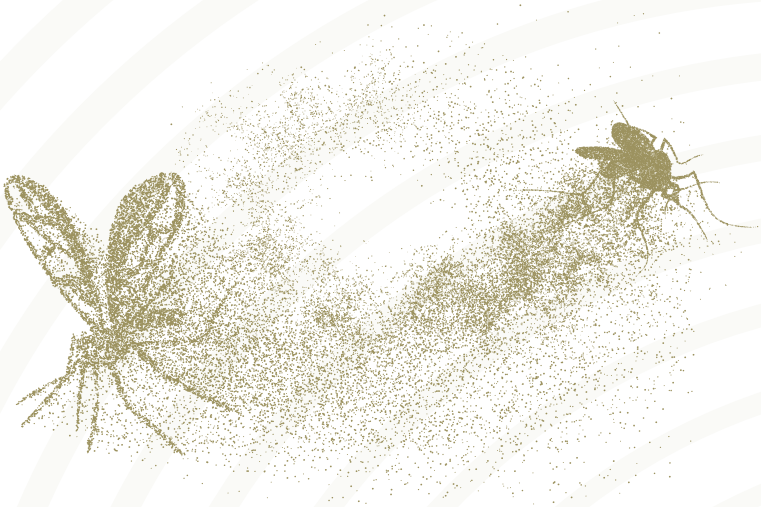
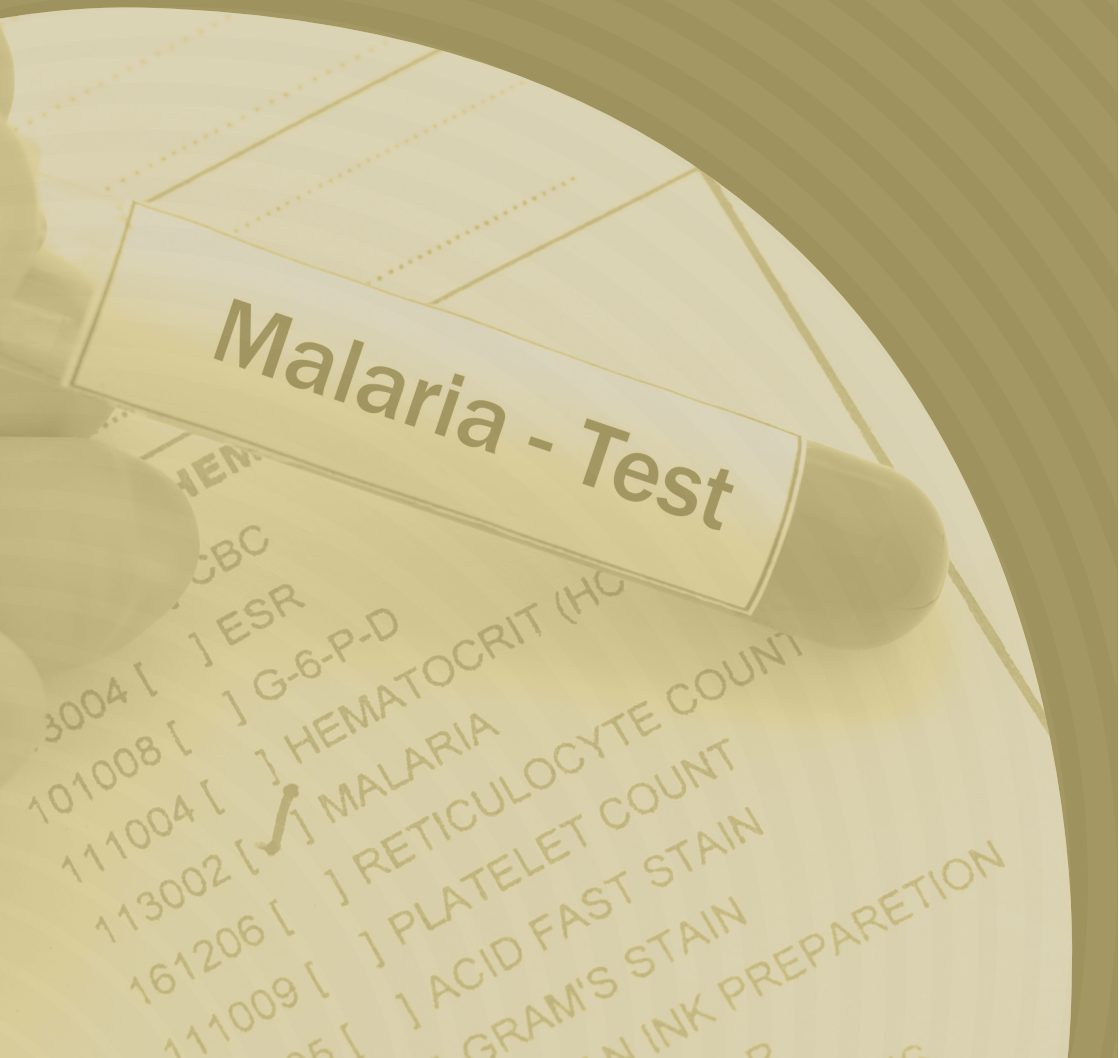
وزارة الصحة
Ministry of Health

Malaria Elimination Proagram

NATIONAL MALARIA DRUG POLICY



Third Edition 2018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] ACID FAST STAIN
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INK PREPARETION

Kingdom Of Saudi Arabia
Ministry Of Health

Deputy Minister Of Public Health Office
General Directorate Of Vector Borne & Zoonotic Diseases

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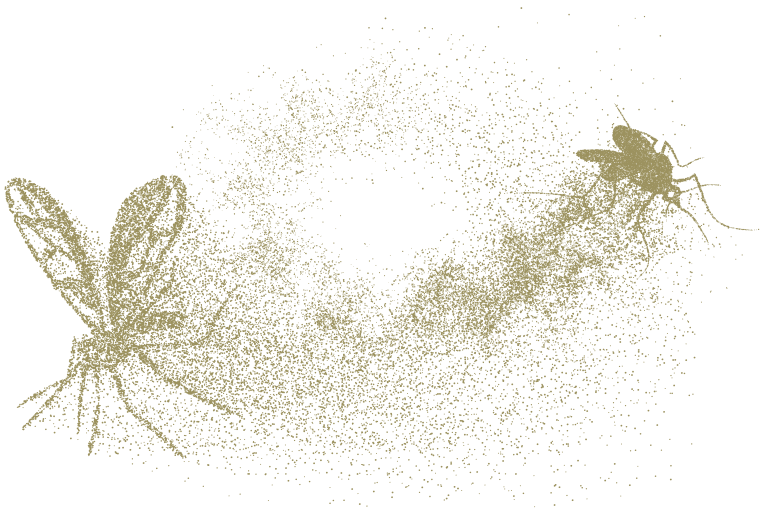

MALARIA

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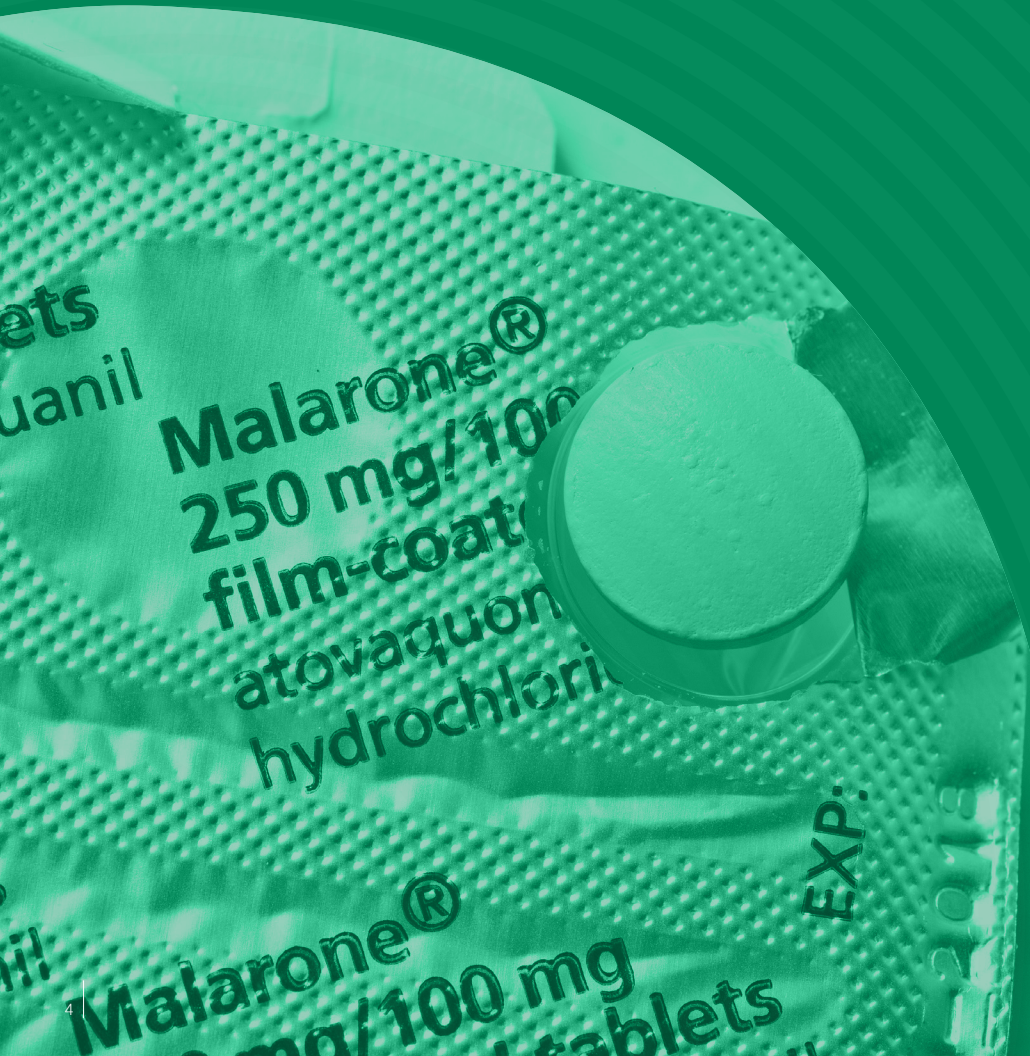
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CONTENTS:


Malaria : - + ✓

ABBREVIATIONS:

ACT	Artemisinin-based combination therapy
AL	Artemether plus Lumefantrine combination
AS	Artesunate
AS+SP	Artesunate + Sulfadoxine / Pyrimethamine combination
BW	body weight
CT	Combination therapy
CQ	Chloroquine
DEET	N,N diethyl-m-toluamide (an insect repellent)
DIC	Disseminated Intravascular Coagulation
G6PD	Glucose-6-phosphate dehydrogenase
HIV/AIDS	Human immunodeficiency virus/ acquired Immunodeficiency syndrome
HRP2	Histidine-rich protein 2
INR	International Normalized Ratio
I.V.	Intravenous
I.M.	Intramuscular
ITN.	Insecticidal Treated Nets.
K13	Plasmodium falciparum Klech13 mutation
MOH	Ministry Of Health
MQ	Mefloquine
PCR	Polymerase chain reaction
P. f	Plasmodium falciparum
P. m	Plasmodium malariae
P. o	Plasmodium ovale
P. v	Plasmodium vivax
Pf HRP2	Plasmodium falciparum Histidine-rich protein-2
PQ	Primaquine
RBC	Red Blood Cells
RCT	Randomized Controlled Trial
RDT	Rapid Diagnostic Test
SP	Sulfadoxine – Pyrimethamine
SCA	Sickle Cell Anemia
SCD	Sickle Cell Disease
PLDH	Parasite Lactic Dehydrogenase
WBC	White Blood Cells
WHO	World Health Organization

Chapter 1:

Introduction

1.1 Malaria is a life-threatening infection caused by Plasmodium species and transmitted by some species of anopheles mosquitoes.

According to the WHO malaria report, there were 212 million new cases of malaria worldwide in 2015 (range 148–304 million) and an estimated 429 000 malaria deaths (range 235 000–639 000) worldwide. Approximately 90% of the disease burden occurs in Africa followed by the South-East Asia (7%). and the Eastern Mediterranean Region (2%).

Five known species of Plasmodium can cause human malaria (Plasmodium falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi). Severe and complicated malaria infection is mainly caused by P. falciparum which is responsible for most of malaria related deaths.

1.2 Malaria in Saudi Arabia:

In Saudi Arabia, there were 5382-reported malaria cases in year 2016; however only 272 cases were locally acquired, and all were P. falciparum infection. From total malaria, cases the P. falciparum was represented 72.9%, P. vivax 26.4%, and P. malariae 0.7%. All local acquired cases were from the southwest regions (Jazan & Asser), while the imported cases were mainly from Yemen, India and Sudan. The annual incidence rate varies widely depending upon population movement and early arrival of heavy rainfall, with the peak of transmission occurring between October and March.

1.3 Malaria During Hajj Season:

Hajj in Islam is the fifth pillar of the five Islam pillars. More than 2 millions of pilgrims from different countries of the world come to Makkah during Hajj season every year. Some of these countries, particularly from Africa and Asia are malaria endemic. People coming for Hajj from all countries stay in Makkah and Madinah Almunawwarah, where there is no prevalence of malaria vector mosquitoes and no possibility for malaria transmission. However, there are certain precautionary measures to be applied during Hajj season for more precautions as follows:

1 – Measures applied before inlet of Pilgrims:

- Spray of all Health Care Facilities, governmental and private institutes together with all pilgrims camps with Residual Insecticides. Besides, all agricultural farms surrounding the holy places are subjected to aerial spraying with aircrafts insecticides.
- Configuration of epidemiological surveillance team at Hajj Entry ports to monitor all suspected cases and apply necessary measures.

2 - Measures applied during Hajj season:

- Configure epidemiology investigation team for follow-up of malaria cases (for proper diagnosis and treatment).
- Secure malaria drugs and malaria treatment policy for all Health Care Facilities.

Chapter 2:

Goals & Criteria for change of drug policies

2.1 Goals:

This drug policy is based on practical issues to meet the following objectives:

2.1.1 Prompt and effective treatment of all confirmed malaria cases in order to relieve illness, prevents complications and cure the infection.

2.1.2 Prevent or delay the emergence and spread of resistance to antimalarial drugs.

2.1.3 Reduction/interruption of transmission in endemic areas and prevention of the resumption of transmission to areas free of local malaria transmission.

2.1.4 Prevention of relapse in P. vivax and P. ovale infection.

2.2 Determinants of Antimalarial treatment policy:

The main determinant of antimalarial treatment policy is the therapeutic efficacy of the antimalarial medicine in use.

Other important determinants include: changing patterns of malaria-associated morbidity and mortality; consumer and provider dissatisfaction with the current policy; and the availability of alternative medicine, strategies and approaches.

2.3 ACT resistance and its criteria:

Artemisinin resistance have been reported from south east Asia. It is defined as delayed parasite clearance (partial resistance) following treatment with an artemisinin derivative monotherapy, or after treatment with an Artemisinin combination therapy (ACT).
There is no evidence that higher levels of Artemisinin resistance have emerged in Saudi Arabia or its neighbouring countries.
The Plasmodium falciparum resistance to ACT could be linked either to the artemisinin derivative or to the ACT drug partner.

To confirm resistance to the artemisinin derivatives, the following criteria must be documented:

1. The proportion of patients with persistent parasitemia by microscopy at 72 hours (day 3) after treatment with ACT or artemisinin derivative as monotherapy should be ≥ 10% or if it is < 10% but increasing with time.
2. The percentage of patients carrying K13 resistance-validated mutations of ≥ 5%.

Resistance to the ACT partner drug can be confirmed if the percentage of patients with persistent parasitemia at 28^{th} or 42^{nd} day after treatment with ACT is ≥ 10. At this point, re-infection must be excluded by applying PCR test. If re infection is excluded, then the ACT regime must be changed.

Chapter 3:

Clinical presentation & Diagnosis

3. 1 Clinical presentation:

Malaria symptoms manifest approximately 7 – 14 days after introduction of Plasmodium parasite in human circulation by infected Anopheline mosquito. Prolonged incubation period has been reported in P.vivax.

Signs and symptoms vary, most patients experience fever as the major manifestation. Common associated symptoms include headache, back pain, myalgia, nausea, vomiting, diarrhea, and cough.

Untreated P. falciparum infection can lead to coma, generalized convulsions, hyper parasitaemia, anemia, fluid and electrolyte imbalance which may lead to acid-base disturbances, renal failure, hypoglycemia, hyperpyrexia, cerebral malaria, hemoglobinuria, circulatory collapse and shock, spontaneous bleeding, disseminated intravascular coagulation (DIC), pulmonary edema and death.

3.2 Diagnosis:

The most important factors that determine patient's survival in P. falciparum malaria are early diagnosis and early administration of appropriate therapy. Thus, high index of suspicion by concerned doctor or medical personnel for malaria infection in endemic areas, careful travel and blood transfusion history are essential for early recognition of the disease in areas of no or low transmission.

Parasitological confirmation of malaria is a crucial part of case management and should be provided by microscopic examination of peripheral blood, if microscopy is not available Rapid Diagnostic Tests should be used to guide for the provision of proper treatment, in the meantime the blood smear should be taken and examined as conditions permits.

Laboratory confirmation is obtained by demonstration of malaria parasites in blood films (thick and thin film). This remains the gold standard method for the diagnosis, identification of Plasmodium

species and estimation of parasite load (density). Parasite density is quantified by counting ≥ 200 WBC and expressed as number of parasites per 200 WBC or converted to number of parasites per microliter (WHO Basic Malaria Microscopy Ref list).

Giemsa stain is recommended for identification of Plasmodium species and for parasite count. It should be used in all health facilities throughout the Kingdom.

Repeated blood films examinations for 4 times within 24 hours may be needed to demonstrate the presence of parasites particularly in low parasitemia or in non-specialized or busy laboratories.

Avoid delay of blood film preparation from venous blood collected in anticoagulant since this could lead to false negative results and distortion of parasite morphology.

3.2.1 Reporting of malaria blood smear result:

A. Parasite per microliter of blood:

This method is preferred for its easiness, simplicity and acceptable accuracy. The number of parasites is counted in relation to the number of leukocytes in the thick film. Although the most accurate count is obtained when the patient's true white cell count is known. The number of leukocytes in 1 microliter of blood is assumed to be (8000), with wide variations among individuals, but the figure is accepted as reasonably accurate.

$$\frac{\text{Number of parasites counted} \times 8000}{\text{Number of leucocytes counted}} = \text{Parasites per microliter of blood}$$

B.Th. "plus" system

This is an old semi-quantitative method which is simple but far less accurate for establishing parasite density in thick blood films, Table (1).

Table (1): semi-quantitative method for parasite density in thick blood films

Degree of parasitaemia	Parasite estimate
+	1-10 parasites per 100 thick film microscopic fields
++	11-100 parasites per 100 thick film microscopic fields
+++	1-10 parasites per one thick film microscopic field
++++	> 10 parasites per one thick film microscopic field

3.3 Malaria Rapid Diagnostic Tests (RDTs):

A Rapid Diagnostic Test (RDT) is an alternate test to confirm the diagnosis of malaria infection by detecting specific malaria antigens in the patient's blood.

3.3.1. Three target enzymes or proteins are available for Rapid Diagnostic Testing RDT:

- P. falciparum Histidine Rich Protein 2 (Pf HRP2) which identify recent P. falciparum infection with very high sensitivity (95%, (Confidence Interval 93.5 – 96.2%) if the parasite density of >100 (parasite/µl) and high specificity (93%, (CI 93 – 99.4 %)
- Parasite specific Lactate Dehydrogenase (P. LDH) which identify P. falciparum and other species is less sensitive and more specific than Pf HRP2 which has the advantage of differentiating P. falciparum PLDH from other Plasmodium species i.e. vivax, ovale and malariae) (85% sensitive if the parasite density >100 (parasite/µl))
- Plasmodium anti-Aldolase pan test which react to all Plasmodia species.

The application of RDTs improves the speed and accuracy of P. falciparum diagnosis. However, it has some disadvantages including its inability to assess the parasite load and that the HRP2 can remain detectable in the blood for up to four weeks after the complete parasitological cure and may thus give false positive results.

3.3.2 Reports of Plasmodium falciparum that lack the HRP2 enzyme from South America, South East Asia and east Africa are increasing. This mutant P. falciparum will escape the detection by HRP2 dependent RDT

In 2015–2017, PfHRP2/3 gene deletions were reported from both high and low transmission areas in the China– Myanmar border, India, Ghana, Congo, Eritrea, Uganda, and Rwanda.

The HRP2 mutation is not reported in Saudi Arabia but may be seen in imported malaria from countries where this mutation is prevalent. The preventive medicine department in the region should be notified if PfHRP2 mutation is suspected (i.e. patients with confirmed Plasmodium falciparum malaria by either microscopic examination or PLDH or Aldolase based RDT but negative HRP2).

3.3.2 Advantage of RDTs

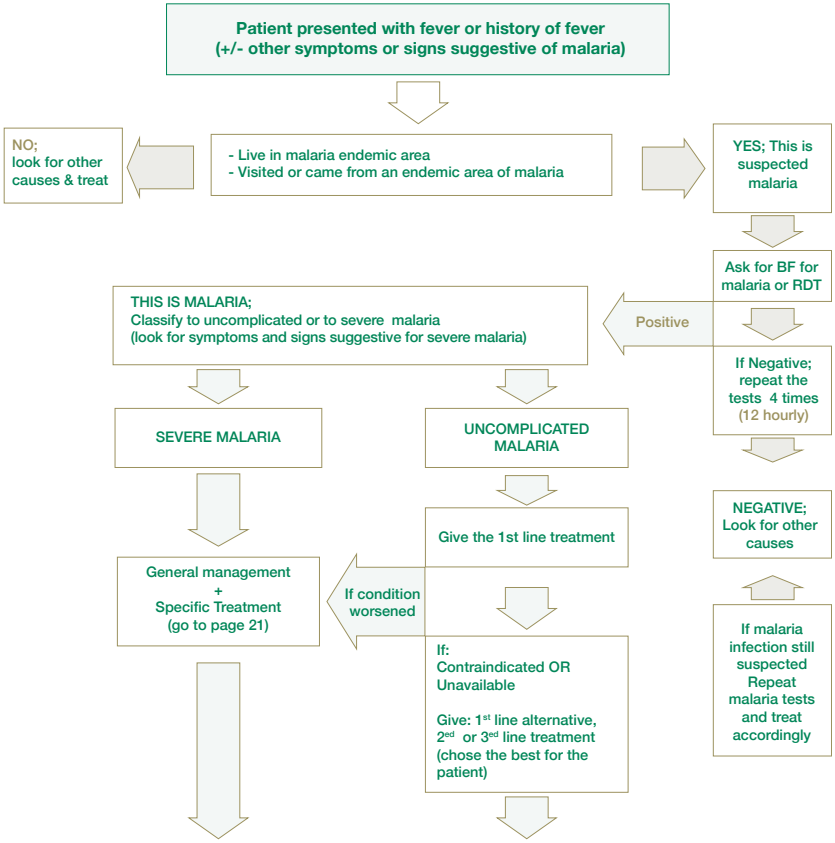
- Relatively easy to use with minimal training required
- Relatively rapid, giving timely results
- Little or no manipulation of sample required, can be performed in places without laboratories
- Most of the RDTs do not require refrigeration, hence tests can be performed where there is no power supply
- Uses whole blood (prick or venous blood-prick preferred).

3.3.3 Thick and thin blood films stained with Giemsa stain should be taken from all patients suspected to have malaria (including all patients with positive RDTs) and examined under the microscope, about 200 microscopic field should be examined before writing a negative result.

Once Malaria diagnosed, appropriate antimalarial treatment should be started immediately guided by:

- Type of plasmodium species and stages of malaria parasites.
- Clinical status of patient: Uncomplicated or Severe, or pregnancy.
- Drug sensitivity of the infected parasite: area where parasite acquired.
- Previous exposure to anti-malarial drugs.

Malaria Diagnosis and Treatment, KSA



First line treatment of uncomplicated malaria: (ARTESUNATE + SP); alternative (ARTESUNATE + MEFLOQUINE)
Second Line Treatment of uncomplicated malaria:: (ARTEMETHER + LUMEFANTRINE)
Third Line Treatment of uncomplicated malaria: (oral QUININE + DOXYCYCLINE)

Chapter4:

Malaria case definition & Case classification

4.1. DEFINITION OF MALARIA CASE:

A patient who presents with symptoms of malaria and a positive parasitological test (microscopy or RDT)

4.1.1 CLINICAL MALARIA (PROBABLE MALARIA):

Patients who present with signs and symptoms of malaria without parasitological confirmation and receive antimalarial treatment, it can be uncomplicated or severe. The national guidelines recommendation is to confirm or exclude malaria by repeated microscopic examination for 4 times within first 24 hours.

4.1.2 PARASITOLOGICAL MALARIA (CONFIRMED MALARIA):

Patients with signs and symptoms with parasitological confirmation done by blood film microscopy, RDT, or molecular diagnostic test (in the context of malaria elimination) are considered as confirmed malaria.

It can be asymptomatic, uncomplicated or severe.

4.1.3 CARRIER STATE:

A carrier state of malaria is the person who is asymptomatic but harbors the Plasmodium species in one of two forms:

1. Person who is carrying the sexual form (gametocyte) with no signs and symptoms of malaria.
2. Patients who had some degree of natural resistance to Plasmodium infection either due to

acquired factors like the development of partial immunity after repeated attacks of malaria or due to certain genetic factors like:

- Persons who are negative for the Duffy blood group have red blood cells that are resistant to infection by P. vivax
- Persons who have the sickle cell trait are relatively protected against severe P. falciparum malaria.

4.2 Case classification:

Malaria case can be classified according to many factors, depending on the appearance of signs and symptoms and the severity of infection.

4.2.1 A symptomatic malaria:

A person with no signs or symptoms but had a parasitological positive (asexual form) peripheral blood test, usually found during surveys or medical checks.

4.2.2 Uncomplicated malaria:

Uncomplicated malaria with signs and symptoms of malaria without signs of severity or evidence of vital organs dysfunction.

4.2.3 Severe falciparum malaria:

Complicated P. falciparum malaria or Severe Malaria occurs when the infection causes or is likely to cause acute organ failures and death.

The definition of severe and/or complicated malaria is the presence of P. falciparum infection with one or more of the following conditions/ complications in the absence of other alternative etiology

1. Cerebral malaria:
    - Abnormal behavior.
    - Impaired level of consciousness
        i. A Glasgow coma scale GCS of less than 11 in adults
        ii. A Blantyre coma scale of less than three in Pediatrics.
    - Seizures.
    - Coma.
2. Hyper parasitemia: P. falciparum parasitemia > 5% in non-immune patients or > 10% in immune, presence of late stages like trophozoites or schizonts in peripheral blood.
3. Hypoglycemia: Blood or Plasma glucose of less than 2.2 mmol/L or <40 mg/dl, hypoglycemia occurs more frequently in pregnant ladies, and those who received treatment with quinine.

4. Renal impairment: (urine output less than 400ml/24h, plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L or black water fever.
5. Severe anemia-HB: Less than 7g/100ml in adults (hematocrit < 15 % in children). Or evidence of ongoing hemolytic anemia.
6. Coagulopathy (DIC).
7. Severe thrombocytopenia: (Platelets less than 50000/ µl or evidence of bleeding).
8. Jaundice: serum bilirubin of >50 µmol/L (3mg/dl) with parasite count of >100,000/ µl
9. Pulmonary complication:
   - Acute respiratory distress syndrome (ARDS)
   - Acute lung injury (ALI)
   - Pulmonary edema (Respiratory rate >30/min, CXR finding compatible with pulmonary edema with O2 saturation of < 92% on room air)
10. Shock.
11. Acidosis: A base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L
12. Prostration in children: (inability to sit or feed).

4.2.4 Patients at risk for severe malaria:

- Patients with delayed diagnosis and/ or inappropriate treatment.
- Visitors to malaria endemic area from non-endemic area.
- Pregnant women especially primigravida's
- Children under five years
- Severe anemia
- Sickle cell anemia
- Post Splenectomy.
- Resistant P. falciparum infection.
- Immuno-suppressed persons including HIV/AIDS and patients on immunosuppressive medications
- In hypo-endemic area, all ages are at risk.

Chapter 5:

Treatment of uncomplicated P. falciparum Malaria

5.1 Combination Therapy (CT):

Combination Therapy in malaria is the simultaneous use of two or more blood schizontocidal drugs with independent modes of action and thus unrelated biochemical targets in the parasite. The concept is based on the potential of the combined drugs to improve therapeutic efficacy and to delay the development of resistance to the individual components of the combination.

5.2 Artemisinin Based Combination Therapy (ACT):

Artemisinin and its derivatives (Artesunate, Artemether and dihydro-artemisinin) produce rapid clearance of parasitaemia and rapid resolution of symptoms. The Artemisinin compounds are active against all species of malaria parasites that infect humans and are generally well tolerated. These drugs also have the advantage, from a public health perspective as it reduces gametocyte carriage and thus the transmission of malaria.

5.3 Treatment of uncomplicated falciparum Malaria:

- A great number of patients with uncomplicated malaria can be successfully treated on outpatient basis, provided that the patients are followed-up to full recovery and disappearance of parasitemia.
- Delaying appropriate anti-malarial treatment may increase the risk of developing serious complications and progression to severe malaria.
- Malaria in pregnancy caries grave risks of maternal death and significant risk of miscarriage, stillbirth or neonatal death. Once recognized, it should be promptly and effectively treated preferably as inpatient.

- The emergence of drug resistance is a major concern in the management of malaria. Therefore, when treatment is commenced, patients on anti-malarial chemotherapy should strongly be persuaded to comply fully with the given treatment even if their symptoms have improved. Investing a little time in providing this information should result in better compliance.

5.4 First-line treatment of uncomplicated malaria:

5.4.1 Artesunate (AS) + Sulfadoxine-Pyrimethamine (SP):

This is currently available as separate scored tablets containing either 50 mg or 100 mg of Artesunate (AS), and tablets containing 500 mg of sulfadoxine + 25 mg of pyrimethamine. The total recommended treatment dose is 4 mg/kg, with therapeutic range of 2 - 10 mg/kg BW of Artesunate given once a day for 3 days and a single administration of Sulfadoxine/ Pyrimethamine (25/1.25 mg base/kg BW) on day one, Table (2a & b).

Table (2a): Dosage schedule for «Artesunate (AS) + Sulfadoxine-Pyrimethamine (SP) tabs:

Age in years	Weigh in Kgs	Day 1		Day 2	Day 3
		SP (500 S+25 P mg tab)	AS (50mg tab)	AS (50mg tab)	AS (50mg tab)
5 - 11 Months	5 - 10 Kgs	½	½	½	½
1 - 6 years	11 - 24 Kgs	1	1	1	1
7 - 13 years	25 - 50 Kgs	2	2	2	2
> 13 years	> 50 Kgs	3	4	4	4

** A single dose of primaquine (0.25 mg base/kg bw, maximum dose 15 mg) should be added on the first day of treatment to ACT for uncomplicated falciparum malaria as a gametocytocidal medicine.*

Table (2b): Summery of first line treatment of uncomplicated P. falciparum malaria

Body weight in Kg	Artesunate daily dose for 3 days	Sulfadoxine – Pyrimethamine dose (single dose)	Primaquine single dose
5 to < 10 kg	25 mg	250 mg / 12.5 mg	Not recommended
10 to < 25 kg	50 mg	500 mg / 25 mg	0.25 mg/kg
25 to < 50 kg	100 mg	1000 mg / 50 mg	7.5 mg
50 to 100 kg	200 mg	1500 mg / 75 mg	15 mg
>100 kg	2 mg/kg	1500 mg / 75 mg	15 mg

5.4.2: Artesunate (AS) + Mefloquie (MQ) combination therapy

Artesunate (AS) + Mefloquie (MQ) combination therapy is recommended if the use of Sulfadoxine – Pyrimethamine (SP) is contraindicated or not recommended as in:

- Clinical or laboratory diagnosis of G6PD deficiency.
- Allergy to Sulfadoxine or Pyrimethamine.
- Severe anemia.
- If P. falciparum malaria infection acquired in countries with known resistance to Sulfadoxine – Pyrimethamine (SP) as in Sudan, Sub Saharan Africa and South-East Asia.

The recommended dose of Mefloquine is 15 - 20 mg/kg given in one or two divided dose 8 - 12 hours apart, a higher dose of Mefloquine given as 8 (5 – 11) mg/kg/dose daily for 3 days is needed if malaria is acquired in south east Asia.

Both adult and pediatric fixed dose formulations of Artesunate and Mefloquine are currently not available in our formulary but both medications are available in sperate doses, Artesunate is available as 50 mg and 100 mg tablets and Mefloquine is available as 250 mg tablets.

5.4.3. Delayed parasite clearance:

In case of detectable parasitemia of the asexual form of the parasite at 72 hours or more from the start of ACT treatment, delayed parasite clearance is suspected.

Please refer to item 5.6.4.2 Page for further management.

5.4.4. Treatment Failure:

Treatment failure is defined as; failure to resolve or recurrence of fever and/or parasitemia within 2 weeks of the start of treatment, it is divided into:

1/ Early treatment failure (1-3 days of treatment).

2/ Late treatment failure (after 4 days up to 6 weeks).

5.4.5 Causes of treatment failure:

- Poor adherence to treatment.
- Low or incomplete dose.
- Abnormal individual pharmacokinetics.
- Drug resistance.

5.4.6 Treatment failure management:

- Failure within 14 days; Shift to the second line immediately.
- Failure after 14 days; this may be due to recrudescence or re-infection so it can be retreated with the first-line drug. In recrudescence, the first-line drug should be effective in most of the cases.

5.5. Second-line treatment:

5.5.1. Artemether-lumefantrine (Coartem):

Artemether-lumefantrine is currently available as co-formulated tablets (Coartem) containing 20 mg of artemether and 120 mg of Lumefantrine.

The total recommended treatment is a six-dose regimen of artemether-lumefantrine twice daily for 3 days, Table (3).

Table (3): Dosage schedule for (Artemether 20 mg + Lumefantrine 120 mg)*

Age in years	Weigh in Kgs	Day1**		Day2		Day3	
		AM	PM	AM	PM	AM	PM
< 5 kg		Was not recommended					
< 3 years	5 – 14	1	1	1	1	1	1
3 - 8 years	15 – 24	2	2	2	2	2	2
9 - 14 years	25 -34	3	3	3	3	3	3
> 14 years	> 34	4	4	4	4	4	4

** A single dose of primaquine (0.25 mg base/kg bw, maximum dose 15 mg) should be added on the first day of treatment to ACT for uncomplicated falciparum malaria as a gametocytocidal medicine.*
*** The second dose on the first day should be given any time between 8h and 12h after the first dose. Dosage on the second and third days is twice a day (morning and evening).*

An advantage of this combination is that Lumefantrine is not available as a mono-therapy and has never been used by itself for the treatment of malaria. Recent evidence indicates that the therapeutic response and safety profile in young children of less than 10 kg is similar to that in older children, and artemether-lumefantrine is now recommended for patients > 5 kg. Lumefantrine absorption is enhanced by co-administration with fat. Low blood levels, with resultant treatment failure, could potentially result from inadequate fat intake, and so it is essential that patients are informed of the need to take this ACT with milk or fat-containing food – particularly on the second and third days of treatment.

5.5.2 Single dose primaquine as gametocytocidal drug for P. falciparum:

It is recommended to add a single dose of primaquine (0.25 mg base/kg bw, maximum dose 15 mg) to ACT for uncomplicated falciparum malaria as a gametocytocidal medicine) if there is no contra indication to Primaquine. (WHO Guidelines for malaria treatment, 3rd edition 2015).

Primaquine is contraindicated in

- G6PD deficiency
- Pregnancy
- Children less than 6 months of age
- Lactating mothers for babies less than 6 months of age
- Known hypersensitivity to Primaquine

5.6. Third line treatment:

ACT is the recommended first and second line treatments for uncomplicated P. falciparum infection in Saudi Arabia however if both are not available or in the presence of a contra indication to their use like allergy to Artesunate and/or Artemether then a third line regimen should be used

For adult patients with uncomplicated P. falciparum malaria who can take orally one of the following options is recommended as third line treatment

- Oral Atovaquone 250 mg /Proguanil 100 mg (Malarone) four adult tablets once daily for 3 days. The drug is recommended to be taken with food or a fatty drink.

or

- Oral Quinine + Doxycycline for 7 days.
- Avoid taking Doxycycline with milk or milk products as it may decrease the absorption
- Doxycycline is contra indicted in pregnancy, lactating mothers, children < 8 years of age, patients with hypersensitivity to tetracyclines and systemic lupus erythromatosus patients .
- Atovaquone /Proguanil combination is associated with lower side effects than Quinine/ Doxycycline and Quinine/ Clindamycin combination therapies.
- Quinine and Clindamycin is the preferred anti-malarial regimen in pregnant women with uncomplicated P. falciparum malaria during first trimester of pregnancy.

5.7. Use of monotherapy is not recommended for the treatment of malaria due to rapid development of resistance.

The continued use of prolonged duration of Artesunate alone or any other partner drug like Sulfadoxine – Pyrimethamine (SP) or Mefloquine alone will compromise the values of ACT regimens in the future.

Chapter 6:

Management of severe and complicated falciparum malaria:

6.1 Key-Points: (Treatment objectives)

The main primary objectives of treatment of severe and complicated falciparum malaria are to prevent mortality and morbidity of the patients,

The secondary objectives are prevention of recrudescence, interruption of transmission and delaying emergence of resistance.

6.2.1 True Medical Emergency

Severe and complicated malaria is a true medical emergency associated with severe multi systemic complications, warranting ICU care for close monitoring and timely appropriate management of:

- Coma
- Hypoglycemia is a common complication necessitating frequent blood glucose monitoring.
- Fluids, electrolytes and acid base derangements should be managed properly.
- The diagnosis of malaria should preferably be confirmed by a positive blood film.
- Repeated examinations are necessary to confirm the diagnosis and to assess the parasitic response to anti-malarial drugs.
- If malaria smear examination is not immediately available, do urgent RDTs, prepare thick& thin blood smears and start anti-malarial treatment urgently.
- Repeated assessment of parasitemia are mandatory for management and follow up.
- Good nursing care is always crucial.

6.2.2 Pre-referral treatment:

A patient with severe malaria can deteriorate rapidly. Early administration of specific antimalarial treatment is life-saving.

All suspected or confirmed severe malaria cases should receive a full first dose of parenteral Artesunate therapy - if no facility for parenteral therapy then oral Artesunate therapy - before patient referral to another health care center with admission facility.

Rectal suppositories of Artesunate can be used for pediatrics < 6 years if IV treatment is not possible.

The rectal Artesunate therapy is not recommended for older children and adult patients.

Starting the first dose of available and appropriate anti-malarial drug is very important to decrease malaria morbidity but should not delay the patient referral.

6.3 Management of severe and complicated P. falciparum malaria should include:

6.3.1 Specific antimalarial treatment:

If severe or complicated malaria is anticipated, parenteral treatment should be started without any delay.

6.3.2 Supportive treatment = Good nursing care:

Metabolic and supportive care is equally important to ameliorate treatable complications.

6.4. Specific Anti malarial treatment

6.4.1. first line recommended treatment, Table (4):

- Intra Venous ARTESUNATE based combination treatment is the treatment of choice for severe and complicated P. falciparum malaria in Saudi Arabia.
- Children weighting < 20 kg should receive a higher dose of IV Artesunate as 3 mg/kg per dose at 0, 12, 24, 48 and 72 hours.
- Adults and children weighting 20 kg or more should receive IV Artesunate 2.4 mg/kg per dose at 0, 12, 24, 48 and 72 hours.
- If the patient remains critically ill and cannot take orally, then daily dose of IV Artesunate

can be continued until able to take oral ACT (max 7 days).

- Artesunate monotherapy is not recommended, addition of a long acting partner drug (i.e. Sulfadoxine-Pyrimethamine (SP) or Mefloquine or Lumefantrine) is required to maintain the necessary anti-malarial effect and prevent recrudescence of malaria, once the patient condition improved and he/she is able to take orally then start the recommended ACT therapy
- The choice of the long acting partner drug depends upon variable factors including patient comorbidities, malaria complication, G6PD status and the information about P. falciparum resistance in the country or region of acquiring the malaria infection.
- The recommended duration of IV Artesunate therapy is 72 hours, however, if the patient recovered early and able to take orally then the minimum duration of Intravenous Artesunate therapy is 24 hours (i.e. 3 doses of IV Artesunate) before starting full ACT treatment orally.
- A patient who is unable to take orally will be treated as severe malaria with intravenous Artesunate until he is able to take orally.
- All Saudi patients and residents in Saudi Arabia for 3 years and patients from non-endemic or hypo endemic countries with parasitemia level of 5% or more will be treated as severe malaria
- All male patients with severe and complicated malaria should have G6PD screening among the admission investigation if available

Table (4): Summary of recommended treatment for severe and complicated Plasmodium falciparum malaria .

Body weight	IV Artesunate dose	Dose frequency	Notes
< 20 kg	3 mg / kg / dose	At 0, 12, 24, 48 and 72 hours Daily dose of IV Artesunate until the patient can take orally and oral ACT can be given.	After the first 24 hours of IV Artesunate, if the patient improved and can take orally then oral ACT can be started. Rapid decline of parasitemia index is expected with Artesunate treatment. If asexual form of the parasite is seen at 72 hours or more, Plasmodium falciparum resistance is suspected (see below for further management).
20 kg or more	mg/kg/dose		

6.4.2. Delayed Plasmodium falciparum clearance:

- In case of detectable parasitemia of the asexual form of the parasite at 72 hours or more from the start of ACT treatment, delayed parasite clearance is suspected, and this may suggest partial or relative P. falciparum resistance, it is suggested to do the followings:
- Continue Artemisinin derivative treatment until undetectable parasitemia (max 7 days).
- Notify preventive medicine department in the region to follow the patient and arrange for Plasmodium falciparum Klech13 (K13) mutation.
- Arrange for parasitemia level daily until (0) level is achieved, then on day 7,14,28 and 42.
- Use Primaquine 0.25 mg/ kg (max of 15 mg) single dose at the end of treatment as gametocidal drug to prevent the transmission in the community (unless Primaquine is contra indicated).
- Continue follow up of the patient until clinical and parasitological cure is achieved.

6.4.3. Second line recommended treatment

If Artesunate is not available then:

Intra muscular ARTEMETHER 3.2mg/kg asa loading dose followed by 1.6 mg / kg/dose daily (max 7 days) until the patient can take oral ACT.

6.4.4. Third line recommended treatment

If both Artesunate and Artemether are not available

QUININE (I.V.) is the third option in severe and complicated malaria

Loading dose of 20 mg/kg in 5% dextrose over 4 hrs, followed by daily dose of 10 mg/kg over 4 hrs. at every 8 hrs. intervals for 7 days (max 1800 mg/day). The treatment should be shifted to the oral administration of quinine (10 mg/kg every 8 hours) as soon as the patient is safely able to take and tolerate oral treatment. A 7 days course of doxycycline can be given in order to ensure radical cure. The first (adult) dose of doxycycline is 200 mg, followed by daily doses of 100 mg for 7-10 days.

Patients who received Mefloquine chemoprophylaxis should NOT receive a loading dose of 20 mg/kg IV quinine.

[NB: doxycycline is contraindicated in children < 8 years and in pregnant women].

The following side effects of Quinine should be monitored:

- Hypoglycemia. Which is a complication of severe malaria, can be aggravated by both Quinine and Quinidine.
- Cardiac monitoring is crucial during treatment with Quinine or quinidine as QT and QRS wave changes might appear.
- Visual disturbances.
- Auto toxicity
- CNS (vertigo, syncope, confusion)

- Infusion treatment should be continued until parasitaemia is <1% or until oral treatment can be started and tolerated. Oral Quinine should then be started and continued for 3-7 days.

6.5 Exchange transfusion:

- Exchange transfusion is not recommended for management of severe complicated and uncomplicated malaria.
- The theoretical benefits of exchange transfusion by removing the parasitized RBC are not proven to be beneficial in any powered randomized controlled trial.
- The risks of exchange transfusion are high (fluid overload, hypocalcemia, line related infections allergic reactions etc.) and clearly out way unproven benefits and thus not recommended.
- In 2013 CDC conducted an analysis of cases of severe malaria treated with exchange transfusion and no mortality benefit was seen.
- Our current guidelines, CDC and WHO guidelines do not recommend exchange transfusion as a treatment for severe and complicated malaria.

6.6. Primaquine 0.25 mg (max 15 mg) once either before patient discharge or at the 3rd day of ACT treatment should be added as gametocidal drug to stop disease transmission UNLESS contra indicated.

Check the result of G6PD level on admission before use of Primaquine.

Primaquine should NOT be given in cases of:

- **Known hypersensitivity to primaquine**
- **Severe G6PD deficiency**
- **Pregnancy**
- **Children<6months**
- **Lactating women: (if infant is < 6 months age)**

Antimalarial drugs available in KSA:

Artesunate 50mg + Sulfadoxine 500mg/Pyrimethamine 25mg tabs
Artesunate 100mg + Sulfadoxine 500mg/Pyrimethamine 25mg tabs
Artemether 20mg + Lumefantrine tabs 120mg (Coartem)
Artemether ampoule 20mg and 80mg I/M
Artesunate ampoule 60mg I/V
Artesunate suppositories 50mg, 100mg, 200mg and 400mg
Quinine phosphate tabs 300mg
Quinine phosphate ampoules 600mg
Chloroquine phosphate tablets and ampoules 250mg
Chloroquine phosphate Syrup 50mg/5ml
Sulfadoxine tabs 500mg/Pyrimethamine tabs 25mg (Fansidar)
Primaquine tabs 7.5mg and 15mg
Mefloquine tabs 250mg
Atovaquone 250mg-Proguanil 100mg tabs (Malarone)

6.7: Management of malaria complications, Table (5):

Table (5): Clinical management of severe manifestations and complications of P. falciparum malaria:

Manifestations/complications	Suggested Immediate management
COMA (cerebral malaria)	Maintain airway, place the patient on his/her side, exclude other causes of coma (e.g.hypoglycemia, meningitis);avoid harmful ancillary treatment as corticosteroids, heparin and adrenaline. Intubate if necessary.
Hyperpyrexia	Administer tepid sponging ,fanning, cooling blankets and antipyretic; avoid aspirin
Hypoglycemia	Check blood glucose, correct hypoglycemia
Severe anemia	Blood Transfusion.
Acute pulmonary edema	Prop the patient up at angle of 45, give oxygen, diuretics, stop intravenous fluids, Intubate if needed .
Acute renal failure	Exclude pre- renal failure causes, check fluid balance and electrolytes; early haemodialysis / peritoneal dialysis
Bleeding and Coagulopathy	Transfuse FFP
Metabolic acidosis	Exclude or treat hypoglycemia, hypovolaemia and septicemia.
Shock	Exclude septicemia, blood culture; give parenteral antibiotics, correct shock.

Chapter 7:

Treatment of P. falciparum malaria in Specific Risk-Groups

7.1. Treatment of malaria in pregnancy:

7.1.1 Uncomplicated malaria

- Pregnant women have more tendency to develop severe malaria particularly hypoglycemia.
- Malaria in pregnancy is associated with increased risk of hypoglycemia, thrombocytopenia, pulmonary edema, abortion, stillbirth, low birth weight, maternal and neonatal death.
- Close observation for hypoglycemia, pulmonary edema and severe anemia is essential before and during anti-malarial treatment.
- Progression of P. falciparum malaria in pregnancy from uncomplicated to severe and complicated malaria can be rapid and thus it is recommended to admit pregnant women with malaria for close observation.
- Diagnosis of falciparum malaria in pregnancy can be difficult due to low level parasitemia because of parasites sequestration in the placenta.
- Congenital malaria is rare complication of malaria in pregnancy, it is seen more commonly with P. vivax than P. falciparum.

7.1.2 Treatment of uncomplicated malaria in pregnancy

- Oral Quinine + Clindamycin for 7 days is the recommended first line therapy in first trimester.
- Artemisinin based combination therapy (ACT) is the recommended first line therapy for second and third trimester.
- Artemether–lumefantrine (ACT) for 3 days is associated with high safety profile and cure rate as compared to the other ACT combinations.

- Artesunate + Clindamycin for 7 days is an effective and safe treatment regimen for both complicated and uncomplicated P. falciparum malaria in pregnancy.
- In a recent NEJM study comparing 4 ACT regimens (Artemether–Lumefantrine, Amodiaquine – Artesunate, Mefloquine-Artesunate, and Dihydroartemisinin–Piperaquine) in African pregnant women with P. falciparum malaria, Artemether–lumefantrine was associated with the fewest adverse effects and acceptable cure rates of 95%. While the Mefloquine-Artesunate combination provides 97% cure rate but with significant increase in the minor adverse effects.
- Artesunate + Mefloquine (ACT) can be used in 2nd and 3rd trimesters of pregnancy.
- Sulfadoxine/Pyrimethamine can increase neonatal icterus if used in 3rd trimester.
- Primaquine and Doxycycline are contra indicated all over the pregnancy

7.1.3 Treatment of severe and complicated P. falciparum malaria in pregnancy.

- Intra Venous Artesunate is the treatment of choice all over the pregnancy including the first trimester.
- IV Artesunate 2.4 mg/kg / dose at 0, 12, 24, 48 and 72 hours.
- If the patient improves and can take orally then complete her treatment with either oral Artesunate and Clinamycin for 7 days or with oral Artemether–lumefantrine (ACT) for 3 days if in 2nd or 3rd trimesters.
- If the patient remains critically ill or cannot take orally, then continue daily dose of IV Artesunate and Clindamycin to complete 7 days of treatment.

7. 2. Treatment in infants & children :

7.2.1 Key points:

- Infants and young children who live in or visited a malarious area are more susceptible to malaria infection and to its severe complications
- Symptom of malaria in children include fever, headache, vomiting, aches and pains, irritability and food refusal.
- Malaria infection in children mimic many other acute febrile illness, therefore laboratory confirmation with microscopy or RDT is mandatory in all suspected cases.
- Malaria infection may co-exist with other febrile illness in children
- Delay in treating P. falciparum malaria in infants and young children can have fatal consequences, particularly for more severe infections.

- Malaria in Children < 5 years should be considered severe and treated in hospital.
- Case fatality rates of severe malaria are high in infants so it is highly recommended to start anti-malarial drug immediately in case of suspicion
- In treating young children, it is important to ensure accurate dosing and retention of the administered dose, as infants are more likely to vomit or regurgitate antimalarial treatment than older children or adults.
- The lack of infant formulations of most antimalarial drugs often necessitates division of tablets, which can lead to inaccurate dosing.
- Artemisinin derivatives are safe and well tolerated by young children
- The recommended treatment for uncomplicated malaria in children is Artesunate (AS) + Sulfadoxine-Pyrimethamine (SP) (Table …) as first line, Artemether-lumefantrine (Coartem) (Table …) as a second line and oral Quinine + Doxycycline for 7 days as a third line (Table …).
- 1st and second line treatment are not recommended in infants < 5 Kg weight or < 3 months of age, instead parenteral or rectal artesunate can be given
- Mefloquine is not recommended in children < 15 Kg weight
- Rectal administration of a single dose of artesunate as pre-referral treatment reduces the risks of death.
- Children weighing less than 20 kg should receive a higher parenteral dose of artesunate (3 mg/kg/dose) than larger children and adults (2.4 mg/kg/dose)
- In case of vomiting or severe illness Artesunate by parenteral or rectal route should be considered depending on the situation.
  - Infants < 3 months: Parenteral or rectal Artesunate
  - Infants > 3 months and young children: ACT (crushed and dissolved)

7.2.2 Artemether or artesunate suppositories:

- Artemether suppositories: 4 mg/ kg (loading dose), then 2 mg/ kg daily (maintenance dose) for 5 days
- Artesunate suppositories: children: 5-10mg/kg (once daily for 5 days)

7.2.3 Severe malaria in children:

- Life saving and should be treated in ICU
- Symptoms and signs include; repeated convulsions, respiratory distress, hypoglycemia, severe anaemia and coma
- Good nursing care and careful monitoring are always required
- Specific treatment should be initiated as soon as possible (Artesunate IV as first line, Artemether IM as second line, Quinine IV as third line) (table ….)

N.B. Malaria in Children < 5 years should be considered severe and treated in hospital,

7.3. Co-existing morbidities:

7.3.1 HIV infection:

There is considerable geographic overlap between malaria and HIV, resulting in substantial numbers of individuals with co-infection. HIV-related immuno-suppression may lead to more severe manifestations of malaria.

Co-infected pregnant women are more likely to have symptomatic malaria infections, anemia, placental malaria infection, and low birth weight.

Treatment of Plasmodium falciparum malaria with ACT regimens containing Sulfadoxine-Pyrimethamine should not be given to HIV-infected patients receiving cotrimoxazole (Trimethoprim - Sulfamethoxazole) prophylaxis as this increases the risk of sulfonamide-induced adverse drug reactions.

For information on drug-drug interactions between anti-retroviral therapy and anti-malarial drugs used either for therapy or chemoprophylaxis we recommend to visit Liverpool HIV drug interactions at https://www.hiv-druginteractions.org

7.3.2 Treatment of malaria in Glucose 6-phosphate dehydrogenase deficiency:

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a X linked genetic disorder that affects 400 million people worldwide. The prevalence of G6PD deficiency Saudi Arabia is 3.6 – 8.4 % in males, 6.2% in Yemen and 26% in Oman.
- Glucose 6-phosphate dehydrogenase (G6PD) may provide relative protection from severe malaria, but G6PD are not immune to malaria infection.
- Both malaria infection and some anti-malarial increase the risk of RBC hemolysis in G6PD patient.
- G6PD screening is recommended for all male patients with severe and complicated malaria and all patients with malaria and severe hemolysis, black water fever or renal failure.
- Artesunate + Mefloquine should replace the use of Artesunate + Sulfadoxine/Pyrimethamine as a first line in the treatment of both complicated and uncomplicated malaria.
- In the treatment of P. falciparum malaria; Sulfadoxine / Pyrimethamine and Primaquine are contraindicated.

7.3.3. Treatment OF malaria in Sickle Cell Disease patients:

Sickle cell disease is the most common inherited hematological disorder in Saudi Arabia, Sickle cell anemia, Sickle- Beta Thalassemia are the two most common forms mainly in the Eastern

province, Al Hasa, and in the South West provinces (Jazan and Asir) where active foci of malaria transmission do exist.

- Patients with Sickle cell disease (Sickle cell anemia, Sickle beta thalassemia) have higher mortality and morbidity from malaria infection and they require urgent admission, timely and appropriate use of effective anti-malarial drugs.
- A study from Kenya (Blood 2010 116:1663-1668) has shown that the mortality of SCA children who had malaria was about 10 times higher than non sicklers malaria patients.
- Malaria infection in sickle cell disease patient induce more hemolysis, rapid decline of the hemoglobulin level and urgent demand for packed red blood cells transfusion.
- Poor correlation between the parasitemia level and the severity of the infection i.e. Plasmodium falciparum malaria may be severe and complicated at relatively lower parasitemia levels.
- Sickle cell anemia patients with auto splenectomy are at a higher risk for severe and complicated malaria. The spleen plays an important role in the protection from severe malaria by reducing the parasitemia level by removing the infected RBC from the circulation. SCA patients have an impaired splenic function; either due to anatomical atrophy of the spleen from repeated infarctions or due to functional asplenia.
- Due to high mortality of malaria in Sickle cell anemia patient, the policy recommends admission of all SCA patients with malaria infection to a hospital for close observation, early and appropriate anti malarials, and hemolysis treatment.
- The drugs recommended for the first and second line P. falciparum malaria treatment (Artesunate, Artemether, Mefloquine, Sulfadoxine-pyrimethamine, Lumefantrine, Clindamycin) are safe for use in sickle cell anemia patients.
- SCD patients traveling to malaria endemic destination should receive appropriate advices on malaria protection including malaria chemoprophylaxis.
- Sickle cell trait confers partial protection against severe P. falciparum malaria which provided relative survival advantage of sickle cell trait persons and may explain the similar geographical distribution of Sickle cell gene and malaria worldwide.
- This relative protection is incomplete and not protective from malaria infection, thus sickle cell trait persons traveling to an endemic malaria region require malaria protection including Chemoprophylaxis if indicted for other travelers.
- Atovaquone / Proguanil (Malarone), Mefloquine, Doxycycline and Chloroquine can be used for malaria chemoprophylaxis for both sickle cell disease and sickle cell trait persons.

Chapter 8:

Treatment of P. vivax and other forms of Malaria:

8.1. Treatment of Malaria caused by P.vivax, P. ovale or P. malariae:

P.vivax, the second most important species causing human malaria, accounts for 40% of malaria cases worldwide and is the dominant malaria species outside Africa. It is prevalent in endemic areas in the Middle East, Asia. In Africa, it is rare except in the Horn of Africa and it is almost absent in West Africa.

In most areas where P. vivax is prevalent, malaria transmission rates are low, and the affected populations therefore achieve little immunity to this parasite. Consequently, people of all ages are at risk. The other two human malaria parasite species P. malariae and P. ovale are generally less prevalent but are distributed worldwide especially in the tropical areas of Africa.

Among the well-known species of Plasmodium that affect humans, only P.vivax and P. ovale form Hypnozoites, which are dormant parasite stage in the liver that can result in multiple relapses of infection, weeks to years after the primary infection. The objective of treating malaria caused by these two species is to cure both the blood stage and the liver stage infections (radical cure), and thereby prevent both relapse and recrudescence.

8.1.1 P.vivax :

- Chloroquine 25 mg base/kg divided over 3 days, combined with primaquine 0.25 mg/kg (for Adult 15 mg), taken with food for 14 days is the treatment of choice for Chloroquine-sensitive infections.
- ACTs combined with primaquine for Chloroquine-resistant P. vivax malaria.
- In mild-to-moderate G6PD deficiency, primaquine 0.75 mg base/kg bw should be given once a week for 8 weeks. In severe G6PD deficiency, primaquine is contraindicated and should not be used.

Severe P.vivax malaria manifestations that have been reported are cerebral malaria, severe

anaemia, severe thrombocytopenia and pancytopenia, jaundice, spleen rupture, acute renal failure. Severe anaemia and pulmonary oedema are not uncommon. Prompt treatment and case management should be the same as for severe and complicated falciparum malaria

8.1.2 P. ovale.

The recommended treatment for malaria caused by P. ovale is the same as that given to achieve radical cure in P.vivax malaria.

8.1.3 P. malariae and P. knowlesi:

P. malariae and P. knowlesi should be treated with the standard regimen of Chloroquine as for P. vivax malaria, but does not require radical cure as no Hypnozoites are formed in infection with this species.

8.2 Pre-referral treatment options:

The risk of death from severe malaria is greatest in the first 24 h, yet in most malaria endemic countries, the transit time between referral and arrival at appropriate health facilities is usually prolonged thus delaying the commencement of appropriate antimalarial treatment, during which time the patient may deteriorate or die. It is recommended that patients are treated with the first dose of one of the recommended treatments by the parenteral route if possible or by the intra-rectal route before referral (unless the referral time is very short).

The administration of Artemisinin derivatives by rectal route as pre-referral treatment is feasible even at a community level.

Chapter 9:

Malaria Prevention and Chemoprophylaxis

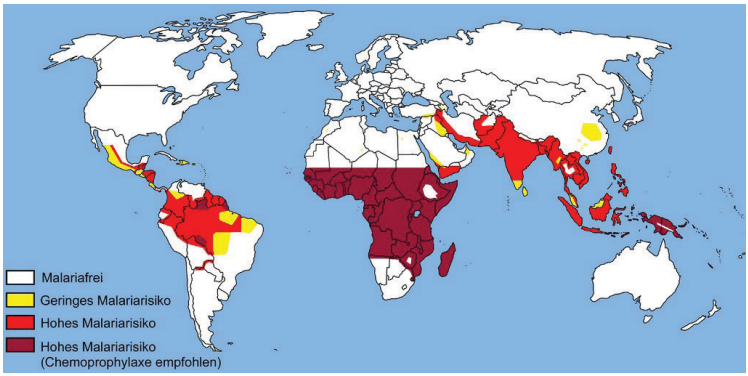
9.1 Awareness of risk

The risk of being bitten by a mosquito and the type of malaria transmitted varies, depending on the country you're visiting, MAP (1), and the time of the year. Measures to avoid bites should always be taken. If malaria is prevalent in an area you're travelling to, you would be wise to take preventive medicine. Areas of greatest risk are those where there's a high prevalence of multi-resistant P. falciparum malaria.

There are guidelines on risk and preferable preventive regimens for each of the regions described below.

- Sub-Saharan Africa.
- South Asia.
- South East Asia.

MAP (1): Global malaria endemicity



For optimal prevention of malaria, protection from mosquito bites is essential – even if you're taking preventive medicines.

9.2 Avoidance of mosquito bites

Mosquitoes bite particularly at twilight and at night, so measures of personal protection should be taken during this time. Sleep in rooms that are properly screened with screen nets over the windows and doors. Avoid unscreened entry points to the room. Air-conditioned rooms are good, too.

Spray the room with an insecticide before entering to kill any mosquitoes that have got inside during the day. Otherwise, you should use a mosquito net around your bed, impregnated with an insecticide such as pyrethrum (a harmless substance manufactured on the basis of extract of chrysanthemum) or other pyrithroids.

Wearing long trousers, long-sleeved clothing and thick socks to protect from mosquito bites and should be worn outside immediately after sunset. It may be hard to follow such advice in hot climate. Light colors are less attractive to mosquitoes.

9.2.1 Application of mosquito repellent creams:

Mosquito repellent containing DEET (chemical name N,N-diethyl-meta-toluamide) is recommended for persons during outdoors movement which is the most effective form of bite-preventive treatment.

It is important that the manufacturer's recommendations are not exceeded, particularly when using it on small children.

Insect repellents containing 20 to 50 per cent DEET will effectively repel mosquitoes when applied to exposed skin.

9.2.2 Insecticide-treated mosquito nets

When sleeping outdoors or in an unscreened room, have an insecticide-treated mosquito net around the bed. This significantly reduces the risk of bites.

The net should be small-meshed, with no holes, and tucked in under the bottom sheet. During the day, it should be rolled up, so mosquitoes and other insects can't get inside while it's not in use.

Insecticide-treated net (ITN) lasts for six months, depending on how much the net is used and stored condition.

It is highly recommended for every traveler to malaria endemic area to take his/her own net with him/her because ITNs may not be found there. And if he/she is staying for more than 6 months he/she can use long lasting insecticide-treated nets (LLITN).

9.3 Preventive medicines

Taking medicines to prevent malaria is essential, when visiting an area where malaria is prevalent. The problem can be in choosing the most appropriate antimalarial chemoprophylactic for the

country to be visited. It is also needed to take into account the individual circumstances. Because resistance to Chloroquine and other drugs is spreading, preventive (prophylactic) medicines that were effective five years ago may no longer be so. The geographic spread of Chloroquine resistance in the malarial parasite Plasmodium falciparum is increasing. It exists throughout sub-Saharan Africa, Southeast Asia, and the Indian subcontinent. The most appropriate drug(s) will depend on the country to be visited and the individual circumstances.

9.4. Malaria Chemoprophylaxis.

100 million travelers visit countries/regions with active malaria transmission annually. The risk of acquiring malaria for travelers is variable and depends on multiple epidemiological factors including:

- The epidemiology of malaria in the travel destination.
- The duration of the stay.
- The occupation, the activities and the style of living during travel
- The preventive measures used by the individual and the local health authority.

Malaria prevention advice should be evidence based, using sound and updated epidemiological data. The following variables should be considered for the recommendation of antimalarial chemoprophylactic drugs.

- The predominant Plasmodium species and the P. falciparum resistance in the destination country.
- Individual considerations like the sex, age, co morbid illness, concomitant drugs, allergies, pregnancy, etc

Malaria in Saudi Arabia is unstable. The annual incidence of locally acquired malaria is variable but remain very low (less than 100 cases per year in the last 5 years).

Plasmodium falciparum malaria is reported from few active foci in the rural area of Jazan and Asir, South West of Saudi Arabia. The high land of Asir province including the main cities (Abha, Khamis Mushaitt), and the islands in Jazan province (Farsan) are free of malaria transmission.

9.4.1 Population at risk for malaria is Saudi Arabia

The population at risk for Malaria in Saudi Arabia are:

- Army personnel and other employees working at the Southern borders in Jazan and Asir regions.
- Travelers to countries with active malaria transmission like Sub-Saharan Africa and South-East Asia.
- Pilgrimage for Hajj or Umra from countries / regions with active malaria transmission

9.4.2 Recommendation for Chemoprophylaxis for the army personnel working at the southern borders of Saudi Arabia

9.4.2.1: Atovaquone 250 mg–Proguanil 100 mg (Malarone) one tablet daily is the recommended chemoprophylactic drug for army personnel.

- Start 2 days before arrival.
- One tablet daily during the stay
- Continue for 5 days after leaving the destination.
- should be taken with a meal rich in fats (e.g. yoghurt).
- Avoid Atovaquone-Proguanil in patients with renal impairment (GFR <50 ml/min/1.7 m2 BSA).
- The most frequent side effects are gastrointestinal symptoms and headache.
- Atovaquone- Proguanil is contra indicated in patients with allergy to any of the two components.

9.4.2.2: Alternatives chemoprophylactic regimens.

Doxycycline 100 mg once daily, starting 2 days before travel, continuing throughout the stay and for 4 weeks after leaving.

9.4.2.3: Mefloquine 250 mg once weekly is not recommended for the army personnel and pilots, divers, due to the neuropsychiatric side effects.

9.5: The use of Atovaquone 250 mg–Proguanil 100 mg (Malarone) twice weekly provide adequate chemoprophylactic effect, 2 studies have shown similar protective effect to weekly Mefloquine and daily Atovaquone/Proguanil. The twice weekly dosing is currently under evaluation.

9.6: Emergency stand by treatment

Emergency standby treatment is recommended for the army personnel deployed in remote areas if they have malaria symptoms (fever, rigors, dark urine etc.) and they cannot reach safely to any health care facility within 24 hours of onset. Clear written instructions for its use are required before deployment.

- Emergency stand by therapy is additive measure and not a replacement for chemoprophylaxis
- Standby emergency treatment should be started only if it is unfeasible to consult a doctor or reach a diagnosis within 24 hours of the onset of fever.
- Artesunate 200 mg daily for 3 days and Fansidar 3 tabs once are recommended.
- Atovaquone – Proguanil (Malarone) is not recommended for emergency standby treatment unless no other alternative is available due to concerns on resistance and to minimize the drug toxicity.

9.7 Chemoprophylaxis for the travelers to malaria endemic destinations, Table (6)

9.7.1 Mefloquine 250 mg once weekly is recommended for travelers to countries or regions with P. falciparum Chloroquine resistance.

- Strat 2- 3 weeks before travel, continue throughout the stay and for 4 weeks after leaving the malaria endemic destination.
- Mefloquine is taken after meals with plenty of fluids
- Mefloquine chemoprophylaxis can be continued long periods of stay up to one year.

9.7.2 Contraindications to Mefloquine use are

- Allergy to mefloquine, quinine or quinidine.
- Current of previous history of psychiatric disorder including; depression, anxiety disorder, psychosis, schizophrenia, suicide attempts, suicidal thoughts, convulsions and epilepsy.
- Any of the above mentioned psychiatric disorders in a first-degree relative.
- Heart block and prolonged QT interval.
- Chronic liver disease.
- Blackwater fever.
- Children/ infants less than 5 kg weight
- Halofantrine use; avoid halofantrine use for 4 months after last dose of Mefloquine.
- Avoid Mefloquine in certain high-risk travelers like; pilots, divers, armed personnel, dangerous missions and travelers to countries with high prevalence of Mefloquine resistance like Thailand-Myanmar borders.
- Dizziness, balance disorder, tinnitus and vertigo are rare side effects of Mefloquine but may persist for few months after discontinuation.

9.7.3 Atovaquone 250 mg–Proguanil 100 mg (Malarone) one tablet daily is an alternative drug if Mefloquine is contra indicated (see above for more information), start 2 days before travel, continue during the stay and for 5 days after leaving the destination.

9.7.4 Doxycycline is the third option for malaria chemoprophylaxis

- The recommended dose is 100 mg daily
- Start 2- 3 days before travel, then daily throughout the stay and for 4 weeks after leaving the malaria endemic area
- It is contra indicated in pregnant women and children less than 8 years of age.

- Doxycycline is very effective drug for malaria chemoprophylaxis, but the GIT side effects and photosensitivity limit its use.
- Doxycycline should be taken with plenty of water, users should avoid lying down for one hour after taking the drug to minimize the risk of esophageal irritation.

9.7.5 Chloroquine is recommended for travelers to countries/ regions where P. falciparum is still sensitive to chloroquine

- Chloroquine-resistant falciparum malaria is reported from all WHO regions except Central America north of the Panama Canal, Haiti & the Dominican Republic).
- It remains effective against other Plasmodium species (vivax, ovale, malariae and knowlesi).
- Chloroquine 2 tablets (310 mg base) once weekly
- Start 1-2 weeks before travel, weekly throughout the stay and for 4 weeks after leaving the destination.

Table (6): Recommended malaria chemoprophylaxis for travellers

Drug	Dose	Available tablets	Duration
Travelers to countries or regions with P. falciparum chloroquine resistance.			
Mefloquine	One tablet once weekly	250 mg	Start 2 weeks before travel, throughout the stay and 4 weeks after leaving.
Atovaquone / proguanil	One tablet daily	Atovaquone 250 mg–Proguanil 100 mg	Start 2 days before travel, daily throughout and 5 days after leaving
Doxycycline	One tablet daily	100 mg	Start 2 days before travel, daily throughout and 28 days after leaving
For travelers to countries or regions with P. falciparum Chloroquine sensitive.			
Chloroquine	One tablet once weekly	250 mg (155 mg base)	Start 2 weeks before travel, throughout the stay and 4 weeks after leaving.

9.7.6 Long-term use of chemoprophylaxis:

No evidence of harm from the prolonged use of Mefloquine, Chloroquine, Proguanil and doxycycline if tolerated

Atovaquone/Proguanil (Malarone): limited data suggest no evidence of harm from prolonged use up to 1 year

9.8 Pregnancy and breastfeeding:

- Pregnant women are discouraged by the World Health Organization from travelling to malarious regions especially to areas with Chloroquine resistant malaria, because malaria increases the risk of abortion, premature birth, still-birth and maternal death.
- Just as for children, an extra effort should be made to protect them from mosquitoes and malaria if they're obliged to travel.
- Mefloquine 250 mg once weekly can be used as chemoprophylaxis in 2nd and 3rd trimesters.
- Atovaquone / Proguanil combination (Malarone) is not recommended for malaria chemoprophylaxis during pregnancy due to insufficient data, however animal studies and limited data from inadvertent human use during pregnancy did not show teratogenicity's or major side effects.
- Doxycycline and Primaquine are contra indicated during pregnancy and for lactating mothers.
- Chloroquine is safe during all trimesters of pregnancy, but most of the countries with active foci for malaria transmission are chloroquine resistant.
- Mefloquine and Chloroquine are safe for lactating mothers.
- Atovaquone/ Proguanil is not recommended for lactating mothers due to limited data but can be used if there is no other alternative.

9.9 Children: (Protecting children against malaria)

9.9.1 Remember to use:

- Mosquito repellent
- Insecticide treated nets (ITNs) or Long lasting insecticidal nets(LLINs)
- Regular chemoprophylaxis

9.9.2 Net advice:

Mosquito nets are available for cots and small beds. Babies should be kept under one as much as possible between dusk and dawn.

According to the World Health Organization, it's not advisable to take infants and young children to areas where there's malaria, especially if there's Chloroquine-resistant falciparum malaria (WHO, 2015).

If travel to malaria endemic area is a must, extra care should be taken to protect small children. It is vital to get qualified medical help if a child develops a fever during or after a trip to a malarious region, even if every possible thing has been done to avoid catching the disease.

9.9.3 Medicines for children:

- Preventive medicines should be given to breastfed, as well as bottle-fed, babies because they're not protected by the mother's medicine passing into the breast milk.
- Mefloquine is not recommended for children < 3 months of age or weighing less than 5 kg.
- Doxycycline is contraindicated in children < 8 years of age.
- The currently available strength of Atovaquone 250 mg + Proguanil 100 mg is for adult use and should not be used for chemoprophylaxis in children weighing less than 40 kg, Table (7).
- Keep all antimalarial medicines in childproof containers out of children's reach. Chloroquine can be fatal to children if the recommended dose is exceeded.

Table (7): Malaria chemoprophylaxis in children

Weight	Dose	Tablets
< 10 kg	Not recommended	
11 – 20 kg	Atovaquone 62.5 mg/ Proguanil 25 mg	1 pedia tab
21- 30 kg	Atovaquone 125 mg/ Proguanil 50 mg	2 pedia tabs
31- 40 kg	Atovaquone 187.5 mg/ Proguanil 75 mg	3 pedia tabs
40 or more	Atovaquone 250 mg/ Proguanil 100 mg	One adult tab

Chapter 10:

Travel Advice

10.1 Travellers could be at risk of malaria infection in 91 countries around the world, mainly in Africa, Asia and the Americas. Indeed, the risk for travellers of contracting malaria is highly variable from country-to-country and even between areas in a country. It may also vary according to the season, being highest at the end of the rainy season. In Saudi Arabia, the risk of malaria infection is restricted in the villages located on the Saudi border with the Republic of Yemen only in Jazan and Aseer regions. People traveling to these villages or to the malaria endemic countries, where the active malaria transmission occurs need to take chemoprophylaxis prior to, during, and upon return from their travel. Personal protective measures are also highly recommended to prevent mosquito bites including sleeping under long-lasting insecticidal nets, and using protective clothing and insect repellents. Further information can be obtained from the following link: https://www.moh.gov.sa

10.1.1 People infected with malaria often experience fever, chills and flu-like illness at first. Left untreated, the disease can lead to severe complications and, in some cases, death. Malaria symptoms appear after a period of seven days or longer. Fever occurring in a traveller within three months of possible exposure is a medical emergency that should be investigated immediately.

10.1.2 Some groups of travellers, especially young children, pregnant women and individuals with a weak immune system, are at particular risk of developing serious illness if they become infected with malaria. In pregnant women, malaria increases the risk of maternal death, miscarriage, stillbirth and low birth weight, as well as the associated risk of neonatal death. For further advices, please contact the appropriate travel health centers illustrated in Table (8).

Table (8): List of travel health centers in the KSA according to regions

No	Region	Selected health center
1	Riyadh (3)	Atiqa Primary Health care center (PHC) Al-Mohammadiyah PHC Airport Health Monitoring center
2	Makkah	Al-Raeyah PHC
3	Al-Madinah (2)	Preventive Medicine Clinics Complex Al-Safiyah PHC
4	Hail	Sharaaf PHC
5	Al-Qaseem	Al-Shamasi PHC
6	Eastern province (3)	Al-Mazrouiyah PHC Ras Tanura PHC Al-Khobar PHC
7	Northern province	Public Health at Directorate of Health Affairs
8	Aseer	Central Abha PHC
9	Al-Baha	Al-Baha PHC
10	Najran	Al-Dhubad PHC
11	Jazan	Airport PHC
12	Tabuk	Al-Saadah PHC
13	Al-Jouf	Al-Shalhoob PHC
14	Jeddah (2)	Al-Sulimaniyah PHC Al-Nahdah PHC
15	Al-Taif	Masarah PHC
16	Hafr Al-Baten	Al-Faisaliyah PHC
17	Al-Hassa	Al-Faisaliyah PHC
18	Bishah	Bishah Airport PHC
19	Al-Qunfudah	Al-Khalidiyah PHC
20	Al-Qurayyat	Al-Mohammadiyah PHC

Chapter 11:

Glossary

11.1 Artemisinin-based combination therapy (ACT):

A combination of artemisinin or one of its derivatives with an antimalarial drug of a different class and mode of action.

11.2 Asexual cycle:

Two separate cycles of asexual reproduction of malaria parasite in the human host, one in the liver, called the exo-erythrocytic cycle, and the other in the blood, known as the erythrocytic cycle. The erythrocytic cycle of the malaria parasite in host start from merozoites invasion of red blood cells to schizonts rupture (merozoite → ring stage → trophozoite → schizont → merozoite). Duration approximately 48 h in P. falciparum, P. ovale and P. vivax and 72 hr. in P. malariae.

11.3 Asexual parasitemia:

It is the presence of asexual parasites in host red blood cells. The level of asexual parasitemia can be expressed in several different ways. The percentage of infected red blood cells; the number of infected cells per unit volume of blood; the number of parasites seen in (1-100) microscopic fields in a high-power examination of a thick blood film or the number of parasites seen per 200–1000 white blood cells in a high power examination of a thick blood film.

11.4 Cerebral malaria Severe P. falciparum malaria with cerebral manifestations, usually including impaired level of consciousness, convulsions and/or coma.

11.5 Combination treatment (CT):

A combination of two or more different classes of antimalarial medicines with unrelated mechanisms of action.

11.6 Cure:

Is the elimination of the symptoms (clinical cure) and asexual blood stages of the malaria parasite(parasitological cure) that caused the patient or caregiver to seek treatment.

11.7 Drug resistance:

The World Health Organization defines resistance to antimalarial as the ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a medicine given in doses equal to or higher than those usually recommended but within the tolerance of the subject, provided drug exposure at the site of action is adequate. Resistance to antimalarial arises because of the selection of parasites with genetic mutation or gene amplifications that confer reduced susceptibility.

11.8 Gametocytes:

Sexual stages of malaria parasites present in the host RBC.

11.9 Hypnozoites:

Persistent (Dormant) liver stages of P. vivax and P. ovale malaria that remains dormant in host hepatocytes for an interval (most often 3 – 45 weeks) before maturing to hepatic schizont. These then burst and release merozoite, which infect red blood cells. Hypnozoites are the source of relapses.

11.10 Malaria pigment (haemozoin):

A dark brown granular pigment formed by malaria parasites as a by-product of hemoglobin catabolism. The pigment is evident in mature trophozoite and schizonts. They may also be present in white blood cells (peripheral monocytes and polymorpho nuclear neutrophils) and in the placenta.

11.11 Merozoites:

Parasites released into the host bloodstream when a hepatic or erythrocytic schizonts bursts. These then invade the RBC.

11.12 Monotherapy:

Antimalarial treatment with a single medicine (either a single active compound or a synergistic combination of two compounds with related mechanism of action).

11.13 Plasmodium:

A genus of protozoan, blood parasites that includes the causal agents of malaria. Plasmodium falciparum, P. malariae, P. ovale and P. vivax cause malaria in humans. Human infections with P. Knowlesi have been reported from South-East Asia but no documented report of imported or locally transmitted P. knowlesi malaria in Saudi Arabia till date.

11.14 Pre-erythrocytic development:

The life-cycle of the malaria parasite when it first enters the host. Following inoculation into a human by the female anopheles mosquito, sporozoites invade parenchyma cells in the host liver and multiply within the hepatocytes for 5 –12 days, forming hepatic schizonts. These then burst liberating merozoites into the bloodstream, which subsequently invade red blood cells.

11.15 Radical Cure:

In P. vivax and P. ovale infections comprise a cure as defined above plus prevention of relapses by killing Hypnozoites.

11.16 Rapid diagnostic test (RDT):

An antigen-based stick, cassette or card test for malaria in which a line indicates the presence of plasmodia antigens.

11.17 Recrudescence:

A Latin word that means the revival or reappearance in active existence. Malaria recrudescence is described when parasitaemia falls below detectable levels and then later increases to a patent parasitaemia. (It is the recurrence of asexual parasitaemia after treatment of the infection that caused the original illness.) This results from incomplete clearance of parasitaemia due to inadequate or ineffective treatment (drug resistance or improper choice of medication). It is, therefore, different from a relapse in P. vivax and P. ovale infections, and it differs from a new infection or re-infection (as identified by molecular genotyping in endemic areas).

11.18 Recurrence:

The recurrence of asexual parasitaemia following treatment can be caused by a recrudescence, a relapse (in P. vivax and P. ovale infections only) or a new infection.

11.19 Relapse:

The recurrence of asexual parasitaemia in P. vivax and P. ovale malaria deriving from persisting liver stages. Relapse occurs when the blood stage infection has been eliminated but Hypnozoites persist in the liver and mature to form hepatic schizonts. After variable intervals of weeks to months, the hepatic schizonts burst and liberate merozoites into the bloodstream.

11.20 Ring stage:

Young stage is usually ring-shaped intra-erythrocytic malaria parasites; before malaria pigment is evident under microscopy.

11.21 Schizont:

Mature malaria parasites in host liver cells (hepatic schizonts) or red blood cells (erythrocytic schizonts) that are undergoing nuclear division. This process is called schizogony.

11.22 Selection pressure:

Resistance to antimalarials emerges and spreads because of this elective survival advantage that resistant parasites have in the presence of antimalarials to which they are resistant. Selection pressure describes the intensity and magnitude of the selection process, the greater of the proportion of parasites in a given population exposed to concentrations of an antimalarial that allows proliferation of resistant, but not sensitive parasites, the greater the selection pressure.

11.23 Severe falciparum malaria:

Acute falciparum malaria with signs of severity and/or evidence of vital organ dysfunction.

11.24 Sporozoites:

Motile malaria parasites that are infective to humans, inoculated by a feeding female anopheles mosquito, that invade hepatocyte.

11.25 Transmission intensity:

The intensity of malaria transmission measured by the frequency with which people living in an area are bitten by anopheles mosquitoes carrying Sporozoites. This is often expressed as the annual entomological inoculation rate (EIR), which is the average number of inoculations of malaria parasites received by one person in one year.

11.26 Trophozoite:

Stage of development of the malaria parasite within host red blood cells from the ring stage to just before nuclear division. Mature trophozoite contains visible malaria pigment.

11.27 Uncomplicated malaria:

Symptomatic infection with malaria parasitaemia without signs of severity and / or evidence of vital organ dysfunction.

11.28 First and second line Treatment:

First-line treatments are those recommended in the national treatment guidelines as the medicine of choice to treat malaria. Second-line treatments are those used for treatment failure, or if the patient is allergic or unable to tolerate the first-line treatment.

11.29 Vectorial capacity:

It is a series of biological features that determine the ability of mosquitoes to transmit plasmodium.

Chapter 12:

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April 25

WORLD MALARIA DAY