FT Health Combating Malaria

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Researchers warn victory remains a long way off

The biggest threat to the campaign against malaria is the perception that the war has already been won, writes *Andrew Ward*

Success can be a dangerous thing in the world of global health policy. Deaths from malaria have fallen by 42 per cent since 2000 and incidence of the disease is down by a quarter.

This is due in large part to a surge of international financial support for anti-malaria efforts from just $100m in 2000 to almost $1.84bn in 2012. An estimated 3.3m lives have been saved as a result. Yet, far from trumpeting these statistics, leaders of the global campaign against malaria are worried about complacency.

"It is part of human nature that people always want to move on to the next thing," says James Whiting, executive director of Malaria No More UK. "There is a danger that people think malaria has been 'done' and start to shift attention elsewhere."

If this were to happen, says Mr Whiting, the gains of the past decade could quickly vanish. "Whenever I go to meet a politician to talk about funding, I take a chart with me showing what happened the last time momentum was lost," he says.

"The first big push against malaria made huge progress between the 1950s and 1970s, but things stalled in the 1980s and 1990s and you saw the disease come surging back," he adds.

There have already been warning signs. A dip in deliveries of mosquito nets treated with insecticide – one of the most effective measures against the parasitic infection – was accompanied by a slowing of the decline in malaria deaths in 2011 and 2012.

Even after years of progress, malaria remains one of the world's biggest killers, responsible for 627,000 deaths in 2012. About 90 per cent of these were in Africa and 460,000 of them were children under five.

One of the world's biggest killers: 627,000 people died from malaria in 2012 PA

"The fact that so many people are dying from mosquito bites is one of the greatest tragedies of the 21st century," says Margaret Chan, director-general of the World Health Organisation. "If political commitment wanes, the great progress that has been achieved could be undone, in some places in a single transmission season."

Much of the success of the past decade has been driven by the Global Fund to Fight Aids, Tuberculosis and Malaria – a consortium of governments, international bodies and private donors set up to tackle three diseases that have ravaged Africa and other parts of the developing world.

Donor nations last year pledged $12bn to the Global Fund between 2014 and 2016 – an increase of 30 per cent from the $9.2bn donated over the two prior years, but short of the $15bn target set by the fund's leaders.

"We're doing everything we can to keep up the sense of urgency," says Ray Chambers, the special envoy responsible for financing the health programmes within the UN's Millennium Development Goals. "With a big push over the next two years, we can try to get down to about 100,000 [annual] childhood [malaria] deaths, from about 400,000 now. But funding is a challenge."

Strong economic growth in parts of Africa should help, by allowing local governments to spend more on health and by lifting people out of the squalid living conditions in which malaria prospers.

But Suprotik Basu, chief executive of Mr Chambers' team, says the disease is still holding back economic development on the continent.

In parts of Ghana, for example, malaria treatment costs up to a quarter of household income for poorer people. Including lost productivity, the annual cost of malaria to Africa is estimated at $8bn-$12bn.

"Many African nations are on course to become middle-income countries," says Mr Basu. "We are doing everything we can to break the back

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Gold miner and the metal itself help in fight against the disease

Case study

Andrew Jack looks at how a business in Ghana is taking a leading role

When AngloGold Ashanti began a malaria control programme at its gold mine in Obuasi in the Ashanti region of southwest Ghana in 2005, the main local hospital was handling 6,800 cases of the disease a month.

Almost a decade later, and after an annual investment of $1.5m, it has cut that volume to about 100 a month, and as low as 47 in March. "This is very positive," says Sylvester Segbaya, director of the company's malaria control programme. "We've sharply reduced the burden."

Often nature works synergistically, generating problems and solutions in the same place. This applies to gold mining, which often brings large volumes of people close to areas of stagnant water in humid climates where mosquitoes can breed.

The industry risks harbouring – if not encouraging malaria – through artisanal mining processes, during which gold is washed and sorted with water, and more generally by bringing employees into high-risk areas.

Yet both the mining companies and the precious metal itself can play an important role in tackling the disease. The juxtaposition of a lethal disease and large companies extracting gold is beginning to mobilise greater efforts to tackle malaria.

With 2,500 of the malaria cases among AngloGold Ashanti's own employees a decade ago – amounting to a third of its workforce – there was a strong element of self-interest in it doing more.

With an average of three days absence per infection, the company estimated it was losing 7,500 man-days a month and spending $660,000 a year on treatment. Malaria caused absenteeism from employment and from schools in the local community.

Watchful: a mine worker at the Ashanti goldfields mine in Obuasi, Ghana Reuters

"Malaria from the very word 'go' is a big problem," Mr Segbaya says. "We saw it affecting the productivity of our employees and everything else. Even when staff got back to work, they were not as fit and strong as they used to be, and had lower output. It was harming our operations."

The company placed great emphasis on indoor residual spraying to kill and deter mosquitoes, carrying out programmes every six months. Large-scale government programmes had been carried out several decades ago, but since neglected.

It also launched larviciding in selected places to kill mosquito eggs. More recently, AngloGold has ensured that all suspected cases are confirmed with testing ahead of treatment.

It has begun to distribute bed nets alongside government programmes, although Mr Segbaya says there is still some debate on their value at the company.

"The challenge we saw was that people had the option to use the nets or not," he argues. "We didn't want to leave the results to individual's discretion. Data have shown that people use them only 40 or 50 per cent of the time."

However, the company's success in this area has led to its appointment – unusual for a business – as the principal recipient of a grant in Ghana for bed net distribution by the Global Fund to fight Aids, TB and Malaria. It also advises the US President's Malaria Initiative on insecticide spraying.

> 'Government support has been very limited. We had to follow with the funding'

Just as importantly, the company has begun to expand its programme to its other mines in Ghana and the various countries where it operates, including Guinea, Mali and Tanzania.

Its thinking has also helped inspire other mining companies to wage war on malaria, including Newmont of the US and Kinross of Canada.

Critics say that larger companies could be doing more to tackle malaria, for instance increasing the focus on artisanal mining communities.

Many people also point to the primary role of government in operating malaria control programmes.

Mr Segbaya says: "The problem is always that government support has been very limited. We had to follow with the funding."

In the absence of sufficient public sector financing and activity, Mr Segbaya says he is working with Ghana's government to create "a national fund overseen by high-profile people with integrity, and with companies to make their contribution".

Meanwhile, there is another important role that gold plays in the fight against malaria.

Trevor Keel, head of technology at the World Gold Council, says the metal is an essential part of modern rapid diagnostic tests for those infected with the parasite. Some 200m kits are distributed globally each year.

The malaria antibody is attached to gold nanoparticles during manufacture. These will attract any malaria antigens in a blood sample. That turns the particles from red to purple, resulting in a "positive" two-line readout on the device.

"Without the gold, these tests would be useless," says Mr Keel.

His organisation is now working on support for the development of a new thermal contrast technology that will improve the sensitivity of standard rapid diagnostic tests.

More generally, gold itself is finding new applications, both in diagnostics for a wider range of diseases and even in some treatments, such as for dysentery.

Gold may find a broader range of medical uses, while the businesses that extract it are mobilising to tackle the malaria with which mining can all too often be associated.

Telecoms help pave way to improved net benefits

Costs Increased efficiency keeps the price of prevention down, says *Rose Jacobs*

Perhaps the reason Martin Edlund is optimistic about the procurement and distribution of anti-malaria tools is his experience in the field.

A co-founder of the charity Malaria No More, he witnessed a successful step-change in malaria net distribution in Senegal starting in 2008.

A year earlier, the World Health Organisation had changed the rules on net coverage. While previously it had recommended focusing distribution efforts on pregnant women and children below the age of five, now it was aiming for universal coverage.

That meant that the old practices – for example, handing out net vouchers at neonatal clinics – were no longer sufficient. "How do you find adult males and give them these nets," Mr Edlund recalls asking. There was no obvious mechanism, and yet the answer was, in the end, relatively simple: a walking census.

The group teamed up with the Peace Corps and began visiting villages, finding out how many people lived in each, and telling them when they would be back with the appropriate number of nets. They even managed to reduce the problem of people selling the nets on rather than using them themselves by writing the name of the head of household and the village on each.

In other words, the last mile – shorthand for the final steps a product or service must take to reach the individuals who will use it – was less of a problem than had been feared.

But Mr Edlund does not think this will always be the case. "You might be able to do a mass campaign with prevention tools, but not malaria diagnostics," he explains.

"People need to be able to access diagnostic tools when and where they come across a fever that might be malaria." However, he believes solutions to problems of access are not far off.

Some of these come from the very industry that gave rise to the term "last mile": telecommunications. Thanks to widespread mobile phone use in African countries plagued by malaria, experts hope for a future in which malaria infection could be tracked in near real-time, and treated accordingly.

> 'Would the growing middle classes be willing to pay for a net?'

This falls into what the UN's Population Fund describes as a "pull" model of distribution: demand-driven and targeted. But technology should also aid more traditional "push" approaches, under which governments and charities roughly forecast how much of a product will be needed in a certain area, then make sure the appropriate quantity is available.

Patrick Kuchar, malaria branch chief at the US Centers for Disease Control and Prevention, cites a project in Tanzania that turned physical vouchers for nets – slips of paper easily lost and hard to safeguard against counterfeiting – into electronic codes delivered to phones and good for one net per code. Other pilot projects send health workers regular text message reminders about, say, running a diagnostic test or urging patients to buy nets. Others send messages directly to patients, alerting them when it is time to take a dose of their prescribed medicine.

As for procurement, the costs of prevention tools, diagnostics and medicines fell significantly between 2005 and 2012, according to a study published last year in the Malaria Journal.

However, higher prices and new products mean that procurement efficiencies will remain important.

Mr Kuchar says that technology should aid centralised buying, alongside help from the US President's Malaria Initiative. It offers guidance to charities and governments on how to forecast accurately the amount of drugs, diagnostic tests and nets they will need, and how to procure them centrally.

In turn, this gives manufacturers the confidence to produce products in high enough numbers that they can achieve economies of scale.

It is not a marginal concern. While the Roll Back Malaria campaign estimates the global cost for malaria control and elimination peaked in 2009-10, it does not expect total costs to fall much below $5bn before 2020, roughly split between Africa and Asia, with much smaller amounts demanded by the Middle East, Eurasia and the Americas.

Building networks: distributing mosquito nets in Uganda Alamy

Within this, procurement costs remain significant – they are estimated to account for about 40 per cent of the money put towards malaria by the Global Fund, one of the world's most important funding sources for anti-malaria measures.

Meanwhile, the team at Malaria No More is investigating the degree to which individuals might start sharing the burden.

Mr Edlund points out that many of the countries facing malaria already shoulder the vast bulk of the costs as their economies grow – a virtuous circle, since the economic progress comes at least in part on the back of successes so far in the fight against malaria.

As the middle class in these regions grows, too, might real markets develop for some of these products?

"By now, hundreds of millions of families have owned nets and used them and seen the benefits," Mr Edlund says. "Would these families be willing to pay for a net?

Call for greater penalties for peddlers of fake remedies

Under scrutiny: Cambodian officials inspect a pharmacy in their continuing search for counterfeit drugs Getty

Counterfeits Few people are being brought to court anywhere in the world for manufacturing useless copies of drugs, writes *Andrew Jack*

In 2012, customs officers in the Angolan port of Luanda decided to inspect a shipment of hi-fi speakers. Inside, they found large quantities of concealed drugs: not narcotics but medicines offering just as much profit for their distributors – and potentially far greater harm for their purchasers.

The seizure contained 32m tablets of pills labelled as Coartem, one of the most effective drugs against malaria (see separate article overleaf), but when analysed they were found to contain no "active pharmaceutical ingredient" at all.

This high-profile case highlighted the extent of counterfeiting. Large quantities of a product purporting to be a life-saving medicine were to be sold to patients. Yet they would have done nothing to treat malaria, but rather exposed many to risk of death.

The Angola shipment was traced to Guangzhou, in China's industrial heartland. Despite the country's pre-eminent role in developing artemisinin, one of the two active ingredients in Coartem, China is also by far the largest hub of counterfeit manufacturing – especially for malaria treatments. Indian producers have also been identified as producing fake antimalarials.

Yet no prosecutions have taken place in China, and few people have been brought to court anywhere else for counterfeit medicines in general – let alone faking malaria medicines. Most of the investigations that have taken place have focused on higher-priced drugs for patients in richer countries such as cancer treatments.

Ironically, Coartem is available free to a large number of patients across Africa and other parts of the developing world, thanks to substantial donor support from the Global Fund to Fight Aids, TB and Malaria, the US President's Malaria Initiative, and a range of other projects, companies and individuals. That process has created a powerful brand that unscrupulous intermediaries seek to exploit.

Andrew Jackson, head of global corporate security at Novartis of Switzerland, the pharmaceutical group that developed and produces the treatment, says: "When you donate something to governments or their agents in many African countries, and it has a certain street value, a lot is going to leak out of the system."

He says that an important problem has been the diversion of donated Coartem from clinics to so as to sell it to patients – engineering a shortage of supplies where they are available free and creating an alternative market for private vendors to exploit.

In the absence of a firmly controlled pharmacy distribution chain, or the requirement for doctors' prescriptions to help restrict access to regulated outlets, Coartem is available for sale.

That process may reduce the drug's effectiveness even when it is genuine, since stocks lose their potency after they have gone out of date, or if they have been transported and stored in high temperatures or humidity.

Pirated versions of a drug are a more serious problem. Counterfeiters have proved highly effective in producing successive generations of fakes to keep up with efforts by the original producers to differentiate them. Label changes, special characters and even holograms are quickly copied.

Amir Attaran, a professor at the law and medicine faculties of the University of Ottawa, is among those calling for an international treaty and tougher national laws that would increase the penalties for counterfeit drugs. Penalties for fake medicines – unlike narcotics – are usually modest fines or criminal sentences and are not a primary focus for law enforcement bodies.

> 'People will make money wherever there is an opportunity'

He says international action has stalled, not only because of the lack of reliable information about the extent of the problem but also because of disputes over definitions.

Health experts have long been divided on the distinction between cheap, poorly manufactured "substandard" drugs and intentional counterfeits.

"I see this as a legal or criminal issue, and only secondarily a medical one," Prof Attaran says.

In the absence of tougher laws, donors, police and manufacturers have increased the exchange of information to identify and track counterfeiters.

Yet so far, only a small number of prosecutions of intermediaries and sellers of fake antimalarials have taken place in Africa, with no convictions against the real counterfeiters.

There has also been much discussion – in developed and poorer countries alike – of the use of bar codes and other detection systems, combined with scanners and mobile phones to verify unique numbers as a way to authenticate medicines.

Some experts question their value, and say that they create a false sense of security, can be circumvented and may not work at all in rural areas.

"Everyone thinks technology is cool," says Mr Jackson. "But we should invest heavily in enforcement, inspection and intelligence exchange.

"We are certainly seeing more and more diverted and fake Coartem. People will make money wherever there is an opportunity."

In the meantime, he says, improved education for patients about the risks of counterfeits is needed. "People have blind trust in the drugs they buy, but they are not all OK."

Improving situation: thanks to advancements in the treatment of malaria, since 2000 there has been a 42 per cent drop in the number of deaths from the disease Alamy

Race is on to find new treatments

Drugs The threat of drug resistance spreading has prompted a hunt for fresh remedies, says *Andrew Ward*

Mao Zedong may seem an unlikely hero of the battle against malaria. During his leadership of China in the 1960s, universities were shut down and scientists banished to the countryside as part of the Cultural Revolution.

But an exception was made for a research programme into treatments for malaria, which was ravaging the army of Beijing's North Vietnamese allies during their jungle battles with US-backed South Vietnam.

An effective drug was developed using a chemical compound called artemisinin extracted from the sweet wormwood plant – a herb used in Chinese medicine for centuries.

It took until the late 1990s for the treatment to gain wider usage, when Novartis of Switzerland bought the Chinese patent for an artemisinin-based combination therapy (ACT) with a cure rate of 95 per cent.

The Basel-based drugmaker had originally eyed its potential as a premium-priced product to sell to tourists and countries' militaries but in 2001 agreed to make it available to the World Health Organisation and its partners at cost price. Since then, Novartis has supplied more than 600m treatments on a non-profit basis in more than 60 countries, with many millions more treatments coming from generic producers.

Coartem, Novartis's brand name for the drug, remains one of the most important weapons in the fight against malaria and has played a big role in the 42 per cent drop in deaths from the disease since 2000.

However, there are fears its days may be numbered because of signs of rising resistance to the treatment in southeast Asia. ACT-resistant strains of the Plasmodium parasite responsible for malaria have been detected in Cambodia, Myanmar, Thailand, Vietnam and Laos.

The big fear is that these strains could spread to India or Africa. The WHO has warned this could have "dire" consequences and imperil progress made over the past 15 years.

"Given the ever-increasing levels of population movement in Asia and the Pacific, the geographic scope of the problem could widen quickly, posing a health security risk for many countries in the region," the WHO said.

With the clock ticking on artemisinin-based drugs, the race is on to develop a new generation of treatments.

Novartis announced last November that it had discovered a potential new drug based on a class of compounds called imidazopyrazines, in a research programme backed by the Wellcome Trust and Medicines for Malaria Venture.

Initial studies have shown it has the potential to block the plasmodium parasite at an earlier stage of infection and to stop it recurring. This would give it an important advantage over existing treatments, which are only effective against the disease at its most acute stage.

Thierry Diagana, head of the Novartis Institute for Tropical Diseases, says the breakthrough "could provide a path towards elimination of the disease". However, there are years of work ahead before a medicine will be patented.

'The geographic scope of the problem could widen quickly'

In the meantime, GlaxoSmithKline is hoping to provide an alternative by offering the first vaccine against malaria. After 30 years of work, GSK plans to seek European regulatory approval for its RTS,S vaccine this year.

If successful, the WHO has indicated it could make a recommendation on the vaccine next year, clearing the way for its adoption by governments across Africa and other malaria-hit regions.

In clinical trials, the vaccine cut incidence of the disease among young children aged between five and 17 months by nearly half, and among infants aged six to 12 weeks by about a quarter.

These success rates are much lower than those associated with other childhood vaccines and the trial results were a disappointment to some in the health community who had been hoping for a "silver bullet".

But Allan Pamba, head of GSK in east Africa, who has been closely involved in development of the vaccine, says a success rate of nearly half is more than enough to justify its adoption given the number of lives this could save.

An estimated 627,000 people worldwide died from malaria in 2012 – most of them children under the age of five in Africa.

"The antimalarial drugs we have are great, but resistance is growing," says Mr Pamba. "We need new tools."

So far, GSK has invested about $350m on development, with another $260m to come in the final push to launch.

The UK-based company has said the price will be based on the cost of production plus 5 per cent, with the profit ploughed back into further research and development on tropical diseases.

"We could have put these resources into developing another Viagra or statin or diabetes drug, any of which would have promised a much surer return on investment," says Mr Pamba. "The only rationale for developing this product is its social impact."

GSK cites its malaria work as evidence of a broader commitment to Africa, which also includes donations of drugs to fight neglected tropical diseases such as soil-transmitted helminth infections and affordable access programmes for its HIV drugs.

For a company battered in the past year by allegations of corruption in China and several other countries, the launch of the world's first malaria vaccine would help enhance GSK's global image.

But Mr Pamba says the project is about much more than public relations. As Africa's economy develops, GSK is increasingly looking at the continent's commercial potential. The company last month announced plans to invest £130m in Africa over the next five years to boost manufacturing capacity.

By reducing the $12bn annual cost of malaria to the African economy, GSK hopes to hasten the day when it can treat the continent like an ordinary market.

An effective vaccine may at last be in sight

Opinion
JOE COHEN

In 1987, I started work on an ambitious project to develop a vaccine against malaria.

In the 1980s, as vaccines helped tackle killer diseases such as polio and measles, hopes were high that a similar approach could end the deadly cycle of malaria.

While huge progress has been made during the past decade, thanks to bed nets, better treatments and diagnostic tools, it still claims hundreds of thousands of lives each year – mostly young African children.

The need for new approaches is as relevant now as it was then.

It is exhilarating to think that nearly 30 years later, this may finally be within reach. The investigational vaccine we have been working on is being tested in late-stage trials across Africa.

We will submit the vaccine for assessment by the European Medicines Agency this year. All being well, the world might have its first vaccine against malaria in a few years.

Setting out on a career as a molecular biologist in 1984, I'd planned to head into academia. But a job advert caught my eye, offering the chance to join a group developing a hepatitis B vaccine.

My application was successful and became part of the team that created the first vaccine based on genetic engineering technology.

When I was asked three years later to lead a malaria vaccine project I jumped at the chance. I didn't think I would still be working on it three decades later. But malaria is tough to crack.

It is caused by a parasite rather than a bacterium or virus. Parasites are experts at evading the body's immune system. No vaccine exists against any human parasite anywhere.

The malaria parasite can alter its appearance and composition to avoid detection.

Once in the body, it spends minutes in the bloodstream before hiding in the liver, where it becomes harder to target.

There it differentiates and replicates before bursting into the bloodstream, invading and destroying red blood cells and causing symptoms from headaches to seizures and, all too often, death.

Our approach focused on advances in molecular biology and immunology to target the malaria parasite before and during liver cell infection.

We trialled our candidate vaccine in healthy adult volunteers in the US then, with proof of concept in hand, in Africa, starting in adults and progressing towards testing in children.

Data from a late-stage trial that is still in progress suggest the candidate vaccine can almost halve the number of malaria cases in children aged five to 17 months, on top of reductions from bed nets and other tools.

This seems modest, but each year there are more than 100m malaria cases in African children under five. Easing this disease burden would have enormous human, social and economic benefits.

The other big challenge is financing. In the late 1990s, ready to start clinical trials in Africa, we understood the cost of developing this vaccine would be hundreds of millions of dollars. Those who would eventually use the vaccine – children in Africa – could not be expected to pay for it.

We have been fortunate. Not only has the support and commitment of GlaxoSmithKline been constant, but we found a way of sharing the cost and risk by joining with the Path Malaria Vaccine Initiative, a non-profit group, to develop the vaccine.

The partnership continues and is one of the bedrocks of the project, as are our multiple collaborations with leading African scientists. This type of public-private partnership could be a model for similar projects.

If the candidate vaccine is approved and recommended by global and national public health policy makers, we need to make sure it reaches the people who need it.

Having it sit on a shelf because it is too expensive would be unthinkable for me and for the hundreds of researchers in Africa, the US and Europe.

After three decades of fighting malaria, I'm retired, but certainly not tired. I'm still a consultant to the project. Innovation against malaria does not end here.

The RTS,S candidate vaccine is not perfect and, if approved, it will need to be implemented with other antimalarial measures.

We will always need to look for better approaches to stay ahead and, I hope, to make malaria history.

Joe Cohen PhD is an adviser to the malaria vaccine project at GSK

Still battling on: Dr Joe Cohen

Statistics fail to reveal the true picture of India's health

Asia

More accurate reporting is needed, writes *Amy Kazmin*

In the early 1950s, India, newly independent from British rule, went on the offensive against malaria, with a well-coordinated programme to spray the insecticide DDT in areas with high levels of the disease to prevent the mosquitoes breeding.

The results were so encouraging – a 99 per cent drop in reported cases – that in 1958 New Delhi renamed its programme the National Campaign for the Eradication of Malaria, optimistic that mosquito-borne illness could be eliminated.

Instead, the programme faltered, because of lack of public co-operation, weak morale among spraying teams and inadequate supervision.

Mosquitoes developed resistance to DDT and malaria bounced back with a vengeance, rising to a peak of about 6.5m reported cases in 1976.

"Gradually, the system got corrupted," says Dr Manish Kakkar, head of zoonotic diseases at the Public Health Foundation of India. "There were reversals and resurgence."

Today, India's government claims to be making renewed strides in malaria control. The World Health Organisation estimates that by 2015 India's malaria incidence and fatalities will be down to 50-70 per cent of their 2002 levels.

But with serious questions about the credibility of official data – and few signs of an intensive, long-term effort to reduce mosquito breeding – health experts say malaria still threatens the lives of many.

"The danger is still there," says Amit Sengupta, co-convener of the People's Health Movement India, a non-governmental organisation. "It isn't something you can be complacent about."

India's National Vector Borne Disease Control Board says malaria incidence has fallen from about 3m cases a year in the mid-1990s to some 1m in 2012.

It also says deaths have dropped from an average of 1,050 a year for 16 years from 1995 to 519 in 2012.

But these numbers are acknowledged seriously to underreport incidence and fatalities, as officials only count those cases confirmed by a test at a government health facility.

Many malaria patients in rural India – whether they recover or succumb – are treated by local private doctors or never see a health worker at all, and so do not appear on the government's radar for official testing and diagnosis.

"Everybody accepts that if you only rely on data based on cases that smear positive, you would miss something by an order of magnitude of 10 to 100 times," says Dr Sengupta.

Some of India's worst affected areas are conflict zones such as Chhattisgarh – where radical Maoist rebels control vast swaths of territory and the government has little presence – or remote border areas.

"It's difficult to obtain insights into the malaria programme in India," says Dr Kakkar. "It's a case where the information is not only deficient, but there are questions about the credibility of what is available."

India's true malaria burden is a matter of intense debate. The WHO estimates malaria kills 15,000 Indians annually. But researchers working on the innovative Million Deaths Survey – which used so-called "verbal autopsies" to assign likely causes to 122,000 unexplained deaths in India from 2001 to 2003 – say the real toll is far higher.

'Technology gives a temporary edge, but the parasite is also moving to outwit you'

In a 2010 article in *The Lancet,* the Million Deaths survey researchers said a more "plausible" range was 125,000 to 277,000 fatalities a year, mostly in rural areas.

New Delhi, however, has questioned the accuracy of verbal autopsies, which use relatives' recollections of a person's fatal illness to make a postmortem diagnosis, and argued malaria deaths are overestimated.

Meanwhile, a government-appointed panel developed a method for estimating malaria deaths that resulted in a sharply higher figure than the current official estimate. But health officials are planning a further study on the methodology, which is unlikely to be accepted for at least a year.

India is not alone in struggling accurately to assess its malaria burden. The WHO says just 14 per cent of global malaria cases are detected and reported through official surveillance systems. In turn, these are too weak and inconsistent even to reflect malaria trends in countries accounting for about 85 per cent of the global burden.

While some professionals even question whether India's malaria trend is declining, others say research suggests incidence and death are falling.

In recent years, artemisinin combination therapy and rapid diagnostic tests have been more widely available, improving treatment success rates.

But Dr Sengupta warns India's current decline could be part of a cycle of temporary "small victories" followed by renewed malaria resurgence, unless there is a more determined, concerted effort to control mosquito breeding.

He also notes a worrying rise in the more dangerous falciparum malaria as a percentage of all Indian malaria cases.

"Marginally, the health system has improved with new drugs and rapid diagnostic tests being used," he says. "It's an infusion of technology that temporarily gives you an edge. But the parasite is also moving to outwit you.

"If you can put in place public health measures that eliminate places where mosquitoes breed, you would probably see a more permanent secular change."

Complexity of life-cycle also offers opportunities

Science New methods of controlling the spread of the disease are being tested, but they need time to be developed, reports *Clive Cookson*

From the biological point of view, malaria is a particularly complex disease. It is caused by an unusual pathogen, the protozoan Plasmodium parasite, which has an extremely involved lifestyle shuttling between two hosts: mosquitoes and humans.

This triangular complexity involving protozoa, people and insects presents a formidable problem to scientists looking for new treatments. But it can also be seen as an opportunity, because there are potentially more points of attack than for simpler diseases. And these can be illuminated by new molecular techniques such as genomics and proteomics.

One of the most urgent jobs is to discover how and why Plasmodium becomes resistant to artemisinin, which has been the most effective antimalarial drug available.

In January, an international team announced a breakthrough in the journal *Nature*, after using a battery of technologies to identify a genetic marker of artemisinin resistance.

The scientists first created a Plasmodium strain in the laboratory that resisted high levels of artemisinin and compared its DNA with the non-resistant parent strain. This revealed a specific mutation in a gene called K13 that marked the resistant parasite. Then field work in Cambodia, where artemisinin resistance is emerging most strongly, showed that the same K13 mutation characterised the phenomenon in the wild.

Chris Plowe of the University of Maryland summarised the importance of the discovery. "This new marker gives us a tool that will make it possible to map the distribution of artemisinin resistance very quickly," he says. "There are a number of important research questions that need to be answered, but in the meantime knowing the distribution of K13 resistant genotypes will be very useful in planning malaria elimination efforts."

Another important example of the contribution that a battery of high-tech approaches can make to understanding malaria was published in *Nature* in February. Scientists from Glasgow University and the Wellcome Trust Sanger Institute have identified the factor that Plasmodium must produce to begin the process of passing from human to mosquito. Blocking this essential step in the parasite's life cycle could open the way to drugs that prevent transmission of malaria.

The researchers identified a regulatory protein that triggers the development of male and female forms of Plasmodium. These specialised sexual cells, called gametocytes, are responsible for infecting the mosquito and initiate transmission of the disease.

Any drug developed to disable this transmission switch is likely to be an "altruistic intervention", taken by infected adults to prevent them passing on the disease. Researchers believe parents would agree to do so for the sake of their children.

Vaccines are one of the most active fields of malaria science, as researchers look for improvements on RTS,S, the only product that has shown some efficacy in extensive clinical trials (*see Joe Cohen, Page 4*). While public health experts welcome RTS,S they recognise that more effective "second-generation vaccines" will be needed if humanity is ever to achieve the dream of eliminating malaria.

The World Health Organisation Malaria Vaccine Technology Roadmap, published last November, lists 27 vaccine candidates in clinical trials.

One promising example at Oxford university is a vaccine that enlists the cellular arm of the human immune system to attack Plasmodium, generating CD8 T-cells. Most other vaccines rely on the antibodies they raise, rather than on immune cells.

The Oxford candidate combines attenuated doses of two viruses, one derived from a chimpanzee common cold virus and the other from a strain of the old smallpox vaccine.

If trials of the Oxford vaccine in Africa this year give encouraging results, it may be combined with RTS,S to give a vaccine that attacks malaria on both fronts, with antibodies and killer T-cells.

Another approach focuses on Plasmodium's residence in mosquitoes rather than in people. Last year, researchers at Michigan State University reported in the journal *Science* that they had established a stable and inheritable bacterial infection in malaria-transmitting Anopheles mosquitoes that makes them immune to Plasmodium parasites.

The Wolbachia bacteria are in effect acting as a vaccine to prevent malarial infection of the mosquitoes.

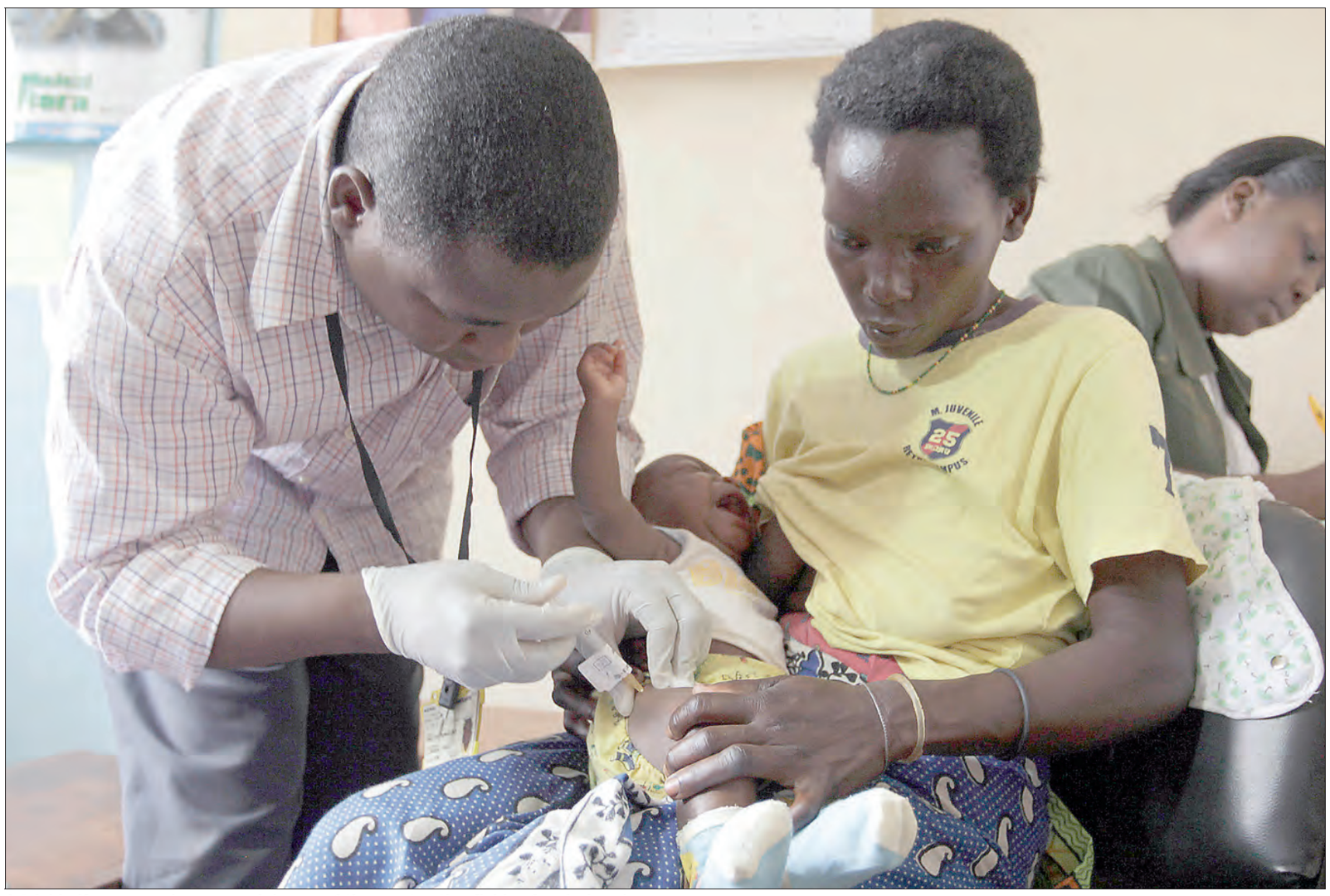
In the Michigan experiment, the Plasmodium-preventing infection with Wolbachia bacteria passed down 34 generations of mosquito before the study ended. The idea is that a Wolbachia-infected strain of mosquito, once released, will spread bacteria through the wild insect population. But extensive field testing will be required to confirm that it works.

A study at Pennsylvania State University, published in February in *Nature Scientific Reports*, showed the effects of Wolbachia infection vary considerably with environmental conditions, particularly temperature.

"Much of the work on the Wolbachia-malaria interaction has been conducted under highly simplified laboratory conditions," says Courtney Murdock of Penn State. "These results suggest that the development of this promising control technology requires an improved understanding of how mosquitoes, Wolbachia and malaria parasites will interact in diverse transmission settings."

Similar comments could be made about much of the promising research into this most complex of diseases.

A long and winding road leads from great work in the lab to effective deployment in the field.



A trial in Kenya: vaccine research is one of the most active fields of malaria science Reuters

> The triangular complexity involving protozoa, people and insects presents a formidable problem

Favoured way to fight disease faces increased resistance

Insecticides An alternative to impregnated bed nets has yet to be found, says *Rose Jacobs*

Even the most predictable problems cannot always be averted. Ahead of a World Health Organisation (WHO) endorsed, internationally embraced and remarkably successful push to fight malaria with insecticide-treated mosquito nets – an effort that started in earnest about a decade ago – some scientists had qualms.

The history of medicine has shown that successive generations of bugs tend to develop resistance to chemicals designed to kill them – and do so with greater speed and ease when they are up against only one type of poison.

Yet only one class of insecticides, those made of pyrethroid, a compound with low toxicity for mammals but high toxicity for insects, was being used on the nets.

The reason for this was simple: the World Health Organisation had approved only one insecticide and that was pyrethroid-based. The chances of another meeting the group's standards were low.

"A number of people thought we just didn't have the time [to wait for an alternative]," says Janet Hemingway, a professor at the Liverpool School of Tropical Medicine, pointing out the challenge of finding chemicals that not only had the right levels of toxicity, but also suitable longevity and the ability to bleed into polyester netting.

The clock was ticking. By 2004, malaria was claiming 1.8m lives a year, according to an analysis by researchers at the Institute for Health Metrics and Evaluation at the University of Washington, in Seattle. Insecticide-treated nets were the most effective means available for prevention.

In 2007, the WHO extended its recommendations for net usage from pregnant women and young children to universal coverage in malarial regions, contributing significantly, experts agree, to a more than 40 per cent reduction in malaria mortality rates globally since 2000.

But insecticide resistance poses a serious threat to this success, says the WHO. Resistance has been identified in 64 countries, or nearly two-thirds of those suffering from malaria transmission. India and sub-Saharan Africa are the worst affected.

The degree to which this is increasing infection and death rates – or will in the future – is less clear.

A team of researchers, including Ms Hemingway, recently conducted a review of studies investigating the relationship, but hesitated to draw conclusions given the wide range of methods and standards of research.

Patrick Kuchar, malaria branch chief at the US Centers for Disease Control and Prevention, points out that it may be "we are seeing resistance in more places because we're looking for it in more places".

Torn nets add complications. "Initially, we were expecting that the life of the insecticide would be the limiting factor of their practical, useful lifespan and what we're finding now is that their physical integrity fails before the insecticide is entirely used up," says Mr Kuchar.

The WHO has recommended immediate action to tackle resistance to insecticides, whose presence greatly enhances the effectiveness of bed nets. Unfortunately, that is easier said than done. According to Ms Hemingway, development of non-pyrethroid insecticides for this kind of malaria control was "something of a cottage industry" for many years.

This was, in part, because the focus of agricultural insecticide research switched from creating chemicals that are sprayed and kill bugs on contact to those delivered via plants that target insects' digestive systems. Potential profits for a bug spray to fight disease are not sufficient to attract much industry interest.

Public-private partnerships are attempting to address the problem, but viable alternatives to pyrethroid-treated nets are still six to seven years off, according to Ms Hemingway. In the meantime, spraying insecticides in homes and other buildings may grow in importance, despite it being less practical to deliver than nets. This is because, while pyrethroid is used most often in such spraying, other insecticides have also been approved. Scientists hope that, by taking pyrethroid in and out of use, resistant bugs will die out, since they will lack the competitive advantage they possess in pyrethroid's presence.

More broadly, as the favourite means of fighting malaria – the bed net – faces waning effectiveness, diagnostic tools and treatment will play a more important role. But prevention measures remain essential.

"The nets are effective in most situations," says Mr Kuchar. "They continue to provide a barrier mechanism, and you build that culture of net use and acceptability in people, so when the next generation of nets come along, they'll be ready for them."

And so – for all their faults – pyrethroid-treated nets are not being abandoned. In fact, funding for them remains a key concern for experts most alert to the problem of insecticide resistance.

Ms Hemingway points out that universal net coverage in Africa requires delivery of 150m nets a year. In 2012, the global community did not manage half that number.

Cover up: nets are still proving to be effective in most situations Getty

Experts say victory is a long way off

Continued from Page 1

of this disease over the next five to 10 years, so we can gradually hand over the baton to national governments as the problem becomes more manageable."

Mr Chambers reports growing interest from companies in Africa to co-operate with anti-malaria programmes as a way to help boost development.

He cites the case of a safari tourism company in southern Africa that is working with local health agencies, motivated by a desire to declare its base malaria-free to attract foreign visitors.

Mr Whiting says researchers have estimated that, by 2035, the world economy will see a return of $208bn on the international investment in fighting malaria. With an insecticide-treated bed net costing just £3 to protect a family of four for four years, campaigners say the programme is one of the most cost-effective in global health.

Mosquito net ownership in sub-Saharan Africa has risen from about 3 per cent of the population in 2000 to just over half, helping reduce malaria mortality rates among children by about 54 per cent.

Other measures have included insecticide spraying, improved diagnostic tests and widened distribution of antimalarial drugs.

"All the donors have agreed there must be no backsliding, because that would put at risk the gains from all the investment put in so far," says Mr Basu.

"If you take your eye off the ball even for a few months, malaria comes roaring back," he explains.

The biggest donors to the Global Fund have been the US, which pledged $4bn in the latest financing round last December, the UK ($2.7bn), France ($1.5bn) and Japan ($800m). The Bill & Melinda Gates Foundation, run by the Microsoft founder and his wife, underscored its powerful role by donating up to $500m.

Mr Chambers says rising powers such as China, India and Brazil have started to show more interest in global health challenges as they grow in stature.

China, in particular, has an increasing commercial stake in Africa that could encourage it to take a bigger role.

"In the next several years I expect we will see the Bric countries standing shoulder to shoulder with the traditional donor nations," says Mr Chambers.

Just under a third of Global Fund resources has been allocated to fighting malaria over the next two years, with half going to HIV/Aids and 18 per cent to TB. "These diseases are interconnected, because if you are infected with one, you become more vulnerable to the others," says Mr Basu.

$500m

Amount donated by the Gates Foundation

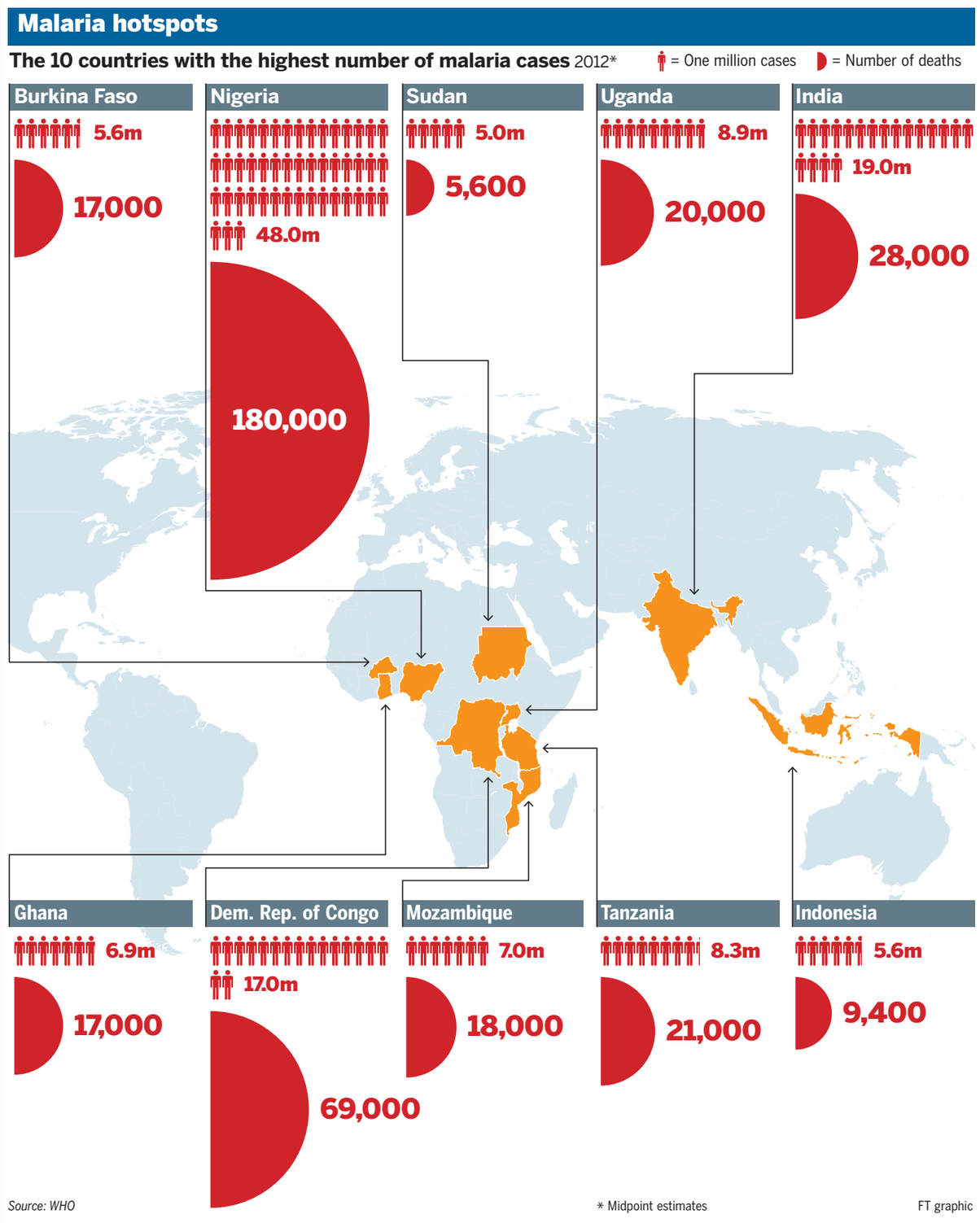
Another threat to progress comes from resistance to antimalarial drugs and insecticides. Drug resistance has so far been limited to southeast Asia, but scientists fear it could spread through infected travellers.

There are sources of encouragement too, including a promising new treatment under development by Novartis and a vaccine from GlaxoSmithKline.

"If we keep up this rate of progress over the next five to six years, we will start to get into more challenging territory of eradication in many countries," says Mr Whiting. "That last mile is always the hardest."

Malaria hotspots

The 10 countries with the highest number of malaria cases 2012* = One million cases = Number of deaths



Source: WHO * Midpoint estimates FT graphic

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