plan the delivery of social and health services.

> 'If there is no improvement in the service there is really no point in us bothering'

Karina, a 36-year-old Cuban doctor working alongside Angolan nurses as part of a broader Cuban healthcare mission, says many of her patients have been slow to put health recommendations into practice.

"They use their mosquito nets even when they have holes in," she says.

There are also signs that local bureaucrats and public health workers have not been 100 per cent behind the effort. One of 20 volunteers attached to the Ndala-Mulemba post, says that full-time nurses and administrative staff have been uncooperative.

"The nurses arrive late and there are a lot of delays," the volunteer complains. "If there is no improvement in the service, there is really no point in us bothering. We are really de-motivated."

Vaccines and chemicals used to treat drinking water have sometimes been unavailable. And efforts to encourage people to register births [only about a third of babies are currently catalogued] have run into inflexible administrative processes.

To cap it all, the provincial government has not paid the volunteers the $50 monthly stipend for nearly a year.

Domingo Dinis, a 30-year-old volunteer who also works as a nurse, agrees. "It's been going on for months and we still haven't had a response from the provincial government. It really creates a problem, because when the bureaucrats don't respond, people blame us."

Already four of 20 volunteers have stopped working.

Nkanga Guimerães, a doctor and child health specialist at Unicef, says that vaccination and anti-malaria programmes are having a positive impact, but efforts to revitalise these programmes are necessary.

"It is only the beginning, but it is being threatened by small things," he says.

Worse still, the other elements of an ambitious primary health care pilot scheme being developed in the town are not panning out as hoped.

Few private clinics have responded to the municipality's call to help in the public sector.

Even the long-suffering Cubans are complaining. Karina says she spends three hours a day stuck in traffic, travelling to the clinic where she works.

"You waste a lot of time in traffic. It annoys you a lot," she says.

"We came here to work after all. It is a rich country, but they don't know how to take advantage."

Activists worry about 'black hole' of Burma

South-east Asia

Tim Johnston on a source of resistant disease untouched by global funding

All day the boats chug back and forth across the sluggish Moei river below the Wang Pha clinic in western Thailand, carrying everything from timber and tea to migrants and malaria.

The Moei forms the border between Thailand and Burma, but if it is a negligible barrier to goods, people, and disease, it is a huge one in the fight against malaria.

South-east Asia does not have the same kinds of infection rates that are seen in Africa: the average person around Wang Pha gets an infectious bite about 0.6 times a year, compared with more than 300 times for parts of Tanzania.

However, the Thai-Cambodian and Thai-Burmese borders have the dubious distinction of being the source of resistance to anti-malarial drugs.

Chloroquine and melfloquine, both huge pharmacological breakthroughs in their day, met their match in the jungles of south-east Asia and surrendered.

And it is in this area that doctors such as François Nosten first started to notice tolerance to the drug artemesinin, the newest and current best hope against malaria.

"I can still get the same number of patients cured, but it takes a little bit longer," says Prof Nosten, the director of the Shoklo Malaria Research Unit, a collaboration between Oxford University in the UK and Thailand's Mahidol University.

No one is entirely sure what is happening with artemesinin tolerance. Around the Cambodian town of Pailin, where it was first observed, it now takes artemesinin-based combination therapy (ACT) five to seven days to clear the parasite from the bloodstream, up from 48 hours when it was first used.

Prof Nosten says Shoklo has studied the genome of the tolerant strain and has yet to find significant differences. He even suggests it is possible the strain has always existed but has only recently become noticeable because ACTs have eliminated most of the sensitive parasites, leaving the tolerant ones.

Shoklo has its offices and main laboratory in the Thai city of Mae Sot and runs a series of clinics up and down the Burma border. Prof Nosten says the work of the Global Fund and other agencies is having a significant impact in Thailand and Cambodia, but Burma is a "black hole", a source of disease untouched by international funding.

> 'We have the tools, the drugs, even the money. The only problem is the politics'

He says that, as artemesinin tolerance spreads, Burma is a disaster waiting to happen: "You can probably stop it in Cambodia, you can probably stop it in Thailand, but if it reaches Burma you have lost."

The answer, Prof Nosten believes, is to democratise diagnosis and treatment.

Since simple, cheap and reliable diagnosis kits have become available, Shoklo has experimented with training villagers to diagnose and treat locals. The faster a patient is treated, the less chance of extending the cycle of infection.

"You need to get the guy to the clinic within 48 hours, and how can you do that if the clinic is five hours walk away?" he asks.

The programme has had an extraordinary effect. In 2007, the Shoklo network treated 60,000 cases of *falciparum* malaria; last year it treated 35,000.

The problem is Burma, but in this case it is not that the area just across the river is a war zone, nor is it the result the legendary intransigence of the Burmese authorities: it is what the blue line of the Moei represents to the international authorities funding the fight against malaria.

"You have all the money being concentrated on this side of the border," says Prof Nosten. "Research is global and they see the border as a wall."

A short walk across the border from the Wang Pha clinic, lies Koko Hospital, sleepy in the baking heat of the late dry season. Dr Naw Baw, the hospital director, has tried to set up a similar scheme, but she has no money and the terms of Prof Nosten's funding prohibits him from sharing his.

"Different organisations have different ideas, and some are frightened to come here," is all she will say of international reluctance to fund projects.

It is an attitude that infuriates Prof Nosten. He understands why Thailand would be reluctant to give some of its hard-won Global Fund money to Burma, and is unsurprised that Burma – which again became eligible for Global Fund grants last year – has not spared any for the remote border region opposite Wang Pha.

What he cannot understand is why the funding has been structured so as to make it difficult to obtain money for cross-border programmes.

"If we stop at the border, we will not be able to stop resistance," he says. "We have the tools, the drugs, even the money. The only problem is the politics."