

GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF MALARIA IN ZAMBIA

FOURTH EDITION

2014



Foreword

Malaria is still a major cause of sickness and death in Zambia. Children under five years of age and pregnant women are at risk of serious illness, but malaria affects all levels of society. The Ministry of Health (MoH) is absolutely dedicated to ensuring that this disease is addressed at all levels and on all fronts. The MoH approach to ensure maximum impact on malaria focuses on the integration of the most effective prevention and treatment tools. Both indoor residual spraying (IRS) of insecticides and large-scale use of long-lasting insecticide-treated nets (LLINs) will be promoted to have the most rapid and sizable impact on the transmission of the disease. The importance attached to the management of malaria at the community level, availability of the most effective medicines at all levels of the health system, and use of the newest diagnostic tools including rapid diagnostic tests to ensure proper diagnosis at lower health facilities and at the community level are all key approaches to ensure the highest possible quality of case management.

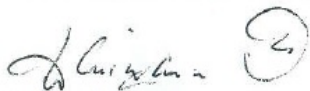
With this combination of approaches, the MoH aims to have a dramatic impact on the level of malaria in the country.

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 fourth edition guidelines are intended to provide useful updated information to all health

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workers on the diagnosis and management of malaria at all levels of the health care system. It also contains additional information such as a chapter on malaria prophylaxis for special populations.

I hope that these guidelines will continue to serve as an important source of reference material for general malaria management. I equally 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.

A handwritten signature in black ink, which appears to read 'Davy Chikamata', is written over a circular stamp. The stamp contains some illegible text and a central emblem.

Dr Davy Chikamata
Permanent Secretary
Ministry of Health

Acknowledgements

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

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Dr Elizabeth Chizema-Kawesha

Director

Disease Control, Surveillance and Research

Acronyms

ACT	Artemisinin-based combination therapy
ADR	Adverse drug reaction
AL	Artemether-lumefantrine
cm	Centimeter
CHA	Community health assistants
CHW	Community health workers
CRF	Case Report Form
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
IMCI	Integrated Management of Childhood Illness
IPTp	Intermittent preventive treatment
ITNs	Insecticide-treated nets
IV	Intravenous
kg	Kilogram
LLINs	Long-lasting insecticide-treated nets
mg	Milligram
ml	Millilitre
Mm Hg	Millimetre of mercury
µL	Micro litre
MoH	Ministry of Health
NMCP	National Malaria Control Programme

RBC	Red blood cell
RDT	Rapid diagnostic test
SP	Sulfadoxine-pyrimethamine
UNICEF	United Nations Children's Fund
WHO	World Health Organization
ZPVC	Zambia Pharmacovigilance Centre

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Chapter 1: Introduction

1.1 Introduction

Malaria is a protozoa infection of the genus *Plasmodium*. It is transmitted through the bite of an infected female mosquito belonging to the genus *Anopheles* (*An.*). In Zambia, there are three species that can transmit human malaria: *An. gambiae*, *An. arabiensis*, and *An. funestus*. They differ from many other mosquitoes common in Zambia by being late-night feeders (thus the rationale for sleeping under insecticide-treated mosquito nets [ITNs]). Malaria is generally endemic throughout the country although the country is stratified by high (hyper-endemic), moderate (meso-endemic), and low (hypo-endemic) areas. Urban areas of the country, including Lusaka, tend to have very low transmission. Malaria is by and large more prevalent in rural parts of Zambia.

Five species of *Plasmodium* (*P.*) parasites cause infections in humans: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*. Each species has a different biological pattern through which it affects humans. The most common species that is clinically significant and causes the most lethal form of malaria is *P. falciparum*.

In Zambia, *P. falciparum* accounts for more than 95% of malaria cases, with *P. malariae* comprising 3%, and *P.*

ovale 2%. *P. vivax* is rare in Zambia and no documented cases of *P. knowlesi* have been reported in Zambia to date.

Tremendous efforts have been made to reduce the burden of malaria in the country; the national incidence rate is now 373 cases per 1,000 people (Ministry of Health [MoH] (a), 2012). The malaria parasite prevalence of infection in children under five years of age has decreased from 22.1% in 2006 to 14.9% in 2012 (MoH (c), 2012).

The National Malaria Control Centre estimates that there are fewer than 4,000 deaths per year due to malaria (MoH (a), 2012). Malaria also has an impact on pregnant women, contributing significantly to maternal deaths, maternal anaemia, premature delivery, and low-birth-weight infants. Hospital admissions due to malaria and fatality rates have also increased during the same period.

Since 2003, the MoH has adopted the use of artemisinin-based combination therapy (ACT) as treatment for uncomplicated malaria in order to reduce the malaria disease burden in Zambia.

This *Guidelines* document presents revised treatment recommendations based on the latest available evidence. Key updated policy decisions found in this document are summarized below.

Uncomplicated malaria (see section 2.2 for definition)

1. First-line treatment:
 - a. Artemether-lumefantrine (AL), an ACT (children below 5 kg of weight should be treated under medical supervision).
 - b. Sulphadoxine-pyrimethamine (SP) for children below 5 kg of weight.
 - c. Alternative first-line choice for uncomplicated malaria is dihydroartemisin-piperaquine.
2. Second-line treatment:
 - a. In case of failure of the first-line medicine in all age groups, quinine is the medicine of choice.

Severe malaria (see section 2.3 for definition)

1. Injectable artesunate is the drug of choice in adults and children with severe malaria.
2. If injectable (IV) artesunate is unavailable, artemether (intramuscular [IM]) or quinine (IV/IM) are suggested alternatives.
3. Following initial parenteral treatment for a minimum of 24 hours, 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.

Pre-referral treatment

1. The first option should be to give IM artesunate or

rectal artesunate; if that is not available, then give IM quinine.

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

Adults: One or more artesunate suppositories inserted in rectum. Dose should be given once and followed as soon as possible by definitive therapy for malaria.

A patient who is given IM quinine as pre-referral treatment will need a second dose in just 4 hours. However, a patient who receives IM artesunate as pre-referral treatment will be due for a second dose after 12 hours, allowing sufficient time to reach the hospital to which they have been referred.

Malaria in pregnancy

1. Uncomplicated malaria
 - a. First-line treatment
 - i. Quinine in the first trimester of pregnancy.
 - ii. Artemether-lumefantrine in the second and third trimesters of pregnancy.

- b. Second-line treatment in second and third trimesters
 - i. Quinine should be used in all cases of failure of first-line treatment.
2. Severe malaria
 - a. Quinine in the first trimester of pregnancy.
 - b. Injectable artesunate in the second and third trimesters of pregnancy.
3. Intermittent preventive treatment during pregnancy (IPTp)
 - a. Sulphadoxine-pyrimethamine should be used for IPTp during the second and third trimesters of pregnancy on a monthly basis at all scheduled antenatal care visits.

1.2 Policy on Parasite-Based Diagnosis

In view of the national malaria treatment policy with ACT as first-line treatment of uncomplicated malaria, the fact that malaria is the number one killer disease in most areas of the country, and the frequent misdiagnosis of malaria in the absence of laboratory confirmation:

- Parasite-based diagnosis with microscopy or rapid diagnostic tests (RDTs) should be part of malaria case management in all health facilities.
- All suspected malaria cases shall be subjected to

parasite-based diagnosis and treatment initiated in accordance with the test result. For children below five years presenting with fever to the first level of health care, treatment should be initiated according to the Integrated Management of Childhood Illness (IMCI) guidelines (WHO/UNICEF, 2008).

- The two methods to be used for parasitological diagnosis in this policy are microscopy and RDTs. The choice between RDTs and microscopy will depend on:
 - Local circumstances.
 - Level of health care including the skills available.
 - The usefulness of microscopy for diagnosis of other diseases.
 - Health system infrastructure for laboratory services in the country.

In this respect:

- Microscopy will be deployed in the public health sector according to the current national laboratory policy.
- RDTs will be deployed in all health facilities. However, priority will be given to facilities where deployment of microscopy may not be possible.
- In the private sector, all private health facilities managing fever cases will follow the recommended policy of using microscopy or RDTs for parasitological confirmation of malaria.
- RDTs will also be deployed at the community

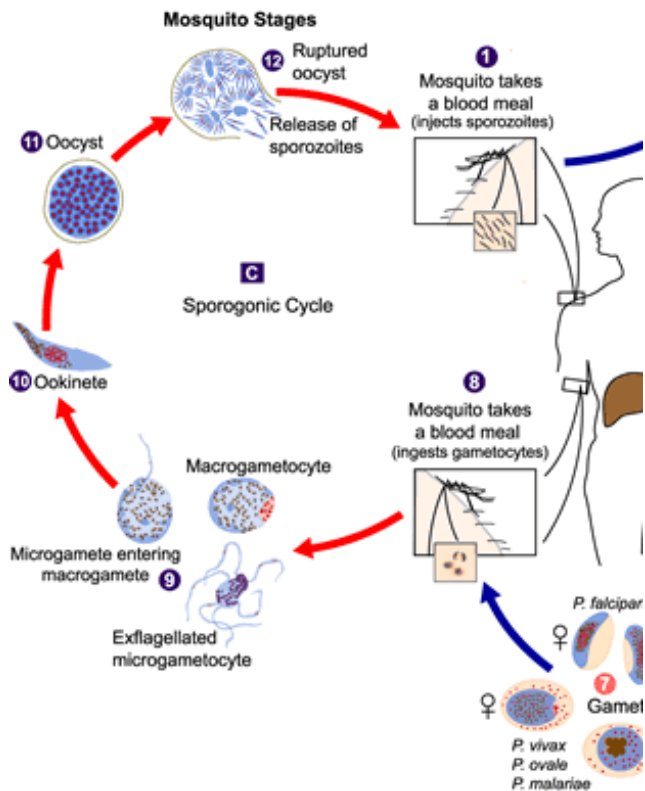
level in the context of integrated community case management (iCCM) of malaria.

- The type of RDTs to be deployed in the country will be guided by high sensitivity, specificity, and stability in the field guided by the performance and pre-qualification schemes of the World Health Organization (WHO). However, practical experience and operational evidence will continue to be carefully monitored and evaluated.

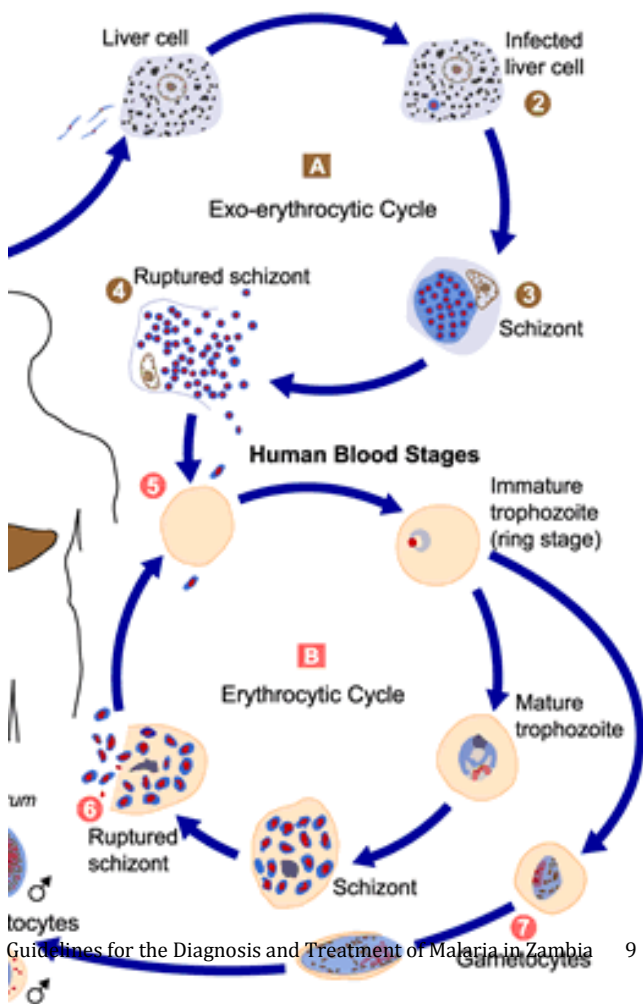
1.3 Pathogenesis of Malaria

Human infection begins when a female *Anopheles* species mosquito inoculates *Plasmodia* sporozoites into the blood system while feeding. Once inside the body, the parasite moves to the liver, where it enters a hepatocyte and develops. From the liver it enters the blood stream and multiplies inside the red blood cells. Capillaries in major organs are occluded and organ function is impaired. This complex life cycle of development of the *Plasmodium* parasite gives way to the different clinical symptoms in the human host (see Figure 1).

Figure 1: Life cycle of the malaria parasite



Human Liver Stages



Source: Centers for Disease Control and Prevention, 2013

The invasion, alteration, and destruction of red blood cells by the malaria parasites, local and systemic circulatory changes, and the related metabolic abnormalities are all important in the pathophysiology of malaria.

P. falciparum is especially lethal as it invades red blood cells of all ages making the infection difficult to be destroyed by the human immune system. *P. vivax* and *P. ovale* invade only young reticulocytes.

P. falciparum has a natural affinity for soft tissues causing sequestration in the brain, kidneys, and blood vessels, and consequently causing extremely high levels of parasitaemia, pronounced anaemia, and cerebral malaria—factors that contribute to the severity of the disease.

Drug resistance to *P. falciparum* has also been shown to develop faster than with other *Plasmodium* strains. It is owing to these factors that malaria infection that is predominantly due to *P. falciparum* causes grave consequences.

Chapter 2: Clinical Features

2.1 Introduction

The incubation period of malaria ranges from 10 to 14 days depending on the parasite species. The first attacks are usually more severe and may persist for weeks, if untreated. Malaria infection is a serious condition that can lead to severe malaria or death if treatment is delayed. Relapse occurs when parasites persisting in the liver reinvade the bloodstream (this is common with *P. ovale* and *P. vivax*).

The onset of malaria caused by *P. falciparum* may be challenging to diagnose. It is characterized by fever, which may be continuous, recurring, or irregular. If the acute attack is treated rapidly using effective medicines, the disease is usually mild and recovery uneventful. If inadequately treated in an individual, sequestration of infected red blood cells in the deep tissues can cause serious complications leading to severe malaria and death.

In areas of intense transmission such as Zambia, *P. falciparum* malaria during pregnancy is extremely dangerous to both the mother and the unborn baby. It is also particularly dangerous in children under five years of age and visitors from areas of low or no malaria transmission.

Malaria may manifest clinically either as an acute uncomplicated disease or as severe malaria. In areas of intense transmission, high proportions of infected persons have partial immunity to malaria and are often asymptomatic. A careful assessment of the patient with suspected malaria is essential in order to differentiate between the acute uncomplicated and severe disease, as this has therapeutic and prognostic implications.

2.2 Clinical Manifestations

Clinical manifestations may be categorized into symptoms of uncomplicated malaria and those of severe malaria.

2.3 Uncomplicated Malaria

Early symptoms are usually non-specific and are often characterized by intermittent febrile illness. Fever is the most common symptom. Headache, aching joints, back pain, nausea, vomiting, and general discomfort usually accompany fever.

It should be noted that the patient may not present with fever but may have had a recent history of fever. This is due to the natural malaria cycle. A history of fever during the previous two days along with other symptoms of malaria is a clinical basis for suspecting malaria.

It is equally important to note that fever is a common

symptom for other infections besides malaria, such as ear infections, measles, and respiratory infections. Malaria has been nicknamed "The Great Imitator" because of this. The possibility of other infections, either co-existing with malaria or as the sole cause of fever, should always be borne in mind when determining the diagnosis. It is therefore important to exclude other causes of fever.

In children, the onset of malaria may be characterized, in the early stages, only by symptoms like poor appetite, restlessness, cough, diarrhoea, malaise, and loss of interest in the surroundings.

2.4 Severe Malaria

P. falciparum infection in the presence of any life-threatening condition is considered as severe malaria. Some of the life-threatening conditions include signs and symptoms such as:

- Cerebral malaria, defined as coma not attributable to any other cause in a patient with *P. falciparum* malaria
- Generalized convulsions (more than two episodes within 24 hours)
- Coma or altered level of consciousness
- Drowsiness or lethargy
- Prostration (inability to sit or stand without support)

- Acute pulmonary oedema (adult respiratory distress syndrome)
- Hypotension and shock (systolic blood pressure of less than 50 mm Hg in children 1–5 years of age and less than 80 mm Hg in adults (cold moist skin, low blood pressure, collapse)
- Persistent/excessive vomiting
- Abnormal bleeding (spontaneous or prolonged bleeding from puncture sites)
- Fluid and electrolyte disturbances
- Acute renal failure (failure to pass urine or passing very little urine—less than 400 ml in 24 hours in adults and less than 2 ml per kg in 24 hours in children)
- Jaundice

In addition, relevant laboratory indicators include:

- Hyperparasitaemia (proportion of parasitized red cells >5% in the non-immune and >10% in the semi-immune population)
- Acidosis (metabolic) (plasma bicarbonate <15 mmol/L)
- Severe normocytic anaemia (haemoglobin (Hb) <5g/dl or packed cell volume [PVC] < 15%)
- Hyperlactataemia (lactate >5 mmol/L)

- Renal impairment (creatinine >265 µmol/L)
- Haemoglobinuria
- Hypoglycaemia (blood glucose <2.2 mmol/L or <40 mg/dl)

These severe manifestations can occur singly or, more commonly, in combination in the same patient.

Table 1: Signs and symptoms of malaria

UNCOMPLICATED MALARIA	SEVERE AND COMPLICATED MALARIA
Fever	Severe anaemia (Hb <5 g/dl)
Headache	Jaundice
Sweats and chills	Drowsiness
Body pains	Convulsions
Acute gastroenteritis	Respiratory distress
Nausea	Unconsciousness/coma
	Change in behavior
	Hyperparasitaemia
	Prostration (i.e., generalized weakness, inability to stand or walk)
	Abnormal bleeding
	Dehydration
	Hepatomegaly
	Splenomegaly

2.5 Occurrence Indicators of Severe Malaria

Table 2 shows the difference in the severe manifestations of malaria in adult and paediatric populations.

Table 2: Occurrence indicators of severe malaria

Clinical manifestation	Frequency of occurrence	
	Children	Adults
Prostration	+++	+++
Impaired consciousness	+++	++
Respiratory distress	+++	++
Multiple convulsions	+++	+
Circulatory collapse	+	+
Pulmonary oedema	+	+
Abnormal bleeding	+	+
Jaundice	+	+++
Haemoglobinuria	+	+
Laboratory indices		
Severe anaemia (Hb <5 g/dl)	+++	+
Hypoglycaemia	+++	++
Acidosis	+++	++
Hyperlactataemia	+++	++
Renal impairment	+	+++
Clinical and Laboratory Features of Severe Malaria		
Key: +++ High ++ Moderate + Rare - None		

Chapter 3: Diagnosis

3.1 Introduction

Early diagnosis and prompt effective treatment are of vital importance in the management of malaria. The signs and symptoms of malaria are nonspecific. Diagnosis based on clinical features alone has very low specificity and often results in over-treatment. Confirmatory diagnosis plays an important supportive role in clinical care.

Diagnosis of malaria should be based on parasitological confirmation (laboratory). A careful medical history and a physical examination should be performed. A complete history should include common symptoms of malaria, age, place of residence, recent history of travel, previous treatment(s), and other illnesses. In children, refusal to eat or feed and decreased activity should be noted. A history of fever in the last 48 hours with or without other symptoms of malaria or a current history of fever (temperature $\geq 37.5^{\circ}\text{C}$) is adequate ground for suspicion of malaria but does not constitute a confirmatory diagnosis. A parasitological confirmation of malaria is recommended; it improves the differential diagnosis of fever, improves fever case management, and reduces unnecessary use of antimalarial medicines. Antimalarial treatment on the basis of clinical suspicion of malaria should only be considered in situations where a parasitological diagnosis is not

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immediately accessible.

Parasitological confirmation (laboratory) is done by examining either a blood smear/slide or malaria RDT. Molecular testing can also be used to confirm a diagnosis of malaria. In the presence of suggestive signs and symptoms of malaria with negative microscopy or RDT results, a re-evaluation of the patient to rule out the presence of any other cause of fever for children under the age of five, further evaluation, classification, and treatment should be performed according to the IMCI guidelines (refer to Chapter 4: Integrated Management of Childhood Illness and Appendix A1-A2).

3.2 Confirmatory (Laboratory) Diagnosis

A parasitological confirmation of malaria improves the differential diagnosis of fever, improves fever case management, and reduces unnecessary use of antimalarial medicines. It also assists the health care provider to monitor the patient's response to treatment. Parasite density (particularly in areas of low endemicity) is an important indicator of severity of disease. However, in areas of high endemicity the general population may tolerate very high levels of parasitaemia with less severity in the clinical manifestation.

3.3 Light Microscopy

Among the advantages of light microscopy:

- It is cheap (apart from the initial investment in the procurement of the microscope, the operational cost is low, especially in areas of very high patient load).
- In skilled hands, it is sensitive.
- It can differentiate between species.
- It can determine parasite density levels.
- It can also be used for the diagnosis of other medical conditions.
- It can be used to monitor treatment response.

In Zambia, the Giemsa stain technique is currently recommended.

The standard examination of a thick film is at least 100 microscope fields, examined at a magnification of 600X to 700X. The limit of detection is approximately 10 to 12 parasites per microlitre of blood, which corresponds to approximately 0.004% parasitaemia.

Requirements for this method include: slide, sterile lancets, 70% methanol or 70% isopropanol, cotton wool, slide box (to protect drying blood films), marker or pencil, staining jar, Giemsa stock solution, distilled (or ordinary) water, and measuring cylinder.

Thin smears are first fixed by dipping in methanol before staining. For rapid diagnosis, the stock solution is diluted to 10–15% at which concentration staining duration is 10 to 15 minutes. Slow staining, which gives clearer results, takes about 30 to 45 minutes, and the concentration of the stain is 3%. Examination is done using a 100X oil immersion lens objective and a 10X or 7X eye-piece.

Parasite numbers are normally counted as either the number of parasites per microscope field or per white blood cells (leucocytes). If the latter is used, considering an average leucocyte count of 8000/microlitre, the parasite density count can be expressed as:

$$\text{Parasite/microlitre of blood} = \frac{\text{Number of parasites counted} \times \text{total WBC}}{\text{(number of WBC counted)}}$$

This means that if 200 white blood cells are counted, the parasites are multiplied by 40, and if 500 white blood cells are counted the parasites are multiplied by 16.

The presence of signs and symptoms of disease with a negative blood smear/slide does not preclude the diagnosis of malaria, particularly in endemic areas with high transmission. In the event that slide results are not conclusive or indeterminate by the laboratory technician, a rapid diagnostic test (RDT) could be performed to counter-check the status of the patient.

Microscopy should be used in the following situations:

- Where there is a well-functioning laboratory, unless the workload is excessively high, in which case RDTs can be used.
- RDTs are not intended to replace malaria microscopy and, therefore, all laboratory staff well-trained in malaria diagnostics are encouraged to use microscopy whenever possible.
- Blood slide examination is recommended to confirm the diagnosis in patients with suspected severe malaria; an RDT can be done if microscopy is not available. Patients with symptoms and signs of severe malaria should be started on antimalarial treatment immediately while waiting for the results of diagnostic tests, especially if it takes up to 2 hours before the results will become available.

3.4 Rapid Diagnostic Tests (RDTs) and Antigen Detection Tests

RDTs detect antigens derived from malaria parasites in lysed blood. The antigens include histidine-rich proteins (HRP I or II) produced by trophozoites and young (but not mature) gametocytes of *P. falciparum* and parasite lactate dehydrogenase (pLDH) produced by both asexual and sexual forms of the parasite.

RDTs have the following advantages:

- They are rapid.
- They are sensitive (based on results from WHO (b), 2012).
- They do not require skilled personnel.
- They do not require infrastructure.

RDTs are a laboratory commodity and should be ordered like any other laboratory supply. It is therefore the responsibility of the laboratory personnel to undertake the necessary quality assurance procedures in the use of RDTs.

The limitations of RDTs include:

- They cannot quantify parasitaemia.
- A limited possibility of false positive results.
- HRP II antigen-based RDTs are not recommended for follow-up of patients after treatment, as they may remain positive for up to 35 days following effective antimalarial treatment and parasite clearance.

RDTs should be used in the following situations:

- In health facilities where there are no microscopy services.
- In health facilities where there are no trained or poorly trained laboratory staff.
- During times when the laboratory is closed, such as nights, weekends, or when the laboratory staff is away.

- In very busy health facilities with insufficient staff to perform blood slides on all patients who need them, especially in outpatient clinics.
- In emergency cases that need very urgent malaria results in the outpatient or inpatient department.
- At community level by community health workers as part of a planned home-based care or screening programmes, such as iCCM.

3.5 Supportive Investigations

Other laboratory investigations that might be indicated in patients with malaria particularly in the presence of features of severity include:

Investigations to rule out complications:

- Haemoglobin
- Blood glucose estimation (children and patients with altered consciousness)
- Prothrombin time
- Bilurubin
- Urea and creatinine
- Chest X-ray
- Full blood count

Investigations for differential diagnosis:

- Lumbar puncture to exclude meningitis
- Blood culture
- Urine examination
- Chest X-ray

Chapter 4: Integrated Management of Childhood Illness

The Integrated Management of Childhood Illness (IMCI) is an approach to the management of illnesses specifically targeted at children aged five years and below. IMCI teaches health workers an effective approach for assessing and treating the most common childhood illnesses (such as malaria) at first-level health facilities. Children aged five years and below are particularly vulnerable to malaria, and its consequences are usually more serious than in older persons.

The cornerstones of IMCI are early recognition and prompt treatment of fever. Fever is one of the most common symptoms of malaria. The prompt management of fever minimizes the chances of disease complications. The updated IMCI Guidelines for Malaria are presented in Appendix A2 and are described further below (WHO/UNICEF, 2008).

The following are recommended steps in the management of fever in children under five years at first-level health facilities:

Ask and check for the general danger signs:

- Is the child able to drink or breast feed?

- Does the child vomit everything?
- Has the child had any convulsions?
- Is the child lethargic or unconscious (or prostrated)?

A child with any general danger sign has severe disease and needs urgent attention. Complete the assessment and commence appropriate treatment for severe disease.

4.1 Assessment of Fever

Ask: does the child have fever?

- Check to see if the child has a history of fever, feels hot, or has a temperature of 37.5°C or above.
- Ask whether the child has a history of fever or if the child has had any fever with this illness. Use words for “fever” that the caretaker understands. Make sure the caretaker understands what fever is.

Ask about (or measure) fever in ALL sick children.

- For how long? If more than 7 days, has the fever been present every day?

Ask, look, and feel for other causes of fever such as:

- Stiff neck
- Cough and/or difficulty breathing
- Ear infection
- Measles

- Diarrhoea

A child with fever and stiff neck may have meningitis. A child with meningitis needs urgent treatment with injectable antibiotics and referral to a hospital.

4.2 Classification of Fever

If the child has fever, classify for fever and for anaemia using the IMCI tables (WHO/UNICEF, 2008). Other causes of fever in children are classified under pneumonia and acute ear infection. Here we shall only classify for fever and anaemia.

There are two possible classifications for fever:

- Very severe febrile disease
- Malaria

Look at Appendix A2 and classify as shown in Table 3 below:

Table 3: Malaria classification according to Integrated Management of Childhood Illness (IMCI) guidelines

Signs	Classify as	Treatment
<ul style="list-style-type: none"> • Any general danger • Stiff neck 	Very severe febrile disease	<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Malaria test POSITIVE 	Malaria	<ul style="list-style-type: none"> • Give recommended first-line oral antimalarial • Give one dose of paracetamol in clinic for high fever (38.5° C or above) • Advise caregiver when to return

		<p>immediately</p> <ul style="list-style-type: none"> • Follow up in 3 days if fever persists • If fever is present every day for more than 7 days, refer for treatment
<ul style="list-style-type: none"> • Malaria test negative • Other cause of fever PRESENT 	<p>Fever: no malaria</p>	<ul style="list-style-type: none"> • 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 caregiver 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

4.3 Very Severe Febrile Disease

If the child with fever has any general danger sign or a stiff neck, classify the child as having **VERY SEVERE FEBRILE DISEASE**.

Treatment

A child with fever and any general danger sign or stiff neck may have meningitis, severe malaria (including cerebral malaria), or sepsis. It is not possible to distinguish between these severe diseases without laboratory tests. A child classified as having **VERY SEVERE FEBRILE DISEASE** needs urgent referral. Before referring, you will give several treatments for the possible severe diseases.

Give the child an initial dose of available first-line treatment choice (injectable [IV] artesunate if available) for severe malaria. Also give the first dose of an appropriate antibiotic for meningitis or other severe bacterial infection. Give treatment to prevent low blood sugar. Give paracetamol if there is a high fever.

4.4 Malaria

If a general danger sign or stiff neck is not present, look at the yellow row in Table 3. Because the child has a fever (by history, feels hot, or temperature 37.5°C or above) and is in a high malaria-risk area, classify the child as having **MALARIA**.

In Zambia the risk of malaria is high throughout the year; therefore, fever in a child may be due to malaria.

However, a diagnostic test needs to be performed and only then can a treatment choice be determined based on the test results.

Treatment

Treat a child classified as having MALARIA with an oral antimalarial (e.g., artemether-lumefantrine [AL]) if a RDT or microscopy for malaria is positive or if you are unable to test for malaria. If the malaria test is negative, look for other causes of fever.

Also, give paracetamol to a child with high fever (auxiliary temperature of 38.5°C or above).

Most viral infections last less than a week. A fever that persists every day for more than 7 days may be a sign of typhoid fever or other severe disease. If the child's fever has persisted every day for more than 7 days, refer the child for additional assessment.

4.5 Classify Anaemia

There are three classifications for a child with anaemia (Table 4). These are:

- SEVERE ANAEMIA
- ANAEMIA

- NO ANAEMIA

Severe Anemia

If the child has severe palmar pallor, this classifies the child as having SEVERE ANAEMIA.

Treatment

Children classified as having SEVERE ANAEMIA are at risk of death from malaria and heart failure. These children need urgent referral to a hospital where their treatment can be monitored, as they may need blood transfusion.

Anaemia

If the child has some palmar pallor, classify the child as having ANAEMIA.

Table 4: Assessment for anaemia

Symptoms	Classification	Action
Severe palmar pallor	SEVERE ANAEMIA	Refer URGENTLY to hospital.
Some palmar pallor	ANAEMIA	<ul style="list-style-type: none"> • Give iron/folate. • Do a rapid diagnostic test (RDT) or microscopy for malaria. • If malaria test is positive or unable to do test, treat with oral malaria medications. • If malaria test is negative, look for other causes. • Give mebendazole or albendazole if child is one year or older and has not had a dose in the previous six months. • Advise caretaker of symptoms that require an immediate return to the clinic. • Follow up in 14 days.
No palmar pallor	NO ANAEMIA	<ul style="list-style-type: none"> • Give routine vitamin A every six months from six months of age. • Give mebendazole or albendazole if child is one year or older and has

		<p>not had a dose in the previous six months.</p> <ul style="list-style-type: none"> • Advise caretaker of symptoms that require an immediate return to the clinic.
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Treatment

A child with some palmar pallor may have anaemia and should be given iron and folate. Treat the child with iron unless the child has a severe illness (pink classification in Table 4). Children with a severe illness may recover better if they are not given iron and folate.

Children with anaemia should be given antimalarial medicines, since anaemia may be due to malaria. Before giving an antimalarial, do a RDT or microscopy to check for malaria. If the malaria test is positive or if you are unable to do the test, give an antimalarial to the child. If the malaria test is negative, look for other causes of anaemia.

Hookworm and whipworm infections contribute to anaemia because the loss of blood from the gut results in iron deficiency. Give the child mebendazole or albendazole if he has anaemia and is one year of age or older and has not had a dose of mebendazole or albendazole in the last six months.

Advise the caretaker of a child with some palmar pallor to return for follow-up in 14 days.

No Anaemia

If the child has no palmar pallor, classify as NO ANAEMIA.

Treatment

Give the child routine vitamin A every six months from six months of age. Advise the caretaker about symptoms that would require an immediate return to the clinic.

Chapter 5: Management of Uncomplicated Malaria at All Levels

5.1 Introduction

Prompt diagnosis and early appropriate treatment are vital elements of the effective management of malaria at all levels of health care provision. The principal objectives are to shorten the course of illness, prevent the illness from becoming severe, prevent death or sequelae from severe malaria, and prevent transmission of malaria.

In order to achieve these objectives, uncomplicated malaria must be diagnosed early and correct treatment administered without delay. All health facilities should be able to manage uncomplicated malaria.

5.2 Treatment of Uncomplicated Malaria

The first-line drug for the treatment of uncomplicated malaria in Zambia is artemether-lumefantrine (AL) given over three consecutive days. If AL is ineffective or contraindicated, the alternative first-line treatment is dihydroartemisinin/ piperaquine, given as a three-day oral treatment.

Dosage

AL is co-formulated at a dose of 20 mg artemether and 120

mg lumefantrine given daily over three days. Table 5 shows recommended doses according to age, weight, and average dosage requirements. If the drug is vomited or spat out within 30 minutes, the dose should be repeated. If more than two consecutive episodes of vomiting occur, parenteral artesunate should be administered.

The correct dosage for AL is determined by weight. It is administered at intervals of 0, 8, 24, 36, 48, and 60 hours (twice daily for three days). It is recommended that the first dose, whenever possible, should be given by directly observed therapy (DOT).

To enhance absorption and ensure desired treatment outcome, it is preferable to administer AL after meals (preferably containing fatty foods). See Table 5 for recommended doses.

Table 5: Recommended doses of artemether-lumefantrine (AL)

Weight (kg)	Age (yrs.) (approx.)	Number tablets, per dose (give twice daily)	A+L / dose	Total no. tablets to be given over three days
5–<15	2 months–<3 years	1	20 mg A + 120 mg L	6
15–25	3–<9	2	40 mg A + 240 mg L	12
25–35	9–12	3	60 mg A + 360 mg L	18
>35	>12	4	80 mg A + 480 mg L	24

It is more accurate to use weight than age to determine dosage, as shown in Figure 2.

Figure 2: Recommended dosing of artemether-lumefantrine (AL) by weight.

BODY WEIGHT	DAY 1		DAY 2		DAY 3	
	☀ morning	🌙 8 hours after	☀ morning	🌙 evening	☀ morning	🌙 evening
5 kg to less than 15 kg	☉	1 Tablet am 1 Tablet pm	☉	1 Tablet am 1 Tablet pm	☉	1 Tablet am 1 Tablet pm
15 kg to less than 25 kg	☉☉	2 Tablets am 2 Tablets pm	☉☉	2 Tablets am 2 Tablets pm	☉☉	2 Tablets am 2 Tablets pm
25 kg to less than 35 kg	☉☉☉	3 Tablets am 3 Tablets pm	☉☉☉	3 Tablets am 3 Tablets pm	☉☉☉	3 Tablets am 3 Tablets pm
Adults and children 35 kg & above	☉☉☉☉	4 Tablets am 4 Tablets pm	☉☉☉☉	4 Tablets am 4 Tablets pm	☉☉☉☉	4 Tablets am 4 Tablets pm

5.3 Management of Fever

The management of fever is a key element in the case management of malaria.

This is especially important in children under the age of five years with temperatures of 38.5°C or more. Fever can be controlled with antipyretics and/or physical measures.

Patients with hyperpyrexia (38.5°C and above) should be given an anti-pyretic drug like paracetamol or aspirin every 4 to 6 hours (maximum 4 doses in 24 hours) until symptoms resolve. Children below 12 years should not be given aspirin because of the risk of developing Reye's syndrome and gastrointestinal bleeding.

Physical measures for reducing temperature include: exposure of the patient (reduce number of clothes), fanning, and tepid sponging (using a cloth to cool the child). Because of the logistic difficulties in obtaining tepid (lukewarm) water, this intervention could be challenging. Using cold water in place of tepid water could be hazardous to the patient and, therefore, should never be encouraged.

5.4 Treatment Failure or Non-Response to Treatment

Treatment failure is defined as the failure of an appropriately given antimalarial to control malaria in a patient. Treatment failures may result from drug resistance, poor adherence, or unusual pharmacokinetic properties in that individual. Monitoring treatment failure is very important because it can signal the appearance of antimalarial resistance. Non-response to treatment is the lack of effect of the antimalarial due to other causes such as not giving the appropriate dose, vomiting, etc.

Treatment failure within 14 days of receiving an ACT is very unusual. When a patient returns within 14 days after adequate completion of treatment with AL with symptoms of malaria, treatment failure should be considered.

To determine true treatment failure (i.e., the antimalarial

does not work even when taken appropriately), it is important to determine from the patient's history whether he or she has other reasons for the treatment not to have worked. Reasons for such non-responses may include:

- Vomiting the drug
- Inadequate dosage
- Fever/symptoms from a cause other than malaria
- Non-adherence to treatment
- Poor drug absorption or interaction with other drugs
- Poor drug quality (e.g., counterfeit drug)

If none of these reasons for non-response to treatment are present and there is still parasitaemia, then there is high likelihood that treatment has failed. In patients who continue with fever after 14 days, re-infection should be considered.

5.5 Management of Treatment Failure and Non-Response

The following recommendations should be followed after a full history and examination:

- If a cause for non-response is identified (e.g., antimalarial was vomited), such cause must be addressed and treatment reinstated with a first-line antimalarial.

- In a facility where laboratory facilities 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 several weeks after treatment.**
- In a facility where laboratory facilities are available, a blood smear should be performed. If parasites (trophozoites) are found, change the treatment to the second-line drug (quinine tablets; see Table 6). If parasites are not found, then other causes for the symptoms should be sought and treated accordingly.
- If the blood smear is negative and no other obvious causes are found, refer the patient to the next level of health facility for proper management.

Table 6: 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

This table is based on a dose of 10 mg/kg body weight

every 8 hours for 7 days using tablets containing 300 mg quinine salt.

Appropriate management of treatment failure or non-response is important because the patient may progress to severe malaria, and resistant parasites may be present and transmitted to others. Refer to Appendix A for additional information.

5.6 Integrated Community Management of Malaria (iCCM)

5.6.1 Initial care and care-seeking

According to iCCM, when a child has a fever, the caregiver should seek treatment promptly. The tasks to be carried out at this level include:

- Recognize the symptom of fever and danger signs (see Chapter 2) and promptly seek appropriate care.
- Correctly use the first-line medicine (AL).
- Reduce body temperature with measures such as tepid sponging, fanning, or giving paracetamol, if indicated.
- Use oral rehydration salts (ORS) in case of diarrhoea and/or vomiting.
- Continue feeding, especially very young children.

5.6.2 Diagnosis and treatment by community health workers (CHWs) and community health assistants (CHAs)

This category refers to community members selected by the communities and trained in management of common illnesses including malaria. These may include volunteer CHWs and CHAs. The CHWs and CHAs are supplied with materials for diagnosis and treatment of uncomplicated malaria. Tasks at this level include:

- Carrying out diagnoses according to their training and recognizing danger signs. RDTs when available should be used in all cases of fever to confirm malaria before treatment.
- Administering the first-line medicine (AL). In addition, measures to reduce body temperature should be recommended, such as tepid sponging, fanning, and giving paracetamol. Follow-up should be conducted with patients, particularly children below five years and pregnant women.
- Providing education to the community on the need for compliance to treatment, recognition of danger signs, and prevention of malaria.

5.7 Referral

CHWs and CHAs should make early referral to a health facility in case of danger signs and treatment failures. Referred patients should be accompanied to the health facility or a referral letter sent with the patient indicating treatment given and when.

Criteria for referral to a health facility (Appendix A1):

- 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 diarrhoea.
- 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 nose, gums, and other sites.
- Passing dark or little or no urine.
- High fever (above 39°C).
- Severe dehydration (loose skin and sunken eyes).
- Anaemia.

Chapter 6: Management of Severe Malaria

P. falciparum is the most common species that can lead to severe malaria. Severe malaria is a medical emergency! Delay in diagnosis and appropriate treatment may lead to serious complications and even death. The key features of effective case management of severe malaria are early recognition, assessment by a qualified health worker, referral to a higher facility where necessary, and appropriate antimalarial and supportive therapy.

6.1 Features of Severe Malaria

The features of severe malaria are described in detail in Chapter 2. The following laboratory investigations should be done whenever severe malaria is suspected and laboratory capacity is available at the health facility level.

6.1.1 Urgent laboratory investigations

- Thick and thin blood smears for malaria parasites
- RDTs used only if microscopy is not available
- Blood glucose
- Hematocrit/or haemoglobin
- Lumbar puncture to exclude meningitis if signs and symptoms are suggestive

6.1.2 Other laboratory investigations

The following investigations (if available) are also essential to the management of a severe case of malaria:

- **Plasma creatinine or urea:** there is no need to measure both, as creatinine is more useful.
- **Electrolytes:** these may occasionally reveal a correctable abnormality such as hyponatraemia (low sodium level). Measuring creatinine and electrolytes is most valuable when acute renal failure threatens or develops.
- **Full blood cell count and differential white cell count:** sometimes these may indicate the possibility of an additional diagnosis.
- **Blood gases, pH, and anion gap:** acidaemia is an indicator of severe disease in both conscious and unconscious patients.
- **Plasma and cerebrospinal fluid lactate concentrations:** these are raised in lactic acidosis; high levels are associated with a poor prognosis.
- **Blood culture:** this is done to exclude other serious infections such as septicemia.
- **Chest X-ray:** may identify pulmonary oedema or lobar consolidation. It may be of value in assessing respiratory distress syndrome.

None of these investigations should delay treatment in a

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patient who is suspected of having severe malaria!

All life-threatening conditions and the presence of any danger sign in a patient with fever and parasitological evidence of malaria should be considered as possible severe malaria and referred to a facility or admitted to hospital without delay for appropriate management.

6.2 Treatment of Severe Malaria

Severe malaria is a medical emergency, and it demands urgent clinical assessment and treatment. If the facility does not have the capacity, the patient should be referred. The patient, especially if comatose, should be managed in a special observation unit or an intensive care unit (ICU). Severe malaria should be managed initially as described in Table 7.

Table 7: Initial management of severe malaria

1. Clear and maintain airway, where indicated.
2. If comatose, position semi-prone or on side.
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. Take blood for diagnostic smear/slide or rapid

diagnostic test (RDT), haematocrit, and other laboratory tests.

6. Exclude hypoglycaemia and monitor blood glucose (every 2 to 4 hours).
7. Obtain specimens to exclude meningitis and other conditions where indicated.
8. Start antimalarial chemotherapy.
9. Start treatment for hypoglycaemia, meningitis and other conditions where indicated.
10. Monitor urine output. If necessary insert urethral catheter.
11. Plan first 8 hours of intravenous fluids, including diluents for antimalarial medicine, glucose therapy, and blood transfusion, if necessary.
12. If auxiliary temperature exceeds 38.5°C, take measures to lower temperature.
13. In case of convulsions, start anticonvulsant therapy and monitor patient closely.

Notes:

1. The patient's fluid requirements should be assessed regularly. Look for evidence of fluid depletion or overload. Calculate the appropriate rate of infusion. Children with metabolic acidosis may benefit from a

resuscitation bolus of fluid, preferably a plasma expander such as normal saline. Naso-gastric infusion is an alternative route.

2. The most common indication for blood transfusion is severe anaemia (Hb less than 5 g/dl). The decision whether to transfuse should not rely only on the haematocrit and/or Hb level but should also be based on assessment of the patient's overall medical condition.
 - If the patient's life is at risk by associated acidosis and shock, packed cell or whole blood transfusion should be given urgently.
 - If the patient has spontaneous bleeding, fresh whole blood or platelet infusion should be given.
 - If the patient has congestive cardiac failure due to anaemia, even when Hb is more than 5 g/dl, transfusion with packed cells should be given.
3. Urinary catheterization is necessary.
4. A central venous pressure line may be necessary if pulmonary oedema is suspected and may be useful in a patient with shock or impending renal failure.
5. For patients in coma or respiratory distress, the need for intubation and mechanical ventilation may be considered.

6.2.1 Antimalarial treatment

- Injectable artesunate is the drug of choice for adults and children with severe malaria.
- If injectable artesunate is unavailable, artemether (IM) or quinine (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 and complete treatment with an effective oral antimalarial using a full course of an effective ACT (e.g., AL).

6.2.1.1 Injectable artesunate

For severe (complicated) malaria, intravenous (IV) artesunate is recommended as described below:

1. Each vial of injectable artesunate must be reconstituted with 1 ml of sodium bicarbonate, which is supplied together with the vial of artesunate. Shake for 2 to 3 minutes until the powder is completely dissolved and the solution is clear.
2. Dilute with 5 ml of 5% dextrose solution or water for injection or normal saline (0.9% sodium chloride).
3. The solution should be prepared freshly for each administration and should not be stored.
4. Dose = 2.4 mg/kg body weight, or 0.24 ml/kg body weight (round up to nearest ml).
5. Withdraw into syringe and inject intravenously over 5

minutes.

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

1. Each vial of injectable artesunate must be reconstituted with 1 ml of sodium bicarbonate, which is supplied together with the vial of artesunate. Shake for 2 to 3 minutes until the powder is completely dissolved and the solution is clear.
2. Dilute with 2 ml of 5% dextrose solution or water for injection or normal saline (0.9% sodium chloride).
3. The solution should be prepared freshly for each administration and should not be stored.
4. Dose = 2.4 mg/kg body weight, or 0.12 ml/kg body weight (round up to nearest ml)
5. Withdraw into syringe and inject slowly. Should be injected into the upper, outer quarter of the anterior of the thigh.

Do not inject artesunate into the buttocks!

Recommended Dosing Schedule

Children: Artesunate 2.4 mg/kg of body weight IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day.

Adults: Artesunate 2.4 mg/kg body weight IV or IM given

on admission (time = 0), then at 12 h and 24 h, then once a day.

Give 2.4 mg/kg body weight IV or IM stat, repeat after 12 hours and 24 hours, then once daily afterward.

After initial parenteral treatment for a minimum of 24 hours, once the patient regains consciousness and can take medications orally, discontinue parenteral therapy and commence full course of artemether-lumefantrine.

There should be an interval of at least 8 hours between the last dose of artesunate and the first dose of artemether/lumefantrine.

6.2.1.2 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 (or isotonic fluid if hypoglycaemia is excluded) per kg body weight by IV infusion over 4 hours. After 8 hours, give a maintenance dose of 10 mg/kg body weight over 4 hours, repeated every 8 hours until patient can swallow, then oral quinine 10 mg/kg body weight every 8 hours to complete a 7-day course of treatment.

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 4 hours and then every 8 hours. This should be given preferably on the Guidelines for the Diagnosis and Treatment of Malaria in Zambia 53

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 (or isotonic fluid if hypoglycaemia is excluded) per kg body weight by IV infusion over 4 hours. After 8 hours, give a maintenance dose of 10 mg/kg body weight (maximum 600 mg) over 4 hours, repeated every 8 hours until patient can swallow or after coma resolution, then oral quinine 10 mg/kg body weight every 8 hours to complete a 7-day course of treatment.

By IM injection: 10 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 4 hours and then every 8 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:

$$\text{Drip rate per minute} = \frac{\text{Amount of fluid to be given} \times 20 \text{ (drop factor)}}{\text{Time in minutes over which to be given}}$$

6.2.2 Monitoring of patients with severe malaria

All patients with severe malaria should be monitored closely to prevent complications, as described in Table 8.

Table 8: Key observations and their implications for patients with severe malaria

Regular Observation (Clinical signs)	Possible Abnormal Observation	Appropriate Action
Axillary temperature	If temperature remains high > 38.5°C or rises despite exposure and fanning	Give paracetamol if not given in the past 4 hours 24 hours of therapy Reconsider your diagnosis while continuing treatment
Shock, if cold peripheries, delayed capillary refill (one second)	< 90 mmHg systolic in an adult, and < 50 mmHg in infants and children	Review fluid balance, urine output, infusion rate and haemocrit If hypovolaemic, give saline infusion where indicated 30 ml/kg 0.9% saline in 1 hour then reassess Look for haemorrhage Take blood for bacteriological culture Give broad spectrum antibiotic (for possible bacteremia)
Urine output	Oliguria: < 400 mls in an adult in 24 hrs or < 200 mls in infants and children in 24 hrs	Review fluid output and status of hydration Correct fluid deficiency if

		necessary Assess for acute renal failure
Coma score	Deterioration See Appendix B for Glasgow and Blantyre Coma Scale [see Appendix B] if suspected)	Immediately check for blood glucose (treat hypoglycaemia) Reconsider other diagnoses Repeat lumbar puncture
Convulsions	These can recur, or develop for the first time during treatment and may be due to hyperpyrexia, hyperglycaemia, or electrolyte imbalance	Give anticonvulsant drugs Check axillary temperature, if > 38.5 °C treat as above Check blood glucose (treat hypocalcaemia if suspected) Check fluid balance Check electrolytes
Bleeding from venipuncture sites or spontaneous (DIC) due to decrease	Prolonged bleeding time suggesting disseminated intravascular coagulation due to decrease fibrinogen and thrombocytes	Check bleeding time Cross match blood Give fresh whole blood as needed to correct blood loss and bleeding tendency (20 mls/kg for children, 2 units in adults)

Observations are aimed at:

- Controlling the delivery of medicines and infusion fluids.
- Detecting the development of complications of malaria.
- Detecting toxic and adverse reactions of medicines given.
- Documenting the patient's recovery.

Pre-referral treatment of patients with suspected severe malaria

If a patient presents at the health centre with severe malaria, pre-referral treatment before transfer to the next level of care should be given as follows:

- Perform an RDT; if positive, start on injectable artesunate. The results of the RDT should be sent with the patient to the next level.

In remote rural areas or peripheral clinics where IV infusion is not possible, give rectal artesunate and only give quinine or artemether 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 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.

Chapter 7: Managing Complications of Severe Malaria

7.1 Introduction

A body temperature of 38.5°C and above is considered as hyperpyrexia and should be treated to avoid complications. Antipyretics such as paracetamol, aspirin (not in children under 12 years), and nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are effective in reducing body temperature. The latter two, however, carry the risk of causing gastrointestinal bleeding. Crushed paracetamol tablets or syrup (15 mg/kg) may be washed down a nasogastric tube. Tepid sponging, exposure, and fanning are also effective ways of reducing temperature.

7.2 Hyperpyrexia

Convulsions, if left untreated, can cause complications including death. They are common in children with severe malaria but are relatively rare in adults. The general principles for the care of patients with convulsions should be as follows:

- Urgently STOP the convulsion with an anticonvulsant.
- Maintain a clear airway.
- Nurse the patient in a semi-prone position.

- Monitor vital signs (temperature, pulse rate, respiratory rate, and blood pressure).

7.2.1 Anticonvulsant drugs

- **DIAZEPAM** 10 mg by slow injectable injection in adults, and 0.5 mg/kg intrarectally (rectal) in children, or intramuscular (IM) if intrarectal cannot be done.
- **PHENOBARBITONE** 10–15 mg/kg IM injection is the best treatment for repeated convulsions.

If IV administration is not possible, use the rectal route. Give at a dose of 0.5–1.0 mg/kg. For rectal administration, withdraw the IV preparation into a syringe, and then remove the needle. Insert about 5 cm length of a naso-gastric tube into the rectum, inject the diazepam into the naso-gastric tube and thereafter flush with 5 ml of water. If a naso-gastric tube is not available, use a syringe without a needle.

Treat convulsions with diazepam. Give a slow bolus of IV diazepam 0.15 mg/kg (maximum 10 mg for adults). **If convulsions persist after 10 minutes**, repeat rectal diazepam treatment once. **Should convulsions continue despite a second dose**, give a further dose of rectal diazepam or phenobarbitone 20 mg/kg as a loading dose IM or IV. **If convulsions persist**, repeat phenobarbitone 6 mg/kg after a 20-minute interval (to make three doses).

Note: Make sure the patient has received glucose and that

the temperature is controlled.

Diazepam should not be used in infants below 1 month of age. Instead use phenobarbitone 20 mg/kg IM or IV. If convulsions persist, repeat phenobarbitone 10 mg/kg after 30 minutes.

7.3 Severe Anaemia

Severe anaemia should be considered a medical emergency that may result in death.

Indication for urgent blood transfusion

Blood transfusion should be considered if the haematocrit falls below 15% or haemoglobin concentration is < 5 g/dl. Packed cells should be given; in cases of hypovolemic shock, whole blood is preferred. This general recommendation still needs to be tailored to each individual case.

Patients with very low Hb may also have the following conditions:

- Signs of heart failure
- Signs of respiratory distress
- Hyperparasitaemia
- Impaired consciousness

Management of life-threatening anaemia (Hb < 5 g/dl)

associated with malaria

- 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.

How to administer blood

Packed cells are given at 10 ml/kg and whole blood at 20 ml/kg. 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. Transfuse slowly (4 to 6 hours per unit).

Drip: drops/mm =

Volume to be transfused in ml x 20 (or 15) drop factor
Time of transfusion in hours (4 to 6 hours) x 60 minutes

1 ml whole blood = 20 drops

1 ml packed cell = 15 drops

Fresh blood is preferred because it contains clotting factors and platelets. Transfusion should be carefully monitored for hypersensitivity reactions.

Note: Impaired tissue oxygenation (which may present as lethargy, breathlessness, or confusion) in anaemia is due to

impaired oxygen-carrying capacity by red blood cells, which cannot be corrected by fluid infusions and/or giving oxygen.

Diuretics are given only when the patient's renal function is adequate. Give small intravenous doses of furosemide 20 mg as necessary during the blood transfusion to avoid circulatory overload. For children give 1 mg/kg body weight.

POINT TO REMEMBER: Children with anaemia due to malaria may be hypovolemic and can die of shock.

Follow-up after discharge

After discharge, it is important to continue monitoring the patient's condition:

- Discharge the patient on folic acid and ferrous sulphate (do not give ferrous sulphate to patients with sickle cell disease).
- Review after 14 days to check haemoglobin or haematocrit level.
- Continue treatment with folic acid and ferrous sulphate for at least three months.
- Encourage patients to use other preventive measures such as ITNs.

7.4 Haemoglobinuria

Haemoglobinuria (black water fever) associated with malaria is uncommon and usually presents in adults as severe disease with anaemia and renal failure. In cases of haemoglobinuria, antimalarial treatment should not be stopped. The medicine of choice is injectable artesunate. If injectable artesunate, is not available give quinine or artemether.

If a patient develops haemoglobinuria while on quinine treatment, switch to artemether IM if available. If the haematocrit is below 20%, transfuse whole blood. Monitor central venous pressure to avoid overload and hypovolemia. If oliguria develops and blood urea and serum creatinine levels rise (i.e., if acute renal failure develops), peritoneal dialysis or haemodialysis may be required. Refer to a dialysis unit or centre.

7.5 Hypoglycaemia

Hypoglycaemia must be ruled out in all patients with severe malaria.

7.5.1 Clinical features

Hypoglycaemia is an important manifestation of severe malaria. It occurs in three different (but potentially overlapping) groups of patients:

- Patients with severe disease, especially young children.
- Patients treated with quinine, as a result of quinine-induced hyperinsulinaemia.
- Pregnant women, either on admission or following quinine treatment.

In conscious patients, hypoglycaemia may present with classical symptoms of anxiety, sweating, dilatation of the pupils, breathlessness, oliguria, a feeling of coldness, tachycardia, and light-headedness. This clinical picture may develop into deteriorating consciousness, generalized convulsions, extensor posturing, shock, and coma.

The diagnosis is easily overlooked because all these clinical features also occur in severe malaria itself. Deterioration in the level of consciousness may be the only sign.

If possible, confirm by biochemical testing, especially in the high-risk groups mentioned above.

7.5.2 Management of Hypoglycaemia

- Do a blood sugar test.
- If a blood sugar test cannot be done, then comatose or severely ill patients should be given a stat dose of 10% dextrose (125 ml as an infusion in adults or 5 ml/kg body weight in children). This should be given by intravenous injection slowly.

- Monitoring of the clinical condition and blood sugar must continue even if hypoglycaemia is initially controlled and the patient is receiving injectable glucose.

For children

- All children with severe malaria should be assumed to have hypoglycaemia and receive treatment as above even where a test cannot be done.
- Following the bolus dose of 10% dextrose, oral feeds should be encouraged. For children who are unable to take food orally, a naso-gastral tube should be inserted and feeds initiated. Where dextrose is not available, mix 20 g of sugar (about 4 level teaspoons) with 200 ml of clean water; give 50 ml of this solution orally.

7.6 Metabolic Acidosis

Deep breathing with recession of the lower chest wall in the absence of localizing chest signs suggests metabolic acidosis. Acidosis commonly accompanies cerebral malaria or anaemia. A systolic blood pressure below 50 mm Hg (in children) and below 80 mm Hg in the supine position (in adults) indicates a state of shock. Correct any reversible cause of acidosis (in particular, dehydration in severe anaemia).

Convulsions may contribute to lactic acidosis; therefore,

prevention of further seizures may be beneficial. If haemoglobin is above 5 g/dl, give 20 ml/kg of isotonic saline by intravenous infusion over 30 minutes. If the Hb is less than 5 g/dl, give a blood transfusion (whole blood 10 ml/kg over 30 minutes and a further 10 ml/kg over 1 to 2 hours without diuretics). Monitor response by continuous clinical observation supported by repeated measurement of acid/base status, Hb, blood sugar, and urea and electrolyte levels.

7.7 Referral

If patients require dialysis or intensive care, or if blood transfusion services are not available, patients should be referred to a higher level facility.

Chapter 8: Malaria in Pregnancy

8.1 Introduction

Malaria in pregnancy is a major concern in Zambia. Pregnant women are particularly at risk due to the lowered acquired partial immunity during pregnancy. Although *P. falciparum* infection during pregnancy does not always result in maternal illness, it may lead to placental malarial infection, and to serious adverse health outcomes in both the mother and the fetus. The risk factors for high transmission areas such as Zambia include: primigravidity, secundigravidity, young maternal age (less than 18 years old), second trimester, and HIV infection. Malaria in pregnancy may present as acute symptomatic disease or as chronic anaemia. In low transmission areas, all pregnant women are at risk. In these areas, the risk for pregnant women to get severe malaria is higher than in non-pregnant women, and the mother or her fetus might die from hypoglycaemia, cerebral malaria, or severe anaemia.

Adverse pregnancy outcomes include spontaneous abortion, stillbirth, severe maternal anaemia, and low birth weight (weight <2500grams). Low birth weight is as a result of prematurity and/or intrauterine growth retardation. Severe maternal anaemia among women may lead to maternal death. Low birth weight is the single most important risk factor for neonatal and infant death.

Malaria prevention and control during pregnancy requires a three-pronged approach: effective case management of malaria infections, use of insecticide-treated bed nets (ITNs), and intermittent preventive treatment (IPTp) in areas of high transmission. These should be delivered as a package of antenatal care.

8.2 Clinical Features

Clinical features vary depending on the endemicity of the disease. At the moment, Zambia has areas of both stable and low transmission. This means that malaria in pregnancy will often be asymptomatic, with anaemia being the main maternal manifestation of the infection in stable malaria areas, with quite severe anaemia in areas of low transmission. With severe anaemia, the main effect on the baby is low birth weight. Other effects may include: preterm delivery, intrauterine growth retardation, perinatal death, low Apgar scores, and intrauterine fetal death.

8.3 Diagnosis

It should be noted that malaria parasites may be sequestered in the placenta and thus may not be detected by examining a peripheral blood smear. A negative slide is therefore not a definitive confirmation of the absence of malaria parasites in pregnancy. However, a malaria rapid diagnostic test (RDT) may detect the presence of parasites

even when they are sequestered in the placenta.

8.4 Treatment

Uncomplicated malaria

The antimalarial medicine considered safe in the first trimester of pregnancy is oral quinine. Quinine is effective and can be used in all trimesters of pregnancy including the first trimester. In the absence of quinine, and where the potential benefits outweigh the risks, AL can be used to treat uncomplicated malaria in the first trimester. In reality, women often do not declare their pregnancies in the first trimester, so early pregnancies will often be exposed inadvertently to the available first-line treatment.

There is increasing experience with artemisinin derivatives in the second and third trimesters. There have been no adverse effects on the mother or fetus. For Zambia, the use of artemisinin-based combination therapy (ACT), specifically artemether-lumefantrine (AL), in the second and third trimesters of pregnancy is recommended to treat uncomplicated malaria.

Severe malaria

Pregnant women, particularly in the second and third trimesters, are more likely to develop severe malaria than other adults, often complicated by pulmonary oedema and hypoglycaemia. Maternal mortality is approximately 50%,

which is higher than in non-pregnant adults. Fetal death and premature labour are common. Parenteral antimalarials should be given to pregnant women with severe malaria in full doses without delay. Treatment must not be delayed and should be started with quinine in the first trimester and injectable artesunate in the second and third trimesters.

Fever in pregnancy

A pregnant woman with fever should be evaluated like any adult patient presenting with fever before instituting treatment for malaria.

8.5 Intermittent Preventive Treatment (IPTp)

Sulphadoxine-pyrimethamine (SP) is the medicine of choice for IPTp. One adult treatment dose (3 tablets) is given monthly after quickening (16 weeks following the last menstrual period). The same adult treatment dose of SP (3 tablets) should be given monthly (at least 4 weeks apart) during the second and third trimesters at every scheduled antenatal care visit. The total number of doses recommended for the entire duration of pregnancy is three or more doses, under direct observation when possible.

HIV-positive pregnant women on co-trimoxazole prophylaxis for *Pneumocystis jirovecii* should not be given SP. This is because co-trimoxazole has some protective effects against malaria and there is an increased

risk of serious adverse events if co-trimoxazole is administered concurrently with SP, especially in the context of underlying HIV infection.

Pregnant women who are intolerant to SP should be counseled about effective personal protective measures such as the use of ITNs.

8.6 Health Education

All pregnant women should be counseled on effective malaria prevention. These include:

- Attend antenatal clinic and receive IPTp.
- Sleep under ITNs at night.
- Seek medical attention promptly whenever they are sick.
- After birth, protect the newborn baby with ITNs.

Chapter 9: Antimalarial Medicines

9.1 Introduction

This chapter provides a summary of antimalarial medicines in common use in Zambia. It also provides information on the principles of combination therapy.

The Zambia National Formulary and other reference material should be used if further information is required.

The malaria treatment policy in Zambia recommends the use of artemether-lumefantrine (AL) as the first-line medicine for treating uncomplicated malaria. If AL is not available, dihydroartemisinin-piperaquine should be used. In situations where artemisinin-based combination therapy (ACT) is contraindicated, sulphadoxine-pyrimethamine (SP) should be used, except during the first trimester of pregnancy. Quinine is the first-line medicine for treatment of uncomplicated malaria during the first trimester of pregnancy. For severe and complicated malaria, artesunate is the recommended first-line medicine for all population categories except pregnant women in the first trimester of pregnancy, when parenteral quinine is preferred.

9.2 Combination Therapy

Combination therapy refers to the use of two or more antimalarial medicines with different biochemical targets in

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the parasite, which are synergistic or additive or complementary in their effect.

The use of two or more medicines that have the same biochemical target in the parasite, such as sulphadoxine-pyrimethamine, chlorproguanil-dapsone, or atovaquone-proguanil, is not considered combination therapy. Similarly, the use of two medicines that have no significant schizonticidal effect when used as monotherapy is not considered combination therapy.

Combination therapy in antimicrobial treatment is a well-known principle used to slow down the development of resistance of microbial pathogens. It has been used in the treatment of HIV/AIDS, tuberculosis, and cancer. This principle has now been extended to the treatment of malaria.

Combination therapies can either be fixed dose, where all components are co-formulated in a single tablet, or free combinations, where the components are in separate tablets or capsules but are co-administered.

The underlying theory to combination therapy in malaria is based on the fact that resistance to antimalarial medicines arises from the selection of mutations.

An effective combination should include an effective short half-life medicine and a compatible longer half-life partner antimalarial medicine. This shortens the duration of

treatment, while at the same time reducing the likelihood of development of resistance. The combination must also be amenable to good patient compliance.

A number of combination formulations comprising an artemisinin medicine and another antimalarial medicine have recently been developed. Many such combinations have been found to be efficacious and effective. The combinations have generally included a fast-acting artemisinin component with a slower-acting effective antimalarial medicine. Examples include: artesunate-SP, artemether-lumefantrine, and dihydroartemisinin-piperaquine. Such combinations are referred to as artemisinin-based combination therapies (ACTs).

The recommended first-line medicine for treating uncomplicated malaria in the current malaria treatment policy, artemether-lumefantrine, is one such combination.

9.3 Artemether-lumefantrine

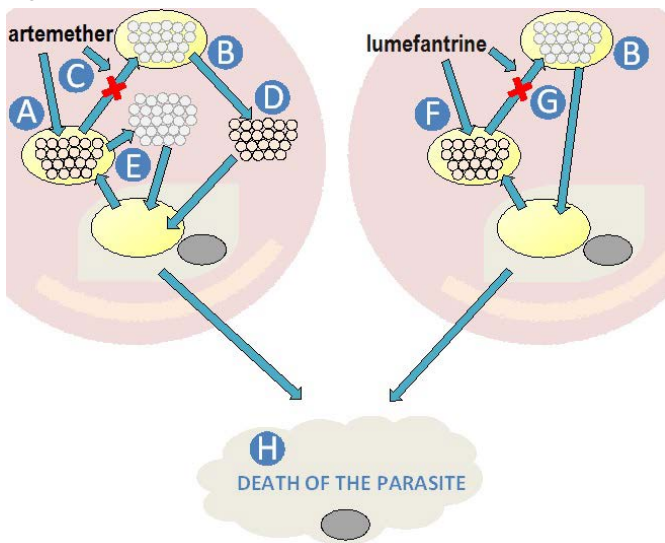
AL is the first-line medicine for the management of uncomplicated malaria in Zambia.

Presentation

It is currently available as a co-formulated tablet presented in a blister packet containing 20 mg artemether and 120 mg lumefantrine.

A dispersible fixed-dose AL tablet developed specifically for infants and children weighing between 5 kg and 35 kg is now available. The new sweet-tasting paediatric formulation of AL 20 mg/120 mg is designed to quickly disperse in small amounts of water, making it easier for caregivers to administer and for sick children to take.

Figure 3: Mode of action of artemether-lumefantrine.



Source: Adapted from Coartem (Artemether-Lumefantrine) Monograph, 5th edition. November 2005.

Artemether and lumefantrine work at different points in the

Plasmodium life cycle, making emergence of resistance unlikely. As shown in Figure 3, parasites in the infected erythrocytes ingest and degrade haemoglobin and concentrate the iron in a food vacuole in the form of toxic haem (A). Normally, the haem is then made harmless by conversion to haemozoin (B).

Artemether is concentrated in the food vacuole. It then splits into an endoperoxide bridge as it interacts with haem, blocking conversion to haemozoin (C), destroying existing haemozoin, and releasing haem (D) and a cluster of free radicals into the parasite (E).

Lumefantrine (F) also targets haem, preventing its detoxification (G). Toxic haem and free radicals are jointly responsible for the death of the parasite (H). Artemether provides rapid onset of action to kill the parasite; lumefantrine has a slower onset but its longer-acting activity prevents reappearance or recrudescence of the parasite.

Efficacy

The combination has schizonticidal as well as gametocytocidal activity. The artemether component is fast-acting, reducing parasite load significantly within a few hours of administration. The lumefantrine component is slower acting but lasts longer, thereby providing therapeutic activity for a longer period.

AL is well tolerated and has shorter parasite clearance times than chloroquine or quinine, as well as a rapid symptomatic response. As a result, patients may be tempted to not complete the treatment course. It is important to encourage the patient to complete the course in order to achieve the desired treatment outcomes.

Indications

Treatment of uncomplicated malaria in both adults and children except in the first trimester of pregnancy and children below 5 kg body weight.

Dosage

For dosage, refer to Chapter 5 on management of uncomplicated malaria.

Adverse effects

The common adverse effects reported include: sleep disorders, headache, dizziness, palpitations, abdominal pain, anorexia, diarrhoea, vomiting, nausea, pruritis, rash, cough, arthralgia, and myalgia.

Contraindications

Due to insufficient safety data, AL is currently not recommended for use in the first trimester of pregnancy and in children below 5 kg body weight.

Caution

Use with caution in patients with severe hepatic or renal

insufficiency. No specific studies have been carried out in these patients; therefore, no specific dose-adjustment recommendation can be made. Driving and use of machinery is not recommended due to risk of dizziness and fatigue. Special care should be taken with patients previously treated with halofantrine, mefloquine, or quinine.

9.4 Dihydroartemisinin-piperaquine (DHA-PQ)

DHA-PQ is an alternative first-line option for the management of uncomplicated malaria in Zambia. It should be used only if AL is unavailable.

Presentation

There are two co-formulated versions of DHA-PQ: one contains 20 mg DHA and 160 mg PQ, whereas the other contains 40 mg DHA and 320 mg PQ.

Mode of action

DHA is the main active metabolite of artemisinin derivatives including both artemether and artesunate. It attains high concentrations in *P. falciparum*-infected red blood cells and exerts a mechanism of action as described in section 9.3 for artemether. Piperaquine is a bisquinolone whose precise mechanism of action is not fully understood, although it may be similar to that of chloroquine, which binds to toxic haem within *P. falciparum* and prevents its

detoxification.

Efficacy

This combination has excellent schizonticidal activity. The DHA component is rapid acting, reducing parasite load significantly within a few hours of administration. The PQ component is slower acting but lasts longer, thereby providing therapeutic activity for a longer period.

The therapeutic efficacy of DHA-PQ has been extensively evaluated in studies in adults and children in South/Southeast Asia and sub-Saharan Africa. When compared directly to AL, it has been shown to be non-inferior to AL for the treatment of uncomplicated *P. falciparum* malaria in children in a multi-centre trial in Burkina Faso, Kenya, Mozambique, Uganda, and Zambia. The day 28 polymerase chain reaction-corrected cure rate among Zambian children aged 6 to 59 months was 95% for both DHA-PQ and AL. In the multi-centre trial, significantly fewer DHA-PQ recipients experienced reinfection up to day 42 as compared to those treated with AL.

Indications

Treatment of uncomplicated malaria in both adults and children except in the first trimester of pregnancy and children below 5 kg body weight.

Dosage

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The standard dose is one half to one tablet daily for three days (Table 9).

Table 9: Dosage recommendations for dihydroartemisinin-piperaquine (DHA-PQ)

Body weight (kg)	Daily dose (mg) DHA	Daily dose (mg) PQ	Number of tablets per dose
5 to <7	10	80	½ x 20 mg/160 mg tablet
7 to <13	20	160	1 x 20 mg/160 mg tablet
13 to <24	40	320	1 x 40 mg/320 mg tablet
24 to <36	80	640	2 x 40 mg/320 mg tablet
36 to <75	120	960	3 x 40 mg/320 mg tablet
75 to 100	160	1280	4 x 40 mg/320 mg tablet
>100	No data	No data	No data

Adverse effects

The common adverse effects reported include: headache, nausea, vomiting, dizziness, fever, cough, myalgias, arthralgias, and abdominal pain. DHA-PQ had potential to prolong the QT interval.

Contraindications

Due to insufficient safety data, DHA-PQ is currently not

recommended for use in the first trimester of pregnancy and in children below 5 kg body weight. This combination should not be used in patients with a family history of sudden death, congenital QTc interval prolongation, or any other condition known to prolong the QTc interval.

Caution

Use with caution in patients with severe hepatic or renal insufficiency. No specific studies have been carried out in these patients; therefore, no specific dose-adjustment recommendation can be made.

9.5 Sulfadoxine-pyrimethamine (SP)

This is the first-line medicine for the management of uncomplicated malaria in children who weigh less than 5 kg. It is also the recommended medicine for intermittent presumptive treatment in pregnancy.

Presentation

SP is a tablet containing 500 mg sulphadoxine and 25 mg pyrimethamine. It is the only formulation widely available on the Zambian market.

Suspension and injectable forms are also available in some countries.

Mode of action

SP belongs to the antifolate group of antimalarials.

Sulphadoxine works synergistically with pyrimethamine against the parasite-specific enzymes dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR). The combination works best at the mature trophozoite to early schizont stage. The medicines inhibit parasite synthesis of folate, which is essential for DNA replication and therefore cell growth. Pyrimethamine binds and inhibits DHFR and sulphadoxine inhibits DHPS by acting as analogues of para-aminobenzoic acid (PABA), a folate precursor.

Efficacy

These medicines are highly active blood schizonticides against *P. falciparum* but are less effective against other species. There is no cross-resistance with the 4-aminoquinolines, mefloquine, quinine, halofantrine, or the artemisinin derivatives. They do not have gametocytocidal activity.

Sulpha-pyrimethamine combinations have a long half-life so they can be given as a single-dose treatment, thereby increasing compliance. This property, however, provides potent selective pressure for parasite resistance in areas of high transmission.

The medicines are generally well tolerated. The medicine may be given with an antipyretic to achieve temperature control. The onset of action of the medicine is slow;

therefore it takes a while before symptomatic relief is achieved.

Indications

According to current treatment policy in Zambia, SP is indicated for the following:

- Treatment of uncomplicated malaria in both adults and children.
- First-line treatment of children below 5 kg body weight with uncomplicated malaria.
- First-line treatment in the case of hypersensitivity to AL.
- IPT in pregnancy.

Dosage

Single-dose treatment containing 25 mg/kg body weight sulphadoxine plus 1.25 mg/kg body weight pyrimethamine.

Recommended single adult dose is 1500 mg sulphadoxine plus 75 mg pyrimethamine (i.e., 3 tablets).

Table 10: Sulphadoxine-pyrimethamine dosage schedule for children

Weight (kg)	Age (years)	Number of tablets
5–10	2–11 months	0.5
10–14	1–2	0.75
15–20	3–5	1
21–30	6–8	1.5
31–40	9–11	2
41–50	12–13	2.5
>50	14 and above	3

Medicine disposition

Both sulphadoxine and pyrimethamine are highly protein-bound with relatively long mean elimination half-lives. Sulphadoxine has a half-life of around 180 hours and pyrimethamine about 95 hours. Pyrimethamine is extensively metabolized whereas only a small proportion of sulphadoxine is metabolized (to acetyl and glucuronide derivatives). Excretion is mainly in the urine. Both medicines cross the placental barrier and are also detected in breast milk.

Adverse effects

Serious adverse reactions to sulpha medicines are rare. When they occur they include severe cutaneous reactions, such as Steven Johnson syndrome and toxic epidermal necrolysis. Toxic epidermal necrolysis appears to be more

common in HIV-infected patients. These serious cutaneous adverse reactions are fatal in 10% to 20% of cases. They are not dose-dependent and cannot be predicted by a history of allergy to sulfa medicines. Health workers are encouraged to document data on these events and report through the pharmacovigilance system described in Chapter 11 of these guidelines.

Contraindications

SP is contraindicated in patients with hypersensitivity to sulpha medicines or to pyrimethamine and in hepatic or renal dysfunction.

9.6 Artesunate

Artesunate is the medicine of choice for the treatment of severe malaria in all categories of patients.

Presentation

Artesunate is dispensed as a powder of artesunic acid. This must be dissolved in sodium bicarbonate (5%) to form sodium artesunate. The solution is then diluted in approximately 5 ml of 5% dextrose and given by IV injection or by intramuscular (IM) injection to the anterior thigh. The solution should be freshly prepared prior to administration and should never be stored. Where available, artesunate is the preferred treatment for severe malaria in adults and children.

Mode of action

All artemisinins used today are prodrugs of the biologically active metabolite dihydroartemisinin, which is active during the stage when the parasite is located inside red blood cells. Although there is no consensus regarding the mechanism through which artemisinin derivatives kill the parasites, several lines of evidence indicate that artemisinins exert their antimalarial action by perturbing redox homeostasis in malaria parasites. When the parasite that causes malaria infects a red blood cell, it consumes haemoglobin within its digestive vacuole, a process that generates oxidative stress.

Medicine disposition

Artesunate can be administered rapidly through IV injection over 3 to 5 minutes or as an IM injection. In addition, the drug only requires two doses on the first day of treatment and once daily thereafter. In settings where IV or IM administration is not feasible, artesunate solution may be given rectally until vascular access is available.

Artesunate administered by IV or IM injection has proven superior to quinine in large, randomized controlled trials in both adults and children. Artesunate is associated with a mortality rate that is approximately 30% lower than that of quinine. Reasons for this difference include reduced incidence of hypoglycaemia, easier administration, and more rapid action against circulating and sequestered

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parasites. Artesunate is now recommended for treatment of all cases of severe malaria.

Indications

Treatment of choice in severe and complicated malaria in all population groups.

Dosage

Refer to Chapter 6 on management of severe malaria for IM and IV dosage.

Adverse effects

Artesunate is very well tolerated with few drug-related side effects. Drug interactions through the cytochrome P450 system are possible, but no serious interactions have been noted. The side effects from the artemisinin class of medications are similar to the symptoms of malaria: nausea, vomiting, anorexia, and dizziness. Mild blood abnormalities have also been noted.

9.7 Quinine

Quinine is the first-line medicine for the management of uncomplicated malaria in the first trimester of pregnancy and the second-line alternative for patients with severe malaria.

Presentation

Quinine is available in many different tablet and injectable

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salt formulations. The most common are quinine hydrochloride, quinine dihydrochloride, and quinine sulphate.

Tablets containing 200 mg and 300 mg base and injections containing 150 mg/ml and 300 mg/ml in 2 ml ampoules are available.

The salts hydrochloride, dihydrochloride, and sulphate contain 82%, 82% and 82.6% of quinine base respectively.

Mode of action

Quinine has greatest activity on the mid- to late-trophozoite stage of the parasite. Its mode of action is similar to amodiaquine. It acts on the parasite food vacuole.

Efficacy

Quinine is an alkaloid extracted from the bark of the cinchona tree. It is a blood schizonticide effective against *P. falciparum* infections, including chloroquine-resistant strains. It is also effective against parasites resistant to SP.

Evidence of resistance to quinine requires documentation. To date, very little resistance has been reported.

Indications

- Alternative treatment of severe and complicated malaria in all population groups.
- First-line treatment for uncomplicated malaria during

first trimester of pregnancy.

- Second-line treatment in case of treatment failure with first-line treatment.

Dosage

Refer to Chapter 6 on management of severe malaria for IM and IV dosage.

Medicine disposition

Quinine is rapidly absorbed when orally taken and peak plasma concentrations are reached within 1 to 3 hours. It is highly protein-bound and is distributed throughout body fluids. It readily crosses the placental barrier and the blood-brain barrier.

Quinine is extensively metabolized in the liver. It has an elimination half-life of 10 to 12 hours in healthy individuals and is excreted in urine, mainly as hydroxylated metabolites.

There are some pharmacokinetic variations, depending on the age and malaria status. The volume of distribution is less in young children than in adults, and the rate of elimination is slower in the elderly than in young adults. In patients with acute malaria, the volume of distribution is reduced and systemic clearance is slower than in healthy subjects. These changes are proportional to the severity of disease.

Use in pregnancy

Quinine is safe in pregnancy. Therapeutic doses do not induce abortion or labour.

The stimulation of contractions and evidence of fetal distress associated with its use may be attributable to fever and other effects of malaria.

Adverse effects

The common adverse reactions of quinine include: tinnitus, headache, hot and flushed skin, nausea, abdominal pain, rashes, visual disturbances, confusion, hypoglycaemia (especially after parenteral administration), and cardiovascular effects. They rarely justify withdrawal of the medicine, when they occur alone. They are normally reversible.

Dose-related adverse effects largely affect the cardiovascular, gastrointestinal, and central nervous systems. They usually arise from excessive infusion, but also from accumulation following oral administration.

Quinine can cause severe hypotension if injected too rapidly. Enhanced cardiac toxicity may occur in individuals who have taken mefloquine for malaria prophylaxis. Quinine may cause hypoglycaemia since the medicine stimulates secretion of insulin.

Chapter 10: 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.

10.1 Risk Groups

Risk groups that should be given antimalarial chemoprophylaxis include:

- Patients with sickle cell disease.
- 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.

Sickle cell disease

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

Dosage: 25 mg pyrimethamine and 100 mg dapsone tablet taken once per week, preferably in the morning.

Visitors (non-immunes) to Zambia

The options include mefloquine, atovaquone-proguanil, and doxycycline. The most appropriate prophylactic antimalarial medicines prescribed should be taken in the correct doses. Doses should be taken prior to arrival in Zambia, continued during the stay, and continued following departure from Zambia. Visitors are encouraged to use other effective protective measures such as the use of insecticide-treated nets (ITNs), staying indoors in screened areas at dusk, and using insect repellents.

Note: Despite the use of malaria chemoprophylaxis, if the patient develops fever they should promptly seek medical attention.

See Appendix D for more information about antimalarial prophylaxis for travellers.

Chapter 11: Pharmacovigilance

A pharmacovigilance system provides the means by which the safety of medicines, once they have been released onto the market for use by the public, can be monitored in order to ensure that they fulfill their intended role in society (alleviating human suffering). There is need for continued surveillance of safety and efficacy of pharmaceutical products that are used in clinical practice.

The continuous evaluation of these products' benefit and harm will help to achieve the ultimate goal to make safer and more effective treatment available to patients.

11.1 Definitions

Pharmacovigilance. Science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problems.

Adverse drug reaction (ADR). A response to a medicine which is noxious (harmful) and unintended, and which occurs at doses normally used in humans. This description emphasizes the response of a patient, in which individual factors may play an important role, and that the phenomenon is noxious (an unexpected therapeutic response, for example, may be a side effect but not an adverse reaction).

Unexpected adverse reaction. An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the medicine.

Medicine/drug. A pharmaceutical product, used in or on the human body for the prevention, diagnosis, or treatment of disease, or for the modification of physiological function.

Side effect. Any unintended effect of a pharmaceutical product occurring at doses normally used by a patient, which is related to the pharmacological properties of the medicine. Essential elements in this definition are the pharmacological nature of the effect, that the phenomenon is unintended, and that there is no deliberate overdose.

Adverse event or experience. Any untoward medical occurrence that may present during treatment with a medicine but that does not necessarily have a causal relationship with this treatment. The basic point here is the coincidence in time without any suspicion of a causal relationship.

Serious adverse event. Any event that:

- Is fatal.
- Is life-threatening.
- Is permanently/significantly disabling.

- Requires or prolongs hospitalization.
- Causes a congenital anomaly.
- Requires intervention to prevent permanent impairment or damage.

Signal. Reported information on a possible causal relationship between an adverse event and a medicine when the relationship has been previously unknown or incompletely documented. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

11.2 Why pharmacovigilance is needed in Zambia

During the last few decades, it has been demonstrated by a number of studies that morbidity due to medicines is one of the major health problems. This situation is beginning to be recognized as a concern by health professionals and the public.

There is very limited information available on ADRs in Zambia. However, the National Medicine Policy acknowledges the widespread inappropriate use of medicines in the country. In this situation, one may expect the likelihood of a higher incidence of ADRs than may be on record.

The large number of sub-standard and counterfeit products circulating on the Zambian market, the lack of independent Guidelines for the Diagnosis and Treatment of Malaria in Zambia 97

medicine information, and the irrational use of medicines compound the likelihood of a higher incidence of ADRs than is actually known.

Medicine monitoring is a useful tool for detecting ADRs and counterfeit and substandard quality problems. ADR monitoring helps to ensure that patients obtain safe and efficacious products.

The effectiveness of a national post-marketing surveillance programme is directly dependent on the active participation of health workers. Health workers are in the best position to report on suspected ADRs observed in their everyday patient care.

All health care providers should report ADRs as part of their professional responsibility, even if they are doubtful about the precise relationship with the given medication.

How to recognize ADRs

Since ADRs may act through the same physiological and pathological pathways as different diseases, they are difficult and sometimes impossible to distinguish. However, the following step-wise approach may be helpful in assessing possible medicine-related ADRs:

- Ensure that the medicine ordered is the medicine received and actually taken by the patient at the dose advised.

- Verify that the onset of the suspected ADR was after the medicine was taken, not before, and discuss carefully the observation made by the patient.
- Determine the time interval between the beginning of medicine treatment and the onset of the event.
- Evaluate the suspected ADR after discontinuing the medicines or reducing the dose, and monitor the patient's status (dechallenge).
- Analyze the alternative causes (other than the medicine) that could on their own have caused the reaction.
- Use relevant up-to-date literature and personal experience as a health worker on medicines and their ADRs and verify if there are previous conclusive reports on this reaction.

The Zambia Pharmacovigilance Centre is a very important resource for obtaining information on ADRs. The manufacturer of the medicine can also be a resource to consult.

What should be reported?

For “new” medicines: report all suspected reactions, including minor ones.

For established or well-known medicines: report all serious or unexpected (unusual) suspected ADRs.

- Report if an increased frequency of a given reaction is observed.
- Report all suspected ADRs associated with medicine-medicine, medicine- food, or medicine-food supplements interactions.
- Report ADRs in special fields of interest such as medicine abuse and medicine use in pregnancy and during lactation.
- Report when suspected ADRs are associated with medicine withdrawals.
- Report ADRs occurring from overdose or medication error.
- Report when there is a lack of efficacy or when suspected pharmaceutical defects are observed.
- Report all medicine-related problems (e.g., product quality problems, suspected counterfeit products).

How to report ADRs

Case Report Forms (CRF) may be obtained from the District, Provincial, and Zambia Pharmacovigilance Centre (ZPVC).

A sample of the CRF is provided in Appendix C. However, if report forms are not available, a copy can be made from the sample form or the form at <http://www.zamra.co.zm/index.php/report-adverse-medicine-reaction>. Further, verbal reports from members of

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the public may be accepted by a health worker who will in turn transcribe the information onto a CRF.

The completed CRF should be sent to the district or provincial pharmacovigilance coordinator or direct to the ZPVC.

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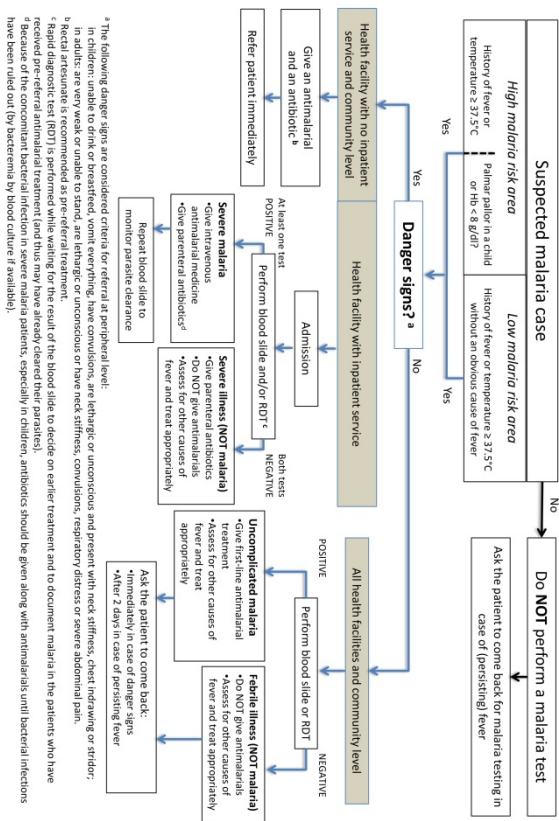
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http://www.who.int/entity/maternal_child_adolescent/documents/IMCI_chartbooklet/en/index.html. Accessed January 14, 2014.

Appendix A1: Algorithm for Malaria Diagnosis and Treatment, First Visit



^a The following danger signs are considered criteria for referral at peripheral level:

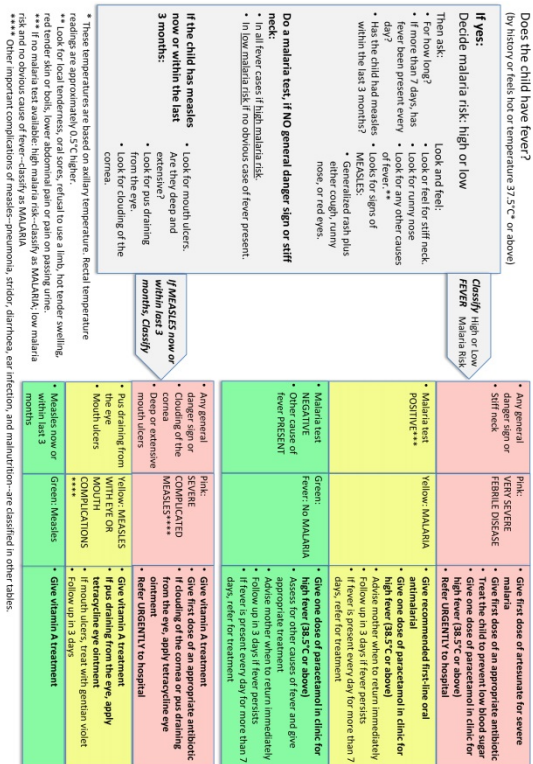
In children: unable to drink or breastfeed, vomit everything, have convulsions, are lethargic or unconscious and present with neck stiffness, chest indrawing or stridor;
In adults: are very weak or unable to stand, are lethargic or unconscious or have neck stiffness, convulsions, respiratory distress or severe abdominal pain.

^b Rectal artemesinate is recommended as pre-referral treatment.

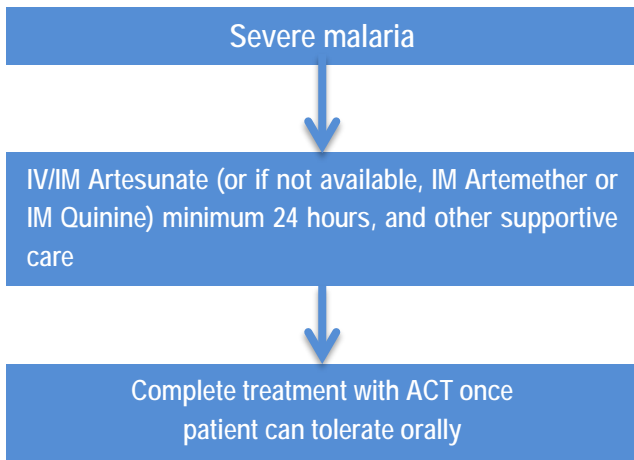
^c Rapid diagnostic test (RDT) is performed while waiting for the result of the blood slide to decide on earlier treatment and to document malaria in the patients who have received pre-referral antimalarial treatment (and thus may have already cleared their parasites).

^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).

Appendix A2: Updated for Integrated Management of Childhood Illness (IMCI) Algorithm



Appendix A3: Algorithm for Management of Severe Malaria



Appendix B: Glasgow and Blantyre Coma Scales

Table B1. THE GLASGOW COMA SCALE (indication – above 12 years and adults)

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.”

The Glasgow Coma Scale can be used repeatedly to assess improvement or deterioration of patient’s 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 command	5
	Localizes pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1

Table B2. THE BLANTYRE COMA SCALE (indication – children 9 months to 12 years)

A state <3 is considered at “unarousable coma”.

Test	Response	Score
Eye movement	Directed e.g.	
	Caregiver’s face	1
	Not directed	0
Verbal response	Appropriate cry	
	Moan or inappropriate cry	1
	None	0
Best motor response	Localizes painful stimuli	2
	Withdraws limb from pain	1
	Non-specific or absent response	0

Appendix C: Adverse Medicine Reaction Reporting Form



PHARMACEUTICAL REGULATORY AUTHORITY NATIONAL PHARMACOVIGILANCE UNIT

ADVERSE MEDICINE REACTION/MEDICINE QUALITY PROBLEM REPORT FORM

PATIENT DETAILS		Sex: <input type="radio"/> Male <input type="radio"/> Female		Date of Birth or age:	
Medical initials:		Weight (kg): <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		DD <input type="text"/> - MM <input type="text"/> - YYYY <input type="text"/>	
Health Facility:		Height (cm): <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		Pregnant: <input type="radio"/> Yes <input type="radio"/> No	
				Breastfeeding: <input type="radio"/> Yes <input type="radio"/> No	
SUSPECTED MEDICINES					
Give name(s) of medicine and batch number if known					
Medicine/Vaccine	Route	Dosage	Date started	Date stopped	Reason for use
OTHER MEDICINES TAKEN in last 28 days (including self-medication & herbal remedies)					
Give name(s) of medicine and batch number if known					
Medicine/Vaccine	Route	Dosage	Date started	Date stopped	Reason for use
DESCRIPTION OF PROBLEM (ADVERSE REACTION OR MEDICINE QUALITY PROBLEM)					
Describe the problem (please provide as much detail as possible and include any results of relevant supportive laboratory data and other investigations). For Product quality Problems indicate: Name(s), Batch Number, Name of the Manufacturer, Product License Number, Dosage form & strength, Expiry Date, Size/Type of container and source of the medicine (attach additional pages if necessary)					
Date reaction started:		Date reaction stopped:			
SERIOUSNESS OF REACTION (tick)		OUTCOME (tick)			
Death due to reaction		Recovered (indicate date of recovery)			
Life Threatening		Not yet recovered			
Congenital abnormality		Fatal (indicate date of death)			
Involved or prolonged Hospitalisation		Unknown			
Permanently or significantly disabling		SEQUELAE if Yes, describe			
Required intervention to prevent permanent impairment or damage		Yes			
		No			
ADDITIONAL INFORMATION e.g. medical history, allergies, dechallenge and rechallenge results, previous exposure to suspected medicines etc. (attach additional pages if necessary)					
REPORTER'S DETAILS					
Full name:					
Profession:					
Contact Address:					
Telephone number(s):					
Email address:					
Name of Health Facility:					
SEND TO: National Pharmacovigilance Unit, Pharmaceutical Regulatory Authority, P.O. Box 31890, Lusaka. Telephone: +260-211-220088/220066/220109 Fax: +260-211-238458 E-mail: npvu@pra.gov.zm					

Appendix D: The Use of Antimalarials for Prophylaxis In Travellers

Generic name: **Atovaquone-Proguanil**

Tablet size	Adult dosage	Pediatric dosage	Adverse effects
250 mg atovaquone and 100 mg proguanil (adult)	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 tablet daily;	Not recommended for prophylaxis for children weighing < 5 kg, pregnant women, and women breastfeeding infants weighing < 5 kg.
62.5 mg atovaquone and 25 mg proguanil (pediatric)		body weight 21–30kg, 2 pediatric tablets daily;	Take with food; do not use in persons with creatinine clearance < 30 mL/min; common adverse events include nausea, abdominal pain, and headache;
		body weight 31–40 kg, 3 pediatric tablets daily;	occasional adverse events include transient increase in transaminase levels with treatment doses; rare adverse events include rash.
		body weight > 40 kg, 1 adult tablet daily	

Generic name: **Doxycycline**

Tablet size	Adult dosage	Pediatric dosage	Adverse effects
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)	Take at approximately the same time each day while in the malarious area and for 4 weeks after leaving such areas. Contraindicated in children < 8 years of age and pregnant women. Contraindicated in persons with hypersensitivity to tetracyclines.

Generic name: **Mefloquine**

Tablet size	Adult dosage	Pediatric dosage	Adverse effects
250 mg	One tablet orally once weekly; begin 1–2 days before travel and continue for 4 weeks after travel	<p>Body weight \leq 9 kg, 5 mg per kg weekly;</p> <p>body weight 10–19 kg, a quarter tablet;</p> <p>body weight 20–30 kg, a half tablet;</p> <p>body weight 31–45 kg, a three-quarter tablet;</p> <p>body weight \geq 46 kg, 1 tablet</p>	<p>Begin \geq 2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas.</p> <p>Contraindicated in people allergic to mefloquine or related compounds (quinine, quinidine) and in people with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures.</p> <p>Use with caution in persons with psychiatric disturbances or a previous history of depression. Not recommended for persons with cardiac conduction abnormalities.</p>

Cover photo: PATH/Laura Newman