Everyday Practice

Rational approach to the treatment of malaria

N. VALECHA, A. SRIVASTAVA, V. P. SHARMA

INTRODUCTION

Over 2000 million people in about 95 countries of 3 continents (Asia, Africa and America) are at risk of getting malaria and worldwide the number of clinical cases is estimated to be over 100 million with more than 1 million deaths each year.

Countries of the Southeast Asian (SEA) region experienced a resurgence of the disease in the mid 1970s and have switched from the eradication to the control concept by decentralizing the programmes through their primary health care systems. This approach produced good results and the rising trend of malaria was stabilized to around 3 million cases annually for about 5 to 6 years. However, the incidence of *Plasmodium falciparum* (Pf) infections continued to rise. In 1970 these constituted 20% of the total cases but in 1991 they had risen to 41%.

EPIDEMIOLOGY

The incidence of malaria in different countries in this region is shown in Fig. 1. India contributed 68% of the total followed by Sri Lanka (9.7%) and Thailand (9.2%) while Maldives reported only 25 imported cases (unpublished SEARO data, 1994).

Although the situation seems to be improving in some countries in many others it is deteriorating at an alarming rate. Reporting of cases is inadequate and an estimate of world trends indicates that, excluding Africa, the world figure averaged around 5 million cases to which the SEA region contributed nearly 3 million.

Figure 2 shows the malaria profile in India for the period 1961–93. It is apparent that the malaria control had considerable success with the morbidity figure in 1965 touching 0.1 million cases and no deaths. Thereafter the incidence started rising and reached a record figure of 6.4 million cases in 1976. Subsequent to the introduction of a modified plan for control of malaria, the figure came down to 2.0 million cases in 1984 since when the incidence has been static. The failure to eradicate the disease is linked to chloroquine resistance and the increase of Pf infection (Fig. 3).

CLINICAL FEATURES

These vary from mild to severe and complicated according to the species of parasite present, the patient's immune state,

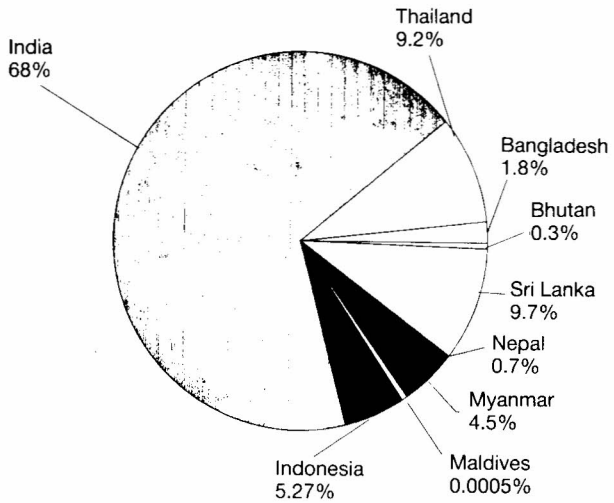

FIG 1. Country-wise malaria incidence in the Southeast Asian region

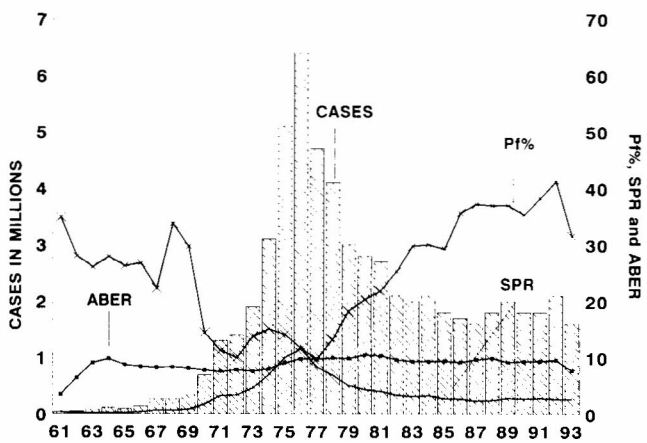

FIG 2. Malaria incidence in India (1961–93) Pf% per cent of Pf cases SPR slide positivity rate ABER annual blood examination rate

the intensity of the infection and the presence of concomitant conditions. The disease tends to be particularly severe in children and pregnant women.[1] The first symptoms of malaria are non-specific: lack of well being, headache, fatigue and muscle pain followed by fever. In some patients headache, chest pain, abdominal pain, arthralgia, myalgia or diarrhoea may be prominent and suggest an alternative diagnosis. The classic malarial paroxysms in which fever spikes (with chills and rigors) at regular intervals are not common in Pf infections but tertian periodicity is often seen in *Plasmodium vivax* (Pv) infections after an initial phase of irregular fever. Most patients with uncomplicated infections have few signs other than mild anaemia and, in some cases, a palpable spleen.

Severe manifestations and complications

In patients with Pf infection complications can occur if treat-

Malaria Research Centre, Indian Council of Medical Research, 22 Sham Nath Marg, New Delhi 110054, India
N. VALECHA, A. SRIVASTAVA, V. P. SHARMA

Correspondence to N. VALECHA

FIG 3. Chloroquine resistance and *P. falciparum* foci in India (1988)

ment is delayed or if they have impaired immunity. These include cerebral malaria, hypoglycaemia, lactic acidosis, non-cardiogenic pulmonary oedema, renal impairment and haematological abnormalities.

Cerebral malaria. Coma is the characteristic feature and is associated with a mortality of 20% despite treatment. There is a diffuse symmetric encephalopathy[1] and focal neurological signs are unusual. Convulsions, which are usually generalized, occur in 50% of adults and a higher proportion of children surviving cerebral malaria. Approximately 10% of these children particularly those who have had hypoglycaemia, repeated seizures and deep coma have residual neurological deficit. Anaemia and jaundice are common.

PRINCIPLES OF CHEMOTHERAPY

Antimalarial drugs have varying degrees of activity against different species of malarial parasites at different stages of development.[2] The life cycle of the parasite is depicted in Fig. 4. Accordingly the drugs can be classified into the following groups (Fig. 5, Table I):

Tissue schizonticides (used for casual prophylaxis). These drugs act on the pre-erythrocytic stages of the parasite (primary tissue forms or primary exo-erythrocytic forms) thus completely preventing invasion of red blood cells.

Tissue schizonticides (used as antirelapse drugs). These act on the exo-erythrocytic stages or tissue forms of Pv and *P. ovale* and are able to achieve radical cure of these infections.

TABLE I. Action of commonly used drugs on the developmental cycle of malarial parasites

Drug	Sporozoites	Tissue phase during incubation period	Erythrocytic phase		Latent tissue plant (responsible for relapses)	Development gametocytes in the mosquito (sporontocidal action)	Chemical class of the relevant antimalarial compound
			Asexual parasites	Sexual forms (gametocytes)			
Quinine	No action	No action	Fast action	Active against Pv and *P. malariae**	No action	No action	Cinchona alkaloids
Mepacrine	No action	No action	Fast action	As quinine	No action	No action	9-aminoacridines
Chloroquine Amodiaquine	No action	No action	Fast action	As quinine	No action	No action	4-aminoquinolines
Primaquine	No action	Active but not used for prophylaxis	Active but only in toxic doses	Direct and fast action on all species particularly Pf	Highly active	Highly active	8-aminoquinolines
Proguanil	No action	Active particularly on Pf	Active but relatively slow	No direct action	No action	Highly active	Biguanides
Pyrimethamine	No action	Probably as proguanil	As proguanil	No evidence of direct action	Some action on Pv	Little evidence	Diaminopyrimidines
Sulphones and Sulphonamides	No action	Possible action	Moderate action when given alone	As pyrimethamine	Little evidence		Sulphones and sulphonamides comprise a large number of short and long acting compounds
Mefloquine	Probably no action	Probably no action	Marked action	As quinine	Probably no action	Probably no action	Quinolinemethanols
Artemisinin	No action	No action	Marked action	No action	Probably no action	Probably no action	Sesquiterpene lactone

* no direct action on Pf Pv *Plasmodium vivax* Pf *Plasmodium falciparum*

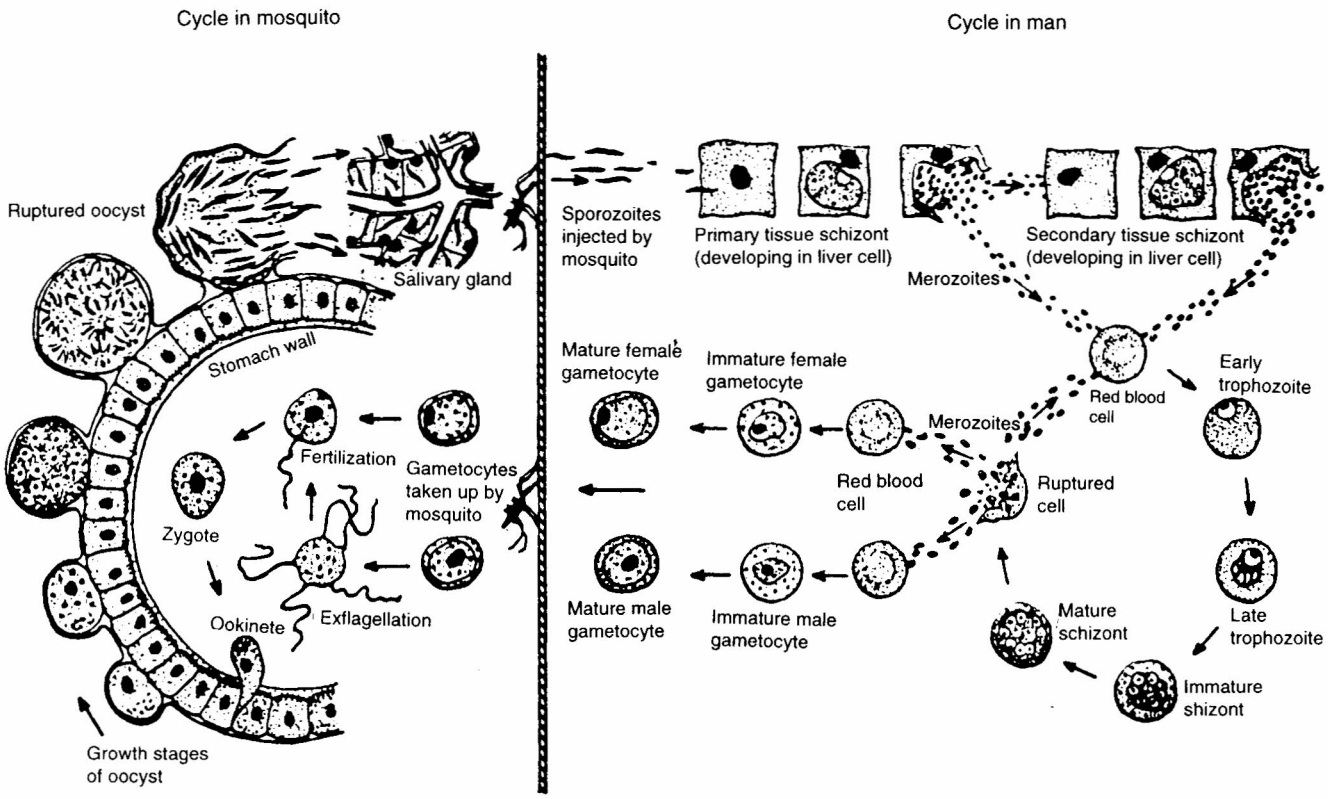

FIG 4. Life cycle of malarial parasite

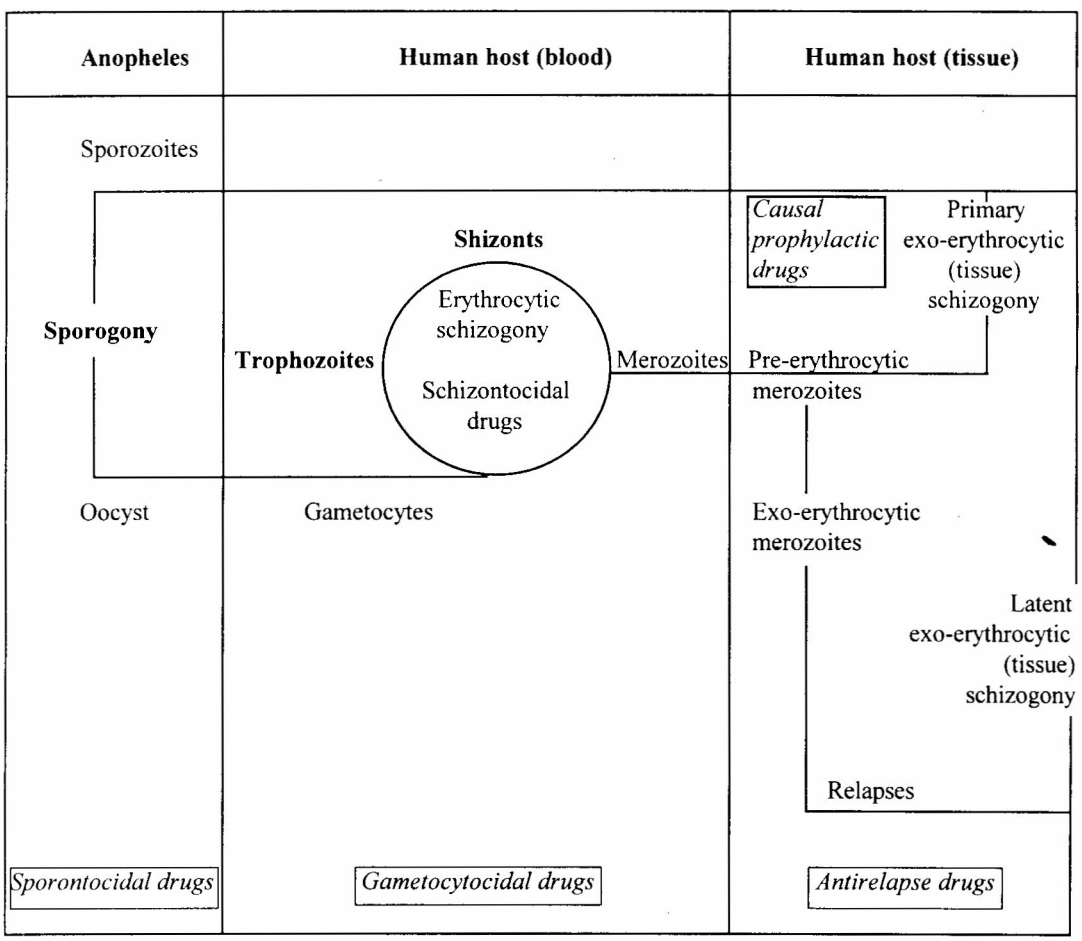

FIG 5. Action of antimalarial compounds on different parts of the life cycle of *Plasmodia* in the mosquito and man

Schizonticides (Blood schizonticides or schizonticidal drugs). These achieve clinical cure of infection. They also act on sexual erythrocytic forms of Pv, *P. ovale* and *P. malariae.*

Gametocytocides. These drugs destroy all sexual forms including those of Pf. They also act on the developmental stages of the malarial parasite in the anopheles.

TREATMENT OF AN UNCOMPLICATED ATTACK

There are two main types of drug administration:[3]

Presumptive treatment

This assumes that every case of fever is due to malaria and pending the result of a blood slide examination 600 mg base of chloroquine is given in a single dose. This is often the only practical and effective approach in community based programmes. However, if a patient with fever reports to a clinician and other obvious causes for it are ruled out, a peripheral blood smear is prepared for examination of the malarial parasite and presumptive treatment should be given only if there is a delay in obtaining the report. Otherwise further treatment should be started after receiving the report and would depend on the infecting species.

Radical treatment

If the blood smear is positive for malaria then full doses of chloroquine and primaquine should be given. The World Health Organization (WHO) recommends that for Pv and Pf infections chloroquine is given in a total dose of 1500 mg base over a period of 3 days in the following manner:

Day 1: Chloroquine 600 mg base followed 6 hours later by 300 mg
Day 2: Chloroquine 300 mg base
Day 3: Chloroquine 300 mg base

Patients should be advised to take the drug after meals and that it will take 48 hours before the signs and symptoms subside.

When the patient has already received presumptive treatment he or she should be given only 900 mg chloroquine to complete the dose of 1500 mg. However, if there is a gap of more than 7 days between the presumptive therapy and radical treatment then a full course of 1500 mg chloroquine base should be given.

In India the population is partly immune to malaria and no cases of chloroquine resistance to Pf have yet been reported. Therefore, under the National Programme for Control of Malaria, a single dose of 600 mg base of chloroquine is given after confirmation of diagnosis (as in radical treatment).[3] However, relapses sometimes occur in Pv infection. To prevent these, primaquine should be given in a dose of 15 mg per day for 5 days. This drug destroys the latent forms of the parasite (hypnozoites in the liver). While administering primaquine one should remember that[4]

1. It should not be given where active transmission is continuing.
2. It should not be given to infants and pregnant women.
3. It should never be prescribed to patients known to have glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.
4. It should be discontinued if the patient has side-effects such as cyanosis or haematuria.

It is not necessary to give antirelapse treatment to all cases of Pv infections who live in areas where the transmission levels are high. The patients should be given the full course of chloroquine and warned of a possible relapse. If the symptoms recur, they should be treated with another course of chloroquine or a combination of chloroquine and primaquine.[4] If primaquine is not available, the relapse can be treated with chloroquine alone. The WHO recommends 15 mg/day of primaquine for 14 days. In India the former schedule is preferred because of operational reasons and safety.

For Pf infection, primaquine should be given in a single dose of 45 mg to eliminate the sexual forms of the parasite or the gametocytes. The gametocytes do not cause clinical signs and symptoms, but transmit the disease via mosquitoes. A single dose of primaquine eliminates gametocytes from the blood. If primaquine is not available chloroquine should be given.

While most of the cases will respond to treatment, some may show recrudescence within 28 days. If this occurs even after taking the full dose of 1500 mg of chloroquine (and non-compliance by the patient or vomiting are excluded), it means that chloroquine resistant strains of Pf are present in that particular area. The response of the parasite to chloroquine can be graded as described below.[5]

Sensitivity ('S') is defined as 'clearance of asexual' parasitaemia as seen in the blood smear within 7 days of starting treatment by administering 1.5 g of chloroquine base without subsequent recrudescence within a period of 28 days.

Resistance (R) has three grades.

R I. The blood smear shows clearance of asexual parasites within 7 days after starting treatment with 1.5 g of chloroquine base followed by their reappearance within 8 to 28 days.
R II. The blood smear shows reduction to 25% of the pretreatment asexual parasites but no clearance.
R III. The blood smear shows no marked reduction, that is parasitaemia persists at the 75% level after the administration of 1.5 g of chloroquine base.

If after 48 hours of treatment, the parasite count decreases to 25% of the original value, the organism can be assumed to be sensitive to chloroquine. However, if the count persists at the 75% level after 48 hours, then other drugs should be given[6] (Fig. 6).

For adults a combination of sulphadoxine or sulphalene 1000 to 1500 mg with pyrimethamine 50 to 75 mg in a single dose (2 to 3 tablets of the combination) is recommended.

If the patient is sensitive to sulphonamides or Pf is resistant to the sulphadoxine–pyrimethamine combination then quinine sulphate 600 mg, 3 times a day for 7 days in combination with tetracycline 1 to 2 g daily for 7 days should be given. The oral use of quinine should be restricted otherwise the effectiveness of this valuable drug for complicated cases of malaria may be lost.

P. malariae infections are also encountered in some parts of our country and may cause serious renal complications. These patients should be treated with chloroquine in a dose of 150 mg over 3 days. Primaquine is not given because

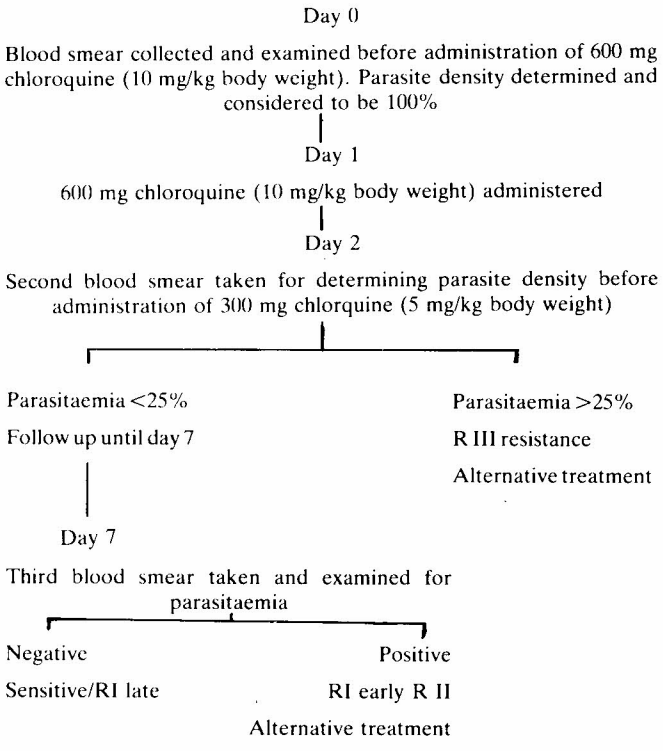

FIG 6. Simplified *in vivo* test system for detecting chloroquine resistance in *P. falciparum*

relapses do not occur due to *P. malariae*. Mixed infections with Pv and Pf should be treated as for Pf. Figure 7 depicts a scheme of treatment.

NEWER DRUGS

The diminishing efficacy of existing antimalarial drugs, because of increasing numbers of drug resistant parasite strains, has made prophylaxis and treatment of the disease a therapeutic challenge. Many new drugs have been introduced in various countries in the recent past. Their indiscriminate use has led to development of drug resistant strains of Pf to them as well. In India, so far only chloroquine, amodiaquine, sulphapyrimethamine, quinine, tetracycline and primaquine are officially registered for use. The artemisinin group of drugs are likely to be introduced in the near future.

Mefloquine

Mefloquine, a quinolinemethanol, chemically related to quinine, is a potent long acting blood schizonticide active against parasites resistant to 4-aminoquinolines, sulphonamide–pyrimethamine combinations and quinine. It is also effective in a single oral dose (usually 15 mg/kg base) and so avoids patient non-complicance.[7]

At present, no parenteral formulation is available as the drug is irritating to the peripheral vein walls. The main adverse reactions are dizziness, nausea, vomiting, diarrhoea and abdominal pain, but these are all self-limiting. Dose-related sinus bradycardia has also been reported. There has been increasing concern about reports of serious neurological and psychiatric side-effects following the therapeutic and prophylactic use of mefloquine. Considering this the WHO recommends that persons involved in tasks requiring fine coordination and spatial discrimination should not be administered prophylactic mefloquine.

Halofantrine

This is an aminoalcohol and a member of the 9-phenanthrenemethanol class of drugs. It has some disadvantages—poor solubility in water, inter- and intra-subject variation in bioavailability and slow absorption. It may be useful in areas where mefloquine is not effective.[8]

Artemisinin

This is an antimalarial compound which was isolated in China from the aerial parts of the plant *Artemisia annua*.[9] It is a sesquiterpene lactone with a bridged peroxide linkage. A number of derivatives such as artemether, arteether and artesunate are available. Data from 23 trials (on 1891 patients), comparing an artemisinin derivative with other antimalarials have shown that the fever clearance time compared with intravenous quinine was shortened by 17% (to 7.7 hours) and parasite clearance by 32% (19.8 hours). Artesunate appears to have a more rapid action than the other derivatives. No serious toxicity was observed but the recrudescence rate is high when the drug is used alone. A 50% recrudescence rate following a 3-day treatment schedule has been reported and the use of mefloquine or other long acting antimalarials has been recommended to prevent this phenomenon. This is a valuable drug for rapid parasitological and clinical recovery in cases of severe and complicated malaria.

Antibiotics

Certain antibiotics (tetracyclines and clindamycin) have useful antimalarial properties. Erythromycin, chloramphenicol and rifampicin have antimalarial activity *in vitro* but have not yet found clinical application.

VACCINES

The life cycle of Pf is complex and thus the task of designing an effective vaccine has been difficult. Most vaccines which have been targeted against the sporozoite stage of the parasite, have been based on the NANP (Asn-Ala-Asn-Pro) repeat sequence of the circumsporozoite protein. This sequence has been obtained by chemical synthesis and the synthetic hybrid (SPf66) vaccine has been found to be safe, non-toxic, immunogenic and protective.[10]

A double blind efficacy trial conducted in Colombia, South America showed a 34% protective efficacy against the first or only episodes, being highest among children aged 1 to 4 years (77%) and adults older than 45 years (67%). The estimated protective efficacy against second episodes was 51%.

CHEMOPROPHYLAXIS

Chloroquine is the best and safest drug for prophylaxis. The dose is 600 mg base in the first week followed by 300 mg base once a week. It prevents the clinical signs and symptoms and is a suppressive prophylactic. It can protect against malaria due to the non-falciparum species, will suppress the strains of Pf that have low levels of resistance and may reduce mortality due to chloroquine resistant Pf infections.[11] Daily proguanil in a dose of 200 mg in addition to

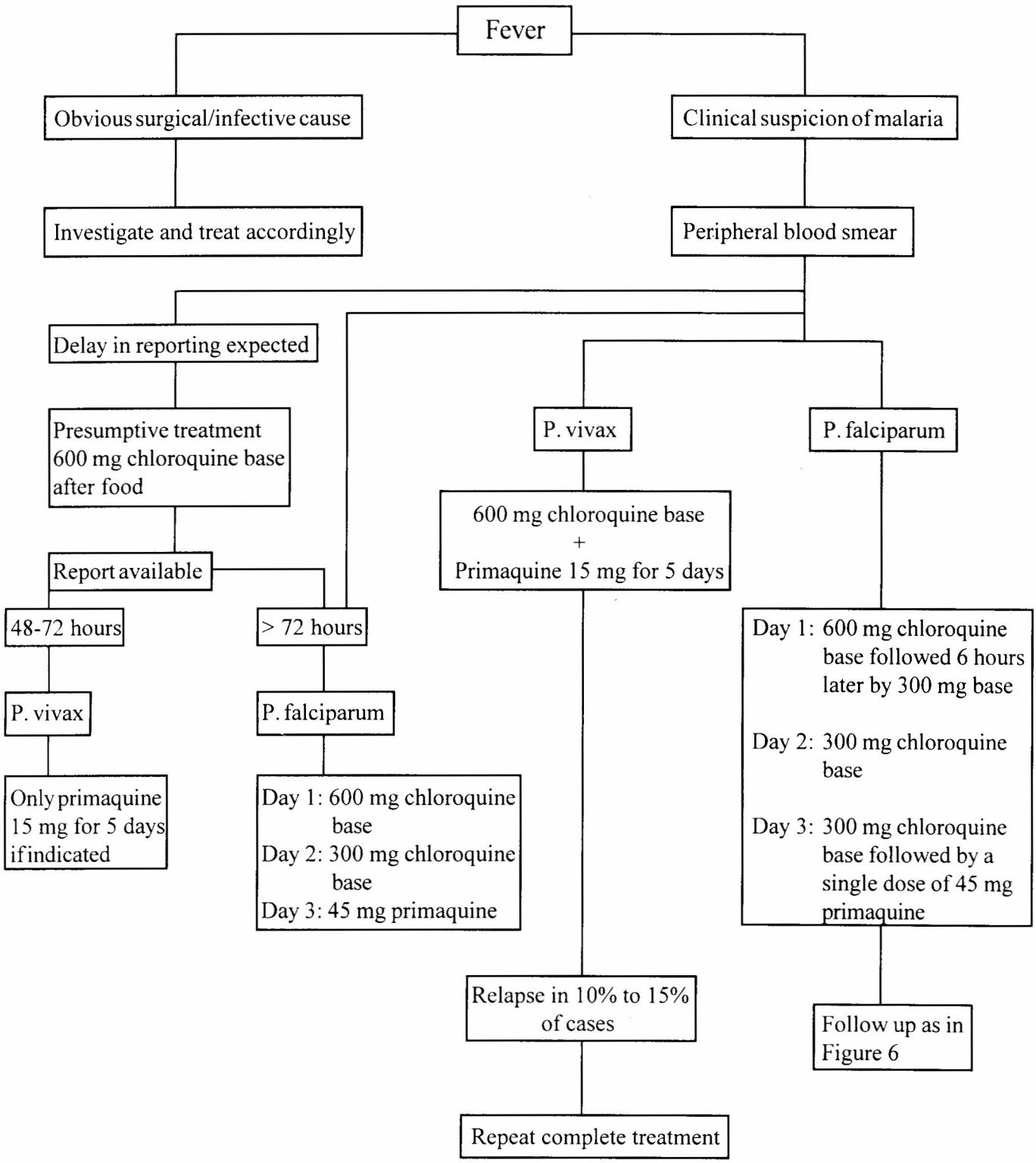

FIG 7. Flow diagram showing an approach to the treatment of malaria

chloroquine is more effective in regions where chloroquine resistance occurs.

Prophylactic drugs should not be prescribed routinely. They are indicated for only special risk groups such as pregnant women, non-immune travellers and non-immune persons living in closed communities in endemic areas for fixed periods (e.g. labour forces and police and army units).

THE FUTURE

For effective implementation of a global strategy, it is necessary that there be sustained political commitment at all levels of the government and private sector. Also control and prevention of malaria should be an integral part of health systems and should be coordinated with the relevant development programmes in non-health sectors.

IMPORTANT POINTS

1. Always determine the species and stage of the malarial parasite in the peripheral blood smear.
2. Gametocytes/sexual forms of parasite are not responsible for the clinical syndrome.
3. It is important to determine whether the patient has already been treated with antimalarial drugs. Patients who have parasitaemia and are likely to have received treatment within 3 to 7 days may have been 'treatment failures'. Those who have been treated with drugs within the previous 24 to 36 hours may be at risk of adverse drug interactions if other drugs are administered.
4. Wait 48 hours for clinical and parasitological recovery and then reassess the patient.
5. The problem of drug resistance has been encountered in Pf and not in Pv or *P. malariae* infection.
6. Relapses occur only in Pv and *P. ovale* infections.
7. Primaquine is used as an antirelapse drug in Pv and for preventing transmission in Pf. It has no role in curing an acute attack.
8. Treatment is essentially the same in children. The dose of chloroquine is 10 mg/kg followed 6 hours later by 5 mg/kg on day 1 and 5 mg/kg on days 2 and 3.
9. Chloroquine and quinine are safe during pregnancy.
10. The sulphonamide–pyrimethamine combination is not needed for treatment of Pv infections. It has limited efficacy and slower action in these cases. Use these drugs only in chloroquine resistant cases of Pf.

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