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The problem of *Plasmodium falciparum* drug resistance in Africa south of the Sahara

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The resistance of P. falciparum *malaria to dihydrofolate reductase inhibitors, to the 4-aminoquinolines (in particular, chloroquine), and to the combination sulfadoxine–pyrimethamine is reviewed in the light of past and the most recent findings. Considering the gravity of the situation following the recent discovery of resistance of* P. falciparum *to chloroquine among the semi-immune populations of Africa south of the Sahara, a few suggestions are made for a realistic and rational approach to the drug resistance problem. Some questions that may be worthy of applied field research are briefly mentioned and governments are invited to take the necessary action to ensure better control of the procurement, distribution, and use of antimalarials.*

The relatively recent discovery of resistance to chloroquine in *Plasmodium falciparum* in East Africa, first in the non-immune and more recently among the semi-immune population, is certainly a matter of serious concern. This concern is even more justified by the actions being promoted by African countries for the prevention or reduction of malaria mortality and reduction of morbidity through the use of drugs.

An assessment of the present situation with regard to *P. falciparum* sensitivity to different antimalarials in tropical Africa may provide some guidance for a more correct selection and better utilization of drugs for both chemotherapy and chemoprophylaxis of *P. falciparum* infections. With this in mind, an attempt has been made to update the available information on the *P. falciparum* drug resistance problem in tropical Africa and to discuss briefly its implications.

RESISTANCE OF *P. FALCIPARUM* TO DIHYDROFOLATE REDUCTASE INHIBITORS

This group of compounds includes proguanil, chlorproguanil, pyrimethamine, and cycloguanil embonate. These drugs have been used mainly for prophylaxis or presumptive treatment; for radical treatment, pyrimethamine is given in combination with long-acting sulfonamides, especially in chloroquine-resistant *P. falciparum* malaria. Another member of this group is trimethoprim, which has been used very rarely for the radical treatment of *P. falciparum*, in combination with sulfa drugs.

Resistance of *P. falciparum* to pyrimethamine in tropical Africa was detected as early as 1954 (*1*). In subsequent years, *P. falciparum* resistance to dihydrofolate reductase inhibitors was discovered in several countries of West and East Africa, to the extent that in 1970 it was possible to talk of the "saga of pyrimethamine resistance in Africa" (*2*).

A map (Fig. 1) showing the distribution of resistance to dihydrofolate reductase inhibitors in tropical Africa has been drawn on the basis of published information on *P. falciparum* resistance to proguanil, chlorproguanil, pyrimethamine, and cycloguanil embonate up to 1970. More recently, pyrimethamine resistance has been reported from northern Liberia (Björkman, personal communication) and Kenya (*3*) and this is also shown in the map. In Liberia, the distribution of pyrimethamine resistance was found to be patchy; in the absence of pyrimethamine resistance, chlorproguanil was given as a prophylactic for a few years without the parasite becoming resistant to the drug, whereas chlorproguanil resistance developed quickly in the presence of pyrimethamine resistance. This is an interesting experience, since cross-resistance among different dihydrofolate reductase inhibitors is a very common, even though not a constant, phenomenon.

In conclusion, *P. falciparum* resistance to dihydrofolate reductase inhibitors is a widespread phenomenon in subtropical Africa and perhaps much more common than the map would indicate if anecdotal evidence is taken into account.

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Fig. 1. Countries in tropical Africa where *P. falciparum* resistance to one or more dihydrofolate reductase inhibitors has been documented.

RESISTANCE OF *P. FALCIPARUM* TO 4-AMINOQUINOLINES

In 1970, it was possible to state that *P. falciparum* resistance to chloroquine had never been convincingly demonstrated in the African continent (*4*). In the following years, however, reports from Ethiopia (*5*), Nigeria (*6*), the Sudan (*7*), and Zambia (*8*) raised very strong suspicions that chloroquine-resistant *P. falciparum* malaria had emerged in those countries. They were not accepted as definite proof simply because the criteria established by WHO for the confirmation of resistance had not been fully respected.

The first well documented case of *P. falciparum* resistance to chloroquine was reported in 1979 in an American tourist who had contracted the disease in Kenya (*9*). Since then, cases of *P. falciparum* resistant to chloroquine have continued to be found at an unrelenting speed among non-immune persons visiting East Africa (*10–12*).

Chloroquine resistance of *P. falciparum* at the RI

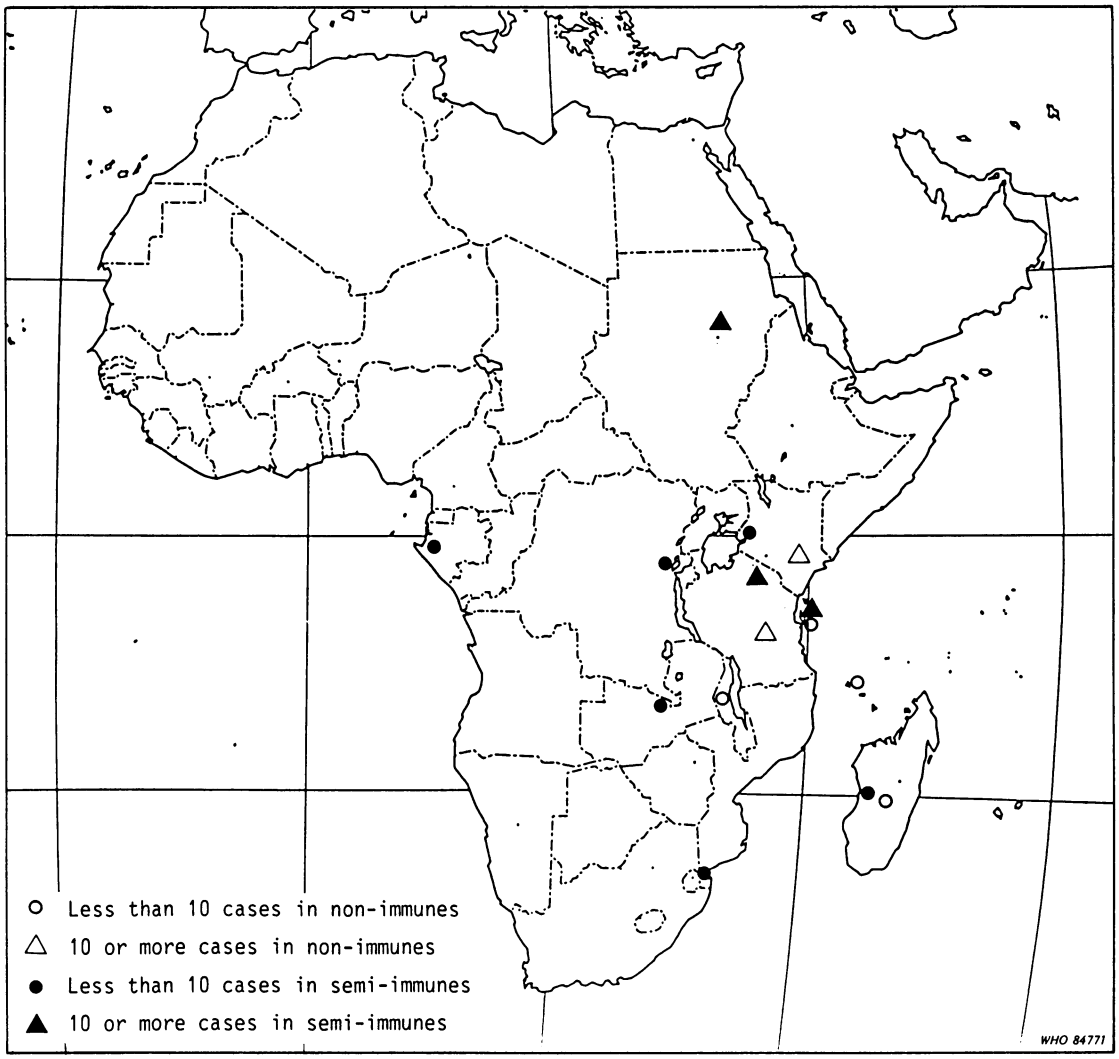

Fig. 2. Distribution of *P. falciparum* chloroquine resistance in tropical Africa: status as at October 1983.

level was found among semi-immune persons in the United Republic of Tanzania from 1981 onwards[a] (*13*, *14*) and in Kenya (*15*). Resistance at the RII and RIII levels among semi-immune persons has been found more recently in Gabon (*16*), Madagascar (*17*), the Sudan,[b] the United Republic of Tanzania (Zanzibar) (*18*), Zaire (*19*), and Zambia (*20*), and among non-immune persons in Kenya (*22*) and the United Republic of Tanzania (*22–24*). The latest reports of *P. falciparum* resistance to chloroquine have come from Mozambique[c] and Malawi (*25*). Of importance is the presence of *P. falciparum* resistance to amodiaquine (RII level) in Zanzibar (*46*). In recent years, we have thus witnessed a rapid development of chloroquine-resistant *P. falciparum* and its spread from East Africa to other countries of the continent (Fig. 2). However, although the phenomenon

[a] VERNAJ, F. ET AL. *Chloroquine-resistant malaria cases imported from Tanzania.* Unpublished document, WHO/MAL.81.943 (1981).

[b] AL TAWIL, N. & AKOOD, M. A. *Response of falciparum malaria to a standard regimen of chloroquine in Khartoum Province, Sudan.* Unpublished document, WHO/MAL.83.991 (1983).

[c] ALMEIDA FRANCO, L. T. WHO unpublished report (no number), 1983.

requires further investigation, especially in West Africa, and continuous monitoring, the distribution of resistant parasites and their degree of resistance is far from being uniform.

From published and unpublished information, an evaluation has been made of *in vitro* tests for chloroquine sensitivity in *P. falciparum* by probit analysis of log/dose response from 3–8 point assay[d] and the results are summarized in Table 1 and Fig. 3. The regression lines indicate that, on the basis of the micro *in vitro* tests carried out in different areas, the *P. falciparum* populations showed significant differences with regard to chloroquine sensitivity. Highly sensitive populations prevailed at Shirati (United Republic of Tanzania) in 1979–80 and at Buyo (Ivory Coast) in 1983, whilst incipient resistance was found at Mto-wa-Mbu (United Republic of Tanzania) in 1981 and by 1982 resistant populations were well represented at Shirati and Lambaréné (Gabon) and even more so in Zanzibar (United Republic of Tanzania).

[d] GRAB B. & WERNSDORFER, W. H. *Evaluation of* in vitro *tests for drug sensitivity in* Plasmodium falciparum*: probit analysis of log/dose response test from 3–8 point assay.* Unpublished document, WHO/MAL.83.990 (1983).

RESISTANCE OF *P. FALCIPARUM* TO PYRIMETHAMINE–SULFADOXINE

P. falciparum malaria resistant to the combination pyrimethamine–sulfadoxine (Fansidar) has recently been reported from East Africa. It has been detected among non-immune persons visiting Kenya (*26, 27*) and the United Republic of Tanzania (*27–30*) and in a semi-immune person in the latter country (*31*). One case of *P. falciparum* resistant to pyrimethamine–dapsone (Maloprim) has also been found in a non-immune person visiting Kenya (*32*). These preliminary reports on *P. falciparum* resistance to pyrimethamine–sulfadoxine and pyrimethamine–dapsone should be viewed with great concern. These drug combinations have never been widely used in Africa for the treatment of malaria and the distribution of the resistant parasites and their degree of resistance is little known because of the lack of extensive surveys and of suitable *in vitro* test methods.

The resistance of *P. falciparum* to pyrimethamine is quite widespread on the African continent and it would appear that, once established, it can remain

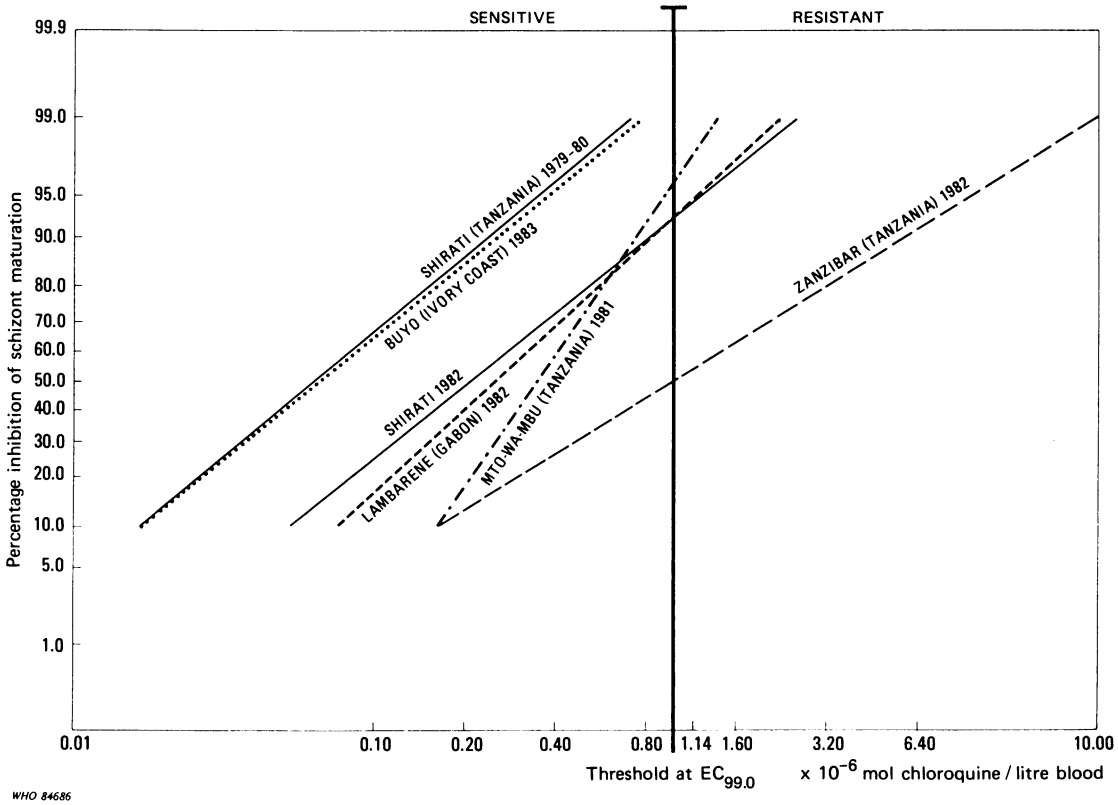

Fig. 3. Inhibition of schizont maturation in the *in vitro* chloroquine microtest, showing probit regression lines for six different studies.

Table 1. Results of an evaluation of *in vitro* tests for chloroquine sensitivity in *P. falciparum* by probit analysis of log/dose response from 3–8 point assays.

Country/location	Year	Number of isolates	Slope	Variance of slopes	Plotting points at various levels of effective concentration of chloroquine				
					EC_{10}	EC_{50}	EC_{90}	EC_{95}	EC_{99}
U. Rep. of Tanzania/Shirati (1)	1979–80	73	2.229	0.008	0.017	0.066	0.247	0.359	0.726
U. Rep. of Tanzania/Mto-wa-Mbu	1981	21	3.920	0.051	0.163	0.345	0.733	0.907	1.354
U. Rep. of Tanzania/Shirati (2)	1982	30	2.169	0.099	0.054	0.210	0.819	1.204	2.483
U. Rep. of Tanzania/Zanzibar	1982	30	1.652	0.007	0.160	0.955	5.695	9.449	24.442
Gabon/Lambaréné	1982	14	2.485	–	0.0774	0.2537	0.8317	1.1645	2.1907
Ivory Coast/Buyo	1983	19	2.19	0.11	0.017	0.066	0.255	0.373	0.776

and spread even many years after the withdrawal of the drug.[e] The resistance of *P. falciparum* to pyrimethamine–sulfadoxine seems to be linked to the presence of parasites highly resistant to pyrimethamine, as the presence of a medium level of pyrimethamine resistance *per se* does not seem to preclude the curative effect of the combination of drugs (*33*). It may also be a necessary condition for the development of resistance to the combination that *P. falciparum* parasites should be resistant to both pyrimethamine and sulfadoxine, a likely event since sulfonamides have been widely used in Africa for other bacterial diseases. The reservations expressed in 1969 concerning the use of long-acting sulfonamides in association with pyrimethamine for the treatment of *P. falciparum* malaria in Africa (*34*) have now become more relevant in the light of recent findings. It is also important to remember that pyrimethamine–sulfadoxine should not be given during the first three months of pregnancy or to infants and that cases of agranulocytosis associated with pyrimethamine–dapsone (*35–37*) and cases of Stevens-Johnson syndrome following pyrimethamine–sulfadoxine prophylaxis (*38–39*) have been reported recently.

RESISTANCE OF *P. FALCIPARUM* TO QUININE

In Africa south of the Sahara, *P. falciparum* has always proved to be highly sensitive to quinine and there do not appear to be any reports of quinine resistance from this part of the world. However, variations in the response of *P. falciparum* to quinine may occasionally be encountered and, since there may be some association between quinine resistance and chloroquine resistance (*40*), the sensitivity of *P. falciparum* to quinine should be monitored in those areas where chloroquine resistance is already established.

DISCUSSION

Large-scale vector control operations are at present not feasible for malaria control programmes in tropical Africa, owing to the magnitude of the administrative, operational, technical, and logistic problems encountered in the area. The most recent attempt to reduce specific mortality and morbidity by making drugs available to the rural African population is being greatly jeopardized by the appearance and rapid spread of drug-resistant *P. falciparum* malaria. At this stage, what seems to be urgently required is a judicious selection and proper use of the available compounds and the promotion of research activities that may answer some outstanding questions.

Some elements that may be worthy of consideration are summarized below.

Antimalarials are used for prophylaxis and treatment. From what has been said above about the resistance of *P. falciparum* to chloroquine, it would appear that this drug should no longer be used for chemoprophylaxis in the tropical African environment.

Despite the widespread *P. falciparum* resistance to dihydrofolate reductase inhibitors, some clinicians still recommend proguanil at the increased daily dosage of 200 mg (adult dosage) as a prophylactic (*41*, *42*). This view is not unchallenged. Proguanil is not recommended in WHO-supported programmes because of the lack of sufficient documented evidence of the efficacy of proguanil in the presence of pyrimethamine resistance and the ease with which resistance to dihydrofolate reductase inhibitors develops under drug pressure. Chlorproguanil may have some advantages over proguanil since it is retained in the

[e] KOUZNETSOV, R. L. ET AL. *Spread of pyrimethamine-resistant strains of* Plasmodium falciparum *into new areas of north-east Tanzania in the absence of drug pressure.* Unpublished document, WHO/MAL/80.926 (1980).

human body much longer than proguanil. From recent experiences, it would appear that its administration at regular intervals for the protection of vulnerable groups of the population may be recommended, but only in the absence of pyrimethamine resistance; this greatly limits its use on a large scale.

Long-acting sulfonamides with pyrimethamine cannot be recommended for chemoprophylaxis and their use should be reserved for the radical treatment of *P. falciparum* infections resistant to chloroquine (*43*).

Primaquine has a sporontocidal and gametocytocidal effect. It can be added to the drugs used for the radical treatment of *P. falciparum* infections, especially if treatment facilities become more easily available. This may curtail the transmission of drug-resistant parasites. Appropriate studies may be indicated, even in areas where the transmission potential is very high.

The discovery of chloroquine-resistant *P. falciparum* among the semi-immune populations of Africa is an undeniable proof of the potential gravity of the present situation. However, there is no reason for generalizing from only a few, though well established, facts. Studies on the distribution of chloroquine resistance in *P. falciparum* in Africa are still fragmentary and from these reports (some shown in Fig. 3) and others that have appeared in the literature (*44*, *45*), it is evident that there are still large areas in Africa where chloroquine is highly effective. The situation may be in an evolutionary phase, hence the necessity to study chloroquine sensitivity of *P. falciparum* in different geographical areas of tropical Africa and to monitor it in subsequent years. Concurrently, proper guidance in the use of 4-aminoquinolines should be derived from past and more recent epidemiological experiences.

From the knowledge at present available it would appear that chloroquine resistance has been selected and enhanced by drug pressure. In *P. falciparum* chloroquine resistance has been found in Madagascar where the drug has been used for chemoprophylaxis in schoolchildren since 1949; it has also been found in the United Republic of Tanzania where enormous quantities of the drug have been imported in recent years and used for both chemoprophylaxis and treatment. The evolution of *P. falciparum* chloroquine sensitivity in the Shirati area in the north of the United Republic of Tanzania is also interesting and informative (Fig. 3): chloroquine was introduced in this area in 1978 and continued to be administered at regular intervals up to the end of 1982 as a chemosuppressant in schoolchildren up to 10 years of age.

There is certainly a need for a more rational use of chloroquine. In endemic areas where *P. falciparum* is still sensitive to 4-aminoquinolines, these drugs can and must still be used for the radical treatment of the disease, but they must be given at sufficiently high doses to obtain radical cure. In many areas of tropical Africa, a radical cure is no longer attainable with a single-dose treatment (10 mg base per kg body weight) as was the case a few years ago. Great difficulties are to be expected if the single dose has to be replaced by the 3-day treatment (25 mg total dose of base per kg) and simple trials may be required in different countries. Cases not responding to the 3-day chloroquine treatment should be given quinine for five days or a single dose of 1500 mg of sulfadoxine and 75 mg pyrimethamine (adult dose). Under no circumstances should pyrimethamine–sulfadoxine (Fansidar) be used for radical treatment of *P. falciparum* infections in areas where the parasites are still fully sensitive to the 4-aminoquinolines.

There is an urgent need for African governments to formulate and implement a malaria drug policy aimed at controlling the importation and production of antimalarial drugs, their distribution to the private and public sectors, and their utilization.

RÉSUMÉ

LE PROBLÈME DE LA RÉSISTANCE AUX MÉDICAMENTS DE *PLASMODIUM FALCIPARUM* EN AFRIQUE SUBSAHARIENNE

La situation actuelle en ce qui concerne la sensibilité de *P. falciparum* aux inhibiteurs de la dihydrofolate-réductase, aux amino-4 quinoléines (notamment la chloroquine), à l'association sulfadoxine-pyriméthamine et à la quinine en Afrique tropicale est examinée à la lumière de l'expérience antérieure comme des résultats les plus récents. La résistance largement répandue de *P. falciparum* aux antifoliques et, ce qui est plus important, l'implacable propagation de la résistance de ce même parasite aux amino-4 quinoléines, constituent les traits les plus marquants et les plus inquiétants qui se dégagent de cette étude.

L'examen de la littérature sur le sujet montre que l'on assiste à une modification de la réponse à la chloroquine chez des souches de *P. falciparum* prélevés dans plusieurs pays d'Afrique. D'où l'urgence de mener d'autres études sur la distribution de ce phénomène dans différentes régions géographiques du continent et d'en surveiller l'évolution dans les années à venir. Le problème de la résistance à la chimiothérapie est sans doute préoccupant, mais l'affolement n'est pas de mise. Ce dont on a besoin de toute urgence, c'est d'une sélection judicieuse et d'une bonne utilisation des produits existants. A cet effet on peut tirer des données épidémiologiques, ou mieux, des recherches de terrain esquissées dans l'article, de précieuses indications.

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