Kingdom of Cambodia

Nation Religion King

National Treatment Guidelines for Malaria in Cambodia

June 2022

National Center for Parasitology, Entomology, and Malaria Control

1. Preface

Malaria though a preventable and curable disease, continues to be a serious public health Malaria though a preventable and curable disease, continues to be a serious public health issue. The World Malaria Report (2021) estimated 241 million malaria cases globally in 2020, and it was the cause of an estimated 627,000 deaths. An increase of 69,000 deaths compared to that in the previous year. The 2021 World Malaria Report estimates malaria incidence in the Western Pacific Region at 2 cases per 1000 populations at risk and the mortality rate at 0.4 per 100,000 populations at risk. However, Cambodia had the third-highest malaria incidence in the Western Pacific Regions after Papua New Guinea and the Solomon Islands.

The National Strategic Plan for Elimination of Malaria (2011 to 2025) was approved by **Samdech Akak Moha Sena Badei Techo HUN SEN, Prime Minister** of Cambodia in 2011. Since then, Cambodia has made significant strides. Malaria cases have reduced significantly from 106,905 cases in 2011 to only 4,329 confirmed malaria cases in 2021., malaria was responsible for over 150 deaths in 2011, the elimination effort has resulted in no recorded deaths from malaria since 2018, thereby achieving the goal to halt malaria mortality by 2020 ahead of schedule. Malaria transmission is focalized in 21 out of 25 provinces in the country.

It is imperative that every malaria control intervention be implemented with the highest degree of coverage and quality. Selection and spread of drug-resistant malaria strains will occur more rapidly with inappropriate treatment regimens, inadequate patient adherence, and use of substandard quality pharmaceuticals. Accordingly, the Ministry of Health (MoH) is publishing this updated version of the National Treatment Guidelines for Malaria, incorporating the latest information, comments, and suggestions presented at National Treatment Guideline Dissemination Workshop, May 2022. The meetings gathered experts and key stakeholders from the Ministry of Health, WHO, and technical partners to consider the latest malaria surveillance and research findings including Therapeutic Efficacy Studies (TES) to refine and improve existing treatment guidelines.

As in the previous version, these guidelines are designed for all health care providers at all levels of the public health, the military, police, and community health network to provide uniform and quality malaria case management.

The updated Guidelines. serve the goals set before, i.e., to aggressively reduce morbidity, prevent deaths from malaria, reduce the impact of resistant malaria parasite strains, to preserve the current arsenal of malaria treatments in the phase of malaria elimination. The MOH seeks to focus on the following strategies at the community, health center, and referral hospital levels:

- Prompt, safe, effective, and quality treatment with Artemisinin-based Combination Therapy (ACT), following early detection, to cure the disease and prevent progression to severe malaria
- Early identification, referral, and treatment of severe cases to prevent deaths

- Administration of gametocides to interrupt the transmission from human to vector mosquitoes
- Application of quality and full course of drugs against hypnozoites to prevent relapse
- Close monitoring of drug efficacy to inform decision-making in malaria treatment policies

The strategies will be supported by an enabling environment provided by strong program leadership, effective program management, smooth coordination between central and provincial levels, and harnessing modern innovation and research.

The new edition is one of the tools that will push malaria elimination further and make the dream of malaria-free Cambodia come true.

The Ministry of Health is grateful to the National Center for Parasitology Entomology and Malaria Control (CNM) for its strong leadership and to WHO and other technical partners for their assistance in making this new edition available.

Prof. Dr. MAM BUNHENG

Minister of Health

2. Table of contents

3. Acknowledgements

The National Treatment Guidelines for Malaria in Cambodia (2022) was updated through an inclusive process, consisting of a series of meetings and workshops with extensive reviews of best practices and current research with members of the Diagnosis and Treatment Technical Working Group between March 2022 and June 2022.

The following members of the National Center for Parasitology, Entomology and Malaria Control (CNM) are gratefully acknowledged for their strong coordination and participation in the process of and valuable contribution to updating: Dr. Huy Rekol, Dr. Lek Dysoley, Dr.Chea Nguon, Dr. Boukheng Thavrin, Dr. Meas Tha, Dr. Chea Huch, Dr. Siv Sovannaroth, Dr. Po Ly, Dr. Srey Sophanaroth, Dr. Saing Sam Ath, Dr.Tol Bunkea, and Ph. Ouk Rada.

The National Center for Parasitology, Entomology and Malaria Control (CNM) expresses sincere gratitude to the members of the Diagnostic and Treatment Technical Working Group and all others who participated actively in various developmental and review meetings and for their valuable contributions (in alphabetical order):

CHAI	Bunmeng Chhun, Yucheng Tsai, Hoi Ching Cheung, Somaya Iqubal, Thea Song
CRS	Dr. Sok Pun, Dr. Chy Say, Peng Sovann
MC	Dr. Lieven Vernaeve , Mom Sokly
PMI	Dr. Michael Thigpen, Dr. Saad El-Din Hassan, Dr Rida Slot
UNOPS	Dr. Mohammad Naeem DURRANI, Dr. Muhammed Farooq Sabawoon, Dr Sodavuth Preap
URC	Dr. Soy Ty Kheang, Dr. Nguon Sokomar, Dr. Top Samphornarann
WHO	Dr. Luciano Tuseo, Dr Zaixing Zhang, , Dr. Pascal Ringwald

Substantial comments and valuable input to the document were provided by experts from the following organizations, which provided detailed comments (in alphabetical order): Clinton Health Access Initiative (CHAI), Catholic Relief Services (CRS), Malaria Consortium (MC), US President's Malaria Initiative (PMI), United Nations Office for Project Services (UNOPS), University Research Co., LLC (URC), Mahidol Oxford Tropical Medicine Research Unit (MORU), Armed Forces Research Institute of Medical Sciences(AFRIMS), Institute Pasteur Cambodia(IPC) and the World Health Organization (WHO).
Finally, Dr. Jean Olivier Guintran, WHO consultant, is acknowledged explicitly for his invaluable contribution throughout the whole process.

4. Acronyms and abbreviations

ACT	Artemisinin-based Combination Therapy
ACPR	Adequate clinical and parasitological response
AFS	Active fever screening
AHA	Acute hemolytic anemia
AL	Artemether-Lumefantrine
AS	Artesunate
AS-MQ	Artesunate-Mefloquine
AS-PYR	Artesunate-Pyronaridine
CI	Confidence interval
CNM	National Center for Parasitology, Entomology and Malaria Control
CQ	Chloroquine
DDF	Department of Drug and Food
DHA-PPQ	Dihydroartemisinin-Piperaquine
DOT	Directly Observed Treatment
FDC	Fixed-Dose Combination
FDH	Former District Hospital
G6PD	Glucose-6-Phosphate Dehydrogenase
Hb	Haemoglobin
HC	Health center
HRP2	Histidine-Rich Protein 2
iDES	Integrated drug efficacy surveillance
IV	Intravenous
IM	Intramuscular
IPTf	Intermittent preventive treatment of malaria for forest goers
IPTi	Intermittent preventive treatment of malaria in infants
IPTp	Intermittent preventive treatment of malaria in pregnancy
MEAF	Malaria Elimination Action Framework
MIS	Malaria Information System
MMW	Mobile Malaria Worker
MOH	Ministry of Health
NCAMM	National competency assessment of malaria microscopists
NCG	National core group

NMRL	National Malaria Reference Laboratory
NRL	National reference laboratory
OD	Operational District
PCR	Polymerase Chain Reaction
P.f	*Plasmodium falciparum*
PHD	Provincial Health Department
P.k	*Plasmodium knowlesi*
P.v	*Plasmodium vivax*
pLDH	Plasmodium lactate dehydrogenase
PQ	Primaquine
QA	Quality assurance
RBC	Red blood cell
RDT	Rapid diagnostic test
RH	Referral hospital
SMC	Seasonal malaria chemoprevention
SOPs	Standard operating procedures
TDA	Targeted drug administration
TES	Therapeutic efficacy studies
T-Hb	Total Hemoglobin
TOT	Training of Trainers
VMW	Village Malaria Worker
WHO	World Health Organization

5. Glossary

Adherence: compliance with a regimen (chemoprophylaxis or treatment) or with procedures and practices prescribed by a health care worker

Adverse drug reaction: a response to a medicine that is harmful and unintended and which occurs at doses normally used in humans

Adverse event, serious: any untoward medical occurrence in a person exposed to a biological or chemical product, which is not necessarily causally related to the product, and results in death, requirement for or prolongation of inpatient hospitalization, significant disability or incapacity or is life-threatening

Annual blood examination rate: the number of people receiving a parasitological test for malaria per unit population per year

Antimalarial medicine: a pharmaceutical product used in humans for the prevention, treatment or reduction of transmission of malaria

Artemisinin-based combination therapy: a combination of an artemisinin derivative with a longer-acting antimalarial drug that has a different mode of action

Case, confirmed: malaria case (or infection) in which the parasite has been detected in a diagnostic test, i.e. microscopy, a rapid diagnostic test or a molecular diagnostic test

Case, malaria: occurrence of malaria infection in a person in whom the presence of malaria parasites in the blood has been confirmed by a diagnostic test. A suspected malaria case cannot be considered a malaria case until parasitological confirmation. A malaria case can be classified as imported, indigenous, induced, introduced, relapsing or recrudescent (depending on the origin of infection); and as symptomatic or asymptomatic.

Case, presumed: case suspected of being malaria that is not confirmed by a diagnostic test

Case, recrudescent: 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 recrudescent case must be distinguished from reinfection and relapse, in case of *P. vivax* and *P. ovale*.

Case, relapsing: malaria case attributed to activation of hypnozoites of *P. vivax* or *P. ovale* acquired previously

Case, suspected malaria: illness suspected by a health worker to be due to malaria, generally on the basis of the presence of fever with or without other symptoms

Case detection, active: detection by health workers of malaria cases at community and household levels, sometimes in population groups that are considered at high risk. Active case detection can consist of screening for fever followed by parasitological examination of all febrile patients or as parasitological examination of the target population without prior screening for fever.

Case detection, passive: detection of malaria cases among patients who, on their own initiative, visit health services for diagnosis and treatment, usually for a febrile illness

Case follow-up: periodic re-examination of patients with malaria (with or without treatment)

Case investigation: collection of information to allow classification of a malaria case by origin of infection, i.e. imported, indigenous, induced, introduced, relapsing or recrudescent

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 < 11, Blantyre coma scale < 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 mechanisms of action

Coverage, universal: access to and use of appropriate interventions by the entire population at risk of malaria

Cure: elimination from an infected person of all malaria parasites that caused the infection

Cure, radical: elimination of both blood-stage and latent liver infection in cases of *P. vivax* and *P. ovale* infection, thereby preventing relapses

Diagnosis: the process of establishing the cause of an illness (for example, a febrile episode), including both clinical assessment and diagnostic testing

Diagnosis, molecular: use of nucleic acid amplification-based tests to detect the presence of malaria parasites

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

Dosage regimen (or treatment regimen): prescribed formulation, route of administration, dose, dosing interval and duration of treatment with a medicine

Dose: quantity of a medicine to be taken at one time or within a given period

Drug efficacy: capacity of an antimalarial medicine to achieve the therapeutic objective when administered at a recommended dose, which is well tolerated and has minimal toxicity

Drug resistance: the ability of a parasite strain to survive and/or multiply despite the absorption of a medicine given in doses equal to or higher than those usually recommended

Drug, gametocidal: a drug that kills male and/or female gametocytes, thus preventing them from infecting a mosquito

Drug, schizontocidal: a drug that kills schizonts, either in the liver or the blood

Erythrocytic cycle: portion of the life cycle of the malaria parasite from merozoite invasion of red blood cells to schizont rupture. The duration is approximately 24 hours in *P. knowlesi*, 48 hours in *P. falciparum*, *P. ovale* and *P. vivax* and 72 hours in *P. malariae*.

Fixed-dose combination: a combination in which two antimalarial medicines are formulated together in the same tablet, capsule, powder, suspension or granule

Gametocyte: sexual stage of malaria parasites that can potentially infect anopheline mosquitoes when ingested during a blood meal

Hyperparasitaemia: a high density of parasites in the blood, which increases the risk that a patient's condition will deteriorate and become severe malaria

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 (even longer in some cases), before activation and development into a pre-erythrocytic schizont, which then causes a blood-stage infection (relapse)

Infection, mixed: malaria infection with more than one species of Plasmodium

Infection, reservoir of: any person or animal in which plasmodia live and multiply, such that they can be transmitted to a susceptible host

Infection, submicroscopic: low-density blood-stage malaria infections that are not detected by conventional microscopy

Intermittent preventive treatment in infants: a full therapeutic course of sulfadoxine-pyrimethamine delivered to infants in co-administration with DTP2/Penta2, DTP3/Penta3 and measles immunization, regardless of whether the infant is infected with malaria

Intermittent preventive treatment in pregnancy: a full therapeutic course of antimalarial medicine given to pregnant women at routine prenatal visits, regardless of whether the woman is infected with malaria

Malaria infection: presence of Plasmodium parasites in blood or tissues, confirmed by diagnostic testing

Mass drug administration: administration of antimalarial treatment to all age groups of a defined population or every person living in a defined geographical area (except those for whom the medicine is contraindicated) at approximately the same time and often at repeated intervals

Mass screening, testing and treatment: screening of an entire population for risk factors, testing individuals at risk and treating those with a positive test result

Medicine safety: characteristics of a medicine that reflects its potential to cause harm, including the important identified risks of a drug and important potential risks

Monotherapy: antimalarial treatment with a single active compound or a synergistic combination of two compounds with related mechanisms of action

Parasitaemia: presence of parasites in the blood

Parasitaemia, asymptomatic: The presence of asexual parasites in the blood without symptoms of illness

Parasite clearance time: time between first drug administration and the first examination in which no parasites are present in the blood by microscopy

Parasite density: number of asexual parasites per unit volume of blood or per number of red blood cells

Plasmodium: genus of protozoan blood parasites of vertebrates that includes the causal agents of malaria. *P. falciparum*, *P. malariae*, *P. ovale* and *P. vivax* cause malaria in humans. Human infection with the monkey malaria parasite *P. knowlesi* and very occasionally with other simian malaria species may occur in tropical forest areas.

Prequalification: process to ensure that health products are safe, appropriate and meet stringent quality standards for international procurement

Preventive chemotherapy: use of medicines either alone or in combination to prevent malaria infections and their consequences

Prophylaxis: any method of protection from or prevention of disease; when applied to chemotherapy, it is commonly termed "chemoprophylaxis"

Rapid diagnostic test: immunochromatographic lateral flow device for rapid detection of malaria parasite antigens

Recrudescence: recurrence of asexual parasitaemia of the same genotype(s) that caused the original illness, due to incomplete clearance of asexual parasites after antimalarial treatment

Recurrence: reappearance of asexual parasitaemia after treatment, due to recrudescence, relapse (in *P. vivax* and *P. ovale* infections only) or a new infection

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: recurrence of asexual parasitaemia in *P. vivax* or *P. ovale* infections arising from hypnozoites

Ring form (ring stage, ring-stage trophozoite): young, usually ring-shaped malaria trophozoites, before pigment is evident by microscopy

Schizont: stage of the malaria parasite in host liver cells (hepatic schizont) or red blood cells (erythrocytic schizont) that is undergoing nuclear division by schizogony and, consequently, has more than one nucleus

Sensitivity (of a test): measured as the proportion of people with malaria infection (true positives) who have a positive result

Severe anaemia: haemoglobin concentration of < 5 g/100 mL (haematocrit < 15%)

Severe falciparum malaria: acute falciparum malaria with signs of severe illness and/or evidence of vital organ dysfunction

Specificity (of a test): measured as the proportion of people without malaria infection (true negatives) who have a negative result

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

Treatment, anti-relapse: antimalarial treatment designed to kill hypnozoites and thereby prevent relapses or late primary infections with *P. vivax* or *P. ovale*

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

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

Treatment, preventive: intermittent administration of a full therapeutic course of an antimalarial either alone or in combination to prevent malarial illness by maintaining therapeutic drug levels in the blood throughout the period of greatest risk

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

Trophozoite: The stage of development of malaria parasites growing within host red blood cells from the ring stage to just before nuclear division. Trophozoites contain malaria pigment that is visible by microscopy.

Uncomplicated malaria: symptomatic malaria parasitaemia without signs of severity or evidence of vital organ dysfunction

6. Diagnosis & treatment of malaria in Cambodia

Partial resistance of *P. falciparum* to artemisinin was first confirmed along the Cambodia–Thailand border just over a decade ago. Drug monitoring has been central to tracking the evolution of antimalarial resistance and adapt treatment regimen accordingly. In 2016 Cambodia had to modify the first-line artemisinin-based combination therapy (ACT) when resistance to piperaquine had emerged.

In 2018, the National Centre for Parasitology Entomology and Malaria Control (CNM) launched a malaria intensification plan targeting hard to reach populations located using more granular village data and hotspot mapping. Additional village malaria workers (VMWs) were deployed and mobile malaria workers (MMWs) were assigned close to high-risk forested areas. Passive and active case detection were intensified and the number of malaria test increased from 253,631 in 2018 to 612,759 in 2019. Village malaria workers and mobile malaria workers have played a central role, responsible for 80% of all malaria testing in 2021.

Since early 2020, *P. falciparum* cases are systematically investigated and classified to localize active foci. In November 2020, the CNM started to operate intensified focus responses to accelerate *P. falciparum* elimination. The focalized innovative approaches includee Targeted Drug Administration (TDA), Intermittent Preventive Treatment for forest goers (IPTf) and weekly active fever screening (AFS) in active foci across five provinces. Quality assurance of microscopy have been enhanced by establishing a national reference laboratory and provincial quality assurance laboratories.

Malaria testing remained steady in 2021 with 818,729 tests performed. No deaths from malaria have been recorded since 2018 and the number of reported malaria cases has dropped rapidly from 76,804 in 2017 to 4,329 in 2021. During the same period, reported severe malaria cases decreased from 2,052 to only 27. *P. falciparum* is now at historically low levels (only 361 cases in 2021) and confined to difficult to reach forest areas. Men are at greatest risk, accounting for 81% of all infections, and *P. vivax* now the dominant malaria species. Glucose-6-phosphate dehydrogenase (G6PD) quantitative testing and radical cure to eliminate the dormant liver stage parasites were recently expanded to 324 health facilities across the country.

The threat of *P. falciparum* resistance to the available ACT requires the country to remain vigilant and sustain drug efficacy surveillance to detect and rapidly adapt drug policy if necessary.

7. Objectives of MEAF 2021-2025

The Malaria Elimination Action Framework (MEAF) 2021-2025 is an amendment to the previous strategies. It builds on the previous framework (2016-2020) and carries forward the same vision of a malaria-free Cambodia. The national commitment is now to end malaria transmission of *P. falciparum* by 2023 and *P. vivax* by 2025.

The three objectives with one enabling environment are:

Objective 1: Early detect and effectively and safely treat 100% of cases, and provide effective personal protection to at least 90% of the high-risk population

Objective 2: Intensify focal interventions to interrupt transmission in endemic locations with highest risk (including mobile migrant population/forest goers) to reach API less than 0.1 for *P. falciparum* by 2023 and all species by 2025

Objective 3: Investigate, clear, document and follow up 100% of cases and foci to interrupt transmission and prevent re-establishment

Enabling environment: Strengthening program leadership to maintain effective program management and coordination at central and provincial levels and harness innovation and research.

The specific objectives related to diagnosis and treatment are the following:

- All suspected malaria patients receive a parasitological test within 48 hours of symptom onset.
- All suspected malaria patients from private sector providers are referred to a public sector facility.
- All patients with confirmed malaria receive first-line anti-malarial treatment and other treatment regimens according to National Treatment Guidelines.
- All targeted villages with full coverage of diagnosis and treatment for all confirmed cases within 48 hours of symptom onset by community networks (VMW/MMW)
- All confirmed cases among MMP and other underserved populations are diagnosed and treated within 48 hours of symptom onset.
- All patients with confirmed severe malaria are treated according to National Treatment Guidelines.
- All national, provincial and referral hospitals, and testing labs are qualified for malaria services and comply with quality assurance guidelines.
- Foster interventions to impact infection reservoir in high risk locations and communities.
- Implement interventions to stop transmission in active foci.
- Strengthen Procurement and Supply Management Systems (PSM).
- Test and regularly monitor drug efficacy.

8 Changes from the 2014 edition

This new edition of the National Guidelines for the treatment of malaria contains updated recommendations based on new evidence in line with the most recent World Health Organization (WHO) guidance. Adaptation has been made on the basis of local priorities, malaria epidemiology, parasite resistance and national resources.

Since the last 2014 edition, the following major changes have occurred in Cambodia:

- Evolution of malaria epidemiology and ecosystem: transmission is now restricted to foci at the proximity of forested areas and the country is now engaged in the final efforts to eliminate *P. falciparum* malaria.
- Occurrence and spread of *P. falciparum* parasites resistant to Dihydroartemisinin-Piperaquine
- *P. vivax* is now the most frequent species and new tools and new drugs regimens are available for effective and safe radical cure in the prospect of its elimination.

The following table describes the major changes compared to the 2014 edition:

Table 8.1 Major changes from the 2014 National Treatment Guidelines

Diagnosis of malaria • Added detailed instructions for identification of danger signs and immediate referral of severe febrile diseases • Differentiated case definition of suspected uncomplicated malaria for public health facilities, private sector and VMW/MMW levels • Added detailed instructions for patients with recurrent malaria • Additional guidance for patients with a negative malaria test
Treatment of uncomplicated *P. falciparum* • First and second line treatment updated • Systematic gametocytocidal single-dose treatment is now recommended • Added instructions on counselling to patients • Added detailed instructions to manage suspected treatment failure • Added descriptions of alternative treatments under evaluation
Treatment of uncomplicated *P. vivax* and *P. ovale* • Universal access to G6PD quantitative testing is now available at health facility level • Added primaquine radical treatment of *P. vivax* and *P. ovale* according to G6PD status • Added instructions on counselling to patients • Added instructions on monitoring of safety and adherence of radical treatment • Added detailed instructions for the detection and management of acute hemolytic anemia • Added descriptions of alternative treatments under evaluation

Treatment of uncomplicated *P. malariae* or *P. knowlesi* • First and second line treatment updated
Treatment of severe malaria • Pre-referral treatment withdrawn • Artesunate IV followed by ACT is now the preferred treatment of severe malaria including for pregnant women in first trimester with increased dosing for young children • Added detailed instructions for continuing supportive care, monitoring and management of complications
Efficacy of antimalarial medicines • Updated section including therapeutic efficacy studies, integrated drug efficacy surveillance and molecular resistance markers
Targeted drug administration and chemoprevention in special risk groups • New section including targeted drug administration and intermittent preventive treatment for forest goers in active foci
Safety of antimalarial medicines • New section including pharmacovigilance, reporting, investigation and management of adverse drug reactions
Quality of Diagnosis & Treatment • New section including quality assurance of diagnosis and antimalarial medicines, competency assessment, supervisions and performance evaluation

9 Diagnosis of malaria

9.1 Clinical assessment of patients with fever

The signs and symptoms of malaria are non-specific. Malaria is suspected clinically primarily on the basis of fever or a history of fever. Fever is defined as a recent (less than 7 days) perception of fever (usually with chills and sweats) or elevated axillary temperature (≥ 37.5°C) if measured.

Other usual manifestations include chills, sweat, headaches, body or joint pains, malaise, nausea, or vomiting. Physical examination may reveal pallor and hepatosplenomegaly. But there is no combination of signs or symptoms that reliably distinguishes malaria from other causes of fever.

The priority is to detect danger signs of a severe febrile disease caused by malaria or another infection.

Ask the patient and/or the accompanying person about:

- History of fever, chills
- Headache, neck stiffness, convulsions
- Rash, skin problem
- Runny nose, earache, sore throat
- Cough, difficult breathing
- Difficult drinking, eating, vomiting
- Diarrhea
- Missed vaccinations (check the vaccination card for children)

Examine the patient carefully:

- Temperature, pulse, blood pressure
- Respiration rate
- Chest inspection and auscultation
- Dehydration signs
- Rash or skin infection (wounds, abscess)
- Severe pallor
- Weight, weight/height ratio (malnutrition)
- Throat, eyes, and ears
- Cervical lymph nodes
- Abdomen palpation
- Neck stiffness, bulging fontanel (infant)

9.2 Patients with danger signs of a severe febrile disease

Severe febrile disease is a life-threatening medical emergency, and oral treatment is impossible and/or insufficient.

Look for one of the following danger signs of severe febrile disease:

Table 9.1. Danger signs of severe febrile disease

Danger signs for detection by health facilities	Danger signs for detenction by VMW/MMWs
• Coma or altered consciousness • A Glasgow coma score < 11 in adults or a Blantyre coma score < 3 in children • Unable to fix/follow objects with eyes • Unable to localize a painful stimulus	• Unusually sleepy or unconscious • Does not respond when touched/spoken to
• Prostration • Generalized weakness so that the person is unable to sit, stand or walk without assistance • Not able to drink or feed	• Not able to sit, stand or walk without assistance • Not able to drink or feed
• Multiple convulsions • More than two episodes within 24 hours of Involuntary spasms of body parts	• Repeated body spasms
• Respiratory distress • Difficult, rapid, or deep breathing • Chest in-drawing, nasal flaring	• Difficult breathing • Chest indrawing, fast breathing (>30 /min for adults, >40/min for children age 1-5 years)
• Severe pallor	• Severe pallor
• Jaundice	• Yellow eyes and skin
• Abnormal bleeding • Blood from the nose, gums • Hematemesis or melaena	• Vomiting of blood • Blood from the nose, gums • Black feces without an identified cause
• Circulatory collapse – Shock • Systolic blood pressure < 70 mm Hg in children or < 80 mm Hg in adults • Cool peripheries or prolonged capillary refill	
• Oliguria • Urine output <400ml/24h	

A patient with any danger sign of severe febrile disease should be immediately referred to the closest hospital for appropriate parenteral treatment and careful supportive care, and

close clinical monitoring.

9.3 Diagnosis of uncomplicated malaria by VMW/MMWs

In Cambodia, the incidence of malaria is very low, and risk is restricted exclusively to individuals who have been exposed to malaria with defined risk factors. Most febrile illnesses are not due to malaria. For accelerated elimination, VMW/MMWs are deployed into and at proximity of active transmission areas. They operate both passive and active case detection and, therefore, sometimes requested to test asymptomatic individuals most at-risk in addition to febrile patients. VMWs/MMWs should identify the patients potentially exposed to malaria during the previous month according to risk factors.

Case definition of suspected uncomplicated malaria for VMWs/MMWs:

In the absence of danger sign, every patient presenting with

- **a fever or history of fever or chills or sweat**

OR

- **any of the following risk factors in the previous month:**
  - Stayed or traveled into the forested area/endemic region
  - Received a malaria treatment for malaria infection
  - Lived or worked with a confirmed malaria case

⇒ See Annex 1: Job Aid – Diagnosis & Treatment flow chart for VMW/MMWs

All cases of suspected malaria should have a rapid diagnosis test (RDT) to confirm the diagnosis.

⇒ See Annex 2: Job Aid – Instruction to perform RDT
⇒ See Annex 3: Job Aid – Interpretation of RDT result

9.4 Diagnosis of uncomplicated malaria in public hospitals and health center/health posts

In Cambodia, the incidence of malaria is very low, and risk is restricted exclusively to individuals who have been exposed to malaria with defined risk factors. Most febrile illnesses are not due to malaria. Health staff should identify the patients potentially exposed to malaria during the previous month according to risk factors.

Case definition of suspected uncomplicated malaria in public hospitals and health centers/health posts:

In the absence of a danger sign, every patient presenting with

- **a fever or history of fever or chills or sweat**

AND

- **any of the following risk factors in the previous month:**
  - Stayed or traveled into the forested area/endemic region
  - Received a malaria treatment for malaria infection
  - Lived or worked with a confirmed malaria case

In health centers, all cases of suspected malaria should have a rapid diagnosis test (RDT) to confirm the diagnosis.

⇒ See Annex 2: Job Aid – Instruction to perform RDT
⇒ See Annex 3: Job Aid – Interpretation of RDT result

In hospitals, all cases of suspected malaria should have a parasitological test (microscopy or RDT) to confirm the diagnosis.

For the management of a new fever episode, quality-assured microscopy and RDTs are equivalent in terms of performance for the diagnosis of uncomplicated malaria.

High-quality microscopy service for the diagnosis of malaria are not available in all hospitals. It requires trained staff, well-maintained equipment, a regular supply of reliable reagents, clean water and electricity, and a well-executed quality management system.

In hospitals, RDTs are an option for testing suspected uncomplicated malaria in outpatient departments with a high caseload. Health staff might be trained to perform RDTs where the quality of microscopy is not assured. RDTs are also needed for diagnostic testing for malaria when the laboratory is closed or microscopy is not available (after working hours).

⇒ See standard operating procedures for microscopy and reference for microscopy quality assurance in Operational Manual for Quality Assurance of Malaria Diagnosis

9.5 Diagnosis of uncomplicated malaria in the private sector

The Public Private Mix (PPM) program has been minimized in 2018. Private care providers are no longer allowed to perform RDTs and provide treatment for malaria.

Case definition of suspected uncomplicated malaria in the private sector:

In the absence of a danger sign, every patient presenting with

- **a fever or history of fever or chills or sweat**

AND

- **any of the following risk factors in the previous month:**

- Stayed or traveled into the forested area/endemic region
- Received a malaria treatment for malaria infection
- Lived or worked with a confirmed malaria case

All cases of suspected malaria in the private sector should be referred to the closest public health facility for a parasitological diagnosis (microscopy or RDT).

9.6 Parasitological diagnosis of malaria

In Cambodia, the selected RDTs detect *P. falciparum* histidine-rich protein-2 (PfHRP2) and *P. vivax* specific pLDH.

The other less frequent malaria species – *P. ovale, P. malariae* and *P. knowlesi* – have been documented by microscopy or PCR in the country but cannot be detected by current RDTs. The relapsing simian malaria *P. cynomolgi* has also been identified in humans by PCR in the western part of the country.

RDTs with pan-malarial antigens (pLDH or aldolase) are available. Their performance for the detection of *P. vivax* has improved in recent years but their sensitivity for the other species is still low. In addition, *P. knowlesi* is frequently misdiagnosed as *P. malariae* by microscopy and requires confirmation by PCR.

Any case of high parasitaemia with "*P. malariae*-like" parasites in or near an area where long- or pig-tailed macaque monkeys live should be treated as *P. knowlesi* and confirmed by PCR if possible.

9.7 Rapid diagnosis tests under evaluation

The following products are under development and might be available with appropriate improved performance in the close future:

- More sensitive RDT
- RDT specific of current *P. falciparum* infection
- RDT detecting *P. ovale*, *P. malariae* and *P. knowlesi* using Pan-pLDH or aldolase antigens

10 Patients with negative malaria test

When a patient is tested negative for malaria, antimalarial medicine should not be given.

There should be additional investigations, including taking a detailed history of illness, careful physical examination, and extra laboratory tests to rule out alternative causes of fever requiring specific treatment.

Only patients with a positive diagnostic test for malaria should receive antimalarial treatment. In addition, patient should be assessed for other causes of fever, and specific treatment should be provided in addition to the antimalarial treatment, if needed.

The following alternative causes of fever should be investigated:

- Viral upper respiratory tract infections, sore throat
- Otitis media and tonsillitis
- Pneumonia
- Gastroenteritis
- Typhoid
- Urinary tract infection
- Skin infection
- Measles
- Sepsis
- Meningitis
- Dengue
- Zika
- Chikungunya
- Japanese encephalitis
- Leptospirosis
- Rickettsia
- Scrub typhus

11 Treatment of uncomplicated *P. falciparum* malaria

11.1 First-line treatment of uncomplicated *P. falciparum* malaria

Uncomplicated malaria is a malaria infection without evidence of vital organ dysfunction.

The first-line treatment of uncomplicated *P. falciparum* is artesunate-mefloquine (AS-MQ)

Note: First- and second-line treatments for *P. vivax* and other species of malaria are the same as the first- and second-line treatments for *P. falciparum* malaria.

Do not give artesunate-mefloquine (AS-MQ) if:

- Patient has history of psychiatric disorders, epilepsy or seizures

⇒ Refer to hospital

- Patient was treated with AS-MQ treatment in the last 28 days

11.2 See Section 11.4 Treatment of uncomplicated malaria caused by *P. vivax, P. ovale, P. malariae* or *P. knowlesi*

11.2.1 Current efficacy of antimalarial medicines in Cambodia

Efficacy of AS-MQ and AS-PYR on *P.vivax* blood stages have been evaluated by TES recently with a 28-day follow-up. Reliable distinction between re-infections, relapses and recrudescences is currently not possible with *P. vivax*.

Table 11.6. Recent estimates of drug efficacy on *P. vivax* in Cambodia

Drug	Year	N	ACPR	95% CI
AS-PYR	2018	120	100%	-
AS-MQ	2018	180	100%	-
AS-PYR	2020	87	98%*	95-100
AS-MQ	2020	114	100%	-

*One recurrence

11.2.2 Treatment of blood stage *P. vivax, P. ovale, P. malariae* or *P. knowlesi* infections

Moderate level of *P. vivax* resistance to chloroquine has been documented in other parts of South-East Asia but *P.vivax, P. ovale, P. malariae* and *P. knowlesi* are all sensitive to ACTs containing piperaquine, mefloquine or lumefantrine.

***P.vivax, P. ovale, P. malariae* and *P. knowlesi* malaria should be treated by first-line ACT (AS-MQ).**

In addition to providing first-line ACT as treatment for uncomplicated blood stage of *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* infections, VMW/MMWs should

- refer patients to heath centers

- follow up on patients' treatment compliance

Artesunate-mefloquine (AS-MQ) fixed-dose combination is available in 25/50 mg and 100/200 mg tablets. Dosing is best using weight; if ascale is not available, use age categories.

⇒ See Section 11.1 First-line treatment of uncomplicated *P. falciparum* malaria for contraindications for AS-MQ and mode of administration
⇒ See Table 11.1. AS-MQ daily dosing for uncomplicated malaria
⇒ See Annex 4: Job Aid – Treatment of uncomplicated malaria
⇒ See Annex 5: Counselling for the treatment of uncomplicated malaria

If pediatric AS-MQ 25/50mg tablets are not available for procurement, AS-PYR 20/60mg sachets could be procured as substitute for first-line treatment for children 5–17kg.

⇒ See Table 11.2. AS-PYR daily dosing for uncomplicated malaria in children
⇒ See Annex 6: Job Aid – Alternative pediatric treatment of uncomplicated malaria

11.2.3 Prevention of *P. vivax* and *P. ovale* relapses

The only drugs with significant activity against the hypnozoites are the 8-aminoquinolines (primaquine and tafenoquine). The total dose of primaquine given is the main determinant of radical curative efficacy. In the standard regimen, primaquine is given once a day at 0.25 mg/kg body weight for 14 days (total dose of 3.5 mg/kg). In vivo assessments suggest that tolerance of *P. vivax* to primaquine is greater in eastern Asia and Oceania than elsewhere, and higher doses are often proposed (total dose of 7 mg/kg per day).

In G6PD-normal patients, primaquine is remarkably safe, well tolerated and highly efficacious in preventing relapse. In a significant proportion of G6PD-deficient patients, however, the 14-day regimen of primaquine induces dose-dependent, potentially severe hemolysis.

As G6PD deficiency is an X-linked disorder, there are two distinct G6PD genotypes in males (wild type and hemizygous) but three in females (wild type, homozygous and heterozygous). The five genotypes in males and females translate into three phenotypes: G6PD normal and G6PD deficient in both males and females and G6PD intermediate (with an enzyme activity 30–80% of normal) in heterozygous females only. The enzymatic activity decides on the likelihood that the patient develops acute hemolytic anemia (AHA) during a 14-day regimen of primaquine for radical cure.

Any person (male or female) with red blood cell G6PD activity < 30% of the normal (adjusted male median) activity has G6PD deficiency and will experience hemolysis if they receive the 14-day regimen of primaquine for radical cure. Heterozygous females with higher G6PD activities may still show substantial hemolysis during a 14-day primaquine radical cure regimen.

***P. vivax* and *P. ovale* malaria cases and mixed infection cases that involve *P. vivax* or *P. ovale* should be considered for radical cure treatment with a 14-day or 8-week regimen of primaquine, depending on G6PD activity level of the patient.**

Primaquine is strictly contraindicated for:

- pregnant or breastfeeding women

– infants aged < 6 months

⇒ Radical treatment can be proposed after the delivery and breastfeeding period.

11.2.4 G6PD quantitative testing

The G6PD status of patients should be known before administration of radical treatment with primaquine.

For both male and female patients with a positive RDT or microscopy result for *P. vivax*, *P. ovale* and mix infection, a G6PD test will be performed by health facility staff to determine eligibility for safe radical cure.

A rapid quantitative G6PD test should be used at points of care level.

For the currently available SD Biosensor STANDARD G6PD test, results are displayed in unit per gram of hemoglobin (U/g Hb), and the G6PD status of the patient (normal, intermediate, or deficient) should be interpreted as per the following table:

Table 11.7. Thresholds for interpretation of SD Biosensor STANDARD G6PD test result

G6PD activity U/g Hb	Male	Female
≥ 6.1	Normal	Normal
≥ 4.0 – 6.0		Intermediate
≤ 3.9	Deficient	Deficient

Interpretation of the G6PD Test results should only be performed when Hb level is greater than 7g/dL.

If the measured value of the T-Hb test is less than or equal to 7g/dL, a T-Hb confirmatory test should be performed.

If hemoglobin ≤ 7 g/dL, the primaquine treatment will not be started.

⇒ See Annex 7: Job Aid – Instruction for quantitative G6PD testing with SD Biosensor

⇒ See Annex 8: Job Aid – Instruction to perform quality control of SD Biosensor

11.2.5 Treatment of patients with normal G6PD activity

Patients with normal G6PD activity should be treated with primaquine at 0.25-0.5 mg/kg body weight once a day for 14-days with appropriate counselling.

Primaquine is available in 7.5mg base tablets. Weight-based dosing is shown in the following table.

Table 11.8. Primaquine dosing for 14-day radical cure regimen

Weight range (kg)	Dose (mg base)	Number of 7.5mg base tablets, per day	Dose range (mg base/kg)
20-<31	7.5	1	0.38-0.25
31-<46	15	2	0.48-0.33
46-<61	22.5	3	0.49-0.33
≥ 61	30	4	0.49-0.33

⇒ See Annex 9: Job Aid – Diagnosis & Treatment flow chart for health facilities

11.2.6 Treatment of females with intermediate G6PD activity

In females with intermediate G6PD activity, consider giving primaquine at 0.75 mg/kg body weight once a week for 8 weeks with appropriate counselling and close medical supervision.

Table 11.9. Primaquine dosing for 8-week radical cure regimen

Weight range (kg)	Dose (mg base)	Number of 7.5mg tablets, per week	Dose range (mg base/kg)
10-<15	7.5	1	0.75-0.54
15-<23	15	2	1.00-0.68
23-<30	22.5	3	0.98-0.78
30-<40	30	4	1.00-0.78
40-<50	37.5	5	0.94-0.76
50-<60	45	6	0.90-0.76
≥ 60	52.5	7	≤ 0.87

⇒ See Annex 9: Job Aid – Diagnosis & Treatment flow chart for health facilities

11.2.7 Treatment of patients with G6PD deficiency

In patients with G6PD deficiency, consider giving primaquine at 0.75 mg/kg body weight once a week for 8 weeks with appropriate counselling and close medical supervision.

⇒ See Annex 9: Job Aid – Diagnosis & Treatment flow chart for health facilities
⇒ See Table 11.9. Primaquine dosing for 8-week radical cure regimen

11.2.8 Counselling and monitoring of patients treated by primaquine radical cure

Primaquine causes dose-limiting abdominal discomfort when taken on an empty stomach and should always be taken with food.

All patients treated by primaquine should get **initial counselling**:

- to recognize symptoms and signs of adverse event, especially acute hemolytic anemia (AHA)
- to stop primaquine and be told where to seek care should these signs develop
- to report adverse events and adherence to the treatment by phone calls or VMW/MMWs' in-person visits on D3, D7, D14 for the 14-day treatment; and for the 8 week treatment, to report adverse events and adherence to the treatment during visits to the health center on D3 and D7 and by phone calls or VMW/MMWs in-person weekly visits starting on D14 of the 8-week treatment
- to understand the importance of full adherence to complete the treatment

⇒ See Annex 10: Counselling for patient with P. vivax malaria who tested G6PD deficient or intermediate
⇒ See Annex 11: Counselling for patients with P. vivax malaria who tested to be G6PD normal

Patients who receive primaquine for radical cure will be monitored for treatment adherence and tolerance: Patients will be followed up for adherence to treatment by either the health center staff or the VMW/MMW. If a VMW/MMW is present in the village, he/she will follow up with the patient on D3, D7, and D14 for the 14-day treatment and weekly starting on D14 for the 8-week treatment. He/she will ask the the patients about the number of tablets taken, check the number of tablets remaining, monitor the patient's treatment adherence form, and record the treatment adherence data in the paper-based checklist and Malaria Information System (MIS) App. During these visits, he or she will ask for side effects or symptoms of hemolysis (AHA). When identifying side effects, he/she will refer the patient to the closest health center or directly to the hospital if the patient experiences severe side effects. If there is no VMW/MMW in the village, the health center staff will call the patient on D3, D7, and D14 for the 14-day treatment and weekly starting on 14 for the 8-week treatment to check the treatment adherence and tolerance and then report the information in the MIS.

⇒ See Annex 12: Patient's follow-up card for primaquine radical cure
⇒ See Annex 13: Checklist for monitoring of radical treatment by VMWs

Patients receiving a weekly regimen will have close medical monitoring during the first week of the 8-week treatment with hemoglobin measurement at the health center on Day 0 before the first dose, on day 3, and on day 7 before administration of the second dose.

If hemoglobin ≤ 7g/dl on D0, the 8-week primaquine treatment will not be started.

If hemoglobin ≤ 7g/dl, on D3 or on D7, or the hemoglobin drops ≥ 25% comparing to D0, the patient will be referred to a hospital for medical assessment and supervision and the treatment interrupted.

11.2.9 Diagnosis and management of acute hemolytic anemia (AHA)

At the community level, VMWs should check for the following signs and symptoms in patients receiving primaquine for radical cure, and if VMWs identify any one of the above symptoms, the patient needs to be referred to the health center immediately:

- **Dark urine (urine with blood)**
- **Pallor (pale skin or yellow skin, eyes, or lips)**
- **Shortness of breath**
- **Back pain**
- **Increased heart rate**

⇒ See Annex 12: Patient's follow-up card for primaquine radical cure
⇒ See Annex 13: Checklist for monitoring of radical treatment by VMWs

At the health center level, the health worker should question detailed history of symptoms and conduct clinical assessment to check for the following signs and symptoms:

- **Pallor, yellowing of skin and eyes**
- **Shortness of breath after activity, rapid breathing**
- **Increased heart rate, palpitations, tachycardia**
- **Back pain**

In addition, he/she should **observe the urine of the patient against the Hillmen colour chart**

Urine should be placed in a clear glass container and held up against a white piece of paper, in a well illuminated area.

A score of 5 or above is considered evidence of hemoglobinuria.

In the presence of hemoglobinuria or one of the AHA symptoms, report the event to Department of Drugs and Food (DDF) on an adverse drug reaction report and refer the patient immediately to the closest provincial hospital.

⇒ See Annex 14: Adverse drug reaction report – DDF pharmacovigilance center

At the hospital level, the referred patient will be questioned for detailed history and subject to careful clinical assessment to verify and confirm clinical signs and symptoms of AHA.

In addition, the following set of laboratory investigations is required:

- Hemoglobin and hematocrit
- Creatinine and urea
- Hemoglobinuria confirmed by urine stick

⇒ See Annex 14: Adverse drug reaction report – DDF pharmacovigilance center
⇒ See Annex 15: investigation of reported adverse reaction after PQ radical treatment

When a patient presents with signs and symptoms of AHA following the administration of primaquine, the patient should be managed in line with the following sequence:

- Stop primaquine treatment immediately
- Admit the patient
- Give oral hydration

If hemoglobin > 7 g/dL and no evidence of concurrent hemolysis:

Prescribe careful fluid management with monitoring of urine color and hemoglobin

If hemoglobin ≤ 7 g/dL, or hemoglobin < 9 g/dL with concurrent signs of hemolysis:

Give a blood transfusion

11.2.10 Alternative radical cure treatment regimens under evaluation

The following regimens are under evaluation. They might be available in the future if proven better in terms of effectiveness or safety than the current recommended regimen:

- Tafenoquine single dose
- Primaquine with higher dose for 7 days

11.3 Treatment of recurrent uncomplicated malaria

⇒ Patients with recurrent malaria

- Patient is a pregnant woman in the first trimester

⇒ See Section 11.6 Treatment of uncomplicated malaria in pregnancy

In this document, the day of malaria diagnosis is referred to as Day 0 (D0).

Artesunate-mefloquine (AS-MQ) fixed-dose combination is available in 25/50 mg and 100/200 mg tablets. Dosing is best using weight; if a scale is not available, use age categories.

Table 11.1. AS-MQ daily dosing for uncomplicated malaria

Weight (kg)	Age	Tablets	Number of tablets		
			Day 0	Day 1	Day 2
5-<9	6-11 months	25/50 mg	1	1	1
9-<18	1-6 years	25/50 mg	2	2	2
18-<30	7-12 years	100/200 mg	1	1	1
≥30	≥13 years	100/200 mg	2	2	2

⇒ See Annex 4: Job Aid – Treatment of uncomplicated malaria
⇒ See Annex 5: Counselling for the treatment of uncomplicated malaria

If pediatric AS-MQ 25/50mg tablets are not available for procurement, AS-PYR 20/60mg sachets could be procured as substitute as first-line treatment for children 5–17kg.

Table 11.2. AS-PYR daily dosing for uncomplicated malaria in children

Weight (kg)	Sachets	Number of sachets		
		Day 0	Day 1	Day 2
5- < 8	20/60 mg	1	1	1
8- < 15	20/60 mg	2	2	2
15- < 18	20/60 mg	3	3	3

⇒ See Annex 6: Job Aid – Alternative pediatric treatment of uncomplicated malaria

Mode of administration:

Directly Observed Treatment (DOT) for the first dose: the first dose of ACT is given immediately on D0 and should be observed by the health care provider or VMW/MMW.

Follow up on Treatment Adherence by VMW/MMW: patient should take subsequent doses at D1 and D2, ideally in the presence of a VMW/MMW. This activity could be implemented only in villages with VMW/MMW.

11.3.1 Current efficacy of antimalarial medicines in Cambodia

Western Cambodia has been the epicenter of multidrug-resistant *P. falciparum* for many years. Artemisinin resistance was first reported in 2009 from western Cambodia and has since spread throughout the Greater Mekong Subregion. Following WHO recommendations, the strategy is to switch to an alternative ACT when the efficacy of the first-line treatment falls below 90%. Cambodia started using artesunate-mefloquine (AS-MQ) in 2000, then changed its first-line treatment to dihydroartemisinin-piperaquine (DHA-PIP) in 2010, then changed back to artesunate-mefloquine (AS-MQ) in 2016-2017.

Therapeutic efficacy studies (TES) have been conducted for more than 20 years by the CNM. The table below reports main results of the drug efficacy collected between 2011 and 2019. Studies are gray shaded when the estimated efficacy falls below the 90% threshold.

The resistance to DHA-PIP emerged in 2013 in the western part and had spread to the eastern part in 2016. The efficacy of the first-line ACT AS-MQ has been monitored annually between 2016 and 2019. Efficacy was well above 95% with only 4 recrudescence in total. Optimal efficacy of artesunate-pyronaridine (AS-PYR) is well documented in both the eastern and the western part of the country. In contrast, efficacy of artesunate-amodiaquine (AS-AQ) and artemether-lumefantrine (AL) have been measured below 90% in the western part.

Table 11.3. Recent estimates of drug efficacy in Cambodia

Drug	Year	N	Adequate clinical and parasitological response	95% Confidence Interval (CI)

(ACPR)				
DHA-PIP - West	2011-13	143	85%	77-91
DHA-PIP - East	2011-13	276	98%	95-99%
DHA-PIP - East	2016	107	78%	65-84%
AS-AQ	2016	63	81%	69-89%
AS-PYR - West	2016	121	87%	79-92%
AS-MQ	2016	65	100%	-
AS-MQ	2017	162	99%*	96-100%
AS-PYR - East	2017	59	98%*	91-100%
AS-MQ	2018	121	99%*	96-100%
AS-PYR - West	2018	100	99%*	97-100%
A-L -West	2018-19	37	85%	68-94%
A-L -East	2018-19	92	99%*	91-100%
AS-MQ	2019	110	98%**	94-100%
AS-MQ	2020	34	100%	-

*One recrudescence **two recrudescences

See Annex for references.

11.3.2 Gametocytocide treatment to reduce transmission

The use of primaquine as a gametocytocide has a particular role in programs to eliminate *P. falciparum* malaria.

A single dose of 0.25 mg base/kg is effective in blocking infectivity to mosquitos and is unlikely to cause serious toxicity in people with any level of Glucose-6-Phosphate Dehydrogenase (G6PD) activities. Thus, the G6PD status of the patient does not have to be known before primaquine is used for this indication.

For *P. falciparum* malaria, a single dose of primaquine as gametocytocide treatment is given at the same time as the first dose of the first-line treatment.

Primaquine causes dose-limiting abdominal discomfort when taken on an empty stomach and should always be taken with food.

Table 11.4. Primaquine dosing as gametocytocide treatment for uncomplicated *P. falciparum* malaria

Weight (kg)	Dose	Tablets	Number of tablets Day 0
< 20	None	-	-
20-49	7.5mg	7.5mg	1
≥ 50	15mg	7.5mg	2

Primaquine is strictly contraindicated for:

- pregnant or breastfeeding women
- infants aged < 6 months

⇒ see Annex 4: Job Aid – Treatment of uncomplicated malaria

11.3.3 Alternative antimalarial medicines under evaluation

In the context of evolving multi-drug resistance, the following alternative drug combinations have been evaluated by clinical trials in Cambodia and proposed as alternatives in the event of failure of existing first- and second-line drugs:

- atovaquone–proguanil–artesunate–pyronaridine (ATQ-PG-AS-PYR)
- artemether–lumefantrine–amodiaquine (A-L-AQ)
- dihydroartesunate–piperaquine–mefloquine (DHA-PIP-MQ)

The table below details results of recent clinical trials conducted in Cambodia. Combinations with efficacy below the WHO recommended 95% threshold to select a new first-line treatment are shaded in gray.

Table 11.5. Results of recent clinical trials of alternative antimalarial medicines

Drug		Year	N	ACPR	95% CI
ATQ-PG	North	2018-19	98	90%	82–95%
ATQ-PG-AS	North	2018-19	97	92%	83-96%
A-L-AQ	West	2018-19	38	92%	76-97%
A-L-AQ	East	2018-19	92	98%	91-99%
DHA-PIP-MQ	West	2015-17	89	96%	93-99%
DHA-PIP-MQ	East	2015-17	46	100%	92-100%

11.4 Treatment of uncomplicated malaria caused by *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi*

11.4.1 Current efficacy of antimalarial medicines in Cambodia

Efficacy of AS-MQ and AS-PYR on *P.vivax* blood stages have been evaluated by TES recently with a 28-day follow-up. Reliable distinction between re-infections, relapses and recrudescences is currently not possible with *P. vivax*.

Table 11.6. Recent estimates of drug efficacy on *P. vivax* in Cambodia

Drug	Year	N	ACPR	95% CI
AS-PYR	2018	120	100%	-
AS-MQ	2018	180	100%	-
AS-PYR	2020	87	98%*	95-100
AS-MQ	2020	114	100%	-

*One recurrence

11.4.2 Treatment of blood stage *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* infections

Moderate level of *P. vivax* resistance to chloroquine has been documented in other parts of South-East Asia but *P.vivax, P. ovale, P. malariae* and *P. knowlesi* are all sensitive to ACTs containing piperaquine, mefloquine or lumefantrine.

***P.vivax, P. ovale, P. malariae* and *P. knowlesi* malaria should be treated by first-line ACT (AS-MQ).**

In addition to providing first-line ACT as treatment for uncomplicated blood stage of *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* infections, VMW/MMWs should

- refer patients to heath centers
- follow up on patients' treatment compliance

Artesunate-mefloquine (AS-MQ) fixed-dose combination is available in 25/50 mg and 100/200 mg tablets. Dosing is best using weight; if ascale is not available, use age categories.

⇒ See Section 11.1 First-line treatment of uncomplicated *P. falciparum* malaria for contraindications for AS-MQ and mode of administration
⇒ See Table 11.1. AS-MQ daily dosing for uncomplicated malaria
⇒ See Annex 4: Job Aid – Treatment of uncomplicated malaria
⇒ See Annex 5: Counselling for the treatment of uncomplicated malaria

If pediatric AS-MQ 25/50mg tablets are not available for procurement, AS-PYR 20/60mg sachets could be procured as substitute for first-line treatment for children 5–17kg.

⇒ See Table 11.2. AS-PYR daily dosing for uncomplicated malaria in children
⇒ See Annex 6: Job Aid – Alternative pediatric treatment of uncomplicated malaria

11.4.3 Prevention of *P. vivax* and *P. ovale* relapses

The only drugs with significant activity against the hypnozoites are the 8-aminoquinolines (primaquine and tafenoquine). The total dose of primaquine given is the main determinant of radical curative efficacy. In the standard regimen, primaquine is given once a day at 0.25 mg/kg body weight for 14 days (total dose of 3.5 mg/kg). In vivo assessments suggest that tolerance of *P. vivax* to primaquine is greater in eastern Asia and Oceania than elsewhere, and higher doses are often proposed (total dose of 7 mg/kg per day).

In G6PD-normal patients, primaquine is remarkably safe, well tolerated and highly efficacious in preventing relapse. In a significant proportion of G6PD-deficient patients, however, the 14-day regimen of primaquine induces dose-dependent, potentially severe hemolysis.

As G6PD deficiency is an X-linked disorder, there are two distinct G6PD genotypes in males (wild type and hemizygous) but three in females (wild type, homozygous and heterozygous). The five genotypes in males and females translate into three phenotypes: G6PD normal and G6PD deficient in both males and females and G6PD intermediate (with an enzyme activity 30–80% of normal) in heterozygous females only. The enzymatic activity decides on the likelihood that the patient develops acute hemolytic anemia (AHA) during a 14-day regimen of primaquine for radical cure.

Any person (male or female) with red blood cell G6PD activity < 30% of the normal (adjusted male median) activity has G6PD deficiency and will experience hemolysis if they receive the 14-day regimen of primaquine for radical cure. Heterozygous females with higher G6PD activities may still show substantial hemolysis during a 14-day primaquine radical cure regimen.

***P. vivax* and *P. ovale* malaria cases and mixed infection cases that involve *P. vivax* or *P. ovale* should be considered for radical cure treatment with a 14-day or 8-week regimen of primaquine, depending on G6PD activity level of the patient.**

Primaquine is strictly contraindicated for:

- pregnant or breastfeeding women
- infants aged < 6 months

⇒ Radical treatment can be proposed after the delivery and breastfeeding period.

11.4.4 G6PD quantitative testing

The G6PD status of patients should be known before administration of radical treatment with primaquine.

For both male and female patients with a positive RDT or microscopy result for *P. vivax*, *P. ovale* and mix infection, a G6PD test will be performed by health facility staff to determine eligibility for safe radical cure.

A rapid quantitative G6PD test should be used at points of care level.

For the currently available SD Biosensor STANDARD G6PD test, results are displayed in unit per gram of hemoglobin (U/g Hb), and the G6PD status of the patient (normal, intermediate, or deficient) should be interpreted as per the following table:

Table 11.7. Thresholds for interpretation of SD Biosensor STANDARD G6PD test result

G6PD activity U/g Hb	Male	Female
≥ 6.1	Normal	Normal
≥ 4.0 – 6.0		Intermediate
≤ 3.9	Deficient	Deficient

Interpretation of the G6PD Test results should only be performed when Hb level is greater than 7g/dL.

If the measured value of the T-Hb test is less than or equal to 7g/dL, a T-Hb confirmatory test should be performed.

If hemoglobin ≤ 7 g/dL, the primaquine treatment will not be started.

⇒ See Annex 7: Job Aid – Instruction for quantitative G6PD testing with SD Biosensor
⇒ See Annex 8: Job Aid – Instruction to perform quality control of SD Biosensor

11.4.5 Treatment of patients with normal G6PD activity

Patients with normal G6PD activity should be treated with primaquine at 0.25-0.5 mg/kg body weight once a day for 14-days with appropriate counselling.

Primaquine is available in 7.5mg base tablets. Weight-based dosing is shown in the following table.

Table 11.8. Primaquine dosing for 14-day radical cure regimen

Weight range (kg)	Dose (mg base)	Number of 7.5mg base tablets, per day	Dose range (mg base/kg)
20-<31	7.5	1	0.38-0.25
31-<46	15	2	0.48-0.33
46-<61	22.5	3	0.49-0.33
≥ 61	30	4	0.49-0.33

⇒ See Annex 9: Job Aid – Diagnosis & Treatment flow chart for health facilities

11.4.6 Treatment of females with intermediate G6PD activity

In females with intermediate G6PD activity, consider giving primaquine at 0.75 mg/kg

body weight once a week for 8 weeks with appropriate counselling and close medical supervision.

Table 11.9. Primaquine dosing for 8-week radical cure regimen

Weight range (kg)	Dose (mg base)	Number of 7.5mg tablets, per week	Dose range (mg base/kg)
10-<15	7.5	1	0.75-0.54
15-<23	15	2	1.00-0.68
23-<30	22.5	3	0.98-0.78
30-<40	30	4	1.00-0.78
40-<50	37.5	5	0.94-0.76
50-<60	45	6	0.90-0.76
≥ 60	52.5	7	≤ 0.87

⇒ See Annex 9: Job Aid – Diagnosis & Treatment flow chart for health facilities

11.4.7 Treatment of patients with G6PD deficiency

In patients with G6PD deficiency, consider giving primaquine at 0.75 mg/kg body weight once a week for 8 weeks with appropriate counselling and close medical supervision.

⇒ See Annex 9: Job Aid – Diagnosis & Treatment flow chart for health facilities
⇒ See Table 11.9. Primaquine dosing for 8-week radical cure regimen

11.4.8 Counselling and monitoring of patients treated by primaquine radical cure

Primaquine causes dose-limiting abdominal discomfort when taken on an empty stomach and should always be taken with food.

All patients treated by primaquine should get **initial counselling**:

- to recognize symptoms and signs of adverse event, especially acute hemolytic anemia (AHA)
- to stop primaquine and be told where to seek care should these signs develop
- to report adverse events and adherence to the treatment by phone calls or VMW/MMWs' in-person visits on D3, D7, D14 for the 14-day treatment; and for the 8 week treatment, to report adverse events and adherence to the treatment during visits to the health center on D3 and D7 and by phone calls or VMW/MMWs in-person weekly visits starting on D14 of the 8-week treatment
- to understand the importance of full adherence to complete the treatment

⇒ See Annex 10: Counselling for patient with P. vivax malaria who tested G6PD

deficient or intermediate

⇒ See Annex 11: Counselling for patients with P. vivax malaria who tested to be G6PD normal

Patients who receive primaquine for radical cure will be monitored for treatment adherence and tolerance: Patients will be followed up for adherence to treatment by either the health center staff or the VMW/MMW. If a VMW/MMW is present in the village, he/she will follow up with the patient on D3, D7, and D14 for the 14-day treatment and weekly starting on D14 for the 8-week treatment. He/she will ask the the patients about the number of tablets taken, check the number of tablets remaining, monitor the patient's treatment adherence form, and record the treatment adherence data in the paper-based checklist and Malaria Information System (MIS) App. During these visits, he or she will ask for side effects or symptoms of hemolysis (AHA). When identifying side effects, he/she will refer the patient to the closest health center or directly to the hospital if the patient experiences severe side effects. If there is no VMW/MMW in the village, the health center staff will call the patient on D3, D7, and D14 for the 14-day treatment and weekly starting on 14 for the 8-week treatment to check the treatment adherence and tolerance and then report the information in the MIS.

⇒ See Annex 12: Patient's follow-up card for primaquine radical cure

⇒ See Annex 13: Checklist for monitoring of radical treatment by VMWs

Patients receiving a weekly regimen will have close medical monitoring during the first week of the 8-week treatment with hemoglobin measurement at the health center on Day 0 before the first dose, on day 3, and on day 7 before administration of the second dose.

If hemoglobin ≤ 7g/dl on D0, the 8-week primaquine treatment will not be started.

If hemoglobin ≤ 7g/dl, on D3 or on D7, or the hemoglobin drops ≥ 25% comparing to D0, the patient will be referred to a hospital for medical assessment and supervision and the treatment interrupted.

11.4.9 Diagnosis and management of acute hemolytic anemia (AHA)

At the community level, VMWs should check for the following signs and symptoms in patients receiving primaquine for radical cure, and if VMWs identify any one of the above symptoms, the patient needs to be referred to the health center immediately:

- **Dark urine (urine with blood)**
- **Pallor (pale skin or yellow skin, eyes, or lips)**
- **Shortness of breath**
- **Back pain**
- **Increased heart rate**

⇒ See Annex 12: Patient's follow-up card for primaquine radical cure

⇒ See Annex 13: Checklist for monitoring of radical treatment by VMWs

At the health center level, the health worker should question detailed history of symptoms and conduct clinical assessment to check for the following signs and symptoms:

- **Pallor, yellowing of skin and eyes**
- **Shortness of breath after activity, rapid breathing**
- **Increased heart rate, palpitations, tachycardia**
- **Back pain**

In addition, he/she should **observe the urine of the patient against the Hillmen colour chart**

Urine should be placed in a clear glass container and held up against a white piece of paper, in a well illuminated area.

A score of 5 or above is considered evidence of hemoglobinuria.

In the presence of hemoglobinuria or one of the AHA symptoms, report the event to Department of Drugs and Food (DDF) on an adverse drug reaction report and refer the patient immediately to the closest provincial hospital.

⇒ See Annex 14: Adverse drug reaction report – DDF pharmacovigilance center

At the hospital level, the referred patient will be questioned for detailed history and subject to careful clinical assessment to verify and confirm clinical signs and symptoms of AHA.

In addition, the following set of laboratory investigations is required:

- Hemoglobin and hematocrit
- Creatinine and urea
- Hemoglobinuria confirmed by urine stick

⇒ See Annex 14: Adverse drug reaction report – DDF pharmacovigilance center
⇒ See Annex 15: investigation of reported adverse reaction after PQ radical treatment

When a patient presents with signs and symptoms of AHA following the administration of primaquine, the patient should be managed in line with the following sequence:

- Stop primaquine treatment immediately
- Admit the patient
- Give oral hydration

If hemoglobin > 7 g/dL and no evidence of concurrent hemolysis:

Prescribe careful fluid management with monitoring of urine color and hemoglobin

If hemoglobin ≤ 7 g/dL, or hemoglobin < 9 g/dL with concurrent signs of hemolysis:

Give a blood transfusion

11.4.10 Alternative radical cure treatment regimens under evaluation

The following regimens are under evaluation. They might be available in the future if proven better in terms of effectiveness or safety than the current recommended regimen:

- Tafenoquine single dose
- Primaquine with higher dose for 7 days

11.5 Treatment of recurrent uncomplicated malaria

11.5.1 Patients with recurrent malaria

The continued use of a medicine encourages the selection of resistant *P. falciparum* parasites and their spread.

Many recurrent malaria cases are missed because patients are not asked whether they received antimalarial treatment within the preceding 1–2 months. Patients who present with malaria should be asked this question routinely.

If a patient received IPTf/TDA within 28 days prior to a confirmed malaria diagnosis, they should be referred to a hospital. An investigation as to whether the patient had completed the full regimen for IPTf is needed. If the full dose of IPTf was completed, the second-line treatment should be given to treat the current malaria infection; if not, the first-line treatment should be given.

Recurrent P. vivax malaria

Recurrence of *P. vivax* and *P. ovale* malaria are considered relapses or reinfections.

Patients with recurrence of *P. vivax* or *P. ovale* should receive a first-line ACT treatment and radical cure according to the patient's G6PD status.

Recurrent P. falciparum malaria

Recurrence of *P. falciparum* malaria can result from either a re-infection or a recrudescence due to treatment failure.

Treatment failure occurs when malaria parasites are not completely cleared from the body and return later as a recrudescence.

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 medicines.

Recurrent P. falciparum malaria after 28 days

Recurrence of fever and parasitemia may be due to either recrudescence or a new infection.

If PCR genotyping of parasites is available to make the distinction between a recrudescence and a re-infection, recrudescences should be treated by second line treatment, while re-infections should be treated with first-line ACT.

If PCR genotyping of parasites is not available, the patient should receive a first-line ACT.

Recurrent P. falciparum malaria within 28 days

The recurrence is considered as a treatment failure that 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 medicines.

When possible, treatment failure **must be confirmed parasitologically with microscopy** as *P. falciparum* histidine-rich protein-2 (PfHRP2)-based tests may remain positive for weeks after the initial infection, even without recrudescence.

The first cause of reccurence to rule-out is an **incorrect treatment intake** with wrong:

- duration of treatment (less than 3 doses over 3 days)
- dosing (incorrect weight or dosing)
- drug regimen (not the first-line recommended ACT)
- drug intake (vomiting after less than 1 hour)

If an incorrect treatment was given during the initial malaria case, the patient should be treated with the first-line ACT and told to come back immediately if not better within 3 days or if fever reoccurs within one month.

If the treatment was correctly administered, the patient should be referred to the hospital for parasitological confirmation with microscopy and treated with second line ACT if positive.

11.5.2 Second-line treatment of uncomplicated *P. falciparum* malaria

Patients with recurrent uncomplicated *P. falciparum* within 28 days after correct intake of a first-line treatment should receive artesunate-pyronaridine (AS-PYR) as second-line treatment.

If the patient had received IPTf/TDA within 28 days prior to confirmed malaria diagnosis, the patient needs to be referred to the hospital.

Artesunate-pyronaridine (AS-PYR) is **available in fixed-dose combination** with 20/60 mg sachets of granules for children < 20kg and 60/180 mg tablets for adults.

Table 11.10. AS-PYR daily dosing for uncomplicated malaria

Weight (kg)	Formulation	Number of sachets or tablets		
		Day 0	Day 1	Day 2
5-<8	20/60 mg sachet	1	1	1
8-<15	20/60mg sachet	2	2	2
15-<20	20/60 mg sachet	3	3	3
20-<24	60/180mg tablet	1	1	1
24-<45	60/180mg tablet	2	2	2
45-<65	60/180mg tablet	3	3	3
≥65	60/180mg tablet	4	4	4

Do not give artesunate-pyronaridine (AS-PYR) if:

- Patient is a a pregnant woman in the first trimester

⇒ See section “Treatment of uncomplicated malaria in pregnancy”

11.6 Treatment of uncomplicated malaria in pregnancy

Pregnant women with uncomplicated *P. falciparum* or *P. vivax* malaria have increased risks for abortion, stillbirth, premature delivery and low infant birth weight. They should be advised to take adequate prevention measures and personal protection when living in areas with residual transmission. They should be advised not to visit forests during the pregnancy.

All women of childbearing age should be asked about the possibility that they are pregnant before they are given antimalarial agents.

For all pregnant women:

Primaquine is contraindicated during pregnancy. Do not prescribe primaquine as gametocytocide to reduce transmission or as radical cure treatment for the prevention of *P.vivax* and *P. ovale* relapses.

For pregnant women with uncomplicated malaria during the first trimester:

In reality, women often do not declare their pregnancy in the first trimester or may not yet be aware that they are pregnant and therefore will often be exposed inadvertently to the available first-line treatment. There is no need for those women to have their pregnancy interrupted because of this exposure.

The antimalarial medicines considered safe in the first trimester of pregnancy are quinine, chloroquine, clindamycin and proguanil. There is insufficient information on the safety of ACT during the first trimester of pregnancy to recommend it.

During the first trimester, treat pregnant women with uncomplicated malaria with 7 days of quinine. If quinine is not available, treat with first-line ACT.

Quinine is available in 300mg tablets.

The dosing regimen is 2 tablets (10mg/kg) every 8 hours for 7 days.

Pregnant women with uncomplicated malaria during the second and third trimester should be treated with the first-line ACT.

Pregnant women with severe malaria should be treated similarly to non-pregnant women.

Table 11.11. Preferred malaria treatment according to pregnancy status

	Uncomplicated *P. falciparum* malaria	Uncomplicated *P. vivax* malaria	Severe malaria
First trimester*	Qunine 7 days	Quinine 7 days	Artesunate IV + ACT 3 days
Second/third trimester	ACT 3 days	ACT 3 days	Artesunate IV + ACT 3 days
Not pregnant	ACT 3 days + single dose PQ	ACT 3 days + PQ 14 days/PQ 8 weeks	Artesunate IV + ACT 3 days

*ACT as alternative treatment if Quinine tablets are not available

Treatment of mixed infections

- To treat any mixed infection of *P. vivax* or *P. ovale* with other species, follow the relevant recommended *P. vivax* treatment regimens.

⇒ See Section 11.4 Treatment of uncomplicated malaria caused by *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi*

- To treat mixed infections that do not involve *P. vivax* or *P. ovale*, refer to the relevant *P. falciparum* treatment regimen.

⇒ See Section 11 Treatment of uncomplicated *P. falciparum* malaria

12 Treatment of severe malaria

Severe malaria is most commonly caused by infection with *P. falciparum*, although *P. vivax* and *P. knowlesi* can also cause severe disease. Unless the condition is diagnosed and treated promptly, a patient with severe malaria may deteriorate rapidly and experience vital organ dysfunction and death.

12.1 Pre-referral treatment

The recommended pre-referral treatment options are intramuscular artesunate, rectal artesunate for children <6 years, intramuscular artemether or intramuscular quinine, and immediate referral. None of these options has been retained considering the very low incidence of severe malaria in the country (fewer than 30 cases in 2021) and usually short referral time to hospitals where intravenous treatment can be administered.

12.2 Assessment of severe febrile disease in hospital

Parasitological diagnosis

At the hospital level, microscopy is the preferred option for the assessment of severe febrile disease because initial quantification of parasite density is a marker of severity.

High-quality microscopy services for the diagnosis of malaria are not available in some hospitals. It requires trained staff, well-maintained equipment, a regular supply of reliable reagents, clean water and electricity, and a well-executed quality management system.

RDTs might be used to assess severe febrile disease in hospitals where quality of microscopy is not assured. RDTs are also needed when laboratory is closed, or microscopy is not available (after working hours).

If microscopy reading is not immediately available, RDT is helpful to guide initial emergency treatment.

If parasitological confirmation of malaria is not readily feasible, make a blood film and start treatment for severe malaria on the basis of the clinical presentation.

In general, the greater the parasite density in the peripheral blood, the higher the likelihood that severe disease is present. Nevertheless, as the parasites in severe falciparum malaria are usually sequestered in capillaries and venules, patients may present with severe malaria with very low peripheral parasitemia.

Microscopy is also needed for follow-up of parasite density until full parasite clearance.

RDTs for detecting PfHRP2 antigen cannot be used to monitor the response to treatment, as they can remain positive for up to 4 weeks after clearance of parasitemia.

Additional investigations in presence of other specific signs might be:

- Blood glucose, hemoglobin, urea, creatinine and electrolytes
- Urine strip test for hemoglobin, glucose, proteins
- Lumbar puncture (if unconscious, neck stiffness or bulging fontanel)
- Thoracic x-ray (if cough, fast or difficult breathing, abnormal auscultation)

12.3 Diagnosis of severe malaria

Severe malaria is defined by the presence of *P. falciparum, P. vivax* or *P. knowlesi* asexual parasitemia together with one or more of the followings:

Table 12.1. Signs of severe malaria

Clinical signs or conditions	
Impaired consciousness	A Glasgow coma score < 11 in adults or a Blantyre coma score < 3 in children
Multiple generalized convulsions	2 or more episodes within a 24-hour period
Prostration	Inability to sit upright, stand or walk without assistance or inability to drink in children too young to sit
Respiratory distress	Respiratory rate > 30/min in adults, > 40 in children, often with chest indrawing
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
Circulatory collapse - Shock	Compensated with normal blood pressure, decompensated with systolic blood pressure < 70 mm Hg in adults and < 50 mm Hg in children, with signs of impaired perfusion in peripheries
Abnormal bleeding	From nose, gums, hematemesis, or melena
Oliguria or anuria	Urine output < 400ml/24 hours
Jaundice	Yellow-colored eyes or skin
Laboratory abnormalities	
Hyperparasitemia	4% of RBC with malaria parasites
Hypoglycemia	Blood glucose < 2.2 mmol/l or 40mg/dl
Hemolysis	Plasma or serum bilirubin > 50 µmol/L
Renal impairment	Creatinine > 265 µmol/L or blood or urea > 20 mmol/L

Disseminated intravascular coagulopathy	
Severe anemia	Hemoglobin concentration <5g/dl or hematocrit < 15% in children < 12 years of age; and < 7 g/dL and < 20%, respectively, in adults
Acidosis	Base deficit of > 8 mEq/L or, bicarbonate < 15 mmol/L or lactate ≥ 5 mmol/L
Hemoglobinuria	

⇒ See Annex 16: Blantyre and Glasgow coma scales

Patients with *P. falciparum* parasites densities > 10% are considered to have severe malaria even if they do not have evidence of vital organ dysfunction.

P. vivax infection is much less likely to progress to severe malaria than P. falciparum infection. 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 hyperparasitemia is defined with parasite density > 100 000/µL, and jaundice with parasite density > 20 000/µL.

12.4 Diagnosis of other severe febrile diseases

There is considerable clinical overlap between bacteremia, pneumonia and severe malaria, and these conditions may coexist. Severe febrile disease can also result from meningitis, encephalitis, typhoid fever, septicemia, or severe dengue.

12.5 Emergency measures

- Admit the patient to an acute illness ward or room or intensive care unit if available for close monitoring.
- Clear the airway and check how the patient is breathing.
- Rapidly assess circulation and resuscitate as necessary.
- For unconscious patients, insert a nasogastric tube and aspirate stomach contents, place the patient in the recovery position.
- Establish intravenous access. Ensure hydration and fluid balance with normal saline or Ringer lactate.
- Provide oxygen to patients with proven or suspected hypoxia (oxygen saturations < 90%).
- Make sure to look for other treatable causes of coma. Meningitis should be excluded by lumbar puncture.
- Give parenteral antibiotic therapy.

12.6 Antimalarial treatment of severe malaria

Administer injectable malaria treatment:

Preferred option for the treatment of severe malaria is artesunate IV injection.

- Weigh the patient, and calculate the dose according to body weight (mg per kg).
- Give 2.4mg/kg (higher dose of 3mg/kg for children less than 20kg), bolus injected slowly after a 10mg/ml dilution.

⇒ See Annex 17: Job Aid - Treatment of severe cases with artesunate IV
⇒ See Annex 19: Dosing tables for artesunate IV and artesunate IM

- The second dose of artesunate IV injection should be given after 12h and then every 24h if necessary.
- Give parenteral treatment for a minimum of 24h (3 doses), even if the patient is able to tolerate oral medication earlier.
- Thereafter, give a full course of the first-line ACT.

If intravenous (IV) injection is not possible, artesunate intramuscular (IM) injection into the anterior thigh is also possible using a 20mg/ml dilution.

⇒ See Annex 18: Instructions to prepare artesunate IV and artesunate IM
⇒ See Annex 19: Dosing tables for artesunate IV and artesunate IM

If artesunate injectable is not available, the following alternative treatments are acceptable:

- **Artemether IM**: 3.2mg/kg intramuscularly given at admission, then 1.6mg/kg per day

⇒ See Annex 20: Dosing table for artemether IM

- **Quinine IV infusions** must be administered with careful rate-controlled slow infusion in dextrose over 4 hours. The infusion rate should not exceed 5mg/kg per hour. It requires a first loading dose of 20mg/kg, then 10mg/kg every 8 hours.

12.7 Treatment of severe malaria in pregnancy

Severe falciparum malaria is associated with substantially higher mortality in pregnancy than in non-pregnant women. Hypoglycemia and pulmonary oedema are more frequent, and obstetric complications and associated infections are common. Severe malaria usually precipitates premature labour, and stillbirth or neonatal death is common.

For pregnant women in all trimesters, the treatment of severe malaria is the same as for non-pregnant patients with artesunate injectable followed by full course of first-line ACT.

⇒ See Section 12.6 Antimalarial treatment of severe malaria
⇒ See Section 11.6 Treatment of uncomplicated malaria in pregnancy

12.8 Management of complications

Look carefully for the following complications and administer specific treatment:

- Bacterial infection
- Hypoglycemia
- Convulsions
- Over- or underhydration
- Shock or severe dehydration
- Acute renal failure
- Pulmonary edema

⇒ See Annex 21: Guidelines for the management of complications

12.9 Supportive care and monitoring of severe malaria

Frequent monitoring of parasitemia (every 12h) is important during the first 2–3 days of treatment to monitor the parasite response to the antimalarial medicine.

Close monitoring of the patient with severe malaria is critical because the clinical situation changes quickly. The most important observations are pulse, respiratory rate and pattern, blood pressure, temperature, and level of consciousness.

Reduce high body temperatures by administering paracetamol as an antipyretic. Tepid sponging and fanning may make the patient comfortable.

Provide good nursing care. This is vital, especially if the patient is unconscious.

Pay careful attention to the patient's fluid balance to avoid over- or underhydration.

Record urine output and look for the appearance of brown or black urine (hemoglobinuria) or oliguria, which may indicate acute kidney injury.

Monitor blood glucose frequently and correct hypoglycemia if present.

Carry out regular control of hematocrit and hemoglobin concentration.

13 Interventions to interrupt transmission in active foci

All foci receive a set of malaria interventions as per their classification and their vulnerability and receptivity scores. The active *P. falciparum/*mix foci should be managed actively, with activities implemented every month for one full year to fully eliminate transmission in the foci and ensure Elimination of *P. falciparum* by 2023. Residual and cleared-up foci should be appropriately covered with case management and vector control interventions to prevent the reintroduction of malaria.

For more information, refer to surveillance guidelines.

13.1 Active Fever Screening (AFS) in active foci

The objective of house-to-house fever screening is to detect and treat malaria cases as early as possible in active foci.

AFS consist of weekly fever door-to door screening using RDT. It is operated by VMWs/MMWs and should cover the whole village as well as neighboring worksites and forest settlements.

13.2 Targeted drug administration (TDA) in active foci

The objective is to quickly reduce the parasite biomass in most at risk populations (male aged 15-49) to accelerate the interruption of malaria transmission in R1 foci. This is expected to impact *P. falciparum* as well as other species of malaria.

The TDA consists of the administration of a full 3-day ACT treatment within the focus for two consecutive months at the beginning of focus response activities.

14 Chemoprevention in special risk groups

Chemoprevention is the use of antimalarial medicines for prophylaxis and for preventive treatment. The objective of preventive treatment is to prevent malarial illness by maintaining therapeutic drug levels in the blood throughout the period of greatest risk.

WHO currently recommends intermittent preventive treatment of malaria in pregnancy (IPTp) or infants (IPTi) and seasonal malaria chemoprevention (SMC) in areas with moderate-to-high malaria transmission in Africa. None of these options are appropriate for Cambodia.

14.1 Intermittent preventive treatment for forest goers (IPTf) in active foci

The objective of this pre-exposure chemoprevention is to reduce the risk of getting malaria for all forest goers residing in active foci.

IPTf consists of the administration of a full 3-day ACT treatment in people who plan to work in forested areas within the following month. The intervention is delivered house-to-house by VMWs during the household visits for weekly active fever screening. The preventive ACT treatment can be repeated with a minimum period of one month between each treatment and for 3 consecutive months maximum.

14.2 Chemoprophylaxis for travelers

For travelers to areas with active transmission, malaria may be prevented by taking drugs that inhibit liver-stage development (causal prophylaxis) or drugs that kill asexual blood stages (suppressive prophylaxis).

In the prospect of prevention of malaria re-establishment, people resident in Cambodia travelling to malaria endemic countries should be advised to take appropriate chemoprophylaxis.

Current recommended regimen are atovaquone + proguanil, primaquine, chloroquine, mefloquine, doxycycline or tafenoquine. The appropriate regimen should be selected according to the drug resistance profile of the visited country, the level of malaria transmission and the duration of the travel.

⇒ See different options of chemoprophylaxis for adult travellers in annex 22

Please refer to WHO guidelines for the latest information.

15 Efficacy of antimalarial medicines

15.1 Resistance to antimalarials

Treatment failure is defined as the inability to clear malarial parasitemia or prevent recrudescence after administration of a therapeutic regime of a recommended antimalarial medicine, regardless of whether clinical symptoms are resolved. Drug resistance is only one of several factors that may cause treatment failure. Confirmation and characterization of parasite resistance requires additional tools (in-vitro or ex-vivo tests, analysis of molecular markers and measurement of drug concentrations in the blood).

15.2 Therapeutic Efficacy Studies (TES)

Prospective evaluations of patients' clinical and parasitological responses to treatment for uncomplicated malaria according to the WHO protocol were repeated every year in selected sites. Over the last 3 years, it has been difficult to recruit enough patients to obtain interpretable information on drug efficacy because of the marked decrease in number of *P. falciparum* malaria cases.

15.3 Integrated Drug Efficacy Surveillance (iDES)

Monitoring of drug efficacy will be integrated into the routine surveillance system. All patients will receive the full, supervised, recommended treatment, and followed up to confirm the complete cure.

Malaria cases are diagnosed (with species identification) by an RDT and/or microscopy on Day 0. Microscopy is mandatory for detecting recurrent parasitemia during follow-up and on the last day of follow-up. The minimum data must be collected at least twice: on the first day of treatment (Day 0) and on the specified last day of follow-up. For *P. falciparum*, the appropriate follow-up period is 42 days for drugs with a long half-life like artesunate–mefloquine and artesunate–pyronaridine. If feasible, additional follow-up on Day 3 and then weekly on Days 7, 14, 21, 28 and 35 is recommended. The blood slides must be read within 24h by a quality assured microscopy laboratory. Patients and referent care providers should be immediately informed about the result and those with a positive result be quickly treated with the second line treatment.

Dry blood spots on filter paper are collected for PCR/genotyping and used to confirm Day 0 diagnosis by PCR, distinguish between reinfection and recrudescence in case of reappearance of parasitemia and to look for molecular markers of drug resistance.

For *P. vivax*, the follow-up period is 28 days for asexual stages and 3 months for relapses.

15.4 Molecular resistance markers

Increased copy numbers of *P. falciparum* multidrug resistance 1 protein (Pfmdr1) and *P. falciparum* plasmepsin 2–3 (Pfpm2–3) have been associated with *P. falciparum* resistance to

mefloquine and piperaquine resistance, respectively. Resistance of *P. falciparum* to artemisinin is strongly associated with point mutations in the propeller region of the PfKelch13 gene. Systematic collection of dried blood spots on filter papers for analysis of validated molecular markers every year can be used to monitor trends. The aim is to collect data from a sample large enough to obtain significant results. While molecular markers can be used to monitor trends, clinical data will nevertheless be needed to inform treatment policies. The frequency of parasites with a given resistance marker can be estimated at the desired level of geographical aggregation (province or district) and mapped.

15.5 Criteria for drug policy change

TES/Integrated drug efficacy surveillance is the means to monitor drug efficacy. For artesunate–mefloquine (AS-MQ) and artesunate–pyronaridine (AS-PYR), the key outcome indicator of drug efficacy monitoring is the proportion of patients with treatment failure by the end of follow-up (day 42 for *P. falciparum* and Day 28 for *P. vivax*).

In line with WHO recommendations, a change in the treatment policy is required when the failure rate of the first-line drug is ≥ 10%.

A new antimalarial medicine should have a parasitological cure rate of > 95% to be adopted as first or second line.

16 Safety of antimalarial medicines

16.1 Pharmacovigilance system and reporting of adverse drug reactions

The Department of Drug and Food (DDF) manages the pharmacovigilance center and web-based system for the reporting of adverse reactions. All health facilities should be trained to enter information on a generic report to report adverse drug reaction on a dedicated web portal or transmit the paper version to DDF.

⇒ See Annex 14: Adverse drug reaction report – DDF pharmacovigilance center

In addition, CNM has developed specific MIS App for the follow-up of patients treated by primaquine for *P. vivax* radical cure. VMW/MMWs and health facilities use it to report suspicions of primaquine induced adverse reactions on their smartphones or tablets.

A similar system will be developed to capture and report adverse reactions possibly induced by ACTs administered for TDA or IPTf in active foci.

16.2 Investigations and management of reported adverse drug reactions

Reported severe adverse drug reactions should be investigated to compile clinical and laboratory evidences and assess whether they are induced by PQ or other antimalarial drugs.

All reported severe adverse drug reaction after PQ radical treatment should be investigated.

⇒ See Annex 15: Investigation of reported adverse reaction after PQ radical treatment

17 Quality of diagnosis & treatment

17.1 Pre-qualification and registration of diagnosis tests and antimalarial medicines

WHO has established an international mechanism to prequalify manufacturers of RDTs and antimalarials on the basis of their compliance with internationally recommended standards of manufacture and quality.

RDTs and ACTs available at points of care should be prequalified by WHO.

17.2 Quality assurance (QA) of microscopy

When targeting elimination, a comprehensive and active quality assurance (QA) program of malaria laboratory diagnosis is of key importance. Quality assurance of malaria microscopy is required to ensure the efficiency, cost-effectiveness and accuracy of test results continuously and systematically. The primary objective is to ensure that health care professionals and patients have full confidence in the laboratory result.

An operational manual for quality assurance of malaria diagnosis has been developed in line with basic principles and concepts recommended by WHO. The main components of the QA are outlined as well as a comprehensive set of standard operating procedures (SOPs), checklists, and standard forms.

The parasitological laboratory at CNM is designated as the National Malaria Reference Laboratory (NMRL) with a national core group (NCG) of highly qualified microscopists (WHO-certified Level 1/2).

Microscopists should be CNM-certified Level A or Level B by standard national competency assessment of malaria microscopists (NCAMM) and regularly re-trained to maintain their competency. Supervision of malaria laboratories and slide cross-checking must be conducted regularly to evaluate the performance of the microscopists continuously.

17.3 Quality assurance of rapid diagnostic tests

The quality assurance of malaria diagnosis by RDTs should be in line with the WHO recommendations on RDT procurement, post purchase RDT lot testing, storage and performance.

WHO pre-qualified selected products meet the following the evaluation criteria:

- For the detection of *P. falciparum* and *P. vivax* in all transmission settings, the panel detection score against *P. falciparum* samples should be at least 75% at 200 parasites/µL;
- The false-positive rate should be less than 10%; and
- The invalid rate should be <5%.

WHO recommends **post purchase RDT lot testing** at the Research Institute for Tropical Medicine – Philippines.

RDTs must be transported and stored in accordance with the manufacturer's instructions.

17.4 Quality assurance of quantitative G6PD test

The user manual of the SD Biosensor STANDARD G6PD system details the quality control procedures.

A Control test is required when opening a new test device packaging (new lot number) or whenever the result does not agree with the test result expected.

A Check Strip test is required when using the analyzer for the first time; whenever the result does not agree with the test result expected; when replacing the batteries or cleaning the analyzer; or when dropping the analyzer.

Storage of Test Kit: The sealed pouch containing the test device may be stored at 2°C to 30°C (36°F to 86°F) out of direct sunlight. Perform test at 15°C to 40°C (59°F to 104°F).

⇒ See Annex 8: Job Aid – Instruction to perform quality control of SD Biosensor

17.5 Quality assurance of antimalarial medicines

As the national drug regulatory authority, the Department of Drug and Food (DDF) ensures that the antimalarial medicines are of acceptable quality, through market regulation, inspections, and law enforcement.

17.6 Capacity building

Training manuals are developed for in-service training courses on diagnosis and treatment which are planned and organized by CNM, providing Training of Trainers (TOT) to Provincial Health Departments (PHDs) and Operational Districts (ODs) at regular intervals. PHDs in collaboration with ODs then provide cascade training to HCs, and HCs provide cascade training to VMWs/MMWs, with PHDs/ODs support. The main objective is to provide supplemental information and instructions for training, so that all trainings conducted use standardized training curriculum throughout the country.

Optimal periodicity of regular in-service trainings for health facility staff is of 2 years. In addition, special courses might also be organized when significant changes must be operated at points of care level. For example, MMWs may need additional specific training for their outreach activities.

Job aids should be developed and provided to health facilities and VMWs.

17.7 Supervisions

In health facilities, supportive supervision and quality assurance assessments should be

performed quarterly by PHDs/ODs and CNM. VMWs should attend monthly meetings or quarterly for integrated VMWs at health center level. Supervision MIS App including check-list, scoring tools to assess competency of VMW/MMWs are available on tablets.

18 Monitoring and evaluation of diagnosis & treatment

Several indicators in the table below are included in the Monitoring & Evaluation framework of the MEAF 2021-2025 to monitor the outcome and coverage of diagnosis and treatment interventions. Annual targets have been defined in line with the MEAF objectives. Data elements are collected on real-time through the MIS and main indicators can be visualized on the CMN MIS platform on request.

Table 18.1 Indicators in MEAF 2021-2025 to monitor diagnosis and treatment interventions

	2021	2022	2023	2024	2025
Annual blood Examination Rate: Number of parasitological tests per 100 population	4	4	4	4	4
Percentage of *P. falciparum* and mix cases that received treatment according to NTG	>95%	>95%	>99%		
Percentage of *P. vivax* cases that received treatment according to NTG	60%	75%	85%	>95%	100%
Percentage of care providers with adequate case management practices observed during supervision	100%	100%	100%	100%	100%
Percentage of points of care with a sufficient closing stock balance of RDTs or antimalarials	100%	100%	100%	100%	100%

19 References

References on malaria diagnosis

WHO/UNICEF (2011) Integrated Management of Childhood Illness: Caring for Newborns and Children in the Community. Manual for the Community Health Worker.

WHO (2011) Universal access to malaria diagnostic testing: an operational manual.

WHO (2014) Policy brief on malaria diagnostics in low-transmission settings

WHO (2015) Training materials on the use of malaria RDT

WHO/FIND/CDC (2017) Malaria rapid diagnostic test performance. Results of WHO product testing of malaria RDTs: round 7 (2015-2016).

WHO (2016) Malaria microscopy quality assurance manual – Ver. 2 - January 2016

WHO (2019) Recommended selection criteria for procurement of malaria rapid diagnostic tests - Information Note

CNM (2019) Quality Assurance of Malaria Diagnosis - Operational Manual

References on malaria treatment

WHO (2005) Pocket book of hospital care for children: Guidelines for the management of common illnesses with limited resources.

WHO (2010) Good procurement practices for artemisinin-based antimalarial medicines - March 2010

WHO (2013) Management of severe malaria – A practical handbook. Third edition

WHO (2015) Guidelines for the treatment of malaria. Third edition - April 2015.

WHO (2015) Policy brief on single-dose primaquine as a gametocytocide in Plasmodium falciparum malaria - January 2015

WHO (2016) Testing for G6PD deficiency for safe use of primaquine in radical cure of *P. vivax* and *P. ovale* – Policy brief - October 2016

WHO (2019) The use of artesunate-pyronaridine for the treatment of uncomplicated malaria – Information note - October 2019

WHO (2020) Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010–2019)

WHO (2021) Malaria terminology, 2021 update

WHO (2022) Guidelines for malaria treatment – Update 18 February 2022

CNM (2020) Training manual for Diagnosis & treatment – Facilitator guide

References on drug efficacy in Cambodia

Mairet-Khedim et al. (2021) Clinical and In Vitro Resistance of Plasmodium falciparum to Artesunate-Amodiaquine in Cambodia. Clin Inf Dis 2021;73(3):406–13

Peto et al. (2022) Triple therapy with artemether–lumefantrine plus amodiaquine versus artemether–lumefantrine alone for artemisinin-resistant, uncomplicated falciparum malaria: an open-label, randomised, multicentre trial. Lancet Infect Dis 2022

Wojnarski et al (2020) Atovaquone-Proguanil in Combination with artesunate to treat multidrug-resistant P. falciparum malaria in Cambodia: An Open-Label Randomized Trial.

Leang et al. (2019) Efficacy and Safety of Pyronaridine-Artesunate plus Single- Dose Primaquine for the Treatment of Malaria in Western Cambodia. Antimicrob Agents Chemother 63:e01273-19

Leang et al. (2016) Efficacy and Safety of Pyronaridine-Artesunate for Treatment of Uncomplicated Plasmodium falciparum Malaria in Western Cambodia. Antimicrob Agents Chemother 60:3884 –3890.

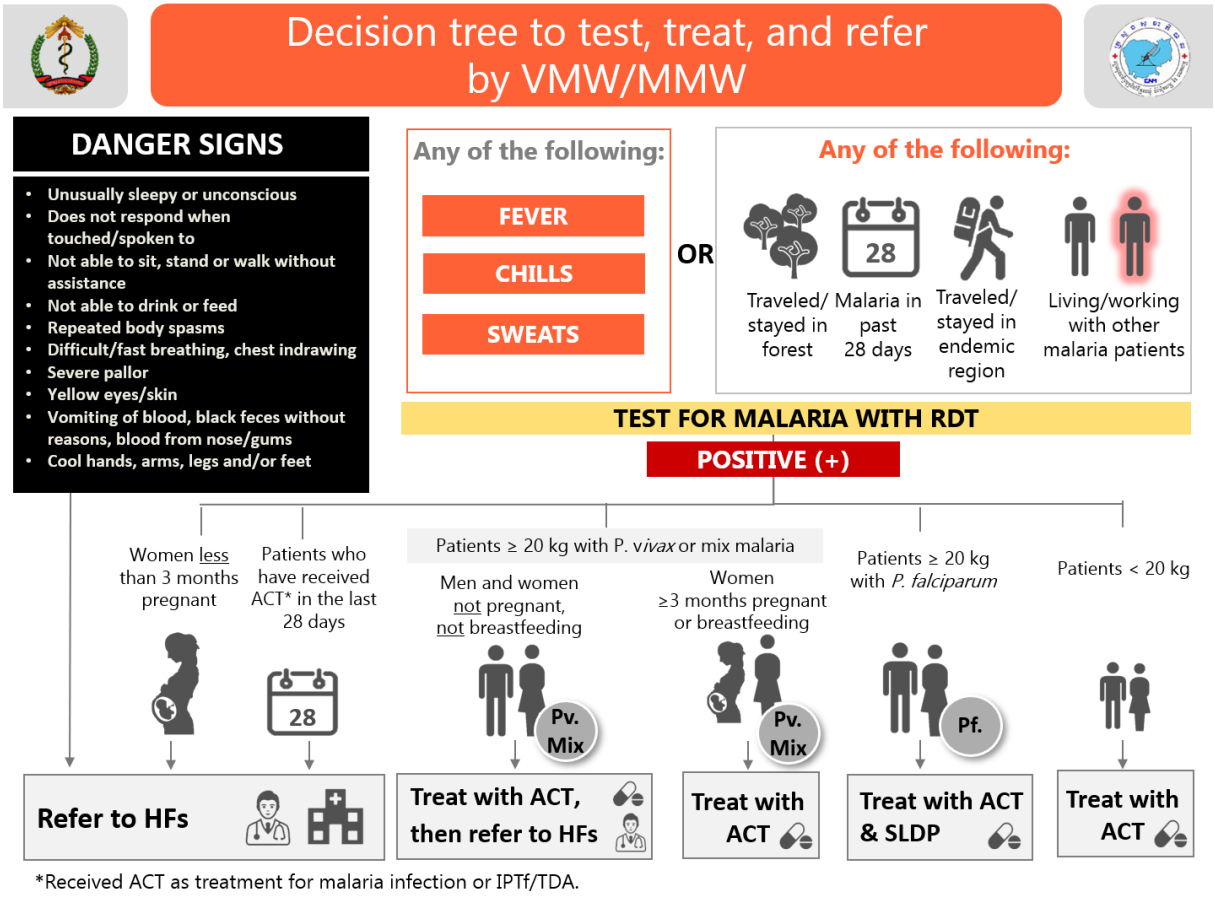
Leang et al. (2015) Evidence of Plasmodium falciparum Malaria Multidrug Resistance to Artemisinin and Piperaquine in Western Cambodia: Dihydroartemisinin-Piperaquine Open-Label Multicenter Clinical Assessment. Antimicrob Agents Chemother 59:4719 –4726.

Van der Pluijm et al. (2020) Triple artemisinin-based combination therapies versus artemisinin-based combination therapies for uncomplicated Plasmodium falciparum malaria: a multicentre, open-label, randomised clinical trial. Lancet 2020; 395: 1345–60.

Jacob et al. (2021) Genetic surveillance in the Greater Mekong subregion and South Asia to support malaria control and elimination. eLife 2021;10:e62997

Annexes

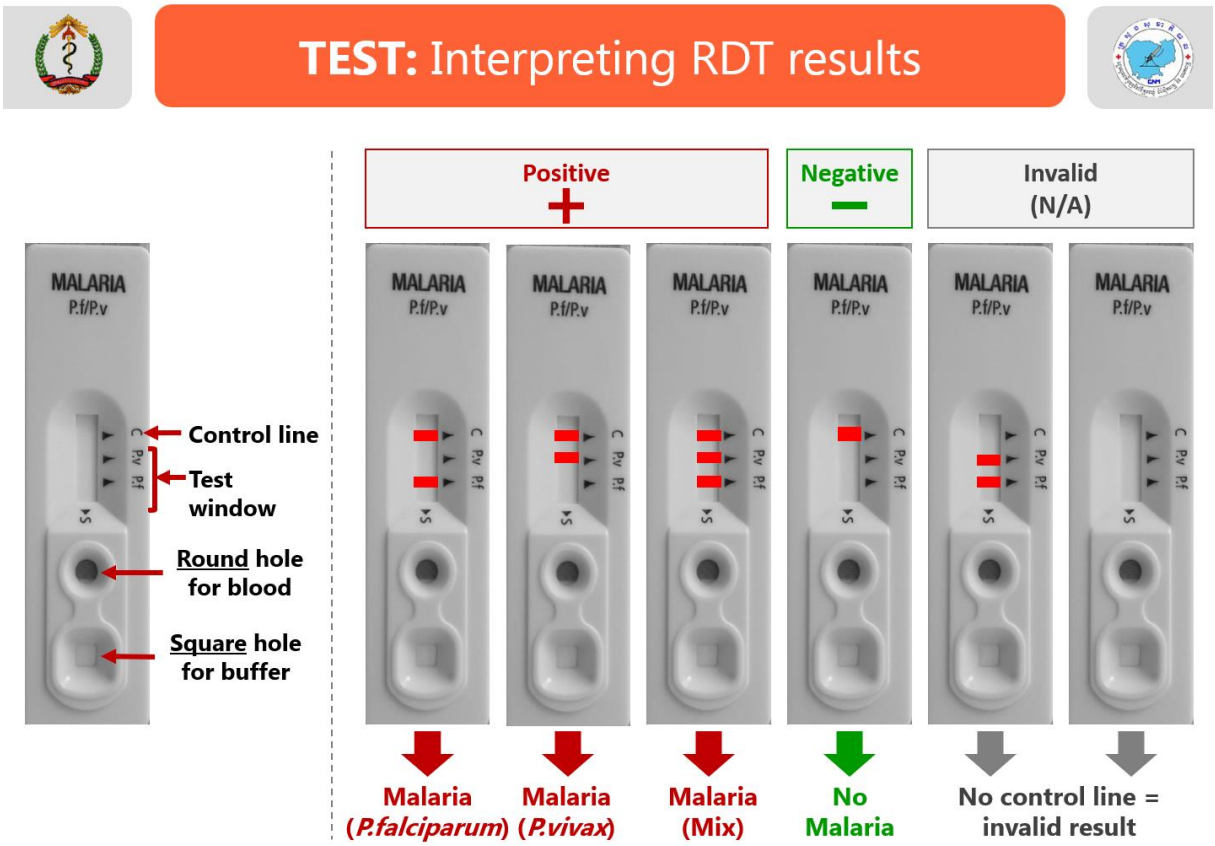
Annex 1: Job Aid – Diagnosis & Treatment flow chart for VMW/MMWs



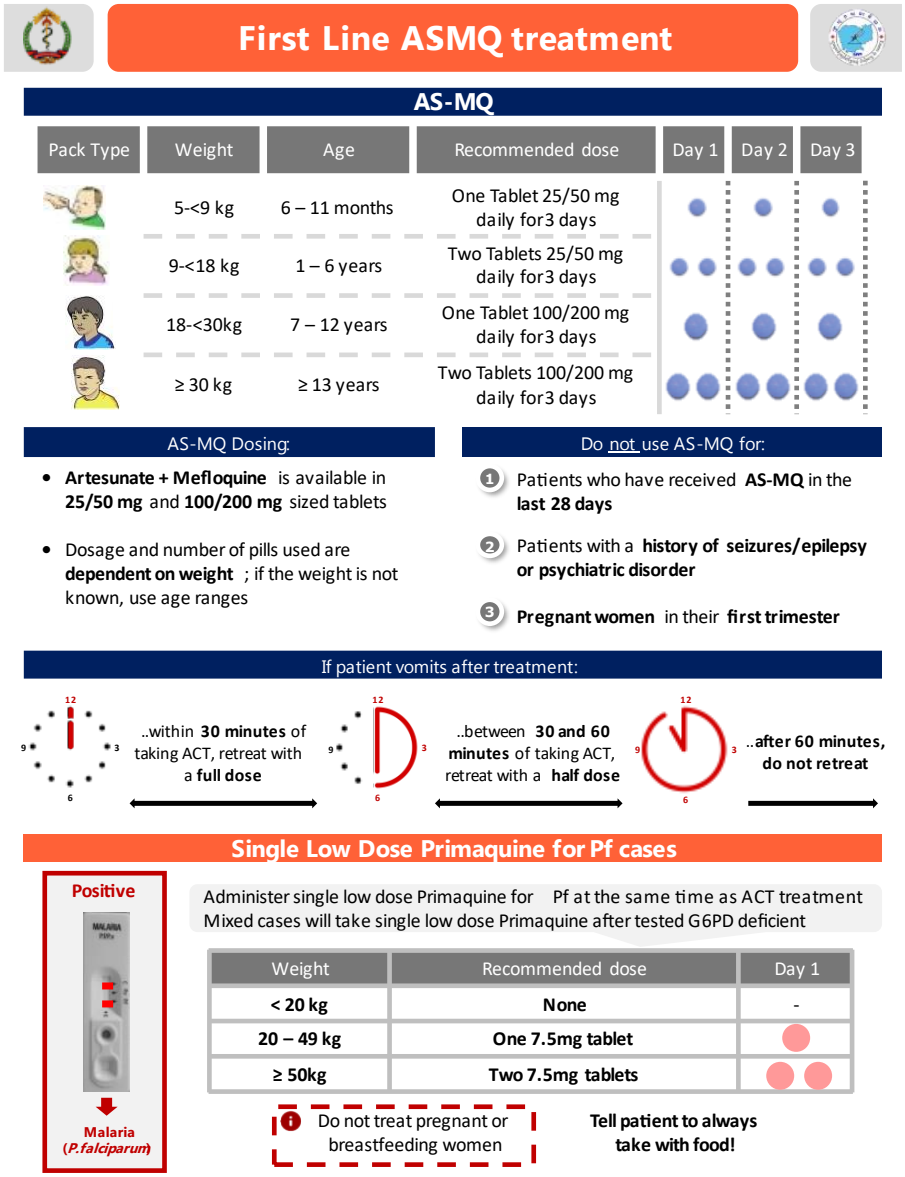
*Received ACT as treatment for malaria infection or IPTf/TDA.

Annex 2: Job Aid - Instruction to perform RDT

Annex 3: Job Aid – Interpretation of RDT result



Annex 4: Job Aid – Treatment of uncomplicated malaria



Annex 5: Counselling for the treatment of uncomplicated malaria

1. Take at least 10 minutes for patient counselling.
2. Praise the patient for coming to seek care early.
3. Reassure them; tell them that they will be cured soon.
4. Let them hold the blister of drugs as you explain how to take the tablets:
   - Tell them it is better to eat some food before taking tablets
   - If they vomit within 30 minutes of taking tablets, take another dose to replace it
   - If they vomit within one hour, take half the dose
5. Ask them to repeat what you have told them. If something in the description is wrong, explain again.
6. Ask if they have any question.
7. Tell them to come back if condition gets worse or if they still have fever after 3 days.

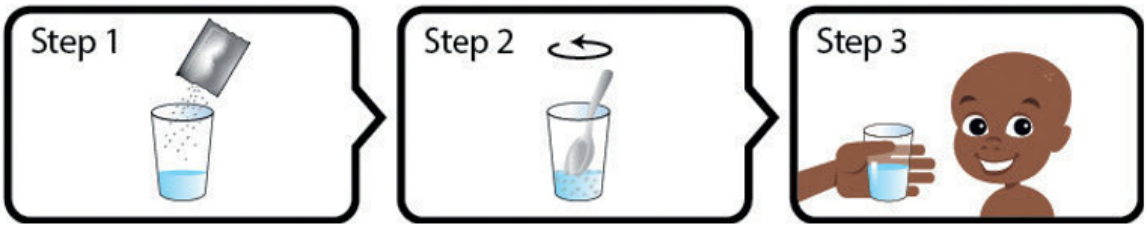
Annex 6: Job Aid – Alternative pediatric treatment of uncomplicated malaria

Alternative AS-PYR pediatric treatment

AS-PYR - Pyramax (Weight: 5 – <18kg; Age: 0 – 6 years)

ACT Type	Weight	Recommended dose	Day 1	Day 2	Day 3
Artesunate/ pyronaridine (Pyramax) 60/20 mg sachets	5 – <8 kg	One Sachet daily for 3 days			
	8 – <15 kg	Two Sachets daily for 3 days			
	15 – <18 kg	Three Sachets daily for 3 days			

Instruction for Use



Step 1. Put granule in a little water.
Step 2. Stir gently until a uniform suspension is obtained.
Step 3. Give now. Make sure the child drinks all the suspension.
Add a little water and repeat until all the suspension is taken.

If patient vomits after treatment:

..within **30 minutes** of taking ACT, retreat with a **full dose**

..between **30 and 60 minutes** of taking ACT, retreat with a **half dose**

..**after 60 minutes, do not retreat**

Single Low Dose Primaquine for Pf cases

- **No Primaquine is provided for children under 20kg**

Annex 7: Job Aid – Instruction for quantitative G6PD testing with SD Biosensor

SD BIOSENSOR G6PD TEST

G6PD Testing Instruction Job Aid
May 2022

Prepare the machine, test device and buffer (step 1-9) BEFORE doing the blood collection (step 10).

1. Check the room temperature is between 15-40°C.
2. Put on gloves.

3. Insert the code chip when using tests from a new or different box (skip this step for the tests from the same box)

4. Check the expiration date printed on the test device pouch.

5. Ensure the code number on the screen matches with that on the test device pouch.

6. Open the pouch and take out the test device.

7. Insert the test device until it will not go any further.

8. When 'OPE' appears on the screen, open the chamber flap.

9. Check the expiration date, then open the buffer tube and place it on a rack.

10. Clean the finger with an alcohol swab, then prick it and remove the first drop with gauze. Put used lancet in sharp bin immediately.

11. Hold the stem of EZI tube horizontally, then touch the tip of the EZI tube to the blood drop. Fill to black line (10µL).

12. Mix the blood sample with extraction buffer by squeezing and releasing the EZI tube bulb 8- 10 times.

13. Discard used EZI tube in a sharp bin (or a biohazard waste bin).

14. Take a new EZI tube.

15. Hold the stem of the EZI tube horizontally, then touch its tip to the blood-buffer mix. Do not cover hole on bulb. Fill to black line (10µL).

16. Apply the sample to the specimen application hole of the test device.

17. Close the chamber immediately after applying and 'CLO' will appear on the screen. If not, restart from step 1 using a new test.

18. Wait for 2 min for the test result to appear on the screen. Check the date and report the results. Hb must be >7g/dL to interpret G6PD.

19. Remove the used test device and discard it in sharp bin or biohazardous waste bin.

Interpretation of the results

1. Check the hemoglobin result:
Interpretation of the G6PD Test results should only be performed when Hb level is >7g/dL. Perform a confirmatory test if Hb level is ≤ 7g/dL. **No treatment provided to Hb level ≤ 7g/dL.**

2. Check the G6PD result according to the below table and provide radical cure:

- daily Primaquine for 14 days to **G6PD normal patients**
- weekly Primaquine for 8 weeks to **G6PD intermediate and deficient patients*** (*to be implemented after receiving training from CNM)

G6PD activity	Male	Female
≥ 6.1	Normal	Normal
≥ 4.1 – 6.0		Intermediate
≤ 4.0	Deficient	Deficient

Annex 8: Job Aid – Instruction to perform quality control of SD Biosensor

SD BIOSENSOR G6PD TEST

G6PD Quality Control Job Aid
May 2022

Steps for Internal Quality Control – Check strip & Quality Control Kit

*Use the **check strip** when:*

- Using your analyzer for the first time
- The result does not agree with the test result expected
- Replacing the batteries or cleaning the analyzer
- You have dropped the analyzer

1. Switch on the analyzer and press Left and Right button together for 3 seconds to enter the check strip test mode.

2. When the 'CHE' appears on the screen, insert the check strip.

3. Wait 10 seconds

4. If there is any problem for the analyzer, 'EEE' error message will appear on the screen. Otherwise, 'OK' message will appear on the screen.

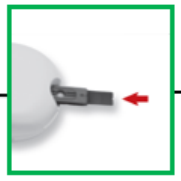
*Use the **Quality Control** when:*

- Every time a new kit of test strips is opened, use 2 test strips to do one level 1 control & one level 2 control

1. Check the expiration date, code number on the foil pouch, and ensure code number on the codechip matches

2. Open the foil pouch and take a test device out

3. Hold the test device with thumb and index finger so that the upper test device is facing upwards.



4. Insert the test device completely into the test device slot of a G6PD Analyzer.

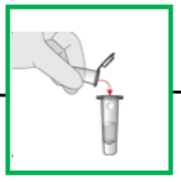
5. 'OPE' displays. **Press the left button for 3 seconds. "C" mark will be appeared on the screen. "C" mark represents control test mode**

6. Open the measurement chamber flap.

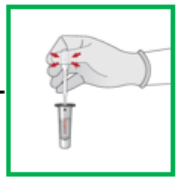
7. Check the expiry date printed on the control bottle.

8. Open the control bottle and take a tube out of the bottle.

9. Open an extraction buffer pouch and take an extraction buffer out of the pouch. Check the expiration date.

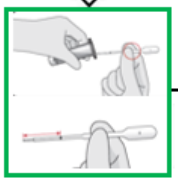


10. Put the control tablet into the extraction buffer.

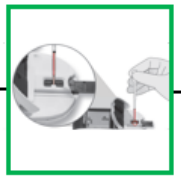


11. Mix the collected specimen with extraction buffer, pressing and releasing a new Ezi tube 8 to 10 times.

12.Discard the used Ezi tube. Take out an unused Ezi tube.



13. Hold the Ezi tube horizontally and touch the tip of Ezi tube. Capillary action will automatically draw the control material to the black line and stop.



14. Apply the control mixture to the test device

15. 'CLo' will appear on the scree. Close the measurement chamber flap. Discard the used Ezi tube in a biosafety box.

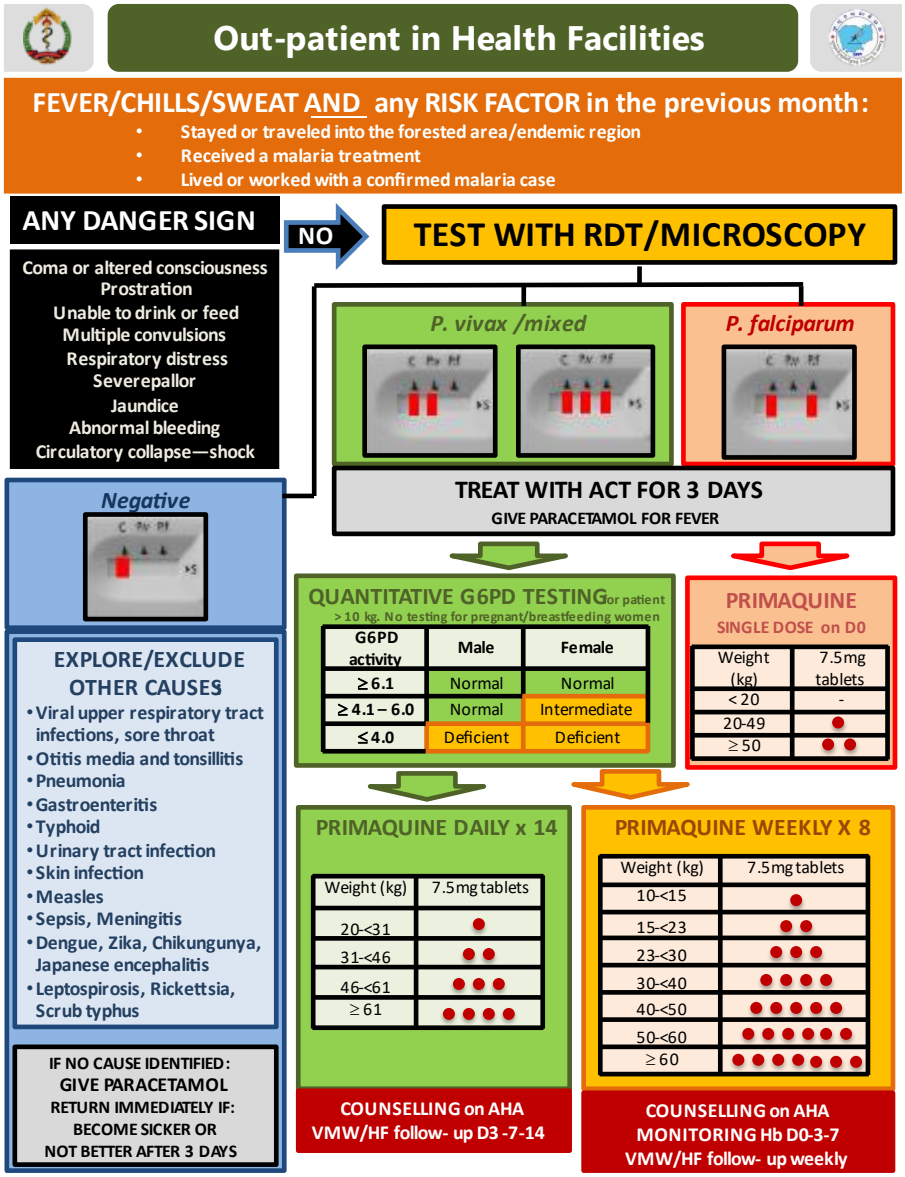
16. After 2 minutes of reaction time, the test result will appear on the screen.

[Control Range]

	G6PD	T-Hb
Level 1	0.1-3.0 U/g Hb	6.0-12.0 g/dL
Level 2	6.0-17.0 U/g Hb	13.0-20.0 g/dL

If the test result shows out of range of indicated control range, repeat the test.
If the control values fall repeatedly outside of the established control ranges, then stop using the STANDARD G6PD system and please contact PHD/OD. PHD/OD will contact CNM for further actions.

Annex 9: Job Aid – Diagnosis & Treatment flow chart for health facilities



Annex 10: Counselling for patient with P. vivax malaria who tested to be G6PD deficient or intermediate

Patients with vivax malaria usually have parasites that stay hidden in the liver and enter blood later, which will make the patient sick again with malaria symptoms.

To get rid of these parasites from the liver, it is recommended that patients who have vivax malaria receive treatment with primaquine every day for 14 days as long as they have normal levels of glucose-6-phosphate dehydrogenase (G6PD).

Unfortunately, the test has detected what is called G6PD deficiency. You have a low amount of G6PD in the red blood cells that carry oxygen in the blood around the body. You do not feel anything wrong but your red blood cells can get broken or get damaged more easily if you take certain medications, such as primaquine. It could result in a large number of their red blood cells being damaged and make you sick.

You may also have a higher risk of anemia when you take the following medications: Dapsone, Nitrofurantoin, Ciprofloxacin, Norfloxacin, Cotrimoxazole, Chloramphenicol, Sulfa-drugs, Aspirin. It could also be caused by food: Fava beans, soya beans or bitter melon.

You can receive a weekly primaquine treatment under strict monitoring. You better take it with food to reduce stomach irritation. There is still a very small risk that your red blood cells would be damaged and make you sick. In most cases, this can be corrected by stopping primaquine treatment when these symptoms develop. In rare cases, some patients may need a blood transfusion in hospital to replace the red blood cells that were damaged. The most common symptoms are fatigue, shortness of breath after activity, rapid breathing, pallor, and increased heart rate, yellowing of skin and eyes, or dark, tea colored urine or back pain. In rare cases, some patients may need a blood transfusion in hospital to replace the red blood cells that were damaged.

For this reason, you must come back to the health center on D3 and D7 during the first week. We'll test your blood and ask you if you have any of the following 5 symptoms:

1- Pallor, yellowing of skin and eyes
2- Shortness of breath after activity, rapid breathing
3- Increased heart rate, palpitations, tachycardia
4- Back pain
5- Dark colored urine

If you have one of these symptoms, do not wait. You should visit the closest health center immediately and tell that you are taking primaquine treatment. If the health center is closed, then you should go to the nearest hospital.

If well tolerated during the first week, you should take the treatment once every week for 8 weeks. The treatment will not be efficient if you stop before. We'll visit or phone you weekly and at the end of the treatment to check if you have completed the 8-week treatment.

Annex 11: Counselling for patients with P. vivax malaria who tested to be G6PD normal

Patients with vivax malaria usually have parasites that stay hidden in the liver and enter blood later, which will make the patient sick again with malaria symptoms. This can result in frequent recurrences of vivax malaria. Having malaria recurrence frequently can make your body weaker due to lowering of the red blood cells in your body, and it can affect your ability to work or take care of your family when you are sick. To get rid of these parasites from the liver, it is recommended that patients who have vivax malaria receive treatment with primaquine every day for 14 days as long as they have normal levels of glucose-6-phosphate dehydrogenase (G6PD). Taking primaquine will kill and eliminate hidden parasites in the liver and make the patient less likely to have recurrence of the infection.

For patients like you, tested with a normal G6PD level, taking primaquine treatment is generally very well tolerated and most people able to complete the full 14 days course. You better take it with food to reduce stomach irritation.

However, there is still a very small risk that the test was not interpreted properly or did not detect a mild G6PD deficiency. Your red blood cells would be damaged and make you sick. In most cases, this can be corrected by stopping primaquine treatment when these symptoms develop. In rare cases, some patients may need a blood transfusion in hospital to replace the red blood cells that were damaged.

For this reason, we are going to follow you up by phone calls on D3 and D7 during the first week. We'll ask you if you have some of the following 5 symptoms:

1- Pallor, yellowing of skin and eyes
2- Shortness of breath after activity, rapid breathing
3- Increased heart rate, palpitations, tachycardia
4- Back pain
5- Dark colored urine

If you have one of these symptoms, do not wait for the phone call. You should visit the closest health center immediately and tell that you are taking primaquine treatment. If the health center is closed, then you should go to the nearest hospital.

If well tolerated during the first week, you should take the treatment once every day for 14 days. The treatment will not be efficient if you stop before. We'll visit or phone you on day 3, 7, and at the end of the treatment to check if you have completed the 14 days treatment.

Annex 12: Patient's follow-up card for primaquine radical cure

Patient Treatment and Information Form for Patient to Track their Treatment Course

For *P. falciparum*, *P. knowlesi* and *P. malariae* malaria patients

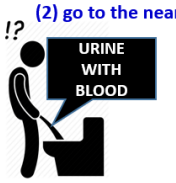
1. Complete the **3-day full treatment dose** based on the instruction provided by your health provider.
2. A treatment provider or village malaria worker (VMW) will support you to complete your medication. He/she will **visit your house to follow up** on your medication **on Day 3** after you get the treatment.

For *P. vivax*, *P. ovale* and mixed malaria patients

1. In addition to the **3-day full treatment dose of ACT**, radical cure is provided for all *P. vivax, P. ovale* and mixed malaria patients. G6PD normal patients complete **14-day Primaquine**, and G6PD intermediate and deficient patients complete 8-week Primaquine.
2. For 14-day Primaquine, a treatment provider or village malaria worker (VMW) will support you to complete your medication. He/she will **call or visit your house to follow up** on your medication **on Day 3, Day 7 and Day 14** after you get the treatment.
3. For 8-week Primaquine, patients are required to travel back to HC on **Day 3 and Day 7** for checking the hemoglobin level before receiving the next dose. From Week 3, the completion of the medication will be supervised by HC or VMW via phone call or visits.
4. **What do I do if I miss a dose?** Continue taking your medication according to your schedule. Do not take 2 doses at the same time.

If you take the full dose of medication, you reduce the chance of relapse and prevent transmission of malaria to your household and colleagues

If you experience any of these signs and symptoms below, stop taking primaquine and
(1) go to visit the original health provider (health centers or hospitals) immediately
(2) go to the nearest hospital immediately, if the health center is closed or you have traveled to other areas




Pallor, yellow skin and eyes


Shortness of breath, rapid breathing


Back pain


Increased heart rate, palpitations, tachycardia

For all patients - How can you protect yourself from malaria?

1 
Sleep under bed nets at all times

2 
Wear long sleeved clothes
Particularly in the evening and in the forest

3 
If you or a family member has a fever, go for malaria testing at nearest health facilities or VMW/MMW

Patient ID: ____ Patient Name: ____ Sex: M / F Weight (kg): ____ Species: Pf / Pv / mix / Pk / Po / Pm

Date of G6PD test: ____ G6PD value: ____ U/g Hb Hemoglobin level: ____ g/dL G6PD level: ____ Current Village: ____

HF Name: ____ HF Phone No.: ____ Assigned Hospital Name: ____ Assigned Hospital Phone No.: ____

ACT (for all patients)

	Date	Checked when completed
DAY 0 *		☐
DAY 1		☐
DAY 2		☐

SLD PRIMAQUINE (only for Pf patients)

	Date	Checked when completed
DAY 0 *		☐

PRIMAQUINE (only for Pv, Po & mixed patients)

G6PD normal (14-day PQ)

	Date	Checked when completed		Date	Checked when completed
DAY 0 *		☐	DAY 7		☐
DAY 1		☐	DAY 8		☐
DAY 2		☐	DAY 9		☐
DAY 3		☐	DAY 10		☐
DAY 4		☐	DAY 11		☐
DAY 5		☐	DAY 12		☐
DAY 6		☐	DAY 13		☐

G6PD intermediate & deficient (8-week PQ)

	Date	Checked when completed
Week 1 *		☐
Week 2		☐
Week 3		☐
Week 4		☐
Week 5		☐
Week 6		☐
Week 7		☐
Week 8		☐

Please take the medications with food to reduce stomach irritation. Please take this card with you all the time!
***Record for D0 to be filled at HF after observation of treatment intake**

Annex 13: Checklist for monitoring of radical treatment by VMWs

Job Aid – VMW's Checklist for adherence and side effect monitoring for P. Vivax Radical Cure

1 When arriving at patient house,

a) Check the patient adherence follow-up form (14-day PQ for G6PD normal and 8-week PQ for G6PD intermediate and deficient) and verify the amount of remaining medication

b) Ask patients if there was any history of side effects after taking the medicine.

c) If the patient has not completed the medication yet, ask the patients what are the reasons

2 Ask the patient about any history of side effects or signs and symptoms of acute hemolytic anemia (AHA), since the day of taking the medicine, or since the previous visit by VMW on day 3, day 7 and day 14 (14-day PQ), or the previous week (8-week PQ).

Urine with blood
*Examine patient's urine in a bottle, and compare with the urine color chart

Pallor (pale skin or yellow eyes, nails or lips)
*Examine patient skin, eyelids, nails and lips

Shortness of breath
*Ask and observe the patients

Back pain
*Ask and observe the patients

Increased heart rate
*Ask and observe the patients

3 VMWs must report the data to MIS via phone

If VMW finds any dangerous sign among above 5 symptoms with the patient, please:

1 – Call the HC staff to consult if the patient needs to be referred, or, refer the patients to HCs (without consult)

2 – Record the actions taken in MIS app

Version: May 2022

Annex 14: Adverse drug reaction report – DDF pharmacovigilance center

ក្រសួងសុខាភិបាល
នាយកដ្ឋានឱសថ ចំណីអាហារ បរិក្ខារពេទ្យ
និងគ្រឿងសំអាង

ព្រះរាជាណាចក្រកម្ពុជា
ជាតិ សាសនា ព្រះមហាក្សត្រ

CONFIDENTIAL
see reverse side for directions

ដាស់ដាក់
សូមអាន ការណែនាំខាងក្រោយ

របាយការណ៍ស្តីអំពីប្រតិកម្មរំខានរបស់ឱសថ
ADVERSE DRUG REACTION REPORT

ព័ត៌មានអ្នកជំងឺ /PATIENT INFORMATION

ឈ្មោះ/Full Name:..... ភេទ/Sex: ☐ស្រី/ F ☐ប្រុស/ M អាយុ/ Age : .....(ឆ្នាំ/Y) ទម្ងន់/Weight: .....(Kg)
មានផ្ទៃពោះ/Pregnancy: ☐គ្មាន/No ☐មាន/Yes (ខែទី/In which month.....) ទូរស័ព្ទទំនាក់ទំនង/Telephone:.....

ឱសថសង្ស័យថាមានប្រតិកម្មរំខាន / SUSPECTED DRUGS

ឈ្មោះឱសថ (លេខឡុត និង ថ្ងៃផុតកំណត់) Drug Name (Batch and Expiry date)	ផ្លូវប្រើប្រាស Route	កំរិតប្រើ Dosage	គោលបំណងក្នុងការប្រើប្រាស Reason for Use	ថ្ងៃចាប់ផ្តើមប្រើ Date Started	ថ្ងៃឈប់ប្រើ Date Stopped

ឱសថប្រើប្រាស់រួមជាមួយឱសថសង្ស័យខាងលើ (រួមទាំងឱសថបុរាណ) / OTHER MEDICINES IN USE (INCLUDING HERBAL MEDICINES)

ប្រតិកម្មរំខានរបស់ឱសថដែលកើតមាន / ADVERSE DRUG REACTIONS

ថ្ងៃចេញរោគសញ្ញា/Onset Date: ..... ថ្ងៃបាត់រោគសញ្ញា/ Stopped : .....

សូមរៀបរាប់ពីរោគសញ្ញា/Description :.....
.....
.....
.....

ភាពធ្ងន់ធ្ងរបស់ប្រតិកម្មរំខាន/Severity of ADRs:
☐ស្រាល/Mild ☐មធ្យម/Moderate ☐ធ្ងន់ធ្ងរ/Severe
☐ស្លាប់/Fatal ☐មិនដឹង/Unknown

យោបល់ផ្សេងៗ/Other comments:.....
.....
.....

ព័ត៌មានអ្នករាយការណ៍/REPORTER INFORMATION

ឈ្មោះ/Name:.....
☐វេជ្ជបណ្ឌិត/Medical Doctor ☐ទន្តបណ្ឌិត/Dentist
☐ឱសថការី/Pharmacist ☐គិលានុបដ្ឋាក/Nurse
អ្នកជំងឺទៀត/Others:.....
ទូរស័ព្ទ/Telephone:.....

ថ្ងៃទី/Date: ...../...../.....
ហត្ថលេខា/Signature
.....

សូមកុំបំពេញទីនេះ:/For Official Use Only
លេខចុះបញ្ជី:.....
ថ្ងៃទទួល:.....
អ្នកទទួល:.....

Annex 15: Investigation of reported adverse reaction after PQ radical treatment

Date of investigation: __/__/20__
Name of investigator: _____ □ PHD □ OD □CNM □ other _____

Patient name: _____ Sex: __ Age: __ __ Weight (kg): __ __

Date of G6PD test: __/__/20__ Name of HC: _____
Qualitative RDT - Type: _____ Result: Non-deficient □ Deficient □
Quantitative test – Type: _____ Result: ___. __ UI/g Hb - Hb ___. __ g/dl

Date start of PQ treatment: __/__/20__ Dosing per day: __ __mg for __ __days
Date end of PQ treatment: __/__/20__

Date of clinical check: __/__/20__
Name of HC □ Hospital □ _____ Name of health worker _____
Date onset of reported symptoms: __/__/20__
Reported signs and symptoms: □ Pallor, yellowing of skin and eyes**;** □ Shortness of breath after activity, rapid breathing**;** □ Increased heart rate**;** □ Back pain**;** □ Dark colored urine
Other symptoms: _____
HR __ per min; BP __/__ mmHg; RR __ per min
Clinical examination – Other signs and complains: _____
Biology if possible: Hemoglobin ___. __ g/dl; Hematocrit __ __% Creatinine ___ Urea ___
Hemoglobinuria: □ Confirmed by urine stick; □ Suspected by color chart score ____ >5

Discharge □ Referral/Admission to hospital □ - Name of hospital: _____

Treatment:
□ Interruption of PQ □ Hydration with careful fluid management, monitoring of urine color and hemoglobin
□ Blood transfusion with □ Hemoglobin < 7 g/dL □ Hemoglobin < 9 g/dL with concurrent hemolysis

Patient Status: □ Currently hospitalized □ Discharged after __ __ days, □ Death

---

Conclusion by investigator: Signature _____
□ Confirmed Acute Hemolytic Anemia (AHA) □ Suspected AHA
□ Another Adverse Drug Reaction _____
□ Mild □ Moderate □ Severe □ Fatal

Official use by CNM:

□ Adverse Drug reaction report completed and sent to DDF pharmacovigilance unit.

Annex 16: Blantyre and Glasgow coma scales

Blantyre coma scale applicable to children who have not learnt to speak.

Type of response	Response	Score
Best motor	Localizes painful stimulus	2
	Withdraws limb from pain	1
	Nonspecific or absent response	0
Verbal	Appropriate cry	2
	Moan or inappropriate cry	1
	None	0
Eye movements	Directed	1
	Not directed	0
Total		0–5

Glasgow coma scales for adults and children > 5 years

Type of response	Response	Score
Eyes open	Spontaneously	4
	To speech	3
	To pain	2
	Never	1
Best verbal	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
Best motor	Obeys commands	6
	Purposeful movements to painful stimulus	5
	Withdraws to pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1
Total		3-15

Annex 17: Job Aid - Treatment of severe cases with artesunate IV

ARTESUNATE I.V FOR SEVERE MALARIA

1 WEIGH THE PATIENT

CALCULATE DOSE

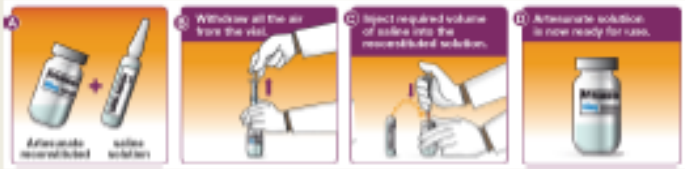
In ml and number of vials needed
Concentration: 10mg/ml

2 RECONSTITUTE

With 1ml bicarbonate solution vial

3 DILUTE IN 5ml

Saline solution or Dextrose 5%



4 ADMINISTER I.V.

Slow bolus 3-4ml per minute
If i.v. not possible, consider i.m. injection
Refer to guidelines for different dilution

5 SCHEDULE

Dose 1: on admission (0 Hour)
Dose 2: 12 hours later
Dose 3: 24 hours after first dose

Intravenous route (IV) Concentration: 10mg/ml			
Weight (Kg)	**60 mg vials**	**mg**	**ml**
< 7	1	20	2
7 - 10	1	30	3
11 - 13	1	40	4
14 - 16	1	50	5
17 - 20	1	50	5
21 - 25	1	60	6
26 - 29	2	70	7
30 - 33	2	80	8
34 - 37	2	90	9
38 - 41	2	100	10
42 - 45	2	110	11
46 - 50	2	120	12
51 - 54	3	130	13
55 - 58	3	140	14
59 - 62	3	150	15
63 - 66	3	160	16
67 - 70	3	170	17
71 - 75	3	180	18
76 - 79	4	190	19
80 - 83	4	200	20
84 - 87	4	210	21
88 - 91	4	220	22
92 - 95	4	230	23
96 - 100	4	240	24

Annex 18: Instructions to prepare artesunate IV and artesunate IM

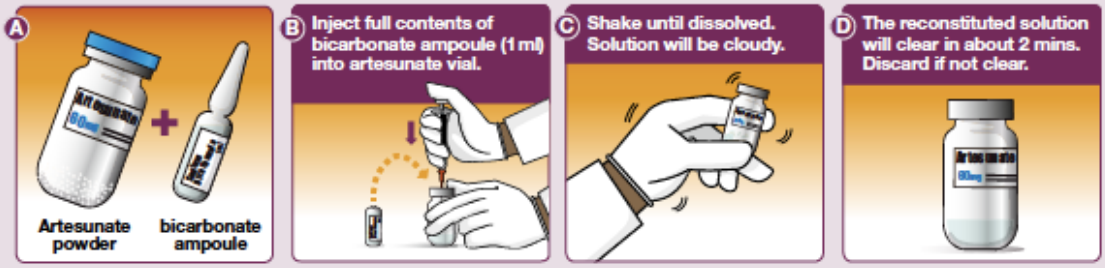
1 WEIGH THE PATIENT

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 + bicarbonate ampoule (immediately before use)



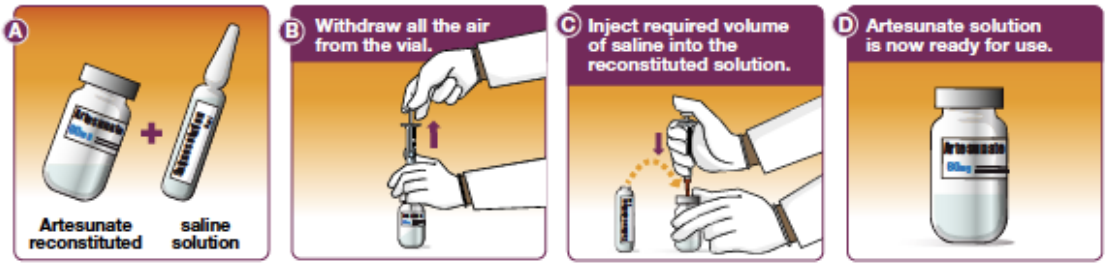
4 DILUTE

- Reconstituted artesunate + saline solution (or dextrose 5%)
- Volume for dilution

	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	10 mg/ml	20 mg/ml

IMPORTANT

Water for injection is not an appropriate dilutant



Annex 19: Dosing tables for artesunate IV and artesunate IM

Artesunate can be given by intravenous route (IV) or intramuscular route (IM).

IV is the preferred route of administration.

Dose:

For children < 20 kg: 3.0 mg/kg

For children ≥20 kg and adults: 2.4 mg/kg

Less than 20 kg

For intravenous route (IV)

Concentration: 10 mg/ml

$$\frac{3.0\ \text{mg} \times \text{body weight (kg)}}{\text{IV artesunate solution concentration } 10\ \text{mg/ml}}$$

Round up to the next whole number

Example:

Dose needed (ml) for 8 kg child:

$$\frac{3.0 \times 8}{10} = 2.4\ \text{ml}$$

2.4 ml rounded up to 3 ml

Weight kg	Dose mg	Dose ml
6 - 7	20	2
8 - 10	30	3
11 - 13	40	4
14 - 16	50	5
17 - 20	60	6

For intramuscular route (IM)

Concentration: 20 mg/ml

$$\frac{3.0\ \text{mg} \times \text{body weight (kg)}}{\text{IM artesunate solution concentration } 20\ \text{mg/ml}}$$

Round up to the next whole number

Example:

Dose needed (ml) for 8 kg child:

$$\frac{3.0 \times 8}{20} = 1.2\ \text{ml}$$

1.2 ml rounded up to 2 ml

Weight kg	Dose mg	Dose ml
6 - 7	20	1
8 - 10	30	2
11 - 13	40	2
14 - 16	50	3
17 - 20	60	3

More than 20 kg

Concentration: 10 mg/ml

$$\frac{2.4\ \text{mg} \times \text{body weight (kg)}}{\text{IV artesunate solution concentration } 10\ \text{mg/ml}}$$

Round up to the next whole number

Example:

Dose needed (ml) for 26 kg child:

$$\frac{2.4 \times 26}{10} = 6.24\ \text{ml}$$

6.24 ml rounded up to 7 ml

Weight kg	Dose mg	Dose ml
20 - 25	60	6
26 - 29	70	7
30 - 33	80	8
34 - 37	90	9
38 - 41	100	10
42 - 45	110	11
46 - 50	120	12
51 - 54	130	13
55 - 58	140	14
59 - 62	150	15
63 - 66	160	16
67 - 70	170	17
71 - 75	180	18
76 - 79	190	19
80 - 83	200	20
84 - 87	210	21
88 - 91	220	22
92 - 95	230	23
96 - 100	240	24

Concentration: 20 mg/ml

$$\frac{2.4\ \text{mg} \times \text{body weight (kg)}}{\text{IM artesunate solution concentration } 20\ \text{mg/ml}}$$

Round up to the next whole number

Example:

Dose needed (ml) for 26 kg child:

$$\frac{2.4 \times 26}{20} = 3.12\ \text{ml}$$

3.12 ml rounded up to 4 ml

Weight kg	Dose mg	Dose ml
20 - 25	60	3
26 - 29	70	4
30 - 33	80	4
34 - 37	90	5
38 - 41	100	5
42 - 45	110	6
46 - 50	120	6
51 - 54	130	7
55 - 58	140	7
59 - 62	150	8
63 - 66	160	8
67 - 70	170	9
71 - 75	180	9
76 - 79	190	10
80 - 83	200	10
84 - 87	210	11
88 - 91	220	11
92 - 95	230	12
96 - 100	240	12

Annex 20: Dosing table for artemether IM

Weight	Day 1		Day 2-5	
	Dose (mg/kg)	Ampules	Dose	Ampules
50 kg	3.2	2	1.6	1
25 kg	3.2	1	1.6	½
12.5 kg	3.2	½	1.6	¼

Annex 21: Guidelines for the management of complications

Bacterial infection

Treatment with IV broad-spectrum antibiotics should be given to all patients with severe malaria: Ampicillin 50mg/kg 6 hourly plus gentamicin 7.5mg daily
If signs of meningitis:

- Children: benzyl penicillin 60mg/kg plus chloramphenicol 25mg/kg 6 hourly
- Adults: benzyl penicillin 5 million IU plus 1g chloramphenicol 6 hourly

Hypoglycemia

Children: Dilute 50% glucose 1ml/kg in an equal volume of Norma cellar or D5W and give by slow IV injection over a period of 5 minutes. (Example: a child weighing 16kg would receive 16 x 1ml = 16ml 50% glucose diluted to 32ml). Then follow with a continuous infusion of 5% or ideally 10% dextrose.
Adults: infuse 50ml of 50% glucose over 15 minutes. Recheck blood glucose 15 minutes after the end of the infusion. If blood glucose is still <40 mg/dl, repeat glucose infusion as above.

Prolonged convulsions (> 5 minutes)

Maintain the airway. Turn the patient on his or her side to reduce the risk of aspiration. Do not attempt to force anything into the patient's mouth. Check blood glucose and treat if <40 mg/dl. Monitor vital signs every 15 minutes and record
Treat with:

- Diazepam 0.3mg/kg (up to a maximum 10mg), slow IV injection over 2 minutes,

OR

- Diazepam 0.5mg/kg per rectum: administered by 1ml syringe into the rectum

Over or under hydration

Use IV fluids, such as 4% dextrose 0.18% saline or 5% dextrose (ideally with added sodium 2mmol/kg/day). The following maintenance fluid volumes are recommended:

Weight	Fluid requirement
< 5kg	150ml/kg/day
5-10kg	120ml/kg/day
11-19kg	80 ml/kg/day
20-30kg	60ml/kg/day
Child >30kg and adult	50ml/kg/day

Shock or severe dehydration

Use normal (0.9%) saline (NaCl) or Ringer's lactate.
Children: infuse 20ml/kg of normal saline (or Ringer's lactate) over 15 minutes. (Example: a child of 15kg would receive 15 x 20ml = 300ml)
Adults: infuse 1000ml of normal saline (or Ringer's lactate) over 30 minutes. Reassess the patient. If there is no improvement in hydration or circulation, give a second infusion (children: 20ml/kg normal saline; adults: 1000ml normal saline). Reassess the patient. If there is no improvement in hydration or circulation, give a third infusion

(Children: 20ml/kg normal saline; adults: 1000ml normal saline). Reassess the patient. If there is still no improvement in circulation or hydration, infuse 20ml/kg of blood over 60 minutes.

Acute renal failure

Children:

- Acute renal failure is suggested by a urine output of < 0.5ml/kg/hour (oliguria). Blood concentrations of urea and creatinine are usually raised. Check that oliguria is not due to dehydration or shock by giving test infusion(s) of 20ml/kg normal saline. If, despite correction of dehydration or shock urine, output is still <0.5ml/kg/hour, give IV furosemide 3mg/kg. If urine output remains <0.5ml/kg/hour, assume that renal failure is established, and restrict fluids to insensible loss (30ml/kg/day: equivalent to 300ml/day for a child weighing 10kg) plus urine output.

Adults:

- Acute renal failure is suggested by oliguria (urine output < 400ml in 24 hours). Check that oliguria is not due to dehydration or shock by giving test infusion(s) of 1000ml normal saline. Once dehydration is corrected, give a single dose of furosemide 40mg. If oliguria persists (< 30ml/hour), increase the dose in a stepwise fashion at 60-minute intervals to 100mg, 200mg (one hour infusion), and finally 400mg (two hours infusion). If urine output remains < 30ml/hour, assume that renal failure is established, and restrict fluids to insensible loss (approximately 1000ml/day) plus urine output.

Pulmonary edema

Check for increased respiratory rate, chest signs (crackles on auscultation), and hepatomegaly. If pulmonary edema is suspected, position the patient upright, give oxygen, stop IV fluids and give furosemide 1mg/kg.

Annex 22: Different options of chemoprophylaxis for adult travelers

Drug/Presentation		Dose	Start before	End after	Contraindication
Atovaquone-proguanil	Daily	1	1-2 day	7 days	Pregnant or lactating women
Doxycycline 100mg	Daily	1	1-2 days	4 weeks	Pregnant women, children <8 years
Primaquine 30mg base	Daily	1	1-2 day	7 days	Pregnant or lactating women, G6PD deficiency
Mefloquine 228 mg base	Weekly	1	1-2 weeks	4 weeks	Psychiatric condition, Seizure disorder
Tafenoquine 200mg	Weekly	1	3 days	1 week	Pregnant or lactating women, children, G6PD deficiency
Chloroquine 300mg base	Weekly	1	1-2 weeks	4 weeks	Chloroquine resistance

*Please refer to WHO guidelines for the latest information.