FT Health Combating Malaria

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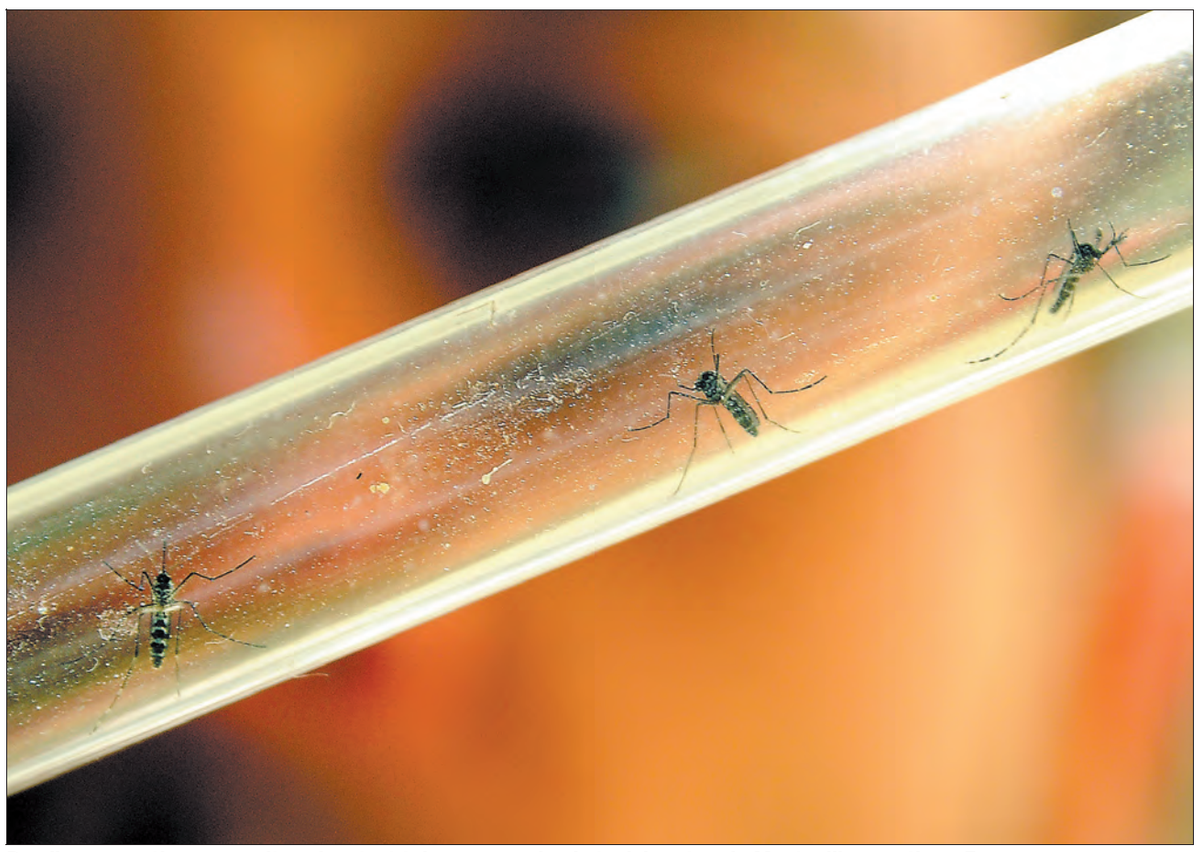
More push required in fight against mass killer



Deadly enemy: tiger mosquitoes in a test tube are examined at a laboratory in Montpellier, southern France Getty Images

Progress runs alongside fear that an infectious disease claiming 660,000 lives a year is slipping off the agenda, writes *Andrew Jack*

Since the start of this century, the fight against malaria has made a substantial inroad into one of the world's most serious infectious diseases, saving more than one million lives.

Yet global political leaders must decide in the coming months on fresh support for global health programmes and finalise the replacement for the 2015 Millennium Development Goals, which may no longer explicitly refer to diseases such as malaria. That risks reversing progress on a task that remains far from complete.

As Margaret Chan, the head of the World Health Organisation (WHO), cautioned in its latest report on the disease: "Behind the statistics and graphs lies a great and needless tragedy: malaria – an entirely preventable and treatable disease – still takes the life of an African child every minute."

Her agency estimates that 660,000 people die from malaria each year and 219m are infected, causing personal tragedy and slowing economic development in some of the poorest regions of the world.

The number of those afflicted has dropped significantly as funds have risen for the distribution of highly effective tools to combat the disease: drugs, diagnostics, insecticides and bed nets. International support for the battle against malaria rose from $100m in 2000 to $1.8bn last year. Domestic spending has risen steadily to above $600m.

That reflects political commitment, with many African countries increasing their own budgets for health. Leaders from eight southern African nations have pledged to move towards malaria elimination, and their Asia-Pacific counterparts are doing the same. China, already the source of the most effective antimalarial treatment, is becoming more active in developing cheap and high-quality medicines for Africa, and studying ways to enhance surveillance and control of the disease. At the same time, China remains a source of counterfeit and substandard drugs. There is concern that, as an intensifying push against the disease is required, the momentum is slowing because of austerity measures squeezing governments' ability to provide assistance. Compared with estimated spending of $5.1bn a year, only $2.3bn is being provided. "It feels there is a bit of a turning point," says Sylvia Meek, technical director of the Malaria Consortium, the UK-based charity. "A lot has been achieved but there is still so much more to do. We need to avoid any backsliding."

> 'Behind the statistics and graphs lies a great and needless tragedy'

The number of insecticide-treated bed nets distributed in Africa fell from a peak of 145m in 2010 to 66m in 2012. Such nets have a lifespan of just two to three years and it is estimated that more than half of all households in sub-Saharan Africa rely on them. Free distribution has helped ensure wide availability but undermined incentives for sustainable for-profit local net production. Furthermore, mosquito resistance to the present generation of insecticides has been detected in 64 countries, highlighting the growing need for incentives and research efforts to develop new products. Other problems await. A decade after their introduction, artemisinin combination therapies (ACTs) are available at low cost and on a large-scale from a variety of competing producers but, while they remain highly effective, the troubling signs are of emerging resistance to ACTs in four countries in southeast Asia. That has

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Commentary
Dr Fatoumata Nafo-Traoré of Roll Back Malaria

Protagonists dig deeper in their efforts to crush a complex foe

Close quarters: an electron micrograph image of the head of a female *Anopheles arabiensis* mosquito Science Photo Library

Mosquitoes Changes in the insect's behaviour have made it tougher for scientists engaged in the battle, says *Sarah Murray*

According to ancient Chinese warlord Sun Tzu, the key to success in combat is to know your enemy. This principle is being taken seriously in the war on malaria. While part of it involves studying how the behaviour of different mosquito species affects malaria transmission, scientists are digging deeper. They want to know their foe's genetic make up so that they can alter it.

The enemy is complex. About 500 malaria mosquito species are distributed around the world, with about 50 transmitting malaria. Why only some species or populations are efficient vectors, or carriers, of malaria remains unclear.

Understanding breeding patterns or whether a malaria-transmitting mosquito lives mainly inside or outside can help advance disease transmission and control techniques.

While most malaria transmission occurs in sub-tropical areas of Africa, the US and Asia, mosquitoes have different behavioural patterns. For a start, *Anopheles gambiae*, the species that transmits malaria, prefer to bite humans while *Anopheles quadriannulatus*, a non-vector species, stick to animals.

Variations are found in when and where mosquitoes bite, with *Anopheles gambiae* feeding and resting indoors while *Anopheles arabiensis* function outdoors. Worryingly, research has found that some of these behavioural patterns are changing in response to human interventions.

"The use of insecticides inside has caused changes in mosquito behaviour," explains Igor Sharakhov, an entomology professor at Virginia Polytechnic Institute and State University. "They have become more active outdoors and more active early in the day, not just at night."

This has implications for outdoor workers such as forest workers, fishermen and farm labourers, as well as victims of natural disasters or wars living in temporary shelters, and has prompted research into clothing impregnated with insecticide.

Evidence indicates that the range of mosquito forms is increasing. A team of researchers from the London School of Hygiene & Tropical Medicine has found that in parts of West Africa, different molecular types of *Anopheles gambiae* have been interbreeding, creating a more complex range of forms.

Interbreeding has the potential to accelerate the spread of insecticide resistance, says David Conway, the professor who led the research, "because the gene can enter the population without having to wait for a new mutation".

Prof Conway warns that the finding does not signal a major threat to malaria control. "But it's a warming that we need to understand these populations that we are trying to control because it could make insecticide use less effective," he says.

As well as tracking mosquitoes through field research, the study of genetics is seen as having great potential. Progress in understanding the biological blueprint of the insects is bringing researchers closer to the possibility of genetically editing mosquitoes.

Much of the data generated so far is on VectorBase, a website that makes available genomes and related information on five vectors, including mosquitoes. Frank Collins, one of the project's principal investigators, sees many uses for the data. Before even entering the realm of genetic modification, he argues that an understanding of the mosquito genome could help advance the development of new control products such as insecticides.

> 'The insect has become more active outdoors and more active early in the day, not just at night'

"These could target features of mosquito genomes that are not represented in mammalian genomes," says Prof Collins, who is professor of biological sciences at Indiana's University of Notre Dame. "So you might be able to develop something that is less toxic to non-target organisms."

Understanding mosquito behaviour at the molecular level makes possible entirely new kinds of control techniques. Identifying the mechanism through which a mosquito finds a human host might allow the development of a false host that is in fact a toxic trap. Another approach would be to edit mosquitoes' genes to render them incapable of transmitting the disease. In one project demonstrating the feasibility of this approach, researchers at Virginia Polytechnic Institute and State University used gene disruption to change the eye colour of a mosquito.

At Johns Hopkins Malaria Research Institute in Baltimore researchers have genetically modified a bacterium commonly found in a mosquito's intestine so that it secretes proteins that are toxic to the malaria parasite.

Researchers from the University of Irvine and Oxitec, an Oxford university spin-out biotech company, have been developing flightless mosquitoes that could help control the spread of diseases such as malaria and dengue fever.

"Now it's getting more exciting because we are discovering all these genetic tools that we can apply to malaria," says Prof Sharakhov.

Researchers seek out man-made alternatives to natural remedies

Drugs

Long development process starts to pay, writes *Andrew Jack*

Many thousands of years after nature evolved the most effective current treatments for malaria, researchers aim to introduce man-made alternatives to help keep ahead of the parasite.

Artemisinin, derived from the Chinese sweet wormwood plant, remains the ingredient of choice in drugs to cure the disease but comes with a problem. Its complex nature means that manufacturers have until now struggled to find cheaper and more consistent synthetic equivalents.

Global production over the past decade since the widespread introduction of artemisinin combination therapies (ACTs) has been hampered by weather, land for cultivation and other uncertain growing conditions, as well as market manipulations to further restrict supply and push up the price.

That is beginning to change. In one of a number of such collaborations under way, this month the French drug company Sanofi unveiled plans for large-scale semi-synthetic production of artemisinin, following a painfully long and complex process of development.

Building on work by the US non-profit business One-WorldHealth, the company Amyris and the University of California, Berkeley, Sanofi has finalised plans to produce 35 tonnes of artemisinin this year, rising to 50-60 tonnes a year from 2014 – enough for 80-150m treatments.

The elaborate work involves fermentation of artemisinic acid in Bulgaria, photochemistry to transform it into artemisinin in Italy and processing and mixing with other drugs such as amodiaquine, one of the company's existing antimalarial combinations. Sanofi has pledged to produce it on a no-profit, no-loss basis to help keep treatments affordable.

A farmer with the artemesia crop

"Promoting a steady and affordable supply of high-quality artemisinin is a critical part of our efforts to eradicate malaria," says Steve Davis, president of PATH, the Seattle-based non profit group that helped support the work.

Artificial artemisinin is not the only example of a public-private partnership beginning to show results. David Reddy, head of the Medicines for Malaria Venture (MMV), describes a new "challenge" model to accelerate traditional drug development techniques.

Designed in conjunction with the Queensland Institute of Medical Research, it permits healthy volunteers to be injected with small quantities of malaria-infected red blood cells. The evolution of the parasite in the body is observed using sophisticated Polymerase Chain Reaction tests. That minimises the dangers and speeds up traditional drug testing, which was conducted in patients exposed to malaria naturally in endemic regions.

Mr Reddy cites MMV's work in developing common pharmacokinetic tests and making widely available libraries of experimental compounds owned by normally intensely competitive and secretive companies. That has so far allowed it to identify and circulate a "malaria box" of 400 potential drugs to more than 100 research teams around the world.

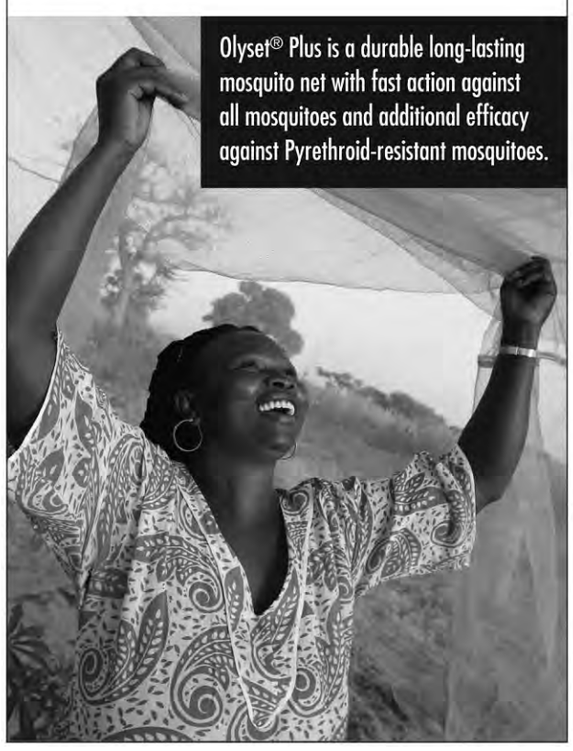
"There's not a lot of profit to be made in malaria," he says. "The last thing companies want to do is waste their money on drugs that will not measure up. If you can begin a common understanding of what drugs are needed and the criteria for selection, and not reinvent the wheel, that creates savings and de-risks the work for industry." Promising pre-clinical discoveries have been made by university researchers in countries including South Africa, as well as in companies in more developed and emerging economies alike.

Regulatory innovation is under way, such as the pioneering authorisation last year by the European Medicines Agency of Pyramax, a drug developed with Shin Poong of South Korea and MMV, under its "article 58" rule.

That offers approval of a medicine by a well-respected organisation but for use in developing countries rather than within the EU, where the risks and benefits would be different.

Nature has not been standing still, either. The emergence of malaria strains resistant to artemisinin in southeast Asia is pushing researchers to seek entirely new classes of compounds. Paul Herrling, chairman of the Novartis institute for tropical diseases, which developed Coartem, the first ACT, cites promising advances with several experimental medicines.

"We want to continue to be a major player in malaria," he says. While sharing much of its expertise with MMV, the company is developing on its own the most advanced compound – codenamed 609 – partly because "MMV is not particularly swimming in money" and it hopes to generate a modest return on the drug.



Push required in fight against killer

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led to calls from specialists such as Professor Nick White at Oxford university for an intensive campaign to saturate the region with the latest drugs in an effort to wipe out the malaria parasite entirely.

It points to the need to continue investing in research and development. The malaria drug pipeline looks healthy, with a range of experimental medicines under test. These offer the prospects of shorter cures, a shift away from reliance on ACTs and alternative treatments for *Plasmodium vivax*, the second most common type of malaria in Asia.

Work on developing a malaria vaccine is continuing, though interim findings of the most advanced product – GlaxoSmith Kline's RTSS – suggest only modest protection in children.

A sharp debate might be expected, therefore, over the costs of adding another product to the "armatorium" and the stretching of fragile health systems with the purchase and distribution of RTSS.

There are many competing demands ahead as far as the use of existing tools is concerned. Intermittent preventive treatment for pregnant mothers has a powerful effect in reducing the risk of infection in the newly born. Seasonal malaria chemoprevention for children aged three to 59 months has been shown to reduce illness. The former

Rob Newman, of the WHO, says data collection is vital

tool has much scope for improved uptake; the latter has barely been used to date.

Dr Fatoumata Nafo-Traoré, head of the Roll Back Malaria partnership of public and private organisations, praises African leaders' efforts against the disease but warns that "the inadequate dissemination, uptake and application of research results within African countries themselves have created a needless separation of research and policy setting."

Scope exists for greater efficiencies, partly by breaking down barriers between "vertical" diseases. Malaria has boosted funding for bed nets that also tackle lymphatic filariasis (elephantiasis). The latter's community drug workers, however, could be used more to help with bednet distribution. The product they give out – ivermectin – also kills mosquitoes. The Global Fund to Fight Aids, TB and Malaria, the largest conduit of multilateral donor support, is seeking a fresh injection of funds this year after a restructuring designed to target spending more effectively.

Nigeria and the Democratic Republic of Congo alone are estimated to account for 40 per cent of malaria deaths globally. With India, they are host to 40 per cent of all infections. This suggests the need for greater focus in the fight against the disease if the greatest short-term impact is to be achieved.

> 'Every suspected case should get a diagnostic, be treated and tracked'

Yet Prof Sir Richard Feachem from the University of California San Francisco argues that excessive attention on high-incidence countries comes at the expense of 34 lower incidence ones that have good prospects of eliminating malaria. He calls for more concentration on "hotspots and hot pops" – the latter being the population of migrant adult males, who are becoming the most important infected group.

Tighter targeting of malaria will be essential, such as when protecting the rubber tappers in Myanmar who work at night, rendering bednets useless. The Malaria Consortium is studying the use of insecticide-impregnated wristbands to keep mosquitoes at bay.

Despite the closure by the Global Fund of its unit supporting an affordable medicines facility, more partnership with unregulated private vendors of drugs seems inevitable while widespread lack of stock exists in public clinics.

More generally, the "three Ts" – test, treat and track – need greater resources. Without more monitoring, and support from health workers, it is impossible fully to understand malaria or tackle it. "In the very highest burden countries we don't have the hard, real data to say whether we are on track," says Rob Newman, head of the WHO's global malaria programme. "Every suspected case should get a diagnostic, be treated and tracked in a surveillance system. That data to make informed decisions is going to be critical."

Yeast process gives rise to research progress

Science Re-engineering a familiar ingredient and the discovery of new compounds mark big steps in fighting the disease, writes *Clive Cookson*

Looking to the future: the discovery of a promising new class of antimalarial compounds has fuelled optimism in the fight against the disease Getty Images

When it comes to science, malaria can no longer be regarded as a neglected disease. Spending on malaria research and development rose rapidly during the first decade of this century – propelled by increased commitments from charitable foundations such as Gates and Wellcome, as well as the pharmaceutical industry and government agencies such as the US National Institutes of Health – and is running at around $700m a year.

Given the long time lag in medical research between discovery and commercial application, as safety and efficacy of drugs and vaccines are tested in clinical trials, it is too soon to see spectacular results from the extra R&D funding. But several scientific papers and announcements over the past few months have given encouraging indications of new weapons in the battle against malaria.

The recent development with most immediate commercial application was the publication this month in the journal Nature of a new production process for artemisinin, the key ingredient of the combination therapies recommended by the World Health Organisation. At the same time Sanofi, the French pharmaceutical group, announced plans for large-scale production of artemisinin, using the new process, in collaboration with two non-profit organisations, PATH and OneWorld Health.

Besides its importance for the fight against malaria, the announcement is also significant because it heralds the first industrial-scale application of "synthetic biology", the discipline that takes genetic manipulation to a stage beyond the simple addition of one or two genes.

The nine-year programme to develop a cheaper and more reliable source of artemisinin – a natural product derived until now from the sweet wormwood plant – has involved extensive re-engineering of baker's yeast to make the yeast cells convert glucose into artemisinic acid in a fermenter. This precursor molecule is then transformed into artemisinin itself through a more conventional chemical process catalysed by light.

Engineering the yeast to produce commercially viable quantities of artemisinic acid required the insertion into yeast of enzyme genes from the sweet wormwood plant and, equally importantly, various DNA control regions to make sure that the enzyme production switches on and off in the correct sequence.

Several partners took part in the artemisinin programme, which started in the lab of synthetic biology pioneer Jay Keasling at the University of California, Berkeley, and continued through research by Amyris, a biotech start-up company, and Sanofi.

> '[ELQ-300] is one of the first drugs to kill the malaria parasite in all three stages of its life cycle'

The yield is now 25 grammes of artemisinic acid per litre of yeast fermentation culture – enough for Sanofi to make 35 tonnes of artemisinin this year and 50 to 60 tonnes in 2014, which corresponds to about 100m doses of malaria treatment.

Artemisinic acid will be produced in a fermentation facility in Bulgaria and converted into artemisinin at Sanofi's Garessio drug factory in Italy.

Operating on a no-profit, no-loss production model, Sanofi expects to sell artemisinin at the lower end of the price range of the plant-derived product. Its factory could supply one third to a half of world demand, but the company says it wants to avoid driving plant-based producers out of business. The idea is to smooth out the unevenness of supply and price fluctuations that have characterised the artemisinin market so far.

The other big news recently on the drug development front was the discovery of a very promising class of antimalarial compounds, published last month in the journal, Science Translational Medicine.

This project, involving an international research team funded by the non-profit Medicines for Malaria Venture and the National Institutes of Health, is far further from commercial application than the artemisinin process but could eventually be more important.

The new compounds, which go by the tongue-twisting name of 4(1H)-quinolone-3-diarylethers, show strong activity in lab tests against *Plasmodium faciparum* and P vivax, the parasite species that causes most malaria cases.

The "lead compound" in this group, known as ELQ-300, acts against the parasite at several stages of its life cycle. ELQ-300 is extremely potent when tested in mice with malaria, although this does not necessarily mean that it will work so well in humans when clinical trials start a year or two from now.

"This is one of the first drugs ever to kill the malaria parasite in all three stages of its life cycle," said Dennis Kyle, professor of global health at the University of South Florida.

"So it may become part of a new generation therapy that not only treats sick people and prevents them from getting ill but also blocks the transmission of malaria from mosquitoes to humans . . . If the drug can break the parasite life cycle, we may ultimately eradicate the disease."

Wiping such a complex disease as malaria off the fact of the earth may seem like a fantasy but epidemiologists insist that, armed with the right drugs, vaccines, diagnostics and mosquito control measures, we can do it. As a recent paper in the journal Science put it, "malaria elimination can proceed like a ratchet, country by country and region by region, culminating in global eradication".

Supply of vital weapon cries out for raised funding

Under cover: a Zimbabwean woman puts her child into a bed, protected by an impregnated net Reuters

Bed nets Fits and starts in assistance from donors hamper efforts to increase production and delivery, writes *Sarah Murray*

With bed net distribution to sub-Saharan Africa having fallen since the 2010 peak, all eyes are on the next funding replenishment round of the Global Fund to Fight Aids, Tuberculosis and Malaria. For while some of the bottlenecks to net distribution are logistical and regulatory, what the scaling up of delivery really requires is funding.

"There are many threats to maintaining the game in malaria control but the biggest one is financial constraints," says Scott Filler, a senior technical adviser on malaria at the Global Fund.

What most people agree on is that the distribution of bed nets has proved one of the most powerful tools in the battle against mosquitos. Nets not only provide a barrier preventing them from biting people, when treated with insecticide, they also kill mosquitoes on impact, reducing their numbers.

"Nets have played a huge rule in helping us achieve the progress we've made in the past decade and will remain a critical piece in helping rid the world of malaria," says Christopher Helfrich, director of the United Nations Foundation's Nothing But Nets initiative. This, a grassroots campaign, raises awareness and funding to fight malaria by encouraging members of the public to donate at least $10 to buy nets.

In terms of donor funding, trends have not been encouraging. According to the World Health Organisation's 2012 World Malaria Report, funding available for malaria prevention and control is currently far below what is needed to achieve global malaria targets.

The WHO estimates that to achieve universal access to malaria interventions, $5.1bn will be required every year between 2011 and 2020. Yet in 2011, only $2.3bn was available.

In addition to the downturn in funding, logistics provide an additional hurdle. Distributing bulky mosquito nets – particularly when it comes to reaching remote rural areas – is not always easy.

"You only need to see a truckload of 10,000 of these to realise what a logistical challenge it is to get a net from a port into an individual's hands," says Mr Filler.

"And it's one thing in an urban environment but we also have to distribute to places that are very hard to access by road," he adds. "So the last mile is often the most expensive and challenging."

What has eased are the bureaucratic and regulatory hurdles to getting nets distributed, with many countries having lowered taxes and import fees for nets. "There were some growing pains at the ports, but we're moving past that and most countries are no longer doing this for the first time," says Mr Filler. "So they are now much more adept at getting these nets out there."

Debates have at times raised the question of whether more efficient distribution of nets could be achieved by creating an affordable but for-profit market for nets.

Some have argued that market-based mechanisms would create a more sustainable supply than relying on donor funding, which – as the current recession and corresponding downturn in funding has demonstrated – ebbs and flows in line with economic shifts and political priorities. However, the main obstacle to this has been the fact that it remains too difficult to produce nets that are cheap enough for target communities, which include some of the world's poorest people. "When you have so little discretionary income, it's hard to think of preventive modalities," says Mr Filler.

Early experiments with subsidised nets never achieved the scale of distribution that has been seen with free net deliveries. As a result, the market remains highly dependent on public funding.

"The commercial market has grown but it's still less than 5 per cent of the global market," says Adam Flynn, UK sales manager for global vector control for Sumitomo of Japan, which has committed substantial philanthropic resources to its Olyset net programme. Sumitomo is one of the few companies manufacturing nets in Africa. Through a partnership with A to Z Textile Mills in Tanzania, including the provision of a royalty-free technology licence, the factory has been producing insecticide-impregnated nets since 2003.

While many look to this model as a means of spreading the economic benefits of malaria prevention to local communities, the ups and downs in funding also have a big impact for manufacturers such as A to Z – and the challenges can be equally great at times when funding suddenly start to flow again.

"You go from empty factories to having to employ 1,000 people, getting the mills turning again and trying to deal with penalties for late delivery," says Mr Flynn. "The fits and starts nature of donor funding is difficult for manufactures to deal with."

As a result, focus is on the Global Fund Fourth Replenishment, the name given to the organisation's efforts to secure financing for 2014-2016. "Funding is the foundation stone of it all," says Mr Flynn.

Protection bid aims at children

Seasonal targeting

Programme focuses on rainy season, says *Charles Batchelor*

An ambitious programme to protect children under five against malaria during the most dangerous months of the rainy season is being introduced across west Africa but funding constraints are a drag on progress.

Initial studies of the effect of seasonal malaria chemoprevention (SMC) at eight sites in Senegal, Mali, Ghana, Gambia and Burkino Faso achieved a 75 per cent reduction in malaria episodes, including severe malaria, and a possible reduction in child mortality of one in 1,000 with no reports of serious adverse affects.

These early successes led the World Health Organisation to draw up a set of implementation guidelines last November that have been adopted by 10 countries in the Sahel region of Africa. "This intervention has been shown to be effective, cost-effective, safe and feasible for the prevention of malaria among children less than five years of age," the WHO says.

"This is now being rolled out in countrywide programmes over the forthcoming malaria transmission season starting in July and for the next four months," says Peter Olumese, medical officer in the WHO's global malaria programme. "We had a meeting with the 10 countries where we thought this would be a useful strategy. We wanted to plan along with them and provide support."

More than 85 per cent of the estimated 216m annual cases of clinical malaria and 90 per cent of the 655,000 deaths occur in Africa south of Sahara. The vast majority of cases and deaths occur in young children.

"Across the Sahel sub-region most childhood malaria mortality and morbidity occurs during the rainy season, which is generally short," the WHO says. "Giving effective malaria treatment at intervals during this period has been shown to prevent illness and death from malaria in children."

The pilot studies involved a range of anti-malarial medicines administered on a monthly or bi-monthly basis. This led to the WHO recommending a course of amodiaquine plus sulphadoxine-pyrimethamine (AQ+SP) for children aged between three and 59 months at monthly intervals up to a maximum of four doses in areas of highly seasonal malaria transmission.

The areas thought most suitable for this approach were where more than 60 per cent of clinical malaria cases occurred within the four-month period of the rainy season, where the incidence of infection was greater than 10 per cent in the target age group and where the AQ+SP combination retained more than 90 per cent efficacy.

"How widely this programme is implemented depends on the resources and the money these countries have," says Dr Olumese. "It represents good value for money because the effect is significant but most countries depend on external funding and this recommendation [from the WHO] has come midway in their funding cycle."

Private sector role remains elusive

Provision Ending a free market treatment supply initiative is not universally supported, writes *Andrew Jack*

The US government may be among the strongest defenders of the free market but it has found itself in unusual company in recent months as part of an escalating campaign to undermine programmes supporting private sector involvement in the distribution of malaria treatments.

Late last year, a curious coalition including both the US president's Malaria Initiative and Oxfam, the UK-based development charity, claimed victory with the decision by the Global Fund to Fight Aids, TB and Malaria to wind down its unit overseeing the Affordable Medicines Facility – malaria (AMFm).

The idea behind the AMFm was pragmatic. Even if the best long-term approach to distributing malaria treatments is via the public health system with no direct charge to patients, failures in supply and the long distance to clinics mean many buy drugs from private vendors. By subsidising the high cost of artemisinin in combinating therapies (ACTs), the scheme would make the best drugs available more cheaply than substandard or inappropriate alternatives such as chloroquine.

"Providing drugs should not be restricted solely to the public sector because there will never be enough money," says Prof Barry Bloom at Harvard School of Public Health, who conducted an evaluation of the AMFm and regrets its axing. "Working together with the private sector strikes me as an experiment worth pursuing and not killing."

Since 2009, the programme had subsidised nearly 320m artemisinin-combination treatments in Cambodia, Ghana, Kenya, Madagascar, Niger, Nigeria, Tanzania and Uganda, at a cost of more than $460m underwritten by donors including those governments that channelled support through the Global Fund.

To its critics, the AMFm risked undermining public sector provision of healthcare, imposing costs that reduced access for the poorest, draining off supplies of ACTs from public clinics and risking greater abuse of a valuable antimalarial drug by handing its use to non-medically trained people. "Just 40 months away from the Millennium Development Goal deadline . . . progress is being threatened by the support of some donors for the Affordable Medicines Facility–malaria," wrote Oxfam in a report last summer that spelled out its doubts.

Painful reality: a Cambodian boy has his finger pricked for a blood sample during screening Getty

More practically, there were concerns that the subsidy would prove ineffective, with intermediaries profiting from donor subsidies while adding mark-ups to make the final price of ACTs to patients higher and less affordable than less desirable alternative treatments.

Some observers suggest that Oxfam took an ideological stance against involving the private sector, while US opposition – in turn driving ambivalence towards the AMFm by the World Health Organisation, a beneficiary of its support – reflected a reluctance by Washington-based "Beltway bandits" to lose a share of funding and control.

Others retort that there were just as strong beliefs, economic lobbies and individual careers that benefited from the continuation of the AMFm and that the programme's evaluation was restricted in a way that prevented full assessment of its effectiveness. Prof Bloom's evaluation concluded that the AMFm pilot was successful in increasing availability, decreasing retail prices and increasing market share of quality-assured ACTs. It found in five of eight pilot countries, that ACTs were "dramatically" more available and prices for patients were reduced. It did not assess the impact on morbidity and mortality.

The idea of working with the private sector is not yet dead. While the global fund will no longer support the AMFm centrally, it will still permit subsidies by individual recipient countries that choose to use them. Meanwhile, there is little doubt that in the absence of easily accessible and affordable healthcare, the private sector will continue to play a significant role in tackling malaria. The Center for Health Market Innovations, which promotes ways of improving privately delivered health care, is among groups trying to research the role of "informal providers" in more detail.

Hans Ritvield from Novartis, who coordinates access programmes for Coartem, the first and most widely used ACT, says his company is making a loss on sales to the public sector at $1 per treatment. It plans to expand a programme of offering the drug at a range of higher prices between $4 and $12 for Africa's emerging middle class to make the product self sustaining.

More generally, critics and supporters alike agree on one thing. The advent of low-cost, rapid diagnostic tests makes it essential that ACTs are only supplied to those with confirmed cases of malaria. Otherwise, drugs will be misused, supplies wasted and non-malaria illnesses inadequately treated.

The next wave of pilot programmes – including some under way from Unitaid, the Geneva-based donor – will focus on incentives for private vendors to sell medicines and diagnostics responsibly. "We need to look at different options for rapid diagnostic tests," says Rob Newman, head of the WHO's global malaria programme. "It is a false dichotomy to talk about being 100 per cent for or against the private sector. Countries need to decide how important it is, and we all need to work to generate the evidence."

The AMFm may be dead but the search for successors is already under way.

Falling impact shifts focus to politics

Elimination

The need for fresh approaches remains, writes *Andrew Jack*

Richard Feachem brandishes a sheet of paper showing four maps of the world that shift from almost universally bright red in 1900 to green with a more modest central belt of intermittent red in 2025. The colours portray malaria's declining impact.

At the start of the last century, the disease was transmitted in countries from Chile to Sweden and affected almost every nation. Today, it remains present in 99 and, within a decade, he believes the "malaria map" could shrink significantly further.

"Five years ago, talk of elimination was not acceptable," says Sir Richard, head of the global health group of the University of California San Francisco. "Today, it's mainstream."

While global eradication of malaria may be impossible, some specialists argue that its elimination from many more countries is feasible and control at a manageable level is possible in others, provided that resources are sustained and allocated.

Since 2008, Armenia, Morocco, Turkmenistan and the United Arab Emirates have joined a list totalling 111 countries that are malaria-free. A further 34 he classifies as malaria-eliminating, with considerable scope to remove the burden of the disease as soon as 2015.

Progress is not easy. Sir Richard's team estimates that there have been 75 resurgences globally since 1930, as political attention and funding shifted elsewhere.

Today, he worries about the trade-off as the Global Fund to Fight Aids, TB and Malaria focuses on high-incidence countries at the expense of lower incidence ones with greatest potential for elimination. There is also the need for new tools and approaches, as the disease shifts from *Plasmodium falciparum* in children and pregnant women to *Plasmodium vivax* affecting adult males – often migrant groups.

While some parts of the hot and wet tropical areas of Africa present a rate of transmission that

'Five years ago, talk of elimination was not acceptable. Today, it is mainstream'

may prove too difficult to eliminate with current technology, he argues that climatic conditions are less of a brake elsewhere.

"Elimination requires a lot of spending, for surveillance and a much better ability to tackle cases and outbreaks," cautions Sylvia Meek, technical director of the Malaria Consortium, a British-based charity.

"It needs much more investment than most countries are willing to provide. The difficulty is how to maintain political commitment when malaria is no longer seen as a problem."

Vaccines Test setbacks demonstrate formidable nature of the adversary

Disappointing results from clinical trials of the leading candidate among antimalarial vaccines have demonstrated once again just how formidable an adversary is the malaria parasite, **writes Charles Batchelor**.

A Phase 3 trial among more than 15,000 six-12-week-olds at 11 sites across seven African countries of the RTS,S vaccine showed lower efficacy than an earlier Phase 2 trial with children aged five-17 months. RTS,S, which targets the parasite in the human liver, is being developed by Glaxo SmithKline in a public-private partnership with the Path Malaria Vaccine Initiative

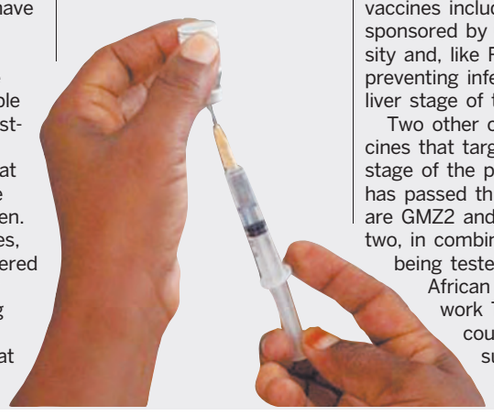
The latest trial showed efficacy rates of 31 per cent against clinical malaria and 37 per cent against severe malaria (involving serious organ failure). This compared with rates of 56 per cent and 47 per cent respectively among the older infants.

"This was a bit of a surprise," said Joe Cohen, adviser to the GSK Malaria Vaccine Project and co-inventor of the vaccine. "We can speculate on the reasons [for lower efficacy]. The infants have more immature immune systems than older children. The vaccine was administered at the same time as routine vaccines for tetanus and polio so there may have been some interference between them."

The latest results have come from a larger sample than the Phase 2 field testing trial among the older infants. "The lesson is that small trials don't give the full picture," said Dr Cohen.

Despite these difficulties, analysis of the data gathered from the Phase 3 trial of RTS,S alone is continuing with researchers drawing comfort from the fact that the side effects appeared to be no different to those experienced after taking the standard vaccines against childhood illness.

"There are currently no licensed malaria vaccines," says Vasee Moorthy, technical officer at the World Health Organisation (WHO). "Clinical testing of RTS,S is at least five to 10 years ahead of other candidate vaccines. WHO will make evidenced-based policy recommendations on RTS,S in 2015 based on the full results of the Phase 3 trial, including site-specific efficacy and the booster dose data."



Three of the other malaria vaccine projects are at the Phase 2 stage while there are also promising approaches earlier in development, according to Dr Moorthy. The three Phase 2 vaccines include ME-TRAP, sponsored by Oxford university and, like RTS,S, aimed at preventing infection at the liver stage of the pathogen.

Two other candidate vaccines that target the blood stage of the pathogen after it has passed through the liver, are GMZ2 and MSP3. These two, in combination, are being tested by the African Malaria Network Trust in four countries in sub-Saharan Africa.

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Efforts to gain control meet resistance

Insecticides Regulatory obstacles stand in the way of innovation, writes *Sarah Murray*

In the field of vector control, as the development of pyrethroids is known, the race is on to come up with new forms before growing resistance to this common form of man-made insecticides reverses recent gains in the battle against malaria.

While promising alternatives are on the horizon, regulatory obstacles threaten to slow the process of putting new insecticides to work.

Pyrethroid insecticides – which are less environmentally harmful and pose a lower threat to non-insect life than products such as DDT – have long been the preferred form of mosquito control. Evidence is emerging that a growing number of mosquitoes are developing resistance to them.

While it is not yet known to what extent this is causing the failure of treated bed nets or indoor wall spraying campaigns, the danger is approaching, says Janet Hemingway, director of the Liverpool School of Tropical Medicine and professor of insect molecular biology. "We cannot assume we're going to have pyrethroids as a viable control tool for much longer," says Prof Hemingway, who is former chief executive of the Vector Control Consortium.

The IVCC, a non-profit collaboration, was launched with $50m from the Bill & Melinda Gates Foundation and is working with the chemical industry to develop new insecticides.

Part of the reason behind the creation of the IVCC was that the flow of innovation in public health insecticides had dried up.

Public health objectives no longer met those of the agrochemical industry, which developed pyrethroids in the 1980s, when what the agriculture industry required "was something that killed everything with six legs and a couple of wings", says Prof Hemingway.

The small size of the market for malaria insecticides and the fact that this market is driven by public funding – with orders dependent on the tender process – has made the business case for the development of new products hard to establish.

A worker in Mumbai, India, administers an antimalarial fumigation spray PA

The IVCC has therefore acted as a catalyst for innovation by providing donor funding to cover early-stage development costs, as well as a skill base companies can tap into.

"It's helping unblock some of the barriers to getting innovation moving," says Mark Birchmore, head of the vector control unit at Syngenta, the Swiss agribusiness group, which is working with the IVCC. "And the IVCC's convening power allows us to have a dialogue that helps shape the innovation portfolio so that we're focusing on the right things."

Because of the length of time needed to develop new insecticides, the approach has been two-pronged. Existing insecticides have been reformulated, with the first, Syngenta's Actellic, going into use last year. Reformulating existing products can fill the gap between increased pyrethroid resistance and the appearance of new insecticides.

"That's quicker to do because the active ingredient is already registered," says Tom McLean, the IVCC's chief operating officer.

Moreover, developing pyrethroid products that incorporate other ingredients can extend their life, since it takes mosquitoes longer to develop resistance to an insecticide that contains a combination of chemicals.

Insecticides with entirely new active ingredients are set to come on to the market in the next five to seven years. However, in addition to the length of time required to develop products, regulation presents additional hurdles.

As well as going through the regulatory approval processes of individual countries, vector control products are assessed by the World Health Organisation's pesticide evaluation scheme. "That evaluation scheme ends up being a de facto regulatory scheme because at least two of the big donor organisations typically don't allow recipients of aid money to buy products that aren't recommended by the WHO," says Mr Birchmore.

The WHO's four-phase evaluation process can take several years, he explains. "And that's a lot longer than it would take to register a product in the most challenging country from a time point of view."

Mr McLean argues that the WHO's evaluation process can act as a disincentive to companies to develop new products because they are required to invest heavily in demonstrating that a product is safe and effective and then must make that data publicly available.

"It produces a barrier to innovation among industry partners that's severe at the moment," he says. "There are a number of companies saying they will not bring new products through until this is sorted out."

> 'There are a number of companies saying they will not bring new products through'

The IVCC is exploring mechanisms – such as periods of exclusivity or payment of premiums for innovators – that could provide greater incentives for companies to participate in the development of new insecticides.

"We have to draw a reasonable balance between rewarding companies for creating the innovative products that we need without creating monopolies that are then unduly exploited," he says.

"But this problem has been solved elsewhere and the solutions could be applied in this case."

Chance discovery Unintended consequence of drug highlights potential benefits of integration with other 'neglected tropical disease' programmes

When Moses Bockarie was conducting fieldwork in Papua New Guinea in the 1990s, he noticed a striking side effect when he decided he would take ivermectin, the medicine he was giving to local people to protect them against lymphatic filariasis (elephantiasis), **writes Andrew Jack**. Mosquitoes that bit him in the laboratory died rapidly afterwards.

The chance discovery added a new and more positive twist to a concern that animal researchers had identified a decade earlier when examining an unintended consequence of using the drug on cattle. Their dung did not decompose because the impregnated faeces killed the flies that usually swarmed around it.

It highlighted a broader message that is even more relevant and useful today. Tighter integration of malaria programmes with other still more "neglected tropical diseases" can provide mutual benefit and offer more effective protection against a range of different debilitating illnesses.

"Ivermectin to kill mosquitoes has become a hot topic," says Prof Bockarie, director of the Centre for Neglected Tropical Diseases at the Liverpool School of Tropical Medicine, who has noticed a surge of recent publications on the matter. While ivermectin's toxicity may be short lived and its potency in different types of mosquito vary, its impact is spreading with growing "mass drug administration" programmes in Africa to tackle lymphatic filariasis and onchocerciasis (river blindness).

Even when it no longer proves lethal, residual levels in the blood may be enough to disrupt the parasite. Ivermectin is a well-studied and well-tolerated medicine.

In a number of African countries ivermectin is now distributed twice a year – albeit often in the dry season when transport is easier.

Timing its use, however, with the peak malaria biting period could help reduce the burden of the three diseases simultaneously – as well as that of scabies.

That is not the only advantage of adopting a less "vertical" single disease-focused approach. Long-lasting insecticide impregnated bednets increasingly provided to tackle malaria are also effective in reducing the burden of lymphatic filarasis. Nonetheless, Mr Bockarie says many organisations contracted to provide nets to fight malaria would do well to talk with longer-standing community drug administrators for lymphatic filariasis and onchocerciasis. "Some groups are really not talking to each other," he says.

A final synergy with malaria comes from another neglected tropical disease: worms. Deworming programmes run in schools in Kenya have allowed researchers to get accurate information from children of the extent to which bednets distributed to their homes are actually being put to use.

Such feedback – which suggests that fewer nets are slept under than are distributed to the public – will prove useful in improving coverage and the accompanying education efforts to boost use. With money increasingly tight, cross fertilisation between disease networks could prove ever more a necessity than an unintended bonus.