KINGDOM OF SAUDI ARABIA
DEPUTY MINISTER OF PUBLIC HEALTH OFFICE
DIRECTORATE GENERAL OF COMMUNICABLE DISEASES
DIRECTORATE OF VECTOR CONTROL DISEASES
MALARIA ELIMINATION PROGRAM

NATIONAL MALARIA DRUG POLICY

Second Edition 2015

Review Board:

A.MOH (Head Quarter)

1) Dr. Bin Saeed , Abdulaziz Abdullah	Deputy- Minister for Public Health
2) Dr. Abdullah , M Assiri	Assistant Deputy- Minister for Preventive Health
3) Dr. Al-Hakeem ,Raafat F.	Director General of Communicable Diseases
4) Dr. Al-Zahrani,Mohammed H.	Malaria Elimination Program Director
5) Dr. Al-Barrak, Ali M	Director General For Saudi Centers for Disease Control & Prevention
6) Dr. Al Hazmi , M.M.	Consultant of infectious diseases KSA
7) Dr. Alhelal , Mohammad Abdullah	Malaria Specialist
8) Dr. Khairi,Taj-elsir M.	Epidemiologist -Malaria Elimination program
9) Dr. Ibrahim , Ali Adam	Public Health physician – Malaria Elimination program
10) Mr. Alhogail , Abdullah	Malaria Elimination program
11) Dr. Eltigani , Rahma	Public Health physician – Malaria Elimination program
12) Mr.Almojam, Suliman.	lab specialist – Malaria Elimination program

B.MOH (Regions)

Dr. Alshahrani, Ali Mohammed - Dr. Alghamdi,Faisal - Dr. Alghamdi,Saeid Abdulaziz-Dr.Almitairy,Majid Matar - Dr.Alzahrani,Abdullah Gainan - Dr. Alfaify ,Sulaiman Qassim - Dr.Alhwitan , Abdullah - Dr.Alhawsa ,Abdulrahman Faye - Dr.Qasem , AlanaziSulaiman - Mr.Almadi, Saad Mohammed - Dr.Hamzi ,Ali - Dr.Haider,Adel - Mr. Abdelmohsin Abdoon, Mr. Elamin, Yousif Eldirdiry - Dr. Abuzaid A. Abuzaid – Dr. Alsahli, Ahmed - Dr.Aljamri,Tajudin - Dr.Ali,Ibrahim Saeed M. Dr.Mohamed,Tarig A/Gader - Dr.Humattalla,Abdulla M. - Mr. Alattas,Mohammed Salim - Mr.AlGallee,Abdullah Mohammed- Mr.Al Gafeese, Ali Nasser-Mr. Alsuhibani ,Khalid Sulaiman - Mr. Ghoneim,Salah -Mr. Aburukbh,Sami Misfer–Mr. Alshihri,Saad Saeed - Mr. Alghamdi,Saeid Abdullah -Mr. AL.Shalawi,Meshal Abdullah - Mr. Alassiri , Abdullah Ibraheem-Mr. Alfaify , Mussa Salman - Mr.Alzumea, Mohammed Saleh – Mr. AlRowis, Mohammed M.- Mr. Nasser , AlBekairy Saleh - Mr. Ghormallah , Alzahrani Ahmed -Mr. AL.Shalawi,Mohammed Abdullah - Mr.Alghunaimi ,Salem Ibrahim - Mr.Alfozan,Abdulaziz Abdullah - Mr.Alnsiri,Abdullah,Abdulaziz- Mr. Alwan,Yahya Hussein Ahmed – Mr. Alturky, Turky Abdulaziz -Mr.Sadi, Ahamed M . - Mr.Bakkari, Mohammed A.- Mr. Alfaifi,Abdullah A. - Mr.Mashragi,Ibraheem G. - Mr.Otaif, Ismaeel H. - Mr.Almosailhi ,Ahmed H. - Mr. Omar, Abdiasiis.

WHO Experts :

Dr. Atta, Hoda Y. (Regional advisor, RBM / EMRO / WHO**)**

Dr. Zamani, Ghasem. (EMRO / WHO**)**

Dr. Adeel, A.A. (WHO temporary advisor KSA**)**

Dr. Kondrashion A. (WHO consultant**)**

Dr. Bosman A. (M.O. WHO HQ**)**

CONTENTS :

Abbreviations:

ACT	**Artemisinin-based combination therapy**
ACMP	**Advisory committee on Malaria Prevention**
AL	**Artemether plus Lumefantrine combination**
AS	**Artesunate**
AS+SP	**Artesunate + Sulfadoxine / Pyrimethamine combination**
BW	**body weight**
CT	**Combination therapy**
CQ	**Chloroquine**
G6PD	**glucose-6-phosphate dehydrogenase**
HIV/AIDS	**human immunodeficiency virus/ acquired Immunodeficiency syndrome**
HRP2	**histidine-rich protein 2**
I.V.	**Intravenous**
I.M.	**Intramuscular**
MQ	**Mefloquine**
PfHRP2	***Plasmodium falciparum* Histidine-rich protein-2**
PQ	**primaquine**
RCT	**randomized controlled trial**
RDT	**rapid diagnostic test**
SP	**Sulfadoxine - Pyrimethamine**
WHO	**World Health Organization**

Chapter 1: Glossary

1.1 Artemisinin-based combination therapy (ACT): A combination of artemisinin or one of its derivatives with an antimalarial of a different class and mode of action.

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

1.3 Asexual parasitaemia: The presence in host red blood cells of asexual parasites. The level of asexual parasitaemia 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.

1.4 Cerebral malaria: Severe *P. falciparum* malaria with cerebral manifestations, usually including coma (Glasgow coma scale < 11, Blantyre coma scale < 3). Malaria with coma persisting for > 30 min after a seizure is considered to be cerebral malaria.

1.5 Combination treatment (CT): A combination of two or more different classes of antimalarial medicines with unrelated mechanisms of action.

1.6 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.

1.7 Drug resistance: The World Health Organization (WHO) 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.

1.8 Gametocytes: Sexual stages of malaria parasites present in the host red blood cells.

1.9 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.

1.10 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.

1.11 Merozoites: Parasites released into the host bloodstream when a hepatic or erythrocytic schizonts bursts. These then invade the red blood cells.

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

1.13 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 the monkey malaria parasite, *P. Knowles*i have also been reported from forested regions of South-East Asia.

1.14 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.

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

1.16 Rapid diagnostic test (RDT): An antigen-based stick, cassette or card test for malaria in which a colored line indicates the presence of plasmodia antigens.

1.17 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).

1.18 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.

1.19 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.

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

1.21 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.

1.22 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.

1.23 Severe anaemia: Haemoglobin concentration of < 5 g/100 ml (haematocrit< 15%).

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

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

1.26 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.

1.27 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.

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

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

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

Chapter 2: Goals & Criteria for change

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 Introduction:

Malaria is a life threatening infection caused by Plasmodium species and transmitted by some species of anopheles mosquitoes.
About 3.2 billion people – almost half of the world's population mainly in the tropical and subtropical areas is at risk of malaria with 149 – 303 millions of acute infections and 236000 – 635000 deaths annually.

Four well known species of Plasmodium cause human malaria (*P. falciparum, P. vivax, P. ovale* and *P. malariae*), *P. falciparum* is responsible for the severe and complicated cases, which might result in death if not promptly treated with effective drugs. Recently, human infections with the monkey malaria parasite, *P. Knowlesi* have also been reported from forested regions of South-East Asia.

In Saudi Arabia, there were 2305 reported malaria cases in year 2014, however only 51 cases were locally acquired and all *were Plasmodium falciparum* infection. From total malaria cases the *Plasmodium falciparum was represented 38.80%, Plasmodium vivax 60.80%, Plasmodium ovale 0.20% and Plasmodium malariae 0.20%.* 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.

2.3 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.

2.4 Criteria for Antimalarial treatment policy changes :

It is now recommended that a change of first-line treatment should be initiated if the total failure proportion exceeds 10%. (WHO malaria treatment guidelines) That is to add: careful clinical and parasitological follow up of the patients is highly required. However, it is acknowledged that a decision to change may be influenced by a number of additional factors including the prevalence and geographical distribution of reported treatment failures.

Chapter 3: Clinical presentation & Diagnosis

3. 1 Clinical presentation:

Malaria symptoms manifest approximately 7 – 14 days after introduction of parasite in human circulation by infected 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, haemoglobin-uria, circulatory collapse and shock, spontaneous bleeding (disseminated intravascular coagulation), 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 microscopy. Where microscopy is not available RDTs 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) that remain the gold standard method for the diagnosis, identification of plasmodium species and estimation of parasite load or density by parasite density 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 4 times may be needed (This should be done within 24 hours) to demonstrate the presence of parasites particularly in low parasitaemia 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.

3.3 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.

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 *Plasmodium falciparum* PLDH from other *Plasmodium* species i.e. *vivax*, *ovale* and *malariae*) (93.2% 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.

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).

Note:

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 antimalarials.

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) but with no features of severe malaria is defined as having uncomplicated malaria or simple malaria.

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.

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 is the person or animal that shows no symptoms of a disease but harbors the infectious agent of that disease and is capable of transmitting it to others).

In malaria it occurs in two forms:

1. Person who is carrying the sexual form (gametocyte) with no signs and symptoms of malaria usually due to incomplete treatment.
2. Patients who had some degree of natural resistance to one parasite species or another.

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 *Plasmodium 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 *Plasmodium 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 3 in Pediatrics.
    - Seizures.
    - Coma.

2.Hyperparasitaemia: *P. falciparum* parasitaemia > 10% (Parasitized RBCs > 5% in non-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)**.**

Note: The diagnosis should preferably be confirmed microscopically.

4.2.4 Patients at risk for severe malaria:

- Visitors to endemic area from non-endemic area.
- Under five years In hyper-endemic area..
- Patients with severe anaemia.
- In hypo-endemic area, all ages are at risk.
- Splenectomized patients.
- Resistant *P. falciparum* infection.
- Delayed or inappropriate treatment.
- Immuno-suppressed persons (HIV)
- Patients on immunosuppressive drugs
- Young children
- Pregnant women especially primigravidas

Chapter 5: Treatment of Falciparum Malaria

5.1 Combination Therapy (CT):

Combination Therapyin 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 parasitaemia.
- Delaying the treatment may increase the possibility of developing serious complications.
- 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.
- Treatment failures should be closely monitored.

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 50 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.

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.

5.4.2 Treatment Failure:

Treatment failure is defined as; failure to resolve or recurrence of fever and/or parasitaemia 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 4 weeks).

5.4.3 Causes of treatment failure:

a) Poor adherence to treatment.
b) Low or incomplete dose.
c) Abnormal individual pharmacokinetics.
d) Drug resistance.

5.4.4 Treatment failure management:

1) Failure within 14 days; Shift to the second line immediately.
2) 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:

Artemether-lumefantrine (Coartem):

This is currently available as co-formulated tablets 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.

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.

Single dose primaquine as gametocytocide for 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) (WHO Guidelines for malaria treatment, 3rd edition 2015).

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)**

5.6 Management of severe and complicated falciparum malaria:

5.6.1 Key-Points: (Treatment objectives)

The main objective is to prevent the patient from dying; secondary objectives are prevention of disabilities, prevention of recrudescence, interruption of transmission and delaying emergence of resistance. Severe and complicated malaria is a true medical emergency associated with severe multi systemic complications, warranting ICU care for close monitoring and subsequent management of:

- Coma
- Hypoglycemia is a common complication necessitating frequent 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 then to assess the parasitic response to anti-malarial drugs.
- If malaria smear examination is not available, prepare a thick& thin smear and start treatment urgently.
- (Parasite count) is mandatory for management and follow up.
- Good nursing care is always required.

5.6.2 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 dose of parenteral or rectal medication BEFORE transferred to hospital

5.6.3 Management should include:

1. Specific antimalarial treatment:

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

Parenteral ARTESUNATE (I.V.) is the first option for the treatment of severe and complicated falciparum malaria. Children weighting < 20 kg should receive a higher dose of Artesunate (3 mg/kg BW per dose) than larger children and adults (2.4 mg/kg bw per dose) unless otherwise contraindicated i.e. first trimester of pregnancy.

If the first option is not available then

Parenteral ARTEMETHER (I.M.) 3.2mg/kg (1.6 mg/Kg initially, and again after 12 hours on the first day). Then 1.6 mg/Kg daily for the next 6 days .

Or

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

2. Supportive treatment = Good nursing care:

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

3. Severe Malaria is a Medical Emergency:

- After rapid assessment and confirmation of the diagnosis, full doses of parental or rectal Antimalarial treatment should be started immediately with whichever effective Antimalarial is available
- Rectal route may be a suitable alternative pre-referral in severely ill children.

5.6.4 Specific Antimalarial drugs:

It is essential that Antimalarial treatment in full doses is given as soon as possible in severe malaria. Two classes of drugs are currently available for the parenteral treatment of severe malaria: the artemisinin derivatives (Artesunate, Artemether) and the cinchona alkaloids (quinine).

5.6.4.1 ARTESUNATE I.V:

2.4 mg /kg bw is given twice on the first day (at zero hour and 12 hours), then once daily for next 6 days. Shift to oral route immediately when the patient conditions permit.

*Artesunate can also be given intramuscular.

5.6.4.2 ARTEMETHER I/M:

3.2mg/kg (1.6 mg/Kg initially, and again after 12 hours on the first day). Then 1.6 mg/Kg daily for the next 6 days.

5.6.4.3 QUININE DIHYDROCHLORIDE:

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.

[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)

Note :

- 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.
- In the management of severe malaria cases due to *P. falciparum,* Primaquine (0.25 mg once) should be added as gametocidal drug to stop disease transmission but no need to add Primaquine in cases of malaria due to *P. vivax or P. malariae* or *P. ovale* as quinine has gametocytocidal effect on them.

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)

Chapter 6 : management of severe manifestations:

6.1 Clinical management of severe manifestations and complications of malaria:

Manifestations/complications	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 lancillary treatment as corticosteroids, heparin and adrenaline. Intubate if necessary.
Hyperpyrexia	Administer tepid sponging ,fanning, cooling blankets and antipyretic
Hypoglycemia	Check blood glucose, correct hypoglycemia
Severe anemia	Transfuse with fresh blood
Acute pulmonary edema	Prop the patient up at angle of 45, give oxygen, diuretics, stop intravenous fluids, Intubate if needed and add positive end-expiratory pressure.
Acute renal failure	Exclude pre- renal failure causes, check fluid balance and blood electrolytes; if there is renal failure do haemodialysis / peritoneal dialysis
Bleeding and Coagulopathy	Transfuse with screened fresh blood or plasma , give vitamin K injection.
Metabolic acidosis	Exclude or treat hypoglycemia, hypovolaemia and septicemia. If severe add haemodialysis.
Shock	Exclude septicemia, take blood for culture; give parenteral antibiotics, correct shock.

Chapter 7 : Specific Risk-Groups

7.1 Treatment of malaria in pregnancy:

7.1.1 Uncomplicated malaria

- Pregnant women with symptomatic acute malaria are a high- risk group, and must receive effective antimalarials. Malaria in pregnancy is associated with abortion, stillbirth, low birth weight, increased anaemia and, in low transmission areas, an increased risk of severe malaria.
- First trimester: quinine + Clindamycin to be given for 7 days.
- ACT should be used if it is the only effective treatment available.
- In Second and third trimesters: ACT can be used if it is known to be effective. In KSA (Artesunate + Clindamycin, or quinine + Clindamycin to be given for 7 days.)

7.1.2 Severe and complicated Malaria

- Artesunate I.V. (All Trimesters) …. If not available
- Quinine I.V.

7. 2 Treatment in infants:

Malaria is common in infants and under 2 years old children in endemic areas, as immunity acquired from the mother wanes after 3-6 months of age.

Case fatality rates of severe malaria are high in infants so it is highly recommended to start antimalarials immediately in case of suspicion. Accurate diagnosis is important. Infants are more likely intolerant to antimalarials because of vomiting, regurgitation, and gastrointestinal intolerance.

Artemisinin derivatives appear to be safe and well tolerated by young children.

Delay in treatment may have fatal consequences, so every effort should be made to give oral treatment and ensure that it is retained by the infant. 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), in cases of vomiting or severe illness parenteral or rectal Artesunate should be given

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

- Artemether suppositories: 4 mg/ kg (loading dose), then 2 mg/ kg daily (maintenance dose) for 5 days
- Artesunate suppositories: Adult: 10-15mg/kg, children: 5-10mg/kg (once daily for 5 days)

N.B. Artemether and Artesunate suppositories can be used as a pre-referral treatment

7. 3 Co-existing morbidities:

- **HIV infection :**

There is considerable geographic overlap between malaria and HIV, resulting in substantial numbers of individuals with co-infection. Worsening HIV-related immuno-suppression may lead to more severe manifestations of malaria.. Co-infected pregnant women are more likely to have symptomatic malaria infections, anaemia, placental malaria infection, and low birth weight.

Treatment or intermittent preventive treatment (IPT) with sulfadoxine-pyrimethamine should not be given to HIV-infected patients receiving cotrimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis as this increases the risk of sulfonamide-induced adverse drug reactions.

Chapter 8: Treatment of 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.

8.3 Management in epidemic situations:

Drug treatment should be as simple as possible, with simple dosing schedules and a minimum need for monitoring. Therefore, the simple once a day regimens and the ease of drawing and administering intramuscular artemether make this a suitable alternative for severe malaria in most epidemic situations.

Chapter 9: MALARIA PREVENTION

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 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 *Plasmodium 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.

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 Chemoprophylactic drugs in current use.

The following points should be considered when choosing antimalarial chemoprophylactic drugs.

1. The type of malaria in the area to be visited.
2. The risk of being bitten by a mosquito.
3. Individual considerations:
    1. Pregnancy
    2. Breastfeeding.
    3. Psychotic illness.
    4. Is it for a child?
    5. Concomitant medication.

9.4.1 Chloroquine:

This is taken weekly and is the preferred drug in areas without resistance to Chloroquine. It is used in combination with Proguanil in areas with low resistance. This combination is becoming less effective due to increasing resistance to Chloroquine, particularly in Africa. Proguanil is taken daily and is an alternative to Chloroquine, in areas with Chloroquine resistant. Although resistance to Proguanil has developed over the last years it is still being used as an alternative to Chloroquine in areas of Chloroquine resistance.

However, it's still the recommended combination for the Indian subcontinent and various other low risk parts of the world. Both drugs should be started one week before travel and continued for a further four weeks after leaving the malarious area.

9.4.2 Mefloquine:

Mefloquine is more effective in areas of Chloroquine-resistant malaria, i.e. over 90 per cent in Africa. It's main side-effects are mood changes and depression in some people. Other milder side-effects include sleep disturbances and abnormal dreams.

It is taken weekly at a dose of one tab (250mg) and should be started two - four weeks before travelling, so that 2-4 doses should be taken before departure. This enables blood levels of the drug to reach a protective level**.**

Mefloquine should be continued for four weeks after leaving the malarious area. It should not be taken by people with a history of psychiatric disturbances (including depression) or convulsions.

9.4.3 Malarone :

Malarone is also considered to have similar effectiveness as Mefloquine. Long-term use of Malarone requires specialist advice.

It is taken daily and should be taken with a meal rich in fats (e.g. yoghurt) or a milky drink to avoid the risk of it's not being adequately absorbed from the gastrointestinal tract.

Malarone should be started two to three days before travel and only needs to be continued for a week after leaving the malarious area.

9.4.4 Doxycycline:

No evidence of harm in long-term use. Photosensitivity and antibiotic resistance may also develop. It is contraindicated in pregnancy and in children < 8 years.

9.5 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.

9.6 Children: (Protecting children against malaria)

9.6.1 Remember to use:

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

9.6.2 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.

9.6.3 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.

Chloroquine and Proguanil may be given safely to babies and young children, but the doses used are much smaller than those recommended for adults.

Mefloquine may be given from three months onwards. There's little experience with this medicine in children less than three months or weighing less than 5kg and it's not recommended in these cases.

Doxycycline is contraindicated in children < 8 years of age.

Adult Malarone (250mg atovaquone + 100mg proguanil) should not be given to children weighing less than 40kg.

For administration, antimalarial medicines may be crushed and mixed with jam, banana, or similar foods. Syrup formulations are available for certain medicines, but they have shorter shelf-lives in tropical areas.

Remember to keep all antimalarial medicines in childproof containers out of children's reach. Chloroquine can be fatal to children if the recommended dose is exceeded.

Chapter 10: Travel Advice

10.1 If a travel to a malarious area is anticipated, chemoprophylaxis and personal protective measures are of paramount importance.

10.2 Medicines for pregnant women:

Both **Chloroquine and Proguanil** have no special risk for pregnant women and should be administered together.
Pregnant women who use Proguanil may benefit by also taking a daily folic acid supplement.

In countries where resistance to Chloroquine is high, it may be necessary for the doctor to prescribe **Mefloquine.**
The decision to prescribe **Mefloquine** is made up after weighing the benefits of preventing malaria, versus the harmful effects, that malaria can impart on both the mother and foetus.
In scenarios where other medicines are not effective, the benefits of using Mefloquine may outweigh the risks.
If pregnant women accidentally take Mefloquine during pregnancy, there's no reason to terminate the pregnancy.
Malarone should be avoided unless there's no suitable alternative. Pregnant women who use Malarone may benefit by also taking a daily folic acid supplement.
Doxycycline should not be taken by pregnant women.

10.3 Medicines for breastfeeding mothers:

Breastfeeding mothers can safely take Chloroquine and Proguanil, but not enough of these medicines passes into the breast milk in order to provide protection for the child.

Doxycycline and Malarone shouldn't be taken by breastfeeding mothers.

Medical advice should be urgently sought if fever or flu-like illness is developed within one year of visiting a malarious area especially if these symptoms appear within three months of returning - even if you have been taking preventive medicines.

10.4 Long-term malaria prophylaxis:

The ACMP guidance notes the following

Mefloquine	**No evidence of harm in long-term use if tolerated in the short-term**
Doxycycline	**No evidence of harm in long-term use. Evidence suggest that it may be used safely**
Atovaquone/Proguanil (Malarone)	**No evidence of harm in long-term use. Evidence suggests that it can be used confidently for travel up to one year and possibly, longer, but only with caution until more post-licensing experience is available.**
Chloroquine and Proguanil	**Both are considered safe for long-term use.**

Chapter 11: References

1. **Beg MA et al. (2002).** Cerebral involvement in benign tertian malaria. American Journal of Tropical Medicine and Hygiene, 67:230–232.

2. **Dorsey G et al. (2007).** Combination therapy for uncomplicated falciparum malaria in Ugandan child: a randomized control trial. Journal of American Medical Association, 297:2210–221

3. **Fanello CI et al. (2007).** A randomized trial to assess the safety and efficacy of Artemether - lumefantrine (Coartem) for the treatment of uncomplicated Plasmodium falciparum malaria in Rwanda. Transactions of the Royal Society of Tropical Medicine and Hygiene, , 101:344–350

4. **Faye B et al. (2007).** Efficacy and tolerability of four antimalarial combinations in the treatment of uncomplicated Plasmodium falciparum malaria in Senegal. Malaria Journal, 6:80.

5. **Hay SI et al. (2004).** The global distribution and population at risk of malaria: past, present, and future. Lancet, 4:327–336.

6. **Iqbal J, Khalid N, Hira PR. (2002).** Comparison of two commercial assays with expert microscopy for confirmation of symptomatically diagnosed malaria. Journal of Clinical Microbiology, 40:4675–678.

7. **Mendis K et al. (2001).** The neglected burden of Plasmodium vivax malaria. American Journal of Tropical Medicine and Hygiene, 64:97–106.

8. **Nzila A, Alzahranil (2013).** Drugs for the treatment of malaria in the Kingdom of Saudi Arabia. Saudi Med J; Vol. 34 (6): 569-578.

9. **Sinclair D. et al. (2009).** Artemisinin-based combination therapy for treating uncomplicated malaria. Cochrane Database of Systematic Reviews,:CD007483.

10. **Tjitra E. (2001).** Improving the diagnosis and treatment of malaria in Eastern Indonesia [dissertation]. In: *Menzies School of Health Research.* Darwin, Australia, Northern Territory University.

11. **WHO (2015).** Guidelines for malaria treatment, 3rd edition.

12. **WHO (2012).** Management of severe malaria: a practical handbook – 3rd edition.

13. **WHO (2010).** Basic Malaria Microscopy 2nd Edition.
http://apps.who.int/iris/bitstream/10665/44208/1/9789241547826_eng. pdf

Http://apps.who.int/iris/bitstream/10665/79317/1/9789241548526_eng.pdf