DISEASE WATCH | FOCUS

Malaria

BACKGROUND

Causative agent. Malaria is caused by single-celled protozoan parasites of the genus *Plasmodium*. Four species infect humans by entering the bloodstream: *Plasmodium falciparum,* which is the main cause of severe clinical malaria and death; *Plasmodium vivax*; *Plasmodium ovale*; and *Plasmodium malariae*. Inoculation of parasite sporozoites occurs via the bite of infected blood-feeding female mosquitoes of the genus *Anopheles*. In humans, the parasites multiply exponentially in the liver, releasing merozoites that develop and multiply in infected red blood cells. With a blood meal, mosquitoes ingest *Plasmodium* gametocytes, which undergo another reproductive phase inside the mosquito before being transferred to another human host.

Current global status. Malaria is responsible for 273 million clinical cases and 1.12 million deaths annually. More than 40% of the global population (>2.1 billion people) is estimated to be at risk.

Distribution. Malaria occurs in 100 countries, but is mainly confined to poor, tropical areas of Africa, Asia and Latin America (FIG.1). More than 90% of malaria cases occur in tropical Africa, particularly among young children and pregnant women.

RECENT DEVELOPMENTS

New basic knowledge. The availability of the genome sequences of the three components of the malaria life cycle, *P. falciparum*[1], *Anopheles gambiae*[2] and humans[3], provides a wealth of information and unique opportunities for the development of better control tools. Integrated analyses of the genome sequence, DNA polymorphisms, and mRNA and protein expression profiles will lead to greater understanding of the molecular basis of vector–human–parasite interactions and provide insights for the development of intervention strategies to treat malaria[4].

The discovery of fosmidomycin and drugs that inhibit the non-mevalonate pathway of isoprenoid biosynthesis in *P. falciparum* demonstrate the value of genomics in identifying new drug targets and new antimalarials[5]. Examination of the genome sequences has also led to the identification of molecular markers for antimalarial resistance, including polymorphisms in *pfcrt*, *dhfr*, *dhps* and *pfmdr1* that are associated with resistance to chloroquine, sulfadoxine–pyrimethamine (SP)[6,7], mefloquine, quinine and artemisinin (FIG. 2).

The genome sequences will also promote vaccine development through the identification of several potential antigens[8,9]. Scanning of the genomes for desired properties, such as surface expression or limited antigenic diversity[1], together with microarray and proteomic data on stage-specific expression[10], enables the identification of potential antigens expressed at different stages of the *P. falciparum* life cycle.

In addition, recent findings have significant implications for the development of new strategies for malaria control[11,12]. Germline transformation of *A. gambiae* was achieved using the piggyBac transposable element marked with enhanced green fluorescent protein (EGFP), which was injected into mosquito embryos[11]. Transgenic *Anopheles stephensi* mosquitoes have been engineered that express *Plasmodium berghei* antiparasitic genes in their mid-gut epithelium, thereby rendering them inefficient vectors for malaria[12]. Crystal structures of *P. falciparum* dihydrofolate reductase-thymidylate synthase (DHFR-TS) also provide possible approaches for the design of new antimalarial drugs[13].

New tools and intervention methods.
Malaria is a particular problem in cases of severe disease, when patients might be unconscious, unable to take medicine by mouth and cannot reach a hospital in time for intravenous drug administration. Rectal artesunate, developed with support from the TDR and expected to provide an interim treatment while patients can be transferred to hospital, has received approval from the US Food and Drug Administration. Studies in Sudan[14] and Ghana[15] showed rapid clinical response with no significant adverse effects or signs of toxicity.

A low-cost combination of chlorproguanil and dapsone has been developed by a public–private partnership as an alternative to SP, the use of which is already limited in some areas of Africa owing to the appearance of resistant parasites. Phase III trials[16] were completed in 2001 and it has been approved by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) for the treatment of uncomplicated *P. falciparum* infections in adults and children more than three months of age.

Maintaining the effectiveness of antimalarial drugs is a key aspect of malaria control and one strategy is the use of combination therapy. Fourteen double-blind, placebo-controlled trials of artesunate-based combinations were conducted in Africa and Peru, and results indicated that combination therapy might offer an effective method to counter drug resistance. The use of artesunate in combination with chloroquine, amodiaquine, SP or mefloquine, consistently showed better cure rates, greater and more rapid parasite killing, and less gametocyte carriage than treatment with the single agents, and the toxicities of the combinations were similar to that of the single agents. Chloroquine alone was highly ineffective, and although this was improved by combination with artesunate, cure rates were still poor. Results with SP varied with geographical location and, although SP combination treatment is unsuitable in East Africa, where SP resistance is already established, it could be effective in other areas[17]. The combination of amodiaquine with artesunate had a more consistent pattern and resulted in high cure rates[18], but there was significant resistance in Kenya.

Given the limited impact of control strategies, an effective malaria vaccine is needed. Malaria vaccines are being developed to target the parasite at different stages in its life cycle. The number of antigens that deserve study as vaccine candidates continues to increase[10]. Those under development include: a recombinant chimeric virus-like particle

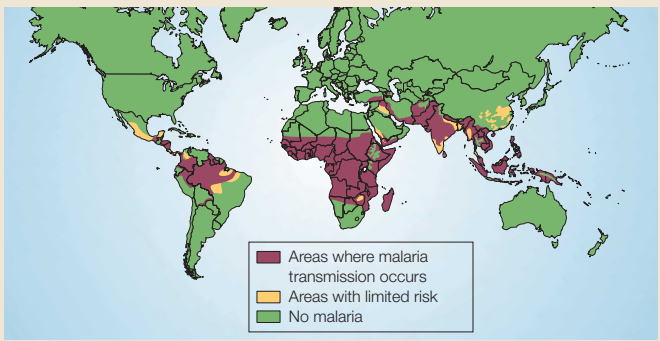

Figure 1 | Global distribution of malaria

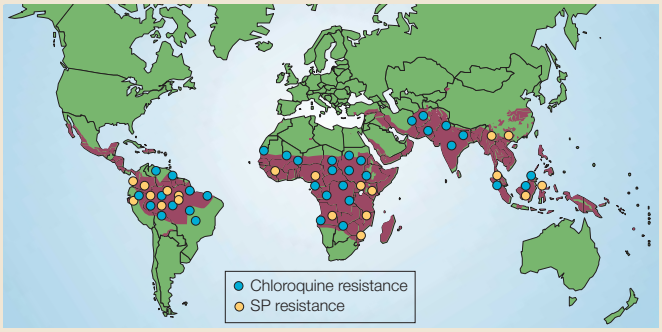

Figure 2 | Antimalarial drug resistance

composed of wild-type hepatitis B virus surface antigen fused to a fragment of *P. falciparum* circumsporozoite surface protein (CSP) (RTS,S)[19]; a synthetic multiple antigenic peptide vaccine based on CSPs[20]; merozoite surface protein-1 (MSP-1)[21]; and recombinant receptor-binding domains of erythrocyte-binding proteins formulated in human-compatible adjuvants[22,23].

Results of two studies in Tanzania to assess the impact of intermittent preventive treatment in infants (IPTi) — administration of a full treatment dose of an antimalarial drug at specific times during the first year of life — indicate that this is an important strategy in malaria control. Both a single dose of SP[24], administered to infants at 2, 3 and 9 months of age at the time of routine vaccination in areas of moderate malaria transmission, and amodiaquine[25], administered every two months at child health visits, reduce the occurrence of malaria and anaemia. Additional double-blind studies (in Ghana and Kenya) to assess the impact of IPTi in different epidemiological situations are in progress to validate the strategy in malaria control.

New strategies, policies and partnerships. Social, economic, political, behavioural and health-system factors all affect, and are affected by, disease patterns and disease-control efforts. Research to elucidate these factors is important for effective disease-control programmes, and product development and implementation[26]. The artesunate combination clinical trials (described above) were accompanied by social, economic and behavioural research examining access to care and patient behaviour, as well as the economic effects (including 'willingness to pay') on the individual patient, the community and the health sector.

Methods have been developed, and implementation strategies tested, for home management of malaria, showing that treatment of children in the early stages of malaria can prevent progression to severe disease. Four studies on home management of malaria, in Burkina Faso, Ghana, Uganda and Nigeria, were completed during 2000–2001. In the Burkina Faso study, which involved 67,500 children under five, there was evidence that antimalarials can reduce progression to severe disease[27]. A fourfold increase in the percentage of children treated led to a 53% reduction in the proportion of sick children that progressed to severe malaria at low cost. In Nigeria, the study aimed to understand when and why healthcare would be sought for childhood illnesses in three rural communities[28]. It showed that high temperature and loss of appetite were associated with malaria, and therefore with chloroquine use, whereas coughing and difficulty in breathing were associated with antibiotic use. The ability of healthcare workers to make these distinctions in medication use will provide the foundation for health education in promoting appropriate early treatment of childhood fevers.

The achievements described above highlight the value of working in partnership for controlling malaria. The artesunate combination trials were a multi-partner endeavour and provided evidence that allowed the WHO Roll Back Malaria partnership to recommend artemisinin-based combinations. In addition, they led to the formation of a consortium of institutions to develop fixed-dose co-formulations of artesunate with amodiaquine or mefloquine. This project (known as FACT) is jointly managed by Médecins Sans Frontières (MSF) and the TDR.

CONCLUSIONS AND FUTURE OUTLOOK

Malaria remains a major problem in developing countries. Important achievements have been made in the past years, which will contribute significantly to malaria control. They include exploitation of the *P. falciparum*, *A. gambiae* and human genomes, development of new drugs and new vaccine candidates, development and implementation of combination therapy, intermittent preventive treatment and home management of malaria.

The main challenges include overcoming the spread of drug-resistant *P. falciparum* through the use of combination therapy and appropriate early detection and monitoring of drug resistance, ensuring that the implementation of IPT on a large scale does not interfere with the expanded programme of immunization (EPI) and developing appropriate mechanisms for sustainable and effective implementation of the home management strategy over time and on a much larger scale.

These challenges will only be alleviated, and the control strategies achieve maximum impact, if additional resources are deployed to strengthen malaria research and control communities in countries where the new tools will be used. Continued and sustained efforts are needed to develop control tools through research and development in partnership.

Information source: Touré, Y. T. and Oduola A.
TDR Reference Group on Malaria: Yongyuth, Y., Jacobs-Lorena, M., Heggenhougen, H. K., Borjkman, A., Trape, J. F., and Doumbo, O. TDR/WHO, 20 Avenue Appia, CH-1211 Geneva, Switzerland. e-mail: DiseaseWatch.Malaria@who.int
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