Malaria and drug resistance

Although the malaria parasite has developed resistance to chloroquine in parts of Africa, chloroquine is still effective in preventing mortality and will remain the first choice in anti-malarial drugs for a long time to come

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The emergence and spread of resistance to chloroquine in WHO's African Region has very serious implications for malaria control throughout the continent. Drug resistance has been defined as “the ability of a parasite to multiply or to survive in the presence of concentrations of a drug that would normally destroy parasites of the same species or prevent their multiplication.” In short, what is happening is that chloroquine treatment offered to malaria sufferers in some areas is no longer giving them relief.

Prior to 1978, there had been a number of reports of treatment failures from different parts of the Region. Some of these reports were critically investigated and refuted. Some were unable to withstand critical examination whilst others did not offer any opportunities for challenge. During this period, small doses of chloroquine as low as 5 mg chloroquine base per kilogramme bodyweight were found to be adequate in effecting clearance of Plasmodium falciparum parasites in some East and West African countries. Chloroquine had also been used extensively in a number of countries for mass chemoprophylaxis programmes without any signs of the emergence of drug resistance.

Consequently, while resistance to chloroquine was emerging and spreading in South America and South-East Asia in the 1950s and 1960s, malaria experts were fairly optimistic that Africa would not be affected by the phenomenon. There were however a few who were not so confident and who predicted that with increasing use of the drug, the phenomenon would sooner or later emerge in Africa. A few also predicted that resistance to the drug would initially spread from South-East Asia to East Africa through population movements and would then cross the continent to West Africa.

In fact drug resistance did appear first in East Africa, but West Africa is still free from it. And it is not easy to attribute the emergence of the problem in East Africa to the movement of people from South-East Asia. The first reports of resistance to chloroquine in the Region came in 1978 when non-immune outsiders who had acquired their infections while visiting Kenya and Tanzania were found to have chloroquine-resistant P. falciparum infections.

Systematic studies on the sensitivity of P. falciparum to anti-malaria drugs began in the two countries as a result of the reports, and resistance has been confirmed among semi-immune indigenous populations in several areas. Since then the phenomenon has been confirmed and reported successively in a number of Eastern, Central and Southern African countries. In the Comoros—the island state lying between Madagascar and mainland Africa—the report is based on the detection of chloroquine-resistant parasites in an individual who is believed to have acquired his infection in the country. The true situation has yet to be assessed.

The reports from the other countries are all based on studies carried out by research scientists who are interested in the subject. Information on the geographical distribution and the rate and extent to which the degree of resistance is growing and spreading in these countries is unfortunately only fragmentary at this stage. The available information is limited to a few localities where studies have been carried out.

It is however reassuring that chloroquine is still effective in preventing mortality in all those areas. It still remains and will continue to remain the first choice in anti-malarial drugs for a long time to come. A state of despair and hopelessness that would arise if chloroquine proved no longer effective and
had to be replaced by alternative drugs has not been reached and is unlikely to be reached in the foreseeable future.

**No easy solution**

The life cycle of the malaria parasite as it passes from mosquito to human and back would suggest that the reduction and eventual interruption of transmission should be very easy. However, for a wide variety of technical, operational, administrative and financial reasons which need not be dwelt on here, large-scale vector control operations for reducing and ultimately interrupting transmission are not yet feasible, especially in the rural areas of most sub-Saharan African countries where malaria is endemic.

This unfortunate situation is unlikely to change in the foreseeable future. So the only feasible means of reducing the harmful effects of malaria in most African countries is to prevent or reduce malaria-related mortality and morbidity. This can be effectively achieved by developing the widest possible network of facilities and services for the prompt diagnosis or recognition and adequate treatment of malaria cases, as well as for protecting vulnerable groups of the population such as pregnant women. In addition, personal and community protective measures can be encouraged, such as the use of mosquito bed-nets, insect repellents, screening of houses, burning of mosquito coils and spraying of rooms in the evening.

Protecting pregnant women implies the regular administration of an adequate dose of chloroquine. For reasons that are not yet very clear, the protective immunity of women is depressed during pregnancy, especially during the first pregnancy, and they are therefore very vulnerable to the disease.

Infants and young children under five years are also highly vulnerable to the disease; this is due to early loss of maternal protective immunity passed on during pregnancy and the time it takes to acquire an adequate level of natural protective immunity. Consequently it was advocated in the past that this age-group, and even schoolchildren, should be protected through large-scale chemoprophylaxis programmes.

The current policy, however, is to discourage and discontinue such programmes. Firstly, they have proved to be not only very expensive but also ineffective, with little or no impact on health status. It is difficult to ensure adequate coverage and regular administration to the individuals at risk, and invariably there are interruptions because of drug shortages or logistic problems. Secondly, there are fears that the long-term administration of anti-malaria drugs in sufficient doses to prevent parasitaemia will interfere with the development of natural protective immunity. Thirdly, the long-term administration of chloroquine for as long as five or six years is likely to hasten the appearance of toxic effects from the drug. Fourthly, the large-scale use of chloroquine, especially in small doses, seems likely to encourage the emergence and spread of drug-resistant strains of *P. falciparum*. Finally, it is clear that mortality and suffering in this age-group can effectively be prevented or reduced by ensuring prompt diagnosis or recognition and adequate treatment of acute illness. On the other hand, there is no objection to individual chemoprophylaxis based on sound medical advice.

So far, resistance has been detected mainly in *P. falciparum*, which not only causes the most severe forms of the disease but also accounts for over 90 per cent of infections in most areas of tropical Africa where malaria is endemic. Against this background, it becomes readily recognisable that in a strategy almost entirely dependent on the rational deployment of anti-malaria drugs the emergence and spread of drug-resistant malaria parasites is bound to pose serious public health problems.

Should the intensity of resistance to chloroquine become very great, there is still only a very limited range of alternative drugs and treatment regimens. The effective management of recrudescences and treatment failures could be increasingly difficult if resistance to the alternative drugs also emerged. Compared to chloroquine, the available alternative drugs have worse side-effects. Besides, the alternative treatment regimens are more costly, so patients are less likely to comply with them. And developing new, safer and more effective anti-malaria drugs is a slow and expensive process, so it is not clear how soon such drugs might be available.

It cannot be over-emphasised that formulating and vigorously pursuing ra-
tional policies and measures aimed at maintaining for as long as possible the efficacy of the currently available anti-malaria drugs, especially chloroquine, will be a matter of great importance.

Certain basic measures need to be adopted in all areas where *P. falciparum* is or may be a public health problem. Extensive use of a drug is clearly a major contributory factor to the emergence and spread of drug resistant parasites. Large-scale abuse and misuse of drugs, which results in the administration of sub-curative doses, has been observed in some countries and should be prevented. This applies equally to the mass administration of drugs. So there is a need to draw up policies aimed at controlling the importation, production, distribution and use of anti-malaria drugs. This applies especially to the second-line drugs, such as Fansidar. Fansidar—which should be held in reserve and used for cases that fail to respond adequately to chloroquine or amodiaquine—can be obtained without prescription in some countries and is being misused on a large scale. This is dangerous since it could encourage resistance to the drug.

Intensive education and information of health personnel and the general public are needed to promote sound knowledge and correct use of anti-malaria drugs. It is also necessary to develop effective and efficient mechanisms for the prompt referral and adequate management of severe and complicated cases of malaria and treatment failures, particularly in areas where there is resistance to chloroquine.

This calls for the formulation of standard treatment regimens for different levels in the health care delivery systems, and appropriate drugs should be available in adequate quantities at the different levels. At each level, the personnel responsible for the diagnosis and management of malaria should be given adequate training appropriate to the tasks they are required to perform. Village or community health workers have to learn the criteria for recognising all forms of malaria (acute without complications, severe with or without complications, and treatment failures) and giving correct treatment. And at the centres designated for managing referral cases, correct clinical diagnosis and parasitological confirmation of cases will be as crucial as their proper management. Alternative drugs should be readily available at these centres, and the drug policies and standard treatment regimens should be under continuous review and modified as appropriate. This will call for an initial assessment of the response to various treatment regimens and subsequent continuous monitoring at all levels.

Where there are no laboratory facilities, response should be based on clearly defined clinical criteria. Where there are laboratory facilities, response should be based largely on clinical criteria but selected cases could be assessed by a combination of clinical and parasitological response. Depending on the availability of resources and the size of the country, one or more special teams capable of both *in vivo* and *in vitro* testing of sensitivity should be established.

An information system, which should be as simple as possible, ought to be developed. The system should provide an alarm mechanism which will enable a special team to respond promptly to changes in the adequacy of response to treatment, moving into the area to carry out detailed investigations mainly by the *in vivo* method. The *in vitro* method should on the whole be used sparingly. There should be as much exchange of information as possible between countries within the framework of technical cooperation.

Who should play an important and active role through technical collaboration with, and support to, the member countries. It can do so by disseminating relevant technical information, providing the services of consultants, supplies and equipment, organizing meetings for exchange and discussion of experience, offering training and strengthening national training capabilities, and mobilising resources in support of national, subregional and regional anti-malaria activities.

Finally, the only logical means of preventing or reducing the emergence and spread of *P. falciparum* drug-resistance is to reduce or interrupt its transmission. Who should therefore make every possible effort to stimulate and intensify research aimed at improving existing tools or developing new ones which will make the reduction and eventual interruption of malaria in Africa feasible and affordable by the countries.