

# 1. INTRODUCTION

## 1.1 Background

Malaria is an important cause of death and illness in children and adults in tropical countries. Mortality, currently estimated at over a million people per year, has risen in recent years, probably due to increasing resistance to antimalarial medicines. Malaria control requires an integrated approach comprising prevention including vector control and treatment with effective antimalarials. The affordable and widely available antimalarial chloroquine that was in the past a mainstay of malaria control is now ineffective in most *falciparum* malaria endemic areas, and resistance to sulfadoxine–pyrimethamine is increasing rapidly. The discovery and development of the artemisinin derivatives in China, and their evaluation in South-East Asia and other regions, have provided a new class of highly effective antimalarials, and have already transformed the chemotherapy of malaria in South-East Asia. Artemisinin-based combination therapies (ACTs) are now generally considered as the best current treatment for uncomplicated *falciparum* malaria.

These treatment guidelines recommend antimalarials for which there is adequate evidence of efficacy and safety now, and which are unlikely to be affected by resistance in the near future. Much of the world's symptomatic malaria is treated in peripheral health centres or remote villages, where facilities are limited. The aim is therefore to provide simple and straightforward treatment recommendations based on sound evidence that can be applied effectively in most settings.

These guidelines are based on a review of current evidence and are developed in accordance with WHO's standard methodology. Clinical evidence has been assessed in an objective way using standard methods. The number of anti-malarial drug trials published has doubled in the past seven years, so these guidelines have a firmer evidence base than previous treatment recommendations. Inevitably, information gaps remain, however, and so the guidelines will remain under regular review and will be updated as new evidence becomes available. There are also difficulties when comparing results from different areas, as levels of drug resistance and background immunity vary. Where transmission levels and, consequently, immunity are high, the malaria symptoms are self-limiting in many patients, in particular in adults, so that drugs that are only partially effective may appear still to work well in many cases, misleading patients and doctors alike. But in the same location, the young child who lacks immunity to illness caused by *P. falciparum* may die if ineffective drugs are given.

The treatment recommendations given in these guidelines aim for effective treatment for the most vulnerable and therefore take all the relevant factors into account. These factors include laboratory measures, such as tests for *in vitro* antimalarial susceptibility and validated molecular markers of resistance, the pharmacokinetic and pharmacodynamic properties of the different antimalarials, and clinical trial results. Cost is a factor that has been taken into consideration in antimalarial treatment policy and practices. However, there are increasing international subsidies for antimalarials. Efficacy (both now and in the future) and safety have therefore taken precedence when making the recommendations. The malaria treatment guidelines given below are brief; for those who wish to study the evidence base in more detail, a series of annexes is provided.

## 1.2 Objectives and target audience

The purpose of this document is to provide comprehensible, global, evidence-based guidelines to help formulate policies and protocols for the treatment of malaria. Information is presented on the treatment of:

- uncomplicated malaria, including disease in special groups (young children, pregnant women, people who are HIV-positive, travellers from non-malaria endemic regions) and in epidemics and complex emergency situations;
- severe malaria.

The guidelines do not deal with preventive uses of antimalarials, such as intermittent preventive treatment or chemoprophylaxis.

The guidelines are aimed primarily at policy-makers in ministries of health. The following groups should also find them useful:

- public health and policy specialists working in hospitals, ministries, non-governmental organizations and primary health care services;
- health professionals (doctors, nurses and paramedical officers).

The guidelines provide a framework for the development of specific and more detailed treatment protocols that take into account national and local malaria drug resistance patterns and health service capacity (see Annex 2). They are not intended to provide a comprehensive clinical management guide for the treatment of malaria. However, where there are controversies about specific clinical practices, and evidence is currently available to provide information to guide decision-making about these practices, that information has been included.

### 1.3 Methods used in developing the guidelines and recommendations

These guidelines have been developed in accordance with the *WHO Guidelines for Guidelines Development*.<sup>1</sup> In order to ensure that the guidelines are based on the best current evidence, WHO commissioned two academic centres to identify, compile and critically review published and unpublished studies of antimalarial treatments. The collated evidence was then reviewed by the Technical Guidelines Development Group made up of a broad spectrum of experts on malaria, malaria control programmes, and treatment guidelines methodology. A large number of external reviewers with a wide range of expertise were also involved in developing the guidelines.

In assessing the available information on treatment options, four main types of information were considered, and should also be considered by countries seeking to adapt the guidelines.<sup>2</sup> Wherever possible, systematic reviews of randomized trials that directly compare two or more treatment alternatives in large populations were identified and used as the basis for recommendations. It is clear that such evidence does not exist for all options, but recommendations on these options still need to be made. Other information including studies measuring cure rates but not directly comparing treatments, pharmacological assessments and surveillance data about resistance patterns have therefore also been considered.

In relation to malaria, as with other diseases, systematic reviews are not the sole basis for decision-making: the large differences in transmission intensity, and thus baseline immunity, in treatment populations and in resistance patterns all have major effects on treatment responses. Any statistical analysis that combines the results of individual studies has to take due account of these factors and be interpreted accordingly. However, such analyses do not obviate the need for a systematic and comprehensive review of all available trials before reaching decisions about treatment recommendations.

Treatments for malaria, like those for many infectious diseases, must be considered from the perspective of community or public health benefits and harms as well as from that of the patient. In some instances, therefore, the recommendations provided here are based on public health considerations as well as the potential individual benefits.





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<sup>1</sup> The process is described in detail in Annex 1.

<sup>2</sup> A guide to assist country adaptation of these guidelines is provided in Annex 2.

Cost-effectiveness studies have not been included in the information considered by the Technical Guidelines Development Group at this stage for two reasons: there are very few completed, generalizable cost-effectiveness studies that relate to the main treatment options being considered and the price of the antimalarials concerned is extremely fluid, rendering such studies unreliable. However, as relevant information becomes available, it will be considered for inclusion in future editions of the guidelines.

For clarity, these guidelines have adopted a simple descriptive approach; this may be revised in future editions. They are presented as a central unreferenced main document containing the recommendations. Summaries of the recommendations are given in boxes. Symbols for the evidence used as the basis of each recommendation (in order of level of evidence) are:

-  formal systematic reviews, such as a Cochrane Review, including more than one randomized controlled trial;
-  comparative trials without formal systematic review;
-  observational studies (e.g. surveillance or pharmacological data);
-  expert opinion/consensus.

In addition, for each policy or treatment question leading to a recommendation, a brief summary of evidence is provided in a separate evidence box. Full reviews of the evidence and references are provided in annexes. If pharmacokinetics studies have been included as part of the deliberations, this is noted in the main document.<sup>3</sup>

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<sup>3</sup> Details of the pharmacology of antimalarials are provided in Annex 3.

## 2. THE CLINICAL DISEASE

Malaria is caused by infection of red blood cells with protozoan parasites of the genus *Plasmodium*. The parasites are inoculated into the human host by a feeding female anopheline mosquito. The four *Plasmodium* species that infect humans are *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Occasional infections with monkey malaria parasites, such as *P. knowlesi*, also occur.

The first symptoms of malaria are nonspecific and similar to the symptoms of a minor systemic viral illness. They comprise: headache, lassitude, fatigue, abdominal discomfort and muscle and joint aches, followed by fever, chills, perspiration, anorexia, vomiting and worsening malaise. This is the typical picture of uncomplicated malaria. Residents of endemic areas are often familiar with this combination of symptoms, and frequently self-diagnose.

Malaria is therefore frequently overdiagnosed on the basis of symptoms alone. Infection with *P. vivax* and *P. ovale*, more than with other species, can be associated with well-defined malarial paroxysms, in which fever spikes, chills and rigors occur at regular intervals. At this stage, with no evidence of vital organ dysfunction, the case-fatality rate is low (circa 0.1% for *P. falciparum* infections – the other human malarias are rarely fatal) provided prompt and effective treatment is given. But if ineffective drugs are given or treatment is delayed in falciparum malaria, the parasite burden continues to increase and severe malaria may ensue. A patient may progress from having minor symptoms to having severe disease within a few hours. This usually manifests with one or more of the following: coma (cerebral malaria), metabolic acidosis, severe anaemia, hypoglycaemia and, in adults, acute renal failure or acute pulmonary oedema. By this stage, mortality in people receiving treatment has risen to 15–20%. If untreated, severe malaria is almost always fatal.

The nature of the clinical disease depends very much on the pattern and intensity of malaria transmission in the area of residence, which determines the degree of protective immunity acquired and, in turn, the clinical disease profile. Where malaria transmission is “stable” – meaning where populations are continuously exposed to a fairly constant rate of malarial inoculations – and if the inoculation rates are high – entomological inoculation rate (EIR) >10/year –, then partial immunity to the clinical disease and to its severe manifestations is acquired early in childhood. In such situations, which prevail in much of sub-Saharan Africa and parts of Oceania, the acute clinical disease described above is almost always confined to young children who suffer high parasite densities and acute clinical disease. If untreated, this can progress very rapidly to severe malaria. In stable and high-transmission areas, adolescents and adults are partially immune and rarely suffer clinical disease,

although they continue to harbour low blood-parasite densities. Immunity is reduced in pregnancy, and can be lost when individuals move out of the transmission zone.

In areas of unstable malaria, the situation prevailing in much of Asia and Latin America and the remaining parts of the world where malaria is endemic, the rates of inoculation fluctuate greatly over seasons and years. EIRs are usually  $<5$ /year and often  $<1$ /year. This retards the acquisition of immunity and results in people of all ages, adults and children alike, suffering acute clinical malaria, with a high risk of progression to severe malaria if untreated. Epidemics may occur in areas of unstable malaria when inoculation rates increase rapidly. Epidemics manifest as a very high incidence of malaria in all age groups and can overwhelm health services. Severe malaria is common if effective treatment is not made widely available.

Thus in areas of high transmission, it is children who are at risk of severe malaria and death, whereas in areas of low or unstable transmission, all age groups are at risk.

## 3. TREATMENT OBJECTIVES

### 3.1 Uncomplicated malaria

The objective of treating uncomplicated malaria is to cure the infection. This is important as it will help prevent progression to severe disease and prevent additional morbidity associated with treatment failure. Cure of the infection means eradication from the body of the infection that caused the illness. In treatment evaluations in all settings, emerging evidence indicates that it is necessary to follow patients for long enough to document cure (see section 6.1). In assessing drug efficacy in high-transmission settings, temporary suppression of infection for 14 days is not considered sufficient by the group.

The public health goal of treatment is to reduce transmission of the infection to others, i.e. to reduce the infectious reservoir.<sup>4</sup>

A secondary but equally important objective of treatment is to prevent the emergence and spread of resistance to antimalarials. Tolerability, the adverse effect profile and the speed of therapeutic response are also important considerations.

### 3.2 Severe malaria

The primary objective of antimalarial treatment in severe malaria is to prevent death. Prevention of recrudescence and avoidance of minor adverse effects are secondary. In treating cerebral malaria, prevention of neurological deficit is also an important objective. In the treatment of severe malaria in pregnancy, saving the life of the mother is the primary objective.

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<sup>4</sup> Further information on antimalarials and malaria transmission is provided in Annex 4.

## 4. DIAGNOSIS OF MALARIA

Prompt and accurate diagnosis of malaria is part of effective disease management and will, if implemented effectively, help to reduce unnecessary use of antimalarials.<sup>5</sup> High sensitivity of malaria diagnosis is important in all settings, in particular for the most vulnerable population groups, such as young children, in which the disease can be rapidly fatal. High specificity can reduce unnecessary treatment with antimalarials and improve differential diagnosis of febrile illness.

The diagnosis of malaria is based on clinical criteria (clinical diagnosis) supplemented by the detection of parasites in the blood (parasitological or confirmatory diagnosis). Clinical diagnosis alone has very low specificity and in many areas parasitological diagnosis is not currently available. The decision to provide antimalarial treatment in these settings must be based on the prior probability of the illness being malaria. One needs to weigh the risk of withholding antimalarial treatment from a patient with malaria against the risk associated with antimalarial treatment when given to a patient who does not have malaria.

### 4.1 Clinical diagnosis

The signs and symptoms of malaria are nonspecific. Malaria is clinically diagnosed mostly on the basis of fever or history of fever. The following WHO recommendations are still considered valid for clinical diagnosis.<sup>6</sup>

- In general, **WHO**, clinical diagnosis of uncomplicated malaria should be based on the degree of exposure to malaria and a history of fever in the previous 3 days with no features of other severe diseases.
- In young children, **WHO**, clinical diagnosis should be based on a history of fever in the previous 24 h and/or the presence of anaemia, for which pallor of the palms appears to be the most reliable sign in young children.

The WHO/UNICEF strategy for Integrated Management of Childhood Illness (IMCI)<sup>7</sup> has also developed practical algorithms for management of the sick child presenting with fever where there are no facilities for laboratory diagnosis.

<sup>5</sup> Further information on the diagnosis of malaria is provided in Annex 5.

<sup>6</sup> WHO Expert Committee on Malaria. Twentieth report. Geneva, World Health Organization, 2000 (WHO Technical Report Series, No. 892).

<sup>7</sup> IMCI information package, 1999. Geneva, World Health Organization, 1999 (document WHO/CHS/CAH/98.1).

## 4.2 Parasitological diagnosis

The introduction of ACTs has increased the urgency of improving the specificity of malaria diagnosis. The relatively high cost of these drugs makes waste through unnecessary treatment of patients without parasitaemia unsustainable. In addition to cost savings, parasitological diagnosis has the following advantages:

- improved patient care in parasite-positive patients owing to greater certainty that the patient has malaria;
- identification of parasite-negative patients in whom another diagnosis must be sought;
- prevention of unnecessary exposure to antimalarials, thereby reducing side-effects, drug interactions and selection pressure;
- improved health information;
- confirmation of treatment failures.

The two methods in use for parasitological diagnosis are light microscopy and rapid diagnostic tests (RDTs). Light microscopy has the advantage of low cost and high sensitivity and specificity when used by well-trained staff. RDTs for detection of parasite antigen are generally more expensive, but the prices of some of these products have recently decreased to an extent that makes their deployment cost-effective in some settings. Their sensitivity and specificity are variable, and their vulnerability to high temperatures and humidity is an important constraint. Despite these concerns, RDTs make it possible to expand the use of confirmatory diagnosis. Deployment of these tests, as with microscopy, must be accompanied by quality assurance. Practical experience and operational evidence from large-scale implementation are limited and, therefore, their introduction should be carefully monitored and evaluated.

The results of parasitological diagnosis should be available within a short time (less than 2 h) of the patient presenting. If this is not possible, the patient must be treated on the basis of a clinical diagnosis.

The choice between RDTs and microscopy depends on local circumstances, including the skills available, the usefulness of microscopy for other diseases found in the area, and the case-load. Where the case-load of fever patients is high, microscopy is likely to be less expensive than RDTs. Microscopy has further advantages in that it can be used for speciation and quantification of parasites, and identification of other causes of fever. However, most malaria patients are treated outside the health services, for example, in the community,

in the home or by private providers; microscopy is generally not feasible in such circumstances, but RDTs may be.

The following conclusions and recommendations are based on evidence summarized by recent WHO consultations, especially the Technical Consultation on the Role of Parasitological Diagnosis in Malaria Case Management in Areas of High Transmission, held in Geneva from 25 to 26 October 2004 (report in preparation).

### 4.3 Where malaria transmission is low to moderate and/or unstable

Parasitological confirmation of the diagnosis of malaria is recommended. This should be provided by microscopy or, where not available, RDTs. Low to moderate transmission settings<sup>8</sup> include many urban areas in Africa, and the low transmission season in areas with seasonal malaria.

In settings where malaria incidence is very low, parasitological diagnosis for all fever cases may lead to considerable expenditure to detect only a few patients who are actually suffering from malaria. In such settings, health workers should be trained to identify, through the history, patients that have been exposed to malaria risk before they conduct a parasitological test.

### 4.4 In stable high-transmission settings

Malaria is usually the most common cause of fever in children under 5 years of age in these areas. Antimalarial treatment should therefore be given to children with fever (>37.5 °C) or a history of fever and no other obvious cause. Malaria is the most likely cause of their illness and there is as yet no evidence to show that the benefits of parasitological diagnosis in this highly vulnerable group outweigh the risks of not treating false negatives. In children of 5 years of age and above, malaria becomes progressively less likely as a cause of fever, as immunity is acquired. In these older children and in adults, malaria diagnosis should be based on a parasitological confirmation. Parasitological diagnosis should be promoted in pregnant women, to improve the differential diagnosis of fever and to reduce unnecessary use of antimalarials in pregnancy. Parasitological diagnosis is also particularly important in settings with a high prevalence of HIV/AIDS because of the high incidence of febrile disease that is not malaria in HIV-infected patients.

<sup>8</sup> Transmission intensity is conventionally expressed in terms of EIR (see section 2). There is as yet no consensus on criteria for determining the thresholds between high, and low to moderate transmission settings. Suggested criteria include: the proportion of all children under 5 years of age with patent parasitaemia, and the incidence of individuals with the spleen palpable below the umbilicus in children aged 2–9 years. The IMCI guidelines recommend that areas in which fewer than 5% of young children with fever have malaria parasitaemia should be considered as low-transmission settings.

## 4.5 Malaria parasite species identification

In areas where two or more species of malaria parasites are common, only a parasitological method will permit a species diagnosis. Where mono-infection with *P. vivax* is common and microscopy is not available, it is recommended that a combination RDT which contains a pan-malarial antigen is used. Alternatively, RDTs specific for falciparum malaria may be used, and treatment for vivax malaria given only to cases with a negative test result but a high clinical suspicion of malaria. Where *P. vivax*, *P. malariae* or *P. ovale* occur almost always as a co-infection with *P. falciparum*, an RDT detecting *P. falciparum* alone is sufficient. Anti-relapse treatment with primaquine should only be given to cases with confirmed diagnosis of vivax malaria.

## 4.6 In epidemics and complex emergencies

In epidemic and complex emergency situations, facilities for parasitological diagnosis may be unavailable or inadequate to cope with the case-load. In such circumstances, it is impractical and unnecessary to demonstrate parasites before treatment in all cases of fever. However, there is a role for parasitological diagnosis even in these situations (see section 11.1).

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| <p>In areas of low to moderate transmission, prompt parasitological confirmation of the diagnosis is recommended before treatment is started. This should be achieved through microscopy or, where not available, RDTs.</p>  |  |
| <p>In areas of high stable malaria transmission, the prior probability of fever in a child being caused by malaria is high. Children under 5 years of age should therefore be treated on the basis of a clinical diagnosis of malaria. In older children and adults including in pregnant women, a parasitological diagnosis is recommended before treatment is started.</p> |  |
| <p>In all suspected cases of severe malaria, a parasitological confirmation of the diagnosis of malaria is recommended. In the absence of or a delay in obtaining parasitological diagnosis, patients should be treated for severe malaria on clinical grounds.</p>  |  |

## 5. RESISTANCE TO ANTIMALARIAL MEDICINES<sup>9</sup>

Resistance has arisen to all classes of antimalarials except, as yet, to the artemisinin derivatives. This has increased the global malaria burden and is a major threat to malaria control. Widespread and indiscriminate use of antimalarials places a strong selective pressure on malaria parasites to develop high levels of resistance. Resistance can be prevented, or its onset slowed considerably, by combining antimalarials with different mechanisms of action and ensuring very high cure rates through full adherence to correct dose regimens.

### 5.1 Impact of resistance

Initially, at low levels of resistance and with a low prevalence of malaria, the impact of resistance to antimalarials is insidious. The initial symptoms of the infection resolve and the patient appears to be better for some weeks. When symptoms recur, usually more than two weeks later, anaemia may have worsened and there is a greater probability of carrying gametocytes (which in turn carry the resistance genes) and transmitting malaria. However, the patient and the treatment provider may interpret this as a newly acquired infection. At this stage, unless clinical drug trials are conducted, resistance may go unrecognized. As resistance worsens the interval between primary infection and recrudescence shortens, until eventually symptoms fail to resolve following treatment. At this stage, malaria incidence may rise in low-transmission settings and mortality is likely to rise in all settings.

### 5.2 Global distribution of resistance

Resistance to antimalarials has been documented for *P. falciparum*, *P. vivax* and, recently, *P. malariae*.

In *P. falciparum*, resistance has been observed to almost all currently used antimalarials (amodiaquine, chloroquine, mefloquine, quinine and sulfadoxine–pyrimethamine) except for artemisinin and its derivatives. The geographical distributions and rates of spread have varied considerably.

*P. vivax* has developed resistance rapidly to sulfadoxine–pyrimethamine in many areas. Chloroquine resistance is confined largely to Indonesia, East Timor, Papua New Guinea and other parts of Oceania. There are also documented reports

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<sup>9</sup> Further information on the emergence, spread and prevention of resistance to antimalarials is provided in Annex 6.

from Peru. *P. vivax* remains sensitive to chloroquine in South-East Asia, the Indian subcontinent, the Korean peninsula, the Middle East, north-east Africa, and most of South and Central America.

### 5.3 Assessing resistance

The following methods are available for assessing resistance to antimalarials:

- *in vivo* assessment of therapeutic efficacy (see section 6.1),
- *in vitro* studies of parasite susceptibility to drugs in culture,
- molecular genotyping.

## 6. ANTIMALARIAL TREATMENT POLICY

National antimalarial treatment policies should aim to offer antimalarials that are highly effective. The main determinant of policy change is the therapeutic efficacy and the consequent effectiveness of the antimalarial in use. Other important determinants include: changing patterns of malaria-associated morbidity and mortality; consumer and provider dissatisfaction with the current policy; and the availability of new products, strategies and approaches.

### 6.1 Assessment of *in vivo* therapeutic efficacy

This involves the assessment of clinical and parasitological outcomes of treatment over a certain period following the start of treatment, to check for the reappearance of parasites in the blood. Reappearance indicates reduced parasite sensitivity to the treatment drug. As a significant proportion of treatment failures do not appear until after day 14, shorter observation periods lead to a considerable overestimation of the efficacy of the tested drug. This is a particular problem at low levels of resistance and with low failure rates. The current recommended duration of follow-up is  $\geq 28$  days in areas of high as well as low to moderate transmission. Assessment over only 14 days, the period previously recommended in areas of high transmission, is no longer considered sufficient. Antimalarial treatment should also be assessed on the basis of parasitological cure rates. Where possible, blood or plasma levels of the antimalarial should also be measured in prospective assessments so that drug resistance can be distinguished from treatment failures due to pharmacokinetic reasons.

In high-transmission settings reinfection is inevitable, but cure of malaria (i.e. prevention of recrudescences) is important as it benefits both the patient, by reducing anaemia, and the community, by slowing the emergence and spread of resistance. In the past, “clinical” and “parasitological” cure rates were regarded separately, but with increasing appreciation of the adverse effects of treatment failure, the two are now considered together. Persistence of parasitaemia without fever following treatment has previously not been regarded seriously in high-transmission situations. This still represents a treatment failure and is associated with anaemia. Slowly eliminated antimalarials provide the additional benefit of suppressing malaria infections that are newly acquired during the period in which residual antimalarial drug levels persist in the body. On the other hand, these residual drug levels do provide a selection pressure for resistance. In these treatment recommendations, the curative efficacy of the antimalarials has taken precedence over these considerations.

## 6.2 Criteria for antimalarial treatment policy change

These malaria treatment guidelines recommend that antimalarial treatment policy should be changed at treatment failure rates considerably lower than those recommended previously. This major change reflects the availability of highly effective drugs, and the recognition both of the consequences of drug resistance, in terms of morbidity and mortality, and the importance of high cure rates in malaria control.

It is now recommended that a change of first-line treatment should be initiated if the total failure proportion exceeds 10%. However, it is acknowledged that a decision to change may be influenced by a number of additional factors, including the prevalence and geographical distribution of reported treatment failures, health service provider and/or patient dissatisfaction with the treatment, the political and economical context, and the availability of affordable alternatives to the commonly used treatment.

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| In therapeutic efficacy assessments, the cure rate should be defined parasitologically, based on a minimum of 28 days of follow-up. Molecular genotyping using PCR technology should be used to distinguish recrudescing parasites from newly acquired infections. |  |
| Review and change of the antimalarial treatment policy should be initiated when the cure rate with the current recommended medicine falls below 90% (as assessed through monitoring of therapeutic efficacy).  |  |
| A new recommended antimalarial medicine adopted as policy should have an average cure rate $\geq 95\%$ as assessed in clinical trials.   |  |

## 7. TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA

### 7.1 Assessment

Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence of vital organ dysfunction. In acute falciparum malaria there is a continuum from mild to severe malaria. Young children and non-immune adults with malaria may deteriorate rapidly. Detailed definitions of severe malaria are available (see section 8.1) to guide practitioners and for epidemiological and research purposes but, in practice, any patient whom the attending physician or health care worker suspects of having severe malaria should be treated as such initially. The risks of under-treating severe malaria considerably exceed those of giving parenteral or rectal treatment to a patient who does not need it.

### 7.2 Antimalarial combination therapy

To counter the threat of resistance of *P. falciparum* to monotherapies, and to improve treatment outcome, combinations of antimalarials are now recommended by WHO for the treatment of falciparum malaria.

Antimalarial combination therapy is the simultaneous use of two or more blood schizontocidal drugs with independent modes of action and thus unrelated biochemical targets in the parasite. The concept is based on the potential of two or more simultaneously administered schizontocidal drugs with independent modes of action to improve therapeutic efficacy and also to delay the development of resistance to the individual components of the combination.

Drug combinations such as sulfadoxine–pyrimethamine, sulfalene–pyrimethamine, proguanil–dapson, chlorproguanil–dapson and atovaquone–proguanil rely on synergy between the two components. The drug targets in the malaria parasite are linked. These combinations are operationally considered as single products and treatment with them is not considered to be antimalarial combination therapy. Multiple-drug therapies that include a non-antimalarial medicine to enhance the antimalarial effect of a blood schizontocidal drug (e.g. chloroquine and chlorpheniramine) are also not antimalarial combination therapy.

The rationale for combining antimalarials with different modes of action is twofold: (1) the combination is often more effective; and (2) in the rare event that a mutant parasite that is resistant to one of the drugs arises de novo during the course of the infection, the parasite will be killed by the other drug. This mutual protection is thought to prevent or delay the emergence of resistance. To realize the two advantages, the partner drugs in a combination must be independently effective. The possible disadvantages of combination treatments are the potential for increased risk of adverse effects and the increased cost.

Artemisinin and its derivatives (artesunate, artemether, artemotil, dihydroartemisinin) produce rapid clearance of parasitaemia and rapid resolution of symptoms. They reduce parasite numbers by a factor of approximately 10 000 in each asexual cycle, which is more than other current antimalarials (which reduce parasite numbers 100- to 1000-fold per cycle). Artemisinin and its derivatives are eliminated rapidly. When given in combination with rapidly eliminated compounds (tetracyclines, clindamycin), a 7-day course of treatment with an artemisinin compound is required; but when given in combination with slowly eliminated antimalarials, shorter courses of treatment (3 days) are effective. The evidence of their superiority in comparison to monotherapies has been clearly documented.

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**Interventions:** single drug (oral AQ, MQ or SP) compared with single drug in combination with AS (both oral)

**Summary of RCTs:** one meta-analysis of 11 RCTs has been conducted. This found a clear benefit of adding 3 days of AS to AQ, MQ or SP for uncomplicated malaria. The combination treatment resulted in fewer parasitological failures at day 28 and reduced gametocyte carriage compared to the baseline value. Adding AS treatment for 1 day (6 RCTs) was also associated with fewer treatment failures by day 28 but was significantly less effective than the 3-day regimen (OR: 0.34; 95% CI: 0.24–0.47;  $p < 0.0001$ ).

**Expert comment:** the addition of AS to standard monotherapy significantly reduces treatment failure, recrudescence and gametocyte carriage.

**Basis of decision:** systematic review.

replace monotherapy with oral ACTs given for 3 days.

<sup>a</sup> See also Annex 7.1.

In 3-day ACT regimens, the artemisinin component is present in the body during only two asexual parasite life-cycles (each lasting 2 days, except for *P. malariae* infections). This exposure to 3 days of artemisinin treatment reduces the number of parasites in the body by a factor of approximately one hundred million ( $10^4 \times 10^4 = 10^8$ ). However, complete clearance of parasites is dependent on the partner medicine being effective and persisting at parasitocidal concentrations until all the infecting parasites have been killed. Thus the partner compounds need to be relatively slowly eliminated. As a result of this the artemisinin component is “protected” from resistance by the partner medicine provided it is efficacious and the partner medicine is partly protected by the artemisinin derivative. Courses of ACTs of 1–2 days are not recommended; they are less efficacious, and provide less protection of the slowly eliminated partner antimalarial.

The artemisinin compounds are active against all four species of malaria parasites that infect humans and are generally well tolerated. The only significant adverse effect to emerge from extensive clinical trials has been rare (circa 1:3000) type 1 hypersensitivity reactions (manifested initially by urticaria). These drugs also have the advantage from a public health perspective of reducing gametocyte carriage and thus the transmissibility of malaria. This contributes to malaria control in areas of low endemicity.

Non-artemisinin based combinations (non-ACTs) include sulfadoxine–pyrimethamine with chloroquine (SP+CQ) or amodiaquine (SP+AQ). However, the prevailing high levels of resistance have compromised the efficacy of these combinations. There is no convincing evidence that SP+CQ provides any additional benefit over SP, so this combination is not recommended; SP+AQ can be more effective than either drug alone, but needs to be considered in the light of comparison with ACTs. The evidence is summarized next page.

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**Interventions:** oral SP+CQ compared with oral SP

*Summary of RCTs:* no RCTs with reported results for day 28 outcomes. Five subsequent RCTs found insufficient evidence of any difference in rates of treatment failure at days 14 and 21, respectively, between CQ+SP and SP alone, and gave no information on adverse events.

*Expert comment:* increasing resistance to CQ in all settings means that neither of the options is recommended.

*Basis of decision:* RCT.

do not use CQ+SP.

**Interventions:** oral SP+AQ compared with oral AQ or oral SP

*Summary of RCTs:* one systematic review of SP+AQ compared with AQ alone with day 28 follow-up found no significant difference in day 28 outcomes.

Three subsequent RCTs also found no significant differences in cure rates and levels of adverse events.

One systematic review of SP+AQ compared with SP alone, found no significant difference in rates of day 28 cure or adverse events. One subsequent RCT found higher rates of day 28 cure and mid-adverse events with the combination compared to SP alone.

*Expert comment:* in some areas where AQ+SP has been deployed, failure rates of this combination have increased rapidly.

*Basis of decision:* systematic review.

if more effective medicines (ACTs) are not available and AQ and SP are effective,<sup>b</sup> AQ+SP may be used as an interim measure.

<sup>a</sup> See also Annex 7.2.

<sup>b</sup> Efficacy >80%.

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**Interventions: oral ACTs compared with oral non-artesunate combinations**

*Summary of RCTs:* 1 RCT compared AS (for 3 days)+SP with AQ+SP. The total failure excluding new infections at day 28 was similar in the 2 groups (13% in the AS+SP group compared to 22% in the AQ+SP group; OR: 0.59; 95% CI: 0.29–1.18); total number of recurrent infections, including reinfections, was higher with AS+SP (29% with AS+SP, 17% with AQ+SP, OR: 0.49; 95% CI: 0.27–0.87).

*Expert comment:* the above result is probably due to the efficacy of AQ that remains high, while SP failure is on the increase. In areas where AQ+SP has been adopted as first-line treatment, the impression is that there has been rapid development of resistance to AQ. This also makes both AQ and SP unavailable for use as an ACT component.

*Basis of decision:* expert opinion.

if more effective ACTs are not available and both AQ and SP are effective,<sup>b</sup> then AQ+SP may be used as an interim measure.

<sup>a</sup> See also Annex 7.3.

<sup>b</sup> Efficacy >80%.

## 7.3 The choice of artemisinin-based combination therapy options

Although there are some minor differences in oral absorption and bioavailability between the different artemisinin derivatives, there is no evidence that these differences are clinically significant in current formulations. It is the properties of the partner medicine that determine the effectiveness and choice of combination. ACTs with amodiaquine, atovaquone-proguanil, chloroquine, clindamycin, doxycycline, lumefantrine, mefloquine, piperazine, pyronaridine, proguanil-dapsone, sulfadoxine-pyrimethamine and tetracycline have all been evaluated in trials carried out across the malaria-affected regions of the world. Some of these are studies for product development.

Though there are still gaps in our knowledge, there is reasonable evidence on safety and efficacy on which to base recommendations.

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**Interventions:** oral AL, AS+AQ, AS+MQ, AS+SP

*Summary of RCTs:* AL 6-dose regimen compared with 4-dose regimen; 6 doses resulted in higher cure rate in 1 trial in Thailand (RR: 0.19; 95% CI: 0.06–0.62).

AS+MQ compared with AL 6-dose regimen; systematic review including 2 small RCTs from Thailand. Higher proportion of patients with parasitaemia at day 28 with AL but difference not statistically significant. One additional RCT in Lao People's Democratic Republic also reported higher proportions of patients with parasitaemia at day 42 with AL but also not statistically significant.

AS+AQ compared with AL 6-dose regimen; 1 trial in Tanzania found a significantly higher proportion of parasitological failures on day 28 with AS+AQ.

No trials of AL compared with AS+SP.

*Expert comment:* the efficacy of ACTs with AQ or SP as partner medicines is insufficient where cure rates with these medicines as monotherapies is less than 80%. The efficacy of AL and AS+MQ generally exceeds 90% except at the Thai-Cambodian border, where AL failure rate was 15%.

*Basis of decision:* expert opinion.

Use the following ACTs: AL (6-dose regimen), AS+AQ, AS+MQ, AS+SP.

In areas with AQ and SP resistance exceeding 20% (PCR-corrected at day 28 of follow-up), use AS+MQ or AL.

<sup>a</sup> See also Annex 7.4

The following ACTs are currently recommended (alphabetical order):

- artemether-lumefantrine,
- artesunate + amodiaquine,
- artesunate + mefloquine,
- artesunate + sulfadoxine–pyrimethamine.

amodiaquine + sulfadoxine–pyrimethamine may be considered as an interim option where ACTs cannot be made available, provided that efficacy of both is high.

Several available drugs that were considered by the Technical Guidelines Development Group are currently not recommended.

- Chlorproguanil-dapsone has not yet been evaluated as an ACT partner drug, so there is insufficient evidence of both efficacy and safety to recommend it as a combination partner.

- Atovaquone-proguanil has been shown to be safe and effective as a combination partner in one large study, but is not included in these recommendations for deployment in endemic areas because of its very high cost.
- Halofantrine has not yet been evaluated as an ACT partner medicine and is not included in these recommendations because of safety concerns.
- Dihydroartemisinin (artemimol)-piperaquine has been shown to be safe and effective in large trials in Asia, but is not included in these recommendations as it is not yet available as a formulation manufactured under good manufacturing practices, and has not yet been evaluated sufficiently in Africa and South America.

Several other new antimalarial compounds are in development but do not yet have a sufficient clinical evidence to support recommendation here.

Although for many countries, artemether-lumefantrine and artesunate + mefloquine may give the highest cure rates, there may be problems of affordability and availability of these products. Also, there is currently insufficient safety and tolerability data on artesunate + mefloquine at the recommended dose of 25mg/kg in African children to support its recommendation there. Trials with mefloquine monotherapy (25mg/kg) have raised concerns of tolerability in African children. Countries may therefore opt instead to use artesunate + amodiaquine and artesunate + sulfadoxine–pyrimethamine, which may have lower cure rates because of resistance. Although still effective in some areas, sulfadoxine–pyrimethamine and amodiaquine are widely available as monotherapies, providing continued selection pressure, and it is likely that resistance will continue to worsen despite deployment of the corresponding ACTs. This may be a particular problem in settings where sulfadoxine–pyrimethamine is being used for intermittent preventive treatment in pregnancy; artesunate + sulfadoxine–pyrimethamine should probably not be used in such settings.

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| The treatment of choice for uncomplicated falciparum malaria is a combination of two or more antimalarials with different mechanisms of action.  |  |
| ACTs are the recommended treatments for uncomplicated falciparum malaria.  |  |
| The following ACTs are currently recommended:<br>– artemether-lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, artesunate + sulfadoxine-pyrimethamine.   |  |
| The choice of ACT in a country or region will be based on the level of resistance of the partner medicine in the combination:<br>– in areas of multidrug resistance (South-East Asia), artesunate + mefloquine or artemether-lumefantrine<br>– in Africa, artemether-lumefantrine, artesunate + amodiaquine; artesunate + sulfadoxine-pyrimethamine. |  |
| The artemisinin derivative components of the combination must be given for at least 3 days for an optimum effect.  |  |
| Artemether-lumefantrine should be used with a 6-dose regimen.  |  |
| Amodiaquine + sulfadoxine-pyrimethamine may be considered as an interim option in situations where ACTs cannot be made available.  |  |

## 7.4 Practical aspects of treatment with recommended ACTs

This is currently available as co-formulated tablets containing 20 mg of artemether and 120 mg of lumefantrine. The total recommended treatment is a 6-dose regimen of artemether-lumefantrine twice a day for 3 days.

**Table 1.**

| Body weight in kg<br>(age in years) |         | No. of tablets at approximate timing of dosing <sup>a</sup> |     |      |      |      |      |
|-------------------------------------|---------|---|-----|------|------|------|------|
|                                     |         | 0 h   | 8 h | 24 h | 36 h | 48 h | 60 h |
| 5–14                                | (<3)    | 1   | 1   | 1    | 1    | 1    | 1    |
| 15–24                               | (≥3–8)  | 2   | 2   | 2    | 2    | 2    | 2    |
| 25–34                               | (≥9–14) | 3   | 3   | 3    | 3    | 3    | 3    |
| >34                                 | (>14)   | 4   | 4   | 4    | 4    | 4    | 4    |

<sup>a</sup> The regimen can be expressed more simply for ease of use at the programme level as follows: the second dose on the first day should be given any time between 8 h and 12 h after the first dose. Dosage on the second and third days is twice a day (morning and evening).

An advantage of this combination is that lumefantrine is not available as a monotherapy and has never been used by itself for the treatment of malaria. Recent evidence indicates that the therapeutic response and safety profile in young children of less than 10 kg is similar to that in older children, and artemether-lumefantrine is now recommended for patients ≥ 5 kg. Lumefantrine absorption is enhanced by co-administration with fat. Low blood levels, with resultant treatment failure, could potentially result from inadequate fat intake, and so it is essential that patients or carers are informed of the need to take this ACT with milk or fat-containing food – particularly on the second and third days of treatment.

This is currently available as separate scored tablets containing 50 mg of artesunate and 153 mg base of amodiaquine, respectively. Co-formulated tablets are under development. The total recommended treatment is 4 mg/kg bw of artesunate and 10 mg base/kg bw of amodiaquine given once a day for 3 days.

**Table 2.**

| Age         | Dose in mg (No. of tablets) |       |       |                      |       |       |
|-------------|-----------------------------|-------|-------|----------------------|-------|-------|
|             | Artesunate (50 mg)          |       |       | Amodiaquine (153 mg) |       |       |
|             | Day 1                       | Day 2 | Day 3 | Day 1                | Day 2 | Day 3 |
| 5–11 months | 25 (1/2)                    | 25    | 25    | 76 (1/2)             | 76    | 76    |
| ≥1–6 years  | 50 (1)                      | 50    | 50    | 153 (1)              | 153   | 153   |
| ≥7–13 years | 100 (2)                     | 100   | 100   | 306 (2)              | 306   | 306   |
| >13 years   | 200 (4)                     | 200   | 200   | 612 (4)              | 612   | 612   |

This combination is sufficiently efficacious only where 28-day cure rates with amodiaquine monotherapy exceed 80%. Resistance is likely to worsen with continued availability of chloroquine and amodiaquine monotherapies. More information on the safety of artesunate + amodiaquine is needed from prospective pharmacovigilance programmes.

This is currently available as separate scored tablets containing 50 mg of artesunate, and tablets containing 500 mg of sulfadoxine and 25 mg of pyrimethamine.<sup>11</sup> The total recommended treatment is 4 mg/kg bw of artesunate given once a day for 3 days and a single administration of sulfadoxine-pyrimethamine (25/1.25 mg base/kg bw) on day 1.

**Table 3.**

| Age         | Dose in mg (No. of tablets) |       |       |                                    |       |       |
|-------------|-----------------------------|-------|-------|------------------------------------|-------|-------|
|             | Artesunate (50 mg)          |       |       | Sulfadoxine-pyrimethamine (500/25) |       |       |
|             | Day 1                       | Day 2 | Day 3 | Day 1                              | Day 2 | Day 3 |
| 5–11 months | 25 (½)                      | 25    | 25    | 250/12.5 (½)                       | –     | –     |
| ≥1–6 years  | 50 (1)                      | 50    | 50    | 500/25 (1)                         | –     | –     |
| ≥7–13 years | 100 (2)                     | 100   | 100   | 1000/50 (2)                        | –     | –     |
| >13 years   | 200 (4)                     | 200   | 200   | 1500/75 (3)                        | –     | –     |

While a single dose of sulfadoxine–pyrimethamine is sufficient, it is necessary for artesunate to be given for 3 days for satisfactory efficacy. This combination is sufficiently efficacious only where 28-day cure rates with sulfadoxine–pyrimethamine alone exceed 80%. Resistance is likely to worsen with continued availability of sulfadoxine–pyrimethamine, sulfalene–pyrimethamine and cotrimoxazole (trimethoprim-sulfamethoxazole).

This is currently available as separate scored tablets containing 50 mg of artesunate and 250 mg base of mefloquine, respectively. Co-formulated tablets are under development but are not available at present. The total recommended treatment is 4 mg/kg bw of artesunate given once a day for 3 days and 25 mg base/kg bw of mefloquine usually split over 2 or 3 days.

<sup>11</sup> A similar medicine with tablets containing 500 mg of sulfalene and 25 mg of pyrimethamine is considered to be equivalent to sulfadoxine-pyrimethamine.

**Table 4.**

| Age         | Dose in mg (No. of tablets) |       |       |                     |           |         |
|-------------|-----------------------------|-------|-------|---------------------|-----------|---------|
|             | Artesunate (50 mg)          |       |       | Mefloquine (250 mg) |           |         |
|             | Day 1                       | Day 2 | Day 3 | Day 1               | Day 2     | Day 3   |
| 5–11 months | 25 (1/2)                    | 25    | 25    | –                   | 125 (1/2) | –       |
| ≥1–6 years  | 50 (1)                      | 50    | 50    | –                   | 250 (1)   | –       |
| ≥7–13 years | 100 (2)                     | 100   | 100   | –                   | 500 (2)   | 250 (1) |
| >13 years   | 200 (4)                     | 200   | 200   | –                   | 1000 (4)  | 500 (2) |

Two different doses of mefloquine have been evaluated, 15 mg base/kg bw and 25 mg base/kg bw. The lower dose is associated with inferior efficacy and is not recommended. To reduce acute vomiting and optimize absorption, the 25 mg/kg dose is usually split and given either as 15 mg/kg (usually on the second day) followed by 10 mg/kg one day later, or as 8.3 mg/kg per day for 3 days. Pending development of a co-formulated product, malaria control programmes will have to decide on the optimum operational strategy of mefloquine dosing for their populations. Mefloquine is associated with an increased incidence of nausea, vomiting, dizziness, dysphoria and sleep disturbance in clinical trials, but these are seldom debilitating and in general, where this ACT has been deployed, it has been well tolerated.

## 7.5 Incorrect approaches to treatment

In endemic regions, some semi-immune malaria patients could be cured using partial treatment with effective medicines (i.e. use of regimens that would be unsatisfactory in patients with no immunity). This had led in the past to different recommendations for patients considered to be semi-immune and those considered to be non-immune. Another potentially dangerous practice is to give only the first dose of the treatment course for patients with suspected but unconfirmed malaria, with the intention of giving full treatment if the diagnosis is eventually confirmed. Neither practice is recommended. If malaria is suspected and the decision to treat is made, then a full effective treatment is required whether or not the diagnosis is confirmed by a test.

With the exception of artemether-lumefantrine, the partner medicines of all other ACTs have been previously used as monotherapies, and still continue to be available as such in many countries. Their continued use as monotherapies can potentially compromise the value of ACTs by selecting for drug resistance. The withdrawal of artemisinins and other monotherapies is recommended.

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| Partial treatments should not be given even when patients are considered to be semi-immune or the diagnosis is uncertain. A full course of effective treatment should always be given once a decision to give antimalarial treatment has been reached. |  |
| The artemisinins and partner medicines of ACTs should not be available as monotherapies.   |  |

## 7.6 Additional aspects of clinical management

Some patients cannot tolerate oral treatment, and will require parenteral or rectal administration for 1–2 days until they can swallow and retain oral medication reliably. Although such patients may not show signs of severity, they should receive the same antimalarial dose regimens as for severe malaria (see section 8.4).

Some patients may have no signs of severity but on examination of the blood film are found to have very high parasitaemia. The risks associated with high parasitaemia vary depending on the age of the patient and on transmission intensity. Thus cut-off values and definitions of hyperparasitaemia also vary. Patients with high parasitaemias are at an increased risk of treatment failure and of developing severe malaria, and therefore have an increased risk of dying. These patients can be treated with the oral ACTs recommended for uncomplicated malaria. However, they require close monitoring to ensure that the drugs are retained and that signs of severity do not develop, and they may require a longer course of treatment to ensure cure. Details of definitions and management are provided in sections 8.1 and 8.15.

Fever is a cardinal feature of malaria, and is associated with constitutional symptoms of lassitude, weakness, headache, anorexia and often nausea. In young children, high fevers are associated with vomiting, including of

medication, and seizures. Treatment is with antipyretics and, if necessary, tepid sponging. Care should be taken to ensure that the water is not too cool as, paradoxically, this may raise the core temperature by inducing cutaneous vasoconstriction. Paracetamol (acetaminophen) 15 mg/kg bw every 4 h is widely used; it is safe and well tolerated given orally or as a suppository. Ibuprofen (5 mg/kg bw) has been used successfully as an alternative in malaria and other childhood fevers, although there is less experience with this compound. Acetylsalicylic acid (aspirin) should not be used in children because of the risks of Reye’s syndrome. There has been some concern that antipyretics might attenuate the host defence against malaria, as their use is associated with delayed parasite clearance. However, this appears to result from delaying cytoadherence, which is likely to be beneficial. There is no reason to withhold antipyretics in malaria.

**Interventions:** oral paracetamol, oral nonsteroidal antiinflammatory drugs, mechanical methods

*Summary of RCTs:* a systematic review of 12 trials ( $n = 1509$ ) in children using paracetamol.

Systematic review of 3 randomised trials in adults did not provide any evidence that antipyretic medicines prolonged illness.

In 2 trials, where all children received an antipyretic medicine, physical methods resulted in a higher proportion of children without fever at one hour ( $n = 125$ , RR: 11.76; 95% CI: 3.39–40.79). In a third trial ( $n = 130$ ), which only reported mean change in temperature, no difference was detected.

*Expert comment:* symptomatic treatment of fever is indicated and is particularly important in small children in whom fever can cause seizures and induce vomiting (more likely if core temperature is  $>38^\circ\text{C}$ ). Mechanical antipyretic measures, such as exposure and fanning cause a transient reduction in temperature, oral antipyretics may be more effective for reducing temperature.

use paracetamol or ibuprofen for treating fever (particularly if temperature is  $>38.5^\circ\text{C}$ ). Mechanical methods have an additive effect.

An antipyretic medicine and physical methods for fever reduction should be administered to children with fever. This is particularly important in children when core temperature is  $\geq 38.5^\circ\text{C}$ .

Paracetamol (acetaminophen) and ibuprofen are the preferred options for reducing fever.

Vomiting is common in acute malaria and may be severe. Antiemetics are widely used. There have been no studies of their efficacy in malaria, and no comparisons between different antiemetic compounds, although there is no evidence that they are harmful.

Generalized seizures are more common in children with falciparum malaria than in those with the other malarias. This suggests an overlap between the cerebral pathology resulting from malaria and febrile convulsions. Sometimes these seizures are the prodrome of cerebral malaria. If the seizure is ongoing, the airway should be maintained and anticonvulsants given (parenteral or rectal benzodiazepines or intramuscular paraldehyde). If it has stopped, the child should be treated as indicated in section 7.6.3 if core temperature is above 38.5 °C. There is no evidence that prophylactic anticonvulsants are beneficial in otherwise uncomplicated malaria.

## 7.7 Operational issues in treatment management

To optimize the benefit of deploying ACTs, and to have an impact on malaria, it will be necessary to deploy them as widely as possible – this means at most peripheral health clinics and health centres, and in the community. Deployment through the formal public health delivery system alone will not reach many of those who need treatment. In several countries, they must also be available through the private sector. Ultimately, effective treatment needs to be available at community or household level in such a way that there is no financial or physical barrier to access. The strategy to secure full access must be based on an analysis of the national and local health systems, and will often require adjustment based on programme monitoring and operational research. The dissemination of clear national treatment guidelines, use of appropriate information, education and communication materials, monitoring both of the deployment process, access and coverage and provision of adequately packaged and presented antimalarials are needed to optimize the benefits of providing these new effective treatments widely.

At all levels, from the hospital to the community, education is vital to optimizing antimalarial treatment. Clear guidelines in the language understood by the local users, posters, wall charts, educational videos and other teaching materials, public awareness campaigns, education of and provision of information

materials to shopkeepers and other dispensers can all improve the understanding of malaria and the likelihood of improved prescribing and adherence, appropriate referral, and minimizing the unnecessary use of antimalarials.

To achieve the desired therapeutic effectiveness, a drug must be intrinsically efficacious and must be taken in the correct doses at the proper intervals. Patient adherence is a major determinant of the response to antimalarials, as most treatments are taken at home without medical supervision. There have been few studies of adherence. These suggest that 3-day regimens of medicines such as ACTs are adhered to reasonably well, provided that patients or carers are given an adequate explanation at the time of prescribing. Prescribers, shopkeepers or vendors should therefore give a clear and comprehensible explanation of how to use the medicines. Co-formulation is probably a very important contributor to adherence. User-friendly packaging, such as blister packs, also encourage completion of the treatment course and correct dosing.

Many of the antimalarials available in malaria endemic areas are substandard in that the manufacturing processes have been unsatisfactory, or their pharmaceutical properties do not meet the required pharmacopoeial specifications. Counterfeit tablets and ampoules containing no antimalarials are a major problem in some areas. These may result in fatal delays in appropriate treatment, and may also give rise to a mistaken impression of resistance. WHO, in collaboration with other United Nations agencies, has established an international mechanism to pre-qualify manufacturers of artemisinin compounds and ACTs on the basis of compliance with internationally-recommended standards of manufacturing and quality. It is the responsibility of national ministries of Health and regulatory authorities to ensure the quality of antimalarials provided through both the public and private sectors, through regulation, inspection and law enforcement.

Rare but serious adverse effects are often not detected in clinical trials and can only be detected through pharmacovigilance systems operating in situations of wide population use. There are few data from prospective Phase IV post-marketing studies on rare but potentially serious adverse effects of antimalarials. Chloroquine has the best-documented adverse effect profile. The safety profiles of the artemisinin derivatives, mefloquine and sulfadoxine–pyrimethamine are supported by a reasonable evidence base, but mainly from large clinical trials.

The neurotoxicity observed in animals treated with artemisinin derivatives has prompted large prospective assessments in humans, but no evidence of neurotoxicity has been found. Concerns over the risk of severe liver or skin reactions to sulfadoxine-pyrimethamine treatment have receded with increasing numbers of negative reports. More data are needed on the newer drugs and on amodiaquine as well. There is also an urgent need to obtain more information on the safety of antimalarials, in particular the ACTs, in pregnancy. It is recommended that countries or regions should consider establishing pharmacovigilance systems if they have not already done so.

## 7.8 Management of treatment failures

Treatment failure within 14 days of receiving an ACT is very unusual. Of 39 trials of artemisinin or its derivatives, which together enrolled 6124 patients, 32 trials (4917 patients) had no failures at all by day 14. In the remaining 7 trials, failure rates at day 14 ranged from 1% to 7%. The majority of treatment failures occur after 2 weeks of initial treatment. In many cases failures are missed because patients presenting with malaria are not asked whether they have received antimalarial treatment within the preceding 1–2 months. Recurrence of falciparum malaria can be the result of a reinfection, or a recrudescence (i.e. failure). In an individual patient it may not be possible to distinguish recrudescence from reinfection, although if fever and parasitaemia fail to resolve or recur within 2 weeks of treatment then this is considered a failure of treatment. Wherever possible treatment failure must be confirmed parasitologically – preferably by blood slide examination (as HRP2-based tests may remain positive for weeks after the initial infection even without recrudescence). This may require transferring the patient to a facility with microscopy; transfer may be necessary anyway to obtain second-line treatment. Treatment failures may result from drug resistance, poor adherence or unusual pharmacokinetic properties in that individual. It is important to determine from the patient's history whether he or she vomited previous treatment or did not complete a full course. Treatment failures within 14 days should be treated with a second-line antimalarial (see section 7.8.3).

Recurrence of fever and parasitaemia more than 2 weeks after treatment, which could result either from recrudescence or new infection, can be retreated with the first-line ACT. Parasitological confirmation is desirable but not a precondition. If it is a recrudescence, then the first-line treatment should still be

effective in most cases. This simplifies operational management and drug deployment. However, reuse of mefloquine within 28 days of first treatment is associated with an increased risk of neuropsychiatric sequelae and, in this particular case, second-line treatment should be given. If there is a further recurrence, then malaria should be confirmed parasitologically and second-line treatment given.

On the basis of the evidence from current practice and the consensus opinion of the Guidelines Development Group, the following second-line treatments are recommended, in order of preference:

- alternative ACT known to be effective in the region,
- artesunate + tetracycline or doxycycline or clindamycin,
- quinine + tetracycline or doxycycline or clindamycin.

The alternative ACT has the advantages of simplicity, and where available, co-formulation to improve adherence. The 7-day quinine regimes are not well tolerated and adherence is likely to be poor if treatment is not observed.

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| Alternative ACT known to be effective in the region.   |  |
| Artesunate (2 mg/kg bw once a day) + tetracycline (4 mg/kg bw four times a day) or doxycycline (3.5 mg/kg bw once a day) or clindamycin (10 mg/kg bw twice a day). Any of these combinations to be given for 7 days. |  |
| Quinine (10 mg salt/kg bw three times a day) + tetracycline or doxycycline or clindamycin. Any of these combinations to be given for 7 days.   |  |

## 7.9 Treatment in specific populations and situations

Pregnant women with symptomatic acute malaria are a high-risk group, and must receive effective antimalarials. Malaria in pregnancy is associated with low birth weight, increased anaemia and, in low-transmission areas, an increased

risk of severe malaria. In high-transmission settings, despite the adverse effects on fetal growth, malaria is usually asymptomatic in pregnancy. There is insufficient information on the safety and efficacy of most antimalarials in pregnancy, particularly for exposure in the first trimester, and so treatment recommendations are different to those for non-pregnant adults. Organogenesis occurs mainly in the first trimester and this is therefore the time of greatest concern for potential teratogenicity, although nervous system development continues throughout pregnancy. The antimalarials considered safe in the first trimester of pregnancy are quinine, chloroquine, proguanil, pyrimethamine and sulfadoxine–pyrimethamine. Of these, quinine remains the most effective and can be used in all trimesters of pregnancy including the first trimester. In reality women often do not declare their pregnancies in the first trimester and so, early pregnancies will often be exposed inadvertently to the available first-line treatment. Inadvertent exposure to antimalarials is not an indication for termination of the pregnancy.

There is increasing experience with artemisinin derivatives in the second and third trimesters (over 1000 documented pregnancies). There have been no adverse effects on the mother or fetus. The current assessment of benefits compared with potential risks suggests that the artemisinin derivatives should be used to treat uncomplicated falciparum malaria in the second and third trimesters of pregnancy, but should not be used in the first trimester until more information becomes available. The choice of combination partner is difficult. Mefloquine has been associated with an increased risk of stillbirth in large observational studies in Thailand, but not in Malawi. Amodiaquine, chlorproguanil-dapsone, halofantrine, lumefantrine and piperazine have not been evaluated sufficiently to permit positive recommendations. Sulfadoxine–pyrimethamine is safe but may be ineffective in many areas because of increasing resistance. Clindamycin is also safe, but both medicines (clindamycin and the artemisinin partner) must be given for 7 days. Primaquine and tetracyclines should not be used in pregnancy.

Despite these many uncertainties, effective treatment must not be delayed in pregnant women. Given the disadvantages of quinine, i.e. the long course of treatment, and the increased risk of hypoglycaemia in the second and third trimesters, ACTs are considered suitable alternatives for these trimesters. In practice, if first-line treatment with an artemisinin combination is all that is immediately available to treat in the first trimester of pregnancy pregnant women who have symptomatic malaria, then this should be given. Pharmacovigilance programmes to document the outcome of pregnancies where there has been exposure to ACTs, and if possible documentation of the development of the infant, are encouraged so that future recommendations can stand on a firmer footing.

**Interventions:** oral AS+MQ, oral CQ alone, oral quinine, oral quinine + clindamycin

*Summary of RCTs:* four randomized and two quasi-randomized trials with 513 pregnant participants. There were fewer treatment failures with AS+MQ than with quinine in one trial (day 63: RR: 0.09; 95% CI: 0.02–0.38; 106 participants). Data for other comparisons are scant. Where trials reported adverse outcomes, there were no differences reported between treatments in terms of effect on the mother or the fetus.

*Expert comment:* systematic summaries of safety suggest that the artemisinin derivatives are safe in the second and third trimesters of pregnancy. One large observational study in Thailand suggests an increased risk of stillbirth associated with MQ but this was not found in a study conducted in Malawi. There are as yet insufficient safety data about the use of artemisinin derivatives in the first trimester of pregnancy.

*Basis of decision:* expert opinion.

for the first trimester of pregnancy: quinine +/- clindamycin.

For second and third trimesters:

the ACT being used in the country/region, or  
artesunate + clindamycin,  
quinine + clindamycin.

**First trimester:** quinine + clindamycin<sup>a</sup> to be given for 7 days.  
ACT should be used if it is the only effective treatment available.

**Second and third trimesters:** ACT known to be effective in the country/region or artesunate + clindamycin to be given for 7 days or quinine + clindamycin to be given for 7 days.

<sup>a</sup> If clindamycin is unavailable or unaffordable, then the monotherapy should be given.

The amounts of antimalarials that enter breast milk and are therefore likely to be consumed by the breast-feeding infant are relatively small. The only exception to this is dapsone, relatively large amounts of which are excreted in breast milk (14% of the adult dose), and pending further data this should not be prescribed. Tetracyclines are also contraindicated because of their effect on the infant's bones and teeth.

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| Lactating women should receive standard antimalarial treatment (including ACTs) except for tetracyclines and dapson, which should be withheld during lactation. |  |
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### *Choice of antimalarial drug*

In endemic countries, malaria is common in infants and children under 2 years of age. Immunity acquired from the mother wanes after 3–6 months of age, and the case-fatality rate of severe malaria in infants is higher than in older children. Furthermore, there are important differences between infants and older children in the pharmacokinetics of many medicines. Accurate dosing is particularly important in infants. Despite this, few clinical studies focus specifically on this age range, partly because of ethical considerations relating to the recruitment of very young children to clinical trials, and also because of the difficulty of repeated blood sampling. In the majority of clinical studies, subgroup analysis is not used to distinguish between infants and older children. Infants are more likely to vomit or regurgitate antimalarial treatment than older children or adults. Taste, volume, consistency and gastrointestinal tolerability are important determinants of whether the child retains the treatment. Mothers often need advice on techniques of medicine administration and the importance of administering the medicine again if it is immediately regurgitated. With the increasing failure of chloroquine and sulfadoxine–pyrimethamine as front-line antimalarials, the challenge is now to find safe alternatives in this age group. Fortunately the artemisinin derivatives appear to be safe in, and well tolerated by young children, and so the choice of ACT will be determined largely by the safety and tolerability of the partner drug. The limited information available does not indicate particular problems with currently recommended ACTs in infancy.

### *Dosing*

Although dosing based on body area is recommended for many drugs in young children, for the sake of simplicity, dosing of antimalarials has been traditionally based on weight. The weight-adjusted doses of antimalarials in

<sup>12</sup> A detailed review of the available data on safety of antimalarials in infants is provided in Annex 3, section A3.17.

infants are similar to those used in adults. For the majority of antimalarials, however, the lack of an infant formulation necessitates the division of adult tablets, which leads to inaccurate dosing. There is a need to develop infant formulations for a range of antimalarials in order to improve the accuracy and reliability of dosing.

Delay in treating falciparum malaria may have fatal consequences, particularly for more severe infections. Every effort should be made to give oral treatment and ensure that it is retained. In situations where it is not possible to give parenteral treatment, a sick infant who vomits antimalarial medicine treatment repeatedly, has a seizure or is too weak to swallow reliably should be given artesunate by the rectal route, pending transfer to a facility where parenteral treatment is possible. Large trials assessing the impact of this strategy on mortality have recently been undertaken in remote rural areas, but results are not yet available. Pharmacological and trial evidence concerning the rectal administration of artesunate and other antimalarial drugs is provided in section 8.7.

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| The acutely ill child requires careful clinical monitoring as they may deteriorate rapidly.                        |  |
| ACTs should be used as first-line treatment for infants and young children.  |  |
| Referral to a health centre or hospital is indicated for young children who cannot swallow antimalarials reliably. |  |

Travellers who acquire malaria are often non-immune adults either from cities with little or no transmission within endemic countries, or visitors from non-endemic countries. Both are likely to be at a higher risk of malaria and its consequences because they have no immunity to malaria. Within the malaria endemic country they should in principle be treated according to national policy. Travellers who return to a non-endemic country and then develop malaria present particular problems and, have a high case fatality rate. Doctors may be unfamiliar with malaria and the diagnosis may be delayed, relevant antimalarials may not be registered and/or therefore available. If the patient falls ill far from a major health facility, availability of antimalarials can be a life-threatening issue despite registration. On the other hand prevention of

emergence of resistance and transmission are of less relevance outside malaria endemic areas. Thus monotherapy may be given if it can be assured to be effective. Furthermore cost of treatment is usually not a limiting factor. The principles underlying the recommendations given below are that effective medicines should be used to treat travellers; if the patient has taken chemoprophylaxis, then the same medicine should not be used for treatment. The treatment for *P. vivax*, *P. ovale* and *P. malariae* in travellers should be the same as for these infections in patients from endemic areas (see section 9).

In the management of severe malaria outside endemic areas, there may be delays in obtaining artesunate, artemether or quinine. If parenteral quinidine is available but other parenteral drugs are not, then this should be given with careful clinical and electrocardiographic monitoring (see section 8).

**Interventions:** atovaquone–proguanil, halofantrine, quinine, quinine + clindamycin, artemether-lumefantrine

*Summary of RCTs:* three RCTs (total 259 patients) report effective treatment with all interventions listed although the artemether-lumefantrine regimen was only 4 doses and therefore less effective. In one trial using halofantrine significant prolongation of the QT interval was noted.

*Expert comment:* halofantrine is not recommended because of significant cardiotoxicity compared to other treatments.

*Basis of decision:* RCTs and expert opinion.

the following antimalarials are suitable for use in travellers returning to non-endemic countries:

- artemether-lumefantrine (6-dose regimen),
- atovaquone–proguanil,
- quinine + doxycycline or clindamycin.

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| <b>For travellers returning to non-endemic countries:<sup>a</sup></b>  |  |
| <ul style="list-style-type: none"><li>– atovaquone–proguanil (15/6 mg/kg, usual adult dose, 4 tablets once a day for 3 days);</li><li>– artemether–lumefantrine (adult dose, 4 tablets twice a day for 3 days);</li><li>– quinine (10 mg salt/kg bw every 8 h) + doxycycline<sup>b</sup> (3.5 mg/kg bw once a day) or clindamycin (10 mg/kg bw twice a day); all drugs to be given for 7 days</li></ul>  |  |
| <b>For severe malaria:</b>   |  |
| <ul style="list-style-type: none"><li>– the antimalarial treatment of severe malaria in travellers is the same as shown in section 8;</li><li>– travellers with severe malaria should be managed in an intensive care unit;</li><li>– haemofiltration or haemodialysis should be started early in acute renal failure or severe metabolic acidosis;</li><li>– positive pressure ventilation should be started early if there is any breathing pattern abnormality, intractable seizure or acute respiratory distress syndrome.</li></ul> |  |

<sup>a</sup> Halofantrine is not recommended as first-line treatment for uncomplicated malaria because of cardiotoxicity.

<sup>b</sup> Doxycycline should not be used in children under 8 years of age.

## 7.10 Coexisting morbidities

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Increasing numbers of people in malaria endemic areas are living with HIV infection. It is becoming increasingly apparent that, as HIV progresses and immunosuppression worsens, the manifestations of malaria also worsen. In pregnant women, the adverse effects on birth weight are increased. In patients with partial immunity to malaria, the severity of the infection is increased. There is insufficient information at the present time on how HIV infection modifies the therapeutic response to antimalarials. However, increasing parasite burdens and reduced host immunity, both of which occur with HIV infection, are associated with increased treatment failure rates. At this time, there is insufficient

<sup>13</sup> Further information on malaria treatment and HIV/AIDS is provided in Annex 8.

information to modify the general malaria treatment recommendations for patients with HIV/AIDS. Current UNAIDS/WHO recommendations on the prophylaxis of opportunistic infections with cotrimoxazole (trimethoprim-sulfamethoxazole) in people living with HIV/AIDS remain unchanged (see below). However, treatment with sulfadoxine–pyrimethamine should not be given to patients on cotrimoxazole as there is probably an increased risk of sulfa-related adverse effects (and in any case as both medicines have similar antimalarial activity, the malaria infection is likely to be resistant to sulfadoxine–pyrimethamine). Depending on the malaria transmission setting, HIV-infected individuals are at increased risk of asymptomatic parasitaemia, clinical malaria or severe and complicated malaria. Therefore, they have an even greater need for malaria control measures than individuals not infected with HIV.

**Interventions:** oral ACTs, oral SP

*Summary of RCTs:* none.

*Expert comment:* observational studies suggest that malaria is more severe in patients co-infected with HIV. There is concern that severe adverse reactions to sulfonamides may be more frequent in HIV patients receiving cotrimoxazole (trimethoprim-sulfamethoxazole) for prophylaxis against opportunistic infections who are treated with SP for malaria.

*Basis of decision:* expert opinion.

there is insufficient evidence to recommend modifications to antimalarial treatment regimens in patients infected with HIV.

SP should be avoided for malaria treatment in HIV-infected patients receiving cotrimoxazole prophylaxis.

Patients with HIV infection who develop malaria should receive standard antimalarial treatment regimens as recommended in the relevant sections of the guidelines.

Treatment or intermittent preventive treatment with sulfadoxine-pyrimethamine should not be given to HIV-infected patients receiving cotrimoxazole (trimethoprim-sulfamethoxazole) prophylaxis.

Malaria and malnutrition frequently coexist. There are only a few studies of antimalarial medicine disposition in people with malnutrition, although many antimalarial drug efficacy studies have been conducted in populations and settings where malnutrition was prevalent (see Annex 3, section A3.17.2).

### *Changes in drug kinetics in malnutrition*

Drug absorption may be reduced owing to diarrhoea and vomiting, rapid gut transit and atrophy of the bowel mucosa. Absorption of intramuscular and possibly intrarectal drugs may be slower and diminished muscle mass may make it difficult to administer repeated intramuscular injections. The volume of distribution of some drugs would be expected to be larger and plasma concentrations lower. Hypoalbuminaemia, resulting from decreased synthesis as dietary deficiency occurs, could lead to an increase in the concentration of unbound drug; this may increase metabolic clearance, but hepatic dysfunction may reduce the metabolism of some drugs.

### *Antimalarial drugs and protein energy malnutrition*

There are limited studies of the effect of malnutrition on chloroquine, doxycycline, quinine, sulfadoxine–pyrimethamine and tetracycline, and not all of these studies were conducted in patients with malaria. There is insufficient evidence to suggest that the dosages in mg/kg bw of any antimalarial should be changed in patients with malnutrition.

There are no studies in malnourished patients of amodiaquine, artemisinin derivatives, artemether-lumefantrine, atovaquone–proguanil, clindamycin, mefloquine or primaquine.

|  |  |
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| Although there are many reasons why drug kinetics may be different in malnourished patients as compared with those who are well nourished, there is insufficient evidence to change current mg/kg bw dosing recommendations. |  |
|--|--|

## 8. TREATMENT OF SEVERE FALCIPARUM MALARIA<sup>14</sup>

### 8.1 Definition

In a patient with *P. falciparum* asexual parasitaemia and no other obvious cause of their symptoms, the presence of one or more of the following clinical or laboratory features classifies the patient as suffering from severe malaria<sup>15</sup>:

**Clinical manifestation:**

- Prostration
- Impaired consciousness
- Respiratory distress (acidotic breathing)
- Multiple convulsions
- Circulatory collapse
- Pulmonary oedema (radiological)
- Abnormal bleeding
- Jaundice
- Haemoglobinuria

**Laboratory test:**

- Severe anaemia
- Hypoglycaemia
- Acidosis
- Renal impairment
- Hyperlactataemia
- Hyperparasitaemia

### 8.2 Treatment objectives

The main objective is to prevent the patient from dying, secondary objectives are prevention of recrudescence, transmission or emergence of resistance and prevention of disabilities.

The mortality of untreated severe malaria is thought to approach 100%. With anti-malarial treatment the mortality falls to 15–20% overall, although within the broad definition are syndromes associated with mortality rates that are lower (e.g. severe anaemia) and higher (metabolic acidosis). Death from severe malaria often occurs within hours of admission to hospital or clinic, and so it is essential that therapeutic concentrations of antimalarial are achieved as soon as possible.

<sup>14</sup> Further information is provided in Annex 9.

<sup>15</sup> Full details of the definition and prognostic factors are provided in WHO Severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2000;94(Suppl. 1):1–90, and *Management of severe malaria: a practical handbook*, 2nd ed. Geneva, World Health Organization, 2000.

Management of severe malaria comprises four main areas: clinical assessment of the patient, specific antimalarial treatment, adjunctive therapy and supportive care.

### 8.3 Clinical assessment

Severe malaria is a medical emergency. The airway should be secured in unconscious patients and breathing and circulation assessed. The patient should be weighed or body weight estimated so that drugs, including antimalarials and fluids can be given on a body weight basis. An intravenous cannula should be inserted and immediate measurements of blood glucose (stick test), haematocrit/haemoglobin, parasitaemia and, in adults, renal function should be taken. A detailed clinical examination should be conducted, with particular note of the level of consciousness and record of the coma score. Several coma scores have been advocated. The Glasgow coma scale is suitable for adults, and the simple Blantyre modification or children's Glasgow coma scale are easily performed in children. Unconscious patients should have a lumbar puncture for cerebrospinal fluid analysis to exclude bacterial meningitis.

The degree of acidosis is an important determinant of outcome; the plasma bicarbonate or venous lactate level should therefore be measured if possible. If facilities are available, arterial or capillary blood pH and gases should be measured in patients who are unconscious, hyperventilating or in shock. Blood should be taken for cross-match, and (if possible) full blood count, platelet count, clotting studies, blood culture and full biochemistry should be conducted. The assessment of fluid balance is critical in severe malaria. Respiratory distress, in particular with acidotic breathing in severely anaemic children, often indicates hypovolaemia and requires prompt rehydration and, where indicated, blood transfusion (see also section 8.10.3).

### 8.4 Specific antimalarial treatment

It is essential that antimalarial treatment in full doses is given as soon as possible in severe malaria. Two classes of drugs are currently available for the parenteral treatment of severe malaria: the cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives (artesunate, artemether and artemotil). Although there are a few areas where chloroquine is still effective, parenteral chloroquine is no longer recommended for the treatment of severe malaria because of widespread resistance. Intramuscular sulfadoxine-pyrimethamine is also not recommended.

Quinine treatment for severe malaria was established before modern trial methods were developed. Several salts of quinine have been formulated for parenteral use, but the dihydrochloride is the most widely used. Peak concentrations following intramuscular quinine in severe malaria are similar to those following intravenous infusion. Pharmacokinetic modelling studies suggest that a loading dose of quinine of twice the maintenance dose (i.e. 20 mg salt/kg bw) reduces the time to reach therapeutic plasma concentrations. After the first day of treatment, the total daily maintenance dose of quinine is 30 mg salt/kg bw (usually divided into three equal administrations at 8 h intervals).

**Interventions:** *high first dose of quinine (loading dose 20 mg/kg bw) compared with non-loading dose regimen*

*Summary of RCTs:* a systematic review of two small trials showed shorter parasite and fever clearance time with high first-dose regimens but the trials were too small to show an impact on mortality.

*Pharmacokinetic studies:* a 20 mg salt/kg bw loading dose results in effective blood levels of quinine being reached by the end of a 4-h infusion or within 4 h of i.m. administration. If a loading dose is not given, therapeutic concentrations may not be reached in the first 12 h of treatment.

*Basis of decision:* pharmacokinetic studies.

use a loading dose of quinine of 20 mg salt/kg bw.

**Interventions:** *quinine i.m. compared with quinine by i.v. infusion*

*Summary of RCTs:* one small trial of limited power did not demonstrate large differences.

*Expert comment:* peak plasma concentrations are similar for both routes of administration. However, quinine i.m. may be erratically absorbed in severe malaria, particularly in patients with shock.

*Basis of decision:* pharmacokinetic studies.

rate-controlled i.v. infusion is the preferred route of quinine administration, but if this cannot be given safely, then i.m. injection is a satisfactory alternative.

**Interventions:** *quinine, rectal compared with quinine by i.m or i.v. infusion*

*Summary of RCTs:* one systematic review of 8 trials detected no difference in effect on parasites, clinical illness between the rectal group and either i.m or i.v. groups. Some studies however excluded patients with severe malaria.

*Expert comment:* quinine dihydrochloride is locally irritant, quinine gluconate is less irritant.

*Basis of decision:* systematic review.

there is insufficient evidence to recommend rectal administration of quinine unless parenteral administration is not possible and no other effective options are available.

<sup>a</sup> See also Annex 9.1–9.3.

Various artemisinin derivatives have been used in the treatment of severe malaria including artemether, artemisinin (rectal), artemotil and artesunate. The pharmacokinetic properties of artesunate are superior to those of artemether and artemotil as it is water soluble and can be given either by intravenous or intramuscular injection. Randomised trials comparing artesunate and quinine from South-East Asia show clear evidence of benefit with artesunate. In the largest multi-centre trial, which enrolled 1461 patients (including 202 children <15 years old), mortality was reduced by 34.7% compared to the quinine group. The results of this and smaller trials are consistent and suggest that artesunate is the treatment of choice for adults with severe malaria.

There are, however, still insufficient data for children, particularly from high transmission settings to make the same conclusion. An individual patient data meta-analysis of trials comparing artemether and quinine showed no difference in mortality in African children.

Although artesunate has better pharmacokinetic properties than artemether or artemotil, there are relatively few published comparative clinical trials. Concerns have been raised, regarding the possibility that the intrinsic benefits of artemether as an antimalarial may have been negated by its erratic absorption following intramuscular injection. Artemotil is very similar to artemether, but very few trials have been conducted.

**Interventions: AS i.v. compared with quinine i.v. infusion**

*Summary of RCTs:* multi-centre trials enrolling 1461 patients, with mortality in the AS vs QN being 15% vs 22%. There was a relative reduction in mortality of 34.7% (95% CI: 18.5–47.6%;  $p = 0.002$ ) in the AS group. QN was associated with hypoglycaemia (RR: 3.2,  $p = 0.009$ ). Clear evidence of mortality benefit with artesunate.

*Expert comment:* trials mainly in Asian adults, more information needed in children in higher transmission settings. There are no RCTs comparing AS with artemether i.m.

*Basis of decision:* RCT

AS is the recommended first choice in areas of low-malaria transmission.

**Interventions: artemether i.m. compared with quinine i.v. infusion**

*Summary of RCTs:* systematic review of 11 RCTs; analysis across all trials showed lower mortality with artemether, but this was not significant in an analysis of adequately concealed trials (RR: 0.8; 95% CI: 0.52–1.25). Within these, in an individual patient data analysis of 1919 adults and children, the odds ratio for deaths in artemether recipients was 0.8 (95% CI: 0.62–1.02). In the prospectively defined subgroup analysis of adults with multisystem failure, there was a significant difference in mortality in favour of artemether.

*Expert comment:* artemether i.m. is erratically absorbed in severe malaria particularly in patients with shock.

*Basis of decision:* systematic review.

artemether i.m. is an acceptable alternative to quinine i.v. infusion.

**Interventions: artemotil i.m. compared with quinine by i.v. infusion**

*Summary of RCTs:* systematic review of two trials; the trials had insufficient power to show a difference.

*Expert comment:* insufficient clinical trials and pharmacokinetic data to warrant a recommendation.

*Basis of decision:* systematic review.

do not use artemotil unless alternatives are not available.

**Interventions:** artemisinin derivatives, rectal, compared with quinine by i.v. infusion

*Summary of RCTs:* systematic review of three trials; the trials had insufficient power to show a difference.

However, rectal artesunate has superior effect in reducing parasite densities compared to quinine (i.v. or i.m.) at 12 and 24 hours after administration.

*Expert comment:* pharmacokinetic studies suggest highly variable but adequate absorption of rectal artemisinin and rectal artesunate. Rectal formulations have been developed for pre-referral use.

*Basis of decision:* systematic review.

use artemisinins rectally for complete treatment only when parenteral antimalarial treatment is not possible.

<sup>a</sup> See also Annex 9.4–9.7.

Quinidine commonly causes hypotension and concentration-dependent prolongation of ventricular repolarization (QT prolongation). Quinidine is thus considered more toxic than quinine and should only be used if none of the other effective parenteral drugs are available. Electrocardiographic monitoring and frequent assessment of vital signs are required if quinidine is used.

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| Severe malaria is a medical emergency.<br>After rapid clinical assessment and confirmation of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay with whichever effective antimalarial is first available.   |  |
| Artesunate 2.4 mg/kg bw i.v. or i.m. given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended choice in low transmission areas or outside malaria endemic areas  |  |
| For children in high transmission areas, the following antimalarial medicines are recommended as there is insufficient evidence to recommend any of these antimalarial medicines over another for severe malaria:<br><ul style="list-style-type: none"> <li>– artesunate 2.4 mg/kg bw i.v. or i.m. given on admission (time = 0), then at 12 h and 24 h, then once a day;</li> <li>– artemether 3.2 mg/kg bw i.m. given on admission then 1.6 mg/kg bw per day;</li> <li>– quinine 20 mg salt/kg bw on admission (i.v. infusion or divided i.m. injection), then 10 mg/kg bw every 8 h; infusion rate should not exceed 5 mg salt/kg bw per hour.</li> </ul> |  |

## 8.5 Practical aspects of treatment

Artemisinin is formulated as a suppository for rectal administration. Artemether and artemotil are formulated in oil and are given by intramuscular injection. They are both absorbed erratically, particularly in very severely ill patients. Artesunate is soluble in water and can be given either by intravenous or intramuscular injection. There are also rectal formulations of artesunate, artemether and dihydroartemisinin.

The dosing of artemisinin derivatives has been largely empirical. The doses recommended here are those that have been most widely studied. The only recent change is the higher maintenance dose of parenteral artesunate recommended (2.4 mg/kg bw), which is based on pharmacokinetic and pharmacodynamic studies and by extrapolation from studies with oral artesunate. Expert opinion is that the previously recommended maintenance dose of 1.2 mg/kg bw may have been insufficient in some patients.

Artesunate is dispensed as a powder of artesunic acid. This is dissolved in sodium bicarbonate (5%) to form sodium artesunate. The solution is then diluted in approximately 5 ml of 5% dextrose and given by intravenous injection or by intramuscular injection to the anterior thigh. The solution should be prepared freshly for each administration and should not be stored.

Artemether and artemotil are dispensed dissolved in oil (groundnut, sesame seed) and given by i.m. injection into the anterior thigh.

Whereas many antimalarials are prescribed in terms of base, for historical reasons quinine doses are often recommended in terms of salt (usually sulfate for oral use and dihydrochloride for parenteral use). Recommendations for doses of this and other antimalarials should state clearly whether the salt or base is being referred to (doses with different salts must have the same base equivalents). Quinine must never be given by intravenous injection, as lethal hypotension may result. Quinine dihydrochloride should be given by rate-controlled infusion in saline or dextrose solutions at a rate not exceeding 5 mg salt/kg bw per hour. If this is not possible then it should be given by intramuscular injection to the anterior thigh, not the buttock (to avoid sciatic nerve injury). The first dose should be split, 10 mg/kg bw to each thigh. Undiluted quinine dihydrochloride at a concentration of 300 mg/ml is acidic (pH 2) and painful when given by intramuscular injection, so it is best either formulated or diluted to concentrations of 60–100 mg/ml for intramuscular injection. Gluconate

salts are less acidic and better tolerated than the dihydrochloride salt when given by the intramuscular and rectal routes.

As the first dose (loading dose) is the most important in the treatment of severe malaria, this should be reduced only if there is clear evidence of adequate pre-treatment before presentation. Although quinine can cause hypotension if administered rapidly, and overdose is associated with blindness and deafness, these adverse effects are rare in the treatment of severe malaria. The dangers of insufficient treatment (i.e. death from malaria) exceed those from excessive treatment initially. After the second day of parenteral treatment, if there is no clinical improvement or in acute renal failure, the maintenance doses of quinine given by infusion should be reduced by one-third to avoid accumulation.

The dosage of artemisinin derivatives does not need adjustment in vital organ dysfunction. Quinine (and quinidine) levels may accumulate in severe vital organ dysfunction. If there is no clinical improvement or the patient remains in acute renal failure the dose should be reduced by one-third after 48 h. Dosage adjustments are not necessary if patients are receiving either haemodialysis or haemofiltration. Dosage adjustment by one-third is necessary in patients with hepatic dysfunction.

## 8.6 Follow-on treatment

Following initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with an effective oral anti-malarial. Current practice is to continue the same medicine orally as given parenterally to complete a full 7 days of treatment. In non-pregnant adults, doxycycline is added to either quinine, artesunate or artemether and should also be given for 7 days. Doxycycline is preferred to other tetracyclines because it can be given once daily, and does not accumulate in renal failure. But as treatment with doxycycline only starts when the patient has recovered sufficiently, the doxycycline course finishes after the quinine, artemether or artesunate course. Where available, clindamycin may be substituted in children and pregnant women, as doxycycline cannot be given to these groups. Although following parenteral treatment with a full course of oral ACT (artesunate + amodiaquine or artemether-lumefantrine) is theoretically a good alternative, this has not been evaluated in clinical trials.

The recommendation from experts' opinion is to complete treatment in severe malaria following parenteral drug administration by giving a full course of combination therapy, ACT or quinine + clindamycin or doxycycline. Regimens containing mefloquine should be avoided if the patient presented initially with impaired consciousness. This is because of an increased incidence of neuropsychiatric complications associated with mefloquine following cerebral malaria.

## 8.7 Pre-referral treatment options<sup>16</sup>

The risk of death from severe malaria is greatest in the first 24 h, yet in most malaria endemic countries, the transit time between referral and arrival at appropriate health facilities is usually prolonged thus delaying the commencement of appropriate antimalarial treatment, during which time the patient may deteriorate or die. It is recommended that patients are treated with the first dose of one of the recommended treatments by the parenteral route if possible or by the intra-rectal route before referral (unless the referral time is very short). This could be intramuscular artemether, artesunate or quinine, or a rectal formulation of artemisinin or artesunate.

| The following may be given:                          |  |
|--|--|
| – artesunate or artemisinin by rectal administration |  |
| – artesunate or artemether i.m.                      |  |
| – quinine i.m.                                       |  |

The administration of an artemisinin by the rectal route as pre-referral treatment is feasible even at the community level.

There is insufficient evidence to show whether rectal artesunate is as good as intravenous or intramuscular options in the management of severe malaria. The recommendation, therefore, is to use artesunate or artemisinin suppositories only as pre-referral treatment and to refer the patient to a facility where complete parenteral treatment with artesunate, quinine or artemether

<sup>16</sup> Further information is provided in Annex 9.8

can be instituted. If, however, referral is impossible, rectal treatment should be continued until the patient can tolerate oral medication, at which point a full course of the recommended ACT for uncomplicated malaria in the locality can be administered.

### Artemisinin derivatives

Artemisinin suppositories are not widely available. Doses used have been variable and empiric: 10–40 mg/kg bw (at 0, 4 or 12, 24, 48 and 72 h). Some studies have given a maintenance dose of one- to two-thirds of the initial dose. Artesunate suppositories\* are given in a dose of 10 mg/kg bw daily. The individual suppositories contain either 50, 100 or 400 mg of artesunate. Recommendations for artesunate suppositories for pre-referral treatment of severe malaria are provided in Tables 5 and 6.

### Initial (pre-referral) treatment with rectal artesunate

The appropriate single dose of artesunate given by suppository should be administered rectally as soon as the presumptive diagnosis of severe malaria is made. In the event that an artesunate suppository is expelled from the rectum within 30 min of insertion, a second suppository should be inserted and, especially in young children, the buttocks should be held together, for 10 min to ensure retention of the rectal dose of artesunate.

one or more artesunate suppositories inserted in the rectum, dose as indicated in Table 5. The dose should be given once and followed as soon as possible by definitive therapy for malaria.

**Table 5.**

| Weight (kg) | Artesunate dose | Regimen (single dose)  |
|-------------|-----------------|--|
| <40         | 10 mg/kg bw     | Use appropriate no. of 100-mg rectal suppositories (see Table 6) |
| 40–59       | 400 mg          | One 400-mg suppository   |
| 60–80       | 800 mg          | Two 400-mg suppositories   |
| >80         | 1200 mg         | Three 400-mg suppositories                                       |

\* It should be noted that the clinical trial data with rectal artesunate relate to a single suppository formulation and presentation<sup>17</sup> which has well characterized absorption kinetics and so cannot necessarily be extrapolated to other rectal formulations of artesunate.

<sup>17</sup> This product is being developed by the UNDP/UNICEF/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

one or more artesunate suppositories inserted in the rectum as indicated in Table 6. The dose should be given once and followed as soon as possible by definitive therapy for malaria.

**Table 6.**

| Weight (kg) | Age          | Artesunate dose (mg) | Regimen (single dose)      |
|-------------|--------------|----------------------|----------------------------|
| 5–8.9       | 0–12 months  | 50                   | One 50-mg suppository      |
| 9–19        | 13–42 months | 100                  | One 100-mg suppository     |
| 20–29       | 43–60 months | 200                  | Two 100-mg suppositories   |
| 30–39       | 6–13 years   | 300                  | Three 100-mg suppositories |
| >40         | >14 years    | 400                  | One 400-mg suppository     |

### *Quinine*

The intrarectal dose used in treatment trials in Africa was either 12 mg/kg bw quinine base every 12 h without a loading dose, or 8 mg/kg bw every 8 h, also without a loading dose. The retention and absorption of quinine is dependent on pH. Results with gluconate salts (pH 4.5) cannot be extrapolated to more acidic solutions (such as the dihydrochloride salt, pH 2).

## 8.8 Adjunctive treatment

In an attempt to reduce the unacceptably high mortality of severe malaria, various adjunctive treatments for the complications of malaria have been evaluated in clinical trials. These are summarized in Table 7 and further information is given in sections 8.9 and 8.10.

**Table 7.**

| Manifestation/complication   | Immediate management <sup>a</sup>   |
|--|---|
| Coma (cerebral malaria)  | Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatment such as corticosteroids, heparin and adrenaline; intubate if necessary.           |
| Hyperpyrexia   | Administer tepid sponging, fanning, cooling blanket and antipyretic drugs.  |
| Convulsions  | Maintain airways; treat promptly with intravenous or rectal diazepam or intramuscular paraldehyde.  |
| Hypoglycaemia (blood glucose concentration of <2.2 mmol/l; <40 mg/100ml) | Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion.   |
| Severe anaemia (haemoglobin <5 g/100ml or packed cell volume <15%)       | Transfuse with screened fresh whole blood   |
| Acute pulmonary oedema <sup>b</sup>                                      | Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure/continuous positive airway pressure in life-threatening hypoxaemia.  |
| Acute renal failure  | Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure add haemofiltration or haemodialysis, or if unavailable, peritoneal dialysis. The benefits of diuretics/dopamine in acute renal failure are not proven. |
| Spontaneous bleeding and coagulopathy                                    | Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets if available); give vitamin K injection.  |
| Metabolic acidosis   | Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe add haemofiltration or haemodialysis.   |
| Shock  | Suspect septicaemia, take blood for cultures; give parenteral antimicrobials, correct haemodynamic disturbances.  |
| Hyperparasitaemia  | See section 8.14.   |

<sup>a</sup> It is assumed that appropriate antimalarial treatment will have been started in all cases.

<sup>b</sup> Prevent by avoiding excess hydration.

## 8.9 Continuing supportive care

Patients with severe malaria require intensive nursing, in an intensive care unit if possible. Following the initial assessment and the start of antimalarial treatment, clinical observations should be made as frequently as possible. These should include recording of vital signs, with an accurate assessment of respiratory rate and pattern, coma score, and urine output. Blood glucose should be checked, using rapid stick tests every 4 h if possible, particularly in unconscious patients. Convulsions should be treated promptly with intravenous or rectal diazepam or intramuscular paraldehyde.

Fluid requirements should be assessed individually. Adults with severe malaria are very vulnerable to fluid overload and there is a thin dividing line between underhydration, and thus worsening renal impairment, and overhydration, with the risk of precipitating pulmonary oedema. If the patient becomes oliguric (< 0.4 ml of urine/kg bw per hour) despite adequate rehydration, and the blood urea or creatinine are rising or already high, then fluids should be restricted to replace insensible losses only. Children, on the other hand, are more likely to be dehydrated and may respond well to a bolus of fluid. The fluid regimen must also be tailored around infusion of the antimalarial drugs. Central venous pressure should be maintained at 0–5 cm. If the venous pressure is elevated (usually because of excessive fluid administration), the patient should be nursed with the head raised at an angle of 45° and, if necessary, intravenous furosemide should be given. If available, haemofiltration should be started early for acute renal failure or severe metabolic acidosis unresponsive to rehydration.

If blood glucose is < 2.2 mmol/l then hypoglycaemia should be treated immediately (0.3–0.5 g/kg bw of glucose). Hypoglycaemia should be suspected in any patient who deteriorates suddenly. Stick tests may overestimate the frequency of hypoglycaemia, so laboratory confirmation may be necessary.

Patients with acute pulmonary oedema should be nursed in an upright position and given oxygen, and filling pressures on the right side of the heart should be reduced with whichever treatments are available (loop diuretics, opiates, venodilators, venesection, haemofiltration, dialysis). The right-sided pressure should be reduced to the lowest level compatible with an adequate cardiac output. Positive pressure ventilation should be started (if available) early if the patient becomes hypoxic.

Fewer than 5% of patients with severe malaria develop clinically significant disseminated intravascular coagulation. These patients should be given fresh blood transfusions and vitamin K. Patients with secondary pneumonia should be given empirical treatment with a third-generation cephalosporin, unless admitted with clear evidence of aspiration, in which case penicillin or clindamycin

is adequate. Children with persistent fever despite parasite clearance may have a systematic *Salmonella* infection, although in the majority of cases of persistent fever no other pathogen is identified after parasite clearance. Urinary tract infections are common in catheterized patients. Antibiotic treatments should take account of likely local antibiotic sensitivity patterns.

## 8.10 Additional aspects of clinical management

The differential diagnosis of fever in a severely ill patient is broad. Coma and fever may result from meningoencephalitis or malaria. Cerebral malaria is not associated with signs of meningeal irritation (neck stiffness, photophobia, Kernig sign) but the patient may be opisthotonic. As untreated bacterial meningitis is almost invariably fatal, a diagnostic lumbar puncture should be performed to exclude this condition. There is also considerable clinical overlap between septicaemia, pneumonia and severe malaria – and these conditions may coexist. In malaria endemic areas particularly, where parasitaemia is common in the young age group, it is often impossible to rule out septicaemia in a shocked or severely ill obtunded child. Where possible, blood should always be taken on admission for culture, and if there is any doubt, empirical antibiotic treatment should be started immediately along with antimalarial treatment.

Many other supportive strategies and interventions have been proposed in severe malaria, but very few are supported by evidence of benefit, and many have proved harmful.

Heparin, prostacyclin, deferoxamine, pentoxifylline, low molecular weight dextran, urea, high-dose corticosteroids, acetylsalicylic acid, deferoxamine, anti-tumour necrosis factor antibody, cyclosporin, dichloroacetate, adrenaline and hyperimmune serum have all been suggested – but none of these is recommended. Evidence on use of corticosteroids is summarized in the box below.

**Interventions: corticosteroids i.v.**

*Summary of RCTs:* one systematic review and no additional trials. No significant difference in mortality; increased risk of gastrointestinal bleeding.

*Expert comment:* no additional information.

*Basis of decision:* systematic review.

do not use corticosteroids.

<sup>a</sup> See also Annex 9.9.

Severe metabolic acidosis is common but apart from correction of hypovolaemia and anaemia, no specific treatment is of proven value. Significant electrolyte abnormalities are relatively unusual, and potassium supplementation is often not required in the acute phase. The optimum fluid resuscitation regimens, the thresholds for blood transfusion, the role of exchange transfusion, and the management of seizures remain areas of uncertainty, and these are discussed in more detail below. The optimum body positioning in comatose patients, and the timing and type of feeding in patients who remain unconscious for > 24 h have not been studied. It is generally agreed that early ventilation for respiratory abnormalities and early management of renal failure or severe metabolic acidosis are beneficial. In acute renal failure, haemofiltration is associated with a lower mortality, and more rapid correction of biochemical abnormalities compared with peritoneal dialysis. There have been no comparative trials of haemodialysis and haemofiltration.

Patients, especially children with severe malaria may be dehydrated. However, the degree of fluid depletion varies considerably. As a result, it is not possible to give general recommendations on fluid replacement. Each patient must be individually assessed and fluid resuscitation based on estimated deficit. In high-transmission settings where severe malaria is confined to childhood, children commonly present with severe anaemia and hyperventilation (sometimes termed “respiratory distress”). In the past this was ascribed to “anaemic heart failure” (i.e. pulmonary oedema), and sometimes diuretics were administered. It is now clear that this syndrome is not a result of anaemic heart failure, but results from severe metabolic acidosis and anaemia, and so should be treated by blood transfusion. In general children tolerate rapid fluid resuscitation better than adults, and are less likely to develop pulmonary oedema. In adults, there is a very thin dividing line between overhydration, which may produce pulmonary oedema, and underhydration contributing to

shock and worsening acidosis and renal impairment. Careful and frequent evaluations of the jugular venous pressure, peripheral perfusion, venous filling, skin turgor and urine output should be made. Where there is uncertainty over the jugular venous pressure, and if nursing facilities permit, a central venous catheter should be inserted and the central venous pressure measured directly. The optimum rate of resuscitation, the role of colloids compared with crystalloids, and the optimum electrolyte composition of the replacement fluid have not been determined.

Severe malaria is associated with rapid development of anaemia as infected and uninfected erythrocytes are removed from the circulation. In areas of high stable transmission, severe anaemia in young children is the principal manifestation of severe falciparum malaria. Ideally fresh blood should be transfused, and the patient's relatives are often willing donors. However, in most settings cross-matched virus-free blood is in short supply. As with fluid resuscitation, there have not been enough studies to provide strong evidence-based recommendations, so the recommendations given here are based on expert opinion. In high-transmission settings, blood transfusion is recommended for children with a haemoglobin level of  $< 5$  g/100 ml (haematocrit  $< 15\%$ ). Mortality as a direct result of anaemia rises at lower haemoglobin levels. In low-transmission settings, a threshold of 20% (haemoglobin 7 g/100ml) is recommended. These general recommendations still need to be tailored to the individual, as the pathological consequences of rapid development of anaemia are worse than those of acute on chronic anaemia, where there has been adaptation and a compensatory right shift in the oxygen dissociation curve (Annex 9.10).

There have been many anecdotal reports and several series claiming benefit for EBT in severe malaria but no comparative trials, and there is no consensus on whether it reduces mortality or how it might work. The rationale for EBT has been variously proposed as:

- removing infected red blood cells from the circulation and therefore lowering the parasite burden (although only the circulating relatively non-pathogenic stages are removed – and this is also achieved rapidly with artemisinin derivatives);
- reducing rapidly both the antigen load and the burden of parasite-derived toxins, metabolites and toxic mediators produced by the host;
- replacing the rigid unparasitized red cells by more deformable cells and therefore alleviating microcirculatory obstruction.

EBT requires intensive nursing and a relatively large volume of blood, and carries significant risks. There is no consensus on the indications, benefits and dangers involved, or on practical details such as the volume of blood that should be exchanged. It is therefore not possible to make any recommendation regarding the use of EBT.

Seizures are common in cerebral malaria, particularly in children. The treatment of convulsions in cerebral malaria with intravenous (or, if not possible, rectal) benzodiazepines or intramuscular paraldehyde is similar to that for repeated seizures from any cause. In a large double-blind placebo-controlled evaluation of a single intramuscular injection of 20 mg/kg bw of phenobarbital (phenobarbitone) in children with cerebral malaria there was a reduction in seizures but a significant increase in mortality in phenobarbital recipients. This resulted from respiratory arrest, and was associated with additional benzodiazepine use. Clearly the 20 mg/kg dose of phenobarbital should not be given without respiratory support, but it is not known, whether a lower dose would be effective and safer or whether, if ventilation is given, mortality would not be increased. In the absence of further information, prophylactic anticonvulsants are not recommended.

**Interventions:** *phenobarbital i.v.*

*Summary of RCTs:* systematic review of three trials. In the two trials with adequate blinding, death was more common with phenobarbital.

*Expert comment:* no additional information.

*Basis of decision:* systematic review.

avoid routine use of phenobarbital.

<sup>a</sup> See also Annex 9.11.

The threshold for administering antibiotic treatment should be low in severe malaria. Septicaemia and severe malaria are associated and there is diagnostic overlap, particularly in children. Unexplained deterioration may result from a supervening bacterial infection. Although enteric bacteria (notably *Salmonella*) have predominated in most trial series, a variety of bacteria have been cultured from the blood of patients diagnosed as having severe malaria, and so broad-spectrum antibiotic treatment should be given initially.

## 8.11 Treatment during pregnancy

Pregnant women, particularly in the second and third trimesters of pregnancy are more likely to develop severe malaria than other adults, often complicated by pulmonary oedema and hypoglycaemia. Maternal mortality is approximately 50%, which is higher than in non-pregnant adults. Fetal death and premature labour are common. The role of early Caesarean section for the viable live fetus is unproven, but is recommended by many authorities. Obstetric advice should be sought at an early stage, the paediatricians alerted, and blood glucose checked frequently. Hypoglycaemia should be expected and is often recurrent if the patient is receiving quinine. Antimalarials should be given in full doses. Severe malaria may also present immediately following delivery. Postpartum bacterial infection is a common complication in these cases. Falciparum malaria has also been associated with severe mid-trimester haemolytic anaemia in Nigeria. This often requires transfusion, in addition to antimalarial treatment and folate supplementation.

Parenteral antimalarials should be given to pregnant women with severe malaria in full doses without delay. Artesunate or artemether are preferred over quinine in the second and third trimesters because quinine is associated with recurrent hypoglycaemia. Recent evidence shows that in non pregnant adults with severe malaria in areas of low transmission, artesunate was superior to quinine, reducing mortality by 35% compared to quinine, which makes artesunate the preferred option in the second and third trimesters. In the first trimester, the risk of hypoglycaemia associated with quinine is lower, and the uncertainties over the safety of the artemisinin derivatives are greater. However, weighing these risks against the above evidence in favour of the efficacy of artesunate, and until more evidence becomes available, both artesunate and quinine may be considered as options. Treatment must not be delayed so if only one of the drugs artesunate, artemether or quinine is available it should be started immediately.

**AS, artemether, quinine (all parenteral)**

*Summary of RCTs:* none.

*Expert comment:* complications of severe malaria are more frequent in pregnant women than in non-pregnant adults. Artesunate reduces the mortality of severe malaria in non pregnant adults compared with quinine in low transmission situations. The artemisinin derivatives (artesunate and artemether) may also have safety advantages compared with quinine in the second and third trimesters of pregnancy because they do not cause recurrent hypoglycaemia. In the first trimester, the risk of hypoglycaemia associated with quinine is lower, and the uncertainties over the safety of the artemisinin derivatives are greater.

*Basis of decision:* expert opinion.

use the parenteral antimalarial treatment locally available for severe malaria in full doses. Where available, AS is the first, and artemether the second option in the second and third trimesters.

In the first trimester, until more evidence becomes available, both artesunate and quinine may be considered as options.

## 8.12 Management in epidemic situations

Management of severe falciparum malaria in epidemic situations will often take place in temporary clinics or in situations in which staff shortages and high workloads make intensive care monitoring difficult. Drug treatment should therefore be as simple and safe as possible, with simple dosing schedules and a minimum need for monitoring. Artesunate has been shown to reduce mortality of severe malaria, but with the current artesunate formulation, drawing the drug into a syringe takes two dissolution-dilution steps. In some circumstances this may not be possible. Parenteral quinine requires either intravenous infusions or a three times a day intramuscular regimen, plus monitoring of blood glucose. Thus the simple once a day regimens and the ease of drawing up and administering intramuscular artemether make this a suitable alternative for severe malaria in most epidemic situations. Experience with artesunate suppositories in epidemic situations is limited. Their use may be appropriate in severely ill patients who are unable to swallow oral medication when intramuscular artemether (or quinine by intravenous infusion) is unavailable. If artesunate suppositories are used, patients should be moved as soon as possible to a facility where intramuscular or intravenous therapy can be started.

When the patient cannot be moved, continued treatment with rectal artesunate is appropriate until oral drugs can be taken. It is essential that a full course of antimalarial treatment is completed.

In epidemic settings where the need for simplicity is paramount, intramuscular artemether is the drug of choice for severe malaria in all trimesters of pregnancy.

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| Artesunate by the intravenous route is the treatment of choice, but if not possible, artemether by the intramuscular route is the preferred alternative for severe malaria in pregnancy during a malaria epidemic. |  |

### 8.13 Hyperparasitaemia<sup>18</sup>

Patients with high parasite counts are known to be at increased risk of dying, although the relationship between parasite counts and prognosis varies at different levels of malaria endemicity. Many hyperparasitaemic patients have evidence of vital organ dysfunction but there is a large subgroup in which no other manifestations of severe disease are present. These patients have symptoms and signs compatible with a diagnosis of uncomplicated malaria in association with a high parasite count (sometimes termed uncomplicated hyperparasitaemia). The relevance for treatment is firstly the increased risk of progressing to severe malaria, and secondly the generally higher treatment failure rates. This is of particular concern as resistance to antimalarials is most likely to arise in patients with heavy parasite burdens and little or no immunity. In a low-transmission area in north-west Thailand, the overall mortality of uncomplicated falciparum malaria was 0.1%, but in patients with parasitaemia of >4% it was 3%. In areas of moderate or high transmission, much higher parasitaemias are often well tolerated, however. There is not enough evidence to provide a firm recommendation on the definition of hyperparasitaemia, although  $\geq 5\%$  parasitaemia in a low-transmission setting and  $\geq 10\%$  in a higher transmission setting are commonly used.

<sup>18</sup> Further information is provided in Annex 9.12

Available evidence indicates that use of oral treatment under close supervision is effective in the treatment of patients with hyperparasitaemia who have no other features of severe malaria. Parenteral treatment should, however, be substituted at any time if there is concern. The rapidity of action of the artemisinin derivatives makes them ideal drugs. The standard treatment course should be given, as there is insufficient information on the safety of higher doses of the partner drug. Alternatively, the first dose of artemisinin derivative can be given parenterally or rectally to ensure adequate absorption, followed by a full course of ACT. Mefloquine-containing regimens in which the tablets are dispensed separately should be given such that mefloquine is given on days 2 and 3, rather than day 1, when it is better tolerated, with a lower incidence of early vomiting.

The optimum duration of treatment for hyperparasitaemia is still unresolved. Data to support the suggestion that patients should be treated conservatively with 7 days of an artemisinin derivative, plus a full course of partner medicine (e.g. artesunate 7 days + mefloquine 25 mg/kg bw divided over 2 days) are lacking. A longer ACT course than is recommended for uncomplicated malaria may not be possible in places where only fixed-dose combinations are available.

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| <p>Hyperparasitaemic patients with no other signs of severe disease should be treated with oral artemisinin derivatives under the following conditions:</p> <ul style="list-style-type: none"> <li>– patients must be monitored closely for the first 48 h after the start of treatment,</li> <li>– if the patient does not retain oral medication, parenteral treatment should be given without delay.</li> </ul> |  |
| <p>Non-immune patients with parasitaemia of &gt; 20% should receive parenteral antimalarial treatment.</p>   |  |

## 9. TREATMENT OF MALARIA CAUSED BY *P. VIVAX*, *P. OVALE* OR *P. MALARIAE*<sup>19</sup>

*P. vivax*, the second most important species causing human malaria, accounts for about 40% of malaria cases worldwide and is the dominant malaria species outside Africa. It is prevalent in endemic areas in the Middle East, Asia, Oceania and Central and South America. In Africa, it is rare except in the Horn and it is almost absent in West Africa. In most areas where *P. vivax* is prevalent, malaria transmission rates are low, and the affected populations therefore achieve little immunity to this parasite. Consequently, people of all ages are at risk. The other two human malaria parasite species *P. malariae* and *P. ovale* are generally less prevalent but are distributed worldwide especially in the tropical areas of Africa.

Among the four species of *Plasmodium* that affect humans, only *P. vivax* and *P. ovale* form hypnozoites, parasite stages in the liver that can result in multiple relapses of infection, weeks to months after the primary infection. Thus a single infection causes repeated bouts of illness. This affects the development and schooling of children and debilitates adults, thereby impairing human and economic development in affected populations. The objective of treating malaria caused by *P. vivax* and *P. ovale* is to cure both the blood stage and the liver stage infections, and thereby prevent both relapse and recrudescence. This is called radical cure. Infection with *P. vivax* during pregnancy, as with *P. falciparum*, reduces birth weight. In primigravidae, the reduction is approximately two-thirds of that associated with *P. falciparum* (110 g compared to 170 g), but this adverse effect does not decline with successive pregnancies as with *P. falciparum* infections. Indeed, in the one large series in which this was studied, it increased. Reduction in birth weight (<2500 g) increases the risk of neonatal death.

### 9.1 Diagnosis

The clinical features of uncomplicated malaria are too non-specific for a clinical diagnosis of the species of malaria infection to be made. Diagnosis of *P. vivax* malaria is based on microscopy. Although rapid diagnostic tests based on immunochromatographic methods are available for the detection of non-falciparum malaria, their sensitivities below parasite densities of 500/μl are low. Their relatively high cost is a further impediment to their wide use in endemic areas. Molecular markers for genotyping *P. vivax* parasites have been developed to assist epidemiological and treatment studies but these are still under evaluation.

<sup>19</sup> Further information is provided in Annex 10.

## 9.2 Susceptibility of *P. vivax*, *P. ovale* and *P. malariae* to antimalarials

There are very few recent data on the *in vivo* susceptibility of *P. ovale* and *P. malariae* to antimalarials. Both species are regarded as very sensitive to chloroquine, although there is a single recent report of chloroquine resistance in *P. malariae*. Experience indicates that *P. ovale* and *P. malariae* are also susceptible to amodiaquine, mefloquine and the artemisinin derivatives. Their susceptibility to antifolate antimalarials such as sulfadoxine-pyrimethamine is less certain. *P. vivax* susceptibility has been studied extensively, and now that short-term culture methodologies have been standardized, clinical studies have been supported by *in vitro* observations. *P. vivax* is still generally very sensitive to chloroquine, although resistance is prevalent and increasing in some areas, notably Oceania, Indonesia and Peru (see Annex A.6.4). Resistance to pyrimethamine has increased rapidly in some areas, and sulfadoxine-pyrimethamine is consequently ineffective. There are insufficient data on current susceptibility to proguanil and chlorproguanil, although resistance to proguanil was selected rapidly when it was first used in *P. vivax* endemic areas. In general, *P. vivax* is sensitive to all the other antimalarial drugs; it is more sensitive than *P. falciparum* to the artemisinin derivatives, and slightly less sensitive to mefloquine (although mefloquine is still effective). In contrast to *P. falciparum*, asexual stages of *P. vivax* are susceptible to primaquine. Thus chloroquine + primaquine can be considered as a combination treatment. The only drugs with significant activity against the hypnozoites are the 8-aminoquinolines (bulaquine, primaquine, tafenoquine). There is no standardized *in vitro* method of drug assessment for hypnozoitocidal activity. *In vivo* assessment suggests that tolerance of *P. vivax* to primaquine in East Asia and Oceania is greater than elsewhere.

## 9.3 Treatment of uncomplicated vivax malaria

There have been fewer studies on the treatment of malaria caused by *P. vivax* than of falciparum malaria – only 11% of 435 published before 2004. For chloroquine-sensitive vivax malaria (i.e. in most places where *P. vivax* is prevalent) the conventional oral chloroquine dose of 25 mg base/kg bw is well tolerated and effective. Some have advocated lower total doses, but this is not recommended as it might encourage the emergence of resistance. Chloroquine is given in an initial dose of 10 mg base/kg bw followed by either 5 mg/kg bw at 6 h, 24 h and 48 h or, more commonly, by 10 mg/kg bw on the second day

and 5 mg/kg bw on the third day. It is also clear that if ACT treatment is given, the response is as good as or better than in falciparum malaria. The exception to this is a regimen containing sulfadoxine-pyrimethamine. It appears that *P. vivax* has developed resistance to sulfadoxine-pyrimethamine more rapidly than has *P. falciparum*, so that artesunate + sulfadoxine-pyrimethamine may not be effective against *P. vivax* in many areas.

There are relatively few data on treatment responses in chloroquine-resistant vivax malaria. Studies from Indonesia indicate that amodiaquine is efficacious, and there is some evidence that mefloquine and quinine can also be used. The artemisinin derivatives would also be expected to be highly effective, and artemether-lumefantrine could be an alternative treatment. However, there are insufficient clinical data to confirm this.

To achieve radical cure, relapses must be prevented by giving primaquine. The frequency and pattern of relapses varies geographically, however. It has become clear in recent years that whereas 50–60% of *P. vivax* infections in South-East Asia relapse, the frequency is lower in Indonesia (30%) and the Indian subcontinent (15–20%). Some *P. vivax* infections in the Korean peninsula (now the most northerly of human malarias) have an incubation period of nearly one year. Thus the preventive efficacy of primaquine must be set against the prevalent relapse frequency. It appears that the total dose of 8-aminoquinoline given is the main determinant of curative efficacy against liver-stage infection. There is no evidence that the short courses of primaquine widely recommended (such as 5-day regimens) have any efficacy. Primaquine should be given for 14 days. The usual adult oral dose is 15 mg base (0.25 mg/kg bw per day) but in South-East Asia, particularly Indonesia, and in Oceania, higher doses (0.5 mg base/kg bw per day) are required. Primaquine causes abdominal discomfort when taken on an empty stomach; it should always be taken with food.

There has been debate as to whether primaquine should be given in endemic areas. Repeated vivax malaria relapses are debilitating at any age, but if reinfection is very frequent, then the risks of widespread use of primaquine may exceed the benefits. In low-transmission areas, the benefits of deploying primaquine are considered to exceed the risks, but in areas of sustained high transmission (such as on the island of New Guinea), *P. vivax* infection is very frequent, immunity is acquired, and the risks of widespread deployment of primaquine are considered to outweigh the benefits.

***Primaquine and glucose-6-phosphate dehydrogenase deficiency***

The inherited sex-linked deficiency in glucose-6-phosphate dehydrogenase (G6PD) is associated with some protection against falciparum malaria, but increased susceptibility to oxidant haemolysis. The prevalence of G6PD deficiency varies but can be as high as 30%. There are many different genotypes, each with different levels of deficiency. Primaquine is an oxidant and causes variable haemolysis in G6PD-deficient individuals. Fortunately primaquine is eliminated rapidly and so haemolysis is self-limiting provided no further medicine is taken. Screening for G6PD deficiency is not generally available outside hospitals, although rapid tests are under development. Many patients are therefore unaware of their G6PD status. If a patient is known to be severely G6PD deficient then primaquine should not be given. For the majority of patients with mild variants of the deficiency, primaquine should be given in a dose of 0.75 mg base/kg bw once a week for 8 weeks. If significant haemolysis occurs on treatment then primaquine should be stopped.

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| Chloroquine 25 mg base/kg bw divided over 3 days, combined with primaquine 0.25 mg base/kg bw, taken with food once daily for 14 days is the treatment of choice for chloroquine-sensitive infections. In Oceania and South-East Asia the dose of primaquine should be 0.5 mg/kg bw.                                  |  |
| Amodiaquine (30 mg base/kg bw divided over 3 days as 10 mg/kg bw single daily doses) combined with primaquine should be given for chloroquine-resistant vivax malaria.  |  |
| In moderate G6PD deficiency, primaquine 0.75 mg base/kg bw should be given once a week for 8 weeks. In severe G6PD deficiency, primaquine should not be given.  |  |
| Where ACT has been adopted as the first-line treatment for <i>P. falciparum</i> malaria, it may also be used for <i>P. vivax</i> malaria in combination with primaquine for radical cure. Artesunate + sulfadoxine-pyrimethamine is the exception as it will not be effective against <i>P. vivax</i> in many places. |  |

## 9.4 Treatment of severe vivax malaria

Although *P. vivax* malaria is considered to be a benign malaria, with a very low case-fatality ratio, it may still cause a severe and debilitating febrile illness. It can also very occasionally result in severe disease as in falciparum malaria. Severe vivax malaria manifestations that have been reported are cerebral malaria, severe anaemia, severe thrombocytopenia and pancytopenia, jaundice, spleen rupture, acute renal failure and acute respiratory distress syndrome. Severe anaemia and acute pulmonary oedema are not uncommon. The underlying mechanisms of severe manifestations are not well understood.

Prompt and effective treatment and case management should be the same as for severe and complicated falciparum malaria (see section 8).

## 9.5 Treatment of malaria caused by *P. ovale* and *P. malariae*

Resistance of *P. ovale* and *P. malariae* to antimalarials is not well characterized and infections caused by these two species are considered to be generally sensitive to chloroquine. Only one study, conducted in Indonesia, has reported resistance to chloroquine in *P. malariae*. The recommended treatment for the relapsing malaria caused by *P. ovale* is the same as that given to achieve radical cure in vivax malaria, i.e. with chloroquine and primaquine. *P. malariae* should be treated with the standard regimen of chloroquine as for vivax malaria, but it does not require radical cure with primaquine as no hypnozoites are formed in infection with this species.

*P. ovale* mainly occurs in areas of high stable transmission where the risk of re-infection is high. In such settings, primaquine treatment is not indicated.

## 9.6 Monitoring therapeutic efficacy for vivax malaria

The antimalarial sensitivity of vivax malaria needs monitoring, to track and respond to emerging resistance to chloroquine. The 28-day *in vivo* test for *P. vivax* is similar to that for *P. falciparum* (see Annex 6), although the interpretation is slightly different. Genotyping may distinguish a reinfection from a recrudescence and from acquisition of a new infection, but it is not possible to distinguish reliably between a relapse and a recrudescence as they derive from the same infection. If parasitaemia recurs within 16 days of administering treatment then relapse is unlikely, but after that time, relapse cannot be distinguished from a recrudescence. Any *P. vivax* infection that

recurs within 28 days, whatever its origin, must be resistant to chloroquine (or any other slowly eliminated antimalarial) provided adequate treatment has been given. In the case of chloroquine, adequate absorption can be confirmed by measurement of the whole blood concentration at the time of recurrence. Any *P. vivax* infection that has grown *in vivo* through a chloroquine blood concentration  $\geq 100$  ng/ml must be chloroquine resistant. Short-term *in vitro* culture allows assessment of *in vitro* susceptibility. There are no molecular markers yet identified for chloroquine resistance. Antifolate resistance can be monitored by molecular genotyping of the gene that encodes dihydrofolate reductase (*Pvdhfr*).

## 10. MIXED MALARIA INFECTIONS

Mixed malaria infections are common. In Thailand, despite low levels of malaria transmission, one-third of patients with acute *P. falciparum* infection are co-infected with *P. vivax*, and 8% of patients with acute vivax malaria have simultaneous *P. falciparum* infection. Mixed infections are underestimated by routine microscopy. Cryptic *P. falciparum* infections can be revealed in approximately 75% of cases by the RDTs based on the histidine-rich protein 2 (HRP2) antigen, but such antigen tests are much less useful (because of their lower sensitivity) in detecting cryptic vivax malaria. ACTs are effective against all malaria species and are the treatment of choice. Radical treatment with primaquine should be given to patients with confirmed *P. vivax* and *P. ovale* infections except in high transmission settings where the risk of re-infection is high.

## 11. COMPLEX EMERGENCIES AND EPIDEMICS

When large numbers of people are displaced within malaria endemic areas there is an increased risk of a malaria epidemic, especially when people living in an area with little or no malaria transmission move to an endemic area (e.g. displacement from highland to lowland areas). The lack of protective immunity, concentration of population, breakdown in public health activities and difficulties in accessing insecticides, insecticide-treated nets and effective treatment, all conspire to fuel epidemic malaria, in which morbidity and mortality are often high. Such circumstances are also ideal for the development of resistance to antimalarials. For these reasons, particular efforts must be made to deliver effective antimalarial treatment to the population at risk.

### 11.1 Diagnosis

In epidemic and complex emergency situations, facilities for laboratory diagnosis may be either unavailable or so overwhelmed with the case-load that parasite-based diagnosis is impossible. In such circumstances, it is impractical and unnecessary to demonstrate parasites before treatment in all cases of fever. Once an epidemic of malaria has been confirmed, and if case numbers are high, treatment based solely on the clinical history is appropriate in most cases, using a full treatment course. However, parasite-based diagnosis is essential to:

- diagnose the cause of an epidemic of febrile illness,
- monitor and confirm the end of an epidemic,
- follow progress in infants, pregnant women, and those with severe malaria.

As the epidemic wanes, the proportion of fever cases investigated parasitologically can be increased. It is important to monitor the clinical response to treatment wherever possible, bearing in mind that other infections may also be present. In mixed falciparum/vivax epidemics, parasitaemia should be monitored in order to determine a species-specific treatment.

### 11.2 Use of rapid diagnostic tests in epidemic situations

RDTs offer the advantage of simplicity and speed in epidemic situations, but heat stability may be a problem and false-negative results may be seen. A negative result should not automatically preclude treatment, especially in severe clinical disease. Current experience with RDTs indicates that they are useful for confirming the cause and end-point of malaria epidemics, but they should not be relied on as the sole basis for treatment. They should also be backed up with adequate quality assurance, including temperature stability testing.

### 11.3 Management of uncomplicated malaria in epidemics

Malaria epidemics are emergencies in which populations at risk in epidemic-prone areas are mainly non-immune or only partially immune. The principles of treatment are the same as elsewhere (see section 7); the antimalarial to be used in epidemics (and complex emergencies) must be highly efficacious ( $\geq 95\%$  cure), safe and well tolerated so that adherence to treatment is high. Complete courses of treatment should always be given in all circumstances.

The rapid and reliable antimalarial effects of ACTs and their gametocytocidal properties, which reduce transmission, make them ideal for treatment in a malaria epidemic. An active search should be made for febrile patients to ensure that, as many cases as possible are treated, rather than relying on patients to come to a clinic.

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|---|--|
| ACTs are recommended for antimalarial treatment in epidemics in all areas with the exception of countries in Central America and the Island of Hispaniola, where chloroquine and sulfadoxine-pyrimethamine still have a very high efficacy against falciparum malaria. Chloroquine 25 mg base/kg bw divided over 3 days, combined with primaquine 0.25 mg base/kg bw, taken with food once a day for 14 days is the treatment of choice for chloroquine-sensitive <i>P. vivax</i> infections. In Oceania and South-East Asia the dose of primaquine should be 0.5 mg/kg bw. |  |
| In situations where ACTs are not immediately available, the most effective alternative should be used until ACTs become available.  |  |

### 11.4 Areas prone to mixed falciparum/vivax malaria epidemics

Resistance of *P. vivax* to chloroquine has been reported from South-East Asia and Oceania but is probably limited in distribution. There is insufficient knowledge at present to allow specific recommendations to be made for treatment of *P. vivax* epidemics in areas of suspected resistance. ACTs (except artesunate + sulfadoxine-pyrimethamine) should be used for treatment as they are highly effective against all malaria species. In areas with pure vivax epidemics, and where drug resistance has not been reported, chloroquine is the most appropriate drug once the cause of the epidemic has been established.

## 11.5 Use of gametocytocidal drugs to reduce transmission

ACTs reduce gametocyte carriage markedly, and therefore reduce transmission. This is very valuable in epidemic control. In the only randomized comparison reported, ACTs had a greater effect than primaquine on gametocyte carriage. In circumstances where an ACT is not used, a single oral dose of primaquine of 0.75 mg base/kg bw (45 mg base maximal for adults) combined with a fully effective blood schizonticide could be used to reduce transmission provided that it is possible to achieve high coverage (> 85%) of the population infected with malaria. This strategy has been widely used in South-East Asia and South America, although its impact has not been well documented. The single primaquine dose was well tolerated and prior testing for G6PD deficiency was not required. There is no experience with its use in Africa, where there is the highest prevalence of G6PD deficiency in the world. Primaquine should not be given in pregnancy. Whether there is any additional benefit in combining primaquine with an ACT is unknown. There is insufficient evidence to recommend this.

## 11.6 Anti-relapse therapy in vivax malaria epidemics

Anti-relapse therapy for vivax malaria is impractical in most epidemic situations because of the duration of treatment and poor compliance. If adequate records are kept, it can be given in the post-epidemic period to patients who have been treated with blood schizonticides. Primaquine 0.25–0.5 mg base/kg bw daily doses should be given for 14 days, as there is no evidence that shorter courses are effective. Compliance with radical (anti-relapse) treatment is often poor and the drug should ideally be given under supervision, which is very difficult in epidemic situations. Appropriate health education should be provided to assist malaria control and encourage adherence.

## 11.7 Mass treatment

Mass treatment (mass drug administration) of all or a large section of the population whether symptoms are present or not) has been carried out in the past, usually in conjunction with insecticide residual spraying, as a way of controlling epidemics. Analysis of 19 mass drug administration projects during the period 1932–1999 did not draw definitive conclusions because study designs were so variable.<sup>20</sup> Many projects were unsuccessful, although a

<sup>20</sup> von Seidlein L, Greenwood BM. Mass administration of antimalarial drugs. *Trends in Parasitology*, 2003, 19:790–796.

reduction in parasite prevalence and some transient reduction in mortality and morbidity occurred in some cases. Reduced transmission was seen only in one study, in Vanuatu, where the population concerned was relatively small, well defined and controlled.

There is no convincing evidence for the benefits of mass treatment. Mass treatment of symptomatic febrile patients is considered appropriate in epidemic and complex emergency situations. Whenever this strategy is adopted, a full treatment course should be given.