Guidelines for Management of **Malaria** in Zimbabwe

Diagnosis & Management of Uncomplicated and Severe Malaria

MINISTRY OF HEALTH AND CHILD CARE
ZIMBABWE

REVISED JUNE 2015

Foreword

IN ZIMBABWE, MALARIA continues to be a major public health problem. Over half of the population of approximately 13 million is at risk of contracting malaria. However important milestones have been achieved over the recent years; around 500,000 cases and between 400 to 500 deaths are being recorded annually, from an average of 1.5 million cases and 1,000 deaths annually five to 10 years ago. Various strategies are in place to prevent and control malaria. Case management is one of the extremely important strategies alongside integrated vector control, prevention of malaria in pregnancy, social and behaviour change communication, epidemic preparedness and response, monitoring and evaluation and operational research.

Malaria is undergoing an epidemiological transition and in response to this changing epidemiology and transmission patterns, Zimbabwe's malaria control strategy is similarly evolving. The National Malaria Strategic Plan aims to have reduced transmission from 22 cases per 1,000 population in 2012, to 10 per 1,000 in 2017, while deaths are targeted to be reduced to near zero. Currently, seven districts in the country are implementing malaria pre-elimination activities, and the aim is to increase these to approximately one-third of the country by 2017.

In 2008, Zimbabwe changed its malaria treatment policy following wide spread resistance to Chloroquine and Sulphadoxine/Pyrimethamine to more efficacious anti-malarial medicines for treating uncomplicated malaria. The first-line treatment for uncomplicated malaria is currently an Artemisinin-based combination therapy (ACT) called Artemether-Lumefantrine while the second line is oral Quinine. However in line with the minimum standards advocated for by the Southern African Development Community region (which is slowly moving to elimination of malaria) and the latest World Health Organization guidelines, the country has adopted the introduction of a second-line ACT, namely Artesunate-Amodiaquine.

Oral Quinine will remain an alternative second line medicine. Given the evidence on the enhanced efficacy of parenteral Artesunate over Quinine as treatment for severe malaria, case management guidelines are also being adapted to introduce this new treatment, while pre-referral Artesunate suppositories will be used, starting at the community level. In addition, single low-dose Primaquine will be introduced in the treatment regimen of cases in elimination areas to reduce the risk of mosquitoes obtaining the parasites from infected persons.

Malaria case management is guided by treatment guidelines, which are a set of instructions directing the utilization of anti-malarial medicines in the country. The guidelines are continuously reviewed and updated whenever appropriate by the case management technical subcommittee, which advises the Ministry of Health and Child Care through the National Malaria Control Program on malaria case management issues. The subcommittee directs the development of treatment guidelines and case management policies. The guidelines also stipulate that all suspected malaria cases are to be confirmed with rapid diagnostic tests and/or microscopy before receiving treatment.

It is against this background that the malaria treatment guidelines were developed to guide and standardise the implementation of the malaria treatment policy from rural health centres to central hospitals. The treatment guidelines cover all aspects of malaria case management, including diagnosis, management of uncomplicated and severe malaria, and intermittent preventive treatment in pregnancy. Guidelines for the management of malaria at the community level will be developed from these.

It is my sincere hope that all the health workers will adhere to these guidelines in the management of malaria and prevent unnecessary suffering and loss of lives.

Brigadier General (Dr) G. Gwinji
Secretary for Health and Child Care

Photo: PSI/ E. Gaus

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Definition of Abbreviations and Acronym

ACT	Artemisinin-based combination therapy
AL	Artemether-Lumefantrine
ASAQ	Artesunate (AS)-Amodiaquine (AQ) Co-formulated (ASAQ)
DOT	Directly Observed Therapy
HRP2	Histidine rich protein 2
IM	Intramuscular
IV	Intravenous
P. falciparum	*Plasmodium falciparum*
pLDH	Parasite lactate dehydrogenase
RDT	Rapid diagnostic test

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Malaria is a major public health problem in Zimbabwe with about 50% of the population living in risk areas.

Photo: PSI/ E. Gaus

Background Information

MALARIA is a disease caused by infection with the parasite of the genus *Plasmodium.* This occurs when one is bitten by an infected female *Anopheles* mosquito (the vector). There are two important vector species responsible for transmission of malaria in Zimbabwe. These are *Anopheles gambiae* and *Anopheles fenustus.* The most common infection in Zimbabwe is with the parasite species *Plasmodium falciparum (P. falciparum).* There are other species of parasites that are not common in this country such as *Plasmodium vivax, malariae, ovale* and *knowlesi.* Infections by these malaria parasites may be acquired if one travels to countries where these parasites are found. *P. falciparum* is the most common cause of severe malaria, but *vivax* and *knowlesi* can also cause severe disease.

Malaria is a major public health problem in Zimbabwe with about 50% of the population living in malaria transmission areas. It accounts for 20 to 30% of outpatient attendances and 12% of inpatients. The most effective control and prevention strategy for malaria is through prevention of mosquito bites (vector control and personal protection/prevention strategies). The peak transmission period is between the months of November and April. Malaria incidence in Zimbabwe has progressively declined over the last decade from 155 cases/1,000 population in 2003 to 29/1,000 in 2013. Vector control measures and appropriate case management through deployment of rapid diagnostic tests (RDTs) and efficacious medicines that impact transmission enabled this change. It is therefore critical that when patients contract malaria, proper case management is instituted as this is part of malaria control.

The most effective prevention for malaria is through prevention of mosquito bites

Malaria can rapidly deteriorate if not promptly diagnosed and treated

Malaria can rapidly deteriorate from uncomplicated to severe disease if it is not promptly diagnosed and appropriately treated. The appropriate management of severe malaria is very crucial as mortality from untreated severe malaria is almost universal. Vulnerable groups such as children under five years, pregnant women and those immunocompromised are at high risk of severe morbidity and mortality from malaria if not timeously and properly managed. Inappropriate use of first line medicines for malaria over years has contributed to the emergence of Chloroquine resistant strains of *P. falciparum* in most parts of Asia and Sub-Saharan Africa, including Zimbabwe.

Thus the approach to the diagnosis of malaria has shifted emphasis from clinical diagnosis, using symptoms and signs, to infection confirmation by RDT in the outpatient setting and blood slide microscopy on all patients requiring admission or re-presenting within two weeks of treatment. A confirmed parasitological diagnosis prevents the unnecessary treatment of those who do not have malaria thereby allowing an alternative diagnosis to be sought early. Microscopy for inpatients who are mostly deemed to have severe malaria also enables quantifying the parasite density, identifying the blood stages, including the presence of gametocytes, and speciating the type of parasite involved. Other blood parasites that cause similar symptoms to malaria, such as the haemolymphatic stage of Human African Trypanosomiasis, can be found on a peripheral smear in patients who reside or have visited areas where transmission of both parasites occurs. Therefore an approach that favours parasitological confirmation makes the management of malaria safe and cost effective.

These guidelines have been made for clinicians to fulfil the following objectives:

1. 

To standardise the approach to diagnosis and management of malaria

2. 

To provide information on the appropriate medicines, doses and supportive management of both uncomplicated and severe malaria

3. 

To provide health workers with a quick reference text for the management of uncomplicated and severe malaria

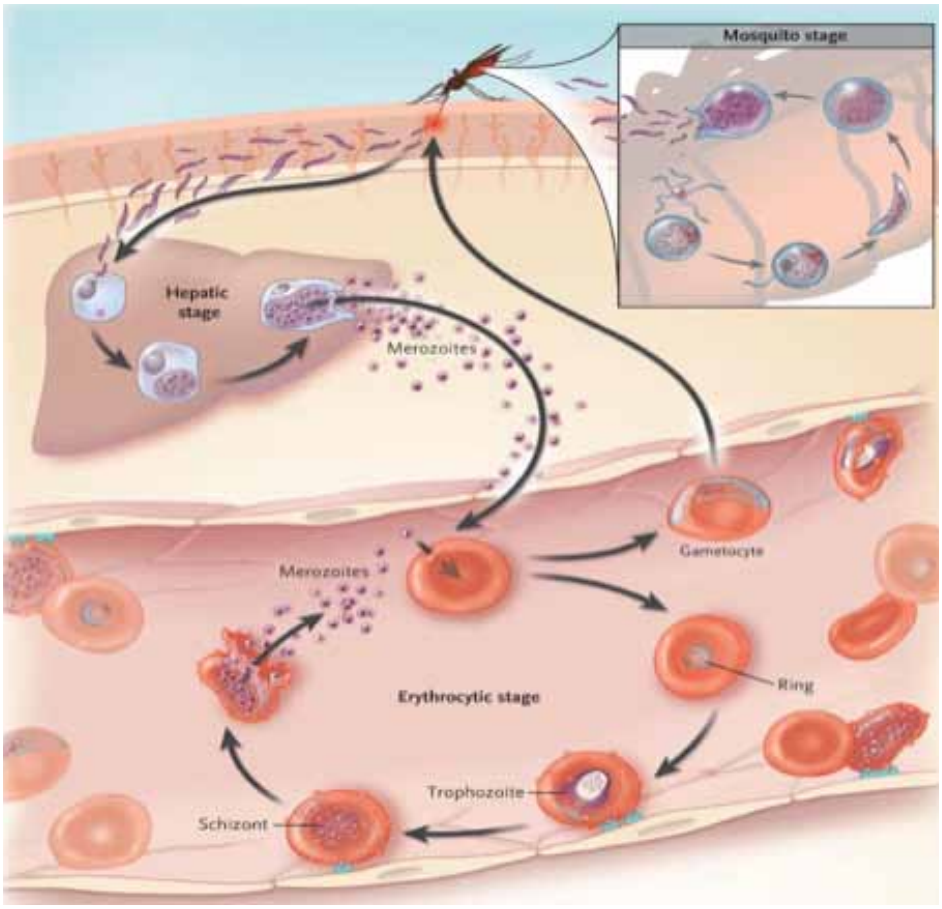
PATHOLOGY

When an infected female *Anopheles* mosquito bites a person during a blood meal, it injects sporozoites into the blood stream. These sporozoites circulate to the liver where they invade hepatocytes. In the liver, the sporozoites develop into merozoites after a brief period during which the person has no symptoms (one week to two weeks for *P. falciparum*). The merozites are released into the circulation and these invade red cells (erythrocytes) where they appear as ring forms of trophozoites that further develop to schizonts. The schizonts lyse (rupture) red cells releasing merozoites that infect more red cells. This cycle is the asexual erythrocytic stage of the infection. This invasion and subsequent repeated lysis of red cells during this asexual stage is responsible for the symptoms of malaria.

The invasion and subsequent repeated lysis of red cells during the asexual stage is responsible for the symptoms of malaria

Some parasites do not continue with the asexual cycle but instead develop into gametocytes that can be taken up by a mosquito during a meal, resulting in sexual reproduction in the vector to produce more infectious sporozoites.

FIGURE 1 Life Cycle *P. falciparum*



Source: NEJM 2008

Malaria Diagnosis

MICROSCOPY VERSUS RAPID DIAGNOSTIC TESTS (RDTS)

Microscopy is still the gold standard for the diagnosis of malaria

Microscopy is still the gold standard for the diagnosis of malaria; however it requires technical expertise and can be time consuming when case loads are high. Present day RDTs have a high specificity and sensitivity, approaching that of microscopy. They are based on the detection of malaria parasite proteins in patients' blood. The tests currently in use in Zimbabwe are based on detecting histidine rich protein 2 (HRP2), which is stable at high temperatures and only detects *P. falciparum,* and parasite lactate dehydrogenase (pLDH) that will also detect the other *Plasmodium* spp. (*vivax, ovale* and *malariae*). However these tests remain positive for two weeks after treatment. *(see Treatment of Uncomplicated Malaria)*

Advantages of a Confirmed Parasitological Diagnosis over Clinical Diagnosis:

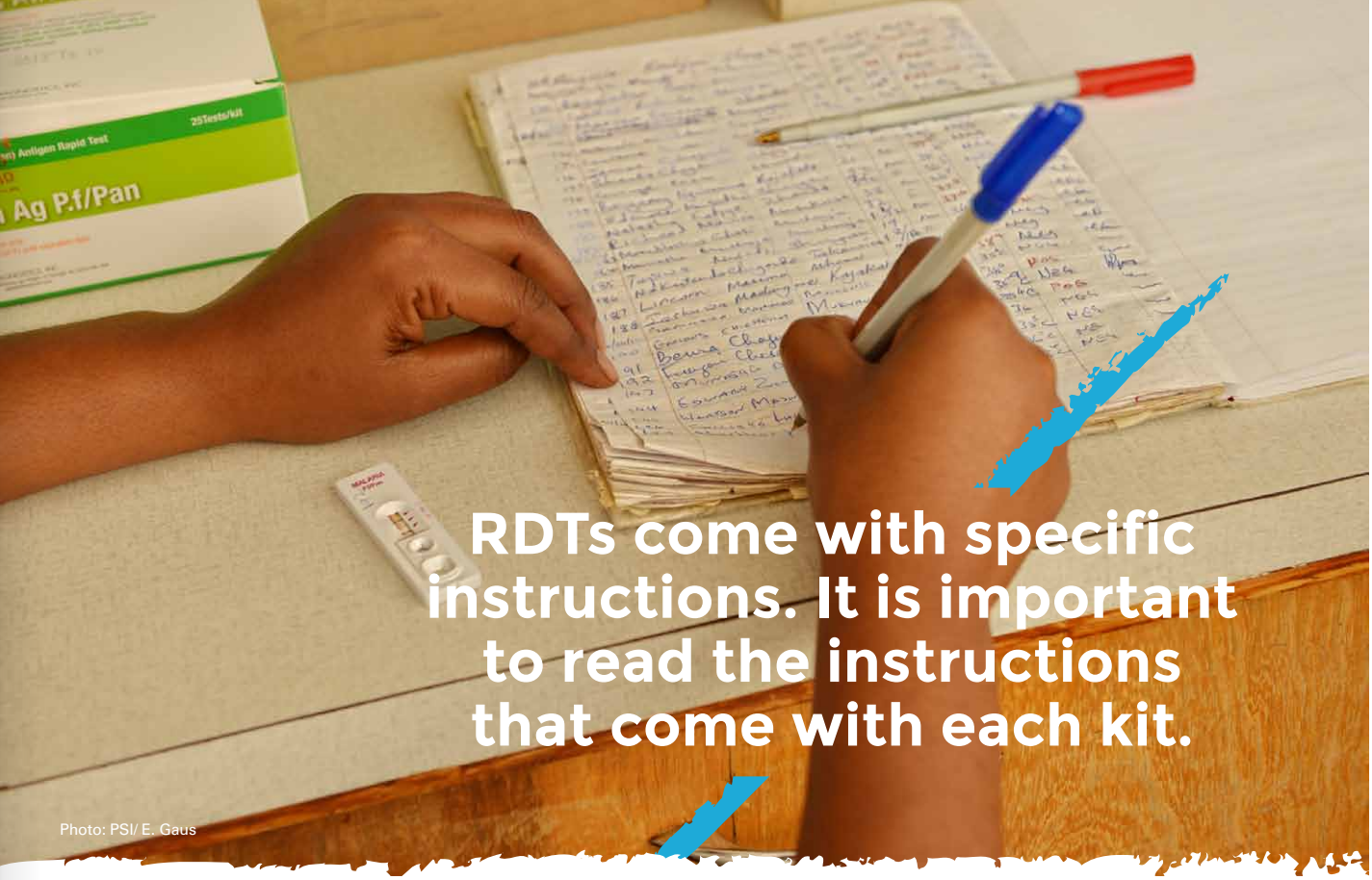
- Cost-effective, particularly if health workers believe negative results.
- Enables alternative diagnoses to be sought early.
- Prevents unnecessary exposure to medicines and the associated side effects.
- Reduces chances of malaria parasite resistance to medicines through selection pressure.
- Leads to more accurate health information by reducing over-diagnosis of malaria.
- Enables confirmation of treatment failures.

Where RDTs Should be Deployed:

- To trained community-based health workers.
- All rural clinics.
- District and provincial hospitals.
- Central hospitals in emergency departments.
- Private health institutions including in emergency departments.

Microscopy Should Still be Used for:

- All admitted malaria patients to improve follow up.
- Confirming co-infections.
- Those with a recent travel history to countries where other malaria species (e.g. *P. vivax*) are reported.
- Suspected treatment failure.
- Patients who have received treatment within the preceding two weeks.



RDTs come with specific instructions. It is important to read the instructions that come with each kit.

Photo: PSI/ E. Gaus

PERFORMING AN RDT

As indicated, there are various types of RDTs and each comes with specific instructions. It is therefore important to read the instruction manual/insert that comes with each kit to know how to collect and apply the patient's blood and the kit's Buffer solution to the kit's cassette or card. Two types of RDTs are currently approved for use in Zimbabwe. These are the *P. falciparum* band specific for *P. falciparum* (HRP2) and the Pan band for *P. vivax*, *ovale* and *malariae* (pLDH).

The RDT is based on immunochromatography where antibody-antigen (malaria) complex is transported with the aid of a Buffer solution along nitrocellulose paper for another antibody-antigen-antibody reaction in the test window. When there is a positive antibody-antigen reaction with the antibody imbedded on the nitrocellulose paper, a coloured band will appear in the test window.

Specific Steps to Performing an RDT:

1. Assemble all the supplies you will need, including:

- **a)** Test packet
- **b)** Alcohol swab
- **c)** Sterile lancet
- **d)** Examination gloves
- **e)** Buffer
- **f)** Watch or clock to use as a timer

2. **Place all these supplies on a table.**

3. **Check for the expiry date and do not use if the date has passed.**

4. **Put on a new pair of examination gloves. This protects self and patient from possible infection with blood-borne diseases, including HIV-AIDS.**

5. **The following should be in the test packet:**

a) The blood transfer device (loop, capillary tube, pipette, or other) is used to collect blood and transfer it to the test cassette or card.

b) The desiccant sachet protects the test from humidity before the packet is opened. (Discard once the packet is opened.)

c) The test cassette is used to conduct the test.

6. **Write the patient's name on the cassette.**

7. **Clean the patient's fourth finger with alcohol swab, because that finger:**

a) Is least used.

b) Is least inconvenient if finger becomes sore.

c) Is less likely to be infected.

d) May have thinner skin.

8. **Allow cleaned finger to air dry. (Don't blow or wipe finger.)**

9. **Open lancet and prick the finger, preferably towards the side of the pulp (ball) of the finger. (Pricking the midline or tip is more painful.)**

10. **Check to be sure the finger-prick will produce enough blood, and then discard the lancet in the sharps container.**

a) Discard the lancet in an appropriate sharps container immediately after using it.

b) Never set the lancet down before discarding it.

c) Never discard the lancet in a non-sharps container.

d) Never use a lancet on more than one person.

11. **Ensure a good-sized drop of blood is on the finger before collecting.**

12. **Collect the droplet of blood using the blood collection device.**

13. **Collect just to the mark. Do not lift the tip of the pipette or tube as this will allow air bubbles to enter.**

14. **Add the drop of blood to the lower well (hole). Do not deposit blood on the plastic edges of the well.**

15. **Discard the blood collection device after use.**

16. **Add exactly the correct number of drops of Buffer. Hold the bottle vertically.**

17. **Wait the correct time per test instructions (e.g. 15 minutes) after adding Buffer before reading test results.**

18. **Remove and discard your gloves at this time.**

Reading an RDT

Wait for 15 to 30 minutes and read the results as follows *(Figure 2)*:

− **Negative** for *P. falciparum* malaria: Only one pink coloured band appears in the window 'C'.

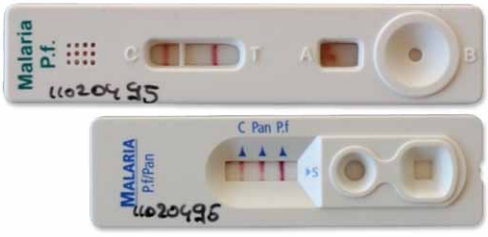
\+ **Positive** for *P. falciparum* malaria: Two bands appear, one on the control 'C' and another one on 'P.f' in the test window.

\+ **Positive** for mixed infection (*P. falciparum*, *vivax*, *ovale*, *malariae*): All three bands appear in the test window ('C', 'P.f' and 'Pan').

\+ **Positive** for non *P. falciparum* infection: Two bands appear on 'C' and 'Pan'.

\ **Invalid:** No control band appears on device. Repeat the test with a new device, making sure the procedure is properly followed.

FIGURE 2 Two and Three Line RDTs Positive for *P. falciparum* or Mixed Infection, Respectively



Uncomplicated Malaria

INTRODUCTION

Medicines should be easily administered, have a fast therapeutic response with minimal side effects

The effective and correct treatment of uncomplicated malaria is critical for the following reasons:

- To effect complete cure of the infection
- To prevent progression of the infection to severe, complicated disease and mortality
- To reduce infection transmission in the community by reducing the infectious reservoir of parasite carriers
- To prevent emergence of resistant malaria parasites, thus safeguarding the current anti-malarial medicines

The medicines used for the treatment should be safe, tolerable, easily administered, and have a fast therapeutic response with minimal side effects.

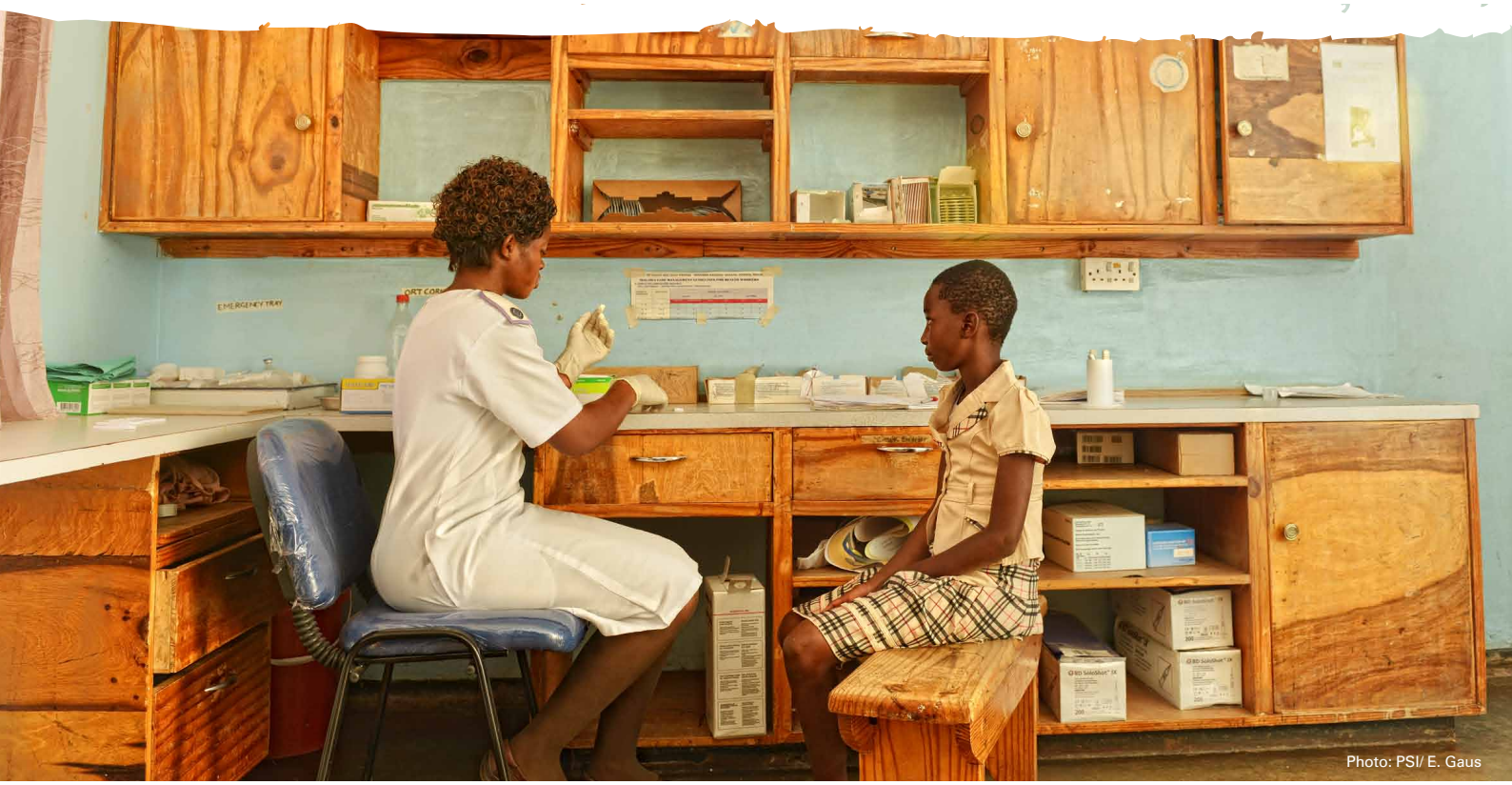


Photo: PSI/ E. Gaus

CLINICAL SUSPICION OF UNCOMPLICATED MALARIA

The diagnosis of malaria is dependent on an appropriate history and symptoms suggestive of malaria and appropriate clinical signs supporting the diagnosis.

Diagnosis of malaria is dependent on appropriate history, symptoms and clinical signs supporting it

Symptoms Suggestive of Uncomplicated Malaria Include the Following:

- Fever
- Chills/rigors
- Headache
- Nausea/anorexia
- Joint pains
- Lethargy/malaise
- Sweating

Signs of Malaria May Include:

- Fever, usually above 37.5 degrees Celsius.
- An enlarged spleen, especially in children and in adults without immunity to malaria.

A complete history should be taken, in addition to specifically enquiring about:

- The above symptoms.
- Travel to malarious areas within one to six weeks or usual residence in malaria area.
- Pregnancy, as pregnant women are more prone to contracting malaria and tend to easily progress to severe malaria.
- HIV sero-positivity, as patients with advanced immunosuppression are more likely to contract malaria and to progress to severe disease.
- Nutrition, as malnourished children might not have a fever and will most likely present with non-specific complaints.
- Previous treatment of malaria.

A clinical suspicion of uncomplicated malaria should be made if there is fever and other suggestive symptoms as listed above, in addition to:

- Enlarged spleen in the non-immune, semi-immune adults or in children.
- Absence of signs of severe disease.

CONFIRMATION OF MALARIA

Once malaria is suspected an RDT must be performed for confirmation

Once malaria is suspected, then an RDT must be performed for confirmation, as below.

- **If the RDT is positive,** then the patient has malaria.*
- **If the RDT is negative a**nd malaria is still suspected, perform microscopy.
- **If the smear is negative,** consider other causes of fever.

Re-assess the patient and repeat the test if other causes of fever are not found and there is persistence of symptoms.

Please note: *Confirmation of malaria does not necessarily mean the absence of other diseases that may also cause fever.*

**If the patient has been treated for malaria in the previous two weeks, it is possible that the RDT will be positive due to lingering antibodies, not an active new infection. Therefore it is important to ask about previous, especially recent, treatment for malaria. If the patient has received an antimalarial medicine within the previous two weeks, refer him/her to a centre that can conduct microscopy. These patients need to have a diagnosis confirmed with a positive blood slide. If the slide is positive, the treatment will depend on the type of antimalarial the patient had recently received.*

TREATMENT

Treatment should be given to those patients where the diagnosis of malaria has been confirmed by a positive RDT or slide for malaria. This is first and foremost a good clinical practice that ensures patients are investigated for other causes of illnesses if negative for malaria. It also safeguards against the misuse of the anti-malarial medicines for treating those who do not need them and prevents subsequent development of resistant parasites in the community as a result of overuse of anti-malarial medicines. Confirmation of the diagnosis of malaria also safeguards against giving the patient the wrong treatment.

1st First Line Treatment of Uncomplicated Malaria: Artemether-Lumefantrine (Coartemether)

Each tablet of co-formulated Coartemether contains Artemether 20 mg and 120 mg Lumefantrine.

TABLE 1 Treatment Schedule for Coartemether: Children ≥5 kg Body Weight (>Six Months) and Adults

WEIGHT IN KILOGRAMS (KG)	AGE IN YEARS	DOSAGE (NUMBER OF TABLETS TAKEN ORALLY)					
		DAY ONE		DAY TWO		DAY THREE	
		START DOSE	AFTER 8 HOURS	AM	PM	AM	PM
5 - <15	6 months - <3 years	1	1	1	1	1	1
15 - <25	3 - <8	2	2	2	2	2	2
25 - <35	8 - <14	3	3	3	3	3	3
≥35 & Adults	≥14	4	4	4	4	4	4

- Coartemether is taken twice a day for three days, for a total of six doses.
- Always ensure that a full course of three days (six doses) is taken, even if the patient is feeling better.
- If the initial dose (stat dose) of Coartemether is vomited within 30 minutes, repeat the dose.
- ***If vomiting persists, treat as severe malaria.***
- To ensure adherence, it is desirable to give the initial dose (stat dose) as a Directly Observed Therapy (DOT).
- If there is no improvement after 48 hours, confirm possible treatment failure with microscopy before giving second line treatment for uncomplicated malaria. *(see Second Line Treatment for Uncomplicated Malaria)*
- If there is reappearance of signs and symptoms suggestive of malaria after the patient initially recovered and within 28 days of treatment, transfer to a centre where there is microscopy for testing and treatment with second line if testing confirms malaria.

2nd Second Line Treatment of Uncomplicated Malaria: Artesunate (AS)-Amodiaquine (AQ) Co-formulated (ASAQ)

Each tablet of ASAQ may contain Artesunate 25 mg and Amodiaquine 67.5 mg base, Artesunate 50 mg and Amodiaquine 135 mg base OR Artesunate 100 mg and Amodiaquine 270 mg base. Dosage is 4 mg/kg body weight Artesunate and 10 mg/kg Amodiaquine base taken orally once daily for three days.

TABLE 2 Treatment Schedule for Second Line Therapy (ASAQ) for Patients ≥5 kg Body Weight or Over Two Months

WEIGHT RANGE IN KILOGRAMS	APPROXIMATE AGE RANGE	DOSAGE	DAY 1	DAY 2	DAY 3
5 - <9	>2 months - <12 months	25 mg Artesunate 67.5 mg Amodiaquine	1 tablet	1 tablet	1 tablet
9 - <18	1 year - <6 years	50 mg Artesunate 135 mg Amodiaquine	1 tablet	1 tablet	1 tablet
18 - <36	6 years - <14 years	100 mg Artesunate 270 mg Amodiaquine	1 tablet	1 tablet	1 tablet
≥36	14 years and above	100 mg Artesunate 270 mg Amodiaquine	2 tablets	2 tablets	2 tablets

- If there is a weight age disparity, the weight of the patient should be used for dosing.
- ASAQ should not be taken with a fatty meal.
- If unable to swallow tablets (this does not include those unable to swallow due to severe malaria), the tablet can be crushed and dissolved in water.
- Should there be vomiting within a half an hour of dosing, another dose of ASAQ should be repeated.
- The first dose should be given as DOT.
- If there is no improvement after 48 hours, repeated vomiting of the medication or symptoms progress, treat as severe malaria.

CAUTION

- ASAQ should not be co-administered with Efavirenz.
- ASAQ should be administered with caution in patients taking Zidovudine since both have overlapping side-effects (Neutropenia – Pancytopenia). Use only if there is no safer alternative, and carefully follow up.
- ASAQ should not be used in the first trimester of pregnancy.
- ASAQ can be used during breastfeeding.
- In patients who cannot tolerate ASAQ or where ASAQ is contraindicated, the second line treatment of choice is oral Quinine with Clindamycin or Doxycycline. *(see Alternative Second Line Treatment of Uncomplicated Malaria)*

ALTERNATIVE 2nd

Alternative Second Line Treatment of Uncomplicated Malaria

For adults unable to tolerate ASAQ, give Oral Quinine with Doxycycline or Clindamycin given for a total of seven days.

Each Quinine tablet contains Quinine sulphate 300 mg.

TABLE 3 Treatment Schedule for Alternative Second Line Therapy: Adults

MEDICINE	DOSE	DOSING FREQUENCY	DURATION
Quinine tablet	600 mg	Every 8 hours	7 days
Doxycycline tablet or Clindamycin tablet	100 mg	Once daily	7 days
	300 mg	Every 8 hours	7 days

- If for any reason Quinine is given as monotherapy (without Doxycycline or Clindamycin), it should be given for a total of seven days.
- Doxycycline is contraindicated in children below age of eight years and in pregnant women.
- Clindamycin is used in place of Doxycycline in pregnancy during the first trimester and children under the age of eight years. *(see Treatment in Special Groups: Uncomplicated Malaria in Pregnancy)*

SPECIAL GROUPS

Treatment in Special Groups:
Uncomplicated malaria in infants and Pregnant Women not eligible for treatment with Coartemether

TABLE 4 Treatment of Infants <5 kg Body Weight

MEDICINE	DOSE	DOSING FREQUENCY	DURATION
Quinine (Oral)	10 mg per kg body weight	Every 8 hours	7 days

TABLE 5 Treatment Schedule for Uncomplicated *P. falciparum* Malaria in Pregnancy

TRIMESTER/APPROXIMATE GESTATION								
1ST TRIMESTER- BEFORE QUICKENING	2ND TRIMESTER AFTER QUICKENING AND 3RD TRIMESTER							
			DOSAGE (NUMBER OF TABLETS TAKEN ORALLY)					
			DAY 1		DAY 2		DAY 3	
MEDICINE	MEDICINE		STAT	AFTER 8 HRS	AM	PM	AM	PM
Oral Quinine 600mg and Clindamycin 300mg tablets every 8 hrs for 7 days	1st line	Artemether 20mg and Lumefantrine 120mg (Coartemether) tablets	4	4	4	4	4	4
	2nd line	Artesunate (AS)- Amodiaquine (AQ)	200 mg AS 540 mg AQ		200 mg AS 540 mg AQ		200 mg AS 540 mg AQ	

SUPPORTIVE THERAPY

Supportive therapy appropriate for age to relieve symptoms such as headache, fever and nausea may be given in addition to the above anti--malarial medicines. Take note that medicines such as Aspirin may not be appropriate in children; however Paracetamol or paediatric formulations of Ibuprofen can be prescribed. Consult *Essential Medicines List of Zimbabwe* for further information.

Photo: PSI/ E. Gaus

TREATMENT OF UNCOMPLICATED MALARIA IN ELIMINATION AREAS

The current success registered in the control of malaria has been due to aggressive vector control interventions and the use of rapidly acting and efficacious Artemisin-based combination therapies (ACTs) that have an effect on *P. falciparum* gametocytes. Artemisinins particularly target and clear the asexual blood stages of the parasite that are responsible for clinical disease and death. The Artemisinins also have action against young immature gametocytes leaving mature gametocytes persistent in the circulation for possible uptake and infection of mosquitos thus enabling malaria transmission to continue.

Medicines against gametocytes will have a profound impact on reducing new malaria infections in areas of low malaria transmission

In areas of low malaria transmission where symptomatic infections contribute substantially to malaria transmission, the use of medicines against gametocytes will have a profound impact on reducing new malaria infections. Primaquine, an 8-aminoquinoline, has strong gametocytocidal properties superior to all current anti-malarial medicines in use. Primaquine is particularly effective against the mature gametocytes and when used in combination with ACTs reduces the duration of gametocyte carriage.

Gametocyte concentrations that are below levels that can be detected by ordinary microscopy have been shown to persist 14 days after successful treatment of clinical malaria. Effectively malaria transmission is possible from these “cured cases.” Treatment protocols that have ACT together with Primaquine clear the circulating gametocytes that persist after ACT treatment alone, thereby rendering most patients gametocyte free by day 14.

Primaquine can cause severe haemolysis when administered to patients with G6PD deficiency

Primaquine has the potential to cause severe haemolysis when administered to patients with Glucose-6-phosphate dehydrogenase (G6PD) deficiency. Like other haemoglobinopathies, G6PD deficiency in carriers has some protective effect against malaria. It is prevalent in areas where malaria transmission occurs, including most of Sub-Saharan Africa. The actual incidence and severity of G6PD deficiency in Sub-Saharan Africa, including Zimbabwe, has not been fully established. The standard dose of Primaquine for elimination of gametocytes in *P. falciparum* malaria infection is 0.75 mg/kg body weight when administered to patients without G6PD deficiency.

Due to the challenges of deploying facilities for G6PD testing in resource constrained areas, the World Health Organization (WHO) has recommended the use of a reduced dose of **Primaquine 0.25 mg base/kg body weight single dose** to ameliorate the chances of clinically significant haemolysis where G6PD assay has not been done.

The following patients should be given Primaquine 0.25 mg base/kg body weight with first dose of ACT:

Uncomplicated malaria:

- Above one year old
- Body weight above 10kg
- Not pregnant

Do not give Primaquine to the following:

- Patients with severe malaria *(see Severe Malaria for definition)*
- Pregnant and breastfeeding patients
- Known history of G6PD deficiency
- Pallor or existing anaemia, haemoglobin <8gm/dl
- Patients on medications likely to cause haemolysis
- Patients on medicines likely to cause bone marrow suppression
- Patients taking Zidovudine

Dosage Schedule for Primaquine:

Primaquine comes as a tablet: 26.3 mg Primaquine phosphate equivalent to 15 mg Primaquine base.

- Mix 15 ml water with one crushed tablet of 15 mg Primaquine base, making a suspension of 1 mg/ml.
- The dose of Primaquine should be given with the first dose of ACT.

TABLE 6 Dosage Schedule for Primaquine and Coartemether by Weight for Patients 10 - <30 kg

WEIGHT IN KILOGRAMS (KG)	DOSE (1 MG/ML OF PRIMAQUINE SOLUTION) + COARTEMETHER
10 - <14	3 mls + 1 tablet Coartemether stat
14 - <18	4 mls + 1 tablet Coartemether stat for <15 kg 4 mls + 2 tablets Coartemether for 15 - <18 kg
18 - <22	5 mls + 2 tablets Coartemether stat
22 - <26	6 mls + 2 tablets Coartemether stat for 22 - <25 kg 6 mls + 3 tablets Coartemether stat for 25 - <26 kg
26 - <30	7 mls + 3 tablets Coartemether stat

- **Patients ≥30 kg can be given treatment in tablet form**

TABLE 7 Dosage Schedule for Primaquine and Coartemether by Weight for Patients ≥30 kg

WEIGHT IN KILOGRAMS (KG)	DOSE (15 MG PRIMAQUINE BASE TABLET) + COARTEMETHER
30 - <41	½ tablet + 3 tablets Coartemether stat for 30 - <35 kg ½ tablet + 4 tablets Coartemether stat for 35 - <41 kg
≥41	1 tablet + 4 tablets Coartemether stat

Adverse effects of Primaquine

Adverse effects are highly unlikely at this lower dose, but closely monitor patients that develop the following as they may be experiencing life threatening haemolysis:

- Back pain
- Dark urine
- Jaundice
- Worsening fever
- Headache with dizziness and breathlessness (symptomatic anaemia)

UNCOMPLICATED NON-*FALCIPARUM* MALARIA

P. vivax, the second most important species causing human malaria, is the dominant malaria species outside Africa. It is prevalent in endemic areas in Asia, Central and South America, Middle East and Oceania. In Africa, it is rare, except in the Horn, and it is almost absent in West Africa. *P. malariae* and *P. ovale* are generally less prevalent, but they are distributed worldwide, especially in the tropical areas of Africa. *P. vivax* and *P. ovale* form hypnozoites (dormant stage), parasite stages in the liver, which can result in multiple relapses of infection weeks to months after the primary infection. Thus, a single infection causes repeated bouts of illness.

The prevalence of non-*falciparum* malaria in Zimbabwe is estimated to be less than 2%. However due to movements of people across countries, especially from the Horn of Africa, it is necessary that health workers are prepared to manage non-*falciparum* malaria.

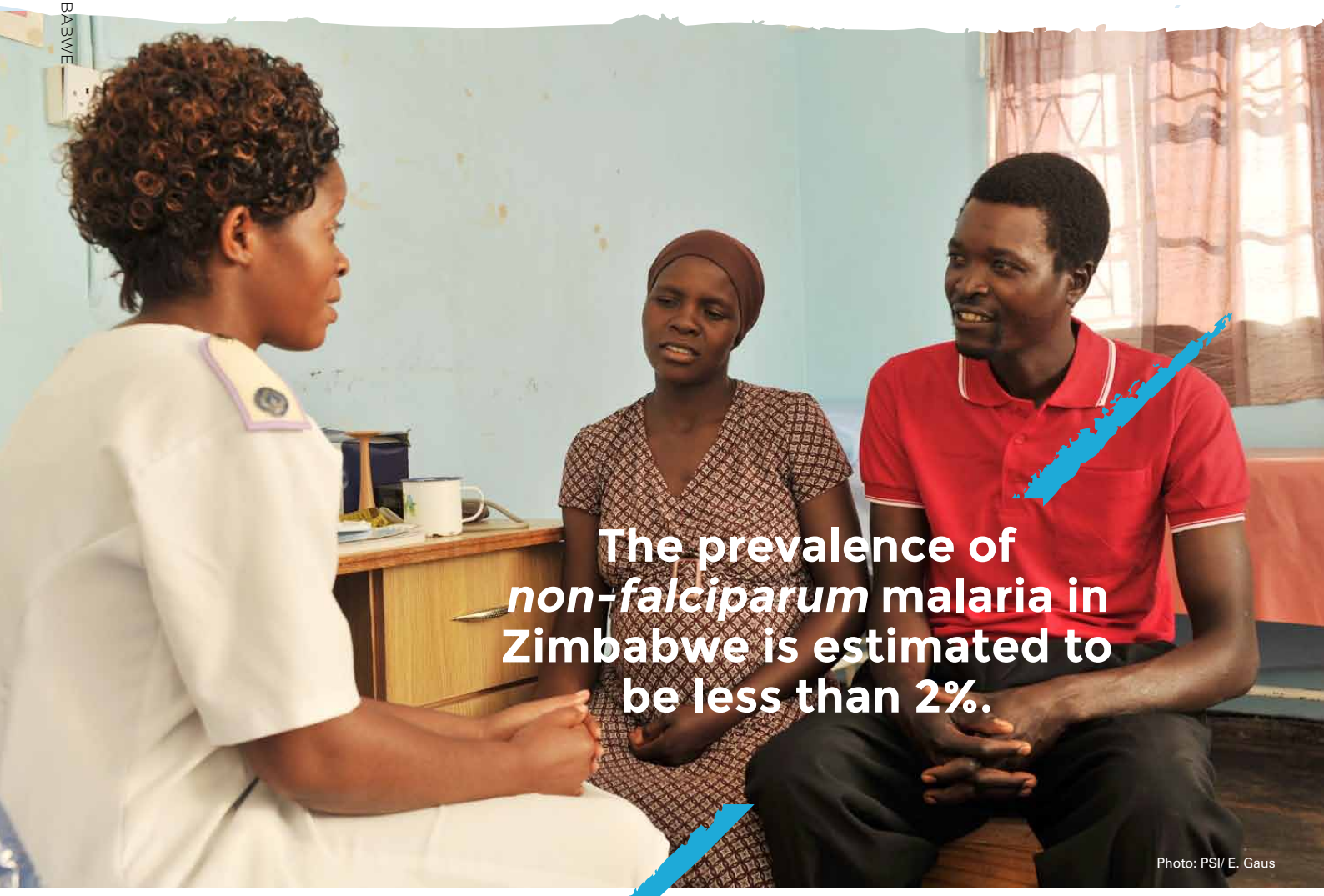


Photo: PSI/ E. Gaus

Diagnosis of Non-*falciparum* Malaria

The clinical features of uncomplicated malaria are not sufficiently specific to allow a clinical diagnosis of the species of malaria infection. Diagnosis of non-*falciparum* malaria must be made by microscopy or a combination (Pan) RDT with good accuracy. Molecular markers for genotyping of *P. vivax* parasites have been developed to assist epidemiological and treatment studies, but are not generally available for routine clinical use.

Diagnosis of non-*falciparum* malaria must be made by microscopy or a combination (Pan) RDT

Treatment of Uncomplicated Non-*falciparum* Malaria

The goal for treatment of *P. vivax* infections is to cure infection and to prevent relapses by clearing hypnozoites from the liver. *P. vivax* remains sensitive to Chloroquine in most parts of the world with exception of few areas. The following are the medicines and guidelines for treatment selection:

Treatment of P. vivax and P. ovale

- Patients WITHOUT G6PD deficiency - Give an ACT (as for *P. falciparum* malaria above) combined with Primaquine, an anti-relapse medicine, at a dose of 0.25 mg base/kg body weight, taken with food once daily for 14 days.
- Patients WITH moderate G6PD deficiency - Give Primaquine at a dose of 0.75 mg base/kg body weight, once a week for eight weeks.
- Primaquine should not be used in patients with severe G6PD deficiency.

Treatment of P. malariae

- Treat as for *P. falciparum* malaria

Treatment for mixed infections of P. falciparum and other Plasmodium species

- Give an ACT along with a 14-day course of Primaquine for mixed infections including *P. vivax* and/or *P. ovale*.
- Treat as for *P. falciparum* malaria if mixed infection includes *P. malariae*.

Severe Malaria

The mortality of untreated severe malaria is almost 100%

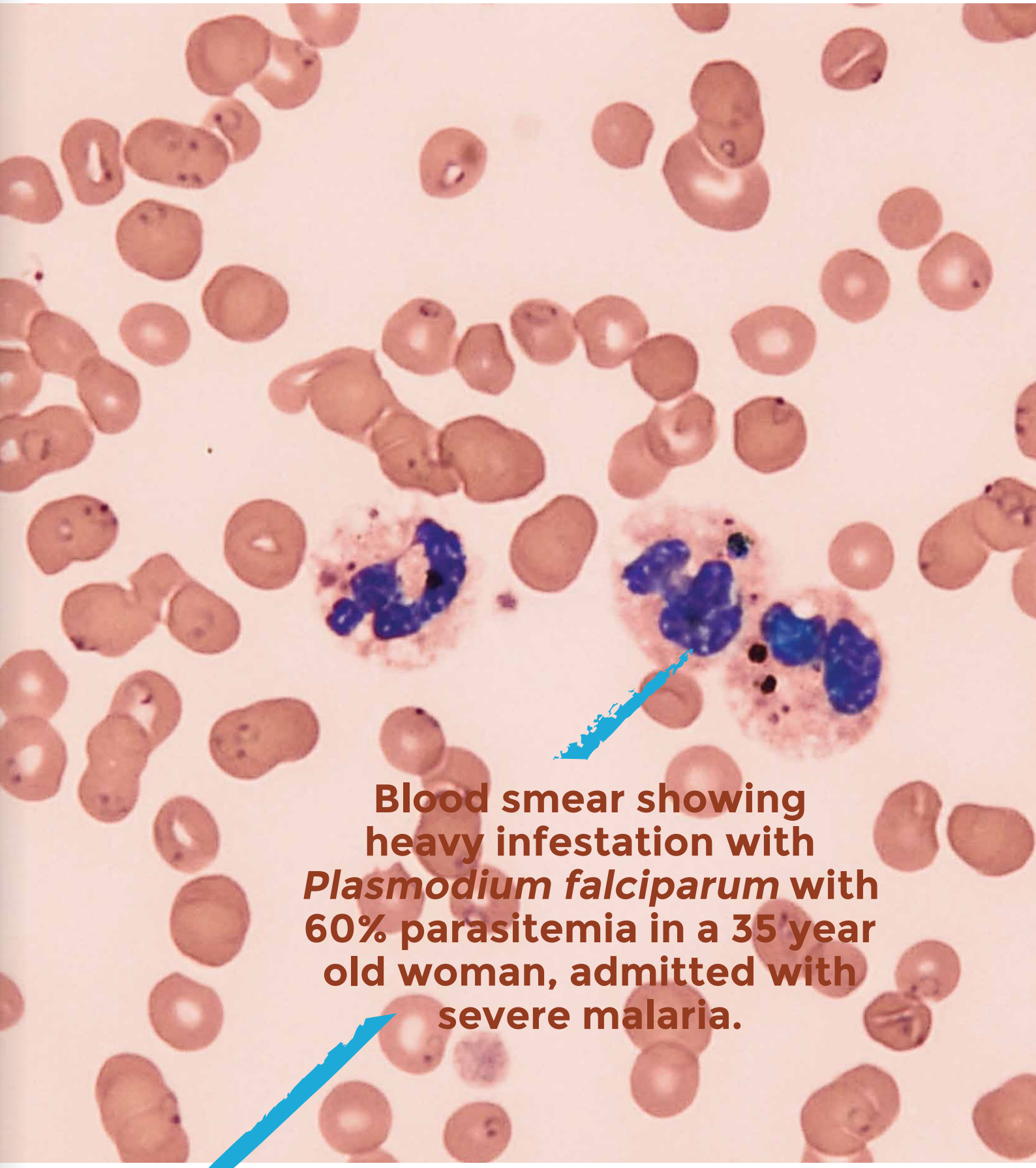
The mortality of untreated severe malaria is almost 100% and death often occurs within a few hours after admission. It is therefore critical that the diagnosis be made early and treatment instituted as soon as possible. Almost any organ system can be affected in severe malaria.

CLINICAL FEATURES OF SEVERE MALARIA

- Impaired consciousness (including unrousable coma)
- Prostration: generalized weakness so that the patient is unable to sit, stand or walk without assistance
- Multiple convulsions: more than two episodes within 24 hours
- Deep breathing and respiratory distress (acidotic breathing)
- Acute pulmonary oedema and acute respiratory distress syndrome
- Circulatory collapse or shock: systolic blood pressure <80mm Hg in adults and <50mm Hg in children
- Acute kidney injury
- Clinical jaundice plus evidence of other vital organ dysfunction
- Abnormal bleeding

TABLE 8 Characteristics of Severe Malaria

CLINICAL MANIFESTATIONS	POOR PROGNOSTIC FEATURES
Physical findings • Prostration • Impaired consciousness • Respiratory distress • Repeated convulsions/fits • Shock/circulatory collapse • Abnormal bleeding • Jaundice • Anuria or Oligouria • Macroscopic haemoglobinuria ("Coca-Cola" urine) • Pulmonary oedema **Abnormal Laboratory results** • Severe normocytic anaemia • Hypoglycaemia • Hyperlactatemia • Metabolic acidosis • Elevated transaminases • Hyperbilirubinaemia • Disseminated intravascular coagulation	**Physical findings** • Coma with extensor posturing • Tachypnoea, laboured respirations • >3 fits in 24 hours • Systolic BP less than 80mm Hg despite volume replacement • Retinal haemorrhage, purpura, ecchymosis • Fluid and electrolytes abnormalities **Abnormal Laboratory results** • Haemoglobin <5gm/dL packed cell volume, Hematocrit <15% • Blood glucose (<2.2mmol/l or <40 mg/dl) • Plasma HCO3 <15mmol/l, blood pH <7.25 • Serum creatinine >265µmol/l • Venous lactate >5mmol/l • Parasiteamia >10% • Transaminases 3 times upper limit • Serum bilirubin >50µmol/l **Radiological Findings** • Pulmonary oedema



Blood smear showing heavy infestation with *Plasmodium falciparum* with 60% parasitemia in a 35 year old woman, admitted with severe malaria.

INVESTIGATIONS

The presence of at least one of the following also indicates severity:

- **Anaemia (Full Blood Count)**
  This is indicated by haemoglobin levels of <5.5gm/dL in patients who normally stay in areas of all-year-round transmission of malaria, and Hb ≤ 7.5gm in patients who are non-immune are significant and require transfusion. The rate of fall of the Hb may be more important than absolute figures on determining transfusion.
- **Hypoglycaemia (Glucometer, Dextrostix or Random Blood Sugar)**
  This is indicated by glucose levels less than 3.4 mmol/l. Actual blood sugars and glucometers are more accurate than Dextrostix.
- **Renal impairment (Urea & Electrolytes)**
- **Hyperparasitaemia (Microscopy)**
  Generally patients who stay in moderate to high transmission areas tend to tolerate high parasite counts in their blood. This is, however, not so in non-immune patients or those who stay in low transmission areas as they rapidly progress to severe malaria. A count of ≥ 10% for patients who stay in moderate to high transmission areas and ≥ 5% for those in low transmission areas is generally accepted as hyperparasitaemia.
- **Acidosis (Arterial blood gases or plasma lactate)**
- **Pulmonary oedema (CXR)**

It is important to realise that the frequency of occurrence of these severe features differ between children and adults. These differences are shown in Table 9.

WARNING SIGNS IN CHILDREN UNDER FIVE YEARS

The most common, most important complications of *P. falciparum* infection in children include the following:

- Cerebral malaria
- Severe anaemia
- Respiratory distress (acidosis) and hypoglycaemia

The following are particularly important signs of severity in children:

- Hyperpyrexia
- Unable to drink or breastfeed
- Persistent vomiting
- Unable to sit or stand
- Fits or convulsions
- Lethargy or unconsciousness

See Appendices 1 and 2 for coma scales that may be used with adults and children to help assess a patient's neurological status. The scales should be repeated to assess patient improvement or deterioration.

TABLE 9 Signs and Symptoms of Severe Malaria in Adults and in Children

SIGN OR SYMPTOM	ADULTS	CHILDREN
Duration of illness	5–7 days	Shorter (1–2 days)
Respiratory distress/deep breathing (acidosis)	Common	Common
Convulsions	Common (12%)	Very common (30%)
Posturing (decorticate/decerebrate and opisthotonic rigidity)	Uncommon	Common
Prostration/obtundation	Common	Common
Resolution of coma	2–4 days	Faster (1–2 days)
Neurological sequelae after cerebral malaria	Uncommon (1%)	Common (5-30%)
Jaundice	Common	Uncommon
Hypoglycaemia	Less common	Common
Metabolic acidosis	Common	Common
Pulmonary oedema	Uncommon	Rare
Renal failure	Common	Rare
CSF opening pressure	Usually normal	Usually raised
Bleeding/clotting disturbances	Up to 10%	Rare
Invasive bacterial infection (co-infection)	Uncommon (<5%)	Common (10%)

TREATMENT

Severe malaria is a medical emergency. A rapid assessment should be done and treatment commenced promptly. The following are important aspects of initial management:

- Check that the airway is patent; if necessary, provide an oral airway for children with seizures.
- Provide oxygen for children with proven or suspected hypoxia (oxygen saturations <90%). Children at high risk for hypoxia include those with seizures (generalized, partial or subtle seizures), children with severe anaemia and those with impaired perfusion (delayed capillary refilling time, weak pulse or cool extremities).
- Provide manual or assisted ventilation with oxygen in case of inadequate breathing.
- Nursing must include all the well-established principles of the care of unconscious children: lay the child in the lateral or semi-prone position, turn them frequently (every 2 hours) to prevent pressure sores, and provide prospective catheterization to avoid urinary retention and wet bedding. An unconscious child with possible raised intracranial pressure should be nursed in a supine position with the head raised ~30°.

- Correct hypoglycaemia (threshold for intervention: blood glucose <3mmol/l) with 200 to 500 mg/kg of glucose. Immediately give 5 ml/kg of 10% dextrose through a peripheral line, and ensure enteral feeding or if not possible, maintain with up to 5 ml/kg per hour of 10% dextrose. If only 50% dextrose is available, dilute one volume of 50% dextrose with four volumes of sterile water to get 10% dextrose solution (e.g. 0.4 ml/kg of 50% dextrose with 1.6 ml/kg of water for injection or 4 ml of 50% with 16 ml of water for injection). Administration of hypertonic glucose (>20%) is not recommended, as it is an irritant to peripheral veins.
- In any child with convulsions, hyperpyrexia and hypoglycaemia should be excluded.
- Treat convulsions with intravenous Diazepam, 0.3 mg/kg as a slow bolus ('push') over two minutes or 0.5 mg/kg body weight intrarectally. Diazepam may be repeated if seizure activity does not stop after 10 minutes. Midazolam may be used (same dose) instead of Diazepam by either the intravenous or buccal route.
- Patients with seizures not terminated by two doses of Diazepam should be considered to have status epilepticus and given Phenytoin (18 mg/kg loading dose, then a maintenance dose of 5 mg/kg per day for 48 hours). If this is not available or fail to control seizures, give Phenobarbitone (15 mg/kg intramuscularly or a slow intravenous loading dose, then a maintenance dose of 5 mg/kg per day for 48 hours). When Phenobarbitone is used, monitor the patient's breathing carefully, as it may cause respiratory depression requiring ventilatory support. High-dose (20 mg/kg) Phenobarbitone may lead to respiratory depression and increases the risk for death. Be prepared to use 'bag and mask' manual ventilation if the patient breathes inadequately or to use mechanical ventilation if available.
- Fluid balance maintenance in children who are unable to tolerate or take oral fluids should be by intravenous infusion of fluids at 3–4 ml/kg per hour.
- Give a blood transfusion to correct severe anaemia.
- Paracetamol at 15 mg/kg body weight every 4 hours may be given orally or rectally as an antipyretic to keep the rectal temperature below 39°C. Tepid sponging and fanning will make the patient more comfortable.
- Avoid harmful ancillary medicines such as corticosteroids, heparin and adrenaline.

ARTESUNATE INJECTION

1st First Line Treatment for Severe Malaria: Injectable Artesunate

First line treatment for severe malaria should be initiated promptly after parasitological diagnosis of the disease using an RDT or microscopy. Microscopy should be done, even if initial diagnosis was made using an RDT, so the parasite speciation and quantification can be determined.

- The dose for intravenous Artesunate, the preferred route of administration, is 2.4 mg/kg body weight.[1]
- Artesunate is presented as a vial of 60 mg powder together with a 1 ml ampoule of Sodium bicarbonate.
- The solution is diluted with Normal Saline or 5% Dextrose.

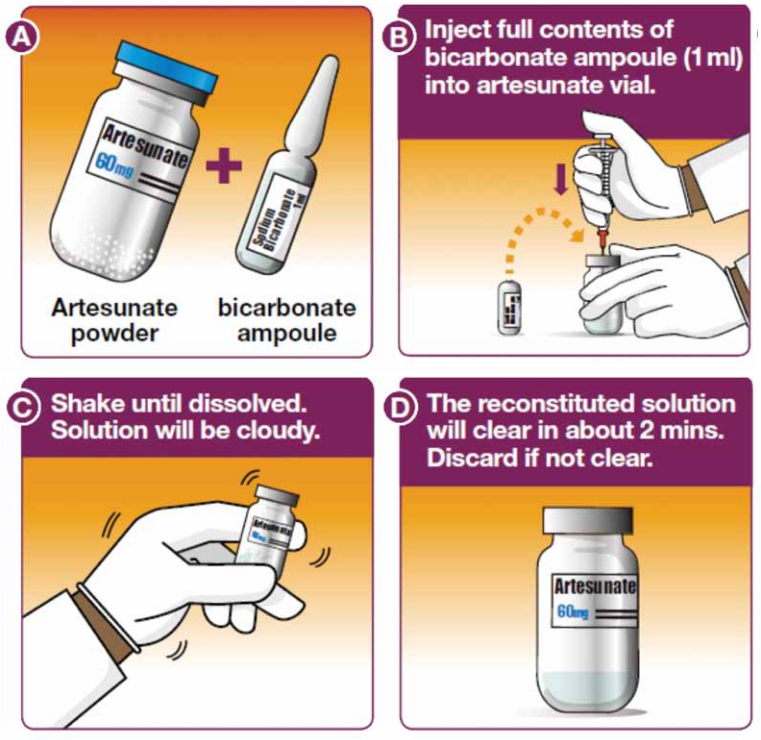
PREPARATION OF ARTESUNATE

1. Weigh the patient.

2. Determine the number of vials needed.

WEIGHT	<26 KG	26 - <51 KG	51 - <76 KG	≥76 KG
60 mg vial	1	2	3	4

3. Reconstitute, as shown in the pictures below. *Activate the medicine immediately before use: Artesunate powder + Bicarbonate ampoule.*



1 For those 20kg or less the dose can be up to 3 mg/kg body weight.

4. Dilute, according to the table and pictures below.

Reconstituted Artesunate + Normal Saline (or Dextrose 5%).

IMPORTANT: Water for injection is not an appropriate dilutant.

	INTRAVENOUS (IV)	INTRAMUSCULAR (IM)
Bicarbonate solution volume	1 ml	1 ml
Saline solution volume	5 ml	2 ml
Total volume	6 ml	3 ml
Artesunate 60 mg solution concentration	10 mg/ml	20 mg/ml

5. Calculate the dose.

Calculate and withdraw the required dose in ml according to route of administration:

FOR IV ROUTE

CONCENTRATION: 10 MG/ML

$$\frac{\text{2.4 mg x body weight (kg)}}{\text{IV Artesunate solution concentration 10 mg/ml}}$$

Example: Dose needed (ml) for 26 kg child:

$$\frac{2.4 \times 26}{10} = 6.24 \text{ ml} \rightarrow \textbf{7 ml*}$$

*Round up to the next whole number

Weight (kg)	Dose	
	mg	ml
5 - <9	20	2
9 - <13	30	3
13 - <17	40	4
17 - <21	50	5
21 - <26	60	6
26 - <30	70	7
30 - <34	80	8
34 - <38	90	9
38 - <42	100	10
42 - <46	110	11
46 - <51	120	12
51 - <55	130	13
55 - <59	140	14
59 - <63	150	15
63 - <67	160	16
67 - <71	170	17
71 - <76	180	18
76 - <80	190	19
80 - <84	200	20
84 - <88	210	21
88 - <92	220	22
92 - <96	230	23
≥96	240	24

FOR IM ROUTE

CONCENTRATION: 20 MG/ML

$$\frac{\text{2.4 mg x body weight (kg)}}{\text{IV Artesunate solution concentration 20 mg/ml}}$$

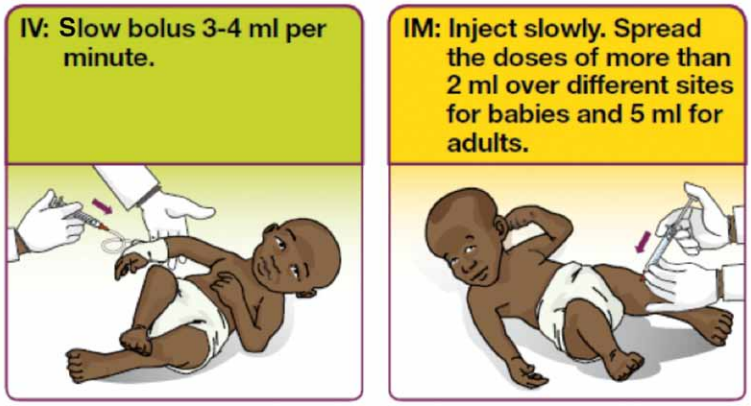
Example: Dose needed (ml) for 26 kg child:

$$\frac{2.4 \times 26}{20} = 3.12 \text{ ml} \rightarrow \textbf{4 ml*}$$

*Round up to the next whole number

Weight (kg)	Dose	
	mg	ml
5 - <9	20	1
9 - <13	30	2
13 - <17	40	2
17 - <21	50	3
21 - <26	60	3
26 - <30	70	4
30 - <34	80	4
34 - <38	90	5
38 - <42	100	5
42 - <46	110	6
46 - <51	120	6
51 - <55	130	7
55 - <59	140	7
59 - <63	150	8
63 - <67	160	8
67 - <71	170	9
71 - <76	180	9
76 - <80	190	10
80 - <84	200	10
84 - <88	210	11
88 - <92	220	11
92 - <96	230	12
≥96	240	12

6. **Administer, according to the instructions below.**



DOSING SCHEDULE

- Give three parenteral doses over 24 hours as indicated below.
- Give parenteral 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 a full three-day course of recommended first line oral Artemisinin Combination Therapy (ACT). 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 seven days.**
- A course of injectable Artesunate should always be followed by a three-day course of ACT. *(see Table 1)*
- Prepare a fresh solution for each injection.
- Discard any unused solution.
- Continue to evaluate the patient regularly for improvement or deterioration.
- Continue supportive treatment and monitoring as required in all patients with severe malaria.

IF IV ARTESUNATE IS UNAVAILABLE, IV QUININE IS THE ALTERNATIVE FOR PATIENTS WITH SEVERE MALARIA.

- **IMPORTANT:** IV Quinine is the medicine of choice to treat SEVERE MALARIA in children weighing <5 kg and pregnant women in the first trimester.
- Weigh the patient. Adults who are unable to stand are estimated to be 60 kg for purposes of administering Quinine.
- An IV line should be established.
- Rapidly measure blood glucose using the available means (glucometer, Dextrostix).
- Commence Quinine following the regimens shown in Table 10 below.

TABLE 10 Dosage for Intravenous Quinine

CHILDREN IV DOSE	ADULT IV DOSE
Loading Quinine 20 mg/kg diluted in 10 ml/kg body weight 5% Dextrose or Normal Saline over four hours.	**Loading** Quinine 20 mg/kg body weight diluted in 500 ml 5% Dextrose or Normal Saline over four hours.
After 8 hours Quinine 10 mg/kg body weight diluted in 10 ml/kg weight 5% Dextrose or Normal Saline over four hours.	**After 8 hours** Quinine 10 mg/kg body weight diluted in 500 ml 5% Dextrose or Normal Saline over four hours.
Repeat Doses Quinine 10 mg/kg diluted in 10 ml/kg of 5% Dextrose or Normal Saline every eight hours. Each dose given over four hours until patient is able to take orally to complete seven days.	**Repeat Doses** Quinine 10 mg/kg body weight diluted in 500 ml 5% Dextrose or Normal Saline every eight hours. Each dose is given over four hours until patient is able to take orally to complete seven days.

Note: *Do not give a loading dose of Quinine if the patient has been taking Quinine in the preceding 24 to 48 hours. This also applies if the patient has been on Mefloquine prophylaxis.*

Avoid using IV infusion of Quinine in young children as pre-referral treatment at the local health centre because monitoring of fluid balance may be inadequate in addition to tendency to develop hypoglycaemia.

- 10% Dextrose is the preferred solution for giving Quinine in most instances to ameliorate hypoglycaemia.
- In children, give maintenance fluids in between the Quinine infusions using Dextrose (2.5%, 5% or 10%), infused at a rate of 5 ml/kg body weight per hour.

- In adults alternate Normal Saline with 5% Dextrose (125 ml/hr or one litre given over eight hours will provide sufficient fluids for maintenance).
- Monitoring for hypoglycaemia should be done every four hours by available means (glucometer or Dextrostix) and managed appropriately. If the blood sugar is less than 3.4 mmol/l, give 20 ml of 50% Dextrose to adults. In children, use 25% Dextrose, which is made by diluting 50% Dextrose with water for injection in the ratio of 1:1 and give 2 ml/Kg of the 25% solution if the blood glucose is less than 3.4 mmol/l.
- Once the patient is able to take oral medication, Doxycycline 100 mg daily where appropriate or Clindamycin 300 mg three times a day should be given to complete seven days.

Please refer to Table 11 for additional recommendations for adjunctive treatment for severe malaria.

TABLE 11 Adjunctive Treatment for Severe Malaria

CONDITION	POSSIBLE INTERVENTION
Coma (Depressed LOC)	• Ensure ABC (Airway, Breathing & Circulation) of resuscitation. Manage airway with intubation if required. Give 02. • Secure IV access. • Check for hypoglycaemia. • Investigate for other causes, including lumbar puncture to exclude meningitis
Convulsion	• Maintain airway with patient in lateral position to prevent aspiration. • Treat with IV or Rectal Diazepam per rising need.
Hypo-glycaemia	• Correct hypoglycaemia with 50% Dextrose IV bolus in adults. • In children, give 25% Dextrose by diluting 50% Dextrose with injection water 1:1. This can be given per naso-gastric tube.
Acute Pulmonary oedema	• Prop patient head up at 45°, give oxygen. • Provide IV diuretics. • Review IV fluids (stop IV rehydration). • Consider intubation and ventilation.
Severe Anaemia	• Transfuse depending on patient clinical condition and signs. Generally, patients from high transmission areas may tolerate lower haemoglobin levels.
Acute Kidney injury	• Assess hydration status to rule out pre-renal cause. • Consider early peritoneal dialysis or haemodialysis if the patient is adequately fluid-replaced, but with reduced urine output of <0.4 ml/kg body weight per hour.
Shock/ Circulatory collapse	• Look out and investigate for sepsis. • Consider inotropic support and care in high care facilities. • Consider adding empirical antibiotics. Use anaerobic cover if aspiration is suspected.

Other Considerations:

- Exchange transfusion for hyperparasitaemia is not useful.
- Where there is bleeding-coagulopathy, consider disseminated intravascular coagulation (DIC). Fresh frozen plasma or cryoprecipitate or whole blood can be given.

SPECIAL GROUPS

Medicines for Severe Malaria in Special Groups

TABLE 12 Medicines for Treatment of Severe Malaria in Pregnancy

TRIMESTER/APPROXIMATE GESTATION	
1ST TRIMESTER OR BEFORE QUICKENING	**2ND AND 3RD TRIMESTERS AFTER QUICKENING**
• IV Quinine as outlined for adult patients • Switch to Oral Quinine and Clindamycin as soon as the patient is able to tolerate. Complete seven days of treatment for both medicines	• IV Artesunate as outlined for adults • Switch to Oral Coartemether once patient is able to tolerate. Complete the full three day course of treatment

TABLE 13 Medicines for Treatment of Severe Malaria in Children Weighing <5 kg

TREATMENT
• Administer IV Quinine as outlined above. • Switch to Oral Quinine to complete seven days as soon as the patient can tolerate oral medication. *(see Treatment of Uncomplicated Malaria)*

MEDICINES USED TO TREAT SEVERE MALARIA IN HIV POSITIVE PATIENTS ARE THE SAME AS PATIENTS WITHOUT HIV INFECTION.

Medicine Information

Potential Adverse Effects of Medicines Used in Treatment of Malaria

ARTEMETHER-LUMEFANTRINE (COARTEMETHER)

Well-tolerated with minor side effects. Take with fatty meal, e.g. milk

Coartemether is generally well-tolerated. It may cause the following minor side effects: abdominal pain, nausea and vomiting, sometimes diarrhoea. Headache and dizziness may also occur. Unfortunately most of these symptoms are also associated with malaria, making it difficult to differentiate side effects from the actual disease. Coartemether is well-absorbed when taken with a fatty meal (e.g. a glass of milk).

ARTESUNATE-AMODIAQUINE

May cause upset stomach, mild pruritus and nausea. Avoid taking with fatty meal

Side effects will primarily be from Amodiaquine which has an almost similar side effect profile to Chloroquine. Amodiaquine is better palatable than Chloroquine. Patients may experience gastrointestinal upset and mild pruritus. Adults may experience a strange sensation of impending doom. Amodiaquine can produce neutropenia/agranulocytosis. Acute poisoning may produce similar presentation as Chloroquine poisoning (headache, gastrointestinal upset, loss of vision, convulsions, hypotension, cardiac instability) but with less cardiotoxicity. Avoid taking with fatty meals.

HOWEVER: In people with HIV/AIDS and uncomplicated *P. falciparum* malaria, avoid ASAQ if on treatment with Efavirenz.

ARTESUNATE PARENTERAL

Well-tolerated, side effects may include dizziness, mild tinnitus and upset stomach

Artesunate is generally well-tolerated, with some side effects being indistinguishable from the symptoms of malaria itself. Some dizziness, mild tinnitus and gastrointestinal disturbances have been noted. There may be a mild rise in liver enzymes. Delayed haemolysis has been reported in patients treated for malaria with high parasitaemia (5-10%). The phenomenon of delayed haemolysis may occur 7 to 21 days after the successful treatment of severe malaria.

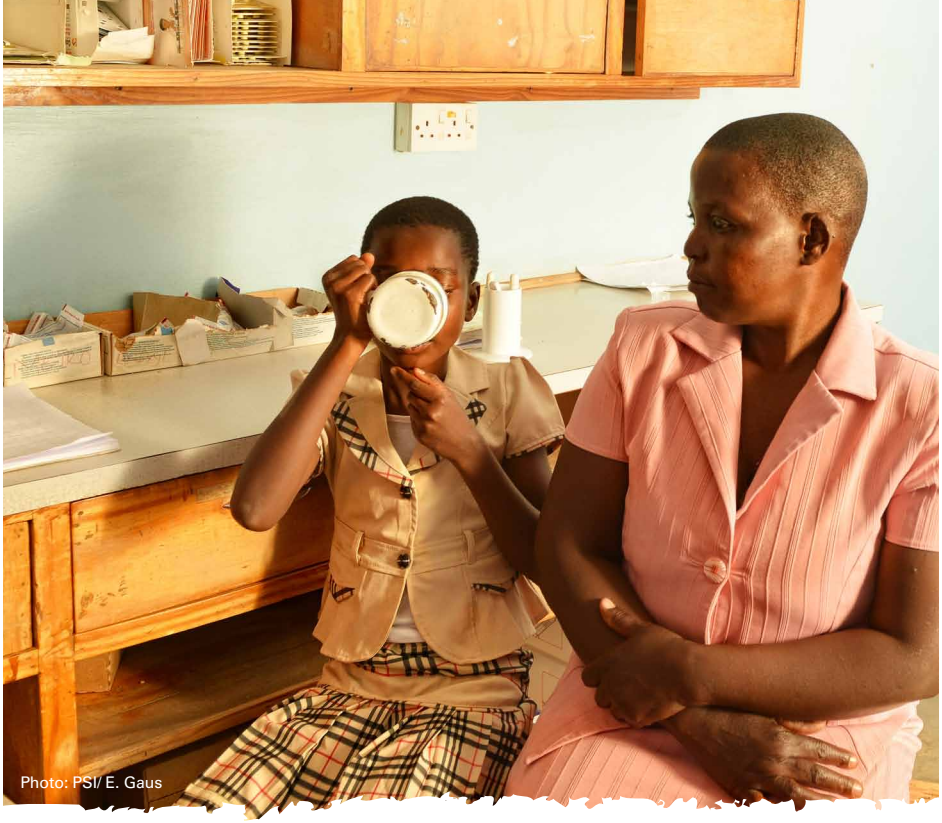


Photo: PSI/ E. Gaus

QUININE

The most common side effect of Quinine is tinnitus associated with muffled (reduced) hearing that is reversible on completion of the treatment. In addition, there may be dizziness with vertigo resulting in nausea and sometimes vomiting. The above side effects usually set in within two to three days of treatment and there is no need to discontinue treatment. Hypoglycaemia is a recognised side effect particularly in the severely ill patients requiring IV Quinine. Hypotension may occur after excessive or rapid infusion. Cardiotoxicty causing dysrhythmias is uncommon but can occur in patients who were on Mefloquine for prophylaxis.

Side effects may include: tinnitus, reduced hearing, nausea, vomiting

DOXYCYCLINE

Doxycycline may cause a photosensitive dermatitis in some patients. Abdominal discomfort, anorexia and vomiting may occur. Doxycycline should not be prescribed to pregnant women and children less than eight years of age as it causes dental discolouration.

Not for pregnant women and children less than eight years

CLINDAMYCIN

Clindamycin should be discontinued if a patient develops diarrhoea after commencing treatment (this may progress to life threatening antibiotic associated pseudomembranous colitis). Abdominal discomfort, nausea, anorexia and vomiting may also occur but do not warrant discontinuation of treatment unless very severe. Mild skin rash is unimportant but progression to erythema multiform may rarely occur.

Stop if patient develops diarrhoea after commencing treatment

Pre-referral Treatment

Rapid and effective treatment of malaria is very important to prevent long standing disability or death. Patients with severe malaria can rapidly deteriorate if treatment to reduce the level of parasitaemia is not quickly instituted. This is particularly so in those who stay far from health centres where anti-malarial injectables can be given. Deterioration from fever and subtle early symptoms of uncomplicated malaria to severe complicated disease with central nervous system involvement can occur within hours especially in the non-immune, pregnant and young children.

PRE-REFERRAL TREATMENT AT THE COMMUNITY LEVEL

When a patient presents with signs and symptoms of severe malaria as a referral from the community based health workers he/she may have been given Rectal Artesunate. This would be more likely if the patient was unable to take any medication orally and the time to get to the referral centre was more than six hours.

Rectal Artesunate is given as follows:

The dose of Rectal Artesunate is 10 mg per kg body weight, to patients weighing 5 kg or more.

Where the weight of the patient is not immediately known dose according to the table below:

TABLE 14 Dosing of Rectal Artesunate by Age

AGE (YEARS)	ARTESUNATE DOSE
6 months - <1 Year	50 mg STAT
1 - <3	100 mg STAT
3 - <5	200 mg STAT
5 - <14	300 mg STAT
14 - <16	400 mg STAT
≥16	600 mg STAT

The weight of patients above 16 years and all adults has been assumed to be an average of 60 kg. When Artesunate is given according to known body weight, do not exceed 1200 mg.

- Do not give Rectal Artesunate to children weighing <5 kg (<6 months).
- Artesunate suppositories come in doses of 50 mg, 100 mg and 400 mg.
- To get to the required dose, one or more suppositories can be given in combination to get to the total dose required being considerate not to exceed three suppositories.
- If the suppository is expelled within 30 minutes, the dose should be repeated by insertion of another suppository.
- In children, the buttocks should be held together for 10 minutes to ensure retention.
- Once the Rectal Artesunate has been given, immediately refer the patient to the nearest health centre for further management.

PRE-REFERRAL TREATMENT AT THE PRIMARY HEALTH CENTRE

- All severe cases of malaria should be referred to hospital for further treatment.
- After a positive RDT, also make blood smears (thick and thin smears) and label these with the date and PATIENT'S NAME. Both the thick and thin smears should accompany the patient to hospital.
- In patients weighing ≥5 kg, give Rectal Artesunate as indicated above. *(see Severe Malaria, Treatment)*

OR

- Administer an initial dose of IV Artesunate as indicated above. *(see Severe Malaria, Treatment)*

OR

- If unable or difficult to establish IV access, administer an initial dose of Artesunate IM *(see Severe Malaria, Treatment)* and transfer without delay.
- Administer injection slowly.
- IM Injection volumes >5 ml should be spread over different injection sites.

OR

- **In adults, administer Quinine IV:** IV Quinine loading dose of 20 mg per kg body weight is diluted in 500 ml of Normal Saline or 5% Dextrose infused over four hours. Do not exceed 1200 mg of loading dose.

After eight hours subsequent doses should be administered at 10 mg per kg body weight diluted in Normal Saline or 5% Dextrose

- **In children, administer Quinine IV:** IV Quinine loading dose of 20 mg/kg body weight is diluted in 10 ml/kg body weight 5% Dextrose or Normal Saline infused over 4 hours. After eight hours subsequent doses should be administered at 10 mg/kg body weight diluted in 10 ml/kg of 5% Dextrose or Normal Saline every eight hours infused over four hours

Additional Supportive Measures for Patients with Severe Malaria Awaiting Transfer:

- Maintain airway by appropriately positioning the patient in a left lateral position with the chin extended if patient is in a coma or convulsing. Administer oxygen if available. Patients with pulmonary oedema should be propped up and given IV diuretics.
- Give IV 25% Dextrose for hypoglycaemia in children as 1 ml 50% Dextrose per kg body weight diluted 1:1 with water for injection. This can also be given orally or via nasogastric tube if IV access is not readily secured. Where the child is still able, continue to breastfeed.
- Give Parenteral anti-emetics to adults with persistent vomiting as needed.
- Address hyperpyrexia through physical means, such as tepid sponging and fanning. Antipyretics, such as Paracetamol, may be given where appropriate.
- Where available, treat convulsions with either IV or rectal diazepam.

A clear legible referral letter stating the date, name of patient, brief history, diagnosis and the pre-referral treatment given must accompany the patient to the next level of care. Complete the malaria referral form. *(see Appendix 3)*

Patients that have received Rectal Artesunate should receive the second dose of Artesunate 12 hours after the first dose.

See Figure 3 for a flow chart for diagnosis and management of *P. falciparum* infections.

FIGURE 3 Flow Chart for Assessment of a Suspected *P. falciparum* Malaria Case and Management of a Confirmed *P. falciparum* Malaria Case

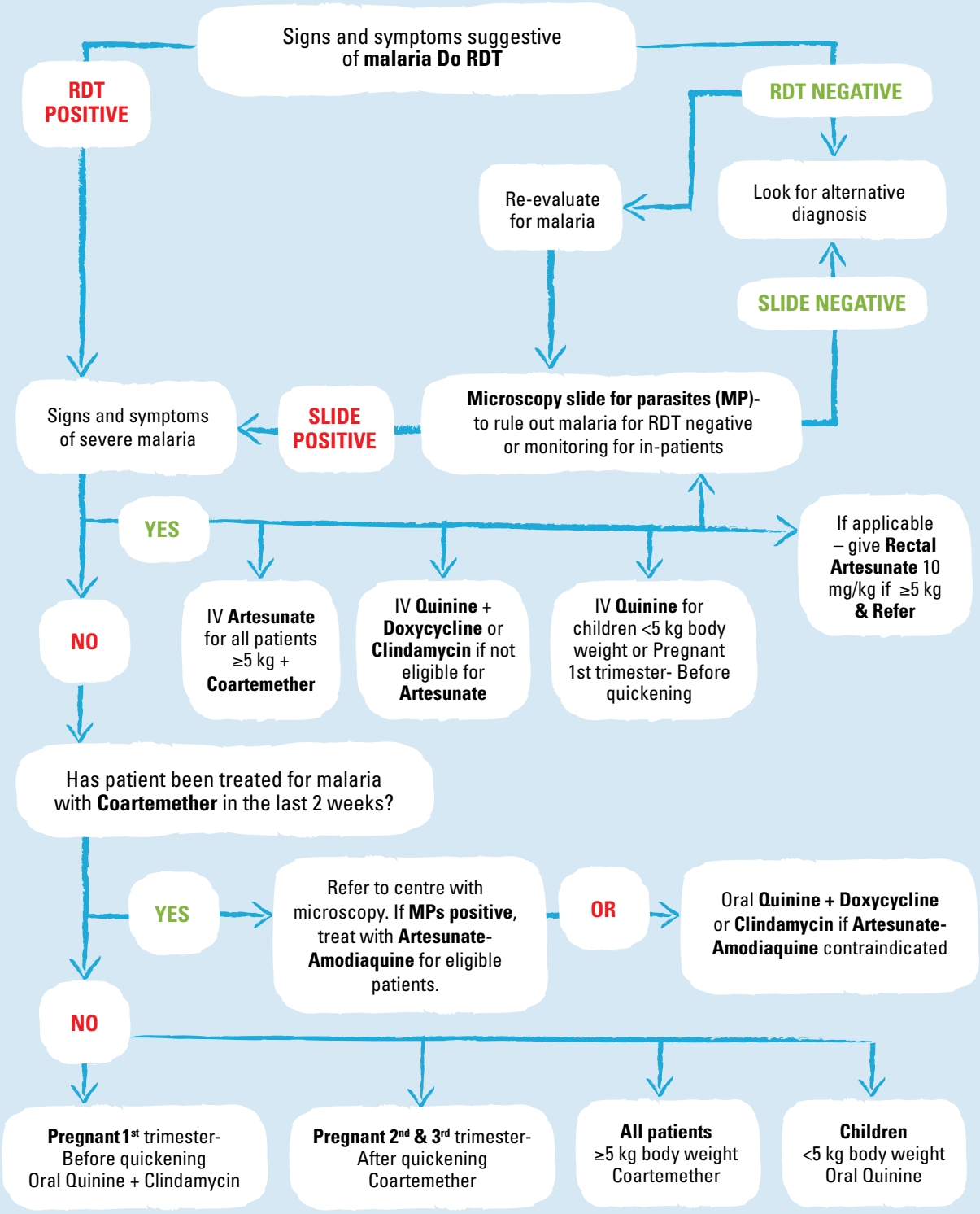


Photo: PSI/ E. Gaus

Appendices

Appendix 1. Glasgow Coma Scale

TYPE OF RESPONSE	RESPONSE	SCORE
Eyes open	Spontaneously	4
	To speech	3
	To pain	2
	Never	1
Best verbal	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
Best motor	Obeys commands	6
	Purposeful movements to painful stimulus	5
	Withdraws to pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1
Total		3–15

A state of unrousable coma is reached at a score of <11. This scale can be used repeatedly to assess improvement or deterioration.

- The normal score is 15.
- If the score is less than or equal to eight, the patient is considered to be comatose.

Appendix 2. Blantyre Coma Scale (for use in preverbal young children)

TYPE OF RESPONSE	RESPONSE	SCORE
Best motor	Localizes painful stimulus	2
	Withdraws limb from pain	1
	Nonspecific or absent response	0
Verbal	Appropriate cry	2
	Moan or inappropriate cry	1
	None	0
Eye movements	Directed (e.g. follows mother's face)	1
	Not directed	0
Total		0–5

- A score of zero to three is bad. A child with this score is seriously ill.
- A score of five is good/normal.

Appendix 3. Health Facility Malaria Referral Form

HEALTH FACILITY MALARIA REFERRAL FORM

MINISTRY OF HEALTH AND CHILD CARE
NATIONAL MALARIA CONTROL PROGRAMME

Name	Sex	Age	Address	Village:
Date seen at HF:	RDT done? Yes/No Result: Pos/Neg Coartemether given by VHW? Yes/No Coartemether course finished? Yes/No			Referred by:
Date referred from HF:				Blood slides taken and enclosed: Yes/No Result: Positive/Negative
Next of kin:	Traditional medicine: (name)			
Symptoms & duration (days)* Headache Fever Shivering Vomiting Abdominal pain Diarrhea Fits Consciousness disorder Other symptoms	*Signs** Fever Persistent vomiting Pallor Jaundice Poor urine output Uremic frost "Coca-cola" urine Breathlessness Mucosal bleeding Convulsions Coma			*Reason for referral** Cerebral Severe Non-responsive to Coartemether Non-responsive to Quinine Pregnant Other Reasons
Pulse:_____/min	Temperature: ____°C	Blood Pressure___/___ mmHg		Respiration___/min

Treatment: Medicines Dose Time Given	Medicine	Dose	Time/Date given
	1. 2. 3. 4. 5. 6.		
Prescription dated:			
Comments:			
Signed (Name):		**Designation:**	**Time of referral:**

* Tick all that are appropiate

Appendix 4. Malaria Deaths Investigation Form

MALARIA DEATHS INVESTIGATION FORM

MINISTRY OF HEALTH AND CHILD CARE
NATIONAL MALARIA CONTROL PROGRAMME

Province: Code:		District: Code:	
Name of Facility: Code:		Date form completed: ____/____/____	
Name of deceased:	Patient No:	Age:	Sex:
Address (where resided):			
If female, pregnant? (Y/N):	If pregnant, estimated gestation (weeks):		
Had pregnant patient received IPTp? (Y/N):	If yes, indicate number of doses given:		
Which areas did the deceased visit in the past 2- 6 weeks:			
Date of onset of symptoms:			
Was RDT performed before presenting to the primary health facility? (Y/N) Date: Result: positive (P.f./Pan)/negative			
Was Coartemether taken before presenting to the primary health facility? (Y/N) Date: Was Rectal Artesunate given before presenting to the primary health facility? (Y/N) Date:			

List all details of the patient's visit to the first facility visited:

Health facility name:_____ Level of facility: (PHC/Secondary/Tertiary)
Presentation Date: _____ Time: _____

RDT performed? (Y/N) _____ Result positive (*P.f.*/Pan)/negative_____

Malaria slide taken? (Y/N)_____ Result (positive[1]/negative) _____

Type of malaria diagnosed (uncomplicated/severe) _____

Antimalarial medicines given:

Name: _____ Dose: _____ Route: (Oral/PR/IM/IV) Time given: _____ DOT[2]? (Y/N)

Other medicines given (specify):

Name: _____ Dose: _____ Route: (Oral/PR/IM/IV) Time given: _____

Date and time referred to the next level: Date:_____ Time: _____

Reason for referral: _____

List all details of the patient's treatment at the second level referral centre:

Health facility name: _____ Presentation Date: _____ Time:_____

Malaria slide taken? (Y/N) ___ Date slide taken: _____ Date result received: _____
Result: (Positive[3]/Negative)_____

Type of malaria diagnosed (uncomplicated/severe)

Antimalarial medicines given (Y/N): Specify

Name: _____Dose:____ Route: (Oral/PR/IM/IV)____ Time given: _____

Name: _____Dose:____ Route: (Oral/PR/IM/IV)____ Time given: _____

Antibiotics given (Y/N): Specify

Name: _____Dose:_____Route: (Oral/PR/IM/IV)____ Time given: _____

Other medicines given (Y/N) Specify

Name: _____Dose:_____ Route: (Oral/PR/IM/IV)____ Time given: _____

Ancillary treatment (Y/N) (specify): Blood transfusion, glucose, Ringer lactates, Dialysis, Other?

Date and time referred to the next level: Date:_____ Time:_____

Reasons for referral:

List all details of the patient's treatment at the tertiary level referral centre:

Health facility name: _____ Presentation Date: _____ Time: _____

Malaria slide taken? (Y/N) Result: (Positive[4]/Negative)

Type of malaria diagnosed (Uncomplicated/Severe)

Antimalarial medicines given (Y/N): Specify

Name: _____Dose: ____ Route: (Oral/PR/IM/IV) Stat dose Date: ____Time: _____

Name: _____Dose: ____ Route: (Oral/PR/IM/IV) Stat dose Date: ____ Time: _____

Antibiotics[5] given (Y/N): Specify

Name: _____Dose: ____ Route: (Oral/PR/IM/IV) Stat dose Date: _____Time: _____

Name: _____Dose: ____Route: (Oral/PR/IM/IV) Stat dose Date: ____ Time: _____

Other medicines given (Y/N) Specify

Name: _____Dose: ____Route: (Oral/PR/IM/IV) Stat dose Date: _____Time: _____

Name: _____Dose: ____ Route: (Oral/PR/IM/IV) Stat dose Date: _____Time: _____

Others:

Name: _____Dose: _____Route: (Oral/PR/IM/IV) Stat dose Date: ____Time: _____

Ancillary treatment (Y/N) Specify:

Blood transfusion (Y/N) type Dose: _____ First cycle Date: _____ Time: _____

Glucose (Y/N) Dose: ____Route: (Oral/IM/IV) Stat dose Date: _____Time: _____

Ringer lactates (Y/N) Dose: _____ First infusion Date: _____ Time: _____

Dialysis (Y/N) First cycle Date: _____Time: _____

Others:

Name: _____ Dose: _____ Route: (Oral/PR/IM/IV) Stat dose Date: _____Time: _____

Name: _____Dose: _____Route: (Oral/PR/IM/IV) Stat dose Date: _____Time: _____

Tick all complications observed at the health facility or listed in the documentation			
	Multiple convulsions		Altered level of consciousness (confusion, drowsiness or coma)
	Severe anaemia (Hb <5g/dl)		Bleeding tendencies
	Jaundice (yellowness of the eyes)		Shock
	Haemoglobinuria ("Coca-cola" coloured urine)		Hypoglycaemia
	Acute renal failure		Hyperparasitaemia (>5% in non-immunes)
	Respiratory distress (difficulty in breathing, fast breath)		Other (specify) _____
Duration of illness:	Date of death:	Time:	
Was any other concurrent illness present? (Y/N) If Yes, state the illness:			
Health provider's comments[6]:			
Signed (Name):	**Qualifications:**	**Date:**	
Comments by Head of institution:			
Signed (Name):	**DMO/MO/DNO/CO**	**Date:**	

1 Indicate species and density of parasites.
2 Directly observed treatment.
3 Indicate species and density of parasites.
4 Indicate species and density of parasites.
5 Clindamycin or Doxycycline if given as antimalarials should not be indicated here as antibiotics.
6 The health worker who managed/treated this patient should fill in this part indicating all other relevant information that may not have been captured in the form.

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PRIMARY HEALTH CARE
A HEALTHY NATION
MINISTRY OF HEALTH AND CHILD CARE
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