EXECUTIVE SUMMARY

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

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

TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA

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

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

- Pregnancy

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

Second and third trimesters:

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

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

TREATMENT OF SEVERE MALARIA

- Severe malaria is a medical emergency. After rapid clinical assessment and confirmation of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay with whichever effective antimalarial is first available.
- For adults, artesunate IV or IM:
  - artemether or quinine is an acceptable alternative if parenteral artesunate is not available.
- For children, artesunate IV or IM
  - artemether or quinine is an acceptable alternative if parenteral artesunate is not available.
- Give parenteral antimalarials in the treatment of severe malaria for a minimum of 24 h, once started (irrespective of the patient's ability to tolerate oral medication earlier) and, thereafter, complete treatment by giving a complete course of:
  - an ACT;
  - artesunate plus clindamycin or doxycycline;
  - quinine plus clindamycin or doxycycline.
- If complete treatment of severe malaria is not possible, patients should be given pre-referral treatment and referred immediately to an appropriate facility for further treatment. The following are options for pre-referral treatment : rectal artesunate, quinine IM, artesunate IM, artemether IM.

TREATMENT OF UNCOMPLICATED *P. VIVAX* MALARIA

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

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

MALARIA DIAGNOSIS

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

TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA

- Artemisinin-based combination therapies should be used in preference to sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) for the treatment of uncomplicated *P. falciparum* malaria.

  Strong recommendation, moderate quality evidence.
- ACTs should include at least 3 days of treatment with an artemisinin derivative.

  Strong recommendation, high quality evidence.
- Dihydroartemisinin plus piperaquine (DHA+PPQ) is an option for the first-line treatment of uncomplicated *P. falciparum* malaria worldwide.

  Strong recommendation, high quality evidence.
- Addition of a single dose primaquine (0.75 mg/kg) to ACT treatment for uncomplicated falciparum malaria as an antigametocyte medicine, particularly as a component of pre-elimination or an elimination programme.

TREATMENT OF SEVERE *P. FALCIPARUM* MALARIA

- Intravenous (IV) artesunate should be used in preference to quinine for the treatment of severe *P. falciparum* malaria in adults.

  Strong recommendation, high quality evidence.

TREATMENT OF UNCOMPLICATED *P. VIVAX* MALARIA

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

  Weak recommendation, moderate quality evidence.
- At least a 14-day course of primaquine is required for the radical treatment of *P. vivax.*

  Strong recommendation, very low quality evidence.

BOX 6.1

Summary of recommendations on **PARASITOLOGICAL DIAGNOSIS**

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

7. TREATMENT OF UNCOMPLICATED *P. FALCIPARUM* MALARIA

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

7.1 Definition of uncomplicated malaria

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

7.2 Rationale for antimalarial combination therapy

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

7.2.1 Non-artemisinin based combination therapy

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

BOX 7.1

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

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

GRADE evaluation (*see* Annex 7, tables A7.1.1–A7.1.4)
In trials comparing AQ+SP to the recommended ACTs, the performance of AQ+SP is highly variable. Treatment failure rates at day 28 (after polymerase chain reaction [PCR] adjustment) are as high as 16% in Uganda and 24% in Rwanda. In addition, AQ+SP is less effective at reducing gametocyte carriage than combinations containing an artemisinin derivative. AQ+SP performed adequately in trials from Senegal in 2003, Burkina Faso in 2005, and Madagascar in 2006.

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

7.2.2 Artemisinin-based combination therapy

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

in combination with slowly eliminated antimalarials. With this shorter 3-day course, the complete clearance of all parasites is dependent on the partner medicine being effective and persisting at parasiticidal concentrations until all the infecting parasites have been killed. Thus, the partner compounds need to be relatively slowly eliminated. This also results in the artemisinin component being protected from resistance by the partner medicine, while the partner medicine is also partly protected by the artemisinin derivative.

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

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

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

Box 7.2

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

▶ **ACTs should include at least 3 days of treatment with an artemisinin derivative.**
Strong recommendation, high quality evidence

GRADE evaluation (*see* Annex 7, Table A7.2.1)
In trials comparing the addition of 3 days of artesunate to sulfadoxine-pyrimethamine with adding 1 day of artesunate, there was a significant reduction in treatment failure at day 28 with the 3-day combination (5 trials, 1634 participants; relative risk [RR] 0.62, 95% confidence interval [CI] 0.55–0.69).

7.3 ACT options

Although there are some minor differences in oral absorption and bioavailability between the different artemisinin derivatives, there is no evidence that these differences are clinically significant in currently available formulations. It is the properties of the partner medicine that determine the efficacy and choice of combination. Resistance to the artemisinins' partner medicines compromises the efficacy of the ACT.

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

BOX 7.3

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

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

GRADE evaluation (*see* Annex 7, tables A7.3.1–A7.3.3)
In clinical trials directly comparing DHA+PPQ and the currently recommended ACTs, DHA+PPQ was at least as effective at treating uncomplicated *P. falciparum* malaria (as measured by PCR adjusted treatment failure) as:

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

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

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

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

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

7.3.1 Deployment considerations affecting choice

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

Resistance and tolerability to the partner medicines of artemisinins in ACTs may affect choice. In many countries, artemether plus lumefantrine, artesunate plus mefloquine or dihydroartemisinin plus piperaquine may give the highest cure rates. The main reason for restricting the use of AS+MQ in African children so far has been excessive vomiting associated with mefloquine at the recommended dose of 25 mg/kg. However, a recent study[8] found that in children weighing 10–20 kg (mean age of the study population was 4.5 ± 1.7 years) the tolerability of AS+MQ is as good as with artemether-lumefrantrine.

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

7.4 Management of treatment failures

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

Wherever possible, treatment failure must be confirmed parasitologically – preferably by blood slide examination (as *P. falciparum* histidine-rich protein-2 (*Pf*HRP2)-based tests

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

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

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

7.4.1 Failure within 14 days

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

7.4.2 Second-line antimalarial treatments

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

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

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

7.4.3 Failure after 14 days

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

BOX 7.4

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

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

7.5 Practical aspects of treatment with recommended ACTs

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

7.5.1 Artemether plus lumefantrine

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

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

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

7.5.2 Artesunate plus amodiaquine

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

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

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

7.5.3 Artesunate plus mefloquine

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

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

Mefloquine is associated with an increased incidence of nausea, vomiting, dizziness, dysphoria and sleep disturbance in clinical trials, but these are seldom debilitating – where this ACT has been deployed it has been well tolerated. To reduce acute vomiting and optimize absorption, the 25 mg/kg dose is usually split and given either as 15 mg/kg

(usually on the second day) followed by 10 mg/kg one day later, or as a daily dose of 8.3 mg/kg for 3 days. (*see* Annex 3, Sections A3.5, A3.6.3,)

7.5.4 Artesunate plus sulfadoxine-pyrimethamine

This is currently available as separate scored tablets containing 50 mg of artesunate and tablets containing 500 mg of sulfadoxine and 25 mg of pyrimethamine.[9]

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

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

7.5.5 Dihydroartemisinin plus piperaquine

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

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

7.5.6 Artesunate plus tetracycline or doxycycline or clindamycin

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

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

7.6 Incorrect approaches to treatment

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

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

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

In endemic regions, some semi-immune malaria patients could be cured using an incomplete dose or treatment regimens that would be unsatisfactory in patients with no immunity. In the past, this had led to different recommendations for patients considered as semi-immune and those considered as non-immune. This practice is no longer recommended. A full treatment course with a highly effective ACT is required whether or not the patient is considered to be semi-immune.

Another potentially dangerous practice is to give only the first dose of the treatment course for patients with suspected but unconfirmed malaria, with the intention of giving full treatment if the diagnosis is eventually confirmed. This practice is also unsafe and not recommended. If malaria is suspected and the decision to treat is made, then a full effective treatment is required whether or not the diagnosis is confirmed by a test.

With the exception of lumefantrine, the partner medicines of all other ACTs have been used previously as monotherapies, and amodiaquine, mefloquine and SP continue to be available as monotherapy in many countries. Despite recommendations and warnings, artemisinin derivatives are available as monotherapy in the market place in many countries, and they are being used as such for the treatment of uncomplicated malaria. The continued use of artemisinins or any of the partner medicines, such as monotherapies, can compromise the value of ACTs by selecting for drug resistance.

7.7 Additional considerations for clinical management

7.7.1 Can the patient take oral medication?

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

7.7.2 Use of antipyretics

Fever is a cardinal feature of malaria, and is associated with constitutional symptoms of lassitude, weakness, headache, anorexia and often nausea. In young children, high fevers are associated with vomiting, often regurgitating their medication, and seizures. Treatment is with antipyretics and, if necessary, fanning and tepid sponging. Antipyretics

should be used if core temperatures > 38.5 °C. Paracetamol (acetaminophen) 15 mg/kg every 4 hours is widely used; it is safe and well tolerated, given orally or as a suppository. Ibuprofen (5 mg/kg) has been used successfully as an alternative in malaria and other childhood fevers, although there is less experience with this compound. Acetylsalicylic acid (aspirin) should not be used in children because of the risks of Reye's syndrome.

7.7.3 Use of antiemetics

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

7.7.4 Management of seizures

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

7.8 Operational issues in treatment management

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

7.8.1 Home-based management of malaria

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

7.8.2 Health education

At all levels, from the hospital to the community, education is vital to optimizing antimalarial treatment. Clear guidelines in the language understood by the local users, posters, wall charts, educational videos and other teaching materials, public awareness campaigns, education and provision of information materials to shopkeepers and other dispensers can all improve the understanding of malaria. This will increase the likelihood of improved prescribing and adherence, and appropriate referral, and will minimize the unnecessary use of antimalarials.

7.8.3 Adherence to treatment

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

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

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

7.8.4 Quality assurance of antimalarial medicines

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

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

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

7.8.5 Pharmacovigilance

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

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

7.9 Treatment in specific populations and situations

7.9.1 Pregnant women

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

7.9.1.1 First trimester

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

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

7.9.1.2 Second and third trimesters

There is increasing experience with artemisinin derivatives in the second and third trimesters (over 1500 documented pregnancies). There have been no adverse effects on the mother or fetus. The current assessment of benefits compared with potential risks suggests

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

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

BOX 7.5

RECOMMENDATIONS: *treatment of uncomplicated falciparum malaria in pregnancy*

▶ **First trimester:**

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

▶ **Second and third trimesters:**

- ACT[b] known to be effective in the country/region or artesunate plus clindamycin to be given for 7 days or quinine plus clindamycin to be given for 7 days.
  Pharmacovigilance programmes need to be established to continually monitor safety of antimalarial medicines in all trimesters, including inadvertent exposures in the early first trimester.

a. If clindamycin is unavailable or unaffordable, then the monotherapy should be given.
b. With the exception of DHA+PPQ for which there is insufficient information in second and third trimesters of pregnancy to use as first-line therapy.

7.9.2 Lactating women

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

BOX 7.6

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

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

7.9.3 Infants and young children

7.9.3.1 Choice of antimalarial drug

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

The artemisinin derivatives are safe and well tolerated by young children, and so the choice of ACT will be determined largely by the safety and tolerability of the

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

Delay in treating *P. falciparum* malaria in infants and young children may have fatal consequences, particularly for more severe infections. The uncertainties noted above should not delay treatment with the most effective drugs that are available, with attention to accurate dosing and ensuring the administered dose is retained, as infants are more likely to vomit or regurgitate antimalarial treatment than older children or adults. Taste, volume, consistency and gastrointestinal tolerability are important determinants of whether the child retains the treatment. Mothers often need advice on techniques of medicine administration and the importance of administering the drug again if it is regurgitated within an hour of administration. Because deterioration in infants can be rapid, there should be a much lower threshold for the use of parenteral treatment.

7.9.3.2 Dosing

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

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

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

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

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

BOX 7.7

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

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

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

7.9.4 Large adults

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

7.9.5 Travellers

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

given below are that effective medicines should be used to treat travellers; if the patient has taken chemoprophylaxis, then the same medicine should not be used for treatment. The treatment for *P. vivax*, *P. ovale* and *P. malariae* in travellers should be the same as for these infections in patients from endemic areas (*see* Section 9).

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

BOX 7.8

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

▶ **For travellers returning to non-endemic countries with uncomplicated malaria:**[a]

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

▶ **For severe malaria:**

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

a. Halofantrine is not recommended as first-line treatment for uncomplicated malaria because of cardiotoxicity.
b. Doxycycline should not be used in children under 8 years of age.

BOX 7.9

Summary recommendations on the **TREATMENT OF FALCIPARUM MALARIA IN SPECIAL GROUPS**

▶ **Pregnancy**

First trimester:

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

Second and third trimesters:

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

▶ **Lactating women**

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

▶ **Infants and young children**

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

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

Uncomplicated falciparum malaria:

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

Severe malaria:

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

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

7.10 Co-existing morbidities

7.10.1 HIV infection

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

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

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

BOX 7.10

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

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

7.10.2 Severe malnutrition

Malaria and malnutrition frequently coexist. There are only a few studies of antimalarial drug disposition in people with malnutrition, although many antimalarial drug efficacy studies have been conducted in populations and settings where malnutrition was prevalent (*see* Annex 3, Section A3.15.2).

7.10.2.1 Changes in drug kinetics in malnutrition

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

7.10.2.2 Antimalarial drugs and protein energy malnutrition

There are limited data of the effect of malnutrition on chloroquine, doxycycline, quinine, sulfadoxine-pyrimethamine and tetracycline, and not all of these studies were conducted in patients with malaria. There is insufficient evidence to suggest that the dosages (in mg/kg body weight) of any antimalarial should be changed in patients with malnutrition. There are no studies in malnourished patients taking amodiaquine, artemisinin derivatives, artemether plus lumefantrine, atovaquone plus proguanil, clindamycin, mefloquine or primaquine.

BOX 7.11

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

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

8. TREATMENT OF SEVERE *P. FALCIPARUM* MALARIA

8.1 Definition

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

Clinical features:

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

Laboratory findings:

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

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

8.2 Treatment objectives

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

The mortality of untreated severe malaria (particularly cerebral malaria) is thought to approach 100%. With prompt, effective antimalarial treatment and supportive care the mortality falls to 15–20% overall; although within the broad definition there are syndromes associated with mortality rates that are lower (e.g. severe anaemia) and higher (metabolic acidosis). Death from severe malaria often occurs within hours of admission to hospital or clinic, so it is essential that therapeutic concentrations of a highly effective antimalarial are achieved as soon as possible. Management of severe malaria comprises four main areas: clinical assessment of the patient, specific antimalarial treatment, adjunctive therapy and supportive care.

8.3 Clinical assessment

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

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

8.3.1 Diagnosis

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

The following sections, from 8.4 to 8.6 have been revised to reflect the change of treatment of severe falciparum malaria in children

8.4 Specific antimalarial treatment

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

8.4.1 Artemisinin derivatives

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

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

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

BOX 8.1a

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

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

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

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

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

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

Other consideration

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

BOX 8.1b

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

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

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

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

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

Other consideration

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

8.4.2 Quinine

Quinine treatment for severe malaria was established before modern clinical trial methods were developed. Several salts of quinine have been formulated for parenteral use, but the dihydrochloride is the most widely used. Peak concentrations following intramuscular quinine in severe malaria are similar to those following intravenous infusion. Pharmacokinetic modelling studies suggest that a loading dose of quinine (i.e. 20 mg salt/kg body weight – twice the maintenance dose) reduces the time needed to reach therapeutic plasma concentrations. The maintenance dose of quinine (10 mg salt/kg

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

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

8.4.3 Quinidine

Quinidine commonly causes hypotension and concentration-dependent prolongation of ventricular repolarization (QT prolongation). Quinidine is thus considered more toxic than quinine and should only be used if no other effective parenteral drugs are available. Electrocardiographic monitoring and frequent assessment of vital signs are required if quinidine is used.

8.5 Follow-on treatment

Following initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with an effective oral antimalarial using a full course of an effective ACT (artesunate plus amodiaquine or artemether plus lumefantrine or dihydroartemisinin plus piperaquine) or artesunate (plus clindamycin or doxycycline) or quinine (plus clindamycin or doxycycline). Doxycycline is preferred to other tetracyclines because it can be given once daily, and does not accumulate in renal failure. But as treatment with doxycycline only starts when the patient has recovered sufficiently, the 7-day doxycycline course finishes after the quinine, artemether or artesunate course. Where available, clindamycin may be substituted in children and pregnant women; doxycycline cannot be given to these groups. Regimens containing mefloquine should be avoided, if the patient presented initially with impaired consciousness. This is because of an increased incidence of neuropsychiatric complications associated with mefloquine following cerebral malaria.

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

8.6 Pre-referral treatment options

The risk of death from severe malaria is greatest in the first 24 h, yet, in most malaria endemic countries, the transit time between referral and arrival at health facilities able to administer intravenous treatment is usually prolonged; this delays the commencement of appropriate antimalarial treatment. As during this time the patient may deteriorate or die,

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

BOX 8.2

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

- **If complete treatment for severe malaria (as recommended in Section 8.4) is not possible, patients with severe malaria should be given pre-referral treatment and referred immediately to an appropriate facility for further treatment.**
  - The following are options for pre-referral treatment:
    • rectal artesunate • quinine IM • artesunate IM • artemether IM.
  - In young children of less than 5 years of age, the use of rectal artesunate (10 mg/kg) has been shown to reduce the risk of death and permanent disability.

8.6.1 Pre-referral and continued treatment with rectal artemisinins

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

There is insufficient evidence to show whether rectal artesunate is as good as intravenous or intramuscular options in the management of severe malaria. The recommendation, therefore, is to use artesunate or artemisinin suppositories only as pre-referral treatment and to refer the patient to a facility where complete parenteral treatment with artesunate, quinine or artemether can be instituted. If, however, referral is impossible, rectal treatment should be continued until the patient can tolerate oral medication; at this point, a full course of the recommended ACT for uncomplicated malaria in the locality can be administered.

8.6.2 Dosing for antimalarials given by rectal route

8.6.2.1 Initial (pre-referral) treatment with rectal artesunate

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

8.6.2.2 Artemether

Doses used have been variable and empiric: 10–40 mg/kg body weight (at 0, 4 or 12, 24, 48 and 72 h). Some studies have given a maintenance dose of one to two thirds of the initial dose.

8.6.2.3 Quinine

The intrarectal dose used in treatment trials in Africa was either 12 mg/kg BW quinine base (as Quinimax®, a cinchona alkaloid combination containing 96.1% quinine, 2.5% quinidine, 0.68% cinchonine, and 0.67% cinchonidine as gluconate salts) every 12 h without a loading dose, or 8 mg/kg BW every 8 h without a loading dose. The retention and absorption of quinine is dependent on pH. Results with gluconate salts (pH 4.5) cannot be extrapolated to more acidic solutions (such as the dihydrochloride salt, pH 2).

BOX 8.3

Summary of recommendations on the **TREATMENT OF SEVERE FALCIPARUM MALARIA**

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

8.7 Practical aspects of treatment

8.7.1 Artemisinins

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

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

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

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

8.7.2 Quinine

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

As the first (loading) dose is the most important in the treatment of severe malaria, this should be reduced only if there is clear evidence of adequate pre-treatment before

presentation. Although quinine can cause hypotension if administered rapidly, and overdose is associated with blindness and deafness, these adverse effects are rare in the treatment of severe malaria. The dangers of insufficient treatment (i.e. death from malaria) exceed those from excessive treatment initially.

8.7.3 Adjustment of dosing in renal failure or hepatic dysfunction

The dosage of artemisinin derivatives does not need adjustment in vital organ dysfunction. Quinine (and quinidine) levels may accumulate in severe vital organ dysfunction. If the patient remains in acute renal failure or has hepatic dysfunction, then the dose should be reduced by one third after 48 h. Dosage adjustments are not necessary if patients are receiving either haemodialysis or haemofiltration.

8.8 Adjunctive treatment

In an attempt to reduce the unacceptably high mortality of severe malaria, various adjunctive treatments for the complications of malaria have been evaluated in clinical trials. These are summarized in Table 8.1, and further information is given in sections 8.9 and 8.10.

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

Manifestation/complication	Immediate management[a]
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatment, such as corticosteroids, heparin and adrenaline; intubate if necessary.
Hyperpyrexia	Administer tepid sponging, fanning, a cooling blanket and antipyretic drugs. Paracetamol is preferred over more nephrotoxic drugs (e.g. NSAIDs[b]).
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam or intramuscular paraldehyde. Check blood glucose.
Hypoglycaemia	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion.
Severe anaemia	Transfuse with screened fresh whole blood.
Acute pulmonary oedema[c]	Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure/ continuous positive airway pressure in life-threatening hypoxaemia.
Acute renal failure	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure add haemofiltration or haemodialysis, or if unavailable, peritoneal dialysis.

Table 8.1 *continued*

Manifestation/complication	Immediate management[a]
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets, if available); give vitamin K injection.
Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe, add haemofiltration or haemodialysis.
Shock	Suspect septicaemia, take blood for cultures; give parenteral broad-spectrum antimicrobials, correct haemodynamic disturbances.

a. It is assumed that appropriate antimalarial treatment will have been started in all cases
b. Non-steroidal anti-inflammatory drugs
c. Prevent by avoiding excess hydration

8.9 Continuing supportive care

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

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

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

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

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

8.10 Additional aspects of management

8.10.1 Treatments not recommended

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

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

8.10.2 Fluid therapy

The degree of fluid depletion varies considerably in patients with severe malaria. As a result, it is not possible to give general recommendations on fluid replacement. Each patient must be individually assessed and fluid resuscitation based on estimated deficit. In high-transmission settings, children commonly present with severe anaemia and hyperventilation (sometimes termed "respiratory distress") resulting from severe metabolic acidosis and anaemia; they should be treated by blood transfusion. In general, children tolerate rapid fluid resuscitation better than adults; they are less likely to develop pulmonary oedema. In adults, there is a very thin dividing line between over-hydration, which may produce pulmonary oedema, and under-hydration contributing to shock, worsening acidosis and renal impairment. Careful and frequent evaluations of the jugular venous pressure, peripheral perfusion, venous filling, skin turgor and urine output should be made. Where the nursing facilities permit, a central venous catheter should be inserted and the central venous pressure measured directly (target 0–5 cm H_2O).

8.10.3 Blood transfusion

Severe malaria is associated with rapid development of anaemia as infected and uninfected erythrocytes are haemolysed and/or removed from the circulation by the spleen. Ideally fresh cross-matched blood should be transfused. However, in most settings cross-matched virus-free blood is in short supply. As with fluid resuscitation, there have not been enough studies to provide strong evidence-based recommendations on the indications for transfusion, so the recommendations given here are based on expert opinion. In high-transmission settings, blood transfusion is generally recommended for children with a haemoglobin level of < 5 g/100ml (haematocrit < 15%). In low-transmission settings, a threshold of 20% (haemoglobin 7 g/100 ml) is recommended. However, these general recommendations still need to be tailored to the individual, as the pathological consequences of rapid development of anaemia are worse than those of chronic or acute

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

8.10.4 Exchange blood transfusion

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

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

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

8.10.5 Use of anticonvulsants

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

8.10.6 Concomitant use of antibiotics

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

severe malaria; so broad-spectrum antibiotic treatment should be given initially until a bacterial infection is excluded.

8.11 Treatment of severe malaria in special groups during pregnancy

8.11.1 Treatment during pregnancy

Women in the second and third trimesters of pregnancy are more likely to develop severe malaria than other adults, and, in low-transmission settings, this is often complicated by pulmonary oedema and hypoglycaemia. Maternal mortality is approximately 50%, which is higher than in non-pregnant adults. Fetal death and premature labour are common.

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

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

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

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

and *P. ovale* are generally less prevalent, but they are distributed worldwide, especially in the tropical areas of Africa. Further information on treatment is provided in Annex 9.

Among the four species of *Plasmodium* that affect humans, only *P. vivax* and *P. ovale* form hypnozoites, parasite stages in the liver, which can result in multiple relapses of infection weeks to months after the primary infection. Thus, a single infection causes repeated bouts of illness. The objective of treating malaria caused by *P. vivax* and *P. ovale* is to cure (radical cure) both the blood stage and the liver stage infections, and, thereby, prevent both recrudescence and relapse, respectively. Infection with *P. vivax* during pregnancy, as with *P. falciparum*, reduces birth weight. In primigravidae, the reduction is approximately two thirds of that associated with *P. falciparum* (110 g compared with 170 g), but this adverse effect does not decline with successive pregnancies, unlike with *P. falciparum* infections.

9.1 Diagnosis

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

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

There are very few recent data on the in vivo susceptibility of *P. ovale* and *P. malariae* to antimalarials. Both species are regarded as very sensitive to chloroquine, although there is a single recent report of chloroquine resistance in *P. malariae*. Experience indicates that *P. ovale* and *P. malariae* are also susceptible to amodiaquine, mefloquine and the artemisinin derivatives. Their susceptibility to antifolate antimalarials, such as sulfadoxine-pyrimethamine, is less certain.

P. vivax susceptibility has been studied extensively and, now that short-term culture methodologies have been standardized, clinical studies have been supported by in vitro observations. *P. vivax* is generally still sensitive to chloroquine, although resistance is prevalent and increasing in some areas (notably Indonesia, Peru and Oceania). Resistance to pyrimethamine has increased rapidly in some areas, and sulfadoxine-pyrimethamine is, consequently, ineffective. There are insufficient data on current susceptibility to proguanil and chlorproguanil, although resistance to proguanil was selected rapidly when it was first used in *P. vivax* endemic areas.

In general, *P. vivax* is sensitive to all the other antimalarial drugs and slightly less sensitive to mefloquine (although mefloquine is still effective). In contrast to *P. falciparum*, asexual stages of *P. vivax* are susceptible to primaquine. Thus, chloroquine plus primaquine can be considered as a combination treatment. The only drugs with significant activity against the hypnozoites are the 8-aminoquinolines (buloquine, primaquine, tafenoquine).

There is no standardized in vitro method of drug assessment for hypnozoiticidal activity. In vivo assessment suggests that tolerance of *P. vivax* to primaquine in eastern Asia and Oceania is greater than elsewhere.

9.3 Treatment of uncomplicated vivax malaria

9.3.1 Blood stage infection

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

9.3.1.1 Chloroquine-resistant vivax malaria

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

BOX 9.1

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

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

GRADE evaluation (see Annex 9, tables A9.6.1 and A9.6.2)
Two trials compared DHA+PPQ to alternative ACTs (AL6 and AS+AQ) in Indonesia where all groups were also given primaquine to clear the liver stage parasites. DHA+PPQ reduced the number of relapses by day 42 compared to AL (1 trial, 126 participants; RR 0.16, 95% CI 0.07–0.38; moderate quality evidence) and AS+AQ (1 trial, 84 participants; RR 0.16, 95% CI 0.05–0.49; moderate quality evidence). There are no trials comparing DHA+PPQ and AS+MQ in *P. vivax* mono-infection.
At day 42, the patients in the DHA+PPQ groups were also less likely to be anaemic, although this data includes participants with *P. falciparum* mono-infection at baseline, and recurrence of *P. falciparum* was also lower with DHA+PPQ. This effect is likely to be a prophylactic effect related to the longer half-life of DHA+PPQ.

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

9.3.2 Liver stage infection

To achieve a radical cure, relapses must be prevented by giving primaquine. The frequency and pattern of relapses varies geographically. Whereas 50–60% of *P. vivax* infections in South-East Asia relapse, the frequency is lower in Indonesia (30%) and the Indian subcontinent (15–20%). Some *P. vivax* infections in the Korean peninsula (now the most northerly of human malarias) have an incubation period of nearly one year. Moreover, the *P. vivax* populations emerging from hypnozoites commonly differ from the populations that caused the acute episode. Activation of heterologous hypnozoites populations is the most common cause of the first relapse in patients with vivax malaria. Thus, the preventive efficacy of primaquine must be set against the prevalent relapse frequency. It appears that the total dose of 8-aminoquinoline given is the main determinant of curative efficacy against liver-stage infection. In comparison with no primaquine treatment, the risk of relapse decreased by the additional milligram per kilogram body weight of primaquine given. Primaquine should be given for 14 days.

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

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

14-day regimen is significantly better at reducing relapses (6 trials, 1072 participants; OR 0.24, 95% CI 0.12–0.45). The usual adult oral dose is 15 mg base (0.25 mg/kg body weight per day), but in South-East Asia, particularly Indonesia, and in Oceania, higher doses (0.5 mg base/kg body weight per day) are required. Primaquine causes abdominal discomfort when taken on an empty stomach; it should always be taken with food.

There has been debate as to whether primaquine should be given in endemic areas. Repeated vivax malaria relapses are debilitating at any age, and so they must be prevented. However, in situations where transmission is intense with a high rate of re-infection, simply preventing relapses is unlikely to lower the incidence of infection or disease. Therefore, in areas of sustained high transmission, the benefits of the widespread deployment of primaquine are not considered to outweigh the risks associated with this medication. In low-transmission areas, on the other hand, the benefits of primaquine in preventing relapses will exceed its risks and its routine use to prevent relapses is recommended in patients who are not G6PD-deficient.

BOX 9.2

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

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

GRADE evaluation (*see* Annex 9, table A9.7.1)
A 14-day course of primaquine significantly reduces the relapse rate of *P. vivax* compared to a 5-day course (2 trials, 186 participants; RR 0.1, 95% CI 0.03–0.35; low quality evidence).

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

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

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

9.3.2.1 Primaquine and glucose-6-phosphate dehydrogenase deficiency

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

are found only in areas where malaria is or has been endemic. There are a large number of different genotypes, each with different levels of deficiency. Primaquine is an oxidant and causes variable haemolysis in G6PD-deficient individuals. Primaquine also causes methemoglobinaemia. The severity of haemolytic anaemia is related to primaquine dosing and the variant of the G6PD enzyme. Fortunately, primaquine is eliminated rapidly and so haemolysis is self-limiting provided no further drug is taken. Screening for G6PD deficiency is not generally available outside hospitals, although rapid tests are under development. Many patients are, therefore, unaware of their G6PD status. If a patient is known to be severely G6PD deficient, then primaquine should not be given. For the majority of patients with mild variants of the deficiency, primaquine should be given in a dose of 0.75 mg base/kg body weight once a week for eight weeks. If significant haemolysis occurs on treatment, then primaquine should be stopped.

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

BOX 9.3

Summary of recommendations on the **TREATMENT OF UNCOMPLICATED VIVAX MALARIA**

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

9.4 Treatment of severe *P. vivax* malaria

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

that have been reported are cerebral malaria, severe anaemia, severe thrombocytopenia and pancytopenia, jaundice, splenic rupture, acute renal failure and acute respiratory distress syndrome. Severe anaemia and acute pulmonary oedema are not uncommon. The underlying mechanisms of severe manifestations are not fully understood. Prompt and effective treatment and case management should be the same as for severe and complicated falciparum malaria (*see* Section 8).

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

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

9.6 Monitoring therapeutic efficacy for vivax malaria

The antimalarial sensitivity of vivax malaria needs monitoring to track and respond to emerging resistance to chloroquine. The 28-day in vivo test for *P. vivax* is similar to that for *P. falciparum*, although the interpretation is slightly different. Genotyping can distinguish a relapse or recrudescence from acquisition of a new infection, but it is not possible to distinguish reliably between a relapse and a recrudescence as they derive from the same infection. Relapse is unlikely if parasitaemia recurs within 16 days of administering treatment but, after that time, relapse cannot be distinguished from a recrudescence. Any *P. vivax* infection that recurs within 28 days, whatever its origin, must be resistant to chloroquine (or any other slowly eliminated antimalarial) provided adequate treatment has been given. In the case of chloroquine, adequate absorption can be confirmed by measurement of the whole blood concentration at the time of recurrence. Any *P. vivax* infection that has grown in vivo through a chloroquine blood concentration of > 100 ng/ml must be chloroquine resistant. Short-term in vitro culture allows assessment of in vitro susceptibility. There are no molecular markers yet identified for chloroquine resistance. Antifolate resistance can be monitored by molecular genotyping of the gene that encodes dihydrofolate reductase *(Pvdhfr)*. Since ACTs are increasingly being used for the treatment of vivax infections in situations where it is resistance to chloroquine, the sensitivity of *P. vivax* to ACTs must also be routinely monitored.