FT HEALTH
Combating Malaria

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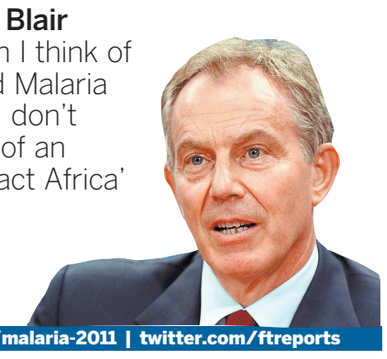
On FT.com

Tony Blair
'When I think of World Malaria Day, I don't think of an abstract Africa'



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Hopes still high that killer can be beaten

The death rate is falling, but chances of eradication are tempered by realities of cost and science, writes **Andrew Jack**

Safety net: keeping mosquitoes off a boy in Sierra Leone. Producing anti-mosquito nets locally can help distribution. Report, Page 5. Alamy

From sprawling Nigeria to feuding Ivory Coast, staff and volunteers across Africa are racing to distribute mosquito nets.

If they do not beat the coming rainy season, flooding will block transport routes just as malaria surges and claims many lives.

In the fight against one of the world's worst infectious diseases, the 2010 target for "universal distribution" of long-lasting insecticide-impregnated nets to places in need has not been met, but there has been significant progress in recent months.

"It was an incredible year," says Ray Chambers, the United Nations' special envoy on malaria.

"We fell a bit short, but I believe with greater certainty than ever that we are closer to our goal of achieving near-zero deaths from malaria by 2015."

His optimism is shared by many in the field.

There has been impressive progress in tackling a disease that kills nearly 800,000 a year and infects hundreds of millions more, imposing a heavy healthcare cost and slowing development.

This hope is tempered by the burden of history, the limitations of inadequate existing policies, the challenges of science and evolution, and the soaring costs required for success at a time of international austerity.

There has been a sharp uptake in funding for malaria programmes since the middle of the last decade, with foreign donors alone now providing an estimated $1.8bn annually and a few countries, such as the UK, have recently increased support.

While some companies sell questionable products such as mosquito buzzers that have no proved effect, a legitimate industry has also grown up around products that have been shown to work.

Funding from governments and philanthropists channelled through public-private partnerships has helped stimulate innovation, with tests advancing on GlaxoSmithKline's malaria vaccine that could be ready by 2015.

There is also a growing pipeline of new, more rapidly acting, drugs.

Furthermore, the growing use of diagnostic tests in countries such as Senegal has come with intriguing findings, suggesting that the burden of malaria may be less than previously believed. Costs have been saved by limiting the use of drugs to confirmed cases.

There have been other types of innovations too, from the use of community volunteers to diagnose and treat the illness, to text messaging to help with epidemiology and stock control.

Net Guarantee and Pledge Guarantee for Health offer bridge financing to countries seeking to overcome slow disbursement by donors.

Looking to the future, Oliver Sabot from the Clinton Health Access Initiative supports "cash on delivery to sustain the gain", linking future donor support to achieving and maintaining a lower malaria burden.

Political leadership has intensified, with the Norwegian government last week hosting a meeting on elimination, and the African Leaders' Malaria Alliance (Alma) now boasting 39 heads of state willing to take greater direct responsibility for tackling the disease.

As a result, a dozen countries in Africa – and more than 30 others where the disease is endemic – have seen deaths from malaria more than halve in recent years. In 2010, Morocco and Turkmenistan joined the list of those to have eliminated malaria.

Yet greater leadership will be needed in the face of multiple challenges. The first comes from governments.

Funding has stagnated at only a third of the estimated $6bn required each year.

Some existing donors have pared back, while new contributors such as China and the oil-rich Gulf States, let alone many of the countries at greatest risk themselves, are only starting to come forward.

Progress in tackling the disease provides a pretext for donors to turn their attention away, risking a reversal of all the gains.

"It's guaranteed: next year, if we take our foot off the pedal, we'll go back to where we were five years ago," warns Pape Moussa Thior, head of Senegal's malaria programme.

Awa Coll Seck, head of Roll Back Malaria, an advocacy partnership, chides western governments for reducing financial assistance, and failing to meet pledges to harmonise and co-ordinate aid programmes to reduce reporting requirements.

She is also critical of governments in the most affected countries. "Alma has a lot of potential but needs to take big decisions, with African leaders talking to their peers on the G8 and the G20 to keep malaria high on the development agenda."

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There is more room for hope than ever

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Combating Malaria

Vaccines Partnerships boost success hopes

The world's first large-scale clinical trial of a malaria vaccine has just completed enrolment, writes **Clive Cookson**.

In seven African countries, 15,640 babies and young children are receiving the so-called RTS,S vaccine being developed by GlaxoSmithKline in a public-private partnership with the Path Malaria Vaccine Initiative (MVI).

This Phase 3 efficacy trial began in May 2009, when the first child was vaccinated in Bagamoyo, Tanzania, and will continue until the end of 2012, with follow-ups for another year. Although initial results are expected late this year, the final analysis will not be ready until late 2014.

Meanwhile, encouraging results continue to emerge from the analysis of Phase 2 trials. Early this year, the journal Lancet Infectious Diseases published the results of a study involving 894 babies in Tanzania and Kenya, who were randomly assigned to receive three shots each of either RTS,S or a rabies vaccine during 2007 and 2008.

Those who received RTS,S were 53 per cent less likely to suffer malaria after eight months and 46 per cent less likely after 15 months, indicating the vaccine maintained efficacy.

As the clinical trials proceed toward possible commercial registration of RTS,S in 2015, attention is turning to how much the mass vaccination of babies against malaria will cost and how it will be funded.

Andrew Witty, GSK chief executive, pledged last year that RTS,S would be priced at just 5 per cent above cost – a far lower margin than usual for new vaccines in the industrialised world – and any profits would be reinvested to combat developing world diseases.

The company has not yet said what that price is likely to be, though this will probably emerge this year. The cost will be determined by GSK after discussions with the World Health Organization, and the Global Alliance for Vaccines and Immunisation (GAVI), which will be meeting many of the costs of vaccination, and the Gates Foundation, which has contributed $200m to the development of RTS,S through MVI. (GSK has already contributed $300m).

If the Phase 3 results match Phase 2's, RTS,S will reduce the number of African children who die of malaria from the current 800,000 every year.

But its 50 per cent efficacy is low compared with vaccines for other diseases, so much research is going on to develop malaria vaccines that offer better protection. MVI's aim is to have one with 80 per cent efficacy available by 2025.

One possibility is to increase the efficacy of RTS,S. Last year, GSK launched a collaboration with Crucell, the Dutch biotechnology company recently bought by Johnson & Johnson, to develop a malaria vaccine using RTS,S with Crucell's Ad35.CS.

The idea, backed by pre-clinical research, is that the two work in combination.

The antigen, a protein from the malaria parasite designed to help the human immune system fight infection, is administered with a chemical "adjuvant" in the case of RTS,S and carried by a harmless virus in the case of Ad35.CS.

While most malaria vaccine projects, including RTS,S and Ad35.CS, are based on "sub-unit" antigens – small parts of the parasite – US companies Sanaria and Seattle BioMed are pursuing vaccines made from whole parasites weakened by irradiation or genetic manipulation.

These are high-tech versions of traditional vaccines and, according to their promoters, are more likely to induce strong protection against malaria than the sub-unit vaccines.

An entirely different approach is the "transmission blocking vaccine", which interrupts the life cycle of the parasite inside the mosquito, by inducing antibodies that prevent the parasite from maturing in the insect after it takes a blood meal from a vaccinated human.

MVI is supporting a project by Johns Hopkins University in Baltimore and the US-based Sabin Vaccine Institute to develop such a vaccine.

While this would not stop someone from getting malaria nor lessen its symptoms, it would limit its spread by stopping mosquitoes that fed on a vaccinated person from transmitting malaria to new hosts.

Rapid tests come with challenges

Diagnostics

Charis Gresser says potential will only be fulfilled if prescribing habits and patient expectations change

RDTs – tests that can detect malaria without the need for microscopy – have become widespread

Pedro Sa Da Bandeira /malaria consortium

When a child develops a fever in sub-Saharan Africa, the one treatment that he or she is likely to get is antimalarials.

It is easy to see why this would be the default. Malaria is widespread in many African countries and can kill if left untreated.

Why take that risk, health workers reason, if they have access to effective and safe drugs? But a significant development in the diagnosis of malaria is challenging this long-standing practice of treatment based on clinical symptoms alone.

Rapid diagnostic tests (RDT) – kits that can pick up the presence of malaria parasites in the blood without the need for microscopy – have become widespread. Five years ago, relatively few RDTs were distributed. Now that figure has probably risen to more than 100m last year. The public health implications of this could be profound.

Richard Murphy, medical adviser with Médecins sans Frontières, the charity, says the group has long been a proponent of RDT in the field. "We want to be precise in our use of antimalarials because we think overtreatment can lead to drug resistance. We want the medicine to match the disease so people will be confident about our treatments.

"When we are precise about diagnosis we can then learn about the epidemiology of non-malarial fevers and can begin to address other reasons for morbidity and mortality."

The growth of RDT use has not been without problems. There are more than 200 products on the market and test performance varies widely.

To help establish some coherence, the World Health Organization started publishing data that compared the performance of different kits. Additionally the agency, together with the Foundation for Innovative Diagnostics (Find), offers a service to test RDTs that have already been purchased.

Clearer guidelines on what to expect from them now informs donors' procurement plans.

The rise in RDT use also raises other issues. The first are the logistical and economic challenges of delivering them where they are needed. That ranges from storage to monitoring their use. And in countries where many seek private sector medical treatment, public health experts worry about getting the incentive structure right so they will not just be available but also used.

Olusoji Adeyi, director of the Affordable Medicines Facility-malaria (AMFm) at the Global Fund to Fight Aids, Tuberculosis and Malaria, says: "We need to find the right financial incentives for the pharmacy, some form of financial bundling of the treatment with the diagnostic, so that the shop owner makes the same amount of money whether the test result is negative or positive."

But one of the biggest obstacles may be behaviour.

Prescribing habits can be hard to change and many factors can cause this to become entrenched. To start with, clinicians may not be used to using the tests.

They may also worry about the reliability of RDTs and prefer their diagnostic skills, especially if the test is negative. And patients may not be content to be told they do not have malaria and there is no medicine for what ailments they do have.

Stephen O'Brien, the UK international development minister, says: "Changing prescribing by doctors is as important as getting RDTs out to people.

> 'We want to be precise with antimalarials – overtreatment can lead to drug resistance'

"Test results risk being ignored unless we help change prescribing behaviour and the expectation of patients that they will always get an antimalarial.

"Unless this behaviour change happens, this excellent new technology will not reach its full potential."

One of the biggest challenges is what healthcare workers do if the test is negative. To put it simply, if a child's fever is not malaria, what is it? The range of possibilities is considerable, including typhoid, dengue fever, influenza, pneumonia and meningitis.

Jane Cunningham, technical officer at TDR, a tropical disease research programme based at the WHO, says: "There are large gaps in our knowledge of the underlying epidemiology [of non-malarial fevers] in the developing world. We need more research to inform case management and the diagnostic research and development agenda."

Researchers are also looking for data on what happens when RDTs are widely available. A paper analysing RDT and anti-malarial use in Senegal reported that the results of the tests were taken into account by those dispensing drugs and, over time, this led to a big reduction in the antimalarials consumed.

The paper estimates that roughly half a million unnecessary artemisinin-based combination therapies courses were averted. The widespread use of diagnosis also allowed public health agencies to better estimate the actual incidence of malaria, which in turn helped guide the procurement of drugs.

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Rising resistance worries in Cambodia

Families with children on the Thai-Cambodia border queue up while WHO staff take blood samples Getty

Drug efficacy

The problem is also spreading to the Thai-Burma border, a problem hotspot, notes **Tim Johnston**

In the rundown town of Pailin in north-western Cambodia, something strange and worrying is happening: where artemisinin-based drugs once took two days to clear malarial infections, this is now taking up to 10 days.

Could this be the beginning of the end for a therapy that is now the weapon of choice against one of the world's biggest killers?

Artemisinin, a drug that was known to ancient Chinese herbalists but has only been rediscovered in the past few decades, has become the silver bullet against malaria, but the news from Pailin is causing grave concerns.

Pailin lies amid the scrub of north-western Cambodia, known principally for being one of the last refuges of the murderous Khmer Rouge regime.

It has an equally grim reputation for being the nursery of resistance to generation after generation of antimalarial drugs.

No one is entirely sure why this area is the source of so much resistance – the prevalence of malaria is much higher in any number of African countries – but it was here that long-standing antimalarials chloroquine and mefloquine first showed signs of stumbling.

"Recently, there have been signs that the efficacy of artemisinin-based combination therapy and artesunate monotherapy have declined in western Cambodia," according to a landmark paper by Arjen Dondorp and colleagues in the New England Journal of Medicine in 2009.

"Artemisinin resistance would be disastrous for global malaria control," the paper continues with understatement.

What is particularly worrying is that the longer clearance times seem to be spreading to the Thai-Burma border, another hotspot of resistance to traditional drugs.

Artemisinin is still effective, but it is taking significantly longer to clear the bloodstream of the plasmodium falciparum parasite, which causes the most severe disease.

Researchers say it is still unclear exactly what is causing the change and more work needs to be done, but progress is being hampered by a shortage of funds.

The Bangkok-based Mahidol-Oxford Research Unit, leading malaria research in south-east Asia, has been hit by reduced aid budgets and the appreciation of the Thai baht and will have a €400,000 ($580,000) shortfall this year.*

Given the limited information on what is happening at a molecular level, researchers such as François Nosten, the head of the Shoklo Malaria Research Unit on the Thai-Burma border, are reluctant to use the word "resistance", preferring the less loaded term "tolerance".

> 'The only way to suppress malaria is to provide everyone with access to rapid diagnostics and treatment'

The longer clearance times "could be a complex mixture of things," says Prof Nosten.

"It could be genetic mutations; or it may be factors related to the patient, the type of haemoglobin [the body's oxygen carrying molecules]; or maybe the spleen is not removing the dead parasites as it should; or it could be related to the immune system," says Prof Nosten, who was a co-author on the 2009 New England Journal study.

Prof Nosten and Nicholas White, professor of tropical medicine at Mahidol University, led the 20-year campaign to overcome western bureaucratic resistance to artemisinin-based therapy and are launching a 14-nation survey to see if tolerance is spreading.

"If we find similar signs elsewhere, it would be a real emergency," says Prof Nosten.

"What you don't want is this presumed tolerant parasite to spread to Africa, because the transmission rates are much higher there and it is much harder to stop mutation."

"My view is that the only way to suppress malaria effectively is to give everyone access to rapid diagnostics and rapid treatment," he says, defining "rapid" as ideally within 24 hours and certainly within 48 hours. This is a huge challenge in the more remote areas of countries such as the Congo and Burma.

"It would not solve the problem on its own, but it would buy time to come up with drugs that are not tolerant," says Dr Nosten.

There are some promising ones in the pipeline.

The Shoklo Malaria Research Unit, part of the Mahidol-Oxford Research Unit, is doing human trials on a drug known as OZ439, a synthetic artemisinin substitute developed by the Medicines for Malaria Venture, a non-profit group supported by organisations as diverse as the Gates Foundation, ExxonMobil and the Dutch foreign ministry.

Initial trials have been encouraging, showing it could be as effective as artemisinin at lower doses, but it is too early to say if it has the same drawbacks as its naturally-occurring cousin. Even if it passes current trials, it is not likely to be widely available for at least another five years.

Novartis is researching a drug it has dubbed NITD 609, one of a class of spiroindolones, which block protein synthesis in the parasites. The drug is progressing towards human trials.

** For more information or to make a donation visit: www.shoklo-unit.com*

Health warning Ineffective buzzers

Flying to a malarial zone but forgotten to bring your tablets? Hate the thought of having to apply repellent every evening and sleep under a bed net? Just relax in your airline seat with a drink and purchase a handy duty-free electronic buzzer. The appeal is tempting, writes **Andrew Jack**, but the reality is dangerous and potentially lethal.

Despite repeated scientific studies showing buzzers do nothing to prevent mosquito bites or stop the spread of malaria, a mini industry of manufacturers continues to produce devices. Many are sold by reputable intermediaries including international airlines.

Cathay Pacific, for instance, offers MozStop, made by Akita of Japan, in its in-flight catalogue. "This convenient, chemical-free, ultrasonic mosquito repeller keeps those annoying mozzies away," claims the airline's duty-free magazine.

"I consider it grossly unethical," says Bart Knols, a scientist whose campaigning blog Malaria World has in recent months pushed BA, Finnair and KLM to drop similar products. "People could come back with malaria or even die as a result."

The idea behind electronic buzzers is that they replicate the sound of the male mosquito's wing beats, frightening away already "pregnant" females. "The whole theory is complete nonsense," says Mr Knols. "We know mosquitoes will take a blood meal even before they have been inseminated."

In 2005, Which, the British consumer body, put a volunteer into a sealed chamber with anopheles mosquitoes, to test a range of insect repellents from creams and coils to plug-in vaporisers.

The unanimous verdict on four brands of buzzers was that they did not reduce biting.

A comprehensive review of 10 scientific studies published in 2009 for the Cochrane Collaboration concluded bluntly: "There was no suggestion in the field studies that electronic mosquito repellents show any promise as a preventive measure against malaria."

Some companies have been referred to trading standards officers. In 2002, the US Federal Trade Commission criticised Florida-based Lentek International's MosquitoControl device for "false and unsubstantiated claims".

Manufacturers have since tweaked their claims or dropped or modified their products.

Prince Lionheart's Lovebug for children claims that it "emits a safe, barely audible tone that imitates the sound of a dragonfly's wing beat – the mosquito's natural predator. Effectiveness may vary in individual situations . . . For protection from malaria consult your doctor or pharmacist."

Moziban says its buzzer "emits a harmless electronic sound proved to repel the female mosquitoes" while adding it "does not offer protection against insect borne diseases such as malaria."

Just as malaria continues to evolve, so too do those seeking to make money from it, regardless of the science.

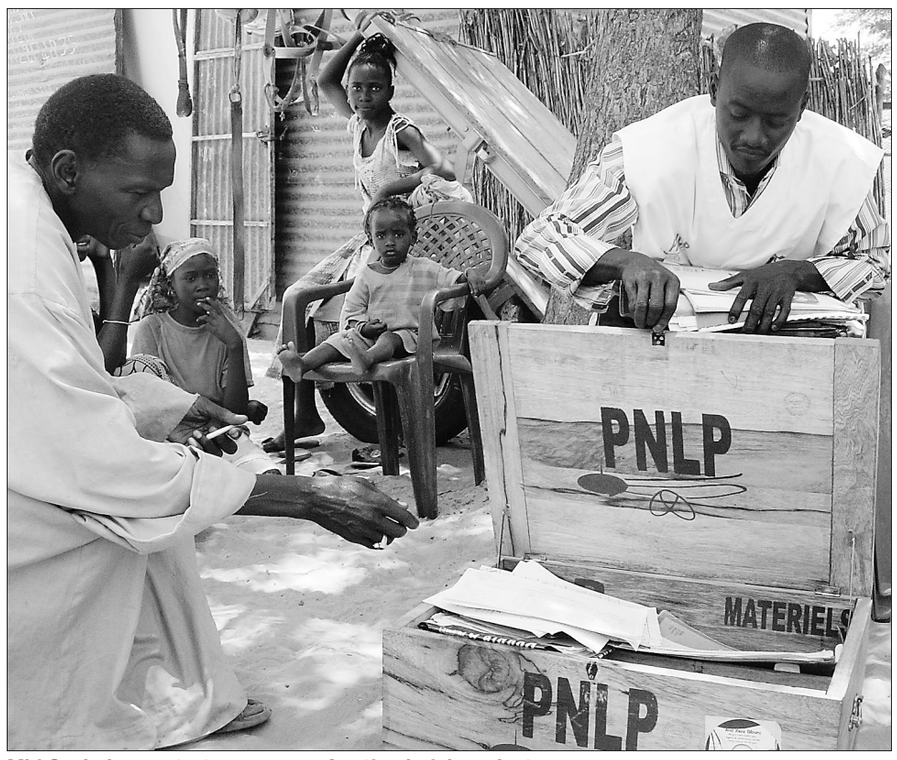
Bart Knols: buzzer theory is 'nonsense'

Combating Malaria

Reliable diagnoses help reduce incidence

Senegal

Community-based volunteers are helping the fight, says **Andrew Jack**



Mbi Seck demonstrates a range of antimalarial products — Andrew Jack

Mbi Seck runs a finger down a list of people from his village of Kassine suspected of having malaria. Hardly any bear the positive sign written against their name to confirm the diagnosis.

His presence reflects strong progress in Senegal in tackling what was until recently one of the country's greatest scourges.

"In the past, we saw lots of cases but now there are not so many," says Mr Seck.

He is one of a thousand "Pecadom" volunteers – a French acronym for home-based community workers – who are selected by villagers and form the backbone of efforts to tackle malaria in the country's inaccessible rural regions.

In 2005 alone, Senegal estimated it had 2,000 deaths from malaria and 2m infections – a heavy toll on children and adults alike.

The Global Fund to Fight Aids, Tuberculosis and Malaria, which channels international support, suspended an initial $3m grant because of disappointing progress.

Since then, a turnround has taken place, driven by strong community groups, firm political leadership, widespread application of the best international thinking on treatment, diagnosis and prevention – and more than $130m in fresh donor support.

By 2009, it estimated that deaths of children under five years had fallen by a third and there were just 174,000 infections.

"It was a big trauma in 2005," says Pape Moussa Thior, the dapper doctor running the country's malaria programme, who demonstrates his efficiency with swift decisions and rapid replies to requests by e-mail and telephone.

"We reinforced our capacity, increased staffing and decided to put in place all the recommendations of the World Health Organization."

With a new organisation and a reworked plan, Dr Thior was able to co-ordinate fresh funding from the Global Fund.

In 2006, more rapidly than many other countries, Senegal switched from older malaria drugs to artemisinin combination therapy (ACT), providing dearer but more effective treatment.

It then began to accelerate the distribution of insecticide-impregnated mosquito nets.

Modou Diagne Fada, Senegal's minister of health and prevention, credits his country's political leadership, and strong tradition of medical training and academic research.

He also cites the contribution of the Pecadom system – introduced in 2008 to help treat people who would otherwise not have the ability to walk or ride long distances for treatment. "We think it will be adopted as a model for west Africa and beyond," he says.

Dr Thior stresses another aspect of the programme that has proved pivotal to progress: reliable measurement.

By introducing reliable rapid diagnostic tests in 2007, which have since been distributed to village-level Pecadoms, his team has been able accurately to identify and quantify malaria for the first time.

> 'We reinforced our capacity, increased staffing and put in place all the recommendations of the WHO'

In the past, drugs were often given pointlessly, to those with malaria-like symptoms, particularly fevers, that were in fact caused by other diseases.

Microscopic examination of blood samples allows accurate diagnosis, but was rarely available and costly for doctors and patients.

Tests have allowed Senegal to save substantial sums on ACTs, although Dr Thior regrets that Global Fund rules require the money to be repaid rather than channelled to other malaria activities.

They have also revised the burden of malaria downwards substantially – suggesting it may long have been overestimated in many countries.

The country's fight against malaria is far from over.

A previous strategy on distributing bed nets to "vulnerable groups" – pregnant mothers and children under five – shifted the burden to the next age group, with unprotected older children becoming regularly infected.

Now, with the help of local and international non-governmental organisations, Senegal is rushing to provide "universal" coverage of bed nets ahead of the coming rainy season, after which villages will become inaccessible and the burden of infection will rise.

The Peace Corps has helped develop a distribution model that works closely with communities, taking a census of the number of sleeping places to be covered, and then distributing nets that are removed from their packaging and marked with the recipient's name to reduce the temptation to sell them.

The Senegalese singer Youssou N'Dour and his Surround Sound foundation have launched song contests, public announcements on radio and television, and text messages to remind people to use nets nightly, for their whole family, throughout the year.

And activists such as Momar Khoudia Diop, who lost his 12-year old daughter to malaria, have launched awareness raising activities, including inspections where those who do not use their nets properly are fined.

Dr Thior's main concern is the threat of a resurgence in the disease, if funders wrongly believe it has been defeated and turn their attention elsewhere.

Mbi Seck's worry is about those villagers with negative malaria diagnoses but who have other diseases for which there are currently no treatments available.

'The biggest challenge is access to the market'

ACT production

African drugmakers call for more donor help. **Katrina Manson** reports

A little over a year ago, east Africa produced a rather special yellow pill.

Made by Quality Chemical Industries, a Ugandan company backed by international private equity and an Indian drugs firm, it was the region's first home-made combined antimalarial therapy.

In July, it received World Health Organization pre-qualification for its production, an industry and donor-wide green light.

That means a region that suffers so badly from the illness can start treating it too. But although the $32m factory can produce up to 6m doses a day, output reaches only 2m. Instead of employing 600 people, it employs 280.

If expanded, it could even produce 12m doses a day, boosting output enough to serve the entire region.

But something in the system is desperately wrong.

"The biggest challenge we have is access to market. We don't get the orders," says Emmanuel Katongole, chief executive.

"Several international agencies and governments subsidise export, particularly India, and they render local production almost impossible," he explains.

Experts are agreed that artemisinin-based combined therapies (known as ACTs), such as those produced by Quality Chemical Industries, are the best first-line treatment for malaria, but prices and supply still have far to go.

Donors have started pouring billions of dollars into a threefold strategy: insecticide-treated bed nets; indoor residual spraying; and viable treatment that is widespread and affordable.

However, only one in five antimalarial treatments is an ACT, not enough are produced and although many public health services provide them free, the over-the-counter price of a course tends to be a costly $10.

Moreover, most Africans rely not on public health services – which are often poorly resourced, hard to reach and short of everything from electricity to medicine, if they function at all – but on the private sector.

In Uganda, about 60 per cent of those seeking healthcare pay for it; in postwar Democratic Republic of Congo it is 85 per cent; and in Africa's most populous nation, Nigeria, it is 95 per cent. For too long, donors have not thought enough about the circumstances of those they are trying to help.

> 'Donors are full of good intentions but keep trying the same things'

"The donor community is full of good intentions but tends to keep trying to do the same old thing – directing 100 per cent of its effort to 5 per cent of the channels," says Olusoji Adeyi, director of an initiative to lower the price of malaria medicine on behalf of The Global Fund to Fight Aids, Tuberculosis and Malaria.

The Fund, which in east Africa has spent $157m on supplying insecticide-treated bed nets and $196m on treatments, has now done deals with six ACT manufacturers in India, China and Europe in the first phase of an eight-country pilot that is going well thus far.

The Fund subsidises 95 per cent of the cost of production, and the ACTs have ended up on shelves in Kenya and Ghana for less than a dollar. So far, there are orders worth $70m for 75m treatments.

"It's a game-changer. With hindsight, it seems amazing this has not been attempted before," says Dr Adeyi, who says several east African manufacturers will meet in Nairobi at the end of May to discuss joining the scheme.

Quality Chemical Industries, at the head of the queue, has had no luck.

Its sole buyer for now is the Ugandan government, which supplies pills free of charge, but the company is also in talks with the Kenyan government. The crucial thing will be how far donors can support the company.

Price negotiations are tricky. Mr Katongole produces a course of 24 for $1.90 but has $1.50 in his sights. Competitors, mostly in India, can still undercut them at $1.40. "It's not price alone we must look at," says Mr Katongole.

He cites other benefits such as employment and boosting terms of trade.

Ambrose Talisuna, epidemiologist and director of Medicines for Malaria Venture, which lobbies to reduce drug costs, cautions: "The quality of local drugs tends to be worse and the price higher."

Yet he believes regional ACT production is critical, not only for its economic benefits, but because it might help tackle other problems related to domestically produced antimalarial drugs that flood the market. These include rising resistance, counterfeits and substandard goods.

In Ghana, skilled counterfeiters produce pills that contain no ACT, constituting a potentially lethal placebo.

For Dr Talisuna, that is another reason to back local manufacturers.

Proximity may be the best policy

Bed nets

Production in Africa may help boost economies, writes **Sarah Murray**

Home-made solution: A to Z Textiles produces mosquito nets in Arusha, Tanzania, giving local workers a regular source of income Getty

It is widely agreed that insecticide impregnated bed nets are an effective and low-cost method of reducing malaria death and infection rates. What is subject to debate, however, is how best to manufacture and distribute them.

Often it is the "last mile" that proves most difficult for manufacturers, governments and aid agencies, with stories of nets languishing in warehouses because of an absence of local distribution networks.

Some fundraisers have also focused on generating funding for the nets, at the expense of distribution considerations.

"The most critical part is getting the nets out to hang over children's beds," says Mikkel Vestergaard Frandsen, chief executive of Vestergaard Frandsen, the Switzerland-based company that is one of the largest producers of bed nets. "A lot of logistics co-ordination is needed."

He says partners such as aid agencies or ministries of health are mainly responsible for local distribution. "But we offer a lot of support in getting the nets to regional depots, so that the organisations can take them on from there."

While Vestergaard Frandsen manufactures its nets in Vietnam, some argue there is a need for more local net manufacturing in Africa, where most cases of the disease occur.

"When you have proximity to the market, there is a health benefit," says Adam Flynn, sales and marketing manager at Sumitomo Chemical, which makes its Olyset nets in partnership with A to Z Textiles in Arusha, Tanzania.

He adds: "If nets have long lead times coming from Asia, by the time they arrive they may have to wait in storage until the wet season has cleared – and in the interim people are suffering."

However, those making the case for more local manufacturing are not only thinking about overcoming distribution challenges. Local production, they argue, could play a role in boosting income levels in malarial areas, particularly in Africa.

"If you're looking at how to put into effect health improvements in poor countries, you need the inputs and the hospitals, but you also need economic development," says Michael Jennings, senior lecturer at the department of development studies at the School of Oriental and African Studies in London, which conducted a study commissioned by Sumitomo Chemical about the economic impact of local production.

In the study, 71 per cent of the employees at the factory said their salary was helping their children go to school, while 75 per cent said it allowed them to support family and relations.

"Some 90 per cent of Tanzanians are in informal employment, so having a regular wage is a rarity," says Mr Flynn. "And if we all agree that disease and poverty are intertwined, there is a benefit to manufacturing in Africa."

At present, Sumitomo Chemical is one of the few companies to have established manufacturing on the continent. Since 2003, A to Z has been manufacturing Olyset nets under a royalty-free agreement through a joint venture with Sumitomo.

> 'If disease and poverty are intertwined, there is a benefit to manufacturing in Africa'

At its peak, the facility in Arusha was employing about 8,000 people and covering the bulk of requirements for east Africa. However, production has fallen recently, leading to the loss of 850 jobs.

Part of the reason, says Mr Flynn, is that the mandate from the United Nations for universal coverage – which led to a sharp rise in net production and demand in recent years – is coming to an end.

He also blames donor procurement policies, which emphasise the need to buy nets at the lowest cost, which has led to greater purchasing from more price-competitive Asian manufacturers.

The cost factor has also become more important to the donor community as aid budgets have tightened in the wake of the global economic slowdown.

"The prevailing procurement policy, which is very price-focused, is not taking into account the broader developmental impacts of local manufacturing," says Mr Flynn.

Other barriers exist to net manufacturing in Africa, however.

Vestergaard Frandsen has been looking at 16 countries to assess the extent to which the company could manufacture in them.

"It's not so much a matter of price, it's more a lack of infrastructure that prevents us," says Mr Vestergaard Frandsen.

"If a machine breaks down in Burkina Faso, you'd have to wait four weeks to get spare parts flown from Germany – but if a machine breaks down in Hanoi, you can pick up the spare parts from around the corner."

Prof Jennings argues that the developmental benefits of local procurement in terms of income generation may, in some cases, outweigh such challenges. However, because these benefits are harder to quantify, they may be overlooked.

"One of the dangers in international development and aid is that there's a great emphasis on efficiency," he says.

"And that's an unarguable good – aid should be spent efficiently. But the question is, how do you define efficiency?"

Scheme can help mother and child

Prophylaxis

But there are fears that the costs may outweigh the benefits, reports **Jack Serle**

The insidious burden of malaria sometimes passes down the generations, as it can move through the placenta from mother to unborn child, resulting in low birth weight, anaemia and stunted growth.

Yet two doses of an anti-malarial drug during pregnancy can protect both mother and child.

This intermittent preventive therapy (IPT) consists of 1500mg of sulphadoxine and 75mg of pyrimethamine and is given twice. The treatment remains in the woman's blood long enough to prevent reinfection.

It can also stop malaria crossing from the placenta into the foetus in up to 90 per cent of cases. Administering it at antenatal clinics is a simple way of combining antenatal and anti-malarial care.

Yet despite its obvious benefits, IPT has seen low uptake. According to the World Health Organization (WHO) the proportion of women returning for the essential second dose is as low as 2.4 per cent in Angola.

IPT uptake is limited by attendance at clinics; this is not easy for women living in countries that have few rural transport links.

Good results in pregnant women have led to the development of IPT in infants. Administering a full therapeutic dose at set points in the first year of life, regardless of whether the infant is infected, reduces the burden of disease.

However, no national malaria programme has implemented IPT in infants, despite the ability to deliver it simply with other childhood vaccinations.

This lack of enthusiasm stems from concerns of a "rebound", malaria flaring up in two year olds who have outgrown the programme, and its effects on the overall burden of disease, which may not make it worth the cost.

"Not a lot of malaria occurs in the first year of life," says Professor Brian Greenwood of the London School of Hygiene & Tropical Medicine. "Infants are protected by their mother's antibodies crossing the placenta."

The transition zone from the southern Sahara to tropical savannah has a short malaria season. The overwhelming majority of infections are in children aged one to five and come in the months that follow the rains.

"It's like a flu epidemic; everyone gets malaria, it's very traumatic," says Prof Greenwood.

"Everyone in a community knows someone who has lost a child to malaria at that time of the year."

This has kindled debate over the relative merits of using IPT in under-fives. While effective – it confers 80-90 per cent protection – administering the programme to a diffuse, rural population every month would require a network of health workers.

Brian Greenwood: 'Everyone in a community knows someone who has lost a child to malaria'

However, Prof Greenwood says: "It is something that we can do now – for the next five or 10 years." He adds: "Hopefully, by then we'll have vaccines and better insecticides."

Whether the cost of this programme is outweighed by its benefits remains to be determined.

The logistics of rolling out IPT in children are significant says Prof Greenwood. The reluctance of national governments to adopt it for infants is also a deterrent.

As Prof Greenwood says: "You do the research; the WHO says it has their blessing. Then, it's up to the governments to decide if they want to go through the process of implementing it."

Researchers probe creative ways to kill mosquitoes

Insecticides

Clive Cookson stresses that the rapid evolution of resistance highlights the urgent need for replacement compounds

If humanity is ever to vanquish malaria the war will have to be won on several fronts, with attacks not only on the parasites that cause the disease but also on the mosquitoes that transmit it.

Alongside new funding for drugs and vaccines against the plasmodium parasites that cause malaria, donors and companies are increasing investment in "vector control", as people in the field call the battle against malarial anopheles mosquitoes.

Only when transmission levels and parasite loads in human populations have been reduced through co-ordinated mosquito control campaigns will drugs and vaccines have a chance of driving the disease towards elimination.

The days of large-scale, indiscriminate and environmentally harmful spraying with the now-outlawed pesticide DDT are long gone.

Campaigns are much better focused, through the provision of long-lasting insecticide treated nets (LLINs) and indoor residual spraying (IRS) – coating with insecticide the walls and ceilings of houses or huts, where mosquitoes settle before and between blood meals.

At the heart of the campaign is the Innovative Vector Control Consortium, based at the UK's Liverpool School of Tropical Medicine, which was set up in 2005 with a $50.7m grant from the Gates Foundation followed by a further $50m last year.

"When we set up the IVCC, we knew that insecticide resistance was going to be a big issue, but we didn't realise quite how important it would become," says Janet Hemingway, IVCC chief executive. "Resistance to pyrethroids [the most widely used mosquito killers] is rampaging through vector populations in Africa."

The rapid evolution of resistance to existing insecticides highlights the urgent need for replacements. No new mosquito killer has reached the public health market since the 1980s.

The source of new anti-mosquito compounds has always been the much larger and more profitable agricultural market.

This worked well in the old days when farmers coated crops with broad-spectrum insecticides that could be transferred relatively easily to the public health market, says Prof Hemingway, but is less relevant now that more specific, systemic pesticides are developed for agricultural applications.

Even so, there is still scope for "repurposing" agricultural insecticides. The leading contender is chlorfenapyr, a broad-spectrum insecticide developed by BASF, the German chemical company, and launched on the crop protection market in 1995.

Last year, BASF agreed to collaborate with IVCC and the London School of Hygiene and Tropical Medicine to develop malaria prevention products based on chlorfenapyr, including bed nets and wall sprays.

Chlorfenapyr – sold under a variety of trade names such as Phantom or Pylon in the US, Citrex and Sunfire in Latin America, and Rampage and Secure in the Asia-Pacific region – is used mainly for killing insects on vegetable and fruit crops. The company hopes the chemical's good safety record and low toxicity to mammals will lead to quick approval in the public health market, possibly as soon as next year.

"The mode of action is quite different from pyrethroid insecticides, which disrupt insects' central nervous systems," says Susanne Stutz, the BASF chemist in charge of developing chlorfenapyr for public health.

"Chlorfenapyr is a pyrrole compound that works by disrupting energy production in the mitochondria in insect cells."

Another priority is to find a way to prolong the active life of insecticides on bed nets and wall coverings. Vestergaard Frandsen, based in Switzerland and the largest manufacturer of treated bed nets, is leading the way with a wall covering called ZeroVector Durable Lining.

Durable Lining is a simple woven cloth – impregnated with insecticide – that can be nailed to the walls of huts and houses. The insecticide remains active for at least three years. Most IRS applications to hard walls lose effectiveness in six to nine months.

Looking further ahead, IVCC hopes that collaboration with academic researchers and the chemical industry will produce three new active ingredients for mosquito control by 2020.

But killing mosquitoes is not necessarily the only way to control them. Pheromones, the sex attractant chemicals that can lure insects into traps from a considerable distance at very low concentrations, have not yet been developed to work as effectively for anopheles mosquitoes as for other pests, says Prof Hemingway.

She sees potential in developing better mosquito repellents that would stop the insects entering homes: "We need a super-repellent that works much better than Deet [the standard ingredient in consumer products]."

Another long-term prospect is the "sterile insect" approach being pioneered by Oxitec, a biotechnology company based near Oxford.

The idea is to release vast numbers of male mosquitoes, sterilised by genetic engineering, that would mate with all available females and swamp the fertile wild males in the vicinity.

This approach is showing promise with the aedes mosquitoes that spread dengue, but Oxitec scientists have found it hard to engineer sterility into the anopheles species.

Vector controller: one research priority is to find a way to prolong the active life of insecticides Dreamstime

Hopes are still high

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A second set of challenges relates to vested interests and conservatism in the field.

A dozen countries still allow the best drug against malaria – artemisinin – to be used on its own as a "monotherapy", undermining its efficacy.

Many more have been reluctant to focus on the best available international drugs, judged by price and quality, favouring domestic industrial policy over public health.

Authorities have been slow to adopt newer treatments, whether injectable artesunate for severe malaria, or drug combinations such as DHA-PPQ, which has been shown to work over several years and is desperately needed in Cambodia, where existing artemisinin treatments do not.

Drug development partnerships and other competing agencies need to co-operate more to reduce duplication and costs.

And advocates have proved reluctant to engage with the private sector, when the reality in many countries is that most patients seek healthcare from doctors and pharmacies outside under-resourced public health systems.

Companies need to adapt too. The one-off surge in bed net orders is already over and producers are feeling the squeeze.

Sumitomo's Tanzanian net factory is under threat, and fewer producers may undermine sustainable and affordable supplies for a commodity that needs to be replaced every three to four years.

The third and perhaps largest challenge is the malaria parasite itself.

It has defied efforts at eradication, adapting to overcome older drugs and insecticides.

Two countries that were making strong progress – Rwanda and Zambia – showed recent reversals.

New studies in Tanzania and Burkina Faso suggest that far more malaria-spreading mosquitoes may live and bite outdoors than was previously believed, undermining the value of indoor spraying and bed nets.

Rob Newman, head of the malaria programme at the World Health Organization, cautions that if there is any prospect of achieving a 2015 objective of near-zero deaths, "it requires an extraordinary intensification of what we have been doing" and increasing surveillance to tailor policies much more to local needs.