Case management

GUIDE FOR **PARTICIPANTS**

World Health Organization

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TRAINING MODULE ON **MALARIA CONTROL**

World Health Organization

CONTENTS

Foreword

Malaria is a major global public health problem and a leading cause of morbidity and mortality in many countries. In 2010, an estimated 3.3 billion people (about half of the world population) lived in areas where malaria is a health risk for the population. Malaria caused some 216 million cases with up to 655 000 deaths in 2010. Approximately 80% of the cases and 90% of the deaths occur in Africa while the remaining cases and deaths occur mainly in the South-East Asia and Eastern Mediterranean Regions.

The WHO global malaria control and elimination strategy aims to achieve a 50% reduction in the malaria burden by 2010 compared to the levels in 2000, and at least a 75% reduction in malaria incidence and deaths by 2015. These goals are relevant for high-burden countries which implement malaria control programmes.

Elimination of malaria is defined as the complete interruption of the chain of local malaria transmission. Elimination programmes require more technical malaria expertise than standard malaria control programmes, especially in malaria epidemiology and entomology.

To achieve the objectives of malaria control and elimination programmes, appropriately planned and targeted delivery of essential malaria interventions is critical, including: early diagnostic testing of suspected malaria and prompt treatment of confirmed cases with effective artemisinin-based combination therapy (ACT); and application of appropriate vector control interventions, particularly the use of insecticide-treated nets (ITNs/LLINs) and indoor residual spraying (IRS).

This training module on malaria case management has been developed to support the staff involved in malaria control and elimination programmes in the effective organization of malaria diagnosis and case management services.

Abbreviations

ACT	Artemisinin-based combination therapy
ANC	Antenatal clinic
ARDS	Adult respiratory distress syndrome
ATP	Antimalarial treatment policy
CBP	Community-based providers
DIC	Disseminated intravascular coagulation
DNA	Deoxyribonucleic acid
G6PD	Glucose-6 phosphate dehydrogenase
HMM	Home-based management of malaria
HRP-2	Histidine-rich protein 2
IMCI	Integrated management of childhood illness
IPT	Intermittent preventive treatment
LMIS	Logistics management and information system
PCR	Polymerase chain reaction
PCV	Packed cell volume
pLDH	Parasite lactate dehydrogenase
RBC	Red blood cell
RDT	Rapid diagnostic test
SBET	Standby emergency treatment
TET	Therapeutic efficacy testing
TNF	Tumor necrosis factor
WBC	White blood cell

Acknowledgements

Methodology

The content of the training module is based on the 2nd edition of the *WHO guidelines for the treatment of malaria* and other evidence-based technical documents on the diagnosis and treatment of malaria (http://www.who.int/malaria/publications).

The module was developed through a rigorous process involving a Technical Expert Committee representing malaria training and academic institutions, malaria researchers, country programme managers, and WHO regional offices, who guided the process of reviewing and updating the module. The process included the following steps:

▸ Three technical expert group consultations (7–9 April 2008; 14–16 October 2008 and 15–17 April 2009) were held in Geneva to review the existing WHO training materials on malaria case management and identify areas for update in view of the current status of developments in new tools, technologies and strategies for malaria control focusing mainly on the changing disease epidemiology.

▸ Technical experts were commissioned to incorporate the recommended updated information in the module.

▸ The revised module was then reviewed for content and completeness by the technical expert committee, the WHO technical staff and external experts in malaria case management.

▸ The module was field-tested in several national and international courses.

▸ Based on feedback from field tests, and in consultation with technical experts, the text was finalized for publication.

Introduction

This training module focuses on providing guidance to malaria programme managers and other malaria specialists on the current recommended approaches used in planning and delivery of malaria case management services. It is designed to provide guidance on all aspects of malaria diagnosis and case management.

The module can be used both for in-service training programmes and for pre-service training curricula of health workers in relevant fields of health studies. It can be used for stand-alone training sessions or together with training modules dealing with other aspects of malaria control and elimination.

The module uses a problem-solving approach to facilitate the understanding of malaria case management, and is designed to promote good practice through practical application, involving individual and team work.

The training is most efficiently delivered through an institutionalized training programme that can ensure regular provision of the course. In areas that do not have an institutionalized programme, the training can be organized by national, provincial or district programmes, in collaboration with local partners.

The module is in two parts, the *Guide for Participants* and the *Guide for Tutors.* For each group of participants the topics to be covered can be selected to suit their specific training needs.

Potential users of the *Guide for Participants*

The guide is designed for health professionals engaged in planning and implementation of malaria control and elimination programmes, particularly those involved in malaria case management services.

Objectives

At the end of the training course, participants should have acquired the skills and competence necessary to:

▶ understand the basis of malaria diagnosis and treatment;

▶ plan and implement malaria case management services;

▶ understand antimalarial treatment policy formulation;

▶ understand the use of evidence for decision-making.

Running the training course

To facilitate learning by all participants, the teaching of this subject will encourage the participants to learn from each other as well as from the tutors and facilitators, particularly in the group discussions. Each participant will therefore be expected to take part actively throughout the course. In working through the Learning Units, there will be opportunities to put into practice, individually or collectively, what has been learnt.

The tutor and the facilitators

The tutor should have extensive experience in the management of malaria and be able to help the participants to solve a wide range of problems. The facilitators, who work closely with the tutor, will also be able to spend time with the individual participants for discussion and explanation.

Presentations

Formal presentations (e.g. lectures) by the tutor will be kept to a minimum and will take the form of an explanation of the principles, basic knowledge, and experience with the class in plenary sessions. Most of the information provided in such sessions is already contained in this guide and the participants will not need to take extensive notes. A lecture will usually be combined with a demonstration. The participants will be asked frequently to present their work in plenary session. This will provide experience on how to make a presentation, both by presenting and by learning from the observations and suggestions made during discussion.

Demonstrations

Demonstrations will be used: *(i)* to illustrate some procedures for the diagnosis and management of malaria that will be carried out later by the participants, and *(ii)* to study specimens that participants should be able to recognize and equipment that they should be able to use.

Discussions

Discussions will be based on subjects taken from the Learning Units which will be read during small group and plenary sessions. In these exercises, a facilitator will lead the discussions on the selected subjects. These sessions provide opportunities for the participants to give their individual opinions, to develop ideas and to learn from one another.

Practical sessions

The course will include as many practical sessions as feasible in order to provide as much practical experience as possible in all aspects of malaria case management. In some sessions, each facilitator will work with a small group of four or five participants; by limiting the size of the groups, the participants will receive extensive individual attention and increased opportunities for learning and practice.

Small group discussions

These will often take place during presentations by the tutor and as separate exercises (in small groups) before or after a formal presentation. This will enable participants to discuss issues with colleagues, to share ideas, opinions and experiences, and to draw their own conclusions from discussions in plenary.

The small group discussions are considered to form a particularly valuable component of the course. The participants are encouraged to take full advantage of these sessions and to contribute actively in discussions. At each group work session there should be a change of moderator and reporter to ensure that every participant gains experience in these roles and that the tasks are shared equitably.

Clinical work and visits to health facilities

Whenever possible, sessions will take place at clinics, outpatient departments and inpatient wards. This will give practical experience of real-life situations and the problems that may arise in the course of the participants' daily work. The management of severe malaria at a health facility will be studied through examination of patients' health facility records.

Use of the *Guide for Participants*

This *Guide for Participants* contains instructional materials designed to enable the course participants to achieve the objectives stated earlier. The guide is divided into a series of Learning Units. It is necessary to acquire the skills and knowledge described in each unit in the sequence before progressing to the next in the series; otherwise it may prove difficult to achieve the objectives of subsequent units. This progressive step-wise learning process begins with Learning Unit 1, where participants will answer questions on their knowledge about the management of malaria in their own country or place of work, and concludes with Learning Unit 12, at which stage the main components of malaria case management and a number of important programmatic issues will have been covered.

Participants will follow the group training activities using the *Guide for Participants* plus other materials provided by the tutor. The way in which the tutor and facilitators should make the best use of the *Guide for Participants* and *Guide for Tutors* will become apparent in working through the training module.

During the course, the *Guide for Tutors* will be available only to the tutor and facilitators. Upon completion of the course/module, each participant should receive a copy of the *Guide for Tutors* so that they can use it for further training and reference.

Evaluation

Judging whether or not the course was successful involves answering the following questions:

> ▶ *How well did the group learn?*

This may be determined by evaluating the performance of the participants as they work through the Learning Units and again at the end of the training.

> ▶ *How did the participants view the training?*

Participants' answers to this question will give valuable information on how useful they find this type of training, especially if they provide a short evaluation during the course and a longer one at the end of the module.

Evaluation of the participants

Progress and achievements will be evaluated by the tutor, the facilitators, and by the participants themselves. As well as general assessment during the group activities, a number of quizzes and tests will be used. The evaluation is intended to provide a helpful opportunity for participants to measure their progress, and as a contribution to the learning process.

Whether this module is used for group training or individual learning, assessment of progress made by the trainee in gaining skills and competence in the subject matter is essential. In a training course, this can be accomplished by means of a pre-test and a post-test, using a multiple-choice questionnaire (MCQ). The pre-test will be given before the trainee reads the *Guide for Participants* the post-test will be administered after all the Learning Units have been completed. At the end of these sessions the tutor will analyse the results to identify topics that were not fully understood. The tutor may also explain to individual participants where mistakes were made and areas where improvement is needed.

The evaluation of the participant's progress also includes assessment of classroom, practical and field activities, degree of group participation, etc. including how the group work was presented in plenary sessions, and the degree of clarity.

Evaluation of the training by the participants

The entire training activity, including the organization and content of the course, the suitability of the learning methods, and the quality of the teaching, competence of the tutors and facilitators will be assessed by the participants through a questionnaire, and at a plenary feedback and discussion session after the completed questionnaires have been analysed. The questionnaire is completed anonymously so that participants may answer fully and frankly. All participants are encouraged to make suggestions for improvement on the part of the tutor and facilitators as well as in the content of the course and the training facilities. The objective of the plenary session is to ascertain whether an issue raised by one or more persons has the consensus of the whole group, and to be able to judge its importance. This exercise provides useful feedback for evaluating the training activity and for planning similar activities so that future participants may benefit from this experience.

LEARNING UNIT **1**

The malaria situation in the place where you work

Purpose of this session:
During this session you will:

- **Describe the malaria situation in the country or area where you work**
- **Outline the main components of the national malaria control policy in your country**
- **Indicate the major challenges and obstacles to achieving malaria control in your place of work**

This Learning Unit contains a series of questions designed to stimulate your thoughts about the malaria situation in the country where you work. If your answers relate only to part of the country, specify precisely which part of the country is concerned. Answer clearly and briefly those questions on which you have a definite opinion.

The responses will be reviewed during a discussion led by the tutor.

Please write only single - or few - word points under these questions. Do not write long comments or essays, as we will be discussing the questions together afterwards. Answering all these questions should take only about 15 minutes.

Question 1

a. *What is malaria?*

b. *Which species of Plasmodia are responsible for malaria in your country?*

Question 2

In your area does malaria occur all year round or does it occur during particular seasons or periods of the year? (specify the seasons or period)

Question 3

On average, how many episodes of malaria do you think a child may have in a year, in your area?

Question 4

On average, how many episodes of malaria do you think an adult may have in a year, in your area?

Question 5

a. *What methods are available for making a parasitological diagnosis of malaria in your country?*

b. *Suggest approximately what proportion of malaria treatments are based on a parasitological diagnosis, and among theses, indicate the proportion tested by each of the available methods.*

....

....

Question 6

What are the principal components of the national malaria control programme in your country? [This should be just a list – not a discussion of whether or how well the programme is carried out].

....

....

Question 7

a. *What is the national policy recommendation for first-line treatment, and what is the regimen/dose?*

....

....

b. *Is this the treatment that patients actually receive? If not, explain why not, and in roughly what proportion of cases something else is used, and what are these alternative therapies?*

....

....

c. *Do you think the recommended treatment is effective?*

....

....

d. *Where do people obtain their antimalarial medicines?*

....

....

e. *What proportion of children who need an antimalarial medicine for parasitologically confirmed malaria infection actually receive one?*

....

....

Question 8

On average how many cases of severe malaria are seen at your place of work per year?

....

....

Question 9

How many deaths are due to severe falciparum malaria in a year?

Question 10

Is there a specific period during the year when most cases of severe falciparum malaria occur? If so, state which period.

Question 11

Do you think that most of the patients with severe falciparum malaria in your area are brought to a health facility? If not, explain why.

Question 12

a. *What proportion of the deaths occurring at home are among people who did not receive medical care? If you consider the proportion to be relatively high, explain why this is the case.*

b. *What factors result in delay of patients with severe falciparum malaria reaching a health facility?*

Question 13

What is the national policy recommendation for the treatment of severe falciparum malaria? and what is the recommended regimen?

Question 14

What are the major constraints in your country, or place of work, to a satisfactory treatment of severe falciparum malaria?

Question 15

What do you expect from this training? List at least three expectations.

Question 16

Approximately what proportion of pregnant women receive, during their pregnancy, (a) any doses of antimalarial drugs for 'intermittent presumptive therapy' (IPTp), (b) two or more doses of IPTp?

LEARNING UNIT **2**

Basic facts about malaria

Learning Objectives:
by the end, participants should be able to...

● **Name the species of parasites causing human malaria and describe their geographical distribution**

● **Describe the life cycle of Plasmodium and correlate the events in the life cycle with the pathogenesis and clinical features of malaria**

● **Define the terms: relapse, reinfection, periodicity, paroxysms, recrudescence**

● **Describe the relationship between the clinical features and parasitaemia**

● **Describe the biological characteristics of the different Plasmodium species and the clinical features associated with malaria caused by each of them**

● **Define uncomplicated and severe malaria**

2.1   Introduction

The word *malaria* is based on the association between the "bad air" of marshes where the anopheline mosquitoes breed and human infection by *Plasmodium* species. Malaria has afflicted the world's human population for thousands of years and continues to do so today. The earliest references to malaria in recorded history are descriptions of splenomegaly with fever from China in the Nei Ching Canon of Medicine in 1700 BC and from Egypt in the Ebers Papyrus in 1570 BC. Hippocrates clearly recognized the syndrome of malaria

and its relationship to marshes. Literary references to malaria appear in Homer's Iliad and in the works of Chaucer and Shakespeare. European travellers to India, sub-Saharan Africa and South America were decimated by malaria from the 16th to the 19th centuries.

Malaria remains one of the main global health problems of our time, causing an estimated 216 million clinical cases and 655 000 deaths in 2010, with about 90% of deaths and 80% of cases occurring in Africa, south of the Sahara. Malaria transmission occurs in 90 countries and territories between latitudes 45° N and 40° S. These countries have tropical or subtropical zones with optimal climatic conditions that favour the development of anopheline mosquitoes and malaria parasites.

2.2   Definition and etiology

Malaria is a parasitic infectious disease caused by protozoan parasites of the genus *Plasmodium* and is transmitted by mosquitoes. It is characterized by recurrent symptoms of chills, fever and generalized body pain. The four *Plasmodium* species of human malaria are: *P. falciparum*, *P. vivax, P. ovale* and *P. malariae*. There are also increasing reports of human infections with the monkey malaria parasite *P. knowlesi* in forested regions of South-East Asia.

▸ *Plasmodium falciparum* is found worldwide, mainly in tropical and subtropical areas. It is the main species that causes severe, potentially fatal malaria.

▸ *Plasmodium vivax* is found mainly in Asia, Latin America, and in some parts of Africa. Recent evidence shows that *P. vivax* can cause severe illness. *P. vivax (*also *P. ovale)* has dormant liver stages, the hypnozoites, which can become activated and invade the blood to cause clinical relapse several months or years after the infecting mosquito bite. *P.vivax* does not infect individuals who are negative for the Duffy blood group, as are many residents of sub-Saharan Africa.

▸ *Plasmodium ovale* is found mostly in the countries of west Africa and the islands of the western Pacific. It is biologically and morphologically very similar to *P. vivax.* However, unlike *P. vivax,* it is able to infect individuals who are negative for the Duffy blood group. This explains the greater prevalence of *P. ovale* (rather than *P. vivax)* in west Africa.

▸ *Plasmodium malariae* is found worldwide. *P. malariae* causes a persistant chronic infection which may be lifelong. A small number of patients develop serious complications such as the nephrotic syndrome.

▸ *Plasmodium knowlesi* is found in Malaysia, Thailand and other South East Asian countries. It is mainly transmitted in forests and along forest fringes. Under the microscope, it is indistinguishable from *P. malariae.* It can cause severe disease and death in some individuals.

2.3 Modes of transmission

There are three main modes of malaria transmission: the bite of an infected female anopheline mosquito (the main method of transmission); accidental transmission via blood transfusion or needle stick injury; and congenital transmission from mother to child during pregnancy or parturition.

The female anopheline mosquito is the vector of malaria parasites. There are more than 400 species of *Anopheles* mosquitoes throughout the world, but only some 60 of these are vectors of malaria under natural conditions, of which 30 are vectors of major importance.

Most areas have multiple species of *Anopheles*, and different species occur in different parts of the world. The most efficient vector species, which predominate in Africa, are *A. gambiae*, *A. arabiensis*, and *A. funestus*. Other vectors common in Asian countries include *A. stephensi*, *A. minimus,* and *A. dirus.*

2.3.1 Life cycle of malaria

Humans acquire malaria from sporozoites transmitted by the bite of an infected female anopheline mosquito. The sporozoites then travel through the bloodstream to the liver within about 30 minutes, where they invade hepatocytes and mature to become tissue schizonts (pre-erythrocytic schizogony). Tissue schizonts are a central feature of all plasmodium species that infect humans. They amplify the infection by producing large numbers of merozoites (10 000 – 30 000) from each sporozoite-infected hepatocyte.

Each merozoite released from the liver is capable of infecting a human red blood cell (RBC) and establishing the asexual cycle of replication in the red blood cells. The asexual cycle starts with merozoite invasion and continues to schizont rupture (merozoite → ring stage → mature trophozoite → schizont → merozoites), leading to invasion of more red blood cells. Some intraerythrocytic parasites develop into the sexual forms, the gametocytes, which are necessary for the sexual reproductive cycle that takes place in the vectors.

When potent gametocytes are ingested by a female anopheline mosquito during a blood meal, micro- and macrogametocytes mature to become male and female gametes. Fertilization of the female gametes produces diploid zygotes which mature to become ookinetes. Ookinetes then undergo a meiotic reduction division to produce haploid sporozoites, which migrate to the salivary glands of the mosquito and subsequently reinfect humans. In the *P. vivax* and *P. ovale* life cycles, some sporozoites can lie dormant in the liver cells for months or years after the initial bloodstream infection and do not cause symptoms during this time. The dormant forms, called hypnozoites, eventually mature to become tissue schizonts which release infectious merozoites, resulting in a clinical relapse.

2.3.2   Malaria transmission by mosquitoes

The parasite incubation period in the vector mosquito, known as extrinsic incubation, is temperature-dependent. *P. falciparum* takes 8–11 days to complete the mosquito phase at an optimal ambient temperature of 28°C and 22 days at 20°C. The temperature of the mosquito gut equals that of its surroundings; a low environmental temperature therefore results in a longer development time for the parasite in the mosquito. *P. falciparum* is unable to develop below 19°C while *P. vivax* can develop in the mosquito at temperatures as low as 16°C; consequently *P. vivax* transmission is found in some areas where the average temperature is too low for *P. falciparum* transmission. Due to this difference in temperature sensitivity, *P. falciparum* is common in tropical regions while *P. vivax* prevails in both tropical and temperate cold regions (see Figure 2.1).

2.3.3   Other modes of transmission

Transmission via blood transfusion, accidental needle stick, or needle sharing, leads to transfer of asexual stages of the parasite. The incubation period of the disease is therefore much shorter than it is after transmission of sporozoites by mosquito bite. Transfusion of blood infected with *P. vivax* and *P. ovale* parasites does not lead to clinical relapse because pre-erythrocytic schizogony does not occur and hence the dormant hepatic forms are not produced.

Transmission of malaria across the placenta from mother to fetus is diagnosed when parasitaemia is found in the neonate within seven days of birth, or later if there has not been any other possibility of transmission to the neonate (by blood or mosquito bite). Despite the high prevalence of placental infection, congenital transmission of malaria is rare.

2.4   Biological and clinical characteristics of different malaria species

The parasite incubation period, known as the intrinsic incubation period, differs for each parasite species. The incubation period of *P. falciparum* is 9–14 days, *P. vivax* 12–17 days, *P. ovale* 16–18 days and *P. malariae* 18–37 days. The erythrocytic cycle, which is responsible for clinical paroxysms, takes about 48 hours in *P. falciparum, P. vivax,* and *P. ovale* infections (tertian cycle), but lasts about 72 hours with *P. malariae* infection (quartan cycle).

The malaria parasite species also differ in the number of merozoites they produce in the exo-erythrocytic and erythrocytic phases and the type of the red blood cells they invade. *P. falciparum* produces the greatest number of merozoites in both phases followed by *P. vivax. P. falciparum,* which is responsible for the severe forms of malaria, infects red blood cells of all ages, unlike *P. malariae* which infects older red blood cells, and *P. vivax* and *P. ovale* which infect young red cells.
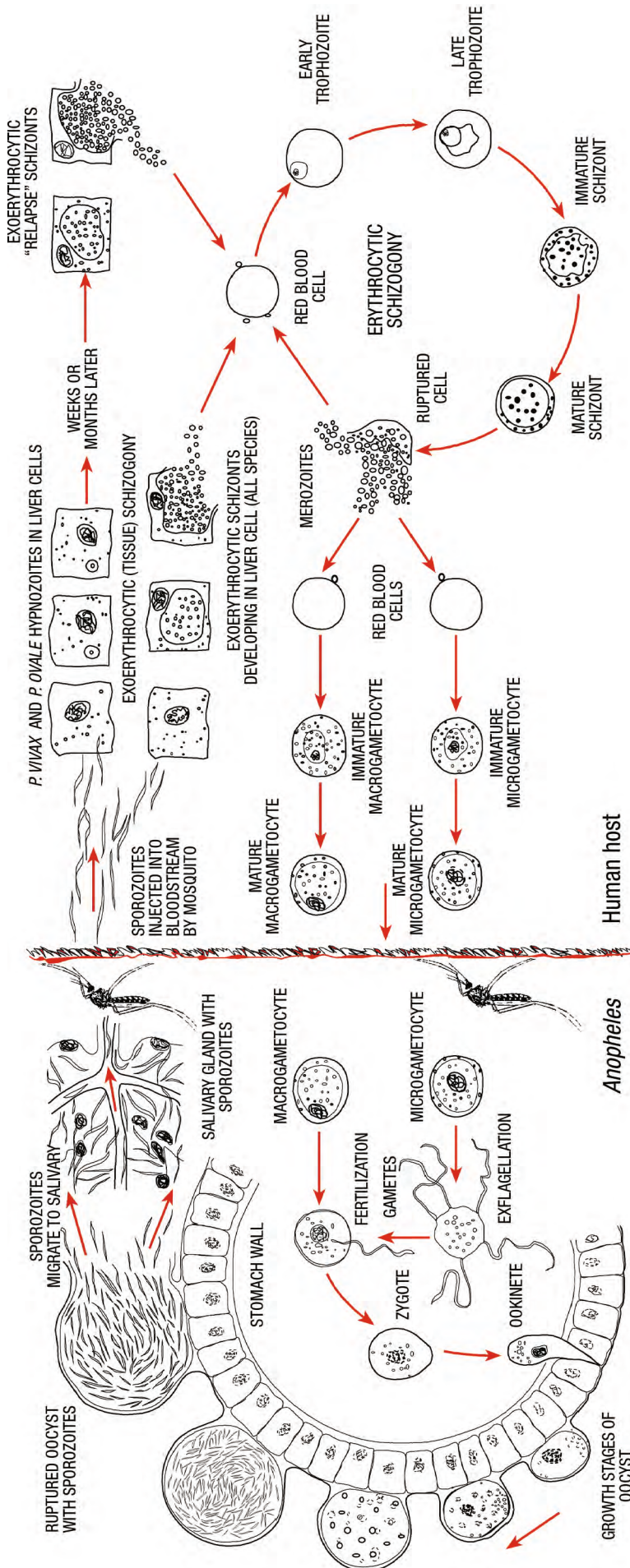
Figure 2.1   Life-cycle of malaria parasites

2.5   Classification of malaria endemicity

Endemicity of malaria describes the intensity of malaria transmission in a given community or region and can be classified according to parasite rates. Based on intensity of transmission, populations or regions may be classified as follows:

Stable malaria areas – In these regions:
- ▸ transmission occurs all year round, though there may be seasonal variations;
- ▸ older children and adults in the community have partial immunity which protects them from severe forms of malaria;
- ▸ young children are susceptible to severe malaria.

Unstable malaria areas – In areas with low transmission:
- ▸ intermittent transmission may be annual, biannual (twice a year) or variable;
- ▸ malaria epidemics tend to occur;
- ▸ immunity to malaria is usually low or absent.

2.5.1   Classification based on spleen and parasite rates

The spleen rate is the proportion (expressed as a percentage) of enlarged spleens in a sample of the population, usually children aged 2–9 years. The parasite rate is the proportion of a given population with malaria parasites in the blood. Based on these two indices, malaria endemicity can be classified as described in the table below (Table 2.1).

Table 2.1 Classification of malaria endemicity by spleen and parasite rates.

Type	Spleen rate	Parasite rate
Hypoendemicity	≤ 10% of children aged 2–9 years	≤ 10% of children aged 2–9 years
Mesoendemicity	11–50% of children aged 2–9 years	11–50% of children aged 2–9 years
Hyperendemicity	Constantly > 50% in children aged 2–9 years; also high in adults (> 25%)	Constantly > 50% in children aged 2–9 years
Holoendemicity	Constantly > 75% in children aged 2–9 years, but low in adults	Constantly > 75% in infants aged 0-11 months

In areas of high endemicity the level of immunity to malaria in the community tends to be high and consequently the prevalence of asymptomatic malaria infections is high.

2.5.2   Clinical classification

In clinical terms, malaria can be classified in two major forms: as follows:

Uncomplicated malaria

This is symptomatic malaria with parasitaemia without signs of severity or evidence of vital organ dysfunction. Most cases of malaria in children in the tropics are of this type.

The main manifestations of uncomplicated malaria include fever, chills, rigors, headaches, and body pains. Others are malaise, nausea, vomiting, and joint weakness. Physical examination may reveal pallor and hepatosplenomegaly.

Severe malaria

This refers to acute *P. falciparum* malaria with signs of severity or evidence of vital organ dysfunction. A patient is regarded as having severe falciparum malaria if there are asexual forms of *P. falciparum* in a blood film and any of the following clinical or laboratory features (see box 2.1) are present:

Box 2.1 Clinical and laboratory features of severe malaria.	
Clinical features of severe malaria	**Laboratory features of severe malaria**
▸ impaired consciousness or unarousable coma	▸ hypoglycaemia
▸ prostration	▸ metabolic acidosis
▸ multiple convulsions	▸ severe normocytic anaemia
▸ deep breathing, respiratory distress	▸ haemoglobinuria
▸ circulatory collapse or shock	▸ hyperparasitaemia
▸ clinical jaundice	▸ hyperlactataemia
▸ abnormal spontaneous bleeding	▸ renal impairment
▸ pulmonary oedema (radiological)	

See LEARNING UNIT 4 for more details regarding the definition of severe malaria.

LEARNING UNIT **3**

Management of uncomplicated malaria

Learning Objectives:
by the end, participants should be able to...

● **Demonstrate competence in the clinical assessment of a suspected case of malaria**

● **List the advantages of parasitological diagnosis**

● **Recall the WHO recommendations on parasitological diagnosis**

● **Describe the methods for preparation of blood film, staining and microscopic examination for diagnosis of malaria**

● **Explain the mechanism of the malaria rapid diagnostic tests (RDT)**

● **State the advantages and disadvantages of malaria microscopy and RDTs**

● **State the recommended guidelines for the treatment of uncomplicated malaria**

● **Describe the supportive care for uncomplicated malaria**

● **Define the term ''drug resistance'' in malaria and list the methods for assessment of drug resistance**

● **Indicate the role of follow-up for case management at all levels of health services**

3.1   Management of uncomplicated falciparum malaria

3.1.1   Diagnosis of uncomplicated falciparum malaria

A. Clinical assessment

Taking the case history of a patient with suspected malaria

The general information relevant to malaria includes:

- age – severe forms are commoner in children under 5 years of age in areas with stable malaria transmission;
- place of residence – malaria should be suspected in people who live in endemic areas;
- history of travel – individuals in malaria-free areas who present with suggestive symptoms should be asked about any recent travel to a malaria-endemic area; if there has been such travel, it is important to find out about use of prophylaxis;
- pregnancy history in women of child-bearing age.

Clinical features of uncomplicated disease:

- history of fever
- febrile paroxysms
- chills
- rigors
- headaches and other body aches
- other symptoms are: vomiting , joint pains , weakness , cough, nausea

Clinical features of severe disease:

- impaired consciousness or unarousable coma
- prostration
- failure to feed
- multiple convulsions
- deep breathing, respiratory distress
- circulatory collapse or shock
- clinical jaundice
- abnormal spontaneous bleeding
- pulmonary oedema

Physical examination of a patient with suspected malaria

Check for fever, i.e. body temperature ≥ 37.5°C (axillary)

Examine for pallor, particularly in children and pregnant women

Examine for features of possible severe disease (see Learning Unit 4).

Prompt and accurate diagnosis of malaria is part of effective disease management and will help to ensure appropriate treatment for patients as well as reducing the inappropriate use of antimalarials. A high level of sensitivity of malaria diagnosis is important in all settings, particularly for the most vulnerable population groups, such as children, in which the disease can be fatal. A high level of specificity of diagnosis can improve the differential diagnosis of febrile illness and reduce the unnecessary use of medicines and overuse of antimalarials.

Clinical criteria may be applied for the empirical diagnosis of malaria but a parasite-based test is required for confirmation of the diagnosis of malaria infection.

Clinical diagnosis of malaria

The signs and symptoms of malaria are non-specific. This means that many other infections can cause signs and symptoms identical to those caused by malaria. Malaria is suspected clinically mainly on the basis of fever or history of fever in settings where exposure to infection may have occurred. Clinical diagnosis of uncomplicated malaria is only justifiable when a diagnostic testing is not available. Current WHO recommendations for such situations are:

▶ In settings where the risk of malaria is low, clinical diagnosis of uncomplicated malaria should be based on the degree of exposure to malaria and a history of fever in the previous three days, in the absence of features of other severe diseases;

▶ In settings where the risk of malaria is high, clinical diagnosis should be based on a history of fever in the previous 24 hours and/or the presence of anaemia, for which pallor of the palms appears to be the most reliable sign in young children, in the absence of features of other severe diseases.

B. Parasitological diagnosis

Parasitological diagnosis is required for confirmation of the diagnosis of malaria. It is recommended for all suspected malaria cases in all transmission settings. The advantages of parasitological diagnosis are:

a. improved care of parasite-positive patients owing to greater certainty that the cause of the present illness is malaria;

b. identification of parasite-negative patients for whom another diagnosis must be sought;

c. prevention of unnecessary use of antimalarials, thereby reducing the risk of adverse side-effects and drug interactions;

d. confirmation of treatment failures; and

e. improved malaria case detection and reporting.

The two main methods in routine use for parasitological confirmation of malaria are light microscopy and rapid diagnostic tests (RDTs). For the management of a new fever episode, quality-assured microscopy and RDTs are equivalent in terms of performance for the diagnosis of uncomplicated malaria. In addition, molecular diagnosis (e.g. polymerase chain reaction / PCR) is usually applied in research settings, and in surveillance in areas where elimination of malaria is in progress. Serological tests for malaria have no place in the management of febrile patients.

Parasitological diagnosis should be available within a short time (less than 2 hours) of clinical examination of the patient. If this is not possible, the patient should be treated on the basis of a clinical diagnosis.

> **WHO recommendations on parasitological diagnosis**
>
> Following are the WHO recommendations on malaria diagnosis[1]:
>
> ▸ Prompt parasitological confirmation by microscopy or RDTs is recommended in all patients suspected of malaria before treatment is started.
>
> ▸ Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not accessible.

In settings of low to moderate and/or unstable transmission, which include many urban areas in Africa and the low transmission season in areas with seasonal malaria, health workers should be trained to identify, through the case history, patients who have been exposed to malaria risk before a parasitological test is ordered.

Malaria species identification: in areas where two or more malaria species are common, either malaria microscopy or certain RDTs can provide a species-specific diagnosis. Where *P. falciparum* and non-falciparum malaria are both prevalent and commonly occurring as single-species infections, if microscopy is not available, it is recommended to use combination RDTs that detect all species and distinguish *P. falciparum* and non-falciparum malaria.

In epidemic-prone zones, good quality malaria diagnosis must be available, not only for case management but also for surveillance, i.e. investigation of an unexpected increase in cases of fever. During outbreak investigations and field surveys, RDTs have the advantage of allowing both detection and immediate treatment of malaria-positive cases. When the positivity rate is very low, it becomes difficult to maintain the interest and skills of microscopists and their capacity to implement an effective quality management system based on slide cross-checking (because of problems of sensitivity).

In complex emergency situations, there are several logistic and practical advantages to using RDTs rather than microscopy: rapid deployment in the field, less training needed than for microscopy, no need for an electricity supply, immediate availability of results for treatment of positive cases in the field, and potential for testing more cases. However, if the patient has received previous antimalarial treatment, a microscopic examination of blood film for malaria is recommended to investigate possible treatment failure.

[1.] *Guidelines for the treatment of malaria. Second edition.* 2010. World Health Organization, Geneva. http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf

Basic malaria microscopy

Microscopy has a high degree of sensitivity and specificity when performed well. In addition, it allows quantification of malaria parasites and identification of the infecting species. It is inexpensive and considered to be the "gold standard" against which the sensitivity and specificity of other methods must be assessed. A skilled microscopist is able to detect asexual parasites at densities of fewer than 10 per microlitre (µl) of blood but under typical field conditions the limit of sensitivity is approximately 100 parasites per µl.

Types of stains

Many differential stains have been developed for the detection of malaria parasites but the Romanowsky stains that stain the nucleus red and cytoplasm blue have proved the most adaptable and reliable for routine work.

Giemsa stain, an alcohol-based Romanowsky stain, is the "gold standard". It is the most commonly used stain and the best for routine diagnosis due to its applicability to both thick and thin blood films, its stability during storage and its constant and reproducible staining quality over a range of temperatures.

Field stain, most widely used aqueous-based stain, is a good method to stain thick smears but not suitable for thin smears. Field stain has the advantage that the film is stained extremely quick. It is useful in laboratories where the workload is high but variable results may occur during routine use, thereby reducing its widespread application. Other stains include Leishman's stain solution which uses methanol as solvent and therefore, useful to stain thin smears; Wright's stain can be used if rapid results are needed but it is not optimal for blood parasites.

Thick smears are more sensitive for detecting the presence of parasites, and thin smears can provide more details for species determination. This requires a skilled microscopist. If an experienced microscopist is not available, RDTs should be used.

Slide examination

- Giemsa stained thick and thin blood smears are the basis for microscopic diagnosis of malaria.
- Before starting parasite count, 100 fields of the thick smear at a magnification of 700 (equivalent to 0.25µl of blood) are examined to establish presence of parasites and their species. If diagnosis of species is uncertain, a further 100 fields should examined to identify a potential mixed infection.
- Thin smears are not routinely examined to diagnose malaria in a patient except when there is technical problems with the thick smears (e.g lost during the staining, auto-fixed, unreadable for other reason), when confirmation of the species is difficult or uncertain in the thick smear or when the parasite density is very high. Examine the thin smear until the presence and species of malaria parasites have been identified, or up to at least 800 fields before declaring the slide negative.
- The limit of detection by experienced microscopists is usually 10–20 parasites per µl of blood. Therefore a negative slide does not exclude the possibility that the patient may have malaria parasites in the blood. Following a negative result, examination of the blood should be repeated after a few hours.
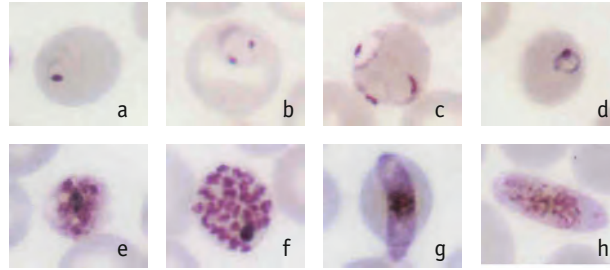
Figure 3.1   **Microscopic appearance of different stages of *P. falciparum* trophozoites (a-d), schizonts (e, f), female (g) and male (h) gamaetocytes**

Parasite density

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

Methods of counting malaria parasites in thick blood films

Parasites per microlitre (µl)

The following is a practical method which has an adequate degree of accuracy. It is based on the number of parasites per µl of blood in a thick film, 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 0.25µl of blood (100 fields, using a x7 ocular and a x100 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, parasite density is calculated using following counting procedure:

Count parasites and leukocytes separately using two tally counters.

i. If, after 200 leukocytes have been counted, 100 or more asexual parasites have been identified, record the results in the record form, showing parasites per 200 leukocytes.

ii. If, after 200 leukocytes have been counted, 99 or less asexual parasites have been counted, continue counting until 500 leukocytes have been counted and record the parasites per 500 leukocytes.

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

$$\text{Parasite density (parasites per µl)} = \frac{\text{number of parasites counted} \times 8000}{\text{number of leukocytes counted}}$$

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. The microscopist should report if gametocytes are seen but should not include them in the count. It is rarely possible to differentiate the gametocytes of *P. vivax* and *P. malariae* from the asexual parasites with sufficient accuracy.

The plus system

The "plus system" is an old, simplified method of enumerating parasites in thick blood films. However it is less accurate for establishing parasite density in thick smears and therefore it is no longer recommended. It indicates the relative parasite count using a plus code from one to four, as follows:

- ▸ +   = 1–10 parasites per 100 oil-immersion thick smear fields;
- ▸ ++   = 11–100 parasites per 100 oil-immersion thick smear fields;
- ▸ +++   = 1–10 parasites per thick smear field;
- ▸ ++++   = >10 parasites per thick smear field.

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

Advantages of light microscopy

- ▸ Low direct costs in areas of high patient turnover, if the infrastructure to maintain the service is available;
- ▸ Highly sensitive and specific in identifying parasite species and stages when used by well-trained staff;
- ▸ Differentiation between *Plasmodium* species and the stages of the parasite;
- ▸ Determination of parasite densities;
- ▸ Can be used to diagnose many other conditions for example (thick film) trypanosomiasis, leukaemia, leucocytosis, eosinophilia, and (thin film) various types of anaemia such as hypochromic or macrocytic.

Disadvantages of light microscopy

- ▸ Need for adequate training/retraining and supervision of laboratory staff;
- ▸ Need to rely on electricity;
- ▸ Time required for confident interpretation;
- ▸ Need to maintain quality assurance and control of laboratory services.

Rapid diagnostic tests

Malaria rapid diagnostic tests (RDTs) detect malaria-specific antigens derived from the blood stages of malaria parasites. The presence of antigen is indicated by a result line across a nitrocellulose strip. RDTs provide a useful support to clinical diagnosis of malaria and a valid alternative to microscopy for the clinical diagnosis of uncomplicated malaria, particularly where good quality microscopy services are not readily available. The sensitivity and specificity of RDTs in detecting falciparum and vivax malaria are comparable to field microscopy.

RDTs are widely used in many countries for the diagnosis of malaria. They have the potential to improve diagnosis and the rational use of antimalarial medicines, and also contribute to quality of care by excluding malaria in febrile patients whose illness has another cause. Different formats of RDTs are available: dipsticks, cards and cassettes – the last more widely used because of ease of use.

Mechanism of action of rapid diagnostic tests

There are different types of malaria RDTs, and the principles are essentially the same for them all. Whole blood is used for the tests, usually obtained from a finger-prick.

RDTs are lateral flow immunochromatographic antigen-detection tests, which rely on the capture of dye-labelled antibodies to produce a visible band on a strip of nitrocellulose. In the case of malaria RDTs, the dye-labelled antibody first binds to a parasite antigen and the resultant complex is captured on a strip by a band of bound antibody, forming a visible line. A control line gives information on the integrity of the antibody-dye conjugate but does not confirm that the RDT can detect parasite antigen.

Some RDTs detect only one species, *P. falciparum*, some detect this species in combination with one or more of the other three species of human malaria parasites (*P. vivax, P. ovale* and *P. malariae*), and some RDTs detect all of these species. The commercially available RDTs target the *Plasmodium falciparum* Histidine-Rich Protein 2 (HRP2), the plasmodium lactate dehydrogenase (pLDH) and/or aldolase (common to all malaria species). Different variants of pLDH are present in the commercially available RDTs: pLDH-Pan (common to all human malaria species), pLDH-Pf (present only in *P. falciparum*), pLDH-Pv (present only in *P. vivax*) and pLDH-Pvom (present in all species except *P. falciparum*).

RDT specific for *P. falciparum*

This is an antigen capture assay using a monoclonal antibody against *P. falciparum* HRP2. It is used to confirm falciparum malaria and also to exclude falciparum malaria in cases of unexplained fever, thereby indicating the need to investigate other possible causes. A potential problem with this test is that the circulating antigen may be detectable for 2–3 weeks after the elimination of viable parasites. A positive test may therefore not always indicate the presence of active infection, but it supports the diagnosis of uncomplicated *P. falciparum* if the patient has not been treated with antimalarial medicines in the previous few weeks. If the patient has received previous antimalarial treatment, a microscopic examination of a blood film for malaria is recommended to investigate possible treatment failure.

The example (Fig. 3.2) provided shows the appearance of the result line in a test which is positive for *P. falciparum*. Absence of the control line indicates that the test is invalid and should be discarded. The patient needs to be tested with a new RDT.

Combination RDTs

This is an antigen capture assay, in cassette format, using monoclonal antibodies targeting both *P. falciparum* antigens (HRP2 or pLDH-Pf) as well as antigens of the other parasite species (aldolase or pLDH-Pan or pLDH-Pv or pLDH-Pvom); these can be in various combinations. Clearance of pLDH is 5–6 days, significantly shorter than the clearance of HRP2.

Malaria Generic Pf RDT Results Guide

NEGATIVE RESULT

POSITIVE RESULTS

Plasmodium *falciparum*

Note: Test is positive even if the test line is faint.

INVALID RESULTS

No Control Line

Note: Repeat the test using a new RDT if no control line appears.
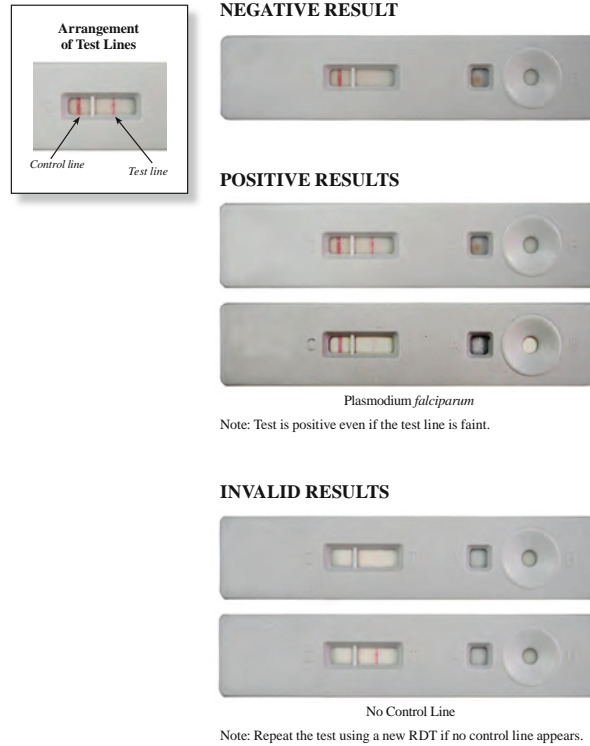
Figure 3.2   Malaria generic *P. falciparum* RDT

Malaria Generic Pf-Pan RDT Results Guide

NEGATIVE RESULT

Negative

Arrangement of Test Lines

C - Control line   T2 test line   T1 test line

POSITIVE RESULTS

P. falciparum

Non-falciparum (*P. vivax, P. ovale, P. malariae* or a mixed infection of these)

P. falciparum

P. falciparum monoinfection or 'Mixed' Infection

NOTE: Test is positive even if the line in the test window is faint.

INVALID RESULTS

No Control Line

No Control Line

Repeat the test using a new RDT if no control line appears.

Figure 3.3   Malaria *P. falciparum*-Pan RDT

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The example provided (Fig. 3.3) shows the appearance of the result line in a test showing positivity for *P. falciparum*, positivity for non-falciparum malaria as well as positivity for *P. falciparum*/mixed species malaria. The absence of the control line indicates that the test is invalid and should be discarded. The patient needs to be tested with a new RDT.

RDTs are vulnerable to exposure to high temperatures and require proper conditions of transport and storage. In places with high number of malaria tests per day, rapid diagnostic tests (RDTs) are generally more expensive than microscopy.

Advantages of RDT

▸ Ability to provide rapid results permitting immediate treatment on site;

▸ Fewer requirements for training and skilled personnel;

▸ Do not rely on electricity;

▸ Reinforcement of patient confidence in the diagnosis and in the health service in general.

Disadvantages RDT

▸ It is a qualitative test giving only a positive or a negative result;

▸ Inability, in the case of some RDTs, to distinguish new infections from a recently and effectively treated infection; this is due to the persistence of certain target antigens (e.g. HRP2) in the blood for 1–3 weeks after effective treatment;

▸ Unpredictable sensitivity in the field; this can be reduced by careful procurement, testing, and good transport and storage. WHO facilitates lot (batch) testing prior to field deployment.

Polymerase chain reaction

The polymerase chain reaction (PCR) uses enzymes to mass replicate and amplify a portion of a deoxyribonucleic acid (DNA) strand for easier analysis, such as searching for genes of interest. This technique may be used in certain situations, such as for identifying morphologically similar species (*P. malariae* and *P. knowlesi*), for efficacy testing to distinguish new infections from relapses and recrudescences, and for population screening in special elimination or containment projects. It is presently not indicated in day-to-day clinical practice.

3.1.2   Treatment of uncomplicated falciparum malaria

The objective of treating uncomplicated malaria is to cure the infection – elimination from the body of the parasites that caused the illness. This is important as it will help prevent progression to severe disease and prevent additional morbidity associated with treatment failure. The public health goal of treatment is to reduce transmission of the infection to others. Another important objective of treatment is to prevent the emergence and spread of resistance to antimalarial medicines.

To improve treatment outcomes and to counter the development of resistance to monotherapies, WHO recommends combinations of antimalarials for the treatment of falciparum malaria[2].

[2.] *Guidelines for the treatment of malaria. Second edition.* 2010.World Health Organization, Geneva. http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf

Antimalarial combination therapy is the simultaneous use of two or more blood schizonticidal medicines with independent modes of action, i.e. acting on unrelated targets in the parasite. The rationale for antimalarial combination therapy is two-fold:

▶ The combination is often more effective than a monotherapy.

▶ In the rare event of a mutant parasite that is resistant to one of the medicines arising de novo during the course of the infection, the parasite will be killed by the other medicine. This is thought to prevent or delay the emergence of resistance.

Treatment of uncomplicated malaria consists of provision of (a) effective antimalarial medicines, (b) supportive care and (c) proper counselling.

A. Artemisinin-based combination therapy

These are combinations in which one of the components is artemisinin and its derivatives (artesunate, artemether, and dihydroartemisinin). These compounds produce rapid clearance of parasitaemia and quick resolution of symptoms and they are eliminated rapidly. Therefore, when given in combination with rapidly eliminated compounds (tetracyclines, clindamycin), a 7-day course of treatment with an artemisinin compound is required, but when given in combination with slowly eliminated antimalarials, shorter courses of treatment are sufficient. Several trials have shown conclusively that combination therapy is superior to monotherapies.

In contrast to other antimalarial medicine groups, the artemisinins have marked effects on all stages of the parasite, with viability declining soon after the start of treatment. The artemisinins have gametocytocidal effects on *P. falciparum*, and this may help to reduce transmission. They are made available as fixed-dose formulations or co-administered therapy.

Artemether plus lumefantrine

This is currently available as a fixed-dose formulation with dispersible or standard tablets containing 20mg of artemether and 120mg of lumefantrine.

> **THERAPEUTIC DOSE:** The recommended treatment is a 6-dose regimen over 3 days. The dosing is based on the number of tablets per dose according to pre-defined weight bands (5–14kg: 1 tablet; 15–24kg: 2 tablets; 25–34kg: 3 tablets; and > 34kg: 4 tablets), given twice a day for 3 days. This corresponds to a target dose of 1.7/12mg/kg body weight (bw) per dose of artemether-lumefantrine, respectively, given twice a day for 3 days, with a therapeutic dose range of 1.4–4mg/kg of artemether and 10–16mg/kg of lumefantrine.

An advantage of this combination is that lumefantrine is not available as a monotherapy and has never been used alone for the treatment of malaria. Lumefantrine absorption is enhanced by co-administration with fat. It is therefore preferable to take this artemisinin-based combination therapy (ACT) with or immediately after a meal – particularly on the second and third days of treatment. A flavoured dispersible tablet paediatric formulation of artemether-lumefantrine is now available, facilitating its use in young children.

Artesunate plus amodiaquine

This combination is currently available as a fixed-dose formulation with tablets containing 25/67.5, 50/135 or 100/270mg of artesunate and amodiaquine. Blister packs of separate scored tablets containing 50mg of artesunate and 153mg base of amodiaquine are also available.

> **Therapeutic dose: A target dose of 4mg/kg/day artesunate and 10mg/kg day amodiaquine once a day for 3 days, with a therapeutic dose range between 2–10mg/kg/day artesunate and 7.5–15mg/kg/day amodiaquine.**

This combination was found to be sufficiently efficacious only where 28-day cure rates with amodiaquine monotherapy exceeded 80%. Resistance is likely to increase with continued availability of chloroquine and amodiaquine monotherapies. More information on the safety of artesunate plus amodiaquine is needed from prospective pharmacovigilance programmes.

Artesunate plus mefloquine

Blister packs with separate scored tablets containing 50mg of artesunate and 250mg of mefloquine base are available.

> **Therapeutic dose: A target dose of 4mg/kg/day artesunate given once a day for 3 days and 25mg base/kg of mefloquine either split over 2 days as 15mg/kg and 10mg/kg, or 8.3mg/kg/day mefloquine once a day for 3 days. The therapeutic dose range is between 2–10mg/kg/day of artesunate and 7–11mg/kg/day of mefloquine.**

Mefloquine was found to be associated with an increased incidence of nausea, vomiting, dizziness, dysphoria and sleep disturbance in clinical trials, but these side effects are seldom debilitating, and where this ACT has been deployed it has been well tolerated.

Artesunate plus sulfadoxine-pyrimethamine

This is currently available as separate scored tablets containing 50mg of artesunate and 500mg of sulfadoxine and 25mg of pyrimethamine.*

> **Therapeutic dose: A target dose of 4mg/kg/day artesunate given once a day for 3 days and a single administration of 25/1.25mg/kg sulfadoxine-pyrimethamine on day 1, with a therapeutic dose range between 2–10mg/kg/day artesunate and 25–70/1.25–3.5mg/kg sulfadoxine-pyrimethamine.**

This combination was sufficiently efficacious only where 28-day cure rates with sulfadoxine-pyrimethamine alone exceeded 80%. Resistance is likely to increase with continued availability of sulfadoxine-pyrimethamine, sulfalene-pyrimethamine and cotrimoxazole (trimethoprim-sulfamethoxazole).

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* A similar medicine with tablets containing 500mg of sulfalene and 25mg of pyrimethamine is considered to be equivalent to sulfadoxine-pyrimethamine.

Dihydroartemisinin plus piperaquine

This is currently available as a fixed-dose combination with tablets containing 40mg of dihydroartemisinin and 320mg of piperaquine.

> **THERAPEUTIC DOSE: A target dose of 4mg/kg/day dihydroartemisinin and 18mg/kg/day piperaquine once a day for 3 days, with a therapeutic dose range between 2–10mg/kg/day dihydroartemisinin and 16–26mg/kg/day piperaquine.**

B. Supportive care for uncomplicated malaria

▸ **Use of antipyretics:** Fever is a cardinal feature of malaria. It may be associated with vomiting and seizures, and causes great discomfort. For fever management paracetamol should be used and, if necessary, tepid sponging of the body. Paracetamol at a dose of 15mg/kg given at 4-hour intervals has been effective in fever management. Ibuprofen (5mg/kg) may also be used. A systematic review of several randomized control trials did not show any deleterious effect from the use of antipyretics, and consequently their use is encouraged especially in children prone to seizures.

▸ **Use of anti-emetics:** Vomiting is common in malaria and anti-emetics are frequently prescribed. However their efficacy has not been studied and documented.

▸ **Management of convulsions:** Generalized seizures are common in children with falciparum malaria compared to other forms of malaria. When seizures occur the airways should be maintained and an anticonvulsant given (intramuscular paraldehyde, or rectal or parenteral benzodiazepine). Multiple convulsions are a sign of severe malaria.

C. Follow up/health education

At all levels, from the hospital to the community, education is vital to optimizing antimalarial treatment. Clear guidelines in the language understood by the local users, posters, wall charts, educational videos and other teaching materials, public awareness campaigns, education of and provision of information materials to shopkeepers and other dispensers can all improve the understanding of malaria and the likelihood of improved prescribing and adherence, appropriate referral, and minimizing the unnecessary use of antimalarials.

There is also a need for prescribers, shopkeepers and vendors to give a clear and comprehensive explanation to the patient or carer on how to use the medicine.

Concepts such as the community management of malaria should be explained to patients and caregivers during follow-up visits.

3.1.3   Management of treatment failures[4]

Treatment failure is defined as failure to clear the malaria parasitaemia +/- resolve clinical symptoms following full regimen of antimalarial treatment. Antimalarial drug resistance can cause treatment failure but not all treatment failure is due to parasite resistance to medicines.

Antimalarial drug resistance refers to the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a medicine given in doses equal to or higher than those usually recommended but within tolerance of the subject, provided that the medicine gains access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action[5,6]. There are several factors contributing to treatment failure and these include antimalarial drug resistance, poor adherence or inadequate drug exposure (under dosing, vomiting, poor or erratic absorption) and substandard medicines.

Treatment failure within first 14 days

With the advent of ACTs the approach to treatment failure in clinical settings has been slightly modified. Owing to the potency of the ACTs, treatment failure within 14 days of receiving an ACT is very unusual. The majority of treatment failures occur after 2 weeks of initial treatment. Recurrence of falciparum malaria may be the result of a reinfection, or a recrudescence (i.e. treatment failure). In an individual patient it may not be possible to distinguish between recrudescence and reinfection, although if fever and parasitaemia fail to resolve, or recur within 2 weeks of treatment, then treatment is considered to have failed.

Wherever possible, treatment failure should be confirmed parasitologically, preferably by blood slide examination. HRP-2-based tests may remain positive for weeks after the initial infection even without recrudescence. This may require referring the patient to a facility where microscopy is available; referral may also be necessary to obtain second-line treatment. It is important to determine from the patient's history whether the antimalarial medicine was vomited or whether the full course was not completed. Treatment failures should be treated with a second-line antimalarial.

Treatment failure after 14 days

Recurrence of fever and parasitaemia more than two weeks after treatment could result either from recrudescence or new infection. This distinction can only be made through parasite genotyping by PCR which is not routinely used in patient management. Thus to simplify operational management and medicine deployment, all presumed treatment failures after two weeks of initial treatment should be considered as new infections, especially in areas of high transmission, and be treated with the first-line ACT. However, reuse of mefloquine within 60 days of first treatment is associated with an increased risk of neuropsychiatric reactions and in this particular situation, second-line treatment not containing mefloquine should be given.

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[4] Adapted from *Guidelines for the treatment of malaria. Second edition. 2010.*World Health Organization, Geneva. http://whqlibdoc. who.int/publications/2010/9789241547925_eng.pdf

[5] WHO (1973). Chemotherapy of malaria and resistance to antimalarials: report of a WHO Scientific Group. *WHO Technical Report Series,* No 529, 1973.

[6] Bruce-Chwatt LJ et al. *Chemotherapy of malaria, revised 2nd ed.* Geneva, World Health Organization, 1986.

Recommended second-line antimalarial treatments

On the basis of the evidence from current practice and the consensus opinion of the Guidelines Development Group, the following second-line treatments are recommended, in order of preference:

- ▸ alternative ACT known to be effective in the region;

- ▸ artesunate plus tetracycline or doxycycline or clindamycin;

- ▸ quinine plus tetracycline or doxycycline or clindamycin.

The alternative ACT has the advantages of simplicity, and where available, co-formulation to improve adherence. The 7-day quinine regimens are not well tolerated and adherence is likely to be poor if treatment is not observed.

3.2   Management of non-falciparum malaria

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

3.2.1   Diagnosis of non-falciparum malaria

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

3.2.2   Treatment of uncomplicated non-falciparum malaria

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

- ▸ For chloroquine-sensitive vivax malaria (as in most places where *P. vivax* is prevalent), oral chloroquine at a dose of 25mg/kg is well tolerated and effective. It is given at an initial dose of 10mg/kg followed by either 5mg/kg at 6h, 24h and 48h or, more commonly 10mg/kg

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on the second day and 5mg/kg on the third day. This should be combined with primaquine, anti-relapse medicine, at a dose of 0.25mg base/kg bw, taken with food once daily for 14 days in patients without G6PD deficiency. In Oceania and South-East Asia however, the dose of primaquine should be 0.5mg/kg bw.

▶ There is evidence that amodiaquine, mefloquine and quinine are effective in the treatment of chloroquine-resistant vivax malaria. An ACT based on amodiaquine or mefloquine or piperaquine, rather than monotherapy, is the recommended treatment of choice. Such ACTs should be administered with primaquine as is for chloroquine sensitive vivax malaria.

▶ patients with moderate G6PD deficiency, primaquine 0.75mg base/kg bw should be given once a week for 8 weeks. Primaquine should not be used in patients with severe G6PD deficiency.

▶ Where ACT has been adopted as the first-line treatment for falciparum malaria, it may also be used for vivax malaria in combination with primaquine for radical cure. Artesunate plus sulfadoxine-pyrimethamine is the exception because this treatment is not effective against *P. vivax* in many places.

P. ovale and *P. malariae* infections are considered to be generally sensitive to chloroquine. Treatment for *P. ovale*, relapsing malaria, is the same as for *P. vivax*, i.e. with chloroquine and primaquine. *P. malariae* forms no hypnozoites and, therefore, treatment with only chloroquine is sufficient.

ACT is recommended for mixed infections of *P. falciparum* and other species. A 14-day course of primaquine should be given for mixed infections including *P. vivax* and/or *P. ovale*.

3.3   Exercises

3.3.1   Clinical exercises

Exercice 3.1

    a. *What is the main symptom of malaria?*

....

....

    b. *List some of the clinical features of uncomplicated malaria.*

....

....

    c. *What are the criteria for clinical diagnosis of malaria?*

....

....

Exercice 3.2

a. *What are the advantages of parasitological diagnosis of malaria?*

b. *What laboratory tests should be done?*

Exercice 3.3

List at least three causes of fever other than malaria that you would consider in a child.

Exercice 3.4

a. *Who should receive antimalarial treatment?*

b. *Which antimalarial medicine would you give to a patient with a confirmed diagnosis of malaria?*

c. *What antimalarial medicine would you give a pregnant woman with uncomplicated malaria in the first trimester?*

Exercice 3.5

a. *Write four key messages you would give a patient about taking antimalarial medicines at home.*

b. *What would you do for a 2-year old child who returns with persistent symptoms three or more days after initial malaria treatment?*

3.3.2   **Case studies**

PATIENT A

The place: Rural district in a falciparum malaria endemic region.

The patient: A boy aged 5 years is brought to your hospital's outpatient department. The mother says he was well until this morning when he woke up and said he was feeling tired and refused his breakfast. When the mother touched him he felt hot and she gave him a half tablet of paracetamol. When you examine, you find a well-nourished 20kg child, alert, not pale, and with axillary temperature of 38.5°C. The rest of the physical examination is normal.

● **Question 1**

What action would you take?

....

....

● **Question 2**

Examination of thick blood smear revealed asexual *P. falciparum* parasites.
a. *What treatment would you give the child?*

....

b. *At what dose?*

....

c. *By which route?*

....

....

● **Question 3**

What will you tell the mother?

....

....

PATIENT B

The place: Rural district in malaria endemic setting.

The patient: A girl aged 36 months is brought to you with a history of fever for two days and ear pain for one day. On examination you find that she is in fair general condition, weighs 20kg, with temperature 39.2°C and discharge of pus from the left ear. Other systems are normal. RDT reveals positive test result.

Question 1

What diagnosis would you make?

Question 2

What treatment would you prescribe?

Question 3

What have you learnt from this patient concerning malaria?

Question 4

If the malaria slide was negative, would you give antimalarial medicines?

PATIENT C

The place: Rural community of falciparum malaria endemic country.

The patient: A boy aged 4½ years wakes up in the morning and takes only tea without milk. He is rather quiet with hot body. The mother gives him a half tablet of chloroquine. That day when he returned from school he was apparently well. The chloroquine was stopped. Two days later in the evening he develops a fever and vomits. The mother then gives another half tablet of chloroquine. The following morning he again refuses food, and he has a low-grade fever to touch. The mother decides to come to the clinic.

Question 1

Was the mother right to give the chloroquine?

Question 2

Why or why not?

Question 3

Why did the child get better after the first dose of chloroquine?

Question 4

What actions would the health worker at the clinic take?

Question 5

Diagnostic test with an HRP2-detecting RDT revealed positive test result.
How would you treat this patient?

PATIENT D

The place: Urban district in a country highly endemic for malaria.

The patient: A boy aged 6 years wakes up in the morning and refuses to eat. He is rather quiet but does not have fever. The mother gives two tablets of artemether-lumefantrine (AL). That day when he returned from school he was apparently well. The AL was stopped. Two days later in the evening he develops a fever and vomits. The mother then gives another 2 tablets of AL. The following morning he again refused food, and he had a low-grade fever to touch. The mother decides to take the child to the clinic.

Question 1

a. Was the mother right to give the AL?

b. Why or why not?

Question 2

a. Should the mother have stopped the treatment after the initial first dose of AL?

b. Why or why not?

Question 3

How should the health worker manage this patient?

LEARNING UNIT **4**

Management of severe malaria

Learning Objectives:
by the end, participants should be able to...

● **Define severe malaria**
● **Discuss the host-parasite interaction that contributes to the pathogenesis of severe malaria**
● **List the determinants of severe malaria and identify groups at high risk**
● **Make a diagnosis of severe falciparum malaria**
● **Specify the emergency and supportive measures and follow-up guidance for malaria patients with different types of complications**
● **Describe the recommended antimalarial chemotherapeutic regimen for severe malaria**

4.1   Diagnosis of severe malaria

4.1.1   Characteristics of severe falciparum malaria

Severe falciparum malaria is characterized by evidence of vital organ dysfunction. Severe falciparum malaria should be diagnosed if there are asexual forms of *P. falciparum* in a blood film from a patient showing any of the following clinical features or laboratory findings.

Clinical features:

- impaired consciousness or unrouseable coma (Glasgow coma scale < 11 for adults or Blantyre coma scale < 3 for children – see Annex 1). Retinal haemorrhages are common in falciparum malaria comatose patients;

- prostration, i.e. generalized weakness so that the patient is unable walk or sit up without assistance (affected children are unable to feed);

- multiple convulsions – more than two in 24 hours;

- deep breathing, respiratory distress (acidotic breathing);

- circulatory collapse or shock, systolic blood pressure < 70mmHg in adults and < 50mmHg in children;

- jaundice with evidence of other vital organ dysfunction;

- abnormal spontaneous bleeding;

- pulmonary oedema (presence of rapid breathing with bilateral basal crackles in the lungs).

Laboratory findings:

- hypoglycaemia (blood glucose < 2.2mmol/litre or < 40mg/dl);

- metabolic acidosis (plasma bicarbonate < 15mmol/litre);

- severe normocytic anaemia (Hb < 5g/dl, packed cell volume < 15%);

- haemoglobinuria;

- hyperparasitaemia ;

- hyperlactataemia (lactate > 5mmol/litre);

- acute kidney injury (serum creatinine 265mmol/litre or greater).

Note that:

a) Each of the individual clinical features is important for the diagnosis of severe falciparum malaria;

b) An individual patient may have any single complication or any combination of the complications listed above;

c) A patient with one or more of the complications may go on to develop others;

d) Other possible diagnoses in such a patient must be carefully considered.

4.1.2 Risk groups for severe falciparum malaria

Any infection with *P. falciparum* can become severe if treatment is delayed or inadequate. However, people who have been repeatedly exposed to falciparum malaria develop partial immunity and are less likely to experience severe falciparum malaria.

Those most at risk are:

▶ children in areas of high endemicity – especially those aged from 6 months to 5 years;

▶ people of all ages in areas of low endemicity;

▶ residents of areas where there is little or no falciparum malaria who travel to a high transmission area: this may involve travel within a single country or between countries;

▶ people returning to highly endemic areas after a few years' residence in area with little or no falciparum malaria;

▶ non-immune pregnant women (at risk of some specific complications);

▶ internally-displaced persons moving from an area of low transmission to an area of high transmission;

▶ patients who have had a splenectomy.

4.1.3 Diagnosis of severe falciparum malaria

A correct diagnosis should be based upon a complete case history, a physical examination, and laboratory investigations.

Both thick and thin blood films should be examined, or malaria antigen detection by RDT should be done, to demonstrate the presence of *P. falciparum* asexual parasites.

However, it is important to note that:

▶ Waiting for a blood smear result must not be allowed to delay the start of treatment unduly: if clinical features strongly suggest severe falciparum malaria, treatment may be started before the results are available.

▶ Occasionally blood films may be negative even though the patient is suffering from severe falciparum malaria. Following a negative result, blood films should be repeated, e.g. every 6 hours.

▶ Some types of RDTs (HRP-2 tests) may remain positive for about a month after an acute infection has been successfully treated.

▶ A positive blood film does not prove that severe falciparum malaria is the only cause of the severe illness. Other possible causes should also be considered.

4.2 Pathophysiology of severe falciparum malaria

In studying this section it should be remembered that some of the factors and theories outlined are well established, while others remain speculative.

After reading, the content of this section should be discussed with colleagues in the group and then in plenary session. List the ways in which understanding the pathophysiology helps in determining the correct treatment.

4.2.1 Mechanism of malarial disease

The possible effects of malarial infection cover an enormous range, from completely asymptomatic infection to severe fatal disease. Many factors are believed to influence the clinical manifestations of infection: some of these factors are known beyond doubt, while others remain speculative.

Factors known to influence the severity of disease in a malaria infection

► The species of parasite. *P. falciparum* causes almost all cases of severe malaria, but it also, more commonly, causes mild disease or asymptomatic infection. However, *P. vivax* is being increasingly recognized as a cause of severe malaria;

► The immunity of the individual. Adults who have lived all their life in an endemic area are less susceptible to severe disease than:
  – adults who visit an endemic area for the first time
  – young children living in the same endemic area

► Pregnancy, especially first and second pregnancies;

► The availability and efficacy of antimalarial medicines;

► The degree of parasite drug-resistance that prevails locally;

► HIV/AIDS, especially in pregnant women;

► Some genetically inherited conditions in the human host, e.g. sickle-cell trait, ß-thalassemia, and probably G6PD deficiency have a protective effect;

► Other factors that may affect the severity of illness, although not yet proven:
  – *the particular strain of* **P. falciparum.** Are some strains more virulent than others? There is evidence to suggest that this is so, but no real proof;
  – *the age at which first infection takes place.* Perhaps very early infections – in the first three months of life when maternal antibodies still convey some protection against parasite multiplication or disease – cause partial protection with less risk of severe disease;
  – *the intensity of transmission.* If transmission is very intense, first infections in infants will tend to occur very early in life. There is evidence that the pattern and severity of disease in children differs according to the local transmission pattern;
  – *other differences between people.* Specific histocompatibility antigens, human leucocyte antigens (HLA) class I and class II molecules are probably associated with protection against severe malaria;
  – *the extent of the individual response to an infection,* e.g. the rate and degree of production of cytokines such as tumour necrosis factor (TNF);
  – *the number of sporozoites* injected by the mosquito, or by several mosquitoes.

4.2.2   How parasites cause severe disease

Microvascular obstruction of vital organs

In falciparum malaria, a consistent pathological feature is the sequestration of red blood cells containing maturing parasites (schizonts, large trophozoites) in deep capillaries and venules. This phenomenon is observed in many different organs and tissues, including the brain, lungs, heart, bone marrow and gut. It seems likely that sequestration is involved in complications such as altered consciousness and acidosis, through pathophysiological mechanisms that are not fully understood.

Some survivors of cerebral malaria have neurological sequelae, some of which correspond to abnormalities that have been shown on computed tomography (CT) scans, but most of which are manifested as neurological deficits, epilepsy, or subtle long-term defects of learning and behaviour. Sequestration contributes to microvascular obstruction and mechanical obstruction causes hypoxia. In addition, sequestered parasites, which are known to be highly active metabolically, may use up vital substances such as glucose, so that these are not available to host cells, such as brain cells. The parasites may also release substances, e.g. lactate or toxins, free iron, and toxic oxygen radicals that are directly injurious to local host tissues.

It is thought that sequestration may also serve to concentrate schizonts in vital tissues. Rupture of schizonts may then stimulate the release of large quantities of cytokines locally with a powerful local effect even if cytokine levels in the general circulation are not particularly high.

Sequestration appears to be confined to *P. falciparum* and does not occur in *P. vivax* infection. At approximately 12–14 hours of development, *P. falciparum* parasites begin to exhibit a high molecular weight protein strain-specific to this variant – *Plasmodium falciparum* Erythrocytic Membrane Protein1 (*pf*EMP1) – on the surface of infected red blood cells which mediate attachment to vascular endothelium. This is associated with knob-like projections from the erythrocyte membrane. The red cells progressively adhere to the walls of venules and capillaries (cytoadherence) in vital organs, producing sequestration. There is also formation of 'rosettes' by unparasitized red blood cells within microvasculature.

In vitro, a parasitized cell may attract unparasitized red cells which adhere to its surface to form a rosette.

Cytokines

It is possible, but still not proven, that excessive production of pro-inflammatory cytokines may cause severe disease in addition to fever. The cytokine TNF is known to be secreted by the individual in response to malaria. Large quantities of TNF circulate in severe falciparum malaria, especially in fatal cases, and TNF is known to be capable of causing many of the symptoms, signs and complications that are typical of severe malaria, e.g. coma, hypoglycaemia, acidosis, anaemia and respiratory distress syndrome. The ratio of pro-inflammatory to anti-inflammatory cytokines has been observed to be high in fatal cases of malaria.
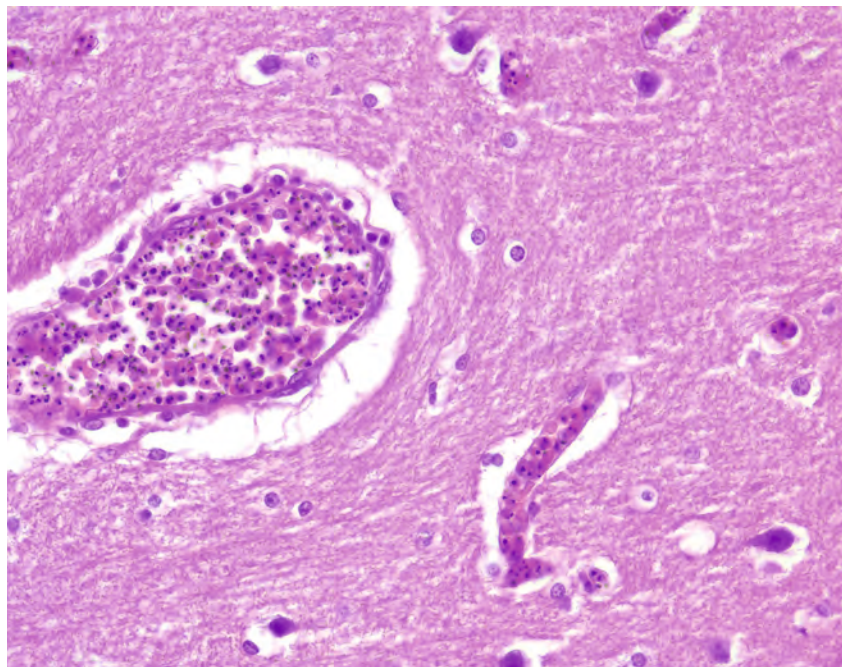
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Figure 4.1: Brain tissue from a patient who died of cerebral malaria, showing microvascular sequestration of parasitised red blood cells in both capillaries and small venules, with mild perivascular oedema aroud the larger vessels.

4.2.3   Processes contributing to specific complications

Altered consciousness or coma

It is believed that altered consciousness or coma (cerebral malaria) is caused by sequestration of parasites in the brain. However, complete obstruction to blood flow is unlikely, since the survivors rarely have any permanent neurological deficit. Other processes may cause or contribute to altered consciousness or coma.

Hypoglycaemia

Hypoglycaemia may be due to impaired production or release of glucose in the liver, and to increased intake in the tissues. In children, hypoglycaemia complicates other childhood infections in addition to malaria. Though hypoglycaemia may develop during any period of prolonged fasting, the mechanisms involved remain unclear.

Another mechanism leading to hypoglycaemia, most commonly but not exclusively seen in pregnant women, may develop during the course of treatment with quinine, or quinidine where it is still used. These medicines stimulate the production of insulin which contributes to hypoglycaemia.

Convulsions

In relation to a convulsion, unconsciousness occurs both during the convulsion (ictal) and for a period of up to several hours after the convulsion (post-ictal). Convulsions may be due to the direct effect of parasites in the brain, or may result from accompanying metabolic disorders,

e.g. hypoglycaemia, severe acidosis, hyponatraemia or hypoxia. A very high temperature may exacerbate any of these causes of convulsion, or may itself trigger a convulsion.

Raised intracranial pressure

The majority of children with cerebral malaria have a high opening pressure of the cerebrospinal fluid, indicating raised pressure in the brain and spinal column. The presence of high pressure may vary over time. It has also been observed in some adults. The cause of raised intracranial pressure is not clear, but it is probably largely due to cerebral oedema. Additional contributing factors may include the increased mass of red blood cells sequestered in the brain, and the dilatation of vessels in the brain in response to mechanisms triggered by parasite sequestration and schizont rupture. Raised intracranial pressure is not the cause of coma or of death in the majority of cases. It may, however, play a part in pathogenesis or affect the course of the disease in ways that are not yet understood.

Anaemia

Anaemia is partly due to the destruction of red blood cells that contain parasites. Several other mechanisms may accelerate the development of anaemia: non-parasitised red cells are destroyed more quickly than normal during malarial illness and the bone marrow does not function adequately to replace them. Anaemia is exacerbated if there is abnormal bleeding, intravascular haemolysis or renal failure.

Acidosis

Acidosis is probably due to a relative shortage of oxygen in tissues occupied by sequestered parasites. This shortage of oxygen is made worse when there is hypovolaemia and/or severe anaemia, as both of these conditions may impair the supply of oxygen to tissues. Lack of oxygen forces tissues to obtain energy by other biochemical pathways not dependent on oxygen; one result is the release of lactic acid, leading to metabolic acidosis. There is evidence that medicines containing salicylates, which are often given to lower the fever, may exacerbate the metabolic acidosis. Concomitant gram-negative septicaemia aggravates the acidosis.

Acute renal failure

Acute renal failure – acute tubular necrosis – is a common complication in adults, but is rarely seen in children. It is fully reversible if the patient is kept alive for long enough, usually between a few days to three weeks, e.g. by peritoneal dialysis. Renal failure is most likely to develop if there has been a period of low blood pressure or shock. Sequestration is also observed in the kidneys.

Pulmonary oedema and acute respiratory distress syndrome

Pulmonary oedema (non cardiogenic) may result from excessive fluid replacement by intravenous infusion, especially if there is renal failure. Acute respiratory distress syndrome (ARDS) appears to be due to a direct effect of parasites sequestered in the lungs, possibly through release of cytokines. Both of these complications are unusual in children in endemic areas.

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Haemoglobinuria

Haemoglobinuria results from the rapid breakdown of red blood cells in the circulation (massive intravascular haemolysis).

Jaundice

Jaundice is more common in adults than in children and is due partly to haemolysis and partly to liver dysfunction.

Shock

Shock is due to inadequate cardiac output and poor tissue perfusion. In some patients it may occur concurrently with bacteraemia.

Bleeding disorders

In falciparum malaria, the platelet count is typically low. Nevertheless, spontaneous bleeding is rare in both children and adults. When it develops it results from disseminated intravascular coagulation (DIC).

4.2.4   Severe non-falciparum malaria

P. vivax and more recently *P. knowlesi* have been recognized as causes of severe malaria particularly in Asia and in certain forested areas of South-East Asia respectively. Severe vivax malaria may present with pathologies similar to severe *P. falciparum* malaria and can be fatal. Severe anaemia, respiratory distress, multiple organ failure and impaired consciousness (cerebral malaria) occur in all age groups but the risk is greatest among young children and pregnant women.

4.3 Treatment of severe malaria

The main objective of treatment is to prevent the patient from dying; secondary objectives are prevention of recrudescence, transmission or emergence of resistance and prevention of disabilities.

Special attention is required because severe falciparum malaria is a common cause of avoidable death and because correct early treatment and careful nursing can greatly improve the outcome. The following special measures are indicated:

▶ antimalarial medicines should be given parenterally if possible, under close supervision;

▶ treatment should be undertaken in hospital if possible;

▶ medicines that are ineffective and potentially dangerous should not be used.

Under ideal conditions the severely ill patient, especially one who is comatose, should be managed in an intensive care unit. Where this is not possible, as in most endemic areas, the

health worker has to provide emergency care. Frontline health workers must be appropriately trained to a very high level to fulfill their essential role in patient management. Meticulous nursing care can be life-saving, especially for the unconscious patient.

4.3.1   Immediate supportive treatment

In severe malaria, the patient has a number of life-threatening complication(s) which can be fatal if not urgently treated. Some of the most urgent measures that will be required are to:

▸ **Start immediate resuscitation measures,** paying particular attention to the airways;

▸ **Establish an intravenous infusion,** which is necessary to administer medicines and fluids;

▸ **Correct hypoglycaemia** if present by infusing dextrose over a period of 3–5 minutes. This can be done by any one of the following procedures:

  i)   0.5–1ml/kg of 50% dextrose diluted with an equal volume of normal saline given by slow intravenous infusion over several minutes in children;

  ii) 20–50ml of 50% dextrose given as intravenous bolus in adults;

  iii) for other strengths of dextrose, calculate the volume accordingly;

  iv) where intravenous access is impossible, give sugar solution by nasogastric tube (NGT);

  v)   re-check blood glucose 2–4 hourly during the course of treatment, particularly in comatose patients.

▸ **Control convulsions:** correct hypoglycaemia if it is present and and give rectal paracetamol if the temperature is above 39°C. If the convulsions continue for more than 5 minutes give diazepam by slow intravenous injection (0.15ml/kg bw, maximum 10mg for adults). In children always calculate according to weight in order to avoid dangerous respiratory depression. Diazepam can be given intra-rectally (0.5–1.0mg/kg bw) only if injection is not possible. Monitor the breathing carefully. If the first dose of diazepam fails to control convulsions, a second dose may be given after 10 minutes. If seizures continue, give paraldehyde (0.1ml/kg IM - repeat after 30 minutes if necessary); or phenytoin (18mg/kg infused over 20 minutes as a loading dose, followed by 2.5mg/kg twice daily for 48 hours). If you have given two doses of diazepam and seizures continue, and if phenobarbitone is the only additional anticonvulsant drug available, you may give phenobarbitone (15mg/kg IM or IV loading dose, then 5mg/kg daily for 48 hours), but extreme vigilance is necessary because these two drugs (phenobarbitone and diazepam) in combination may cause respiratory arrest - monitor breathing continuously and be ready to give assisted ventilation, by bag-and-mask if a manual ventilator is not available.

4.3.2   Continued supportive treatment

▸ **Assess the patient's fluid requirements.** Look for evidence of fluid depletion or overload in order to determine the appropriate rate of infusion. Children with severe metabolic acidosis may benefit from a resuscitation bolus of fluid, preferably a plasma expander, e.g. normal saline. The usual route for fluid infusion is intravenous; if this cannot be achieved alternatives are intra-osseous or nasogastric infusions. Intra-osseous infusion may be performed when there is life threatening hypovolaemia, under strict sterile procedure.

▸ **Reduce body temperature if greater than 39.5ºC.** This is best done by giving paracetamol, by mouth if possible, alternatively by suppository. In addition, remove the patient's clothes and start tepid sponging and fanning from the sides or back of the patient. Relatives can help with this task.

▸ **Consider the need for blood transfusion.** The most common indication for blood transfusion is severe anaemia (Hb < 5g/dl). Assess the patient's clinical condition rather than relying on the haemotocrit and/or Hb level. *"Does the patient need blood?"* is a more important question than *"What is the PCV/Hb?"*

If the patient's life is threatened by anaemia-associated acidosis, or by shock, or the parasitaemia is so high that a critical drop is predictable, packed cells (10ml/kg in children) or whole blood transfusion should be given urgently with frusemide as follows:

▹ if the patient has spontaneous bleeding give whole fresh blood if available or a platelet transfusion if possible;

▹ where blood is unavailable, give pre-referral treatment and refer the patient;

▹ if the patient is unconscious, insert a nasogastric tube and start the procedures for management of the comatose patient.

▸ **Decide whether to insert a urinary catheter.** This is necessary if either acute renal failure or pulmonary oedema is suspected, in order to guide fluid balance.

▸ **Decide whether a central venous pressure line is to be set up.** This is of most value where pulmonary oedema is suspected, and may be useful in the patient with shock or impending renal failure. It requires the necessary facilities, sterile procedures, expertise and a sufficient number of trained staff to use it properly.

▸ **Consider the need for intubation and mechanical ventilation if the necessary facilities are available.**

4.3.3   Specific antimalarial treatment

After rapid clinical assessment and confirmation of the diagnosis, appropriate and correct regimen of parenteral antimalarial medicines should be administered to patients with severe malaria without delay.

> *WHO recommended antimalarials for the treatment of severe malaria*
>
> Following are the recommendations on the treatment of severe malaria
>
> ▸ Artesunate 2.4mg/kg bw IV or IM given on admission (time = 0), then at 12h and 24h, then once a day is the recommended treatment.
>
> ▸ Artemether, or quinine, is an acceptable alternative if parenteral artesunate is not available: artemether 3.2mg/kg bw IM given on admission then 1.6mg/kg bw per day; or quinine 20mg salt/kg bw on admission (IV infusion or divided IM injection), then 10mg/kg bw every 8 hours; infusion rate should not exceed 5mg salt/kg bw per h.

Artesunate IV or IM should be used in preference to parenteral quinine for the treatment of severe malaria.

Artesunate: 2.4mg/kg IV or IM given on admission (time = 0) then at 12 and 24 hours, then once a day until the patient can swallow. It is available in ampoules, containing 60mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution.

Reconstitution: the vial of artesunate powder should be mixed with 1ml of 5% sodium bicarbonate solution (provided) and shaken 2–3 minutes for better dissolution. The solution should be prepared freshly for each administration and should not be stored. Then:

IV administration: add 5ml of 5% glucose or normal saline to make the concentration of artesunate as 10mg/ml and administer by slow infusion;

IM administration: add 2ml of 5% glucose or normal saline to make the concentration of artesunate as 20mg/ml.

If artesunate is not available, then give artemether as follows:

Artemether: 3.2mg/kg bw IM (loading dose) followed by 1.6mg/kg daily until the patient can swallow.

If both artesunate and artemether cannot be administered, give quinine as follows:

Quinine: 20mg dihydrochloride salt/kg bw (loading dose) diluted in 10ml isotonic fluid/kg by IV infusion over 4 hours; followed by 8 hourly maintenance dose of quinine 10mg salt/kg bw over 4 hours, calculated from the beginning of the previous infusion, until the patient can swallow.

If for any reason quinine cannot be administered by IV infusion, quinine dihydrochloride can be given in the same dosages by IM injection in the anterior thigh (not in the buttock). The dose of quinine should be divided between two sites – half the dose in each anterior thigh. If possible, for IM use, quinine should be diluted in normal saline to a concentration of 60–100mg salt/ml.

Doxycycline and tetracycline should not be used in children under 8 years of age and pregnant women.

Parenteral antimalarials in the treatment of severe malaria should be given for a minimum of 24 hours, once started (irrespective of the patient's ability to tolerate oral medication earlier). If the patient can swallow, thereafter, the treatment should be completed by giving a complete course of one of the following:

► full course of the recommended first-line ACT;

► artesunate (2mg/kg once daily) plus either clindamycin (10mg/kg twice a day) or doxycycline (3.5mg/kg once a day) or tetracycline (4mg/kg four times daily) to complete a 7-day course of treatment;

► quinine (10mg salt/kg, 8-hourly) plus either clindamycin (10mg/kg twice a day), or doxycycline (3.5mg/kg once a day) or tetracycline (4mg/kg four times daily) to complete a 7-day course of treatment.

In patients requiring more than 48 hours of quinine parenteral therapy, the maintenance dose should be reduced by one-third to one-half (i.e. 5–7mg salt/kg bw every 8 hours).

Total daily doses of intravenous quinine are as follows:

Adults:

- first day of treatment: 30–40mg salt/kg bw;
- second day of treatment: 30mg salt/kg bw;
- third day of treatment and subsequent days: 15mg salt/kg bw.

Children:

- first day of treatment: (first day of treatment): 20–25mg salt/kg bw;
- second day of treatment: 20mg salt/kg bw;
- third day of treatment and subsequent days: 10mg salt/kg bw.

Treatments that are contraindicated:

- corticosteroids
- other anti-inflammatory agents
- other agents given for cerebral oedema (urea, invert sugar)
- low molecular weight dextran
- epinephrine (adrenaline)
- heparin
- pentoxifylline (oxpentifylline)
- hyperbaric oxygen
- cyclosporin (cyclosporin A)

4.3.4   Pre-referral treatment

At peripheral health facilities where complete parenteral treatment with artesunate, quinine or artemether cannot be instituted, patients with severe malaria should be given pre-referral treatment and referred immediately to an appropriate facility for definitive treatment.

The following are options for pre-referral treatment:

- artesunate suppositories: 10mg/kg bw single dose. Artesunate suppositories are currently available in 50mg and 200mg formulations. If the suppository is expelled from the rectum within 30 minutes of insertion, re-insert another dose and, especially in young children, the buttocks should be held together for 10 minutes to ensure retention of the suppository;
- quinine IM: 10mg salt/kg bw initial dose given through the anterior thigh;
- artesunate IM: 2.4mg/kg bw initial dose given through the anterior thigh;
- artemether IM: 3.2mg/kg bw initial dose given through the anterior thigh.

If referral is impossible, rectal treatment should be continued until the patient can tolerate oral medication; at this point, a full course of the recommended ACT for uncomplicated malaria in

the locality can be administered. However, referral is essential for patients with severe anaemia requiring blood transfusion, and those with multiple convulsions, renal failure and bleeding.

4.3.5   Continuing treatment and nursing care

Continuing care calls for close cooperation between medical and nursing staff. Responsibility for various observations must be allocated according to the availability and expertise of personnel. Proper nursing care of the unconscious patient, in an intensive care unit if available, is of utmost importance in patients with cerebral malaria. The patient must be turned every two hours and not allowed to lie in a wet bed. Particular attention must be paid to pressure points and the patient should be nursed on his/her side to avoid aspiration of fluids. Sufficient nutritional support is necessary for patients who have a prolonged illness.

Following are the parameters to be monitored on a routine basis:

▸ level of consciousness (see Blantyre and Glasgow coma scales in Annex 1);

▸ vital signs: blood pressure, temperature, pulse rate and respiratory rate;

▸ fluid input and output. Examine regularly for signs of dehydration or fluid over load;

▸ urine volume, colour and specific gravity;

▸ blood glucose;

▸ parasitaemia;

▸ haemoglobin (Hb/Ht) if anaemia is suspected to be worsening;

▸ occurrence of convulsions;

▸ uterine contractions and fetal heart rate in pregnant women.

A record chart should be kept on which the important complications of the patient's illness are summarized; the treatment prescribed, and all important observations are recorded at suitable intervals. Special attention should be given to pregnant women with severe malaria as they are prone to developing severe anaemia, hypoglycaemia and pulmonary oedema; they should be monitored very closely.

A sample chart is provided (Table 4.1). This chart should be modified according to local facilities and experience. Table 4.2 indicates some of the important observations during treatment and their implications. A decision is taken on how frequently observations should be made; this should be as often as possible with the avail-able staff (e.g. every four hours), but will also depend on the particular circumstances of each patient and the severity, stage and complications of the illness. For example, blood glucose should be checked hourly in a co-matose pregnant woman receiving intravenous quinine, but less frequently in a man whose condition is steadily improving. Observations (see Table 4.3) should be aimed at:

▸ controlling the delivery of medicines and infusion fluids;

▸ detecting the development of complications of malaria;

▸ detecting toxic effects and side-effects of medicines being administered;

▸ documenting the patient's recovery.

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Table 4.1   **Management of severe malaria: daily observation sheet (acute phase)**

Date of admission: ..../............./............   **Time (h/min):** ..../............

Name of patient: ....

Record No.		Hours										
Age:												
Sex: .... M ☐ F ☐												
Weight		1			4			8				
Medicines given before admission (including OPD)	Real time (h) minutes											
Investigations done on admission	Temperature (2x/day) Pulse (2x/day)											
Parasite count	Respiratory rate (2x/day)											
Haemotocrit/Hb	Blood pressure (2x/day)											
Blood sugar	Glasgow/Blantyre coma scale (3x/day)											
Urine analysis												
Cerebral spinal fluid (CSF)	Convulsions (Y N)											
Blood group	Able to drink (Y N)											
	Able to sit (Y N)											
	Parasite count											
	Haemotocrit/Hb											
	Blood sugar											
	iv artesunate or quinine in mg											
	iv fluids – dextrose saline											
	Other medicines, e.g. iv diazepam/antibiotics											
	Urine volume											
	Blood transfusion											

Hours

12				16				20				24			

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Table 4.2   Management of severe malaria: observation sheet (convalescence phase – discharge)

Name of patient: ....

Date of admission: ..../........./...........   **Time (h/min):** ..../........./...........

	Frequence of observations	DAY		DAY		DAY		DAY		DAY		DAY ...	
Record No.	**Hours**	**0**	**12**	**0**	**12**	**0**	**12**	**0**	**12**	**0**	**12**	**0**	**12**
	Real time(hour/min)												
Rectal/axillary temperature (°C)	12 hourly												
Level of consciousness (Glasgow/Blantyre coma scale)	12 hourly												
Pulse per minute	12 hourly												
Respiratory rate (per minute)	12 hourly												
Blood pressure (mmHg)	once in 24 hours												
Haematocrit (%) or Hb (g/dl)	on day 3 and day 7												
Parasite count per mm³	On day 3 & day 7												
Oral quinine (mg)	3 times daily												
First-line antimalarial (ACT)	When patient can take oral treatment*												
Other medication (specify)													
Brief comments													

* At least after 24 hours of parenteral treatment

Outcome and follow up visits

100% recovery / with sequelae (specify) / death /unknown (absconded)
Fever clearance time (day/h) ....   Coma recovery time (day/h) ....
Parasitaemia clearance time (day / h) ....

Table 4.3   Observations during treatment

Regular observations	Possible abnormality	Appropriate actions
A. CLINICAL		
Breathing	Increased rate or difficulty Deep breathing in children	Review urine output and fluid balance. Assess lung, heart and liver size. Chest X-ray if available. If pulmonary oedema is demonstrated, or seems likely, prop the patient up, give oxygen, IV frusemide 2–4mg/kg. Treat acidosis with normal saline and bicarbonate.
Body temperature	rectal temperature: > 40°C OR axillary temperature: > 39.5°C	Give paracetamol (rectal or oral) if not already given within past 4 hours. Tepid sponging and fanning. Aspirin can be given to adults (instead of paracetamol) but not to children.
	If temperature remains high or rises despite 24 hours of antimalarial therapy	Reconsider your diagnosis, while continuing treatment.
Blood pressure (BP)	Falls: < 80mmHg systolic in an adult, and < 50mmHg in infants and children. In children, BP is not always reliable: check for peripheral perfusion, looking at nailbed refill.	Review fluid balance, urine output, quinine infusion rate and haematocrit. Give plasma or saline infusion if hypovolaemia is present. Look for haemorrhage. Take blood for bacteriological culture if facilities are available. Give broad spectrum antibiotic for possible sepsis.
Fluid balance (use input and output chart); weigh patients as accurately as possible. Catheterize if acute renal failure or pulmonary oedema is suspected.	Oliguria: < 17ml/hour in an adult or < 0.3ml/kg/hour in infants and children	Review adequacy of hydration and infusion. Correct deficit if necessary. Prevent or manage acute renal failure if suspected. Give fluid challenge 20ml/kg of normal saline with frusemide 2–3mg/kg. Dialysis if this fails.
Coma score	Deterioration	Immediately check blood glucose. Reconsider other diagnoses. Provide appropriate nursing care for the unconscious patient.
Convulsions (subtle convulsions can be easily missed)	These can recur, or develop for the first time during treatment. They may be due to malaria, to high fever, abnormal blood glucose levels, or electrolyte imbalance. **Convulsions often precede coma.**	Check rectal temperature; if > 39°C, manage as above. Check blood glucose and fluid balance; check electrolytes if possible as there is risk of hyponatraemia. Correct any imbalance; give anticonvulsant medicine. Maintain the airway. Treat promptly with IV or rectal diazepam or IM paraldehyde.
Prolonged bleeding from vein puncture sites or spontaneous haemorrhage	Disseminated intravascular coagulation (DIC)	Check bleeding time. Cross-match blood. Give whole fresh blood or platelet infusion as needed to correct blood loss and bleeding tendency.

U4

Regular observations	Possible abnormality	Appropriate actions

B. LABORATORY

Regular observations	Possible abnormality	Appropriate actions
Blood glucose	Falls < 2.2mmol/l (40mg/dl)	Review infusion; a child will become hypoglycaemic if deprived of glucose for more than 12–24 hours. Give IV 50% dextrose (1ml/kg) diluted with an equal volume of normal saline.
Packed cell volume OR Haemoglobin	Falls < 15% OR < 5g/dl	Cross-match blood: consider need for transfusion with whole blood or packed cells (10ml/kg). Repeat Hb or haematocrit at regular intervals.
Parasitaemia	Remains high for 2–3 days, or remains positive for > 5 days. Commonly remains at the initial level for 12–24h, even when medicines are fully effective, then falls.	Review adequacy of antimalarial medicine and dosage. Consider alternative or give an additional medicine. Artemisinin derivatives are so effective that exchange transfusion is usually unnecessary.

If facilities are available for platelet counts, prothrombin or partial thromboplastin times should be checked.

Box 4.1 and 4.2 indicate some of the errors that may be encountered in the diagnosis and management of severe falciparum malaria.

Box 4.1 Errors in the diagnosis of severe malaria
▸ Failure to think of malaria in a patient with either typical or atypical illness
▸ Failure to elicit a history of exposure (travel history) – including travel within a country with variable transmission
▸ Misjudgment of severity
▸ Failure to do a thick blood film in a non-immune patient
▸ Failure to identify *P. falciparum* in a dual infection with P. vivax (the latter may be more obvious)
▸ Missed hypoglycaemia
▸ Failure to diagnose alternative or associated infections (bacterial, viral, etc.)
▸ Misdiagnosis making an alternative diagnosis in a patient who is actually suffering from malaria (e.g. influenza, viral encephalitis, hepatitis, scrub typhus, etc.)
▸ Failure to recognize respiratory distress (metabolic acidosis)
▸ Failure to carry out an ophthalmoscopic examination for the presence of papilloedema, and malarial retinopathy

---

Box 4.2 Errors in the management of severe malaria

▶ Inadequate nursing care
▶ Errors of fluid and electrolyte replacement
  – failure to control the rate of intravenous infusion
▶ Delay in starting antimalarial therapy
▶ Use of an inappropriate medicine
  – ineffective antimalarial medicine
  – unjustified withholding of an antimalarial treatment
  – dosage of antimalarial medicine not correctly calculated
  – inappropriate route of administration
  – unjustified cessation of antimalarial treatment
  – failure to adjust the dose to prevent cumulative effects of antimalarial medicines
  – failure to switch patients from parenteral to oral therapy as soon as they can take oral medication
  – unnecessary continuation of chemotherapy beyond the recommended length of treatment
  – failure to review antimalarial treatment in a patient whose condition is deteriorating
▶ Failure to elicit a history of recent intake of medicines
▶ Failure to identify or treat metabolic acidosis
▶ Unnecessary endotracheal intubation
▶ Unduly delayed endotracheal intubation (when it is indicated and possible)
▶ Failure to prevent or control convulsions
▶ Failure to recognize minor ("subtle") convulsions
▶ Failure to recognize and treat severe anaemia
▶ Delay in considering obstetrical intervention in late pregnancy
▶ Failure to recognize and manage pulmonary oedema
▶ Undue delay in starting peritoneal dialysis or haemodialysis
▶ Failure to pass a nasogastric tube to prevent aspiration pneumonia
▶ Failure to cover with antibiotics if the decision is taken to delay lumbar puncture

U4

4.4 Assessment of recovery

4.4.1 How to assess the patient's recovery

Your records and observations will provide some indications of patient recovery e.g. lowering temperature, decreasing parasite count, and an improving coma score.

In addition, the patient's ability to drink, eat, talk, sit, stand or walk should be recorded.

When a patient has recovered, an assessment should be made of possible sequelae of the disease or the treatment. In particular you should:

Perform a neurological examination

In particular, assess the patient's functional capacity to hold and use objects, ability to feed, the gait and posture. Try to determinate whether the patient can do the things that he or she was

able to do before the illness began. For a young child this requires asking parents or guardians about the child's previous activities.

Assess vision and hearing

Use the best available methods. Simple bedside measures can be used, especially for infants and children (e.g. does the child turn his/her head towards a noise? does the child watch the mother when she moves?). Use audiometry and vision charts if these are available.

Repeat packed cell volume (PCV) or haemoglobin and blood films

Optimally these should be repeated on day 7 and day 14 after recovery and again one month later. It is important to check on day 7 whether the haemoglobin is continuing to fall. If it is, there may be another cause of anaemia that needs to be investigated. By day 14 full recovery should have taken place.

4.4.2   Review and synopsis

When the patient is discharged, a summary should be prepared of the events of the patient's illness, indicating the distinguishing features of the illness and the patient's responses to treatment. A form to enter this information could be attached to the other record sheets.

KEY POINTS

▸ Severe malaria is a medical emergency requiring nursing, medical and laboratory staff to be alert at all times. Prompt action is especially important for high-risk groups such as young children and pregnant women.

▸ Artesunate IV or IM should be used in preference to quinine IV or IM for the treatment of severe malaria.

▸ The management of the patient is as important as chemotherapy and here the nurse has a crucial role to play.

▸ Regular monitoring of the core temperature, respiration (rate and depth), blood pressure, level of consciousness and other vital signs is essential. These observations will make it possible to identify the late onset of important complications such as hypoglycaemia, metabolic acidosis, pulmonary oedema and shock. Urine output should be recorded.

▸ Laboratory measurements should include regular checks on PCV, Hb, glucose, urea or creatinine (also electrolytes and arterial blood gases when possible).

▸ A proportion of children who survive cerebral malaria have neurological sequelae which persist into the convalescent period.

▸ It is important to retest PCV and Hb one month after discharge, especially if the patient was anaemic.

4.5   Exercise

4.5.1   Picture quiz

The picture plates provided below are intended to help the participants to interpret physical signs of severe disease in children and adults, decide on differential diagnoses, and determine tests that need to be carried out.
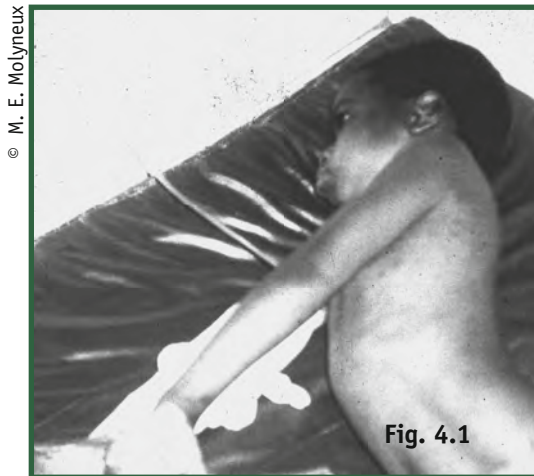
Fig. 4.1

Fig. 4.2
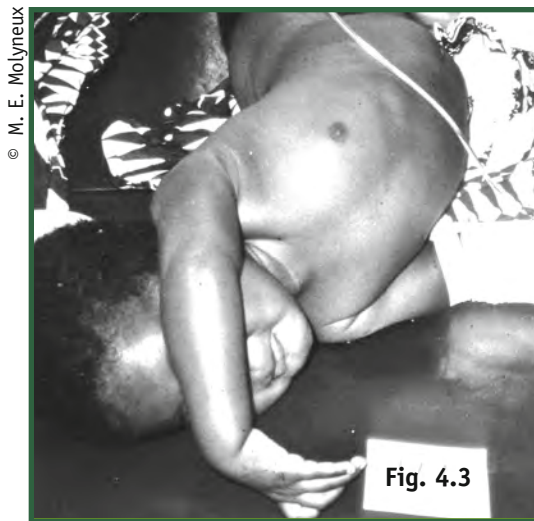
Fig. 4.3

The children seen in Figures 4.1, 4.2 and 4.3 were all brought to a clinic in an area where *P. falciparum* is hyperendemic. Each child is unconscious and has a heavy *P. falciparum* parasitaemia. The children are 3 to 5 years old. They are febrile (axillary temperature: 38°C–40°C). They have been immunized against measles, diphtheria, tetanus, and whooping-cough through the EPI services.

Question 1

What do pictures 1–3 show?

Question 2

What is the differential diagnosis?

U4

Question 3

What tests should be carried out?

....

....

The children seen in Figures 4.4 and 4.5 each have a short history of fever followed by progressive loss of consciousness. Both are in deep coma and have a heavy *P. falciparum* parasitaemia. They are 3 and 4 years old. Neither has been immunized against the common childhood diseases.

Fig. 4.4

Fig. 4.5

Question 4

What do the pictures seen in Figures 4.4 and 4.5 show?

....

....

Question 5

What could be the explanation for this?

....

....

The patient seen in pictures of Figure 4.6 has *P. falciparum* malaria. She was admitted in coma, treated with quinine and recovered consciousness. Two days later she had a convulsion and collapsed into coma again.

© R. Maude

Fig. 4.6

Question 6

What are the possible causes of the convulsion and subsequent coma?

Question 7

What investigations would you carry out to ascertain the causes?

Question 8

How will you manage this patient?

Figure 4.7 shows the supportive treatment given to a patient with severe falciparum malaria.

© Tran Tinh Hien

Fig. 4.7

Question 9

What exactly does the picture seen in Figure 4.7 show?

Question 10

What is the most frequent complication in severe falciparum malaria that leads the physician to carry out this procedure?

Question 11

What are the complications to be feared in carrying out this procedure in rural hospitals?

Figures 4.8 and 4.9 refer to the clinical and radiological presentation of a woman soon after delivery.

She has severe falciparum malaria with hyperparasitaemia and the condition shown in Figures 4.8 and 4.9 was preceded by difficulty in breathing with an increased respiratory rate.

Fig. 4.8

Fig. 4.9
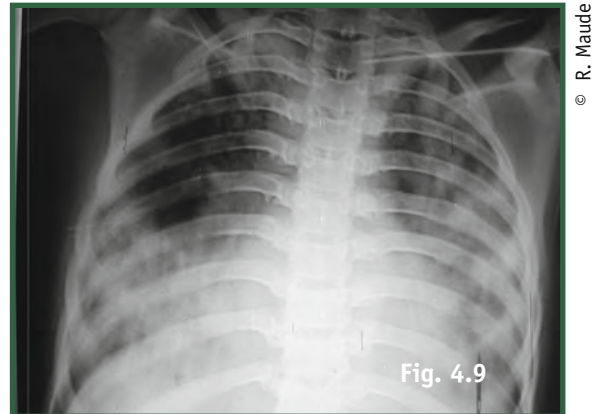
Question 12

What is the condition suggested by these pictures?

Question 13

What is the differential diagnosis for this condition?

4.5.2 **Case studies**

PATIENT A

The place: A rural district hospital catering for population living in high transmission setting.

The patient: A girl aged 4 years is brought to the outpatient department of your hospital by her mother, late in the evening.

The child was well until yesterday morning (36 hours ago), when she began to have fever. Yesterday she took meals but seemed indifferent; today she has refused food, but has drunk a little. The mother says the child had a "fit" this morning; she regained consciousness immediately. For the past few hours the child has been increasingly drowsy, and for the last hour has been unconscious.

At the examination the child is well-nourished, unconscious, and not dehydrated. The axillary temperature is 40.2°C; pulse rate 120s/min, regular; blood pressure 90/70mmHg. There is no neck stiffness and no rash. The pupils are equal; a few retinal haemorrhages seen; no papilloedema. Some yellowish sticky fluid is seen filling the left external auditory meatus. Reflexes are normal.

Question 1

If facilities are limited, which laboratory tests are essential for this child as a guide for immediate action?

....

....

Question 2

a. *Among the possible tests, blood glucose should have been included. Why does this have priority in this case?*

....

....

b. *In this patient 2ml venous blood was taken into a fluoride oxalate sample tube and sent to the laboratory to determine the blood glucose level. The result will be available two hours later. Should you wait for the result of the blood glucose test if it will take two hours?*

....

....

c. *If not, what should be done?*

....

....
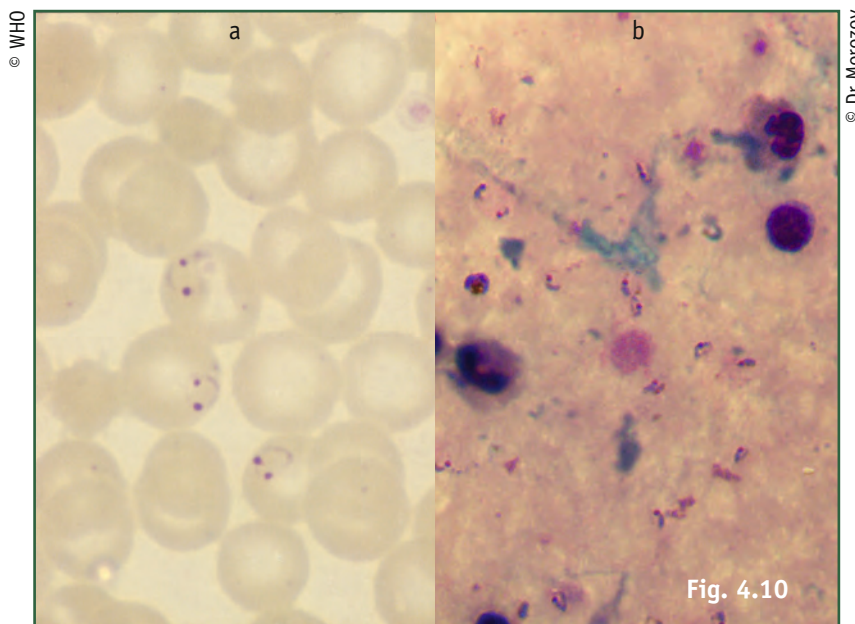
Question 3

In this child the blood glucose level was 1.0mmol/1(18mg/dl); 50% dextrose was given intravenously, but the child remained unconscious.

What does this suggest?

....

....

Question 4

Figure 4.10 shows thin (a) and thick (b) blood films from this patient as seen under the high-power microscope (magnification x700).

Fig. 4.10

a. *What does the film show?*

....

....

b. *What species of parasite is present?*

....

....

c. *How heavy is the infection?*

....

....

d. *How could you quantify it more accurately?*

....

....

Question 5

If a child has *P. falciparum* parasitaemia "++++" with hypoglycaemia:

a. Does this exclude a diagnosis of meningitis?

b. Neck stiffness was assessed in this patient. Is it still necessary to do the lumbar puncture?

c. Does clear colourless cerebrospinal fluid exclude meningitis?

Question 6

In this patient microscopy of the cerebrospinal fluid showed 3 WBC/mm³ and 7 RBC/mm³ (normal)

a. Could the ear discharge be important in this patient?

b. What should be done about it?

Question 7

What is your decision on how to proceed with antimalarial treatment?
a. *Which medicine(s) to use?*

b. *By which route?*

c. *What is the correct dosage and schedule?*

Question 8

Apart from antimalarial medicine(s), is any other medicine therapy indicated for this patient?

Question 9

How should fluid replacement be given?

Question 10

The haematocrit is 19%. What are the implications of the levels of parasitaemia and haematocrit in this patient?

a. Should a transfusion be given?

b. If blood transfusion is or becomes necessary, how should the blood be given?

Question 11

What clinical observations should be made during the course of treatment in this patient?

Question 12

What laboratory tests should be repeated (and when) during treatment?

Question 13

What should be followed up after the child has recovered?

PATIENT B

The place: A rural clinic in an area where *P. falciparum* is hyperendemic. Various antimalarial medicines are available, but intravenous infusions cannot be given.

The patient: A child aged 20 months became feverish two days ago and has vomited several times today. One hour ago the child had a convulsion, described by the mother as a repetitive twitching of limbs and mouth, followed by unresponsiveness for a few minutes. The child is now febrile (39.3°C), conscious, and able to localize and respond to a painful stimulus. Malaria rapid diagnostic test shows a positive result for *P. falciparum.* The child repeatedly vomits any antimalarial medicine given by mouth.

Question 1

a.   *Does the child have cerebral malaria?*

b.   *What should be done about the convulsions?*

Question 2

The district hospital is 30km away; the journey will probably take several hours by bus.
a.   *Should the patient be referred to hospital?*

b.   *What treatment should be given in the meantime?*

Question 3

On arrival at the district hospital, the child was still unable to take oral medication and was admitted. A thick blood smear showed *P. falciparum* rings "++++" and he was given quinine IV. On the third day, there had been some improvement but the child was still febrile and the parasitaemia reduced a little.

Does this suggest that the child has drug-resistant malaria?

Question 4

The child was able to feed and take oral medication on the third day.

Should the parenteral treatment with quinine be continued?

....

....

Question 5

On completion of the treatment, a further blood test showed gametocytes "+".

What should be done about the gametocytes present in the blood after treatment?

....

....

PATIENT C

The place: A country where *P. falciparum* is hyperendemic.

The patient: A male economist aged 28 years, was born and brought up locally, but attended university in northern Europe for five years. He returned home last month.

One week ago he developed fever. He decided this could not be malaria because he had grown up in a malaria-endemic area and believed he was therefore immune. Two days ago he became confused, especially at night. He stayed in bed and was attended by a servant who called the doctor today because the patient was increasingly confused. The last urine he had passed was a small volume of very dark fluid 24 hours ago.

On examination, the patient was a well-nourished adult man. He was afebrile with a rectal temperature of 36.5ºC. He was restless but could give brief appropriate answers to questions, and could localize the site of a painful stimulus. He was jaundiced and his mucous membranes were pale. There was some bleeding from the gums, and there were a few retinal haemor-rhages in both eyes.

Question 1

a. *What is the differential diagnosis?*

....

....

b. *Was the patient right to think he was immune to malaria? Justify your answer.*

....

....

Question 2

The thick blood film shows *P. falciparum* rings "++++" and the thin blood film shows that 26% of red cells are parasitized.

a. *What else should be looked for in the thin blood film?*

....

....

b. *What other tests are necessary to investigate the bleeding tendency?*

....

....

c. *What treatment is needed for the bleeding?*

....

....

Question 3

The patient has not passed urine for 24 hours.
What kind of investigations and actions are appropriate?

....

....

Question 4

15ml of dark brown urine was obtained by catheter. The urine 'stix' tests showed albumin "++", blood "++++", conjugated bilirubin "++", urobilinogen "++". Microscopy of the urine showed no cells and a few casts.

How are the results of the urine test to be interpreted?

....

....

Question 5

Acute renal failure is confirmed.

a. *Is it possible that the kidneys may recover?*

....

....

b. *What therapy should be given to this patient with acute renal failure?*

....

....

PATIENT D

The place: A country with hyperendemic *P. falciparum* malaria in low-lying areas but no malaria transmission on the high central plateau.

The patient: A woman aged 19 years, resident of the highlands, was brought to a clinic in the malaria-endemic area. The medical officer recorded that the patient gave a history of fever for the past three days with rigors and vomiting. On examination she was febrile with an axillary temperature of 39.1°C and slightly jaundiced. She was fully conscious. A thin blood smear examined for 10 minutes revealed no malaria parasites. Because she was living in the non-malaria highland area and has negative thin blood smear, the doctor considered it unlikely that she was suffering from malaria, so he diagnosed hepatitis and advised rest and a fat-free diet.

Question 1

a. *Do you think the medical officer was right to decide that this patient did not have malaria? Justify your answer.*

b. *Could the doctor have done better with:*
   i. The history?

   ii. The investigations?

Question 2

Two days later the patient was brought back to the clinic by anxious relatives. She had become drowsy and was not answering questions properly. On examination the patient was afebrile, slightly jaundiced and confused. She could not answer questions but could withdraw her hand from a painful stimulus. The possible diagnoses considered were fulminant hepatitis, sickle-cell crisis, relapsing fever and cholecystitis. Malaria was ruled out because she was not febrile. Treatment was started urgently with tetracycline intravenously and enemas to empty the large bowel. She remained unconscious and her temperature rose to 38°C; a blood film now showed scanty *P. falciparum* parasitaemia. This was considered "probably incidental" because low-grade parasitaemia was common among young adults in the area.

a. *What errors were made in clinical judgement?*

73

b. What errors were made in the treatment of the patient?

....

....

Question 3

The next day the patient was increasingly febrile and the parasitaemia had increased. The parenteral artesunate (IV or IM), the preferred antimalarial medicine for the treatment of severe malaria, was out of stock. Therefore, quinine 20mg base/kg was given intravenously to run over one hour in normal saline, to be repeated 8-hourly. Twenty-four hours later the patient became increasingly breathless. There were no signs in the chest but pneumonia was diagnosed and treated with penicillin. Twelve hours later the patient was still breathless and suddenly had a convulsion. Her level of consciousness deteriorated and she died ten hours later.

a. What errors were made in the administration of quinine?

....

....

b. What errors were made in the diagnosis of clinical complications?

....

....

PATIENT E

The place: A country endemic for *P. falciparum* and *P. vivax* malaria.

The patient: A boy aged 16 years who was brought to a clinic. His friend told the doctor that the patient had a history of fever for the past 7 days. Two days before admission, the patient went to a private clinic and was diagnosed with influenza. He was given some medication but did not improve. On examination the patient was febrile and jaundiced, with stupor. Blood smear examination showed *P. vivax* parasites.

Question 1

Could cerebral malaria be the cause of the patient's stupor?

....

....

Question 2

What should be investigated in this patient?

....

....

Question 3

What is the case management if repeated blood smears show only P. vivax parasites, and blood glucose and lumbar puncture are normal?

....

....

Question 4

If the patient had a haematocrit/PCV of 18%, or Hb 5.1g/dl, what should be done?

....

....

Question 5

To prevent relapse of the P. vivax *infection, when could the patient be given primaquine?*

....

....

Question 6

What further antimalarial treatment will this patient require?

....

....

Question 7

What precautions should be taken with this treatment?

....

....

PATIENT F

The place: A country where *P. falciparum* malaria is transmitted in forested areas but not in the main cities.

The patient: A man aged 30 years who had a holiday in the forest one month before admission to hospital. He became ill seven days ago, with chills, sweating and headache. He went to a private clinic and was diagnosed with upper respiratory tract infection. He was prescribed an antibiotic and his condition seemed to improve, but yesterday he developed rigors and persistent vomiting. A blood film at the private clinic showed *P. falciparum* malaria with 10% parasitaemia, and oral quinine (600mg every 8 hours) was prescribed. He took 3 doses. Today he is referred to hospital because of stupor. His temperature is 39ºC, pulse 100/min, and blood pressure 120/80mmHg.

Question 1

What tests are urgently required?

Question 2

Blood glucose was 1.7mmol/l (30mg/dl), and the patient was given an infusion of 50ml of 50% dextrose. After dextrose infusion, the patient became alert.

a. What antimalarial treatment should be given to the patient?

b. If parenteral artesunate, the preferred antimalarial medicine for severe malaria, is not available and IV quinine is given, should this patient be given a loading dose of quinine?

Question 3

If the patient had renal failure and was not given quinine before admission, should he be given a loading dose of quinine?

Question 4

If the patient had jaundice and renal failure, how is the dose of quinine adjusted?

Question 5

If the patient's consciousness does not improve after dextrose infusion and he has convulsions, what should be done?

PATIENT G

The place: A country where *P. falciparum* malaria is hyperendemic.

The patient: A woman aged 30 years who was admitted to hospital because of high fever with dyspnoea. Twenty days before admission, she had fever which did not subside after taking paracetamol. Today she developed dyspnoea and came to the hospital. On examination, her temperature was 38°C, pulse rate 120/min, respiratory rate 28/min, and blood pressure 130/88mmHg. The chest X-ray showed increased interstitial shadowing and a normal heart size compatible with non-cardiogenic pulmonary oedema. The blood smear showed *P. falciparum* parasitaemia.

Question 1

What is the possible cause of tachypnoea in this patient?

Question 2

The patient was given furosemide (30mg) and oxygen therapy via nasal cannula (with oxygen flow 5 l/min). Half an hour later, the patient had not improved and arterial blood gas showed PaO$_2$ 48 Torr. What should be done?

Question 3

When should the patient be started on positive-end expiratory pressure (PEEP) assisted ventilation?

Question 4

If central venous pressure (CVP) is measured to evaluate the patient's volume status, what level of CVP should be maintained?

Question 5

What other severe malaria manifestations or complications are often associated with pulmonary oedema?

LEARNING UNIT **5**

Hospital visit

Learning Objectives:
by the end, participants should be able to...

● **Describe the profile of malaria patients with uncomplicated and severe malaria seen in the hospital in the past year**
● **Take a history and conduct a clinical examination of (a) a patient with severe malaria, and (b) a patient with an uncomplicated febrile illness, who are being treated in the hospital**
● **Assess the basis for diagnosis and the details of the management of the patients reviewed in the second bullet above**

This is a very important part of the course. There will be an opportunity for participants to discuss their observations with each other and with their tutor at the end of the visit. In order to get an understanding of the malaria burden in the district, the participants should extract from the hospital records the following information:

▶ Number, age distribution and seasonality of patients with (a) severe malaria and (b) uncomplicated malaria seen in the hospital in the past year.

▶ Numbers of diagnostic tests and blood slides examined for malaria in the past years and the proportion positive for malaria, recorded parasite densities, and the species of malaria parasites identified

The participants should observe clinicians on history taking and clinical examination of (a) a patient with an uncomplicated febrile illness, and (b) a patient with severe malaria, who are being treated in the hospital. Finally, they should provide a critical assessment of how the patients have been diagnosed and managed for malaria in the hospital.

LEARNING UNIT **6**

Malaria in pregnancy

Learning Objectives:
by the end, participants should be able to...

● **Describe the relationship between malaria and pregnancy**
● **List measures to prevent malaria during pregnancy**
● **State the justification, indications, advantages, recommended medicines and their dosage and timing, for intermittent preventive treatment (IPT)**
● **State the recommended therapeutic regimens for the treatment of uncomplicated and severe malaria during pregnancy**

6.1   Effects of malaria on pregnancy

The symptoms and complications of malaria in pregnancy vary according to transmission intensity and the level of acquired immunity. Pregnant women living in areas of low or unstable malaria transmission have little or no immunity to malaria, and are at higher risk of developing severe malaria than are non-pregnant adults living in the same area.

In these areas, malaria is a major cause of maternal anaemia, spontaneous abortion, stillbirth, premature delivery, low birth weight (birth weight < 2.5kg), neonatal death and maternal death. In non-immune women, severe malaria symptoms (hypoglycaemia, cerebral malaria, and pulmonary oedema being particular problems) are more common in pregnancy.

In stable transmission settings, the deleterious impact of malaria is particularly apparent in first and second pregnancies. Partial clinical immunity acquired during years of exposure

to the malaria parasite prior to pregnancy does not prevent infection, but does reduce the risk of severe disease. Clinical malaria is not, therefore, a prominent feature of infection during pregnancy, and the major detrimental effects of infection are low birth weight (LBW) and maternal anaemia.

HIV infection impairs pregnant women's ability to control *P. falciparum* infection. Women with HIV infection are more likely to have symptomatic malaria infections and to have an increased risk of an adverse birth outcome due to malaria. In the presence of HIV infection, placental malaria appears to be independent of the number of pregnancies, so that the risk of placental malaria is similar in HIV-infected multigravidae and HIV-negative primagravidae.

Severe anaemia, exacerbated by malaria, is an important complication of pregnancy in many tropical countries. Especially in communities where chronic hookworm anaemia is prevalent, high output anaemic cardiac failure may develop in late pregnancy.

Asymptomatic hypoglycaemia may occur in pregnant women with malaria before antimalarial treatment, and pregnant women with uncomplicated or severe malaria are particularly vulnerable to quinine-induced hypoglycaemia.

There is an increased risk of pulmonary oedema precipitated by fluid overload or by the sudden increase in peripheral resistance, or autotransfusion of hyperparasitaemic blood from the placenta, which occurs just after delivery.

6.2 Treatment of uncomplicated malaria in pregnancy

Pregnant women with symptomatic acute malaria are a high-risk group, and require effective antimalarial medication. There is insufficient information on the safety and efficacy of most antimalarial medicines in pregnancy, particularly for exposure in the first trimester, and treatment recommendations differ from those for non-pregnant adults. Therefore as a standard practice for the administration of any medicine pregnant women, all women of child-bearing age should be asked whether they are, or could possibly be, pregnant before an antimalarial medicine is prescribed. The following are the antimalarial medicines recommended for the treatment of uncomplicated falciparum malaria during pregnancy:

▸ In the first trimester, give a 7-day course of quinine plus clindamycin. ACTs are not recommended as routine treatment in early pregnancy because their safety has not been fully established. An ACT is indicated only if (i) it is the only treatment immediately available, (ii) if treatment with 7-day quinine plus clindamycin fails, or (iii) if there is uncertainty about the patient's compliance with a 7-day course of treatment.

▸ In the second and third trimesters, give an effective ACT. Acceptable alternative treatments are 7-day quinine plus clindamycin, or 7-day artesunate plus clindamycin.

For the treatment of non-falciparum malaria in pregnancy, chloroquine, which is the treatment of choice for *P. vivax* (chloroquine-sensitive), *P. ovale* and *P. malaria*, is safe in pregnancy. For more detail refer to section 3.2.2 of Learning Unit 3.

6.3 Treatment of severe malaria in pregnancy

A pregnant woman with severe malaria should be given a parenteral antimalarial medicine in full doses without delay. Parenteral artesunate is more effective than parenteral quinine in reducing the risk of death from severe malaria.

Although safety data on the use of artemisinins in the first trimester are limited, saving the mother's life is the primary objective, and both artesunate (IV or IM) and quinine (IV or IM) may be considered as options.

In the second and third trimesters, parenteral artesunate is preferred over parenteral quinine, because of its antimalarial efficacy and because quinine is associated with recurrent hypoglycaemia. For more information on the therapeutic doses of these medicines refer to section 4.3.3 of Learning Unit 4.

6.4 Intermittent preventive treatment (IPT) of malaria in pregnancy

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Intermittent preventive treatment during pregnancy (IPTp) is a strategy to prevent the consequences of malaria infections among pregnant women living in areas of moderate to high transmission of *P. falciparum*. IPTp involves the administration of a curative treatment dose of an effective antimalarial medicine at predefined intervals during pregnancy, beginning after quickening (the time at which foetal movements are first felt by the mother) in the second trimester. Sulfadoxine-pyrimethamine (500mg sulfadoxine and 25mg pyrimethamine per tablet) is currently the only recommended antimalarial medicine for IPTp. The benefits of IPTp include reduced incidence of malaria in pregnancy, reduced risk of malaria-related anaemia in pregnancy, and reduced rate of low birth weight.

WHO recommends that all pregnant women at risk of falciparum infection in countries in sub-Saharan Africa with stable malaria transmission receive IPT with SP during the scheduled ANC visit. The first dose should be administered as early as possible during the 2nd trimester of gestation (determined by the onset of "quickening" or by fundal height by ANC personnel). Each SP dose should be given at least 1 month apart and up to delivery."

In areas where > 10% of pregnant women are infected with HIV, a third dose should be given.

As a policy, the medicines for IPT are taken under direct observation of treatment (DOT) during the ANC visit.

6.5   Exercises

6.5.1   Case study

PATIENT A

The place: A country where *P. falciparum* malaria is transmitted in forested areas but not in the main cities.

The patient: A woman aged 25 years is brought to the outpatient department of the central hospital in the capital. She is a local resident, the wife of a business executive, and is in the seventh month (28 weeks) of her first pregnancy.

The patient became ill five days ago, with chills, sweating and headaches. An antibiotic was prescribed and her condition seemed to improve, but yesterday she developed rigors and persistent vomiting. A blood film at the local clinic showed malaria parasites, and oral quinine (600mg every 8 hours) was prescribed. She took two doses.

Today she has been referred to your hospital because of restlessness and increasing mental confusion. Examination shows a semiconscious woman who is unable to speak. She withdraws her hand from a painful stimulus but cannot localize a stimulus applied to the sternum or forehead. There is no neck stiffness, jaundice, pallor or rash. Axillary temperature is 39°C, pulse rate 90/min, blood pressure 110/70mmHg. The uterine fundus is palpable (26–28 weeks), and the fetal heart can be heard.

Question 1

What tests are urgently required?

Question 2

If the blood glucose is 1.2mmol/l (22mg/dl) what treatment should be given?

Question 3

The blood film shows *P. falciparum* rings "++++", and the cerebrospinal fluid is normal except for low glucose.

a.   What antimalarial medicine should be administered and by which route?

Assume that the patient is 6 months pregnant and parenteral quinine is the only available parenteral medicine.

b. *Should a loading dose of quinine be given? Justify your answer.*

c. *What nursing procedures are important during this treatment?*

d. *In a health unit without facilities for parenteral therapy, what alternative treatment could be considered?*

Question 4

After six hours the patient becomes increasingly restless. The respiratory rate increases to 40/minute. The blood glucose level is normal.

Under these conditions, what diagnostic steps should be taken?

Question 5

A chest X-ray gives the picture shown (Fig. 6.1). What is the diagnosis and treatment?

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Fig. 6.1
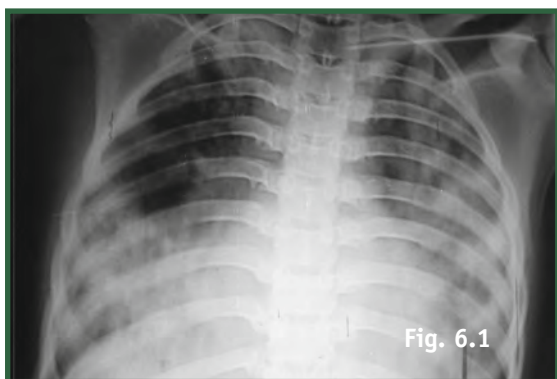
Question 6

What other observations are particularly important in this patient?

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Question **7**

What other questions should this patient's relatives be asked?

....

....

6.5.2   Group work

Work in three groups (A, B, C) and discuss the following questions.

Group A

Suggest possible reasons for the increased susceptibility of pregnant women to malaria. In high transmission areas, why are primigravid women more susceptible to *P. falciparum* than are secundagravid women, and why are multigravid women less susceptible than the latter? In what ways may malaria in pregnancy endanger *(i)* the mother and *(ii)* the baby?

Group B

What special precautions should be taken for *(i)* uncomplicated malaria and *(ii)* severe malaria in pregnancy? Discuss the rationale, dosage and timing for the administration of IPTp. Are any special measures required for the hospital delivery of a patient with severe malaria?

Group C

Discuss the opportunities provided by pregnancy for appropriate health promotion activities relevant to malaria. Are there any beliefs and cultural practices in countries that might endanger a pregnant woman or her child if she has malaria?

LEARNING UNIT **7**

Management of fever at first level health facility

Learning Objectives:
by the end, participants should be able to…

● **Manage a patient with fever at primary care level using the syndromic approach**
● **Describe the general danger signs in a patient with fever**
● **Classify a case of fever according to the recommended criteria for areas of low and high transmission**
● **Select appropriate treatment according to the classification**
● **Correctly identify cases for referral and state appropriate pre-referral treatment**
● **Identify the most appropriate case management where referral is not possible**

7.1   Introduction

WHO has developed guidelines for the integrated management of childhood illnesses (IMCI) for the correct assessment and treatment of the major causes of child mortality. These guidelines are designed to assist health workers at first level health facility. The sections below provide a brief description of the IMCI guidelines for the management of fever.

7.2   Assessment of a patient with fever

All patients with fever as a main symptom (history of fever or feels hot or has an axillary temperature of 37.5°C or above) should be quickly checked for general danger signs and features of severe malaria for immediate care if any one of these signs or features is present.

Check for general danger signs

A general danger sign is present if the patient:

▶ is not able to drink or breastfeed;

▶ vomits everything;

▶ has had convulsions;

▶ is lethargic or unconscious.

Patient with a general danger sign should be referred immediately to hospital where appropriate treatments are available. Danger signs are assessed as follows:

ASK the following:

1. Is the patient able to drink or breastfeed?
A patient has the sign "not able to drink or breastfeed " if he/she is not able to swallow or suck when offered a drink or, for a young child, breast milk.

2. Does the patient vomit everything?
A patient has the sign "repeated vomiting" if he/she vomits everything and is unable to hold down food, fluids, etc.

3. Has the patient had convulsions?
Ask if the patient has had convulsions during this current illness. Use words which will be understood, like "fits" or "spasms" or local terminology.

LOOK for the following:

Is the patient is lethargic or unconscious?

▶ A patient has the sign "lethargic or unconscious" if he/she is not awake/alert or drowsy and does not show interest in what is happening around, or has mental disturbance.

▶ A patient with a general danger sign should be given pre-referral treatment without delay and refered immediately. If there is no general danger sign, assess for any other sign of severe malaria. Some patients may not have any of the 4 general danger signs but other signs of severe malaria (see below).

ASK and LOOK for the following:

1. Does the patient have any other sign of severe malaria?

- ► Severe palm pallor
- ► Difficult in breathing
- ► Passing dark or little urine
- ► Jaundice (yellow eyes)
- ► Bleeding from injection or venepuncture sites

A patient who has any one of the signs of severe malaria above should be given pre-referral treatment and referred for further management.

2. Does the patient have any other signs suggesting another cause of fever?

- ► Check for a stiff neck.
- ► See whether the patient's nose is running (specially for children below 5 years).
- ► Look for signs of measles (specially for children below 5 years).
- ► Look for other signs of local infection such as tender swelling.

If a child has any general danger sign, then the case is classified as VERY SEVERE FEBRILE DISEASE OR VERY SEVERE MALARIA (see Table 7.1).

7.3 Classification of fever without danger signs

If the patient has fever and no danger signs, classify or diagnose the cause of fever on the basis of malaria risk.

The IMCI guidelines classify fever on the basis of three levels of malaria risk:

- ► high malaria risk: areas where the malaria positivity rate among febrile children attending first-line health facilities is consistently above 5%;
- ► low malaria risk: areas where the malria positivitiy rate among febrile children attending first. line health facilities is consistently below 5%;
- ► no malaria risk: areas where no local malaria transmission is reported.

Note: the patient should be classified on the basis of the travel history during the previous 3 months. If the patient has spent one or more nights in a high malaria risk area in the previous 3 months, he or hse should be considered at high malaria risk.

In high malaria risk areas, all febrile patients should be suspected as malaria and tested accordingly.

In low malaria risk areas, malaria should be strongly suspected only in patients with no obvious cause of fever and such cases should be test for malaria.

Using the IMCI algorithms, there are three possible classifications of a case assessed for fever according to the tables on the ASSESS & CLASSIFY chart.

Perform microscopy or rapid diagnostic test

In all patients with non-severe febrile illness, parasitological diagnosis is recommended before treatment with antimalarials. In areas of high malaria risk, parasitological confirmation of malaria by microscopy or RDTs should be carried out for all febrile children and adults with no danger signs, while in areas of low malaria risk, only in those children and adults without any other obvious cause of fever.

A blood test is considered positive if the blood slide taken from the patient and examined by microscopy shows malaria parasites, or when using RDTs, when the test reads positive for malaria antigens in the blood. The test is reported negative if the blood properly examined by microscopy did not show any malaria parasites, or if a well performed RDT test was found negative for malaria antigen.

Children above five years of age or adults with a positive slide should be classified or diagnosed as having malaria. When using IMCI algorithms for children under five years of age, follow the classifications below.

If the patient has fever with no general danger sign but with a positive malaria test, the case should be classified as MALARIA. If there is no general danger sign and the malaria test is negative, the case should be classified as FEVER: NO MALARIA (see Table 7.1).

The patient should be assessed for any other apparent cause of fever such as pneumonia, ear infection, dysentery, sore throat or local infection, all of which are common causes of fever in children under five.

Table 7.1   Classification of fever in areas of high risk of malaria transmission

Does the child have fever?
(by history or feels hot or temperature 37.5°C or above)

If yes, decide malaria risk: high or low

Then ask:
- ☐ For how long?
- ☐ If more than 7 days, has fever been present every day?
- ☐ Has the child had measles within the last 3 months?

Look and feel:
- ☐ Look or feel for stiff neck
- ☐ Look for runny nose

Look for signs of measles:
- ☐ Generalized rash, and
- ☐ One of these: cough, runny nose, or red eyes

Look for any other cause of fever

Do a malaria test if NO any general danger sign or stiff neck

- ☐ **HIGH MALARIA RISK:** do a malaria test in all fever cases
- ☐ **LOW MALARIA RISK:** do a malaria test if no obvious cause of fever
- ☐ Look for mouth ulcers

CLASSIFY FEVER

HIGH MALARIA RISK

Signs	Classify	Treatment
☐ Any general danger sign, or ☐ Stiff neck	**Pink:** VERY SEVERE FEBRILE DISEASE	☐ Give first dose of artesunate or quinine for severe malaria ☐ Give first dose of an appropriate antibiotic ☐ Treat the child to prevent low blood sugar ☐ Give one dose of paracetamol in clinic for high fever (≥ 38.5°C) ☐ Refer URGENTLY to hospital
☐ Malaria test POSITIVE	**Yellow:** MALARIA	☐ Give recommended first line oral antimalarial ☐ Give one dose of paracetamol in clinic for high fever (≥ 38.5°C) ☐ Advise mother when to return immediately ☐ Follow-up in 3 days if fever persists ☐ If fever is present every day for more than 7 days, refer for assessment
☐ Malaria test NEGATIVE. ☐ Runny nose PRESENT, or ☐ Measles PRESENT, or ☐ Other cause of fever PRESENT	**Green:** FEVER: NO MALARIA	☐ Assess for possible bacterial cause of fever and treat with appropriate drugs ☐ Give one dose of paracetamol in clinic for high fever (≥ 38.5°C) ☐ Advise mother when to return immediately ☐ Follow-up in 2 days if fever persists ☐ If fever is present every day for more than 7 days, refer for assessment

LOW MALARIA RISK

Signs	Classify	Treatment
☐ Any general danger sign, or ☐ Stiff neck	**Pink:** VERY SEVERE FEBRILE DISEASE	☐ Give first dose of artesunate or quinine for severe malaria ☐ Give first dose of an appropriate antibiotic ☐ Treat the child to prevent low blood sugar ☐ Give one dose of paracetamol in clinic for high fever (≥ 38.5°C) ☐ Refer URGENTLY to hospital
☐ Malaria test POSITIVE	**Yellow:** MALARIA	☐ Give recommended first line oral antimalarial ☐ Give one dose of paracetamol in clinic for high fever (≥ 38.5°C) ☐ Advise mother when to return immediately ☐ Follow-up in 3 days if fever persists ☐ If fever is present every day for more than 7 days, refer for assessment
☐ Malaria test NEGATIVE, or ☐ Runny nose PRESENT, or ☐ Measles PRESENT, or ☐ Other cause of fever PRESENT	**Green:** FEVER: NO MALARIA	☐ Assess for possible bacterial cause of fever and treat with appropriate drugs ☐ Give one dose of paracetamol in clinic for high fever (≥ 38.5°C) ☐ Advise mother when to return immediately ☐ Follow-up in 2 days if fever persists ☐ If fever is present every day for more than 7 days, refer for assessment

NO MALARIA RISK and no travel to malaria risk area

Signs	Classify	Treatment
☐ Any general danger sign ☐ Stiff neck	**Pink:** VERY SEVERE FEBRILE DISEASE	☐ Give first dose of an appropriate antibiotic. ☐ Treat the child to prevent low blood sugar ☐ Give one dose of paracetamol in clinic for high fever (≥ 38.5°C) ☐ Refer URGENTLY to hospital
☐ No general danger signs ☐ No stiff neck	**Green:** FEVER	☐ Assess for possible bacterial cause of fever and treat with appropriate drugs ☐ Give one dose of paracetamol in clinic for high fever (≥ 38.5°C) ☐ Advise mother when to return immediately ☐ Follow-up in 2 days if fever persists ☐ If fever is present every day for more than 7 days, refer for assessment

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*   These temperatures are based on axillary temperature. Rectal temperature readings are approximately 0.5°C higher.

** If no malaria test is available: high malaria risk – classify as Malaria; low malaria risk and no other obvious cause of fever – classify as Malaria

*** Look for local tenderness, refusal to use a limb, hot tender swelling, red tender skin or boils, lower adbominal pain or pain in passing urine.

7.4   Treatment of fever

A patient with fever and any general danger sign or stiff neck may have severe malaria (including cerebral malaria), meningitis or sepsis. It may not be possible to distinguish between these severe diseases without further laboratory tests.

A patient classified as having very severe febrile disease needs urgent pre-referral treatment and referral. Pre-referral treatment should include a single pre-referral administration of rectal artesunate or, if not available, intramuscular injection of quinine or artemether, and first dose of an appropriate antibiotic for meningitis or other severe bacterial infection.

Other urgent treatments for severe febrile disease may include:

- ▸ correction of any metabolic defect including treatment to correct hypoglycaemia;
- ▸ supportive therapy as indicated (e.g. diazepam or paraldehyde for convulsions; paracetamol for fever ≥ 38.5°C).

A patient classified as having malaria should be treated with the appropriate first line ACT. If in addition the patient has other problems, classify and treat according to IMCI guidelines for children below 5 years or the national treatment guidelines for children above 5 years and adults.

Where referral is not possible

In situations where referral is not possible, the patient should be kept at the health unit and treatment with an appropriate parenteral or rectal antimalarial continued according to the national guidelines. When the patient is able to tolerate oral administration, a full dose of the locally recommended ACT should be given.

However every effort must be made to refer the patient as he/she may require other forms of intensive care. In the following situations patients must always be referred because they will die if they are not sent promptly to an appropriate health facility:

- ▸ still unconscious after 2 days of treatment with quinine or artemether;
- ▸ uncontrollable convulsions;
- ▸ severe pallor;
- ▸ renal failure;
- ▸ pregnant women with severe malaria.

LEARNING UNIT **8**

Community case management of malaria (CCM)

Learning Objectives:
by the end, participants should be able to...

- **Explain the rationale behind the strategy for CCM**
- **Describe the role of home caregivers in CCM**
- **Describe the role of community-based providers in CCM**
- **Describe the diagnostic and treatment procedures for CCM**
- **Define integrated community case management (iCCM) of childhood illnesses**
- **Indicate key components and actions that will facilitate delivery of iCCM**

8.1 Rationale for community management of malaria

Effective interventions against malaria are available, yet the burden persists, largely because most people at risk have little or no access to them for various reasons, including physical access and affordability. Most malaria cases occur in remote and rural areas and among marginalized populations, ethnic minorities and forest dwellers in Africa, Asia and Latin America, who have limited access to formal health care. With very limited transport facilities in these settings, the likelihood of reaching a functional health facility in a timely manner remains very low.

In order to improve access to prompt and effective case management of malaria, especially in remote, underserved areas with high malaria transmission, WHO recommends community case management of malaria (a strategy formerly known as 'home management of malaria'),

in the context of the integrated Community Case Management (iCCM) of childhood illness. Through this strategy, antimalarial treatment is made available close to the home by community health workers. CCM was originally based on presumptive treatment of all cases of suspected malaria, but is now being redefined to include the use of malaria rapid diagnostic tests (RDTs) by community-based providers to confirm a diagnosis of malaria before dispensing antimalarial treatment.

Community management of malaria enables access to diagnosis and treatment of malaria to extend beyond the reach of health facilities. CCM requires that simple and reliable diagnostic tests, effective and appropriate treatment with first-line ACTs for uncomplicated malaria, early identification and pre-referral treatment for severe malaria, as well as guidance on referral for other illnesses, are provided at the community level through trained community-based providers, such as community health workers, mother coordinators and private vendors.

8.2 Management of malaria cases in the community

8.2.1 Recognition of malaria illness by caregivers in the home

Caregivers (parents and guardians) or patients themselves should recognize malaria illness early and take appropriate action as indicated below:

▸ For patients with a history of fever (hot body) for the past 24 hours (in settings where the risk of malaria is high) or 72 hours (in settings where the risk of malaria is low), caregivers should immediately contact the designated community-based provider to access prompt malaria diagnostic testing and effective antimalarial medicines.

8.2.2 Diagnosing malaria illness by community-based provider

The designated community-based providers should assess the condition of the patient, look for danger signs and symptoms of severe disease and take appropriate action as indicated below:

▸ Patients with fever and one or more danger signs or severe symptoms should be classified as having SEVERE FEBRILE DISEASE – probably malaria, and urgent action should be taken (see section 8.2.3).

▸ Patients with uncomplicated suspected malaria (history of fever in the past 2 days or raised temperature) should be tested for malaria parasites using RDTs.

In addition, the patient should be assessed for other causes of fever, and specific treatment should be provided in addition to the antimalarial treatment, if needed.

8.2.3 Provision of effective antimalarial treatment by community-based provider

Before initiating the treatment, the community-based providers should check whether the patient (i) has already been treated for malaria in the past 2 weeks and (ii) took the full course of treatment as required. Then the following actions should be taken as appropriate:

▸ Patients classified as having a *severe febrile disease* should be given:
  ▹ pre-referral treatment (artesunate suppositories);
  ▹ immediate referral to the nearest health centre or hospital; and
  ▹ a referral note indicating details of what was observed, what treatment was given and when it was given.
▸ Patients with positive RDT results for malaria with no features of severe disease should receive a full course of the recommended first-line ACT. Clear advice and instructions on treatment schedules should also be provided to the caretakers or to the patients.
▸ Patients with negative RDT results for malaria should NOT receive antimalarial medicine BUT should be referred to health facilities for further assessment and appropriate treatment.
▸ Patients with persisting or recurrent fever within 2 weeks following an initial full course of antimalarial treatment should be referred to health facilities as soon as possible.
▸ Patients with persisting or recurrent fever within 2 weeks following an incomplete initial course of antimalarial treatment should receive a full course of the recommended first-line ACT.

8.2.4 Supportive treatment and counseling of the patient

Patient with uncomplicated malaria may require additional supportive therapy to correct conditions such as high fever and dehydration. In addition the caretakers and/or patients should be instructed on administering the treatment schedules and how to provide supportive care. The community-based providers should provide:

▸ paracetamol and advise caregiver and/or patient to use tepid sponging and fanning in the case of high fever (axillary temperature above 38°C in children);
▸ oral Rehydration Salt (ORS) and advise increased intake of clean water or other fluids in case of dehydration or diarrhoea. For infants, encourage mothers to provide extra breast-feeding;
▸ advice to the caregiver and/or patient to return within 72 hours (3 days) if fever, and any other signs of illness, persist following treatment. For all patients who come back, a full assessment should be done and appropriate action taken:
  ▹ if the patient developed signs and symptoms of severe illness, give pre-referral treatment and refer to the nearest health facility for further management,
  ▹ if the patient has not taken the complete treatment course, administer 1st-line treatment,
  ▹ if patient has taken a full course of the treatment and still has clinical signs and symptoms of malaria, refer to the nearest health facilities.

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The caregiver and/or the patient can play an important role in the management of the patient. Following treatment by the community-based provider, the caregiver should:

▶ watch for changes in the patient's clinical condition and take appropriate action if deterioration occurs;

▶ complete the patient's treatment course; and

▶ offer supportive care to the patient, including ensuring there is increased fluid intake, recommended feeding practices and measures to reduce fever.

8.3   Integrated community case management (iCCM) of childhood illnesses

In addition to malaria, pneumonia, diarrhoea and malnutrition are among the leading causes of death among children aged 2 to 59 months. It is common for a child to have two or more of these conditions at the same time and the child needs treatment for each of them. Furthermore, there is often a significant overlap in the clinical manifestation of pneumonia and malaria. The introduction of simple and rapid diagnostic testing (RDTs) at community level allows not only for targeted malaria treatment but also for early identification of non-malarial febrile illnesses which need proper management. This underscores the need, especially in malaria endemic settings, to integrate malaria diagnosis and treatment with the other recommended community-based interventions for major childhood illnesses, which include community case management of pneumonia, diarrhoea and malnutrition. WHO and UNICEF jointly recommend a strategy for integrated community case management (iCCM) of childhood illnesses which include malaria, pneumonia, diarrhoea and malnutrition.

In the context of iCCM, the community-based providers should assess the condition of the sick child, look for and identify signs and symptoms of severe diseases, malaria, pneumonia, diarrhoea and malnutrition, and take appropriate action as indicated below:

▶ A child with one or more of the following danger signs should be classified as having Severe Disease:
  ▷ cough for 21 days or more
  ▷ diarrhoea for 2 weeks or more
  ▷ diarrhoea with blood in the stool
  ▷ fever for 7 days or more
  ▷ convulsions
  ▷ not able to drink or breastfeed
  ▷ repeated vomiting
  ▷ chest in-drawing
  ▷ lethargic or unconscious
  ▷ stiff neck

> ▷ red on the MUAC (Mid-Upper Arm Circumference) strap
> ▷ swelling of both feet

Any child classified as having severe disease should be given an appropriate pre-referral treatment and referred without delay to the nearest health facility with a referral note. The pre-referral treatment recommended for iCCM include:

> ▷ artsunate suppositories for febrile patients with convulsions, repeated vomiting, unable to swallow or with altered consciousness;
> ▷ first line ACT for febrile patients with danger signs other than the three listed above;
> ▷ antibiotic for febrile patients with cough plus chest indrawing if they can take medicines by mouth;
> ▷ ORS for patients with diarrhoea and who can drink.

▶ A child without a severe disease can be managed by the community-based providers as follows:

> ▷ A child with fever (reported or current) for less than 7 days and who is living in malaria endemic areas should be tested for malaria parasites using RDTs. The child with positive malaria RDTs test should be classified as uncomplicated malaria and should be given the recommended first line ACT. The child should be assessed also for other possible diseases (e.g. pneumonia) and receive additional treatment as appropriate. Patients with negative RDT results, and without any symptoms or signs of other diseases (e.g. fast breathing, diarrhoea), should be instructed to return for a follow-up visit within 3 days and/or anytime if the child is still sick. During the follow-up visit, look for signs of illness again. Refer the child if the child is not improving.
> ▷ A child with cough plus fast breathing and/or chest indrawing should be classified as pneumonia. An antibiotic (amoxicillin) should be given to the patients if they can oral medication.
> ▷ A child with loose stools (3 or more in 24 h) for less than 7 days should be classified as having diarrhoea. These patients should receive ORS and zinc if they can drink.

In addition to assessing the child's condition and providing treatment, the community-based provider should advise the family on home care for the sick patient, and follow up until the child is well. If the child does not improve with home care, then refer the child to a health facility for assessment and treatment.

In order to facilitate successful implementation of the iCCM strategy, countries need to incorporate iCCM activities in the overall malaria strategic and implementation plans. Following are key components and actions that will facilitate delivery of iCCM at country level.

1. Policy setting and coordination

▶ Undertake a needs assessment and situation analysis for community-based treatment services.

▶ Undertake mapping of current CCM programme activities and partners.

▶ Establish a national coordination mechanism for CCM.

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▶ Ensure appropriate national policies and guidelines are in place to allow treatment with ACTs, antibiotics, ORS and zinc at the community level.

2. Costing and financing

▶ Undertake a costing exercise that covers all required CCM programme elements and ensure that necessary programme funds are secured.

3. Human resources

▶ Ensure that the roles and expectations of community health workers and communities themselves are clear and well articulated.

▶ Develop a comprehensive basic and refresher training plan for community-based providers, including strategies for retention, incentives and recruitment.

4. Supply chain management

▶ Ensure that appropriate "child friendly" medicines and supplies for CCM are included in the national essential medicines list and registered for use in the country.

▶ Develop a procurement plan, inventory control, supply logistics system for CCM with standard operating procedures.

5. Service delivery and referral

▶ Ensure that appropriate guidelines for clinical assessment, diagnosis, management and referral are in place, including plans for rational use of medicines (and RDTs where applicable).

▶ Develop referral systems for CCM.

6. Communication and social mobilization

▶ Develop appropriate communication and social mobilization plan and strategy, including prevention and management of community illness for policy makers, local leaders, health providers, community-based providers and communities.

▶ Ensure that appropriate materials and messages for CCM are defined, targeting the community and other groups.

7. Supervision and performance quality assurance

▶ Develop a supervision plan and appropriate tools to support effective supervision.

▶ Ensure that supervisors are trained, have access to appropriate supervision tools, resources to conduct supervision (i.e. vehicles, fuel, etc.) and provide skills coaching for community-based providers.

8. Monitoring and evaluation and health information systems

▶ Develop a comprehensive monitoring framework and system for all CCM components which is integrated within the national health sector plan and health information system.

LEARNING UNIT **9**

Malaria chemoprophylaxis and standby treatment

Learning Objectives:
by the end, participants should be able to...

- Specify the indications for antimalarial chemoprophylaxis
- State the medicines recommended for antimalarial chemoprophylaxis and the criteria for their selection
- Indicate the rationale for standby emergency treatment (SBET) of malaria
- State the indications for SBET
- Give appropriate guidance for travellers carrying SBET

9.1 Malaria chemoprophylaxis

9.1.1 Target groups for chemoprophylaxis

The role of chemoprophylaxis in malaria control has considerably reduced in the last two decades. In the past, WHO recommended that pregnant women and young children in malaria-endemic areas should receive a full course of antimalarial treatment on their first contact with the antenatal and postnatal services, followed by weekly chemoprophylaxis with chloroquine.

The implementation of this policy was limited by a number of factors, including: spread of chloroquine resistance, poor compliance with a weekly regimen throughout pregnancy and childhood, cost.

Long-term chemoprophylaxis is no longer recommended for young children or pregnant women. For pregnant women and infants in areas of moderate to high transmission, intermittent preventive treatment (IPT) is currently the strategy of choice. Chemoprophylaxis is now only recommended as a short term measure for international travellers to malaria-endemic areas and for military personnel, police and labour forces serving in highly endemic areas.

9.1.2   Recommended antimalarial prophylaxis

No prophylactic regimen gives complete protection but good chemoprophylaxis (adherence to the recommended medicine regimen) does reduce the risk of fatal disease.

Depending on the malaria risk in the area to be visited and the local patterns of resistance to antimalarial medicine, the recommended medicine may be chloroquine, chloroquine plus proguanil, mefloquine, or doxycycline:

▶ Chloroquine alone can only be recommended for areas where malaria is due exclusively to *P. vivax* or fully chloroquine-sensitive *P. falciparum*.

▶ Chloroquine+proguanil can be recommened for areas where both *P. vivax* and *P. falciparum* malaria transmission co-exist and where chloroquine resistance is emerging. For these areas, atovaquone+proguanil can be used as an alternative that can be started the day before travel.

▶ Atovaquone-proguanil, doxycycline or mefloquine (selected according to reported resistance pattern) are recommended for areas with *(i)* high risk of *P. falciparum* malaria, in combination with reported antimalarial drug resistance; *(ii)* moderate/low risk of *P. falciparum* malaria, in combination with reported high levels of drug resistance.

All antimalarial medicines have specific contraindications and possible side-effects. Adverse reactions attributed to chemoprophylaxis are common but most are minor and do not affect the activities of the traveller. Serious adverse reactions are rare. The risk of medicine-associated adverse effects should be weighed against the risk of malaria and local medicine resistance patterns. Because of the risk of side-effects, chemoprophylaxis should not be prescribed in the absence of malaria risk.

Most countries have specific advice to their citizens on malaria prophylaxis when travelling to malaria-endemic regions[7].

9.2   Standby emergency treatment for different risk groups

A traveller who develops fever one week or more after entering an area where there is a risk of malaria should consult a physician or qualified malaria laboratory immediately to obtain a correct diagnosis and safe and effective treatment. In principle, travellers can be treated with ACT according to the national policy in the country they visit.

[7.] More information on malaria prophylaxis for travellers is available in the annually updated WHO publication *International travel and health*.http://www.who.int/ith

Because of the spread of counterfeit and substandard medicines in some resource-poor settings, travellers may prefer to buy a reserve antimalarial treatment before departure so that they can be confident of medicine quality should they become ill. Although many travellers will be able to obtain proper medical attention within 24 hours of the onset of fever, this is not always possible, particularly for travellers staying in remote locations. In such situations, travellers are advised to carry antimalarial medicines for self-administration ("stand-by emergency treatment").

Stand-by emergency treatment (SBET) may also be indicated for travellers in some occupational groups, such as aircraft crews, who make frequent short stops in endemic areas over a prolonged period of time. Such travellers may choose to reserve chemoprophylaxis for high-risk areas and seasons only. However, they should continue to take measures to protect against mosquito bites and be prepared for an attack of malaria: they should always carry a course of antimalarial medicines for SBET, seek immediate medical care in case of fever, and initiate SBET if prompt medical help is not available.

In addition, SBET – combined with protection against mosquito bites – may be indicated for those who travel for one week or more to remote rural areas where there is multiresistant malaria but a very low risk of infection, and the risk of side-effects of chemoprophylaxis may outweigh that of contracting malaria. This may be the case in certain border areas of Thailand and neighbouring countries in south-east Asia, as well as parts of the Amazon basin.

Successful SBET depends essentially on travellers' behaviour, and health advisers need to take time to explain the strategy. Travellers provided with SBET should be given clear and precise written instructions on the recognition of symptoms, when and how to take the treatment, possible side-effects, and the possibility of medicine failure. Travellers should realize that self-treatment is a first-aid measure, and that they should still seek medical advice as soon as possible.

In general, travellers carrying SBET should observe the following guidance:

▶ Consult a clinician immediately if fever occurs one week or more after entering an area with malaria risk.

▶ If it is impossible to consult a physician and/or establish a diagnosis within 24h of the onset of fever, start the SBET and seek medical care as soon as possible for complete evaluation and to exclude other serious causes of fever.

▶ Do not treat suspected malaria with the same medicines used for prophylaxis.

▶ Vomiting of antimalarial medicines is less likely if fever is first lowered with antipyretics.

▶ A second full dose should be taken if vomiting occurs within 30 min of taking the medicine. If vomiting occurs 30–60min after a dose, an additional half-dose should be taken. Vomiting with diarrhoea may lead to treatment failure because of poor medicine absorption.

▶ Complete the stand-by treatment course and resume antimalaria prophylaxis one week after the first treatment dose. To reduce the risk of medicine interactions, at least 12h should elapse between the last treatment dose of quinine and resumption of mefloquine prophylaxis.

The medicine options for SBET are in principle the same as for treatment of uncomplicated malaria. The choice will depend on the type of malaria in the area visited and the chemo-prophylaxis regimen taken.

9.3 Case study

PATIENT A

The place: A city where there is no *P. falciparum* malaria transmission.

The patient: A woman aged 24 years who made a 2-month visit to a part of the country where malaria is endemic. For malaria prophylaxis she took mefloquine (250mg weekly), but discontinued this on return to the city. Twelve days later she felt tired and had a mild headache. The following evening she became febrile and began to vomit. Her general practitioner referred her to hospital. On examination, she was febrile with a temperature of 39.5ºC. There were no other abnormalities. Thick and thin blood films showed *P. falciparum* trophozoites with 20% parasitized erythrocytes. Quinine was immediately started by intravenous route (loading dose of quinine 20mg salt/kg given in 4 hours, followed by 10mg salt/kg every 8 hours for a total of 10 days) to attempt a rapid reduction of the parasitaemia. During the second infusion a nurse reported that the patient could not communicate. On examination, she was conscious with open eyes but unable to speak. There was no spontaneous movement of her limbs but reflexes were normal. There was no neck stiffness or retinal haemorrhage.

Question 1

What is the neurological lesion?

Question 2

What important investigations should be carried out immediately?

Question 3

Is it possible that a person who has mefloquine prophylaxis may develop malaria?

Question 4

Should dexamethasone be used in this patient? Justify your answer.

LEARNING UNIT **10**

National antimalarial treatment policy

Learning Objectives:
by the end, participants should be able to...

● **Define "antimalarial treatment policy" (ATP)**
● **List the purposes of the ATP**
● **List the components of the ATP**
● **Describe how an ATP is formulated, monitored and updated**
● **Describe how the ATP utilizes available systems for quality control and quality assurance of antimalarial medicines**

10.1   Antimalarial treatment policy

10.1.1   Definition of antimalarial treatment policy (ATP)

The ATP is a set of recommendations and regulations concerning antimalarial medicines and their utilization in the country. This policy is continuously evaluated, reviewed and updated whenever appropriate by the national malaria control programme.

10.1.2   Purpose of the ATP

The purpose of the ATP is to ensure the efficient use of the available resources to maximize the reduction in mortality and morbidity due to malaria.

The specific objectives of an ATP are to:

▶ provide rapid and long-lasting cure for malaria patients;

▶ reduce morbidity, including malaria-related anaemia;

▶ prevent the progression of uncomplicated malaria to severe and potentially fatal disease;

▶ reduce the transmission of the infection and infectious reservoir;

▶ minimize the emergence and spread of resistance to antimalarial medicine.

10.1.3   Information in an ATP document

A well-written ATP will usually contain information on:

▶ decision on whether a sick patient requires antimalarial treatment;

▶ recommended treatment for uncomplicated and for severe malaria;

▶ chemoprophylaxis for various risk groups;

▶ criteria for review of antimalarial treatment policy;

▶ regulation and deployment of antimalarial medicines.

10.1.4   Preparation of a national ATP

The available information on malaria parasite medicine resistance in the country and on the currently recommended medicines and their roles in malaria management is considered.

The antimalarial medicines are then selected using the criteria below:

▶ efficacy and proven effectiveness against prevalent malaria species;

▶ safety;

▶ simplicity of dosage;

▶ cost effectiveness; and

▶ acceptability for consumers and prescribers.

10.1.5   Criteria for changing an ATP

The main determinant of policy change is the therapeutic efficacy and the consequent effectiveness of the antimalarial in use. Other important determinants are changing patterns of malaria-associated morbidity and mortality; consumer and provider dissatisfaction with current policy; and the availability of new products, strategies and approaches.

In therapeutic efficacy assessments, the cure rate should be defined parasitologically, based on a minimum of 28 days of follow-up. Molecular genotyping using PCR technology should be used to distinguish recrudescent parasites from newly acquired infections. It is currently recommended that a review and change of the antimalarial treatment policy should be initiated

when the cure rate with the current recommended medicine falls below 90% (as assessed through monitoring of therapeutic efficacy). However, a decision to change may be influenced by a number of factors, including the prevalence and geographical distribution of reported treatment failures, health service provider and/or patient dissatisfaction with the treatment, the political and economical context, and the availability of affordable alternatives to the commonly used medicine. A new recommended antimalarial medicine adopted as policy should have an average cure rate ≥95% as assessed in clinical trials.

10.1.6   Monitoring the ATP

It is necessary to maintain continued monitoring of the efficacy of the present therapy and alternatives, preferably at the sites used for initial testing. The availability, acceptability and affordability of effective medicines to the consumer should also be monitored. Through social research methods, ranging from focus groups to interviews, information can be obtained on consumers' use of antimalarial medicines, health-seeking behaviour, incentives for making their choice of therapy and compliance with recommendations. The opinion of providers and adherence to the policy and quality of care should also be followed up. The impact of any possible change in policy also needs to be assessed using appropriate indicators in order to assist national policy-makers to review the policy.

10.2   Pharmacovigilance

Appropriate surveillance systems should be set up for monitoring adverse medicine reactions. Such a system should take into account that adverse effects and tolerance of the medicine may compromise disease management by altering the provider and consumer confidence and adherence. In addition, the proportion of severe and life-threatening events may influence whether the medicine is appropriate for first-line therapy.

Rare adverse effects, which may be serious, are unlikely to be detected during clinical trials. Detection of rare effects requires pharmacovigilance systems operating in settings where the medicine is widely used in the population. There are few data from prospective phase IV post-marketing studies on rare, but potentially serious, adverse effects of antimalarials.

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The safety profiles of the artemisinin derivatives, mefloquine, and sulphadoxine-pyrimethamine are supported by an adequate evidence base, mainly from large clinical trials. Neurotoxicity observed in animals treated with artemisinin derivatives prompted large-scale prospective assessments in humans, but no evidence of neurotoxicity has been found.

More data are needed on the newer medicines. There is also an urgent need to obtain more information on the safety profiles of antimalarials, in particular the ACTs, in pregnant women.

WHO recommends that countries or regions should consider establishing pharmacovigilance systems if these are not already in place.

10.3   Quality assurance of malaria diagnosis and antimalarial medicines

10.3.1   Microscopy

Traditional microscopy is most reliable in an expert's hands, but it is much less sensitive and precise in routine practice, due to errors in collection, processing or examination of slides, interpretation and reporting. The sources of errors are many and depend on the competence of laboratory technicians, physical limitations in the workplace, the quality of supplies, the condition of microscopes and the workload.

Quality assurance programmes for traditional microscopy, developed in the 1950s and 1960s, emphasized validation by the re-checking of slides by expert or senior microscopists. The main activity was re-examination of all positive slides and a random sample (10%) of negative ones. Less importance was accorded to species identification, and there was no emphasis on quantification. In some settings, cross-checking is blinded, and feedback, if sent, refers only to discrepancies in positivity and species identification, not to the quality of slide processing. Routine systems do not provide for continuous monitoring of individual technicians and laboratories.

While competency testing is the main method for assessing technicians, it is used in only a few settings. Validation of slides read is commoner and allows for monitoring of performance over time and detection of additional problems, such as poor staining, poor slide preparation, inadequate supplies and equipment and other factors affecting performance in malaria microscopy. The currently recommended practical method is regular evaluation of the proportion of agreement between first reading and expert re-examination of at least 10 slides per month (5 randomly selected positive slides and 5 randomly selected negative slides). These numbers are manageable in most settings, and validators can cope with the workload.

Poor performance detected by slide cross-checking can be remedied by a variety of strategies, such as retraining, regular consultative visits and improving supplies and equipment, depending on the type of problem identified. Continuous monitoring and evaluation of individual laboratories and technicians should be established by means of a supervisory checklist. The quality of microscopes, the quality of reagents and training of staff in quality assurance in central and peripheral laboratories should be assured at national or subnational level. Technicians should be trained to detect malfunctioning microscopes and to use simple methods for maintenance, should also be able to recognize errors in processing slides and know how to prevent them.

A quality assurance system requires a national reference laboratory or centre for setting standard operating procedures and providing training and reference materials, including slide banks with reference slides and a competent workforce of senior microscopists and trainers. A functional quality assurance system requires adequate investment, which may be offset by improved cost–effectiveness of malaria diagnosis and improved confidence of health workers in the results of microscopy.

10.3.2 Rapid diagnostic tests

Antigen-detecting rapid diagnostic tests (RDTs) are important for parasitological confirmation of a diagnosis of malaria when microscopy is not available. Many tests are sold commercially, but most can be used to detect only *P. falciparum* antigens (histidine-rich protein 2 [HRP-2] and plasmodium lactate dehydrogenase) or a combination of *P. falciparum* antigens (HRP-2) and antigens of other parasite species (pLDHPv, pLDHPvom) or common to all parasite species (pLDHPan and aldolase).

Rapid diagnostic tests are affected by various conditions of manufacture, storage and use, which can impair their accuracy and reliability. They are also subject to degradation by heat and moisture, and most manufacturers specify storage at 4–30°C. The tests should be stored centrally, in air-conditioned facilities when possible. Storage in the field should be under similar conditions to those used for medicines. Transport in the sun in non-air-conditioned vehicles and the length of storage at high temperatures should be minimized.

Quality assurance must become an integral part of the budgets and implementation plans for use of RDTs. The aim is to ensure the accuracy of the tests in the hands of the end-users. Quality assurance includes monitoring the technical standard of the tests, pre-purchase or post-purchase testing of a sample of tests, training and supervision of users and control of storage and transport to minimize unfavourable environmental effects.

Health workers should know how to manage negative results, as RDTs are not infallible, even when prepared and interpreted correctly. A clinical algorithm should be designed for treatment of patients with negative results but who have symptoms of severe malaria, while other causes of illnesses are being investigated.

In order to assess the quality of RDTs that have had typical storage and distribution in remote areas, the results should be compared with those of microscopy at a few sentinel sites, with slides stained on site and checked centrally. The person in charge of quality assurance should also be in charge of monitoring results.

The preparation and interpretation of RDTs by health workers should be monitored three to six months after training, and remedial training should be given as required. During supervisory visits, interpretation of a set of prepared RDTs should be re-tested, and the preparation technique should be assessed; diagnosis and treatment records should be reviewed.

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10.3.3 Antimalarial medicines

Quality assurance generally includes all activities and responsibilities required to ensure that pharmaceutical products meet quality specifications in their final dosage form. Good manufacturing practice is an aspect of quality assurance that ensures that products are consistently produced and controlled to the standards appropriate to their use and to the standards required by the medicine regulatory authority. The main aim of good manufacturing practice is to diminish the risk, inherent in any pharmaceutical production, of unexpected cross-contamination, incorrect labelling or human error. WHO has consolidated the good manufacturing practices of various countries into standardized procedures, applicable to all manufacturers.

Quality control is the part of good manufacturing practice that addresses operations and decisions about the quality of a product. In particular, quality control involves sampling, specifications, testing and documentation and procedures to ensure that the necessary tests are carried out, and that products are not released for use, sale or supply until their quality has been judged to be satisfactory.

Samples for quality control should be collected as close to the end-user as possible and sent for analysis to well-recognized reference laboratories at national or regional level. A two-level system of testing can be used, with basic testing at sentinel sites at the periphery, and the referral of 100% of failed or doubtful samples and 5–10% of passed samples to the national reference laboratory for verification.

Simple test methods are available for quality assurance of pharmaceuticals under field conditions, for rapid detection of counterfeit and substandard pharmaceuticals. Some are commercially available and assembled in self-contained kits in suitcases. These systems allow basic quality control of selected essential medicines, including artemether and artesunate, with sufficient supplies to run 1000–3000 tests. Testing includes both physical testing (visual inspection and tablet or capsule disintegration test) for rapid identification of counterfeits and preliminary assessment of medicine solubility and availability, and chemical analysis (simplified colour reactions and semiquantitative thin-layer chromatography tests) for rapid checking of a medicine's identity and for semiquantitative analysis of the amount of active pharmaceutical ingredient present.

10.4   Group work

Work in three groups (A, B, C) and discuss the following questions.

Group A
1. Discuss the antimalarial drugs used at each level of health care in your country or at your place of work.
2. Compare and contrast the antimalarial treatment policies in your countries or work places.
3. Discuss the steps leading to change of antimalarial treatment policy.

Group B
Outline the process and challenges involved in the introduction of the new treatment policy in your country or place of work.

Group C
Discuss the implementation of the new antimalarial drug treatment policy in your country or place of work.

LEARNING UNIT **11**

Routine surveillance and operational research in case management

Learning Objectives:
by the end, participants should be able to...

- **Describe the role of evidence-based decisions in malaria case management**
- **Describe the systems for routine surveillance for evidence gathering**
- **Demonstrate an understanding of therapeutic efficacy trials of antimalarial medicines**
- **Describe the principles of operational research**
- **Identify operational research issues related to malaria case management**

11.1 Role of evidence-based decisions in malaria case management

The appropriate use of evidence is now one of the core strategies for malaria control. For the formulation of malaria treatment guidelines and protocols, it is important that relevant evidence is gathered in a systematic and reliable way. Systematic review of evidence was the basis for the development of the *WHO Guidelines for the Treatment of Malaria*; these guidelines are reviewed periodically as new evidence emerges.

In using the guidelines for decision-making it is important to take account of the strength or quality of the evidence. In general terms the evidence may be derived from *(i)* formal systematic reviews *(ii)* randomized control trials *(iii)* observational studies, and where none of these is available, *(iv)* consensus of expert opinions.

Wherever possible, systematic reviews of randomized control trials that directly compare two antimalarial treatment alternatives in large populations should be used as the basis for recommendations. Such evidence does not exist for all treatment options, but recommendations on these options still need to be made. Other information, including studies measuring cure rates but not directly comparing treatments, pharmacological assessments and surveillance data on resistance patterns could also be considered.

In addition to the systematic review of evidence, other issues that may guide decision-making concerning antimalarial interventions include individual or population perspective of benefits and harms, and cost-effectiveness.

11.2 The systems for routine surveillance for evidence gathering

A reliable malaria surveillance system provides data in a manner that is representative of changes within a given population. This often involves the use of sentinel sites which allow for consistent longitudinal data gathering and documentation of trends. At the start a core group of monitoring and evaluation experts (from the national malaria control programme, ministry of health, universities and national reference laboratory) should be established to coordinate all activities including training, supervision, collection and analysis of data, and to forward recommendations to the treatment policy makers. The minimal requirements for establishing a sentinel site are the availability of trained and motivated clinical and laboratory personnel and a laboratory equipped for blood film examinations. Additionally there should be application of appropriate guidelines for management of malaria, and adequate record-keeping for monitoring the trend of response to antimalarial medicines. The scope of activities at a sentinel site would include:

► case management and monitoring of trends in morbidity and mortality (continuous);
► therapeutic efficacy monitoring of antimalarial medicines (annual or biennial):
  ▷ uncomplicated malaria: ACTs
► quality assessment of diagnostics and medicines;
► periodic testing of insecticide susceptibility ;
► pharmacovigilance activities;
► operational research.

11.2.1 Choice of a sentinel site

The following characteristics should be considered in setting up sentinel sites:
► local population density;
► accessibility to the site and feasibility of close supervision;
► malaria transmission intensity and seasonality;

▸ population mobility and migration;

▸ malaria treatment failures reported by the health information systems.

11.2.2 Therapeutic efficacy testing

The rapid spread of antimalarial drug resistance over the last few decades has increased the need for monitoring the efficacy of antimalarial medicines, in order to ensure proper management of clinical cases, to allow early detection of changing patterns of resistance, and to indicate where national malaria treatment policies should be revised.

Based on the current WHO protocol, the monitoring procedure includes in vivo testing (therapeutic efficacy testing) which involves the repeated assessment of parasitological outcomes of treatment during a fixed period of follow-up, in order to detect any reappearance of symptoms and signs of clinical malaria and/or parasites in the blood, which would indicate reduced parasite sensitivity to the particular medicine. Therapeutic efficacy testing follows a set of criteria for the selection of patients, the administration of a standard treatment regimen of the appropriate medicine, and clinical and parasitological examinations at the stipulated follow-up period (28 days for chloroquine, or longer periods for medicines with a long elimination half-life). The protocol is designed for use in the assessment of antimalarial medicines or medicine combinations used routinely for treatment of uncomplicated falciparum malaria (chloroquine, sulfadoxine-pyrimethamine, amodiaquine, artemisinin-based combination therapies and others). The methods and procedures for therapeutic efficacy testing including sample size calculations, screening evaluation, enrolment evaluation, informed consent procedures, treatment, evaluation of patient follow-up, definition of study end-points and determination of study outcomes are detailed and explained in Annex 2.

11.3 Group work

Work in three groups (A, B, C) and discuss the following questions.

Group A
How is malaria being treated in your country or place of work?

Group B
What is the malaria disease burden in your country or place of work?

Group C
What operational research in malaria case management is done in your country or place of work?

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LEARNING UNIT **12**

Programmatic aspects of case management

learning objectives:
by the end, participants should be able to...

- Describe the policies and procedures for the procurement of antimalarial commodities
- Discuss medicine management in the context of a malaria control programme
- Discuss partnership coordination and role of the private sector in malaria case management
- Describe the use of health information systems and reporting in malaria case management

12.1 Procurement of antimalarial commodities

It is important to classify malaria illness into uncomplicated and severe malaria, and to identify the population at risk and the needs for prevention of malaria, in order to determine which commodities are needed to manage each situation. Sufficient quantities of commodities are needed at different levels of health care – community/home, primary care facility, district/zone and higher referral facilities.

Annex 3 details quantification of required antimalarial commodities (medicines and diagnostics) using morbidity methods as well as medicine management information systems in health facilities.

At community level only the oral first-line antimalarial medicine (as per national antimalarial treatment policy) is required.

At first level primary care facilities additional injection or rectal preparations are needed to provide pre-referral treatment in more serious cases. RDTs for parasitological diagnosis and blood slide preparation for dispatch to a higher level are also needed at the primary care level.

At the secondary (district) health facility, oral medicines, injection medicines, supportive treatment, blood slides, RDT kits and other basic laboratory tests should be available to manage severe malaria.

A tertiary referral health facility should also have supplies to manage the serious complications of severe malaria.

12.1.1   Supplies for malaria case management

The supplies needed for malaria case management include:

- ► oral and parenteral antimalarial medicines according to national policy;
- ► supportive medicines such as paracetamol, medicines to treat complications, e.g. 50% dextrose solution, and medicines to treat intercurrent infections, particularly antibiotics;
- ► consumables like syringes, intravenous cannulae, IV fluid/blood perfusion sets;
- ► reagents, slides, microscopes for blood slide microscopy, RDT kits;
- ► equipment and reagents to determine levels of blood glucose, urea and electrolytes, to analyse cerebrospinal fluid, and for blood cultures.

The quantity of medicines needed is estimated, and any undue variation in requirement forecasted. The consumption data for different age groups by weight, and special categories like pregnant women, should be determined. Some categories of medicines, e.g. artemether-lumefantrine, are packaged according to body weight/age.

12.1.2   Responsibility of the programme manager for drug management

Drug management and supply requires team work. The programme manager needs to work with pharmacy staff to ensure that accurate amounts of medicines are procured on time. The medicines must be transported and stored in a secure place with correct temperature, humidity and special environment for specified medicines. The regulations governing the storage and administration of medicines must be known and applied.

12.1.3   Distribution of antimalarial commodities

The flow of medicines is monitored by recording in stock cards or stock books. This information can also be stored electronically. The amount to be procured is determined on the basis of the stocks. There is a hierarchy for the level of storage of medicines from the national level through levels of sub-national stores to the primary care level. Medicines may be distributed from the central national store to lower levels by the PUSH method, or ordered from lower levels according to local need by the PULL method.

To avoid medicines expiring inadvertently, the strategy 'First In First Out' and 'First Expiring First Out' should be applied. Each health facility is expected to produce a stock status report and submit it to the higher pharmacy services level. A minimum re-order quantity 'buffer stock' should be determined and maintained.

Similar principles are applied in maintaining the supply chain for other supplies such as laboratory reagents and other items. The cost of procurement, distribution and storage of commodities should be determined and budgeted.

12.2 Partnership coordination and role of the private sector

In many countries up to 60% of the population seeks treatment for malaria from the private sector. Private sector facilities are those which are not owned and run directly by government departments; they include hospitals, surgeries, pharmacies, medicine stores, laboratories and others.

National malaria control programmes can usefully interact with the private sector for the benefit of the overall effort to improve malaria case management. In particular, the national malaria programme should take the initiative in the following areas for cooperation:

▶ collaborating with private sector to ensure that national policies such as antimalarial treatment polices are followed nationally by all providers;

▶ supporting the private sector to increase population access to appropriate treatment for malaria;

▶ facilitating the access of private sector providers to cost-effective medicines;

▶ obtaining malaria-related data from the private sector for accurate effective national planning;

▶ ensuring that the medicines used in both the private and public sectors are of high quality.

12.3 Health system utilization and integration of malaria with other programmes

Interaction of national malaria control programmes with other national programmes is important for addressing malaria-related cross-cutting issues and for making best use of human and other resources.

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Following are some of the other relevant programmes:

▶ Integrated Management of Childhood Illness

▶ Reproductive Health/Safe Motherhood

▶ Child and Adolescent Health

▶ Expanded Programme on Immunization

▶ Health Information

In many settings, particularly at lower health facility levels, the same health workers are the implementers of all of these programmes. Consequently, it is extremely important to ensure the integration of the following activities:

▶ training of health workers;

▶ conducting supervision visits and compiling site reports;

▶ transportation for field work;

▶ integration of malaria activities with other programmes, e.g. administration of antimalarial medicines for IPT in pregnancy during ANC visits.

12.4   Use of health information system and reporting

The malaria data that needs to be collected includes:

▶ morbidity data – the number of cases seen in the health facility;

▶ mortality data – total deaths and case fatality rates;

▶ utilization of health facilities – numbers for each group of users.

The data has to be classified into age groups such as < 5 year-old children, 15–49 year-old women, and other adults. The collected data should be timely, complete, analysed and reported to those who use it. Annex 4 summarizes the current indicators relevant for malaria case management.

The advantages to be derived from the data include:

▶ epidemics can be diagnosed and managed promptly;

▶ more accurate determination of the quantities of supplies required is possible;

▶ health system strengths and weaknesses are identified, and weaknesses can be rectified.

The information collected can be used in monitoring and evaluation of the malaria control programme. The malaria control programme should coordinate with the private sector, nongovernmental organizations, the pertinent United Nations agencies and other international agencies, to compile an all-inclusive case management data base.

12.5   Group work

Work in three groups (A, B, C) and discuss the following questions.

Group A

Explain the logistics, practices and cycle of procurement of malaria commodities in your country or place of work.

Group B

This group should discuss resource mobilization, partnership coordination, and the role of the private sector in malaria control programmes.

Group C

This group should discuss the use of health information systems and reporting.

ANNEX 1
Coma scales

Table An 1.1 The Glasgow coma scale (for adults)

Parameter	Response	Score
Eyes opens	spontaneously	4
	to speech	3
	to pain	2
	never	1
Best verbal response	orientated	5
	confused	4
	inappropriate words	3
	incomprehensible sounds	2
	none	1
Best motor response	obeys commands	6
	localizes pain	5
	withdrawal from pain	4
	flexion to pain	3
	extension to pain	2
	none	1
	Total score	**3–15**

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

Table An 1.2. The Blantyre coma scale (for children)

Parameter	Response	Score
Best motor response	localizes painful stimulus[a]	2
	withdraws limb from pain[b]	1
	nonspecific or absent response	0
Best verbal response	appropriate cry	2
	moan or inappropriate cry	1
	none	0
Eye movements	directed (e.g. follows mother's face)	1
	not directed	0
	Total score	**0–5**

A state of unrousable coma is reached at a score of < 3. This scale can be used repeatedly to assess improvement or deterioration.

[a] Rub knuckles on patient's sternum.

[b] Firm pressure on thumbnail bed with horizontal pencil.

ANNEX 2
Procedures involved in therapeutic efficacy study

The therapeutic efficacy study protocol is designed for use in the assessment of antimalarial medicines or medicine combinations used routinely for treatment of uncomplicated falciparum malaria. It comprises a series of activities, including sample size calculations, screening evaluation, enrolment evaluation, informed consent procedures, directly observed treatment, evaluation of patients during follow up, definition of study end-points and determination of study outcomes. These study methods and procedures are described below.

A2.1 Sample size considerations

The required sample size is defined as the total number of patients who can be assigned a clinical outcome at the end of the study (i.e. adequate clinical and parasitological response or failure due to recrudescence, after confirmation with PCR correction). After the initial sample size calculation, an additional 20% should be added to account for patients who are likely to be either lost during follow-up, withdraw or are excluded after detection of reinfection, with PCR correction[1].

For single-arm efficacy studies, which were recommended by the Technical Expert Group on Malaria Chemotherapy in 2008, sample size should be determined using classical statistical methods. The calculation is based on an expected proportion of treatment failures in the study population and the desired levels of confidence (95%) and precision (5%). For example, in the case of a medicine with an expected failure rate of 5%, a confidence level of 95% and a precision level of 5%, a minimum of 73 patients should be enrolled. An additional 20% should be added for the reasons outlined above. If the treatment failure rate is unknown, a clinical failure rate of 50% should be assumed. In order for the study to be representative, a minimum sample of 50 patients is required, regardless of the rates of failure. Several statistical software packages are available that facilitate the calculation of sample sizes for clinical trials.

Details on sample size calculation for comparative, randomized studies of two or more antimalarial agents are described in the protocol.

A2.2 Screening evaluation

A rapid screening procedure should be used in an outpatient setting to identify patients who may meet enrolment criteria. The exact procedures used, the clinical and laboratory evaluations performed, and the sequence in which they are done during screening may vary from site to site. The typical screening data set includes age, sex, temperature, and body weight and height. If the local situation, available resources, and capacity of the outpatient unit permit, initial blood slide examination and haemoglobin concentration (or haematocrit) can be performed on all patients

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[8.] Stepniewska K, White NJ (2006). Some considerations in the design and interpretation of anti-malarial drug trials in uncomplicated falciparum malaria. *Malaria Journal,* 5:127.

during the screening procedure. Alternatively, these tests can be limited to febrile patients. If possible, a record book should be kept in which all cases screened are entered, with information on age, sex, address, temperature, blood film, and, if applicable, reason for exclusion from study. This information can be very useful for data interpretation and can provide clues about the rate of transmission.

A2.3 Initial clinical evaluation/enrolment evaluation

All patients meeting the basic enrolment criteria during the screening procedure should be evaluated in greater depth by clinical staff. Special care should be taken to detect the presence or early signs of febrile diseases other than malaria, as these will probably necessitate exclusion of the patient from the evaluation. Among paediatric populations, the most frequent confounding condition is lower respiratory tract infections: cough or difficult breathing, together with fast breathing, is an indicator for identifying and excluding patients suffering from such conditions. Fast breathing is defined as a respiratory frequency ≥ 50/minute in infants < 12 months of age and ≥ 40/minute in children aged 12–59 months. Other relatively common febrile conditions are otitis media, tonsillitis, measles and abscesses. Patients with these conditions should not be enrolled, but obviously need to be treated both for malaria (if they have parasitaemia) and the other infection as appropriate. A case record form should be used to record the general information and clinical observations for each patient passed from screening into the study sent from screening. Particular care should be taken to record detailed instructions on how to find the patient's home to ensure that follow-up at home is possible should the patient fail to return to the health facility for scheduled visits.

A2.4 Informed consent

Formal informed consent must be obtained from all patients meeting the enrolment criteria. The procedure for obtaining consent should conform to international and local guidelines for research on human subjects. The study should be fully explained to patients or parents/guardians, including potential benefits and risks.

A2.5 Treatment

Patients meeting all enrolment criteria should receive treatment only after they have had the study fully explained to them and have willingly provided their informed consent. All antimalarial treatment should be given by study team members under observation using established treatment regimens for the medicine under assessment. If more than one treatment is being studied, patients meeting all enrolment criteria should be randomly assigned to their treatment arm. Although this protocol is not intended to be a comparative clinical trial, such randomization is highly recommended. Randomization is best achieved, and more likely to avoid introduced bias, by strictly following a computer-generated randomization list, although other methods (e.g. coin toss) have been used.

Enrolled patients should be observed for at least 30 minutes after treatment to ensure that they do not vomit the medicine. If vomiting occurs within 30 minutes of treatment, the full treatment

dose should be repeated. Ancillary treatments, such as antipyretics, may be required and should be provided to patients by the study team. Patients with persistent vomiting (i.e. necessitating more than a single repeat dose) should be excluded from the study and immediately referred to the health facility staff for appropriate management.

Once the complete enrolment and treatment procedure is finished, the patient should be given a schedule for routine follow-up visits. It is also important to ensure that the patient (or patient's parent or guardian) knows that, if symptoms return at any time during the follow-up period, he or she should return immediately to the assessment team for re-evaluation, even if it is not a regularly scheduled follow-up day.

Due to the need for supervising treatment on an outpatient basis, the therapeutic efficacy test system is suitable for all medicines requiring a single dose administration or daily dosing for up to three days. As the therapeutic efficacy test relates to the treatment of non-complicated, non-severe falciparum malaria, it involves only the oral administration of medicines

A2.6 Recommended duration of follow-up

Studies of directly observed treatment for uncomplicated malaria are prospective evaluations of clinical and parasitological responses on days 0, 1, 2, 3, 7, 14, 21 and 28 (35 and 42). The day the patient is enrolled and receives the first dose of medicine is traditionally day 0. Follow-up for 28 days is recommended as the minimum duration for medicines with elimination half-lives of less than 7 days (amodiaquine, artemisinin derivatives, atovaquone-proguanil, chloroquine, halofantrine, lumefantrine, quinine and sulfadoxine-pyrimethamine). Patients should always be advised to return on any day during the follow-up period if symptoms return and not to wait for scheduled visit day. Blood films for parasite count should be obtained and examined on scheduled days or on any other day the patient spontaneously returns.

For medicines with longer elimination half-lives (mefloquine, piperaquine), longer follow-up periods are necessary. Although a follow-up period of 42 days is optimal for most medicines, long periods of follow-up for routine monitoring might not always be feasible for national malaria control programmes. Lengthy study duration increases the risk that more patients will be lost to follow-up, reducing the study's validity and subsequently its sensitivity to reveal the true level of failure. Thus, as a compromise, a 28-day follow-up is recommended as the minimum standard to allow national malaria control programmes to capture most failures with most medicines, except mefloquine and piperaquine, for which the minimum follow-up should be 42 days[9].

Studies of 28 days or longer duration risk loss to follow-up and should be accompanied by molecular assessments (PCR genotyping) to distinguish recrudescence from reinfection. Assessment over only 14 days, the period previously recommended in areas of high transmission, is no longer considered sufficient. If surveillance programmes do not have access to molecular techniques, studies of 14 days duration without PCR adjustments can still provide useful information on failing medicines (i.e. to justify their replacement) – but they cannot be used to justify inclusion or continued recommendation. In areas of low to moderate transmission,

[9]. Stepniewska K et al. (2004). *In vivo assessment of drug efficacy against Plasmodium falciparum malaria: duration of follow-up. Antimicrobial Agents and Chemotherapy,* 48:4271–4280.

the use of molecular methods is recommended, but is not strictly essential if the likelihood of reinfection is relatively small. PCR genotyping involves comparison of polymorphic parasite genes, usually those encoding variable blocks within PfMSP2, and also sometimes PfMSP1 and PfGLURP, in whole blood samples taken during the acute and recurrent infections.

Antimalarial treatment should also be assessed on the basis of parasitological cure rates. Where possible, blood or plasma levels of the antimalarial should also be measured in prospective assessments so that medicine resistance can be distinguished from treatment failures due to pharmacokinetic reasons.

A2.7 Follow-up schedule

The day when the patient is enrolled and receives the first dose of medicine is traditionally designated Day 0. Thereafter, the schedule calls for clinical reassessments to be made on Days 1, 2, 3 and 7, then weekly for the remainder of the follow-up period i.e. on Days 14, 21 and 28 (35, 42). Patients should always be advised to return on any day during the follow-up period if symptoms return and not to wait for scheduled visit day. Blood films for parasite count should be obtained and examined on Days 2, 3, 7, 21 and 28 (35, 42) or on any other day if the patient spontaneously returns.

Additionally, blood films should be obtained whenever parasitological reassessment is requested by the clinical staff for reasons of patient safety. Study patients should be closely monitored in order to minimize risk. Haemoglobin status is typically reassessed on Day 14 and Day 28 and every 7 days thereafter until study completion. Because many medicines require multiple day dosing, the initial visits are critical not only for the efficacy assessment but also for patient safety; defaulters at this stage will not have received a complete course of treatment and may be at risk. The ultimate success of the study rests on minimizing loss to follow-up.

While patients can be encouraged to return on their own for scheduled follow-up visits, it is essential that provisions be made ahead of time for locating patients at home if they do not attend as requested. This requires obtaining very detailed directions to the home during enrolment and study team members familiar with the community who can be responsible for home visits. The schedule for treatment and follow-up examination must be followed rigorously to ensure integrity of the data. Patients who fail to appear on Day 1 and Day 2 and miss one dose of the treatment are withdrawn from the study definitively. After Day 3, patients who fail to appear on Day 7 but present on Day 8 {likewise Days 14/15, Days 21/ 22, and Days 28/29 (35/36, 42/43)} may still be included in the study group. Deviation from the protocol of more than 1 day cannot be allowed, both for the safety of the patient and for the relevance of the data.

A2.8 Rescue treatment

Rescue treatment is defined as a second-line treatment that is given to a study patient when a treatment failure has been identified. The choice of this treatment depends on the medicine under assessment: ideally, the rescue treatment would use a medicine that has an established efficacy and safety record in the case of infections resistant to the treatment under assessment and that may or may not be the officially recommended second-line malaria treatment in the

country in question. Patients experiencing severe deterioration in clinical status during the study should be referred immediately for appropriate inpatient care. However, most study patients should not develop severe illness – in fact, the study design aims to provide sufficiently close patient monitoring to allow for intervention before severe illness can develop.

A2.9 Data analysis

Computer-based applications have been prepared by WHO to provide assistance in all aspects of data management and analysis[10].

The Kaplan-Meier method is preferred for statistical analysis of data on medicine efficacy. The advantage of survival analysis is that it takes into account data on patients who were lost to follow-up or withdrawn from the study, in particular patients with reinfection. All the baseline and follow-up data collected on a patient until the day of censoring—the last day the patient was observed and was not classified as a failure—can be included in the analysis, even for patients who do not complete the study. This method also allows for calculation of mean time to failure and gives a reasonably unbiased estimate of failure rates. Although Kaplan-Meier analyses can be done manually, use of a computer programme to perform the calculations facilitates the analysis and reduces the possibility of errors.

The usual per-protocol method can be used in parallel. In the per-protocol method, all patients who cannot be evaluated (i.e. those withdrawn, lost to follow-up or reinfected as confirmed by PCR) are removed from the numerator and the denominator. For comparisons with previous studies, results from both types of analyses, Kaplan-Meier and per-protocol, can be reported.

A2.10 Definition of study end-points

Valid study end-points include treatment failure (early treatment failure, late clinical failure, late parasitological failure), completion of follow-up without treatment failure (adequate clinical and parasitological response), loss to follow-up, withdrawal from the study and protocol violation.

Results should be expressed as the proportion of adequate clinical and parasitological response (or proportion of early treatment failure, late clinical failure or late parasitological failure) before and after adjustment by PCR. Importantly, even if follow-up periods longer than 28 days are required, the results at day 28 should always be reported in addition to the failure rate at day 42.

It is recommended that studies that include patient follow-up periods longer than 14 days use molecular techniques to differentiate recrudescences from reinfections. While most of these infections may in fact be reinfections, two issues make their appropriate classification problematic. First, the usual PCR techniques used for this purpose are insufficiently sensitive to pick up minority populations of parasites present at Day 0. It is therefore possible that "new" parasites identified during follow-up actually represent recrudescence of parasites from a resistant minority population that was present from the start rather than true reinfections. Second, once a reappearance of parasites has been identified, the patient would receive rescue

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[10.] WHO (2009). *Methods for surveillance of antimalarial drug efficacy.* World Health Organization, Geneva, http://www.who.int/malaria/publications/atoz/9789241597531/en/index.html

treatment (in areas of high transmission, this would occur only when in combination with fever; in areas of low to moderate transmission, it would occur regardless of presence of fever). Provision of additional treatment at this point would make further interpretation of follow-up for that patient impossible and potentially "mask" a true treatment failure. In other words, there is a possibility, albeit relatively small, that a recrudescence might have occurred at a later point during follow-up in a patient experiencing, and being treated for, a reinfection. In either case, classification of all of these reinfections as treatment successes would lead to underestimation of true failure rates. Classifying all reinfections as treatment failures would lead to overestimation of true failure rates (and would render PCR unnecessary). For consistency, it is recommended that reinfections (as well as PCR unclassifiable results) be classified as protocol violations, as would be the case if the patient had self-treated during follow-up: the implications for bias are essentially the same in both circumstances.

Guidelines for calculating the cumulative success or failure rate or the proportion of adequate clinical and parasitological response or treatment failure on PCR-corrected results are provided below:

End-point for day X (X = 28 or 42)	Cumulative success or failure rate (Kaplan-Meier analysis)	Proportion (per-protocol analysis)
Adequate clinical and parasitological response at day X	Success	Success
Early treatment failure	Failure	Failure
Late clinical failure before day 7	Failure	Failure
Late clinical failure or late parasitological failure on or after day 7		
• falciparum recrudescence*	Failure	Failure
• falciparum reinfection*	Censored day of reinfection	Excluded from analysis
• other species with falciparum recrudescence	Failure	Failure
• other species with falciparum reinfection	Censored day of reinfection	Excluded from analysis
• other species infection	Censored day of infection	Excluded from analysis
• undetermined or missing PCR	Excluded from PCR-corrected analysis but included as failures for PCR-uncorrected analysis	Excluded from analysis
Loss to follow-up	Censored last day of follow-up according to timetable	Excluded from analysis
Withdrawal and protocol violation	Censored last day of follow-up according to timetable before withdrawal or protocol violation	Excluded from analysis

*As defined by WHO (2008b)[11]

For PCR-uncorrected results, all late clinical failures and late parasitological failures on or after day 7 are considered as failures.

[11.] WHO (2008b). *Methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations. Geneva,* World Health Organization. http://www.who.int/malaria/resistance.

A2.11 Methods of measurement and laboratory examinations

Physical examination

A standard physical examination will be performed at baseline (day 0 before dosing) and on days 1, 2, 3, 7, 14, 21, 28, (35 and 42). A complete medical history, demographic information and contact details will be taken at baseline.

Body weight

Body weight will be recorded on day 0 to the nearest kilogram on a Salter scale or on a hanging scale for young children. The scales will be properly calibrated. Patients should not wear excessive clothing while being weighed as this can overestimate their true weight. All young children should only wear undergarments while being weighed. The screening weight will be used to satisfy the inclusion or exclusion for nutrition status as well as to calculate the dose (number of tablets) to be administered. The reliability of the scales will be verified before the study begins and checked at regular intervals.

The circumference of the left mid-upper arm will be measured, at the mid-point between the elbow and the shoulder, and will be recorded to the nearest 0.2cm. Oedema will be assessed by thumb pressure for 3s on the dorsal surface of both feet.

Body temperature

Axillary (or oral, tympanic, or rectal) temperature will be measured at baseline (day 0 before dosing) and on days 1, 2, 3, 7, 14, 21, 28, (and day 35 and 42, if relevant). Temperature will be measured with a thermometer that has a precision of 0.1°C. Temperature will also be measured as clinically indicated. If the result is < 36.0°C, the measurement will be repeated. The same route should be used throughout the study.

The quality of the temperature-taking technique and the thermometers should be assessed regularly. Thermometers should be tested in a water-bath of known temperature before the study begins and at regular intervals thereafter.

Microscopic blood examination

Thick and thin blood films for parasite counts should be obtained and examined at screening on day 0 to confirm adherence to the inclusion and exclusion criteria. Thick blood films will be also examined on days 2, 3, 7, 14, 21, 28, (35 and 42) or on any other day if the patient returns spontaneously and parasitological reassessment is required. Specimens must be labelled anonymously (screening number or study number, day of follow-up, date).

A fresh Giemsa stain dilution should be prepared at least once a day and possibly more often, depending on the number of slides to be processed. Giemsa-stained thick and thin blood films are examined at a magnification of 1000x to identify the parasite species and to determine the parasite density.

Three blood slides per patient will be obtained: two thick blood smears and one thin blood smear. One slide will then be stained rapidly (10% Giemsa for 10–15min) for initial screening, while the others will be retained. If the patient is subsequently enrolled, the second slide will

be stained more carefully (e.g. 2.5–3% Giemsa for 45–60min), and slower staining will also be used for all slides obtained at follow-up visits. The study number of the patient, the date and the day of follow-up is recorded either on the frosted edge of the slide or on the glass with a permanent glass pen.

The thick blood smear for initial screening is used to count the numbers of asexual parasites and white blood cells in a limited number of microscopic fields. The adequate parasitaemia for enrolment is at least one parasite for every three white blood cells, corresponding to approximately 2000 asexual parasites per µl, for high transmission areas or at least one parasite for every six white blood cells, corresponding to approximately 1000 asexual parasites per µl, for low-to-moderate transmission areas.

The second blood smear is used to calculate the parasite density, by counting the number of asexual parasites in a set number of white blood cells (typically 200) with a hand tally counter. Once a field has been started, it must be counted to completion; the final number of white blood cells will therefore rarely be exactly 200. If more than 500 parasites have been counted before 200 white blood cells have been reached, the count will be stopped after the reading of the last field has been completed. Parasite density, expressed as the number of asexual parasites per µl of blood, will be calculated by dividing the number of asexual parasites by the number of white blood cells counted and then multiplying by an assumed white blood cell density (typically 6000–8000 per µl).

$$\text{Parasite density (per µl)} = \frac{\text{Number of parasites counted} \times (6000 - 8000)}{\text{Number of leukocytes counted}}$$

The same technique will be used to establish the parasite count on each subsequent blood film. When the number of asexual parasites is less than 100 per 200 white blood cells in follow-up smears, counting will be done against at least 500 white blood cells (i.e. to completion of the field in which the 500th white blood cell is counted). A blood slide will be considered negative when examination of 100 fields of thick film or 1000 white blood cells reveals no asexual parasites. The presence of gametocytes on an enrolment or follow-up slide should be noted, but this information will not contribute to basic evaluation.

In addition, 100 fields of the second thick film should be examined to exclude mixed infections; in case of any doubt, the thin film will be examined for confirmation. If examination of the thin film is not conclusive, the patient will be excluded from the analysis after complete treatment and follow-up.

Two qualified microscopists will read all the slides independently, and parasite densities will be calculated by averaging the two counts. Blood smears with discordant results (differences between the two microscopists in presence of parasite species diagnosed, or difference in parasite density of > 50%) will be re-examined by a third, independent microscopist, and parasite density will be calculated by averaging the two closest counts.

Haematological assessment (optional)

Haematological assessment should be done by measuring haematocrit or haemoglobin, when possible. Haematocrit can be measured by means of the microhaematocrit method. In healthy persons, the haematocrit (expressed as %) is roughly 3 times the haemoglobin concentration when the latter is expressed in grams per dl. This ratio is maintained in normocytic anaemia, but in most of the tropical forms of chronic anaemia the ratio is 3.3, denoting a hypochromic type of anaemia.

For valid comparisons between the Day 0, Day 14 and 28 (42), either haematocrit readings or the quantitative determination of haemoglobin levels are required. Enrolment requires a haemoglobin value above 5.0g/dl or a haematocrit above 15%.

Previous antimalarial medicine use (optional)

A history of previous antimalarial medicine use or the presence of antimalarial medicines in the urine or blood is not an exclusion criterion. However, the information on previous medicine use should be carefully collected and recorded for each patient. Screening of the urine for detection of antimalarial medicines is desirable since it may give an indication of current medicine use in the population, and this information can be used to stratify the results.

A history of adverse reactions to antimalarials or other medicines is vital medical information that should be marked with a red pen or a highlighter on the patient record form. While such reactions are rather rare and relatively mild with chloroquine, quinine and mefloquine, they may be life-threatening with medicines containing sulfonamides. In the case of a history of allergic reactions to medicines, the precise nature of which cannot be elucidated, it is advisable to exclude the patient from tests involving sulfonamides.

A2.12 Classification of the therapeutic response

The WHO standard protocol classifies outcomes of efficacy studies into the following four categories: early treatment failure, late clinical failure, late parasitological failure, and adequate clinical and parasitological response. These classifications rely on the presence or absence of fever or other signs of clinical malaria and presence of parasitaemia during the course of follow-up. These are defined as follows:

Classification of treatment outcomes in studies of antimalarial medicine efficacy in areas of low, moderate and intense transmission.

Treatment outcome	Symptoms and signs
Early treatment failure	Development of danger signs or severe malaria on days 1–3 in the presence of parasitaemia Parasitaemia on day 2 higher than the day 0 count irrespective of axillary temperature Parasitaemia on day 3 with axillary temperature ≥ 37.5°C Parasitaemia on day 3 that is ≥ 25% of count on day 0.
Late treatment failure	
Late clinical failure	Development of danger signs or severe malaria on any day between day 4 and day 28 (42) in the presence of parasitaemia in patients who did not previously meet any of the criteria of early treatment failure Presence of parasitaemia with axillary temperature ≥ 37.5°C (or history of fever) on any day from day 4 to day 28/42, in patients who did not previously meet any of the criteria of early treatment failure.
Late parasitological failure	Presence of parasitaemia on any day from day 7 to day 28 (42) and axillary temperature < 37.5°C in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure
Adequate clinical and parasitological response	Absence of parasitaemia on day 28 (42), irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure

A2.13 Interpretation of therapeutic efficacy study results

The test system aims at the assessment of the proportion of all treatment failures (early plus late treatment failures) in the sample of patients included in the study. The statistical procedure adapted for the interpretation of the results allows testing of the hypothesis that the proportion of treatment failures is above a certain level in the study area, and, therefore, a decision to change is deemed necessary. A high proportion of early treatment failures to the first-line antimalarial medicine is per se a strong indicator of the need for changing the first line treatment. In practice, in most situations the proportion of early treatment failures will not be unacceptably high; a full investigation with a 14 day follow-up period is needed to determine the extent of the problem.

The haematological response should be evaluated on a sample basis, not on an individual basis. Analysis of haemoglobin in individuals is important clinically, but does not indicate medicine resistance. The group of children with anaemia, i.e. with an initial haemoglobin of less than 8g/dl (or haematocrit of less 25%), should be re-evaluated on day 14. Experience has shown that in African children with anaemia, the average haemoglobin levels on day 14 will have improved by 1.5-2g/dl (or Ht by 56.5%) within 14 days of effective treatment. Haematological response can be analysed only if at least 30–40% of children have malaria-associated anaemia on Day 0.

In the past, "clinical" and "parasitological" cure rates were considered separately but with increasing appreciation of the adverse effects of treatment failure, the two are now considered together. Persistence of parasitaemia was not previously regarded as serious in high transmission settings. However, it represents a treatment failure and is associated with anaemia. It is now recommended that a change of first-line treatment should be initiated if the proportion of treatment failures (after correcting for reinfection using PCR) exceeds 10%.

ANNEX 3
Quantification of antimalarial commodities

A3.1   Quantification of medicine requirements

The quantities of antimalarial medicines required can be estimated by the standard morbidity method or the consumption method, which are generally used for large-scale forecasting of medicine requirements for annual or semi-annual procurement cycles. Before starting quantification by either method, the following steps must be completed:

▶ nominate the official (senior pharmacist, medical officer or senior administrator) responsible for the quantification. A person(s) with experience in large-scale quantification of antimalarial medicines should be consulted at this stage;

▶ form a coordination working group (composed of senior medical administrators or clinicians, managers of the health information system, pharmacists and a finance officer);

▶ define the target coverage for the quantification (by geographical area and health facility or community level), specifically for medicines in the national malaria treatment policy;

▶ consider whether the needs of the facilities for which medicine requirements are being quantified are expanding or contracting, in the light of the health sector development plan of the country and the expected impact on consumption of antimalarial medicines of the policy on pricing and accessibility of medicines;

▶ consider how the estimates will be affected by existing prescribing patterns (i.e. malaria treatment based on presumptive diagnosis) and the expected extent of change in prescribing practices (i.e. after introduction or expansion of malaria rapid diagnostic tests);

▶ make a realistic plan for completion of the quantification, on the basis of whether it is to be centralized (managed at central level) or decentralized (each facility compiling its own estimates, which are reviewed and consolidated at the district and provincial levels before submission to the procurement office).

The last step is particularly relevant for decentralized systems, in which quantification is based on the consumption method.

A3.1.1 Morbidity method

The morbidity method may be most appropriate for quantifying medicine requirements in the following situations:

▶ available consumption data are incomplete or unreliable;

▶ prescribing patterns are not cost-effective, and systematic improvement is required (e.g. persistent reliance on clinical diagnosis in all age groups despite the availability of microscopy and rapid diagnostic tests);

▶ previous budget for medicine procurement was insufficient to meet requirements; or

▶ health facilities are new or rapidly expanding or a new antimalarial treatment is being introduced, so that past consumption data are not a reliable guide to future requirements.

This is the method of choice for estimating antimalarial medicine requirements in countries in the early phase of implementation of artemisinin-based combination treatments.

Step 1. Prepare a list of medicines to be quantified

The list should contain the antimalarial medicines in the national guidelines for treatment of falciparum malaria (both uncomplicated and severe) and the other species (see Table An3.1).

Table An3.1 The currently recommended antimalarial medicines

Malaria disease	*P. falciparum*	*P. vivax*	*P. malariae*	*P. ovale*
Uncomplicated first-line	ACTs: - AL - AS+AQ - AS+MQ - AS+SP - DHA+PPQ	CQ plus PQ	CQ	CQ
second-line	- Alternative ACT - AS+TET or DOXY or CLIN - QNN+TET or DOXY or CLIN	- AS+AQ plus PQ - AS+MQ plus PQ - DHA+PPQ plus PQ		
Severe	- AS IV/IM - AM IM - QNN IV/IM - AT IM			

AL: artemether-lumefantrine; AM: artemether ; AS: artesunate; AQ: amodiaquinine; CLIN: clindamycin; CQ: chloroquine; DHA+PPQ: dihydroartemisinin-piperaquine;
DOXY: doxycycline; MQ: mefloquine; PQ: primaquine; QNN: quinine;
SP: sulfadoxine-pyrimethamine; TET: tetracycline.

Step 2. Establish the standard treatment course

Standard treatment courses across the range of different age groups must be established. It is preferable to calculate average regimens, on the basis of observed or reported practices, to make the estimate of requirements more realistic. As these data are often not available, the ideal regimens from standard treatment guidelines are generally used in the morbidity method.

The standard courses of treatment are shown for *P. vivax* malaria in Table An3.2, for uncomplicated falciparum malaria during the first trimester of pregnancy and for intermittent preventive treatment with sulfadoxine–pyrimethamine in Table An3.3, and for severe malaria in Table An 3.4. The correlations between age and weight should be derived from national data that reflect the actual anthropometric and nutritional status of the population.

Table An3.2 **Standard treatment courses of chloroquine, amodiaquine and primaquine for _P._ vivax malaria**

Age	< 4m	4–11m	1–2y	3–4y	5–7y	8–10y	11–13y	14+y
Weight	5-6kg	7-10kg	11-14kg	15-18kg	19-24kg	25-35kg	36-50kg	50+kg
Medicine (strength)								
CQ (total dose)								
100mg base tabs								
150mg base tabs								
50mg base/5 ml								
AQ (total dose)								
153mg base tabs								
200mg base tabs								
PQ (total dose)								
5mg base tabs								
7.5mg base tabs								
15mg base tabs								

CQ, chloroquine; AQ, amodiaquine; PQ, primaquine

Table An3.3 **Standard treatment courses for treatment of uncomplicated falciparum malaria during the first trimester of pregnancy, and for intermittent preventive treatment (IPTp) with sulfadoxine/pyrimethamine**

Medicine	Daily dose (tablets)	Duration of treatment	Total tablets per treatment/IPTp
Quinine sulfate 300mg tabs	2 tabs x 3 times daily	7 days	42 tabs
Sulfadoxine-pyrimethamine 500-25mg tabs for IPTp	3 tabs in single dose	repeated 2–3 times (2nd and 3rd trimesters)	6–9 tabs

Table An3.4 **Standard treatment courses for treatment of severe malaria, both the loading dose and the maintenance dose to be repeated during the first 48 hours of treatment**

Age	< 4m	4–11m	1–2y	3–4y	5–7y	8–10y	11–13y	14+y
Weight	5-6kg	7-10kg	11-14kg	15-18kg	19-24kg	25-35kg	36-50kg	50+kg
Medicine (strength)								
Artesunate IV/IM Loading dose _Maintenance_ (first 72 hours)								
Artemether IM Loading dose _Maintenance_								
Quinine Loading dose _Maintenance_								

Step 3. Estimate the number of malaria episodes requiring treatment in health facilities

The morbidity method requires information on the population by age group; the actual or projected incidence of malaria; patient attendance at health facilities; and malaria treatment practices (actual or expected). Information from the routine health management information system is often incomplete or not available, and special surveys of representative samples of health facilities might not be possible. It may therefore be necessary, instead, to estimate patient contacts with health facilities that result in malaria treatment.

Step 4. Calculate the quantities of medicines for each type of standard malaria treatment

The expected frequency of malaria episodes per age group treated in health facilities is multiplied by the amount of antimalarial medicine required per corresponding age group, estimated on the basis of the national malaria treatment guidelines. The expected requirement of each medicine is the sum of the needs estimated for each age group. An example of calculation of the requirements for artesunate plus sulfadoxine-pyrimethamine or artesunate plus mefloquine in areas of intense transmission is given in Table An 3.5. The total number of treatment courses needed for each age group, f, is obtained by multiplying the number of febrile episodes expected to be treated as malaria (a x b), by the percentage expected attendance to the health facilities served by the medicine distribution system (c). The proportion of patients expected to be tested by microscopy or RDTs (d_1), should be multiplied by the positivity rate (d_2). A certain proportion of patients will not be tested and treated on the basis of clinical diagnosis only (e). The extent of reduction of treatment due to laboratory confirmation of diagnosis, (d_1), is influenced by coverage of laboratory services (microscopy and rapid diagnostic tests) and expected compliance with negative results by health providers. See the example below.

Example (from the Table An 3.5)

In the 7–13 age group

> The total number of febrile episodes expected to be treated as malaria =
> (a x b) = 25 000 x 2 = 50 000

but …

> The number of episodes expected to be seen in health facilities =
> 50 000 x c = 50 000 x 0.4 = 20 000

however, after laboratory confirmation …

> The number of episodes to be treated =
> 20 000 x d_1 x d_2 = 20 000 x 0.6 x 0.2 = 2400

To this number, febrile patients seen in health facilities and treated on a clinical basis should be added:

> a x b x c x e = 25 000 x 2 x 0.4 x 0.4 = 8000

An example of calculation of the requirements for artemether-lumefantrine in areas of low transmission is given in Table An3.6. The method of calculation and the factors are the same as for Table An 3.5

Table An3.5   Morbidity method: example for AS+SP, AS+AQ, AS+MQ in high transmission areas

Age-groups (years)	Population (a)	Febrile episodes per year treated as malaria(b)	% attendance at health facility(c)	% tested (d1)	% positive (d2)	% treated on clinical basis (e)	No. of treatment courses (f)
< 1	6 000	2	50	40	30	60	4 320
2–6	16 000	4	50	50	40	50	22 400
7–13	25 000	2	40	60	20	40	10 400
≥ 14	53 000	1	20	70	10	30	3 922
Total	100 000						41 042
TOTAL REQUIREMENTS (f) = (a x b x c x d1 x d2) + (a x b x c x e)							

Table An3.6   Morbidity method: example for AL in low transmission areas

Age-groups (years)	Population (a)	Febrile episodes per year treated as malaria(b)	% attendance at health facility(c)	% tested (d1)	% positive (d2)	% treated on clinical basis (e)	No. of treatment courses (f)
< 3	11 000	50	50	40	10	60	1 760
3–8	17 000	50	50	50	10	50	2 338
9–13	21 000	25	40	60	5	40	903
≥ 14	51 000	25	20	60	5	40	1 097
Total	100 000						6 097
TOTAL REQUIREMENTS (f) = (a x b x c x d1 x d2) + (a x b x c x e)							

The morbidity method allows estimation of total requirements in medicines for large-scale forecasting, as part of annual procurement cycles. The estimates obtained using this method should be compared with estimates derived from the consumption method, even if based on a sample of health facilities with good stock records. This can indicate the actual medicine delivery capacity of the health facilities and might lead to reconsideration of some of the assumptions made for the morbidity estimates.

For special life-saving and relatively expensive medicines, i.e. those used for the management of severe malaria (Table An 3.4), estimates must be based on both morbidity records (number of malaria inpatients) and previous consumption data (based on a sample of health services with inpatient facilities). In countries where parenteral artemisinin formulations have been introduced recently, for which consumption data are not available, the consumption of quinine ampoules can be used to estimate the requirements for artesunate or artemether ampoules. This requires conversion into equivalent amounts of parenteral treatment courses for adults for both medicines, according to the following formulas (derived from Table An 3.4).

A3.1.2 Consumption method

The consumption method is based on records of past consumption of individual medicines, adjusted by stock-outs and projected changes in medicine use. The method requires inventory

records of past consumption for all medicines eligible for procurement. If the records of past consumption are accurate and rational, this method gives an adequate prediction of future needs and is the method of choice in large, well-established medicine supply systems with long experience of uninterrupted supply.

Since malaria transmission is seasonal, consumption data for the past 12 months should be reviewed. If medicine requirements are to be estimated for a six-month period (semi-annual procurement cycle), the consumption data for the same six-month period of the previous year must be used. The most accurate records are stock records and distribution reports from central, regional and district warehouses. Consumption is calculated from these records as:

Total consumption (for a specified period) =

opening stock + medicines received − closing stock

Dispensing records from health facilities could also be used, in principle, but this approach is reliable only if records are well kept and complete. It might be difficult to obtain consumption data from patient registers, even if treatments are recorded, because this information is not routinely reported in health management information systems.

Records of stock-outs are important for calculating consumption precisely. The simplest approach is to divide the total consumption by the number of months reviewed and correct by the average number of months of stock rupture, as follows:

Adjusted average monthly consumption =

$$\frac{\text{Consumption during the review period}}{\text{No. of months in review period} - \text{No. of months of stock-out in review period}}$$

A3.2   Medicine management information system in health facilities

A reliable management information system is vital for coordinating a medicine distribution network. It is a recording and reporting system for inventories, costs, receipt and issue of medicines. Therefore, the forms, records and reports form the core of the supply information system, carrying specific information on medicine needs, movement and associated financial transactions.

The most important is the stock record of each item in the inventory. At a minimum, there should be a space on the form to describe each item (one for each course-of-therapy blister pack in the case of artemisinin-based combination treatments), its stock reference number and unit of issue (e.g. boxes of 30 treatment units). The stock record documents all transactions related to an item. Columns and rows appear below the standard information to record the source of each delivery and the particular health facility to which each item was issued, the quantities received and issued, the balance and the expiry date of each new lot received. Some stock records contain additional information, such as re-order level, re-order interval, re-order quantity, lead time and estimated consumption rate. Many variations exist, but the sample stock record shown below (Figure An3.1) contains the most important features.

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GENERIC NAME: artemether-lumefantrine   STRENGTH: 20mg/120

INVENTORY NUMBER: XXXX   DOSAGE FORM: tablet

UNIT OF ISSUE: (6 x 2 tablets) x 30   UNIT PRICE: US$ .....

Date	Source/ recipient	Quantity received	Quantity issued	Balance	Expiry date	Signature
15/9/05	Inventory			120	06/2006	
17/9/05	Clinic A		10			
23/9/05	HC A		30			
25/9/05	Clinic B		10			
26/9/05	Clinic C		10			
1/10/05	Hospital		40			
3/10/05	HP A		5			
3/10/05	CMS	400			07/2007	
5/10/05	Clinic B		10		06/2006	
8/10/05	HC A		30		5–06/2006 25–07/2007	
12/10/05	Clinic A		10			
15/10/05	Clinic C		10			
23/10/05	Hospital		40			
29/10/05	HP B		5			
1/11/05	HP A		5			
				305		

HC, health centre; HP, health post; CMS, central medical store

Figure An3.1 Example of a stock record card

For artemisinin-based combination treatments, separate stock record cards should be maintained for each course-of-therapy blister pack in its unit of presentation (e.g. Coartem® is available in dispenser boxes containing 30 individual treatment courses). To facilitate stock inventory control, the stock record form should state the number of boxes and not the individual treatment courses. The medical store unit must make regular, periodic counts of the actual stock on hand to ensure that the stock balance on the inventory records is correct. Available stocks in all locations should be counted as scheduled and compared with the balance recorded on the respective cards.

The stock record form makes it possible to calculate consumption over a certain period, according to the method described in section An3.1.1.2 (Consumption = opening stock + medicines received − closing stock). In the example shown in Figure An3.1, consumption during the period 15 September 2005 to 1 November 2005 was 120 + 400 − 305 = 215 unit forms (i.e. 215 x 30 = 6450 individual treatment courses). The stock record card can be used to calculate monthly consumption: the consumption in October 2005 in the example was 60 + 400 − 355 = 105 unit forms (i.e. 105 x 30 = 3150 individual treatment courses).

The stock record card in the example refers to paediatric doses of artemether–lumefantrine (15–25kg of body weight) in a district medical store receiving medicine from a central medical store and delivering it to the hospital, health centres, several clinics and health posts. As

standard amounts of medicines are delivered according to health facility level (clinics, 10 boxes; health posts, 5 boxes), the system in use in this example is probably a "push" system, whereby medicine allocations for distribution are determined according to the expected consumption at peripheral level. While no stock ruptures are recorded on this stock record card, it is important to evaluate the stores of health facilities, as stock rupture is more likely in a "push" than in a "pull" system guided by consumption patterns at peripheral health facilities.

As individual health facilities are the end-users of medical supplies, it is essential to maintain information from those facilities in order to monitor consumption. Various methods of calculating re-order quantities exist (including that described above, but they are all based on monthly consumption. Monthly consumption is determined from the stock card and recorded on a monthly stock recording form. An example of a monthly stock management form for medicines and laboratory supplies is shown in Fig. An3.2.

District ....   Health unit ....   Month ....

Item	Duration of stock-out			Stock management (treatment courses)						
	None	<1 week	>1 week	Safety stock	Opening stock	Closing stock	Monthly consumption	Expected variation	Lead time	Quantity re-ordered
Name of first-line medicine										
1. ACT Prepack 1										
2. ACT Prepack 2										
3. ACT Prepack 3										
4. ACT Prepack 4										
5. Second-line medicine										
6. Parenteral quinine										
7. Artemisinin suppositories										
8. Sulfadoxine-pyrimethamine for IPT										
Additional medicines or supplies:										
9.										
10.										
Laboratory supplies:										
11. Giemsa stain										
12. Malaria slides										
13. RDTs										
14. Lancets										

Opening stock: *stock at beginning of month*; closing stock: *balance at end of month*
ACT = artemisinin-based combination therapy; IPT = intermittent preventive treatment; RDT = rapid diagnostic test.

Figure An3.2 Model monthly stock management form for medicines and laboratory supplies

Individual health facilities report to district offices, which report to regional offices, which report to the central office. The reports are used to assess medicine use, to project medicine needs and to revise budgets. Their ultimate goal is managing the reliable movement of supplies from the source to the end-user the least expensively and to track stored items and to protect from loss, damage, theft or waste. The success of the information system depends primarily on well-trained, well-organized and well-supervised staff.

A3.3 Management of routine ordering

A3.3.1 Calculation of safety stocks

In order to convert the estimated medicine requirements into potential orders to cover consumption between two cycles of orders from the same supplier, the amount of medicines that must be held in stock should be calculated. As it is impossible to forecast demand with complete accuracy or to be certain about the supplier's performance, a certain amount of medicine must be stocked to absorb fluctuations in supply and demand and to reduce the risk for stock-outs. High stock levels, however, increase inventory costs (personnel, storage, risks of spoilage, expiry and theft), and most public pharmaceutical systems calculate the minimum safety stock needed to protect against stock ruptures.

The commonest method for estimating safety stock needs is to determine the average lead time for each item from the current supplier (interval from the time the order is placed to the time the medicines reach the central warehouse) and the average consumption. Invoices from suppliers can be used to calculate the average lead time for the last few procurements. The safety stock is calculated by multiplying the adjusted average monthly consumption by the expected lead time, as follows:

$$SS = Ca \times LT,$$

where   *SS* is the safety stock,

       Ca is the average monthly consumption, adjusted for stock rupture, and

       LT is the lead time between initiation of purchase order and receipt of medicines in the warehouse, also calculated in months.

The safety stocks of vital items must be increased when consumption varies or when the lead time is uncertain. The simplest approach is to add an arbitrary multiplier to the basic formula, for example, to multiply the safety stock by 1.5.

A public medicine distribution system generally has three types of stores: one or more primary stores, which receive purchases and generally serve a whole country, region or province; intermediate stores, which receive the medicines distributed by the primary stores and are often on the site of a regional or district hospital; and health facility stores, which receive the medicines distributed by the intermediate stores. The physical size of the store at each level is determined by the demand for medicines and by the supply frequency. The stock levels within the supply system and the number of supply points at each level constitute the supply pipeline. The number of levels, the frequency of requisition and delivery and the amount of safety stock at each level will influence the amount of medicines needed to fill the supply pipeline.

A3.3.2 Time and quantity for re-ordering

A new order should be placed once the stock has reached a minimal level. In many situations, the minimal stock level (re-order level) is calculated in the same way as the safety stock, i.e. by multiplying the average lead time by the average quantity consumed during the same period.

Once the basic inventory has been established, the question is how much medicine should be ordered. Several formulas are available, but one of the most commonly used is the consumption-based re-ordering formula, in which the quantity of medicines to re-order is based on the adjusted average monthly consumption multiplied by the sum of the lead time and procurement period plus the safety stock level, after removal of stock on order and stock in inventory. This is expressed as:

$$Qo = Ca \times (LT + PP) + SS - (Si + So),$$

where Qo is the quantity of medicines to be re-ordered in the next procurement period;

        Ca is the average monthly consumption, adjusted for stock rupture;

        LT is the lead time;

        PP is the procurement period;

        SS is the safety stock;

        Si is the stock in inventory, i.e. the working stock plus the safety stock; and

        So is the stock on order but not yet received.

As artemisinin-based combination treatments are available in three to four different course-of-therapy blister packs, calculation of the quantities to re-order requires a review of the consumption (from stock records) of each type of blister pack, adjusted for stock rupture.

Ordering also requires forecasts of future needs, the least predictable variable in a re-ordering formula. The amounts calculated from the formula should be adjusted for the expected seasonality of malaria or epidemic risk. If annual purchasing is for staggered deliveries or scheduled purchasing (e.g. at six-month intervals), the order to be delivered before the malaria transmission season should be increased, on the basis of consumption during the last comparable season. Consumption of antimalarial medicines during the four-month malaria transmission season can represent 60–70% of annual consumption.

In countries prone to epidemics of malaria, an appropriate epidemic stock of anti¬malarial medicines must be added to the quantities to be re-ordered. The history and extent of past malaria epidemics and their geography (epidemic-prone districts) will guide the amount and strategic placement of such stocks. Because of the relatively short shelf-life of artemisinin-based combination therapies (generally 18–20 months residual shelf-life at port of entry), the epidemic stock must be rotated with the routine stock to avoid the risk of expiration of medicines with a short shelf-life.

A3.3.3   Quantification of annual requirements

Once the initial quantification has been completed by the morbidity or the consumption method, the following steps must be completed to convert the estimated medicine requirements into potential orders.

▶ Estimate requirements on the basis of the number of supply points at each level, their frequency of requisition and delivery, the amount of safety stock at each level, in line with the overall plan of starting and expanding the distribution of antimalarial medicines;

▶ Consider the impact of lead time, including time to place an order, production time, time for shipment, customs clearance and arrival in the central warehouse;

▶ Adjust the amounts for damage, spoilage, expiration and theft; many systems allow at least 10% for losses. A percentage of loss must be allowed in quantifying vital items: artemisinin-based combination treatments are more attractive to thieves than other medicines because of their high price in the private sector;

▶ Adjust the quantity to be ordered according to pack size (multiples of 25, 30 or 50 individual treatment units, according to the supplier), as well as the minimal order size required by the supplier;

▶ Estimate total procurement costs on the basis of current medicine prices from local suppliers and international procurement agencies;

▶ Adjust the estimated budget for expected price increases due to anticipated international devaluation, devaluation of local currency and possible increases in shipping costs;

▶ Reduce the estimated quantities to conform to budget realities, if necessary.

A3.4   Management of medicine distribution

Storage and distribution costs represent a significant component of the health budget, and transport costs can be very high, especially in large countries with low population densities. In many endemic countries, a six- or three-month re-order interval (or annual orders with staggered deliveries at six- or three-month intervals) is useful for reducing inventory costs for artemisinin-based combination treatments. This also allows regular replenishment of the inventory with new supplies with adequate residual shelf-life.

Staggered deliveries make it possible to manage the distribution of smaller amounts of artemisinin-based combination treatments, which might be appropriate in countries in the early phase of implementation, with limited experience in the inventory and distribution of high-value medicines available in different course-of-therapy blister packs with a relatively limited shelf-life. To a certain extent, staggered delivery gives the requisitioner flexibility to adjust deliveries in cases of high inventory levels due to unexpectedly low consumption or difficulties in distribution. Reduction is generally easier than increase, as the production of artemisinin-based combination treatment is generally complex. Repeated requests for delay or reduction of expected deliveries can, however, be a cause for litigation, as suppliers might ask to be reimbursed for unanticipated warehousing costs.

Artemisinin-based combination treatments may initially be distributed by a "push" system, in which the central level determines the quantities of medicines to be delivered to lower levels. This system is useful if peripheral staff has limited experience in assessing needs and managing an inventory of these new medicines and there is uncertainty about demand exceeding the supply (making rationing necessary).

The next step is to select an appropriate re-supply interval. Generally, deliveries are made at intervals of one to three months, depending on availability, capacity and transport costs, as well as order size and storage capacity at each level of the distribution system. Other factors, such as expiry dates and security against theft, should also be taken into consideration in selecting appropriate re-supply intervals.

In the management of the distribution of malaria medicines, both the seasonality of malaria and the reliability of transport during the rainy season should be taken into account. Delivery frequency and volume must be scheduled to work around road interruptions due to rain. In remote areas that are difficult to reach, adequate supplies of artemisinin-based combination treatments must be delivered and stored at least one month before the start of the malaria season, in locally accessible warehouses, preferably in health facilities.

A detailed plan must be drawn up of the time required for processing requisitions and organizing deliveries at each level of medical store, including the time required for transport. One practical approach to planning such requirements is to calculate the number of days per month needed for processing requisitions and deliveries at each distribution level (from central to intermediate warehouses up to health facility stores) and to mark the requirements in days on a planning chart. This detailed plan should include the time required for preparing deliveries and organizing transport before the rainy season for destinations with poor access.

A3.5 Quantification of rapid diagnostic test requirements

Many countries are introducing rapid tests for the diagnosis of malaria to extend parasitological confirmation of malaria to areas and health facilities where there is no microscopy. As these tests are relatively new, relatively expensive and have a limited shelf-life (a maximum of two years), quantification of the requirements for these rapid diagnostic tests needs special attention.

Before quantifying the requirements for the public sector, it is important to:

▶ define the target coverage for quantification, indicating by geographical area the number of health facilities that will be using the tests, stratified by health care system level (hospitals, health centres, clinics, dispensaries, health units, health posts);

▶ consider whether the number of health facilities for which requirements are being quantified will be increasing or decreasing during the period covered by the quantification, as part of health sector development in the country;

▶ provide preliminary estimates of expected variations in the use of health facilities after the introduction of the new malaria treatment policy and the expected impact of the policy on pricing, access to medicines and on health service utilization. In countries where rapid diagnostic tests have been introduced, consumption data from selected districts or regions where both the tests and artemisinin-based combination treatment are deployed should be used to estimate

requirements for rapid diagnostic tests. Consumption data should preferably cover at least two years after introduction. If the consumption data are from areas prone to malaria epidemics, the likelihood that fewer rapid diagnostic tests might be required in normal years should be considered.

In countries where rapid diagnostic tests have never been used, alternative methods for estimating requirements must be used, based on the principle that a rapid diagnostic test is required where microscopy is not available The public sector demand can be estimated from records of the number of febrile patients treated for malaria (i.e. the number of suspected malaria cases) for whom no microscopy was performed in public health services. In practice, the overall demand of the public sector for rapid diagnostic tests can be estimated by subtracting the total number of cases examined by microscopy from the total number of reported cases of malaria in public health facilities (in areas where the proportion of tested cases over total reported cases is low).

If rapid diagnostic tests are to be used at all levels of the health care system, the following formula should be applied to data for the most recent calendar year:

> Public sector rapid diagnostic test demand =
>
>   No. of malaria cases reported − No. of microscopy examinations for malaria

The estimated demand for rapid diagnostic tests must then be adjusted by the completeness of reporting and the target proportion of patients with probable malaria to be tested.

Completeness of reporting can vary according to health facility level. If high-level health facilities (i.e. hospitals and health centres with microscopy capability) have more complete reporting than lower-level health facilities, the estimated need for rapid diagnostic tests will be artificially reduced, or underestimated. If possible, the total number of malaria cases should be corrected for completeness of reporting, by dividing the total number by the proportion of health facilities, of all existing facilities, that report data within a nationally established time frame.

Because of the specific programmatic requirements for rapid diagnostic testing, including training, maintenance of the cold chain and quality assurance, quantification of requirements should be adjusted to meet the needs of the operational plans set by the malaria programme. In most situations, rapid diagnostic tests will not be used at all levels of the health care system, some health facility levels might not be included at the time of introduction of the tests, and operational coverage might increase over time. For example, if peripheral health posts are targeted for introduction of RDTs and 20% of the reported cases of malaria are treated at this level, the overall requirement for rapid diagnostic tests should be increased proportionally by 20%. Some countries might plan to use rapid diagnostic tests in all health facilities without microscopy, while others might plan to use them as part of home-based management. Estimates of requirements at community level should take into account the expected number of fever episodes that will be tested by community-based health providers over a certain period as part of the operational plan for community-based malaria case management.

ANNEX 4
Indicators for malaria case management

Indicator 1	Confirmed malaria cases (number and rate)
Numerator and denominator	*Numerator.* Number of confirmed malaria cases (by microscopy or RDT) reported by health facilities (passive detection), active case detection or by community workers per year. *Denominator for rate.* Population (<5 years, all ages) living in areas at risk of malaria.
Breakdown	Age group, species, location (district, health facility catchment area), method of detection (PCD, ACD, community).
Purpose	Measures trend of malaria morbidity and highlights location and quantity of ongoing malaria transmission. This indicator is the most important measure of progress and management in low-incidence areas.
Data collection	Method: Health management information systems. Data from community and active case detection forms should be added to total numbers but should be identified as a separate subset.
Data collection	Tools: Health facility records, registers and community health forms
References	1. Guidelines for the treatment of malaria. Geneva, World Health Organization, 2010;
	2. World malaria report 2005. Geneva, Roll Back Malaria/World Health Organization/UNICEF 2005 (WHO/HTM/MAL/2005.1102);
	3. Framework for monitoring progress and evaluating outcomes and impact. Geneva, World Health Organization/Roll Back Malaria, 2000 (WHO/CDS/RBM/2000.25);
	4. WHO Expert Committee on Malaria. Twentieth report. Geneva, World Health Organization, 2000 (WHO Technical Report Series, No. 892).

Indicator 2	Malaria test positivity rate (for microscopy, slide positivity rate)
Numerator and denominator	*Numerator.* Number of parasitologically confirmed malaria cases (by microscopy or RDT). *Denominator.* Number of suspected malaria cases tested. Non febrile cases should be not be included.
Breakdown	Location (district, health facility catchment area), type of diagnostic test (microscopy or RDT).
Purpose	Malaria test positivity rate (TPR) monitors impact of program on malaria transmission. This indicator is not as affected by RDT stock-outs and interruption of microscopy services as the number or rate of confirmed cases because denominator does not include suspected cases that are not tested.
Data collection	Method: Health management information systems. Data from community and active case detection forms should be added to total numbers but should be identified as a separate subset. Tools: Health facility records, registers and community health forms.
References	1. Guidelines for the treatment of malaria. Geneva, World Health Organization, 2010;
	2. Muir DA. Anopheline mosquitoes: vector reproduction, life cycle and biotope. In: Malaria: principles and practice of malariology Volume II (Wernsdorfer WH, McGregor I, eds). New York:Churchill Livingstone, 1988; pp. 1045-1054;
	3. Disease surveillance guidelines. WHO SME/GMP. Draft 2010.

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Indicator 3	Percentage of suspected malaria cases that undergo laboratory diagnosis
Numerator and denominator	*Numerator.* Number of suspected malaria cases for which parasitological test (microscopy or RDT) was performed. *Denominator.* Number of suspected malaria cases. Use data from passive detection only; exclude data from active case detection
Breakdown	Location (district, health facility catchment area), type of diagnostic test (microscopy or RDT)
Purpose	An indicator of quality of surveillance—the higher the proportion of supect cases tested, the more likely that number of confirmed cases reported represents true rate of malria. Target should be 100% of suspected cases receiving laboratory testing. This indicator shows capacity of malaria programme to expand rationale treatment of malaria based on definitive diagnosis. Both programme implementation and health system capacity influence these achievements.
Data collection	Method: health management information systems. Data from community and active case detection forms should be added to total numbers but should be identified as a separate subset. Tools: Health facility records, registers and community health forms. Same as other surveillance data.
References	Framework for monitoring progress and evaluating outcomes and impact. Geneva, World Health Organization/Roll Back Malaria, 2000 (WHO/CDS/RBM/2000.25);

Indicator 4	In-patient malaria cases (number and rate)
Numerator and denominator	*Numerator.* Cases with a discharge diagnosis of malaria. (<5 years, all ages) *Denominator for rate.* Population (<5 years, all ages) living in areas at risk of malaria. **It is assumed that all cases would have had a parasite-based test for malaria (microscopy and/or RDT) and discharge diagnosis was based on test results.** In-patient cases can be from hospitals or non-hospital facilities with in-patient beds.
Breakdown	Age group, location (district, health facility catchment area).
Purpose	As marker of severe disease and death, monitors impact of program on severe disease. This indicator may show differential impact of improved treatment over decreased transmission since prompt, appropriate treatment specifically attenuates clinical progression from uncomplicated to severe disease.
Data collection	Method: health management information systems. Tools: In-patient discharge records, both hospitals and other health facilities with in-patient beds.
References	Framework for monitoring progress and evaluating outcomes and impact. Geneva, World Health Organization/ Roll Back Malaria, 2000 (WHO/CDS/RBM/2000.25).

Indicator 5	In-patient malaria deaths (number and rate)
Numerator and denominator	*Numerator.* Deaths with a diagnosis of malaria at death (<5 years, all ages) Deaths can be from hospitals or non-hospital facilities. *Denominator for rate.* Population (<5 years, all ages) living in areas at risk of malaria.
Breakdown	Age group, location (district, health facility catchment area).
Purpose	Monitors impact of program on severe disease and death. May show differential impact of improved treatment over decreased transmission since prompt, appropriate treatment specifically attenuates clinical progression from uncomplicated to severe disease and death. The operational target for monitoring the RBM target of near-zero preventable malaria deaths (by 2015) would be elimination of in-patient malaria deaths.
Data collection	Method: health management information systems. Tools: In-patient discharge records, both hospitals and other health facilities with in-patient beds. Reported deaths from any health facility, even those with out-patient services only, should be included in reported routine data
References	1. World malaria report 2005. Geneva, Roll Back Malaria/World Health Organization/UNICEF 2005 (WHO/HTM/MAL/2005.1102); 2. WHO Expert Committee on Malaria. Twentieth report. Geneva, World Health Organization, 2000 (WHO Technical Report Series, No. 892).

Indicator 6	**Percentage of out-patient malaria cases that received appropriate antimalarial treatment according to national policy**
Numerator and denominator	*Numerator.* Number of malaria cases receiving appropriate anti-malarial treatment at health facility.
	Denominator. Number of out-patient malaria cases expected to be treated at health facility with appropriate anti-malarial medicine.
	This number comes from surveillance data and is based on national treatment policy. If the information system does not collect number of patients treated, then number of ACTs received or dispensed can be taken as a surrogate numerator.
Breakdown	Species, location (district, health facility catchment area).
Purpose	Measures the capacity of health system and programme to ensure access to and delivery of appropriate anti-malarial treatment for those coming to health facilities.
	Provides useful information about difference between treatment of patients and amount of anti-malarial medicines distributed at various levels.
Data collection	Numerator (number of patients treated) comes from logistic information and denominator (number expected to be treated) comes from surveillance data.
	Surrogate indicator/denominator. Number of anti-malarial medicines dispensed would come from district, provincial, and national medicine store rooms and their information systems.
References	1. Guidelines for the treatment of malaria. Geneva, World Health Organization, 2010;Malaria Control;
	2. Muir DA. Anopheline mosquitoes: vector reproduction, life cycle and biotope. In: Malaria: principles and practice of malariology Volume II (Wernsdorfer WH, McGregor I, eds). New York:Churchill Livingstone, 1988; pp. 1045-1054.

Indicator 7	**Percentage of pregnant women attending ANC receiving at least 2 doses of intermittent preventive therapy (IPTp)**
Numerator and denominator	*Numerator.* Number of pregnant women receiving second dose of IPT
	Denominator. Number of pregnant women with at least one ANC visit.
Breakdown	Location (district, health facility catchment area)
Purpose	Monitoring coverage of adequate IPT in pregnant women. At least 80% of pregnant women attending ANC should receive at least two doses of IPT. This indicator is used mostly in high-transmission countries.
Data collection	Method: health management information systems.
	At ANC clinics. Part of routine monthly reporting of logistic information from health facility to district
References	A Strategic Framework for Malaria Prevention and Control during Pregnancy in the African Region. AFRO/ MAL/04/01. 2004. WHO Regional Officer for Africa. Brazzaville.
	Framework for monitoring progress and evaluating outcomes and impact. Geneva, World Health Organization/ Roll Back Malaria, 2000 (WHO/CDS/RBM/2000.25).

Indicator 8	**Percentage of health facilities without stock-outs of first-line antimalarial medicines and diagnostics, by month**
Numerator and denominator	*Numerator.* Number of health facilities, in areas at risk of malaria, without stock-outs of first-line anti-malarial medicine (according to national policy), and RDT in a month
	Denominator. Number of reporting health facilities in the same areas at risk of malaria
Breakdown	Location (district, health facility catchment area), type of commodity (antimalarials, RDTs).
Purpose	Health facilities should have a continuous (every day) supply of first-line anti-malarial medicine [ACT] and RDT. This indicator monitors supply chain at the health facility and helps programmes take immediate action following the detection of stock-outs.
Data collection	Routine monthly health facility logistics data.
References	Framework for monitoring progress and evaluating outcomes and impact. Geneva, World Health Organization/ Roll Back Malaria, 2000 (WHO/CDS/RBM/2000.25).