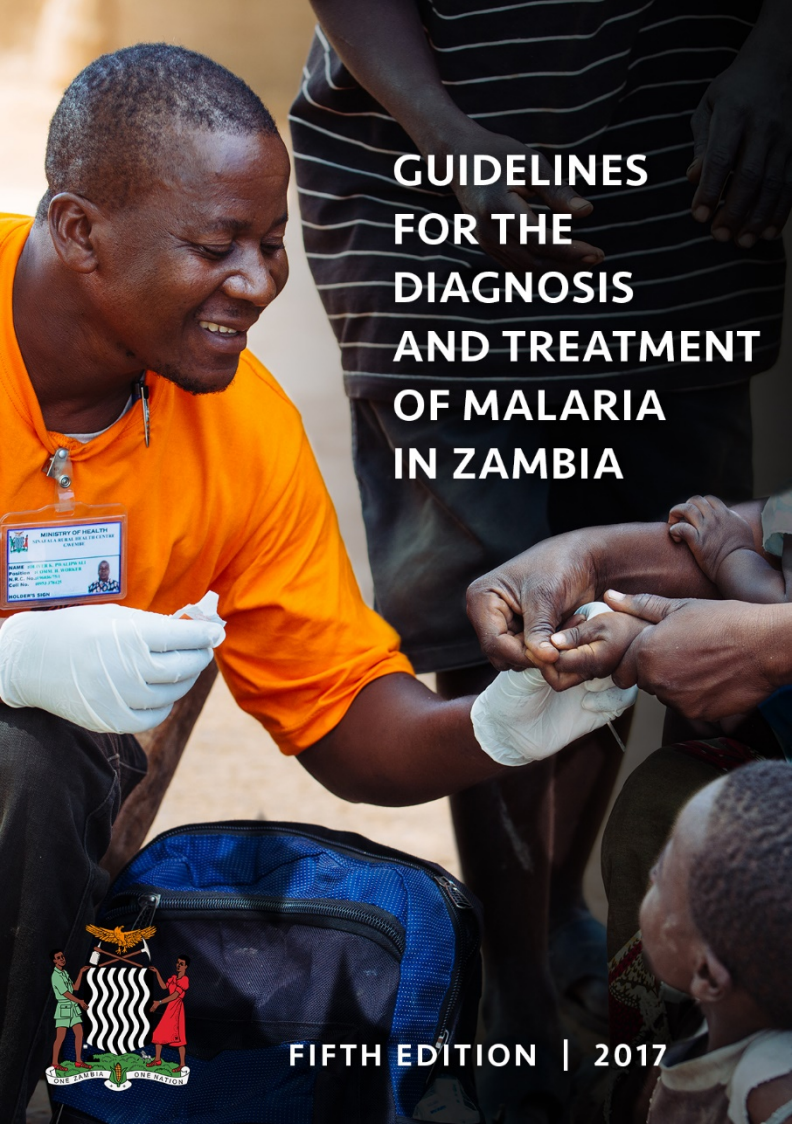
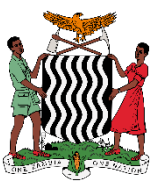


GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF MALARIA IN ZAMBIA

FIFTH EDITION | 2017

Guidelines for the Diagnosis and Treatment of Malaria in Zambia

Fifth Edition
2017



NATIONAL MALARIA
ELIMINATION CENTRE
Lusaka, Zambia

Previous editions of the Guidelines for the Diagnosis and Treatment of Malaria in Zambia were produced in 2010 and 2017.

Foreword

Malaria remains a major public health problem in Zambia, despite significant progress made in fighting the disease in the last decade. Malaria prevalence varies across districts with 14 million Zambians at risk, including the most vulnerable groups, such as pregnant women and children.

The country's last two iterations of the National Malaria Strategic Plan (NMSP) aimed to reduce transmission through multiple strategies, including the distribution of long-lasting insecticide-treated mosquito nets (LLINs), increased indoor residual spaying (IRS), improved case management using rapid diagnostic tests (RDTs), and treatment with artemisinin-based combination therapy (ACT). In the current NMSP (2017–2021), Zambia will continue to scale up malaria interventions in pursuit of a malaria-free nation.

In Zambia, case management coverage has greatly improved through strengthening of general health services and the provision of adequate diagnostics and medicines according to national guidelines. The national objective is to ensure that 100% of all suspected malaria cases in all districts receive parasitological (microscopy or RDT) analysis and

100% of parasitologically confirmed malaria cases receive prompt (within 24 hours), effective antimalarial treatment. Universal coverage, service for anyone who requires it, with early diagnosis and effective treatment is a key strategy in reducing morbidity and mortality.

It is with this background that I sincerely welcome the revisions made in the Guidelines for the Diagnosis and Treatment of Malaria in Zambia to reflect the updated policy recommendations. These fifth edition guidelines are intended to provide information to all health workers on the diagnosis and treatment of malaria at all levels of the health care system.

I hope that these guidelines will continue to serve as an important source of reference material for general malaria management. I want to take this opportunity to thank all the organizations and individuals that have provided both technical and financial support to ensure a successful revision of the guidelines.

Dr Jabbin Mulwanda

Permanent Secretary, Health Services

Zambia Ministry of Health

Acknowledgments

The revision of the previous edition of the Guidelines for the Diagnosis and Treatment of Malaria in Zambia have been made possible through the concerted efforts of the National Malaria Elimination Centre (NMEC) together with its many collaborating partners. The NMEC would therefore like to thank all individuals and organisations that put in a tremendous amount of work to ensure that the information was updated, leading to the production of this fifth edition.

The Ministry of Health would especially like to acknowledge the contribution of the following individuals: Dr Anthony Yeta, Dr Mutinta Mudenda, Dr John Banda, Dr Busiku Hamainza, Mr Moonga Hawela, Mr Tadious Chimombe, Mr Donald Mukumbuta, Mr Jacob Chirwa from NMEC, Mr Boyd Mwanashimbala (MOH – Clinical Care), Dr Patricia Mupeta Bobo (MOH), Professor James Chipeta (University of Zambia School of Medicine), Professor Bellington Vwalika, Dr Brown Kamanga, Dr Mable Mutengo, Dr Evans Mulendele, Mr Jimmy Hangoma (University Teaching Hospital), Ms Jane Banda (Cancer Disease Hospital), Dr Sebastian Hachizovu (Tropical Disease Research Centre), Dr Chomba Sinyangwe (US President's Malaria Initiative), Dr

Carrie Nielsen (US President's Malaria Initiative/CDC), Dr Phil Thuma (Macha Research Trust), Mr Nyambe Lyoko (Zambia Medicines Regulatory Authority), Mr Morgan Phiri (Churches Health Association of Zambia), Ms Sarah Shankwaya (Programme for Advancement of Malaria Outcomes), and Ms Victoria Kalota (Malaria Care), Dr John Miller (PATH MACEPA), Dr. Freddie Masaninga (World Health Organization).

We also acknowledge comments and suggestions made by partners through the Malaria Case Management Technical Working Group.

Dr Elizabeth Chizema

Director National Malaria Elimination Programme

Ministry of Health

Acronyms

ACT	Artemisinin-based combination therapy
ADR	Adverse drug reaction
cm	Centimeter
CHA	Community heath assistant
CHW	Community health worker
CFR	Case fatality rate
DIC	Disseminated intravascular coagulation
DHA-PQ	Dihydroartemisinin-piperaquine
Hb	Haemoglobin
HIV	Human immunodeficiency virus
HMIS	Health management information system
iCCM	Integrated community case management
IM	Intramuscular
IPTp	Intermittent preventive treatment
ITN	Insecticides-treated net
IV	Intravenous
kg	Kilogram
KL	Micro litre
LLIN	Long-lasting insecticide-treated net
mg	Milligram
ml	Millilitre
Mm Hg	Millimetres of mercury
MOH	Ministry of Health
NMEC	National Malaria Elimination Centre
NMSP	National Malaria Strategic Plan
RBC	Red blood cell
RDT	Rapid diagnostic test
SP	Sulphadoxine-pyrimethamine
WHO	World Health Organization

Table of Contents

1. Introduction

Malaria is one of the major public health problems in Zambia. Despite significant progress made over the past decade, malaria continues to be a major cause of morbidity and mortality in the country, resulting in approximately 6 million cases and 2000 deaths annually. Malaria prevalence varies across districts with over 14 million Zambians at risk, including the most vulnerable groups, such as pregnant women and children.[1]

All four species of *Plasmodium* are found in Zambia with 98% of cases caused by *P. falciparum* both as a mono- and co-infection with other *Plasmodium* species. Mono infections with non-*P. falciparum* account for less than 2% of cases and are most commonly caused by *P. malariae*.[2,3]

Malaria is curable when effective treatment is commenced early. The national objective as indicated in the National Malaria Elimination Strategic Plan (NMSP) 2017–2021 is to ensure that 100% of all suspected malaria cases in all districts receive parasitological (microscopy or rapid diagnostic test [RDT]) diagnosis and 100% of parasitologically confirmed malaria cases receive prompt (within 24

hours), effective antimalarial treatment.[4] Delay in treatment may lead to serious consequences including death.

Artemesinin-based combination therapies (ACTs) are recommended for the treatment of uncomplicated malaria in Zambia. By combining two active ingredients with different mechanisms of action, ACTs are the most effective antimalarial medicines currently available. However, caution must be taken to avoid misuse in order to guard against the emergence of resistance as has been reported elsewhere.[5–7]

These guidelines have been primarily developed for health care providers in Zambia involved in the diagnosis and treatment of malaria in both public and private health facilities. However, other groups that may find these guidelines useful include public health practitioners, nongovernmental organizations, agencies that are partners in health or malaria, research institutions, the pharmaceutical industry, and medical and health institutions.

2. Clinical features

Fever is the cardinal symptom of malaria. The other features may include rigors, chills, headache, myalgia, arthralgia, anorexia, nausea, and vomiting. The features of malaria are non-specific and can mimic other diseases like viral infections, bacterial infections (e.g., enteric fever) among others.[8–10] Therefore, all clinically suspected malaria cases should be promptly confirmed either by microscopy or malaria RDT.

3. Diagnosis

3.1 Rapid diagnostic test

In all cases of suspected malaria, RDTs should be used for prompt confirmation. RDTs are based on the detection of circulating parasite antigens.[11,12] Several types of RDTs are available (http://www.wpro.who.int/sites/rdt), some can only detect *P. falciparum*, while others can detect other parasite species as well. The Ministry of Health through the NMEC rolled out and recommended RDTs that only detect *P. falciparum* for use in the public and private health sector in Zambia.

Since there are different types of RDTs, the test insert leaflet should always be read properly and instructions followed accurately. Failure to observe these criteria can lead to incorrect results. It should be noted that *P. falciparum* Histidine Rich Protein–Ri (PfHRP-2) based kits may show positive results up to four weeks after successful treatment and parasite clearance. In these cases, results should be correlated with microscopic diagnosis. Therefore, PfHRP-2 RDTs should not be used on the patient whose results were positive for malaria within 14 days.

Prompt diagnosis and complete treatment of malaria aims to:

- Cure
- Prevent the progression of uncomplicated malaria to severe disease
- Prevent deaths
- Interrupt transmission
- Minimize risk of emergence of drug resistant parasites

3.2 Microscopy

Microscopy of thick and thin blood smears remains the gold standard for confirmation of diagnosis of malaria. The advantages of microscopy are:

- High specificity when used by a competent microscopist.
- Ability to quantify the parasite load.
- Ability to distinguish different species of malaria parasites and their different stages.
- Ability to detect other blood parasites and conditions.
- It helps in monitoring the response to treatment.

4. Treatment of uncomplicated malaria

All confirmed uncomplicated malaria cases diagnosed by RDT or microscopy should be promptly treated with effective recommended first line antimalarial medicines and, currently, the recommended medicines for uncomplicated malaria in Zambia are ACTs. These recommended ACTs are Artemether-lumefantrine (AL) and Dihydroartemisin-Piparaquine (DHA-PQ). DHA-PQ preferably must not be used as first line treatment of uncomplicated malaria in areas where there is active DHA-PQ mass drug administration. Both children of all ages 13–15 and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) must be treated with an ACT (see respective dosage details in Tables 1 and 2).[13] An alternative first line medicine where ACTs are not recommended is Quinine.

MONOTHERAPY OF ORAL ARTEMISININ DERIVATIVES IS BANNED IN ZAMBIA

Artemisinin derivatives are the only rapidly acting antimalarials as of now and if used alone, can lead to the development of artemisinin resistance. Hence, they should not be administered as monotherapy for uncomplicated malaria. The only artemisinin derivatives monotherapy are Injectable Artesunate and Injectable Artemether and strictly only for treatment of severe malaria.

Table 1. Dosage schedule for Artemether-Lumefantrine (AL).

Body weight (kg)	AL dose (mg) given twice daily for 3 days (the first two doses must be 8 hours apart)
*5 to < 15	20 + 120
15 to < 25	40 + 240
25 to < 35	60 + 360
≥ 35	80 + 480

*Note that infants of less than 5 kg must be treated with the same dosage as those of 5 to <15 kg (see refs 13, 14, and 15).

Source: Adapted from 2015 World Health Organization Guidelines for treatment of malaria 3rd Edition.

Table 2. Dosage schedule for Dihydroartemisin-Piperaquine (DHA-PQ)

Body weight (kg)	DHA-PQ dose (mg) given daily for 3 days
5 to < 8	20 + 160
8 to < 11	30 + 240
11 to < 17	40 + 320
17 to < 25	60 + 480
25 to < 36	80 + 640
36 to < 60	120 + 960
60 to < 80	160 + 1280
> 35	200 + 1600

Source: Adapted from 2015 World Health Organization Guidelines for treatment of malaria 3RD Edition

4.1 Treatment of uncomplicated malaria in pregnancy

4.1.1 First trimester of pregnancy

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

4.1.2 Second and third trimester of pregnancy

Use AL or DHA-PQ in the second and third trimesters of pregnancy, in the usual adult dose.

4.2 Treatment of mixed infections

For all mixed infections, treat with ACTs as per the respective ACT drug regimen. Where malaria species confirmation is not available, treat as *P. falciparum.* However, anti-relapse treatment with primaquine can be given for 14 days if *P. malariae* is confirmed in a mixed infection, and in such circumstances wherever possible check for Glucose 6 Dehydrogenase deficiency.

4.3 General recommendations for the management of uncomplicated malaria

- The first dose should be given under observation.
- The dose should be repeated if vomiting occurs within half an hour of antimalarial intake.
- The patient should be asked to report back if the situation deteriorates or if there is no improvement after 48 hours.
- The patient should also be examined and investigated for concurrent illnesses.
- Counsel the patient to complete treatment.
- Educate the patient on prevention of malaria.

5. Treatment failure/drug resistance

5.1 Definition of treatment failure

Treatment failure is defined as the failure of antimalarial medicine to treat malaria. Treatment failures may be caused by:

- Parasite resistance to antimalarials.
- Poor drug quality.
- Unusual pharmacokinetic properties in an individual.
- Inadequate dosage.
- Vomiting.
- Non-adherence to treatment.
- Fever/symptoms from a cause other than malaria.

Treatment failure within 14 days of receiving an ACT is very unusual. When a patient returns within 14 days of ACT treatment with symptoms of malaria, treatment failure should be considered. If fever persist after 14 days, re-infection should be suspected (see section on pharmacovigilance).

5.2 Management of treatment failure

The following recommendations should be followed after a taking a patient's full history and performing an examination:

- If a cause for non-response is identified, such cause must be addressed and treatment reinstituted with a first-line antimalarial.
- In cases where appropriate treatment adherence has been determined:
    - In a facility where laboratory services are not available and malaria is still suspected, the patient should be referred to a health centre or a district hospital for parasitological microscopic confirmation; do not use RDTs because they may remain positive for 14 days or more after treatment.
    - In a facility where laboratory services are available, a blood smear should be performed. If parasites (trophozoites) are found, change the treatment to the second-line medicine (quinine tablets; see Table 3). If parasites are not found, then other

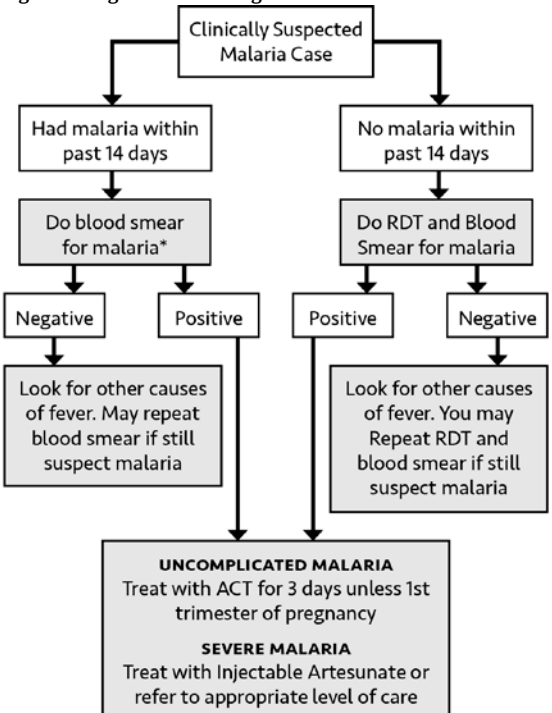
causes of the symptoms should be determined and treated accordingly.

- If the blood smear is negative and no other obvious causes are found, refer the patient to the next level for further management.

Table 3: Administration of oral quinine (salt, 300 mg tablet) for different age groups

Age (years)	Number of tablets per dose
<1	0.25
1–3	0.5
4–6	0.75
7–11	1
12–15	1.5
>15	2

Figure 1. Algorithm for Diagnosis and Treatment of Malaria



*Note: If blood smear not available, may do RDT but keep in mind that RDT may remain positive for 2–4 weeks after a recently treated malaria illness. Treatment for a POSITIVE RDT in this circumstance should be correlated with expert microscopy results.

6. Integrated community case management

6.1 Initial care and care-seeking

According to integrated community case management (iCCM) the roles of a caregiver with a child with fever include:

- Recognizing the symptom of fever and danger signs (see Chapter 7 and promptly seek appropriate care.
- Correctly using the prescribed first-line medicine.
- Reducing body temperature with measures such as exposure of patient, fanning, or giving paracetamol, if indicated.
- Appropriately using oral rehydration salts in case of diarrhea and/or vomiting.
- Continuing feeding, especially very young children.

6.2 Diagnosis and treatment by community health workers and community health assistants

In the iCCM approach the community health workers (CHWs) and community health assistants (CHAs) are

provided with diagnostic tools and medicines for the management of common childhood illnesses including the treatment of uncomplicated malaria. Their roles in the management of uncomplicated malaria include:

- Carrying out diagnoses according to their training and recognizing danger signs.
- Using RDTs in all cases of fever to confirm malaria before treatment.
- Administering the first-line medicine.
- Administering pre-referral treatment when danger signs are recognized.
- Instituting measures to reduce body temperature.
- Following up with patients, particularly children under five years of age.
- Providing education to the community on the need for compliance to treatment, recognition of danger signs, and prevention of malaria.
- Advising when to return if the condition persists.

6.3 Referral

CHWs and CHAs should make early referral to a health facility in case of danger signs and persistence of the

illness. Referred patients should be accompanied to the health facility with a referral note indicating patient details, the condition, the treatment given, and when the treatment took place.

Criteria for referral to a health facility:

- All pregnant women with fever.
- Changes in behavior (unconsciousness, confusion, convulsions, and inability to recognize relatives).
- Failure to retain oral medication or food/fluids (vomiting).
- Severe diarrhea.
- Inability to eat or drink.
- Failure to respond to treatment (i.e., if symptoms persist after 48 hours).
- Difficulty in talking, sitting up, or walking.
- Unexplained heavy bleeding from the nose, gums, and other sites.
- Passing dark or little or no urine.
- High fever (above 38.5°C).
- Severe dehydration (loose skin and sunken eyes).
- Anemia.

6.4 Pre-referral treatment

When severe illness or danger signs are noticed the following pre-referral procedures must be instituted.

Where intramuscular injections of artesunate are not available, treat children older than six months and less than six years with a single rectal dose of artesunate and refer immediately to an appropriate facility for further care. Do not use rectal artesunate in older children and adults. Rectal artesunate should be dosed by weight, but age can be used if a weight cannot be easily determined (Table 4).

Table 4. Rectal artesunate pre-referral dosing

Age	Over 6 months to less than 3 years	Over 3 years to less than 6 years
Weight range	From 5 kg to less than 14 kg	From 14 kg to 20 kg
Dose	100mg	200mg

For children older than six years of age and adults, if able to take oral medication give a dose of available ACT.

7. Severe malaria

7.1 Definition

Severe *P. falciparum* malaria is defined as symptomatic malaria with evidence of dysfunction in one or more vital organs (see below) occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia. It may progress from uncomplicated malaria or be of sudden onset, particularly in non-immunes.

7.1.1 Features of severe malaria

Clinical features

Cerebral malaria: Impaired consciousness (or a Glasgow coma score <11 in adults or a Blantyre coma score <3 in children), multiple convulsions (more than two episodes in 24 hours).

Prostration: Generalized weakness so that the person is unable to sit, stand, or walk without assistance.

Severe malarial anaemia: Haemoglobin concentration ≤5 g/dL or a haematocrit of ≤15% in children under 12 years of age (<7 g/dL and <20%, respectively, in adults) with a parasite count >10 000/μ.

Pulmonary oedema: Radiologically confirmed or oxygen saturation <92% on room air with a respiratory rate >30/min, often with chest indrawing and crepitations on auscultation.

Metabolic acidosis: Severe acidosis manifests clinically as rapid, deep, laboured breathing.

Shock: Compensated shock is defined as capillary refill ≥3 seconds or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock (hypotention) is defined as systolic blood pressure <70 mm Hg in children or <90 mm Hg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).

Acute renal failure: Urine output of less than 400 mls in 24 hours (less than 1 ml/kg in children)

Severe anaemia, and/or bleeding: Severe normocytic anaemia (Hb less than 5 g/dl, packed cell volume less than 15%) / abnormal spontaneous bleeding

Jaundice: Plasma or serum bilirubin >50 μmol/L (3 mg/dL) with a parasite count >100 000/μL

Significant bleeding: Including recurrent or prolonged bleeding from the nose, gums, or venepuncture sites; haematemesis or melaena

Haemoglobinuria (black water fever): Characterised by the passage of dark (Coca-Cola coloured) urine.

Laboratory features

Metabolic acidosis: A base deficit of >8 mEq/L or, if not available, a plasma bicarbonate level of <15 mmol/L or venous plasma lactate ≥5 mmol/L or pH of <7.35.

Hypoglycaemia: Blood glucose less than 2.2 mmol/l or less than 40 mg/dl.

Hyperparasitaemia: Greater than 2% or
100 000/µl in low intensity transmission areas or greater than 5% or 250 000/µl in areas of high stable malaria transmission intensity.

Renal impairment: Plasma or serum creatinine >265 µmol/L (3 mg/dL) or blood urea >20 mmol/L.

Hyperparasitaemia: *P. falciparum* parasitaemia >10%.

7.2 Management of severe malaria

7.2.1 Initial management of severe malaria

If the capacity to manage severe malaria is not available in the facility, the patient must be referred to a higher level of care immediately after stabilizing the patient

and giving the first dose of appropriate antimalarial treatment (refer to section 7.3.1 or 7.3.2). The patient, especially if comatose, should be managed in a special observation unit or an Intensive Care Unit and the following measures undertaken:

1. Confirm the malaria diagnosis.
2. If comatose, manage the airway, breathing, and circulation (ABC) and position in semi-prone or on left side and insert urethral catheter, nasogastric tube and IV access.
3. Weigh patient (particularly children), if possible, and calculate dosage per body weight.
4. Make rapid clinical assessment and look for signs of meningitis and other conditions.
5. Get blood for glucose, hemoglobin, urea, creatinine, electrolytes, and others as may be indicated.
6. Start antimalarial treatment.
7. Start treatment for other complications as may be indicated and monitor the patient regularly.

7.3 Antimalarial treatment

In the general population, injectable artesunate is the drug of choice for adults and children with severe malaria.

If injectable artesunate is unavailable, artemether (intramuscular [IM]) or quinine (intravenous [IV]/IM) are recommended alternatives.

Following initial parenteral treatment for a minimum of 24 hours, once the patient can tolerate oral therapy, it is essential to continue with a complete course of an effective appropriate oral antimalarial.

7.3.1 Injectable artesunate

For severe malaria, IV artesunate is recommended as described below:

1. Each vial of injectable artesunate must be reconstituted with 1 ml of sodium bicarbonate which is normally supplied together with the vial of artesunate. Shake for 3–5 minutes until the powder is completely dissolved and the solution is clear.
2. Dilute with 5 ml normal saline (0.9% sodium chloride) or 5% dextrose solution.

Caution! Artesunate should not be diluted with water for injection and the prepared solution should be used within ONE HOUR of preparation after which it should be discarded.

3. Dose: Those less than 20 kg should be given 3 mg/kg, while those who are 20 kg and above should be given at 2.4 mg/kg body weight.
4. Withdraw into syringe and inject intravenously at a rate of 3–4 ml per minute.

If IV administration is not possible, artesunate may be given by IM injection as described below:

1. Each vial of injectable artesunate must be reconstituted with 1 ml of sodium bicarbonate, which is normally supplied together with the vial of artesunate. Shake for 3–5 minutes until the powder is completely dissolved and the solution is clear.
2. Dilute with 2 ml of normal saline (0.9% sodium chloride) or 5% dextrose solution.
3. The prepared solution should be used within one hour of preparation after which it should discarded.

4. Dose: Those less than 20 kg should be given 3 mg/kg while for those 20 kg and above should be given 2.4 mg/kg body weight.
5. Withdraw into a syringe and inject slowly.
    a. The maximum volume to be administered at each site is 5 ml.
    b. The preferred site for IM administration is the upper, outer quarter of the anterior of the thigh.

Do not inject artesunate into the buttocks!

Recommended dosing schedule of artesunate

2.4 mg/kg of body weight (or 3 mg /kg body if weight is less than 20 kg) IV or IM given as follows:

- On admission (time = 0).
- Repeat after 12 hours.
- Repeat 24 hours after the initial dose.
- Thereafter repeat once daily for a maximum of six days if the patient is still not able to tolerate oral medication.

After the initial parenteral treatment for a minimum of 24 hours, and once the patient regains consciousness and can take medications orally, discontinue parenteral therapy and commence the full course of an oral ACT. There should be an interval of at least eight hours between the last dose of artesunate and the first dose of an oral ACT.

7.3.2 Quinine

Children—by intravenous (IV) injection:

- Loading dose of 20 mg/kg body weight (maximum 1200 mg) diluted in 10 ml/kg of 5% or 10% dextrose by IV infusion over four hours. (In case of a diabetic patient with malaria, use isotonic fluid with two hourly monitoring of blood sugar.)
- After eight hours, give a maintenance dose at 10 mg/kg body weight over four hours, and repeat every eight hours until patient can swallow.
- Then use oral quinine at 10 mg/kg body weight every eight hours to complete a seven-day course of treatment.

Children—by intramuscular (IM) injection:

- 10 mg/kg body weight diluted in saline or water for injection (to a concentration of 60–100 mg salt/ml), repeated after four hours and then every eight hours. This should be given preferably on the anterior thigh. A maximum of 3 ml should be injected into one site. This route does not recommend a loading dose.

Adults—by IV injection:

- Loading dose of 20 mg/kg body weight (maximum 1200 mg) diluted in 10 ml/kg of 5% or 10% dextrose per kg body weight by IV infusion over four hours.
- After eight hours, give a maintenance dose of 10 mg/kg body weight (maximum 600 mg) over four hours, repeated every eight hours until patient can swallow or after coma resolution, then oral quinine 10 mg/kg body weight every eight hours to complete a seven-day course of treatment.

Adults—by IM injection:

- l0 mg/kg body weight (maximum 1200 mg) diluted in saline or water for injection (to a concentration of 60–100 mg salt/ml), repeated after four hours and then every eight hours. This should be given preferably on the anterior thigh. A maximum of 3 ml should be injected into one site. If the amount to be injected exceeds 3 ml, use multiple sites. **A loading dose is not recommended** when administering quinine by this route.

The drip rate is calculated as follows:

$$\text{Drops per minute} = \frac{\text{Amount of solution (mL/hour) x drop factor}}{\text{Time in minutes over which to be given}}$$

It is also important to manage the underlying condition in these patients.

7.4 Monitoring of patients with severe malaria

- Patients with severe malaria should be monitored regularly.
- All complications should be managed accordingly (see Chapter 7).

- Particular attention should be paid to the care of the critically ill with measures such as monitoring of the airway, breathing and circulation, insertion of IV access, feeding via nasogastric tubes where indicated, twice-hourly turning, monitoring of input and output of fluids, urinary catheterization, etc.
- Laboratory investigations:
    - Repeat the blood slide every 24 hours until there is zero parasitaemia.
    - Other laboratory parameters should be repeated as per protocol.

7.5 Pre-referral treatment of patients with suspected severe malaria

If a patient presents at the health facilities with signs and symptoms of severe malaria and requires to be transferred to the next level of care, the following should be done before transferring:

- Perform an RDT or microscopy.
- If RDT-positive, give the first dose of injectable artesunate.

- Refer the patient immediately after stabilization. The results of the RDT should be sent with the patient to the next level.

NOTE! If microsropy/RDT is not possible and severe malaria is suspected, give the first dose of injectable artesunate before referring to the next level of care.

- In remote rural areas or peripheral clinics where IV infusion may not possible, give rectal artesunate if available. Artemether or quinine IM may be given only if artesunate is unavailable.
- For conscious children younger than five years of age, encourage the caregiver to continue feeding to avoid hypoglycaemia.
- In suspected severe malaria cases where meningitis and septicemia cannot be ruled out, administer a broad-spectrum antibiotic.
- Control fever by the use of antipyretics, or use physical methods such as tepid sponging, fanning, or reducing the amount of clothing that the patient is wearing.

Where complete treatment of severe malaria is not possible but injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate facility for further care. Where

intramuscular artesunate is not available, use intramuscular artemether or, if that is not available, use intramuscular quinine.

7.6 Managing complication of severe malaria

Management of specific complications are tabulated below and also detailed elsewhere.[13,16,17]

Coma (cerebral malaria)

Immediate management: Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g., hypoglycaemia, bacterial meningitis), insert urinary catherter, intubate if necessary. Avoid harmful ancillary treatments.

Hyperpyrexia

Crushed paracetamol tablets or syrup (15 mg/kg) may be washed down a naso-gastric tube. Tepid sponging, exposure, and fanning are also effective ways of reducing temperature.

Convulsions

The general principles for the care of patients with convulsions should be as follows:

- Maintain a clear airway.
- Urgently STOP the convulsion with an anticonvulsant (intravenous or rectal diazepam, lorazepam, midazolam, or intramuscular paraldehyde).
- Check blood glucose.
- Nurse the patient in a semi-prone position.

Convulsions in children:

- Use diazepam 0.5–1.0 mg/kg rectally or intramuscular (IM) if intrarectal cannot be done. This can be repeated twice.
- If convulsions persist, give a bolus of phenobarbital, 20 mg/kg IV over 20 minutes or IM WITH respiratory support, followed by maintenance doses of 10 mg/kg in two divided doses at least 30 minutes after the bolus for recurrent convulsions.

Convulsions in adults:

- Give a slow bolus of IV diazepam 5–10 mg. If convulsions continue, give a second dose. If

they persist, phenobarbitone 20 mg/kg over 20 minutes as a loading dose (maximum 100 mg) IM or IV. If convulsions persist repeat phenobarbitone at 6 mg/kg after a 20-minute interval. *Note: Make sure the patient has received glucose and that the temperature is controlled.*

Hypoglycaemia

- Check random blood sugar (RBS).
- Correct hypoglycaemia and maintain with glucose-containing infusion.

Hypoglycaemia in children:

- A bolus of 5 mls/kg of 10% dextrose may be given, followed by a continuous infusion of either 10% or 5% dextrose. If IV access is not possible, give 50% dextrose via nasogastric tube.

Hypoglycaemia in adults:

- Provide a bolus of 100 ml of 25% or 50% dextrose, intravenously followed by a continuous infusion of 5% or 10% dextrose.

- Where IV fluids are not recommended, 50% dextrose could be repeated every 25 to 30 minutes until the target of 6 mmol/L is achieved.
- Check the blood sugar every 30 to 60 minutes aiming at a RBS of 6mmol/L.
- In cases of hypoglycemia due to quinine-induced hyperinsulinemia, the drug can be substituted for another potent antimalarial drug where possible, or continuous infusion of 5–10% dextrose can be instituted as the hypoglycaemia can be recurrent and protracted.

Severe anaemia

- Careful clinical examination for signs of severe anaemia (palms and mucus membranes) should be done as well as signs of cardiac failure—in children difficulties in feeding, with sweating and hepatomegaly are more reliable features as oedema (swelling of the feet and abdomen) may not always be obvious (other features of heart failure: respiratory distress, tachycardia, raised jugular venous pressure, gallop rhythm on auscultation)

- In high-transmission settings, blood transfusion is generally recommended for children with a haemoglobin level of <5 g/100 ml (haematocrit < 15%).
- Administer oxygen 2.5 L/mm to improve oxygen delivery.
- Prop the patient up with pillows or clothing.
- Collect blood for cross-match and Hb estimations and transfuse as appropriate.
- Give packed cells at l0 ml/kg; in cases of hypovolemic shock, whole blood at 20 ml/kg is preferred.
- An intravenous stat (bolus) dose of a loop diuretic like furosemide at 1 to 2 mg/kg may be given (provided the blood pressure is not low) during blood transfusion to avoid circulatory overload.

Acute pulmonary oedema

Prop patient up, give oxygen, give a diuretic (frusemide at 1 mg/kg IV bolus in children and 40 mg IV stat in adults), stop intravenous fluids, intubate where necessary.

Acute kidney injury

Exclude dehydration and heart failure, and then refer.

Hypotension/shock

- Administer intravenous saline or Ringer's lactate if serum lactate normal.
- If the patient has associated anaemia, a blood transfusion should be given.
- Monitor the central venous pressure while infusing the fluids, keeping it at 0–5 cm of H2O to avoid fluid overload.
- Dopamine infusion can be started at a dose of 0.5 mcg/kg/minute.
- Third generation cephalosporins or Benzyl penicillin with Gentamicin can be administered to cover for bacteremia.

Spontaneous bleeding and coagulopathy

Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets, if available); give vitamin K injection (1 mg IM stat in children, 30mg IM stat in adults).

Bleeding and coagulation abnormalities

Severe thrombocytopenia will require a platelet transfusion. Fresh frozen plasma may be considered when platelets are unavailable.

Disseminated intravascular coagulation (DIC) can be confirmed by measuring plasma concentrations of fibrinogen and fibrin degradation products. Treatment of DIC involves administration of fresh whole blood or fresh frozen plasma and injection of Vitamin K 10 mg (1 mg in children). Patients with expanded blood volume on central venous pressure assessment should receive an exchange transfusion with fresh blood, to avoid fluid overload.

Hemoglobulinuria ('Black water fever')

Due to hemoglobinemia, the hemoglobin estimation may be unreliable. Treatment of hemoglobulinuria is directed at treatment of the anaemia and renal failure.

7.7 Concomitant use of antibiotics

After the start of antimalarial treatment, unexplained deterioration may result from a supervening bacterial infection. Septicaemia and severe malaria may occur concurrently particularly in children. Thus broad-

spectrum antibiotic treatment should be given with antimalarial drugs if bacterial infection is also suspected. Antibiotic treatment should be based on culture and sensitivity results or, if not available, local antibiotic sensitivity patterns.

8. Malaria prophylaxis

Malaria prophylaxis is not necessary for persons living in an area with a high malaria transmission pattern because it may lower one's resistance to the disease. Prophylaxis may, however, be used in sickle cell disease patients and in non-immune visitors because of risk for severe disease. It is important to note that chemoprophylaxis does not offer 100% protection.

8.1 Risk groups

Risk groups that should be given antimalarial chemoprophylaxis include:

- Patients with sickle cell disease.
- Visitors from low-risk regions to high-risk regions.
- Visitors from countries and/or areas where there is no malaria transmission (non-immunes).
- Patients who have had a splenectomy.
- Patients taking cytotoxic or immunosuppressive medicines for malignant disease.

8.2 Sickle cell disease

The recommended prophylaxis is Deltaprim (Maloprim). This is a combination tablet containing pyrimethamine and dapsone used for malaria prophylaxis.

Dosage for adults: (1 tablet) 12.5 mg pyrimethamine and 100 mg dapsone tablet taken once per week, preferably in the morning.

Dosage for children 5–10 years of age: 1/2 tablet taken once per week, preferably in the morning.

Dosage for children less than five years of age: 1/4 tablet taken once per week, preferably in the morning.

8.3 Visitors (non-immunes) to Zambia

The options include mefloquine, atovaquone-proguanil (Malarone), and doxycycline. Begin taking mefloquine two weeks prior to arrival in Zambia, continued weekly during the stay, and continued weekly for two weeks following departure from Zambia. Begin taking atovaquone-proguanil 1-2 days before travel, daily during the visit and 7 days after leaving Zambia. Begin taking doxycycline prior to arrival and continue to take for 4 weeks after leaving Zambia. Visitors are

encouraged to use other effective protective measures such as long-lasting insecticide-treated nets (LLINs) and using insect repellents among others.

Note: If the patient develops fever despite taking malaria chemoprophylaxis they should promptly seek medical attention.

See Annex 6 for more information about antimalarial prophylaxis for travellers.

9. Pharmacovigilance

Pharmacovigilance is the practice of monitoring the safety and efficacy of medicines for purposes of early detection and prevention of unwanted adverse outcomes. This is a critical component of patient care where healthcare professionals have a particularly important role to play. However, pharmacovigilance requires active participation of all stakeholders including patients, caregivers, general members of the public, pharmaceutical manufacturers, healthcare professionals and medicines regulators.

In Zambia, the pharmacovigilance system is coordinated by the Zambia Medicines Regulatory Authority (ZAMRA).

ZAMRA receives all adverse drug reaction reports, manages the national ADR database, distributes reporting forms, conducts causality assessment on received ADRs, and provides feedback to the reporters.

10. References

1. *Zambia 2015 National Malaria Indicator Survey*, Ministry of Health Zambia, April 2016.
2. Sitali L, Chipeta J, Miller JM, Moonga HB, Kumar N, Moss WJ, Michelo C. Patterns of mixed Plasmodium species infections among children six years and under in selected malaria hyper-endemic communities of Zambia: population-based survey observations. *BMC Infect Dis*. 2015 May 2;15:204. doi: 10.1186/s12879-015-0935-7.
3. Laban NM, Kobayashi T, Hamapumbu H, Sullivan D, Mharakurwa S, Thuma PE, Shiff CJ, Moss WJ, Southern Africa International Centers of Excellence for Malaria Research. Comparison of a PfHRP2-based rapid diagnostic test and PCR for malaria in a low prevalence setting in rural southern Zambia: implications for elimination. *Malar J*. 2015 Jan 28;14:25. doi: 10.1186/s12936-015-0544-3.
4. Zambia Ministry of Health, *Zambia Malaria Elimination Strategic Plan 2017-2021*, 2016.
5. Thu AM, Phyo AP, Landier J, Parker DM, Nosten FH. Combating multidrug-resistant Plasmodium falciparum malaria. *FEBS J*. 2017 Jun 5. doi: 10.1111/febs.14127. [Epub ahead of print]

6. Thanh NV, Thuy-Nhien N, Tuyen NT, Tong NT, Nha-Ca NT, Dong LT, Quang HH, Farrar J, Thwaites G, White NJ, Wolbers M, Hien TT. Rapid decline in the susceptibility of Plasmodium falciparum to dihydroartemisinin-piperaquine in the south of Vietnam. *Malar J*. 2017 Jan 13;16(1):27. doi: 10.1186/s12936-017-1680-8.
7. Imwong M, Jindakhad T, Kunasol C, Sutawong K, Vejakama P, Dondorp AM. An outbreak of artemisinin resistant falciparum malaria in Eastern Thailand. *Sci Rep*. 2015 Nov 30;5:17412. doi: 10.1038/srep17412.
8. Crawley J, Chu C,Mtove G, Nosten F. Malaria in children. *Lancet*. 2010;375:1468–81.
9. John CJ. Malaria (Plasmodium). In: Kliegman R, Nelson WE, editors. *Nelson textbook of Paediatrics, vol. 1*. 20th ed. Philadelphia: Elsevier/ Saunders; 2016. p. 1709–21.
10. Centre for Disease Control (CDC). *Treatment of Malaria (Guidelines for Clinicians)*. Available at: http://www.cdc. gov/malaria/diagnosis_treatment/clinicians1.html. Accessed 13 August 2017.
11. Abba K, Deeks JJ, Olliaro P, Naing CM, Jackson SM, Takwoingi Y, Donegan S, Garner P. Rapid diagnostic tests for diagnosing uncomplicated P.

falciparum malaria in endemic countries. *Cochrane Database Syst Rev*. 2011 Jul 6;(7):CD008122. doi: 10.1002/14651858.CD008122.pub2. Review.
12. Odaga J, Sinclair D, Lokong JA, Donegan S, Hopkins H, Garner P. Rapid diagnostic tests versus clinical diagnosis for managing people with fever in malaria endemic settings. *Cochrane Database Syst Rev*. 2014 Apr 17;(4):CD008998. doi: 10.1002/14651858.CD008998.pub2. Review.
13. WHO. *Guidelines for treatment of malaria*. 3rd edition, 2015. Available at: http://www.who.int/malaria/publications/atoz/9789241549127/en/. Accessed 13th August 2017.
14. Sinclair D, Zani B, Donegan S, Olliaro P, Garner P. Artemisinin-based combination therapy for treating uncomplicated malaria. *Cochrane Database Syst Rev*. 2009 Jul 8;(3):CD007483. doi: 10.1002/14651858.CD007483.pub2. Review.
15. Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin-piperaquine for treating uncomplicated Plasmodium falciparum malaria. *Cochrane Database Syst Rev*. 2014 Jan 20;(1):CD010927. doi: 10.1002/14651858.CD010927.

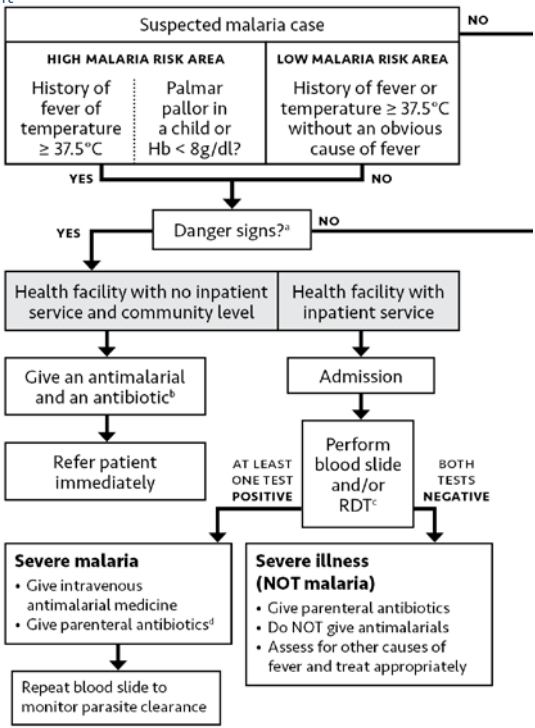
16. Srikanta Basu1 & Puneet Kaur Sahi. Malaria: An Update. *Indian J Pediatr* (July 2017) 84(7):521–528 DOI 10.1007/s12098-017-2332.
17. *Management of Severe Malaria: A practical hand book*. Second edition. World Health Organization. Geneva, 2000.

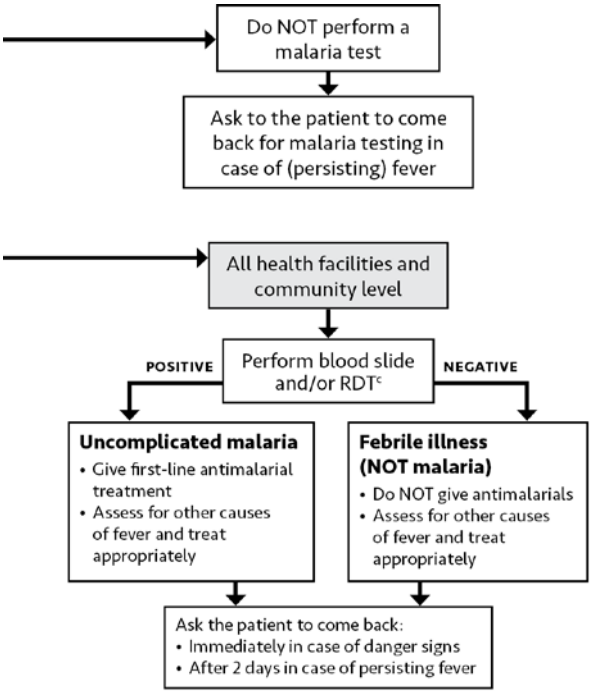
Recommended further readings

- Malaria in India. Guidelines for its control. National Vector Borne Disease Control Programme. Available at: http://www.nvbdcp.gov.in/malaria-new.html
- National drug policy on malaria (2013). Ministry of Health /Directorate of Clinical Care and Diagnostics, Zambia. Available at: http://www.nvbdcp.gov.in
- Rapid diagnostic tests. Website of WHO Regional Office for the Western Pacific. Available at: http://www.wpm.who.int/sites/rdt
- WHO Guidelines for the treatment of malaria, second edition. Geneva: World Health Organization (2010). Available at: http://www.who.int/malaria/publication/atoz/9789241547925/enindex.html

- Regional guidelines for the management of severe falciparum malaria in small hospitals, World Health Organization, Regional Office for South-East Asia (2006). New Delhi: WHO/ SEARO. Available at: http://www.searo.who.int/entity/malaria/documents/Gudeline_Sevmal_SMHosp/en/
- Regional guidelines for the management of severe falciparum malaria in large hospitals. World Health Organization, Regional Office for South-East Asia (2006). New Delhi: WHO/ SEARO. Available at: http://www.searo.who.int/entity/malaria/documents/SEA_GUidelines_Servmal_LH/en/
- Bloland PB. Drug resistance in malaria. WHO/CDS/CSR/DRS/2001.4. 2001. Available at: http://www.who.int/csr/resources/publications/drugresist/malaria.pdf.
- Kochar DK, Das A, Kochar SK, Saxena AV, Sirohi P, Garg S, Kochar A, Khatri MP, Gupta V (2009). Severe Plasmodium vivax malaria: A report on serial cases from Bikaner in northwestern India. Am J Trop Med Hyg 80 (2): 194–8.

Annex 1: Algorithm for malaria diagnosis and treatment, first visit





a The following danger signs are considered criteria for referral at peripheral level:
In children: inability to drink or breask feed, vomiting everything, convulsion, lethargic or unconscious, neck stiffness, chest indrawing, or stridor.
In adults: weak or unable to stand, lethargic or unconscious, neck stiffness, convulsions, respiratory distress or severe abdominal pain.

b Rectal artesunate is recommended as pre-referral treatment.

c Rapid diagnostic test (RDT) is performed while waiting for the result of the blood slide to decide on earlier treatment and to document malaria in the patients who have received pre-referral antimalarial treatment (and thus may have already cleared their parasites).

d Because of the concomitant bacterial infection in severe malaria patients, especially in children, antibiotics should be given along with antimalarials until bacterial infections have been ruled out (by bacteremia by blood culture if available).

Annex 2. Integrated management of childhood illness algorithm

Does the child have fever?

(by history or feels hot or temperature 37.5°C or above)

If yes:

Decide malaria risk: high or low

Then ask:

- For how long?
- If more than 7 days, has fever been present every day?
- Has the child had measles within the last 3 months

Look and feel:

- Look or feel for stiff neck
- Look for runny nose
- Look for any other causes of fever**
- Look for signs of MEASLES:
  - Generalized rash plus either cough, runny nose, or red eyes

Classify FEVER
High or low malaria risk

Do a malaria test, if NO general danger sign or stiff neck:

- In all fever cases if **high malaria risk**.
- In **low malaria risk** if no obvious cause of fever present.

If the child has measles now or within the last 3 months:

- Look for mouth ulcers. Are they deep and extensive?
- Look for pus draining from the eye.
- Look for clouding of the cornea.

If MEASLES now or within last 3 months, classify

† These temperatures are based on axillary temperature. Rectal temperature readings are approximately 0.5°C higher.

** Look for local tenderness, oral sores, refusal to use a limb, hot tender swelling, red tender skin or boils, lower abdominal pain or pain on passing urine.

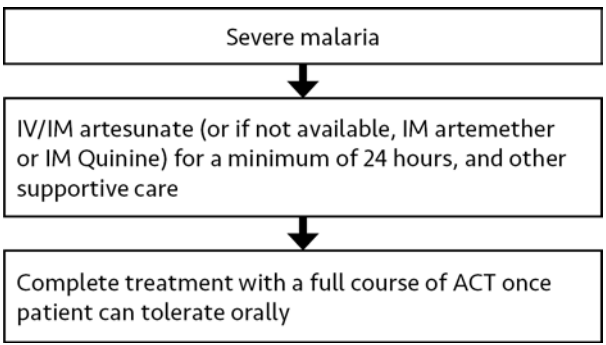
*** If no malaria test available:
High malaria risk—classify as MALARIA
Low malaria risk and no obvious cause of fever—classify as MALARIA

**** Other important complications of measles—pneumonia, stridor, diarrhoea, ear infection, and malnutrition—are classified in other tables.

• Any general danger sign or • Stiff neck	Pink: VERY SEVERE FEBRILE DISEASE	• **Give first dose of artesunate for severe malaria** • **Give first dose of an appropriate antibiotic** • **Treat the child to prevent low blood sugar** • **Give one dose of paracetamol in clinic for high fever (38.5°C or above)** • **Refer URGENTLY to hospital**
• Malaria test POSITIVE ***	Yellow: MALARIA	• **Give recommended first-line oral antimalarial** • **Give one dose of paracetamol in clinic for high fever (38.5°C or above)** • Advise mother when to return immediately • Follow up in 3 days if fever persists • If fever is present every day for more than 7 days, refer for treatment
• Malaria test NEGATIVE • Other cause of fever PRESENT	Green: Fever: No MALARIA	• **Give one dose of paracetamol in clinic for high fever (38.5°C or above)** • Assess for other causes of fever and give appropriate treatment • Advise mother when to return immediately • Follow up in 3 days if fever persists • If fever is present every day for more than 7 days, refer for treatment

• Any general danger sign or • Clouding of the cornea • Deep or extensive mouth ulcers	Pink: SEVERE COMPLICATED MEASLES ****	• **Give vitamin A treatment** • **Give first dose of an appropriate antibiotic** • **If clouding of the cornea or pus draining from the eye, apply tetracycline eye ointment** • **Refer URGENTLY to hospital**
• Pus draining from the eye • Mouth ulcers	Yellow: MEASLES WITH EYE OR MOUTH COMPLICATIONS****	• **Give vitamin A treatment** • **If pus draining from the eye, apply tetracycline eye ointment** • If mouth ulcers, treat with gentian violet • Follow up in 3 days
• Measles now or within last 3 months	Green: Measles	• **Give vitamin A treatment**

Annex 3. Algorithm for management of severe malaria



Annex 4. Glasgow Coma Scale (only applicable to patients above 12 years old)

To calculate the Glasgow Coma Scale, take the score for each section, and then add the three figures together to obtain a total score. A score of <10 is considered as a state of "unarousable coma". This scale can be used repeatedly to assess patient improvement or indeed a deteriorating condition.

Test	Response	Score
Eyes open	Spontaneously	4
	To speech	3
	To pain	2
	Never	1
Best verbal response	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
Best motor response	Obeys commands	5
	Localizes pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1

Annex 5: The Blantyre Coma Scale (used in children ages 9 months to 12 years old)

This coma scale is used in children aged between 9 months and 12 years.

A score ≤2 is considered "unarousable coma"

Test	Response	Score
Eyes open	Directed (e.g., toward care giver's face)	1
	Not directed	0
Best verbal response	Appropriate cry	2
	Moan or inappropriate cry	1
	None	0
Best motor response	Localizes pain stimuli	2
	Withdraws limb from pain	1
	Non-specific or absent response	0

Annex 6. The use of anti-malarials for prophylaxis in travelers

Prophylaxis in sickle cell disease

Generic name: Pyrimethamine+Dapsone (Deltaprim/maloprim)

Tablet size	Adult dosage	Paediatric dosage
1 tablet of deltaprim contains 12.5 mg pyrimethamine +100 mg dapsone	1 tablet taken once per week, preferably in the morning	Children 5–10 years: ½ tablet taken once per week preferably in the morning Children less than 5 years: ¼ tablet taken once per week, preferably in the morning

Adverse effects

Side effects at the recommended dose are rare. Cyanosis has been reported for higher doses or if taken for prolonged periods. It is contraindicated in those with a sulphonamide sensitivity.

Generic name: Atovaquone-Proguanil

Tablet size	Adult dosage	Paediatric dosage
250 mg atovaquone and 100 mg proguanil (adult) 62.5 mg atovaquone and 25 mg proguanil (pediatric)	One tablet orally once daily; begin 1–2 days before travel and continue for 7 days after travel	Body weight 11–20 kg: 1 pediatric table daily Body weight 21–30kg: 2 pediatric tablets daily Body weight 31–40 kg: 3 pediatric tablets daily Body weight > 40 kg: 1 adult tablet daily

Adverse effects

Not recommended for prophylaxis for children weighing less than 5 kg, pregnant women, and women breastfeeding infants weighing less than 5 kg.

Take with food; do not use in persons with creatinine clearance less than 30 mL per minute; common adverse

events include nausea, abdominal pain, and headache; occasional adverse events include transient increase in transaminase levels with treatment doses; rare adverse events include rash.

Generic name: Doxycycline

Tablet size	Adult dosage	Paediatric dosage
Doxycycline 100 mg	One tablet orally once daily; begin 1–2 days before travel and continue for 4 weeks after travel	≥ 8 years old, 2 mg per kg of body weight orally once daily (max. dosage, 100 mg/day)

Adverse effects

Should be taken at approximately the same time each day while in the malarious area and for four weeks after leaving such areas. Contraindicated in children under eight years old and pregnant women. Contraindicated in persons with hypersensitivity to tetracyclines.

Generic name: Mefloquine

Tablet size	Adult dosage	Pediatric dosage
Mefloquine 250 mg	One tablet orally once weekly; begin 1–2 days before travel and continue for 4 weeks after travel	Body weight ≤ 9 kg, 5 mg per kg weekly; body weight 10–19 kg, a quarter tablet; body weight 20–30 kg, a half tablet; body weight 31–45 kg, a three-quarter tablet; body weight ≥ 46 kg, 1 tablet

Mefloquine should be taken at least two weeks before travel to malarious areas. While in the malarious area it should be taken weekly on the same day of the week and for four weeks after leaving such areas.

Adverse effects

It is contraindicated in people allergic to mefloquine or related compounds (quinine, quinidine) and in people with active depression, a recent history of depression, generalised anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures.

Persons with psychiatric disturbances or a previous history of depression should use with caution. It is not recommended for persons with cardiac conduction abnormalities.