Swaziland National
Malaria Diagnosis and Treatment Guidelines

Version 2.1
July 2017

Kingdom of Swaziland
Ministry of Health
National Malaria Control Programme

TABLE OF CONTENTS

GLOSSARY

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

Asexual cycle. The life-cycle of the malaria parasite in humans by which new parasites arise from a single organism, and inherit the genes of that parent only; it does not involve the fusion of gametes.

Parasitemia. Is the quantitative content of parasites in the blood. It is used as a measurement of parasite load in the organism and an indication of the degree of an active parasitic infection. To be expressed as number of parasites per microliter of blood.

Cerebral malaria. Malaria infection of the Central Nervous System characterised by Confusion, it is one of the most serious complications of malaria that may develop when the disease goes untreated or uncontrolled

Combination treatment. A combination of two or more different classes of antimalarial medicines with unrelated mechanisms of action. The purpose is to forestall development of drug resistance.

Complicated malaria. Patient with a peripheral parasitaemia and signs of involvement of vital organs such as the brain, kidney or lungs.

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

Drug resistance. The ability of a parasite strain to survive and/or multiply despite the administration and adequate absorption of a medicine given in doses equal to, or higher than, those usually recommended but within the tolerance of the subject.

Gametocytes. Sexual stages of malaria parasites that are infective to the Mosquito host.

Glucose-6-phosphate dehydrogenase deficiency (G6PD). A hereditary condition in which red blood cells break down when the body is exposed to certain drugs or the stress of infection.

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

Plasmodium. A genus of protozoan vertebrate blood parasites that includes the causal agents of malaria. *Plasmodium falciparum*, *P. malariae*, *P. ovale*, *P. vivax* and *P. knowlesi* cause malaria in humans.

Primaquine. An 8-aminoquinoline antimalarial drug used extensively in the radical treatment of P. vivax and P. ovale malaria, and as a single dose gametocytocide in falciparum malaria.

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

Recrudescence. The presence of asexual parasites after treatment of the infection from the same parasite clone that caused the original illness.

Relapse. The recurrence of asexual parasitaemia in *P. vivax* and *P. ovale* malaria deriving from

persisting liver stages. Relapse occurs when the blood stage infection has been eliminated but hypnozoites persist in the liver and mature to form hepatic schizonts.

Selection pressure. Resistance to antimalarials emerges and spreads because of the selective survival advantage that resistant parasites have in the presence of antimalarials that they are resistant to. Selection pressure describes the intensity and magnitude of the selection process; the greater the proportion of parasites in a given parasite population exposed to concentrations of an antimalarial that allow proliferation of resistant, but not sensitive parasites, the greater is the selection pressure.

Severe anaemia. Haemoglobin concentration of <5 g/dl or haematocrit<15%.

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

Transmission intensity. The intensity of malaria transmission, as measured by the frequency of bites by anopheline mosquitoes carrying malaria sporozoites. This is often expressed as the annual entomological inoculation rate (EIR), which is the number of inoculations of malaria parasites received by one person over a given period of time (typically in one year).

Treatment failure. Patients continue to have parasitaemia with or without symptoms despite administration of antimalarials. This can be due to non-compliance, inadequate therapeutic blood levels or drug resistance in the parasite.

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

ACRONYMS

ACT	artemisinin-based combination therapy
AIDS	acquired immunodeficiency syndrome
AL	artemether lumefantrine
DEET	N,N-Diethyl-meta-toluamide
G6PD	glucose-6-phosphate dehydrogenase
HIV	human immunodeficiency virus
HMIS	Health Management Information Systems
HRP-II	histidine-rich protein II
IPTp	intermittent preventive therapy for pregnancy
IRS	indoor residual spraying
LLIN	long-lasting insecticide-treated nets
NMCP	National Malaria Control Programme
ORS	oral rehydration salt
pLDH	parasite lactate dehydrogenase
PQ	primaquine
RDT	rapid diagnostic test
SADC	Southern African Development Community
SP	sulfadoxine pyrimethamine
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organisation

FOREWORD

Case management of malaria has undergone profound changes over the years since the introduction and widespread use of rapid diagnostic testing (RDT) in 2010 and artemisinin-based combination therapy (ACT). Scale-up of malaria preventative and control interventions over the last decade resulted in substantial declines in mortality and morbidity of the disease. Sustaining these gains in the future will depend on the health system performance. Treatment provides individual benefits by curing infection and preventing progression to severe disease as well as community-level benefits by reducing the infectious reservoir and averting the emergence and spread of drug resistance.

Swaziland utilizes artemether lumefantrine (AL), a form of artemisinin-based combination therapy (ACT) that is recommended by the WHO, as the first-line treatment for uncomplicated malaria. AL has gametocytocidal effects, in addition to potent asexual stage effectiveness, that will also target the sexual stage (transmissible stage) of the parasite. This provides the additional benefit of reducing transmission.

These revised guidelines outline the use of artesunate as the first-line treatment for severe and complicated malaria, as recommended by the WHO. Compared with quinine, artesunate is easier to administer and has shown to be more effective at reducing mortality among patients diagnosed with severe malaria. This will translate to better patient outcomes and less lives lost.

Single, low-dose primaquine (0.25mgdoseperkg) in addition to artemisinin-based combination therapies (ACTs) is used for the treatment of uncomplicated *P. Falciparum* malaria. Primaquine is the only commercially available drug that kills the mature (stage IV and V) gametocytes of *P. falciparum* that cause transmission of infection from humans to mosquitoes thus treating with primaquine will potentially reduce transmission.

The purpose of these guidelines is to ensure effective case management of malaria at all health facilities. The guidelines include both local best practices in malaria diagnosis and treatment and recommendations by international experts based on the most current research in malaria diagnosis and treatment. As Swaziland targets malaria elimination, the guidelines will be regularly updated to incorporate new knowledge and research in our fight against malaria.

_____

Dr. Simon Zwane
Principal Secretary
Ministry of Health, Swaziland

ACKNOWLEDGEMENTS

Contributing Authors

Version 2.1 (2017)

The members of the Swaziland Malaria Elimination Advisory Group (SMEAG) Case Management Committee contributed to the revision and finalization of Version 2.1 of these guidelines in 2017:

- Mr Mbongiseni Mathobela, National Malaria Control Program
- Dr Ezeogu Austin, Mbabane Government Hospital
- Dr Kalungero Muhindo, Good Shepherd Hospital
- Dr Getahun Tsegaye Tesfa, Raleigh Fitkin Memorial Hospital
- Dr Gezahegne Agegne, Raleigh Fitkin Memorial Hospital
- Dr Mukemba Jackson, Hlathikulu Government Hospital
- Dr Kevin Makadzange, World Health Organisation (WHO)
- Mrs Nomcebo Nhlabatsi, National Malaria Control Program
- Mr Stanley Chitundu, National Malaria Control Program
- Mr Manik Saini, Clinton Health Access Initiative (CHAI)
- Mr Siphesihle Nhlabatsi, Central Medical Stores
- Sister Xolisiwe Dlamini, Emergency Preparedness and Response (EPR)
- Ms Glenys Sikhondze, National Malaria Control Programme
- Mr Makhoselive Dlamini, National Malaria control Programme
- Mr Sibonakaliso Vilakati, National Malaria control Programme
- Sindisiwe S. Dlamini, Swaziland Health Laboratory Services
- Philton Ndzinisa, Swaziland Health Laboratory Services
- Sister Thelma Mkhumane, Lobamba Clinic Sister
- Busi Mamba' Mbabane Public Health Unit

Section 1.Introduction

This document provides guidelines on prevention, diagnosis and treatment of uncomplicated and severe, complicated malaria at all health facilities in Swaziland. It details the signs and symptoms of the disease, the diagnostic process and management procedures for uncomplicated and severe, complicated malaria. The purpose of the document is to provide healthcare workers with case management guidance based on a review of the current evidence-based literature and the local context; to standardise malaria case management in Swaziland; and to align all healthcare workers to the policies in definitive diagnosis and appropriate treatment. This document was drafted through wide consultation with local and international stakeholders and will be reviewed and updated as necessary.

1.1 Malaria Elimination in Swaziland

As a low malaria transmission country, Swaziland was identified by the African Union Health Ministers and the Southern African Development Community (SADC) as a country ready to pursue malaria elimination. Swaziland's initial malaria elimination strategic plan (2008 – 2015) described the key interventions required to eliminate malaria by 2015. Although it fell short of that goal, many successes were achieved that culminated in only 68 local cases observed in the 2015/2016 transmission season. This updated strategic plan details the actions that will take Swaziland over the final hurdles and eliminate malaria by 2020. All progress made to-date has been made possible with strong financial support from both the government and the Global Fund.

This strategic plan envisions a malaria-free Swaziland with the goal of eliminating malaria by 2020. Four objectives have been identified:

Objective 1: Strengthen surveillance, monitoring and evaluation systems to ensure that 100% of suspected cases are tested and all confirmed cases and transmission foci are reported and investigated by 2020.

Objective 2: Ensure universal access to malaria case management and appropriate vector control interventions for targeted populations by 2020.

Objective 3: Achieve 100% community and health worker knowledge, attitudes, behaviours and practices on malaria prevention and elimination by 2020.

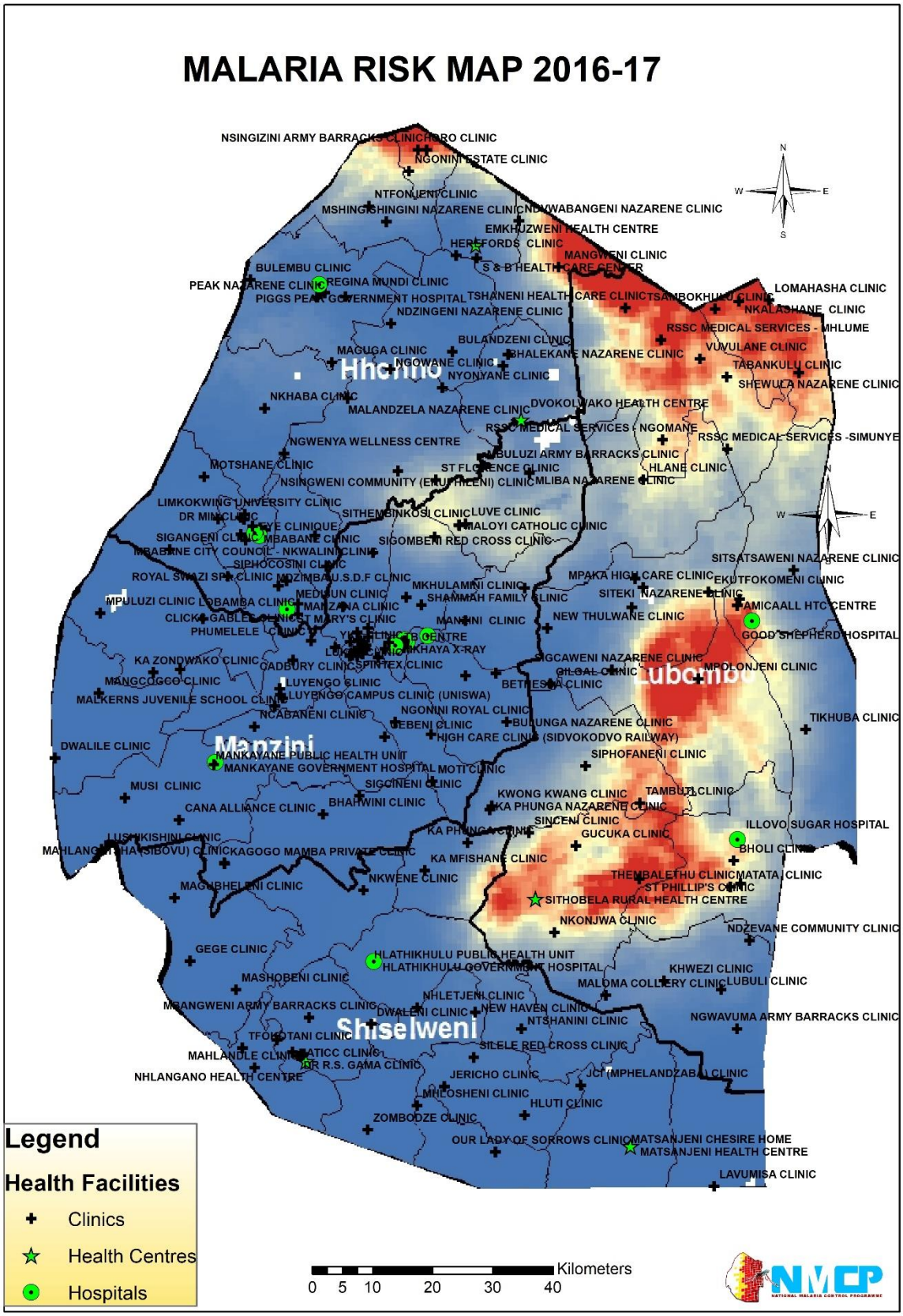
Objective 4: Strengthen programme management capacity for malaria elimination at all levels by 2020.

1.2 Malaria Epidemiology in Swaziland

Malaria is an infectious disease caused by the Plasmodium parasite and transmitted via mosquito bites. Female mosquitoes of the genus *Anopheles* are infected when they take their blood meals from an infected human. They then transmit the parasite when they bite an uninfected human. Once in the human body, the parasites multiply in the liver and then infect red blood cells.

Malaria transmission has remained most prevalent along Swaziland's eastern border, particularly in the Lubombo and north eastern Hhohho regions. Transmission occurs in the rainy season between November and May, with a peak in February and March, and occurs mainly in the Lowveld zone of the country. Malaria transmission is unstable and closely related to the level of rainfall and the presence of imported malaria cases from neighbouring high-endemic countries, which varies considerably each year. Based on previously identified cases, Figure 1 shows areas at-risk for transmission in Swaziland (in red) based on multiple factors including climate and environment.

Figure 1. Malaria At-Risk Areas in Swaziland



SECTION 2. GUIDELINES FOR DIAGNOSIS AND TREATMENT OF UNCOMPLICATED MALARIA

Uncomplicated or mild malaria is defined as symptomatic malaria without signs of severity or evidence of vital organ dysfunction. However, **if the patient does not receive prompt and effective treatment, uncomplicated malaria can rapidly advance to severe and complicated malaria, which could lead to death.** Vulnerable groups for severe and complicated malaria include pregnant women, children under 5 years of age, and immune-compromised individuals. Members of these groups require special attention, immediate treatment, and diligent follow-up to prevent advancement to severe disease.

2.1 Assessment of Uncomplicated Malaria

Diagnosis of uncomplicated malaria should be based on a clinical assessment of the patient as well as the results of parasitological diagnosis by either rapid diagnostic test (RDT) and/or microscopy. When the result of a parasitological diagnosis is negative, the healthcare worker should seek an alternative diagnosis. A complete assessment of uncomplicated malaria should include clinical features, patient history and laboratory assessment.

Patient History

As part of the clinical assessment of the patient, the patient history should include an evaluation of exposure to areas of transmission and exposure to the vector. Obtaining an exposure history to an area of high transmission is of paramount importance to determine the patients' risk of malaria infection. The healthcare worker must weigh the various components of risk for infection.

- **Travel history** –All suspected malaria patients should be asked their travel history, particularly in the last two months before presentation. Take note of patients who have travelled to high transmission regions, especially the Lowveld and Lubombo plateau of Swaziland, Mozambique and other endemic countries. Timing of travel is also important; in general, patients will present signs and symptoms within one month of *P. falciparum* infection.
- **Seasonality of transmission** – Whether the patient was exposed during high or low transmission season will alter their risk of malaria infection. High transmission season in Swaziland is November to April.
- **Exposure to vectors** – The anopheles mosquito takes blood meals at sundown, and risk is substantially reduced if patients reside in screened homes, use long-lasting insecticide-treated nets (LLINs), utilise N,N-Diethyl-meta-toluamide DEET. Patients who have reduced their exposure to the vector will have reduced chance of infection.

Patient's previous exposure to antimalarial medication should always be determined. If patient has undertaken a course of AL within the past 14 days, then clinician must determine whether it was a case of treatment failure or non-compliance. This would be highly unusual, but microscopy will provide definitive guidance (see "Treatment Failure" in **Section 2.3**).

Physical Examination

A complete physical examination should be carried out in all patients to identify signs and symptoms of malaria. There are no physical findings that are specific for malaria, although a combination of the following signs and symptoms would suggest uncomplicated malaria and prompt a laboratory

confirmation test for malaria.

Signs and Symptoms of Uncomplicated Malaria
• Fever >37.5°C or history of fever within past 48 hours with no other apparent cause; although fever is often characteristic of malaria, fever may be absent at times due to the cyclical nature of the disease • Headache • Shivering, chills • Joint pains and generalised body ache • Nausea, vomiting, abdominal pain, diarrhoea, thirst, and/or poor appetite • Motor weakness • Infants may present with increased irritability and refusal to feed • Anaemia, as evidenced by examination of conjunctiva, nail beds that demonstrate pallor

Laboratory Values

Malaria diagnosis should be based on clinical assessment and the results of a malaria RDT and/or microscopy.

SPECIAL NOTE

Healthcare workers will test all patients with a fever of >37.5°C and or with a history of fever in the past week or one of the above signs and symptoms.
A rapid diagnostic test (RDT) and/or microscopy must be conducted for every suspected malaria case. At the **clinic** level, antimalarial treatment should *only* be prescribed when RDT results are positive. At the **hospital** and **health centre** level, the final diagnosis and the prescription of antimalarial treatment should be guided by the results of Microscopy.

Malaria RDTs are similar to rapid tests for other diseases, including HIV. Before conducting the test, the expiration date must be noted. RDTs should not be removed from their sealed packets until right before use. After explaining the purpose of the test to the patient, blood should be taken by finger prick and the blood transfer device included in the kit used to place the recommended amount of blood on the RDT sample well. Buffer is then added according to manufacturer instructions. Results should be ready in exactly 20 minutes.

If the RDT and/or microscopy result is negative, alternative causes of fever should be investigated. If there is a high suspicion of malaria in a RDT-negative patient and if there is no other cause of fever,

the healthcare worker should seek a second laboratory confirmation test.

SPECIAL NOTE

If there is strong clinical suspicion of malaria despite a negative RDT (e.g., non-*P. falciparum* malaria),[1]**clinics** should refer the patient to a high-level health facility for microscopy. At the **hospitals** and **health centres**, RDTs and microscopy should be repeated until parasitaemia is confirmed or refuted. Clinicians should avoid treating for malaria unless there is parasitological laboratory confirmation.

Differential Diagnosis Considerations

The history of present illness should include the standard questions to identify the source of the fever. The healthcare worker should ask targeted questions to identify other common causes of fever:

- Runny nose (viral illness),
- Ear pain/discharge (otitis media),
- History of bloody diarrhoea (enteritis)

Other questions to help identify fever aetiology should be pursued:

- Any exposure to sick contacts
- History of recent medications (including malaria treatment) or herbal remedies.

Differential diagnosis of fever is broad, and other causes of fever should also be investigated. Co-infections occur regularly. The high prevalence of HIV/AIDS leads to an increase in the presence of febrile disease that is not malaria, thereby further complicating the diagnosis of malaria. The common causes of fever in Swaziland are listed below.

Differential Diagnosis: Common Causes of Fever in Swaziland
• Upper respiratory tract infections (common cold, pharyngitis/tonsillitis, otitis media, sinusitis)
• Diarrhoea
• Skin/soft tissue infections
• Pneumonia
• Urinary tract infections
• Meningitis

2.2 Definitive Diagnosis

Prompt and accurate diagnosis is part of effective disease management. In an elimination setting, symptom-based clinical judgment alone is not appropriate and confirmation by a parasitological diagnostic test is required before treatment is given. Diagnosis of malaria should be based both on clinical criteria and on the detection of parasites in the blood (also known as parasitological or

[1]More than 99% of all malaria cases in Swaziland are *P. falciparum*, but non-*P. falciparum* malaria is possible. Note that *P. falciparum* malaria is the deadliest.

confirmatory diagnosis).

In accordance with World Health Organisation (WHO) recommendations for low transmission settings, **the malaria diagnosis policy in Swaziland is to conduct a parasitological diagnostic test on *all* suspected malaria cases.**

The commonly used methods of parasitological diagnosis are microscopy and malaria rapid diagnostic tests (RDTs). One or both methods is/are available at all health facilities in Swaziland.

Parasitological Diagnosis at Health Facilities
• Clinics: RDTs only (a slide should be taken if RDT is positive) • Health centres: RDTs and microscopy • Hospitals: RDTs and microscopy

Microscopy

Examination of blood smears by light microscopy is the "gold standard" for malaria diagnosis. Malaria microscopy is done by examining Giemsa stained thick and thin blood smears by light microscopy for presence of malaria parasites. Microscopy allows for the quantification of malaria parasites and identification of infecting species.

Rapid Diagnostic Tests (RDTs)

Malaria RDTs are immunochromatographic tests that detect specific antigens produced by malaria parasites that are present in the blood of an infected or recently infected individual. Malaria RDTs can assist in making a rapid, accurate diagnosis of malaria when microscopy-based diagnosis is not available or is unreliable. Some RDTs can detect only one species (*P. falciparum*) while others detect one or all other species of the parasite (*P. vivax, P. malariae, and P. ovale*). To ensure malaria elimination of all malaria infections, Swaziland will us PF/PAN kits for malaria Diagnosis.

RDTs should not be used to monitor response to therapy or to confirm suspected treatment failure. RDTs detect antigens produced by the parasite which may be present in the blood of infected individual days *after* successful treatment. Several studies suggest that parasite antigens can persist for up to 30 days after successful treatment. Microscopy should therefore be ordered to determine if

the parasite has been successfully cleared on patient follow up post treatment.

2.3 Uncomplicated Malaria Treatment

Drug Therapy for Uncomplicated Malaria
• First-line treatment for all (excluding pregnant women and infants <1 year): Artemether Lumefantrine (AL) and a single low-dose of primaquine • First-line treatment for pregnant women in their 2nd and 3rd trimesters and lactating women: artemether lumefantrine (AL) • First-line treatment for pregnant women in their 1st trimester: oral quinine • Second-line treatment: oral quinine • AL and oral quinine are effective against all malaria strains and therefore should be used for all malaria cases.

Artemether Lumefantrine (AL) and Single low-dose Primaquine

Artemether lumefantrine (AL) is the first-line treatment for uncomplicated malaria for all children and adults, including pregnant women in their second and third trimester and lactating women with mild malaria. **It should not be used in pregnant women in their first trimester**. It is available at all facilities in co-formulated tablets containing 20 mg of artemether and 120 mg of lumefantrine. **Tablets should be kept in the blister packs until immediate consumption.**

The combination of artemether and lumefantrine interferes with the conversion of haem to the non-toxic haemozoin (haem is toxic to the malaria parasite) and also inhibits nucleic acid synthesis. This treatment rapidly clears the parasite and parasite gametocytes from the blood and reduces malaria symptoms.

Primaquine phosphate is a member of the 8-aminoquinoline group of drugs that includes tafenoquine and primaquine. Each tablet contains 26.3 mg of primaquine phosphate (equivalent to 15 mg of primaquine base). The dosage is customarily expressed in terms of the base. A single dose 0.25mg base/kg primaquine is recommended by WHO in addition to artemisinin combination treatment (ACTs) for uncomplicated falciparum malaria as a gametocytocidal medicine, particularly as a component of pre-elimination or elimination programs and is unlikely to cause a serious toxicity in subjects with any of the G6PD variants[2].

SPECIAL NOTE
A single 0.25mg base/kg primaquine dose should be given to all patients with parasitologically-confirmed P. falciparum malaria on the first day of treatment in addition to an ACT, except for pregnant women and infants < 1 year of age.

Artemether lumefantrine (AL)

- **Treatment dosage:** Twice a day for three days (6 doses).
- For all patients, **the first treatment dose should be directly observed**- if the patient vomits within 30 minutes of dosing, the patient must be re-dosed as the dose will have been ineffective**.**
- The second dose on the first day should be given anytime between 8 and 12 hours after the

[2]WHO, 2012.

first dose (whatever time of the day or night this may be). Dosage on the second day is twice a day (morning and evening).

- The total dose is based on weight, but if a scale is not available, AL should be dosed based on age:

Table 1.Dosing Schedule for Artemether Lumefantrine

Body Weight (age)	No. of Tablets & Timing of Dosing					
	Day 1		Day 2		Day 3	
	1st dose	8hrs later	Morning	Evening	Morning	Evening
5-14 kg (<3 yrs)	1	1	1	1	1	1
15-24 kg (≥3-8 yrs)	2	2	2	2	2	2
25-34kg (≥9-14 yrs)	3	3	3	3	3	3
≥ 34kg (>14 yrs)	4	4	4	4	4	4

- **Treatment absorption:** Lumefantrine absorption is enhanced by co-administration with fat. Low blood levels, with resultant treatment failure could potentially result from inadequate fat intake so it is essential that patients or caregivers are informed of the need to take AL with fat containing food, particularly on the second and third day of treatment. For infants and small children that cannot take tablets, the pills can be crushed and mixed with a small amount of milk or water.[3] It is important the child drinks the full drink the medicine is mixed into, do not make up using a large volume of liquid.

- **Reported side effects:** Overall side effects from AL are rare, and when they occur, they are mild:
  - Dizziness
  - Fatigue
  - Anorexia
  - Nausea
  - Vomiting
  - Abdominal pain
  - Palpitations
  - Myalgia
  - Sleep disorders
  - Arthralgia
  - Headache and
  - Rash have been reported.

All healthcare workers and patients are therefore advised to identify all adverse effects and report them to the NMCP via the pharmacovigilance unit. The Programme will document all reports and use the information to make future drug policy decisions.

- **Contraindications:**
  - Patients with history of arrhythmias
  - clinically relevant bradycardia
  - heart failure
  - family history of sudden death or of congenital QT interval prolongation
  - Persons with known hypersensitivity to either of the components in AL
  - Severe malaria
  - First trimester of pregnancy

AL has a short shelf life of less than two years. It is a highly hygroscopic chemical compound, and

[3]Juma, 2008.

moisture and temperature of 30°C and above severely affects the efficacy of the drug. Proper cool chain management throughout the supply chain is critical.

Artemether Lumefantrine Patient Counselling
• You must take the full course of 6 doses exactly as directed, even if you feel better before the end of the treatment. • Take this medicine with food, preferably fatty foods (for example emasi, fat cakes, full cream milk, fatty meats, foods made with butter). • Drink plenty of fluid (ORS or water) to keep hydrated while you are sick so you feel better sooner.

Primaquine

- **Treatment dosage:** A single 0.25mg/kg dose of primaquine with first dose of ACT
- For all patients, **the dose should be directly observed**- if the patient vomits within 30 minutes of dosing, the patient must be re-dosed as the dose will have been ineffective**.**
- The total dose is based on weight.

Table 2. Dosing schedule for Primaquine (7.5mg and 15mg tablet)

Weight (kg)	Number of tablets 7.5mg	Number of tablets 15mg	Dose in mg
10-15	0.5	-	3.75
16-30	1	0.5	7.5
31-45	1.5	-	11.25
>45	2	1	15

- **Treatment absorption:** Primaquine may be taken with or without food. It is recommended

that primaquine be taken with food to avoid a stomach upset.

- **Reported side effects:** No side effect is likely, but the most common:
  - Is feeling sick after taking the medicine
  - Fever
  - Skin rash
  - Vomiting
  - Stomach cramps
  - Headache
  -

- Rare but serious side effects may include:
  - Pale nails
  - Shortness of breath
  - Dizziness on standing
  - Pale colour (anaemia)
  - Dark urine
  - Fast heartbeat
  - Confusion
  - Bluish colour of skin
  - Nails or lips
  - Itching of skin
  - Swelling of face
  - Neck
  - Body and difficulty breathing.

The Programme will document all reports and use the information to make future drug policy decisions.

- **Contraindications:**
  - Acutely ill patients suffering from systemic disease manifested by tendency to granulocytopenia, such as rheumatoid arthritis and lupus erythematosus.
  - Also patients receiving concurrently other potentially haemolytic drugs or depressants of myeloid elements of the bone marrow.
  - Pregnant women and infants <1 year of age
  - Use of Primaquine in patients receiving quinine
- Primaquine has a shelf life of two years. It is a highly hygroscopic chemical compound, and must be protected from light and stored at 25° C; excursions permitted to 15° C – 30° C. Proper cool chain management throughout the supply chain is critical.

Primaquine Patient Counselling
• You must check the colour of your urine, if you notice dark to very dark urine (reddish-brown) or experience nausea, vomiting, stomach or back pain, please return to the health facility.

Quinine

Due to its effectiveness and long safety record in pregnancy, oral quinine will be used as the first-line treatment for mild malaria in pregnant women in their first trimester.
Oral quinine is also the second-line treatment for uncomplicated malaria.

- **Treatment schedule and dosage:** Dosage based on weight 10 mg/kg 3 times daily for 7 days.

The maximum dosage for adults is 600mg 3 times a day for 7 days.

- **Treatment absorption:** Oral quinine sulphate can be taken with or without food.
- **Reported side effects**:
    - Dizziness
    - Ringing in the ears
    - Blurred vision
    - Tremors

At the recommended dosages, these symptoms are not severe enough to stop treatment and will subside spontaneously when administration of the drugs ends. Hypoglycaemia may be caused by quinine.

- **Contraindication:** No contraindication to the oral administration of the drug within the above dosage.

Table 3. Dosing Schedule for Oral Quinine (300 mg tablet)

Body Weight (Age)	No of Tablets (3 times a day for 7 days)
4-6 kg (2-4 months)	**
6-10 kg (4-12 months)	**
10-19 kg (1-5 years)	1/2
20-35 kg (5-10 years)	1
36-50 kg (10-13 years)	1 ½
>50 kg (>13 years)	2

**Note: All children weighing less than 10kg should be admitted and treated with parenteral quinine.

Supportive Treatment

Apart from fever, a patient with uncomplicated malaria may require additional treatment to correct conditions such as dehydration and anaemia. If the patient is unable to take the treatment for prolonged period (24 hours), they should return to the health facility for potential hydration, anti-nausea, or anti-emetics and referral for inpatient care if necessary.

Table 4. Supportive Treatment

Condition	Treatment and Notes
High fever (>39°C) and body aches	• Give paracetamol and advise patient to receive tepid sponging and fanning to bring fever down
Dehydration or diarrhoea	• Give oral rehydration salt (ORS) • Advise to take increased amounts of water or other fluids • In the case of infants, encourage mothers to provide extra breast-feeding
Anaemia	• Take ferrous sulphate and folic acid for 30 days • Refer severe anaemia to a higher level health facility

Health Promotion and Counselling

To ensure adherence to treatment, the first treatment dose for all patients should be directly observed

and the following counselling messages should be provided:

- Explain the dosing schedule, use probing questions to confirm the patient's understanding
- Emphasise that all doses must be taken even if the patient feels better after a few doses
- Recommend paracetamol for symptoms of fever and body aches
- If vomiting occurs within 30 minutes after receiving the drug orally the dose should be repeated; if vomiting occurs after this time, continue with planned dosing schedule
- Advise patients to go immediately to the nearest health facility if the condition deteriorates at any time, or if symptoms have not resolved after three days
- Alert patients that a surveillance agent from the NMCP will be conducting a household follow-up within 48 hours

Healthcare workers should also promote the following messages to malaria patients:

- Take personal protection measures such as accepting indoor residual spraying (IRS), sleeping under a long-lasting insecticide-treated net (LLIN) every night during the malaria season, using mosquito coils, repellents, and insecticides
- Use personal protection measures and chemoprophylaxis when travelling to a malarious region in Swaziland or in another country
- Remove stagnant water bodies within the community to prevent vector breeding
- Seek immediate treatment if they have similar signs and symptoms
- Educate friends and family on malaria prevention

Treatment Failure

Recurrence of *P. falciparum* malaria can be the result of a re-infection with a new parasite or a recrudescence of original infection, otherwise known as treatment failure. Treatment failure is defined as a failure to achieve the desired therapeutic response (i.e. clearance of parasite) after the initiation of therapy. Treatment failure may result from poor adherence to treatment, pharmacokinetics (poor absorption), and drug resistance. Treatment failure within 14 days of receiving an ACT is very unusual.[4]

Treatment failure should be suspected if patient deteriorates clinically at any time or if symptoms persist 3 to 14 days after initiation of therapy in accordance with the recommended treatment regimen. To determine whether there has been treatment failure, the healthcare worker must determine from the patient's history (1) whether he or she vomited treatment or did not complete a full treatment course and (2) whether there is persistent parasitaemia in the patient's blood despite successful treatment.

Clinic level – Because persistent parasitaemia can only be confirmed by microscopy,[5] clinics should refer patients with suspected treatment failure to hospitals and health centres for microscopy confirmation.

- **Hospital or health centre level** – At hospitals and health centres, malaria microscopy should be conducted.

Only confirmed cases of malaria treatment failure should be treated with the second-line antimalarial treatment: oral quinine. In cases of non-adherence or non-completion of medicine, repeat a full course of the first-line drug. Other potential differential diagnosis should be sought and managed if

[4]WHO, 2006.

[5]Use of RDTs is not recommended in suspected treatment failure because the parasite antigen persists in the blood after successful clearance of malaria from the bloodstream. Thus RDTs should not be used after malaria treatment has been instituted. Only microscopy can quantify parasite count and expected decrement on medications.

parasitaemia has cleared in the patient.

Management of Non-*P. falciparum* Malaria

Non-*P. falciparum* cases are extremely rare in Swaziland. The procedures for management of such cases are the same as that for *P. falciparum* malaria. For laboratory-confirmed *P. vivax* and *P. ovale* malaria cases, primaquine may also need to be prescribed, along with AL, to prevent the relapse of the disease.

Treatment of such infections will be a combination of ACT (AL for 3 days) and primaquine for duration of 5 days.

Anaemia (Hb<8g/dl) and known G6PD deficient patients should be excluded from treatment with primaquine.

Table 5. Dosing schedule for Primaquine (7.5mg and 15mg tablet) for radical treatment of P. vivax and P. ovale (Daily dose for 5 days)

Weight (kg)	Number of tablets 7.5mg	Number of tablets 15mg	Dose in mg
10-15	1	0.5	7.5
16-30	2	1	15
31-45	3	1.5	22.5
>45	4	2	30

2.4 Supportive Health System

The implementation of an effective case management policy requires the support of a strong health system that provides regular training and mentoring for clinicians and laboratory technicians, enables proper storage and inventory management of pharmaceutical and health products, and ensures quality diagnosis by both RDTs and microscopy.
As Swaziland conducts a malaria elimination campaign, prompt reporting of every malaria case becomes critical, as interventions must target community outbreaks and each patient will be followed up by a National Malaria Control Programme (NMCP) surveillance agent.

Malaria Notification Policy

The immediate notification of all confirmed malaria cases in Swaziland within 24hours is mandatory. All malaria cases are to be rapidly reported through the Immediate Disease Notification System (IDNS). All health facilities should be equipped with the IDNS tool where the details of the malaria case are to be recorded by the healthcare worker, including the contact information and travel history of the case. The healthcare worker then **calls the toll-free number 977** to relay the details of the case to the Ministry of Health's Epidemic Preparedness and Response (EPR) Unit. A response to this case is then mounted by the National Malaria Control Programme following notification of the malaria case. Routine monthly reporting of malaria cases is also done by the **Health Management Information Systems (HMIS)** via their regular data collection methods. **The number of cases reported to the IDNS**

should match the monthly totals reported by the health facility to the HMIS.

Reporting Requirements for Confirmed Malaria Cases
• Promptly notify cases within 24hours to Immediate Disease Notification System (977), ensure contact details and travel history is captured and reported • On a monthly basis, all cases should be tallied and reported to the Health Management Information System (HMIS)

Patient Follow-Up

NMCP surveillance agents will conduct a case investigation for every patient with a positive malaria test within 48 hours after they have received treatment. The agents will carry out a complete case, travel and exposure history. The surveillance agents will also perform RDTs on community members residing within 500m of the malaria patient and refer all patients testing positive with RDTs to the nearest clinic.

Supply Management of Pharmaceutical and Health Products

RDTs and anti-malarias must be maintained between 4°C and 30°C at all times to ensure efficacy.

SECTION 3.GUIDELINES FOR DIAGNOSIS AND TREATMENT OF SEVERE AND COMPLICATED MALARIA

Severe malaria is defined as the detection of *P. falciparum* malaria in the peripheral blood with signs of severity and/or evidence of vital organ dysfunction. Severe and complicated malaria is a medical emergency. Delay in diagnosis leads to rapid deterioration and death.

The key to effective management is early recognition, prompt referral from clinic level to a higher level of care, and appropriate antimalarial and supportive therapy prior to transfer. In Swaziland, heightened vigilance for severe and complicated malaria is warranted due to the decrease in natural immunity and the high prevalence of HIV-related immune-suppression.

3.1 Assessment of Severe and Complicated Malaria

Patient History

Relatives and caretakers of the patient should be questioned about the patient's exposure to transmission, including whether the patient resides in a malarious region and/or has recently travelled to a malaria-endemic area (see "Patient History" in **Section 2.1**).

Relatives and caretakers should also be questioned on the patient's previous treatment with antimalarials or other drugs, recent fluid intake and urine output, and recent or past history of convulsions. This information should be taken into consideration during drug therapy and supportive treatment.

Clinic Referral of Suspected Severe and Complicated Malaria

In Swaziland, severe and complicated malaria is managed at hospitals and health centres. At the clinic level, if any of the signs and symptoms of severe and complicated malaria are identified and the patient is living in or has travelled to a malaria area, the patient should be immediately referred to the closest hospital or health centre.
Danger signs for severe febrile illness are detailed in **Annex C**; these are also the criteria for referral to a higher-level facility.

SPECIAL NOTE

Severe and complicated malaria is a **medical emergency** and should only be treated at the hospital and health centre. Any clinic receiving a patient with signs and symptoms of severe and complicated malaria must *immediately* **refer** the patient to the nearest hospital or health centre.
The clinic should **contact EPR on 977**to organise transportation if an ambulance is not readily available.
Pre-referral treatment:2.4 mg/kg IM artesunate injection should be administered. If artesunate is not available, pre-referral treatment: 10 mg/kg IM quinine at a dilution of <60 mg/ml should be administered. (Refer to table7)

The risk of death from severe and complicated malaria is greatest in the first 24 hours, and the time between referral and arrival at appropriate facility cannot be delayed, as the patient may deteriorate or die. Administration of antimalarials to patients with severe and complicated malaria as pre-referral

treatment has been shown to improve patient's outcomes.[6]The following pre-referral and supportive treatment for severe and complicated malaria should be administered at the clinic level.

- **Pre-referral antimalarial treatment** – Immediately administer intramuscular (IM) artesunate (2.4 mg/kg) (if artesunate is unavailable, administer quinine 10mg/kg IM at a dilution of <60mg/ml) while organising transport to higher-level healthcare facility.
- **Hydration and glucose** – The patient may have low blood sugar from the infection. If the patient can swallow give sugar water or oral rehydration salt (ORS) and for babies, expressed milk. Where there is a qualified staff member, administer 50% glucose IV.
- **Fever management** – Encourage the caretaker to undertake sponging along the journey to keep the temperature down. Paracetamol can be used if patient is able to take oral medication.
- **Referral documentation** – Record all findings and drugs given in the referral letter.

Physical Examination

Once a patient has arrived at a health centre or hospital, a full physical examination should be undertaken. The vital signs (i.e., respiratory rate, heart rate and blood pressure, cardiac/circulatory system, pulmonary and neurological examination) should be carefully and quickly performed to direct supportive measures.

- **Cardiovascular system** – Particular attention should be made to assess the cardiovascular system to determine if they are intravascularly depleted (i.e., low blood pressure, rapid pulse, dry mucous membranes, sluggish capillary refill[7]) or have pulmonary oedema (i.e., S3, jugular vein distension, rales). Patients may have metabolic acidosis due to poor perfusion and tissue hypoxia; this is manifested by deep breathing. Severe anaemia itself can contribute to hypoxia resulting in tachypnoea and cardiac failure; examine conjunctive and nail bed for pallor.
- **Respiratory system** – Respiratory status should be examined carefully; determine if they are in heart failure with fluid overload. Provide supplemental oxygen as needed.
- **Neurological system** – Neurologic abnormalities secondary to severe malaria can occur particularly in children. This includes the development of seizures. Seizures are often subtle and can manifest as abnormal eye movements, drooling and subtle repetitive movements of limbs, lip smacking, etc. It is important to look for these subtle signs of seizures as treatment of them can resolve mental status abnormalities. If the patient has evidence of a decreased attention, a detailed neurological examination to quantify the degree of encephalopathy or coma should be done; patients with mental status changes should undergo lumbar puncture, if there is no evidence of increased intracranial pressure, to rule out bacterial meningitis. Hypoglycaemia, which can be secondary to malaria infection can also result in decrease in mental status and coma. This should be assessed for by finger stick glucose; if one cannot check glucose levels, empiric administration of dextrose should be considered.
- **Bacterial infections** – Patients with malaria can have concomitant bacterial infections including pneumonia (assess for lobar abnormalities on lung examination), Salmonella bacteraemia or gastroenteritis, especially in patients with anaemia. Disseminated intravenous coagulation can be detected by examining the skin carefully for petechiae in the mouth,

[6]Gomes, 2009.

[7]Capillary refilling is tested by pressing firmly on the pulp of a finger and estimating the time required for blood to return after pressure into the nailbed after it is released. In a normal person with good cardiac output and digital perfusion, capillary refilling should take less than 3 seconds. Longer than this may suggest hypovolaemia.

conjunctiva and extremities.

Clinical Features of Severe and Complicated Malaria	
• Prostration (extreme weakness) • Impaired consciousness • Respiratory distress; deep breathing • Multiple convulsions • Circulatory collapse • Pulmonary oedema • Abnormal bleeding	• Jaundice • Haemoglobinuria; red-coloured urine due to destruction of red cells and release of haemoglobin • Shock • Decreased urine output

Laboratory Values

Every suspected malaria patient should be confirmed parasitologically by RDTs and or microscopy and treatment should be started immediately after malaria is confirmed. If the tests are negative and the clinician has strong suspicions of malaria then the clinician can start the empiric therapy on his/her clinical judgement while repeating RDT test after 6-8hours from initial test. Further adjustment of therapy including discontinuation of antimalarials can be made after examination of negative multiple slides and or when an alternative aetiology is found.

SPECIAL NOTE

In all suspected cases of severe and complicated malaria, parasitological confirmation of the diagnosis of malaria is recommended.

Additional investigations to determine the severity of disease and prognosis should be undertaken where feasible. Laboratory diagnostic studies for severe and complicated malaria include:

Laboratory Features of Severe and Complicated Malaria	
Severe anaemia	Haemoglobin <7g/dl, hct<20%
Hypoglycaemia	blood glucose <2.2 mmol/l
Acidosis	arterial pH <7.35
Renal impairment	Serum creatinine >265 μmol/litre or Rapidly rising creatinine (>2.5 μmol/kg/day) or Urine output <400 ml/day (adult)
Hyperparasitaemia	≥3+ or ≥5% infected red cells
Coagulopathy	Disseminated intravenous coagulation

3.2 Management of Severe and Complicated Malaria

Artesunate

The first-line treatment for severe and complicated malaria is **artesunate** except for pregnant women in their 1st trimester and children under 5kg. Artesunate is an Artemisinin derivative that rapidly clears the parasite from the blood and reduces malaria symptoms. Compared to other antimalarials available

for the treatment of severe malaria, artesunate reduces the risk of mortality as well as the incidence of convulsions, coma, and risk of the patient developing hypoglycaemia. Artesunate is easy to administer through IV injection and does not require rate controlled infusion or cardiac monitoring. There are two methods of administration for artesunate: intravenous (IV) and intramuscular (IM). For severe and complicated malaria, **IV administration is the route of choice**. Artesunate is available as ampoules containing 60mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution.

Drug Therapy for Severe Malaria

Severe and Complicated Malaria

- Pre-referral treatment: Intramuscular (IM) artesunate
- First-line treatment (including pregnant women in their 2nd and 3rd trimesters and lactating women): Intravenous (IV) or Intramuscular (IM) artesunate
- First-line treatment for pregnant women in their 1st trimester: Intravenous (IV) or Intramuscular (IM) quinine

If artesunate unavailable:

- Pre-referral treatment: Intramuscular (IM) quinine
- First-line treatment: Intravenous (IV) and Intramuscular(IM) quinine
- First-line treatment for pregnant women: intravenous (IV) and (IM) quinine

Table 6. Dosing Schedule for Artesunate in Severe and Complicated Malaria

Method of Administration	Dosing Schedule
Intravenous (IV)	• Loading dose: 2.4 mg/kg for adults and 3mg/kg for children<20kg – IV injection administered over 5 minutes – Omit loading dose if patient received pre-referral IM artesunate within 12 hours. • Maintenance dose: 2.4 mg/kg for adults and 3mg/kg for children<20kg • Administered at 12 and 24 hours after loading dose then once daily until oral AL is tolerated • Once started, administer IV artesunate for at least 24 hours (irrespective of the patient's ability to tolerate oral medication earlier)
Intramuscular (IM)	• IM artesunate may cause sterile abscesses and should be given only when IV therapy is not possible • After an RDT has tested positive, IM artesunate should be given on thigh not buttock • 2.4 mg/kg IM artesunate injection for pre-referral treatment
Oral (following IV and IM administration)	• **Once the patient is able to tolerate oral medication (after at least 24 hours since initial artesunate dose), change to AL**

In the absence of artesunate or when it is contra indicated, IV and IM quinine may be given for the treatment of severe malaria.

IV and IM artesunate is the first-line treatment for severe and complicated malaria, as it is the most potent drug and will have the greatest therapeutic benefit in patients that are severely ill

Quinine

IM and IV quinine is used first line in severe and complicated malaria, in the absence of artesunate injection. Where artesunate is available, it should be used first line in preference to quinine.

There are three methods of administration for quinine: intravenous (IV), intramuscular (IM), and oral. For severe and complicated malaria, IV administration is the route of choice.

Table7. Dosing Schedule for Quinine in Severe and Complicated Malaria

Method of Administration	Dosing Schedule
Intravenous (IV)	• Loading dose: 20 mg quinine salt/kg – Omit the loading dose if the patient has had an adequate dose of quinine (>40 mg salt/kg) in the previous 2 days – The loading dose should be given as an IV infusion over 4 hours • Maintenance dose: 10 mg Quinine salt/kg – The maintenance dose must be given every 8 hours – The maintenance dose should be given as an infusion over 4 hours – If IV therapy is still required after 48 hours, the maintenance dose should be reduced to 7 mg salt/kg to avoid the risk of accumulation – A minimum of 3 doses of IV quinine should be given before changing to oral treatment • Volume of infusion – Dilute quinine in 5% dextrose, 10% dextrose, 4% dextrose or D51/2 normal saline – Dilute quinine to a total volume of 10 ml/kg (the same volume is used for both loading and maintenance doses) and infuse over 4 hours – To avoid overloading the patient with IV fluids, the volume of the quinine infusion must be taken into account when calculating the total 24-hour fluid requirement • IV quinine can cause hypoglycaemia; blood glucose should therefore be monitored every 4 hours
Intramuscular (IM)	• IM quinine may cause sterile abscesses and should be given only when IV therapy is not possible • Dilute quinine 1 part in 5 (1ml quinine plus 4ml of dilution solution) with normal (0.9%) saline • Divide the dose into 2 separate injections and administer by deep IM injection into both anterior thighs; IM quinine should not be injected into the buttock
Oral (following IV and IM administration)	• **Once the patient is able to tolerate oral medication, treatment should be completed with oral quinine 10 mg salt/kg every 8 hours to complete the remainder of a total of 7 days of quinine treatment or switch to AL**

Supportive Treatment

In addition to administering antimalarial treatment, healthcare workers should also provide the following support treatment for patients with severe and complicated malaria.

- Clear the airway and check that the patient is breathing
- Establish IV access
- Take blood for malaria parasites, blood glucose, and haemoglobin. Urea and electrolytes, blood gas, and blood culture are also extremely useful, but may not be feasible at all facilities
- Rapidly assess circulation, hydration and nutritional status, and resuscitate as necessary with D5/normal (0.9%) saline

- For unconscious patients, insert a naso-gastric tube and aspirate stomach contents to prevent aspiration pneumonia. Place the patient in the recovery position, and perform a lumbar puncture to exclude meningitis
- Treat convulsions lasting 5 minutes or more
- Treat hypoglycaemia (blood glucose <2.2 mmol/l)
- If haemoglobin is <5 g/dl and patient has respiratory distress, transfuse blood
- Start antibiotic therapy if indicated

The management of the patient with severe malaria is as important as drug therapy and here the nurse has a crucial role to play. The following measures should be undertaken:

- Meticulous nursing care should be given to unconscious patients
- The treatment observation chart for inpatients has to be filled in correctly
- Aspiration pneumonia is a potentially fatal complication, and must be dealt with immediately by clearing airway and consider administration of metronidazole if an aspiration event occurs
- A careful record of fluid intake and output must be kept, the appearance of black urine noted and specific gravity measured
- The speed of infusion of fluids should be checked frequently; insertion sites for intravenous lines should be monitored
- Changes in the level of consciousness, occurrence of convulsions or changes in behaviour of the patient must be reported immediately
- For children, if rectal temperature rises above 39°C, vigorous tepid sponging and fanning must be applied and paracetamol given

Additional guidelines for management of complications resulting from severe and complicated malaria is outlined in **Annex D**. Complications include: cerebral malaria; convulsions; anaemia; renal failure; hypoglycaemia; fluid, electrolyte, and acid-base disturbances; pulmonary oedema, circulatory collapse (“algid malaria”); spontaneous bleeding and disseminated intravascular coagulation; hyperpyrexia; hyperparasitaemia; and malarial haemoglobinuria.

SECTION 4.GUIDELINES FOR MALARIA PROPHYLAXIS AND PREVENTION

There is no safe, effective and affordable anti-malarial drug that can be used for chemoprophylaxis on a large scale. Secondly, it should be well understood that no drug can guarantee absolute and complete protection against malaria. Therefore, the use of personal protective measures such as the use of long-lasting insecticide-treated nets (LLINs), insect repellents, and protective clothing is recommended when travelling.

All patients travelling to malaria-endemic areas should be counselled to take precautions to prevent mosquito bites. Chemoprophylaxis should be recommended to those travelling to malaria endemic areas outside of Swaziland, two weeks before travelling (especially Mozambique) particularly those with high risk exposure and lowered immunity (i.e. pregnant women, children under 5years of age, immune-compromised individuals).

Finally, all patients who travel to malaria endemic areas should be counselled that if they develop fever, they should present to their health care facility promptly for a malaria diagnostic test. Early recognition and treatment of malaria will prevent serious complications.

4.1 Chemoprophylaxis

Antimalarial chemoprophylaxis should be recommended for those travelling to malaria endemic settings outside of Swaziland, Mefloquine is the chemoprophylaxis of choice, while doxycycline and atovaquone/proguanil recommended when mefloquine is not feasible.

Malaria Chemoprophylaxis
• First-choice prophylaxis (excluding pregnant women in their 1st trimester and children <3months): weekly mefloquine • Alternative prophylaxis (excluding children under 5kg, pregnant women and elderly adults): daily atovaquone/proguanil • Alternative prophylaxis for all (excluding children under 8years of age and pregnant women): daily doxyclycline

NOTE: There is no safe malaria chemoprophylaxis for pregnant women in their 1st trimester and

children <3months.

Table 8. Dosing Schedule for Chemoprophylaxis

Chemoprophylaxis	Dosage Schedule and Notes
Mefloquine	• One dose per week: begin one - two weeks prior to travel), weekly during travel, and for 4 weeks upon return • Contraindicated in patients with history of anxiety or depression; counsel if development of anxiety or neuropsychiatric side effects to discontinue • May be taken for up to 6 months
Doxycycline	• Daily dosing during travel and for 30 days upon return • Side effect: photosensitivity, must take with food
Atovaquone/proguanil	• Daily dosing during travel and for 7 days upon return • Fewer side effects • More expensive than mefloquine and doxycycline

Pregnancy: Intermittent preventive therapy (IPTp) is not recommended for pregnant women in low transmission settings such as Swaziland. If travelling to high transmission area and at risk for vector exposure, mefloquine is safest option. Doxycycline and atovaquone/proguanil are contraindicated in pregnancy.

Mefloquine

- **Treatment schedule and dosage –** Dosage based on weight (4.6 mg base/kg);
    - Weekly intake (taken on the same day each week),
    - Starting 2 weeks before travel (at least one week before travel),
    - Take throughout travel if it a week or more
    - Take for 4 weeks on return from trip
- **Treatment absorption –**Mefloquine should not be taken on an empty stomach. It should be

taken with food and at least a full glass of water (240 mL).

- **Reported side effects** – Dizziness mild to moderate gastrointestinal disturbances
    - Nausea
    - Vomiting
    - abdominal pain
    - diarrhoea

- **Contraindications**
    - Persons with known hypersensitivity
    - Persons with a history of severe neuropsychiatric disease
    - Pregnant women in the first trimester
    - Infant less than 3 months
    - Persons who have received treatment with mefloquine in the previous 4 weeks
    - Persons performing activities requiring fine coordination and spatial discrimination

Table9. Dosing Schedule for Mefloquine (250 mg tablet)

Body Weight (age)	No. of Tablets & Timing of Dosing					
	Week before of travel	Each week of travel	Week 1 after travel	Week 2 after travel	Week 3 after travel	Week 4 after travel
<5 kg (<3 months)	-	-	-	-	-	-
5-12 kg (3-23 months)	1/4	1/4	1/4	1/4	1/4	1/4
13-24 kg (2-7 years)	½	1/2	½	1/2	1/2	1/2
25-35 kg (8-10 years)	¾	3/4	¾	3/4	3/4	¾
>36 kg (>11 years)	1	1	1	1	1	1

Doxycycline

- **Treatment schedule and dosage** – Dosage based on weight (2 mg base/kg);
    - Daily intake
    - Starting 1-2 days before travel,
    - Take daily throughout travel
    - Take for 4 weeks on return from travel
- **Treatment absorption** – A full glass of water should be taken with doxycycline.
- **Reported side effects** –
    - Vomiting
    - Diarrhoea
    - Nausea
    - Loss of appetite

Doxycycline may cause photosensitivity (sunburns); counsel patients to avoid sun or wear long sleeves

or sunscreen.

- **Contraindications**
  - Children less than 8 yrs
  - Pregnant women

Table 10. Dosing Schedule for Doxycycline (100 mg tablet)

AGE	No. of Tablets & Timing of Dosing							
	d-2	d-1	d	d+1	d+2	…	d+27	d+28
>8years	1	1	1	1	1	1	1	1

Note: d = total number of days travelling to malaria-endemic region; d-1 = day before travel; d+1 = day after travel

Atovaquone/Proguanil

- **Treatment schedule and dosage** – Dosage based on weight;
  - daily intake
  - Starting 1-2 days before travel
  - Take throughout travel
  - Take for 7 days after leaving malarious region.
- **Treatment absorption** –Atovaquone/proguanil should be taken with food or a milky drink
- **Reported side effects** –
  - Abdominal pain
  - Nausea
  - Vomiting
  - Headache.
- **Contraindications**
  - Persons with severe renal impairment (creatinine clearance <30 ml/min)
  - Not recommended for children <5kg
  - Not recommended for pregnant and lactating women feeding infants weighing <5 kg

Table11. Dosing Schedule for Atovaquone/Proguanil
(250 mg atovaquone and 100 mg proguanil co-formulated tablet)

Body Weight	No. of Tablets & Timing of Dosing									
	d-2	d-1	D	d+1	d+2	d+3	d+4	d+5	d+6	d+7
11-21kg	1/4	1/4	1/4	1/4	1/4	1/4	1/4	1/4	1/4	1/4
21-31kg	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2
31-40kg	3/4	3/4	3/4	3/4	3/4	3/4	3/4	3/4	3/4	3/4
>40kg	1	1	1	1	1	1	1	1	1	1

Note: d = total number of days travelling to malaria-endemic region; d-1 = day before travel; d+1 = day after travel

4.2 Personal Protection and Counselling

Healthcare workers should counsel travellers to reduce risk of infection by minimising exposure during vector biting hours (i.e. sundown), residing in screened residence, sleeping under LLINs, applying liberal amounts of N,N-Diethyl-meta-toluamide (DEET)-based insect repellents and pyrethroid-based insecticides, and using mosquito coils.

Healthcare workers should encourage those living in the malarious areas of Swaziland (e.g., Lowveld

and the Lubombo plateau) and vulnerable groups (i.e., pregnant women, children under 5years of age, and immuno-compromised individuals) to use personal protection measures to decrease risk of malaria transmission. These include allowing spray operators to spray the household during the annual IRS campaign, regularly sleeping under LLINs, removing stagnant waters in the communities where the vector could breed, wearing long sleeves during the peak biting hours (i.e., sundown), and using mosquito coils, repellents, and insecticides.

REFERENCES

Amexo, M, R Tolhurst, G Barnish, and I Bates. “Malaria misdiagnosis: effects on the poor and vulnerable.” *Lancet*364(9448):1896-8. November2004.

De Oliveira, AM, J Skarbinski, PO Ouma, et al. “Performance of malaria rapid diagnostic tests as part of routine malaria case management in Kenya.”*American Journalof Tropical Medicine andHygiene*; 80(3):470-4. March 2009.

Gomes, M, M Faiz, J Gyapong, M Warsame, T Agbenyega, A Babiker, F Baiden, EYunus, F Binka, and C Clerk. “Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial.” *The Lancet*373(9663):557-566. 2009.

Hopkins, Heidi, Lisa Bebell, Wilson Kambale, Christian Dokomajilar, Philip J. Rosenthal, and Grant Dorsey.“Rapid Diagnostic Tests for Malaria at Sites of Varying Transmission Intensity in Uganda.”*Journal of Infectious Diseases* 2008:197.February 2008.

Juma, Elizabeth A, Charles O Obonyo, Willis S Akhwale, and Bernhards R Ogutu. “A randomized, open label, comparative efficacy trial of artemetherlumefantrine suspension versus artemetherlumefantrine tablets for treatment of uncomplicated Plasmodium falciparum malaria in children in western Kenya.” *Malaria Journal* 7:262. December 2008.

Mayxay M, Newton PN, Yeung S, Pongvongsa T, Phompida S, Phetsouvanh R, White NJ. “Short communication: An assessment of the use of malaria rapid tests by village health volunteers in rural Laos.” *Tropical Medicine and International Health*. 2004.

Molyneux, ME, TE Taylor, et al.“Clinical features and prognostic indicators in paediatric cerebral malaria: A study of 131 comatose Malawian children.”*Quarterly Journal of Medicine*. 1989.

Njama-Meya, D, TD Clark, B Nzarubara, S Staedke, MR Kamya, and G Dorsey. “Treatment of malaria restricted to laboratory-confirmed cases: a prospective cohort study in Ugandan children.”*Malaria Journal*6:7. January 2007.

Singh, N, AK Mishra, MM Shukla, SK Chand, and PK Bharti. “Diagnostic and prognostic utility of an inexpensive rapid on site malaria diagnostic test (ParaHIT f) among ethnic tribal population in areas of high, low and no transmission in central India.” *BMC Infectious Diseases*. 2005.

Swarthout, TD, H Counihan, RK Senga, and I van den Broek. “Paracheck-Pf accuracy and recently

treated Plasmodium falciparum infections: is there a risk of over diagnosis?" *Malaria Journal.*2007.

Swaziland National Malaria Control Programme (NMCP).*Annual Report*. 2007.

Swaziland National Malaria Control Programme (NMCP). *Annual Report*. 2016.

Swaziland NMCP.*Malaria Elimination Strategic Plan, 2008-2013*. July2008.

Swaziland NMCP.*Malaria Elimination Strategic Plan, 2015-2020*. July2014.

SwazilandNMCP.*National Malaria Conference Report.* May 2016.

Teasdale, G and B Jennett. "Assessment of coma and impaired consciousness. A practical scale."*Lancet* 2(7872):81-4. July1974.

Tjitra, E, S Suprianto, J McBroom, BJ Currie, and NM Anstey. "Persistent ICT malaria P.f/P.vpanmalarial and HRP2 antigen reactivity after treatment of Plasmodium falciparum malaria is associated with gametocytemia and results in false-positive diagnoses of Plasmodium vivax in convalescence" *Journal of Clinical Microbiology*. 2001.

White, NJ."The treatment of malaria."*New England Journal of Medicine* 12;335(11):800-6.September 1996.

World Health Organisation (WHO).*Guidelines for the Treatment of Malaria 3rd Edition*. 2015.

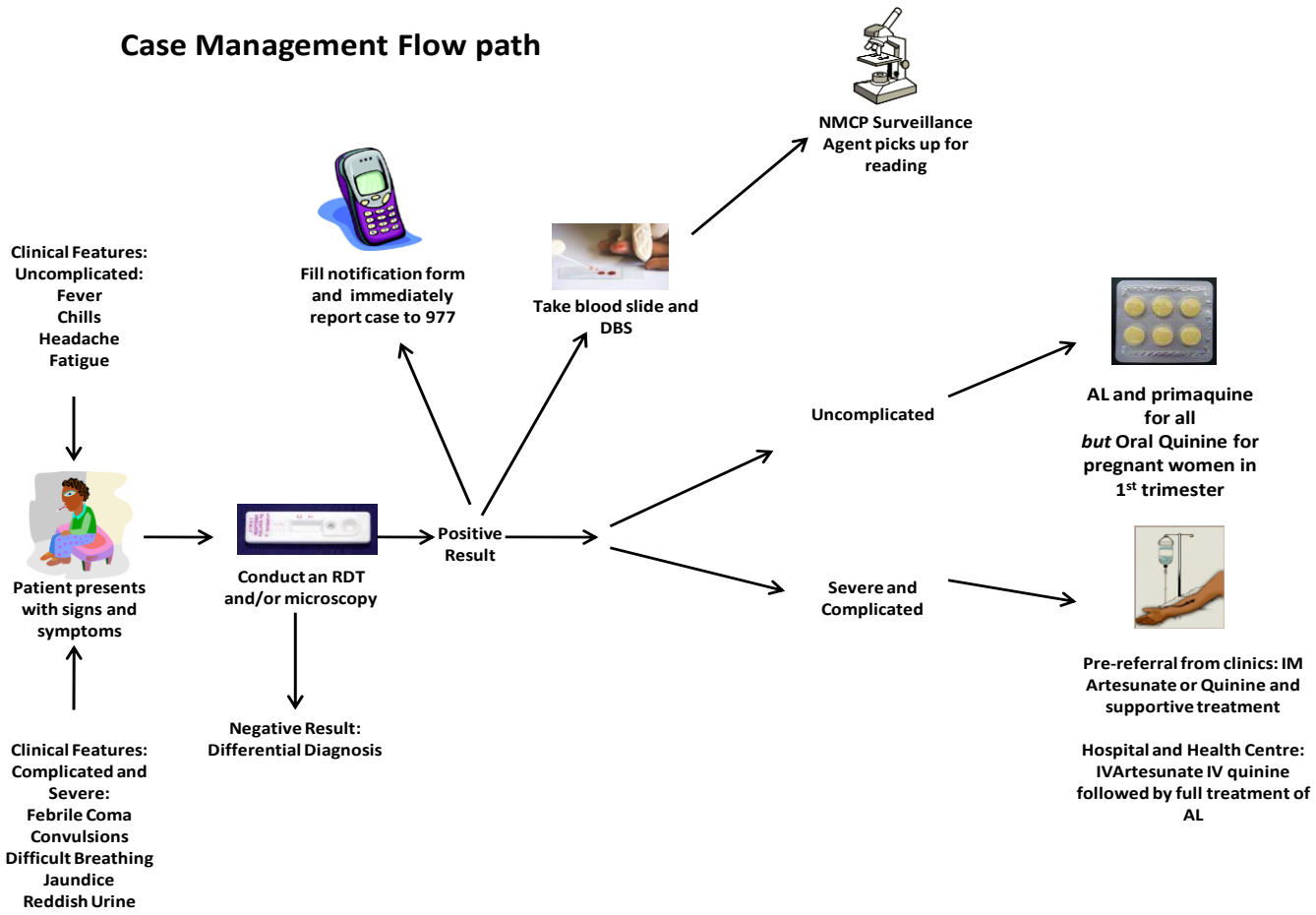
WHO.*Malaria Microscopy Quality Assurance Manual* version 1. February 2009.

WHO and Foundation for Innovative New Diagnostics (FIND).*Results of Malaria RDT Product Testing Round One*. 2008.

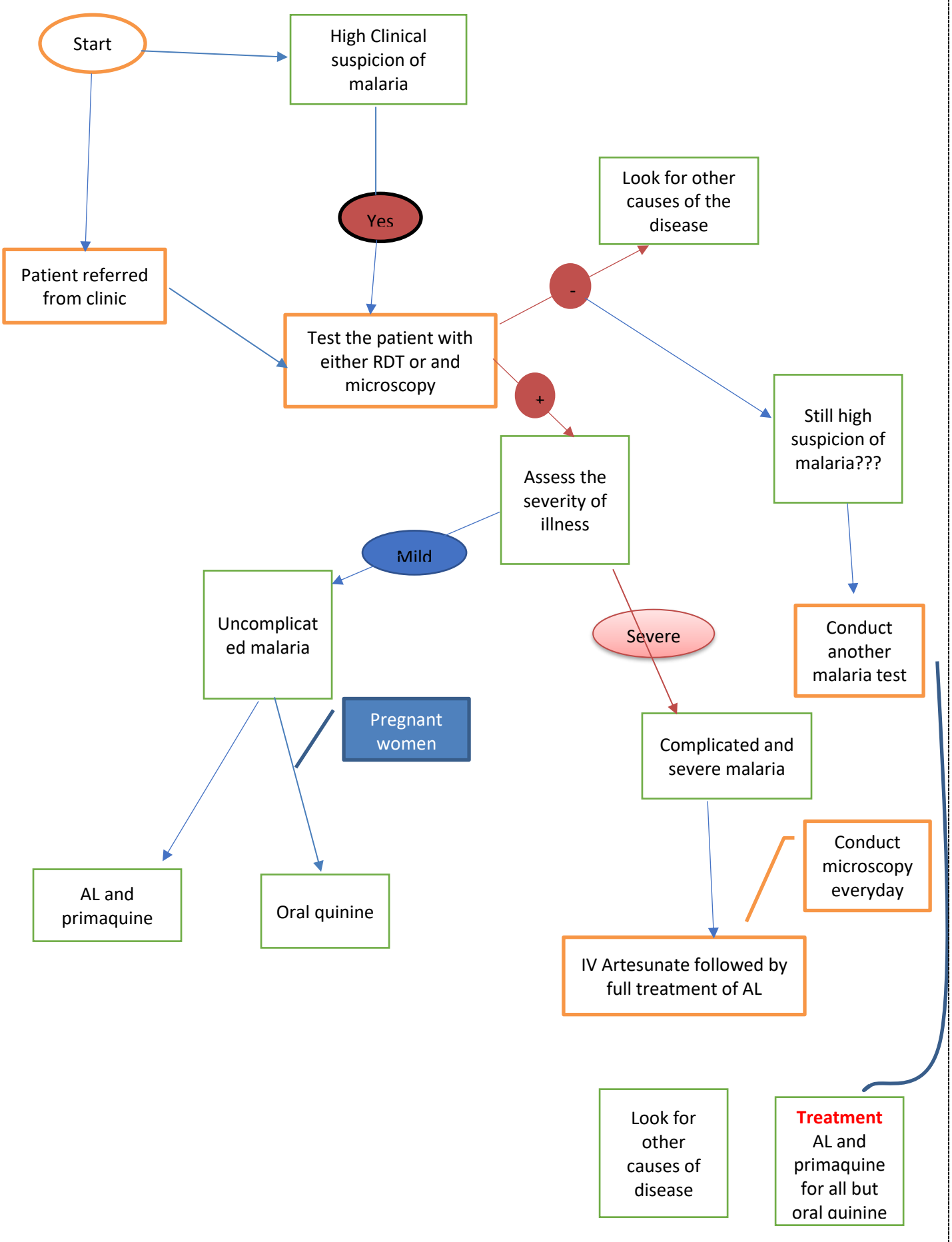
WHO.*Updated WHO Policy Recommendation: Single dose Primaquine as a gametocytocide in Plasmodium falciparum malaria.* October 2012.

ANNEX A. FLOW CHARTS FOR CASE MANAGEMENT

A.1 Malaria Case Management at Clinics



A.2 Malaria Case Management at Hospitals and Health Centres



ANNEX B. DANGER SIGNS OF SEVERE FEBRILE ILLNESS

Whenever malaria is suspected, healthcare workers must assess patient for signs of severe and complicated malaria.
Only uncomplicated malaria is managed at the clinic level.
Patients with signs of severe disease should be referred to the hospital or health centre urgently.

Ask	Look, Listen, Feel

• Is the patient able to drink?
• Has the patient had convulsions (fits)?
• Does the patient vomit repeatedly?
• How much urine does the patient pass?
  – Very little?
  – None at all?
  – Is it dark?
	• Is the patient abnormally sleepy, difficult to wake, or confused?
	• Is the patient unresponsive to pain (coma)?
	• Does the patient have shortness of breath, or difficult of breathing (respiratory distress or signs of pulmonary oedema)?
	• Does the patient have a weak rapid pulse?
	• Does the patient have severe anaemia (paleness of lower eyelids, palms, and tongue)?
	• Does the patient have yellow eyes (jaundice)?
	• Does the patient have severe dehydration? Look for:
	  – Sudden weight loss
	  – Loose skin
	  – Sunken eyes
	  – Dry mouth
	• Is the patient bleeding with no known cause?
	• Is the patient unable to stand or sit?

High Risk Groups for Severe Disease • Pregnant women • Children under 5 • Immunocompromised patients	

If the patient has fever or history of fever in past 48 hours and the answer to any of these questions is yes, the patient has severe febrile illness, possibly severe and complicated malaria.
The patient's life is in danger. Urgent treatment is needed to save the patient's life.

Supportive Treatment Before Referral

- Immediately administer intramuscular (IM) quinine
- The patient may have low blood sugar; if the patient can swallow give sugar water, oral rehydration salt (ORS) or for babies expressed milk; administer 5% glucose IV if possible
- Encourage the caretaker to undertake sponging along the journey to keep down temperature
- If rapid diagnostic test (RDT) can be performed without delay, it should be performed and the results noted in referral letter
- Record all findings and drugs given in referral letter

Note: This applies to clinics only.

ANNEX C. MANAGEMENT OF SEVERE AND COMPLICATED MALARIA

C.1 Cerebral Malaria

Clinical Features in Adults

- Comatose/the depth of consciousness being variable;
- Convulsions are common in adults
- Retinal bleeding is associated with a poor prognosis in adults; papilla oedema is rare
- Retinopathy is the most specific clinical sign for coma due to malaria (i.e., true cerebral malaria); rarely patients with cerebral malaria have normal retinal exam; the absence of retinopathy should raise the suspicion of a second process causing coma
- A variety of transient abnormalities of eye movement
- Fixed jaw closure and tooth grinding (bruxism) are common; pouting may occur or a pout reflex may be elicited (by stroking the sides of the mouth)
- Mild neck stiffness occurs but neck rigidity and photophobia are normally absent
- Motor abnormalities such as decerebrate rigidity, decorticate rigidity (arms flexed and legs stretched), and opisthosomas occur
- Opening pressure at lumbar puncture is usually normal in adults, but may be elevated
- Cerebrospinal fluid (CSF) is clear, with fewer than 10 white cells/µl; the protein is raised, as is the CSF lactic acid concentration

Clinical Features in Children

- The earliest symptom of cerebral malaria in children is usually fever (37.5-41°C), followed by failure to eat or drink. Vomiting and coughing are common; diarrhoea is unusual
- The history of symptoms preceding coma may be very brief; commonly one or two days
- A child who loses consciousness after a febrile convulsion should not be considered to have cerebral malaria unless coma persists for more than 0.5 hour after the convulsion
- The depth of coma may be assessed according to the Glasgow Coma Scale for adults or the Blantyre Coma Scale for children and continued monitoring of this score
- Always exclude or treat hypoglycaemia
- Convulsions are common before or after the onset of coma; they are significantly associated with morbidity and sequelae and need prompt treatment (anti-seizure medication, fever control)
- In some children the breathing is laboured and noisy; in others, deep breathing with a clear chest suggests acidosis
- A few children have cold, clammy skin, with core-to-skin temperature difference of 10ºC. Some of these patients are in a state of shock with systolic blood pressure <50 mmHg
- In patients in profound coma, corneal reflexes or “doll’s eye” movements may be absent
- In some children, extreme opisthosomas is present which may lead to a mistaken diagnosis of tetanus or meningitis
- CSF opening pressure is variable; it is raised more frequently than in adults, and is sometimes very high
- Leukocytosis (increased white blood cells) is not unusual in severe disease and does not necessarily imply an associated bacterial infection (this is also true in adults)
- A proportion of children (about 10%) who survive cerebral malaria have neurological sequelae which persist into the convalescent period. Sequelae may take the form of hemiparesis (mild paralysis of half of the body), cerebellar ataxia (loss of balance while walking), cortical blindness, severe hypotonia (low muscle tone), mental retardation, generalised spasticity, or aphasia and

behavioural changes

Management in Adults

- Give meticulous nursing care to the comatose patient
- Consider a urethral catheter using a sterile technique, to follow fluid balance
- Keep an accurate record of fluid intake and output
- Monitor and record the level of consciousness, temperature, respiratory rate, blood pressure, and vital signs frequently
- Treat convulsions and any other signs of complications

Management in Children

- A rapid initial examination should be carried out to assess:
  - Hydration
  - Anaemia
  - Pulmonary oedema
  - Level of consciousness
  - Hyperpyrexia
- Immediate tests must include:
  - Perform malaria RDT
  - Thick and thin blood films
  - Haematocrit
  - Finger-prick blood glucose
  - Lumbar puncture
- If parasitological confirmation is delayed more than one hour, treatment should be started immediately before the diagnosis is confirmed
- Treat convulsion if the child has convulsions
- Any child with convulsions should be examined for hyperpyrexia and hypoglycaemia and given appropriate treatment
- Simple practical manoeuvres, such as tepid sponging and fanning, should be employed to try to

keep the rectal temperature below 39°C. Relatives can be instructed to do this
- Paracetamol, 10 mg/kg of body weight given every 4 to 6 hours, may also be given as an antipyretic

Avoid in Patients with Cerebral Malaria

- Corticosteroids
- Other anti-inflammatory agents
- Other agents given for cerebral oedema (urea, invert sugar)
- Low molecular weight dextran
- Epinephrine (adrenaline)
- Heparin
- Epoprostenol (prostacyclin)
- Pentoxifylline (oxpentifylline)
- Hyperbaric oxygen
- Cyclosporine A

C.2 Convulsions

Management in Adults and Children

- Maintain the airway
- Turn the patient on his or her side to reduce the risk of aspiration
- Do not attempt to force anything into the patient's mouth
- Check blood glucose and treat if <2.2 mmol/l (see below)
- Treat with:
  - diazepam, 0.3 mg/kg (up to a maximum 10 mg), as a slow IV injection over 2 minutes; or diazepam, 0.5 mg/kg per rectum, administered by inserting a 1-ml syringe (without a needle) into the rectum; or
  - phenobarbitone, Phenobarbital 15-20 mg/kg, slow IV push; or
  - phenytoin, 18 mg/kg diluted in a 1000 ml normal saline, infused over 20 min; or
  - paraldehyde, 0.2-0.4 ml/kg
- If the patient continues to convulse, give further doses of diazepam or paraldehyde every 10 minutes (up to a maximum of 3 doses of either drug)
- Treat patients who have multiple (3 or more) or prolonged (lasting 30 minutes or more) convulsions with a loading dose of IM Phenobarbital, 10–15 mg/kg

C.3 Anaemia

Clinical Features in Adults

- Anaemia is common in severe malaria. The rate of development and degree of anaemia depend on the severity and duration of parasitaemia. In some children, repeated untreated episodes of otherwise uncomplicated malaria may lead to anaemia. In other children, severe anaemia may develop rapidly in association with hyperparasitaemia. In these cases, acute destruction of parasitised red cells is responsible.
- Anaemia is often associated with secondary bacterial infection, retinal haemorrhage and

pregnancy.

Clinical Features in Children

- Children with severe anaemia may present with tachycardia and dyspnoea. Anaemia may contribute both to cerebral signs, confusion, restlessness, coma, and retinal haemorrhages, and to cardiopulmonary signs such as gallop rhythm, cardiac failure, hepatomegaly and pulmonary oedema.

Management in Adults

- The need for blood transfusion must be addressed with great care in each individual. Not only the level of the haematocrit or haemoglobin concentration but also the density of parasitaemia and the clinical condition of the patient must be taken into account
- A diuretic is usually not indicated.

Management in Children

- The need for blood transfusion must be addressed with great care in each individual child. Not only the level of the haematocrit or haemoglobin concentration but also the density of parasitaemia, their volume and tissue perfusion status and the clinical condition of the patient must be taken into account.
- In general and with the provision mentioned above, a haematocrit of less than 15% or haemoglobin<5g/dl in a normally hydrated child is an indication for blood transfusion (20ml/kg over 3-4 hours). In children with respiratory distress (mostly due to acidosis), an initial transfusion is required with the utmost urgency (10 ml of packed cells or 20 ml of whole blood per kg of body weight, the first 10ml/kg over 30 minutes, the second 10ml/kg over 2 hours).
- A diuretic is usually not indicated as many of these children are hypovolemic. If there is volume overload, furosemide, 1-2 mg/kg of body weight up to a maximum of 20 mg, may be given intravenously.

C.4 Renal Failure

Clinical Features in Adults and Children

- Renal failure as a complication of malaria is virtually confined to adults.
- There is a rise in serum creatinine and urea, oliguria (scanty urination, <4ml/kg per hour in adults and <5ml/kg per hour in children) and eventually anuria (no urination) due to acute tubular necrosis.
- Acute renal failure is usually reversible.
- In children, renal failure is rare and poor urine output is often secondary to dehydration.

Management in Adults and Children

- Patients must be catheterised so that urine output can be measured accurately.
- Exclude dehydration or shock (hypovolemic) by clinical examination, including measurement of jugular or central venous pressure, and blood pressure drop between the patient lying supine and when propped up to 45C. Give a test infusion of 1000ml of normal saline (0.9%).
- For Adults: Once dehydration is corrected, give a single dose of furosemide, 40mg IV. If oliguria persists, increase furosemide dose in a stepwise fashion at 60 minute intervals to 100mg, 200mg

(1 hour infusion), and finally 400mg (2 hour infusion).

- For Adults: If urine output remains <4ml/kg per hour, assume renal failure is established and restrict fluids to approximately 1000ml/day plus urine output.
- Peritoneal dialysis should not be undertaken lightly. If possible, refer the patient to a dialysis unit or centre.

C.5 Hypoglycaemia

Clinical Features in Adults

- Hypoglycaemia (blood glucose <2.2 mmol/l) is an important manifestation of *P. falciparum* malaria. It occurs in three different groups of patients, which may overlap:
  - Patients with severe disease, especially young children;
  - Patients treated with quinine, as a result of a quinine-induced hyperinsulinemia;
  - Pregnant women, either on admission or following quinine treatment.
- In conscious patients, hypoglycaemia may present with classic symptoms of anxiety, sweating, dilatation of the pupils, breathlessness, laboured and noisy breathing, oliguria, a feeling of coldness, tachycardia and light-headedness. This clinical picture may develop into deteriorating consciousness, generalised convulsions, extensor posturing, shock and coma.
- The diagnosis is easily overlooked because all these clinical features also occur in severe malaria itself. Deterioration in the level of consciousness may be the only sign. If hypoglycaemia is suspected clinically in an unconscious person and it is not possible to check the blood glucose, give a presumptive infusion of glucose 50% as described below.

Management in Adults

- If hypoglycaemia is detected by blood testing or suspected on clinical grounds, insert an IV line and give 50% glucose, 50 ml by intravenous bolus injection
- Follow with an intravenous infusion of 5% or 10% glucose
- Continue to monitor blood glucose levels every 15 minutes (using a “stix” method if available, or clinically and biochemically if not) in order to regulate the glucose infusion.
- If blood glucose is still <2.2 mmol/l, repeat glucose infusion as above.
- If it is not possible to insert an IV line and the patient is unconscious, give 1ml/kg 50% dextrose via naso-gastric tube.
- Give oral sugar solution and food once the patient regains consciousness.

Management in Children

- Unconscious children should be given glucose regularly to prevent starvation hypoglycaemia. It is most conveniently provided as 5% dextrose in water infusion, but if this is likely to lead to fluid overload, smaller volumes of more concentrated glucose may be given at regular intervals.
- If hypoglycaemia occurs, it should be treated with 10% glucose, up to 5.0 ml/kg, in an equal volume of any infusion fluid, followed by a slow intravenous infusion of 10% glucose to prevent recurrence of hypoglycaemia.
- Monitoring of blood glucose level should continue (see above) even after apparent recovery, since

hypoglycaemia may recur.
- Give breast milk or sugar solution once the patient regains consciousness.

C.6 Fluid, Electrolyte, and Acid-Base Disturbances

Clinical Features in Adults

- Patients with severe *P. falciparum* malaria often show the following on admission: clinical evidence of hypovolemic (low jugular venous pressure, postural hypotension, and oliguria with high urine specific gravity) and clinical signs of dehydration (reduced ocular tension and decreased skin turgor).
- Acidotic breathing (hyperventilation) may develop in severely ill patients who are in shock, hypoglycaemic, hyperparasitaemic, or in renal failure. Lactic acidosis is a common complication and both blood and CSF lactic acid concentrations are raised. Perfusion is improved by correcting hypovolemic.

Management in Adults

- Look for evidence of dehydration and hypovolemic:
  - Reduced ocular tension
  - Reduced skin turgor
  - Cool extremities
  - Postural drop in blood pressure (as the patient is propped up from the lying-down position to 45° or to standing position)
  - Reduced peripheral venous filling
  - Low jugular venous pressure
  - Reduced urine output
  - High urine specific gravity
  - Urine sodium concentration less than 20 mmol/l
- If there is evidence of dehydration give modest volumes of isotonic fluids (0.9% saline or D5%/1/2 normal saline dextrose) by intravenous infusion, but avoid fluid overload
  - Check if the patient does not have severe malnutrition
  - Patients with severe malnutrition should not be given large volumes of IV fluids
  - If patient is markedly dehydrated, infuse 1000 ml of normal saline over 30 minutes as a bolus and check blood pressure
  - Reassess and give a second 1000 ml infusion if no improvement in blood pressure and clinical exam and symptoms
  - If after the 3rd infusion there is no improvement, give 20ml/kg of blood over 60 minutes
  - Give presumptive treatment with antibiotics to all patients who are in shock.
- Monitor blood pressure, urine volume (every hour)
- Improve oxygenation
  - Clear airway
  - Increase concentration of inspired oxygen
  - Support ventilation artificially, if necessary

Clinical Features in Children

- Patients with severe *P. falciparum* malaria often show the following on admission: clinical evidence of hypovolemic (low jugular venous pressure, postural hypotension, and oliguria with high urine specific gravity) and clinical signs of dehydration (reduced ocular tension and decreased

skin turgor).

- Acidotic breathing-hyperventilation-may develop in severely ill patients who are in shock, hypoglycaemic, hyperparasitaemic, or in renal failure. Lactic acidosis is a common complication and both blood and CSF lactic acid concentrations are raised. Perfusion is improved by correcting hypovolemic.
- The best clinical indications of mild to moderate dehydration in children are decreased peripheral perfusion, deep (acidotic) breathing, decreased skin elasticity, raised blood urea (>6.5 mmol/l), increased thirst, loss of about 3-4% of total body weight and evidence of metabolic acidosis.
- In children presenting with oliguria and dehydration, examination of urine usually reveals a high specific gravity, low urinary sodium, and normal urinary sediment, indicating simple dehydration rather than renal failure, which is rare in children.

Management in Children

- Careful rehydration with isotonic saline is mandatory, with frequent examination of the jugular venous pressure, blood pressure and chest
  - Check if the patient does not have severe malnutrition. Patients with severe malnutrition should not be given large volumes of IV fluids.
  - If severe dehydration, infuse 20ml/kg of normal saline over 30 minutes as a bolus and check blood pressure.
  - Reassess and give a second 20ml/kg infusion if no improvement in blood pressure and clinical exam and symptoms.
  - If after the 3rd infusion there is no improvement, give 20ml/kg of blood over 60 minutes.
  - Give presumptive treatment with antibiotics to all patients who are in shock.
- Where facilities for monitoring and maintenance of adequate sterility exist, fluid balance may be adjusted in accordance with direct measurement of the central venous pressure through a central venous catheter
- If, after careful rehydration, urine output over 24 hours is less than 4 ml/kg of body weight, furosemide can be given intravenously, initially at 2 mg/kg of body weight, then doubled at hourly intervals to a maximum of 6 mg/kg of body weight (given over 15 minutes)

C.7 Pulmonary Oedema

Clinical Features in Adults and Children

- Pulmonary oedema is a grave complication of severe malaria, with a high mortality (over 80%). Pulmonary oedema may appear several days after treatment has been started and at a time when the patient's general condition is improving and the peripheral parasitaemia is diminishing. It must be differentiated from iatrogenically produced pulmonary oedema resulting from IV fluid overload. Hyperparasitaemia, renal failure and pregnancy are often associated, as well as hypoglycaemia and metabolic acidosis. The first indication of impending pulmonary oedema is an increase in the respiratory rate, which precedes the development of other pulmonary signs. Check for crackles (rales) on auscultation and hepatomegaly.
- Hypoxia may cause convulsions and deterioration in the level of consciousness and the patient may die within a few hours.

Management in Adults and Children

- Keep patient upright; raise the head of the bed or lower the foot of the bed
- Give a high concentration of oxygen by any convenient method available, including mechanical

ventilation

- Give the patient a diuretic, such as furosemide 40 mg (1mg/kg), by intravenous injection. If there is no response, increase the dose progressively to a maximum of 200 mg
- In well-equipped intensive care units, mechanical ventilation with positive end expiratory pressure (PEEP), a wide range of vasoactive drugs and haemodynamic monitoring will be available
- If there is over hydration/fluid over load:
  - Stop all intravenous fluids
  - Use haemofiltration immediately, if available
- If there is no improvement, withdraw 250 ml of blood initially by venesection into a blood transfusion donor bag so that it can be given back to the patient later

C.8 Circulatory Collapse ("Algid Malaria")

Clinical Features in Adults and Children

- Some patients are admitted in a state of collapse, with a systolic blood pressure less than 80 mmHg in the supine position (less than 50 mmHg in children); a cold, clammy, cyanotic skin; constricted peripheral veins; rapid feeble pulse.
- Circulatory collapse is also seen in patients with pulmonary oedema or metabolic acidosis, and following massive gastrointestinal haemorrhage. Dehydration with hypovolemic may also contribute to hypotension.
- Possible sites of associated infection should be sought, e.g. lung, urinary tract (especially if there is an indwelling catheter), meningitis, intravenous injection sites, intravenous lines.

Management in Adults and Children

- Correct hypovolemic with an appropriate plasma expander (fresh blood, plasma, polygeline or dextran 70). If these are not available give isotonic saline (D5/NS).
- Take a blood culture (where possible) and start patient on broad-spectrum antibiotics immediately e.g. combined treatment with benzylpenicillin and gentamicin
- Once the results of blood culture and sensitivity testing are available, give the appropriate antibiotic
- Maintain central venous pressure between 0 and 5 cm H2O (if hypotension persists dopamine may be given through a central line)

C.9 Spontaneous Bleeding and Disseminated Intravascular Coagulation

Clinical Features in Adults and Children

- Bleeding gums, epistaxis, petechiae, and subconjunctival haemorrhages may occur. Disseminated intravenous coagulation, complicated by clinically significant bleeding (e.g., haematemesis or melaena), occurs in fewer than 10% of patients; it seems to occur more often in non-immune patients. Thrombocytopenia is common, and is not related to other measures of coagulation or to plasma fibrinogen concentrations; in most cases it is unaccompanied by bleeding. The platelet

count usually returns to normal after successful treatment of the malaria.

Management in Adults and Children

- Transfuse fresh blood, clotting factors or platelets as required
- Give vitamin K, 10 mg, by slow IV injection and for a child, administer 0.5mg/kg.

C.10 Hyperpyrexia

Clinical Features in Adults and Children

- Hyperpyrexia is more common in children and is associated with convulsions, delirium, and coma. In visitors not acclimatised to living in hot countries, it must be differentiated from heat stroke. Sustained very high body temperatures (42°C and above), rarely seen in malaria, may cause permanent severe neurological sequelae. There is evidence that high body temperature in pregnant women contributes to foetal distress.

Management in Adults

- Monitor temperature frequently
- If the temperature is above 39°C, give 1 g of paracetamol orally in addition to fanning and tepid sponging

Management in Children

- Monitor temperature frequently
- If rectal temperature is above 39ºC, apply vigorous tepid sponging and fanning, and give paracetamol, 10 mg/kg of bodyweight by mouth, suppository or nasogastric tube given every 4 to 6 hours.

C.11 Hyperparasitaemia

Clinical Features in Adults and Children

- In general, and especially in non-immune subjects, high parasite densities (above 5% or +++++) and peripheral schizontaemia are associated with severe disease. However, in hyper-endemic areas, partially immune children can tolerate surprisingly high densities (20-30%) often without clinical symptoms.

Management in Adults and Children

- An initial dose of parenteral antimalarial therapy should be given immediately, even if the patient can take medication by mouth

C.12 Malarial Haemoglobinuria

Clinical Features in Adults and Children

- Malarial haemoglobinuria (“black water fever”) is uncommon and usually presents in adults as

severe disease with anaemia and renal failure.

- Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and some other erythrocyte enzyme deficiencies may develop vascular haemolysis and haemoglobinuria when treated with oxidant drugs such as primaquine.

Management in Adults and Children

- Continue appropriate antimalarial treatment if parasitaemia is present
- Transfuse fresh blood to maintain haematocrit above 15%
- Monitor jugular or central venous pressure to avoid fluid overload and hypovolemic
- If oliguria develops and blood urea and serum creatinine levels rise, peritoneal dialysis or haemodialysis may be required
- If patient taking quinine develops profound haemoglobinuria and haemolytic anaemia (very rare event), oral AL should be administered

ANNEX D. COMA SCALES

D.1 Coma Score in Adults: Glasgow Coma Score

The Glasgow Coma Score (GCS)[8] has limited applicability to children, especially below the age of 36 months (where the verbal performance of even a healthy child would be expected to be poor). Blantyre Coma Score should be used for young children.

The GCS is scored between 3 and 15, with 3 being the worst and 15 the best. It is composed of three parameters: best eye response (E), best verbal response (V), and best motor response (M). When describing a GCS score, it is important to break it down to its components; e.g., E3V3M5 rather than

[8]Teasdale, 1974.

"GCS 11."

Table 10.The Glasgow Coma Score (GCS)

Best Eye Response (E) – highest possible score: 4	
1	No eye opening
2	Eye opening to pain *Note: Patient responds to pressure on the patient's fingernail bed; if this does not elicit a response, supraorbital and sternal pressure or rub may be used.*
3	Eye opening to verbal command *Note: Not to be confused with an awaking of a sleeping person; such patients receive a score of 4, not 3.*
4	Eyes open spontaneously
Best Verbal Response (V) – highest possible score: 5	
1	No verbal response
2	Incomprehensible sounds *Note: Moaning but no words*
3	Inappropriate words *Note: Random or exclamatory articulated speech, but no conversational exchange*
4	Confused *Note: The patient responds to questions coherently but there is some disorientation and confusion.*
5	Orientated *Note: Patient responds coherently and appropriately to questions such as the patient's name and age, where they are and why, the year, month, etc.*
Best Motor Response (M) – highest possible score: 6	
1	No motor response
2	Extension to pain *Note: Adduction of arm, internal rotation of shoulder, pronation of forearm, extension of wrist, decerebrate response*
3	Abnormal flexion to pain *Note: Adduction of arm, internal rotation of shoulder, pronation of forearm, flexion of wrist, decorticate response.*
4	Flexion/Withdrawal to pain *Note: Flexion of elbow, supination of forearm, flexion of wrist when supra-orbital pressure applied; pulls part of body away when nailbed pinched.*
5	Localises to pain *Note: Purposeful movements towards painful stimuli; e.g., hand crosses mid-line and gets above clavicle when supra-orbital pressure applied.*
6	Obeys commands *Note: The patient does simple things as asked.*

Table 2.Interpretation of the Glasgow Coma Score (GCS)

GCS Score	Interpretation
15	Fully awake
13-14	Mild brain injury
9-12	Moderate brain injury
4-8	Severe brain injury (generally accepted definition of coma)
3	Deep coma or death

NOTE: Refer to ICU when the score is less than 11

D.2 Coma Score in Children: Blantyre Coma Score

The Blantyre Coma Scale (BCS)[9] is a modification of the Glasgow coma scale suitable to use in preverbal children. The scale uses motor and crying responses to pain and includes the ability to watch. It can be used to assess young children with cerebral malaria.

Like the GCS, the components are of the BCS are eye movement score, best verbal response, and best motor response. For each area of assessment, determine patient response and add for total score. This provides an objective measurement of mental status and provides prognostic information.

Table 3.The Blantyre Coma Score (BCS)

Eye Movement Score (E) – highest possible score: 1	
0	Fails to watch or follow
1	Watches or follows (e.g., mother's face)
Best Verbal Response (V) – highest possible score: 2	
0	No vocal response to painful stimulus
1	Moan or abnormal cry with painful stimulus
2	Cries appropriately with painful stimulus, or, if verbal, speaks
Best Motor Response (M) – highest possible score: 2	
0	No response or inappropriate response
1	Withdraws limb from painful stimulus (pressure with horizontal pencil on nail bed of finger or toe)
2	Localises painful stimulus (pressure with blunt end of pencil on sternum or supraorbital ridge)

Table 4.Interpretation of the Blantrye Coma Score (BCS)

BCS Score	Interpretation
5	Maximum score; good
1-4	Abnormal
0	Minimum score; poor

NOTE: refer to ICU when the score is less than 3

ANNEX E: MALARIA AND HIV

Prompt diagnosis and effective antimalarial treatment should be provided for all uncomplicated malaria cases, especially in HIV-infected patients, given their increased risk of anaemia, severe malaria and malaria related mortality

A large number of HIV patients either live in areas where malaria transmission occurs, or travel to these areas. The burden of HIV-malaria co-infection is highest in Southern Africa, since this is where HIV prevalence is high, particularly in rural areas and where the malaria burden is mostly in adults due to the unstable malaria transmission precluding their acquiring immunity. Substantial interaction between malaria and HIV/ AIDS occurs at many levels:

- Overlap of symptoms of the two diseases, especially fever, may result in HIV-positive patients with malaria presenting late to health facilities and the diagnosis of malaria being missed:
- Although acute malaria causes a temporary increase in replication of HIV and hence in plasma viral load, there is no evidence that malaria has a substantial effect on the clinical progression of HIV infection, HIV transmission or response to antiretroviral treatment;

[9] Molyneux, 1989.

- HIV infected individuals who live in areas of stable malaria transmission and are thus expected to be malaria semi-immune, are at increased risk of symptomatic parasitaemia and/or may exhibit higher levels of peripheral parasitaemia than semi immune adults who are HIV – negative

Management of HIV-Infected Patients with Uncomplicated Malaria

It is unclear how HIV infection modifies the therapeutic response to antimalarials. Increased P. falciparum parasite burden and reduced host immunity, both of which occur with HIV infection, may be associated with an increased risk of anaemia delayed parasite clearance and increased failure rates,

- Patients with HIV infections who develop malaria should receive the recommended antimalarial regimens, although more closely monitored, to ensure an adequate response.
- There are limited data regarding interactions of antimalarials with antiretroviral drugs. Pharmacological interactions between certain antiretrovirals (ARVs) and antimalarial drugs are theoretically possible and might lead to toxicity or sub-therapeutic drug levels.
  - Patients receiving protease inhibitors and the NNRTI delavirdine should avoid halofantrine;
  - HIV-infected children receiving artesunate plus amodiaquine are at increased risk of neutropenia, particularly if taking zidovudine;
  - Hepatotoxicity developed in healthy volunteers given artesunate plus amodiaquine and efavirenz

Management of HIV-Infected Patients with Severe and Complicated Malaria

HIV-infected patients who are malaria non-immune are at higher risk of dying from malaria. Patients co-infected with HIV/AIDS and malaria should be admitted for treatment and close monitoring.

- As HIV progresses and immuno-suppression worsens, the risk of severe malaria increase
- The incidence of severe malaria increased 1.7 – 2.7 folds in adults and up to 9.6 fold in children, and case fatality rates in hospitalized severe malaria cases increased by up to 8.8 – fold in patients co-infected with HIV.
- Renal failure has been identified as a particular complication in this group of patients
- Secondary bacterial infection is common and empiric antibiotic treatment should be considered, e.g. a third generation cephalosporin.
- Electrolyte disturbances are common and close monitoring is essential