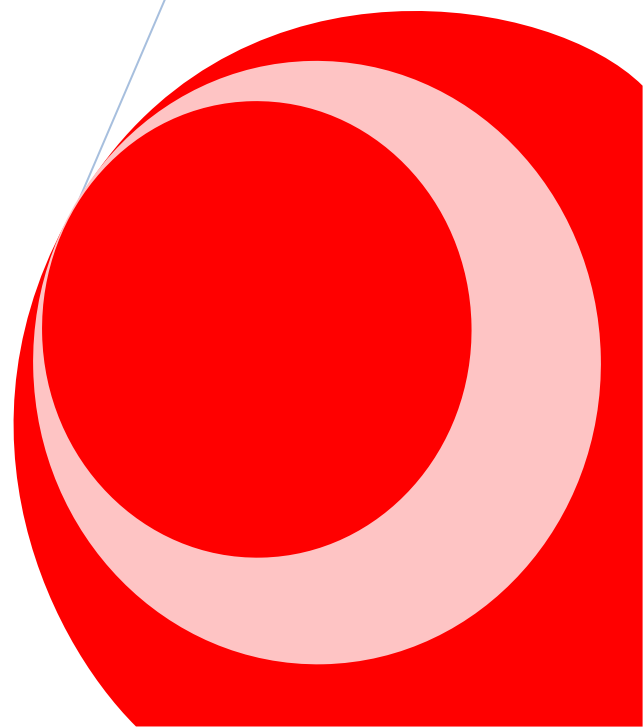




Federal Republic of Nigeria

# **National Guidelines for Diagnosis and Treatment of Malaria**

Third Edition



**NATIONAL GUIDELINES FOR DIAGNOSIS AND TREATMENT OF MALARIA – 3rd Edition**

**Federal Ministry of Health  
National Malaria and Vector Control Division  
Abuja-Nigeria**

**May 2015**

## **FOREWORD**

Over the years, the Federal Government in collaboration with its supporting partners, has put several interventions in place to control the scourge of the disease in the country. Case management of malaria is pivotal to the efforts to eliminate malaria in Nigeria. To this end, several interventions and strategies to reduce morbidity and prevent deaths have been introduced in line with the Federal Government aspiration of reducing malaria to a level where it will no longer be a major public health concern by 2020.

To rapidly promote this, the Federal Government has banned the use of ineffective medicines such as chloroquine and all oral artemisinin monotherapies and has also strengthened the system to detect fake and unwholesome medicines while also monitoring pharmacovigilance in collaboration with NAFDAC.

The Artemisinin based Combination Treatments (ACTs) adopted by Nigeria for the treatment of uncomplicated malaria still remain the best available antimalarial medicines globally and are very efficacious in the country.

In line with the World Health Organization recommendation, the country has adopted the Test, Treat and Track (3T) strategy with all suspected cases of malaria properly diagnosed using Rapid Diagnostic Tests or microscopy, treated promptly with recommended ACT if the result is positive and documented.

New community based strategies such as Seasonal Malaria Chemoprevention (SMC) and Integrated Community Case Management (iCCM) which focus on children less than 5 years who are most vulnerable have also been introduced while private sector interventions which make antimalarial medicines available at highly subsidised rate are being scaled up.

This guideline would be widely disseminated to health care facilities; both private and public across Nigeria as an important step in standardizing diagnosis and treatment practices. Accordingly, it is imperative for the health care providers in the country to strictly comply with this guideline to harmonize malaria management practices within the country.

We acknowledge and appreciate the support provided by international funding agencies and supporting partners.

The Federal government is committed to achieving its target of slide positivity rate of less than 5% by the year 2020. I therefore encourage all health care providers at the various health facilities and within the communities to avail themselves of the opportunities offered by this guideline with a view to “rolling back” malaria from Nigeria.



**Linus Awute, mni**  
**Permanent Secretary**  
**Federal Ministry of Health**

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We also appreciate the contributions of representatives of academic institutions and research centres for their quality inputs to the development of this document.

It is our hope that this document will provide the necessary guide required for the effective management of malaria in Nigeria.



**Dr Bridget Okoeguale**  
**Director, Public Health**  
**Federal Ministry of Health**

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The responsibility for the interpretation and use of the materials in this guidelines lies with the reader, however, all issues arising from this document should be appropriately directed to:

**Dr. Nnenna Ezeigwe**

The National Coordinator

National Malaria Elimination Programme

Abia House, Central Business District, Abuja, Nigeria

E-mail: [drnnenna.ezeigwe@nmcp.gov.ng](mailto:drnnenna.ezeigwe@nmcp.gov.ng)

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## GLOSSARY

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

**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.

**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.

**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.

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

**Malaria pigment (haemozoin):** A dark brown granular pigment formed by malaria parasites as a by-product of haemoglobin catabolism. The pigment is evident in mature *trophozoites* and *schizonts*. They may also be present in white blood cells (peripheral monocytes and polymorphonuclear neutrophils) and in the placenta.

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

**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.

**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.

**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.

**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).

**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.



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

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

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

## **LIST OF ABBREVIATIONS**

<b>AA:</b>	Artesunate - amodiaquine
<b>ACTs:</b>	Artemisinin-based Combination Treatments
<b>ADR:</b>	Adverse Drug Reaction(s)
<b>AL:</b>	Artemether - lumefantrine
<b>bw</b>	Body weight
<b>CSF:</b>	Cerebrospinal fluid
<b>DHP:</b>	Dihydroartemisinin - piperaquine
<b>DOT</b>	Directly Observed Therapy
<b>DTET</b>	Drug Therapeutic Efficacy Test
<b>ECG:</b>	Electrocardiogram
<b>FCT:</b>	Federal Capital Territory
<b>GIT:</b>	Gastrointestinal Tract
<b>G6PD:</b>	Glucose 6-Phosphate Dehydrogenase Deficiency
<b>Hb:</b>	Haemoglobin
<b>HBSS:</b>	Sickle Cell Haemoglobin
<b>HIV:</b>	Human Immunodeficiency Virus
<b>HRP-2:</b>	Histidine Rich Protein-2
<b>IM:</b>	Intramuscular
<b>IPT</b>	Intermittent Preventive Treatment
<b>IV:</b>	Intravenous
<b>kg</b>	Kilogramme
<b>LGA:</b>	Local Government Area
<b>LLIN:</b>	Long Lasting Insecticidal Nets
<b>MAPS:</b>	Malaria Action Programme for States.
<b>MP:</b>	Malaria Parasite
<b>mg</b>	Milligramme
<b>NAFDAC:</b>	National Agency for Food and Drug Administration and Control
<b>NGT:</b>	Nasogastric Tube
<b>PCR:</b>	Polymerase Chain Reaction
<b>PCV:</b>	Pack Cell Volume
<b>PPMVs:</b>	Patent and Proprietary Medicine Vendors
<b>QA:</b>	Quality Assurance
<b>QC:</b>	Quality Control
<b>RDTs:</b>	Rapid Diagnostic Test
<b>RMCs:</b>	Role Model Care-givers
<b>SOPs:</b>	Standard Operating Procedures
<b>SuNMaP:</b>	Support for National Malaria Programme
<b>TNF:</b>	Tumour Necrosis Factor
<b>USAID:</b>	United States Agency for International Development
<b>WBCs:</b>	White Blood Cells
<b>WHO:</b>	World Health Organization

## EXECUTIVE SUMMARY

Malaria case management remains a vital component of the malaria control strategies. This entails early diagnosis and prompt treatment with effective antimalarial medicines recommended for use in the country. This guideline has been reviewed to reflect the aspirations of the Federal Government to rapidly scale up malaria interventions to achieve pre-elimination status. It is also in tandem with the 2014 – 2020 National Malaria Strategic Plan as well as WHO Treatment Guidelines.

This third edition of the guidelines emphasizes the importance of parasitological confirmation of malaria cases through microscopy or Rapid Diagnostic Test and also provides clear and easy-to-understand steps required in carrying out the listed procedures.

The summary of the key recommendations provided in these guidelines is presented below.

- Prompt parasitological confirmation by microscopy or RDTs is required in all patients suspected of malaria before treatment.
- Artemisinin-based combination therapies (ACTs) are the recommended treatments for uncomplicated *P. falciparum* malaria.
- The following ACTs are recommended for use in Nigeria; Artemether-lumefantrine, Artesunate-amodiaquine.
- Artemisinin and its derivatives should not be used as monotherapy in the treatment of uncomplicated malaria.
- Oral Quinine is the recommended medicine for the treatment of uncomplicated malaria in the first trimester of pregnancy.
- ACTs is the recommended treatment of uncomplicated malaria in the second and third trimesters of pregnancy.
- Treat infants less than 5kg with ACTs under supervision by the health care provider
- Severe malaria is a medical emergency. After rapid clinical assessment and confirmation of diagnosis where feasible, commence immediate treatment with parenteral medication. Intravenous artesunate is the treatment for severe *P.falciparum* malaria.
- In treating severe malaria, children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.
- Parenteral artemether or quinine is an acceptable alternative only if artesunate is not available.
- Parenteral antimalarial medicines in the treatment of severe malaria should be administered for a minimum of 24 hours once started (irrespective of the patient's ability to tolerate oral medication earlier) and thereafter, complete treatment with a complete course of an ACT.
- In settings where complete treatment of severe malaria is not possible, patients should be given pre-referral treatment and referred immediately to an appropriate facility for further treatment. The recommended pre-referral treatment options include any of these; artesunate IM or rectal artesunate or quinine IM, in the order of preference
- The recommended chemoprophylaxis for non immune visitors will be as available in the visitor's country of origin or as recommended in Nigeria.
- Sulphadoxine-pyrimethamine (SP) is the recommended medicine for Intermittent Preventive Treatment in Pregnancy.

## **INTRODUCTION**

Malaria has remained a major public health problem in Nigeria; children under the age of five and pregnant women are the most affected. Malaria has impacted negatively on the economy with about 132 billion Naira lost to the disease as cost of treatment and loss in man-hours.

The launch of the Roll Back Malaria initiative in April 25, 2000 and the commitment of all African leaders to fight the disease which kills over one million children and pregnant women every year was commendable.

One of the key strategies to control malaria is effective case management. In 2005, the National Malaria Treatment Policy recommended the use of Artemisinin based Combination Therapy. These medicines still remain the most efficacious antimalarial treatments available. The National Drug Therapeutic Efficacy Tests (DTET) conducted in 2009-2010 demonstrated high efficacy of the recommended artemisinin combination treatments. The Federal Ministry of Health is also currently conducting DTET for the recommended ACTS and also evaluating other artemisinin-based combination treatments in the country.

Until recently, malaria treatment has been based mainly on clinical diagnosis in Nigeria, evidence of decline in the incidence of malaria in many parts of the country has necessitated the adoption of parasitological diagnosis before treatment.

With the availability of parasite-based rapid diagnostic kits, which complements the standard microscopy and consistent with the WHO recommendations, it is now imperative that cases of suspected malaria should have parasitological confirmation before treatment. This allows for targeted treatment, accurate estimation of true malaria cases, and rational deployment of antimalarial drugs.

## **1.0 OVERVIEW OF THE GUIDELINES FOR DIAGNOSIS AND TREATMENT OF MALARIA**

### **Objectives**

The objectives of this document are to provide guidelines for:

- the diagnosis of malaria using malaria rapid diagnostic tests (mRDTs) or microscopy
- treatment of uncomplicated malaria
- management of severe malaria
- chemoprophylaxis and preventive treatment of malaria

### **Target audience**

- Health care providers at all levels

## **1.1 Health Care Levels and their Roles in Malaria Management**

Management of malaria occurs at the community, and at the three health facility levels:

### **Community based Care**

Informal health care providers in the communities are Role Model Care Givers (RMC), Voluntary Village Health Workers (VHWs) and the Proprietary Patent Medicine Vendors (PPMVs). These are trained to recognize basic symptoms of uncomplicated malaria and treat them.

### **Level I**

This includes such facilities as the Primary Health Care Clinics, Dispensaries and Health posts. They are expected to be available in all the political wards and communities in the country. The cadre of staff found in this level include Nurses, Community Health Officers, Community Health Extension Workers, Pharmacy technicians etc. These are trained to provide comprehensive management for uncomplicated malaria and also initiate appropriate treatment before referring suspected cases of severe malaria to higher facilities. Occasionally, there may be medical officers and pharmacists and trained microscopist at this level of health care delivery. Mainstay of diagnosis is the use of Rapid Diagnostic Test kits.

### **Level II**

This level consists of Comprehensive health centres, Cottage hospitals, General hospitals and some private hospitals. At this level, there is capacity to carry out microscopy and other basic laboratory services and also treat severe malaria in addition to providing in-patient care. Each LGA is expected to have at least one of this.

The cadre of staff found at this level are medical officers, pharmacists, medical laboratory scientists, nurses, Community Health Officers etc. Parasite based confirmation with microscopy shall be used to confirm suspected cases of malaria; however RDTs may be used at this level as appropriate.

### **Level III**

This represents the highest level of medical care in the country. The facilities include Teaching hospitals, Specialist hospitals and Federal Medical centres. Some General and private hospitals also belong to this category. At least, one of these categories is found in each state of the Federation and provide specialized health care services. The cadres of health workers found here include, among others, specialists in various health disciplines.

Parasite based confirmation with microscopy shall be used to confirm all cases with febrile illnesses. Malaria RDTs may also be used at this level as appropriate.

## 1.2 Epidemiology and Clinical Disease

Malaria is an infectious disease caused by the parasite of the genus *Plasmodium*, transmitted mostly by the bite of an infected female anopheles mosquito. There are five species of the parasite causing human malaria, namely, *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi* in Nigeria, however, only *P. falciparum*, *P. ovale* and *P. malariae* have been reported in the surveys on malaria. *Plasmodium falciparum* is the commonest species causing about 97% of uncomplicated malaria and it also the species most responsible for the severe form of the disease that leads to death in the country. *Plasmodium vivax* does not occur in indigenous Nigerians.

Malaria transmission is stable in Nigeria. Children under the age of five, pregnant women and non-immune visitors from non-endemic areas are particularly more susceptible than the general population.

Based on clinical and laboratory profiles, malaria can be classified as uncomplicated or severe. Patients with malaria can die when the disease is not appropriately classified. Failure to recognize severe malaria may be fatal.

### a. Uncomplicated malaria:

This is symptomatic malaria that has no vital organ dysfunction or life threatening manifestations.

### b. Severe malaria:

This is when there is *P. falciparum* asexual parasitaemia and no other confirmed cause of their symptoms; and the presence of life threatening clinical or laboratory features.

## 2.0 HISTORY

A complete history should include:

- General information such as age, place of residence and recent history of travel within or outside the country.
- Enquiry about the following symptoms:-
  - Fever
  - Chills (feeling cold) and rigors (shaking of the body)
  - Headache
  - Joint weakness or tiredness
- Also ask for the symptoms of other common childhood diseases
  - Cough or respiratory distress
  - Diarrhoea
  - Ear pain and skin rashes in the last three months.

## 3.0 DIAGNOSIS OF MALARIA

Malaria can be diagnosed based on clinical and laboratory evaluations.

### 3.1 Clinical Assessment

The signs and symptoms of malaria are non-specific. However, clinical suspicion is based on fever or history of fever in the last 24 hrs and/or the presence of anaemia. It is important to note that clinical

diagnosis alone may result in over-diagnosis of malaria; hence, parasitological confirmation is strongly recommended.

Clinical signs may include amongst other symptoms:

- Elevated body temperature  $\geq 37.5^{\circ}\text{C}$ .
- Enlarged spleen or liver, especially in children.
- Pallor (children/pregnant women)
- Exclude signs of severe disease.

### **3.2 Parasitological Diagnosis**

The changing epidemiology of malaria due to scale up of interventions and the introduction of ACTs have increased the urgency of improving the specificity of malaria diagnosis. Parasitological diagnosis has the following advantages:

- Improved patient care in parasite-positive patients;
- Identification of parasite-negative patients in whom another diagnosis must be sought;
- Prevention of unnecessary use of antimalarials, reduction of frequency of adverse effects, especially in those who do not need the medicines, and reduced pressure of selecting new drug for resistant parasites;
- Improved malaria case detection and reporting;
- Treatment monitoring and follow up to confirm treatment failures/successes.

#### **Parasitological confirmation is recommended in all suspected cases of malaria.**

Efforts should be made to explore the opportunities for a parasitological diagnosis. This guideline discourages all forms of empirical treatment that is not based on parasitological diagnosis.

Prompt and accurate diagnosis is part of effective disease management. High sensitivity of malaria diagnosis is important to identify positive cases of malaria in all settings. High specificity is vital to identify negative cases, which can reduce unnecessary treatment with antimalarial medicines and improve differential diagnosis of febrile illness.

The two methods in routine use for parasitological diagnosis are **Light Microscopy** and **Rapid Diagnostic Tests** (RDTs). The latter detect parasite-specific antigens or enzymes and some have a certain ability to differentiate species. **Deployment of microscopy and RDTs must be accompanied by quality assurance.**

Other tests outside the routine clinical setting such as **Polymerase Chain Reaction** (PCR)-based techniques are used for parasite diagnosis under special circumstances in tertiary institutions and research (for instance resistance testing).

Antimalarial treatment should be limited to test positive cases. The negative cases should be reassessed for other common causes of fever. Parasitological diagnosis promotes effective case management of malaria.

Generally, microscopy should be the mainstay of malaria diagnosis (as it reveals the malaria parasites) at facilities with laboratories such as some comprehensive health centres, secondary and tertiary healthcare levels (including the private health facilities). Quality assured malaria RDTs should be used in the primary healthcare level as well as the community. Malaria RDTs should be used in the public and private sectors.

**Parallel testing with microscopy and RDT is not recommended.** Should there be a continued suspicion of malaria after a particular test has been performed; a second test preferably based on another method should be done.

Malaria RDTs for detecting *PfHRP-2* can be useful for patients who have recently received incomplete antimalarial treatment, in whom malaria microscopy can be negative. If initial blood film examination is negative in patients with manifestations compatible with severe malaria, a series of blood films should be examined at 6-12-hour intervals, or an RDT (preferably one detecting *PfHRP-2*) should be performed. If both the slide examination and the RDT results are negative then it is unlikely that an individual has malaria. An alternate cause of the illness should be sought and patient treated or referred as may be applicable.

The results of parasitological diagnosis should be available within two hours of the patient presenting.

### **Microscopy**

Microscopy is the standard method for parasitological diagnosis of malaria. This is done by examining a stained thick or thin blood smear for the presence of malaria parasites. Thick films are recommended for parasite detection and quantification while thin films are recommended for species identification.

Microscopic examination of stained blood films by a highly skilled microscopist has a sensitivity range of 86-98% with a lower sensitivity in detecting low parasitaemias ( $\leq 320/\mu\text{l}$ ). Various factors such as the stage of the malaria infection and previous medication may reduce parasitaemia below the detectable threshold and necessitate repeat examination.

### **Malaria Rapid Diagnostic Tests (mRDT)**

Malaria Rapid Diagnostic Test (mRDT) is a device which detects specific antigens (proteins) produced by malaria parasites. They (mRDTs) are lateral flow immunochromatographic antigen detection tests which rely on the capture of dye-labelled antibodies to produce a visible band on a strip of nitrocellulose.

They provide a useful guide to the presence of clinically significant malaria infection. They complement microscopy based diagnosis where such services are not available. However, RDTs should not replace microscopy as the sole means of malaria diagnosis.

There are different types of RDTs but the commonest ones are broadly of two categories;

- those based on the identification of the *Plasmodium falciparum* histidine rich protein 2 (PfHRP2) and
- those based on the identification of the plasmodium lactate dehydrogenase enzyme (pLDH) and aldolase enzyme.

The former detects the presence of the plasmodium protein whether dead or alive. To that end, HRP-2 based RDTs tend to be very sensitive, but slightly less specific because there could be some false positive as they persist after death of the parasite for up to 5-weeks.



The pLDH RDTs and aldolase on the other hand are produced by all Plasmodium species as part of the glycolytic process and should be viable for the test to be positive. Hence they are slightly less sensitive but more specific. *Plasmodium falciparum* is the most predominant species in Nigeria and justifies the programmatic deployment of quality-assured HRP-2 based RDTs. Most RDTs have a sensitivity of 95% at parasite densities of 200/μl of blood.

The sensitivity of malaria RDTs is determined by the:

- Species of parasite (poor sensitivity in detecting *P. malariae* and *P. ovale*)
- Number of parasites present in the blood
- Condition of the RDT
- Correctness of technique used to perform the test
- Correctness of interpretation by the reader
- Parasite viability and variation in production of antigen by the parasite.

### **The Choice between Rapid Diagnostic Tests (RDTs) and Microscopy**

The choice between RDTs and microscopy depends on local circumstances, including the skills available, patient case-load, epidemiology of malaria and the possible use of microscopy for the diagnosis of other diseases. Where the case-load of fever patients is high, microscopy is likely to be less expensive than RDTs, but may be less operationally feasible. Microscopy has further advantages in that it can be used for speciation and quantification of parasites, and to assess response to antimalarial treatment. Microscopy can also be used in the identification of other causes of fever.

However, a major drawback of light microscopy is its requirement for well-trained, skilled staff and, usually, an energy source to power the microscope. In many areas, malaria patients are treated outside of the formal health services, e.g. in the community, in the home or by private providers; microscopy is generally not feasible in many such circumstances, but RDTs may be possible.

Although RDTs for detection of parasite antigen are generally more expensive, their deployment may be considerably cost effective in many of these settings. The sensitivities and specificities of RDTs are variable, and their vulnerability to high temperatures and humidity is an important constraint. Despite these concerns, RDTs make it possible to expand the use of confirmatory diagnosis.

In the diagnosis of severe malaria cases, microscopy is a preferred option; it not only provides the diagnosis of malaria, but it is useful in assessing other important parameters in a severely ill patient. In situations where an RDT has been used to confirm malaria, this allows for a rapid institution of antimalarial treatment, however, where possible a microscopic examination is recommended to enhance the overall management of the patient.

## Summary Box 1: Diagnosis of Malaria

- Prompt parasitological confirmation by microscopy or RDT is recommended in all patients suspected of malaria before treatment is initiated.
- Treatment solely on the basis of clinical suspicion should only be considered in children less than five years when a parasitological diagnosis is not accessible

## 4.0 TREATMENT OF UNCOMPLICATED MALARIA

### 4.1 Treatment Objectives:

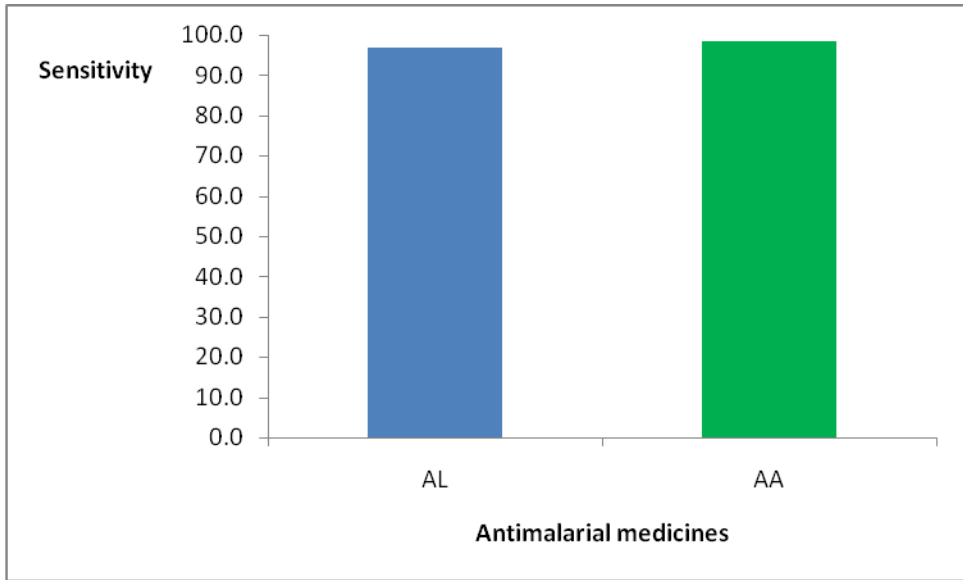
The main objective of treating uncomplicated malaria is to cure the infection as quickly as possible. Prompt treatment prevents progression to severe disease and the additional morbidity associated with treatment failure. Cure of the infection means eradication, from the body, of the asexual parasites that caused the disease. Additional objective is to prevent transmission of gametocytes, which develop from asexual parasites. If the latter are not quickly eliminated, they could result in the emergence and spread of resistance to antimalarial medicines.

### 4.2 Artemisinin- based Combination Treatments

Artemisinin- based Combination Treatments (ACTs) are the currently recommended treatments for uncomplicated malaria globally. ACTs are medicines consisting of an artemisinin derivative and another effective long acting schizonticidal antimalarial medicine.

### 4.3 Recommended treatments

Artemether-Lumefantrine (AL) is the medicine of choice while Artesunate-Amodiaquine (AA) is the alternate medicine for the treatment of uncomplicated malaria in Nigeria. The 2009-2010 Drug Therapeutic Efficacy Tests carried out on these medicines in the country showed sensitivities of 99.1 and 96.9 for AA and AL respectively confirming that they remain efficacious treatments for uncomplicated *P. falciparum* malaria (see below)



PCR-corrected efficacy of artemeter-lumefantrine (AL) or artesunate-amodiaquine (AA) at various drug therapeutic efficacy testing sites in Nigeria between 2009 and 2010.

[Source: Technical report of Drug Efficacy Studies 2009/2010, Federal Ministry of Health]

### ***Artemether-Lumefantrine***

Artemether-Lumefantrine is available in fixed dose combinations as co-formulated tablets and dispersible tablets for children. Tablet strengths (artemether/lumefantrine) available are 20mg/120mg; 40mg/240mg; and 80mg/480mg (Tables 1 and 2). These new higher strengths provide for less pill load per dose.

Table 1: Showing Artemether-Lumefantrine in the 20/120 formulations

Medicines*	Dosage form	Presentation	Strength
Artemether-Lumefantrine	Tablet	Co-formulated	20mg artemether - 120mg lumefantrine per tablet
Artemether-Lumefantrine	Dispersible tablet (Children)	Co-formulated	20mg artemether - 120mg lumefantrine per tablet

Table 2: Showing Artemether-Lumefantrine in the *higher strength* formulations

Medicines	Dosage form	Presentation	Strength
Artemether - lumefantrine 40-240	Tablet	Co-formulated	40mg Artemether – 240mg Lumefantrine per tablet
Artemether-Lumefantrine 80-480	Tablet	Co-formulated	80mg Artemether – 480mg Lumefantrine per tablet

Table 3: Dosage regimens for Artemether-Lumefantrine treatment (different strength formulations) of uncomplicated malaria (tablet splitting is not recommended):

Weight	No. of tablets / dose (20/120)mg tab	No. of tablets /dose (40/240)mg tab	No. of tablets/dose (80/480)mg tab
5-<15kg	1 tab twice daily x 3days	NA	NA
15-<25kg	2 tabs twice daily x 3days	1 tab twice daily x 3days	NA
25-<35kg	3 tabs twice daily x 3days	NA	NA
≥35kg	4 tabs twice daily x 3days	2 tabs twice day x 3 days	1 tab twice/day x 3 days

Tables 1, 2 and 3 show the dosage regimens of AL for the treatment of uncomplicated malaria. It is important to emphasize that the **6 doses** must be taken by the patient. Absorption of the medicine is enhanced by fatty meals\*.

### **Artesunate-Amodiaquine**

Artesunate-Amodiaquine is available as co-formulated tablets. The recommended dosing regimen for Artesunate-Amodiaquine is shown in the Table 5 below. It is important to emphasize that the **3 daily doses** must be taken by the patient.

Table 5: Showing dosage regimen for co formulated Artesunate-Amodiaquine treatment of uncomplicated malaria:

Weight / Age	Tablet strength	Dosage regimen
4.5kg-<9kg 2months-11 months	25mg/67.5mg	1 tablet once daily for three days
>9kg-<18kg >1 year-5 years	50mg/135mg	1 tablet once daily for three days

>18kg-<36kg >6 years-13 years	100mg/270mg	1 tablet once daily for three days
36kg and above 14 years and above	100mg/270mg	2 tablets once daily for three days

#### 4.4 Other ACTs available for the treatment of uncomplicated malaria

- Artesunate-Mefloquine
- Dihydroartemisinin-piperaquine
- Artemisinin-Piperaquine

#### 4.5 Treatment Failure

ACT regimens should provide 3-day treatment with an artemisinin derivative.

With adequate treatment, patient should respond within two days of commencing treatment as indicated by rapid disappearance of fever and other symptoms of malaria and clearance of asexual parasites.

If the patient shows evidence of inadequate response: (for example, persistence of fever, asexual parasites or deterioration in clinical condition, do the following:

- Evaluate the patient and review diagnosis.
- Ensure that appropriate dose of the medicine has been given
- Do further Investigations to rule out other causes of fever

In the absence of other causes of fever, and in the presence of persistent asexual parasites, the patient should be treated with the alternate medicine; in the case of AL, treat with AA and vice versa.

#### 4.6 Use of Monotherapy

The use of single antimalarial agents such as Artemether, Artesunate, Amodiaquine or Sulphadoxine -Pyrimethamine (SP) are not recommended in the treatment of uncomplicated malaria. In Nigeria, the use of Sulphadoxine-Pyrimethamine is restricted to pregnant women as Intermittent Preventive Treatment (IPT).

Chloroquine (tablets or injectable) is prohibited for the treatment of *P. falciparum* malaria, either as a single antimalarial agent or in combination with other antimalarial molecule.

#### 4.7 Practical issues in Management of Uncomplicated Malaria

##### **Antipyretic measures**

If body temperature is greater than 38.5°C:

- In children, give paracetamol; 10 - 15mg/kg every 6 – 8 hours, or when necessary but not exceeding 4 doses in 24 hours.
- Advise caregiver to tepid sponge the child (wipe the body with towel soaked in lukewarm water) and take off unnecessary clothing
- In adults, give 500-1000 mg of paracetamol every 6-8 hours, or when necessary but not exceeding 4 doses in 24 hours.

### **Persistent Vomiting**

- If a patient vomits within 30 minutes of taking the medicine, repeat the dose.
- If the patient vomits again he should be managed with parenteral antimalarial until the vomiting stops and thereafter completes normal course of ACT.

### **Febrile Seizures**

If a patient has a seizure and does not recover within 30 minutes from the seizure, it should be considered as severe malaria.

## **5.0 TREATMENT OF UNCOMPLICATED MALARIA IN SPECIAL GROUPS**

### **5.1 Children less than 5kg**

Malaria in children less than 5kg can be serious and may progress to severe disease with increased risk of dying if not treated promptly. Artemisinin-based combination treatments are safe and well tolerated by young children. ACTs can be used in uncomplicated malaria in infants and young children but attention must be given to accurate dosing and the care provider must ensure that the administered dose is retained. **Treat infants weighing < 5 kg with uncomplicated *P. falciparum* malaria with an ACT at the same mg/kg bw target dose as for children weighing 5 kg.**

### **5.2 Pregnant women and Lactating mothers**

Falciparum malaria during pregnancy carries a high mortality for the foetus and increased morbidity for the pregnant woman

#### **First Trimester**

The safety of the ACTs during the first trimester has not been established for a definite recommendation on their use, therefore treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with 7 days of quinine + clindamycin. However, use an ACT if quinine is not available, or it is not possible to ensure /guarantee adherence to complete 7 day treatment with quinine

#### **Second and third trimesters**

The ACTs are the preferred treatments for uncomplicated malaria.

#### **Lactating mothers**

Lactating mothers should be treated with recommended ACTS.

## **6.0 COMMUNITY MANAGEMENT OF MALARIA**

The management of uncomplicated malaria has been expanded into the community to promote early detection, diagnosis and prompt treatment of malaria. Community-Oriented Resource Persons (CORPs) are a broad group of people based at the community and trained in the treatment and diagnosis of malaria within the communities. They include Role Model Caregivers (RMC), Community-Directed Distributors (CDDs) and other categories of community health workers.

Private sector resource persons such as Community Pharmacists (CPs) and Patent Proprietary Medicine Vendors (PPMVs) are also recognized as CORPs and have been empowered to carry out parasite based diagnosis of malaria using Rapid Diagnostic Tests (RDTs) and initiating appropriate treatment. They are also trained to recognize signs of severe malaria and other severe presentations (Danger signs) and to support the referral process. (See **pages 33 and 34** for algorithms for diagnosis and treatment of malaria at facilities and communities).

Recommended medicines for the treatment of malaria at community level is as recommended for the treatment of uncomplicated malaria.

**Key Messages for use of Oral Medicines at Home for children under 5 years of age**

- Tablets or dispersible formulations are preferred as oral medications
- Determine the appropriate medicine and dosage according to weight or age charts
- Tell the patient or the caregiver the reasons for giving the medicine
- Demonstrate how to take or give the correct doses
- Watch the patient take the medicine
- Explain that the treatment course must be completed even when the patient feels well
- Tell the patient or parent that the medicines are not to be shared with other family members
- Advise patient or caregiver on when to return to the health worker
- Check that the patient or caregiver understands the instructions before leaving

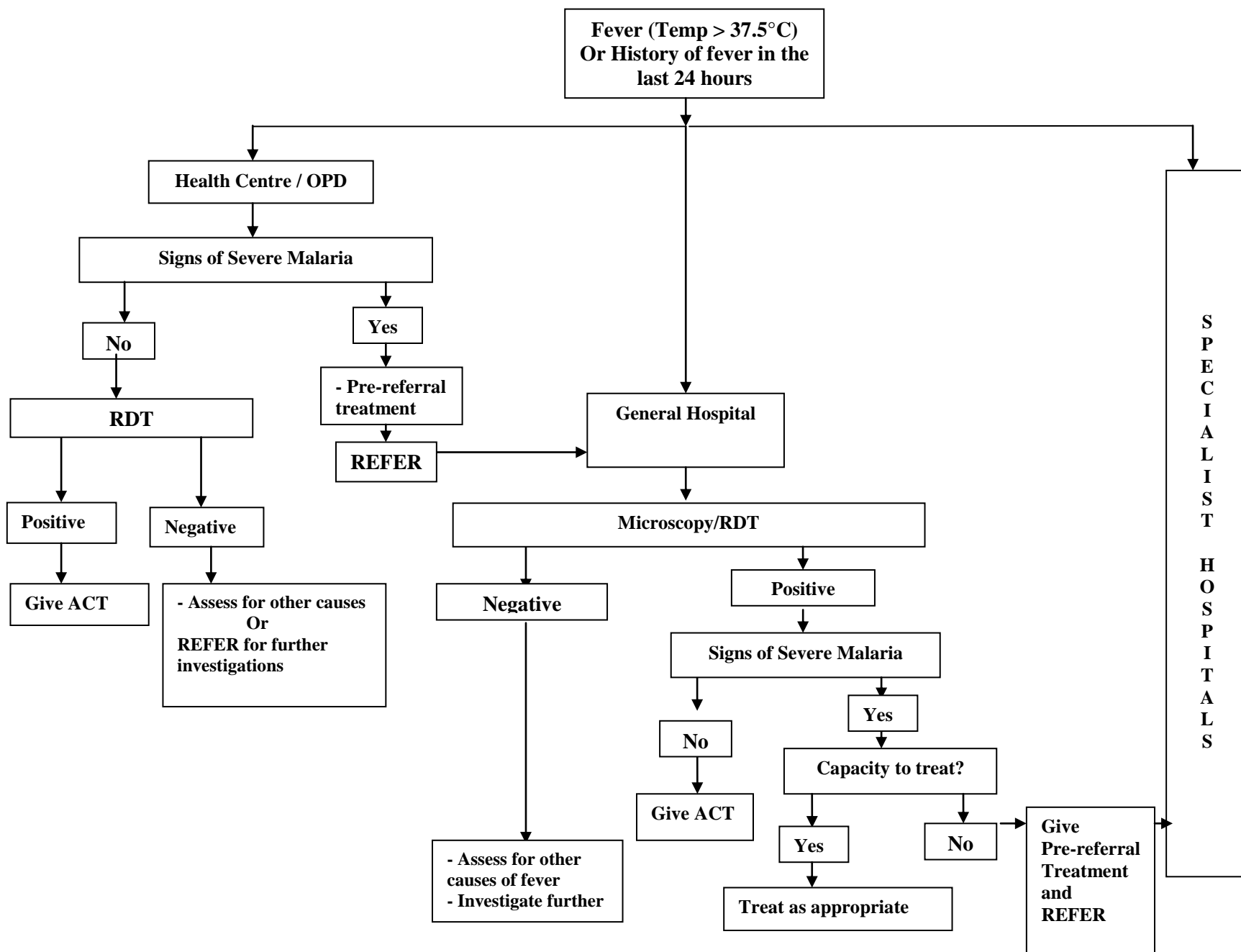
**Follow up**

- Counsel the patient to return immediately if:
  - patient's condition worsens and/ or the patient develops symptoms and/or signs of severe disease, (see section 7.3)
  - fever persists for two days after commencement of treatment
- When patient returns,
  - Check that patient complied with treatment regimen
  - Do complete assessment to rule out any other possible cause of the fever, if fever persists
  - Repeat or do blood smear for malaria parasites, and
  - Refer or manage as necessary

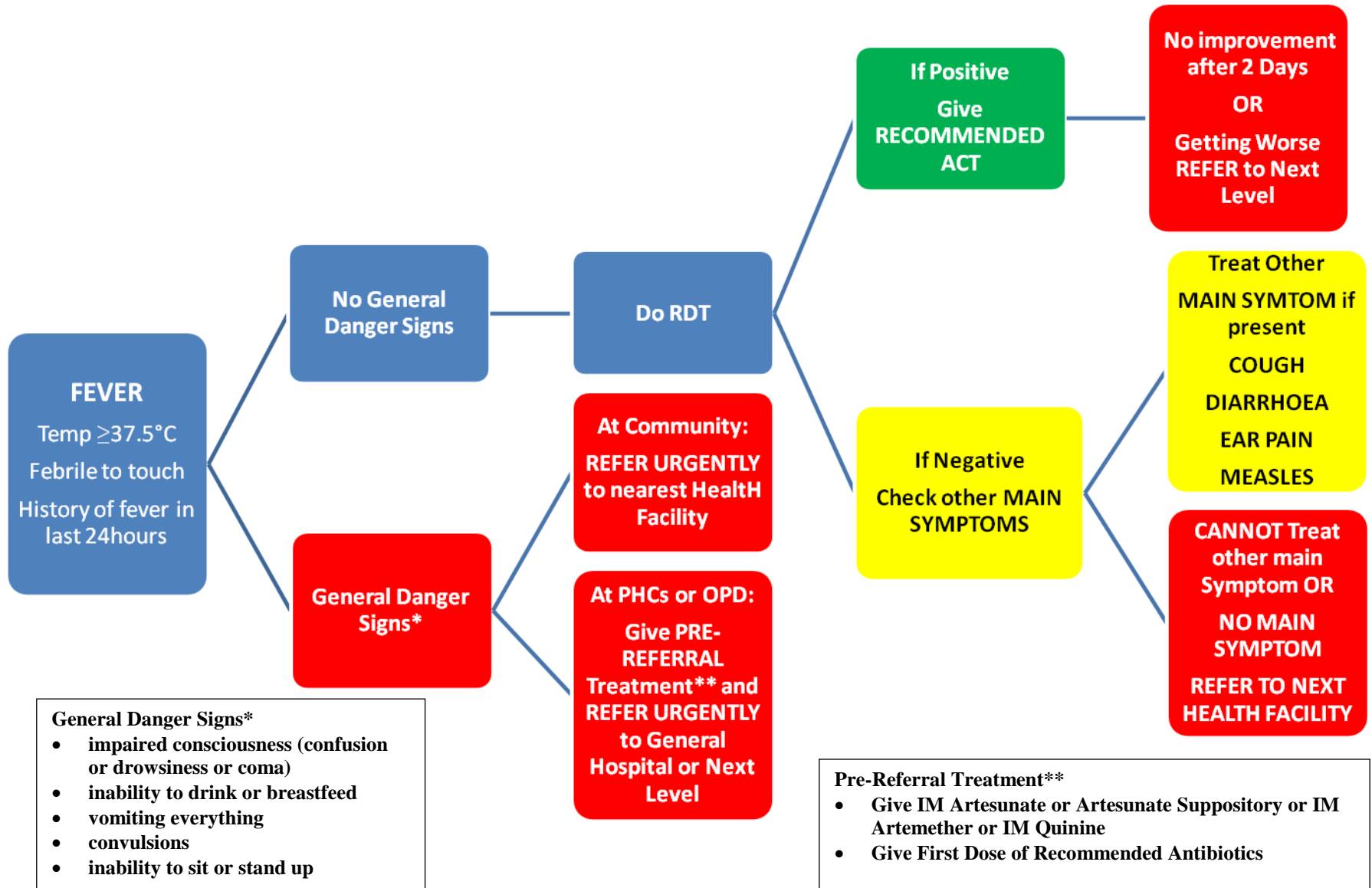




**ALGORITHM FOR FACILITY BASED MANAGEMENT OF MALARIA AT DIFFERENT LEVELS OF HEALTH CARE IN NIGERIA**



**ALGORITHM FOR MANAGEMENT OF SUSPECTED MALARIA AT COMMUNITY OR FIRST LEVEL HEALTH FACILITIES OR OUT PATIENT DEPARTMENTS**



## 7.0 ASSESSMENT AND MANAGEMENT OF SEVERE MALARIA

### 7.1 Key Recommendations on Management of Severe Malaria

Below are the key recommendations in relation to management of severe malaria in Nigeria.

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Severe malaria is a medical emergency requiring in-patient care. After rapid clinical assessment and confirmation of the diagnosis, **full doses of parenteral artesunate** treatment should be started without delay. *If parenteral artesunate is not available other effective (see below) parenteral antimalarial should be commenced.*

- *For children  $\leq 20\text{kg}$ , artesunate 3 mg/kg BW IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended treatment.*
  - *For adults and children  $>20\text{kg}$ , artesunate 2.4 mg/kg Body Weight (BW) IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended treatment. There is no upper limit to the total dose of artesunate.*
  - Artemether, or quinine, is an acceptable alternative if parenteral artesunate is not available: artemether 3.2 mg/kg BW IM given on admission then 1.6mg/kg BW per day; or quinine 20 mg salt/kg BW on admission (IV infusion or divided IM injection), then 10 mg/kg BW every 8 h; infusion rate should not exceed 5 mg salt/kg BW per hour.
  - **Give parenteral antimalarials in the treatment of severe malaria for a minimum of 24hours, once started** (irrespective of the patient's ability to tolerate oral medication earlier), and, thereafter, complete treatment by giving a complete course of the recommended ACT. *(ACTs containing Mefloquine should however be avoided if the patient had cerebral malaria because of the increased risk of seizures, encephalopathy and psychosis).*
  - At community or health facility levels where complete management of severe malaria is not possible, patients with severe malaria should be given pre-referral treatment and referred immediately to an appropriate facility for further treatment.
    - The following options for pre-referral treatment are recommended in a ranked order:
      - For children: artesunate IM; or rectal artesunate; or artemether IM; or quinine IM.
      - For adults: artesunate IM; or artemether IM; or quinine IM.
- 

### 7.2 Introduction

Patients with severe malaria are at immediate risk of dying due to multiple organ dysfunction. It is important to complete any assessment very rapidly so that treatment can be instituted promptly and in the appropriate health facility with the right complement of staff to manage the patient. It is also important to appreciate that the patient is at risk of dying from either the direct effect of malaria or from other complications that may have set in. Hence, in the care of severe malaria patients there will be the need for specific antimalarial treatment, the capacity to correct any of the complications and the ability to monitor or provide other forms of supportive care. Where the patient presents in a facility with no appropriate complement of staff or facilities, pre-referral treatment should be administered and the patient promptly referred to a higher level facility.

## 7.2 Definition

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

- **Impaired consciousness:** A Glasgow Coma Score <11 in adults or a Blantyre Coma Score <3 in children.
- **Prostration:** Generalized weakness so that the person is unable to sit, stand or walk without assistance
- **Multiple convulsions:** More than two episodes within 24hours
- **Acidosis:** A base deficit of >8 meq/L or, if unavailable, a plasma bicarbonate of <15mmol/L or venous plasma lactate  $\geq$  5 mmol/L. Severe acidosis manifests clinically as respiratory distress-rapid, deep and laboured breathing.
- **Hypoglycaemia:** Blood or plasma glucose <2.2mmol/L (<40mg/dL).
- **Severe malarial anaemia:** A haemoglobin concentration  $\leq$  5g/dL or a haematocrit of  $\leq$  15% in children <12 years of age (<7g/dl and <20% respectively in adults) together with a parasite count >10,000/ $\mu$ L.
- **Renal impairment:** (acute kidney injury): Plasma or serum creatinine >265 $\mu$ mol/L (3mg/dL) or blood urea > 20 mmol/L
- **Jaundice:** Plasma or serum bilirubin > 50 $\mu$ mol/L (3mg/dL) together with a parasite count >100,000/  $\mu$ L.
- **Pulmonary oedema:** Radiologically confirmed, or oxygen saturation <92% on room air with a respiratory rate >30/minute, often with chest indrawing and crepitations on auscultation.
- **Significant bleeding:** including recurrent or prolonged bleeding from nose, gums or venepuncture sites; hematemesis or melaena
- **Shock:** Compensated shock is defined as capillary refill  $\geq$ 3 seconds or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure less than 70 mm Hg in children or < 80 mm Hg in adults with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
- **Hyperparasitaemia:** Red blood cell *P.falciparum* parasitaemia >10%.

### Definition of severe non-falciparum malaria

Severe malaria due to other species of plasmodia is still a rare event in Nigeria. However for the purposes of effective management of malaria in visitors to the country, it is important that health care workers acquaint themselves with the case definition for other species.

**Severe vivax malaria** is defined as above but with no parasite density thresholds.

**Severe knowlesi malaria** is also defined as above with two differences

1. *P. knowlesi* hyperparasitaemia: Parasite density >100,000/uL
2. Jaundice and parasite density >20,000/uL

### Explanatory notes on the features of severe malaria

### **Anaemia**

Anaemia occurs as a result of destruction of parasitized red blood cell by the spleen, TNF mediated depression of erythropoiesis and immune mediated haemolysis.

### **Cerebral Malaria**

For a diagnosis of cerebral malaria, the following criteria should be met:

- *Coma*: Motor response to noxious stimuli is non-localising or absent. However management should be instituted once there is an altered consciousness.
- *Exclusion of other encephalopathies*
- *Confirmation of P. falciparum infection*
- Abnormal neurological manifestations
- Convulsions may be as a result of very high temperature, hypoglycaemia, hypoxaemia, severe anaemia or the effect of herbal concoction.

### **Hypoglycaemia**

This may occur as a result of decreased intake, increased glucose utilization; antimalarial mediated reduction, glycogen depletion or impaired gluconeogenesis.

### **Acidosis**

This is due to elevated levels of lactic acid which results from tissue anaerobic glycolysis, particularly in skeletal muscles.

### **Breathing difficulties**

Patients with severe malaria may present with difficulty in breathing as a result of any of the following:

- Heart failure resulting from severe anaemia.
- Pulmonary oedema (following administration of excessive fluids) usually there is frothing from the mouth and marked respiratory distress.
- Acidosis causes deep and rapid respiration.
- Aspiration

### **Acute kidney injury**

Acute kidney injury occurs due to low blood pressure as a result of dehydration or shock.

### **Haemoglobinuria**

This is as a result of excessive breakdown of red blood cells by parasites or drugs like sulphonamides and primaquine, especially in G6PD deficiency patients.

## **7.3 Who are the people at risk for severe malaria?**

- Children < 5 years
- Pregnant women especially those with first and second pregnancies
- People returning or coming to Nigeria after living in malaria free areas
- People who have had splenectomy

## 7.4 Clinical evaluation of patients for severe malaria

### History

In addition to the general history taken in patient with uncomplicated malaria you should ask about the following

***In all patients ask about:-***

- Recent history of travel (to identify those coming from malaria free areas to areas of high transmission or those who have travelled to areas with haemorrhagic fevers which may mimic malaria)
- *Extreme weakness* (Prostration) which is inability to eat and drink or do anything without support. In a patient with suspected uncomplicated malaria, progressive weakness should immediately alert you that the patient may be developing severe malaria.
- *Abnormal behaviour or altered consciousness*
- *Convulsions*: ask about the number of episodes, part of the body involved, previous history and time of onset of last episode.
- *Time of last drink or food* since the onset of the illness.
- *Fast breathing* which may occur due to pulmonary oedema or acidosis.
- *Reduced urinary output* (time patient last passed urine).
- *Colour of urine*: whether dark or coca-cola coloured (this may suggest excessive breakdown of red blood cells or dehydration).
- *Pregnancy*: in adult females.
- **Drug History**: Ask about antimalarial drugs, salicylates and herbal concoctions that may influence treatment or cause some of the symptoms.
- **Previous illnesses**: Ask about any history of recent febrile illness and treatment which may suggest treatment failure or relapse (consider typhoid, malaria and other infections)

### Ask history to exclude other severe diseases

#### Physical Examination

In the physical examination you should aim at

- Assessing for the presence of signs of severe malaria.
- Identifying other possible causes of disease.

#### **a. Central Nervous System**

It is important to assess the level of consciousness using an objective scale in order to facilitate proper evaluation of the progress of the patient. Available scales for assessing level of consciousness include the AVPU scale, Glasgow coma scale or the Blantyre coma scale.

The AVPU scale is as shown below

**A** = alertness (the patient is spontaneously alert)

**V** = response to voice command (the patient respond to his/her name)

**P** = response to pain (the patient feels pain or cry if a child)

**U** = unresponsive. (Patient does not respond at all to noxious stimuli)

**b. Ocular examination**

The fundus of the eyes should be examined to exclude presence of papilloedema and retina haemorrhages. The latter if present is highly suggestive of cerebral malaria

**c. Respiratory System**

- Check for respiratory distress (fast, deep or laboured breathing)
- Listen to the chest for rales or other added sounds.

**d. Cardiovascular**

- Examine the rate, rhythm and volume of the pulse.
- Cold extremities or poor capillary refill at the tips of the fingers (*delay for >3 seconds*).
- Check blood pressure

**e. Abdomen**

- Feel for the spleen and the liver

**Differential Diagnosis:**

- Meningitis - Patient may have a stiff neck.
- Encephalopathy- Repeated convulsions or deep coma.
- Diabetes Mellitus- Patient may be dehydrated, acidotic or in coma.
- Septicaemia- Usually very ill and toxic with warm extremities.
- Epilepsy- Usually no temperature and will have history of convulsions before.
- Acute renal failure from other causes- usually associated with reduced or no urine output
- Viral hemorrhagic fevers (Ebola, Lassa, Dengue etc)- usually associated with jaundice and bleeding tendency and history of contact

**7.5 Parasitological Diagnosis of Severe Malaria**

Every suspected case of severe malaria should have a parasitological diagnosis before treatment. Advantage can be taken of the availability of mRDT to rapidly establish the diagnosis by the bedside. Blood smears can be sent to the laboratory for quantification of the parasite density and subsequent monitoring of patient's progress.

**7.6 Other Laboratory Investigations**

Other laboratory investigations are conducted with the aim to assess complications, exclude other possible causes of severe febrile illnesses and monitor the patients' progress.

Recommended tests to be routinely performed include:

- Haematocrit (PCV) and/or Haemoglobin concentration
- Blood sugar level
- Lumbar puncture in unconscious patients.
- Urinalysis
- Blood culture
- Feto-maternal surveillance in pregnant women

Other tests that could be required subject to the patients' specific situation and available facilities include:

- Blood electrolytes, urea and creatinine
- Chest X-ray
- Complete blood count
- Blood gases (PO<sub>2</sub>, PCO<sub>2</sub> and pH)

**Practice points on diagnosis of severe malaria:**

- High index of suspicion in patients with fever and any of the features discussed above.
- Where confirmation of diagnosis is not immediately feasible, treatment should be commenced while appropriate specimen should be obtained for subsequent lab analysis.
- Bacterial infection may co-exist in patients with severe malaria. This possibility must be borne in mind and blood samples drawn to exclude concomitant sepsis.

## 7.7 Treatment

Severe malaria is a medical emergency requiring in-patient care. Deaths from severe malaria can result either from direct effect of the disease or the complications. The provider should attend to the immediate threats to life first.

### Treatment of complications

#### Coma or unconscious patient

- Ensure airway is patent; gentle suction of nostrils and the oro-pharynx.
- Make sure the patient is breathing.
- Nurse the patient lying on the side or with the head sideways.
- Insert a naso-gastric tube (NGT).
- Establish an intravenous line. It will be necessary for giving drugs and fluids.
- Correct hypoglycaemia:

**Children:** 0.5 ml/kg of 50% dextrose diluted to 10-15%.

**Adults:** 25 ml of 50% dextrose.

-Where intravenous access is not possible, give dextrose or any sugar solution through the naso-gastric tube.

#### Convulsions

- Ensure patent airway and that the patient is breathing.
- Correct hypoglycaemia or control temperature.
- In children give rectal diazepam 0.5 mg/kg or IM paraldehyde 0.1 ml/kg. If convulsions continue, give IM phenobarbitone 10-15 mg/kg.
- In adults give 10 mg diazepam IV.



### Severe dehydration or shock

- Give 20-30 ml/kg of normal saline and reassess the patient within 30 minutes to decide on the next fluid requirement according to the degree of dehydration.
- After correction of the fluid deficit it is important to reduce the maintenance fluid to two thirds of the required volume when the patient is well hydrated.

### Severe Anaemia

- Give urgent blood transfusion to patients with **severe anaemia** in heart failure. **The blood must be screened to ensure that it is HIV, Hepatitis B and C negative.**
- Use packed cells (10 ml/kg in children) or whole blood (plus frusemide).
- Where blood is not available, give pre-referral treatment and **refer urgently** to a health facility with blood transfusion services.

## Specific Antimalarial Treatment

### Treatment Objectives

**The primary objective of antimalarial treatment in severe malaria is to prevent the patient from dying.** The secondary objectives are prevention of disabilities and occurrence of recrudescence.

**The antimalarial medicine recommended for the treatment of severe malaria in Nigeria is injectable (IV/IM) Artesunate.** Where this is not readily available, intramuscular artemether or intravenous/ intramuscular quinine can be used as alternatives.

#### 1. Artesunate

The artemisinin derivative artesunate is now firmly established as the treatment of choice for severe malaria. The largest randomised clinical trials ever conducted in severe falciparum malaria have shown a highly significant reduction in mortality with intravenous or intramuscular artesunate compared with parenteral quinine. This reduction in mortality was not associated with an increase in neurological sequelae in artesunate treated survivors. Furthermore artesunate is simpler and safer to use than quinine and proved highly cost-effective.

#### *Recommended Dosage for injectable artesunate:*

Previously artesunate was recommended to be administered at a dose of 2.4mg/kg in all age groups and for all weight categories. However pharmacokinetic studies in children with severe malaria receiving intramuscular artesunate suggest that there is underexposure relative to older children and adults to both artesunate and the biologically active metabolite dihydroartemisinin (DHA) at that dose. It therefore became necessary to adjust to dose of artesunate in children 20kg and less.

### Standard Operating Procedures for the Preparation and Administration of Injection

#### Artesunate using 60 mg Vial

Recommended steps that must be followed to prepare and administer artesunate injection safely and correctly using the 60 mg vial.

1. Weigh the patient and record the exact weight.
2. Determine the number of 60mg vials needed.
3. Calculate the dose and millilitres of artesunate needed for administration.
4. Gather materials and check expiry dates.
5. Reconstitute artesunate powder with 1 ml of 5% sodium bicarbonate and shake until clear; 2-4 minutes.
6. Dilute the reconstituted artesunate with normal saline based on route of administration; 5 ml for IV and 2 ml for IM.
7. Re-check the dose calculation and withdraw the required dose for the route of administration.
8. Administer injectable artesunate.
9. Plan the dosing schedule.

Calculate the dose and millilitres of artesunate needed for administration.  
 Determine the route of injectable artesunate: intravenous (IV) or intramuscular (IM).  
 Use the following calculations:

**Intravenous injection:**

20kg and less	Above 20kg
$\frac{3.0 \text{ mg} \times \text{body weight (kg)}}{10 \text{ mg/ml}}$	$\frac{2.4 \text{ mg} \times \text{body weight (kg)}}{10 \text{ mg/ml}}$

**Intramuscular injection**

20kg and less	Above 20kg
$\frac{3.0 \text{ mg} \times \text{body weight (kg)}}{20 \text{ mg/ml}}$	$\frac{2.4 \text{ mg} \times \text{body weight (kg)}}{20 \text{ mg/ml}}$

Round up to the next 0.5 ml (e.g. 1.2=1.5 ml 1.6=2 ml)

Give 3 parenteral doses of injection artesunate in the first 24 hours; first dose on admission (time zero), second dose 12 hours after the first dose and third dose at 24 hours after the first dose.

- There is no upper limit to the total dose of artesunate

Where artesunate is not available, severe malaria can be treated with artemether or quinine as alternatives. Their dosages are as indicated below:

**2. Artemether**

The initial dose of Artemether is 3.2/kg bw by intramuscular injection (anterior thigh). The maintenance dose is 1.6mg/kg bw daily.

**Note:**

*There is insufficient data on Artemotil or Arteether, hence they are not recommended for severe malaria.*

### **3. Quinine**

It is administered by either IV or IM route, depending on the availability of infusion facilities.

*Recommended dosage:*

#### ***Intravenous quinine***

*Children:*

Give 20 mg/kg of Quinine dihydrochloride **salt** as loading dose diluted in 10 ml/kg of 4.3% dextrose in 0.18% saline or 5% dextrose over a period of 4 hours. Then 12 hours after the start of the loading dose, give 10 mg **salt** /kg infusion over 4 hours every 8 hours until when patient is able to take orally.

Then give a full dose of recommended ACT.

*Adults:*

Quinine dihydrochloride 20 mg/kg of **salt** to a maximum of 1.2gm (loading dose) diluted in 10 ml/kg isotonic fluid by intravenous infusion over 4 hours then, 8 hours after the start of the loading dose, give 10 mg/kg **salt** to a maximum of 600 mg over 4 hours every 8 hours patient is able to take orally.

Then give a full dose of recommended ACT.

#### **NOTE:**

- If intravenous quinine is required for over 48 hours, reduce the dose to 5-7mg/kg to avoid toxicity. A practical way of doing this is to reduce the dosing frequency to every 12 hours

#### ***Intramuscular Quinine:***

Where intravenous access is not possible give quinine dihydrochloride intramuscularly at a dosage of 20 mg/kg **salt** (loading dose), diluted to 60mg/ml, and continue with a maintenance dose of 10mg/kg 8hourly until patient is able to take orally.

Thereafter give full dose of recommended ACT.

**NOTE: Intramuscular injections should be given with sterile precautions into the anterior or lateral thigh, NOT THE GLUTEAL REGION.**

### **Treatment of severe malaria in pregnancy**

#### **First trimester**

Current body of evidence is yet to be conclusive on the safety of artemisinin derivatives in the first trimester. However, available evidence has placed Artesunate above all other available treatments. Since the risk of death from severe malaria far outweighs the potential risk of artesunate to the foetus, it is therefore recommended for the treatment of malaria during the first trimester.

#### **Second and third trimesters**

Injectable artesunate is recommended for these periods. In addition to the superior efficacy it has added the added advantage of not contributing to hypoglycaemia which is very common when severe malaria occurs in the second and third trimesters of pregnancy. There should also be close monitoring of maternal and foetal wellbeing.



## **Supportive Treatment**

### *High temperature*

- Give paracetamol (rectal) if temperature is  $>38.5^{\circ}\text{C}$ , in children, also tepid sponge (wipe the body with towel soaked in lukewarm water), avoid over-clothing.

### *Pulmonary oedema*

- Prop up the patient at an angle of 45degrees, give oxygen and frusemide 2-4 mg/kg IV, stop intravenous fluids and exclude other causes of pulmonary oedema.

### *Renal failure*

- Give fluids if patient is dehydrated 20 ml/kg of normal saline and challenge with frusemide 1-2 mg/kg.
- Pass a urinary catheter to monitor urinary output.
- If patient does not pass urine within the next 24 hours refer for peritoneal or haemodialysis.
- Exclude pre-renal causes

### *Profuse bleeding*

- Transfuse with screened fresh whole blood, give pre-referral treatment and refer urgently.

### *Other possible treatments:-*

- If meningitis is suspected, and cannot be immediately excluded by a lumbar puncture, appropriate antibiotics should be given.
- Other severe diseases should be treated accordingly.

## **Treatments not recommended**

The following drugs have no role in the treatment of severe malaria.

- Corticosteroids and other anti-inflammatory agents
- Agents used for cerebral oedema e.g. Urea
- Adrenaline
- Heparin

## **Nursing and Quality of Care**

Severe malaria is a serious condition and the clinicians and nurses should closely monitor patients. Therefore nursing care should include all the following:-

### **1. Monitor vital signs**

- Pulse
- Temperature
- Respiratory rate
- Blood pressure

These should be monitored at least every 6 hours but may be more frequent at the initial stages.

## **2. Monitor input and output**

A strict 24-hour input / output chart should be kept in all patients with severe malaria. Examine regularly for signs of dehydration or fluid overload.

## **3. Monitoring unconscious patient**

Unconscious or comatose patients need close monitoring of all vital signs more regularly to assess their progress. Monitor the level of consciousness at least every 6 hours. Patients should be turned in bed regularly to avoid bedsores.

## **4. Drug chart**

A drug chart where all drugs given are recorded should be kept and should include dose given, time given and number of times a day.

## **5. Pregnant women**

They should be monitored closely ensuring the wellbeing of the foetus and preventing the development of maternal hypoglycaemia. Watch out for signs of severe anaemia and pulmonary oedema.

## **Laboratory monitoring**

### **6. Monitor the parasitaemia**

Do blood smears daily. If high after 2-3 days, review adequacy of the medicine dosages.

### **7. Monitor blood glucose**

Do blood glucose level or maintain with dextrose containing infusion

### **8. Monitor Haemoglobin / haematocrit**

## **Assessment of recovery**

When the patient recovers, assess for possible residual problems of the disease or treatment.

- Assess the ability of the patient to do what he/she was able to do before the illness.
- Assess vision and hearing by asking whether they can see or hear; for children use objects or noisy rattles respectively.
- Organize for follow up of the patient.
- Management of residual disability might require a multi-disciplinary approach.

## **Pre-Referral Treatment**

The risk of death for severe malaria is greatest in the first 24 hours. To survive, a patient with severe illness must get access rapidly to a health facility where parenteral treatment and other supportive care can be given safely and as appropriate. The affected patient may die on the way to hospital or be admitted with advanced disease and complications. It is recommended that the patients be treated with one of the following recommended pre referral treatment.

The following options for pre-referral treatment are recommended:

### **Intramuscular pre- referral treatment**

- i. Artesunate 2.4mg/kg stat (see Annex 8)
- ii. Quinine dihydrochloride at a dosage of 10 mg/kg salt diluted to 60mg/ml intramuscularly at the anterolateral aspect of the thigh given at divided sites.

### Artesunate suppositories

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

**Adults:** One or more Artesunate Suppositories inserted in rectum as indicated in Table below. Dose should be given once and followed as soon as possible by definitive therapy for malaria.

### Intra-rectal pre-referral treatment

Intra-rectal artemether at the dose of 10-40mg/kg body weight and intra-rectal quinine at 12mg/kg body weight can also be used as alternative based on availability. These should be administered with a syringe without the needle

### Dosage regimen for Artesunate suppositories in children

Weight (kg)	Age	Artesunate	Dosage Regimen (Single Dose)
<10	<12months	50mg	One 50mg Suppository
10 – 19	1yr -5yr months	100 mg	One 100 mg Suppository
20 – 29	6 - <10years	200 mg	Two 100 mg Suppositories
30 – 39	10 - 13 years	300 mg	Three 100 mg Suppositories
> 40	> 13 years	400 mg	Four 100 mg Suppository

### Summary Box 3: Management of Severe Malaria

- Severe malaria is a medical emergency. Patient should be admitted for investigation and treatment.
- Artesunate 3mg/Kg (in children <20Kg) Or 2.4mg/kg (in older children or Adults) IV or IM given at time 0, 12 and 24 hours, then once daily until patient can tolerate oral medications is the recommended treatment.
- Artemether or Quinine are acceptable alternatives if parenteral artesunate is not available.
- Give parenteral antimalarial medicines in the treatment of severe malaria for a minimum of 24hours, once started (irrespective of the patient's ability to tolerate oral medications earlier) and thereafter complete treatment by giving a complete course of ACT.
- If confirmatory diagnosis is not immediately feasible, treatment should be commenced without delay while appropriate specimen should be obtained for subsequent laboratory analysis

## 8.0 CHEMOPREVENTION AND CHEMOPROPHYLAXIS

### 8.1 Intermittent Preventive Treatment

Pregnant women are at a higher risk of malaria than other adults. In high transmission areas, such as Nigeria, malaria may be asymptomatic during pregnancy. Intermittent Preventive Treatment (IPT) with *Sulfadoxine-Pyrimethamine* (SP) reduces malaria related complications during pregnancy.

The SP should be given as single adult dose of 3 tablets (each tablets contains 500 mg Sulphadoxine and 25 mg Pyrimethamine) at scheduled antenatal care visits. Three (3) or more doses given one month apart are currently recommended. First dose should be given after quickening (early second trimester or following the onset of the first foetal movement).

Pregnant women, who are HIV positive and are on *Co-trimoxazole* chemoprophylaxis, should not receive IPT with SP, due to the increased risk to the adverse effects of the *Sulphonamides*.

An additional preventive measure is to promote the use of Long Lasting Insecticide Nets (LLINs).

### 8.2 Malaria Chemoprophylaxis

Malaria chemoprophylaxis is not recommended for individuals living in areas of intense transmission, however, people with sickle cell anaemia and non-immune visitors are expected to be on regular chemoprophylaxis and these risk categories of patients should be targeted with other preventive interventions e.g. LLINs

#### 8.2.1 Non immune Visitors

The recommended chemoprophylaxis for non-immune visitors should be available in the visitor's country of origin. The following options are recommended for use in Nigeria; Mefloquine, and Atovaquone-Proguanil. Doses should be taken prior to arrival in Nigeria and continued during the stay and following departure from the country.

##### **Mefloquine**

Mefloquine given at a dose 5mg per kg weekly (approximately 250mg of base in an adult weekly) should be started 2-3 weeks prior to arrival, weekly in country and thereafter for two to three weeks after departure.

##### **Atovaquone-Proguanil**

Atovaquone-Proguanil is a fixed dose combination that is administered daily, commencing 1-2 days prior to arrival, then continuing throughout the stay and thereafter for 7 days after departure. Atovaquone-Proguanil given according to weight is given below:

Weight (kg)	Total Daily Dose	Dosage Regimen
11 – 20kg	62.5 mg/25 mg	1 Paediatric Tablet daily
21 – 30kg	125 mg/50 mg	2 Paediatric Tablets as a single daily dose
31 – 40kg	187.5 mg/75 mg	3 Paediatric Tablets as a single daily dose
>40kg	250 mg/100 mg	1 Tablet (adult strength) as a single daily dose

#### 8.2.2 Sickle Cell Anaemia



The current practice among health care practitioners in Nigeria has been to give proguanil to individuals with sickle cell anaemia and counsel them to sleep under LLIN. The evidence based on the clear benefits of proguanil has been equivocal. At present, no medicine is recommended for Sickle cell anaemia as chemoprophylaxis. Sickle cell anaemia individuals with suspicion of malaria should report to the facilities for prompt diagnosis and treatment.

### **8.3 Seasonal Malaria Chemoprevention**

Seasonal Malaria Chemoprevention (SMC) is defined as “the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest risk.”

“Seasonal Malaria Chemoprevention is recommended in areas of highly seasonal malaria transmission throughout the Sahel sub-region. A complete treatment course of sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) should be given to children aged 3–59 months at monthly intervals, beginning at the start of the transmission season, up to a maximum of four doses during the transmission season (provided both drugs retain sufficient antimalarial efficacy.”

The recommended dosing schedule by age is:

Age	Dosage
infants 3–11 months old	<ul style="list-style-type: none"><li>• half of a 150mg tablet of AQ base given once daily for 3 days</li><li>• and a single dose of half a 500/25mg tablet of SP</li></ul>
children 12–59 months	<ul style="list-style-type: none"><li>• a full tablet of 150mg AQ base given once daily for 3 days</li><li>• and a single dose of a full tablet of 500/25mg SP</li></ul>

The single dose of SP is given only on the first day, at the same time as the first dose of AQ.

The target areas for implementation are those in which:

- malaria transmission and the majority (> 60%) of clinical malaria cases occur during a short period of about 4 months; in Nigeria, the states where SMC is recommended are; Kebbi, Sokoto, Zamfara, Katsina, Kano, Jigawa, Bauchi, Yobe and Borno.
- the clinical attack rate of malaria is greater than 0.1 attack per transmission season in the target age group; and
- SP + AQ remains efficacious (> 90% efficacy).

#### *Contraindications*

SMC should not be given to:

- a child with an acute febrile illness or to severely ill children unable to take oral medication;
- an HIV-positive child receiving co-trimoxazole prophylaxis;
- a child who has received a dose of either SP or AQ during the past month; and
- a child who is allergic to either SP or AQ.

### **8.3.1 SMC Plus Package**

The prevalence of malnutrition in the sahelian region during the raining season has necessitated the inclusion of nutritional component to seasonal malaria chemoprevention where feasible. To this end, lipid based nutritional supplements could be given as part of the 4 – month treatment course for SMC. These complementary interventions have been found to reduce the burden of child mortality.

## **8.4 Integrated Community Case Management**

Integrated Community Case Management (iCCM) is the curative treatment to children at homes within communities for Malaria, pneumonia and diarrhoea and identification and referral of newborn requiring further medical attention. It is an equity-focused strategy to improve access to life-saving curative interventions for common childhood illness to children within communities where access to facility-based services is low.

### *Medicines for iCCM*

The medicines deployed for the implementation of iCCM include the following:

Dispersible Amoxicillin 125 mg tablets Artemether-lumefantrine; (20mg/120mg tablets), Artesunate-Amodiaquine (50/135mg) for uncomplicated malaria

Rectal Artesunate for pre-referral patients

Low osmolality ORS

Zinc 20mg tablets

Paracetamol tablets

The strategy is delivered as a package to the community and is jointly coordinated by the Family Health programme, Malaria and the National Primary Health Care Development Agency with collaboration with other ministries, line programmes and agencies.

## **9.0 ANTIMALARIAL DRUG RESISTANCE**

Antimalarial drug resistance is defined as the ability of a parasite strain to survive and/or multiply despite the proper administration and absorption of an antimalarial medicine in the dose normally recommended.

It has resulted in a global resurgence of malaria and it is a major threat to malaria control. Widespread and indiscriminate use of antimalarial drugs places a strong selective pressure on malaria parasites to evolve mechanisms of resistance. Prevention of antimalarial drug resistance is one of the main goals of these antimalarial treatment recommendations. Resistance can be prevented by combining antimalarial medicines with different mechanisms of action, and ensuring very high cure rates through full adherence to correct dose regimens.

### **9.1 Antimalarial drug resistance in Nigeria**

Appreciable resistance of *P. falciparum* has developed to monotherapeutic agents previously used in Nigeria, such as Chloroquine and Sulphadoxine-pyrimethamine. There is no evidence to support the emergence of resistance to Artemisinin derivatives in Nigeria.

The term treatment failure refers to failure to clear parasitaemia after administration of antimalarial treatment and/or failure of resolution of clinical symptoms.

Among causes of treatment failures are:

*National Guidelines for Diagnosis and Treatment of Malaria*

- Incorrect dosing
- Problems of treatment compliance
- Poor drug quality
- Interactions with other drugs
- Compromised drug absorption
- Mis-diagnosis of the patient
- Resistance

## **10.0 PHARMACOVIGILANCE**

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse drug reactions or any other drug related problems such as drug abuse and misuse, medication errors, lack of efficacy and counterfeits.

An Adverse Drug Reaction (ADR) is a response to a medicine which is noxious (harmful) and unintended, and occurs at doses normally used in man for prophylaxis (prevention), diagnosis or therapy (treatment) of disease or the modification of physiological function

The recent medicine mishap in Nigeria has increased the need to ensure the quality, safety and efficacy and the rational use of deployed medicines hence it is mandatory for all levels of care to be involved in Pharmacovigilance.

In all suspected cases of adverse drug reactions, the Pharmacovigilance form from NAFDAC should be completed at all levels of care. It is necessary to complete all section of the adverse drug reaction form.

Completed ADR forms should be sent to the following:

- The National Pharmacovigilance Centre (NPC) – NAFDAC
- Plot 2032 Olusegun Obasanjo Way, Wuse Zone 7, Abuja
- Through NAFDAC offices in the 36 states & FCT
- Reports can also be scanned & emailed to [npcadr@nafdac.gov.ng](mailto:npcadr@nafdac.gov.ng)  
By Telephone: 08086899571 or 07098211221

The NAFDAC has evolved a more specific and organized system where patients report directly to the National PV centre (NPC).

The current growing need in PV system in developing countries has gone beyond the usual way of reporting by healthcare providers and marketing authorization holders to a more specific and organized system where patients report directly to the National PV center (NPC). This has become necessary as a result of decentralization of medical care to trained volunteers in hard to reach communities who now administer treatments without strict supervision.

NAFDAC has now developed a system which avail consumers of antimalarials and other medicines the opportunity to directly report adverse drug reactions (ADR's) to PVC unit of NAFDAC through a text message to a short code to some mobile networks. This system of reporting is termed '**PHARMACOVIGILANCE RAPID ALERT SYSTEM FOR CONSUMER REPORTING**' (PRASCOR).

### **How the Short Code Service works**

Consumers who takes medicine and experiences an ADR/untoward effect/unexpected effect is encouraged to send text message to a prepaid short code; **20543** using one of the three major networks operating in the country; **MTN, Etisalat and Globacom**.

An auto-response is sent to the consumer (Sender).

Information to be sent includes the following:

- Suspected medicine
- Suspected ADRs
- Drug details:
  - Batch number
  - NAFDAC Registration number
  - Expiration number
  - Name and Address of Manufacturer

## 11.0 SUMMARY PHARMACOLOGY OF ANTIMALARIAL DRUGS

### Amodiaquine

Amodiaquine is a Mannich base 4 amino-quinoline that interferes with parasite haem detoxification. It is more effective than chloroquine in both chloroquine sensitive and resistant *P.falciparum* infections. However, there is cross-resistance between chloroquine and amodiaquine.

It is available as tablets containing 200mg of amodiaquine base as the hydrochloride and as 153.1 mg base as chlorohydrate. It is readily absorbed in the GIT and rapidly converted in the liver to the active metabolite, desethylamodiaquine. Desethylamodiaquine is responsible for all the antimalarial effect. Adverse effect of amodiaquine includes abdominal discomfort and vomiting weakness and when used for prophylaxis it causes agranulocytosis. Amodiaquine is recommended as a partner drug in artemisinin based combination therapy.

### Sulphadoxine-Pyrimethamine

Sulphadoxine is a slowly eliminated Sulfonamide. It is used in a fixed dose combination of 20 parts Sulphadoxine with 1 part Pyrimethamine given orally or intramuscularly. It is available as tablet containing 500mg Sulphadoxine and 25mg Pyrimethamine, and in ampoules containing similar concentration of the 2 components for intramuscular use.

The medicine is no longer recommended for the treatment of malaria in Nigeria. However, it has been proven to be effective for use for Intermittent Preventive Treatment during pregnancy.

Sulphadoxine is readily absorbed from the GIT. It is widely distributed in body tissues and fluids and crosses the placental into foetal circulation. It is also readily detectable in breast milk. It is excreted predominantly as the unchanged drug.

Adverse effect includes nausea vomiting and diarrhoea. Hypersensitivity reaction may occur as well as photosensitivity and a variety of dermatological adverse reaction. It may also cause a crystaluria and interstitial nephritis. Pyrimethamine is a di-amino pyrimidine that is also used in the treatment of toxoplasmosis and pneumocystic carini pneumonia. Like sulphadoxine, it is rapidly absorbed from the GIT. Prolonged administration may cause depression of haematopoiesis due to interference with folate metabolism.

### Quinine

It is an alkaloid derived from the bark of cinchona tree. It is an isomer of quinidine. Like other structurally related drugs, it is effective against matured trophozoites of *P.falciparum* and against matured sexual forms of *P.falciparum*, *vivax* and *malariae*. It is available as both tablets and injectable solutions. It is rapidly and almost absorbed from the GIT and also after IM in severe malaria. It is widely distributed throughout the body tissues, and fluids including CSF and, breast milk. Toxicity includes mild form of tinnitus, impaired high tuned hearing, headache, nausea, dizziness, vomiting, abdominal pain, diarrhoea and vertigo. Hypersensitivity reaction may also occur. Intravascular haemolysis that may progress to life threatening haemolytic uremic syndrome can also occur. Thrombocytopenia and haemolytic anaemia. Other adverse effect includes cardiac rhythm disturbances, hypotension and hypoglycaemia.

### Artemisinin and its derivatives

Artemisinin and its derivatives, artemether, dihydro-artemisinin, artesunate and artemotil are sesquiterpenelactones. These drugs are potent and rapidly acting blood schizonticides active against all plasmodium species. These medicines kill all stages of young rings to schizonts and young gametocytes.

Artemisinin itself is now less frequently used compared to its derivatives; dihydro-artemisinin, artemether, artesunate and artemotil. It is converted to dihydro-artemisinin.

Artesunate is a sodium salt of the hemisuccinate ester of artemisinin. It is soluble in water but has poor stability in aqueous solution at neutral or acidic pH. In the injectable form, artesunic acid is drawn up in sodium bicarbonate to form sodium artesunate immediately before injection. It is available as tablet, ampoules for IM or IV, rectal capsules, and as co-formulation with amodiaquine. It is rapidly absorbed after oral, rectal and IM administration and is almost entirely converted to dihydro-artemisinin, the active metabolite. It is rapidly eliminated from the body.

Artemether is methyl ether of dihydro-artemisinin. It is more lipid soluble than artemisinin or artesunate. It can be given as an oil based intramuscular injection or orally, and as co-formulation with lumefantrine. Absorption after oral administration is rapid. After IM administration, absorption is variable particularly after administration in children with poor peripheral perfusion. It is metabolized to dihydro-artemisinin, the active metabolite.

In general, artemisinin and its related derivatives are well tolerated. These drugs in general are less toxic than other currently available antimalarial medicines. Mild GIT disturbances, dizziness, elevated liver enzymes and minor ECG abnormalities and reticulo-cytopaenias have been reported after the use of these drugs. Potentially, serious adverse effects are related to Type I hypersensitivity reactions. Neurotoxicity has been reported in experimental animals and largely has not been found in humans. Currently, clinical resistance has not been reported to this class of antimalaria.

Lumefantrine is an aryl amino alcohol. It is structurally related to halofantrine. It is highly effective against *P.falciparum*. It is available as oral preparation as co-formulation with artemether. Following oral administration, bioavailability is variable but can be improved by co administration with fatty foods. Toxicity includes nausea, abdominal discomfort, headache and dizziness. It does not significantly prolong the ECG Q-T interval

## ANNEX 1:

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

Criterion	Characteristics of diagnostic test	Target cases and clinical setting	Recommended diagnostic tests	
			RDT <sup>e</sup>	Microscopy
Parasite density	RDTs give only a positive or a negative test result.  Microscopy can show parasite density.	Uncomplicated malaria	Yes	Yes
		Severe malaria on admission	Not alone <sup>a</sup>	Yes
		Follow-up of admitted patients <sup>b</sup>	No	Yes
Antigen persistence.	RDTs detect persisting antigens after parasite clearance <sup>c</sup> . Microscopy gives a negative result as soon as the parasite is cleared from patient's blood.	Confirmed malaria with persisting fever despite antimalarial treatment.	No	Yes
		Cases of suspected malaria not previously tested for malaria.	Yes	Yes
		Persisting fever in people who did not receive antimalarial treatment.	Yes	Yes
Time for test completion	RDTs can be performed relatively quickly.	Settings with low work-load per health worker, e.g small health facilities.	Yes	Yes
	Microscopy requires more time.	Settings with high work-load per health worker, e.g outpatient departments of hospitals.	Yes	Yes
Competence and training requirements.	RDTs are relatively easy to perform.	Health workers with limited training in laboratory procedures or settings with limited resources for supervision <sup>d</sup> .	Yes	No
	Microscopy is more complex and requires the competence of a trained microscopist <sup>d</sup> .	Settings in which specific training in microscopy can be given and a laboratory quality management system is functioning <sup>d</sup> .	No	Yes

<sup>a</sup> This diagnostic test should not be used exclusively, and the other test is necessary.

<sup>b</sup> Parasite density is required to monitor response to treatment.

<sup>c</sup> RDTs to detect pLDH may give positive results up to 5-6 days after disappearance of the parasites, while those to detect HRP-2 may give positive results up to 1-5 weeks after the disappearance of the parasite.

<sup>d</sup> Both diagnostic techniques require minimum specific training.

<sup>e</sup> Both diagnostic requires regular supervisory support.

Modified from the WHO Malaria Case Management Guidelines (2015).

## **ANNEX 2:**

### **BLOOD SMEARS FOR MICROSCOPY**

#### **Blood smears-preparation and staining**

Blood should be taken from a finger prick, when possible, with thick and thin film prepared on the same slide. Blood collected in anticoagulant causes morphological changes to the parasite if left for too long before examination. Anticoagulant also causes thick smears not to stick well onto the slide thus requiring a longer time to dry.

The specimen should be clearly labelled and be accompanied with correctly completed form (clinical request or field form). A thick film exposed to alcohol or placed in a hot oven to “quickly” dry the blood renders the film unreadable as the erythrocytes cannot de-haemoglobinize. If blood films in high temperature environments are not stained within a couple of days, the films will be autofixed.

Smears stored in humid and hot conditions facilitate the growth of fungus and bacteria. Similarly, dusty conditions cause the formation of deposits making the smear unreadable or the deposits might be confused for parasites leading to a false result. Smears, both stained and unstained must be protected from the voracious appetites of cockroaches, flies and ants and should where possible be stored in slide boxes.

The smears need to be well stained with Giemsa stain to facilitate the reading, (parasite staging, species identification and determination parasite counts. A stain can either be commercial or prepared in-house. It is imperative that each batch be checked by comparing batches of new staining solution with the old on the same group of thick and thin films. Appropriate documentation indicating source, batch number, date of preparation/manufacture and other information on the quality stain such as concentration and staining time and the result should be done. .

Dilution/buffer solutions should the pH controlled (pH, 7.2). Unfiltered stain and metallic scum of the staining solution leaves a precipitate on the thick film which are often confused with parasites. Therefore, stains should be filtered before use. The Giemsa working solution should be prepared daily for optimal staining reaction.

Maintenance of a microscope is very important and should be done regularly since our environment is dusty. It is an expensive piece of equipment that in poor condition cannot aid the microscopist to read the slide. Humid atmosphere can cause the growth of fungus especially on the lens. Other problems are the bad alignment of the microscope, immersion oil not wiped from the objective and condenser leaving a coating.

Frosted-end slides should be used in preparing the blood smear lancets, lancets should be sterile for single use. Recycled slides should not be used for malaria microscopy.

#### **Recommended procedure notes**

- Make a thick and a thin film on the same slide.
- Stain with Giemsa stain. (See box below for rapid staining method)
- Examine under a high power objective starting with thick and then thin film. The thick film is used to establish the presence of malaria parasites and parasite enumeration, while the thin film is for parasite speciation
- Report type of parasite(s) seen, developmental stage and parasite count as parasite/200 – 500 (or more) WBCs of parasite/ $\mu$ l blood
- Relevant standard operating procedure (SOPs) should be followed in all processes.



- Quantitative method of determining parasite density (in parasites/ul of blood) is recommended to follow-up the outcome of treatment.
- If blood slide is negative, it is recommended that further investigations for the cause of disease including repeating blood slide after 24 hours should be carried out. If the repeat slide is positive, treat accordingly.

### **Rapid Staining Method**

- 1. Fix the thin film by briefly dipping the film into methanol.*
- 2. Avoid contact between the thick film and methanol, as methanol and its vapours quickly fix the thick film, and make it not to stain well.*
- 3. Using a test tube or a small container to hold the prepared stain, make up a 10% solution of Giemsa in the buffered water by mixing three drops of Giemsa from the stock solution, using the Pasteur pipette, with 1 ml of buffered water. Each slide needs approximately 3 ml of stain to cover it.*
- 4. Depending on whether you are using a staining tray, plate or rack, place the slides to be stained face down on the curved staining tray or face upwards on the plate or rack until each slide is covered with stain, or gently pour the stain onto the slides lying face upwards on the plate or rack.*
- 5. Stain the films for 8–10 min. Prior validation of the stain should be done for each batch of prepared stain to determine appropriate staining time*
- 6. Gently wash the stain from the slide by adding drops of clean water. Do not pour the stain directly off the slides, or the metallic-green surface scum will stick to the film, ruining it for microscopy.*
- 7. When the stain has been washed away, place the slides in the drying rack, thin film side downwards, to drain and dry. Ensure that films do not scrape the edge of the rack.*

### **Malaria Parasite Density Determination**

This is a practical method of acceptable accuracy. The number of parasites per microlitre of blood in a thick film is counted in relation to a standard number of leukocytes (6000 per microlitre of blood). Although there are variations in the number of leukocytes between healthy individuals and even greater variations between individuals in ill health, this standard allows for reasonable comparisons. If possible, the absolute patient WBC count should be used.

#### *Step 1*

(a) In routine practice, using a x100 oil immersion objective and a 10x eyepiece, parasite quantitation is performed against 200 or 500 WBCs.

(b) If, after counting 200 WBC, 100 or more parasites are found, record the results in terms of number of parasites/number of WBC counted.

(c) If less than 100 parasites are found after counting 200 WBCs, parasite quantification should be continued until 500 WBCs are counted. All parasites in the final field are counted even if the count exceeds 500 WBCs.

*Step 2*

Parasite density can be determined using the true WBC where available. If unavailable, the common practice is to assume a WBC of 6000/ $\mu$ l of blood. In each case, the parasite density can be calculated using the formula:

$$\frac{\text{Number of parasite counted} \times 6,000}{\text{Number of leukocytes count}} = \text{parasites per microlitre (or absolute WBC)}$$

**Note:** It is normal practice to count the asexual parasites species present and to note and record the presence of sexual stages (gametocytes) seen. This is particularly important when monitoring the response to schizonticidal drugs, which would not be expected to have any effects on the gametocytes.

### **ANNEX 3:**

#### **MALARIA RAPID DIAGNOSTIC TESTS**

##### **Brief information on malaria RDTs**

- Detects antigen, not parasites
- Parasite load is not quantified
- RDTs could remain positive even after the patient has taken ACTs - RDTs to detect pLDH may give positive results up to 5-6 days after disappearance of the parasites, while those to detect HRP-2 may give positive results up to 1-5 weeks after the disappearance of the parasite.
- Occasionally, test could be negative in the presence of parasites
- RDTs degraded by excessive heat may not function properly
- Limited shelf life (18 – 24 months)
- RDTs could exist as combo test (having a combination of two antigens (e.g HRP-2 and pLDH))

**Accuracy is dependent on following the prescribed procedures.**

##### ***Appropriate Storage of RDTs***

- Determine a cool place in your facility for RDTs storage. Storage temperature should not go beyond 35°C
- Keep RDTs in a cool place where drugs are stored in the facility.
- Do not expose RDTs to direct sunlight
- Do not keep RDTs in a car parked in the sun (temperature may sometimes rise beyond what RDTs can tolerate)
- Open a pack only when you are ready to use them

##### **Just before and RDT is done**

- Be ready to use the results to inform treatment
- Check that the RDT has not expired
- Put on latex gloves
- Read the instructions in order to do it well

##### **Materials required before doing an RDT**

An RDT contains the following:

- alcohol swab
- sterile lancet
- a blood transfer device
- Buffer solution

The following items must also be available:

- Watch or clock to use as a timer
- Marker to write patients' data on RDT
- Sharp container(s)/safety boxes for used lancets & blood transfer device
- Waste bin for used alcohol swabs, cotton wool, gloves etc

### **Recommended Procedure notes**

Note: It is pertinent to follow specific instructions on various RDT types before use.

1. *Wear your latex gloves.*
2. *Open an RDT cassette and write the name of the patient and date.*
3. *Swab patient's fourth finger (the left hand of a right handed person) with methylated spirit and allow to dry (this will ensure that the patient's blood collects and not spread around the finger).*
4. *Take an unused lancet and prick the tip of the swabbed finger and discard lancet in the sharps quickly (do not re-cap the lancet).*
5. *Get the blood transfer device and collect the recommended volume of blood*
6. *Dispense the blood in the well (allow the transfer device to touch the pad in the blood well before releasing the content so that the blood collected is deposited fully – insufficient blood can give a false result).*
7. *Dispose blood transfer device immediately (do not leave on your table)*
8. *Put the recommended drops of buffer in the buffer well (ensure that the buffer container faces the well vertically, a little above the RDT cassette – do not allow buffer to spill on the side of the well)*
9. *Note the time immediately by writing the start time on the cassette. Also indicate the stop time by adding the recommended time for the test. For example, if you were to read the test result after 15 minutes, add 15 minutes to the start time to get the stop time.*
10. *Interpret the result at the recommended time and not after as this could give you a false result.*

**ANNEX 4:**

**QUALITY ASSURANCE FOR MALARIA DIAGNOSIS WITH MICROSCOPY**

The quality assurance (QA) of malaria diagnosis is a system designed to continuously and systematically improve the efficiency, cost-effectiveness, reliability and accuracy of test results. It is critical that QA ensures:

- the health workers have full confidence in the laboratory results
- the diagnostic results are of benefit to the patient and the community.

These demands can only be met through a commitment to QA that ensures that microscopic services are staffed by competent and motivated staff supported by both effective training and supervision and a logistics system that provides an adequate and continual supply of quality reagents and essential equipment which are maintained in working order.

The principles and concepts of QA for microscopic diagnosis of malaria are similar to those for microscopic diagnosis of other communicable diseases, such as other protozoan diseases, tuberculosis and helminth infections. This provides a potential for the integration of laboratory services where it is feasible and cost-effective.

Quality assurance on malaria microscopy and RDT should be supported and promoted to ensure that high quality of malaria diagnosis is provided at all levels. This will be done through regular training (using the standard national curriculum), competency assessment, and supervision of the microscopists.

Good procurement practices should also be promoted to ensure that the appropriate equipment and consumables are procured for malaria microscopy.

For the RDTs, in-country lot testing should be conducted upon arrival in the country to ensure that they conform to the manufacturer's standard at the manufacturing site (quality control check) and followed up with periodic quality-control testing at the facilities, medical stores or in the communities where they are used.

As in microscopy, on-the-job training and supervision should be strengthened to ensure that health workers correctly perform the RDTs and treatment decisions of suspected malaria patients are based on the test results.

**ANNEX 5**

**SUMMARY OF CHECK-LIST FOR INTERNAL QUALITY ASSURANCE FOR MALARIA MICROSCOPY**

Category	Check List Questions	Yes	No
<b>Laboratory Design</b>	There is sufficient working surface for each member of the laboratory staff.		
	The electric microscope(s) are not located directly in front of a window but face a blank wall.		
	The laboratory has access to a clean water supply.		
	There is hand washing facilities.		
	There is good ambient lighting at all times (including cloudy weather).		
	There is an adequate electrical supply for the microscope(s).		
	There is adequate storage space for reagents, equipment, and storage of slides.		
	There is a safe waste management system.		
	Laboratory chairs and/or stools are suitable for microscopy.		
<b>Quality of the Microscope</b>	The microscope(s) is binocular and electrically powered.		
	The microscope lamp(s) has sufficient power to provide good illumination at small aperture settings.		
	The light source can be centred.		
	The microscope(s) have Plan C x 100 objectives.		
	Blood smears are able to be brought into sharp focus x 100 oil immersion magnification.		
	The stage movement mechanism is precise and stable.		
<b>Microscope Slides</b>	Microscope slides are clean.		
	Microscope slides are not oily to the touch.		
	Microscope slides do not have scratches or surface aberrations.		
	Microscope slides do not give a blue background colouration (microscopically at x100) after staining.		
	Microscope slides do not have fungal contamination.		
	Slides are protected against fungal contamination (in high humidity settings).		
<b>Methanol</b>	Methanol is AR grade.		
	Methanol is supplied to the laboratory is in the original sealed container as supplied by the manufacturer, and is not repackaged by the supplier.		

Category	Check List Questions	Yes	No
	Methanol is not oily (test – place some methanol on the fingers, it should not be sticky).		
	There is no deformation or blistering of red blood cells in the thin blood film (this is caused by poor quality methanol).		
	The methanol used for slide fixing is stored in moisture-proof containers.		
<b>Giemsa Stain</b>	Only stain prepared from high quality Giemsa powder is used.		
	Commercial Giemsa stain is supplied to the laboratory in the original sealed.		
	The stain is within the manufacturer’s expiry date.		
	The laboratory has a Stain QC Register recording the batch number and expiry date of supplies received the QC results on each batch (staining time, staining quality, and optimal pH of use) and any problems encountered.		
	Stock stain is stored in a dark glass bottle tightly sealed.		
	Stock stain is not stored in direct sunlight or near a heat source.		
	The stock stain used by the laboratory was prepared less than two years ago.		
	Stained blood films do not contain stain precipitate.		
<b>Diluted Giemsa stain</b>	Stock stain is always diluted in buffer to the correct pH.		
	The diluted stain contains no stain precipitate.		
	The surface of the diluted stain does not have an oily appearance. For horizontal slide staining (using a staining rack) this is best observed after the stain has been added to the slides. This effect can be caused by poor quality methanol used to prepare Giemsa stain from powder.		
	Diluted stain is always discarded within 15 minutes of preparation.		
<b>Thick blood films</b>	>95% of thick films have the correct thickness. It should be just possible to read newsprint through the thick film while it is still wet.		
	There is flaking in the centre of the smear (a hole in the centre of the thick film) in <2% of the thick films.		
	100% of the thick films are correctly stained.		
	None of the thick films contain stain precipitate contamination.		
	There a protocol for the preparation of thick films of the correct thickness from patients with severe anaemia.		
	Slide warmers may be used with caution in high humidity settings.		

Category	Check List Questions	Yes	No
<b>Thin blood Films</b>	>95% of the thin films have a smooth semi-circular tail.		
	In >95% of the thin films the red cells are just touching and not overlapping in approximately 20%–30% of the film (the reading area).		
	No thin films have water damage (retractile artefacts inside the red cells).		
	Thin films are fixed immediately after drying.		
<b>Staining</b>	The laboratory has a pH meter that reads to 2 decimal places.		
	The pH meter is calibrated with calibration buffers according to manufacturer’s directions.		
	pH adjusted buffer always used to prepare diluted Giemsa.		
	The pH of the buffer is calibrated for each batch of Giemsa.		
	Slides are always washed in water of the same pH as the buffer used for Giemsa dilution.		
	The diluted Giemsa is always prepared in a clean measuring cylinder.		
	There is an absolute rule that the diluted Giemsa stain is discarded in <15 minutes after preparation.		
	The trophozoite chromatin stains red to “rusty red”.		
	The trophozoite cytoplasm stains blue to strong blue.		
	The thick film background is stained light pink to grey.		
	The red cells in the thin film are stained pink.		
	The nuclear lobes of the polymorphs are stained significantly darker than the cytoplasm.		
	Slides are always washed from the thin film end.		
	All slides are washed gently by a technique that “floats” the stain off with minimal without disturbing the thick film.		
Laboratory staff who perform staining have protective clothing to protect their personal clothing.			
<b>Counting</b>	The laboratory reports the actual number of trophozoites when required against 500 (200) WBC.		
<b>Slide Reading Times</b>	All laboratory staff who report malaria examination results read a minimum of 10 thick blood films each month.		
	Laboratory staff always read a minimum of 100 fields before reporting a film as negative.		



Category	Check List Questions	Yes	No
	There is no pressure on microscopists to read slides more quickly than the standard reading time (such as end of day, “urgent cases”).		
	Is there a laboratory protocol that ensures that microscopists do not continuously read malaria slides for more than 3 hours without a 30 minute break?		
<b>Species identification</b>	Thin films are available for species identification where a mixed infection is suspected or species identification is unclear on the thick film.		

## **ANNEX 6**

### **QUALITY CONTROL IN LABORATORY DIAGNOSIS OF MALARIA**

The main focus of QC is on reproducibility (precision) of results. The programme is used within the laboratory for checking its own performance. Quality control (QC) is the responsibility of the laboratory chief but all laboratory personnel must be involved.

Standard operating procedures (SOPs) need to be developed, depending on the type of analyses carried out at each level of the health services so that tests can be performed in an acceptable standard way. The SOPs should state clearly the minimum QC for each method or test. By standardizing test procedures, it allows easier clinical and epidemiological interpretation of the results. Troubleshooting guides for equipment, reagents and methods would be useful additions to the more isolate laboratories where “instant” help is not available.

With such a multitude of steps involved in processing of a specimen, errors can occur at any stage. Laboratory management needs to be aware where errors can happen to reduce the possibility of their occurrence. Therefore, all stages from the preparation through to the examination must be monitored. Below quality controls issues will focus on microscopy and rapid tests. The general points are equally pertinent for all techniques.

#### **Slide cross-checking**

Cross- checking in malaria diagnosis is part of supervision activities and involves the re examination of a proportion of positive and negatives slides from each laboratory. Cross checking of slides provides the supervisor with information about the accuracy of the examination by scientist and criteria for improvement if required. An idea about the quality of the preparation can also be ascertained.

**ANNEX 7:**


<b>DOSES, VIALS, AND VOLUME FOR INTRAVENOUS ARTESUNATE DOSE USING 60MG VIALS</b>					
				<b>Vial dose</b>	60 mg
				<b>ml of 5% Na Bicarbonate required for reconstitution</b>	1 ml
				<b>ml of normal saline required for dilution for IV injection</b>	5 ml
				<b>Total volume after reconstitution and dilution</b>	<b>6 ml</b>
<b>Weight in Kg</b>	<b>Dose in mg (3.0 mg/kg) rounded up to next whole number for &lt; 20kg</b>	<b>Number of 60 mg vials needed</b>	<b>ml required from each vial for 10 mg/ml concentration</b>	<b>Total ml per IV dose</b>	
< 5 kg	15mg	1	1.5ml	1.5 ml	
5 to 7 kg	20 mg	1	2 ml	2 ml	
8 to 10 kg	30 mg	1	3 ml	3 ml	
11 to 13kg	40 mg	1	4 ml	4 ml	
14 to 17kg	50 mg	1	5 ml	5 ml	
18 to 20kg	60 mg	1	6 ml	6 ml	
<b>Weight in Kg</b>	<b>Dose in mg (2.4 mg/kg) rounded up to next whole number for &lt; 20kg</b>	<b>Number of 60 mg vials needed</b>	<b>ml required from each vial for 10 mg/ml concentration</b>	<b>Total ml per IV dose</b>	
21 to 25	60 mg	1	6 ml	6 ml	
26 to 29	70 mg	2	6ml + 1ml	7ml	
30 to 33	80 mg	2	6ml + 2ml	8 ml	
34 to 37	90 mg	2	6ml + 3ml	9 ml	
38 to 41	100 mg	2	6ml + 4ml	10 ml	
42 to 45	110 mg	2	6ml + 5ml	11 ml	
46 to 50	120 mg	2	6ml + 6ml	12 ml	
51 to 54	130 mg	3	6ml +6ml + 1ml	13 ml	
55 to 58	140 mg	3	6ml +6ml+2ml	14 ml	
59 to 62	150 mg	3	6ml +6ml +3ml	15 ml	
63 to 66	160 mg	3	6ml +6ml + 4ml	16 ml	
67 to 70	170 mg	3	6ml +6ml +5ml	17 ml	
71 to 75	180 mg	3	6ml+ 6ml +6ml	18 ml	
76 to 79	190 mg	4	6ml+ 6ml +6ml+1ml	19 ml	
80 to 83	200 mg	4	6ml+ 6ml +6ml+2ml	20 ml	
84 to 87	210 mg	4	6ml+ 6ml +6ml+3ml	21 ml	
88 to 91	220 mg	4	6ml+ 6ml +6ml+4ml	22 ml	
92 to 95	230 mg	4	6ml+ 6ml +6ml+5ml	23 ml	
96 to 100	240 mg	4	6ml+ 6ml +6ml+6ml	24 ml	

**ANNEX 8:**

<b>DOSES, VIALS, AND VOLUME FOR INTRAMUSCULAR ARTESUNATE DOSE USING 60MG VIALS</b>					
				<b>Vial dose</b>	60 mg
				<b>ml of 5% Na Bicarbonate required for reconstitution</b>	1 ml
				<b>ml of normal saline required for dilution for IM injection</b>	2 ml
				<b>Total volume after reconstitution and dilution</b>	<b>3 ml</b>
<b>Weight in Kg</b>	<b>Dose in mg (3.0 mg/kg) rounded up to next whole number for &lt; 20kg</b>	<b>Number of 60 mg vials needed</b>	<b>ml required from each vial for 20 mg/ml concentration</b>	<b>Total ml per IM dose</b>	
< 5 kg	15mg	1	1 ml	1 ml	
5 to 7 kg	20 mg	1	1 ml	1 ml	
8 to 10 kg	30 mg	1	1.5 ml	1.5 ml	
11 to 13kg	40 mg	1	2 ml	2 ml	
14 to 17kg	50 mg	1	2.5 ml	2.5 ml	
18 to 20kg	60 mg	1	3 ml	3 ml	
<b>Weight in Kg</b>	<b>Dose in mg (2.4 mg/kg) rounded up to next whole number for &lt; 20kg</b>	<b>Number of 60 mg vials needed</b>	<b>ml required from each vial for 20 mg/ml concentration</b>	<b>Total ml per IM dose</b>	
21 to 25	60 mg	1	3 ml	3 ml	
26 to 29	70 mg	2	3ml + 1ml	4 ml	
30 to 33	80 mg	2	3ml + 1ml	4 ml	
34 to 37	90 mg	2	3ml + 2ml	5 ml	
38 to 41	100 mg	2	3ml + 2ml	5 ml	
42 to 45	110 mg	2	3ml + 3ml	6 ml	
46 to 50	120 mg	2	3ml + 3ml	6 ml	
51 to 54	130 mg	3	3ml + 3ml + 1ml	7 ml	
55 to 58	140 mg	3	3ml + 3ml + 1ml	7 ml	
59 to 62	150 mg	3	3ml + 3ml + 2ml	8 ml	
63 to 66	160 mg	3	3ml + 3ml + 2ml	8 ml	
67 to 70	170 mg	3	3ml + 3ml + 3ml	9 ml	
71 to 75	180 mg	3	3ml + 3ml + 3ml	9 ml	
76 to 79	190 mg	4	3ml+3ml+3ml+1ml	10 ml	
80 to 83	200 mg	4	3ml+3ml+3ml+1ml	10 ml	
84 to 87	210 mg	4	3ml+3ml+3ml+2ml	11 ml	
88 to 91	220 mg	4	3ml+3ml+3ml+2ml	11 ml	
92 to 95	230 mg	4	3ml+3ml+3ml+3ml	12 ml	
96 to 100	240 mg	4	3ml+3ml+3ml+3ml	12 ml	

**ANNEX 9: Pharmacovigilance form**

**NATIONAL PHARMACOVIGILANCE CENTRE (NPC) NIGERIA**

<p>National Agency for Food and Drug Administration &amp; Control (NAFDAC), Headquarters Office Plot 2032 Olusegun Obasanjo Way Wuse Zone 7 Abuja</p>  <p><b>FORM FOR REPORTING OF SUSPECTED ADVERSE DRUG REACTIONS</b></p> <p><i>IN STRICT CONFIDENCE</i></p> <p>Tel: 08086899571 or Fax: 09-5241108</p>					
<b>1. * PATIENT'S DETAILS</b>					
Full Name or Initials: _____ Patient Record No: _____ AGE/DATE OF BIRTH: _____ SEX: M <input type="checkbox"/> F <input type="checkbox"/> WEIGHT (kg): _____ HOSPITAL/Treatment Centre: _____					
<b>2. * ADVERSE DRUG REACTION (ADR)</b>					
<p><b>A. DESCRIPTION</b></p>   <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">DATE Reaction Started</td> <td style="width: 50%;">DATE Reaction Stopped</td> </tr> <tr> <td> </td> <td> </td> </tr> </table>	DATE Reaction Started	DATE Reaction Stopped			<p><b>C. OUTCOME OF REACTION</b> TICK AS APPROPRIATE</p> <p><input type="checkbox"/> Recovered fully      <input type="checkbox"/> Recovered with disability (Specify) _____</p> <p><input type="checkbox"/> Congenital Abnormality (Specify) _____      <input type="checkbox"/> Life Threatening (Specify) _____</p> <p><input type="checkbox"/> Death      <input type="checkbox"/> Others (specify) _____</p>
DATE Reaction Started	DATE Reaction Stopped				
<p><b>B. Was Patient Admitted Due to ADR</b>      Yes <input type="checkbox"/>      No <input type="checkbox"/></p> <p>If Already Hospitalized, Was it Prolonged Due to ADR      Yes <input type="checkbox"/>      No <input type="checkbox"/></p> <p>Duration of Admission (days) _____</p> <p>Treatment of Reaction: _____</p>					
<b>3. * SUSPECTED DRUG (Including Biologicals Traditional/Herbal Medicines &amp; Cosmetics)</b>					
<p><b>A. DRUG DETAILS</b> (State name and other details if available / Attach product label / Sample (if available))</p> Brand Name: _____ Generic Name: _____ Batch No: _____ NAFDAC No: _____ Expiry Date: _____ Name & Address of Manufacturer: _____					
<b>B. Indications for Use</b>	<b>Dosage</b>	<b>Route of Administration</b>	<b>Date Started</b>	<b>Date Stopped</b>	
<b>4. * CONCOMITANT MEDICINES</b> (All medicines taken within the last 3months including herbal and self medication)					
<b>Brand or Generic Name</b>	<b>Dosage</b>	<b>Route</b>	<b>Date Started</b>	<b>Date Stopped</b>	<b>Reason for Use</b>
<b>5. * SOURCE OF REPORT:</b>					
Name of Reporter: _____ Address: _____ Profession: _____ Signature: _____ Tel No/E-mail: _____					
<b>*: MANDATORY FIELDS</b>					

## **SELECTED FURTHER READING**

1. The WHO Guidelines and Manuals and other materials from which the recommendations in this National Guidelines for Diagnosis and Treatment of Malaria were derived are:
2. Guidelines for the treatment of malaria, 2<sup>nd</sup> Ed. Geneva World Health Organization, 2010, <http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html>.
3. Management of severe malaria: a practical handbook 3<sup>rd</sup> Edition. World Health Organization (WHO) 2010\*
4. Assessment and Monitoring of Antimalarials Drugs Efficacy for the Treatment of Uncomplicated Falciparum Malaria: World Health Organization (WHO) 2003
5. The use of Malaria Rapid Diagnostic Tests, World Health Organisation 2004
6. Stephen Oguiche, Henrietta U. Okafor, Ismaila Watila, Martin Meremikwu, Philip Agomo, William Ogala, Chimere Agomo, Godwin Ntadom, Olajide Banjo, Titilope Okuboyejo, Gboye Ogunrinde, Friday Odey, Olugbemiga Aina, Tolulope Sofola, and Akintunde Sowunmi Efficacy of Artemisinin-Based Combination Treatments of Uncomplicated Falciparum Malaria in Under-Five-Year-Old Nigerian Children. *Am. J. Trop. Med. Hyg.*, 91(5), 2014, pp. 925–935.\*
7. Malaria Consortium: Treatment of Severe Malaria with Injectable Artesunate, Trainers Guide for National Trainers.

**EDITORIAL TEAM**

Dr Bolatito Aiyenigba	FHI360/Malaria Action Programme for States
Dr David Shekarau	National Malaria Elimination Programme, Abuja
Dr Evelyn Kabakwu	Consultant, Malaria Community Case Management
Dr Godwin Ntadom	National Malaria Elimination Programme, Abuja
Dr Jamilu Ibrahim Nikau	National Malaria Elimination Programme, Abuja
Dr John Collins	Department of Paediatrics, University of Jos
Dr John Kpamor	Malaria Consortium
Dr Nnamdi Nwaneri	National Malaria Elimination Programme, Abuja
Dr Nnenna Ogbulafor	National Malaria Elimination Programme, Abuja
Dr Olufemi Ajumobi	National Malaria Elimination Programme, Abuja
Dr Oluseye Babatunde	World Health Organization, Nigeria
Dr Peter Olumese	World Health Organization, Geneva
Dr Ruth Aisabokhae	Clinton Health Access Initiative
Dr Yetunde Oke	Malaria Action Programme for States
Pharm Ewomazino Ogedegbe	Association of Reproductive and Family Health
Pharm Ngozi Etolue	National Malaria Elimination Programme, Abuja
Professor Akintunde Sowunmi	University College Hospital, Ibadan
Professor Francis Useh	University of Calabar
Professor Martin Meremikwu	University of Calabar
Professor Olugbenga Mokuolu	University of Ilorin
Professor Stephen Oguche	University of Jos
Professor Uche Henrietta Okafor	University of Nigeria
Professor Wellington Oyibo	Lagos University Teaching Hospital, Idi Araba, Lagos
Professor William Ogala	Ahmadu Bello University, Zaria