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FOREWORD TO THE THIRD EDITION

Malaria kills more people than any other single disease in Uganda. It is the most frequent cause of attendance at health facilities.

Most attacks of malaria which occur in Uganda are uncomplicated. Although uncomplicated malaria does not often cause death, it must be diagnosed early and treated promptly because:

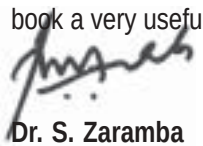
i. It may deteriorate and become severe in which case the risk of death of the patient is high.
ii. It causes economic loss since people who are sick are not able to work or attend school.

This third edition of the guide on 'Management of Uncomplicated Malaria' has been written to include the new policy on malaria case management.

Following a review of information on malaria treatment available within and outside Uganda by a committee of experts, the Ministry of Health has changed the national policy on malaria treatment from Chloroquine + Sulfadoxine/Pyrimethamine combination to Artemisinin-based Combination Therapy (ACTs). Henceforth:

i. Artemether/Lumefantrine is the first line treatment for uncomplicated malaria and Artesunate + Amodiaquine the alternative. For a pregnant woman during the first trimester and for children less than 5kg body weight ACTs are not recommended. Quinine should be used instead.
ii. The recommended second line medicine is oral quinine for all patients.
iii. Parenteral quinine is the recommended treatment for severe and complicated malaria in all patients. However parenteral artemisinin derivatives may be used if quinine is contraindicated or not available.
iv. Sulfadoxine/Pyrimethamine is the recommended medicine for intermittent preventive treatment (IPT) during pregnancy.
v. For the treatment of clinical malaria during pregnancy, quinine is the recommended treatment.

Health workers, particularly those working in health centres and clinics, will find this book a very useful working tool.



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Ministry of Health

ACKNOWLEDGEMENT

The Ministry of Health acknowledges with thanks, the efforts of all individuals and institutions that contributed towards the review of the Second Edition and compilation and production of this Third Edition of the book especially the following:

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ACRONYMS & ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
AL	Artemether/Lumefantrine
CFI	Community Focused Interventions
DDHS	District Director of Health Services
HSD	Health Sub - District
IM	Intramuscular
IMCI	Integrated Management of Childhood illnesses
IPT	Intermittent Preventive Treatment
ITN	Insecticide Treated Net
MCP	Malaria Control Programme
MOH	Ministry of Health
NDA	National Drug Authority
NGO	Non Governmental Organization
OPD	Out Patients Department
OTC	Over - the - Counter Medicine
RDT	Rapid Diagnostic Tests
SP	Sulfadoxine-Pyrimethamine
UNEPI	Uganda National Expanded Program on Immunisation
UNICEF	United Nations Children's Fund
WHO	World Health Organisation

INTRODUCTION

Malaria is the most common disease in all parts of Uganda. It does not only lead to illness and death but also has long term consequences on child development such as low birth weight, chronic anaemia, reduced growth and in some cases severe neurological complications. Health unit records indicate that malaria accounts for 25%-40% of out-patient attendances, 20% of in-patient admissions and 9-14% of in-patient deaths. Children aged below five years and pregnant women are the most affected.

The main objective of malaria control in Uganda is to reduce morbidity and mortality, and the social and economic losses due to malaria. This can be largely achieved through a combination of interventions particularly the following:

i. Early diagnosis and prompt, correct and effective treatment of malaria cases in health facilities and in communities;
ii. Vector control through the use of insecticide treated mosquito nets, indoors residual insecticide spraying and environmental management;
iii. Intermittent preventive treatment of malaria in pregnant mothers.

This guide on management of uncomplicated malaria will provide information on:

- Diagnosis of malaria
- Treatment of cases of uncomplicated malaria
- Counseling of the patients
- What to do in cases of severe malaria
- Malaria in pregnancy
- Malaria prevention and control
- Pharmacovigilance

How to use this guide

This guide provides health workers with the most important facts about malaria and its transmission and management. The illustrations facilitate understanding and can also be used when counseling patients.
The following system is used to highlight certain points:

☆	**Important** points for you to remember or do.
☛	**Common mistakes**.

CHAPTER 1

INFORMATION ON MALARIA AND ITS TRANSMISSION

1.1 What is malaria?

Malaria is an acute febrile illness caused by malaria parasites. There are four types of malaria parasites which infect humans namely; *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae*. Of these, *P. falciparum* is the most common in Uganda.

Human beings are infected through the bite of a female Anopheles mosquito, which is carrying malaria parasites.

1.2 How does malaria transmission occur?

A number of conditions have to be fulfilled before malaria transmission can take place. These are:

a. A reservoir of parasites in the human population from which the mosquito can pick up the infection. Some people carry malaria parasites without being sick and these parasites (gametocytes) are taken up by the mosquitoes.
b. Presence of breeding sites for the mosquitoes. These are stagnant water bodies such as pits, puddles, fish ponds, and water collections at the edges of swamps, creeks and rivers (where the water does not flow rapidly).
c. Suitable climatic conditions for the mosquito to survive and for the parasite to develop within the mosquito. Mosquitoes live and grow in warm, moist climates, with relative humidity above 60%. Malaria parasites develop inside mosquitoes when the mean daily temperature is above 18^0 C *(*for *P. falciparum)*.

☛ **Some people believe that one can get malaria by eating mangoes, new millet or maize, drinking dirty water or walking in the rain. This is not true! Those people believe this because malaria is most common in association with the rainy season when mangoes, maize and millet are plentiful. Actually there is more malaria in association with rains because there are more mosquitoes**

In addition to the bite of an infective mosquito, malaria can also be transmitted by blood transfusions and from mother to child through the placenta; but this is not common. Figure 1 is a diagrammatic representation of malaria transmission; figure 2 outlines the life cycle of Anopheles mosquitoes and figure 3 outlines the life cycle of malaria parasites in humans

and mosquitoes. You can use these figures to counsel your patients.

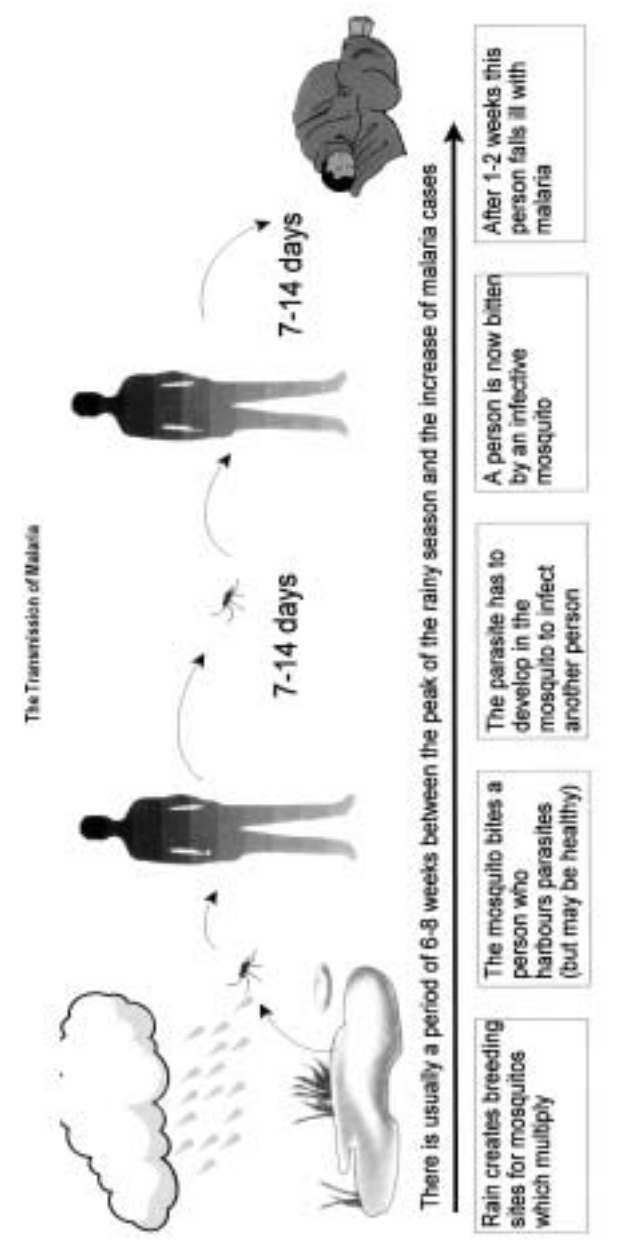


Figure 1: The transmission of Malaria

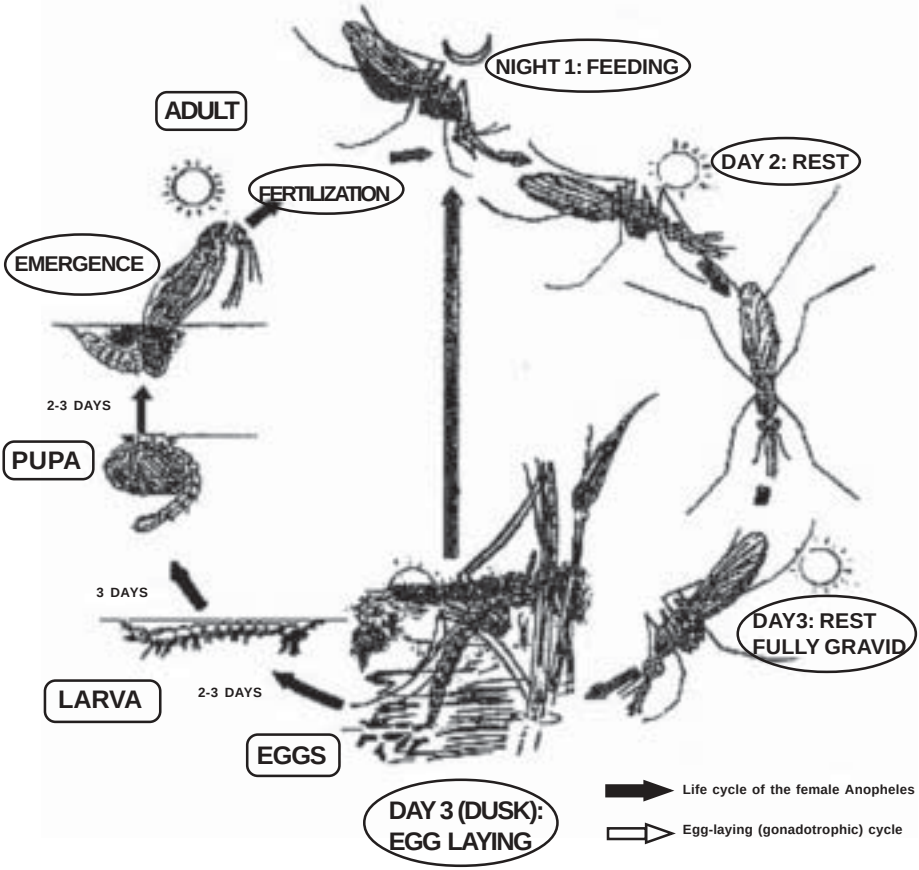


Figure 2: The life cycle of Anopheles mosquitoes

NIGHT 1: FEEDING	The female Anopheles mosquito has to search for and take a blood meal. If she fails she rests during the day and searches again the following night.
DAY 2: RESTING	During the day the mosquitoes rest in cool, shaded, humid places. *An. gambiae* and *An. funestus* prefer to feed indoors and to rest indoors after feeding. A fed female mosquito begins to digest the blood and her eggs begin to develop.
NIGHT 2: RESTING	The mosquito is half gravid. She continues to rest. Blood digestion and egg production continue. She may leave the house and change the resting place.
DAY 3: RESTING	The mosquito is fully gravid. She continues to rest. Egg production is completed.
DAY 3 (DUSK): EGG LAYING	The gravid mosquito flies to a suitable water collection and lays 50 to 150 eggs. She then goes to search for another blood meal to start the cycle again.
LARVA	The eggs hatch into larvae in 2 to 3 days. The larvae feed by filtering algae and other material from the water. During the following 3 days they undergo 3 moults.
PUPA	After the third moult the larvae continue to feed and grow. Then they become mobile pupae. The pupa does not feed; but it breathes through 2 air trumpets while the adult develops internally.
EMERGENCE	After 2 to 3 days the adult emerges. The pupa splits and a soft limp adult climbs out. The adult dries and hardens and then flies off.
FERTILIZATION	The male mosquitoes form mating swarms usually at twilight. During copulation the male mosquito deposits spermatozoa into the spermatheca of the female.

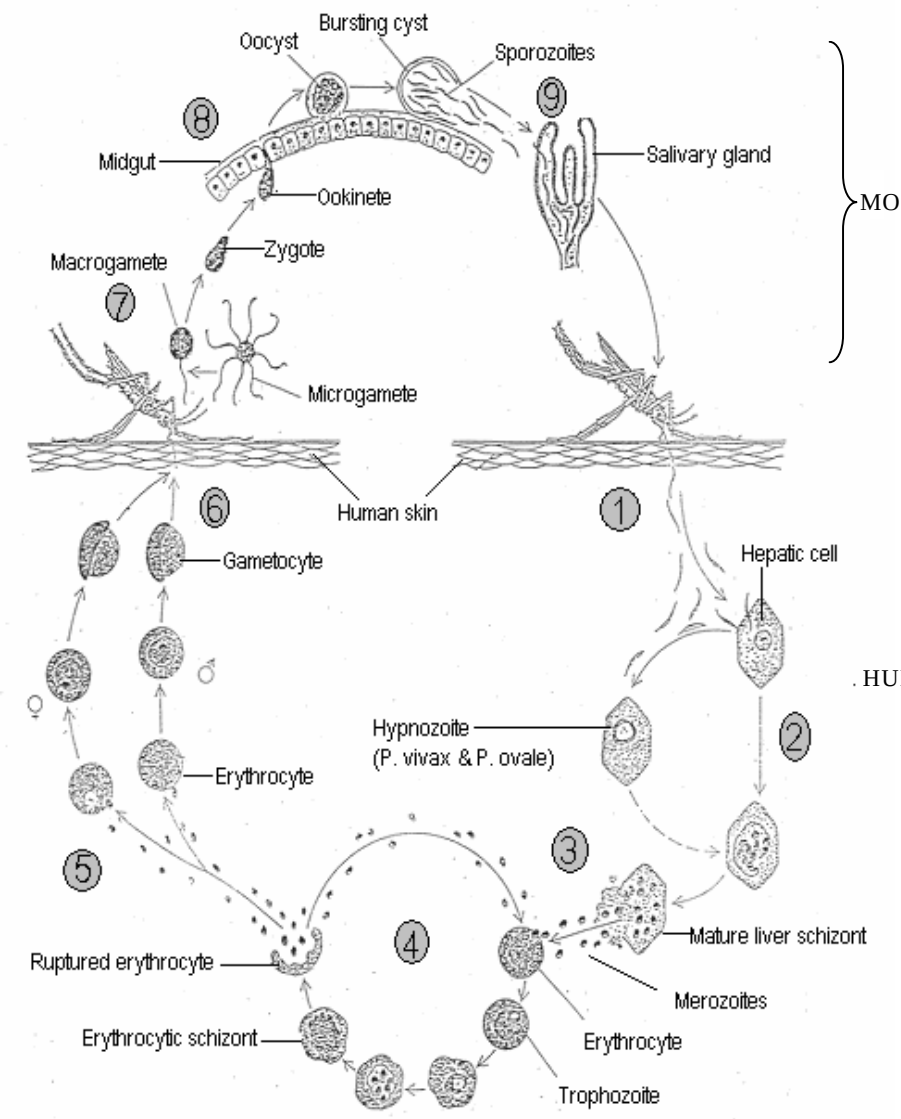

Bursting cyst
Oocyst
Sporozoites
8
9
Midgut
Salivary gland
Ookinete
MOSQUITO
Zygote
Macrogamete
7
Microgamete
Human skin
6
1
Gametocyte
Hepatic cell
♀
♂
. HUMAN
Hypnozoite
(P. vivax & P. ovale)
2
Erythrocyte
3
5
Mature liver schizont
4
Ruptured erythrocyte
Merozoites
Erythrocytic schizont
Erythrocyte
Trophozoite

Figure 3: The life cycle of malaria parasites in humans and mosquitoes

The life cycle of the malaria parasites is divided between two hosts: the mosquito and the human.

1. The malaria parasites (in the form of SPOROZOITES) which are injected from the salivary glands of the mosquito into the blood when an infective mosquito bites a human rapidly enter liver cells.
2. Within the liver cells the sporozoites proliferate into another form of the malaria parasites called MEROZOITES. For P. vivax and P. ovale some malaria parasites remain dormant for some time and are called HYPNOZOITES. The collection of merozoites within the liver cell is called a LIVER SCHIZONT.
3. Rupture of the liver schizonts releases merozoites into the blood where they enter red blood cells (erythrocytes) to begin a phase of asexual reproduction.
4. Within the erythrocytes the malaria parasites first assume a form called TROPHOZOITES and then multiply by binary fission to become many merozoites. The collection of merozoites within the erythrocyte is called an ERYTHROCYTIC SCHIZONT. Rupture of erythrocytic schizonts releases many merozoites which then infect other red blood cells. This cycle is repeated indefinitely.
5. Eventually some merozoites differentiate into sexual forms called GAMETOCYTES.
6. The gametocytes within their erythrocytes may be ingested by a mosquito.
7. In the mosquito gut, lysis of the erythrocytes frees gametocytes to develop into GAMETES. Each male gamete develops into eight sperm-like MICROGAMETES which fertilize the female MACROGAMETES to form ZYGOTES.
8. The resulting zygotes become OOKINETES which penetrate the mosquito's mid-gut wall and multiply to form another form of malaria parasites called sporozoites. The bags of sporozoites on the mosquito gut wall are called OOCYSTS
9. Rupture of the oocyst releases sporozoites that infect the mosquito's salivary glands.

CHAPTER 2

DIAGNOSIS OF MALARIA

2.1 How does malaria present?

The symptoms of malaria, particularly the fever, are related to the rupture of parasitized red blood cells (erythrocytes). This releases toxic substances which in turn cause a rapid onset of fever together with all the other symptoms and complications. The classical malaria fever is intermittent - it comes and goes many times.

> **Remember that fever in malaria is intermittent; that means, it comes and goes many times. Therefore the body temperature may be normal during a clinic visit, but will rise later.**

Three phases can be distinguished in a typical attack of malaria:

i. The **cold stage** is when the patient feels cold and shivers.
ii. The **hot stage** is when the patient feels hot.
iii. The **sweating stage** is associated with profuse sweating and relief of symptoms.

When people are frequently exposed to malaria, they develop partial protection or immunity, against malaria. In such people (with partial immunity) the above stages may not be observed. Also in people who have had partial treatment with antimalarial medicines these classical stages may not be pronounced.

2.2 History and physical examination

The diagnosis of malaria entails taking a history of the illness, performing a physical examination and carrying out relevant investigations where possible.

☆ **The 'Integrated Management of Childhood Illnesses' (IMCI) is an approach to assist health workers in identifying, classifying and treating sick children between the ages of 2 months and 5 years. Health workers trained in IMCI should follow the steps given by the IMCI charts when dealing with sick children.**

2.2.1 History

☞ **Often history taking is omitted. However, it is only with a good history that you will be able to manage your patient adequately!**

Ask the patient or caretaker and/or observe the following:

- What is the presenting complaint? (See Box 1)
- Have there been or are there any danger signs now? (See Box 2)
- Look for signs and symptoms of other diseases (see Box 3)
- Also establish when the illness began, how it began and inquire if medicines have been taken, especially antimalarials. If medicines have been taken establish type, dose, and duration of treatment. Establish whether the medicines were not vomited.

Box 1: Symptoms of uncomplicated malaria

Children under 5 years

- fever (raised temperature detected by thermometer or touch) or a history of fever
- loss of appetite
- weakness
- lethargy
- vomiting

Older children and adults

- fever (raised temperature detected by thermometer or touch) or a history of fever
- loss of appetite
- nausea
- vomiting
- headache
- joint pains
- muscle aches
- weakness
- lethargy

Box 2: Danger signs of severe illness

- convulsions or fits within the last two days or at present
- not able to drink or breast-feed
- vomiting everything
- altered mental state (lethargy, drowsiness, unconsciousness or confusion)
- prostration or extreme weakness (unable to stand or sit without support)
- severe respiratory distress or difficult breathing
- severe anaemia (severe pallor of palms and mucous membranes)
- severe dehydration (sunken eyes, coated tongue, lethargy, inability to drink)

☆	**A patient presenting with fever and any danger sign(s) should be managed as a case of severe malaria.**

2.2.2 Physical examination

☆	**Always take the temperature, weigh the patient and carry out a general examination of your patient. See Box 3.**

Box 3. Common signs of uncomplicated malaria

Raised Temperature (above 37.5 °c *par* axilla)
Mild anaemia (mild pallor of palms and mucous membranes); occurs commonly in children
Dehydration (dry mouth, coated tongue and sunken eyes). In adults, sunken eyes are usually a sign of severe dehydration.
Enlarged spleen (in acute malaria it may be minimally enlarged, soft and mildly tender)

An enlarged spleen due to malaria calls for no additional treatment.

Also **check for danger signs** (see Box 2) which require immediate action. What to do if danger signs are present is detailed in Chapter 5 of this guide.

☆	**Checking for danger signs is particularly important in those most at risk of severe malaria: that is children aged less than 5 years, non-immune adults and pregnant women.**

Look carefully at the patient and answer the following questions:

a) Level of consciousness:

- Is the patient awake and attentive?
- Is the patient oriented and interested in, or aware of the surroundings
- In young children:
  - Does the child look at the mother or caretaker?
  - Does the child follow an object moved in front of his/her eyes?
  - Does the child react to loud noises?

One or more negative answers indicate reduced consciousness!

b) Respiration:

- Is the patient breathing faster than normal for his age? (see table 1)
- In young children:
  - Is there chest in-drawing?
  - Is there nose flaring?
  - Is the child grunting?

If one or more of the above is present, there is respiratory distress!

Table 1: Respiratory rate in children

If the child is	The child has fast breathing if you count
2 months up to 12 months	50 breaths per minute or more
12 months up to 5 years	40 breaths per minute or more

c) Severe anaemia:

Look at the tongue, the conjunctivae and the palms.

- Are these parts very pale?

If so, there is severe anaemia!

d) Dehydration:

- Is the mouth dry?
- Are the eyes sunken?
- Pinch the skin (of the abdomen in children or forehead in adults) between your thumb and index finger and then suddenly let go. Does the skin go back very slowly?

If the answer to one or more of the above questions is yes, then there is dehydration!

☆	**If any danger signs are present, follow the steps outlined in chapter 5 of this guide for immediate action!**

If no danger signs are present, continue the examination and identify **any other disease** which may be responsible for the fever and any other symptoms. (See Box 4)

- Inspect the skin thoroughly for skin rashes (measles, chicken pox)
- Check for abscesses (pyomyositis, cellulitis)
- Check the neck for stiffness (meningitis)
- Check in the mouth whether the tonsils are big, red or have pus discharge (tonsillitis)
- Is the nose running, the mucus pus-like (purulent)?
- Check the ears for otitis. Is there ear pain or discharge?

☆	**If you find any other disease which may be responsible for the fever, treat accordingly!**

Box 4: Other diseases to be looked for

- respiratory tract infection
- urinary tract infection
- meningitis
- otitis media
- tonsillitis
- abscess
- skin sepsis
- measles or other virus infections with rashes

If there are no danger signs (Box 2) and/or complications and no other diseases (Box 4) a patient with fever is considered to be a case of uncomplicated malaria.

☆	**Remember to use the weight and/or age to determine the right dose of antimalarial treatment especially in young children!**

2.3 Laboratory diagnosis

2.3.1 Microscopic examination of a blood smear

The 'gold standard' of malaria diagnosis is the examination of blood smears for malaria parasites. However, the reliability of microscopy depends a lot on the expertise and experience of the person who makes stains and examines the blood smears.

Where laboratory facilities exist, blood examination for malaria parasites should be done for the following groups of patients:

- Patients who present with features of severe malaria.
- Patients who have taken antimalarial treatment for 2 days and symptoms persist. Laboratory examinations are very important for these patients to rule out other causes of their symptoms. These examinations should also provide a report on the characteristics of the White Blood Cells (i.e. increased, reduced or with fewer nuclear lobes).
- Children under four (4) months with symptoms of uncomplicated malaria.
- Pregnant women with symptoms of uncomplicated malaria.

If these patients are found positive with malaria parasites, they should always be given the appropriate antimalarial treatment. Even when the blood smear is negative, these patients should be treated for malaria if the clinical presentation strongly suggests malaria. (See Chapter 3)

* **When requesting a malaria test from the laboratory you should always insist on being given a result which also indicates how many parasites were seen (see appendix 5). This information will help you to monitor your patient's response to treatment if repeated tests are done.**

The detection of malaria parasites through microscopy has the following limitations:

- Failure to see the parasites in a blood smear does not necessarily mean that the patient has no malaria.
- In areas with high malaria transmission (i.e. most parts of Uganda) many people, particularly children below 10 years of age, have malaria parasites in their blood, even when they are not sick.

In these cases the laboratory results are difficult to interpret.

Remember: Any patient with fever or a history of fever within the last 24 hours without evidence of other diseases should be treated for malaria even with a negative blood smear for malaria parasites.

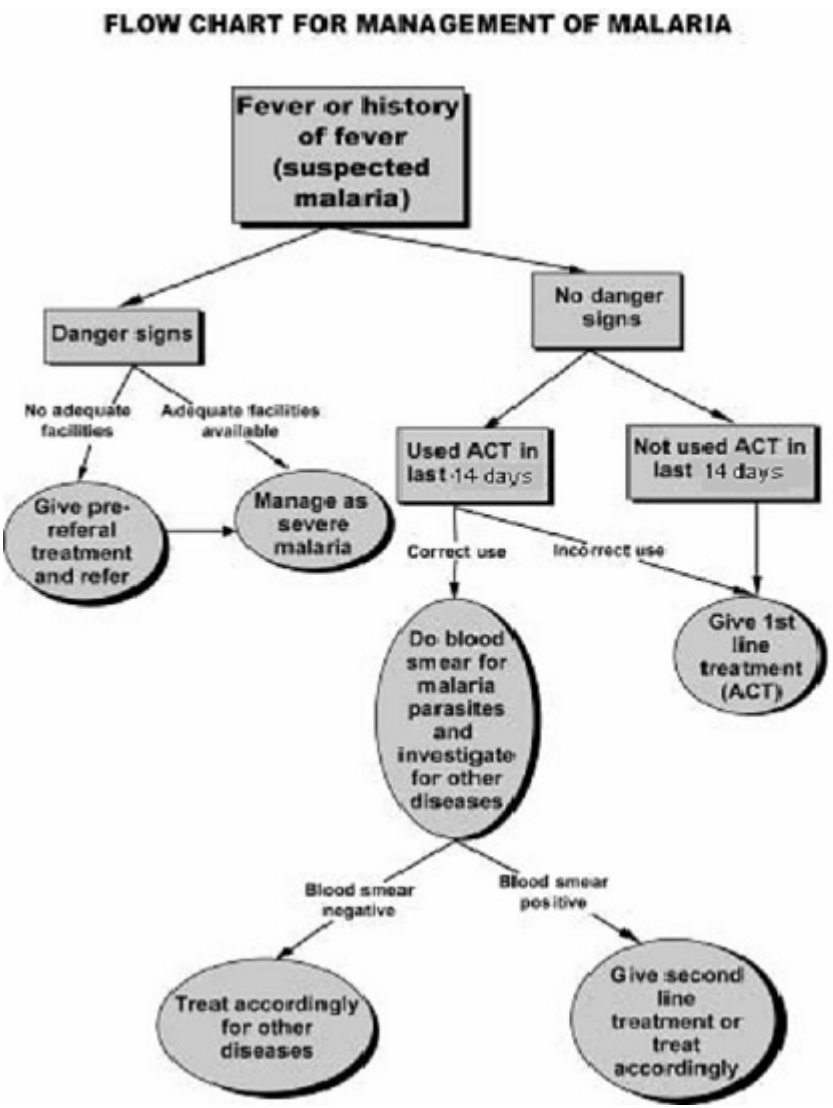
2.3.2 Malaria Rapid Diagnostic Tests (RDTs)

Malaria rapid diagnostic tests are used to detect the presence of antigens from malaria parasites in blood using antibodies. These tests can be performed by persons who have little technical expertise and experience. However, they have the following limitations:

- In most parts of Uganda, children have malaria parasites in their blood, even when they are not sick. When tested the RDTs will be positive.
- By detecting antigens from both dead and living malaria parasites the tests may be positive in patients who have already been successfully treated.
- Extremes of temperature and moisture can lead to degradation of RDTs

Given the current limitations of RDTs, their use should be considered only in special situations (such as verifying malaria epidemics, children under 4 months of age); **and their routine use is therefore not recommended**.

Figure 4:


FLOW CHART FOR MANAGEMENT OF MALARIA
Fever or history of fever (suspected malaria)
Danger signs
No danger signs
No adequate facilities
Adequate facilities available
Used ACT in last 14 days
Not used ACT in last 14 days
Give pre-referal treatment and refer
Manage as severe malaria
Correct use
Incorrect use
Do blood smear for malaria parasites and investigate for other diseases
Give 1st line treatment (ACT)
Blood smear negative
Blood smear positive
Treat accordingly for other diseases
Give second line treatment or treat accordingly

CHAPTER 3

TREATMENT OF UNCOMPLICATED MALARIA

3.1 General principles of treatment

* **Any patient with fever or a history of fever within the last 24 hours without evidence of other diseases should be treated for malaria even with a negative blood smear for malaria parasites.**

A number of medicines exist which can treat malaria. However, not all of them can be used for widespread treatment because of potential side effects or a very high resistance of malaria parasites. Artemisinin-based Combination Therapies (ACTs) are new and effective medicines that are recommended by WHO. The Ministry of Health has therefore, selected an ACT called **Artemether/Lumefantrine** (COARTEM®) as first line medicine for the treatment of uncomplicated malaria.

When treating a patient with uncomplicated malaria you should always keep the following points in mind:

* **Always give a full course of treatment: the right number of tablets over the right number of days.**
* **Give the medicine orally unless the patient vomits repeatedly.**
* **If symptoms persist but there are no danger signs (Box 2), wait at least 48 hours before you change the treatment.**

Malaria parasites may develop resistance against antimalarial medicines. This means that the medicine is not able to cure the patient or, after initial improvement the symptoms come back within 14 days.

Note: If a patient does not respond to the first line medicine after 2 days and no laboratory facility is available, give the second line medicine if there is no evidence of any other cause of the fever.

The flow chart (figure 2) summarizes the correct management of uncomplicated malaria. You should take some time to study it.

☞ **Patients often change treatment after only a few hours or a day if fever and other symptoms do not immediately disappear. This is not correct! Be sure to tell your patients that it may take between 24 and 48 hours before symptoms disappear.**

3.2 First line Treatment of uncomplicated malaria with Artemether/Lumefantrine (Coartem®).

Artemether/Lumefantrine (See Appendix 1) is the recommended first line medicine for the treatment of uncomplicated malaria.
The first dose should be given under supervision of the health worker. It should preferably be taken with food or fluids. **Fatty meals or milk improve absorption of this medicine.**
If vomiting occurs within half ($^1/_2$) an hour of swallowing the medicine, the dose should be repeated and the attendant should receive a replacement dose from the health worker.

Pregnant women in the first trimester of pregnancy should not take Artemether/ Lumefantrine. (See Chapter 4 for instructions on treatment of malaria in pregnancy). Artemether/Lumefantrine is contraindicated for children below 5Kg body weight. Such patients should be treated with quinine.

Artemether/Lumefantrine (Coartem®) is available as co-formulated tablets containing 20mg Artemether and 120mg Lumefantrine per tablet. The dose ranges from 1 tablet 12 hourly to 4 tablets 12 hourly (depending on the patient's body weight or age) for 3 days.
To assist you to find the correct dosage of Coartem®, table 2 gives the number of tablets for various weight-ranges/age groups.

Table 2: Dosage of Coartem® tablets (Artemether 20mg & Lumefantrine 120 mg)

Weight (Kg)	Age	Day 1	Day 2	Day 3	Colour Code
5-14	From 4 months up to 3 years	1 tablet twice a day, 12 hourly	1 tablet twice a day, 12 hourly	1 tablet twice a day, 12 hourly	Yellow
15-24	From 3 years up to 7 years	2 tablets twice a day, 12 hourly	2 tablets twice a day, 12 hourly	2 tablets twice a day, 12 hourly	Blue
25-34	From 7 years up to 12 years	3 tablets twice a day, 12 hourly	3 tablets twice a day, 12 hourly	3 tablets twice a day, 12 hourly	Brown
> 35	From 12 and above	4 tablets twice a day, 12 hourly	4 tablets twice a day, 12 hourly	4 tablets twice a day, 12 hourly	Green

*** Coartem has a shelf life of only two years and is not stable at temperatures exceeding 30 degrees Celsius. It is hygroscopic (takes up water) and should be taken as soon as the blister pack has been opened.**

3.3 Alternative first line treatment of uncomplicated malaria with Artesunate + Amodiaquine

Artesunate + Amodiaquine combination treatment can be used as first line treatment for uncomplicated malaria in situations when Artemether/Lumefantrine is not available.

Separate scored tablets contain 50mg of Artesunate and 153mg base of Amodiaquine, respectively. Co-formulated tablets are not available at present.

Available from different manufacturers either in separate blister packs or as single course-of-therapy packs. Tablets need to be divided for children below 1 year of age.

Table 3: The WHO recommended dosage for AS+AQ is the following:

	Artesunate			Amodiaquine		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5 -11 months	25 mg (1/2 tab)	25 mg (1/2 tab)	25 mg (1/2 tab)	76 mg (1/2 tab)	76 mg (1/2 tab)	76 mg (1/2 tab)
1-6 years	50 mg (1 tab)	50 mg (1 tab)	50 mg (1 tab)	153 mg (1 tab)	153 mg (1 tab)	153 mg (1 tab)
7-13 years	100 mg (2 tabs)	100 mg (2 tabs)	100 mg (2 tabs)	306 mg (2 tabs)	306 mg (2 tabs)	306 mg (2 tabs)
>13 yrs	200 mg (4 tabs)	200 mg (4 tabs)	200 mg (4 tabs)	612 mg (4 tabs)	612 mg (4 tabs)	612 mg (4 tabs)

Other available combination treatments for uncomplicated malaria are:

i. Artesunate + Sulfadoxine/Pyrimethamine
ii. Artesunate + Mefloquine
iii. Amodiaquine + Sulfadoxine/Pyrimethamine

Dosages for these medicines are in annex 3. New antimalarial medicines are on trial and may soon be on the market.

3.4 Second lineTreatment of uncomplicated malaria with quinine tablets

Quinine tablets are the **second line medicine** for the treatment of uncomplicated malaria. This means it should only be given when the first line medicine (Artemether/ Lumefantrine) has failed or when it is contra-indicated.

Quinine tablets (300 mg salt) are given as a dose of 10 mg/kg (up to a maximum of 600mg) every 8 hours for 7 days.

Table 4: Dosage of quinine tablets (quinine 300mg salt)

Age	Weight	Dose (to be given every 8 hours for 7 days)
3 months up to 1 year	5 kg up to 10 kg	75 mg (¼ tab)
1 year up to 5 years	10 kg up to 18 kg	150 mg (½ tab)
5 years up to 7 years	18 kg up to 24 kg	225 mg (¾ tab)
7 years up to 10 years	24 kg up to 30 kg	300 mg (1 tab)
10 years up to 13 years	30 kg up to 40 kg	375 mg (1¼ tab)
13 years up to 15 years	40 kg up to 50 kg	450 mg (1½ tab)
15 years and over	over 50 kg	600 mg (2 tab)

3.5 Supportive treatment and counseling for uncomplicated malaria.

Good management of uncomplicated malaria does not consist of antimalarial treatment alone. It also should include the following supportive treatment:

- antipyretic treatment
- fluids and food
- counseling

3.5.1 Antipyretic treatment

If the fever is high (axillary temperature 38.5 C and above) an antipyretic should be given. Children below 8 years of age should only receive Paracetamol while older children and adults can be given either Paracetamol or Aspirin. The dosage of Paracetamol is 10mg per Kg body weight up to maximum of 1000mg eight hourly.

Table 5: The dosage of Paracetamol (500mg)

Age group	Number of tablets (500 mg Paracetamol)	Maximumnumber of tablets per day
From 2 months up to 3 years	125 mg (¼ tab)	3/4
From 3 years up to 7 years	250 mg (½ tab)	1½
From 7years up to 10 years	500 mg (1 tab)	3
From 10 years up to15 years	750 mg (1½ tab)	4½
15 years and above	1000 mg (2 tab)	6

In addition to the anti-pyretic, undressing and tepid sponging with luke-warm (tepid) water can be used to lower the temperature.

3.5.2 Fluid and food

Patients with fever lose a lot of fluid through sweating and respiration. They should be encouraged to drink plenty of fluids to avoid **dehydration**!

* **A patient with fever should take plenty of fluids at short intervals.**

Although a sick person should not be forced to eat, care must be taken that the energy supply is sufficient. Light foods or fruit juices should be offered frequently. Babies should continue to be breast-fed

3.5.3 Counseling

A patient can comply with the treatment a lot better if he/she fully understands why and how to take the treatment and what to expect during its course. Therefore, you should explain to the patient or the caretaker the following:

- That the cause of the illness is malaria. The disease is characterized by fever and is transmitted by mosquitoes.
- The correct way to take the medicines
- In order to be totally cured, the patient must take the full course of treatment.
- Symptoms may not disappear immediately after taking the first dose. Improvement may take up to two days.
- The patient should consult a health worker immediately if symptoms worsen or if they persist beyond two days.
- The patient should take another dose if he/she vomits the medicine within 30 minutes.
- The patient should not change treatment by himself/herself.
- Before you give any medication, always ask about a history of reactions and avoid medicines which caused serious reactions in the same patient

Make sure that the patient understands the illness and its treatment while at home. Talk to the patient about the prevention and control of malaria, emphasizing the importance of sleeping under insecticide treated nets.

CHAPTER 4

MALARIA IN PREGNANCY

Malaria in pregnancy is always a serious disease and must be treated promptly. It can lead to abortion, still-birth, premature delivery and low birth weight. It may also lead to maternal ill health such as severe anaemia.

4.1 Treatment of uncomplicated malaria during pregnancy

Any pregnant woman presenting with fever should be treated for malaria. Throughout pregnancy, quinine should be used as the first line treatment. During the first trimester (first 12 weeks of pregnancy) it is not recommended to take ACTs at all.

However after the first trimester, if there are no suitable alternatives, ACTs may be used as first line treatment. The doses of quinine and ACTs during pregnancy are the same as those for adults who are not pregnant.

4.2 Intermittent preventive treatment (IPT) of malaria during pregnancy

During pregnancy a woman can have malaria parasites in her placenta without any signs of malaria. In fact, even a blood test will not detect parasites that are hidden in the placenta. However, malaria harms the baby by interfering with its oxygen and nutrient supply.

To prevent the ill effects of malaria during pregnancy, all pregnant women should receive two (2) doses of SP as preventive treatment.

* **The first dose of SP (3 tablets) is given as directly observed treatment during the 4th to 6th months of pregnancy.**

* **The second dose of SP (3 tablets) is given as directly observed treatment during the 7th to 9th months of pregnancy.**

* **There must be an interval of at least one month (4 weeks) between the doses of SP.**

* **To prevent new malaria infections, pregnant women should be advised to sleep under insecticide treated nets.**

CHAPTER 5

WHAT TO DO IN CASES OF SEVERE MALARIA

What to do depends on the services available at the health facility. Where there are no facilities to manage severe and complicated malaria, the patient should be referred to the next level of care as quickly as possible.

Before referral, the following measures should be taken:

- Inject 10 mg/kg body weight of Quinine I.M. into the anterior part of the thigh after dilution as shown in Box 5.

Box 5: Dilution of Quinine for I.M. injection

- A 2ml ampoule of Quinine contains 600mg of quinine (300mg/ml).
- Add twice the volume of water for injection (4ml) to get 600mg of quinine in 6 ml of solution
- Each ml of the solution will contain 100 mg of Quinine
- Calculate the volume (ml) of the diluted quinine needed (you require 0.1ml/kg). The dose of the diluted quinine required = **0.1ml x Body Weight in Kg**
- If the total solution to be injected is more than 3 ml, split the volume in two and inject one half in each thigh. **Do not inject into the buttock!**

- Control temperature (undressing, fanning, tepid sponging, Paracetamol);
- If the patient has convulsions, control convulsions (5 mg rectal Diazepam in children, or 10 mg I.V. Diazepam in adults).
- Any patient who has had convulsions or is drowsy should be given sugar solution orally if conscious or through a nasogastric tube if unconscious;
- If the patient is dehydrated, give oral fluids (if necessary through nasogastric tube);
- Counsel the patient or caretaker on the need for referral;
- Write a referral note stating the treatment given and the time.

* **You should do everything you can to make sure the patient reaches the hospital! If you are in a Hospital or Health Centre IV, follow the appropriate guidelines for management of severe malaria.**

CHAPTER 6

MALARIA PREVENTION AND CONTROL

6.1 What determines malaria transmission?

1. Malaria is a febrile disease caused by infection with malaria parasites. The most common malaria parasite in Uganda is *P. falciparum.* Others are *P. vivax, P. ovale and P. malariae. P. falciparum* is the most virulent malaria parasite. It is the parasite that causes severe and complicated malaria and is therefore responsible for practically all deaths due to malaria. Malaria parasites are transmitted mainly through infective mosquito bites and rarely by blood transfusions and from mother to foetus through the placenta.
2. Mosquitoes breed in stagnant water. The mosquitoes which most commonly transmit malaria in Uganda are *Anopheles gambiae and Anopheles funestus*. These two mosquitoes breed in clean fresh water and they prefer to feed on humans indoors at night and to rest indoors after feeding.
3. Human behaviour influences malaria transmission. Population movements from non-endemic to endemic areas expose susceptible people to infection. Agricultural and commercial activities such as irrigation, valley dams, fish ponds, brick making, hoof marks create breeding sites for mosquitoes.
4. Suitable environmental conditions such as a warm humid climate with plenty of rain favour the breeding and longevity of mosquitoes and the multiplication of malaria parasites inside the mosquitoes.

6.2 How can malaria be controlled?

Malaria can be controlled by preventing mosquitoes from reaching and biting humans, reducing the population of mosquitoes and reducing the malaria parasite load in the human population.

a. Prevention of contact between mosquitoes and humans

This can be achieved through use of insecticide treated mosquito nets, screening of houses, site selection and other feasible interventions.

i. Use of insecticide treated mosquito nets.

The best way to prevent bites is to sleep under insecticide treated mosquito nets. Such nets create a physical barrier which prevents man-mosquito contact. They also repel and kill mosquitoes.

ii. Screening of houses

Screening of houses by putting mesh in windows, doors, and ventilators reduces the entry of mosquitoes into the houses. Doors and windows should also be closed early in the evening.

iii. Site selection

Residential houses should be built far away from marshes and other collections of stagnant water where mosquitoes breed.

b. Reduction of the mosquito population

Reduction of the mosquito population can be achieved by destruction of adult mosquitoes and larvae and reduction of breeding sites.

i. Destruction of adult mosquitoes

- Spraying of the internal walls of human dwellings with residual insecticides
- Use of insecticide treated mosquito nets (ITN)

ii. Destruction of mosquito larvae

- Intermittent cleaning and drying of water containers and intermittent crop irrigation at least once every 7 days ensures that mosquitoes do not have sufficient time to complete their breeding cycle.
- Putting chemicals (e.g. temephos, pirimiphos-methyl), fish (e.g. *Gambusia affinis*) or bacteria (*Bacillus thuringiesis israelensis*) that kill larvae into stagnant water bodies (larviciding) interrupts the mosquito breeding cycle.

iii. Reduction of mosquito breeding sites

- Peridomestic sanitation e. g. reducing breeding places around the home by proper disposal of broken utensils and plastic bags, old tyres and filling in holes in the ground.
- Environmental management e. g. constructing drainage channels for storm water and rivers and drainage of stagnant water bodies.
- Water management e. g. protection of sources of water for domestic, agricultural or industrial use

c. Destruction of malaria parasites

Reduction of malaria parasites can be achieved through case management and preventive treatment.

1. *Early diagnosis and prompt treatment of malaria cases (Case management)*

- Effective treatment reduces the length of morbidity and the risk of mortality. Those who are successfully treated also cease to serve as sources of malaria parasites.

2. *Preventive treatment.*

- Intermittent preventive treatment of pregnant women reduces the risk of poor pregnancy outcomes e. g. maternal anaemia, maternal death, abortion and low birth weight babies
- Chemoprophylaxis for special risk groups (e.g. sicklers, non-immune visitors, children prone to very frequent febrile convulsions) reduces the risk of morbidity and mortality.

d. Advocacy, health education, and social mobilisation

Provision of malaria control interventions requires aggressive advocacy among decision makers at all levels and the public at large. Uptake of these interventions calls for a continuous and concerted effort by health workers in mobilizing and educating the public.

CHAPTER 7:

MONITORING AND REPORTING ADVERSE MEDICINE REACTIONS

Pharmacovigilance

Pharmacovigilance is concerned with the detection, assessment and prevention of adverse reactions to medicines.
For the purpose of the Pharmacovigilance programme, a medicine is defined as "Any substance administered to human beings for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function". This definition includes prescribed medicines, over-the-counter medicine, vaccines, herbal medicines and biologicals including blood and blood-related products such as serum and plasma.

Why is Pharmacovigilance important?

Medicine monitoring is of tremendous value as a tool for detecting adverse medicine reactions and specifically in relation to counterfeit and substandard products. Adverse medicine reaction monitoring is to help ensure that patients obtain safe and efficacious products.

The information collected during the pre-marketing phase of a medicine is inevitably incomplete with regard to possible adverse reactions. This is mainly because:

- Tests in animals are insufficiently predictive of human safety.
- In clinical trials the patients are selected and limited in number, the conditions of use differ from those in clinical practice and the duration of trials is limited.
- Information about the rare but serious adverse reactions, toxicity, uses in special groups (such as children, the elderly or pregnant women) or during interactions is often incomplete or unavailable.

Thus, post marketing surveillance is important to permit detection of less common, but sometimes very serious adverse medicine reactions.

HOW TO RECOGNISE ADVERSE MEDICINE REACTIONS

Since adverse medicine reactions may act through the same physiological and pathological pathways as different diseases, they are difficult and sometimes impossible to distinguish. However, the following step- wise approach may be helpful in assessing possible medicine-related adverse reactions:

- Ensure that the medicine prescribed is the medicine received and actually taken by the patient at the dose advised. The regimens for the ACTs used for treatment of uncomplicated malaria have been specified in this guide.
- Verify that the onset of the suspected adverse medicine reaction was after the medicine was taken, (not before) and discuss carefully the observation made by the patient.
- Determine the time interval between the beginning of the medicine treatment and the onset of the suspected adverse reaction.
- If the adverse reaction is serious and outweighs the benefit of treatment then discontinue the medicine and change to an alternative one. You should discontinue any medicine that has caused an irreversible adverse reaction and change to an appropriate alternative. The broad choices available to you are between the first and second line malaria treatments.
- Look for alternative causes (other than the medicine) that could on their own have caused the reaction.
- Report any adverse medicine reactions to the National Pharmacovigilance Centre through the in-charge of the health facility and the office of the District Director of Health Services (DDHS).

WHAT SHOULD BE REPORTED

It should be routine practice to report suspected adverse reactions of all medicines including vaccines. These may be adverse reactions that are known or new to you or other health workers. Once you have recognized and investigated an adverse reaction as described above it is important to notify the National Pharmacovigilance Centre of those reactions that you consider moderate or severe. Irreversible adverse reactions of any severity should also be reported. Below are other examples of what should be reported:

- Suspected reactions to medicines that have recently been introduced into the country such as ACTs.
- Severe adverse reactions of established or well- known medicines such as quinine should be reported.
- Report an increased frequency of a known reaction.
- Report all suspected adverse reactions associated with interactions between one medicine and another, medicine and herbal treatment, and medicine and food supplements.
- Report adverse medicine reactions in special cases such as medicine abuse and use in pregnancy and during lactation. It is important to follow-up mothers

who mistakenly took ACTs in the first trimester of a pregnancy to find out if there were any effects on the newborn.

- Report when adverse reactions are associated with medicine withdrawals.
- Report when suspected pharmaceutical defects are observed.
- Report adverse medicine reactions occurring from overdose or medication error.

☞ **Report all suspected adverse reactions that you consider of clinical importance as soon as possible**

HOW TO REPORT

Complete the reporting form a copy of which is in appendix 4. This form should be available at your health unit or can be requested for. The effectiveness of a national Pharmacovigilance Programme is dependent on the active participation of all health workers since they are in the best position to report on suspected adverse medicine reactions observed in their every day patient care.

Report forms should be sent to the DDHS offices or National Drug Authority (NDA) Regional Offices and then forwarded to the National Pharmacovigilance Centre at NDA,
Plot 46/48, Lumumba Avenue,
P.O. Box 23096, Kampala,
Fax: 255758, 342921,
Hotline: 041 344052,
E-mail: ndaug@nda.or.ug
www.nda.or.ug

APPENDIX 1:

INFORMATION ON ARTEMETHER/LUMEFANTRINE (COARTEM®)

1. Presentation

COARTEM® (Coartemether) is a fixed medicine combination for oral use containing artemether 20 mg and lumefantrine 120 mg per tablet. Artemether is the methyl ether derivative of artemisinin.

2. Pharmacology and Pharmacokinetics

The anti-malarial principal is extracted from the plant *Artemisia annua, L.* Other artemisinin derivatives include artesunate, dihydroartemisinin and arteether. Artemisinin derivatives have been used for treatment of fever in China for many years and have been found to be safe and efficacious. These compounds are potent blood schizontocidal and gametocytocidal products against *P. falciparum*. They are the most rapidly effective antimalarial medicines known, producing clinical improvement within 1-3 days after starting treatment. When used as monotherapy, recrudescence is unacceptably high. It has therefore been found necessary to combine it with a longer acting medicine in this case, Lumefantrine.

Lumefantrine is an aryl amino alcohol similar to quinine, mefloquine and halofantrine

Artemether is rapidly absorbed and metabolized to dihydroartemisinin by the liver and is eliminated through the foecal route and through the kidneys. Fatty meals improve absorption of this medicine. Absorption on an empty stomach is very poor. Both the parent medicine and its metabolite are detectable in blood 30 minutes after ingestion. Plasma peak concentrations (Cmax) of both compounds are achieved 2 hours after administration. The terminal half-life of artemether is approximately 2 hours; and that of its metabolite dihydroartemisinin slightly longer. It is highly bound to plasma proteins.

Artemether is a sesquiterpene lactone with a peroxide bridge. The peroxide moiety appears to be responsible for its anti-malarial activity. It has a broad activity on the parasite ranging from very young ring forms to mature schizonts. Artemether acts by the haem-catalysed intraparasitic production of highly reactive carbon center of free radicals. The site of action is the food vacuole of the malaria parasite.

3. Indications

COARTEM® is recommended as the first line medicine for uncomplicated *P. falciparum* malaria. It is not recommended for prophylaxis or for treating severe forms of malaria as an initial treatment but can be used to complete the course of quinine.

4. Use in pregnancy and lactation

The safety of artemether in pregnancy and lactation has not been established and, therefore, artemether is contraindicated in the first trimester. Also, artemether is not recommended for children below 5 kg body weight.

5. Medicine interactions

Both artemether and lumefantrine are metabolized in the liver by the enzyme CYP3A4 but do not inhibit this enzyme at therapeutic concentrations. It is prudent to avoid co-administration with medicines that are metabolized through the liver especially those that share the same metabolic pathway for example halofantrine, quinine and mefloquine.

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6. Adverse effects

The common adverse effects reported include, headache, sleep disorders, dizziness, palpitations, abdominal pain, anorexia, vomiting, nausea, pruritus, skin rash, cough, arthralgia and myalgia.

7. Dose schedule

COARTEM® is available as co-formulated tablets containing 20 mg of artemether and 120 mg of lumefantrine. The dose of COARTEM® ranges from 1 tablet 12 hourly to 4 tablets 12 hourly (depending upon the weight of the patient) for 3 days.

8. Shelf life

Coartem has a shelf life of only two years and is not stable at temperature exceeding 30 degrees Celcius. It is hygroscopic and should be taken as soon as the blister pack has been opened.

APPENDIX 2:

INFORMATION ON AMODIAQUINE + ARTESUNATE COMBINATION

1. Presentation

Various manufacturers have different compositions of artesunate and amodiaquine. The recommended composition is co-packaged as artesunate 50 mg and Amodiaquine hydrochloride USP equivalent to amodiaquine base of 153.1mg.

2. Pharmacology and Pharmacokinetics

Amodiaquine is effective against the erythrocytic stages of all 4 species of plasmodium falciparum. Amodiaquine accumulates in the parasite's lysosomes and prevents breakdown of haemoglobin on which the parasite depends for its survival.

Amodiaquine hydrochloride is readily absorbed from the gastrointestinal tract. It is rapidly converted in the liver to the active metabolite desethylamodiaquine, only a negligible amount of amodiaquine is being excreted unchanged in the urine. The plasma elimination half-life of desethylamodiaquine varies from 1 to 10 days or more. About 5% of the total administered dose is recovered in urine while the rest is metabolised in the body. Amodiaquine and desethylamodiaquine have been detected in the urine several months after administration.

Artesunate is a water-soluble hemisuccinate derivative of artemisinin. Artesunate and its active metabolite dihydroartemisinin are potent blood schizonticides, active against the ring stage of the parasite.
Artesunate binds tightly to parasitized erythrocyte membranes. The functional group responsible for antimalarial activity of artesunate is endoperoxide bond. Release of an active oxygen species from this bond kills the parasite if accumulated in the erythrocytes. It also suppresses the production or activity of antioxidant enzymes in the erythrocytes, causing lysis of the parasitic cell due to the highly reactive free oxygen radicals. It reduces gametocyte carriage rate.

Pharmacokinetic data for Artesunate in humans are sparse, with no data demonstrating the rate or extent of absorption or the systemic distribution of artesunate. Artesunate is rapidly hydrolyzed to the active metabolite dihydroartemisinin. The oral formulation is probably hydrolysed completely before entering the systemic circulation. Peak serum levels occur within one hour of an oral dose of artesunate and persist for up to 4 hours.

Dihydroartemisinin has a plasma elimination half-life of less than 2 hours, which may slow the development of resistance to artesunate.

3. Indications

Amodiaquine - artesunate combination kit is indicated in the treatment of uncomplicated cases of malaria caused by Plasmodium *falciparum*.

4. Use in pregnancy and lactation

Although no data are available for amodiaquine, chloroquine, a structurally similar 4-aminoquinoline with the same spectrum of activity and similar adverse reaction profile is known to cross the placental barrier. Caution should be observed when the medicine is administered during pregnancy.

Little experience has been gained with the use of artesunate in pregnancy. It should be used with extreme caution in pregnancy during the first trimester.

Therefore, risk benefit ratio should be considered before administering amodiaquine - artesunate combination kit in pregnancy as enough safety data is not available.

5. Medicine interactions

The incidence of agranulocytosis is higher when amodiaquine is combined with other antimalarials. Idiosyncratic medicine induced involuntary movements have occurred when amodiaquine is combined with chloroquine.

Since magnesium trisilicate and kaolin are known to decrease the gastrointestinal absorption of chloroquine when administered simultaneously, it is likely that this also follows for amodiaquine.

Concomitant administration of chloroquine at recommended doses for malaria chemoprophylaxis during pre-exposure prophylaxis of rabies with intradermally administered rabies vaccine may interfere with the antibody response to the vaccine. However, the clinical significance of this interaction remains to be clearly established but should be considered and may have relevance in the case of amodiaquine.

Artesunate has a minimal effect on hepatic cytochrome P450 activity and does not appear to influence the metabolism of mefloquine, a medicine likely to be used in combination with artesunate.

Artesunate does not inhibit the formation of carboxy-primaquine, a metabolite of primaquine.

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6. Contraindications

Amodiaquine - artesunate combination kit is contraindicated in patients with known hypersensitivity to amodiaquine or 4-aminoquinolines and artesunate or artemisinin derivatives. Because of resistance and risk of major toxicity, amodiaquine is not recommended for the prophylaxis of malaria. Amodiaquine is also contraindicated in patients with hepatic disorders.

7. Precautions

They are mainly pertaining to amodiaquine in the amodiaquine - artesunate combination kit.

Amodiaquine is no longer recommended for chemoprophylaxis of falciparum malaria because its use is associated with hepatic toxicity and agranulocytosis.

Severe neutropenia can occur. Large doses of amodiaquine have been reported to produce syncope, spasticity, convulsions and involuntary movements.

Amodiaquine may cause blood dyscrasias, hepatitis, peripheral neuropathy and haemolytic anaemia. If long term therapy is given, regular ophthalmic examination is recommended.

Because amodiaquine may concentrate in the liver, the medicine should be used with caution in patients with hepatic disease or alcoholism and in patients receiving hepatotoxic medicines.

Since hemolysis and acute renal failure has been reported to occur in a few patients with glucose 6-phosphate dehydrogenase deficiency receiving chloroquine, this should also be considered when using amodiaquine.

8. Adverse effects

Agranulocytosis and other blood dyscrasias, hepatitis and peripheral neuropathy have been reported occasionally after amodiaquine usage alone. Administration of quinoline type medicines has been associated with hemolytic anaemia.

In therapeutic doses used for malaria. amodiaquine may occasionally cause nausea, vomiting, diarrhoea, vertigo and lethargy. Abdominal pain, headache and photosensitivity have been reported with amodiaquine. When given for long periods, it sometimes causes corneal deposits, visual disturbances and bluish - grey pigmentation of the finger nails, skin and hard palate. These reactions clear somewhat slowly, on stopping treatment. However, because of the occasional development of irreversible retinopathy,

regular ophthalmic examinations should be carried out if the medicine is used over a long period. The medicine can also cause irregular heart beats and tremors.
Prophylactic use of amodiaquine is associated with an unacceptably high incidence of serious toxicity. Approximately 1 in 2000 patients develop agranulocytosis. Serious hepatotoxicity has also been reported. Minor adverse effects are similar to those of chloroquine, although pruritus is less of a problem. Artesunate and other related artemisinin derivatives have been widely used in China, with no reports of any serious adverse reactions. Medicine induced fever can occur. Neurotoxicity has been observed in animal studies but not in humans. In view of the uncertainty about toxic effects, caution should be exercised when more than one 3 day treatment is given. Cardiotoxicity has been observed following administration of high doses.

In healthy volunteers, a reversible reduction in reticulocyte counts was the dose limiting adverse effect of artesunate, occurring with doses of 16.88mg/Kg.
Possible medicine related adverse effects include dizziness, itching, vomiting, abdominal pain, flatulence, headache, bodyache, diarrhoea, tinnitus and increased hair loss, macular rash, reduction in neutrophil counts and convulsions. However, it is likely that many of these effects are disease-related rather than medicine-induced.
Occasional skin rash and pruritus has been observed with artesunate.

9. Overdosage

This is mainly pertaining to amodiaquine in the amodiaquine - artesunate combination. Intoxication with amodiaquine is far less frequent than chloroquine poisoning. However, large doses of amodiaquine have been reported to produce syncope, spasticity, convulsions and involuntary movements.

The usual signs and symptoms of an overdose are headache, vertigo and vomiting; the more severe manifestations including cardiac arrhythmias, convulsions and coma. The most dramatic feature is visual disturbance, including sudden loss of vision, which is usually transitory.

Other symptoms include itching, cardiovascular abnormalities, dyskinesia, neuromuscular and haematological disorders and hearing loss.

Nausea, vomiting, diarrhoea, headache, drowsiness, blurred vision, blindness, convulsions, coma, hypotension, cardiac arrhythmias, cardiac arrest, and impaired respiration are the characteristic features of amodiaquine poisoning. ECG may show inverted or flattened T waves, widening of QRS, ventricular tachycardia and fibrillation. Hypokalemia may be present.

No data available for overdosage of artesunate.

10. Treatment of over-dosage

Treatment of overdosage is supportive and must be prompt since acute toxicity can progress rapidly, possibly leading to vascular collapse and respiratory and cardiac arrest. Early endotracheal intubation and mechanical ventilation may be necessary. Early gastric lavage followed by administration of activated charcoal may provide some benefit in reducing absorption of the medicine. These should be preceded by measures to correct cardiac and severe cardiovsacular disturbances, if present and by respiratory support. Diazepam IV may control seizures and other manifestations of CNS stimulation. Seizures caused by anoxia should be corrected by oxygen and other respiratory support. Defibrillators and cardiac pacemakers may be required.

11. Storage

Keep in a cool, dry, dark place.

12. Dose schedule

See Appendix 3.

APPENDIX 3:

WORLD HEALTH ORGANISATION (WHO) RECOMMENDED COMBINATION THERAPIES FOR UNCOMPLICATED FALCIPARUM MALARIA

1. Artemether/Lumefantrine

Co-formulated tablets contain 20mg of Artemether (A) and 120mg of Lumefantrine (L)

At present available as single-source product under the proprietary name of Coartem®. In addition to its commercial presentation, it is also available in different course-of-therapy packs for different population groups, supplied at cost through WHO and UNICEF for public sector use in endemic developing countries.

The WHO recommended dosage is the following:

	Tablets containing 20mg of artemether and 120mg of lumefantrine					
	0 hours	8 hours	24 hours	36 hours	48 hours	60 hours
5-14 kg	1	1	1	1	1	1
15-24 kg	2	2	2	2	2	2
25-34 kg	3	3	3	3	3	3
>34kg	4	4	4	4	4	4

Note: Simplification of the above for ease of use at the program level is as follows: 2nd dose on the first day should be given anytime between 8 to 12 hours of the first dose. Doses on the 2nd and 3rd days is twice a day (morning and evening).

1. Artesunate + Amodiaquine

Separate scored tablets contain 50mg of artesunate and 153mg base of amodiaquine, respectively. Co-formulated tablets are not available at present.

Available from different manufacturers either in separate blister packs or as single course-of-therapy packs. Tablets need to be divided for children below 1 year of age.

The WHO recommended dosage for AS+AQ is the following:

	Artesunate (50mg)			Amodiaquine (153mg)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5 -11 months	25 ($^1/_2$ tab)	25($^1/_2$ tab)	25($^1/_2$ tab)	76($^1/_2$ tab)	76($^1/_2$ tab)	76($^1/_2$ tab)
1-6 years	50 (1 tab)	50(1 tab)	50(1 tab)	153(1 tab)	153(1 tab)	153(1 tab)
7-13 years	100(2tabs)	100(2tabs)	100(2tabs)	306(2tabs)	306(2tabs)	306(2tabs)
>13 yrs	200(4tabs)	200(4tabs)	200(4tabs)	612(4tabs)	612(4tabs)	612(4tabs)

3. Artesunate + Sulfadoxine/Pyrimethamine

Separate scored tablets containing 50mg of artesunate and 500mg of sulfadoxine + 25mg pyrimethamine, respectively. Co-formulated tablets are not available.

Available from different manufacturers either in separate blister packs as single course-of-therapy packs. Tablets need to be divided for children below 1 year of age.

The WHO recommended dosage of Artesunate + SP is the following:

	Artesunate (mg)			Sulfadoxine/Pyrimethamine (mg/mg)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5 -11 months	25 ($^1/_2$ tab)	25 ($^1/_2$ tab)	25 ($^1/_2$ tab)	250/12.5 ($^1/_2$ tab)	0	0
1-6 years	50 (1 tab)	50 (1 tab)	50 (1 tab)	500/25 (1 tab)	0	0
7-13 years	100 (2 tabs)	100 (2 tabs)	100 (2 tabs)	1000/50 (2tabs)	0	0
>13 years	200 (4tabs)	200 (4tabs)	200 (4tabs)	1500/75 (3tabs)	0	0

4. Artesunate + Mefloquine

Separate scored tablets containing 50mg of artesunate and 250mg base of mefloquine, respectively. Co-formulated tablets are not available at present.

Available from manufacturers either in separate blister packs or as single course-of-therapy packs. Tablets need to be divided for children below 1 year of age.

The WHO recommended dosage is the following:

	Artesunate (50mg)			Mefloquine (250mg)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5 -11 months	25 ($^1/_2$ tab)	25 ($^1/_2$ tab)	25 ($^1/_2$ tab)	0	125 ($^1/_2$ tab)	0
1-6 years	50 (1 tab)	50 (1 tab)	50 (1 tab)	0	250 (1 tab)	0
7-13 years	100 (2 tabs)	100 (2 tabs)	100 (2 tabs)	0	500 (2 tabs)	250 (1 tab)
> 13 years	200 (4 tabs)	200 (4 tabs)	200 (4 tabs)	0	1000 (4 tabs)	500 (2 tabs)

5. Amodiaquine + Sulfadoxine/Pyrimethamine

Separate scored tablets containing 153mg base of amodiaquine, and 500mg of sulfadoxine + 25mg pyrimethamine, respectively. Co-formulated tablet, are not available.

Available from manufacturers either in separate blister packs or as course-of-therapy packs. Tablets need to be divided for children below 1 year of age[1].

[1] One manufacturer supplies course-of-therapy blister packs also for children below 1 year of age, and this is being deployed as part of the malaria treatment policy in Rwanda since 2002.

The WHO recommended dosage is the following:

	Amodiaquine (153mg)			Sulfadoxine/Pyrimethamine (500/25mg/mg)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5 -11 months	76 ($^1/_2$ tab)	76 ($^1/_2$ tab)	76 ($^1/_2$ tab)	250/12.5 ($^1/_2$tab)	0	0
1-6 years	153 (1 tab)	153(1 tab)	153 (1 tab)	500/25 (1 tab)	0	0
7-13 years	306 (2 tabs)	306 (2 tabs)	306 (2 tabs)	1000/50 (2 tabs)	0	0
> 13 years	612 (4 tabs)	612 (4 tabs)	612 (4 tabs)	1500/75 (4 tabs)	0	0

APPENDIX 4: FORM FOR REPORTING SUSPECTED ADVERSE MEDICINE REACTIONS

CONFIDENTIAL

(See Reverse for Instructions)

REPORT ON SUSPECTED ADVERSE REACTIONS

REPUBLIC OF UGANDA
MINISTRY OF HEALTH

A. Patient's details

Surname			
Other Names			
Age		Sex	Weight (Kgs)
OPD No.		Health Facility name	
District			

B. Drug Details (Including vaccines and other health care products)

Suspected Drug Brand Name ➡		Generic Name ➡	
Indication: Why was the drug prescribed or taken		Manufacturing / Expiry date ➡	
Date ➡ Started	Date ➡ Stopped	Daily ➡ Dose	Route ➡
			Diluent details ➡
Prescribed? YES ☐ NO ☐	**OTC?** YES ☐ NO ☐		Lot / Batch No.➡

C. Reaction Details

• Headache ☐	• Shock / Collapse ☐	• Skin reaction ☐	Date Reaction Started ➡
• Diarrhea ☐	• Nausea or vomiting ☐	• Convulsions ☐	Date of notification of Reaction ➡
• Anaphylaxis ☐	• Severe local reaction ☐	• Injection site abscess ☐	
• Other(specify)			Date Reaction Stopped ➡

Treatment given: Yes ☐ No ☐ If yes specify

Was patient admitted? YES ☐ NO ☐ Duration of admission (days) ➡

Outcome: Continuing ☐ Recovered ☐ Fatal ☐ Date of death

D. Other Drugs Used (Including self medication, vaccines, herbal preparations) **Tick box** ☐ **if no drug taken**

	1	2	3	4	5
Name of drug					
Indication					
Daily dose					
Date started					
Date ended					

Comments: Please use this space to record other information e.g. relevant history, allergies, failure of efficacy, counterfeit, test result, follow up data etc.

F. Reporter Details

Name:		Designation:	
Postal address:		Telephone / Fax:	
Signature:		**Date:**	

If you would like information about other adverse reactions associated with the suspected drug, please tick this box ☐

Thank you for your cooperation.

Guide on filling the Adverse Drug Reactions (ADR) reporting form

1. For the purpose of the pharmacovigilance programme, a drug or medicine is defined as, 'Any substance administered to human beings for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. This definition includes prescribed medicines, over-the-counter medicines, vaccines, herbal medicines and biologicals including blood and blood-related products e.g. serum, plasma etc.

2. All health professionals in Uganda can report any suspected adverse drug reaction directly to NDA.

3. Please note that identities of the patient, reporting Doctor, Pharmacist, Nurse and health facility will be kept strictly confidential.

4. Please report any adverse reaction experienced by a patient even if you are not certain the product caused the adverse reaction or even if you do not have all the details.

5. This form can also be used to report product quality problems such as suspected contamination, questionable stability, defective components, poor packaging / labeling and/or therapeutic failures.

7. The completed suspected ADR report should be sent to the office of the District Director of Health Services (DDHS) to be forwarded to National Drug Authority at the address given below.

8. Date of Notification: Date a patient reports to the health facility.

9. The form must be forwarded to the next level (HSD/DDHS) within 24-48 hours of notification

The Executive Secretary / Registrar
National Drug Authority
National Pharmacovigilance Centre
Plot 46 -48 Lumumba Avenue
P.O. BOX 23096 Kampala, UGANDA
Tel: 255665 / 347391 /2 / Hotline: 344052 Fax:255758
Email: ndaug@nda.org.ug
Web site: www.nda.or.ug

APPENDIX 5:

ENUMERATION OF MALARIA PARASITES

In addition to definitive diagnosis of malaria and differential diagnosis of the species of malaria parasites, microscopical examination also enables their number in a unit volume of blood to be determined. Knowledge of the degree of parasitaemia may be of diagnostic and prognostic value in the case of severe *P. falciparum* malaria infection and helps in following up the changes produced by treatment.

1. Method of counting malaria parasites in thin blood films

To count parasites as a percentage of red cells on the thin film, use two tally counters, one for red cells and the other for parasites. Count all the red cells in an oil immersion field, then all the parasites in the same field. Repeat the exercise until 500 red cells have been counted. Percentage parasitaemia is then the total number of parasites x 100 divided by the total number of red cells counted.

$$\text{Percentage of Parasitaemiea} = \frac{\text{Number of Parasites counted (total) x 100}}{\text{Number of red blood cells counted (total)}}$$

2. Methods of counting malaria parasites in thick blood films

I. Parasites per µl (microlitre)

The following is a practical method of adequate accuracy. It is based on the number of parasites per µl of blood in a thick film, these being assessed in relation to a predetermined number of leukocytes. An average of 8000 leukocytes per µl is taken as the standard. Despite inaccuracies due to variations in the number of leukocytes between individuals in normal health and greater variations in ill health, this standard allows for reasonable comparisons. Before counting begins, the equivalent of 0.25 µl of blood (100 fields, using a 7 x ocular and a 100 x oil-immersion objective) should be examined in the thick film to determine the parasite species and stages that may be present. When this has been established, a suitable counting method for positive blood films is:

i. To count parasites and leukocytes separately using two tally-counters.

   a. If, after 200 leukocytes have been counted, 10 or more parasites have been identified, record the results in the record form, showing parasites per 200 leukocytes;

b. If, after 200 leukocytes have been counted, 9 or less parasites have been counted, continue counting until 500 leukocytes have been counted and record the parasites per 500 leukocytes.

ii. In each case, the parasite count in relation to the leukocyte count can be converted to parasites per µl by the simple mathematical formula:

$$\frac{\text{No. of parasites counted} \times 8000}{\text{No. of leukocytes counted}} = \text{parasites per µl}$$

This means that if 200 leukocytes are counted, the parasites are multiplied by 40, and if 500 leukocytes are counted the parasites are multiplied by 16.

iii. It is normal practice to count all the species present and to include both sexual and asexual parasites together. Occasionally a separate count is made of the gametocytes of *Plasmodium falciparum* but when this is done, they should still be included in the general parasite count. It is rarely possible to separate the gametocytes of *P. vivax* or *P. malariae* from the asexual parasites with sufficient accuracy to justify a gametocyte count.

II. The Plus System

A more simplified method of enumerating parasites in thick blood films is to use the plus system. This indicates the relative parasite count and entails using a code of from one to four pluses, as follows:

+	= 1-10 parasites per **100 thick film** fields	= 4-40 parasites per mm^3
++	= 11-100 parasites per **100 thick film** fields	= 40-400 parasites per mm^3
+++	= 1-10 parasites per **one thick film** field	= 400-4,000 parasites per mm^3
++++	= more than 10 parasites per **one thick film** field	= 4,000-40,000 parasites per mm^3

This system should be used only when it is not possible to undertake the more acceptable parasite count per µl of blood.