United Republic of Tanzania

Ministry of Health and Social Welfare

National Guidelines for Diagnosis and Treatment of Malaria

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Foreword

These National Guidelines for Malaria Diagnosis and Treatment serve as a reference to diverse health profession cadres in all levels of health care delivery in Tanzania. They provide a framework for development of different field manuals for malaria diagnosis and treatment and related pharmaceutical supplies protocols.

The broad objective of these guidelines is to provide standard management reference for the care of patients with malaria at different levels of health care in both the public and private sector.

Since the publication of the previous “National Guidelines for Malaria Diagnosis and Treatment 2006” much progress has been made in the treatment of uncomplicated malaria, notably, increased access in public health facilities to confirmation of diagnosis of malaria using Rapid Diagnostic Test , the ban on oral monotherapy antimalarials, in particular oral Artemisinin monotherapy, and clear evidence of benefits of Artesunate injection in the treatment of severe malaria in reducing malaria mortality compared to quinine injection. The new guidelines also provide a revised schedule for administration of Intermittent Preventive Treatment in Pregnancy in line to WHO policy. In general these guidelines provide updated, practical approaches to aspects of diagnosis and treatment of malaria based on sound evidence.

Artemether-Lumefantrine will continue to be the first line treatment for uncomplicated malaria, as its efficacy remains within acceptable limits. This medicine is indicated for all age groups, with the exception of pregnant women in the first trimester with uncomplicated malaria, who should be treated with quinine. Injectable Artesunate is the medication of choice for treatment of severe malaria. Sulfadoxine-Pyrimethamine remains the medicine of choice for Intermittent Preventive Treatment of malaria in pregnancy but with an increased frequency of administration. The aim of Intermittent Preventive Treatment is to prevent the worst effects of malaria infection in pregnancy rather than to ensure clinical cure.

It is expected that with effective nation-wide coverage of effective vector control interventions such as the use of long lasting insecticide treated nets, larval source management and indoor residual spraying, complemented by large-scale deployment of artemisinin based combination treatment, malaria transmission can be greatly reduced.

This would be followed in time by a corresponding change in the clinical epidemiological profile and a risk of epidemics, if control measures are not sustained.

The Ministry would like to thank all those who participated in the preparations of these guidelines.

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List of abbreviations

ACT	Artemisinin based Combination therapy
ADDO	Accredited Drug Dispensing Outlet
ADR	Adverse Drug Reaction
AIDS	Acquired Immunodeficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (Alanine transaminase)
ALu	Artemether-Lumefantrine
AMFm	Affordable Medicine Facility for malaria
ANC	Ante Natal Clinic
AO	Acridine Orange
AQUAMAT	African Quinine vs. Artesunate Malaria Trial
ARV	Antiretroviral
AST	Aspartate aminotransferase
BS	Blood Slide
CHMTs	Council Health Management Teams
CHW	Community Health Workers
CPT	Co-trimoxazole Preventive Therapy
CSF	Cerebro-spinal Fluid
DIC	Disseminated intravascular coagulation
DLDB	*Duka la Dawa Baridi* (Drug Shop)
DOT	Direct Observed Treatment
DPQ	Dihydroartemisinin-Piperaquine
EIR	Entomological Inoculation Rate
FEFO	First Expiry, First Out
FeFo	Ferrous Sulphate Folic Acid
Hb	Haemoglobin
HF	Health Facility
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
HRP2	Histidine-rich Protein-2
HW	Health Workers
ICCM	Integrated Community Case Management
IDSR	Integrated Disease Surveillance and Response
IHI	Ifakara Health Institute
IM	Intra muscular
IMCI	Integrated Management of Childhood Illness
IPC	Interpersonal communication
IPD	In Patient Department
IPTp	Intermittent Preventive Treatment of Pregnant Women
IRS	Indoor Residual House-spraying
IV	Intravenous
LLINs	Long Lasting Insecticide treated Nets
M&E	Monitoring and Evaluation
MFT	Mass Fever Treatment
MMAM	*Mpango wa Maendeleo ya Afya ya Msingi* (Primary Health Services Development Programme)
MMTSP	Malaria Medium Term Strategic Plan
MoF	Ministry of Finance
MoHSW	Ministry of Health and Social Welfare
mRDTs	malaria Rapid Diagnostic Tests
MSaT	Mass Screening and Treatment
MSD	Medical Stores Department
MTCT	Mother To Child Transmission
MTPR	Malaria Test Positivity Rate

MTR	Malaria Test Rate
NHLQATC	National Health Laboratory and Quality Assurance Training Centre
NMCP	National Malaria Control Programme
OPD	Out Patient Department
ORS	Oral Rehydration Salts
ORT	Oral Rehydration Therapy
PHLB	Private Health Laboratory Board
pLDH	Plasmodium Lactate Dehydrogenase
PR	Pulse Rate
QA	Quality Assurance
QAACT	Quality Assured ACT
QARDT	Quality Assured RDT
RCH	Reproductive and Child Health
RDT	Rapid Diagnostic Test
RR	Respiratory Rate
SCD	Sickle cell disease
SME	Surveillance, Monitoring and Evaluation
SOP	Standard Operating Procedures
SP	Sulfadoxine-Pyrimethamine
Swiss TPH	Swiss Tropical and Public Health Institute
TDHS	Tanzania Demographic and Health Survey
TFDA	Tanzania Food and Drug Authority
THMIS	Tanzania HIV/AIDs and Malaria Indicator Survey
UNICEF	United Nations Children's Fund
USAID	United States of America International Development Agency
VC	Vectorial Capacity
WHO	World Health Organization

Definition of selected terms

Anaemia: Reduction of red blood cells or haemoglobin (Hb) concentration or both below the normal range for the age and sex of the individual.

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

Cerebral malaria: Severe P. falciparum 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.

Chemoprophylaxis: This is the regular use of antimalarial drugs to prevent development of malaria parasites following any possible inoculation.

Clinical/probable (not tested) malaria case: These are suspected malaria cases that did not receive a diagnostic test for malaria but were nevertheless treated as malaria. The terms "clinical" and "probable" are interchangeable and widely used in the past.

Combination therapy: Refers to the use of two or more antimalarial drugs with independent mode of action and different biochemical targets in the parasite, which are synergistic or additive, or complementary in their effect.

Confirmed malaria (malaria test positive): Suspected malaria case in whom malaria parasites have been demonstrated by microscopy or a rapid diagnostic test. The definition implies that the case displayed symptoms of malaria as well as the presence of parasites. Note that for some suspected cases with a positive test, particularly in populations that have acquired immunity to malaria, the febrile illness may in fact be due to other causes. Nevertheless, a diagnosis of confirmed malaria is still given. If a concurrent disease is suspected, it should be further investigated and treated.

Confirmed not malaria (malaria test negative): Suspected malaria cases for whom a malaria diagnostic test was negative. These would normally be given a diagnosis other than malaria. It is possible that some patients that test negative by microscopy or RDT can have very low levels of parasitaemia that are only detectable by more sensitive techniques such as polymerase chain reaction (PCR)[1] testing. Such low levels of parasitaemia are not thought to be clinically significant although they may contribute to transmission in low transmission settings.

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

Drug resistance: In malaria this is defined as the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended, but within the limit of 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 and blood cells.

Hypnozoites: Persistent liver stages of P. vivax and P. ovale malaria that remain dormant in host hepatocytes for an interval (most often 3-45 weeks) before maturing to hepatic schizonts. These

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[1] Polymerase chain reaction or PCR is a very sensitive test that can detect very small amounts of genetic material from parasites.

then burst and release merozoites, which infect red blood cells. Hypnozoites are the source of relapses.

Malaria epidemic. Occurrence of new cases of malaria clearly exceeding the number expected at that particular time and place.

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

Pharmacovigilance: This is a set of activities related to the detection, assessment, understanding and prevention of adverse drug reaction. The noxious (harmful) and unintended response to a medicine administered at therapeutic doses is known as **Adverse Drug Reaction (ADR)**

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.

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

Radical cure: In *P.vivax* and *P.ovale* infections only, this comprises a cure as defined above plus prevention of relapses by killing hypnozoites.

Rapid Diagnostic Test: A qualitative technique which specifically detects antigens produced by malaria parasites. They are developed as a stick, cassette or card test in which coloured line indicates that plasmodial antigens have been detected.

Severe malaria: In a patient with *P.falciparum* asexual parasitaemia and no other obvious cause of symptoms, the presence of one or more of the following clinical features classifies the patient as suffering from severe malaria; Behavioural Changes, prostration/extreme weakness, coma, Respiratory distress, convulsions, vomiting everything, inability to drink or breast feed, circulatory collapse/shock, pulmonary oedema, bleeding tendency/DIC, jaundice, acute renal failure, and haemoglobinuria.

Suspected malaria case: All patients presenting with signs and symptoms suggesting malaria. The criteria for recognizing suspected malaria is fever or history of fever.

Transmission intensity: The intensity of malaria transmission is measured by the frequency with which people living in an area are bitten by anopheline mosquitoes carrying sporozoites. This is expressed as the **Entomological Inoculation Rate (EIR)**. The EIR therefore is the number of infectious mosquito bites received per person per unit time.

Treatment failure: A failure to clear malaria parasitaemia and/or resolve clinical symptoms despite the administration of an antimalarial.

Uncomplicated malaria: Infection with malaria parasitaemia with non-specific symptoms including; headache, fatigue, abdominal discomfort, muscle and joint aches, usually followed by fever, chills, perspiration, anorexia and vomiting.

Vectorial capacity: The expression of the efficiency of the mosquito vector and the magnitude of the infective parasite pool in humans. This is important as the interventions which are used to reduce the mosquito's daily survival rate will also affect the vectorial capacity.

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1 Introduction: The National Guidelines for Diagnosis and Treatment of Malaria in the Context of the Tanzania Malaria Control Strategy

Malaria is a disease caused by the protozoan parasite of the genus *Plasmodium* and is transmitted by the bite of an infected female anopheline mosquito. There are four *Plasmodium* species that can infect humans; *P. falciparum, P. vivax, P. ovale, and P. malariae.*

P. falciparum is the most virulent species and can be fatal. The case fatality rate of severe falciparum malaria can reach up to 10% even in well-equipped hospitals. *P. vivax* malaria on the other hand is an acute but not life-threatening illness and is associated with anaemia and splenomegaly. Furthermore *P. vivax* and *P. ovale* can stay dormant in the liver as hypnozoites for up to several months or even years after inoculation by the anopheline mosquito.

Plasmodium falciparum is the most common species and predominates across sub-Saharan Africa. *P. vivax* predominates in the subtropics and coexists with *P. falciparum* in Asia, the tropical Americas and the Horn of Africa. *P. ovale* is found in Africa and sporadically in South-East Asia and the western Pacific. *P. malariae* has a similar geographical distribution to *P. falciparum* but its incidence is patchy.[1]

1.1 The epidemiology of malaria

The transmission of the diseases is influenced by a number of factors:

- Distribution of the mosquito vector species
- Vectorial capacity of the mosquito vector species
- Temperature and humidity
- Patients' immunity status
- Intensity of the infection – infecting *Plasmodium* species
- Presence of other co-morbidities e.g. Malnutrition, HIV/AIDS

The vectorial capacity (VC) is the expression of the efficiency of the mosquito vector and the magnitude of the infective parasite pool in humans. This is important as the interventions which are used to reduce the mosquito's daily survival rate will also affect the vectorial capacity. Another important factor in the epidemiology of the diseases is the Entomological Inoculation Rate (EIR). This is the number of infectious mosquito bites received per person per unit time.[2]

In situations where the EIR <10 per year malaria transmission is unstable and is considered to be low-to-moderate in intensity.

In situations where rates of EIR are > 10 per year, malaria transmission is high and stable.

Malaria endemicity can be sub-divided into four different levels (*table 1*):

Table 1: Classification of malaria endemicity levels

Criterion	Hypoendemic	Mesoendemic	Hyperendemic	Holoendemic
Spleen rate 2 – 9 years	0 – 10%	11 – 50%	50%+	75%+
Parasite Prevalence	0 – 10%	11 – 50%	50%+	75%+
Stability	Unstable	Unstable	Stable	Stable
Types of Epidemic	True	Seasonal		
Entomological Inoculation Rate	<0.25	0.25 - 10	11 – 140	>140

Source: Systems for the early detection of Malaria Epidemics in Africa, WHO, 2006

Holoendemic

This signifies an area where transmission occurs all year long. Malaria is stable with severity of the disease occurring in children under the age of five; Parasite prevalence in 2-9 years is >75%. Mortality is highest in the first and second year of life. The population is continuously exposed to a constant, high rate of malarial inoculations and acquires partial immunity to clinical disease. A large proportion of sub-Saharan Africa falls under this classification.

Hyperendemic

Areas where there is intense year round transmission, with periods of no transmission during the dry season; these areas are referred to as **stable transmission**. Parts of sub-Saharan Africa fall under this classification. Transmission peaks during the long rainy season, and occurrence of severe disease spikes in children under the age of five. Parasite prevalence in 2-9 year olds is >50%.

Mesoendemic

Areas with regular but seasonal transmission; referred to as **unstable malaria transmission**. Cerebral malaria is common in children and pregnant women; infection is tolerated well in adults. Transmission is seasonal under normal rainfall conditions; in times of drought, transmission intensity declines. Parasite prevalence in 2-9 year olds is between 11-50%.

Hypoendemic

Areas where transmission is intermittent and very low. Vector species are difficult to find and parasite prevalence in 2-9 year olds is between 0-10%.

Current proven malaria control interventions lead to the reduction in the basic reproduction rate of malaria parasites by reducing human infectivity due to prompt, effective treatment of patients, and by reducing the vectorial capacity through mosquito control measures.

These interventions include; Indoor Residual House-spraying (IRS) which reduces the daily survival of the mosquito, Long Lasting Insecticide Nets (LLINs) which reduce the human biting rate of the mosquito and to a lesser extent the daily survival rate, while Artemisinin

based Combination therapies (ACTs) reduce the parasite reservoir. ACTs are also gametocidal and can therefore reduce transmission if coverage is sufficiently wide.[3]

1.2 The epidemiology of malaria in Tanzania

Climatic conditions are favourable for transmission almost throughout the entire country. Mainland Tanzania is conventionally classified as having stable perennial to stable seasonal malaria in over 80% of the country. The remaining 20% of the country has highly seasonal and unstable malaria transmission and is considered prone to malaria epidemics. The southern and central part of the country has a single main rainy season (November-May) while east, north and north-west Tanzania experiences bimodal rainfall (October-December and March-May). Transmission peaks occur at the end of each rainy season.

The country has five main malaria epidemiological strata (table 2).

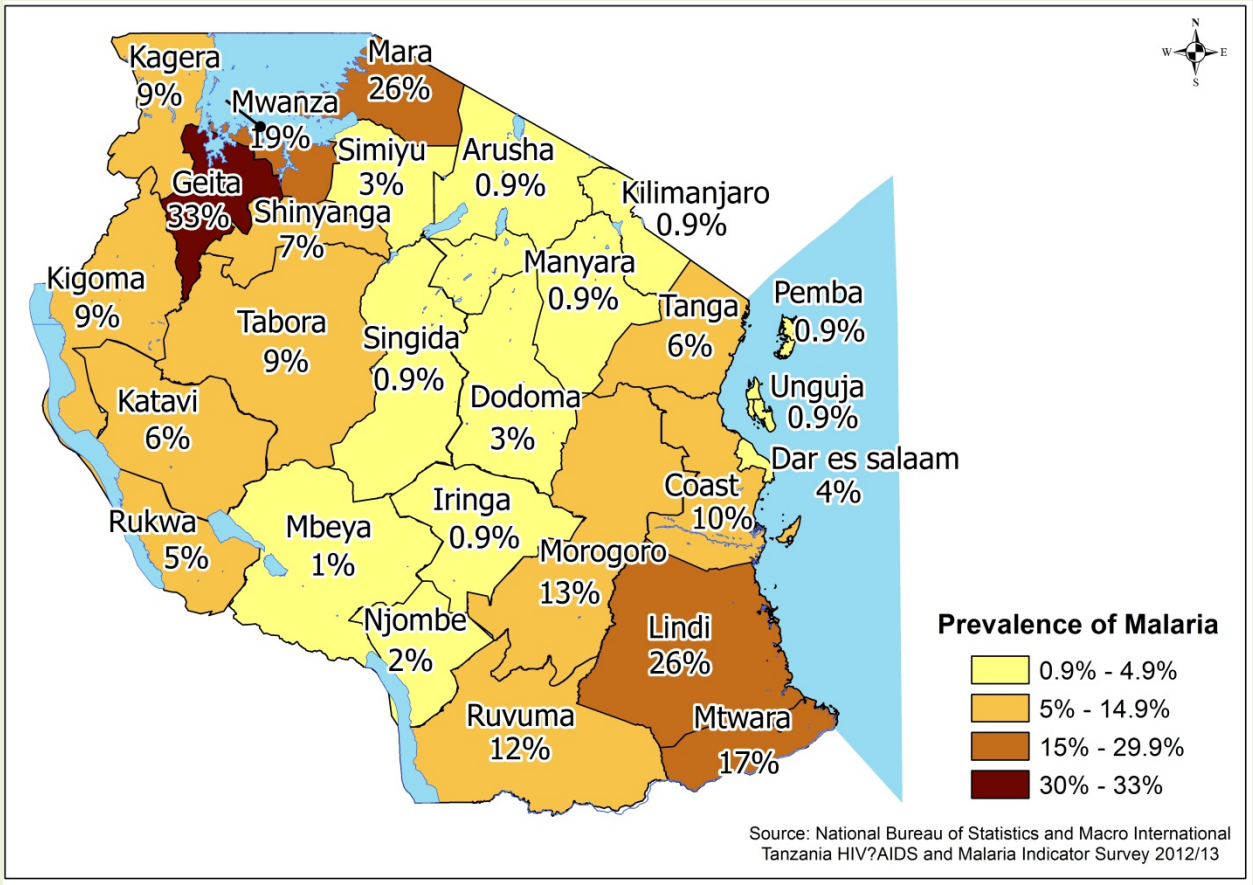
Table 2: Stratification of malaria endemicity, seasonality and transmission intensity in Tanzania

Stratum	Regions	Endemicity	Seasonality	Pattern	Transmission
Coastal belt, eastern and southern lowlands	Lindi, Mtwara, Pwani, Dar es Salaam and part of Morogoro, Tanga, and Ruvuma	Meso	Perennial	Bimodal	Stable
Northern Highlands	Manyara, Arusha part of Kilimajaro and Tanga	Hypo	Highly Seasonal	Bimodal	Unstable No-malaria in some areas
Central plateau	Dodoma, Singida and part of Tabora	Meso-Hypo	Seasonal to Highly Seasonal	Unimodal	Stable – Unstable
Southern Highlands	Iringa, Mbeya, Njombe, part of Ruvuma and Rukwa	Hypo (with areas of meso)	Seasonal	Unimodal	Unstable stable and No-malaria in some areas:)
Lake Victoria, Tanganyika and Nyasa basins	Kigoma, Katavi, Simiyu, Mara, Mwanza, Geita, Shinyanga, Kagera, part of Mbeya, Rukwa, Ruvuma and Njombe	Meso	Perennial	Bimodal (lake Victoria basin) Unimodal (lake Tanganyika and Nyasa basins)	Stable

Over 93% of the mainland Tanzanian population lives in areas where malaria is transmitted. The most vulnerable groups are children under five and pregnant women. Other vulnerable groups include people living with HIV/AIDs.

The most recent population based survey – the Tanzania HIV/AIDs and Malaria Indicator Survey (THMIS, 2011/2012)[4] shows a marked decline in malaria prevalence from 18% reported in the 2007/2008 survey to 10%. THMIS results are used to assess malaria transmission intensity in the country. There is a marked variation in prevalence with the highest being in the Great Lake zone (9-33%), followed by southern lowlands (6-26%). The regions with the lowest prevalence are central and northern zones (<1%). *Figure 1* summarises malaria prevalence by region.

Figure 1: Malaria prevalence in children 6-59 months, THMIS 2011/2012



Plasmodium falciparum is the main parasite responsible for 96% of malaria infections in Mainland Tanzania, the remaining being attributed to other plasmodia, mainly *P. malariae* and *P. ovale*. The principal malaria vectors are the *Anopheles gambiae* complex and *Anopheles funestus.*

1.3 The National Guidelines for Diagnosis and Treatment of Malaria

1.3.1 The strategic context

The National Malaria Medium Term Strategic Plan (MMTSP 2008-2013) is the road map for malaria control in the country. MMTSP has two core strategies; (a) Malaria Diagnosis and Treatment and (b) Integrated Vector Management.

The goal of appropriate malaria diagnosis and treatment is to reduce morbidity and mortality. The National Guidelines for Diagnosis and Treatment of Malaria (NGDTM, 2006) have been guiding the National Malaria Control Programme (NMCP) to achieve this goal. The guiding principle of the national antimalarial treatment policy is to promote safe, effective, good quality, affordable and accessible antimalarial treatment.

Updating antimalarial treatment policies is the culmination of efforts on several levels; analysis of the technical, social and economic issues related to malaria control; consensus building on antimalarial drug resistance; review of new recommendations from the global level on updated evidence for malaria treatment; and selection of options among policy makers, researchers, regional and health personnel and other relevant stakeholders.

1.3.2 Rationale of guidelines update

In recent years it had become increasingly clear from both updated generic WHO guidelines on the treatment of malaria[5] and local level evidence in the country that case management of malaria needed to be updated accordingly.

The epidemiology of malaria in the country is changing; a number of research studies and the current THMIS (2011/12) have shown a marked reduction in the prevalence of malaria. [6,7] These significantly lower rates of parasitaemia were indicative of an urgent need for reviewing the specificity and accuracy of malaria diagnosis.

The NMCP has introduced malaria Rapid Diagnostic Tests (mRDTs) at all levels of health care delivery since 2009 with the aim of improving malaria case detection and reducing over diagnosis and, eventually, overtreatment. In the updated case management guidelines, it is now mandatory to parasitologically confirm all febrile patients suspected of malaria before treatment.

Confirmation of malaria diagnosis improves the quality of patient care by (1) ensuring that only malaria positive cases receive treatment, (2) improving management of non-malarial febrile illnesses, and (3) improving malaria disease surveillance by recording true cases only.

The recommended first line treatment for uncomplicated malaria changed from Sulfadoxine-Pyrimethamine (SP) to Artemisinin Based Combination Therapy (ACT) in 2006, and Artemether-Lumefantrine (ALu) was selected as the drug of choice; while quinine remained as the second line therapy as well as the medicine of choice for severe malaria.

Starting from 2007 Artemether-Lumefantrine (ALu) has been deployed in all public health facilities through assistance from developing partners, mainly The Global Fund and US President's Malaria Initiative (PMI). The Affordable Medicine Facility for malaria (AMFm) was introduced in 2010 to improve access and affordability to quality assured ACTs in the private sector.

Evidence from therapeutic efficacy studies conducted in sentinel sites in the country reveal that *P. falciparum* remains highly sensitive to the first line drug – ALu.[8]

There is evidence from multicentre studies carried out in Africa that injectable Artesunate is superior in efficacy to quinine for the treatment of severe malaria.

The multi –centre study carried out over a five year period in hospitals across nine Sub-Saharan African countries and enrolled 5,425 children with severe malaria. AQUAMAT was

carried out in nine hospitals in countries with high endemicity including; Mozambique, Tanzania, Kenya, Uganda, Rwanda, the Democratic Republic of Congo, Nigeria, Ghana, and Gambia.

The largest randomized trial conducted in Africa children with severe malaria through the African Quinine vs. Artesunate Malaria Trial (AQUAMAT) showed a significant reduction in mortality (22.5%) in the artesunate group when compared to the quinine group.[9]

The incidence of convulsions, coma and hypoglycaemia after leaving the hospital was also significantly reduced in the artesunate group compared to those treated with quinine. It was also observed that there was no significant difference in the incidence of severe neurological sequelae. From this evidence, WHO has recommended injectable artesunate to be used in preference to quinine for the treatment of severe *P. falciparum* malaria in adults and children. Artesunate also has a number programmatic and logistical advantages over quinine, as it does not require rate-controlled infusion or cardiac monitoring.[10]

Hence, these guidelines promote the use of injectable artesunate as the medicine of choice in the treatment of severe malaria. Injectable Artemether or Quinine is the alternative treatment where injectable artesunate is contraindicated.

During the last few years, WHO has observed a slowing of efforts to scale-up intermittent preventive treatment of pregnant women (IPTp) for malaria with Sulfadoxine-Pyrimethamine (SP) in a number of countries in Africa. While there are several reasons for this but, confusion among health workers about SP administration for IPTp may also be playing a role. For this reason, WHO clarified its recommendations on IPTp[11], and urged national health authorities to disseminate these recommendations widely and ensure their correct application. Based on the above suggestions, these guidelines endorse a new IPTp administration arrangement for all pregnant women at each scheduled antenatal care visit from the second trimester.

1.3.3 Broad objective

The broad objective of these guidelines is to provide standard management reference for the care of patients with malaria. They form part of the National Drug Policy and recommendations also, provide the indications for malaria case management at the appropriate level of health care in the public and private sectors.

1.3.4 Specific objectives

- To stimulate at what level of health care delivery, specific antimalarial drugs should be made available at all times
- To promote prompt and accurate malaria diagnosis
- To promote rationale antimalarial drug management
- To promote intermittent preventive therapy for malaria in pregnancy
- To provide consistent guidance to prescribers and users on the appropriate use of chemoprophylaxis for specific at risk groups
- To provide information to health care managers and service providers on the detection of antimalarial drug resistance, the management of pharmaceutical and other commodities for diagnosis and treatment of Malaria

1.4Choice of antimalarial medicines

The following antimalarial medicines are recommended for treatment of malaria in Tanzania.

- The medicine of choice for the treatment of uncomplicated malaria remains Artemether-Lumefantrine (ALU)
- The alternative medicine for the treatment of uncomplicated malaria, where there is no response to Artemether-Lumefantrine or it is contraindicated, is Dihydroartemisinin-Piperaquine (DPQ)
- The medicine of choice for treatment of severe malaria is Injectable Artesunate
- The alternative treatments for severe malaria are Injectable Quinine or Injectable Artemether
- The medicine of choice for uncomplicated malaria in pregnant women during the first trimester is Quinine
- The medicine for Intermittent Preventive Treatment in pregnancy at each scheduled antenatal care visit, remains Sulfadoxine-Pyrimethamine (SP)

2 Management of Malaria and Health Care Delivery in Tanzania

In Tanzania, there are four categories of health care delivery:

- Category I: Community - Home, Village/Community Primary Health Care Post, Pharmacy, Accredited Drug Dispensing Outlet (*Duka la Dawa Muhimu or ADDO*)
- Category II: Dispensary
- Category III: Health Centre
- Category IV: Hospital

The categories mentioned above should not be viewed as a rigid sequence of referral from category I - II - III - IV. Instead, a well-trained health worker should be able to recognize the severity of malaria and refer the patient directly to the most appropriate category of care consistent with that condition.

2.1Community

Providers and caregivers

Home-based management of malaria (HMM) is one of the recommended strategies for improving access to prompt and effective treatment of malaria episodes, which makes use of trained community members living as close as possible to where the patients live. Parents and guardians awareness on the importance of early care of malaria patients is a crucial aspect for appropriate and prompt malaria treatment.

- Parents/guardians
- Community Health Workers (CHW) and other Community Owned Resource Persons (CORPs)
- Dispensing staff of Accredited Dispensing Drug Outlets (ADDOs *duka la dawa muhimu*)

Community based providers are equipped and supported to give health education on malaria prevention, malaria diagnosis using mRDT, treatment of children with uncomplicated malaria, pre-referral treatment and encouraging early health care seeking behaviour

Household Malaria Management

Diagnosis and types of services provided should include the following:

- Health education and promotion
- Identification of signs and symptoms of uncomplicated and severe malaria
- Use of mRDTs to support clinical diagnosis
- Treatment of uncomplicated malaria in children
- Pre-referral treatment for severe malaria
- Where referral is made, a referral note should be written
- Supportive care (fanning-*kupepea* and antipyretics)

- Encourage early health care seeking behaviour and referral to the nearest facility

Commodities for Household Malaria Management

- mRDTs
- Artemether-Lumefantrine (ALu) tablets
- Paracetamol
- Sharp safety disposal box
- Examination gloves
- Oral rehydration therapy (ORT)

Household malaria management commodities are part of the recommended package in the Community Based Health Care kit

2.2 Dispensary

At the dispensary a more detailed history should be taken and a more extensive clinical examination should be performed. Laboratory investigations for malaria parasites should be available throughout. This level of health care is critical to promote appropriate management of uncomplicated malaria and for pre-referral care of severe cases.

Staffing

- Clinical Officers
- Assistant Clinical Officers
- Trained Nurses/Public Health Nurses
- Pharmaceutical Assistants and Medical attendants (Nurse Assistants/Auxiliaries, Laboratory Assistants)

Dispensary staff, are trained to perform mRDT and administer antimalarial medication intramuscularly when indicated

Diagnosis is based on

- Clinical history and physical examination
- Malaria RDT and/or blood smear for malaria parasites

Types of services provided

- Treatment of uncomplicated malaria
- Pre-referral treatment of severe malaria cases with intra-muscular antimalarials
- Treatment of severe malaria cases where referral is not possible
- Patient education & promotion
- Identification of patients with anaemia for the purpose of treatment and/or referral

- Identification of patients with severe disease and treatment failures for referral with the case summary
- Detection of hypoglycaemia (where available)
- Estimation of haemoglobin (where available)

Type of treatment provided

- Antimalarials:

Artemether-Lumefantrine (ALu) tablets

Injectable antimalarials (Artesunate)

SP tablets for Intermittent Preventive Treatment

- Analgesics/antipyretics: Paracetamol and Aspirin[12]
- Anticonvulsant medicines: Diazepam (injectable) and Phenobarbitone (injectable/tablets)
- Oral Rehydration Salt (ORS)
- Exposure and Fanning (*kupepea)*
- Correction of hypoglycaemia: Sugar solution, Dextrose 10% or 25% or 50% solution (where available)

2.3 Health centre

At the health centre, better resources for differential diagnosis and patient monitoring are available. Therefore, a more detailed history should be taken, more extensive clinical investigation should be performed; mRDT and/or a blood smear for malaria parasites should be done. This level of care is critical for the care of severe malaria cases referred from lower level.

Staffing

- Assistant Medical Officer
- Clinical Officer
- Assistant Clinical Officer
- Public Health Nurse
- Nurse Midwives
- Medical Attendants (Nurse Assistants/auxiliaries)
- Laboratory Technicians/Assistants
- Pharmaceutical Technicians/Assistants

Health centre staff are trained to perform mRDT, microscopic diagnosis of malaria and to administer antimalarial medication intramuscularly and/or intravenously, when indicated

Diagnosis is based on:

- Clinical history and physical examination
- Malaria RDT and/or blood smear for malaria parasites

Type of services provided

- Treatment of uncomplicated and severe malaria cases
- Patient monitoring in severe malaria
- Health education and promotion
- Identification of patients with severe disease and treatment failures and/or referral with case summary
- Identification of patients with anaemia for the purpose of treatment and/or referral
- Detection and correction of hypoglycaemia
- Detection and correction of anaemia
- Pre-referral treatment

Type of treatment available

- Antimalarials

Artemether-Lumefantrine (ALu) tablets

Injectable antimalarials (artesunate)

SP tablets for Intermittent Preventive Treatment

- Analgesics/anti-pyretics: paracetamol, aspirin (not for children under 12 years of age)
- Anticonvulsants medicines: diazepam (Injectable) and phenobarbitone (Injectable/tablet)
- Oral rehydration salts (ORS)
- Intravenous fluids: dextrose 5%, sodium chloride 0.9% (normal saline), sodium lactate compound (ringer lactate/hartmann's solution) and dextrose saline
- Dextrose 10%, 25% and 50% solutions for correction of hypoglycaemia
- Exposure and fanning (*kupepea*)

Blood transfusion services are not usually available at the health centre

2.4Hospital

Staffing:

- Medical Specialists
- Medical Officers
- Assistant Medical Officers
- Clinical officers

- Nursing Officers
- Assistant Nursing Officers
- Public Health Nurses A and B
- Nurse Midwives
- Medical Attendants (Nursing Assistant/Auxiliaries)
- Laboratory Technicians/Assistants
- Pharmacists and/or Pharmaceutical Technicians/Assistants
- Other Medical Cadres

Diagnosis

At this level there is sufficient clinical expertise for diagnosis of severe malaria and its complications and adequate differential diagnosis. There should also be greater efficiency and accuracy in mRDT and microscopic diagnosis of malaria including identification of species, sexual and asexual forms and performance of quantitative parasite counts.

Diagnosis is based on:

- Clinical history and physical examination
- Laboratory tests, radiology and other supportive tests

Laboratory tests available include:

Urgent test for suspected severe malaria patients:

- Blood smear for malaria parasites
- Blood glucose
- Lumbar puncture for CSF examination
- Full blood picture including Hb

Other supportive tests:

- Urinalysis including haemoglobinuria
- Basic biochemical tests
- Liver function tests - including bilirubin, ALT, AST and ALP
- Serum creatinine and blood urea
- Electrolytes including sodium, potassium, chloride, bicarbonate and lactate
- Cultures – blood, CSF and urine

Type of services provided

- Treatment of uncomplicated and severe malaria cases
- Health education & promotion
- Identification of patients with complicated conditions that cannot be managed at district/regional hospitals (e.g. renal failure, uncontrollable convulsions, etc.) for treatment at consultant hospitals

- Identification of patients with anaemia for the purpose of treatment
- Patient monitoring
- Blood transfusion services
- Intensive care

Type of treatment available

- Antimalarials
- Artemether-Lumefantrine (ALu) tablets
- Injectable antimalarials (Artesunate)
- SP tablets for Intermittent Preventive Treatment

Other recommended antimalarial medicines may be available both for oral or parenteral treatment: e.g. Dihydroartemisinin-Piperaquine (DPQ) tablets, alternative injectable antimalarials: Artemether or quinine

- Analgesics/antipyretics: paracetamol, aspirin (not for children under 12 years of age)
- Anticonvulsant medicines: Injectable Diazepam and Phenobarbitone (injectable /tablet)
- Oral rehydration salts (ORS)
- Intravenous fluids: Dextrose 5%, sodium chloride 0.9% (normal saline), sodium lactate compound (Ringer Lactate/Hartmann's solution) and dextrose saline
- Blood transfusion services
- Correction of hypoglycaemia: dextrose10%, 25% and 50% solution
- Exposure and fanning (*kupepea*)

3 Diagnosis of Malaria

Prompt and accurate diagnosis of malaria is part of effective disease management. The diagnosis of malaria is based on clinical suspicion and on the detection of parasites in the blood (parasitological or confirmatory diagnosis). The aim of malaria diagnosis is to assist in the treatment of the disease and not in clearing asymptomatic infections.

A positive clinical identification of malaria is based on exclusion diagnosis, therefore symptoms and signs of other common febrile illness have to be elicited through history and examination.

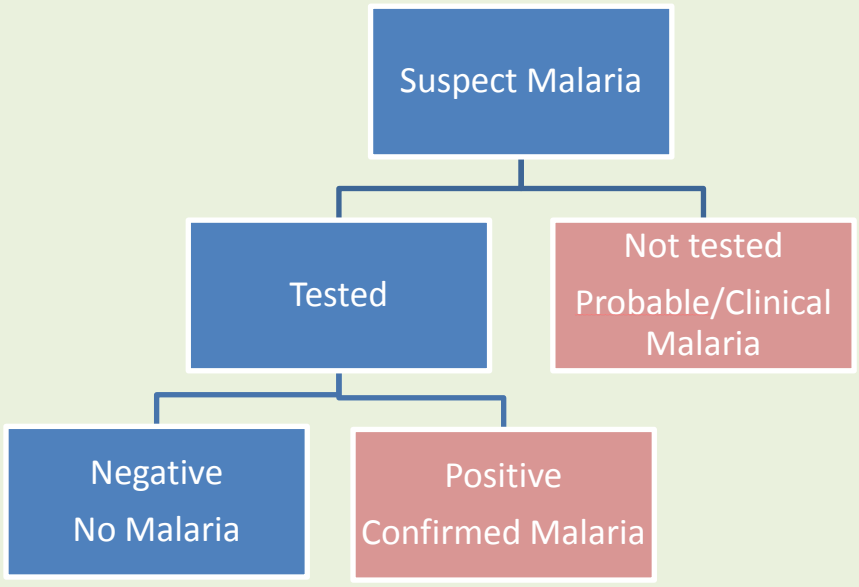
The two recommended methods in routine use for parasitological diagnosis are malaria microscopy and malaria-Rapid Diagnostic Tests (mRDT). Quality microscopy remains the gold standard for parasitological diagnosis of malaria.

The benefit of parasitological diagnosis depends entirely on health care providers adhering to the results when managing the patient. The exception is where the severity of disease justifies the use of antimalarials in test negative cases.

3.1Malaria Case Definition

Not all cases of malaria receive a diagnostic test. Thus, it is necessary to distinguish between suspected malaria cases, probable cases and confirmed cases[13]. The relationship between these categories is shown diagrammatically in figure 2[14]:

Figure 2: Malaria case classification in the control phase



Suspected malaria case

This is a patient suspected of having malaria. The criteria for recognizing suspected malaria is fever or history of fever. All suspected cases of malaria should be given a diagnostic test either by microscopy or rapid diagnostic test (RDT).

Clinical/probable (not tested) malaria case

These are suspected malaria cases that did not receive a diagnostic test for malaria but were nevertheless treated as malaria. The terms “clinical” and “probable” are interchangeable and were widely used in the past.

Confirmed malaria (malaria test positive)

A suspected malaria case in which malaria parasites have been demonstrated by microscopy or a rapid diagnostic test, the definition implies that the case displayed symptoms of malaria as well as the presence of parasites. It should be noted that for some suspected cases with a positive test, particularly in populations that have acquired immunity to malaria, febrile illness may in fact be due to other causes. Nevertheless, in such instances, a diagnosis of confirmed malaria is still given. If a concurrent disease is suspected it should be further investigated and treated.

Confirmed no malaria (malaria test negative)

Suspected malaria cases for which a malaria diagnostic test was negative. These would normally be given a diagnosis other than malaria. It is possible that some patients that test negative by microscopy or RDT can have very low levels of parasitaemia that are only detectable by more sensitive techniques such as polymerase chain reaction (PCR)[15] testing. Such low levels of parasitaemia are not thought to be clinically significant although they may contribute to transmission in low transmission settings.

Uncomplicated and severe malaria cases

Malaria cases can be split into uncomplicated or severe cases.

Uncomplicated malaria: is defined as symptomatic malaria without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction.

Severe malaria: In a patient with *P. falciparum* asexual parasitaemia and no other obvious cause of symptoms the presence of one or more of features (listed in chapter 5: management of severe malaria) classifies the patient as suffering from severe malaria.

In general, uncomplicated malaria cases are treated as out-patient cases while severe malaria is managed as in-patient[16]*. Therefore, out-patient and in-patient malaria cases are considered as proxies for uncomplicated and severe malaria cases, respectively*[17]

3.2 Clinical diagnosis of malaria

Malaria is an acute disease which exhibits non-specific signs and symptoms. Malaria is clinically suspected mostly on the basis of fever or a history of fever. Diagnosis based on clinical features alone, especially in low and moderate malaria transmission settings, has very low specificity and results in low malaria diagnosis accuracy.

As noted above, early symptoms of malaria are non-specific and similar to the symptoms of a minor systemic viral illness. They comprise: headache, fatigue, abdominal discomfort, muscle and joint aches, usually followed by fever, chills, perspiration, anorexia vomiting and worsening of malaise. Malaria is, therefore, frequently over-diagnosed on basis of symptoms (clinical diagnosis) alone. At this early stage of disease, if it is malaria, clinically it is classified (diagnosed) as uncomplicated malaria.

However, if the disease progresses to severe form it is diagnosed as severe malaria, the usual cause being delayed treatment or the use of ineffective treatment. Vital organ dysfunction is an indication of severe malaria. Severe malaria usually manifests with one or more of the following: coma (cerebral malaria), severe anaemia, metabolic acidosis, hypoglycaemia, acute renal failure or pulmonary oedema. By this stage of the disease, the case fatality in people receiving treatment is typically 10-20%. However, if left untreated, severe malaria is fatal in the majority of cases.

In Tanzania the commonest presentations of severe malaria are severe anaemia and cerebral malaria.

3.2.1 Malaria clinical diagnosis at Community level

Management of malaria at the community level is still a big challenge, mainly due to the lack of capacity to correctly diagnose malaria.

Therefore, communities should be empowered to identify symptoms and encourage appropriate management of uncomplicated malaria through early health care seeking behaviour.

Communities should also be empowered to identify severe malaria symptoms for immediate referral to the nearest health care facility.

3.2.2 Malaria diagnosis at health facility level

In a health facility, detailed history should be taken and a thorough physical examination made in order to diagnose malaria. A careful assessment of a patient with suspected malaria is essential in order to differentiate between uncomplicated and severe disease.

In children under five years of age, IMCI practical algorithms for management of sick child should be used to ensure full assessment and appropriate case management of children, in particular in the primary level health facilities.

Laboratory investigations should always be done in all health facilities, to confirm malaria clinical diagnosis

3.3 Differential diagnoses of malaria

Malaria features may mimic other diseases, therefore, care should be taken when diagnosing malaria and other diseases that may have similar clinical presentation should also be considered. Apart from malaria, the most common causes of acute fever in outpatient children under 5 years of age (in approximate descending order of frequency) are[18]:

- Upper respiratory tract infections, including otitis media and tonsillitis (mostly of viral origin)
- Other viral diseases (influenza, human herpesvirus 6, parvovirus B19, Epstein-Barr virus, cytomegalovirus)
- Pneumonia
- Gastroenteritis
- Urinary tract infection
- Typhoid fever
- Skin infection (abscess, cellulitis)
- Sepsis due to bacteraemia
- Meningitis

3.4 Parasite-based malaria diagnosis: confirmed malaria

The two recommended diagnostics tests for routine confirmation of malaria diagnosis are quality malaria microscopy and quality mRDT.

Malaria RDTs have made accurate malaria diagnosis potentially accessible to virtually all suspected patients; previously such diagnosis was restricted to people close to clinics or laboratories at which microscopy-based diagnosis could be maintained.

According to MoHSW policy, malaria microscopy is a diagnostic investigation based in an established health laboratory. It requires a well-trained skilled staff to perform it, in the minimum a Laboratory Assistant. Malaria microscopy needs an energy source preferable electricity to power the microscope.

Malaria RDTs are diagnostic investigations which are not necessary based in a health laboratory. The policy allows the test site for mRDT to be outside the established health laboratories, as long as it is performed by a trained and certified person.

Thus, malaria laboratory investigations may be performed depending on the capacity of the facility and the clinical indications. Malaria tests should be made available to all malaria suspected cases. Additional supportive urgent laboratory investigations should be made available for all patients to further investigate the patient.

3.4.1 The role of malaria laboratory investigations

Under the current epidemiological and clinical settings, malaria laboratory investigations are essential to:

- Improve the quality of patient care by confirming parasite-positive patients
- Improve the quality of patient care by identifying parasite-negative patients in whom another diagnosis must be looked for

- Prevent unnecessary use of antimalarials, reducing frequency of adverse effects, especially in those who do not need the medicines, and medicine pressure selection for resistant parasites
- Improve malaria disease surveillance by reporting confirmed (true) cases
- Confirmation of treatment failure by malaria microscopy

3.4.2 Malaria Rapid Diagnostic Tests (mRDTs)

Malaria RDTs are qualitative techniques which specifically detect antigens (proteins) produced by malaria parasite. The tests can be done by minimally trained personnel, and are rapid as results can be obtained within 20 minutes.

There are two main groups of commercially available mRDTs:

- Specific antigen mRDT; detects one species of human malaria parasites
- Pan specific antigen mRDT; detects all human species of malaria parasites

The common malaria antigens detected by mRDTs are:

- Histidine-rich Protein-2 (HRP2). This antigen is expressed by cell membrane of red blood cells parasitized *by P. falciparum*, hence heat stable. It is a highly sensitive antigen for *P. falciparum* only
- Plasmodium Lactate Dehydrogenase (pLDH). This antigen is an enzyme with antigenic properties produced by all *Plasmodium* species. It is heat unstable
- Aldolase is an enzyme with antigenic properties, produced by all *Plasmodium* species. It is heat unstable

The above antigens are component of available RDTs for malaria. They can be presented alone or in combination in the same device.

The target antigens for mRDTs and the detected plasmodium species are summarized in *Table 3*.

Table 3: Common target antigens for commercially available mRDTs devices

Antigen Device/Species	HRP-2	pLDH	Aldolase
P. falciparum specific	√	√	
P. vivax specific		√	
Pan-specific (all species)	√	√	√

In Tanzania the recommended mRDT in public health facilities is a pan specific device which is able to detect two antigens: HRP2 and pLDH

HRP2 device specific for P.falciparum is the alternative mRDT

The criteria for choice of mRDTs are explained in Appendix A.

3.4.3 Malaria microscopy

Malaria microscopy is a skilled exercise requiring great care at each step of the standard operating procedures and precise visual and differential skills.

Microscope for detection of malaria parasites

A reliable and well maintained binocular microscope is essential for accurate malaria microscopy. A binocular microscope with a x7 or x10 eyepiece, a quality immersion oil (refractive index of 1.5) and lens (x100) with a built-in electrical light source is the **"gold standard"**[19].

Stains for detecting malaria parasites

Many stains have been developed for the detection of malaria parasites. The Romanowsky stains have proved the most adaptable and reliable for routine work.

Routine blood slides are judged to be of good quality if smeared and stained as recommended in the Standard Operating Procedures.

Giemsa stain:

The **Giemsa stain** is one of the Romanowsky stains. The alcohol based stain is the **"gold standard".** It is recommended for routine diagnosis due to its applicability to both thick and thin blood films, its stability during storage and its constant and reproducible staining quality over a range of temperatures.

Quality Giemsa stain used in a reliable and well maintained binocular microscope is the recommended "gold standard" for routine parasite-based malaria diagnosis in health laboratories

For reporting of results of thick and thin blood smears for malaria parasites, see Appendix B.

Other stains

Field stain

Field's stain is a version of a Romanowsky stain, used for rapid processing of the specimens. It is useful in laboratories where the workload is low and an excellent stain when used properly. Improperly managed field stain tends to increase false positive due to cross contamination in case of many slides processed at the same time thereby it is not recommended for routine malaria diagnosis.

Acridine Orange stain

This is a fluorescent dye which uses a special microscope for malaria diagnosis. Acridine Orange (AO) is a practical alternative technique for the laboratory diagnosis of malaria in Tanzania. The most notable advantage of the AO method is its promptness; results are readily available within 3–10 minutes. However, species differentiation may be difficult. The AO special microscopes need a stable electrical power source to ensure the continuation of service to the patients.

3.4.4 Which routine malaria test to use at health facility

All patients suspected of having malaria must be confirmed by malaria microscopy or mRDT. It improves the accuracy of malaria diagnosis and ensures that ACT treatment is given to those who really need it.

Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not feasible.

All patients suspected of having malaria must be confirmed by quality malaria microscopy or mRDT. The two malaria parasite-based investigations complement each other to ensure 24-hours access to all suspected patients

- A quality assurance programme for microscopy and RDT is a prerequisite to implementing appropriate malaria diagnostic services and consequently, to improving malaria case management (see chapter 12)
- For the management of a new suspected uncomplicated malaria case both quality microscopy and quality mRDT have adequate sensitivity for the diagnosis of malaria
- In all suspected severe malaria cases microscopy is recommended. For severe malaria management there is the need to assess parasite density for monitoring of treatment response. However mRDT should also be performed at admission to guide treatment due to possible operational delays of malaria microscopy results. In cases where malaria non-response to treatment is suspected in-patients who initially tested positive, microscopy is the recommended test. In this instance, malaria RDTs are not recommended because parasite antigens persist up to 4 weeks after parasitaemia has cleared
- To maximise the benefits of malaria diagnosis at different levels of health care and in different clinical settings, the strategic framework outlined in *Table 4* below should be adhered to

Table 4: Strategic framework for selection of routine malaria test to be used at different levels and in different clinical settings

Health facility level	Clinical setting	• Condition/Remarks	Microscopy	RDT
Community (CHW, ADDO)	Screening of febrile patients	• Community member received adequate training and supervision • regular commodity supply • proper storage • Compliance with blood safety procedures	NA	Yes *
Dispensary without lab facilities	Screening of suspected malaria patients at OPD	• Non lab trained health care workers to be trained	NA	Yes
	Follow up of patients previously tested positive and with persistent malaria symptoms (suspect drug failure)	• RDTs not to be used due to persistent antigenaemia.	NA	No
	Screening of Severe illness before referral	•	NA	No
Dispensary with lab facility	Screening of suspected malaria patients at OPD	• Non lab trained health care workers to be trained	No	Yes
		• Certified ** personnel available • low workload • quality assurance in place • electricity available	Yes	No
Health Centre and Hospital with lab facilities	Screening of suspected malaria patients at OPD	• Low workload • quality assurance in place, • certified ** personnel available • electricity available	Yes	No
	Screening of suspected malaria patients at OPD	• high workload • peak hours • quality assurance not in place, • certified ** personnel not available, • electricity not available	No	Yes
	Severe malaria cases upon admission	• Parasite density needed	Yes	Yes
	Follow up of admitted patients	• Parasite density needed	Yes	No
	Follow up of patients previously tested positive and with persistent malaria symptoms (suspect drug failure)	• RDTs not to be used due to persistent antigenaemia	Yes	No
Malaria outbreak investigation		•	No	Yes
Malaria epidemic follow up		• Blood slides are taken in the field for later examination by qualified personnel • RDTs not to be used due to persistent antigenaemia	Yes	No
Community surveys		• Blood slides are taken in the field for later examination by qualified personnel	Yes	Yes
Malaria testing at first antenatal attendance			No	Yes
**** use of RDTs for household malaria management depends on availability of appropriate supportive strategic framework at this level***				
***** Microscopist should be certified after attending special training on malaria microscopy under NMCP supervision***				

4 Management of Uncomplicated Malaria

The management of a patient with malaria will be determined by the clinical presentation for both uncomplicated or severe disease and confirmation by a parasite-based laboratory test.

The objectives of treatment of uncomplicated malaria are:

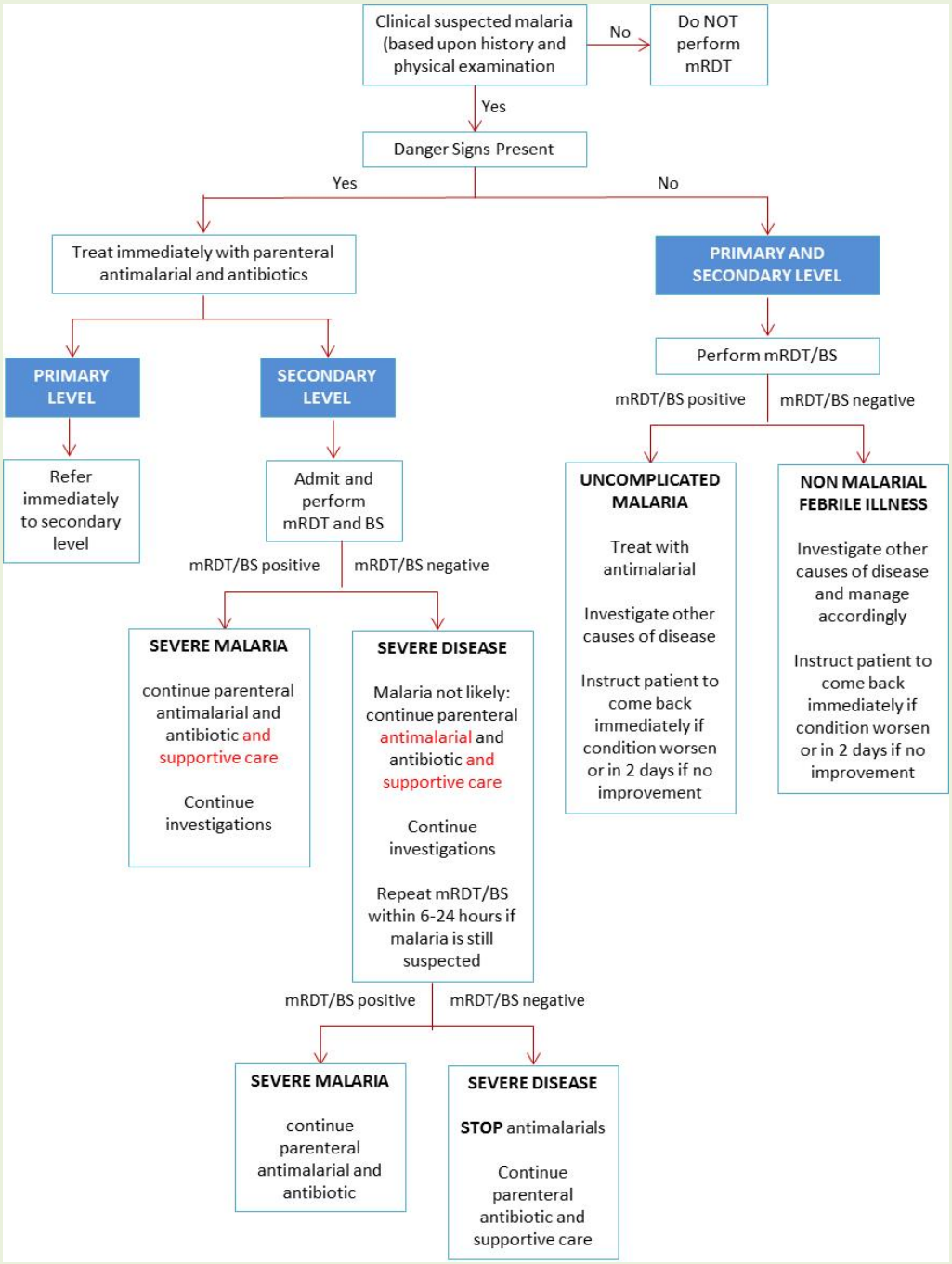
- *To provide rapid and long lasting clinical and parasitological cure*
- *To reduce morbidity including malaria related anaemia*
- *To halt the progression of simple disease into severe and potentially fatal disease*

In order to achieve these objectives, uncomplicated malaria must be diagnosed early and the correct treatment administered without delay. Since the progression towards severe and fatal disease is rapid, especially in children under five years of age, it is recommended that diagnosis and treatment of uncomplicated malaria should be done within 24 hours from the onset of symptoms. It is recommended that parasitological results be available in short time of the patient presenting to a health facility.

4.1 Management of a patient with suspected malaria

The flow chart in *Figure 3* illustrates the sequence of actions when managing a patient with suspected malaria. *See also appendix C; IMCI algorithm for a child with fever.*

Figure 3: Management of a patient with suspected malaria using mRDT and/or microscopy



Note to the malaria management algorithm

General Danger signs:

- In children: unable to drink or breastfeed, vomit everything, convulsions, lethargic or unconscious, neck stiffness, chest in drawing or stridor; (see Appendix C)
- In adults: very weak or unable to stand, lethargic or unconscious, neck stiffness, convulsions, respiratory distress or severe abdominal pain

4.2 Clinical features of uncomplicated malaria

Diagnosis of malaria begins with clinical assessment of patients, through detailed history taking and recording of signs and symptoms. Malaria signs and symptoms are non-specific and may mimic symptoms of systemic viral illnesses or other disease conditions. The occurrence of malaria signs and symptoms may differ in children and adults. The main features of malaria are included in *Table 5*.

Table 5: Clinical features of uncomplicated malaria and expected frequency in children below 5 years of age and adults

Features	< 5 years	>5 years and adults
Fever	+ + +	+
Headache	+	+ +
Joint pains	+	+ +
Malaise	+	+ +
Vomiting/diarrhea	+ + +	+
Body ache	+	+ +
Poor appetite	+ +	+ +
Body weakness	+ +	+ +
Pallor	+ + +	+
Enlarged spleen	+ +	+

4.3 Treatment of uncomplicated malaria using combination therapy

Combination therapy is defined as the simultaneous use of two or more blood schizontocidal drugs with independent modes of action to improve therapeutic efficacy and also to delay the development of resistance to the individual components of the combination.

Artemisinin-based combination treatment (ACT) is recommended by WHO to be used for the treatment of uncomplicated malaria. ACTs are combinations in which one of the components is Artemisinin and its derivatives (Artesunate, Artemether, and Dihydroartemisinin) and the other component is an antimalarial with a known good efficacy profile (e.g. Lumefantrine, Piperaquine, Mefloquine, Amodiaquine).

The Artemisinin compounds are active against all four species of malaria parasites that infect humans and are generally well tolerated.

Artemisinin and its derivatives (Artesunate, Artemether, and Dihydroartemisinin) should not be used as monotherapy

For the ACTs to eliminate at least 90% of the parasitaemia, a 3-day course of the Artemisinin is required. This ensures that only about 10% of the parasitaemia is present for clearance by the partner medicine.

Uncomplicated malaria treatment should include at least 3 days with an Artemisinin derivatives (ACT) for an optimum effect

Fixed-dose combinations (the components are mixed in the same tablet) are highly preferable to the loose individual medicines co-blistered or co-dispensed (the components of the combination therapy are in separate tablets). It promote adherence to treatment and reduces the potential for selective use of the medicines as monotherapy.

In Tanzania the ACT of choice for the treatment of uncomplicated malaria is Artemether-Lumefantrine (ALu).The alternative medicine for the treatment of uncomplicated malaria, where there is no response to Artemether-Lumefantrine or it is contraindicated, is Dihydroartemisinin-Piperaquine (DPQ).

4.4Treatment of uncomplicated malaria with medicine of choice: Artemether-Lumefantrine

Artemether-Lumefantrine *(ALu) is the medicine of choice for the treatment of uncomplicated malaria. As long as its monitored efficacy remains within acceptable limits of 90% and above*

An added advantage of this combination is that Lumefantrine is not available as a monotherapy for the treatment of malaria.

Medicine description

Artemether-Lumefantrine (ALu) is an oral fixed combination tablet of 20mg Artemether – a derivative of Artemisinin, and 120mg Lumefantrine.

Artemether is effective against all human malaria parasites species. It has a rapid schizonticidal action against *Plasmodium falciparum*. Recrudescence is therefore frequent when it is used as a monotherapy. Lumefantrine is an aryl amino alcohol. It has a longer elimination half-life of up to 10 days and is associated with a low recrudescence rate, but has a slower onset of action. ALu therefore combines the benefits of the fast onset of action of Artemether with the long duration of action and high cure rate of Lumefantrine in a single oral formulation. It is highly efficacious even against multi medicine resistant malaria parasites with clearance of the parasites from the blood within 2 days.

Available formulations

Standards Tablets: Fixed formulation Artemether 20 mg, Lumefantrine120mg

Dispersible tablets: Fixed formulation for children, Artemether 20 mg, Lumefantrine120mg (5–14 kg: 1 tablet; 15–24 kg: 2 tablets) [20].

Indications:

Treatment of choice for uncomplicated malaria

Contraindications

Hypersensitivity to either Artemether or Lumefantrine

Not recommended

First trimester of pregnancy

Adverse effects of Artemether-Lumefantrine (ALu)

While the overall incidence of side effects to ALu is low, the common adverse effects reported include sleep disorders, headache, dizziness, nausea, anorexia, abdominal pain, pruritus, rash, cough, palpitation, arthralgia and myalgia.

Lumefantrine does not cause prolongation of QT intervals and therefore it is safe in patients with cardiac illness.

Medicine interactions

The manufacturer of artemether-lumefantrine recommends avoiding the following: grapefruit juice; antiarrhythmics, such as amiodarone, disopyramide, flecainide, procainamide and quinidine; antibacterials, such as macrolides and quinolones; all antidepressants; antifungals such as imidazoles and triazoles; terfenadine; other antimalarials; all antipsychotic drugs; and beta blockers, such as metoprolol and sotalol.

However, there is no evidence that co-administration with these drugs would be harmful (WHO 2010).

Artemether-Lumefantrine administration

- The first dose of Artemether-Lumefantrine should preferably be administered at the health facility as direct observed treatment (DOT)
- When administering Artemether-Lumefantrine, if the medicine is vomited or spat out within 30 minutes, the dose should be repeated
- ALu should be taken with meals to enhance its absorption

Dosage regimen

The recommended treatment is a 6-dose regimen over a 3-day period.

The dosing is based on the number of tablets per dose according to pre-defined weight bands (5–14 kg: 1 tablet; 15–24 kg: 2 tablets; 25–34 kg: 3 tablets; and > 34 kg: 4 tablets), given twice a day for 3 days.

The above recommended regimen approach is more convenient, rather than the use of extrapolates to 1.7/12 mg/kg body weight of Artemether and Lumefantrine, respectively, per dose, given twice a day for 3 days, with a therapeutic dose range of 1.4–4 mg/kg of Artemether and 10–16 mg/kg of Lumefantrine.

Treatment on the basis of clinical suspicion alone should only be considered when parasitological diagnosis is not accessible

The recommended dosing schedule for ALu (strength 20/120 mg) is reported in *table 6.*

Table 6: Dosage schedule of Artemether 20mg & Lumefantrine 120 mg 'ALu' (number of tablets recommended at approximate timing of dosing)

		Day 1		Day 2		Day 3	
Kg	Dose	1st	2nd	3rd	4th	5th	6th
	Hours	0 (*)	8	24	36	48	60
	Age (years)	tablets	tablets	tablets	tablets	tablets	Tablets
up to 15	0 to 3	1	1	1	1	1	1
15 up to 25	3 up to 8	2	2	2	2	2	2
25 up to 354	8 up to 12	3	3	3	3	3	3
35 and above	12 and above	4	4	4	4	4	4
(*) 0 hours means the time of starting medication (see appendix D for time schedule for 1st and 2nd dose)							

For practical purposes, a simpler dosage regimen is recommended in order to improve compliance: the first dose should be given as DOT; the second dose should strictly be given after 8 hours; subsequent doses could be given twice daily (morning-evening) in the second and third day of treatment until completion of 6 doses

Non response to ALu may be due to:

- Vomiting the medicine
- Inadequate dosage
- Poor quality of the medicine
- Fever/symptoms from a cause other than malaria
- Parasite resistance to the medicine (rare)

Management of non-response to malaria treatment with ALu

Treatment failure within 14 days of receiving an ACT in malaria confirmed patient is unusual. Where a confirmed patient returns between 4 to 14 days after treatment with ALu complaining of continued symptoms of malaria, non-response should be considered and the following recommendations followed after a full history, examination and laboratory tests:

- Where laboratory facilities are not available and malaria is still suspected, treatment with DPQ should be started immediately with strict follow up
- Where laboratory facilities are available, a blood smear (and not RDT) should be examined. If parasites are found, treatment with DPQ should be started and treatment failure recorded. If parasites are not found other causes for the symptoms should be sought and treated accordingly

Patients should be instructed to return to the health facility in 2 days if symptoms persist or immediately if condition worsens

Health workers should immediately refer cases that fail to respond to the recommended medicine regimen for further investigations and appropriate management

4.5 Other ACT options for the treatment of uncomplicated malaria

Recommended ACTs options for the treatment of uncomplicated malaria are those with a minimum 3-day course.

The partner medicines in an Artemisinin based combination must, independently, be sufficiently efficacious in treating malaria. Reported resistance to a partner medicine is a significant factor, thus, the higher rates of resistance to a partner medicine the lower the recommendation for the ACT in question.

Efficacious combinations improve treatment outcomes; in parasites resistant to one of the medications in the combination, then the other antimalarial medicine by ensuring that parasites are killed. This mutual protection is thought to prevent or delay the emergence of resistance especially to Artemisinin compounds.

In Tanzania *P. falciparum* treatment failure to following medicines is present and has been reported; a mean treatment failure rate of 25.5% for Sulfadoxine-Pyrimethamine and 11.5% for Amodiaquine[21].

The most recommended regimens are fixed dose combination regimens. These ensure that patients take both medicines together in the right dose. Patient adherence to treatment is also a major determinant of the response to antimalarial medicines, as most treatments are taken at home without medical supervision.

There is no concrete evidence on the safety of Artemisinin in the first trimester of pregnancy so ACT should be avoided in first trimester patients with uncomplicated.

4.5.1 Dihydroartemisinin-Piperaquine (DPQ)

Medicine description

The recommended formulation is an oral fixed combination tablet of Dihydroartemisinin- a derivative of Artemisinin and Piperaquine.

Dihydroartemisinin is the main active metabolite of the Artemisinin derivatives. It has cure rates, toxicity and medicine interaction close to those of other oral Artemisinin derivatives.

Piperaquine is an antimalarial compound belonging to the 4-aminoquinolines.

The exact mechanism of action of Piperaquine is still unknown. It is reasonable to assume that the compound has similar targets as chloroquine considering the close structural resemblance.

Piperaquine is highly active *in vitro* against both chloroquine-sensitive and chloroquine-resistant isolates of *P. falciparum*.

Piperaquine is less toxic than chloroquine or Amodiaquine. However similar cardiovascular side-effects could be seen manifesting such as sinus bradycardia, asymptomatic prolongation of QT interval, which correlates with the food-dependent plasma levels of Piperaquine. Due to this finding Piperaquine (DPQ) should be administered with water without food to minimize these side effects.

The prolonged duration of post-treatment of the Piperaquine combination is evidence for the benefit of Piperaquine as a partner medicine in ACTs.

Available formulation

- Fixed-dose combination with tablets containing Dihydroartemisinin and Piperaquine
- Two strengths for the above formulation:

  40 mg DHA + 320 mg PPQ

  20 mg DHA + 160 mg PPQ (for paediatric formulation)

Indications

- The alternative medicine of choice for the treatment of uncomplicated malaria
- Treatment of uncomplicated malaria where ALu is contraindicated
- Treatment of uncomplicated malaria where ALu has failed

Contraindications

- Hypersensitivity to either Dihydroartemisinin or Piperaquine

Adverse effects

- DPQ does cause sinus bradycardia and asymptomatic prolongation of QT interval. Therefore it is to be given with caution in patients with cardiac illness
- Other known adverse effects related to treatment are, nausea, anorexia, body weakness (asthenia), dizziness and headache

Dosage regimen

A target dose: 4 mg/kg/day of Dihydroartemisinin and 18 mg/kg/day of Piperaquine. Once a day for 3 days

The *table 7* below gives guidanceon dosage schedule for malaria treatment using two different strength DPQ tablets for different pre-defined groups of body weights.

Table 7: *Dosage schedule for DPQ: 4 mg/kg/day Dihydroartemisinin and 18 mg/kg/day Piperaquine once a day for 3 days,*

Body Weight (kg)	Daily dose (mg)		Tablet strength and number of tablets per dose
	Piperaquine	**Dihydro artemisinin**	
5 to <7	80	10	½ x 160mg / 20mg tablet
7 to <13	160	20	1 x 160mg / 20mg tablet
13 to <24	320	40	1 x 320mg / 40mg tablet

Body Weight (kg)	Daily dose (mg)		Tablet strength and number of tablets per dose
	Piperaquine	**Dihydro artemisinin**	
24 to <36	640	80	2 x 320mg / 40mg tablets
36 to <75	960	120	3 x 320mg / 40mg tablets
75 to 100	1,280	160	4 x 320mg / 40mg tablets

4.5.2 Artesunate-Amodiaquine

Available formulations

- Fixed –dose formulation with tablets containing 25/67.5 mg, 50/135 mg or 100/270 mg of artesunate and Amodiaquine
- Separate tablets: containing 50 mg of artesunate and 153 mg base of Amodiaquine respectively

Indications:

Treatment of uncomplicated malaria

Not recommended

First trimester of pregnancy

Dosage regimen

A target dose artesunate: 4 mg/kg/day and 10 mg/kg/day Amodiaquine once a day for 3 days (see *table 8*).

Table 8: Dosing Schedule for Artesunate-Amodiaquine

Body weight ranges (age ranges)	Co-blistered tablets of artesunate and amodiaquine	Fixed dose combination artesunate / amodiaquine tablet
≥4.5kg to < 9 kg (2 to 11 months)	½ tablet of amodiaquine ½ tablet of artesunate per day for 3 days	1 tablet (25mg artesunate/67.5 mg amodiaquine) per day for 3 days
≥9kg to <18kg (1 to 5 years)	1 tablet of amodiaquine 1 tablet of artesunate per day for 3 days	1 tablet (50mg artesunate/135 mg amodiaquine) per day for 3 days
≥18kg to <36kg (6 to 13 years)	2 tablets of amodiaquine 2 tablets of artesunate per day for 3 days	1 tablet (100mg artesunate/270 mg amodiaquine) per day for 3 days
≥ 36kg (14 years and above)	4 tablets of amodiaquine 4 tablets of artesunate per day for 3 days	2 tablets (100mg artesunate/270 mg amodiaquine) per day for 3 days

4.5.3 Artesunate - Mefloquine

Available formulations

This is currently available as blister packs with separate scored tablets containing 50 mg of artesunate and 250 mg base of mefloquine, respectively.

Adverse effects

Mefloquine is associated with an increased incidence of nausea, vomiting, dizziness, dysphoria and sleep disturbance in clinical trials, but these are seldom incapacitating. Where this ACT has been deployed it has been well tolerated.

Indications:

Treatment of uncomplicated malaria.

Not recommended

First trimester of pregnancy.

Dosage regimen

The target dose is artesunate 4 mg/kg/day given once a day for 3 days, and 25 mg/kg of mefloquine split over 2 days as 15 mg/kg and 10 mg/kg. See *Table 9*.

Table 9: Dosing Schedule for Artesunate-Mefloquine*

Age	Dose in mg (no. of tablets)					
	Artesunate			Mefloquine (base)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5–11 months	25 (½)	25	25	–	125 (½)	–
1–6 years	50 (1)	50	50	–	250 (1)	–
7–13 years	100 (2)	100	100	–	500 (2)	250 (1)
>13 years	200 (4)	200	200	–	1000 (4)	500 (2)

***Alternatively the total dose of mefloquine may be split into three, with one third of the dose being taken on days 1, 2 and 3*

4.6Management of fever

Patients with high fever (38.5^{0}C and above) should be given an anti-pyretic medicine like paracetamol (*Table 10*) or aspirin every 4 to 6 hours (maximum 4 doses in 24 hours) until symptoms resolve, usually after two days. Children below 12 years should not be given aspirin because of the risk of developing Reye's syndrome.

Table 10: Treatment schedule for paracetamol (500mg) tablets dosage for children: 10 mg/Kg bwt

Age (years)	Weight (Kg)	Dose
2 months up to 3 yr	4 up to 14	¼
3 up to 5	14 up to 19	½
5 up to 12	19 up to 35	1
12 up to 14	35 up to 45	$1^1/_2$
14 and above	45 and above	2

4.7Recommendations to be given to uncomplicated malaria patient/caretakers

The time of consultation, testing and prescription is a unique and critical opportunity for the health care provider to counsel and advise the patient or the caretaker. In this occasion health education messages should focus on the following:

- Importance of compliance to the parasitological results, antimalarial treatment if test positive, and further investigation if test negative
- Doses, schedules and route
- When to return immediately; worsening conditions especially when fever remains high, excessive vomiting and extreme weakness

- Continue with feeding and fluid intake
- When to return for follow up to the health facility; If symptoms persist after completing correct treatment
- Personal protection measures especially use of long lasting insecticide treated nets

The benefit of parasitological diagnosis depends entirely on health providers adhering to the results when managing patients with uncomplicated malaria

5 Management of Severe Malaria

Severe *Plasmodium falciparum* malaria is a medical emergency. Delay in diagnosis and provision of in appropriate treatment may lead to serious complications and even death. In Tanzania the commonest presentations of severe malaria are severe anaemia and cerebral malaria.

The objectives of treatment of severe malaria are:

To prevent death

To prevent further complications and disabilities

5.1 Principles for the management of severe malaria

In the management of all cases of severe malaria, concerns about prevention of recrudescence, use of Injectable monotherapy in the first 24 hours instead of combination therapies and avoidance of minor side effects are not primary objectives.

Death from severe malaria often occurs within hours of admission to hospital or clinic, so it is essential that highly effective management be achieved as soon as possible.

Management of severe malaria comprises of four main areas; rapid clinical assessment, management of emergency condition, specific antimalarial treatment and supportive care.

5.1.1 Rapid clinical assessment of the patient

Severe malaria is a potentially fatal medical emergency, thus assessment of the patient's condition must be conducted with minimum loss of time. An open airway should be secured in unconscious patients and breathing and circulation assessed. The patient should be weighed or body weight estimated, so that medicines, including antimalarials and fluids, can be given accordingly. Differential diagnosis must be made, malaria tests and relevant supportive investigation performed, see section 3.4.

5.1.2 Management of emergency conditions

After the rapid assessment, open airway should be secured in unconscious patients, breathing supported if necessary and circulation maintained. Convulsions and coma should be managed and severe dehydration corrected.

5.1.3 Specific antimalarial treatment

After above rapid clinical assessment and provisional diagnosis, while waiting for parasite-based confirmatory investigation results, parenteral antimalarial treatment should be started without delay with whichever first available recommended effective antimalarial.

5.1.4 Supportive care

In an attempt to reduce the high mortality of severe malaria caused by complications, supportive treatments should be provided for any complication which appears. Supportive treatment is determined by level of health care delivery and existing capacity.

5.2 Clinical features and conditions related to severe malaria

5.2.1 Features of severe malaria

If the disease progress to a severe form it is diagnosed as severe malaria. Categorisation of a case as severe malaria is due to evidence of vital organ dysfunction. One or more of the features in *Table 11* indicate severe malaria.

Table 11: Features of severe malaria

Clinical features	Description/criteria
Prostration/extreme weakness	Unable to stand or sit up without support
Impaired consciousness	Altered level of consciousness Coma
Change of behaviour	Hallucinations, delusions, agitation Acute state of confusion
Convulsions	Repetitive abnormal muscular movements
Respiratory distress (due to lactic acidosis and/or pulmonary oedema)	*Acidotic breathing*: deep and laboured breathing *Pulmonary oedema*: laboured breathing, restlessness, blood stained frothy sputum
Bleeding tendency/DIC	Easy/prolonged bleeding
Jaundice	Yellow colouration of mucus membranes
Circulatory collapse/shock*	Low systolic BP ** and fast pulse rate ***
Vomiting everything	Throwing up after every feed/drink
Inability to drink or breast feed	Not able to swallow

** Shock: cold extremities, capillary refill delayed for ≥ 3 seconds (when a nail of the thumb is pressed); weak and fast pulse;*

*** Low systolic BP <50 mmHg in children and <90 mmHg in adults;*

**** Fast pulse rate ≥150 per minute in children and ≥100 beats per minute in adults;*

The occurrence of features associated to severe malaria are related to the age of the patient and are summarised in *Table 12.*

Table 12: Clinical features of severe malaria and expected frequency by age group

Clinical features- severe malaria	<5 years	>5 and adults
Duration of illness	Short (1-2 days)	5-7 days
Behavioural Changes	+	+++
Prostration/Extreme weakness	+++	+++
Posturing (decorticate/decerebrate and opistotonic rigidity)	+++	+
Coma	+++	++
Resolution of coma	1-2 days	2-4 days
Neurological sequelae after cerebral malaria	++ (5-30%)	+ (1%)
Respiratory distress	+++	++
Metabolic acidosis	++	++
Convulsions	+++ (30%)	+ (12%)
Hypoglycemia	++	+
Vomiting everything	++	+
Inability to drink or breast feed	++	+
Circulatory collapse/Shock	+	++
Pulmonary oedema	+	+
Bleeding tendency /DIC	+	++ (up to 10%)
Jaundice	+	+++
Acute Renal Failure	+	++
Haemoglobinuria	+	++
Invasive Bacterial co-infection	++ (10%)	+ (<5%)
+ = less common, ++ = common, +++ = Very common		

5.2.2 Conditions related to severe malaria

Malaria infection may cause vital organ dysfunction and death. The common conditions associated with severe malaria and the corresponding laboratory indices are listed in *Table 13*.

Table 13: Common conditions observed in severe malaria cases

		Frequency of condition by agegroup	
Condition	**Corresponding Laboratory Indices**	**<5 years**	**>5 and adults**
Severe malarial anaemia	Hb <5g/dl in children or 7g/dl in pregnant women	+++	+
Haemoglobinuria	Dark brown or Positive Hb on dipstick urine	+	++
Pulmonary oedema	Chest X-ray findings	++	++
Hyperparasitaemia	> 250 000/µL in areas of high stable malaria transmission intensity or >100 000/µL in low intensity transmission areas	++	+
Metabolic acidosis	Arterial pH <7.3, Plasma lactate > 5 mmol/L or Plasma bicarbonate < 15 mmol/L	+++	++
Acute renal failure	Oliguria urine output <0.3 ml/kg/hr in children and <17ml/hr in adults Raised serum creatinine >265 mmol/L	+	+++
Hypoglycaemia	Glucose <2.5 mmol/L	+++	++
Uraemia	BUN >6.7 mmol/L	+	+++
Hyponatraemia	<130 mmol/L	+	+

5.2.3 Supportive investigations for suspected severe malaria ill patients

Laboratory diagnosis of malaria can be complemented with other laboratory tests such as:

- Blood glucose estimation in patients with altered consciousness
- Haematocrit and/or haemoglobin estimation
- Lumbar puncture to exclude meningitis at hospital and health centre levels (if facilities for LP assessment are available)

The following investigations, if available, are also helpful in the management of severely ill patient suspected of having severe malaria:

- Serum creatinine or urea- to assess Kidney function
- Electrolytes- for early detection of acute renal failure
- Full blood cell count and differential white cell count for additional diagnosis of other infectious diseases
- Blood gases, pH and anion gap- to diagnose acidosis

N.B. Plasma and cerebrospinal fluid lactate concentrations. These are raised in metabolic acidosis. High levels are associated with a poor prognosis

Radiological investigation:

- Chest X-ray; look for pulmonary oedema or lobar consolidation

5.3 Treatment of severe malaria

The medicine of choice for treatment of severe malaria is Injectable Artesunate

Injectable Quinine is to be used when Artesunate is contraindicated (in case of allergy, medicine interaction or non-response) and when not available

Give Injectable antimalarials in the treatment of severe malaria for a minimum of 24 hours, even if the patient can tolerate oral medication earlier than 24 hours, and thereafter, complete treatment by giving a complete course of Artemether-Lumefantrine**.**

5.3.1 Artesunate for injection

Description of medicine

Artesunate is a water-soluble derivative of Artemisinin. The only Artemisinin analogue that can be given intravenously, it produces rapid parasite clearance in *falciparum* malaria.

Available formulations

Three formulations are available: 30mg, 60mg and 120mg of Artesunate for injection.

The recommended formulation for public sector is 60mg.

Package details are in *Table 14*:

Table 14: Artesunate for injection package by strength

Strength	30 mg	60 mg	120 mg
Artesunate for injection	1 vial of 30 mg	1 vial of 60 mg	1 vial of 120 mg
Sodium bicarbonate 5%	1 ampoule of 0.5 ml	1 ampoule of 1 ml	1 ampoule of 2.5 ml
Sodium chloride	1 ampoule of 2.5 ml	1 ampoule of 5 ml	1 ampoule of 10 ml

Indications

Medicine of choice for treatment of severe malaria.

Dosage

Artesunate for injection should be administered in a dose of 2.4 mg/kg body weight IV or IM given on admission (time = 0 hour), then at 12 hours and 24 hours.

Children weighting less than 20 kg should receive a higher dose of artesunate: 3 mg/kg/dose with the same schedule as indicated above (0, 12, 24 hours). The higher dose will ensure a drug exposure equivalent to older children and adults.

If the patient can tolerate oral medication after 24 hours provide a full treatment course of ALu. Initiate the first dose of ALu 8 hours after the last injection.

Administration and dosage (60 mg strength)

Injectable Artesunate has 2-steps dilutions.

Step 1: The powder for injection should be diluted with 1ml of 5% sodium bicarbonate solution (provided in each box) and shaken vigorously 2-3 minutes for better dissolving till the solution becomes clear.

Step 2:

- For slow intravenous infusion (3-4 minutes), add 5 ml of 5% dextrose or normal saline, to obtain a Artesunate concentration of 10 mg/ml
- For deep intra-muscular injection, add 2 ml of 5% dextrose or normal saline to obtain a Artesunate concentration of 20 mg/ml

Dilution

The quantity for reconstitution and dilution of different strength are shown in *Table 15.*

Table 15: Quantity for dilution of Artesunate for injection

Route	IV injection			IM injection		
Strength	30 mg	60 mg	120 mg	30 mg	60 mg	120 mg
Sodium bicarbonate 5%	0.5	1	2	0.5	1	2
Normal saline or 5% of glucose	2.5	5	10	1	2	4
Total (ml)	3	6	12	1.5	3	6
Artesunate concentration (mg/ml)	10	10	10	20	20	20

The powder form for injection is difficult to dissolve, care should be taken to ensure that it is completely dissolved before parenteral administration. If the solution is cloudy or a precipitate is present, the parenteral preparation should be discarded. Dissolved artesunate should always be used immediately after 2nd dilution

Never store diluted Artesunate for further use

See also Appendix Ea and Eb; Artesunate injection dilution, administration and dosage.

5.3.2 Alternative medicine for treatment of severe malaria: Injectable Quinine

Injectable Quinine is the alternative treatment for severe malaria where injectable *Artesunate* is contraindicated (in case of allergy, medicine interaction or non-response) or non availability.

Whereas many antimalarials are prescribed in terms of base, for historical reasons quinine doses are often recommended in terms of salt. Several salts of quinine have been formulated for parenteral use, but the dihydrochloride is the most widely used.

Undiluted quinine dihydrochloride at a concentration of 300 mg/ml is acidic (pH 2) and painful when given by intramuscular injection, so it is best either formulated or diluted to concentrations of 60–100 mg/ml for intramuscular injection.

Formulation*:*

- Injection 600 mg in 2 mls

Indications:

- Acceptable alternative choice for treatment of severe malaria
- Medicine of choice for treatment of severe malaria in first trimester of pregnancy

Contraindications

- Hypersensitivity to quinine
- Optic neuritis
- Myasthenia gravis

Use in pregnancy and lactation

Quinine is safe in pregnancy. In therapeutic doses it does not induce labour. Uterine contractions and foetal distress associated with the use of quinine, may be attributable to fever and effects of malaria disease. The risk of quinine induced hypoglycaemia is however greater in pregnant women than in non-pregnant.

Adverse effects

- Cinchonism (tinnitus, muffled hearing, sometimes vertigo or dizziness)
- Hypotension especially if injected rapidly by the intravenous route
- Hypoglycaemia, through stimulation of secretion of insulin from pancreatic beta cells. Hypoglycaemia is particularly likely to develop after intravenous infusion in pregnancy since beta cells are more susceptible to a variety of stimuli at that time
- Injection sterile abscess

Administration of intravenous quinine;

- Quinine 10 mg/kg body weight of salt
- Diluted in 5-10 ml/kg body weight of 5% dextrose or dextrose-saline
- Infused over 4 hours and repeated every 8 hours
- The total volume given will depend on the patient's overall fluid balance

The **drop rate** is calculated as follows:

$$\text{Drop rate per minute} = \frac{\text{amount of fluid to be infused (in ml)}}{\text{time period to be infused (in minutes)}} \times \text{(drop factor)}$$

Table 16 illustrates dilution schedules and drop rates for intravenous quinine administration:

Table 16: Dilution schedule and drop rate for intravenous Quinine administration

Age (years)	Weight(kg)	Quinine dose	Volume of undiluted quinine solution (300mg/ml)	Amount of fluid to be infused (in 4 hours)	Drop rate per minute
2 up to 4 months	4 up to 6	60 mg	0.2 ml	50 ml	4 drops
4 up to 9 months	6 up to 8	90 mg	0.3 ml	100 ml	8 drops
9 up to 12months	8 up to 10	120 mg	0.4 ml	100 ml	8 drops
12 up to 3yrs	10 up to 14	150 mg	0.5 ml	100 ml	8 drops
3 up to 5	15 up to 19	180 mg	0.6 ml	150 ml	13 drops
5 up to 8	19 up to 25	210 mg	0.7 ml	200 ml	17 drops
8 up to 12	25 up to 36	300 mg	1.0 ml	250 ml	21 drops
12 up to 14	36 up to 50	420 mg	1.4 ml	350 ml	30 drops
14 up to 16	50 up to 60	540 mg	1.8 ml	500 ml	42 drops
16 and above	60 and above	600 mg	2.0 ml	500 ml	42 drops

Dilution of quinine for intra-muscular use

- Quinine Dihydrochloride injection (300 mg/ml) for intra-muscular use
- Dose of 10 mg of salt/kg bodyweight (not exceeding a maximum dose of 600mg)
- Dilution: diluted four times in water for injection to a concentration of 60 mg/ml. This dilution will minimize the risk of sterile abscess formation
- Preferably the dose should be calculated for each single patient according to the body weight. *Table 17* summarises guidance dosage

Table 17: Dilution schedule for intra-muscular Quinine administration (Dose = 10 mg/kg of body weight)

Age (years)	Weight (Kg)	Volume of undiluted Quinine (300 mg/ml)	Volume of diluents (to add to each dose)	Total volume of diluted Quinine (60 mg/ml)
2 up to 4 months	4 up to 6	0.2 ml	0.8 ml	1.0 ml
4 up to 9 months	6 up to 8	0.3 ml	1.2 ml	1.5 ml
9 up to 12 months	8 up to 10	0.4 ml	1.6 ml	2.0 ml
12 months up to 3yrs	10 up to 14	0.5 ml	2.0 ml	2.5 ml
3 up to 5	15 up to 19	0.6 ml	2.4 ml	3.0 ml
5 up to 8	19 up to 25	0.7 ml	2.8 ml	3.5 ml
8 up to 12	25 up to 35	1.0 ml	4.0 ml	5.0 ml
12 up to 14	35 up to 50	1.4 ml	5.6 ml	7.0 ml
14 up to 16	50 up to 60	1.8 ml	7.2 ml	9.0 ml
16 and above	60 and above	2.0 ml	8.0 ml	10.0 ml

5.3.3 Other medicines for treatment of severe malaria: Injectable Artemether

Artemether is a lipid soluble Methylether of Dihydroartemisinin

Formulation

Formulation advised by the WHO are ampoules of injectable solutions for intramuscular injection containing 80 mg artemether in 1 ml oil solution for adults or 40 mg artemether in

ml for paediatric use.

Administration and Dosage:

Artemether should be administered in a dose of 3.2 mg/kg body weight loading dose IM stat then 1.6mg/kg body weight (time = 0h then at 24 hrs and 48 hrs). See *table 18* for reference.

If the patient can tolerate oral medication after 24 hours provide a full treatment course of ALu, Initiate the first dose of ALu 8 hours after the last injection.

Table 18: Artemether Injectable dosage by weight

Weight	Loading dose		Second and subsequent doses	
	0 hrs		24, 48, …., hrs	
	Dose	Strength	Dose	Strength
Weight	3.2 mg/Kg	80 mg/ml	1.6 mg/kg	80 mg/ml
Kg	mg	ml	mg	ml
<5	16	0.2	8	0.1
5-8	26	0.3	13	0.2
9-12	38	0.5	19	0.2
13-16	51	0.6	26	0.3
17-20	64	0.8	32	0.4
21-25	80	1.0	40	0.5
26-29	93	1.2	46	0.6
30-33	106	1.3	53	0.7
34-37	118	1.5	59	0.7
38-41	131	1.6	66	0.8
42-45	144	1.8	72	0.9
>45	160	2.0	80	1.0

Artemether injections need additional supplies such as tuberculin syringes.

Artemether injectable can be deployed effectively in malaria epidemics (see section 7.5).

5.3.4 Other medicines for treatment of severe malaria: Rectal Artesunate

Available formulation:

Suppositories 50 mg.

Suppositories 200 mg.

Dosage

10 mg / kg of body weight (see *table 19*).

Indication:

Rectal Artesunate can be administered as a pre-referral medication.

Table 19: dosage regimen for artesunate suppositories for different age groups (10mg/kg body weight)

Weight (Kg)	Age	Artesunate (mg)
<10 kg	<12 months	50mg
10-19 kg	1-5 years	100mg
20-29 kg	6- <10 years	200mg
30-39 kg	10-13 years	300mg
>40 kg	>13 years	400mg

5.4Adjunctive management of severe malaria

In an attempt to reduce the unacceptably high mortality of severe malaria, patients require intensive care. Clinical observations should be made as frequently as possible. See *table 20*.

Table 20: Immediate clinical management of complications due to severe malaria

Condition	Immediate management
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis)
Hyperpyrexia	Fanning and antipyretic medicines. Paracetamol is preferred over other medicines
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam or Intramuscular paraldehyde. Check blood glucose
Hypoglycaemia	Check blood glucose, correct hypoglycaemia and maintain with glucose containing infusion
Severe anaemia	Transfuse with screened fresh whole blood
Acute pulmonary oedema	Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids
Acute renal failure	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure add haemofiltration or haemodialysis
Spontaneous bleeding and Coagulopathy	Transfuse with screened fresh whole blood and give vitamin K injection
Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and septicemia. If severe, add or refer for haemofiltration or haemodialysis
Shock	Suspect septicaemia, take blood for cultures; give parenteral broad-spectrum antimicrobials, correct haemodynamic disturbances

5.5 Management of severe malaria by levels of health facility

The transit time between referral and arrival at appropriate health facilities is usually prolonged thus delaying the commencement of appropriate antimalarial treatment.

During this time the patient may deteriorate or die. It is recommended that patients are treated with the first dose of one of the recommended parenteral treatments before referral (unless the referral time is very short). This could be intramuscular Artesunate, Artemether, or Quinine.

5.5.1 Management of severe malaria at community level (Home and ADDO)

Management should include

- Early recognition of symptoms and signs defining severe malaria with appropriate early health care seeking behaviour
- Control of fever by the use of anti-pyretics and fanning (kupepea)
- Continued feeding and fluid intake
- Immediate referral to the nearest health care facility

5.5.2 Management of severe malaria at dispensary level

Management should include

- Early diagnosis of severe malaria based upon a complete history, physical examination Taking and reporting of blood smear/mRDT must not be allowed to delay treatment unduly
- Provision of pre-referral treatment with i/m Artesunate
- Immediate referral with clinical summary, to the nearest health care facility where resources for the continuing care of patients with severe malaria are available

General management

Assessment and resuscitation

- Airway – ensure airway is open with no foreign objects
- Put the patient in semi prone position
- Breathing – ensure there is adequate respiratory movement
- Circulation – measure pulse rate and blood pressure
- Blood slide for malaria parasites (do not wait for results)
- Blood glucose estimation by glucose strips
- Hb estimation

Pre-referral treatment

- Administration of i/m Artesunate
- In suspected severe malaria where meningitis and septicaemia cannot be ruled out, a broad-spectrum antibiotic (e.g. Chloramphenicol) should be administered
- Correction of hypoglycaemia by using oral sugar-water
- Control fever with anti-pyretics and fanning (kupepea)
- Control convulsion with diazepam

5.5.3 Management of severe malaria at health centre level

Management should include

- Early diagnosis of severe malaria based upon a complete history, physical examination and blood smear/RDT for malaria parasites. Taking and reporting of blood smear must not be allowed to delay treatment unduly
- Provision of appropriate treatment intravenously/intramuscularly. Artesunate injection should be given on admission (time = 0 hour), then at 12 hours and 24 hours (in the first 24 hours irrespective of the patient's ability to tolerate oral medication earlier) and, thereafter, complete treatment by a full course of ALu. Initiate the first oral dose 8 hours after the last injection
- Treatment of hypoglycaemia. Hypoglycaemia remains a major problem in the management of severe malaria especially in young children and pregnant women. It should be deliberately looked for and treated accordingly
- Referral with clinical summary to the nearest hospital when clinical need dictates (e.g. blood transfusion or intensive care)

General management

Assessment and resuscitation

- Airway – ensure airway is open with no foreign objects
- Put the patient in semi prone position
- Breathing – ensure there is adequate respiratory movement
- Circulation – measure pulse rate and blood pressure
- Blood slide for malaria parasites (do not wait for results)
- Blood glucose estimation by glucose strips/glucometer
- Hb estimation

Insert intravenous cannula

- Blood samples for random blood glucose (RBG), full blood picture (FBP), serum creatinine, liver function tests (bilirubin, AST, ALT, ALP) and serum electrolytes
- Start dextrose-saline or dextrose 5% infusion

Insert naso-gastrict tube (if indicated)

- For feeding and medication

Insert urethral catheter (if indicated)

- Urine for dipstick
- Urinary output measurement

Nursing care and monitoring

- Fluid input and output chart
- Level of consciousness
- Temperature, PR, RR and BP
- Feeding
- Changing position every 2 hours

Investigations

- Hb, Glucose, Creatinine, Electrolytes if indicated

5.5.4 Management of severe malaria at hospital level

Management should include:

Early diagnosis of severe malaria based upon a complete history, physical examination and blood smear/RDT for malaria parasites. Taking and reporting of blood smear and other investigations must not be allowed to delay treatment unduly.

- Provision of appropriate treatment intravenously/intramuscularly. Artesunate injection should be given on admission (time = 0 hour), then at 12 hours and 24 hours (in the first 24 hours irrespective of the patient's ability to tolerate oral medication earlier), and thereafter, complete treatment by a full course of ALu. Initiate the first oral dose 8 hours after the last injection
- General management, nursing care and monitoring
- Treatment of complications e.g. blood transfusion
- Treatment of hypoglycaemia. Hypoglycaemia remains a major problem in the management of severe malaria especially in young children and pregnant women. It should be deliberately looked for and treated accordingly
- Laboratory investigations for other complications where indicated

General management

Assessment and resuscitation

- Airway – ensure airway is open with no foreign objects
- Put the patient in a semi prone position
- Breathing – ensure there is adequate respiratory movement
- Circulation – measure pulse rate and blood pressure
- Blood slide for malaria parasites (do not wait for results)
- Blood glucose estimation by glucose strips/glucometer
- Hb estimation
- Insert intravenous cannula

- Blood samples for random blood glucose (RBG), full blood picture (FBP), serum creatinine, liver function tests (bilirubin, AST, ALT, ALP) and serum electrolytes
- Start dextrose-saline or dextrose 5% infusion

Insert naso-gastrict tube (if indicated)

- For feeding and medication

Insert urethral catheter (if indicated)

- Urine for dipstick
- Urinary output measurement

Nursing care and monitoring

- Fluid input and output chart
- Level of consciousness
- Temperature, PR, RR and BP
- Feeding
- Changing position every 2 hours

Investigations

Investigations of severe malaria at hospital level are shown in *table 21.*

Table 21: Investigations of severe malaria at hospital level

Essential	If indicated
Blood film for malaria parasites/RDT	Blood culture and sensitivity
Blood glucose estimation	Chest radiograph
Full blood picture	Cerebrospinal fluid analysis
Urinalysis (including detection of Hb)	Urine culture and sensitivity
Biochemical tests:	Serum lactate, serum bicarbonate, serum creatinine, liver function tests (bilirubin, AST, ALT, ALP) arterial pH and serum electrolytes

5.6Monitoring of patients with severe malaria

All patients with severe malaria should be closely monitored clinically as described in *table 22*.

Table 22: Important clinical observations and their implications during treatment of severe malaria

Regularly observe	Possible observation	Appropriate action
Breathing	Increased respiratory rate: • *< 2 months: 60 or more*	- Check position of the patient - Put the patient in semi-prone (Fowler's) position

Regularly observe	Possible observation	Appropriate action
	per minute • *2 up to 12 months: 50 or more per min* • *1 yr up to 5 yrs: 40 or more per min* • *5 yrs and above: 20 or more per min* Or difficulty in breathing	- Give oxygen if there is respiratory distress - Review urine output - Examine lung, heart and size of the liver - Chest X ray if available - If pulmonary oedema is demonstrated, or seems likely treat appropriately
Axillary temperature	*≥38.5^{0}C* *If temperature remains high or rises despite 24 hours of artesunate therapy*	- Give paracetamol if not given within the past 4 hours - Fanning (*kupepea*) - Reassess and investigate for other possible causes while continuing treatment
Shock	Cold extremities, capillary refill delayed for ≥ 3 seconds (when a nail of the thumb is pressed); weak and fast pulse; BP Falls: • *<90 mmHg systolic in an adult* • *< 50 mmHg in infants and children (using paediatric cuff)*	- Review fluid balance, urine output, and haematocrit - If hypovolaemic/dehydrated give saline infusion where indicated - Evidence recommends not to give bolus (rapid) infusion to severely ill children in shock if not dehydrated, it is associated with increased mortality - Look for haemorrhage - Take blood for bacteriological culture and sensitivity if facilities are available - Give broad spectrum antibiotic (for possible gram negative bacteraemia) if confirmed or sepsis suspected
Urine output	Oliguria: • *<17 ml/hr in an adult or* • *<0.3 ml/kg/hr in infants and children*	- Review fluid input and status of hydration - Correct fluid deficit if necessary - Prevent or manage acute renal failure if suspected - Catheterize if acute renal failure
Coma score	Deterioration *See appendix F for Glasgow and Blantyre coma scale*	- Reassess and investigate for other possible causes while continuing treatment - Immediately check blood glucose (correct hypoglycaemia if suspected) - Lumbar puncture
Convulsions	These can recur, or develop for the first time during treatment and may be due to fever, abnormal blood glucose or electrolyte imbalance or other causes	- Check axillary temperature if ≥38.5^{0}C , treat as above - Check blood glucose (correct hypoglycaemia if suspected) - Check fluid balance - Check electrolytes if possible (to detect hyponatraemia) - Give anticonvulsant medicines

Regularly observe	Possible observation	Appropriate action
Bleeding from venepuncture sites or spontaneous haemorrhage	Prolonged bleeding time suggesting *Disseminated intravascular coagulopathy* (DIC)	- Check bleeding time - Grouping and cross matching blood - Give whole fresh blood as needed to correct blood loss and bleeding tendency (20 ml/kg for children, 2 units in adults)

Laboratory indices should be also frequently monitored to establish the appropriate actions to be taken (see *table 23*).

Table 23: Important observations and their implications during treatment of severe malaria: laboratory parameters

Regularly observe	Possible observation	Appropriate action
Blood glucose	Falls below 2.5 mmol/L (<45 mg/dl) OR <3.0 mmol/L (54mg/dl) in malnourished children	- Ask when last fed. A child will become hypoglycaemic if deprived of glucose for more than 12 hours - Give IV 10 or 25% glucose bolus - Review infusion - Maintain feeding
Haematocrit	Falls to 12% or below	- Grouping and cross-matching blood - Give blood transfusion 10 mls/kg body weight of packed cells - Repeat haemoglobin and haematocrit at regular intervals - Consider transfusion if in cardiac failure even if Hb is >4g/dl
Haemoglobin	Falls to 4g/dl or below	
Parasitaemia	Remains high 2-3 days or remains positive for >5 days Parasitaemia commonly remains at the initial level for 12-24 hours even if medicines are fully effective	- Take BS for malaria parasites daily until the results are negative - Review adequacy of antimalarial dosage - Consider alternative medicine (Quinine)

5.7Emergency management of severe malaria

5.7.1 Convulsions

Convulsions are common in children with severe *P. falciparum* malaria but are relatively rare in adults. The general principles for the care of patients with convulsions should be as follows:

- Maintenance of a clear airway
- Monitoring of vital signs: temperature, pulse rate, respiratory rate and blood pressure
- Nurse the patient in a semi-prone position

- Check blood glucose where possible, or give IV dextrose

Administer anticonvulsant medicines:

- Diazepam 0.15 mg/ kg (maximum 10 mg for adults.) slow bolus IV injection
- In children, diazepam rectal route should be used. Give a dose of 0.5-1.0 mg/ kg. Draw the IV preparation into a small syringe and remove the needle. Insert 5 cm of a naso-gastric tube into the rectum. Inject the diazepam into the naso-gastric tube and flush it with 5 ml of water. If a naso-gastric tube is not available, use a syringe without a needle. Hold buttocks together for few minutes to ensure retention and absorption of the medicine
- If convulsions persist after 10 minutes repeat rectal diazepam treatment as above. Should convulsions continue despite a second dose, give a further dose of rectal diazepam or phenobarbitone 20 mg/ kg IM or IV after another 10 minutes

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

5.7.2 Hypoglycaemia

Check blood glucose every 4 hours. If blood glucose level falls to< 2.5 mmol/L or level of consciousness deteriorates.

In children

- Give 5 ml/kg of 10% dextrose OR 2.5 ml/kg of 25% dextrose as bolus
- If 50% dextrose solution is available, it should be diluted to make 25% by adding an equal volume of water for injection or normal saline

In adults

- Give 125 mls of 10% dextrose OR 50 mls of 25% dextrose as bolus

Where dextrose is not available, sugar water should be prepared by mixing 20 gm of sugar (4-level tea spoons) with 200 ml of clean water. 50 ml of this solution is given ORALLY or by naso-gastric tube if unconscious

5.7.3 Hypotension

Give colloid fluids (plasma expander) or blood if haemoglobin is less than 5g/dl.

5.7.4 Pulmonary oedema

Check for

- Restlessness
- Frothy sputum
- Basal crepitations
- Low oxygen saturation (< 95%)

Give

- Oxygen
- IV furosemide
- Mechanical ventilation may be needed

5.7.5 Metabolic Acidosis

In malaria patients metabolic acidosis is attributed to **lactic acidosis.**

Check for

- Respiratory distress, deep and laboured breathing

Give

- Oxygen
- Correct hypovolaemia

6 Anaemia in relation to Malaria

6.1 The relation between malaria and anaemia

The aetiology of anaemia in malaria endemic areas is often multi-factorial, with different causes interacting in a vicious cycle of nutritional deficiencies, infections and inherited red blood cell disorders. However, malaria remains one of the main contributors.

In endemic areas, malaria clinical diagnosis is based on a history of fever in the previous 24 h and/or the presence of anaemia, for which pallor of the palms appears to be the most reliable sign in young children. In the same settings malaria in pregnancy is associated with increased anaemia.

Anaemia can result from repeated or persistent malaria infections, which may result from inadequate treatment, parasite resistance or no treatment at all. Anaemia, weakness and febrile episodes are characteristic of these cases. Anaemia due to malaria may develop rapidly following an acute malaria attack or insidiously over a period of time as described above.

On the other hand, severe anaemia in young children is the principal manifestation of severe *falciparum* malaria. Severe malaria is associated with rapid development of anaemia as infected and uninfected erythrocytes are removed from the circulation. Mortality as a direct result of anaemia rises at lower haemoglobin levels.

Children commonly present with severe anaemia and hyperventilation (sometimes termed “respiratory distress”). In the past this was ascribed to “anaemic heart failure” (i.e. pulmonary oedema), and sometimes diuretics were administered. It is now clear that this syndrome is not a result of anaemic heart failure, but results from severe metabolic acidosis and anaemia, and so should be treated by blood transfusion.

Anaemia is defined as reduction of red blood cells or haemoglobin (Hb) concentration or both below the normal range for the age and sex of the individual (see *table 24*).

Anaemia due to malaria is usually normocytic and normochromic in nature. During the course of malaria infection, red blood cells are destroyed.

Table 24: Normal Haemoglobin concentration levels by ages and sex

Category	Hb g/dl
Newborn	13.5 - 20
Children less than 6 years	11 - 13
Adult females, not pregnant	12 - 16
Adult females, pregnant	11 - 15
Adult males	13 - 17

6.2 Clinical presentation and classification of anaemia

6.2.1 Clinical presentation of anaemia

In areas of high malaria endemicity the association between malaria and anaemia is strong. However, patients presenting with anaemia and malaria are frequently not treated correctly because their symptoms and signs are often missed. All patients, especially pregnant women and young children, presenting to health facilities with malaria should be checked carefully for anaemia. This should be done by asking about anaemia related symptoms and checking for physical signs.

Ask for (symptoms):

- Tires or is fatigued easily
- Inability to feed and drink (Infants and children)
- Dizziness and breathlessness on exertion in pregnant women
- History of eating soil (especially in children or pregnant women)

Look for (signs):

- Pallor (palms, soles, nails beds, conjunctivae and tongue)
- Signs of respiratory distress (nasal flaring, chest in-drawing and deep breathing or grunting)
- Signs of congestive heart failure (dyspnoea, tachycardia, gallop rhythm, basal crepitations, oedema, puffy eyes, raised jugular venous pressure and enlarged tender liver)

6.2.2 Classification of anaemia according to severity

A classification based on severity of anaemia provides an ideal approach on its management. The following classification is based on IMCI protocol (see **Appendix** G).

Mild/moderate anaemia, Hb 8.5-11 g/dl

- Some pallor

Severe anaemia, Hb <8.5 g/dl

- Severe palmar pallor
- Excessive tiring
- Dyspnoea or breathlessness
- Warm hands
- Peripheral oedema: pedal pitting
- Tachycardia, collapsing pulse, wide pulse pressure and gallop rhythm
- Ejection systolic murmur (‘flow’ murmur)

Life threatening anaemia, Hb<5g/dl

Respiratory distress

- Nasal flaring
- Chest in-drawing
- Deep breathing or grunting

Congestive heart failure

- Pulmonary oedema: basal crepitations
- Peripheral oedema: pedal, periorbital and sacral.
- Circulatory congestion: raised jugular venous pressure and enlarged tender liver
- Tachycardia
- Gallop rhythm

6.3 Management of malarial anaemia

6.3.1 Management of mild/moderate anaemia (8.5 up to 11 g/dl) associated with malaria

Features

- Some pallor, body weakness

Management

Patients with some pallor or moderate anaemia (Hb 8.5 - 11 g/dl) need to be treated for malaria, as persistent parasitaemia is a cause of anaemia by dyserythropoiesis and haemolysis. Iron and folic acid speed up haematological recovery after malaria and should be given at least for three months. It is also important to treat hookworm infestation in children, as this is a common cause of iron deficiency anaemia.

Folic acid tablets administration

- Start a 3 months treatment course (5 mg daily)

Ferrous sulphate tablets administration

- Start a three months course at dose of 6 mg/kg of elemental iron daily
- Adults need 200mg ferrous sulphate (one tablet) three times daily

6.3.2 Management of severe anaemia (Hb 5 up to <8.5g/dl) associated with malaria

Features

- Severe palmar pallor, excessive tiring, dyspnoea or breathlessness, warm hands, peripheral oedema, pedal pitting, tachycardia, collapsing pulse, wide pulse pressure and gallop rhythm, ejection systolic murmur ('flow' murmur)

Management

This condition can be managed through outpatient services with close monitoring OR can be admitted depending on the severity of the above features

- Test and eventually treat malaria (see chapter 3 and 4)
- Perform full blood count to investigate morphological type
- Do other investigations to identify other underlying causes of anaemia e.g. stool sample for hookworm and treat accordingly
- Give oral haematenics for at least three months
- Advise to return immediately if condition worsens
- Follow up after 15 days

6.3.3 Life threatening anaemia (Hb < 5g/dl) associated with malaria

Features

- Respiratory distress
- Congestive heart failure

Treatment

This is a medical emergency.

- Admit the patient
- Treat malaria as severe malaria with parenteral antimalarials (see management of severe malaria)
- Prop the patient up with pillows or clothing
- Administer oxygen (2.5 L/min in adults, 1.0-2.0 L/min in children) to improve oxygen delivery
- Draw blood for grouping and cross matching

Indications for urgent blood transfusion

- Hb equal or less than 4 g/dl and/or
- Signs of heart failure
- Signs of respiratory distress

Administration of blood

- Use packed cell (10 ml/kg in children) or whole blood 20 ml/kg body weight
- Transfuse slowly (4-6 hours per unit)

$$\text{Drip: drops/min} = \frac{\text{volume to be transfused in ml} \times 20\text{(or 15) drop factor}}{\text{time of transfusion in hours (4-6 hours)}} \times 60 \text{ minutes}$$

N.B. ***1ml whole blood= 20 drops***

1ml packed cell= 15 drops

- Where blood is not available, give pre-referral treatment and refer urgently to a health facility with blood transfusion services
- Diuretics: Frusemide (IV/IM) for an adult 40 mg or 1 mg/kg bodyweight for children

Children with malarial anaemia are hypovolaemic

Follow-up after discharge

- Start folic acid and ferrous sulphate (do not give ferrous sulphate to sickle cell patients)
- Review after 14 days to check on haemoglobin or haematocrit level
- Continue treatment for at least three months
- Encourage patients to protect themselves from being bitten by mosquitoes by sleeping under an Insecticide Treated Net (ITN)

6.3.4 Management of anaemia associated with malaria in pregnancy

In anaemic pregnant women, even if there are no signs or symptoms of malaria, perform malaria test preferably mRDT, if positive give an effective antimalarial appropriate for the gestational age; if negative investigate for other causes of anaemia (see section 7.1.4).

7 Management of Malaria in Special Situations and Groups

7.1 Malaria in pregnancy

Malaria is an important cause of morbidity and mortality for the pregnant woman, the foetus and the new-born.

During pregnancy, the naturally acquired partial immunity to malaria declines. The decline in immunity is most pronounced during the first and second pregnancy. The reasons for the decline in immunity are yet to be determined. Pregnant women, especially primigravidae, are more susceptible to malarial infection than non-pregnant women.

Malaria infection is often covert during pregnancy. Pregnant women with symptomatic acute malaria are a high-risk group, and they must promptly receive effective antimalarial treatment. In primigravidae malaria tends to be more frequent and the attacks more severe.

7.1.1 Effects of malaria in pregnancy

The effects of malaria in pregnancy to the foetus and new-born are related to malaria endemicity, with abortion or stillbirth more common in areas of low endemicity and intrauterine growth retardation more common in areas of high endemicity [22].

In high-transmission settings, though usually asymptomatic, the adverse effects of malaria to the pregnant woman include anaemia. Conversely, in low-transmission areas, malaria is common to be clinically evident and pose an increased risk of severe malaria and death. *Table 25* summarizes the effects of malaria in pregnancy.

Table 25: Effects of malaria on morbidity among pregnant woman, foetus and new born

	Pregnant Woman	Foetus	New born
Morbidity	Severe malaria (*)	Intrauterine growth retardation	Low birth weight
	Anaemia	Congenital Infection	Prematurity
	Premature labour		Congenital /neonatal malaria
(*) especially cerebral malaria and pulmonary oedema			

7.1.2 Management of uncomplicated malaria in pregnancy

Early diagnosis and effective case management of malaria illness in pregnant women is crucial in preventing the progression of uncomplicated malaria to severe disease and death.

Clinical features of uncomplicated malaria

The clinical presentation of malaria during pregnancy is often hidden. Some pregnant women will present with the suggestive features of uncomplicated and/or severe malaria (see chapters 4 and 5). However in others, anaemia may be the only recognizable clinical feature.

Diagnosis of uncomplicated malaria in pregnancy

Diagnosis should follow the general principles of diagnosis of malaria based on accurate history taking, complete physical examination and appropriate laboratory tests as in any other malaria patients.

Treatment of uncomplicated malaria

In reality, women often do not declare their pregnancies in the first trimester or are not yet aware that they are pregnant; so all women of child bearing age should be asked about the possibility of being pregnant before being given antimalarials, a standard practice for the administration of any medicine in potentially pregnant women, should be observed. Nevertheless, early pregnancies will often be exposed inadvertently to the available first-line treatment in the population, mostly ACTs.

During history taking and physical examination, it is particularly important to elicit signs and symptoms of uncomplicated malaria. Whenever malaria is suspected, laboratory confirmation of malaria parasites should be performed. A negative peripheral blood slide result does not rule out the presence of placental parasitaemia. However, malaria RDT is considered a reliable indicator of placental infection[23].

Malaria treatment in the first trimester of pregnancy

Presently, Artemisinin derivatives cannot be recommended for treatment of malaria in the first trimester of pregnancy. However, they should not be withheld if treatment is considered to be life saving for the mother and other antimalarial are not available or considered to be unsuitable. Data from prospective studies are limited, but Quinine is considered safe in the first trimester of pregnancy.

Pregnant women in the first trimester with uncomplicated falciparum malaria should be treated with quinine tablets for seven days

Administration of oral quinine: Quinine is safe in pregnancy, in therapeutic doses it does not induce labour. Uterine contractions and foetal distress with the use of quinine may be attributable to fever and effects of malaria disease.

- Quinine Tablet strength 300 mg (salt)
- Quinine tablets (salt) should be given for 7 days at a dose of 10 mg/kg every 8 hours, for treatment of uncomplicated malaria in 1st trimester
- Do not exceed a maximum dose of 600mg per day

Malaria treatment in second and third trimester of pregnancy

There is increasing experience with Artemisinin derivatives in the second and third trimesters. There have been no adverse effects on the mother or foetus. Assessment of benefits compared with potential risks suggests that the Artemisinin derivatives should be used to treat uncomplicated *falciparum* malaria in the second and third trimesters of pregnancy. Adequate information on the choice of drug combination partner is crucial.

ALu is well tolerated and safe in pregnancy during second and third trimester. (See also section 4: Management of uncomplicated malaria).

During the second and third trimesters of pregnancy Artemether-Lumefantrine should be used as medicine of choice for treatment of uncomplicated malaria

7.1.3 Management of severe malaria in pregnancy

Pregnant women infected with malaria are at risky group i.e. they are more susceptible to develop severe malaria. Maternal mortality due to severe malaria is higher than in non-pregnant adults. Foetal death and premature labour are common.

Clinical features of severe malaria in pregnancy

Women in the second and third trimesters of pregnancy are more likely to develop severe malaria than other adults, often complicated by pulmonary oedema and hypoglycaemia.

The following are commonly presenting features:

- high fever
- hyperparasitemia
- low blood sugar
- severe haemolytic anaemia
- cerebral malaria
- pulmonary oedema

Diagnosis of severe malaria in pregnancy

Diagnosis of severe malaria in pregnancy should follow the general principles of diagnosis of malaria based on accurate history taking, complete physical examination and appropriate laboratory tests.

Treatment of severe malaria in pregnancy

The primary objective of antimalarial treatment in severe malaria is to prevent death. In the treatment of severe malaria in pregnancy, saving the life of the mother is the primary objective.

The medicine of choice for treatment of severe malaria in the first trimester of pregnancy is IV Quinine (see chapter 5).

The medicine of choice for treatment of severe malaria in 2nd and 3rd trimester of pregnancy is Injectable Artesunate (see chapter 5).

Quinine is associated with an increased risk of hypoglycaemia in late pregnancy, and it should be used only if Artesunate injectable is not available. (See specific antimalarial treatment in section 5: Management of severe malaria).

7.1.4 Anaemia associated with malaria in pregnancy

A Pregnant woman with haemoglobin (Hb) level of <11 g/dl (or haematocrit <33%) is considered anaemic. The aetiology of anaemia in pregnancy is multi-factorial. In primigravidae, malaria is the major contributor to anaemia. Malaria infection in pregnancy worsens pre-existing conditions of anaemia; the risk of maternal mortality, especially in the face of complications such as abortion and haemorrhage, is increased by anaemia and which can be a direct cause of mortality due to cardiac failure. Anaemia can also contribute to stillbirth and low birth weight.

In Tanzania, **the major** causes of anaemia in pregnancy are:

- Malaria
- Hookworm and schistosomiasis infestation (due to increased blood loss)
- Iron and folate deficiency (due to poor dietary intake and increased demand due to pregnancy)
- Chronic infection including TB, HIV/AIDS
- Deliveries at short intervals (less than 3 years)

There are three approaches for addressing the maternal anaemia problem:

- Early diagnosis
- Treatment
- Prevention

Management of mild/moderate anaemia (Hb 8.5 up to 11 g/dl) in pregnancy

Perform appropriate investigations (malaria test (BS/mRDT), peripheral blood film, RBC indices, WBC total and differential, urinalysis, and stool examination)

Treat the cause of anaemia if determined

Give the following medicines

- Full course of oral quinine in the first trimester or ALu in second and third trimesters if the patient is positive for a malaria test
- Combined ferrous sulphate 200mg + folic acid 0.25mg (FeFo) twice daily for three months
- Antihelminthics (e.g. mebendazole from second trimester)
- Treat schistosomiasis if the patient lives in areas with high schistosomiasis transmission (after delivery).

Monitor response to treatment

- Clinical response
- Hb measurement is recommended every 2 weeks until Hb reaches 11 g/dl
- Reticulocyte count

For non-responding patients other investigations should be considered e.g. bone marrow aspiration.

Management of severe anaemia (Hb < 8.5 g/dl) in pregnancy

Severe anaemia has to be aggressively treated before the woman goes into labour. During labour a patient may go into cardiac failure because of the increased work of the heart. Likewise, the shunting of the blood to the circulation from the placental bed after delivery may overload the circulation and precipitate cardiac failure.

Aims of treatment

- Correct anaemia and improve Hb concentration to a safe level (> 8.5 g/dl) before the patient goes into labour
- Avert congestive cardiac failure by increasing the oxygen carrying capacity

Management of severe anaemia

Gestational age should determine the appropriate approach for the management of severe anaemia in pregnancy. Before 36 weeks of gestational age and if the patient is not in cardiac failure the treatment should be as for the above moderate anaemia. If in failure and after 36 weeks of gestational age with or without failure:

- Treat the cause if determined
- Give blood transfusion (preferably packed cells)
- Continue with combined iron and folic acid up to 3 months after delivery
- Follow up the patient every 2 weeks until Hb reaches 11 g/dl

7.1.5 Prevention of anaemia during pregnancy

Routine prevention of anaemia is part of the antenatal care in all RCH clinics. During the scheduled ANC visits the following services are offered to pregnant women:

- Combined ferrous sulphate 200mg + folic acid 0.25mg (FeFo) once daily
- Intermittent Preventive Treatment (see below)
- Early detection of anaemia
- Hb screening
- Symptom sign surveillance
- De-worming as indicated in the focused antenatal care (FANC)
- Treatment of any underlying infection

Malaria test and treatment at first ANC attendanceAll women should be advised on appropriate diet during pregnancy and on personal malaria protection using long lasting insecticide treated nets (LLINs).

7.1.6 Prevention of malaria during pregnancy

Controlling the effects of malaria infection on the pregnant woman and the foetus requires a balanced programme of effective case management of malaria illness and prevention of the consequences of asymptomatic infection. Evidence based effective preventive interventions are required. These interventions consist of intermittent preventive treatment and use of insecticide treated nets.

Intermittent preventive treatment in pregnancy (IPTp)

Intermittent preventive treatment (IPT) is the administration of antimalarials in full therapeutic doses at predetermined intervals during pregnancy even if individuals have no signs of malaria. IPT should not be considered as chemoprophylaxis; the woman is not protected from infection and still could be infected after taking IPT.

The aim of IPT is to prevent adverse effects of malaria on both mother and fetus, including maternal anaemia, foetal loss, premature delivery, intrauterine growth retardation, and delivery of low birth-weight infants.

The medicine of choice for IPT is Sulfadoxine/Pyrimethamine (SP)

SP remains the medicine of choice for IPT. It is particularly important that medicines used in pregnancy are known to be safe; SP is a medicine with a long half-life and still effective when used as IPT.

There is convincing evidence[24] showing that it is beneficial for both the pregnant woman and her baby to receive more than 2 doses of SP (IPTp), and that as many as 4 or 5 doses of SP are safe in pregnancy.

IPTp with SP is recommended for all pregnant women at each scheduled antenatal care visit. The first IPTp-SP dose should be administered as early as possible during the 2nd trimester of gestation

- Each SP dose should be given at least 1 month apart
- The last dose of IPTp with SP can be administered up to the time of delivery, without safety concerns. Taking SP in the last four months of pregnancy is not associated with kernicterus (jaundice in the new-born) as previously thought; therefore it is safe to give SP right up until the time of delivery
- SP can be given either on an empty stomach or with food
- SP can be administered safely with combined ferrous sulphate 200 mg + folic acid 0.25 mg (FeFo)
- In exceptional cases where a pregnant woman is taking folic acid at a daily dose equal or above 5 mg, she should not take it together with SP as this counteracts its efficacy
- SP should not be administered to women receiving cotrimoxazole prophylaxis

IPT should be administered as direct observed treatment (DOT) during an antenatal care visit

- If malaria is diagnosed after administration of IPT with SP a full treatment with antimalarials should be given according to the guidelines (see chapter 4 or 5)
- IPT is not a contraindication to tetanus toxoid injection and the two can be administered simultaneously
- Pregnant women who are known to have hypersensitivity to sulfonamides (most commonly skin rashes) should not receive SP for IPT. No other medicine should be used for IPT. Currently, no alternative medicine is recommended for IPT apart from SP
- If a woman is treated for malaria with an antimalarial at the ANC visit or in the 4 weeks before, it is not necessary to give her SP as well. She should be instructed to return in about a month for her next ANC visit and IPTp-SP should be given at that time

Long Lasting Insecticide Treated Net (LLIN)

Pregnant women should be advised to sleep under Long Lasting Insecticide Treated Nets (LLINs) at night and to take other personal protective measures to reduce contact with mosquitoes.

Mothers should be encouraged to protect their newborn infants with LLINs

7.2 Malaria in neonates

Though rare, congenital and neonatal malaria does occur. A significant proportion of neonates with malaria may be missed in the wards on the assumption that the disease condition is rare. Neonatal malaria is defined as symptoms attributable to malaria with evidence of ring forms of malaria parasite in the blood of an infant within the first twenty-eight days (4 weeks) of life.

Congenital malaria is defined as symptoms attributable to malaria with evidence of ring forms of malaria parasite in the blood of an infant within the first seven days (1 week) of life.

Congenital or acquired malaria in this age group is life threatening and requires immediate treatment.

The signs and symptoms resemble those seen in the new-born with septicaemia.

7.2.1 Clinical features of malaria in the neonatal period

The clinical features of malaria in the new-born include:

- Fever
- Lethargy
- Unable to breastfeed
- Vomiting
- Irritability
- Respiratory distress
- Seizures
- Jaundice
- Pallor
- Hepatosplenomegaly

Laboratory findings will include the presence of malaria parasites, hyperbilirubinaemia, anaemia (Hb<13.5 g/dl), hypoglycaemia and acidosis.

7.2.2 Management of neonatal malaria

- Neonates with suspected malaria should be admitted to hospital immediately as they can deteriorate quickly and die at home
- Symptoms and signs of neonatal malaria mimic serious bacterial infection. Therefore, a thorough investigation should be done

Assessment and resuscitation

- Airway: ensure airway is open
- Breathing: ensure there is adequate respiratory movements, give oxygen if there is cyanosis
- Circulation: measure pulse rate

Investigations

- FBP
- blood sugar
- blood culture and sensitivity, blood slide for malaria parasite, serum electrolytes

Treatment

- Broad spectrum antibiotic as provided in the Standard Treatment Guidelines (STG)
- Parental Artesunate is recommended as 1st line treatment for neonates and infants below 5kg with severe malaria. Injectable quinine remains a suitable alternative where Artesunate is not available
- If a neonate is not able to breast feed, give 10% glucose IV 60ml/kg/24hours
- Give blood transfusion if HB is <10g/dl

Nursing care and monitoring

- Monitor vital signs (PR, RR & Temperature)
- Monitor input/output
- Check BS for malaria parasite daily
- Ensure feeding
- Advise on use of LLINs

7.3Malaria and HIV/AIDS

Malaria and HIV infections are both endemic in Tanzania and co–infection is common. The two diseases are the most important health problems in the country, being among the high ranking causes of morbidity and mortality.

Recent studies have documented in detail the consequences of HIV infection on malaria; observing that HIV infection is associated with increased prevalence and severity of clinical malaria and impaired response to antimalarial treatment.[25] One review emphasises that this is dependent on; age, immune-depression and previous immunity to malaria.

Previous studies with less effective regimens suggested that increasing HIV-related immunosuppression was associated with decreased treatment response, increased parasite burdens and reduced host immunity. All these factors are now known to occur with HIV infection and are associated with increased treatment failure rates.

Patients infected with HIV are often on medications which include; cotrimoxazole as prophylaxis and/or antiretroviral (ARVs). However there is limited information on drug interactions between ARVs and ACTs.

In HIV-infected pregnant women, the adverse effects of placental malaria on birth weight are reported to increase.

7.3.1 Clinical features of malaria in HIV/AIDS

Worsening HIV-related immunosuppression may lead to more severe manifestations of malaria. In stable endemic areas, HIV-infected patients with partial immunity to malaria may suffer more frequent and higher density infections; while in areas of unstable transmission, HIV infection is associated with an increased risk of severe malaria and malaria-related deaths.

Clinical features of uncomplicated malaria in HIV/AIDS

Fever

Fever is a major symptom of both AIDS related opportunistic infections and malaria. Patients with AIDS often present with fever, which may be intermittent or continuous. The acute fever due to malaria could be masked with the prolonged fever of HIV/AIDS. In stable transmission areas, patients may suffer fever more frequent.

One should always consider a possibility of malaria in AIDS patients presenting with fever.

Anaemia

Anaemia may be a feature of both AIDS and malaria.

Headache

Headache may be a feature of both AIDS and malaria. However, the other causes of headache in AIDS patients such as cerebral toxoplasmosis, meningitis and intracranial tumours should be ruled out.

Other constitutional symptoms

Diarrhoea, joint aches and general body weakness can manifest in both, AIDS and malaria. These symptoms tend to be chronic in AIDS and acute in malaria, hence the risk of malaria symptoms being masked by AIDS related symptoms is significant.

Clinical features of severe malaria in HIV / AIDS

HIV infection is associated with an increased risk of severe malaria and malaria-related deaths, especially in low transmission areas.

Severe malaria in HIV/AIDS patients frequently presents as cerebral malaria or severe anaemia.

Cerebral malaria

AIDS patients with cerebral malaria may present with central nervous system manifestations (CNS) such as altered level of consciousness, prostration and convulsions.

It is important to note that the manifestation of cerebral malaria resembles the CNS manifestation of HIV/AIDS e.g. convulsions, prostration and coma

Severe malaria anaemia

A patient with severe anaemia due to malaria may present with severe pallor with or without heart failure.

The presence of severe anaemia in HIV/AIDS patients may reflect an advanced disease or co-morbidity with malaria

7.3.2 Diagnosis of malaria in HIV/AIDS

Diagnosis should follow the general principles of diagnosis of malaria based on accurate history taking, complete physical examination and appropriate laboratory tests as in any other malaria patient.

Consider the possibility of malaria in HIV/AIDS patients presenting with fever, pallor, headache and the other constitutional symptoms. More extensive work up should be performed to exclude other infective causes of fever.

In stable malaria transmission areas where resident population has partial immunity to malaria, the attacks may be frequent with higher density infections.

In suspected cerebral malaria in a HIV/AIDS patient, emphasis should be put on cerebrospinal fluid (CSF) examination to rule out other life threatening conditions such as bacterial and cryptococcal meningitis

7.3.3 Treatment of uncomplicated and severe malaria in HIV /AIDS

If malaria is diagnosed, depending on classification of the malaria diagnosis, a full treatment with antimalarials should be given according to the guidelines (see chapter 4 and 5).

However it should be noted that, clearance of parasitaemia may not necessarily be accompanied by clearance of symptoms (fever) due to the presence of other underlying infections. HIV/AIDS infected adults with low CD4 cell counts may be more susceptible to treatment failure of anti-malaria drugs.

7.3.4 Malaria and HIV/AIDS in pregnancy

HIV infected pregnant women are at an increased risk of infection with malaria parasites and are more likely to develop clinical malaria. Their parasite density is increased compared to non-HIV infected pregnant women and they tend to have a diminished response to antimalarial treatment. HIV and malaria co-infected pregnant women are also at very high risk of anaemia and placental malaria. Pregnant women with dual infection have poorer birth outcomes (foetal loss, pre-term delivery, low birth weight).[26] A considerable proportion of children born to women with HIV and malaria are of low birth weight and are more likely to die during infancy. Malaria infection during pregnancy may be associated with increased risk of *mother to child transmission* (MTCT) of HIV.

The World Health Organization recommends exclusive breast feeding until six months for children born to HIV-infected mothers, whose HIV status is negative or undocumented.

Breastfeeding should be accompanied with complementary feeding until the child is 12 months of age[27].

7.3.5 Effect of malaria on HIV infected children

The effects of malaria on HIV infected children include increased risk of illness and anaemia. All clinical outcomes such as severity of anaemia, transfusion, hospitalization rates, coma and hypoglycaemia were higher in HIV-infected children than in HIV-negative children in a study carried out in Kenya.[28] Although HIV infection increases the prevalence and severity of clinical malaria in children, it does not undermine the response to treatment with antimalarial medicines in uncomplicated malaria.[29] In one particular study it was observed that although treatment of uncomplicated malaria with Artesunate plus Amodiaquine was highly effective in patients on antiretroviral therapy (ARV) there was a significant 7-8 fold increased risk of neutropenia 14 days after initiation of treatment among HIV-infected children compared to uninfected children.[30] WHO therefore recommends that treatment of malaria in HIV-infected patients receiving Zidovudine or Efavirenz should as much as possible avoid Amodiaquine containing ACT regimens[31].

Treatment in HIV-infected patients on zidvudine or efavirenz should, if possible, avoid Amodiaquine-containing ACT regimens

7.3.6 Prevention

intermittent preventive treatment in HIV infected pregnant women

Pregnant women who are infected with HIV and receiving co-trimoxazole preventive therapy (CPT), do not need to receive concurrent treatment with SP for IPTp[32].

HIV positive pregnant women should be referred to PMTCT services and should always be protected by LLINs

Co-trimoxazole preventive therapy according to the PMTCT guidelines is recommended for all pregnant women infected with HIV, regardless from the clinical stage, to prevent malaria, Pneumocystis carinii pneumonia and toxoplasmosis

Prevention for the people living with HIV/AIDS

As people living with HIV/AIDS in areas of high transmission are particularly vulnerable to malaria, their protection using Long Lasting Insecticide Treated Nets (LLINs) is a high priority.

HIV infected individuals with advanced immunosuppression (CD4 T-cell count ≤ 200 µl) should receive co-trimoxazole prophylaxis until their CD4 count is above 200 µl to prevent them from respiratory tract infections and malaria

7.4 Malaria and chemoprophylaxis in sickle cell disease

Sickle cell disease (SCD) is an inherited blood condition. SCD also known as sickle-cell disorder is where the sickle cell gene responsible for the production of abnormal haemoglobin S is inherited from both parents.

In areas where malaria is common, SCD patients have low risk or malaria infection[33]. However, when they do get malaria it is associated with high risk of morbidity and mortality[34].

Malaria is the most common precipitating cause of crises in sickle cell disease in malaria-endemic countries[35].

It is recommended to give routine malaria prevention medicines (chemoprophylaxis) to individuals with SCD in areas where malaria is endemic. This helps to reduce SCD crises and all the problems that go along with it.

7.4.1 Malaria prevention in sickle cell disease

No suitable malaria medicine is currently available for chemoprophylaxis in individuals with sickle cell disease.

Chloroquine as a chemoprophylaxis in SCD is no longer recommended, as it does not provide an adequate level of protection.

Alternative medicines, such as proguanil, have not been assessed for long-term benefits and harms[36].

Malaria chemotherapy in SCD may not be necessary in low transmission malaria areas.

The emphasis of malaria prevention for SCD suffers is on the use of Long Lasting Insecticide Nets (LLINs); access to prompt diagnosis and treatment; and health education on risks associated with malaria in SCD.

Treatment of malaria in sickle cell disease

If malaria is diagnosed, depending on classification of the malaria diagnosis, full treatment with antimalarials should be given according to the guidelines on the treatment of uncomplicated malaria or severe malaria. (See chapter 4 or 5).

7.5 Non-immune travellers and malaria chemoprophylaxis

Prevention of malaria among healthy, non-immune persons who travel to a malarious area involves multiple strategies such as mosquito avoidance (by use of insecticide bed nets and repellents) and use of antimalarials medicines to kill any parasite that are contracted from residual mosquito bites.

Chemoprophylaxis is the regular use of antimalarial medicines to prevent development of malaria parasites following any possible inoculation.

All recommended primary chemoprophylaxis regimens involve taking a medicine before, during, and after travel to the malaria risk country.

The risk for travellers to acquire malaria differs substantially from region to region and from traveller to traveller, even within the same region. This variability is a function of the intensity of transmission within the various regions, duration, season and type of travel.

Travellers who have symptoms of malaria should be advised to seek medical evaluation as soon as possible but not to stop their chemoprophylaxis regimen.

7.5.1 Chemoprophylaxis for non-immune travellers

For non-immune travellers, Tanzania is a destination where chloroquine-resistant malaria is present. In addition to mosquito avoidance measures, the recommended chemoprophylaxis options are proguanil, atovaquone-proguanil, doxycycline, and mefloquine (see *table 26*).

Table 26: Medicines indicated for chemoprophylaxis

	Indications	Adult	Children	Pregnancy	Start	Finish
Proguanil	Non-Immune Stay >3 months	200 mg daily	3mg/kg daily	Yes	1 week before	4 weeks after
Mefloquine	Non-Immune Stay <3 months	250 mg weekly	5 mg/kg weekly	Avoid	4 weeks before	4weeks after
Proguanil/ Atovaquone	Up to 28 days	1 tab daily	See 9.6.4	Avoid	1-2 days before	1week after
Doxycycline	Up to 6 months	100 mg daily	>12 years	Avoid	1week before	4weeks after

Chemoprophylaxis for non-immune pregnant women

Non-immune pregnant women should ideally not travel to malarious areas unless absolutely necessary. Proguanil prophylaxis should be taken during the first three months (first trimester) of pregnancy; mefloquine prophylaxis may be taken from the fourth month of pregnancy onwards.

Chemoprophylaxis is currently not recommended for pregnant women living in malaria endemic areas. Instead, intermittent preventive treatment (IPT) is recommended (see chapter 7.1.6).

7.5.2 Medicines for malaria Chemoprophylaxis

Mefloquine

This medicine is structurally similar to quinine. It is a potent long acting blood schizonticide effective against all malaria parasites including *P.falciparum* parasites resistant to 4

aminoquinolines (chloroquine and amodiaquine), SP and quinine. However, resistance to mefloquine develops very fast.

Available formulation

Tablet 250mg mefloquine base.

Indications

Prophylaxis against malaria.

Contraindications

- History of allergy to mefloquine
- Pre-existing neurological or psychiatric disease including epilepsy
- Concomitant use of halofantrine, SP, quinine, anti-convulsants and beta blockers e.g propranolol
- Treatment with mefloquine in the previous 4 weeks
- Pregnancy during the first trimester
- Persons undertaking fine co-ordination and spatial discrimination e.g drivers, pilots, machine operators

Use in pregnancy and lactation

- Mefloquine should be used in pregnancy only if there are compelling medical reasons
- Pregnancy should be avoided during and for three months after completing prophylaxis
- Prophylactic use during pregnancy should be avoided in the first three months
- Nursing mothers should be advised not to breast feed while taking mefloquine

Adverse effects

Dizziness,sinus bradycardia, sinus arrhythmia, neuropsychiatric disorders

Dose for chemoprophylaxis

- Adult: 250 mg weekly
- Children: 5mg/kg weekly

<u>Proguanil Hydrochloride</u>

Proguanil is a valuable medicine for causal prophylaxis. It kills the pre-erythrocytic (liver) stages of *Plasmodium* species. It has slow schizonticidal action on the erythrocytic forms but is highly effective against *Plasmodium falciparum.* It is less active against *P. Vivax*.

For those staying longer than three months in an endemic area Proguanil is recommended.

Dose for chemoprophylaxis

- Adult: 200 mg daily

- Children: 3 mg/kg body weight daily

The medicine can normally be used continuously for a period of up to five years. Proguanil should be taken one week before travelling to an endemic area. It should be continued throughout exposure and 4 weeks after returning from an endemic area.

Indications

Proguanil is the recommended medicine where chemoprophylaxis is indicated. It is not recommended for the treatment of malaria.

Precautions

The medicine should be used with caution in patients with renal impairment. The medicine can delay metabolism of the anticoagulant warfarin. The medicine is considered to be safe in pregnancy and lactation at prophylactic doses, but folate supplementation is advised.

Adverse effects

At normal dosage levels the side effect most commonly encountered is mild gastric intolerance. This usually subsides as treatment continues. Occasionally mouth ulceration, stomatitis, anorexia, nausea, diarrhoea, and irreversible hair loss may occur; overdose may cause haematuria, renal irritation, gastric discomfort and vomiting. The medicine should be used with care in persons with liver or kidney dysfunction.

Available formulation

Tablets of 100 mg proquanil hydrochloride containing 87 mg proquanil base.

Note

Proguanil is currently not recommended or used for treatment of malaria either alone or in combination with other antimalarial medicines.

Doxycycline

Indications

Prophylaxis

Treatment of malaria in combination with other antimalarial medicines (e.g. Artesunate or Quinine)

Dose for prophylaxis

Adult dose is 100 mg daily. To be given from 12 years of age and above.

Can normally be used continuously for a period of at least 6 months (professional guidance is required).

A trial course should be taken before departure if this regimen is being used for the first time; it can be used to detect the likelihood of developing allergic reactions. Doxycycline needs to be started one week before exposure and continued throughout exposure and for 4 weeks after return from malaria endemic area.

Contraindications

Doxycycline is contraindicated during pregnancy, breastfeeding, and in those with systemic lupus erythematosis, porphyria and children aged less than 12 years because permanent discolouration of teeth can occur.

It should be used with caution by women on oral contraceptive pills as it may reduce the effectiveness of the pills.

Adverse effects

Occasionally the medicine causes anorexia, nausea and diarrhoea. Long term use may lead to super-infections such as candida infection and sore tongue (glossitis) and on rare occasions hepatitis, colitis and blood dyscrasias.

Prolonged use can lead to skin photosensitivity. Sunscreens can be used to counter this effect, and if the reaction is severe, alternative prophylaxis should be used. Heartburn is a common side effect, so the capsule should be taken with a full glass of water.

Proguanil Hydrochloride/Atovaquone

Indications

Treatment of uncomplicated *falciparum* malaria.

Prophylaxis of malaria particularly where resistance toward other antimalarial medicines is suspected.

Contraindications

Contraindications include renal impairment, diarrhoea or vomiting. The medication should be avoided in pregnancy and during breastfeeding. Concomitant administration with tetracycline, rifampicin, indinavir and metoclopromide is also not advised, due to reduced plasma concentration of atovaquone.

Side effects

Some side effects: Nausea, vomiting, mouth ulcers, stomatitis, diarrhoea, abdominal pain, anorexia, fever, headache, dizziness, insomnia, cough, visual disturbance, angioedema, blood dyscrasia, and hair loss.

Caution: operating machinery and other activities, which require full attention and fine motor coordination, should be avoided when using this medication.

Formulation and strength available

Adult strength formulation (tablets):

- Proguanil hydrochloride 100 mg
- Atovaquone 250 mg

Paediatric formulation (tablets):

- Proguanil hydrochloride 25 mg
- Atovaquone 62.5 mg

Dose for chemoprophylaxis

Adult dosage—one tablet, started 1-2 days before travel, taken daily during exposure, and for 7 days after leaving the malarious region.

Child dosage—Paediatric-strength tablet (25 mg Proguanil with 62.5 mg Atovaquone) is available.

The dosage is based on weight:

- 10 kg-20 kg 1 paediatric-strength tablet
- 21-30 kg 2 paediatric-strength tablets
- 31-40 kg 3 paediatric-strength tablets
- More than 40 kg 1 adult-strength tablet

7.6Seasonal Malaria Chemoprevention

With the changing epidemiology of malaria, there is a progressive paradigm shift from a "one size fits all" approach, to the targeting of malaria control strategies to specific populations and/or locations for maximal effectiveness. In keeping with this approach, WHO is now recommending a new intervention against *Plasmodium falciparum* malaria: Seasonal Malaria Chemoprevention (SMC).This intervention has been shown to be effective, cost-effective, safe, and feasible for the prevention of malaria among children less than 5 years of age in areas with highly seasonal malaria transmission[37].

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

Seasonal Malaria Chemoprevention (SMC) is recommended in areas of highly seasonal malaria transmission.

NMCP has not yet set up implementation arrangements for SMC and is currently promoting operational research to explore the best therapeutics to be adopted and the suitable areas to be targeted by the intervention.

7.7Malaria epidemics

A malaria epidemic is defined as the occurrence of new cases of malaria clearly exceeding the number expected at that particular time and place. Malaria epidemics should be clearly differentiated from area with high intensity seasonal transmission that occurs in several areas of Tanzania.

High morbidity and mortality usually occurs during an epidemic. In Tanzania the numbers of admissions, blood transfusions and deaths during malaria outbreaks have been found to be 4-5 times higher in epidemic than in non-epidemics years.

Generally there is an inverse relationship between the usual intensity of malaria transmission and the risk of epidemics. Unstable malaria transmission areas, such as fringe highlands and semi-arid zones, are more prone to malaria epidemics.

In Tanzania about 20% of the districts are classified as malaria epidemic prone and people living in those areas are at a higher risk of malaria epidemics. The results of the 2012 THMIS suggest malaria transmission is decreasing. If greatly reduced; it will be followed in time by a corresponding change in the clinical epidemiological profile and an increased risk of epidemics, if control measures are not sustained.

Factors associated with unexpected increases in malaria transmission include:

- Failure of malaria control measures; impaired antimalarial medicine supply or efficacy, may contribute to the occurrence of outbreaks
- Movements of non-immune population to areas with sustained malaria transmission (refugees, seasonal labourers)
- Man-made (environmental modification) or natural (climatic)

7.7.1 Measures to be considered during malaria epidemics

- Improved diagnosis and treatment
- Indoor residual house spraying
- Community mobilization and participation
- Community health education about malaria control in the epidemic area
- Enhance use of ITNs

7.7.2 Malaria diagnosis and treatment in epidemic situations

In epidemic situations, facilities for malaria tests may be unavailable or inadequate to cope with the case load. In such circumstances, it may be impractical and unnecessary to demonstrate presence of parasites before treatment in all cases of fever. Once a malaria epidemic has been confirmed, and if case numbers are high, treatment based solely on the clinical history is appropriate in most cases, using a full treatment course.

It is also useful to monitor the proportion of parasitologically confirmed cases during an epidemic, the Malaria Test Positivity Rate (SPR). As the epidemic wanes, the proportion of fever cases investigated for parasites can be increased. It is important to monitor the clinical response to treatment wherever possible; bearing in mind that other causes of fever may be involved.

However, parasite-based diagnosis is essential to:

- Diagnose and confirm the cause of an epidemic of febrile illness both in health facilities and communities. Rapid diagnostic tests (RDTs) offer the advantage of simplicity and speed in epidemic situations
- Follow up the progress of the epidemic and confirm the end. In this case microscopy is preferred since HRP2 may be positive for several weeks after the parasitological clearance
- Microscopy may be needed also to follow progress in admitted severe malaria cases

Treatment of uncomplicated malaria cases during a malaria outbreak

Malaria epidemics are emergencies in which populations at risk are mainly non-immune or only partially immune. The aim of malaria case management in such situation is to prevent the occurrence of severe disease and, ultimately, deaths.

All suspect cases of malaria should be given a full therapeutic dose of antimalarial medicines according to the guidelines (see chapter 4).

Mass fever treatment (MFT)

MFT is an active search for febrile patients in the community to ensure that as many patients as possible receive adequate treatment in the event of a malaria epidemic MFT at community level is a temporary necessity in emergency situations when medical staffs are dealing with overwhelming malaria caseloads during a confirmed malaria epidemic. This approach requires that sufficient and appropriate antimalarials are available and mobile treatment teams can be deployed in affected areas within a week from the detection of the outbreak.

Mass screening and treatment (MSaT)

MSaT is a possible alternative to MFT during a malaria epidemic if enough resources are available. MSaT refers to screening all people in a population with an mRDT and providing treatment to those with a positive test result. This intervention is based on the assumption that most of the people who can serve to infect mosquitoes will have high enough levels of parasites or antigen in their blood to be detected at the time of screening.

Management of severe malaria cases

Management of severe malaria in epidemic situations will often take place in temporary clinics or situations in which staff shortages and high workloads make intensive care monitoring difficult. Medical treatment should therefore be as safe as possible, with simple dosing schedules and a minimum need for monitoring.

Due to the high workload and to facilitate care of the patients, the medication of choice for pre-referral management and for treatment of severe cases during a malaria epidemic is intramuscular **Artemether**. Artemether injectable is and oil solution and offers some advantages compared to the other injectable antimalarials. It doesn't require the two steps reconstruction of Artesunate and has a simpler schedule compared to Quinine. Hence, its administration during emergencies, where numerous patients are expected to be managed for severe malaria at the same time, offers several advantages. However artesunate and injectable quinine are acceptable alternative treatments in case Arthemeter is not available. The principles of treatment of severe malaria are described in chapter 5.

7.7.3 Malaria epidemic preparedness and commodities stock management

It is essential to ensure that adequate supplies of diagnostics and antimalarial medicines are available by establishing and maintaining stocks at national and district level to deal with the eventuality of an epidemic. These stocks will need to be continuously rotated to ensure that commodity shelf-lives do not expire. Replenishment assumes prompt release, transport and customs clearance of commodities (if required).

7.7.4 Prevention of malaria during epidemics

During malaria epidemics there is an increased risk of malaria infection for the whole population. Therefore, all the population should be protected by ITNs and other personal protection measures.

8 Artemisinin Resistance Containment

One of the major threats to sustained malaria control and elimination is the emergence of malaria parasites that are resistant to Artemisinins. These medicines are the basis for artemisinin-based combination therapies (ACTs), the most potent weapon in treating *falciparum* malaria.

Resistance to previous generations of antimalarials spread rapidly around the world, resulting in increases in child mortality and an untold number of deaths.

Evidence of resistance to artemisinins has been identified and confirmed in South East Asia[38]. The world needs to mobilize continuously to contain artemisinin resistance in these hotspots and to stop its spread to new areas. This is a threat that should be taken seriously.

The WHO has developed a Global Plan for Artemisinin Resistance Containment (GPARC); endemic countries are on the front line of resistance management, and they should lead implementation of the GPARC by implementing the following effective measures:

- Monitoring therapeutic efficacy of medicines of choice and alternative treatments
- Ensuring access to parasitological diagnosis for all malaria suspected patients
- Ensuring access to quality-assured ACTs for confirmed cases
- Banning the use of ACT-based monotherapies

8.1 Monitoring therapeutic efficacy of medicine of choice and recommended alternative treatments

8.1.1 The role of therapeutic efficacy in artemisinin resistance containment

Regular therapeutic efficacy monitoring and surveillance are critical for identifying new foci of artemisinin resistance rapidly and guiding containment and prevention activities.

The primary objective of monitoring therapeutic efficacy is to evaluate the sensitivity of the recommended 1st and 2nd line antimalarial medicines.

The country regularly monitors the efficacy of the ACTs in use to ensure that the appropriate ACT is being deployed.

Therapeutic efficacy involves measurement and reporting of parasite clearance on day 3 after treatment with ACTs, as parasite clearance beyond day 3 is the first signals of artemisinin resistance.

According to the WHO protocol, national malaria control programmes should evaluate the efficacy of first- and second-line antimalarial medicines at sentinel sites at least once every 24 months (WHO, 2009).

8.1.2 Field methods for assessing the sensitivity of antimalarials

Close follow-up of routine cases in the health care facilities: regular monitoring of sensitivity of antimalarial medicine is by following-up of confirmed cases of malaria that do not

respond to antimalarial treatment. It is recommended that this good clinical practice is done routinely in ensure early detection and management of clinical failures.

Should a patient return between 4 to 14 days after treatment with recommended antimalarial medicine with continued symptoms of malaria, after first ruling out other causes of disease, non-response should be considered.

Causes of non-response (treatment failures) to antimalarial treatment include:

- *Vomiting the medicine*
- *Inadequate dosage*
- *Fever/symptoms from a cause other than malaria*
- *Poor quality of the medicine*
- *Parasite resistance to the medicine*

The clinician should indicate treatment failure if the patient has taken the antimalarial medicine appropriately i.e. according to the correct dosage and duration. The clinician should carry out further investigations to rule out other causes, if malaria is still suspected re-confirm by microscopy and change the antimalarial medication to the second line treatment according to national guidelines. If the clinician observes frequent occurrence of suspected non response to first line antimalarial therapy, he/she should alert relevant authorities.

The used patient register must have the needed information when record is reviewed.

Therapeutic efficacy of antimalarial medicines: is the second way to monitor the sensitivity of the antimalarial medicine. It is *in vivo* medicine sensitivity tests using standard/approved scientific protocols.

Through this method a WHO standard protocol for therapeutic testing is used. The protocol provides the minimum essential information for deciding on malaria treatment policy. It provide basic data on currently recommended 1st and 2nd line medicines, where necessary, possible replacement medicines.

The artemisinin resistance containment measures in effect at country level ensure the already established national implementation framework on antimalarial therapeutic testing is operational as per recommendations.

8.2 Role of parasitological diagnosis for all malaria suspected patients in artemisinin resistance containment

As the malaria transmission and malaria burden decreases in the country, the proportion of fevers due to malaria will continue to decrease. Without appropriate diagnosis, more ACTs will be wasted on non-malarial febrile illnesses, potentially increasing the risk for selecting for resistant parasites. To reduce the number of patients without malaria taking ACTs, all suspected cases of malaria should be diagnosed parasitologically before treatment.

Administering ACT to a person who does not have malaria does not, in itself, cause resistance; the problem arises when that person is later exposed to malaria. If this occurs relatively soon after the ACT were taken while therapeutic levels are adequate, the presence of the two medicines makes selection of a resistant parasite unlikely; if exposure occurs later, when only the partner medicine may be present in the blood at a sub therapeutic level, resistant parasites may be selected.

Malaria endemic countries are of greatest concern, because people in these areas are more likely to be bitten by an infected mosquito at a time when only the partner medicine is present in blood.

If the partner medicine becomes less effective or ineffective, it no longer provides an adequate shield for the artemisinin derivative in the ACT. As a result, parasites resistant to artemisinin and its derivatives may develop, threatening the effectiveness and longevity of ACTs.

Artemisinin resistance containment measure at country level is to always treat confirmed cases to ensure that parasites are exposed to therapeutic level of ACTs.

8.3 Access to quality-assured ACTs for confirmed cases

When manufactured and administered in adherence with treatment guidelines, combination therapies are not only more effective than monotherapies, but the mutual protection provided by two medicines reduces the chance that resistance will emerge. The mutual protection of combined medicines in the ACTs is obtained through quality-assured products.

The effective measure on artemisinin resistance containment at country level is to ensure sustainable availability of quality-assured ACTs in both the private and public sector.

8.4 Enforced ban on the use of ACT-based monotherapies

8.4.1 The contribution of oral artemisinin monotherapy in ACT resistance

Unlike ACTs, which require only 3 days to result in high cure rates, oral artemisinin-based monotherapies require 7 days for comparable efficacy, and many patients stop taking them after only a few days, when their symptoms have diminished significantly. When adherence is incomplete, parasites in a patient's blood are exposed to a sub curative dose; while the most sensitive parasites are eliminated, the more resistant ones can survive and be transmitted to others. As a result, the use of oral artemisinin-based monotherapies may hasten the spread of artemisinin resistance.

8.4.2 Enforcement of the ban on the use of antimalarial oral monotherapy.

The effective measures at country level is to:

- Ban the use of Artemisinin based oral Monotherapy
- Stop local manufacture which aims at distribution of oral artemisinin-based monotherapies
- Strengthen regulation of medicine markets to non-use of oral artemisinin-based monotherapies

9 Behaviour Change Communication for Malaria Treatment

9.1 Key BCC issues for diagnosis and treatment of malaria

In the Malaria Medium Term Strategic Plan (MMTSP), Behaviour Change Communication is a key supporting strategy. The NMCP Communication Strategy has been developed, to support the two main/core strategies that were identified in the National Malaria Medium Term Strategic Plan 2008-2013 (MMTSP); Malaria prevention and malaria treatment. The communication strategy identifies the main messages to be used in addressing the challenges in each core strategy, as well as, the tools and channels to communicate these messages.

Within the context of the Malaria Communication Strategy, the following issues have been identified as the key gaps in knowledge on malaria diagnosis and treatment to be addressed by the communication plan (*Table 27*).

Table 27: Malaria case management communication gaps and needs

Communication Gaps/Needs
a) Awareness of Signs and Symptoms of Malaria
b) Early treatment seeking behaviour (patients, especially children must receive treatment within 24 hours of detection)
c) Correct treatment of patients (both at home and at health centres (the right medicines and treatment guidelines)
d) Importance of completing treatment, key to fighting treatment failure and prevention of parasite developing resistance to medicines
e) Adherence to test results (health professionals and the general public)
f) Importance of pregnant mothers going promptly to the health facilities to get quality malaria management when they feel sick (safe and effective treatment based on proper diagnosis)
g) Importance of improving interpersonal communication between providers and client on diagnosis and treatment of malaria
h) Correct diagnosis of malaria at health facilities.
i) Importance of follow-up visits in the health facility in case symptoms persist or condition worsen

The framework for implementing malaria diagnosis and treatment BCC/IEC is included in *Table 28*:

Table 28: Framework for implementing malaria diagnosis and treatment BCC/IEC

Strategy	Communication gap	Communication objective	Main message	Message delivery channels	Desired Action
IPTp	Inadequate knowledge on IPTp	Increase knowledge among pregnant women on IPTp Increase proportion of pregnant women who take 2 or more IPT doses	IPTp ensure safety of unborn child & pregnant woman Make sure you get 2 or more doses You need 4 ANC visits to ensure safe pregnancy	Mass Media: Radio spots, TV, IPC: health providers Print Materials (leaflets, posters, brochures), Community mobilization	Pregnant women get 2 or more IPTp doses and attend all ANC appointments
Diagnosis	*Low awareness of S&S of Malaria*	Increase knowledge on S&S	Recognize S&S act properly Don't wait for all S&S	Mass Media: Radio spots, TV, IPC: health providers Print Materials (leaflets, posters, brochures), Community mobilization	Care takers recognize S&S and act quickly
	Poor adherence to test results	Act according to test results	Lab test are accurate More harm if results are disregarded		HW & patients treat malaria based on lab results
Treatment	*Delayed treatment seeking behaviour*	Increase proportion of community who seek prompt treatment	Seek treatment as soon as S&S are recognized Appropriate IPC friendly skills to patients Counselling caretakers on early seeking behaviour	Mass media: TV and Radio spots Print media IPC in health facilities CORPs: community interactions	Treatment for malaria sought within 24 h
	incorrect treatment	Increase proportion of community given correct treatment	Right ACT, right dose Complete the dosage		Correct treatment to medicine sellers & caretakers
	Failure to complete treatment		Complete the dosage Full dosage ensures recovery		Patients complete prescribed treatment

10 Management of Commodities for Malaria Diagnosis and Treatment

Coordination to ensure a consistent supply of pharmaceutical commodities for malaria diagnosis and treatment is an important function of the NMCP.

Artemisinin based combination therapy (ACT), Artesunate injection and Malaria Rapid Diagnostic Tests (mRDT) are the most used Pharmaceutical malaria commodities. They are centrally supplied to the public sector through the Integrated Logistics System (ILS).

The management procedures such as ordering, distribution, storage, inventory control, prescribing, dispensing, use and reporting must be strictly followed as prescribed in all levels to ensure uninterrupted supply. Pharmaceutical malaria commodities should be used based on the treatment guidelines to maximise their rational use.

10.1 Quantification and ordering pharmaceutical malaria commodities for public sector facilities

10.1.1 Quantification and ordering at national level

The public procurement agency for health related commodities known as Medical Stores Department (MSD) has responsibilities of procuring, storing and distribution of all health commodities and medical equipment including malaria commodities.

MSD through Pharmaceutical Services Section (PSS) of MoHSW receives guidance from the NMCP, which provides the information on product specifications, the quantities of products and delivery schedules for procurement purposes. NMCP forecasts once a year, and reviews the forecasting on a biannual basis, reviewing what is available in the country and what is in the pipeline.

The consumption based quantification is the preferred method for maintaining adequate antimalarial medicines and mRDT supplies in the country. In public health facilities there is an established supply system, which accomodate the implementation of consumption-based quantification. However, in operation both reported morbidity (clinical) data and consumption (inventory) data are compared and used in quantification.

10.1.2 Ordering pharmaceuticals in the Regional and District Hospitals

There is a system in place for procurement by the regions and districts. The system requires all procurement for malaria commodities to be done with MSD. Regions/Districts are allowed to buy from the other sources only when they can demonstrate that MSD does not have the commodities they require in stock. The MSD procurement system allows for emergency procurement when there is national stock-out of malaria commodities. The maximum quantity for emergency procurement system is established in the Public Procurement Act (PPA), 2004.Regional and District pharmacists and facility In-charges are expected to order their requirements according to their respective needs. Prior to initiating

orders, the pharmacist or pharmacy In-charge should make sure that there is adequate information on the expected number of patients with malaria to be tested by mRDT and treated with ACT/other antimalarials in a defined period of time (usually quarterly). He/she, in collaboration with colleagues, must determine what to order, quantities and source of supply. The order should be submitted to the relevant authorities, such as the Hospital Therapeutic Committee, for endorsement and approval. The amounts to be ordered must be determined by using standard quantification procedures.

10.2 Storage and distribution of pharmaceutical malaria commodities in public sector

10.2.1 National level storage and distribution

ACT, mRDT and other sensitive items are stored in the high value section of MSD warehouses, where custodianship is by the appointed staff. The delivery and storage of the malaria commodities is coordinated from the MSD central level.

Good distribution practices require at a minimum: a well-designed and managed system, stocked with constant supply of medicines; that medicines are kept in good condition throughout the distribution process; that the quality of medicines is ensured, loss is minimized;, reporting, inventory, ensuring security, grouping routes in the most efficient manner, adequate vehicles for delivery, delivery documentation and providing information for forecasting needs. The MSD has a well-established distribution system that adheres to these tenants, including the following documentation: sales invoices, delivery notes, good received notes, and claim and verification forms.

The distribution of health products to the health facilities from the MSD zonal stores is managed using the Integrated Logistics Systems (ILS) on a quarterly basis. Malaria pharmaceutical commodities are stored in MSD zonal warehouses and distributed to health care facilities.

10.2.2 Regional and district level storage and distribution

The Integrated Logistics System has been introduced in Tanzania to manage various categories of health supplies including essential medicines in public dispensaries, health centres, and hospitals (including faith-based and not-for-profit organizations). Facilities order quantities of each commodity according to their needs and within their budget using standard request forms known as Report and Request Forms (R&R Forms). The ILS captures consumption data through request forms.

The appropriate authority at regional, district and health facility level will then receive medicines and related supplies based on quarterly cycles. At the Hospital level, Therapeutic Committee receives the commodities. A Goods Received Note (GRN) is filled as acknowledgement for the receipt of the products in good order and condition. Any

discrepancy between the order sent out and goods received must be recorded and feedback communicated to the issuing MSD office using a Verification and Claim Form.

Medicines and related supplies must be stored appropriately in accordance with Good Storage Practices (GSP) so as to avoid deterioration and/or damage of the products.

Medicines and related supplies should be ordered and issued from a store using approved documents. It is important that the pharmacist or pharmacy in-charge to make sure, by comparing orders with clinical records and average health facility workload, that orders for medicines and related supplies are genuine and quantities ordered or issued are within the normal consumption pattern. Medicines and related supplies should be issued on the basis of FEFO (First Expiry, First Out).

Health facilities should maintain a rational and accountable distribution system through proper inventory control of medicines and related supplies. Tracking, stock inventory and management should follow the stipulated procedures.

10.2.3 Distribution chain of malaria pharmaceutical products in private sector

The formal private-for-profit health sector includes hospitals, health centres, dispensaries, pharmacies, and Acredited Medicine Dispensing Outlets (ADDOs). The private sector forms the cornerstone of the MOHSW's home management of malaria strategy to increase access to effective treatment. Frequency of orders made byprivate sector facilities will beon a demand-driven basis even in case of supply of subsidized malaria commodities.

Anti-malarial manufacturers distribute their medicines through a range of national- and regional-level wholesalers in Tanzania. Most multinational manufacturers have selected agents' in-country who has exclusive importation rights for their products. These agents then either distribute the product to other areas of the country through their own networks or provide the product to another importer or wholesaler for distribution ("horizontal distribution").

If the product is imported, the distribution chain from manufacturer to importer includes:

- The importer who places an order with a relevant supplier
- The supplier who provides a pro-forma invoice to the importer, who forwards it to TFDA for approval and deduction specified percent (%) of the invoice value (as a regulatory fee)
- The supplier sending the consignment to the importer. Upon arrival the consignment is inspected by TFDA and the Tanzania Revenue Authority to ensure the quality of the products and for tax collection purposes; Most importers hire clearing agents to handle these procedures and ensure the products arrive at the importers' warehouse in a timely manner

The entire procurement process including approvals for relevant authority can take between 1-2 weeks while importation from overseas can take as much as 3-4 months. Procurement of products from domestic suppliers is simpler and faster in most cases.

Supportive interventions for the malaria commodities management in the private sector includes; training, supervision, medicine monitoring, improving regulatory environment, improving access and adherence to suggested price where subsidy mechanisms are in place.

10.2.4 Distribution chain of malaria commodities for Home Malaria Management

Home malaria management requires establishing a commodities distribution chain up to community level (community health workers). In this case diagnostics and medicines are managed by the nearby health facility through the standard supply chain. The health facility in charge is responsible for requisition of the products, temporary storage and distribution to the end point. Community leaders are responsible for the appropriate storage and use at the end point.

10.3 Monitoring of malaria case management commodities

10.3.1 National monitoring of malaria commodities management activities

NMCP and Pharmaceutical Services Section (PSS) in collaboration with development partners has been implementing end use verification for the purpose of assessing the availability of malaria commodities at the health facility level and MSD on a quarterly basis.

A verification team visit quarterly health facilities and MSDs zonal warehouses, and produce a quarterly report which provides a snapshot of stock availability of malaria commodities. Whenever stock imbalances are detected, NMCP then conducts re-distribution to mitigate stock-outs.

10.3.2 Regional and district monitoring of malaria commodities management activities

The RHMT/CHMT or hospital management team, during routine supervision, should look at all aspects of good pharmaceutical services including stock availability, expired stocks, ordering, storage, inventory control, distribution, dispensing and usage of malaria commodities.

10.4 Quality assurance for malaria diagnosis

10.4.1 Malaria tests quality assurance

The primary aim of malaria test quality assurance (QA) programme is to ensure that malaria parasite-based diagnosis services are manned by competent staff, supported by effective training and supervision that maintains a high level of staff competency and performance and by a logistics system that provides and maintains an adequate level of supply of reagents, devices and equipment.

Quality assurance involves all processes for ensuring quality of diagnosis from the time when the test kit is manufactured to the time when it is used, and from the time when a specimen is collected, received in the testing site, processed, and interpreted to the time when results are dispatched to the client.

10.4.2 Objectives and framework for malaria tests quality assurance

The diagnostic unit of MoHSW through NMCP is responsible for overseeing malaria parasite based diagnosis.

The long-term aim is fully functional malaria testing national QA system with the benchmarking and competency accreditation of all routine performers of malaria tests.

The malaria laboratory tests QA programme objectives are:

- Ensuring quality product supplies to both malaria RDTs and microscopy
- Improving the overall competency and performance of malaria microscopy and mRDT at all levels of the laboratory services
- Sustaining the highest level of accuracy (both in sensitivity and specificity) in confirming the presence of malaria parasites
- Systematically monitoring laboratory procedures, consumables, devices, equipment and the results of laboratory diagnosis
- Establishing a clear hierarchical reporting system for results of QA

The framework for malaria test quality assurance is included in *Table 29.*

Table 29: Main activities for malaria diagnosis QA system

Main activities	Malaria tests	
	mRDT	Microscopy
Ensure continuous quality product supply	Forecast, select according to established national criteria, procure from manufacturer under WHO-FIND continuous evaluation program, plan delivery schedules and perform	Quantify, select national recommended techniques with equipment & reagent and procure from manufacturer with GMP

Main activities	Malaria tests	
	mRDT	Microscopy
	batch (lot) test	
Improve competency and performance	Appropriate training and follow-ups to non and laboratory personnel on SOPs, safety precautions and proper waste disposal	Refresher trainings and follow-up for laboratory personnel on good laboratory practices with focus to SOPs
Describe QA procedures and reporting system	Description of methodology, activities, levels of implementation, management checklist/tools and lines of reporting	Description of activities, levels of implementation, management checklist/tools and lines of reporting

10.4.3 Laboratory quality assurance management at national level

The main functions of the national quality assurance system are:

- Preparation of the quality management plan
- To set quality standards for testing sites and performances
- To support the national malaria reference laboratory
- Designing and updating standard operating procedures (SOP) and job aids
- To scale up the system of accredition of points of care performing malaria tests
- To set up a system of certification of microscopists
- Perform RDT lot testing
- Provide minimum specification for laboratory reagents and equipment for malaria microscopy
- Follow up procurement of quality equipment and reagents
- Monitoring the quality management system

The main actors and their respective functions of laboratory quality assurance management at national level are:

- NMCP case management head
- NMCP diagnostic focal person
- NMCP commodities and logistics focal person
- National health laboratory and quality assurance training centre (NHLQATC)malaria focal person
- National malaria quality assurance core facilitators team

10.4.4 Laboratory quality assurance management at district level

The main functions of the quality assurance system at district level are:

- Supervision of laboratories and points of care performing mRDT
- Monitoring competence in malaria testing
- Cross checking routine blood slide results (validation)
- Temperature monitoring of RDT storage in health facilities

The main actors and their respective functions of laboratory quality assurance management at district level are:

- District laboratory technologist
- District malaria IMCI focal person

10.4.5 Laboratory quality assessment at health facility level

The activities to be performed at points of care where malaria testing facilities are available are the following:

- Supervision visits
- Monitoring the competence of malaria tests performers (microscopts and RDTs performers) by direct observation
- Quality control of routine BS for malaria (preparation and validation)
- Monitoring RDTs stability
- Internal quality check (if applicable)
- Quality of RDT performed at community level (if applicable)

10.5 Malaria therapeutic and laboratory devices quality assurance procedures

ACTs and Artesunate Injection: TFDA quality control laboratory has been prequalified by WHO as a WHO quality control laboratory. TFDA implements quality assurance testing; i.e. preliminary testing upon entry and post-market surveillance.

Two random sampling procedures are used, the lot or batch testing at the point of entry or post marketing, and cohort events monitoring through surveillance.

TFDA quality assurance system for ACTs is performed through:

- Port of Entry screening test where a sample is randomly selected from each batch of imported antimalarial agents subjected to preliminary testing; only batches that

comply with screening tests are allowed into the market. This is applicable when the number ofbatchesand the quantities per batch are reasonable for the exercise. If this is not the case, then 10% of the batches are randomly selected and samples are collected from the selected batches, if they pass the test then they are considered a representation of the entire shipment. To minimize this challenge, NMCP and MSD are working in ensuring that the numbers of batchesper consignment are reasonable and manageable

- Once the products are in the market, they are again sampled during Post Marketing Surveillance. Testing and tracking of malaria commodity performance is mandatory after entry. This is a countrywide surveillance in which antimalarials are sampled according to guidelines documented in the sampling plan

Procedure in case of a product failing QC testing

A recall is instituted in the case of ACT or Artesunate injection or RDT product failing QC testing. For public health facilities, commodities are recalled through the DMO then sent to MSD. These commodities are destroyed after verification and approval from relevant authorities (TFDA and MoFEA). MSD will then make a claim for replacement of these commodities from the manufacturer/supplier. For the private sector, TFDA is responsible for managing a recall through the wholesalers by the distributors. These products will subsequently be disposed of in accordance with the TFDA Act.

mRDT lot testing

The quality control sampling procedure for RDT(WHO sampling protocol) consists of a sample of 150 tests per lot for each consignment is collected from those products with a shelf-life less than 18 months and 175 tests per lot for those with more than an 18 month shelf–life and shipped to the identified WHO pre-qualified laboratory. This is done on a quarterly basis as per the procurement plan i.e. whenever a new consignment arrives.

10.6 Pharmacovigilance

Adverse drug reactions (ADRs) are inevitable consequences of pharmacotherapy. It is well known that all medicines carry the potential to produce both desirable and undesirable effects. No medicine is absolutely safe under all circumstances of use or in all patients and ADRs may occur even if a medicine is correctly selected and dosed.

All medicines undergo safety assessment during the development process, before being declared fit for human consumption. However, the populations treated once the medicine hits the market are clearly different from the ones studied during development. New safety hazards are therefore likely to be discovered once the medicine is prescribed widely also to elderly, polymorbid patients, children and women of childbearing age. Even medicines that show no teratogenic potential in animals may cause harm to the unborn child and it is not until pregnant patients are exposed that these effects will be recognised. Patients are not followed as closely and intensively as study participants, therefore unwanted effects can go

unrecognised for quite a while. Also medication will often be prescribed for far longer periods of time than the ones studied before registration, unveiling problems related to chronic use.

This explains the need for intensive and pro-active post-marketing surveillance applying different scientific approaches.

10.6.1 Importance of pharmacovigilance

The most important aspects of pharmacovigilance are:

- The continuous evaluation of medicine safety and efficacy will help to make safer and more effective treatment available to patients
- Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or medicine interactions is often incomplete or not available
- Monitoring after effects of accidental use of contraindicated medicines for specific groups (e.g. pregnant women in the first trimester and new-borns under 5kg of body weight)
- Data derived from the surveillance assists the regulatory authorities to make evidence-based decisions
- Early detection of ADR may prevent or reduce ADR related morbidity and mortality

10.6.2 Clinical presentation of adverse medicine reactions

ADRs may present with non-specific symptoms and signs and can at times mimic features of some diseases; hence, it is difficult to distinguish between ADR and clinical features of the treated condition. However, the following step-wise approach may be helpful in assessing possible medicine-related ADRs:

- Ensure that the medicine prescribed is the medicine dispensed and actually used by the patient at the dose advised
- Verify that the onset of the suspected ADR was after taking the medicine
- Determine the time interval between the beginning of medicine treatment and the onset of the event
- Evaluate the suspected ADR after discontinuing the medicines and monitor the patient’s status
- Analyse the alternative causes (other than the medicine) that could on their own have caused the reaction
- Use relevant up-to-date literature on medicines and their adverse reactions and verify if there are previous conclusive reports on this reaction
- Fill in the ADR reporting form (yellow form) and submit to the relevant authority as instructed

- Manage the patient accordingly, including referral to appropriate level
- Make all necessary arrangements for patient follow up

10.6.3 Reporting adverse drug reactions

Spontaneous method using yellow form

The report of suspected adverse reaction to medicines or vaccines (yellow form) is the recommended form for reporting suspected ADRs. The operational challenge is the low reporting rates. It is a passive surveillance method which encourages health professionals and others to look for adverse effects and report safety concerns and submits to the TFDA as per instructions. Reporting is entirely dependent on the initiative and motivation of the reporters. This method is commonly referred to as “spontaneous” or “voluntary” or “passive” reporting system.

Who should report?

All health care providers (specialists, medical doctors, clinical officers, pharmacists or nurses) should report ADRs as part of their professional responsibility, even if they are doubtful about the precise relationship with the prescribed medication.

What should be reported?

All suspected adverse medicine reactions should be reported, both to common or new medicines.

How to report

The Tanzania Food and Drug Authority (TFDA) has developed ADR reporting form (yellow form) as provided in appendix H. Reporting forms are distributed by TFDA zonal offices and should be available at DMO’s office. At district level, the DMO is responsible for distributing forms to all health facilities both public and private. Yellow forms can be filled by any health care provider. The forms come with a prepaid postage stamp and once completed they should be posted to TFDA.

What happens after reporting?

Upon receipt of the forms, TFDA is responsible for sending an acknowledgement letter to the ADR reporter. In addition, TFDA is responsible for conducting causality assessment of reported ADR and taking appropriate actions such as product recall if necessary, de-registering the product, amendment of indications or summary of product characteristics.

Active pharmacovigilance method

Active (or proactive) safety surveillance means that active measures are taken to detect adverse events. This is managed by active follow-up after treatment and the events may be detected by asking patients directly or screening patient records; this is best done prospectively. The most comprehensive method is cohort event monitoring (CEM), it

records all clinical events and not just suspected adverse reactions. Event monitoring involves actively and systematically asking for reports of the events.

A CEM programme is essentially an observational study of a new medicine in the early post marketing phase.

Preliminary information from Tanzania CEM ALu safety study indicates this product is safe as no new ADR has been registered to date[39]. The estimated sample size for the referenced CEM study was 10,000 patients.

11 Malaria Surveillance, Monitoring and Evaluation

11.1 Monitoring and Evaluation of NMCP MTSP

Monitoring is the routine tracking of the key elements of program performance through record keeping, regular reporting, surveillance systems and periodic surveys. Monitoring assists program managers to determine which areas require greater effort and may pinpoint areas that might contribute to an improved response. Monitoring is also necessary to inform any evaluation of programs conducted, as monitoring provides contextual information to assist with interpretation. Indicators selected for monitoring will be different depending on the reporting level within the health system and the epidemiological situation. At the global level, the main focus of the monitoring process is outcome indicators to monitor trends in coverage of recommended interventions, as elaborated above. At the national and sub-national levels, the emphasis will be on utilizing programmatic records, health system data, and sentinel site data to monitor inputs, processes, and outputs.

Formal impact evaluation is required to determine and document the extent to which any expectant population-level results are attributable to a particular intervention or set of interventions, as measured through outcome and impact indicators. A more pragmatic definition of impact for the purposes of this plan is defined as the estimation of overall program impact on malaria morbidity and mortality brought about by all control initiatives and programs combined, irrespective of their financing source(s).

The NMCP M&E plan [40]

The focus of this plan is to provide a roadmap for evaluating the effect of the scale-up of the Tanzania NMCP on population-level outcome coverage indicators and impact endpoints of malaria morbidity and child mortality due to malaria and all-causes. A secondary objective is to evaluate the incremental effect of the delivery systems used to distribute ITNs and behaviour change communication messages.

11.2 Reporting malaria cases and malaria related rates

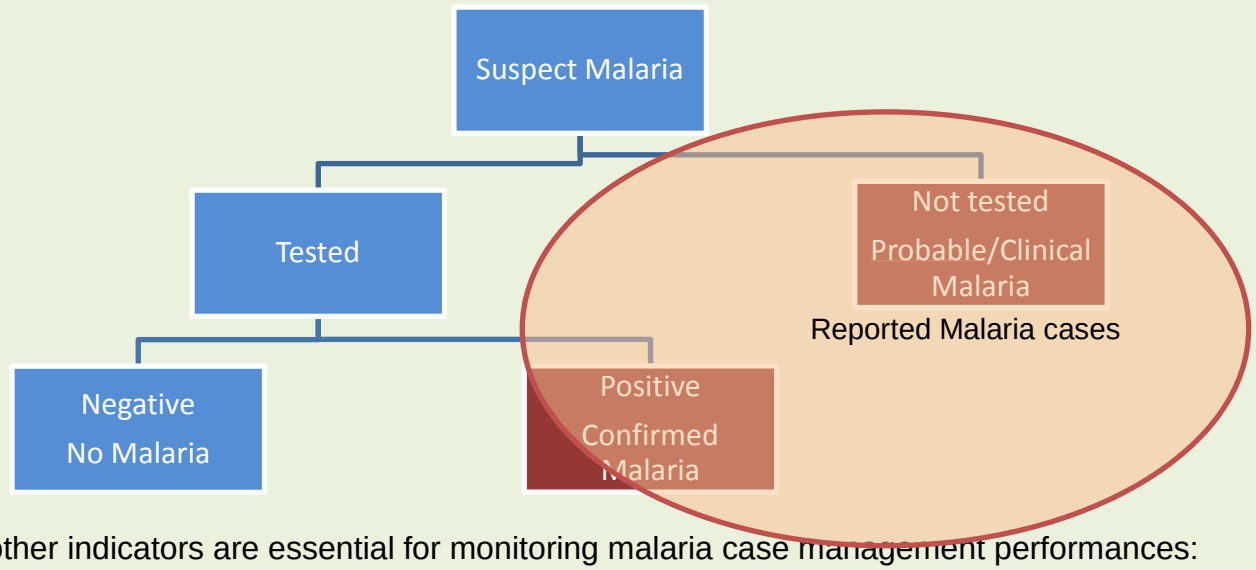
In the control phase not all cases of malaria may receive a diagnostic test. Thus, it is necessary to distinguish between suspected malaria cases, probable cases and confirmed cases[41]. For comprehensive malaria case definition see chapter 3.

There are three major indicators for **monitoring malaria case management**:

- **Suspected malaria cases**: all patients tested for malaria and all patients not tested for malaria but treated with antimalarials
- **Confirmed malaria cases**: all patients tested for malaria with a positive test result
- **Clinical/probable malaria case**: all patients not tested for malaria but treated with antimalarials

- There are only two reported malaria cases indicators: malaria confirmed cases and malaria clinical/probable cases. Malaria suspect cases and negative malaria tests should not be reported as malaria cases (*figure 4*)

Figure 4: Reported malaria cases based on the malaria case definition



Two other indicators are essential for monitoring malaria case management performances:

Malaria Test Rate (MTR): The MTR is the proportion of malaria tests (BS and RDT) performed over the number of malaria suspect cases. Programs should ensure that the percentage of suspected cases receiving a diagnostic test is 100%, by continually monitoring the indicator, finding out why some health facilities achieve less than 100% (e.g. because of RDT stock outs or lack of training, lack of adherence to algorithm) and taking appropriate action. As diagnostic testing is expanded, it is expected that the number of confirmed malaria cases will increase while the number of probable cases will decrease (suspected cases may decrease if more restricted guidance on who should be tested is developed), hence it can be difficult to obtain an accurate picture of trends in malaria cases. Slide and RDT positivity rates might provide some information on disease trends but could be influenced by a change in the composition of the population being tested as testing is made more widely available (it will not be possible to use the percentage of all attendances that are due to malaria as an indicator since the indicator will also be affected by the change in diagnostic practice).

Malaria Test Positivity Rate (MTPR): the MTPR is calculated by dividing the number of positive malaria tests over the number of malaria tests performed. It can be tracked to provide information on trends in malaria. In some settings slide positivity rates have decreased from 30-60% to <10% in response to control measures within 2-3 years. Test positivity rates can vary by season and the peak test positivity rate seen during a season may be quite different from the annual average.

For comprehensive **evaluation** of the malaria burden in communities and success of malaria control measures, confirmed reported malaria cases should be analysed against the population (malaria incidence).

Confirmed malaria cases (<5 years old and total) per 1,000 population. The number of malaria cases fluctuates with malaria transmission seasons and can be useful in assessing the success of preventive programs and demand for treatment in the public and private sectors. However, the variable is also sensitive to changes in reporting rates, diagnostic practices and utilization of health facilities. Care should be taken to ensure that there is consistency in reporting over time by examining trends in health facility reporting rates, annual blood examination rates and total outpatient attendances. If there have been changes in these variables, then it may be more informative to examine trends in test positivity rates (slide or RDT positivity rate) or confine analysis to a subset of health facilities that have reported consistently over time.

11.3 Routine reporting systems

Two primary *routine* reporting systems exist for malaria surveillance; the national Health Management Information System (HMIS) and Integrated Disease Surveillance and Response (IDSR) strategy. HMIS is the system used in the health sector to collect routine data from all health facilities. Malaria information collected as part of HMIS includes: numbers of malaria and anaemia cases, provision of IPTp, bed net vouchers and iron/folate to ANC clients, and deaths attributes to malaria.

In addition to the health facility and district based monitoring of malaria for timely action, health facility-based data collection and reporting through the IDSR system is also currently implemented. The IDSR is a strategy that assists health workers to detect and respond to diseases of epidemic potential, public health importance, and those targeted for eradication and elimination. Information from this strategy is intended to enable health teams to respond quickly to outbreaks, set priorities, plan interventions, mobilize and allocate resources. However, the IDSR system, which captures data from health centres and hospitals, is usually aggregated and lacks the essential breakdown by geographical area, which is important for targeting areas at higher risk. The issue of gathering and reporting surveillance data through the IDSR system in such a way that it captures timely data from most peripheral health facilities including community based approaches needs to be strengthened.

11.3.1 Malaria in the Health Management Information System

The HMIS is the system used in the health sector to collect routine data from all health facilities. The objectives of the HMIS are to provide data for measuring/monitoring the following key impact indicators over time: 1) Standardized laboratory-confirmed malaria, cumulative incidence per year, among children less than5 years, everyone older, and pregnant women; 2) Intermittent preventative therapy uptake among pregnant women; and 3) Standardized crude laboratory-confirmed malaria death rates among children less than 5 years, everyone older, and pregnant women.

In the past, many of the malaria cases were diagnosed clinically, which is usually non-specific fever cases, although malaria laboratory confirmation of clinical diagnosis is

conducted in all hospitals and health centres. This information is reported annually through Council Health Management Teams (CHMTs) and the Health Statistics Abstract. Data flows from the health facility level up to the central level, where it is compiled, analysed, and reported. The NMCP is currently working with selected sentinel districts to improve and standardize diagnostic procedures through capacity building exercises focusing on use of laboratory diagnostic procedures, data recording, and data reporting. In future therefore, trends in malaria incidence, IPTp and malaria related deaths for impact evaluation purposes will come from the health facility surveillance system.

Current HMIS strengthening should focus on improving human resource capacity, timely reporting so as to accommodate data demand for specific programs, and improving the quality of data recording and reporting. Specific recommendations for strengthening coordination of programs and improving the quality of data include: hiring and/or training focal people at the health facility and district level to ensure complete and accurate reporting; and improvements in existing data collection tools as needed to ensure accurate and standardized reporting of data for ascertaining data for impact indicators. Further review of the system is currently underway, with the goal of finding ways to respond to the data demands of specific programs in a timely fashion. In addition, implementation of a revised Reproductive and Child Health Information System is currently underway.

With the curret efforts to scale up mRDT at all levels of the health care delivery system, definitive malaria diagnosis has been introduced in health facilities without formal laboratory services. In general, uncomplicated malaria cases are treated as outpatient cases while severe malaria cases are managed as in patients[42]. For reporting purposes, therefore, outpatient and inpatient malaria cases are considered as proxies for uncomplicated and severe malaria cases, respectively[43].

The revised HMIS (2012) now includes more precise malaria indicators listed below:

OPD

Confirmed Malaria: malaria cases with a positive malaria test result either mRDT or blood smear (< 1 month, 1-11 months, 1-4 years, 5+ years, Male and Female);

Clinical Malaria: probable malaria cases not tested but treated with antimalarials (< 1 month, 1-11 months, 1-4 years, 5+ years, Male and Female);

Anaemia: clinically or laboratory diagnosed (< 1 month, 1-11 months, 1-4 years, Male and Female;

Total OPD attendances: all cases attending OPD (< 1 month, 1-11 months, 1-4 years, 5+ years, Male and Female);

Suspect malaria cases: not reported at OPD but can be estimated by summing up the number of malaria tests performed and the number of clinical malaria cases [Not included in current HMIS];

Total malaria test: number of patients tested by mRDT or Microscopy [Not included in current HMIS].

Admission and Deaths

The number of in-patient malaria cases and deaths should be taken from the discharge register for discharges in which malaria is the primary diagnosis. Diagnosis at the time of admission should not be used for surveillance reporting purposes. Inpatient cases with a primary discharge diagnosis of malaria should have a positive test for malaria during the hospitalization. If parasite based testing is not available, then discharge diagnosis based on clinical grounds and response to treatment is used to assign primary discharge diagnosis. The predictive value of discharge diagnosis on clinical grounds is considered to be higher than for uncomplicated malaria and can be used for surveillance purposes if testing is not available.

Inpatient malaria cases are known to fluctuate with malaria transmission seasons and are sensitive to changes induced by malaria control activities, decreasing rapidly when high coverage with two or more malaria interventions has been achieved e.g. within 60 days. However, the rapidity of change in malaria admissions and deaths may be influenced by initial levels of transmission with more gradual change in areas with higher transmission intensity (and parasite prevalence in children).

In-patient cases should be confirmed by parasitological diagnosis. In situations where parasitological testing is not performed then an in-patient diagnosis is, nevertheless, considered to be more specific than an outpatient diagnosis and trends are likely to reflect real changes in malaria cases although there is also a possibility of over-diagnosis.

Confirmed Malaria Admission: malaria admission with a positive malaria test results either mRDT or blood smear (< 1 month, 1-11 months, 1-4 years, 5+ years, Male and Female);

Clinical Malaria Admission: probable malaria admission not tested but treated with antimalarials and with a malaria discharge diagnosis. (< 1 month, 1-11 months, 1-4 years, 5+ years, Male and Female);

Severe Anaemia Admission: patients with anaemia primary discharge diagnosis either clinical or laboratory confirmed (< 1 month, 1-11 months, 1-4 years, Male and Female);

Total Admissions: number of patients admitted (< 1 month, 1-11 months, 1-4 years, Male and Female);

Confirmed Malaria Death deaths due to malaria, with positive malaria test results either mRDT or blood smear (< 1 month, 1-11 months, 1-4 years, 5+ years, Male and Female);

Clinical Malaria Death: probable death due to malaria, not tested but treated with antimalarials and with a malaria discharge diagnosis. (< 1 month, 1-11 months, 1-4 years, 5+ years, Male and Female);

Severe Anaemia Death: death due to anneamia, with death primary discharge diagnosis either clinical or laboratory confirmed (< 1 month, 1-11 months, 1-4 years, Male and Female);

Total Deaths: number of patients died during the admission (< 1 month, 1-11 months, 1-4 years, 5+ years, Male and Female).

RCH

IPTp 1: ANC attendances receiving first IPTp;

IPTp 2: ANC attendances receiving second IPTp;

IPTp 3+: ANC attendances receiving third and more IPTp;

Antenatal malaria test: first ANC attendances receiving a malaria test;

Antenatal malaria test positive: first ANC attendances with a positive malaria test;

Antenatal TNVS: ANC attendances received a LLIN discount voucher;

Infant TNVS: infant attendances received a LLIN discount voucher.

Laboratory

Total Blood Slides/Total mRDT: The number of patients tested (and the related malaria test rate, see above) is an important malaria indicator. Ideally all suspected cases of malaria, based on clinical signs and symptoms, should be tested. The number of patients tested for malaria can be affected by seasonality, availablility of tests, attendances to the health facility. The number of people tested should be approximately half of the people attending an OPD, especially children;

Blood Slides/mRDT Positives: Malaria parasite-based testing is primarily done by microscopy and rapid diagnostic test (RDT). In areas of high malaria transmission, because of acquisition of immunity, parasitaemia is not always related to the primary cause of illness that was responsible for the patient to seek care. In low transmission settings, parasitaemia is more likely to be related to the presenting illness;

Blood Slides Positive by *Plasmodium* species: In areas with more than one species of *Plasmodium* it is useful to monitor the percentage of cases due to *P. falciparum* as this can provide information on the likelihood of observing severe cases. In areas where control measures are extended the proportion of cases due to *P. falciparum* may decrease; *P. vivax* appears to be respond less quickly to control measures because it is able to tolerate a greater range of environmental conditions and because the hypnozoite stage enables infections persist in the absence of mosquito transmission;

Hb (<5 years of age):

<5g/dl: is an indicator of life threatening anaemia and it is a proxy indicator of severe malarial anaemia. It is influenced by seasonality and vary according to intensity of malaria transmission. It is usually a very sensitive indicator of changes in malaria transmission;

<7 g/dl: is an indicator of severe anaemia and it is a proxy indicator of malaria transmission intensity in the community;

Hb 7 - <11 g/dl: is an indicator of mild-moderate anaemia.

Hb (pregnant women):

<8.5 g/dl: is an indicator of severe anaemia and it is a proxy indicator of malaria transmission intensity in the community;

Hb 8.5 - <11 g/dl: is an indicator of mild-moderate anaemia.

Blood Tranfusions (<5 years of age): it is a proxy indicator of severe malaria and it is influenced by seasonality and intensity of malaria transmission in the area.

Pharmacy (Malaria Commodities)

This indicator monitors supply chain at the peripheral level (health facility) and helps programmes take immediate action following the detection of stock-outs. In Tanzania some of the indicators are included in the mobile phone based *SMS for life* and *ILS gateway* platforms[44].

Artemether Lumefantrine: received and dispensed, stock levels by category;

SP: received and dispensed, stock levels;

Artesunate Inj: received and dispensed, stock levels;

Quinine Tab: received and dispensed, stock levels;

mRDT: received and dispensed, stock levels.

11.3.2 Malaria passive surveillance within the Integrated Disease Surveillance and Response Strategy (IDSR)

IDSR is a strategy that assists health workers and the MoHSW to detect and respond to diseases of epidemic potential, public health importance, and those targeted for eradication and elimination. Information from this strategy is collected weekly and is intended to enable health teams to respond quickly to outbreaks, set priorities, plan interventions, mobilize and allocate resources. For the NMCP, the purpose of passive weekly surveillance is to provide denominator data for measuring the proportion of malaria epidemics detected and appropriately responded to within 2 weeks of onset at the national level. Since a high proportion of suspected and probable cases are not malarious fevers, these cases do not provide good measures for malaria surveillance; malaria surveillance is therefore be based on confirmed cases. It is also important to report the different categories (suspected, probable and confirmed malaria cases) separately - it is not helpful to aggregate these numbers (e.g. to report probable plus confirmed cases) since the final values are not comparable over time as the incidence of malaria in the community changes. To increase the timeliness electronic reporting currently developed.

The followings are the malaria indicators included in the weekly IDSR reports in Tanzania (see attached sheet):

- **Total Malaria Tests**

- **Total Malaria Positive Tests**
- **Total Clinical Cases**

11.3.3 Malaria active surveillance (malaria case detection)

Active malaria case detection (AMCD) is defined as detection by health workers of malaria infections at community and household level in population groups that are considered to be at high risk. Active case detection can be conducted as fever screening followed by parasitological examination of all febrile patients or as parasitological examination of the target population without prior fever screening. In Tanzania there are currently two indications for AMCD: a) sentinel population surveillance and b) focal screen and test.

Sentinel population surveillance

Pregnant woman and infants attending RCH clinics are considered easy to reach sentinel population. Although data collected through this system in not representative of malaria trends in the community, it is a useful source to monitor longitudinal malaria morbidity trends, seasonal variation and intensity of transmission in different ecological strata. : 1) there is high coverage in antenatal attendances and measles vaccination (over 90%); 2) this population represents a homogeneous group that can be followed up longitudinally; 3) this population is easily reachable; 4) these data can provide prospective/longitudinal indications of malaria trends; 5) this system does not require extensive financial resources and is easily implementable under existing routine health care delivery systems; 6) low-levels of training are required; 7) data are easily recorded and reported using a modified information system; 9) there is the potential to add Haemoglobin testing in the same facilities to monitor anaemia prevalence; and 10) this data collection system will provide a service to the target population as asymptomatic positive cases will be treated immediately.

All pregnant women attending the ANC for the first time should be tested for malaria using an RDT. If the test is positive then the women should be prescribed a full course of antimalarial according to gestational age. If the woman is eligible IPTp, then SP should be administered as well.

Selective/focal malaria screen and testing

Focal screen and treatment (FSaT) is an active case detection performed in a defined and small geographic area. This variation of mass fever screening and testing active search advocated for malaria epidemic response (see malaria epidemic section of the guidelines). FSaT can be performed in non-epidemic situations like screening a household, village, or hot spot.

Appendix

Appendix A: Choice of Malaria Rapid Diagnostic Tests (mRDTs)

Malaria RDT detection rate focuses on consistency of performance for registered mRDT. It is not a single measure of mRDT clinical sensitivity, nor positivity rate against the panel of malaria parasites, but rather a combined measure of positivity rate along with inter-test and inter-lot (inter-batch) consistency.

The above described *detection rate* of mRDTs is a WHO and FIND (Foundation for Innovative New Diagnostics) evaluation program procedure[45] to assess the performance of commercially available malaria RDTs and allow direct product comparisons that would assist agencies and governments in making procurement decisions.

In broad terms the *detection rate* of mRDT product is the percentage of malaria samples in the panel giving a positive result by two mRDTs per lot at the lower parasite density (200 parasites/μL) and a single RDT per lot at the higher parasite density (2000 or 5000 parasites/μL).

For detecting *P. falciparum* in low to moderate transmissions areas, it is highly advisable to select RDTs with a *P. falciparum* panel detection score well above 50% at 200 parasites/μL[46].

For detecting *P. vivax* in low to moderate transmissions areas; the panel detection score for *P. vivax,* should be equivalent to those for *P. falciparum* – well above 50% at 200 parasites/μL.

Plasmodium falciparum mRDT tests targeting HRP2 antigen demonstrated the highest detection rates[47]..

MoHSW technical recommendation in the choice of mRDT:

The MoHSW recommends the following minimum criteria for selection of mRDT to be used in the public sector:

Malaria RDT device

- Malaria antigen Pf/Pan which detects all four human parasite with heat stable specific Pf (HRP2) antigen as an independent component
- Format of the test: cassette is preferred
- Registration: it should be registered by Public Health Laboratory Board in the Tanzania

Performance

- Product for procurement is short listed from the performance assessment results of WHO-FIND malaria RDTs continuing evaluation programme

- False positive rate less than 10% (i.e. sensitivity of 90% and above)
- Invalid rate less than 5% (i.e. without visible control line)
- Detection rate: malaria RDTs with minimum detection rate of 90% for *P. falciparum* and 75% for *P.vivax* at low parasitaemia of 200 parasites/μL [48]
- Heat stability at 40°C temperatures show test line; intended for storage, transport and use.

The manufacturer should provide:

- Complete packing; kit comprises all required gargets required for testing
- Individual packed test in moisture-proof container
- Product support such as larger lot, bulk buffer
- Blood-transfer device (pipette, dropper etc)
- Pickers and
- Swab

Appendix B: Reporting of blood smear results

Parasites per microliter of blood:

In this method it is assumed that 1 microliter (μl) of blood contains 8,000 white blood cells (WBC). The number of parasites counted relative to the number of leucocytes counted can thus be converted to the number of parasites per μl of blood by the simple formula given below:

$$\frac{\textit{Number of parasites x 8000 WBC}}{\textit{Number of leucocytes counted}} = \textbf{Parasite count per } \mu l$$

In practice, this means that if 200 leucocytes are counted (denominator in the formula), the number of parasites should be multiplied by 40 and if 500 hundred are counted, the number of parasites is multiplied by 16. This is the preferred method of reporting.

Appendix C: Integrated Management of Childhood Illness algorithm for child with fever

Does the child have fever?				
If yes, then ask: for how long?				
Look and Feel	*Test*	*Test Result*	*Classify*	*Identify Treatment/Management*
Any General danger sign Neck stiffness	Do not Perform a mRDT Test	Not Applicable	SEVERE MALARIA and/or VERY SEVERE FEBRILE DISEASE	• Give Artesunate injectable IM (first dose) • Give first dose of an appropriate antibiotic • Treat the child to prevent low blood sugar • Give one dose of paracetamol in the clinic for high fever (38.5 C or above) • Refer URGENTLY to the hospital
Fever By history, within 48 hours Feels hot Temperature 37.5 C or above No danger signs	mRDT available: Perform a mRDT	mRDT Positive	CONFIRMED MALARIA	• Treat with first line antimalarial (ALu) for three days; give first ALu dose as DOT in the clinic • Give one dose of paracetamol in the clinic for high fever (38.5 C or above) • Investigate for other causes of fever • Advise mother /guardian to return immediately if condition worsen • Follow up in 2 days if fever persist • If fever is present every day for more than 7 days, refer for assessment • Advise the mother/guardian on use of ITN (Insecticide Treated Nets)
		mRDT Negative	FEBRILE ILLNESS (NOT MALARIA)	• Investigate for other causes of fever and manage accordingly • Give one dose of paracetamol in the clinic for high fever (38.5 or above) • Advise mother/guardian to return immediately if condition worsen • Follow up in 2 days if fever persist or immediately if condition worsen • If fever is present every day for more than 7 days, refer for assessment • Advise the mother/guardian on use of ITN
		mRDT Invalid	Not applicable	Repeat RDT and then continue according to results
	mRDT not available	Not applicable	CLINICAL MALARIA or Other FEBRILE ILLNESS	• Treat with first line antimalarial (ALu) for three days; give first ALu dose as DOT in the clinic • Give one dose of paracetamol in the clinic for high fever (38.5 or above) • Investigate for other causes of fever • Advise mother /guardian to return immediately if condition worsen • Follow up in 2 days if fever persist or immediately if condition worsen • If fever is present every day for more than 7 days, refer for assessment • Advise the mother/guardian on use of LLIN

Appendix D: Time schedule for 1st and 2nd dose of Artemether-Lumefantrine

1st dose	2nd dose	3rd dose
1:00 AM	9:00 AM	8:00 PM
2:00 AM	10:00 AM	8:00 PM
3:00 AM	11:00 AM	8:00 PM
4:00 AM	12:00 PM	8:00 PM
5:00 AM	1:00 PM	8:00 AM
6:00 AM	2:00 PM	8:00 AM
7:00 AM	3:00 PM	8:00 AM
8:00 AM	4:00 PM	8:00 AM
9:00 AM	5:00 PM	8:00 AM
10:00 AM	6:00 PM	8:00 AM
11:00 AM	7:00 PM	8:00 AM
12:00 PM	8:00 PM	8:00 AM
1:00 PM	9:00 PM	8:00 AM
2:00 PM	10:00 PM	8:00 AM
3:00 PM	11:00 PM	8:00 AM
4:00 PM	12:00 AM	8:00 AM
5:00 PM	1:00 AM	8:00 PM
6:00 PM	2:00 AM	8:00 PM
7:00 PM	3:00 AM	8:00 PM
8:00 PM	4:00 AM	8:00 PM
9:00 PM	5:00 AM	8:00 PM
10:00 PM	6:00 AM	8:00 PM
11:00 PM	7:00 AM	8:00 PM
12:00 AM	8:00 AM	8:00 PM

Dozi ya kwanza		Dozi ya 2		Dozi ya 3	
7:00	usiku	3:00	asubuhi	2:00	usiku
8:00	usiku	4:00	asubuhi	2:00	usiku
9:00	usiku	5:00	asubuhi	2:00	usiku
10:00	alfajiri	6:00	mchana	2:00	usiku
11:00	alfajiri	7:00	mchana	2:00	asubuhi
12:00	alfajiri	8:00	mchana	2:00	asubuhi
1:00	asubuhi	9:00	mchana	2:00	asubuhi
2:00	asubuhi	10:00	jioni	2:00	asubuhi
3:00	asubuhi	11:00	jioni	2:00	asubuhi
4:00	asubuhi	12:00	jioni	2:00	asubuhi
5:00	asubuhi	1:00	usiku	2:00	asubuhi
6:00	mchana	2:00	usiku	2:00	asubuhi
7:00	mchana	3:00	usiku	2:00	asubuhi
8:00	mchana	4:00	usiku	2:00	asubuhi
9:00	mchana	5:00	usiku	2:00	asubuhi
10:00	jioni	6:00	usiku	2:00	asubuhi
11:00	jioni	7:00	usiku	2:00	usiku
12:00	jioni	8:00	usiku	2:00	usiku
1:00	usiku	9:00	usiku	2:00	usiku
2:00	usiku	10:00	alfajiri	2:00	usiku
3:00	usiku	11:00	alfajiri	2:00	usiku
4:00	usiku	12:00	alfajiri	2:00	usiku
5:00	usiku	1:00	asubuhi	2:00	usiku
6:00	usiku	2:00	asubuhi	2:00	usiku

Appendix E1: Preparation and administration of Injectable Artesunate

	Use the IM route only if the IV route is not feasible	
Step 1 **Reconstitute**	Inject contents of the sodium bicarbonate ampoule (1ml) into Artesunate vial (60mg) Shake for 2-3 minutes Wait till completely dissolved and solution is clear **Artesunate is now reconstituted into a solution of 60mg/ml**	
Step 2 **Dilute**	For intravenous injection (IV)	For intramuscular injection (IM)
	Dilute with 5%Dextrose/0.9% saline 5ml	Dilute with 5%Dextrose/0.9% saline 2ml
	Total (with 1ml sodium bicarbonate) 6ml	Total (with 1ml sodium bicarbonate) 3ml
	Concentration of IV solution is 10mg/ml artesunate	**Concetration of IV solution is 20mg/ml artesunate**
Step 3 **Calculate dose**	Dose: 2.4 mg per kg of body weight divided by the concetration of IV solution (10mg/ml) $\frac{\text{Body weigh} \times 2.4}{10}$ =dose needed in ml >Round up to nearest ml	Dose: 2.4mg per kg of body weight divided by the concetration of IM solution (20mg/ml) $\frac{\text{Body weight} \times 2.4}{20}$ dose needed in ml **>Round up to nearest ml**
Step 4 **Inject**	Draw the required dose into the syringe Inject intravenously over about 5 minutes **Discard any solution not used within 1 hour**	Draw the required dose into the syringe Inject slowly **Discard any solution not used within 1 hour**
Step 5 Repeat **Injection**	Dosing schedule 0hrs,12hrs,24hrs,48hrs until patient can take oral medication Administer for a minimum of 24hours (3 doses), even if the patient can take oral medication and follow -up with a full 3-day course of ACT	

Precautions:

- Inject immediately after reconstitution
- Discard any solution not used within 1 hour
- Discard if solution is not clear
- Do not use in intravenous drip

Appendix E2: Artesunate injectable dose chart

Dose: 2.4 mg/kg of body weight, 3.0 mg/kg of body weight for children below 20 kg

Weight	Dose	ml per dose strength 60mg		Vials of Artesunate 60mg needed**
		i/v	i/m*	
Kg	mg/kg	10 mg/ml	20 mg/ml	
<5	**3**	1.5	1	1
5-8	**3**	2	1	1
9-12	**3**	4	2	1
13-16	**3**	5	3	1
17-20	**3**	6	3	1
21-25	**2.4**	6	3	1
26-29	**2.4**	7	4	2
30-33	**2.4**	8	4	2
34-37	**2.4**	9	5	2
38-41	**2.4**	10	5	2
42-45	**2.4**	11	6	2
46-50	**2.4**	12	6	2
51-54	**2.4**	13	7	3
55-58	**2.4**	14	7	3
59-62	**2.4**	15	8	3
63-66	**2.4**	16	8	3
67-70	**2.4**	17	9	3
71-75	**2.4**	18	9	3
76-79	**2.4**	19	10	4
80-83	**2.4**	20	10	4
84-87	**2.4**	21	11	4
88-91	**2.4**	22	11	4
92-95	**2.4**	23	12	4
96-100	**2.4**	24	12	4

*Half the i/v dose rounded up to 1ml

**Full vial(s) might not be required for a given weight band. The left-over solution must be discarded within 1hr of preparation and must not be reused

Appendix F: Coma scales

The Glasgow coma scale

The **Glasgow Coma Scale** is a neurological scale that aims to give a reliable, objective way of recording the conscious state of a person for initial as well as subsequent assessment. A patient is assessed against the criteria of the scale, and the resulting points give a patient score between 3 (indicating deep unconsciousness) and 14.

		Score
Eyes open:	Spontaneously	4
	To speech	3
	To pain	2
	Never	1
Best verbal response:	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
Best motor response:	Obeys command	5
	Localises pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1
	Total	3-14

A state of unrousable coma is reached at a score of <10.

This scale can be used repeatedly to assess improvement or deterioration.

The Blantyre coma scale

The **Blantyre coma scale** is a modification of the Glasgow Coma Scale, designed to assess malarial coma in children, including those who have not learned to speak.

		Score
Best motor response:	Localises painful stimulus ([a])	2
	Withdraws limb from pain ([b])	1
	Non-specific or absent response	0
Verbal response:	Appropriate cry	2
	Moan or inappropriate cry	1
	None	0
Eyes movements:	Directed (e.g. Follow mother's face)	1
	Not directed	0
	Total	0-5

A state of unrousable coma is reached at a score of <3

This scale can be used repeatedly to assess improvement or deterioration

[a] rub knuckles on patient's sternum

[b] firm pressure on thumbnail bed with horizontal pencil

AVPU scale

The **AVPU scale** (an acronym from "alert, voice, pain, unresponsive") is a simplified system to measure and record a patient's responsiveness, indicating their level of consciousness. It is the IMCI recommended coma scale.

		Score
A	**Alertness** (is the patient alert?)	0
V	Response to **voice** command (does the patient respond to his/her name?)	1
P	Response to **pain** (does the patient feel pain?)	2
U	**Unresponsive** (patient does not respond at all)	3

The level of consciousness worsen as you move down in the scale

Appendix G: Classification and management of anaemia by severity in children one week up to 5 years of age according to IMCI[49]

Signs	Classification	Action
Severe palmar pallor	SEVERE ANAEMIA	• Refer urgently to health facilities where blood transfusion services are available
Some palmar pallor	ANAEMIA	• Give folic acid and iron for three months • Give mebendazole to a child aged 1 year and above if has not received it in the previous 6 months • Follow up in 14 days to check for severity of anaemia; if no deterioration continue with iron and folic acid for three months
No palmar pallor	NO ANAEMIA	• No additional treatment

Appendix H: Adverse Medicine Reaction Reporting Form

TANZANIA FOOD AND DRUG AUTHORITY

REPORT OF SUSPECTED ADVERSE REACTION TO MEDICINES OR VACCINES

Note: Identities of reporter, patient and institution will remain confidential

I. PARTICULARS OF PATIENT	
Patient Initials or Record No.: - _____ Date of Birth (dd-mm-yyyy) or age:-_____	Sex: - Male ❑ Female ❑ Weight in kg:-_____

II. DETAILS OF ADVERSE REACTION	
Description of reaction: …… …… ……	Date Reaction Started__/__/__ Date Reaction Stopped (if known) __/__/__ Onset latency…….

Health related information: Medical history (e.g. hepatic, renal, HIV), allergies, pregnancy, smoking, alcohol use, etc.

Please write any relevant medical and laboratory results including dates (if done)

……

III. DETAILS OF SUSPECTED MEDICINE/VACCINE USED							
Name of suspected medicine(s)/ vaccine(s) Specify brand name or manufacturer if known	**Dosage**	**Frequency**	**Route**	**Therapy Date**		**Batch. No & Expiry date (If known)**	**Reason for use**
				Start	**Stop**		
1.							
2.							
3.							
Other medicines used at the same time and or one month before (including herbal medicines)							
1.							
2.							
3.							

IV. MANAGEMENT OF ADVERSE REACTION	
Reaction subsided after stopping the suspected medicine/reducing the dose: ❑ Yes ❑ No ❑Unknown	
Reaction reappeared after reintroducing medicine: ❑ Yes ❑ No ❑ Not applicable	
Seriousness of the Reaction **(please tick all that apply):**	
❑ Discomfort but able to work	❑ Caused persistent disability or incapacity
❑ Discomfort could not work	❑ Caused a congenital anomaly
❑ Required or prolonged hospitalization	❑ Patient Died
❑ Life threatening	❑ Others, please give details……....…….
Treatment of adverse reaction ❑ No ❑ Yes **(if yes please specify)**: ……	
Outcome of the reaction ❑Not yet recovered;❑ Recovered (Date): __/__/__❑Died (Date): __/__/__ ❑Unknown	
Cause of death……	

V. THERAPEUTIC FAILURE
PLEASE WRITE IF THE MEDICINE(S)/VACCINE(S) SHOWED LACK OF EFFICACY BELOW : (Continue at the back)

VI. MEDICATION ERRORS
PLEASE WRITE DETAILS OF MEDICATION ERRORS BELOW:
PLEASE WRITE ANY OTHER RELEVANT ADDITIONAL INFORMATION BELOW :

VII. PARTICULARS OF REPORTER /HEALTH CARE PROVIDER	
Name: _____ Profession: _____	Name and Address of the health facility:
Contact phone No: _____ E-mail: _____	_____
Signature: _____ Date of this report: ___/___/___	_____
❑ *Please tick if you wish to receive information about other local reports associated with the suspected medicine(s)*	

Thank you for your cooperation	*Submission of an ADR case report does not discredit the competence of the reporter.*	*Ref No. (for official use)*

First Fold

Guide to filling the form

How to report?

- Dully fill in the form as required
- Use a separate form for each patient
- Report direct to TFDA through the following addresses:-

Mail : Tanzania Food and Drug Authority,

P. O. Box 77150, Dar es Salaam

Fax:: 22- 2450793

An Adverse Medicine Reaction (ADR) is defined as a reaction which is noxious and unintended, and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological function.

What to report?

Please report all undesirable patient effect suspected to be associated with medicines, cosmetics or medical devices use.

Report even if:

- You're not sure that the product caused the event
- You don't have all the details

Moisten g[illegible] for few seconds

Second Fold

POSTAGE WILL BE PAID BY LICENCEE

No postage stamp required

If posted in Tanzania

BUSINESS REPLY SERVICE LICENCE No. BRS 01

TO: THE DIRECTOR GENERAL

TANZANIA FOOD AND DRUG AUTHORITY

P. O. BOX 77150

DAR ES SALAAM

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[15] Polymerase chain reaction or PCR is a very sensitive test that can detect very small amounts of genetic material from parasites

[16] With the exception of some low-transmission and elimination countries that may admit uncomplicated malaria cases to ensure full adherence to treatment or radical cure

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[42] (with the exception of some low-transmission and elimination countries that may admit uncomplicated malaria cases to ensure full adherence to treatment or radical cure)

[43]WHO Regional Office for Africa, Brazzaville, 1994. The concept of inpatient malaria cases serving as a proxy for severe malaria cases in Africa is contained in the WHO document, "Information systems for the evaluation of malaria programs. A practical guide. AFRO/CTD/94.3"

[44] Roll Back Malaria, 2010. SMS for Life, Tanzania Pilot Project, Final Report

[45] WHO 2009. product testing of malaria RDTs, performance summary results, rounds 1 and 2 (2008-2009)

[46] WHO 2010. Information note on recommended selection criteria for procurement of malaria rapid diagnostic tests (RDTs); 16 September 2010

[47] WHO, FIND, 2009, Malaria rapid diagnostic test performance summary results of WHO product testing of malaria RDTs: rounds 1 and 2 (2008-2009)

[48] WHO-Geneva; Technical Consultation meeting for RDT experts on parasitological confirmation of malaria diagnosis; October 2009

[49] Modified from the IMCI protocol for district health workers