KINGDOM OF CAMBODIA

NATION RELIGION KING

National Treatment Guidelines

for Malaria in the Kingdom of Cambodia

May 2012

World Health Organization

PREFACE

Malaria, which has plagued humankind since ancient times, continues to be one of the most important and devastating infectious diseases in the world. Half of the world's population, 3.3 billion people, living in 106 countries are at risk of contracting the disease. In Cambodia, despite the limited areas of the country where transmission occurs (forested hilly areas), an estimated 3.2 million people, living within 2km of forest, are at risk of malaria. Around 62,770 malaria episodes were treated by the public health services during 2011 alone. Malaria in Cambodia is also a key contributor to anemia, complications during pregnancy, low-birth weight and poor child growth. More importantly, current malaria treatment and control efforts in Cambodia may be hampered by the emergence and spread of artemisinin resistance, which has been recently detected in the western part of the country along the Thai-Cambodia border. Artemisinin monotherapy and use of substandard and counterfeit antimalarials in the private sector are among some of the challenges in case management of malaria faced in Cambodia.

To successfully implement the National Strategic Plan on Malaria Elimination by 2025 supported and adopted by Samdech Decho Hun Sen, Prime Minister of Cambodia, the Ministry of Health is publishing this revised version of the National Treatment Guidelines for Malaria, incorporating updated information on new ACT formulations recommended at the National Malaria Drug Policy meeting held in April 2010, in accordance with the local needs and the anti-malarial drug sensitivity monitoring. The specific Artemisinin-based combination therapy (2 anti-malarial drugs used in a fixed-dose combination) is recommended according to a consensus reached among national and international experts.

These guidelines are designed for doctors and staff of each level of the public health facilities (referral hospital, health centre and health post), the private sector as well as at the community level (through village malaria workers) for improved case management of malaria and to reduce its mortality.

The main aim of this publication is to provide all those involved in the management of malaria in different sectors and levels with clear and practical guidelines for the early diagnosis and prompt and appropriate treatment of malaria. The Information is presented here on treatment of:

- uncomplicated malaria
- severe or complicated malaria

The guidelines do not deal with preventive uses of anti-malarial, such as intermittent preventive treatment or chemoprophylaxis except for temporary travelers to malaria endemic areas.

It is the Ministry of Health's earnest hope that these guidelines will facilitate the effective, appropriate and timely diagnosis and treatment of malaria and thus contribute to a significant decrease in the burden of the disease in the country. The Ministry of Health would like to thank the World Health Organization for its collaboration in updating this new edition.

GOAL AND OBJECTIVES OF THE NATIONAL MALARIA CONTROL PROGRAMME

Goal: To move towards pre-elimination of malaria across Cambodia with special efforts to contain artemisinin resistant P.falciparum malaria.

Objectives:

1. To improve access to early malaria diagnosis and treatment services.
2. To decrease drug pressure for selection of artemisinin resistant malaria parasites.
3. To improve access to preventive measures and specifically prevent transmission of artemisinin resistant malaria parasites.
4. To increase community awareness and behavior change among the population at risk.
5. To provide effective management (including information systems and surveillance) and coordination.

Broad Aims of Malaria Case Management

- To cure infection and reduce morbidity and mortality
- To reduce the infectious reservoir

Specific Objectives of Malaria Case Management

- Early detection and prompt effective treatment to cure the infection and prevent progression to severe disease
- Proper management of severe disease to prevent death
- Prevent drug resistance
- Reduce malaria transmission

Components of Malaria Case Management

- Prompt parasitological diagnosis
- Treatment with effective drugs
- Referral (and pre-referral treatment when indicated)
- Counseling and Follow up of patient
- Issues related to diagnosis: policy and quality assurance

- Drugs: supply and management; safety (pharmacovigilance), quality (regulation issues) and therapeutic efficacy

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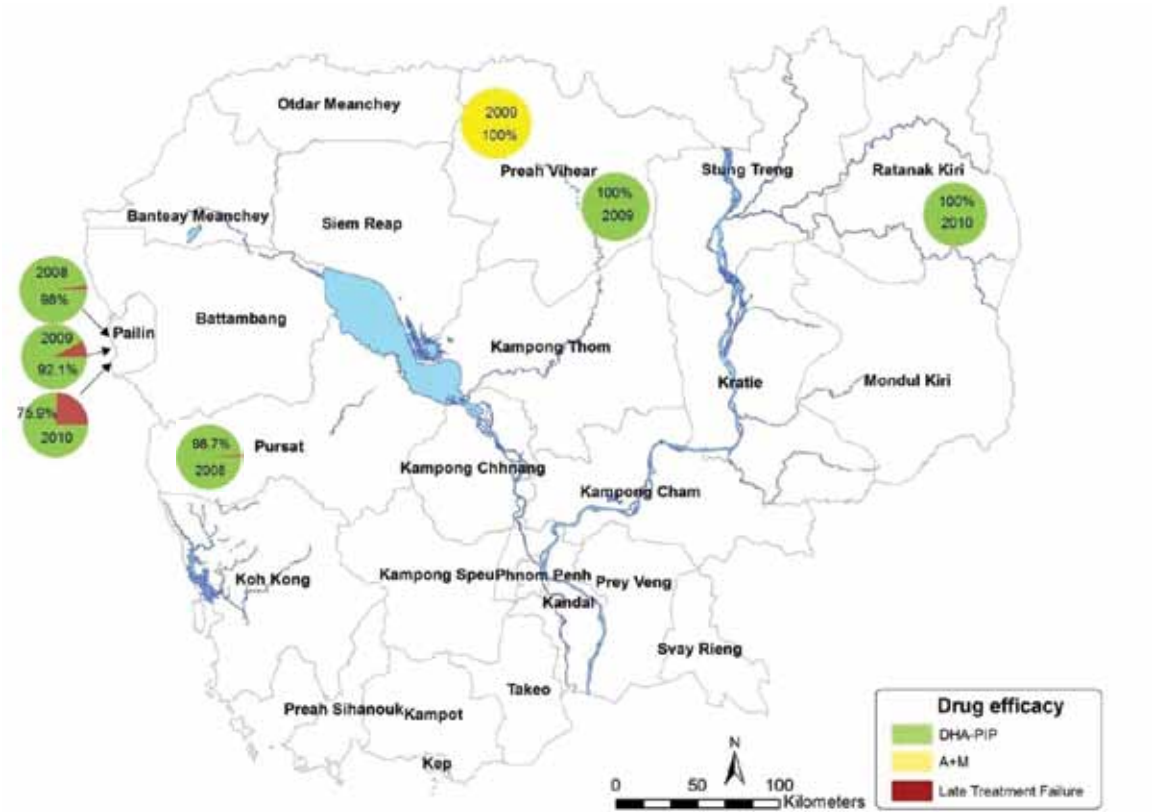
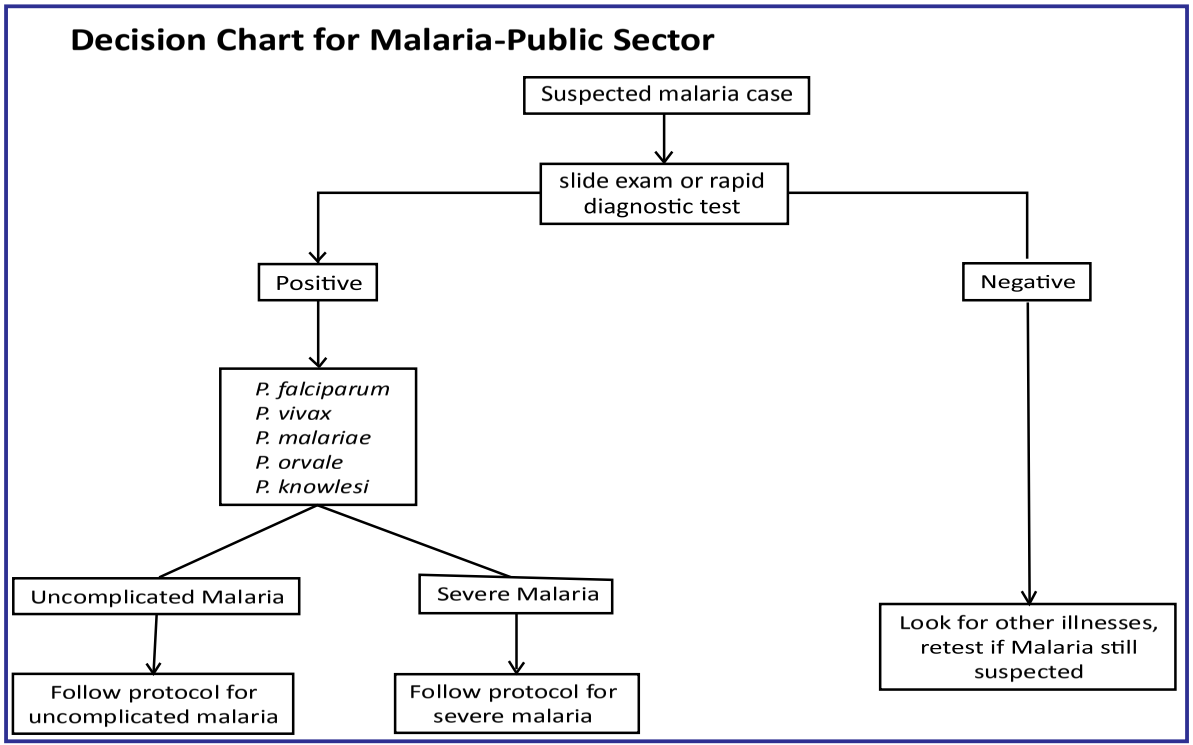
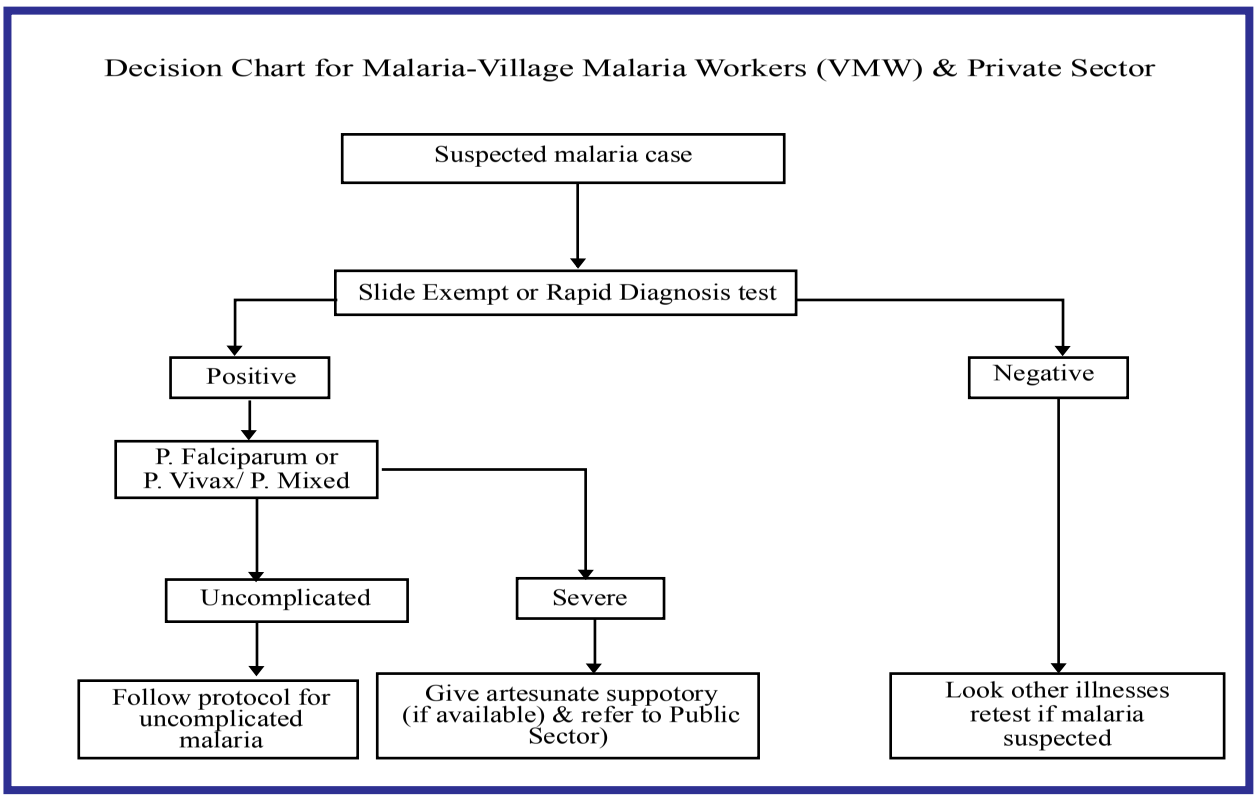
1. Distribution of first line antimalarial drug efficacy in Cambodia



2. Key References for Diagnosis and Treatment of Malaria




Decision Chart for Malaria-Village Malaria Workers (VMW) & Private Sector
Suspected malaria case
Slide Exempt or Rapid Diagnosis test
Positive
Negative
P. Falciparum or P. Vivax/ P. Mixed
Uncomplicated
Severe
Follow protocol for uncomplicated malaria
Give artesunate suppotory (if available) & refer to Public Sector)
Look other illnesses retest if malaria suspected

Essential Anti-Malarial Drugs

Table 1: List of anti-malarial drugs used for routine treatment

Drug	Health Facility where drugs are used			
	RH/FDH	HC/HP	VMW/MMW	Private*
Dihydroartemisinin-Piperaquine (tab)	Yes	Yes	Yes	Yes
Artesunate (supp)	Yes	Yes	Yes	Yes
Artesunate (IV)	Yes	Yes	No	No
Artemether (IM)	Yes	Yes	No	No
Tetracycline	Yes	Yes	No	No
Doxycycline	Yes	Yes	No	No
Quinine tablet	Yes	Yes	No	No
Quinine (IV)	Yes	Yes	No	No
Artesunate + melfloquine	Yes	Yes	Yes	Yes
Atovaquone + Proquanil	*	*	*	No
Primaquine	*	*	*	No

IV = intravenous, IM = intramuscular, supp = suppository

*Introduction of these drugs will proceeded progressively for selected level and /or facilities depending on CNM decision after capacity assessment.

Table 2: Responsibility of health care system in malaria case management

Clinical Manifestations	Health service where treatment is indicated				
	RH/FDH	Deleted this column	HC/HP	VMW/MMW	Private**
Uncomplicated malaria	Yes	Yes	Yes	Yes	Yes
Malaria in pregnancy	Yes	Yes	Yes	Yes	Refer to public sector
Malaria in children under 5 years old	Yes	Yes	Yes	Yes	Refer to public sector
Severe and Complicated malaria	Yes	Yes	Artesunate Suppository & Refer		

** Ban on sale of all anti -malarial drugs in private sector after 2015.

3. MALARIA DIAGNOSIS

The only way to be sure of that a patient has malaria is if he/she has a positive diagnostic test ("confirmed" malaria). All suspected malaria cases should receive parasite-based diagnosis before treatment, in all sectors.

Treatment for malaria should not be initiated until the diagnosis has been confirmed through parasite-based diagnosis ("confirmed" malaria).

3.1 Patient history

Risk factors for malaria:

- New settlers with known people in malaria transmission area
- Live or work in the forest
- Pregnant women
- Children
- Not using bed net in high transmission areas
- Refusal of or delay in seeking medical care
- Misdiagnosis

Medical and drug history:

- Malaria episode presence in the past
- Drugs taken during last month (eg, artesunate, Mefloquine, DHA-PIP; A+M;Malarine)
- Any other illnesses or drug allergy
- Medical and surgical history of other illnesses

3.2 Uncomplicated malaria features

Uncomplicated malaria symptomatology

Fever - Chills - Sweating

Other common signs:

Headache, back or muscle pain, gastrointestinal complaints (nausea, vomiting, diarrhea), abdominal swelling, enlarged spleen or liver.

3.3 Severe or complicated malaria definition[1]

Signs of uncomplicated malaria with one or more of the following:

- **Prostration** (inability to sit upright without support or to drink)
- **Impaired consciousness** (modified Glasgow score ≤ 9 in adult and children > 5 years old or Blantyre coma score ≤ 2 in children who have not learned to speak)
- **Respiratory distress** (sustained nasal flaring, intercostals recession and deep or fast breathing i.e. RR > 25/min in adults, RR > 40/min in children)
- **Multiple convulsions** (>1/24h)
- **Circulatory collapse** (BP < 50 mmHg before 5 years old or BP < 80 mmHg above 5 years old, cool peripheries, weak pulses)
- **Pulmonary oedema** (radiological features)
- **Abnormal bleeding**
- **Jaundice**
- **Macroscopic haemoglobinuria**
- **Severe anaemia *or very pale color*** (Hb<5g/dl or Ht<15 %)
- **Hypoglycaemia** (glycaemia < 2.2 mmol/l or < 0.4 g/l)
- **Metabolic acidosis** (plasma bicarbonate < 15 mmol/l)
- **Hyperlactaemia** (plasma lactate > 5 mmol/l)
- **Hyperparasitaemia** (*++++ or* >200 000 parasites/µl)
- **Renal failure *or scanty urine, oliguria*** (urine output < 400 ml/24h or plasma creatinine> 265 µmol/l in adult or urine output < 12 ml/kg/24h or plasma creatinine above the age-related normal range, persisting after rehydration in children)
- **Frequent vomiting *(vomiting everything*** with inability to retain food or medicines)

[1] Severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* (2000) **94**, supplement 1

If you see these signs:

-ALWAYS make a blood smear

-Start treatment immediately even without any thin-thick blood smear result

Remember

- It is possible (though unusual) for a patient with severe malaria to have a negative blood slide. If there is no other obvious cause of the illness, the health worker should treat for malaria if there is a high suspicion of malaria even where the slide is negative.
- A patient with malaria may have another disease at the same time.

3.4. Differential diagnosis:

The symptoms of malaria are very similar to many other infections especially in children. It is possible to have malaria and another infection at the same time.

Differential diagnosis for uncomplicated malaria:

- Viral infections (influenza or common cold, measles, dengue)
- Bacterial infections (ear, throat or chest).

Differential diagnosis for severe or complicated malaria:

- Meningitis or encephalitis
- Typhoid fever
- Septicaemia
- Pneumonia
- Dengue haemorrhagic fever (in children)
- Eclampsia (in pregnant women).
-

3.5. Diagnostic tests for malaria

3.5.1 Microscopic examination of a blood slide:

Definitive diagnosis can only be made with a blood slide examination this remains the Gold Standard for Malaria diagnosis.

3.5.2. Rapid diagnostic tests (RDT): "dipstick"

Can diagnose *P. falciparum* and other types of malaria, including *P. vivax*

It is important to use a combination RDT test that differentiates between *P. falciparum* and *P. vivax* malaria. Use of an RDT that identifies *P. falciparum* only is not recommended.

Remember:

The thin-thick blood smear can sometimes be negative during severe malaria. A blood smear examination is preferred over the RDT in severe cases, as it has the added advantage of not detecting only parasites, but can also be used to diagnosis other possible illness or define the extent of severity of the malaria infection.

3.6 Summary

Definitive diagnosis can only be made with a blood slide examination or a rapid diagnostic test.

If it is impossible to have a blood slide or a rapid diagnostic test examined, refer to the nearest public health facility where diagnosis is possible.

Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not accessible[2].

[2] *Guidelines for the treatment of malaria – 2nd edition.* WHO, 2010.

4. TREATMENT OF UNCOMPLICATED MALARIA IN ADULTS

4.1. Principles

Recommendations by the National Malaria Programme for ***P. falciparum, P. vivax or P. malariae*** **malaria** are as follows:

1st line treatment:

- **Dihydroartemisinin-Piperaquine (DHA-PIP) + Primaquine***

OR

- **Artesunate + Mefloquine (A+M) + Primaquine ***

2nd line treatment:

- **Quinine + Doxycycline/tetracycline + Primaquine ***

National Malaria Program recommends using atovaquone-proguanil or Artesunate +Pyronaridine with directly observed treatment (DOT) and strict follow up for 28 days for P.falciparum in Pailin province and other areas of ACT resistance in western Cambodia (please see table 1 page 9 and request special instruction from CNM)

4.2. Treatment according to RDT or thin-thick blood smear results

4.2.1. Positive RDT or thin-thick blood smear

The 1st line treatment for *P. falciparum, P. vivax, P. malariae or mixed infections:*

- DHA-PIP (dihydroartemisinin + piperaquine) for 3 days: dihydroartemisinin (DHA) 40 mg tablets and piperaquine (PIP) 320 mg tablets.
- Give Primaquine:
  - P. Falciparum , P. malariae: single dose 45mg

- P. vivax, P. ovale: 45mg/week x 8 weeks

OR

- Artesunate 50mg + Mefloquine 250mg (A+M)
- Give Primaquine:
  - P. Falciparum , P. malariae: single dose 45mg
  - P. vivax, P. ovale: 45mg/week x 8 weeks

Primaquine is recommended by the World Health Organization (WHO). In Cambodia, Primaquine is suggested for G6PD deficiency people if the Primaquine study show safety. Some health care providers may wish to test patient for G6PD deficiency before treatment. **(please see table 1 page 9 and request special instruction from CNM)**

Schedule for DHA-PIP (40 mg/320mg)

Weight (kg)	Age (years)	Number of Tablets			
		Dihydroarteminisinin-Piperaquine			
		Day 1	Day 2	Day 3	Total
≥ 40kg – 79kg	> 15 yrs	3 tablets	3 tablets	3 tablets	9 tablets
≥ 80 kg		4 tablets	4 tablets	4 tablets	12 tablets

Schedule for A+M5

		Number of tablets					
Weight (kg)	Age (years)	*Artesunate*			*Mefloquine*		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
w≥40	>15	4	4	4	2	2	1

Recommendations:

- Give the dosage by weight; if there is no scale, treat by age.
- It is important to give the correct dose (if the treatment is incomplete, the patient may have relapses)
- Explain to the patient:

- Causes of malaria and how to prevent it
- The importance of compliance to the treatment and of taking all the tablets
- The possibility of having side effects (Common side effects include anaemia, headache, heart rhythm disturbances)
- The importance of consulting Doctor before the stage of severe malaria.

DHA-PIP Adverse effects

Adverse effects are rare. Most of them are due to piperaquine affecting the digestive tract (nausea, diarrhea, loss of appetite etc). Rare allergic reactions (rash, pruritus) have also been reported.

Important notes about the treatment by A+M or DHA-PIP :

1. Resistance to Mefloquine alone exists already in Cambodia.
2. To stop resistance from spreading, give the correct dosage of " A+M or DHA-PIP" according to the patient's weight.
3. Watch all patients swallowing the first tablets on D_1 and observe for 1 hour after its intake.
4. To avoid vomiting after the first tablets:
   - Lower the patient's fever with damp cloths and give paracetamol 30-60 minutes before the anti-malarial drugs are administered; ask the family to fan the patient.
   - Let the patient rest for 30-60 minutes before treatment (especially children < 5 years old).
   - Make sure the child is calm and not afraid, when the patient has to take the medicine.
5. If the patient already took quinine, you must wait for 12 hours after the last quinine dose before giving $A+M_5$ (Artesunate + Mefloquine) to the patient.

Contra-indications[3]:

Do not give Mefloquine:

- To patients who have received Mefloquine in the previous 4 weeks
- To patients with a history of allergy to Mefloquine
- To patients on digoxin or β-blocker
- To patients with cardiac disorder
- To patients with epileptic disorder
- To patients with a psychiatric disorder
- To patients with a kidney failure or liver failure

Such patients should be treated with quinine + Doxycycline/tetracycline for 7 days.

Pregnant Women

- Quinine is safe for pregnant women in all three trimesters.
- A+M is safe for pregnant women only for second and third trimesters.
- DHA-PIP is safe for pregnant women in second and third trimesters, but unknown safety in first trimester.

4.2.2. Negative RDT or thin-thick blood smear:

- If the RDT is negative and the clinical signs are typical for malaria, re-test, or look for other illnesses as per sector protocol (see decision charts on pages 7-8)
- If the RDT is negative and the clinical signs don't suggest malaria, do not treat like malaria; look for another illness.
- If symptoms persist, ask for another RDT or blood slide

[3] The use of antimalarial drugs Report of a WHO Informal Consultation. WHO, Geneva, 13-17 November 2000

4.2.3. If RDT and/or thin-thick blood smear are not available:

- If you cannot have any RDT or slide result within the same day: admit, observe the patient and wait for the results.
- If there is no possibility of RDT or slide results, refer the patient based on the clinical signs and symptoms.

In case of severe or complicated malaria, start treatment with Artesunate IV (or if not available, then artemether IM) and DHA-PIP
(See guidelines for severe malaria, pages 22 to 34)

4.3. Follow-up of uncomplicated malaria:

4.3.1. 1st line treatment failure by DHA-PIP or A+M:

If a patient returns with symptoms, it may be a different disease or the patient did not take the treatment appropriately (inadequate absorption or incomplete treatment).

1) If the patient's compliance is doubtful, then re-treat with DHA-PIP (dihydroartemisinin + piperaquine) or A+M
2) If the patient did complete his/her 3-day treatment with DHA-PIP or A+M and comes back before the 28th day after treatment, give **quinine + doxycycline/tetracycline**
3) Repeat the Primaquine single dose in case of P.falciparum and 8 weekly doses in case of P.vivax
4) If the patient comes back after the 28th day after treatment, suspect a new malaria infection and treat with DHA-PIP (dihydroartemisinin + piperaquine) or A+M according to the RDT or slide results

If symptoms persist despite taking a complete treatment with DHA-PIP (dihydroartemisinin + piperaquine) or A+M and if the patient did not vomit any tablets, then the parasite could be drug resistant

Record treatment failure in the register
It is important for National Malaria Centre to know about such cases

4.3.2. Parasitological monitoring:

1. In health centres or health posts not equipped with microscope:
   - Monitor the clinical improvement
   - If symptoms persist, refer the patient to the nearest referral hospital, where according to the slide results, he/she will be treated or not with quinine + doxycycline

<u>Note:</u> RDTs are not suitable for follow-up after treatment. They often remain positive up to and even after D_{14}, even though all the parasites have been killed

2. In referral hospitals and health centres equipped with a microscope:
   - Make a slide 72 hrs after treatment to confirm the negativity of the slide or the decrease of the parasitaemia compared to the Day of Admission (D1)
   - If the parasitaemia decreased between D1 and testing 72 hrs after treatment, make another slide on D7 to confirm its negativity
   - If the parasitaemia did not decrease from D1 and testing 72 hrs after treatment, refer the patient to the nearest referral hospital, where he/she will be treated with quinine + doxycycline.

4.4. 2nd line treatment by quinine + Doxycycline/tetracycline for all malaria species

4.4.1. Treatment:

Dosage:

1) The dose of quinine is 10 mg/kg x 3 times/24 hours (30mg/kg/day)
2) The dose of Doxycycline is 100mg x 2 times/24 hours for adults (2mg/kg x 2 times/24 hours for children >8 years).
   Or tetracycline 8.3mg/kg x 3 times / 24 hours (25mg/kg/day)
3) **The quinine + Doxycycline/tetracycline treatment must be given for 7 days.**
4) If possible, treat the patient by weight. Otherwise, treat by age.

Contraindications:

Doxycycline/tetracycline is not recommended for Children under 8 years old and pregnant women

Recommendations:

1) Quinine is safe for pregnant women if used in the correct dose.
2) For small children, crush tablets and mix with water and sugar.
3) Explain to the patient:
   - Side effects of quinine (vertigo, nausea, tinnitus)
   - The importance of taking a correct treatment for 7 days
   - Not to take quinine as a preventive medicine for malaria
   - To take antimalarial drugs only after making a dipstick or blood test
   - The causes and prevention measures of malaria

4.4.2. Parasitological monitoring under quinine + doxycycline/tetracycline:

1) Ask all patients to return 72 hrs after beginning treatment and D_7 after the start of treatment to check treatment efficacy.

2) Make a slide 72 hrs after beginning treatment, only if symptoms persist. Always make a slide on D_7.
3) A positive slide 72 hrs after beginning treatment does not always mean that the parasite is resistant to the treatment. Importance should be given to parasite count between D_1 and D_3. If the parasite count on D_3 is higher than on D_1: admit and observe patient carefully. Repeat blood smear on D_4 to confirm treatment failure and contact CNM.
4) A positive slide on D_7 may mean treatment failure.

4.4.3. Treatment failure by quinine + doxycycline/tetracycline:

1. If blood slide remains positive (trophozoites are present) on D7, treat for a total of 10 days, until D10.
2. If blood slide remains positive on D10, treat for a total of 14 days, until D14.
3. On D14, if trophozoites are still present, check if the correct dose was taken.
4. If so, contact the next level of referral.

Remember:
A slide positive only for gametocytes has no clinical significance and does not indicate anti-malarial drug failure.

5. TREATMENT OF SEVERE OR COMPLICATED MALARIA IN ADULTS

5.1. Different treatment guidelines for severe or complicated malaria

5.1.1a. 1st line treatment Artesunate IV / IM + DHA-PIP + Primaquine

Treat with Intravenous (IV) Artesunate. If not available then treat with Intramuscular (IM) artemether. Followed by a full oral course of DHA-PIP once the patient can swallow. PLUS single dose Primaquine.

CAUTION!

Do not confuse intravenous (IV) Artesunate vial with intramuscular (IM) artemether ampoules! Read the label carefully before administering to the patient.

Dosage:

Give Artesunate IV 2.4mg/kg body weight at the following times:

- On admission give dose 1
- After 12 hours dose 2
- After 12 more hours dose 3
- Continue treatment every 24 hours to the maximum of seven doses
- Give Primaquine *and* full 3-day oral dose of DHA-PIP when the patient can swallow

Examples: Artesunate IV

Patient Weight (Kg)	AS mg/kg	Total Dose (mg)	No. of vials (60mg)	5% sodium bicarbonate (ml)	Normal saline/ 5% dextrose
50 Kg	2.4	120	2	2	10ml *
25 Kg	2.4	60	1	1	5ml
12.5 Kg	2.4	30	0.5	0.5	2.5ml

* Note: 60mg IV + 1ml 5% Sodium bicarbonate + 5ml Normal Saline or 5% Dextrose = 6mls

Examples: Artesunate IM

Patient Weight (Kg)	AS mg/kg	Total Dose (mg)	No. of vials (60mg)	5% sodium bicarbonate (ml)	Normal saline/ 5% dextrose
50 Kg	2.4	120	2	2	4ml *
25 Kg	2.4	60	1	1	2ml
12.5 Kg	2.4	30	0.5	0.5	1ml

* Note: 60mg IM + 1ml 5% Sodium bicarbonate + 2ml normal saline or water = 3mls

5.1.1b. 1st line treatment artemether IM + DHA-PIP + Primaquine:

Dosage:

D_1 (day of admission) **Give artemether 3. 2 mg/kg (IM)**
D_2 **Give artemether 1.6 mg/kg (IM)**
From D_3 to D_5 **Give artemether 1. 6 mg/kg each day (IM)**
From D_6 **Give DHA-PIP for full three days dose + single dose of Primaquine**

Intravenous fluids are required when treating a patient with artemether IM. Most patients with severe or complicated malaria are unable to eat or drink. They need intravenous fluid.

Maintenance intravenous (IV) fluid:

Give intravenous fluid of 500 ml × 3 for 24 hours: give 2 bottles of dextrose 5% or dextrose 10%, plus 1 bottle of saline of 0.9%. (Give the patient an infusion depending on his/her hydration status).

Recommendations:

1) If you cannot weigh the patient, estimate the patient's weight.
2) If the patient has regained consciousness and is able to swallow tablets **before the 5th day** of treatment by artemether IM, always give A+M$_5$ or DHA- Piperaquine watch the patient swallow the first dose of tablets.

Example:

For a patient who weighs 50 kg, give:

on D$_1$ give : artemether 3.2 mg × 50 = 160 mg IM

Note: in 1 ampoule there is 80 mg of artemether, therefore you need to inject 2 ampoules IM as a single dose.

From D$_2$ to D$_5$, give:

Artemether 1.6 mg × 50 = 80 mg IM

That is 1 ampoule as a single dose each day.

From D$_6$, give: DHA-Piperaquine during 3days

5.1.2. Artesunate suppositories before referring to Referral Hospital:

Start treatment with suppositories of Artesunate 200 mg before the patient goes to the nearest referral hospital. (Cf. table 5 page 50)

Weight (kg)	Age (years)	Artesunate suppositories (mg)	No. of suppositories
≥ 40kg	> 15 yrs	200	**2**

Before referring, fill the referral form including dosage of drug administered and timing.

Maintenance of intravenous (IV) fluid:

Give intravenous fluid of 500 ml × 3 for 24 hours: give 2 bottles of dextrose 5% or dextrose 10%, plus 1 bottle of saline of 0.9%. (Give the patient an infusion depending on his/her hydration status).

Contraindications[4]*:*

Artesunate or artemether is not recommended during the 1st trimester of pregnancy.
Preferably give IV Quinine for at least 7 days followed by full oral treatment when the patient is able to swallow.

Recommendations:

- If you cannot weigh the patient, estimate the patient's weight.
- If less than one vial is needed per dose the remaining portion should be discarded if not immediately used for another patient. It must not be kept for more than 1 hour after reconstitution.
- Dosage should be rounded up to next whole number in mls, e.g. for a child requiring 4.3mls, round up to 5mls.
- IV injection should be given as a slow direct injection for 4-5 mins.
- Inject immediately after preparation
- Discard any solution if not used within one hour of reconstitution
- Prepare a fresh solution for each administration.
- If the patient has regained consciousness and is able to swallow tablets before the 5th day of treatment by Artesunate IV/IM or

[4] Guideline for the treatment of malaria second edition. WHO, Geneva, 2010

artemether IM always give DHA-PIP and Primaquine and watch the patient swallow the first dose of tablets.

5.1.3. 2nd line treatment with Quinine IV + Doxycycline/tetracycline

Dosage and treatment protocol:

D_1 (day of admission)

1st infusion:

500 ml dextrose 10% + quinine dihydrochloride 10 mg/kg over 4 hours (40 drops/minute)

2nd infusion:

500 ml dextrose 10% + quinine 10 mg/kg over 8 hours (20 drops/minute)

3rd infusion:

500 ml dextrose 10% + quinine 10 mg/kg over 8 hours (20 drops/minute)

D_2

Give 3 infusions at 8-hours intervals, identical to the 3rd infusion of D_1:

500 ml dextrose 10% + quinine 10 mg/kg (20 drops/minute)

From **D_3** to **D_7**

If the patient has regained consciousness and is able to take oral tablets:

STOP THE INFUSION

- Give quinine 10mg/kg x 3 times per day (every 8 hours) to complete 7 days course
- Plus Doxycycline/tetracycline100mg for adult x 1 time per day (every

24 hours) to complete 7 days course

(See Tables 6a and 6b, pages 52-53).

If the patient has not recovered from coma:

- Give drugs and infusions as on D_2

Recommendations:

If you cannot weigh the patient, estimate his/her weight.

- Always use a 10% dextrose infusion as quinine can cause hypoglycemia.
- If Doxycycline is not available, substitute/replace with tetracycline
- Doxycycline and tetracycline should not be used for children under 8 years old; use Clindamycine if available (5mg/kg per day).

To make dextrose 10%: add 50 ml of dextrose 50% to 500 ml of dextrose 5% for infusion

- Start oral treatment when the patient regain consciousness and can swallow.
- Treatment with quinine and tetracycline/doxycycline should be continued for 7 days.
- If the patient goes home before finishing the tablets, explain to the patient how and when to take the tablets.
- Explain that it is necessary to take all the tablets to make sure that malaria does not come back and to prevent drug resistance development.

Important notes about quinine:

- One ampoule of 2 ml contains 600 mg of quinine dihydrochloride.
- In case of a renal failure (if the patient passes only a small amount of dark urine and appears well hydrated), reduce after 24 hours the

dose of quinine by 50%, i.e. quinine 5 mg/kg in an 8-hour infusion, 3 times per 24 hours.

- If haemoglobinuria occurs, **DO NOT STOP or REDUCE QUININE.** If anaemia is severe, transfuse.

5.2. Follow-up of severe malaria

5.2.1. Clinical monitoring

Clinical surveillance of a severe malaria patient relies on a daily clinical examination, looking for the clinical improvement of the patient compared to admission day:

- Temperature (if > 39°C – sponge patients or wrap children in moist towel)
- Blood pressure and pulse
- Respiratory rate (if respiratory rate increases, slow the infusion down and raise the head of the bed)
- Fluid intake and urine output
- Rate of infusions monitoring
- Anaemia monitoring
- Keep the patient clean and do not allow lying on wet bed.

Care of the comatose patient

- Assess and monitor coma by using the modified Glasgow coma scale for adults or Blantyre coma scale for children (page 36-42).
- Maintain the airways (remove denture) – nurse the patient on their side, with the neck extended and the mouth clear of mucus etc.
- Turn the patient every hour (ask the patient's family for help).
- Keep a record of fluid intake and output.
- Insert a urethral catheter by sterile technique.
- If the diagnosis of malaria in a comatose patient is not clear – consider doing a lumbar puncture.
- Always examine for hypoglycaemia and treat it.

5.2.2. Parasitological monitoring:

1) All patients with severe malaria should have a daily blood slide performed until there are 2 consecutive negative slides.
2) The daily blood slide results including parasitaemia (counting of parasites) will help you to see if the patient is improving.
3) Always take a blood slide on D_7 to see if malaria is cured.
4) If the blood slide on D_7 shows presence of gametocytes, that is not a treatment failure and no special treatment is needed.

5.3. Additional treatments

5.3.1. Rehydration

Check for signs of dehydration:

- Decreased skin turgor
- Dry mucous membranes
- Oliguria
- Rapid pulse
- Hypotension

Adults: Give infusion of Ringer Lactate or saline 0.9% 1000 ml over 1 hour.

Children:

- For severely dehydrated children, give an infusion of saline 0.9% or Lactate Ringer 20-30 ml/kg in 1-2 hours.
- For mildly dehydrated children, give an infusion of saline 0.9% or Lactate Ringer 5ml/kg/h or give ORS through nasogastic tube 20 ml/kg/h until rehydrated.

Monitor intake and output:

- Especially in prolonged coma
- Measure oral intake (oral or intravenous fluid) and urine output (volume of urine)
- Record intravenous fluid administration
- Take vomiting into account

5.3.2. Treatment and prevention of convulsions:

1) Reduce fever: sponge with cool water, fan the patient and give paracetamol (15 mg/kg per dose).
2) Give diazepam (VALIUM®)[5]:
   - *for children:* 0.5 mg/kg per rectum (maximum 10 mg per dose) using a syringe without needle
   - *for adults:* 1 ampoule of 10 mg IV, IM or per rectum
3) Give diazepam every 15 minutes until convulsion stops.

DO NOT give ASPIRIN – it is dangerous with severe malaria.

5.3.3. Glycaemia stabilization:

Evaluation of blood glucose level:

1) Use dextrostix if available *(glycaemia <2.2 mmol/l or <0.4g/l)*.
2) If you do not have dextrostix, look for clinical signs of hypoglycaemia:
   - All patients with malaria, with problems of consciousness (confusion, coma) especially children and pregnant women.
   - Patients who had awaken from coma and become comatose again.
   - Patients with convulsions.
   - Patients whose coma deepens despite anti-malarial treatment.

Treatment of hypoglycaemia:

Adults:

Give IV infusion (50 ml) of dextrose 50% (never give bolus 50% dextrose, it must be diluted to at least twice it volume to prevent vascular infarction): followed by an infusion of dextrose 10%. Repeat once when the patient's condition does not improve.

[5] Vidal 1999

Children:

Give IV infusion (1ml/kg) of dextrose 50% followed by an infusion of dextrose 10%. Repeat once when the patient's condition does not improve.

5.3.4. Renal status evaluation:

The patient is passing adequate amount of urine:

- *Adults:* Normal > 450 ml/24hours
- *Children:* Normal > 2 ml/kg/hour

Stop rehydration efforts when the patient is clinically rehydrated.

If the patient is passing less than 450 ml/24hours:

- Check hydration status, rehydrate if necessary.
- If hydration status is normal, monitor urine output and compensate for volume, plus 10 ml/kg for insensible loss.

If the patient is not passing any urine and appears well hydrated, carry out the furosemide test.

FUROSEMIDE (LASILIX®) TEST:

Only give furosemide when you are sure the patient is rehydrated.

Note: children very rarely require furosemide.

Adults: give 40 mg of furosemide slowly IV over 15 minutes.

Children: give 2 mg/kg of furosemide slowly IV.

Test results:

- If the patient urinates: the prognosis is good and the patient is likely to recover.
- If the patient does not urinate:

- Repeat the test 1 hour later by using 80 mg of furosemide (or 4 mg/kg for children).
- If still no urine after 1 hour, give 120 mg of furosemide (or 8 mg/kg for children).

- If the patient still does not urinate: restrict fluids to cover losses plus 10 ml/kg for insensible loss.
- If possible transfer the patient for peritoneal dialysis.
- Do not give diuretics before rehydrating the patient.

5.3.5. Anaemia treatment:

Anaemia may be caused by:

- haemolysis and haemoglobinuria
- haemorrhage
- bacterial sepsis

Treatment:

Transfuse if haematocrit is below 15% or haemoglobin is less than 6 g/dl.

1) Use fresh whole blood 20 ml/kg or packed red cells 10 ml/kg (packed red cells are preferred in children)
2) Although administration of iron will not help if anaemia is due to haemolysis, severe anaemia is usually due to many causes. Therefore anaemic patients should be given iron and foliate tablets to take home, and advice about iron-rich foods.

5.3.6. Treatment of other co-infections:

Prevent pulmonary infections:

- position the patient correctly on the side
- remove secretions by suction

Prevent urinary infections:

- use sterile urinary catheters
- wash hands
- use sterile gloves
- clean and disinfect the urogenital area before inserting the catheter

Treatment of co-infections:

1) If there are signs of pulmonary infection:
   - Raised respiratory rate
   - Cough
   - Crepitations on auscultation

Treat quickly with antibiotics according to the Clinical and Therapeutic Guideline, Referral Hospitals of the Ministry of Health.

2) If there are signs of septicaemia:
   - Hypotension
   - Cold, clammy skin
   - Rapid, week pulse

Treat quickly with antibiotics according to the Clinical and Therapeutic Guideline, Referral Hospitals of the Ministry of Health.

5.3.7. Management of Other Complications:

Acute pulmonary oedema (APO)

This serious condition can be recognized by:

- increased respiratory rate
- fine crepitations on auscultation

APO can be caused by overhydration (fluid overload), or by the malaria parasite damaging the lungs directly.

Treatment:

1. Keep the patient upright
2. Stop or slow down all IV fluids
3. Give the patient a high concentration of oxygen
4. Give the patient furosemide 40 mg IV
5. If the patient still does not urinate, increase progressively furosemide until 120 mg IV

Spontaneous bleeding and DIC (disseminated intravascular coagulation)

Clinical features:

- Bleeding gums, epistaxis, petechiae, subconjonctival haemorrhage
- Haematemesis or melaena

Treatment:

1. Continue IV fluid administration
2. Transfuse fresh whole blood
3. Slow IV injection of vitamin K may be helpful: 10 mg for adults

Haemoglobinuria:

Clinical findings:

- Patient with a G6PD deficiency who have taken Primaquine
- Black water fever (haemoglobinuria associated with anaemia and kidney failure) can occur when the patient has taken quinine inappropriately.

Treatment:

1. Continue appropriate antimalarial treatment
2. Transfuse fresh whole blood if needed
3. Peritoneal dialysis is sometimes needed

6. MANAGEMENT OF MALARIA IN CHILDREN

6.1. Clinical diagnosis of malaria in children:

Uncomplicated malaria features[6]*:*

- History of travelling to or inhabiting endemic area
- Paroxysms of high fever at 39-40°C
- Stomach discomfort in infants and young children with nausea, vomiting and sometimes diarrhoea
- Algid syndrome: crying and restlessness in infant and young child, headache in older ones, often associated with an acute and distend abdomen (which might simulate a surgical abdomen)
- Neurological syndrome: drowsiness, confusion, meningism, evocative of encephalitis
- Splenomegaly is common and might be associated to hepatomegaly
- Broncho-tracheal signs: cough is common with sometimes a labial herpes (which might be confusing)

Notes:

It can be very difficult to differentiate uncomplicated malaria from severe malaria in children presenting neurological signs. Indeed, high fever can itself explain a transient delirium, which disappears as the temperature drops back to normal. Fever can also induce convulsion in children up to 4-5 years old but convulsions generally occur only once.

As a child's clinical condition deteriorates rapidly (sometimes 2-3 days after fever starts), treatment for severe or complicated malaria is strongly recommended and as early as possible.
(For severe or complicated malaria signs cf. page 11)

[6] Martin Danis et Jean Mouchet. Paludisme. Universités Francophones, Ellipses/Aupelf, 1991

6.2. Treatment of uncomplicated malaria in children:

6.2.1. Treatment according to RDT or thin-thick blood smear results:

P. falciparum, P. vivax, P. malariae or mixed infections:

The 1st line treatment for uncomplicated *P. falciparum*, *P. vivax*, *P. malariae* and mixed infection malaria in children is:

- Dihydroartemisinin + piperaquine 2-4mg/ kg DHA and 20mg/kg piperaquine.
- Primaquine 0.75mg/Kg single dose for P. falciparum
- Primaquine 0.75mg/Kg per week x 8 weeks for P. vivax

Or

- (A+M) +Primaquine

Remarks:

National Malaria Program recommends using atovaquone-proguanil with directly observed treatment (DOT) and strict follow up for 28 days for P.falciparum in Pailin province and other areas of ACT resistance in western Cambodia (please request special instruction from CNM)

Dosage:

For children from 3 months to < 15 years old, the 1st line treatment is as follows:

Dihydroartemisinin – Piperaquine (DHA-PIP) (40 mg/320mg)

Weight (kg)	Age (years)	Day 1	Day 2	Day 3	Total Tablets
5 ≤ BW < 10	3 ms ≤ a <1 yr	½ tablet	½ tablet	½ tablet	**1 ½ tablets**
10 ≤ BW < 19	1 yr ≤ a < 5 yrs	1 tablet	1 tablet	1 tablet	**3 tablets**
19 ≤ BW < 30	5 yrs ≤ a < 10 yrs	1½ tablets	1½ tablets	1½ tablets	**4 ½ tablets**
30 ≤ BW < 40	10 yrs ≤ a < 15 yrs	2 tablets	2 tablets	2 tablets	**6 tablets**

6.2.2. Quinine + Doxycycline/tetracycline:

2nd line treatment

Use quinine + Doxycycline/tetracycline only if the **1st line treatment has failed** or if the patient is **contraindicated** to dihydroartemisinin + piperaquine
Do not give Tetracycline/Dxycycline to chidren age 8 years or less.

Dosage:

1) The dose of quinine is 10 mg/kg x 3 times/24 hours (30mg/kg/day)
2) The dose of Doxycycline is 100mg x 2 times/24 hours for adults (2mg/kg x 2 times/24 hours for children >8 years)

   Or

   Tetracycline 8.3mg/kg x 3 times / 24 hours (25mg/kg/day)
3) The quinine + Doxycycline/tetracycline treatment must be given for 7 days.
4) If possible, treat the patient by weight. Otherwise, treat by age.

6.3. Treatment of severe malaria in children:

6.3.1. Artesunate IV or artemether IM plus DHA-PIP and Primaquine

Indication:

This is the 1st line treatment for severe malaria (page 22-25)

Maintenance intravenous fluid:

CHILDREN OVER 25 Kg WEIGHT:

Give intravenous fluid of 500 ml × 3 for 24 hours: give 2 bottles of dextrose 5% or dextrose 10%, plus 1 bottle of saline 0.9%.

CHILDREN 25 Kg OR LESS:

Calculate the amount of infusion fluid required as follows:

Bodyweight	Infusion fluid
< 10 kg	100 ml/kg/24hours
10 – 25 kg	60-90 ml/kg/24hours

Use dextrose 10% or dextrose 5%. Alternate with saline 0.9% aiming at keeping a ratio of 2 parts dextrose solution to 1 part saline.

Recommendations:

1) If you cannot weigh the patient, estimate the patient's weight.
2) If less than one vial is needed per dose the remaining portion should be discarded if not immediately used for another patient. It must not be kept for more than 1 hour after reconstitution.
3) Dosage should be rounded up to next whole number in mls, e.g. for a child requiring 4.3mls, round up to 5mls.
4) IV injection should be given as a slow direct injection for 4-5 mins.
5) Inject immediately after preparation
6) Discard any solution if not used within one hour of reconstitution
7) Prepare a fresh solution for each administration.
8) If the patient has regained consciousness and is able to swallow tablets before the 5th day of treatment by artesunate IV/IM or artemether IM always give DHA-PIP and Primaquine and watch the patient swallow the first dose of tablets.

Examples: Artesunate IV

Patient Weight (Kg)	AS mg/kg	Total Dose (mg)	No. of vials (60mg)	5% sodium bicarbonate (ml)	Normal saline/ 5% dextrose
25	2.4	60	1	1	5ml
12.5	2.4	30	0.5	0.5	2.5ml

* Note: 60mg IV + 1ml 5% Sodium bicarbonate + 5ml Normal Saline or 5% dextrose = 6mls

Examples: Artesunate IM

Patient Weight (Kg)	AS mg/kg	Total Dose (mg)	No. of vials (60mg)	5% sodium bicarbonate (ml)	Normal saline/ 5% dextrose
25	2.4	60	1	1	2ml
12.5	2.4	30	0.5	0.5	1ml

* Note: 60mg IM + 1ml 5% Sodium bicarbonate + 2ml normal saline or water = 3mls

Examples: Artemether IM

On **D_1**, give **artemether 3. 2 mg × 12.5kg = 40 mg** (= ½ ampoule) if Artesunate IV is not available

In a 1 ml ampoule there is 80 mg of artemether, therefore for this patient you need to inject IM:

$$\frac{1 \times 40}{80} = 0.5 \text{ ml (= 40 mg)}$$

Use a 1 or 2 ml syringe to measure 0.5 ml of artemether.

From **D_2** to **D_5**, give **artemether 1.6 mg × 12.5 = 20 mg IM** (= ¼ ampoule)

In a 1 ml ampoule there is 80 mg of artemether, therefore you need to inject IM until D_5:

$$\frac{1 \times 20}{80} = 0.25 \text{ ml (= 20 mg)}$$

Use a 1 or 2 ml syringe to measure 0.25 ml of artemether (if at all possible, use a tuberculin syringe to measure exactly).

On **D_6** give **DHA-PIP as an oral dose for 3 days + Primaquine**

6.3.2. Artesunate suppositories before referring to referral hospital:

Start the treatment with suppositories of Artesunate 50mg (5-10mg/kg) before the patient goes to the nearest referral hospital.

Weight (kg)	Age (years)	Artesunate suppositories (mg)	No. of suppositories
5 ≤ BW < 10	3 ms ≤ a <1 yr	50	1
10 ≤ BW < 19	1 yr ≤ a < 5 yrs	50	2
19 ≤ BW	5 yrs ≤ a < 14 yrs	200	1

Give the patient an infusion depending on his/her hydration status.

Note

If the patient's transportation lasts for more than 24 hours, repeat suppository dosage of Artesunate (10mg/kg/day for a total of 5 days) and give A+M5 or DHA-Piperaquine when the patient recovers or at the end of treatment

Suppositories of Artesunate 50mg are safe, easy to use and proved to be as effective as parenteral artemether IM or Artesunate IV in severe malaria treatment.

Suppositories should be inserted blunt end first in the anal canal. If the suppository is expelled within 1 hour, a new one should be inserted. If the suppository is expelled a 2nd time also, replace it only if you can see that it has been expelled.

6.3.3. Quinine IV + Doxycycline/Tetracycline

(Cf. dosage, recommendations, follow-up of a severe malaria, additional treatments page 26-34)

7. MANAGEMENT OF MALARIA IN PREGNANT WOMEN

7.1. Clinical diagnosis of malaria in pregnant women[7]:

Same clinical features as in adult malaria except that the risk of evolution into severe or complicated malaria, in case of infection by *P. falciparum*, is faster and that relapses in infections by *P. vivax* and *malariae* are more common.

Adequate treatment is important because of high risks of premature delivery, congenital infection, low birth weight and stillbirth.

Hypoglycaemia, anaemia and pulmonary oedema are common complications of malaria in pregnant woman.

7.2. Treatment of uncomplicated malaria in pregnant women:

7.2.1. *P. falciparum, P. vivax or P. malariae*:

- Quinine is safe for pregnant women in all three trimesters.
- A+M is safe for pregnant women only for second and third trimesters.
- DHA-PIP is safe for pregnant women in second and third trimesters, but unknown safety in first trimester.

7.2.1.1. During the 1st trimester of pregnancy:

The 1st line treatment for *P. falciparum, P. vivax, P. malariae or mixed infections:*

GIVE QUININE ALONE FOR 7 DAYS

(Cf. table 6a-b page 51)

Martin Danis et Jean Mouchet. Paludisme. Universités Francophones, Ellipses/Aupelf, 1991

7.2.1.2. During the 2nd and 3rd trimester of pregnancy:

The 1st line treatment for *P. falciparum, P. vivax, P. malariae or mixed infections:*

- DHA-PIP (Dihydroartemisinin + Piperaquine) for 3 days

OR

- Artesunate + Mefloquine (A+M) for 3 days

(Cf. tables 1 and 2, pages 47-48)
(Cf. Recommandations page 14-19)

7.3. Treatment of severe malaria in pregnant women:

7.3.1. During the 1st trimester of pregnancy:

Give infusions of QUININE alone followed by per oral treatment when the patient is able to swallow for at least 7 days

(Cf. dosage, recommendations, follow-up of a severe malaria, additional treatments page 26-34)

7.3.2. During the 2nd-3rd trimester of pregnancy:

Give infusions Artesunate IV or IM injection followed by 3 days DHA-PIP or A+M 3days

7.4. Screening for asymptomatic malaria in pregnant women

- Screen all pregnant women for malaria during each anti-natal visit in health facilities located in malaria areas.
- Screen all pregnant women on monthly basis for malaria who live in Village Malaria Worker (VMW) during 2nd and 3rd trimester of pregnancy.