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The fight against malaria continues

Eliminating bad air

Malaria is a 'disease of poverty', and is spreading as the parasite's resistance to cheap medicines grows. There are hopes that public–private partnerships will help in the development and testing of new drugs, diagnostic tests and vaccines. But the most vulnerable groups, including pregnant women and children, must be involved in clinical trials.

By **Marion de Boo**

A generation ago hopes were high that malaria would soon be eradicated. But in Africa the disease has continued to spread as the malaria parasite has developed resistance to the most commonly used antimalarial drugs, and mosquitoes have became resilient to insecticides. In many countries, economic upheavals, armed conflicts and complex emergencies have also led to the breakdown of malaria control programmes and the collapse of primary health services.

Each year, malaria kills more than a million people in Africa, most of them children under five years of age. Health experts say that malaria is the world's leading cause of child mortality, killing one child every 30 seconds. Other vulnerable groups include pregnant women, travellers and HIV-infected people. Worldwide, over 3 billion people live under the threat of malaria. About 90% of acute malaria cases occur in sub-Saharan Africa. The World Bank estimates that malaria costs the continent more than US$12 billion each year in healthcare expenditures and lost productivity. Stopping malaria would provide an enormous boost to the economies and the development prospects of many African countries.

Bad air

For centuries it was believed that malaria – from the Italian *mala aria*, 'bad air' – was caused by evil vapours from marshes. Not until 1898 was it proven that the disease is caused by a parasite, *Plasmodium falciparum*, transmitted by female mosquito. In Africa, the mosquito *Anopheles gambiae* is an important vector of the disease. The *Plasmodium* parasites develop in the stomach of the mosquito and are transmitted to humans during a blood meal. The parasites are transported via the bloodstream to the victim's liver, where they invade liver cells and multiply. After 9–16 days, the parasites return to the bloodstream and enter the red blood cells where they reproduce again, destroying the cells. In a short time, the patient develops a fever. Other symptoms include weakness, muscle pain, headache, shivering and vomiting. If left untreated, malaria can lead to severe anaemia, coma and death.

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The battle against malaria is being waged on several fronts: preventive medicines, diagnostic testing and vaccines. The research and the necessary clinical trials are very expensive, however, and the pharmaceutical industry is willing to provide only part of the funding. A number of new initiatives, involving partnerships between the public and private sectors, are offering fresh hope that that this devastating disease will one day be eliminated.

Growing resistance

'Malaria is a disease of poverty', says molecular geneticist Charles Mgone, director of the European and Developing Countries Clinical Trials Partnership (EDCTP). 'Many poor countries can not afford to put in place universal diagnostic tests, particularly in rural areas, and patients may not be able to afford expensive medicines. The pharmaceutical industry is reluctant to invest in this type of research, since it's a very expensive venture. So for the poor it's a double whammy'.

Malaria is a curable disease. However, many of the traditional, affordable antimalarial drugs, including chloroquine and sulfadoxine–pyrimethamine (SP or Fansidar), have lost their clinical effectiveness as the parasite's resistance has grown. The use of other drugs for malaria treatment and prevention is dictated by the level of drug resistance in each country where the disease is endemic.

The most promising new treatments are based on artemisinin, a compound extracted from the shrub *Artemisia annua*. In China, artemisinin (*qinghaosu*) has been used in traditional medicine to treat fever for over 2000 years. Since 2001, the WHO has recommended artemisinin-based combination therapies (ACTs) for uncomplicated malaria. ACTs use a combination of antimalarials. While numerous countries, including most African nations, have changed their official malaria treatment policies, cost remains a major barrier to rolling out ACTs at country level. Because ACTs cost up to 20 times as much as older medications, they remain unaffordable in many malaria-endemic countries.

Safe, affordable and accessible

Renewed efforts are now being made to tackle this lack of access to affordable antimalarial drugs through public–private partnerships. Many new malaria drugs are being developed and tested thanks to a combination of public and private funding. Philanthropic organizations, such as the Bill and Melinda Gates Foundation,

NGOs and development agencies have joined forces with large pharmaceutical companies.

One important initiative is Medicines for Malaria Venture (MMV), a non-profit organization based in Geneva. After just seven years, MMV is managing the largest-ever portfolio of antimalarial drug research, with over 25 projects in different stages of R&D. MMV hopes to register at least one new antimalarial before 2010, and to maintain a continuous supply of new drugs in the pipeline. Another is the Drugs for Neglected Diseases Initiative (DNDi), which has developed two new antimalarial combinations in collaboration with industry partners.

Unfortunately, no good treatments are available yet for children with severe or cerebral malaria, according to Mgone. 'In Africa, where chemotherapy remains the main form of treatment, intravenous quinine is still used to treat children, even though the drug is poorly tolerated and can have a number of toxic side-effects. Some Southeast Asian countries prefer to use artemisinin-based treatments'.

For adults, the WHO now recommends an intravenous artemisinin-based drug, artesunate, for the treatment of severe malaria in 'low-transmission' areas where malaria is present but not

Anopheles gambiae: the face of the enemy

widespread. However, more research is needed to determine its efficacy in children in high-transmission regions in Africa. That's why a new €5.3 million trial, funded by EDCTP and sponsored by MMV, has recently been launched in Gabon and Malawi. The trial will evaluate the efficacy of two intravenous artesunate dosing regimens for children with severe malaria, in the hope of reducing the number of injections required from five to just three per child.

Malaria in pregnancy

Apart from children, pregnant women are the other main risk group that deserves special attention. 'Pregnant women are particularly vulnerable', says Feiko ter Kuile of the Liverpool School of Tropical Medicine in the UK. 'Each year, more than 30 million women in Africa become pregnant in malaria-endemic areas. African women have developed significant immunity by the time they become pregnant for the first time. That's why most malaria infections remain without symptoms and rarely result in a fever. Because they don't feel ill, they don't seek treatment, so that the infection remains undetected and untreated. These 'silent' infections are very harmful to the developing foetus'.

Ideally, every pregnant woman should receive an insecticide-treated bednet and at least two treatment doses of an effective antimalarial drug, such as sulfadoxine-pyrimethamine (SP). This combination of interventions has been shown to be very effective. According to a review in a special issue of *The Lancet Infectious Diseases* published in February 2007, successful prevention of malaria in pregnancy by drugs and insecticide-treated bednets reduces the risk of severe maternal anaemia by 38%, low birthweight by 43%, and perinatal mortality by 27% among women in their first and second pregnancies.

'Unfortunately, SP resistance is now spreading all over Africa, making the search for safe and effective alternative antimalarial drugs a global research priority', says ter Kuile. 'The available arsenal of drugs for both treatment and prevention of malaria in pregnancy is extremely limited and resistance to these drugs is developing rapidly. While overall malaria drug development has advanced considerably over the past five years, resulting in significant improvements in the treatment options for children, pregnant women have lagged behind because of their systematic exclusion from regulatory trials. There is hope, however, as a series of studies in Southeast Asia suggest that several of the newly developed candidates for children are also very effective and appear to be safe in pregnant women'.

Knowledge of how to use these drugs safely during pregnancy is still lacking, however. To rectify this, a group of experts from 25 research institutions, including 12 in Africa, decided to create the Malaria in Pregnancy (MiP) Consortium. Their aim is to ensure that the most promising of these new candidates are studied as speedily and effectively as possible using standardized and systematic approaches. These multi-centre approaches are commonly used in the developed world but have not yet been widely applied in Africa, according to ter Kuile. 'Typically, it took over 10 years to evaluate promising new interventions such as bednets or intermittent preventive treatment with SP for malaria in pregnancy, resulting in significant delays in their implementation'. The MiP Consortium hopes to cut this timeline in half within the next five years. Malaria in Pregnancy is funded by the Bill and Melinda Gates Foundation and is seeking additional funding from EDCTP and other major donors.

Diagnostics

In any effort to manage malaria, prompt and accurate diagnosis and effective treatment are essential. The clinical diagnosis of malaria is not always very easy, however, as the many of the initial symptoms are similar to those of other diseases, like the flu. 'In many places, anyone with a high fever is considered to be a case of malaria', Mgone says. 'Indiscriminate use of antimalarial drugs for treating any fever has led to an increase in drug resistance. That's why priority is now being given to the development of new, inexpensive and easy-to-use diagnostic tests that can help ensure that artemisinin-based combination therapies are used only when really necessary, that is, for true malarial fever'.

Mgone's view is supported by Pètra Mens, a researcher at the Royal Tropical Institute (KIT), Amsterdam, who recently completed a comparative clinical diagnostic study in Kenya and >

Tanzania, in collaboration with Kenya Medical Research Institute in Nairobi and the Aga Khan Hospital in Dar es Salaam. Blood samples were collected from 338 children suspected of having uncomplicated malaria in health clinics in the two countries. The study found that diagnoses of malaria based solely on clinical signs can lead to overdiagnosis. Clearly, laboratory confirmation is essential.

Traditionally, malaria is detected by examining blood under the microscope for presence of the very small malaria parasites. This can be labour-intensive and time-consuming, and many remote villages may not have good microscopy facilities or anyone trained to use them. When poorly performed, microscopy is an unreliable technique and a substantial number of patients with low numbers of parasites in their blood may be missed. The KIT is playing a leading role in the development of alternative, so-called rapid diagnostic tests (RDTs) that can demonstrate the presence of malaria parasites within minutes. As yet, however, these tests can continue to give positive results for some time after successful treatment has been completed, and they may also fail to detect low numbers of parasites. While there is much room for improvement, KIT parasitologist Henk Schallig believes that RDTs 'have the potential to circumvent some of the drawbacks of standard microscopy. Together with the Foundation for Innovative New Diagnostics (FIND), a product development partnership, we have started a research programme to develop and improve these tests'.

Vaccine development

Probably the best solution to control malaria would be a good vaccine that offers protection against the multiple forms of the malaria parasite. At present, several prototype vaccines are being tested. 'However, this has proven more complex and is taking longer than expected', says Chris Janse of the Centre for Infectious Diseases at Leiden University Medical Centre. 'Ever since the early 1980s, when the first genes of malaria parasites were cloned, scientists have been announcing that an effective vaccine would become available within the next 5–10 years, but this has never happened. We don't expect to find an effective vaccine, giving long-lasting protection to 80–100% of the population, any time soon'.

Vaccines produced by recombinant technology or peptide synthesis have not worked very well so far. Different parasite-specific features and characteristics of the interactions between the human immune system and the parasites, might explain the difficulties in developing effective intervention strategies. The completion of the *Plasmodium falciparum* genome sequence in late 2002 was an enormous step forward in malaria research, allowing the search to begin in earnest for new drugs and vaccines to combat the disease. The new genomic data is proving invaluable in increasing our understanding of the parasite and its interaction with mosquitoes and humans.

Why is it so complicated to develop a good vaccine? One reason, says Janse, is that 'humans don't easily develop an effective immune response against the malaria parasite. And relatively little is known about how to boost the right immune response. Besides, the malaria parasite spends most of its life cycle well hidden inside liver cells or red blood cells. In the meantime, it keeps changing its identity. The proteins on the outside of its cell membrane are changing continuously, in order to mislead the human immune system. That makes it even harder to choose the right proteins to make an effective vaccine'.

Charles Mgone agrees that there is still a long way to go. 'The most promising candidate vaccine is unlikely to be released before the year 2015'. Developed by GlaxoSmithKline, the vaccine is now being tested in phase III trials in various countries in Africa. 'It won't be a magic bullet', Mgone says, 'but with malaria, any protection is good'.

The malaria vaccine testing centre at Radboud University Nijmegen Medical Centre is unique in Europe. Recent studies by researcher Teun Bousema, who is presently working in Tanzania, have shown that far more people than previously thought can suffer from sub-clinical malaria without showing any symptoms. These people are carrying the malaria parasites, which may be transmitted by mosquitoes to new victims. Bousema recommends the development of transmission blocking vaccines in order to stop the malaria parasites being passed on to other people.

Charles Mgone acknowledges that the fight will be a long one, but he remains optimistic. 'Africa is a wide and a poor continent. But in the end we will win. One day, malaria will be beaten'. ■

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