

NATIONAL GUIDELINES FOR THE TREATMENT OF MALARIA, SOUTH AFRICA 2019



health

Department:
Health
REPUBLIC OF SOUTH AFRICA

GUIDELINES FOR THE TREATMENT OF MALARIA IN SOUTH AFRICA

September 2019 UPDATE

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PREFACE

South Africa has played a leading role in the control of malaria for almost a century and has dramatically reduced its burden of malaria since 2000. This has paved the way for our commitment to eliminate malaria. However, climatic conditions favourable for malaria transmission, budget constraints and a high burden of malaria in some of our neighbouring countries make it essential that malaria control is maintained while moving the elimination agenda forward.

However, this success brings its own challenges, including the fact that a significant number of malaria cases in South Africa are now imported (i.e. not locally transmitted). Late presentation especially to health facilities in malaria-free areas is problematic. Thus, health professionals throughout South Africa, in both the malaria-endemic and malaria-free areas, all need to develop and maintain their knowledge and skills in malaria diagnosis and treatment.

These guidelines are based on the 3rd Edition of the WHO Guidelines (Published 2015) World Health Organization's Guidelines for the treatment of malaria. Additional literature surveys have been undertaken. Factors that were considered in the choice of therapeutic options included effectiveness, safety, and impact on malaria transmission and on the emergence and spread of antimalarial drug resistance. On-going surveillance is critical given the spread of artemisinin resistance in Southeast Asia, although not yet confirmed anywhere in Africa. The guidelines on the treatment of malaria in South Africa aim to facilitate effective, appropriate and timeous treatment of malaria, thereby reducing the burden of this disease in our communities. This is essential to further reduce the malaria case fatality rates currently recorded in South Africa, to decrease malaria transmission and to limit resistance to antimalarial drugs.

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- Prof. Lucille Blumberg (SAMEC Chairperson), Prof. John Frean, Dr Natalie Mayet, Dr Jaishree Raman (National Institute for Communicable Diseases of the National Health Laboratory Service)
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MP MATSOSO

DIRECTOR-GENERAL: DEPARTMENT OF HEALTH

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ABBREVIATIONS

ACT	Artemisinin-based combination therapy
ARDS	Acute respiratory distress syndrome
CDC	Communicable Disease Control
CHC	Community Health Centre
CNS	Central nervous system
CVP	Central venous pressure
DIC	Disseminated intravascular coagulation
ECG	Electrocardiogram
GCS	Glasgow Coma Scale
G-6-PD	Glucose-6-phosphate dehydrogenase
MCC	Medicines Control Council
MVBD	Malaria and other vector-borne diseases
NSAIDS	Non-steroidal anti-inflammatory drugs
PHC	Primary healthcare
RDT	Rapid diagnostic tests
SP	Sulfadoxine-pyrimethamine
SAMEC	South African Malaria Elimination Committee
WHO	World Health Organization

DISCLAIMER

This material is intended for use by healthcare professionals. It has been compiled from information currently available and although the greatest care has been taken, the Department of Health and its South African Malaria Elimination Committee (SAMEC) do not accept responsibility for errors or omissions. Readers are directed to the reference articles for further information and should exercise their own professional judgment in confirming and interpreting the findings presented in the publication. These guidelines were issued in 2019 by the National Department of Health and replace all previous guidelines.

SUMMARY

Plasmodium falciparum (*P. falciparum*) accounts for the majority of malaria cases in southern Africa and may be associated with severe and fatal disease. Almost all South Africans, including residents of seasonal malaria transmission areas in the country, are non-immune and are therefore at increased risk of developing severe malaria.

Approach to management

The diagnosis and management of malaria, especially falciparum malaria, is urgent. As signs and symptoms of malaria are very non-specific, a **high index of suspicion** is the most important element in the diagnosis of malaria. Malaria should be suspected in any person presenting with any of the symptoms listed below, who has a history of travel to, or residence in, a malaria transmission area. Delayed diagnosis, underassessment of disease severity and inappropriate treatment are associated with significantly increased morbidity and mortality. Classically, malaria presents with fever, rigors, headache and body pains, but the clinical features are non-specific and may be confused with many other diseases, especially influenza. A definitive diagnosis should be made promptly by demonstrating the parasite on microscopy of a blood smear or by using a malaria rapid diagnostic test. Disease severity should be assessed carefully with both clinical and laboratory tests. Malaria is a notifiable disease.

Confirm diagnosis and assess severity

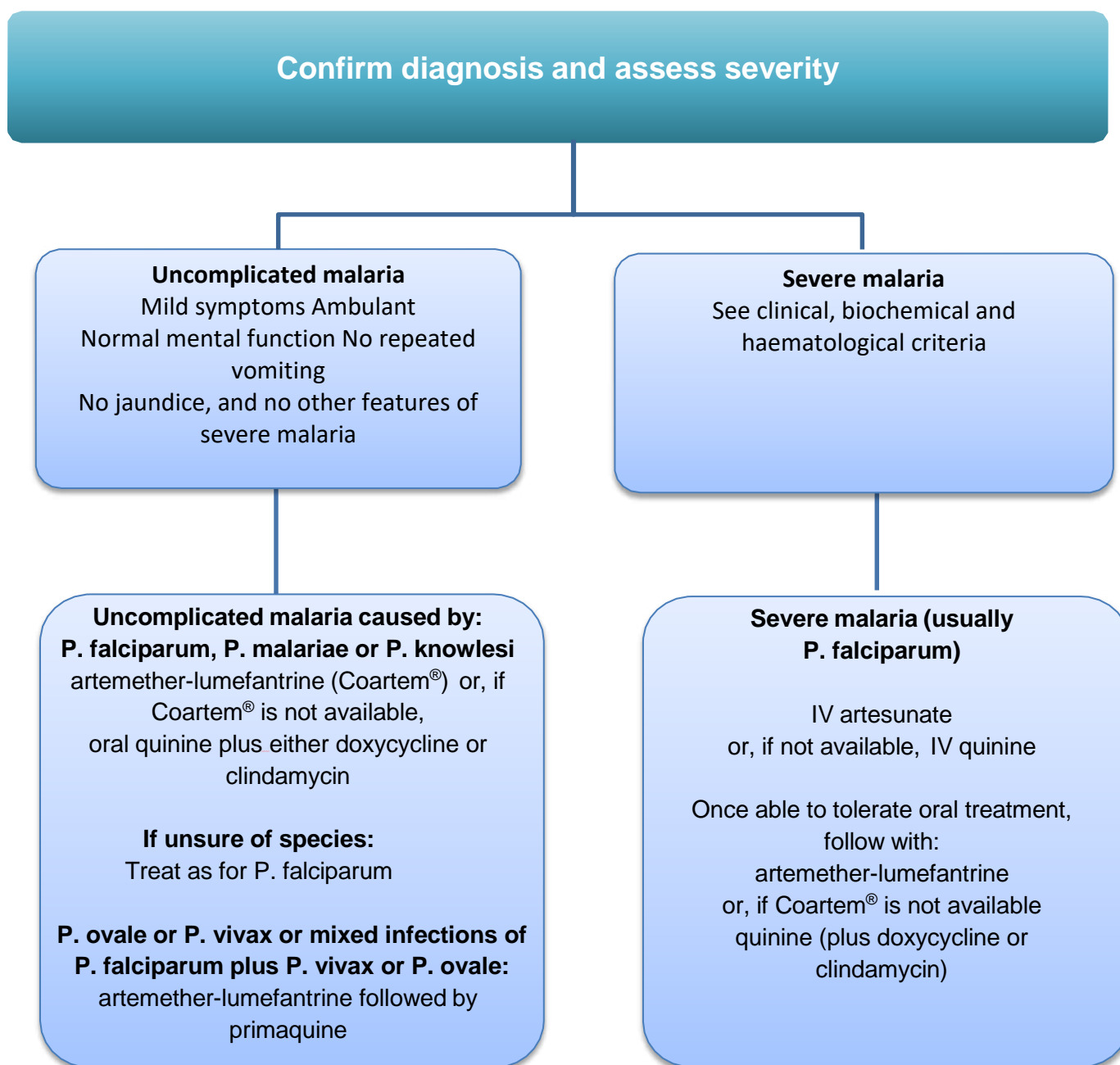


Figure 1. Algorithm for the management of malaria in South Africa

Uncomplicated malaria

For uncomplicated malaria, artemether-lumefantrine (Coartem®) is recommended for first-line therapy. Oral quinine plus either doxycycline or clindamycin should only be used if artemether-lumefantrine is unavailable or contraindicated. High-level resistance precludes the use of both chloroquine and sulfadoxine-pyrimethamine for the treatment of falciparum malaria. Given its associated safety concerns, halofantrine should not be used.

Key patient information for outpatient treatment should include the following:

- take all doses as directed, even if feeling better sooner. Artemether-lumefantrine should be taken with a fat-containing meal or drink
- it is important that the patient drinks enough fluids, and takes paracetamol (not anti-inflammatories) to treat their fever
- the patient should expect improvement of symptoms within 24 to 48 hours and to return to the health facility if they remain unwell or their temperature is not settling by day three
- the patient should return to the health facility immediately if vomiting, or if the patient deteriorates in any way (e.g. becomes sleepy, confused, jaundiced)

Referral criteria

As disease progression can occur rapidly in non-immune patients, careful monitoring during at least the initial 24 hours of treatment is essential.

Definite indications for hospital admission include:

- any feature of severe malaria
- danger signs
- high risk groups
- suspected treatment failure (including reappearance of parasites within six weeks of treatment)

Danger signs include:

- unable to drink or breastfeed
- repeated vomiting
- recent history of convulsions
- lethargy
- unable to sit or stand

High risk groups include:

- pregnant and postpartum women
- infants and young children
- elderly persons (older than 65 years)
- splenectomised persons
- immunocompromised persons (including HIV-infected)
- persons with comorbid conditions

Severe malaria

Severe malaria is a medical emergency. Unless falciparum malaria is promptly diagnosed and treated, the clinical picture may deteriorate rapidly. Severe malaria carries a 10 to 40 per cent case fatality rate, often in spite of treatment. Patients should be treated promptly with intravenous (or intramuscular) artesunate or quinine (if artesunate not available) in the highest level of care available. For severe malaria, intravenous artesunate (or if contraindicated or unavailable, intravenous quinine) for at least 24 hours, is recommended and should be followed by a full treatment course of artemether-lumefantrine as soon as the patient can tolerate oral treatment. Patients with severe malaria all require hospital admission. The major complications of malaria include cerebral malaria, hypoglycaemia, anaemia, renal failure, acute respiratory distress syndrome (ARDS) and metabolic acidosis. These complications carry high mortality rates especially in children, pregnant woman and in those living with HIV and AIDS. These complications require specific management and close monitoring.

Clinical features of severe malaria:

- impaired consciousness
- prostration, i.e. unable to sit, stand or walk without assistance
- multiple convulsions: more than two episodes in 24 hours
- acidotic breathing and respiratory distress
- acute pulmonary oedema and acute respiratory distress syndrome
- circulatory collapse or shock
- anuria
- jaundice
- abnormal bleeding

Laboratory and other findings in severe malaria:

- hypoglycaemia ($<2.2\text{mmol/l}$ or $<40\text{mg/dl}$)
- metabolic acidosis (plasma bicarbonate $<15\text{mmol/l}$)
- severe normocytic anaemia ($<7\text{g/dl}$)
- hyperparasitaemia
- haemoglobinuria
- hyperlactataemia (lactate $>5\text{mmol/l}$);
- renal impairment (serum creatinine $>265\mu\text{mol/l}$)
- pulmonary oedema (radiological)

1. INTRODUCTION

Since 2000, the burden of malaria morbidity and mortality has been reduced substantially. Implementing more effective treatments for uncomplicated malaria (artemether- lumefantrine) and severe malaria (intravenous artesunate), as well as strengthening of mosquito vector control and malaria information systems, were among the measures that contributed to improved malaria control. These advances paved the way toward the South African Department of Health refocusing its efforts to work towards malaria elimination.

Achieving the ambitious target of malaria elimination depends on all healthcare workers in malaria endemic and non-endemic areas optimising their management of malaria cases, including 1) encouraging early treatment seeking within 24 to 48 hours; 2) maintaining a high index of suspicion to ensure prompt diagnostic testing of all patients with malaria symptoms who are resident in, or have recently travelled to, a malaria area;

3) in those who test malaria positive, assessing disease severity and starting effective treatment immediately depending on disease severity; 4) notifying each and every case (including all imported cases in non-endemic areas) and 5) monitoring adequacy of response to treatment.

For severe malaria, survival rates are significantly greater following parenteral artesunate than parenteral quinine treatment in both adults and children, so artesunate is the preferred treatment whenever available promptly. Follow-up treatment with primaquine (a section 21 product) is essential to ensure radical cure of *P. ovale* and *P. vivax* malaria.

These guidelines have been compiled using both international and local information. The relentless development of drug resistance in malaria parasites, most notably in *P. falciparum*, has necessitated on-going updates of treatment and chemoprophylaxis policies globally. While recommended treatments are currently considered highly effective in South Africa, the rapid spread of resistance to all available antimalarials in South East Asia is a major concern. New information arising from on-going monitoring of malaria prevalence and distribution, as well as resistance to antimalarial drugs, will inform future guidelines.

2. MALARIA TREATMENT OBJECTIVES

The main objectives of malaria treatment are to:

- prevent mortality
- prevent disease progression and development of severe malaria
- reduce morbidity
- eliminate parasitaemia and stop further transmission
- limit the emergence and spread of drug resistance

3. PARASITE SPECIES

More than 90 per cent of human malaria infections in sub-Saharan Africa are due to *P. falciparum* while the remainders are due to *P. ovale*, *P. vivax*, or *P. malariae*. Occasionally mixed infections occur. Human infection with the monkey malaria parasite, *P. knowlesi*, has been reported from forested regions of Southeast Asia but not yet in sub-Saharan Africa. Malaria species are usually differentiated by microscopy. Young ring forms of all species look similar, but older stages and gametocytes have species specific characteristics. However, *P. knowlesi* is frequently misdiagnosed as *P. malariae*.

4. RISK GROUPS

Pregnant (and post-partum) women, young children, the elderly, splenectomised and immunocompromised persons (including HIV-infected persons) are the groups at highest risk for the development of severe *P. falciparum* malaria.

Non-immune individuals are particularly vulnerable. South Africans, including residents in areas where malaria transmission occurs, are non-immune.¹

¹Partial immunity may be acquired after long-term, repeated exposure to *P. falciparum* infection, as seen in residents of perennial high transmission areas in sub-Saharan Africa, such as parts of Mozambique, Malawi, Tanzania, the Democratic Republic of Congo, and Uganda.

5. CLINICAL PRESENTATION AND DIAGNOSIS

As signs and symptoms of malaria are very non-specific, a **high index of suspicion** is the most important element in the diagnosis of malaria. Malaria should be suspected in any person presenting with an acute febrile illness and any of the symptoms listed below, who has a history of travel to, or residence in, a malaria transmission area.

5.1. Malaria transmission

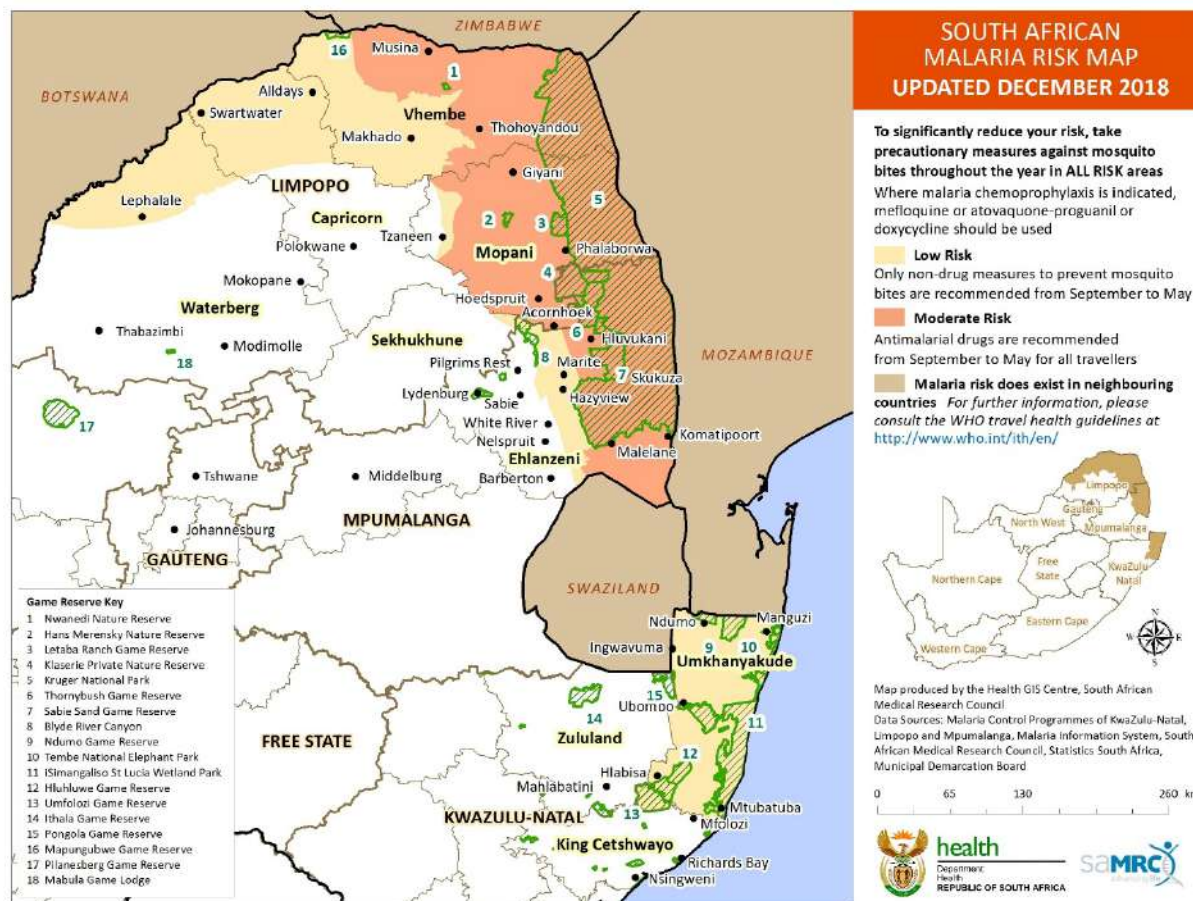


Figure 2. Distribution of malaria risk areas in South Africa - 2019

Malaria transmission areas in South Africa include north-eastern KwaZulu-Natal and low altitude areas of Mpumalanga and Limpopo, particularly those bordering Zimbabwe, Mozambique and Swaziland (Figure 2). Very rarely, malaria is contracted in the North West and Northern Cape, adjacent to the Molopo and Orange rivers, respectively. In South Africa malaria transmission occurs typically between the months of September and May.

Occasionally, infected mosquitoes are accidentally transported to non-endemic areas and transmit malaria, a form of the disease called Odyssean (taxi/suitcase/airport) malaria. Gauteng, because of its large and mobile population, is most frequently affected, but Odyssean malaria can occur anywhere. The diagnosis is often delayed or missed, and there is a high rate of severe or fatal infection (case fatality rate 11 per cent during the 2014 to 2016 period). Needlestick and transfusion or transplant-related malaria may occur unexpectedly, with similar poor outcomes.

Malaria transmission occurs in almost all countries in sub-Saharan Africa with the exception of Lesotho. Malaria transmission also occurs in parts of Central and Southeast Asia, Yemen, the Middle East, and in the Caribbean and Central and South America. Within each country, geographical distribution, transmission intensity and species of malaria vary and up-to-date information on global malaria risk is summarised by the World Health Organization (See <http://www.who.int/ith/2015-ith-county-list.pdf?ua=1>).

5.2. Symptoms and signs

Common malaria symptoms and signs include:

- fever, chills, perspiration, rigors (cold shivers/hot sweats)
- headache
- muscle/joint aches
- malaise
- lethargy, lassitude, fatigue
- loss of appetite (in older children and adults), poor feeding (in young children)
- abdominal discomfort, diarrhoea, nausea, vomiting
- cough (in young children)
- splenomegaly (in patients from areas of high intensity malaria transmission)

ONSET: Symptoms and signs of falciparum malaria may present as early as seven days after exposure, with a usual range of 10 to 21 days elapsing after being bitten by an infected vector mosquito. Longer incubation periods may occur in patients who have failed chemoprophylaxis (usually due to poor adherence or inappropriate chemoprophylaxis) or have been on selected antibiotics (e.g. cotrimoxazole, tetracycline, macrolides, chloramphenicol and quinolones). Very rarely, incubation periods for *P. falciparum* of six to 18 months have been recorded. Malaria due to infections with *P. vivax*, *P. ovale* or *P. malariae* can take up to 12 months to first manifest clinically, with relapses occurring months or even years later, if primaquine is not taken to ensure radical cure.

DIFFERENTIAL DIAGNOSIS: Presentation of falciparum malaria is very variable and may mimic many other diseases (and *vice versa*) including influenza, viral hepatitis, meningitis, encephalitis, septicaemia, typhoid fever, tick bite fever, gastroenteritis, viral haemorrhagic fever, trypanosomiasis, HIV seroconversion illness, urinary tract infection and relapsing fever.

DISEASE PROGRESSION: Non-immune patients with uncomplicated malaria are at significant risk of disease progression to severe falciparum malaria. Life-threatening complications can develop rapidly in these patients. These complications occur almost invariably as a result of delay in diagnosis and/or delay in treatment of an uncomplicated infection, the use of ineffective therapy or under-dosing with effective drugs.

5.3. Laboratory diagnosis

A diagnosis of malaria cannot be confirmed or excluded clinically. Since the clinical presentation is non-specific and may mimic many other diseases, each patient's blood should be examined immediately using a malaria antigen rapid diagnostic test (RDT) or microscopy of thick and thin blood smears to confirm or exclude the diagnosis. However, in some cases, a negative smear or RDT may not exclude the diagnosis. If the initial RDT or blood film examination is negative in patients with symptoms compatible with malaria and no other cause can be determined, a series of RDT or blood films should be examined at 6-12 hour intervals. Repeat tests should continue until the diagnosis is confirmed, the patient has recovered, or another definitive diagnosis has been made. A blood test for parasites should be done irrespective of the time of the year or whether or not the patient has taken chemoprophylaxis or travelled to a malaria endemic area.

In the majority of malaria cases, examination of correctly stained blood smears will reveal malaria parasites. Examination of the peripheral blood smear will give an indication of the parasite density as well as the species of parasite. **High levels of parasitaemia (more than four per cent or equal to or more than three + or more than 100 000 asexual parasitized red blood cells/ μ l)² should be treated as severe malaria.** Importantly, the converse may not be true, with severe disease sometimes occurring with low parasitaemias in the peripheral blood. The interpretation of a low parasite count must always be considered in conjunction with the patient's clinical condition and other laboratory results (See Section 5.2 and Section 7).

A number of commercial rapid diagnostic tests (RDTs) are available for early diagnosis in health facilities where microscopy is not immediately available. These RDT kits detect parasite antigens, namely, histidine-rich protein 2 (or parasite lactate dehydrogenase or aldolase). Most RDTs will only detect *P. falciparum*, although some can detect the other malaria species but are less sensitive for these. The *P. falciparum*-specific RDTs are generally highly sensitive; however, performance is dependent on the correct storage, usage, interpretation of results and quality of RDT used. The test may be negative early in the disease, and false positives may be encountered occasionally. RDTs should be used only for diagnosis of acute malaria infections, and not for follow-up, as they may remain positive for several weeks, even after successful treatment.

²The parasite density refers to the parasite load in the peripheral blood expressed semi-quantitatively (1 to 4+) or as the percentage of red blood cells (RBCs) infected or quantitatively as the number of asexual parasite infected RBCs per microlitre. Quantification is often inaccurate and does not necessarily reflect the total parasite load in the patient.

Additional diagnostic methods are offered by reference and some private laboratories. Polymerase chain reaction (PCR) is highly sensitive and specific but is not practical for routine diagnosis. It is useful to resolve difficult species identification, scanty mixed- species infections, and to detect very low-level infections, e.g. when treatment has already been given. The quantitative buffy coat (QBC) method is used in some private laboratories. It is theoretically more sensitive than blood film examination, but is technically demanding and not appropriate for general use. See Annexure 3 for more information about additional laboratory tests for malaria diagnosis.

If the diagnosis of malaria cannot be confirmed (unavailability of RDTs and microscopy or negative test results), the decision to commence malaria therapy should be made on clinical grounds, based on whether exposure to malaria parasites was possible and the severity of the clinical features. In cases of severe malaria, a blood smear or rapid malaria test is likely to be positive. However, occasionally patients with severe malaria may have a negative smear due to sequestration of parasitised red blood cells. In patients who are treated empirically for malaria, it is imperative to collect a blood specimen before treatment and to continue to look for alternative diagnoses and to follow up patients very carefully. A malaria smear is indicated in patients with malaria symptoms and a negative RDT, to exclude non-falciparum malaria.

For both RDTs and microscopy, on-going training and supervision, as well as quality assurance programmes, are needed to ensure reliable malaria diagnosis and inform case management, as well as targeting of malaria control and elimination interventions. All malaria diagnostic laboratories should belong to an external quality assessment (proficiency testing) scheme. Laboratories should ideally participate in slide re-checking arrangements. Quality system recommendations for South Africa are available (see National Department of Health website: www.health.gov.za).

5.4. Referral criteria

Danger signs include:

- unable to drink or breast feed
- repeated vomiting
- recent history of convulsions
- lethargy
- unable to sit or stand

High risk groups include:

- pregnant and postpartum women
- infants and young children
- elderly persons (older than 65 years)
- splenectomised persons
- immune compromised persons (including HIV-infected)

As disease progression can occur rapidly in non-immune patients, careful monitoring during at least the initial 24 hours of treatment is essential.

Definite indications for hospital admission include:

- any feature of severe malaria (See Section 7)
- danger signs
- high risk population groups
- suspected treatment failure (including reappearance of parasites within six weeks of treatment)

5.5. Malaria notification

MALARIA IS A CATEGORY 1 NOTIFIABLE DISEASE

The RAPID notification of all malaria cases in South Africa is mandatory. Due to the high malaria burden in especially the malaria endemic provinces but also in the non-endemic areas, it is critical that each malaria case is reported to facilitate public health interventions to stop malaria transmission and implement vector control methods. Prompt notification of malaria cases to the local health authorities provides essential information needed for the Malaria Control Programmes to target their interventions efficiently and effectively. This is even more critical now that South Africa is working towards the ambitious target of malaria elimination. Wherever possible, mobile technology, such as Malaria Connect and the NMC APP, should be used to ensure notification within 24 hours to enable prompt response and follow-up by the Malaria Control Programme.

The procedure for notifiable medical conditions is as follows:

Malaria is a category 1 notifiable medical condition thus must be reported/notified within 24 hours of diagnosis. Comprehensive details of the new notification procedures are detailed in the **Standard Operating Procedures for Paper based reporting of Notifiable Medical Conditions (NMC)** – version 2.0 and on the inside front cover page of the NMC Case Notification Booklet – version 2.0 June 2018; both documents are available at each Health Establishment and are also obtainable by emailing NMCsurveillanceReport@nicd.ac.za or via the NICD website www.nicd.ac.za

Every doctor or nurse (health care provider) who diagnoses a patient with malaria must immediately submit an electronic or written notification to the NMC national surveillance system as well as to the local authority by following the process below;

Paper-based notification

- Complete the NMC Case Notification Form - version 2.0 January 2018 **(the GW17/5 form is no longer in use).**
- The NMC Case Notification Form must be completed as soon as possible and preferably whilst the patient is still with the healthcare provider to ensure that all required details are completed. Notification information is crucial for case and contact tracing and management to ensure disease containment.
- The NMC Case Notification Form must be completed as detailed in the NMC Case Notification Form Completion Guide summarised on the back cover page of the NMC case notification booklet.
- Once the NMC case notification form has been completed, send the form to

NMCsurveillanceReport@nicd.ac.za or fax to [086 639 1638](tel:0866391638) or NMC hotline [072 621 3805](tel:0726213805). **A copy/photograph of the form can be sent via sms or whatsapp to [072 621 3805](tel:0726213805).**

- Send the top copy of the completed NMC case notification form to the NMC surveillance team (details above) and to the malaria focal person at Sub-District/District
- Details of the Health Establishment NMC focal person and the District NMC focal person are given on the cover page of the NMC case notification booklet.
- The middle copy of the form (blue) must be attached to the patient referral letter if the patient is being referred. If not, then it must be kept in the patient file.
- The bottom copy of the form (pink) must remain in the NMC Case Notification Booklet. Once the NMC Case Notification Booklet is complete, send the pink forms to the NICD for archiving.

The notifying Health Establishment will receive feedback pertaining to the reported case within 3 days of a paper based notification

Electronic notification via the NMC web or mobile APP (from April 2018)

- Download the NMC APP at <https://mstrmobile.nicd.ac.za/nmc/> or your mobile APP Play Store or via the NICD website.
- Open the new case tab which contains the NMC case notification form and complete the required details.
- Upon completion click save to save the captured details

The notification will automatically be sent to all relevant focal people at Health Establishment, Sub-District, District, Province & National levels.

The notifying health care provider will receive immediate feedback pertaining to receipt of the reported case.

Comprehensive details on how to capture and send the notification are provided in the NMC APP user manual; also available on the NICD website.

6. MANAGEMENT OF UNCOMPLICATED MALARIA

Patients should receive prompt treatment with artemether-lumefantrine (oral quinine only if artemether-lumefantrine is contraindicated or unavailable)

The majority of patients with uncomplicated malaria can be treated at primary healthcare level. Since delays in the initiation of treatment increase morbidity and mortality, effective treatment should be started as soon as malaria is diagnosed at clinic or hospital level. All patients should be observed for vomiting at the health facility for one hour after the initial dose, and a repeat dose given if needed.

The choice of chemotherapy for malaria is based on:

- the species of parasite (although initial treatment should be the same, a 14 day primaquine course is needed for radical cure of *P. ovale* and *P. vivax*)
- patient characteristics (age, pregnancy, co-morbidity, allergies, concomitant medications)
- the presence or absence of vomiting (repeated vomiting indicates the need for parenteral treatment)

6.1 Uncomplicated *P. falciparum* malaria

It is critical to differentiate between uncomplicated and severe/high-risk malaria). Patients with uncomplicated malaria include those who have mild symptoms, are ambulant and have no evidence of organ dysfunction either clinically or on laboratory tests and in whom the parasite count is less than four per cent or 3+ (see Section 7: Severe malaria, for details). Uncomplicated malaria may rapidly progress to severe malaria if the patient is not treated promptly with an effective antimalarial.

6.1.1. Chemotherapy

6.1.1.1. Artemether-lumefantrine

The recommended treatment for patients with uncomplicated malaria is the fixed dose artemisinin-based combination therapy (ACT), artemether-lumefantrine (Coartem®). Artemether-lumefantrine should also be used to treat uncomplicated malaria in pregnant women in the second and third trimester, and may be considered as an alternative to quinine plus clindamycin during the first trimester of pregnancy (See Section 8.1.2).

The WHO recommends artemisinin-based combination therapies (ACTs) as the best current treatment for uncomplicated falciparum malaria, as ACTs are associated with rapid clinical and parasitological response, improved cure rates, decreased malaria transmission and have the potential to delay antimalarial drug resistance. Artemether-lumefantrine has the advantages of a short treatment course (six doses over three days) and good tolerability. However, artemether-lumefantrine is only indicated for the treatment of uncomplicated malaria as there is no evidence of its efficacy in more severe disease, for which parenteral artesunate (or parenteral quinine) is required.

Table 1. Dosage of artemether-lumefantrine

ARTEMETHER-LUMEFANTRINE (oral) One tablet contains artemether 20 mg plus lumefantrine 120 mg.	5 -<15 kg#: One tablet stat, followed by one tablet after eight hours and then one twice daily on each of the following two days (total course = six tablets) 15-<25 kg: Two tablets stat, followed by two tablets after eight hours and then two twice daily on each of the following two days (total course = 12 tablets) 25-<35 kg: Three tablets stat, followed by three tablets after eight hours and then three twice daily on each of the following two days (total course = 18 tablets) 35-<65 kg: Four tablets stat, followed by four tablets after eight hours and then four twice daily on each of the following two days (total course = 24 tablets). >65 kg*: Dose as for those above 35 kg, although inadequate experience in this weight group justifies closer monitoring of treatment response. <i>NOTE: Administer with food/milk containing at least 1.2 g fat (e.g. ~100ml milk) to ensure adequate absorption.</i>
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WHO states that it can be used for children weighing less than 5 kg. (See 8.2.1) A flavoured dispersible tablet has been formulated for use in young children, but is not yet registered for use in South Africa.

* An adult tablet containing 80mg artemether and 480 mg lumefantrine has been formulated that allows adults to be dosed with one tablet stat, followed by one tablet after eight hours and then one tablet twice daily on each of the following two days (total course = six tablets). This formulation is not yet registered for use in South Africa.

- The recommended artemether-lumefantrine (Coartem®) dosage regimen is six doses administered over a three-day period. The number of tablets per dose should be according to body weight as listed in **Table 1**.
- Adequate absorption of the lumefantrine component is critically dependent on co- administration with food or drink containing at least 1.2 g fat (e.g. ~ 100 ml full cream milk). It is essential that patients or caregivers are informed of the need to take this ACT with or immediately after a meal or milk – particularly on the second and third days of treatment.
- No adequate experience has been acquired in the use of artemether-lumefantrine in patients weighing more than 65 kg, although the WHO and other agencies recommend its use in these patients. However, patients weighing more than 85 kg may be at an increased risk of treatment failure (see below).
- Artemether-lumefantrine is well tolerated. Adverse effects identified include sleep disturbances, headaches, dizziness, palpitations, abdominal pain, anorexia, cough, arthralgia, myalgia, asthma and fatigue. Rarely, hypersensitivity reactions have been reported.
- Although there is no evidence of iatrogenic cardiotoxicity in these groups, the manufacturer advises against administration to patients with clinical conditions resulting in QTc prolongation, a family history of congenital prolonged QT syndrome or sudden death or those with other risk factors for cardiac conductivity, such as hypokalaemia or hypomagnesaemia.
- Although the magnitude of potential drug interactions is likely to be small relative to the far greater effect of co-administration with fat, a number of drug interactions have been reported:
 - artemether and or dihydroartemisinin concentrations may be increased by ketoconazole, but decreased by lopinavir+ritonavir, darunavir+ritonavir, nevirapine, efavirenz, etravirine and rifampicin
 - lumefantrine concentrations may be increased by lopinavir+ritonavir, darunavir+ritonavir, ketoconazole and possibly nevirapine, but decreased by rifampicin, efavirenz, mefloquine and etravirine
 - the manufacturer recommends avoiding concomitant administration with other medications that prolong the QT interval, such as class IA (quinidine, procainamide, disopyramide); or class III (amiodarone, sotalol) antiarrhythmic agents; antipsychotics (pimozide, ziprasidone); antidepressants; certain antibiotics (macrolide antibiotics, fluoroquinolone antibiotics, imidazole, and triazole antifungal agents); certain non-sedating antihistamines (terfenadine, astemizole); cisapride; or medications that are metabolised by the cytochrome enzyme CYP2D6 that also have cardiac effects (e.g., flecainide, imipramine, amitriptyline, clomipramine)
- Very young children (under three years), particularly if underweight for age, may be at increased risk of treatment failure, probably due to lower drug concentrations; therefore, their responses to treatment must be monitored more carefully.

For those at increased risk of treatment failure, ensuring full adherence (and co- administration with fat) and monitoring their response to treatment is particularly important. Ideally they should be seen at least daily until their treatment has been completed and then ideally on day 14 and 28 to monitor for late treatment failures. Alternative artemether-lumefantrine dosage regimens for these vulnerable groups are currently under evaluation.

For patients weighing more than 85 kg, we advise extending the treatment course to FIVE days, administering FOUR tablets per dose, given twice daily for a total of 10 doses (off-label recommendation).

6.1.1.2. Quinine

Table 2. Doses of quinine (plus either doxycycline or clindamycin)

QUININE (oral) One tablet usually contains 300 mg quinine sulphate	10 mg salt/kg body weight every eight hours for seven days. In the past, maximum doses have been recommended, but there is no evidence or justification for this practice. For obese patients, less of the drug is often distributed to fat than other tissues; therefore they should be dosed on an estimate of lean body weight or ideal body weight. Patients who are heavy but not obese require the same mg/kg doses as lighter patients. As data is limited on the relationship between dose, drug exposure and treatment outcome in large and obese patients, treatment providers should follow up their treatment response more closely whenever possible.
DOXYCYCLINE (oral) One capsule / tablet contains 50 or 100 mg doxycycline	Use in combination with quinine: 100 mg (or 2.2 mg/kg in children) twice daily for at least seven days. NOTE: Avoid in pregnancy and children under eight years old.
CLINDAMYCIN (oral) One tablet contains 150 mg clindamycin	Use in combination with quinine in pregnancy and children under eight years: 10 mg/kg twice daily for seven days

When artemether-lumefantrine is not available or is contraindicated (e.g. a history of allergy to artemisinin or lumefantrine), uncomplicated malaria can be treated with oral quinine plus either doxycycline or clindamycin (**Table 2**). In infants weighing less than five kilograms, the preferred treatment is quinine plus clindamycin, as artemether-lumefantrine use in this weight band is off-label; however, the WHO recommends that it can be used in infants weighing less than five kilograms with uncomplicated malaria.

Provided the full seven-day treatment course is completed, quinine is a rapidly-acting, effective antimalarial drug for both uncomplicated (oral quinine) and severe malaria (IV quinine) acquired in sub-Saharan Africa. Quinine resistance is rare in this area, although increasing slowly in Southeast Asia.

- Quinine therapy should be continued for seven to ten days.
- Quinine should ideally be used as directly observed treatment of inpatients, due to the poor tolerability and thus poor adherence with this seven-day regimen. Shortened courses of quinine (three days) cannot be recommended for treatment, given their poor efficacy. If discharge prior to treatment completion is unavoidable, it is most important that patients (or caregivers) understand that it is essential to complete the course of seven to ten days of quinine (with doxycycline or clindamycin).
- Oral quinine therapy is recommended in uncomplicated malaria but the initial doses of quinine should be administered intravenously if the patient is vomiting repeatedly.
- The addition of a second, effective, antimalarial drug, i.e. doxycycline or clindamycin (**Table 2**), is indicated to ensure complete parasite clearance and improve cure rates. One of these agents should be added as soon as can be tolerated (usually two to three days after commencement of the quinine), to ensure that possible adverse effects from the quinine are not confused with those of the second agent. In patients' under eight years old or during pregnancy, clindamycin should be used rather than doxycycline.
- Minor adverse effects, causing a syndrome known as cinchonism (mild hearing impairment (notably high tone deafness), tinnitus, headache, nausea and slight visual disturbances) occur in up to 70 percent of patients with therapeutic quinine concentrations and are not an indication to discontinue therapy.
- Hypoglycaemia is the most frequent serious adverse reaction and it is particularly common in young children, pregnant women and elderly patients. Quinine toxicity presents with central nervous system (CNS) disturbances (primarily visual and auditory) and cardiovascular abnormalities (hypotension, heart block, ventricular arrhythmias) and can be confused with severe malaria.
- Cardiotoxicity is particularly related to rapid infusion of quinine, which should always be given by slow infusion over two to four hours.
- Hypersensitivity reactions to quinine have been reported, including urticarial rash, bronchospasm, flushing, fever, antibody-mediated thrombocytopenia, haemolytic anaemia and haemolytic-uraemic syndrome. Hepatic injury and psychosis occur very rarely.

6.1.2. General management

All first doses of drugs must be given under supervision and patients must be observed for at least an hour, as vomiting is common in patients with malaria. Treatment must be repeated if the patient vomits within the first hour. Vomiting is one of the commonest reasons for treatment failure

It is easy to underestimate the disease severity and complications may arise despite apparent appropriate chemotherapy. Patients with malaria should be carefully assessed and closely monitored. The clinical and parasitological response of patients to treatment should be monitored regularly; in particular, their mental state, respiratory rate, jaundice and urine output require careful attention. Adequate fluids should be given, and antipyretics (paracetamol) administered when needed. Ibuprofen has been used but there is less experience with this compound. Other non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin should be avoided as they may increase the risk of renal failure in patients with malaria.

6.1.3. Patient information for outpatient treatment

For patients who are treated as outpatients, they (and or their caregivers) should be well informed about the importance of full adherence and the urgency of returning to a health facility should their condition not improve as expected.

Key patient information for outpatient treatment should include the following:

- take all doses as directed, even if feeling better before treatment is completed. artemether-lumefantrine should be taken with a fat-containing meal or drink
- it is important that the patient drinks enough fluids and takes paracetamol (not anti-inflammatories) to treat fever
- to expect improvement of symptoms within 24-48 hours and to return to the health facility if they remain unwell or their temperature is not settling by day three
- to return to the health facility immediately if vomiting, or if the patient deteriorates in any way (e.g. becomes sleepy, confused, jaundiced)

Patients should show a clinical response to therapy within 24 - 48 hours. A repeat peripheral blood smear should be performed where possible after 72 hours of treatment. For patients treated for uncomplicated malaria with an artemisinin-based combination therapy, a positive malaria blood smear 72 hours after starting antimalarials may be a predictor of subsequent treatment failure and provides a simple screening measure for artemisinin resistance (or poor adherence). Artemisinin resistance is highly unlikely if the proportion of patients still parasitaemic on day three is less than three to five per cent, but further studies are indicated if this proportion is higher.

Malaria treatment failure may manifest as failure to respond clinically or the development of danger signs or severe malaria or persistence of parasitaemia for more than seven days or, most commonly but less frequently recognised, the reappearance of parasites on microscopy within six weeks. Rapid diagnostic tests must not be used for follow-up, as they may remain positive for several weeks, even after successful treatment. On a malaria peripheral blood smear, the presence of gametocytes, the stage of malaria parasite's life cycle responsible for malaria transmission, does not indicate treatment failure, as these may be present for several weeks after successful treatment.

Treatment failure may be due to:

- parasite resistance to the antimalarial drug used
- under-dosing
- vomiting of oral medication
- non-compliance with medication
- failure to take fatty food or milk with artemether-lumefantrine, leading to poor absorption of lumefantrine component
- re-infection (apparent treatment failure)
- relapse due to *P. ovale* or *P. vivax*, because of failure to take primaquine for radical cure of hypnozoites

Treatment failures after completing a full course of either the three-day artemether-lumefantrine or seven-day quinine (plus doxycycline or clindamycin) regimen are rare, as both these treatments have high cure rates. A patient who fails treatment and manifests features of severe malaria or danger signs should be treated with intravenous artesunate, or quinine if artesunate is not available. Patients who have failed first-line treatment with artemether-lumefantrine should then be given a seven to ten-day course of quinine with either doxycycline or clindamycin. Treatment failures following quinine treatment of uncomplicated malaria could be treated with a full course of artemether-lumefantrine, provided severe malaria complications are carefully excluded.

6.2. Treatments not recommended for *P. falciparum* malaria

- Monotherapies (single antimalarial agents used on their own) are not recommended for the treatment of falciparum malaria. Artemisinin derivatives should never be used as monotherapy as this could select for resistance and compromise the value of artemisinin-based combination therapies (ACTs).
- Neither chloroquine nor sulfadoxine-pyrimethamine are recommended, given high-level resistance in most parts of the world, including South Africa.
- Mefloquine is registered only for prophylaxis and not treatment, given the higher incidence of severe psychiatric adverse effects associated with treatment doses.
- Halofantrine should not be used, given the associated cardiotoxicity, variable bioavailability and drug interactions.
- Clindamycin and doxycycline are slow-acting antimalarials and should never be used as monotherapy, but are added to quinine treatment regimens to improve cure rates.
- Homeopathic preparations are not recommended, as there is no scientific evidence to demonstrate their efficacy in the treatment of malaria (and minimal safety data are available).

6.3. Reducing the transmissibility of treated *P. falciparum* infections in areas of low intensity transmission

South Africa is working towards malaria elimination. As a component of pre-elimination or elimination programmes the WHO recommends adding a single low primaquine dose of 0.25 mg/kg to full artemether-lumefantrine treatment to patients with *P. falciparum* malaria (except pregnant women, infants aged under six months and women breastfeeding infants aged under six months) to further reduce malaria transmission. Plans are underway to implement this in selected areas as part of the elimination strategy.

Table 3. Primaquine dose for reducing *P. falciparum* transmission in areas of low transmission intensity

Body weight (kg)	Single primaquine dose (mg base)
10 to <25 (kg)*	3.75 mg
25 to <50	7.5 mg
50 to 100	15 mg

* Dosing of young children weighing less than 10kg would require an alternative formulation or tablet strength <7.5mg

Gametocytes are the sexual stage of the falciparum malaria lifecycle responsible for malaria transmission between human hosts and mosquito vectors. Although artemether- lumefantrine reduces gametocyte carriage to some extent, primaquine is the only currently available antimalarial that is also effective against mature gametocytes. A WHO expert panel reviewed the safety of primaquine as a *P. falciparum* gametocytocide and concluded that a single primaquine dose of 0.25 mg/kg is unlikely to cause serious toxicity, even in people with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

6.4. Treatment of non-falciparum infections

The parasite species should be reliably confirmed microscopically. If unsure of the species, standard treatment for *P. falciparum* should be administered. The preferred treatment in non-falciparum infections is artemether-lumefantrine. For *P. vivax* or *P. ovale* a follow-on treatment course of primaquine is essential to eradicate the residual hepatic phase to prevent relapse (called radical cure). Primaquine is contraindicated in severe G-6-PD deficiency, pregnant women, and infants under six months of age.

At present *P. ovale*, *P. malariae* and *P. knowlesi* are generally chloroquine-sensitive, but cases of chloroquine-resistant *P. vivax* have been documented in Oceania, Brazil, and Indonesia. Patients with pure non-falciparum malaria infections should be treated with artemether-lumefantrine if acquired in areas with chloroquine resistance, or if chloroquine sensitivity in that area is unknown. Chloroquine treatment can only be considered for uncomplicated infections of pure non-falciparum species acquired in areas where chloroquine sensitivity has been confirmed recently.

In sub-Saharan Africa, a minority (less than ten per cent) of malaria infections are due to the non-falciparum species, namely *P. vivax*, *P. ovale*, or *P. malariae*. In South Africa, *P. ovale* is the most common non-falciparum malaria. Infections contracted in Asia, the Caribbean, Central America and the Middle East are most frequently due to *P. vivax*.

Generally, disease due to infection with the non-falciparum malarias is uncomplicated, although both *P. vivax* and *P. knowlesi* (and more rarely, *P. ovale*) can result in severe and sometimes fatal malaria (usually complicated by respiratory distress). Anemia may complicate chronic *P. ovale* infections, while *P. vivax* infection during pregnancy reduces the birth weight of the infant. Repeated *P. malariae* infections may be associated with the nephrotic syndrome in children. Severe malaria, regardless of species, should be treated with intravenous artesunate or quinine.

Table 4. Dosage of chloroquine and primaquine

CHLOROQUINE (oral) Confirmed non- falciparum malaria only one tablet contains 150 mg chloroquine base	Adults: 1.5 g over three days, as follows: Initially 600 mg, followed by 300 mg six to eight hours later, and 300 mg once daily on second and third days.	Children: Initial dose: 10 mg base/kg then 5 mg base/kg six to eight hours later, and 5 mg base/kg once daily on second and third days.
PRIMAQUINE (oral)* One tablet usually contains 26.3 mg primaquine phosphate = 15 mg primaquine base. *Not registered in South Africa; provision for Section 21 use.	Adults: 15 mg base daily for 14 days following standard treatment, or 0.25–0.5 mg base/kg daily for 14 days. In mild G-6-PD deficiency (10-60% residual G-6-PD activity): 45 mg base once a week for eight weeks. <i>Contraindicated in pregnant women and women who are breastfeeding a child under six months of age.</i>	Children: 0.25–0.3 mg base/kg daily for 14 days. In mild G-6-PD deficiency: 0.5-0.8 mg base/kg weekly for eight weeks. <i>Contraindicated in children under six months of age.</i>

As primaquine is not currently registered for use in South Africa, it must be obtained on a named-patient basis from Sanofi Aventis under Section 21 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) following authorisation from the Medicines Control Council. Delay in accessing primaquine does not compromise patient health. Primaquine should be given for 14 days at the recommended dosages (**Table 4**). Primaquine is contraindicated in children under six months of age and during pregnancy. In pregnant women eradication of the hepatic stage must be delayed until after delivery. Patients with severe G-6-PD deficiency (less than ten per cent residual enzyme activity) should not receive primaquine due to the risk of severe haemolytic anemia. There is no proven treatment alternative for these patients, although continuing weekly prophylactic chloroquine (usually for three years) may be effective. Primaquine may be taken by patients with mild deficiency of G-6-PD (10 - 60 percent residual enzyme activity) at a reduced dose of 0.5 - 0.8 mg/kg body weight once a week for eight weeks. Such patients should be evaluated for anaemia and haemoglobinuria at three, seven and 10 days after the start of primaquine.

6.5. Treatment of mixed *Plasmodium* species infections

The severity of the falciparum infection should dictate choice of initial therapy. If doubt exists about the presence of other *Plasmodium* species in addition to *P. falciparum*, the patient should be treated for *P. falciparum*, as this is the species most frequently associated with severe malaria complications. For *P. vivax* or *P. ovale* a follow-up course of primaquine is essential to eradicate the residual hepatic phase to prevent relapse.

In patients with confirmed or suspected mixed infections i.e. *P. falciparum* with either *P. vivax* or *P. ovale*, the standard therapy for uncomplicated (or severe) *P. falciparum* malaria is artemether-lumefantrine (or intravenous artesunate or quinine) plus a follow-up course of primaquine is recommended. A mixed infection of *P. falciparum* and *P. malariae* or *P. knowlesi* should be managed as for falciparum malaria. The preferred treatment in uncomplicated mixed infections is artemether-lumefantrine, with intravenous artesunate or quinine recommended for severe infections.

7. MANAGEMENT OF SEVERE MALARIA

Severe malaria is a medical emergency. Unless falciparum malaria is promptly diagnosed and treated, the clinical picture may deteriorate rapidly. Severe malaria carries a 10 to 40 per cent case fatality rate in spite of treatment. Patients should be treated promptly with intravenous artesunate or quinine (where artesunate is not available) in the highest level of care available.

7.1. WHO definition of severe malaria

WHO defines severe falciparum malaria as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia:

Clinical features:

- impaired consciousness
- prostration, i.e. unable to sit, stand or walk without assistance
- multiple convulsions: More than two episodes in 24 hours
- acidotic breathing and respiratory distress
- acute pulmonary oedema and acute respiratory distress syndrome
- circulatory collapse or shock
- anuria
- jaundice
- abnormal bleeding

Laboratory and other findings:

- hypoglycaemia ($<2.2\text{mmol/l}$ or $<40\text{mg/dl}$)
- metabolic acidosis (plasma bicarbonate $<15\text{mmol/l}$)
- severe normocytic anaemia (haemoglobin concentration $<7\text{g/dL}$ or a haematocrit of $<20\%$)
- hyperparasitaemia
- haemoglobinuria
- hyperlactataemia (lactate $>5\text{mmol/l}$)
- renal impairment (serum creatinine $>265\text{ }\mu\text{mol/l}$)
- pulmonary oedema (radiological)

Severe vivax malaria is defined as for falciparum malaria but with no parasite density thresholds. Severe knowlesi malaria is defined as for falciparum malaria but with two differences: *P. knowlesi* hyperparasitaemia is defined as a parasite density >100 000/µl and *P. knowlesi* jaundice is defined as jaundice plus a parasite density >20 000/µl.

7.2. Management of severe malaria at the PHC level

Any patient presenting with clinical features of severe malaria at a primary healthcare (PHC) facility or community health centre (CHC) must be given pre-referral treatment and rapidly transferred to the nearest hospital as an emergency (to reach the hospital within six hours of diagnosis).

7.2.1. Pre-transfer antimalarial drug treatment

If any significant delay (more than six hours) is expected in getting the patient from the PHC/CHC facility to treatment at the nearest hospital, give **one** of the following parenteral antimalarial drug treatments (if available):

- IM artesunate 2.4 mg/kg stat (off-label use) (see annex 2), **or**
- IM quinine 20 mg salt/kg stat (divided into 10 mg/kg diluted to a concentration of 60-100 mg/mL administered into each anterior thigh).³

7.2.2. Pre-transfer general management

- If unconscious, nurse the patient in the lateral or semi-prone position to avoid aspiration.
- Check blood glucose and correct hypoglycaemia if present.
- If hypotensive or in shock, commence IV fluid resuscitation with normal saline.
- If in respiratory distress, administer oxygen.
- Reduce high body temperature (more than 39°C) by administering paracetamol and fanning.
- Control convulsions with intravenous or rectal diazepam. Convulsions may be due to hypoglycaemia.

³Undiluted quinine dihydrochloride is acidic and painful when given as an intramuscular injection. To avoid sciatic nerve injury, quinine should not be injected into the buttock.

7.3. Management of severe malaria at the hospital level

Management of severe malaria comprises four main areas: Clinical assessment of the patient, specific antimalarial treatment, laboratory investigations and management of the complications.

7.3.1. Initial clinical assessment and management

- The airway should be secured in unconscious patients and breathing and circulation assessed.
- The patient should be weighed or body weight estimated so that drugs, including antimalarials, and fluids can be given on a body weight basis.
- An intravenous cannula should be inserted and an immediate measurement of blood glucose (rapid test) done.
- A detailed clinical examination should be conducted, with particular note of the level of consciousness and record of the coma score.
- In patients with depressed level of consciousness and meningism, bacterial meningitis and viral encephalitis must be considered in the differential diagnosis in addition to cerebral malaria, and examination of the CSF may be indicated in addition to peripheral blood examination for malarial parasites.
- The degree of acidosis is an important determinant of outcome; the plasma bicarbonate or venous lactate level should be measured if possible. If facilities are available, arterial or capillary blood pH and gases should be measured in patients who are unconscious, hyperventilating or in shock.
- Submit blood urgently for full blood count, platelet count, and ideally parasite density as well as urea, creatinine and electrolytes. Obtain results urgently.

7.3.2. Chemotherapy

The WHO now recommends intravenous artesunate as the treatment of choice for severe malaria in children and adults. Intravenous quinine is an effective alternative for the treatment of severe malaria in children and adults in South Africa in facilities without prompt access to intravenous artesunate.

7.3.2.1. Artesunate

ARTESUNATE (intravenous)	Patients weighing >20 kg: 2.4 mg/kg at 0, 12 and 24 hours then daily until patient is able to tolerate oral treatment. Children weighing <20 kg: 3 mg/kg at 0, 12 and 24 hours then daily until patient is able to tolerate oral treatment.
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Administration: Administer 2.4 mg/kg (or 3 mg/kg if <20 kg) IV at 0, 12 and 24 hours then daily until patient is able to tolerate oral treatment. Dissolve 60 mg artesunate powder in 1ml five per cent sodium bicarbonate solution (supplied with the artesunate powder) and add 5ml five per cent dextrose (or 0.9% sodium chloride) to give a solution of 10 mg/ml for injecting as a bolus into an IV cannula. Once reconstituted, artesunate solution is not stable and should be administered within 30 minutes; solution not administered within 30 minutes should be discarded. At least three IV doses (at 0, 12, and 24 hours) should be given for severe malaria before switching to oral therapy can be considered. Patients

should then complete a full course (six doses) of artemether-lumefantrine as outlined in section 6.1.1.1

Administer 2.4 mg/kg IM (off-label use) if required for pre-transfer antimalarial treatment. Note that the concentration for IM is 20 mg/ml. See Annex 2.

Safety: Artesunate has excellent safety and tolerability. Common adverse events include gastrointestinal disturbance (nausea, vomiting, anorexia) and dizziness. Rare events include haematological disorders (neutropenia, reduced reticulocyte count, anaemia, eosinophilia), elevated AST and transient ECG abnormalities without reports of significant clinical effects. Delayed haemolysis starting more than one week after artesunate treatment of severe malaria in hyperparasitaemic patients has been reported in African children and non-immune European travellers. The WHO describes this post-treatment haemolysis as a predictable event related to the life-saving effect of artesunate and recommends that hyperparasitaemic patients must be followed up carefully to identify and treat late-onset anaemia. Hypersensitivity reactions occur very rarely. Animal studies have documented neurotoxicity and teratogenicity, but there is no evidence of similar effects in humans.

7.3.2.2. Quinine

Intravenous quinine administration should always be given by slow, rate-controlled intravenous administration, never by bolus (rapid) injection. Where intravenous quinine administration is not feasible, not available or is considered unsafe, the intramuscular route may be used initially.

Quinine loading dose: In severe malaria a loading dose must be given as a slow infusion to achieve therapeutic concentrations as quickly and safely as possible. The loading dose is 20 mg/kg body weight of quinine dihydrochloride salt, diluted in 5-10 ml/kg body weight of five per cent dextrose water given by slow intravenous infusion over four hours. The loading dose is given strictly according to body weight. The disposition of quinine in very obese patients is not known. It has been suggested that there is a ceiling dose above which quinine should not be given, but there is no evidence to support this. No loading dose is to be given and ECG monitoring is necessary if the patient has definitely received treatment doses of mefloquine, quinine (more than 40 mg/kg in the previous two days), quinidine or halofantrine (in the last 24 hours). If in doubt, the loading dose should be given in these cases.

Quinine maintenance dose: Eight hours after starting the loading dose, a maintenance dose of 10mg/kg body weight of quinine dihydrochloride salt, diluted in 5-10 ml/kg of a dextrose-containing solution should be commenced and infused over two to four hours. Intravenous quinine should be administered every eight hours until the patient can tolerate oral medication (usually by 48 hours).

- Do not confuse the doses of salt and base; for historical reasons quinine doses are usually prescribed as salt (10 mg of salt = 8.3 mg of base).
- The dose of IV quinine should be reduced to 10 mg/kg 12 hourly (or 7 mg/kg 8 hourly) on the third day of treatment if parenteral therapy is required for more than 48 hours because there

has been no significant improvement in the clinical condition of the patient, or acute kidney injury has developed or persisted (see 7.5.4).

- Where facilities for IV infusion do not exist, quinine can be given IM in the same dosage. The required dose, diluted in normal saline, to between 60 and 100 mg/ml, should be divided with half the total dose injected in each anterior thigh.
- *For obese patients:* The maintenance dose should preferably be calculated according to ideal body weight. Ideal body weight (IBW) can be estimated for adults using the following formula:
Males: $IBW\ (kg) = 0.9 \times \text{height in cm} - 88$
Females: $IBW\ (kg) = 0.9 \times \text{height in cm} - 92$

Once able to tolerate oral treatment: Patients should be given a full six-dose course of artemether-lumefantrine (or complete seven to ten days of quinine plus either doxycycline or clindamycin as per the recommendations for uncomplicated malaria in Section 6). The use of additional doxycycline or clindamycin does not add initial therapeutic benefit for severe malaria and may contribute to drug side effects so should only be added once the patient is improving.

Safety: Quinine has a narrow therapeutic window, although serious side effects (cardiovascular or nervous system) during treatment of severe malaria are unusual. The most frequent side effect during intravenous therapy is hypoglycaemia, especially in pregnant women and children. Minor adverse effects, causing a syndrome known as cinchonism (mild hearing impairment (notably high tone deafness), tinnitus, headache, nausea and slight visual disturbances) occur in up to 70 per cent of patients with therapeutic quinine concentrations and are not an indication to discontinue therapy. Hypotension, heart block, ventricular arrhythmias, and neurological problems, including convulsions and visual disturbances, occur rarely.

Complications associated with inappropriate use of intravenous quinine that have contributed to malaria-related deaths in South Africa include:

- failure to administer a quinine loading dose
- too rapid administration of quinine loading (or maintenance) doses – IV quinine should always be infused over four hours
- repeated administration of quinine loading doses following clinical deterioration in patients already receiving quinine maintenance therapy
- untreated hypoglycaemia and inadequate monitoring of glucose levels

7.3.3. General management

The following measures should be applied in the management of all patients with definitively diagnosed or clinically suspected severe malaria:

- patients should be admitted to the highest level of care available, ideally an intensive care unit. Good nursing care is vital.
- antimalarial chemotherapy, ideally injectable artesunate, must be commenced urgently. (see section 7.2) Quinine may be used if artesunate not available.

- if parasitological confirmation of malaria is not readily available in very ill patients with a febrile disease with no other obvious cause, a blood film should be made and treatment started on the basis of the clinical presentation and likelihood of malaria.
- doses must be calculated based on the recommended mg/kg body weight. It is therefore important, whenever possible, to weigh the patient. If quinine treatment is used, do not confuse the doses of salt and base. Quinine doses are usually prescribed as salt (10 mg of salt = 8.3 mg of base).
- other treatable causes of coma (e.g. meningitis, hypoglycaemia) should be excluded
- a rapid initial check of the blood glucose level and frequent monitoring for hypoglycaemia are important. Where this is not possible and the patient has a depressed level of consciousness and/or convulsions, glucose should be given as a 50 per cent dextrose solution intravenously. See section 7.5.2.
- regular monitoring of the core (e.g. tympanic or sublingual) temperature, respiratory rate, blood pressure, level of consciousness and other vital signs is mandatory.
- laboratory measurements should include regular checks of haemoglobin, glucose, urea and creatinine, electrolytes and liver functions, acid-base status where possible and parasite density.
- monitor fluid balance carefully. Avoid over- and under-hydration. Fluid overload is extremely dangerous as it may precipitate potentially fatal respiratory failure. Hypovolaemia, however, may potentiate renal failure, metabolic acidosis and circulatory collapse. Accurate recording of fluid input and output is essential as fluid balance should be according to urine output and normal and excess fluid loss.
- monitor urine output constantly and carefully observe for the appearance of haemoglobinuria.
- reduce high body temperatures (more than 39°C) with fanning and antipyretics (paracetamol). Ibuprofen has been used but there is less experience with this compound. Other non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin should be avoided as they may increase the risk of renal failure in patients with malaria.
- the threshold for administering antibiotic treatment should be low in severe malaria. Septicaemia and severe malaria are associated and there is substantial diagnostic overlap, particularly in children living in areas of moderate and high malaria transmission intensity. A broad-spectrum antibiotic e.g. a 3rd generation cephalosporin, is recommended for children with suspected severe malaria until a bacterial infection is excluded, and for adults with severe malaria if there is evidence of bacterial co-infection.
- in adult patients, stress ulcer prophylaxis should be considered. No studies have been performed specifically in patients with severe malaria, but stress ulcer prophylaxis has been shown to be effective in reducing upper gastrointestinal haemorrhage in general ICU populations in resource-rich settings. Stress ulcer prophylaxis can be provided using H₂-receptor blockers such as ranitidine or proton pump inhibitors such as omeprazole.
- the role of exchange transfusion in severe malaria is controversial and there are no controlled studies or meta-analyses yet supporting its use. Exchange transfusion may be considered as an adjunctive therapy in selected patients with persistent acidosis and/or multi-organ impairment unresponsive to first-line treatment, or in patients with hyperparasitaemia in whom

the parasite count increases despite appropriate chemotherapy. The value of exchange transfusion or red cell exchange transfusion should be regarded as experimental until further data become available. The requirements for exchange transfusion include a safe blood supply, a skilled operator and a haemodynamically stable patient. The exchange volume should be four to ten liters of blood for an adult.

7.4. Fluid management in severe malaria

Fluid requirements should be assessed individually. Adults with severe malaria are very vulnerable to fluid overload, while children are more likely to be dehydrated.

The approach to fluid management in malaria patients has become clearer over the last five years, due to improved understanding of the pathophysiology at the microcapillary level in these patients. It is now understood that fluid loading has a limited effect on the obstructed microvascular circulation in malaria. Adults with severe malaria have an increase in vascular permeability, so extra fluid loading may lead to complications such as pulmonary and cerebral oedema. Clinical examination is notoriously unreliable when deciding fluid status, and fluid resuscitation decisions should not be based solely on physical examination. Careful frequent evaluation of jugular venous pressure, peripheral perfusion, venous filling, skin turgor, urine output and laboratory investigations such as lactate and central venous oxygen saturation, are required.

- Rapid bolus infusion of colloid or crystalloids is contraindicated.
- In adults, there is a very thin divide between over-hydration (which may produce pulmonary oedema) and under-hydration, which contributes to shock, worsening acidosis and renal impairment, so a conservative fluid approach is considered best.
- If a patient is anuric, it is unlikely that fluid resuscitation will lead to recovery of renal function and early renal replacement therapy (RRT) is the treatment of choice.
- In the setting of acute kidney injury and oliguria, small fluid boluses (5 ml/kg titrated against effect) can be considered, but clinicians should maintain a low threshold for initiating RRT.
- If an adult with severe malaria has adequate blood pressure (mean arterial blood pressure of more than 65 mm Hg) and urine output (more than 0.5 ml/kg per hour), the evidence suggests little advantage in prescribing any fluid beyond crystalloid at a maintenance rate of 1 to 2 ml/kg per hour, with the selection of crystalloid therapy guided by plasma electrolytes and glucose.
- Respiratory distress with acidotic breathing in severely anaemic children may indicate hypovolaemia and will require prompt initiation of rehydration (Ringer's solution or normal saline and, where indicated, blood transfusion), but care should be taken as excessive administration of fluids may lead to pulmonary oedema. See section 7.5.5 for correct fluid management.

7.5. Management of malaria complications

7.5.1. Severe malarial anaemia

Definition: Malaria patients with a haemoglobin concentration <7 g/dl or a haematocrit of less than 20 per cent may be considered at increased risk although the WHO definition of severe malarial anaemia for research purposes is stricter i.e.:

A parasite count of more than 10000/μl with

- ADULTS: a haemoglobin concentration <7 g/dl or a haematocrit of less than 20 per cent, or
- CHILDREN (under 12 years of age): a haemoglobin concentration <7 g/dl or a haematocrit of less than 20 per cent

Anaemia may have many causes, but is a common complication of malaria, especially in young children and pregnant women. It occurs as a result of haemolysis and/or bone marrow dysfunction. Delayed haemolysis may occasionally follow artesunate treatment of hyper parasitaemic non-immune patients (see section 7.3.2.1).

7.5.2. Hypoglycaemia

Definition: Blood or plasma glucose <2.2 mmol/l (<40 mg/dl);

Hypoglycaemia is common in severe malaria, particularly in pregnant women, young children, and patients treated with intravenous quinine. **Blood glucose should be monitored every four to six hours;** in severe malaria, many of the usual diagnostic features of hypoglycaemia (sweating, anxiety, dilated pupils or tachycardia) may be absent and the diagnosis may be overlooked. Hypoglycaemia should always be excluded in malaria patients with decreased levels of consciousness or convulsions.

Management: Give an intravenous bolus of 50 per cent glucose, 1 ml per kg over 10 minutes, preferably piggy-backed into an intravenous infusion. Thereafter, blood glucose levels should be checked frequently (at least every hour), as rebound hypoglycaemia is common. Maintenance with 10 per cent dextrose may be necessary.

7.5.3. Cerebral malaria

Definition: Decreased level of consciousness (See Glasgow and Blantyre Coma Scores, Annex 1), agitation or confusion or multiple convulsions (two or more episodes within 24 hours).

Cerebral malaria can resemble bacterial or viral infections of the central nervous system, or any cause of raised intracranial pressure. The clinical features are not specific; the patient may be flaccid or spastic, and may exhibit decorticate, decerebrate or opisthotonic posturing. Papilloedema or cerebral oedema is not usually found. It is very important to exclude hypoglycaemia. If meningitis is suspected, a lumbar puncture should be performed. Cerebral malaria may occur as an isolated complication, or as part of multi-organ failure. Convulsions may be subtle and occur as a result of cerebral malaria, accompanying fever or hypoglycaemia.

Management:

- Maintain airway, place patient on his/her side, apply supportive measures and exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis).
- Treat convulsions promptly with standard anticonvulsant drugs (e.g. diazepam 0.3 mg/kg, max 10 mg, by slow IV injection over two minutes or 0.5-1.0 mg/kg rectally). Patients with recurrent seizures and those that are not terminated by two doses of benzodiazepine given 10 minutes apart should be considered to have status epilepticus and given intravenous phenytoin at a loading dose of 18 mg/kg over 20 minutes; this should be followed by maintenance doses of 5mg/kg/day for 48 hours.
- Avoid harmful ancillary treatment such as corticosteroids, mannitol, heparin and

adrenaline. Prophylactic anticonvulsants are not recommended.

7.5.4. Renal failure

Definition: A serum creatinine $>265 \mu\text{mol/l}$ (3 mg/dl) or blood urea $>20 \text{ mmol/l}$ or a rapidly rising creatinine of $>2.5 \mu\text{mol/kg/day}$, and/or a urine output of less than 0.5 ml/kg/hr (or less than 200 ml/12 hr in adults).

Renal failure is generally an early complication of severe malaria and is much more common in adult patients than in children, although in children a raised blood urea on admission also has prognostic significance. Renal dysfunction in malaria develops as a consequence of hypovolaemia, sequestration of parasitised red cells in the renal vasculature, intravascular haemolysis and haemoglobinuria. This may lead to acute tubular necrosis and renal failure. Acute renal failure is usually reversible with appropriate management.

Management:

- Dehydration, if present, must be corrected carefully. When patients present in a polyuric phase it is critical to replace fluid losses adequately. However, excessive administration of fluids should be avoided to minimise the risk of pulmonary oedema. Patients who develop pulmonary oedema have worse outcomes than those with renal failure. Meticulous attention to fluid intake and output is essential to avoid fluid overload.
- Serum or plasma creatinine concentrations should always be measured on admission and then daily if serum creatinine is $>2 \text{ mg/dl}$ ($>177 \mu\text{mol/l}$).
- As AKI in the acute phase of severe malaria develops rapidly and is often compounded by severe metabolic acidosis, RRT should be instituted earlier rather than later in the diseases process. Early referral for dialysis is recommended if the serum creatinine is rising by more than $2.5 \mu\text{mol/kg/day}$. Veno-venous haemofiltration is the most effective mode of dialysis in malaria.
- Patients with impaired renal function require approximately 30 per cent reduction in maintenance quinine dihydrochloride salt to 7 mg/kg every eight hours (or 10 mg/kg every 12 hours), after 48 hours of treatment with the full dose. Quinine is not removed by dialysis. No dosage adjustment is required for artesunate.

7.5.5. Circulatory collapse

Definition: Decompensated shock is defined as systolic blood pressure less than 70 mm Hg in children or less than 80 mm Hg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill). Compensated in children is defined as capillary refill more than three seconds or temperature gradient on leg (mid to proximal limb), but no hypotension.

Circulatory collapse may be seen in patients with metabolic acidosis, severe anaemia, dehydration, ARDS, a ruptured spleen or septicaemia. Clinical assessment can be a more reliable indication of circulatory collapse than blood pressure measurement in children as the correct cuff size is often unavailable and children are able to maintain normal blood pressure despite severe circulatory collapse more efficiently than adults.

Management: Suspect septicaemia; take blood cultures and start broad-spectrum antibiotics e.g. 3rd generation cephalosporin. Rapid fluid loading in adults or children with severe malaria is dangerous. These are general guides to fluid replacement, but each patient needs individual assessment of their fluid requirements:

- hypoglycaemia, which is particularly common in children and pregnant women, should be corrected immediately.
- then, the following fluid management recommendations should be adjusted to individual needs:
 - **children:** Correct fluid deficits over three to four hours with 0.9% ('normal') saline at 3–5 ml/kg/h, then switch to maintenance five per cent dextrose (2– 3 ml/kg/h). If solutions containing 0.45% saline/5% dextrose are available, then these are preferred for initial resuscitation.
 - **adults:** There is no single fluid prescription appropriate for all adults with SFM. The disease's protean manifestations occur in a range of patients with a variety of co-morbidities. However, in general, the available data support a conservative fluid resuscitation strategy (Figure 3).⁴

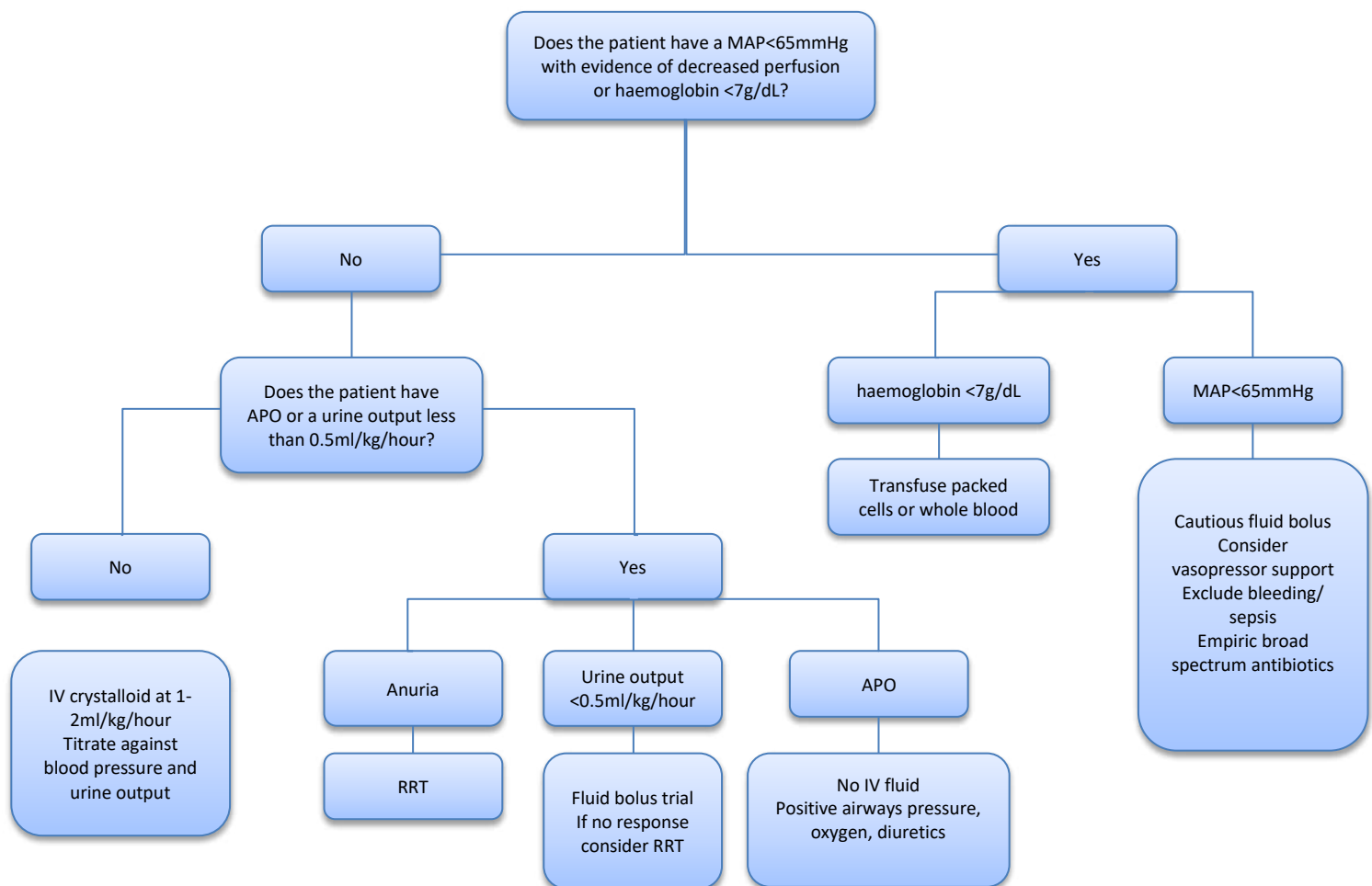


Figure 3. Suggested fluid management for adults with severe malaria.

⁴ Hanson J et al (2014). The fluid management of adults with severe malaria. Critical Care 18 (6):642.

All of the proposed supportive care measures may not be available at sites where patients with severe malaria are initially managed. Early transfer to centers where these services are available is indicated, when possible. Maintenance fluid: The suggested 1 to 2 mL/kg per hour should take into consideration and include other administered fluids: antibiotic therapy, vasopressor infusions, and so on. Crystalloid: Based on plasma electrolytes, consider balanced solutions if available. Fluid bolus: 5 mL/kg crystalloid over 15 minutes; titrate bolus frequency against clinical response. APO, acute pulmonary edema; IV, intravenous; MAP, mean arterial pressure; RRT, renal replacement therapy, hemofiltration preferred if available.

- do NOT use colloids.
- in refractory or recurrent hypoglycaemia, after correction of the low blood glucose with intravenous hypertonic dextrose (0.3–0.4g/kg), check that the intravenous line is patent and fluid infusion rate is correct, or stop blood transfusions and restart five per cent dextrose infusion. Rarely, it may be necessary to give 10 per cent glucose infusions for maintenance after correction of hypoglycaemia. These can be prepared by dilution of 50 percent glucose (usually 50 ml) in 450–500 ml of five per cent dextrose.

7.5.6. Metabolic acidosis

Definition: A base deficit of more than eight mEq/l or, if unavailable, a plasma bicarbonate of less than 15 mmol/l or venous plasma lactate more than five mmol/l. Severe acidosis manifests clinically as respiratory distress – rapid, deep and laboured breathing. Metabolic acidosis, especially lactic acidosis, is an important indicator of severe malaria, even if no other complications are present, and is a poor prognostic sign. Other causes for increased respiratory rate may be excluded with a chest X-ray. Metabolic acidosis may present as shock and/or respiratory distress; in children severe anaemia may present with metabolic acidosis.

Management: The most important cause of the lactic acidosis is microvascular obstruction through sequestration of parasitised red blood cells in the microcirculation. Hypovolaemia or shock, hypoglycaemia and seizures can also contribute.

- Correct any reversible cause of acidosis, in particular dehydration, hypoglycaemia, septicaemia, convulsions and severe anaemia.
- Optimise fluid status and correct hypotension. Take care not to give excessive fluid. Prompt therapy with parenteral artesunate will itself contribute to the control of acidosis as parasites are killed and further sequestration is reduced. Bicarbonate infusion is not generally recommended. Consider haemodialysis (or haemofiltration) in severe metabolic acidosis.

Anaemia contributes to metabolic acidosis in children and should be managed as follows:

- If Hb \leq 7g/dl: Give packed cells 10-20 ml/kg over four to six hours IVI;
If deep breathing, reduced skin turgor, cool peripheries or disturbed consciousness: Give packed cells 10 ml/kg intravenously over one hour then 10 ml/kg intravenously over one to four hours.
- If Hb >7 g/dl: If solutions containing 0.45% saline/five per cent dextrose are available, then these are preferred for initial resuscitation at 3–5 ml/kg/h for three to four hours, then switch to maintenance 2–3 ml/kg/h. Alternatively use five per cent dextrose or 0.9% ('normal') saline.

7.5.7. Respiratory distress

Definitions:

- Mild: Sustained nasal flaring and/or mild intercostal indrawing (recession).
- Severe: The presence of either marked indrawing (recession) of the bony structure of the lower chest wall or deep (acidotic) breathing.
- Pulmonary oedema: Radiologically confirmed, or oxygen saturation less than 92 per cent on room air with a respiratory rate >30/min, often with chest indrawing and crepitations on auscultation.

An increase in the respiratory rate, bilateral crepitations, clinical and laboratory evidence of cyanosis, confusion, agitation, or an arterial oxygen saturation of less than 92 per cent, should alert the clinician to the possibility of ARDS. Pulmonary oedema as a result of iatrogenic fluid overload, or pneumonia, should also be considered.

Acute respiratory distress syndrome (ARDS) is an uncommon, but often-fatal complication of severe malaria, and is a particularly severe problem in pregnancy. ARDS may appear several days after chemotherapy has been started and the general condition of the patient appears to have improved.

Management: Fluids must be restricted, and IV fluids stopped in acute pulmonary oedema. Prop patients up at an angle of 45°. Give oxygen, and diuretics should be given where indicated. Provide ventilatory support with positive end expiratory pressure, or continuous positive airway pressure, in severe hypoxaemia.

7.5.8. Hepatic dysfunction

Definition: Plasma or serum bilirubin >50 µmol/l (3 mg/dl) with a parasite count >100 000/µl.

Although a raised indirect (unconjugated) bilirubin due to haemolysis is a frequent finding in malaria, the clinical presence of jaundice indicates severe malaria, while the finding of raised hepatic transaminases (more than three times normal) should alert the clinician of the probability of severe malaria (or hepatotoxicity). The presence of jaundice combined with renal failure and acidosis is a poor prognostic sign.

7.5.9. Bleeding

Definition: Spontaneous bleeding, including recurrent or prolonged bleeding from nose, gums or venepuncture sites; haematemesis or melaena and / or thrombocytopenia (<20 000/µl).

Thrombocytopenia does not, in itself, indicate disseminated intravascular coagulation and is usually not accompanied by bleeding. Moderate degrees of thrombocytopenia are seen in the majority of malaria patients (including in uncomplicated malaria cases), but bleeding is not common. However, severe degrees of thrombocytopenia (<20 000/µL) may be an indication of severe malaria and may be associated with bleeding. If it does occur, bleeding usually accompanies renal, pulmonary or hepatic complications and is associated with severe thrombocytopenia and coagulopathy. Stress-related gastrointestinal haemorrhage may occur in severely ill patients. With effective malaria treatment, platelet counts return to normal within a few days. DIC is mostly associated with multi-organ failure or hyperparasitaemia, and may in some cases be due to secondary bacterial infection or

septicaemia. Thrombocytopenia is not related to other measures of coagulation (prothrombin time, partial thromboplastin time) or to plasma fibrinogen concentrations. Plasma fibrinogen is usually in the high normal or slightly elevated.

Management: Transfuse with screened, fresh whole blood, if indicated, and available; give platelet transfusions if the platelet count is very low or there is evidence of bleeding; alternatively, give red cell concentrate plus fresh frozen plasma and vitamin K injection.

7.5.10. Secondary infections

The threshold for administering antibiotic treatment should be low in severe malaria. Septicaemia and severe malaria are associated and there is diagnostic overlap, particularly in children. HIV co-infected patients may be at an increased risk of these co- infections. This syndrome is associated with high mortality. Unexplained deterioration may result from a supervening bacterial infection. Although enteric bacteria (notably salmonellae) have predominated in most trial series, a variety of bacteria have been cultured from the blood of patients diagnosed as having severe malaria, and so broad-spectrum antibiotic treatment should be given initially until a concomitant bacterial infection is excluded.

Secondary bacterial infections that may complicate malaria include aspiration pneumonia, urinary tract infections in catheterised patients and nosocomial infections in hospitalised patients.

Management: Antibiotics should be administered to all children with suspected severe malaria, and any patient in whom septicaemia is suspected. A broad-spectrum antibiotic should be administered to cover both Gram-positive and Gram-negative bacteria e.g. a 3rd generation cephalosporin.

7.5.11. Hyperparasitaemia

Definition: More than four per cent of circulating red cells contain parasites or more than 3+ asexual *P. falciparum* parasitaemia on peripheral smear in non-immune patients (or more than 10 per cent in semi-immune patients).

In general, peripheral parasite counts above four per cent should be regarded as severe malaria as this is associated with increased mortality while more than two per cent has a higher risk of treatment failure and they are considered an important source of antimalarial drug resistance. The peripheral parasite count does not accurately reflect the parasite load. Low parasite counts do not exclude severe malaria or complications, and a parasite count must always be interpreted together with the clinical picture and other laboratory findings. In highly endemic malarious areas, semi-immune persons may tolerate high parasite densities (up to 10 per cent), without clinical symptoms and complications. The presence of schizonts of *P. falciparum* in a peripheral blood smear is an important indicator of severe malaria.

Management: People with uncomplicated *P. falciparum* hyperparasitaemia (>4% or >200 000/μL) are at increased risk for severe malaria and death as well as for treatment failure. They thus require close monitoring, and, if feasible, admission to hospital. Whenever possible, give 24-48 hours of parenteral artesunate before the standard 3-day artemether-lumefantrine treatment. If parenteral artesunate is

not promptly available, ensure full adherence and co-administration with a fat-containing drink or food to ensure optimal absorption of each oral artemether-lumefantrine dose, and monitor response to treatment more closely.

7.5.12. Malarial haemoglobinuria

Intravascular haemolysis leads to anaemia, passage of haemoglobin in the urine, and varying degrees of renal failure. The condition is seen in patients with G-6-PD deficiencies who are treated with antimalarial drugs, notably oxidant drugs like primaquine. The condition occasionally occurs in patients with severe malaria and in those with malaria treated with quinine.

Management: It is important to continue full dose antimalarial treatment in patients with confirmed malaria; including quinine if artesunate is not immediately available. However, primaquine must be delayed until patients have recovered from their severe malaria; avoided in patients with severe G-6-PD deficiency and used with caution in patients with mild G-6-PD deficiency (See Section 6.4). Transfusion of fresh blood or (preferably) packed cells for severe anaemia to maintain a haematocrit of more than 20 per cent. Avoid fluid overload; monitor urine output, respiratory rate, and check for chest crepitations. Start renal dialysis when indicated.

7.5.13. Splenic rupture

Splenic rupture is a rare complication of malaria, and is more common in *P. vivax* infections.

8. TREATMENT OF MALARIA IN HIGH-RISK GROUPS

All those who are non-immune are at high risk for the development of severe falciparum malaria. One can assume that all South Africans living in the malaria areas in this country and all South African travellers are non-immune. Pregnant (and post-partum) women, young children, the elderly, splenectomised and immunocompromised persons, including those co-infected with HIV and AIDS, are particularly vulnerable.

8.1. Pregnancy

Pregnant women, particularly in the second and third trimesters of pregnancy, are more likely to develop severe malaria and have a higher malaria-related mortality rate than other adults. Malaria in pregnancy is more frequently associated with complications such as cerebral malaria, hypoglycaemia, and pulmonary oedema/ARDS. In addition, maternal malaria increases the risk of spontaneous abortion, stillbirth, premature delivery, low birth weight (a leading cause of child mortality) and rarely, congenital malaria. Foetal distress may occur peripartum. The risk of severe malaria extends into the early postpartum period. It is important to follow up pregnant women treated for malaria, and their infants, more closely to promptly diagnose and adequately manage any complications of malaria in pregnancy.

8.1.1. Diagnosis of malaria in pregnancy

A high index of suspicion is the most important element in the diagnosis of malaria. Malaria is more frequently missed or misdiagnosed in pregnancy and needs to be differentiated from complications of pregnancy e.g. intrauterine sepsis, eclampsia, or pyelonephritis, as signs and symptoms may be similar.

Suspect malaria if the patient is resident in, or has travelled to, a malaria transmission area. A history of visiting a malaria transmission area should be explored in all pregnant women with fever. A malaria smear or malaria antigen test is mandatory for any pregnant patient with fever and a history of malaria exposure; if initially negative, repeat regularly and urgently (not waiting for fever peaks) until the diagnosis is confirmed, the patient is recovered, or another definitive diagnosis is made.

It is critical to differentiate between uncomplicated and severe malaria. However, uncomplicated malaria may progress rapidly to severe malaria in pregnancy if the patient is not treated urgently and appropriately.

All pregnant women with malaria must be admitted to hospital and those with severe malaria should be transferred to the highest level of care promptly available.

8.1.2. Management of uncomplicated malaria in pregnancy

In the second and third trimesters artemether-lumefantrine should be used to treat uncomplicated malaria. In the first trimester of pregnancy, the treatment of choice to date has been quinine plus clindamycin. However, a recent meta-analysis suggests that artemether-lumefantrine can also be used during the first trimester. Doxycycline and primaquine are contraindicated throughout pregnancy.

With the doses recommended to treat malaria, the benefits of artemether-lumefantrine and quinine plus clindamycin therapy during pregnancy outweigh any risks, so using a less effective therapy cannot be considered. Both quinine and artemether-lumefantrine are effective; however, a meta-analysis of 6 randomised controlled trials from sub-Saharan Africa and Thailand for uncomplicated falciparum malaria in the 2nd and 3rd trimesters showed that artemisinin-based combinations were more effective than oral quinine, with faster parasite clearance, lower treatment failures, and higher mean birth weights. There were no differences in foetal deaths and congenital abnormalities [Renée J. Burger *et al*]. Sub-optimal absorption of artemether-lumefantrine and a higher treatment failure rate has been shown in pregnant women on the Thai-Burmese border, but not in Uganda or Tanzania. As a high-risk group, the response to treatment of pregnant women should be more closely monitored [Tarning J *et al*].

Quinine is challenged by poor tolerability which, in addition to complex and lengthy (7- day) dosing regimen, often results in poor compliance. Quinine's main adverse effect in pregnancy is hypoglycaemia and glucose levels should be more closely monitored. Compared with artemisinin-based combination treatment of uncomplicated malaria in the 2nd and 3rd trimester, quinine is also associated with more tinnitus, dizziness, and vomiting. Quinine may be oxytocic, but this effect may be due to the malaria itself. The incidence of quinine-related teratogenesis is unknown, although congenital abnormalities, notably CNS anomalies and limb defects have been occasionally reported with quinine use in the first trimester.

Artemether-lumefantrine is now an alternative for the treatment of uncomplicated malaria in the first trimester of pregnancy. No evidence of the artemisinin-related embryotoxicity observed in animals was found in 1599 well documented pregnancies followed prospectively after artemisinin-based (n=654) or quinine based (n=945) treatment of uncomplicated malaria. Compared to quinine, artemisinin use during the first trimester was not associated with an increased risk of miscarriage, still births or congenital anomalies. Neither was any significant difference seen in a sensitivity analysis restricted to the exposure during the embryo-sensitive period (6-12 weeks). Key limitations of this study include the inability to control for confounding by indication in the African studies, the paucity of data on potential confounders, the limited statistical power to detect differences in congenital anomalies, and the lack of assessment of cardiovascular defects in newborns [Dellicour S *et al*].

8.1.3. Management of severe malaria in pregnancy

- Intravenous artesunate is recommended for severe malaria in all trimesters of pregnancy as it has been shown to be highly effective. Once patients can tolerate oral medication, they should complete a full course (six doses) of artemether-lumefantrine (or a total of at least seven days of oral quinine plus clindamycin).
- If parenteral artesunate is unavailable, parenteral quinine should be started immediately until parenteral artesunate is obtained. Hypoglycemia is common and is often recurrent if the patient is receiving quinine, and may be refractory to glucose administration. Hypoglycemia must be considered urgently in any pregnant woman with malaria who presents with convulsions,

confusion or a depressed level of consciousness.

- It may be difficult to differentiate cerebral malaria from eclampsia. If a pregnant woman living in a malaria area has fever, headaches or convulsions and malaria cannot be excluded, it is essential to treat the woman for both malaria and eclampsia.
- Respiratory failure due to ARDS is a particular problem of malaria in pregnancy, and is difficult to manage and carries a high mortality rate. **It is critical therefore to monitor fluid balance very carefully.** Fluid overload may potentiate the development of ARDS. Hypovolaemia however, may potentiate renal failure, metabolic acidosis and circulatory collapse. Accurate recording of fluid input and output is essential. ARDS commonly occurs several days after treatment is initiated.
- Obstetric advice should be sought early. The role of an early caesarean section for the viable foetus is unproven. Termination of pregnancy is generally not indicated. Severe malaria may present immediately after delivery.
- Postpartum bacterial infection is a common complication and should be managed appropriately.

8.1.4. Management of malaria in lactating and postpartum women

In lactating women, uncomplicated malaria should be treated with artemether- lumefantrine, and IV artesunate OR quinine used together with clindamycin for severe malaria.

The risk of severe malaria extends into the early postpartum period. Postpartum bacterial infection is a common complication in these patients.

8.2. Infants and young children

Infants and young children (especially those under five years) are particularly at risk for severe malaria and complications can develop very rapidly. The symptoms of malaria in children may differ from those in adults. Poor feeding, lethargy, irritability, coughing and convulsions (frequently subtle), are important presenting features in children.

8.2.1. Managing uncomplicated malaria in young children

In children weighing more than five kilograms, with uncomplicated malaria, recommended treatment is artemether-lumefantrine. The WHO recommends that uncomplicated malaria in infants weighing less than five kilograms be treated with artemether-lumefantrine at the same mg/kg target dose as infants weighing more than five kilograms. As infants and young children have a higher risk of developing complicated malaria, they should ideally be admitted for treatment under close supervision.

For children under five kilograms bodyweight, with uncomplicated malaria, an alternative option is quinine plus clindamycin. As there is no quinine syrup available, it can be difficult to administer to children. Crushed tablets mixed in mashed bananas, chocolate syrup or jam can be used to make the quinine more palatable, although food effects on bioavailability have not been studied.

Young children who are vomiting but have no other indications of severe malaria should be given the recommended maintenance doses of parenteral artesunate (3 mg/kg, if <20 kg body weight; 2.4 mg/kg

if >20 kg) or quinine (10 mg/kg) until the child can take medication orally. Particular care must be taken to ensure that the correct dosage according to bodyweight is administered. Once oral intake is tolerated a full treatment course of artemether-lumefantrine must be administered.

8.2.2. Managing severe malaria in young children

Intravenous artesunate (3 mg/kg) is the preferred treatment for severe malaria in young children weighing under 20 kg; children weighing more than 20 kg should be dosed at 2.4 mg/kg. Doses should be given at 0, 12 and 24 hours, and then daily until the patient can tolerate oral treatment. Intravenous quinine is an alternative for severe malaria in children when the loading dose of 20 mg/kg must also be used (See section 7.3.2.2). Particular care must be taken to ensure that the correct dosage is administered according to body weight. Where intravenous artesunate/quinine is not promptly available, or cannot be given safely, initial administration of quinine by deep intramuscular injection using scrupulous aseptic technique, should be considered prior to referral. When given intramuscularly, quinine dihydrochloride should be diluted to reduce pain and prevent sterile abscess formation. Dilutions to between 60 and 100 mg/ml should be made.

General management of severe malaria in young children:

- check airway, breathing, circulation (ABC).
- hypoglycaemia, cerebral malaria, anaemia, and metabolic acidosis are important complications.
- agitation and respiratory distress (as a result of metabolic acidosis) are ominous signs
- fluid boluses are not recommended. Rehydration using crystalloids should be administered over three to four hours. (see 7.5.5).
- secondary bacterial infections, including septicaemia, are common and broad-spectrum antibiotics e.g. third generation cephalosporins should be given to children with severe malaria.
- renal failure and acute respiratory distress syndrome are rare in young children
- meningitis is important in the differential diagnosis of malaria with a depressed level of consciousness or convulsions.
- convulsions in children with malaria may be subtle, and could be due to hypoglycaemia, cerebral malaria or pyrexia.

8.3. Patients with HIV and AIDS

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-infected 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, particularly in rural areas, where HIV prevalence is high, and where the malaria burden is mostly in adults due to unstable malaria transmission precluding their acquiring immunity. Substantial interaction between malaria and HIV and 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 or delayed.

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

8.3.1. Managing uncomplicated malaria in HIV-infected patients

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 delay in treatment seeking, increased risk of anaemia, delayed parasite clearance and increased treatment failure rates.

- Patients with HIV infection who develop malaria should receive the recommended antimalarial regimens, although more closely monitored, to ensure an adequate response.
- Pharmacological interactions between certain antiretrovirals (ARVs) and antimalarial drugs are theoretically possible and might lead to toxicity or sub-therapeutic drug levels.
 - Co-treatment with artemether-lumefantrine and efavirenz-based antiretrovirals reduces lumefantrine concentrations with a higher risk of treatment failure. An extension of the duration of artemether-lumefantrine treatment to five days is proposed.
 - HIV-infected children receiving artesunate plus amodiaquine are at increased risk of neutropenia, particularly if taking zidovudine.
 - Although amodiaquine is not available or recommended in South Africa, it is important to note that hepatotoxicity has developed in healthy volunteers given artesunate plus amodiaquine and efavirenz.
 - Although sulfadoxine-pyrimethamine is not recommended for the treatment of malaria in South Africa, it is important to note that sulfadoxine-pyrimethamine (SP) should be avoided in those taking cotrimoxazole.

8.3.2. Managing severe malaria in HIV-infected patients

HIV-infected patients who are malaria non-immune are at higher risk of severe malaria and of dying from malaria. Patients co-infected with HIV and AIDS and malaria should be admitted for treatment and close monitoring at the highest level of care promptly available.

- As HIV progresses and immune suppression worsens, the risks of severe malaria increase.
- The incidence of severe malaria increased 1.7-2.7-fold in adults and up to 9.6-fold in children, and case fatality rates in hospitalised 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 given, e.g. a third generation cephalosporin.
- Electrolyte disturbances are common and close monitoring is essential.

9. CONCLUSIONS

Significant advances since 2000 have led to substantial decreases in the burden of malaria in South Africa, across Africa and globally. The widespread deployment of artemisinin-based treatments for uncomplicated malaria (artemether-lumefantrine) and severe malaria (IV artesunate) have played a key role. However, important challenges remain, including artemisinin resistance spreading in Southeast Asia (although not yet confirmed anywhere in Africa), and the fact that the majority of malaria cases in South Africa are now imported (i.e. not locally transmitted), and often presented late to health facilities in malaria-free areas. Thus, health professionals throughout South Africa, in both the malaria endemic and malaria free areas, all need to develop and maintain their knowledge and skills in malaria diagnosis and treatment. These guidelines and the key resources listed below aim to assist to ensure prompt diagnosis and effective treatment, both essential to reduce the unacceptably high malaria case fatality rates currently recorded in South Africa.

AVAILABLE PRODUCTS

Trade name	Active ingredient	Registered by:
Adco-quinine® injectable	quinine dihydrochloride	Adcock Ingram
Aspen-quinine® oral	quinine sulphate	Aspen Pharmacare
Coartem® oral	artemisinin-lumefantrine	Novartis South Africa (Pty) Ltd
Garsun® injectable	artesunate	Equity Pharmaceuticals (Pty) Ltd

USEFUL LINKS

WHO Guidelines for the Treatment of Malaria 3rd Edition (2015):

www.who.int/malaria/publications/atoz/9789241549127/en/

WHO TMIH Supplement on Severe Malaria (2014):

<http://www.who.int/malaria/publications/atoz/who-severe-malaria-tmih-supplement-2014.pdf>

WHO Training materials on the use of Rapid Diagnostic Tests

<http://www.who.int/malaria/areas/diagnosis/rapid-diagnostic-tests/job-aids/en/>

MMV injectable artesunate tool kit: user guide, job aid (poster) and training video

<http://www.mmv.org/access/injectable-artesunate-tool-kit>

Global Health Network Basic Malaria Microscopy Learner's Guide

<https://globalhealthtrainingcentre.tghn.org/elearning/basic-malaria-microscopy/>

World Health Organization International Travel and Health 2015 Malaria Update

<http://www.who.int/ith/2015-ith-chapter7.pdf?ua=1>

World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases (TDR) 2015. Methods Manual: Microscopy for the detection, identification and quantification of malaria parasites on stained thick and thin blood films in research settings.

apps.who.int/iris/bitstream/10665/163782/1/9789241549219_eng.pdf

World Health Organization Malaria Microscopy Quality Assurance Manual – Version 2 (2016)

apps.who.int/iris/bitstream/10665/204266/1/9789241549394_eng.pdf

Centers for Disease Control and Prevention. Malaria diagnosis and treatment in the United States.

https://www.cdc.gov/malaria/diagnosis_treatment/

National Institute of Allergy and Infectious Diseases. Malaria.

<https://www.niaid.nih.gov/topics/malaria/Pages/default.aspx>

UpToDate Search <http://www.uptodate.com/contents> for:

- diagnosis of malaria
- treatment of uncomplicated falciparum malaria in non-pregnant adults and children
- overview of malaria in pregnancy
- overview of non-falciparum malaria in non-pregnant adults and children
- treatment of severe malaria
- HIV and malaria

World Health Organization. Overview of Malaria Elimination

<http://www.who.int/malaria/areas/elimination/overview/en/>

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ANNEXURE 1: ASSESSMENT OF THE LEVEL OF CONSCIOUSNESS

The Glasgow Coma Scale

Best motor response	Score
Carrying out request (obeying command)	6
Localising response to pain	5
Withdraws to pain	4
Flexor response to pain	3
Extensor posturing to pain	2
No response to pain	1
Best verbal response	
Orientated	5
Confused conversation	4
Inappropriate speech	3
Incomprehensible speech	2
None	1
Eye opening	
Spontaneous eye opening	4
Eye opening in response to speech	3
Eye opening to response to pain	2
No eye opening	1

An overall scale is made by adding the score in the three areas assessed, e.g:

3 No response to pain + no verbalisation + no eye opening = 3

≤8 Severe injury

9-12 Moderate injury

13-15 Minor injury

Blantyre paediatric coma scale (for children under five years)

Motor response	
Localises to pain	2
Withdraws from pain stimuli	1
No response	0
Verbal response	
Appropriate cry	2
Inappropriate cry/moan	1
No cry	0
Eye response	
Directed	1
Not Directed	0

4-5 Normal




2-3 Mild impairment

0-1 Severe impairment


ANNEXURE 2: GUIDELINES FOR ADMINISTRATION OF INJECTABLE ARTESUNATE FOR SEVERE MALARIA.

Please refer to product package insert

GUIDELINES FOR ADMINISTRATION OF INJECTABLE ARTESUNATE FOR SEVERE MALARIA

PRODUCT DESCRIPTION
Dose: For children > 20 kg and adults: 2.4 mg/kg
IV is the route of administration.
Please refer to the patient information leaflet for more information.
* Water for injection is not an appropriate diluant



**WHO
RECOMMENDED
TREATMENT**





1 WEIGH THE PATIENT

2 DETERMINE THE NUMBER OF VIALS NEEDED

Weight	less than 25 kg	26-50 kg	51-75 kg	76-100 kg
60 mg vial	1	2	3	4

3 RECONSTITUTE





■ Activate the drug: artesunate powder + bicarbonate ampoule (immediately before use)

4 DILUTE

■ Reconstitute artesunate + saline solution (or dextrose 5%)
■ Volume for dilution

	IV
Bicarbonate solution volume	1 ml
Saline solution volume	5 ml
Total volume	6 ml
Artesunate 60 mg solution concentration	10 mg/ml

IMPORTANT

Water for injection is not an appropriate diluant

5 CALCULATE THE DOSE

■ Calculate and withdraw the required dose in ml for intravenous administration:

For intravenous route (IV)
Concentration: 10 mg/ml
3.0 mg x body weight (kg)
IV artesunate solution concentration 10 mg/ml
(Round up to the next whole number)

Example:
Dose needed (ml) for 8 kg child:
 $\frac{3.0 \times 8}{10} = 2.4 \text{ ml}$
2.4 ml rounded up to 3 ml

Weight kg	Dose mg	Dose ml
6 - 7	20	2
8 - 10	30	3
11 - 13	40	4
14 - 16	50	5
17 - 20	60	6

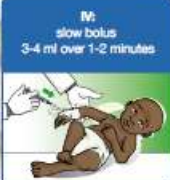
Concentration: 10 mg/ml
2.4 mg x body weight (kg)
IV artesunate solution concentration 10 mg/ml
(Round up to the next whole number)

Example:
Dose needed (ml) for 26 kg child:
 $\frac{2.4 \times 26}{10} = 6.24 \text{ ml}$
6.24 ml rounded up to 7 ml

Weight kg	Dose mg	Dose ml
20 - 25	60	6
26 - 29	70	7
30 - 33	80	8
34 - 37	90	9
38 - 41	100	10
42 - 45	110	11
46 - 50	120	12
51 - 54	130	13
55 - 58	140	14
59 - 62	150	15
63 - 66	160	16
67 - 70	170	17
71 - 75	180	18
76 - 79	190	19
80 - 83	200	20
84 - 87	210	21
88 - 91	220	22
92 - 95	230	23
96 - 100	240	24

6 ADMINISTER

IV slow bolus
3-4 ml over 1-2 minutes



7 DOSING SCHEDULE

- Give 3 IV doses over 24 hours as indicated in the opposite table.
- Give IV doses for a minimum of 24 hours once started irrespective of the patient's ability to tolerate oral treatment earlier.

- Day 1** Dose 1: on admission (0 Hours)
Dose 2: 12 hours later
- Day 2** Dose 3: 24 hours after first dose

- When the patient can take oral medication, prescribe an appropriate oral combination antimalarial regimen. The first dose of ACT should be taken between 8 and 12 hours after the last injection of artesunate.
- Until the patient is able to take oral medication, continue parenteral treatment (one dose a day) for a maximum of 7 days.
- A course of injectable artesunate should always be followed by a 3-day course of ACT.
- Evaluate the patient's progress regularly.

IMPORTANT

- Prepare a fresh solution for each administration.
- Discard any unused solution after use.

References: 1. World Health Organization (WHO) List of Prequalified Medicinal Products (<http://apps.who.int/prequal/QueryProductRegistry.aspx?list=ms>): artesunate injectable, reference N° MA051, prequalified on 05-Nov-2010.
2. World Health Organization, Management of Severe Malaria - A practical handbook - Third edition - April 2013 - (<http://www.who.int/malaria/publications/whos6041548529/en/index.html>)

This document is intended to demonstrate to health workers how to prepare and administer injectable artesunate, a treatment for severe malaria. It is not intended to provide personal medical advice. The responsibility for the interpretation and use of this material lies with the reader. In no event shall MMV be liable for damages arising from its use. © 2014 Medicines for Malaria Venture (MMV). All rights reserved. A copy of this document can only be made upon MMV's written authorization.

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ANNEXURE 3: ADDITIONAL DIAGNOSTIC TESTS FOR MALARIA

Malaria PCR is useful in certain circumstances, but is not generally appropriate as the primary diagnostic method in routine diagnostic laboratories. If malaria is suspected for clinical, epidemiological or laboratory (e.g. unexplained thrombocytopenia) reasons, and initial laboratory tests are negative, they should be repeated.

Indications for PCR* are:

1. To exclude or confirm a diagnosis of malaria in patients with suspected malaria who are repeatedly smear or RDT negative.
2. To exclude or confirm a diagnosis of malaria in patients with suspected malaria who have discrepant rapid antigen and smear test results that are not due to malaria treatment.
3. To determine the *Plasmodium* species present, if in doubt, in smear-positive malaria patients. (Note that combo RDT results are often incorrectly interpreted as mixed species infections in *P. falciparum* malaria; the solution is technologist training, and correlation with microscopy.)

Contraindications for PCR are:

1. If referral entails delays that could contribute to detrimental outcomes for the patient.
2. As a primary diagnostic method instead of, or in addition to, microscopy and RDTs.
3. To follow response to treatment (likewise for RDTs), as these tests will stay positive for a period even if the clinical and parasitological response is satisfactory.
4. To determine the parasite load (likewise for RDTs), as these are not quantitative tests.

*Or suitable validated digital microscopy (e.g. Parasight P0002, Sight Diagnostics Ltd, Jerusalem, Israel), if PCR is not readily available.

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Guidelines for the treatment of malaria Directorate: Malaria (Civitas Building, Room 836, North Tower)		
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