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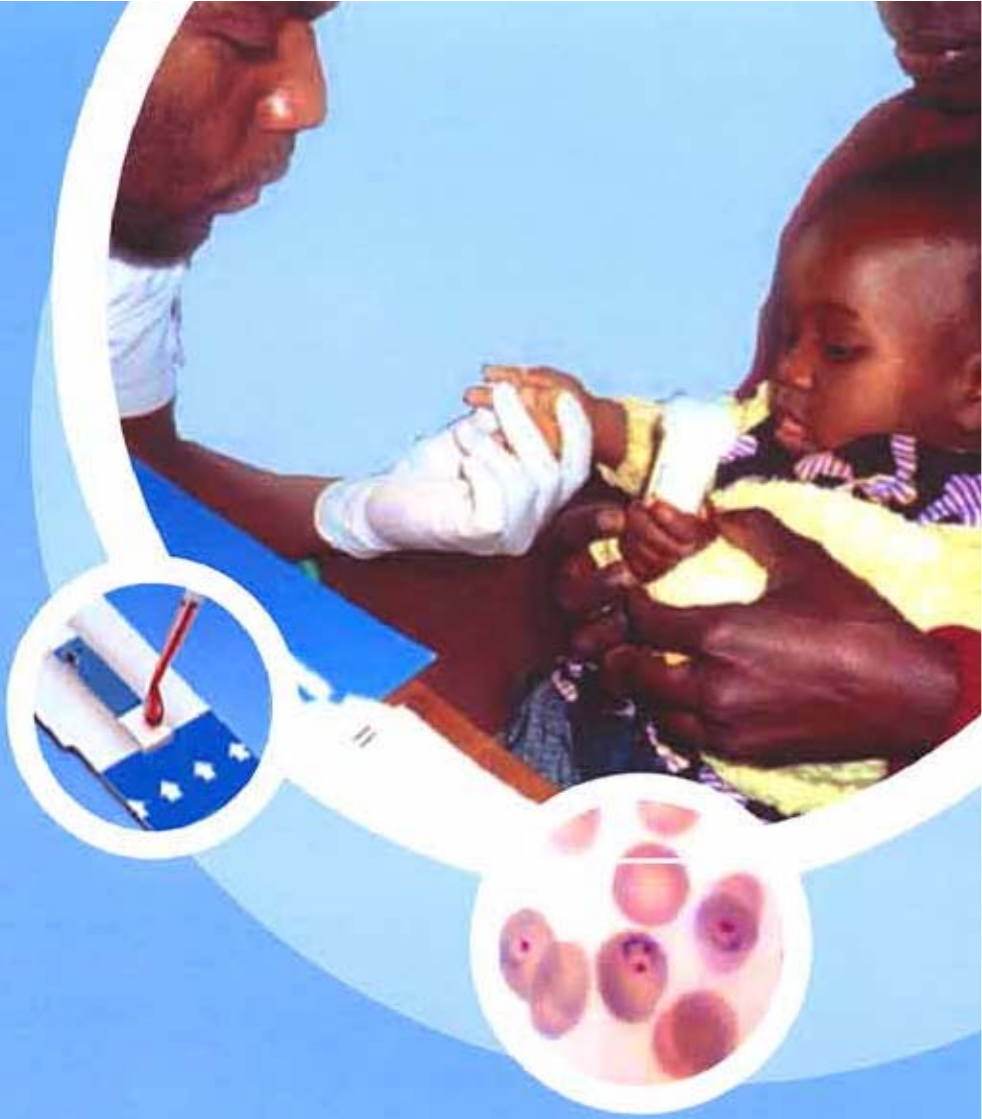

Guidelines for the Treatment of Malaria in South Africa 2010

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REPUBLIC OF SOUTH AFRICA

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PREFACE

Considerable success has been achieved in the control and management of malaria in South Africa in recent years. This is despite the ongoing development of parasite and vector resistance to drugs and insecticides, respectively. It gives me great pleasure to introduce these guidelines on the treatment of malaria in South Africa.

The objectives of these publications are to provide all those involved in the management of malaria with clear and practical guidelines for the diagnosis and appropriate treatment of malaria.

The intended treatment outcomes are the prevention of malaria morbidity and mortality. In addition, the recommendations are intended to contribute to reduced malaria transmission and to limit resistance to antimalarial drugs.

These guidelines are based on the 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.

The previous guidelines were compiled in August 2002. Advances in the availability of antimalarial drugs, reduced malaria transmission intensity, increased drug resistance and changes in respect of health care delivery in South Africa have prompted revision of these guidelines.

It is hoped these guidelines will facilitate effective, appropriate and timeous treatment of malaria, thereby reducing the burden of this disease in our communities and in South Africa.

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Dr A Motsoaledi, MP
Minister of Health
08/02/2010

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Dr KS Chetty
Acting Director-General: Department of Health
08/02/2010

ABBREVIATIONS

ACT	Artemisinin-based combination therapy
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
CDC	Communicable Disease Control
CNS	Central nervous system
CVP	Central venous pressure
DIC	Disseminated intravascular coagulation
ECG	Electrocardiogram
GCS	Glasgow Coma Score
G-6-PD	Glucose-6-phosphate dehydrogenase
KZN	KwaZulu-Natal
MVBD	Malaria and Other Vector Borne Diseases
MAG	Malaria Advisory Group
NSAIDS	Non-steroidal anti-inflammatory drugs
NDoH	National Department of Health
PEEP	Positive end-expiratory pressure
RDT	Rapid diagnostic tests
SP	Sulfadoxine-pyrimethamine
SCAT	Subcommittee for Chemoprophylaxis and Treatment
WHO	World Health Organization
UCT	University of Cape Town

SUMMARY

Plasmodium 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 are non-immune and are therefore at risk for developing severe malaria.

The diagnosis and management of malaria is urgent. Delayed diagnosis 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 rapid malaria antigen test.

For uncomplicated malaria, artemether-lumefantrine (Coartem®) is recommended for first-line therapy. Alternatively quinine plus either doxycycline or clindamycin can be used if artemether-lumefantrine is unavailable or contra-indicated. High-level resistance precludes the use of chloroquine for falciparum malaria. Sulfadoxine-pyrimethamine (SP) and halofantrine are no longer recommended.

For severe malaria, quinine (with the addition of doxycycline or clindamycin) or intravenous artesunate is recommended. Patients with severe malaria will require hospital admission. All patients with malaria require careful clinical and parasitological follow-up. The major complications of malaria include: cerebral malaria, hypoglycaemia, anaemia, renal failure, acute respiratory distress syndrome (ARDS) and metabolic acidosis, and these carry high mortality rates especially in children, pregnant women and in those living with HIV/AIDS. These complications require specific management.

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 Malaria Advisory Group do not accept responsibility for errors or omissions. Readers are referred to the reference articles for further information and should exercise their own professional judgement in confirming and interpreting the findings presented in the publication. These guidelines were issued in 2010 by the National Department of Health, and replace all previous guidelines.

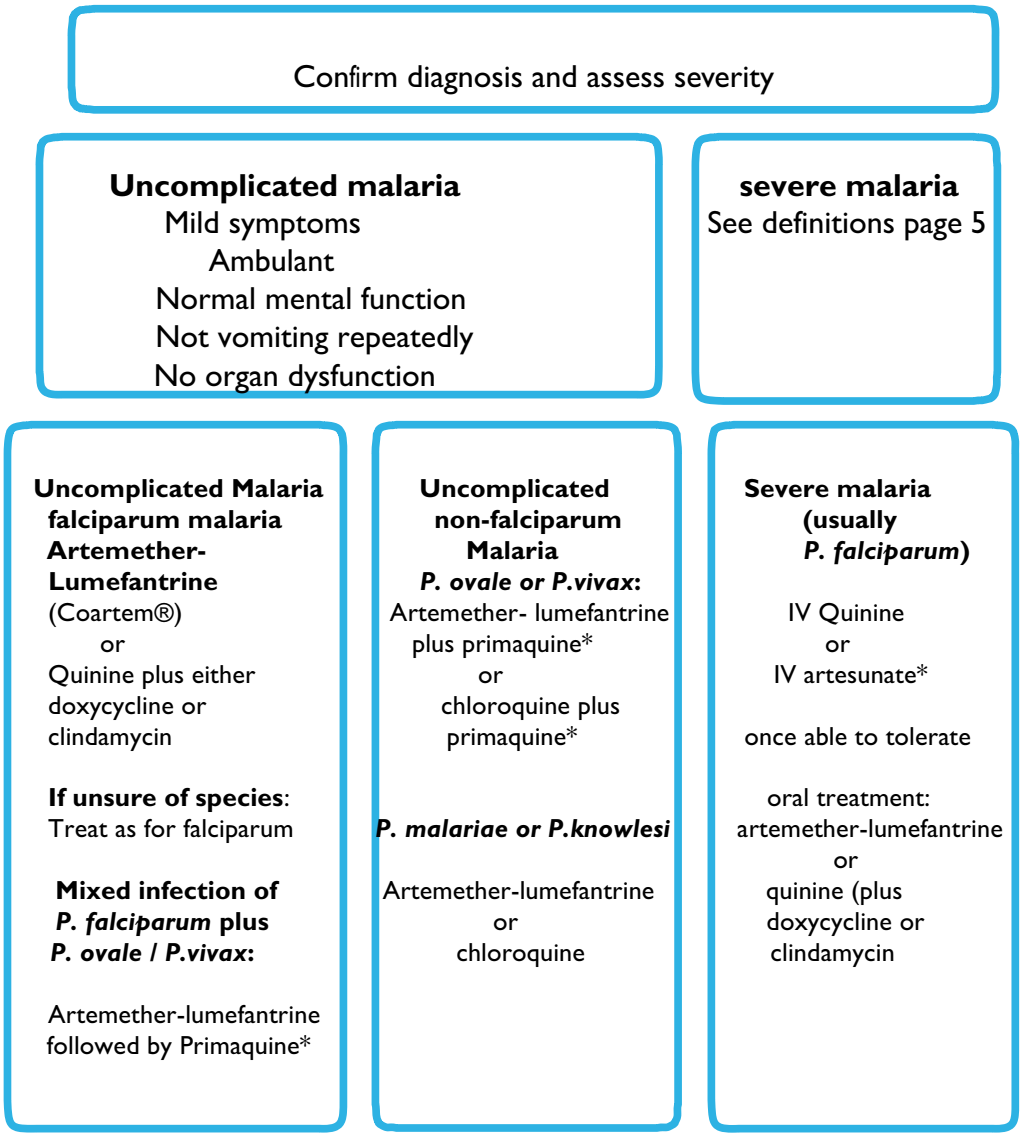

Figure 1: Algorithm for the management of Malaria in South Africa

* Although not registered for use in South Africa, provision has been made for compassionate use

1. INTRODUCTION

The relentless development of drug resistance in malaria parasites, most notably in *P. falciparum,* has necessitated ongoing updates of chemoprophylaxis and treatment policies globally.

In South Africa, chloroquine resistance was first demonstrated in KwaZulu-Natal (KZN), and later in Mpumalanga Provinces. This prompted a policy change from chloroquine to sulphadoxine-pyrimethamine (SP) as first-line treatment for uncomplicated malaria in KZN in 1988 and in Mpumalanga and Limpopo Provinces in 1997.

The development of significant SP resistance in KZN led to a further policy change in 2001, with artemether-lumefantrine replacing SP as first line treatment for uncomplicated *P. falciparum* infections. Subsequently, in December 2004, Limpopo Province also replaced SP with artemether-lumefantrine. Mpumalanga Province used SP-artesunate in the public sector from 2001 to end of 2005, but has deployed artemether-lumefantrine since January 2006.

In order to combat the continuous pattern of drug resistance developing sequentially to antimalarials used as monotherapy (single drug therapy), combination chemotherapy, preferably including an artemisinin derivative, is recommended. Additional benefits of artemisinin-based combination therapy (ACT) include improved treatment outcomes and a decrease in malaria transmission, resulting in greater cost-effectiveness.

These guidelines have been compiled using both international and local information. In South Africa there is ongoing monitoring of malaria prevalence and distribution, and the therapeutic efficacy of antimalarial drugs. New information arising from such monitoring activities will inform future guidelines.

2. OBJECTIVES

The objectives of malaria treatment are:

- To prevent mortality;
- to prevent disease progression and development of severe malaria;
- to reduce morbidity;
- to eliminate parasitaemia to minimise transmission; and
- to limit the emergence and spread of drug resistance.

3. PARASITE SPECIES

More than 90% of human malaria infections in sub-Saharan Africa are due to *Plasmodium falciparum* while the remainder are due to *Plasmodium ovale, Plasmodium vivax,* or *Plasmodium malariae*. Occasionally mixed infections occur. Rarely, human infection with

the monkey malaria parasite, *P. knowlesi*, has also been reported from forested regions of Southeast Asia. Almost all severe and complicated malaria infections are due to *P. falciparum*.

4. RISK GROUPS

South Africans, including residents in areas where malaria transmission occurs, are non-immune. High-risk groups for the development of severe *P. falciparum* malaria in South Africa include non-immune travellers to malaria areas and residents (of all age groups) in malaria areas. Pregnant (and post-partum) women, young children, the elderly, splenectomised and immunocompromised individuals are particularly vulnerable. There are increasing data on the interaction between HIV and malaria, showing that non-immune patients co-infected with HIV have a higher risk of severe malaria and malaria-related mortality. There is also evidence of increased clinical episodes of malaria and higher parasite densities in semi-immune individuals who are HIV infected. Partial immunity may be acquired after long-term, repeated exposure to *P. falciparum* infection, as occurs in residents of perennial high transmission areas, such as in parts of Mozambique, Malawi, Tanzania and some other sub-Saharan African countries.

5. CLINICAL PRESENTATION AND DIAGNOSIS

As signs and symptoms of malaria are 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 (Section 5.2), who has a history of travel to, or residence in, a malaria transmission area.

5.1 Malaria transmission

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

Malaria transmission occurs in almost all countries in sub-Saharan Africa with the exception of Lesotho, and year-round transmission with seasonal disease incidence peaks is usual. 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.

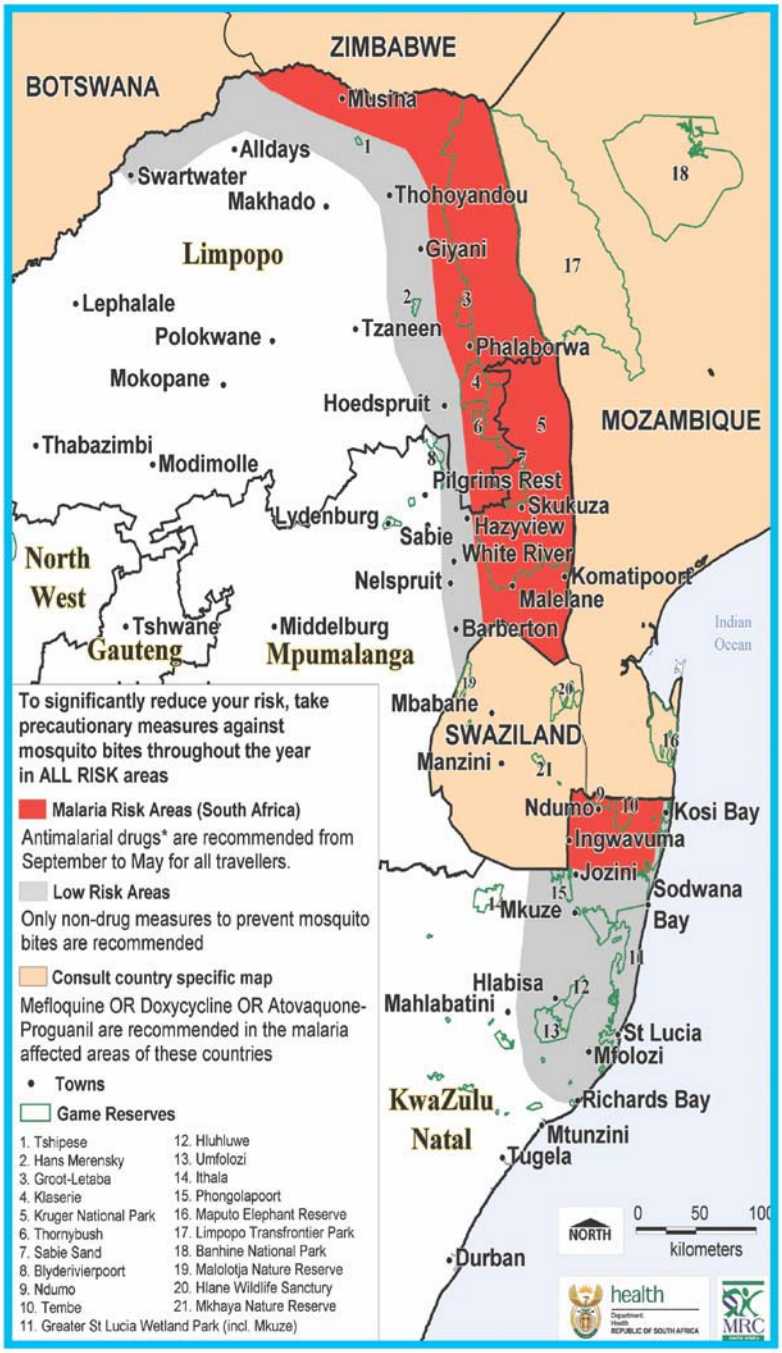

Figure 2: Distribution of malaria risk in South Africa

5.2 Symptoms and signs

Table 1: Symptoms and signs of malaria

Uncomplicated malaria signs and symptoms	Danger signs	High risk groups
• Fever • Headache • Rigors (cold and shiver/hot sweats) • Myalgia • Weakness • Dizziness • Loss of appetite/poor feeding • Diarrhea, nausea and vomiting • Cough • Splenomegaly	• Unable to drink or • Breastfeed • Repeated vomiting • Recent history of convulsions • Lethargy • Unable to sit or stand	• Pregnant (and postpartum) women • Infants and young children • Elderly patients (>65 years) • Splenectomised patients • Immunocompromised patients, including patients with HIV/AIDS • Non-immune patients

Severe malaria: clinical features	Severe malaria: biochemical features	Severe malaria: haematological features
• Prostration • Impaired consciousness • Multiple convulsions • Respiratory distress (acidotic breathing) • Circulatory collapse • Acute respiratory distress syndrome (ARDS) • Abnormal bleeding • Jaundice • Haemoglobinuria	• Renal impairment: serum creatinine >265 µmol/liter or rapid rising creatinine (>2.5 µmol/kg/day) or urine output <400ml/day (adult) • Acidosis: plasma bicarbonate <15 mmol/liter or serum lactate >5 mmol/liter • Hepatic impairment: transminases >3 times normal Hypoglycaemia: blood glucose <2.2 mmol/liter • Hypoxia: PO_2 <8 Kpa in a room air	• Parasitaemia: ≥4% or ≥3+ • Anaemia: haemoglobin < 6g/dl or haematocrit <20% • Malaria pigment in ≥5% neutrophilis • Schizonts of *P.falciparum* in peripheral blood smear • Evidence of DIC

Symptoms and signs of malaria may present as early as 7 days after exposure, with a usual range of 10 - 21 days elapsing after being bitten by an infected 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 6 - 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.

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

Non-immune patients with uncomplicated malaria are at significant risk of disease progression to severe *P. 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 treatment of an uncomplicated infection, the use of ineffective therapy or under-dosing with effective drugs.

In a febrile patient with no obvious other cause of fever, in whom no recent history

of visiting or living in a malaria area is forthcoming, malaria should still be excluded as infected mosquitoes have occasionally been documented to travel long distances by road, rail or air transport.

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 rapid diagnostic test or microscopy of blood smear to confirm or exclude the diagnosis. A blood test for parasites should be done irrespective of the time of the year or whether or not the patient has taken chemoprophylaxis.

In the majority of malaria cases, examination of correctly stained blood smears will reveal malaria parasites. However, a negative smear does not exclude the diagnosis; repeat specimens should be examined regularly and urgently (without waiting for fever peaks), until the diagnosis is confirmed, the patient has recovered, or another definitive diagnosis is made. Examination of the peripheral blood smear will give an indication of the species of parasite as well as the parasite density. High levels of parasitaemia (>4% or ≥3+)* should be treated as severe malaria. Importantly, the converse may not be true, with severe disease also 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 7. Management of severe malaria).

A number of commercial rapid diagnostic tests (RDTs) are available for early diagnosis in health facilities where microscopy is not immediately available. These kits detect parasite antigen, namely, histidine-rich protein 2 (or lactate dehydrogenase or aldolase). The majority of the RDTs will only detect *P. falciparum,* although some can detect the other malaria species but are less sensitive for these. The RDTs for *P. falciparum* are generally highly sensitive. Performance is, however, dependent on the correct storage, usage and interpretation of results and the quality of the particular RDT used. 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. The test may be negative early in the disease, and false positives may be encountered rarely.

If the diagnosis of malaria cannot be confirmed (unavailability of laboratory tests or negative tests), 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 parasitized red blood cells. In patients who are treated empirically for malaria, it is imperative to continue to look for alternative

*The parasite density referes to the parasite load in the peripheral blood expressed semi-quantitatively (1-4+) or as a percentage of infected red blood cells. Quantification is often inaccurate and does not necessary reflect the total parasite load in patient.

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.

5.4 Referral criteria

Ideally all patients with malaria should be treated in hospital, particularly if they present to health facilities in areas where malaria transmission does not occur. Clinical judgement should always be applied. Definite indications for hospital admission include:

- Any feature of severe malaria (Table 1);
- Danger signs (Table 1);
- High risk population groups (Table 1);
- Suspected treatment failure (including reappearance of parasites within 6 weeks of treatment).

5.5 Malaria notification

Malaria is a notifiable disease.

The notification of all malaria cases in South Africa is mandatory. As thousands of malaria cases present each year in non-malaria areas as well as in malaria transmission areas, it is critical that these cases all get notified to the local authority to facilitate adequate provision of malaria diagnosis and management resources to healthcare facilities in these areas.

The procedure for notifiable medical conditions is as follows:

1. Healthcare worker (not necessarily a medical doctor) diagnoses (preferably a definitive diagnosis) and immediately notifies the malaria case to the local authority using GW17/5 or applicable notification form, as some of the important information required on the notification form may not be available after the patient has left the healthcare facility. If possible, the malaria species should be specified in the notification form.
2. Local authority/hospital/district (whoever is responsible for disease containment) submits the GW17/3 summary of cases and GW17/4 summary of deaths forms weekly.
3. Regional/district office health information unit will collate and use this information to plan and monitor the impact of malaria control and case management interventions.

6. MANAGEMENT OF UNCOMPLICATED MALARIA

Patients should receive prompt treatment with the most effective regimen available.

Treatment should ideally be initiated in hospital, particularly when patients present in non-malaria areas or are among the high-risk population groups (Table 2). In malaria areas the majority of patients with uncomplicated malaria can be treated at primary health care level.

The choice of chemotherapy for malaria is based on:

- the severity of disease;
- the known or suspected resistance pattern of the parasite in the area where the malaria infection was acquired;
- the species of parasite;
- patient characteristics (age, pregnancy, co-morbidity, allergies, concomitant medications); and
- the presence or absence of vomiting.

Drug choices may change over time with the development of parasite resistance or the availability of new antimalarial treatments.

6.1 Uncomplicated *P. falciparum* malaria

It is critical to differentiate between uncomplicated and severe/high-risk malaria (Table 1). 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 4% (see Section 7: Severe malaria, for details). However, uncomplicated malaria may rapidly progress to severe malaria if the patient is not treated appropriately.

6.1.1 Chemotherapy

Artemether-lumefantrine

The recommended treatment for patients with uncomplicated malaria, including all patients over 5 kg in bodyweight and women in the second and third trimesters of pregnancy, is the fixed dose artemisinin-based combination therapy (ACT), artemether-lumefantrine (Coartem®).

The WHO recommends ACTs as the best current treatment for uncomplicated falciparum malaria, as they have the advantages of rapid clinical and parasitological response, improved cure rates, decreased malaria transmission and the potential to delay antimalarial drug resistance. Artemether-lumefantrine has the advantages of a shorter treatment course (6 doses over 3 days) and far better tolerability than the only effective alternative, quinine. However, its indication is limited to the treatment of uncomplicated malaria as there is no evidence of its efficacy in more severe disease.

ARTEMETHER-LUMEFANTRINE (oral) 1 tablet contains artemether 20 mg plus lumefantrine 120 mg.	**5 -<15 kg:** One tablet stat, followed by one after 8 hours and then one twice daily on each of the following two days (total course = 6 tablets) **15-<25 kg:** Two tablets stat, followed by two after 8 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 after 8 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 after 8 hours and then four twice daily on each of the following two days (total course = 24 tablets). **>65 kg:** Dose as for >35 kg above, although inadequate experience in this weight group justifies closer monitoring of treatment response. *NOTE: Administer with food/milk containing at least 1.3 g fat (100 ml milk) to ensure adequate absorption.*

- The recommended artemether-lumefantrine (Coartem®) dosage regimen is six doses administered over a 3-day period. The number of tablets per dose should be according to body weight (above).
- Adequate absorption of the lumefantrine component is critically dependent on co-administration with food or drink containing at least 1.3 g fat (e.g. 100 ml milk). It is essential that patients or carers are informed of the need to take ACT with or immediately after a meal or milk – particularly on the second and third days of treatment.
- This drug has been best studied in patients weighing less than 65 kg and thus is not yet registered for use in patients weighing greater than 65 kg, although evidence in this group is generally positive. The WHO, however, recommends use in patients >65 kg. Patients >80 kg may be at increased risk of treatment failure. Monitor response to treatment carefully, and consider using a 5-day regimen.
- 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 the magnitude of potential drug interactions is likely to be small relative to the far greater effect of co-administration with fat, 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 antihistaminics (terfenadine, astemizole), cisapride or medications that are metabolized by the cytochrome enzyme CYP2D6, which also have cardiac effects (e.g. flecainide, imipramine, amitriptyline, clomipramine).
- As mefloquine decreases lumefantrine efficacy, monitor artemether-

lumefantrine treatment response closely in patients recently treated with mefloquine.

- Young children (<5 years) may be at increased risk of treatment failure, probably due to lower drug concentrations; monitor response to treatment carefully. A flavoured dispersible tablet has been formulated for young children, but is not yet registered for use in South Africa.
- For those at increased risk of treatment failure, consider administering same number of tablets as indicated based on weight over 5 days at 0, 8, 24, 48, 72 and 96 hours (off-label).

Quinine (plus either doxycycline or clindamycin)

QUININE (oral) 1 tablet usually contains 300 mg quinine sulphate	10 mg salt/kg body weight (maximum usually 600 mg) every 8 hours for 7 days.
DOXYCYCLINE (oral) 1 capsule/tablet contains 50 or 100 mg doxycycline	Use in combination with quinine as soon as oral medication can be tolerated: 3.5 mg/kg daily for at least 7 days. NOTE: Avoid in pregnancy and children under 8 years old.
CLINDAMYCIN (oral) 1 tablet contains 150 mg clindamycin	Use in combination with quinine in pregnancy and children <8 years as soon as oral medication can be tolerated: 10 mg/kg twice daily for 7 days

In children ≤5 kg in bodyweight and in all pregnant patients in the first trimester, the recommended chemotherapy is quinine plus clindamycin. When artemether-lumefantrine is not available or is contra-indicated (history of allergy to artemisinins or lumefantrine), uncomplicated malaria can also be treated with quinine plus either doxycycline or clindamycin. Quinine is a rapidly-acting, effective antimalarial drug used for both uncomplicated and severe malaria acquired in sub-Saharan Africa. Quinine resistance is rare in this area, although increasing slowly in Southeast Asia.

- It is advisable that quinine only be used as observed treatment of inpatients, due to the poor tolerability and thus poor adherence with this 7-day regimen.
- Oral quinine therapy is recommended in uncomplicated malaria but the initial doses of quinine should be administered intravenously if the patient is vomiting repeatedly.
- Quinine therapy should be continued for 7-10 days.
- The addition of a second, effective, antimalarial drug, i.e. doxycycline or clindamycin, 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 2-3 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 less than 8 years old or during pregnancy, clindamycin should be used rather than doxycycline or other tetracyclines.

- Shortened courses of quinine (3 days) cannot be recommended for treatment. It is most important that patients (or caregivers) understand that it is essential to complete the course of 7-10 days of quinine (with doxycycline or clindamycin) as adherence with this poorly-tolerated treatment is generally low.
- 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% of patients during quinine therapy and are not an indication to discontinue therapy. Major side effects include arrhythmias, hypersensitivity and hypoglycaemia.
- Hypoglycaemia is the most frequent serious adverse reaction. 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.

6.1.2 General management

It is easy to underestimate the severity of disease 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, the mental state, respiratory rate 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) should be avoided as they may increase the risk of renal failure in patients with malaria.

If patients with uncomplicated malaria cannot be admitted to hospital for treatment, they (or their caregivers) should be warned of the symptoms and signs of severe malaria and advised of the urgency of returning for hospitalisation and appropriate treatment.

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.

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 after 72 hours is a good predictor of subsequent treatment failure and provides a simple screening measure for artemisinin resistance. Artemisinin resistance is highly unlikely if the proportion still parasitaemic on day 3 is less than 3-5%, 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 (Table 1) or persistence of parasitaemia for >7 days or reappearance of parasites on microscopy within 6 weeks. Rapid diagnostic tests should 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); or
- Relapse due to *P. ovale* or *P. vivax*, because of failure to treat hypnozoites with primaquine.

Treatment failures after completing a full course current first-line therapy of either the 3-day artemether-lumefantrine or 7-day quinine (plus doxycycline or clindamycin) regimen are rare, as both these treatments have high cure rates. Patients who have failed first-line treatment with artemether-lumefantrine should then be given a 7-10 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 (Table 1). A patient who fails treatment and manifests features of severe malaria or danger signs should be treated with intravenous artesunate or quinine.

6.2 Treatments not recommended for *P. falciparum* malaria

- Monotherapies (antimalarial agents used on their own) are no longer 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 treatments (ACTs); taking artemisinin monotherapies for less than 7 days is strongly associated

with treatment failure (recrudescence of infection).

- Chloroquine is not recommended following the emergence of high-level resistance in most parts of the world, including South Africa.
- Sulphadoxine-pyrimethamine is no longer recommended in South Africa, due to the availability of more effective combination therapy, coupled with high-level resistance in some parts of the country.
- Mefloquine is registered only for prophylaxis but not treatment, given the higher incidence of severe psychiatric adverse effects associated with treatment doses.
- Halofantrine treatment is not advisable given the associated cardiotoxicity, variable bioavailability and drug interactions in patients who have taken mefloquine prophylaxis.
- 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.

6.3 Treatment of non-falciparum infections

In sub-Saharan Africa, a minority (<10%) of the malaria infections are due to one of the non-falciparum species, namely *P. vivax, P. ovale,* or *P. malariae*. 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 *P. vivax* and *P. knowlesi* have rarely caused severe malaria (usually complicated by respiratory distress), and repeated *P. malariae* infections may be associated with the nephrotic syndrome in children. The parasite species should be reliably confirmed microscopically. If unsure of the species, standard treatment for *P.falciparum* should be administered.

P. ovale, P. malariae and *P. knowlesi* are currently chloroquine-sensitive, but cases of chloroquine-resistant *P. vivax* have been documented in Oceania, Brazil, and Indonesia.
In South Africa *P. ovale* is the most common of the non-falciparum malarias. Anaemia may complicate chronic *P. ovale* infection. Pure infections of non-falciparum species can be treated with artemether-lumefantrine (see page 8), or chloroquine (or quinine) monotherapy.
For *P. vivax or P. ovale* a follow-up course of primaquine* is essential to eradicate the residual hepatic phase to prevent relapse.

CHLOROQUINE (oral) non-falciparum malaria only 1 tablet contains 150 mg chloroquine base	**Adults**: 1.5 g over 3 days, as follows: initially 600 mg, followed by 300 mg 6-8 hours later, and 300 mg once daily on second and third days.	**Children**: Initial dose: 10 mg base/kg then 5 mg base/kg 6-8 hours later, and 5 mg base/kg once daily on second and third days.
PRIMAQUINE (oral)* 1 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 mg base/kg daily for 14 days. In mild G-6-PD deficiency (10-60% residual G-6-PD activity): 45 mg base weekly once a week for six to eight weeks.	**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 8 weeks. *Contraindicated in children under 1 year old.*

Primaquine is not currently registered for use in South Africa, so must be obtained on a named-patient basis under Section 21 of the Medicines and Related Substances Act following authorisation from the Medicines Control Council. This delay in accessing primaquine does not compromise patient health. Primaquine should be given for 14 days at the recommended dosages. Primaquine is contra-indicated in children less than 1 year of age and during pregnancy. In pregnant women eradication of the hepatic stage must be delayed until after delivery. Patients with severe glucose-6-phosphate dehydrogenase (G-6-PD) deficiency (<10% residual enzyme activity) should not receive primaquine due to the risk of severe haemolytic anaemia. There is no proven alternative for these patients, although continuing weekly prophylactic chloroquine (usually for 3 years) may be effective. Primaquine may be taken by patients with mild deficiency of G-6-PD (10 - 60% residual enzyme activity) at a reduced dose of 0.5 - 0.7 mg/kg body weight once every 7 days for 8 weeks. Such patients should be evaluated for anaemia and haemoglobinuria at 3, 7, and 10 days after the start of primaquine.

6.4 Treatment of mixed *Plasmodium* species infections

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 of 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 severity of the falciparum infection should dictate choice of initial therapy. Doubt frequently exists about the presence of *P. falciparum* in addition to other *Plasmodium* species. The patient should then be treated for *P. falciparum*, as this is the species most frequently associated with severe infections and complications.

7. MANAGEMENT OF SEVERE MALARIA

Severe malaria is a medical emergency. Unless *P. falciparum* malaria is promptly diagnosed and treated, the clinical picture may deteriorate rapidly. Treated severe malaria carries a 10 – 40% mortality burden. Patients should be treated in the highest level of care available.

For the definition of severe malaria and danger signs, as well as a list of high-risk population groups, see Table 1 (page 5).

Management of severe malaria comprises 4 main areas: clinical assessment of the patient, specific antimalarial treatment, general management, and management of the complications of severe malaria.

7.1 Initial assessment

- 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.
- A lumbar puncture for cerebrospinal fluid analysis to exclude bacterial meningitis should be considered in unconscious patients.
- The degree of acidosis is an important determinant of outcome; the plasma bicarbonate or venous lactate level should therefore 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 measurement of urea, creatinine and electrolytes and obtain results urgently.
- The assessment of fluid balance is critical in severe malaria. Respiratory distress, with acidotic breathing, in severely anaemic children, often indicates hypovolaemia and requires prompt rehydration and, where indicated, blood transfusion.

7.2 Chemotherapy

Intravenous quinine is the drug of choice for the treatment of severe malaria in children in South Africa and in adults without prompt access to intravenous artesunate. The World Health Organization now recommends intravenous artesunate as the treatment of choice for severe malaria in adults.

7.2.1 Quinine

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

Quinine loading dose: In severe malaria a loading dose must be given. The rationale for the loading dose is to rapidly reach a therapeutic level. The loading dose is quinine dihydrochloride salt, 20 mg/kg body weight diluted in 5-10 ml/kg body weight of 5% dextrose water given by slow intravenous infusion over 4 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 if the patient has definitely received treatment doses of mefloquine, quinine (more than 40 mg/kg in the previous 2 days), or quinidine or halofantrine (in the last 24 hours). If in doubt the loading dose should be given. In these cases, ECG monitoring is necessary.

Quinine maintenance dose: Eight hours after starting the loading dose, a maintenance dose of quinine dihydrochloride salt, 10 mg/kg diluted in 5-10 ml/kg body weight of a dextrose-containing solution should be commenced and infused over 4 hours. Intravenous quinine should be administered every 8 hours until the patient can take oral medication (usually by 48 hours). If a treatment dose of mefloquine has been taken in the 12 hours before severe malaria treatment starts, ECG monitoring would be advisable.

- The dose of IV quinine should be reduced to 5-7 mg/kg 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 renal failure has developed. The dose of quinine should be reduced in renal failure (See 7.4.4).
- Where facilities for IV infusion do not exist, quinine can be given IM in the same dosage. The required dose, diluted to between 60 mg and 100 mg/ml, should be given as half the dose in each anterior thigh.

For obese patients: the maintenance dose should be calculated according to ideal body weight. Ideal body weight (IBW) can be calculated for adults by a formula as follows:

Males: IBW (Kg) = 0.9 x height in cm - 88
Females: IBW (Kg) = 0.9 x height in cm - 92

Once able to tolerate oral treatment: patients should be given a full 6-dose course of artemether-lumefantrine or complete 7 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. They should be added once the patient is improving.

Safety: Quinine has a narrow therapeutic window, although serious side effects (cardiovascular or nervous system) during antimalarial treatment 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% of patients during quinine therapy 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;
- rapid administration of quinine loading doses;
- repeated administration of quinine loading doses following clinical deterioration in patients already receiving quinine maintenance therapy;
- hypoglycaemia and inadequate monitoring of glucose levels.

7.2.2 Artesunate

ARTESUNATE (intravenous)* * Not registered in South Africa; provision for Section 21 use.	2.4 mg/kg at 0, 12 and 24 hours then daily until patient is able to tolerate oral treatment.

Although not yet registered in South Africa, there is provision for compassionate use of IV artesunate in terms Section 21 of the Medicines and Related Substances Act, and it can be obtined at selected sentinel hospitals through the IV artesunate access programme.

Administration: Administer 2.4 mg/kg at 0, 12 and 24 hours then daily until patient is

able to tolerate oral treatment. Dissolve artesunate powder 60 mg in 1 ml 5% sodium bicarbonate solution and add 5 ml 5% dextrose (or 0.9% sodium chloride) solution (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 2–3 IV doses should be given for severe malaria before switching to oral therapy can be considered. Patients should then complete a full course (6 doses) of artemether-lumefantrine (or 7 days of oral quinine plus either doxycycline or clindamycin).

Safety: Artesunate has excellent safety and tolerability. Common adverse events include gastro-intestinal disturbance (nausea, vomiting, anorexia) and dizziness. Rare events include haematological disorders (neutropenia, reduced reticulocyte count, anaemia, eosinophilia), elevated AST and transient ECG abnormalities without clinical effect. Hypersensitivity reactions occur very rarely. Animal studies have documented neurotoxicity and teratogenicity, but there is no evidence of similar effects in humans.

7.3 General management

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

- Patient should be admitted at the highest level of care available, ideally an intensive care unit. Good nursing care is vital;
- Appropriate antimalarial chemotherapy must be commenced urgently. Ideally the drug should initially be given intravenously(see Section 7.2);
- If parasitological confirmation of malaria is not readily available, a blood film should be made and treatment started on the basis of the clinical presentation, in very ill patients with febrile disease with no other obvious cause;
- Doses must be calculated on a mg/kg of body weight basis. 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 50% dextrose solution intravenously. See Section 7.8.2;
- Regular monitoring of the core 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. Frequent central venous pressure (CVP) monitoring is recommended; maintain the CVP at between 0-5 cm of water. Consider risk of bleeding due to thrombocytopenia when inserting CVP line;

- Monitor urine output constantly and carefully observe for the appearance of haemoglobinuria;
- Reduce high body temperatures (> 39°C) with paracetamol (or ibuprofen) and vigorous tepid sponging and fanning. Avoid aspirin-containing compounds and non-steroidal anti-inflammatory drugs other than ibuprofen;
- 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. A broad-spectrum antibiotic e.g. a 3rd generation cephalosporin is recommended.

7.4 Management of malaria complications

7.4.1 Severe anaemia

Definition: A haemoglobin level < 6 g/dl or a haematocrit < 20%.
Anaemia 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. Severe anaemia may manifest as cardiac failure, shock, hypoxia or confusion. Some patients may also have other causes contributing to their anaemia.
Management: Transfuse with screened fresh whole blood. Caution should be exercised and fluid overload should be avoided. If no fresh blood is available, packed red cell concentrate may be used.

7.4.2 Hypoglycaemia

Definition: A blood glucose level <2.2 mmol/l.
Hypoglycaemia is common in severe malaria, particularly in pregnancy, children, and patients on intravenous quinine. Blood glucose should be monitored 4-6 hourly. Hypoglycaemia may not always present with classical symptoms of sweating, anxiety, dilatation of pupils or tachycardia. Hypoglycaemia should always be excluded in patients with malaria who present with depressed levels of consciousness, including coma and convulsions.

Management: Give 50% dextrose water intravenously as a bolus:

- Adults: 50 ml;
- Children: 1 ml/kg body weight of 50%.

This should be followed by continuous intravenous infusion of 5 or 10% dextrose solution. Avoid fluid overload.

7.4.3 Cerebral malaria

Definition: A depressed level of consciousness (using Glasgow or Blantyre coma scores – Annexes 1, page 33 and 34), agitation or confusion.
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, or may exhibit meningism or symmetrical upper motor neurone signs. 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 occur as a result of cerebral malaria, accompanying fever or hypoglycaemia.

Management: Prophylactic anticonvulsants are currently not recommended. Treat convulsions with standard anticonvulsant drugs and supportive measures. Supportive measures include monitoring of level of consciousness and effective protection of the airway (particularly when the Glasgow Coma Score is <9). Avoid harmful ancillary treatment such as corticosteroids, mannitol, heparin and adrenaline.

7.4.4 Renal failure

Definition: A serum creatinine greater than 265 µmol/l, or a rapidly rising creatinine of more than 2.5 µmol/kg/day, and/or a urine output of less than 0.5 ml/kg/hr (or less than 400 ml/day in an adult).
Renal failure is generally an early complication of malaria in adults, and occurs rarely in children. Renal dysfunction in malaria develops as a consequence of hypovolaemia, sequestration of parasitized 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. A central venous catheter should be inserted where possible and maintained between 0-5 cm of water. Meticulous attention to fluid intake and output is essential to avoid fluid overload.

Early dialysis is recommended, where available, as renal failure in malaria occurs against a background of a hypercatabolic state. Early referral for dialysis is recommended if the serum creatinine is rising by more than 2.5 µmol/kg/day.Veno-venous haemofiltration is the most effective mode of dialysis in malaria.

Patients with impaired renal function require a reduction in maintenance quinine dihydrochloride salt to 5-7 mg/kg every 8 hours, after 48 hours of treatment with the full dose. Quinine is not removed by dialysis. No dosage adjustment is required for artesunate.

7.4.5 Circulatory collapse

Definition: Systolic blood pressure less than 80 mmHg in adults (>13 years) or a systolic blood pressure <50 mmHg at any age or clinical features of circulatory collapse.
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.

Use the following signs to indicate circulatory collapse in children:

- Tachycardia;
- Cool/cold and clammy extremities e.g. limbs;
- Mottled/pale skin indicating poor perfusion.

Management: Ideally, a central venous catheter should be inserted and hypovolaemia corrected with an appropriate volume expander (blood or plasma) or isotonic saline. Suspect septicaemia; take blood cultures and start broad-spectrum antibiotics e.g. 3rd generation cephalosporin. Start inotropes if the CVP is >5 cm of water and the patient is still shocked.

7.4.6 Metabolic acidosis

Definition: plasma bicarbonate <5 mmol/l or serum lactate >5 mmol/l.
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: Correct any reversible cause of acidosis, in particular dehydration, hypoglycaemia, septicaemia, convulsions and severe anaemia. Take care not to give excessive fluid. The routine use of bicarbonate is not recommended. Consider haemodialysis (or haemofiltration) in severe metabolic acidosis.

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

- If Hb ≤6 g/dl: give packed cells 10-20 ml/kg over 4-6 hours ivi;
- If deep breathing, reduced skin turgor, cool peripheries or disturbed consciousness: give packed cells 10 ml/kg intravenously over 1 hour then 10 ml/kg intravenously over 1-4 hours;
- If Hb >6 g/dl: give crystalloid (0,9% saline) or Ringers lactate 10-20 ml/kg intravenously over 4 hours (rate of infusion based on clinical judgment).

7.4.7 Respiratory distress

Definition: An increase in the respiratory rate, bilateral crepitations, clinical and laboratory evidence of cyanosis, confusion, agitation, or an arterial oxygen saturation of less than 90%, 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. 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/continuous positive airway pressure in severe hypoxaemia.

7.4.8 Hepatic dysfunction

Definition: Although a raised indirect bilirubin due to haemolysis is a frequent finding in malaria, the clinical presence of jaundice or the finding of raised hepatic transaminases (≥3 x normal) should alert the clinician of the probability of severe malaria. The presence of jaundice combined with renal failure and acidosis is a poor prognostic sign.

7.4.9 Disseminated intravascular coagulation (DIC)

Definition: Spontaneous bleeding and coagulopathy.
DIC is rare in patients with severe malaria. Moderate degrees of thrombocytopenia are seen in the majority of cases of uncomplicated malaria, but bleeding is not common. However, severe degrees of thrombocytopenia may be an indication of severe malaria and may be associated with bleeding. 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.

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.

7.4.10 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 also be at an increased risk. 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 (3rd generation cephalosporin) should be administered to all children with severe malaria, and any patient in whom septicaemia is suspected. Although secondary bacterial infection is more common in children, most guidelines recommend antibiotics for adults too as the features of bacterial and malarial sepsis overlap. A broad-spectrum antibiotic should be administered to cover both Gram-positive and Gram-negative bacteria e.g. a 3rd generation cephalosporin.

7.4.11 Hyperparasitaemia

Definition: ≥4% or ≥3+ asexual *P. falciparum* parasitaemia on peripheral smear.
In general, peripheral parasite counts above 4% should be regarded as severe malaria as this is associated with increased mortality. 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. The peripheral parasite count does not accurately reflect the parasite load. In highly endemic malarious areas, semi-immune persons may tolerate high parasite densities, 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: The patient should be managed with a rapidly acting effective antimalarial drug, preferably artesunate, for 7 days. The use of artemether-lumefantrine in hyperparasitaemia has not yet been studied and it is possible that the 3-day course of artemisinsin-derivative would be too short. As hyperparasitaemia increases the risk of malaria complications (which are often underdiagnosed) and of malaria mortality, initial intravenous quinine therapy should be considered if artesunate is not available. The patient should be especially closely monitored for complications, even if these are not present initially. Exchange transfusion possibly has a role to play in patients with hyperparasitaemia whose parasite counts increase or fail to decrease significantly despite appropriate therapy.

7.4.12 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 also occurs in patients with severe malaria and in those with malaria treated with quinine.

Management: Continue appropriate malaria chemotherapy; quinine may be continued (primaquine must be avoided in patients with G-6-PD deficiency). Supportive therapy should include blood transfusions for severe anaemia, adequate fluids and renal dialysis where indicated.

7.4.13 Exchange transfusion

The role of exchange transfusion in severe malaria is controversial and there are no controlled studies to support its use. Exchange transfusion may be considered for use in selected patients, e.g. patients with hyperparasitaemia in whom the parasite count increases despite appropriate chemotherapy, and patients who develop multi-organ dysfunction despite appropriate chemotherapy. The requirements for exchange transfusion include a safe blood supply, a skilled operator and a haemodynamically stable patient. The exchange volume should be 4-10 liters of blood for an adult.

7.4.14 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 *P. 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 individuals, including those co-infected with HIV/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 carefully follow up pregnant women treated for malaria, and their infants, 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 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 (repeated if initially negative) or malaria antigen test is mandatory for any pregnant patient with fever and a history of malaria exposure.

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 available.

8.1.2 Management of uncomplicated malaria in pregnancy

In the first trimester of pregnancy, the treatment of choice for uncomplicated malaria is quinine plus clindamycin. In the second and third trimesters artemether-lumefantrine may be considered. Doxycycline is contraindicated throughout pregnancy.

Quinine has proved to be safe when used in normal therapeutic doses, and since the risks of malaria are great, using a less effective therapy cannot be considered. Quinine's main adverse effect in pregnancy is hypoglycaemia and patients should be closely monitored for this. Quinine may be oxytoxic, but this effect may also be due to the malaria itself. The incidence of teratogenesis is unknown, although congenital abnormalities, notably CNS anomalies and limb defects have been occasionally reported with quinine use in the first trimester. With the doses used to treat malaria, the benefits of quinine therapy outweigh any risks.

Artemether-lumefantrine is an alternative for the treatment of malaria in the second and third trimesters of pregnancy. There is increasing experience with the artemisinin derivatives in the 2nd and 3rd trimesters of pregnancy, and no adverse effects on the mother or human foetus have been documented to date. However, sub-optimal absorption of artemether-lumefantrine has been shown in pregnant women in the second and third trimester with uncomplicated malaria. Some animal studies have shown teratogenicity, particularly with high doses. Avoid the artemisinins in the first trimester of pregnancy if an effective and safe alternative is promptly available, as limited human data are available and animal studies show adverse effects.

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

8.1.3 Management of severe malaria in pregnancy

- For severe malaria, quinine is recommended for treatment in the first trimester. Artesunate is highly effective in the second and third trimester. Both should be given intravenously. Once patients can tolerate oral medication, they should complete a full course (6 doses) of artemether-lumefantrine (or 7 days of oral quinine plus clindamycin).
- Obstetric advice should be sought early.
- The role of early caesarean section for the viable live fetus is unproven.
- Termination of pregnancy is generally not indicated.
- 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 (maintain CVP <5 cm H_2O). ARDS commonly occurs several days after treatment is initiated.
- 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 <5 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 over 5 kg in body weight with uncomplicated malaria, recommended treatment is artemether-lumefantrine or quinine plus clindamycin. As children have a higher risk of developing complicated malaria, they should ideally be admitted for treatment under close supervision.

For children ≤5 kg body weight with uncomplicated malaria the treatment of choice is quinine plus clindamycin. This is because of the risk of rapid development of complications. 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.

Children who are vomiting but who have no other indications of severe malaria should be given the recommended maintenance doses (10 mg/kg) of parenteral quinine until the child can take medication orally. Particular care must be taken to ensure that the correct dosage according to body weight is administered. Once oral intake is confirmed then switch to either artemether-lumefantrine or quinine plus clindamycin (depending on the child's age).

8.2.2 Managing severe malaria in young children

Intravenous quinine is indicated for severe malaria in children and the loading dose of 20 mg/kg must be used. Particular care must be taken to ensure that the correct dosage is administered according to body weight. Where intravenous quinine is not promptly available, or cannot be given safely, initial administration of quinine by deep intra-muscular 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;
- Children who present with shock and acidosis should be given a bolus (20 ml/kg) of fluid, either colloid (plasma) OR crystalloid (Ringers lactate, or normal saline if this is unavailable);
- 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.

Future treatment options: Artemisinin derivatives have been shown to be safe and highly effective in children with severe malaria and multidrug-resistant malaria. Pre-referral treatment with rectal artesunate has been shown to reduce mortality in children being transferred to a hospital from a primary healthcare facility where parenteral treatment

is not safely available. Rectal artesunate is not yet registered for use in South Africa. Intravenous artesunate is currently only authorised for use in adults (on a named patient basis under Section 21 of the Medicines and Related Substances Act in South Africa), but is being evaluated for the treatment of severe malaria in African children. When these products become available they are expected to provide a safer and possibly more effective alternative to quinine.

8.3 Malaria and HIV/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, since this is where HIV prevalence is high, particularly in rural areas and where the malaria burden is mostly in adults due to the unstable malaria transmission precluding their acquiring immunity. Substantial interaction between malaria and HIV/AIDS occurs at many levels:

- Overlap of symptoms of the two diseases, especially fever, may result in HIV-positive patients with malaria presenting late to health facilities and the diagnosis of malaria being missed;
- Although acute malaria causes a temporary increase in replication of HIV and hence in plasma viral load, there is no evidence that malaria has a substantial effect on the clinical progression of HIV infection, HIV transmission or response to antiretroviral treatment;
- HIV-infected individuals who live in areas of stable malaria transmission and are thus expected to be malaria semi-immune, are at increased risk of symptomatic parasitaemia and/or may exhibit higher levels of peripheral parasitaemia than semi-immune adults who are HIV-negative.

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 an increased risk of anaemia, delayed parasite clearance and increased failure rates.

- Patients with HIV infection who develop malaria should receive the recommended antimalarial regimens, although more closely monitored, to ensure an adequate response.
- There are limited data regarding interaction of antimalarials with antiretroviral drugs. Pharmacological interactions between certain antiretrovirals (ARVs) and antimalarial drugs are theoretically possible and might lead to toxicity or sub-therapeutic drug levels.

- Patients receiving protease inhibitors and the NNRTI delavirdine should avoid halofantrine;
- HIV-infected children receiving artesunate plus amodiaquine are at increased risk of neutropenia, particularly if taking zidovudine;
- Hepatotoxicity developed in healthy volunteers given artesunate plus amodiaquine and efavirenz

(Note: neither halofantrine nor amodiaquine is recommended for malaria treatment in South Africa).

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/AIDS and malaria should be admitted for treatment and close monitoring at the highest level of care available, preferably a level 2 or level 3 hospital.

- As HIV progresses and immunosuppression 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 considered, e.g. a third generation cephalosporin.
- Electrolyte disturbances are common and close monitoring is essential.

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ANNEX 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

ANNEX 1: Assessment of the Level of Consciousness

Blantyre Paediatric Coma Scale

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

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