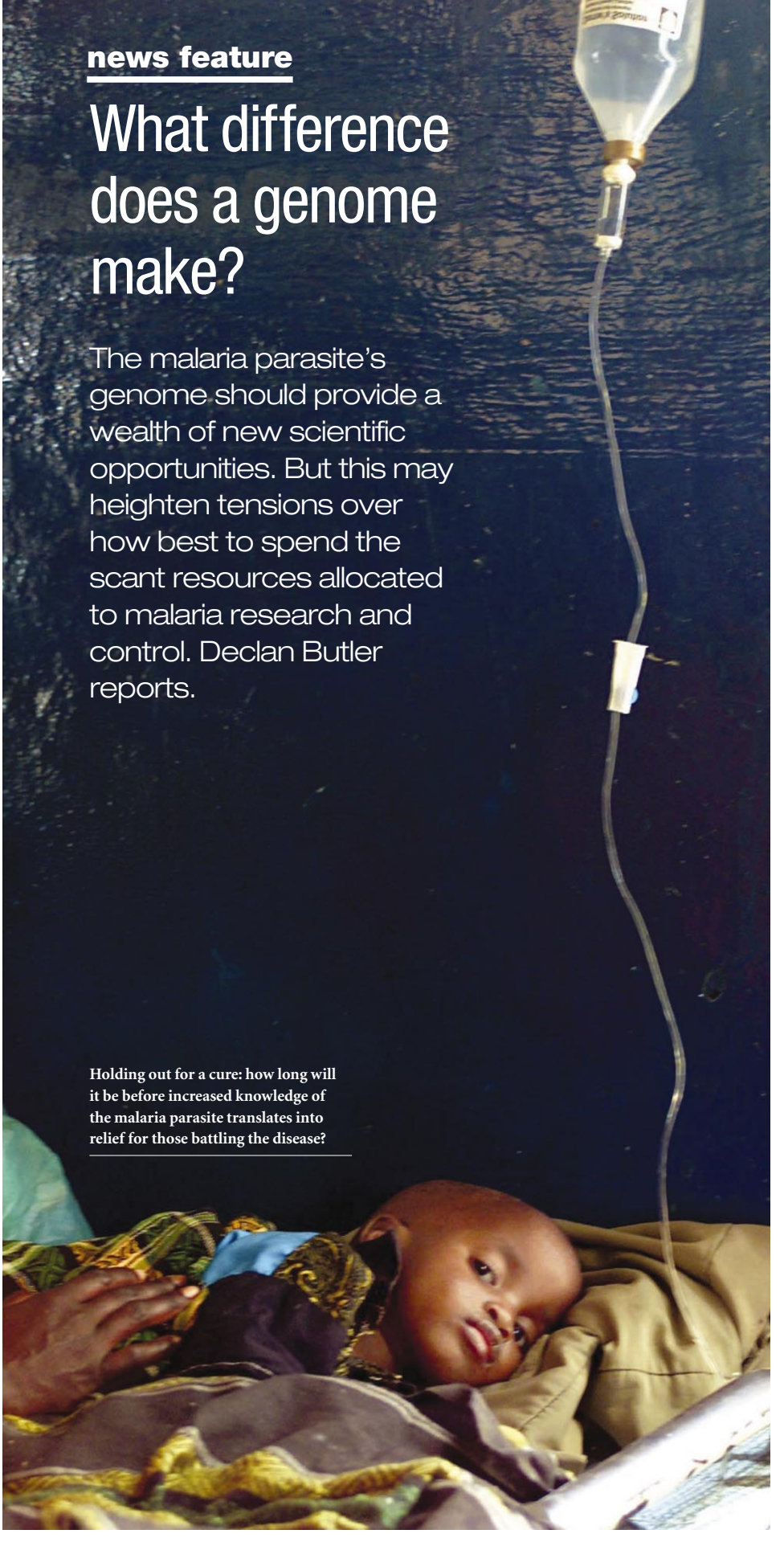
What difference does a genome make?

The malaria parasite's genome should provide a wealth of new scientific opportunities. But this may heighten tensions over how best to spend the scant resources allocated to malaria research and control. Declan Butler reports.



Holding out for a cure: how long will it be before increased knowledge of the malaria parasite translates into relief for those battling the disease?

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The yellow international vaccination card tucked inside my passport describes malaria as "a serious and sometimes fatal disease, endemic in many tropical and subtropical countries. You cannot be vaccinated against it, but you can protect against mosquito bites, and take antimalaria tablets regularly. If you get a fever within two years after your return, tell your doctor you have recently been in a malarious country."

Behind this bland warning lies a human catastrophe. Malaria kills more than a million people a year — or at least one person every 30 seconds — almost all of them in sub-Saharan Africa. Up to 500 million people suffer from the disease, with varying degrees of severity. Many are too poor to have access to protection and treatment, and existing drugs are rapidly losing their potency as the parasite evolves resistance to our limited pharmaceutical armoury.

In this week's *Nature*, an international team describes the complete genome sequence of *Plasmodium falciparum*, the deadliest malaria parasite[1]. But how will this milestone influence the battle to defeat this devastating disease? Certainly, it will rejuvenate our understanding of the parasite's biology and its interactions with its human host. It will also generate new approaches and targets for drug and vaccine discovery.

But unfortunately, the availability of the *P. falciparum* genome does not herald the parasite's impending doom. The biggest bottlenecks often lie downstream, in getting funds and industrial expertise to move promising drugs and vaccines from the lab to the market. And, as experience with AIDS has shown, economic forces and inadequate health infrastructure can prevent Africa's poorest from benefiting from effective new treatments.

At least the outlook has improved in the past few years, with a series of new initiatives being launched to tackle malaria. In 1997, research agencies, charities and aid donors met with scientists in Dakar, Senegal, to explore ways forward. This led to the creation of the international Multilateral Initiative on Malaria, which aims to train African scientists and bridge the divides between bench researchers and field workers, and between developed and developing-world scientists. In 1998, Gro Harlem Bruntland, director-general of the World Health Organization (WHO), added political momentum by launching Roll Back Malaria, a global push in research and control that aims to halve deaths from the disease by 2010. And in July last year, the G8 leading industrialized nations pledged US$1.3 billion to the Global Fund to Fight AIDS, Tuberculosis and Malaria.

But budgets for malaria research and control still fall massively short of what is required, making Bruntland's goal of rolling back malaria a distant dream. The world currently spends around $200 million each year

on the disease, a figure that should be boosted this year by a further $100 million for control from the G8-backed global fund. But this is a mere fraction of the sums made available for bioterrorism research in the wake of last year's anthrax attacks, and will do little to lessen the human misery caused by malaria.

Against this cash-strapped background, the flood of information that will flow from the *P. falciparum* genome is likely to exacerbate tensions between those who want to invest in developing new drugs and vaccines, and others who believe that the money would be better spent on improving existing countermeasures, such as insecticide-impregnated bednets. "Many would argue that children in Africa are dying for want of access to simple existing methods," says David Heymann, the WHO's executive director for communicable diseases. "Others would argue that more effective tools will serve the poor better."

Time trials

It's a delicate balance to strike, and one that must take into account the timescale over which information from genomics and other high-throughput biological analyses are likely to yield practical tools for malaria control. The *P. falciparum* genome should rapidly start churning out new drug targets that may move speedily into clinical trials. But old hands of malaria research, such as Louis Miller of the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, feel that it will take longer — perhaps two decades — to convert genomic information into effective vaccines. More ambitious schemes, such as releasing transgenic mosquitoes that are unable to transmit malaria (see page 429), lie further away still.

New targets for antimalarial drugs are badly needed. For decades, doctors in developing countries have depended on chloroquine or a combination of two drugs known as Fansidar to treat malaria. Both chloroquine and Fansidar are reasonably cheap, and were very effective. But they are now useless across large swathes of Africa because the parasite has grown resistant to them.

Of the 1,223 new drugs registered between 1975 and 1996, only three were antimalarials[2]. And the handful of new antimalarial drugs currently being developed come from just three families of compounds — quinolines, antifolates and artemesinins — the first two of which are already succumbing to resistance.

The *P. falciparum* genome should yield new drug families. Putative enzymes, which are generally the most effective targets for drug development, can be identified from sequence data. And because the *P. falciparum* genome project has made its data freely available on the Internet, the opportunities can already be glimpsed. In 1999, German researchers identified an enzyme in a biochemical pathway for fatty-acid synthesis in the parasite[3], for which an inhibitory drug, fosmidomycin, had already been developed for an entirely different purpose — treating recurrent urinary infections. It is now in late-stage clinical trials as an antimalarial.

The outlook for vaccines is less certain, and acute funding shortages leave researchers divided over the importance of genomics in identifying parasite molecular signatures, or antigens, that the human immune system can be made to attack. Some researchers complain that they can't test all the antigens that have already been identified. "If there were an extra $100 million to spend on malaria-vaccine research, I would allocate very little of it to exploring the parasite genome," says Adrian Hill of the University of Oxford, UK. He argues that the main problem is finding ways to make the human immune system respond more strongly to existing *P. falciparum* antigens. Another researcher puts it more bluntly: "If more money were spent on developing existing vaccine candidates rather than hyping the genome, I think lives would be saved sooner."

But Henk Stunnenberg of the University of Nijmegen in the Netherlands disagrees. He argues that vaccine developers need to be more ruthless in weeding out candidate vaccines at earlier stages, while exploring the wider range of antigens that the parasite's genome will provide. "If one is honest, a substantial number of promising candidates fell through in preclinical and clinical trials, but are still sold as steps forward," Stunnenberg claims. "Having more targets raises justified hope that we will succeed in developing effective vaccines."

Others argue that the genome will allow 'rational' vaccine design based on antigens' function and the way in which they stimulate the immune system. But Louis Schofield, a malaria researcher at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, warns against excessive optimism. "A plethora of new vaccine candidates will be useless without a thorough understanding of total parasite biology," he says. That will mean exploring both the *P. falciparum* and human genomes to gain insight into the interaction between host and parasite. It may also require require malaria research labs to retool and restaff to emphasize bioinformatics, proteomics and large-scale studies of protein–protein interactions — not least because *P. falciparum* undergoes profound changes in patterns of protein production at different stages of its life cycle.

While bench researchers debate how the *P. falciparum* genome should influence their priorities, other initiatives are trying to address the bottleneck that lies downstream: the difficulty of pushing to market promising drug and vaccine candidates that would be seen as commercial liabilities under the pharmaceutical industry's usual rules — where profits come from drugs that can be mass-marketed at developed-world prices.

The Geneva-based Medicines for Malaria Venture (MMV), for instance, was launched in 1998 to kickstart discovery and development of new families of antimalarial drugs. Its goal is to raise $30 million annually from public and private donors to register a new, affordable antimalarial every five years. Drug companies have provided project-management expertise and technologies such as combinatorial chemistry and high-throughput screening. With seven drug-discovery and five development projects under way, the MMV now has the largest antimalarial drug pipeline since the Second World War, says its chief executive officer, Christopher Hentschel. So far, however, the scheme has attracted funds of just $15 million per year — a fraction of what is needed — with $5 million coming from one individual, Microsoft chairman Bill Gates.

Gates' philanthropy is also underwriting the Malaria Vaccine Initiative, based in Rockville, Maryland, which aims to do for vaccines what the MMV is doing for drugs. It was launched in 1999 and is supported by $50 million from the Bill and Melinda Gates Foundation.

Setting priorities

Unfortunately, drug- and vaccine-development efforts must compete for limited funds with fundamental research into the malaria parasite and the costs of programmes to control malaria in the field. And given the enormity of the current death toll, many public-health experts argue that the latter must be given high priority (see Correspondence, page 431).

Tikki Pang, the WHO's director of research policy and cooperation, argues that this contentious debate must be informed by something that is currently lacking: rigorous, independent cost–benefit analyses of the value of expanding and improving existing countermeasures, such as bednets and education, compared with investing for the future in genomics-based research to produce new drugs and vaccines.

Almost everyone can agree, however, that it would be desirable to help the countries most severely afflicted by malaria to commit the resources needed to combat the disease, and to train their researchers to get involved. Sadly, much remains to be done. The Multilateral Initiative on Malaria has made progress, but many African researchers argue that other developed-world research groups and funders need to rethink their priorities. Kevin Marsh, director of the Kenya Medical Research Institute–Wellcome Trust unit in Kilifi, on the Kenyan coast, argues that donors have "massively underestimated" the needs, and too often provide short-term funding with little strategic vision. This has created "a group of high-level research assistants, but not international-calibre scientists", he says.

Genomics is sometimes portrayed as a

great leveller, allowing any scientist with Internet access to query sequence databases and make discoveries. But African scientists complain that so far they have been sidelined. "First-world scientists pursuing genomic research are generally not working in collaboration with endemic-area scientists and local institutions," agrees Gerald Keusch, director of the US National Institutes of Health's Fogarty International Center in Bethesda, Maryland. "If the promise of the parasite genomes is to be realized, there needs to be a greater effort to develop trusting, transparent and collaborative relationships with institutions in the countries where the fruits of malaria and mosquito genome research will be used."

Inclusive effort?

Winston Hide, director of the South African National Bioinformatics Institute in Cape Town, is annoyed that efforts to sequence the genomes of *P. falciparum* and its mosquito vector, *Anopheles gambiae*[4], did not include developing-country groups. Although Hide accepts that most African labs are not equipped to undertake the sequencing itself, he says they could have been involved in the analysis, which would also have given them early access to unpublished information.

Malcolm Gardner, lead author of the *P. falciparum* genome paper, says that the consortium has gone out of its way to put preliminary sequence data on the Internet. The *Plasmodium* Genome Database has also been made available on CD-ROM to take into account poor Internet access in developing countries, he adds.

But there are precedents for using genome projects to build scientific infrastructure in a developing country — albeit one richer than those in sub-Saharan Africa. In July 2000, some 30 labs in the Brazilian state of São Paulo published the first complete genome of a plant pathogen, the bacterium *Xylella fastidiosa*, which causes disease in orange trees[5]. And with the genomes of *P. falciparum* and other tropical parasites now becoming available, the South African government has pledged US$40 million over ten years to create a national bioinformatics network centred on Hide's institute, which he hopes will become a hub for the whole of Africa.

Disappointment over the involvement of African scientists in malaria research is nothing, however, compared with the despair with which public-health experts view the disparity between the demand for malaria control in Africa and the supply of resources and trained staff. The WHO Commission on Macroeconomics and Health, an expert panel set up by Bruntland that recently reported on global health needs[6], argued that, to control malaria effectively, funding for its control needs to rise to $2.5 billion annually by 2007, and to $3.1 billion by 2015. At present, only a handful of sub-Saharan African countries have been able to raise their spending on malaria control to the level needed even to meet the more modest goals of Roll Back Malaria.

"Control will not make much progress unless the international community is willing to tackle the gross underfunding and major problems of health-service infrastructure in Africa," concludes Anne Mills, a health economist at the London School of Hygiene and Tropical Medicine and a member of the WHO Commission on Macroeconomics and Health. "Individual disease initiatives can only go so far when basic health infrastructure is weak or non-existent."

Mills' message applies across the entire spectrum of malaria research and control. While biomedical scientists and public-health experts argue over the relative merits of investing in genomics, drug and vaccine development, or the application of existing control measures, what's really needed is more money across the board.

With the resources currently available, say health economists, talking about defeating malaria is like promising to build a $100-million skyscraper with just $1 million in the bank. The stark truth is: if we don't bankroll the effort, we won't roll back malaria. ■

Declan Butler is *Nature*'s European correspondent.

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Multilateral Initiative on Malaria
http://mim.nih.gov
Roll Back Malaria
www.rbm.who.int
Global Fund to Fight AIDS, Tuberculosis and Malaria
www.globalfundatm.org
Medicines for Malaria Venture
www.mmv.org
Malaria Vaccine Initiative
www.malariavaccine.org

WHO/TDR/CRUMP

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Despite the use of insecticidal bednets (top), drug programmes (middle) and pesticides (above), many Africans remain at risk from malaria.

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