GUIDELINES
FOR THE TREATMENT
OF MALARIA

Third edition

World Health
Organization

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OF MALARIA

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Contents

Glossary

Artemisinin-based combination therapy (ACT). A combination of an artemisinin derivative with a longer-acting antimalarial that has a different mode of action.

Asexual cycle. The life cycle of the malaria parasite in the host, from merozoite invasion of red blood cells to schizont rupture (merozoite → ring stage → trophozoite → schizont → merozoites). The duration is approximately 24 h in *Plasmodium knowlesi*, 48 h in *P. falciparum*, *P. ovale* and *P. vivax* and 72 h in *P. malariae*.

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

Asymptomatic parasitaemia. The presence of asexual parasites in the blood without symptoms of illness.

Cerebral malaria. Severe *P. falciparum* malaria with coma (Glasgow coma scale < 11, Blantyre coma scale < 3); malaria with coma persisting for > 30 min after a seizure.

Combination treatment. A combination of two or more classes of antimalarial drug with unrelated mechanisms of action.

Cure. Elimination of the malaria parasites that caused the treated illness.

Drug resistance. The ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended, provided the exposure is adequate. Resistance to antimalarial agents arises because of the selection of parasites with genetic changes (mutations or gene amplifications) that confer reduced susceptibility.

Gametocytes. The sexual stages of malaria parasites that infect anopheline mosquitoes when taken up during a blood meal.

Fixed-dose combination. A combination in which two antimalarial drugs are formulated together in the same tablet, capsule, powder, suspension or granule.

Hyperparasitaemia. A high density of parasites in the blood, which increases the risk of deterioration to severe malaria (although the risk varies in different endemic areas according to the level of transmission) and of subsequent treatment failure. In this document, the term is used to refer to a parasite density > 4% (~ 200 000/µL). Patients with *P. falciparum* parasite densities > 10% and patients with *P. knowlesi* parasite densities > 100 000/µL (~ 2%) are considered to have severe malaria even if they do not have evidence of vital organ dysfunction.

Hypnozoites. Persistent liver stages of *P. vivax* and *P. ovale* malaria that remain dormant in host hepatocytes for 3–45 weeks before maturing to form hepatic schizonts, which then burst and release merozoites that infect red blood cells. This is the cause of relapses.

Malaria pigment (haemozoin). A dark-brown granular material formed by malaria parasites as a by-product of haemoglobin digestion. Pigment is evident in mature trophozoites and schizonts. It may also be phagocytosed by monocytes, macrophages and polymorphonuclear neutrophils.

Merozoite. Parasite released into the host bloodstream when a hepatic or erythrocytic schizont bursts. The merozoites then invade red blood cells.

Monotherapy. Antimalarial treatment with a single medicine: either a single active compound or a synergistic combination of two compounds with related mechanisms of action.

***Plasmodium*.** A genus of protozoan vertebrate blood parasites that includes the causal agents of malaria. *P. falciparum*, *P. malariae*, *P. ovale* (two species) and *P. vivax* cause malaria in humans. Human infections with the monkey malaria parasite *P. knowlesi* and very occasionally with other simian malaria species may occur in forested regions of South-East Asia.

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

Radical cure. This term refers to both cure of blood-stage infection and prevention of relapses by killing hypnozoites (in *P. vivax* and *P. ovale* infections only).

Rapid diagnostic test (RDT). An antigen-based stick, cassette or card test for malaria in which a coloured line indicates the presence of plasmodial antigens.

Recrudescence. Recurrence of asexual parasitaemia following antimalarial treatment comprising the same genotype(s) that caused the original illness. This results from incomplete clearance of asexual parasitaemia because of inadequate or ineffective treatment. It must be distinguished from re-infection (usually determined by molecular genotyping in endemic areas). Recrudescence is different from relapse in *P. vivax* and *P. ovale* infections.

Recurrence. Recurrence of asexual parasitaemia after treatment, due to recrudescence, relapse (in *P. vivax* and *P. ovale* infections only) or a new infection.

Relapse. Recurrence of asexual parasitaemia in *P. vivax* and *P. ovale* malaria deriving from persisting liver stages; occurs when the blood-stage infection has been eliminated but hypnozoites persist in the liver and mature to form hepatic schizonts. After an interval of weeks or 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 by microscopy.

Schizont. Mature malaria parasite in host liver cells (hepatic schizont) or red blood cells (erythrocytic schizont) that is undergoing nuclear division by a process called schizogony.

Selection pressure. Resistance to antimalarial agents emerges and spreads because of the survival advantage of resistant parasites in the presence of the drug. The selection pressure reflects the intensity and magnitude of selection: the greater the proportion of parasites in a given population exposed to concentrations of an antimalarial agent that allow proliferation of resistant but not sensitive parasites, the greater is 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.

Sporozoite. Motile malaria parasite that is infective to humans, inoculated by a feeding female anopheline mosquito, that invades hepatocytes.

Transmission intensity. This is the frequency with which people living in an area are bitten by anopheline mosquitoes carrying human malaria sporozoites. It is often expressed as the annual entomological inoculation rate, which is the average number of inoculations with malaria parasites received by one person in 1 year.

Trophozoite. The stage of development of malaria parasites growing within host red blood cells from the ring stage to just before nuclear division. Mature trophozoites contain visible malaria pigment.

Uncomplicated malaria. Symptomatic malaria parasitaemia with no signs of severity and/or evidence of vital organ dysfunction.

Vectorial capacity. Number of potential new infections that the population of a given anopheline mosquito vector would distribute per malaria case per day at a given place and time.

Abbreviations

ACT	artemisinin-based combination therapy
bw	body weight
CI	confidence interval
DTP	diphtheria, tetanus and pertussis (vaccine)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
G6PD	glucose-6-phosphate dehydrogenase
HRP2	histidine-rich protein 2
IPTp	intermittent preventive treatment in pregnancy
IPTi	intermittent preventive treatment in infancy
PCR	polymerase chain reaction
*Pf*HRP2	*Plasmodium falciparum* histidine-rich protein-2
*p*LDH	*parasite*-lactate dehydrogenase
Pvdhfr	*Plasmodium vivax* dihydrofolate reductase gene
RDT	rapid diagnostic test
RR	relative risk, or risk ratio
SMC	seasonal malaria chemoprevention
SP	sulfadoxine–pyrimethamine

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EDITION

EXECUTIVE SUMMARY

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Malaria case management, consisting of early diagnosis and prompt effective treatment, remains a vital component of malaria control and elimination strategies. This third edition of the WHO *Guidelines for the treatment of malaria* contains updated recommendations based on new evidence particularly related to dosing in children, and also includes recommendations on the use of drugs to prevent malaria in groups at high risk.

Core principles

The following core principles were used by *the Guidelines* Development Group that drew up these *Guidelines*.

1. Early diagnosis and prompt, effective treatment of malaria

Uncomplicated falciparum malaria can progress rapidly to severe forms of the disease, especially in people with no or low immunity, and severe falciparum malaria is almost always fatal without treatment. Therefore, programmes should ensure access to early diagnosis and prompt, effective treatment within 24–48 h of the onset of malaria symptoms.

2. Rational use of antimalarial agents

To reduce the spread of drug resistance, limit unnecessary use of antimalarial drugs and better identify other febrile illnesses in the context of changing malaria epidemiology, antimalarial medicines should be administered only to patients who truly have malaria. Adherence to a full treatment course must be promoted. Universal access to parasitological diagnosis of malaria is now possible with the use of quality-assured rapid diagnostic tests (RDTs), which are also appropriate for use in primary health care and community settings.

3. Combination therapy

Preventing or delaying resistance is essential for the success of both national and global strategies for control and eventual elimination of malaria. To help protect current and future antimalarial medicines, all episodes of malaria should be treated with at least two effective antimalarial medicines with different mechanisms of action (combination therapy).

4. Appropriate weight-based dosing

To prolong their useful therapeutic life and ensure that all patients have an equal chance of being cured, the quality of antimalarial drugs must be ensured and antimalarial drugs must be given at optimal dosages. Treatment should maximize the likelihood of rapid clinical and parasitological cure and minimize transmission from the treated infection. To achieve this, dosage regimens should be based on the patient's weight and should provide effective concentrations of antimalarial drugs for a sufficient time to eliminate the infection in all target populations.

Recommendations

All cases of suspected malaria should have a parasitological test (microscopy or Rapid diagnostic test (RDT)) to confirm the diagnosis.

Both microscopy and RDTs should be supported by a quality assurance programme.
Good practice statement

Treating uncomplicated *P. falciparum* malaria

Treatment of uncomplicated P. falciparum malaria

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following recommended artemisinin-based combination therapies (ACT):
- artemether + lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- dihydroartemisinin + piperaquine
- artesunate + sulfadoxine – pyrimethamine (SP)

Strong recommendation, high-quality evidence

Duration of ACT treatment

ACT regimens should provide 3 days' treatment with an artemisinin derivative.
Strong recommendation, high-quality evidence

Revised dose recommendation for dihydroartemisinin + piperaquine in young children

Children < 25kg treated with dihydroartemisinin + piperaquine should receive a minimum of 2.5 mg/kg body weight (bw) per day of dihydroartemisinin and 20 mg/kg bw per day of piperaquine daily for 3 days.
Strong recommendation based on pharmacokinetic modelling

Reducing the transmissibility of treated P. falciparum infections

In low-transmission areas, give a single dose of 0.25 mg/kg bw primaquine with ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. Testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency is not required.
Strong recommendation, low-quality evidence

Treating uncomplicated *P. falciparum* malaria in special risk groups

First trimester of pregnancy

Treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with 7 days of quinine + clindamycin.
Strong recommendation

Infants less than 5kg body weight

Treat infants weighing < 5 kg with uncomplicated *P. falciparum* malaria with ACT at the same mg/kg bw target dose as for children weighing 5 kg.
Strong recommendation

Patients co-infected with HIV

In people who have HIV/AIDS and uncomplicated *P. falciparum* malaria, avoid artesunate + SP if they are being treated with co-trimoxazole, and avoid artesunate + amodiaquine if they are being treated with efavirenz or zidovudine.
Good practice statement

Non-immune travellers

Treat travellers with uncomplicated *P. falciparum* malaria returning to non-endemic settings with ACT.
Strong recommendation, high-quality evidence

Hyperparasitaemia

People with *P. falciparum* hyperparasitaemia are at increased risk for treatment failure, severe malaria and death and should be closely monitored, in addition to receiving ACT.
Good practice statement

Treating uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria

Blood stage infection

If the malaria species is not known with certainty, treat as for uncomplicated *P. falciparum* malaria.
Good practice statement

In areas with chloroquine-susceptible infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria with either ACT (except pregnant women in their first trimester) or chloroquine.
Strong recommendation, high-quality evidence

In areas with chloroquine-resistant infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria (except pregnant women in their first trimester) with ACT.
Strong recommendation, high-quality evidence

Treat pregnant women in their first trimester who have chloroquine-resistant *P. vivax* malaria with quinine.
Strong recommendation, very low-quality evidence

Preventing relapse in *P. vivax* or *P. ovale* malaria

The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.
Good practice statement

To prevent relapse, treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency) with a 14-day course (0.25-0.5 mg/kg bw daily) of primaquine in all transmission settings.
Strong recommendation, high-quality evidence

In people with G6PD deficiency, consider preventing relapse by giving primaquine base at 0.75 mg/kg bw once a week for 8 weeks, with close medical supervision for potential primaquine-induced haemolysis.
Conditional recommendation, very low-quality evidence

When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine.
Good practice statement

Pregnant and breastfeeding women

In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, on the basis of G6PD status, treat with primaquine to prevent future relapse.
Conditional recommendation, moderate-quality evidence

Treating severe malaria

Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of ACT (add single dose primaquine in areas of low transmission).
Strong recommendation, high-quality evidence

Revised dose recommendation for parenteral artesunate in young children

Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.
Strong recommendation based on pharmacokinetic modelling

Parenteral alternatives where artesunate is not available

If artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.
Conditional recommendation, low-quality evidence

Treating cases of suspected severe malaria pending transfer to a higher-level facility (pre-referral treatment)

Pre-referral treatment options

Where complete treatment of severe malaria is not possible but injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate facility for further care. Where intramuscular artesunate is not available use intramuscular artemether or, if that is not available, use intramuscular quinine.
Strong recommendation, moderate-quality evidence

Where intramuscular injection of artesunate is not available, treat children < 6 years with a single rectal dose (10mg/kg bw) of artesunate, and refer immediately to an appropriate facility for further care. Do not use rectal artesunate in older children and adults.
Strong recommendation, moderate-quality evidence

Chemoprevention for special risk groups

Intermittent preventive treatment in pregnancy

In malaria-endemic areas in Africa, provide intermittent preventive treatment with SP to all women in their first or second pregnancy (SP-IPTp) as part of antenatal care. Dosing should start in the second trimester and doses should be given at least 1 month apart, with the objective of ensuring that at least three doses are received.
Strong recommendation, high-quality evidence

Intermittent preventive treatment in infants

In areas of moderate-to-high malaria transmission of Africa, where SP is still effective, provide intermittent preventive treatment with SP to infants (< 12 months of age) (SP-IPTi) at the time of the second and third rounds of vaccination against diphtheria, tetanus and pertussis (DTP) and vaccination against measles.
Strong recommendation

Seasonal malaria chemoprevention

In areas with highly seasonal malaria transmission in the sub-Sahel region of Africa, provide seasonal malaria chemoprevention (SMC) with monthly amodiaquine + SP for all children aged < 6 years during each transmission season.
Strong recommendation, high-quality evidence

Antimalarial drug quality

National drug and regulatory authorities should ensure that the antimalarial medicines provided in both the public and the private sectors are of acceptable quality, through regulation, inspection and law enforcement.
Good practice statement

Monitoring the efficacy of antimalarial drugs

All malaria programmes should regularly monitor the therapeutic efficacy of antimalarial drugs using the standard WHO protocols.
Good practice statement

National adaptation and implementation

The choice of ACTs in a country or region should be based on optimal efficacy, safety and adherence.
Good practice statement

Drugs used in IPTp, SMC and IPTi should not be used as a component of first-line treatments in the same country or region.
Good practice statement

When possible, use:
- fixed-dose combinations rather than co-blistered or loose, single-agent formulations; and
- for young children and infants, paediatric formulations, with a preference for solid formulations (e.g. dispersible tablets) rather than liquid formulations.

Good practice statement

1 | INTRODUCTION

1.1 | BACKGROUND

Malaria remains an important cause of illness and death in children and adults in countries in which it is endemic. Malaria control requires an integrated approach, including prevention (primarily vector control) and prompt treatment with effective antimalarial agents. Since publication of the first edition of *the Guidelines for the treatment of malaria* in 2006 and the second edition in 2010, all countries in which *P. falciparum* malaria is endemic have progressively updated their treatment policy from use of monotherapy with drugs such as chloroquine, amodiaquine and sulfadoxine–pyrimethamine (SP) to the currently recommended artemisinin-based combination therapies (ACT). The ACTs are generally highly effective and well tolerated. This has contributed substantially to reductions in global morbidity and mortality from malaria. Unfortunately, resistance to artemisinins has arisen recently in *P. falciparum* in South-East Asia, which threatens these gains.

The treatment recommendations in this edition of *the Guidelines* have a firm evidence base for most antimalarial drugs, but, inevitably, there are still information gaps. *The Guidelines* will therefore remain under regular review, with updates every 2 years or more frequently as new evidence becomes available. The treatment recommendations in the main document are brief; for those who wish to study the evidence base in more detail, a series of annexes is provided, with references to the appropriate sections of the main document.

1.2 | OBJECTIVES

The objectives of *the Guidelines* are to:

- assist policy-makers to design and refine effective national treatment policies on the basis of the best available evidence;
- help hospital and clinical care providers to design and refine effective treatment protocols on the basis of the best available evidence;
- promote the use of safe, effective malaria treatment; and
- protect currently effective malaria treatment against the development of resistance.

1.3 | SCOPE

The Guidelines provide a framework for designing specific, detailed national treatment protocols, taking into account local patterns of resistance to antimalarial drugs and health service capacity.

The Guidelines provide evidence-based recommendations on:

- the treatment of uncomplicated and severe malaria in all age groups and situations, including in young children, pregnant women, people who are HIV positive, travellers from non-malaria-endemic regions and in epidemics and complex emergency situations; and
- the use of antimalarial drugs as preventive therapy in healthy people living in malaria-endemic areas who are high risk, in order to reduce morbidity and

mortality from malaria. The two approaches used are intermittent preventive treatment (IPT) and seasonal malaria chemoprevention (SMC).

No guidance is given in this edition on the use of antimalarial agents to prevent malaria in people travelling from non-endemic settings to areas of malaria transmission. This is available in the WHO, International travel and health guidance.[1]

1.4 | TARGET AUDIENCE

The Guidelines are designed primarily for policy-makers in ministries of health, who formulate country-specific treatment guidelines. Other groups that may find them useful include health professionals (doctors, nurses and paramedical officers) and public health and policy specialists working in hospitals, research institutions, medical schools, non-governmental organizations and agencies that are partners in health or malaria control, the pharmaceutical industry and primary health-care services.

1.5 | METHODS USED TO MAKE THE RECOMMENDATIONS

This third edition of *the Guidelines for the treatment of malaria* was prepared in accordance with the latest WHO standard methods for guideline development.[2] This involves planning, "scoping" and needs assessment, establishment of a guideline development group, formulation of key questions (population, participants or patients; intervention or indicator; comparator or control; outcome: "PICO"), commissioning reviews, applying Grading of Recommendations Assessment, Development and Evaluation (GRADE) to the quality of the evidence and making recommendations.[3] This method (see Annex 1) ensures a transparent link between the evidence and the recommendations.

1.5.1 | SOURCES OF EVIDENCE

After the scoping meeting, the Cochrane Infectious Diseases Group at the Liverpool School of Tropical Medicine in Liverpool, England, was commissioned to undertake systematic reviews and to assess the quality of the evidence for each priority question. All the reviews involved extensive searches for published and unpublished trials and highly sensitive searches of the Cochrane Infectious Diseases Group trials register, the Cochrane Central Register of Controlled Trials, MEDLINE®, Embase and LILACS. All the reviews are published on line in the Cochrane Library.

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[1] WHO International travel and health. Geneva : World Health Organization; 2014 (http://www.who.int/ith/en/).
[2] WHO handbook for guideline development. Geneva: World Health Organization; 2012 (http://www.who.int/kms/guidelines_review_committee/en/).
[3] Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, for the GRADE Working Group. Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations 2008. BMJ 336:924-926.

When little evidence was available from randomized trials, the group considered published reviews of non-randomized studies.

A subgroup on dosing reviewed published studies from MEDLINE® and Embase on the pharmacokinetics and pharmacodynamics of antimalarial medicines. They also used raw data from the WorldWide Antimalarial Resistance Network, a repository of clinical and laboratory data on pharmacokinetics and dosing simulations in individual patients, including measurements using validated assays of concentrations of antimalarial medicines in plasma or whole blood. The data came either from peer-reviewed publications or were submitted to regulatory authorities for drug registration. Population pharmacokinetics models were constructed, and the concentration profiles of antimalarial medicines in plasma or whole blood were simulated (typically 1000 times) for each weight category to inform dose recommendations.

1.5.2 | QUALITY OF EVIDENCE

The quality of the evidence from systematic reviews was assessed for each outcome and rated on a four-point scale, after consideration of the risk for bias (including publication bias) and the consistency, directness and precision of the effect estimates. The terms used in the quality assessments refer to the confidence that the guideline development group had in the estimate and not to the scientific quality of the investigations reviewed:

Quality of evidence	Interpretation
High	The group is very confident in the estimates of effect and considers that further research is very unlikely to change this confidence.
Moderate	The group has moderate confidence in the estimate of effect but considers that further research is likely to have an important impact on their confidence and may change the estimate.
Low	The group has low confidence in the estimate of effect and considers that further research is very likely to have an important impact on their confidence and is likely to change the estimate.
Very low	The group is very uncertain about the estimate of effect.

1.5.3 | FORMULATION OF RECOMMENDATIONS

The systematic reviews, the GRADE and other relevant materials were securely provided to all members of the Guideline Development Group. Recommendations were formulated after considering the quality of the evidence, the balance of benefits and harm and the feasibility of the intervention based on the four core principles listed in the executive summary. Although cost is a critical factor in setting national antimalarial treatment policies, cost was not formally considered. The dose recommendations were designed to ensure equivalent exposure of all patient groups to the drug. A revised dose regimen was recommended when there was sufficient evidence that the dose should be changed in order to achieve the target exposure. The Guideline Development Group discussed both the proposed wording of the recommendations and the rating of its strength. Areas of disagreement were resolved through extensive discussions at the meetings, e-mail and teleconferencing. The final draft was circulated to the Guideline Development Group and external peer reviewers. The external comments were addressed where possible and incorporated into the revised guidelines. Consensus was reached on all the recommendations, strength of evidence and the wording of *the guidelines*. Voting was not required at any stage.

Factor considered	Rationale
Balance of benefits and harm	The more the expected benefits outweigh the expected risks, the more likely it is that a strong recommendation will be made. When the balance of benefits and harm is likely to vary by setting or is a fine balance, a conditional recommendation is more likely.
Values and preferences	If the recommendation is likely to be widely accepted or highly valued, a strong recommendation is more likely.
Feasibility	If an intervention is achievable in the settings in which the greatest impact is expected, a strong recommendation is more likely.

1.5.4 | TYPES OF RECOMMENDATIONS

Three types of recommendations are presented in *the guidelines*

- *Treatment recommendations:* These recommendations were formulated using the GRADE approach, supported by systematic reviews of the evidence, with formal assessment of the quality of evidence, that were used by the panel in making the recommendations. However, a small number of treatment recommendations are not accompanied by GRADE tables, and these have been labelled as 'evidence not

graded'. These recommendations were made when the panel considered there to be such limited evidence available on alternatives to current practice that they could do little but recommend the status quo pending further research.

• *Dosing recommendations:* These recommendations were formulated using mathematical modelling, based on summaries of systematically collected pharmacokinetic data, to predict drug exposures in people of different body-weights, particularly those who are generally under-represented in clinical trials such as young infants.

• *Good practice statements:* These statements reflect a consensus among the panel, that the net benefits of adherence to the statement are large, unequivocal and the implications of the statement are common sense. These statements are made to re-emphasize the basic principles of good care, or good management practice with implementation, such as quality assurance of antimalarial medicines.

1.5.5 | STRENGTH OF RECOMMENDATIONS

Each recommendation was then classified as strong or conditional:

Strength of recommendation	Interpretation		
	For policy-makers	**For clinicians**	**For patients**
Strong	This recommendation can be adopted as policy in most situations.	Most individuals should receive the recommended course of action.	Most people in your situation would want the recommended course of action.
Conditional	Substantial debate should be conducted at national level, with the involvement of various stakeholders.	Be prepared to help individuals in making a decision that is consistent with their own values.	The majority of people in your situation would want the recommended course of action, but many would not.

1.5.6 | PRESENTATION OF EVIDENCE (RECOMMENDATIONS)

For clarity, *the guidelines* are presented in a simple descriptive form in the main document, with the recommendations. The recommendations are summarized in boxes at the start of each section (green), an evidence box (blue) is presented for each of the recommendation with a link made to the the GRADE profiles and decision tables. The complete GRADE tables, the pharmacokinetics underlying dose revisions, and additional references are provided in annexe 4.

1.5.7 | FUNDING

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

1.5.8 | MANAGEMENT OF CONFLICTS OF INTEREST

All members of the guideline development group and external expert reviewers made declarations of interest, which were managed in accordance with WHO procedures and cleared by the Legal Department. The WHO Guideline Steering Group and the co-chairs of *the Guidelines* Development Group were satisfied that there had been a transparent declaration of interests. No case necessitated the exclusion of any of the Guideline Development Group member or an external peer reviewer. The members of the guideline development group and a summary of declaration of interest listed in Annex 1.

1.5.9 | DISSEMINATION

The guidelines will be disseminated as a printed publication and electronically on the WHO web site in three languages (English, French and Spanish). A library of all supporting documentation will be also available on the web site. WHO headquarters will work closely with the regional and country offices to ensure the wide dissemination of *the guidelines* to all malaria endemic countries. There will also be dissemination through regional, sub-regional and country meetings. Member States will be supported to adapt and implement these guidelines (further details on national adaptation and implementation provided in Chapter 14).

1.5.10 | UPDATING

The evidence will be reviewed regularly and updated every 2 years or more frequently as new evidence becomes available. A mechanism will be established for periodic monitoring and evaluation of use of the treatment guidelines in countries.

1.5.11 | USER FEEDBACK

An online survey was carried out to obtain feedback from users of the second edition of *the Guidelines for the treatment of malaria*, and the responses were used in updating this edition.

**2 | CLINICAL MALARIA
AND EPIDEMIOLOGY**

2.1 | ETIOLOGY AND SYMPTOMS

Malaria is caused by infection of red blood cells with protozoan parasites of the genus *Plasmodium* inoculated into the human host by a feeding female anopheline mosquito. The five human *Plasmodium* species transmitted from person to person are *P. falciparum*, *P. vivax*, *P. ovale* (two species) and *P. malariae*. Increasingly, human infections with the monkey malaria parasite *P. knowlesi* are being reported from the forested regions of South-East Asia and particularly the island of Borneo.

The first symptoms of malaria are nonspecific and similar to those 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. In young children, malaria may also present with lethargy, poor feeding and cough. At this early stage of disease progression, with no evidence of vital organ dysfunction, a rapid, full recovery is expected, provided prompt, effective antimalarial treatment is given. If ineffective or poor-quality medicines are given or if treatment is delayed, particularly in *P. falciparum* malaria, the parasite burden often continues to increase and the patient may develop potentially lethal severe malaria. Disease progression to severe malaria may take days but can 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. If left untreated, severe malaria is fatal in the majority of cases.

2.2 | CLASSIFICATION OF ENDEMICITY

The nature of the clinical disease depends strongly on the background level of acquired protective immunity, which is a consequence of the pattern and intensity of malaria transmission in the area of residence.[4]

Where the transmission of malaria is stable, i.e. where populations are continuously exposed fairly constantly to a high frequency of malarial inoculation (entomological inoculation rate, > 10/year), partial immunity to clinical disease and a reduced risk of developing severe malaria are acquired in early childhood. The pattern of acquired immunity is similar across the sub-Sahel region, where malaria transmission is intense only during the 3- or 4-month rainy season and relatively low at other times. In both these situations, clinical disease is confined mainly to

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[4] High transmission area: hyperendemic or holoendemic area in which the prevalence rate of *P. falciparum* parasitaemia among children aged 2–9 years is > 50% most of the year. In these areas, virtually all exposed individuals have been infected by late infancy or early childhood. Moderate transmission area: mesoendemic area in which the prevalence rate of *P. falciparum* parasitaemia among children aged 2–9 years is 11–50% during most of the year. The maximum prevalence of malaria occurs in childhood and adolescence. Low transmission area: hypoendemic area in which the prevalence rate of *P. falciparum* parasitaemia among children aged 2–9 years is ≤ 10% during most of the year. Malaria infection and disease may occur at a similarly low frequency at any age, as little immunity develops.

young children, who may develop high parasite densities that can progress very rapidly to severe malaria. In contrast, in these settings adolescents and adults are partially immune and seldom suffer clinical disease, although they often continue to have low blood-parasite densities. Immunity is modified in pregnancy, and it is gradually lost, at least partially, when individuals move out of the endemic areas for long periods (usually many years).

In areas of unstable malaria transmission, which prevail in much of Asia and Latin America and the remaining parts of the world where malaria is endemic, the intensity of malaria transmission fluctuates widely by season and year and over relatively small distances. *P. vivax* is an important cause of malaria in these regions. The entomological inoculation rate is usually < 5/year and often < 1/year, although there are usually small foci of higher transmission in areas in which asymptomatic parasitaemia is common. The generally low transmission retards acquisition of immunity, so that people of all ages—adults and children alike—suffer from acute clinical malaria, with a significant risk for progression to severe malaria if it is untreated. Epidemics may occur in areas of unstable malaria transmission when the inoculation rate increases rapidly because of a sudden increase in vectorial capacity. Epidemics manifest as a very high incidence of malaria in all age groups and can overwhelm health services. In epidemics, severe malaria is common if prompt, effective treatment is not widely available. Non-immune travellers to a malaria endemic area are at particularly high risk for severe malaria if their infections are not detected promptly and treated effectively.

With effective malaria control, such as population-wide coverage with effective vector control and wide-scale deployment of ACTs, the number of inoculations is usually greatly reduced. This will be followed in time by a corresponding change in the clinical epidemiology of malaria in the area and an increasing risk for an epidemic if control measures are not sustained (see Annex 2).

3RD

EDITION

3 | DIAGNOSIS OF MALARIA

Recommendations on malaria diagnosis

All cases of suspected malaria should have a parasitological test (microscopy or Rapid diagnostic test (RDT)) to confirm the diagnosis.
Both microscopy and RDTs should be supported by a quality assurance programme.
Good practice statement

Prompt, accurate diagnosis of malaria is part of effective disease management. All patients with suspected malaria should be treated on the basis of a confirmed diagnosis by microscopy examination or RDT testing of a blood sample. Correct diagnosis in malaria-endemic areas is particularly important for the most vulnerable population groups, such as young children and non-immune populations, in whom falciparum malaria can be rapidly fatal. High specificity will reduce unnecessary treatment with antimalarial drugs and improve the diagnosis of other febrile illnesses in all settings.

WHO strongly advocates a policy of "test, treat and track" to improve the quality of care and surveillance (section 13).

3.1 | SUSPECTED MALARIA

The signs and symptoms of malaria are non-specific. Malaria is suspected clinically primarily on the basis of fever or a history of fever. There is no combination of signs or symptoms that reliably distinguishes malaria from other causes of fever; diagnosis based only on clinical features has very low specificity and results in overtreatment. Other possible causes of fever and whether alternative or additional treatment is required must always be carefully considered. The focus of malaria diagnosis should be to identify patients who truly have malaria, to guide rational use of antimalarial medicines.

In malaria-endemic areas, malaria should be suspected in any patient presenting with a history of fever or temperature ≥ 37.5 **°**C and no other obvious cause. In areas in which malaria transmission is stable (or during the high-transmission period of seasonal malaria), malaria should also be suspected in children with palmar pallor or a haemoglobin concentration of **<** 8 g/dL. High-transmission settings include many parts of sub-Saharan Africa and some parts of Oceania.

In settings where the incidence of malaria is very low, parasitological diagnosis of all cases of fever may result in considerable expenditure to detect only a few patients with malaria. In these settings, health workers should be trained to identify patients who may have been exposed to malaria (e.g. recent travel to a malaria-endemic area without protective measures) and have fever or a history of fever with no other obvious cause, before they conduct a parasitological test.

In all settings, suspected malaria should be confirmed with a parasitological test. The results of parasitological diagnosis should be available within a short time (< 2 h) of the patient presenting. In settings where parasitological diagnosis is not possible, a decision to provide antimalarial treatment must be based on the probability that the illness is malaria.

In children < 5 years, the practical algorithms for management of the sick child provided by the WHO–United Nations Children's Fund (UNICEF) strategy for Integrated Management of Childhood Illness[5] should be used to ensure full assessment and appropriate case management at first-level health facilities and at the community level.

3.2 | PARASITOLOGICAL DIAGNOSIS

The benefit of parasitological diagnosis relies entirely on an appropriate management response of health care providers. The two methods used routinely for parasitological diagnosis of malaria are light microscopy and immunochromatographic RDTs. The latter detect parasite-specific antigens or enzymes that are either genus or species specific.

Both microscopy and RDTs must be supported by a quality assurance programme. Antimalarial treatment should be limited to cases with positive tests, and patients with negative results should be reassessed for other common causes of fever and treated appropriately.

In nearly all cases of symptomatic malaria, examination of thick and thin blood films by a competent microscopist will reveal malaria parasites. Malaria RDTs should be used if quality-assured malaria microscopy is not readily available. RDTs for detecting *Pf*HRP2 can be useful for patients who have received incomplete antimalarial treatment, in whom blood films can be negative. This is particularly likely if the patient received a recent dose of an artemisinin derivative. If the initial blood film examination is negative in patients with manifestations compatible with severe malaria, a series of blood films should be examined at 6–12-h intervals, or an RDT (preferably one detecting *Pf*HRP2) should be performed. If both the slide examination and the RDT results are negative, malaria is extremely unlikely, and other causes of the illness should be sought and treated.

This document does not include recommendations for use of specific RDTs or for interpreting test results. For guidance, see the WHO manual *Universal access to malaria diagnostic testing*.[6]

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[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 October 2009).

[6] Universal access to malaria diagnostic testing—an operational manual. Revised. Geneva: World Health Organization; 2013 (http://www.who.int/entity/malaria/publications/atoz/9789241502092/en/index.html).

In patients with suspected severe malaria and in other high-risk groups, such as patients living with HIV/AIDS, absence or delay of parasitological diagnosis should not delay an immediate start of antimalarial treatment.

At present, molecular diagnostic tools based on nucleic-acid amplification techniques (e.g. loop-mediated isothermal amplification or PCR) do not have a role in the clinical management of malaria.

Where *P. vivax* malaria is common and microscopy is not available, it is recommended that a combination RDT be used that allows detection of *P. vivax* (*p*LDH antigen from *P. vivax)* or pan-malarial antigens (Pan-*p*LDH or aldolase).

3RD

EDITION

4 | TREATMENT OF UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA

Treating uncomplicated *P. falciparum* malaria

Treatment of uncomplicated P. falciparum malaria

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following recommended ACTs:
- artemether + lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- dihydroartemisinin + piperaquine
- artesunate + sulfadoxine–pyrimethamine (SP).

Strong recommendation, high-quality evidence

Duration of ACT treatment

ACT regimens should provide 3 days' treatment with an artemisinin derivative.
Strong recommendation, high-quality evidence

Revised dose recommendation for dihydroartemisinin + piperaquine in young children

Children weighing <25kg treated with dihydroartemisinin + piperaquine should receive a minimum of 2.5 mg/kg bw per day of dihydroartemisinin and 20 mg/kg bw per day of piperaquine daily for 3 days.
Strong recommendation based on pharmacokinetic modelling

Reducing the transmissibility of treated P. falciparum infections

In low-transmission areas, give a single dose of 0.25 mg/kg bw primaquine with ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. G6PD testing is not required.
Strong recommendation, low-quality evidence

4.1 | DEFINITION OF UNCOMPLICATED MALARIA

A patient who presents with symptoms of malaria and a positive parasitological test (microscopy or RDT) but with no features of severe malaria is defined as having uncomplicated malaria (see section 7.1 for definition of severe malaria).

4.2 | THERAPEUTIC OBJECTIVES

The clinical objectives of treating uncomplicated malaria are to cure the infection as rapidly as possible and to prevent progression to severe disease. "Cure" is defined as elimination of all parasites from the body. The public health objectives of treatment are to prevent onward transmission of the infection to others and to prevent the emergence and spread of resistance to antimalarial drugs.

4.3 | TREATMENT OF *P. FALCIPARUM* MALARIA

4.3.1 | ARTEMISININ-BASED COMBINATION THERAPY

Treatment of uncomplicated *P. falciparum* malaria

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with an ACT.
Strong recommendation, high-quality evidence

GRADE (Annex 4, A4.1 and A4.2)
In the absence of resistance to the partner drug, the five recommended ACTs have all been shown to achieve a PCR - adjusted treatment failure rate of < 5% in many trials in several settings in both adults and children (*high-quality evidence*).

Other considerations
The guideline development group decided to recommend a menu of approved combinations, from which countries can select first- and second-line treatment.

Sinclair D, Zani B, Donegan S, Olliaro PL, Garner P. Artemisinin-based combination therapy for treating uncomplicated malaria. Cochrane Database Systemat Rev 2009; 3:CD007483. doi: 10.1002/14651858.CD007483.pub2.

Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin-piperaquine for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database of Systemat Rev 2014;1:CD010927. doi: 10.1002/14651858.CD010927.

ACT is a combination of a rapidly acting artemisinin derivative with a longer-acting (more slowly eliminated) partner drug. The artemisinin component rapidly clears parasites from the blood (reducing parasite numbers by a factor of approximately 10 000 in each 48-h asexual cycle) and is also active against the sexual stages of parasite that mediate onward transmission to mosquitos. The longer-acting partner drug clears the remaining parasites and provides protection against development of resistance to the artemisinin derivative. Partner drugs with longer elimination half-lives also provide a period of post-treatment prophylaxis.

The five ACTs recommended for treatment of uncomplicated *P. falciparum* malaria are:

- artemether + lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- artesunate + SP
- dihydroartemisinin + piperaquine.

4.3.2 | DURATION OF TREATMENT

Duration of ACT treatment

ACT regimens should provide 3 days' treatment with an artemisinin-derivative.
Strong recommendation, high-quality evidence

GRADE (see Annex 4, A4.3)
In four randomized controlled trials in which the addition of 3 days of artesunate to SP was compared directly with 1 day of artesunate with SP:

- Three days of artesunate reduced the PCR-adjusted treatment failure rate within the first 28 days from that with 1 day of artesunate (RR, 0.45; 95% CI, 0.36–0.55, four trials, 1202 participants, *high-quality evidence*).
- Three days of artesunate reduced the number of participants who had gametocytaemia at day 7 from that with 1 day of artesunate (RR, 0.74; 95% CI, 0.58–0.93, four trials, 1260 participants, *high-quality evidence*).

Other considerations
The guideline development group considered that 3 days of artemisinin derivative are necessary to provide sufficient efficacy, promote good adherence and minimize the risk of drug resistance resulting from incomplete treatment.

A 3-day course of the artemisinin component of ACTs covers two asexual cycles, ensuring that only a small fraction of parasites remain for clearance by the partner drug, thus reducing the potential development of resistance to the partner drug. Shorter courses (1–2 days) are therefore not recommended, as they are less effective, have less effect on gametocytes and provide less protection for the slowly eliminated partner drug.

4.3.3 | DOSING OF ACTS

ACT regimens must ensure optimal dosing to prolong their useful therapeutic life, i.e. to maximize the likelihood of rapid clinical and parasitological cure, minimize transmission and retard drug resistance.

It is essential to achieve effective antimalarial drug concentrations for a sufficient time (exposure) in all target populations in order to ensure high cure rates. The dosage recommendations below are derived from understanding the relationship between dose and the profiles of exposure to the drug (pharmacokinetics) and the resulting therapeutic efficacy (pharmacodynamics) and safety. Some patient groups, notably younger children, are not dosed optimally with the "dosage regimens recommended by manufacturers, which compromises efficacy and fuels resistance. In these guidelines when there was pharmacological evidence that certain patient groups are not receiving optimal doses, dose regimens were adjusted to ensure similar exposure across all patient groups.

Weight-based dosage recommendations are summarized below. While age-based dosing may be more practical in children, the relation between age and weight differs in different populations. Age-based dosing can therefore result in under-dosing or over-dosing of some patients, unless large, region-specific weight-for-age databases are available to guide dosing in that region.

Factors other than dosage regimen may also effect exposure to a drug and thus treatment efficacy. The drug exposure of an individual patient also depends on factors such as the quality of the drug, the formulation, adherence and, for some drugs, co-administration with fat. Poor adherence is a major cause of treatment failure and drives the emergence and spread of drug resistance. Fixed-dose combinations encourage adherence and are preferred to loose (individual) tablets. Prescribers should take the time necessary to explain to patients why they should complete antimalarial course.

Artemether + lumefantrine

(For further details, see Annex 5, A5.3.)

Formulations currently available: Dispersible or standard tablets containing 20 mg artemether and 120 mg lumefantrine, and standard tablets containing 40 mg artemether and 240 mg lumefantrine in a fixed-dose combination formulation. The flavoured dispersible tablet paediatric formulation facilitates use in young children.

Target dose range: A total dose of 5 – 24 mg/kg bw of artemether and 29 – 144 mg/kg bw of lumefantrine

Recommended dosage regimen: Artemether + lumefantrine is given twice a day for 3 days (total, six doses). The first two doses should, ideally, be given 8 h apart.

Body weight (kg)	Dose (mg) of artemether + lumefantrine given twice daily for 3 days
5 to < 15	20 + 120
15 to < 25	40 + 240
25 to < 35	60 + 360
≥ 35	80 + 480

Factors associated with altered drug exposure and treatment response:

• Decreased exposure to lumefantrine has been documented in young children (<3 years)as well as pregnant women, large adults, patients taking mefloquine, rifampicin or efavirenz and in smokers. As these target populations may be at increased risk for treatment failure, their responses to treatment should be monitored more closely and their full adherence ensured.

• Increased exposure to lumefantrine has been observed in patients concomitantly taking lopinavir- lopinavir/ritonavir-based antiretroviral agents but with no increase in toxicity; therefore, no dosage adjustment is indicated.

Additional comments:

• An advantage of this ACT is that lumefantrine is not available as a monotherapy and has never been used alone for the treatment of malaria.

• Absorption of lumefantrine is enhanced by co-administration with fat. Patients or caregivers should be informed that this ACT should be taken immediately after food or a fat containing drink (e.g. milk), particularly on the second and third days of treatment.

Artesunate + amodiaquine

(For further details see Annex 5, A5.1 and A5.4.)

Formulations currently available: A fixed-dose combination in tablets containing 25 + 67.5 mg, 50 + 135 mg or 100 + 270 mg of artesunate and amodiaquine, respectively

Target dose and range: The target dose (and range) are 4 (2–10) mg/kg bw per day artesunate and 10 (7.5–15) mg/kg bw per day amodiaquine once a day for 3 days. A total therapeutic dose range of 6–30 mg/kg bw per day artesunate and 22.5–45 mg/kg bw per dose amodiaquine is recommended.

Body weight (kg)	Artesunate + amodiaquine dose (mg) given daily for 3 days
4.5 to < 9	25 + 67.5
9 to < 18	50 + 135
18 to < 36	100 + 270
≥ 36	200 + 540

Factors associated with altered drug exposure and treatment response:

- Treatment failure after amodiaquine monotherapy was more frequent among children who were underweight for their age. Therefore, their response to artesunate + amodiaquine treatment should be closely monitored.
- Artesunate + amodiaquine is associated with severe neutropenia, particularly in patients co-infected with HIV and especially in those on zidovudine and/or cotrimoxazole. Concomitant use of efavirenz increases exposure to amodiaquine and hepatotoxicity. Thus, concomitant use of artesunate + amodiaquine by patients taking zidovudine, efavirenz and cotrimoxazole should be avoided, unless this is the only ACT promptly available.

Additional comments:

- No significant changes in the pharmacokinetics of amodiaquine or its metabolite desethylamodiaquine have been observed during the second and third trimesters of pregnancy; therefore, no dosage adjustments are recommended.
- No effect of age has been observed on the plasma concentrations of amodiaquine and desethylamodiaquine, so no dose adjustment by age is indicated. Few data are available on the pharmacokinetics of amodiaquine in the first year of life.

Artesunate + mefloquine

(For further details, see Annex 5, A5.4 and A5.10.)

Formulations currently available: A fixed-dose formulation of paediatric tablets containing 25 mg artesunate and 55 mg mefloquine hydrochloride (equivalent to 50 mg mefloquine base) and adult tablets containing 100 mg artesunate and 220 mg mefloquine hydrochloride (equivalent to 200 mg mefloquine base)

Target dose and range: Target doses (ranges) of 4 (2 – 10) mg/kg bw per day artesunate and 8.3 (5 – 11) mg/kg bw per day mefloquine, given once a day for 3 days

Body weight (kg)	Artesunate + mefloquine dose (mg) given daily for 3 days
5 to < 9	25 + 55
9 to < 18	50 + 110
18 to < 30	100 + 220
≥ 30	200 + 440

Additional comments:

- Mefloquine was associated with increased incidences of nausea, vomiting, dizziness, dysphoria and sleep disturbance in clinical trials, but these symptoms are seldom debilitating, and, where this ACT has been used, it has generally been well tolerated. To reduce acute vomiting and optimize absorption, the total mefloquine dose should preferably be split over 3 days, as in current fixed-dose combinations.

• As concomitant use of rifampicin decreases exposure to mefloquine, potentially decreasing its efficacy, patients taking this drug should be followed up carefully to identify treatment failures.

Artesunate + sulfadoxine–pyrimethamine

(For further details, see Annex 5, A5.4 and A5.13.)

Formulations: Currently available as blister-packed, scored tablets containing 50 mg artesunate and fixed dose combination tablets comprising 500 mg sulfadoxine + 25 mg pyrimethamine. There is no fixed-dose combination.

Target dose and range: A target dose (range) of 4 (2–10) mg/kg bw per day artesunate given once a day for 3 days and a single administration of at least 25 / 1.25 (25–70 / 1.25–3.5) mg/kg bw sulfadoxine / pyrimethamine given as a single dose on day 1

Body weight (kg)	Artesunate dose given daily for 3 days (mg)	Sulfadoxine / pyrimethamine dose (mg) given as a single dose on day 1
5 to < 10	25 mg	250 / 12.5
10 to < 25	50 mg	500 / 25
25 to < 50	100 mg	1000 / 50
≥ 50	200 mg	1500 / 75

Factors associated with altered drug exposure and treatment response: The low dose of folic acid (0.4 mg daily) that is required to protect the fetuses of pregnant women from neural tube defects do not reduce the efficacy of SP, whereas higher doses (5 mg daily) do significantly reduce its efficacy and should not be given concomitantly.

Additional comments:

• The disadvantage of this ACT is that it is not available as a fixed-dose combination. This may compromise adherence and increase the risk for distribution of loose artesunate tablets, despite the WHO ban on artesunate monotherapy.
• Resistance is likely to increase with continued widespread use of SP, sulfalene–pyrimethamine and cotrimoxazole (trimethoprim-sulfamethoxazole). Fortunately, molecular markers of resistance to antifols and sulfonamides correlate well with therapeutic responses. These should be monitored in areas in which this drug is used.

Dihydroartemisinin + piperaquine

(For further details, see Annex 5, A5.8.)

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Revised dose recommendation for dihydroartemisinin-piperaquine in young children

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Children weighing <25kg treated with dihydroarteminsinin + piperaquine should receive a minimum of 2.5 mg/kg bw per day of dihydroartemisinin and 20 mg/kg bw per day of piperaquine daily for 3 days.
Strong recommendation based on pharmacokinetic modelling

The dosing subgroup reviewed clinical efficacy and safety data together with all available dihydroartemisinin-piperaquine pharmacokinetic data (6 published studies and 10 studies from the WWARN database; total 652 patients) and then conducted simulations of piperaquine exposures for each weight group. These showed lower exposure in younger children with higher risks of treatment failure. The revised dose regimens are predicted to provide equivalent piperaquine exposures across all age groups. The subgroup also reviewed preliminary results from an unpublished study using doses similar to those now recommended in this guidelines (n=100).

Other considerations
This dose adjustment is not predicted to result in higher peak piperaquine concentrations than in older children and adults, and as there is no evidence of increased toxicity in young children, the GRC concluded that the predicted benefits of improved antimalarial exposure are not at the expense of increased risk.

Tarning J, Zongo I, Some FA, Rouamba N, Parikh S, Rosenthal PJ, et al. Population pharmacokinetics and pharmacodynamics of piperaquine in children with uncomplicated falciparum malaria. Clin Pharmacol Ther 2012;91:497–505.

The WorldWide Antimalarial Resistance Network DP Study Group. The effect of dosing regimens on the antimalarial efficacy of dihydroartemisinin–piperaquine: a pooled analysis of individual patient data. PLoS Med 2013;10: e1001564.

Formulations: Currently available as a fixed-dose combination in tablets containing 40 mg dihydroartemisinin and 320 mg piperaquine and paediatric tablets contain 20 mg dihydroartemisinin and 160 mg piperaquine.

Target dose and range: A target dose (range) of 4 (2–10) mg/kg bw per day dihydroartemisinin and 18 (16–27) mg/kg bw per day piperaquine given once a day for 3 days for adults and children weighing ≥ 25 kg. The target doses and ranges for children weighing < 25 kg are 4 (2.5–10) mg/kg bw per day dihydroartemisinin and 24 (20–32) mg/kg bw per day piperaquine once a day for 3 days.

Recommended dosage regimen: The dose regimen currently recommended by the manufacturer provides adequate exposure to piperaquine and excellent cure rates (> 95%), except in children < 5 years, who have a threefold increased risk

for treatment failure. Children in this age group have significantly lower plasma piperaquine concentrations than older children and adults given the same mg/kg bw dose. Children weighing < 25 kg should receive at least 2.5 mg/kg bw dihydroartemisinin and 20 mg/kg bw piperaquine to achieve the same exposure as children weighing ≥ 25 kg and adults.

Dihydroartemisinin + piperaquine should be given daily for 3 days.

Body weight (kg)	Dihydroartemisinin + piperaquine dose (mg) given daily for 3 days
5 to < 8	20 + 160
8 to < 11	30 + 240
11 to < 17	40 + 320
17 to < 25	60 + 480
25 to < 36	80 + 640
36 to < 60	120 + 960
60 < 80	160 + 1280
>80	200 + 1600

Factors associated with altered drug exposure and treatment response:
- High-fat meals should be avoided, as they significantly accelerate the absorption of piperaquine, thereby increasing the risk for potentially arrhythmogenic delayed ventricular repolarization (prolongation of the corrected electrocardiogram QT interval). Normal meals do not substantially alter the absorption of piperaquine.
- As malnourished children are at increased risk for treatment failure, their response to treatment should be monitored closely.
- Dihydroartemisinin exposure is lower in pregnant women.
- Piperaquine is eliminated more rapidly by pregnant women, shortening the post-treatment prophylactic effect of dihydroartemisinin + piperaquine. As this does not affect primary efficacy, no dosage adjustment is recommended for pregnant women.

Additional comments: Piperaquine prolongs the QT interval by approximately the same amount as chloroquine but by less than quinine. It is not necessary to perform an electrocardiogram before prescribing dihydroartemisinin + piperaquine, but this ACT should not be used in patients with congenital QT prolongation or who have a clinical condition or are on medications (see Annex 5.14) that prolong the QT interval. There has been no evidence of piperaquine-related cardiotoxicity in large randomized trials or in extensive deployment.

4.4 | RECURRENT FALCIPARUM MALARIA

Recurrence of *P. falciparum* malaria can result from re-infection or recrudescence (treatment failure). Treatment failure may result from drug resistance or inadequate exposure to the drug due to sub-optimal dosing, poor adherence, vomiting, unusual pharmacokinetics in an 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 of treatment.

When possible, treatment failure must be confirmed parasitologically. This may require referring the patient to a facility with microscopy or LDH-based RDTs, as *P. falciparum* histidine-rich protein-2 (*Pf*HRP2)-based tests may remain positive for weeks after the initial infection, even without recrudescence. Referral may be necessary anyway to obtain second-line treatment. In individual patients, it may not be possible to distinguish recrudescence from re-infection, although lack of resolution of fever and parasitaemia or their recurrence within 4 weeks of treatment are considered failures of treatment with currently recommended ACTs. In many cases, treatment failures are missed because patients are not asked whether they received antimalarial treatment within the preceding 1 – 2 months. Patients who present with malaria should be asked this question routinely.

4.4.1 | FAILURE WITHIN 28 DAYS

The recommended second-line treatment is an alternative ACT known to be effective in the region. Adherence to 7-day treatment regimens (with artesunate or quinine both of which should be co-administered with + tetracycline, or doxycycline or clindamycin) is likely to be poor if treatment is not directly observed; these regimens are no longer generally recommended. The distribution and use of oral artesunate monotherapy outside special centres is strongly discouraged, and quinine-containing regimens are not well tolerated.

4.4.2 | FAILURE AFTER 28 DAYS

Recurrence of fever and parasitaemia > 4 weeks after treatment may be due to either recrudescence or a new infection. The distinction can be made only by PCR genotyping of parasites from the initial and the recurrent infections.

As PCR is not routinely used in patient management, all presumed treatment failures after 4 weeks of initial treatment should, from an operational standpoint, be considered new infections and be treated with the first-line ACT. However, reuse of mefloquine within 60 days of first treatment is associated with an increased risk for neuropsychiatric reactions, and an alternative ACT should be used.

4.5 | REDUCING THE TRANSMISSIBILITY OF TREATED *P. FALCIPARUM* INFECTIONS IN AREAS OF LOW-INTENSITY TRANSMISSION

Reducing the transmissibility of *P. falciparum* infections

In low-transmission areas, give a single dose of 0.25 mg/kg bw primaquine with ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. G6PD testing is not required.
Strong recommendation, low-quality evidence

GRADE (see Annex 4, A4.4)
In an analysis of observational studies of single-dose primaquine, data from mosquito feeding studies on 180 people suggest that adding 0.25 mg/kg primaquine to treatment with an ACT can rapidly reduce the infectivity of gametocytes to mosquitoes.

In a systematic review of eight randomized controlled trials of the efficacy of adding single-dose primaquine to ACTs for reducing the transmission of malaria, in comparison with ACTs alone:

- Single doses of > 0.4 mg/kg bw primaquine reduced gametocyte carriage at day 8 by about two thirds (RR, 0.34; 95% CI, 0.19–0.59, two trials, 269 participants, *high-quality evidence*); and
- Single doses of primaquine > 0.6 mg/kg bw reduced gametocyte carriage at day 8 by about two thirds (RR, 0.29; 95% CI, 0.22–0.37, seven trials, 1380 participants, *high-quality evidence*).

There have been no randomized controlled trials of the effects on the incidence of malaria or on transmission to mosquitos.

Other considerations
The guideline development group considered that the evidence of a dose–response relation from observational studies of mosquito feeding was sufficient to conclude the primaquine dose of 0.25mg/kg bw significantly reduced *P .falciparum* transmissibility.

Graves PM, Gelband H, Garner P. Primaquine or other 8-aminoquinoline for reducing P. falciparum transmission. Cochrane Database Systemat Rev 2014; 6:CD008152. doi: 10.1002/14651858.CD008152.pub3.

White NJ, Qiao LG, Qi G, Luzzatto L. Rationale for recommending a lower dose of primaquine as a Plasmodium falciparum gametocytocide in populations where G6PD deficiency is common. Malar J 2012;11:418.

The population benefits of reducing malaria transmission with gametocytocidal drugs such as primaquine require that a very high proportion of treated patients receive these medicines and that there is no large transmission reservoir of asymptomatic parasite carriers. This strategy is therefore likely to be effective only in areas of low-intensity malaria transmission, as a component of pre-elimination or elimination programmes.

In light of concern about the safety of the previously recommended dose of 0.75 mg/kg bw in individuals with G6PD deficiency, a WHO panel reviewed the safety of primaquine as a *P. falciparum* gametocytocide and concluded that a single dose of 0.25 mg/kg bw of primaquine base is unlikely to cause serious toxicity, even in people with G6PD deficiency.[7] Thus, where indicated a single dose of 0.25mg/kg bw of primaquine base should be given on the first day of treatment, in addition to an ACT, to all patients with parasitologically confirmed *P.falciparum* malaria except for pregnant women, infants < 6 months of age and women breastfeeding infants < 6 months of age, because there are insufficient data on the safety of its use in these groups. (For further details, see Annex 5, A5.11.)

Dosing table based on the most widely currently available tablet strength (7.5mg base)

Body weight (kg)	Single dose of primaquine (mg base)
10[a] to < 25	3.75
25 to < 50	7.5
50 to 100	15

[a] Dosing of young children weighing < 10 kg is limited by the tablet sizes currently available.

4.6 | INCORRECT APPROACHES TO TREATMENT

4.6.1 | USE OF MONOTHERAPY

The continued use of artemisinins or any of the partner medicines alone will compromise the value of ACT by selecting for drug resistance.

As certain patient groups, such as pregnant women, may need specifically tailored combination regimens, single artemisinin derivatives will still be used in selected referral facilities in the public sector, but they should be withdrawn entirely from the private and informal sectors and from peripheral public health care facilities.

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[7] Recht J, Ashley E, White N. Safety of 8-aminoquinoline antimalarial medicines. Geneva: World Health Organization; 2014 (http://who.int/malaria/publications/atoz/9789241506977/en/).

Similarly, continued availability of amodiaquine, mefloquine and SP as monotherapies in many countries is expected to shorten their useful therapeutic life as partner drugs of ACT, and they should be withdrawn wherever possible.

4.6.2 | INCOMPLETE DOSING

In endemic regions, some semi-immune malaria patients are cured by an incomplete course of antimalarial drugs or by a treatment regimen that would be ineffective in patients with no immunity. In the past, this led to different recommendations for patients considered semi-immune and those considered non-immune. As individual immunity can vary considerably, even in areas of moderate-to-high transmission intensity, 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 a treatment course to patients with suspected but unconfirmed malaria, with the intention of giving the full treatment if the diagnosis is confirmed. This practice is unsafe, could engender resistance, and is not recommended.

4.7 | ADDITIONAL CONSIDERATIONS FOR CLINICAL MANAGEMENT

4.7.1 | CAN THE PATIENT TAKE ORAL MEDICATION?

Some patients cannot tolerate oral treatment and will require parenteral or rectal administration for 1–2 days, until they can swallow and retain oral medication reliably. Although such patients do not show other signs of severity, they should receive the same initial antimalarial treatments recommended for severe malaria (see chapter 7, 7.4.). Initial rectal or parenteral treatment must always be followed by a full 3-day course of ACT.

4.7.2 | USE OF ANTIPYRETICS

In young children, high fevers are often associated with vomiting, regurgitation of medication and seizures. They are thus treated with antipyretics and, if necessary, fanning and tepid sponging. Antipyretics should be used if the core temperature is > 38.5 °C. Paracetamol (acetaminophen) at a dose of 15 mg/kg bw every 4 h is widely used; it is safe and well tolerated and can be given orally or as a suppository. Ibuprofen (5 mg/kg bw) has been used successfully as an alternative in the treatment of malaria and other childhood fevers, but, like aspirin and other non-steroidal anti-inflammatory drugs, it is *no longer recommended* because of the risks of gastrointestinal bleeding, renal impairment and Reye's syndrome.

4.7.3 | USE OF ANTI-EMETICS

Vomiting is common in acute malaria and may be severe. Parenteral antimalarial treatment may therefore be required until oral administration is tolerated. Then a full 3-day course of ACT should be given. Anti-emetics are potentially sedative and may have neuropsychiatric adverse effects, which could mask or confound the diagnosis of severe malaria. They should therefore be used with caution.

4.7.4 | MANAGEMENT OF SEIZURES

Generalized seizures are more common in children with *P. falciparum* malaria than in those with malaria due to other species. This suggests an overlap between the cerebral pathology resulting from falciparum malaria and febrile convulsions. As seizures may be a prodrome of cerebral malaria, patients who have more than two seizures within a 24-h period should be treated as for severe malaria. If the seizures continue, the airways should be maintained and anticonvulsants given (parenteral or rectal benzodiazepines or intramuscular paraldehyde). When the seizure has stopped, the child should be treated as indicated in section 7.10.5, if his or her core temperature is > 38.5 °C. There is no evidence that prophylactic anticonvulsants are beneficial in otherwise uncomplicated malaria, and they are not recommended.

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EDITION

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

Treating uncomplicated *P. falciparum* malaria in special risk groups

First trimester of pregnancy

Treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with 7 days of quinine + clindamycin.
Strong recommendation, very low- quality evidence

Infants less than 5kg body weight

Treat infants weighing < 5 kg with uncomplicated *P. falciparum* malaria with an ACT at the same mg/kg bw target dose as for children weighing 5 kg.
Strong recommendation, very low- quality evidence

Patients co-infected with HIV

In people who have HIV/AIDS and uncomplicated *P. falciparum* malaria, avoid artesunate + SP if they are also receiving co-trimoxazole, and avoid artesunate + amodiaquine if they are also receiving efavirenz or zidovudine.
Good practice statement

Non-immune travellers

Treat travellers with uncomplicated *P. falciparum* malaria returning to non-endemic settings with an ACT.
Strong recommendation, high-quality evidence

Uncomplicated hyperparasitaemia

People with *P. falciparum* hyperparasitaemia are at increased risk of treatment failure, severe malaria and death so should be closely monitored, in addition to receiving an ACT.
Good practice statement

Several important patient sub-populations, including young children, pregnant women and patients taking potent enzyme inducers (e.g. rifampicin, efavirenz), have altered pharmacokinetics, resulting in sub-optimal exposure to antimalarial drugs. This increases the rate of treatment failure with current dosage regimens. The rates of treatment failure are substantially higher in hyperparasitaemic patients and patients in areas with artemisinin-resistant falciparum malaria, and these groups require greater exposure to antimalarial drugs (longer duration of therapeutic concentrations) than is achieved with current ACT dosage recommendations. It is often uncertain how best to achieve this. Options include increasing individual doses, increasing the frequency or duration of dosing, or adding an additional antimalarial drug. Increasing individual doses may not, however, achieve the desired exposure (e.g. lumefantrine absorption becomes saturated), or the dose may be toxic due to transiently high plasma concentrations (piperaquine, mefloquine, amodiaquine, pyronaridine). An additional advantage of lengthening the duration of treatment (by giving a 5-day regimen) is that it provides additional exposure of the asexual cycle to the artemisinin component as well as augmenting exposure to the partner drug. The acceptability, tolerability, safety and effectiveness of augmented ACT regimens in these special circumstances should be evaluated urgently.

5.1 | PREGNANT AND LACTATING WOMEN

Malaria in pregnancy is associated with low-birth-weight infants, increased anaemia and, in low-transmission areas, increased risks for severe malaria, pregnancy loss and death. In high-transmission settings, despite the adverse effects on fetal growth, malaria is usually asymptomatic in pregnancy or is associated with only mild, non-specific symptoms. There is insufficient information on the safety, efficacy and pharmacokinetics of most antimalarial agents in pregnancy, particularly during the first trimester.

5.1.1 | FIRST TRIMESTER

First trimester of pregnancy

Treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with 7 days of quinine + clindamycin.
Strong recommendation

Evidence supporting the recommendation (see Annex 4, A4.5)
Data available were not suitable for evaluation using the GRADE methodology, as there is no /almost no evidence for alternative treatment using ACT.

Safety assessment from published prospective data on 700 women exposed in the first trimester of pregnancy has not indicated any adverse effects of artemisinin-derivatives on pregnancy or on the health of the fetus or neonate.

The currently available data are only sufficient to exclude a ≥ 4.2-fold increase in risk of any major defect detectable at birth (background prevalence assumed to be 0.9%), if half the exposures occur during the embryo-sensitive period (4–9 weeks post-conception).

Other considerations
The limited data available on the safety of artemisinin-derivatives in early pregnancy allow for some reassurance in counselling women accidentally exposed to an artemisinin-derivative early in the first trimester. There is no need for them to have their pregnancy interrupted because of this exposure.

In the absence of adequate safety data on the artemisinin-derivatives in the first trimester of pregnancy the Guideline Development Group was unable to make recommendations beyond reiterating the status quo.

McGready R, Lee SJ, Wiladphaingern J, et al. Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study. Lancet Infect Dis. 2012;12:388-96.

Mosha D, Mazuguni F, Mrema S, et al. Safety of artemether-lumefantrine exposure in first trimester of pregnancy: an observational cohort. Malar J. 2014; 13: 197e.

Because organogenesis occurs mainly in the first trimester, this is the time of greatest concern for potential teratogenicity, although development of the nervous system continues throughout pregnancy. The antimalarial medicines considered safe in the first trimester of pregnancy are quinine, chloroquine, clindamycin and proguanil.

The safest treatment regimen for pregnant women in the first trimester with uncomplicated falciparum malaria is therefore quinine + clindamycin (10mg/kg bw twice a day) for 7 days (or quinine monotherapy if clindamycin is not available). An ACT or oral artesunate + clindamycin is an alternative if quinine + clindamycin is not available or fails.

In reality, women often do not declare their pregnancy in the first trimester or may not yet be aware that they are pregnant. Therefore, all women of childbearing age should be asked about the possibility that they are pregnant before they are given antimalarial agents; this is standard practice for administering any medicine to potentially pregnant women. Nevertheless, women in early pregnancy will often be exposed inadvertently to the available first-line treatment, mostly ACT. Published prospective data on 700 women exposed in the first trimester of pregnancy indicate no adverse effects of artemisinins (or the partner drugs) on pregnancy or on the health of fetuses or neonates. The available data are sufficient to exclude a ≥ 4.2-fold increase in risk of any major defect detectable at birth (background prevalence assumed to be 0.9%), if half the exposures occur during the embryo-sensitive period (4–9 weeks post-conception). These data provide assurance in counselling women exposed to an antimalarial drug early in the first trimester and indicate that there is no need for them to have their pregnancy interrupted because of this exposure.

5.1.2 | SECOND AND THIRD TRIMESTERS

Experience with artemisinin derivatives in the second and third trimesters (over 4000 documented pregnancies) is increasingly reassuring: no adverse effects on the mother or fetus have been reported. The current assessment of risk–benefit suggests that *ACTs should be used* to treat uncomplicated falciparum malaria in the second and third trimesters of pregnancy. The current standard six-dose artemether + lumefantrine regimen for the treatment of uncomplicated falciparum malaria has been evaluated in > 1000 women in the second and third trimesters in controlled trials and has been found to be well tolerated and safe. In a low-transmission setting on the Myanmar–Thailand border, however, the efficacy of the standard six-dose artemether + lumefantrine regimen was inferior to 7 days of artesunate monotherapy. The lower efficacy may have been due to lower drug concentrations in pregnancy, as was also recently observed in a high-transmission area in Uganda and the United Republic of Tanzania. Although many women in the second and third trimesters of pregnancy in Africa have been exposed to artemether + lumefantrine, further studies are under way to evaluate its efficacy, pharmacokinetics and safety in pregnant women. Similarly, many pregnant women in Africa have been treated with amodiaquine alone or combined with SP or artesunate;

however, amodiaquine use for the treatment of malaria in pregnancy has been formally documented in only > 1300 pregnancies. Use of amodiaquine in women in Ghana in the second and third trimesters of pregnancy was associated with frequent minor side-effects but not with liver toxicity, bone marrow depression or adverse neonatal outcomes.

Dihydroartemisinin + piperaquine was used successfully in the second and third trimesters of pregnancy in > 2000 women on the Myanmar–Thailand border for rescue therapy and in Indonesia for first-line treatment. SP, although considered safe, is not appropriate for use as an artesunate partner drug in many areas because of resistance to SP. If artesunate + SP is used for treatment, co-administration of daily high doses (5 mg) of folate supplementation should be avoided, as this compromises the efficacy of SP. A lower dose of folate (0.4–0.5 mg bw/day) or a treatment other than artesunate + SP should be used.

Mefloquine is considered safe for the treatment of malaria during the second and third trimesters; however, it should be given only in combination with an artemisinin derivative.

Quinine is associated with an increased risk for hypoglycaemia in late pregnancy, and it should be used (with clindamycin) only if effective alternatives are not available.

Primaquine and tetracyclines should not be used in pregnancy.

5.1.3 | DOSING IN PREGNANCY

Data on the pharmacokinetics of antimalarial agents used during pregnancy are limited. Those available indicate that pharmacokinetic properties are often altered during pregnancy but that the alterations are insufficient to warrant dose modifications at this time. With quinine, no significant differences in exposure have been seen during pregnancy. Studies of the pharmacokinetics of SP used in IPTp in many sites show significantly decreased exposure to sulfadoxine, but the findings on exposure to pyrimethamine are inconsistent. Therefore, no dose modification is warranted at this time.

Studies are available of the pharmacokinetics of artemether + lumefantrine, artesunate + mefloquine and dihydroartemisinin + piperaquine. Most data exist for artemether + lumefantrine; these suggest decreased overall exposure during the second and third trimesters. Simulations suggest that a standard six-dose regimen of lumefantrine given over 5 days, rather than 3 days, improves exposure, but the data are insufficient to recommend this alternative regimen at present. Limited data on pregnant women treated with dihydroartemesinin + piperaquine suggest lower dihydroartemisinin exposure and no overall difference in total piperaquine exposure, but a shortened piperaquine elimination half-life was noted. The data on artesunate + mefloquine are insufficient to recommend an adjustment of dosage. No data are available on the pharmacokinetics of artesunate + amodiaquine in pregnant women with falciparum malaria, although drug exposure was similar in pregnant and non-pregnant women with vivax malaria.

5.1.4 | LACTATING WOMEN

The amounts of antimalarial drugs that enter breast milk and are consumed by breastfeeding infants are relatively small. Tetracycline is contraindicated in breastfeeding mothers because of its potential effect on infants' bones and teeth. Pending further information on excretion in breast milk, primaquine should not be used for nursing women, unless the breastfed infant has been checked for G6PD deficiency.

5.2 | YOUNG CHILDREN AND INFANTS (INCLUDING THOSE WHO ARE MALNOURISHED)

Artemisinin derivatives are safe and well tolerated by young children; therefore, the choice of ACT is determined largely by the safety and tolerability of the partner drug.

SP (with artesunate) should be avoided in the first weeks of life because it displaces bilirubin competitively and could thus aggravate neonatal hyperbilibinaemia. Primaquine should be avoided in the first 6 months of life (although there are no data on its toxicity in infants), and tetracyclines should be avoided throughout infancy. With these exceptions, none of the other currently recommended antimalarial treatments has shown serious toxicity in infancy.

Delay in treating *P. falciparum* malaria in infants and young children can have fatal consequences, particularly for more severe infections. The uncertainties noted above should not delay treatment with the most effective drugs available. In treating young children, it is important to ensure accurate dosing and retention of the administered dose, 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 drug administration and the importance of administering the drug again if it is regurgitated within 1 h of administration. Because deterioration in infants can be rapid, the threshold for use of parenteral treatment should be much lower.

5.2.1 | OPTIMAL ANTIMALARIAL DOSING IN YOUNG CHILDREN

Although dosing on the basis of body area is recommended for many drugs in young children, for the sake of simplicity, antimalarial drugs have been administered as a standard dose per kg bw for all patients, including young children and infants. This approach does not take into account changes in drug disposition that occur

with development. The currently recommended doses of lumefantrine, piperaquine, SP, artesunate and chloroquine result in lower drug concentrations in young children and infants than in older patients. Adjustments to previous dosing regimens for dihydroartemisinin + piperaquine in uncomplicated malaria and for artesunate in severe malaria are now recommended to ensure adequate the drug exposure in this vulnerable population. The available evidence for artemether + lumefantrine, SP and chloroquine does not indicate dose modification at this time, but young children should be closely monitored, as reduced drug exposure may increase the risk for treatment failure. Limited studies of amodiaquine and mefloquine showed no significant effect of age on plasma concentration profiles.

In community situations where parenteral treatment is needed but cannot be given, such as for infants and young children who vomit antimalarial drugs repeatedly or are too weak to swallow or are very ill, give rectal artesunate and transfer the patient to a facility in which parenteral treatment is possible. Rectal administration of a single dose of artesunate as pre-referral treatment reduces the risks for death and neurological disability, as long as this initial treatment is followed by appropriate parenteral antimalarial treatment in hospital. Further evidence on pre-referral rectal administration of artesunate and other antimalarial drugs is given in section 7.5.

5.2.2 | OPTIMAL ANTIMALARIAL DOSING IN INFANTS

Infants less than 5kg body weight

Treat infants weighing < 5 kg with uncomplicated *P. falciparum* malaria with an ACT at the same mg/kg bw target dose as for children weighing 5 kg.
Strong recommendation

Evidence supporting the recommendation (see Annex 4, A4.6)
Data available were not suitable for evaluation using the GRADE methodology.

In most clinical studies, subgroups of infants and older children were not distinguished, and the evidence for young infants (< 5 kg) is insufficient for confidence in current treatment recommendations. Nevertheless despite these uncertainties, infants need prompt, effective treatment of malaria. There is limited evidence that artemether + lumefantrine and dihydroartemisinin + piperaquine achieve lower plasma concentrations in infants than in older children and adults.

Other considerations
The Guideline Development Group considered the currently available evidence too limited to warrant formal evidence review at this stage, and was unable to recommend any changes beyond the status quo. Further research is warranted.

The pharmacokinetics properties of many medicines in infants differ markedly from those in adults because of the physiological changes that occur in the first year of life (Annex 5). Accurate dosing is particularly important for infants. The only antimalarial agent that is currently contraindicated for infants (<6 months) is primaquine.

ACT is recommended and should be given according to body weight at the same mg/kg bw dose for all infants, including those weighing < 5 kg, with close monitoring of treatment response. The lack of infant formulations of most antimalarial drugs often necessitates division of adult tablets, which can lead to inaccurate dosing. When available, paediatric formulations and strengths are preferred, as they improve the effectiveness and accuracy of ACT dosing.

5.2.3 | OPTIMAL ANTIMALARIAL DOSING IN MALNOURISHED YOUNG CHILDREN

Malaria and malnutrition frequently coexist. Malnutrition may result in inaccurate dosing when doses are based on age (a dose may be too high for an infant with a low weight for age) or on weight (a dose may be too low for an infant with a low weight for age). Although many studies of the efficacy of antimalarial drugs have been conducted in populations and settings where malnutrition was prevalent, there are few studies of the disposition of the drugs specifically in malnourished individuals, and these seldom distinguished between acute and chronic malnutrition. Oral absorption of drugs may be reduced if there is diarrhoea or vomiting, or rapid gut transit or atrophy of the small bowel mucosa. Absorption of intramuscular and possibly intrarectal drugs may be slower, and diminished muscle mass may make it difficult to administer repeated intramuscular injections to malnourished patients. The volume of distribution of some drugs may be larger and the plasma concentrations lower. Hypoalbuminaemia may reduce protein binding and increase metabolic clearance, but concomitant hepatic dysfunction may reduce the metabolism of some drugs; the net result is uncertain.

Small studies of the pharmacokinetics of quinine and chloroquine showed alterations in people with different degrees of malnutrition. Studies of SP in IPTp and of amodiaquine monotherapy and dihydroartemisinin + piperaquine for treatment suggest reduced efficacy in malnourished children. A pooled analysis of data for individual patients showed that the concentrations of lumefantrine on day 7 were lower in children < 3 years who were underweight for age than in adequately nourished children and adults. Although these findings are concerning, they are insufficient to warrant dose modifications (in mg/kg bw) of any antimalarial drug in patients with malnutrition, however, their response to treatment should be monitored more closely.

5.3 | LARGE AND OBESE ADULTS

Large adults are at risk for under-dosing when they are dosed by age or in standard pre-packaged adult weight-based treatments. In principle, dosing of large adults should be based on achieving the target mg/kg bw dose for each antimalarial regimen. The practical consequence is that two packs of an antimalarial drug might have to be opened to ensure adequate treatment. For obese patients, less drug is often distributed to fat than to other tissues; therefore, they should be *dosed on the basis of an estimate of lean body weight, ideal body weight*. Patients who are heavy but not obese require the same mg/kg bw doses as lighter patients.

In the past, maximum doses have been recommended, but there is no evidence or justification for this practice. As the evidence for an association between dose, pharmacokinetics and treatment outcome in overweight or large adults is limited, and alternative dosing options have not been assessed in treatment trials, it is recommended that this gap in knowledge be assessed urgently. In the absence of data, treatment providers should attempt to follow up the treatment outcomes of large adults whenever possible.

5.4 | PATIENTS CO-INFECTED WITH HIV

There is considerable geographical overlap between malaria and HIV infection, and many people are co-infected. 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 areas of stable endemic malaria, HIV-infected patients who are partially immune to malaria may have more frequent, higher-density infections, while in areas of unstable transmission, HIV infection is associated with increased risks for severe malaria and malaria-related deaths. Limited information is available on how HIV infection modifies therapeutic responses to ACTs. Early studies suggested that increasing HIV-related immunosuppression was associated with decreased treatment response to antimalarial drugs. There is presently insufficient information to modify the general malaria treatment recommendations for patients with HIV/AIDS.

Therapeutic interactions must be taken into consideration (See Annex 5, 5.14). Studies on prophylaxis with trimethoprim + sulfamethoxazole in HIV-infected children and adults show significant protection against malaria, even in areas with high rates of antifolate resistance. In studies of drug interactions between antiretroviral medicines and ACTs, HIV-co-infected individuals on trimethoprim + sulfamethoxazole and antiretroviral treatment, particularly zidovudine-containing regimens, had high rates of neutropenia when artesunate + amodiaquine was used for malaria treatment. HIV-infected children had a seven- to eightfold increased risk for neutropenia 14 days after starting of artesunate + amodiaquine than HIV-uninfected children. Hepatotoxicity has been documented when efavirenz was given with artesunate + amodiaquine, which may be due to inhibition of CYP2C8-

mediated amodiaquine metabolism by efavirenz. Data on the safety of nevirapine-based regimens in people receiving amodiaquine + artesunate are lacking, but lower levels of amodiaquine and its metabolite desethylamodiaquine have been reported when they were given together with nevirapine.

More data are available on use of artemether + lumefantrine with antiretroviral treatment. A study in children with uncomplicated malaria in a high-transmission area of Africa showed a decreased risk for recurrent malaria after treatment with artemether + lumefantrine in children receiving lopinavir–ritonavir-based antiretroviral treatment as compared with non-nucleoside reverse transcriptase inhibitor-based antiretroviral treatment. Evaluation of pharmacokinetics in these children and in healthy volunteers showed significantly higher exposure to lumefantrine and lower exposure to dihydroartemisinin with lopinavir–ritonavir-based antiretroviral treatment, but no adverse consequences. Conversely, efavirenz-based antiretroviral treatment was associated with a two- to fourfold decrease in exposure to lumefantrine in healthy volunteers and malaria-infected adults and children, with increased rates of recurrent malaria after treatment. Close monitoring is required. Increasing artemether + lumefantrine dosing with efavirenz-based antiretroviral treatment has not yet been studied. Exposure to lumefantrine and other non-nucleoside reverse transcriptase inhibitor-based antiretroviral treatment, namely nevirapine and etravirine, did not show consistent changes that would require dose adjustment.

Studies of administration of quinine with lopinavir–ritonavir or ritonavir alone in healthy volunteers gave conflicting results. The combined data are insufficient to justify dose adjustment. Single-dose atovaquone – proguanil with efavirenz, lopinavir–ritonavir or atazanavir–ritonavir were all associated with a significantly decreased area under the concentration–time curve for atovaquone (two- to fourfold) and proguanil (twofold), which could well compromise treatment or prophylactic efficacy. There is insufficient evidence to change the current mg/kg bw dosing recommendations; however, these patients should also be monitored closely.

5.5 | PATIENTS CO-INFECTED WITH TUBERCULOSIS

Rifamycins, in particular rifampicin, are potent CYP3A4 inducers with weak antimalarial activity. Concomitant administration of rifampicin during quinine treatment of adults with malaria was associated with a significant decrease in exposure to quinine and a five-fold higher recrudescence rate. Similarly, concomitant rifampicin with mefloquine in healthy adults was associated with a there-fold decrease in exposure to mefloquine. In adults co-infected with HIV and tuberculosis who were being treated with rifampicin, administration of artemether + lumefantrine resulted in significantly lower exposure to artemether, dihydroartemisinin and lumefantrine (nine-, six- and there-fold decreases, respectively). There is insufficient evidence at this time to change the current mg/kg bw dosing recommendations; however, as these patients are at higher risk of recrudescent infections they should be monitored closely.

5.6 | NON-IMMUNE TRAVELLERS

Non-immune travellers

Treat travellers with uncomplicated *P. falciparum* malaria returning to non-endemic settings with an ACT.
Strong recommendation, high-quality evidence

GRADE (see Annex 4, A4.1 and A4.2)
Studies have consistently demonstrated that the five WHO recommended ACTs have less than 5% PCR-adjusted treatment failure rates in settings without resistance to the partner drug (*high quality evidence*).

Other considerations
The Guideline Development Group considered the evidence of superiority of ACTs over non-ACTs from endemic settings to be equally applicable to those travelling from non-endemic settings.

Travellers who acquire malaria are often non-immune people living in cities in endemic countries with little or no transmission or are visitors from non-endemic countries travelling to areas with malaria transmission. Both are at higher risk for severe malaria. In a malaria-endemic country, they should be treated according to national policy, provided the treatment recommended has a recent proven cure rate > 90%. Travellers who return to a non-endemic country and then develop malaria present a particular problem, and the case fatality rate is often high; doctors in non-malarious areas may be unfamiliar with malaria and the diagnosis is commonly delayed, and effective antimalarial drugs may not be registered or may be unavailable. However prevention of transmission or the emergence of resistance are not relevant outside malaria-endemic areas. If the patient has taken chemoprophylaxis, the same medicine should not be used for treatment. Treatment of *P. vivax*, *P. ovale* and *P. malariae* malaria in travellers should be the same as for patients in endemic areas (see section 6).

There may be delays in obtaining artesunate, artemether or quinine for the management of severe malaria outside endemic areas. If only parenteral quinidine is available, it should be given, with careful clinical and electrocardiographic monitoring (see section 7).

5.7 | UNCOMPLICATED HYPERPARASITAEMIA

Uncomplicated hyperparasitaemia is present in patients who have ≥ 4% parasitaemia but no signs of severity. They are at increased risk for severe malaria and for treatment failure and are considered an important source of antimalarial drug resistance. In falciparum malaria, the risk for progression to severe malaria with vital organ dysfunction increases at higher parasite densities. In low-transmission settings, mortality begins to increase when the parasite density exceeds 100 000/ µL (~2% parasitaemia). On the north-west border of Thailand, before the general introduction of ACT, parasitaemia > 4% without signs of severity was associated with a 3% mortality rate (about 30-times higher than from uncomplicated falciparum malaria with lower densities) and a six-times higher risk of treatment failure. The relationship between parasitaemia and risks depends on the epidemiological context: in higher-transmission settings, the risk of developing severe malaria in patients with high parasitaemia is lower, but "uncomplicated hyperparasitaemia" is still associated with a significantly higher rate of treatment failure.

Patients with a parasitaemia of 4–10% and no signs of severity also require close monitoring, and, if feasible, admission to hospital. They have high rates of treatment failure. Non-immune people such as travellers and individuals in low-transmission settings with a parasitaemia > 2% are at increased risk and also require close attention. Parasitaemia > 10% is considered to indicate severe malaria in all settings.

It is difficult to make a general recommendation about treatment of uncomplicated hyperparasitaemia, for several reasons: recognizing these patients requires an accurate, quantitative parasite count (they will not be identified from semi-quantitative thick film counts or RDTs), the risks for severe malaria vary considerably, and the risks for treatment failure also vary. Furthermore, little information is available on therapeutic responses in uncomplicated hyperparasitaemia. As the artemisinin component of an ACT is essential in preventing progression to severe malaria, absorption of the first dose must be ensured (atovaquone – proguanil alone should not be used for travellers presenting with uncomplicated hyperparasitaemia). Longer courses of treatment are more effective; both giving longer courses of ACT and preceding the standard 3-day ACT regimen with parenteral or oral artesunate have been used.

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EDITION

6 | TREATMENT OF UNCOMPLICATED MALARIA CAUSED BY *P. VIVAX*, *P. OVALE*, *P. MALARIAE* OR *P. KNOWLESI*

Treating uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria

Blood stage infection

If the malaria species is not known with certainty, treat as for uncomplicated *P. falciparum* malaria.
Good practice statement

In areas with chloroquine-susceptible infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria with either an ACT (except pregnant women in their first trimester) or chloroquine.
Strong recommendation, high-quality evidence

In areas with chloroquine-resistant infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria (except pregnant women in their first trimester) with an ACT.
Strong recommendation, high-quality evidence

Treat pregnant women in their first trimester who have chloroquine-resistant *P. vivax* malaria with quinine.
Strong recommendation, very low-quality evidence

Preventing relapse in *P. vivax* or *P. ovale* malaria

The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.
Good practice statement

To prevent relapse, treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known no to be G6PD deficient, and people with G6PD deficiency) with a 14-day course (0.25-0.5 mg/kg bw daily) of primaquine in all transmission settings.
Strong recommendation, high-quality evidence

In people with G6PD deficiency, consider preventing relapse by giving primaquine base at 0.75 mg/kg bw once a week for 8 weeks, with close medical supervision for potential primaquine-induced adverse haematological effects.
Conditional recommendation, very low-quality evidence

When the G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine.
Good practice statement

Pregnant and breast feeding women

In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, on the basis of G6PD status, treat with primaquine to prevent future relapse.
Conditional recommendation, moderate-quality evidence

P. vivax is the second most important causative agent of human malaria. Approximately 35% of the world's population is at risk. *P. vivax* accounts for approximately 9%[8] of malaria cases worldwide and is the dominant malaria species outside Africa. *P. vivax* is prevalent in endemic areas in Asia, Central and South America, the Middle East and Oceania. In Africa, *P. vivax* is relatively uncommon, except in the Horn of Africa. In West Africa, *P. vivax* is rare except in Mauritania and Mali. In most areas in which *P. vivax* is prevalent, malaria transmission rates are low, and the affected populations therefore achieve little immunity. Consequently, people of all ages are at risk. The exception is the island of New Guinea, where transmission in some parts is intense. The other human malaria parasite species *P. malariae* and *P. ovale* (two sympatric species) are generally less prevalent, but they are distributed worldwide, especially in the tropical areas of Africa. During the past decade, there have been many reported human infections with *P. knowlesi,* a simian parasite in the forested areas of South-East Asia. In parts of the island of Borneo, this is now the main species causing malaria. Further information is provided in Annex 6.

Of the species of *Plasmodium* that affect humans, only *P. vivax* and *P. ovale* form hypnozoites, which are dormant parasite stages in the liver that cause relapses of infection weeks to years after the primary infection. Thus, a single mosquito inoculation may result in repeated bouts of illness. *P. vivax* exists in two general forms: the more prevalent tropical form, which causes malaria that relapses at frequent intervals (typically every 3 weeks unless slowly eliminated antimalarial drugs are given, in which case the interval is 5–7 weeks) and tends to be less susceptible to primaquine; and a temperate form, in which there may be a long (~9-month) incubation period or a similarly long interval between primary illness and relapse. The temperate form of *P. vivax* is more sensitive to primaquine. Infection with *P. vivax* during pregnancy reduces the birth weight of the infant, as does *P. falciparum*. In primigravidae, the birth weight reduction is approximately two thirds of that associated with *P. falciparum* (110 g compared with 170 g), but this adverse effect does not decrease with successive pregnancies, unlike in *P. falciparum* infections. *P. knowlesi* infections in humans are potentially dangerous; the patient may deteriorate rapidly because this parasite has a 24-h asexual cycle (quotidian) and so the parasite burden may expand rapidly, resulting in severe and sometimes fatal illness.

6.1 | THERAPEUTIC OBJECTIVE

The objective of treating malaria caused by *P. vivax* and *P. ovale* is to cure both blood-stage and liver-stage infections (called radical cure), thereby preventing recrudescence and relapse, respectively.

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[8] WHO. World malaria report 2014. Geneva: World Health Organization; 2014 (http://who.int/malaria/publications/world_malaria_report_2014/en/).

6.2 | DIAGNOSIS

The clinical features of uncomplicated malaria are non-specific, and diagnosis of malaria requires blood testing. Malaria species are usually differentiated by microscopy. Young ring forms of all species look similar, but older stages and gametocytes have species-specific characteristics, except for the two forms of *P. ovale*, which appear identical. *P. knowlesi* malaria is frequently misdiagnosed as *P. malariae*, so any case of high parasitaemia with "*P. malariae-like*" parasites in or near an area where long- or pig-tailed macaque monkeys live should be treated as *P. knowlesi* until proved otherwise. *P. knowlesi* infections require confirmation by PCR. RDTs based on lateral flow immunochromatography are available for the detection of *P. vivax*, and their performance has improved in recent years, although their sensitivity for the other non-falciparum malarias is low. Molecular genotyping of *P. vivax* parasites is less useful in studies of therapeutic efficacy than in falciparum malaria as relapses may be due to either the same genotype that caused the initial illness or a different one.

6.3 | SUSCEPTIBILITY OF *P. VIVAX*, *P. OVALE*, *P. MALARIAE* AND *P. KNOWLESI* TO ANTIMALARIAL DRUGS

Few recent data are available on the susceptibility of *P. ovale, P. malariae* and *P. knowlesi* to antimalarial agents in vivo. These species are all regarded as sensitive to chloroquine, although chloroquine resistance was reported recently in *P. malariae*. Experience indicates that *P. ovale* and *P. malariae* are also susceptible to amodiaquine, mefloquine and the artemisinin derivatives and to ACT. Their susceptibility to antifolate antimalarial drugs, such as SP, is less certain. *P. knowlesi* is also sensitive to quinine, mefloquine, atovaquone – proguanil and artemether + lumefantrine and severe knowlesi malaria responds well to artesunate.

The susceptibility of *P. vivax* has been studied extensively, and, now that short-term culture methods have been standardized, the results of clinical studies are supported by *in vitro* observations. *P. vivax* is generally still sensitive to chloroquine, but resistance is increasing. High-level resistance to chloroquine is prevalent throughout the island of New Guinea, in Oceania and in parts of Indonesia. Lower-level resistance is found in other parts of South-East Asia and parts of South America. On the Indian subcontinent where most of the world's *P. vivax* malaria occurs, the parasites are mainly sensitive to chloroquine. Resistance to pyrimethamine has increased rapidly in some areas, rendering SP ineffective. There are insufficient data on current susceptibility to proguanil, although resistance to proguanil was selected rapidly when it was first used in areas endemic for *P. vivax* malaria.

In general, *P. vivax* is sensitive to all the other antimalarial drugs. In contrast to *P. falciparum*, asexual stages of *P. vivax* are also susceptible to primaquine. Thus, chloroquine + primaquine can be considered as a combination treatment for

blood-stage infections, in addition to providing radical cure. The only drugs with significant activity against the hypnozoites are the 8-aminoquinolines (primaquine, bulaquine, tafenoquine). There is no standardized *in vitro* method for assessing the hypnozoiticidal activity of antimalarial drugs. *In vivo* assessments suggests that tolerance of *P. vivax* to primaquine is greater in eastern Asia and Oceania than elsewhere.

6.4 | TREATMENT OF BLOOD-STAGE INFECTION

Treating uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria

In areas with chloroquine-susceptible infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale, P. malariae* or *P. knowlesi* malaria with either an ACT (except pregnant women in their first trimester) or chloroquine.
Strong recommendation, high-quality evidence

In areas with chloroquine-resistant infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria (except pregnant women in their first trimester) with an ACT.
Strong recommendation, high-quality evidence

GRADE (see Annex 4, A4.7 and A4.8)

In a systematic review of ACTs for the treatment of *P. vivax* malaria, five trials were conducted in Afghanistan, Cambodia, India, Indonesia and Thailand between 2002 and 2011 with a total of 1622 participants which compared ACTs directly with chloroquine. In comparison with chloroquine:

- ACTs cleared parasites from the peripheral blood more quickly (parasitaemia after 24 h of treatment: RR, 0.42; 95% CI, 0.36–0.50, four trials, 1652 participants, *high-quality evidence*); and
- ACTs were at least as effective in preventing recurrent parasitaemia before day 28 (RR, 0.58; 95% CI, 0.18–1.90, five trials, 1622 participants, *high-quality evidence*).

In four of these trials, few cases of recurrent parasitaemia were seen before day 28 with both chloroquine and ACTs. In the fifth trial, in Thailand in 2011, increased recurrent parasitaemia was seen after treatment with chloroquine (9%), but was infrequent after ACT (2%) (RR, 0.25; 95% CI, 0.09–0.66, one trial, 437 participants).

ACT combinations with long half-lives provided a longer prophylactic effect after treatment, with significantly fewer cases of recurrent parasitaemia between day 28 and day 42 or day 63 (RR, 0.57; 95% CI, 0.40–0.82, three trials, 1066 participants, *moderate-quality evidence*).

Other considerations

The guideline development group recognized that, in the few settings in which *P. vivax* is the only endemic species and where chloroquine resistance remains low, the increased cost of ACT may not be worth the small additional benefits. Countries where chloroquine is used for treatment of vivax malaria should monitor for chloroquine resistance and change to ACT when the treatment failure rate is > 10% at day 28.

Gogtay N, Kannan S, Thatte UM, Olliaro PL, Sinclair D. Artemisinin-based combination therapy for treating uncomplicated Plasmodium vivax malaria. Cochrane Database Systemat Rev 2013; 10:CD008492. doi: 10.1002/14651858.CD008492.pub3.

6.4.1 | UNCOMPLICATED *P. VIVAX* MALARIA

In areas with chloroquine-sensitive P. vivax

For chloroquine-sensitive vivax malaria, oral chloroquine at a total dose of 25 mg base/kg bw is effective and well tolerated. Lower total doses are not recommended, as these encourage the emergence of resistance. Chloroquine is given at an initial dose of 10 mg base/kg bw, followed by 10 mg/kg bw on the second day and 5 mg/kg bw on the third day. In the past, the initial 10-mg/kg bw dose was followed by 5 mg/kg bw at 6 h, 24 h and 48 h. As residual chloroquine suppresses the first relapse of tropical *P. vivax* (which emerges about 3 weeks after onset of

the primary illness), relapses begin to occur 5–7 weeks after treatment if radical curative treatment with primaquine is not given.

ACTs are highly effective in the treatment of vivax malaria, allowing simplification (unification) of malaria treatment; i.e. all malaria infections can be treated with an ACT. The exception is artesunate + SP, where resistance significantly compromises its efficacy. Although good efficacy of artesunate + SP was reported in one study in Afghanistan, in several other areas (such as South-East Asia) *P. vivax* has become resistant to SP more rapidly than *P. falciparum*. The initial response to all ACTs is rapid in vivax malaria, reflecting the high sensitivity to artemisinin derivatives, but, unless primaquine is given, relapses commonly follow. The subsequent recurrence patterns differ, reflecting the elimination kinetics of the partner drugs. Thus, recurrences, presumed to be relapses, occur earlier after artemether + lumefantrine than after dihydroartemisinin + piperaquine or artesunate + mefloquine because lumefantrine is eliminated more rapidly than either mefloquine or piperaquine. A similar temporal pattern of recurrence with each of the drugs is seen in the *P. vivax* infections that follow up to one third of acute falciparum malaria infections in South-East Asia.

In areas with chloroquine-resistant P. vivax

ACTs containing piperaquine, mefloquine or lumefantrine are the recommended treatment, although artesunate + amodiaquine may also be effective in some areas.

In the systematic review of ACTs for treating *P. vivax* malaria, dihydroartemisinin + piperaquine provided a longer prophylactic effect than ACTs with shorter half-lives (artemether + lumefantrine, artesunate + amodiaquine), with significantly fewer recurrent parasitaemias during 9 weeks of follow-up (RR, 0.57; 95% CI, 0.40–0.82, three trials, 1066 participants). The half-life of mefloquine is similar to that of piperaquine, but use of dihydroartemisinin + piperaquine in *P. vivax* mono-infections has not been compared directly in trials with use of artesunate + mefloquine.

In the first-trimester of pregnancy, quinine should be used in place of ACTs (section 5.1).

6.4.2 | UNCOMPLICATED *P. OVALE*, *P. MALARIAE* OR *P. KNOWLESI* MALARIA

Resistance of *P. ovale*, *P. malariae* and *P. knowlesi* to antimalarial drugs is not well characterized, and infections caused by these three species are generally considered to be sensitive to chloroquine. In only one study, conducted in Indonesia, was resistance to chloroquine reported in *P. malariae*.

The blood stages of *P. ovale*, *P. malariae* and *P. knowlesi* should therefore be treated with the standard regimen of ACT or chloroquine, as for vivax malaria.

6.4.3 | MIXED MALARIA INFECTIONS

Mixed malaria infections are common in endemic areas. For example, in Thailand, despite low levels of malaria transmission, 8% of patients with acute vivax malaria also have *P. falciparum* infections, and one third of acute *P. falciparum* infections are followed by a presumed relapse of vivax malaria (making vivax malaria the most common complication of falciparum malaria).

Mixed infections are best detected by nucleic acid-based amplification techniques, such as PCR; they may be underestimated with routine microscopy. Cryptic *P. falciparum* infections in vivax malaria can be revealed in approximately 75% of cases by RDTs based on the *Pf*HRP2 antigen, but several RDTs cannot detect mixed infection or have low sensitivity for detecting cryptic vivax malaria. ACTs are effective against all malaria species and so are the treatment of choice for mixed infections.

6.5 | TREATMENT OF THE LIVER STAGES (HYPNOZOITES) OF *P. VIVAX* AND *P. OVALE*

Preventing relapse in *P. vivax* or *P. ovale* malaria

To prevent relapse, treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient and people with G6PD deficiency) with a 14-day course of primaquine in all transmission settings.
Strong recommendation, high-quality evidence

In people with G6PD deficiency, consider preventing relapse by giving primaquine base at 0.75 mg base/kg bw once a week for 8 weeks, with close medical supervision for potential primaquine-induced adverse haematological effects.
Conditional recommendation, very low-quality evidence

6.5.1 | PRIMAQUINE FOR PREVENTING RELAPSE

To achieve radical cure (cure and prevention of relapse), relapses originating from liver hypnozoites must be prevented by giving primaquine. The frequency and pattern of relapses varies geographically, with relapse rates generally ranging from 8% to 80%. Temperate long-latency *P. vivax* strains are still prevalent in many areas. Recent evidence suggests that, in endemic areas where people are inoculated frequently with *P. vivax*, a significant proportion of the population harbours dormant but "activatable" hypnozoites. The exact mechanism of activation of dormant hypnozoites is unclear. There is evidence that systemic parasitic and bacterial infections, but not viral infections, can activate *P. vivax* hypnozoites, which explains why *P. vivax* commonly follows *P. falciparum* infections in endemic areas where both parasites are prevalent. Thus, the radical curative efficacy of primaquine must be

set against the prevalent relapse frequency and the likely burden of "activatable" hypnozoites. Experimental studies on vivax malaria and the relapsing simian malaria *P. cynomolgi* suggest that the total dose of 8-aminoquinoline given is the main determinant of radical curative efficacy. In most therapeutic assessments, primaquine has been given for 14 days. Total doses of 3.5 mg base/kg bw (0.25 mg/kg bw per day) are required for temperate strains and 7 mg base/kg bw (0.5 mg/kg bw per day) is needed for the tropical, frequent-relapsing *P. vivax* prevalent in East Asia and Oceania. Primaquine causes dose-limiting abdominal discomfort when taken on an empty stomach; it should always be taken with food.

Primaquine formulation: If available, administer scored tablets containing 7.5 or 15 mg of primaquine. Smaller-dose tablets containing 2.5 and 5 mg base are available in some areas and facilitate accurate dosing in children. When scored tablets are not available, 5 mg tablets can be used.

Therapeutic dose: 0.25–0.5 mg/kg bw per day primaquine once a day for 14 days (see Annex 5, A5.11).

Use of primaquine to prevent relapse in high-transmission settings was not recommended previously, as the risk for new infections was considered to outweigh any benefits of preventing relapse. This may have been based on underestimates of the morbidity and mortality associated with multiple relapses, particularly in young children. Given the benefits of preventing relapse and in the light of changing epidemiology worldwide and more aggressive targets for malaria control and elimination, *the group now recommends that primaquine be used in all settings*.

6.5.2 | PRIMAQUINE AND GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

Any person (male or female) with red cell G6PD activity < 30% of the normal mean has G6PD deficiency and will experience haemolysis after primaquine. Heterozygote females with higher mean red cell activities may still show substantial haemolysis. G6PD deficiency is an inherited sex-linked genetic disorder, which is associated with some protection against *P. falciparum* and *P. vivax* malaria but increased susceptibility to oxidant haemolysis. The prevalence of G6PD deficiency varies, but in tropical areas it is typically 3–35%; high frequencies are found only in areas where malaria is or has been endemic. There are many (> 180) different G6PD deficiency genetic variants; nearly all of which make the red cells susceptible to oxidant haemolysis, but the severity of haemolysis may vary. Primaquine generates reactive intermediate metabolites that are oxidant and cause variable haemolysis in G6PD-deficient individuals. It also causes methemoglobinaemia. The severity of haemolytic anaemia depends on the dose

of primaquine and on the variant of the G6PD enzyme. Fortunately, primaquine is eliminated rapidly so haemolysis is self-limiting once the drug is stopped. In the absence of exposure to primaquine or another oxidant agent, G6PD deficiency rarely causes clinical manifestationsso, many patients are unaware of their G6PD status. Screening for G6PD deficiency is not widely available outside hospitals, but rapid screening tests that can be used at points of care have recently become commercially available.

- In patients known to be G6PD deficient, primaquine may be considered at a dose of 0.75 mg base/kg bw once a week for 8 weeks. The decision to give or withhold primaquine should depend on the possibility of giving the treatment under close medical supervision, with ready access to health facilities with blood transfusion services.
- Some heterozygote females who test as normal or not deficient in qualitative G6PD screening tests have intermediate G6PD activity and can still haemolyse substantially. Intermediate deficiency (30–80% of normal) and normal enzyme activity (> 80% of normal) can be differentiated only with a quantitative test. In the absence of quantitative testing, all females should be considered as potentially having intermediate G6PD activity and given the 14-day regimen of primaquine, with counselling on how to recognize symptoms and signs of haemolytic anaemia. They should be advised to stop primaquine and be told where to seek care should these signs develop.
- If G6PD testing is not available, a decision to prescribe or withhold primaquine should be based on the balance of the probability and benefits of preventing relapse against the risks of primaquine-induced haemolytic anaemia. This depends on the population prevalence of G6PD deficiency, the severity of the prevalent genotypes and on the capacity of health services to identify and manage primaquine-induced haemolytic reactions.

6.5.3 | PREVENTION OF RELAPSE IN PREGNANT OR LACTATING WOMEN AND INFANTS

Preventing relapse in pregnant or lactating women

In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, on the basis of G6PD status, treat with primaquine to prevent future relapse.
Conditional recommendation, moderate-quality evidence

GRADE (see Annex 4, A4.11)
In a systematic review of malaria chemoprophylaxis in pregnant women, chloroquine prophylaxis against *P. vivax* during pregnancy was directly evaluated in one trial conducted in Thailand in 2001. In comparison with no chemoprophylaxis:

- Chloroquine prophylaxis substantially reduced recurrent *P. vivax* malaria (RR, 0.02; 95% CI, 0.00−0.26, one trial, 951 participants, moderate-quality evidence).

Radeva-Petrova D, ter Kuile FO, Sinclair D, Kayentao K, Garner P. Drugs for preventing malaria in pregnant women in endemic areas: any drug regimen versus placebo/no treatment. Cochrane Database Systemat Rev 2014; 10:CD000169. doi: 10.1002/14651858.CD000169.pub3.

Primaquine is contraindicated in pregnant women, infants < 6months of age and in lactating women (unless the infant is known not to be G6PD deficient).

As an alternative, chloroquine prophylaxis could be given to suppress relapses after acute vivax malaria during pregnancy. Once the infant has been delivered and the mother has completed breastfeeding, primaquine could then be given to achieve radical cure.

Few data are available on the safety of primaquine in infancy, and in the past primaquine was not recommended for infants. There is, however, no specific reason why primaquine should not be given to children aged 6 months to 1 year (provided they do not have G6PD deficiency), as this age group may suffer multiple relapses from vivax malaria. The guideline development group therefore recommended lowering the age restriction to 6 months.

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EDITION

7 | TREATMENT OF SEVERE MALARIA

Treating severe malaria

Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of an ACT (add single dose primaquine in areas of low transmission).
Strong recommendation, high-quality evidence

Revised dose recommendation for parenteral artesunate in young children

Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.
Strong recommendation based on pharmacokinetic modelling

Parenteral alternatives when artesunate is not available

If parenteral artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.
Conditional recommendation, low-quality evidence

Treating cases of suspected severe malaria pending transfer to a higher-level facility (pre-referral treatment)

Pre-referral treatment options

Where complete treatment of severe malaria is not possible but injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate facility for further care. Where intramuscular artesunate is not available use intramuscular artemether or, if that is not available, use intramuscular quinine.
Strong recommendation, moderate-quality evidence

Where intramuscular injections of artesunate are not available, treat children < 6 years with a single rectal dose (10 mg/kg bw) of artesunate, and refer immediately to an appropriate facility for further care. Do not use rectal artesunate in older children and adults.
Strong recommendation, moderate-quality evidence

Mortality from untreated severe malaria (particularly cerebral malaria) approaches 100%. With prompt, effective antimalarial treatment and supportive care, the rate falls to 10–20% overall. Within the broad definition of severe malaria some syndromes are associated with lower mortality rates (e.g. severe anaemia) and others with higher mortality rates (e.g. acidosis). The risk for death increases in the presence of multiple complications.

Any patient with malaria who is unable to take oral medications reliably, shows any evidence of vital organ dysfunction or has a high parasite count is at increased risk for dying. The exact risk depends on the species of infecting malaria parasite, the number of systems affected, the degree of vital organ dysfunction, age, background immunity, pre-morbid, and concomitant diseases, and access to appropriate treatment. Tests such as a parasite count, haematocrit and blood glucose may all be performed immediately at the point of care, but the results of other laboratory measures, if any, may be available only after hours or days. As severe malaria is potentially fatal, any patient considered to be at increased risk should be given the benefit of the highest level of care available. The attending clinician should not worry unduly about definitions: the severely ill patient requires immediate supportive care, and, if severe malaria is a possibility, parenteral antimalarial drug treatment should be started without delay.

7.1 | DEFINITIONS

7.1.1 | SEVERE FALCIPARUM MALARIA

For epidemiological purposes, **severe falciparum malaria** is defined as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia.

- *Impaired consciousness:* A Glasgow coma score < 11 in adults or a Blantyre coma score < 3 in children
- *Prostration:* Generalized weakness so that the person is unable to sit, stand or walk without assistance
- *Multiple convulsions:* More than two episodes within 24 h
- *Acidosis:* A base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, laboured breathing).
- *Hypoglycaemia:* Blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL)
- *Severe malarial anaemia:* Haemoglobin concentration ≤ 5 g/dL or a haematocrit of ≤ 15% in children < 12 years of age (< 7 g/dL and < 20%, respectively, in adults) with a parasite count > 10 000/μL
- *Renal impairment:* Plasma or serum creatinine > 265 μmol/L (3 mg/dL) or blood urea > 20 mmol/L
- *Jaundice:* Plasma or serum bilirubin > 50 μmol/L (3 mg/dL) with a parasite count > 100 000/ μL
- *Pulmonary oedema*: Radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation
- *Significant bleeding:* Including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena

- *Shock:* Compensated shock is defined as capillary refill ⩾ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children or < 80 mm Hg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).
- *Hyperparasitaemia: P. falciparum* parasitaemia > 10%.

7.1.2 | SEVERE VIVAX AND KNOWLESI MALARIA

Severe vivax malaria is defined as for falciparum malaria but with no parasite density thresholds.

Severe knowlesi malaria is defined as for falciparum malaria but with two differences:

- *P. knowlesi* hyperparasitaemia: parasite density > 100 000/µL
- Jaundice and parasite density > 20 000/µL.

7.2 | THERAPEUTIC OBJECTIVES

The main objective of the treatment of severe malaria is to prevent the patient from dying. Secondary objectives are prevention of disabilities and prevention of recrudescent infection.

Death from severe malaria often occurs within hours of admission to a hospital or clinic, so it is essential that therapeutic concentrations of a highly effective antimalarial drug be achieved as soon as possible. Management of severe malaria comprises mainly clinical assessment of the patient, specific antimalarial treatment, additional treatment and supportive care.

7.3 | 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 antimalarial drugs and fluids, can be given appropriately. An intravenous cannula should be inserted, and blood glucose (rapid test), haematocrit or haemoglobin, parasitaemia and, in adults, renal function should be measured immediately. 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 is easily performed in children. Unconscious patients should undergo 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 concentration should 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-matching, a full blood count, a platelet count, clotting studies, blood culture and full biochemistry (if possible). Careful attention should be paid to the patient's fluid balance in severe malaria in order to avoid over- or under-hydration. Individual requirements vary widely and depend on fluid losses before admission.

The differential diagnosis of fever in a severely ill patient is broad. Coma and fever may be due to meningoencephalitis or malaria. Cerebral malaria is not associated with signs of meningeal irritation (neck stiffness, photophobia or Kernig's 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. When possible, blood should always be taken on admission for bacterial culture. In malaria-endemic areas, particularly where parasitaemia is common in young age groups, it is difficult to rule out septicaemia immediately in a shocked or severely ill obtunded child. *In all such cases, empirical parenteral broad-spectrum antibiotics should be started immediately, together with antimalarial treatment.*

7.4 | TREATMENT OF SEVERE MALARIA

It is essential that full doses of effective parenteral (or rectal) antimalarial treatment be given promptly in the initial treatment of severe malaria. This should be followed by a full dose of effective ACT orally. Two classes of medicine are available for parenteral treatment of severe malaria: artemisinin derivatives (artesunate or artemether) and the cinchona alkaloids (quinine and quinidine). Parenteral artesunate is the treatment of choice for all severe malaria. The largest randomized clinical trials ever conducted on severe falciparum malaria showed a substantial reduction in mortality with intravenous or intramuscular artesunate as compared with parenteral quinine. The reduction in mortality was not associated with an increase in neurological sequelae in artesunate-treated survivors. Furthermore, artesunate is simpler and safer to use.

7.4.1 | ARTESUNATE

Treating severe malaria

Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of an ACT.
Strong recommendation, high-quality evidence

GRADE (see Annex 4, A4.12)
In a systematic review of artesunate for severe malaria, eight randomized controlled trials with a total of 1664 adults and 5765 children, directly compared parenteral artesunate with parenteral quinine. The trials were conducted in various African and Asian countries between 1989 and 2010.
In comparison with quinine, parenteral artesunate:

- Reduced mortality from severe malaria by about 40% in adults (RR, 0.61; 95% CI, 0.50–0.75, five trials, 1664 participants, *high-quality evidence*);
- Reduced mortality from severe malaria by about 25% in children (RR, 0.76; 95% CI, 0.65–0.90, four trials, 5765 participants, *high-quality evidence*); and
- Was associated with a small increase in neurological sequelae in children at the time of hospital discharge (RR, 1.36; 95% CI, 1.01–1.83, three trials, 5163 participants, *moderate-quality evidence*), most of which, however, slowly resolved, with little or no difference between artesunate and quinine 28 days later (*moderate-quality evidence*).

Other considerations
The guideline development group considered that the small increase in neurological sequelae at discharge after treatment with artesunate was due to the delayed recovery of the severely ill patients, who would have died had they received quinine. This should not be interpreted as a sign of neurotoxicity. Although the safety of artesunate given in the first trimester of pregnancy has not been firmly established, the guideline development group considered that the proven benefits to the mother outweigh any potential harm to the developing fetus.

Sinclair D, Donegan S, Isba R, Lalloo DG. Artesunate versus quinine for treating severe malaria. Cochrane Database Systemat Rev 2012;6:CD005967. doi: 10.1002/14651858.CD005967.pub4.

Revised dose recommendation for parenteral artesunate in young children with severe malaria

Children weighing less than 20 kg should receive a higher parenteral dose of artesunate (3 mg/kg/dose) than larger children and adults (2.4 mg/kg/dose) to ensure equivalent drug exposure.
Strong recommendation based on pharmacokinetic modelling

The dosing subgroup reviewed all available pharmacokinetic data on artesunate and the main biologically active metabolite dihydroartemisinin following administration of artesunate in severe malaria (published pharmacokinetic studies from 71 adults and 265 children). Simulations of artesunate and dihydroartemisinin exposures were conducted for each age group. These showed underexposure in younger children. The revised parenteral dose regimens are predicted to provide equivalent artesunate and dihydroartemisinin exposures across all age groups.

Other considerations
Individual parenteral artesunate doses between 1.75 and 4 mg/kg have been studied and no toxicity has been observed. The GRC concluded that the predicted benefits of improved antimalarial exposure in children are not at the expense of increased risk.

Hendriksen IC, Mtove G, Kent A, Gesase S, Reyburn H, Lemnge MM, et al. Population pharmacokinetics of intramuscular artesunate in African children with severe malaria: implications for a practical dosing regimen. Clin Pharmacol Ther 2013;93:443–50.

Zaloumis SG, Tarning J, Krishna S, Price RN, White NJ, Davis TM, McCaw JM, Olliaro P, Maude RJ, Kremsner P, Dondorp A, Gomes M, Barnes K, Simpson JA. Population pharmacokinetics of intravenous artesunate: a pooled analysis of individual data from patients with severe malaria. CPT Pharmacometrics Syst Pharmacol. 2014;3:e145.

Artesunate is dispensed as a powder of artesunic acid, which 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 into the anterior thigh.

The solution should be prepared freshly for each administration and should not be stored. Artesunate is rapidly hydrolysed in-vivo to dihydroartemisinin, which provides the main antimalarial effect. Studies of the pharmacokinetics of parenteral artesunate in children with severe malaria suggest that they have less exposure than older children and adults to both artesunate and the biologically active metabolite dihydroartemisinin. Body weight has been identified as a significant covariate in studies of the pharmacokinetics of orally and rectally administered artesunate, which suggests that young children have a larger apparent volume of distribution for both compounds and should therefore receive a slightly higher dose of parenteral artesunate to achieve exposure comparable to that of older children and adults.

Artesunate and post-treatment haemolysis

Delayed haemolysis starting >1 week after artesunate treatment of severe malaria has been reported in hyperparasitaemic non-immune travellers. Between 2010 and 2012, there were six reports involving a total of 19 European travellers with severe malaria who were treated with artesunate injection and developed delayed haemolysis. All except one were adults (median age, 50 years; range, 5–71 years). In a prospective study involving African children, the same phenomenon was reported in 5 (7%) of the 72 hyperparasitaemic children studied. Artesunate rapidly kills ring-stage parasites, which are then taken out of the red cells by the spleen; these infected erythrocytes are then returned to the circulation but with a shortened life span, resulting in the observed haemolysis. Thus, post-treatment haemolysis is a predictable event related to the life-saving effect of artesunate. Hyperparasitaemic patients must be followed up carefully to identify late-onset anaemia.

7.4.2 | PARENTERAL ALTERNATIVES WHEN ARTESUNATE IS NOT AVAILABLE

Parenteral alternatives when artesunate is not available

If parenteral artesunate is not available, use intramuscular artemether in preference to quinine for treating children and adults with severe malaria.
Strong recommendation, high-quality evidence

GRADE (see Annex 4, A4.13 and A4.14)

A systematic review of intramuscular artemether for severe malaria comprised two randomized controlled trials in Viet Nam in which artemether was compared with artesunate in 494 adults, and 16 trials in Africa and Asia in which artemether was compared with quinine in 716 adults and 1447 children. The trials were conducted between 1991 and 2009.

In comparison with artesunate, intramuscular artemether was not as effective at preventing deaths in adults in Asia (RR, 1.80; 95% CI, 1.09–2.97; two trials, 494 participants, *moderate-quality evidence*).

Artemether and artesunate have not been directly compared in randomized trials in African children.

In comparison with quinine:
- Intramuscular artemether prevented a similar number of deaths in children in Africa (RR, 0.96; 95% CI, 0.76–1.20; 12 trials, 1447 participants, *moderate-quality evidence*).
- Intramuscular artemether prevented more deaths in adults in Asia (RR, 0.59; 95% CI, 0.42–0.83; four trials, 716 participants, *moderate-quality evidence*).

Other considerations

Indirect comparisons of parenteral artesunate and quinine and of artemether and quinine were considered by the guideline development group with what is known about the pharmacokinetics of the two drugs. They judged the accumulated indirect evidence to be sufficient to recommend parenteral artesunate rather than intramuscular artemether for use in all age groups.

Esu E, Effa EE, Opie ON, Uwaoma A, Meremikwu MM. Artemether for severe malaria. Cochrane Database Systemat Rev 2014;9:CD010678. doi: 10.1002/14651858.CD010678.pub2.

Artemether

Artemether is two to three times less active than its main metabolite dihydroartemisinin. Artemether can be given as an oil-based intramuscular injection or orally. In severe falciparum malaria, the concentration of the parent compound predominates after intramuscular injection, whereas parenteral artesunate is hydrolysed rapidly and almost completely to dihydroartemisinin. Given intramuscularly, artemether may be absorbed more slowly and more erratically than water-soluble artesunate, which is absorbed rapidly and reliably after intramuscular injection. These pharmacological advantages may explain the clinical superiority of parenteral artesunate over artemether in severe malaria.

Artemether is dispensed dissolved in oil (groundnut, sesame seed) and given by intramuscular injection into the anterior thigh.

Therapeutic dose: The initial dose of artemether is 3.2 mg/kg bw intramuscularly (to the anterior thigh). The maintenance dose is 1.6 mg/kg bw intramuscularly daily.

Quinine

Quinine treatment for severe malaria was established before the methods for modern clinical trials were developed. Several salts of quinine have been formulated for parenteral use, but the dihydrochloride is the most widely used. The peak concentrations after intramuscular quinine in severe malaria are similar to those after intravenous infusion. Studies of pharmacokinetics show that a loading dose of quinine (20 mg salt/kg bw, twice the maintenance dose) provides therapeutic plasma concentrations within 4 h. The maintenance dose of quinine (10 mg salt/kg bw) is administered at 8-h intervals, starting 8 h after the first dose. If there is no improvement in the patient's condition within 48 h, the dose should be reduced by one third, i.e. to 10 mg salt/kg bw every 12 h.

Rapid intravenous administration of quinine is dangerous. 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 bw per h.

Whereas many antimalarial drugs are prescribed in terms of base, for historical reasons quinine doses are usually recommended in terms of salt (usually sulphate for oral use and dihydrochloride for parenteral use). Recommendations for the doses of this and other antimalarial agents should state clearly whether the salt or the 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 solution. If this is not possible, it should be given by intramuscular injection to the anterior thigh; quinine should not be injected into the buttock in order to avoid sciatic nerve injury. The first dose should be split, with 10 mg/kg bw into 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 to administer it either in a buffered formulation or diluted to a concentration 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, it 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 of excessive initial treatment.

7.5 | PRE-REFERRAL TREATMENT OPTIONS

Treating cases of suspected severe malaria pending transfer to higher-level facilities (pre-referral treatment)

Where complete treatment of severe malaria is not possible but injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate facility for further care. Where intramuscular artesunate is not available use intramuscular artemether or, if that is not available, use intramuscular quinine.
Strong recommendation, moderate-quality evidence

Where intramuscular injections of artesunate are not available, treat children < 6 years with a single rectal dose (10mg/kg bw) of artesunate, and refer immediately to an appropriate facility for further care. Do not use rectal artesunate in older children and adults.
Strong recommendation, moderate-quality evidence

GRADE (see Annex 4, A4.15 and A4.16)
In a systematic review of pre-referral treatment for suspected severe malaria, in a single large randomized controlled trial of 17 826 children and adults in Bangladesh, Ghana and the United Republic of Tanzania, pre-referral rectal artesunate was compared with placebo.

In comparison with placebo:
- Rectal artesunate reduced mortality by about 25% in children < 6 years (RR, 0.74; 95% CI, 0.59–0.93; one trial, 8050 participants, *moderate-quality evidence*).
- Rectal artesunate was associated with more deaths in older children and adults (RR, 2.21; 95% CI, 1.18–4.15; one trial 4018 participants, *low-quality evidence*).

Other considerations
The guideline development group could find no plausible explanation for the finding of increased mortality among older children and adults in Asia who received rectal artesunate, which may be due to chance. Further trials would provide clarification but are unlikely to be done. The group was therefore unable to recommend its use in older children and adults.

In the absence of direct evaluations of parenteral antimalarial drugs for pre-referral treatment, the guideline development group considered the known benefits of artesunate in hospitalized patients and downgraded the quality of evidence for pre-referral situations. When intramuscular injections can be given, the group recommends intramuscular artesunate in preference to rectal artesunate.

Okebe J, Eisenhut M. Pre-referral rectal artesunate for severe malaria. Cochrane Database Systemat Rev 2014;5:CD009964. doi: 10.1002/14651858.CD009964.pub2.

The risk for 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 a health facility where intravenous treatment can be administered is usually long, thus delaying the start of appropriate antimalarial treatment. During this time, the patient may deteriorate or die. It is therefore recommended that patients, particularly young children, be treated with a first dose of one of the recommended treatments before referral (unless the referral time is < 6 h).

The recommended pre-referral treatment options for children < 6 years, in descending order of preference, are intramuscular artesunate; rectal artesunate; intramuscular artemether; and intramuscular quinine. For older children and adults, the recommended pre-referral treatment options, in descending order of preference, are intramuscular injections of artesunate; artemether; and quinine.

Administration of an artemisinin derivative by the rectal route as pre-referral treatment is feasible and acceptable even at community level. The only trial of rectal artesunate as pre-referral treatment showed the expected reduction in mortality of young children but unexpectedly found increased mortality in older children and adults. As a consequence, rectal artesunate is recommended for use only in children aged < 6 years and only when intramuscular artesunate is not available.

When rectal artesunate is used, patients should be transported immediately to a higher-level facility where intramuscular or intravenous treatment is available. If referral is impossible, rectal treatment could be continued until the patient can tolerate oral medication. At this point, a full course of the recommended ACT for uncomplicated malaria should be administered.

The single dose of 10 mg/kg bw of artesunate when given as a suppository should be administered rectally as soon as a presumptive diagnosis of severe malaria is made. If the suppository is expelled from the rectum within 30 min of insertion, a second suppository should be inserted and the buttocks held together for 10 min to ensure retention of the dose.

7.6 | ADJUSTMENT OF PARENTERAL DOSING IN RENAL FAILURE OR HEPATIC DYSFUNCTION

The dosage of artemisinin derivatives does not have to be adjusted for patients with vital organ dysfunction. However quinine accumulates in severe vital organ dysfunction. If a patient with severe malaria has persisting acute kidney injury or there is no clinical improvement by 48 h, the dose of quinine should be reduced by one third, to 10 mg salt/kg bw every 12 h. Dosage adjustments are not necessary if patients are receiving either haemodialysis or haemofiltration.

7.7 | FOLLOW-ON TREATMENT

The current recommendation of experts is to give parenteral antimalarial drugs for 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 can tolerate oral medication, before giving the oral follow-up treatment.

After initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with an effective oral antimalarial drug by giving a full course of effective ACT (artesunate + amodiaquine, artemether + lumefantrine or dihydroartemisinin + piperaquine). If the patient presented initially with impaired consciousness, ACTs containing mefloquine should be avoided because of an increased incidence of neuropsychiatric complications. When an ACT is not available, artesunate + clindamycin, artesunate + doxycycline, quinine + clindamycin or quinine + doxycycline can be used for follow-on treatment. Doxycycline is preferred to other tetracyclines because it can be given once daily and does not accumulate in cases of renal failure, but it should not be given to children < 8 years or pregnant women. As treatment with doxycycline is begun only when the patient has recovered sufficiently, the 7-day doxycycline course finishes after the artesunate, artemether or quinine course. When available, clindamycin is preferred in children and pregnant women.

7.8 | 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 and should include monitoring of vital signs, coma score and urine output. Blood glucose should be monitored every 4 h, if possible, particularly in unconscious patients.

7.9 | MANAGEMENT OF COMPLICATIONS

Severe malaria is associated with a variety of manifestations and complications, which must be recognized promptly and treated as shown below.

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

Manifestation or 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 treatments, intubate if necessary.
Hyperpyrexia	Administer tepid sponging, fanning, a cooling blanket and paracetamol.
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam, lorazepam, midazolam or intramuscular paraldehyde. Check blood glucose.
Hypoglycaemia	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion. Although hypoglycaemia is defined as glucose < 2.2 mmol/L, the threshold for intervention is < 3 mmol/L for children < 5 years and < 2.2 mmol/L for older children and adults.
Severe anaemia	Transfuse with screened fresh whole blood.
Acute pulmonary oedema[b]	Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure or continuous positive airway pressure in life-threatening hypoxaemia.
Acute kidney injury	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure, add haemofiltration or haemodialysis, or, if not available, peritoneal dialysis.
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] Prevent by avoiding excess hydration

7.10 | ADDITIONAL ASPECTS OF MANAGEMENT

7.10.1 | FLUID THERAPY

Fluid requirements should be assessed individually. Adults with severe malaria are very vulnerable to fluid overload, while children are more likely to be dehydrated. The fluid regimen must also be adapted to the infusion of antimalarial drugs. Rapid bolus infusion of colloid or crystalloids is contraindicated. If available, haemofiltration should be started early for acute kidney injury or severe metabolic acidosis, which do not respond to rehydration. As the degree of fluid depletion varies considerably in patients with severe malaria, it is not possible to give general recommendations on fluid replacement; each patient must be assessed individually and fluid resuscitation based on the 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 adults, there is a very thin dividing line between over-hydration, which may produce pulmonary oedema, and under-hydration, which contributes to shock, worsening acidosis and renal impairment. Careful, frequent evaluation of jugular venous pressure, peripheral perfusion, venous filling, skin turgor and urine output should be made.

7.10.2 | BLOOD TRANSFUSION

Severe malaria is associated with rapid development of anaemia, as infected, once 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 for fluid resuscitation, there are not enough studies to make strong evidence-based recommendations on the indications for transfusion; 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/100 mL (haematocrit < 15%). In low-transmission settings, a threshold of 20% (haemoglobin,

7 g/100 mL) is recommended. These general recommendations must, however, be adapted to the individual, as the pathological consequences of rapid development of anaemia are worse than those of chronic or acute anaemia when there has been adaptation and a compensatory right shift in the oxygen dissociation curve.

7.10.3 | EXCHANGE BLOOD TRANSFUSION

Many anecdotal reports and several series have claimed the benefit of exchange blood transfusion in severe malaria, but there have been no comparative trials, and there is no consensus on whether it reduces mortality or how it might work. Various rationales have been proposed:

- removing infected red blood cells from the circulation and therefore lowering the parasite burden (although only the circulating, relatively non-pathogenic stages are removed, and this is also achieved rapidly with artemisinin derivatives);
- rapidly reducing 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 easily deformable cells, 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 exchange blood transfusion.

7.10.4 | 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 substantial diagnostic overlap, particularly in children in areas of moderate and high transmission. Thus broad-spectrum antibiotic treatment *should be given* with antimalarial drugs to all children with suspected severe malaria in areas of moderate and high transmission until a bacterial infection is excluded. After the start of antimalarial treatment, unexplained deterioration may result from a supervening bacterial infection. Enteric bacteria (notably *Salmonella*) predominated in many trial series in Africa, but a variety of bacteria have been cultured from the blood of patients with a diagnosis of severe malaria.

Patients with secondary pneumonia or with clear evidence of aspiration should be given empirical treatment with an appropriate broad-spectrum antibiotic. In children with persistent fever despite parasite clearance, other possible causes of fever should be excluded, such as systemic *Salmonella* infections and urinary tract infections, especially in catheterized patients. In the majority of cases of persistent fever, however, no other pathogen is identified after parasite clearance. Antibiotic treatment should be based on culture and sensitivity results or, if not available, local antibiotic sensitivity patterns.

7.10.5 | 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 bw of phenobarbital to children with cerebral malaria, the frequency of seizures was reduced but the mortality rate was increased significantly. This resulted from respiratory arrest and was associated with additional use of benzodiazepine. *A 20 mg/kg bw dose of phenobarbital should **not** be given without respiratory support.* It is not known whether a lower dose would be effective and safer or whether mortality would not increase if ventilation were given. In the absence of further information, prophylactic anticonvulsants are not recommended.

7.10.6 | TREATMENTS THAT ARE NOT RECOMMENDED

In an attempt to reduce the high mortality from severe malaria, various adjunctive treatments have been evaluated, but none has proved effective and many have been shown to be harmful. Heparin, prostacyclin, desferroxamine, pentoxifylline, low-molecular-mass dextran, urea, high-dose corticosteroids, aspirin anti-TNF antibody, cyclosporine A, dichloroacetate, adrenaline, hyperimmune serum, *N*-acetylcysteine and bolus administration of albumin are not recommended. In addition, use of corticosteroids increases the risk for gastrointestinal bleeding and seizures and has been associated with prolonged coma resolution times when compared with placebo.

7.11 | TREATMENT OF SEVERE MALARIA DURING PREGNANCY

Women in the second and third trimesters of pregnancy are more likely to have 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 antimalarial drugs should be given to pregnant women with severe malaria in full doses without delay. *Parenteral artesunate is the treatment of choice in all trimesters.* Treatment must not be delayed. If artesunate is unavailable, intramuscular artemether should be given, and if this is unavailable then parenteral quinine should be started immediately until artesunate is obtained.

Obstetric advice should be sought at an early stage, a paediatrician 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 after delivery. Postpartum bacterial infection is a common complication and should be managed appropriately.

7.12 | TREATMENT OF SEVERE *P. VIVAX* MALARIA

Although *P. vivax* malaria is considered to be benign, with a low case-fatality rate, it may cause a debilitating febrile illness with progressive anaemia and can also occasionally cause severe disease, as in *P. falciparum* malaria. Reported manifestations of severe *P. vivax* malaria include severe anaemia, thrombocytopenia, acute pulmonary oedema and, less commonly, cerebral malaria, pancytopenia, jaundice, splenic rupture, haemoglobinuria, acute renal failure and shock.

Prompt effective treatment and case management should be the same as for severe *P. falciparum* malaria (see section 7.4). Following parenteral artesunate, treatment can be completed with a full treatment course of oral ACT or chloroquine (in countries where chloroquine is the treatment of choice). A full course of radical treatment with primaquine should be given after recovery.

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**8 | MANAGEMENT OF MALARIA CASES
IN SPECIAL SITUATIONS**

8.1 | EPIDEMICS AND HUMANITARIAN EMERGENCIES

Environmental, political and economic changes, population movement and war can all contribute to the emergence or re-emergence of malaria in areas where it was previously eliminated or well controlled. The displacement of large numbers of people with little or no immunity within malaria-endemic areas increases the risk for malaria epidemics among the displaced population, while displacement of people from an endemic area to an area where malaria has been eliminated can result in re-introduction of transmission and a risk for epidemics in the resident population.

Climate change may also alter transmission patterns and the malaria burden globally by producing conditions that favour vector breeding and there by increasing the risks for malaria transmission and epidemics.

8.1.1 | PARASITOLOGICAL DIAGNOSIS DURING EPIDEMICS

In the acute phase of epidemics and complex emergency situations, facilities for laboratory diagnosis with good-quality equipment and reagents and skilled technicians are often not available or are overwhelmed. Attempts should be made to improve diagnostic capacity rapidly, including provision of RDTs. If diagnostic testing is not feasible, the most practical approach is to treat all febrile patients as suspected malaria cases, with the inevitable consequences of over-treatment of malaria and potentially poor management of other febrile conditions. If this approach is used, it is imperative to monitor intermittently the prevalence of malaria as a true cause of fever and revise the policy appropriately. This approach has sometimes been termed "mass fever treatment". This is not the same as and should not be confused with "mass drug administration", which is administration of a complete treatment course of antimalarial medicines to every individual in a geographically defined area without testing for infection and regardless of the presence of symptoms (see section 10).

8.1.2 | MANAGEMENT OF UNCOMPLICATED FALCIPARUM MALARIA DURING EPIDEMICS

The principles of treatment of uncomplicated malaria are the same as those outlined in section 4. Active case detection should be undertaken to ensure that as many patients as possible receive adequate treatment, rather than relying on patients to come to a clinic.

8.1.3 | MANAGEMENT OF SEVERE MALARIA DURING EPIDEMICS

The principles of treatment of severe malaria during epidemics are the same as those outlined in section 7. In humanitarian emergencies, when there are many patients and many present late, effective triage, with immediate resuscitation and treatment, are essential. In epidemic situations, severe malaria is often managed in temporary clinics or in situations in which staff shortages and the high workload make intensive case monitoring difficult.

8.1.4 | EPIDEMICS OF MIXED FALCIPARUM AND VIVAX OR VIVAX MALARIA

ACTs (except artesunate + SP) should be used to treat uncomplicated malaria in mixed-infection epidemics, as they are highly effective against all malaria species. In areas with pure *P. vivax* epidemics, ACTs or chloroquine (if prevalent strains are sensitive) should be used.

8.1.5 | ANTI-RELAPSE THERAPY FOR *P. VIVAX* MALARIA

Administration of 14-day primaquine anti-relapse therapy for vivax malaria may be impractical in epidemic situations because of the duration of treatment and the difficulty of ensuring adherence. If adequate records are kept, therapy can be given in the post-epidemic period to patients who have been treated with blood schizontocides.

8.2 | MALARIA ELIMINATION SETTINGS

8.2.1 | USE OF GAMETOCYTOCIDAL DRUGS TO REDUCE TRANSMISSION

ACT reduces *P. falciparum* gametocyte carriage and transmission markedly, but this effect is incomplete, and patients presenting with gametocytaemia may be infectious for days or occasionally weeks, despite ACT. The strategy of using a single dose of primaquine to reduce infectivity and thus *P. falciparum* transmission has been widely used in low transmission settings.

Use of primaquine as a *P. falciparum* gametocytocide has a particular role in programmes to eliminate *P. falciparum* malaria. The population benefits of reducing malaria transmission by gametocytocidal drugs require that a high proportion of patients receive these medicines. WHO recommends the addition of a single dose of primaquine (0.25

mg base/kg bw) to ACT for uncomplicated falciparum malaria as a gametocytocidal medicine, particularly as a component of pre-elimination or elimination programmes. A recent review of the evidence on the safety and effectiveness of primaquine as a gametocytocide of *P. falciparum* indicates that a single dose of 0.25 mg base/kg bw is effective in blocking infectivity to mosquitos and is unlikely to cause serious toxicity in people with any of the G6PD variants. Thus, the G6PD status of the patient does not have to be known before primaquine is used for this indication.

8.3 | ARTEMISININ-RESISTANT FALCIPARUM MALARIA

Artemisinin resistance in *P. falciparum* is now prevalent in parts of Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. There is currently no evidence for artemisinin resistance outside these areas. The particular advantage of artemisinins over other antimalarial drugs is that they kill circulating ring-stage parasites and thus accelerate therapeutic responses. This is lost in resistance to artemisinin. As a consequence, parasite clearance is slowed, and ACT failure rates and gametocytaemia both increase. The reduced efficacy of artemisinin places greater selective pressure on the partner drugs, to which resistance is also increasing. This situation poses a grave threat. In the past chloroquine resistant parasites emerged near the Cambodia–Thailand border and then spread throughout Asia and Africa at a cost of millions of lives. In Cambodia, where artemisinin resistance is worst, none of the currently recommended treatment regimens provides acceptable cure rates (> 90%), and continued use of ineffective drug regimens fuels the spread of resistance. In Cambodia use of atovaquone–proguanil instead of ACT resulted in very rapid emergence of resistance to atovaquone.

In this dangerous, rapidly changing situation, local treatment guidelines cannot be based on a solid evidence base; however, the risks associated with continued use of ineffective regimens are likely to exceed the risks of new, untried regimens with generally safe antimalarial drugs. At the current levels of resistance, the artemisinin derivatives still provide significant antimalarial activity; therefore, longer courses of treatment with existing or new augmented combinations or treatment with new partner medicines (e.g. artesunate + pyronaridine) may be effective. Studies to determine the best treatments for artemisinin-resistant malaria are needed urgently.

It is strongly recommended that single-dose primaquine (as a gametocytocide) be added to all falciparum malaria treatment regimens (section 4.5). For the treatment of severe malaria in areas with established artemisinin resistance, it is recommended that parenteral artesunate and parenteral quinine be given together in full doses, as described in section 7.4.

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9 | ARTEMISININ-BASED COMBINATION THERAPIES NOT CURRENTLY RECOMMENDED FOR GENERAL USE

The pipeline for new antimalarial drugs is healthier than ever before, and several new compounds are in various stages of development. Some novel antimalarial agents are already registered in some countries. The decision to recommend antimalarial drugs for general use depends on the strength of the evidence for safety and efficacy and the context of use. In general, when there are no satisfactory alternatives, newly registered drugs may be recommended; however, for global or unrestricted recommendations, considerably more evidence than that submitted for registration is usually required, to provide sufficient confidence for their safety, efficacy and relative merits as compared with currently recommended treatments.

Several new antimalarial drugs or new combinations have been introduced recently. Some are still in the pre-registration phase and are not discussed here. Artesunate + pyronaridine, arterolane + piperaquine, artemisinin + piperaquine base and artemisinin + napththoquine are new ACTs, which are registered and used in some countries. In addition, there are several new generic formulations of existing drugs. None of these yet has a sufficient evidence base for general recommendation (i.e. unrestricted use).

A systematic review of **artesunate + pyronaridine** included six trials with a total of 3718 patients. Artesunate + pyronaridine showed good efficacy as compared with artemether + lumefantrine and artesunate + mefloquine in adults and older children with *P. falciparum* malaria, but the current evidence for young children is insufficient to be confident that the drug is as effective as currently recommended options. In addition, regulatory authorities noted slightly higher hepatic transaminase concentrations in artesunate + pyronaridine recipients than in comparison groups and recommended further studies to characterize the risk for hepatotoxicity. Preliminary data from repeat-dosing studies are reassuring (see Annex 4, A4.17).

Arterolane + piperaquine is a combination of a synthetic ozonide and piperaquine phosphate that is registered in India for use only in adults There are currently insufficient data to make general recommendations.

Artemisinin + piperaquine base combines two well-established, well-tolerated compounds. It differs from previous treatments in that the piperaquine is in the base form, the artemisinin dose is relatively low, and the current labelling is for only a 2-day regimen. There are insufficient data from clinical trials for a general recommendation, and there is concern that the artemisinin dose regimen provides insufficient protection against resistance to the piperaquine component.

Artemisinin + naphthoquine is also a combination of two relatively old compounds that is currently being promoted as a single-dose regimen, contrary to WHO advice for 3 days of the artemisinin derivative. There are currently insufficient data from rigorously conducted randomized controlled trials to make general recommendations (see Annex 4, A4.18).

Many ACTs are generics. The bioavailability of generics of currently recommended drugs must be comparable to that of the established, originally registered product, and the satisfactory pharmaceutical quality of the product must be maintained.

3RD EDITION

10 | MASS DRUG ADMINISTRATION

Mass antimalarial drug administration has been used extensively in various forms over the past 80 years. The objective is to provide therapeutic concentrations of antimalarial drugs to as large a proportion of the population as possible in order to cure any asymptomatic infections and also to prevent reinfection during the period of post-treatment prophylaxis.[9] Mass drug administration rapidly reduces the prevalence and incidence of malaria in the short term, but more studies are required to assess its longer-term impact, the barriers to community uptake, and its potential contribution to the development of drug resistance.[10] In an analysis of 38 mass drug administration projects carried out since 1932,[11] only one was reported to have succeeded in interrupting malaria transmission permanently. In this study, chloroquine, SP and primaquine were provided weekly to the small population of Aneityum Island in Vanuatu for 9 weeks before the rainy season, in combination with distribution of insecticide-treated nets.[12]

There is considerable divergence of opinion about the benefits and risks of mass antimalarial drug administration. As a consequence, it has been little used in recent years; however, renewed interest in malaria elimination and the emerging threat of artemisinin resistance has been accompanied by reconsideration of mass drug administration as a means for rapidly eliminating malaria in a specific region or area. During mass campaigns, every individual in a defined population or geographical area is requested to take antimalarial treatment at approximately the same time and at repeated intervals in a coordinated manner. This requires extensive community engagement to achieve a high level of community acceptance and participation. The optimum timing depends of the elimination kinetics of the antimalarial (e.g. in current initiatives using dihydroartemisinin + piperaquine, the drug is given monthly for 3 months at treatment doses, as the residual piperaquine levels suppress reinfections for 1 month). Depending on the contraindications for the medicines used, pregnant women, young infants and other population groups may be excluded from the campaign. Thus, the drugs used, the number of treatment rounds, the optimum intervals and the support structures necessary are all context-specific and are still subject to active research. In the past, vivax elimination programmes were based on pre-seasonal mass radical treatment with primaquine (0.25 mg/kg/for 14 days) without testing for G6PD deficiency or monitoring primaquine-induced haemolysis, although in some cases interrupted regimens were used: 4 days' treatment, 3 days of no treatment, then continuation to complete the course (usually 11 days) if the drug was well tolerated.[13]

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[9] White NJ. How antimalarial drug resistance affects post-treatment prophylaxis. Malar J 2008;11:7–9.

[10] Poirot E, Skarbinski J, Sinclair D, Kachur SP, Slutsker L, Hwang J. Mass drug administration for malaria. Cochrane Database Systemat Rev 2013;11:CD008846. doi: 10.1002/14651858.CD008846.pub2.

[11] von Seidlein L, Greenwood BM. Mass administration of antimalarial drugs. Trends Parasitol 2003;19:790–6.

[12] Kaneko A, Taleo G, Kalkoa M, Yamar S, Kobayakawa T, Björkman A. Malaria eradication on islands. Lancet 2000;356:1560–4.

[13] Kondrashin A, Baranova AM, Ashley EA, Recht J, White NJ, Sergiev VP. Mass primaquine treatment to eliminate vivax malaria: lessons from the past. Malar J 2014;13:51.

Both mass drug administration and mass screening and treatment require that a high proportion of the target population is reached by the intervention. This requires informed, enthusiastic community participation and comprehensive support structures.

Once mass drug administration is terminated, if malaria transmission is not interrupted or importation of malaria is not prevented, then 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.[14] If malaria is not eliminated from the target population, then mass drug administration may provide a significant selective pressure for the emergence of resistance. The rebound in malaria may be associated temporarily with higher morbidity and mortality if drug administration was maintained long enough for people to lose herd immunity against malaria. For this reason, mass drug administration should not be started unless there is a good chance that focal elimination will be achieved. In some circumstances (e.g. containment of artemisinin-resistant *P. falciparum*), elimination of only one species may be the objective.

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[14] Vectorial capacity: number of new infections that the population of a given anopheline mosquito vector would distribute per case per day at a given place and time, assuming the human population is not immune. Factors affecting vectorial capacity include: the density of female anophelines relative to humans; their longevity, frequency of feeding and propensity to bite humans; and the length of the extrinsic (i.e. in the mosquito) cycle of the parasite.

3RD

EDITION

11 | CHEMOPREVENTION IN SPECIAL RISK GROUPS

Chemoprevention for special risk groups

Intermittent preventive treatment of malaria in pregnancy

In malaria-endemic areas in Africa, provide intermittent preventive treatment with SP to all women in their first or second pregnancy (SP-IPTp) as part of antenatal care. Dosing should start in the second trimester and doses should be given at least 1 month apart, with the objective of ensuring that at least three doses are received.
Strong recommendation, high-quality evidence

Intermittent preventive treatment in infants

In areas of moderate-to-high malaria transmission in Africa, where SP is still effective, provide intermittent preventive treatment with SP to infants (< 12 months of age) (SP-IPTi) at the time of the second and third rounds of vaccination against DTP and vaccination against measles.
Strong recommendation

Seasonal malaria chemoprevention

In areas with highly seasonal malaria transmission in the sub-Sahel region of Africa, provide seasonal malaria chemoprevention (SMC) with monthly amodiaquine + SP for all children < 6 years during each transmission season.
Strong recommendation, high-quality evidence

Chemoprevention is the use of antimalarial medicines for prophylaxis and for preventive treatment. The use of medicines for chemoprophylaxis is not addressed in detail in the current guidelines, beyond a short description of general condition of use.

Malaria may be prevented by taking drugs that inhibit liver-stage (pre-erythrocytic) development (causal prophylaxis) or drugs that kill asexual blood stages (suppressive prophylaxis). Causal prophylactics (atovaquone + proguanil, primaquine) can be stopped soon after leaving an endemic area, whereas suppressive prophylactics must be taken for at least 4 weeks after leaving the area in order to eliminate asexual parasites emerging from the liver weeks after exposure. For travellers, chemoprophylaxis is started before entering the endemic area to assess tolerability and for slowly eliminated drugs to build up therapeutic concentrations.

The objective of preventive treatment is to prevent malarial illness by maintaining therapeutic drug levels in the blood throughout the period of greatest risk. Current WHO-recommended malaria chemopreventive therapies include IPTp, IPTi and SMC.

11.1 | INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY WITH SULFADOXINE–PYRIMETHAMINE

Intermittent preventive treatment in pregnancy (IPTp)

In malaria-endemic areas in Africa, provide SP-IPTp to all women in their first or second pregnancy as part of antenatal care. Dosing should start in the second trimester and doses should be given at least 1 month apart, with the objective of ensuring that at least three doses are received.
Strong recommendation, high-quality evidence

GRADE (see Annex 4, A4.19)
In a systematic review of IPTp, seven trials involving direct comparison of two doses of SP with three or more doses monthly were evaluated. The trials were conducted in Burkina Faso, Kenya, Malawi, Mali and Zambia between 1996 and 2008.

In comparison with two doses of SP, three or more doses:
- Increased the mean birth weight by about 56 g (95% CI, 29–83; seven trials, 2190 participants, *high-quality evidence*);
- Reduced the number of low-birth-weight infants by about 20% (RR, 0.80; 95% CI, 0.69–0.94; seven trials, 2190 participants, *high-quality evidence*);
- Reduced placental parasitaemia by about 50% (RR, 0.51; 95% CI, 0.38–0.68; six trials, 1436 participants, *high-quality evidence*); and
- Reduced maternal parasitaemia by about 33% (RR, 0.68; 95% CI, 0.52–0.89; seven trials, 2096 participants, *high-quality evidence*).

The trials conducted to date have not been large enough to detect or exclude effects on spontaneous miscarriage, stillbirth or neonatal mortality (*very low-quality evidence*).

Other considerations
The guideline development group noted that the beneficial effects were obvious in women in their first and second pregnancies. There was less information on women in their third or later pregnancy, but the available information was consistent with benefit.

Kayentao K, Garner P, van Eijk AM, Naidoo I, Roper C, Mulokozi A, et al. Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine–pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. JAMA 2013;309:594–604.

Malaria infection during pregnancy is a major public health problem, with substantial risks for the mother, her fetus and the newborn. WHO recommends a package of interventions for preventing and controlling malaria during pregnancy, which includes promotion and use of insecticide-treated nets, appropriate case management with prompt, effective treatment and, in areas with moderate to high transmission of *P. falciparum*, administration of IPTp-SP.

In the systematic review summarized in the box above, the reduction in risk for low birth weight was consistent for a wide range of levels of resistance to SP. The group that received three or more doses also had less placental malaria. There were no differences in serious adverse events between the two groups. On the basis of these results, *WHO now recommends that, in areas of moderate-to-high malaria transmission of Africa, IPTp-SP be given to all pregnant women at each scheduled antenatal care visit,* starting as early as possible in the second trimester, provided that the doses of SP are given at least 1 month apart. The objective is to ensure that at least three doses are received.

In several countries in Africa, some *P. falciparum* parasites carry quintuple mutations (triple *Pfdhfr* and double *Pfdhps*), which are associated with therapeutic failure of SP treatment. IPTp-SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes in areas where a high proportion (> 90%) of *P. falciparum* parasites carry these quintuple mutations. Therefore, IPTp-SP should still be administered to women in these areas. In areas where *P. falciparum* carrying six mutations (either *Pfdhfr* 164 or *Pfdhps* 581) are prevalent, the efficacy of IPTp-SP may be compromised. It is unclear by how much.

There are currently insufficient data to define the level of *P. falciparum* transmission at which IPTp-SP may cease to be cost-effective from a public health point of view. Furthermore, the natural fluctuations in malaria incidence from year to year, the low cost of the intervention and the challenges of IPTp re-introduction after withdrawal indicate that caution must be exercised in discontinuing IPTp-SP because of recent reductions in transmission. More data will be needed to allow the formulation of more specific guidelines.

11.2 | INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN INFANTS WITH SULFADOXINE–PYRIMETHAMINE

Intermittent preventive treatment in infants

In areas of moderate-to-high malaria transmission in Africa, where SP is still effective, provide intermittent preventive treatment with SP to infants (< 12 months of age) (SP-IPTi) at the time of the second and third rounds of vaccination against diphtheria, tetanus and pertussis (DTP) and vaccination against measles. *Strong recommendation – from 2010, evidence not re-evaluated*

Evidence supporting the recommendation (see Annex 4, A4.20)
The recommendation is based on a pooled analysis of 6 randomised pacebo controlled studies on SP-IPTi conducted in areas of moderate to high transmission of malaria:

- SP-IPTi delivered through EPI provides an overall protection in the first year of life against clinical malaria [30.3% (95% CI: 19.8%–39.4%)], anaemia [21.3% (95% CI: 8.3%–32.5%)], hospital admissions associated with malaria parasitaemia [38.1% (95% CI 12.5%–56.2%)], and all-cause hospital admissions [22.9% (95% CI: 10.0%–34.0%)]. SP-IPTi offers a personal protection against clinical malaria for a period of approximately 35 days following the administration of each dose.

Other considerations
The recommendation was formulated at the fourth consultative meeting of the Technical Expert Group (TEG) of Preventive Chemotherapy, GMP, WHO, April 2009 which reviewed all evidence available at the time. The evidence was not re-evaluated during this guideline process and therefore the quality of evidence has not been formally assessed.

Aponte JJ, Schellenberg D, Egan A, et al. Efficacy and safety of intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in African infants: a pooled analysis of six randomised, placebo-controlled trials. Lancet. 2009 ;374:1533-42.

The vast majority of malaria cases and deaths in Africa occur in young children. The key interventions recommended to prevent and control malaria in this vulnerable group include use of insecticide–treated nets or indoor residual spraying, prompt access to diagnosis and treatment and, in areas of Africa with moderate to high transmission of *P. falciparum*, administration of IPTi. This consists of co-administration of a full therapeutic course of SP with the second and third vaccinations against DTP and vaccination against measles delivered in the Expanded

Programme on Immunization at routine schedules—usually at 10 weeks, 14 weeks and about 9 months of age—to infants at risk for malaria.[15]

WHO recommends co-administration of SP-IPTi in areas with moderate-to-high malaria transmission (annual entomological inoculation rate ≥ 10) of Africa, and where parasite resistance to SP is not high, defined as a prevalence of the Pfdhps 540 mutation of ≤ 50%.

The studies showed no evidence of any adverse effects of SP-IPTi on infants' serological responses to vaccines (DTP, polio, hepatitis B, *Haemophilus influenzae* B, yellow fever or measles). A rebound effect in terms of greater susceptibility to malaria after termination of SP-IPTi, although reported in some studies, was not found in the pooled analysis.

SP-IPTi should not be given to infants receiving a sulfa-based medication for treatment or prophylaxis, including co-trimoxazole (trimethoprim–sulfamethoxazole), which is widely used as prophylaxis against opportunistic infections in HIV-infected infants.

Surveillance of molecular markers of SP resistance should accompany SP-IPTi, in particular the distribution and prevalence of *Pfdhps* 540 mutations, which is a surrogate measure of SP efficacy.

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[15] Policy recommendation on intermittent preventive treatment during infancy with sulphadoxine-pyrimethamine (SP-IPTi) for *Plasmodium falciparum* malaria control in Africa. Geneva: World Health Organization; 2010 (http://www.who.int/malaria/news/WHO_policy_recommendation_IPTi_032010.pdf).

11.3 | SEASONAL MALARIA CHEMOPREVENTION WITH AMODIAQUINE + SULFADOXINE– PYRIMETHAMINE

Seasonal malaria chemoprophylaxis

In areas with highly seasonal malaria transmission in the sub-Sahel region of Africa, provide SMC with monthly amodiaquine + SP for all children < 6 years during each transmission season.
Strong recommendation, high-quality evidence

GRADE (see Annex 4, A4.21)
In a systematic review SMC was directly compared with no prophylaxis in seven trials with a total of 12 589 children. All the trials were conducted in West Africa, and six of seven trials were restricted to children < 5 years.
In comparison with no chemoprophylaxis, SMC:
- Prevented up to 75% of malaria episodes (rate ratio, 0.26; 95% CI, 0.17–0.38; six trials, 9321 participants, *high-quality evidence*);
- Prevented up to 75% of severe malaria episodes (rate ratio, 0.27; 95% CI, 0.10–0.76; two trials, 5964 participants, *high-quality evidence*); and
- May be associated with a reduction in mortality (risk ratio, 0.66; 95% CI, 0.31–1.39; six trials, 9533 participants, *moderate-quality evidence*).

These effects remained even when use of insecticide-treated nets was high (two trials, 5964 participants, *high-quality evidence*).

The current regimen (amodiaquine + SP) caused vomiting after the first dose in some children (*high-quality evidence*).

Meremikwu MM, Donegan S, Sinclair D, Esu E, Oringanje C. Intermittent preventive treatment for malaria in children living in areas with seasonal transmission. Cochrane Database Systemat Rev 2012;2:CD003756. doi: 10.1002/14651858.CD003756.pub4.

Throughout the Sahel subregion, most mortality and morbidity from malaria among children occurs during the rainy season, which is generally short. The interventions currently recommended by WHO for the control of malaria are use of insecticide-treated nets and/or indoor residual spraying for vector control, prompt access to diagnostic testing of suspected malaria and treatment of confirmed cases. SMC is defined as intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent illness, with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest risk.

SMC is therefore recommended in areas of highly seasonal malaria transmission throughout the Sahel subregion. A complete treatment course of amodiaquine + SP should be given to children aged 3–59 months at monthly intervals, beginning at the start of the transmission season, to a maximum of four doses during the transmission season (provided both drugs retain sufficient antimalarial efficacy).

The results of clinical trials indicate that a high level of protection against uncomplicated clinical malaria is likely to be maintained for 4 weeks after administration of each course of amodiaquine + SP; thereafter, protection appears to decay rapidly.

Treatment of breakthrough *P. falciparum* infections during the period of SMC should not include either amodiaquine or SP, and, in areas where SMC is implemented, alternative antimalarial combinations containing neither amodiaquine nor SP must be made available for the treatment of clinical malaria in the target age group.

IPTi and SMC should not be administered concomitantly; therefore, IPTi should not be used in target areas for SMC. SMC should not be given to children with severe acute illness or who are unable to take oral medication, or to HIV-positive children receiving co-trimoxazole, or children who have received a dose of either amodiaquine or SP during the past month or children with allergy to either drug.

12 | QUALITY OF ANTIMALARIAL MEDICINES

Antimalarial drug quality

National drug and regulatory authorities should ensure that the antimalarial medicines provided in both the public and the private sectors are of acceptable quality, through regulation, inspection and law enforcement.
Good practice statement

The two general classes of poor-quality medicines are those that are *falsified* (counterfeit), in which there is criminal intent to deceive and the drug contains little or no active ingredient (and often other potentially harmful substances), and those that are *substandard*, in which a legitimate producer has included incorrect amounts of active drug and/or excipients in the medicine, or the medicine has been stored incorrectly or for too long and has degraded. Falsified antimalarial tablets and ampoules containing little or no active pharmaceutical ingredients are a major problem in some areas. They may be impossible to distinguish at points of care from the genuine product and may lead to under-dosage and high levels of treatment failure, giving a mistaken impression of resistance, or encourage the development of resistance by providing sub-therapeutic blood levels. They may also contain toxic ingredients.

Substandard drugs result from poor-quality manufacture and formulation, chemical instability or improper or prolonged storage. Artemisinin and its derivatives in particular have built-in chemical instability, which is necessary for their biological action but which causes pharmaceutical problems both in their manufacture and in their co-formulation with other compounds. The problems of instability are accelerated under tropical conditions. The requirement for stringent quality standards is particularly important for this class of compounds. Many antimalarial drugs are stored in conditions of high heat and humidity and sold beyond their expiry dates.

In many malaria-endemic areas, a large proportion of the antimalarial drugs used are generic products purchased in the private sector. They may contain the correct amounts of antimalarial drug, but, because of their formulation, are inadequately absorbed. Antimalarial medicines must be manufactured according to good manufacturing practice, have the correct drug and excipient contents, be proved to have bioavailability that is similar to that of the reference product, have been stored under appropriate conditions and be dispensed before their expiry date.

Tools to assess drug quality at points of sale are being developed, but the capacity of medicines regulatory agencies in most countries to monitor drug quality is still limited. Legal and regulatory frameworks must be strengthened, and there should be greater collaboration between law enforcement agencies, customs and excise authorities and medicines regulatory agencies to deal more effectively with falsified medicines. Private sector drug distribution outlets should have more information and active engagement with regulatory agencies. WHO, in collaboration with other United Nations agencies, has established an international mechanism to prequalify manufacturers of ACTs on the basis of their compliance with internationally recommended standards of manufacture and quality. Manufacturers of antimalarial medicines with prequalified status are listed on the prequalification web site.[16]

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[16] Prequalification programme: A United Nations programme managed by WHO. Geneva: World Health Organization; 2009 (http://apps.who.int/prequal/).

3RD

EDITION

13 | **MONITORING THE EFFICACY AND SAFETY OF ANTIMALARIAL DRUGS AND RESISTANCE**

Monitoring of antimalarial drug efficacy and safety, and resistance

All malaria programmes should regularly monitor the therapeutic efficacy of antimalarial drugs using the standard WHO protocols.
Good practice statement

When adapting and implementing these guidelines, countries should also strengthen their systems for monitoring and evaluating their national programmes. The systems should allow countries to track the implementation and impact of new recommendations, better target their programmes to the areas and populations at greatest need and detect decreasing antimalarial efficacy and drug resistance as early as possible. See also Annex 7.

13.1 | ROUTINE SURVEILLANCE

WHO promotes universal coverage with diagnostic testing and antimalarial treatment and strengthened malaria surveillance systems. In the "test, track, treat" initiative, it is recommended that every *suspected* malaria case is tested, that every *confirmed* case is treated with a quality-assured antimalarial medicine and that the disease is tracked by timely, accurate surveillance systems. Surveillance and treatment based on confirmed malaria cases will lead to better understanding of the disease burden and enable national malaria control programmes to direct better their resources to where they are most needed.

13.2 | THERAPEUTIC EFFICACY

Monitoring of therapeutic efficacy in falciparum malaria involves assessing clinical and parasitological outcomes of treatment for at least 28 days after the start of adequate treatment and monitoring for the reappearance of parasites in blood. The exact duration of post-treatment follow-up is based on the elimination half-life of the partner drug in the ACT being evaluated.

PCR genotyping should be used in therapeutic monitoring of antimalarial drug efficacy against *P. falciparum* to distinguish between recrudescence (true treatment failure) and new infections.

An antimalarial medicine that is recommended in the national malaria treatment policy should be changed if the total treatment failure proportion is ≥ 10%, as assessed in vivo by monitoring therapeutic efficacy. A significantly declining trend in treatment efficacy over time, even if failure rates have not yet fallen to the ≥ 10% cut-off, should alert programmes to undertake more frequent monitoring and to prepare for a potential policy change.

Assessing therapeutic responses is more difficult in vivax malaria than in falciparum malaria, as relapses cannot be distinguished from recrudescence or reinfection. Relapse of tropical *P. vivax* infection may occur about 3 weeks after treatment. However these early relapses (or any newly acquired infections) should be suppressed by therapeutic doses of slowly eliminated antimalarial drugs such as chloroquine, mefloquine and piperaquine. Reappearance of parasitaemia within 28 days of treatment (whether relapse, recrudescence or re-infection) can therefore still be used as a proxy measure of resistance.

13.3 | RESISTANCE

Antimalarial drug resistance is the ability of a parasite strain to survive and/or multiply despite administration and absorption of an antimalarial drug given in doses equal to or higher than those usually recommended, provided that drug exposure is adequate. Resistance to antimalarial drugs arises because of selection of parasites with genetic changes (mutations or gene amplifications) that confer reduced susceptibility. Resistance has been documented to all classes of antimalarial medicines, including the artemisinin derivatives, and it is a major threat to malaria control. Widespread inappropriate use of antimalarial drugs 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 antimalarial drugs with different mechanisms of action and ensuring high cure rates through full adherence to correct dose regimens. If different drugs with different mechanisms of resistance are used together, the emergence and spread of resistance should be slowed.

Clinical and parasitological assessment of therapeutic efficacy should include:

- confirmation of the quality of the antimalarial medicines tested;
- molecular genotyping to distinguish between re-infections and recrudescence and to identify genetic markers of drug resistance;
- studies of parasite susceptibility to antimalarial drugs in culture; and
- measurement of antimalarial drug levels to assess exposure in cases of slow therapeutic response or treatment failure.

13.4 | PHARMACOVIGILANCE

Governments should have effective pharmacovigilance systems (such as the WHO pregnancy registry) to monitor the safety of all drugs, including antimalarial medicines. The safety profiles of the currently recommended antimalarial drugs are reasonably well described and supported by an evidence base of several thousand participants (mainly from clinical trials); however, rare but serious adverse drug reactions will not be detected in clinical trials of this size, particularly if they occur primarily in young children, pregnant women or people with concurrent

illness, who are usually under-represented in clinical trials. Rare but serious adverse drug reactions are therefore detected only in prospective phase IV post-marketing studies or population-based pharmacovigilance systems. In particular, more data are urgently needed on the safety of ACTs during the first trimester of pregnancy and on potential interactions between antimalarial and other commonly used medicines.

3RD

EDITION

14 | NATIONAL ADAPTATION OF THE
GENERIC FRAMEWORK FOR MALARIA
DIAGNOSIS AND TREATMENT, AND
IMPLEMENTATION

> ## National adaptation and implementation
>
> The choice of ACT in a country or region should be based on optimal efficacy, safety and adherence.
> *Good practice statement*
>
> Drugs used in IPTp, SMC and IPTi should not be used as a component of first-line treatment in the same country or region.
> *Good practice statement*
>
> When possible:
> - use fixed-dose combinations rather than co-blistered or loose, single-agent formulations; and
> - for young children and infants, use paediatric formulations, with a preference for solid formulations (e.g. dispersible tablets) rather than liquid formulations.
>
> *Good practice statement*

These guidelines provide a generic framework for malaria diagnosis and treatment policies worldwide; however, national policy-makers will be required to adapt these recommendations on the basis of local priorities, malaria epidemiology, parasite resistance and national resources.

14.1 | NATIONAL DECISION-MAKING

National decision-makers are encouraged to adopt inclusive, transparent, rigorous approaches. Broad, inclusive stakeholder engagement in the design and implementation of national malaria control programmes will help to ensure they are feasible, appropriate, equitable and acceptable. Transparency and freedom from financial conflicts of interest will reduce mistrust and conflict, while rigorous evidence-based processes will ensure that the best possible decisions are made for the population.

14.2 | INFORMATION REQUIRED FOR NATIONAL DECISION-MAKING

Selection of first- and second-line antimalarial medicines will require reliable national data on their efficacy and parasite resistance, which in turn require that appropriate surveillance and monitoring systems are in place (see section 13). In some countries, the group adapting *the guidelines* for national use might have to re-evaluate the global evidence base with respect to their own context. The GRADE tables in Annex 4 may serve as a starting-point for this assessment.

Decisions about coverage, feasibility, acceptability and cost may require input from various health professionals, community representatives, health economists, academics and health system managers.

14.3 | OPPORTUNITIES AND RISKS

The recommendations made in these guidelines provide an opportunity to improve malaria case management further, to reduce unnecessary morbidity and mortality and to contribute to continued efforts towards elimination. Failure to implement the basic principles of combination therapy and rational use of antimalarial medicines will risk promoting the emergence and spread of drug resistance, which could undo all the recent gains in malaria control and elimination.

14.4 | GENERAL GUIDING PRINCIPLES FOR CHOOSING A CASE MANAGEMENT STRATEGY AND TOOLS

14.4.1 | CHOOSING A DIAGNOSTIC STRATEGY

The two methods currently considered suitable for routine patient management are light microscopy and RDTs. Different strategies may be adopted in different health care settings. The choice between RDTs and microscopy depends on local circumstances, including the skills available, the patient case-load, the epidemiology of malaria and use of microscopy for the diagnosis of other diseases. When the case-load of patients with fever is high, the cost of each microscopy test is likely to be less than that of an RDT; however, high-throughput, high-quality microscopy may be less operationally feasible. Although several RDTs allow diagnosis of both *P. falciparum* and *P. vivax* infections, microscopy has further advantages, including accurate parasite counting (and thus identification of high parasite density), prognostication in severe malaria, speciation of other malaria parasites and sequential assessment of the response to antimalarial treatment. Microscopy may help to identify other causes of fever. High-quality light microscopy requires well-trained, skilled staff, good staining reagents, clean slides and, often, electricity to power the microscope. It requires a quality assurance system, which is often not well implemented in malaria-endemic countries.

In many areas, malaria patients are treated outside the formal health services, e.g. in the community, at home or by private providers. Microscopy is generally not feasible in the community, but RDTs might be available, allowing access to confirmatory diagnosis of malaria and the correct management of febrile illnesses.

The average sensitivity of HRP2-detecting RDTs is generally greater than that of RDTs for detecting *p*LDH of *P. falciparum*, but the latter are slightly more specific because the HRP2 antigen may persist in blood for days or weeks after effective treatment. HRP2-detecting RDTs are not suitable for detecting treatment failure. RDTs are slightly less sensitive for detecting *P. malariae* and *P. ovale*. The WHO Malaria RDT Product Testing programme provides comparative data on the performance of RDT products to guide procurement. Since 2008, 210 products have been evaluated in five rounds of product testing.[17, 18]

For the diagnosis of severe malaria, microscopy is preferred, as it provides a diagnosis of malaria and assessment of other important parameters of prognostic relevance in severely ill patients (such as parasite count and stage of parasite development and intra-leukocyte pigment). In severe malaria, an RDT can be used to confirm malaria rapidly so that parenteral antimalarial treatment can be started immediately. Where possible, however, blood smears should be examined by microscopy, with frequent monitoring of parasitaemia (e.g. every 12 h) during the first 2–3 days of treatment in order to monitor the response.

14.4.2 | CHOOSING ACT

In the absence of resistance, all the recommended ACTs have been shown to result in parasitological cure rates of > 95%. Although there are minor differences in the oral absorption, bioavailability and tolerability of 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 and the level of resistance to it that determine the efficacy of a formulation.

Policy-makers should also consider:
- local data on the therapeutic efficacy of the ACT,
- local data on drug resistance,
- the adverse effect profiles of ACT partner drugs,
- the availability of appropriate formulations to ensure adherence,
- cost.

In parts of South-East Asia, artemisinin resistance is compromising the efficacy of ACTs and placing greater selection pressure on resistance to the partner medicines. Elsewhere, there is no convincing evidence for reduced susceptibility to the artemisinins; therefore, the performance of the partner drugs is the determining factor in the choice of ACT, and the following principles apply:

- Resistance to mefloquine has been found in parts of mainland South-East Asia where this drug has been used intensively. Nevertheless, the combination with artesunate is very effective, unless there is also resistance to artemisinin.

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[17] Malaria rapid diagnostic test performance. Results of WHO product testing of malaria RDTs: round 5. Geneva: World Health Organization; 2014 (http://who.int/malaria/publications/atoz/9789241507554/en/).

[18] Information note on recommended selection criteria for procurement of malaria rapid diagnostic tests (RDTs). Geneva: World Health Organization; 2014 (http://who.int/malaria/publications/atoz/rdt_selection_criteria/en/).

Resistance to both components has compromised the efficacy of artesunate + mefloquine in western Cambodia, eastern Myanmar and eastern Thailand.

- Lumefantrine shares some cross-resistance with mefloquine, but this has not compromised its efficacy in any of the areas in which artemether + lumefantrine has been used outside South-East Asia.
- Until recently, there was no evidence of resistance to piperaquine anywhere, but there is now reduced susceptibility in western Cambodia. Elsewhere, the dihydroartemisinin + piperaquine combination is currently highly effective.
- Resistance to SP limits its use in combination with artesunate to the few areas in which susceptibility is retained.
- Amodiaquine remains effective in combination with artesunate in parts of Africa and the Americas, although elsewhere resistance to this drug was prevalent before its introduction in an ACT.

14.5 | CONSIDERATIONS IN USE OF ARTEMISININ-BASED COMBINATION THERAPY

Oral artemisinin and its derivatives (e.g. artesunate, artemether, dihydroartemisinin) should not be used alone. In order to simplify use, improve adherence and minimize the availability of oral artemisinin monotherapy, fixed-dose combination ACTs are strongly preferred to co-blistered or co-dispensed loose tablets and should be used when they are readily available. Fixed-dose combinations of all recommended ACT are now available, except artesunate + SP. Fixed-dose artesunate + amodiaquine performs better than loose tablets, presumably by ensuring adequate dosing. Unfortunately, paediatric formulations are not yet available for all ACTs.

The choice of ACT in a country or region should be based on optimal efficacy and adherence, which can be achieved by:

- minimizing the number of formulations available for each recommended treatment regimen,
- using, where available, solid formulations instead of liquid formulations, even for young patients.

Although there are some minor differences in the oral absorption and bioavailability of different artemisinin derivatives, there is no evidence that such differences in currently available formulations are clinically significant. It is the pharmacokinetic properties of the partner medicine and the level of resistance to it that largely determine the efficacy and choice of combinations. Outside South-East Asia, there is no convincing evidence yet for reduced susceptibility to the artemisinins; therefore, the performance of the partner drug is the main determinant in the choice of ACT, according to the following principles:

- Drugs used in IPTp, SMC or chemoprophylaxis should not be used as first-line treatment in the same country or region.

- Resistance to SP limits use of artesunate + SP to areas in which susceptibility is retained.

Thus, in the majority of malaria-endemic countries, first-line ACTs remain highly effective, although resistance patterns change over time and should be closely monitored.

14.6 | CHOOSING AMONG FORMULATIONS

Use of fixed-dose combination formulations will ensure strict adherence to the central principle of combination therapy. Monotherapies should not be used, except as parenteral therapy for severe malaria or SP chemoprevention, and steps should be taken to reduce and remove their market availability. Fixed-dose combination formulations are now available for all recommended ACTs except artesunate + SP.

Paediatric formulations should allow accurate dosing without having to break tablets and should promote adherence by their acceptability to children. Paediatric formulations are currently available for artemether + lumefantrine, dihydroartemisinin + piperaquine and artesunate + mefloquine.

14.7 | OTHER OPERATIONAL ISSUES IN MANAGING EFFECTIVE TREATMENT

Individual patients derive the maximum benefit from an ACT if they can access it within 24–48 h of the onset of malaria symptoms. The impact in reducing transmission at a population level depends on high coverage rates and the transmission intensity. Thus, to optimize the benefits of deploying ACTs, they should be available in the public health delivery system, the private sector and the community, with no financial or physical barrier to access. A strategy for ensuring full access (including community management of malaria in the context of integrated case management) must be based on analyses of national and local health systems and may require legislative changes and regulatory approval, with additional local adjustment as indicated by programme monitoring and operational research. To optimize the benefits of effective treatment, wide dissemination of national treatment guidelines, clear recommendations, appropriate information, education and communication materials, monitoring of the deployment process, access and coverage, and provision of adequately packaged antimalarial drugs are needed.

14.7.1 | COMMUNITY CASE MANAGEMENT OF MALARIA

Community case management is recommended by WHO to improve access to prompt, effective treatment of malaria episodes by trained community members living as close as possible to the patients. Use of ACTs in this context is feasible, acceptable and effective.[19] Pre-referral treatment for severe malaria with rectal artesunate and use of RDTs are also recommended in this context. Community case management should be integrated into community management of childhood illnesses, which ensures coverage of priority childhood illnesses outside of health facilities.

14.7.2 | HEALTH EDUCATION

From the hospital to the community, education is vital to optimizing antimalarial treatment. Clear guidelines in the language understood by 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 improve the understanding of malaria. They will increase the likelihood of better prescribing and adherence, appropriate referral and unnecessary use of antimalarial medicines.

14.7.3 | ADHERENCE TO TREATMENT

Patient adherence is a major determinant of the response to antimalarial drugs, as most treatments are taken at home without medical supervision. Studies on adherence suggest that 3-day regimens of medicines such as ACTs are completed reasonably well, provided that patients or caregivers are given an adequate explanation at the time of prescribing or dispensing. Prescribers, shopkeepers and vendors should therefore give clear, comprehensible explanations of how to use the medicines. Co-formulation probably contributes importantly to adherence. User-friendly packaging (e.g. blister packs) also encourages completion of a treatment course and correct dosing.

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[19] Ajayi IO, Browne EN, Bateganya F, Yar D, Happi C, Falade CO, 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. Malar J 2008;7:190.

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3RD

EDITION

LIST OF ANNEXES

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Annex 1 | Preparation of the guidelines

The guideline development process

Since the first and second editions of *the guidelines* were issued in 2006 and 2010, respectively, WHO methods for preparing guidelines have continued to evolve. This third edition of *the Guidelines for the treatment of malaria* was prepared in accordance with the updated WHO standard methods for guideline development.[1] This involved planning, "scoping" and needs assessment, establishment of a guidelines development group, formulation of key questions (PICO questions: population, participants or patients; intervention or indicator; comparator or control; outcome), commissioning reviews, Grading of Recommendations, Assessment, Development and Evaluation (GRADE) and making recommendations. This method ensures a transparent link between the evidence and the recommendations. The GRADE system is a uniform, widely adopted approach based on explicit methods for formulating and evaluating the strength of recommendations for specific clinical questions on the basis of the robustness of the evidence.

The Technical Guidelines Development Group, co-chaired by Professor Fred Binka and Professor Nick White (other participants are listed below), organized a technical consultation on preparation of the third edition of *the Guidelines*. Declarations of conflicts of interest were received from all participants.

A WHO guideline steering group facilitated the scoping meeting, which was convened in February 2013, to set priorities and identify which sections of the second edition of *Guidelines* were to be reviewed and to define potential new recommendations. Draft PICO questions were formulated for collation and review of the evidence. A review of data on pharmacokinetics and pharmacodynamics was considered necessary to support dose recommendations, and a subgroup was formed for this purpose.

After the scoping meeting, the Cochrane Infectious Diseases Group at the Liverpool School of Tropical Medicine in Liverpool, England, was commissioned to undertake systematic reviews and to assess the quality of the evidence for each priority question. The reviews involved extensive searches for published and unpublished reports of trials and highly sensitive searches of the Cochrane Infectious Diseases Group trials register, the Cochrane Central Register of Controlled Trials, MEDLINE®, Embase and LILACS. All the reviews will be published on line in the Cochrane Library. When insufficient evidence was available from randomized trials, published reviews of non-randomized studies were considered.

A subgroup of the GDG on dosage recommendations reviewed published studies from MEDLINE® and Embase on the pharmacokinetics and pharmacodynamics of antimalarial medicines. For analyses of pharmacokinetics and simulations of dosing, they used raw clinical and laboratory data from the Worldwide Antimalarial Resistance Network on the concentrations of antimalarial agents in plasma or

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[1] WHO handbook for guideline development. Geneva: World Health Organization; 2012 (http://www.who.int/kms/guidelines_review_committee/en/).

whole blood measured with validated assays in individual patients. The data had either been included in peer-reviewed publications or been submitted to regulatory authorities for drug registration. Population pharmacokinetics models were constructed, and the plasma or whole blood concentration profiles of antimalarial medicines were simulated (typically 1000 times) for different weight categories.

The guideline development group met in two technical meetings, in November 2013 and June 2014, to develop and finalize recommendations based on the GRADE tables constructed on the basis of answers to the PICO questions. The new *Guidelines* were written by a subcommittee of the group. At various times during preparation of *the guidelines*, sections of the document or recommendations were reviewed by external experts and users who were not members of the group; these external peer reviewers are listed below.

Treatment recommendations were agreed by consensus, supported by systematic reviews and review of information on pharmacokinetics and pharmacodynamics. Areas of disagreement were discussed extensively to reach consensus; voting was not required.

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Declaration of interests

Participants in the technical consultation for the review of *the 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 the declared interests had direct relevance to the deliberations or recommendations of the meeting, the panel members with declared interests were excluded from the subcommittees on GRADE and recommendations and the drafting group. The declared interests, as per WHO regulations, were cleared through the Legal Department of WHO.

Dr K. Barnes reported being a recipient of grants from the Malaria Medicine Venture to undertake clinical trials to evaluate novel antimalarial medicines.

Dr F. Binka reported being a member of the INDEPTH network that was a recipient of a research grant from the Bill and Melinda Gates Foundation to conduct Phase IV post licensure studies on "Eurartesim".

Dr P. Garner reported receiving a grant from Department of International Development (UK) to help ensure global guidelines and decisions are based on reliable evidence.

Dr N. Valecha reported serving as an investigator for clinical trial supported by the Department of Science and Technology India, and Ranbaxy Laboratories Limited. There were no monetary benefits and no conflicts with the subject of this review.

Professor N. White reported being an advisor to all pharmaceutical companies developing new antimalarial medicines. This is done on a pro-bono basis, it does not include consultancy fees nor any form of remuneration.

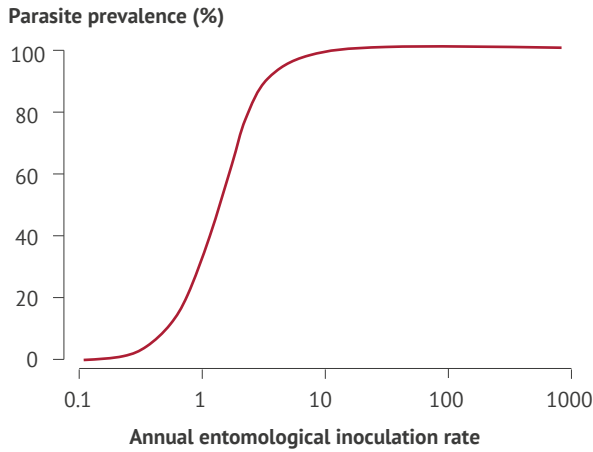# Annex 2 | Malaria transmission and antimalarial medicines

Principles of malaria transmission

Malaria is spread among people by mosquitoes belonging to the genus *Anopheles*. The female mosquito is infected by gametocytes, the sexual stages of the malaria parasite, when they take a blood meal from an infected person. Male and female gametocytes then fuse to form zygotes (ookinetes), which embed in the gut wall as oocysts and then undergo further development in the insect for 6–12 days. The mature oocysts rupture to liberate motile sporozoites, which migrate to the mosquito salivary glands to await inoculation into humans through the bite of the mosquito carrying them (*1*).

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 (EIR), which is the number of infectious mosquito bites received by an individual in 1 year. The EIR determines to a large extent the epidemiology of malaria and the pattern of clinical disease in an area. The upper end of the EIR range is found in a few parts of tropical Africa, where rates of 500–1000 can be reached (*2*). At the lower end of the range, EIRs of ≤ 0.01 are 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 the EIRs are < 10 and often 1–2, and situations of stable but seasonal malaria, as in much of West Africa, where the EIR is 10–100.

The proportion of infected mosquitoes in a locality reflects the capacity of the vectors to transmit malaria (vectorial capacity) and the number of infected and infectious humans in the area. Lowering the infectivity of infected persons to mosquito vectors contributes to reducing malaria transmission and eventually to reducing the incidence and prevalence of the disease. The relation between EIR and the prevalence of malaria is, however, complex: it is affected by vectorial capacity, the pattern of acquisition and loss of immunity to malaria and access to effective drug treatment in the area. The hypothetical relation represented in Figure A2.1 assumes no drug treatment. In areas of low transmission, where the EIR is < 1 or 2, a reduction in the inoculation rate will result in an almost proportionate reduction in the prevalence (and incidence rate) of malaria. When the EIR exceeds 10, there is great redundancy in the infectious reservoir, and larger reductions in transmission are required to make a significant impact on malaria prevalence. Experience with major interventions, such as use of insecticide-treated nets and artemisinin-based combination therapy, suggests that effective transmission-reducing interventions reduce mortality and even morbidity in most situations (1–4).

Figure A2.1. Relation between entomological inoculation rate and parasite prevalence (on the assumption that no infections are treated)



Effect of medicines on malaria transmission

Medicines can reduce malaria transmission by two mechanisms (*5*): early, effective treatment and reducing infectivity.

Early, effective treatment of a malaria blood infection with any antimalarial medicine will reduce gametocytaemia by eliminating the asexual blood stages from which gametocytes derive. The faster the clearance of asexual blood parasites, the greater the reduction in infectivity. The potent anti-infective properties of artemisinins result partly from rapid clearance of parasites. In *P. vivax, P. malariae* and *P. ovale* infections, gametocytes are susceptible to all the antimalarial drugs, have a short developmental period (2–3 days) and have short-lived mature gametocytes. Effective treatment of the asexual blood infection alone abolishes infectivity to mosquitoes. In *P. falciparum* infections, gametocytes take longer to develop (7–10 days), and for most of this time they are sequestered in the microcirculation (particularly in the bone marrow and spleen). Treated *P. falciparum* infections may remain infectious for more than 1 week after patients have been successfully treated unless they also take a specific anti-gametocyte medication (primaquine, see below).

Infectivity can be lowered either by a direct effect on gametocytes (gametocytocidal effect; primaquine) or on the parasite developmental stages in the mosquito (sporontocidal effect; antifols, atovaquone) or by killing feeding mosquitoes (endectocidal effect; avermectins). The antimalarial drugs used to treat the asexual stages of *P. falciparum* do not reduce the infectivity of mature infective gametocytes (*3–5*). Sulfadoxine–pyrimethamine in fact increases gametocyte carriage, but it also reduces the infectivity of drug-sensitive parasites. Artemisinins are the most potent gametocytocidal drugs of those currently used to treat acute malaria (*6–11*). They kill young gametocytes, preventing new infective gametocytes from entering the circulation, but they have less effect on mature gametocytes that may

be present in the circulation at the time of treatment (*6*). The 8-aminoquinoline primaquine acts on mature gametocytes rapidly, reducing their transmissibility to mosquitoes and accelerating gametocyte clearance (*12–20*). Thus, addition of primaquine to ACTs in the treatment of *P. falciparum* infections rapidly and potently reduces the transmissibility of the treated infection (Figure A2.2).

Figure A2.2. Dose–response relations for primaquine in reducing the infectivity of *Plasmodium falciparum*-infected individuals to anopheline mosquitoes
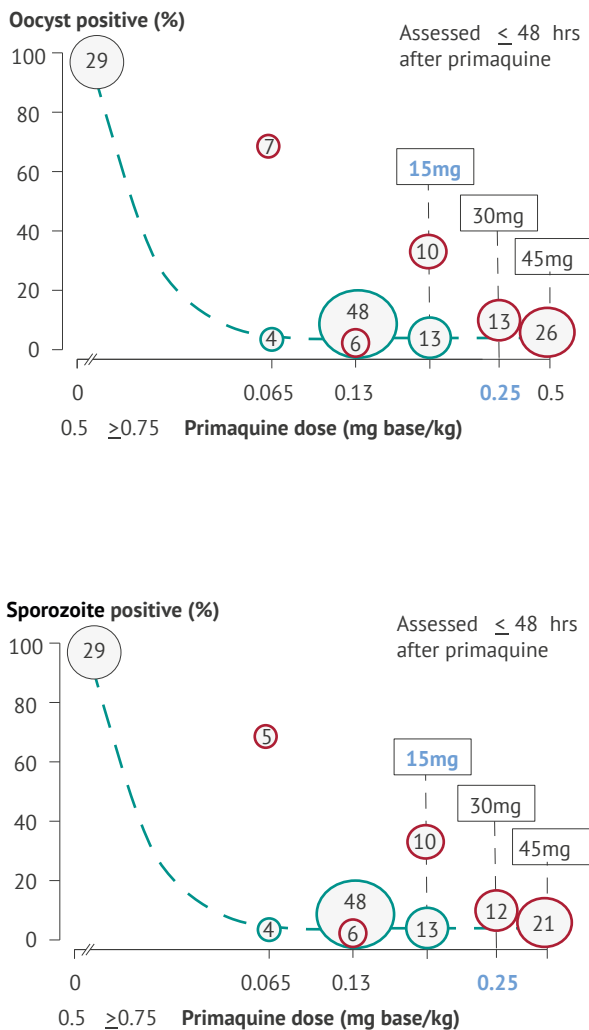
Pooled data from all studies conducted (*17*). Vertical axes show the proportions of fed anopheline mosquitoes that were infected. Oocyst formation (upper graph) and sporozoite formation (lower graph) assessed from blood sampled 48 h after a dose of primaquine. Primaquine given with an artemisinin derivative is shown in green, and primaquine given with no antimalarial medicine or a non-artemisinin derivative is shown in red. In these studies, 29 patients received no primaquine. The size of the circle is proportional to the number of patients in each group (shown within). Corresponding adult primaquine doses are indicated in squares.

In areas of low-to-moderate transmission

The most direct consequences of lowering parasite infectivity by the use of medicines are seen in areas of low transmission, where symptomatic patients contribute significantly to the infectious reservoir. Reducing infectiousness has a significant impact on malaria transmission and thus the prevalence of infection and the incidence of disease.

In areas of high-transmission

In high-transmission areas, infected but asymptomatic people 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, symptomatic patients comprise only a minority of the infective reservoir (*21–23*). In high-transmission settings, a considerable reduction in transmission rates is required to reduce parasite prevalence (and incidence of disease). Adding transmission-blocking drugs to antimalarial treatment is not cost–effective. As malaria control intensifies in highly endemic countries, however, transmission rates are declining; infectivity-reducing drug regimens may therefore further reduce transmission and play an important role in sustaining achievements.

Thus, the use of antimalarial medicines specifically to reduce infectivity:
- is justified in low-transmission settings and
- will be beneficial in high-transmission settings when transmission rates have been lowered by effective malaria control.

Strategies to reduce the transmission of drug-resistant parasites

Continued use of an antimalarial drug 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 are accompanied by more gametocytaemia than those that are sensitive (*6, 7, 24*). Furthermore, drug resistance leads to recrudescence associated with higher rates of gametocyte carriage than primary infections. Thus, cumulatively drug-resistant infections generate more gametocytaemia and therefore greater transmission potential than sensitive ones (*25, 26*). Secondly, under some circumstances, gametocytes carrying resistant genes may be more infectious to mosquitoes, producing greater numbers of oocysts and infecting a higher proportion of mosquitoes than those carrying sensitive genes (*27*). There is some evidence that mosquito control measures preferentially eliminate drug-resistant parasites (*28*). This evidence is supported by field experience in:

- Zimbabwe, where house spraying with insecticides to reduce malaria transmission was associated with a decrease in drug resistance (*29*), and
- focal regions in India and Sri Lanka, where a combination of intense vector-control measures and switching to an effective medicine led to significant reductions and, in some instances, even elimination of chloroquine-resistant *P. falciparum* from those foci.

As one of the earliest features of drug resistance is increased gametocyte carriage, addition of a transmission-blocking drug such as primaquine will negate this transmission advantage and slow the spread of resistance.

Summary and conclusions

Antimalarial medicines play an important role in reducing malaria transmission and in curtailing the spread of drug-resistant parasites. Good access to diagnosis and early, effective treatment will reduce malaria transmission. Antimalarial medicines with specific gametocytocidal activity (e.g. artemisinin derivatives, primaquine) will reduce falciparum malaria transmission even further, particularly in areas of low transmission.

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Annex 3 | Malaria diagnosis

Symptom-based (clinical) diagnosis

Malaria is a common cause of fever and illness in endemic areas (*1*, *2*). Malaria cannot be diagnosed accurately with any one set of clinical criteria, as the signs and symptoms (fever, chills, headache and anorexia) are non-specific 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 prevalent species of malaria parasite and other prevailing causes of fever (*3*). The concurrent incidence of other diseases with malaria may also affect its presentation. HIV/AIDS increases the risk for malaria illness and the progression to severe malaria, although the risk also depends on the malaria transmission intensity in the area and the age of the patient. HIV/AIDS also increases the incidence of febrile diseases that are not malaria, further complicating symptom-based diagnosis of malaria (*4*).

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 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 use of the more restrictive criteria in clinical algorithms resulted in only trivial savings in drug costs in comparison with the use of a fever-based diagnosis, and, in areas of high prevalence, greatly increased the probability of missing malaria infections (*7*). The diagnosis of malaria therefore requires blood testing.

Light microscopy

Microscopy not only provides a highly sensitive, specific diagnosis of malaria when performed well but also allows quantification of malaria parasites and identification of the infecting species. Light microscopy involves relatively high costs for training and supervision, and the accuracy of diagnosis is strongly dependent on the competence of the microscopist. Microscopy technicians may also contribute to the diagnosis of non-malarial diseases.

Although nucleic acid amplification-based tests are more sensitive, light microscopy is still considered the "field standard" against which the sensitivity and specificity of other methods must be assessed. A skilled microscopist can detect asexual parasites at a density of < 10 per μL of blood, but under typical field conditions, the limit of sensitivity is approximately 100 parasites per μL (*8*). This limit of detection approximates the lower end of the pyrogenic density range. Thus, microscopy provides good specificity for diagnosing malaria as the cause of a presenting febrile illness. More sensitive methods allow detection of an increasing proportion of cases of incidental parasitaemia in endemic areas, thus reducing the specificity of a positive test. Light microscopy has other important advantages:

- low direct costs, if laboratory infrastructure to maintain the service is available;
- high sensitivity, if the performance of microscopy is high;
- differentiation of Plasmodia species;
- determination of parasite densities – notably identification of hyperparasitaemia;
- detection of gametocytaemia;
- allows monitoring of responses to therapy and
- can be used to diagnose many other conditions.

Good performance of microscopy can be difficult to maintain, because of the requirements for adequate training and supervision of laboratory staff to ensure competence in malaria diagnosis, electricity, good quality slides and stains, provision and maintenance of good microscopes and maintenance of 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*).

Rapid diagnostic tests

Rapid diagnostic tests (RDTs) are immuno-chromatographic tests for detecting parasite-specific antigens in a finger-prick blood sample. Some tests allow detection of only one species (*P. falciparum*); others allow detection of 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 various formats, e.g. dipsticks, cassettes and cards. Cassettes and cards are easier to use in difficult conditions outside health facilities. RDTs are relatively simple to perform and to interpret, and they do not require electricity or special equipment.

Since 2012, WHO has recommended that RDTs should be selected in accordance with the following criteria, based on the results of the assessments of the WHO Malaria RDT Product Testing programme (*13*):

- For detection of *P. falciparum* in all transmission settings, the panel detection score against *P. falciparum* samples should be at least 75% at 200 parasites/μL.
- For detection of *P. vivax* in all transmission settings the panel detection score against *P. vivax* samples should be at least 75% at 200 parasites/μL.
- The false positive rate should be less than 10%.
- The invalid rate should be less than 5%.

Current tests are based on the detection of histidine-rich protein 2 (HRP2), which is specific for *P. falciparum*, pan-specific or species-specific *Plasmodium* lactate dehydrogenase (*p*LDH) or pan-specific aldolase. The different characteristics of these antigens may affect their suitability for use in different situations, and these should be taken into account in programmes for RDT implementation. The tests have many potential advantages, including:

- rapid provision of results and extension of diagnostic services to the lowest-level health facilities and communities;

- fewer requirements for training and skilled personnel (for instance, a general health worker can be trained in 1 day); and
- reinforcement of patient confidence in the diagnosis and in the health service in general.

They also have potential disadvantages, including:

- inability, in the case of *Pf*HRP2-based RDTs, to distinguish new infections from recently and effectively treated infections, due to the persistence of *Pf*HRP2 in the blood for 1–5 weeks after effective treatment;
- the presence in countries in the Amazon region of variable frequencies of HRP2 deletions in *P. falciparum* parasites, making HRP2-based tests not suitable in this region;
- poor sensitivity for detecting *P. malariae* and *P. ovale*; and
- the heterogeneous quality of commercially available products and the existence of lot-to-lot variation.

In a systematic review (*14*), the sensitivity and specificity of RDTs in detecting *P. falciparum* in blood samples from patients in endemic areas attending ambulatory health facilities with symptoms suggestive of malaria were compared with the sensitivity and specificity of microscopy or polymerase chain reaction. The average sensitivity of *Pf*HRP2-detecting RDTs was 95.0% (95% confidence interval [CI], 93.5–96.2%), and the specificity was 95.2% (93.4–99.4%). RDTs for detecting *p*LDH from *P. falciparum* are generally less sensitive and more specific than those for detecting HRP2, with an average sensitivity (95% CI) of 93.2% (88.0–96.2%) and a specificity of 98.5% (96.7–99.4%). 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 diagnoses. The criteria for selecting RDTs or microscopy are listed in Table A3.1.

Table A3.1. Technical strengths and limitations of RDTs and microscopy to be taken into account in selecting the best option in different clinical situations and settings

Criterion	Characteristic of diagnostic test	Target cases and clinical setting	Recommended diagnostic test	
			RDT	Microscopy
Parasite density	RDTs give only a positive or a negative result. Microscopy can also show parasite density.	Uncomplicated malaria	Yes	Yes
		Severe malaria on admission	Not alone[a]	Yes
		Follow-up of admitted patients[b]	No	Yes

Criterion	Characteristic of diagnostic test	Target cases and clinical setting	Recommended diagnostic test	
			RDT	Microscopy
Antigen persistence	RDTs detect persisting antigens after parasite clearance.[c]	Confirmed malaria with persisting fever despite antimalarial treatment	No	Yes
	Microscopy gives a negative result as soon as the parasite is cleared from the patient's blood.	Cases of confirmed malaria not previously tested for malaria	Yes	Yes
		Persisting fever in people who did not receive antimalarial treatment	Yes	Yes
Electricity supply	RDTs do not require electricity.	Health centres and hospitals	Yes	Yes
	Microscopy requires a reliable electricity supply.	Health workers in the community and at health posts	Yes	No
Time for test completion	RDTs can be performed relatively quickly.	Settings with low work-load per health worker, e.g. small health facilities and facilities in areas of low endemicity	Yes	Yes
	Microscopy requires more time.	Settings with high work-load per health worker, e.g. outpatient departments of hospitals or health centres in areas of high endemicity	Yes	Not alone[a]

Criterion	Characteristic of diagnostic test	Target cases and clinical setting	Recommended diagnostic test	
			RDT	Microscopy
Competence and training requirements	RDTs are relatively easy to perform. Microscopy is more complex and requires the competence of a trained microscopist.[d]	Health workers with limited training in laboratory procedures or in settings with limited resources for supervision[d]	Yes	No
		Settings in which specific training in microscopy can be given and a laboratory quality management system is functioning[e]	Yes	No

[a] This diagnostic test should not be used exclusively, and the other test is necessary.

[b] Parasite density is required to monitor response to treatment.

[c] RDTs to detect pLDH may give positive results up to 5–6 days after disappearance of the parasite, while those to detect HRP2 give positive results up to 1–5 weeks after disappearance of the parasite.

[d] Both diagnostic techniques require minimum specific training.

[e] Both diagnostic techniques require regular supervisory support.

Diagnosis with either microscopy or RDTs is expected to reduce overuse of antimalarial medicines by ensuring that treatment is given only to patients with confirmed malaria infection, as opposed to treating all patients with fever (15). Although providers of care may be willing to perform diagnostic tests, they do not, however, always respond appropriately to the results. This is especially true when they are negative. It is therefore important to ensure the accuracy of parasite-based diagnosis and also to demonstrate this to users and to provide them with the resources to manage both positive and negative results adequately (16).

Immunodiagnosis and nucleic acid amplification test 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 (17).

Techniques to detect parasite nucleic acid, e.g. polymerase chain reaction and loop-mediated isothermal amplification, are highly sensitive and very useful for detecting mixed infections, in particular at low parasite densities that are not detectable by conventional microscopy or with RDTs. They are also useful for studies of drug resistance and other specialized epidemiological investigations (18); however, they are not generally available for large-scale field use in malaria-endemic areas, nor are they appropriate for routine diagnosis in endemic areas where a large proportion of the population may have low-density parasitaemia.

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These techniques may be useful for population surveys and focus investigation in malaria elimination programmes.

At present, nucleic acid-based amplification techniques have no role in the clinical management of malaria or in routine surveillance systems (*19*).

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Annex 4 | Grading of Recommendations Assessment, Development and Evaluation (GRADE) for assessing the quality of evidence

This Annex gives the results of Grading of Recommendations, Assessment, Development and Evaluation (GRADE) based on responses to questions of importance to patient outcomes (population, participants or patients; intervention or indicator; comparator or control; outcome: PICO) and the resulting recommendations. The GRADE system is a uniform, widely adopted approach based on explicit methods for formulating and evaluating the strength of recommendations for specific clinical questions on the basis of the robustness of the evidence. The method ensures a transparent link between the evidence and the recommendations (see section 1.5 and Annex 1).

Questions:

A4.1	Are artemisinin-based combinations superior to non-artemisinin combinations for treating confirmed *P. falciparum* malaria?	
A4.2	Is dihydroartemisinin + piperaquine a safe, effective alternative to other WHO-approved ACTs?	
A4.3	Are ACTs containing 3 days of an artemisinin derivative more effective than ACTs containing 1 day of an artemisinin derivative?	
A4.4	Does addition of a single dose of 0.25 mg/kg base primaquine to ACTs reduce *P. falciparum* transmission to a greater extent than ACTs alone in areas of low transmission?	
A4.5	Are artemisinin-derivatives safe in the first trimester of pregnancy?	
A4.6	Should infants with uncomplicated malaria receive higher mg/kg bw doses of ACT than older children?	
A4.7	In settings where *P. vivax* parasites are susceptible to chloroquine, do ACTs improve the cure rate to a greater extent than chloroquine?	
A4.8	In settings where *P. vivax* parasites are resistant to chloroquine, do ACTs improve the cure rate and reduce the relapse rate to a greater extent than chloroquine?	
A4.9	Do 14-day courses of primaquine reduce relapse rates to a greater extent than shorter courses in people treated for *P. vivax* malaria?	
A4.10	What is the optimal primaquine regimen for radical cure of *P. vivax* malaria in people with G6PD deficiency?	
A4.11	In settings where *P. vivax* parasites are susceptible to chloroquine, is chloroquine prophylaxis during pregnancy safe and effective?	
A4.12	Is parenteral artesunate superior to parenteral quinine in preventing death from severe malaria?	

A4.13	Is parenteral artesunate superior to intramuscular artemether in preventing death from severe malaria?	
A4.14	Is intramuscular artemether superior to parenteral quinine in preventing death from severe malaria?	
A4.15	For pre-referral treatment, do intramuscular antimalarial drugs reduce the number of deaths to a greater extent than rectal artesunate in adults and children with signs of severe malaria?	
A4.16	Does pre-referral rectal artesunate reduce the number of deaths in adults and children with signs of severe malaria to a greater extent than placebo?	
A4.17	Is artesunate + pyronaridine a safe, effective alternative to other WHO-approved ACTs?	
A4.18	Is artemisinin + naphthoquine a safe, effective alternative to other WHO-approved ACTs?	
A4.19	Are three or more doses of sulfadoxine–pyrimethamine during pregnancy more effective than two doses?	
A4.20	In areas of moderate-to-high malaria transmission where SP is still effective, does intermittent treatment with SP alongside routine vaccination reduce morbidity and mortality compared to no intervention?	
A4.21	Does seasonal malaria chemoprevention reduce morbidity and mortality from malaria to a greater extent than no intervention?	

A4.1 Are artemisinin-based combinations superior to non-artemisinin combinations for treating confirmed *P. falciparum* malaria?

Balance of desirable and undesirable effects

Desirable	Undesirable
Studies have consistently demonstrated that the five WHO-recommended ACTs result in < 5% PCR-adjusted treatment failures in settings with no resistance to the partner drug (*high-quality evidence*).	Increased cost

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
High			

Rationale for the recommendation

The Guideline Development Group decided to recommend a "menu" of approved combinations from which countries can select first- and second-line therapies. Modelling studies suggest that having multiple first-line ACTs available for use may help to prevent or delay the development of resistance.

Recommendation

Treat adults and children with uncomplicated *P. falciparum* malaria (including infants, pregnant women in their second and third trimesters and breastfeeding women) with ACT.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

- The WHO-approved first-line ACT options are: artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, dihydroartemisinin + piperaquine and artesunate + sulfadoxine–pyrimethamine.
- These options are recommended for adults and children, including infants, lactating women and pregnant women in their second and third trimester.
- In deciding which ACTs to adopt in national treatment policies, national policy-makers should take into account: the pattern of resistance to antimalarial drugs in the country, the relative efficacy and safety of the combinations, their cost, the availability of paediatric formulations and the availability of co-formulated products.
- Fixed-dose combinations are preferred to loose tablets or co-blistered products.

A4.2 Is dihydroartemisinin + piperaquine a safe, effective alternative to other WHO-approved ACTs?

Balance of desirable and undesirable effects

Desirable	Undesirable
A PCR-adjusted treatment failure rate of < 5% has been seen consistently in trials of dihydroartemisinin + piperaquine (*high-quality evidence*).	A few more patients receiving dihydroartemisinin + piperaquine than those given artesunate + mefloquine had a prolonged QT interval (*low-quality evidence*), and a few more patients receiving dihydroartemisinin + piperaquine than those given artesunate + mefloquine or artemether + lumefantrine had borderline QT prolongation.
Dihydroartemisinin + piperaquine has a longer half-life than artemether + lumefantrine, and fewer new infections occur within 9 weeks of treatment with dihydroartemisinin + piperaquine (*high-quality evidence*).	
Dihydroartemisinin + piperaquine and artesunate + mefloquine have similar half-lives, and a similar frequency of new infections is seen within 9 weeks of treatment (*moderate-quality evidence*).	No sudden cardiac deaths have been reported.

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
High			

Rationale for the recommendation

The Guideline Development Group recommended dihydroartemisinin + piperaquine for use in 2009 but re-evaluated the evidence in 2013 because additional data on its safety had become available.

The group noted the small absolute prolongation of the QT interval with dihydroartemisinin + piperaquine but was satisfied that the increase was of comparable magnitude to that observed with chloroquine and was not important clinically.

The group also noted that the drug has been extensively studied, and no sudden unexpected cardiac episodes have been reported.

Recommendation

Dihydroartemisinin + piperaquine is recommended for general use.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

- A systematic review showed that the dosing regimen of dihydroartemisinin + piperaquine currently recommended by the manufacturers leads to sub-optimal drug concentrations and an increased risk of treatment failure in young children. The group recommends a revised dosing regimen based on pharmacokinetic models.
- Further studies of the risk for QT interval prolongation have been requested by the European Medicines Agency.

Dihydroartemisinin + piperaquine versus artemether + lumefantrine for treating people with proven uncomplicated *P. falciparum* malaria in Africa

Patients or population: Patients with uncomplicated *P. falciparum* malaria
Settings: Malaria-endemic settings in Africa
Intervention: Dihydroartemisinin + piperaquine once daily for 3 days
Comparison: Artemether + lumefantrine twice daily for 3 days
Source: Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD010927. DOI: 10.1002/14651858.CD010927

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (trials)	Quality of evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	Artemether + lumefantrine	Dihydroartemisinin + piperaquine				
Treatment failure on day 28	PCR-unadjusted		RR 0.34 (0.30 to 0.39)	6200 (9 trials)	⊕⊕⊕⊕ High[1-4]	Important
	23 per 100	8 per 100 (7 to 9)				
	PCR-adjusted		RR 0.42 (0.29 to 0.62)	5417 (9 trials)	⊕⊕⊕⊕ High[1-3,5]	Important
	3 per 100	1 per 100 (1 to 2)				
Treatment failure on day 63	PCR-unadjusted		RR 0.71 (0.65 to 0.78)	3200 (2 trials)	⊕⊕⊕⊕ High[1,3,4,6,7]	Important
	45 per 100	32 per 100 (29 to 35)				
	PCR-adjusted		RR 0.72 (0.50 to 1.04)	2097 (2 trials)	⊕⊕⊕⊕ High[1,3,7-9]	Critical
	6 per 100	4 per 100 (3 to 6)				

The assumed risk is the mean risk of the control group across studies; the corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio; PCR, polymerase chain reaction

[1] No serious risk of bias: Trials generally have little risk of bias. Exclusion of studies with high or unclear risk for selection bias or detection bias did not change the result.
[2] No serious inconsistency: All the trials had similar results, and statistical heterogeneity was low.
[3] No serious indirectness: The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.
[4] No serious imprecision: The 95% CI implies appreciable benefit, and the meta-analysis is adequately powered to detect this result.
[5] No serious imprecision: Although there is a benefit in favour of dihydroartemisinin + piperaquine, the PCR-adjusted treatment failure rate was < 5% with both drugs.
[6] No serious inconsistency: At this time, there is inconsistency between trials; both show a benefit with dihydroartemisinin + piperaquine, but the size of the benefit differs.
[7] Seven studies in east, west and southern Africa had outcomes at day 42, when dihydroartemisinin + piperaquine still had an advantage over artemether + lumefantrine for PCR-unadjusted treatment failure (RR, 0.60; 95% CI; 0.53 to 0.67, seven studies, 3301, *high-quality evidence*) and for PCR-adjusted treatment failure (RR, 0.58; 95% CI, 0.41 to 0.81, seven studies, 2559 participants, *high-quality evidence*).
[8] No serious inconsistency: The treatment failure rate with dihydroartemisinin + piperaquine was < 5% in both trials.
[9] No serious imprecision: Both ACTs performed well in these two trials, with low rates of treatment failure.

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Dihydroartemisinin + piperaquine versus artesunate + mefloquine for treating people with proven uncomplicated *P.falciparum* malaria in Asia

Patients or population: Patients with uncomplicated *P.falciparum* malaria
Settings: Malaria-endemic settings in Asia
Intervention: Dihydroartemisinin + piperaquine once daily for 3 days
Comparison: Artesunate + mefloquine once daily for 3 days
Source: Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD010927. DOI: 10.1002/14651858.CD010927.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk: Artesunate + mefloquine	Corresponding risk: Dihydroartemisinin + piperaquine				
Treatment failure on day 28	PCR-unadjusted		RR 1.02 (0.28 to 3.72)	3487 (8 trials)	⊕⊕⊕⊕ High[1–4]	Important
	2 per 100	2 per 100 (1 to 8)				
	PCR-adjusted		RR 0.41 (0.21 to 0.8)	3467 (8 trials)	⊕⊕⊕⊕ High[1,2,3,5]	Important
	1 per 100	0 per 100 (0 to 1)				
Treatment failure on day 63	PCR-unadjusted		RR 0.84 (0.69 to 1.03)	2715 (5 trials)	⊕⊕⊕⊝ Moderate[1,6–8]	Important
	12 per 100	10 per 100 (8 to 13)				
	PCR-adjusted		RR 0.5 (0.3 to 0.84)	2500 (5 trials)	⊕⊕⊕⊕ High[1,7–9]	Critical
	3 per 100	2 per 100 (1 to 3)				

The assumed risk is the mean risk of the control group across studies; the corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio; PCR, polymerase chain reaction

[1] No serious risk of bias: Trials generally have little risk of selection or detection bias. Exclusion of trials with high or unclear risk of bias did not change the result.
[2] Downgraded by 1 for serious inconsistency: in six trials, very few recurrences of parasitaemia were found in both groups. Two trials conducted mainly in areas in Thailand with multi-drug resistance showed increased risks for recurrent parasitaemia with artesunate + mefloquine.
[3] No serious indirectness: The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam.
[4] No serious imprecision: Overall, no significant difference between treatments; however, dihydroartemisinin + piperaquine may be superior where *P.falciparum* is resistant to mefloquine.
[5] No serious imprecision: Overall, a statistically significant benefit with dihydroartemisinin + piperaquine, although the benefit may be present only where there is resistance to mefloquine.
[6] Downgraded by 1 for serious inconsistency: of the five trials, one in Thailand in 2005 showed a statistically significant benefit with dihydroartemisinin + piperaquine, one in Myanmar in 2009 showed a benefit with dihydroartemisinin + piperaquine, and three found no difference.
[7] No serious indirectness: The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar and Thailand.
[8] No serious imprecision: Overall, no significant difference between treatments. Although some trials found statistically significant differences, these may not be clinically important.
[9] Downgraded by 1 for serious inconsistency: Slight variation among trials, only one showing a statistically significant benefit with dihydroartemisinin + piperaquine.

Dihydroartemisinin + piperaquine versus artemether + lumefantrine for uncomplicated *P. falciparum* malaria

Patients or population: Patients with uncomplicated *P. falciparum* malaria
Settings: Malaria-endemic areas
Intervention: Dihydroartemisinin + piperaquine
Comparison: Artemether + lumefantrine
Source: Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD010927. DOI: 10.1002/14651858.CD010927

Outcome		No. of participants with adverse events (95% CI)		No. of participants (trials)	Quality of the evidence (GRADE)
		Artemether + lumefantrine	Dihydroartemisinin + piperaquine		
Serious adverse events (including deaths)		6 per 1000	10 per 1000 (6 to 17)	7022 (8 trials)	Moderate[1–4]
Gastroenterological	Early vomiting	2 per 100	3 per 100 (2 to 5)	2695 (3 trials)	Moderate[2,3,5,6]
	Vomiting	9 per 100	9 per 100 (8 to 11)	6761 (9 trials)	Moderate[2,3,5,6]
	Nausea	2 per 100	2 per 100 (1 to 7)	547 (2 trials)	Low[2,3,5,7]
	Diarrhoea	12 per 100	12 per 100 (10 to 14)	4889 (7 trials)	Moderate[2,3,5,6]
	Abdominal pain	19 per 100	16 per 100 (12 to 20)	911 (5 trials)	Low[2,3,5,8]
	Anorexia	15 per 100	14 per 100 (12 to 17)	3834 (5 trials)	Moderate[2,3,5,6]
Neuro-psychiatric	Headache	27 per 100	33 per 100 (25 to 44)	309 (2 trials)	Low[2,3,5,8]
	Sleeplessness	1 per 100	3 per 100 (1 to 9)	547 (2 trials)	Low[2,3,5,7]
	Dizziness	3 per 100	4 per 100 (2 to 11)	547 (2 trials)	Low[2,3,5,7]
	Sleepiness	0 per 100	0 per 100 (0 to 0)	384 (1 trial)	Low[2,3,5,7]
	Weakness	17 per 100	18 per 100 (15 to 21)	1812 (5 trials)	Moderate[2,3,5,6]

Cardio-respiratory	Cough	42 per 100	42 per 100 (40 to 45)	4342 (5 trials)	Moderate[2,3,5,6]
	Coryza	68 per 100	66 per 100 (60 to 72)	832 (2 trials)	Low[1,2,3,8]
	Prolonged QT interval (adverse event)	3 per 100	2 per 100 (1 to 5)	1548 (1 trial)	Low[8,10,11]
	Prolonged QT interval (Bazett correction)	7 per 100	9 per 100 (6 to 11)	1548 (1 trial)	Low[5,8,11]
	Prolonged QT interval (Fridericia correction)	0 per 100	0 per 100 (0 to 2)	1548 (1 trial)	Low[5,8,11]
Musculoskeletal or dermatological	Pruritis	2 per 100	4 per 100 (2 to 6)	2033 (5 trials)	Moderate[2,3,5,6]
	Facial oedema	0 per 100	0 per 100 (0 to 0)	384 (1 trial)	Low[2,3,5,7]

The assumed risk for adverse events in the artemether + lumefantrine group is an average across trials; the corresponding risk associated with dihydroartemisinin + piperaquine (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, confidence interval; RR, risk ratio

[1] No serious risk of bias: All but one of the trials were open label; however, we did not downgrade for this outcome.

[2] No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.

[3] No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.

[4] Downgraded by 1 for serious imprecision: No statistically significant difference was detected between treatments; however the sample size does not exclude the possibility of rare but clinically important differences.

[5] Downgraded by 1 for risk of bias: The majority of trials were open label.

[6] No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences.

[7] Downgraded by 1 for serious imprecision: There are limited data.

[8] Downgraded by 1 for serious imprecision: The result does not reach statistical significance.

[9] No serious imprecision: The total number of participants is high, and the findings are precise.

[10] Downgraded by 1 for serious risk of bias: This trial was unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.

[11] No serious indirectness: This single trial was conducted in children in Burkina Faso, Kenya, Mozambique, Uganda and Zambia.

Dihydroartemisinin + piperaquine versus artesunate + mefloquine for treating uncomplicated *P.falciparum* malaria

Patients or population: Patients with uncomplicated *P.falciparum* malaria
Settings: Malaria-endemic areas
Intervention: Dihydroartemisinin + piperaquine
Comparison: Artesunate + mefloquine
Source: Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD010927. DOI: 10.1002/14651858.CD010927

Outcome		No. of participants with adverse events (95% CI)		No. of participants (trials)	Quality of the evidence (GRADE)
		Artesunate + mefloquine	Dihydroartemisinin + piperaquine		
Serious adverse events (including deaths)		8 per 1000	9 per 1000 (4 to 18)	3522 (8 trials)	Moderate[1–4]
Gastroenterological	Early vomiting	7 per 100	6 per 100 (5 to 8)	4114 (9 trials)	Moderate[2,3,5,6]
	Nausea	20 per 100	14 per 100 (12 to 16)	4531 (9 trials)	Moderate[3,5,7,8]
	Vomiting	13 per 100	8 per 100 (6 to 10)	2744 (5 trials)	Moderate[3,5,7,8]
	Anorexia	15 per 100	13 per 100 (11 to 15)	3497 (6 trials)	Low[3,5,7,9]
	Diarrhoea	6 per 100	8 per 100 (6 to 11)	2217 (5 trials)	Moderate[3,5,7,8]
	Abdominal pain	11 per 100	11 per 100 (9 to 13)	3887 (7 trials)	Moderate[3,5,7,10]
Neuro-psychiatric	Headache	12 per 100	10 per 100 (8 to 12)	2039 (4 trials)	Low[3,5,8,11]
	Dizziness	36 per 100	26 per 100 (24 to 28)	4531 (9 trials)	Moderate[3,5,7,8]
	Sleeplessness	21 per 100	10 per 100 (8 to 13)	2551 (6 trials)	Moderate[3,5,7,8]
	Fatigue	8 per 100	3 per 100 (2 to 6)	872 (2 trials)	Low[5,7,12]
	Nightmares	10 per 100	1 per 100 (0 to 7)	220 (1 trial)	Low[5,12]
	Anxiety	11 per 100	1 per 100 (0 to 4)	522 (1 trial)	Low[5,12]
	Blurred vision	9 per 100	4 per 100 (2 to 9)	464 (1 trial)	Low[5,12]
	Tinnitus	9 per 100	4 per 100 (1 to 11)	220 (1 trial)	Low[5,12]

Cardio-respiratory	Palpitations	18 per 100	11 per 100 (8 to 15)	1175 (3 trials)	Moderate[3,5,7,8]
	Cough	10 per 100	8 per 100 (5 to 12)	1148 (1 trial)	Low[5,9]
	Dyspnoea	9 per 100	3 per 100 (1 to 10)	220 (1 trial)	Low[5,13]
	Prolonged QT interval (adverse event)	4 per 100	5 per 100 (3 to 9)	1148 (1 trial)	Low[9,14,15]
	Prolonged QT interval (Bazett correction)	4 per 100	9 per 100 (5 to 15)	1148 (1 trial)	Low[5,9,15]
	Prolonged QT interval (Fridericia correction)	5 per 100	4 per 100 (3 to 8)	1148 (1 trial)	Low[5,9,15]
Musculoskeletal/ dermatological	Arthralgia	6 per 100	5 per 100 (3 to 9)	1148 (1 trial)	Moderate[5,10,14]
	Myalgia	6 per 100	6 per 100 (4 to 10)	1148 (1 trial)	Moderate[5,10,14]
	Urticaria	2 per 100	1 per 100 (0 to 4)	719 (2 trials)	Low[5,13]
	Pruritus	3 per 100	2 per 100 (1 to 4)	872 (2 trials)	Low[5,13]
	Rash	1 per 100	0 per 100 (0 to 7)	220 (1 trial)	Low[5,13]

The assumed risk for adverse events in the artesunate + mefloquine group is the average risk across trials; the corresponding risk with dihydroartemisinin + piperaquine (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, confidence interval.

[1] No serious risk of bias: Only eight of the 11 reports made any comment on serious adverse events. None of these eight trials was blinded.

[2] No serious inconsistency: None of the eight trials found statistically significant differences.

[3] No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.

[4] Downgraded by 1 for imprecision: These trials do not exclude the possibility of rare but clinically important adverse effects.

[5] Downgraded by 1 for serious risk of bias: All trials were open label.

[6] No serious imprecision: The 95% CI around the absolute effect is narrow and excludes clinically important differences.

[7] No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.

[8] No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect.

[9] Downgraded by 1 for serious imprecision: This result does not reach statistical significance.

[10] No serious imprecision: No difference was found between treatments, and the sample is large enough for detection of any differences.

[11] Downgraded by 1 for serious inconsistency: There is moderate heterogeneity among trials.

[12] Downgraded by 1 for serious indirectness: Only two trials assessed this outcome.

[13] Downgraded by 1 for imprecision: Limited data available, and the result is not statistically significant.

[14] Downgraded by 1 for serious risk of bias: This trial is unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.

[15] No serious indirectness: This single large trial was conducted in adults and children in India, the Lao People's Democratic Republic and Thailand.

A4.3 Are ACTs containing 3 days of an artemisinin derivative more effective than ACTs containing 1 day of an artemisinin derivative?

Balance of desirable and undesirable effects

Desirable	Undesirable
Fewer patients taking ACTs containing 3 days of an artemisinin derivative experience treatment failure within the first 28 days (*high-quality evidence*).	
Fewer participants taking ACTs containing 3 days of an artemisinin derivative have gametocytaemia at day 7 (*high-quality evidence*).	

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
High			

Rationale for the recommendation

The Guideline Development Group considers that 3 days of an artemisinin derivative are necessary to provide sufficient efficacy, promote good adherence and minimize the risk for drug resistance due to incomplete treatment.

Recommendation

The first-line ACT should contain at least 3 days' treatment with an artemisinin derivative.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

- Longer ACT treatment may be required to achieve > 90% cure rate in areas with artemisinin-resistant *P. falciparum*, but there are insufficient trials to make definitive recommendations.

Are ACTs containing 3 days of an artemisinin derivative more effective than ACTs containing 1 day of an artemisinin-derivative?

Patients or population: Adults and children with uncomplicated malaria
Settings: Malaria-endemic settings
Intervention: Artesunate 4 mg/kg bw once daily for 3 days plus sulfadoxine–pyrimethamine on day 1
Control: Artesunate 4 mg/kg bw once daily for 1 day plus sulfadoxine–pyrimethamine on day 1
Source: Kramer C, Sinclair D. Artemisinin-based combination treatments containing three days of artemisinin versus combinations containing one day of artemisinin.
Unpublished analysis including four studies[1-4]

Outcome	Illustrative comparative risks (95% CI)			Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	**Corresponding risk**					
	Artesunate 1 day	**Artesunate 3 days**					
Parasitological failure	At day 14			RR 0.36 (0.27 to 0.5)	1276 (4 studies)	⊕⊕⊕⊕ High[5-8]	Important
	19 per 100	7 per 100 (5 to 10)					
	At day 28 PCR-unadjusted			RR 0.62 (0.54 to 0.71)	1260 (4 studies)	⊕⊕⊕⊕ High[5-8]	Important
	47 per 1000	25 per 100 (21 to 31)					
	At day 28 PCR-adjusted			RR 0.45 (0.36 to 0.55)	1202 (4 studies)	⊕⊕⊕⊕ High[5-8]	Critical
	33 per 100	14 per 100 (12 to 18)					

Gametocytaemia					
	At day 7	RR 0.74 (0.58 to 0.93)	1260 (4 studies)	⊕⊕⊕⊕ High[5-7,8]	Important
	20 per 100	15 per 100 (12 to 19)			
	At day 14	RR 0.8 (0.57 to 1.14)	1199 (4 studies)	⊕⊕⊕⊖ Moderate[5,7,8]	Important
	11 per 100	8 per 100 (6 to 12)			
	At day 28	RR 0.36 (0.14 to 0.92)	898 (4 studies)	⊕⊕⊕⊖ Moderate[5,7,9]	Important
	3 per 100	1 per 100 (1 to 3)			

Assumed risk is the mean risk of the control group across studies; the corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio; ACT, artemisinin-based combination therapy; PCR, polymerase chain reaction

1 Obonyo CO, Ochieng F, Taylor WRJ, Ochola SA, Mugitu K, Olliaro P. Artesunate plus sulfadoxine-pyrimethamine for uncomplicated malaria in Kenyan children: a randomized, double blind, palcebo-controlled trial. Transactions of the Royal Society of Tropical Medicine and Hygiene 2003;97:585-91.

2 Obonyo CO, Taylor W, Ekvall H, Kaneko A, ter Kuile F, Olliaro P. Effect of artesuante plus sulfadoxine-pyrimethamine on haematological recovery and anaemia, in Kenyan children who uncomplicated, Plasmodium falciparum malaria. Annals of Tropical Medicine and Parasitology 2006;101(4):281-295.

3 Priotto G, Kabalyenga J, Pinoges L, Ruiz A, Eriksson T, Coussement F. Artesunate and sulfadoxine-pyrimethamine combinations for the treatment of uncomplicated Plasmodium falciparum malaria in Uganda: A randomized, double-blind, placebo-controlled trial. Transactions of the Royal Society of Tropical Medicine and Hygiene 2003;97(3):325-330.

4 von Seidlin L, Milligan P, Pinder M, Bojang K, Anyalebechi C, Gosling R. Efficacy of artesunate plus pyrimethamine-sulphadoxine for uncomplicated malaria in Gambian children: a double blind, randomised, controlled trial. Lancet 2000;355:352-57. No serious risk of bias: All four studies adequately concealed allocation and reported double blinding.

5 No serious inconsistency: All four studies found reductions with 3 days of artesunate, although there was some variation in the size of this effect.

6 No serious indirectness: The four trials were conducted in children with uncomplicated P. falciparum malaria in the Gambia, Kenya, Malawi and Uganda. The same screening methods and inclusion criteria were used. Sulfadoxine–pyrimethamine was the partner antimalarial drug in all four trials. Resistance to sulfadoxine–pyrimethamine was noted at three study sites, parasitological failure with sulfadoxine–pyrimethamine alone being seen in 10–13% of participants in the Gambia, 27% in Kenya and 25% in Uganda.

7 No serious imprecision: The confidence intervals are narrow, and the intervals comprise clinically important effects.

8 No serious imprecision: The confidence intervals are narrow and do not include no effect.

9 Downgraded by 1 for serious imprecision: As gametocytaemia at this time was rare in both groups, the studies have inadequate power to confidently detect important differences.

A4.4 Does addition of a single dose of 0.25 mg/kg bw primaquine base to ACTs reduce *P.falciparum* transmission to a greater extent than ACTs alone in areas of low transmission?

Recommendation

In low-transmission areas, also give a single dose of 0.25 mg/kg bw primaquine to reduce onward transmission of P. falciparum. G6PD testing is not necessary (except for pregnant and breastfeeding women and infants aged < 1 year).

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	Conditional			

Remarks

- This recommendation excludes high-transmission settings, as symptomatic patients make up only a small proportion of the total population carrying gametocytes within a community, and primaquine is unlikely to affect transmission.
- A major concern of national policy-makers in using primaquine has been the small risk for haemolytic toxicity in G6PD-deficient people, especially where G6PD testing is not available.
- Life-threatening haemolysis is considered unlikely with the 0.25mg/kg bw dose and without G6PD testing.

Balance of desirable and undesirable effects

Desirable	Undesirable
Single doses of primaquine > 0.4 mg/kg bw reduced gametocyte carriage at day 8 by around two thirds (*moderate-quality evidence*).	People with severe G6PD deficiency are at risk for haemolysis. At this dose, however, the risk is thought to be small; there are insufficient data to quantify this risk.
There are too few trials of doses < 0.4 mg/kg bw to quantify the effect on gametocyte carriage (*low-quality evidence*).	
Analysis of observational data from mosquito feeding studies suggests that 0.25 mg/kg bw may rapidly reduce the infectivity of gametocytes to mosquitoes.	

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
		Low	

Rationale for the recommendation

The Guideline Development Group considered the evidence on dose–response relations in the observational mosquito-feeding studies of reduced transmissibility with the dose of 0.25 mg/kg bw and the judgement of the WHO Evidence Review Group (November 2012). Their view was that the potential public health benefits of single low-dose (0.25 mg/kg bw) primaquine in addition to an ACT for falciparum malaria, without G6PD testing, outweigh the potential risk for adverse effects.

Single-dose primaquine for preventing transmission of *P. falciparum* parasites when given with artemisinin-based treatments

Patients or population: People with symptomatic malaria
Settings: Malaria-endemic areas
Intervention: Short-course primaquine plus malaria treatment including an artemisinin derivative
Control: Malaria treatment with an artemisinin derivative alone
Sources: Graves PM, Gelband H, Garner P. Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission. Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD008152. DOI: 10.1002/14651858.CD008152.pub4.
White NJ, Qiao LG, Qi G, Luzzatto L. Rationale for recommending a lower dose of primaquine as a *Plasmodium falciparum* gametocytocide in populations where G6PD deficiency is common. Malar J 2012;11:418.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comment
	Assumed risk	Corresponding risk				
	ACT	ACT + primaquine				
Malaria incidence, prevalence or entomological inoculation rate	–	–	–	0 trials	–	
People infectious to mosquitoes	–	–	–	0 trials	–	Limited observational data from mosquito feeding studies suggests that 0.25 mg/kg bw may rapidly reduce the infectivity of gametocytes to mosquitoes.

Participants with gametocytes on microscopy or PCR[1] (day 8)					
	Dose < 0.4 mg/kg bw		RR 0.67 (0.44 to 1.02)	223 (1 trial)	⊕⊕⊕⊖ [2-4] Low
	34 per 100	23 per 100 (15 to 35)			
	Dose 0.4–0.6 mg/kg bw		RR 0.30 (0.16 to 0.56)	219 (1 trial)	⊕⊕⊕⊖ [2,4-6] Moderate
	35 per 100	11 per 100 (6 to 20)			
	Dose > 0.6 mg/kg bw		RR 0.29 (0.22 to 0.37)	1380 (7 trials)	⊕⊕⊕⊕ High [7-9]
	30 per 100	9 per 100 (7 to 11)			
Mean percentage change in haemoglobin (Hb)[10]	15% mean drop in Hb from baseline in the control group	Mean drop in Hb from baseline in the intervention groups was 3% lower (10% lower to 4% higher)		101 (1 trial)	⊕⊖⊖⊖ Very low [10,11]

Assumed risk is the mean risk of the control group across studies. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; ACT, artemisinin-based combination therapy; RR, risk ratio; AUC, area under the concentration–time curve

[1] AUC estimates ($log1_0$ AUC for days 1–43) are included as footnotes for each dosing stratum.
[2] No serious risk of bias: Includes one trial with no risk of bias detected.
[3] Downgraded by 2 for very serious imprecision: One small trial with CIs that include 50% reduction and no effect.
[4] No data on percentage reduction in log_{10} AUC for days 1–43 at this dose
[5] Downgraded by 1 for serious imprecision: A single trial with few events
[6] Not downgraded for serious indirectness: This is a single trial in a single setting.
[7] Includes seven trials, with 11 comparisons: One trial included five separate comparisons of artesunate + amodiaquine, dihydroartemisinin + piperaquine, artesunate + mefloquine and artemether + lumefantrine.
[8] No serious inconsistency: While there is marked quantitative heterogeneity, the studies with no demonstrable effect had few events. Not downgraded.
[9] Percentage reduction in log_{10} AUC for days 1–43: range, 21.1–87.5%. We included four trials with 12 comparisons. We excluded one trial as having a high risk of bias due to small sample size and large difference in baseline gametocyte count in the two groups.
[10] One trial reported a relative decrease in haemoglobin against baseline in both groups on days 8, 15, 29 and 43 in all participants irrespective of G6PD status. No difference at any time between participants receiving primaquine and those that not did not. We present the data for day 43 in this table.
[11] Downgraded by 2 for very serious indirectness: the percentage of people with large drops in haemoglobin, not the mean change in the population, is the important safety outcome, and the estimates are averages in a small population (N = 99) that includes people with normal G6PD function. The study is therefore unlikely to detect effects in a small subgroup with a relatively uncommon adverse event.

A4.5 Are artemisinin-derivatives safe in the first trimester of pregnancy?

Balance of desirable and undesirable effects

Desirable	Undesirable
	Published prospective data on 700 women exposed in the first trimester of pregnancy have not indicated any adverse effects of artemisinin-derivatives on pregnancy or on the health of the fetus or neonate.
	The currently available data are only sufficient to exclude a ≥ 4.2-fold increase in risk of any major defect detectable at birth (background prevalence assumed to be 0.9%), if half the exposures occur during the embryo-sensitive period (4–9 weeks post-conception).

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low

Rationale for the recommendation

In the absence of adequate safety data on the artemisinin-derivatives in the first trimester of pregnancy the Guideline Development Group was unable to make recommendations beyond reiterating the status quo.

Recommendation

Treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with 7 days of quinine + clindamycin.

Treat pregnant women in their first trimester who have chloroquine-resistant *P. vivax* malaria with quinine.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

Previous data indicated that the antimalarial medicines considered safe in the first trimester of pregnancy are quinine, chloroquine, clindamycin and proguanil. This evidence was not revisited during this guideline process.

The limited data available on the safety of artemisinin-derivatives in early pregnancy allow for some reassurance in counselling women accidentally exposed to an artemisinin-derivative early in the first trimester, and there is no need for them to have their pregnancy interrupted because of this exposure.

McGready R, Lee SJ, Wiladphaingern J, et al. Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study. Lancet Infect Dis. 2012;12:388–96.

Mosha D, Mazuguni F, Mrema S, et al. Safety of artemether-lumefantrine exposure in first trimester of pregnancy: an observational cohort. Malar J. 2014; 13: 197e.

A4.6 Should infants with uncomplicated malaria receive higher mg/kg doses of ACT than older children?

Balance of desirable and undesirable effects

Desirable	Undesirable
	There is some evidence that artemether + lumefantrine and dihydroartemisinin + piperaquine may achieve lower plasma concentrations in infants than in older children and adults.

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low

Rationale for the recommendation

The Guideline Development Group considered the currently available evidence too limited to warrant formal evidence review at this stage, and was unable to recommend any changes beyond the status quo. Further research is warranted.

Recommendation

Treat infants weighing < 5 kg with uncomplicated *P. falciparum* malaria with an ACT. The weight-adjusted dose should achieve the same mg/kg bw target dose as for children weighing 5 kg.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

A4.7 In settings where *P. vivax* parasites are susceptible to chloroquine, do ACTs improve cure rate to a greater extent than chloroquine?

Balance of desirable and undesirable effects

Desirable	Undesirable
ACTs clear parasites more quickly than chloroquine (*high-quality evidence*).	
ACTs with long half-lives provide a longer period of suppressive post-treatment prophylaxis against relapses and new infections (*high-quality evidence*).	
Simplified national protocols for all forms of uncomplicated malaria.	
Adequate treatment of undiagnosed *P. falciparum* in mixed infections.	

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
High			

Rationale for the recommendation

The Guideline Development Group recognized that, in the few settings in which *P. vivax* is the only endemic species and where chloroquine resistance remains low, the increased cost of ACT may not be worth the small additional benefits. In these settings, chloroquine may still be considered, but countries should monitor chloroquine resistance and change to ACT when the treatment failure rate is > 10% on day 28.

Recommendation

In areas with chloroquine-susceptible *P. vivax*, treat adults and children with uncomplicated non-falciparum malaria with either chloroquine or ACT.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	Conditional			

Remarks

Current methods cannot distinguish recrudescence from relapse or relapse from newly acquired infections, but the aim of treatment is to ensure that the rates of recurrent parasitaemia of any origin are < 10%.

Primaquine has significant asexual stage activity against vivax malaria and augments the therapeutic response to chloroquine. When primaquine is given routinely for 14 days, it may mask low-level chloroquine resistance and prevent vivax recurrence within 28 days.

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A4.8 In settings where *P. vivax* parasites are resistant to chloroquine, do ACTs improve cure rate and reduce relapse rate to a greater extent than chloroquine?

Balance of desirable and undesirable effects

Desirable	Undesirable
ACTs clear parasites more quickly than chloroquine (*high-quality evidence*).	
ACTs are at least as effective as chloroquine in preventing recurrent parasitaemia before day 28 (*high-quality evidence*).	
ACTs with long half-lives (artesunate + mefloquine, dihydroartemisinin + piperaquine) provide a longer period of suppressive post-treatment prophylaxis against relapses and new infections (*high-quality evidence*).	
Adequate treatment of undiagnosed *P. falciparum* in mixed infections.	

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
High			

Rationale for the recommendation

The Guideline Development Group recognized that, in the few settings in which *P. vivax* is the only endemic species and where chloroquine resistance remains low, the increased cost of ACT may not be worth the small additional benefits. In these settings, chloroquine may still be considered, but countries should monitor chloroquine resistance and change to ACT when the treatment failure rate is > 10% on day 28.

Recommendation

In areas with chloroquine-resistant *P. vivax*, treat adults and children with uncomplicated *P. vivax* malaria with ACT (including infants, pregnant women in their second and third trimester and breastfeeding women).

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

Current methods do not distinguish recrudescence from relapse or relapse from newly acquired infection, but the aim of treatment is to ensure that the rates of recurrent parasitaemia of any origin is < 10% within 28 days.

When primaquine is not given for radical cure, slowly eliminated ACT that prevents recurrent parasitaemia before day 28 should be used (dihydroartemisinin + piperaquine or artesunate + mefloquine).

Primaquine has significant asexual stage activity against vivax malaria and augments the therapeutic response to chloroquine. When primaquine is given routinely for 14 days, it may mask low-level chloroquine resistance and prevent vivax recurrence within 28 days.

When primaquine is given routinely for 14 days, ACTs with shorter half-lives (artemether + lumefantrine, or artesunate + amodiaquine) may be sufficient to keep the rate of recurrent parasitaemia before day 28 below 10%.

Artemisinin-based combination therapy versus chloroquine for uncomplicated *P. vivax* malaria

Patient or population: Adults and children with uncomplicated *P. vivax* malaria
Settings: Malaria-endemic areas in which chloroquine is still effective for the first 28 days
Intervention: Artemisinin-based combination therapy
Comparison: Chloroquine
Source: Gogtay N, Kannan S, Thatte UM, Olliaro PL, Sinclair D. Artemisinin-based combination therapy for treating uncomplicated *Plasmodium vivax* malaria. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD008492. DOI: 10.1002/14651858.CD008492.pub3.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	Chloroquine	ACT				
Remaining parasitaemia at 24 h	52 per 100	22 per 100 (19 to 26)	RR 0.42 (0.36 to 0.50)	1652 (4 studies[1])	⊕⊕⊕⊕ High[2-5]	Important
Still febrile after 24 h	29 per 100	16 per 100 (12 to 20)	RR 0.55 (0.43 to 0.7)	990 (2 studies[6])	⊕⊕⊕⊝ Moderate[2,4,5,7]	Important
Effective treatment of blood-stage infection as assessed by recurrent parasitaemia before day 28	3 per 100	2 per 100 (1 to 6)	RR 0.58 (0.18 to 1.90)	1622 (5 studies[8])	⊕⊕⊕⊕ High[2,3,4,9]	Critical

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Post-treatment prophylaxis as assessed by recurrent parasitaemia between day 28 and day 42, 56 or 63	With primaquine		RR 0.27 (0.08 to 0.94)	376 (1 study[10])	⊕⊕⊖⊖ Low[11,12]	Important
	6 per 100	2 per 100 (0 to 6)				
	Without primaquine		RR 0.57 (0.40 to 0.82)	1066 (3 studies[13])	⊕⊕⊕⊖ Moderate[3,5,14]	Important
	40 per 100	23 per 100 (16 to 33)				
Serious adverse events	0 per 100	0 per 100 (0 to 2)	RR 1 (0.14 to 7.04)	1775 (5 studies[8])	⊕⊕⊕⊕ High[2–4,9]	Important

Assumed risk is the mean risk of the control group across studies. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio; ACT, artemisinin-based combination therapy

[1] These four studies are from Afghanistan, Cambodia, Thailand, India and Indonesia.

[2] No serious study limitations: Three studies adequately concealed allocation to be at low risk of selection bias. Removal of the remaining trials did not substantially change the result.

[3] No serious inconsistency: The findings of all the trials are consistent.

[4] No serious indirectness: The findings of these studies can reasonably be applied to other settings with similar transmission and resistance patterns.

[5] No serious imprecision: The studies show a clinically and statistically significant benefit of ACT.

[6] These two studies are from Afghanistan, Cambodia, Thailand, India and Indonesia.

[7] Downgraded by 1 for serious inconsistency: In one additional trial which could not be included in the meta-analysis, fever clearance was not significantly different between groups.

[8] These five studies are from Afghanistan, Cambodia, Thailand, India and Indonesia.

[9] No serious imprecision: No clinically important difference between ACTs and chloroquine. Although the 95% CI around the relative effect is very wide, recurrent parasitaemia before day 28 and serious adverse events were very rare; consequently, the 95% CI around the absolute effect is very narrow.

[10] This single multi-site study was conducted in Cambodia, Thailand, India and Indonesia.

[11] Downgraded by 1 for serious indirectness: This study delayed primaquine until day 28; therefore, the course was not completed until day 42, the last day of the trial. The effect might not be present if primaquine is given in the usual way (on completion of 3 days of ACT). The period of follow-up was not long enough to fully assess this effect; the inevitable relapse might simply be delayed, rather than a reduction in clinical episodes.

[12] Downgraded by 1 for serious imprecision: Although the result is statistically significant, the 95% CI is wide and includes the possibility of no appreciable benefit.

[13] One study continued follow-up until day 56, one to day 42 and one to day 63. (Primaquine was administered to the participants after day 63.)

[14] Downgraded by 1 for serious indirectness: Both studies were conducted in Afghanistan where primaquine is not recommended because of a high prevalence of G6PD deficiency. The period of follow-up was not long enough to fully assess this effect; the inevitable relapse might simply be delayed, rather than a reduction in clinical episodes.

Dihydroartemisinin-piperaquine versus alternative artemisinin-based combination treatment for uncomplicated *P. vivax* malaria

Patients or population: Adults and children with uncomplicated *P. vivax* malaria
Settings: Settings with high transmission of *P. vivax* (chloroquine resistance is also reported as high)
Intervention: Dihydroartemisinin + piperaquine
Comparison: Alternative ACTs
Source: Gogtay N, Kannan S, Thatte UM, Olliaro PL, Sinclair D. Artemisinin-based combination therapy for treating uncomplicated *Plasmodium vivax* malaria. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD008492. DOI: 10.1002/14651858.CD008492.pub3.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	Alternative ACT	Dihydroartemisinin + piperaquine				
Effective treatment of blood-stage parasites as assessed by recurrent parasitaemia before day 28	35 per 100	7 per 100 (3 to 17)	RR 0.20 (0.08 to 0.49)	334 (3 studies[1])	⊕⊕⊕⊝ Moderate[2–5]	
Post-treatment prophylaxis as assessed by recurrent parasitaemia between days 28 and 42	With primaquine					
	34 per 100	7 per 100 (3 to 16)	RR 0.21 (0.1 to 0.46)	179 (2 studies)	⊕⊕⊝⊝ Low[5–8]	
	Without primaquine					
	33 per 100	13 per 100 (5 to 37)	RR 0.40 (0.14 to 1.10)	66 (1 study)	⊕⊝⊝⊝ Very low[9–11]	

Assumed risk is the mean risk of the control group across studies. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio; DHA-P: dihydroartemisinin + piperaquine; ACT: Artemisinin-based combination therapy.

[1] These three studies are from Papua New Guinea and Indonesia.

[2] No serious risk of bias: Allocation was adequately concealed in these studies, resulting in a low risk of bias.

[3] Downgraded by 1 for serious inconsistency: There was some clinical heterogeneity between trials. Dihydroartemisinin + piperaquine did not perform as well in Papua New Guinea as it has elsewhere; however, it was still superior to artemether + lumefantrine and artesunate+sulfadoxine–pyrimethamine.

[4] No serious indirectness: Studies included adults and children and were conducted in areas where transmission is high and chloroquine resistance is well documented.

[5] No serious imprecision: Both limits of the 95% CI suggest an appreciable clinical benefit with dihydroartemisinin + piperaquine.

[6] Downgraded by 1 for serious risk of bias: Losses to follow-up were high (> 20% at this time).

[7] No serious inconsistency: Statistical heterogeneity was low.

[8] Downgraded by 1 for serious indirectness: One trial delayed administration of primaquine until day 28; therefore, the course will not have been completed until the last day of the trial. The second trial offered unsupervised primaquine to all participants on completion of ACT. This reflects normal practice, but it is not clear how many participants completed their course. The period of follow-up was not long enough to fully assess this effect; the inevitable relapse might simply be delayed, rather than a reduction in clinical episodes.

[9] Downgraded by 1 for serious risk of bias: Losses to follow-up were high (> 20% at this time).

[10] Downgraded by 1 for serious indirectness: Only one study assessed this outcome. Recurrent parasitaemia was higher with all three ACTs than seen elsewhere, and the results are therefore not easily extrapolated to other sites.

[11] Downgraded by 1 for serious imprecision: The 95% CI of the effect estimate is wide and includes an important clinical benefit and no difference between treatments.

A4.9 Do 14-day courses of primaquine reduce relapse rates to a greater extent than shorter courses in people treated for *P. vivax* malaria?

Balance of desirable and undesirable effects

Desirable	Undesirable
14-day courses of primaquine added to chloroquine reduce relapse rates to a greater extent than chloroquine alone (*high-quality evidence*).	Primaquine is known to cause haemolysis in people with G6PD deficiency.
14-day courses of primaquine added to chloroquine may result in fewer relapses than 7-day courses (*low-quality evidence*).	Of the 15 trials included in the Cochrane review, 12 explicitly excluded people with G6PD deficiency; in three trials, it was unclear whether participants were tested for G6PD deficiency or excluded. None of the trials reported serious or treatment-limiting adverse events.

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
High			

Rationale for the recommendation

Primaquine has not previously been recommended in high-transmission settings, where the risk of new infections was considered to outweigh any benefits of reduced spontaneous relapses.

In the light of changing epidemiology worldwide and more aggressive targets for malaria control and elimination, the group now recommends primaquine for radical cure of *P. vivax* in all settings.

Recommendation

To prevent future relapse, treat people with P. vivax or P. ovale malaria with a 14-day course of primaquine (except pregnant or breastfeeding women and people with G6PD deficiency).

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

The widely used primaquine regimen of 0.25 mg base/kg bw per day for 14 days is based on studies of long-latency Korean *P. vivax*.

In South-East Asia and Oceania, *P. vivax* relapses at 3-week intervals and is more resistant to primaquine. Consequently, higher doses of primaquine have been used (0.375 –0.5 mg base/kg bw per day), but there are few data from comparative trials.

Primaquine is contraindicated in pregnancy and lactation < 6 months post partum, unless the infant has been tested for G6PD deficiency. It could be given to women who have delivered and ceased breastfeeding.

A4.10 What is the optimal primaquine regimen for radical cure of *P. vivax* malaria in people with G6PD deficiency?

Balance of desirable and undesirable effects

Desirable	Undesirable
There are no comparative trials of the efficacy or safety of primaquine in people with G6PD deficiency.	Primaquine is known to cause haemolysis in people with G6PD deficiency.
	Of the 15 trials included in the Cochrane review, 12 explicitly excluded people with G6PD deficiency; in three trials, it was unclear whether participants were tested for G6PD deficiency or excluded. None of the trials reported serious or treatment-limiting adverse events.

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
			Very low

Rationale for the recommendation

In the absence of evidence to recommend alternatives, the Guideline Development Group considers a regimen of 0.75 mg/kg bw primaquine given once weekly for 8 weeks to be the safest for people with G6PD deficiency.

Recommendation

In people with G6PD deficiency, consider relapse prevention with primaquine at 0.75 mg base/kg bw once a week for 8 weeks.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	Conditional			

Remarks

Primaquine is contraindicated in pregnancy and lactation, unless the infant has been tested for G6PD deficiency. It could be given to women once they have delivered and ceased breastfeeding.

Primaquine (14 days) versus no intervention or placebo for preventing relapses in people with *P. vivax* malaria treated for blood-stage infection with chloroquine

Patients or population: People with *P. vivax* malaria[1]
Intervention: Primaquine (0.25 mg/kg bw) for 14 days plus chloroquine (25 mg/kg bw for 3 days)
Comparison: Chloroquine alone (25 mg/kg bw for 3 days)
Source: Galappaththy GNL, Tharyan P, Kirubakaran R. Primaquine for preventing relapse in people with *Plasmodium vivax* malaria treated with chloroquine. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD004389. DOI: 10.1002/14651858.CD004389.pub3.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	No primaquine	Primaquine 14 days				
P. vivax relapse defined as reappearance of *P. vivax* parasitaemia > 30 days after starting primaquine	8 per 100	5 per 100 (4 to 6)	RR 0.60 (0.48 to 0.75)	1740 (10 studies)	⊕⊕⊕⊕ High[2-5]	Important
Serious adverse events	None reported	None reported	Cannot be estimated	1740 (10 studies)	[6]	Important
Other adverse events	None reported	None reported	Cannot be estimated	1740 (10 studies)		Important

The assumed risk is the median risk in the control group; the corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio

[1] Studies conducted in Ethiopia, India (4), Pakistan (4) and Thailand.
[2] No serious study limitations: Three studies were at high risk of bias; however, they contributed only 15.5% weight to the pooled effect estimates, and their removal from the sensitivity analysis did not alter the results appreciably.
[3] No serious inconsistency: Results were consistent within subgroups based on duration of follow-up < 6 months or > 6 months and whether treatment was supervised or not; the I[2] value for the pooled effect estimate from the 10 trials was 30%.
[4] No serious indirectness: The trials included children and were done in transmission settings and countries representative of the vivax malaria burden. The outcome used was the best estimate currently available in the absence of widely available validated molecular techniques to differentiate relapse from new infections.
[5] No serious imprecision: The upper and lower limits of the 95% CI of the pooled relative risk indicate appreciable benefit with chloroquine + primaquine for 14 days. The total number of events was < 300, but the total sample size was larger than the optimal information size, given the magnitude of risk reduction.
[6] Of the 15 trials included in the Cochrane review, 12 explicitly excluded people with G6PD deficiency; in three trials, it was unclear whether participants were tested for G6PD deficiency or excluded. None of the trials reported serious or treatment-limiting adverse events.

14-day course of primaquine versus 7-day course to reduce spontaneous relapse of *P. vivax* in people treated for blood-stage infections with chloroquine

Patients or population: People with *P. vivax* malaria[1]
Intervention: Primaquine (0.25 mg/kg bw) for 14 days plus chloroquine (25 mg/kg bw for 3 days)
Comparison: Primaquine (0.25 mg/kg bw) for 7 days plus chloroquine alone (25 mg/kg bw for 3 days)
Source: Galappaththy GNL, Tharyan P, Kirubakaran R. Primaquine for preventing relapse in people with *Plasmodium vivax* malaria treated with chloroquine. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD004389. DOI: 10.1002/14651858.CD004389.pub3.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	7 days primaquine	14 days primaquine				
P. vivax relapse defined as reappearance of *P. vivax* parasitaemia > 30 days after starting primaquine	42 per 100	19 per 100 (11 to 34)	RR 0.45 (0.25 to 0.81)	126 (1 study)	⊕⊕⊝⊝ low[2,3]	Critical
Severe adverse events	None reported	None reported	Cannot be estimated	126 (1 study)	–	Important
Other adverse events	Not reported	Not reported	Cannot be estimated	126 (1 study)	–	Important

The assumed risk is the median risk in the control group; the corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio

[1] This single study was conducted in Colombia.

[2] Serious indirectness: The trial authors did not include children < 15 years. Another trial in the same area by the same group of investigators immediately afterwards included children. The results for 3 days of primaquine versus 14 days of primaquine did not differ in children from that in adults. Duration of follow-up was 2 months. While this ensures detection of early relapse, it does not cover relapses after 2 months. The relapse rates at 6 months showed that most relapses occur by 2 months. The effects of 7 days of primaquine were assessed in only one trial. We therefore downgraded the evidence by 1.

[3] Serious imprecision: Although the upper and lower limits of the 95% CI of the risk ratio in this trial showed statistically significant, clinically appreciable benefit with 14 days of primaquine over 7 days of primaquine, the total number of events was 38 and the sample size of the trial was 104. This is lower than the optimal information size. We downgraded the evidence by 1.

A4.11 In settings where *P. vivax* parasites are susceptible to chloroquine, is chloroquine prophylaxis during pregnancy safe and effective?

Balance of desirable and undesirable effects

Desirable	Undesirable
Chloroquine prophylaxis reduced recurrent P. vivax malaria in pregnant women (*moderate-quality evidence*).	

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
	Moderate		

Rationale for the recommendation

Recommendation

Primaquine is contraindicated in pregnant or breastfeeding women with *P. vivax* malaria. Therefore, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then treat with 14 days of primaquine to prevent future relapse.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	Conditional			

Remarks

Chloroquine prophylaxis to prevent *P. vivax* malaria during pregnancy

Settings: Malaria-endemic areas
Intervention: Chloroquine prophylaxis
Comparison: Placebo
Source: Radeva-Petrova D, Kayentao K, ter Kuile FO, Sinclair D, Garner P. Drugs for preventing malaria in pregnant women in endemic areas: any drug regimen versus placebo or no treatment. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD000169. DOI: 10.1002/14651858.CD000169.pub3.

Maternal outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	**Corresponding risk**			
	Placebo	**Chloroquine prophylaxis**			
Clinical malaria	–	–	–	–	–
P. vivax parasitemia	7 per 100	0 per 100 (0 to 2)	RR 0.02 (0.00 to 0.26)	951 (1 study)	⊕⊕⊕⊝ Moderate[1–3]
Severe anaemia in third trimester	–	–	–	–	–
Anaemia in third trimester	509 per 1000	484 per 1000 (458 to 514)	RR 0.95 (0.90 to 1.01)	951 (1 study)	⊕⊕⊕⊝ Moderate[1,2,4]
Adverse events					

The assumed risk is the median risk in the control group; the corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio

[1] No serious risk of bias: This study had a low risk of bias in all domains.
[2] No serious indirectness: This study was conducted in Thailand between 1998 and 2001. Chloroquine was administered as four tablets at enrolment, followed by two tablets once a week until delivery.
[3] Downgraded by 1 for serious imprecision: Although the intervention appeared to prevent all episodes of *P. vivax* malaria, there were few events, even in the control group.
[4] Downgraded by 1 for serious imprecision: The finding of a small clinical benefit did not reach statistical significance.

A4.12 Is parenteral artesunate superior to parenteral quinine in preventing death from severe malaria?

Balance of desirable and undesirable effects

Desirable	Undesirable
In both adults and children, parenteral artesunate prevented more deaths than parenteral quinine (*high-quality evidence*). For intravenous administration, artesunate is given as a bolus, whereas quinine requires slow infusion. For intramuscular administration, artesunate is given in a smaller volume than quinine.	Artesunate is associated with a small increase in neurological sequelae at the time of hospital discharge (*moderate-quality evidence*). The difference is no longer evident on day 28 after discharge (*moderate-quality evidence*).

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
High			

Rationale for the recommendation

The Guideline Development Group considered the small increase in neurological sequelae at discharge associated with artesunate to be due to prolonged recovery of severely ill patients who would have died if they had received quinine. This should not be interpreted as a sign of neurotoxicity.

Although the safety of artesunate in the first trimester of pregnancy has not been firmly established, the group considered that the proven benefits to the mother outweigh the potential harms to the developing fetus.

Recommendation

Treat adults and children with severe malaria with intravenous or intramuscular artesunate for at least 24 h (including infants, pregnant women in all trimesters and lactating women).

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

Parenteral artesunate is recommended as first-line treatment for adults, children, infants and pregnant women in all trimesters of pregnancy.

Artesunate versus quinine for treating children with severe malaria

Patients or population: Children with severe malaria
Settings: Malaria-endemic areas
Intervention: Artesunate
Comparison: Quinine
Source: Sinclair D, Donegan S, Isba R, Lalloo DG. Artesunate versus quinine for treating severe malaria. Cochrane Database of Systematic Reviews 2012, Issue 6. Art. No.: CD005967. DOI: 10.1002/14651858.CD005967.pub4.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	Quinine	Artesunate				
Death	109 per 1000	83 per 1000 (71 to 98)	RR 0.76 (0.65 to 0.9)	5765 (4 studies[1])	⊕⊕⊕⊕ High[2-5]	Critical
Neurological sequelae on day 28	11 per 1000	14 per 1000 (8 to 22)	RR 1.23 (0.74 to 2.03)	4857 (1 study)	⊕⊕⊕⊝ Moderate[6-9]	Important
Neurological sequelae at discharge	28 per 1000	38 per 1000 (28 to 51)	RR 1.36 (1.01 to 1.83)	5163 (3 studies)	⊕⊕⊕⊝ Moderate[2-4,11]	Important
Time to hospital discharge (days)	See comment	See comment	Not estimable	113 (3 studies)	⊕⊕⊕⊝ Moderate[2,4,12,13]	Important

| Hypoglycaemia episodes | 30 per 1000 | 19 per 1000 (13 to 26) | RR 0.62 (0.45 to 0.87) | 5765 (4 studies[1]) | ⊕⊕⊕⊕ High[2-4,14] | Important |

Assumed risk is the mean risk of the control group across studies. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio

[1] One large multicentre trial and two small trials compared artesunate with quinine in children aged < 15 years. In addition, one large multicentre study included a subgroup of 202 children in this age group.

[2] No serious study limitations: All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome.

[3] No serious inconsistency: There was no statistical heterogeneity between the trials ($I^2 = 0\%$).

[4] No serious indirectness: Most of the data are from the single multicentre trial with centres in the Democratic Republic of Congo, the Gambia, Ghana, Kenya, Mozambique, Nigeria, Rwanda, Uganda and the United Republic of Tanzania, where the established, standard doses of artesunate and quinine (with loading dose) were used. The median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group.

[5] No serious imprecision: Both limits of the 95% CI of the pooled effect imply an appreciable clinical benefit with artesunate. The number of people who must be treated to prevent one childhood death is 38.

[6] Serious study limitations: 41/170 (24%) patients with neurological sequelae at discharge were not available for assessment at day 28.

[7] No serious inconsistency: Not applicable, as only one trial.

[8] No serious indirectness: This trial was conducted in 11 centres in Africa, with standard dosing of artesunate and quinine. The nature of the neurological sequelae is not described.

[9] No serious imprecision: The 95% CI around the absolute effect is narrow. The worst-case scenario is a 1.2% increase in neurological sequelae at day 28.

[11] Serious imprecision: The effect estimate indicates clinically important harm; however, the 95% CI includes the possibility of no clinically important difference between the two interventions.

[12] No serious inconsistency: None of the trials found evidence of a large difference between the two treatment groups.

[13] Serious imprecision: We were unable to pool the data as they were reported only as medians and range or intraquartile range. There is no evidence of a clinically important benefit with artesunate on this outcome.

[14] No serious imprecision: The result is statistically significantly in favour of artesunate. The sample size is adequate to detect a 40% risk reduction with 80% power and 95% confidence.

Artesunate versus quinine for treating adults with severe malaria

Patient or population: Adults with severe malaria
Settings: Malaria-endemic areas
Intervention: Artesunate
Comparison: Quinine
Source: Sinclair D, Donegan S, Isba R, Lalloo DG. Artesunate versus quinine for treating severe malaria. Cochrane Database of Systematic Reviews 2012, Issue 6. Art. No.: CD005967. DOI: 10.1002/14651858.CD005967.pub4.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	Quinine	Artesunate				
Death	241 per 1000	147 per 1000 (121 to 181)	RR 0.61 (0.5 to 0.75)	1664 (5 studies[1])	⊕⊕⊕⊕ High[2-5]	Critical
Neurological sequelae at day 28	–	–	–	–	–	Important
Neurological sequelae at discharge	3 per 1000	9 per 1000 (2 to 44)	RR 2.97 (0.6 to 14.64)	1259 (1 study[6])	⊕⊕⊕⊖ Moderate[7-10]	Important
Time to hospital discharge (days)	See comment	See comment	Not estimable	113 (2 studies)	⊕⊕⊕⊖ Moderate[11-14]	Important

| Hypoglycaemia episodes | 47 per 1000 | 17 per 1000 (9 to 32) | RR 0.36 (0.19 to 0.68) | 1372 (2 studies) | ⊕⊕⊕⊕ High[11,13,15,16] | Important |

Assumed risk is the mean risk of the control group across studies. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio

[1] One large multicentre trial and four smaller trials assessed artesunate vs quinine in adults.

[2] No serious study limitations: Two of the smaller studies did not conceal allocation, and none of the studies was blinded; however, most data are from studies in which allocation was concealed, and the lack of blinding is unlikely to introduce bias for an objective outcome such as death.

[3] No serious inconsistency: The point estimates of all five trials favoured artesunate. No significant statistical heterogeneity was detected ($I^2 = 0$%).

[4] No serious indirectness: All five trials were conducted in Asia but in a variety of settings (Bangladesh, India, Indonesia, Myanmar, Thailand and Viet Nam), and included age groups > 15–16 years. Of the four small trials, two did not give the loading dose of quinine, but there was no statistical heterogeneity between these two trials and the large multicentre trial, in which the loading dose was given.

[5] No serious imprecision: Both limits of the 95% CI imply a clinically important benefit with artesunate.

[6] Only one trial measured the incidence of neurological sequelae in adults, reported as unpublished data from the authors.

[7] No serious study limitations: This trial was unblinded, but the nature of the sequelae makes observer or reporting bias unlikely.

[8] No serious inconsistency: Not applicable, as only one trial.

[9] No serious indirectness: This trial was conducted in sites in four countries in Asia with the standard doses of artesunate and quinine (with loading dose). Of the 10 sequelae that occurred in this trial (the additional two were in children), five were psychiatric sequelae, four were a persistent problem with balance, and two were hemiparesis.

[10] Serious imprecision: Neurological sequelae appear to be rare after severe malaria in adults; however, the 95% CI includes the possibility of clinically important harm with artesunate.

[11] No serious study limitations: The large multicentre study adequately concealed allocation and can be considered at low risk of bias. The smaller trial did not did not. Neither trial was blinded.

[12] No serious inconsistency: Neither trial found a statistically significant difference in time to hospital discharge.

[13] No serious indirectness: This evidence is from multiple sites in Asia (Bangladesh, India, Indonesia and Myanmar), and both trials used standard drug doses.

[14] Serious imprecision: We were unable to pool data because of the way in which they were presented, but there is no evidence of a benefit on this outcome with artesunate.

[15] No serious inconsistency: There was no statistical heterogeneity ($I^2 = 0$%).

[16] No serious imprecision: This result is statistically significantly in favour of artesunate. The sample size was adequate to detect a 75% risk reduction with 80% power and 95% confidence.

A4.13 Is parenteral artesunate superior to parenteral quinine in preventing death from severe malaria?

Balance of desirable and undesirable effects

Desirable	Undesirable
In children > 12 years and adults, parenteral artesunate probably prevents more deaths than intramuscular artemether (*moderate-quality evidence*).	
No randomized controlled trials have been conducted in children aged ≤ 12 years.	

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
	Moderate		

Rationale for the recommendation

Indirect comparisons of artesunate and quinine and of artemether and quinine were considered by the Guideline Development Group, with what is known about the pharmacokinetics of the two drugs. The group considered that the accumulated indirect evidence is sufficient to recommend artesunate over artemether for all age groups.

Recommendation

Treat children and adults with severe malaria with parenteral artesunate for at least 24 h.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

Intramuscular artemether should be considered only when parenteral artesunate is not available.

Artemether versus artesunate for treating adults with severe malaria

Patient or population: Adults with severe malaria
Settings: Malaria-endemic countries
Intervention: Intramuscular artemether
Comparison: Intravenous or intramuscular artesunate
Source: Esu E, Effa EE, Opie ON, Uwaoma A, Meremikwu MM. Artemether for severe malaria. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD010678.
DOI: 10.1002/14651858.CD010678.pub2.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	Artemether	Artesunate				
Death	148 per 1000	81 per 1000 (50 to 136)	RR 0.55 (0.34 to 0.92)	494 (2 studies)	⊕⊕⊕⊝ Moderate[1-4]	Critical
Coma resolution time	–	–	Not pooled	494 (2 studies)	⊕⊕⊕⊝ Moderate[1,3,5,6]	Important
Neurological sequelae at discharge	–	–	–	–		Important
Parasite clearance time	–	–	Not pooled	494 (2 studies)	⊕⊕⊕⊝ Moderate[1,3,6,7]	Important
Fever clearance time	–	–	Not pooled	494 (2 studies)	⊕⊕⊝⊝ Low[1,3,6,8]	Important

Assumed risk is the mean risk of the control group across studies. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio

[1] No serious risk of bias: The trials were generally well conducted and had a low risk of bias.
[2] No serious inconsistency: There is no statistical heterogeneity.
[3] No serious indirectness: The two studies were conducted in Thailand and Viet Nam; both compared intramuscular artemether with intravenous artesunate in adults.
[4] Downgraded by 1 for serious imprecision: These trials and the meta-analysis have inadequate power to detect a difference in mortality or to prove equivalence.
[5] No serious inconsistency: Both studies suggest an advantage with artesunate, although this was statistically significant only in the small trial.
[6] Downgraded by 1 for serious imprecision: These data could not be pooled.
[7] No serious inconsistency: Neither study found a difference between treatments.
[8] No serious inconsistency: One trial found no statistically significant difference, and the other, small trial found a benefit with artesunate.

A4.14 Is intramuscular artemether superior to parenteral quinine in preventing death from severe malaria?

Balance of desirable and undesirable effects

Desirable	Undesirable
In children, artemether is probably equivalent to quinine in preventing death (*moderate-quality evidence*). In children > 5 years and adults, artemether may be superior to quinine (*moderate-quality evidence*). Artemether is easier to administer, requiring a smaller fluid volume for intramuscular injection.	

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
	Moderate		

Rationale for the recommendation

The Guideline Development Group considered the possible superiority, the ease of administration and the better adverse-event profile of artemether as sufficient to recommend artemether over quinine as a second-line treatment option for severe malaria.

Recommendation

If parenteral artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	Conditional			

Remarks

Quinine is retained as an option for treating severe malaria when artesunate or artemether is not available or is contraindicated.

Artemether versus quinine for treating children with severe malaria

Patient or population: Children with severe malaria
Settings: Malaria-endemic countries
Intervention: Intramuscular artemether
Comparison: Intravenous or intramuscular quinine
Source: Esu E, Effa EE, Opie ON, Uwaoma A, Meremikwu MM. Artemether for severe malaria. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD010678. DOI: 10.1002/14651858.CD010678.pub2.

| Outcome | Illustrative comparative risks (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Importance of the outcome to decision-making |
| | Assumed risk | Corresponding risk | | | | |
	Quinine	Artemether				
Death	170 per 1000	164 per 1000 (129 to 204)	RR 0.96 (0.76 to 1.2)	1447 (12 trials)	⊕⊕⊕⊖ Moderate[1–4]	Critical
Coma resolution time	The mean time in control groups ranged from 17.4 to 42.4 h.	The mean time was 5.45 h shorter in the intervention groups (7.90 to 3.00 h shorter)	–	358 (6 trials)	⊕⊕⊖⊖ Low[3,5–7]	Important
Neurological sequelae at discharge	220 per 1000	185 per 1000 (145–235)	RR 0.84 (0.66 to 1.07)	968 (7 trials)	⊕⊕⊖⊖ Low[1–3,8]	Important
Parasite clearance time	The mean time in control groups ranged from 22.4 to 61.3 h.	The mean time was 9.03 h shorter in the intervention groups (11.43 to 6.63 h shorter)		420 (7 trials)	⊕⊕⊕⊖ Moderate[1,3,7,9]	Important

| Fever clearance time | The mean time in control groups ranged from 18 to 61 h. | The mean time was 3.73 h shorter in the intervention groups (6.55 to 0.92 h shorter) | – | 457 (8 trials) | ⊕⊕⊝⊝ Low[3,10–12] | Important |

Assumed risk is the mean risk of the control group across studies, as given in footnotes. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio

[1] No serious risk of bias: Various risks of bias, but exclusion of trials with high or unclear risk of selection bias did not change this result.

[2] No serious inconsistency: None of the individual trials found statistically significant effects, and there was no statistical heterogeneity between trials.

[3] No serious indirectness: Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine.

[4] Downgraded by 1 for serious imprecision: These trials and the meta-analysis had inadequate power to detect a difference or to prove equivalence.

[5] Downgraded by 2 for serious risk of bias: Four of the six trials had unclear risk of selection bias. When these four trials are excluded, the result becomes nonsignificant.

[6] No serious inconsistency: Statistically significant differences were seen in only two of the six trials; however, statistical heterogeneity between trials was low, and the result of the meta-analysis is significant.

[7] No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect.

[8] Downgraded by 2 for very serious imprecision: These trials and the meta-analysis have inadequate power to detect a difference or to prove equivalence. The 95% CI is very wide and includes clinically important differences and no effect.

[9] Downgraded by 1 for serious inconsistency: The mean difference in parasite clearance time ranged from a 2-h increase with artemether to a 15-h decrease.

[10] Downgraded by 1 for serious risk of bias: Four of the seven trials had unclear risks of selection bias. When these four trials are excluded, the result becomes nonsignificant.

[11] Downgraded by 1 for serious inconsistency: The mean difference in fever clearance time ranged from a 25-h increase with artemether to an 18-h decrease.

[12] No serious imprecision: The meta-analysis has adequate power to detect this effect. The result is statistically significant but may not be clinically important.

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Artemether versus quinine for treating adults with severe malaria

Patients or population: Adults with severe malaria
Settings: Malaria-endemic countries
Intervention: Intramuscular artemether
Comparison: Intravenous or intramuscular quinine
Source: Esu E, Effa EE, Opie ON, Uwaoma A, Meremikwu MM. Artemether for severe malaria. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD010678. DOI: 10.1002/14651858.CD010678.pub2.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	Quinine	Artemether				
Death	208 per 1000	123 per 1000 (87 to 173)	RR 0.59 (0.42 to 0.83)	716 (4 studies)	⊕⊕⊕⊝ Moderate[1-4]	Critical
Coma resolution time	–	–	Not pooled	683 (3 studies)	⊕⊕⊝⊝ Low[1,5,6]	Important
Neurological sequelae at discharge	4 per 1000	12 per 1000 (1 to 111)	RR 2.92 (0.31 to 27.86)	560 (1 study)	⊕⊕⊝⊝ Low[7,8]	Important
Parasite clearance time	–	–	Not pooled	716 (4 studies)	⊕⊕⊕⊝ Moderate[1,3,6,9]	Important
Fever clearance time	–	–	Not pooled	716 (4 studies)	⊕⊕⊝⊝ Low[1,3,6,10]	Important

Assumed risk is the mean risk of the control group across studies, as given in footnotes. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio

[1] No serious risk of bias: The trials were generally well conducted and with low risk of bias.

[2] No serious inconsistency: Statistically significant differences were seen in only one of the four studies; however, statistical heterogeneity among the trials was low, and the results of the meta-analysis are statistically significant.

[3] No serious indirectness: All four trials compared intramuscular artemether with intravenous quinine in adults: two studies in Thailand, one each in Papua New Guinea and Viet Nam.

[4] Downgraded by 1 for serious imprecision: These trials and the meta-analysis had inadequate power to detect a difference in mortality or to prove equivalence.

[5] Downgraded by 1 for serious inconsistency: One trial found a shorter median coma resolution time with quinine, and one trial found no difference; the third trial reported mean coma recovery time incompletely.

[6] Downgraded by 1 for imprecision: The data could not be pooled.

[7] No serious risk of bias: This single trial had a low risk of bias.

[8] Downgraded by 1 for serious imprecision: Neurological sequelae in adults were uncommon. This trial had inadequate power to detect or exclude clinically important differences.

[9] No serious inconsistency: The two largest studies both found shorter median clearance times with artemether.

[10] Downgraded by 1 for inconsistency: One trial found a shorter median fever clearance time with quinine, and two trials found a shorter time with artemether.

A4.15 For pre-referral treatment, do intramuscular antimalarial drugs reduce the number of deaths to a greater extent than rectal artesunate in adults and children with signs of severe malaria?

Balance of desirable and undesirable effects

Desirable	Undesirable
No studies of direct comparison of rectal artesunate with parenteral antimalarial drugs for pre-referral treatment. In hospital care, parenteral artesunate reduces the number of deaths to a greater extent than parenteral quinine (*high-quality evidence*) and probably reduces the number of deaths from that with intramuscular artemether (*moderate-quality evidence*).	

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
	Moderate		

Rationale for the recommendation

In the absence of direct comparative evaluations of parenteral antimalarial drugs for pre-referral treatment, the Guideline Development Group considered the known benefits of artesunate in hospitalized patients and downgraded the quality of evidence for use in pre-referral situations. When intramuscular injections can be given, the panel recommends intramuscular artesunate in preference to rectal artesunate.

Recommendation

In settings where complete treatment of severe malaria is not possible but injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate facility for further care.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

This recommendation applies to all people with suspected severe malaria, including infants, lactating women and pregnant women in all trimesters.

Where intramuscular artesunate is not available, use rectal artesunate (in children < 6 years), intramuscular artemether or intramuscular quinine.

A4.16 Does pre-referral rectal artesunate reduce the number of deaths in adults and children with signs of severe malaria to a greater extent than placebo?

Balance of desirable and undesirable effects

Desirable	Undesirable
Pre-referral rectal artesunate probably reduces mortality in children aged < 6 years (*moderate-quality evidence*).	Older children and adults may be at increased risk for mortality, although the reasons for this finding from a single study are unclear (*low-quality evidence*).

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
	Moderate		

Rationale for the recommendation

In people with signs of severe malaria living in remote areas, prompt antimalarial treatment and prompt referral prevent mortality.

The Guideline Development Group could find no plausible explanation for the finding of increased mortality among older children and adults in Asia, which may be due to chance. Further trials would help clarify this but are unlikely to be done. The group was therefore unable to recommend its use in older children and adults.

Recommendation

In settings where intramuscular injections are not available, give children aged < 6 years a single rectal dose of artesunate, and refer immediately to an appropriate facility for further care.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

The current evidence suggests that, in older adults and children, more deaths occur with rectal artesunate than with placebo. Rectal artesunate should not be used unless other treatment options are not available.

Rectal artesunate versus placebo for pre-referral treatment of severe malaria in children

Patients or population: Children aged < 5 years with severe malaria
Settings: Rural settings in Africa and Asia where parenteral treatment is not available
Intervention: Rectal artesunate plus referral for definitive treatment
Comparison: Placebo plus referral for definitive treatment
Source: Okebe J, Eisenhut M. Pre-referral rectal artesunate for severe malaria. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD009964. DOI: 10.1002/14651858.CD009964.pub2.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk — Placebo	Corresponding risk — Rectal artesunate				
All-cause mortality Follow-up: 7–30 days	In Asia					Critical
	31 per 1000	14 per 1000 (7 to 26)	RR 0.44 (0.23 to 0.82)	2010 (1 study)	⊕⊕⊝⊝ Low[1-4]	
	In Africa					
	44 per 1000	36 per 1000 (28 to 46)	RR 0.81 (0.63 to 1.04)	6040 (1 study)	⊕⊕⊝⊝ Low[1,2,3,5]	
	Overall					
	41 per 1000	30 per 1000 (24 to 38)	RR 0.74 (0.59 to 0.93)	8050 (1 study)	⊕⊕⊕⊝ Moderate[1,2,3,6]	

The assumed risk is the risk of the control group in the single study. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio

[1] No serious risk of bias: Allocation was concealed, and trial participants and staff were blinded to treatment allocation.
[2] Downgraded by 1 for serious inconsistency: In Asia, older children and adults were also randomized to artesunate or placebo, and mortality was significantly higher in those given rectal artesunate; the cause is unclear.
[3] No serious indirectness: This trial was conducted in community settings in Bangladesh, Ghana and the United Republic of Tanzania.
[4] Downgraded by 1 for serious imprecision: The number of events was low.
[5] Downgraded by 1 for serious imprecision: The 95% confidence interval is wide and includes no difference.
[6] No serious imprecision: The result is statistically significant, and the study had adequate power to detect this effect.

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Rectal artesunate versus placebo for pre-referral treatment of severe malaria in adults

Patients or population: Children aged > 6 years and adults with severe malaria
Settings: Rural settings where parenteral treatment is not available
Intervention: Rectal artesunate plus referral for definitive treatment
Comparison: Placebo plus referral for definitive treatment
Source: Okebe J, Eisenhut M. Pre-referral rectal artesunate for severe malaria. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD009964.
DOI: 10.1002/14651858.CD009964.pub2.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	Placebo	Rectal artesunate				
All-cause mortality Follow-up: 7–30 days	7 per 1000	15 per 1000 (8 to 29)	RR 2.21 (1.18 to 4.15)	4018 (1 study)	⊕⊕⊝⊝ Low[1-4]	Critical

The assumed risk is the risk of the control group in the single study. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio

[1] No serious risk of bias: Allocation was concealed, and trial participants and staff were blinded to treatment allocation.
[2] Downgraded by 1 for serious inconsistency: Rectal artesunate appears beneficial in children < 5 years and harmful in older children and adults. This finding is difficult to explain.
[3] No serious indirectness: This trial was conducted in a single setting in Bangladesh.
[4] Downgraded for serious imprecision: There were few deaths in adults in this trial: 31/2009 in treated and 14/2009 in controls.

A4.17 Is artesunate + pyronaridine a safe, effective alternative to other WHO-approved ACTs?

Balance of desirable and undesirable effects

Desirable	Undesirable
Artesunate + pyronaridine may be as effective as artemether + lumefantrine and artesunate + mefloquine in adults and older children (*moderate-quality evidence*). The current evidence for young children is insufficient to be confident that the drug is as effective as other recommended options.	Elevated results of liver function tests found four times more frequently with artesunate + pyronaridine than with the other antimalarial drugs (*moderate-quality evidence*).

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
	Moderate		

Rationale for the recommendation

The Guideline Development Group agreed that the data were promising, but they were unable to recommend this combination for general use at this time. Additional data are required on efficacy in children < 5 years and safety, especially with repeated dosing.

Recommendation

Artesunate + pyronaridine is not recommended for general use.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
			Conditional	

Remarks

In areas with multiple drug resistance where there are few alternatives, use of artesunate + pyronaridine may be considered.

Artesunate + pyronaridine versus artemether + lumefantrine for treating people with proven uncomplicated falciparum malaria

Patients or population: Adults and children with uncomplicated falciparum malaria
Settings: Malaria-endemic areas in Africa and Asia
Intervention: Artesunate + pyronaridine once daily for 3 days
Comparison: Artemether + lumefantrine twice daily for 3 days
Source: Bukirwa H, Unnikrishnan B, Kramer CV, Sinclair D, Nair S, Tharyan P. Artesunate plus pyronaridine for treating uncomplicated *Plasmodium falciparum* malaria. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD006404. DOI: 10.1002/14651858.CD006404.pub2.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	Artemether + lumefantrine	Artesunate + pyronaridine				
Treatment failure on day 28	PCR-unadjusted		RR 0.60 (0.40 to 0.90)	1720 (2 studies)	⊕⊕⊕⊝ Moderate[1-4]	Important
	7 per 100	4 per 100 (3 to 6)				
	PCR-adjusted		RR 1.69 (0.56 to 5.10)	1650 (2 studies)	⊕⊕⊕⊝ moderate[1,2,3,5]	Important
	1 per 100	1 per 100 (0 to 4)				
Treatment failure on day 42	PCR-unadjusted		RR 0.85 (0.53 to 1.36)	1691 (2 studies)	⊕⊕⊕⊝ moderate[1,2,3,5]	Important
	17 per 100	15 per 100 (9 to 23)				
	PCR-adjusted		RR 1.53 (0.73 to 3.19)	1472 (2 studies)	⊕⊕⊝⊝ Low[1,6,3,5]	Critical
	2 per 100	3 per 100 (1 to 6)				

Assumed risk is the mean risk of the control group across studies; the corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio; PCR, polymerase chain reaction

[1] No serious risk of bias: Both studies were well conducted with low risk of bias.

[2] No serious inconsistency: The trend was towards benefit with artesunate + pyronaridine in both trials but reached statistical significance in only one.

[3] Downgraded by 1 for serious indirectness: The two trials were conducted in children aged 3 months – 12 years in study sites in Africa and Asia. In both trials, only 152 children aged < 5 years received artesunate + pyronaridine, and only 115 children in total were randomized to artesunate + pyronaridine in Asia. Further, adequately powered studies in children in Africa and adults and children in Asia would be needed to generalize this result.

[4] No serious imprecision: The result is statistically significant and the meta-analysis is adequately powered; however, these multi-centred trials are underpowered to show equivalence at country level. Not downgraded.

[5] No serious imprecision: No substantial difference found between the two ACTs; however, these multi-centred trials are underpowered to show equivalence at country level. Not downgraded.

[6] Downgraded by 1 for serious inconsistency: Although statistical heterogeneity was low, PCR-adjusted treatment failure was > 5% in the one study with children aged < 5 years.

Artesunate + pyronaridine versus artesunate + mefloquine for treating people with proven uncomplicated *P. falciparum* malaria

Patients or population: People with uncomplicated falciparum malaria
Settings: Malaria-endemic areas in Africa and Asia
Intervention: Artesunate + pyronaridine once daily for 3 days
Comparison: Artesunate + mefloquine once daily for 3 days
Source: Bukirwa H, Unnikrishnan B, Kramer CV, Sinclair D, Nair S, Tharyan P. Artesunate plus pyronaridine for treating uncomplicated *Plasmodium falciparum* malaria. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD006404. DOI: 10.1002/14651858.CD006404.pub2.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	Artesunate + mefloquine	Artesunate + pyronaridine				
Treatment failure on day 28	PCR-unadjusted		RR 0.35 (0.17 to 0.73)	1200 (1 study)	⊕⊕⊕⊝ Moderate[1–4]	Important
	4 per 100	2 per 100 (1 to 2)				
	PCR-adjusted		RR 0.38 (0.14 to 1.02)	1187 (1 study)	⊕⊕⊕⊝ Moderate[1–3,5]	Important
	2 per 100	1 per 100 (0 to 2)				
Treatment failure on day 42	PCR-unadjusted		RR 0.86 (0.57 to 1.31)	1146 (1 study)	⊕⊕⊕⊝ Moderate[1,2,3,5]	Important
	8 per 100	7 per 100 (5 to 11)				
	PCR-adjusted		RR 1.64 (0.89 to 3.00)	1116 (1 study)	⊕⊕⊝⊝ Low[1–3,5,6]	Critical
	4 per 1000	6 per 100 (3 to 11)				

Assumed risk is the mean risk of the control group across studies. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio; PCR, polymerase chain reaction

[1] No serious risk of bias: This study was well conducted with low risk of bias.

[2] No serious inconsistency: Not applicable, as only one trial.

[3] Downgraded by 1 for serious indirectness: Of the 1271 children and adults aged > 5 years enrolled in this study, 81.3% (1033) were enrolled and treated in study sites in Asia (Cambodia, India, Thailand, Viet Nam) and only 18.7% (237) in Africa (Burkina Faso, Côte d'Ivoire, United Republic of Tanzania). Further studies in African children are necessary to generalize this result.

[4] No serious imprecision: The result is statistically significant, and the meta-analysis is adequately powered; however, this multi-centred trial is underpowered to show equivalence at country level. Not downgraded.

[5] No serious imprecision: No clinically important differences found between ACTs; however, this multi-centred trial is underpowered to show equivalence at country level. Not downgraded.

[6] PCR-adjusted treatment failure with artesunate + pyronaridine was just > 5%.

Hepatic toxicity of pyronaridine in comparison with other antimalarial drugs

Patients or population: People with uncomplicated falciparum malaria
Settings: High- and low-transmission settings for *P. falciparum* and *P. vivax* malaria
Intervention: Pyronaridine alone or with an artemisinin derivative
Comparison: Another antimalarial drug
Source: Bukirwa H, Unnikrishnan B, Kramer CV, Sinclair D, Nair S, Tharyan P. Artesunate plus pyronaridine for treating uncomplicated *Plasmodium falciparum* malaria. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD006404. DOI: 10.1002/14651858.CD006404.pub2.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	Comparator antimalarial	Pyronaridine alone or with artesunate				
Elevated alanine aminotransaminase activity Grade 3, 4 toxicity	2 per 1000	10 per 1000 (3 to 30)	RR 4.17 (1.38 to 12.61)	3523 (4 studies)	⊕⊕⊕⊝ Moderate[1-4]	Important
Elevated aspartate aminotransferase activity Grade 3, 4 toxicity	2 per 1000	8 per 1000 (2 to 29)	RR 4.08 (1.17 to 14.26)	3528 (4 studies)	⊕⊕⊕⊝ Moderate[1-4]	Important
Elevated alkaline phosphatase activity Grade 3, 4 toxicity	2 per 1000	1 per 1000 (0 to 5)	RR 0.62 (0.15 to 2.51)	2606 (3 studies)	⊕⊕⊕⊝ Moderate[1,2,3,5]	Important
Elevated bilirubin Grade 3, 4 toxicity	3 per 1000	6 per 1000 (2 to 19)	RR 1.92 (0.59 to 6.24)	3067 (3 studies)	⊕⊕⊝⊝ Low[1,2,3,6]	Important

Assumed risk is the mean risk of the control group across studies. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio

[1] No serious risk of bias: The studies were well conducted, although the data analysis was not clearly independent of the drug manufacturer in three of the studies.

[2] No serious inconsistency: Statistical heterogeneity was low.

[3] Downgraded by 1 for serious indirectness: Only 232 children aged < 5 years were included in these trials.

[4] No serious imprecision: The 95% CI is wide, and there are few events. Larger trials would be necessary for the group to have full confidence in this result, but it was not downgraded.

[5] No serious imprecision: The 95% CI is narrow and probably excludes clinically important differences.

[6] Downgraded by 1 for serious imprecision: The 95% CI is wide and includes no difference in clinically important effects.

A4.18 Is artemisinin + naphthoquine a safe, effective alternative to other WHO-approved ACTs?

Balance of desirable and undesirable effects

Desirable	Undesirable
The current evidence is insufficient to allow confidence in the estimates of benefit.	The current evidence is insufficient to allow confidence in the estimates of harm.

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
			Very low

Rationale for the recommendation

The Guideline Development Group noted that the trials conducted to date involved evaluation of this drug in 1- and 2-day regimens, which do not meet the current WHO recommendation for 3-day regimens of ACTs.

Recommendation

Artemisinin + naphthoquine is not recommended for general use.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
				Strong

Remarks

Artemisinin + naphthoquine versus artemether + lumefantrine for treating people with proven uncomplicated *P. falciparum* malaria

Patients or population: Adults and children with uncomplicated *P. falciparum* malaria
Settings: Malaria-endemic settings
Intervention: Artemisinin + naphthoquine; 1-day course
Comparison: Artemether + lumefantrine twice daily for 3 days
Source: Isba R, Zani B, Gathu M, Sinclair D. Artemisinin–naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria. *Cochrane Database of Systematic Reviews* 2015, Issue 2. Art. No.: CD011547. DOI: 10.1002/14651858.CD011547

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	Artemether + lumefantrine	Artemisinin + naphthoquine				
Treatment failure on day 28	PCR-unadjusted		RR 1.54 (0.27 to 8.96)	297 (2 studies)	⊕◯◯◯ Very low[1–4]	Important
	1 per 100	2 per 100 (0 to 9)				
	PCR-adjusted		RR 3.25 (0.13 to 78.69)	295 (2 studies)	⊕◯◯◯ Very low[1–4]	Critical
	0 per 100	0 per 100 (0 to 0)				
Fever clearance: fever on day 2	2 per 100	10 per 100 (1 to 76)	RR 5.90 (0.73 to 47.60)	123 (1 study)	⊕◯◯◯ Very low[5–7]	Important
Parasite clearance: parasitaemia on day 2	2 per 100	0 per 100 (0 to 6)	RR 0.15 (0.01 to 2.92)	297 (2 studies)	⊕◯◯◯ Very low[1–3,8]	Important
Gametocytaemia on day 7	2 per 100	3 per 100 (0 to 34)	RR 1.97 (0.18 to 21.14)	123 (1 study)	⊕◯◯◯ Very low[5–7]	Important

Assumed risk is the mean risk of the control group across studies. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio; PCR, polymerase chain reaction

[1] No serious risk of bias: One study adequately concealed allocation and thus had a low risk of selection bias. In the other study, the process of randomization and allocation concealment was unclear.
[2] No serious inconsistency: Statistical heterogeneity was low.
[3] Downgraded by 1 for serious indirectness: Only two studies, in Benin and Cote d'Ivoire, evaluated this comparison. Further studies in additional settings are required before this result can be generalized.
[4] Downgraded by 2 for very serious imprecision: Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. Both trials are significantly underpowered.
[5] No serious risk of bias: This study adequately concealed allocation and thus had a low risk of selection bias.
[6] Downgraded by 1 for serious indirectness: Study in Cote d'Ivoire. Further studies in additional settings are required before this result can be generalized.
[7] Downgraded by 2 for very serious imprecision: This trial was small and the result has a very wide 95% confidence interval, including appreciable benefit and harm.
[8] Downgraded by 2 for very serious imprecision: The result has a very wide 95% confidence interval, including appreciable benefit and harm.

Artemisinin + naphthoquine versus dihydroartemisinin + piperaquine for treating people with proven uncomplicated *P. falciparum* malaria

Patient or population: Adults and children with uncomplicated *P. falciparum* malaria
Settings: Malaria-endemic settings
Intervention: Artemisinin + naphthoquine; 1-day course
Comparison: Dihydroartemisinin + piperaquine; 3-day course
Source: Isba R, Zani B, Gathu M, Sinclair D. Artemisinin-naphthoquine for treating uncomplicated *Plasmodium falciparum* malaria. *Cochrane Database of Systematic Reviews* 2015, Issue 2. Art. No.: CD011547. DOI: 10.1002/14651858.CD011547

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	**Corresponding risk**				
	Dihydroartemisinin + piperaquine	**Artemisinin + naphthoquine**				
Treatment failure on day 28	PCR-unadjusted		Cannot be estimated	143 (1 study)	⊕◯◯◯ Very low[1,2,3]	Important
	0 per 100	0 per 100				
	PCR-adjusted		Cannot be estimated	143 (1 study)	⊕◯◯◯ Very low[1,2,3]	Important
	0 per 100	0 per 100				
Treatment failure on day 42	PCR-unadjusted		RR 0.91 (0.13 to 6.26)	143 (1 study)	⊕◯◯◯ Very low[1,2,3]	Important
	3 per 100	3 per 100 (0 to 19)				
	PCR-adjusted		RR 0.19 (0.01 to 3.82)	141 (1 study)	⊕◯◯◯ Very low[1,2,3]	Critical
	3 per 100	0 per 100 (0 to 11)				
Fever clearance: fever on day 2	0 per 100	0 per 100	Cannot be estimated	144 (1 study)	⊕◯◯◯ Very low[1,2,4]	Important
Parasite clearance: parasitaemia on day 2	0 per 100	4 per 100 (0 to ?)	RR 6.29 (0.33 to 119.69)	144 (1 study)	⊕◯◯◯ Very low[1,2,5]	Important
Gametocytaemia: on day 7	8 per 100	11 per 100 (4 to 30)	RR 1.38 (0.52 to 3.70)	144 (1 study)	⊕◯◯◯ Very low[1,2,5]	Important

Assumed risk is the mean risk of the control group across studies. The corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio; PCR, polymerase chain reaction

[1] No serious risk of bias: Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias.
[2] Downgraded by 1 for serious indirectness: This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized.
[3] Downgraded by 2 for very serious imprecision: Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. This trial is significantly underpowered.
[4] Downgraded by 2 for very serious imprecision: This trial is small. No participants in either group had fever on day 2.
[5] Downgraded by 2 for very serious imprecision: The result has a very wide 95% confidence interval, including appreciable benefit and harm.

A4.19 Are three or more doses of sulfadoxine–pyrimethamine during pregnancy more effective than two doses?

Balance of desirable and undesirable effects

Desirable	Undesirable
Three or more doses of sulfadoxine–pyrimethamine during pregnancy increase mean birth weight and reduce the number of low-birth-weight infants to a greater extent than two doses (*high-quality evidence*).	No adverse effects have been reported.

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
High			

Rationale for the recommendation

The Guideline Development Group noted that effects were seen in women in their first and second pregnancy. Less information was available on women in their third or later pregnancy, but this information was consistent with benefit.

Recommendation

In malaria-endemic areas, give sulfadoxine–pyrimethamine to all pregnant women in their first or second pregnancy monthly from the start of the second trimester.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

Three or more doses of sulfadoxine–pyrimethamine versus two doses to all pregnant women

Settings: Malaria-endemic areas
Intervention: Three or more doses of sulfadoxine–pyrimethamine
Comparison: Two doses of sulfadoxine–pyrimethamine
Source: Kayentao K, Garner P, Maria van Eijk A, Naidoo I, Roper C, Mulokozi A, et al. Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine + pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. JAMA 2013;309:594–604.

Maternal outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	**Corresponding risk**			
	Sulfadoxine–pyrimethamine (2 doses)	**Sulfadoxine–pyrimethamine (≥ 3 doses)**			
Severe anaemia in 3rd trimester	34 per 1000	25 per 1000 (16 to 38)	RR 0.73 (0.48 to 1.11)	2196 (6 studies)	⊕⊕⊝⊝ Low[1-4]
Anaemia in 3rd trimester	509 per 1000	484 per 1000 (458 to 514)	RR 0.95 (0.90 to 1.01)	2088 (7 studies)	⊕⊕⊕⊝ Moderate[1,5-7]
Parasitaemia at delivery	92 per 1000	63 per 1000 (48 to 82)	RR 0.68 (0.52 to 0.89)	2096 (7 studies)	⊕⊕⊕⊝ Moderate[1,8-10]

The assumed risk is the median risk in the control group; the corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio

[1] No serious inconsistency: Statistical heterogeneity is low.
[2] Downgraded by 1 for serious risk of bias: The strongest effect was seen in a trial at high risk of selection bias; removal of this trial removes the statistical significance. None of the three trials was blinded, and all had a high attrition rate.
[3] No serious indirectness: These three studies were conducted in Kenya (1996), Burkina Faso (2005) and Malawi (2005) in women in their first or second pregnancy.
[4] Downgraded by 1 for serious imprecision: These trials had inadequate power. To detect a 25% relative reduction in severe anaemia confidently would require a sample size of over 12 000.
[5] Downgraded by 1 for serious risk of bias: Two trials were at high risk of selection bias, three were unblinded and four had a high attrition rate.
[6] No serious indirectness: The four studies were conducted in Kenya (1996), Zambia (2004), Burkina Faso (2005) and Malawi (2005) in women in their first or second pregnancy.
[7] No serious imprecision: This meta-analysis has adequate power to detect an effect.
[8] Downgraded by 1 for serious risk of bias: Two of the three studies were at high risk of selection bias. All three had a high attrition rate.
[9] No serious inconsistency: A subgroup analysis suggests that the effect may be larger in women infected with HIV.
[10] No serious indirectness: These three trials were conducted in Kenya (1996), Zambia (2004) and Malawi (2005) in women in their first or second pregnancy. In two trials, the analysis was stratified by HIV status.

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Three or more doses of sulfadoxine–pyrimethamine versus two doses: all pregnant women

Settings: Malaria-endemic areas
Intervention: Three or more doses of sulfadoxine–pyrimethamine
Comparison: Two doses of sulfadoxine–pyrimethamine
Source: Kayentao K, Garner P, Maria van Eijk A, Naidoo I, Roper C, Mulokozi A, et al. Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine + pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. JAMA 2013;309:594–604.

Fetal outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Sulfadoxine–pyrimethamine (2 doses)	Sulfadoxine–pyrimethamine (≥ 3 doses)			
Miscarriage	0 per 1000	0 per 1000 (0 to 0)	RR 1.43 (0.88 to 2.33)	2471 (6 studies)	⊕⊖⊖⊖ Very low[1–4]
Stillbirth	30 per 1000	34 per 1000 (24 to 46)	RR 1.14 (0.85 to 1.55)	2676 (7 studies)	⊕⊖⊖⊖ Very low[1,2,3,5]
Neonatal mortality	21 per 1000	18 per 1000 (12 to 28)	RR 0.88 (0.57 to 1.35)	2405 (6 studies)	⊕⊖⊖⊖ Very low[1,2,3,5]
Preterm birth	122 per 1000	116 per 1000 (55 to 111)	RR 1.28 (0.90 to 1.82)	2579 (7 studies)	⊕⊕⊖⊖ Low[2,6–8]
Low birth weight	167 per 1000	134 per 1000 (115 to 157)	RR 0.80 (0.69 to 0.94)	2190 (7 studies)	⊕⊕⊕⊕ High[2,9–11]

Mean birth weight	Mean birth weight in the control groups ranged from 2722 g to 3239 g.	Mean birth weight in the intervention groups was 56 g higher (29 to 83 g higher).		2190 (7 studies)	⊕⊕⊕⊕ High[2,9–11]
Placental parasitaemia	63 per 1000	32 per 1000 (24 to 43)	RR 0.51 (0.38 to 0.68)	1436 (6 studies)	⊕⊕⊕⊕ High[2,9,11,12]
Cord blood haemoglobin	–	–	–	–	–

The assumed risk is the median risk in the control groups; the corresponding risk (and its 95% CI) is calculated by applying the relative effect of the intervention (and its 95% CI) to the assumed risk. CI, confidence interval; RR, risk ratio

[1] Downgraded by 1 for serious risk of bias: Two studies were at high risk of selection bias, and all three were unblinded and at high risk of attrition bias.

[2] No serious inconsistency: Statistical heterogeneity was low.

[3] No serious indirectness: The three studies were conducted in Kenya (1996), Malawi (2005) and Burkina Faso (2008) in women in their first or second pregnancy.

[4] Downgraded by 2 for serious imprecision: The trials had inadequate power to detect an effect. Confident detection of a 25% reduction in mortality would require a sample size of over 25 000.

[5] Downgraded by 2 for serious imprecision: The trials had inadequate power to detect an effect. Confident detection of a 25% reduction in mortality would require a sample size of over 14 000.

[6] Downgraded by 1 for serious risk of bias: Two of the four studies were at high risk of selection bias and three at high risk of attrition bias.

[7] No serious indirectness: These four studies were conducted in Kenya (1996), Zambia (2004), Malawi (2005) and Burkina Faso (2008) in women in their first or second pregnancy.

[8] Downgraded by 1 for serious imprecision: The 95% CI does not exclude what may be clinically important effects. Confident detection of a 25% reduction in pre-term birth would require a sample size of > 2500.

[9] No serious risk of bias. Two studies are at low risk of bias. Removal of the trials with high risk of bias did not influence the effect estimate.

[10] No serious indirectness: These studies were conducted in Kenya (1996), Zambia (2004), Malawi (2005 and 2006), Mali (2008) and Burkina Faso (2008) in women in their first or second pregnancy.

[11] No serious imprecision: The sample size is sufficiently large to detect a difference between the two drug regimens, and the result is statistically significant.

[12] No serious indirectness: These studies were conducted in Kenya (1996), Zambia (2004), Malawi (2005) and Mali (2008) in women in their first or second pregnancy.

A4.20 In areas of moderate-to-high malaria transmission where SP is still effective, does intermittent treatment with SP alongside routine vaccination reduce malaria morbidity and mortality compared to no intervention?

Balance of desirable and undesirable effects

Desirable	Undesirable

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low

Rationale for the recommendation

The recommendation was formulated at the fourth consultative meeting of the Technical Expert Group (TEG) of Preventive Chemotherapy, GMP, WHO, April 2009 which reviewed all evidence available at the time. The evidence was not re-evaluated during this guideline process and therefore the quality of evidence has not been formally assessed.

Recommendation

In areas of moderate-to-high malaria transmission where SP is still effective, provide intermittent preventive treatment with SP to infants (< 12 months of age) (SP-IPTi) at the time of the second and third rounds of vaccination against diphtheria, tetanus and pertussis (DTP) and vaccination against measles.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

This recommendation made in 2009 is included in the Malaria Treatment Guidelines to bring together all major recommendations about the use of anti-malarial drugs in malaria endemic areas.

The recommendation is based on a pooled analysis of 6 randomised pacebo controlled studies on SP-IPTi conducted in areas of moderate to high transmission of malaria:

- SP-IPTi delivered through EPI provides an overall protection in the first year of life against clinical malaria [30.3% (95% CI: 19.8%–39.4%)], anemia [21.3% (95% CI: 8.3%–32.5%)], hospital admissions associated with malaria parasitemia [38.1% (95% CI 12.5%–56.2%)], and all-cause hospital admissions [22.9% (95% CI: 10.0%–34.0%)]. SP-IPTi offers a personal protection against clinical malaria for a period of approximately 35 days following the administration of each dose.

Aponte JJ, Schellenberg D, Egan A, et al. Efficacy and safety of intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in African infants: a pooled analysis of six randomised, placebo-controlled trials. Lancet. 2009 ;374:1533–42.

A4.21 Does seasonal malaria chemoprevention (SMC) reduce malaria morbidity and mortality to a greater extent than no intervention?

Balance of desirable and undesirable effects

Desirable	Undesirable
SMC prevents up to three quarters of malaria episodes (*high-quality evidence*).	The current regimen of amodiaquine + sulfadoxine–pyrimethamine causes vomiting in some children (*high-quality evidence*).
SMC prevents up to three quarters of severe malaria episodes (*high-quality evidence*).	
SMC may cause a small reduction in mortality (*moderate-quality evidence*).	

Overall quality of evidence for all critical outcomes

High	Moderate	Low	Very low
High			

Rationale for the recommendation

The Guideline Development Group endorsed the previous recommendation for SMC made by the WHO Technical Expert Group on Preventive Chemotherapy in May 2011, subsequently reviewed and endorsed by the WHO Malaria Policy Committee, in January 2012.

Recommendation

In areas with highly seasonal malaria transmission, provide SMC with monthly amodiaquine + sulfadoxine–pyrimethamine for all children < 6 years during each transmission season.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
Strong				

Remarks

The target areas for implementation are those where:

- malaria transmission and most clinical malaria cases occur during a short period of about 4 months;
- the clinical attack rate of malaria is > 0.1 episode per child during the transmission season; and
- amodiaquine + sulfadoxine–pyrimethamine remains efficacious (> 90% efficacy). SMC should not be given to children with severe current illness, who are already taking co-trimoxazole or with a known allergy to amodiaquine or sulfadoxine–pyrimethamine.

Seasonal malaria chemoprevention (SMC) versus placebo to reduce malaria morbidity and all-cause mortality

Patient or population: Children aged < 5 years
Settings: Areas with seasonal transmission
Intervention: Regular full treatment doses of antimalarial medicines (amodiaquine + sulfadoxine–pyrimethamine, artesunate + sulfadoxine–pyrimethamine or sulfadoxine–pyrimethamine alone) every 1–2 months during the malaria transmission season
Comparison: Placebo
Source: Meremikwu MM, Donegan S, Sinclair D, Esu E, Oringanje C. Intermittent preventive treatment for malaria in children living in areas with seasonal transmission. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD003756. DOI: 10.1002/14651858.CD003756.pub4.

Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance of outcome to decision-making
	Assumed risk	Corresponding risk				
	Placebo	SMC				
Clinical malaria	2.5 episodes per child per year[3]	0.7 episodes per child per year (0.4 to 1.0)	Rate ratio 0.26 (0.17 to 0.38)	9321 (6 studies)	⊕⊕⊕⊕ High[1,2]	Critical
Severe malaria	35 episodes per 1000 children per year[4]	9 episodes per 1000 children per year (4 to 27)	Rate ratio 0.27 (0.1 to 0.76)	5964 (2 studies)	⊕⊕⊕⊕ High[2]	Critical
Death from any cause	3 per 1000 per year	2 per 1000 per year (1 to 5)	Risk ratio 0.66 (0.31 to 1.39)	9533 (6 studies)	⊕⊕⊕⊖ Moderate[5]	Critical
Moderately severe anaemia	67 per 1000 per year	47 per 1000 per year (35 to 65)	Risk ratio 0.71 (0.52 to 0.98)	8805 (5 studies)	⊕⊕⊕⊖ Moderate[6]	Important

				9533 (6 studies)	⊕⊕⊕⊖ Moderate[7]	Important
Serious drug-related adverse events	–	–	–	9533 (6 studies)	⊕⊕⊕⊖ Moderate[8]	Important
Non-serious adverse events	–	–	–			

The assumed risk is based on the sum of events and participants in the control groups in the trials, unless stated otherwise in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, confidence interval; SMC, seasonal malaria chemoprevention

[1] The trials were conducted in children aged < 5 years in Burkina Faso, the Gambia, Ghana, Mali (two) and Senegal. In three studies, amodiaquine + sulfadoxine–pyrimethamine administered monthly, in two studies sulfadoxine–pyrimethamine was given every 2 months, and in one study sulfadoxine–pyrimethamine + artesunate was given monthly. Two studies, in which insecticide-treated nets were also distributed, showed that the benefits remained even when use of bednets was > 90%.

[2] There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.

[3] The incidence of malaria in the control groups was 2.88 episodes per child per year in Burkina Faso, 2.4 in Mali and 2.25 in Senegal.

[4] The incidence of severe malaria in the control groups was 32 per 1000 children per year in Burkina Faso and 37 per 1000 children per year in Mali.

[5] Downgraded by 1 for imprecision: There were very few deaths in these trials, and none of the trials had adequate power to detect an effect on mortality. Larger trials are necessary for this effect to be established confidently. A reduction in the number of deaths would be consistent with the high-quality evidence of a reduction in severe malaria.

[6] There was substantial heterogeneity among these five trials, and the trials in the Gambia and Ghana did not show an effect. Downgraded by 1 for inconsistency. There was no reason to downgrade for study limitations, directness or precision.

[7] No drug-related serious adverse events were reported. Downgraded by 1 for precision, as trials of this size have inadequate power to fully detect or exclude rare, serious adverse events.

[8] Downgraded by 1 for study limitations. All seven trials reported observed adverse events; however, the adequacy of the methods used to collect these data is unclear in some trials. The only adverse event found to be statistically more common with SMC was vomiting after amodiaquine + sulfadoxine–pyrimethamine.

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# Annex 5 | Pharmacology of antimalarial drugs

A5.1 | AMODIAQUINE

Therapeutic indications

Amodiaquine in combination with artesunate is indicated for the treatment of uncomplicated *P. falciparum* or *P. vivax* malaria and is considered to be effective against *P. ovale, P. knowlesi* and *P. malariae* (*1*). It may also be used as follow-on treatment in severe malaria when the patient is well enough to take oral medication.

Amodiaquine plus sulfadoxine–pyrimethamine (SP) is given at full treatment doses at monthly intervals as seasonal malaria chemoprevention to young children (aged 3–59 months) in areas of seasonal, high-intensity malaria transmission. This combination is currently recommended in the Sahel region of sub-Saharan Africa in areas where malaria transmission is intense and where the majority (>60%) of clinical malaria cases occur during a short period (≤ 4 months) (*2*).

Artesunate–amodiaquine should not be used for prophylaxis, as its accumulation increases the risks for hepatotoxicity and agranulocytosis (*1*).

Structure and mechanism of action
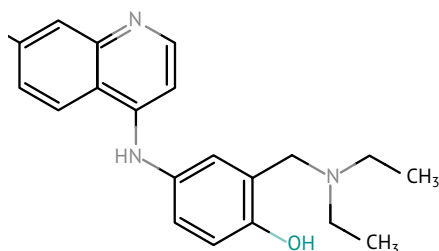
Molecular mass: 355.9

Amodiaquine is a Mannich base 4-aminoquinoline that is similar in structure and mechanism of action to chloroquine. Amodiaquine is converted to its active metabolite desethylamodiaquine and is thought to act by accumulating inside the parasite food vacuole and interfering with haem detoxification. Amodiaquine is effective against some parasite strains that are resistant to chloroquine, although some cross-resistance exists (*1, 3*).

Pharmacokinetics

The pharmacokinetic parameters of amodiaquine is presented in Table A5.1.

Table A5.1. Pharmacokinetic parameters reported for amodiaquine and its active metabolite desethylamodiaquine in studies of currently recommended dosages for treatment of uncomplicated malaria or seasonal malaria chemoprevention (range of mean or median values reported).

Parameter	Amodiaquine	Desethylamodiaquine
C_{max} (ng/mL)	5.2–39.3	161–751
T_{max} (h)	0.5–2.0	2.71-47.9
Elimination $T_{1/2}$ (h)	3.3–12.4	90–240
Vd/f (L/kg)	311–1010	62.4–252
Cl/f (L/h per kg)	14–57.8	0.61–0.74
$AUC_{0-infinity}$ (ng.h/mL)	39.3–602	14700–40339

Amodiaquine is readily absorbed from the gastrointestinal tract and rapidly converted by the cytochrome P450 (CYP) enzyme CYP2C8 into desethylamodiaquine, which contributes nearly all the antimalarial effect. While amodiaquine is eliminated rapidly, desethylamodiaquine is eliminated more slowly, with a terminal half-life of 4–10 days (*4–13*).

Safety

Adverse events

Artesunate–amodiaquine is generally well tolerated but is associated with a higher incidence of gastrointestinal disturbances, including nausea and abdominal pain, than other ACTs (*14, 15*). Other commonly reported adverse events include cough, anorexia, insomnia, fatigue and weakness (*4, 6, 16–18*). Serious adverse events associated with amodiaquine are neutropenia and hepatotoxicity (*19–22*). While these effects were most often associated with prolonged use of amodiaquine (as prophylaxis), they have also been observed with short-course artesunate–amodiaquine treatment. Less common events that have been reported include arrhythmia, bradycardia, vomiting, extrapyramidal effects and pruritus (*14, 15, 23, 24*). Eye disorders, varying in type and severity have been reported, including transient accommodation disorders and corneal opacification, which regressed once treatment was stopped, and, very rarely, irreversible retinopathy (*3*).

Amodiaquine + SP is generally well tolerated in children, and no serious adverse events have been reported (*9, 25–28*); however, a tendency to higher frequencies of vomiting, loss of appetite, fever and mild-to-moderate skin reactions have been reported after administration of amodiaquine + SP as compared with placebo.

Contraindications

Amodiaquine should not be administered to patients with known hypersensitivity and should be avoided in patients with a history of hepatotoxicity, hepatic impairment, neutropenia or retinopathy.

Cautions

Although seasonal malaria chemoprevention with amodiaquine + SP is generally effective in preventing malaria, breakthrough infections may occur. It is important that parents or guardians continue to use other malaria prevention measures (such as insecticide-treated bednets) and monitor their children; they should seek medical attention immediately in the event of febrile illness. Should malaria infection occur while the child is on amodiaquine + SP, the treatment chosen should not include either amodiaquine or SP.

Cardiovascular effects have been reported during high-dose treatment with other 4-aminoquinoline derivatives. There is no evidence, however, that an overdose of amodiaquine causes any of the life-threatening cardiovascular complications seen with overdose of chloroquine. Caution should nevertheless be exercised in treating patients who have recently taken another antimalarial drug with cardiovascular side-effects, such as quinine or mefloquine.

Pragmatic dosing

Fixed dose artesunate + amodiaquine result in better treatment efficacy than loose tablets (29). Antimalarial dosing has often been based on age because access to formal health services or functioning weighing scales is often limited in malaria-endemic countries. While age-based dosing is more practical, it carries a risk for potential under- or over-dosing of more patients. Large datasets of weight-for-age have been used to determine suitable age-based dosing for African children (*30*), which resulted in higher proportions of patients receiving therapeutic doses of artesunate and amodiaquine. To simplify dosage recommendations in other regions, anthropometric data should be collated for each malaria-endemic region and the data re-modelled accordingly.

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References

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A5.2 | ARTEMETHER

Therapeutic indications

- Intramuscular artemether is an alternative for treatment of severe malaria when parenteral artesunate is not available. Although artemether was superior to quinine in the treatment of severe malaria in adults (but not in children), its absorption is unpredictable, which may affect treatment responses in the most severely ill patients.
- Artemether is an alternative for pre-referral treatment of severe malaria in adults when parenteral artesunate is not available and in children when neither parenteral nor rectal artesunate is available.
- Artemether is also used in a fixed-dose oral combination with lumefantrine (see A5.3) for the treatment of uncomplicated malaria caused by *P. falciparum, P. vivax, P. ovale, P. malariae* or *P. knowlesi* parasites.

Structure and mechanism of action
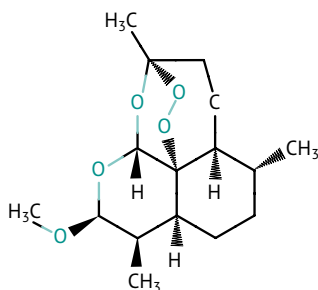
Molecular mass 298.4

Artemether is the methyl ether derivative of dihydroartemisinin. It is two- to threefold less active than dihydroartemisinin, its active metabolite. The ethers are metabolized to dihydroartemisinin to a lesser extent than artesunate. Like the other artemisinin derivatives, artemether has broad stage specificity against blood-stage parasites, from the ring stages through to early schizonts. It also reduces gametocyte carriage, limiting malaria transmission from the treated infection (*1, 2*).

Pharmacokinetics

Table A5.2 shows the pharmacokinetic parameters of artemether when given by intramuscular injection for the treatment of severe malaria. The pharmacokinetics of oral artemether when given in the fixed-dose combination with lumefantrine for the treatment of uncomplicated malaria is shown in section A5.3.

Table A5.2. **pharmacokinetic parameters estimated for artemether and its active metabolite dihydroartemisinin in studies of currently recommended doses of intramuscular artemether for treatment of severe malaria (range of mean or median values reported)**

Parameter	Artemether	Dihydroartemesinin
C_{max} (ng/mL)	171–540	15–405
T_{max} (h)	1.5–10.0	1.3–7.4
Elimination $T_{1/2}$ (h)	5.7–7.0	5.1
AUC (µg.h/mL)	0.81–5.8	0.19–5.04
Vd (L/kg)	3.5–8.6	2.05
CL (L/h per kg)	0.44–1.38	7.16–8.99
K_a (/h)	0.031–0.044	–

Note that the estimates of Vd and Cl assume complete bioavailability.

Artemether is a water-insoluble, lipid-soluble compound and is therefore given either as an oil-based intramuscular injection or orally. It is absorbed slowly and erratically after intramuscular administration in severe malaria (Figure A5.2) (*3, 4*). Artemether is approximately 95% bound to plasma proteins. It is converted, primarily by CYP3A4 and to a lesser extent by CYP2B6, CYP2C9 and CYP2C19, into dihydroartemisinin. While dihydroartemisinin is responsible for most of the antimalarial action after oral administration, the concentrations of artemether parent compound predominate after intramuscular administration in severe falciparum malaria. Artemether also undergoes auto-induction but to a lesser extent than artemisinin. Both artemether and dihydroartemisinin are eliminated within 7 h of administration (*3, 5–10*).

Figure A5.2. Individual concentration–time profiles for artemether after the first intramuscular dose of 3.2 mg/kg to 10 adult Vietnamese patients with severe falciparum malaria (2).
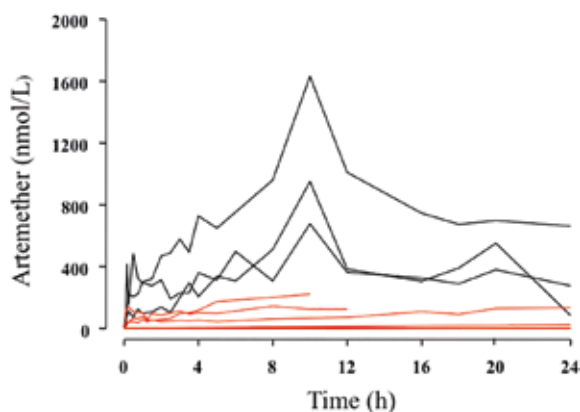
Safety

Adverse effects

Artemether is generally very well tolerated after both oral and intramuscular administration. It has similar side-effects to other artemisinin derivatives, including hypersensitivity reactions (risk estimate, 1 in 3000), mild gastrointestinal disturbance, dizziness, reticulocytopenia, neutropenia and elevated liver enzyme activity. Although no electrocardiographic abnormalities were found in most studies, bradycardia and very slight prolongation of the QT interval have been reported. While studies in experimental animals show neurotoxicity after parenteral artemether, clinical, neurophysiological and pathological studies in humans have not shown similar findings.

Contraindications

Artemether is contraindicated in patients with known hypersensitivity to any artemisinin derivative.

Cautions

A marked increase in the concentration of artemether in the cerebrospinal fluid of patients with meningitis was observed, prompting researchers to advise caution in treating patients with signs of meningitis (2, 10, 11).

Patients with acute renal failure have higher maximum concentrations, higher exposure, a lower volume of distribution and a longer elimination half-life of artemether than people without renal failure (6).

Drug interactions

See Table A5.14.

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A5.3 | ARTEMETHER–LUMEFANTRINE

Therapeutic indications

- Artemether–lumefantrine is indicated for the treatment of uncomplicated *P. falciparum* or *P. vivax* malaria and is considered effective against *P.ovale, P.knowlesi* and *P. malariae.*
- Artemether–lumefantrine may also be used as follow-on, but not initial, treatment in severe malaria when the patient is well enough to take oral medication.
- Artemether–lumefantrine is not indicated for malaria prophylaxis.

Structure and mechanism of action

For artemether: See A5.2
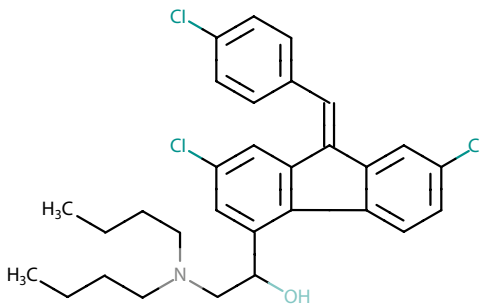
Molecular mass 528.9

Lumefantrine (benflumetol) is a fluorene derivative belonging to the aryl amino-alcohol group of antimalarials, which includes quinine, halofantrine and mefloquine (*1*). It is thought to work similarly to the other members of the group by preventing haem detoxification within the parasite food vacuole, thus causing accumulation of the toxic haem complex (*2*). Lumefantrine is not available as and has not been used as monotherapy, which should slow the selection and spread of resistance to this drug.

Pharmacokinetics

The pharmacokinetic parameters of artemether–lumefantrine are presented in Table A5.3 (*6–29*).

Table A5.3. Pharmacokinetic parameters estimated for artemether, lumefantrine and their respective active metabolites, dihydroartemisinin and desbutyllumefantrine in studies of currently recommended doses of artemether– lumefantrine used for treatment of acute malaria (range of mean or median values reported).

Parameter	Artemether	Dihydroartemisinin	Lumefantrine	Desbutyl-lumefantrine
C_{max} (ng/mL)	5.2–190	26–205	4456–28 300	19.3–89
Day 7 concentration (ng/mL)	–	–	156–1310	4
T_{max} (h)	0.5–2.13	0.8–3.0	2–66.3	8–62.7
K_a (/h)	–	–	0.06–0.82	–
AUC	40–385 ng.h/mL	90–382 ng.h/mL	207–2730 µg.h/mL	5.4 µg.h/mL
Elimination $T_{1/2}$ (h)	0.86–5.16	1–2.3	32.7–275	137–141
Cl/f (L/h per kg)	1.46–41.26	3.48–13.61	0.077–0.104	10.0
Vd/f (L/kg)	9.85–143.5	1.038–35.6	0.4–8.9	730–977

Artemether is more lipophilic than other artemisinin derivatives and is readily absorbed from the gastrointestinal tract, reaching peak plasma concentrations within 2 h of oral administration. It is then converted, primarily by CYP3A4 and to a lesser extent by CYP2B6, CYP2C9 and CYP2C19 enzymes, into dihydroartemisinin which is responsible for most of the antimalarial action. Artemether also undergoes auto-induction (3). Both artemether and dihydroartemisinin are eliminated rapidly.

Lumefantrine is highly lipophilic and is more readily absorbed when co-administered with fatty foods or milk (4, 5, 7). Its bioavailability and the time to reach maximum concentrations vary within and between individuals, primarily due to fat-dependent absorption. The absorption of lumefantrine is close to saturation at currently recommended doses, so increasing the dose does not result in a proportional increase in exposure (6, 11); similar non-linear relations between dose and bioavailability are well described for other highly lipophilic drugs. Lumefantrine exhibits high plasma protein binding (99.7%) and has an elimination half-life of ~3 days. It is extensively metabolized in the liver, primarily by the CYP3A4 enzymes (2, 30). Its active metabolite is desbutyl-lumefantrine (31).

Safety

Adverse events

Artemether–lumefantrine has a wide therapeutic index and is generally well tolerated, with reported side-effects such as nausea, dizziness and headache that are not easily distinguishable from symptoms of acute malaria (*13, 28, 32–35*). Artemether–lumefantrine does not significantly prolong the QTc interval (*36*).

Contraindications

Artemether–lumefantrine should not to be administered to patients with known hypersensitivity to either artemether or lumefantrine.

Cautions

Artemether–lumefantrine has not been studied extensively in patients > 65 years or children weighing < 5 kg. so these patients should be monitored closely when taking this medication.

The manufacturer advises against administration to patients with congenital or clinical conditions resulting in QTc prolongation, a family history of congenital long QT syndrome or sudden death or those with electrolyte abnormalities such as hypokalaemia or hypomagnesaemia, which may affect cardiac conductivity, although there is no evidence for iatrogenic toxicity in these groups (*37*).

Drug interactions

See Table A5.14.

Dosage recommendations

Formulations currently available: Dispersible or standard tablets containing 20 mg of artemether and 120 mg of lumefantrine in a fixed-dose combination formulation. The flavoured dispersible tablet paediatric formulation facilitates use in young children.

Dose optimization: To evaluate the feasibility of dose optimization, a population model of the pharmacokinetics of lumefantrine was constructed at the Mahidol–Oxford Tropical Medicine Research Unit from pooled concentration–time data for 1390 patients in four countries (Papua New Guinea, Thailand, Uganda, United Republic of Tanzania). Body weights from 8 to 70 kg were well represented. A saturation model was used to describe the dose-limited absorption. The current dose recommendations resulted in similar day-7 lumefantrine plasma concentrations in all non-pregnant patients, except for the smallest children (weighing 5–14 kg). Because of dose-limited absorption, however, it is uncertain whether increases in individual doses would result in predictably higher lumefantrine exposure in these young children. Extended or more frequent dosing regimens should be evaluated prospectively in this age group.

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A5.4 | ARTESUNATE

Therapeutic indications

- Parenteral (intravenous or intramuscular) artesunate is indicated for the initial treatment of severe malaria.
- Rectal artesunate is indicated as pre-referral treatment for severe malaria.
- Artesunate–amodiaquine, artesunate–mefloquine or artesunate–SP are indicated for the treatment of acute uncomplicated *P. falciparum, P. vivax, P. ovale, P. knowlesi* or *P. malariae* malaria.

Structure and mechanism of action

Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is obtained by the reduction of artemisinin, a sesquiterpene lactone endoperoxide (*1*). *In vivo*, artesunate is rapidly converted to its active metabolite dihydroartemisinin. The mechanism of action of the artemisinin derivatives is not well-defined but involves cation-mediated generation of reactive intermediates and reduction of the peroxide bridge.
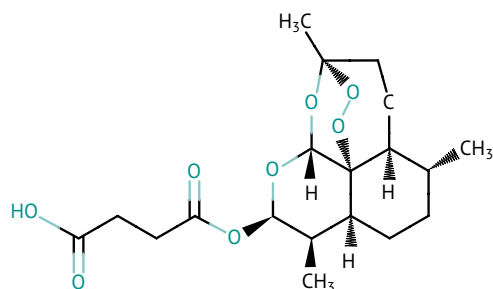
Artesunate, like other artemisinin derivatives, kills all erythrocytic stages of malaria parasites, including the ring stages and early schizonts, as well as the gametocytes responsible for continuing transmission, although it has only partial activity against the mature stage V gametocytes. It is essentially inactive against extra-erythrocytic forms, sporozoites, liver schizonts and merozoites. Artesunate is more water-soluble than other artemisinins and therefore can be administered intravenously. It can also be given orally, rectally or by the intramuscular route.

Molecular mass: 384.4

Pharmacokinetics

The pharmacokinetic parameters of intravenous, intramuscular, rectal and oral artesunate are presented in Table 5.4 (*1–32*). Artesunate is rapidly absorbed and biotransformed into its active metabolite dihydroartemisinin by plasma esterases, with a possible contribution from CYP2A6 enzymes. While dihydroartemisinin accounts for nearly all the antimalarial activity of oral artesunate, artesunate contributes more significantly to the antimalarial effect after intravenous administration. Peak concentrations of artesunate are reached within a few minutes of parenteral administration; thereafter, artesunate is rapidly eliminated. Plasma protein binding of dihydroartemisinin is approximately 93%. Dihydroartemisinin is metabolized in the gut and liver by glucuronidation and is excreted in the urine.

Table A5.4. Pharmacokinetic parameters of artesunate and its active metabolite, dihydroartemisinin (DHA), when given intravenously, intramuscularly or rectally for the treatment of severe malaria or orally for the treatment of uncomplicated malaria (range of mean or median values reported).

	Intravenous		Intramuscular		Rectal		Oral	
	Artesunate	DHA	Artesunate	DHA	Artesunate	DHA	Artesunate	DHA
C_{max} (ng/mL)	1140–29 644	340–3007	660–2192	62.5–1584	90–894	180–1279	34–451	900–2043
T_{max} (min)	2	9–17.4	8	1.4–40.5	42–54	12–138	30–84	54–120
AUC (µg.h/mL)	505–2051	1107–2559	855	1496	692	2402–2786	0.113–0.419	1.217–3.745
Elimination $T_{1/2}$ (min)	9–25.2	20.7–95.4	11.5–48.2	32–52.7	51	18–81	54	48–150
Cl/f (L/h per kg)	1.27–3.12	0.73–2.16	2.7–4.26	1.08–1.21	5.9	1.5–2.64	0.61–15.4	0.63–1.66
Vd/f (L/kg)	0.08–0.24	0.75–2.22	0.44–2.16	0.77–1.79	2.06	0.6–2.8	0.63-3.35	1.45–3.00

Safety

Pregnancy

In experimental animals, dose-dependent fetal toxicity was observed after administration of artesunate in the first trimester and was more likely to occur with increased duration of treatment (*1*). There is no evidence that artemisinin derivatives are teratogenic in humans, but experience is still limited. While the possible risk for teratogenicity limits the use of artemisinin derivatives in the treatment of uncomplicated malaria in women in the first trimester, treatment of severe malaria with artesunate is recommended as it is potentially life-saving for the mother. Artesunate has been successfully and safely administered in the second and third trimesters of pregnancy (*1, 33*).

Adverse events

Artesunate is generally well-tolerated and has a better safety profile than quinine in severe malaria (*34–37*). It has similar side-effects to other artemisinin derivatives, including hypersensitivity reactions (risk estimate, 1 in 3000), gastrointestinal disturbances, cough, rash, arthralgia, dizziness and delayed haemolysis. Clinically, the most significant effect is haemolysis, which has been reported up to weeks after treatment (*38*) (see section 7.4.1). Dose-dependent neutropenia was observed in Cambodia, where an oral dose of 6 mg/kg bw artesunate for 7 days resulted in significantly lower neutrophil counts than in those patients given 2 or 4 mg/kg bw (*39*). Other adverse effects observed in animal models, such as hepatotoxicity and neurotoxicity, have not been observed in clinical studies at therapeutic doses (*40–42*). Although there is a theoretical concern about bradycardia and QTc

prolongation associated with artemisinin derivatives, particularly at high doses, this has not been seen with artesunate (*16*).

Contraindications

Artesunate is contraindicated in patients with known hypersensitivity to artesunate or artemisinin derivatives.

Cautions

As lower plasma concentrations of artesunate and dihydroartemisinin are reported in young children with severe anaemia, it is important to monitor their response to treatment closely.

While use of artesunate in patients with renal or hepatic impairment has not been studied extensively, the limited data available (and the known metabolism and excretion of drug) do not suggest that artesunate would be toxic to renally or hepatically impaired individuals. Nevertheless, caution is advised in treating these patients.

Drug interactions

See Table A5.14.

Dosage optimization

For the treatment of uncomplicated malaria, the target dose of artesunate remains 4 mg/kg bw daily, with a daily dose range of 2–10 mg/kg bw. Children weighing < 25 kg with severe malaria had lower exposure to intravenous or intramuscular artesunate and its active metabolite dihydroartemisinin than older children and adults given the same dose of 2.4 mg/kg bw (*9*), which was attributed to an increased clearance rate in younger children. This may increase the risk for treatment failure, which can be fatal in severe malaria. The Mahidol–Oxford Tropical Medicine Research Unit performed nonlinear mixed-effects population pharmacokinetics modelling in order to inform WHO dosage recommendations for ensuring equivalent exposure to the drug for all target populations. These models confirmed that young children (< 25 kg/5 years) should receive a slightly higher dose of 3 mg/kg (see section 7.4.1), which is still within the therapeutic range prescribed by the manufacturer and does not raise safety concerns.

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# A5.5 | ATOVAQUONE–PROGUANIL

Therapeutic indications

• The combination atovaquone–proguanil is indicated for the prophylaxis of malaria.
• Atovaquone–proguanil may also be considered for the treatment of uncomplicated malaria in travellers outside malaria-endemic areas and for use in combination with artesunate and primaquine as an alternative treatment for uncomplicated malaria, where WHO recommmended treatments are not available or not effective.

Structure and mechanism of action
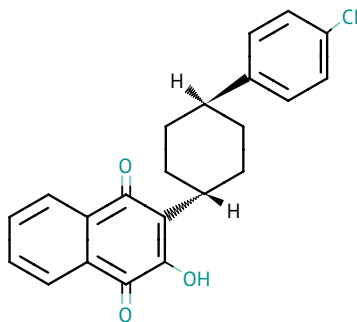
Molecular mass: 366.8

Atovaquone is a hydroxynaphthoquinone with antimalarial activity against all stages of all *Plasmodium* species (*1*). It is an ubiquinone analogue that inhibits the transport of several parasite enzymes and interferes with the cytochrome electron transport system, resulting in the collapse of the mitochondrial membrane potential (*1*, *2*). Atovaquone–proguanil is seldom used in endemic areas because of the propensity for emergence of high-grade resistance to atovaquone from single mutations in the *cyt b* gene (*3*).

Molecular mass: 253.7
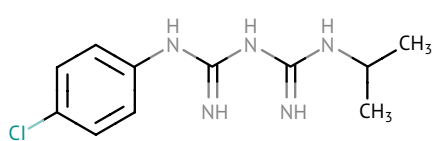
Proguanil is a biguanide compound that is active against all stages of the malaria parasite life cycle. *In vivo*, it is converted into an active triazine metabolite, cycloguanil, which acts by inhibiting dihydrofolate reductase (*2, 4*).

The combination of atovaquone and proguanil is synergistic, but it is the parent compound rather than the metabolite that synergizes, independently of its antifol metabolite, lowering the effective concentration at which atovaquone collapses the mitochondrial membrane potential (*4*).

Pharmacokinetics

Table A5.5 summarizes the pharmacokinetic parameters of atovaquone–proguanil (*5–13*). Atovaquone is a highly lipophilic compound, and there is considerable inter-individual variation in its absorption. Atovaquone–proguanil should be taken at the same time each day with food or a milky drink, as atovaquone is generally poorly absorbed from the gastrointestinal tract; the absolute oral bioavailability is approximately 23% when taken with food (*14*). In contrast, proguanil is readily absorbed from the gastrointestinal tract, reaching peak concentrations within approximately 5 h of administration. Atovaquone is 99% bound to plasma proteins and has a long plasma half-life (~2–3 days) because of enterohepatic recycling. It is excreted almost exclusively in the faeces as unchanged drug (*14*). Proguanil is 75% protein bound and undergoes hepatic biotransformation via CYP2C19 (and possibly CYP3A4) into the antifolate metabolite cycloguanil (*10, 14*). Between 40 and 60% of proguanil is excreted by the kidneys (*14*). The apparent clearance (Cl/f) of both atovaquone and proguanil is related to body weight (*14*). While most of the pharmacokinetics of proguanil and cycloguanil is comparable in adults and children, the elimination half-life of atovaquone is shorter in children (*9, 14*). The plasma concentrations of atovaquone and proguanil in women in the second and third trimesters of pregnancy are approximately half those of non-pregnant adults (with and without acute malaria) as a result of a greater Vd and increased oral clearance.

Table A5.5. Pharmacokinetic parameters of atovaquone, proguanil and cycloguanil in studies of currently recommended doses for malaria prophylaxis or treatment (range of mean or median values reported).

Parameter	Atovaquone	Proguanil	Cycloguanil
C_{max} (ng/mL)	634–13 270	560–751	37–67
T_{max} (h)	5.1–5.7	4.4–5.2	6.4–6.9
Elimination $T_{1/2}$ (h)	29–134	8.0–17.6	15.6–22.6
AUC	2.67–27.63 µg.days/mL	7.2–15.4 µg.h/mL	0.6–1.8 µg.h/mL
Cl/f (L/h per kg)	0.09–0.32	0.71–1.23	–
Vd/f (L/kg)	4.7–13	13.4–22.9	–

Safety

Pregnancy

Atovaquone–proguanil is regarded as safe in pregnancy, as no evidence of adverse effects associated with its use was found in studies in pregnant humans or experimental animals (*2, 7, 8, 14*).

Adverse effects

Generally atovaquone–proguanil is well tolerated. The side-effects of atovaquone–proguanil are similar in children and adults (*9, 14*). The most common adverse effects reported are headache, cough and gastrointestinal disturbances (such as abdominal pain, nausea, vomiting and diarrhoea). Other adverse events occur rarely, such as dizziness and oral ulceration, and, very rarely, blood disorders including neutropenia and anaemia and skin reactions such as photosensitivity rash and erythema multiforme. Raised liver enzyme activities, hepatitis and hepatic failure have been reported. Allergic reactions including anaphylaxis, angioedema, Stevens–Johnson syndrome and vasculitis may rarely occur. Pancytopenia in patients with severe renal impairment treated with proguanil has been reported, probably because of drug accumulation (*15*).

Contraindications

Atovaquone–proguanil is contraindicated in patients with known serious hypersensitivity reactions to atovaquone or proguanil. It is also contraindicated as malaria prophylaxis in patients with severe renal impairment because of the high risk for pancytopenia.

In the elderly, doses should be selected cautiously, taking into account the greater frequency of decreased hepatic, renal or cardiac function, higher systemic exposure to cycloguanil and a greater frequency of concomitant disease or other drug therapy (*14*).

Drug interactions

See Table A5.14. The main concern is the approximate twofold reduction in plasma concentrations of both atovaquone and proguanil (*7*, *8*), which could leave pregnant women more susceptible to malaria infection or at risk for treatment failure. Further clinical and dose-optimization studies in pregnancy are required. Additional strategies are strongly advised for pregnant women taking atovaquone–proguanil for malaria prevention.

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A5.6 | CHLOROQUINE

Therapeutic indications

- Chloroquine is indicated for the treatment of uncomplicated malaria due to *P. vivax, P. malariae, P. ovale* and *P. knowlesi* (*1*).
- Chloroquine is no longer recommended for prophylaxis against *P. falciparum* (except in some parts of Central America) but may be used to prevent *P. vivax* infections.

Structure and mechanism of action
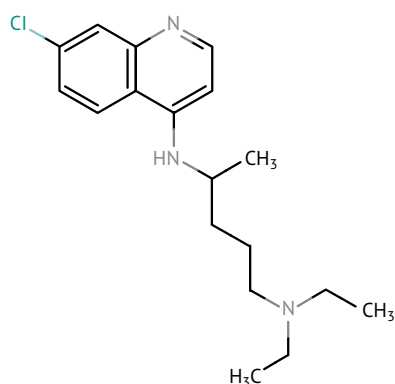
Chloroquine is a 4-aminoquinoline that inhibits intraparasitic haem detoxification (*2*); it may also interfere with the biosynthesis of nucleic acids. Chloroquine reaches high concentrations in the parasite's food vacuole. Chloroquine resistance is associated with genetic mutations in genes encoding trans-membrane proteins of the parasite's food vacuole (PfCRT and PfMDR) (*3*).

Molecular weight: 319.9

Pharmacokinetics

Table A5.6 summarizes the pharmacokinetic properties of chloroquine (*4–15*). Chloroquine is rapidly and almost completely absorbed from the gastrointestinal

tract after oral administration (*16*). Plasma protein binding is approximately 55%. Chloroquine is extensively distributed in body tissues and fluids, including the placenta and breast milk. It is metabolized in the liver by CYP2C8 and CYP3A4 enzymes, mainly to monodesethylchloroquine, which has similar antimalarial activity (*17*). The drug is eliminated slowly from the body , with ~55% eliminated via the kidneys.

Table A5.6. Pharmacokinetic properties of chloroquine and desethylchloroquine in studies of currently recommended doses for malaria prophylaxis or treatment (range of mean or median values reported).

Parameter	Chloroquine	Desethylchloroquine
C_{max} (ng/mL)	283–1430	89–220
T_{max} (h)	2.7–6.9	–
AUC (µg.h/mL)	8.2–140	23.1–64.3
Elimination $T_{1/2}$ (h)	108–291	175–290
Cl/f (L/h per kg)	0.23–0.80	0.1–0.16
Vd/f (L/kg)	31.8–262	12.6

Safety

Pregnancy

At the doses used for treatment or prophylaxis of *P. vixax, P. ovale* or *P. malaria*, chlororoquine is considered safe in pregnancy (*18,19*). The chloroquine concentrations achieved are reportedly lower during pregnancy, particularly in the second and third trimesters (*11,21)*, although one studies showed no such difference (*20*). The response of pregnant patients to treatment should be monitored closely.

Adverse effects

Chloroquine is generally well tolerated at therapeutic doses. Large doses used for the treatment of rheumatoid arthritis are associated with a higher frequency of adverse events than the lower doses used in malaria. Pruritus is a common side-effect and is more severe in dark-skinned individuals. Other less common side-effects include headache, hepatitis, elevated liver enzyme, various skin eruptions and gastrointestinal disturbances, such as nausea, vomiting and diarrhoea. Taking chloroquine with food helps to avoid gastrointestinal intolerance. Chloroquine causes slight widening of the QRS complex and QT intervals in electrocardiography but has not been associated with conduction disturbances or arrhythmia at therapeutic doses. 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 hair loss. Blood disorders, such as aplastic anaemia, are extremely uncommon.

Acute overdosage is very dangerous, and death can occur within a few hours. The patient may progress from feeling dizzy and drowsy with headache and gastrointestinal upset, to sudden visual loss, convulsions, hypokalaemia, hypotension and cardiac arrhythmia. Overdosed patients require intensive care.

Contraindications

Chloroquine is contraindicated in patients with known hypersensitivity to chloroquine or any aminoquinoline compounds.

Caution

Use with caution in patients with psoriasis, neurological (e.g. epilepsy), retinal, or gastrointestinal disorders, as chloroquine may exacerbate these underlying conditions. The drug should also be administered with caution to patients with retinal or visual impairment or hepatic impairment.

Drug interactions

See Table A5.14.

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A5.7 | CLINDAMYCIN

Therapeutic indications

Clindamycin is used in combination with artesunate or quinine for severe or uncomplicated malaria.

Structure and mechanism of action
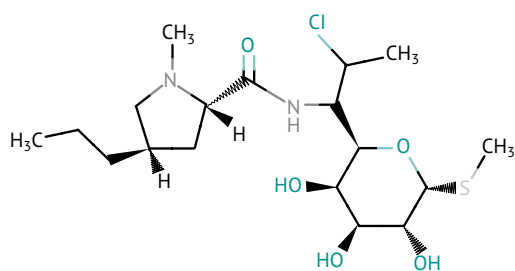
Clindamycin is a lincosamide antibiotic derived from lincomycin. Its mechanism of action involves inhibition of microbial protein synthesis by preferential binding to the 50S ribosomal subunit and interference with peptide chain initiation (1, 2).

Molecular mass: 425.0

Pharmacokinetics

The pharmacokinetic parameters reported for clindamycin are summarized in Table A5.7. Clindamycin is rapidly absorbed after oral administration, with an oral bioavailability of approximately 90% (3). It is widely distributed in body fluids and tissues, including bone, but insignificant levels are reached in cerebrospinal fluid. Clindamycin also crosses the placenta and appears in breast milk (4). It is about 90% bound to plasma proteins and accumulates in leukocytes, macrophages and bile (3). The half-life of clindamycin may be prolonged and clearance reduced in neonates and patients with renal impairment (5, 6). Clindamycin is metabolized by CYP3A4 enzymes in the liver into the active *N*-demethyl and sulfoxide metabolites and some inactive metabolites (7). About 10% of a dose is excreted in the urine as active drug or metabolites and about 4% in faeces; the remainder is excreted as inactive metabolites. Excretion is slow and takes place over many days. Although clearance is reduced slightly in patients with markedly reduced renal function, dose modification is not considered necessary (3). Clindamycin is not effectively removed from the body by dialysis.

Table A5.7. Pharmacokinetic parameters of clindamycin (range of mean or median values reported).

Parameter	Clindamycin
C_{max} (ng/mL)	2.5–14
T_{max} (h)	0.75–3.0
AUC (µg.h/mL)	24.63–26.87
Elimination $T_{elimination}$ (h)	1.9–3.57
Cl/f (L/h)	10.0–26.52
Vd/f (L)	49.1–132.6
Ka	0.967

Safety

Studies of reproductive toxicity with clindamycin in experimental animals revealed no evidence of impaired fertility or harm to the fetus. Although data on its use during pregnancy in humans are limited, clindamycin is regarded as safe for use in pregnancy.

Adverse events

Clindamycin is generally well tolerated after oral administration. Its major disadvantage is its potential to cause antibiotic-associated diarrhoea, leading to overgrowth of *Clostridium difficile* and pseudomembranous colitis (*3*). Other adverse effects include nausea, vomiting, abdominal pain or cramps, rash or pruritis. High doses of clindamycin may cause a metallic taste in the mouth. Rarely, clindamycin therapy has been associated with anaphylaxis, blood dyscrasia (leukopenia, agranulocytosis, eosinophilia, thrombocytopenia), erythema multiforme, polyarthritis, jaundice, raised liver enzymes and hepatotoxicity. Some parenteral formulations contain benzyl alcohol, which may cause fatal "gasping syndrome" in neonates.

Contraindications

Clindamycin is contraindicated in patients with known hypersensitivity to clindamycin or lincomycin.

Cautions

Clindamycin should be used with caution in patients with gastrointestinal diseases as they may be at greater risk for pseudomembranous colitis. Caution is also advised in administering clindamycin to severely ill elderly patients, who may be more likely than younger patients to develop diarrhoea. The longer elimination half-life of clindamycin in neonates means that its plasma concentration may be significantly higher than in older children (*5*, *6*). For this reason, close monitoring

of organ function is required when clindamycin is administered to neonates, particularly if they were premature. Clearance of clindamycin is reduced in patients with moderate-to-severe liver disease, so dosage modification (increasing the interval between doses) may be needed.

Greater bioavailability, higher serum protein binding, lower plasma drug clearance and a smaller steady-state volume of distribution have been found in patients with HIV/AIDS than in healthy volunteers (*10, 13*). Although the clinical significance of these findings has not yet been established, close monitoring of these patients is recommended (Drug interactions. See Table A5.14).

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binding of clindamycin in sera of patients with AIDS. Antimicrob Agents Chemother 1996;40:1134–8.

A5.8 | DIHYDROARTEMISININ−PIPERAQUINE

Therapeutic indications

Dihydroartemisinin–piperaquine is indicated for the treatment of uncomplicated *P. falciparum* or *P. vivax* malaria (*1*) and is likely to be very effective in *P. ovale*, *P. knowlesi* and *P. malariae* malaria. It may also be used as follow-on treatment in severe malaria once the patient is well enough to take oral medication.

Structure and mechanism of action
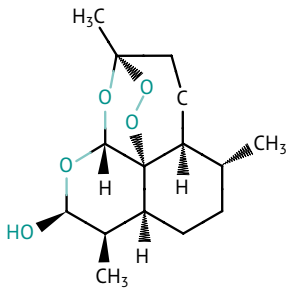
Dihydroartemisinin is a sesquiterpene peroxide and an active metabolite of artesunate and artemether (*2*, *3*). The mechanism of action of the artemisinin derivatives is not known but involves cation-mediated generation of reactive intermediates and reduction of the peroxide bridge.

Molecular mass: 284.4

Piperaquine is a bisquinoline compound of the 4-aminoquinoline group of antimalarial drugs that include chloroquine (*2*). Piperaquine is thought to act similarly to chloroquine, which accumulates inside the parasite food vacuole and inhibits parasite-mediated haem detoxification, causing accumulation of the toxic haem complex (*4*).
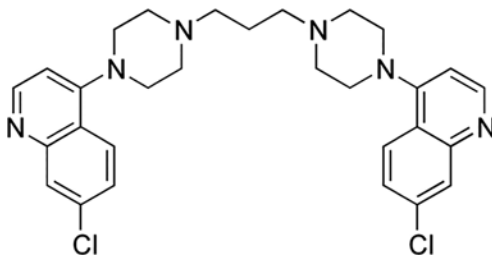
Molecular mass: 535.5

Piperaquine is also effective against chloroquine-resistant malaria parasites (*5*, *6*). In chloroquine resistance, mutations in the genes encoding trans-membrane parasite food vacuole proteins are thought to result in efflux of chloroquine, so that it cannot accumulate at its site of action (*7*). These mutated parasite membrane proteins are considered to be unable to efflux the bulky bisquinoline structure (*4*).

Pharmacokinetic parameters

Dihydroartemisinin–piperaquine is readily absorbed from the gastrointestinal tract, with peak plasma concentrations reached within 1–3 h for dihydroartemisinin and 3–6 h for piperaquine. Piperaquine is extensively distributed throughout the body, with more than 99% bound to plasma proteins (*3, 8–19*).

Dihydroartemisinin has a smaller volume of distribution and plasma protein binding of 44–93%. Elimination of dihydroartemisinin is much more rapid (elimination half-life, about 1 h) than that of piperaquine (2–4 weeks) (*3, 9, 10, 15*).

Table A5.8. Pharmacokinetic parameters of dihydroartemisinin and piperaquine in studies of manufacturer-recommended dosages in patients treated for acute uncomplicated malaria (range of mean or median values reported).

Parameter	Dihydroartemisinin	Piperaquine
C_{max} (ng/mL)	366–698	71.6–730
T_{max} (h)	0.97–2.8	1.48–5.7
$AUC_{0-infinity}$	0.84–1.95 ng.h/mL	24.1–49.5 µg.h/mL
Day-7 concentration (ng/mL)	–	22.7–64
K_a (per h)	–	0.08
Vd/f (L/kg)	1.47–3.59	529–877
Cl/f (L/h per kg)	1.19–2.16	0.85–1.85
Elimination $T_{1/2}$	0.85–1.40 h	13.5–28 days

Safety

Adverse events

Overall, dihydroartemisinin–piperaquine was well tolerated in large randomized controlled trials. The adverse effects reported included nausea, diarrhoea and vomiting, as well as anorexia, anaemia, dizziness, headache, sleep disturbance and cough (*2, 20–28*).

Although there was no evidence of cardiotoxicity in large randomized trials and extensive use of dihydroartemisinin–piperaquine, piperaquine does prolong the QT interval on electrocardiography (reflecting ventricular repolarization) by approximately the same amount as chloroquine (but by less than quinine) (*29, 30*). In a study in healthy volunteers, dihydroartemisinin–piperaquine increased the QTc interval by 45.2, 35.5 and 21.0 ms in people who took each dose with a high (~1000 kcal) or low (~400 kcal) fat/calorie meal and in fasting conditions, respectively; none had a QTc interval greater than 500 ms (*2*). Significant prolongation of the QTc interval may cause potentially life-threatening ventricular tachyarrhythmia, but there is no evidence that this has occurred with piperaquine, despite its extensive use.

Contraindications

Dihydroartemisinin–piperaquine should not be administered to patients with known hypersensitivity to either dihydroartemisinin or piperaquine (*2*). It should not be used in patients with congenital QTc prolongation or who have a clinical condition or are on medication that results in QTc interval prolongation.

Cautions

In view of the lack of evidence on the safety of dihydroartemisinin–piperaquine in patients > 70 years of age, in infants weighing < 5 kg and in patients with renal or hepatic impairment, patients in these populations should be monitored closely when this combination is administered.

Drug interactions

See Table 5.14.

Dosage recommendations

The previous edition of the *WHO Guidelines for the treatment of malaria* recommended target oral doses of 2–10 mg/kg dihydroartemisinin and 16–26 mg/kg piperaquine to be taken daily for 3 days (*1*). The dosing schedule recommended by the manufacturers, however, results in some individuals at the upper end of the weight band receiving much lower doses of piperaquine and dihydroartemisinin than this target. Furthermore, the weight-adjusted dosage recommendation for dihydroartemisinin–piperaquine was the same for all age groups, even though their pharmacokinetic parameters do not scale linearly with weight (*31*). Children aged <5 years have higher body weight-adjusted oral clearance of piperaquine than other age groups (*8,14,33*) and therefore have lower exposure to piperaquine, placing them at increased risk for treatment failure.

The WorldWide Antimalarial Resistance Network analysed pooled data from individual patients to determine the influence of dosing schedules on the clinical efficacy of dihydroartemisinin–piperaquine (*32*). Twenty-four published and two unpublished studies (with a total of 7072 patients) were included in the analysis. After correction for reinfection by parasite genotyping, the Kaplan–Meier estimates of cure rates were high 97.7% (95% CI, 97.3%–98.1%) at day 42 and 97.2% (95% CI 96.7%–97.7%) at day 63. Overall, 28.6% (979/3429) of children aged 1–5 years received a total dose of piperaquine < 48 mg/kg (the lower limit previously recommended by WHO), giving a risk that was 2.3–2.9-fold greater than that of other age groups. This sub-optimal dosing was associated with higher treatment failure rates at day 63 (94.4%; 95% CI, 92.6–96.2%; $p < 0.001$). After adjustment for confounding factors, the mg/kg bw dose of piperaquine was found to be a significant predictor of recrudescence, the risk increasing by 13% (95% CI, 5.0–21%) for every 5-mg/kg bw decrease in dose ($p = 0.002$). In a multivariable model, increasing the target minimum total dose of piperaquine for children aged 1–5 years from 48 mg/kg bw to 59 mg/kg bw was predicted to halve the risk for treatment failure and was needed to cure more than 95% of these young patients. The increased

exposure was not associated with gastrointestinal toxicity in the 10 studies in which this could be assessed.

On the basis of the evidence of sub-optimal dosing of young children, the Mahidol–Oxford Tropical Medicine Research Unit performed nonlinear mixed-effects population pharmacokinetics modelling in order to inform WHO dosage recommendations for ensuring equivalent piperaquine exposure for all target populations. Selection of the published models included for simulating the target exposure in adult patients (*9*, *11*, *18*) was based on use of an appropriate structural pharmacokinetic model, sufficient data collection and adequate predictive performance. Exposure to piperaquine was then simulated with the population pharmacokinetic estimates and between- and within-patient variation reported for each of the paediatric data sets available (unpublished data from the WorldWide Antimalarial Resistance Network, *8*, *19*). The results were reported as medians and interquartile ranges for day-7 concentrations. Peak concentrations for 1000 patients were simulated for each body weight. Examples are shown in Figures A5.8.1 and A5.8.2.

Figure A5.8.1. Simulated maximum piperaquine concentrations based on the current recommendations of the manufacturer of Eurartesim®, the current revised WHO dosing recommendations and population pharmacokinetics reported by Tarning et al. (9). The broken horizontal black lines are the maximum 75th percentile expected after dosing with the manufacturer-recommended dose regimen.
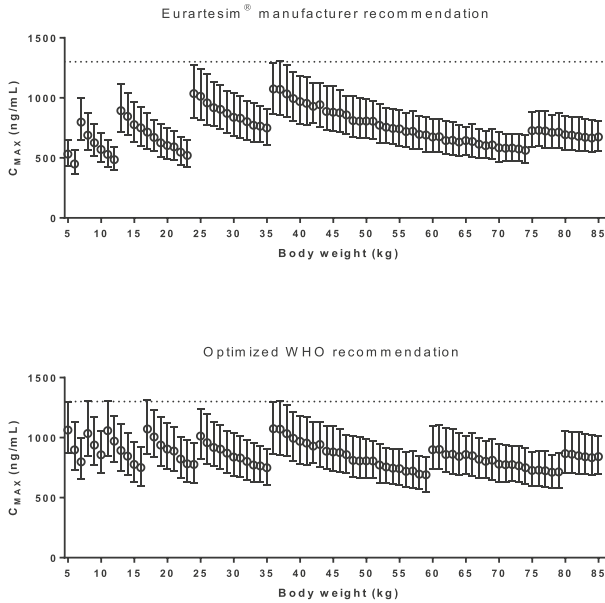
Figure A5.8.2 **Simulated day-7 piperaquine capillary plasma concentrations based on the current recommendations of the manufacturer of Eurartesim® and the current revised WHO dosing recommendations, using population pharmacokinetic parameters reported by Tarning et al. (8). The solid horizontal black lines indicate a previously defined therapeutic day-7 concentration (13).**
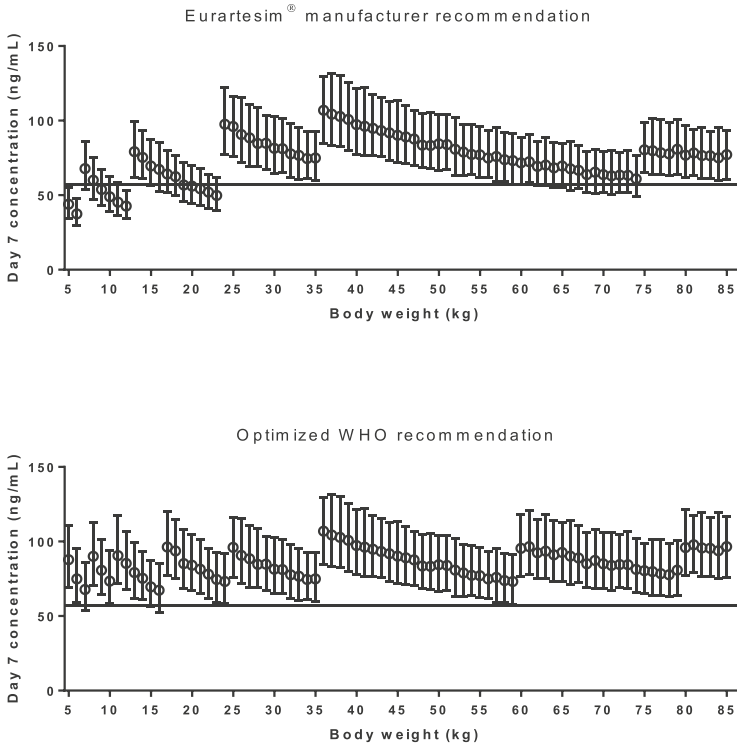
The revised WHO dosage recommendations selected ensure that the piperaquine exposure of young children (C_{max}, day-7 concentration) is equivalent to that of older children and adults, while using as few weight bands as possible and minimizing the use of half-tablets. Equivalent exposure in all weight groups is achievable with increases in mg/kg bw dosage of up to 20% in those weighing <25kg or >80kg; Importantly, this is not predicted to result in higher maximum (C_{max}) or day-7 concentrations of piperaquine than those already observed in adult patients given the doses currently recommmended by the manufacturer. Any further simplification of these recommendations will require a prospective study of the safety of slightly higher mg/kg doses.

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A5.9 | DOXYCYCLINE

Therapeutic indications

Doxycycline is indicated for the prophylaxis of malaria. It is also used as co-treatment with quinine or artesunate as follow-up treatment for severe malaria or in combination for uncomplicated falciparum malaria.

Structure and mechanism of action
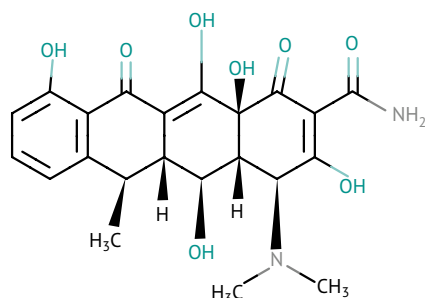
Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline, with uses similar to those of tetracycline. It is preferred to tetracycline because of its longer half-life, more reliable absorption and better safety profile in renal insufficiency. It is a slow-acting antimalarial drug that works by inhibiting protein synthesis through disruption of the normal function of the apicoplast in malaria parasites (*1, 2*).

Molecular mass: 444.4

Pharmacokinetics

The reported pharmacokinetic parameters of doxycycline are summarized in Table A5.9. Doxycycline is highly lipophilic and is rapidly and almost completely absorbed after oral administration. While the absorption of tetracyclines is known to be affected by the ingestion of food, that of doxycycline is not markedly changed. As milk significantly reduces absorption and the peak plasma concentrations of doxycycline, it should not be administered with milk or other dairy products.

Doxycycline is widely distributed in body fluids and tissues, including bone marrow, breast milk, liver and spleen, and it crosses the placenta. It is approximately 90% bound to plasma proteins. Like other tetracycline compounds, it undergoes enterohepatic recirculation, which slows clearance. Excretion occurs primarily through chelation in the gastrointestinal tract and to a much lesser extent via renal elimination (*3–22*). The elimination half-life of doxycycline is not affected by impaired renal function, renal failure or haemodialysis. Therefore, dose adjustment is not warranted for patients with renal impairment.

Table A5.9. Pharmacokinetic parameters of doxycycline in studies of it's use for prophylaxis or treatment of malaria (range of mean or median values reported).

Parameter	Doxycycline
C_{max} (µg/mL)	3.06–6.90
T_{max} (h)	1.5–6.0
AUC (µg.h/mL)	39.0–108.4
Elimination $T_{1/2}$ (h)	8.8–22.4
Cl/f (mL/h per kg)	29.5–112.0
Vd/f (L/kg)	0.75–1.83
K_a (per h)	0.26–1.03

In patients with malnutrition, doxycycline clearance is increased and total exposure to the drug is reduced; however, the plasma concentration remains within the therapeutic range (*16*). Therefore, dose adjustment is not warranted.

Safety

Adverse effects

Doxycycline has side-effects similar to those of other tetracyclines (*4*). Gastrointestinal effects, such as nausea, vomiting and diarrhoea, are common, especially with higher doses, and are due to mucosal irritation. Oral doxycycline should be administered with food if gastrointestinal upset occurs. Dry mouth, glossitis, stomatitis, dysphagia and oesophageal ulceration have also been reported. The incidence of oesophageal irritation can be reduced by administration of doxycycline with a full glass of water.

Tetracyclines, including doxycycline, discolour teeth and cause enamel hypoplasia in young children. Tetracyclines are deposited in deciduous and permanent teeth during their formation and in calcifying areas in bone and nails; they interfere with bone growth in fetuses and young infants.

Other reported side-effects are enterocolitis and inflammatory lesions in the ano-genital region, candidal vaginitis, skin reactions such as maculopapular and erythematous rashes, exfoliative dermatitis and photosensitivity. Patients should be warned to avoid excessive exposure to the sun while taking doxycycline.

Hypersensitivity reactions such as urticaria, angioneurotic oedema, anaphylaxis, anaphylactoid purpura, pericarditis and exacerbation of systemic lupus erythematosus may occur. Severe adverse effects are rare; they include benign intracranial hypertension in adults and haematological abnormalities such as haemolytic anaemia, thrombocytopenia, neutropenia and eosinophilia. Thrombophlebitis has been reported with prolonged intravenous administration.

Contraindications

Doxycycline is contraindicated in individuals with known hypersensitivity to tetracyclines. It is also contraindicated in pregnancy and in children < 8 years (*2, 4, 23*). Fatal liver necrosis has been reported with doxycycline use in pregnancy. In addition, doxycycline crosses the placenta and may cause discoloration of teeth and possible bone growth retardation in the fetus. Doxycycline use is not advocated for children < 8 years in whom the teeth are still developing because of the possibility of permanent tooth discoloration and bone growth retardation.

Caution

Doxycycline should be used with caution in patients with gastric or intestinal diseases such as colitis, who may be at greater risk for pseudomembranous colitis. Caution is advised in administering doxycycline to patients with established systemic lupus erythematosus, as it might worsen their condition. Drug interactions: See Table 5.14.

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A5.10 | MEFLOQUINE

Therapeutic indications

Mefloquine is indicated for the chemoprophylaxis of malaria caused by all species. In combination with artesunate, it is also recommended for treatment of uncomplicated malaria.

Structure and mechanism of action
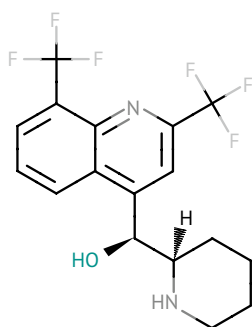
Mefloquine, a 4-methanolquinoline, is structurally related to quinine and belongs to the aryl amino-alcohol group of drugs (*1*). Mefloquine has two racemic forms, *erythro-* and *threo-*, each composed of a pair of enantiomers, of which the racemic mixture of the *erythro-* enantiomers is the most active against malaria parasites (*1*). Its mechanism of action is not fully understood but is thought to involve inhibition of parasite-mediated haem detoxification, a common mechanism of action of quinoline antimalarials. A more recent proposal is that it inhibits endocytosis of the cytosol by the parasite (*2*). Mefloquine has approximately the same stage specificity of action as quinine, killing primarily the large ring and trophozoite asexual parasites. It has no significant pre-erythrocytic activity.

Molecular mass: 378.3

Pharmacokinetics

The pharmacokinetic parameters of mefloquine used with artesunate for the treatment of uncomplicated malaria and for chemoprophylaxis in healthy subjects (*3–23*) are summarised in Table A5.10.

Table A5.10. Pharmacokinetic parameters of mefloquine in studies of currently recommended dosages when used for prophylaxis or treatment of acute malaria (range of mean or median values reported).

Parameter	Prophylaxis	Treatment
C_{max} (ng/mL)	722–2259	1000–3279
T_{max} (h)	4.5–31	15–72
Elimination $T_{1/2}$ (days)	1.03–19.1	8.1–15.2
$AUC_{0-infinity}$ (µg/mL.days)	15.6–48.0	12.8–63.6
Cl/f (L/h per kg)	0.016–0.095	0.016–0.174
Vd/f (L/kg)	1011–1460	7.87–31.8

Inter-individual differences in absorption result in different times to reach maximum concentrations. The pharmacokinetic parameters of mefloquine are altered in malaria: patients with malaria have higher plasma concentrations and eliminate mefloquine more rapidly than healthy volunteers, possibly because of interruption of entero-hepatic cycling (24). The pharmacokinitic parameters of mefloquine are also highly stereospecific (3–5). Mefloquine is extensively distributed in the body; it crosses the blood–brain-barrier and the placenta and is found in breast milk (21). It accumulates in erythrocytes, with an erythrocyte-to-plasma ratio of about 2:1 (24). Approximately 98.2% of mefloquine is bound to protein. In the liver, it is metabolized by CYP3A4, largely to an inactive metabolite (24). Mefloquine has a long elimination half-life (⩽ 3 weeks). Excretion occurs primarily via the bile and faeces as unchanged drug and metabolites, with a small proportion excreted unchanged in the urine.

While mefloquine has no effect on the pharmacokinetics of dihydroartemisinin, concomitant administration of artesunate decreases the maximum concentration and increases the clearance rate and volume of distribution of mefloquine (6, 24). Delaying the dose of mefloquine to the second day of artesunate administration increases its estimated oral bioavailability substantially, probably as an indirect effect of rapid clinical improvement (10). Administration with food does not alter the kinetics of artesunate–mefloquine (10, 17).

The pharmacokinitic parameters of mefloquine are similar in children and adults (4, 23). Peak mefloquine concentrations in whole blood are lower during pregnancy than in non-pregnant individuals (8, 21). As the overall efficacy of the drug does not appear to be affected, however, dosage adjustment is not warranted for pregnant women.

Safety

Adverse events

Although mefloquine is associated with higher incidences of central nervous system and gastrointestinal adverse effects than other ACTs, it is generally well tolerated when given in combination with artesunate for the treatment of uncomplicated malaria. Mefloquine has been associated with seizures, anxiety, irritability, dizziness, paranoia, suicidal ideation, depression, hallucinations and violence in patients treated for malaria and in people on long-term mefloquine prophylaxis (*20, 24–31*). Such neuropsychiatric adverse effects generally resolve after discontinuation of mefloquine. The estimated incidence of seizures, encephalopathy or psychotic reactions ranges from 1 in 10 000 healthy people receiving chemoprophylaxis, 1 in 1000 malaria patients in Asia, 1 in 200 malaria patients in Africa to 1 in 20 patients recovering from cerebral malaria. Mefloquine should therefore not be given to patients who have had cerebral malaria. Mefloquine prophylaxis should be avoided in travellers who require fine motor coordination or in whom sudden onset of dizziness or confusion may be hazardous, such as pilots and drivers. Travellers and their companions should be advised to monitor for adverse effects such as restlessness, anxiety, depression or confusion, and, if these occur, to discontinue mefloquine and seek medical attention.

The most frequently reported adverse effect with treatment is vomiting or gastrointestinal disturbances, which tend to affect adherence and efficacy. Early vomiting was a predictor of treatment failure in patients given mefloquine for uncomplicated malaria (*32*). Mefloquine has been associated rarely with hepatitis, polyneuropathy, thrombocytopenia, pneumonia, skin rashes or irritation, sinus bradycardia and visual impairment (*33–42*). Adverse events appear to be associated with high concentrations of the (–)-enantiomer rather than of the drug overall and to be more frequent in women than men (*20, 43*).

Contraindications

Mefloquine is contraindicated in patients with known hypersensitivity to mefloquine or related compounds (e.g. quinine and quinidine). It should not be prescribed for follow-up treatment after cerebral malaria or for prophylaxis in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia or another major psychiatric disorder, or with epilepsy or a history of convulsions (*24*).

Caution

Given the lack of evidence on the safety of mefloquine in severe hepatic impairment, such patients should be monitored carefully because of a potential increase in the risk for adverse events. Clinical trials show no or only small, clinically insignificant alterations in the electrocardiogram after administration of mefloquine (*39, 44*); however, caution should be exercised in administering mefloquine to patients with cardiac disease.

The teratogenic and embryotoxic effects of mefloquine observed in experimental animals and the high rate of spontaneous abortions seen in one small study of mefloquine prophylaxis in pregnant women (*45*) have raised concern about the safety of mefloquine in pregnancy. Large clinical studies have not, however, revealed such adverse outcomes, allaying concern that mefloquine might be associated with stillbirth (*46–48*). Prophylactic doses of mefloquine in the second and third trimesters of pregnancy also appear to be effective and are not associated with adverse maternal or fetal outcomes (*49*, *50*). However, gastrointestinal side-effects, including nausea and vomiting, are more common in pregnant women treated with mefloquine than those treated with SP (*29*).

Drug interactions

See Table A5.14.

Dose optimization

For the treatment of uncomplicated malaria in combination with artesunate, the recommended total dose of mefloquine is 25 mg/kg bw, which gives a higher cure rate than the previously recommended dose of 15 mg/kg bw. A pharmacokinetics model predicted that initial use of the lower (15-mg/kg bw) dose of mefloquine resulted in a greater likelihood of selecting resistant mutants than *de novo* use of the higher (25-mg/kg bw) dose (*51*). Giving mefloquine in two or three doses improves its tolerability and oral bioavailability. The fixed-dose combination of artesunate + mefloquine given daily for 3 days is preferred.

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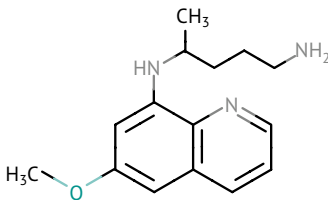
A5.11 | PRIMAQUINE

Therapeutic indications

Primaquine is indicated for radical cure of *P. vivax* or *P. ovale* malaria; for presumptive anti-relapse therapy (terminal prophylaxis) in people extensively exposed to *P. vivax* or *P. ovale*; to reduce onward transmission of *P. falciparum* malaria in programmes to eliminate *P. falciparum* malaria and in areas threatened by resistance of *P. falciparum* to artemisinins; and as an alternative for primary prophylaxis against all malaria species.

Except in primary prophylaxis, primaquine is used in conjunction with an effective blood schizonticide: either ACT, or chloroquine for vivax or ovale malaria.

Structure and mechanism of action

Primaquine is an 8-aminoquinoline, which is highly active against the exoerythrocytic forms (hypnozoites) and the sexual stages of malaria parasites (gametocytes). It has weak activity against the asexual blood stages of *P. vivax* and has negligible activity against *P. falciparum*. Although *P. falciparum* gametocyte clearance takes days, gametocytes are sterilized within hours; therefore, the effect of primaquine on oocyst and sporozoite formation (and thus onward transmission of the treated infection) precedes its effect on gametocyte carriage (*1*).

Molecular mass: 259.4

Hepatic metabolism of primaquine produces reactive intermediate metabolites that generate toxic intracellular oxidative species. The parent compound itself is relatively inactive. The precise mechanism of action of primaquine is not fully understood, but it is thought that the reactive intermediates disrupt the metabolic processes of plasmodial mitochondria and interfere with electron transport in the parasite (*2*, *3*). There is no evidence for acquired resistance to its hypnozoitocidal or gametocytocidal activities.

Pharmacokinetics

Primaquine is rapidly absorbed from the gastrointestinal tract, reaching peak concentrations within 1–4 h, with a bioavailability of about 96% (*4*). Primaquine is biotransformed by two main routes: by monoamine oxidase to the predominant, but inactive, metabolite carboxyprimaquine, which is relatively slowly eliminated; and via CYP2C19, CYP2D6 and CYP3A4 in the liver, which generate the reactive intermediates responsible for antimalarial effects and haemolytic toxicity (*5–7*). Genetic polymorphisms that decrease CYP2D6 enzyme activity reduce bioactivation of primaquine and may result in treatment failure. Primaquine is extensively distributed in the body. About 75% of primaquine in plasma is bound to proteins,

and high concentrations occur in erythrocytes. Primaquine crosses the placenta, but it is uncertain whether significant amounts occur in breast milk (*8*).

Both primaquine and carboxyprimaquine are excreted mainly through the biliary tract and can be found in faeces within 24 h of administration (*8*). Primaquine is also excreted in the urine as unchanged drug. Conflicting results have been reported on the effects of gender on the disposition of primaquine, some studies reporting increased exposure and hence greater side-effects in women and others reporting no effect of gender (*9–11*). In view of the relatively small samples in each of these studies, the findings should be interpreted cautiously. The pharmacokinetics of a single oral dose of 15 mg did not appear to be altered in patients with severely impaired renal function and end-stage renal dysfunction (*12*).

The pharmacokinetic parameters of primaquine are summarized in Table A5.11 (*4, 7, 9–18*).

Table A5.11. pharmacokinetic parameters of primaquine and carboxyprimaquine in studies in healthy volunteers and patients (range of mean or median values reported).

Parameter	Primaquine	Carboxyprimaquine
C_{max} (ng/mL)	65–295	343–2409
T_{max} (h)	1.8–4.0	4–8
Elimination T (h)	3.5–8.0	15.7–16.9
AUC (ng.h/mL)	443–1978	3831–47 085
Cl/f (L/h per kg)	0.31–1.19	–
Vd/f (L/kg)	2.92–7.94	–

Safety

Adverse events

While primaquine is generally well tolerated, it may cause dose-related gastrointestinal discomfort, including abdominal pain, nausea and vomiting (*19–22*). Administration with food improves tolerability. Hypertension and cardiac arrhythmia have been reported rarely. The most important adverse effect is haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and the degree of haemolysis is proportional to the dose, duration of exposure, and degree of G6PD deficiency. Leukopenia, methaemoglobinaemia with cyanosis and granulocytopenia may also occur. Fortunately, primaquine is eliminated rapidly, so that haemolysis stops once the drug is stopped. Patients should discontinue primaquine if they pass red or black urine, or have symptomatic anaemia.

Contraindications

Primaquine is contraindicated in patients with known hypersensitivity to primaquine or related compounds and in patients with severe G6PD deficiency or severe nicotinamide adenine dinucleotide (NADH) methaemoglobin reductase deficiency. Primaquine crosses the placenta and may cause haemolysis in a G6PD-deficient fetus; it is therefore not recommended for use during pregnancy or during breastfeeding unless the G6PD status of the infant is known. Use of primaquine in infants < 6 months is not advised because of lack of data on its safety.

Caution

The different variants of G6PD deficiency are associated with significantly different risks for haemolysis. The African A– variant is at the less severe end of the spectrum of severity, and the Mediterranean variant (which predominates in southern Europe, the Middle East and Central Asia) is at the more severe end (*23*). Administration of a single dose of 0.25 mg base/kg bw as a gametocytocide is considered to confer no significant haemolytic risk in people with any of the variants; therefore, testing for GDPD deficiency is not required before this single dose administration. The regimens necessary for radical cure may, however, cause significant, occasionally life-threatening haemolyisis in G6PD-deficient patients; therefore, testing for G6PD deficiency is recommended before radical cure regimens. Unfortunately, testing is not widely available, so an individual decision on whether to prescribe radical a curative regimen depends on an assessment of the potential risks of haemolytic toxicity and the benefits of preventing relapse. This assessment must be based on knowledge of the prevalence and severity of G6PD deficiency in the patient's ethnic group and the risks and impact of vivax relapse in the area. Caution is also advised in treating patients with systemic diseases associated with an increased risk for granulocytopenia, such as rheumatoid arthritis and systemic lupus erythematosus.

Drug interactions

See Table A5.14.

Dose optimization

The dosages recommended for radical cure of *P. vivax* or *P. ovale* malaria, presumptive anti-relapse therapy (0.25 mg base/kg bw per day for 14 days for "temperate strain infections" and 0.50 mg base/kg bw per day for 14 days for tropical, frequently relapsing infections) and primary prophylaxis (0.5 mg/kg bw base up to maximum oral dose of 30 mg daily) remain unchanged. WHO now recommends a single, low dose (0.25 mg/kg bw) to reduce onward transmission of *P. falciparum* malaria in programmes to eliminate *P. falciparum* malaria and in areas threatened by resistance of *P. falciparum* to artemisinins (*24*). This lower dose is safer and was considered to be as effective in reducing transmissibility on the basis of the limited available

data from assessments of direct transmission blocking in mosquito feeding studies, which is considered therapeutically more relevant than gametocyte clearance (*1, 25–27*). The feasibility of achieving this lower dosage in young children would be enhanced by the availability of a pre-qualified 3.75-mg primaquine tablet.

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A5.12 | QUININE

Therapeutic indications

Parenteral quinine is indicated for the treatment of severe malaria. Oral quinine is used in the treatment of uncomplicated malaria, particularly in the first trimester of pregnancy, or as an alternative treatment when an effective ACT is not promptly available.

Structure and mechanism of action
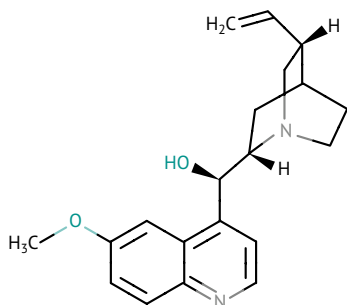
Quinine is an alkaloid derived from the bark of the cinchona tree that belongs to the aryl amino alcohol group of drugs (*1*). It is one of four antimalarial cinchona alkaloids and is the L-stereoisomer of quinidine. Quinine kills large ring and trophozoite asexual parasites and is gametocytocidal against *P. vivax, P. ovale* and *P. malariae* but not *P. falciparum* malaria (*2*). The mechanism of action of quinine is not clearly understood, although it is thought to involve inhibition of parasite haem detoxification inside the food vacuole.

Molecular mass: 324.4

Pharmacokinetics

The pharmacokinetic parameters of quinine are presented in Table A5.12 (*2–33*). Quinine is rapidly absorbed after both oral and parenteral administration. It is widely distributed throughout the body and is detectable in cerebrospinal fluid, breast milk and the placenta (*2*). Quinine undergoes extensive hepatic biotransformation, predominantly via CYP3A4 enzymes as well as CYP2C9, CYP1A2 and CYP2D6, into several metabolites. Quinine is both a substrate and an inhibitor of CYP2D6. The initial metabolite, 3-hydroxyquinine, contributes approximately 10% of the antimalarial activity of the parent compound. Up to 20% of administered drug is excreted unchanged by the kidneys, and small amounts may appear in bile and saliva (*34, 35*).

Table A5.12. Pharmacokinetic parameters of quinine reported with currently recommended doses used for the treatment of patients with severe or uncomplicated malaria (range of mean or median values reported).

Parameter	Quinine
C_{max} (µg/mL)	5.27–17.9
AUC (µg.h/mL)	9.20–449
T_{max} (h)	1.0–5.9
Elimination T (h)	3.21–26
Cl (mL/min per kg)	0.22–4.99
Vd (L/kg)	0.45–4.24

The pharmacokinetics of quinine is altered significantly by malaria infection (*2–4*). Both the apparent volume of distribution and systemic clearance are reduced in proportion to disease severity, resulting in higher plasma quinine levels in patients with severe malaria. As a result, quinine accumulates with standard maintenance dosing regimens (10 mg salt/kg bw every 8 h), unless the patient starts to recover. As a consequence, if there is no clinical recovery within 48 h, the dosage is reduced by one third (to 10 mg salt/kg bw every 12 h). In patients who are in acute renal failure, quinine clearance is determined by the overall disease severity and hepatic function. In addition, plasma-protein binding, mainly to the acute-phase protein α1-acid glycoprotein, increases from about 80% in healthy subjects to around 90% in patients with malaria (*36*).

The exposure of pregnant women to quinine was generally lower and elimination more rapid than that in non-pregnant patients (*23, 28*). The disposition of quinine changes with age, with slightly higher concentrations observed in children < 2 years (*24*). In children with protein energy malnutrition, clearance is significantly reduced, the elimination half-life is significantly longer but the maximum concentration significantly lower than in controls (*20, 31, 32*). Quinine pharmacokinetics, including total clearance normalized to ideal body weight, is not significantly altered in obese patients; thus, the maintenance dose of quinine in these patients should be based on ideal body weight rather than on total body weight (*6, 33*). Quinine clearance is significantly lower in elderly patients, posing a potential risk for drug accumulation and toxicity (*26*).

A5

Safety

Adverse events

Because of its narrow therapeutic index, quinine has frequent adverse effects (*2, 6, 8, 28, 37*). The side-effects commonly seen after administration of treatment doses are referred to as "cinchonism". Mild forms are characterized by tinnitus, slight impairment of hearing, headache, nausea, dizziness, dysphoria and sometimes disturbed vision. Impairment of high tone hearing is usually concentration-

dependent and reversible. More severe manifestations include vertigo, vomiting, abdominal pain, diarrhoea, marked auditory loss and visual symptoms, including loss of vision. An important side-effect of quinine is hyperinsulinaemic hypoglycaemia, which is particularly common in young children, pregnant women and elderly patients. Quinine also causes prolongation of the QTc interval (typically by about 10%), although cardiotoxic effects are much less frequent than those of quinidine. Hypotension and cardiac arrest may occur if the drug is given too rapidly (such as in an intravenous bolus); intravenous formulations should therefore be given by infusion not exceeding a rate of 5 mg/kg bw per hour. Venous thrombosis may occur after intravenous administration, while pain, necrosis and abscess formation may occur with acidic intramuscular injections. Hypersensitivity reactions to quinine have also been reported, including urticaria, bronchospasm, flushing of the skin, fever, antibody-mediated thrombocytopenia, haemolytic anaemia and haemolytic–uraemic syndrome. Hepatic injury and psychosis occur very rarely.

Quinine has been used as an abortifacient, but there is no evidence that it causes abortion, premature labour or fetal abnormalities (*28, 34*). Quinine therefore remains the drug of choice during the first trimester of pregnancy. It may also be used safely in the second and third trimesters of pregnancy, although poor compliance because of 7-day treatment course and low tolerability may compromise its efficacy, and there is a high rate of hyperinsulinaemic hypoglycaemia.

Overdosage of quinine may cause oculotoxicity, including blindness from direct retinal toxicity, and cardiotoxicity, and can be fatal (*38*). Cardiotoxic effects include conduction disturbances, angina and hypotension leading to cardiac arrest. Treatment is largely supportive, with particular attention to maintenance of blood pressure, glucose and renal function and to treating any arrhythmias.

Contraindications

Quinine is contraindicated in patients with known hypersensitivity to quinine or any of the cinchona alkaloids.

Caution

Although caution should be exercised when administering quinine to patients who have heart rhythm disorders or heart disease, there is little evidence of cardiotoxicity in patients with malaria. Quinine metabolites may cause oxidative haemolysis in people with G6PD deficiency. Caution is also advised in treating patients with kidney or liver disease, as the drug may accumulate (*10, 18, 19, 39–41*).

Drug interactions

See Table A5.14.

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A5.13 | SULFADOXINE–PYRIMETHAMINE

Therapeutic indications

Sulfadoxine–pyrimethamine (SP) is indicated in areas of moderate to high malaria transmission intensity for intermittent preventive treatment of malaria in pregnant women in their first and second pregnancy and in infants. SP is used in combination with amodiaquine for seasonal malaria chemoprevention in children in areas with highly seasonal malaria transmission, and, in the few areas in which it remains effective, SP can be used with artesunate for the treatment of acute uncomplicated malaria.

Structure and mechanism of action
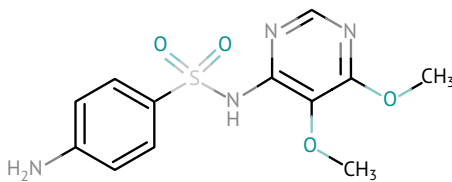
Sulfadoxine is a sulfonamide antimicrobial, which acts by inhibiting the activity of dihydropteroate synthetase and thus synthesis of folic acid by bacteria and protozoa. Sulfadoxine is active predominantly against the later development stages of asexual parasites (*1*).

Molecular mass: 310.3
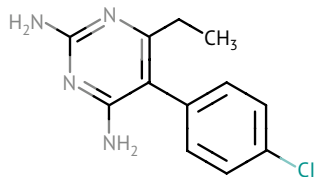
Pyrimethamine inhibits dihydrofolate reductase and thereby the synthesis of folic acid by protozoa. It is again active predominantly against the later development stages of asexual parasites (*1*).

Molecular mass: 248.7

Seasonal malaria chemoprevention (see section 11.3) with SP + amodiaquine should not be implemented in areas with high levels of resistance to SP or amodiaquine (*2*).

Intermittent preventive treatment (see sections 11.1 and 11.2): In areas with moderate levels of resistance to SP, intermittent preventive treatment remains effective in both pregnant women and infants, but the effectiveness decreases with high levels of resistance (*3–8*). The greatest protection in pregnancy is achieved by use of insecticide-treated nets in combination with an effective regimen of intermittent preventive treatment (*9, 10*). Adequate, consistent use if nets and other preventive measures is particularly important in areas where resistance to SP and malaria transmission intensity are high.

Artesunate + SP should not be used for the treatment of uncomplicated malaria in areas with established SP resistance. Some studies have indicated an increase in gametocyte carriage at low levels of resistance, further compromising the useful therapeutic life of this antimalarial drug (*11–13*)

Pharmacokinetics

The pharmacokinetic parameters of sulfadoxine and pyrimethamine are presented in Table A5.13. Both sulfadoxine and pyrimethamine are readily absorbed from the gastrointestinal tract after oral administration. Plasma protein binding is about 90% for both drugs. Sulfadoxine usually, but not always, has a longer elimination half-life than pyrimethamine. Pyrimethamine has a larger volume of distribution than sulfadoxine and is concentrated in kidneys, lungs, liver and spleen. Like sulfadoxine, pyrimethamine crosses the placental barrier and passes into breast milk. Sulfadoxine is metabolized mainly by the liver, undergoing varying degrees of acetylation, hydroxylation and glucuronidation. Pyrimethamine is also metabolized in the liver and, like sulfadoxine, is excreted mainly through the kidneys. The renal clearance of sulfadoxine is reported to vary with pH: a decrease in urinary pH from 7.5 to 5.5 decreased renal clearance by a factor of 2 (*1, 14–25*).

Table A5.13. pharmacokinetic parameters of sulfadoxine and pyrimethamine in studies of currently recommended dosages for the treatment, seasonal chemoprevention or intermittent preventive treatment of malaria (range of mean or median values reported).

Parameter	Sulfadoxine	Pyrimethamine
C_{max}	57.9–217.8 µg/mL	86–860 ng/mL
T_{max} (h)	3.7–63	2.4–41.1
Elimination $T_{1/2}$	4.1–10.9 days	60–450 h
AUC	15.9–66.3 µg.h/mL	21 787–106 065 ng.h/mL
Vd	263–660 mL/kg	2.32–7.20 L/kg
Cl/f	13.9–71.1 mL/day per kg	335–1776 mL/h per kg
Day-7 concentration	30.9–84.2 µg/mL	56.8–143.1 ng/mL

The interaction between artesunate and SP has been investigated (*24, 25*). Although the volume of distribution of pyrimethamine increased slightly on co-administration with artesunate, this is unlikely to be clinically significant, as total exposure and concentrations up to day 7 were not affected (*25*).

Safety

Adverse events

At the recommended doses, SP is generally well tolerated. The adverse effects reported are mainly those associated with sulfonamides, including gastrointestinal disturbances, headache, dizziness and skin reactions such as photosensitivity, rash, pruritus, urticaria and slight hair loss (*1*, *26–29*). Potentially fatal skin reactions, namely erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis, may also occur (*1*). Leukopenia, thrombocytopenia, megaloblastic anaemia, haemolytic anaemia (probably related to G6PD deficiency), crystalluria, haematuria, oliguria and hepatitis have also been reported. There have been isolated case reports of serum sickness, allergic pericarditis and pulmonary infiltrates resembling eosinophilic or allergic alveolitis.

Contraindications

SP, alone or in combination with amodiaquine or artesunate, is contraindicated in:

- individuals with known hypersensitivity to pyrimethamine, sulfonamides and related compounds;
- patients with documented megaloblastic anaemia due to folate deficiency;
- premature or newborn infants in the first 2 months of life, because of the immaturity of their enzyme systems; and
- HIV-infected patients receiving cotrimoxazole prophylaxis against opportunistic infections.

Caution

If skin eruptions, cytopenia or a bacterial or fungal super-infection occurs, use of SP should be discontinued. Caution is advised in repeated administration of SP to patients with blood dyscrasias and those with renal or hepatic failure, in whom the drugs accumulate.

Drug interactions

See Table 5.14.

Dose optimization

Dosing of antimalarial medicines has often been based on age, because access to formal health services or functioning weighing scales is often limited in malaria-endemic countries. While age-based dosing is more practical, it could result in under- or over-dosing in more patients. The accuracy of age-based dosing of SP could be improved by collating data on weight-for-age for each malaria-endemic region, as has been done for sub-Saharan African children in relation to administration of artesunate + amodiaquine (*30*).

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A5.14 | DRUG INTERACTIONS REPORTED FOR CURRENTLY RECOMMENDED ANTIMALARIAL DRUGS

Antimalarial drug	Demonstrated interactions	Potential interactions
Amodiaquine	**Increased plasma concentration and elevated liver enzyme activities with efavirenz (1)** **Decreased plasma concentration with nevirapine (2)** **Increased risk for neutropenia with zidovudine-containing regimens and trimethoprim + sulfamethoxazole (3)**	Increased risk for cardiac events with anti-arrythmic agents (4, 5) Visual loss or disturbances with mefloquine (6) Caution with inhibitors of CYP2C8 and CYP2A6[a] May inhibit CYP2D6 and CYP2C9 (7)

Antimalarial drug	Demonstrated interactions	Potential interactions
Artemether	*Increased plasma concentration* with ketoconazole (*8*) *Decreased plasma concentration* with darunavir + ritonavir (*9*), lopinavir + ritonavir (*10*, *11*), nevirapine (*12*, *13*), efavirenz (*12*, *14*), etravirine (*9*) and rifampicin (*15*)	Caution with inhibitors and inducers of CYP3A4 (*16*, *17*), although these will probably not have a large effect on antimalarial activity as the main effect is to change the ratio of artemether to dihydroartemisinin
Artesunate	*Increased plasma concentration* with nevirapine (*18*)	
Atovaquone	*Decreased plasma concentration* with rifampin (*19*), rifabutin (*19*), efavirenz (*20*), lopinavir + ritonavir (*20*) and atazanavir + ritonavir (*20*) Increased plasma concentrations of zidovudine (*21*)	Reduced plasma concentration with metoclopramide[a] and tetracycline[a] Increased plasma concentrations of etravirine (*22*), saquinavir (*22*) and warfarin (*23*)
Chloroquine	*Increased plasma concentration* with paracetamol (*24*) *Reduced metabolism and clearance* with cimetidine (*25*) *Reduced absorption* with antacids and kaolin (*26*) Reduced bioavailability of ampicillin (*27*) and praziquantel (*28*); reduced therapeutic effect of thyroxine (*29*) Increased plasma concentration of cyclosporine (*30*) Reduced plasma concentration of methotrexate (*31*) Reduced antibody response to primary immunization with intradermal human diploid-cell rabies vaccine (*32*)	Increased convulsions with mefloquine (*33*) Increased risk for acute dystonic reactions with metronidazole (*34*) Antagonises effects of anti-epileptics (*35*)
Clindamycin	*Delayed absorption* with aluminium salts and kaolin (*36*) Prolongs effects of neuromuscular blocking agents, and may lead to respiratory depression (*37*)	Possible antagonism and cross-resistance with macrolides (*38*) and chloramphenicol (*39*) Antagonizes parasympathomimetics, such as neostigmine

Antimalarial drug	Demonstrated interactions	Potential interactions
Dihydroartemisinin	***Reduced plasma concentration* when artesunate (40) or artemether (41) is given with ritonavir**	May result in slight decrease in CYP1A2 activity[a]
Doxycycline	***Decreased absorption* with antacids, bismuth subsalicylate (42), proton pump inhibitors (43) and oral iron preparations (44)** *Enhanced metabolism by hepatic enzyme inducers* such as antiepileptics (45-47) (carbamazepine, phenytoin, phenobarbital), rifampicin (48) and chronic alcohol use (49)	May potentiate the effect of oral anticoagulants (50) May reduce efficacy of oral contraceptives (51)
Lumefantrine	*Increased plasma concentration* with darunavir + ritonavir (9), lopinavir + ritonavir (11) and ketoconazole (8) *Decreased plasma concentration* with mefloquine (17), **rifampicin (15), efavirenz (12, 14)** and etravirine (9)	Prolongation of QTc interval with quinine (52) Caution with strong CYP3A4 inducers and drugs with cardiac effects that are metabolized by CYP2D6 (due to inhibition of CYP2D6 by lumefantrine[a]) May reduce efficacy of hormonal contraceptives[a]
Mefloquine	*Increased plasma concentration* with ketoconazole (53) and ampicillin (54) **Decreased plasma concentration and more rapid elimination with rifampicin (55)** Reduces plasma concentration of ritonavir (56) and anticonvulsants[a] (Note: use in patients with epilepsy contraindicated)	Increased risk for cardiac events with calcium channel blockers, digoxin, amiodarone, quinine, quinidine, quinolones and medicines that cause β-adrenergic blockade[a] Potential reduced effectiveness of live typhoid vaccine (57, 58) Potential increased plasma concentration with tetracycline (59) Increased risk of nephrotoxicity with quinine or chloroquine[a]

Antimalarial drug	Demonstrated interactions	Potential interactions
Piperaquine	None reported	Increased plasma concentration and potential increased toxicity with verapamil, indinavir, lopinavir + ritonavir, HMG-CoA reductase inhibitors (statins) and cyclosporin[a] *In-vitro* metabolism by CYP3A4 increased (*60*) and thus reduced plasma concentration and potentially reduced effectiveness with barbiturates, chronic alcohol use, rifampicin, efavirenz, nevirapine, phenytoin or carbamazepine[a] Increased risk for cardiac events with drugs that prolong the QTc interval[a]
Primaquine	*Decreased plasma concentration* of carboxyprimaquine with quinine (*61*) *Increased plasma concentrations* of primaquine and carboxyprimaquine with dihydroartemisinin–piperaquine, artesunate–pyronaridine and chloroquine (*62, 63*)	Adverse haematological effects with myelosuppressants[a] Strong CYP2D6 inhibitors or inducers are predicted to reduce efficacy (*64*) Inhibits metabolism of alcohol, leading to alcohol accumulation (*65*)
Proguanil	*Reduced plasma concentrations* with efavirenz (*20, 66*), lopinavir + ritonavir (*20*) and atazanavir + ritonavir (*20*) Reduced conversion of proguanil to cycloguanil by oestrogens (*67*)	May potentiate warfarin (*68*) May reduce effectiveness of live typhoid vaccine (*57*)
Sulfadoxine–pyrimethamine	Reduced effectiveness with high doses >5mg of folic acid (*69*) Avoid concurrent trimethoprim or trimethoprim + sulfamethoxazole due to increased risk for severe cutaneous reactions (*70*)	Additive haematological toxicity with myelosuppressants such as methotrexate, daunorubicin and cytarabine (71) Hepatotoxicity with lorazepam (72) Kaolin (73) may reduce absorption May displace quinine, phenytoin and warfarin from plasma protein, possibly increasing toxicity(71)

Antimalarial drug	Demonstrated interactions	Potential interactions
Quinine	*Increased plasma concentrations* with cimetidine (*74*) and ketoconazole (*75*) **Reduced plasma concentrations with nevirapine (76), rifampicin (77, 78) and ritonavir (79)** Increased plasma concentration of digoxin (*80*)	Omeprazole, nifedipine, troleandomycin and erythromycin may inhibit quinine metabolism, leading to its accumulation (*81*). QTc interval may be prolonged with antiarrhythmic agents such as flecainide and amiodarone[a] Ventricular arrhythmia may occur with antihistamines such as terfenadine and with antipsychotic drugs such as thioridazine.[a]

Major effects of likely clinical relevance are highlighted in bold.

[a] Information obtained from product package insert

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Annex 6 | Treatment of *Plasmodium vivax, P. ovale, P. malariae* and *P. knowlesi* infections

A6.1 | INTRODUCTION

Plasmodium vivax accounts for approximately half of all malaria cases outside Africa (*1–3*). It is prevalent in the Middle East, Asia, the Western Pacific and Central and South America. With the exception of the Horn, it is rarer in Africa, where there is a high prevalence of the Duffy-negative phenotype, particularly in West Africa, although cases are reported in both Mauritania and Mali (*3*). In most areas where *P. vivax* is prevalent, the malaria transmission rates are low (except on the island of New Guinea). Affected populations achieve only partial immunity to this parasite, and so people of all ages are at risk for *P. vivax* malaria (*3*). Where both *P. falciparum* and *P. vivax* are prevalent, the incidence rates of *P. vivax* tend to peak at a younger age than for *P. falciparum*. This is because each *P. vivax* inoculation may be followed by several relapses. The other human malaria parasite species, *P. malariae* and *P. ovale* (which is in fact two sympatric species), are less common. *P. knowlesi*, a simian parasite, causes occasional cases of malaria in or near forested areas of South-East Asia and the Indian subcontinent (*4*). In parts of the island of Borneo, *P. knowlesi* is the predominant cause of human malaria and an important cause of severe malaria.

Of the six species of *Plasmodium* that affect humans, only *P. vivax* and the two species of *P. ovale* (*5*) form hypnozoites, which are dormant parasite stages in the liver that cause relapse weeks to years after the primary infection. *P. vivax* preferentially invades reticulocytes, and repeated illness causes chronic anaemia, which can be debilitating and sometimes life-threatening, particularly in young children (*6*). Recurrent vivax malaria is an important impediment to human and economic development in affected populations. In areas where *P. falciparum* and *P. vivax* co-exist, intensive malaria control often has a greater effect on *P. falciparum*, as *P. vivax,* is more resilient to interventions.

Although *P. vivax* has been considered to be a benign form of malaria, it may sometimes cause severe disease (*7*). The major complication is anaemia in young children. In Papua province, Indonesia (*7*), and in Papua New Guinea (*8*), where malaria transmission is intense, *P. vivax* is an important cause of malaria morbidity and mortality, particularly in young infants and children. Occasionally, older patients develop vital organ involvement similar to that in severe and complicated *P. falciparum* malaria (*9, 10*). During pregnancy, infection with *P. vivax*, as with *P. falciparum*, increases the risk for abortion and reduces birth weight (*11, 12*). In primigravidae, the reduction in birth weight is approximately two thirds that associated with *P. falciparum*. In one large series, this effect increased with successive pregnancies (*11*).

P. knowlesi is a zoonosis that normally affects long- and pig-tailed macaque monkeys. It has a daily asexual cycle, resulting in a rapid replication rate and high parasitaemia. *P. knowlesi* may cause a fulminant disease similar to severe falciparum malaria (with the exception of coma, which does not occur) (*13*, *14*). Co-infection with other species is common.

A6.2 | DIAGNOSIS

Diagnosis of *P. vivax*, *P. ovale*, and *P. malariae* malaria is based on microscopy. *P. knowlesi* is frequently misdiagnosed under the microscope, as the young ring forms are similar to those of *P. falciparum*, the late trophozoites are similar to those of *P. malariae*, and parasite development is asynchronous. Rapid diagnostic tests based on immunochromatographic methods are available for the detection of *P. vivax* malaria; however, they are relatively insensitive for detecting *P. malariae* and *P. ovale* parasitaemia. Rapid diagnostic antigen tests for human *Plasmodium* species show poor sensitivity for *P. knowlesi* infections in humans with low parasitaemia (*15*).

A6.3 | TREATMENT

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

A6.3.1 | TREATMENT OF *P. VIVAX* MALARIA

Blood-stage infection

P. vivax is highly sensitive to artemisinin derivatives, which clear parasitaemia and resolve symptoms very rapidly (*16*). Artemisinin-based combination therapy (ACT) is therefore rapidly effective (*17–20*). All the currently recommended ACT is all highly effective against *P. vivax* malaria, with the exception of artesunate + sulfadoxine–pyrimethamine in some areas (because of resistance to sulfadoxine–pyrimethamine). Thus, ACTs may be used to treat the blood stage of all malarias. Chloroquine remains an effective treatment for vivax malaria in many areas, but in others susceptibility has declined. In Oceania and Indonesia, high-level resistance of *P. vivax* to chloroquine is prevalent (*21*).

Tropical *P. vivax* usually relapses around 3 weeks after the start of treatment and thereafter at 3-week intervals. This is the pattern seen after treatment with quinine or an artemisinin derivative only (*22*), but, after treatment with chloroquine or other slowly eliminated antimalarial drugs, the first relapse is suppressed by the residual drug levels. As a result, the first relapse is delayed and typically presents 5–6 weeks after the start of treatment. Chloroquine, piperaquine, and mefloquine

reliably suppress this first relapse. The more rapidly eliminated amodiaquine and lumefantrine (in ACT) provide less relapse suppression, and therefore relapses occur earlier after these treatments. Whether the total number of relapses is reduced by slowly eliminated antimalarial drugs remains to be determined.

Prevention of relapse

The radical curative efficacy of primaquine varies geographically (*23*), although there is no evidence for acquired resistance. The frequent-relapsing tropical strains prevalent in South-East Asia and Oceania require a higher primaquine dose for radical cure than strains found elsewhere. Failure of standard primaquine therapy (15 mg daily for 14 days; 0.25 mg/kg bw per day; total dose, 3.5 mg base/kg bw) to prevent relapse has since been reported in Oceania, South-East Asia, the Americas and on occasion in other locations. Because adherence (and often drug quality) were not confirmed in most of these studies, all these reports may not represent failure of the 0.25-mg/kg bw per day primaquine regimen. A systematic review of 87 clinical trials of primaquine dosing and relapse in vivax malaria, with data for 59 735 patients enrolled in 156 treatment arms, conducted in 20 countries, was reported recently (*24*). The median rate of recurrence after a very low dose (total dose, ≤ 2.5 mg/kg bw) primaquine in 44 studies was 25% (range, 0–90%) at 4–6 months, while that in 82 studies with a dose of > 2.5 to ≤ 5 mg/kg bw was 6.7% (range, 0–59%). High-dose (> 5 mg/kg bw) primaquine regimens (assessed in 28 treatment arms) were associated with a median recurrence rate of 0% (range, 0–15%) at 1 month. In 18 studies with control arms, the effectiveness of a very low-dose regimen of primaquine was no different from that in patients who did not receive primaquine (odds ratio, 0.60; 95% confidence interval [CI], 0.33–1.09, $p = 0.09$), whereas a significant benefit of the low-dose regimens was reported in 50% (6/12) of studies (overall odds ratio, 0.14; 95% CI, 0.06–0.35, $p < 0.001$). Two studies of a total of 171 patients showed much greater effectiveness of high-dose primaquine than a control (odds ratio, 0.03; 95% CI, 0.01–0.13; $p < 0.0001$). Figure A6.1 illustrates these findings.

Figure A6.1. Forest plots showing effectiveness of different doses of primaquine in radical cure of vivax malaria. Very low dose = total dose, ≤ 2.5 mg/kg bw, low dose = > 2.5 to ≤ 5 mg/kg bw, high dose = > 5 mg/kg bw.

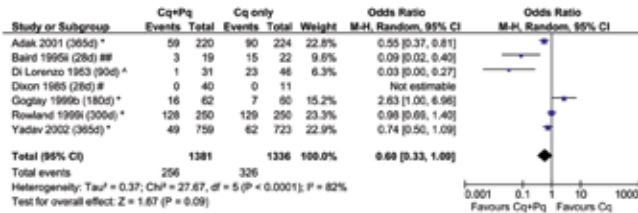* Indian subcontinent; ^ USA (Korea); ^^ USA (Chesson); # Thailand; ## Indonesia: + Ethiopia.

Study or Subgroup	Cq+Pq Events	Total	Cq only Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Adak 2001 (365d) *	59	220	90	234	22.8%	0.55 [0.37, 0.81]
Baird 1995i (28d) ##	3	19	15	22	9.6%	0.09 [0.02, 0.40]
Di Lorenzo 1953 (90d) ^	1	31	23	46	6.3%	0.03 [0.00, 0.27]
Dixon 1985 (28d) #	0	40	0	11		Not estimable
Goglay 1999b (180d) *	16	62	7	60	15.2%	2.63 [1.00, 6.95]
Rowland 1999i (300d) *	128	250	129	250	23.3%	0.98 [0.69, 1.40]
Yadav 2002 (365d) *	49	759	62	723	22.9%	0.74 [0.50, 1.09]
Total (95% CI)		**1381**		**1336**	**100.0%**	**0.60 [0.33, 1.09]**
Total events	256		326			

Heterogeneity: Tau² = 0.37; Chi² = 27.67, df = 5 (P < 0.0001); I² = 82%
Test for overall effect: Z = 1.67 (P = 0.09)

Favours Cq+Pq   Favours Cq

Figure 7 Forest plot of the effectiveness of very low dose primaquine in studies with a control arm.

Study or Subgroup	Cq+Pq Events	Total	Cq only Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Alving 1953 (120d) *	0	348	137	355	6.0%	0.00 [0.00, 0.04]
Alving 1960 (120d) ^^	16	60	71	74	10.9%	0.02 [0.00, 0.06]
Goglay 1999a (180d) *	0	63	7	60	5.7%	0.06 [0.00, 1.01]
Leslie 2004 (270d) *	74	383	86	212	13.7%	0.35 [0.24, 0.51]
Looareesuwan 1999 (28d) #	2	441	2	445	8.4%	1.01 [0.14, 7.20]
Luxemburger 1999(63d) #	3	43	38	69	10.9%	0.06 [0.02, 0.22]
Pukrittayakamee1994(28d)#	0	25	0	30		Not estimable
Pukrittayakamee2000(28d)#	0	22	0	21		Not estimable
Rajgor 2003 (180d) *	6	103	13	101	11.9%	0.42 [0.15, 1.15]
Rowland 1999i (300d) *	32	100	49	100	13.2%	0.49 [0.28, 0.87]
Walsh 2004 (56d) #	3	12	8	10	8.2%	0.08 [0.01, 0.63]
Yeshiwondim 2010 (157d) +	4	132	9	108	11.2%	0.34 [0.10, 1.15]
Total (95% CI)		**1732**		**1585**	**100.0%**	**0.14 [0.06, 0.35]**
Total events	140		420			

Heterogeneity: Tau² = 1.49; Chi² = 62.22, df = 9 (P < 0.00001); I² = 86%
Test for overall effect: Z = 4.27 (P < 0.0001)

Favours Cq+Pq   Favours Cq

Figure 8 Forest plot of the effectiveness of low dose primaquine in studies with a control arm.

Study or Subgroup	Cq+Pq Events	Total	Cq only Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Baird 1995i (28d) ##	4	26	20	23	48.4%	0.03 [0.01, 0.14]
Leslie 2008 (330d) *	1	54	22	68	51.6%	0.04 [0.01, 0.30]
Total (95% CI)		**80**		**91**	**100.0%**	**0.03 [0.01, 0.13]**
Total events	5		42			

Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
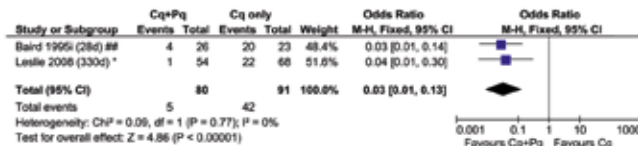Test for overall effect: Z = 4.86 (P < 0.00001)

Favours Cq+Pq   Favours Cq

Figure 9 Forest plot of the effectiveness of high dose primaquine in studies with a control arm. Footnote for Figures 7, 8 and 9: * Indian subcontinent; ^ USA (Korea), ^^ USA (Chesson), # Thailand, ## Indonesia, + Ethiopia.

 In addition there was a higher risk for relapse after standard primaquine therapy (equivalent to 15 mg daily) among people weighing > 70 kg. Thus, it is recommended that a higher dose regimen (0.5 mg base/kg bw; total, 7 mg/kg bw over 14 days) be given in South-East Asia and Oceania, where tropical frequent-relapse strains are prevalent. Elsewhere, where relapse rates are lower, the lower dose is effective and therefore recommended (0.25 mg base/kg bw; total, 3.5mg/kg bw over 14 days).

Figure A6.2. Dose–response relations for the radical curative efficacy of primaquine in Thailand (22). *P. vivax* recurrence (presumed relapse) within 28 days of regimens of artesunate and different durations of primaquine (30 mg base per day) to adults is shown. The grey circle shows the recurrences in adults receiving artesunate and primaquine at 60 mg daily for 7 days. The blue-centred black diamond show the rates with primaquine alone. The difference between primaquine at 30 mg/day with and without artesunate reflects recrudescence (A; arrowed) and that between primaquine at 30 mg/day with artesunate and primaquine at 60 mg/day presumably reflects relapses (B; arrowed).
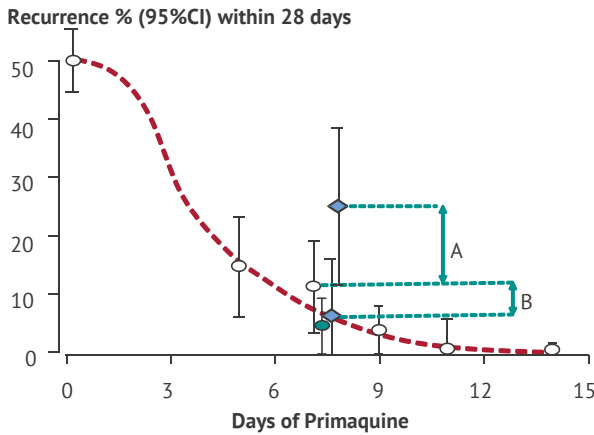
An important question is whether the current 14-day primaquine regimen can be shortened. Seven-day regimens are used commonly in the Americas. Pukrittayakamee et al. (*22*) compared different durations of treatment for vivax malaria in Thailand and showed that a 30-mg adult dose given twice daily for 7 days (n = 43) was not inferior to the standard 14-day course of 30 mg/day once daily (n = 42) and was not associated with a greater incidence of adverse effects (Figure 6.2). Durand et al. (*25*) evaluated the efficacy of three primaquine regimes – 0.5 mg/kg bw per day for 5 days (150 mg total), 0.5 mg/kg bw per day for 7 days (210 mg total) or 0.25 mg/kg per day for 14 days (210 mg total) – to prevent *P. vivax* malaria relapses in Loreto, Peru. Each group consisted of 180 patients; 90% completed follow-up. The relapse rates were similar with the 7- and 14-day regimes (16/156 = 10.3% and 22/162 = 13.6%, *p* = 0.361) and higher in the 5-day group (48/169 = 28.4%, *p* < 0.001 and *p* = 0.001, respectively). More information is needed on the tolerability, safety and efficacy of this approach. Primaquine is metabolized via cytochrome P450 mixed function oxidases (principally 2D6) to reactive intermediates, which mediate radical curative efficacy and haemolytic toxicity. Patients with loss-of-function polymorphisms in CYP2D6 may not generate sufficient metabolites for efficacy and may have relapses despite full adherence to primaquine radical curative regimens.

As primaquine also has weak but significant activity against blood-stage parasites (*16*), the radical cure regimen of chloroquine and primaquine for vivax malaria conforms to the definition of combination therapy. Combinations of chloroquine and primaquine may therefore mask low-level chloroquine resistance.

Assessment of resistance

As *P. vivax* cannot be cultured continuously in vitro, it is more difficult to determine its in-vitro sensitivity to antimalarial drugs (although short-term cultures do provide reliable results). In-vivo assessment of the therapeutic efficacy of drugs against *P. vivax* malaria is compounded by difficulties in distinguishing recrudescence due to drug-resistant infections from relapse. Recurrence occurring within 16 days of starting treatment for a primary infection is almost certainly recrudescence and thus represents therapeutic failure. A recurrence between days 17 and 28 may be either a recrudescence due to chloroquine-resistant parasites or a relapse; however, a relapse or a newly acquired infection should still be suppressed by residual chloroquine levels within 28 days. Beyond day 28, recurrences are increasingly likely to represent relapses or newly acquired infections (*26*). Recurrent vivax parasitaemia in the presence of chloroquine blood levels > 100 ng/mL is likely to represent resistance, whatever the origin of the recurrence.

A6.3.2 | TREATMENT OF SEVERE AND COMPLICATED VIVAX OR KNOWLESI MALARIA

P. vivax and *P. knowlesi* are very sensitive to artemisinin derivatives (*14*, *16*). Prompt, effective management should be the same as for severe and complicated falciparum malaria (see section 7).

A6.3.3 | TREATMENT OF MALARIA CAUSED BY P. OVALE, P. MALARIAE AND P. KNOWLESI

Infections with *P. ovale* (both species), *P. malariae* and *P. knowlesi* are considered to be generally sensitive to chloroquine. A single study in Indonesia reported resistance of *P. malariae* to chloroquine (*27*). The recommended treatment for radical cure of *P. ovale* relapsing malaria is the same as that for *P. vivax*, i.e. ACT or chloroquine combined with primaquine (total dose, 3.5 mg base/kg bw). The high prevalence of G6PD deficiency in areas endemic for *P. ovale* indicates that caution should be exercised in use of primaquine, as stated below. *P. malariae* and *P. knowlesi* do not form hypnozoites and so do not require radical cure with primaquine.

A6.3.4 | ADVERSE EFFECTS AND CONTRAINDICATIONS

Chloroquine is generally well tolerated. Common side-effects include mild dizziness, nausea, vomiting, abdominal pain and itching, and dosing of primaquine is limited by abdominal discomfort at doses > 1 mg/kg bw. In general, primaquine is well tolerated at individual doses ≤ 0.5 mg base/kg bw if given with food. Some methaemoglobinaemia is common but is very seldom dangerous. The main adverse effect of primaquine is oxidant haemolysis, which can be severe, resulting in haemoglobinuria ("blackwater") and severe anaemia. Although some red cell loss may occur in normal subjects, patients who are G6PD deficient are particularly vulnerable.

Figure A6.3. Geographical distribution of G6PD deficiency genotypes (*28*).
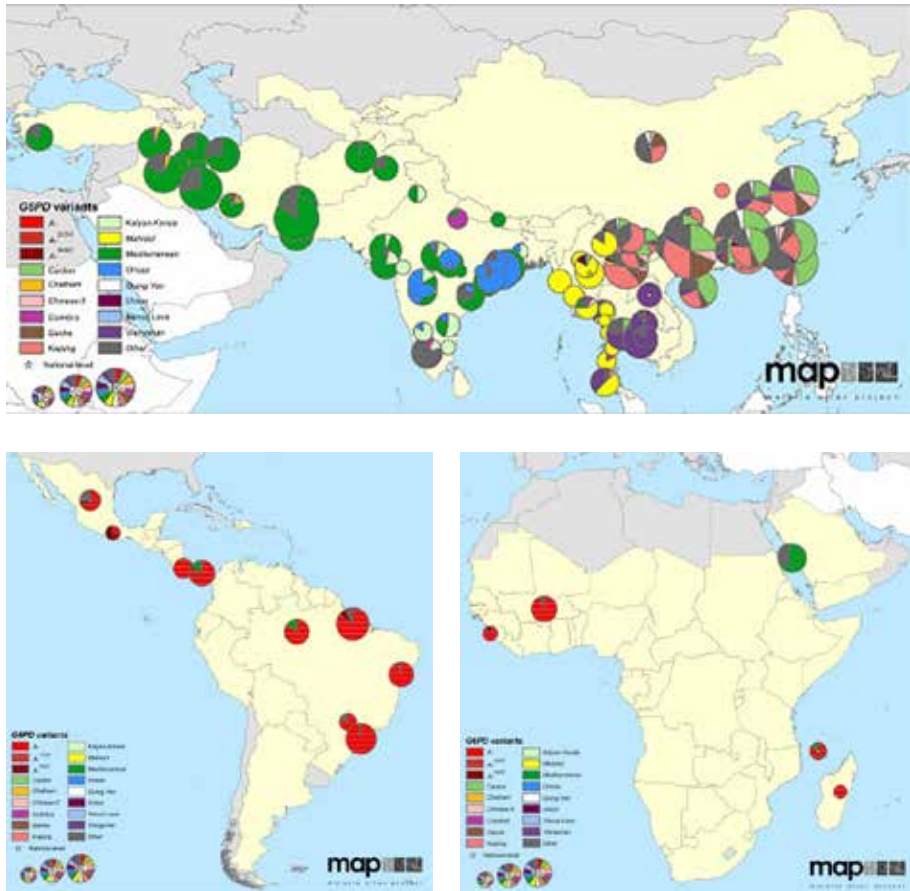
G6PD deficiency is very common, with a prevalence typically ranging from 3% to 35% in tropical areas (Figure A6.3). There are over 180 genetic G6PD variants, nearly all conferring an unstable enzyme, which degrades more rapidly than the normal variant. This renders older red cells vulnerable to oxidant damage (*28*). G6PD is X-linked; thus, males have only one G6PD allele (they are either normal or deficient hemizygotes), whereas females have two (so can be homozygous G6PD normal, homozygous G6PD deficient or heterozygous). Hemizygous males and homozygous females have full expression of G6PD deficiency: the level of G6PD activity in their mature red cells is nearly always 15% of normal or less. Heterozygous females usually have only partial deficiency, and they have been referred to as having "intermediate" deficiency, although, because X-inactivation is a random event that takes place early in embryonic life (termed Lyonization), the proportion of these two cell types is very variable. Thus, although the average ratio of G6PD-deficient to normal red cells is 50:50, some individuals may have a ratio of 70:30 or even more unequal ratios. The severity of oxidant haemolysis in heterozygous females therefore varies from that observed in hemizygous males (if the majority of their red cells are G6PD deficient) to very little haemolysis (if the majority of their red cells are G6PD normal). Importantly, if > 30% of their red cells are not G6PD deficient, heterozygous females will be identified as "normal" in current screening tests.
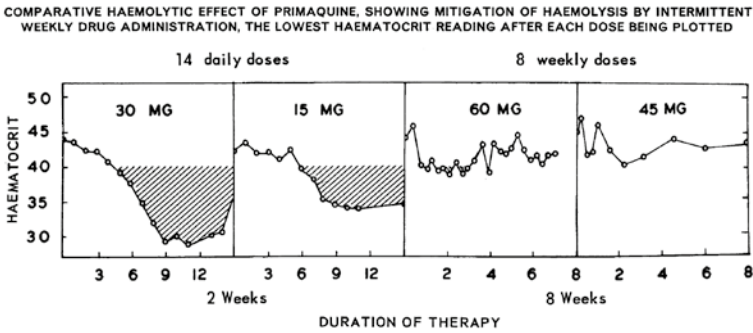
At a population level, the overall fall in haemoglobin in heterozygous females will be, on average, one half of that seen in hemizygous male and homozygous females (*29, 30*). From a clinical standpoint, heterozygotes with > 80% G6PD normal red cells (i.e. < 20% G6PD-deficient red cells) are very unlikely to develop severe haemolytic anaemia. Except in severely deficient individuals, haemolysis typically starts after 1 or 2 days of treatment (when all the remaining red cell oxidant defences have been exhausted). The extent of haemolysis with primaquine depends on the degree of G6PD deficiency and the primaquine dose. Two of the most prevalent G6PD variants represent the two ends of the severity spectrum, with the Mediterranean variant (the main variant found in Europe, West and Central Asia and northern India) being among the most severe and the African A– variant (found in sub-Saharan Africa and in African-Americans) being among the mildest (Figure A6.4). There is also substantial variation in G6PD activity among individuals with the same genotype and even within the same individual over time. With less severe G6PD variants, primaquine-induced haemolysis typically becomes evident after 1 or 2 days of exposure, when the oxidant defences of all the older erythrocytes have been depleted (*29–31*). If primaquine is continued in people with the African A– variant, haemolysis lessens and the haemoglobin concentration starts to rise again, despite further drug administration, as reticulocytes enter the circulation to replace the haemolysed cells.

Figure A6.4. Red cell survival and degree of anaemia following daily primaquine in different G6PD deficiency variants. On the left, red cell survival with different daily doses of primaquine given to adults with the African A− variant of G6PD deficiency. On the right, the average fractional fall in haemoglobin concentration by day 7 (time of the usual nadir) with daily primaquine dosing in people with four different G6PD deficiency variants.
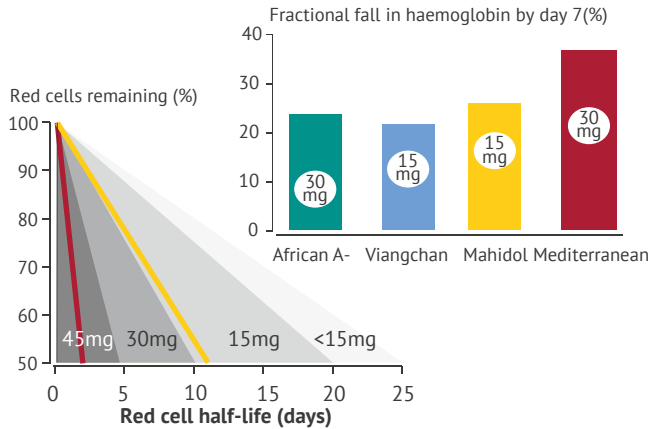
These young red cells entering the circulation contain five times more G6PD than the oldest red cells and so are relatively resistant to the haemolytic effect. Further haemolysis does, however, occur with higher doses (*31*). In contrast, in the Mediterranean variant, haemolysis continues if primaquine is not stopped, and life-threatening anaemia may result. In six decades of primaquine use in approximately 200 million people, 14 deaths have been reported. If the estimate is confined to reports with known denominators, the estimated mortality rate is 1 in 621 428. All but one death occurred subsequent to multiple dosing to prevent vivax malaria relapse (*32, 33*).

Figure A6.5. Haemolysis following different primaquine regimens in people with A- G6PD deficiency. Weekly administration ameliorates the anaemia by allowing haematological recovery after each dose.

COMPARATIVE HAEMOLYTIC EFFECT OF PRIMAQUINE, SHOWING MITIGATION OF HAEMOLYSIS BY INTERMITTENT WEEKLY DRUG ADMINISTRATION, THE LOWEST HAEMATOCRIT READING AFTER EACH DOSE BEING PLOTTED

To reduce the risk for haemolysis of individuals who have G6PD deficiency, an intermittent primaquine regimen of 0.75 mg base/kg bw weekly for 8 weeks can be given, under medical supervision. This regimen was safe and effective in people with the African A– genotype (*34*) (Figure A6.5). Although the regime has been recommended for some 50 years, relatively few studies have been conducted of its efficacy or safety.

The risk for severe haemolysis is virtually confined to G6PD-deficient individuals, which is why testing is so important (*33*). In non-G6PD-deficient individuals, a high dose of primaquine (30 mg/day) has been shown to be safe and effective for both daily prophylaxis and radical treatment. Primaquine is not recommended during pregnancy or in infants < 6 months, as limited data are available on its safety in these groups.

A6.4 | MONITORING THERAPEUTIC EFFICACY

The sensitivity of *P. vivax* to antimalarial drugs must be monitored in order to improve the treatment of vivax malaria, in particular in view of its emerging resistance to chloroquine. A modified version of the standard WHO in-vitro test for determining the antimalarial sensitivity of *P. falciparum* has been used successfully for assessing the sensitivity of *P. vivax* populations and for screening the efficacy of new antimalarial drugs (*35–37*). WHO recently introduced a revised protocol for *in-vivo* monitoring of the therapeutic efficacy of chloroquine in *P. vivax* malaria, which includes measurement of blood chloroquine levels to assess exposure, and use of molecular markers (only available for the *Pvdhfr* gene). Better understanding of the molecular mechanisms underlying drug resistance in *P. vivax* is needed to improve monitoring of chloroquine resistance.

A6.5 | REFERENCES

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# Annex 7 | Resistance to antimalarial medicines

A7.1 | INTRODUCTION

Resistance to antimalarial drugs is a major threat to the control and elimination of malaria. The greatest problem with antimalarial drug resistance is with *Plasmodium falciparum*. All geographical areas are affected, with the exception of Central America, and the worst affected is mainland South-East Asia, where parasites with reduced susceptibility to all the available antimalarial medicines are now prevalent. Resistance to chloroquine in *P. falciparum* has spread across most of the world and caused millions of deaths. Yet, chloroquine resistance appears to have arisen de novo and then spread on only a few occasions. In contrast, resistance to antifolate drugs and atovaquone arises frequently (e.g. antifolate resistance rose to high levels within 2 years of the initial deployment of proguanil in peninsular Malaya in 1947), and it can be induced readily in both *P. falciparum* and *P. vivax* (*1*). Against a background of chloroquine resistance, mefloquine resistance arose over a 6-year period on the north-west border of Thailand (*2*). Genetically encoded resistance to the artemisinin derivatives in *P. falciparum* has emerged recently in South-East Asia and is now affecting therapeutic responses to ACTs (*3–5*). Piperaquine resistance has begun to emerge in Cambodia. Resistance also occurs in *P. vivax;* high-level resistance to chloroquine is prevalent in Indonesia and Papua New Guinea, and lower levels of resistance have been reported in several other areas of Asia and the Americas (*6*). Antifol resistance is also common in *P. vivax*. There are very few reports of resistance in *P. malariae* or *P. ovale* (although there have also been very few studies).

Currently, there are no "bedside" tests for determining the susceptibility of malaria parasites to antimalarial medicines. Monitoring is therefore needed to determine geographical trends in susceptibility and the emergence and spread of drug resistance to guide treatment choices and planning.

A7.2 | DEFINITION

Antimalarial drug resistance is defined as the ability of a parasite strain to survive or multiply despite the proper administration and absorption of an antimalarial drug at the recommended dose. Drug resistance to an antimalarial compound reflects a right-hand shift in the concentration–effect (dose–response) relation (Fig. A7.1).

Figure A7.1 The concentration–effect relationship.
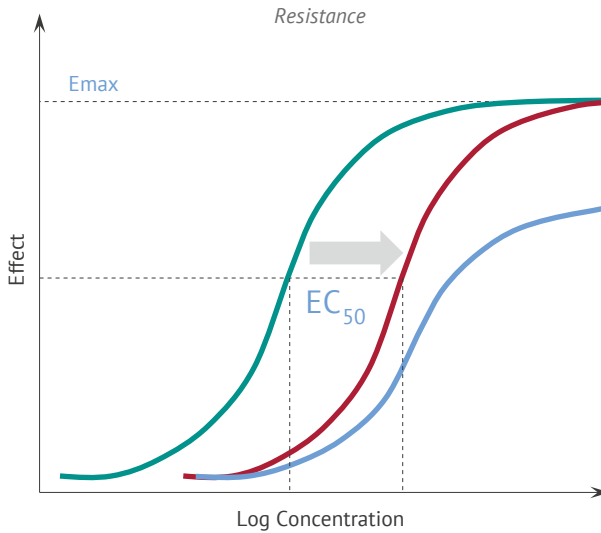
Resistance is a right-hand shift in the concentration–effect relation for a particular malaria parasite population. It may be a parallel shift (red) from the "normal" profile (green), or, in some circumstances, the slope changes or the maximum achievable effect (E_{max}) is reduced (blue). The effect measured in vivo is parasite killing (reflected by reduction in parasite density), and that in vitro is usually a measure of parasite development, such as schizont maturation or uptake of ³H-hypoxanthine or some other labelled substrate. The concentration associated with half of the maximum effect is the EC_{50}. In-vitro susceptibility tests usually report EC_{50} (termed IC_{50}).

A7.2.1 | PHARMACOKINETICS

The pharmacokinetic properties of antimalarial drugs vary widely in different individuals, so that infective malaria parasites may encounter very different blood concentrations of antimalarial medicines in patients who receive similar mg/kg bw doses (Figure A7.2). Clinical characterization of resistance should therefore also include measurement of blood or plasma concentrations to distinguish true resistance from inadequate drug exposure. 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, such as proguanil), it is also necessary if possible to show adequate conversion to the active metabolite.

Figure A7.2 Pharmacokinetics and pharmacodynamics of antimalarial drugs.
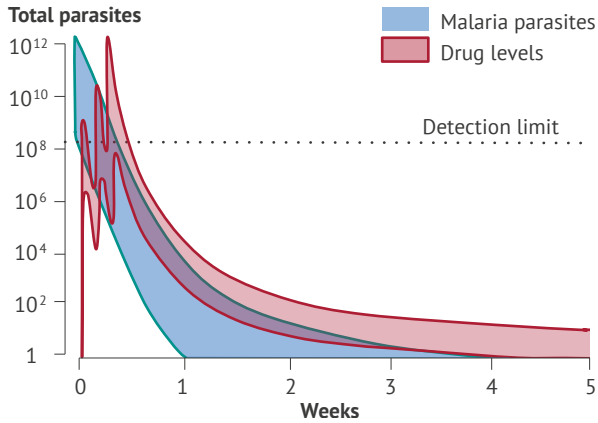
Shows the range of total numbers of parasites in the body (blue) and antimalarial drug concentrations in blood (red) that typically occur in adult patients after administration of a slowly eliminated antimalarial drug. When the drug is combined with an artemisinin derivative to form an ACT, the initial decrease in parasite numbers is much greater (section A7.4).

A7.2.2 | LEVELS OF RESISTANCE

The main consequence of antimalarial drug resistance is treatment failure. At low levels of resistance, there are no early treatment failures, but the proportion of patients with late recrudescence increases. As the level of resistance rises, recrudescence occurs earlier and earlier, until, with high-grade resistance, eventually parasitaemia fails to clear or, worse still, continues to increase (7). Slowing of parasite clearance is an indicator of increasing resistance. In artemisinin resistance, slow parasite clearance is the main manifestation of resistance (reflecting loss of susceptibility of the ring-stage parasites) (3). Increasing rates of gametocytaemia are another important manifestation, which may precede detectable increases in treatment failure rates (8). This is an important driver of the spread of antimalarial drug resistance.

Antimalarial drug resistance is not the only cause of "treatment failure", which is failure to clear malaria parasitaemia or to resolve clinical symptoms despite use of an antimalarial drug at correct doses. Incorrect dosing, incomplete adherence (compliance), poor drug quality, interactions with other drugs, compromised drug absorption, vomiting of the medicine, unusual pharmacokinetics or misdiagnosis of the disease are other causes. Treatment failure is dangerous for the patient and also for the community, as it increases malaria transmission and fuels the emergence and spread of antimalarial drug resistance.

A7.3 | EMERGENCE AND SPREAD OF ANTIMALARIAL DRUG RESISTANCE

A7.3.1 | MOLECULAR BASIS

The genetic events that confer antimalarial drug resistance (without seriously damaging the parasites) are spontaneous and rare. They occur independently of the drug but are then selected by the drug, which kills sensitive parasites but not resistant ones. The resistance mechanisms that have been described to date are mutations or changes in the copy number of genes related either to the drug targets (e.g. *Pfdhfr*) or to the pumps (e.g. *Pfmdr*) that affect intraparasitic concentrations of the drug. A single genetic event may be all that is required to confer resistance, or multiple unlinked events may be necessary (epistasis). *P. falciparum* parasites in South-East Asia appear constitutionally to have an increased propensity to develop drug resistance.

A7.3.2 | DEVELOPMENT OF RESISTANCE

The development of resistance can be considered in two parts: the initial rare genetic event, which produces the resistant mutant, and the subsequent selection process, in which the survival advantage in the presence of the antimalarial drug leads to preferential transmission of resistant mutants and, thus, to the spread of resistance. In the absence of the antimalarial drug, resistant mutants usually have a survival disadvantage. Provided the mutations have not gone to fixation (i.e. while wild-type parasites are still prevalent), this "fitness cost" of the resistance mechanism may result in a decrease in the prevalence of resistance once the selection pressure is removed. This happened in Malawi when chloroquine was withdrawn: susceptibility to chloroquine returned (*9*). Resistance to one drug may select for resistance to another when the mechanisms of resistance are similar (cross-resistance). There are many parallels with antibiotic resistance, particularly to anti-tuberculosis drugs, for which, as for malaria, transferable resistance genes are not involved in resistance (*10, 11*). In experimental models, resistance mutations can be selected without passage through the mosquito (i.e. during mitotic cell

division) by exposing large numbers of malaria parasites (either in vitro, in animals or, as was done in the past, in volunteers) to sub-therapeutic drug concentrations *(12)*. This allows growth of any spontaneously emerging resistant mutants while suppressing the majority drug-sensitive parasite population. The same factors underlie the selection of resistance in natural parasite populations. This explains why under-treatment of hyperparasitaemic individuals is such a potent source of resistance *(13)*.

The factors that determine a propensity for antimalarial drug resistance to develop include (*7, 14*):

- the intrinsic frequency with which the genetic changes occur:
- the degree of resistance (the rightwards shift in the concentration–effect relation (Figure A7.1) conferred by the genetic change;
- the fitness cost of the resistance mechanism;
- the proportion of all transmissible infections that are exposed to the drug (selection pressure);
- the number of parasites exposed to the drug;
- the concentrations of drug to which these parasites are exposed;
- the pharmacokinetics and pharmacodynamics of the antimalarial drug(s);
- individual (dosing, duration, adherence) and community patterns of drug use (quality, availability, distribution);
- the immunity profile of the community and the individual; and
- the simultaneous presence of other antimalarial drugs or substances in the blood to which the parasite is not resistant.

The emergence of resistance reflects the product of the probability of de-novo emergence (a rare event) and of subsequent spread. Because de-novo resistance arises randomly among malaria parasites, non-immune patients infected with large numbers of parasites who receive inadequate treatment (because of poor drug quality, poor adherence, vomiting of an oral treatment, etc.) are such an important source of de-novo resistance (*13*). This underlines the importance of correct prescribing, good adherence to prescribed drug regimens and the provision of treatment regimens that are still highly effective in hyperparasitaemic patients. Immunity provides a powerful "brake" on the emergence of resistance by reducing the chances that resistant parasites can survive and spread.

The spread of resistant mutant malaria parasites is facilitated by 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 (*15*). Slowly eliminated drugs, such as mefloquine (terminal elimination half-life ($t_{\frac{1}{2}\beta}$), 2–3 weeks), piperaquine ($t_{\frac{1}{2}\beta}$ 4 weeks) and chloroquine ($t_{\frac{1}{2}\beta}$ 1–2 months), persist in the blood and provide a selective filter for weeks or months after drug administration has ceased.

A7.3.3 | 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 propagation of resistance *(7, 16)*. Epidemiological studies clearly implicate low-transmission settings, where patients often have little or no immunity, as the source of drug resistance. Resistance in *P. falciparum* to chloroquine, sulfadoxine–pyrimethamine, mefloquine, atovaquone and now artemisinins all originated in South-East Asia. Chloroquine and pyrimethamine resistance spread subsequently to Africa (*17*).

In low-transmission areas, although asymptomatic carriage is common in focal areas, a high proportion of malaria infections are symptomatic, and selection of drug resistance therefore takes place in the context of treatment. Large numbers of parasites (>10^8) in an individual usually encounter antimalarial drugs at concentrations that are maximally effective. But, in some patients, for the reasons mentioned earlier, the blood concentrations of antimalarial drugs are much lower and may select for resistance. Immunity considerably reduces the emergence of resistance (*7*). Host defence contributes a major anti-parasitic effect, and so any spontaneously generated drug-resistant mutant malaria parasite must contend not only with the concentrations of antimalarial drug present but also with host immunity (*18*). 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 antimalarial drugs, both to eliminate the rare de-novo resistant mutants and to stop them from being transmitted (i.e. like 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 (*18*). Even if a resistant mutant parasite 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. In high-transmission settings, individuals are commonly infected with many different parasite genotypes, which increases the possibility of out-breeding of multi-genic resistance mechanisms or competition in the feeding anopheline mosquito (*19*). In areas of high malaria transmission, people still receive antimalarial treatment throughout their lives (often inappropriately for other febrile infections), but these "treatments" are largely unrelated to the peaks of parasitaemia. This substantially reduces the probability of selecting resistant parasites.

A7.3.4 | PHARMACOKINETICS OF ANTIMALARIAL DRUGS AND SELECTION OF RESISTANCE

Absorption and disposition

The probability of selecting a de-novo mutation depends on the degree of resistance that results from it. If a single mutation confers high-level resistance, selection occurs readily; however, resistance usually develops in a series of steps, the initial step being low-level resistance. If the range of blood concentrations achieved in a patient considerably exceeds the concentrations that result in 90% inhibition of multiplication (IC_{90} values) for the most resistant mutant (IC_{90}^{R}), then resistance cannot be selected in the acute phase of treatment, as even the resistant mutants are prevented from multiplying. If, however, the peak concentrations are close to or below the IC_{90}^{R}, resistance may be selected (*20*). Peak drug concentrations are determined mainly by absorption, distribution volume and dose. Several antimalarial drugs (notably lumefantrine, atovaquone and, to a lesser extent, mefloquine) are lipophilic, hydrophobic and variably absorbed (inter-individual variation in bioavailability of up to 20-fold); the distribution volumes also vary substantially among individuals. This results in considerable inter-individual variation in peak blood concentrations of the drugs (*21*). As a result, some patients may have very low levels despite receiving "correct dosing" (previous dosing recommendations for young children have often been too low); usually, however, under-dosing results from incorrect dosing. The main sources of under-dosing globally are incorrect self-medication, because of poor adherence to a 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 at home (*22*). Quality-assured drugs, education, correct prescribing, optimized doses, good adherence and high-quality packaging and formulations therefore play major roles in preventing the emergence of antimalarial drug resistance.

Drug elimination rates

In high-transmission settings, a person who takes an antimalarial drug for symptomatic malaria exposes not only the parasites that are causing that infection but also all the newly acquired infections that emerge from the liver during the drug's elimination phase. The longer the terminal elimination half-life of the drug, the greater the exposure. Slow drug elimination is particularly relevant to the spread of resistance and is less important for de-novo selection (*13, 15, 23*). Some rapidly eliminated antimalarial drugs (e.g. the artemisinin derivatives) never present an intermediate concentration to infecting malaria parasites, because they are eliminated completely within the 2-day life cycle of the asexual parasite (*20*). Others (e.g. desethylamodiaquine, pyronaridine, mefloquine, piperaquine and

chloroquine) have elimination half-lives of weeks or months and thus present a lengthy selection opportunity. Obviously, the greater the degree of resistance (i.e. the higher the IC_{90}^R relative to the IC_{90} for susceptible parasites, IC_{90}^S), the wider is the window of selection opportunity ([20]). Selection occurs only during the terminal phase if prevalent parasites are inhibited by these low concentrations. As the prevalence and degree of resistance rise, these low concentrations become ineffective, and so selection no longer occurs during the terminal elimination phase. With the exception of the artemisinin derivatives, maximum antimalarial parasite reduction ratios (kill rates) do not usually exceed 1000-fold per cycle ([24]). Following hepatic schizogony, exposure of at least two asexual cycles (4 days) to therapeutic drug concentrations is required to eradicate the blood-stage parasites emerging from the liver (suppressive prophylaxis). As a result, rapidly eliminated drugs such as the artemisinin derivatives or quinine provide little or no selection during the elimination phase ([20]).

## A7.3.5 | SPREAD OF RESISTANCE

The spread of resistance is determined by the reproductive advantage conferred by the resistance mechanism. This results from the increased gametocyte carriage associated with resistance (both from the primary infection and from subsequent recrudescence), the "donors" and the selective pressure from residual concentrations of slowly eliminated antimalarial drug in potential recipients ([15]).

Resistance encoded by multiple mutations at a single locus generally occurs in two overlapping phases: in phase 1, the drug is better tolerated by the parasites, but the therapeutic doses still usually clear the infection; in phase 2, clinical failures start to occur. As the second phase is very rapid, it is essential that surveillance programmes be in place and are 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 surveillance is still vital to detect early signs of resistance.

A7.4 | PREVENTION OF RESISTANCE BY USE OF COMBINATION THERAPY

The theory underlying combination treatment of tuberculosis, leprosy and HIV infection is well known; it also applies to malaria (*7, 10, 11, 13, 21, 24*). Combination therapy slows the emergence of resistance. If two drugs with different modes of action and, therefore, different resistance mechanisms are used in combination, the per-parasite probability of developing resistance to both drugs is the product of their individual per-parasite probabilities. The lower the de-novo per-parasite probability of developing resistance, the greater is the delay in the emergence of resistance.

The ideal pharmacokinetics for an antimalarial drug has 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 for a combination to be effective in a 3-day regimen, the elimination half-life of at least one component must exceed 24 h. Artemisinin derivatives are particularly effective in combinations with other antimalarial drugs because of their high killing rates (parasite reduction rate, around 10 000-fold per cycle), lack of adverse effects and the absence of significant resistance outside South-East Asia (*2*). Combinations of artemisinin derivatives (which are eliminated very rapidly) given for 3 days with slowly eliminated drugs, such as lumefantrine, mefloquine and piperaquine, 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 the slowly eliminated partner unprotected (*25*). Resistance can arise in any parasite and could therefore arise within the residual parasites that have not yet been killed by the artemisinin derivative; however, the number of parasites exposed to the partner drug alone represents a tiny fraction (< 0.00001%) of those present in an acute symptomatic infection. Furthermore, these residual parasites "see" relatively high levels of the partner, and, even if susceptibility is reduced, these levels may be sufficient to eradicate the infection (Figure A7.3). The long tail of low concentrations does, however, provide a selective filter for resistant parasites acquired from elsewhere and therefore contributes to the spread of resistance once it has developed. 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 effective in stopping resistance and also in reducing the incidence of malaria (*2*). In that location, the mefloquine−artesunate ACT remained highly effective for 15 years, before artemisinin resistance emerged and failure rates increased again.

Figure A7.3. Pharmacokinetics and pharmacodynamics of ACTs.
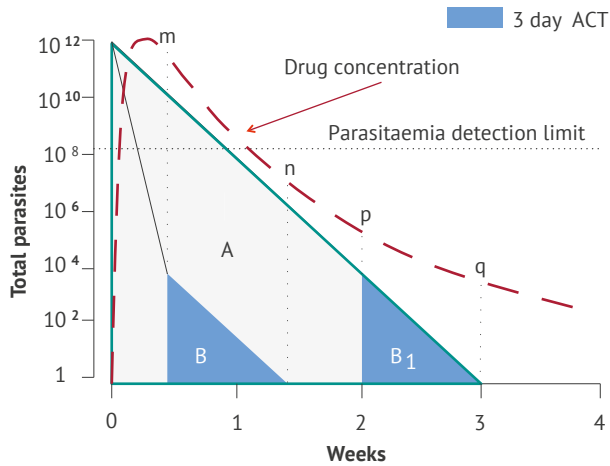
The artesunate + mefloquine combination is shown as an example. If no artesunate is given, the number of parasites exposed to mefloquine alone is shown by the area of A; when the combination is administered for 3 days, the number of parasites exposed to mefloquine alone is shown by the area of B (100 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 (p to q). If a parasite containing a de-novo mefloquine-resistant mutation were to occur, it 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 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.

A7.5 | MONITORING ANTIMALARIAL DRUG RESISTANCE

A7.5.1 | MONITORING METHODS

Clinical methods

The rapid spread of antimalarial drug resistance over the past few decades shows the importance of monitoring for proper management of clinical cases, early detection of changing patterns of resistance and indicating where national malaria treatment policies should be revised. Recommendations and methods for testing therapeutic efficacy in vivo are described in detail in WHO publications (*26, 27*). They involve assessing the outcome of treatment during a fixed period of follow-up (≥ 28 days) to detect malaria recurrence, i.e. any reappearance of symptoms and signs of clinical malaria and/or parasites in the blood. When possible, this is accompanied by at least one measurement of the slowly eliminated partner antimalarial drug in blood or plasma (usually on day 7 as all patients must be seen on this day in therapeutic assessments). Methods have been developed for measuring the concentrations of several antimalarial drugs in dried blood spots on filter paper, which considerably facilitates field studies (*28*). In endemic areas, recrudescence can be distinguished from reinfection by molecular genotyping (*27*).

Assessing resistance to artemisinins

Recrudescence rates are less informative in assessing resistance to artemisinins, as these drugs are given in combination. The key measure is the parasite clearance rate, which is measured from the log-linear decrease in parasite density, which occurs after a variable lag phase from the start of treatment (Figure A7.4). In-vivo methods for assessing artemisinin resistance require frequent measurement of parasite counts (at least three counts in the first 24 h) in patients with high enough parasite counts (at least 10 000/µL), from which parasite clearance rates are derived. The result is usually expressed as the parasite clearance half-life ($PCt_{1/2}$) (*29, 30*). The $PCt_{1/2}$ values of fully sensitive infections are usually < 3 h, whereas those of resistant infections are > 5 h, although there is some overlap. The levels of artemisinin and its derivatives are usually not measured, as these drugs are eliminated rapidly and their assessment requires immediate plasma separation, centrifugation and storage at −70 °C (*28*).

Figure A7.4. Parasite clearance curves. After a variable lag phase, parasitaemia decreases log-linearly. The slope of the linear segment gives the parasite clearance rate, from which the parasite clearance half-life ($PCt_{1/2}$) is derived. This is independent of the initial parasite density, whereas the parasite clearance time is strongly dependent on initial density. Artemisinin resistance (red profile) is associated with slowing of parasite clearance, typically to $PCt_{1/2} > 5$ h.
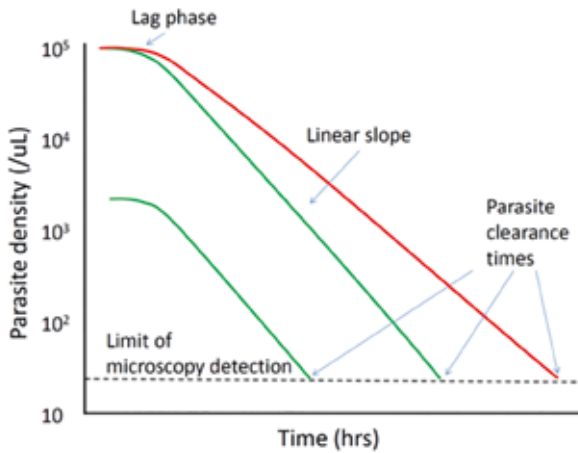
Laboratory methods

Other indirect methods to assess antimalarial resistance include in-vitro studies of parasite susceptibility to drugs in culture, studies of point mutations or duplications in parasite resistance genes with molecular methods and measurement of the concentrations of antimalarial drugs in blood. These provide valuable early warning signs of resistance. In-vitro tests for *P. falciparum* have been available for several decades, but there is still substantial variation in methods, analysis and performance between laboratories. In-vitro testing for *P. vivax* in fresh blood samples is still confined to research centres. In-vitro assessment of artemisinin resistance in *P. falciparum* requires testing for ring-stage susceptibility in special assays, as the results of conventional testing do not correlate well with parasite clearance rates (*3*).

Understanding of the molecular basis of antimalarial drug resistance has increased considerably in recent years. In many cases, multiple genetic changes are involved, but genotyping of malaria parasites (usually from a filter paper blood spot) by polymerase chain reaction can be used operationally to identify the principle genetic correlate of resistance. Reduced susceptibility to sulfadoxine–pyrimethamine is predicted well as single nucleotide polymorphisms in the *Pfdhfr* and *Pfdhps* genes for *P. falciparum* and *Pvdhfr* genes, and detection of these mutations is valuable in determining resistance patterns. Polymorphisms in the chloroquine resistance transporter gene *Pfcrt* predict resistance to chloroquine and to a lesser extent amodiaquine, and polymorphisms in the cytochrome bc1 complex gene (*cytbc1*) predict resistance to atovaquone. Amplification of the wild-type *Pfmdr1* gene is

associated with resistance to mefloquine and to a lesser extent lumefantrine, whereas mutations in the gene are associated with resistance to chloroquine and amodiaquine. Artemisinin resistance is associated with mutations in the "propeller region" of the *P. falciparum* kelch protein gene on chromosome 13 (PfK13).

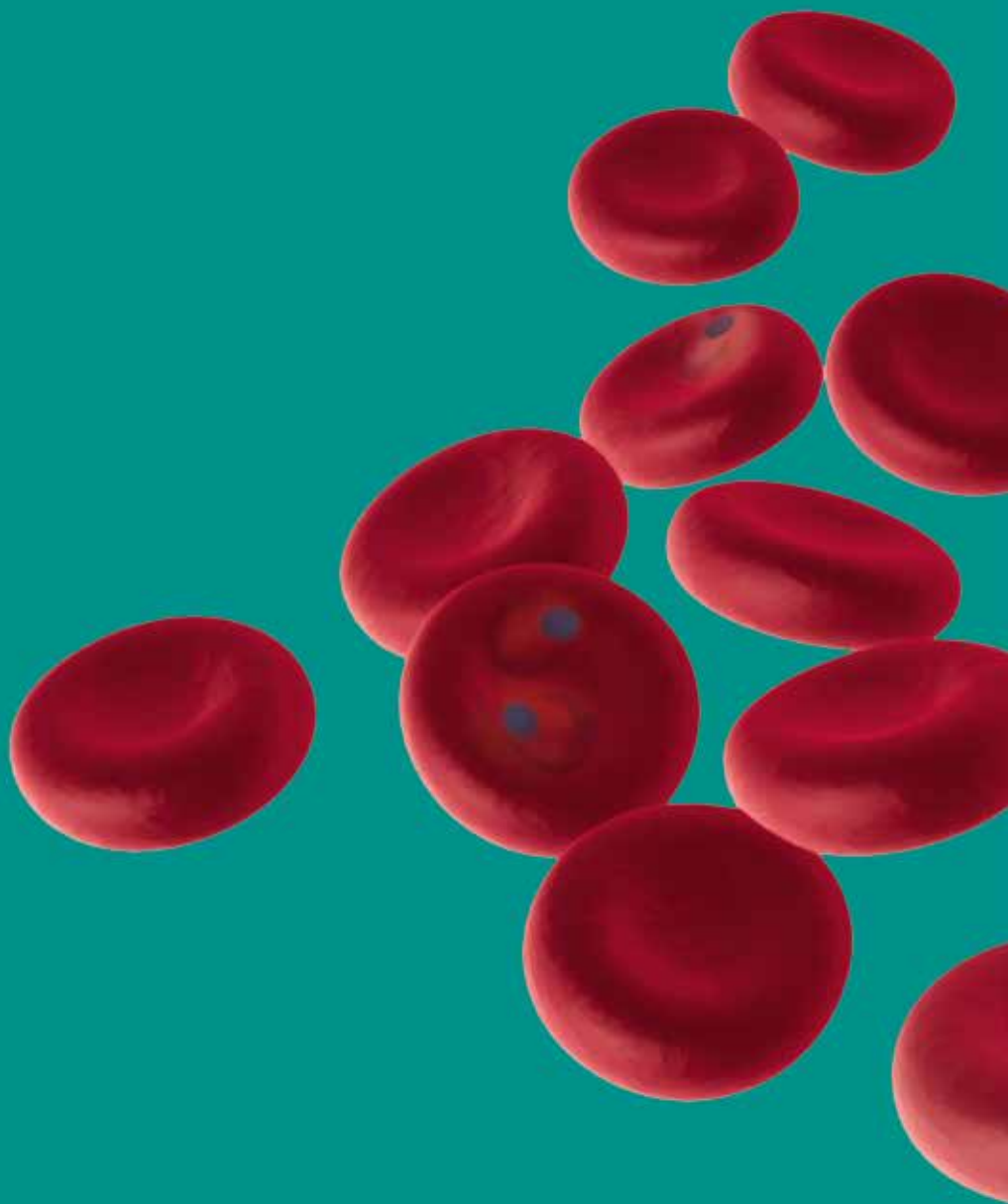## A7.5.2 | REPORTING OF TREATMENT FAILURES

Reports of treatment failure and decreased drug sensitivity have often provided an important first indication of more widespread resistance in an area. Although such evidence may be biased, it can be collected without much effort at peripheral health centres. Reports of treatment failure are particularly useful if accompanied by measurement of the level of the (slowly eliminated) antimalarial drug at the time of recurrent infection (to assess exposure) and storage of blood samples for molecular genotyping and, if possible, parasite culture. If such reports are standardized and registered, they can make a valuable contribution to national early-warning systems and facilitate cost-effective monitoring by national programmes (*26*).

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30. Flegg JA, Guérin PJ, Nosten F, Ashley EA, Phyo AP, Dondorp AM, et al. Optimal sampling designs for estimation of *Plasmodium falciparum* clearance rates in patients treated with artemisinin de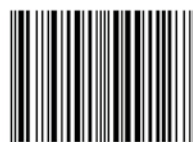rivatives. Malar J 2013;12:e411.