



*GUIDELINES
FOR THE TREATMENT
OF MALARIA*

Second edition



Guidelines for the treatment of malaria

Second edition



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GLOSSARY

Artemisinin-based combination therapy (ACT). A combination of artemisinin or one of its derivatives with an antimalarial or antimalarials of a different class.

Asexual cycle. The life-cycle of the malaria parasite in host from merozoite invasion of red blood cells to schizont rupture (merozoite → ring stage → trophozoite → schizont → merozoites). Duration approximately 48 h in *Plasmodium falciparum*, *P. ovale* and *P. vivax*; 72 h in *P. malariae*.

Asexual parasitaemia. The presence in host red blood cells of asexual parasites. The level of asexual parasitaemia can be expressed in several different ways: the percentage of infected red blood cells, the number of infected cells per unit volume of blood, the number of parasites seen in one microscopic field in a high-power examination of a thick blood film, or the number of parasites seen per 200–1000 white blood cells in a high-power examination of a thick blood film.

Cerebral malaria. Severe *P. falciparum* malaria with cerebral manifestations, usually including coma (Glasgow coma scale < 11, Blantyre coma scale < 3). Malaria with coma persisting for > 30 min after a seizure is considered to be cerebral malaria.

Combination treatment (CT). A combination of two or more different classes of antimalarial medicines with unrelated mechanisms of action.

Cure. Elimination of the symptoms and asexual blood stages of the malaria parasite that caused the patient or caregiver to seek treatment.

Drug resistance. The World Health Organization (WHO) defines resistance to antimalarials as the ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a medicine given in doses equal to or higher than those usually recommended but within the tolerance of the subject, provided drug exposure at the site of action is adequate. Resistance to antimalarials arises because of the selection of parasites with genetic mutations or gene amplifications that confer reduced susceptibility.

Gametocytes. Sexual stages of malaria parasites present in the host red blood cells.

Hypnozoites. Persistent liver stages of *P. vivax* and *P. ovale* malaria that remain dormant in host hepatocytes for an interval (most often 3–45 weeks) before maturing to hepatic schizonts. These then burst and release merozoites, which infect red blood cells. Hypnozoites are the source of relapses.

Malaria pigment (haemozoin). A dark brown granular pigment formed by malaria parasites as a by-product of haemoglobin catabolism. The pigment is evident in mature trophozoites and schizonts. They may also be present in white blood cells (peripheral monocytes and polymorphonuclear neutrophils) and in the placenta.

Merozoites. Parasites released into the host bloodstream when a hepatic or erythrocytic schizont bursts. These then invade the red blood cells.

Monotherapy. Antimalarial treatment with a single medicine (either a single active compound or a synergistic combination of two compounds with related mechanism of action).

Plasmodium. A genus of protozoan vertebrate blood parasites that includes the causal agents of malaria. *Plasmodium falciparum*, *P. malariae*, *P. ovale* and *P. vivax* cause malaria in humans. Human infections with the monkey malaria parasite, *P. knowlesi* have also been reported from forested regions of South-East Asia.

Pre-erythrocytic development. The life-cycle of the malaria parasite when it first enters the host. Following inoculation into a human by the female anopheline mosquito, sporozoites invade parenchyma cells in the host liver and multiply within the hepatocytes for 5–12 days, forming hepatic schizonts. These then burst liberating merozoites into the bloodstream, which subsequently invade red blood cells.

Radical cure. In *P. vivax* and *P. ovale* infections only, this comprises a cure as defined above plus prevention of relapses by killing hypnozoites.

Rapid diagnostic test (RDT). An antigen-based stick, cassette or card test for malaria in which a coloured line indicates that plasmodial antigens have been detected.

Recrudescence. The recurrence of asexual parasitaemia after treatment of the infection with the same infection that caused the original illness. This results from incomplete clearance of parasitaemia due to inadequate or ineffective treatment. It is, therefore, different to a relapse in *P. vivax* and *P. ovale* infections, and it differs from a new infection or re-infection (as identified by molecular genotyping in endemic areas).

Recurrence. The recurrence of asexual parasitaemia following treatment. This can be caused by a recrudescence, a relapse (in *P. vivax* and *P. ovale* infections only) or a new infection.

Relapse. The recurrence of asexual parasitaemia in *P. vivax* and *P. ovale* malaria deriving from persisting liver stages. Relapse occurs when the blood stage infection has been eliminated but hypnozoites persist in the liver and mature to form hepatic schizonts. After variable intervals of weeks to months, the hepatic schizonts burst and liberate merozoites into the bloodstream.

Ring stage. Young usually ring-shaped intra-erythrocytic malaria parasites, before malaria pigment is evident under microscopy.

Schizonts. Mature malaria parasites in host liver cells (hepatic schizonts) or red blood cells (erythrocytic schizonts) that are undergoing nuclear division. This process is called schizogony.

Selection pressure. Resistance to antimalarials emerges and spreads because of the selective survival advantage that resistant parasites have in the presence of antimalarials to which they are resistant. Selection pressure describes the intensity and magnitude of the selection process; the greater the proportion of parasites in a given parasite population exposed to concentrations of an antimalarial that allows proliferation of resistant, but not sensitive parasites, the greater the selection pressure.

Severe anaemia. Haemoglobin concentration of < 5 g/100 ml (haematocrit $< 15\%$).

Severe falciparum malaria. Acute falciparum malaria with signs of severity and/or evidence of vital organ dysfunction.

Sporozoites. Motile malaria parasites that are infective to humans, inoculated by a feeding female anopheline mosquito. The sporozoites invade hepatocytes.

Transmission intensity. The intensity of malaria transmission measured by the frequency with which people living in an area are bitten by anopheline mosquitoes carrying sporozoites. This is often expressed as the annual entomological inoculation rate (EIR), which is the number of inoculations of malaria parasites received by one person in one year.

Trophozoites. Stage of development of the malaria parasites within host red blood cells from the ring stage and before nuclear division. Mature trophozoites contain visible malaria pigment.

Uncomplicated malaria. Symptomatic infection with malaria parasitaemia without signs of severity and/or evidence of vital organ dysfunction.

Vectorial capacity. Number of new infections the population of a given vector would distribute per case per day at a given place and time, assuming conditions of non-immunity.

ABBREVIATIONS

ACT	artemisinin-based combination therapy
AL	artemether plus lumefantrine combination
AQ	amodiaquine
AS	artesunate
AS+AQ	artesunate plus amodiaquine combination
AS+MQ	artesunate plus mefloquine combination
AS+SP	artesunate plus sulfadoxine-pyrimethamine combination
BW	body weight
CI	confidence interval
CQ	chloroquine
DHA+PPQ	dihydroartemisinin plus piperaquine combination
EIR	entomological inoculation rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
G6PD	glucose-6-phosphate dehydrogenase
HIV/AIDS	human immunodeficiency virus/ acquired immunodeficiency syndrome
HRP2	histidine-rich protein 2
IC ₅₀	concentration providing 50% inhibition
IV	intravenous
IM	intramuscular
MIC	minimum inhibitory concentration
MQ	mefloquine
OR	odds ratio
PCR	polymerase chain reaction
<i>Pf</i> HRP2	<i>Plasmodium falciparum</i> histidine-rich protein-2
<i>p</i> LDH	<i>parasite</i> -lactate dehydrogenase
PQ	primaquine
<i>Pvdhfr</i>	<i>Plasmodium vivax</i> dihydrofolate reductase
RCT	randomized controlled trial
RDT	rapid diagnostic test
RR	relative risk
SP	sulfadoxine-pyrimethamine
WHO	World Health Organization
WMD	weighted mean difference

EXECUTIVE SUMMARY

Malaria case management remains a vital component of the malaria control strategies. This entails early diagnosis and prompt treatment with effective antimalarial medicines. The *WHO Guidelines for the treatment of malaria*, which were first published in 2006, provide global, evidence-based recommendations on the case management of malaria, targeted mainly at policy-makers at country level, providing a framework for the development of specific and more detailed national treatment protocols that take into account local antimalarial drug resistance patterns and health service capacity in the country. This second edition of the guidelines revisits the recommendations based on updated evidence. The same presentation format from the first edition has been mainly kept based on feedback from the end-users. A summary of the key recommendations provided in these guidelines is presented below.

BOX 1. Recommendations unchanged from the first edition of the *Guidelines* (2006)

TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA

- ⊙ Artemisinin-based combination therapies (ACTs) are the recommended treatments for uncomplicated *P. falciparum* malaria.
- ⊙ The following ACTs are recommended:
 - artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, and artesunate plus 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.
- ⊙ Artemisinin and its derivatives should not be used as monotherapy.
- ⊙ Second-line antimalarial treatment:
 - alternative ACT known to be effective in the region;
 - artesunate plus tetracycline or doxycycline or clindamycin; any of these combinations to be given for 7 days;
 - quinine plus tetracycline or doxycycline or clindamycin; any of these combinations should be given for 7 days.

TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA IN SPECIAL RISK GROUPS

- ⊙ Pregnancy
 - First trimester:**
 - quinine plus clindamycin to be given for 7 days (artesunate plus clindamycin for 7 days is indicated if this treatment fails);
 - an ACT is indicated only if this is the only treatment immediately available, or if treatment with 7-day quinine plus clindamycin fails or uncertainty of compliance with a 7-day treatment.

Second and third trimesters:

- ACTs known to be effective in the country/region or artesunate plus clindamycin to be given for 7 days, or quinine plus clindamycin to be given for 7 days.
- ⊙ Lactating women:
 - lactating women should receive standard antimalarial treatment (including ACTs) except for dapsone, primaquine and tetracyclines.
- ⊙ Infants and young children:
 - ACTs for first-line treatment in infants and young children with attention to accurate dosing and ensuring the administered dose is retained.
- ⊙ Travellers returning to non-endemic countries:
 - atovaquone-proguanil;
 - artemether-lumefantrine;
 - quinine plus doxycycline or clindamycin.

TREATMENT OF SEVERE MALARIA

- ⊙ Severe malaria is a medical emergency. 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.
- ⊙ For adults, artesunate IV or IM:
 - artemether or quinine is an acceptable alternative if parenteral artesunate is not available.
- ⊙ For children, artesunate IV or IM
 - artemether or quinine is an acceptable alternative if parenteral artesunate is not available.
- ⊙ Give parenteral antimalarials in the treatment of severe malaria for a minimum of 24 h, once started (irrespective of the patient's ability to tolerate oral medication earlier) and, thereafter, complete treatment by giving a complete course of:
 - an ACT;
 - artesunate plus clindamycin or doxycycline;
 - quinine plus clindamycin or doxycycline.
- ⊙ If complete treatment of severe malaria is not possible, patients should be given pre-referral treatment and referred immediately to an appropriate facility for further treatment. The following are options for pre-referral treatment: rectal artesunate, quinine IM, artesunate IM, artemether IM.

TREATMENT OF UNCOMPLICATED *P. VIVAX* MALARIA

- ⊙ Chloroquine combined with primaquine is the treatment of choice for chloroquine-sensitive infections.
- ⊙ In mild-to-moderate G6PD deficiency, primaquine 0.75 mg base/kg body weight given once a week for 8 weeks. In severe G6PD deficiency, primaquine is contraindicated and should not be used.
- ⊙ Where ACT (exception AS+SP) has been adopted as the first-line treatment for *P. falciparum* malaria, it may also be used for *P. vivax* malaria in combination with primaquine for radical cure. Artesunate plus sulfadoxine-pyrimethamine is not effective against *P. vivax* in many places.

BOX 2. Additional recommendations in the second edition of the *Guidelines* (2010)**MALARIA DIAGNOSIS**

- ⊙ Prompt parasitological confirmation by microscopy or alternatively by RDTs is recommended in all patients suspected of malaria before treatment is started.
- ⊙ Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not accessible.

TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA

- ⊙ Artemisinin-based combination therapies should be used in preference to sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) for the treatment of uncomplicated *P. falciparum* malaria.
Strong recommendation, moderate quality evidence.
- ⊙ ACTs should include at least 3 days of treatment with an artemisinin derivative.
Strong recommendation, high quality evidence.
- ⊙ Dihydroartemisinin plus piperazine (DHA+PPQ) is an option for the first-line treatment of uncomplicated *P. falciparum* malaria worldwide.
Strong recommendation, high quality evidence.
- ⊙ Addition of a single dose primaquine (0.75 mg/kg) to ACT treatment for uncomplicated falciparum malaria as an antigametocyte medicine, particularly as a component of pre-elimination or an elimination programme.

TREATMENT OF SEVERE *P. FALCIPARUM* MALARIA

- ⊙ Intravenous (IV) artesunate should be used in preference to quinine for the treatment of severe *P. falciparum* malaria in adults.
Strong recommendation, high quality evidence.

TREATMENT OF UNCOMPLICATED *P. VIVAX* MALARIA

- ⊙ In areas with chloroquine resistant *P. vivax*, artemisinin-based combination therapies (particularly those whose partner medicines have long half-lives) are recommended for the treatment of *P. vivax* malaria.
Weak recommendation, moderate quality evidence.
- ⊙ At least a 14-day course of primaquine is required for the radical treatment of *P. vivax*.
Strong recommendation, very low quality evidence.

1. INTRODUCTION

1.1 Background

Malaria is an important cause of death and illness in children and adults, especially in tropical countries. Malaria control requires an integrate approach, including prevention (primarily vector control) and prompt treatment with effective antimalarials. Since the publication of the first edition of the guidelines in 2006, most of the countries where *P. falciparum* is endemic have progressively updated treatment policies from the failing chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) to the recommended artemisinin-based combination therapies (ACTs); this is the best current treatment for uncomplicated falciparum malaria. Unfortunately, the implementation of these policies has lagged behind due to various factors such as high costs.

The recommendations given in these guidelines aim to provide simple and straightforward treatment recommendations based on sound evidence that can be applied even in severely resource-constrained settings. To achieve this goal, all relevant factors are taken into account with adjustments for different areas where levels of drug resistance and background immunity vary. These factors include the in vitro antimalarial susceptibility and the pharmacokinetic and pharmacodynamic properties of the different antimalarial medicines. Cost is a factor that should be taken into consideration in antimalarial treatment policy and practices. However, as there are increasing international subsidies for antimalarials, efficacy and safety have taken precedence over costs when making the recommendations. The number of antimalarial drug trials published has continued to increase over the years, with the result that these guidelines have a firmer evidence base than previous treatment recommendations. Inevitably, there are still information gaps, so they will remain under regular review with updates every two years and/or on an ad hoc basis as new evidence becomes available. The malaria treatment recommendations in the main document are brief; for those who may wish to study the evidence base in more detail, a series of annexes with linkages to the appropriate sections of the main document is provided.

1.2 Objectives and target audience

1.2.1 Objectives

The purpose of these guidelines is to provide global, evidence-based recommendations on the treatment of malaria. Information is shown on the treatment of:

- uncomplicated malaria, including disease in special risk groups (young children, pregnant women, people who are HIV positive, travellers from non-malaria endemic

- regions), and in epidemics and complex emergency situations; and
- severe malaria.

The guidelines provide a framework for the development of specific and more detailed national treatment protocols that take into account local antimalarial drug resistance patterns and health service capacity in the country (see Annex 2). They are not intended to provide, or to be used, as a comprehensive clinical management guide/manual for the treatment of malaria.

1.2.2 Target audience

These guidelines are primarily targeted at policy-makers in ministries of health, who formulate country specific treatment guidelines. However, the following groups should also find them useful:

- public health and policy specialists working in hospitals, research institutions, medical schools, nongovernmental organizations and agencies working as partners in health or malaria control, the pharmaceutical industry and primary health-care services; and
- health professionals (doctors, nurses and paramedical officers).

1.3 Methods used in developing the guidelines and recommendations

In the first edition of the *WHO Guidelines for the treatment of malaria* (2006), the methodology for identifying the questions, search and review of evidence is similar to that used in this current update. However, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was not applied then, rather in formulating recommendations, evidence was graded in order of priority as follows:

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

Since the release of the first edition of the guidelines, the WHO's standard methods for guidelines development has evolved and, thus, this second edition was developed in accordance with the updated WHO standard methods for guideline development. This methodology incorporates a transparent link between research evidence and recommendations. The GRADE system, which has been incorporated into this update, is a uniform approach that is being widely adopted. It employs explicit methods, developed by the GRADE Working Group, to formulate and to evaluate the strength of a recommendation based on the robustness of the evidence relating to a specific clinical question. For this second edition of the guidelines, only new recommendations have been subjected to the GRADE process (see Annex 1).

The development, preparation and printing of the guidelines is exclusively funded by the WHO Global Malaria Programme. No external sources of funding either from bilateral technical partners, or from industry, was solicited or used.

1.3.1 Method

The GRADE methodology involves a four-step process:

- *identification* of the clinical questions, and the critical and important outcomes to answer these questions;
- *systematic* reviews of the evidence (using Cochrane methodology) focusing on these outcomes;
- *construction* of GRADE tables to summarize the data and to assess the quality (or robustness) of the evidence;
- *interpretation* of the GRADE tables and the formulation of recommendations.

The first meeting of the Malaria Treatment Guidelines Panel identified several key areas for review of existing recommendations:

- consider adding dihydroartemisinin plus piperaquine to the recommended list of artemisinin-based combination therapies (ACTs) for uncomplicated malaria;
- consider removing amodiaquine plus sulfadoxine-pyrimethamine from the list of recommended antimalarials for uncomplicated malaria;
- reconsider the recommendation of artesunate plus mefloquine in Africa, with specific concerns regarding toxicity/vomiting in children;
- consider the relative effectiveness of IV artesunate instead of quinine for severe malaria;
- assess the role of ACTs in vivax malaria in areas with chloroquine-resistant *P. vivax*;
- consider the best treatment for radical cure of *P. vivax* malaria.

A sub-group of the panel – the “GRADE sub-group” – was formed that prepared and evaluated appropriate, up-to-date systematic reviews and developed GRADE profiles related to these questions.

The quality of the evidence, as assessed by GRADE, is rated on a four-point scale:

- **HIGH quality:** further research is very unlikely to change the confidence in the estimate of effect;
- **MODERATE quality:** further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate;
- **LOW quality:** further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate;
- **VERY LOW quality:** uncertainty about the estimate.

Recommendations were formulated based on the GRADE profiles with the strength of recommendations rated as:

- **weak:** the panel considers that the benefits of the intervention probably outweigh the risks; or
- **strong:** the panel is confident that the benefits of the intervention outweigh the risks.

The recommendations were modified where necessary with further consideration of important factors beyond the scope of evidence so that **strong** recommendations may be made on the basis of **low** quality evidence, and vice versa. These additional values and preferences considered as important to the panel are described alongside presentation of the tables.

1.3.2 Presentation of evidence (recommendations)

For clarity, these guidelines are presented in a simple descriptive form with a central main document containing the recommendations. Summaries of the recommendations are given in boxes together with the summary of the GRADE profiles, where available. In situations where a GRADE table has not been constructed, it is so indicated in the recommendation box. Full reviews of the evidence, the complete GRADE tables and additional references are provided in annexes appropriately referenced in the main document.

2. CLINICAL DISEASE AND EPIDEMIOLOGY

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*. Increasingly, human infections with the monkey malaria parasite, *P. knowlesi*, have also been reported from the forested regions of South-East Asia.

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, usually followed by fever, chills, perspiration, anorexia, vomiting and worsening malaise. Malaria is, therefore, frequently over-diagnosed on the basis of symptoms alone, especially in endemic areas, because of this non-specificity of symptomatology. At this early stage, with no evidence of vital organ dysfunction, the patients can readily be treated with full rapid recovery provided prompt and effective treatment is given. If, however, ineffective medicines are given or if treatment is delayed, particularly in *P. falciparum* malaria, the parasite burden continues to increase and severe malaria may ensue. It is a progression that may occur within a few hours. Severe malaria

usually manifests with one or more of the following: coma (cerebral malaria), metabolic acidosis, severe anaemia, hypoglycaemia, acute renal failure or acute pulmonary oedema. By this stage of the disease, the case fatality in people receiving treatment is typically 10–20%. However, if left untreated, severe malaria is fatal in the majority of cases.

The nature of malaria clinical disease depends greatly on the background level of the acquired protective immunity, a factor which is the outcome of the pattern and intensity of malaria transmission in the area of residence.

Where the transmission of malaria is “stable”, meaning where populations are continuously exposed to a fairly constant, high rate of malarial inoculations (entomological inoculation rate [EIR] >10 per year), partial immunity to the clinical disease and to its severe manifestation 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 mostly confined to young children, who suffer high parasite densities and acute clinical disease. If untreated, this can progress very rapidly to severe malaria; adolescents and adults are partially immune and seldom suffer clinical disease, although they may continue to harbour low blood-parasite densities. Immunity is, however, modified in pregnancy, and it is often gradually lost, at least partially, when individuals move out of the endemic areas for long durations (usually many years).

In areas of unstable malaria, which prevails 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. Entomological inoculation rates are usually <5 per year and often <1 per 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 due to a sudden increase in mosquito vector densities. Epidemics manifest as a very high incidence of malaria in all age groups and can overwhelm health services. Severe malaria is common if prompt effective treatment is not made widely available. Non-immune travellers to a malaria endemic area are at a high risk of acquiring malaria, unless protective measures are taken, and of the disease progressing to fatal severe malaria if infections are not treated promptly and effectively.

With effective malaria control (as with a population-wide coverage with effective vector control and large-scale deployment of ACTs), the number of malaria inoculations can be greatly reduced; this will be followed in time by a corresponding change in the clinical epidemiological profile in the area and a risk of epidemics, if control measures are not sustained.

3. OBJECTIVES OF TREATMENT

3.1 Uncomplicated malaria

The objective of treating uncomplicated malaria is to cure the infection as rapidly as possible. Cure is defined as the elimination from the body of the parasites that caused the illness. This prevents progression to severe disease, and additional morbidity associated with treatment failure. In treatment evaluations, it is necessary to follow patients for sufficient time to appropriately assess cures (*see* Section 5.1).

The public health goal of treatment is to reduce transmission of the infection to others, i.e. to reduce the infectious reservoir and to prevent the emergence and spread of resistance to antimalarial medicines (*see* Annex 4). The adverse effect profile and tolerability of antimalarial medicines, 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. 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. In all cases of severe malaria, prevention of recrudescence and avoidance of minor adverse effects are secondary.

4. RESISTANCE TO ANTIMALARIAL MEDICINES

Resistance to antimalarial medicines has been documented in all classes of antimalarials, including the artemisinin derivatives, and it is a major threat to malaria control. Widespread and indiscriminate use of antimalarials exerts 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. Further information on the emergence, spread and prevention of resistance to antimalarials is provided in Annex 6.

¹ *Methods for surveillance of antimalarial drug efficacy*. Geneva, World Health Organization, 2009. <http://apps.who.int/malaria/docs/drugresistance/Protocol2009.pdf>, accessed 29 October 2009).

² *Methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations. Informal consultation organized by the Medicines for Malaria Venture and cosponsored by the World Health Organization, 29–31 May 2007, Amsterdam, the Netherlands*. Geneva, World Health Organization, 2008. <http://apps.who.int/malaria/docs/drugresistance/MalariaGenotyping.pdf>, accessed 29 October 2009).

4.1 Impact of resistance

Initially, at low levels of resistance and with a low prevalence of malaria, the impact of resistance to antimalarials is insidious. At the early onset of resistance, the initial symptoms of the infection resolve and the patient appears to be better for a short period of time; however, symptoms recur (usually between three to six weeks after treatment), anaemia may worsen and there is a greater probability of carrying gametocytes (which in turn carry the resistance genes). The patient and the treatment provider mostly interpret these early features of resistance as a newly acquired infection. Unless clinical drug trials are conducted at this stage, resistance may go unrecognized. As resistance worsens, the interval between primary infection and recrudescence shortens; eventually symptoms fail to resolve following treatment, with malaria incidence likely to rise in low-transmission settings, and mortality is likely to rise in all settings.

4.2 Global distribution of resistance

Resistance to antimalarials has been documented for *P. falciparum*, *P. malariae* and *P. vivax*. In *P. falciparum*, resistance has been observed in all currently used antimalarials (amodiaquine, chloroquine, mefloquine, quinine, and sulfadoxine-pyrimethamine) and, more recently, in artemisinin derivatives. The geographical distributions and rates of spread have varied considerably.

P. vivax has developed resistance rapidly to sulfadoxine-pyrimethamine in many areas, while resistance to chloroquine is confined largely to Indonesia, Papua New Guinea, Timor-Leste and other parts of Oceania. There are also reports on resistance from Brazil and Peru. *P. vivax* remains sensitive to chloroquine in most of South-East Asia, the Indian subcontinent, the Korean peninsula, the Middle East, north-east Africa, and most of South and Central America.

4.3 Assessing efficacy and resistance

The following methods are available for assessing efficacy and resistance to antimalarials:

- in vivo assessment of therapeutic efficacy;¹
- molecular genotyping to distinguish between re-infections and recrudescence;²
- in vitro studies of parasite susceptibility to drugs in culture.³
- molecular markers.

³ Basco LK. *Field application of in vitro assays for the sensitivity of human malaria parasites to antimalarial drugs*. Geneva, World Health Organization, 2007
http://apps.who.int/malaria/docs/drugresistance/OMS_FieldApplicationInVitroAssays.pdf, accessed 29 Oct. 2009).

5. ANTIMALARIAL TREATMENT POLICY

National antimalarial treatment policies should aim to offer antimalarials that are highly effective.

5.1 Criteria for antimalarial treatment policy change

The main determinant of antimalarial treatment policy is the therapeutic efficacy of the antimalarial medicines 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 alternative medicines, strategies and approaches. Therapeutic efficacy monitoring involves the assessment of clinical and parasitological outcomes of treatment over at least 28 days following the start of adequate treatment to monitor for the reappearance of parasites in the blood. Reappearance of the same genotype indicates reduced parasite sensitivity to the treatment drug.

Antimalarial treatment should be assessed on the basis of parasitological cure rates. The duration of post-treatment follow-up is based on the elimination half-life of the antimalarial medicine being evaluated. The current recommended duration of follow-up is a minimum of 28 days for all antimalarial medicines, while it is extended for longer periods of time depending on elimination half-life (42 days for combinations with mefloquine and piperaquine). When 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 inadequate drug exposure.

In high-transmission settings re-infection is inevitable, but the cure of malaria (i.e. prevention of recrudescence) is important; it benefits both the patient, by reducing anaemia, and the community, by reducing the parasite reservoir and slowing the emergence and spread of resistance. 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 the provision of a period of prophylaxis.

5.2 Therapeutic efficacy cut-offs for changing treatment policy

A change of an antimalarial medicine recommended in the national malaria treatment policy should be initiated if the total treatment failure proportion is $\geq 10\%$, as assessed through in vivo monitoring of therapeutic efficacy. The selection of a new and/or

alternative antimalarial medicine for use at public health level within the context of national treatment guidelines, should be based on an average cure rate of >95%, as assessed in clinical trials.

6. DIAGNOSIS OF MALARIA

Prompt and accurate diagnosis of malaria is part of effective disease management. The diagnosis of malaria is based on clinical suspicion and on the detection of parasites in the blood (parasitological or confirmatory diagnosis). High sensitivity of diagnosis in malaria-endemic areas is particularly important for the most vulnerable population groups, such as young children and the non-immune population, in whom the disease can be rapidly fatal, while high specificity will reduce unnecessary treatment with antimalarials and improve diagnosis of other febrile illnesses in all settings. Thus, high quality malaria diagnosis is important in all settings. Further information on the diagnosis of malaria is provided in Annex 5.

6.1 Clinical diagnosis

The signs and symptoms of malaria are nonspecific. Malaria is clinically suspected mostly on the basis of fever or a history of fever. Diagnosis based on clinical features alone has very low specificity and results in over-treatment. Other possible causes of fever and the need for alternative or additional treatment must always be carefully considered. The WHO recommendations for clinical diagnosis/suspicion of uncomplicated malaria in different epidemiological settings are as follows:⁴

- in settings where the risk of malaria is low, clinical diagnosis of uncomplicated malaria should be based on the possibility of exposure to malaria and a history of fever in the previous three days with no features of other severe diseases;
- in settings where the risk of malaria is high, 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.

In all settings, clinical suspicion of malaria should be confirmed with a parasitological diagnosis. However, in settings where parasitological diagnosis is not possible, the decision to provide antimalarial treatment must be based on the prior probability of the illness being malaria. Other possible causes of fever and need for alternative treatment must always be carefully considered.

⁴ WHO Expert Committee on Malaria. Twentieth report. Geneva, World Health Organization, 2000 in WHO Technical Report Series, No. 892.

In children under five years of age, the WHO/United Nations Children’s Fund (UNICEF) strategy for Integrated Management of Childhood Illness (IMCI)⁵ practical algorithms for management of the sick child should be used to ensure full assessment and appropriate case management of children at the first-level health facilities.

6.2 Parasitological diagnosis

The changing epidemiology of malaria and the introduction of ACTs have increased the urgency of improving the specificity of malaria diagnosis. Parasitological diagnosis has the following advantages:

- improved patient care in parasite-positive patients;
- identification of parasite-negative patients in whom another diagnosis must be sought;
- prevention of unnecessary use of antimalarials, reducing frequency of adverse effects, especially in those who do not need the medicines, and drug pressure selecting for resistant parasites;
- improved malaria case detection and reporting;
- confirmation of treatment failures.

The two methods in routine use for parasitological diagnosis are light microscopy and rapid diagnostic tests (RDTs). The latter detect parasite-specific antigens or enzymes and some have a certain ability to differentiate species. Deployment of microscopy and RDTs must be accompanied by quality assurance. Antimalarial treatment should be limited to test positive cases and negative cases should be reassessed for other common causes of fever. The benefit of parasitological diagnosis depends entirely on health-care providers adhering to the results in managing the patient, except where the severity of the disease justifies the use of antimalarials in test negative cases, considering the possible small risk of false negative tests. The risk of false negative microscopy is higher if the patient has received a recent dose of an artemisinin derivative.

The results of parasitological diagnosis should be available within a short time (less than two hours) of the patient presenting. In the absence or delay of parasitological diagnosis, patients with suspected severe malaria, and other high risk groups, should be treated immediately on clinical grounds.

6.2.1 The choice between rapid diagnostic tests and microscopy

The choice between RDTs and microscopy depends on local circumstances, including the skills available, patient case-load, epidemiology of malaria and the possible use of microscopy for the diagnosis of other diseases. Where the case-load of fever patients is high, microscopy is likely to be less expensive than RDTs, but may be less operationally

⁵ *Integrated management of childhood illness for high HIV settings: chart booklet*. Geneva, World Health Organization, 2008 http://www.who.int/child_adolescent_health/documents/9789241597388/en/index.html, accessed 29 Oct. 2009.

feasible. Microscopy has further advantages in that it can be used for speciation and quantification of parasites, and to assess response to antimalarial treatment. Microscopy can also be used in the identification of other causes of fever. However, a major drawback of light microscopy is its requirement for well-trained, skilled staff and, usually, an energy source to power the microscope.

In many areas, malaria patients are treated outside of the formal health services, e.g. in the community, in the home or by private providers; microscopy is generally not feasible in many such circumstances, but RDTs may be possible. Although RDTs for detection of parasite antigen are generally more expensive, their deployment may be considerably cost effective in many of these settings. The sensitivities and specificities of RDTs 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. Practical experience and operational evidence of best practices from large-scale implementation, though still limited, should guide wide-scale deployment of RDTs on a programmatic level.

In the diagnosis of severe malaria cases, microscopy is a preferred option; it not only provides the diagnosis of malaria, but it is useful in assessing other important parameters in a severely ill patient. In situations where an RDT has been used to confirm malaria, this allows for a rapid institution of antimalarial treatment, however, where possible a microscopic examination is recommended to enhance the overall management of the patient.

6.3 Where malaria transmission is low-to-moderate and/or unstable

Parasitological confirmation of the diagnosis of malaria is strongly recommended. This should be provided by high quality microscopy or, where this is not available, by RDTs. Low-to-moderate transmission settings⁶ include most areas outside Africa. In Africa, this includes many urban areas that have effective malaria control programmes; during the low-transmission season, it includes 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 patients that may have been exposed to malaria (e.g. recent travel to a malaria endemic area, or lack of effective preventive measures) and have symptoms that may be attributable to malaria before they conduct a parasitological test.

⁶ 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.

6.4 In stable high-transmission settings

Parasitological confirmation of the diagnosis of malaria provided by high-quality microscopy or, where this is not available, by RDTs is recommended for all suspected cases of malaria. High-transmission settings include most areas in some parts of Oceania and sub-Saharan Africa. In these settings, slide positivity rate in children under five years of age with fever is more than 5%.

A parasitological confirmation of malaria in stable high-transmission settings is recommended; it improves the differential diagnosis of fever, improves fever case management, and reduces unnecessary use of antimalarial medicines. Antimalarial treatment on the basis of clinical suspicion of malaria should only be considered in situations where a parasitological diagnosis is not accessible. This consideration is of high significance particularly in vulnerable populations (e.g. children under five years of age, pregnant women, suspected severe malaria cases, and in settings with a high prevalence of HIV/AIDS where the patients present with fever or a history of fever and no other obvious cause of the fever is present) in whom the disease can rapidly become fatal.

6.5 Malaria parasite species identification

In areas where two or more species of malaria parasites are common, only the 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. Where *P. vivax*, *P. malariae* or *P. ovale* occur, almost always as a co-infection with *P. falciparum*, an RDT detecting *P. falciparum* alone may be sufficient; the treatment for non-falciparum malaria is given only to cases with a negative test result and where no other obvious cause of illness is present. Anti-relapse treatment with primaquine should only be given to cases with confirmed diagnosis of *P. vivax* or *P. ovale* malaria, and in the absence of contraindications such as glucose-6-phosphate dehydrogenase (G6PD) deficiency.

6.6 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 may be impractical and unnecessary to demonstrate parasites before treatment in all cases of fever (see details in Section 11.1).

BOX 6.1**Summary of recommendations on PARASITOLOGICAL DIAGNOSIS**

- ▶ **Prompt parasitological confirmation by microscopy, or RDTs, is recommended in all patients suspected of malaria before treatment is started.**
- ▶ **Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not accessible.**

7. TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA

To counter the threat of resistance of *P. falciparum* to monotherapies, and to improve treatment outcome, WHO recommends that artemisinin-based combination therapies be used for the treatment of uncomplicated *P. falciparum* malaria (see also Annex 7). Although the evidence base confirming the benefits of artemisinin-based combinations has grown substantially in recent years, there is still substantial geographic variability in the efficacy of available ACT options, underlining the importance of countries regularly monitoring the efficacy of the ACTs in use to ensure that the appropriate ACT option(s) is being deployed.

7.1 Definition of uncomplicated malaria

Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction. The signs and symptoms of uncomplicated malaria are nonspecific. Malaria is, therefore, suspected clinically mostly on the basis of fever or a history of fever.

7.2 Rationale for antimalarial combination therapy

Antimalarial combination therapy is the simultaneous use of two or more blood schizontocidal medicines with independent modes of action and, thus, different biochemical targets in the parasite. The rationale is twofold: *i*) the combination is often more effective; and *ii*) in the very rare event that a mutant parasite resistant to one of the medicines arises *de novo* during the course of the infection, this resistant parasite will be killed by the other antimalarial medicine. This mutual protection is thought to prevent or to delay the emergence of resistance. To realize the two advantages, the partner medicines in a combination must independently be sufficiently efficacious in treating malaria.

7.2.1 Non-artemisinin based combination therapy

Non-artemisinin based combination treatments include sulfadoxine-pyrimethamine plus chloroquine (SP+CQ) or amodiaquine (SP+AQ). The prevailing high levels of resistance to these medicines as monotherapy have compromised their efficacy even in combinations. There is no convincing evidence that chloroquine plus sulfadoxine-pyrimethamine provides any additional benefit over SP, so this combination is not recommended; amodiaquine plus sulfadoxine-pyrimethamine can be more effective than either drug alone; but it is usually inferior to ACTs, and it is no longer recommended for the treatment of malaria.

BOX 7.1

RECOMMENDATION: *withdrawal of non-ACTs for treatment of uncomplicated falciparum malaria*

- ▶ **Artemisinin-based combination therapies should be used in preference to amodiaquine plus sulfadoxine-pyrimethamine for the treatment of uncomplicated *P. falciparum* malaria.**
Strong recommendation, moderate quality evidence

GRADE evaluation (see Annex 7, tables A7.1.1–A7.1.4)

In trials comparing AQ+SP to the recommended ACTs, the performance of AQ+SP is highly variable. Treatment failure rates at day 28 (after polymerase chain reaction [PCR] adjustment) are as high as 16% in Uganda and 24% in Rwanda. In addition, AQ+SP is less effective at reducing gametocyte carriage than combinations containing an artemisinin derivative. AQ+SP performed adequately in trials from Senegal in 2003, Burkina Faso in 2005, and Madagascar in 2006.

Other considerations

The panel's view is that the continued spread of amodiaquine and sulfadoxine-pyrimethamine resistance is likely to reduce the effectiveness of this combination in most African countries and, thus, their use as partners in ACT combinations.

7.2.2 Artemisinin-based combination therapy

These are combinations in which one of the components is artemisinin and its derivatives (artesunate, artemether, dihydroartemisinin). The artemisinins produce rapid clearance of parasitaemia and rapid resolution of symptoms, by reducing parasite numbers 100- to 1000-fold per asexual cycle of the parasite (a factor of approximately 10 000 in each 48-h asexual cycle), which is more than the other currently available antimalarials achieve. Because artemisinin and its derivatives are eliminated rapidly, when given alone or in combination with rapidly eliminated compounds (tetracyclines, clindamycin), a 7-day course of treatment with an artemisinin compound is required (see Annex 3 for details). This long duration of treatment with the artemisinins can be reduced to 3 days when given

in combination with slowly eliminated antimalarials. With this shorter 3-day course, the complete clearance of all 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. This also results in the artemisinin component being protected from resistance by the partner medicine, while the partner medicine is also partly protected by the artemisinin derivative.

An additional advantage from a public health perspective is the ability of the artemisinins to reduce gametocyte carriage and, thus, the transmissibility of malaria. This contributes to malaria control, particularly in areas of low-to-moderate endemicity.

To eliminate at least 90% of the parasitaemia, a 3-day course of the artemisinin is required to cover up to three post-treatment asexual cycles of the parasite. This ensures that only about 10% of the parasitaemia is present for clearance by the partner medicine, thus reducing the potential for development of resistance. Shorter courses of 1–2 days of the artemisinin component of the ACTs would lead to a larger proportion of parasitaemia for clearance by the partner medicine; this is not recommended for the following additional reasons:

- they are less efficacious (except when the partner drug is highly effective),
- they have less of an effect on gametocyte carriage,
- they provide less protection of the slowly eliminated partner antimalarial.

Box 7.2

RECOMMENDATION: *duration of artemisinin component in combination treatment of uncomplicated P. falciparum malaria*

► **ACTs should include at least 3 days of treatment with an artemisinin derivative.**

Strong recommendation, high quality evidence

GRADE evaluation (see Annex 7, Table A7.2.1)

In trials comparing the addition of 3 days of artesunate to sulfadoxine-pyrimethamine with adding 1 day of artesunate, there was a significant reduction in treatment failure at day 28 with the 3-day combination (5 trials, 1634 participants; relative risk [RR] 0.62, 95% confidence interval [CI] 0.55–0.69).

7.3 ACT 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 currently available formulations. It is the properties of the partner medicine that determine the efficacy and choice of combination. Resistance to the artemisinins' partner medicines compromises the efficacy of the ACT.

In addition to the four ACT combinations – artemether plus lumefantrine (AL), artesunate plus amodiaquine (AS+AQ), artesunate plus mefloquine (AS+MQ), and artesunate plus sulfadoxine-pyrimethamine (AS+SP) – already recommended for the treatment of uncomplicated *P. falciparum* malaria there is now sufficient evidence on safety and efficacy of dihydroartemisinin plus piperaquine (DHA+PPQ) for its addition to the list of ACTs options recommended for the treatment of uncomplicated falciparum malaria (see Annex 7, Section A7.1).

BOX 7.3

RECOMMENDATION: DHA+PPQ as a first-line treatment for uncomplicated *P. falciparum* malaria

► **DHA+PPQ is an ACT option for first-line treatment of uncomplicated *P. falciparum* malaria worldwide.** *Strong recommendation, high quality evidence*

GRADE evaluation (see Annex 7, tables A7.3.1–A7.3.3)

In clinical trials directly comparing DHA+PPQ and the currently recommended ACTs, DHA+PPQ was at least as effective at treating uncomplicated *P. falciparum* malaria (as measured by PCR adjusted treatment failure) as:

- artesunate plus mefloquine in Asia (day 63, 3 trials, 1182 participants; RR 0.39, 95% CI 0.19–0.79; *high quality evidence*);
- artemether plus lumefantrine worldwide (day 42, 4 trials, 1492 participants; RR 0.42, 95% CI 0.26–0.67; *high quality evidence*);
- artesunate plus amodiaquine worldwide (day 28, 2 trials, 679 participants; RR 0.47, 95% CI 0.23–0.94; *moderate quality evidence*).

Other considerations

At the time of publication, no DHA+PPQ product has been prequalified by WHO or registered by any stringent medicine regulatory authority.

In summary, the ACT options now recommended for treatment of uncomplicated falciparum malaria in alphabetical order are:

- artemether plus lumefantrine,
- artesunate plus amodiaquine,
- artesunate plus mefloquine,
- artesunate plus sulfadoxine-pyrimethamine,⁷
- dihydroartemisinin plus piperaquine.

⁷ A similar medicine with tablets containing 500 mg of sulfalene and 25 mg pyrimethamine is considered an alternative to sulfadoxine-pyrimethamine.

7.3.1 Deployment considerations affecting choice

Fixed-dose combination (FDC) formulations are strongly preferred and recommended over blistered co-packaged or loose tablets combinations to promote adherence to treatment and to reduce the potential selective use of the medicines as monotherapy. Fixed-dose combination formulations are now available for all recommended ACTs, except artesunate plus SP. Fixed-dose combinations may contribute to delaying artemisinin resistance as they avoid artemisinin monotherapies being distributed (as loose tablets or in co-packaged blisters). As formulating FDCs of ACTs is technically difficult, it is essential that generic FDCs are shown to have satisfactory ingredient compatibility, stability, and similar absorption rates and oral bioavailability to the separate tablets or benchmark reference FDCs.

Resistance and tolerability to the partner medicines of artemisinins in ACTs may affect choice. In many countries, artemether plus lumefantrine, artesunate plus mefloquine or dihydroartemisinin plus piperazine may give the highest cure rates. The main reason for restricting the use of AS+MQ in African children so far has been excessive vomiting associated with mefloquine at the recommended dose of 25 mg/kg. However, a recent study⁸ found that in children weighing 10–20 kg (mean age of the study population was 4.5 ± 1.7 years) the tolerability of AS+MQ is as good as with artemether-lumefantrine.

The low levels of resistance to AQ and SP in some parts of Africa still makes artesunate plus amodiaquine or sulfadoxine-pyrimethamine effective options. However, amodiaquine and sulfadoxine-pyrimethamine remain widely available as monotherapies providing continued selection pressure, and it is likely that resistance will continue to worsen despite the deployment of corresponding ACTs.

7.4 Management of treatment failures

Recurrence of *P. falciparum* malaria can be the result of a re-infection, or a recrudescence (i.e. failure). In an individual patient, it may not be possible to distinguish recrudescence from re-infection, although if fever and parasitaemia fail to resolve or recur within two weeks of treatment then this is considered a failure of treatment. Treatment failures may result from drug resistance, poor adherence or inadequate drug exposure (from under-dosing, vomiting or unusual pharmacokinetic properties in that individual) or substandard medicines. It is important to determine from the patient's history whether he or she vomited the previous treatment or did not complete a full course.

Wherever possible, treatment failure must be confirmed parasitologically – preferably by blood slide examination (as *P. falciparum* histidine-rich protein-2 (PfHRP2)-based tests

⁸ Babacar Faye et al. A Randomized trial of artesunate mefloquine versus artemether lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Senegalese children. *Am. J. Trop. Med. Hyg.* 82(1), 2010, 140-144.

may remain positive for weeks after the initial infection, even without recrudescence). This may require referring the patient to a facility with microscopy. Referral may be necessary anyway to obtain treatment.

In many cases, failures are missed because patients who present with malaria are not asked whether they have received antimalarial treatment within the preceding 1–2 months. This should be a routine question in patients who present with malaria.

7.4.1 Failure within 14 days

Treatment failure within 14 days of receiving an ACT is very unusual, with the majority of treatment failures occurring after two weeks of initial treatment. Of 39 trials with artemisinin or its derivatives, which together enrolled 6124 patients, 32 trials (4917 patients) reported no treatment failures by day 14. In the remaining 7 trials, failure rates at day 14 ranged from 1–7%. Treatment failures within 14 days of initial treatment should be treated with a second-line antimalarial (*see* Section 7.4.2).

7.4.2 Second-line antimalarial treatments

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:

- an alternative ACT known to be effective in the region,
- artesunate plus tetracycline or doxycycline or clindamycin (given for a total of 7 days),
- quinine plus tetracycline or doxycycline or clindamycin (given for a total of 7 days).

The alternative ACT has the advantages of simplicity, and where available, a fixed-dose combination formulation improves adherence. The 7-day regimes are not well tolerated, and adherence is likely to be poor if treatment is not observed. It is essential that the patient and the caregiver understand the importance of completing the full 7-day course of treatment.

7.4.3 Failure after 14 days

Recurrence of fever and parasitaemia more than two weeks after treatment could result either from recrudescence or new infection and this distinction can only be made through parasite genotyping by PCR. Since PCR is not routinely used in patient management, to simplify drug deployment, all presumed treatment failures after two weeks of initial treatment should, from an operational standpoint, be considered as new infections, especially in areas of high transmission, and be treated with the first-line ACT. This simplifies operational management and drug deployment. If the failure is a recrudescence, then the first-line treatment should still be effective in most cases. However, reuse of mefloquine within 60 days of first treatment is associated with an increased risk of neuropsychiatric reactions and, in cases where the initial treatment was AS+MQ, second-line treatment not containing mefloquine should be given instead.

BOX 7.4**Summary of recommendations on TREATMENT FOR UNCOMPLICATED *P. FALCIPARUM* MALARIA**

- ▶ **The treatment of choice for uncomplicated falciparum malaria is a combination of two or more antimalarial medicines with different mechanisms of action.**
- ▶ **ACTs are the recommended treatments for uncomplicated falciparum malaria.**
- ▶ **The artemisinin derivative components of the combination must be given for at least three days for an optimum effect.**
- ▶ **The following ACTs are recommended:**
 - artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, and dihydroartemisinin plus piperaquine.
- ▶ **Fixed-dose combinations are highly preferable to the loose individual medicines co-blistered or co-dispensed.**
- ▶ **The choice of ACT in a country or region will be based on the level of resistance of the partner medicine in the combination:**
 - in areas of multidrug resistance (east Asia), artesunate plus mefloquine, or artemether plus lumefantrine or dihydroartemisinin plus piperaquine are recommended; and
 - in other areas without multidrug resistance (mainly Africa), any of the ACTs including those containing amodiaquine or sulfadoxine-pyrimethamine may still be effective.
- ▶ **Artemisinin and its derivatives should not be used as monotherapy.**
- ▶ **Second-line antimalarial treatment:**
 - alternative ACT known to be effective in the region;
 - artesunate plus tetracycline or doxycycline or clindamycin, any of these combinations should be given for 7 days;
 - quinine plus tetracycline or doxycycline or clindamycin, any of these combinations should be given for 7 days.

7.5 Practical aspects of treatment with recommended ACTs

An increasing variety of formulations and products are available for the recommended artemisinin-based drug combinations. The drug concentrations achieved in an individual patient depend on variables that include the pharmacokinetic properties of the drug, drug quality, and dose taken related to dosing schedules and adherence.

7.5.1 Artemether plus lumefantrine

This is currently available as a fixed-dose formulation with dispersible or standard tablets containing 20 mg of artemether and 120 mg of lumefantrine.

Therapeutic dose. The recommended treatment is a 6-dose regimen over a 3-day period. The dosing is based on the number of tablets per dose according to pre-defined weight bands (5–14 kg: 1 tablet; 15–24 kg: 2 tablets; 25–34 kg: 3 tablets; and > 34 kg: 4 tablets), given twice a day for 3 days. This extrapolates to 1.7/12 mg/kg body weight of artemether and lumefantrine, respectively, per dose, given twice a day for 3 days, with a therapeutic dose range of 1.4–4 mg/kg of artemether and 10–16 mg/kg of lumefantrine.

An advantage of this combination is that lumefantrine is not available as a monotherapy, and it has never been used by itself for the treatment of malaria. Lumefantrine absorption is enhanced by co-administration with fat. It is essential that patients or caregivers are informed of the need to take this ACT immediately after a meal or drink containing at least 1.2 g fat – particularly on the second and third days of treatment. A flavoured dispersible tablet paediatric formulation of artemether plus lumefantrine is now available, enhancing its use in young children (*see* details in Annex 3, sections A3.6.2, A3.7).

7.5.2 Artesunate plus amodiaquine

This is currently available as a fixed-dose formulation with tablets containing 25/67.5 mg, 50/135 mg or 100/270 mg of artesunate and amodiaquine. Blister packs of separate scored tablets containing 50 mg of artesunate and 153 mg base of amodiaquine, respectively, are also available.

Therapeutic dose. A target dose of 4 mg/kg/day artesunate and 10 mg/kg/day amodiaquine once a day for 3 days, with a therapeutic dose range between 2–10 mg/kg/day artesunate and 7.5–15 mg/kg/dose amodiaquine.

This combination was sufficiently efficacious only where 28-day cure rates with amodiaquine monotherapy exceeded 80%. Resistance is likely to worsen with continued availability of chloroquine and amodiaquine monotherapies (*see* Annex 3, Sections A3.2, A3.6.3).

7.5.3 Artesunate plus mefloquine

This is currently available as blister packs with separate scored tablets containing 50 mg of artesunate and 250 mg base of mefloquine, respectively. A fixed-dose formulation of artesunate and mefloquine is at an advanced stage of development.

Therapeutic dose. A target dose of 4 mg/kg/day artesunate given once a day for 3 days and 25 mg/kg of mefloquine either split over 2 days as 15mg/kg and 10mg/kg or over 3 days as 8.3 mg/kg/day once a day for 3 days. The therapeutic dose range is between 2–10 mg/kg/dose/day of artesunate and 7–11 mg/kg/dose/day of mefloquine.

Mefloquine is associated with an increased incidence of nausea, vomiting, dizziness, dysphoria and sleep disturbance in clinical trials, but these are seldom debilitating – where this ACT has been deployed it has been well tolerated. 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 a daily dose of 8.3 mg/kg for 3 days. (see Annex 3, Sections A3.5, A3.6.3,)

7.5.4 Artesunate plus sulfadoxine-pyrimethamine

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.⁹

Therapeutic dose. A target dose of 4 mg/kg/day artesunate given once a day for 3 days and a single administration of 25/1.25 mg/kg sulfadoxine-pyrimethamine on day 1, with a therapeutic dose range between 2–10 mg/kg/day artesunate and 25–70/1.25–3.5 mg/kg sulfadoxine-pyrimethamine.

This combination was sufficiently efficacious only where 28-day cure rates with sulfadoxine-pyrimethamine alone exceeded 80%. Resistance is likely to worsen with continued widespread use of sulfadoxine-pyrimethamine, sulfalene plus pyrimethamine and cotrimoxazole (trimethoprim plus sulfamethoxazole) (see Annex 3, sections A3.3–A3.4, A3.6.3).

7.5.5 Dihydroartemisinin plus piperaquine

This is currently available as a fixed-dose combination with tablets containing 40 mg of dihydroartemisinin and 320 mg of piperaquine.

Therapeutic dose. A target dose of 4 mg/kg/day dihydroartemisinin and 18 mg/kg/day piperaquine once a day for 3 days, with a therapeutic dose range between 2–10 mg/kg/day dihydroartemisinin and 16–26 mg/kg/dose piperaquine (see Annex 3, Section A3.6.4).

7.5.6 Artesunate plus tetracycline or doxycycline or clindamycin

There are no blister co-packaged forms of any of these combination options. These are reserved for very rare occasions of treatment failures to the recommended ACTs and in some special groups, e.g. pregnant women failing ACT treatment. They are dosed separately and should only be used in a hospital setting.

Therapeutic dose. Artesunate (2 mg/kg once a day) plus tetracycline (4 mg/kg four times a day or doxycycline (3.5 mg/kg once a day) or clindamycin (10 mg/kg twice a day). Any of these combinations should be given for 7 days.

7.6 Incorrect approaches to treatment

Artemisinin should not be used as monotherapy, as this will promote resistance to this critically important class of antimalarials. Wherever possible, artemisinin should be used

⁹ A similar medicine with tablets containing 500 mg of sulfalene and 25 mg of pyrimethamine is considered to be equivalent to SP.

in fixed-dose combinations, and otherwise used in combination with another effective antimalarial concurrently or sequentially. As certain patient groups, such as pregnant women and hyperparasitaemic patients, may need specifically tailored combination regimens, artemisinin derivatives as single agents will still be needed in selected facilities in the public sector, but they should be withdrawn from the private and informal sector.

In endemic regions, some semi-immune malaria patients could be cured using an incomplete dose or treatment regimens that would be unsatisfactory in patients with no immunity. In the past, this had led to different recommendations for patients considered as semi-immune and those considered as non-immune. This practice is no longer recommended. A full treatment course with a highly effective ACT is required whether or not the patient is considered to be semi-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. This practice is also unsafe and not 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 lumefantrine, the partner medicines of all other ACTs have been used previously as monotherapies, and amodiaquine, mefloquine and SP continue to be available as monotherapy in many countries. Despite recommendations and warnings, artemisinin derivatives are available as monotherapy in the market place in many countries, and they are being used as such for the treatment of uncomplicated malaria. The continued use of artemisinins or any of the partner medicines, such as monotherapies, can compromise the value of ACTs by selecting for drug resistance.

7.7 Additional considerations for clinical management

7.7.1 Can the patient take oral medication?

Some patients cannot tolerate oral treatment, and they will require parenteral or rectal administration for 1–2 days until they can swallow and retain oral medication reliably. Although such patients may never show other signs of severity, they should receive the same initial antimalarial dose regimens as for severe malaria. Initial parenteral treatment must always be followed by a full 3-day course of ACT (*see* Sections 8.4–8.7).

7.7.2 Use of antipyretics

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, often regurgitating their medication, and seizures. Treatment is with antipyretics and, if necessary, fanning and tepid sponging. Antipyretics

should be used if core temperatures $>38.5^{\circ}\text{C}$. Paracetamol (acetaminophen) 15 mg/kg every 4 hours is widely used; it is safe and well tolerated, given orally or as a suppository. Ibuprofen (5 mg/kg) 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.

7.7.3 Use of antiemetics

Vomiting is common in acute malaria and may be severe. Antiemetics are widely used. There have been no studies of their efficacy in patients with malaria, and no comparisons between different antiemetic compounds; there is no evidence that they are harmful though they can mask severe malaria. Patients that vomit everything, including the medicines, should be managed as severe malaria (*see* Sections 8.4–8.7).

7.7.4 Management of seizures

Generalized seizures are more common in children with *P. falciparum* malaria than in those with the other malarias. This suggests an overlap between the cerebral pathology resulting from malaria and febrile convulsions. As seizures may be a prodrome of cerebral malaria, patients with repeated seizures (more than two seizures within a 24 h period) should be treated as for severe malaria (*see* Sections 8.4–8.7). 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 7.7.2, if core temperature is above 38.5°C . There is no evidence that prophylactic anticonvulsants are beneficial in otherwise uncomplicated malaria, and they are not recommended.

7.8 Operational issues in treatment management

Individual patients derive the maximum benefit from ACTs, if they can access these within 24–48 hours of the onset of malaria symptoms. At a population level, their impact in terms of reducing transmission and delaying resistance depends on high coverage rates. Thus, to optimize the benefit of deploying ACTs, their deployment should target the public health delivery system, the private sector and the community or household. It should also ensure that there is no financial or physical barrier to universal access. The strategy to secure full access (including home-based management of malaria) must be based on an analysis of the national and local health systems, and this may require legislative change and regulatory approval with additional local adjustment based on programme monitoring and operational research. The dissemination of national treatment guidelines with clear recommendations, production and use of appropriate information, education and communication materials, monitoring both of the deployment process, access and coverage, and provision of adequately packaged (user-friendly) antimalarials are needed to optimize the benefits of providing effective treatments widely.

7.8.1 Home-based management of malaria

Home-based management of malaria (HMM) is one of the strategies recommended by WHO to improve access to prompt and effective treatment of malaria episodes through trained community members living as close as possible to where the patients live. Recently, evidence has been produced on the feasibility, acceptability and effectiveness of ACTs used within the context of HMM, supporting HMM as a public health strategy as well as adding to the evidence base for scaling up implementation of HMM with ACTs.^{10,11} Home management of malaria allows for coverage of the health services for malaria to extend beyond the reach of health facilities. It requires that effective and appropriate treatment with first-line ACTs, as well as guidance on referral criteria are provided at the community level through trained community-based providers, such as community health workers, mother coordinators and private vendors. The inclusion of pre-referral treatment with rectal artesunate and RDTs is recommended, where feasible. Further operational research is needed to optimize the use of RDTs within the context of HMM. HMM is now being integrated within the overall platform of the Community Case Management of childhood illnesses (CCM).

7.8.2 Health education

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 and provision of information materials to shopkeepers and other dispensers can all improve the understanding of malaria. This will increase the likelihood of improved prescribing and adherence, and appropriate referral, and will minimize the unnecessary use of antimalarials.

7.8.3 Adherence to treatment

Patient adherence is a major determinant of the response to antimalarials, as most treatments are taken at home without medical supervision. To achieve the desired therapeutic effectiveness, a medicine must be efficacious and it must be taken in the correct doses at the proper intervals. Studies on adherence suggest that 3-day regimens of medicines such as ACTs are adhered to reasonably well, provided that patients or caregivers are given an adequate explanation at the time of prescribing and/or dispensing. Prescribers, shopkeepers and 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 (e.g. blister packs) also encourages completion of the treatment course and correct dosing.

¹⁰ Ajayi IO et al. Feasibility and acceptability of artemisinin-based combination therapy for the home management of malaria in four African sites. *Malaria Journal*, 2008, 7:6. doi:10.1186/1475-2875-7-6

¹¹ Ajayi IO et al. Effectiveness of artemisinin-based combination therapy used in the context of home management of malaria: A report from three study sites in sub-Saharan Africa. *Malaria Journal* 2008, 7:190. doi:10.1186/1475-2875-7-190

7.8.4 Quality assurance of antimalarial medicines

Artemisinin and its derivatives in particular have built-in chemical instability, necessary for their biological action, which causes pharmaceutical problems both in the manufacturing process and in their co-formulation with other compounds. The problems of instability are accelerated under tropical conditions. The requirement to observe stringent quality manufacturing standards is particularly important for this class of compounds.

Counterfeit antimalarial tablets and ampoules containing no or minimal amounts of active pharmaceutical ingredients are also a major problem in some areas. These may lead to under-dosage, and they may result in fatal delays in appropriate treatment; they may also give rise to a mistaken impression of resistance, while also encouraging the development of resistance, especially those delivering a low dose of the antimalarial.

The World Health Organization, in collaboration with other United Nations agencies, has established an international mechanism to prequalify manufacturers of ACTs on the basis of compliance with internationally recommended standards of manufacturing and quality. Manufacturers of antimalarials with prequalified status are listed on the prequalification web site.¹² It is the responsibility of national drug and regulatory authorities to ensure that antimalarial medicines provided through both the public and private sectors are of acceptable quality, through regulation, inspection and law enforcement.

7.8.5 Pharmacovigilance

Rare but serious adverse drug reactions are often not detected in clinical trials, and they can only usually be detected through pharmacovigilance systems operating in situations of wide population use. There are few data from prospective Phase IV post-marketing studies of antimalarials specifically designed to detect rare but potentially serious adverse drug reactions. The safety profiles of the artemisinin derivatives, mefloquine and sulfadoxine-pyrimethamine are supported by a reasonable evidence base (mainly from multiple clinical trials). There have been large case-control studies with artemisinin and its derivatives in humans with evaluation of neurology, audiometry and auditory evoked potentials, and no evidence of neurotoxicity have been documented. Concern remains about the risks of neutropenia and hepatotoxicity associated with amodiaquine, whether used alone or in combination. This risk is increased by drug interactions, e.g. with efavirenz or zidovudine. More data are needed on safety of all of the ACTs, especially exposure in the first trimester of pregnancy, and also on interactions between antimalarials and other commonly used medicines. It is recommended that governments of malaria endemic countries with large-scale deployment of ACTs should consider establishing effective pharmacovigilance systems.

¹² Prequalification programme: a United Nations Programme managed by WHO. Geneva, World Health Organization, 2009 (<http://apps.who.int/prequal/>, accessed 24 October 2009).

7.9 Treatment in specific populations and situations

7.9.1 Pregnant women

Pregnant women with symptomatic acute malaria are a high-risk group, and they must promptly receive effective antimalarial treatment. Malaria in pregnancy is associated with low birth weight, increased anaemia and, in low-transmission areas, an increased risk of severe malaria and death. In high-transmission settings, despite the adverse effects on fetal growth, malaria is usually asymptomatic in pregnancy or associated with only mild, non-specific symptoms. There is insufficient information on the safety and efficacy of most antimalarials in pregnancy, particularly for exposure in the first trimester.

7.9.1.1 First trimester

Organogenesis occurs mainly in the first trimester; this is, therefore, the time of greatest concern for potential teratogenicity, although development of the nervous system continues throughout pregnancy. Although data from prospective studies are limited, antimalarial medicines considered safe in the first trimester of pregnancy are quinine, chloroquine, clindamycin and proguanil. Pregnant women in the first trimester with uncomplicated falciparum malaria should be treated with quinine plus clindamycin for seven days (and quinine monotherapy if clindamycin is not available). Artesunate plus clindamycin for seven days is indicated if this treatment fails.

In reality, women often do not declare their pregnancies in the first trimester or are not yet aware that they are pregnant; so all women of child bearing age should be asked about the possibility of their being pregnant before being given antimalarials, a standard practice for the administration of any medicine in potentially pregnant women. Nevertheless, early pregnancies will often be exposed inadvertently to the available first-line treatment in the population, mostly ACTs. Published prospective data on a limited number of exposed pregnancies in the first trimester ($n = 123$) indicate no adverse effects of artemisinins (and the partner drugs) on pregnancy or on the health of the fetus and neonates. The available data are sufficient to exclude a 5.3-fold or greater increase in risk of overall major birth defects and provide assurance in counselling women following early first trimester exposure, indicating that there is no need for them to seek to have their pregnancy interrupted because of this exposure. However, more data on the safety of artemisinins in early pregnancy are urgently needed. The recently introduced Pregnancy Exposure Registry will shed more light on the risks to patients in the first trimester of pregnancy who are inadvertently exposed to antimalarials, including ACTs.

7.9.1.2 Second and third trimesters

There is increasing experience with artemisinin derivatives in the second and third trimesters (over 1500 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. The choice of combination partner is difficult because of limited information. Mefloquine monotherapy has been associated with an increased risk of stillbirth in large studies in Thailand, but not in Malawi. The current standard six-dose artemether plus lumefantrine regimen has been evaluated in 125 women in the second and third trimesters in a controlled trial for the treatment of uncomplicated falciparum malaria on the Burmese-Thai border. It was well tolerated and safe, but efficacy was inferior to seven days of artesunate monotherapy. Reduced efficacy probably resulted from low drug concentrations in later pregnancy. Although many pregnant women in Africa have been exposed to artemether plus lumefantrine in the second and third trimesters of pregnancy, formal studies to evaluate its efficacy and safety in pregnant women in Africa are still ongoing. Similarly, many pregnant women in Africa have been treated with amodiaquine alone or combined with SP or artesunate; however the use of amodiaquine in pregnancy has only been documented in just over 500 pregnancies (with safety assessments in 450 of them). Amodiaquine use in Ghanaian pregnant women in the second and third trimesters was associated with frequent minor side effects, but it was not associated with liver toxicity or bone marrow depression or adverse neonatal outcome. There is no published information about the combination of amodiaquine and artesunate.

On the Burmese-Thai border, DHA+PPQ has been used successfully in the second and third trimesters of pregnancy in 50 women for rescue therapy and for treatment in 104 pregnant women in West Papua province (Indonesia). Sulfadoxine-pyrimethamine, though considered safe, is compromised for treatment in many areas because of increasing resistance. If AS+SP is used for treatment, the co-administration of high dose (5 mg) daily folate supplementation should be avoided as this compromises the efficacy of SP in pregnancy. Lower folate dosing (0.4–0.5 mg/day) should be used in women receiving AS+SP for the treatment of malaria, or treatments other than SP should be used. Clindamycin is also considered safe, but it must be given for seven days in combination with quinine. Quinine is associated with an increased risk of hypoglycaemia in late pregnancy, and it should be used only if effective alternatives are not available. Primaquine and tetracyclines should not be used in pregnancy.

BOX 7.5

RECOMMENDATIONS: *treatment of uncomplicated falciparum malaria in pregnancy*

► First trimester:

- Quinine plus clindamycin^a to be given for 7 days (artesunate plus clindamycin for 7 days is indicated if this treatment fails).
- An ACT is indicated only if this is the only treatment immediately available, or if treatment with 7-day quinine plus clindamycin fails, or if there is uncertainty about patient compliance with a 7-day treatment.

► **Second and third trimesters:**

- ACT^b known to be effective in the country/region or artesunate plus clindamycin to be given for 7 days or quinine plus clindamycin to be given for 7 days.

Pharmacovigilance programmes need to be established to continually monitor safety of antimalarial medicines in all trimesters, including inadvertent exposures in the early first trimester.

^a If clindamycin is unavailable or unaffordable, then the monotherapy should be given.

^b With the exception of DHA+PPQ for which there is insufficient information in second and third trimesters of pregnancy to use as first-line therapy.

7.9.2 Lactating women

The amounts of antimalarials that enter breast milk and are consumed by the breastfeeding infant are relatively small. Tetracycline is contraindicated in breastfeeding mothers because of its potential effect on the infant's bones and teeth. Primaquine should not be used in nursing women, unless the breastfed infant has been determined not to be G6PD-deficient.

BOX 7.6

RECOMMENDATION: *treatment for lactating women with uncomplicated falciparum malaria*

- **Lactating women should receive the recommended antimalarial treatment (including ACTs), except for primaquine and tetracycline.**

7.9.3 Infants and young children

7.9.3.1 Choice of antimalarial drug

There are important differences in the pharmacokinetic parameters of many medicines in young children. Accurate dosing is particularly important in infants. Despite this, only a few clinical studies have focused specifically on this age range; this is partly because of ethical considerations relating to the recruitment of very young children to clinical trials, and it is 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. As a result, the available evidence in young infants (<5 kg) is insufficient for confident recommendations for any of the ACTs, to the extent that many of the drugs carry label restrictions that they should not be used. Furthermore, dosing is often difficult where paediatric formulations are unavailable.

The artemisinin derivatives are safe 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. Sulfadoxine-pyrimethamine should be avoided in the first weeks of life because it competitively displaces bilirubin with the potential to aggravate neonatal hyperbilirubinemia. Primaquine should also be avoided in the first month and tetracyclines avoided throughout infancy and in children < 8 years of age. With these exceptions there is no evidence for specific serious toxicity for any of the other currently recommended antimalarial treatments in infancy.

Delay in treating *P. falciparum* malaria in infants and young children may have fatal consequences, particularly for more severe infections. The uncertainties noted above should not delay treatment with the most effective drugs that are available, with attention to accurate dosing and ensuring the administered dose is retained, as 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 drug again if it is regurgitated within an hour of administration. Because deterioration in infants can be rapid, there should be a much lower threshold for the use of parenteral treatment.

7.9.3.2 Dosing

Although dosing based on body area is recommended for many drugs in young children, for the sake of simplicity, dosing of antimalarials has traditionally been based on administering a standard dose per kg body weight for all patients (including young children and infants); however, the disposition of many medicines are different from that of older children and adults. The currently recommended doses of lumefantrine, piperaquine, sufladoxine-pyrimethamine and chloroquine achieve substantially lower drug concentrations in young children than older patients. Small studies did not find any effect of age on plasma concentrations of amodiaquine or mefloquine. Although the absorption and disposition of many drugs differ between infants and young children, there are very limited data on antimalarial pharmacokinetics in the first year of life.

For the majority of antimalarials, the lack of an infant formulation necessitates the division of adult tablets; this leads to inaccurate dosing. There are now paediatric formulations and paediatric tablet strengths for some of the antimalarial medicines. These have the potential for improving the effectiveness and accuracy of ACT dosing in young children.

In situations where it is not possible to give parenteral treatment, such as severely sick infants that vomit antimalarial drug treatment repeatedly, or are too weak to swallow, artesunate should be given by the rectal route prior to transfer to a facility where parenteral treatment is possible. Evidence from recent studies demonstrates that in situations where parenteral medication is not possible, using a single dose of rectal artesunate as pre-referral treatment reduces the risk of death or permanent disability (as long as this initial treatment is followed up with appropriate parenteral antimalarial

treatment in the hospital). Further evidence concerning the rectal administration of artesunate and other antimalarial drugs is provided in Section 8.6.

A detailed review of the available data on safety of antimalarials in infants is provided in Annex 3, Section A3.15.1.

BOX 7.7

RECOMMENDATION: *treatment for infants and young children with uncomplicated falciparum malaria*

► **The acutely ill child requires careful clinical monitoring as she/he may deteriorate rapidly.**

- ACTs should be used as first-line treatment for infants and young children with uncomplicated malaria, and careful attention should be paid to accurate dosing and ensuring the administered dose is retained.
- Referral to a health centre or hospital is indicated for young children who cannot swallow antimalarial medicines reliably. If referral is expected to take more than six hours, pre-referral treatment with rectal artesunate is indicated.

7.9.4 Large adults

Large adults are a patient group likely to be at risk of under-dosing when dosed by age or standard pre-packaged adult weight-based treatments, which has received little attention. As the evidence-base of an association between intake dose, pharmacokinetics and treatment outcome in overweight or large adults is limited, and the safety of alternative higher dosing options has not been assessed in treatment trials, these current guidelines caution treatment providers to be vigilant and follow up the treatment outcome in large adults where possible. The gap in knowledge needs to be urgently addressed.

7.9.5 Travellers

Travellers who acquire malaria are often non-immune persons either who reside in cities with little or no transmission within endemic countries, or visitors from non-endemic countries who travel to areas of malaria transmission. Both are likely to be at a higher risk for severe malaria. When within the malaria endemic country, they should be treated according to national policy, provided this has a recent proven cure rate exceeding 90%. Travellers who return to a non-endemic country and then develop malaria present particular problems, and they have a relatively high case fatality rate. Doctors in non-malarious areas may be unfamiliar with malaria, so the diagnosis may be delayed. Effective antimalarials may not be registered or may be unavailable. On the other hand, prevention of transmission or the emergence of resistance is irrelevant outside malaria endemic areas. Thus, monotherapy may be given if it is effective. Furthermore, the 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).

BOX 7.8

RECOMMENDATIONS: *treatment for travellers returning to non-endemic countries with uncomplicated falciparum*

► **For travellers returning to non-endemic countries with uncomplicated malaria:^a**

- atovaquone plus proguanil (15/6 mg/kg [adult dose – 4 tablets] once a day for 3 days)
- artemether plus lumefantrine
- dihydroartemisinin plus piperazine
- quinine plus doxycycline^b or clindamycin

► **For severe malaria:**

- the antimalarial treatment in travellers is the same as shown in Section 8
- travellers with severe malaria should be managed in an intensive care unit

^a Halofantrine is not recommended as first-line treatment for uncomplicated malaria because of cardiotoxicity.

^b Doxycycline should not be used in children under 8 years of age.

BOX 7.9

Summary recommendations on the TREATMENT OF FALCIPARUM MALARIA IN SPECIAL GROUPS

► **Pregnancy**

First trimester:

- quinine plus clindamycin^a to be given for 7 days (artesunate plus clindamycin for 7 days is indicated if this treatment fails);
- an ACT is indicated only if this is the only treatment immediately available, or if treatment with 7-day quinine plus clindamycin fails or if there is uncertainty of compliance with a 7-day treatment.

Second and third trimesters:

- ACT^b known to be effective in the country/region or artesunate plus clindamycin to be given for 7 days or quinine plus clindamycin to be given for 7 days.

► **Lactating women**

- Lactating women should receive standard antimalarial treatment (including ACTs) except for dapson, primaquine and tetracyclines, which should be withheld during lactation.

► **Infants and young children**

- ACTs for first-line treatment in infants and young children with attention to accurate dosing and ensuring the administered dose is retained.
- Referral to a health centre or hospital is indicated for young children who cannot swallow antimalarial medicines reliably. If referral is expected to take more than 6 hours, pre-referral treatment with rectal artesunate is indicated.

► **Travellers returning to non-endemic countries**

Uncomplicated falciparum malaria:

- atovaquone plus proguanil,
- artemether plus lumefantrine,
- dihydroartemisinin plus piperaquine,
- quinine plus doxycycline^c or clindamycin; all drugs to be given for 7 days.

Severe malaria:

- the antimalarial treatment is the same as shown in Section 8.

-
- a. If clindamycin is unavailable or unaffordable, then the monotherapy should be given.
 - b. With the exception of DHA+PPQ for which there is insufficient information in second and third trimesters of pregnancy to use as first-line therapy.
 - c. Doxycycline should not be used in children under 8 years of age.

7.10 Co-existing morbidities

7.10.1 HIV infection

There is considerable geographic overlap between malaria and HIV, resulting in substantial numbers of individuals with co-infection. Worsening HIV-related immunosuppression may lead to more severe manifestations of malaria. In HIV-infected pregnant women, the adverse effects of placental malaria on birth weight are increased. In stable endemic areas, HIV-infected patients with partial immunity to malaria may suffer more frequent and higher density infections; while in areas of unstable transmission, HIV infection is associated with an increased risk of severe malaria and malaria-related deaths. There is limited information at present on how HIV infection modifies the therapeutic responses to ACTs or on interactions between antimalarial medicines and antiretrovirals. Early studies with less effective regimens suggested that increasing HIV-related immunosuppression was associated with decreased treatment response, increased parasite burdens and reduced host immunity. Both of these are now known to occur with HIV infection

and are associated with increased treatment failure rates. At the current time there is insufficient information to modify the general malaria treatment recommendations for patients with HIV/AIDS.

Patients infected with HIV may be receiving other medications, such as cotrimoxazole (trimethoprim plus sulfamethoxazole) as prophylaxis, for opportunistic infections and/or antiretroviral medicines. There is limited information on drug interactions between antiretroviral therapies with ACTs. In one study, treatment of uncomplicated malaria with artesunate plus amodiaquine was highly effective in both HIV-infected and HIV-uninfected children. Importantly, however, there was a significant 7–8-fold increased risk of neutropenia 14 days after initiation of treatment among HIV-infected children compared to uninfected children. About one fifth of the episodes in the HIV-infected group were severe or life threatening. Among the HIV-infected children, the risk of neutropenia was significantly higher among those on antiretroviral regimens containing zidovudine. Hepatotoxicity has been documented when efavirenz was given together with artesunate plus amodiaquine. Given this limited but worrying information, treatment of malaria in HIV-infected patients receiving zidovudine or efavirenz should, if possible, avoid amodiaquine-containing ACT regimens. Although HIV-infection and cotrimoxazole may also depress neutrophil counts, there is insufficient information on the interaction of amodiaquine containing ACT regimens with cotrimoxazole or HIV infection to make recommendations.

BOX 7.10

RECOMMENDATIONS: *treatment for HIV-infected patients with uncomplicated P. falciparum malaria*

- ▶ **Patients with HIV infection who develop malaria should receive prompt, effective antimalarial treatment regimens as recommended in the relevant sections of these guidelines.**
- ▶ **Treatment or intermittent preventive treatment with sulfadoxine-pyrimethamine should not be given to HIV-infected patients receiving cotrimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis.**
- ▶ **Treatment in HIV-infected patients on zidovudine or efavirenz should, if possible, avoid amodiaquine-containing ACT regimens.**

7.10.2 Severe malnutrition

Malaria and malnutrition frequently coexist. There are only a few studies of antimalarial drug 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 A3.15.2).

7.10.2.1 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 (IM) 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.

7.10.2.2 Antimalarial drugs and protein energy malnutrition

There are limited data 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 body weight) of any antimalarial should be changed in patients with malnutrition. There are no studies in malnourished patients taking amodiaquine, artemisinin derivatives, artemether plus lumefantrine, atovaquone plus proguanil, clindamycin, mefloquine or primaquine.

BOX 7.11

RECOMMENDATION: *treatment of uncomplicated falciparum malaria in malnourished patients*

- ▶ **Although there are many reasons why antimalarial pharmacokinetics may be different in malnourished patients as compared with those who are well nourished, there is insufficient evidence to change current mg/kg body weight dosing recommendations.**

8. TREATMENT OF SEVERE *P. FALCIPARUM* MALARIA

8.1 Definition

In a patient with *P. falciparum* asexual parasitaemia and no other obvious cause of symptoms, the presence of one or more of the following clinical or laboratory features classifies the patient as suffering from severe malaria (see also Annex 8).¹³

Clinical features:

- impaired consciousness or unrousable coma
- prostration, i.e. generalized weakness so that the patient is unable walk or sit up without assistance
- failure to feed
- multiple convulsions – more than two episodes in 24 h
- deep breathing, respiratory distress (acidotic breathing)
- circulatory collapse or shock, systolic blood pressure < 70 mm Hg in adults and < 50 mm Hg in children
- clinical jaundice plus evidence of other vital organ dysfunction
- haemoglobinuria
- abnormal spontaneous bleeding
- pulmonary oedema (radiological)

Laboratory findings:

- hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
- metabolic acidosis (plasma bicarbonate < 15 mmol/l)
- severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%)
- haemoglobinuria
- hyperparasitaemia (> 2%/100 000/µl in low intensity transmission areas or > 5% or 250 000/µl in areas of high stable malaria transmission intensity)
- hyperlactataemia (lactate > 5 mmol/l)
- renal impairment (serum creatinine > 265 µmol/l).

¹³ Full details of the definition and prognostic factors are provided in: World Health Organization. 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.

8.2 Treatment objectives

The main objective is to prevent the patient from dying. Secondary objectives are prevention of disabilities and prevention of recrudescence.

The mortality of untreated severe malaria (particularly cerebral malaria) is thought to approach 100%. With prompt, effective antimalarial treatment and supportive care the mortality falls to 15–20% overall; although within the broad definition there 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, so it is essential that therapeutic concentrations of a highly effective antimalarial are achieved as soon as possible. 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. An open airway should be secured in unconscious patients and breathing and circulation assessed. The patient should be weighed or body weight estimated, so that medicines, including antimalarials and fluids, can be given accordingly. 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, including a 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, full blood count, platelet count, clotting studies, blood culture and full biochemistry (wherever possible). 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).

8.3.1 Diagnosis

The differential diagnosis of fever in a severely ill patient is broad. Coma and fever may result from meningoenzephalitis or malaria. Cerebral malaria is not associated

with signs of meningeal irritation (neck stiffness, photophobia or 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 about the diagnosis, empirical antibiotic treatment should be started immediately along with antimalarial treatment.

8.4 Specific antimalarial treatment

It is essential that effective, parenteral (or rectal) antimalarial treatment in full doses is given promptly in severe malaria. Two classes of medicines are available for the parenteral treatment of severe malaria: the cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives (artesunate, artemether and artemotil). Parenteral chloroquine is no longer recommended for the treatment of severe malaria, because of widespread resistance. Intramuscular sulfadoxine-pyrimethamine is also not recommended.

8.4.1 Artemisinin derivatives

Various artemisinin derivatives have been used in the treatment of severe malaria, including artemether, artemisinin, artemotil and artesunate. Randomized trials comparing artesunate and quinine from South-East Asia show clear evidence of benefit with artesunate. In a multi-centre trial, which enrolled 1461 patients (including 202 children < 15 years old), mortality was reduced by 34.7% in the artesunate group when 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.

Until recently there was insufficient evidence to make a similar recommendation in children, from high transmission settings, so the guidelines for this important patient group did not recommend artesunate above treatment with either artemether or quinine. This has now changed with the publication of the AQUAMAT trial*, a multi-centre study conducted in African children hospitalized with severe malaria. This very large randomized controlled trial, which enrolled 5425 children < 15 years of age across Africa, showed a significant mortality reduction by 22.5% in the artesunate group when compared to the quinine group. The incidence of convulsions, coma, and hypoglycaemia developing after hospital was also significantly reduced. Importantly there was no significant difference in the incidence of severe neurological sequelae.

* Artesunate vs. quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label randomized trial. *Lancet* 2010; 376: 1647–57

BOX 8.1a

RECOMMENDATION: IV/IM artesunate treatment for severe *P. falciparum* malaria in adults

- ▶ **Intravenous artesunate should be used in preference to quinine for the treatment of severe *P. falciparum* malaria in adults.** *Strong recommendation, high quality evidence*

GRADE evaluation (see Annex 8, Table A8.1.1)

Intravenous artesunate has been shown to significantly reduce the risk of death from severe malaria compared to intravenous quinine (6 trials, 1938 participants; RR 0.62, 95% CI 0.51–0.75; high quality evidence).

Intravenous artesunate was associated with a lower risk of hypoglycaemia (2 trials, 185 participants; RR 0.46, 95% CI 0.25–0.87; low quality evidence).

No difference has been shown in the risk of serious neurological sequelae (2 trials, 1253 participants, very low quality evidence).

Other consideration

- Artesunate offers a number of programmatic advantages over quinine in terms of not requiring rate-controlled infusion or cardiac monitoring.

BOX 8.1b

RECOMMENDATION: IV/IM artesunate treatment for severe *P. falciparum* malaria in children

- ▶ **Intravenous artesunate should be used in preference to quinine for the treatment of severe *P. falciparum* malaria in children.** *Strong recommendation, high quality evidence*

Intravenous or intramuscular artesunate has been shown to reduce significantly the risk of death from severe malaria compared to intravenous quinine (4 trials, 5765 participants; RR 0.76, 95% CI 0.65–0.90; high quality evidence).

Intravenous artesunate was associated with a lower risk of hypoglycaemia (4 trials, 5765 participants; RR 0.62, 95% CI 0.45–0.87; high quality evidence).

No difference has been shown in the risk of serious neurological sequelae at day 28 (3 trials, 5163 participants, moderate quality evidence).

Other consideration

- Artesunate offers a number of programmatic advantages over quinine in terms of not requiring rate-controlled infusion or cardiac monitoring.

8.4.2 Quinine

Quinine treatment for severe malaria was established before modern clinical 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 (i.e. 20 mg salt/kg body weight – twice the maintenance dose) reduces the time needed to reach therapeutic plasma concentrations. The maintenance dose of quinine (10 mg salt/kg

body weight) is administered at 8-h intervals, starting 8 h after the first dose (see Annex 9, Section A9.3.2).

Rapid administration of quinine is unsafe. Each dose of parenteral quinine must be administered as a slow, rate-controlled infusion (usually diluted in 5% dextrose and infused over 4 h). The infusion rate should not exceed 5 mg salt/kg body weight per hour.

8.4.3 Quinidine

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 no other effective parenteral drugs are available. Electrocardiographic monitoring and frequent assessment of vital signs are required if quinidine is used.

8.5 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 antimalarial using a full course of an effective ACT (artesunate plus amodiaquine or artemether plus lumefantrine or dihydroartemisinin plus piperazine) or artesunate (plus clindamycin or doxycycline) or quinine (plus clindamycin or doxycycline). 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 7-day doxycycline course finishes after the quinine, artemether or artesunate course. Where available, clindamycin may be substituted in children and pregnant women; doxycycline cannot be given to these groups. 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.

The current recommendation from experts' opinion is to give parenteral antimalarials in the treatment of severe malaria for a minimum of 24 h, once started (irrespective of the patient's ability to tolerate oral medication earlier) or until the patient is about to tolerate oral medication, before giving the oral follow-up treatment.

8.6 Pre-referral treatment options

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 health facilities able to administer intravenous treatment is usually prolonged; this delays the commencement of appropriate antimalarial treatment. As during this time the patient may deteriorate or die,

it is recommended that patients be treated with the first dose of one of the recommended treatments before referral (unless the referral time is less than 6 h). Recommended pre-referral treatment options include intramuscular artesunate, artemether, or quinine, or rectal artesunate (*see* Annex 8, Section A8.5). Evidence from recent studies demonstrates that in situations where parenteral medication is not possible and intramuscular injection impractical, using a single dose of rectal artesunate as pre-referral treatment reduces the risk of death or permanent disability in young children.

BOX 8.2

RECOMMENDATION: *pre-referral treatment for severe P. falciparum malaria*

■ **If complete treatment for severe malaria (as recommended in Section 8.4) is not possible, patients with severe malaria should be given pre-referral treatment and referred immediately to an appropriate facility for further treatment.**

- The following are options for pre-referral treatment:
 - rectal artesunate
 - quinine IM
 - artesunate IM
 - artemether IM.
- In young children of less than 5 years of age, the use of rectal artesunate (10 mg/kg) has been shown to reduce the risk of death and permanent disability.

8.6.1 Pre-referral and continued treatment with rectal artemisinins

The administration of an artemisinin derivative by the rectal route as pre-referral treatment is feasible and acceptable 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 can be instituted. If, however, referral is impossible, rectal treatment should be continued until the patient can tolerate oral medication; at this point, a full course of the recommended ACT for uncomplicated malaria in the locality can be administered.

8.6.2 Dosing for antimalarials given by rectal route

8.6.2.1 *Initial (pre-referral) treatment with rectal artesunate*

The 10 mg/kg body weight single dose of artesunate 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.

8.6.2.2 Artemether

Doses used have been variable and empiric: 10–40 mg/kg body weight (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.

8.6.2.3 Quinine

The intrarectal dose used in treatment trials in Africa was either 12 mg/kg BW quinine base (as Quinimax[®], a cinchona alkaloid combination containing 96.1% quinine, 2.5% quinidine, 0.68% cinchonine, and 0.67% cinchonidine as gluconate salts) every 12 h without a loading dose, or 8 mg/kg BW every 8 h 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).

BOX 8.3

Summary of recommendations on the TREATMENT OF SEVERE FALCIPARUM MALARIA

- ▶ **Severe malaria is a medical emergency. After rapid clinical assessment and confirmation of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay with any effective antimalarial first available.**
- ▶ **For adults, artesunate 2.4 mg/kg BW IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended treatment. Artemether, or quinine, is an acceptable alternative if parenteral artesunate is not available: artemether 3.2 mg/kg BW IM given on admission then 1.6 mg/kg BW per day ; or quinine 20 mg salt/kg BW on admission (IV infusion or divided IM injection), then 10 mg/kg BW every 8 h; infusion rate should not exceed 5 mg salt/kg BW per hour.**
- ▶ **For children, artesunate 2.4 mg/kg BW IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended treatment. Artemether, or quinine, is an acceptable alternative if parenteral artesunate is not available: artemether 3.2 mg/kg BW IM given on admission then 1.6 mg/kg BW per day ; or quinine 20 mg salt/kg BW on admission (IV infusion or divided IM injection), then 10 mg/kg BW every 8 h; infusion rate should not exceed 5 mg salt/kg BW per hour.**
- ▶ **Give parenteral antimalarials in the treatment of severe malaria for a minimum of 24 h, once started (irrespective of the patient's ability to tolerate oral medication earlier), and, thereafter, complete treatment by giving a complete course of:**
 - artemether plus lumefantrine,
 - artesunate plus amodiaquine,
 - dihydroartemisinin plus piperaquine,
 - artesunate plus sulfadoxine-pyrimethamine,
 - artesunate plus clindamycin or doxycycline,
 - quinine plus clindamycin or doxycycline.

8.7 Practical aspects of treatment

8.7.1 Artemisinins

Although artesunate has preferable pharmacokinetic properties to artemether or artemotil, as it is water-soluble and can be given either by intravenous or intramuscular injection. Artemether and artemotil are formulated in oil and are given by intramuscular injection. They are both absorbed erratically, particularly in very severely ill patients. There are rectal formulations of artesunate, artemether, artemisinin 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 body weight), 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 body weight 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 then given by IM injection into the anterior thigh.

8.7.2 Quinine

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 bolus 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 body weight 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 body weight 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 (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.

8.7.3 Adjustment of dosing in renal failure or hepatic dysfunction

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 the patient remains in acute renal failure or has hepatic dysfunction, then the dose should be reduced by one third after 48 h. Dosage adjustments are not necessary if patients are receiving either haemodialysis or haemofiltration.

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 8.1, and further information is given in sections 8.9 and 8.10.

Table 8.1 Immediate clinical management of severe manifestations and complications of *P. falciparum* malaria

Manifestation/complication	Immediate management ^a
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, a cooling blanket and antipyretic drugs. Paracetamol is preferred over more nephrotoxic drugs (e.g. NSAIDs ^b).
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam or intramuscular paraldehyde. Check blood glucose.
Hypoglycaemia	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion.
Severe anaemia	Transfuse with screened fresh whole blood.
Acute pulmonary oedema^c	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.

Table 8.1 continued

Manifestation/complication	Immediate management ^a
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 broad-spectrum antimicrobials, correct haemodynamic disturbances.

^a It is assumed that appropriate antimalarial treatment will have been started in all cases

^b Non-steroidal anti-inflammatory drugs

^c Prevent by avoiding excess hydration

8.9 Continuing supportive care

Patients with severe malaria require intensive nursing care, preferably in an intensive care unit where possible. Clinical observations should be made as frequently as possible. These should include monitoring of vital signs, coma score, and urine output. Blood glucose should also be monitored every four hours, if possible, particularly in unconscious patients.

Fluid requirements should be assessed individually. Adults with severe malaria are very vulnerable to fluid overload. Children, on the other hand, are more likely to be dehydrated. The fluid regimen must also be tailored around infusion of the antimalarial drugs. Central venous pressure should be maintained at 0–5 cm. If available, haemofiltration should be started early for acute renal failure or severe metabolic acidosis, which are unresponsive to rehydration.

If blood glucose is <2.2 mmol/l, then hypoglycaemia should be treated immediately (0.3–0.5 g/kg body weight of glucose). Hypoglycaemia should be suspected in any patient who deteriorates suddenly.

Patients with severe malaria with clinically significant disseminated intravascular coagulation should be given fresh whole blood transfusions and vitamin K.

Patients with secondary pneumonia or with clear evidence of aspiration should be given empirical treatment with a third-generation cephalosporin, or the appropriate antibiotic of known sensitivity in that locality. In children with persistent fever despite parasite clearance other possible causes of fever should be excluded. This includes a systemic *Salmonella* infection and urinary tract infections, especially in catheterized patients. However, in the majority of cases of persistent fever, no other pathogen is identified after parasite clearance. Antibiotic treatments should be based on culture and sensitivity results, or, if not available, take into account likely local antibiotic sensitivity patterns.

8.10 Additional aspects of management

8.10.1 Treatments not recommended

Several other supportive strategies and interventions have been used in severe malaria patients in an effort to further reduce the mortality, but very few are supported by evidence of benefit and many have proved harmful.

Heparin, prostacyclin, desferoxamine, pentoxifylline, low molecular weight dextran, urea, high-dose corticosteroids, acetylsalicylic acid, deferoxamine, anti-tumour necrosis factor antibody, cyclosporin, dichloroacetate, adrenaline and hyperimmune serum are not recommended. In addition, the use of corticosteroids increases the risk of gastrointestinal bleeding and seizures, and has been associated with prolonged coma resolution times when compared with placebos (*see* Annex 8, Sections A8.6 and A8.7).

8.10.2 Fluid therapy

The degree of fluid depletion varies considerably in patients with severe malaria. 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, children commonly present with severe anaemia and hyperventilation (sometimes termed “respiratory distress”) resulting from severe metabolic acidosis and anaemia; they should be treated by blood transfusion. In general, children tolerate rapid fluid resuscitation better than adults; they are less likely to develop pulmonary oedema. In adults, there is a very thin dividing line between over-hydration, which may produce pulmonary oedema, and under-hydration contributing to shock, 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 the nursing facilities permit, a central venous catheter should be inserted and the central venous pressure measured directly (target 0–5 cm H₂O).

8.10.3 Blood transfusion

Severe malaria is associated with rapid development of anaemia as infected and uninfected erythrocytes are haemolysed and/or removed from the circulation by the spleen. Ideally fresh cross-matched blood should be transfused. 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 on the indications for transfusion, so the recommendations given here are based on expert opinion. In high-transmission settings, blood transfusion is generally recommended for children with a haemoglobin level of < 5 g/100ml (haematocrit < 15%). In low-transmission settings, a threshold of 20% (haemoglobin 7 g/100 ml) is recommended. However, 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 chronic or acute

anaemia where there has been adaptation and a compensatory right shift in the oxygen dissociation curve.

8.10.4 Exchange blood transfusion

There have been many anecdotal reports and several series claiming benefit for exchange blood transfusion (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; 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; and
- replacing the rigid unparasitized red cells by more deformable cells and, therefore, alleviating microcirculatory obstruction.

Exchange blood transfusion requires intensive nursing care and a relatively large volume of blood, and it 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.

8.10.5 Use of anticonvulsants

The treatment of convulsions in cerebral malaria with intravenous (or, if this is 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 prophylactic intramuscular injection of 20 mg/kg body weight 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 it was associated with additional benzodiazepine use. A 20 mg/kg dose of phenobarbital should not be given without respiratory support, but whether a lower dose would be effective and safer, or whether if ventilation is given, mortality would not be increased is not known. In the absence of further information, prophylactic anticonvulsants are not recommended.

8.10.6 Concomitant use of antibiotics

The threshold for administering antibiotic treatment should be low in severe malaria. Septicaemia and severe malaria are associated and there is a 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; so broad-spectrum antibiotic treatment should be given initially until a bacterial infection is excluded.

8.11 Treatment of severe malaria in special groups during pregnancy

8.11.1 Treatment during pregnancy

Women in the second and third trimesters of pregnancy are more likely to develop severe malaria than other adults, and, in low-transmission settings, this is 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.

Parenteral antimalarials should be given to pregnant women with severe malaria in full doses without delay. Parenteral artesunate is preferred over quinine in the second and third trimesters, because quinine is associated with recurrent hypoglycaemia. In the first trimester, the risk of hypoglycaemia is lower and the uncertainties over the safety of the artemisinin derivatives are greater. However, weighing these risks against the evidence that artesunate reduces the risk of death from severe malaria, both artesunate and quinine may be considered as options until more evidence becomes available. Treatment must not be delayed; so if only one of the drugs artesunate, artemether or quinine is available, then it should be started immediately.

Obstetric advice should be sought at an early stage, the paediatricians alerted, and blood glucose checked frequently. Hypoglycaemia should be expected, and it is often recurrent if the patient is receiving quinine. Severe malaria may also present immediately following delivery. Postpartum bacterial infection is a common complication in these cases.

9. TREATMENT OF MALARIA CAUSED BY *P. VIVAX*, *P. OVALE* OR *P. MALARIAE*

P. vivax, the second most important species causing human malaria, accounts for about 40% of malaria cases worldwide; it is the dominant malaria species outside Africa. It is prevalent in endemic areas in the Asia, Central and South America, Middle East and Oceania. 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 they are distributed worldwide, especially in the tropical areas of Africa. Further information on treatment is provided in Annex 9.

Among the four species of *Plasmodium* that affect humans, only *P. vivax* and *P. ovale* form hypnozoites, parasite stages in the liver, which can result in multiple relapses of infection weeks to months after the primary infection. Thus, a single infection causes repeated bouts of illness. The objective of treating malaria caused by *P. vivax* and *P. ovale* is to cure (radical cure) both the blood stage and the liver stage infections, and, thereby, prevent both recrudescence and relapse, respectively. 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 with 170 g), but this adverse effect does not decline with successive pregnancies, unlike with *P. falciparum* infections.

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.

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 generally still sensitive to chloroquine, although resistance is prevalent and increasing in some areas (notably Indonesia, Peru and Oceania). 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 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 plus primaquine can be considered as a combination treatment. The only drugs with significant activity against the hypnozoites are the 8-aminoquinolines (buloquine, 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 eastern Asia and Oceania is greater than elsewhere.

9.3 Treatment of uncomplicated vivax malaria

9.3.1 Blood stage infection

For chloroquine-sensitive vivax malaria (i.e. in most places where *P. vivax* is prevalent), oral chloroquine at a total dose of 25 mg base/kg body weight is effective and well tolerated. Lower total doses are not recommended, as these might encourage the emergence of resistance. Chloroquine is given in an initial dose of 10 mg base/kg body weight followed by either 5 mg/kg body weight at 6 h, 24 h and 48 h or, more commonly, by 10 mg/kg body weight on the second day and 5 mg/kg body weight on the third day. Recent studies have also demonstrated the efficacy of the recommended ACTs in the treatment of vivax malaria. The exception to this is artesunate plus sulfadoxine-pyrimethamine. Though there has been one study from Afghanistan reporting good efficacy to AS+SP, it appears that *P. vivax* has developed resistance to sulfadoxine-pyrimethamine more rapidly than *P. falciparum* has; hence, artesunate plus sulfadoxine-pyrimethamine may not be effective overall against *P. vivax* in many areas.

9.3.1.1 Chloroquine-resistant vivax malaria

There is evidence that amodiaquine, mefloquine and quinine are effective in the treatment of chloroquine-resistant *P. vivax* malaria. ACTs based on either amodiaquine, mefloquine or piperazine, rather than monotherapy, are the recommended treatment of choice. Two trials have compared DHA+PPQ to alternative ACTs (AL6 and AS+AQ) in Indonesia. There are no trials comparing DHA+PPQ and AS+MQ in *P. vivax* mono-infection.

BOX 9.1

RECOMMENDATION: ACTs for treatment of chloroquine resistant uncomplicated *P. vivax* malaria

- ▶ In areas with chloroquine resistant *P. vivax*, artemisinin-based combination therapies (particularly with those whose partner medicines have long-half lives) are recommended for the treatment of *P. vivax* malaria. *Weak recommendation, moderate quality evidence*

GRADE evaluation (see Annex 9, tables A9.6.1 and A9.6.2)

Two trials compared DHA+PPQ to alternative ACTs (AL6 and AS+AQ) in Indonesia where all groups were also given primaquine to clear the liver stage parasites. DHA+PPQ reduced the number of relapses by day 42 compared to AL (1 trial, 126 participants; RR 0.16, 95% CI 0.07–0.38; moderate quality evidence) and AS+AQ (1 trial, 84 participants; RR 0.16, 95% CI 0.05–0.49; moderate quality evidence). There are no trials comparing DHA+PPQ and AS+MQ in *P. vivax* mono-infection.

At day 42, the patients in the DHA+PPQ groups were also less likely to be anaemic, although this data includes participants with *P. falciparum* mono-infection at baseline, and recurrence of *P. falciparum* was also lower with DHA+PPQ. This effect is likely to be a prophylactic effect related to the longer half-life of DHA+PPQ.

Other considerations

The panel noted the programmatic advantage of these ACTs also being highly effective against *P. falciparum*. This effect is likely to be a prophylactic effect related to the longer half-life of DHA+PPQ.

9.3.2 Liver stage infection

To achieve a radical cure, relapses must be prevented by giving primaquine. The frequency and pattern of relapses varies geographically. 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. Moreover, the *P. vivax* populations emerging from hypnozoites commonly differ from the populations that caused the acute episode. Activation of heterologous hypnozoites populations is the most common cause of the first relapse in patients with vivax malaria. 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. In comparison with no primaquine treatment, the risk of relapse decreased by the additional milligram per kilogram body weight of primaquine given. Primaquine should be given for 14 days.

A Cochrane Review¹⁴ reports both direct and indirect comparison of a 14-day versus 5-day regimen of primaquine. The review reports indirect evidence of the superiority of the 14-day regimen. No difference has been shown between the 5-day regimen and chloroquine alone (3 trials, 2104 participants; odds ratio [OR] 1.04, 95% CI 0.64–1.69), while the

¹⁴ Galappaththy GNL, Omari AAA, Tharyan P. Primaquine for preventing relapses in people with *Plasmodium vivax* malaria. *Cochrane Database of Systematic Reviews*, 2007, Issue 1 (Article No. CD004389). doi: 10.1002/14651858.

14-day regimen is significantly better at reducing relapses (6 trials, 1072 participants; OR 0.24, 95% CI 0.12–0.45). The usual adult oral dose is 15 mg base (0.25 mg/kg body weight per day), but in South-East Asia, particularly Indonesia, and in Oceania, higher doses (0.5 mg base/kg body weight 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, and so they must be prevented. However, in situations where transmission is intense with a high rate of re-infection, simply preventing relapses is unlikely to lower the incidence of infection or disease. Therefore, in areas of sustained high transmission, the benefits of the widespread deployment of primaquine are not considered to outweigh the risks associated with this medication. In low-transmission areas, on the other hand, the benefits of primaquine in preventing relapses will exceed its risks and its routine use to prevent relapses is recommended in patients who are not G6PD-deficient.

BOX 9.2

RECOMMENDATION: *primaquine for the radical treatment of vivax malaria*

- ▶ **At least a 14-day course of primaquine is required for the radical treatment of *P. vivax***
Strong recommendation, very low quality evidence

GRADE evaluation (see Annex 9, table A9.7.1)

A 14-day course of primaquine significantly reduces the relapse rate of *P. vivax* compared to a 5-day course (2 trials, 186 participants; RR 0.1, 95% CI 0.03–0.35; low quality evidence).

Other considerations

In addition, in clinical trials, CQ plus 14 days of primaquine has been shown to be superior to CQ alone in reducing relapses (6 trials, 1071 participants; OR 0.24, 95% CI 0.12–0.45). No difference has been shown between CQ plus 5 days of primaquine and CQ alone (3 trials, 2104 participants).

Formulation. If available, administer scored tablets containing 7.5 mg or 15 mg of primaquine. When there are no scored tablets available, 5 mg tablets can be used.

Therapeutic dose. Dose range between 0.25 and 0.5mg/kg/day primaquine once a day for 14 days (see Annex 3, Section A3.8).

9.3.2.1 Primaquine and glucose-6-phosphate dehydrogenase deficiency

The inherited sex-linked deficiency, G6PD deficiency, is associated with some protection against *P. falciparum* malaria, but there is increased susceptibility to oxidant haemolysis. The prevalence of G6PD deficiency varies, but it can be as high as 30%; high frequencies

are found only in areas where malaria is or has been endemic. There are a large number of different genotypes, each with different levels of deficiency. Primaquine is an oxidant and causes variable haemolysis in G6PD-deficient individuals. Primaquine also causes methemoglobinemia. The severity of haemolytic anaemia is related to primaquine dosing and the variant of the G6PD enzyme. Fortunately, primaquine is eliminated rapidly and so haemolysis is self-limiting provided no further drug 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 body weight once a week for eight weeks. If significant haemolysis occurs on treatment, then primaquine should be stopped.

Primaquine is contraindicated in pregnant women and children less than four years of age. There is no reliable data on the excretion of primaquine in breast milk to warrant it being contraindicated in women who are breast feeding, however, it is recommended that primaquine use in this group of patients should be medically supervised.

BOX 9.3

Summary of recommendations on the TREATMENT OF UNCOMPLICATED VIVAX MALARIA

- ▶ Chloroquine 25 mg base/kg body weight divided over 3 days, combined with primaquine 0.25 mg base/kg body weight, 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 body weight.
- ▶ ACTs combined with primaquine for chloroquine-resistant vivax malaria.
- ▶ In mild-to-moderate G6PD deficiency, primaquine 0.75 mg base/kg body weight should be given once a week for 8 weeks. In severe G6PD deficiency, primaquine is contraindicated and should not be used.
- ▶ Where ACT (exception AS+SP) has been adopted as the first-line treatment for *P. falciparum* malaria, it may also be used for *P. vivax* malaria in combination with primaquine for radical cure. Artesunate plus sulfadoxine-pyrimethamine is not effective against *P. vivax* in many places.

9.4 Treatment of severe *P. vivax* malaria

Although *P. vivax* malaria is considered to be benign malaria, with a very low case-fatality ratio, it may still cause a severe and debilitating febrile illness. It can also occasionally result in severe disease, as in *P. falciparum* malaria. Severe *P. vivax* malaria manifestations

that have been reported are cerebral malaria, severe anaemia, severe thrombocytopenia and pancytopenia, jaundice, splenic 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 fully 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.

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*, although the interpretation is slightly different. Genotyping can distinguish a relapse or recrudescence 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. Relapse is unlikely if parasitaemia recurs within 16 days of administering treatment 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 of > 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*). Since ACTs are increasingly being used for the treatment of vivax infections in situations where it is resistance to chloroquine, the sensitivity of *P. vivax* to ACTs must also be routinely monitored.

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 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 they 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 a risk of severe malaria epidemics (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 people in exposed settings, breakdown in public health and preventive activities, difficulties in accessing effective treatment, concomitant infections and malnutrition all render populations vulnerable to epidemic malaria. Such circumstances are also ideal for the development of parasite resistance to antimalarials. For these reasons, particular efforts must be made to deliver, free-of-charge, effective antimalarial treatment to the populations at risk. The principles below are applicable to epidemics and to all complex emergencies occurring in areas with malaria risk, where appropriate case management should be key.

11.1 Diagnosis

11.1.1 Use of microscopy

In the acute phase of epidemic and complex emergency situations, facilities for laboratory diagnosis are usually either unavailable, destroyed, or so overwhelmed with the case-load that parasite-based diagnosis before treatment in all fever cases is impossible. In

such circumstances, treatment based solely on the clinical history (mass fever treatment, see Section 11.2.1) may be necessary for a proportion of patients. This course of action should only be followed when it has been established that the epidemic is due to malaria and not to some other infectious disease. It is important to monitor the clinical response to such symptom-based treatment, because other infections may also be present. In all circumstances, parasite-based diagnosis is needed to:

- diagnose malaria as the cause of an epidemic of febrile illness;
- monitor the epidemic curve and confirm the end of an epidemic;
- follow progress in infants, pregnant women, those with severe malaria, the severely malnourished, and suspected treatment failures.

The latter can only be done with microscopy. Microscopy capacity is also needed for field quality control of rapid diagnostic tests and it is, therefore, necessary to build this capacity as soon as possible.

11.1.2 Use of rapid diagnostic tests

Rapid diagnostic tests offer the advantage of being quick to perform with less need for skilled laboratory technicians in epidemic situations. However, heat stability may be a problem and false-negative results may be seen. Current experience with RDTs indicates that they are useful for confirming the cause and end-point of malaria epidemics.

11.2 Management of uncomplicated falciparum malaria

Most malaria patients in epidemics and emergencies are non-immune, partially immune, or otherwise vulnerable to severe disease. An active search should be made for febrile patients to ensure that as many patients as possible receive adequate treatment, rather than relying on patients to come to a fixed clinic. The principles of treatment are the same as elsewhere (see Section 7). The antimalarials to be used for treatment must be highly efficacious (>95% cure), safe and well tolerated so that adherence to treatment is high. Complete courses of treatment should always be given in all circumstances. Artemeter-lumefantrine is the default ACT in the Interagency Emergency Health Kit¹⁵ (IEKH 2006) malaria module. Alternatively, ACT as per the national policy can be used.

11.2.1 Mass fever treatment

Mass fever treatment is the treatment of suspected malaria cases on clinical grounds without laboratory confirmation for each patient. This may be a temporary operational necessity in epidemics and in complex emergency situations when medical staff are dealing with overwhelming malaria case-loads during a confirmed malaria epidemic.

¹⁵ http://www.who.int/making_pregnancy_safer/documents/wb1052006in/en/

Whenever this strategy is adopted, a full treatment course should always be given. Mass fever treatment must not be confused with mass drug administration (i.e. the administration (*see* Section 13).

11.3 Areas prone to mixed falciparum/vivax malaria epidemics

During mixed falciparum/vivax malaria epidemics, ACTs (except artesunate plus sulfadoxine-pyrimethamine) should be used for treatment as they are highly effective against all malaria species.

11.4 Areas prone to vivax malaria epidemics

In areas with pure *P. vivax* epidemics, and where drug resistance has not been reported, chloroquine is the most appropriate medicine once the cause of the epidemic has been established. Resistance of *P. vivax* to chloroquine has been reported from Oceania and South-East Asia, but it is probably limited in distribution. Though there is insufficient knowledge at present to allow specific recommendations to be made for treatment of *P. vivax* epidemics in areas of suspected resistance,

11.5 Anti-relapse therapy in vivax malaria epidemics

The 14-day anti-relapse therapy for vivax malaria is impractical in most epidemic situations because of the duration of treatment and poor compliance. Moreover, it is not an effective strategy as long as the risk of re-infection is high. If adequate records are kept, anti-relapse therapy can be given in the post-epidemic period to patients who have previously been treated with blood schizonticides. Primaquine 0.25–0.5 mg base/kg body weight in two divided daily doses should be given for 14 days, as there is no evidence that shorter courses are effective. Appropriate health education should be provided to encourage adherence in situations where primaquine is given without supervision.

11.6 Management of severe falciparum malaria

Management of severe *P. falciparum* malaria in epidemic situations will often take place in temporary clinics or in situations in which staff shortages and high workloads make intensive case monitoring difficult. Drug treatment should, therefore, be as simple and safe as possible, with simple dosing schedules and minimal need for monitoring the treatment. Intramuscular artemether with its simple one-a-day regimen and ease of administration is an attractive treatment option in overburdened epidemic situations, despite the concern about its erratic absorption. In comparison, the current artesunate

formulation for parenteral use requires a two-step dissolution-dilution process. Parenteral quinine requires either intravenous infusions or a three-times-a-day intramuscular regimen, plus the need to monitor blood glucose.

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 administered. It is essential that a full course of antimalarial treatment be completed.

BOX 11.1

Summary recommendations on TREATMENT OF UNCOMPLICATED MALARIA IN EPIDEMIC SITUATIONS

- ▶ **The principles of treatment are the same as in section 7.**
- ▶ **The following ACTs are recommended for antimalarial treatment in *P. falciparum* or mixed *P. falciparum/P. vivax* malaria epidemics:**
 - artemether plus lumefantrine
 - artesunate plus amodiaquine
 - artesunate plus mefloquine
 - dihydroartemisinin plus piperazine.
- ▶ **The 14-day anti-relapse therapy for vivax malaria patients (where applicable) should be postponed to the post-epidemic period.**
- ▶ **Treatment of severe malaria:**
 - artemether by the IM route is an acceptable and practical alternative for treatment of severe falciparum malaria during an epidemic. As soon as intensive case monitoring becomes possible, artesunate (IV or IM route) is the treatment of choice. Quinine can be used where artesunate is not available.”

12. CASE MANAGEMENT IN THE CONTEXT OF MALARIA ELIMINATION

12.1 Use of gametocytocidal drugs to reduce transmission

Two antimalarial medicines have an effect specifically on gametocytes: primaquine and artemisinins. This can be of particular benefit in epidemic control and in programmes aiming for malaria elimination.

Primaquine selectively kills gametocytes. Especially in South-East Asia and South America, before the use of ACTs for the treatment of *P. falciparum* malaria, a single oral dose of 0.75 mg base/kg body weight primaquine (45 mg base maximal for adults) was added to a fully effective blood schizontocide to eliminate gametocytes and thus reduce transmission. Studies on the impact of this strategy are very limited. Where it has been used, the single dose of primaquine 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.

ACTs reduce gametocyte carriage. One randomized comparison of ACTs and primaquine has reported a greater effect for ACT than primaquine on gametocyte carriage. A more recent study compared the added value of primaquine to AS+SP combination in the treatment of falciparum malaria in United Republic of Tanzania. It reported that primaquine clears gametocytes that persist after treatment with AS+SP, including those at a submicroscopic level: this demonstrates an added benefit of combining a single dose of primaquine with an ACT¹⁶. The addition of a single dose of primaquine to ACT treatment is, therefore, recommended in programmes aimed at reducing transmission, provided the risks of haemolysis in G6PD deficient patients are considered. Primaquine should not be given in pregnancy and in children less than 4 years old.

12.2 Mass screening and treatment

Mass screening for parasitaemia and treating all infected persons in a targeted area or population, irrespective of whether they are symptomatic aims to reduce the size of the infectious reservoir in the targeted area. Mass screening and treatment may be indicated in areas where the parasite reservoir (or parasite gene pool) needs to be quickly and selectively reduced. This type of intervention also plays a significant role in reducing the infectious reservoir of parasites in a given location and is very useful in the pre-elimination and elimination phases of malaria control.¹⁷ It requires considerable logistics, capacity and preparation.

¹⁶ Shekalaghe S et al. Primaquine clears submicroscopic *Plasmodium falciparum* gametocytes that persist after treatment with sulphadoxine-pyrimethamine and artesunate. PLoS ONE, 2007, 2: e1023. doi:10.1371.

13. MASS DRUG ADMINISTRATION

There is no evidence of long-term benefits to support mass drug administration (MDA) in large population groups. There is strong logic that MDA should be selected for drug-resistant genotypes of parasites. The larger the population of parasites that is targeted with MDA, the greater the chance that resistance will emerge against the medicines used.

During MDA campaigns, every individual in a defined population or geographical area is required to take antimalarial treatment on a given day, in a coordinated manner, including the people who are not sick and not infected with malaria parasites at the time. Depending on the contraindications of the medicines used, pregnant women, young infants and other population groups are excluded from the campaign. The concept of MDA is based on the notion that if all people living in a given area could be effectively treated and rid of malaria parasites on a synchronized day, and the procedure repeated at intervals once or twice thereafter, the parasite reservoir of malaria in the area could be effectively reduced and eventually eliminated.

An effectively conducted MDA programme will result in a very significant reduction in the parasite prevalence. However, once MDA is terminated, malaria endemicity in the area will eventually return to its original levels (unless the vectorial capacity is reduced in parallel and maintained at a very low level). The time it takes to return to the original levels of transmission will depend on the prevailing vectorial capacity.¹⁸

The rebound may be associated with higher morbidity and mortality if the MDA was maintained long enough for people to lose herd-immunity against malaria. The rebound may have lower consequences in terms of malaria morbidity and mortality if local improvements in housing and the socioeconomic situation have meanwhile resulted in reduced man-vector contact (i.e. people getting fewer mosquito bites), and/or if local access to reliable health services has improved to such a degree that people get diagnosed and treated much earlier in the course of a malaria infection (i.e. infections are treated before progression to severe disease and death, and before gametocytes are generated for transmission to take place). Mass drug administration is generally carried out over relatively short periods of time, while improvements in housing and the socioeconomic situation occur over much longer timeframes.

¹⁷ Mass screening and treatment is not the same as and must not be confused with Mass Drug Administration, which is the administration of a complete treatment course of antimalarial medicines to every individual in a geographically defined area on a specific day.

¹⁸ Vectorial capacity: number of new infections the population of a given vector would distribute per case per day at a given place and time, assuming conditions of non-immunity. Factors affecting vectorial capacity include: (i) the density of female anophelines relative to humans; (ii) their longevity, frequency of feeding and propensity to bite humans; and (iii) the length of the extrinsic (i.e. in the mosquito) cycle of the parasite.

Consistent with this concept, in an extensive analysis of 19 MDA projects carried out over the period 1932–1999,¹⁹ only one study was shown to result in durably reduced transmission. In that particular 1991 study on Aneityum Island, Vanuatu, MDA took place over a 9-week period prior to the rainy season in a population that was relatively small (718 people), well defined (the entire population of a remote island in the Pacific Ocean with minimal contact with the outside world), and well controlled (resulting in 88.3% compliance). Monthly SP treatment and weekly CQ prophylaxis and weekly single dose PQ were given as part of a package of interventions, including intensive health education, a vector control programme based on full coverage ITN and larvivorous fish, and a community microscopy-based surveillance system to prevent reintroduction and checking all fever cases and screening all arrivals on the island. In this small and well-defined study with a 9-year intense follow up, *P. falciparum* had disappeared by week five; *P. vivax* transmission continued for another five years until 1996.²⁰

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

²⁰ Kaneko A et al. Malaria eradication on islands. *Lancet*, 2000, 356:1560–1564.

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ANNEX 1

THE GUIDELINES DEVELOPMENT PROCESS

A1.1 Treatment recommendations

The first edition of the *WHO Guidelines for the Treatment of Malaria* was developed over an 18-month period and was published in 2006. The methodology for identifying the questions, search and review of evidence is similar to that used in this current update. The GRADE methodology was not applied at that time but, in formulating recommendations, evidence was graded in order of priority as follows:

- formal systematic reviews, such as Cochrane reviews, including more than one randomized control trial
- comparative trials without formal systematic review
- observational studies (e.g. surveillance and pharmacological data)
- expert opinions/consensus.

Since the release of the first edition of the guidelines, the WHO standard methods for guidelines development has evolved and, thus, this revised edition (second edition) was developed in accordance with the updated WHO standard methods for guideline formulation.¹ This was organized through a technical consultation on malaria treatment guidelines by the Technical Guidelines Development Group, co-chaired by Professors Fred Binka and Nick White (other participants are listed below). Conflict of interest statements were received from all participants. The first technical consultation was convened in April 2008, at which time the scope of the guidelines review and key questions to be addressed were determined.

Following the first meeting, contracts for systematic search and reviews of relevant evidence were awarded to research groups from the Liverpool School of Tropical Medicine in Liverpool, England. The search strategies employed included a search of the following databases:

- the Cochrane Infectious Diseases Group trials register (up to June 2004)
- the Cochrane Central Register of Controlled Trials (CENTRAL) published in The Cochrane Library (Issue 2, 2004)
- MEDLINE (1966 to June 2004)
- EMBASE (1980 to June 2004)
- LILACS (1982 to June 2004)

The following search terms were used:

- malaria (free text),
- malaria (controlled vocabulary, MESH or EMTREE).

The terms were used in combination with the search strategy for retrieving randomized and controlled clinical trials developed by The Cochrane Collaboration. Key words relative to currently available antimalarial drugs were used for each section of the review. Where indicated, specific authors and research groups were contacted for more information on published work and work in progress.

For the 2009 update (*second edition*) of these guidelines, only new recommendations have been subjected to the GRADE process. The sub-committee developing the GRADE profiles met in October 2008 to develop the GRADE tables based on the systematic reviews and to formulate recommendations. Conclusions were based on universal consensus, and areas of disagreements were extensively discussed and consensus reached. The need for vote casting did not arise (see below for details of the grading process and methodology).

A second technical consultation meeting of the Technical Guidelines Development Group was convened in November 2008, at which time recommendations formulated by the GRADE sub-committee were reviewed and adopted. A drafting committee was established with timelines for the drafting of the accepted guidelines.

The revised draft of the guidelines was sent out for external peer review. Inputs from the external reviewers were shared with the committee. There were no areas of major disagreement, so, in lieu of another meeting, the minor issues were resolved electronically.

The GRADE approach to guidelines development, which was formally adopted by WHO in 2007, is a uniform approach that is becoming adopted globally. It aims to make explicit the link between research evidence and formulation of recommendations, as well as the value judgements and preferences involved.

The GRADE approach involves a four-step process:

1. Identification of the clinical questions, and the critical and important outcomes to answer these questions;
2. Systematic reviews of the evidence (using Cochrane methodology) focusing on these outcomes;
3. Construction of GRADE tables to summarize the data and assess the quality (or robustness) of the evidence; and
4. Interpretation of the GRADE tables and formulation of recommendations.

IDENTIFICATION OF AREAS OF UNCERTAINTY

The first meeting of the Malaria Treatment Guidelines Panel identified areas where updates were being considered. On this basis, a sub-group of the panel, the GRADE sub-committee worked together in preparing appropriate, up-to-date systematic reviews and GRADE profiles. The sub-committee, thereafter, met to decide on the recommendations arising from the evidence and other explicitly stated considerations. The following areas were identified:

- consider adding dihydroartemisinin plus piperazine to the recommended list of ACTs for uncomplicated malaria;
- consider removing amodiaquine plus sulfadoxine-pyrimethamine from the list of recommended antimalarial drugs for uncomplicated malaria;
- reconsider the recommendation of artesunate plus mefloquine in Africa, with specific concerns regarding toxicity/vomiting in children;
- assess the role of ACTs in *P. vivax* malaria in areas without chloroquine resistant *P. vivax*;
- assess the role of ACTs in *P. vivax* malaria in areas with chloroquine resistant *P. vivax*;
- consider the best treatment for radical cure of *P. vivax* malaria; and
- consider the relative effectiveness of IV artesunate instead of quinine for severe malaria.

ASSESSING QUALITY OF EVIDENCE

The GRADE approach starts with a baseline quality for each outcome. Evidence considered by the panel for the purpose of this annex was derived solely from randomized-controlled trials, for which the baseline quality using the GRADE approach is defined as high.

Cochrane reviews were carried out using standard methods. All head-to-head comparisons of ACTs were reviewed. Outcomes for the review, which are reflected in the GRADE assessments, were agreed upon by the Malaria Technical Guidelines Group.

The panel assessed the four GRADE quality components described below across each outcome for each profile and made judgements as to whether each component had: no serious limitations (do not downgrade); serious limitations (downgrade by 1 level); or very serious limitations (downgrade by 2 levels). For each judgement, the justification for the panel's decision is referenced in a footnote below each profile under the appropriate quality component. Specific decision rules were developed over time that seemed appropriate to forming GRADE profiles within this health problem.

1. DESIGN LIMITATIONS: is the design of the trials flawed for a set outcome?

For hard outcomes, such as death, the panel considered the adequacy of the allocation concealment.

For softer outcomes, such as vomiting, the panel also considered blinding.

Sensitivity analyses, excluding poor quality trials, enabled the panel to make judgements about whether variations in methodological quality between trials constituted a limitation or not, and, if so, if this was serious or very serious.

2. INCONSISTENCY: is the effect size similar across trials for a set outcome?

The panel considered the 95% confidence intervals for each trial reporting an outcome and whether they overlapped or not.

The panel also considered the I^2 value and viewed the forest plot to make a judgement.

3. INDIRECTNESS: is there sufficient evidence for your population and drugs of interest for a set outcome?

The panel considered the trial populations, the population of interest and whether they would expect differences in the performance of either the intervention or the control in different settings.

If the panel only had partial information on the performance outcome in the population of interest, then drugs were downgraded by 1 (serious indirectness).

If the panel only had limited information on the performance outcome in the population of interest, then drugs were downgraded by 2 (very serious indirectness).

4. IMPRECISION: are there sufficient data and or clear relative effects for a set outcome?

The panel agreed that the borders of appreciable benefit and harm were a relative risk value of $0.75 < RR < 1.25$.

If the 95% CI for the pooled estimate included appreciable benefit (or appreciable harm) and no significant difference between the intervention and control group, then the panel downgraded by 1 (serious imprecision).

If the 95% CI for the pooled estimate included appreciable benefit and appreciable harm with the intervention, then the panel downgraded by 2 (very serious imprecision).

The GRADE quality rating for RCT evidence may, therefore, be “downgraded” by one, two or three levels from high to moderate to low or very low quality, and it is rated on the following four-point scale:

- **HIGH QUALITY:** further research is very unlikely to change our confidence in the estimate of effect;
- **MODERATE QUALITY:** further research is likely to have an important impact on our confidence in the estimate of effect, and it may change the estimate;
- **LOW QUALITY:** further research is very likely to have an important impact on our confidence in the estimate of effect, and it is likely to change the estimate;
- **VERY LOW QUALITY:** we are very uncertain about the estimate.

(Please note the GRADE approach also describes a method for upgrading the quality of evidence for non-randomized data that is outside the scope of this annex.)

FORMULATION OF RECOMMENDATIONS

In moving from evidence to formulating recommendations, the GRADE process shows the values and preferences that influenced the decision-making process. The GRADE panel identified the critical or important outcomes for answering the clinical questions. The strength of recommendations is rated on a two-point scale:

- *weak:* the panel considers that the benefits of the intervention probably outweigh the risks;
- *strong:* the panel is confident that the benefits of the intervention outweigh the risks.

The guidelines development process and publication was fully funded by WHO. It is planned that the evidence will be reviewed on an annual basis, and that these guidelines will be updated periodically. Similarly, a mechanism for periodically monitoring and evaluating the use of the treatment guidelines in countries will be established.

A1.2 Members of the Guidelines Development Group

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Declaration of interests

Participants of the Technical Consultation on the review of the *WHO Guidelines for the Treatment of Malaria* and the external expert reviewers of the guidelines reported relevant interests, in accordance with WHO procedures. These were discussed extensively by the committee. Although it was considered that none of these declared interests had any direct relevance to the deliberations and recommendations of the meeting, those panel members with declared interests were excluded from the GRADE and recommendations sub-committee and the guidelines drafting sub-committee. The declared interest, as per WHO regulations, was cleared through the Legal Department of WHO.

Dr N. Valecha reported serving as an investigator for clinical trials supported by the Medicine for Malaria Venture (MMV), the Drugs for Neglected Diseases initiative (DNDi) and Ranbaxy Laboratories Limited. There were no monetary benefits and no conflicts with the subject of this review.

Dr L. Sluscker reported having collaborated with the Kenya Medical Research Institute on a study of paediatric Coartem®. The CDC did not receive funds from the manufacturer (Novartis Pharma AG).

Professor A. Bjorkman reported having participated in a study on paediatric Coartem® sponsored by Novartis Pharma AG.

Dr K. Barnes reported being a grants co-recipient from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the Bill and Melinda Gates Foundation (BMGF) and the UK Department for International Development (DfID) to evaluate antimalarial medicines.

Dr G. Mokuolu reported being a co-investigator in a multi-centre study comparing intravenous artesunate and quinine for the treatment of severe malaria in African children. The study is funded by Oxford University, the United Kingdom.

Dr F. ter-Kuile reported grant income from two not-for-profit project drug developers (MMV and DNDi). He also received a previous grant from Novartis Pharma AG, and is currently serving on the Coartem® advisory board for Novartis.

Dr D. Terlouw reported receiving research funding from an organization that supports the development of drugs for tropical diseases, including malaria.

All other members of the committee reported no interests.

ANNEX 2

ADAPTATION OF WHO MALARIA TREATMENT GUIDELINES FOR USE IN COUNTRIES

A2.1 Background

The guidelines provide a global framework and recommendations on the management of malaria, with the primary target being policy-makers in the ministries of health, to enable countries to formulate specific and more detailed national treatment protocols that take into account local antimalarial drug resistance patterns and health service capacity in the country. The guidelines are generic in nature, and they should be adapted by regions and countries.

This annex provides orientation and guidance that the process countries should follow in adapting the content of the generic malaria treatment guidelines provided in the main document.

A2.2 Development process

Each ministry of health should take the lead in the process of developing national malaria treatment guidelines. The proposed four main steps are listed below.

- A national workshop on the malaria treatment guidelines as a first step at country level. This workshop will review any current national malaria treatment guidelines, identify specific issues that need to be addressed and provide major policy recommendations.
- Drafting/updating the national malaria treatment guidelines. Following the national workshop, the national malaria case management committee (or its equivalent) should spearhead the development of new national malaria treatment guidelines in accordance with the standard outline set out below.
- A consensus workshop on the national malaria treatment guidelines should then be arranged to present, discuss and adopt the draft national malaria treatment guidelines.
- Finalization and dissemination. The national malaria treatment guidelines are finalized, officially endorsed and disseminated.

A2.3 Content

It is recommended that national malaria treatment guidelines be presented in a similar way as *WHO Guidelines on the Treatment of Malaria*. The following outline is suggested:

1. General introduction

- Epidemiological situation and parasite distribution
- National drug resistance pattern

2. Diagnosis of malaria

- Clinical diagnosis
- Role of parasitological diagnosis

3. Treatment of *P. falciparum* malaria or the most prevalent species in the country

- Uncomplicated malaria
 - definition
 - treatment objectives
 - treatment recommendations
 - treatment in specific populations and situations
- Severe malaria
 - definition
 - treatment objectives
 - treatment recommendations
 - pre-referral treatment options
 - management in epidemic situations.

4. Treatment of malaria caused by other species

5. Disease management at the different levels of the health care delivery system

6. Annexes

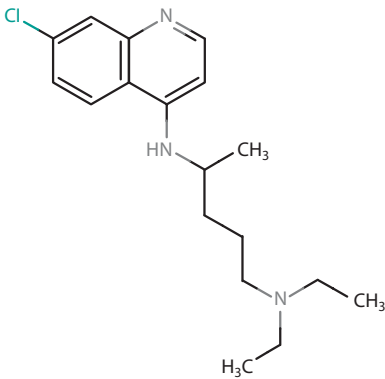
- Relevant annexes should be attached to provide more detailed information on, for example, dosages of drugs, specific data on therapeutic efficacy of antimalarial medicines in the country, other available evidence for treatment recommendation, etc.

ANNEX 3

PHARMACOLOGY OF ANTIMALARIAL MEDICINES

A3.1 Chloroquine

Molecular weight: 436.0



*Chloroquine is a 4-aminoquinoline which has been used extensively for the treatment and prevention of malaria. Widespread resistance has now rendered it virtually useless against *P. falciparum* infections in most parts of the world, although it still maintains considerable efficacy for the treatment of *P. vivax*, *P. ovale* and *P. malariae* infections. As with other 4-aminoquinolines, it does not produce radical cure.*

Chloroquine interferes with parasite haem detoxification (1, 2). Resistance is related to genetic changes in transporters (*PfCRT*, *PfMDR*), which reduce the concentrations of chloroquine at its site of action, the parasite food vacuole.

Formulations

- Tablets containing 100 mg or 150 mg of chloroquine base as phosphate or sulfate.

Pharmacokinetics

Chloroquine is rapidly and almost completely absorbed from the gastrointestinal tract when taken orally, although peak plasma concentrations can vary considerably. Absorption is also very rapid following intramuscular and subcutaneous administration (3–5). Chloroquine is extensively distributed into body tissues, including the placenta and breast milk, and has an enormous total apparent volume of distribution. The relatively small volume of distribution of the central compartment means that transiently cardiotoxic levels may occur following intravenous administration unless the rate of parenteral delivery is strictly controlled. Some 60% of chloroquine is bound to plasma proteins, and the drug is eliminated slowly from the body via the kidneys, with an estimated terminal elimination half-life of 1–2 months. Chloroquine is metabolized

in the liver, mainly to monodesethylchloroquine, which has similar activity against *P. falciparum*.

Toxicity

Chloroquine has a low safety margin and is very dangerous in overdose. Larger doses of chloroquine are used for the treatment of rheumatoid arthritis than for malaria, so adverse effects are seen more frequently in patients with the former. The drug is generally well tolerated. The principle limiting adverse effects in practice are the unpleasant taste, which may upset children, and pruritus, which may be severe in dark-skinned patients (6). Other less common side effects include headache, various skin eruptions and gastrointestinal disturbances, such as nausea, vomiting and diarrhoea. More rarely central nervous system toxicity including, convulsions and mental changes may occur. Chronic use (>5 years continuous use as prophylaxis) may lead to eye disorders, including keratopathy and retinopathy. Other uncommon effects include myopathy, reduced hearing, photosensitivity and loss of hair. Blood disorders, such as aplastic anaemia, are extremely uncommon (7).

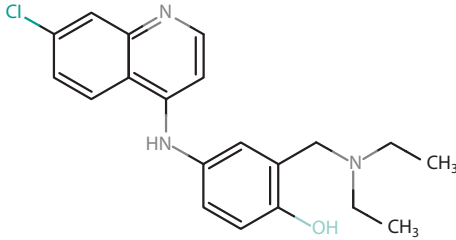
Acute overdose is extremely dangerous and death can occur within a few hours. The patient may progress from feeling dizzy and drowsy with headache and gastrointestinal upset, to developing sudden visual loss, convulsions, hypokalaemia, hypotension and cardiac arrhythmias. There is no specific treatment, although diazepam and epinephrine (adrenaline) administered together are beneficial (8,9).

Drug interactions

Major interactions are very usual. There is a theoretical increased risk of arrhythmias when chloroquine is given with halofantrine or other drugs that prolong the electrocardiograph QT interval; a possible increased risk of convulsions with mefloquine; reduced absorption with antacids; reduced metabolism and clearance with cimetidine; an increased risk of acute dystonic reactions with metronidazole; reduced bioavailability of ampicillin and praziquantel; reduced therapeutic effect of thyroxine; a possible antagonistic effect on the antiepileptic effects of carbamazepine and sodium valproate; and increased plasma concentrations of cyclosporine.

A3.2 Amodiaquine

Molecular weight: 355.9



*Amodiaquine is a Mannich base 4-aminoquinoline with a mode of action similar to that of chloroquine (interference with parasite haem detoxification). It is effective against some chloroquine-resistant strains of *P. falciparum*, although there is cross-resistance.*

Formulations

- Tablets containing 200 mg of amodiaquine base as hydrochloride or 153.1 mg of base as chlorohydrate.

Pharmacokinetics

Amodiaquine hydrochloride is readily absorbed from the gastrointestinal tract. It is rapidly converted in the liver to the active metabolite desethylamodiaquine, which contributes nearly all of the antimalarial effect (10). There are insufficient data on the terminal plasma elimination half-life of desethylamodiaquine. Both amodiaquine and desethylamodiaquine have been detected in the urine several months after administration.

Toxicity

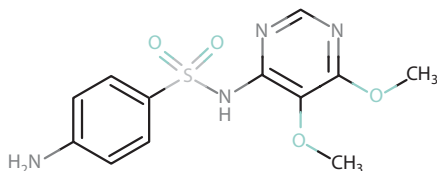
The adverse effects of amodiaquine are similar to those of chloroquine. Amodiaquine is associated with much less pruritus and is more palatable than chloroquine, but is associated with a much higher risk of agranulocytosis and, to a lesser degree, of hepatitis when used for prophylaxis (11). The risk of a serious adverse reaction with prophylactic use (which is no longer recommended) appears to be between 1 in 1000 and 1 in 5000. It is not clear whether the risks are lower when amodiaquine is used to treat malaria. Following overdose cardiotoxicity appears to be much less frequent than with chloroquine. Large doses of amodiaquine have been reported to cause syncope, spasticity, convulsions and involuntary movements.

Drug interactions

There are insufficient data.

A3.3 Sulfadoxine

Molecular weight: 310.3



Sulfadoxine is a slowly eliminated sulfonamide. It is very slightly soluble in water. Sulfonamides are structural analogues and competitive antagonists of p-aminobenzoic acid. They are competitive inhibitors of dihydropteroate synthase, the bacterial enzyme responsible for the incorporation of p-aminobenzoic acid in the synthesis of folic acid.

Formulations

Sulfadoxine is used in a fixed-dose combination of 20 parts sulfadoxine with 1 part pyrimethamine and may be administered orally or by the intramuscular route.

- Tablets containing 500 mg of sulfadoxine and 25 mg of pyrimethamine.
- Ampoules containing 500 mg of sulfadoxine and 25 mg of pyrimethamine in 2.5 ml of injectable solution for intramuscular use.

Pharmacokinetics

Sulfadoxine is readily absorbed from the gastrointestinal tract. Peak blood concentrations occur about 4 h after an oral dose. The terminal elimination half-life is 4–9 days. Around 90–95% is bound to plasma proteins. It is widely distributed to body tissues and fluids, passes into the fetal circulation and is detectable in breast milk. The drug is excreted very slowly in urine, primarily unchanged.

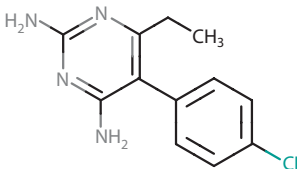
Toxicity

Sulfadoxine shares the adverse effect profile of other sulfonamides, although allergic reactions can be severe because of its slow elimination. Nausea, vomiting, anorexia and diarrhoea may occur. Crystalluria causing lumbar pain, haematuria and oliguria is rare compared with more rapidly eliminated sulphonamides. Hypersensitivity reactions may affect different organ system. Cutaneous manifestations can be severe and include pruritus, photosensitivity reactions, exfoliative dermatitis, erythema nodosum, toxic epidermal necrolysis and Stevens-Johnson syndrome (12). Treatment with sulfadoxine should be stopped in any patient developing a rash because of the risk of severe allergic reactions (13). Hypersensitivity to sulfadoxine may also cause interstitial nephritis, lumbar pain, haematuria and oliguria. This is due to crystal formation in the urine (crystalluria) and may be avoided by keeping the patient well hydrated to maintain a high urine output. Alkalinization of the urine will also make the crystals more soluble.

Blood disorders that have been reported include agranulocytosis, aplastic anaemia, thrombocytopenia, leukopenia and hypoprothrombinaemia. Acute haemolytic anaemia is a rare complication, which may be antibody mediated or associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Other adverse effects, which may be manifestations of a generalized hypersensitivity reaction include fever, interstitial nephritis, a syndrome resembling serum sickness, hepatitis, myocarditis, pulmonary eosinophilia, fibrosing alveolitis, peripheral neuropathy and systemic vasculitis, including polyarteritis nodosa. Anaphylaxis has been reported only rarely. Other adverse reactions that have been reported include hypoglycaemia, jaundice in neonates, aseptic meningitis, drowsiness, fatigue, headache, ataxia, dizziness, convulsions, neuropathies, psychosis and pseudomembranous colitis.

A3.4 Pyrimethamine

Molecular weight: 248.7



Pyrimethamine is a diaminopyrimidine used in combination with a sulfonamide, usually sulfadoxine or dapsone. It exerts its antimalarial activity by inhibiting plasmodial dihydrofolate reductase thus indirectly blocking the synthesis of nucleic acids in the malaria parasite. It is a slow-acting blood schizontocide and is also possibly active against pre-erythrocytic forms of the malaria parasite and inhibits sporozoite development in the mosquito vector. It is effective against all four human malarials, although resistance has emerged rapidly.

Pyrimethamine is also used in the treatment of toxoplasmosis, and isosporiasis and as prophylaxis against *Pneumocystis carinii* pneumonia. Pyrimethamine is no longer used alone as an antimalarial, only in synergistic combination with slowly eliminated sulfonamides for treatment (sulfadoxine, sulfalene) or with dapsone for prophylaxis.

Formulations

Pyrimethamine is currently used mainly in a fixed-dose combination with slowly eliminated sulfonamides, either of 20 parts sulfadoxine with 1 part pyrimethamine (Fansidar®) for which there are oral and parenteral formulations.

- Tablets containing 500 mg of sulfadoxine and 25 mg of pyrimethamine.
- Ampoules containing 500 mg of sulfadoxine and 25 mg of pyrimethamine in 2.5 ml of injectable solution for intramuscular use.

Pharmacokinetics

Pyrimethamine is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur 2–6 h after an oral dose. It is mainly concentrated in the kidneys, lungs, liver and spleen, and about 80–90% is bound to plasma proteins. It is metabolized in the liver and slowly excreted via the kidneys. The plasma half-life is around 4 days. Pyrimethamine crosses the blood-brain barrier and the placenta and is detectable in breast milk. Absorption of the intramuscular preparation is incomplete and insufficiently reliable for this formulation to be recommended (14).

Toxicity

Pyrimethamine is generally very well tolerated. Administration for prolonged periods may cause depression of haematopoiesis due to interference with folic acid metabolism. Skin rashes and hypersensitivity reactions also occur. Larger doses may cause gastrointestinal symptoms such as atrophic glossitis, abdominal pain and vomiting, haematological effects including megaloblastic anaemia, leukopenia, thrombocytopenia and pancytopenia, and central nervous system effects such as headache and dizziness.

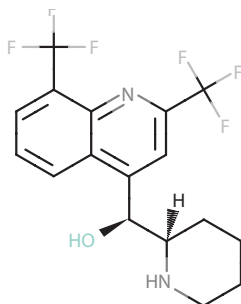
Acute overdosage of pyrimethamine can cause gastrointestinal effects and stimulation of the central nervous system with vomiting, excitability and convulsions. Tachycardia, respiratory depression, circulatory collapse and death may follow. Treatment of overdosage is supportive.

Drug interactions

Administration of pyrimethamine with other folate antagonists such as cotrimoxazole, trimethoprim, methotrexate or phenytoin may exacerbate bone marrow depression. Given with some benzodiazepines, there is a risk of hepatotoxicity.

A3.5 Mefloquine

Molecular weight: 378.3



Mefloquine is a 4-methanolquinoline and is related to quinine. It is soluble in alcohol but only very slightly soluble in water. It should be protected from light. The drug is effective against all forms of malaria.

Formulations

Mefloquine is administered by mouth as the hydrochloride salt (250 mg base equivalent to 274 mg hydrochloride salt).

- Tablets containing either 250 mg salt (United States of America) or 250 mg base (elsewhere).

Pharmacokinetics

Mefloquine is reasonably well absorbed from the gastrointestinal tract but there is marked interindividual variation in the time required to achieve peak plasma concentrations. Splitting the 25 mg/kg dose into two parts given at an interval of 6–24 h augments absorption and improves tolerability (15). Mefloquine undergoes enterohepatic recycling. It is approximately 98% bound to plasma proteins and is widely distributed throughout the body. The pharmacokinetics of mefloquine may be altered by malaria infection with reduced absorption and accelerated clearance (16,17). When administered with artesunate, blood concentrations are increased, probably as an indirect effect of increased absorption resulting from more rapid resolution of symptoms (15). Mefloquine is excreted in small amounts in breast milk. It has a long elimination half-life of around 21 days, which is shortened in malaria to about 14 days, possibly because of interrupted enterohepatic cycling (18–20). Mefloquine is metabolized in the liver and excreted mainly in the bile and faeces. Its pharmacokinetics show enantioselectivity after administration of the racemic mixture, with higher peak plasma concentrations and area under the curve values, and lower volume of distribution and total clearance of the enantiomer than its antipode (21–23).

Toxicity

Minor adverse effects are common following mefloquine treatment, most frequently nausea, vomiting, abdominal pain, anorexia, diarrhoea, headache, dizziness, loss of balance, dysphoria, somnolence and sleep disorders, notably insomnia and abnormal dreams. Neuropsychiatric disturbances (seizures, encephalopathy, psychosis) occur

in approximately 1 in 10 000 travellers receiving mefloquine prophylaxis, 1 in 1000 patients treated in Asia, 1 in 200 patients treated in Africa, and 1 in 20 patients following severe malaria (24–27). Other side effects reported rarely include skin rashes, pruritus and urticaria, hair loss, muscle weakness, liver function disturbances and very rarely thrombocytopenia and leukopenia. Cardiovascular effects have included postural hypotension, bradycardia and, rarely, hypertension, tachycardia or palpitations and minor changes in the electrocardiogram. Fatalities have not been reported following overdosage, although cardiac, hepatic and neurological symptoms may be seen. Mefloquine should not be given with halofantrine because it exacerbates QT prolongation. There is no evidence of an adverse interaction with quinine (28).

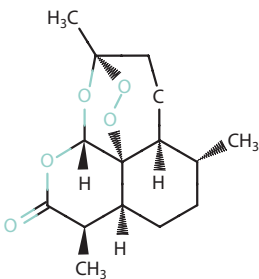
Drug interactions

There is a possible increase in the risk of arrhythmias if mefloquine is given together with beta blockers, calcium channel blockers, amiodarone, pimozide, digoxin or antidepressants; there is also a possible increase in the risk of convulsions with chloroquine and quinine. Mefloquine concentrations are increased when given with ampicillin, tetracycline and metoclopramide. Caution should be observed with alcohol.

A3.6 Artemisinin and its derivatives

A3.6.1 Artemisinin

Molecular weight: 282.3



Artemisinin, also known as qinghaosu, is a sesquiterpene lactone extracted from the leaves of Artemisia annua (sweet wormwood). It has been used in China for the treatment of fever for over a thousand years. It is a potent and rapidly acting blood schizonticide and is active against all Plasmodium species. It has an unusually broad activity against asexual parasites, killing all stages from young rings to schizonts. In P. falciparum malaria, artemisinin also kills the gametocytes – including the stage 4 gametocytes, which are otherwise sensitive only to primaquine. Artemisinin and its derivatives inhibit an essential calcium adenosine triphosphatase, PfATPase 6 (29).

Artemisinin has now largely given way to the more potent dihydroartemisinin and its derivatives, artemether, artemotil and artesunate. The three latter derivatives are converted back in vivo to dihydroartemisinin. These drugs should be given as combination therapy to protect them from resistance.

Formulations

A wide variety of formulations for oral, parenteral and rectal use are available. These include:

- Tablets and capsules containing 250 mg of artemisinin.
- Suppositories containing 100 mg, 200 mg, 300 mg, 400 mg or 500 mg of artemisinin.

Pharmacokinetics

Peak plasma concentrations occur around 3 h and 11 h following oral and rectal administration respectively (30). Artemisinin is converted to inactive metabolites via the cytochrome P450 enzyme CYP2B6 and other enzymes. Artemisinin is a potent inducer of its own metabolism. The elimination half-life is approximately 1 h (31).

Toxicity

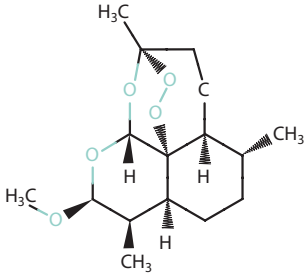
Artemisinin and its derivatives are safe and remarkably well tolerated (32, 33). There have been reports of mild gastrointestinal disturbances, dizziness, tinnitus, reticulocytopenia, neutropenia, elevated liver enzyme values, and electrocardiographic abnormalities, including bradycardia and prolongation of the QT interval, although most studies have not found any electrocardiographic abnormalities. The only potentially serious adverse effect been reported with this class of drugs is type 1 hypersensitivity reactions in approximately 1 in 3000 patients (34). Neurotoxicity has been reported in animal studies, particularly with very high doses of intramuscular artemotil and artemether, but has not been substantiated in humans (35–37). Similarly, evidence of death of embryos and morphological abnormalities in early pregnancy have been demonstrated in animal studies (37a). Artemisinin has not been evaluated in the first trimester of pregnancy so should be avoided in first trimester patients with uncomplicated malaria until more information is available.

Drug interactions

None known.

A3.6.2 Artemether

Molecular weight: 298.4



Artemether is the methyl ether of dihydroartemisinin. It is more lipid soluble than artemisinin or artesunate. It can be given as an oil-based intramuscular injection or orally. It is also coformulated with lumefantrine (previously referred to as benflumetol) for combination therapy.

Formulations

- Capsules containing 40 mg of artemether.
- Tablets containing 50 mg of artemether.
- Ampoules of injectable solution for intramuscular injection containing 80 mg of artemether in 1 ml for adults or 40 mg of artemether in 1 ml for paediatric use.

In a coformulation with lumefantrine:

- Tablets containing 20 mg of artemether and 120 mg of lumefantrine.

Pharmacokinetics

Peak plasma concentrations occur around 2–3 h after oral administration (38). Following intramuscular injection, absorption is very variable, especially in children with poor peripheral perfusion: peak plasma concentrations generally occur after around 6 h but absorption is slow and erratic and times to peak can be 18 h or longer in some cases (39–41). Artemether is metabolized to dihydroartemisinin, the active metabolite. After intramuscular administration, artemether predominates, whereas after oral administration dihydroartemisinin predominates. Biotransformation is mediated via the cytochrome P450 enzyme CYP3A4. Autoinduction of metabolism is less than with artemisinin. Artemether is 95% bound to plasma proteins. The elimination half-life is approximately 1 h, but following intramuscular administration the elimination phase is prolonged because of continued absorption. No dose modifications are necessary in renal or hepatic impairment.

Toxicity

In all species of animals tested, intramuscular artemether and artemotil cause an unusual selective pattern of neuronal damage to certain brain stem nuclei. Neurotoxicity in experimental animals is related to the sustained blood concentrations that follow intramuscular administration (42), since it is much less frequent when the same doses

are given orally, or with similar doses of water-soluble drugs such as artesunate. Clinical, neurophysiological and pathological studies in humans have not shown similar findings with therapeutic use of these compounds (40). Toxicity is otherwise similar to that of artemisinin.

Drug interactions H_2N N CH_3

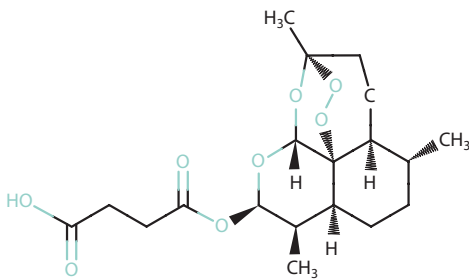
None known. N

NH_2

Cl

A3.6.3 Artesunate

Molecular weight: 384.4



Artesunate is the sodium salt of the hemisuccinate ester of artemisinin. It is soluble in water but has poor stability in aqueous solutions at neutral or acid pH. In the injectable form, artesunic acid is drawn up in sodium bicarbonate to form sodium artesunate immediately before injection.

Artesunate can be given orally, rectally or by the intramuscular or intravenous routes.

Formulations

- Tablets containing 50 mg or 200 mg of sodium artesunate.
- Ampoules for intramuscular or intravenous injection containing 60 mg of anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution.
- Rectal capsules containing 100 mg or 400 mg of sodium artesunate.

Pharmacokinetics

Artesunate is rapidly absorbed, with peak plasma levels occurring 1.5 h, 2 h and 0.5 h after oral, rectal and intramuscular administration, respectively (43–47). It is almost entirely converted to dihydroartemisinin, the active metabolite (30). Elimination of artesunate is very rapid, and antimalarial activity is determined by dihydroartemisinin elimination (half-life approximately 45 min) (40). The extent of protein binding is unknown. No dose modifications are necessary in renal or hepatic impairment.

Toxicity

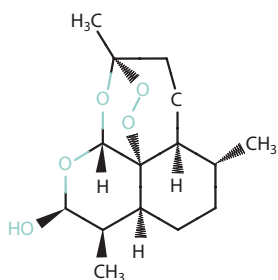
As for artemisinin.

Drug interactions

None known.

A3.6.4 Dihydroartemisinin

Molecular weight: 284.4



Dihydroartemisinin is the main active metabolite of the artemisinin derivatives, but can also be given orally and rectally as a drug in its own right. It is relatively insoluble in water, and requires formulation with suitable excipients to ensure adequate absorption. It achieves cure rates similar to those of oral artesunate. A fixed dose formulation with piperaquine is currently undergoing evaluation as a promising new artemisinin-based combination treatment (ACT).

Formulations

- Tablets containing 20 mg, 60 mg or 80 mg of dihydroartemisinin.
- Suppositories containing 80 mg of dihydroartemisinin.

Pharmacokinetics

Dihydroartemisinin is rapidly absorbed following oral administration, reaching peak levels after around 2.5 h. Absorption via the rectal route is somewhat slower, with peak levels occurring around 4 h after administration. Plasma protein binding is around 55%. Elimination half-life is approximately 45 minutes via intestinal and hepatic glucuronidation (48).

Toxicity

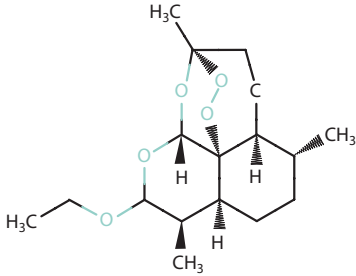
As for artemisinin.

Drug interactions

None known.

A3.6.5 Artemotil

Molecular weight: 312.4



Artemotil is the ethyl ether of artemisinin, and is closely related to the more widely used artemether. It is oil-based so water insoluble. It is given by intramuscular injection only.

Formulations

- Ampoules containing 150 mg of artemotil in 2 ml of injectable solution.

Pharmacokinetics

There is less published information on artemotil than for artemether. Absorption is slower and more erratic, with some patients having undetectable plasma artemotil until more than 24 h after administration.

Toxicity

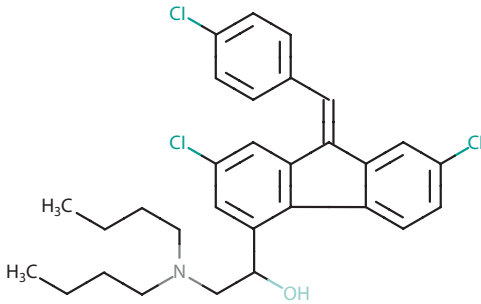
As for artemisinin.

Drug interactions

None known.

A3.7 Lumefantrine (benflumetol)

Molecular weight: 528.9



Lumefantrine belongs to the aryl aminoalcohol group of antimalarials, which also includes quinine, mefloquine and halofantrine. It has a similar mechanism of action. Lumefantrine is a racemic fluorine derivative developed in China. It is only available in an oral preparation coformulated with artemether. This ACT is highly effective against multidrug resistant *P. falciparum*.

Formulations

Available only in an oral preparation coformulated with artemether.

- Tablets containing 20 mg of artemether and 120 mg of lumefantrine.

Pharmacokinetics

Oral bioavailability is variable and is highly dependant on administration with fatty foods (38,49). Absorption increases by 108% after a meal and is lower in patients with acute malaria than in convalescing patients. Peak plasma levels occur approximately 10h after administration. The terminal elimination half-life is around 3 days.

Toxicity

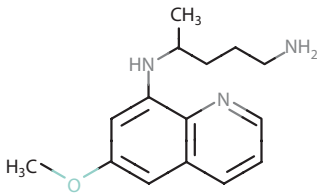
Despite similarities with the structure and pharmacokinetic properties of halofantrine, lumefantrine does not significantly prolong the electrocardiographic QT interval, and has no other significant toxicity (50). In fact the drug seems to be remarkably well tolerated. Reported side effects are generally mild – nausea, abdominal discomfort, headache and dizziness – and cannot be distinguished from symptoms of acute malaria.

Drug interactions

The manufacturer of artemether-lumefantrine recommends avoiding the following: grapefruit juice; antiarrhythmics, such as amiodarone, disopyramide, flecainide, procainamide and quinidine; antibacterials, such as macrolides and quinolones; all antidepressants; antifungals such as imidazoles and triazoles; terfenadine; other antimalarials; all antipsychotic drugs; and beta blockers, such as metoprolol and sotalol. However, there is no evidence that coadministration with these drugs would be harmful.

A3.8 Primaquine

Molecular weight: 259.4



*Primaquine is an 8-aminoquinoline and is effective against intrahepatic forms of all types of malaria parasite. It is used to provide radical cure of *P. vivax* and *P. ovale* malaria, in combination with a blood schizontocide for the erythrocytic parasites. Primaquine is also gametocytocidal against *P. falciparum* and has significant blood stages activity against *P. vivax* (and some against asexual stages of *P. falciparum*). The mechanism of action is unknown.*

Formulations

- Tablets containing 5.0 mg, 7.5 mg or 15.0 mg of primaquine base as diphosphate.

Pharmacokinetics

Primaquine is readily absorbed from the gastrointestinal tract. Peak plasma concentrations occur around 1–2 h after administration and then decline, with a reported elimination half-life of 3–6 h (51). Primaquine is widely distributed into body tissues. It is rapidly metabolized in the liver. The major metabolite is carboxyprimaquine, which may accumulate in the plasma with repeated administration.

Toxicity

The most important adverse effects are haemolytic anaemia in patients with G6PD deficiency, other defects of the erythrocytic pentose phosphate pathway of glucose metabolism, or some other types of haemoglobinopathy (52). In patients with the African variant of G6PD deficiency, the standard course of primaquine generally produces a benign self-limiting anaemia. In the Mediterranean and Asian variants, haemolysis may be much more severe. Therapeutic doses may also cause abdominal pain if administered on an empty stomach. Larger doses can cause nausea and vomiting. Methaemoglobinaemia may occur. Other uncommon effects include mild anaemia and leukocytosis.

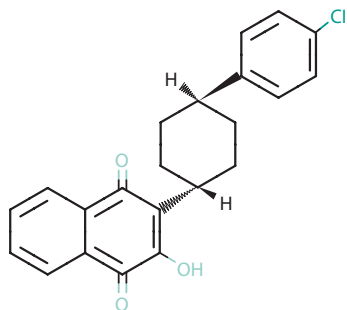
Overdosage may result in leukopenia, agranulocytosis, gastrointestinal symptoms, haemolytic anaemia and methaemoglobinaemia with cyanosis.

Drug interactions

Drugs liable to increase the risk of haemolysis or bone marrow suppression should be avoided.

A3.9 Atovaquone

Molecular weight: 366.8



Atovaquone is a hydroxynaphthoquinone antiparasitic drug active against all Plasmodium species. It also inhibits pre-erythrocytic development in the liver, and oocyst development in the mosquito. It is combined with proguanil for the treatment of malaria – with which it is synergistic. Atovaquone interferes with cytochrome electron transport.

Formulations

Atovaquone is available for the treatment of malaria in a coformulation with proguanil.

- Film-coated tablets containing 250 mg of atovaquone and 100 mg of proguanil hydrochloride for adults.
- Tablets containing 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride for paediatric use.

Pharmacokinetics

Atovaquone is poorly absorbed from the gastrointestinal tract but bioavailability following oral administration can be improved by taking the drug with fatty foods. Bioavailability is reduced in patients with AIDS. Atovaquone is 99% bound to plasma proteins and has a plasma half-life of around 66–70 h due to enterohepatic recycling. It is excreted almost exclusively in the faeces as unchanged drug. Plasma concentrations are significantly reduced in late pregnancy (53).

Toxicity

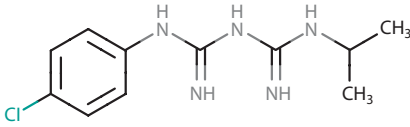
Atovaquone is generally very well tolerated (54). Skin rashes, headache, fever, insomnia, nausea, diarrhoea, vomiting, raised liver enzymes, hyponatraemia and, very rarely, haematological disturbances, such as anaemia and neutropenia, have all been reported.

Drug interactions

Reduced plasma concentrations may occur with concomitant administration of metoclopramide, tetracycline and possibly also acyclovir, antidiarrhoeal drugs, benzodiazepines, cephalosporins, laxatives, opioids and paracetamol. Atovaquone decreases the metabolism of zidovudine and cotrimoxazole. Theoretically, it may displace other highly protein-bound drugs from plasma-protein binding sites.

A3.10 Proguanil

Molecular weight: 253.7



Proguanil is a biguanide compound that is metabolized in the body via the polymorphic cytochrome P450 enzyme CYP2C19 to the active metabolite, cycloguanil. Approximately 3% of Caucasian and African populations and 20% of Oriental people are “poor metabolizers” and have considerably reduced biotransformation of proguanil to cycloguanil (55,56).

Cycloguanil inhibits plasmodial dihydrofolate reductase. The parent compound has weak intrinsic antimalarial activity through an unknown mechanism. It is possibly active against pre-erythrocytic forms of the parasite and is a slow blood schizontocide. Proguanil also has sporontocidal activity, rendering the gametocytes non-infective to the mosquito vector. Proguanil is given as the hydrochloride salt in combination with atovaquone. It is not used alone for treatment as resistance to proguanil develops very quickly. Cycloguanil was formerly administered as an oily suspension of the embonate by intramuscular injection.

Formulations

- Tablets of 100 mg of proguanil hydrochloride containing 87 mg of proguanil base.

In coformulation with atovaquone:

- Film-coated tablets containing 250 mg of atovaquone and 100 mg of proguanil hydrochloride for adults.
- Tablet containing 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride for paediatric use.

Pharmacokinetics

Proguanil is readily absorbed from the gastrointestinal tract following oral administration. Peak plasma levels occur at about 4 h, and are reduced in the third trimester of pregnancy. Around 75% is bound to plasma proteins. Proguanil is metabolized in the liver to the active antifolate metabolite, cycloguanil, and peak plasma levels of cycloguanil occur an hour after those of the parent drug. The elimination half-lives of both proguanil and cycloguanil is approximately 20 h (57, 58). Elimination is about 50% in the urine, of which 60% is unchanged drug and 30% cycloguanil, and a further amount is excreted in the faeces. Small amounts are present in breast milk. The elimination of cycloguanil is determined by that of the parent compound. The biotransformation of proguanil

to cycloguanil via CYP2C19 is reduced in pregnancy and women taking the oral contraceptive pill (59,60,61).

Toxicity

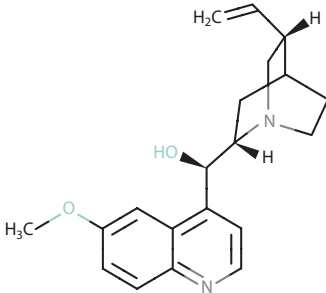
Apart from mild gastric intolerance, diarrhoea and occasional aphthous ulceration and hair loss there are few adverse effects associated with usual doses of proguanil hydrochloride. Haematological changes (megaloblastic anaemia and pancytopenia) have been reported in patients with severe renal impairment. Overdosage may produce epigastric discomfort, vomiting and haematuria. Proguanil should be used cautiously in patients with renal impairment and the dose reduced according to the degree of impairment.

Drug interactions

Interactions may occur with concomitant administration of warfarin. Absorption of proguanil is reduced with concomitant administration of magnesium trisilicate.

A3.11 Quinine

Molecular weight: 324.4



Quinine is an alkaloid derived from the bark of the *Cinchona* tree. Four antimalarial alkaloids can be derived from the bark: quinine (the main alkaloid), quinidine, cinchonine and cinchonidine. Quinine is the L-stereoisomer of quinidine. Quinine acts principally on the mature trophozoite stage of parasite development and does not prevent sequestration or further development of circulating ring stages of *P. falciparum*.

Quinine acts principally on the mature trophozoite stage of parasite development and does not prevent sequestration or further development of circulating ring stages of *P. falciparum*. Like other structurally similar antimalarials, quinine also kills the sexual stages of *P. vivax*, *P. malariae* and *P. ovale*, but not mature gametocytes of *P. falciparum*. It does not kill the pre-erythrocytic stages of malaria parasites. The mechanisms of its antimalarial actions are thought to involve inhibition of parasite haem detoxification in the food vacuole, but are not well understood.

Formulations

- Tablets of quinine hydrochloride, quinine dihydrochloride, quinine sulfate and quinine bisulfate containing 82%, 82%, 82.6% and 59.2% quinine base respectively.
- Injectable solutions of quinine hydrochloride, quinine dihydrochloride and quinine sulfate containing 82%, 82% and 82.6% quinine base respectively.

Pharmacokinetics

The pharmacokinetic properties of quinine are altered significantly by malaria infection, with reductions in apparent volume of distribution and clearance in proportion to disease severity (16,62). In children under 2 years of age with severe malaria, concentrations are slightly higher than in older children and adults (63). There is no evidence for dose-dependent kinetics. Quinine is rapidly and almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur 1–3 h after oral administration of the sulfate or bisulfate (64). It is well absorbed after intramuscular injection in severe malaria (65, 66). Plasma-protein binding, mainly to alpha 1-acid glycoprotein, is 70% in healthy subjects but rises to around 90% in patients with malaria (67–69).

Quinine is widely distributed throughout the body including the cerebrospinal fluid (2–7% of plasma values), breast milk (approximate 30% of maternal plasma concentrations) and the placenta (70). Extensive metabolism via the cytochrome P450 enzyme CYP3A4 occurs in the liver and elimination of more polar metabolites is mainly renal (71, 72). The initial metabolite 3-hydroxyquinine contributes approximately 10% of the antimalarial activity of the parent compound, but may accumulate in renal failure (73). Excretion is increased in acid urine. The mean elimination half-life is around 11 h in healthy subjects, 16 h in uncomplicated malaria and 18 h in severe malaria (62). Small amounts appear in the bile and saliva.

Toxicity

Administration of quinine or its salts regularly causes a complex of symptoms known as cinchonism, which is characterized in its mild form by tinnitus, impaired high tone hearing, headache, nausea, dizziness and dysphoria, and sometimes disturbed vision (7). More severe manifestations include vomiting, abdominal pain, diarrhoea and severe vertigo. Hypersensitivity reactions to quinine range from urticaria, bronchospasm, flushing of the skin and fever, through antibody-mediated thrombocytopenia and haemolytic anaemia, to life-threatening haemolytic-uraemic syndrome. Massive haemolysis with renal failure (“black water fever”) has been linked epidemiologically and historically to quinine, but its etiology remains uncertain (74). The most important adverse effect in the treatment of severe malaria is hyperinsulinaemic hypoglycaemia (75). This is particularly common in pregnancy (50% of quinine-treated women with severe malaria in late pregnancy). Intramuscular injections of quinine dihydrochloride are acidic (pH 2) and cause pain, focal necrosis and in some cases abscess formation, and

in endemic areas are a common cause of sciatic nerve palsy. Hypotension and cardiac arrest may result from rapid intravenous injection. Intravenous quinine should be given only by infusion, never injection. Quinine causes an approximately 10% prolongation of the electrocardiograph QT interval – mainly as a result of slight QRS widening (75). The effect on ventricular repolarization is much less than that with quinidine. Quinine has been used as an abortifacient, but there is no evidence that it causes abortion, premature labour or fetal abnormalities in therapeutic use.

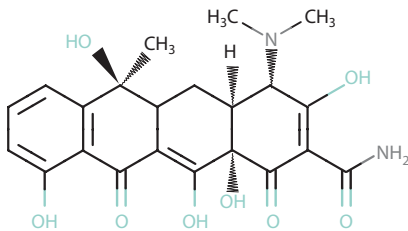
Overdosage of quinine may cause oculotoxicity, including blindness from direct retinal toxicity, and cardiotoxicity, and can be fatal (76). Cardiotoxic effects are less frequent than those of quinidine and include conduction disturbances, arrhythmias, angina, hypotension leading to cardiac arrest and circulatory failure. Treatment is largely supportive, with attention being given to maintenance of blood pressure, glucose, and renal function and to treating arrhythmias.

Drug interactions

There is a theoretical concern that drugs that may prolong the QT interval should not be given with quinine, although whether or not quinine increases the risk of iatrogenic ventricular tachyarrhythmia has not been established. Antiarrhythmics, such as flecainide and amiodarone, should probably be avoided. There might be an increased risk of ventricular arrhythmias with antihistamines such as terfenadine, and with antipsychotic drugs such as pimozide and thioridazine. Halofantrine, which causes marked QT prolongation, should be avoided but combination with other antimalarials, such as lumefantrine and mefloquine is safe. Quinine increases the plasma concentration of digoxin. Cimetidine inhibits quinine metabolism, causing increased quinine levels and rifampicin increases metabolic clearance leading to low plasma concentrations and an increased therapeutic failure rate (77).

A3.12 Tetracycline

Molecular weight: 444.4



*The tetracyclines are a group of antibiotics originally derived from certain *Streptomyces* species, but used mostly in synthetic form. Tetracycline itself may be administered orally or intravenously as the hydrochloride salt or phosphate complex. Both are water soluble, although the intravenous preparation is only stable for a few hours.*

Tetracyclines are inhibitors of aminoacyl-tRNA binding during protein synthesis. They have a broad range of uses, including treatment of some bacterial infections: *Chlamydia*, *Rickettsia*, *Mycoplasma*, Lyme disease, *Brucella*, tularaemia, plague and cholera. Doxycycline is a synthetic tetracycline with a longer half-life, which makes dosing schedules easier.

Formulations

- Capsules and tablets containing 250 mg of tetracycline hydrochloride, equivalent to 231 mg of tetracycline base.

Pharmacokinetics

Some 60–80% of tetracycline is absorbed from the gastrointestinal tract following oral administration. Absorption is reduced by the presence of divalent and trivalent metal ions with which it forms stable, insoluble complexes. Thus absorption may be impaired with food or milk. Formulation with phosphate may improve absorption. Peak plasma concentrations occur 1–3 h after ingestion. Tetracycline is 20–65% bound to plasma proteins. It is widely distributed throughout the body, although less so than the more lipophilic doxycycline. High concentrations are present in breast milk (around 60% of plasma levels), and also diffuse readily across the placenta, and are retained in sites of new bone formation and teeth development. The half-life of tetracycline is around 8 h; 40–70% is excreted in the urine via glomerular filtration. The remainder is excreted in the faeces and bile. Enterohepatic recycling slows down complete elimination.

Toxicity

All the tetracyclines have similar adverse effect profiles. Gastrointestinal effects, such as nausea, vomiting and diarrhoea, are common, especially with higher doses, and are due to mucosal irritation. Dry mouth, glossitis, stomatitis, dysphagia and oesophageal ulceration have also been reported. Overgrowth of *Candida* and other bacteria occurs, presumably due to disturbances in gastrointestinal flora as a result of incomplete absorption of the drug. This effect is seen less frequently with doxycycline, which is better absorbed. Pseudomembranous colitis, hepatotoxicity and pancreatitis have also been reported.

Tetracyclines accumulate in patients with renal impairment and this may renal failure. In contrast doxycycline accumulates less and is preferred in patient with renal impairment. The use of out-of-date tetracycline can result in the development of a reversible Fanconi-type syndrome characterized by polyuria and polydipsia with nausea, glycosuria, aminoaciduria, hypophosphataemia, hypokalaemia, and hyperuricaemia with acidosis and proteinuria. These effects have been attributed to the presence of degradation products, in particular anhydroepitetracycline.

Tetracyclines are deposited in deciduous and permanent teeth during their formation and cause discoloration and enamel hypoplasia. They are also deposited in calcifying areas in

bone and the nails and interfere with bone growth in young infants or pregnant women. Raised intracranial pressure in adults and infants has also been documented. Tetracyclines use in pregnancy has also been associated with acute fatty liver. Tetracyclines should therefore not be given to pregnant or lactating women, or children aged up to 8 years.

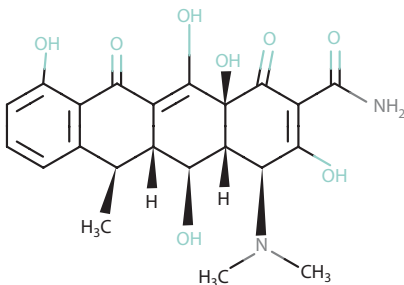
Hypersensitivity reactions occur, although they are less common than for β -lactam antibiotics. Rashes, fixed drug reactions, drug fever, angioedema, urticaria, pericarditis and asthma have all been reported. Photosensitivity may develop, and, rarely, haemolytic anaemia, eosinophilia, neutropenia and thrombocytopenia. Pre-existing systemic lupus erythematosus may be worsened and tetracyclines are contraindicated in patients with the established disease.

Drug interactions

There is reduced absorption of tetracyclines with concomitant administration of cations, such as aluminium, bismuth, calcium, iron, zinc and magnesium. Administration with antacids, iron preparations, dairy products and some other foods should therefore be avoided. Nephrotoxicity may be exacerbated with diuretics, methoxyflurane or other potentially nephrotoxic drugs. Potentially hepatotoxic drugs should be avoided. Tetracyclines produce increased concentrations of digoxin, lithium and theophylline, and decrease plasma atovaquone concentrations and also the effectiveness of oral contraceptives. They may antagonize the actions of penicillins so should not be given concomitantly.

A3.13 Doxycycline (see also Tetracycline)

Molecular weight: 444.4



Doxycycline is a tetracycline derivative with uses similar to those of tetracycline. It may be preferred to tetracycline because of its longer half-life, more reliable absorption and better safety profile in patients with renal insufficiency, where it may be used with caution. It is relatively water insoluble but very lipid soluble. It may be given orally or intravenously.

It is available as the hydrochloride salt or phosphate complex, or as a complex prepared from the hydrochloride and calcium chloride.

Formulations

- Capsules and tablets containing 100 mg of doxycycline salt as hydrochloride.

Pharmacokinetics

Doxycycline is readily and almost completely absorbed from the gastrointestinal tract and absorption is not affected significantly by the presence of food. Peak plasma concentrations occur 2 h after administration. Some 80–95% is protein-bound and half-life is 10–24 h (78). It is widely distributed in body tissues and fluids. In patients with normal renal function, 40% of doxycycline is excreted in the urine, although more if the urine is alkalinized. It may accumulate in renal failure. However, the majority of the dose is excreted in the faeces.

Toxicity

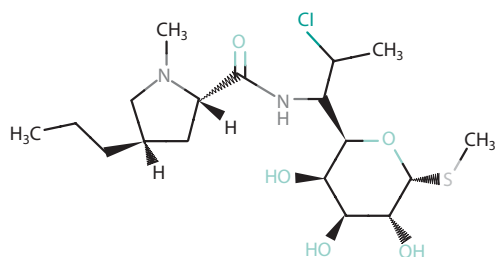
As for tetracycline. Gastrointestinal effects are fewer than with tetracycline, although oesophageal ulceration can still be a problem if insufficient water is taken with tablets or capsules. There is less accumulation in patients with renal impairment. Doxycycline should not be given to pregnant or lactating women, or children aged up to 8 years.

Drug interactions

Doxycycline has a lower affinity for binding with calcium than other tetracyclines, so may be taken with food or milk. However, antacids and iron may still affect absorption. Metabolism may be accelerated by drugs that induce hepatic enzymes, such as carbamazepine, phenytoin, phenobarbital and rifampicin, and by chronic alcohol use.

A3.14 Clindamycin

Molecular weight: 425.0



Clindamycin is a lincosamide antibiotic, i.e. a chlorinated derivative of lincomycin. It is very soluble in water. It inhibits the early stages of protein synthesis by a mechanism similar to that of the macrolides. It may be administered by mouth as capsules containing the hydrochloride or as oral liquid preparations containing the palmitate hydrochloride.

Clindamycin is given parenterally as the phosphate either by the intramuscular or the intravenous route. It is used for the treatment of anaerobic and Gram-positive bacterial infections, babesiosis, toxoplasmosis and *Pneumocystis carinii* pneumonia.

Formulations

- Capsules containing 75 mg, 150 mg or 300 mg of clindamycin base as hydrochloride.

Pharmacokinetics

About 90% of a dose is absorbed following oral administration. Food does not impede absorption but may delay it. Clindamycin phosphate and palmitate hydrochloride are rapidly hydrolysed to form the free drug. Peak concentrations may be reached within 1 h in children and 3 h in adults. It is widely distributed, although not into the cerebrospinal fluid. It crosses the placenta and appears in breast milk. It is 90% bound to plasma proteins and accumulates in leukocytes, macrophages and bile. The half-life is 2–3 h but this may be prolonged in neonates and patients with renal impairment. Clindamycin undergoes metabolism to the active *N*-demethyl and sulfoxide metabolites, and also some inactive metabolites. About 10% of a dose is excreted in the urine as active drug or metabolites and about 4% in the faeces. The remainder is excreted as inactive metabolites. Excretion is slow and takes place over many days. Clindamycin is not effectively removed from the body by dialysis.

Toxicity

Diarrhoea occurs in 2–20% of patients. In some, pseudomembranous colitis may develop during or after treatment, which can be fatal. Other reported gastrointestinal effects include nausea, vomiting, abdominal pain and an unpleasant taste in the mouth. Around 10% of patients develop a hypersensitivity reaction. This may take the form of skin rash, urticaria or anaphylaxis. Other adverse effects include leukopenia, agranulocytosis, eosinophilia, thrombocytopenia, erythema multiforme, polyarthrititis, jaundice and hepatic damage. Some parenteral formulations contain benzyl alcohol, which may cause fatal “gaspings syndrome” in neonates.

Drug interactions

Clindamycin may enhance the effects of drugs with neuromuscular blocking activity and there is a potential danger of respiratory depression. Additive respiratory depressant effects may also occur with opioids. Clindamycin may antagonize the activity of parasymphomimetics.

A3.15 Pharmacology of antimalarials in special groups and conditions

A3.15.1 Safety and tolerability of antimalarials in infants

Infants under 12 months of age constitute a significant proportion of patients in malaria endemic countries. Yet few studies focus specifically on this age range, partly because of ethical dilemmas and also owing to technical difficulties with sampling. Very young children cannot report adverse effects themselves, so detection of these is dependent upon parents and health professionals making observations. In addition, pre-marketing clinical trials for new drugs are not represented by important subpopulations including infants (79), yet there are potentially important pharmacokinetic differences in infants compared to older children and adults (80).

Drug absorption

The gastric pH at birth is usually 6–8 but within a few hours falls to 2 and then rises again until virtual achlorhydria occurs for several days. As the gastric mucosa develops, the acidity increases again until 3 years of age when adult values are attained. The gastric emptying time is prolonged (up to 8 h) in neonates and approaches adult values only after 6 months. Intramuscular injections can also be problematic in young children. Infants with acute or severe malaria may become extremely “shut down” whereby visceral, muscle and skin blood flow is reduced. This may result in slow, erratic or incomplete drug absorption and the consequent delay in achieving therapeutic drug levels at a time when speed and adequacy of drug delivery are crucial.

Distribution

Relatively large total and extracellular body water compartments in infancy lead to larger apparent volumes of distribution. Total body lipids rise steadily after birth for the first 9 months of life but then decrease until adolescence. These changes in body composition can modulate volume of distribution and clearance. Liver mass per body weight is higher in infants than adults and the liver undergoes rapid growth during the first 2 years. The brain is disproportionately large in young children, and the blood brain barrier relatively immature, making a further contribution to volume of distribution. Finally drug distribution is also affected by lower protein binding in infancy with more free drug and thus increased clearance. The former might also lead to a greater risk of toxicity.

Drug metabolism

The cytochrome P450 mixed function oxidase system is the most important biotransformation system incorporating many enzymes and isoenzymes. In general, these enzyme systems are immature at birth. There is therefore relatively slow clearance of most metabolized drugs in the first 2–3 months of life. Between 2 and 6 months clearance is more rapid than in adults and even more so for most drugs from 6 months

to 2 years (elimination half-life for metabolized drugs in infants aged 6 months to 2 years is 0.6 times that in adults).

Renal clearance

Glomerular filtration rate only reaches surface-area-adjusted adult levels at around 6 months of age. Thus for drugs that rely on renal elimination, elimination half-lives in very young infants may be up to 2–3 times longer than in adults. After 2 months, half-lives are shorter (0.35–0.5 times adult values) until about 2 years of age.

A3.15.2 Malnutrition and antimalarials

Malaria and malnutrition frequently coexist. The relationship between malaria and nutritional status is complex and has been the subject of debate for many years (81). Given that a significant proportion of the world's malnourished children live in malaria endemic countries (82) it is important to understand how antimalarial drug disposition may be affected when malnutrition is severe. This section outlines the physiological changes that occur in malnourished patients and discusses how these may influence the pharmacokinetic properties of antimalarials, drawing on the few studies of antimalarial drug disposition in malnutrition that are available

Note: In reviewing the literature it was apparent that many studies were conducted in populations and settings where some degree of malnutrition would have been expected. However, this was only rarely mentioned as a possible confounder for drug efficacy, although there was an occasional comment that obviously malnourished patients appeared to respond differently to treatment than did other patients (83). Several ongoing studies are planning to look specifically at treatment outcomes in this group of patients.

Definitions

There are different ways of classifying malnutrition. Earlier studies employ the Wellcome classification: where body weight is given as a percentage of standard weight (50th percentile of the Harvard value): underweight 80–60%; marasmus 60%; kwashiorkor 80–60% + oedema; marasmic kwashiorkor 60% + oedema. Other studies refer to low weight-for-height (wasting); low weight-for-age (underweight); or low height-for-age (stunting) and use anthropometric indicators and reference standards. Protein-energy malnutrition is defined as a range of pathological conditions arising from coincident lack, in varying proportions, of protein and calories, occurring most frequently in infants and young children and commonly associated with infections (84).

Pharmacokinetics

- *Absorption*

Anorexia, diarrhoea and vomiting are common. Anorexia will affect the absorption of drugs

requiring concomitant administration of fatty foods, and oral bioavailability will be reduced in vomiting patients or those with a rapid transit time. Atrophy of the bowel mucosa, which occurs in severe protein-energy malnutrition, will also hinder absorption.

Children with oedematous lower limbs may be expected to have altered absorption from intramuscular injections. Patients with protein-energy malnutrition frequently have poor peripheral perfusion due to circulatory insufficiency associated with bradycardia, hypotension and a reduced cardiac output. Thus absorption of intramuscular and possibly intrarectal drugs may be expected to be slower than in patients without protein-energy malnutrition. Diminished muscle mass may make repeated intramuscular injections difficult.

- *Distribution*

Total body water increases in proportion to the degree of malnutrition, mainly owing to an expansion of the extracellular fluid (most obvious in oedematous patients). Thus the volume of distribution of some drugs can be expected to be larger and plasma concentrations lower. Albumin is the most important plasma protein for binding of many drugs, but in protein-energy malnutrition hypoalbuminaemia results from decreased synthesis as dietary deficiency occurs. With highly bound drugs this could in theory lead to an increase in the amount of unbound drug, which may increase both the elimination, since more drug is available for metabolism, and potential toxicity. There are other plasma proteins less severely affected by decreased synthesis, and if these are able to bind some free drug then the increase in free fraction might not be as great as anticipated.

- *Metabolism*

Fatty infiltration occurs but jaundice is uncommon unless septicaemia is present. Liver function tests may be abnormal and urea cycle enzymes are decreased. Children with kwashiorkor excreted a higher proportion of unchanged chloroquine before therapy than in the recovery phase (85). This suggests that hepatic function was inadequate during the acute phase of kwashiorkor. Animal studies have demonstrated that some enzyme systems, such as cytochrome P450, have decreased activity in the presence of significant malnutrition.

- *Elimination*

Owing to the reduction in cardiac output, the kidneys receive less than the usual 25% of renal blood flow. Glomerular filtration rate, renal blood flow and tubular function have all been shown to be inadequate, and compounded by concomitant dehydration. Drugs dependent on renal excretion might be expected to have elevated plasma concentrations under such circumstances. Abnormal excretion of drugs into bile has also been described in severe protein-energy malnutrition.

Antimalarials and protein-energy malnutrition

• *Chloroquine*

Few data are available for chloroquine kinetics in malnourished patients. Children with kwashiorkor excreted a higher ratio of chloroquine to its metabolites before nutritional rehabilitation (85). Presumably the metabolism of chloroquine by the liver was affected adversely in protein-energy malnutrition. In a study of chloroquine pharmacokinetics in five children with kwashiorkor (but without malaria), peak plasma concentrations of the drug were approximately one-third of the values for healthy controls (mean 40 + 30 ng/ml compared with 134 + 99 ng/ml), but the times to peak levels and the elimination half-lives were not significantly different, indicating reduced absorption. There was also reduced metabolism of chloroquine to its metabolite, desethylchloroquine, which suggested some impairment of drug metabolism. However, the study did not consider plasma protein binding or drug distribution. Currently there are no recommendations for dose alterations in patients with protein-energy malnutrition (86).

• *Quinine*

Three studies examining the kinetics of quinine in malnourished patients have been published. The first from Nigeria compared the pharmacokinetics of an oral dose of quinine 10 mg/kg in six children with kwashiorkor and seven normal controls who were attending a malaria follow-up clinic (87). The children were aged 1–3 years. Values for total plasma proteins and albumin for children with kwashiorkor were 74% and 67% of those for control children. Absorption of quinine was slower in the kwashiorkor group than in the controls (mean time to maximum concentration (t_{\max}) 2.5 ± 0.3 h compared with 1.5 ± 0.6 h); maximum plasma concentration (C_{\max}) was also lower (1.7 ± 0.5 µmol/l compared with 2.4 + 0.3 µmol/l). Rate of clearance of quinine in kwashiorkor was less than one-third of the value for well-nourished patients (31.5 ± 8.5 mg/min compared with 108.5 ± 34.8 mg/min) and the elimination half-life was also longer (15.0 ± 4.4 h compared with 8.0 ± 1.3 h). The authors concluded that the combination of malabsorption, reduced plasma protein binding and reduced metabolism in the liver was responsible for the differences observed. No dose alterations were suggested.

The second study, in Gabon, compared eight children with non-kwashiorkor global malnutrition (defined as having a ratio of left mid-arm circumference:head circumference of <0.279) with seven children with normal nutritional status (88). The children were aged 9–60 months. Only two were subsequently confirmed to have malaria, although all had been febrile at presentation. Mean serum albumin levels in the two groups were 28.7 and 31.0 respectively. Each child received a loading dose of 16 mg/kg quinine base (25 mg/kg quinine resorcine hydrochloride; Quinimax) by deep intramuscular injection followed by 8 mg/kg at 12 h. The t_{\max} was significantly shorter in malnourished children (1.1 ± 0.4 h compared with 2.2 ± 1.2 h). No difference was observed for C_{\max} , volume of distribution or protein binding. Clearance was significantly faster for malnourished children (4.4 ±

3.6 ml/min/kg compared with 2.3 ± 1.4 ml/min/kg), and half-life shorter (6.3 ± 1.8 h compared with 10.1 ± 3.4 h). Concentration at 12 h was lower in malnourished children (3.3 ± 1.6 mg/ml compared with 5.3 ± 1.6 mg/l). There was a significant correlation between elimination half-life and left mid-arm:head circumference. The ratio between the area under the curve for hydroxyquinine, the main metabolite of quinine, and that for quinine was significantly higher in the malnourished group and significantly correlated with left mid-arm:head circumference ratio, indicating increased metabolism of quinine in malnourished patients. The authors suggest that the administration interval should be reduced to 8 h in malnourished children in order to obtain plasma concentrations of quinine similar to those found in children with normal nutrition.

In the third study, from Niger, 40 children were divided into four groups: normally nourished children with or without cerebral malaria, and malnourished children (>2 SD below the median value for at least two of the following: weight-for-height, weight-for-age and height-for-age) with or without cerebral malaria (89). The age range studied was 24–72 months. Patients with kwashiorkor were excluded. All patients received 4.7 mg/kg quinine base (as 8 mg/kg Quinimax) by intravenous infusion over 4 h. Infusions were repeated every 8 h for children with cerebral malaria. C_{max} was highest in malnourished children, and was higher in those without malaria than with malaria (8.5 ± 4.7 mg/l compared with 7.7 ± 2.0 mg/l); it was lowest in the control groups without and with malaria (3.0 ± 2.1 mg/l and 6.6 ± 3.0 mg/l). There were no differences between the area under the curve for 0–8 h and elimination half-life for the two malnutrition groups and controls with malaria, but all were higher than for controls without malaria. Conversely plasma clearance of quinine and volume of distribution were smaller in these three groups than in controls without malaria. Alpha 1-glycoprotein plasma concentrations and protein-bound fraction of the drug were increased in the three groups. Malnourished children had slower parasite clearance but the difference was not significant. The authors concluded that severe global malnutrition and cerebral malaria have a similar effect on quinine pharmacokinetics in children and that cerebral malaria-mediated modifications of quinine disposition are not potentiated. They recommend that current dosing schedules should not be altered for children with malnutrition.

- *Sulfadoxine-pyrimethamine*

No studies exist of sulfadoxine-pyrimethamine kinetics in malnourished patients. However, observational data from Rwandan refugee children showed that malnourished children (defined as weight-for-height <80% of the reference median with or without oedema) were more likely to have treatment failure than children without malnutrition (86% compared with 58%) (83). Higher initial parasite counts and host immunity, as well as pharmacokinetic differences, may also have contributed to this finding.

- *Tetracycline*

A number of small studies have been conducted on tetracycline kinetics in malnourished adults from India. One study compared the kinetics of intravenous and oral tetracycline in malnourished and normal adult males (90). Compared to the control group, malnourished patients had lower protein binding, shorter elimination half-life and reduced volume of distribution. The authors suggest that in order to keep levels of tetracycline above the minimum inhibitory concentration, the dose interval should be reduced. A similar conclusion was reached by another study that also found more rapid distribution of tetracycline and faster clearance in the malnourished group (91). The same author, in a separate study, also looked at absorption of oral compared with intravenous tetracycline in various types of malnutrition. Oral absorption was slower in patients with protein-energy-malnutrition and pellagra than in patients with anaemia or vitamin B complex deficiency patients and healthy controls. In a third study, patients with nutritional oedema were found to have increased C_{max} and area under the curve values, and reduced clearance and volume of distribution compared with healthy controls (i.e. some differences with non-oedema malnutrition patients) (92).

- *Doxycycline*

There is a single study examining the kinetics of doxycycline given orally to adult patients in India (93). Area under the curve, elimination half-life and plasma protein binding were reduced, and clearance increased in the malnourished group. Renal clearance was similar in controls and malnourished patients. The authors surmised that increased total body clearance of doxycycline might be due to higher metabolism in malnourished patients. Steady state plasma C_{min} levels were lower than in healthy patients but still within the therapeutic range. A change in dose recommendation does not seem necessary given these findings.

- *Other antimalarials*

There are no studies of the kinetics of clindamycin, amodiaquine, artemisinin derivatives (dihydroartemisinin), artemether-lumefantrine, mefloquine or primaquine kinetics in malnourished patients.

Conclusion

There are many reasons why pharmacokinetics may be different in malnourished patients compared to those who are well nourished. However, with the possible exception of quinine, there are insufficient data available for specific dosing changes to be recommended.

A3.16 References

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ANNEX 4

ANTIMALARIALS AND MALARIA TRANSMISSION

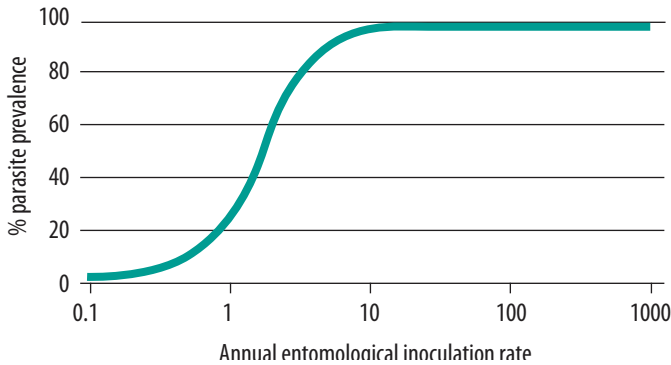
A4.1 Principles of malaria transmission

Malaria is spread among people by a mosquito belonging to the genus *Anopheles*. The female mosquito is infected by gametocytes, the sexual stages of the parasite when it takes a blood meal from an infected person. Gametocytes undergo further development in the insect for a period of 6–12 days, after which transformed parasites as sporozoites can infect a human through the bite of the infected mosquito.

The intensity of malaria transmission in an area is the rate at which people are inoculated with malaria parasites by infected mosquitoes. It is expressed as the annual entomological inoculation rate or EIR, which is the number of infectious mosquito bites received by an individual in one year. The EIR determines to a large extent the epidemiology of malaria and the pattern of clinical disease in an area. The high end of the malaria transmission range is found in a few parts of tropical Africa, where EIRs of 500–1000 can be reached (1). At the low end of the range are EIRs of 0.01 or below, as found in the temperate climates of the Caucasus and Central Asia where malaria transmission is only barely sustained. Between these extremes are situations of unstable seasonal malaria, such as in much of Asia and Latin America, where EIRs lie below 10, and often around 1–2, and situations of stable but seasonal malaria, as in much of West Africa, where the EIR is in the range 10–100.

The proportion of infected mosquitoes in a locality is related to the number of infected and infectious humans in the area; therefore, lowering the infectivity of infected persons to mosquito vectors will contribute to reducing malaria transmission and to eventually reducing the incidence and prevalence of the disease. However, the relationship between EIR and the prevalence of malaria is complex, and it is affected by the extent of immunity to malaria, the pattern of its acquisition and loss, and to whether or not there is effective drug treatment in the area. The hypothetical relationship represented in figure A4.1 assumes no drug treatment. In areas of low transmission where EIRs are below 1 or 2, a reduction in the inoculation rate will result in an almost proportionate reduction in the prevalence (and incidence rate) of malaria. In EIRs in excess of 10, where there is great redundancy in the infectious reservoir, larger reductions in transmission are needed to make a significant impact on malaria prevalence. The experience with major interventions, such as the use of insecticide-treated nets and artemisinin-based combination therapies, suggests, however, that effective transmission-reducing interventions will be beneficial with respect to mortality and even morbidity in most situations (2,3).

Figure A4.1 Relationship between inoculation rate and parasite prevalence (assumes that all infections are untreated)



A4.2 Effect of medicines on malaria transmission

Medicines can lead to reducing malaria transmission by two mechanisms (4).

1. **Early and effective treatment of a malaria blood infection** with any antimalarial will reduce gametocytes by eliminating the asexual blood stages from which gametocytes derive. The faster the clearance of asexual blood parasites the greater the effect on reducing infectivity. The potent anti-infective properties of artemisinins are, therefore, partly due to their rapid parasite clearance action. In *P. vivax*, *P. malariae* and *P. ovale*, gametocytes have a short developmental period (2–3 days) and mature gametocytes are short-lived. Therefore, effective treatment of the asexual blood infection alone will be sufficient to abolish infectivity to mosquitoes. In *P. falciparum*, gametocytes take longer to develop (about 12 days) and mature from a young parasite (merozoite). In the peripheral circulation, mature gametocytes may remain infective for up to several weeks. Hence, infectivity of a *P. falciparum* infection could remain for weeks after the patient has been successfully treated unless a specific anti-gametocyte medication (e.g. primaquine, see below) has been used.
2. **By lowering parasite infectivity** through either a direct effect on gametocytes (gametocytocidal effect) or on the parasite developmental stages in the mosquito (sporonticidal effect) (Table A4.1; Fig. A4.2). Chloroquine, widely used to treat *P. falciparum* disease (asexual blood parasites) in the past, acts against young gametocytes, but it has no suppressive effect on (5) the infectivity of mature infective gametocytes (6), and may even enhance it. In contrast, sulfadoxine-pyrimethamine increases gametocyte carriage but reduces their infectivity (6–8). Artemisinins are the most potent gametocytocidal drugs among those currently being used to treat an asexual blood infection (9–13). They destroy young gametocytes, preventing new infective gametocytes from entering the circulation, but they have less effect on mature

gametocytes, which may be present in the circulation at the time of treatment (12). Primaquine, an 8-aminoquinoline, which is widely used as a hypnozoitocidal drug for the prevention of relapses in *P. vivax*, acts on mature gametocytes and accelerates gametocyte clearance (12). The addition of primaquine to ACTs in the treatment of *P. falciparum* infections will be beneficial, because the latter acts on mature infective gametocytes on which artemisinins have little or no effect (14).

Table A4.1 Effects of some commonly used antimalarials on the infectivity of *P. falciparum* to the mosquito

Drug	Effect of treatment			Overall effect on suppressing infectivity ^a
	<i>Gametocytocidal</i>	<i>Sporonticidal</i>		
	Viability of young sequestered gametocytes	Viability of mature circulating gametocytes	Infectivity of gametocytes to mosquitoes	
Chloroquine	Reduces	No effect (4)	Enhances (5)	+
Sulfadoxine-pyrimethamine	No effect	Increases (5–7)	Suppresses (5–7)	±
Artemisinin derivatives	Greatly reduces (8–11)	Little effect (11)	Unknown	+++
Primaquine	Unknown	Greatly reduces (11)	Unknown	+++
Quinine (4)	No effect	No effect	No effect	None

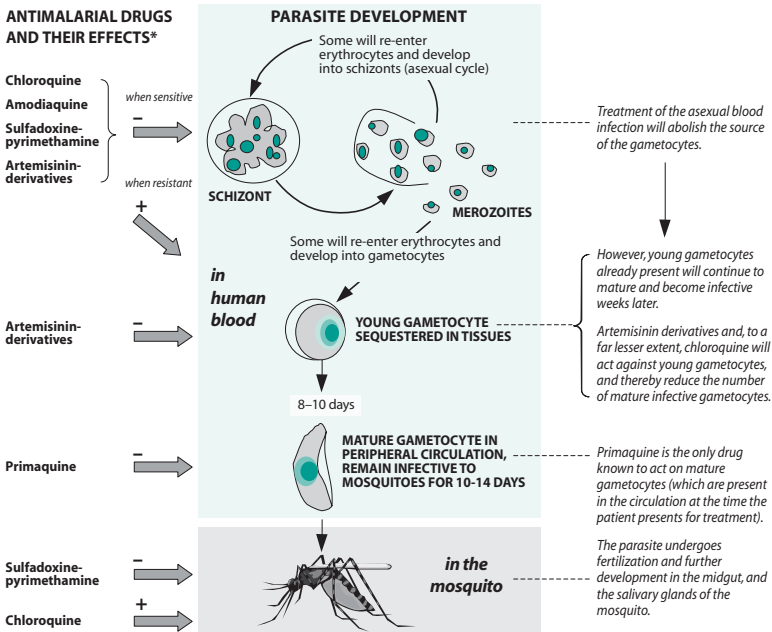
^a ±: No overall effect; +: moderate effect; ++: high effect; +++: very high effect

A4.2.1 In situations of low-to-moderate transmission

The most direct consequences of lowering parasite infectivity by the use of drugs are to be seen in areas of low transmission where symptomatic patients constitute the majority of the infectious reservoir. Here a strategy to shorten the period of infectivity of patients, as well as to reduce the infectiousness of gametocytes, will have a significant impact on malaria transmission. A reduction in transmission would, in these situations, result in an almost proportionate reduction in the prevalence of infection and incidence of disease.

In areas of low-to-moderate transmission, therefore, the provision of prompt and effective treatment to malaria patients is important, both as a means of achieving the therapeutic goal of reducing morbidity and mortality, and the public health goal of reducing transmission. In addition, the use of specific gametocytocidal medicines will help to curtail transmission.

Figure A4.2 Transmission of *Plasmodium falciparum* and the effects of antimalarials



*When parasites are sensitive to the drug unless otherwise stated. Positive and negative arrows indicate the effect of the drug, enhancement (+) and suppression (-), respectively, on the parasite stage or its development.

A4.2.2 In situations of intense transmission

In high-transmission settings, infected but asymptomatic persons constitute an important part of the infectious reservoir. Even though treated cases (mainly children) have higher densities of gametocytes, and infectivity is positively related to gametocyte density, children constitute only a proportion of the infective reservoir (15). This, together with the fact that, in high transmission settings, a considerable reduction in transmission rates is needed to impact on parasite prevalence (and incidence of disease), makes a less compelling case for introducing an infectivity-suppressing component into the treatment schedule. However, as malaria control efforts intensify in highly endemic countries, transmission rates are declining and infectivity-reducing drug regimes will have a useful role to play in sustaining those achievements. The use of antimalarial drugs to reduce infectivity:

- is justified in low-transmission settings;
- will be beneficial in high-transmission settings when transmission rates have been lowered by effective malaria control.

A4.3 Strategies to reduce the transmission of drug-resistant parasites

The continued use of a medicine to which parasites are partially resistant will confer a selective advantage to resistant parasites and favour their transmission. In the presence of the drug, partially resistant infections produce higher gametocyte densities than those that are sensitive (6,7,10,11,16,17). Drug resistance leads to recrudescences, which are associated with higher rates of gametocyte carriage than primary infections. Thus, cumulatively drug resistant infections generate more gametocytes than sensitive ones. Secondly, gametocytes carrying resistant genes have been shown to be more infectious to mosquitoes. They produce higher densities of parasites (oocysts) in the mosquitoes, and they infect a higher proportion of mosquitoes than those carrying sensitive genes (7,8,12). Molecular studies on the transmission of two *P. falciparum* genes linked to chloroquine resistance *PfCRT* and *PfMDR* have shown that gametocytes carrying these genes produce more oocysts and are also more infectious to mosquitoes than gametocytes of the sensitive genotype (17).

Two things important to note are that:

- the continued use of a failing medicine will selectively increase the transmission of drug resistant parasites and hasten their spread;
- early treatment of malaria patients with an effective antimalarial has the greatest chance of limiting the spread of drug-resistant parasites.

A decrease in transmission rates as achieved, for example, by vector control, will curtail the spread of parasites of both sensitive and resistant strains, but evidence suggests that, in the absence of drug pressure, resistant parasites would be at a survival disadvantage compared to sensitive strains (18, 19). Stringent transmission conditions resulting from mosquito-control measures will, therefore, tend to selectively eliminate drug-resistant parasites (20). This is supported by field experiences in:

- Zimbabwe, where house spraying with insecticides to reduce malaria transmission was associated with a decrease in drug resistance (21);
- focal regions in India and Sri Lanka, where a combination of intense vector-control measures and switching to an effective medicine led to a significant reduction and, in some instances, even elimination of chloroquine-resistant *P. falciparum* from the foci; and
- western Thailand, where high levels of mefloquine resistance prevailed in the 1990s and the deployment of insecticide-treated nets and an ACT for malaria treatment was followed by an increase in vitro susceptibility of *P. falciparum* to mefloquine (22).

When parasites become resistant to a medicine used for curative purposes, having anti-infective properties in the same medicine is not likely to help reduce the spread of resistant parasites – it will, to the contrary, favour the spread of resistant parasites over sensitive

ones by conferring a survival advantage on gametocytes that carry resistant genes (23). If, however, a medicine is combined with another that has transmission blocking activity and different biochemical targets in the parasite, then it will block the transmission of parasites resistant to the first. Thus, in an ACT, the artemisinin derivative will reduce the likelihood of emergence and spread of parasites resistant to the partner medicine, because it has short parasite clearance times and anti-infective properties (11,17,24). Likewise, primaquine, when used in combination with a curative medicine, will reduce the transmission of resistant mutants to the latter.

Whilst vector-control methods, such as residual insecticide spraying and the use of insecticide-treated nets, can and will have an effect on the parasite population as a whole, antimalarial medicines that block transmission will take effect only on parasites in the infection which is being treated. This effect will be even smaller in high-transmission settings, because of the infected persons who are ill, and it will constitute only a small proportion of the parasite reservoir treatment; therefore, anti-infective drug treatment will have less effect than vector-control methods in curtailing the spread of resistant parasites.

Other important points are as follows:

- reducing transmission through mosquito control will help reduce the spread of drug resistance;
- a therapeutic strategy to curtail the spread of drug resistant mutants will require a combination of the curative medicines with one, which has infectivity suppressive effects on the parasite targets of the two medicines being different. Both properties residing in the same medicine will be unlikely to protect against the spread of resistant parasites;
- such a therapeutic strategy will be synergistic with mosquito-control methods in preventing the spread of drug resistance.

A4.4 Summary and conclusions

Antimalarial medicines have an important role to play in reducing malaria transmission and in curtailing the spread of drug resistant parasites. Early cure of blood infections, such as by providing good access to diagnosis and treatment will, in itself, be effective in lowering malaria transmission. Antimalarial medicines with specific infectivity suppressive actions (e.g. artemisinin derivatives, primaquine) will reduce malaria transmission even further and at almost all intensities of transmission, but particularly in areas of low transmission.

Mosquito control will be the most effective among the transmission blocking strategies currently available to curtail the spread of drug resistance. Therapeutic strategies to reduce the spread of drug resistant parasites will require using medicines in combination with a partner medicine(s) having infectivity suppressive effects. These should be taken into consideration in the formulation of national treatment policies. Suppression of malaria infectivity should be considered an important activity component in the development of antimalarial medicines.

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ANNEX 5

MALARIA DIAGNOSIS

A5.1 Symptom-based (clinical) diagnosis

Malaria is a common cause of fever and illness in endemic areas (1,2); but it is not possible to accurately diagnose malaria using any one set of clinical criteria, as the signs and symptoms of malaria, e.g. fever, chills, headache and anorexia, are nonspecific and are common to many diseases and conditions. The appropriateness of particular clinical diagnostic criteria varies from area to area according to the intensity of transmission, the species of malaria parasite and other prevailing causes of fever (3). Other diseases co-incident with malaria may also affect its presentation. HIV/AIDS can increase the risk of acquiring malaria or the progression to severe malaria, depending on malaria transmission in the area and the age of the patient; but it can also lead to an increase in the incidence of febrile disease that is not malaria, further complicating symptom-based diagnosis of malaria (4).

The use of detailed weighting and scoring systems for clinical signs and symptoms of malaria may improve the accuracy of clinical diagnosis, but still result in low sensitivity and specificity. Studies in the Gambia achieved a sensitivity of 70–88% and a specificity of 63–82%. These methods may also be too complicated to implement and supervise under operational conditions, and many of the key symptoms and signs of malaria in one area may not be applicable elsewhere (5,6). A review of 10 studies indicated that the use of the more restrictive criteria of clinical algorithms resulted in only trivial savings in drug costs compared with the use of a fever-based diagnosis and, in areas of high prevalence, it greatly increases the probability of missing malaria infections (7).

A5.2 Light microscopy

In addition to providing a diagnosis with a high degree of sensitivity and specificity when performed well, microscopy allows quantification of malaria parasites and identification of the infecting species. Light microscopy involves relatively high costs in training and supervision but, in particular, when the case-load is high, operational costs are low. Microscopy technicians may also be involved in diagnosis of non-malarial diseases.

It is considered to be the “field standard” against which the sensitivity and specificity of other methods must be assessed. A skilled microscopist is able to detect asexual parasites at densities of fewer than 10 per μl of blood, but under typical field conditions the limit of sensitivity is approximately 100 parasites per μl (8). Light microscopy has important advantages:

- low direct costs, if the infrastructure to maintain the service is available,
- high sensitivity, if the quality of microscopy is high,
- differentiation between plasmodia species,
- determination of parasite densities,
- ability to monitor response to therapy,
- ability to be used to diagnose many other conditions.

It can be difficult to maintain good quality of microscopy, for various reasons: the need for adequate training and supervision of laboratory staff; the need to rely on electricity; delays in providing results to patients; and the need to maintain quality assurance and control of laboratory services.

Numerous attempts have been made to improve malaria microscopy, but none has proven to be superior to the classical method of Giemsa-staining and oil-immersion microscopy for performance in typical health-care settings (9).

A5.3 Rapid diagnostic tests

Rapid diagnostic tests are immunochromatographic tests that detect parasite-specific antigens in a finger-prick blood sample. Some tests detect only one species (*P. falciparum*), others detect one or more of the other species of human malaria parasites (*P. vivax*, *P. malariae* and *P. ovale*) (10–12). They are available commercially in different formats, e.g. dipsticks, cassettes or cards. Cassettes and cards are easier to use in difficult conditions outside health facilities.

Rapid diagnostic tests are relatively simple to perform and to interpret, and they do not require electricity or special equipment. WHO recommends that such tests should have a sensitivity of > 95% in detecting plasmodia at densities of more than 100 parasites per μl of blood. WHO maintains a list of RDT manufacturers with ISO 13485:2003 certification as evidence of quality of manufacture, and it evaluates performance of commercially-available tests.

Current tests are based on the detection of histidine-rich protein 2 (HRP2), which are specific for *P. falciparum*, pan-specific or species-specific *Plasmodium* lactate

dehydrogenase (pLDH) or pan-specific aldolase. These antigens have different characteristics, which may affect suitability for use in different situations, and these should be taken into account when developing RDT policy. These tests have many potential advantages, including:

- the ability to provide rapid results;
- fewer requirements for training and skilled personnel (for instance, a general health worker can be trained in one day);
- reinforcement of patient confidence in the diagnosis and in the health service in general.

There are also potential disadvantages, including:

- the likelihood of misinterpreting a positive result as indicating malaria in patients with parasitaemia incidental to another illness, in particular when host immunity is high;
- the inability, in the case of some RDTs, to distinguish new infections from a recently and effectively treated infection; this is due to the persistence of certain target antigens (e.g. HRP2) in the blood for 1–3 weeks after effective treatment;
- unpredictable sensitivity in the field (13–20); this can be reduced by careful procurement, testing, and good transport and storage. WHO facilitates lot (batch) testing prior to field deployment.

Published sensitivities of RDTs for *P. falciparum* range from comparable to those of good field microscopy (>90% at 100–500 parasites/μl of blood) to very poor (40–50%) for some widely used products. Sensitivities are generally lower for other species. The reasons for poor sensitivity may include: poor test manufacture; damage due to exposure to high temperature or humidity; incorrect preparation and interpretation by end-users; and variation in the target antigen (12). Several studies have shown that health workers, volunteers and private sector providers can, with adequate training and supervision, use RDTs correctly and provide accurate malaria diagnosis.

The use of a confirmatory diagnosis with either microscopy or RDTs is expected to reduce the overuse of antimalarials by ensuring that treatment is targeted at patients with confirmed malaria infection, as opposed to treating all patients with fever. However, although providers of care may be willing to perform diagnostic tests, they do not always comply with the results. This is especially true when they are negative. It is, therefore, important to ensure the accuracy of parasite-based diagnosis and demonstrate this to end-users, and to provide them with the resources to adequately manage both positive and negative results.

A5.4 Immunodiagnosis and PCR-based molecular detection methods

Detection of antibodies to parasites, which may be useful for epidemiological studies, is neither sensitive nor specific enough to be of use in the management of patients suspected of having malaria (21).

Techniques to detect parasite DNA, based on the polymerase chain reaction, are highly sensitive and very useful for detecting mixed infections, in particular at low parasite densities. They are also useful for studies on drug resistance and other specialized epidemiological investigations (22), but they are not generally available for large-scale field use in malaria endemic areas.

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ANNEX 6

RESISTANCE TO ANTIMALARIAL MEDICINES

A6.1 Introduction

Currently, there are no bedside tests for determining the susceptibility of the malaria parasite to antimalarials. Monitoring is, therefore, needed to determine geographical trends in susceptibility and the emergence and spread of drug resistance. The information obtained will help guide treatment choices and predictions about future resistance patterns.

The greatest problem with drug resistance occurs with *Plasmodium falciparum*. Resistance of *P. falciparum* is of particular concern because of the enormous burden of disease caused by this species, its lethal potential, the propensity for epidemics, and the cost of candidate replacement drugs for areas with established drug resistance. Chloroquine resistance does occur in *P. vivax*, especially in western Oceania, but there are very few reports of resistance in *P. malariae* or *P. ovale* (although there have also been very few studies).

This annex defines resistance, examines how it arises and spreads, and describes ways in which it can be monitored.

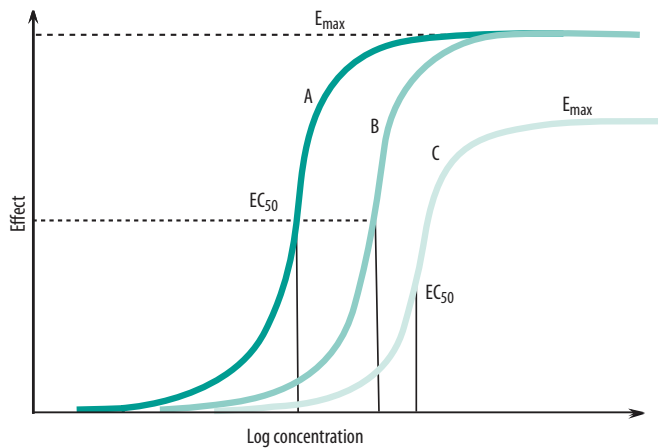
A6.2 Definition

Antimalarial drug resistance is defined as the ability of a parasite strain to survive and/or multiply despite the proper administration and absorption of an antimalarial drug in the dose normally recommended. Drug resistance to an antimalarial compound results in a right shift in the concentration-effect (dose-response) relationship (Fig. A6.1). As the pharmacokinetic properties of antimalarials vary widely in different individuals, the definition of resistance should probably also include a “normal” plasma concentration profile for the active drug concerned or, in the case of a prodrug (a drug that is not active in the ingested form and requires chemical conversion through metabolic processes to become pharmacologically active), a “normal” profile of the biologically active metabolite.

Antimalarial drug resistance is not necessarily the same as malaria “treatment failure”, which is a failure to clear malarial parasitaemia and/or resolve clinical symptoms despite the administration of an antimalarial. So while drug resistance may lead to treatment

failure, not all treatment failures are caused by drug resistance. Treatment failure can also be the result of incorrect dosing, problems of treatment adherence (compliance), poor drug quality, interactions with other drugs, compromised drug absorption, or misdiagnosis of the patient. Apart from leading to inappropriate case management, all these factors may also accelerate the spread of true drug resistance by exposure of the parasites to inadequate drug levels.

Figure A6.1 Drug resistance to an antimalarial compound showing a right shift in the concentration-effect (dose-response) relationship



Note: Resistance is a rightward shift in the concentration-effect relationship for a particular parasite population. This may be a parallel shift (B) from the “normal” profile (A) or, in some circumstances, the slope changes, and/or the maximum achievable effect is reduced (C).

A6.3 Emergence and spread of antimalarial resistance

The development of resistance can be considered in two parts: the initial genetic event, which produces the resistant mutant; and the subsequent selection process in which the survival advantage in the presence of the drug leads to preferential transmission of resistant mutants and, thus, the spread of resistance. In the absence of the antimalarial, resistant mutants may have a survival disadvantage. This “fitness cost” of the resistance mechanism may result in a decline in the prevalence of resistance once drug pressure is removed.

Resistance to one drug may select for resistance to another where the mechanisms of resistance are similar (cross-resistance). There are many parallels with antibiotic

resistance, in particular resistance to anti-tuberculosis drugs where, as for malaria, transferable resistance genes are not involved in the emergence of resistance (1–3). In experimental models, drug-resistant mutations can be selected without mosquito passage (i.e. without meiotic recombination) by exposure of large numbers of malaria parasites (either in vitro, in animals, or, as was done in the past, in volunteers) to sub-therapeutic drug concentrations (4).

Various factors determine the propensity for antimalarial drug resistance to develop (5):

- the intrinsic frequency with which the genetic changes occur;
- the degree of resistance (the shift in the concentration-effect relationship, figure A6.1) conferred by the genetic change;
- the fitness cost of the resistance mechanism;
- the proportion of all transmissible infections that are exposed to the drug (the selection pressure);
- the number of parasites exposed to the drug;
- the concentrations of drug to which these parasites are exposed;
- the pharmacokinetic and pharmacodynamic properties of the antimalarial;
- individual (dosing, duration, adherence) and community (quality, availability, distribution) patterns of drug use;
- the immunity profile of the community and the individual;
- the simultaneous presence of other antimalarials or substances in the blood to which the parasite is not resistant.

The emergence of resistance can be thought of in terms of the product of the probabilities of *de novo* emergence (a rare event) and subsequent spread. Resistant parasites, if present, will be selected when parasites are exposed to “selective” (sub-therapeutic) drug concentrations. “Selective” in this context means a concentration of drugs that will eradicate the sensitive parasites but will still allow growth of the resistant parasite population so that it eventually transmits to another person. Because *de novo* resistance arises randomly among malaria parasites, non-immune patients infected with large numbers of parasites who receive inadequate treatment (either because of poor drug quality, poor adherence, vomiting of an oral treatment, etc.) are a potent source of *de novo* resistance. This emphasizes the importance of correct prescribing, good adherence to prescribed drug regimens, and also provision of treatment regimens that are still highly effective in hyperparasitaemic patients. The principle specific immune response that controls the primary symptomatic infection in falciparum malaria is directed by the variant surface antigen (*PfEMP1*). The parasite population evades this immune response by switching its surface antigen in a specific sequence of changes. The probability of selecting a resistant parasite from the primary infection is the product of the switch rate and the rate of formation of viable resistant parasites.

The subsequent spread of resistant mutant malaria parasites is facilitated by the widespread use of drugs with long elimination phases. These provide a “selective filter”, allowing infection by the resistant parasites while the residual antimalarial activity prevents infection by sensitive parasites. Slowly eliminated drugs, such as mefloquine (terminal elimination half-life ($T_{1/2\beta}$) 2–3 weeks) or chloroquine ($T_{1/2\beta}$) 1–2 months), persist in the blood and provide a selective filter for months after drug administration has ceased.

A6.3.1 Transmission intensity and the selection and spread of resistance

The recrudescence and subsequent transmission of an infection that has generated a *de novo* resistant malaria parasite is essential for resistance to be propagated (5). Gametocytes carrying the resistance genes will not reach transmissible densities until the resistant biomass has expanded to numbers close to those producing illness (>107 parasites) (6). Thus, to prevent resistance spreading from an infection that has generated *de novo* resistance, gametocyte production from the recrudescing resistant infection must be prevented. There has been debate as to whether resistance arises more rapidly in low- or high-transmission settings (7, 8), but, aside from theoretical calculations, epidemiological studies clearly implicate low-transmission settings as the source of drug resistance. Chloroquine resistance and high-level sulfadoxine-pyrimethamine resistance in *P. falciparum* both originated in South-East Asia and, subsequently, spread to Africa (9).

In low-transmission areas, the majority of malaria infections are symptomatic and selection, therefore, takes place in the context of treatment. Relatively large numbers of parasites in an individual usually encounter antimalarials at concentrations that are maximally effective. But in a variable proportion of patients, for the reasons mentioned earlier, blood concentrations are low and may select for resistance.

In high-transmission areas, the majority of infections are asymptomatic and infections are acquired repeatedly throughout life. Symptomatic and sometimes fatal malaria occurs in the first years of life, but, thereafter, it is increasingly likely to be asymptomatic. This reflects a state of imperfect immunity (premunition), where the infection is controlled, usually at levels below those causing symptoms. The rate at which premunition is acquired depends on the intensity of transmission. In the context of intense malaria transmission, people still receive antimalarial treatments throughout their lives (often inappropriately for other febrile infections); but these “treatments” are largely unrelated to the peaks of parasitaemia, thereby reducing the probability of selection for resistance.

Immunity considerably reduces the emergence of resistance (9). Host defence contributes to a major anti-parasitic effect, and any spontaneously generated drug-resistant mutant malaria parasite must contend not only with the concentrations of antimalarial present but also with host immunity. This kills parasites regardless of their antimalarial resistance, and reduces the probability of parasite survival (independently of drugs) at all stages of

the transmission cycle. For the blood-stage infection, immunity acts in a similar way to antimalarials both to eliminate the rare *de novo* resistant mutants and to stop them being transmitted (i.e. like a combination therapy). It also improves cure rates with failing drugs (i.e. drugs falling to resistance), thereby reducing the relative transmission advantage of resistant parasites. Even if a resistant mutant does survive the initial drug treatment and multiplies, the chance that this will result in sufficient gametocytes for transmission is reduced as a result of asexual stage immunity (which reduces the multiplication rate and lowers the density at which the infection is controlled) and transmission-blocking immunity. Furthermore, other parasite genotypes are likely to be present in competition with the resistant parasites for red cells, which increases the possibility of out-breeding of multigenic resistance mechanisms or competition in the feeding anopheline mosquito (10).

The genetic events that confer antimalarial drug resistance (while retaining parasite viability) are spontaneous and rare. They are thought to be independent of the drug. The resistance mechanisms that have been described are mutations in genes or changes in the copy number of genes relating to the drugs target or pumps that affect intraparasitic concentrations of the drug. A single genetic event may be all that is required, or multiple unlinked events may be necessary (epistasis). *P. falciparum* parasites from South-East Asia seem constitutionally to have an increased propensity to develop drug resistance.

A6.3.2 Antimalarial pharmacokinetics and the selection of resistance

A6.3.2.1 Absorption and disposition

The probability of selecting a *de novo* mutation that is resistant to antimalarials during the initial phase of treatment depends on the per-parasite frequency of the genetic event, the number of parasites present, immunity in the infected individual, and the relationship between the drug levels achieved and the degree of resistance conferred by the mutant parasite. If the range of blood concentrations achieved in the patient considerably exceeds the concentrations giving 90% inhibition of multiplication (IC90 values) for the most resistant mutant (IC90R), then resistance cannot be selected in the acute phase of treatment as even the resistant mutants are prevented from multiplying. Conversely, if the degree of resistance provided by the genetic event is very small, the window of opportunity for selection may be negligible. Provided that there is such a window of selection, then the broader the range of peak antimalarial concentrations and the closer the median value approaches IC90R the greater the probability of selecting a resistant mutant in a patient.

Peak drug concentrations are determined by absorption, distribution volume and dose. Several antimalarials (notably lumefantrine, halofantrine, atovaquone and, to a lesser extent, mefloquine) are lipophilic, hydrophobic and very variably absorbed (inter-individual variation in bioavailability up to 20-fold) (11, 12). Inter-individual variation

in distribution volumes tends to be lower (usually less than fivefold) but, taken together with variable absorption, the outcome is considerable inter-individual variation in peak antimalarial blood concentrations. The main sources of underdosing globally are incorrect self-medication, because of poor adherence to the correctly prescribed drug regimen, poor quality drugs, uncontrolled drug availability and purchase of incorrect dose regimens, use of substandard drugs purchased in shops or markets, and incorrect administration in the home. The acute infection is the principal source of *de novo* resistance selection. Quality assured drugs, education, correct prescribing, good adherence, and optimized packaging and formulations, therefore, play pivotal roles in preventing the emergence of antimalarial drug resistance.

A6.3.2.2 Drug elimination rates

In some areas of the world, transmission intensities may be as high as three infectious bites per person per day. A person, in this context, who takes antimalarial treatment for symptomatic malaria exposes not only the parasites causing that infection to the drug, but it also exposes any newly acquired infections that emerge from the liver during the drug's elimination phase; the longer the terminal elimination half-life, the greater the exposure. The length of the terminal elimination half-life is an important determinant of the propensity for an antimalarial to select for resistance (13–15). Some rapidly eliminated antimalarials (e.g. artemisinin derivatives) never present an intermediate drug concentration to infecting malaria parasites, because they are eliminated completely within the two-day life-cycle of the asexual parasite. Others (e.g. mefloquine, chloroquine) have elimination half-lives of weeks or months, and they present a lengthy selection opportunity.

With the exception of the artemisinin derivatives, maximum antimalarial parasite reduction ratios (kill rates) do not exceed 1000-fold per cycle (16). Following hepatic schizogony, exposure of at least two asexual cycles (4 days) to therapeutic drug concentrations is, therefore, required to eradicate the blood-stage parasites emerging from the liver. Even with maximum kill rates in the sensitive parasites and maximum growth rates in the resistant parasites, the resistant parasites only “overtake” the sensitive parasites in the third asexual cycle. Thus, rapidly eliminated drugs (such as the artemisinin derivatives or quinine) cannot select during the elimination phase. Obviously, the greater the degree of resistance conferred by the resistance mutation (i.e. the higher the IC_{90R} relative to the IC₉₀ for susceptible parasites, IC_{90S}), the wider the window of selection opportunity.

Patent gametocyaemia is more likely in recrudescence than primary infections. Therefore, if *de novo* resistance arose in an acute symptomatic treated infection, the transmission probability from the subsequent recrudescence infection (bearing the new resistance genes) would be higher than from an infection newly acquired during the elimination phase of the antimalarial given for a previous infection. This is true even if it attained the same parasite densities (17).

A6.3.3 Spread of resistance

Several mathematical models have been devised to examine the spread of antimalarial drug resistance (10,15,18,19). Spread of resistance is determined by the reproductive advantage conferred by the resistance mechanism. This derives from the increased gametocyte carriage associated with treatment failure (both from the primary infection and from the subsequent recrudescences), the “donors”, and the selective pressure from residual concentrations of slowly eliminated antimalarial in potential recipients. A long elimination half-life results in long periods of post-treatment chemoprophylaxis.

Resistance encoded by multiple mutations at a single locus may occur in two overlapping phases: Phase 1 where the drug is better tolerated by the parasites, but the therapeutic doses still usually clear the infection; and Phase 2 where clinical failures start to occur. This second phase is very rapid, and it is essential that surveillance programmes are in place and capable of monitoring the change from the first to the second phase. Phase 1 may occur faster, in areas of high transmission, but the subsequent phase is slower. Combination therapy significantly slows the rate of evolution of resistance, but it should be instigated before significant resistance to either component is present.

A6.4 Prevention of resistance by use of combination therapy

The theory underlying combination treatment of tuberculosis, leprosy and HIV infection is well known, and it has recently been applied to malaria (4,5,18,20–23). If two drugs with different modes of action and, therefore, different resistance mechanisms are used in combination, then the per-parasite probability of developing resistance to both drugs is the product of their individual per-parasite probabilities.

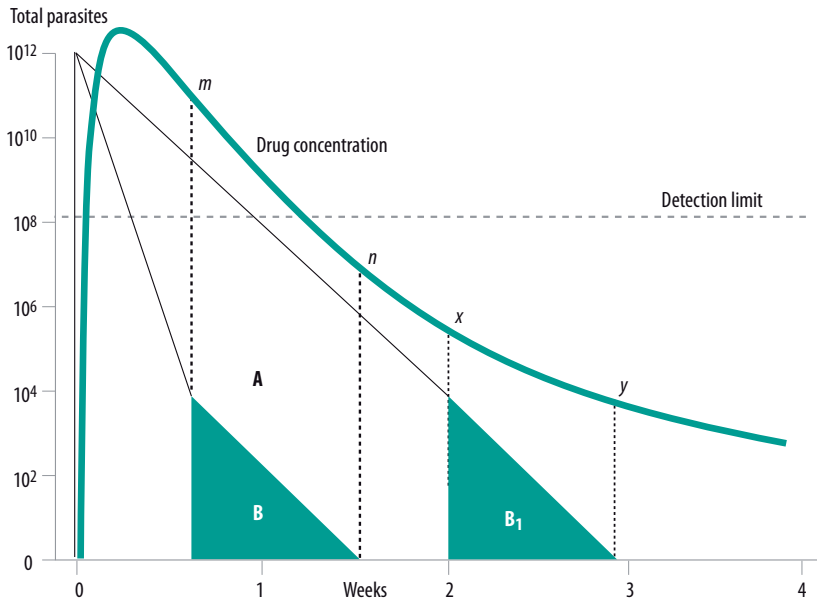
For example, if the per-parasite probabilities of developing resistance to drug A and drug B are both 1 in 1012, then a simultaneously resistant mutant will arise spontaneously in 1 in 1024 parasites. As it is postulated that there are approximately 1017 parasites in the entire world, and a cumulative total of less than 1020 in one year, such a simultaneously resistant parasite would arise spontaneously roughly once every 10 000 years – provided the drugs always confronted the parasites in combination. Thus, the lower the *de novo* per-parasite probability of developing resistance, the greater the delay in the emergence of resistance.

Stable resistance to the artemisinin derivatives has not yet been identified, and cannot yet be induced in the laboratory, which suggests that it may be very rare indeed. *De novo*

resistance to chloroquine is also very rare, and it appears to have arisen and spread only twice in the world during the first decade of intensive use in the 1950s (24). On the other hand, resistance to antifolate and atovaquone arises relatively frequently (e.g. antifolate resistance rose to high levels within two years of the initial deployment of proguanil in peninsular Malaya in 1947) and it can be induced readily in experimental models (14, 21). Against a background of chloroquine resistance, mefloquine resistance arose over a six-year period on the north-west border of Thailand (25). Artemisinin derivatives are particularly effective in combinations with other antimalarials because of their very high killing rates (parasite reduction rate around 10 000-fold per cycle), lack of adverse effects and absence of significant resistance (5).

The ideal pharmacokinetic properties for an antimalarial have been much debated. Rapid elimination ensures that the residual concentrations do not provide a selective filter for resistant parasites; but drugs with this property (if used alone) must be given for at least 7 days, and adherence to 7-day regimens is poor. In order to be effective in a 3-day regimen, elimination half-lives usually need to exceed 24 h. Combinations of artemisinin derivatives (which are eliminated very rapidly) given for 3 days, with a slowly eliminated drug, such as mefloquine, provide complete protection against the emergence of resistance to the artemisinin derivatives if adherence is good, but they do leave the slowly eliminated “tail” of mefloquine unprotected. Perhaps resistance could arise within the residual parasites that have not yet been killed by the artemisinin derivative. However, the number of parasites exposed to mefloquine alone is a tiny fraction (less than 0.00001%) of those present in the acute symptomatic infection. Furthermore, these residual parasites “see” relatively high levels of mefloquine and, even if susceptibility was reduced, these levels may be sufficient to eradicate the infection (Fig. A6.2). The long mefloquine tail does, however, provide a selective filter for resistant parasites acquired from elsewhere, and, therefore, contributes to the spread of resistance once it has developed. Yet on the north-west border of Thailand, an area of low transmission where mefloquine resistance had already developed, systematic deployment of the artesunate-mefloquine combination was dramatically effective in stopping resistance and also in reducing the incidence of malaria (25,26). This strategy is thought to be effective at preventing the *de novo* emergence of resistance at higher levels of transmission, where high-biomass infections still constitutes the major source of *de novo* resistance.

Figure A6.2 Effectiveness of artesunate plus mefloquine combination on parasite levels and resistance



Note: The artesunate plus mefloquine combination. If no artesunate is given, then the number of parasites exposed to mefloquine alone is given by the area of A; with the combination administered for 3 days the number of parasites exposed to mefloquine alone is given by the area of B (100 million times fewer). Furthermore, mefloquine levels are higher (m to n) when confronting B than when confronting the same number of parasites (B_1) if no artesunate is given (x to y). If a parasite containing a *de novo* mefloquine-resistant mutation were to occur, then such a parasite should still be susceptible to artesunate. Thus, the probability of selecting a resistant mutant is reduced by 100 million times; as only a maximum of 100 000 parasites are exposed to mefloquine alone after the fourth day (i.e. in the third cycle), and any artesunate-resistant parasite selected by artesunate initially would always be killed by the accompanying mefloquine. As a result, the combination is more effective, reduces transmission and prevents the emergence of resistance to both drugs.

A6.5 Monitoring of antimalarial drug resistance

A6.5.1 Monitoring methods

The rapid spread of antimalarial drug resistance over the last few decades has increased the need for monitoring in order to ensure proper management of clinical cases, allow

for early detection of changing patterns of resistance, and suggest where national malaria treatment policies should be revised. The monitoring procedures available include therapeutic efficacy testing (also known as *in vivo* testing). This involves the repeated assessment of clinical and parasitological outcomes of treatment during a fixed period of follow-up time to detect any reappearance of symptoms and signs of clinical malaria and/or parasites in the blood, which would indicate reduced parasite sensitivity with the particular drug. Other methods include *in vitro* studies of parasite susceptibility to drugs in culture and studies of point mutations or duplications in parasite resistance genes with molecular methods and antimalarial blood concentration measurement.

A6.5.2 Reporting of treatment failures

Reports of cases of treatment failure and decreased drug sensitivity have often provided important first evidence for more widespread resistance in an area. Although such evidence is subject to bias, it can be collected without much effort at peripheral health centres. If standardized and registered, such reports can make a valuable contribution to national early-warning systems; this facilitates cost-effective monitoring by national programmes.

A6.6 Criteria for antimalarial drug policy change

The WHO 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, as well as 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 other factors; these include: 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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ANNEX 7

UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA

The GRADE tables in this section are based on the Cochrane review titled *Artemisinin-based combination therapies for treating uncomplicated malaria* published in 2009 (1). This review was used to answer specific questions (relating to the current use of ACTs) for the WHO Expert Committee on Malaria. Evidence on the effectiveness of artemether plus lumefantrine in Africa, artesunate plus amodiaquine in Africa and artesunate plus mefloquine in Asia and South America is not presented here, as there were no new questions surrounding their use. An outline of the methodology of this review is given below.

Objective

To compare the effects of ACTs with other available ACT and non-ACT antimalarial combinations for treating uncomplicated *P. falciparum* malaria. This review was limited to ACTs for which co-formulated products are currently available or shortly to be made available. The included drugs were: dihydroartemisinin plus piperazine; artesunate plus mefloquine; artemether plus lumefantrine (six doses); artesunate plus amodiaquine, artesunate plus sulfadoxine-pyrimethamine and amodiaquine plus sulfadoxine-pyrimethamine.

Search methods

A search was conducted in August 2008 of The Cochrane Infectious Disease Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS and the metaRegister of Controlled Trials (mRCT), using “malaria” and “arte*” or “dihydroarte*” as search terms.

Inclusion criteria

Randomized head-to-head comparative trials of ACTs in the treatment of microscopically confirmed, uncomplicated *P. falciparum* malaria in adults and children.

Data collection and analysis

Two authors independently assessed trials for eligibility, risk of bias and extracted data. Primary outcome data was analysed in line with WHO’s protocol for the Assessment and monitoring antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria (2003) and drugs compared using risk ratios and 95% confidence intervals. Secondary outcomes were effects on *P. vivax*, gametocytes, haemoglobin and adverse events.

Results

A total of 47 trials met the inclusion criteria. All five ACT combinations were shown to have failure rates of < 10% in line with WHO recommendations.

A7.1 QUESTION:

Are ACTs superior to AQ+SP for treating *P. falciparum* malaria?

Background

AQ+SP was included as a recommended antimalarial in the first edition of the *WHOMalaria treatment guidelines* only as an interim measure if ACTs were unavailable.

GRADE approach

The benefits and harms of the currently recommended ACTs relative to AQ+SP were assessed using meta-analyses of head-to-head RCTs (search date: August 2008).

1. Is DHA+PPQ superior to AQ+SP for treating uncomplicated *P. falciparum* malaria in Africa? (see GRADE Table A7.1.1)
2. Is AS+MQ superior to AQ+SP for treating uncomplicated *P. falciparum* malaria in Africa? (see GRADE Table A7.1.2)
3. Is AL superior to AQ+SP for treating uncomplicated *P. falciparum* malaria in Africa? (see GRADE Table A7.1.3)
4. Is AS+AQ superior to AQ+SP for treating uncomplicated *P. falciparum* malaria in Africa? (see GRADE Table A7.1.4)

When assessing this evidence, the WHO GRADE panel considered the following factors to be important:

- it is a prerequisite that ACTs have a total failure rate of less than 10% (adjusted to exclude new infections);
- the recommendation concerns ACTs as a replacement for AQ+SP;
- in the absence of evidence to suggest important differences in serious adverse events, and in view of the potentially fatal consequences of inadequate treatment, the only outcome considered to be of critical importance was the PCR-adjusted failure rate;
- the relative effects on *P. vivax* were not considered in this decision-making.

Other considerations

The continued availability of AQ and SP as monotherapies is likely to lead to increased levels of resistance and shorten the useful lifespan of these drugs as partners to the artemisinin derivatives.

Decision

On the basis of these tables, the WHO GRADE panel made a **strong recommendation** that AQ+SP should no longer be recommended as a treatment for uncomplicated *P. falciparum* malaria.

GRADE Table A7.1.1
Is DHA+PPQ superior to AQ+SP for treating uncomplicated *P. falciparum* malaria in Africa?

Quality assessment		Summary of findings						Quality	Importance			
		No. of patients	Effect		Effect							
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	DHA + PPQ	AQ + SP	Relative risk (95% CI)	Absolute		
EFFICACY: total failure (<i>P. falciparum</i>) day 28 PCR adjusted ¹												
2	Randomized trial ²	No serious limitations ^{3,4}	No serious inconsistency ⁵	Serious ^{6,7}	No serious imprecision ⁸	None	14/408 (3.4%)	45/394 (11.4%)	RR 0.3 (0.17–0.54)	80 fewer per 1000 (from 52 fewer to 95 fewer)	MODERATE	CRITICAL
EFFICACY: total failure (<i>P. falciparum</i>) day 28 PCR unadjusted ¹												
2	Randomized trial ²	No serious limitations ³	No serious inconsistency ⁵	Serious ^{6,7}	No serious imprecision ⁸	None	28/422 (6.6%)	77/426 (18.1%)	RR 0.37 (0.25–0.55)	114 fewer per 1000 (from 81 fewer to 136 fewer)	MODERATE	IMPORTANT
TRANSMISSION POTENTIAL: gametocyte development (in those negative at baseline)												
1	Randomized trial	No serious limitations ⁹	Not applicable	Serious ^{6,11}	Very serious ¹⁰	None	7/184 (3.8%)	10/183 (5.5%)	RR 0.7 (0.27–1.79)	17 fewer per 1000 (from 40 fewer to 43 more)	VERY LOW	IMPORTANT
HARMS: serious adverse events (including deaths)												
1	Randomized trial	No serious limitations ⁹	Not applicable	Serious ¹¹	Very serious ¹²	None	0/187 (0%)	0/187 (0%)	Not estimable	Not estimable	VERY LOW	IMPORTANT
HARMS: early vomiting – not reported ¹³												
0	–	–	–	–	–	–	–	–	–	–	–	IMPORTANT

Panel comment: In one of these two trials (Rwanda), the total failure rate (PCR adjusted) with AQ+SP exceeded the maximum 10% that WHO recommends.

Panel conclusion: DHA+PPQ is more effective than AQ+SP at treating *P. falciparum* malaria (moderate quality evidence).

No difference has been shown in the effect on gametocytes (very low quality evidence).

No difference has been shown in the incidence of serious adverse events (very low quality evidence).

1. One trial (2) also reported treatment failure at day 42 and did not show a difference.
2. Burkina Faso (2) and Rwanda (3).
3. No serious limitations: allocation concealment was judged to be at “low risk of bias” in all trials that reported this outcome; laboratory staff were blinded to treatment allocation in one trial.
4. Please note that due to its longer half-life, treatment failure with DHA+PPQ may be underestimated at this point in time.
5. No serious inconsistency: heterogeneity was low.
6. Serious indirectness: due to variable resistance rates to AQ and SP, extrapolation of results to other areas is likely to be unreliable.
7. Trials conducted in Burkina Faso (holoendemic) and Rwanda (transmission not stated); children aged <6 months and pregnant or lactating women were excluded.
8. No serious imprecision: both limits of the 95% CI of the pooled estimate imply appreciable benefit with DHA+PPQ over AQ+SP.
9. No serious limitations: allocation concealment was adequate; the trial was unblinded.
10. Very serious imprecision: the 95% CI is wide including appreciable benefit or harm with each drug over the other.
11. Serious indirectness: only one trial reported this outcome (2).
12. Very serious imprecision: no events were recorded; it is unlikely that trials of this size would detect rare but important serious adverse events.
13. One trial (2) reports vomiting medication on day 0 (as an exclusion criteria not an outcome) and found no difference.

GRADE Table A7.1.2
Is AS+MQ superior to AQ+SP for treating uncomplicated *P. falciparum* malaria in Africa?

Quality assessment		Summary of findings							Quality	Importance		
		No. of patients		Effect								
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	AS + MQ	AQ + SP	Relative risk (95% CI)	Absolute		
EFFICACY: total failure day 28 PCR adjusted ¹												
1	Randomized trial ²	Serious ³	Not applicable	Serious ^{4,5}	Very serious ⁶	None	0/142 (0%)	0/154 (0%)	Not estimable	Not estimable	VERY LOW	CRITICAL
EFFICACY: total failure day 28 PCR unadjusted												
1	Randomized trial ²	Serious ³	Not applicable	Serious ^{4,5}	Very serious ⁷	None	2/144 (1.4%)	2/156 (1.3%)	RR 1.08 (0.15–59)	1 more per 1000 (from 11 fewer to 80 more)	VERY LOW	IMPORTANT
TRANSMISSION POTENTIAL: gametocyte carriage day 7												
1	Randomized trial ²	Serious ³	Not applicable	Serious ^{4,5}	No serious imprecision ⁸	None	0/145 (0%)	19/161 (11.8%)	RR 0.03 (0–0.47)	114 fewer per 1000 (from 63 to 118 fewer)	LOW	IMPORTANT
HARMS: serious adverse events (including deaths)												
1	Randomized trial	Serious ³	Not applicable	Serious ^{4,5}	Very serious ⁹	None	0/145 (0%)	0/161 (0%)	Not estimable	Not estimable	VERY LOW	IMPORTANT
HARMS: early vomiting – not reported												
0	–	–	–	–	–	–	–	–	–	–	–	IMPORTANT

Panel comment: This comparison has only been reported by one trial from Senegal, which had very few events and no conclusion can be made.

Panel conclusion: AS+MQ may be more effective on gametocytes than AQ+SP (low quality evidence).

1. Please note that due to its long half-life, treatment failure with AS+MQ may be underestimated at this point in time.
2. Senegal (4).
3. Serious limitations: allocation concealment was assessed as “unclear” and no blinding is described.
4. Serious indirectness: only one trial from Senegal reported this outcome; extrapolation of this result to other countries is likely to be unreliable.
5. Children aged < 1 year and pregnant or lactating women were excluded.
6. Very serious imprecision: there were no events in this trial.
7. Very serious imprecision: the 95% CI is wide including appreciable benefit and harm with each drug over the other.
8. No serious imprecision: both limits of the 95% CI imply appreciable benefit with AS+MQ over AQ+SP; at day 14 all participants in both groups had cleared their gametocytes.
9. Very serious imprecision: there were no serious adverse events in this trial; a trial of this size would be unlikely to detect rare but important serious adverse events.

GRADE Table A7.1.3
Is AL superior to AQ+SP for treating uncomplicated *P. falciparum* malaria in Africa?

Quality assessment		Summary of findings							Quality	Importance			
		No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations			No. of patients	Effect	
EFFICACY: total failure (<i>P. falciparum</i>) day 28 PCR adjusted – Africa (excluding Burkina Faso)¹													
3	Randomized trial ²	No serious limitations ^{3,4}	No serious inconsistency ⁵	Serious ^{6,7}	No serious indirectness	No serious imprecision ⁸	None	8/460 (1.7%)	67/459 (14.6%)	RR 0.12 (0.06–0.24)	128 fewer per 1000 (from 111 fewer to 137 fewer)	MODERATE	CRITICAL
EFFICACY: total failure (<i>P. falciparum</i>) day 28 PCR unadjusted – Africa (excluding Burkina Faso)													
4	Randomized trial ²	No serious limitations ^{3,4}	No serious inconsistency ⁵	Serious ^{6,7}	No serious indirectness	No serious imprecision ⁸	None	144/978 (14.7%)	398/971 (41%)	RR 0.35 (0.3–0.41)	267 fewer per 1000 (from 242 fewer to 287 fewer)	MODERATE	IMPORTANT
EFFICACY: total failure (<i>P. falciparum</i>) day 28 PCR adjusted – Burkina Faso⁹													
2	Randomized trial ¹⁰	No serious limitations ¹¹	No serious inconsistency ⁵	Very serious ¹²	Very serious ¹³	Very serious ¹³	None	10/360 (2.8%)	8/390 (2.1%)	RR 1.39 (0.55–3.47)	8 more per 1000 (from 9 fewer to 52 more)	VERY LOW	CRITICAL
EFFICACY: total failure (<i>P. falciparum</i>) day 28 PCR unadjusted – Burkina Faso													
2	Randomized trial ¹⁰	No serious limitations ¹¹	No serious inconsistency ⁵	Very serious ¹²	No serious indirectness	No serious imprecision ¹⁴	None	73/423 (17.3%)	22/404 (5.4%)	RR 3.17 (2.01–5.01)	117 more per 1000 (from 55 more to 217 more)	LOW	IMPORTANT
TRANSMISSION POTENTIAL: gametocyte carriage day 14¹⁵													
4	Randomized trial	Serious ¹⁶	No serious inconsistency ⁵	No serious indirectness	No serious imprecision ¹⁷	None	8/761 (1.1%)	19/775 (2.5%)	RR 0.46 (0.21–1.01)	13 fewer per 1000 (from 20 fewer to 0 more)	LOW	IMPORTANT	
HARMS: serious adverse events (including deaths)													
5	Randomized trial	No serious limitations ¹⁸	No serious inconsistency ⁵	No serious indirectness	Very serious ¹³	None	16/1319 (1.2%)	18/1365 (1.3%)	RR 1.08 (0.56–2.08)	1 more per 1000 (from 6 fewer to 14 more)	LOW	IMPORTANT	
HARMS: early vomiting – not reported¹⁹													
0	–	–	–	–	–	–	–	–	–	–	–	–	IMPORTANT

Panel comment:

Data from individual trials showed that failure rates with AQ+SP exceeded the WHO standard of 10% in two out of five trials.

Panel conclusion:

In most areas where it has been studied, AL is more effective than AQ+SP at treating *P. falciparum* malaria (moderate quality evidence).

AL is more effective on gametocytes than AQ+SP (low quality evidence).

No difference has been shown in the incidence of serious adverse events (low quality evidence).

1. Please note due to its longer half-life treatment, failure with AL6 may be underestimated at this point in time.
2. Rwanda (5), Senegal (4) and Uganda (6).
3. No serious limitations: allocation concealment was assessed as “low risk of bias” in two of the three trials; sensitivity analysis removing the trial with unclear concealment did not change the result substantially.
4. Only one trial had adequate blinding.
5. No serious inconsistency: heterogeneity was low.
6. Serious indirectness: there is considerable variability in the efficacy of AQ+SP, which makes extrapolation of results to other settings unreliable.
7. Trials were conducted in Uganda (mesoendemic), Rwanda (transmission not reported) and Senegal (moderate transmission). Children aged <6 months and pregnant or lactating women were excluded.
8. No serious imprecision: both limits of the 95% CI of the pooled estimate imply appreciable benefit with AL6 over AQ+SP.
9. Data was also available from one trial from Burkina Faso at day 42.
10. Burkina Faso (2,7).
11. No serious limitations: allocation concealment was assessed as “low risk of bias” in one trial and unclear in the other; one trial was blinded.
12. Very serious indirectness: the treatment failure rate with AQ+SP seems to be unusually low in Burkina Faso; this result should not be extrapolated to other countries.
13. Very serious imprecision: the 95%CI of the pooled estimate is wide including appreciable benefit and harm with each drug over the other.
14. No serious imprecision: both limits of the 95% CI of the pooled estimate imply appreciable benefit with AQ+SP over AL6.
15. Data was also available for day 7 where gametocyte carriage was significantly lower with AL6.
16. Serious limitations: two of the four trials had inadequate allocation concealment; removing these trials shifted the result significantly in favour of AL6.
17. Serious imprecision: the 95% CI of the pooled estimate includes appreciable benefit with AL6 and no difference between the two drugs.
18. No serious limitations: allocation concealment was assessed as “low risk of bias” in three trials.
19. Two trials reported vomiting of medication on day 0 (as an exclusion criteria not an outcome) and found no difference.

GRADE Table A7.1.4
Is AS+AQ superior to AQ+SP for treating uncomplicated *P. falciparum* malaria in Africa?

Quality assessment		Summary of findings						Effect	Quality	Importance		
		No. of patients	AS + AQ		AQ + SP		Relative risk (95% CI)					
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	AS + AQ	AQ + SP	Absolute			
EFFICACY: total failure (<i>P. falciparum</i>) day 28 PCR adjusted												
5	Randomized trial ¹	No serious limitations ²	Serious ³	No serious indirectness ⁴	Very serious ⁵	None	73/1137 (6.4%)	136/1020 (13.3%)	Not pooled	Not pooled	VERY LOW	CRITICAL
EFFICACY: total failure (<i>P. falciparum</i>) day 28 PCR unadjusted												
7	Randomized trial	No serious limitations ⁶	Serious ⁷	No serious indirectness ⁴	Very serious ⁵	None	635/2089 (30.4%)	718/1888 (38%)	Not pooled	Not pooled	VERY LOW	IMPORTANT
TRANSMISSION POTENTIAL: gametocyte carriage day 14												
3	Randomized trial	No serious limitations ⁸	Serious ⁷	No serious indirectness ⁴	Very serious ⁵	None	8/548 (1.5%)	13/346 (3.8%)	Not pooled	Not pooled	VERY LOW	IMPORTANT
HARMS: serious adverse events (including deaths)												
7	Randomized trial	No serious limitations ⁶	No serious inconsistency ⁹	No serious indirectness ⁴	Serious ¹⁰	None	20/2116 (0.9%)	35/1944 (1.8%)	RR 0.61 (0.36–1.03)	7 fewer per 1000 (from 12 fewer to 1 more)	MODERATE	IMPORTANT
HARMS: early vomiting – not reported												
0	–	–	–	–	–	–	–	–	–	–	–	IMPORTANT

Panel comment: The total failure rate (PCR corrected) with AQ+SP exceeded the WHO standard of 10% in three out of five trials but it was still performing well in Madagascar and Senegal. This variability in performance is likely to reflect variation in resistance to its components.

Panel conclusion: AS+AQ may be more effective at treating gametocytes than AQ+SP (at day 7 not day 14) (very low quality evidence). No difference has been shown in the incidence of serious adverse events (low quality evidence).

1. Madagascar (8), Rwanda (3), Senegal (4), Uganda (6,9).
2. No serious limitations: allocation concealment was assessed as “low risk of bias” in three trials; removing the trials with inadequate concealment did not substantially alter the result; laboratory staff were blinded to allocation in four trials.
3. Serious inconsistency: heterogeneity was high: AS+AQ performed better than AQ+SP in three trials, but AQ+SP was still performing well in Madagascar and Senegal.
4. No serious indirectness: trials were conducted in a variety of African countries. Children aged <6 months and pregnant or lactating women were excluded.
5. Very serious imprecision: data were not pooled; treatment effect is likely to vary between settings.
6. No serious limitations: allocation concealment was assessed as “low risk of bias” in five trials; removal of the trials with inadequate concealment did not substantially alter the result; laboratory staff were blinded to allocation in five trials.
7. Serious inconsistency: heterogeneity was high and so data were not pooled.
8. No serious limitations: allocation concealment was assessed as “low risk of bias” in two trials.
9. No serious inconsistency: heterogeneity was low.
10. Serious imprecision: the 95% CI of the pooled estimate include appreciable benefit with AS+AQ over AQ+SP and no difference between the two drugs.

A7.2 QUESTION:

Is three days of artesunate superior to one day in a combination regime for uncomplicated *P. falciparum* malaria?

GRADE Table A7.2.1
Is artesunate 3 days superior to artesunate 1 day in a combination regime for treating uncomplicated *P. falciparum* malaria?

Quality assessment	Summary of findings				Quality	Importance	
	No. of studies	No. of patients	Effect	Absolute risk			
No. of studies	5	AS 3 days 236/818 (28.9%)	AS 1 day 382/816 (46.8%)	Relative risk (95% CI) RR 0.62	Not pooled	VERY LOW CRITICAL	
Design	Randomized trial	No serious limitations ¹	No serious inconsistency	No serious indirectness ²	No serious imprecision ³	None	
EFFECT: parasitological failure (including re-infections) by day 28 (follow-up 28 days)							

1. No serious limitations: allocation concealment was adequate in five of the studies and unclear in the sixth (10).
2. No serious indirectness: five trials recruited both adults and children and one trial recruited children only.
3. No serious imprecision: the upper border of the 95% CI of the pooled estimate suggests appreciable benefit with artesunate.

A7.3 QUESTION:

Is DHA+PPQ an alternative to the recommended ACTs for treating *P. falciparum* malaria?

Background

DHA+PPQ is a relatively new antimalarial, which was not included as a recommended ACT in the first edition of the *WHO Malaria treatment guidelines*.

GRADE approach

The benefits and harms of DHA+PPQ were assessed using meta-analyses of head-to-head RCTs versus the currently recommended ACTs (search date: August 2008).

1. Is DHA+PPQ an alternative to AS+MQ for treating uncomplicated *P. falciparum* malaria in Asia and South America? (See GRADE Table A7.3.1.)
2. Is DHA+PPQ an alternative to AL6 for treating uncomplicated *P. falciparum* malaria worldwide? (See GRADE Table A7.3.2.)
3. Is DHA+PPQ an alternative to AS+AQ for treating uncomplicated *P. falciparum* malaria worldwide? (See GRADE Table A7.3.3.)

(There were no head-to-head comparisons of DHA+PPQ versus AS+SP.)

When assessing this evidence, the WHO GRADE panel considered the following factors to be important:

- it is a prerequisite that ACTs have a total failure rate of less than 10% (adjusted to exclude new infections);
- the recommendation concerns DHA+PPQ as an alternative, not a replacement, as there are benefits to having a range of available ACTs;
- in the absence of evidence to suggest important differences in serious adverse events, and in view of the potentially fatal consequences of inadequate treatment, the only outcome considered to be of critical importance was the PCR-adjusted failure rate;
- the relative effects on *P. vivax* were not considered in this decision-making.

Other considerations

Some concerns remain that the dose of dihydroartemisinin in the co-formulated product may be sub-optimal. At the time of publication, dihydroartemisinin plus piperaquine was not yet available as a product produced to GMP standards.

Decision

On the basis of these tables, the WHO GRADE panel made a **strong recommendation** that DHA+PPQ be added to the list of recommended ACTs for the treatment of uncomplicated *P. falciparum* malaria worldwide.

GRADE Table A7.3.1
Is DHA+PPQ an alternative to AS+MQ for treating uncomplicated *P. falciparum* malaria in Asia and South America?

Quality assessment		Summary of findings						Quality	Importance			
		No. of patients	Effect		Effect							
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	DHA + PPQ	AS + MQ	Relative risk (95% CI)	Absolute		
EFFICACY: total failure (<i>P. falciparum</i>) day 63 PCR adjusted – Asia ¹												
3	Randomized trial ²	No serious limitations ³	No serious inconsistency ⁴	No serious indirectness ⁵	No serious imprecision ⁶	None	10/604 (1.7%)	21/458 (4.6%)	RR 0.39 (0.19–0.79)	28 fewer per 1000 (from 10 fewer to 37 fewer)	HIGH	CRITICAL
EFFICACY: total failure (<i>P. falciparum</i>) day 63 PCR unadjusted – Asia ¹												
3	Randomized trial ²	No serious limitations ³	No serious inconsistency ⁴	No serious indirectness ⁵	No serious imprecision ⁶	None	73/667 (10.9%)	78/515 (15.1%)	RR 0.73 (0.54–0.98)	41 fewer per 1000 (from 3 fewer to 69 fewer)	HIGH	IMPORTANT
EFFICACY: total failure (<i>P. falciparum</i>) day 63 PCR adjusted – South America												
1	Randomized trial ⁷	No serious limitations ⁸	Not applicable	Serious ⁹	Very serious ¹⁰	None	4/211 (1.9%)	0/224 (0%)	RR 9.55 (0.52–176.35)	Not estimable	VERY LOW	CRITICAL
EFFICACY: total failure (<i>P. falciparum</i>) day 63 PCR unadjusted – South America												
1	Randomized trial ⁷	No serious limitations ⁸	Not applicable	Serious ⁹	No serious imprecision ¹¹	None	12/219 (5.5%)	2/226 (0.9%)	RR 6.19 (1.4–27.35)	47 more per 1000 (from 4 more to 237 more)	MODERATE	IMPORTANT
TRANSMISSION POTENTIAL: gametocyte development (in those negative at baseline)												
4	Randomized trial	No serious limitations ³	No serious inconsistency ⁴	No serious indirectness ¹²	No serious imprecision ¹¹	None	29/814 (3.6%)	8/635 (1.3%)	RR 3.01 (1.37–6.63)	26 more per 1000 (from 5 more to 73 more)	HIGH	IMPORTANT
HARMS: serious adverse events (including deaths)												
8	Randomized trial	No serious limitations ¹³	No serious inconsistency ⁴	No serious indirectness	Very serious ¹⁴	None	12/1465 (0.8%)	8/1152 (0.7%)	RR 0.9 (0.38–2.15)	1 fewer per 1000 (from 4 fewer to 8 more)	LOW	IMPORTANT
HARMS: early vomiting												
5	Randomized trial	Serious ¹⁵	No serious inconsistency ⁴	No serious indirectness	Serious ¹⁶	None	74/833 (8.9%)	88/785 (11.2%)	RR 0.87 (0.66–1.14)	15 fewer per 1000 (from 38 fewer to 16 more)	LOW	IMPORTANT

Panel comment: In these trials, both drugs have total failure rates (PCR adjusted) at day 63 of less than 10% in line with WHO recommendations.

Panel conclusion: DHA+PPQ is at least as effective at treating *P. falciparum* as AS+MQ in Asia (high quality evidence).

DHA+PPQ is not as effective on gametocytes as AS+MQ (high quality evidence).

No difference has been shown in the incidence of serious adverse events (low quality evidence).

1. Data on treatment failure at days 42 and 28 were also available and no differences between the two drugs were shown.
2. Cambodia (11) and Thailand (12, 13).
3. No serious limitations: allocation concealment was judged to be at "low risk of bias" in all trials reporting this outcome; laboratory staff were blinded in two of the trials.
4. No serious inconsistency: heterogeneity was low.
5. No serious indirectness: trials were conducted in Asia (Cambodia and Thailand) in areas of low and unstable transmission; children aged <1 year and pregnant or lactating women were excluded.
6. No serious imprecision: the 95% CI of the pooled estimate includes appreciable benefit with DHA+PPQ over AS+MQ and non-appreciable benefit.
7. Peru (14).
8. No serious limitations: allocation concealment was assessed as "low risk of bias"; no blinding was described in this trial.
9. Serious indirectness: only one trial, conducted in Peru in a low transmission setting; children aged <5 years and pregnant and lactating women were excluded.
10. Very serious imprecision: the 95% CI of the pooled estimate is wide including appreciable benefit or harm with each drug over the other.
11. No serious imprecision: both limits of the 95% CI suggest appreciable benefit with AS+MQ over DHA+PPQ.
12. No serious indirectness: trials conducted in Asia and South America in low and unstable transmission settings.
13. No serious limitations: allocation concealment was judged to be at "low risk of bias" in seven out of eight trials.
14. Very serious imprecision: the 95% CI of the pooled estimate includes appreciable benefit or harm with both drugs over the other.
15. Serious limitations: all trials were open label and judged to at "high risk of bias" for blinding.
16. Serious imprecision: the 95% CI of the pooled estimate includes appreciable benefit with DHA+PPQ over AS+MQ and no difference between the drugs.

GRADE Table A7.3.2
Is DHA+PPQ an alternative to AL6 for treating uncomplicated *P. falciparum* malaria worldwide?

Quality assessment		Summary of findings					Quality	Importance				
		No. of studies	No. of patients	Effect	Relative risk (95% CI)	Absolute						
Efficacy: total failure (<i>P. falciparum</i>) day 42 PCR adjusted ¹			DHA + PPQ	AL								
4	Randomized trial ²	No serious limitations ^{3,4}	No serious inconsistency ⁵	No serious indirectness ⁶	No serious imprecision ⁷	None	24/662 (3.6%)	48/524 (9.2%)	RR 0.42 (0.26–0.67)	53 fewer per 1000 (from 30 fewer to 68 fewer)	HIGH	CRITICAL
Efficacy: total failure (<i>P. falciparum</i>) day 42 PCR unadjusted ¹												
4	Randomized trial ²	No serious limitations ³	Serious ⁸	No serious indirectness ⁶	Serious ⁹	None	143/781 (18.3%)	235/711 (33.1%)	Not pooled	Not pooled	LOW	IMPORTANT
TRANSMISSION POTENTIAL: gametocyte development (in those negative at baseline)												
3	Randomized trial	No serious limitations ¹⁰	Very serious ¹¹	No serious indirectness ¹²	Very serious ¹³	None	25/555 (4.5%)	42/523 (8%)	Not pooled	Not pooled	VERY LOW	IMPORTANT
HARMS: serious adverse events (including deaths)												
4	Randomized trial	No serious limitations ³	No serious inconsistency ⁵	No serious indirectness ⁶	Very serious ¹⁴	None	10/992 (1%)	6/972 (0.6%)	RR 1.61 (0.59–4.41)	4 more per 1000 (from 2 fewer to 20 more)	LOW	IMPORTANT
HARMS: early vomiting												
2	Randomized trial	Serious ¹⁵	No serious inconsistency ⁵	No serious indirectness	Very serious ¹⁴	None	18/575 (3.1%)	13/572 (2.3%)	RR 1.38 (0.68–2.78)	9 more per 1000 (from 7 fewer to 41 more)	VERY LOW	IMPORTANT

Panel comment: In these trials both drugs have total failure rates (PCR adjusted) at day 42 of less than 10% in line with WHO recommendations.
Panel conclusion: DHA+PPQ is more effective at treating *P. falciparum* than AL6 (high quality evidence).
 No difference has been shown in the incidence of serious adverse events (low quality evidence).

1. Data is also available for treatment failure at day 28, but provides no further useful information.
2. Burkina Faso (2), Indonesia (15) and Uganda (16,17).
3. No serious limitations: allocation concealment was adequate in all trials; laboratory staff were blinded in three trials.
4. Please note that due to its longer half-life, treatment failure with DHA+PPQ may be underestimated at this point in time.
5. No serious inconsistency: heterogeneity was low.
6. No serious indirectness: trials were conducted in Africa (Burkina Faso and Uganda) and Asia (Indonesia) in areas of high, moderate and unstable transmission; children aged <6 months and pregnant or lactating women were excluded.
7. No serious imprecision: both limits of the 95% CI of the pooled estimate imply appreciable benefit with DHA+PPQ over AS+MQ.
8. Serious inconsistency: heterogeneity was high so data were not pooled; however, all trials favoured DHA+PPQ but the magnitude of this benefit was variable between settings.
9. Serious imprecision: the unpooled data suggest a significant but variable benefit with DHA+PPQ over AL6.
10. No serious limitations: allocation concealment was adequate in three trials; laboratory staff were blinded in two trials.
11. Serious inconsistency: heterogeneity was high so data were not pooled; two trials showed benefit with DHA+PPQ and one trial found no difference.
12. No serious indirectness: trials were conducted in Africa in moderate to high transmission settings.
13. Very serious imprecision: data not pooled.
14. Very serious imprecision: the 95% CI of the pooled estimate is wide including appreciable benefit and harm with each drug over the other.
15. Serious limitations: staff and participants were unblinded.

GRADE Table A7.3.3
Is DHA+PPQ an alternative to AS+AQ for treating uncomplicated *P. falciparum* malaria worldwide?

Quality assessment		Summary of findings						Quality	Importance			
		No. of patients		Effect		Other considerations	Relative risk (95% CI)					
No. of studies	Design	DHA + PPQ	AS + AQ	Imprecision	Indirectness			Inconsistency	Limitations	Imprecision	Indirectness	Inconsistency
EFFICACY: total failure (<i>P. falciparum</i>) day 28 PCR adjusted ¹												
2	Randomized trial ²	11/326 (3.4%)	22/303 (7.3%)	No serious imprecision ⁷	Serious ⁶	No serious inconsistency ⁵	No serious limitations ^{3,4}	None	RR 0.47 (0.23–0.94)	39 fewer per 1000 (from 4 fewer to 56 fewer)	MODERATE	CRITICAL
EFFICACY: total failure (<i>P. falciparum</i>) day 28 PCR unadjusted ¹												
2	Randomized trial ²	29/344 (8.4%)	54/335 (16.1%)	No serious imprecision ⁷	Serious ⁶	No serious inconsistency ⁵	No serious limitations ³	None	RR 0.53 (0.35–0.81)	76 fewer per 1000 (from 31 fewer to 105 fewer)	MODERATE	IMPORTANT
TRANSMISSION POTENTIAL: gametocyte carriage – not measured ⁸												
2	–	–	–	–	–	–	–	–	–	–	–	IMPORTANT
HARMS: serious adverse events (including deaths)												
1	Randomized trial	0/168 (0%)	3/166 (1.8%)	Very serious ¹⁰	Serious ⁹	Not applicable	No serious limitations ³	None	RR 0.14 (0.01–2.71)	15 fewer per 1000 (from 18 fewer to 31 more)	VERY LOW	IMPORTANT
HARMS: early vomiting												
1	Randomized trial	7/168 (4.2%)	13/166 (7.8%)	Very serious ¹⁰	Serious ⁹	Not applicable	Serious ¹¹	None	RR 0.53 (0.22–1.3)	37 fewer per 1000 (from 61 fewer to 23 more)	VERY LOW	IMPORTANT

Panel comment: In these trials, both drugs have total failure rates (PCR adjusted) at day 28 of less than 10% in line with WHO recommendations.

Panel conclusion: DHA+PPQ is at least as effective at treating *P. falciparum* as AS+AQ (moderate quality evidence). No difference has been shown in the incidence of serious adverse events (very low quality evidence).

1. One trial (18) also reported outcomes at day 42 but losses to follow-up were very high (>20%) at this point in time.
2. Indonesia (18) and Rwanda (3).
3. No serious limitations: allocation concealment was adequate in all trials that reported this outcome; laboratory staff were blinded in all trials.
4. Please note that due to its longer half-life, treatment failure with DHA+PPQ may be underestimated at this point in time.
5. No serious inconsistency: heterogeneity was low.
6. Serious indirectness: only one trial was conducted in Africa (Rwanda, transmission intensity not reported) and one in Asia (Indonesia, unstable transmission); children aged <1 year and pregnant or lactating women were excluded; due to variable resistance rates to amodiaquine, extrapolation to other areas is likely to be unreliable.
7. No serious imprecision: the 95% CI of the pooled estimate includes appreciable and non-appreciable benefit with DHA+PPQ over AS+AQ.
8. Both trials report that there were no significant differences in gametocyte carriage, but figures were not given.
9. Serious indirectness: only one trial (18) assessed this outcome.
10. Very serious imprecision: the 95% CI is wide including appreciable benefit or harm with each drug over the other.
11. Serious limitations: this trial was open label with no blinding of staff or participants.

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ANNEX 8

TREATMENT OF SEVERE *PLASMODIUM FALCIPARUM* MALARIA

The GRADE tables in this section are based on the Cochrane review titled “Artesunate versus quinine for treating severe malaria” published in 2007 (1). A brief outline of the methodology of this review is given below.

Objective

The goal is to compare artesunate with quinine for treating severe malaria.

Inclusion criteria

Randomized controlled trials comparing artesunate with quinine in adults and children with severe malaria who are unable to take medication by mouth.

Search methods

A search was conducted in December 2008 of The Cochrane Infectious Disease Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, ISI Web of Science and the metaRegister of Controlled Trials (mRCT) using “artesunate” and “quinine” as search terms. Conference proceedings were hand searched.

Data collection and analysis

Two authors independently assessed trials for eligibility, risk of bias and extracted data. Outcomes included death, neurological sequelae, coma recovery time, time to hospital discharge, fever clearance time and parasite clearance time, serious adverse effects, hypoglycaemia and other adverse effects. Drugs were compared using risk ratios for dichotomous data, weighted mean difference for continuous data and 95% confidence intervals.

Results

Six trials enrolling 1938 participants met the inclusion criteria. The results are presented below.

A8.1 QUESTION:**Is artesunate superior to quinine in treating severe malaria?****Background**

Artesunate was recommended as an alternative to quinine for treating severe malaria in the first edition of the *WHO guidelines for the treatment of malaria*.

GRADE approach

Artesunate was compared to quinine using meta-analyses of head-to-head RCTs (search date: January 2007).

1. Is artesunate superior to quinine in treating severe malaria? (See GRADE Table A8.1.)

When assessing this evidence the WHO GRADE panel considered the following factors to be important:

- all six studies included in the review were conducted in Asia;
- one large trial enrolling both adults and children provides most of the data but outcomes were not reported separately for children;
- most deaths from severe malaria occur in African children;
- children present with a different picture of severe malaria compared to adults;
- five trials used intravenous artesunate and one trial used intramuscular artesunate.

Other considerations

In contrast to quinine, administration of artesunate does not require cardiac monitoring and, therefore, may be a more practical option in resource-poor settings.

Decision

On the basis of these tables, the WHO GRADE panel made a **strong recommendation** that artesunate should be used in preference to quinine for the treatment of severe malaria in Asia.

GRADE Table A8.1.1
Is artesunate superior to quinine for treating severe malaria in endemic areas?

Quality assessment		Summary of findings					Effect		Quality		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	AS	QN	Relative risk (95% CI)	Absolute	Quality	Importance
EFFICACY: death											
6	Randomized trial	No serious limitations ¹	No serious inconsistency	No serious indirectness ²	No serious imprecision	133/975 (13.6%)	214/963 (22.2%)	RR 0.62 (0.51–0.75)	84 fewer per 1000 (from 56 to 109 fewer)	HIGH	CRITICAL
EFFICACY: neurological sequelae at discharge											
2	Randomized trial	No serious limitations ³	No serious inconsistency	Serious ⁴	Very serious ⁵	8/656 (1.2%)	3/597 (0.5%)	RR 2.21 (0.64–7.63)	6 more per 1000 (from 2 fewer to 33 more)	VERY LOW	CRITICAL
EFFICACY: time to hospital discharge (days)											
1	Randomized trial	Very serious ⁶	Not applicable ⁷	No serious indirectness	Very serious ⁵	59	54	–	MD 0.10 (–1.34 to 1.54)	VERY LOW	IMPORTANT
HARMS: hypoglycaemia (routine monitoring)											
2	Randomized trial	Serious ⁸	No serious inconsistency	Serious ⁹	No serious imprecision	12/96 (12.5%)	24/89 (27%)	RR 0.46 (0.25–0.87)	146 fewer per 1000 (from 35 fewer to 203 fewer)	LOW	CRITICAL

Panel comment: There is very little evidence of artesunate versus quinine in children.

Panel conclusion: Intravenous artesunate is more effective at reducing deaths in severe malaria (high quality evidence).

No difference was shown in the rate of neurological sequelae (very low quality evidence).

Artesunate may result in less hypoglycaemia (low quality evidence).

1. No serious limitations: two out of six trials had inadequate allocation concealment; however, the panel chose not to downgrade for this as a sub-group, analysis excluding these trials did not affect the significance of the result or the absolute magnitude of the effect.
2. No serious indirectness: four trials enrolled adults only, one trial enrolled only children and one large trial enrolled children and adults; in a total of 1938 participants, 1664 were adults and 274 were children; a sub-group analysis of trials which only enrolled adults did not affect the significance of this result and it was, therefore, decided not to downgrade this outcome on the basis of indirectness.
3. No serious limitations: this large RCT was open label although allocation concealment was classified as adequate; of the 10 patients discharged from hospital with residual neurological sequelae, five had psychiatric sequelae, four had persisting problems with balance (one of whom had psychiatric sequelae and tremor) and two had hemiparesis; it was felt that these adverse events were minimally subjective and it was, therefore, decided not to downgrade due to absence of blinding.
4. Serious indirectness: one large trial enrolled both adults and children and one trial enrolled only children; 1259 out of 1533 participants were adults but it was not reported how many adults had data for this outcome; adults are less likely to develop neurological sequelae than children.
5. Very serious imprecision: the 95% CI of the pooled estimate includes appreciable benefit with both artesunate and quinine.
6. Very serious limitations: this trial used inadequate allocation concealment and was open label.
7. Not applicable: only one trial.
8. Serious limitations: one of the two trials used inadequate allocation concealment and was open label.
9. Serious indirectness: one trial enrolled only adults and one trial enrolled only children; 85 participants were adults and 72 were children, but it was not reported how many adults had data for this outcome.

A8.2 QUESTION:

Is a loading dose of quinine (20 mg/kg) superior to no loading dose?

Summary

One systematic review, and one subsequent randomized controlled trial in children, found no significant difference in mortality between quinine regimens with a high initial quinine dose and those with no loading dose. However, parasite and fever clearance times were reduced in the former.

Benefits

One systematic review (search date: 2002, three RCTs, 92 people) (2). One subsequent RCT (3).

The systematic review found no significant difference in mortality between a group receiving a high initial dose of quinine (20 mg salt/kg or 16 mg base/kg given by the intramuscular route or by intravenous infusion) followed by a standard dose of quinine, and one receiving the standard dose but no loading dose (two RCTs, 2/35 (5.7%) died in the group receiving a high initial dose, 5/37 (13.5%) with no loading dose; relative risk: 0.43, 95% CI 0.09–2.15) (2). One of the RCTs (39 children) found no significant difference between the two groups in mean time to recover consciousness (14 h with a high initial dose, 13 h with no loading dose, weighted mean difference (WMD) 1.0 h, 95% CI –8.8 h to +10.8 h) (4). Parasite clearance and fever clearance times were shorter for the high initial dose group than for the group with no loading dose (parasite clearance time: two RCTs, 67 people, WMD 7.4 h, 95% CI –13.2 h to –1.6 h; fever clearance time, two RCTs, 68 people, WMD –11.1 h, 95% CI –20.0 h to –2.2 h). The subsequent RCT (72 children aged 8 months–15 years in Togo, 1999–2000) found no significant difference between the group receiving a high initial dose of IV quinine (20 mg salt/kg over 4 h, then 10 mg salt/kg every 12 h) and that receiving no loading dose (15 mg salt/kg every 12 h) in mortality (2/35 (6%) with a high initial dose, 2/37 (5%) with no loading dose, RR 1.06, 95% CI 0.16–7.1) (3). It also found no significant difference between the two groups for recovery of consciousness (35.5 h with a high initial dose, 28.6 h with no loading dose, WMD +6.9 h, 95% CI –0.6 h to +14.4 h) or time to 100% parasite clearance (48 h compared with 60 h).

Harms

The systematic review found no significant difference between the groups receiving a high initial dose of quinine and no loading dose in rate of hypoglycaemia (two RCTs, 4/35 (11%) hypoglycaemia with a high initial dose, 3/37 (8%) with no loading dose, RR 1.39, 95% CI 0.32–6.00) (2). In one RCT (33 people) included in the review, transient partial hearing loss was significantly increased in the group receiving a high initial dose (10/17 (59%) compared with 3/16 (19%), RR 3.14, 95% CI 1.05–9.38) (5). In another RCT (39 children), there was no significant difference between the two groups in neurological

sequelae (1/18 (6%) with a high initial dose, 2/21 (10%) with no loading dose, RR 0.58, 95% CI 0.06–5.91) (4).

A8.3 QUESTION:

Is intramuscular quinine as effective as intravenous quinine?

Summary

One RCT in children found no significant difference between IM and IV quinine in recovery times or death. However, the study may have lacked the power to detect clinically important differences between treatments.

Benefits

No systematic review. One RCT (59 children aged < 12 years, Kenya, 1989–1990), which compared IM quinine (20 mg salt/kg loading immediately followed by 10 mg salt/kg every 12 h) and with standard-dose quinine given by IV infusion (10 mg salt/kg every 12 h) in severe falciparum malaria (4). The trial found no significant difference in mortality, mean parasite clearance time or recovery time to drinking or walking, but may have lacked the power to detect a clinically important difference (mortality: 3/20 (15%) deaths with IM quinine, 1/18 (5.6%), with IV quinine, RR 2.7, 95% CI 0.3–23.7; mean parasite clearance time: 57 h compared with 58 h, WMD –1.0 h, 95% CI –12.2 h to +10.2 h; mean recovery times to drinking 47 h compared with 32 h, WMD +15 h, 95% CI –5.6 h to +35.6 h; mean recovery times to walking 98 h compared with 96 h, WMD +2.0 h, 95% CI –24.5 h to +28.5 h).

Harms

Neurological sequelae were reported in two children in the IM group, and one child in the IV group had transient neurological sequelae that were not specified 2/20 (10%) compared with 1/18 (5.6%), RR 1.8, 95% CI 0.2–18.2 (4).

A8.4 QUESTION:

Is intramuscular artemether as effective as intravenous quinine?

Summary

Two systematic reviews and three subsequent RCTs found no significant difference in death rates between the groups receiving artemether and quinine for severe malaria.

Benefits

Two systematic reviews (6,7) and three subsequent RCTs (8–10). The first review (search date not reported, seven RCTs, 1919 adults and children) analysed individual participant data (6). It found no significant difference in mortality between IM artemether and quinine given by IV infusion or IM injection (the latter in one RCT only) in severe falciparum malaria (mortality 136/961 (14%) with artemether, 164/958 (17%) with quinine; odds ratio 0.80, 95% CI 0.62–1.02). Parasite clearance was faster with artemether than with quinine (OR 0.62, 95% CI 0.56–0.69). The review found no significant difference in the speed of coma recovery, fever clearance time or neurological sequelae between artemether and quinine (coma recovery time OR 1.09, 95% CI 0.97–1.22; fever clearance time OR 1.01, 95% CI 0.90–1.15; neurological sequelae, OR 0.82, 95% CI 0.59–1.15).

The second review (search date: 1999, 11 RCTs, 2142 people) found a small significant reduction in mortality for IM artemether compared with IV quinine (OR 0.72, 95% CI 0.57–0.91) (7). However, more rigorous analysis excluding three poorer quality trials found no significant difference in mortality (OR 0.79, 95% CI 0.59–1.05). The review found no significant difference in neurological sequelae at recovery between the artemether and quinine groups (OR 0.8, 95% CI 0.52–1.25).

The first subsequent RCT (105 people aged 15–40 years with cerebral malaria in Bangladesh) compared IM artemether (160 mg initially, then 80 mg/kg once daily) with IV quinine (loading dose 20 mg/kg, then 10 mg/kg every 8 h) (8). It found no significant difference in death rates between the artemether and quinine groups (9/51 (18%) compared with 10/54 (19%), OR 0.94, 95% CI 0.35–2.55). Mean fever clearance time and coma recovery time were significantly longer for artemether than for quinine (fever clearance time 58 h compared with 47 h, WMD 11.0 h, 95% CI 1.6–20.4 h; coma recovery time 74 h compared with 53 h, WMD 20.8 h, 95% CI 3.6–38.0 h). There was no significant difference in mean parasite clearance time between artemether and quinine (52 h compared with 61 h, WMD –8.6 h, 95% CI –22.5 h to +5.3 h).

The second subsequent RCT (41 children with severe malaria in Sudan, 40 analysed) compared IM artemether (3.2 mg/kg loading dose, then 1.6 mg/kg once a day) with IV quinine (loading dose 20 mg/kg, then 10 mg/kg every 8 h) (11). It found that artemether significantly increased fever clearance time but found no significant difference between artemether and quinine in time to parasite clearance (mean fever clearance time 30.5 h with artemether, 18 h with quinine, $P = 0.02$; mean parasite clearance time 16 h compared with 22.4 h, $P > 0.05$). There were no deaths in the artemether group, one child died with quinine (0/20 (0%) compared with 1/21 (5%), P value not reported).

The third subsequent RCT (77 comatose children aged 3 months–15 years with cerebral malaria) compared IM artemether (1.6 mg/kg every 12 h) with IV quinine (10 mg/kg every 8 h) (10). It found no significant difference in death rates between the artemether and quinine groups (3/38 (8%) compared with 2/39 (5%), P value not reported). There

was no significant difference between the two groups in mean fever clearance time, coma recovery time and parasite clearance time (fever clearance time 31 h compared with 36 h; coma recovery time 21 h compared with 26 h; parasite clearance time 36 h compared with 41 h; *P* values not reported for any comparison).

Harms

The two systematic reviews (6, 7) and one of the subsequent RCTs (4) found no significant difference in neurological sequelae between the artemether and quinine groups (systematic reviews, see the Benefits section; subsequent trial 3/51 (6%) with artemether, 1/54 (2%) with quinine, RR 3.18, 95% CI 0.34–29.56). However, in the first review, rates for the combined outcome of death or neurological sequelae were lower for artemether than for quinine (OR 0.77, 95% CI 0.62–0.96, *P* = 0.02) (6).

The second subsequent RCT found that one child treated with quinine developed hypoglycaemia (0/20 (0%) with artemether, 1/21 (5%) with quinine (9). It reported no neurological problems in either treatment group after 28 days of follow-up.

The third subsequent RCT found no significant difference in transient neurological sequelae between the artemether and quinine groups (2/38 (5%) compared with 1/39 (3%) (10).

Comment

The third subsequent randomized controlled trial did not use loading doses of either artemether or quinine at the beginning of treatment (10). There was a fourth subsequent RCT (52 people); however, it was not clear whether the participants had severe malaria and the outcomes were poorly reported.

A8.5 QUESTION:

Pre-referral treatment with rectal artesunate: should rectal artesunate be used in preference to quinine?

Summary

There are no data from trials with sufficient statistical power to assess differences in mortality following treatment with rectal artesunate and quinine in people with moderate or severe malaria. The objective of the trials that have been conducted was to establish the safety and efficacy of rectal artesunate as pre-referral treatment where there is no access to parenteral treatment. Comparisons between rectal artesunate and IV artesunate or IV and IM quinine have been carried out to assess parasitological and clinical response in the 12 or 24 h immediately after treatment (11, 12).

Benefits

Two randomized, open-label Phase II and three randomized open label Phase III studies have been conducted in people with moderately severe malaria, i.e. patients who could not take drugs by mouth but did not have features of severe malaria and its complications (11,12). Patients in the artesunate group in the Phase III studies were rescued if their parasitaemia did not decline to below 60% of baseline parasitaemia or if they deteriorated clinically and developed features of severe malaria, convulsions or coma within 24 h of treatment.

Artesunate had a superior effect in all efficacy measures immediately after treatment. In children treated with artesunate, 80/87 (92%) had a parasite density lower than 60% of baseline, compared with 3/22 (14%) of those who received quinine (RR 0.09, 95% CI 0.04–0.19, $P < 0.0001$). In adults, parasitaemia at 12 h was lower than 60% of baseline in 26/27 (96%) in the artesunate group, compared with 3/8 (38%) in the quinine group (RR 0.06, 95% CI 0.01–0.44, $P < 0.001$). The differences were more significant at 24 h. Artesunate and/or dihydroartemisinin were detected in plasma within 12 h in all adults and in 84/87 of the children.

Harms

A single administration of artesunate suppositories at a dose of 10 mg/kg was well tolerated in both children and adults. There was no significant difference in frequency of adverse events (defined as any new symptom, worsening of any existing symptom, sign or abnormal laboratory value) between treatment groups. Other than local reactions at the site of the IM quinine injection in three adult patients, the few adverse events that occurred could have been attributable to falciparum malaria or to pre-existing disease.

A8.6 QUESTION:

Should dexamethasone be given routinely?

Summary

One systematic review found no significant difference in mortality between dexamethasone and placebo, but gastrointestinal bleeding and seizures were more common with dexamethasone.

Benefits

One systematic review (search date: 1999, two RCTs, 143 people with severe/cerebral malaria treated with quinine) compared dexamethasone with placebo over 48 h (13). One

RCT was conducted in Indonesia, the other in Thailand. The review found no significant difference in mortality (14/71 (20%) with dexamethasone, 16/72 (25%) with placebo, RR 0.89, 95% CI 0.47–1.68). One RCT found a longer mean time between start of treatment and coma resolution with dexamethasone (76.0 h compared with 57.0 h, $P < 0.02$) (14), but the other found no significant difference (83.4 h compared with 80.0 h, WMD +3.4 h, 95% CI –31.3 h to +38.1 h) (15).

Harms

The review found that dexamethasone significantly increased gastrointestinal bleeding and seizures compared with placebo (gastrointestinal bleeding 7/71 (10%) with dexamethasone, 0/72 (0%) with placebo, RR 8.17, 95% CI 1.05–63.6; seizures 1/71 (15.5%) compared with 3/72 (4%), RR 3.32, 95% CI 1.05–10.47) (13).

Comment

No effect of the steroid on mortality was shown, but the trials were small. Its effect on disability was not reported.

A8.7 QUESTION:

Should phenobarbital be given to patients?

Cochrane Review, search date: 2004 (16). Three RCTs with a total of 573 participants met the inclusion criteria. All three compared phenobarbital with placebo or no treatment. In the two trials with adequate allocation concealment, death was more common in the anticonvulsant group (RR 2.0, 95% CI 1.20–3.33, fixed effect model). In all three trials, phenobarbital was associated with fewer convulsions than placebo or no treatment (RR 0.30, 95% CI 0.19–0.45, fixed effect model).

A8.8 References

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ANNEX 9

TREATMENT OF *PLASMODIUM VIVAX*, *P. OVALE* AND *P. MALARIAE* INFECTIONS

A9.1 Introduction

Plasmodium vivax is the second major human malaria species; estimates of its contribution to the malaria cases worldwide range from 8–41% (1,2,3), and it is the dominant species of malaria in many areas outside Africa. It is prevalent in the Middle East, Asia, the Western Pacific and Central and South America. It is rarer in Africa and almost absent from West Africa due to the high prevalence of the Duffy negative phenotype (3). In most areas where *P. vivax* is prevalent, malaria transmission rates are low and, therefore, the affected populations achieve only a partial immunity to this parasite. Consequently, people of all ages, adults and children alike, are at risk of acquiring *P. vivax* infections (3). Where both *P. falciparum* and *P. vivax* prevail, the incidence rates of *P. vivax* tend to peak in people of a younger age than those of *P. falciparum* (4). The other two human malaria parasite species, *P. malariae*, which is prevalent at low levels in nearly all malaria endemic areas of the world, and *P. ovale*, which has the most limited distribution of all the species and is prevalent in Africa, New Guinea and the Philippines (5).

Among the four species of *Plasmodium* that affect humans, only *P. vivax* and *P. ovale* have the ability to form hypnozoites (dormant parasite stages in the liver that can result in relapse infections weeks to months after the primary infection). *P. vivax* preferentially invades reticulocytes, and this may lead to anaemia. Repeated infections lead to a chronic anaemia that can be debilitating, thereby impairing human and economic development in affected populations. In areas where both *P. falciparum* and *P. vivax* co-exist, intensive malaria control efforts often result in having a rapid and major impact on *P. falciparum* (leaving *P. vivax* as the residual malaria burden, as it is more resilient to interventions). As a result *P. vivax* is increasing in some regions of the world (3). Appropriate case management of *P. vivax* malaria will help to minimize the global malaria burden.

Although *P. vivax* has been traditionally known to be benign malaria, it causes a severe and debilitating febrile illness. Vivax malaria can also result in severe disease with life-threatening end-organ involvement similar to severe and complicated *P. falciparum* malaria illness. Recent studies in Papua province, Indonesia (6), and Papua New Guinea (7) highlight *P. vivax* as a major cause of malaria morbidity and mortality, particularly in young infants and children, accounting for nearly as high a proportion of severe malaria

episodes in this age group as *P. falciparum*. Severe vivax malaria presents as wide a range of pathologies as is seen in severe *P. falciparum* malaria ranging from toxic shock and cerebral malaria to multiple organ failure (8, 9). During pregnancy, infection with *P. vivax*, as with *P. falciparum*, reduces birth weight due to chronic anaemia, sequestration and pro-inflammatory cytokines in the placenta (10–12), and increases the risk of neonatal death. In primigravidae, the reduction is approximately two thirds that associated with *P. falciparum*, but the effect does not appear to decline with successive pregnancies; indeed, in the one large series in which this was studied, it increased (12).

A9.2 Diagnosis

Diagnosis of vivax malaria is based on microscopy. Rapid diagnostic tests based on immunochromatographic methods are available for the detection of non-falciparum malaria. However, their sensitivities for detecting parasitaemias of $\leq 500/\mu\text{l}$ are low (13–20). The relatively higher cost of *P. vivax* tests compared to those for *P. falciparum* is a further impediment to their large-scale use in endemic areas. Molecular markers for genotyping *P. vivax* parasites are available for the dihydrofolate reductase (*dhfr*) gene, and those for chloroquine resistance are under development.

A9.3 Treatment

The objectives of treatment of vivax malaria are twofold: to terminate the acute blood infection, to cure the clinical symptoms, and to clear hypnozoites from the liver to prevent future relapses. This is known as a radical cure.

Before 2004, there were relatively few studies on the treatment of *P. vivax*. Only 11% of the 435 published antimalarial drug trials have been on *P. vivax* malaria (21). Thereafter, there have been several trials on the efficacy of artemisinin-based combination therapies for the treatment of vivax malaria (22–24).

A9.3.1 Standard oral regimen

Chloroquine monotherapy (25 mg base/kg body weight over 3 days) is recommended as the standard treatment for vivax malaria, because the parasite remains sensitive to chloroquine in much of the world. Primaquine (0.25 or 0.5 mg base/kg body weight in a single daily dose for 14 days) is used as a supplement to the standard treatment for the purpose of eradicating dormant parasites in the liver and preventing relapses. Although shorter 5-day

courses of primaquine have been deployed in the past, evidence indicates that a 14-day regimen is superior in preventing relapses (25, 26). The optimal dose of primaquine differs in geographical areas, depending on the relapsing nature of the infecting strain, and it remains unclear in patients of heavy body weight (27). This combination of chloroquine and primaquine constitutes treatment to achieve radical cure of vivax malaria.

Primaquine also has weak activity against blood stage parasites. The radical cure regimen of vivax malaria with chloroquine and primaquine, therefore, conforms to the definition of a combination therapy. The combination of any antimalarial against *P. vivax* infections with primaquine has improved cure rates (22–24, 28, 29), and it is, therefore, useful in the treatment of chloroquine-resistant *P. vivax* infections.

A9.3.2 Treatment of chloroquine-resistant *P. vivax*

Therapeutic efficacy data available to date indicate that *P. vivax* remains sensitive to chloroquine throughout most of the world (22,30–44) with the exception of Indonesia where high therapeutic failure rates ranging from 5–84% have been reported on day 28 of follow-up (22,29,45–50). There are reports of chloroquine failure as both treatment and prophylaxis against *P. vivax* malaria from several other countries and regions where the species is endemic (51–54). Some of these studies did not measure chloroquine drug concentrations, so that it is questionable whether these findings represented strictly defined chloroquine resistance (35,39,40,42,44,55–58).

Antimalarials that are effective against *P. falciparum* are generally effective against the other human malarias. The exception to this is sulfadoxine-pyrimethamine to which *P. vivax* is commonly resistant. Owing to the high prevalence of *dhfr* mutations in *P. vivax* (*Pvdhfr*), resistance to sulfadoxine-pyrimethamine develops faster in this parasite than in *P. falciparum*, and resistant *P. vivax* become prevalent in areas where this drug is used for the treatment of falciparum malaria (38,59–67).

Artemisinins, when combined with an effective partner medicine, have provided excellent cure rates in both chloroquine sensitive and chloroquine resistant strains of *P. vivax*, as recent following evidence indicates: AL produces comparable cure rates to CQ in the treatment of *P. vivax* which is sensitive to CQ (68,69). In areas of CQ resistance, two ACTs, DHA+PPQ (70, 71) and AS+AQ (70), in combination with primaquine, have provided high cure rates. ACTs with partner medicines that have longer half-lives, such as DHA+PPQ, are more effective in reducing relapses than those with shorter half-lives (70, 71).

Other monotherapies that have been tested for the treatment of *P. vivax* malaria with varying degrees of efficacy including amodiaquine (25–30 mg base/kg body weight given over 3 days), which has been used effectively for the treatment of chloroquine-resistant vivax malaria (72) and has been well tolerated (73–75). The risk of relapse of *P. vivax* malaria without primaquine therapy ranged from 5–80% or more, depending largely upon the

geographic location and, therefore, primaquine must be added for radical cure. Mild nausea, vomiting and abdominal pain are the commonly reported adverse reactions (75).

- **Mefloquine** (15 mg base/kg body weight as a single dose) has been found to be highly effective with a treatment success of 100% (38).
- **Doxycycline** alone (100 mg twice a day for 7 days) provides poor cure rates in *P. vivax* (47).
- **Artemisinin derivatives**, such as monotherapy for 3–7 days, have shown poor efficacy in vivax malaria with day 28 cure rates of 47–77% (23,38,56). The addition of primaquine to these regimes improved the day 28 cure rates to 100% (23,76).
- **Quinine** (10 mg salt/kg body weight three times a day for 7 days) (72) is also effective against CQ resistant *P. vivax*, but it is not an ideal treatment because of its toxicity and consequent poor adherence to this regimen. A study in Thailand has found that treatment of vivax malaria with quinine leads to early relapses. This may be because quinine has a short half-life, and no antihypnozoite activity (38).

The best combinations for the treatment of *P. vivax* are those containing primaquine when given in antihypnozoite doses (28,30,38,40,57,75,77,78).

The recommended treatments for CQ resistant *P. vivax* are, therefore, ACTs (with the exception of AS+SP) combined with primaquine at antihypnozoite doses (see below).

Unlike *P. falciparum*, *P. vivax* cannot be cultured continuously in vitro: so it is more difficult to determine the in vitro sensitivity of *P. vivax* to antimalarials. In vivo assessment of the therapeutic efficacy of drugs against *P. vivax* malaria is also compounded by difficulties in distinguishing recrudescences due to drug-resistant infections from relapses. The interval between the primary and repeat infection can serve as a general guide. If the recurrence appears within 16 days of starting treatment of the primary infection, it is almost certainly a recrudescence due to therapeutic failure. A recurrence between days 17 and 28 may be either a recrudescence by chloroquine-resistant parasites or a relapse. Beyond day 28, any recurrence probably represents a relapse in an infection of chloroquine-sensitive *P. vivax* (79). A recurrent vivax parasitaemia in the presence of chloroquine blood levels exceeding 100 ng/ml, and a parasite genotype identical with the primary infection as detected by polymerase chain reaction, are more suggestive of chloroquine resistance to the primary infection than a relapse infection.

A9.3.3 Preventive therapy for relapses

Primaquine is the only available and marketed drug that can eliminate the latent hypnozoite reservoirs of *P. vivax* and *P. ovale* that cause relapses. *P. vivax* populations emerging from hypnozoites commonly differ from the populations that caused the acute episode (69).

There is no evidence that treatment courses shorter than 14 days are effective in preventing relapses (40,57,80,81). Although 5-day courses of primaquine have been deployed as anti-relapse therapy in some countries in the past, evidence shows that the 14-day course is superior in efficacy (25,26). Relapse rates and primaquine sensitivity vary geographically. The reported incidences of relapses range from 11–26; 7% in India (57,82) to 49–51% in Afghanistan (80). Relapses may occur one to four times after initiation of radical treatment (81,83). In patients treated with chloroquine, the first relapse is often suppressed by pharmacologically active concentrations of chloroquine and, therefore, does not manifest clinically or parasitologically. The first clinically manifested relapse has been reported any time after day 16 and up to four years following the primary infection (84–86). Host immunity is also considered to be a major contributor to the therapeutic response against relapses (87). Risk factors associated with relapses are female sex, higher parasitaemia at baseline, shorter number of days with symptoms prior to baseline, and a lower dose of primaquine (84). Other factors should be considered including body weight, natural relapse rates and local response to primaquine (88).

Hypnozoites of many strains of *P. vivax* are susceptible to a total dose of 210 mg of primaquine (28,38,55,78,80,84,89). Infections with the Chesson strain or primaquine-resistant strains prevalent in southern regions of Oceania and South-East Asia require a higher dosage of primaquine (22.5 mg or 30 mg per day for 14 days for a total dose of 315 mg or 420 mg) to prevent relapses (57,77,90). Primaquine is contraindicated in patients with the inherited enzyme deficiency, glucose-6-phosphate dehydrogenase (91,92) (see Section A9.3.6 on adverse effects and attachment of use of primaquine based on G6PD deficiency screening).

Although the long 14-day course of primaquine is a clear disadvantage, it has been shown that poor adherence to unsupervised 14-day primaquine therapy can be overcome effectively through patient education (93). The lengthy treatment courses and follow-up periods make the assessment of primaquine efficacy difficult. Thus, the identification of *P. vivax* strains that are resistant to chloroquine and/or to primaquine presents major challenges.

Alternative drugs are much needed for the radical treatment of *P. vivax* malaria resistant to chloroquine and/or primaquine. New drugs, tafenoquine and bulaquine, are currently being evaluated as an alternative to primaquine in the prevention of relapses (94). However, this too has haemolytic potential in G6PD-deficient individuals.

A9.3.4 Treatment of severe and complicated vivax malaria

Prompt and effective management should be the same as for severe and complicated falciparum malaria (set out in Section 8 of the main document).

A9.3.5 Treatment of malaria caused by *P. ovale* and *P. malariae*

Resistance of *P. ovale* and *P. malariae* to antimalarials is not well characterized, and these infections are considered to be generally sensitive to chloroquine. Only a single study in Indonesia has reported *P. malariae* resistance to chloroquine (64). The recommended treatment for radical cure of *P. ovale*, relapsing malaria, is the same as that for *P. vivax*, i.e. with chloroquine and primaquine. The high prevalence of G6PD deficiency status in areas endemic for *P. ovale* calls for the same caution in the use of primaquine as stated in Section A9.3.6. *P. malariae* forms no hypnozoites, and so it does not require radical cure with primaquine.

A9.3.6 Adverse effects and contraindications

Chloroquine is generally well tolerated. Common side effects include mild dizziness, nausea, vomiting, abdominal pain and itching (4,72,87).

Primaquine can induce a life-threatening haemolysis in those who are deficient in the enzyme G6PD (see Section A9.3.3). The severity of hemolytic anaemia seems to be related to primaquine dosing and the variant of the G6PD enzyme (108). Methemoglobinemia is associated with G6PD deficiency in malaria patients treated with primaquine (109). A full course of primaquine, given as a daily dose of 0.25 mg base/kg body weight for 14 days, is reported to be safe in populations where G6PD deficiency is either absent or readily diagnosable, but could induce a self-limiting haemolysis in those with mild G6PD deficiency (35,55,57). To reduce the risk of haemolysis in such individuals, an intermittent primaquine regimen of 0.75 mg base/kg weekly for 8 weeks can be given under medical supervision. This regimen is safe and effective (92). In non-G6PD deficient individuals, a high dose of primaquine (30 mg/day) has been shown to be safe and effective for Chesson strain *P. vivax* malaria in South-East Asia during a 28-day follow-up (23,77,90). In regions where prevalence of G6PD deficiency is relatively high, G6PD testing is required before administration of primaquine (see Fig. A9.1). Primaquine is not recommended during pregnancy and in infancy, since limited safety data are available in these groups (79). Abdominal pain and/or cramps are commonly reported when primaquine is taken on an empty stomach. Gastrointestinal toxicity is dose-related, and it is improved by taking primaquine with food. Primaquine may cause weakness, uneasiness in the chest, haemolytic anaemia, methaemoglobinaemia (which occurs in non-haemolysed red cells), leukopenia, and suppression of myeloid series. Therefore, primaquine should not be given in conditions predisposing to granulocytopenia, which includes rheumatoid arthritis and lupus erythematosus.

A9.4 Monitoring therapeutic efficacy

There is a need to monitor the antimalarial sensitivity of *P. vivax* in order to improve the treatment of vivax malaria, in particular in view of its emerging resistance to chloroquine. An in vitro test system has been developed for assessing the parasite's sensitivity to antimalarials (95,96). A modified version of the standard WHO in vitro micro-test for determination of the antimalarial sensitivity of *P. falciparum* has been used successfully for assessing the antimalarial sensitivity of *P. vivax* populations and for screening the efficacy of new antimalarials by measuring minimal inhibitory concentration (MIC), and the concentrations providing 50% and 90% inhibition (IC₅₀), and (IC₉₀) (89, 97). WHO has also recently introduced a revised protocol for in vivo monitoring of the therapeutic efficacy of chloroquine in *P. vivax* malaria (98). The revised protocol includes measurement of blood chloroquine levels, PCR genotyping and the use of molecular markers (only available for the *dhfr* gene) to help clarify and complete the overall picture of drug resistance. A better understanding of the molecular mechanisms underlying drug resistance in *P. vivax* is needed to improve the monitoring of chloroquine resistance.

A9.5 Conclusions and recommendations

The standard oral regimen of chloroquine of 25 mg base/kg body weight given over 3 days plus primaquine at either a low (0.25 mg base/kg body weight per day for 14 days) or high (0.5–0.75 mg base/kg body weight per day for 14 days) dose is effective and safe for the radical cure of chloroquine-sensitive *P. vivax* malaria in patients with no G6PD deficiency.

In areas where infections of drug-resistant *P. falciparum* and/or *P. vivax* are common, drug regimens to treat both species effectively must be used. An artemisinin-based combination treatment (particularly dihydroartemisinin plus piperazine) that does not include sulfadoxine-pyrimethamine would be a good choice.

The use of high-dose primaquine (0.5–0.75 mg base/kg body weight per day for 14 days), with either chloroquine or another effective antimalarial, is essential for trying to prevent relapses of primaquine-resistant or primaquine-tolerant *P. vivax*.

A primaquine regimen of 0.75 mg base/kg body weight once per week for 8 weeks is recommended as anti-relapse therapy for *P. vivax* and *P. ovale* malaria in patients with mild G6PD deficiency.

Increased efforts are needed to evaluate alternative treatments for *P. vivax* strains that are resistant to chloroquine. Urgent needs include establishing in vitro culture of *P. vivax* to permit the assessment of drug susceptibility, research to improve understanding of the molecular mechanisms of drug resistance, and the development of better tools for genotyping *P. vivax*.

A9.6 QUESTION:

What is the best treatment for *P. vivax* malaria in areas of chloroquine resistant *P. vivax*?

Background

As ACTs become widely available and chloroquine resistance becomes more widespread, it is important to assess the effects of ACTs on *P. vivax*.

GRADE approach

The benefits and harms of ACTs versus the standard treatments for *P. vivax* were assessed (search date: January 2009).

1. Are ACTs more effective than CQ in areas of CQ resistant *P. vivax*? (No evidence available.)
2. Are ACTs with primaquine more effective at reducing relapses of *P. vivax* than CQ with primaquine in areas of CQ resistant *P. vivax*? (No evidence available.)
3. Is one ACT (plus primaquine) more effective than another for treatment of *P. vivax* in areas with CQ resistant *P. vivax*? (See GRADE tables 9.6.1 and 9.6.2.)

When assessing this evidence the WHO GRADE panel considered the following factors to be important:

- ACTs do not have a substantial effect on the liver stage of *P. vivax* so radical cure requires primaquine.
- In areas with chloroquine resistance the recommendation concerns ACTs as a replacement for CQ.

Other considerations

The ability of ACTs to delay or reduce relapses due to *P. vivax* is likely to reflect the pharmacokinetics of the drug. DHA+PPQ has a notably longer half-life than AL6 and AS+AQ and a similar half-life to AS+MQ.

Decision

On the basis of this evidence, the WHO GRADE panel made a **weak recommendation** that DHA+PPQ may be superior to AL6 and AS+AQ for the treatment of *P. vivax*.

GRADE Table A9.6.1
Is one ACT (plus primaquine) more effective than another at treating *P. vivax* in areas with CQ resistant *P. vivax*?

Quality assessment		Summary of findings							Quality	Importance	
		No. of patients			Effect						
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	DHA + PPQ	AS + AQ	Relative risk (95% CI)	Absolute	
EFFICACY: recurrence of <i>P. vivax</i> parasitaemia – by day 63 – not reported ¹											
0	–	–	–	–	–	–	–	–	–	–	CRITICAL
EFFICACY: recurrence of <i>P. vivax</i> parasitaemia – by day 42											
1	Randomized trial ²	No serious limitations ³	Not applicable	Serious ⁴	No serious imprecision ⁵	None	3/41 (7.3%)	20/43 (46.5%)	RR 0.16 (0.05–0.49)	391 fewer per 1000 (from 237 fewer to 442 fewer)	MODERATE CRITICAL
EFFICACY: recurrence of <i>P. vivax</i> parasitaemia – by day 28											
1	Randomized trial ²	No serious limitations ³	Not applicable	Serious ⁴	No serious imprecision ⁵	None	0/42 (0%)	11/43 (25.6%)	RR 0.04 (0–0.73)	246 fewer per 1000 (from 69 fewer to 256 fewer)	MODERATE IMPORTANT
EFFICACY: failure to initially clear <i>P. vivax</i> – days 0–3											
1	Randomized trial	No serious limitations ⁶	Not applicable	Serious ⁴	Serious ⁷	–	0/54 (0%)	0/60 (0%)	Not estimable	Not estimable	LOW IMPORTANT
PUBLIC HEALTH BENEFIT: anaemia ⁸											
1	–	–	–	–	–	–	–	–	–	–	IMPORTANT
HARMS: serious adverse events ⁹											
1	–	–	–	–	–	–	–	–	–	–	IMPORTANT

Panel comment: Only one trial has compared DHA-PPQ+PQ versus AS+AQ+PQ for treating *P. vivax*.

Panel conclusion: DHA+PPQ performed significantly better at reducing relapses at day 42 (moderate quality evidence).

There may be some benefit in using DHA+PPQ (drugs with longer half-lives) in reducing the prevalence of anaemia.

1. Due to the long-half life of DHA+PPQ, it is likely that it still provides some prophylactic effect at day 42. There is the possibility that effects seen at day 42 may be lost as follow-up continues.
2. Papua, Indonesia (70), 114 patients randomized to DHA+PPQ or AS+AQ.
3. No serious limitations: sequence generation and allocation concealment were adequate; all participants were offered a course of unsupervised primaquine with no further details given regarding who took or completed this treatment; only laboratory staff were blinded to treatment allocation.
4. Serious indirectness: only one trial was found to be assessing this comparison; it may not be possible to generalize this result in other settings; children aged <1 year and pregnant or lactating women were excluded.
5. No serious imprecision: both limits of the 95% CI imply appreciable benefit with DHA+PPQ over AS+AQ.
6. No serious limitations: sequence generation and allocation concealment were adequate.
7. Serious imprecision: *P. vivax* parasitaemia was successfully cleared in all participants in both groups in this trial; further trials are necessary to confirm the absence of any important differences.
8. One trial (70) found that the proportion anaemic (HB<10 g/dl) was significantly higher in the group treated with AS+AQ on days seven ($P = 0.04$) and 28 ($P = 0.019$), but these figures are for participants with *P. vivax* mono-infection, or *P. falciparum* mono-infection or mixed infection at baseline; both *P. vivax* and *P. falciparum* were more common during follow-up in the group treated with AS+AQ.
9. There were three serious adverse events in the group treated with AS+AQ and none with DHA-PPQ. However these events may have occurred in participants with *P. falciparum* only so they are not included in this table.

GRADE Table A9.6.2
Is one ACT (plus primaquine) more effective than another at treating *P. vivax* in areas with CQ resistant *P. vivax*?

Quality assessment	Summary of findings							Quality	Importance					
	No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations			No. of patients	Effect			
								DHA + PPQ	AL	Relative risk (95% CI)	Absolute			
Efficacy: recurrence of <i>P. vivax</i> parasitaemia – by day 63 – not reported ¹														
0	–	–	–	–	–	–	–	–	–	–	–	–	CRITICAL	
Efficacy: recurrence of <i>P. vivax</i> parasitaemia – by day 42														
1	Randomized trial ²	No serious limitations ³	Not applicable	Serious ⁴	No serious imprecision ⁵	None	5/55 (9.1%)	40/71 (56.3%)	RR 0.16 (0.07–0.38)	473 fewer per 1000 (from 349 fewer to 524 fewer)			MODERATE	CRITICAL
Efficacy: recurrence of <i>P. vivax</i> parasitaemia – by day 28														
1	Randomized trial ²	No serious limitations ³	Not applicable	Serious ⁴	No serious imprecision ⁵	None	1/65 (1.5%)	19/74 (25.7%)	RR 0.06 (0.01–0.44)	242 fewer per 1000 (from 144 fewer to 254 fewer)			MODERATE	IMPORTANT
Efficacy: failure to initially clear <i>P. vivax</i> – days 0–3														
1	Randomized trial ²	No serious limitations ³	Not applicable	Serious ⁴	Serious imprecision ⁶	None	0/90 (0%)	0/85 (0%)	Not estimable	Not estimable			LOW	IMPORTANT
PUBLIC HEALTH BENEFIT: anaemia ⁷														
0	–	–	–	–	–	–	–	–	–	–	–	–	–	IMPORTANT
HARMS: serious adverse events – not reported														
0	–	–	–	–	–	–	–	–	–	–	–	–	–	IMPORTANT

Panel comment: Only one trial has compared DHA+PPQ versus AL6+PQ for treating *P. vivax*.

Panel conclusion: DHA-PPQ performed significantly better at reducing relapses at day 42 (moderate quality evidence).

There may be some benefit in using DHA+PPQ (drugs with longer half-lives) in reducing the prevalence of anaemia.

1. Due to the long half-life of DHA+PPQ, it is likely that it still provides some prophylactic effect at day 42. There is the possibility that effects seen at day 42 may be lost as follow-up continues.
2. In Papua, Indonesia, 175 patients randomized to DHA+PPQ or AL (71). All patients also received 14 days of primaquine starting on day 28; this does not reflect normal practice.
3. No serious limitations: allocation concealment was assessed as "low risk of bias"; laboratory staff were blinded, but there was no other blinding.
4. Serious indirectness: only one trial was identified for this comparison; it may not be possible to generalize this in other settings; children weighing <10 kg and pregnant or lactating women were excluded.
5. No imprecision: both limits of the 95% CI imply appreciable benefit of DHA+PPQ over AL.
6. Serious imprecision: *P. vivax* parasitaemia was successfully cleared in all participants in both groups in this trial; further trials are necessary to confirm the absence of any important differences.
7. One trial (71) found that by day 42 the proportion of patients who were anaemic (Hb<10 g/dl) was significantly lower with DHA+PPQ ($P=0.019$), but these figures are for participants with *P. vivax* mono-infection, or *P. falciparum* mono-infection or mixed infection at baseline. Both *P. vivax* and *P. falciparum* were more common during follow-up in the group treated with AL6.

A9.7 QUESTION:

Is 14 days of primaquine superior to 5 days of primaquine for preventing relapses of *P. vivax*?

Background

Primaquine is the most widely used drug for the treatment of the liver stage of *P. vivax*. Treatment regimes vary between countries.

GRADE approach

The evidence included in this table is based on the Cochrane review titled “Primaquine for preventing relapses in people with *Plasmodium vivax* malaria” published in 2007 (99). For the purposes of these guidelines the outcome measure has been converted from odds ratio (used in the review) to risk ratio for consistency.

1. Is 14 days of primaquine superior to five days of primaquine in preventing relapses of *P. vivax*? (See GRADE Table A9.7.1)

When assessing this evidence the WHO GRADE panel considered the following factors to be important:

- ACTs do not have a substantial effect on the liver stage of *P. vivax* so radical cure requires primaquine.

Other considerations

In addition to the presented direct comparison, the Cochrane review reports indirect evidence of the superiority of the 14-day regimen. No difference has been shown between the five-day regimen and chloroquine alone (3 trials, 2104 participants; OR 1.04, 95% CI 0.64–1.69), while the 14-day regimen is significantly better at reducing relapses (6 trials, 1072 participants; OR 0.24, 95% CI 0.12–0.45).

Decision

The WHO GRADE panel makes a **strong recommendation** that for the radical treatment of *P. vivax* primaquine be given for 14 days.

GRADE Table A9.7.1**Is PQ (14 days) superior to PQ (5 days) in preventing relapses of *P. vivax* in adults and children in endemic areas?**

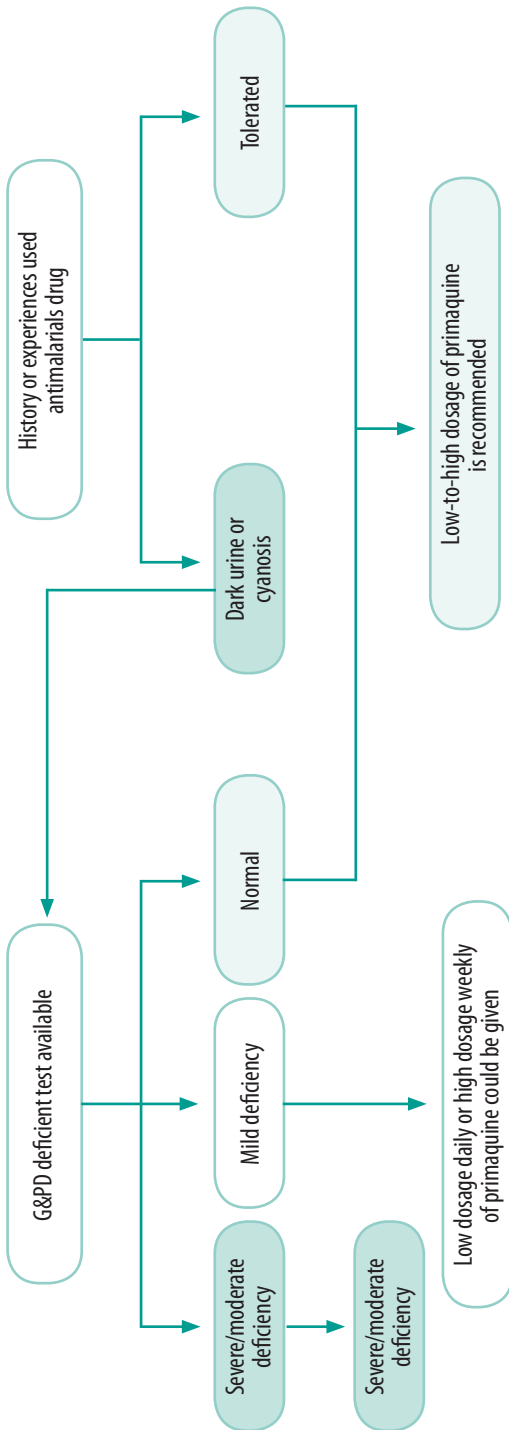
Quality assessment		Summary of findings					Quality	Importance				
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations			No. of patients	Effect		
							PQ (14 d.) + CQ	PQ (5 d.) + CQ	Relative risk (95% CI)	Absolute		
Efficacy: <i>P. vivax</i> parasitaemia detected at > 30 days after starting primaquine												
2	Randomized trial ¹	Serious ²	Not applicable	Serious ³	No serious imprecision ⁴	None	2/94 (2.1%)	24/92 (26.1%)	RR 0.1 (0.03–0.35)	235 fewer per 1000 (from 170 fewer to 253 fewer)	LOW	CRITICAL
Efficacy: <i>P. vivax</i> parasitaemia detected at > 30 days after starting primaquine, excluding new infections by PCR												
1	Randomized trial ⁵	Serious ⁶	Not applicable	Serious ⁷	Very serious ⁸	None	2/31 (6.5%)	4/30 (13.3%)	RR 0.48 (0.1–2.45)	69 fewer per 1000 (from 120 fewer to 193 more)	VERY LOW	CRITICAL

Panel comment: This direct comparison has only been assessed by two small trials.

Panel conclusion: Fourteen days of primaquine may reduce the relapse rate of *P. vivax* > 30 days after primaquine (low quality evidence). However, one very small trial attempted to exclude new infections with PCR and found no statistical difference (very low quality evidence).

1. Brazil (25) and India (26).
2. Serious limitations: in both trials allocation concealment was unclear; Villalobos followed up 61/79 enrolled participants for 90 days (25); Gogtay followed up 77% of enrolled participants for six months (26).
3. Serious indirectness: both trials enrolled adults only although in one trial the definition of adults was people over the age of 12.
4. No serious imprecision: the upper border of the 95% confidence interval of the pooled estimate suggests appreciable benefit with primaquine (14 days) over primaquine (5 days).
5. India (26).
6. Serious limitations: allocation concealment was unclear.
7. Serious indirectness: this trial only recruited people over 12 years of age.
8. Very serious imprecision: the 95% confidence interval includes both appreciable benefit with primaquine (14 days) and appreciable harm.

Figure A9.1 Use of primaquine based on G6PD-deficiency screening



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