

REPUBLIC OF KENYA

# NATIONAL GUIDELINES FOR THE DIAGNOSIS, TREATMENT AND PREVENTION OF MALARIA IN KENYA



**Ministry of Public Health and Sanitation  
Ministry of Medical Services**

*Third Edition*





REPUBLIC OF KENYA

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# NATIONAL GUIDELINES FOR THE DIAGNOSIS, TREATMENT AND PREVENTION OF MALARIA IN KENYA

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Ministry of Public Health and Sanitation  
&  
Ministry of Medical Services

*May 2010*

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**National Guidelines for the Diagnosis, Treatment and Prevention of Malaria in Kenya**

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P. O. Box 19982 KNH Nairobi - 00202, Kenya

**Email:** head.domc@domckkenya.or.ke

**http://**[www.nmcp.or.ke](http://www.nmcp.or.ke)

**Design and Layout**

Scangraphics Kenya Limited

P.O. Box 45037 - 00100 Nairobi, Kenya

**Telephone:** +254 (20) 550 910/ 2066681

**Email:** [info@scangraphics.co.ke](mailto:info@scangraphics.co.ke)

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## PREFACE

The ultimate goal of malaria control is to reduce morbidity and prevent mortality due to malaria thereby mitigating the socio-economic burden of the disease on Kenya. One of the key strategic interventions therefore is to provide early parasitological diagnosis and prompt treatment of malaria using effective medicines.

The Ministries of Health have developed these guidelines for malaria diagnosis, treatment and prevention with an aim of improving malaria case management by all health workers and having a harmonized approach in efforts aimed at the reduction of morbidity and mortality due to malaria.

We currently recommend that as much as possible, a diagnosis of malaria be confirmed before the institution of treatment. The third edition of the guideline contains new information regarding implementation of the policy of diagnosis based treatment of malaria in Kenya. Also new in the guideline is the second line artemisinin based combination treatment for uncomplicated malaria.

The policy document is intended to serve as a guide to all health professionals both pre- and in-service and including those in the private sector, researchers, trainers in medical training institutions and all partners involved in the implementation of malaria case management in Kenya.

These guidelines will continue to be updated periodically taking into consideration continuous monitoring and evaluation and emerging research findings and lessons learned. We have carefully considered the cost effectiveness of recommended interventions. We expect users to continually give feedback regarding the use of relevant sections of the guidelines.



**Dr. S.K Sharif MBS**  
 Director of Public  
 Health & Sanitation



**Dr. Francis Kimani MBS**  
 Director of Medical  
 Services



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We are grateful to the Malaria Interagency Coordinating Committee, members of the Case Management Technical Working Group and staff of the Division of Malaria Control and Division of Child Health for their contributions to the development of this document. We are grateful for the financial support from the United States President's Malaria Initiative (PMI) through MSH/SPS programme as well as support from the United Kingdom's Department for International Development. Technical support was received from the World Health Organization's Kenya Country Office, Inter-country Support Team and Global Malaria Program.

It is our sincere hope that the guidelines will be useful in improving prevention and case management of malaria in Kenya. By implementing the recommendations in the guidelines, there is no doubt that we shall reduce malaria related illnesses and deaths and put Kenya on the path towards a malaria free future.

## ABBREVIATIONS

ACSM	Advocacy communication and social mobilization
ACT	Artemisinin based combination treatment
ADR	Adverse drug reaction
AIDS	Acquired immune-deficiency syndrome
AL	Artemether-lumefantrine
ANC	Antenatal care or clinic
CQ	Chloroquine
CSF	Cerebro-spinal fluid
DHA-PPQ	Dihydroartemisinin-piperaquine
DOMC	Division of Malaria Control
DOT	Directly observed treatment
EPR	Epidemic preparedness and response
GCS	Glasgow coma scale
G6PD	Glucose 6-phosphate dehydrogenase
Hb	Haemoglobin
HIV	Human immune-deficiency virus
HRP2	Histidine-Rich Protein 2
IM	Intramuscular
IMCI	Integrated management of childhood illnesses
IPTp	Intermittent preventive treatment of malaria in pregnancy
IV	Intravenous
kg	kilogram
LLIN	Long lasting insecticidal nets
LMU	Logistics monitoring unit
M&E	Monitoring and evaluation
mg	milligram

ml	millilitre
NSAID	Non-steroidal anti-inflammatory drug
pLDH	Parasite lactate dehydrogenase
PPB	Pharmacy and poisons board
RDT	Rapid diagnostic test
SOP	Standard operating procedure
SP	Sulphadoxine or Sulphalene/pyrimethamine
WBC	White blood cell
WHO/GMP	World Health Organization Global Malaria Program

## GLOSSARY OF TERMS

**Afebrile.** Without fever

**Anaemia.** A reduction in the quantity of the oxygen-carrying pigment haemoglobin in the blood

**Anti-pyretic.** A drug such as paracetamol that relieves fever without affecting the causative agent (in this case the parasite)

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

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

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

**Base.** The main active part of a drug (see also salt)

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

**Cinchonism.** Poisoning caused by an overdose of cinchona or the alkaloids quinine, quinidine, or cinchonine derived from it.

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

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

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

**Endemic.** Occurring frequently in a particular region or population

**Febrile.** With an increase in temperature compared with the normal

**Fever.** An increase in body temperature above the normal temperature i.e. above an oral temperature of 37.5°C.

**Febrile convulsions.** Convulsions occurring in children aged 6 months - 6yrs due to fever caused by infection outside the central nervous system

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

**Hyperpyrexia.** Temperature over 39.5°C

**Hypersensitivity.** An abnormal response to the presence of a particular antigen, which may cause a variety of tissue reactions ranging from serum sickness to an allergy.

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

**Immunity.** All those natural processes which prevent infection, re-infection, or super-infection, or which assist in destroying parasites or limiting their multiplication, or which reduce the clinical effects of infection.

**Lumbar puncture.** The insertion of a needle into the fluid-filled space of the spinal cord in the lumbar region and the removal of a sample of that fluid for examination

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

**Non-immune.** Having no immunity at all to a particular organism or disease

**Parenteral.** The provision of medication into the body by any means other than through the alimentary canal (oral route or rectal), such as by subcutaneous, intramuscular or intravenous injection.

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

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

**Pruritus.** Itching caused by local irritation of the skin or at times nervous disorders.

**Radical cure.** In *P. vivax* and *P. ovale* infections only, this comprises elimination of the symptoms and the asexual blood stages of the malaria parasite plus prevention of relapses by killing hypnozoites.

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

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

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

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

merozoites into the bloodstream.

**Resistance.** See drug resistance.

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

**Salt.** Any compound of a base and an acid, e.g. quinine dichloride or quinine sulphate.

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

**Sensitive.** Possessing the ability to respond to a stimulus.

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

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

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

**Treatment failure.** A failure to achieve the desired therapeutic response after the initiation of therapy. Treatment failure is not synonymous with drug resistance.

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

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





# 1. INTRODUCTION

## 1.1 BACKGROUND

Malaria is one of the leading causes of morbidity and mortality, particularly in children under five years of age in Kenya. *Plasmodium falciparum* is the commonest cause of malaria. Interventions to control malaria in Kenya have been integrated and include:

- ◆ Provision of prompt and effective treatment or malaria case management
- ◆ Vector control using long lasting insecticidal nets, indoor residual spraying and other integrated vector management strategies
- ◆ Prevention and treatment of malaria in pregnancy and
- ◆ Epidemic preparedness and response

The provision of prompt and effective treatment is the cornerstone of malaria case management. The treatment policy for malaria has changed in the last 12 years due to failing therapeutic efficacy from chloroquine (CQ) to sulphadoxine-pyrimethamine (SP) in 1998 and subsequently to the currently recommended artemisinin-based combination therapies (ACTs) in 2004. ACTs are at present the best treatment for uncomplicated malaria and the efficacy of the treatments recommended in this guideline continue to be monitored regularly and information will be used to update policies and guidelines.

## 1.2 OBJECTIVE

The objective of this treatment guideline is to provide the target audience with evidence-based recommendations for the treatment of malaria in Kenya. Information is shown on the treatment of uncomplicated malaria and severe malaria including disease in special risk groups for example young children and pregnant women; as well as chemoprophylaxis for special groups including travellers from non-malaria endemic countries.

## 1.3 TARGET AUDIENCE

These guidelines are intended for: all health professionals (doctors, nurses, clinical officers, pharmacists and other paramedical officers). However, public health and policy specialists working in hospitals, research institutions, medical schools, non-governmental organizations and agencies working as partners in health or malaria control may find it useful.

## 1.4 FORMULATIONS

Only ACTs that are co-formulated (both medicines combined in the same tablet) should be used for the treatment of uncomplicated malaria in Kenya. In order for the ACT to provide its intended benefits of effective treatment and prolongation of the useful therapeutic life of both partner drugs, it is strongly recommended that ACTs should include at least 3 days of treatment with an artemisinin derivative<sup>1</sup>. Paediatric formulations should be used for infants and children in order to ensure the correct dosing. Where available, child friendly formulations (flavoured / liquefiable by dose) should be used. All other previously used monotherapies including oral artemisinins should not be used for treatment of malaria and will not be licensed for this purpose anymore.

## 1.5 DIAGNOSIS BASED TREATMENT

Diagnosis of malaria is based on clinical suspicion and on the detection of parasites in the blood (parasitological or confirmatory diagnosis). It is currently recommended to confirm diagnosis of malaria in all age-groups of patients in all epidemiological settings. The use of a confirmatory diagnosis with either microscopy or RDTs is expected to reduce the overuse of antimalarials by ensuring that treatment is targeted at patients with confirmed malaria infection, as opposed to treating all patients with fever.

Efforts are underway to ensure diagnostic tests are available at all levels of the health care system and this will take some time. Under no circumstances should a patient with suspected malaria be denied treatment, or provided with delayed treatment for lack of a parasitological diagnosis. Clinicians should however endeavour to test patients to confirm malaria even after treatment has been provided.

Although a parasitological diagnosis of malaria is recommended for all patients with suspected malaria, appropriate **treatment should NEVER be delayed or denied** due to inability to test for malaria

<sup>1</sup> World Health Organization 2010. *Guidelines for the treatment of malaria 2<sup>nd</sup> edition*. WHO-GMP Geneva.

## 2. MALARIA IN KENYA

**M**alaria is a disease caused by parasites of the genus *Plasmodium*. Nationally, *Plasmodium falciparum* is the predominant species (98.2 per cent) while *P. malariae*, *P. ovale* is 1.8 per cent often occurring as mixed infections. *P. vivax* may account for up to 40-50 per cent of infections (often mixed with *P. falciparum*) in the Northern and North Eastern parts of Kenya.

### 2.1 EPIDEMIOLOGY OF MALARIA IN KENYA

Kenya has four malaria epidemiological zones, with diversity in risk determined largely by altitude, rainfall patterns and temperature. The zones are:

**Endemic:** Areas of stable malaria have altitudes ranging from 0 to 1,300 metres around Lake Victoria in western Kenya and in the coastal regions. Rainfall, temperature and humidity are the determinants of the perennial transmission of malaria. The vector life cycle is usually short and survival rates are high because of the suitable climatic conditions. Transmission is intense throughout the year, with annual entomological inoculation rates between 30 and 100.

**Seasonal transmission:** Arid and semi-arid areas of northern and south-eastern parts of the country experience short periods of intense malaria transmission during the rainfall seasons. Temperatures are usually high and water pools created during the rainy season provide breeding sites for the malaria vectors. Extreme climatic conditions like the El Niño southern oscillation lead to flooding in these areas, resulting in epidemic outbreaks with high morbidity rates owing to the low immune status of the population.

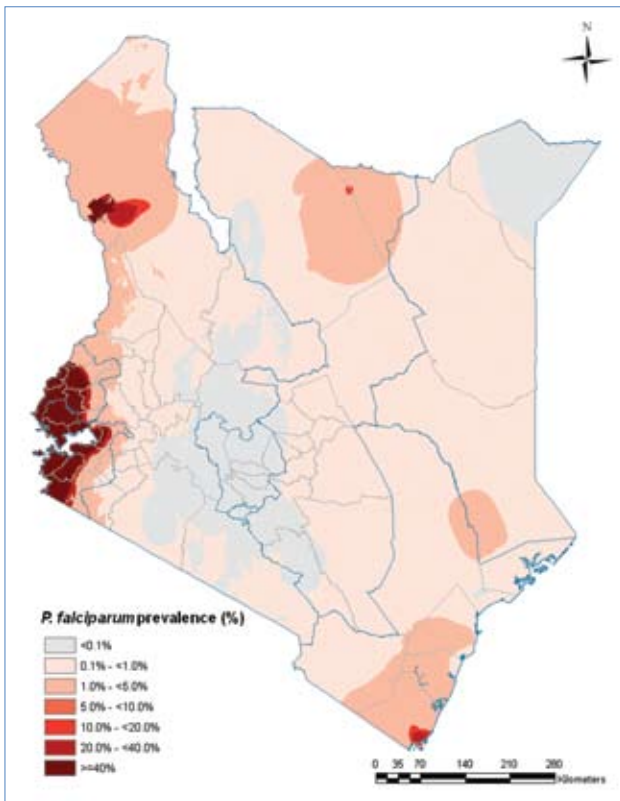
**Epidemic prone areas of western highlands of Kenya:** Malaria transmission in the western highlands of Kenya is seasonal, with considerable year-to-year variation. Epidemics are experienced when climatic conditions favour sustainability of minimum temperatures around 18°C. This increase in minimum temperatures during the long rains favours and sustains vector breeding, resulting in increased intensity of malaria transmission. The whole population is vulnerable and case fatality rates during an epidemic can be up to ten times greater than those experienced in regions where malaria occurs regularly.

**Low risk malaria areas:** This zone covers the central highlands of Kenya including Nairobi. The temperatures are usually too low to allow completion of the sporogonic cycle of the malaria parasite in the vector.

However, the increasing temperatures and changes in the hydrological cycle associated with climate change are likely to increase the areas suitable for malaria vector breeding with the introduction of malaria transmission in areas where it had not existed before.

In 2009, a model-based map of the intensity of *P. falciparum* transmission in Kenya as defined by the proportion of infected children aged 2-10 years in the community was produced. Based on the malaria risk map and the eco-epidemiology of malaria in Kenya, districts have been stratified into 4: Lake stable endemic & Coast seasonal stable endemic (risk class equal to or above 20 per cent); Highland epidemic-prone districts (risk class 5- <20 per cent); Seasonal low transmission including arid and Semi arid districts (risk class less than 5 per cent); low risk districts (risk class less than 0.1 per cent).

**Figure 1: 2009 Kenya malaria endemicity map<sup>2</sup>**



<sup>2</sup> Abdisalan M Noor et al. The risks of malaria infection in Kenya in 2009 BMC Infectious Diseases 2009, 9:180

### 3. CLINICAL FEATURES AND CLASSIFICATION OF MALARIA

Malaria can be classified as either uncomplicated or severe based on clinical presentation.

#### 3.1 UNCOMPLICATED MALARIA

This is characterized by fever in the presence of peripheral parasitaemia. Other features may include chills, profuse sweating, muscle pains, joint pains, abdominal pain, diarrhoea, nausea, vomiting, irritability and refusal to feed. These features may occur singly or in combination.

#### 3.2 SEVERE MALARIA

This is a life threatening manifestation of malaria, and is defined as the detection of *P. falciparum* in the peripheral blood in the presence of any of one or more of the clinical or laboratory features listed below:

- ◆ Prostration (inability or difficulty to sit upright, stand or walk without support in a child normally able to do so, or inability to drink in children too young to sit)
- ◆ Alteration in the level of consciousness (ranging from drowsiness to deep coma)
- ◆ Cerebral malaria (unrousable coma not attributable to any other cause in a patient with *falciparum* malaria)
- ◆ Respiratory distress (acidotic breathing)
- ◆ Multiple generalized convulsions (2 or more episodes within a 24 hour period)
- ◆ Shock (circulatory collapse, septicaemia)
- ◆ Pulmonary oedema
- ◆ Abnormal bleeding (Disseminated Intravascular coagulopathy)
- ◆ Jaundice
- ◆ Haemoglobinuria (black water fever)
- ◆ Acute renal failure - presenting as oliguria or anuria
- ◆ Severe anaemia (Haemoglobin < 5g/dl or Haematocrit < 15%)
- ◆ Hypoglycaemia (blood glucose level < 2.2.mmol/l)
- ◆ Hyperlactataemia

## 4. PARASITOLOGICAL DIAGNOSIS OF MALARIA

The commonly used confirmatory tests to detect the presences of malaria parasites are microscopy or rapid diagnostic tests (RDTs). Quality assurance of microscopy and RDTs is vital for the sensitivity and specificity of the results.

### 4.1 MICROSCOPY

- ◆ Microscopy is the standard method for parasitological diagnosis of malaria and is performed by examining a stained thick or thin blood smear for the presence of malaria parasites.
- ◆ Thick films are recommended for parasite detection and quantification and can be used to monitor response to treatment.
- ◆ Thin films are recommended for species identification.

#### 4.1.1 Recommended procedure for microscopy

- Make a thick or thin blood film on a clean microscope slide
- Stain using giemsa stain\*
- Examine under power 100 oil immersion objective lens starting with the thick followed by the thin film
- Report the type of parasite(s) seen, developmental stage and parasite count as parasites per 200 WBCs or parasites per microlitre of blood
- Ensure you always use relevant Standard Operating Procedures (SOPs) for all processes
- If the blood slide is negative, further investigations for the cause of febrile disease including repeating the blood slide should be carried out.

*\*In the absence of giemsa stain, freshly prepared field stain may be used.*

### 4.2 RAPID DIAGNOSTIC TESTS

Rapid diagnostic tests (RDTs) are immunochromatographic tests based on detection of specific parasite antigens. Tests which detect histidine-rich protein 2 (HRP2) are specific for *P.falciparum* while those that detect parasite lactate dehydrogenase (pLDH) or aldolase have the ability to differentiate between *P.falciparum* and non-*P.falciparum* malaria (vivax, malariae and ovale). With the appropriate training, RDTs are simple to use and are sensitive in detecting low parasitaemia.

The use of RDTs is however not recommended for follow-up as most of the tests remain positive for between 2 to 3 weeks following effective antimalarial treatment and clearance of parasites. They also cannot be used to determine parasite density.

When using RDTs, it is important to adhere strictly to the manufacturer’s instructions especially the time of reading the results. Remember to observe safe medical waste disposal at all times. The recommended RDTs for use in Kenya will be according to the WHO recommendations produced annually.

### 4.3 OTHER PARASITE DETECTION METHODS

Other techniques include detection of antibodies to malaria parasites and also the detection parasite DNA, based on the polymerase chain reaction (PCR). The former is non-specific while the latter is highly sensitive and very useful for detecting mixed infections, in particular at low parasite densities. PCR is currently mainly used in drug efficacy studies. Neither is used for clinical management.



## 5. MANAGEMENT OF UNCOMPLICATED MALARIA

### 5.1 DIAGNOSIS

All patients with fever or history of fever should be tested for malaria and only patients who test positive should be treated for malaria. All patients should also be assessed for other conditions that may cause fever and be managed accordingly.

### 5.2 TREATMENT OF UNCOMPLICATED FALCIPARUM MALARIA

#### 5.2.1 First line treatment in all age groups

The recommended first line treatment for uncomplicated malaria in Kenya is artemether-lumefantrine (AL) currently available as a co-formulated regular or child friendly dispersible tablet containing 20 mg of artemether and 120 mg of lumefantrine. This is administered as a 6-dose regimen given over three days (See table below)

**Table 1: Dosing schedule for artemether-lumefantrine**

Weight in kg	Age in years	Number of tablets per dose					
		Day 1		Day 2		Day 3	
		1st dose	8 hours	24 hours	36 hours	48 hours	60 hours
5 - 14	5 months ≤ 3years	1	1	1	1	1	1
15 - 24	3 - 7years	2	2	2	2	2	2
25 - 34	8 - 11years	3	3	3	3	3	3
above 34	≥ 12 years	4	4	4	4	4	4

- ♦ Malaria patients with HIV/AIDS should be managed according to the same regimen above.
- ♦ In children below 5 kg, if appropriate weight for age, evaluation of other causes of fever including malaria should be undertaken. Where malaria is confirmed, the current recommended treatment is half a tablet of AL given according to the schedule in table 1 under close supervision<sup>3</sup>.

<sup>3</sup> World Health Organization 2010. Guidelines for the treatment of malaria 2nd edition. WHO-GMP Geneva.



- ◆ For children < 24kg, dispersible tablets should be administered where available.
- ◆ Place the tablet in a cup or spoon, add a little water to it, wait a few minutes for tablets to disperse and then administer the resulting suspension to the child.

### 5.2.2 Counselling and follow up

- Directly observe the first treatment dose at the health facility which may be given on an empty stomach
- Show all caregivers of young children how to prepare the dispersible tablet prior to administration. Ensure she/he understands how to administer the same to the child prior to leaving the facility.
- If vomiting occurs within 30 minutes after drug administration, the dose should be repeated.
- Explain the dosing schedule, use probing questions to confirm the patient’s understanding.
- Emphasize that all 6 doses must be taken over 3 days even if the patient feels better after a few doses.
- Advise patients to return immediately to the nearest health facility if the condition deteriorates at any time or if symptoms have not resolved after 3 days.

### 5.2.3 Supportive treatment

- **Fever management:** Administer an antipyretic for fever. The recommended paracetamol is preferred over non-steroidal anti-inflammatory drugs (NSAIDs). Other mechanical methods for reducing temperature include exposure, fanning or tepid sponging.
- **Encourage adequate fluids and nutrition:** Caregivers should be encouraged to give extra fluids and where applicable continue breastfeeding. Feeds and fluid should be administered in small quantities at frequent intervals especially when the child is still very sick.

## 5.3 TREATMENT FAILURE

Treatment failure can be defined as a failure to achieve the desired therapeutic response after the initiation of therapy. Treatment failure is not synonymous with drug resistance. Treatment failure may result from poor adherence to treatment, unusual pharmacokinetic properties in that individual or drug resistance.

Treatment failure could also arise due to a wrong diagnosis and thus initiating the wrong treatment. In evaluating a patient with treatment failure, it is important to determine from the patient's history whether he or she vomited previous treatment or did not complete a full treatment course.

Treatment failures should be suspected if patient deteriorates clinically at any time or symptoms persists 3 - 14 days after initiation of drug therapy in accordance with the recommended treatment regimen.

Development of symptoms 14 days after initiation of therapy where there has been prior clearance of symptoms should be considered as a new infection and be treated with the first line drug.

### 5.3.1 Management of suspected treatment failure

Malaria microscopy should be used to assess suspected treatment failures. Use of RDTs is not recommended. Confirmed cases of treatment failure should be treated with the 2nd line ACT dihydroartemisinin-piperaquine. Other potential differential diagnosis should be sought for and adequately managed. In centres with no microscopy facilities, patients with suspected treatment failures should be referred. In cases of non-adherence with or non-completion of medicine, repeat a full course of the first line drug.

### 5.3.2 Second line treatment in all age groups

The recommended second line treatment for uncomplicated malaria in Kenya is dihydroartemisinin-piperaquine (DHA-PPQ). This is currently available as a fixed-dose combination with adult tablets containing 40 mg of dihydroartemisinin and 320 mg of piperaquine and paediatric tablets containing 20mg dihydroartemisinin and 160mg of piperaquine. These are administered once daily for three days as shown in table 2.

**Therapeutic dose.** A target dose of 4 mg/kg/day dihydroartemisinin and 18 mg/kg/day and piperaquine once a day for 3 days, with a therapeutic dose range between 2 - 10 mg/kg/day dihydroartemisinin and 16 - 26 mg/kg/dose piperaquine.

**Table 2: Dosing schedule for dihydroartemisinin-piperaquine**

Age in years	Number of tablets to be administered on Day 1 at 0 hours	Number of tablets to be administered on Day 2 at 24 hours	Number of tablets to be administered on Day 3 at 48 hours
3 months < 3 years	1 paediatric tablet	1 paediatric tablet	1 paediatric tablet
3 - 5 years	2 paediatric tablets	2 paediatric tablets	2 paediatric tablets
6 - 11 years	1 adult tablet	1 adult tablet	1 adult tablet
12 - 16 years	2 adult tablets	2 adult tablets	2 adult tablets
Above 16 years	3 adult tablets	3 adult tablets	3 adult tablets

## 5.4 TREATMENT OF UNCOMPLICATED VIVAX MALARIA

It is vital to have confirmed lab diagnosis of *P. vivax* malaria before commencing treatment. *P. vivax* has both blood and liver stages. Like falciparum malaria, the recommended treatment for vivax malaria is AL. However, in order to achieve a radical cure and prevent relapses, primaquine, must also be given. Primaquine causes abdominal discomfort when taken on an empty stomach; it should always be taken with food. Primaquine may also cause haemolysis in patients with glucose-6-phosphatase dehydrogenase (G6PD) deficiency.

**Therapeutic dose.** Primaquine dose ranges between 0.25 and 0.5mg/kg/day once a day for 14 days.

## 5.5 M & E INDICATORS

- i. Proportion of patients with fever presenting to health facility who are managed in accordance with national malaria treatment guidelines
- ii. Proportion of patients presenting to health facility with fever and ACT prescribed, who counselling and ACT dispensing tasks performed according to national guidelines

## 6. MANAGEMENT OF SEVERE MALARIA

Severe malaria is a medical emergency. Delay in diagnosis and inappropriate treatment, especially in infants, children and non-immune adults leads to rapid worsening of the situation and is often fatal. The keys to effective management are early recognition, assessment, and appropriate antimalarial and supportive therapy. The commonest cause of severe malaria is *P. falciparum*. Very rarely though, *P. vivax* may also manifest as severe disease.

### 6.1 DIAGNOSIS

The clinical manifestations of malaria severity depend on various factors including age and the levels of malarial immunity. In children the common presentations of severe malaria are severe anaemia, respiratory distress and cerebral malaria. Severe malaria can occur in the absence of fever. An outline of the presentations, their frequency of occurrence and the prognostic value is summarized in the table below.

#### 6.1.1 Clinical features of severe *falciparum* malaria

The clinical features of severe malaria are outlined in tables 3 and 4.

**Table 3: Clinical features of severe *P.falciparum* malaria**

Clinical features	Frequency		Prognostic value	
	Children	Adults	Children	Adults
Prostration	+++	+++	+	+
Altered level of consciousness	+++	++	+++	+++
Multiple convulsions	+++	+	+	++
Respiratory distress	+++	++	+++	+++
Circulatory collapse	+	+	+++	+++
Pulmonary oedema	+	+	+++	+++
Jaundice	+	+++	++	+
Haemoglobinuria	+	+	+	+
Abnormal bleeding	+	+	+++	++

**Table 4: Laboratory features of severe *P. falciparum* malaria**

Laboratory features	Frequency		Prognostic value	
	Children	Adults	Children	Adults
Severe anaemia (Hb < 5 gm/dl or Hct < 15%)	+++	+	+	+*
Hypoglycaemia (blood sugar < 2.2 mmol/l)	+++	++	+++	+++
Hyperparasitaemia	++	+	+/-	++
Renal impairment	+	+++	++	++
Acidosis	+++	++	+++	+++
Hyperlactatemia	+++	++	+++	+++

\* +++: very common; ++: common, +: less common; +/- :data not conclusive

- ◆ In all patients with suspected severe malaria with or without fever or history of fever the use of parasitological diagnosis is recommended
- ◆ Antimalarial treatment should not be withheld if parasitological diagnosis is not possible. Presumptive treatment should be started immediately while efforts to confirm diagnosis are ongoing
- ◆ In settings where resources are available, if 3 consecutive blood slides taken 8 hours apart are negative or the RDT test is negative, alternative causes of illness should be sought.
- ◆ Other investigations to determine severity and prognosis should be undertaken where feasible.

In all suspected cases of severe malaria, a parasitological confirmation of the diagnosis of malaria is recommended. In the absence of or delay in obtaining a parasitological diagnosis, patients should be treated for severe malaria on clinical grounds.

### 6.1.2 Clinical features of severe *P. vivax* malaria

- Severe anaemia
- Severe thrombocytopenia and pancytopenia
- Jaundice
- Splenic rupture
- Acute renal failure
- Acute respiratory distress syndrome.

Prompt and effective treatment and follow-up should be the same as for severe falciparum malaria.

## 6.2 EVALUATION OF SOME CLINICAL MANIFESTATIONS

Along with other clinical and laboratory evaluation for severe malaria, the following should be undertaken as the minimal investigation package for the different clinical scenarios described below:

### 6.2.1 Cerebral malaria

#### Clinical assessment

- a. Assess level of consciousness using coma score (Annex 4).
- b. Determine the presence of severe anaemia by examining for pallor on the palms and conjunctiva
- c. Determine presence of respiratory distress (deep and fast breathing, chest in-drawing)
- d. Determine hydration status (check for sunken eyes, loss of skin turgor, dry tongue and measuring blood pressure).
- e. Assess for renal insufficiency (measuring urine output)
- f. Assess for evidence of disseminated intravascular coagulopathy (spontaneous bleeding from the gums, injection sites, or any other site.
- g. Check for clinical signs of meningitis (stiff neck, Kernig's sign in children, photophobia) cerebral malaria does not cause meningism although patients may present with opisthotonus.

#### Laboratory Tests

Eliminate other causes of alteration in the level of consciousness including Cerebral Spinal Fluid (CSF) analysis to rule out meningitis, blood glucose levels to rule out hypoglycaemia, and other common causes of coma in your environment.

## 6.2.2 Severe anaemia

### Clinical assessment

- a. Determine the presence of severe anaemia by examining for pallor on the palms and conjunctiva
- b. Determine presence of respiratory distress (deep and fast breathing, chest in-drawing)
- c. Assess for evidence of disseminated intravascular coagulopathy (spontaneous bleeding from the gums, injection sites, or any other site).
- d. peripheral oedema)

### Laboratory test

Determine haemoglobin levels, blood group and cross match where applicable.

## 6.2.3 Hypoglycaemia

### Clinical assessment

Assess the level of consciousness

### Laboratory test

Determine the blood glucose level.

## 6.3 TREATMENT OF SEVERE MALARIA

The recommended treatments for severe malaria are parenteral quinine or parenteral artemisinins (artesunate or artemether). The preferred route of administration is the intravenous route. However the intramuscular route can be used as an alternative where intravenous route is not feasible.

### 6.3.1 Quinine administration

- Quinine should only be given as an intravenous infusion and NEVER given as an intravenous (bolus) injection.
- Loading dose should be omitted if patient has received quinine in the last 24 hours or have received mefloquine in the last 7 days
- Quinine is not contraindicated in severe anaemia
- In renal insufficiency the dose of quinine remains unchanged
- In hepatic insufficiency, the dose of quinine should be reduced by 25%
- Hypoglycaemia is a potential side effect of quinine administration particularly in pregnant women and should therefore be administered in a glucose containing infusion.

### 6.3.1.1 Quinine administration in children

#### NOTE

The dosing interval for quinine is between 8 - 12 hours. In order to standardise practice and comply with WHO guidelines, it is therefore recommended to use the dosing interval of 8 hours in children.

#### Administer quinine as follows:

- Put up IV quinine drip 20 mg/kg body weight loading dose in 15mls/kg of 5% dextrose to run over 4 hours.
- 8 hours from the start of the initial dose of quinine, give 10mg/kg in 10mls/kg of isotonic solution (5% dextrose or normal saline) to run in a way as not to exceed 5 mg salt/kg body weight per hour
- Repeat 10mg/kg quinine infusion every 8 hours until the patient can take medication orally.
- Thereafter a complete course of artemether-lumefantrine (AL) is given.
- Alternatively, oral quinine may be given at 10mg/kg every 8 hours to complete a total (parenteral + oral) of 7 days

### 6.3.1.2 Quinine administration in adults

#### Administer quinine as follows:

- A loading dose of quinine 20mg/kg (maximum 1200mg) diluted in 15mls/kg (maximum 500ml) of isotonic solution (5% dextrose or normal saline) is given intravenously to run over 4 hours.
- 8 hours from commencement of the initial dose of quinine, give 10mg/kg (maximum 600mg) diluted in 10mls/kg (maximum 500ml) of isotonic solution (5% dextrose or normal saline) to run over 4 hours.
- Repeat 10mg/kg quinine infusion every 8 hours until the patient can take medication orally.
- Thereafter a complete course of artemether-lumefantrine (AL) is given
- Alternatively oral quinine is continued at 10mg/kg (maximum 600mg) every 8 hours to complete a total of 7 days treatment, in combination with clindamycin or doxycycline also for 7 days.

### 6.3.2 Administration of parenteral artemisinins

Injectable artemisinins may also be used for management of severe malaria.



### 6.3.2.1 Artesunate

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 intravenous injection or by intramuscular 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.

#### Administer artesunate as follows:

- Dissolve artesunic powder with 5% sodium bicarbonate solution (provided with vial).
- Dilute resultant solution with 5ml 5% dextrose
- Administer 2.4 mg/kg stat by slow intravenous injection then 1.2 mg/kg/at 12 hrs and 24 hrs then 1.2mg/kg daily until the patient is able to tolerate oral medications. Artesunate can be given IM at the same dosage and intervals
- Thereafter a complete course of artemether-lumefantrine (AL) is given

### 6.3.2.2 Artemether

Artemether is dispensed as clear oily solution of differing concentrations. Artemether must only be given by intramuscular injection.

#### Administer artemether as follows:

- Artemether administered by the intramuscular route at a loading dose of 3.2 mg/kg IM stat then 1.6 mg/kg/IM daily until the patient is able to tolerate oral medications
- Thereafter a complete course of artemether-lumefantrine is given

In the absence of injectable quinine or artemisinins, patients particularly children with severe malaria who are able to tolerate oral feeds should be given AL or other available ACT to initiate treatment. If the patient is unable to take oral medications, a nasogastric tube should be used to administer AL.

### 6.3.3 Severe malaria patients who may be able to tolerate oral treatment

Patients with the following features:

- Severe anaemia (haemoglobin level of < 5g/dl or haematocrit of < 15% or
- Two or more convulsions within a 24-hr period or
- Hyperparasitaemia and who are stable but show none of the features of prostration, respiratory distress (acidotic breathing) or alteration in the level of consciousness can be treated with AL, DHA-PPQ or oral quinine where ACT is not available. They should however be treated as in-patients for close monitoring. Thus any emerging complications of severe malaria should be managed promptly and appropriately.

## 6.4 SUPPORTIVE TREATMENT

Supportive treatment is crucial in reducing the high mortality associated with severe malaria. The table below highlights specific management for manifestations or complications of severe malaria.

**Table 5: Supportive treatment for manifestations of severe malaria**

Manifestation/Complication	Immediate Management <sup>a</sup>
<b>Coma (cerebral malaria)</b>	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatment, such as corticosteroids, heparin and adrenaline; intubate if necessary. Proper nursing care to avoid aspiration and pressure sores.
<b>Hyperpyrexia</b>	Administer tepid sponging, fanning, a cooling blanket and antipyretic drugs. Paracetamol is preferred over more nephrotoxic drugs (e.g. NSAIDs <sup>b</sup> ).
<b>Convulsions</b>	<b>Maintain airways;</b> treat promptly with: Diazepam ( <i>0.3 mg/kg IV, or 0.5mg/kg by rectal administration</i> ) or Phenobarbitone ( <i>15 mg/kg IM loading dose then a maintenance dose of 4 - 8mg/kg/day for 48 hours</i> ) if convulsions persist. <b>Phenytoin</b> ( <i>18 mg/kg loading dose then maintenance dose of 5 mg/kg/day for 48 hours</i> ) may be used instead of phenobarbitone. Check blood glucose and control temperature

<p><b>Hypoglycaemia</b></p>	<p>Check blood glucose, correct hypoglycaemia correct with glucose (IV or oral), and ensure adequate caloric intake (nutritional support) thereafter. Give (1ml/kg of 50% dextrose bolus diluted as 1 part 50% dextrose to two parts normal saline or 5% dextrose) thereafter maintain with maintain with dextrose containing infusion or ensure oral feeding while continuing to monitor blood glucose level until it is normal and stable.</p>
<p><b>Severe anaemia</b></p>	<p>Transfuse with screened fresh whole blood. as per national blood transfusion guidelines. It is recommended that in the paediatric age group to transfuse for severe malarial anaemia when Hb&lt;4g/dl and that if Hb is between 4 and 5g/dl transfuse if signs of respiratory distress or cardiac failure are present.</p>
<p><b>Fluid and electrolyte imbalance</b></p>	<p>Ensure adequate fluid and electrolyte balance. <i>Note that strict fluid management is vital in the comatose patient. Fluid used in administration of antimalarials and any other transfusions (e.g. blood transfusion) must be calculated as part of the total fluid requirement of the patient.</i></p>
<p><b>Acute pulmonary oedema<sup>a</sup></b></p>	<p>Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure/continuous positive airway pressure in life-threatening hypoxaemia.</p>
<p><b>Acute renal failure</b></p>	<p>Exclude pre-renal causes, check fluid balance and urinary sodium; if renal failure is established add haemofiltration or haemodialysis, or if unavailable, peritoneal dialysis.</p>
<p><b>Spontaneous bleeding and coagulopathy</b></p>	<p>Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets, if available); give vitamin K injection.</p>
<p><b>Metabolic acidosis</b></p>	<p>Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe, add haemofiltration or haemodialysis.</p>
<p><b>Shock</b></p>	<p>Suspect septicaemia, take blood for cultures; give parenteral broad-spectrum antimicrobials, correct haemodynamic disturbances.</p>

<sup>a</sup> It is assumed that appropriate antimalarial treatment will have been started in all cases

<sup>b</sup> Non-steroidal anti-inflammatory drugs

<sup>c</sup> Prevent by avoiding excess hydration

## 6.5 PRE-REFERRAL MANAGEMENT OF SEVERE MALARIA

Since severe malaria is a medical emergency, treatment of a patient with severe malaria should begin in the health centre/dispensary (while waiting for referral) so that life-saving therapy is not delayed.

Upon recognition of severe malaria, pre-referral treatment should be initiated at the peripheral facility using IM quinine. In the absence of quinine, rectal artesunate or IM artemether should be used. All efforts should be made to move the patient to a centre where the expertise and infrastructure exist for the adequate management of severe malaria.

In patients with alteration in the levels of consciousness, parenteral antibiotics (ceftriaxone) should also be administered along with the antimalarial.

If for any reason referral is not possible or delayed, treatment for severe malaria with the use of IM quinine should be continued. Health workers at such facilities should ensure that treatment continues until the patient PHYSICALLY moves to another facility.

### NOTE

It is not enough to give a referral letter and assume that the patient has been referred. The referral letter should be as comprehensive as possible and a health worker should accompany the referred patient

### 6.5.1 Administration of intramuscular quinine

- Quinine **MUST** be diluted (maximum concentration is 100 mg/ml for adults, and 50mg/ml for children) before intramuscular injection.
- A loading dose of 20 mg/kg of quinine (diluted to a maximum 100 mg/ml for adults and 50mg/ml for children) is given by intramuscular injection (preferably the anterior thigh). A maximum of 3ml should be injected into one site. If the amount to be injected exceeds 3ml, multiple sites should be used.
- An example of body weights and dose (ml) of injection is given in Annex 3, Table 19).

### 6.5.2 Administration of parenteral artemisinins

- Administer a start dose of 3.2 mg/kg of artemether solution by the intramuscular route to the anterior thigh.
- 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. Administer a start dose of 2.4 mg/kg of by the intramuscular route to the anterior thigh.

### 6.5.3 Administration of rectal artesunate

- Artesunate for rectal administration is presented in suppositories of different strengths. The appropriate single dose of artesunate should be administered.
- In the event that a suppository is expelled from the rectum within 30 minutes of insertion, a second suppository should be inserted. In young children the buttocks should be held together for 10 minutes to ensure retention of the rectal dose of artesunate.

**Table 6: Rectal artesunate for pre-referral treatment in children<sup>4</sup>**

Weight (kg)	Age	Artesunate dose (mg)	Single dose regimen
5 - 8.9	0 - 12 months	50	One 50 mg suppository
9 - 19	13 - 42 months	100	One 100 mg suppository
20 - 29	43 - 60 months	200	Two 100 mg suppositories
30 - 39	6 - 13 years	300	Three 100 mg suppositories

<sup>4</sup> World Health Organization Artesunate for the treatment of severe malaria. <http://archives.who.int/eml/expcom/expcom15/applications/formulations/artesunate.pdf>

**Table 7: Rectal Artesunate for pre-referral treatment in adults**

Weight (kg)	Artesunate dose (mg)	Single dose regimen
40 - 59	400	One 400 mg suppository
60 - 80	800	Two 400 mg suppositories
> 80	1200	Three 400 mg suppositories

**6.5.4 Referral of the patient**

- Send a clear letter or referral form about the clinical picture, including dosages, times, and route of administration for any medications given
- Carry all blood film examination or slides (if these have been taken) to be sent along with the patient to the referral centre.
- Send potential blood donors
- Ask the guardian to keep the child lying down on their side during the journey
- Accompany or ask a fellow health worker to accompany the patient to the referral centre

**6.6 FOLLOW-UP OF ALL PATIENTS WITH SEVERE MALARIA**

- Monitor for possible complications and manage accordingly
- Monitor Hb levels and give haematinics as appropriate
- Monitor and rehabilitate patients with neurological sequelae

## 7. MALARIA IN PREGNANCY

Pregnancy increases the risk of malaria infection in all women. Malaria during pregnancy causes febrile illness, anaemia and increases the risk of maternal illness and death, miscarriage, stillbirth, low birthweight and neonatal death. Although women in their first and second pregnancies, and all HIV infected women are at greatest risk of the effects of malaria, all pregnant women living in malaria risk areas should be advised on malaria prevention measures and clinical cases of malaria treated promptly with effective antimalarials.

### 7.1 MANAGEMENT OF UNCOMPLICATED MALARIA

#### 7.1.1 Diagnosis

**Table 8: Symptoms and signs of uncomplicated malaria in pregnant women**

TYPE OF MALARIA	SIGNS AND SYMPTOMS USUALLY PRESENT	SIGNS AND SYMPTOMS SOMETIMES PRESENT
<ul style="list-style-type: none"> <li>Uncomplicated malaria</li> </ul>	<ul style="list-style-type: none"> <li>Fever, chills/rigors</li> <li>Headache</li> <li>Muscle and joint pains</li> <li>Nausea and vomiting</li> <li>False labour (uterine contractions)</li> </ul>	<ul style="list-style-type: none"> <li>Enlarged spleen</li> </ul>

- In **all pregnant women** with fever or history of fever the use of parasitological diagnosis is **recommended**.
- At health facilities where malaria diagnostics (microscopy or RDT) are not available, patient with fever or history of fever in whom the health worker suspects malaria and has eliminated other possible causes of fever, should be presumptively classified and treated as malaria.

#### Pregnant women at most risk of malaria infection

- First or second pregnancy in malaria endemic areas
- Immigrants or visitors from areas of low or no malaria transmission
- HIV infected

## 7.1.2 Treatment

### 7.1.2.1 First trimester

The recommended treatment for uncomplicated malaria in the first trimester is a 7-day therapy of oral quinine. Do not withhold artemether-lumefantrine or any other treatment in 1st trimester if quinine is not available. Malaria if untreated can be fatal to the pregnant woman.

### 7.1.2.2 Second and third trimesters

Artemether-lumefantrine is the recommended treatment in the 2nd and 3rd trimesters. Oral quinine may also be used but compliance must be ensured. Dose regimens for quinine and AL are as given in the uncomplicated malaria section.

## 7.1.3 Supportive care

- Prevent hypoglycaemia (particularly if taking quinine)
- Foetal monitoring
- Treatment of anaemia<sup>5</sup>
- Antipyretics

## 7.1.4 Follow-up management

Antenatal Care<sup>6</sup>

## 7.2 MANAGEMENT OF SEVERE MALARIA

Severe malaria in pregnancy is a medical emergency that puts both the lives of the mother and baby at high risk. Aggressive management is essential.

### 7.2.1 Diagnosis

Features of severe malaria in pregnant women are similar to non-pregnant women. These are detailed in section 6.1.1. Pregnant women have an increased risk of quinine induced hypoglycaemia and also complications from severe anaemia.

<sup>5</sup> All pregnant women should receive an iron supplementation during ANC as part of the prevention of anemia.

<sup>6</sup> IPTp with SP should be prescribed in high transmission areas and LLINs given during the ANC visit to all pregnant women



**Table 9: Symptoms and signs of severe malaria in pregnant women**

TYPE OF MALARIA	SIGNS AND SYMPTOMS USUALLY PRESENT	SIGNS AND SYMPTOMS SOMETIMES PRESENT
Severe	Symptoms and signs of uncomplicated malaria plus one or more of the following: <ul style="list-style-type: none"> <li>• Confusion, drowsiness, coma</li> <li>• Fast breathing/ breathlessness/difficulty breathing</li> <li>• Vomiting at every feed or unable to feed</li> <li>• Pale conjunctivae, mucous membranes, tongue and palms</li> <li>• Jaundice</li> </ul>	<ul style="list-style-type: none"> <li>• Convulsions</li> <li>• Severe jaundice</li> <li>• Signs of severe dehydration, especially if woman has been vomiting repeatedly</li> <li>• Sudden weight loss</li> <li>• Sunken eyes</li> <li>• Reduced skin turgor, dry mouth</li> <li>• Reduced amount of urine or no urine at all</li> <li>• Spontaneous bleeding from the gums, skin and vein puncture sites</li> </ul>

**Table 10: Convulsions in pregnancy**

Signs/Symptoms	Severe malaria	Eclampsia*
Recent history of fever, chills(from patient or family)	Yes	No
Temperature	> 38°C	< 38°C
Blood pressure	Diastolic < 90mm hg	Diastolic often > 90mm hg
Enlarged spleen	Yes	No
Jaundice	Yes	No

\* Note that eclampsia is a differential diagnosis in pregnant women presenting with convulsions or alteration in level of consciousness.

In all suspected cases of severe malaria in pregnancy, it is recommended to confirm a diagnosis of malaria parasitologically. In the absence of or delay in obtaining a parasitological diagnosis, it is most important to initiate treatment for severe malaria without delay.

### 7.2.2 Treatment

The recommended medicine for severe malaria in pregnancy is parenteral quinine or parenteral artemisinins (artemether or artesunate). The preferred route of administration is the intravenous route for quinine and artesunate. However the intramuscular route can be used as an alternative where intravenous route is not feasible. Due to the increased risk of hypoglycaemia in pregnant women, a dextrose containing solution must be used for quinine administration.

#### NOTE

Pregnancy is not a contraindication for the use of a loading dose of quinine

### 7.2.3 Pre-referral treatment for severe malaria in pregnancy

- Treatment of a patient with severe malaria should begin in the health centre/dispensary (while waiting for referral) so that life-saving therapy is not delayed
- Upon recognition of severe malaria, initiate treatment with a loading dose of quinine 20mg/kg body weight should be given. Remember to give glucose to prevent hypoglycaemia.
- In the absence of quinine, IM artemether, IM artesunate or rectal artesunate can be administered. All efforts should be made to move the patient to a centre where the expertise and infrastructure exist for the adequate management of severe malaria.
- In patients with alteration in the levels of consciousness, parenteral antibiotics (ceftriaxone) should also be administered along with the antimalarial.
- It is not enough to give a referral letter and assume that the patient has been referred. A health worker should accompany the referred patient to the next level of health care

## 7.3 PREVENTION OF MALARIA IN PREGNANCY

The goal of prevention of malaria in pregnancy is to reduce maternal and perinatal morbidity and mortality associated with malaria. The strategies in prevention of malaria in pregnancy are integrated in the overall antenatal care (ANC) package for maternal health. They include the provision of:

- ◆ Intermittent preventive treatment for malaria in pregnancy (IPTp)
- ◆ Long lasting Insecticidal Nets
- ◆ Provision of prompt diagnosis and treatment of fever due to malaria
- ◆ Health education

### 7.3.1 Intermittent preventive treatment of malaria in pregnancy (IPTp)

IPTp is the presumptive (regardless of whether the woman is infected or not) provision of a full treatment course of an efficacious antimalarial at specific intervals during pregnancy. IPTp has been shown to reduce the risk of placental infection and the associated risk of maternal anaemia, miscarriage, premature deliveries and low birthweight. The current recommended medicine for IPTp is 3 tablets of sulphadoxine/ sulphalene 500mg and pyrimethamine 25mg.

- ◆ IPTp is recommended in areas of high malaria transmission
- ◆ Administer IPTp with each scheduled visit after quickening to ensure women receive a minimum of 2 doses
- ◆ IPTp should be given at an interval of at least 4 weeks (1 month)
- ◆ IPTp should be given under directly observed therapy (DOT) in the antenatal clinic and can be given on an empty stomach.
- ◆ SP as IPTp is safe up to 40 weeks pregnancy and late dosing is beneficial for women presenting late in pregnancy
- ◆ Folic acid tablets should NOT be administered with SP given for IPTp and if need be, may be taken 14 days following administration of IPTp

#### 7.3.1.1 IPTp and HIV+ pregnant women

HIV infection during pregnancy increases the risk of the complications of malaria in pregnancy while malaria infection during pregnancy particularly placental malaria increases the risk of mother to child transmission of HIV.

- Women known to be HIV infected or with unknown HIV status living in areas of high HIV prevalence ( >10% among pregnant women) should receive at least 3 doses of IPTp.

- Pregnant women who are HIV positive and are on daily cotrimoxazole chemoprophylaxis should not be given SP for IPTp
- Pregnant women who are HIV positive and are also taking antiretroviral therapy for PMTCT who are not receiving cotrimoxazole should receive IPTp with SP.

Always ask the mother if she is allergic to sulpha drugs or has experienced side effects to sulpha drugs before giving SP

### 7.3.2 Long lasting insecticidal nets

- LLINs are key in the prevention of malaria in pregnancy.
- Each pregnant woman living in a malaria risk area receives a free LLIN at the first contact visit to the ANC
- Each pregnant woman is shown how to hang the LLIN and encouraged to use the net each and every night during her pregnancy and thereafter.
- LLIN are not a substitute for IPTp and vice versa. Both must be used in order to achieve maximal benefits in the reduction of both maternal and perinatal morbidity and mortality

### 7.3.3 Health education

- Continuous maternal health education should be provided at the ANC encouraging use of all interventions and services and encouraging the pregnant woman to attend all ANC visits as scheduled.

## 8. BASIC TECHNIQUES IN MANAGING MALARIA MEDICINES

### 8.1 CONCEPT OF ESSENTIAL DRUGS

The WHO defines essential drugs as those that are indispensable and necessary for the health needs of the population. They should be available at all times, in the proper dosages forms to all segments of society. Antimalarials are “essential medicines”

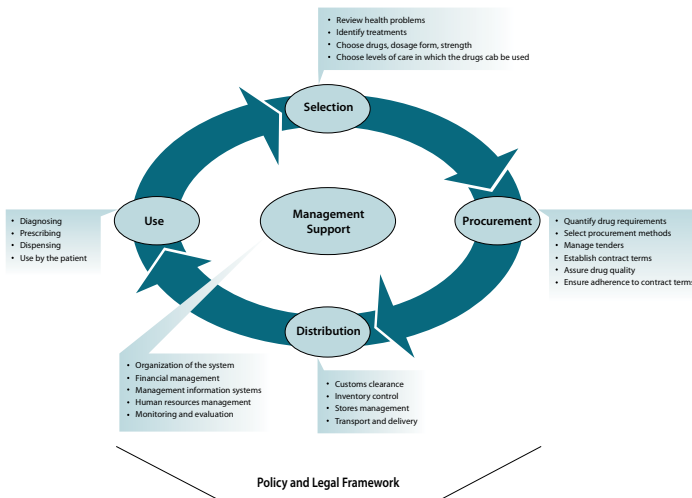
#### 8.1.1 Pharmaceutical management

Pharmaceutical management is a set of practices aimed at ensuring the timely availability and appropriate use of safe, effective, quality medicines and related products and services in any health-care setting.

#### 8.1.2 The pharmaceutical management cycle<sup>7</sup>

The Pharmaceutical Management Cycle is a systematic approach to ensure that medicines at all levels of health care delivery are consistently available and appropriately used. It emphasizes the connections between four drug management activities - selection, procurement, distribution and use. The cycle is depicted below:

**Figure 2: The pharmaceutical management cycle**



<sup>7</sup> The cycle was developed by the Management Sciences for Health Centre for Pharmaceutical Management in collaboration with the World Health Organization’s Action Program on Essential Drugs.

## 8.2 MANAGEMENT OF ANTIMALARIAL MEDICINES

### 8.2.1 Quantification of antimalarial medicines

Quantification is the process of estimating the quantities of antimalarials needed for a specific period of time in order to ensure an uninterrupted supply. Quantification is an important step in procurement and ordering for re-supply. Good quantification ensures the appropriate allocation of funds to enable purchase of the right medicine, in the right quantity and at the right time.

#### 8.2.1.1 The rationale for quantification of antimalarials

- To ensure that there are sufficient quantities to meet clients'/patients' needs and avoid shortages/stock-outs
- To avoid surpluses that may lead to over-stocking, expiries and/or wastage of commodities
- To make informed adjustments to procurement when faced with budgetary constraints

### 8.2.2 Quantification methods

This guideline focuses attention on the two most commonly used methods - consumption and morbidity. The particular method used depends on the type of data available.

#### 8.2.2.1 Consumption method

This is the preferred quantification method for antimalarials. The consumption based method uses historical data on the actual medicines dispensed to patients to calculate the quantity of medicines that will be needed in the future. When using the consumption method for quantification, out of stock periods must be adjusted in the calculation.

#### 8.2.2.2 Morbidity method

The morbidity-based method uses data about diseases and the frequency of their occurrence in the population (incidence or prevalence) or the frequency of their presentation for treatment. It forecasts the quantity of drugs needed for the treatment of specific diseases, based on projections of the incidence of those diseases.

### 8.2.3 Good inventory management

An inventory management system is a cycle of activities comprising ordering, receiving, storage and issuing of antimalarials.

### 8.2.3.1 Ordering

The facility orders supplies periodically from the central medical store using a standard order form.

### 8.2.3.2 Receiving

The facility receives supplies; counter checks against the standard order form and delivery note and records the transaction on a stock/bin card.

### 8.2.3.3 Storage

Malaria medicines and commodities such as RDTs should be stored in optimal conditions to ensure their safety and efficacy in accordance with the principles of good storage practices:

- Good arrangement
- Quality maintenance
- Assured security
- Good inventory control and stock rotation
- Good record keeping

### 8.2.3.4 Issuing

The facility issues supplies to various points of use, using an issue/requisition voucher (S11/S12) and records the issue on the bin card.

### 8.2.3.5 Disposal

Disposal of unusable stock should be carried out according to the guidelines for disposal of pharmaceuticals.

## 8.2.4 Definitions of inventory terms

- **Average monthly consumption:** this refers to the average quantity of commodities consumed per month.
- **Months of stock:** the quantity on hand expressed as the number of months that quantity should last calculated based on the commodity's average monthly consumption.
- **Lead time:** the time interval between when a new stock is ordered and when it is received and available for use
- **Review period:** the routine interval of time between assessments of stock levels to determine if an order should be placed. It is also known as order

interval or re supply interval.

- **Maximum stock level:** the amount of stock above which a facility should not exceed under normal circumstances
- **Minimum stock level:** the amount of stock below which a facility should not fall under normal circumstances
- **Shelf life:** the length of time a product may be stored without compromising its usability, safety, purity or potency.
- **Pipeline:** the entire chain of storage facilities and transportation links through which supplies are moved from manufacturers to clients
- **Stock out days:** Non-availability of any ACT for 2 consecutive days in a month.

### 8.2.5 Types of inventory records

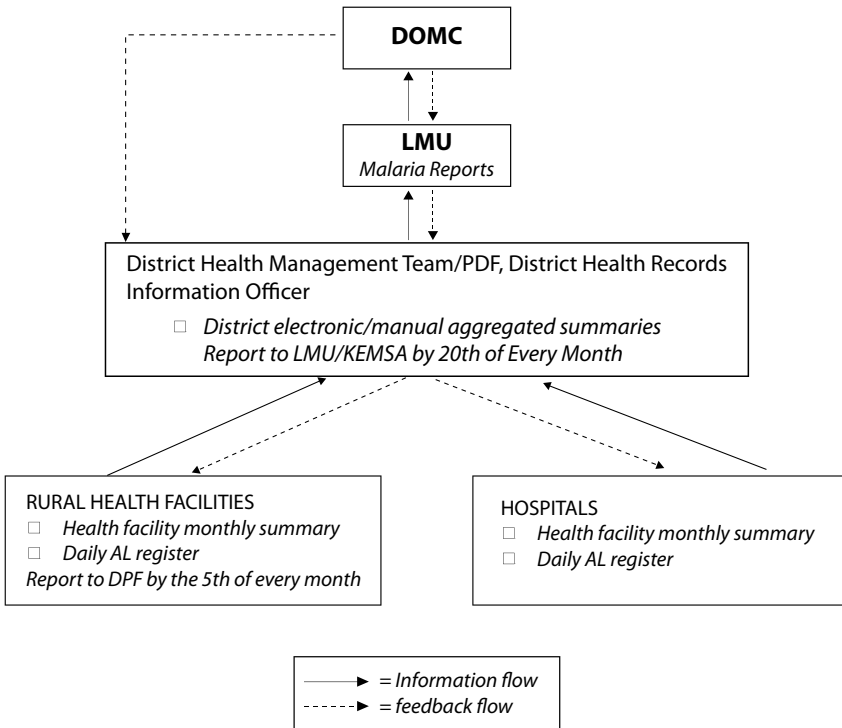
Various forms are used for requisitioning and issuing medicines, financial accounting, and preparing consumption and stock balance reports.

**Table 11: Types of inventory records**

Record type	Source document	Information
Stock keeping records	Bin cards, stock ledger card	Stock at hand Receipts, losses and adjustments
Transaction records	Issue and receipt voucher - (S12, S11), KEMSA delivery notes, Standard order form	Orders, issues and receipts
Consumption records	Daily activity register, health facility monthly summary, District aggregation tool, tally/tick sheet	Consumption data Stock out days Patient numbers



**Figure 3: Flow of logistic management information**



### 8.2.6 M & E LMIS Indicators

- i. National reporting rate
- ii. Proportion of health facilities having no stock-out of all ACTs in a month
- iii. Proportion of health facilities having no stock-out of RDTs in a month

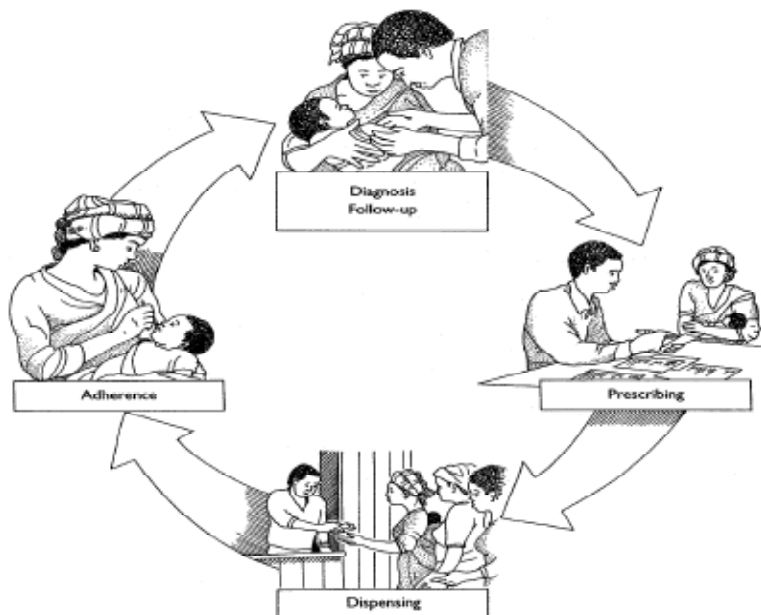
## 8.3 RATIONAL USE OF ANTI-MALARIAL MEDICINES

### 8.3.1 Definition of rational use

The rational use of medicines requires that patients receive medicines appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and the community<sup>8</sup>.

<sup>8</sup> World Health Organization, 1988

**Figure 4: The medicine use cycle**



### 8.3.2 Importance of rational use of medicines

- Irrational medicine use can destroy the benefits of a good pharmaceutical management system and also reduce the therapeutic useful life of an effective medicine
- Resources spent on procurement are lost if the correct drugs are not prescribed and dispensed to the correct patient

### 8.3.3 Factors affecting rational use of medicines

- **Diagnosis** – correct diagnosis based on parasitologically confirmed diagnosis
- **Prescribing** – prescribing /administering the recommended medicine based on the correct diagnosis
- **Dispensing** – correct dispensing (quantity, packaging and labelling) of the prescribed medicine
- **Patient compliance** - patients’ adherence to health worker and label instructions

### 8.3.4 Minimum dispensing information

- Instructions on how to take the drug with directly observed treatment for AL and SP
- Instructions on how long to take the medicine
- Instructions to report any suspected adverse drug reactions (ADR)
- Clear label with appropriate patient and medicine information

## 8.4 PHARMACOVIGILANCE

### 8.4.1 Definitions of key terms

**Pharmacovigilance:** WHO defines pharmacovigilance as the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medicines, biological products, herbals and traditional medicines, with the view to identifying new information about hazards, and preventing harm to patients.

**Adverse drug reaction (ADR)** is a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease. Adverse drug reactions are also called side effects.

**Counterfeits:** WHO defines a counterfeit pharmaceutical product as a product that is deliberately and fraudulently mislabelled with respect to identity and or source.

### 8.4.2 Goals of Pharmacovigilance

- The rational and safe use of medicines
- The evaluation of and communication of the risks and benefits of drugs on the market
- Education and information of patients

### 8.4.3 Adverse drug reactions

Report ALL suspected side effects with medications, especially those where the patient outcome is:

- Death
- Life-threatening (patient would have died if no intervention was undertaken to treat adverse reaction or event)
- Hospitalization (initial or prolonged)
- Disability (significant, persistent or permanent)

- Congenital anomaly
- Required intervention to prevent permanent impairment or damage

**Report even if:**

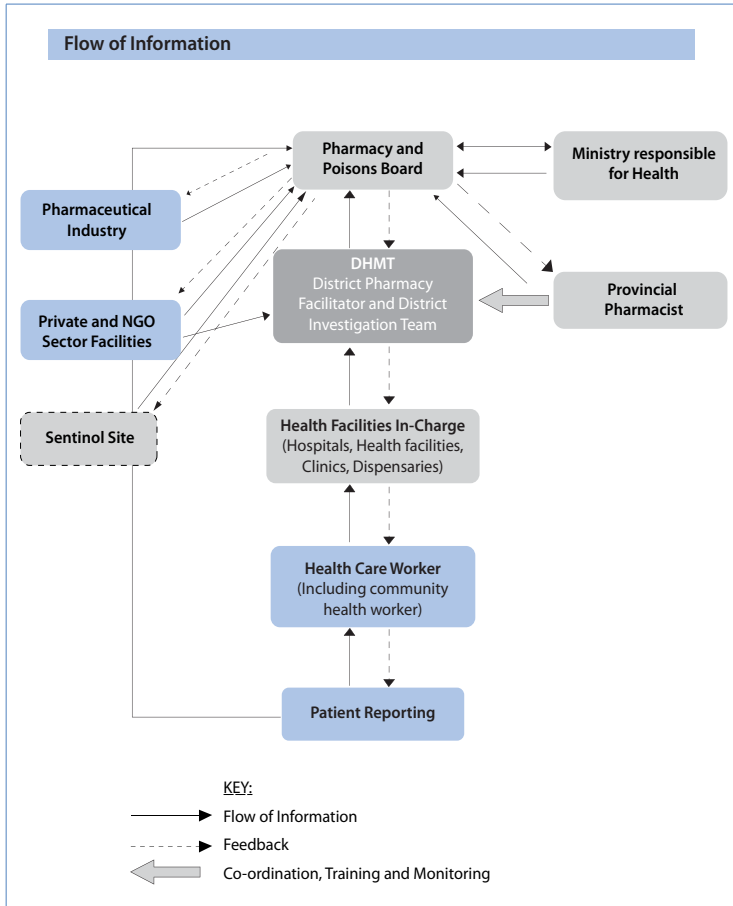
- You are not certain if the drug caused the side effect
- You do not have all the details
- There is nothing to report

**8.4.4 Tools for reporting side effects or adverse drug reactions**

Reporting of side effects is done using:

- Yellow form (PV 1) - form to capture all suspected adverse drug reactions
- White card (PV 4) - alert card to report life threatening drug reactions
- Pink form (PV 6) - form for reporting poor quality medicinal products

**Figure 5: Flow of information on adverse drug reactions**



Feedback to all levels of the system is the responsibility of the Pharmacy and Poisons Board (PPB)

- ◆ All forms should be collected and sent to PPB pharmacovigilance department using the address provided on the forms

**8.4.5 M & E Indicator**

- Number of adverse drug reactions reports received including reports with no adverse reactions reported (zero-reporting).

## 9. MALARIA PREVENTION

### 9.1 CHEMOPROPHYLAXIS FOR NON-IMMUNE POPULATIONS

Chemoprophylaxis is recommended for the following high-risk groups:

#### 9.1.1 Non-immune visitors (tourists)

The recommended medicines for chemoprophylaxis for non-immune persons visiting a malarious area are mefloquine, atovaquone-proguanil or doxycycline)

#### 9.1.2 Patients with sickle cell disease

The currently recommended prophylactic medicine for those with sickle cell disease is still proguanil. Although there is increasing documented resistance to anti-folate drugs, no studies on the effectiveness of proguanil in sickle cell disease have been conducted to recommend otherwise. *It is important for patients with sickle-cell disease to consistently use other malaria prevention methods and to promptly seek treatment for any febrile illness.*

#### 9.1.3 Patients with tropical splenomegaly syndrome

The currently recommended prophylactic medicine for those with tropical splenomegaly syndrome is proguanil. Although there is increasing documented resistance to anti-folate drugs, no studies on the effectiveness of proguanil in this group have been conducted to recommend otherwise.

#### Note

- ◆ Chemoprophylaxis and other preventive measures are not 100% effective. Early medical care should be sought if they develop fever within 3 months of travel to an endemic area, even if adequate prophylaxis has been taken
- ◆ Travellers are encouraged to use other barrier methods (LLINs, insecticide treated materials and repellents) to prevent or reduce bites from mosquitoes
- ◆ Travellers should carry a full course of artemether-lumefantrine (as standby treatment) for use in the event they develop a fever and have no immediate access to health services.

### 9.1.4 Medicines for malaria chemoprophylaxis

#### 9.1.4.1 Mefloquine

Mefloquine is available as tablets of 274mg mefloquine hydrochloride containing 250mg base or tablets of 250mg mefloquine hydrochloride containing 228mg base (United States only). Mefloquine is administered as a weekly dose of 250mg for adults or 5mg base/kg body weight for persons below 36 kg.

It is recommended that Mefloquine prophylaxis is started 2 - 3 weeks before arrival in a malaria risk area, taken throughout the stay and continued for 4 weeks after leaving the area.

**Table 12: Dosing schedule for mefloquine**

Weight	Age	No of tablets per week
< 5 kg	< 3 months	Not recommended
5 - 12 kg	3 - 23 months	¼
13 - 24 kg	2 - 7 yrs	½
25 - 35 kg	8 - 10 yrs	¾
36 and above	11 yrs and above	1

#### **Side effects**

Nausea, vomiting, abdominal pain and diarrhoea. These are most common but are dose related and self-limiting. Other CNS related ones include dysphoria, dizziness, ataxia, headache, some visual and auditory disturbances, sleep disturbances and nightmares, convulsions.

#### **Contraindications**

- ◆ The first trimester of pregnancy
- ◆ Do not administer to patients less than 5 kg.
- ◆ Avoid use in history of seizures and in severe neuro-psychiatric disturbance
- ◆ Do not administer concomitantly with quinine and avoid quinine use after administration of mefloquine

#### **Caution**

- ◆ Mefloquine can compromise adequate immunisation with the live typhoid vaccine.

- ◆ Mefloquine should only be taken 12 hours after administration of the last quinine dose
- ◆ Care should be taken when administering concomitant medications that interfere with cardiac function

#### 9.1.4.2 Proguanil

Proguanil is available as tablets of 100mg of proguanil hydrochloride containing 87mg of proguanil base

#### **Dose**

Proguanil is administered at a daily dose of 3mg/kg daily. Often, the average daily dose is 200mg /day for adults and 100mg/day for children for the duration recommended by the physician.

**Table 13: Dosing schedule for proguanil**

Weight	Age	Number of tablets per day
5 - 8 kg	< 8 Months	¼
9 - 16 kg	8 months - 3 years	½
17 - 24 kg	4 - 7 yrs	¾
25 - 35 kg	8 - 10 yrs	1
36 - 50 kg	11 - 13 yrs	1 ½
50 + kg	14+ yrs	2

#### **Side effects**

Low doses - nausea, diarrhoea, rarely hair loss and mouth ulcers. High doses - vomiting, haematuria and diarrhoea. Symptoms are treated as they appear. There is no specific antidote for proguanil overdose.

#### **Contraindications**

The use of Proguanil is contraindicated in persons with liver or kidney dysfunction.

#### **Caution**

Antacids like magnesium trisilicate decrease absorption of Proguanil.



### 9.1.4.3 Atovaquone – Proguanil (Malarone®/Malanil®)

Atovaquone - proguanil is available as film coated adult tablets containing 250 mg atovaquone and 100mg proguanil hydrochloride or paediatric tablets containing 62.5 mg atovaquone and 25 mg proguanil hydrochloride.

#### **Dose**

It is administered as a daily dose of 1 tablet commencing 1 day before departure to a malaria endemic area, throughout the stay and continuing 7 days after leaving. Adults and children > 40kg should take 1 adult tablet daily. The drug should be taken with food or milk at the same time each day.

**Table 14: Dosing schedule for atovaquone-proguanil for children**

Weight	Number of paediatric tablets
< 11 kg	Not recommended
11 - 20 kg	1
21 - 30 kg	2
31 - 40 kg	3

#### **Side effects**

Abdominal pain, nausea, vomiting, diarrhoea, headache, anorexia and coughing

#### **Contraindications**

- ◆ Persons with hypersensitivity to atovaquone and/ or proguanil.
- ◆ Pregnancy because of lack of data.
- ◆ Caution is indicated in persons with severe renal failure (creatinine clearance)

### 9.1.4.4 Doxycycline

Doxycycline is commonly available as capsules containing 100mg doxycycline hydrochloride. Tablets containing 100mg doxycycline hydrochloride may be available.

#### **Dose**

Doxycycline is administered as a daily dose of 100 mg salt or 1.5mg salt per kg daily. It is taken 1 day before departure to a malaria endemic area and continued daily throughout the stay and for 4 weeks after departure. If tablets are available, fractions

can be administered for patients aged 8 to 13 years.

**Table 15: Dosing schedule for doxycycline**

Weight in kg	Age in years	No of tablets
< 25	< 8	Contraindicated
25 - 35	8 - 10	½
36 - 50	11 - 13	¾
50+	14+	1

**Side effects**

GIT irritation, increased vulnerability to sun-burn (phototoxic reaction), transient depression of bone growth and discoloration of teeth, vaginal candidiasis.

**Contraindications**

Doxycycline shouldn't be used in

- ◆ Children under 8 years of age
- ◆ Pregnant and lactating mothers
- ◆ Persons with hepatic insufficiency
- ◆ Persons with known hypersensitivity to tetracyclines

**Caution**

Doxycycline should not be used for prophylaxis for periods exceeding 4 months. Antacids and milk impair absorption of tetracycline and concurrent administration should be avoided.

**9.2 VECTOR CONTROL**

Integrated vector management is one of the recommended methods to augment other malaria control interventions to reduce transmission of malaria. Vector control must be selective, targeted, site specific and cost effective. The selection of vector control methods should be based on intensity of the disease transmission, vector, human behaviours, the environment and resources available. The community should actively participate in the implementation of these vector control measures especially measures to reduce mosquito breeding within their environments.

Inter-sectoral collaboration involving line ministries, NGOs and the private sector is encouraged in this respect.

The following vector control strategies are available:

- ◆ Use of long lasting insecticidal nets: the use of LLINs is encouraged for all persons living in malaria endemic areas.
- ◆ Indoor residual spraying - both in endemic and epidemic prone areas
- ◆ Larviciding - in focalized breeding sites
- ◆ Screening of house inlets with wire mesh to reduce entry of mosquitoes
- ◆ Environmental management for source reduction of vector density e.g. drainage of breeding sites
- ◆ Biological control measures where feasible - larvivorous fish, growth regulators, BTI (*Bacillus thuringiensis var israeliensis*)
- ◆ Repellents and fumigants

### 9.2.1 M & E Indicators

- i. Proportion of households who own at least 2 LLIN
- ii. Proportion of households in targeted areas sprayed in the last 12 months

## 9.3 EPIDEMIC PREPAREDNESS AND RESPONSE

Malaria interventions are reducing malaria prevalence in many areas, converting them into malaria epidemic zones; therefore there is need to:

- ◆ Strengthen routine surveillance of:
  - Epidemiological indicators i.e. parasite rates (sentinel facilities, community), vectors
  - Meteorological data
- ◆ Ensure availability of buffer stocks for all medicines for uncomplicated and severe malaria, chemicals, spray pumps and LLINs
- ◆ Plan for logistics support

In case of an epidemic threat; conduct:

- ◆ Advocacy and social mobilization
- ◆ Mobilize health workers to provide active surveillance and prompt treatment of cases
- ◆ Warn referral facilities about patient influx and strengthen referral systems
- ◆ Indoor residual spraying and net hanging campaigns.

### 9.3.1 M & E Indicator

- i. Proportion of targeted districts with functional Epidemic Preparedness and Response (EPR) teams and logistics.

## 9.4 ADVOCACY COMMUNICATION AND SOCIAL MOBILIZATION

Advocacy communication and social mobilization are a critical intervention for behavioural change towards improved health practices. The following important information should be provided to patients, caretakers/guardians of young children and community members to:

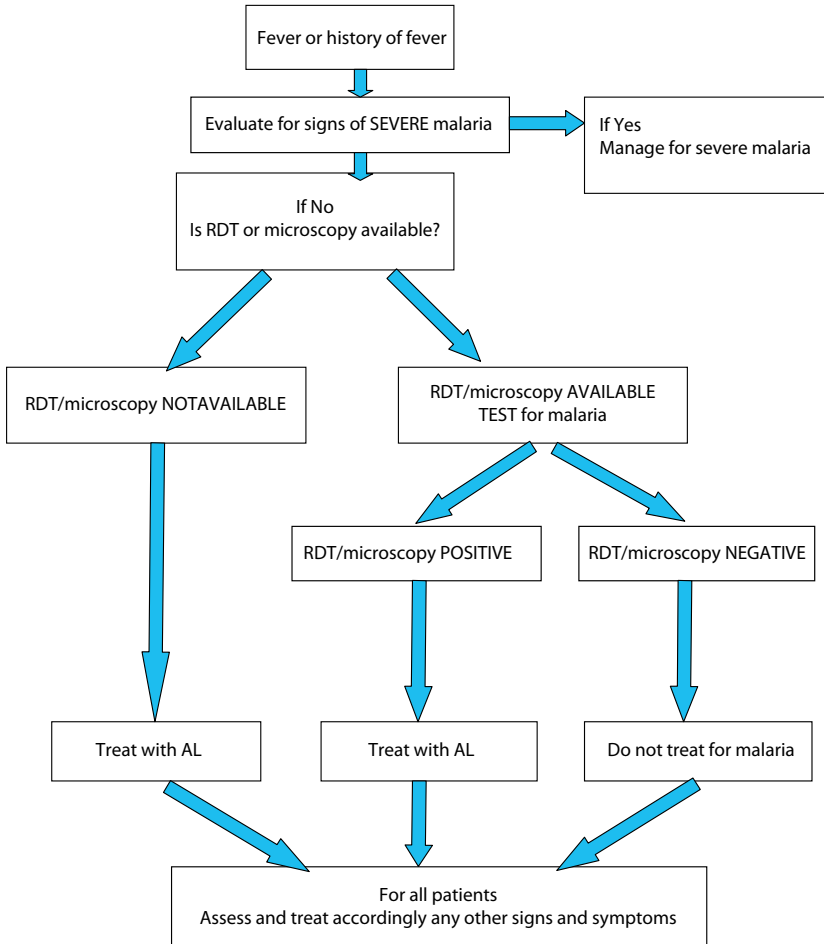
- ◆ Seek prompt diagnosis and correct treatment of all fevers
- ◆ Recognize symptoms and signs of malaria and severe malaria
- ◆ Adhere and complete all prescribed medicines
- ◆ Use appropriate prevention measures especially to sleep under LLIN every night

### 9.4.1 M & E Indicator

- i. Proportion of people reached by ACSM messages on malaria prevention and treatment.

## 10. ANNEXES

### ANNEX 1: ALGORITHM FOR FEVER ASSESSMENT AND MANAGEMENT



## ANNEX 2: THE PHARMACOLOGY OF ANTIMALARIALS

Antimalarials can be classified according to their chemical composition and mode of action. In this guideline, classification based on the mode of action is used.

**Table 16: Common antimalarials classified by mode of action**

Class	Definition	Examples
Blood schizonticidal drugs	Act on (erythrocytic) stage of the parasite thereby terminating clinical illness	Quinine, artemisinins, amodiaquine, chloroquine, lumefantrine, tetracycline, atovaquone, sulphadoxine, clindamycin, proguanil
Tissue schizonticidal drugs	Act on primary tissue forms of plasmodia which initiate the erythrocytic stage. They block further development of the infection	Primaquine, pyrimethamine, proguanil, tetracycline
Gametocytocidal drugs	Destroy sexual forms of the parasite thereby preventing transmission of infection to mosquitoes	Primaquine, artemisinins, quinine <sup>a</sup>
Hypnozoitocidal drugs	These act on persistent liver stages of <i>P. ovale</i> and <i>P. vivax</i> which cause recurrent illness	Primaquine, tafenoquine
Sporozontocidal drugs	These act by affecting further development of gametocytes into oocysts within the mosquito thus abating transmission	Primaquine, proguanil, chlorguanil

<sup>a</sup> Slow acting, cannot be used alone to avert clinical symptoms

<sup>b</sup> Weakly gametocytocidal

## ANNEX 3: ADDITIONAL INFORMATION ON ANTIMALARIALS

Only fixed dose ACTs should be used for the treatment of uncomplicated malaria.

### ARTEMETHER-LUMEFANTRINE (AL)

For information on regular tablets and child friendly dispersible tablets, see section 5.2.1. AL may also be presented as a powder for suspension. Once reconstituted, the suspension must be used as directed and discarded after 3 days.

**Table 17: Dosing Schedule for AL powder for reconstitution**

Body weight in kg	Dosage (in ml) to be administered once a day for three days
3	4.5
4	6
5	7
6	8
7 - 8	10
9 - 10	13
11 - 12	15
13 - 14	18
15 - 17	22
18 - 20	25
21 - 23	29
24 - 26	33
27 - 29	37
30	40

### **Side effects**

Dizziness and fatigue, lack of appetite, nausea, vomiting, abdominal pain, palpitations, muscle pain, joint pain, headache and rash

### **Contraindications**

- ◆ There is limited data on the safety of use in the first trimester pregnancy.
- ◆ Persons with known hypersensitivity to either of the components.

## **DIHYDROARTEMISININ-PIPERAQUINE**

DHA-PPQ is available as both adult and paediatric tablets administered once a day for three days. See section 5.3.2 for dosing information

### **Side effects**

Nausea, diarrhoea, loss of appetite, rash, pruritus

### **Contraindications**

- ◆ Hypersensitivity to any of the components of the combination
- ◆ There is limited data on the safety of use in the first trimester pregnancy.

## **AMODIAQUINE-ARTESUNATE**

### **Dose**

Available as fixed dose combination tablets containing amodiaquine 10 mg /kg daily for three days plus artesunate 4 mg/kg given daily for 3 days.

### **Side effects**

Pruritus, rash, and with higher doses, syncope, spasticity, convulsions and involuntary movements.

### **Contraindications**

- ◆ Hypersensitivity to any of the component medicines
- ◆ Not recommend during the first trimester of pregnancy

## **PRIMAQUINE**

### **Dose**

Primaquine is available as tablets containing 5.0, 7.5 or 15 mg primaquine diphosphate. Dose 0.25 - 0.5 mg / kg once daily for 14 days.

### **Side effects**

The most important adverse effects are haemolytic anaemia in patients with G6PD deficiency.



Therapeutic doses may also cause abdominal pain if administered on an empty stomach. Larger doses can cause nausea and vomiting. Methaemoglobinaemia may occur. Other uncommon effects include mild anaemia and leukocytosis. Overdosage may result in leukopaenia, agranulocytosis, gastrointestinal symptoms, haemolytic anaemia and methaemoglobinaemia with cyanosis.

## QUININE

Quinine is presented as the following tablet strengths:

- ◆ 300 mg quinine dihydrochloride
- ◆ 300 mg quinine hydrochloride
- ◆ 300 mg quinine bisulphate
- ◆ 300 mg quinine sulphate
- ◆ 200 mg quinine sulphate

**Table 18: Quinine tablets equivalence table**

Quinine salt	Number of tablets
300 mg Quinine Dihydrochloride	1
300 mg Quinine Hydrochloride	1
300 mg Quinine Bisulphate	1.5
300 mg Quinine Sulphate	1.5

### **Dose**

Quinine is administered as a seven-day dose of 10 mg /kg salt three times a day every 8 hours; in severe malaria.

**Table 19: Dosing schedule for quinine 200mg tablets**

Weight in kg	No of 200mg tablets
4 - 7	¼
8 - 11	½
12 - 15	¾
16 - 23	1
24 - 31	1 ½
32 - 39	2

**Table 20: Dosing schedule for quinine 300mg tablets**

Weight in kg	No of 300mg tablets
6 - 11	¼
12 - 17	½
18 - 23	¾
24 - 35	1
36 - 47	1 ½
48+	2

For children below the lowest weight category, the dosage of quinine is 10mg/kg and the tablets should thus be reconstituted into a suspension and given based on the weight of the patient. It is important to note that this is not an accurate method for quinine dosing and the reconstitution must be done prior to each dose as the stability of quinine in the liquid used is not known.

***Injectable quinine***

- ◆ Quinine hydrochloride (82% quinine base)
- ◆ Quinine dihydrochloride (82% quinine base)
- ◆ Quinine sulphate (82.6% quinine base) respectively

The ampoules contain 300mg/ml and come as 2 ml or 1 ml ampoules.

### **Quinine for intramuscular injection**

The dosage of IM quinine injection for pre referral treatment is a loading dose of 20mg/kg up to a maximum of 1200 mg

#### **How to give the intramuscular injection**

- ♦ Weigh the patient (if he/she cannot be weighed the following formula can be used to estimate the weight of children under 5 years:  $(\text{age (in years)} \times 2) + 8 = \text{wt in kg}$ )
- ♦ Use a 10 ml sterile syringe. Draw up 5 ml of sterile water for injection. Then into the same syringe, draw up 300 mg (1 ml) from an ampoule of quinine. The syringe now contains 50 mg quinine per ml. Mix the drug by shaking the syringe before injection. \*for the formulation of 600mg/2ml, only one ml is drawn out into the syringe. For the 300mg / ml the whole vial is drawn out while for the 150mg/ml, two vials will be required to make 300 mg.
- ♦ In all situations a maximum of 3ml should be injected into one injection site. If the amount to be injected exceeds 3 ml, half the amount should be injected into each injection site (refer to table below for number of sites).

**Table 21: Dosing schedule for IM injections of quinine**

Dilute quinine to 50 mg/ml - and give based on 10 mg/kg doses

Body weight	Volumes of diluted quinine injection (ml) to be administered	Number of injection sites
Less than 5 kg	1.0ml	one
5.1 - 7.5 kg	1.5ml	one
7.6 - 10kg	2.0ml	one
10.1 - 12.5 kg	2.5ml	one
12.6 - 15 kg	3.0ml	one
15.1 - 17.5 kg	3.5ml	two
17.6 - 20 kg	4.0ml	two
20.1 - 22.5kg	4.5ml	two
22.6 - 25 kg	5.0ml	two
25.1 - 27.5 kg	5.5ml	two
27.6 - 30 kg	6.0ml	two
30.1 - 32.5 kg	6.5ml	three
32.6 - 35 kg	7.0ml	three

***Quinine intravenous infusion***

Intravenous quinine is administered in isotonic fluid; either 5% dextrose or dextrose normal saline as follows. See section on treatment of severe malaria.

***Adults***

- ◆ The first dose 20 mg/kg in 500mls of isotonic fluid given over 4 hours (maximum 1200 mg).
- ◆ Then 8 hours after commencing the initial dose give 10mg/kg in 500mls of isotonic fluid over 4 hours (maximum 600mg).
- ◆ Repeat 10mg/kg 8 hourly until the patient can take orally.
- ◆ Then preferably, give a full treatment course of artemether-lumefantrine or quinine may be continued orally at 10mg/kg three times a day to complete a total of 7 days treatment of quinine

- ◆ Assessment of fluid status should be monitored regularly including urine output.
- ◆ If patient cannot be weighed - IV quinine loading dose should be 900mg. Followed by 600 mg 8 hourly.

### **Children**

- ◆ Put up IV quinine drip (20mg/kg body weight loading dose in 15ml/kg of isotonic fluid) to run over 4 hours.
- ◆ Fluid intake should be calculated according to weight, bolus 20 ml/kg (minimum 10mls/kg) and maintenance 4-6 ml/kg/hr.
- ◆ 8 hours after commencing the initial dose of quinine, give 10mg/Kg in 10mls/kg of isotonic fluid.
- ◆ Repeat 10mg/kg 8 hourly until the patient can take medication orally
- ◆ Then preferably, give a full treatment course of artemether-lumefantrine or quinine may be continued orally at 10mg/kg three times a day to complete a total of 7 days treatment of quinine.

### **Side effects**

The triads of quinine toxicities comprise cinchonism, hypoglycaemia and hypotension. Careful attention should be paid to these and adequate measures taken to correct them.

Cinchonism is characterized by tinnitus, high tone deafness, visual disturbances, headache, dysphoria, nausea and vomiting and postural hypotension all of which disappear on withdrawal of the drug. It is usually mild.

Hypotension is often associated with excessively rapid IV infusion or bolus injection.

Hypoglycaemia is due to the stimulative effect of quinine on the  $\beta$  cells of the pancreas which produce insulin. It is common in pregnancy and very prolonged and severe infection.

Other side effects include nausea, vomiting, diarrhoea, blurred vision, distorted colour perception, photophobia, diplopia and night blindness, cutaneous flushing, pruritus, rashes, fever, and dyspnoea

Black water fever is seen in patients with G6PD enzyme deficiency and malaria treated with quinine. It is characterized by haemolysis, Haemoglobinuria and in severe forms renal failure.

## ANNEX 4: COMA MONITORING SCALES

### THE GLASGOW COMA SCALE

**Table 22: The Glasgow coma scale (for adults and children over 5 yrs)**

Response	Findings	Score
<b>Eye Opening Response</b>	Spontaneous: open with blinking at baseline	4 points
	Opens to verbal command, speech, or shout	3 points
	Opens to pain, not applied to face	2 points
	None	1 point
<b>Verbal Response</b>	Oriented	5 points
	Confused conversation, but able to answer questions	4 points
	Inappropriate responses, words discernible	3 points
	Incomprehensible speech	2 points
	None	1 point
<b>Motor Response</b>	Obeys commands for movement	6 points
	Purposeful movement to painful stimulus	5 points
	Withdraws from pain	4 points
	Abnormal (spastic) flexion, decorticate posture	3 points
	Extensor (rigid) response, decerebrate posture	2 points
	None	1 point

It is recommended to use the simpler Blantyre coma score for children. However, if the GCS is used for children under 5, adjust the verbal response according to the table 23 below.

**Table 23: Adjusted GCS verbal response for children < 5years**

Score	2 to 5 years	0 to 23 months
5	Appropriate words or phrases	Smiles or coos appropriately
4	Inappropriate words	Cries and consolable
3	Persistent cries and/or screams	Persistent inappropriate crying and/or screaming
2	Grunts	Grunts or is agitated or restless
1	No response	No response

To obtain the Glasgow coma score obtain the score for each section add the three figures to obtain a total out of 15.

**Interpretation of symptoms:** Severe: 8 or less; Moderate: 9-12; Mild: 13 or more

## THE BLANTYRE COMA SCALE

The Blantyre coma scale<sup>9</sup> is a modification of the Glasgow coma scale suitable to use in children not yet able to speak. The scale uses motor and crying responses to pain and includes the ability to watch. It can be used to assess young children with cerebral malaria.

**Table 24: The Blantyre coma scale for children < 5 years**

Response	Findings	Score
Eye opening	Directed (e.g. towards mother’s face)	1
	Not directed	0
Best verbal response	Appropriate cry	2
	Inappropriate cry	1
	None	0
Best motor response	Localizes painful stimuli	2
	Withdraws limb from pain	1
	Non-specific or absent response	0

Blantyre coma scale = (best motor response score) + (best verbal response score) + (eye movement score)

### Interpretation of Symptoms

The score can range from 0-5. Any score < 4 is abnormal while 2 or less indicates unrousable coma. The score can be used repeatedly to assess improvement or deterioration

<sup>9</sup> Molyneux ME Taylor TE et al. Clinical features and prognostic indicators in paediatric cerebral malaria: A study of 131 comatose Malawian children. Q J Med. 1989; 71: 441-459.

## ANNEX 5: UPDATED IMCI ALGORITHM

The integrated management of childhood illness (IMCI) algorithm has been updated to reflect the recommendation for confirmation of malaria diagnosis before treatment.

### WHO GENERIC IMCI ALGORITHM

<p><b>Does the child have fever?</b> (by history or feel hot or temperature 37.5°C or above)</p> <p><b>If yes:</b> Decide malaria risk high or low</p> <p><b>Look and feel:</b></p> <ul style="list-style-type: none"> <li>Look or feel for stiff neck.</li> <li>Look or feel for runny nose.</li> <li>Look for signs of local bacterial fever being present every day?</li> <li>Has the child had measles within the last 3 months?</li> <li>Pivax PRESENT</li> </ul> <p><b>TEST POSITIVE</b></p> <p><b>DO MALARIA TEST</b></p> <p>If no general danger sign</p>		<p><b>Classify For Malaria</b></p>	
<p><b>If the child has measles now or within the last 3 months:</b></p> <ul style="list-style-type: none"> <li>Look for mouth ulcers.</li> <li>Are they deep and extensive?</li> <li>Look for pus draining from the eye.</li> <li>Look for clouding of the cornea.</li> </ul>	<p><b>Any general danger sign</b></p> <ul style="list-style-type: none"> <li>Malaria test POSITIVE**</li> </ul>	<p><b>Pink: VERY SEVERE FEBRILE DISEASE</b></p>	<ul style="list-style-type: none"> <li>Give first dose antimalaria for severe malaria</li> <li>Give appropriate antibiotics for apparent bacterial cause of fever</li> <li>Treat the child to prevent low blood sugar</li> <li>Give one dose of paracetamol in clinic (or high dose if severe fever)</li> <li>Refer URGENTLY to hospital</li> <li>Give recommended oral antimalarial</li> <li>Give one dose of paracetamol in clinic (or high dose if severe fever) (38.5°C or above)</li> <li>Advise mother when to return immediately</li> <li>Follow-up in 2 days if fever persists</li> <li>If fever is present every day for more than 7 days, refer for assessment</li> </ul>
<p><b>If the child has measles now or within the last 3 months, Classify</b></p>	<p><b>Malaria test NEGATIVE</b></p> <ul style="list-style-type: none"> <li>Rummy nose PRESENT</li> <li>Other cause of fever PRESENT</li> </ul>	<p><b>Green: FEVER: NO MALARIA</b></p>	<ul style="list-style-type: none"> <li>Give one dose of paracetamol in clinic (or high fever (38.5°C or above)</li> <li>Advise mother when to return immediately</li> <li>Assess for other possible bacterial cause of fever***</li> <li>Follow-up in 2 days if fever persists</li> <li>If fever is present every day for more than 7 days, refer for assessment</li> </ul>
<p><b>If MEASLES now or within last 3 months, Classify</b></p>	<p><b>Any general danger sign or</b></p> <ul style="list-style-type: none"> <li>Clouding of cornea or</li> <li>Deep or extensive mouth ulcers.</li> </ul>	<p><b>Pink: SEVERE COMPLICATED MEASLES**</b></p>	<ul style="list-style-type: none"> <li>Give Vitamin A treatment</li> <li>Give first dose of an appropriate antibiotic</li> <li>Flushing of the cornea or pus draining from the eye: apply antibiotic eye ointment.</li> <li>Refer URGENTLY to hospital</li> </ul>
	<p><b>Pus draining from the eye or</b></p> <ul style="list-style-type: none"> <li>Mouth ulcers.</li> </ul>	<p><b>Yellow: MEASLES WITH EYE OR MOUTH COMPLICATIONS***</b></p>	<ul style="list-style-type: none"> <li>Give Vitamin A treatment</li> <li>If pus draining from the eye, treat eye infection with appropriate eye ointment</li> <li>Refer to hospital with pus draining from the eye</li> <li>Follow-up in 2 days</li> </ul>
	<p><b>Measles now or within the last 3 months</b></p>	<p><b>Green: MEASLES</b></p>	<ul style="list-style-type: none"> <li>Give Vitamin A treatment</li> </ul>

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

\*\* If no malaria test available classify as malaria

\*\*\* Other possible causes of bacterial infection may include urinary tract infection, typhoid, cellulitis and osteomyelitis.

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



## ANNEX 6: THIRD EDITION GUIDELINE REVIEW TEAM

<b>Name</b>	<b>Organization</b>
Agneta Mbithi	Division of Malaria Control
Alex Muturi	Management Sciences for Health
Andrew Nyandigisi	Division of Malaria Control
Anthony Miru	Population Services International
Assumpta Matekwa	Provincial Public Health Nurse - Western
Athuman Chiguzo	Management Sciences for Health
Augustine Ngindu	World Health Organization
Charles Chungu	Centre for Tropical and Travel Medicine
Connie Orata	Management Sciences for Health
Dejan Zurovac	KEMRI/Wellcome Trust Programme
Dorothy Memusi	Division of Malaria Control
Elizabeth Juma	Division of Malaria Control
Ephantus Murigi	Division of Malaria Control
Isaac K Mugoya	KEMRI/Wellcome Trust Programme
James Akudian	Division of Malaria Control
Julius Kimitei	Division of Malaria Control
Mildred Shieshia	Management Sciences for Health
Patricia Njiri	Clinton Foundation
Samwel Kigen	Division of Malaria Control







Ministry of Public Health and Sanitation  
Division of Malaria Control  
P. O. Box 19982 KNH Nairobi - 00202, Kenya  
Email: head.domc@domkenya.or.ke  
<http://www.nmcp.or.ke>