

MALARIA CASE MANAGEMENT

**DESK GUIDE FOR CLINICIANS AND
HEALTH CARE PROVIDERS**

**DIRECTORATE OF MALARIA CONTROL
MINISTRY OF HEALTH
ISLAMABAD**

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**Developed with the Technical Assistance of
The Technical Assistance Management Agency
(TAMA)
Islamabad**

**DIRECTORATE OF MALARIA CONTROL
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ISLAMABAD
October 2007**

Foreword

The Malaria Control Programme in Pakistan dates back to the 1960s when it was directed as the Malaria Eradication Programme. Within a decade it became evident that eradication was too ambitious a goal and the more realistically achievable goal of Malaria control was adopted. The programme was implementing the strategies for control until Pakistan joined the international partnership for Roll Back Malaria (RBM) established by the World Health Organization (WHO) in collaboration with the World Bank, United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP) in 1999 and adopted the RBM strategies for the control of malaria in the country.

Early and appropriate Treatment is a key RBM strategy. Up till 2003 the national programme continued with the treatment policy and protocols of the malaria control era. In the year 2003 the national programme with technical assistance from WHO drafted the first national treatment policy and protocol. A treatment desk guide and training and monitoring manuals based on the policy, were developed and are currently being used in the country.

The national treatment policy was revised in the year 2006 to conform to the WHO most recent guidelines on the radical treatment of falciparum and vivax malaria. The aim is not only to control malaria but to rationalise the use of Antimalarials. Under the new policy mono-therapy and treatment based on clinical diagnosis are being discouraged. Rapid Diagnostic Tests are being introduced in areas where microscopy facilities are not available and artesunate plus sulphadoxine pyrimethamine combination therapy is being promoted for the treatment of uncomplicated falciparum malaria, while chloroquine and primaquine therapy is still reserved for vivax malaria.

This desk guide has been prepared with the aim of providing clinicians and health care providers, both in public and private sector, with guidelines on the management of malaria cases according to the national case management policy. Sufficient details are given to enable the care provider to understand the rationale for the management being recommended and to motivate them to sincerely join the national effort to control malaria in the country.

**Director
Directorate of Malaria Control**

Acknowledgement

The author most gratefully acknowledges the Directorate of Malaria Control, Islamabad, for providing her the opportunity for preparing this guide and the Technical Assistance Management Agency (TAMA), Islamabad for funding the activity.

The activity couldn't have been completed without the help, support and valuable contribution of the following:

1. Dr. Faisal Mansoor, Director National Malaria Control Programme
2. Dr. Mukhtar, Senior scientific Officer, directorate of Malaria control (DOMC), Islamabad
3. Dr Qutbudin Kakar, WHO Technical Officer, DOMC, Islamabad
4. The Provincial Malaria Control coordinators and focal persons (list attached)
5. The participants of the consultative workshop held on September 18, 2007(list attached).

The information contained in this document has been taken from the following sources:

1. Final draft of National Malaria Control Strategy 2007
2. National malaria control programme draft PCI 2007
3. Malaria Case Management ; Desk Guide
4. National Treatment Guidelines for Malaria 2005
5. Malaria Case Management Training Manual
6. WHO Guidelines for the Treatment of Malaria 2006
7. Roll Back Malaria Strategy notes
8. Roll Back Malaria- World Malaria Report 2005
9. WHO EMRO website

Objectives and target audience of the Guidelines

Objectives

The objective of this desk guide is to create awareness among clinicians and care providers:

1. Of the high burden of malaria in the country;
2. The national treatment policy
3. Correct malaria case management
4. Their immense responsibility in the control of malaria in the country

Information is presented on

1. The current situation of malaria in Pakistan
2. Pakistan's national malaria treatment policy
3. Management of malaria:

3.1. Case definitions

- Uncomplicated malaria (UM)
- Malaria treatment failure (MTF)
- Complicate /Severe malaria (SM)

3.2. History and physical examination

3.3. Diagnosis-clinical, Rapid Diagnostic Tests(RDTs), microscopy

4. Antimalarials and their appropriate combinations, dosage and duration of treatment
5. Malaria in vulnerable groups:
 - Children
 - Pregnant women
6. Patient Counseling and education
7. Follow-up of patients
8. Malaria case-management during epidemics and national emergencies

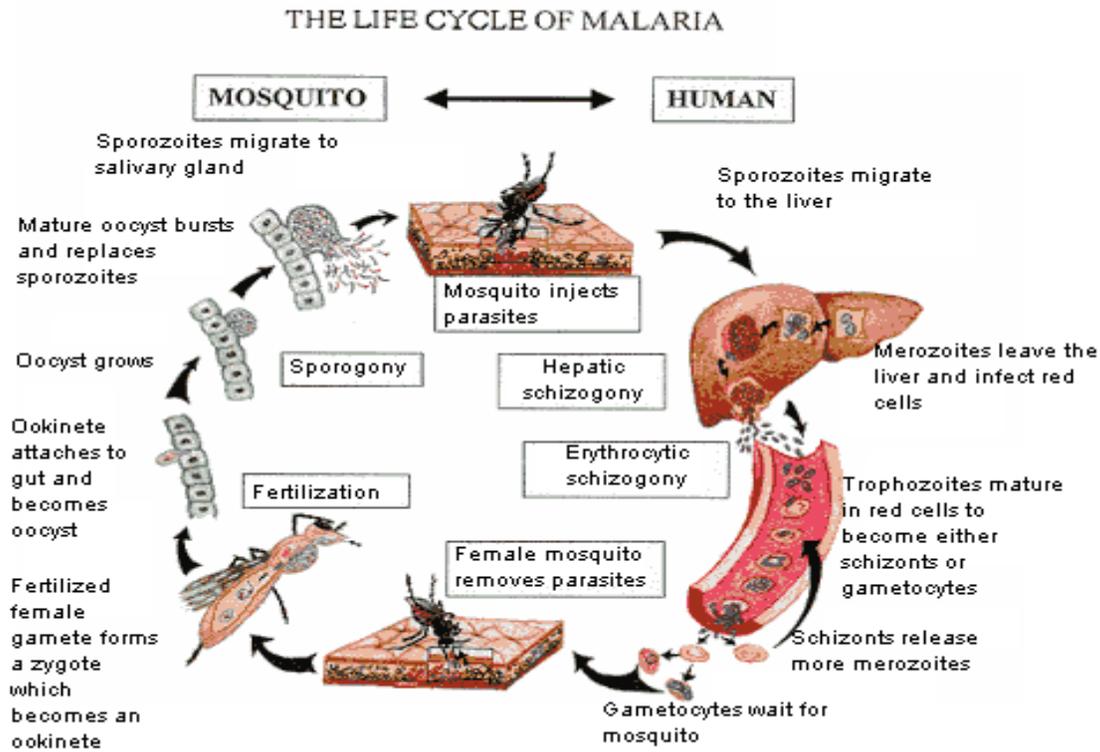
Dr. Tasleem Akhtar, FRCP (Paediatrics)
Consultant TAMA

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Section -1: What is Malaria

Malaria is caused by infection of red blood cells with protozoan parasites of the genus *Plasmodium*. The parasites are inoculated into the human host by a feeding female anopheline mosquito. The four *Plasmodium* species that infect humans are *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. In Pakistan *P. falciparum* and *P. vivax* are the prevalent infecting parasites. There are many species of the vector *Anopheles*. In Pakistan the two major vector species are *Anopheles culicifacies* and *Anopheles stephensi*. *Anopheles* typically breed in natural water bodies with clean, slow moving, warm water, with sufficient aquatic vegetation. However, ecological requirements of particular species may deviate from these typical conditions; *An. stephensi* can easily breed in closed artificial containers and *An. claviger* prefer relatively cold water.



The nature of the clinical disease depends very much on the pattern and intensity of malaria transmission in the area of residence, which determines the degree of protective immunity acquired and, in turn, the clinical disease profile. Where malaria transmission is "stable" – meaning where populations are continuously exposed to a high frequency of malarial inoculations partial immunity to the clinical disease and to its severe manifestations is acquired early in childhood. In such situations, which prevail in much of sub-Saharan Africa and parts of Oceania, the acute clinical disease is almost always

confined to young children who suffer high parasite densities and acute clinical disease. If untreated, this can progress very rapidly to severe malaria. In stable and high-transmission areas, adolescents and adults are partially immune and rarely suffer clinical disease, although they continue to harbor low blood-parasite densities. Immunity is reduced in pregnancy, and can be lost when individuals move out of the transmission zone.

In areas of unstable malaria, the situation prevailing in Pakistan and much of Asia, Latin America and the remaining parts of the world where malaria is endemic, the rates of inoculation fluctuate greatly over seasons and years. This retards the acquisition of immunity and results in people of all ages, adults and children alike, suffering acute clinical malaria, with a high risk of progression to severe malaria if untreated. Epidemics may occur in areas of unstable malaria when inoculation rates increase rapidly. Epidemics manifest as a very high incidence of malaria in all age groups and can overwhelm health services. Severe malaria is common if effective treatment is not made widely available.

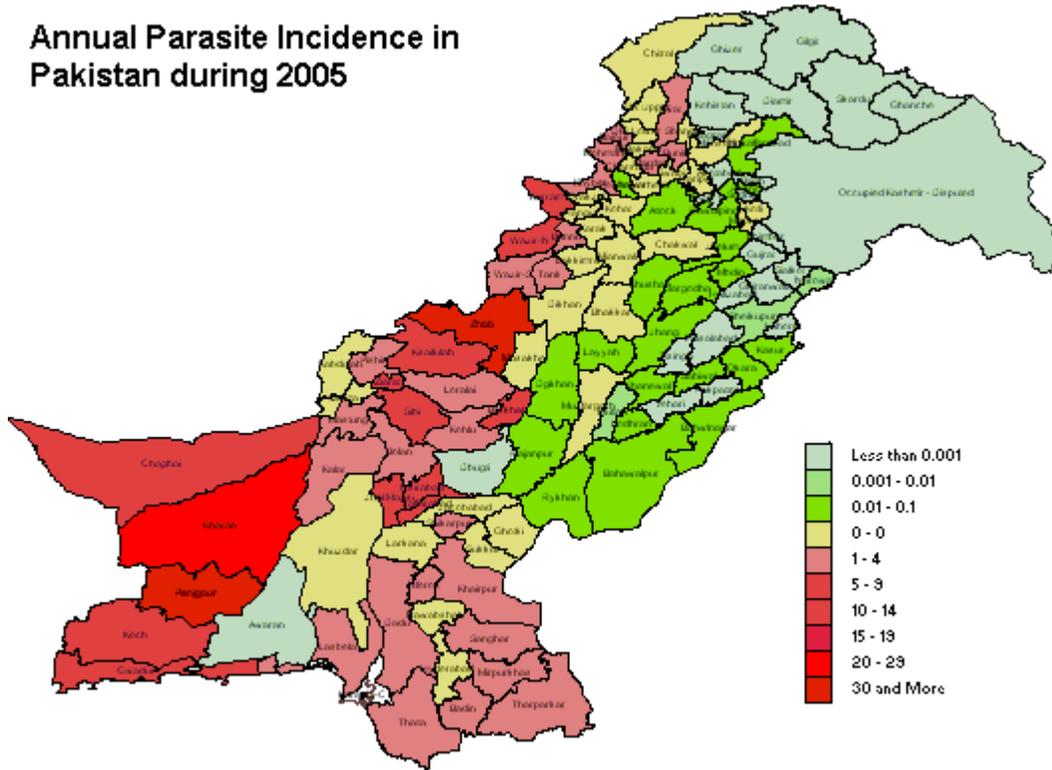
Section-2: Malaria in Pakistan – A Situation analysis

Pakistan is among 107 countries with endemic malaria. Currently Pakistan is listed among moderately endemic countries for malaria. The Pakistan Health Management Information System (HMIS)'s 2006 report shows malaria as the second most frequently reported disease from public health sector facilities. Although at the aggregate level the prevalence of malaria in Pakistan is moderate, there is variation in prevalence from province to province and area to area. In the Province of Baluchistan, the Federally Administered Tribal Area (FATA), 5 districts of Sindh and 14 district of the North West Frontier Province (NWFP), both the overall parasite prevalence and the relative proportion of falciparum malaria are high.

The slide positivity rate for Pakistan is 7% where as it is 16.5% for Balochistan, 17.5% for FATA, 8.9% for NWFP, 6.5% and for Punjab it is 1.5%(all decimals rounded of)

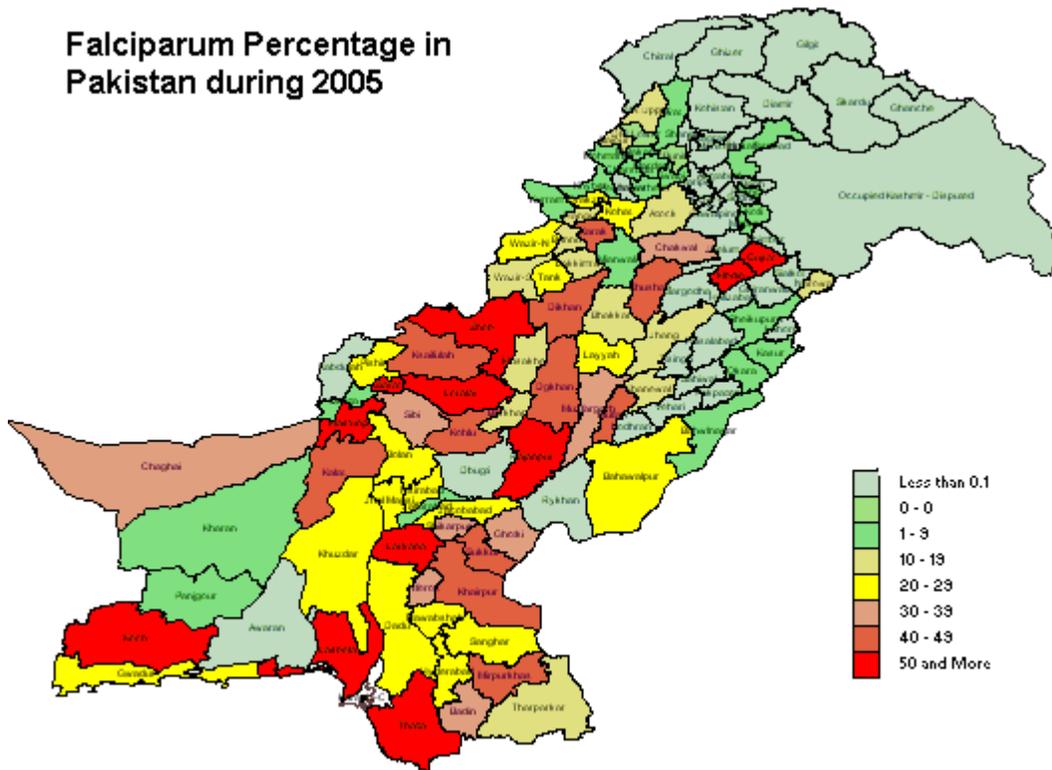
2.1. Distribution and prevalence

Annual Parasite Incidence in Pakistan during 2005



Source: Directorate of Malaria Control, Islamabad

Falciparum Percentage in Pakistan during 2005



Directorate of Malaria Control, Islamabad

The province of Balochistan which is home to about 5% of the population of the country, contributes over 30% of the reported cases while the Punjab province with over 52% of the country population reports less than 10%.

Reported malaria cases by selected subnational area

5 areas	2000	2001	2002	2003	%
Sind			22 458	37 612	30
Baluchistan			33 994	36 794	29
NWFP			20 774	26 791	21
Fata			14 681	13 996	11
Punjab			9 854	9 959	8

Source: World Malaria Report 2005

2.1. Control strategies

Pakistan’s successful Malaria Control Programme of the 1960s and early 1970s was stopped in its tracks by the emergence of resistance to DDT and later chloroquine. As elsewhere the goal was downgraded to control of malaria and treatment and vector control strategies were modified to deal with the challenge of the fast spreading resistance to Antimalarials and insecticides. The well performing system for malaria eradication however went into decline and in some provinces, its was merged with communicable diseases control sections of the general health directorates. The launching of the Roll Back Malaria (RBM) initiative by WHO in partnership with the World Bank, United Nations Children’s Fund (UNICEF), and the United Nations Development Programme (UNDP) in 1998 and the incorporation of the RBM goal in the Millennium Development Goals (MDGs) in 2000, revitalized the world wide effort for the control of malaria. Pakistan joined the RBM Partnership in 1999 and since then is endeavoring to strengthen the malaria control system in the country to achieve the RBM and MDGs goal of halving the number of malaria reported cases by the year 2015.

Pakistan is committed to achieving the RBM and MDGs goal of halving the number of reported cases of malaria by the year 2010. All stakeholders are urged to join the national effort to honour this national commitment

Pakistan’s National Strategy for the Control of Malaria,2007, has been developed within the RBM strategic framework and has the following strategic priorities

- Early Diagnosis and Appropriate Treatment,
- Multiple Prevention,
- Epidemic Preparedness and Behavioral Change Communication and

- Two conditional priorities upon which these strategic priorities depend:
 - Program Management
 - Operational Research

Early diagnosis and prompt appropriate treatment is a key strategy for the control of Malaria. Clinicians and care providers have therefore a key role and responsibility in the control of malaria in the country.

Health care providers in areas with endemic malaria have a special responsibility of reducing the incidence of severe malaria and the malaria specific mortality rate as low as possible

2.3. National Malaria Case Management Policy

The National Malaria Case Management Policy while guided by the WHO guidelines, fully takes into account local epidemiological, biological, and cultural considerations. Malaria in Pakistan is epidemiologically unstable. Peak transmission occurs in the post monsoons months of August to November and as mentioned previously the major vector species are Anopheles culicifacies and Anopheles stephensi and the prevalent causative parasites are Plasmodium vivax and Plasmodium falciparum. Over 40% cases of falciparum are resistant to chloroquine.

Pakistan revised and updated its national malaria treatment policy in 2006 to bring it into conformity with the latest World Health Organisation (WHO)'s recommendations. The WHO guidelines recommend antimalarials for which there is adequate evidence of efficacy and safety, and which are unlikely to be affected by resistance in the near future. The essential new ingredients of the latest policy are:

- Treatment based on clinical diagnosis alone should be reduced by making available Rapid Diagnostic Tests (RDTs) in health facilities where microscopy is not available;
- The use of monotherapy should be discouraged and discontinued and
 - Artemisinin-based combination therapies (ACTs) should be introduced for uncomplicated falciparum malaria.
 - Chloroquine and Primaquine therapy be used for vivax malaria

Monotherapy must be avoided in the treatment of malaria. All clinicians and care providers are urged to use combination therapy as recommended in these guidelines.

2.3.1. Policy Rationale:

The new policy not only aims to counter the widespread high antimalarial resistance in the country but also aims for radical cure of the disease to interrupt transmission in the population. The high prevalence of drug resistance is believed to be due to the indiscriminate and inappropriate use of antimalarials medication on the basis of clinical diagnosis of malaria. While WHO estimates an annual malaria burden of 1.6 million cases for Pakistan, in 2006, the Lady Health Workers alone prescribed over 4.4 million doses and the prescription of these drugs by the private sector amounted to a staggering 70 million doses. The colossal waste of resources is obvious. Implementation of the new policy is aimed to achieve the following major objectives:

- 1) Fast and effective relief for the patient;
- 2) Total elimination of parasite from the patient's body which will result in interruption of transmission of the parasite;
- 3) Containment of the spread of resistance and ;
- 4) Reduction of financial burden on the health care system.

All health care providers are urged to understand the rationale and objectives of the national malaria treatment policy and fully comply with its implementation

Section-3: Clinical Case Management

The responsibility of appropriate case management starts when the patient enters a clinic or health facility or when a health care provider is called to see a patient at home.

3.1. Case Definitions

For the purpose of management malaria cases are categorized as follows:

3.1.1. Uncomplicated malaria (UM)

The case definition for UM is as follows:

- High index of suspicion due to possible exposure to malaria transmission
- Fever or history of fever within last 72 hours (continuous, intermittent or irregular)
- Absence of signs of other diseases

3.1.2. Complicated /Severe malaria (SM)

The case definition for SM is as follows:

- Presence of asexual form of malarial parasite in blood slide examination (BSE) and not other cause of their symptoms in the presence of one or more of the following:

1. Prostration
2. Impaired consciousness
3. Respiratory distress (acidotic breathing)
4. Multiple convulsions
5. Circulatory collapse
6. Pulmonary oedema (radiological)
7. Abnormal bleeding
8. Jaundice
9. Haemoglobinuria
10. Severe anaemia
11. Hypoglycemia
12. Acidosis
13. Renal impairment
14. Hyperlactataemia
15. Hyperparasitaemia

3.1.3. Malaria treatment failure malaria (MTF)

Treatment failures may result from drug resistance, poor adherence or unusual pharmacokinetic properties in that individual. It is important to determine from the patient's history whether he or she vomited previous treatment or did not complete a full course.

The case definition for MTF is as follows:

- Recurrence of asexual parasitaemia detected by blood slide examination after taking a full antimalarial treatment received during the previous 4 weeks

3.2. Clinical Assessment

The general plan for malaria diagnosis and treatment given below, gives the step by step approach to the management of each of the above given types of malaria case.

3.2.1. Case History and Physical Examination

a. Introduction and recording of patients particulars

To develop rapport and a friendly environment greet and introduce yourself and then start recording the following patient's particulars:

Full Name, Name of father or husband in case of married women, Age (in children 5 years or less date of birth should be recorded), full Address, telephone number/ mobile telephone number (if available)

Travel history in the past 4 weeks

In case of married women ask about pregnancy status and month of gestation.

- b. **Record the complaints of the patient.** First let the patient describe his/her complaints unprompted. This helps in identifying the complaint which bothers the patient most.

There are no specific symptoms of malaria: most patients complain of headache, lassitude, fatigue, abdominal discomfort and muscle and joint aches, followed by fever, chills, perspiration, anorexia, vomiting and worsening malaise

Ask about the following:

- Details of treatment, if any, taken by the patient in the past 2 months.
- If you are in non-endemic part of the country, ask the patient about travel history to a malaria endemic area of the country in the past 4 weeks.

c. On Physical examination check:

- The patient's general condition, consciousness level and state of hydration
- The patient's temperature. Fever is present if axillary temperature is above 37.5° C or more than 101° F.
- Clinical anemia by noting the colour of skin, conjunctiva and nails. The colour of nails is especially helpful in the diagnosis of anemia, and the presence of palmar pallor is a good sign of anaemia in children under five.
- Examine the abdomen for enlargement of the spleen. An enlarged, tender spleen, with recent history of fever and anemia, is a clinical predictive indicator of malaria.

A complete physical examination is important in order not to miss conditions with similar presenting complaints and other causes of febrile conditions which may be present

A patient presenting with fever, parasitological confirmation of malaria and any of the following danger sign(s) should be managed as a case of severe malaria.

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

Treatment should not be delayed if parasitological confirmation of malaria

Section-4: Diagnosis

Pakistan's national case management policy discourages treatment on the basis of clinical diagnosis. Care providers are urged to use parasitological confirmation to guide the treatment of malaria following the diagnostic approach described below

Guidelines for selection of method of diagnosis

- Use light microscopy where it is available;
- If microscopy is not available use a falciparum detecting RDT;
- If the test result is negative but strong clinical evidence of malarial infection is present, make a clinical/presumptive diagnosis of vivax malaria and treat as such
- Base treatment on clinical diagnosis only if both microscopy and RDTs are not available

4.1. Clinical Diagnosis

Use the following WHO recommendations for making a clinical diagnosis.

- In general clinical diagnosis of uncomplicated malaria should be based on history of possible exposure to malaria and a history of fever in the previous 3 days with no other obvious causes of fever.
- Various unspecific signs and symptoms may be also present, such as nausea, vomiting, headache, body aches, sweating, rigors, history of intermittent fever. Presence of anemia in children warrants the suspicion of malaria.

4.2. Parasitological diagnosis

The introduction of Artemisinin based combination therapy (ACTs) has increased the urgency of improving the specificity of malaria diagnosis. The relatively high cost of these medicines makes unnecessary treatment of patients without parasitaemia unsustainable.

In addition to cost savings, parasitological diagnosis has the following advantages:

- Improved patient care in parasite-positive patients owing to greater certainty that the patient has malaria;
- Identification of parasite-negative patients in whom another diagnosis must be sought;
- Prevention of unnecessary exposure to Antimalarials, thereby reducing side-effects, drug interactions and selection pressure;
- Improved health information;
- Confirmation of treatment failures.

In Pakistan the following two methods of parasitological diagnosis are recommended by the national malaria control programme:

1. Light microscopy
2. rapid diagnostic Tests (RDTs)

4.2.1. Light microscopy

In Pakistan in the public sector, light microscopy facilities are available in hospitals and at Rural Health Centers (RHCs). In addition to providing a diagnosis with a high degree of sensitivity and specificity when performed well, microscopy allows quantification of malaria parasites and identification of the infecting species. It is inexpensive and is considered to be the “gold standard” against which the sensitivity and specificity of other methods must be assessed. A skilled microscopist is able to detect asexual parasites at densities of fewer than 10 per μl of blood but under typical field conditions the limit of sensitivity is approximately 100 parasites per μl .

Light microscopy has important advantages:

- Low direct costs if the infrastructure to maintain the service is available,
- High sensitivity if the quality of microscopy is high,
- Differentiation between plasmodia species,
- Determination of parasite densities,
- Can be used to diagnose many other conditions.

4.2.2. Rapid diagnostic tests

Rapid diagnostic tests (RDTs) are immuno-chromatographic tests that detect parasite-specific antigens in a finger-prick blood sample. Current tests are based on the detection of histidine-rich protein 2 (HRP2), which is specific for *P. falciparum*, pan-specific or species-specific parasite lactate dehydrogenase (pLDH), or other pan-specific antigens such as aldolase. HRP2 based tests therefore detect only *Plasmodium falciparum* species, pLDH and aldolase based tests detect one or more of the other three species of human malaria parasites (*P. vivax*, *P. malariae* and *P. ovale*) (10–12). RDTs are

available commercially in different formats, as dipsticks, cassettes or cards. Cassettes and cards are easier to use in difficult conditions outside health facilities.

RDTs are simple to perform and interpret, and do not require electricity or special equipment. WHO recommends that such tests should have a sensitivity of > 95% in detecting plasmodia at densities of more than 100 parasites per μl of blood. Programme and project managers should make their own choice among the many products available, using the criteria recommended by WHO (www.wpro.who.int/rdt) as there is as yet no international mechanism for pre-qualification of RDTs.

RDTs have many potential advantages, including:

- The ability to provide rapid results,
- Fewer requirements for training and skilled personnel (a general health worker can be trained in one day),
- Reinforcement of patient confidence in the diagnosis and in the health service in general.

There are also potential disadvantages, including:

- The inability in the case of some RDTs, to distinguish new infections from a recently and effectively treated infection; this is due to the persistence of certain target antigens (e.g. HRP2) in the blood for 1–3 weeks after effective treatment.
- Unpredictable sensitivity in the field (13–20), mainly because test performance is greatly affected by adverse environmental conditions such as high temperature and humidity.
- As for microscopical examination, there is a risk of misinterpreting a positive result as indicating malaria in semi-immune patients with concomitant illness.

Under the national malaria case management policy falciparum detecting RDTs are being provided to facilities where microscopy is not available.

Section-5: Treatment

5.1. Treatment of Uncomplicated Malaria in adults (excluding pregnant women):

5.1.1. The objective of treating uncomplicated malaria is to cure the infection. This is important as it will help prevent progression to severe disease and prevent additional morbidity associated with treatment failure. Cure of the infection means eradication from the body of the infection that caused the illness.

The public health goal of treatment is to reduce transmission of the infection to others, i.e. to reduce the infectious reservoir.

A secondary but equally important objective of treatment is to prevent the emergence and spread of resistance to antimalarials.

Antimalarial combination therapy is the simultaneous use of two or more blood schizontocidal drugs with independent modes of action and thus unrelated biochemical targets in the parasite. Two or more simultaneously administered schizontocidal drugs with independent modes of action improve therapeutic efficacy and also to delay the development of resistance to the individual components of the combination.

ACT should only be given in confirmed falciparum cases

The table below gives the dosage and duration of treatment of uncomplicated malaria in adults excluding pregnant women at all levels of the health care system in Pakistan.

5.1.2. **Drugs, dosages and duration of treatment:** Table-1 gives the recommended drug combinations, dosages and duration of treatment for radical treatment of malaria

Table-1: Radical Treatment of Malaria

Vivax Malaria <ul style="list-style-type: none"> • Slide positive or • Clinically diagnosed 	Radical Treatment				
	Chloroquine (150 mg base tablets)		+	Primaquine (15mg base tablets)	
	Day 1	Day 2	Day 3	One tablet a day for 14 days	
4	4	2			
Falciparum Malaria	Radical Treatment				
	Sulfadoxine pyrimethamine * (500mg +25mg tablets)		+	Artesunate (50 mg tablets)	
	Day 1	Day 2	Day 3		
	SP- 3 + Artesunate 4	Artesunate 4	Artesunate 4		

*

The Artemisinin derivatives and partner medicines of ACTs should not be given as monotherapies and should not be available as monotherapies.

Antimalarials should be taken with water
Ideally the first dose should be given in front of the care provider (DOT)

5.2. Treatment of Severe Malaria

5.2.1. Treatment objectives

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

The mortality of untreated severe malaria is thought to approach 100%. With improvement of the management of severe malaria the case fatality rate of severe malaria can be reduced below 10% overall.

The risk of death from severe malaria is greatest in the first 24 h. It is therefore very important that health care providers at the first level of contact of the patient initiate appropriate antimalarial treatment.

Pakistan's national treatment policy recommends the following management at different levels of the health care system:

5.2.2. Management at peripheral level facilities and private clinics

- In unconscious patients secure the airway
- Take a slide
- Give first dose of Inj. Artemether im (3.2 mg/kg) as a single loading dose or Artesunate suppositories (10 mg/kg)
- Refer to hospital along with slide and evidence of injection

5.2.3. Treatment in Hospitals

- a. **Emergency care:** Severe malaria is a medical emergency. The following must be done immediately the patient arrives in hospital:
- The airway should be secured in unconscious patients
 - Breathing and circulation should be assessed.
 - The patient should be weighed or body weight estimated so that drugs, including antimalarials and fluids can be given on a body weight basis.
 - An intravenous cannula should be inserted and immediate measurements of blood glucose (stick test), haematocrit/haemoglobin, parasitaemia and, in adults, renal function should be taken.
 - A detailed clinical examination should then be conducted, with particular note of the level of consciousness and record of the coma score. The Glasgow coma scale is suitable for adults, and the simple Blantyre modification or children's Glasgow coma scale are easily performed in children.
 - Unconscious patients should have a lumbar puncture for cerebrospinal fluid analysis to exclude bacterial meningitis.
 - The degree of acidosis is an important determinant of outcome; the plasma bicarbonate or venous lactate level should therefore be measured if possible.
 - If facilities are available, arterial or capillary blood pH and gases should be measured in patients who are unconscious, hyperventilating or in shock.
 - Blood should be taken for cross-match, and (if possible) full blood count, platelet count, clotting studies, blood culture and full biochemistry should be conducted.
 - The assessment of fluid balance is critical in severe malaria. Respiratory distress, in particular with acidotic breathing in severely anaemic children, often indicates hypovolaemia and requires prompt rehydration and, where indicated, blood transfusion).

b. Specific antimalarial treatment:

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 cinchona alkaloids (quinine and quinidine) and
- the artemisinin derivatives (artesunate, artemether and artemotil).

Quinidine commonly causes hypotension and concentration-dependent prolongation of ventricular repolarization (QT prolongation). Quinidine is thus considered more toxic than quinine and should only be used if none of the other effective parenteral drugs are available. Electrocardiographic monitoring and frequent assessment of vital signs are required if quinidine is used.

Chloroquine (parenteral) is no longer recommended for the treatment of severe malaria because of widespread resistance. Intramuscular sulfadoxine–pyrimethamine is also not recommended

Recommended treatment is Artesunate which is soluble in water and can be given either by intravenous or intramuscular injection, 2.4 mg//kg bw given on admission (time = 0), then at 12 h and 24 h, than once daily

Artesunate is dispensed as a powder of artesunic acid. This is dissolved in sodium bicarbonate (5%) to form sodium artesunate. The solution is then diluted in approximately 5 ml of 5% dextrose and given by intravenous injection or by intramuscular injection to the anterior thigh. The solution should be prepared freshly for each administration and should not be stored.

Quinine must never be given by bolus intravenous injection, as lethal hypotension may result. It is always given as an constant infusion

Quinine dihydrochloride should be given by rate-controlled infusion in saline or dextrose solutions at a rate not exceeding 5 mg salt/kg bw per hour. If this is not possible then it should be given by intramuscular injection to the anterior thigh, not the buttock (to avoid sciatic nerve injury). The first dose of 20 mg salt/kg bw should be split, 10 mg salt/kg bw to each thigh. Undiluted quinine dihydrochloride at a concentration of 300 mg/ml is acidic (pH 2) and painful when given by intramuscular injection, so it is best either formulated or diluted to concentrations of 60–100 mg/ml for intramuscular injection. Gluconate salts are less acidic and better tolerated than the dihydrochloride salt when given by the intramuscular route.

The dosage of artemisinin and artemisinin derivatives does not need adjustment in vital organ dysfunction. Quinine (and quinidine) levels may accumulate in severe vital organ dysfunction.

The maintenance dose of 10 mg salt/kg bw should be repeated every 8 hours. If there is no clinical improvement or the patient remains in acute renal failure the dose should be reduced by one-third after 48 h. Dosage adjustments are not necessary if patients are receiving either haemodialysis or haemofiltration. Dosage adjustment by one-third is necessary in patients with hepatic dysfunction.

Following initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with an effective oral antimalarial. Current practice is to continue the same medicine orally as given parenterally, i.e. quinine to complete a full 7 days of treatment. In non-pregnant adults, doxycycline is added to quinine and should also be given for 7 days (clindamycin, where available, should be given instead of doxycycline to pregnant women and children, as doxycycline cannot be given to these groups).

Adjunct therapy with corticosteroids is not recommended. No significant difference in mortality between dexamethasone and placebo has been found on systematic review, but gastrointestinal bleeding and seizures were more common with dexamethasone

Malaria treatment failures may result from drug resistance, poor adherence or unusual pharmacokinetic properties in that individual. It is important to determine from the patient's history whether he or she vomited the medicine or did not complete a full course of treatment.

Recurrence of falciparum malaria after treatment can be the result of a re-infection, or a recrudescence (i.e. treatment failure). In an individual patient it may not be possible to distinguish recrudescence from re-infection, although if fever and parasitaemia fail to resolve or recur within 4 weeks of treatment then this is considered a failure of treatment

Wherever possible treatment failure must be confirmed parasitologically by blood slide examination.

HRP2-based tests may remain positive for weeks after the initial infection even without recrudescence and are not helpful in detecting treatment failure

Treatment failure is present if a patient with confirmed malaria has taken the antimalarial treatment in correct dosage according to the national treatment guidelines but fails to clear asexual parasitaemia within 4 weeks of the start of treatment.

Treatment failure within 14 days of receiving an ACT is very rare. The few ACT treatment failures generally occur after 2 weeks of initial treatment, during the 3rd and 4th week after treatment. In many cases failures are missed because patients presenting with malaria are not asked whether they have received full antimalarial treatment within the preceding 1–2 months.

5.3.2. Guidelines for management of malaria treatment failures

- Malaria treatment failures confirmed parasitologically should be treated with a second-line antimalarial.
- Parasitological confirmation is desirable but not an absolute precondition.

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

- alternative ACT known to be effective
- quinine + tetracycline or doxycycline or clindamycin.

The alternative ACT (Artemether + Lumifentrine) has the advantages of simplicity, and where available, co-formulation to improve adherence. The 7-day quinine regimes are not well tolerated and adherence is likely to be poor due to the complexity of the drug regimen (three daily doses for 7 days).

Table:-2: Quinine dosage and duration of treatment

Age	Weight	Drug & Number of tablets Quinine* (300mg tablets)
< 1 yr	5 – 10 kg	¼
1 – 4 yrs	11 – 14 kg	½
5 – 7 yrs	15 – 24 kg	1
8 – 10 yrs	25 – 34 kg	1 ¼
11 – 14 yrs	35 – 50 kg	1 ½
Above 14 yrs	> 50 kg	2

* quinine dosage = 10mg/kg 8 hourly for 7 days

5.4. Incorrect approaches to treatment

In endemic regions, some semi-immune malaria patients could be cured using partial treatment with effective medicines (i.e. use of regimens that would be unsatisfactory in patients with no immunity). This had led in the past to different recommendations for

patients considered to be semi-immune and those considered to be non-immune. **This is no longer recommended.**

Another potentially dangerous practice is to give only the first dose of the treatment course for patients with suspected but unconfirmed malaria, with the intention of giving full treatment once the diagnosis is eventually confirmed. **This is no longer recommended.**

If malaria is suspected and the decision to treat is made, then a full effective treatment is required whether or not the diagnosis is confirmed by a test. Partial treatments should not be given even when patients are considered to be semi-immune or the diagnosis is uncertain. A full course of effective treatment should always be given once the decision has been taken to give antimalarial treatment

Section-6 Treatment in specific populations and situations

6.1. Pregnant women

Pregnant women with symptomatic acute malaria are a high-risk group, and must receive effective antimalarials. Maternal mortality is approximately 50% higher than in non-pregnant women. Fetal death and premature labour are common. Malaria in pregnancy is associated with an increased risk of severe malaria often complicated by pulmonary oedema and hypoglycaemia.

There is insufficient information on the safety and efficacy of most antimalarials in pregnancy, particularly for exposure in the first trimester, and so treatment recommendations are different to those for non-pregnant women. Organogenesis occurs mainly in the first trimester and this is therefore the time of greatest concern for potential teratogenicity, although nervous system development continues throughout pregnancy.

The antimalarials considered safe in the first trimester of pregnancy are quinine, chloroquine, proguanil and sulfadoxine–pyrimethamine. Of these, quinine remains the most effective and can be used in all trimesters of pregnancy

Women often do not declare their pregnancies in the first trimester and so, early pregnancies may often be exposed inadvertently to the available first-line antimalarials. Inadvertent exposure to antimalarials is not an indication for termination of the pregnancy

Current assessment of benefits compared with potential risks suggests that artemisinin derivatives should be used to treat uncomplicated falciparum malaria in the second and third trimesters of pregnancy, but should not be used in the first trimester until more safety information becomes available.

Primaquine and tetracyclines should not be used in pregnancy.

Despite these many uncertainties, effective treatment must not be delayed in pregnant women. Given the disadvantages of quinine, i.e. the long course of treatment, and the increased risk of hypoglycaemia in the second and third trimesters, ACTs are considered suitable alternatives for these trimesters. In practice, if first-line treatment with an artemisinin combination is all that is immediately available to treat in the first trimester of pregnancy pregnant women who have symptomatic malaria, then this should be given.

Pharmacovigilance programmes to document the outcome of pregnancies where there has been exposure to ACTs, and if possible documentation of the development of the infant, are encouraged so that future recommendations can stand on a firmer footing.

6.2. Treatment of malaria in Children

The acutely ill child requires careful clinical monitoring as they may deteriorate rapidly. Referral to a health centre or hospital is indicated for young children who cannot take oral treatment. .

6.2.1. Uncomplicated malaria

The same combination therapies as given above for adults are used to treat malaria in children. Tables below give the age specific dosages for children

Table-3: Chloroquine dosage and duration of treatment for children with P. vivax Malaria

Age	Day 1	Day 2	Day 3
	Chloroquine (150 mg base tablets)	Chloroquine (150 mg base tablets)	Chloroquine (150 mg base tablets)
1 – 11 months	¼	1/4	¼
12 – 35 months	1	1	1
3 – 4 years	1 ¼	1 1/4	1 1/4
5 – 6 years	2	2	2
7 – 14 years	3	3	3

Table-4: Primaquine dosage and duration of treatment for children with P. vivax malaria

Weight in Kg (Age)	Dose No. of tablets to be taken together
5 – 14 Kg (0 – 4 yrs)	Do not give primaquine
15 – 24 Kg (5 – 7 yrs)	¼ once day for 14 days
25 – 35 Kg (8 – 10 yrs)	2/4 once a day for 14 days
36 – 50 Kg (11 – 13 yrs)	¾ once a day for 14 days

Table-5: Artesunate+ Sulfadoxine pyrimethamine dosage and duration of treatment in children with P. falciparum malaria

Age	Day 1		Day 2	Day 3
	Sulfadoxine pyrimethamine (500 + 25 mg tablets)	Artesunate (50 mg tablet)	Artesunate (50 mg tablet)	Artesunate (50 mg tablet)
< 1 year	1/2	1/2	1/2	1/2
1 –6 yrs	1	1	1	1
7 – 13 yrs	2	2	2	2
14 + yrs	3	4	4	4

Children should be given tablets crushed & mixed with sugar solution rather than anti malarial syrups

6.2.2. Severe Malaria

Immediate referral to hospital after

- Clearing airways in unconscious patients
- Giving one of the following pre-referral treatment options
 - a. Artesunate or Artemisinin 10 mg/kg bw by rectal administration
 - b. Inj. Artemether 3.2 mg/kg bw
 - c. Quinine i.m. 10 mg salt /kg bw
- Administering anticonvulsant in patients with convulsions

6.2.2. Supportive Treatment

- **Fever:** In young children, high fevers are associated with vomiting, including of medication, and seizures.

Treatment is with antipyretics Paracetamol (acetaminophen) 15 mg/kg bw every 4 hrs. alternatively Ibuprofen (5 mg/kg bw) may also be used.

Acetylsalicylic acid (aspirin) should not be used in children because of the risks of Reye's syndrome.

If necessary, tepid sponging may be done. Care should be taken to ensure that the water is not too cool as, paradoxically, this may raise the core temperature by inducing cutaneous vasoconstriction.

There has been some concern that antipyretics might attenuate the host defence against malaria, as their use is associated with delayed parasite clearance. However, this appears to result from delaying cytoadherence, which is likely to be beneficial. **There is no reason to withhold antipyretics in malaria.**

- **Vomiting** is common in acute malaria and may be severe. Antiemetics are widely used. There have been no studies of their efficacy in malaria, and no comparisons between different antiemetic compounds, although there is no evidence that they are harmful.
- **Generalized seizures** are more common in children with falciparum malaria than in those with the other malarias. This suggests an overlap between the cerebral pathology resulting from malaria and febrile convulsions. Sometimes these seizures are the prodrome of cerebral malaria. If the seizure is ongoing, the airway should be maintained and anticonvulsants given (parenteral or rectal benzodiazepines or intramuscular paraldehyde).

Section- 7: Patient Counseling and Education

This is a very important part of case management.

7.1. Advice/Counseling re treatment prescribed:

Tell the patient/ caregiver

- The diagnosis which has been made.
- Inform them that malaria is curable provided full treatment as advised is taken.
- Show them each type of tablets prescribed and make sure that they have understood the dosage and duration of treatment. This can be done by asking the patient to repeat the instruction.
- Advise them to drink plenty of water and other liquids. This is very important for children.

- Advise them to take their normal food. No food is contra-indicated in malaria or its treatment.
- Explain to them the danger of self medication and incomplete treatment.
- Tell them to report back (or report to a nearest health facility/provider) if symptoms persist, worsen or new symptoms appear.
- Make sure that they understand when they have to return to the clinic for another visit.

7.2. Counseling for prevention of malaria

Explain to the patient/caregivers the various measures which can prevent future episodes of malaria. Tell them to:

- To use bed nets. Inform them about the availability and cost of bed nets in their area.
- Inform them about vector-control measures being undertaken in their area. Motivate them to cooperate with and assist in the vector control activities of their areas.
- Use of screens on the doors and windows, to reduce the risk of mosquito bites.

Section- 8: Follow up

Follow up of patient is very important under the current strategy for the control of malaria.

The objectives of follow up are:

- 8.1. To monitor clinical improvement;
- 8.2. To ensure parasitological clearance;
- 8.3. To monitor compliance with treatment
- 8.4. To monitor recrudescence due to malaria drug resistance;
- 8.5. To monitor suspected adverse drug effects

Since the aim of treatment is radical cure, it is very important to follow up patients which are still sick to ensure that radical cure has been achieved.

Patients should be advised to return if the illness persists, deteriorates or recurs and if new symptoms appears, and must be motivated to return for another examination.

Patient's/care givers should be informed with precision on where and when to return providing also indication for emergency care in case of need.

Section-9: Malaria case management in epidemics and complex emergencies

7.1. Diagnosis

In epidemic and complex emergency situations, facilities for parasitological diagnosis may be unavailable or inadequate to cope with the case-load. In such circumstances, it is impractical to demonstrate parasitemia before malaria treatment of febrile patients.

However, there is a role for parasitological diagnosis even in these situations: RDTs should be deployed if microscopy is not available..

In all suspected cases of severe malaria, if a delay is expected in obtaining parasitological confirmation of diagnosis, patients should be treated immediately for severe malaria on clinical grounds.

7.2. Treatment

Management of severe falciparum malaria in epidemic situations will often take place in temporary clinics or in situations in which staff shortages and high workloads make intensive care monitoring difficult. Drug treatment should therefore be as simple and safe as possible, with simple dosing schedules and a minimum need for monitoring.

Artesunate has been shown to reduce mortality of severe malaria, but with the current artesunate formulation, drawing the drug into a syringe takes two dissolution-dilution steps. In some circumstances this may not be possible.

Parenteral quinine requires either intravenous infusions or a three times a day intramuscular regimen, plus monitoring of blood glucose.

Intramuscular artemether is the treatment of choice for severe malaria in situations of epidemics and complex emergencies, also for pregnant women

Section 10: Malaria Chemoprophylaxis

Malaria chemoprophylaxis is not recommended for residents in the malaria endemic areas of Pakistan. It should also not be prescribed as a remedy after treatment to prevent re-infections in an endemic area. This section on chemoprophylaxis will enable clinicians and care providers to give correct advice on chemoprophylaxis to compatriots and visitors from abroad.

Malaria chemoprophylaxis is not advised for residents of malaria endemic countries like Pakistan. It should also not be prescribed as a remedy to prevent re-infections in an endemic area.

For travelers the risk of contracting malaria depends on the region visited, the length of stay, time of visit, type of activity, protection against mosquito bites, compliance with chemoprophylaxis etc. Malaria can be severe in the non-immune therefore all visitors from non-malarious areas to a malarious area should be protected by both prevention of mosquito bites and antimalarial chemoprophylaxis. Pregnant women, infants and young children and people who have undergone splenectomy should avoid travel to a malarious area as these people are at higher risk of severe malaria. If travel is unavoidable, these people should observe all preventive measures, and should know where to seek early diagnosis and treatment in case of suspected clinical attack of malaria.

Anti malarial medicines offer protection against clinical attacks of malaria. Correctly taken, appropriate chemoprophylaxis provides 75%–95% protection against acquiring malaria. There is considerable experience on good safety data on most chemoprophylactic regimens recommended for Pakistan.

Malaria can be severe in the non-immune therefore all visitors from non-malarious areas to a malarious area should be protected.

Anti malarial drugs offer protection against clinical attacks of malaria. Correctly taken, appropriate chemoprophylaxis provides 75%–95% protection against acquiring malaria.

The following types of chemoprophylaxis is advised:

12.1. Primary Prophylaxis: Use of antimalarial drugs at recommended dosage, started 1-21 days before departure to a malarious area and continued for the duration of stay and for 1-4 weeks after return. The time required to take chemoprophylaxis either before or after entering the malaria endemic area varies among the different antimalarial medicines. This is of two types:

- **Causal prophylaxis:** This prevents the establishment of infection in the liver by inhibiting the pre-erythrocytic schizogony. Primaquine and proguanil are effective as causal prophylactic drugs. Potential adverse effects on long term use and non-availability of primaquine make it a difficult drug for this purpose. Daily doses of proguanil are therefore recommended for causal prophylaxis, in association with chloroquine in areas where resistance to this drug is not present.
- **Suppressive prophylaxis:** Use of blood schizonticides suppresses the blood forms of the malaria parasite and thus protects against clinical illness. However, *P. vivax* and *P. ovale* may cause relapses from the hypnozoites in liver cells and these cannot be prevented with the use of chemoprophylaxis with blood schizonticides. If *P. vivax* and *P. ovale* relapse occurs after taking malaria chemoprophylaxis, then the patient should receive a full radical treatment with chloroquine, followed by primaquine for two weeks

For long term travelers there are the following alternate options:

- **Chemoprophylaxis only during periods of high malaria transmission:** An option is to take chemoprophylaxis only during periods of high malaria transmission, with the use of stand-by emergency treatment if malaria is contracted. Adopting this option requires careful mosquito avoidance, knowledge of local malaria epidemiology, and prompt access to medical care in the event of a febrile illness. It should be remembered that interruption of chemoprophylaxis at the end of the malaria season is associated with an increased risk of malaria, once the suppressive effect on malaria infection is discontinued.
- **Stand-by emergency treatment (SBET)** is the self-administration of malaria treatment carried by the traveler, and is recommended by the World Health Organization in remote situations where medical attention is not available within 24 hours of the onset of symptoms. It can be recommended either for people taking malaria chemoprophylaxis or for those who visit areas with very low malaria risk and decide not to take chemoprophylaxis. However, the use of SBET requires a knowledgeable and responsible user, always take measure to protect from mosquito bites, always carry of course of antimalarial medicines for SBET, seek immediate medical care in case of fever and take SBET if prompt medical help is not immediately available. Travellers using SBET are exposed to the following risks: i) they might incorrectly treat as malaria potentially serious non-malarious febrile illnesses, ii) fail to seek appropriate medical care promptly, and iii) make mistakes with dosing during self-administration.
SBET is currently recommended as a sole strategy for dealing with malaria risk for travellers from Switzerland and Germany visiting areas of low malaria transmission. This approach is not recommended by UK, US or Canadian authorities.

12.3. Chemoprophylaxis Regimen: Chemoprophylaxis should preferably, be started some time before traveling to a malarious area. The interval varies between 1 day (atovaquone-proguanil, chloroquine-proguanil or doxycycline) up to three weeks

(mefloquine). In addition to assuring adequate blood levels of the drug, this regimen allows for evaluation of any potential side effects (especially with mefloquine). Chemoprophylaxis should continue during all the period of stay in the malarious area and for further period of 1-4 weeks after departure from the area. The chemoprophylaxis should be continued for one week with atovaquone-proguanil, but for 4 weeks with all other chemoprophylaxis regimens.

The following factors should be considered while choosing an appropriate chemoprophylactic regimen:

1. The travel itinerary should be reviewed in detail and compared with the information on areas of risk within a given country to determine whether the traveler will actually be at risk of acquiring malaria.
2. The risk of acquiring chloroquine resistant *P. falciparum* malaria (CRPF) is high in all endemic areas of Pakistan..
3. Any previous allergic or other reaction to the antimalarial drug of choice and the accessibility of medical care during travel must also be determined.

Chemoprophylactic drugs recommended for travelers to Pakistan

Pakistan	Atovaquone/proguanil or doxycycline or mefloquine
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Source; www.malariasite.com/malaria/Prophylaxis.htm

The dosage regimens of medicines used for malaria chemoprophylaxis are given in the table below.

Table- 5: Drugs used for chemoprophylaxis with dosage

Drugs and dosage for chemoprophylaxis				
Drugs	Dosage		Pros and Cons	Adverse Effects
	Adults	Children		
Atovaquone (250 mg) plus Proguanil (100 mg) (Malarone®)	1 tab. once daily	11-20kg: ¼ adult tablet daily 21-30kg: ½ adult tablet daily 31-40kg: ¾ adult tablet daily >40kg: 1 adult tablet daily	Daily dosing; start 1 day before departure and continue for 7 days after exposure; not in pregnancy and lactation	Nausea, vomiting, abdominal pain, diarrhea, increased liver enzyme levels; rarely seizures, rash, mouth ulcers
Doxycycline (100mg)	100mg once daily	1.5mg base/kg once daily (max. 100 mg) <25kg or <8 yr: not recommended 25-35kg or 8-10 yr: 50mg 36-50kg or 11-13	Daily dosing required; start 1 day before departure and continue for 4 weeks after exposure; not in pregnancy	Abdominal discomfort, vaginal candidiasis, photosensitivity, worsening of renal function tests in renal diseases, allergic reactions, blood dyscrasias, esophageal ulceration

		yr: 75mg >50kg or >14 yr: 100mg	and lactation	
Mefloquine (Tablet with 250mg base, 274mg salt)	250 mg base once weekly	5mg of salt/kg once weekly <5kg or <3 mo: not recommended 5-14 kgs: ¼ tab/wk; 15-24 kg: ½ tab/wk; 25-35 kg: ¾ tab/wk; >35 kg: 1 tab/wk	Weekly dosing; start 3 weeks before departure and continue for 4 weeks after exposure; not in first trimester of pregnancy, patients with neuropsychiatric disorders, prior treatment with halofantrine or mefloquine	Dizziness, headache, sleep disorders, nightmares, nausea, vomiting, diarrhea, seizures, abnormal coordination, confusion, hallucinations, forgetfulness, emotional problems including anxiety, aggression, agitation, depression, mood changes, panic attacks, psychotic or paranoid reactions, restlessness, occasional reports of severe intolerance, suicidal ideation and suicide

Source; www.malariasite.com/malaria/Prophylaxis.htm

Section-11: PHARMACOLOGY OF ANTIMALARIAL DRUGS

Only antimalarials recommended under the national treatment policy are included in this section.

Halofantrine has been banned in Pakistan. Health care providers are advised to avoid using halofantrine in any formulation

11.1. Chloroquine

Chloroquine is a 4-aminoquinoline currently being used extensively as a first line treatment for malaria in Pakistan. Over 40% *P. falciparum* resistance to chloroquine is being reported from *P. falciparum* prevalent areas of Pakistan like Baluchistan and Sindh.

Chloroquine interferes with parasite haem detoxification. Resistance is related to genetic changes in transporters (PfCRT, PfMDR), which reduce the concentrations of chloroquine at its site of action, the parasite food vacuole.

As with other 4-aminoquinolines, chloroquine does not produce radical cure of *P. vivax* malaria.

11.1.1. Formulations

Tablets containing 100 mg or 150 mg of chloroquine base as hydrochloride, phosphate or sulfate.

11.1.2. Toxicity

Chloroquine has a low safety margin and is very dangerous in overdosage. At normally recommended doses the drug is generally well tolerated. The principle limiting adverse effects in practice are the unpleasant taste, which may upset children, and pruritus, which may be severe in dark-skinned patients. Other less common side effects include headache, various skin eruptions and gastrointestinal disturbances, such as nausea, vomiting and diarrhoea. More rarely central nervous system toxicity including, convulsions and mental changes may occur.

Acute overdosage is extremely dangerous and death can occur within a few hours. The patient may progress from feeling dizzy and drowsy with headache and gastrointestinal upset, to developing sudden visual disturbance, convulsions, hypokalaemia, hypotension and cardiac arrhythmias. There is no specific treatment, although diazepam and epinephrine (adrenaline) administered together are beneficial.

Acute over dosage with Chloroquine is extremely dangerous and death can occur within a few hours. Chloroquine Injections are not recommended for use in treatment of any form of malaria

11.1.3. Drug interactions

Major interactions are very unusual. There is a theoretical increased risk of arrhythmias when chloroquine is given with halofantrine or other drugs that prolong the electrocardiograph QT interval; a possible increased risk of convulsions with mefloquine; reduced absorption with antacids; reduced metabolism and clearance with cimetidine; an increased risk of acute dystonic reactions with metronidazole; reduced bioavailability of ampicillin and praziquantel; reduced therapeutic effect of thyroxine; a possible antagonistic effect on the antiepileptic effects of carbamazepine and sodium valproate; and increased plasma concentrations of cyclosporine

11.2. Sulfadoxine

Sulfadoxine is a slowly eliminated sulfonamide. It is very slightly soluble in water. Sulfonamides are structural analogues and competitive antagonists of *p*-aminobenzoic acid. They are competitive inhibitors of dihydropteroate synthase, the bacterial enzyme responsible for the incorporation of *p*-aminobenzoic acid in the synthesis of folic acid.

11.2.1. Formulations

Sulfadoxine is used in a fixed-dose combination of 20 parts sulfadoxine with 1 part pyrimethamine and may be administered orally or by the intramuscular route:

- Tablets containing 500 mg of sulfadoxine and 25 mg of pyrimethamine.
- Ampoules containing 500 mg of sulfadoxine and 25 mg of pyrimethamine in 2.5 ml of injectable solution for intramuscular use.

11.2.2. Toxicity

Sulfadoxine shares the adverse effect profile of other sulfonamides, although allergic reactions can be severe because of its slow elimination. Nausea, vomiting, anorexia and diarrhoea may occur. Crystalluria causing lumbar pain, haematuria and oliguria is rare compared with more rapidly eliminated sulphonamides. Hypersensitivity reactions may affect different organ system.

Cutaneous manifestations can be severe and include pruritus, photosensitivity reactions, exfoliative dermatitis, erythema nodosum, toxic epidermal necrolysis and Stevens-Johnson syndrome. Treatment with sulfadoxine should be stopped in any patient developing a rash because of the risk of severe allergic reactions.

Hypersensitivity to sulfadoxine may also cause interstitial nephritis, lumbar pain, haematuria and oliguria. This is due to crystal formation in the urine (crystalluria) and may be avoided by keeping the patient well hydrated to maintain a high urine output. Alkalinization of the urine will also make the crystals more soluble. Other adverse effects, which may be manifestations of a generalized hypersensitivity reaction include fever, hepatitis, myocarditis, pulmonary eosinophilia, fibrosing alveolitis, peripheral neuropathy and systemic vasculitis, including polyarteritis nodosa. Anaphylaxis has been reported only rarely. Other adverse reactions that have been reported include hypoglycaemia,

Blood disorders that have been reported include agranulocytosis, aplastic anaemia, thrombocytopenia, leucopenia and hypoprothrombinaemia. Acute haemolytic anaemia is a rare complication, which may be antibody mediated or associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Jaundice in neonates, aseptic meningitis, drowsiness, fatigue, headache, ataxia, dizziness, convulsions, neuropathies, psychosis and pseudomembranous colitis.

11.3. Pyrimethamine

Pyrimethamine is a diaminopyrimidine used in combination with a sulfonamide, usually sulfadoxine or dapsone. It is a slow-acting blood schizontocide and is also possibly active against pre-erythrocytic forms of the malaria parasite and inhibits sporozoite development in the mosquito vector. It is effective against all four human malarials, although resistance has emerged rapidly. Pyrimethamine is no longer used alone as an antimalarial, only in synergistic combination with slowly eliminated sulfonamides for treatment (sulfadoxine, sulfalene) or with dapsone for prophylaxis.

11.3.1. Formulations

Pyrimethamine is currently used mainly in a fixed-dose combination with slowly eliminated sulfonamides, either of 20 parts sulfadoxine with 1 part pyrimethamine for which there are oral and parenteral formulations:

- Tablets containing 500 mg of sulfadoxine and 25 mg of pyrimethamine.
- Ampoules containing 500 mg of sulfadoxine and 25 mg of pyrimethamine in 2.5 ml of injectable solution for intramuscular use.

11.3.2. Toxicity

Pyrimethamine is generally very well tolerated. Administration for prolonged periods may cause depression of haematopoiesis due to interference with folic acid metabolism. Skin rashes and hypersensitivity reactions also occur. Larger doses may cause gastrointestinal symptoms such as atrophic glossitis, abdominal pain and vomiting, haematological effects including megaloblastic anaemia, leukopenia, thrombocytopenia and pancytopenia, and central nervous system effects such as headache and dizziness.

Acute overdosage of pyrimethamine can cause gastrointestinal effects and stimulation of the central nervous system with vomiting, excitability and convulsions. Tachycardia, respiratory depression, circulatory collapse and death may follow. Treatment of overdosage is supportive.

11.3.3. Drug interactions

Administration of pyrimethamine with other folate antagonists such as cotrimoxazole, trimethoprim, methotrexate or with phenytoin may exacerbate bone marrow depression. Given with some benzodiazepines, there is a risk of hepatotoxicity.

11.4. Artemisinin

Artemisinin also known as qinghaosu, is a sesquiterpene lactone extracted from the leaves of *Artemisia annua* (sweet wormwood). It has been used in China for the treatment of fever for over a thousand years. It is a potent and rapidly acting blood schizontocide and is active against all *Plasmodium* species. It has an unusually broad activity against asexual parasites, killing all stages from young rings to schizonts. In *P. falciparum* malaria, artemisinin also kills the gametocytes – including the stage 4 gametocytes, which are otherwise sensitive only to primaquine.

Artemisinin has now largely given way to the more potent dihydroartemisinin and its derivatives, artemether, artemotil and artesunate. The three latter derivatives are converted back *in vivo* to dihydroartemisinin. These drugs should be given as combination therapy to protect them from resistance.

11.4.1. Formulations

A wide variety of formulations for oral, parenteral and rectal use are available.

These include:

- Tablets and capsules containing 250 mg of artemisinin.
- Suppositories containing 100 mg, 200 mg, 300 mg, 400 mg or 500 mg of artemisinin.

11.4.2. Toxicity

Artemisinin and its derivatives are safe and remarkably well tolerated. There have been reports of mild gastrointestinal disturbances, dizziness, tinnitus, reticulocytopenia, neutropenia, elevated liver enzyme values, and electrocardiographic abnormalities, including bradycardia and prolongation of the QT interval, although most studies have not found any electrocardiographic abnormalities.

The only potentially serious adverse effect reported with this class of drugs is type 1 hypersensitivity reactions in approximately 1 in 3000 patients.

Artemisinin has not been evaluated in the first trimester of pregnancy so should be avoided in first trimester patients with uncomplicated malaria until more information is available.

11.4.3. Drug interactions

None known.

11.5. Artemether

Artemether is the methyl ether of dihydroartemisinin. It is more lipid soluble than artemisinin or artesunate. It can be given as an oil-based intramuscular injection or orally. It is also coformulated with lumefantrine (previously referred to as benflumetol) for combination therapy.

11.5.1. Formulations

- Capsules containing 40 mg of artemether.
- Tablets containing 50 mg of artemether.
- Ampoules of injectable solution for intramuscular injection containing 80 mg of artemether in 1 ml for adults or 40 mg of artemether in 1 ml for paediatric use.

11.5.2. Toxicity

Toxicity is similar to that of artemisinin.

11.5.3. Drug interactions

None known.

11.6. Artesunate

Artesunate is the sodium salt of the hemisuccinate ester of artemisinin. It is soluble in water but has poor stability in aqueous solutions at neutral or acid pH. In the injectable form, artesunic acid is drawn up in sodium bicarbonate to form sodium artesunate immediately before injection. Artesunate can be given orally, rectally or by the intramuscular or intravenous routes. There are no coformulations currently available.

11.6.1. Formulations

- Tablets containing 50 mg or 200 mg of sodium artesunate.
- Ampoules: intramuscular or intravenous injection containing 60 mg of anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution.
- Rectal capsules containing 100 mg or 400 mg of sodium artesunate.

11.6.2. Toxicity

As for artemisinin.

11.6.3. Drug interactions

None known

11.7. Dihydroartemisinin

Dihydroartemisinin is the main active metabolite of the artemisinin derivatives, but can also be given orally and rectally as a drug in its own right. It is relatively insoluble in water, and requires formulation with suitable excipients to ensure adequate absorption. It achieves cure rates similar to those of oral artesunate. A fixed-dose formulation with piperazine is currently undergoing evaluation as a promising new artemisinin-based combination therapy (ACT).

11.7.1. Formulations

- Tablets containing 20 mg, 60 mg or 80 mg of dihydroartemisinin.
- Suppositories containing 80 mg of dihydroartemisinin.

11.7.2. Toxicity

As for artemisinin.

11.7.3. Drug interactions

None known.

11.8. Artemotil

Artemotil previously known as arteether, is the ethyl ether of artemisinin, and is closely related to the more widely used artemether. It is oil-based so water insoluble. It is given by intramuscular injection only.

11.8.1. Formulations

- Ampoules containing 150 mg of artemotil in 2 ml of injectable solution.

11.8.2. Toxicity

As for artemisinin.

11.8.3. Drug interactions

None known.

11.9. Primaquine

Primaquine is an 8-aminoquinoline and is effective against intrahepatic forms of all types of malaria parasite. It is used to provide radical cure of *P. vivax* and *P. ovale* malaria, in combination with a blood schizonticide for the erythrocytic parasites. Primaquine is also gametocytocidal against *P. falciparum* and has significant blood stage activity against *P.*

vivax (and some against asexual stages of *P. falciparum*). The mechanism of action is unknown.

11.9.1. Formulations

- Tablets containing 5.0 mg, 7.5 mg or 15.0 mg of primaquine base as diphosphate.

11.9.2. Toxicity

The most important adverse effects are haemolytic anaemia in patients with G6PD deficiency, other defects of the erythrocytic pentose phosphate pathway of glucose metabolism, or some other types of haemoglobinopathy. In patients with the African variant of G6PD deficiency, the standard course of primaquine generally produces a benign self-limiting anaemia. In the Mediterranean and Asian variants (which are found in north-western part of Pakistan), haemolysis may be much more severe. Therapeutic doses may also cause abdominal pain if administered on an empty stomach. Larger doses can cause nausea and vomiting. Methaemoglobinaemia may occur. Other uncommon effects include mild anaemia and leukocytosis. Overdosage may result in leukopenia, agranulocytosis, gastrointestinal symptoms, haemolytic anaemia and methaemoglobinaemia with cyanosis.

11.9.3. Drug interactions

Drugs liable to increase the risk of haemolysis or bone marrow suppression should be avoided.

11.10. Quinine

Quinine is an alkaloid derived from the bark of the *Cinchona* tree. Four antimalarial alkaloids can be derived from the bark: quinine (the main alkaloid), quinidine, cinchonine and cinchonidine. Quinine is the L-stereoisomer of quinidine.

Quinine acts principally on the mature trophozoite stage of parasite development and does not prevent sequestration or further development of circulating ring stages of *P. falciparum*. Like other structurally similar antimalarials, quinine also kills the sexual stages of *P. vivax*, *P. malariae* and *P. ovale*, but not mature gametocytes of *P. falciparum*. It does not kill the pre-erythrocytic stages of malaria parasites. The mechanisms of its antimalarial actions are thought to involve inhibition of parasite haem detoxification in the food vacuole, but are not well understood.

11.10.1. Formulations

- Tablets of quinine hydrochloride, quinine dihydrochloride, quinine sulfate and quinine bisulfate containing 82%, 82%, 82.6% and 59.2% quinine base, respectively.
- Injectable solutions of quinine hydrochloride, quinine dihydrochloride and quinine sulfate containing 82%, 82% and 82.6% quinine base, respectively.

11.10.2. Toxicity

Administration of quinine or its salts regularly causes a complex of symptoms known as cinchonism, which is characterized in its mild form by tinnitus, impaired high tone hearing, headache, nausea, dizziness and dysphoria, and sometimes disturbed vision. More severe manifestations include vomiting, abdominal pain, diarrhoea and severe vertigo.

Hypersensitivity reactions to quinine range from urticaria, bronchospasm, flushing of the skin and fever, through antibody-mediated thrombocytopenia and haemolytic anaemia, to lifethreatening haemolytic-uraemic syndrome. Massive haemolysis with renal failure ("black water fever") has been linked epidemiologically and historically to quinine, but its etiology remains uncertain.

The most important adverse effect in the treatment of severe malaria is hyperinsulinaemic hypoglycaemia . This is particularly common in pregnancy (50% of quinine-treated women with severe malaria in late pregnancy).

Intramuscular injections of quinine dihydrochloride are acidic (pH 2) and cause pain, focal necrosis and in some cases abscess formation, and in endemic areas are a common cause of sciatic nerve palsy.

Hypotension and cardiac arrest may result from rapid intravenous injection. Intravenous quinine should be given only by infusion, never by injection.

Quinine has been used as an abortifacient, but there is no evidence that it causes abortion, premature labour or fetal abnormalities in therapeutic use.

Overdosage of quinine may cause oculotoxicity, including blindness from direct retinal toxicity, and cardiotoxicity, and can be fatal.

Cardiotoxic effects are less frequent than those of quinidine and include conduction disturbances, arrhythmias, angina, hypotension leading to cardiac arrest and circulatory failure. Treatment is largely supportive, with attention being given to maintenance of blood pressure, glucose and renal function, and to treating arrhythmias.

11.10.3. Drug interactions

Antiarrhythmics, such as flecainide and amiodarone, should be avoided.

There might be an increased risk of ventricular arrhythmias with antihistamines such as terfenadine, and with antipsychotic drugs such as pimozide and thioridazine.

Halofantrine, which causes marked QT prolongation, should be avoided but combination with other antimalarials, such as lumefantrine and mefloquine is safe.

Quinine increases the plasma concentration of digoxin.

Cimetidine inhibits quinine metabolism, causing increased quinine levels and Rifampicin increases metabolic clearance leading to low plasma concentrations and an increased therapeutic failure rate.