



WHO/USAID/USPHS MALARIA COORDINATION MEETING

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THE PLACE OF CHEMOTHERAPY IN ANTIMALARIA PROGRAMMES<sup>1</sup>

1. Introduction

Before this century antimalaria measures consisted mainly of the administration of quinine for the treatment and the prophylaxis of malaria.

After the discovery of the developmental cycle of the malaria parasite at the turn of the century, the emphasis gradually shifted towards antilarval operations, but quinine and new antimalaria drugs continued to be extensively used in clinical practice and for individual and collective prophylaxis. Following the introduction of DDT and during the period of initial success of malaria eradication programmes, house-spraying with residual insecticides has relegated the use of chemotherapeutic measures to a secondary place. In malaria eradication programmes drugs were mainly used in the advanced stages of the programme and under special circumstances. Later on it was realized that house-spraying with residual insecticides has a limited efficacy in some epidemiological situations and that the fast-spreading resistance of malaria vectors to DDT and the rising cost of insecticides severely limit their use. As a consequence, the attention of Public Health Administrators in many countries has once again been drawn towards antimalarial drugs and towards the need of saving lives through antimalaria treatment. The relationship between the two major control methods was put into proper perspective when the revised strategy was presented to the Twenty-second World Health Assembly and summarized in a resolution adopted by the Assembly<sup>2</sup>, calling for the use of all available methods in the most appropriate and economic way.

Although accepted in principle, the implementation of the new strategy was slow for the fear of losing the gains achieved earlier and due to the adherence to classical principles, methodology and procedures.

The well-known limitations of existing drugs, their selective action and the diversity of epidemiological and socio-economic conditions, do not permit to suggest a universally applicable strategy of drug application. Nowadays, the place of chemotherapy in antimalaria activities has to be determined according to realistic health targets that can be attained and maintained, taking into account the properties of the individual drugs, the versatility of epidemiological and socio-economic conditions and the available resources.

2. Use of antimalarial drugs in different types of antimalaria programmes

The health targets that determine the pattern of antimalaria activities and the selection of the various measures (including the use of chemotherapeutic agents) have already been discussed, in general terms, in another document presented to this meeting<sup>3</sup>.

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<sup>2</sup> WHA22.39

<sup>3</sup> The application of integrated methods of malaria control, by J.H. Pull

2.1 In countries or areas where the targets of antimalaria activities are limited to reduction of specific mortality and morbidity

Chemotherapy is often the only operationally, administratively and financially feasible method of malaria control available to the Public Health Officer, particularly in rural areas.

The two targets may be reached most economically by providing antimalarial treatment to sick persons and by systematic mass drug administration to the most vulnerable population groups. For both types of drug administration, only blood schizontocides should be used. A single dose is often sufficient to provide clinical cure in semi-immune persons living in areas where malaria transmission is intense. No radical treatment is justified under such conditions except in particular areas where for special reasons an interruption of malaria transmission is being attempted. The identification of vulnerable groups is the responsibility of the health authorities. In areas of high endemicity such priority groups usually consist of infants, young children, pregnant and nursing mothers. The network of medical establishments in many developing countries is not yet adequate to cope with the protection of the vulnerable groups. Therefore, no effort should be spared to make use, to the greatest possible extent, of responsible collaborators (community leaders, teachers, medical helpers, etc.) and to encourage the participation of the community in the administration of drugs to sick people and to vulnerable groups.

2.2 In countries or areas where the health targets of antimalaria programmes are the reduction of specific morbidity and mortality and the reduction of malaria prevalence

Chemotherapy holds an important place among the antimalaria measures. However, the use of chemotherapeutic agents and of other measures may vary according to the epidemiological and operational conditions and the available resources. In areas where local vectors are endophilic and susceptible to DDT and/or other insecticides, and where human and financial resources permit the performance of efficient house-spraying operations, the role of malaria chemotherapy may be limited to the treatment of malaria cases in hospitals and out-patient clinics. The role of chemotherapy will be considerably greater in the case of malaria epidemics or in development projects exposed to a large influx of malaria cases, where mass drug administration may be instrumental in curtailing malaria epidemics.

Chemotherapy constitutes an essential measure in areas where house-spraying with DDT is not sufficiently effective and the use of alternative insecticides restricted for financial reasons. In respect of the use of antimalaria drugs, the differences between this type of area and areas with serious operational and financial constraints do not so much concern the methods to be employed as the width of their application. Besides providing treatment to sick persons through medical establishments and voluntary collaborators, many antimalaria programmes are able to provide treatment to persons with fever or recent history of fever through surveillance agents who are, at present, often utilized as multi-purpose health workers.

Following unsatisfactory results in many areas, mass drug administration is not usually commended for the protection of entire populations; however, good results were obtained in selected population groups and also in the control of malaria epidemics.

Under particular circumstances and if the financial resources are available, the use of medicated salt may be the method of choice for malaria control in well-organized or isolated groups of population if the salt supply is fully controlled and regular salt intake ensured.

In the socialist countries, the value of chemotherapy was recognized quite early and the drugs were not only used for individual treatment; mass drug administration was practised extensively in the general antimalaria campaign.

### 2.3 In countries or areas where the aim of antimalaria programmes is the elimination of malaria

The place of chemotherapy is well-defined in all phases of the programme. In the attack phase, mass drug administration may be an essential attack measure in areas of intense malaria transmission or in areas where insecticides alone are not effective in interrupting malaria transmission. Mass drug administration is an important measure in combatting epidemics in the other phases of the programme. Presumptive treatment of all persons suspected of malaria, and the radical treatment of all confirmed cases, are the principal methods of malaria control in the consolidation and maintenance phases of the programme when malaria transmission is essentially interrupted.

### 3. Antimalarial drugs and their properties

Bruce-Chwatt wrote in 1956 that "the ideal antimalarial drug combining virtues of casual prophylaxis, suppression, rapid and complete curative action, sporontocidal effect and impossibility to create parasite resistance, together with low toxicity, very slow excretion, palatability and (last, but not least) low cost, is still waiting to be discovered"<sup>1</sup>. This statement, made 20 years ago, still holds true.

Although the intensive search for new antimalarial drugs stimulated by the development and spreading of resistance of P.falciparum to 4-aminoquinolines may lead to the discovery of such an ideal drug, we have to realize that the currently available antimalarials have certain limitations. The properties of these drugs were reviewed by the WHO Scientific Group on the Chemotherapy of Malaria and Resistance to Antimalarial Drugs<sup>2</sup> and will be only briefly summarized in this paper.

3.1 4-aminoquinolines (e.g. chloroquine, amodiaquine) continue to be the most effective drugs for the clinical cure and suppression of vivax, quartan and ovale malaria. This is also the case for falciparum malaria in areas where P.falciparum is still susceptible to 4-aminoquinolines (Africa, Northern and Central America, Asia west of Bangladesh and the Assam State of India). In semi-immune persons, a single dose of chloroquine (often even below 10 mg chloroquine base per kg body weight) is sufficient to terminate a mild attack of falciparum malaria and to achieve radical cure in most of the cases.

In areas where the incidence of chloroquine-resistant strains and the degree of resistance are low, chloroquine, or preferably amodiaquine, may still be of use in the treatment of uncomplicated cases of falciparum malaria. However, alternative antimalarials should be given immediately if the patient's condition starts to deteriorate.

3.2 3-aminoquinolines (e.g. primaquine) are useful for the radical cure of P.vivax, P.malariae and P.ovale infections and highly effective against gametocytes of all species. In areas where the antimalaria activities do not aim at the eradication of the disease and where intensive transmission occurs, they could be used to curtail transmission in epidemic situations.

3.3 Quinine is a highly active blood schizontocide with rapid action. The high efficacy of a single-dose of quinine in semi-immune persons was demonstrated in Africa as long ago as 1901. However, quinine was largely superseded by synthetic antimalarial drugs; it continued to be used on a limited scale for emergency treatment in hospitals. Today, quinine, alone or in combination with other antimalarials, is again being used extensively for the treatment of acute falciparum infections, especially in areas where P.falciparum

<sup>1</sup> Bull. Wld Hlth Org., 1956, 15, 852

<sup>2</sup> Wld Hlth Org. techn. rep. ser., 1973, No. 529

is resistant to 4-aminoquinolines and other chemotherapeutic agents.

3.4 Dihydrofolate reductase inhibitors (e.g. pyrimethamine, proguanil); their use as prophylactic and sporontocidal drugs is limited, at present, to comparatively small areas where malaria parasites are responsive to these drugs. However, in combination with long-acting sulfonamides and sulfones, some of them play an important role in the treatment of falciparum infections resistant to 4-aminoquinolines.

3.5 Sulfonamides and sulfones (e.g. sulfadoxine, sulfalene, dapsons) alone are not used for the treatment and suppression of malaria infections, although field trials in tropical Africa have demonstrated the high effectiveness of these drugs in partially immune Africans. The combination of sulfonamides and sulfones with DHFR inhibitors appears to be highly effective in the treatment and prophylaxis of malaria infections in areas where P.falciparum is resistant to 4-aminoquinolines. The risk of severe reactions associated with the uncontrolled use of large doses of long-acting sulfonamides highlights the need for strict supervision of the treatment.

#### 4. Drug administration for specific purposes

At the time of the world-wide malaria eradication programme a near consensus of opinion was reached with regard to the selection of antimalarial drug schedules, dosages and terminology. The situation has changed with the development of P.falciparum resistance to chloroquine and the conversion of time-limited eradication programmes into long-term control programmes. Since the general epidemiological and socio-economic conditions and the aims of antimalaria programmes vary considerably from country to country, one should expect considerable heterogeneity regarding the use of drugs. However, certain general recommendations can be given below.

##### 4.1 Single-dose treatment

In areas where no chloroquine resistance is reported, the dose of 600 mg chloroquine or amodiaquine base is recommended for the treatment of uncomplicated malaria in adults. In areas where resistance to 4-aminoquinolines is established, sulfadoxine or sulfalene (1 g base) plus 50 mg pyrimethamine could be used. In areas where the degree of P.falciparum resistance to chloroquine is low and long-acting sulfonamides are not available, an increased dose of amodiaquine may be used (900 mg base in two doses).

##### 4.2 Presumptive treatment

The same drugs and dosages of schizontocidal agents as indicated above are used (in P.falciparum areas irrespective of their resistance or susceptibility to 4-aminoquinolines). Of the sporontocidal drugs, primaquine (30-45 mg adult dose) can be used universally. The usefulness of pyrimethamine (25-50 mg) is limited to the areas where the malaria parasites are sensitive to DHFR inhibitors.

##### 4.3 Treatment of acute malaria

In uncomplicated cases of vivax and ovale malaria infections as well as falciparum infections susceptible to chloroquine, the three-day standard treatment with chloroquine can be administered (total of 1500 mg base adult dose in 3 days). In semi-immune persons even a single dose of 4-aminoquinolines will generally be sufficient. In areas where P.falciparum is resistant to chloroquine, a combination of sulfadoxine or sulfalene (1 g) with pyrimethamine (50 mg) may be used. In severe cases of malaria, intravenous quinine infusion (20 mg/kg per day) may be required. This treatment should be followed by the administration of a 3-day standard treatment with chloroquine or amodiaquine, or in the case of an infection with chloroquine-resistant P.falciparum, by the administration of a combined dose of 1 g sulfadoxine and 50 mg pyrimethamine.

#### 4.4 Radical treatment

In the case of P.falciparum infections, the drugs and dosages employed are the same as under 4.3 for clinical cure. For treatment of vivax and ovale infections, it is recommended to complement the chloroquine treatment with the administration of 8-aminoquinolines. Depending on the sensitivity of the P.vivax strains to primaquine the drug may be administered daily for 8 days, 12 days, 14 days, or weekly for 8 or 14 weeks.

#### 4.5 Mass treatment

Chloroquine or amodiaquine are used for the protection of the most vulnerable groups of communities in areas where P.falciparum is susceptible to 4-aminoquinolines. The adult dose of 300 mg base is given at weekly or fortnightly intervals, depending on the levels of transmission and immunity. In areas with chloroquine-resistant P.falciparum, sulfadoxine may be used in combination with pyrimethamine, at intervals of one week (500 mg sulfadoxine + 25 mg pyrimethamine) or 2-4 weeks (1000 mg sulfadoxine + 50 mg pyrimethamine). For the control of malaria epidemics, chloroquine (600 mg base) and primaquine (45 mg base) can be employed in areas with normally susceptible P.falciparum, while the combination of sulfadoxine (1000 mg) and pyrimethamine (50 mg) can be used in areas with chloroquine-resistant strains.

#### 4.6 Chemoprophylaxis

For the protection of indigenous or foreign non-immune persons or groups in areas with normally susceptible parasites, pyrimethamine in a weekly dose of 25 or 50 mg or chloroquine (300 mg weekly) may be used. In areas with chloroquine-resistant P.falciparum the weekly administration of 500 mg sulfadoxine and 25 mg pyrimethamine or of 100 mg dapsona and 12.5 mg pyrimethamine is indicated.

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