

## PREVENTIVE USE OF ANTIMALARIAL DRUGS

### Chemoprophylaxis and Suppression<sup>1</sup>

Chemoprophylaxis (or drug prophylaxis) implies that drugs are used before infection takes place or prior to its manifestation, with the aim of preventing either of these occurrences. Thus drug prophylaxis may refer to absolute prevention of infection (causal prophylaxis) or to suppression of parasitaemia and its symptoms (clinical prophylaxis).

Causal prophylaxis aims at destruction of the pre-erythrocytic forms of the parasite. The drugs employed are primary tissue schizontocides, which eliminate the infection before the merozoites are liberated into the blood stream or, in other words, before the end of the prepatent period.

Clinical prophylaxis or suppression aims at early action on erythrocytic forms when they are released by the primary tissue forms. All blood schizontocides are suppressive drugs when taken in regular small doses. When an effective suppressive is being taken there are no persisting erythrocytic parasites and thus no clinical symptoms of malaria. When administration of the suppressive drugs is continued until complete depletion of the exoerythrocytic and erythrocytic stages of the parasite, no parasitaemia or clinical symptoms appear even after cessation of drug administration. This indicates that suppressive cure of the infection has been achieved. For *P. falciparum* this would occur in about one month from the last infective bite, but for *P. vivax* a much longer period would be required.

Causal prophylaxis is easily attained in falciparum malaria since the parasite in its primary tissue phase is sensitive to some of the drugs used for suppression but the other parasites are not.

Antifolic compounds such as proguanil and pyrimethamine are essentially prophylactic drugs that act on the pre-erythrocytic forms, especially of *P.*

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<sup>1</sup> "Suppression" of parasitaemia does not mean that the parasites are merely held at a low, submicroscopic level during the period of drug administration. In the case of *P. falciparum*, a parasite with brief exoerythrocytic development, the infection is eliminated and no subsequent parasitaemia occurs if drug administration is stopped after having been maintained for at least 4 weeks following exposure to malaria risk. In the case of parasites with persisting exoerythrocytic forms, such as *P. vivax*, parasites may enter the peripheral blood circulation after the drug has been stopped. The interval between discontinuation of the drug and patency is determined by the particular strain of parasite; it will be short for Chesson (tropical) strains and longer for strains from temperate zones.

*falciparum*, present in the liver cells and evolving from the sporozoites. None of the drugs known at present acts on the sporozoites themselves during the short period between their inoculation by the mosquito and their implantation in the liver cells.

Primaquine, a compound of the 8-aminoquinoline group, also has a potent action on the pre-erythrocytic schizonts of all species of human plasmodia. However, it is not used for prophylaxis because of its possible adverse effects.<sup>2</sup>

All therapeutic, i.e., schizontocidal, drugs are good suppressives. When taken in comparatively small doses they eliminate the parasites present in the red blood cells, or at least keep the number of plasmodia at such low levels that they provide protection from the effects of the infection. This can be achieved for prolonged periods when the compound used is appropriate and adequate doses are taken regularly.

Quinine, once the common protective drug, is now seldom, if ever, used for suppression of malaria because large doses were required in some areas and its long-term administration in small doses has been associated with the occurrence of blackwater fever. Chloroquine and amodiaquine are excellent suppressive drugs and have few adverse effects. Various combinations of sulfones or sulfonamides with antifolic compounds are being promoted and increasingly used for the prevention of malaria. It should be remembered that any prophylactic or suppressive drug may fail partially or fully in those malarious areas where there is plasmodial resistance to it.

#### *Individual drug protection*

Anyone visiting or living in a malarious area can protect himself from the disease by taking appropriate drugs. The term "prophylaxis" is often used in a general sense to include the preventive action of any antimalarial compound, although the specific mechanisms of action may be different in different compounds. Thus infection with *P. falciparum* ends in the pre-erythrocytic phase when proguanil or pyrimethamine is used for chemoprophylaxis, the parasites not developing to the erythrocytic stage. When prophylaxis is subsequently stopped on leaving the malarious area, no parasites remain in the body to produce an attack of falciparum malaria. The pre-erythrocytic stage of *P. falciparum* is more sensitive to proguanil than is the erythrocytic stage, so that successful prophylaxis can sometimes be achieved even though

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<sup>2</sup> What amounted to continuous radical treatment was used by the United States Armed Forces in Viet Nam, chloroquine and primaquine being administered together for chemoprophylaxis. With this combination primaquine acts against the tissue phase and chloroquine eliminates the erythrocytic stages of parasites. If continued for a sufficient period after the last infection with *P. vivax* its use results in radical cure of infection with that species (as well as with *P. falciparum*). In the presence of continued reinfection with *P. vivax* the use of primaquine in combination with chloroquine offers no advantage over chloroquine alone: a separate course of radical treatment could be given to eradicate vivax infections when the patient leaves the malarious area.

the trophozoites show resistance to proguanil. In general neither proguanil nor pyrimethamine is active against the pre-erythrocytic stage of *P. vivax*, although pyrimethamine may occasionally be.

With the drugs commonly used for chemoprophylaxis, infection with *P. vivax* proceeds without interruption through the pre-erythrocytic stage, at the end of which a few trophozoites appear in the circulating blood, their presence being demonstrable by subinoculation of blood into a suitable recipient. The parasites rapidly disappear from the blood under the influence of the chemoprophylactic drug, as do their successors when they emerge from the exoerythrocytic stage in the liver from time to time while the drug is being taken. However, if the drug is discontinued on leaving the malarious area and erythrocytic parasites subsequently emerge from the exoerythrocytic stage, they increase in number and an attack of vivax malaria results.

As *P. falciparum* does not have a persistent exoerythrocytic stage in the liver, the rapid destruction of erythrocytic trophozoites as they emerge from the liver means that infection with drug-sensitive strains of this species is eliminated by the chemoprophylactic drug. When the drug is discontinued, 4 weeks after the last possible exposure to infection, no subsequent attacks of falciparum malaria should occur.

Infections with *P. ovale* and *P. malariae* respond in a similar way to *P. vivax* when exposed to the drugs used for chemoprophylaxis.

The drugs commonly used for personal prophylaxis together with the appropriate dosage and the frequency of administration are shown in Table 9. All these drugs are effective from the first day of administration (in areas where the parasites are sensitive to the drugs) but, for reasons explained below, it is advisable that regular drug-taking should start 1–2 weeks before entering the malarious area. The drug should be taken for at least 1 month after leaving the malarious country to ensure that infection with *P. falciparum* is eliminated.

Proguanil is remarkably free from toxic effects. When used for chemoprophylaxis it acts on the pre-erythrocytic stage of *P. falciparum* and on the trophozoites of all 4 species. Resistance of *P. falciparum* to proguanil has been reported from many areas and resistance of *P. vivax* has also been reported (see Chapter 5).

Pyrimethamine is free from toxic effects at the doses recommended for the prophylaxis of malaria. It has much the same activity as proguanil and is also active against the pre-erythrocytic stage of some strains of *P. vivax*. As it has a sweetish taste and accidental poisoning of children has been reported on a number of occasions, the tablets should not be accessible to children.

Amodiaquine and chloroquine are usually well tolerated in the doses recommended for the prophylaxis of malaria. After prolonged administration of amodiaquine pigmentation of the palate, alae nasi and nail beds may be seen. Difficulties in visual accommodation, which may occur with therapeutic doses of chloroquine, are not normally experienced with prophylactic doses.

When high doses of chloroquine are used continuously for a number of years the compound may accumulate in the retina, producing a loss of visual acuity. However, with the dosage (300 mg a week) of chloroquine required for the prevention of malaria this adverse effect is not known to occur unless the drug is taken continuously for more than 6 years, when the cumulative amount exceeds 100 g. Even at this dosage level, chloroquine retinopathy appears to be uncommon.

It has been suggested that, in areas where there is a high level of transmission the amount of drug (e.g., proguanil, chloroquine, amodiaquine) taken for chemoprophylaxis may be doubled.

If the weekly intake of chloroquine base is of the order of 600–700 mg the overall duration of administration should not exceed 3–3½ years. When the strains of parasite present in the area are normally susceptible to the drug being used for prophylaxis any apparent failure of the drug to protect from malaria is more likely to be due to non-compliance with the regular regimen rather than to an inadequate dose being used.

Individual drug protection in areas where the presence of drug-resistant strains of plasmodia has been confirmed presents some difficulty when it comes to the choice of an appropriate compound. This applies particularly to infections with *P. falciparum*. If a high degree of resistance to proguanil or pyrimethamine is present and the parasites respond adequately to the 4-aminoquinolines, chloroquine or amodiaquine is the obvious drug for chemoprophylaxis. In countries or areas where strains of *P. falciparum* are highly resistant to proguanil, pyrimethamine and the 4-aminoquinolines, there is no entirely satisfactory drug or drug combination available at present, although some newer compounds offer considerable promise of being effective and safe. For the time being each case must be given individual attention, in the light of the country or area involved and the probability of the person or persons being infected.

If nonimmune individuals such as tourists are going to spend only a limited amount of time in an area where there are strains of *P. falciparum* resistant to the 4-aminoquinolines, a choice should be made from one of the drugs listed in Table 9. It is advisable to inform the traveller of the possibility of infection occurring in spite of treatment, so that he will seek medical advice should this occur.

If the time to be spent in a resistant area is longer or if infection with *P. falciparum* strains resistant to the 4-aminoquinolines is likely to occur, certain combinations of drugs may be used. A proprietary combination (Maloprim) of pyrimethamine (12.5 mg) and dapsone (100 mg) taken once a week has been widely used with satisfactory results. A further combination consisted of 200 mg proguanil and 25 mg dapsone taken daily. This proved to be very effective in military contingents in south-east Asia, but adverse effects on the blood (agranulocytosis) were seen in some individuals who took the 2 drugs for a period of over 1 year (Black, 1973). The same effects

occurred in subjects given a weekly dose of chloroquine, primaquine and dapsone. The incidence of agranulocytosis was of the order of between 0.1 and 0.5 per 1000 per year in people taking proguanil and dapsone, so the chances of one individual suffering from this condition are very small. However, agranulocytosis can have serious consequences and for this reason the combination should be used without exceeding the usual dosage.

There is also increasing evidence of the value as a preventive drug of a proprietary combination of sulfadoxine (500 mg) with pyrimethamine (25 mg) given at the adult dosage of 1 tablet once a week. Since there are few data on the long-term use of this drug combination it may be preferable to use it only for a limited time (4–6 months) until further information becomes available (Table 10).

A few practical points related to the individual protection of travellers or visitors to malarious areas should be mentioned.

A wide variety of people travel to malarious countries and remain there for varying lengths of time. They comprise tourists (individuals and organized

TABLE 10. COMBINATIONS OF ANTIMALARIAL COMPOUNDS USED FOR TREATMENT OR FOR INDIVIDUAL AND COLLECTIVE PROTECTION

Non-proprietary name	Formulation	Some proprietary names	Dose for prevention (adult)	Dose for treatment (adult)	Remarks
Pyrimethamine and chloroquine sulfate	25 mg + 150 mg (base)	Daraclor	1 or 2 tablets once a week. Children under 6 years of age, $\frac{1}{2}$ a tablet	Not generally used	Mainly for single-dose treatment (presumptive treatment) of cases suspected of malaria infection prior to confirmation of the diagnosis. Used in malaria eradication programmes.
Amodiaquine and primaquine	150 mg (base) + 15 mg (base)	Camoprism	2 tablets once a week for limited periods	2 tablets the first day, 1 tablet on the next 2 days, then 2 tablets once a week for 4–6 weeks	Mainly for limited mass drug administration programmes. To be used with caution in dark-skinned individuals. Also available as Camoprism Infatab at half the dosage of amodiaquine. For limited paediatric use.
Pyrimethamine and dapsone	12.5 mg + 100 mg	Maloprism	2 tablets before exposure, then 1 tablet once a week	Not generally used	To be used for individual protection. Not for children or pregnant women. May be used with caution in areas with resistance of <i>P. falciparum</i> to other drugs.
Chloroquine and chlorproguanil	150 mg + 20 mg	Lapaquin	1 tablet a week	Not normally used	Mainly for individual prevention of malaria, but occasionally used for limited mass drug administration.
Pyrimethamine and sulfadoxine	25 mg + 500 mg	Fansidar Falcidar	1 tablet a week or 2 tablets every 2 weeks <sup>1</sup>	2–3 tablets as a single dose	For treatment of falciparum malaria resistant to chloroquine and other drugs. Liquid formulation available for parenteral use. <sup>2</sup>
Pyrimethamine and sulfalene	25 mg + 500 mg	Metakelfin	As above	As above	Dosage of tablets as above. No injectable formulation available.

<sup>1</sup> For limited periods (3–6 months) in areas where resistance to other drugs has been confirmed.

<sup>2</sup> Each ampoule of 2.5 ml contains 25 mg of pyrimethamine and 500 mg of sulfadoxine.

parties), professional, technical and business people, university staff and students, schoolchildren on holiday travel, missionaries, armed forces personnel, tradesmen and others; and some have their families with them. In certain cases, too, local key personnel require the protection. All require briefing in individual malaria chemoprophylaxis and other measures to protect themselves from malaria. The briefing must be done carefully so that the measures are fully understood, and stress should be laid on the possible effects of failure to take precautions in order to promote the necessary motivation. The subject of what measures to take for individual protection from malaria should be brought up when travellers are receiving their immunizations. Information on areas with a risk of malaria is helpful for such briefing.<sup>3</sup>

The advice on the best protective drug varies according to the intensity of malaria transmission, the degree of exposure to infection and the type of malaria prevalent in the area concerned. It is difficult, if not impossible, to lay down a single rule to fit every situation.

An appropriate drug should be prescribed so that the traveller can obtain sufficient supplies to cover the period of his visit and at least 1 month after leaving the malarious areas. Some method of supervision is necessary to ensure that the tablets are taken. For the individual this may take the form of an entry in a diary at the time the tablets are actually taken. Parents should supervise their children and tour conductors the tourists in their parties. In the armed services stricter supervision is possible.

The drugs, especially chloroquine, are best tolerated when taken after a meal to reduce the occasional occurrence of nausea. It is an advantage to start the drug regimen a few days before departure since the traveller can begin to establish a routine: moreover, the existence of idiosyncrasy to any drug will be discovered while it is still possible to change the active compound. Whatever the drug and the regimen selected, it must be followed with unflinching regularity to be fully effective. One single omission, especially of a weekly dose, interrupts the protective effect. In view of this the regular daily intake of a drug such as proguanil is a distinct advantage.

In addition to the taking of a chemoprophylactic drug, there are many other measures that reduce the chance of malaria infection. The wearing of long sleeves and trousers after dusk decreases the chances of being bitten by anopheline mosquitos; and the application of mosquito repellents to the exposed skin at night has the same effect. Other measures include sleeping under a mosquito net, spraying the room with a pyrethrum knockdown aerosol, protecting living quarters by mosquito screens, avoiding villages at night and siting camps for the nonimmune 1–2 kilometres away from villages or other local habitations.

<sup>3</sup> The latest information together with a map is available in *Weekly Epidemiological Record*, No. 22, 1979 (see Fig. 1 for map).

The traveller should also be warned that vivax malaria may develop after he has stopped taking the drug a month after his return. He should inform his physician of his possible exposure to infection if he becomes ill after his return.

Routine radical treatment for all travellers returning from malarious countries is impracticable and often unnecessary. It could well be given to certain categories of people who have probably been infected with malaria because of the nature of their work, for example field workers, anthropologists, missionaries and personnel of the armed services, but for others it is a matter of individual assessment. A passenger arriving from a malarious area may sometimes be required to take a prescribed course of treatment as part of maintenance phase activities in a country where malaria eradication has been achieved.

Finally, it is important to warn pregnant women that an attack of malaria is a threat to pregnancy and assure them that such drugs as chloroquine and proguanil will have no untoward effect on the fetus. However, combinations of pyrimethamine with sulfonamides are not recommended during the first trimester of pregnancy.

### **Drug Administration in Malaria Control Programmes**

#### *Collective drug protection*

The general protection of groups of people residing in malarious areas and of populations living there permanently can be achieved temporarily by collective chemotherapeutic measures.

This method has been used with success in army units, organized labour forces or similar communities. The rapid excretion of all existing drugs means that they must be administered frequently and regularly. This demands organization, efficient distribution and, above all, persuasion.

In programmes drugs are used to give protection to particular categories of people. In some countries, however, a more general distribution is made in an attempt to protect the whole population. This may be necessary as the immediate first step in an epidemic of malaria, to be followed up by more lasting control measures.

It is obvious that collective drug protection differs only in degree from the mass drug administration described in the next section.

In countries where, for any reason, a malaria eradication programme cannot be undertaken the health service may carry out drug distribution as one of the services provided in the rural areas, the aim being to prevent or reduce the effects of malaria by the use of schizontocidal drugs. Although transmission of the infection cannot be interrupted by this measure alone it has definite beneficial effects, since it not only protects individuals but may also gradually reduce the reservoir of infection by decreasing transmission by the mosquito.

In carrying out such a programme special attention should be paid to a number of factors:

- (1) the value of the method as a public health measure;
- (2) the question whether the programme should attempt to cover the whole population or only specific categories of people;
- (3) the possibility of undesirable long-term side effects on the community;
- (4) the selection of the appropriate drug and dosage; and
- (5) the method of drug distribution and the timing, regularity, frequency and supervision of its management and effects.

With regard to (1), there is no doubt that collective drug distribution is of immediate benefit to the indigenous population living in a malarious area. It has been shown in Africa that regular drug distribution decreases the total amount of sickness from all causes, to some degree reduces absenteeism in schools, and may be followed by modest but definite gains in weight and an increase in blood haemoglobin.

With regard to (2), it is obvious that collective drug distribution must be adapted to the epidemiological conditions of the area. In areas of moderate endemicity and seasonal transmission all groups of the population benefit from drug distribution (adjusted to the start of the transmission period), while in highly endemic areas the long-term protection of the younger more vulnerable age groups is preferable. It is impossible to administer any drug to the entire population or even to a particular category of people with absolute regularity. However, a less than total coverage may, depending on the level of transmission, have an appreciable effect on the amount of malaria.

With regard to (3), the possible undesirable long-term effects of distributing an antimalarial drug regularly should be considered from two angles: the toxic action of the drug and its possible interference in highly endemic areas with acquired tolerance to the infection. As far as the first point is concerned, it seems that, with the exception of mepacrine and some 8-aminoquinolines, the harmful effects of most of the well-known drugs are very few, particularly when assessed in the light of the benefits that the drugs confer. Definite information about the second point is lacking, probably because in all field trials absolute regularity of drug distribution has never been achieved and reinfection, even of short duration, has been sufficient to maintain a degree of immunity.

With regard to (4), the selection of an appropriate drug for collective protection, the general principles outlined in this manual are valid. A good schizontocide, if given at an adequate dosage, acts on all the 4 species of human plasmodia in their asexual stage in the erythrocyte cycle and has a slow effect by attrition on the gametocyte reservoir. For this purpose the 4-aminoquinolines are unsurpassed and there is little to choose between amodiaquine and chloroquine. Proguanil and pyrimethamine have a causal prophylactic effect and also a direct sporontocidal action on the gametocyte reservoir. Their large-scale use is not justified where there is continuous and high-level transmission, because of the probability of the selection of resistant

strains in a population already infected. If these drugs are given, periodic assessment of their effect must be made. Their use in a combined form with a 4-aminoquinoline is much less open to objection. In areas where chloroquine-resistant strains of *P. falciparum* occur the protection to be expected from the 4-aminoquinolines will be less than elsewhere. Furthermore, it is to be expected that their use would exert selective pressure in favour of the resistant strains. The use of alternative drug combinations in restricted areas might be considered, but the widescale use of combinations containing sulfonamides or sulfones entails the risk of inducing sulfonamide resistance in such important pathogenic bacteria as the meningococci.

With regard to (5), the frequency of administration is related not only to the dosage of the drug but also to the convenience of its distribution. In general once-weekly administration is the most appropriate, though fortnightly distribution may be adequate. The frequency of drug administration depends on many local conditions and the level of transmission, but a reasonably strict observance of weekly or fortnightly routines is not too difficult. In schools this regimen is certainly the most suitable and minimizes the effect of a default or two in the weekly drug distribution. It is obvious that in areas of high endemicity the risk of reinfection is greater when treatment is spread more widely. Breaks in this drug distribution in schools owing to holidays are unavoidable.

There is little doubt that in collective drug protection two groups of the population must be given the highest priority: pregnant and nursing women and infants and children. The distribution of drugs to these two groups is not difficult through the normal health service and schools, but a proportion of women and children will always be missed since total drug coverage is almost impossible to achieve in rural areas. In highly malarious areas regular once-weekly or once-fortnightly administration of drugs to small children attending clinics for the under-fives is of special value since malaria can be severe and often fatal in children of this age group.

Drug protection from malaria should be the responsibility of the national health service and the cost must be met mainly by the government, though bilateral or multilateral aid agencies may provide substantial assistance in the organization and expenditure involved.

Table 11 shows the dosage of the main drugs that can be given for collective drug protection in relatively small groups with little immunity or in semi-immune communities living in an endemic area.

At the appropriate dosage none of these drugs taken for general protection has any serious side effects. Proguanil and pyrimethamine have a wider margin of acceptability than the 4-aminoquinolines.

### *Epidemics of malaria*

Epidemics of malaria require special attention. For the control of epidemic malaria in rural communities the above doses are inadequate and the following dosage of fully active schizontocidal drugs is recommended:

	<i>Immediate single adult dose</i>	<i>Follow-up adult dose</i>
Chloroquine	600 mg base	300 mg base once a week
Amodiaquine	600 mg base	400 mg base once a week

Special responsibility lies with the distributors of the drug; they must ensure that the drug is really swallowed and not vomited and that the whole population takes the drug. Drug distribution should continue for 1 month after the confirmed end of the epidemic. The possibility of relapsing vivax and recrudescence of quartan malaria some weeks or months after the cessation of the drug distribution should be taken into account.

TABLE 11. DOSAGE OF DRUGS FOR COLLECTIVE PROTECTION

Drug	Groups with little immunity (adult dosage)	Semi-immune communities in endemic malarious areas (adult dosage)
Proguanil	100-200 mg daily	300 mg once a week <sup>1</sup>
Pyrimethamine	25-50 mg once a week	25 mg once a week <sup>1</sup>
Chloroquine	300-600 mg base once a week	150-300 mg base once a week
Amodiaquine	400 mg base once a week	200-400 mg base once a week

<sup>1</sup> There should be regular monitoring of the response of malaria parasites to these compounds and replacement by alternative drugs if resistance occurs.

Various drug combinations (chloroquine with pyrimethamine; chloroquine with chlorproguanil; amodiaquine with primaquine; pyrimethamine with dapsone) have been used for the protection of relatively small groups, with results ranging from good to disappointing. This is generally related to the regularity and completeness of the method of drug administration and reflects the degree of acceptance of the drugs and the motivation of the population.

The repository drugs have not yet found a well-defined place in malaria control programmes but could be used effectively in special situations.

#### *The use of drugs in malaria control and eradication programmes*

Before describing ways of using antimalarial drugs in malaria eradication programmes it should be stressed that investigation of the response of local strains of parasites to the drugs proposed for use ought to be part of the preparatory phase and the response should be continually monitored. In this way the presence or appearance of drug-resistant strains can be detected early and appropriate alternative drugs be used.<sup>4</sup>

The three main types of treatment with drugs in malaria eradication programmes are: presumptive treatment, mass drug administration and radical treatment.

<sup>4</sup> WHO Technical Report Series No. 529, 1973. *Chemotherapy of malaria and resistance to antimalarials*: Report of a WHO Scientific Group.

### *Presumptive treatment*

This is the treatment given to a person presumed to have or suspected of having malaria. It consists of a single dose of a 4-aminoquinoline together with either a gametocytocide or a sporontocide. The objective of presumptive treatment is to relieve symptoms and prevent transmission until the diagnosis is confirmed and radical treatment can begin.

In practice presumptive treatment consists of administration of 450–600 mg chloroquine or amodiaquine base with the addition of either 30–45 mg primaquine or 25–50 mg pyrimethamine (adult doses). At the same time a blood film is taken and if it is positive a course of radical treatment is given. The doses for children should be reduced proportionately.

In areas where chloroquine-resistant strains of *P. falciparum* are widespread an alternative schizontocide should be given. This may be 50 mg pyrimethamine together with 1 g sulfadoxine or 2 g sulfalene. For presumptive treatment, primaquine (30–45 mg once weekly) may be considered as an addition during the transmission period since pyrimethamine will not affect the gametocytes when pyrimethamine resistance is widespread.

The single-dose treatment of malaria given in clinics or outpatient departments differs from presumptive treatment in that it does not contain a gametocytocide or a sporontocide. It is often used in areas of hyperendemic malaria where there is no malaria eradication programme. In such areas the appropriate schizontocidal component of drugs used for presumptive treatment should be administered for single-dose treatment.

### *Mass drug administration*

Mass drug administration is the distribution of a specified drug to every individual in a given population. This may mean the total population of a malarious area or particular groups such as children, pregnant women, or members of a work force within the total population.

In malaria eradication programmes mass drug administration may be used in localized areas: (1) where small foci continue to persist after transmission has been interrupted elsewhere; (2) for a focal outbreak in the consolidation or maintenance phase in addition to insecticide spraying and other measures; (3) in situations where there is population movement and people congregate from various parts of the country. Mass drug administration may also be used as a supplementary attack phase measure when residual insecticide spraying does not fully interrupt transmission, but it is not a substitute for proper spraying.

Numerous difficulties attend the use of mass drug administration; it is therefore not a procedure that should be adopted without very careful consideration. Operational problems include staff difficulties in administering the drug, the identification of individuals for the purpose of record-keeping, population attitudes and beliefs, and the highly organized and costly system of distribution required to carry out the procedure effectively. Technical

problems include those arising from the frequency of drug administration necessary with the drugs at present available, the difficulty of achieving the total coverage required if the procedure is to be effective, the possible occurrence of side effects, which may be real or imaginary, and the emergence of drug-resistant strains of parasites.<sup>5</sup>

Mass drug administration can be achieved either by direct supervised distribution of tablets or by incorporation of the drug into common salt used for the normal daily preparation of food. The latter form of indirect drug distribution, introduced in Brazil in the 1950s, is often referred to as Pinotti's method.<sup>6</sup>

A number of difficulties have been met in using Pinotti's method in the field. A community may draw its salt from a wide variety of sources; thus there may be considerable problems in trying to channel the supply of salt through a single point where the antimalarial compound is added. It is difficult to ensure the even distribution of the active drug through salt in bulk, and in damp conditions it may concentrate or leach out into one part of the container. The individual consumption of salt differs considerably, hence the range of dosage with the antimalarial varies; some people consume little or no salt and therefore escape the action of the drug. Infants particularly consume little or none and they are therefore the group most at risk. These difficulties have bedevilled the application of what at first sight seemed to be a simple and effective method. In consequence, medicated salt distribution is likely to be of value only in very special circumstances. It proved to be very successful in Guyana, Iran and Suriname, and it may be applicable in other areas where a single source of salt can be identified and controlled. The procedure involves mixing a chloroquine or amodiaquine salt concentrate locally with the salt in bulk. This is done by machinery (e.g. with a concrete mixer) and entails limited capital expenditure. Nevertheless, the whole process demands a fair degree of management, of which only governments or large industrial concerns are capable.

The antimalarial compounds suitable for use with medicated salt are chloroquine and amodiaquine. When pyrimethamine was used for this purpose in the early field trials, rapid development of resistance to the drug invariably followed. Chloroquine has been used most commonly for medicated salt distribution, though amodiaquine base, which is less bitter than chloroquine, was employed with success in Suriname.

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<sup>5</sup> WHO Technical Report Series, No. 375, 1967. *Chemotherapy of malaria: Report of a WHO Scientific Group.*

<sup>6</sup> See PAULINI, E. (1960). Guide-lines for the use of medicated salt (Pinotti's method) in malaria eradication programmes (unpublished document WHO/MEM/1).

The general requirements for this method are as follows:

(1) The salt supply of the population must be such as to ensure that only medicated salt is consumed. This may require legislative action and much public health education.

(2) The salt intake must be regular and well known so that the concentration of the compound in relation to the average daily consumption of the inhabitants can be calculated.

(3) The final concentration of the drug must be adjusted so that the weekly dosage of chloroquine or amodiaquine base is 300–400 mg.

(4) The concentration of chloroquine in the salt must not exceed 4g/kg as beyond this limit the salt becomes bitter.

(5) The mixing and bagging must be such as to prevent irregular drug concentration and leaching out on storage.

(6) A regular follow-up of results is necessary to detect any technical, operational or human difficulties that may prevent consumption of the appropriate dosage, since the application of this ingenious method is more difficult than might be expected.

In all mass drug administration programmes the response of the parasites to the drugs must be continually monitored to ensure early detection of drug resistance. Possible adverse reactions to the drugs in the various age groups should also be borne in mind.

### *Radical treatment*

Radical treatment of vivax malaria has been discussed in detail in Chapter 6. A number of factors may necessitate modification of the amount of primaquine usually given for radical cure of vivax malaria. In addition, in malaria eradication programmes it is usual at the appropriate stage to give radical treatment in all cases of malaria, including those caused by *P. falciparum*, since there may be latent infection with *P. vivax* as well as overt falciparum parasitaemia and since primaquine destroys any surviving gametocytes of *P. falciparum*.

In many programmes the course of radical treatment lasts for only 5 days, during each of which 15 mg primaquine are administered under supervision, 1.5 g chloroquine base also being administered in the first 3 days. The reason for the shortness of the course lies in the necessity to supervise the treatment, which is operationally possible for 5 days but hardly ever for 14 days. This shortened course does not always succeed in eradicating *P. vivax*, but relapses should be picked up by surveillance procedures, as by active or passive case detection and the follow-up of treated cases.

In the south-west Pacific larger amounts of primaquine than usual are required for the radical cure of some strains of *P. vivax*, and daily doses of 22.5 mg primaquine for 14 days are commonly used. Even with this regimen

relapses may occur. This regimen presents operational difficulties if it has to be used as a routine measure in an eradication programme.

Mass radical treatment has been used in some areas, but the areas must be very localized with small numbers of people involved if the operation is to be carried out effectively. Obviously this procedure would be a waste of time if transmission was still going on; thus when it is used for small residual foci it must be combined with effective residual spraying or carried out during that part of the year when there is no transmission. Because of the length of the course of treatment, any movement of people adds to the difficulty of supervising this form of drug distribution.

### **Prevention of Malaria Accidentally Induced by Blood Transfusion**

The subject of accidental transfusion malaria has recently assumed some importance, a large number of such cases having been described and analysed. Various methods of selection of donors in non-malarious areas and the possible use of immunological tests in special circumstances have been discussed. The striking growth in international travel in the past decade has led to the exposure of many potential blood donors to malaria; in consequence, they may be able to transmit malaria when their blood is used for transfusion. Donors are often excluded on the basis of a specified length of time since their exposure to malaria infection. If this results in the exclusion of too large a proportion of the donor panel the use of radical treatment for those suspected of malaria could be considered, possibly in association with serological tests.

In malarious areas nearly all donors are likely to transmit malaria when they give blood for transfusion, so that routine employment of antimalarial drugs is necessary to prevent accidentally induced infection. Transfusions may be given either from *ad hoc* donors in an emergency or from a well organized panel of donors. In the first case the best policy is to treat the recipient: in the second it may be possible to institute routine chemoprophylaxis for all the donors on the panel.

If well supervised routine chemoprophylaxis of the donor panel in a malarious area is not possible, the recipients should receive treatment to destroy any parasites they may receive with the transfused blood. Where parasites are normally sensitive to the 4-aminoquinolines a standard course of chloroquine (1.5 g in 3 days for an adult) eliminates any infection acquired in this way. Where drug-resistant strains are present appropriate alternative treatment should be used (see pp. 131–132). The course can be started the day before a planned transfusion or at the time of transfusion. Exoerythrocytic parasites do not occur in these circumstances and the use of primaquine is not indicated. A combined approach may be possible using chemoprophylaxis for the donor panel and prophylactic treatment for the recipients.

### Cost of Mass Drug Administration

The cost of drugs alone can be relatively easily calculated, although the price of the same compound may vary from country to country because of differences in the suppliers, in transport and in customs duties. However, the total cost of a mass drug distribution scheme is difficult to estimate since it must include operational and evaluation expenses. In a project in Senegal that aims at protecting infants and children up to the age of 14 years the approximate cost in 1972 was US \$0.16 per child per year exclusive of drug administration, the cost of which was estimated at US \$0.04. In this project the drug distribution was carried out through the agricultural cooperatives.

The type and frequency of mass drug administration vary so much from country to country that the cost in one cannot be used to estimate the cost in another. The reported costs from Africa varied in 1973 between US \$0.20 and 0.80 per person per year.<sup>7</sup>

Another estimate prepared in 1973 indicated that in tropical Africa, for a population of 1 million of whom 75 % live in rural areas, the annual cost of drug protection by chloroquine through once-weekly chemoprophylaxis for children and pregnant women and single-dose treatment of malaria attacks in the rest of the population would be about US \$185 000 or approximately US \$0.185 per person per year.<sup>8</sup> This includes the probable expense of drug distribution.

However, the latest estimates, prepared for the Thirty-first World Health Assembly (1978),<sup>9</sup> indicate that single-dose treatment of fever cases (most of them presumably caused by malaria) under tropical African conditions using chloroquine tablets of 100 mg base, at an average dose of 10 mg/kg body weight, for the protection of one million inhabitants would require 4 500 000 tablets. At the price of US \$10 per 1 000 tablets the total cost of the drug (excluding the cost of its distribution) would amount to US \$45 000, the cost per protected inhabitant thus averaging US \$0.05. Because the costs of distribution and evaluation of the results of such a programme vary tremendously from one country to another, since they depend on wages and salaries, transport, and other incidental expenses, the above estimates are only of indicative value, though they may help health administrators to plan the intended antimalaria programmes.

In conclusion, it seems that in most situations it is theoretically possible to prevent malaria by the use of an appropriate drug or combination of drugs.

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<sup>7</sup> WHO Technical Report Series, No. 529, 1973. *Chemotherapy of malaria and resistance to antimalarials*: Report of a WHO Scientific Group.

<sup>8</sup> WHO Technical Report Series, No. 548, 1974. Sixteenth report of the WHO Expert Committee on Malaria.

<sup>9</sup> Malaria control strategy. Report by the Director-General to the Thirty-first World Health Assembly (unpublished WHO document A31.19).

Even when the element of human fallibility is reduced to a minimum, as in conditions of strict military discipline, cases of malaria still occur because absolute regularity of administration has not been achieved; individuals occasionally omit to take the prescribed doses, particularly when the routine is disturbed. It cannot therefore be expected that populations or even particular categories within populations will achieve absolute regularity and it would be impossible to provide adequate supervision to ensure that they did. For these reasons too much must not be expected from mass drug administration, especially as malaria attacks can occur even in responsible people for whom individual chemoprophylaxis has been prescribed.