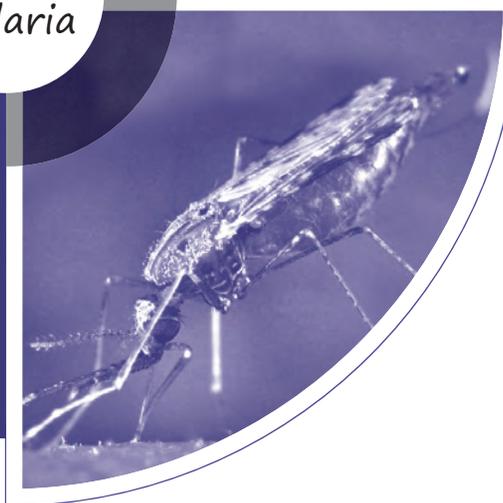
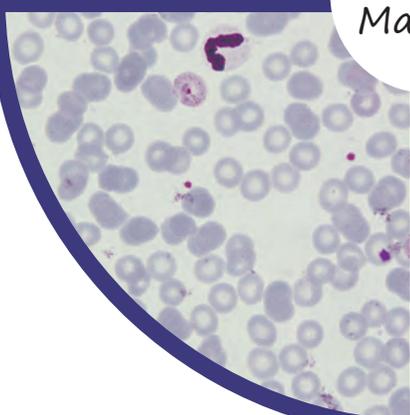


NATIONAL MALARIA TREATMENT PROTOCOL 2019



ZERO
Malaria



Epidemiology and Disease Control Division
Department of Health Services
Teku, Kathmandu

NATIONAL MALARIA TREATMENT PROTOCOL 2019



Epidemiology and Disease Control Division
Department of Health Services

Teku, Kathmandu

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FOREWORD



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Foreword

There had been significant development in the past years in management of malaria. New effective rapid diagnostic tests, upgraded laboratory services, trained human resources, improved surveillance and effective drugs at health care facilities in the country has ensured early and reliable diagnosis of malaria in these areas. This updated National Malaria Treatment Protocol 2019 has simplified the treatment algorithms making it more user friendly to the health-workers in the field who are the front runner for malaria elimination in the country.

The national strategy aims to eliminate the disease by 2025, it is imperative that each case of malaria be identified and treated immediately based on the treatment protocol to prevent further transmission. I am delighted to present this revised National Malaria Treatment Protocol 2019 prepared by the team of experts of Epidemiology & Disease Control Division, Dept. of Health Services, World Health Organization, Save the Children, USAID/PMI and in consultation with national and international experts in the field.

I would like to sincerely thank all those who contributed in producing this excellent national document which can help standardize management of malaria cases in Nepal which is crucial for elimination of malaria from the country.

Dr Sushil Nath Pyakuryal
Director General
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FOREWORD



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Foreword

It gives me immense pleasure to write a few words on the publication of this important standard treatment protocol for malaria.

Malaria continues to be a priority public health problem in Nepal. It affects mainly poor people living in rural areas with limited access to health care services, people living in forest fringe areas and among the migrants returning from high risk malaria areas. With strengthened surveillance, we have been able to detect malaria in the hilly areas of Nepal like Mugu and Bajura, where malaria was not reported before.

Despite all the adversities, with the continued efforts of many involved in the control and prevention of malaria, now the era of malaria intervention has moved on with a target to achieve zero indigenous malaria cases by 2022 and eliminate malaria by 2025. So, there is an imperative need to further ensure that all the suspected cases are tested by quality assured RDT or microscopy and treated immediately. This standard protocol will aide all the health care professionals working in public and private sectors in early diagnosis and management of malaria and rational use of antimalarial drugs. I hope that this National Malaria Treatment Protocol 2019 will be widely used as the guiding document for management of malaria cases in Nepal.

I would like to thank all the participants who have contributed their invaluable suggestions and comments during the revision of this document taking into account all the evidence-based studies and recent developments. I would also like to thank the core team of experts who have put in a tireless effort in ensuring that this protocol encompasses treatment regimen for all of malaria infections that are prevalent in Nepal and ensuring that WHO global recommendations are contextualized to Nepal.

I would like to especially thank the World Health Organization for providing technical support for developing this important standard Malaria Treatment Protocol 2019.

Dr. Bibek Kumar Lal

Director

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ABBREVIATIONS AND ACRONYMS

ACT	Artemisinin-based combination therapy
AL	Artemether – lumefentrine
CQ	Chloroquine
DHA/PPQ	Dihydroartemisinin/piperaquine
FCHV	Female community health volunteer
G6PD	Glucose-6-phosphate dehydrogenase
PCR	Polymerase chain reaction
PfHRP2	Plasmodium falciparum histidine-rich protein-2
RDT	Rapid diagnostic test
SOP	Standard operating procedure

GLOSSARY

Artemisinin-based combination therapy: A combination of an artemisinin derivative with a longer-acting antimalarial drug that has a different mode of action (AL and DHA/PPQ are ACTs being used in the National Malaria Treatment Protocol 2019).

Case management: Diagnosis, treatment, clinical care, counselling and follow-up of symptomatic malaria infections.

Cerebral malaria: Severe *P. falciparum* malaria with impaired consciousness (Glasgow coma scale in adults < 11; Blantyre coma scale in children < 3) persisting for > 1 hour after a seizure.

Chemoprophylaxis: Administration of a medicine, at predefined intervals, to prevent either the development of an infection or progression of an infection to manifest disease.

Combination therapy: A combination of two or more classes of antimalarial medicine with unrelated mechanism of action.

Cure: Elimination of the symptoms and asexual blood stages of the malaria parasite that caused the patient or caregiver to seek treatment.

Diagnosis: The process of establishing the cause of an illness, including both clinical assessment and diagnostic testing.

Molecular diagnosis: Use of nucleic acid amplification-based tests to detect the presence of malaria parasites.

Parasitological diagnosis: Diagnosis of malaria by detection of malaria parasites or Plasmodium-specific antigens or genes in the blood of an infected individual.

Radical cure: Elimination of both blood-stage and latent liver infection in cases of *P. vivax* and *P. ovale* infection, thereby preventing relapses.

Malaria case: Occurrence of malaria infection in a person in whom the presence

of malaria parasites in the blood has been confirmed by a diagnostic test (quality assured RDT or microscopy).

Presumed malaria case: Case suspected of being malaria that is not confirmed by a diagnostic test.

Suspected malaria: A suspected malaria case is an individual with an illness suspected by a health worker to be due to malaria, generally based on the presence of fever with or without other symptoms.

Gametocytes: Sexual stages of malaria parasites present in the host red blood cells that can potentially infect anopheline mosquitoes when ingested during a blood meal.

Hypnozoite: Persistent liver stage of *P. vivax* and *P. ovale* malaria that remains dormant in host hepatocytes for variable periods, from 3 weeks to 1 year (exceptionally even longer), before activation and development into a pre-erythrocytic schizont, which then causes a blood-stage infection (relapse).

Mixed Infection: Malaria infection with more than one species of *Plasmodium*.

Sub-microscopic infection: Low-density blood-stage malaria infections that are not detected by conventional microscopy.

Malaria elimination: Interruption of local transmission (reduction to zero incidence of indigenous cases) of a specified malaria parasite in a defined geographical area as a result of deliberate activities. Continued measures to prevent re-establishment of transmission are required.

Plasmodium: A genus of protozoan vertebrate blood parasites that includes the causal agents of malaria. *Plasmodium falciparum*, *P. malariae*, *P. ovale* and *P. vivax* cause malaria in humans. Human infections with the monkey malaria parasite, *P. knowlesi* have also been reported from forested regions of South-East Asia.

Rapid diagnostic test (RDT): Immunochromatographic lateral flow device (stick, cassette or card test) for rapid detection of malaria parasite antigens.

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

Recrudescence: Malaria case attributed to the recurrence of asexual parasitemia after antimalarial treatment, due to incomplete clearance of asexual parasitemia of the same genotype(s) that caused the original illness. A recrudescence case must be distinguished from reinfection and relapse, in case of *P. vivax* and *P. ovale*.

Reinfection: A new infection that follows a primary infection; can be distinguished from recrudescence by the parasite genotype, which is often (but not always) different from that which caused the initial infection.

Relapse: Malaria case attributed to activation of hypnozoites of *P. vivax* or *P. ovale* acquired previously.

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

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

Treatment failure: Inability to clear malarial parasitaemia or prevent recrudescence after administration of an antimalarial medicine, regardless of whether clinical symptoms are resolved.

First-line treatment: Treatment recommended in national treatment guidelines as the medicine of choice for treating malaria.

Second-line treatment: Treatment used after failure of first-line treatment or in patients who are allergic to or unable to tolerate the first-line treatment.

Presumptive treatment: Administration of an antimalaria drug or drugs to people with suspected malaria without testing or before the results of blood examinations are available.

Radical treatment: Treatment to achieve complete cure. This applies only to *vivax* and *ovale* infections and consists of the use of medicines that destroy both blood and liver stages of the parasite.

EXECUTIVE SUMMARY

Malaria case management, consisting of early diagnosis and prompt effective treatment, remains a vital component of malaria control and elimination strategies. This National Malaria Treatment Protocol 2019 contains updated recommendations based on national adaptation of global WHO recommendations to provide guidance to health workers to ensure that optimal care is provided for malaria patients and contribute to achieving the goal of malaria elimination in Nepal by 2025.

Recommendations

Diagnosis of malaria

- Always obtain a travel history.
- All cases of suspected malaria should have a parasitological test (microscopy or RDT) to confirm the diagnosis. RDTs should be used when microscopy is not feasible.
- Use of both microscopy and RDTs should be supported by a quality assurance programme.

Treating uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria

- ✓ *Treat with chloroquine (3 days) and primaquine (14 days) for P. vivax and P. ovale.*
- ✓ *Treat with chloroquine (3 days) for P. malariae or P. knowlesi.*

Blood stage infection

- 1st line – chloroquine
- 2nd line (chloroquine-resistance infection) – dihydroartemisinin + piperazine

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

- 14-day course of primaquine - (except pregnant women, infants aged < 6 months, and women breastfeeding infants aged < 6 months).
- G6PD testing is encouraged prior to 14 days PQ therapy but in case testing is not available closely supervised 14 days PQ therapy will be given.
- Counselling should be done to patient and followed up on days 3-7-14 days to monitor for adverse effects and compliance with primaquine.

Pregnant or breastfeeding women

- Treat with chloroquine for 3 days. Provide weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, treat with primaquine for 14 days to prevent future relapse.

Treating uncomplicated *P. falciparum* malaria

✓ *Treat with AL (3 Days) and Primaquine on Day 1*

Treatment of uncomplicated *P. falciparum* malaria

- 1st line - artemether + lumefantrine (AL)
- 2nd line - dihydroartemisinin + piperazine (DHA/PPQ)

Reducing the transmissibility of treated *P. falciparum* infections.

- Primaquine single dose of 0.25 mg/kg bw – (except in pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months). Testing for glucose-6-phosphate dehydrogenase (G6PD) is not required.

Pregnant or breastfeeding women

- Treat pregnant women all trimesters and lactating mothers with the first line ACT (AL) as in non-pregnant women. Provide primaquine single dose of 0.25 mg/kg bw after delivery and breastfeeding completed.

Treating severe malaria***Treatment of severe malaria***

- Intravenous or intramuscular artesunate for at least 24 hr. Once a patient has received at least 24 hr of parenteral therapy and can tolerate oral therapy, complete treatment with full course artemether + lumefantrine with single dose primaquine for falciparum and primaquine for radical cure of vivax (14 days).
- Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose).

Pre-referral treatment

- A single intramuscular dose of artesunate and refer to an appropriate facility for further care.

Chemoprophylaxis

- Malaria prophylaxis is not necessary for in-country travel within Nepal.
- Prophylactic medication for malaria is recommended for Nepalese traveling to countries with areas of malaria transmission.
- The medicine of choice depends on the parasite species and resistance profile in the destination country.

1. INTRODUCTION

1.1 Epidemiology

In 1958, the malaria eradication programme was launched in Nepal, as the first national public health programme in the country with the objective of eradicating malaria. Nepal has remarkable achievement in surpassing the targets set by the Millennium Development Goals. Malaria remains a public health priority in Nepal and the country is set for malaria elimination by 2025. The malaria disease distribution has decreased significantly, 1,187 total malaria cases recorded in 2017/18, and distribution is more towards the far-west region of the country as seen in the recent malaria microstratification 2018 (Figure 1).

Large number of Nepalese goes outside the country for work, mainly they visit high malaria endemic States of India like Assam, Gujarat, Maharashtra and West Bengal. Imported malaria through these returning labor forces contributes to the change in epidemiological situation often contributing to the introduced cases which might lead to outbreak if not detected on time. The imported cases contributes to around 50 percent of the total malaria burden. Malaria cases occur throughout the year. Reported incidence is lowest in December-February, rises markedly following the arrival of the monsoon in May and most cases are reported between June and September.

Plasmodium vivax is the predominant species in Nepal and *P. falciparum* is the other important species. The relative proportion of *P. vivax* cases have been increasing from 71 % in 2010 to 95 % in 2018, the proportion of *P. falciparum* is correspondingly on the decline from around 29 % in 2010 to 5 % in 2018. *P. malariae* has not been detected for long time (more than 20 years,) while *P. ovale* has been reported from the private sector among patients returning from Africa.

The country is stratified into 4 risk areas based on the micro-stratification report 2017-18: no risk; low risk; moderate risk and high risk areas. The high and moderate risk areas consist of foothills with river belts, forest fringe areas in terai, hill river valleys, and inner-terai areas, while the low risk areas lie in plain cultivated outer terai mountain, and valleys in the mountains.

Micro-stratification 2017-18

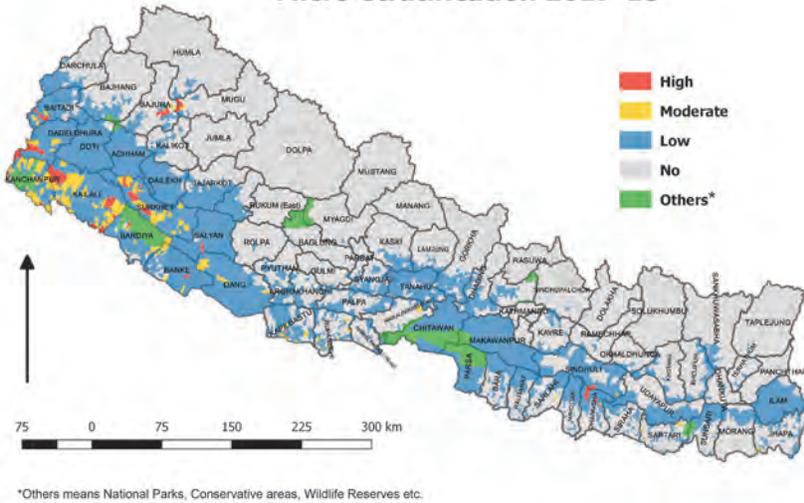


Fig 1: Malaria risk microstratification

1.2 Health care levels and roles in malaria management

Nepal has a comprehensive health infrastructure stretching to Ward level. The four-tier health services delivery system follows a decentralized administrative approach:

- Hospitals
- Primary health care centers (PHC)
- Health posts (HP), and
- Community-based services.

Malaria case management is provided at all the levels except at the community level. The hospitals and PHC provides treatment services for uncomplicated and severe malaria, while the health post provides services for uncomplicated malaria and pre-referral treatment to severe malaria patients before referral to either a PHC or hospital. Community-based services for malaria are currently restricted to referral by Female Community Health Volunteers (FCHVs) based on clinical symptoms and a history of travel to malaria risk area.

1.3 Objectives and core principles of the protocol

Effective malaria case management and surveillance remains part of the major strategy to achieve the elimination goals of the country. The objectives of this guidelines are to provide health workers in Nepal with practical evidence-based recommendations for treatment of malaria.

The recommendations in the protocol is based on the following core principles:

1. Early diagnosis and prompt, 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. All efforts to 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, antimalarial medicines should be administered only to patients who truly have malaria confirmed by quality assured RDT or microscopy. Universal accesses to parasitological diagnosis in all settings should be assured. Adherence to a full treatment course must be promoted.

3. Combination therapy

To help protect current and future antimalarial medicines and facilitate malaria case management and elimination all episodes of malaria should be treated with effective combination therapies.

4. Appropriate dosing

The quality of antimalarial drugs must be ensured, and antimalarial drugs must be given at optimal dosages to maximize the likelihood of rapid clinical and parasitological cure and minimize transmission from the treated infection. The NMTP provides an age/weight band for selecting of drug dosage for practicality when the weighing the patient is not possible. Whenever undernutrition or overweight is suspected, appropriate dose should be given based on patient's weight.

2. DIAGNOSIS OF MALARIA

Recommendations

- Always obtain a travel history.
- All cases of suspected malaria should have a parasitological test (quality assured microscopy or RDT) to confirm the diagnosis.
- PCR technology is not recommended for routine diagnosis of malaria.

2.1 Suspected malaria

The signs and symptoms of malaria are non-specific. Malaria is suspected clinically on the basis of fever or a history of fever. There is no combination of signs or symptoms that reliably distinguishes malaria from other causes of fever. Diagnosis based only on clinical features results in overtreatment. Other possible causes of fever must always be carefully considered. All suspected malaria cases should be confirmed parasitologically and treated with rational use of anti-malarial medicines.

A suspected case of malaria is one in which an individual has an illness suspected by a health worker of being due to malaria, generally based on the presence of fever.

A complete history should also include:

- General information such as age, place of residence.
- Ensure to obtain a history of recent travel within or outside the country.
- Enquiry about the following symptoms:
 - Fever
 - Chills (feeling cold) and rigors (shaking of the body)
 - Headache
 - Joint pain/weakness or tiredness

2.2 Parasitological diagnosis

All suspected malaria cases should have a parasitological test either by quality assured microscopy or RDT to confirm the diagnosis. Quality assured microscopy should be used where available. Only one or the

other should be done, as the sensitivity and specificity of quality assured RDT is similar to microscopy. However, in some specific situations (e.g. monitoring treatment failure or to determine parasite density) microscopy is preferred to RDT. The quality assurance and control of laboratory diagnosis of malaria will be guided by National malaria laboratory plan.

Refer to Annex 4: Species identification of malaria parasites in Giemsa-stained thick blood stained and Annex 5: RDT Result.

2.2.1 Diagnosis of malaria at health posts and primary health centers (PHC)

- The health workers should evaluate the patient clinically with signs and symptoms and history of travel to malaria endemic areas.
- All suspected malaria cases should be tested by RDT for diagnosis. All health post and PHCs should use RDTs for diagnosis of a malaria case. Health posts and PHCs with quality assured malaria microscopy center and human resource should be encouraged to use microscopy to test suspected malaria.
- If features of severe malaria are present, give pre-referral treatment and refer to the hospital or higher centers for further treatment.

2.2.2 Diagnosis of malaria at district hospitals and higher centers

- Microscopy is the main diagnostic tool in the Hospitals. However, RDTs should be made available for use outside of official laboratory operating hours and during excess workload.
- Although detection of parasite DNA based on the polymerase chain reaction are highly sensitive at low parasite densities, they are not recommended and should not be used in the routine case management of malaria. PCR is used in clinical/therapeutic studies in making the distinction between recrudescence and re-infection, as well as in other specialized epidemiological investigations.

2.3 Quality assurance for the malaria diagnostics

The quality assurance (QA) of malaria diagnosis is a system designed to continuously and systematically improve the efficiency, cost-effectiveness, reliability and accuracy of test results and will comply with the National Malaria Lab Plan for quality assurance and quality control.

It is critical that QA ensures:

- the health workers have full confidence in the laboratory results.
- the diagnostic results are of benefit to the patient and the community.

The principles and concepts of QA for microscopic diagnosis of malaria are similar to those for microscopic diagnosis of other communicable diseases, such as other protozoan diseases, tuberculosis and helminth infections. This provides a potential for the integration of laboratory services where it is feasible and cost-effective.

Quality assurance on malaria microscopy and RDT should be supported and promoted to ensure that high quality of malaria diagnosis is provided at all levels. This will be done through regular training (using the standard national curriculum), competency assessment, and supervision of the microscopist.

For the RDTs, WHO pre-qualified products should be selected and ensure that they conform to the manufacturer's standard at the manufacturing site. And followed up with periodic quality-control testing at the facilities, medical stores or in the communities where they are used.

On-the-job training and supervision should be strengthened to ensure that health workers correctly perform the RDTs and make treatment decisions of suspected malaria patients based on the test results.

2.4 Recording and reporting

All the health facilities (health post, primary health care centers, district hospitals and higher centers) enrolling suspected malaria cases for diagnosis and treatment of malaria needs to record the details of each case. All the malaria cases must be notified by SMS/MDIS within 24 hrs of case detection.

Treatment for malaria should be initiated as soon as diagnosis of malaria is established. Further case based investigation and focus investigation should be ensured following the National Malaria Surveillance Guidelines 2019.

3. TREATMENT

Recommendations

Uncomplicated *P. vivax*, *P. ovale*, *P. malariae*, or *P. knowlesi malariae*

- ✓ Treat with Chloroquine (3 Days) and Primaquine (14 days) for *P. vivax* and *P. ovale*.
- ✓ Treat with chloroquine (3 days) for *P. malariae* or *P. knowlesi*.

- **Blood stage infection**

- 1st line – Chloroquine
- 2nd line – dihydroartemisinin + piperazine

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

- 14-day course of primaquine - (except pregnant women, infants aged < 6 months, and women breastfeeding infants aged < 6 months).
- G6PD testing is encouraged prior to 14 days PQ therapy but in case testing is not available closely supervised 14 days PQ therapy will be given.
- Counselling should be done to patient and followed up on days 3, 7 and 14 to monitor for adverse effects and compliance with primaquine (*Refer to Annex: 6*).
- In women who are pregnant or breastfeeding – After completing a 3 day course of chloroquine - weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, treat with primaquine for 14 days to prevent future relapse.

Uncomplicated *P. falciparum* malaria

- ✓ Treat with AL (3 Days) and Primaquine on Day 1.

- **Blood stage infection**

- 3 day treatment with 1st line ACT (AL).
- 1st line - artemether + lumefantrine.
- 2nd line - dihydroartemisinin + piperazine.

- **Reducing the transmissibility of treated *P. falciparum* infections**

- Provide single dose of primaquine 0.25 mg/kg bw – (except in pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months). Testing for glucose-6-phosphate dehydrogenase (G6PD) is not required.

- **Pregnant or breastfeeding women**

- Treat pregnant women all trimesters and lactating mothers with the first line ACT (AL) as in non-pregnant women.
- Provide primaquine single dose of 0.25 mg/kg bw after pregnancy and breastfeeding completed.

Malaria is caused by infection of red blood cells with protozoan parasites of the genus *Plasmodium* inoculated into the human host by a feeding female anopheline mosquito. The human *Plasmodium* species transmitted from person to person are *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Increasingly, human infections with the monkey malaria parasite *P. knowlesi* are being reported from the forested regions of South-East Asia and particularly the island of Borneo.

P. vivax is the most important causative agent of human malaria in Nepal. About 90-95% of malaria cases are due to *P. vivax* and rest due to *P. falciparum*. *P. vivax* and *P. ovale* 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.

3.1 Treatment of uncomplicated *P.vivax*, *P.ovale*, *P.malariae* or *P.knowlesi*

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

P. malariae and *P. knowlesi* only causes blood stage infection.

3.1.1 Blood stage

On the Indian subcontinent where most of the world's *P. vivax* malaria occurs, the parasites are mainly sensitive to chloroquine. A travel history specifically to determine possible infections acquired outside the Indian subcontinent should always be obtained, as this will guide the choice of treatment.

- **First line treatment**

The first line treatment for *P.vivax*, *P.ovale*, *P.malariae* or *P.knowlesi* is chloroquine (CQ) for 3 days. *malaria* is chloroquine (CQ) for 3 days.

Day 1: chloroquine is given at an initial dose of 10 mg base/kg body weight.

Day 2: followed by 10 mg/kg body weight.

Day 3: 5 mg/kg body weight.

When the weight of the patient cannot be determined, dose calculation for chloroquine can be based on Table 3.1. The Table below summarizes the treatment schedule based on approximate age based weight bands.

Table 3.1 Dosage of Chloroquine by age group. (Each tablet of Chloroquine contains 150mg base)

Days	Medicine	AGE (years)				
		< 1 year	1-4	5-9	10-14	> 14
1	Chloroquine tablet (150mg.)	½	1	2	3	4
2	Chloroquine tablet (150 mg.)	½	1	2	3	4
3	Chloroquine tablet (150 mg.)	½	½	1	1½	2
TOTAL		1½	2½	5	7½	10

- **Second line treatment**

The recommended 2nd line option in Nepal is dihydroartemisinin + piperazine (DHA/PPQ). The longer half-life of piperazine gives it an advantage over lumefantrine in the treatment of vivax malaria. It is programmatically most suitable to have the same medicines as second line for both vivax and falciparum malaria. So, DHA/PPQ is also the 2nd line ACT for *P. falciparum* in Nepal.

DHA/PPQ is given over 3 days : dihydroartemisinin at a dose of 4 mg/kg bw per day and 18 mg/kg bw per day piperazine once a day for 3 days (Refer to Table 3.2)

A second line antimalarial (DHA/PPQ) should be used in the following situations:

- Where a patient does not tolerate or has adverse reactions to the first line medicine.
- Recrudescence (treatment failure) - reappearance of symptoms and parasites within 28 days following initial antimalarial treatment of the 1st line drug.
- Suspected chloroquine resistant vivax infection – all cases imported from areas with chloroquine-resistant infections (Mekong Region, Countries in South America and Africa, Indonesia, Timor Leste and PNG) should be considered as potentially CQ resistant and treated with 2nd line medicine.

Table 3.2: Dihydroartemisinin Piperavaquine (DHA/PPQ) Dosing Regimen for the 40mg/320mg formulation

Weight (Kg)	Age (Years)	Dihydroartemisinin(DHA)/Piperaquine (PPQ) 40 mg/320 mg base tablets		
		Day 1	Day 2	Day 3
<10	Under 1	¼ tab	¼ tab	¼ tab
11-24	1-6	1 tab	1 tab	1 tab
24-50	7– 13	1½ tab	1½ tab	1½ tab
50-70	14-18	2 tabs	2 tabs	2 tabs
≥70	≥18	3 tabs	3 tabs	3tabs

3.1.2 Anti-relapse treatment

To prevent relapse, *P. vivax* malaria should be treated in children and adults (except pregnant women, infants aged <6 months, and women breastfeeding infants <6 months) with a 14-day course of primaquine at 0.25 mg/kg body weight per day. When the weight of the patient can not be obtained, dose calculation for primaquine can be based on table 3.3. G6PD deficiency should be done when available.

G6PD Testing and Primaquine Treatment

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. Primaquine generates reactive intermediate metabolites that are oxidant and cause variable haemolysis in G6PD-deficient individuals. The severity of haemolytic anaemia depends on the dose of primaquine and on the variant of the G6PD enzyme.

Screening for G6PD deficiency is not widely available outside major hospitals and RDTs available are not reliable for the diagnosis in females. Fortunately, primaquine is eliminated rapidly (3.5 -8 hours) so haemolysis is self-limiting once the drug is stopped. In Nepal, there have been no documentation of severe adverse reaction despite the long-time use and experience with primaquine. To achieve the goal of malaria elimination and in the light of the public health benefit and significance of achieving radical cure, it is recommended to use the 14 day regimen of primaquine in all cases even where G6PD status or testing is not available. However, all patient receiving primaquine should be properly counselled and closely supervised for detection and management of primaquine-induced hemolysis. The patient should be followed up on Day 3, 7 and 14, both to monitor for adverse effect and to encourage adherence to the 14 days treatment schedule (*See ANNEX 6*).

Table 3.3 Dosage and follow up schedule for primaquine by age group

Days	Medicine	Age in years					Follow-up schedule
		6 months <1*	1-4	5-9	10-14	>14	
1	Primaquine (7.5mg)	Nil	½	1	1 ½	2	
2	Primaquine (7.5mg)	Nil	½	1	1 ½	2	
3	Primaquine (7.5mg)	Nil	½	1	1 ½	2	✓
4-6	Primaquine (7.5mg)	Nil	½	1	1 ½	2	
7	Primaquine (7.5mg)	Nil	½	1	1 ½	2	✓
8-13	Primaquine (7.5mg)	Nil	½	1	1 ½	2	
14	Primaquine (7.5mg)	Nil	½	1	1 ½	2	✓
TOTAL TABLETS		Nil	3½	7	10½	14	

(* 2.5 mg tablet of primaquine should be given, 1 tab daily for 14 days in 6 months - 1 yr)

Note: = Standard 14 days primaquine treatment is recommended ensuring close monitoring of the patients.

3.2 Treatment of P. falciparum malaria

The clinical objectives of treating uncomplicated falciparum malaria are to cure the infection as rapidly as possible and to prevent progression to severe disease. "Cure" is defined as elimination of the parasites from the body. The public health 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.

■ **First line treatment**

The first line treatment for falciparum malaria is artemether + lumefantrine (AL) given over three days (Table 3.4) and a single dose primaquine.

Target dose range of artemether + lumefantrine (AL): Total dose of 5-24 mg/kg - bw of artemether and 29-144 mg /kg- bw of lumefantrine.

- To reduce transmission – Primaquine single dose of 0.25 mg/kg bw – (except in pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months). Testing for glucose-6-phosphate dehydrogenase (G6PD) is not required.
- For ease of monitoring and to ensure compliance, primaquine should be given on day 1 along with the first dose of AL as directly observed treatment.

Table 3.4 Dosage of artemether + lumefantrine by age and weight group

Weight	Age (yrs)	Artemether + Lumefantrine*						Primaquine (0.25mg/kg)
		Day 1		Day 2		Day 3		
		<i>First Dose</i>	<i>After 8hrs</i>	<i>AM</i>	<i>PM</i>	<i>AM</i>	<i>PM</i>	
< 15 kg	< 3	1 tab	1 tab	1 tab	1 tab	1 tab	1 tab	½ tablet (excluding breastfeeding infants less than 6 months of age)
15-25 kg	3-9	2 tabs	2 tabs	2 tabs	2 tabs	2 tabs	2 tabs	1 tablet
25-35 kg	10-14	3 tabs	3 tabs	3 tabs	3 tabs	3 tabs	3 tabs	1.5 tablets
35 kg and Above	≥14	4 tabs	4 tabs	4 tabs	4 tabs	4 tabs	4 tabs	2 tablets

(each tablet of AL contains 20mg/120mg artemether and lumefantrine respectively)

■ **Second line treatment**

The recommended 2nd line option is dihydroartemisinin + piperazine (DHA/PPQ). This is given over 3 days at a dose of dihydroartemisinin 4 mg/kg bw per day and 18 mg/kg bw per day piperazine once a day for 3 days (Table 3.2) and a single dose primaquine.

A second line antimalarial should be used in the following situations:

- Patients not tolerating or adverse reactions to the first line medicine.
- Recrudescence (treatment failure) - reappearance of symptoms and parasites within 28 days following initial antimalarial treatment of the 1st line drug.

3.2.1 Mixed infection:

Mixed malaria infection are common in endemic areas. In Nepal, mixed infection (mostly vivax and falciparum) constitute less than 1 percent of the total case burden. ACTs are effective against all malaria species and is the treatment of choice for blood stage mixed infection. In case of vivax or ovale mixed infection with *P. falciparum*, 14 days of primaquine should be given along with the 1st line ACT (AL) for 3 days. Other mixed infections (*P. malariae* or *P. knowlesi*) should be treated like uncomplicated *P. falciparum* infection.

3.3 Recurrent malaria

Recurrence of malaria can result from re-infection or recrudescence (treatment failure), or relapse in the case of vivax or ovale malaria. Treatment failure may result from drug resistance or inadequate exposure to the drug due to sub-optimal dosing, poor adherence, vomiting, unusual pharmacokinetics in an individual or substandard medicine. It is important to determine from the patient's history whether he or she vomited the previous treatment or did not complete a full course of treatment. Treatment failure must be confirmed parasitologically. This may require referring the patient to a facility with microscopy, as *P. falciparum* histidine-rich protein-2 (*PfHRP2*)-based RDT tests may remain positive for weeks after the initial infection even without recrudescence.

Consultations and referral at the higher centers may also be necessary to initiate second-line treatment. To avoid missing treatment failures patients should always be asked whether they received antimalarial treatment within the preceding 1–2 months.

Recurrence of fever and parasitaemia within 28 days (consider as treatment failure)

If the patient shows evidence of inadequate response: (for example, persistence of fever, asexual parasites or deterioration in clinical condition, do the following:

- Evaluate the patient and review diagnosis.
- Ensure that appropriate dose of the medicine has been given.
- Do further Investigations to rule out other causes of fever.

If initial correct treatment was duly taken, they should be considered treatment failure which should be confirmed by microscopy. All such cases should receive the 2nd line medicine (DHA/PPQ). All efforts should be made to confirm cure on day 28 following treatment with the 2nd line medicine. All suspected treatment failures presenting to the Health Post should be referred to the PHC or hospital for further evaluation and management.

However, if confirmed that the first line medicine was inappropriately dosed, the first line medicine should be repeated. This should not be considered as treatment failure.

Recurrence of fever and parasitaemia > 28 days after treatment may be due to either recrudescence or a new infection. The distinction can be made only by PCR genotyping of parasites from the initial and the recurrent infections. As PCR is not routinely used in patient management, all such patients should from an operational standpoint, be considered new infections (or relapse in the case of vivax/ovale malaria) and be treated with the first-line medicine – CQ for vivax and AL for falciparum following the protocol in sections 3.1 and 3.2 above.

3.4 Treatment of uncomplicated malaria in pregnant women and lactating mothers

- Vivax malaria should be treated with CQ as in non-pregnant women, however the use of primaquine to prevent relapse is contraindicated in pregnancy and lactating mothers. The treatment regimen for pregnant women and lactating mothers presenting with vivax malaria is as below:
 - CQ (25mg/kg) over 3 days to cure the current blood stage infection, then
 - CQ 300mg every week as chemoprophylaxis for the remaining duration of the pregnancy and until the breastfed baby is up to 6 months of age. This is to prevent development of clinical disease by hypnozoites released intermittently from the liver. Once the breastfeed baby is older than 6 months of age, the other should receive a 14 course of primaquine to ensure radical cure.
- Falciparum malaria: Falciparum malaria during pregnancy carries a high mortality for the fetus and increased morbidity for the pregnant woman. Treat pregnant women all trimesters and lactating mothers with the first line ACT (AL) as in non-pregnant women.

4. SEVERE MALARIA

Recommendations

Treatment of severe malaria

- Intravenous or intramuscular artesunate for at least 24 h and until the patient can tolerate oral medication. Once a patient has received at least 24h of parenteral therapy and can tolerate oral therapy, complete treatment with full course artemether + lumefantrine (AL).
- Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose).

Pre-referral treatment

- A single intramuscular dose of artesunate and refer to an appropriate facility for further care.

4.1 Severe *Falciparum* malaria

Severe malaria is most commonly caused by infection with *Plasmodium falciparum*, although *P. vivax* and *P. knowlesi* can also cause severe disease. The risk is increased if treatment of an uncomplicated attack of malaria caused by these parasites is delayed. Recognizing and promptly treating uncomplicated malaria is therefore of vital importance.

High parasitaemia is undoubtedly a risk factor for death from *falciparum* malaria, but the relation between parasitaemia and prognosis varies according to the level of malaria transmission. In low-transmission areas, mortality from acute *falciparum* malaria begins to increase with parasite densities over 100 000/ μ l (~2.5% parasitaemia), whereas in areas of higher transmission much higher parasite densities may be well tolerated. Parasitaemia > 20% is associated with a high risk in any epidemiological context.

A general overview of the features of severe malaria is shown below. The clinical manifestations can occur singly or, more commonly, in combination in the same patient.

Clinical features of severe malaria:

- Impaired consciousness (including unarousable coma): A Glasgow Coma Score <11 in adults or a Blantyre Coma Score <3 in children.
- Prostration: Generalized weakness so that the patient is unable to sit, stand or walk without assistance
- Multiple convulsions: More than two episodes within 24h.
- Deep breathing and respiratory distress (acidotic breathing).
- Acute pulmonary oedema and acute respiratory distress syndrome: Oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultations.
- Circulatory collapse or shock, systolic blood pressure < 80mm Hg in adults and < 50mm Hg in children
- Acute kidney injury/Renal Impairment.
- Clinical jaundice plus evidence of other vital organ dysfunction.
- Abnormal bleeding: Recurrent or prolonged bleeding from nose, gums or venepuncture sites; hematemesis or melaena.

Laboratory and other findings

- Hypoglycaemia (< 2.2mmol/l or < 40mg/dl)
- Metabolic acidosis (plasma bicarbonate < 15mmol/l)
- Severe normocytic anaemia (haemoglobin < 5g/dl, packed cell volume < 15% in children; <7g/dl, packed cell volume < 20% in adults)
- Haemoglobinuria
- Hyperlactataemia (lactate > 5mmol/l)
- Renal impairment: serum creatinine > 265µmol/l (3mg/dl) or Blood urea > 20mmol
- Pulmonary oedema (radiological).
- Hyperparasitaemia: *P. falciparum* parasitaemia > 10%

4.2 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 recrudescence 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.

4.3 Clinical evaluation of patient for severe malaria

In all patients ask about:

- Recent history of travel (to identify those coming from malaria free areas to areas of high transmission or those who have travelled to areas with haemorrhagic fever which may mimic malaria).
- Extreme weakness (Prostration) which is inability to eat and drink or do anything without support.
- Abnormal behaviour or altered consciousness.
- Convulsions: ask about the number of episodes, part of the body involved, previous history and time of onset of last episode.
- Time of last drink or food since the onset of the illness.
- Fast breathing which may occur due to pulmonary oedema or acidosis.
- Reduced urinary output (time patient last passed urine).
- Colour of urine: whether dark or coca-cola coloured (this may suggest excessive breakdown of red blood cells or dehydration).
- Pregnancy: in adult females.
- Ask history to exclude other severe diseases.

Physical examination

A detailed physical examination should be undertaken with the aim at assessing for the presence of signs of severe malaria, prognostics evaluation and identifying other possible causes of disease.

4.4 Laboratory confirmation and test

Every suspected case of severe malaria should have a parasitological diagnosis before treatment. Advantage can be taken of the availability of RDT to rapidly establish the diagnosis by the bedside. Blood smears can be sent to the laboratory for quantification of the parasite density and subsequent monitoring of patient's progress.

Other laboratory investigations are conducted with the aim to assess complications, exclude other possible causes of severe febrile illnesses and monitor the patients' progress.

Recommended tests to be routinely performed include:

- Haematocrit (PCV) and/or Haemoglobin concentration
- Blood sugar level
- Lumbar puncture in unconscious patients.
- Urinalysis

- Blood culture
- Feto-maternal surveillance in pregnant women

Other tests that could be required subject to the patients' specific situation and available facilities include:

- Blood electrolytes, urea and creatinine
- Chest X-ray
- Complete blood count
- Arterial Blood Gas (PO_2 , PCO_2 and pH)

4.5 Treatment

Severe malaria is a medical emergency requiring in-patient care. Deaths from severe malaria can result either from direct effect of the disease or the complications. The provider should attend to the immediate threats to life first.

4.5.1 Specific antimalarial treatment

The antimalarial medicine recommended for the treatment of severe malaria is an initial treatment with injectable (IV/IM) artesunate followed by a full course of AL as soon as the patient is stable enough and able to tolerate oral medication.

Artesunate

Recommended Dosage for injectable artesunate:

- Children less than 20kg – artesunate 3.0 mg/kg bw
- Older children and adults – artesunate 2.4mg/kg bw

Dosage regimen - Give 3 parenteral doses of injection artesunate in the first 24 hours

- first dose on admission (time zero),
- second dose 8 hours after the first dose and
- third dose at 24 hours after the first dose.
- Thereafter every 24 hours until patient is able to tolerate oral medication.

The parenteral antimalarial drugs should be given for a minimum of 24 h once started (irrespective of the patient's ability to tolerate oral medication earlier) or until the patient can tolerate oral medication,

before giving the oral follow-up treatment with single dose of primaquine (PQ)

The method for reconstituting artesunate for injection is provided in Annex 2.

4.5.2 Severe P. Vivax Malaria

Although *P. vivax* malaria is considered to be benign, with a low case-fatality rate, it may cause a debilitating febrile illness with progressive anaemia and can also occasionally cause severe disease, as in *P. falciparum* malaria. Reported manifestations of severe *P. vivax* malaria include severe anaemia, thrombocytopenia, acute pulmonary oedema and, less commonly, cerebral malaria, pancytopenia, jaundice, splenic rupture, haemoglobinuria, acute renal failure and shock.

Prompt effective treatment and case management should be the same as for severe *P. falciparum* malaria (see section 4.5.1). Following parenteral artesunate, treatment can be completed with a full treatment course of oral artemether -lumefantrine and primaquine. A full course of radical treatment (14 days) with primaquine should be given.

4.5.3 Management of specific complications

Severe malaria is associated with a variety of manifestations and complications, which must be recognized promptly and treated as shown in Table 3.5.

Table 3.5 Immediate clinical management of severe manifestations and complications of *P. falciparum* malaria

Manifestation or complication	Immediate management ^a
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatments, intubate if necessary.
Hyperpyrexia	Administer tepid sponging, fanning, a cooling blanket and paracetamol.
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam, lorazepam, midazolam or intramuscular paraldehyde. Check blood glucose.
Hypoglycaemia	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion. Although hypoglycaemia is defined as glucose < 2.2 mmol/L, the threshold for intervention is < 3 mmol/L for children < 5 years and < 2.2 mmol/L for older children and adults.
Severe anaemia	Transfuse with screened fresh whole blood.
Acute pulmonary oedema^b	Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure or continuous positive airway pressure in life-threatening hypoxaemia.
Acute kidney injury	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure, add haemofiltration or haemodialysis, or, if not available, peritoneal dialysis.
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets, if available); give vitamin K injection.
Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe, add haemofiltration or haemodialysis.
Shock	Suspect septicaemia, take blood for cultures; give parenteral broad-spectrum antimicrobials, correct haemodynamic disturbances.

^a It is assumed that appropriate antimalarial treatment will have been started in all cases.

^b Prevent by avoiding excess hydration

4.5.4 Pre-referral treatment

Pre-referral treatment should be provided for suspected severe malaria pending transfer to a higher-level facility. In health facility where complete treatment of severe malaria is not possible, but artesunate injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate facility for further care.

The risk for death from severe malaria is greatest in the first 24 h. The patient may deteriorate or die due to delay in start of anti-malarial due to longer transit time between referral and arrival at a health facility where intravenous treatment can be administered. It is therefore recommended that severe patients be treated with single intramuscular dose of artesunate before referral.

Recommended Dosage for injectable artesunate:

- Children less than 20kg, - artesunate 3.0 mg/kg bw
- Older children and adults – artesunate 2.4mg/kg bw

5. CHEMOPROPHYLAXIS

Malaria chemoprophylaxis

Prophylactic medication for malaria is recommended for Nepalese traveling to countries with areas of malaria transmission, because of the risk for severe disease. Malaria prophylaxis is not necessary for in-country travel within Nepal. It is always necessary to be reminded that chemoprophylaxis is not 100% protective. Those on prophylaxis who develop signs and symptoms suggestive of malaria should seek prompt medical attention to confirm or rule out malaria. Chemoprophylaxis should be combined with other measures to prevent mosquito bites.

The choice of prophylaxis depends on the several factors including the species, resistant profile to antimalarial medicine in the destination country. The available options include:

- a) **Mefloquine:**
- The adult dosage is 250 mg (one tablet) once per week.
 - Children's dosing is by weight (split tablets), at 5mg/kg once per week, to maximum of 250 mg.
 - It is preferable to start 2–3 weeks before arrival in the malaria-risk area to achieve higher pre-travel blood levels and to allow side-effects to be detected before travel so that possible alternatives can be considered.
 - Continue the drug for 4 weeks after leaving malaria-risk area.
 - Advantages: Effective, once per week dosing, long half-life.
 - Minor side effects (fairly common): Headache, nausea, dizziness, sleep disturbance, anxiety, vivid dreams, visual disturbance. Do not usually require stopping the drug.
 - Rare side effects: Seizures, depression, psychosis (1 in 10-17,000). Stop the drug if serious ADR occur.
 - Can be used in pregnancy.
 - Contraindications: Epilepsy or other seizure disorder. Active depression or history of psychosis.
- b) **Doxycycline:**
- The adult dosage is 100 mg once daily. Should be taken at same time each day.

- It should be taken with or after meals and do not lie down for 1 hour after taking, to reduce gastric/esophageal irritation.
- Begin 1 or 2 days before arrival in the malaria-risk area. Continue for 4 weeks after leaving malaria-risk area.
- Advantages: Effective. Low cost. Familiar drug to many people.
- Minor side effects (fairly common): Sun sensitivity, vaginal yeast infection, nausea, gastro-esophageal reflux. etc.
- Contraindications: Do not give to children under 8 years or pregnant women. (Teeth may become permanently stained in unborn and young children).

c) Atovaquone/Proguanil (Malarone)

- Adult preparation is 250 mg/100mg.
- Pediatric preparation is 62.5mg/25 mg.
- Once daily medication.
- Should be started 1-2 days prior to travel and continued for 1 week after the visit to the malaria-risk area.
- It is generally well tolerated, with rare side effects.
- However, the high cost may make it less suitable for longer use for many people.

d) Chloroquine.

- Chloroquine 300 mg base weekly in 1 dose. Start 1 week before departure and continue for 4 weeks after return.
- NOT recommended for travel to African Countries.
- Recommended for prophylaxis to areas with only vivax transmission.

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Annexes

ANNEX 1: Coma scales

1. The Glasgow coma scale

		Score
Eyes open:	Spontaneously	4
	To speech	3
	To pain	2
	Never	1
Best verbal response	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
Best motor response	Obeys command	6
	Localizes pain	5
	Withdrawal	4
	Abnormal flexion to pain	3
	Abnormal extension to pain	2
	None	1
Total: (From 3 to 15)		

To obtain the Glasgow coma score, obtain the score for each section, then add the three figures to obtain a total.

2. Blantyre coma scale

This score has been modified to be applicable to children, including those who have not learned to speak.

Eye movements	Directed (e.g. Follow mothers face)	1
	Not directed	0
Verbal response	Appropriate cry	2
	Moan or inappropriate cry	1
	None	0
Best motor response	Localizes pain stimulus	2
	Withdraws limb from pain	1
	None specific or absent response	0
Total (From 0 to 5)		

To elicit pain during coma evaluation:

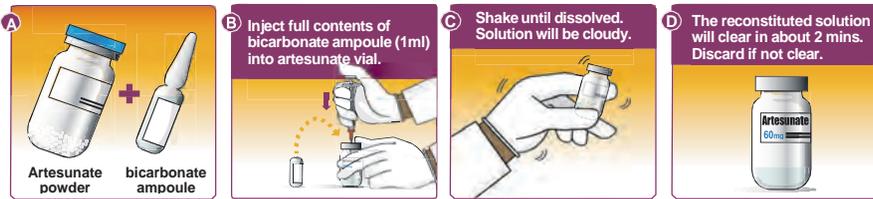
a) Rub knuckles on patient's sternum, or b) Firm pressure on thumb nail with horizontal pencil.

ANNEX 2 : SOP for the preparation and administration of injection artesunate

1. WEIGH THE PATIENT
2. DETERMINE THE NUMBER OF VIALS NEEDED

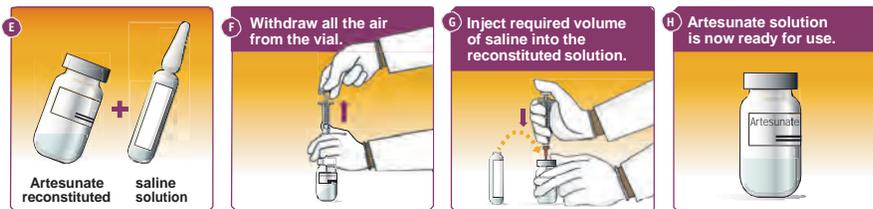
Weight	Less than 25 kg	26-50 kg	51-75 kg	76-100 kg
60 mg Vial	1	2	3	4

3. RECONSTITUTE:
 - Activate the drug: artesunate powder + 1 ml bicarbonate ampoule (immediately before use).



4. CALCULATE THE ARTESUNATE SOLUTION ACCORDING TO ROUTE OF ADMINISTRATION

- Reconstituted artesunate + saline solution (or 5 % dextrose).



	IV	IM
Bicarbonate solution volume	1 ml	1 ml
Saline solution volume	5 ml	2 ml
Total volume	6 ml	3 ml
Artesunate 60 mg solution concentration	10mg/ml	20 mg/ml

5. CALCULATE THE DOSE ACCORDING TO ROUTE OF ADMINISTRATION

	IV			IM		
	Concentration: 10 mg/ml			Concentration: 20 mg/ml		
< 20 kg	$3.0 \text{ mg} \times \text{body weight (kg)}$ IV artesunate solution (10 mg/ml)			$3.0 \text{ mg} \times \text{body weight (kg)}$ IM artesunate solution (20 mg/ml)		
	Dose needed (ml) for 8 kg child = 2.4 ml 2.4 round up to 3 ml			Dose needed (ml) for 8 kg child = 1.2 ml 1.2 ml rounded up to 2 ml		
	Weight (kg)	Dose		Weight (kg)	Dose	
		mg	Ml		mg	ml
	6-7	20	2	6-7	20	1
	8-10	30	3	8-10	30	2
	11-13	40	4	11-13	40	3
	14-16	50	5	14-16	50	4
17-20	60	6	17-20	60	5	

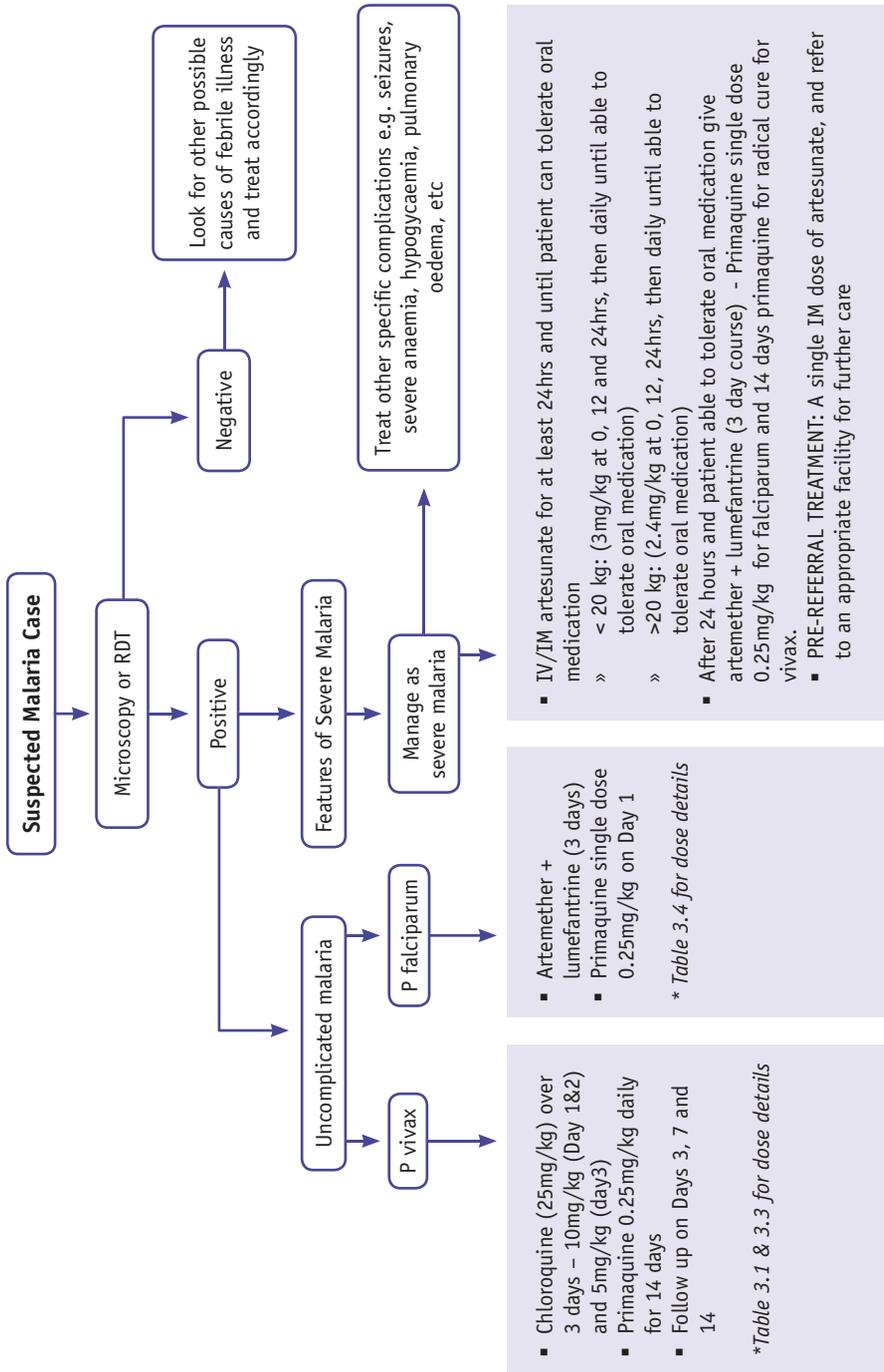
	IV			IM		
	Concentration: 10 mg/ml			Concentration: 20 mg/ml		
>20 kg	$2.4 \text{ mg} \times \text{body weight (kg)}$ IV artesunate solution (10 mg/ml) Dose needed (ml) for 26 kg child = 6.24 ml 6.24 round up to 7 ml			$2.4 \text{ mg} \times \text{body weight (kg)}$ IM artesunate solution (20 mg/ml) Dose needed (ml) for 26 kg child = 3.12 ml 3.12 ml rounded up to 4 ml		
	Weight kg	Dose		Weight kg	Dose	
		Mg	ml		Mg	ml
	20-25	60	6	20-25	60	3
	26-29	70	7	26-29	70	4
	30-33	80	8	30-33	80	5
	34-37	90	9	34-37	90	6
	38-41	100	10	38-41	100	7
	42-45	110	11	42-45	110	8
	46-50	120	12	46-50	120	9
	51-54	130	13	51-54	130	10
	55-58	140	14	55-58	140	11
	59-62	150	15	59-62	150	12
	63-66	160	16	63-66	160	13
	67-70	170	17	67-70	170	14
	71-75	180	18	71-75	180	15
	76-79	190	19	76-79	190	16
	80-83	200	20	80-83	200	17
	84-87	210	21	84-87	210	18

6. ADMINISTER

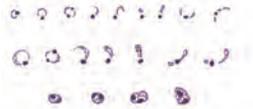
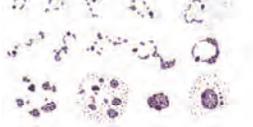
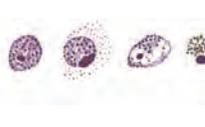
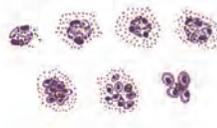
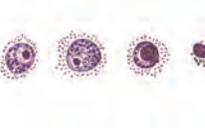
IV: slow bolus 3-4 ml per minute

IM: Inject slowly. Spread the doses of more than 2 ml over different sites for babies and 5 ml for adults

ANNEX 3: Treatment Chart for Suspected Malaria Case



ANNEX 4: Species identification of malaria parasites in giemsa-stained thick blood stained

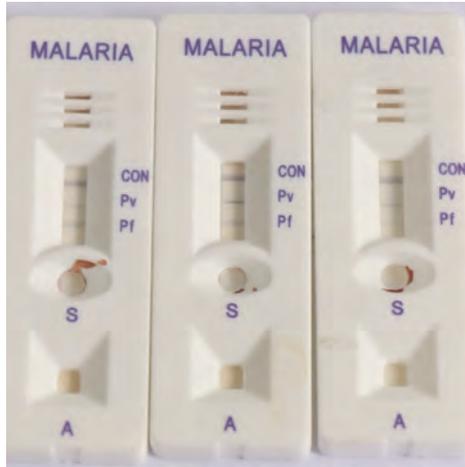
Species		Trophozoite	Schizont	Gametocyte
<i>Plasmodium falciparum</i>	Young, growing trophozoites and/or mature gametocytes usually seen	 <p>Size: small to medium; number: often numerous; shape: ring and comma forms common; chromatin: often two dots; cytoplasm: regular, fine to fleshy; mature forms: sometimes present in severe malaria, compact with pigment as few coarse grains or a mass</p>	 <p>Usually associated with many young ring forms. Size: small, compact; number: few, uncommon, usually in severe malaria; mature forms: 12-30 or more merozoites in compact cluster; pigment: single dark mass</p>	 <p>Immature pointed-end forms uncommon. mature forms: banana-shaped or rounded; chromatin: single, well defined; pigment: scattered, coarse, rice-grain-like; pink extrusion body sometimes present. Eroded forms with only chromatin and pigment often seen.</p>
	All stages seen; Schüffner stippling in 'ghost' or host red cells, especially at film edge	 <p>Size: small to large; number: few to moderate; shape: broken ring to irregular forms common; chromatin: single, occasionally two; cytoplasm: irregular or fragmented; mature forms: compact, dense; pigment: scattered, fine</p>	 <p>Size: large; number: few to moderate, mature forms: 12-24 merozoites, usually 16, in irregular cluster; pigment: loose mass</p>	 <p>Immature forms difficult to distinguish from mature trophozoites. mature forms: round, large; chromatin: single, well defined; pigment: scattered, fine. Eroded forms with scanty or no cytoplasm and only chromatin and pigment present.</p>
<i>Plasmodium ovale</i>	All stages seen; prominent Schüffner stippling in 'ghost' or host red cells, especially at film edge	 <p>Size: may be smaller than <i>P. vivax</i>; number: usually few; shape: ring to rounded, compact forms; chromatin: single, prominent; cytoplasm: fairly regular, fleshy; pigment: scattered, coarse.</p>	 <p>Size: rather like <i>P. malariae</i>; number: few; mature forms: 4-12 merozoites, usually 8, in loose cluster; pigment: concentrated mass.</p>	 <p>Immature forms difficult to distinguish from mature trophozoites. mature forms: round, may be smaller than <i>P. vivax</i>; chromatin: single, well defined; pigment: scattered, coarse. Eroded forms with only chromatin and pigment present.</p>
	All stages seen	 <p>Size: small; usually few; shape: ring to rounded, compact forms; chromatin: single, large; cytoplasm: regular, dense; pigment: scattered, abundant, with yellow tinge in older forms.</p>	 <p>Size: small, compact; number: usually few; mature forms: 6-12 merozoites, usually 8, in loose cluster, some apparently without cytoplasm; pigment: concentrated.</p>	 <p>Immature and certain mature forms difficult to distinguish from mature trophozoites. mature forms: round, compact; chromatin: single, well defined; pigment: scattered, coarse, may be peripherally distributed. Eroded forms with only chromatin and pigment present.</p>

ANNEX 5: RDT result

1. P. vivax positive



2. Mix infection (vivax & falciparum)



CAUSE OF FALSE-NEGATIVE RDT RESULT

- Operator error in preparing the RDT, performing the test or interpreting the result.
- Poor packaging can result in exposure to humidity which will rapidly degrade RDTs.
- Antibody degradation due to heat or incorrect transport or storage, eg. Exposure to high temperatures, freeze-thawing.
- Low expression of the target antigen or variation in the amino acid sequence in the malaria parasite.
- Very low parasite density or target antigen concentration.

ANNEX 6: Patient counselling, detection and management of primaquine-induced hemolysis

i. CHECKLIST FOR PATIENT COUNSELLING

- Explain the benefit of primaquine administration.
- Inquire the patient for a medical history of haemolysis/ bleeding.
- Inform the patient about the risk for acute haemolytic anaemia when taking primaquine.
- Instruct the patient to monitor the color of her or his urine, unusual menstrual bleeding.
- Instruct the patient to stop taking primaquine if her or his urine becomes dark.
- Inform the patient where to seek medical advice if his/her urine becomes dark (the nearest hospital with blood transfusion services).

ii. CHECKLIST OF SYMPTOMS OF ACUTE HAEMOLYTIC ANAEMIA

- Back Pain
- Dark (red or black) urine
- Jaundice
- Fever
- Dizziness
- Breathlessness

iii. CHECKLIST FOR THE MANAGEMENT OF SIDE-EFFECTS

Stop administering primaquine. As primaquine is eliminated rapidly (3.5-8 h), haemolysis is self-limiting once administration is stopped.

- Give oral hydration.
- Refer to an inpatient facility.
- Make a clinical assessment.
- Check haemoglobin or haematocrit.
- Check plasma or serum creatinine or urea (blood urea nitrogen) if possible
- Give a blood transfusion, if necessary, as follows:
 - Hemoglobin < 7g/dl : transfuse
 - Hemoglobin < 9 g/dl with concurrent hemolysis: transfuse
 - Hemoglobin 7-9 g/dl or > 9g/dl and no evidence of concurrent hemolysis: careful fluid management with monitoring of urine colour.

ANNEX 7: Common adverse effects of anti-malarial drugs

	DRUGS	COMMON ADVERSE EVENTS
1	Artemether-lumefantrine	<ul style="list-style-type: none"> ▪ Generally well tolerated. ▪ Reported side-effects such as nausea, dizziness and headache.
2	Chloroquine	<ul style="list-style-type: none"> ▪ Generally well tolerated at therapeutic doses. ▪ Pruritus is a common side effect and is severe in dark skinned individuals. ▪ Other less common side-effects include headache, elevated liver enzyme, skin eruptions, gastrointestinal disturbances such as nausea, vomiting and diarrhea. ▪ Taking chloroquine with food helps to avoid gastrointestinal intolerance.
3	Primaquine	<ul style="list-style-type: none"> ▪ Generally well tolerated. ▪ It may cause dose related gastrointestinal (GI) discomfort, including abdominal pain, nausea and vomiting. ▪ Taking chloroquine with food helps to avoid gastrointestinal intolerance. ▪ The most important adverse effect is hemolysis in patient with G6PD deficiency. Primaquine is eliminated rapidly so that hemolysis stops once the drug is stopped.
4	Artesunate	<ul style="list-style-type: none"> ▪ Well tolerated and has better safety profile than quinine in severe malaria. ▪ Side-effects include hypersensitivity reactions (1 in 3000), GI disturbances, cough, rash, arthralgia, dizziness and delayed hemolysis.
5	Dihydroartemisinin (DHA)/Piperaquine (PPQ)	<ul style="list-style-type: none"> ▪ Nausea, diarrhea, vomiting as well as anorexia, anemia, dizziness, headache, sleep disturbances and cough.

Technical support:

