MINISTRY OF HEALTH MALAYSIA

MANAGEMENT GUIDELINES OF MALARIA IN MALAYSIA

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FOREWORD

Malaysia has come a long way in the prevention and control of malaria since the introduction of the Malaria Eradication Programme in 1960. In 2011, we finally reached the significant milestone of having less than 1 case per 1,000 population and thereby entered the elimination phase. The National Malaria Elimination Strategic Plan was introduced in the same year with the target of “malaria free” status by 2020.

Since the first guidelines in malaria management was published in 1993, several new developments have appeared notably the emergence of *Plasmodium knowlesi* with its diagnostic challenge in identification. The ever growing problem of chloroquine resistance by *Plasmodium falciparum* and the introduction of Artemisinin-based combination therapies (ACTs) require clinicians to enhance their knowledge and skills. Hence, it is timely that the Ministry of Health produce this new guidelines to update all health care workers on the latest clinical evidence of malaria management.

The Management Guidelines of Malaria in Malaysia 2013 covers all aspects in the management including diagnosis, management of severe malaria and malaria chemoprophylaxis. A chapter for the monitoring of treatment response is included to provide a Standard Operating Procedure (SOP) for the National Surveillance of Drug Response against Malaria Parasite. This would facilitate clinicians to monitor and report cases with anti-malaria resistance during the disease follow-up.

It is my sincere hope that all health care personnel will find this guideline useful and utilize it optimally to improve the management of malaria in the country.

Last but not least, I would like to acknowledge the contribution of the technical working group in developing a consensus policy on malaria case management.

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PREFACE

Malaria is a major public-health problem, with over 40% of the world's population (more than 3.3 billion people) are at risk for malaria infection to varying degrees in countries with on-going transmission.

Malaria has been reported in Malaysia even before 1900's. In 1990, there were 50,500 cases in Malaysia. A decade later, in the year 2000, the number of reported cases has reduced to 12,705 cases. In 2012, there were 4,725 cases which is a 63% reduction compared to 2000. The incidence rate in Malaysia has declined to less than 1 per 1,000 population since 1998. There has also been a reduction in the number of malaria deaths from 43 in 1990 to 35 in 2000 and to 16 deaths in 2012. The mortality rate due to malaria has been around 0.001 per 1,000 population since 2006. All figures and rates are inclusive of *P. knowlesi*. The first case of *Plasmodium knowlesi* has been reported in Malaysia in 1965. Based on 2012, *P. knowlesi* accounted for 38% (1813) of all cases which is the highest among all Plasmodium species.

Early diagnosis and prompt treatment are fundamental to malaria control and need to be available wherever malaria occurs. Correct treatment of malarial disease will shorten its duration and largely prevent the development of complications and death, especially in high-risk groups such as young children and pregnant women.

Plasmodium knowlesi followed by *Plasmodium falciparum* causes the most serious form of disease in Malaysia[1]. Infections with this parasite can be fatal in the absence of prompt recognition of the disease. *Plasmodium vivax* may also cause severe infection. Resistance of parasites to antimalarial agents has led to increasing difficulties for the provision of adequate disease management.

This guideline on the management of malaria has been revised and updated based on previous national guidelines (published in year 1993) and the latest WHO guideline (2nd edition). It is intended primarily for healthcare personnel in Malaysia for the management of malaria patients.

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ACRONYM

ACT	Artemisinin-based Combination Therapy
ASMQ	Artesunate / Mefloquine
BD	Bis Die (Latin for twice a day)
BFMP	Blood Film for Malaria Parasite
CVP	Central Venous Pressure
EBT	Exchange Blood Transfusion
EDTA	Ethylenediaminetetraacetic Acid
FDC	Fixed-dose Combination
GCS	Glasgow Coma Scale
G6PD	Glucose-6-Phosphate Dehydrogenase
GI	Gastrointestinal
HDU	High Dependency Unit
ICU	Intensive Care Unit
LDH	Lactate dehydrogenase
NSPEM	National Strategic Plan for Elimination of Malaria
OD	Omne in Die (Latin for once daily)
RDT	Rapid Diagnostic Test
TNF-α	Tumor Necrosis Factor Alpha

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CHAPTER 1: INTRODUCTION

Although malaria control activities over the last few decades have greatly reduced the incidence of malaria in Malaysia, it is still a major public health problem in the hinterland and less developed parts of the country and accounts for a considerable number of cases treated at health clinics and admissions to hospitals. In addition, frequent and affordable travel especially to malaria endemic countries and influx of workers from endemic countries in search of work have kept the number of imported malaria cases on the constant high and pose a real threat of re-introducing malaria into areas which have eliminated the disease.

This book aims to cover various aspects of malaria and its management to assist medical and health personnel in the management of malaria and its complications. If severe cases of malaria are not managed properly, they can lead to complications and death. In our effort to achieve malaria elimination in Malaysia by 2020, there is a need for a standardised up-to-date malaria case management guideline.

1.1 Epidemiology of malaria

Malaria cases in Malaysia have been on the decline from 12,705 cases in 2000 to 4,725 cases in 2012. The incidence rate declined from 0. 55 per 1,000 population in 2000 to 0.16 per 1,000 populations in 2012. For the past decade (2000 – 2012), malaria cases has reduced from 3,918 cases to 1,097 cases in Peninsular Malaysia, from 3,011 cases to 1,571 cases in Sarawak and from 5,776 cases to 2052 cases in Sabah. (Figure 1.1)

There has also been a reduction in the number of malaria deaths from 35 in 2000 and to 16 deaths in 2012. The Case Fatality Rate of malaria has been around 0.3 to 0.5 per 100,000 population since 2006. (Figure 1.2)

1.2 Epidemiology of malaria in 2012

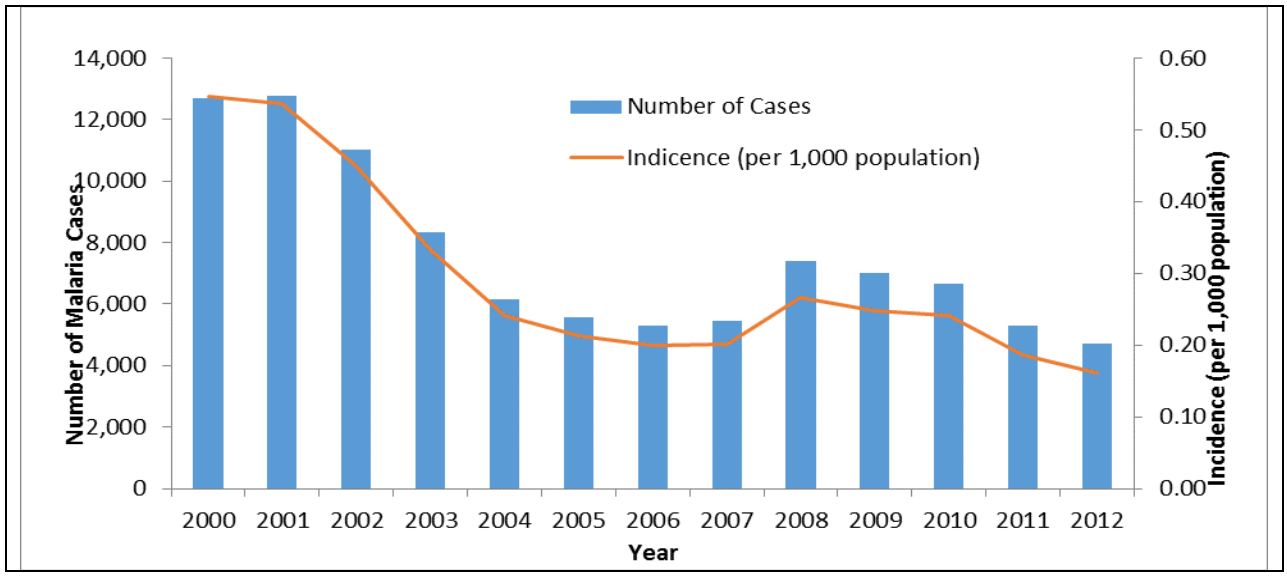
In 2012, of the 4,725 reported cases, 61.6% were human malaria infection and a significant proportions (38.4%) were zoonotic. Among human malaria infection, *P. vivax* accounted for 50.2%, followed by *P. falciparum* (30.7%), *P. malariae* (16.7%) and mixed infection (2.2%).

Of the human malaria, 2051 cases (70.4%) were indigenous cases and a small proportion of 861 cases (29.6%) were imported.

Of the indigenous malaria 74.0% were reported from Sabah followed by 15.9% from Sarawak and 10.1% from Peninsular Malaysia. Of the zoonotic malaria 56.9% were reported from Sarawak followed by 23.3% from Peninsular Malaysia and 19.8% from Sabah.

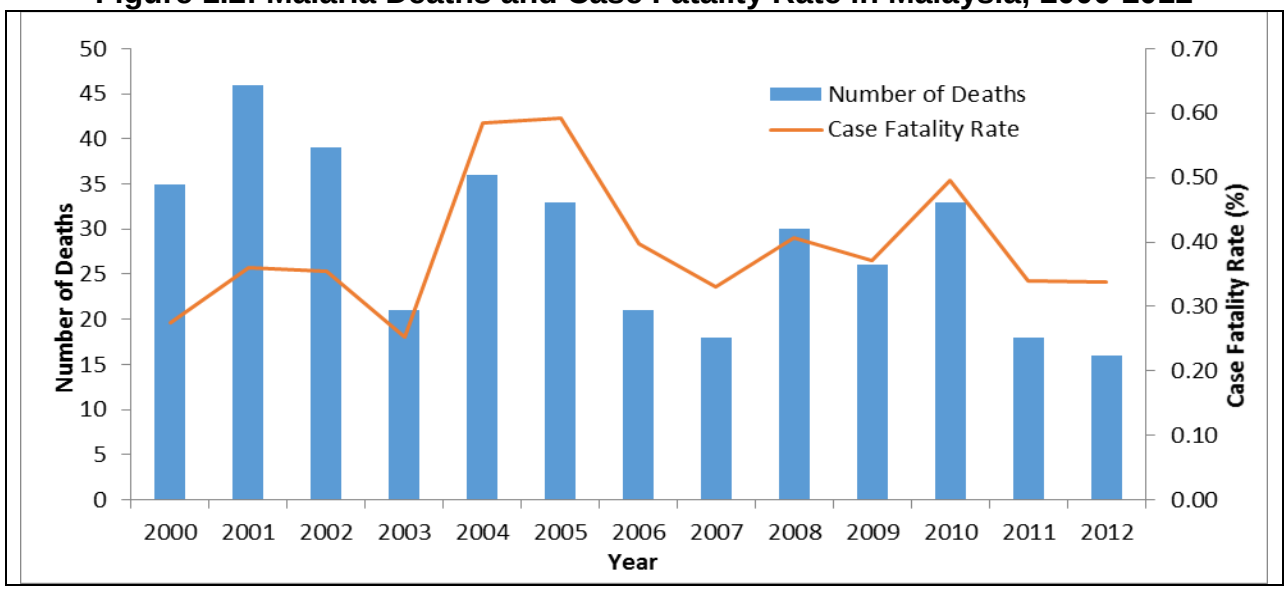
In Peninsular Malaysia, Selangor, Pahang, Kelantan and Perak reported more than 100 cases throughout the year 2012. A big proportion (78.2%) of the cases were among male with only 21.8% among female. About 8.5% of the female patients were pregnant. Children below the age of 5 accounted for 2.5% of all cases whilst those mostly affected were in the age group of 20 – 29 years (25%). About 61.9% of the cases were between the ages of 20 to 49 years.

Figure 1.1: Number and Incidence of Malaria (per 1,000 population) in Malaysia, 2000 – 2012



Source: Vector Borne Disease Sector, Ministry of Health

Figure 1.2: Malaria Deaths and Case Fatality Rate in Malaysia, 2000-2012



Source: Vector Borne Disease Sector, Ministry of Health

1.3 Notification of malaria

Malaria is a notifiable disease under the Communicable Diseases Control Act 1988 which mandates notification within 7 days. However, to ensure early investigation and institution of control measures, all practitioners are to notify malaria cases within 24 hours to the nearest health office.

1.4 National Strategic Plan for Elimination of Malaria (2011-2020)

In 2011, the Malaria Control Programme was reoriented from control to elimination, and MOH formulated the National Strategic Plan for the Elimination of Malaria (NSPEM) (2011 – 2020) with the objective of eliminating locally acquired human-only malaria by 2020.

Seven strategies outlined in the NSPEM (2011 – 2020):

- strengthen Malaria Surveillance System
- intensify control activities using Integrated Vector Management approach
- ensure early detection of cases and prompt treatment
- heighten preparedness and early response to outbreak
- enhance awareness and knowledge on malaria towards social mobilisation and empowerment
- strengthen human resource capacity and
- conduct relevant researches.

One of the seven main strategies is early detection of cases and prompt treatment which advocate for the use of Artemisinin-based Combination Therapy (ACT) as first line treatment for all species.

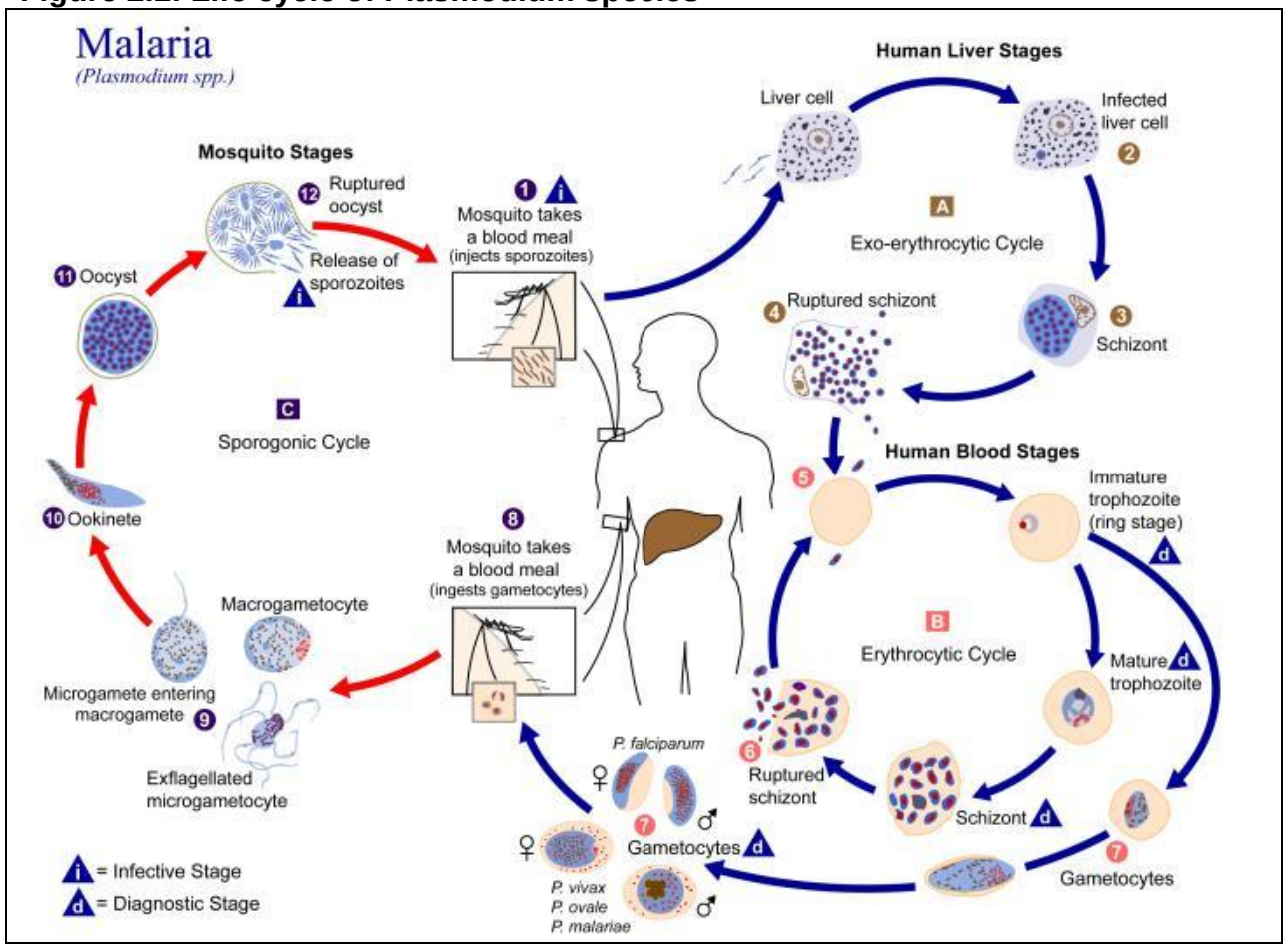
CHAPTER 2: MALARIA PARASITE

2.1 Life cycle

Malaria is caused by infection of red blood cells with protozoan parasites of the genus *Plasmodium*. The parasites are inoculated into the human host by a feeding female anopheline mosquito. The four *Plasmodium* species that are transmitted from humans-to humans are *P. falciparum, P. vivax, P. ovale* and *P. malariae*. Increasingly, human infections with the simian malaria parasite, *P. knowlesi*, have also been reported from the forested regions of Malaysia and other countries in Southeast Asia.

The basic life cycle of all malaria parasites is the same. It comprises of a sexual phase with multiplication in the mosquito (sporogony) and an asexual phase with multiplication in the human (schizogony). (Figure 2.1)

Figure 2.1: Life cycle of Plasmodium species



Source: Image adapted from Laboratory Identification of Parasites of Public Health Concern of the USA government of Centers for Disease Control and Prevention (CDC)[4]

2.2 Pathophysiology

During a blood meal, an infected female Anopheles mosquito injects thousands of malarial sporozoites, which rapidly enter hepatocytes. Reproduction by asexual fission (tissue schizogony) takes place to form a pre-erythrocytic schizont. This part of the life-cycle produces no symptoms.

After a period of time, thousands of merozoites are released into the blood stream to penetrate erythrocytes after attaching via receptors. The time period before merozoites enter the blood from the liver is termed as the pre-patent period; incubation period is about 12 days for *P. falciparum* and *P. knowlesi*, 14 days for *P. vivax* and *P. ovale* and 30 days for *P. malariae*. The clinical symptoms begin after the rupture of the mature schizont-infected erythrocytes, releasing the merozoites and toxic products of the parasite's metabolism into the blood. Most merozoites undergo blood schizogony within erythrocytes to form trophozoites, evolving to schizonts, which rupture to release new merozoites. These then invade new erythrocytes and the erythrocytic cycle (48 hours for *P.falciparum, P.vivax,* and *P.ovale; P.knowlesi* 24 hours*, P.malariae* 72 hours) continues. The rupture of erythrocytes releases toxins that induce the release of cytokines from macrophages, resulting in an increase in body temperature, sometimes resulting in periodicity of fever.

Some merozoites mature within erythrocytes into sexual forms called gametocytes, which reproduce sexually if they are ingested by a mosquito. (Figure 2.1) If left untreated, the parasite counts in a malaria patient keep increasing every 24, 48 or 72 hours, depending on the Plasmodium species.

2.3 Antimalarial drug resistance

Resistance to antimalarials has been documented for *P. falciparum, P. malariae* and *P. vivax*. In *P. falciparum*, resistance has been observed in all currently used antimalarials (amodiaquine, chloroquine, mefloquine, quinine, and sulfadoxine-pyrimethamine) and, more recently, in artemisinin derivatives in certain parts of the world. The geographical distributions and rates of spread of antimalarial drug resistance have varied considerably.

P. vivax has developed resistance rapidly to Fansidar (sulfadoxine-pyrimethamine) in many areas, while resistance to chloroquine is confined largely to Indonesia, Papua New Guinea, Timor-Leste and other parts of Oceania. There are also reports on resistance from Brazil and Peru.

Chloroquine resistant falciparum malaria was first reported in Peninsular Malaysia in 1963.[2] Studies on chloroquine resistant falciparum malaria in the 1960s to 1970s revealed the range of resistance rate from 3.9% to 50.7%, most of it being mild R1 type.

A study in Peninsular Malaysia in 1993 documented the overall resistance to chloroquine as 63.3% and to Sulfadoxine-pyrimethamine as 47.4%. RI, RII and R III[1] rates for chloroquine were 9.1%, 42.4% and 12.1% while for sulfadoxine-pyrimethamine they were 10.5%, 21.1% and 15.8%. Degree and rates of resistance to chloroquine were significantly correlated with pre-treatment parasite density, but not those to sulfadoxine-pyrimethamine.[3]

References:

1. Guidelines for Treatment of Malaria (2nd edition, WHO, 2010)
2. Montgomery, R., and Eyles, D. E. 1963. Chloroquine resistant falciparum malaria in Malaya. Trans. Roy. Soc. Trop. Med & Hyg. 57: 409-16
3. S. Lokman Hakim, S.W.A. Sharifah Roohi, Y. Zurkurnai, A. Noor Rain, S.M. Mansor, K. Palmer, V. Navaratnam and J.W.Mak. Plasmodium falciparum: Increased proportion of severe resistance (RII and RIII) to chloroquine and high rates of resistance to sulfadoxine-pyrimethamine in Peninsular Malaysia after two decades. Transactions of The Royal Society of Tropical Medicine And Hygiene (1996) 90, 294-297
4. The Plasmodium life cycle. Laboratory Identification of Parasites of Public Health Concern of the USA government of Centers for Disease Control and Prevention (CDC).http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/Malaria_il.htm

[1] RI, Delayed Recrudescence: The asexual parasitemia reduces to < 25% of pre-treatment level in 48 hours, but reappears between 2-4 weeks. RI, Early Recrudescence: The asexual parasitemia reduces to < 25% of pre-treatment level in 48 hours, but reappears earlier. RII Resistance: Marked reduction in asexual parasitemia (decrease >25% but <75%) in 48 hours, without complete clearance in 7 days. RIII Resistance: Minimal reduction in asexual parasitemia, (decrease <25%) or an increase in parasitemia after 48 hours.

CHAPTER 3: CLINICAL FEATURES

The incubation period of malaria is variable (refer chapter 2.2); the average being 10–14 days, but may be as short as 7 days or, in exceptional cases, up to 20 years as in *P.malariae* infection.[4] Symptoms occur within 6 weeks of the traveler leaving an endemic area in more than 90% of *P. falciparum* infections, and within 1 year in *P. vivax* infection. For *P. knowlesi,* symptoms occur 9-12 days after a person has visited or worked in a forested or forest-tinge area. There may be a relatively short **prodromal period** of tiredness and aches.

3.1 Symptoms of malaria

The **early** symptoms of malaria are **non-specific** and similar to the symptoms of a minor systemic viral illness e.g. headache, lassitude, fatigue, abdominal discomfort, muscle and joint aches, usually followed by fever, chills, perspiration, anorexia, vomiting and worsening malaise. The most common presentation of malaria is **high fever**. The classical paroxysm begins abruptly with an initial **'cold stage'**, with dramatic rigors during which the patient shakes visibly. This leads to a **'hot stage'** in which the patient has a temperature of more than 40°C, may be restless and excitable and may vomit or convulse, and finally a **'sweating stage'**, when the fever abates and the patient may fall asleep. This paroxysm may last 6–10 hours, and is followed by a prolonged asymptomatic period followed by further rigors in untreated patients. The classic paroxysm is, however, increasingly uncommon in clinical practice.

At early stage of malaria infection, without evidence of vital organ dysfunction, if prompt and effective treatment is given, the patient can experience full rapid recovery. If ineffective medicines are given or if treatment is delayed, especially in *P. knowlesi* and *P. falciparum* malaria, the parasite burden continues to increase every 24 or 48 hours, severe malaria and even death may ensue. This progression may occur within a few hours.

In high-transmission areas, such as in many sub-Saharan Africa, the majority of infections are asymptomatic and infections are acquired repeatedly throughout life. In such areas, symptomatic and sometimes fatal malaria occurs in the first few years of life, but, thereafter, it is increasingly likely to be asymptomatic. This reflects a state of imperfect immunity, where the infection is controlled, usually at levels below those causing symptoms. The rate at which imperfect immunity is acquired depends on the intensity of transmission.[1]

The nature of malarial clinical disease depends greatly on the background level of the acquired protective immunity and intensity of malaria transmission in the area of residence. Non-immune travelers to a malaria endemic area are at a higher risk of acquiring malaria, unless protective measures are taken. Immunity is, however, modified in pregnancy, and it is often gradually lost, at least partially, when individuals move out of the endemic areas for long durations (usually many years).

3.2 Definition of Uncomplicated Malaria

Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction. The signs and symptoms of uncomplicated malaria are non-specific.

3.3 Definition of Severe and Complicated Malaria

Severe malaria usually manifests with one or more of the following: coma (cerebral malaria), metabolic acidosis, severe anaemia, hypoglycaemia, acute renal failure or acute pulmonary oedema. By this stage of the disease, the case fatality in people receiving treatment is typically 10–20%. However, if left untreated, severe malaria is fatal in the majority of cases. Long-term cognitive impairment is also common in children with cerebral malaria.

In a patient with malaria infection and no other obvious cause of symptoms, the presence of one or more of the following clinical or laboratory findings classifies the patient as suffering from severe malaria.

Table 3.1: Clinical Features, Laboratory Findings and Complications of Severe & Complicated Malaria [1, 4]

Clinical features	• Impaired consciousness or unrousable coma • Prostration (*generalized weakness so that the patient is unable walk or sit up without assistance*) • Failure to feed/ not tolerating orally • Convulsion • Deep breathing, respiratory distress (acidotic breathing) • Circulatory collapse or shock, systolic blood pressure < 90 mm Hg *(**please refer to physician for local figure*) in adults and < 50 mm Hg in children • Clinical jaundice and evidence of other vital organ dysfunction • Haemoglobinuria • Abnormal spontaneous bleeding • Pulmonary oedema (*radiological*)
Laboratory findings	• Hypoglycaemia *(blood glucose < 3.0 mmol/l)* • Metabolic acidosis *(plasma bicarbonate < 18 mmol/l)* • Severe normocytic anaemia *(Hb < 8 g/dl, packed cell volume < 24%)* • Haemoglobinuria • Hyperparasitaemia (> *20,000/µl* for *P. knowlesi* or > 100,000/ *µl for other Plasmodium species)* • Hyperlactataemia • Renal impairment
Complications	• Cerebral malaria • Anaemia • Respiratory distress / Acute Respiratory Distress Syndrome (ARDS) • Renal failure • Hypoglycaemia • Circulatory collapse (shock) • Coagulopathy

References:

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6. Singh, B., and C. Daneshvar. *Plasmodium knowlesi* malaria in Malaysia. *Med J Malaysia*. 2010, 65(3): 223-30.

CHAPTER 4: DIAGNOSIS OF MALARIA

4.1 Clinical Diagnosis

The particular clinical diagnostic criteria vary from area to area according to the intensity of transmission, the species of malaria parasite and other prevailing causes of fever[3]. Malaria must be excluded in all febrile patients living in, or returning from, an endemic country, regardless of whether they have been taking antimalarial drugs. All **immigrants** from malaria endemic countries with fever should be given special attention to rule out malaria. Consideration of the possibility of malaria is an important step in diagnosis, particularly outside endemic areas, and a **travel history** should be a routine part of any clinical consultation in febrile patients.

In all settings, **clinical suspicion** of malaria should be **confirmed with a parasitological diagnosis**. However, in settings where parasitological diagnosis is not possible, the decision to provide antimalarial treatment must be based on the prior probability of the illness being malaria. Malaria should be suspected in the presence of thrombocytopenia, relative lymphopenia, atypical lymphocytes, and an elevated *lactate dehydrogenase* (LDH) level. (Box 3.1) Other possible causes of fever and need for alternative treatment must always be carefully considered.

Table 4.1: Investigating suspected malaria[8]

Investigations	Notes
Blood Film for Malaria Parasite (BFMP)	To be done immediately. There is no need to wait for a peak of fever before examining thick and thin blood films. If the initial film is negative, repeat another 2 samples or more especially at peak of fever if symptoms persist.
Full Blood Count (FBC)	In falciparum malaria, the WBC count is generally normal, with relative lymphopenia. Neutrophilia suggests secondary bacterial infection or severe disease. Thrombocytopenia is present in more than 90% of non-immune patients.
Blood Urea & Serum Electrolytes (BUSE)	Sodium, calcium and albumin are low; these usually resolve spontaneously with treatment.
CRP level	C-reactive protein (CRP) is raised
Liver profile	Bilirubin is often raised; in the context of normal liver function, this is related to haemolysis. Although malaria may cause mild elevations of liver enzymes, jaundice in the presence of liver enzyme abnormalities may suggest that other diagnoses (e.g. viral hepatitis) should be considered.
Blood glucose	Blood glucose can be low in severe cases (with high parasitaemia) and during quinine treatment in adults.

4.2 Laboratory Diagnosis

Prompt and accurate diagnosis of malaria is part of effective disease management. The diagnosis of malaria is based on clinical suspicion and on the detection of parasites in the blood (parasitological or confirmatory diagnosis). Once Plasmodium is detected, the

BFMP test should be done daily during hospital stay, weekly tests x 4 during follow-up for all species and additional monthly tests x 11 during follow-up for *P.vivax*.

4.2.1 Tests Available For Laboratory Diagnosis

Several tests are available for laboratory diagnosis of malaria such as Blood Film for Malaria Parasite (BFMP), Polymerase Chain Reaction (PCR) and Rapid Diagnostic Test (RDT) and these will be further elaborated here.

a. Blood Film for Malaria Parasite (BFMP)

Microscopic examination of both thick and thin film remains the gold standard for confirmation of malaria. The thick film is more sensitive for detecting malaria parasites as the blood is more concentrated which allow for a greater volume of blood to be examined. On the other hand, the thin film helps in parasite species identification. (Table 3.1)

Table 4.2: Advantages and limitations of microscopy

Advantages	Limitation
• High sensitivity. It is possible to detect malarial parasites at low densities. • Can quantify the parasite load. • Possible to distinguish the various species of malaria parasite and their different stages.	• Need adequately trained laboratory technician.

i. <u>Specimen</u>

For specimen collection, the thick and thin film should be prepared in one slide and sent in a slide box to the laboratory. Stained the thick (unfixed) and thin film (fixed with methanol) with 10% Giemsa stain in buffered solution with pH7.2 for 10 minutes. Blood taken in EDTA tubes, the anticoagulant should have films made within 2 hours or as soon as possible to minimize morphological changes in the parasites. *If BFMP slides are of poor quality, the medical officer should be informed immediately to send both the slide and blood sample in an EDTA tube to the laboratory. This would help to reduce delay in getting the microscopy results.*

ii. <u>Reporting Format</u>

Quantitative malaria microscopy is more accurate to calculate the number of parasites per micro liter of blood. This method is recommended as it can assist the doctor to assess the disease severity, monitor response to treatment and the patient's progress. The quantitative result should report different stages of parasite and therefore, the laboratory technician has to calculate both the asexual (trophozoites, schizonts) and sexual (gametocytes) stages of the parasite. (Box 4.1 and Box 4.2)

Microscopy results recorded as *P. malariae* should be reported as *P. knowlesi / P. malariae* to guide case management. These findings should be confirmed with PCR.

iii. Laboratory Turnaround Time

Hospital & health clinic with laboratory techinician: Within 1 hour after BFMP slides have reached the laboratory.
Health Care Clinics: Within the same day as taken.

* *Sample sent in EDTA tube may take a longer time to process*

Box 4.1: Method of calculation

When the thick film is examined and if *P. falciparum* parasites are found, they will be counted in the following way:

- Asexual will be calculated against 200 White Blood Cells but in VERY HEAVY infections the number may be 50 WBCs. The higher the number of WBC's counted the more accurate the final calculation.
- Sexual will be counted against WBC's as above.

Please note: A number of assumptions are made here which the doctor should be aware of:

- The number of WBC's per micro-liter of blood is 8,000.
- The number of red blood cells per micro-liter of blood is 5,000,000.
- That one parasite occupies one red blood cell.

Formula for calculation:

$$\frac{\text{No. of parasites}}{\text{No. of WBC's}} \times 8{,}000 = \text{Parasites per µl blood}$$

Box 4.2: Example of Calculation and Reporting

Thick film examined as *P. falciparum*

No. of Asexual	:	100
No of Gametocytes	:	10
No of WBC counted	:	200

Asexual density : $\frac{100}{200} \times 8{,}000 = 100 \times 40$

= 4,000 parasites per µl blood

Sexual density : $\frac{10}{200} \times 8{,}000 = 10 \times 40$

= 400 parasites per µl blood

⇨ Report : = Pf Asexual / sexual
= Pf 4,000 / 400 per µl blood

b. Polymerase Chain Reaction (PCR)

PCR for confirmation and species determination is indicated in certain situation such as;

- With clinical symptoms of malaria but no malaria parasite seen in BFMP
- Mortality cases
- Cases having microscopic appearance of *P.malariae*[10,11]

PCR test is available at the National Public Health Laboratory (MKAK) at Sungai Buloh.

i. Specimen

Whole blood in EDTA or dried blood spot on filter paper are the preferable specimens for PCR analysis. Whole blood via venipuncture in EDTA should be kept in a clean biohazard plastic bag and transported in a cold chain (4°C) within 3-4 hours or minus 20ºC if a longer period is needed for transportation. For dried blood spot prepared on filter papers (Whattman Grade 1), blot approximately 125 µl of blood (about 20 cent size in diameter) on the filter paper and leave to air dry. Label with appropriate ID, i.e. date of sample collection and initials of technician responsible. Dried blood spot should be transported to the laboratory at room temperature in a separate biohazard zip lock plastic bag (if specimens are obtained from more than one patient) within 48 hours. (**Note: A thick and thin film needs to be sent together with whole blood/dried blood spot specimen for microscopy diagnosis**.)

ii. Laboratory Turnaround Time

Nested PCR : 7 working days
qPCR (real time) : 3 working days

c. Rapid Diagnostic Test (RDT)

Rapid Diagnostic Tests are based on the detection of circulating parasite antigens. Rapid antigen detection tests (immunochromatographic tests) cannot replace microscopy but can be supplementary when malaria diagnosis is being performed by relatively inexperienced staff (e.g., in low prevalence areas and outside normal working hours). Result of RDTs should be always interpreted together with the results of microscopy, read by an experienced laboratory technician.

In theory malaria RDTs should have high sensitivity (>95%) and should be highly stable in all situations. Histidine-rich protein-2 is a water-soluble protein produced by trophozoites and young (but not mature) gametocytes of *P. falciparum*. The RDTs that use HRP2 detect *P. falciparum* only. These tests should be used only for diagnosis of acute malaria infections, and not for follow-up, as they may remain positive for several weeks even after successful treatment. *Plasmodium lactase dehydrogenase* (pLDH) and the pan-specific *aldolase* are produced by both asexual and sexual stages (gametocytes) of malaria parasites. There is considerable variability in performance of the pLDH and aldolase-based tests for the non-falciparum species.[9] Because none of

the aldolase-based tests are sufficiently sensitive for the non-falciparum species (including *P. vivax* and *P. knowlesi*), the use of pLDH-based RDTs with high sensitivity is recommended. No commercially available RDTs have been sufficiently sensitive overall for *P. knowlesi*, thus a negative pLDH-RDT or aldolase-based RDT does not exclude the diagnosis of knowlesi malaria. Several types of RDTs are available and information on this is available at the WHO website *(http://www.wpro.who.int/sites/rdt)*.

4.2.2 Quality Checking

Quality checking aims at detecting deficiencies in staff competency, reagent, equipment or infrastructure and work practices which require urgent rectification. The processes involved are shown in Table 4.3.

Table 4.3: Quality Checking Processes

Responsible bodies	Actions
Field sampling/Health Care Clinic /Hospitals	• Sending 100% of microscopy-positive slides and 10% of negative slides to State Vector Laboratory.
State Vector Laboratory/Kota Kinabalu Public Health Laboratory	• Rechecking 100% of positive slides and 10% of negative slides for quality control. • Results reported back to the respective laboratory optimally within one month. • After this all the slides have to be sent to Public Health Lab for quality control checking. • All positive slides for *P. malariae* and *P. knowlesi* to be sent to MKAK for PCR.
Parasitology & Mycology Unit, National Public Health Laboratory (MKAK)	• Rechecking 10% from positive slides and 2% from negative slides, which are sent from State Vector Laboratory for quality control. • Results reported back to the respective laboratory optimally within 5 weeks upon receipt of slides.

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10. Informal Consultation on the Public Health Importance of *Plasmodium knowlesi*. Kuching, Sarawak, Malaysia 22 to 24 February 2011, World Health Organization.
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12. Singh, B., and C. Daneshvar. Human infections and detections of *Plasmodium knowlesi*. Clin. Microbiol.Rev. 2013, 26(2):165.
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CHAPTER 5: MALARIA TREATMENT

The aims of malaria treatment are to alleviate symptoms and to prevent relapses and spread of the disease. WHO recommends the use of Artemisinin Combination Therapy (ACT) as the standard treatment for malaria and discourages the prescription of monotherapy or sub-standard ACT as this will promote resistant plasmodium.

5.1 Treatment of Malaria in Adults

The treatment regimen is as shown in Table 5.1. Treatment of malaria has to be modified in pregnancy due to contraindication for use of certain antimalarials. (Table 5.2)

5.2 Field Treatment

Field treatment for malaria is not advisable as a routine mode of treatment. However, it is still practiced in certain remote areas in Sarawak and probably Sabah due to unforeseen logistic situation. However, this is limited to interior areas where it is only reachable by flying doctor services, the patient with clinically uncomplicated malaria. The treatment should follow treatment guidelines accordingly. However, all malaria cases must be encouraged to be hospitalized.

*As testing for G6PD deficiency is not readily available at field level, patient need to be educated on signs and symptoms of hemolysis i.e. dark colour urine. Patient needs to be advised to stop primaquine immediately if such signs and symptoms are present.

History of previous anti-malarial exposure especially to primaquine can be elicited. If there is no history of adverse reaction to primaquine, then it may be reasonable to assume that there is no G6PD deficiency.

5.3 Presumptive Treatment

Presumptive treatment is given for those patients whom a blood film was taken but the results would not be available at that moment due to logistic reason, like those in very remote areas and risks of defaulting follow-up. This is only done under extreme circumstances. This mode of treatment is given to those in endemic areas with classical symptoms of malaria i.e. fever for more than 3 days with chills and rigors. The treatment should be based on the predominant species in that area. (Refer table 5.2) Sulphadoxine/Pyrimethamine (SP or Fansidar) should not be used for field treatment or presumptive treatment for malaria due to high level of resistance.[4]

Table 5.2: Treatment Regimen for Malaria

DIAGNOSIS	FIRST LINE	ALTERNATIVE	COMMENTS
PLASMODIUM FALCIPARUM			
Plasmodium falciparum **A) Non Complicated** **(i) New Infection**	**Riamet*** (1 tablet: 20 mg artemether/ 120 mg lumefantrine) A 3-day treatment schedule with a total of 6 doses is recommended The patient should receive an initial dose followed by the 2nd dose 8 hours later, then 1 dose BD for the following 2 days **5 - <15kg : 1 tablet per dose** **15 - <25kg : 2 tablets per dose** **25 - <35kg : 3 tablets per dose** **≥35kg : 4 tablets per dose**	Artesunate /Mefloquine (AS+MQ FDC Tablet)* 2 FDC strength – 25mg AS /55 MQ and 100mg AS / 220mg MQ A 3-day treatment schedule, once daily regime 5-8kg : 1 tablet of 25mg AS/55mg MQ 9-17kg : 2 tablets 25mg AS / 55mg MQ 18-29kg : 1 tablet of 100mg AS/ 220mg MQ ≥30kg : 2 tablets of 100mg AS/ 220mg MQ OR Oral Quinine (10mg/kg) 8 hourly with oral Doxycycline 100mg BD for 7 days	The choice of drug should be governed by drug availability and safety. Riamet should be taken with a **fatty meal** eg milk to increase bioavailability If the patient cannot tolerate Riamet or take a high fat diet, AS+MQ will be the preferred option Primaquine 0.75mg/kg (max 45mg) to be given on Day 1 of treatment in addition to artemisin regime and quinine, except for pregnant women and infant < 1 year of age. If G6PD status unknown before use, to use 0.25mg/kg. *_**In pregnancy**_: Limited data on safety of artemisinin exposure during 1st trimester, thus quinine is recommended. Exposure of artemisinin derivatives during 2nd and 3rd trimester have shown no adverse effects on the mother or fetus

DIAGNOSIS	FIRST LINE	ALTERNATIVE	COMMENTS
			Lactating woman Do not use primaquine and tetracycline ***<u>AS + MQ</u>*** • Do not use in pregnancy • May cause seizure in children with epilepsy • Interact with Quinine, Choloroquine and Halofantrine and may cause arrhythmia • Do not repeat AS-MQ regime within 60 days. (Reuse of mefloquine within 60 days of first treatment is associated with increased risk of neuropsychiatric reactions.)
PLASMODIUM FALCIPARUM			
Plasmodium falciparum **A) Non Complicated** **(ii) Treatment Failure or Relapse**	An alternative ACT regimen (as Riamet is used as the first line regimen, so the choice will be AS+MQ and vice versa) Artesunate /Mefloquine (AS+MQ FDC Tablet)* Refer earlier table for dosing	Oral Quinine (10mg/kg) 8 hourly with oral Doxycycline 100mg BD for 7 days	Primaquine 0.75mg/kg(max 45mg) to be given on Day 1 of treatment in addition to artemisin regime and quinine, except for pregnant women and infant < 1 year of age. If possible, check G6PD status before use

DIAGNOSIS	FIRST LINE	ALTERNATIVE	COMMENTS
***Plasmodium falciparum*:** **B) Severe**	Day 1 IV Artesunate 2.4mg/kg at 0 hour, 12 hour, 24 hour and daily subsequently till day 7 ** AND Oral Doxycycline 100mg BD (given together with IV Artesunate) ****Parenteral artesunate should be given for a minimum of 24 hours (3 doses) or until patient can tolerate orally then it can be switched to a complete course of oral ACT either Riamet or AS+MQ** ***For all stages of pregnancy:** IV Artesunate as for normal adults[3]	Day 1 (Loading dose) IV Quinine 20mg salt/kg over 4 hours in D5%. OR IV Quinine 7mg salt/kg over 1 hour followed by 10mg salt/kg over 4 hours Then, IV Quinine 10mg/kg 8 hourly (can give orally if tolerated) for 7 days AND Oral Doxycycline 100mg BD for 7days	IM artesunate or quinine can be given if no venous access available. The drug must be given before transporting patient to a tertiary centre The patient should be managed in an intensive care facility Monitor patient's blood glucose and ECG while on IV quinine ***In renal failure or hepatic dysfunction***, quinine dose should be reduced by one third after 48 h. No dosage adjustments are necessary if patients are receiving haemodialysis Primaquine 0.75mg/kg(max 45mg) to be given on Day 1 of treatment in addition to artemisin regime and quinine, except for pregnant women and infants < 1 year of age. If possible, check G6PD status before use.

DIAGNOSIS	FIRST LINE	ALTERNATIVE	COMMENTS
PLASMODIUM VIVAX / OVALE			
P. vivax, P. ovale **A)New Infection**	Oral Chloroquine 10mg base/kg (max 600mg) stat Then, 5mg base/kg (max 300mg) 6 hours later, Day 2 and Day 3 AND Primaquine 0.5 mg/kg (max 30mg) OD for 14 days		**G6PD**: In patients with mild variants of G6PD deficiency, primaquine should be given in a dose of 0.75 mg base/kg body weight once a week for 8 weeks. If significant haemolysis occurs on treatment, then primaquine should be stopped. In severe *P. vivax*, treatment is as severe *P. falciparum*
B)Treatment Failure or suspected chloroquine resistant	Repeat course: ACT (Riamet) for 3 days AND Primaquine 30mg OD for 14 days **In pregnancy,** The full course of Chloroquine will be given, then followed by 300mg weekly until delivery The full course of Primaquine will only be given post-delivery	ACT (AS+MQ) for 3 days OR Oral Quinine 10mg/kg 8 hourly for 7 days AND Primaquine 30mg OD for 14 days	For adults > 70kg, continue 30 mg daily beyond 14 days until a total cumulative dose of 6 mg/kg is reached
PLASMODIUM MALARIAE/KNOWLESI*			
P.malariae, P.knowlesi **A) New Infection**	**Riamet** (1 tablet: 20mg artemether/120mg lumefantrine)	ACT (AS+MQ) for 3 days OR	**** P. knowlesi* and *P. malariae* cannot be distinguished by microscopy. In Sabah and Sarawak, *P. malariae* is rare;**

DIAGNOSIS	FIRST LINE	ALTERNATIVE	COMMENTS
	A 3-day treatment schedule with a total of 6 doses is recommended. The patient should receive initial dose followed by the 2nd dose 8 hours later, then 1 dose BD for the following 2 days. **5 - <15kg : 1 tablet per dose** **15 - <25kg: 2 tablets per dose** **25 - <35kg: 3 tablets per dose** **≥35kg : 4 tablets per dose**	Oral Chloroquine 10mg base/kg (max 600mg) stat Then, 5mg base/kg (max 300mg) 6 hours later, Day 2 and Day 3	**nearly all reports of *P. malariae* are in fact *P. knowlesi* when tested by PCR. Patient diagnosed by microscopy as *P.malariae* should be presumed to have *P.knowlesi* infection.** It does not require radical cure with primaquine, as no hypnozoites are formed in infection with this species.
B) Severe	Treat as severe P falciparum infection with IV Artesunate AND Oral Doxycycline 100mg BD for 7 days.		

References:

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3. McGready *et al, Lancet ID*, 2012
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CHAPTER 6: MANAGEMENT OF SEVERE AND COMPLICATED MALARIA

Severe malaria is caused by the presence of a high density of asexual forms of Plasmodium in the patient's body. Such a patient needs urgent management at secondary or tertiary hospitals. However, in areas of high malarial endemicity or in outbreak situation, clinical suspicion alone should prompt a therapeutic trial with an appropriate antimalarial drug even if blood smears are negative.

6.1 For treatment

All malaria patients should be admitted. In exceptional cases where this is not possible, uncomplicated malaria can be managed at out-patient clinics with close monitoring.

However, for patients with the following features, admission is **mandatory**:

a. patients with manifestations of severe/ complicated malaria (refer Chapter 3)
b. patients who cannot tolerate orally
c. patients with high parasitaemia (>100 000/µl) [> 20,000/µl for *P.knowlesi*][5]
d. patients with G6PD deficiency
e. all pregnant mothers with acute malaria
f. patients with severe malnutrition
g. children

6.2 Referral to hospitals with specialists

These patients should be referred to hospitals with specialists for further management:

a. all patients with severe and complicated malaria
b. immuno-compromised patients with significant co-morbidities e.g. hepatic or renal dysfunction
c. pregnant mothers

Box 6.1: Steps to referral

When referring patients, ensure

- referral letter and BFMP slides are sent along
- antimalarial treatment is commenced prior to transfer

If referral is not possible

If admission is not possible either to district hospitals or hospitals without specialists, these patients **must be** discussed with the Physicians/ Infectious Disease Specialists regarding the plan of management

.

6.3 Criteria for admission

All patients diagnosed as malaria or suspected malaria should be admitted. In situations where this is not possible, they should be treated and followed up daily by a doctor or assistant medical officer (in area where there is no doctor).

6.4 Criteria for referral to the High Dependency Unit (HDU) or Intensive Care Unit (ICU)

- If a patient has any of the features of severe malaria, the patient should be referred to a hospital with a HDU or ICU.
- All patients with complicated malaria should be referred to the Physician on call.
- An early referral to intensivist should be made for further evaluation and management.
- If the patient cannot be transferred, then the patient should be monitored closely in the district hospital in close consultation with the physician.

6.5 General Management for Severe Malaria

1. Take a complete History and physical examination.
   a. Examine the Glasgow Coma Scale (GCS), presence of neck stiffness, Blood pressure, Pulse rate, Respiratory rate. Examine the fundi as well.
2. Send the following investigations:

   a. Blood for Culture and Sensitivity.
   b. Full Blood Count.
   c. Prothrombin Time (PT), Partial Thromboplastin Time (PTT).
   d. Serum Urea and Electrolytes, Creatinine.
   e. Blood glucose.
   f. Liver Function Test.
   g. Chest X-ray.
   h. Arterial Blood gas.
   i. Serum Lactate (if available)

3. Admit the patient to the ICU or the High Dependency Unit
4. The patient should be referred to the Physician or the Intensivist.
5. Give IV Artesunate (2.4 mg/kg) stat. If this is not possible, give it IM. Administer IV Quinine if IV Artesunate is not available (and IM, if no IV access). For complete dosing, please look at the section on antimalarial treatment.
6. Administer the intravenous antimalarial for at least 24 hours before switching to an oral formulation if the patient improves and can tolerate orally.
7. Close observation of the vital signs, GCS, by the nurses and doctor is of vital importance

8. **Pulmonary oedema is a grave complication of severe knowlesi and falciparum.** It has a high mortality (over 80%in falciparum malaria); the prognosis is better in vivax malaria. Pulmonary oedema may develop several days after chemotherapy has been started, at a time when the patient's general condition is improving and the peripheral parasitaemia is falling.
    a. Close input output monitoring is very important as the patient can develop pulmonary oedema easily if too much fluids are given. Give fluids just enough to maintain the circulation and correct dehydration.
    b. Children with severe malaria who are unable to retain oral fluids should be managed with half normal saline (0.45%) with 5% dextrose with maintenance fluids (3-4ml/kg/hour), and adults at 1-2ml/kg body weight per hour, until the patient is able to take and retain oral fluids.
    c. Rapid fluid boluses are contraindicated in severe malaria resuscitation. Dehydration should be managed cautiously and ideally guided by urine output (with a urine output goal of > 1ml/kg body weight per hour), unless the patient has anuric renal failure or pulmonary oedema, for which fluid management should be tailored to the needs of the patient and reassessed frequently.
9. If the patient's GCS is reduced, look for other causes such as meningitis. A lumbar puncture may then be indicated and antibiotics instituted.
10. There is considerable clinical overlap between septicaemia, pneumonia and severe malaria, and these conditions may coexist .If secondary infections are suspected, then start the patient on a broad spectrum IV antibiotic such as Ceftriaxone 2g OD (after a septic workout is done).
11. Monitor for clinical and parasitological therapeutic response.
12. High fever can be managed by tepid sponging and Paracetamol.

6.6 Management of complications of malaria

Malaria may become a medical emergency without prompt and appropriate treatment. Complications can rapidly set in which may cause death. Most cases of severe malaria are caused by *P. falciparum* infection. Rarely, *P. vivax* or *P. ovale* produce serious complications and even death. In Malaysia, *P. knowlesi* has caused severe malaria and serious complication as a result of hyperparasitaemia.

Table 6.1: Immediate clinical management of severe manifestations and complications of malaria

Manifestations/ Complications	Immediate Management
Coma (cerebral malaria)	• Maintain airways and for ventilator support if necessary; exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatment, such as corticosteroids, heparin and adrenaline.
Convulsions	• Maintain airways; treat promptly with intravenous or rectal diazepam and/ or other anticonvulsants. Check blood glucose, blood urea and serum electrolytes. • Prophylactic anticonvulsants are not recommended.
Hypoglycaemia	• Correct hypoglycaemia and maintain with glucose containing infusion.
Acute renal failure	• Exclude pre-renal causes, check fluid balance and urinary sodium in established renal failure initiate haemofiltration or haemodialysis, or peritoneal dialysis.
Severe Anaemia	• Blood transfusion where indicated.
Acute pulmonary oedema	• Prop patient up at an angle of 45°, give oxygen and other respiratory support as indicated. Adjust fluid therapy appropriately. Diuretics if necessary.
Shock	• Assess hydration status. Give appropriate fluid therapy Achieve CVP measurement 8-12cm H_2O. Suspect septicaemia (bacterial in origin) in unexplained clinical deterioration. Take blood for cultures; give parenteral broad-spectrum antimicrobials and change it according to culture results.

6.7 Adjunct therapy

In an attempt to reduce the unacceptably high mortality of severe malaria, besides appropriate and effective antimalarial drugs, various adjunctive treatments for the complications of malaria have been evaluated in clinical trials. Adjunctive therapy is defined as any additional therapy that modifies physiologic processes caused by malaria. These therapies may act directly on specific biologic pathways altered by malaria or more generally on end-stage factors produced in malaria by a number of different specific processes.

6.7.1 Exchange blood transfusion (EBT)

There is no consensus on the indications, benefits and risk involved on EBT in severe malaria as no randomized clinical trial has ever been conducted on EBT. The procedure requires expertise and intense monitoring, which limits its suitability in resource-limited settings. The rationale for EBT has been variously proposed as:

- Removing infected red blood cells from the circulation and, therefore, lowering the parasite burden
- Reducing rapidly both the antigen load and the burden of parasite-derived toxins and toxic mediators
- Replacing the rigid unparasitized and parasitized red cells by more deformable cells and, therefore, reducing microcirculatory obstruction.

6.7.2 Adjunctive Treatments not recommended

Other supportive strategies and interventions have been used in severe malaria patients in an effort to further reduce the mortality, but very few are supported by evidence of benefit and this includes the use of these listed drugs. [1-3]

- Modulate the immune response to *P. falciparum* (dexamethasone, intravenous immunoglobulin, monoclonal antibodies to TNF-α, pentoxifylline and curdlan sulfate)*
- Reduce iron burden (iron chelation with desferrioxamine or deferipone)
- Reduce oxidative stress (*N*-acetylcysteine [NAC])
- Counteract the prothrombotic state and prevents the formation of rosettes of infected red blood cells (RBCs) (heparin and aspirin)
- Reduce parasitemia (EBT)
- Expand volume and potentially decrease acidosis (albumin)**
- Decrease intracranial pressure and cerebral edema (mannitol and dexamethasone)
- Prevent seizure activity (prophylactic phenobarbital)

Note

* Use of high dose steroid was associated with bleeding and seizures, and prolonged coma resolution time when compared with placebos.

** Albumin is the only adjunctive therapy to date associated with reduced mortality in children with severe malaria from a single, small study. A multicenter randomized clinical trial comparing volume expansion with albumin or saline to treatment with maintenance fluids in febrile children with impaired perfusion is currently being conducted.[4]

6.8 Discharge

All patients diagnosed with malaria must be admitted for the duration of treatment to ensure completion. In high transmission settings, it is important to keep the patients warded until they are cleared of gametocytes which play a crucial role in the spread of malaria and thus of public health concern. Otherwise, the patients can be discharged once they are clinically well with two negative BFMP slides within 48 hours.

6.9 Follow up

Patients should be followed up weekly for a month. Thereafter, follow up for those infected with *P. vivax* infection should be followed up monthly for one year. However, if antimalarial drug resistance is suspected, follow up should be extended; for example, in the case of suspected *P. falciparum* resistance, beyond one month. Such cases should be notified to the state and ministerial level for further action.

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CHAPTER 7: MANAGEMENT OF MALARIA IN PAEDIATRICS

The treatment regimen for pediatric patients is the same as for adults except that the drug dose is adjusted according to the weight of the patient. In addition, drug such as doxycyline is contra-indicated in children less than eight years old. Primaquine should be given to pediatric patients only after they have been screened for G6PD deficiency.

7.1 Uncomplicated malaria

Symptomatic infection with malaria parasitaemia without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction.

Table 7.1: Treatment for Uncomplicated *Plasmodium falciparum* malaria

FIRST LINE TREATMENT

PREFERRED TREATMENT

Artesunate / mefloquine FDC **(ASMQ)**

Weight (kg)	Age	Dose
5-8	6-11 mths	1 ASMQ FDC 25/55mg once daily for 3 days
9-17	1-6 years	2 ASMQ FDC 25/55mg once daily for 3 days
18-29	7-12 years	1 ASMQ FDC 100/220mg once daily for 3 days
>30	>13 years	2 ASMQ FDC 100/220mg once daily for 3 days

ALTERNATIVE TREATMENT

Artemether / lumefantrine (**Riamet**)

Weight (Kg)	Dose
5-14	DI: 1 tab stat then 1 tab again after 8 hours D2-3: 1 tab BD
15-24	D1: 2 tabs stat then 2 tabs again after 8 hours D2-3: 2 tablets BD
25 – 35	D1: 3 tabs stat then 3 tabs again after 8 hours D2-3: 3 tablets BD
>35	D1: 4 tabs stat then again 4 tabs after 8 hours D2-3: 4 tabs BD

Add a **single 0.75 mg base/kg primaquine dose** should be given to **all patients** with confirmed *P. falciparum* malaria on the first day of treatment in addition to an ACT. Check G6PD before giving primaquine.
Avoid ASMQ in children with epilepsy as well.
Riamet should be administered with high fat diet preferable to be taken with milk to enhance absorption
Both ASMQ FDC and Riamet are Artemisinin-based Combination Treatment (ACT).

SECOND-LINE TREATMENT FOR TREATMENT FAILURE

- An alternative ACT (if Riamet were used in the first regimen, use ASMQ for treatment failure and vice-versa)
  OR
- (oral) Artesunate 4mg/kg OD plus clindamycin 10mg/kg bd for a total of 7 days
  OR
- Quinine 10mgsalt/kg 8 hourly plus clindamycin 10mg/kg bd for a total of 7 days.

Add primaquine 0.75mg base /kg single dose OD if gametocyte is present at any time during treatment. Check G6PD before giving primaquine.

Table 7.2: Treatment for Plasmodium *vivax, knowlesi* or *malariae*

Treatment for *Plasmodium vivax*	**Treatment for *Plasmodium knowlesi* or *malariae***
Total chloroquine 25mg base/kg divided over 3 days D1: 10 mg base/kg stat then 5 mg base/kg 6 hours later D2: 5 mg base/kg OD D3: 5 mg base/kg OD **AND** Primaquine* 0. 5 mg base/kg daily for 14 days	Total chloroquine 25mg base/kg divided over 3 days D1: 10 mg base/kg stat then 5 mg base/kg 6 hours later D2: 5 mg base/kg OD D3: 5 mg base/kg OD

NOTE: *Chloroquine should be prescribed as mg base in the drug chart.
P. malariae and *P. knowlesi* do not form hypnozoites, hence do not require radical cure with primaquine

Treatment of chloroquine-resistant *P. vivax, knowlesi or malariae*

- ACT (Riamet or ASMQ) should be used for relapse or chloroquine resistant P.vivax. For radical cure in P vivax, ACT must be combined with supervised 14-day primaquine therapy.
- Quinine 10mg salt/kg three times a day for 7 days is also effective for chloroquine resistant *P. vivax* and this must be combined with primaquine for antihypnozoite activity.
- Mefloquine 15mg/kg single dose combined with primaquine have been found to be effective.

Primaquine may cause life threatening haemolysis in individuals with G6PD deficiency. G6PD testing is required before administration of primaquine. For those found to have mild to moderate G6PD deficiency, an intermittent primaquine regimen of 0.75mg base/kg weekly for 8 weeks can be given under medical supervision. In severe G6PD deficiency primaquine is contraindicated and should not be used

Severe and complicated *P. vivax, knowlesi or malariae* should be managed as for severe falciparum malaria (see below)

7.2 Complicated/severe *Plasmodium falciparum*

All Plasmodium species can potentially cause severe malaria, the commonest being *P. falciparum*. Young children especially those aged below 5 years old are more prone to develop severe or complicated malaria.

Clinical features:	**Laboratory findings:**
• impaired consciousness or unarousable coma • prostration, • failure to feed • multiple convulsions (more than two episodes in 24 h) • deep breathing, respiratory distress (acidotic breathing) • circulatory collapse or shock • clinical jaundice plus evidence of other vital organ dysfunction • haemoglobinuria • abnormal spontaneous bleeding • pulmonary oedema (radiological)	• hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl) • metabolic acidosis (plasma bicarbonate < 15 mmol/l) • severe anaemia (Hb < 5 g/dl, packed cell volume < 15%) • haemoglobinuria • hyperparasitaemia (> 2%/100,000/µl in low intensity transmission areas or > 5% or 250,000/µl in areas of high stable malaria transmission intensity) • hyperlactataemia (lactate > 5mmol/l) • renal impairment

Table 7.3: Treatment for Complicated *Plasmodium falciparum*

FIRST LINE TREATMENT
D 1: IV artesunate 2.4 mg/kg on admission, then repeat again at 12h **D 2-7**: IV artesunate 2.4 mg/kg OD or switch to oral ACT Parenteral artesunate should be given for a minimum of 24h or until patient is able to take orally and thereafter to complete treatment with a complete course of oral ACT (ASMQ or Riamet). Avoid using ASMQ (Artesunate + mefloquine) if patient presented initially with impaired consciousness as increased incidence of neuropsychiatric complications associated with mefloquine following cerebral malaria have been reported. IM artesunate (same dose as IV) can be used in patients with difficult intravenous access. Children with severe malaria should be started should be started on broad-spectrum antibiotic treatment immediately at the same time as antimalarial treatment.
SECOND LINE TREATMENT
D 1: IV Quinine loading 7mg salt/kg over 1 hour followed by infusion quinine 10mg salt/kg over 4 hours then 10mg/kg 8 hourly OR Loading 20mg salt/kg over 4 hours then IV 10mg salt/kg 8 hourly *(Dilute quinine in 250ml of D5% over 4 hours)* **D 2-7**: IV Quinine 10mg/kg 8 hourly AND Doxycycline (>8yrs) (3.5 mg/kg OD) OR Clindamycin (<8yrs) (10 mg/kg/dose bd) given for 7 days Quinine infusion rate should not exceed 5 mg salt/kg body weight per hour Change to oral Quinine if able to tolerate orally. (Max Quinine per dose = 600mg.) Reduce IV quinine dose by one third of total dose if unable to change to Oral quinine after 48hours or in cases with renal failure or liver impairment.

7.3 Congenital malaria

Congenital malaria is uncommon. It can be acquired by transmission of parasites from mother to child during pregnancy or perinataly during labour. Incidence varying from 0.3 to 33% has been reported from both endemic and non-endemic countries. Congenital malaria from *P. vivax* is more commonly reported in Asia whereas infection from *P. falciparum* is mainly described in African countries. Most babies present with symptoms between 10 and 30 days of age (range: 14hr to several months of age). The clinical features of neonatal malaria include anaemia (77%), fever (745), liver and spleen enlargement (68%), poor feeding/lethargy/irritability, jaundice and severe thrombocytopaenia. Congenital malaria may mimic neonatal sepsis and should be considered in the differential diagnosis of neonatal sepsis. All newborn babies of mother with malaria should been screened for congenital malaria.

Treatment for ***P vivax*** **infection**: chloroquine, total dose of 25mg base/kg orally divided over 3 days

D1: 10 mg base/kg stat then 5 mg base/kg 6 hours later
D2: 5 mg base/kg OD
D3: 5 mg base/kg OD

Primaquine is not required for treatment as the tissue/ exo-erythrocytic phase is absent in congenital malaria.

Treatment for ***P.falciparum*** **infection**: quinine 10mg/kg q8 hourly for 1 week.

7.4 Mixed Malaria infections

Mixed malaria infections are not uncommon. ACTs are effective against all malaria species and are the treatment of choice. Treatment with primaquine should be given to patients with confirmed *P.vivax* infection.

References:

1. Dondorp A, *et al*. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): on open-label, randomized trial; Lancet 2010 Nov 13:376(9753): 1647-1657
2. WHO Malaria treatment Guidelines 2010
3. UK Malaria guidelines 2007, Metha PN 2004
4. Neena V. et al. Congenital malaria with atypical presentation: a case report from low transmission area in India. Malaria Journal 2007, 6:43
5. Del Punta et al. Congential Plasmodium vivax malaria mimicking neonatal sepsis: a case report.Malaria Journal 2010, 9:63
6. Red Book 2009

CHAPTER 8: MALARIA CHEMOPROPHYLAXIS

Malaria prevention consists of a combination of mosquito avoidance measures and chemoprophylaxis. The mosquito avoidance measures include insect repellant, wearing long sleeves, long pants, sleeping in a mosquito-free setting or using an insecticide-treated be dnet. The use of *diethyltoluamide* (DEET) 20-50% in lotions, spray or roll-on formulation is safe and effective when applied to the skin of adults and children. Although *diethyltoluamide* may be used in children > 2months, it should be used with caution. Because of their increased surface-area-to-body-mass ratio, children may be at increased risk for toxicity due to greater skin absorption. Low-concentration products should be used and applied sparingly. No antimalarial drug is 100% protective and must be combined with the use of personal protective measures

8.1 Risk of malaria

The risk of acquiring malaria differs substantially from region to region and from traveler to traveler, even within a single country as it depends on several factors such as transmission intensity, duration of stay in the endemic area and the efficacy of preventive measures. Often, the risk to the indigenous population is used as a guideline for the risk to the traveler. Travelers with the highest estimated relative risk for infection are those going to West Africa and Oceania. Travelers going to other parts of Africa, South Asia, and South America have a moderate estimated relative risk for infection. Travelers with lower estimated relative risk are those going to Central America and other parts of Asia. (1) All travelers should seek medical attention in the event of fever during or after return from travel to areas with malaria.

Risk groups include:

a. Travelers or visitors to endemic areas
b. Army personnel
c. Loggers/rubber tappers
d. Workers in endemic areas e.g. dam construction, plantation

Caution:
Patient with severe splenic dysfunction or pregnant women should avoid traveling to endemic areas.

8.2 Chemoprophylaxis

There are two types of chemoprophylaxis: suppressive and causal prophylaxis.

8.2.1 Suppressive prophylaxis

Chloroquine, proguanil, mefloquine, and doxycycline are suppressive prophylactics. This means that they are only effective at killing the malaria parasite once it has entered the erythrocytic stage (blood stage) of its life cycle, and therefore have no effect until the liver stage is complete. That is why these prophylactics must continue to be taken for four weeks after leaving the area of risk.

8.2.2 Causal prophylaxis

Causal prophylactics target not only the blood stages of malaria, but the initial liver stage as well. This means that the user can stop taking the drug seven days after leaving the area of risk. Atovaquone/Proguanil (Malarone) and primaquine are the only causal prophylactics in current use.

8.2.3 Considerations when choosing a drug for malaria prophylaxis

a. Check risk of exposure to malaria and the recommended drugs listed in country-specific tables as in Appendix 1 or updated version on-line in the internet.
b. For all medicines, consider the possibility of drug-drug interactions with other medicines that the person might be taking as well.
c. When deciding which drug to use, consider length of trip, previous adverse reactions and current medical history.
d. Start chemoprophylaxis earlier if there are particular concerns about tolerance to the medications. For example, mefloquine can be started 3–4 weeks in advance to allow potential adverse events (AE) to occur before travel.
e. The use of the same or related drugs that have been taken for prophylaxis is not recommended to treat malaria.

Table 8.1: Advantages and Disadvantages of Chemoprophylaxis

DRUG	ADVANTAGES	DISADVANTAGES
Doxycycline* Dose: 100mg daily Start: 1-2 days before departure Stop: 4 weeks after travel Maximum duration: 2 years **Pediatric Dosage** 1.5mg base/kg once daily (max. 100 mg) <25kg or <8 yr: **Do Not Use** 25-35kg or 8-10 yr: 50mg 36-50kg or 11-13 yr: 75mg >50kg or >14 yr: 100mg	• Some people prefer to take a daily medicine • Good for short trip and last-minute travelers because the drug is started 1-2 days before traveling • Tends to be the least expensive • Doxycycline also can prevent some additional infections (e.g., Rickettsiae and leptospirosis) and so it may be preferred by people planning to do lots of hiking, camping, and swimming in fresh water	• Contraindicated in pregnancy and children <8 years old • Photosensitivity –need to avoid considerable sun exposure • Gastrointestinal (GIT) upset • Vaginal candidiasis
Atovaquone/Proguanil (Malarone) 100/250mg* Dose: 1 tablet daily Start: 1-2 days before departure Stop: 7 days after travel **Pediatric Dosage** **Pediatric tablet** of 62.5 mg atovaquone and 25 mg proguanil: 5-8 kg: 1/2 tablet daily >8-10 kg: 3/4 tablet daily >10-20 kg: 1 tablet daily >20-30 kg: 2 tablets daily >30-40 kg: 3 tablets daily **>40 kg: 1 adult tablet daily**	• Good for last-minute travelers • Good choice for shorter trips • Very well tolerated medicine – side effects uncommon	• Contraindicated in pregnancy or breastfeeding and patient with severe renal impairment • Expensive

DRUG	ADVANTAGES	DISADVANTAGES
Mefloquine (Lariam)** Dose: 250mg weekly Start: 2 weeks before departure Stop: 4 weeks after travel Maximum duration: 1 year **Pediatric Dosage** <15 kg: 5mg of salt/kg; 15-19 kg: 1/4 tab/week; 20-30 kg: 1/2 tab/week; 31-45 kg: 3/4 tab/week; >45 kg: 1 tab/week	• Good choice for long trips because it is taken only weekly • Can be used in second and third trimester of pregnancy and in first trimester if there is no other option	• Cannot be used in areas with mefloquine resistance • Cannot be used in patients with certain psychiatric conditions, patients with epilepsy or cardiac conduction abnormalities • Not a good choice for last-minute travelers and for trips of short duration

***** **Preferred choice for Malaysia**
****** **Alternative**

References:

1. British National Formulary Edition 61 March 2011
2. The World Health Organization provides country-specific advice on malaria prevention.
3. 2007 guidelines are available from the UK Health Protection Agency website
4. Centers for Disease Control and Prevention website. Available at http://www.cdc.gov. Accessed in Jan 2012.

CHAPTER 9: TREATMENT RESPONSE MONITORING

DRS_Annex 1

National Surveillance of Drug Response Against
Malaria Parasite (*P.falciparum, P.knowlesi and P.malariae*)

Note: This form is to be completed for <u>all cases</u> of *P. falciparum, P.knowlesi and P.malariae* seen and treated with the first line drugs at the all hospitals/clinics.

1	INFORMANT									
	Hospital				State					
	Name of Reporting Officer				Designation of Reporting Officer					
	Medical Officer									
	Coordinator									
2	PATIENT'S DEMOGRAPHIC DATA									
	Patient's Initial				Patient's ID (Reg. No/NRIC)					
	Age (Years)		Ethnic		Gender (√)	Male		Female		Body weight (kg)
3	DRUG/MEDICATION HISTORY									
	Day of treatment			Actual number of <u>tablet</u> given to and taken by the patient						
				AL	ASMQ			Others (Specify):		
					Adult dose		Paeds dose	_____		
	D0									
	D1									
	D2									
4	PARASITE RESPONSE									
	Type of parasite (√)			*P.falciparum* ☐		*P.knowlesi* ☐			*P.malariae* ☐	
	Follow-up slide post treatment				Parasite density (per uL blood)					
	Day	Date Due*		Actual Date**	Asexual				Sexual (gametocyte)	
	D0									
	D3									
	D7									
	D14									
	D21									
	D28									
	D56									
5	CASE INVESTIGATION									
	Was this patient treated before for malaria (√)?			No ☐						
				Yes ☐	What type of medication?(If known)					
					When was medication taken? (eg: 1 week/month prior to current treatment)					
	Probable Source of Infection in This Case (√)			Local ☐						
				Imported ☐	From where?					
6	VERIFICATION AND VALIDATION (Epid.Officer/MOH)									
	Name				Signature					

AL=Artemether-Lumefantrine (Riamet) ASMQ=Artesunate-Mefloquine
D0 = Day of starting the treatment
* Enter the date due for the subsequent post-treatment follow-up (D3, D7, D14, D21, D28, D56)
**Enter the actual date of slide collection during follow-up

STANDARD OPERATING PROCEDURE
NATIONAL SURVEILLANCE OF DRUG RESPONSE AGAINST MALARIA PARASITE,
MINISTRY OF HEALTH MALAYSIA

---

1. Organisation and Standard Operating Procedure (refer DRS_Annex 3)

1.1 Medical Officer of Health (MOH) at the District Health Office is responsible to coordinate and monitor surveillance activity.
1.2 Appoint a dedicated staff to act as coordinator (e.g: PPKP).
1.3 Identify all Medical Officers who manage malaria cases (from medical & paediatric wards) at all hospitals in the district.
1.4 Brief the medical officers, Sisters and senior Laboratory Technologist on the surveillance mechanism while patient admitted in the ward and provide the coordinator's contact phone number. The coordinator will continue the surveillance process after patient being discharged from the ward.
1.5 Coordinator to provide and distribute the Surveillance Form (DRS_Annex 1) to MOs/Sisters of the relevant wards
1.6 MOH to instruct the MOs to carry out the surveillance activities.
1.7 MOs complete the Surveillance Form, inform coordinator via phone and return the form to the coordinator once patient is discharge. The coordinator will continue the follow-up procedure and complete the form.
1.8 Coordinator compiles all Surveillance Form and key in data into e-Vekpro completely.
1.9 Coordinator checks the total number of *P. falciparum, P.knowlesi and P.malariae* malaria cases admitted for the month and prepares Reporting Format (DRS_Annex 4) for the MOH to verify and validate.
1.10 Send the Reporting Format (Drs_Annex 4) to State Health Office.
1.11 State KPP will compile reports from all districts, prepares Reporting Format (Drs_Annex 5) and submit to Vector Bourne Disease Section, on a monthly basis to :-

National Anti-Malarial Surveillance,
C/o Malaria Unit,
Vector Bourne Diseases Section,
Disease Control Division, Block E10, Parcel E,
Ministry of Health Malaysia, Precint 1,
62590, Putrajaya.

1.12 Vector Borne Disease Section will compile reports from all states and prepare monthly report.

2. Patient enrolment

2.1 Inclusion criteria :
- 2.1.1 Admit patient
- 2.1.2 Confirmed laboratory diagnosis of the presence of mono-infection asexual stages of *P.falciparum*, *P.knowlesi or P.malariae*.
- 2.1.3 Ability to swallow oral medication.
- 2.1.4 Non-severe and uncomplicated malaria cases treated with first-line treatment regime (refer Guidelines for Management of Malaria 2013).

2.2 Attach the Surveillance Form (**DRS_Annex 1**) to the patient Case Note and enter the information accordingly.
2.3 From the history, acquire the information on previous history of malaria treatment and probable source of infection. Enter the information in Section 5 of the Surveillance Form accordingly.

3. Treatment regime and medication history

3.1 Calculate the artemther-lumefantrine (AL-Riamet) and artesunate-mefloquine (ASMQ-FDC) dosage based on the body weight according to the following regime:-

Treatment regime : 3 days treatment schedule (D0, D1 and D2).
(refer Guidelines for Management of Malaria 2013).

Drug	artemether-lumefantrine (AL-Riamet)	artesunate-mefloquine (ASMQ-FDC)
Dose per day	2 doses (BD)	1 dose (OD)
Total dose	2 X 3 days = total 6 doses	1 X 3 days = total 3 doses
Dosage calculation	5 - < 15 kg : 1 tablet per dose 15 - < 25 kg : 2 tablets per dose 25 - < 35 kg : 3 tablets per dose ≥ 35 kg : 4 tablets per dose	< 10 kg : 1 tablet AS 25mg OD X 3 days, MQ 125mg single dose 10 -20 kg : 2 tablets ASMQ 25/55mg per dose 20 -40 kg : 1 tablet ASMQ 100/220mg per dose ≥ 40kg : 2 tablets ASMQ 100/220mg per dose

3.2 Ascertain the strength of the drug component for each tablet and determine the number of tablet required for each drug.

3.3 Instruct the nurse to supervise the taking of the medication. If the patient vomits within ½ hour of consumption, repeat the dose and indicates that in the appropriate drug column of Section 3 with the initial "rpt'.

3.4 Record the actual number of tablet given to and taken by the patient in Section 3. Record also other concomitants treatment (e.g. paracetamol, antibiotics, etc).
(**NOTE: D0 is the first day of treatment**)

4. Parasite response and monitoring

4.1 Original slide that confirm the diagnosis (D0) must be kept for future reference.

4.2 Clinically monitor the case according to the standard management as per guidelines protocol.

4.3 Repeat BFMP one day after the last dose of AL/ASMQ (D3). Enter the result in Section 4 of the Surveillance Form. (You may repeat BFMP on D1 and D2 if clinically justified e.g. no evidence of clinical improvement or clinically getting worse).

4.4 If the result on D3 is negative, repeat BFMP on D5, D6 and D7. If continue to be negative, discharge the patient. Enter the result of D7 in the Surveillance Form. MOs inform the coordinator and return the form to the coordinator.

4.5 Coordinator arrange for the patient to be followed-up on D14 at patient's house. Inform the patient of the appointed date for the BFMP taking.

4.6 If BFMP negative, enter the result in the Surveillance Form and inform the patient for D21, D28 and D56 visit for similar follow-up. Stress the importance of complete monitoring to ensure compliance.

4.7 If BFMP continues to be negative until D56 or if patient failed to return after 56 days of initiation of treatment, conclude the surveillance.

4.8 If :-

4.8.1 BFMP is positive during any of the follow-up (D3, D5-D7, D14, D21, D28, D56), or

4.8.2 BFMP is repeated and the asexual density is not less than 25% and 50% on D1 and D2 respectively compared to D0 density, or

4.8.3 Patient shows clinical deterioration, concludes the surveillance. If surveillance is concluded because of clinical deterioration, indicate such reason (e.g. "Treatment failure on D2) in Section 4 (just write anywhere).

4.8.4 If conclusion of treatment failure is made on D14, D21, D28 and D56; send both of D0 and the current positive slides to IMR for genotyping. Preferably, send spotted blood sample on filter paper.

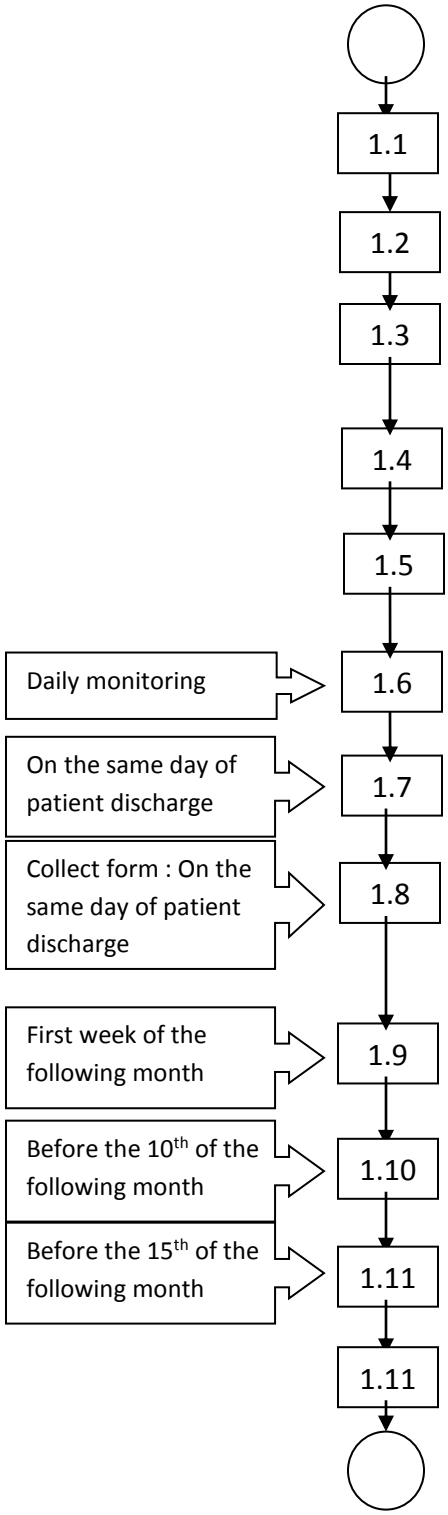
5. Submission of surveillance format

5.1 Once the surveillance is concluded, the coordinator check all the information entered into the Surveillance Form and key in data into e-Vekpro completely. Prepare the report with verification and validation by the MOH.

5.2 Send the report Form to the national coordinator, close the case for surveillance.

National Surveillance of Drug Response Against Malaria Parasite (*P.falciparum, P.knowlesi and P.malariae*)

Standard Operating Procedure Flow Chart :



Prosedure Start

District Health Office – Medical Officer of Health (**MOH**) at the District Health Office is responsible to coordinate and monitor surveillance activity.

District Health Office – MOH Appoint a dedicated staff to act as coordinator (eg: PPKP).

District Health Office – MOH and coordinator identify Medical Officer (**MO**)who incharge and manage malaria cases in district hospital.

District Hospital – MOH/coordinator brief MO's, Sisters and senior Laboratory Technologist on the surveillance mechanism.

District Hospital – Coordinator provides the Surveillance Form (**DRS_Annex 1**)and distribute to the MOs/Sisters of the relevant wards.

District Hospital – MOs begin and carry out the surveillance activities.

District Hospital – MOs complete the Surveillance Form, inform coordinator via phone and return the form to the coordinator once patient is discharge.

District Health Office – Coordinator incharge:
i. Collect form (**DRS_Annex 1**) from MO's
ii. Continue follow-up patient until D56 treatment
iii.Key in data in Vekpro online system completely

District Health Office –
i. Coordinator prepares Reporting Format (**DRS_Annex 4**).
ii. MOH verify and validate the report.

District Health Office – Send the Reporting Format to State Health Office.

State Health Office – State KPP compile and verify/validate report. Send the Reporting Format (**DRS Annex 5**) to Vector Borne Disease Section.

National VBDS – Compile and prepare monthly report.

Prosedure end.

DRS_Annex 4

National Surveillance of Drug Response Against
Malaria Parasite *(P.falciparum, P.knowlesi and P.malariae*)
REPORTING FORMAT (District)

Month ☐ Year ☐

District ☐ Type of Parasite: Pf ☐ Pk ☐ Pm ☐

No.	Hospital	No. of patient admitted for the month	No. of patient enrolled for anti-malaria surveillance for the month	No. of surveillance concluded in the month	No. of surveillance form submitted for the month	No. of resistance cases
Total						

Prepared by:

_____
(Coordinator)

Verified and validated by:

_____
(District health officer)

DRS_Annex 5

National Surveillance of Drug Response Against
Malaria Parasite *(P.falciparum, P.knowlesi and P.malariae*)
REPORTING FORMAT (State)

Month ☐ Year ☐

District ☐ Type of Parasite: Pf ☐ Pk ☐ Pm ☐

No.	Hospital	No. of patient admitted for the month	No. of patient enrolled for anti-malaria surveillance for the month	No. of surveillance concluded in the month	No. of surveillance form submitted for the month	No. of resistance cases
Total						

Prepared by:

_____

Verified and validated by:

_____
(State KPP-Vector)

Appendix 1

MALARIA PROPHYLAXIS RECOMMENDATIONS

Country	Estimated Relative Risk	Drug Resistance	Recommended Chemoprophylaxis	Remarks
Afghanistan	**High**	**Chloroquine**	Doxycline/ mefloquine/ proguanil	
Argentina	**Low**	**None**	Primaquine / doxycycline	*P. vivax* 100%
Bangladesh	**Moderate**	**Chloroquine**	proguanil, doxycycline, or mefloquine	*P. falciparum* 77% *P. vivax* 23%
Botswana	**Very Low**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	
Brazil	**Low**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	
Burma	**Moderate**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	*P. falciparum* 86% *P. vivax* 12% *P. malariae* 2%
Cambodia	**Moderate**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	*P. falciparum* 86% *P. vivax* 12% *P. malariae* 2%
Cameroon	**High**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	
Central African Republic	**High**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	*P. falciparum* 85% *P. malariae*, *P. ovale*, and *P. vivax* 15%
China	**Low**	**Chloroquine Mefloquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	*Along China-Burma border, Hainan* ,Anhui, Guizhou, Henan, and Hubei provinces
Congo	**High**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	
Ethiopia	**Moderate**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	
Gambia	**High**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	
Haiti	**Moderate**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	*P. falciparum* 100%
Kenya	**Moderate**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	*P. falciparum* 85% *P. vivax* 5-10% *P. ovale* up to 5%

Country	Estimated Relative Risk	Drug Resistance	Recommended Chemoprophylaxis	Remarks
Laos	**Very Low**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	*P. falciparum* 95% *P. vivax* 4% *P. malariae* and *P. ovale* 1%
Liberia	**High**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	
Madagascar	**Moderate**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, or mefloquine	
Malaysia** Present in rural areas of Sabah, Sarawak and Peninsular Malaysia.	**Low**	**Chloroquine**	Atovaquone/ proguanil, doxycycline, mefloquine	*P. knowlesi (commonest) 38%* *P. vivax* 31% *P. falciparum* 19% *P. malariae* 10% Mixed 2%
Mexico	**Low**	**None**	Chloroquine, primaquine or doxycycline	*P. vivax 100%*
Namibia	**Moderate**	**Chloroquine**	Atovaquone/ proguanil , doxycycline, or mefloquine	*P. falciparum* 90% *P. malariae*, *P. ovale*, and *P. vivax* 10%
Nigeria	**High**	**Chloroquine**	Atovaquone/ proguanil , doxycycline, or mefloquin	*P. falciparum* 85% *P. ovale* 5-10% *P. vivax* rare
Pakistan	**Moderate**	**Chloroquine**	Atovaquone/ proguanil , doxycycline, or mefloquin	*P. falciparum* 70% *P. vivax* 30%

Source: Adapted from CDC Yellow Book 2010, available at http://wwwnc.cdc.gov)

Appendix 2

DOSAGE GUIDELINES FOR THE TREATMENT OF MALARIA

DRUGS LISTED IN THE MOH FORMULARY

***GUIDANCE ON PRESCRIBING**

The category of prescriber that are authorized to initiate the prescription for the drug in the MOH formulary is listed as:

A*	Consultant / Specialist for Specific Indication Only
A	Consultant / Specialist
A/KK	Consultant / Specialist / Family Physicians Specialist
B	Medical Officer
C	Paramedical Staff
C+	Paramedical Staff Doing Midwifery

No	Generic Name	*Category	Precautions	Adverse Reaction	Contraindications	Interactions
1	Primaquine 7.5 mg base Tablet	B	Use with caution in patients with a deficiency in glucose-6-phosphate dehydrogenase (G6PD) (may cause acute haemolytic anaemia) and patients with a nicotinamide-adenine dinucleotide hydroxide (NADH) methaemoglobin-reductase deficiency (at risk of developing methaemoglobinaemia and cyanosis).	Anaemia, leucocytosis, abdominal pain, methaemoglobinaemia.	Concomitant medications which cause bone marrow suppression, rheumatoid arthritis, lupus erythematosus, G6PD deficiency, pregnancy (suppressive therapy with weekly chloroquine until delivery should be used).	Bone marrow suppression (amphotericin B, antithyroid agents, azathioprine, busulfan) Haemolytic (antidiabetic agents, doxapram, methyldopa, nitrofurans, procainamine, quinidine, quinine, sulfonamide, sulfones, vitamin K)

2	Quinine dihydrochloride 600 mg/2 ml Injection	B	Atrial fibrillation or other serious heart disease, G6PD deficiency, hepatic and renal impairment, history of asthma, may cause significant hypoglycaemia due to quinine-induced insulin release. *During parenteral treatment:* Monitor ECG in elderly patients; monitor blood glucose and electrolyte concentration.	Headache, fever, vomiting, muscle weakness, confusion, blindness, deafness, hypotension, rash, hypoglycaemia, epigastric pain, nausea, vomiting, disseminated intravascular coagulation, thrombocytopenia, hepatotoxicity, interstitial nephritis.	Hypersensitivity to quinine, presence of haemoglobinuria, myasthenia gravis, optic neuritis, tinnitus.	Amiodarone and droperidol (increased risk of ventricular arrhythmias, avoid concomitant use), thioridazine, digoxin, cimetidine, cyclosporine, mefloquine, pancuronium, rifapentine, anticoagulants.
3	Quinine sulphate 300 mg Tablet	B	Atrial fibrillation or other serious heart disease, G6PD deficiency, hepatic and renal impairment, may cause significant hypoglycaemia due to quinine-induced insulin release.	As above.	As above.	As above.
4	Chloroquine phosphate 250 mg Tablet (150 mg Chloroquine base)	C	G6PD deficiency, renal impairment, moderate and severe hepatic impairment, may exacerbate psoriasis or trigger an acute attack of hepatic porphyria (metabolic abnormality), may aggravate myasthenia gravis.	Loss of appetite, nausea, pressure over the stomach, visual disturbances.	Headache, gastrointestinal (GI) disturbances, agitation, anxiety, confusion, delirium, depression, hallucination, visual disturbances, bone marrow suppression (rare), anaphylaxis.	Avoid concomitant use with artemether, lumefantrine, mefloquine. Increased risk of ventricular arrhythmias when given concomitantly with amiodarone, moxifloxacin and droperidol (avoid).

5	Artemether 20mg + Lumefantrine 120mg (Riamet®)	A/KK	Electrolyte disturbances, hepatic impairment, renal impairment, concomitant administration of drugs that prolong QT interval, pregnancy.	Abdominal pain, anorexia, diarrhoea, vomiting, nausea, palpitation, cough, headache, dizziness, sleep disturbances, asthenia, arthralgia, myalgia, cough, fatigue, pruritus, rash.	Hypersensitivity to artemether or lumefantrine. History of arrhythmias, clinically relevant bradycardia and congestive heart failure accompanied by reduced left ventricular ejection fraction. Family history of sudden death or congenital QT interval prolongation. Not recommended in children below 5 kg and during lactation (avoid lactation for at least 1 week after last dose).	Avoid concomitant use with macrolides, quinolones, metoprolol, cimetidine, antipsychotics, antidepressants. Increased risk of ventricular arrhythmias when given with quinine, amiodarone, disopyramide, flecainide (avoid). Caution when used with atazanavir, darunavir, indinavir, lopinavir, ritonavir.
6	Mefloquine HCl 250 mg Tablet	A*	Impaired liver function, cardiac conduction diseases, infants under 3 months (5 kg), epilepsy and psychiatric disorders, lactation (minimal risk); adequate contraception during prophylaxis and for 3 months after stopping treatment is needed.	Nausea, vomiting, dizziness, vertigo, headache, sleep disorders, diarrhoea, abdominal pain, anorexia, neurological and psychiatric disturbances. Rarely, Stevens-Johnson syndrome, atrioventricular block and encephalopathy.	Hypersensitivity to quinine, history of psychosis or convulsions.	Increased risk of ventricular arrhythmias when given with amiodarone and moxifloxacin, possible increased risk with haloperidol (avoid), quinine or related compounds (increased risk of convulsion), increased risk of bradycardia when given with beta-

						blockers, possible increased risk with calcium-channel blockers and digoxin, mefloquine inactivates oral live typhoid vaccines, reduced plasma concentration when given with rifampicin (avoid).
7	Clindamycin HCl 300 mg Capsule	A*	History of GI disease, especially colitis. Renal or hepatic impairment. Perform periodic liver and kidney function tests with prolonged therapy and in neonates and infants. Discontinue immediately if diarrhoea or colitis develops. Clindamycin enters breast milk.	Diarrhoea occasionally with acute colitis (discontinue), pseudomembranous enterocolitis, abdominal pain, GI upset, skin reactions including Stevens-Johnson syndrome (rare), jaundice, hematopoietic changes, vaginitis.	Hypersensitivity to clindamycin or lincomycin.	Neuromuscular blockers (increased levels/effects), erythromycin (avoid concomitant use).
8	Sulfadoxine 500 mg and Pyrimethamine 25 mg Tablet	B	Not recommended for prophylaxis (severe side effects on long-term use), maintain adequate hydration to prevent crystalluria, impaired renal or hepatic function, history of seizure, periodic blood counts are recommended, possible folate deficiency, severe	Nausea, feeling of fullness, headache, pruritus, contact dermatitis, urticaria, rash, rarely Stevens-Johnson syndrome and Lyell's syndrome, photosensitisation. Very rarely, agranulocytosis, thrombocytopenia,	Hypersensitivity to sulphonamides, infants <2 months of age, pregnancy, prophylactic (prolonged) use in patients with renal/hepatic failure or with blood dyscrasias.	Increased antifolate effect: methotrexate, sulfamethoxazole and trimethoprim, trimethoprim alone, zidovudine.

			allergic or bronchial asthma.	aplastic anaemia, liver cell damage.		
9	Doxycycline 100mg Capsule / Doxycycline 100mg Tablet	B	Myasthenia gravis, hepatic impairment.	GI distress, anorexia, maculopapular and erythematous rash, tooth discolouration in children.	Hypersensitivity to tetracycline/doxycycline, porphyria, pregnancy, lactation, children less than 12 years of age.	*Increased levels/effects:* Acitretin, isotretinoin (avoid concomitant use), anticoagulants, methotrexate. *Decreased level/effect:* Penicillin. *Decreased level/effect of doxycycline:* Antacids, ferum.
10	Artesunate 60mg/ml Injection	A	Hepatic or renal insufficiency. Pregnancy (first trimester) and lactation. **Inject immediately after reconstitution. Discard if solution is not clear. Do not use in intravenous drip.**	GI disturbances, dizziness. Transient reduction in reticulocytes, transient increase in transaminases and total bilirubin.	Hypersensitivity to artesunate or artemisinin derivatives.	Antimalarial potentiating action seen with mefloquine, primaquine and tetracycline. Additive effect with chloroquine. Antagonistic effect with pyrimethamine and sulphonamides.
11	Artesunate 100 mg and Mefloquine 220 mg Tablet	A	Severe hepatic impairment, cardiac conduction diseases. Take extra doses in case of vomiting.	*Common* Abdominal pain, nausea, vomiting, diarrhoea, headache, dizziness and insomnia, hyperbilirubinaemia.	Hypersensitivity to mefloquine, quinine, quinidine, artesunate or other artemisinins, history of psychiatric illness, history of epilepsy, pregnancy (first trimester),	Quinine, chloroquine (may cause arrhythmia and may increase the risk of convulsions); halofantrine, amiodarone, disopyramide, tricyclic

				Rare Seizure, depressive syndrome, acute psychosis, acute intravascular haemolysis with haemoglobinuria.	lactation, severe malaria, concurrent or recent halofantrine or ketoconazole therapy.	antidepressants, phenothiazines, haloperidol, ketoconazole, moxifloxacin, metoclopramide (may cause arrthymia); mefloquine concentrations are increased by the co-administration with ampicillin, tetracycline and ketoconazole; mefloquine concentrations are reduced when given together with rifampicin; concurrent administration with ciprofloxacin or ofloxacin may increase the risk of convulsion, mefloquine reduces the plasma levels of anticonvulsants (e.g. carbamazepine, phenobarbital, phenytoin, valproic acid); mefloquine may attenuate oral live

						typhoid vaccine.
12	Artesunate 25 mg and Mefloquine 55 mg Tablet	A	As above.	As above.	As above.	As above.

DRUGS NOT LISTED IN MINISTRY OF HEALTH FORMULARY

No.	Generic Name	Precautions	Adverse Reaction	Contraindications	Interactions
1	Atovaquone 250 mg and Proguanil HCl 100 mg Tablet	Not indicated for severe or complicated malaria. Absorption of atovaquone may be decreased in patients who have diarrhoea or vomiting. Monitor closely and use caution in patients with existing hepatic impairment. Administer with caution to patients with pre-existing renal disease (may use for 3-day treatment in patients with severe renal impairment if benefit outweighs risk). Not for use in patients <5 kg. Delayed cases of *P. falciparum* malaria may occur after stopping prophylaxis. Recrudescent infections of infections following prophylaxis with this agent should be treated with an alternative agent(s).	Abdominal pain, increased transaminases level, nausea, vomiting, diarrhoea, headache, weakness, hallucinations, neutropenia, pancytopenia (with severe renal impairment), photosensitivity. <u>*Rare*</u> Anaphylaxis, hepatitis, Stevens-Johnson syndrome, seizure, psychotic episodes.	Hypersensitivity to atovaquone, proguanil or any component of the formulation. Prophylactic use in severe renal impairment.	*Atovaquone and proguanil may increase the levels/effects of:* Phenothiazines, dapsone, etoposide, hypoglycemic agents, lumefantrine. *The levels/effects of atovaquone and proguanil may be increased by:* Artemether, dapsone, herbs with hypoglycemic properties. *Atovaquone and proguanil may decrease the level/effect of indinavir*. *The levels/effects of atovaquone and proguanil may be decreased by:* Rifamycin derivatives, ritonavir, tetracycline.
2	Atovaquone 62.5 mg and Proguanil HCl 25 mg Tablet				

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23. Package Insert: Quinine Tablet, March 2009.
24. Package Insert: Primaquine Tablet.
25. Package Insert: Fansidar® (Sulfadoxine and Pyrimethamine), 2nd July 2010.
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Appendix 3

SELECTED FURTHER READING

This guidelines and manuals from which the recommendations in this manual were derived are:

1. *Guidelines for the treatment of malaria*, 2nd Ed. Geneva, World Health organization, 2010. http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html.
2. *WHO pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources.* Geneva, World Health organization, 2005.
3. *Universal access to malaria diagnostic testing: an operational manual.* Geneva, World Health organization, 2011. http://whqlibdoc.who.int/publications/2011/9789241502092_eng.pdf.
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