An attack on all fronts

To win the fight against malaria we will need to scale up existing programmes and develop new weapons, say Richard Klausner and Pedro Alonso.

Pregnant women are particularly at risk from malaria.

The global malaria crisis is desperate and worsening, particularly in sub-Saharan Africa. Unless we find ways to control this devastating disease, efforts to reduce poverty, minimize childhood mortality, increase security and strengthen the most vulnerable societies will fail.

During the mid-twentieth century, the international community made decisive progress in its efforts to eradicate malaria from large swathes of the planet, but this momentum slowed during the 1960s with the realization that the available tools — indoor residual spraying with the insecticide DDT, followed by drug chemoprophylaxis — could not eradicate malaria in the regions with the highest rates of infection.

Only recently has there been a renewed political determination to tackle malaria, with initiatives and institutions being established to translate this commitment into action. These include the Roll Back Malaria initiative, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the Malaria Vaccines Initiative. But these efforts are too fragmented and

short-term to succeed. The existing tools and strategies, although reasonably effective, can be greatly improved — if this doesn't happen, then they will get nowhere near eradicating the disease. The resources, policies and capacities to deliver them to those most in need also fall far short of what is required.

What is needed is determined action to deploy existing tools on a vastly greater scale, while investing in their improvement and the creation of new ones. Research must focus on tools that are suited to constraints in the field. Vaccines, for example, are well suited to resource-poor settings, and insecticide-treated bednets, particularly those with long-acting insecticides, are suitable for rural Africa. But the constraints are legion: lack of funds to purchase expensive drugs, the logistical complexity of sustaining labour-intensive indoor residual spraying of insecticides and, most importantly, the weakness of healthcare services in most endemic areas. Strive as we might to eliminate these constraints, the reality is that they are not going to disappear any time soon.

The renewed political commitment to tackle malaria is welcome, but the world now needs to go beyond 'calls to action' and declarations of spectacular targets for reducing the malaria burden — targets that will never be attained if we carry on with business as usual.

Three-pronged attack

Three major tools are currently used to combat malaria: controlling mosquitoes, reducing human–vector contact, and preventing and treating disease with drugs.

Vector control has saved millions of lives worldwide, through indoor residual spraying, environmental management to eliminate breeding sites, and use of mosquito larvicides. Spraying continues to play a major role in malaria control in much of Latin America and in parts of Asia. But its cost, logistical complexity and moderate efficacy make it poorly suited for controlling malaria in rural areas of sub-Saharan Africa.

Reduction of human–vector contact through insecticide-treated bednets is better

suited for malaria control in Africa, enjoys greater community acceptance and is as efficacious as indoor residual spraying. Randomized trials of the nets in diverse settings have established their effectiveness at cutting malaria-related morbidity and mortality. For example, in parts of Africa where malaria is endemic, bednets reduce mortality from all causes among children under five by one-fifth for sustained periods¹. But although they are inexpensive and effective, fewer than 2% of Africans sleep under them². Massive campaigns to increase their use are required as a matter of urgency.

The cornerstone of malaria control worldwide remains effective and inexpensive drugs (see 'Between hope and a hard place', page 926). But resistance of the *Plasmodium* parasite to the most popular drug in Africa, chloroquine, is now widespread and few alternatives have been licensed over the past 20 years, or are in development.

Fresh strategies

Artemisinin derivatives offer great hope for reducing malaria morbidity and transmission. They can be particularly effective in combination with other antimalarials (artemisinin-based combined therapies or ACTs), which should also delay the development of resistance³. But their use has been limited by poor supply of high-quality artemisinin derivatives and by their high costs. These issues have led to vigorous debate about whether ACTs should become standard treatment for malaria in endemic countries. Even if supplies were unlimited, most African countries do not have the financial resources to purchase ACTs^{4,5}.

Besides treatment, malaria drugs also have the potential to prevent the disease and control its spread. Prophylaxis is highly effective for travellers to Africa, but in its present form has limited use among the populations of sub-Saharan Africa. Instead, new strategies for using antimalarials are being tested. For example, intermittent preventive treatment in infants (IPTi) uses existing drugs to protect infants from the worst effects of the disease. Infants receive an antimalarial three times during the first year of life at the time of routine immunization, whether or not they have malaria.

Two studies in Tanzania have shown that IPTi reduces malaria and anaemia in the first year of life by up to 60% (ref. 6). IPTi has the potential to become a major tool for malaria

Preventative measures: spraying with residual insecticides (top) can help to cut the number of hospital admissions with malaria.

control in Africa because it can be delivered through the Expanded Programme on Immunization (EPI), one of the best-functioning systems of regular health contact with young children in Africa.

The IPTi Consortium is an alliance of the World Health Organization (WHO), the UN Children's Fund (UNICEF) and leading research centres in Africa, Europe and the United States, with some US\$28 million of funding provided by the Bill & Melinda Gates Foundation. It has developed a research and implementation agenda that will rapidly resolve outstanding scientific questions about IPTi and move the intervention into policy and practice.

Long-term programme

Operating in parallel with this strategy is intermittent preventive treatment for pregnant women (IPTp). This approach has shown promise when the drugs are administered during antenatal clinic visits⁷, and although efficacy data are limited, it is now a recommended core intervention for improving malaria control during pregnancy. Additional research is needed to assess the safety and efficacy of different

malaria drugs during pregnancy and to evaluate the impact of combined interventions, such as insecticide-treated bednets and IPTp.

Even with plans to improve the use of existing tools, new drugs are urgently needed (see 'Winning the drugs war', page 942), as are financing and distribution mechanisms for their rapid introduction. As with other infectious diseases, prevention must be the mainstay of long-term efforts to control malaria, including the development and introduction of novel forms of environmental vector control (see 'Taking aim at mosquitoes', page 936) and an effective preventive vaccine (see 'Save the children', page 940).

Since the 1930s, it has been understood that "malaria control should not be a campaign, it should be a policy, a long-term programme"⁸. Yet the past four decades have seen few attempts to evaluate the impact of sustained malaria-control programmes that involve scaling up a combination of strategies over a large region, including appropriate treatment, prevention and vector control.

Now is the time to launch and evaluate complementary approaches to malaria control that cover a country or even an entire region of sub-Saharan Africa. Such projects could also generate the crucial evidence required to guide future campaigns. The Bill & Melinda Gates Foundation is currently in discussion with potential partners to assess the possibility of launching just such a research project.

Finally, the biggest challenge confronting the global community — with respect to both existing and future strategies — is to seize the enormous opportunities that already exist to reduce the malaria burden and improve global health. This will be a true test of global responsibility and solidarity. ■

Richard Klausner is executive director of the Global Health Program, Bill & Melinda Gates Foundation, Seattle, Washington. Pedro Alonso is at the Centro de Investigação em Saude da Manhica, Mozambique, and the Center for International Health, Hospital Clinic/IDIBAPS, Universidad de Barcelona, Spain.

1. Lengeler, C. *Cochrane Database Syst. Rev.* Issue 2, CD000363 (2004).
2. *Africa Malaria Report 2003* (WHO/UNICEF, Geneva, 2003); available at www.rbm.who.int/amd2003/amr2003/amr_toc.htm.
3. Adjui, M. *et al. Lancet* **363**, 9–17 (2004).
4. Attaran, A. *et al. Lancet* **363**, 237–240 (2004).
5. Butler, D. *Nature* **429**, 588 (2004).
6. Schellenberg, D. *et al. Lancet* **357**, 1471–1477 (2001).
7. Shulman, C. E. *et al. Lancet* **353**, 632–636 (1999).
8. Boyd, M. *Am. J. Trop. Med.* **19**, 1 (1939).