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MALARIA: CAN WE AFFORD TO WIPE IT OUT?

With a new vaccine on the horizon, the world faces important economic decisions in the fight against the disease

BY KATE KELLAND AND BEN HIRSCHLER
LONDON, DEC 14

Joe Cohen, a scientist tantalisingly close to delivering the world's first malaria vaccine, is on the stump.

After 23 years of painstaking laboratory work and a programme of major trials in seven countries, the 67-year-old

biologist says the clinical case for the vaccine is almost proved. It's a breakthrough moment that could save hundreds of thousands of lives, but when it comes to public health in the developing world, Cohen knows hard science is only half the job. That's why the softly-spoken U.S.-Italian researcher found himself one chilly December evening pitching his life's work to rich-world politicians whose voters will have to

foot the bill, and fielding questions over festive mince pies and wine in a leather and oak-clad room in London's Houses of Parliament.

How cost-effective will the vaccine be compared to tried and tested low-tech approaches like mosquito nets and insecticides, one inquirer asks. Is there any evidence that it will bring down the spread of the disease in general, helping those who



AFRICAN TRIAL: Above, Kenya Medical Research Institute doctors. Right, baby Rehema sleeps before receiving an injection as part of a malaria vaccine trial at a government clinic in Kilifi district on the Kenyan coast, November 2010.

REUTERS/JOSEPH OKANGA



haven't been vaccinated? How long is a shot likely to stay effective? Is there a danger it might foster a false sense of security? As the session goes on, it's clear that enthusiasm for Cohen's work is coupled with wariness among the experts and well-informed lawmakers. The bottom-line question: is the vaccine -- and the global health community's aim of completely eradicating a disease that kills a child every 45 seconds -- really worth the money?

"THE QUESTION IS: WHAT IS THE BEST VALUE FOR OUR DOLLAR?"

It may seem an absurd thing to ask. Malaria threatens half the people on the planet and kills around 800,000 people a year, many of them too young to have even learned to walk. The death rate has come down in the last decade, but full-scale eradication will cost billions and drag funds away from other equally, or possibly even more urgent health efforts. As governments in poor countries and donors from wealthy ones weigh up where to put their money, experts have begun a quiet but fundamental debate about whether wiping out malaria is realistic or even makes economic sense.

"With all of the money and human capacity in the world, there is very little

doubt that we could eliminate malaria. The question is: What is the best value for our dollar? And this is an increasingly pressing question as we look at the global economic climate," says malaria expert Oliver Sabot, who works at the Clinton Health Access Initiative in Boston.

TARGETING THE PARASITE

WHAT IS THE BEST value for our dollar? The answer to that question seems obvious to someone like Loyce Dama Karisa, a Kenyan woman who recently gave birth to her seventh child, a girl called Rehema. Karisa has come in a minibus full of other mothers and babies to a clinic in the mud-and-thatch village of Madamani in the Kilifi district on Kenya's south coast.

GlaxoSmithKline, the British-based drugmaker Cohen works for, is using the clinic as part of Africa's biggest ever medical experiment, giving the vaccine to babies and young children in a trial designed to assess its safety and efficacy. "I wanted my child to get this vaccine," Karisa says. "Malaria is a very bad disease."

In the Kilifi District Hospital, the children's high-dependency unit is full of malaria patients. Listless babies and toddlers lie motionless in adult-sized beds, tangles of tubes taped to their nostrils, arms and legs. One boy has his hands bandaged into stumps to stop him pulling a tube out of his nose. He screams and thrashes about as a

drip is attached to a vein in his foot. Mothers in mint green hospital gowns watch silently. One cradles her tiny sleeping baby's hand in her own while a ceiling fan chops slowly through the hot air, doing nothing to reduce the draining heat.

Families in Kilifi, which despite its lush green vegetation has poor soil for growing crops and high levels of poverty, are almost numb to the ravages of malaria. It's a similar story across the continent: around 90 percent of malaria's victims live in sub-Saharan Africa; most of those are under five.

The disease is caused by a parasite carried in the saliva of mosquitoes. GSK's vaccine goes to work at the point the parasite enters the human bloodstream after a mosquito bite. By stimulating an immune response, it can prevent the parasite from maturing and multiplying in the liver. Without that response, the parasite re-enters the bloodstream and infects red blood cells, leading to fever, body aches and in some cases death.

The vaccine Cohen and his colleagues have developed combines technology from GSK's hepatitis B shot with pieces of the malaria parasite, and adds in a chemical known as an adjuvant to boost the body's immune response further. The result -- the first ever vaccine against a human parasite, as opposed to simple bacteria or viruses -- is a product that could be given alongside standard infant vaccines and has been shown in a Phase II, or mid-stage, clinical trial to reduce the risk of clinical episodes

of malaria in young children by 53 percent over eight months. The pivotal Phase III programme, the one baby Rehema is part of, will inject the last of 16,000 African children by February. If all goes according to plan, the vaccine could be licensed and rolled out as soon as 2015.

GSK's chief executive Andrew Witty says the trials are going well and he's looking forward to bringing the vaccine to market -- something he says won't make shareholders in his company any money, but will make them proud. "This is the first vaccine that has any effect at all against a parasite-borne infection. If we went back 20 or 25 years, people would have said it was impossible," he told Reuters.

An efficacy rate of around 50 percent means the vaccine will be no panacea. Scientists and health experts normally like a success rate of at least 80 percent before a vaccine is accepted for widespread use. There are concerns that the availability of shots could instil a false sense of protection, leading people to neglect other measures like mosquito nets.

But added to the already extensive range of nets, insecticides and anti-malarial drug treatments, the vaccine -- known as RTS,S or Mosquirix -- could prove a powerful new tool.

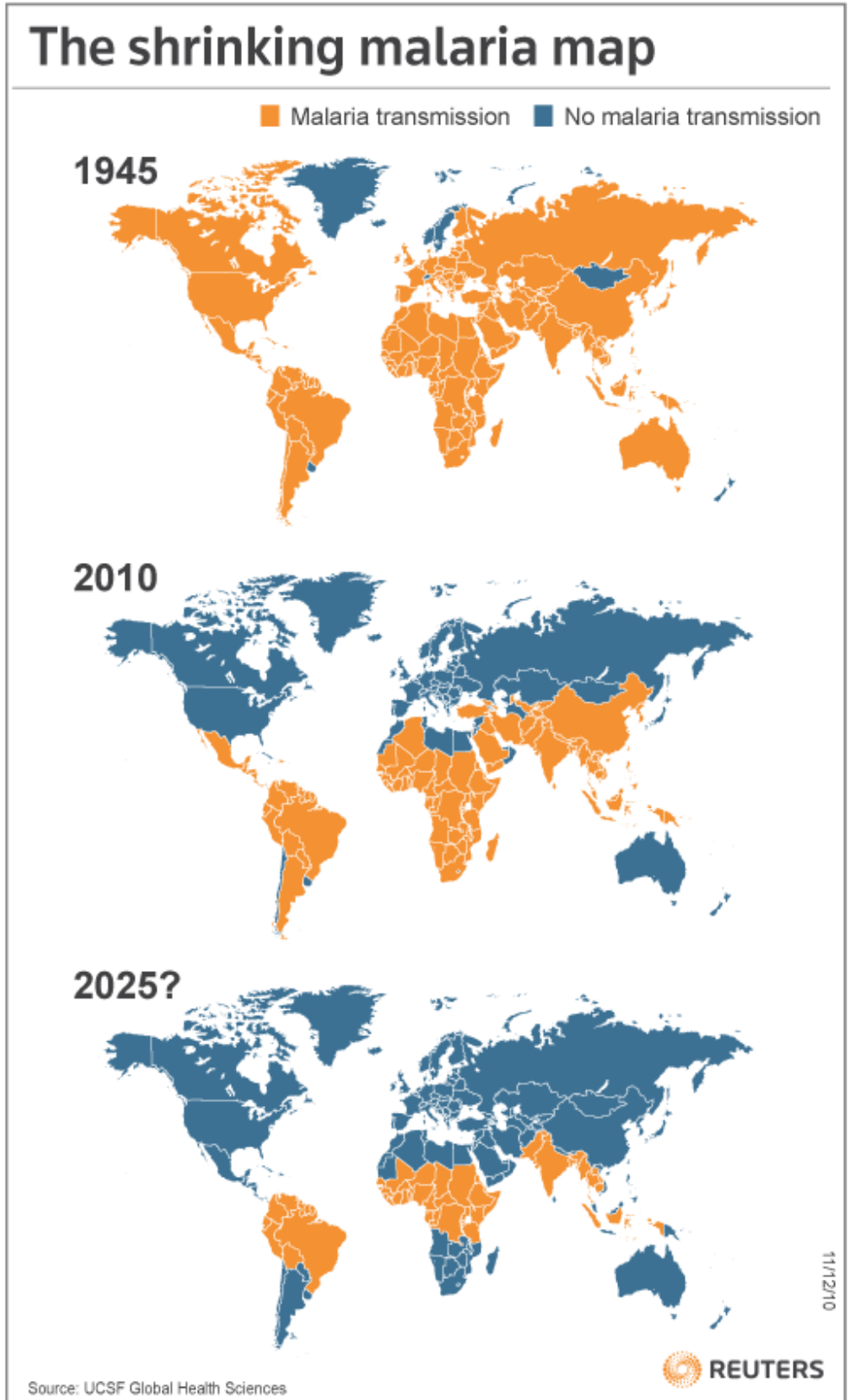
"There are not many scientists who have this incredible opportunity to work on a project and see the realisation of that work being transformed into a vaccine that could save hundreds of thousands of lives," says Cohen, who with his baggy cords, beard and mop of grey hair strikes a contrast with Witty's clean-cut corporate look. "My worst nightmare is that it sits on the shelf for years."

CONVINCING THE FUNDERS

WHETHER THAT HAPPENS WILL depend on securing funding and, crucially, how much the vaccine costs -- a figure health care experts and donors would love to know. GSK has promised it will be cheap, with a profit margin of 5 percent over the cost of making it to be reinvested in new vaccines for malaria and other neglected diseases.

"The last thing in the world we want to do is get to 2014 or 2015, have something that is the world's first vaccine to work against a parasite ... and then say I'm sorry we couldn't figure out a way to make it cheap enough for people in Africa to actually get it," says CEO Witty.

But the company has yet to give an exact figure to enable direct comparison with,



say, the cost of insecticide-treated mosquito nets -- currently available for around \$5 each. Witty points out that mosquito nets typically last around 20 washes, or three to four years, while a vaccine may last a lot

longer. "We want a safe and effective vaccine ... that complements, rather than replaces all the other things that are going on, and that will be priced in that kind of world."

The uncertainty on price is one of

the reasons for the debate about how, where and on what scale the new vaccine -- designed exclusively for children in Africa -- should be used. The cost-benefit analysis that donors must make when they work out where to spend their money is sure to be a lot more complex with this vaccine than with those targeting other diseases such as polio and smallpox. For those diseases, vaccines virtually guarantee (or guaranteed, in the case of smallpox, which was eradicated in 1979) people won't get sick. With malaria, the picture is more complex, given its transmission cycle via mosquitoes and the practical steps that can already be taken to reduce the risk of infection.

"WE ARE NOT GETTING THE TECHNOLOGIES WE KNOW WORK TO THE PEOPLE WHO NEED THEM."

"This is not the elimination or eradication vaccine," says David Brandling-Bennett, deputy director for malaria at the Bill & Melinda Gates Foundation, which said last January it planned to spend \$10 billion over the next decade researching new vaccines and bringing them to poor countries. "And obviously the situation with malaria is very different from the situation with smallpox which relied on a single tool -- a highly effective vaccine that provided solid protection to essentially everyone who had it. We don't have that yet for malaria, and we're under no illusion that we do."

Other vaccines in the pipeline are 10 years away or more. PATH Malaria Vaccine Initiative (MVI), a non-profit organisation based just outside Washington D.C. that has channelled more than \$200 million in grants from the Gates Foundation into the GSK vaccine (alongside more than \$300 million from the drugmaker itself), has a long-term goal of developing a vaccine that is at least 80 percent effective by 2025.

One candidate could be an amended version of the current GSK shot, which the drugmaker has started work on with Dutch biotech company Crucell (now the target of a \$2.3 billion takeover bid from Johnson & Johnson). This would use a common cold virus to "prime" the immune system to get a stronger response, but it is still a year or so



INTERVIEW: GlaxoSmithKline CEO Andrew Witty. Click the picture for video. **REUTERS/SIMON NEWMAN**

of preventing the mosquitoes that bite them from subsequently spreading the malaria parasite. Researchers at Johns Hopkins University believe they have found a way of doing this, and the good news is it could protect against both the type of malaria common in Africa, and the variant that is widespread in Asia. GSK's vaccine only works against the African form.

These are promising leads for the future, but some experts fear the race for smart technology may risk sidelining the effective tools that already exist. "We worry a lot about the science of this, but the reality is that every death from malaria today could be prevented, either by avoiding the malaria case in the first place or treatment at an early stage using existing tools, all costing less than a pint of beer," says Chris Whitty, who works at the London School of Hygiene and Tropical Medicine, advises the British government on malaria, and was one of those at Cohen's appearance in parliament. "The fact is our biggest problem with malaria at the moment is that we are not getting the technologies we know work and are already there to the people who need them."

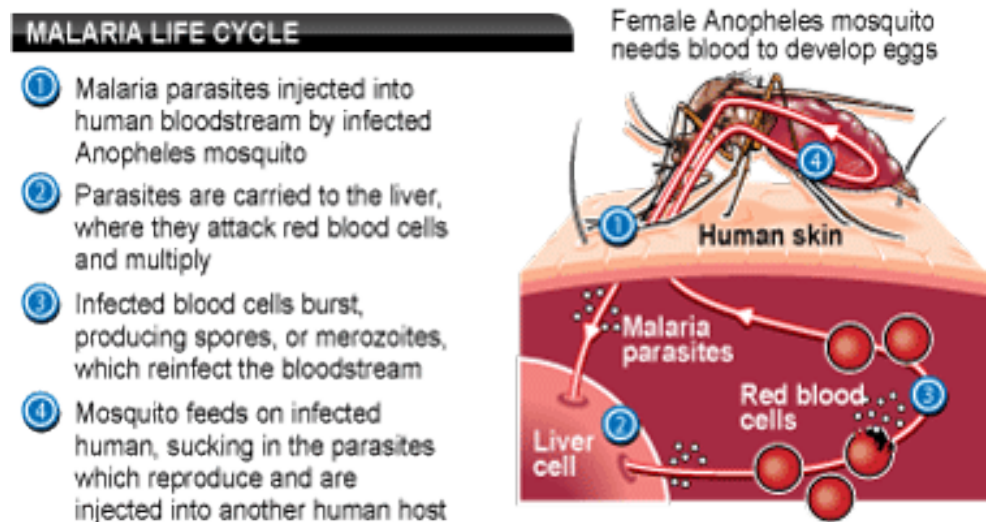
COST EFFECTIVE?

THE SNOWY STREETS OF Swiss ski resort Davos are a long way from the palm trees and mangrove-fringed creeks of Kilifi. But if a malaria vaccine does get into widespread use across Africa, it will in large part be thanks to a novel project to fund vaccines for poor countries

away from starting clinical trials. MVI has also just signed a deal with Merck & Co for a new vaccine project designed to stop the malaria parasite from entering the liver.

Experience shows it won't be easy. Sanaria, a start-up biotech company with funding from MVI, recently found its experimental vaccine protected only five out of 80 volunteers in its first clinical trial. The Maryland-based firm is not giving up but its disappointing results demonstrate the scale of the challenge.

Another, very different approach -- which at first sight looks off the wall -- is to try to vaccinate not humans but mosquitoes. Such a transmission-blocking vaccine would still be injected into people but with the aim

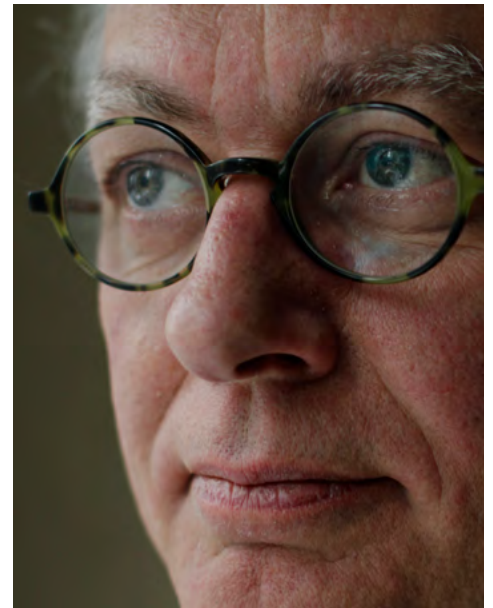


Source: Encyclopedia Britannica

Reuters graphic/Brice Hall



WEIGHING UP THE ODDS: Left, GSK scientist Joe Cohen. Right, PATH MVI's Christian Loucq. REUTERS/THIERRY ROGE, SIMON NEWMAN



"MY WORST NIGHTMARE IS IT SITS ON THE SHELF FOR YEARS."

that was launched 11 years ago at the World Economic Forum, the annual talkfest of the rich and powerful.

Back in January 2000, the inauguration of the Global Alliance for Vaccines and Immunization (GAVI) left many in Davos scratching their heads. The venture sounded worthy, but hardly set the world alight. Media covering Davos were more excited by the Internet stock bubble,

which would soon burst. A few months later, billionaire Bill Gates, who was just embarking on his transformation from software tycoon to philanthropist and who had pledged an initial \$750 million for GAVI, complained that their presentation in Davos was "one of the least inspirational, least informative panels I've seen".

A decade on, though, the alliance can claim remarkable success. It has paid

for the immunisation of 288 million children against diphtheria, tetanus, whooping cough, hepatitis B and Haemophilus influenzae type b (known as Hib), saving more than 5 million lives in the process.

If it wants to beat malaria, the GAVI Alliance will have to up its game even further. It is already \$3.7 billion short on donor money to fund its work through 2015, and that's before any new malaria vaccine.

FINANCIAL ENGINEERING

It's not only biologists, philanthropists and donor governments who are needed to make vaccine projects in poor countries work. Financial engineers -- the bogeymen of the recent crash -- also have a role.

A new kind of bond issue is one of the smart tools deployed to raise money for the GAVI Alliance, a project to bring vaccines to the developing world that was launched in January 2000 at the Davos World Economic Forum. Designed to roll forward future donor pledges into cash-in-hand today, the idea was pioneered in 2005 by Gordon Brown, then British finance minister.

The bonds have struck a chord with institutional investors who appreciate the steady returns and AAA rating of notes on which the World Bank acts as treasurer.

The inaugural \$1 billion bond from the International Finance Facility for Immunisation (IFFIm) was launched in 2006 to mature in November 2011. With a coupon of 5 percent, it's one of 20 such bonds quoted on Reuters and at the end of last week was

yielding around 1.4 percent. Most recently, IFFIm launched its first "kangaroo" bond in Australia, raising A\$400 million with a five-year issue in November.

Banker Gary Smith, who helped set up a sterling offering for HSBC, says the demand is driven by more than altruism.



IN THE LAB: Sanaria Inc., Rockville, Maryland, 2007. REUTERS/JIM YOUNG

"It's very popular in the institutional market, where people understand a good deal when they see it," he says. "It's not a donation; it's an investment. But the mechanics of the product mean the money gets to GAVI sooner and that means

immunisations can start sooner."

IFFIm bonds also slot neatly into ethical funds -- a growing business for the fund management industry -- as testified by holders like Standard Life's UK Ethical Corporate Bond Fund and CBF Church of England Funds.

Retail investors have got in on the act. The IFFIm offer from HSBC last year -- sold to members of the public as a tax-free individual savings account (ISA), as well as to institutions -- raised 266 million pounds, or five times more than expected. A separate retail offering in Japan last year raised \$429 million.

IFFIm's bonds are backed by the governments of Britain, France, Italy, Norway, Spain, the Netherlands, Sweden and South Africa, which have pledged a total of \$5.9 billion to fund vaccines in the developing world over 23 years. Their long-term pledges will be used to repay the bonds.

(Reporting by Ben Hirschler)

Nina Schwalbe, its managing director for policy and performance, says the alliance wants to be ready for the malaria vaccine and is already working on the sums. "We are very enthusiastic about working on this and we are beginning to factor it into our financial projections," she says. "But this vaccine cannot come at any price. In order to be taken on it has to be cost effective."

"WE'RE LOOKING FOR \$10 PER COURSE -- IDEALLY LESS."

What that means is clearly defined by the World Bank: interventions are considered cost-effective if they save a year of healthy life for less than a country's average gross domestic product per head. In simple cash terms that means the difference between a vaccine priced at \$5 and \$15 can be hugely significant, especially at the scale the GAVI Alliance works on: it aims to immunise more than 40 million children a year. "For any vaccine that's introduced, we're looking for less than \$10 per course – and ideally significantly less," Schwalbe told Reuters.

Christian Loucq, director of PATH MVI, says that even with a new vaccine in 2015, wiping out malaria is going to be extremely difficult to achieve, and very pricey.

THE 'E' WORD

IT WAS GATES AND his wife Melinda who on October 17, 2007 first dared to revive what in health circles is known as the "e-word" in relation to malaria. Seizing the moment at a meeting of malaria specialists in Seattle, Gates declared: "We will not stop working until malaria is eradicated." Melinda added that to aspire any lower would be "timid". The World Health Organisation went on to endorse the same ambitious goal.

Talk of eliminating malaria from endemic countries, or eradicating it from the face of the planet, had been considered dangerous and naïve ever since a previous project, the Global Malaria Eradication Programme, was abandoned in 1969. That campaign had succeeded in eliminating malaria from Europe, North America, the Caribbean and parts of Asia and South-Central America, but failed to achieve anything like global reach. What was the point of calling for something that was virtually impossible and almost



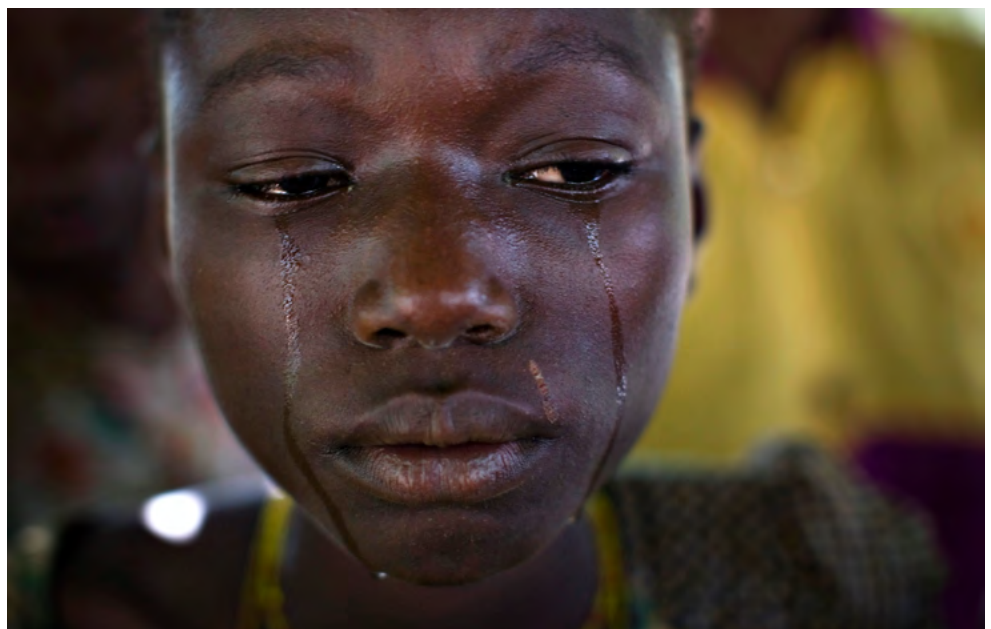
DEALING WITH IT: Above, a woman in Mumbai washes clothes as a health worker fumigates a residential area where cases of malaria have been reported, 2009. Below, war-displaced Mizelede mourns at the funeral of her grandfather, Leon Biliyo, who died from malaria in northeastern Congo in 2009. **REUTERS/ARKO DATTA, FINBARR O'REILLY**

prohibitively expensive?

Richard Feachem, a malaria specialist and director of the Global Health Group at the University of California, San Francisco (UCSF) said the Gates' speeches were a "shock to the system" for the malaria community. "For a couple of decades before that, the e-words were simply not used in polite company," he told a recent meeting of malaria specialists in London. "And then suddenly, here were the richest couple in the world with a foundation largely dedicated to global health saying let's go for eradication."

Three years on, it's too early to judge progress -- most experts say wiping out malaria could take another 50 years. But scrutinising the economic realities of eradicating versus controlling malaria has become a pressing question.

One person who has taken a hard look at the costs and benefits of eliminating malaria, versus controlling it at low levels, is the Clinton Health Access Initiative's Sabot. In a paper published in *The Lancet* in October, Sabot looked at four malaria-endemic countries -- China, Mauritius, Swaziland and



Tanzania – to assess the likelihood that, over 50 years, eliminating malaria would save more money than controlling it. He concluded that elimination had a low chance of saving costs in the first three. In Tanzania, he found only a moderate chance that elimination would be cost-saving.

Sabot and others say countries could focus instead on achieving “controlled low-endemic malaria”, where the disease still infects and might still kill, but no longer ranks as a major health concern. “We know that controlling malaria and bringing it from high levels down to negligible levels is a fantastic investment -- one of the best buys in global health,” he says.

Several malarial countries -- including some in Africa -- have already managed to fight the disease down to levels where death rates barely register. South Africa had 37 deaths from malaria in 2007; Swaziland had 14; Botswana only six. In comparison, South Africa had 350,000 AIDS-related deaths in the same year, while Swaziland had around 10,000 and Botswana had around 11,000.

Why pour so much cash into an ideal whose economic benefits can pale against

other health problems? That question is especially relevant when you understand it’s the jump from keeping malaria at low levels to eradicating it altogether that makes things really costly. Every single last case has to be tracked down and treated, thousands of blood tests conducted and analysed for infection; every border crossing and airport monitored to stop new cases coming in.

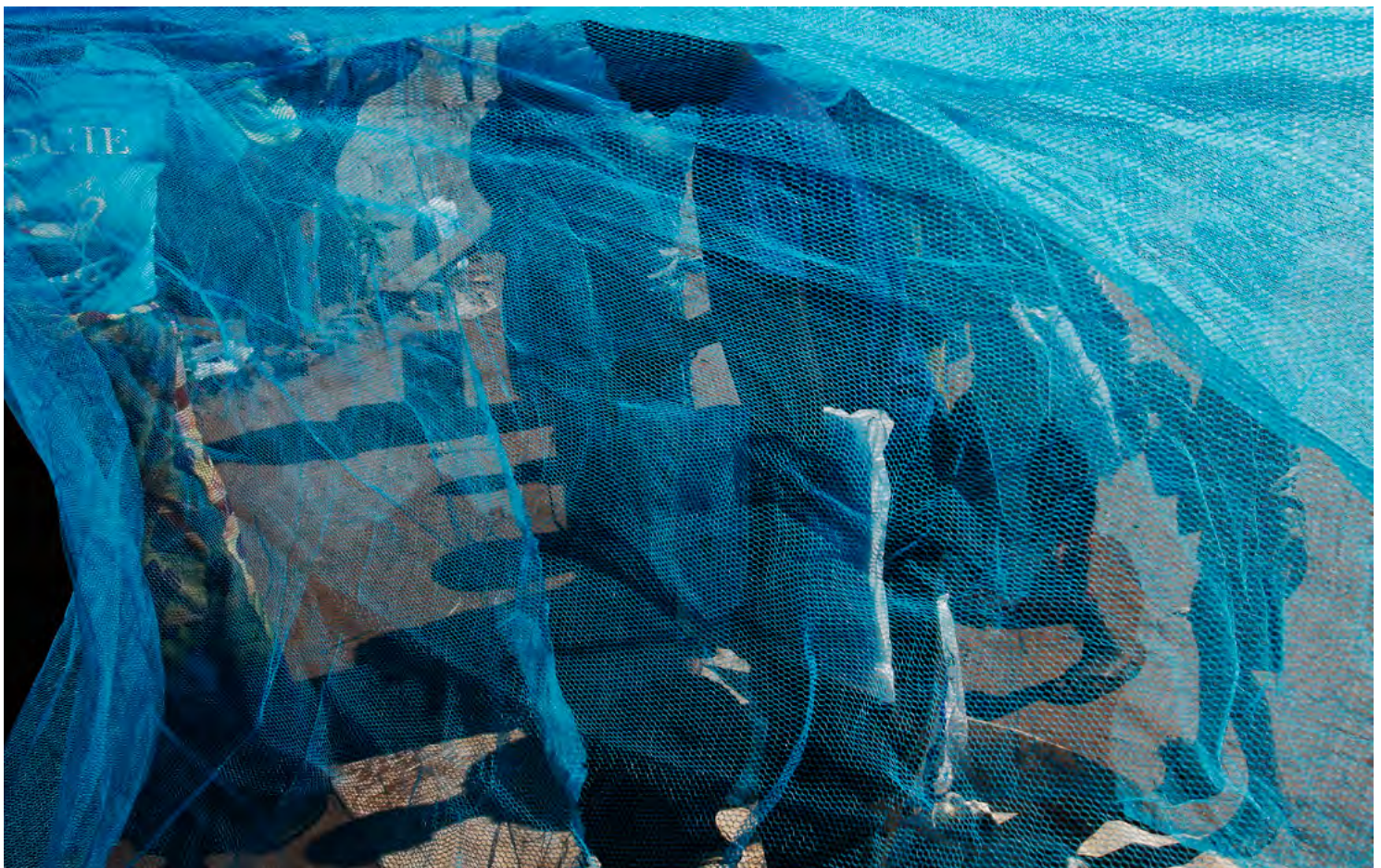
It is an issue that divides experts. MVI’s Loucq thinks it is a price worth paying and draws a comparison with smallpox. “We know that the first 50 percent is easy -- that’s the low-hanging fruit. The next 25 percent are very convenient and only a little bit more difficult to get. But the final 1 percent requires a lot of money and doesn’t look very cost effective,” he says. “For the detection of the last cases, when people were running all over the globe chasing those last few -- the costs of that were enormous -- but they still did it.”

Sabot says it’s at the point where malaria is barely a problem -- even if it remains -- that the economic questions get tougher. “How should the global community be spending its limited pot of resources in



SENSE OF PROTECTION: Above, a worker in the mosquito formulation and vialing room at Sanaria Inc., Rockville, Maryland, 2007. Below, Zambian villagers display a mosquito net offered by the Roll Back Malaria Zambezi Expedition in Matongo village, 2008. **REUTERS/JIM YOUNG, THIERRY ROGE**

malaria?” he asks. “It’s a very open question given this uncertainty on cost-benefit, whether those international institutions would want to invest in elimination as opposed to focusing their investments in control, where there is a very well-known and visible high rate of return.”



MALARIA-FREE TOURISM

OF COURSE THERE ARE reasons to get rid of malaria -- billions of them. In the first part of the 20th century, 178 countries had endemic malaria; now 99 do. Britain and the United States eradicated it in 1952, Australia in 1970. Morocco is the latest place to rid itself of the disease, declaring victory in 2005.

In a recent paper, the UCSF's Feachem identified 32 countries that have now controlled the disease to a point where they could move towards wiping it out. They are all on the fringes of the malaria map. "More than 2 billion people live in the 32 malaria-eliminating countries," he said. "The benefit to these individuals, their countries, their neighbouring countries and the world from continuing to shrink the malaria map is clearly large, even if we cannot fully quantify it or express it in terms of U.S. dollars."

Experts trying to do just that calculate the disease costs African healthcare systems around \$12 billion a year. When you add it all up, malaria lops an estimated 1.3 percent off annual economic growth in the worst-hit countries, which include the likes of Democratic Republic of Congo and Nigeria. It may not sound much but that's around half

the total rate of growth in gross domestic product that a typical industrialised country might expect outside recession.

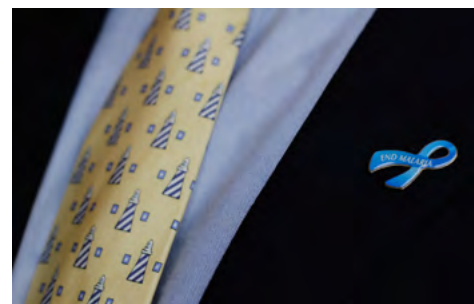
Research shows a firm link between reducing the disease and increasing economic output -- because workers are healthier and take less time off work. Unsurprisingly, children without malaria do better at school.

Though hard to measure, there are other ways cutting malaria is likely to help. Tourists may be more attracted to parts of Africa that are malaria-free, for instance -- a potential boon to places such as Kenya where tourism is one of the main foreign exchange earners. Foreign investors may also be more drawn to countries that have dealt with the problem.

THE SMELL OF WATER

FOR THE PEOPLE OF Kilifi, the debate is little more than a distraction from life's daily battles. Tourists bathe on the region's white sand beaches, but most residents struggle to make ends meet by selling charcoal or picking up casual labour.

"Growing up in an average family with many siblings in the house, we knew when the malaria season came and when one of us in the family had a bout of malaria, we knew it was a question of time before it would



BLUE RIBBON: An 'End Malaria' pin on Christian Loucq's lapel, 2010. REUTERS/SIMON NEWMAN

be the next and the next and the next," says Roma Chilengi, one of the doctors working on the vaccine trials in the district. "By the time it hits you, you have these terrible fevers, these headaches, and the mere smell of water makes you want to vomit."

Chilengi is excited about the prospect of the first malaria vaccine, but wary of hoping for too much after years of seeing other measures like mosquito nets, insecticides and anti-malarial drugs fail to end the disease. As for the price, there's little to dwell on. "All these things cost a lot of money," he says. "But this money is nothing compared to the burden that malaria hits us with."

(Additional reporting by Katy Migiro in Kilifi; Editing by Simon Robinson and Sara Ledwith)

COVER PHOTO:

Iren Salama's baby Pendo receives an injection as part of a malaria vaccine trial at a government clinic vaccine trial in Kilifi district, Kenya, November 2010. REUTERS/JOSEPH OKANGA

FOR MORE INFORMATION CONTACT:

SIMON ROBINSON,
ENTERPRISE EDITOR, EUROPE, MIDDLE EAST
AND AFRICA
+44 20 7542 5458
simon.robinson@thomsonreuters.com

SARA LEDWITH,
TOP NEWS TEAM
+44 7990 4560 467
sara.ledwith@thomsonreuters.com

KATE KELLAND
EMEA Health and Science Correspondent
kate.kelland@thomsonreuters.com

BEN HIRSCHLER
Senior Correspondent, Reuters News
ben.hirschler@thomsonreuters.com