NATIONAL MALARIA TREATMENT PROTOCOL
2015

Editors:
Dr B R Marasini
Dr M P Upadhyay
Dr R R Panthi
Dr Y R Pokhrel
Dr Nihal Singh
Dr Prakash Ghimire
Dr Suman Thapa
Dr Kiran Awasthi
Dr M R Banjara

Epidemiology and Disease Control Division
Department of Health Services
Teku, Kathmandu
Phone: +977.14255796; 14262268
E-mail: ewarsedcd@gmail.com

Revision and Publication support by
World Health Organization
Country Office for Nepal
FOREWORD

I am delighted to present to you the updated National Malaria Treatment Protocol 2015 prepared by the team of experts associated with Epidemiology & Disease Control Division, under the Dept. of Health Services, Ministry of Health. The document is updated based on the new knowledge/skills and availability of technology/tools in diagnosis of disease, detection of G6PD deficiency, and availability of the new treatment regimens in the recent days due to development in medicine science and technology, and prepared on consensus following the recommendations of the National Workshop with various stakeholders including the private sectors.

There have been significant development in clinical management of malaria with the wide availability of different forms/combinations of ACT then and new effective tools for the diagnosis of different specimens of malarial parasites (bi-valent and multi-valent RDTs) and RDT’s for the diagnosis/detection of G6PD deficiency and the best practices that are appropriate to our nation for inclusion in the protocol. Nepal has reached the set Millennium Development Goal on Malaria well ahead of schedule in 2010. The malaria program external review in 2010, mid-term review in 2013 and micro-stratification completed in 2013 has clearly shown that the program requires to change its direction from control to elimination, following which a revised strategy with elimination target of 2015 have already been approved by the ministry. The current Treatment protocol has clearly accommodated the above recommendations and in line with the new strategy targeted towards elimination by 2025.

It gives me great pleasure to announce that. With the rapid progress the malaria program has now entered in the elimination phase. At this important juncture, where the recently promulgated strategy aims to eliminate the disease by 2025, it is imperative that each case be identified and treated immediately based on the treatment protocol. The challenge however lies in implementing the treatment guidelines in both the public and private sectors. Therefore adequate dissemination of the protocol both in the public and private sector is a prerequisite for a successful outcome, for which Epidemiology & Disease Control Division will work in the wide dissemination of the protocol involving both the public and private sectors.

Lastly, I would like to thank all the expert editors, facilitators, resource persons and participants involved in the preparation of this protocol.

Dr. Senendra Raj Uprety
Director General
Department of Health Services
Ministry of Health
PREFACE

It gives me immense pleasure to release this important publication of the Epidemiology & Disease Control Division, Department of Health “National Malaria Treatment Protocol”, revised after 5 years, based on availability of new knowledge and tools in disease detection, diagnosis, detection of G6PD deficiency and appropriate treatment.

Nepal has surpassed the millennium development goals, set for malaria as early as 2010; able to reduce malaria deaths in such an extent that there is no recorded case of deaths due to malaria after 2012. As we move further, the numbers of malaria cases have come near 1000 by 2015; the percentage of imported malaria has increased from about 20% in 2001 to almost half (50%) of total malaria cases by 2015. The current Nepal Malaria Strategic Plan 2014-2025 has envisioned for elimination of malaria by 2025, for which this document plays a vital role as the guiding document/standard protocol for use by various levels of health workers, including the treating physicians.

This protocol will aide all the health care professionals to follow a standard guideline on the rational use of antimalarial drugs for the treatment of cases based on classification (6 ACT + single dose PQ for confirmed Pf ad P mix, 6 CQ + 14 PQ for Pv) and mandatory G6PDd testing of all vivax cases for initiation of PQ paving the path for elimination.

At this juncture, I would like to thank all the editors of the document, expert of the technical working group, participants of the consultative meeting who have provided invaluable inputs to bring this document in this stage. In spite of all our efforts to bring document without any errors, EDCD welcomes any suggestion that would help to improve this document in future editions.

Dr Babu Ram Marasini
Director Epidemiology & Disease Control Division
Department of Health Services
Ministry of Health

December 2015
# TABLE OF CONTENTS

1. Introduction 1  
   1.1 Background 1  
   1.2 Epidemiology of malaria in Nepal 1  
   1.3 Core principles 2  
   1.4 Case definitions 3  
      1.4.1 Sign and Symptoms of Malaria 3  
      1.4.2 Clinically suspected malaria case 3  
      1.4.3 Confirmed malaria case 3  
      1.4.4 Confirmed uncomplicated malaria case 3  
      1.4.5 Severe/complicated malaria case 3  
      1.4.6 Treatment failures 3  
      1.4.7 Recrudescence case 4  
      1.4.8 Relapse case 4  
      1.4.9 Cured case 4  
      1.4.10 Radical cure 4  

2. Diagnosis of Malaria at Different Settings 5  
   2.1 Diagnosis of malaria at Health Posts and Primary Health Care Centers 5  
   2.2 Diagnosis of malaria at district and zonal hospitals 6  
   2.3 Diagnosis of malaria at referral hospitals 6  
   2.4 Clinical diagnosis 6  
   2.5 Light microscopy 7  
   2.6 Rapid diagnostic tests 7  
   2.7 Molecular diagnostic tools 8  

3. Treatment of Malaria 9  
   3.1 Treatment of uncomplicated *P. vivax, P. ovale, P. malariae* and *P. knowlesi* malaria 9  
      3.1.1 Chloroquine sensitive *P. vivax* malaria 10  
      3.1.2 Chloroquine-resistant *P. vivax* malaria 11  
      3.1.3 Treatment of the liver stages (hypnozoites) of *P. vivax* 11  
   3.2 Treatment of uncomplicated *P. falciparum* malaria/ mixed malaria 13  
      3.2.1 Artemisinin-based combination therapy 13  
   3. Treatment of complicated malaria (in tertiary care hospitals) 14  
      3.3.1 General management 15  
      3.3.2 Definitions 15  

4. Diagnosis and Management of Malaria 23  
   4.1 Algorithm for Diagnosis &Treatment of Malaria 24  
   4.2 Malaria Chemoprophylaxis 26  
   4.3 G6PD Deficiency Testing 26  
   4.4 Recording, Reporting and Surveillance of Malaria 27  

5. Appendix 28  
   Appendix 1: Mixed malaria infections, and treatment 28  
   Appendix 2: Participants of consultative meeting for finalization of the NMTP-2015 29  

6. Bibliography 30
List of Tables
Table-1: Dosage of Chloroquine by age group  
Table-2: Chloroquine syrup for young children  
Table-3: Dosage of Chloroquine and Primaquine by age group  
Table-4: The dosages of AL (Coartem ) and a single dose of primaquine by kg body weight  
Table-5: Dosage of Quinine sulphate by body weight in Kg or age  
Table-6: Treatment of Malaria in Children
1.1 Background

The malaria risk micro-stratification report 2013 have clearly identified approximately 13.02 million (47.9%) population of Nepal still are staying in malaria endemic areas (VDCs); out of which ~1 million (3.62%) live in high risk VDCs, 2.66 million (9.8%) live in moderate risk VDCs, and 9.38 million (34.52%) live in low risk VDCs. A total population of 14.13 (52.1%) is estimated to live in VDCs where there is no malaria transmission. It has been shown that only 54 VDC’s are at high risk of malaria, 201 VDCs at moderate risk and 999 VDCs at low risk. The high risk areas consist of foothills with river belts, forest fringe areas in terai, hill river valleys, and inner-terai areas. Low risk VDCs lie in plain cultivated outer terai, mountain, and valleys in the mountains.

1.2 Epidemiology of malaria in Nepal

Confirmed malaria cases gradually dropped from 4895 in 2004 to 1674 by 2014. The proportion of \textit{P. falciparum} infections has declined and reached 13.38\% by 2014. Recorded malaria deaths declined from 156 in 2006 (last outbreak recorded year) to zero deaths by 2012 and able to maintain no malaria related deaths thereafter. The decreasing trend of confirmed malaria cases, case severity with sustaining zero death, have been contributed by increasing the access to diagnosis due to availability of RDT and availability of ACT to public health facilities, high coverage of LLINs in endemic districts and increased socio-economic status of the inhabitants in risk areas. There is encouraging decrease in the indigenous falciparum cases, while it is comparatively slow in case of Plasmodium vivax cases, which is an indication that \textit{P. vivax} may remain a challenge for longer duration for elimination of malaria from Nepal.

Government of Nepal has set a challenging vision of malaria free Nepal by 2025. The goals to achieve the vision of malaria free Nepal by 2025 are: to sustain zero death due to malaria from 2012 onwards; to reduce by 90\%, the incidence of indigenous malaria cases by 2018 (relative to 2012); and to reduce by 70\% the number of VDCs having indigenous malaria cases by 2018 (relative to 2012).
1.3 Core principles

The following core principles were considered at the beginning, which drew up the Guideline.

1. Early diagnosis, prompt and effective treatment of malaria

Uncomplicated falciparum malaria can progress rapidly to severe forms of the disease, especially in people with no or low immunity, and severe falciparum malaria is almost always fatal without treatment.

Therefore, programs should ensure access to early diagnosis and prompt, effective treatment within 24–48 hours of the onset of malaria symptoms.

2. Rational use of antimalarial agents

To reduce the spread of drug resistance, limit unnecessary use of antimalarial drugs and better identify other febrile illnesses in the context of changing malaria epidemiology, antimalarial medicines should be administered only to patients who truly have malaria. Adherence to a full treatment course must be promoted.

Universal access to parasitological diagnosis of malaria is now possible with the use of quality-assured rapid diagnostic tests (RDTs), which are also appropriate for use in primary health care and community settings.

3. Combination therapy

Preventing or delaying resistance is essential for the success of both national and global strategies for control and eventual elimination of malaria. To help protect current and future antimalarial medicines, all episodes of malaria should be treated with at least two effective antimalarial medicines with different mechanisms of action (combination therapy).

4. Appropriate weight-based dosing

To prolong their useful therapeutic life and ensure that all patients have an equal chance of being cured, the quality of antimalarial drugs must be ensured and antimalarial drugs must be given at optimal dosages. Treatment should maximize the likelihood of rapid clinical and parasitological cure and minimize transmission from the treated infection. To achieve this, dosage regimens should be based on the patient’s weight and should provide effective concentrations of antimalarial drugs for a sufficient time to eliminate the infection in all target populations.
1.4 Case definitions

1.4.1 Sign and Symptoms of Malaria
The first symptoms of malaria are nonspecific and similar to the symptoms of a minor systemic viral illness. They comprise:
- Headache,
- Lassitude,
- Fatigue,
- Abdominal discomfort (nausea, vomiting, diarrhea), and
- Muscle and joint aches, usually followed by fever,
- Chills, and/or cough
- Perspiration,
- Anorexia,
- Vomiting and
- Worsening malaise.
- Neurologic complaints (dizziness, confusion, disorientation, coma)

The diagnosis of malaria should also be considered in any person with fever of unknown origin / pyrexia of unknown origin (PUO) regardless of travel history.

1.4.2 Clinically suspected malaria case
A resident of malaria endemic area or a person with a recent travel history to malarious area who presents with history of fever during last three days or patient with symptoms and/or signs of uncomplicated malaria, or patients requiring hospitalization for symptoms and/or signs of malaria, is considered as a case of suspected malaria after the exclusion of other common causes of fever.

1.4.3 Confirmed malaria case
A clinically suspected malaria case showing presence of malarial parasite in the thick/thin blood smear microscopy or detection of parasite specific antigen in the blood of the suspected patient in the laboratory

1.4.4 Confirmed uncomplicated malaria case
A case of malaria confirmed by laboratory (microscopy or RDT), without signs of severity or evidence of vital organ dysfunction.

1.4.5 Severe/complicated malaria case
A confirmed malaria case requiring hospitalization for the treatment due to signs of severity and/or evidence of vital organ dysfunction, which includes:
- Prostration (inability to sit), altered consciousness lethargy or coma
- Breathing difficulties
- Severe anaemia (haemoglobin < 7mg/dl)
- Generalized convulsions/fits
- Inability to drink/vomiting
- Dark and/or limited production of urine
- Jaundice

Generally severe and/or cerebral malaria is caused by Plasmodium falciparum, but not all Pf malaria become severe.

1.4.6 Treatment failures
A confirmed malaria with a history of correct & complete treatment according to nationally recommended anti-malarial medicines, but presents with following:

1.4.6.1 Early treatment failure
- Danger signs or severe malaria on day 1, 2 or 3 in the presence of parasitaemia;
- Parasitaemia on day 2 higher than on day 0, irrespective of axilliary temperature;
• Parasitaemia on day 3 - with axillary temperature 37.5°C;
• Parasitaemia on day 3 - 25% of count on day 0.

1.4.6.2 Late treatment failure

1.4.6.2.1 Late clinical failure
• Danger signs or severe malaria in the presence of parasitaemia on any day between day 4 and day 28 (day 42) in patients who did not previously meet any of the criteria of early treatment failure;
• Presence of parasitaemia on any day between day 4 and day 28 with axillary temperature
• Fever of ≥37.5°C in patients who did not previously meet any of the criteria of early treatment failure

1.4.6.2.2 Late parasitological failure
• Presence of parasitaemia on any day between day 7 and day 28 with axillary temperature
• Fever of < 37.5°C in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure

1.4.6.3 Adequate clinical and parasitological response
• Absence of parasitaemia on day 28, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure

1.4.7 Recrudescence case
The recurrence of malaria sign and symptoms in a patient who have successfully been treated for malaria till follow up period; while the sign and symptoms together with asexual parasitaemia appear once again either due to treatment failure or re-infection (which is difficult to distinguish in absence of molecular tools/genotyping). It is, therefore, different to 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).

1.4.8 Relapse case
P. vivax and P. ovale form hypnozoites, which are dormant parasite stages in the liver that cause relapses of infection weeks to years after the primary infection.

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, which is detected in blood smear in patient who presents with sign and symptoms of malaria after few months/year of antimalarial treatment and disappearance of sign and symptoms for significant duration, till relapse causing fever and parasite release in the blood circulation once again. Recent studies have revealed that some strains of the P. vivax remain in liver for about a month in early relapse cases, while they may remain for one to many years in late relapse cases, the reason for which are not clearly understood.

1.4.9 Cured case
Elimination of the sign and symptoms, plus asexual blood stages malaria parasites that lead the patient or caregiver not to seek further treatment.

1.4.10 Radical cure
P. vivax and P. ovale form hypnozoites, which are dormant parasite stages in the liver that cause relapses of infection weeks to years after the primary infection.

In the cases identified with P. vivax or P. ovale infections; an hypnozoiticidal antimalarial medicine, namely Primaquine is prescribed for 14 days in addition to schizontocidal medicine (ACT or CQ), which is able to kill liver stage malarial parasite stage and prevent relapse. So the antimalarial medicine PQ together with ACT/CQ is considered as radical cure.
Prompt and accurate diagnosis of malaria is part of effective disease management. All patients with suspected malaria should be treated on the basis of a confirmed diagnosis by microscopic examination or RDT testing of a blood sample. Correct diagnosis in malaria-endemic areas is particularly important for the most vulnerable population groups, such as young children and non-immune populations, in whom falciparum malaria can be rapidly fatal. High specificity will reduce unnecessary treatment with antimalarial drugs and improve the diagnosis of other febrile illnesses in all settings.

WHO strongly advocates a policy of “test, treat and track” to improve the quality of care and surveillance. Nepal Malaria Strategic Plan 2014-2025 has stressed to improve quality of and access to early diagnosis and effective treatment of malaria, putting diagnosis and treatment as one of the five strategic objectives.

Malaria diagnosis and treatment both are available free of cost, in public health facilities. Supply of microscopy slides, reagents, RDTs, antimalarial medicines as prescribed by the NMTP (Chloroquine, ACTs, Quinine, Artesunate) are made available by the national malaria program/EDCD, to the most peripheral public health system, where malaria cases are detected. Private sector health care providers, although not fully regulated, coordination at district and higher levels has started to align the diagnosis and treatment as per national protocol. At community level, where malaria microscopy is not available due to non-availability of the trained laboratory personnel, or in health facilities during off hours, RDT’s are utilized for early diagnosis for appropriate and prompt treatment.

Microscopy is available at district level hospitals, Primary Health Care Center and also in most of the health posts of high risk VDCs. As of now Malaria Microscopy is functional in 162 of the 255 VDC’s at risk of malaria, as identified by the malaria risk micro-stratification report developed in 2013. Bi-valent RDTs detecting Pf and Pf are used in those health institutions where malaria microscopy service is not available solely due to no availability of the trained technicians and for emergency purposes. To maintain the quality of malaria microscopy, National Malaria Program in close coordination with Vector Borne Diseases Research and Training Centre, National Public Health Laboratory, WHO, International partner agencies and national academic institute, conducts QA/QC trainings/orientations, annually. There is an existing mechanism for malaria slide cross checking/validation and feedback from regional health Directorate, where the slide validators for the region are located, which is ultimately referred and reported to National Malaria Program on regular intervals.

With the above information, following mechanism has been envisioned to be in place for diagnosis and treatment of malaria cases:

2.1 Diagnosis of malaria at Health Posts and Primary Health Care Centers

At Health Post and Primary Health Care Centers (PHCs), a suspected malaria case may present him/herself to health workers. The health workers (HA/AHW), should evaluate the patient clinically with matching signs and symptoms and history of travel to malaria endemic areas and process for parasitological diagnosis (malaria microscopy or RDT). The suspected patient should be further identified as malaria (PF or Pf or P mix case) or other and provide appropriate treatment following the
protocol (CQ-3 days plus PQ 14 days for PV cases with normal G6PD level; CQ-3 days for identified G6PD deficient patients; ACT 3 days and PQ single dose for Pf- detail annex) and also advice the patient on the importance of adherence to complete treatment and monitoring follow up for evaluating prognosis/treatment failure on day 3, 7, 14 and 28. As far as available thick and thin smear microscopy should be examined for confirming the diagnosis. When Blood smear microscopy is not possible, then bi-valent RDTs may be taken as an alternative to the parasitological diagnosis of the suspected case. Test of G6PD deficiency in all P. vivax cases should be mandatorily done to rationalize PQ prescription and reduce possible adverse effects, if any.

2.2 Diagnosis of malaria at district and zonal hospitals

At district or Zonal Hospital, a suspected malaria case may present him/herself to the doctor/physician, as available. The doctor should evaluate the patient clinically with matching signs and symptoms and history of travel to malaria endemic areas and request for laboratory investigation for confirming the suspicion, including laboratory processing for parasitological diagnosis (malaria microscopy) of malaria.

The Laboratory at the earliest should process thick and thin smear microscopy for the parasitological confirmation of malaria, and should be able to provide laboratory results within 2-3 hrs of specimen collection.

While examining the Thick and Thin smear of the blood from suspected malaria cases, the trained technicians at District/Zonal Hospitals should also record the species and density (as in HMIS form) of the parasites in the patients’ blood smear.

Monitoring follow up on the prognosis/treatment failure on day 3, 7, 14 and 28 shall be carried out, for which the patients/attendants should be informed to visit the hospital for follow up examination/evaluations.

2.3 Diagnosis of malaria at referral hospitals

In referral hospitals, a suspected malaria case may present him/herself to the general practitioner/physician, as available. The general practitioner/physician should evaluate the patient clinically with matching signs and symptoms and history of travel to malaria endemic areas and request for laboratory investigation for confirming the suspicion, including laboratory processing for parasitological diagnosis (malaria microscopy) of malaria.

The Laboratory at the earliest should process for thick and thin smear microscopy for the parasitological diagnosis of malaria, and should be able to provide laboratory results within 2-3 hrs of specimen collection. While examining the Thick and Thin smear of the blood from suspected malaria cases, the trained technicians should also record and report the species and density (as in HMIS form) of the parasites in the patients’ blood smear.

Monitoring follow up on the prognosis/treatment failure on day 3, 7, 14 and 28 should be carried out, for which the patients/attendants should be informed to visit the hospital for follow up examination/evaluations.

Recording of the follow up monitoring results should be maintained at the hospital/lab record files and should be reported as consolidated reports annually to the national program.

2.4 Clinical diagnosis

Clinical diagnosis of malaria often depends on any one set of clinical criteria, as the signs and symptoms of malaria:
1. Fever
2. Chills
3. Headache
4. Anorexia
Clinical diagnoses are nonspecific and are common to many diseases and conditions. The appropriateness of particular clinical diagnostic criteria varies from area to area according to the intensity of transmission, the species of malaria parasite and other prevailing causes of fever. Other diseases co-incident with malaria may also affect its presentation.

Severe malaria is usually recognized by the occurrence of one or more of the following symptoms and signs:
1. Prostration – severe weakness (inability to sit up)
2. Impaired consciousness - Confusion, coma
3. Continuous vomiting
4. Respiratory distress
5. Pallor, unable to walk, collapse
6. Convulsions
7. Jaundice

2.5 Light microscopy

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.

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 can be used for differentiation between plasmodia species, determination of parasite densities, monitoring response to therapy.

It can be difficult to maintain good quality of microscopy, for various reasons: the need for adequate training and supervision of laboratory staff; the need to rely on electricity; delays in providing results to patients; and the need to maintain quality assurance and control of laboratory services.

2.6 Rapid diagnostic tests

Rapid diagnostic tests are immuno-chromatographic tests that are used to detect parasite-specific antigens in a finger-prick blood sample. RDTs are available commercially in different formats such as dipsticks, cassettes or cards. Rapid diagnostic tests are relatively simple to perform and to interpret, and they do not require electricity or special equipment. Specific SOPs should be followed in using the RDTs for testing the suspected cases, using the finger prick/venipuncture blood.

Some RDTs are designed to diagnose one particular species (Plasmodium falciparum) by detecting Plasmodium falciparum specific PfHRP-II antigen. Other RDTs are designed to detect antigen specific to all four human malarial parasites (pan species specific/genus specific) plus species specific antigen distinguishing each human malarial parasite. Rational use of RDT could be helpful in diagnosing human malaria where microscopy is unavailable due to various reasons.

Quality RDT is a valuable complement to microscopy because it helps to expand coverage of parasite based diagnosis to the periphery and minimize exclusively use of clinical diagnosis in starting antimalarial treatment. RDTs are particularly useful for outbreak/epidemic investigation especially in remote areas.

Rapid Diagnostic Tests detecting plasmodium antigen(s) have been successfully introduced into National Malaria Control Program. Increased access to early diagnosis is ensured by availability of RDTs up to SHPs and HPs where microscopy is not feasible. However, clinical management decisions should be based on symptoms/signs plus Laboratory (Microscopy/RDT) results taken together.
Rationale use of these tests, as with microscopy, depends on stringent and functional quality assurance program; NMCP is working closely with NPHL and academic institute in establishing a functional QA system and networking together with defined role of the Regional Health Directorates.

Availability of microscopic laboratory diagnostic facility at sub-health posts / health posts is limited. The necessity for rational use of antimalarials in the face of detection of drug resistant malarial parasites and availability of limited and high cost antimalarial places increasing importance on accuracy of malaria diagnosis.

NMCP has introduced bi-valent RDTs for the diagnosis of *P. falciparum* and *P. vivax* in the sub-health posts / health posts of the high risk districts as early as 2009 and is continued.

The sub-health posts and health posts of the high risk malaria districts will be able to diagnose *P. falciparum* and *P. vivax* by microscopy/RDTs and treat the cases promptly with effective antimalarials.

Detection of antibodies to parasites, particularly in endemic areas is not useful for diagnostic purpose, as parts of the country is still endemic which have people with significant levels of antibodies circulating in their blood, although they may not have active infection at the time of test. So antibody based tests are neither sensitive nor specific enough to be of use for the malaria case management.

### 2.7 Molecular diagnostic tools

Techniques to detect parasite DNA, based on the polymerase chain reaction, are highly sensitive and very useful for detecting mixed infections, in particular at low parasite densities. They are also useful for studies on drug resistance and other specialized epidemiological investigations, but they are not generally available for large-scale field use in malaria endemic areas.
3.1 Treatment of uncomplicated *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi* Malaria

**Blood stage infection**
If the malaria species is not known with certainty, treat as for uncomplicated *P. falciparum* malaria.

*Good practice statement*

**In areas with chloroquine-susceptible infections**, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria with either an ACT (except pregnant women in their first trimester) or Chloroquine.

*Strong recommendation, high-quality evidence*

**In areas with chloroquine-resistant infections**, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria (except pregnant women in their first trimester) with an ACT.

*Strong recommendation, high-quality evidence*

**Treat pregnant women** in their first trimester who have chloroquine-resistant *P. vivax* malaria with Quinine.

*Strong recommendation, very low-quality evidence*

**Preventing relapse in *P. vivax* or *P. ovale* malaria**

The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.

*Good practice statement*

To prevent relapse, treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency) with a 14-day course of primaquine in all transmission settings.

*Strong recommendation, high-quality evidence*

**In people with G6PD deficiency**, consider preventing relapse by giving primaquine base at 0.75 mg/kg body weight once a week for 8 weeks, with close medical supervision for potential primaquine-induced adverse haematological effects.

*Conditional recommendation, very low-quality evidence*

**When the G6PD status is unknown** and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine.

*Good practice statement*

**Pregnant and breastfeeding women**

In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, on the basis of G6PD status, treat with primaquine to prevent future relapse.

*Conditional recommendation, moderate-quality evidence*
**P. vivax** is the most important causative agent of human malaria in Nepal. About 70-85% of malaria cases are due to **P. vivax**.

**P. vivax** forms hypnozoites, which are dormant parasite stages in the liver that cause relapses of infection weeks to years after the primary infection. Thus, a single mosquito inoculation may result in repeated bouts of illness.

**P. vivax** exists in two general forms: the more prevalent tropical form, which causes malaria that relapses at frequent intervals (typically every 3 weeks unless slowly eliminated antimalarial drugs are given, in which case the interval is 5–7 weeks) and tends to be less susceptible to primaquine; and a temperate form, in which there may be a long (~9-month) incubation period or a similarly long interval between primary illness and relapse. The temperate form of **P. vivax** is more sensitive to primaquine.

Infection with **P. vivax** during pregnancy reduces the birth weight of the infant, as does by **P. falciparum**. In primigravidae, the birth weight reduction is approximately two thirds of that associated with **P. falciparum** (110 g compared with 170 g), but this adverse effect does not decrease with successive pregnancies, unlike in **P. falciparum** infections.

The objective of treating malaria caused by **P. vivax** is to cure both blood-stage and liver-stage infections (called radical cure), thereby preventing recrudescence and relapse, respectively.

On the Indian subcontinent where most of the world’s **P. vivax** malaria occurs, the parasites are mainly sensitive to chloroquine.

In general, **P. vivax** is sensitive to all the other antimalarial drugs. In contrast to **P. falciparum**, asexual stages of **P. vivax** are also susceptible to primaquine. Thus, chloroquine + primaquine can be considered as a combination treatment for blood-stage infections, in addition to providing radical cure. The only drugs with significant activity against the hypnozoites are the 8-aminoquinolines (primaquine, bulequine, tafenoquine).

### 3.1.1 Chloroquine sensitive **P. vivax** malaria

For chloroquine-sensitive vivax malaria, oral chloroquine at a total dose of 25 mgbase/kg body weight is effective and well tolerated. Lower total doses are not recommended, as these encourage the emergence of resistance. **Chloroquine is given at an initial dose of 10 mg base/kg body weight, followed by 10 mg/kg body weight on the second day and 5 mg/kg body weight on the third day.** As residual chloroquine suppresses the first relapse of tropical **P. vivax** (which emerges about 3 weeks after onset of the primary illness), relapses begin to occur 5–7 weeks after treatment if radical curative treatment with primaquine is not given. For clarity on the dose for different age groups, below tables (Tables-1 & 2) provides a quick summary/overview.

<table>
<thead>
<tr>
<th>Table-1: Dosage of Chloroquine by age group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*Each tablet of Chloroquine contains 150 mg base*
### Table-2: Chloroquine syrup for young children

<table>
<thead>
<tr>
<th>Day</th>
<th>Less than one year</th>
<th>1 – 4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>One and half tea spoonful (75mg) 1 &amp; ½ (7.5 ml)</td>
<td>Three tea spoonful (150mg)</td>
</tr>
<tr>
<td>2</td>
<td>One and half tea spoonful (75mg) 1 &amp; ½ (7.5 ml)</td>
<td>Three tea spoonful (150mg) 3 (15 ml)</td>
</tr>
<tr>
<td>3</td>
<td>One and half teaspoonful (75mg) 1 &amp; ½ (7.5 ml)</td>
<td>One and half tea spoonful (75mg) 1 &amp; ½ (7.5 ml)</td>
</tr>
</tbody>
</table>

One teaspoonful = 5 ml. of Chloroquine syrup = 50 mg. of Chloroquine base

**Notes:** Chloroquine should not be administered in empty stomach. Repeat the dose, if there is vomiting within half an hour of Chloroquine administration.

### 3.1.2 Chloroquine-resistant *P. vivax* malaria

**ACTs are highly effective in the treatment of vivax malaria, allowing simplification (unification) of malaria treatment; i.e. all malaria infections can be treated with an ACT.** The exception is artesunate + SP, where resistance significantly compromises its efficacy. The initial response to all ACTs is rapid in vivax malaria, reflecting the high sensitivity to artemisinin derivatives, but, unless primaquine is given, relapses commonly follow. The subsequent recurrence patterns differ, reflecting the elimination kinetics of the partner drugs. Thus, recurrences, presumed to be relapses, occur earlier after artemether + lumefantrine than after dihydroartemisinin + piperaquine or artesunate + mefloquine because lumefantrine is eliminated more rapidly than either mefloquine or piperaquine.

ACTs containing piperaquine, mefloquine or lumefantrine are the recommended treatment, although artesunate + amodiaquine may also be effective in some areas. The half-life of mefloquine is similar to that of piperaquine, but use of dihydroartemisinin + piperaquine in *P. vivax* mono-infections has not been compared directly in trials with use of artesunate + mefloquine. In the first-trimester of pregnancy, quinine should be used in place of ACTs.

### 3.1.3 Treatment of the liver stages (hypnozoites) of *P. vivax*

To prevent relapse, *P. vivax* malaria should be treated in children and adults (except pregnant women, infants aged <6 months, women breastfeeding infants <6 months, women breastfeeding older infants unless they are known not to be G6PD deficient and people with G6PD deficiency) with a 14-day course of primaquine (0.25 mg/kg body weight per day) in all transmission settings.

In people with G6PD deficiency, it is considered for preventing relapse by giving primaquine base at 0.75 mg base/kg body weight once a week for 8 weeks, with close medical supervision for closely monitoring potential primaquine-induced adverse haematological effects. Details on dose according to age’s groups could be referred to the table below:

### Table-3: Dosage of Chloroquine and Primaquine by age group

<table>
<thead>
<tr>
<th>Days</th>
<th>Medicine</th>
<th>Age in years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;1</td>
</tr>
<tr>
<td>1</td>
<td>Chloroquine tablet (150mg.)</td>
<td>½</td>
</tr>
<tr>
<td></td>
<td>Primaquine tablet (7.5 mg.)</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>Chloroquine tablet (150 mg.)</td>
<td>½</td>
</tr>
<tr>
<td></td>
<td>Primaquine tablet (7.5 mg.)</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>Chloroquine tablet (150 mg.)</td>
<td>½</td>
</tr>
<tr>
<td></td>
<td>Primaquine tablet (7.5 mg.)</td>
<td>Nil</td>
</tr>
<tr>
<td>4 – 14*</td>
<td>Primaquine tablet (7.5 mg.)</td>
<td>Nil</td>
</tr>
</tbody>
</table>

**Note:** * = Standard 14 days Primaquine treatment is recommended ensuring close monitoring of the patients.
3.1.3.1 Primaquine and glucose-6-phosphate dehydrogenase deficiency

Any person (male or female) with red cell G6PD activity <30% of the normal mean has G6PD deficiency and will experience haemolysis after primaquine. Heterozygote females with higher mean red cell activities may still show substantial haemolysis. G6PD deficiency is an inherited sex-linked genetic disorder, which is associated with some protection against *P. falciparum* and *P. vivax* malaria but increased susceptibility to oxidant haemolysis. The prevalence of G6PD deficiency varies, but in tropical areas it is typically 3–35%; high frequencies are found only in areas where malaria is or has been endemic. In Nepal, a recent study carried out by the national malaria program have shown G6PD deficiency prevalence at a range of 0.5-10% in different ethnic groups inhabiting from east Jhapa to Far west Kanchanpur, the highest being in Rajbanshi in Jhapa and the lowest in Brahman chetri of the general population. There are many (>180) different G6PD deficiency genetic variants; nearly all of which make the red cells susceptible to oxidant haemolysis, but the severity of haemolysis may vary. Primaquine generates reactive intermediate metabolites that are oxidant and cause haemolysis in G6PD-deficient individuals. It also causes methemoglobinemia. The severity of haemolytic anaemia depends on the dose of primaquine and on the variant of the G6PD enzyme. Fortunately, primaquine is eliminated rapidly so haemolysis is self-limiting once the drug is stopped. In the absence of exposure to primaquine or another oxidant agent, G6PD deficiency rarely causes clinical manifestations; so many patients are unaware of their G6PD status. Screening for G6PD deficiency is not widely available outside hospitals, but rapid screening tests that can be used at points of care have recently become commercially available.

In patients known to be G6PD deficient, primaquine may be considered at a dose of 0.75 mg base/kg body weight once a week for 8 weeks. The decision to give or withhold primaquine should depend on the possibility of giving the treatment under close medical supervision, with ready access to health facilities with blood transfusion services.

Some heterozygote females who test as normal or not deficient in qualitative G6PD screening tests have intermediate G6PD activity and can still hemolyse substantially. Intermediate deficiency (30–80% of normal) and normal enzyme activity (>80% of normal) can be differentiated only with a quantitative test. In the absence of quantitative testing, all females should be considered as potentially having intermediate G6PD activity and given the 14-day regimen of primaquine, with counselling on how to recognize symptoms and signs of haemolytic anaemia. They should be advised to stop primaquine and be told where to seek care should these signs develop.

If G6PD testing is not available, a decision to prescribe or withhold primaquine should be based on the balance of the probability and benefits of preventing relapse against the risks of primaquine-induced haemolytic anaemia. This depends on the population prevalence of G6PD deficiency, the severity of the prevalent genotypes and on the capacity of health services to identify and manage primaquine-induced haemolytic reactions.

3.1.3.2 Prevention of relapse in pregnant or lactating women and infants

In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, on the basis of G6PD status, treat with primaquine to prevent future relapse.

Primaquine is contraindicated in pregnant women and in lactating women (unless the infant is known not to be G6PD deficient). As an alternative, chloroquine prophylaxis could be given to suppress relapses after acute vivax malaria during pregnancy. Once the infant has been delivered and the mother has completed breastfeeding, primaquine could then be given to achieve radical cure.
### 3.2. Treatment of uncomplicated *P. falciparum* and mixed malaria

The clinical objectives of treating uncomplicated malaria are to cure the infection as rapidly as possible and to prevent progression to severe disease. “Cure” is defined as elimination of all parasites from the body. The objectives of treatment are to prevent onward transmission of the infection to others and to prevent the emergence and spread of resistance to antimalarial drugs.

#### 3.2.1 Artemisinin-based combination therapy

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with an ACT as below and single dose primaquine for radical treatment.

In the absence of resistance to the partner drug, the five recommended ACTs have all been shown to achieve a PCR - adjusted treatment failure rate of 5% in many trials in several settings in both adults and children.

ACT is a combination of a rapidly acting artemisinin derivative with a longer-acting (more slowly eliminated) partner drug. The artemisinin component rapidly clears parasites from the blood (reducing parasite numbers by a factor of approximately 10,000 in each 48 hrs asexual cycle) and is also active against the sexual stages of the gametocytes that mediate onward transmission to mosquitoes. The longer acting partner drug clears the remaining parasites and provides protection against development of resistance to the artemisinin derivative. Partner drugs with longer elimination half-lives also provide a period of post-treatment prophylaxis.

Globally there are five ACTs recommended for treatment of uncomplicated *P. falciparum* malaria, namely: Artemether + lumefantrine*; artesunate + amodiaquine; artesunate + mefloquine; artesunate + SP; and dihydroartemisinin + piperaquine.

In Nepal, the national malaria program has recommended the use 3 days course of **artemether 20 mg + lumefantrine 120 mg**. The different doses of ACT in different age /weight groups are as in the table below:

<table>
<thead>
<tr>
<th>Body weight (kg.)</th>
<th>ACT Day-1</th>
<th>ACT Day-2</th>
<th>ACT Day-3</th>
<th>Primaquine 0.25 mg/kg body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-14</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>½ tablet</td>
</tr>
<tr>
<td>15-24</td>
<td>2 tablets</td>
<td>2 tablets</td>
<td>2 tablets</td>
<td>1 tablet</td>
</tr>
<tr>
<td>25-34</td>
<td>3 tablets</td>
<td>3 tablets</td>
<td>3 tablets</td>
<td>1.5 tablets</td>
</tr>
<tr>
<td>&gt;35</td>
<td>4 tablets</td>
<td>4 tablets</td>
<td>4 tablets</td>
<td>2 tablets</td>
</tr>
</tbody>
</table>

A 3-day course of the artemisinin component of ACTs covers two asexual cycles, ensuring that only a small fraction of parasites remain for clearance by the partner drug, thus reducing the potential development of resistance to the partner drug. Shorter courses (1–2 days) are therefore not recommended, as they are less effective, have less effect on gametocytes and provide less protection for the slowly eliminated partner drug.
ACT regimens must ensure optimal dosing to prolong their useful therapeutic life, i.e. to maximize the likelihood of rapid clinical and parasitological cure, minimize transmission and retard drug resistance.

It is essential to achieve effective antimalarial drug concentrations for a sufficient time (exposure) in all target populations in order to ensure high cure rates.

The dosage recommendations above are derived from understanding the relationship between dose and the profiles of exposure to the drug (pharmacokinetics) and the resulting therapeutic efficacy (pharmacodynamics) and safety. Some patient groups, notably younger children, are not dosed optimally with the “dosage regimens” recommended by manufacturers, which compromises efficacy and fuels resistance.

Weight-based dosage recommendations are summarized above. While age-based dosing may be more practical in children, the relation between age and weight differs in different populations. Age-based dosing can therefore result in under-dosing or over-dosing of some patients, unless large, region-specific weight-for-age databases are available to guide dosing in that region.

Factors other than dosage regimen may also affect exposure to a drug and thus treatment efficacy. The drug exposure of an individual patient also depends on factors such as the quality of the drug, the formulation, and adherence and for some drugs, co-administration with fat. Poor adherence is a major cause of treatment failure and drives the emergence and spread of drug resistance. Fixed-dose combinations encourage adherence and are preferred to loose (individual) tablets.

Prescribers should take the time necessary to explain to patients why they should complete antimalarial course.

3.3 Treatment of complicated malaria (in tertiary care hospitals)

**Treating severe malaria**

Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication.

Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of an ACT.

*Strong recommendation, high-quality evidence*

**Revised dose recommendation for parenteral artesunate in young children**

Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg body weight per dose) than larger children and adults (2.4 mg/kg body weight per dose) to ensure equivalent exposure to the drug.

*Strong recommendation based on pharmacokinetic modelling*

**Parenteral alternatives, when artesunate is not available**

If parenteral artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.

*Conditional recommendation, low-quality evidence*

Treating cases of suspected severe malaria pending transfer to a higher-level facility (pre-referral treatment):

**Pre-referral treatment options**

Where complete treatment of severe malaria is not possible but injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate...
facility for further care. Where intramuscular artesunate is not available use intramuscular artemether or, if that is not available, use intramuscular quinine. **Strong recommendation, moderate-quality evidence**

Where intramuscular injections of artesunate are not available, treat children < 6 years with a single rectal dose (10 mg/kg body weight) of artesunate, and refer immediately to an appropriate facility for further care. Do not use rectal artesunate in older children and adults. **Strong recommendation, moderate-quality evidence**

### 3.3.1 General management

Mortality from untreated severe malaria (particularly cerebral malaria) approaches 100%. With prompt, effective antimalarial treatment and supportive care, the rate falls to 10–20% overall. Within the broad definition of severe malaria some syndromes are associated with lower mortality rates (e.g. severe anemia) and others with higher mortality rates (e.g. acidosis). The risk for death increases in the presence of multiple complications.

Any patient with malaria who is unable to take oral medications reliably, shows any evidence of vital organ dysfunction or has a high parasite count is at increased risk for dying. The exact risk depends on the species of infecting malaria parasite, the number of systems affected, the degree of vital organ dysfunction, age, background immunity, pre-morbid, and concomitant diseases, and access to appropriate treatment. Tests such as a parasite count, haematocrit and blood glucose may all be performed immediately at the point of care, but the results of other laboratory measures, if any, may be available only after hours or days.

As severe malaria is potentially fatal, any patient considered to be at increased risk should be given the benefit of the highest level of care available. The attending clinician should not worry unduly about definitions: the severely ill patient requires immediate supportive care, and, if severe malaria is a possibility, parenteral antimalarial drug treatment should be started without delay.

### 3.3.2 Definitions

#### 3.3.2.1 Severe falciparum malaria

For epidemiological purposes, severe falciparum malaria is defined as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia.

- **Impaired consciousness:** A Glasgow coma score < 11 in adults or a Blantyre coma score < 3 in children
- **Prostration:** Generalized weakness so that the person is unable to sit, stand or walk without assistance
- **Multiple convulsions:** More than two episodes within 24 hours
- **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. Severe acidosis manifests clinically as respiratory distress (rapid, deep, laboured breathing).
- **Hypoglycaemia:** Blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL)
- **Severe malarial anaemia:** Haemoglobin concentration < 5 g/dL or a haematocrit of 15% in children < 12 years of age (< 7 g/dL and < 20%, respectively, in adults) with a parasite count > 10 000/μl
- **Renal impairment:** Plasma or serum creatinine > 265 μmol/L (3 mg/dL) or blood urea > 20 mmol/L
- **Jaundice:** Plasma or serum bilirubin > 50 μmol/L (3 mg/dL) with a parasite count > 100 000/μl
- **Pulmonary oedema:** Radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation
- **Significant bleeding:** Including recurrent or prolonged bleeding from the nose, gums or
venepuncture sites; haematemesis or melaena

- **Shock:** Compensated shock is defined as capillary refill > 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children or < 80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).

- **Hyperparasitaemia:** *P. falciparum* parasitaemia > 10%

### 3.3.2.2 Severe vivax and knowlesi malaria

Severe vivax malaria is defined as for falciparum malaria but with no parasite density thresholds. Severe knowlesi malaria is defined as for falciparum malaria but with two differences:

- **P. knowlesi hyperparasitaemia:** parasite density > 100 000/μL
- Jaundice and parasite density > 20 000/μL.

### 3.3.2.3 Therapeutic Objectives

The main objective of the treatment of severe malaria is to prevent the patient from dying. Secondary objectives are prevention of disabilities and prevention of recrudescent infection.

Death from severe malaria often occurs within hours of admission to a hospital or clinic, so it is essential that therapeutic concentrations of a highly effective antimalarial drug be achieved as soon as possible. Management of severe malaria comprises mainly clinical assessment of the patient, specific antimalarial treatment, additional treatment and supportive care.

### 3.3.2.4 Clinical Assessment

Severe malaria is a medical emergency. An open airway should be secured in unconscious patients and breathing and circulation assessed. The patient should be weighed or body weight estimated, so that medicines, including antimalarial drugs and fluids, can be given appropriately. An intravenous cannula should be inserted, and blood glucose (rapid test), haematocrit or haemoglobin, parasitaemia and, in adults, renal function should be measured immediately. A detailed clinical examination should be conducted, including a record of the coma score. Several coma scores have been advocated: the Glasgow coma scale is suitable for adults, and the simple Blantyre modification is easily performed in children. Unconscious patients should undergo 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 concentration should 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-matching, a full blood count, a platelet count, clotting studies, blood culture and full biochemistry (if possible). Careful attention should be paid to the patient’s fluid balance in severe malaria in order to avoid over- or under-hydration. Individual requirements vary widely and depend on fluid losses before admission.

The differential diagnosis of fever in a severely ill patient is broad. Coma and fever may be due to meningoencephalitis or malaria. Cerebral malaria is not associated with signs of meningeal irritation (neck stiffness, photophobia or Kernig’s sign), but the patient may be opisthotonic. As untreated bacterial meningitis is almost invariably fatal, a diagnostic lumbar puncture should be performed to exclude this condition. There is also considerable clinical overlap between septicaemia, pneumonia and severe malaria, and these conditions may coexist. When possible, blood should always be taken on admission for bacterial culture. In malaria-endemic areas, particularly where parasitaemia is common in young age groups, it is difficult to rule out septicaemia immediately in a shocked or severely ill obtunded child.

In all such cases, empirical parenteral broad-spectrum antibiotics should be started immediately, together with antimalarial treatment.

Severe malaria is generally caused by *P. falciparum*, but not all *P. falciparum* infection leads to severity. Severe malaria is a medical emergency. In each and every unconscious patient Airway,
Breathing and Circulation (ABC) should be secured including insertion of Foley’s catheter. ABC should be assessed at regular intervals. An airway tube (mouth gag) should be put to secure airway path & prevent the tongue falling back. Breathing should be assessed (if necessary put endotracheal tube in coma patients) by continuous oxygen inhalation. To maintain blood circulation intravenous canula should be inserted with start of 5% Dextrose or Normal saline. Immediate assessment of blood glucose (stick test), haematocrit / haemoglobin, parasitaemia, ECG, renal function tests etc. are necessary. 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.

A detailed clinical examination should be conducted with particular note of the level of consciousness according to Glasgow coma scale in adults and Blantyre coma scale in children.

The assessment of fluid balance is critical in severe malaria. Respiratory distress, in particular with acidosis, breathing in severely anaemic children, often indicates hypovolaemia and requires prompt rehydration and, where indicated, blood transfusion is needed.

Treating physicians should keep in mind that the general conditions in children may deteriorate suddenly. Mortality among pregnant women and children is particularly high.

Differential diagnosis should not be done only on clinical basis because they can also occur in other febrile diseases such as meningitis, encephalitis, septicemia, typhoid fever, leptospirosis and other viral infections that are common in malaria endemic areas. Therefore, the diagnosis must be confirmed by microscopic examination of thick and thin blood smear by an experienced laboratory technician. An inexperienced microscopist may give false results as malaria parasites are confused with artifacts.

3.3.2.5 Clinical manifestation in severe malaria

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostration</td>
<td>Inability to sit</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>Assessment by Glasgow scale in adults or Blantyre scale in children</td>
</tr>
<tr>
<td>Severe pallor</td>
<td>Conjunctiva, tongue, lips, palm pale</td>
</tr>
<tr>
<td>Anuria or oliguria</td>
<td>Urine output &lt;20 ml/hour in adults</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Yellow discoloration of sclera. It is not the indicative sign of Pf but may be the sign of vital organ dysfunction</td>
</tr>
<tr>
<td>Circulatory collapse</td>
<td>Cold extremities, weak peripheral pulse and hypotension (systolic &lt; 80 in adults, and &lt; 70 mm hg in children).</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Deep acidic breathing</td>
</tr>
<tr>
<td>Pulmonary edema or acute respiratory distress syndrome(ARDS)</td>
<td>Tachypnoea, dyspnoea and bilateral rales</td>
</tr>
<tr>
<td>Repeated or prolonged convulsions</td>
<td>Fits comprising of tonic or clonic convulsions followed by loss of consciousness (at least more than 30 mins.) or abnormal behavior</td>
</tr>
<tr>
<td>Abnormal bleeding</td>
<td>Bleeding from gums, nose, veni-puncture sites, GI tract etc</td>
</tr>
<tr>
<td>Hemoglobinuria (Black Water fever)</td>
<td>Dark red or black urine (generally in Pf, may be found in quinine therapy), Anxiety, sweating, palpitation, dilatation of pupils, breathlessness or oliguria</td>
</tr>
<tr>
<td>Hyperparasitemia</td>
<td>10% or more parasitized RBC</td>
</tr>
</tbody>
</table>

3.3.2.6 Presentation of severe malaria in adults and children

It is important to understand that there are considerable differences in the manifestations of severe malaria between adults and children (given below). In Plasmodium falciparum, severe anemia is the most common manifestation in young children while cerebral malaria is the predominant cause of death in older children and adults.
Difference between severe malaria in adults and children

<table>
<thead>
<tr>
<th>Sign or symptoms</th>
<th>Adult</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Common</td>
<td>Very common</td>
</tr>
<tr>
<td>Convulsions</td>
<td>Common</td>
<td>Very common</td>
</tr>
<tr>
<td>Pre-treatment hypoglycemia</td>
<td>Less common</td>
<td>Common</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Less common</td>
<td>Common</td>
</tr>
<tr>
<td>History of cough</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Cerebral malaria</td>
<td>Common</td>
<td>Common in older children</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Very common</td>
<td>Common</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td>Pulmonary Edema, acute respiratory distress syndrome</td>
<td>Less common</td>
<td>Rare</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>Longer (5-7 days)</td>
<td>Shorter (1-2 days)</td>
</tr>
<tr>
<td>Resolution of coma</td>
<td>Longer (2-4 days)</td>
<td>Shorter (1-2 days)</td>
</tr>
</tbody>
</table>

3.3.2.7 Specific anti-malarial treatment

- Antimalarial treatment in full doses should be given as soon as possible in severe malaria. Dosage should be calculated as mentioned in the table below.
- Therapeutic response should be monitored by regular clinical assessment of vitals (temperature, pulse, blood pressure) and conscious level (according to Glasgow and Blantyre coma scale) and fluid balance (maintaining Input and Output chart); and measurement of blood glucose, haemoglobin, electrolytes and renal function test.
- After General management, **Inj. Artesunate 2.4mg/kg** body weight intravenous should be given (time should be maintained), then the same dose intravenous after 12 hrs for the first day followed by the same dose once daily on the next coming days until the patient becomes conscious. After returning consciousness, full course of ACT (Coartem) with single dose (0.75mg/kg body weight) of tab. Primaquine should be given.
- If injection artesunate is not available then inj. Artemether 3.2mg/kg body weight i.m. stat and then 1.6mg/kg body weight i.m. once a day on the next coming days should be given until consciousness returns and then ACT full course orally with the same dose of primaquine.
- If the above medicines are contra-indicated, then inj.quinine 20mg/kg bw by **i.v infusion** as loading dose followed by 10mg/kg bw in every 8 hrs should be given until the consciousness returns. The infusion should not exceed 5mg/kg body weight per hour. After consciousness full course of quinine tab should be given for 7 days with single dose of tab. Primaquine 0.75mg/kg orally.
- After 24 h of treatment with IV artesunate, counts usually fall in a log-normal manner and patient shows signs of clinical improvement in contrast to treatment with quinine infusion which may result in parasite counts often remaining unchanged, and could even rise further, during the first 18–24 h of treatment with quinine.
- Drugs should be given orally as the patient is able to take oral medication.
- Details of treatment are given in tables below.

### Dose of Artesunate

<table>
<thead>
<tr>
<th>Groups</th>
<th>Drug</th>
<th>Dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children: &gt;1 year or &gt; 5 kg body weight &amp; adults</td>
<td>Artesunate INTRAVENOUS or Artemether INTRAMUSCULAR</td>
<td>2.4 mg/kg body weight intravenous on admission (time = 0h), then after 12 h and then once a day. 3.2 mg/kg body weight intramuscular on admission then 1.6 mg/kg body weight per day</td>
<td>The medication should be continued until patient is able to take oral medicines, then switch to oral ACT (6 doses over 3 days in 12 hrs interval)</td>
</tr>
<tr>
<td>Pregnancy in 2nd and 3rd trimester</td>
<td>Artesunate intravenous</td>
<td>2.4 mg/kg body weight intravenous on admission (time = 0h), then after 12 h and then once a day</td>
<td>If the patient is able to take oral medication then switch to oral ACT (6 doses over 3 days)</td>
</tr>
</tbody>
</table>
Artesunate 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.

### 3.3.2.8 Management of Early and Late Treatment Failure Cases

Early and late treatment failure cases should follow second line treatment as it is identified. i.e. administer standard doses of artesunate as an alternate to ACT or CQ depending on the parasite species.

### 3.3.2.9 Formulations of the medicines

**Ampoules**: intramuscular or intravenous injection containing 60 mg of anhydrous artesunaic acid with a separate ampoule of 5% sodium bicarbonate solution.

Rectal capsules containing 100 mg or 400 mg of sodium artesunate.

**Toxicity**: Although mild gastrointestinal disturbances, dizziness and asymptomatic elevated liver enzymes are reported, it is usually self-limiting. No dose modification is necessary in renal or hepatic impairment.

**Adverse Effects**

The only potentially serious adverse effect reported with this class of drugs is type 1 hypersensitivity reactions in approximately 1 in 3000 patients starting with urticaria. The drug must be stopped on appearance of urticaria and treated with 2nd.line drug.

**Oral Medication**

Once patient is able to take oral medication, treatment should be switched to oral ACT and complete course should be given.

**Treatment of children less than 1 year and pregnant women in first trimester of pregnancy with Quinine**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Drug</th>
<th>Dose</th>
<th>Remarks</th>
</tr>
</thead>
</table>
| Children: <1 year of age or <5 kg body weight | Quinine infusion   | **Loading dose:** 20 mg salt/kg body weight on admission intravenous infusion  
**Maintenance dose:** 10 mg/kg body weight in every 8 hr; infusion rate should not exceed 5 mg salt/kg body weight per hour | If the patient is able to take oral medication, then switch to oral quinine to complete total 7 days treatment. |
| Pregnancy: First trimester          | Quinine infusion   | **Loading dose:** 20 mg salt/kg body weight on admission intravenous infusion  
**Maintenance dose:** 10 mg/kg body weight in every 8 hr; infusion rate should not exceed 5 mg salt/kg body weight per hour | Patient able to take oral medication then switch to oral quinine to complete total 7 days treatment. |

**The dosage of Quinine dihydrochloride in the treatment of severe malaria**

**a. Loading dose**

Quinine dihydrochloride 20 mg, salt /kg body weight diluted in 5% dextrose or dextrose saline (10ml/kg body weight) given by intravenous infusion over a period of four hours.

**b. Maintenance dose**

Quinine dihydrochloride 10 mg salt/kg body weight diluted in 5% dextrose or dextrose saline (10ml/kg body weight) given by intravenous infusion.

In adults, the maintenance dose is infused over a period of four hours and the dose is repeated every eight hours until the patient is able to take oral medication.

In children, the maintenance dose is infused over the period of two hours and repeated every 12 hours until the patient is able to take oral medication.
c. Oral dose

When the patient is able to take oral medication then oral quinine sulphate tablets (10 mg salt/kg body weight) is given eight hourly to complete a seven day course of treatment.

Notes:
- During quinine infusion blood sugar examination should be done frequently (every 4 hourly), and sugar supplementation should be provided in order to manage severe hypoglycemia, an adverse reaction due to quinine administration.
- Intravenous quinine should be administered at recommended dosage for the first 48 hours even if acute renal failure or severe jaundice is present, but subsequent dosage should be reduced to half if IV infusion is necessary.

Table-5: Dosage of Quinine sulphate by body weight in Kg or age

<table>
<thead>
<tr>
<th>Weight (Kg)</th>
<th>Age (years)</th>
<th>mg/ (Number of tablets) 3 times a day</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 –10</td>
<td>2-11 months</td>
<td>75 mg. (1/4)</td>
</tr>
<tr>
<td>10.1-14</td>
<td>1-2</td>
<td>150 mg (1/2)</td>
</tr>
<tr>
<td>14.1-20</td>
<td>3-5</td>
<td>225 mg (3/4)</td>
</tr>
<tr>
<td>20.1-30</td>
<td>6-8</td>
<td>300 mg (1)</td>
</tr>
<tr>
<td>30.1-40</td>
<td>9-11</td>
<td>375 mg (1+1/4)</td>
</tr>
<tr>
<td>40.1-50</td>
<td>12-13</td>
<td>450 mg (1+1/2)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>14+</td>
<td>600 mg (2)</td>
</tr>
</tbody>
</table>

Quinine sulphate is available as 300 mg tablets

Continuous and uniform flow of intravenous quinine should be ensured, as a slow infusion will not achieve therapeutic concentration while too rapid infusion may induce cardiac toxicity.
- Monitor pulse, BP at least every 6 hours while the patient is on quinine therapy.
- Avoid erect posture of the acutely sick patient during quinine therapy to prevent postural hypotension.
- If the volume of overload is suspected, the volume of the infusion fluid for the administration of quinine can be reduced to half (i.e., quinine dihydrochloride 10 mg salt/5 ml/kg body weight). However, the duration of infusion is the same as above.
- If the IV infusion is not possible, quinine dihydrochloride can be given by intramuscular injection in the same dosage. The quinine should be diluted in normal saline to a concentration of 60-100mg salt/ml. The diluted quinine is divided into two equal parts and administered in two anterior thighs (one part in each thigh, not in buttock).
- Quinine dihydrochloride is acidic (pH 2) and causes pain, focal necrosis and in some cases leads to abscess formation. It is one of the common causes of sciatic nerve palsy in endemic areas. Hypotension and cardiac arrest may result from rapid intravenous injection. Intravenous quinine should be given only by infusion, never by direct injection.
- If there is no improvement of clinical conditions after 48 hours of parenteral therapy, the maintenance dose of the parenteral quinine should be reduced by one third to one half (i.e., 5 – 7 mg. quinine dihydrochloride).

3.3.2.10 Adverse effects of quinine

Quinine is supplied in the form of ampoules and tablets. Each 2 ml. ampoule contains 600 mg. quinine dihydrochloride and each tablet contains 300 mg. of quinine sulphate.

Over dosage of quinine may cause oculotoxicity, including blindness from direct retinal toxicity, and cardiotoxicity, and can be fatal. Treatment is largely supportive, with attention being given to maintenance of blood pressure, glucose and renal function, and to treating arrhythmias.

3.3.2.11 Drug interactions

There is a theoretical concern that drugs that may prolong the QT interval should not be given with quinine, although whether or not quinine increases the risk of iatrogenic ventricular tachyarrhythmia has not been established. Antiarrhythmics, such as Flecainide and Amiodarone,
should probably 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. Quinine increases the plasma concentration of Digoxin.

3.3.2.12 Use of Other Drugs
If fever is higher and not under control, then tablet paracetamol can be used only to lower the fever. But the use of following drugs in the management of severe malaria is of no beneficial effect and may indeed be harmful and should be avoided:

- Corticosteroids
- Other anti-inflammatory agents
- Agents given for cerebral edema such as urea, mannitol.
- Low molecular weight dextran
- Epinephrine
- Heparin.

3.3.2.13 Malaria in pregnancy
Pregnant women are more likely to develop severe malaria than other adults, often complicated by pulmonary edema and hypoglycaemia. Maternal mortality is approximately 50%, which is higher than in non-pregnant adults. Fetal death and premature labor are common. The role of early Caesarean section for the viable live fetus is unproven, but is recommended by many authorities. Obstetric advice should be sought at an early stage, the pediatricians alerted, and blood glucose checked frequently. Hypoglycaemia should be expected and is often recurrent if the patient is receiving quinine. Antimalarials should be given in full doses.

Severe malaria may also present immediately following delivery. Postpartum bacterial infection is a common complication in these cases. Falciparum malaria has also been associated with severe mid-trimester hemolytic anaemia. This often requires blood transfusion, in addition to anti-malarial treatment and folate supplementation. Parenteral antimalarials should be given to pregnant women with severe malaria in full doses without delay. Artesunate is preferred over quinine in the second and third trimesters because quinine is associated with recurrent hypo-glycaemia. Recent evidence shows that in non pregnant adults with severe malaria in areas of low transmission, artesunate was superior to quinine, reducing mortality by 35% compared to quinine, which makes artesunate the preferred option in the second and third trimesters. In the first trimester, the risk of hypoglycaemia associated with quinine is lower, and the unsafety of artemisinin derivatives is greater. So, Quinine is the recommended drug in first trimester of pregnancy. Treatment should start as soon as possible.

3.3.2.13.1 Treatment of malaria in pregnancy
- Malaria in pregnant women is often more severe leading to anemia and increased risk of abortions/ new born deaths / low birth weight babies.
- Inj. artemesunate is contraindicated in 1st trimester, particularly in the case where both mother and child could be saved. However, one could administer artesunate to save the patient first.
- Approved doses of Quinine (as in table-5) may be given in any trimester of pregnancy for curative treatment of malaria.
- Primaquine should not be given during pregnancy. treating physician should be careful that pregnant women are susceptible to:
  - Severe anemia
  - Hypoglycemia
  - Pulmonary edema and ARDS ( Acute Respiratory Distress Syndrome )
  - Chloroquine and Quinine are the drugs of choice for the treatment ( as per above mentioned tables...........) and not contraindicated in therapeutic doses during pregnancy.

3.3.2.14 Malaria in Children
Generally children tolerate anti-malarial drugs well, although they are more likely:

- to vomit,
to become vulnerable to hypoglycemia,
to have generalized seizures,
relatively resistant to haemodynamic or nephrotoxic abuses

Table- 6: Treatment of Malaria in Children

<table>
<thead>
<tr>
<th>P. vivax- confirmed</th>
<th>Chloroquine over three days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated P. falciparum - confirmed</td>
<td>• Children more than 1 year of age or more than 5 kg, body weight: Coartem.</td>
</tr>
<tr>
<td></td>
<td>• Children less than 1 year of age or less than 5 kg: oral Quinine sulfate 10mg/kg body wt</td>
</tr>
<tr>
<td>Severe malaria- P. falciparum</td>
<td>• Children less than 1 year of age or less than 5 kg body weight: Quinine infusion</td>
</tr>
<tr>
<td></td>
<td>• Children more than 1 year of age or more than 5 kg, bodyweight: parenteral artesunate</td>
</tr>
</tbody>
</table>

Modified Glasgow coma scale for adults

<table>
<thead>
<tr>
<th>Eye opening</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneously</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>To speech</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>To pain</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best verbal response (non-intubated)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oriented and talks</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Disoriented and talks</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Incomprehensible sounds</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Seems able to talk</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Questionable ability to talk</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Generally unresponsive</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best motor response</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal commands</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Localizes to pain</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Withdraws to pain</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Decorticate</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Decerebrate</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Total score

Note: < 9 indicates unarousable coma.

Blantyre coma scale for children

<table>
<thead>
<tr>
<th>Eye movements</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Directed (e.g. towards mother’s face)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Not directed</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Verbal response</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate cry</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Inappropriate cry or moan</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best motor response</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Localizes painful stimuli</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Withdraws limb from pain</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Absent of response or nonspecific</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Total score

Note: <2 score indicates unarousable coma.
These scales should be repeatedly used to assess the improvement or deterioration of the patient’s condition.
## Diagnosis and Management of Malaria

(A brief outline for the Health facilities)

<table>
<thead>
<tr>
<th>Uncomplicated falciparum malaria: Fever or history of fever with high suspicion of malaria and positive RDT or blood slide examination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment:</strong> Tablet ACT (Artemether-lumefantrine) 20mg/120mg (6 doses over 3 days) with single dose tablet primaquine (0.75mg/Kg) on day 0.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uncomplicated Vivax malaria: Fever or history of fever with high suspicion of malaria and positive RDT or blood slide examination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment:</strong> Tablet Chloroquine over 3 days (600mg for the adult) and tablet primaquine 0.25mg/kg daily for 14 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe malaria: Fever or history of fever with high suspicion of malaria and positive RDT or blood slide examination with unconsciousness and/or confused and/or convulsion and/or prostration and/or jaundice and/or severe anaemia and/or acidosis and/or acidosis and/or ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment:</strong> Injection artesunate (2.4mg per kg body weight). First dose instantly and then second dose at 12 hours. Subsequent dose once daily (total dose depends on the condition of the patient’s improvement). Injection artesunate will be followed by tablet artemether-lumefantrine when patient can take orally (with single dose tablet primaquine).</td>
</tr>
</tbody>
</table>

### Preparation for dilution of injection artesunate

- Injection artesunate 60mg/vial should be mixed with 1ml of 5% sodium bicarbonate solution and shaken for 2-3 minutes for better dissolution.

- For I.V.: 5ml of 5% glucose or normal saline should be added to make the concentration 10mg/ml for slow intravenous infusion.

- For I.M.: 2ml of 5% glucose or normal saline should be added to make the concentration of artesunate 20mg/ml for intramuscular injection.

- The total dose of intravenous infusion should be given within 3-4ml/min.
4.1 Algorithm for Diagnosis & Treatment of Malaria

Suspected Malaria Case

Microscopy/RDT

Positive
- \( P\) vivax, \( P\) ovale, \( P\) malariae, \( P\) knowlesi
  - Chloroquine + Primaquine*

Severe complicated Malaria.
Prostration – severe weakness (inability to sit up), Impaired consciousness - Confusion, coma, Continuous vomiting, Respiratory distress, Pallor, unable to walk, collapse, Convulsions, Jaundice
  - Treat as mentioned in section 3.3 with optimum care or Refer to tertiary care centers

Negative
- \( P\) falciparum
  - Treat with ACT for 3 days + single dose PQ as per body wt.

Strong Suspicion of Malaria

Un-complicated Malaria

Look for other febrile illness (JE, Dengue, Meningitis, leptospirosis, etc)
  - Treat as suspected malaria, after excluding all other possible causes

*Primaquine is a hypnozoiticidal antimalarial used in radical treatment of \( P\) vivax malaria and should only be used in G6PD normal individuals.
Suspect Severe Malaria if the patient present with one or more of the following clinical feature

Prostration, impaired consciousness (cerebral malaria), Respiratory distress (acidotic breathing), Multiple convulsions, Circulatory collapse, Pulmonary oedema, Abnormal bleeding, Jaundice, Haemoglobinuria

Start General management as required with:
- Proper Nursing
- Diazepam
- Dextrose
- Cardiac bed + O₂
- Blood transfusion
- Plasma expanders & life-saving drugs
- Management of ARF
- Fresh blood or FFP

Treat SEVERE MALARIA with IV Quinine or IM Artemether

Ask for relevant investigation
- Blood film
- Random blood Sugar
- TWBC
- Hb%, PCV
- Lumber puncture
- Chest X-Ray
- Blood Urea & electrolytes
- PT – PTT platelets count
- LFTs (serum bilirubin
- FDPs or DIMER

Think & exclude possible other causes, history, examination, investigations (TWBC, LP, ...)

Reduce in temperature
Reduce in parasite count
Improving comma scale
Patient ability to: drink, eat, sit, stand, walk...
Not Improved

Assess possible sequelae of disease & treatment
- Perform neurological examination
- Assess vision & hearing
- Repeat Haematocrit on Day 7, Day 14 & 1 month later
- Repeat BFFM on Day 7, Day 14 & 1 month later

Improved
4.2 Malaria Chemoprophylaxis

As of now, there is no malaria transmission in urban areas in Nepal.

People from non-endemic area travelling to endemic area may seek prophylactic course of anti-malarial based on local transmission history and antimalarial resistance status.

For the travelers from non-endemic areas, travelling to malaria endemic areas of Nepal (based on the map in page 1-introduction), Chloroquine 1 tab every day for 7 days, may be taken as a prophylactic dose.

Prophylaxis

Prophylaxis of malaria is used for those who are travelling to malaria risk areas. There is no vaccine against the disease.

For the travelers going abroad on different mission, one should follow WHO guideline for travelers through the web link: http://www.who.int/ith/en/

4.3 G6PD Deficiency Testing

Plasmodium vivax is one of the five species of Plasmodium that can cause malaria in human beings. Although *P. falciparum* is responsible for the majority of cases and deaths from malaria, *P. vivax* has a wider geographical range and is responsible for almost half the cases of malaria outside Africa. Although duffy negative individuals are resistant to *P. vivax* infection, *P. vivax* has been reported from many African countries, albeit at low frequency.

Note: Implement compulsory G6PD testing for confirmed *P. vivax* malaria cases and effective roll over of the radical cure using 3 days CQ+14 days PQ.

In May 2015, the World Health Assembly endorsed the most ambitious targets for malaria control since the eradication era – namely to eliminate malaria from 35 countries and reduce case incidence and mortality rates by 90% globally. *P. vivax* presents a major challenge to achieving these targets; in 2013, it was responsible for 16 million cases globally. It predominates in countries that are prime candidates for elimination, accounting for more than 70% of cases in countries with fewer than 5000 cases of malaria each year.

Not only does *P. vivax* present a barrier to elimination, it can also cause severe disease; severe cases and deaths due to *P. vivax* malaria have been reported from all endemic regions. *P. vivax* survives in cooler climates. It is less responsive to conventional methods of vector control. It is more difficult to detect using current diagnostic techniques. A single infection can give rise to multiple episodes of malaria. Treatment of liver-stage parasite requires a 14-day course of primaquine.

Patients who have a severe deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD) are susceptible to potentially life-threatening destruction of blood cells while taking primaquine. Persons with G6PD deficiency condition do not display any signs of the disease until their red blood cells are exposed to certain chemicals in food or medicine, or to stress.

Symptoms common in men and may include dark urine, enlarged spleen, fatigue, pallor, rapid heart rate, shortness of breath, yellow skin color (jaundice).

Current tests for G6PD deficiency are complex and relatively expensive; thus, many clinicians are reluctant to prescribe primaquine to patients whose G6PD status is unknown. In addition, primaquine cannot be used in pregnant women and infants because of the risk of G6PD deficiency. In the absence of treatment, these populations are prone to multiple relapses.

Guidelines for radical cure over time

» Implement compulsory G6PD testing for confirmed *P. vivax* malaria cases and effective roll over of the radical cure using 3 days CQ+14 days PQ.
In areas where G6PDd is not well understood and test kits are not available, consider assessing the risk/benefit with close medical supervision in weekly regimen. You may radical cure (3 days CQ + 14 days PQ) of the P vivax cases with close monitoring on clinical signs and symptoms (brown urine, gum bleeding, anaemia, etc.), should be started.

In patients known to be G6PD deficient, primaquine may be considered at a dose of 0.75 mg base/kg body weight once a week for 8 weeks. The decision to give or withhold primaquine should depend on the possibility of giving the treatment under close medical supervision, with ready access to health facilities with blood transfusion services.

In order to reduce the transmissibility of treated P falciparum Malaria infections in low transmission areas, give a single dose of 2.5 mg/kg body weight of primaquine with ACT to patients with P falciparum malaria (except pregnant women, infants aged <6 months and women breastfeeding infants aged <6 months) to reduce transmission.

4.4 Recording, Reporting and Surveillance of Malaria

All the health facilities (sub-health post, Health Post, Primary health care centers, district hospitals, District Public health office, Zonal hospitals and tertiary care hospitals) enrolling suspected malaria cases for diagnosis and treatment of malaria needs to record the details of each case in online/paper based malaria case register (malaria case investigation form and national malaria register) and report on a daily/weekly and monthly basis to the national malaria program, at Epidemiology Disease Control Division, based on the requirement of EWARS/IDSRA/MDIS/HMS. Respective district focal points are responsible for validation of the reported cases on a monthly basis and cross reporting to NMCP/EDCD.

Every case needs to be recorded in case investigation form (CIF), so that it could be further analyzed for epidemiological purposes.

Briefly, the CIF contains patient’s case history including demography, diagnostic test results, antimalarial received, previous clinical episodes, travel history for tracking its classification and source of infection, and follow up for understanding the prognosis/treatment outcome.

The detail forms are available in the annex-....
Appendix 1: Mixed malaria infections, and treatment

Mixed malaria is a condition which occurs when there are more than one species involved in causing infection. It has been reported that in South East Asia alone despite having relatively low, seasonal and fewer mosquito bites, more than 30 percent of the Plasmodium falciparum infections are succeeded almost immediately by Plasmodium Vivax infections. In countries like Nepal where there is a presence of both falciparum and vivax malaria mixed infections cannot be neglected as there have been reported incidences of such infections occurring. Furthermore studies have shown that out of one third falciparum cases treated often after a time interval experience a vivax infection. In highly endemic / high transmission areas where frequent infections occur from repeated bites, it is not uncommon that these infections accumulate and henceforth present with multiple genotypes and species. The challenge that lies with these mixed infections is that it cannot be detected with both RDT and microscopy. A sensitive PCR study is the only effective way of diagnosing mixed infections. PCR studies that have been conducted in Asia have often shown mixed infection rates exceeding 20%. Although some epidemiological studies argue that the involvement of vivax offers protection and fatality against mixed infections. However recent studies have proved that vivax infections can also lead to severe infections therefore the likelihood of a mixed infection leading to severe malaria still persists. Therefore any mixed infection that is undiagnosed and untreated might end up being severe and often lead to death. These mixed infections present similar signs and symptoms as that of the severe malaria. The treatment protocol for treating mixed infections is similar to that of falciparum infections plus vivax infections.

Table-4: The dosages of AL (Coartem ) and a single dose of primaquine by kg body weight

<table>
<thead>
<tr>
<th>Body weight (kg.)</th>
<th>Day-1</th>
<th>Day-2</th>
<th>Day-3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACT</td>
<td>ACT</td>
<td>ACT</td>
</tr>
<tr>
<td></td>
<td>First dose (0 hour)</td>
<td>12 hours later</td>
<td>Twice daily -12 hours apart</td>
</tr>
<tr>
<td>5-14</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
</tr>
<tr>
<td>15-24</td>
<td>2 tablets</td>
<td>2 tablets</td>
<td>2 tablets</td>
</tr>
<tr>
<td>25-34</td>
<td>3 tablets</td>
<td>3 tablets</td>
<td>3 tablets</td>
</tr>
<tr>
<td>&gt;35</td>
<td>4 tablets</td>
<td>4 tablets</td>
<td>4 tablets</td>
</tr>
</tbody>
</table>
### Appendix 2: Participants of consultative meeting for finalization of the NMTP-2015

<table>
<thead>
<tr>
<th>S.N.</th>
<th>List of participants</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dr. Senendra Raj Upreti</td>
<td>DoHS</td>
</tr>
<tr>
<td>2</td>
<td>Dr. Babu Ram Marasini</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>3</td>
<td>Dr. GD Thakur</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>4</td>
<td>Dr. Basu Dev Pandey</td>
<td>DoHs</td>
</tr>
<tr>
<td>5</td>
<td>Prof. Dr Kedar P. Baral</td>
<td>PAHS</td>
</tr>
<tr>
<td>6</td>
<td>Prof. Dr. Balman Singh Karki</td>
<td>KIST</td>
</tr>
<tr>
<td>7</td>
<td>Dr. Rajan Poudel</td>
<td>Civil Service Hospital</td>
</tr>
<tr>
<td>8</td>
<td>Dr. Suman Baral</td>
<td>IOM</td>
</tr>
<tr>
<td>9</td>
<td>Dr. Sanjit Karki</td>
<td>PAHS</td>
</tr>
<tr>
<td>10</td>
<td>Dr. Achyut Bikram Hamal</td>
<td>Police Hospital</td>
</tr>
<tr>
<td>11</td>
<td>Dr. Bishow Raj Khanal</td>
<td>VBDRTC</td>
</tr>
<tr>
<td>12</td>
<td>Dr. Yuva Raj Pokherel</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>13</td>
<td>Dr. Ram Raj Panthee</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>14</td>
<td>Dr. Guna Nidhi Sharma</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>15</td>
<td>Dr. Prakash Ghimire</td>
<td>NPO-Malaria, WHO-Nepal</td>
</tr>
<tr>
<td>16</td>
<td>Dr. Shubhesh Raj Kayastha</td>
<td>Seti Zonal Hospital</td>
</tr>
<tr>
<td>17</td>
<td>Dr. Murari Pd. Upadhyay</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>18</td>
<td>Prof. Dr. Prahlad Karki</td>
<td>BPKIHS</td>
</tr>
<tr>
<td>19</td>
<td>Dr. Megha Raj Banjara</td>
<td>TU</td>
</tr>
<tr>
<td>20</td>
<td>Dr. Geeta Shakya</td>
<td>NPHL</td>
</tr>
<tr>
<td>21</td>
<td>Prof. Chitra Kumar Gurung</td>
<td>TU</td>
</tr>
<tr>
<td>22</td>
<td>Dr. Ram K. Baral</td>
<td>BPKIHS</td>
</tr>
<tr>
<td>23</td>
<td>Mr Nabaraj Adhikari</td>
<td>KCMS</td>
</tr>
<tr>
<td>24</td>
<td>Mr. Shishir Kumar Pant</td>
<td>VBDRTC</td>
</tr>
<tr>
<td>25</td>
<td>Mr. Lalan Pd. Shah</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>26</td>
<td>Mr. Chuda Mani Bhandari</td>
<td>CHD/DoHS</td>
</tr>
<tr>
<td>27</td>
<td>Mr. ShambhuNathJha</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>28</td>
<td>BNJnawali</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>29</td>
<td>Mr. Ujjawal Gautam</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>30</td>
<td>Mr. Parashu Ram Shrestha</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>31</td>
<td>Mr. Baikuntha Gautam</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>32</td>
<td>Mr. Sunil Aryal</td>
<td>WHO</td>
</tr>
<tr>
<td>33</td>
<td>Mr. Tulasi Ram Adhikari</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>34</td>
<td>Mr. Uttam Raj Pyakurel</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>35</td>
<td>Mr. Dabal Bdr Bc</td>
<td>EDCD, Teku</td>
</tr>
<tr>
<td>36</td>
<td>Mr. Sandeep Gauro</td>
<td>EDCD, Teku</td>
</tr>
</tbody>
</table>
BIBLIOGRAPHY


WHO Global Malaria Programme, WHO Department of Reproductive Health and Research


World Health Organization, Global Malaria Programme (2014). Emergence and spread of artemisinin resistance calls for intensified efforts to withdraw oral artemisinin-based monotherapy from the market.


