Kingdom of Cambodia

Nation Religion King

Ministry of Health

Surveillance for Malaria Elimination

Surveillance Guidelines
Cambodia 2021 Edition

National Center for Parasitology, Entomology and Malaria Control

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Surveillance for Malaria Elimination

Guidelines

FOREWORD

The Surveillance Guidelines have been developed in line with the Cambodia Malaria Elimination Action Framework (MEAF) 2021-2025 with an overall goal to achieve Elimination of *P. falciparum* malaria with zero indigenous cases by 2023 and Elimination of all species by 2025.

These guidelines are a product of extensive consultations and collaboration between CNM stakeholders, WHO, and technical partners. They provide the strategic framework for the combined set of interventions required for malaria elimination. These are further supplemented with annexed standard operating procedures that translate the guidelines into practical procedures for implementing field operations at all levels.

I am confident that this manual provides the necessary guidance for surveillance to achieve malaria elimination. Therefore, I urge all stakeholders to put all effort into its implementation to enable the country to move towards the vision of malaria-free Cambodia.

Phnom Penh, 27 September, 2021

Professor Eng Huot

Secretary of State

PREFACE

Cambodia has significantly reduced malaria morbidity and mortality over the last ten years and is on the path to Elimination. According to the National Strategic Plan for Elimination of malaria in the Kingdom of Cambodia, the Elimination of malaria is targeted for 2025. In addition, the Malaria Elimination Action Framework for 2021-2025 (MEAF2) reflects new strategic updates based on recent changes in the country's epidemiological and programmatic context.

Beyond that, the improvement of malaria surveillance, stratification, and Elimination are major components of the WHO Global Technical Strategy (GTS) and Malaria Elimination in the Greater Mekong Subregion for 2016-2030. According to the MEAF2, enhancing the surveillance system with early detection, immediate notification, investigation, classification, and emergency response of all cases and foci is required to eliminate *P. falciparum* malaria with zero indigenous cases by 2023.

Given improvements in the epidemiological situation, the country has migrated from the previous four strata classifications found in the last version of the surveillance guidelines (non-endemic, burden reduction, transitional, and Elimination) to targeting Elimination nationwide. This framework will detail how CNM can aggressively pursue Elimination wherever cases are identified in Cambodia.

To strengthen surveillance and operate elimination interventions, a completely new approach is required to build the capacity of health staff in the periphery. These guidelines, along with Standard Operating Procedures, will act as a key catalyst in strengthening health system capacity in Cambodia to achieve malaria Elimination.

Phnom Penh, 20 September, 2021

Director CNM

Dr. HUY REKOL

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ABBREVIATIONS

ACD	Active Case Detection
ACT	Artemisinin-based Combination Therapy
AFS	Active Fever Screening
AHA	Alpha hydroxy acid
API	Annual Parasite Incidence
AS-MQ	Artesunate-Mefloquine
BCC	Behaviour Change Communication
CBNC	Cattle Baited Net Collection
CNM	National Center for Parasitology, Entomology and Malaria Control
DH	District Hospital
DHA-PIP	Dihydro-artemisinin-Piperaquine
G6PD	Glucose-6-Phosphate Dehydrogenase
GIS	Geographic Information System
GMS	Greater Mekong Subregion
HC	Health Center
HLC	Human Landing Collection
HMIS	Health Management Information System
HP	Health Post
IDES	Integrated Drug Efficacy Surveillance
IEC	Information Education Communication
IPT*f*	Intermittent Preventative Treatment for Forest Goers
LAMP	Loop-Mediated Isothermal Amplification
LLIHN	Long-Lasting Insecticidal Hammock Net
LLIN	Long-Lasting Insecticidal Net
M&E	Monitoring and Evaluation
MDR	Multidrug resistance
MEAF	Malaria Elimination Action Framework
MIS	Malaria Information System
MMP	Mobile and Migrant Populations
MMW	Mobile Malaria Workers
MoH	Ministry of Health
NRL	National Reference Laboratory
NTG	National Treatment Guidelines
OD	Operational District
P.f.	Plasmodium *falciparum*
P.v.	Plasmodium *vivax*
PCD	Passive Case Detection
PCR	Polymerase Chain Reaction
PHD	Provincial Health Department
PPM	Public-Private Mix
QA	Quality assurance
RACD	Reactive Case Detection
RCAF	Royal Cambodian Armed Forces
RDT	Rapid Diagnostic Test
REC	Recrudescent
REL	Relapse
RH	Referral Hospital
TDA	Targeted Drug Administration
TES	Therapeutic Efficacy Study
VMWs	Village Malaria Workers
WHO	World Health Organization

GLOSSARY

Active case detection: The detection of malaria infections at the community and household level among population groups that are considered to be 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. Active case detection can be used to fill gaps in the passive case detection system and to detect malaria infections as early as possible in populations that may have a high risk of infection.

Annual blood examination rate: The number of people receiving a parasitological test for malaria per 100 population per year

Case-based surveillance: Every case is reported and investigated immediately.

Case definitions:

- **Confirmed malaria:** Any case in which, regardless of the presence or absence of clinical symptoms, malaria parasites have been demonstrated in a patient's blood by microscopy, a rapid diagnostic test or a molecular diagnostic test.
- **Suspected malaria:** Patient illness suspected by a health worker to be due to malaria. The criteria usually include fever. All patients with suspected malaria should receive a diagnostic test for malaria, by microscopy or a rapid diagnostic test.

Case classification:

- **Imported:** A case the origin of which can be traced to a known malarious area outside the country in which the case was diagnosed.
- **Indigenous:** A case contracted locally with no evidence of importation and no direct link to transmission from an imported case
- **Induced:** A case the origin of which can be traced to a blood transfusion or other form of parenteral inoculation but not by a natural mosquito-borne inoculation.
- **Introduced:** A case contracted locally, with strong epidemiological evidence linking it directly to a known imported case (first generation from an imported case, i.e. the mosquito was infected from a case classified as imported).
- **Locally transmitted:** A case acquired locally by mosquito-borne transmission. Locally acquired cases can be indigenous, introduced or relapsing; the term "autochthonous" is not commonly used.

Case, index: A case of which the epidemiological characteristics trigger additional active case or infection detection. The term is also used to designate the case identified as the origin of infection of one or a number of introduced cases.

Case investigation: Collection of information to allow classification of a malaria case by origin of infection. Case investigation includes administration of a standardized questionnaire to a person in whom a malaria infection is diagnosed.

Case follow-up: Periodic re-examination of patients with malaria. It may involve blood examination and treatment if the patient did not respond to previous medicines. Case follow-up is part of surveillance

Case management: Diagnosis, treatment, clinical care and follow-up of malaria cases.

Case notification: Compulsory reporting of detected cases of malaria by all medical units and medical practitioners, to either the health department or the malaria Elimination service (as laid down by law or regulation).

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

Certification of malaria-free status: Granted by WHO after proof beyond reasonable doubt that the chain of local human malaria transmission by Anopheles mosquitoes has been fully interrupted in an entire country for at least 3 consecutive years.

Elimination: Reduction to zero of the incidence of indigenous infection by human malaria parasites in a defined geographical area as a result of deliberate efforts. Continued measures to prevent re-establishment of transmission are required.

Endemic: Applied to malaria when there is an ongoing, measurable incidence of cases and mosquito-borne transmission in an area over a succession of years.

Epidemic: Occurrence of cases in excess of the number expected in a given place and time.

Eradication: Permanent reduction to zero of the worldwide incidence of infection caused by human malaria parasites as a result of deliberate efforts. Intervention measures are no longer needed once eradication has been achieved.

Evaluation: Attempts to determine as systematically and objectively as possible the relevance, effectiveness and impact of activities in relation to their objectives.

External quality assessment: A system by which a laboratory's performance is checked objectively by an external agency or facility or a reference laboratory.

False negative (or false positive): A negative (or positive) result in a test when the opposite is true.

Focus: A defined, circumscribed locality situated in a currently or former malarious area containing the continuous or intermittent epidemiological factors necessary for malaria transmission.

Gametocyte: The sexual reproductive stage of the malaria parasite present in the host's red blood cells.

Incubation period: The time between infection (by inoculation or otherwise) and the first appearance of clinical signs, of which fever is the commonest.

Line list: Information on cases recorded in rows and columns, with data for each case in columns across one row. The information may include case identification number; demographic factors (patient's name, address, age, sex); clinical factors (date of attendance, type of test, test result, treatment received); intervention factors (house sprayed, insecticide-treated net ownership, preventive therapy).

Local mosquito-borne malaria transmission: Occurrence of human malaria cases acquired in a given area through the bite of infected Anopheles mosquitoes.

Malaria case: Any individual with malaria parasites demonstrated in the blood. The term is equivalent to malaria infection. In settings where malaria is actively being eliminated, a "case" is the occurrence of any confirmed

malaria infection, regardless of the presence or absence of clinical symptoms. Parasite can be detected by microscopy or a rapid diagnostic test. Sub-microscopic infections can be detected by nucleic acid-based amplification (e.g. polymerase chain reaction assays to detect parasite DNA or RNA).

Malaria-free: An area in which there is no continuing local mosquito-borne malaria transmission, and the risk for acquiring malaria is limited to introduced cases.

Malaria incidence: The number of newly diagnosed malaria cases during a specified time in a specified population.

Malaria prevalence: The proportion of a specified population with a malaria infection at a given time.

Mass drug administration: Administration of antimalarial treatment to every member 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. It is usually performed in order to reduce the parasite reservoir of infection radically and thus reduce transmission in a population.

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.

Mass testing and focal drug administration: Testing a population and treating groups of individuals or entire households in which one or more infections is detected.

Mass testing and treatment: Testing an entire population and treating individuals with a positive test result

Monitoring (of programmes): Periodic review of the implementation of an activity, seeking to ensure that inputs, deliveries, work schedules, targeted outputs and other required actions are proceeding according to plan.

National focus register: Centralized computerized database of all malaria foci in a country.

National malaria case register: Centralized computerized database of all malaria cases registered in a country, irrespective of where and how they were diagnosed and treated.

National reference laboratory: This may be part of the central public health laboratory, the National Malaria Country Program (NMCP) or a government institution in academia. It plays an essential role in the preparation of guidelines for standardizing methods, maintaining slide banks, producing locally adapted training materials, providing basic and refresher training, overseeing training activities, assuring the quality of testing and supporting external QA in collaboration with the NMCP.

Outpatient register: List of patients seen in consultation in a health facility, which may include the date of the consultation, patient's age, place of residence, presenting health complaint, test performed and diagnosis.

Parasite prevalence: Proportion of the population in whom Plasmodium infection is detected at a particular time with a diagnostic test (usually microscopy or a rapid diagnostic test).

Passive case detection: Detection of malaria cases among patients who on their own initiative, visit health services for diagnosis and treatment, usually for febrile disease.

Population at risk: Population living in a geographical area in which locally acquired malaria cases occurred in the current and/or previous years.

Pro-active case detection: A type of active case detection conducted that is not triggered by a malaria case. Typically involves screening and treatment in communities and among specific high risk groups.

Proficiency testing: A system in which a reference laboratory sends blood films to a laboratory for examination, and the laboratory receiving the slides is not informed of the correct results until it has reported its findings back to the reference laboratory.

Quality assurance: The maintenance and monitoring of the accuracy, reliability and efficiency of laboratory services. QA addresses all the factors that affect laboratory performance, including test performance (internal and external QC), the quality of equipment and reagents, workload, workplace conditions, training and supervision of laboratory staff and continuous quality improvement. It includes procedures put in place to ensure accurate testing and reporting of results.

Quality control: Assessment of the quality of a test or a reagent. QC also encompasses external QC and reagent QC. External QC is a system in which routine blood slides are crosschecked for accuracy by a supervisor or the regional or national laboratory. Reagent QC is a system for formal monitoring of the quality of the reagents used in a laboratory.

Rapid diagnostic test: An antigen-based stick, cassette or card test for malaria in which a coloured line indicates that plasmodial antigens have been detected.

Rapid diagnostic test positivity rate: Proportion of positive results in rapid diagnostic tests among all the tests performed.

Re-active case detection: A type of active case detection conducted in response to a confirmed case or cluster of cases, in which a population potentially linked to such cases is screened and tested.

Receptivity: Sufficient presence of anopheline vectors and existence of other ecological and climatic factors favoring malaria transmission.

Relapse: Recurrence of asexual parasitaemia in *P. vivax* or *P. ovale* infections arising from hypnozoites. It occurs when the blood-stage infection has been eliminated but hypnozoites persist in the liver and mature to form hepatic schizonts. After an interval, generally from 3 weeks to 1 year, the hepatic schizonts rupture and liberate merozoites into the bloodstream.

Sensitivity (of a test): Proportion of people with malaria infection (true positives) who have a positive test result.

Slide positivity rate: Proportion of slides found positive among the slides examined.

Specificity (of a test): Proportion of people without malaria infection (true negatives) who have a negative test result.

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

Surveillance: That part of the programme designed for the identification, investigation and Elimination of continuing transmission, the prevention and cure of infections and final substantiation of claimed Elimination.

Transmission intensity: Rate at which people in a given area are inoculated with malaria parasites by mosquitoes. This is often expressed as the "annual entomological inoculation rate", which is the number of inoculations with malaria parasites received by one person in a given period of time, usually 1 year.

Transmission season: Period of the year during which mosquito-borne transmission of malaria infection usually takes place.

Vector control: Measures of any kind against malaria-transmitting mosquitoes intended to limit their ability to transmit the disease.

Vector efficiency: Ability of a mosquito species, in comparison with another species in a similar climatic environment, to transmit malaria in nature.

Vectorial capacity: Number of new infections that the population of a given vector would induce per case per day at a given place and time, assuming conditions of non-immunity. Factors affecting vectorial capacity include: (i) the density of female anophelines relative to humans; (ii) their longevity, frequency of feeding and propensity to bite humans; and (iii) the length of the extrinsic cycle of the parasite.

Vulnerability: Either proximity to a malarious area or frequent influx of infected individuals or groups and/or infective anophelines.

TABLE OF CONTENT

PURPOSE OF THE SURVEILLANCE GUIDELINES

These guidelines aim to codify the surveillance strategies to be implemented nationwide to achieve the overall objective of malaria elimination by 2025. The Standard Operation Procedures annexed with these guidelines will serve as a practical guide on how to standardize the implementation of these strategies at the central, peripheral, and community levels.

This guideline is a critical contribution to the strategic framework for malaria elimination in Cambodia. In addition, it gives detailed guidance for field operations to be conducted by district health staff, health center officers, village malaria workers, and other points of care. This manual will be distributed to peripheral staff and outline all surveillance standard operating procedures (SOPs) that each level health staff is expected to follow.

The surveillance guidelines consist of three chapters:

Chapter 01

Overview of the Surveillance Strategy provides an overview of the malaria situation and surveillance strategy for malaria elimination in Cambodia.

Chapter 02

Surveillance for Elimination serves as a practical guide to implement surveillance activities for malaria elimination.

Chapter 03

Data Management and Analysis serve as a practical guide for CNM staff on routine administration and analysis.

Chapter 1 - Overview of the Surveillance Strategy

1.1 Malaria Situation in Cambodia

In Cambodia, malaria transmission is endemic in 21 out of 25 provinces. Transmission occurs primarily in the hot and rainy season between July and November. An estimated 62% of the population lives in malaria at-risk areas or approximately 9.4 million people. Malaria risk is highest in forested or forest-fringe areas in the country's northeastern part (see Figure 1). Out of a total of 55 endemic Operational Districts (ODs), 11 accounted for 85% of all cases reported in the country in 2020.

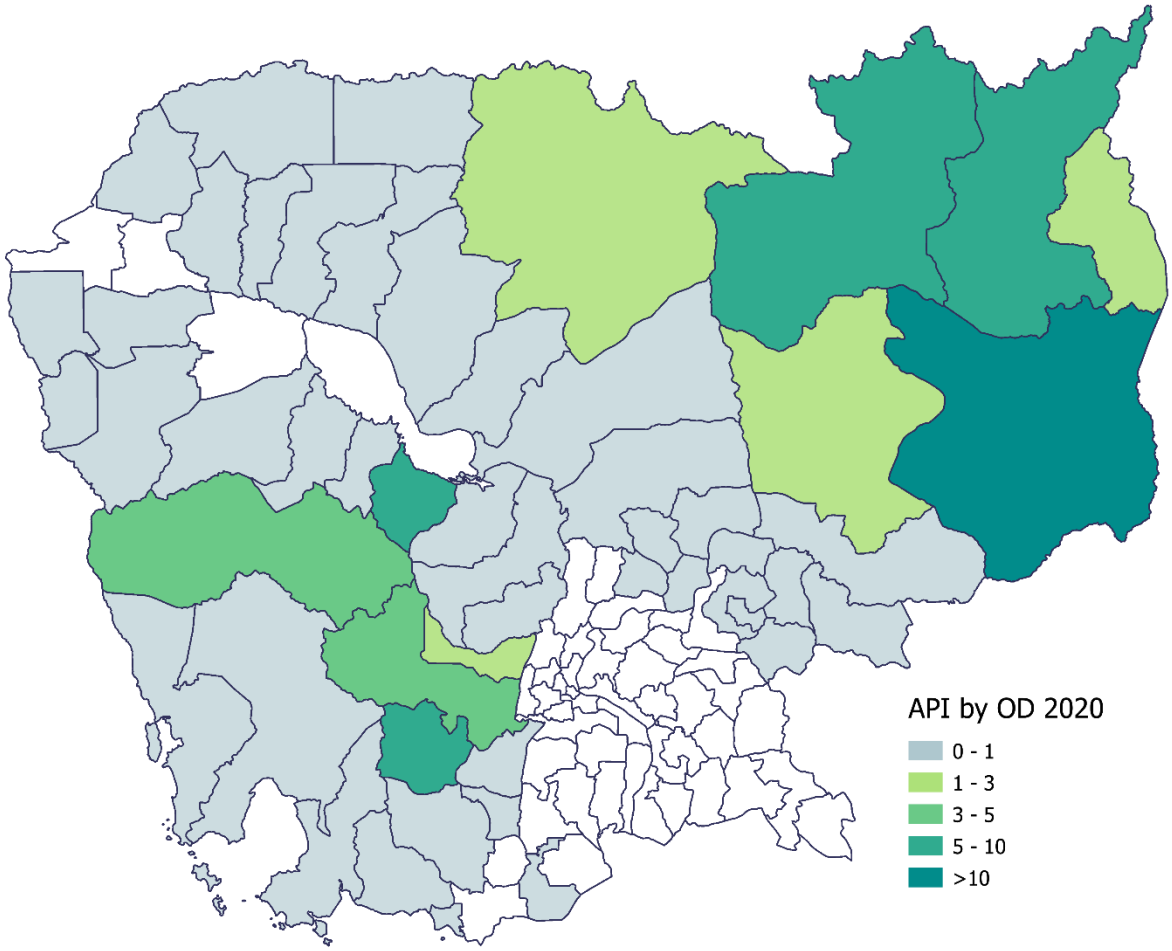

Figure 1: API by operational district, 2020[1]

In 2020, Cambodia recorded 9,161 malaria cases detected by public health facilities and Village Malaria Workers (VMWs) / Mobile Malaria Workers (MMWs), an 82% decrease from 2015. Malaria cases in Cambodia are caused by *Plasmodium falciparum, Plasmodium vivax*, or a mix of both strains. Recent years have focused on eliminating *Plasmodium falciparum* based on its higher morbidity/mortality and the risk of spreading artemisinin resistance. However, its absolute and relative incidence fell dramatically in 2020, thanks partly to the Intensification Plans implemented in the highest-burden villages over the past few years. In 2020, only 10% of malaria cases were due to *P. falciparum*, whereas in 2015, these accounted for 50% of all cases [1].
Conversely, *P. vivax* has not experienced the same declines and is now the dominant species. This highlights the need to scale up access to safe radical cures, which began piloting recently in late 2019. In 2020, *P. vivax* infections accounted for 90% (8,298) of the reported cases.

VMWs remain a key component of malaria elimination efforts. In 2020 VMWs performed more than 73% of tests conducted and treated 61% of total malaria cases. Since April 2018, the public-private mix program (PPM) has been phased out, and suspected cases will be referred and treated only through the public health sector to serve the services better.

An.dirus, An.minimus s.l., and *An.maculatus s.l.* are the main malaria vectors. *An.dirus* is found in forested mountains and foothills, cultivated forests, and rubber plantations, whereas *An.minimus* is located in a wide range

[1] Malaria Information System data

of habitats, from forested areas to open agricultural fields[2]. *An.maculatus* is found in hilly or mountainous areas and breeds in or near-permanent or semi-permanent bodies of clean water such as streams or rivers. These vectors bite during all hours of the evening, but peak biting hours are usually found to be between 8:00 PM and 12:00 PM the next day. No resistance of the main vectors to common insecticides has been documented to date.

1.2 MEAF Surveillance Strategies

As outlined in the Malaria Elimination Action Framework (MEAF) 2021-2025, Cambodia aims to reduce the incidence of malaria to less than 0.1 case per 1000 people at risk for *P. falciparum* by 2020, eliminate *P. falciparum* by 2023, and eliminate all forms of malaria by 2025. To achieve this, the MEAF includes activities to improve and maintain surveillance across the country.

Table 1: MEAF 2021-2025 Objectives and Surveillance Related Sub-Objectives:

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	
1.6	Test and regularly monitor drug efficacy
1.9	Strengthen entomological surveillance of vector-borne diseases with integrated vector management
1.10	Monitor insecticide resistance routinely
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 Plasmodium *falciparum* by 2020 and all species by 2025	
2.1	Utilize risk stratification and mapping to identify and monitor hotspots and deploy intensified network of MMW
2.5	Ensure monitoring, mentoring and supervision for MMW activities in high burden hotpot areas
3) Investigate, clear, document and follow up 100% of cases and foci to interrupt transmission and prevent re-establishment	
3.1	Strengthen capacity for managing, monitoring, and supervising all surveillance activities
3.2	Regularly upgrade system specifications, functions, and the modelling features of Malaria Information System (MIS) to improve visualization, interpretation, and usage of data at all levels
3.3	Improve processes, tools, and trainings to ensure all levels submit complete and accurate reports on time
3.4	Ensure all confirmed cases for all species are notified, investigated, and classified within 24 hours, and responded to within 3 days
3.5	Investigate and classify all new active foci within 7 days
3.7	Detect and respond to all outbreaks within 7 days

[2] Sinka, M.E., Bangs, M.J., Manguin, S. *et al.* The dominant *Anopheles* vectors of human malaria in the Asia-Pacific region: occurrence data, distribution maps and bionomic précis. *Parasites Vectors* **4,** 89 (2011). https://doi.org/10.1186/1756-3305-4-89

1.3 Stratification of MEAF Strategies

The malaria situation in Cambodia is heterogeneous due to variance in malaria transmission dynamics by geographic area, growing multidrug resistance (MDR), and mobility of at-risk populations. In the MEAF 2016-2020, the operational districts in the country were categorized across three phases: Elimination, transitional, and high burden. In the MEAF 2021-2025, the whole country will be in elimination phase given the reduction in cases. Figure 2 displays projected goals of when operation district with higher API should reach a target of API < 1 over the next five years to achieve complete Elimination by 2025. Interventions will be implemented based on operational stratification that allocates each village a particular score / strata based on pre-determined factors (0- no risk, 1- low risk, 2- medium risk, 3- risk, 4- high risk). A village's stratification determines the interventions it receives; however, surveillance activities will be the same across the country. All surveillance activities, such as case investigation and response, foci investigation and response, and TES/iDES studies, will be crucial interventions, especially in the highest risk stratum, to monitor and reduce the high case burden.

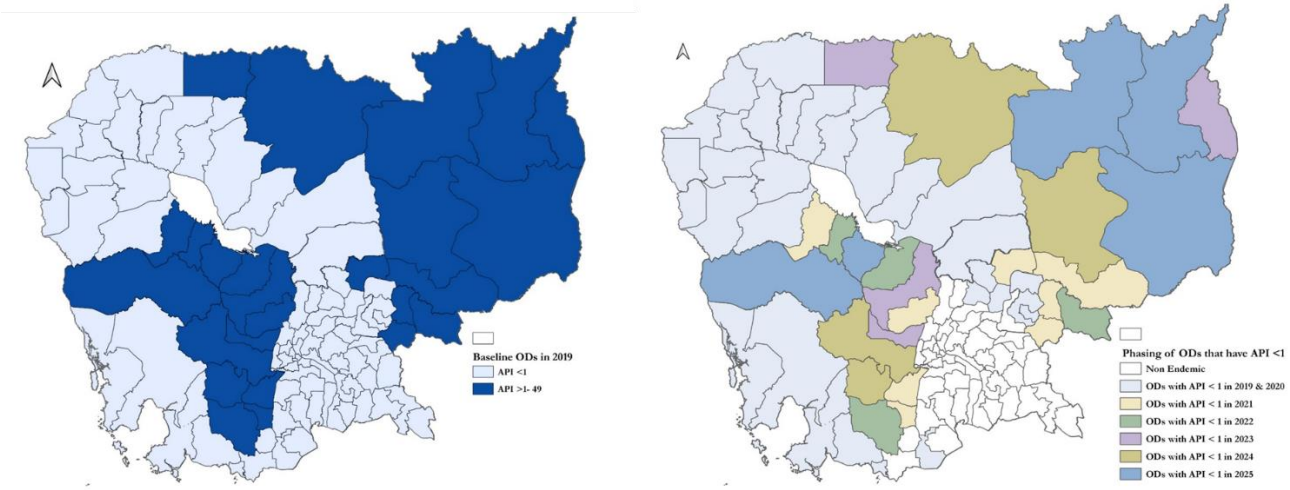

Figure 2: ***Left:*** *Operation districts by low and increased API, baseline in 2019.* ***Right:*** *Geographical timeline of goals for operational districts to reach API < 1 (MEAF 2021-2025).*

1.4 Malaria Case Detection

Malaria case definition in elimination settings refers to any individual with malaria parasites demonstrated in the blood confirmed by microscopy or RDT. The term is equivalent to malaria infection. In settings where malaria is actively being eliminated, a "case" is the occurrence of any confirmed malaria infection, regardless of the presence or absence of clinical symptoms. In that context, the detection of malaria cases can also identify asymptomatic malaria infections.

Parasite can be detected routinely by microscopy or a rapid diagnostic test. Some sub-microscopic infections are low-density blood-stage malaria infections that cannot be detected by conventional microscopy but might be detected by nucleic acid-based amplification (e.g. polymerase chain reaction assays to detect parasite DNA or RNA).

1.4.1 Universal Access to Diagnosis and Treatment

Under the MEAF, early diagnosis of malaria must be universally available with all suspected malaria cases receiving a parasitological test immediately, and maximum 48 hours after symptom onset. To achieve universal early diagnosis, all efforts will be made to provide access to parasitological diagnosis to the whole population at risk. Strong factors such as geographical and financial access will be addressed through adapted policies. In addition, a comprehensive IEC/BCC strategy including community participation will be implemented to favor prompt treatment seeking for malaria related symptoms.

In Cambodia, malaria diagnosis and treatment services are provided through:

- Public Health Facilities: Referral Hospitals (RH), Former District Hospitals (FDH), health centers (HC), and health post (HP)
- Community Health Workers: Village Malaria Workers (VMWs) and Mobile Malaria Workers (MMWs).
- Military and Police health services.

1.4.2 Identification of Malaria Cases

Identification of a suspected case:

Every person presenting to a health facility or community health worker with any of the following symptoms: history of fever, chills, sweat, headache, nausea, vomiting or diarrhea should be carefully assessed to exclude malaria.

The complete, detailed protocol to evaluate a suspected malaria case can be found in the National Treatment Guidelines (NTG).

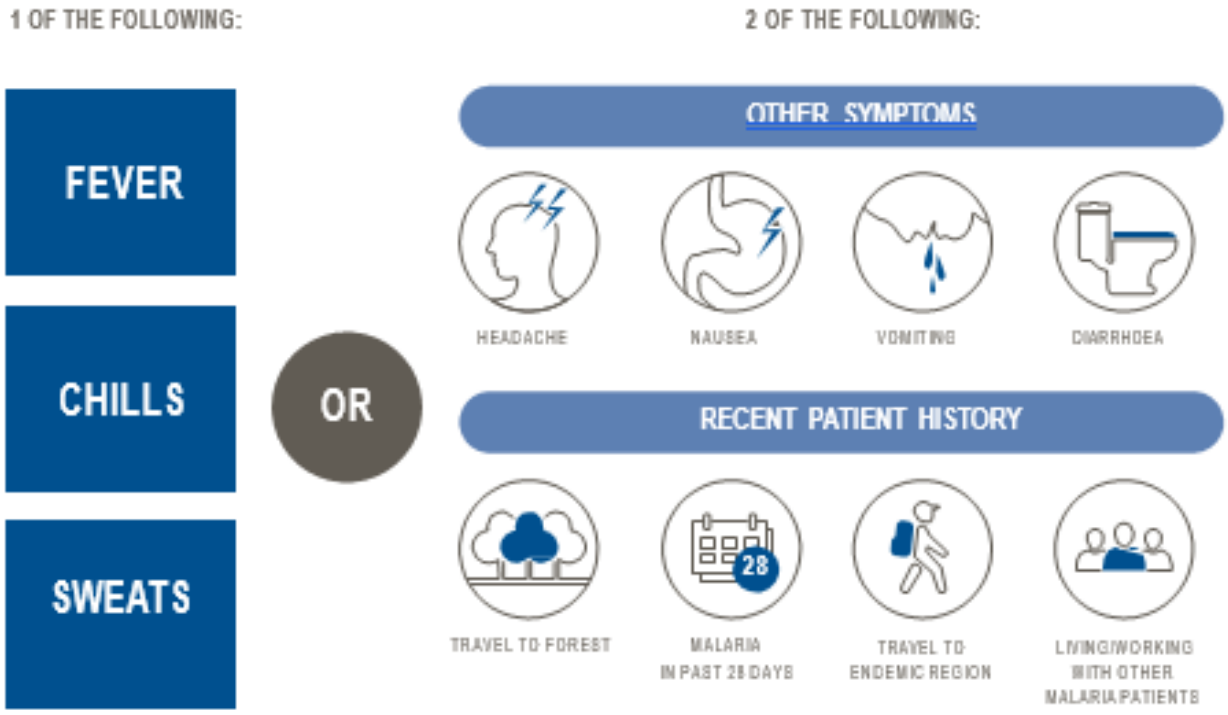

Figure 3: Criteria for malaria diagnostic testing.

Parasitological diagnosis

The two main methods in routine use for parasitological confirmation of malaria are microscopy and rapid diagnostic tests (RDTs). 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. Diagnosis will take place with RDTs at health facility and VMW level, and microscopy at hospital level.

Classification of confirmed cases

Every case will be checked for general danger signs and features of severe malaria for immediate care if present. Confirmed malaria cases are reported as either uncomplicated or severe (see details on signs or symptoms of severe malaria in the NTG).

1.4.3 Treatment of Malaria Case

The aim of treatment of malaria in the context of Elimination is complete parasitological cure, including killing of the parasites in their sexual stages. The treatment should be fully effective and instituted so early that, not only is severe disease prevented, but also the emergence of gametocytes is prevented, so that the risk for transmission from the treated case is minimized.

Artesunate-Mefloquine (AS-MQ) as first line ACT treatment

High frequency of DHA-PPQ failures are now documented over the whole country. By contrast, TES data gives evidence of full efficacy of AS-MQ. WHO prequalified fixed dose combination AS-MQ is the first line ACT treatment recommended in all provinces. While there is no current need to switch regimen, since ASMQ is still efficacious, TES will continue to be implemented in Cambodia alongside IDES studies to monitor the treatment efficacy and inform potential changes in first line treatment.

Gametocytocidal treatment

Health centers, VMWs, and MMWs provide *P. falciparum* patients single low dose primaquine (SLDP) to block the transmission of *P. falciparum* malaria. In 2019, dosing guidelines for Primaquine were updated to introduce 7.5mg formulation to allow for treatment of patients between 20 – 50kg, and 15mg formulation for patients above 50kg.

Plasmodium vivax radical cure

Patients tested positive for *P. vivax* or mix infections will be eligible for safe radical cure with primaquine, the dosage of which will be determined by the results of a G6PD test. To ensure completion of treatment, protocols for follow-up on adherence will be developed based on evidence and feasibility. In addition, building systems for pharmacovigilance is important to monitor for adverse outcomes.

1.5 Basic Concepts about Malaria Elimination

Definition of malaria elimination

Malaria elimination is the interruption of local mosquito-borne malaria transmission and the reduction to zero of the incidence of infection caused by human malaria parasites in a defined geographical area as a result of deliberate efforts. After Elimination is achieved, continued measures to prevent the re-establishment of transmission are required.

The interruption of local transmission by mosquitoes is achieved despite a continued presence of malaria vectors and importation of parasites from abroad through travel and migration. It does not require the Elimination of disease vectors or a complete absence of reported malaria cases: imported malaria cases will continue to be detected, and could, on occasion, lead to the occurrence of introduced cases in which the infection is a first generation of local transmission subsequent to an imported case. In practice, the absence of new cases due to local transmission is an indication of interruption of transmission and cessation of activity of a focus.

Elimination of multi-drug resistant P. falciparum

Since 2008, WHO has coordinated inter-country efforts to contain artemisinin-resistant *P. falciparum* in the Greater Mekong sub-region, with the intention of preventing the spread of artemisinin-resistant *P. falciparum* parasites. It has been found, however, that artemisinin-resistant *P. falciparum* parasites in the area continue to spread and to emerge *de novo*, suggesting that the containment approach was not effective. Further, high level resistance to ACT in Cambodia is documented (resistance to both artemisinin and the partner drug). For this reason, malaria elimination of *P. falciparum* is now the objective for Cambodia by 2023.

Species-specific Elimination

P. falciparum is usually eliminated first because it has a longer incubation interval and shorter incubation period than *P. vivax*. Moreover, *P. vivax* generates persistent hypnozoites that are difficult to cure with current radical primaquine treatment due difficulties with compliance and acceptability. A country may well decide to plan Elimination of one species first, an achievement that would still be a major milestone. However, presently WHO certifies malaria elimination in a country only when all species that cause human malaria have been eliminated. In Cambodia, Elimination of all malaria species is targeted for 2025.

Certification of malaria elimination

The official recognition of malaria-free status granted by WHO after it has been proven beyond reasonable doubt that the chain of local human malaria transmission by Anopheles mosquitoes has been fully interrupted in an entire country for at least 3 consecutive years and there is evidence that the surveillance system is adequately designed to continuously detect cases. The full list of requirements for elimination can be found in the recently published "Preparing for certification for malaria elimination" by WHO[3].

Prevention of re-establishment of transmission

Countries that have eliminated malaria must prevent re-establishment of transmission and must therefore maintain a surveillance system in order to rapidly identify all cases of malaria that might indicate the emergence of transmission, although some activities may be scaled down. Surveillance systems at this stage should be integrated with broader disease surveillance systems, across community, public and private sectors as required. Nationwide early detection and prompt treatment of imported malaria cases that could result in reestablishment of transmission and monitoring of changes in receptivity and vulnerability should be a priority.

Criteria of re-establishment of transmission

Re-establishment of transmission is defined by the occurrence of three or more indigenous malaria cases of the same species per year in the same focus, for three consecutive years.

[3] Preparing for certification of malaria elimination. Geneva: World Health Organization; 2020. Licence: CCBY-NC-SA3.0IGO. https://www.who.int/publications/i/item/9789240005624

Malaria eradication

Malaria eradication is the permanent reduction to zero of the worldwide incidence of infection caused by a particular malaria parasite species. Intervention measures are no longer needed once eradication has been achieved.

Surveillance

In this context, surveillance is defined by the systematic recording, collation, analysis, and utilization of data on patients screened and tested for malaria, the incidence of confirmed malaria cases, and evaluation of the effect of prevention and response activities.

Case-based Surveillance for Elimination

The implementation of malaria case-based surveillance based on specific and rigorous standards defines an elimination program. The central concept of surveillance for Elimination is that identification and investigation of a malaria case and a malaria focus define the presence of malaria transmission.

During Elimination, surveillance is the main intervention, because it aims not only to report morbidity and infections but includes the Elimination of malaria infections, case-by-case and focus-by-focus. The objective of surveillance for Elimination is to shift the focus from just reporting the overall amount of malaria to using the reported data to target the specific drivers of transmission. Surveillance in Elimination is a continuous loop of identifying, reporting, analyzing, and responding to malaria cases with the absence of locally acquired cases and disappearance of active foci as a goal.

Chapter 2 - Surveillance for Elimination

Following country phasing of elimination activities laid out in the MEAF 2016-2020 and given widespread decreases in malaria caseload in Cambodia, all ODs in the country have been targeted for implementing case-based surveillance for elimination activities from 2020 onward.

Malaria case-based surveillance for Elimination aims to detect and notify all malaria infections, ensuring that they are given prompt, efficacious treatment to prevent secondary cases. Then each malaria case should be investigated to determine whether it was locally acquired or imported and to determine risk factors associated with infection. Once a local case of malaria has been detected and notified, a focus investigation is carried out by trained malaria staff to assess the receptivity and vulnerability of an area, what drives transmission, and to determine what interventions are necessary to successfully interrupt transmission. Table 2 below lists additional specific activities to be conducted in all ODs.

Operational objectives of the surveillance for Elimination are:

- Diagnostic testing should be conducted immediately for all suspected cases and be subject to quality control.
- All detected infections be given a fully effective treatment as soon as possible.
- Reporting should cover all health providers and be timely and complete.
- Case-based notification, investigation, and classification should be immediate.
- All cases and foci should be fully investigated, classified, responded to, and reported.
- Records should be kept and stored permanently in the MIS, to guide program implementation, for future reference and to build the evidence base for eventual certification.

Table 2: Components of the surveillance for elimination system

COMPONENTS		Activities
1	**CASE DETECTION**	Passive and Active by Public Health Facilities and VMWs/MMWs
	PROACTIVE CASE DETECTION	Outreach activities conducted by HCs, VMWs, and MMWs in high-risk villages and with at-risk populations
2	**CASE REPORTING**	Immediate notification, case-based, electronic/paper-based
	CASE CLASSIFICATION	For all cases, during notification at all POC
	DOT AND CASE FOLLOW UP	DOT for the first dose is conducted for all cases Adherence to treatment is conducted for *P. vivax* cases,
	REACTIVE CASE DETECTION	For *P. falciparum* or mix LC* or Imported cases and *P. vivax* L1 cases in the village where the case was identified
3	**FOCI INVESTIGATION**	After the first *P. falciparum* or mix L1 case is detected in a village
	FOCI CLASSIFICATION	For all investigated foci, classified as Active, Residual, or Cleared-up and updated yearly
	FOCI MANAGEMENT	For all classified foci

**LC stands for "Local Cambodia" and is one of the case classifications described below. It represents malaria cases believed to have originated within Cambodia but not within the patient's village of residence.*

Figure 1: Night mosqitos capture

2.1 Case Detection

2.1.1 Passive case detection

The detection of malaria cases through rigorous testing of symptomatic populations presenting for care at public hospitals, health centers, and village malaria workers is referred to as passive surveillance. Passive surveillance is the primary approach to disease reporting, monitoring, and response in Cambodia.

In elimination programs, the objective of passive case detection is to treat infections as soon they present at a point of care to reduce the parasite reservoir and prevent secondary transmission. This implies that all symptomatic malaria infected individuals should be identified and treated radically, including gametocytes and *P. vivax* hypnozoites.

Public hospitals and health centers are conducting passive case detection activities and offering malaria testing and treatment services nationwide. However, malaria transmission is mostly focalized in hard-to-reach areas and amongst mobile and migrant populations and forest goers; case management services have to be further made accessible for these hard-to-reach populations.

Village Malaria Workers (VMWs) and Mobile Malaria Workers (MMWs)

VMWs have been deployed in priority areas with the highest malaria transmission based on stratification conducted by CNM. This malaria-focused community health worker program aims to use community engagement and access to help communities to prevent, detect, and treat disease. One male and one female villager are selected as VMWs in each village through community consensus and trained by CNM. The VMWs are responsible for providing case management services to their communities, collecting and reporting data per the national surveillance strategies, and ensuring malaria commodities are available for diagnosis and treatment of malaria patients in their communities. The VMW program also has a very important role to conduct active surveillance and field operations.

MMWs have the same responsibilities as village malaria workers, with a couple of additional responsibilities such as integrating both active and passive case management into daily practices. MMWs are deployed to gain higher access to at-risk MMPs (i.e., forest goers or new settlers) who experience higher rates of malaria. MMWs visit forested areas around their locality twice trips per month, testing at least 20 forest goers in each trip. Stratification of risk will be conducted by CNM regularly and will be used as the basis for expanding and contracting the VMW and MMW programs to address the areas of highest risk in the country.

Village Malaria Workers (VMWs) and Mobile Malaria Workers (MMWs) remain a key component of malaria elimination efforts. Village Malaria Workers (VMWs) contributed to more than 73% of tests conducted in 2020, and 61% of total malaria cases were treated by VMWs/MMWs.

Public-Private Mix (PPM) program

PPM providers are no longer able to test and treat for malaria, however OD staff will continue to provide supervision visits to encourage PPM providers to refer suspected cases of malaria to public health facilities.

RCAF and police health services

Some security forces positioned in endemic areas are exposed to high malaria risk particularly when they operate in forested areas. Their dedicated health services will be supported by CNM to apply adapted preventive measures, provide most efficient diagnosis and treatment protocols and be included into the MIS surveillance network.

The RCAF and Police health services function as public health facilities/VMWs/MMWs.

2.1.2 Active Case Detection

Active case detection is the detection of malaria cases at community and household levels, sometimes in population groups that are considered at high risk. Active case detection is used to fill gaps in the passive case detection system and to detect malaria infections as early as possible in populations that may have a high risk of infection. The ultimate objective of active case detection strategies is to proactively find all malaria infections, whether symptomatic or not, and ensure that they are radically cured so early that they do not generate secondary cases.

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.

1. **Reactive case detection** may be undertaken in response to a confirmed case or cluster of cases, in which a population potentially linked to such index case(s) is screened and tested. The objective is to detect early concomitant infections and to prevent secondary infections.

2. **Proactive case detection** may be conducted in high-risk populations, e.g. mobile-migrant populations at border check points, without being prompted by prior detection of index cases. In Cambodia, this is done through VMWs/MMWs outreach testing activities around the village or in the forest-border areas, or outreach to high-risk populations.

2.2 Immediate Case Based Notification, Investigation, and Classification

(See detail in "SOP FOR IMMEDIATE CASE-BASED NOTIFICATION, INVESTIGATION, AND CLASSIFICATION")

2.2.1 Case-based Notification

Case notification is the compulsory reporting of detected cases of malaria by all points of care and medical practitioners, to either the health department or the malaria elimination service (as laid down by law or regulation).

Objective: Every malaria case is notified on the same day as diagnosis (D0).

All points of care need to report confirmed cases immediately so that a prompt response can be taken. If they have not done so already, all points of care will migrate from the MIS monthly line-list to case-based immediate notification through a dedicated Android application installed on a smartphone or a tablet.

When a test is negative, a shorter notification is done with only the test result and basic patient information of the patient recorded. By contrast, when a case is confirmed, the application captures the same information that is on the MIS line list for patients who are tested positive, including the classification of the case (see 2.2.2). This includes the current village of residence to be selected from a standard drop-down list and the phone number of the patient, among other data points.

All additional details about immediate case-based notification are provided in related "SOP for Immediate Case-based Notification, Investigation, and Classification" in Annex 1.

2.2.2 Case Investigation and Classification

Case classification becomes important during the last stages of Elimination and is the primary reason for case investigations. Case investigation is the collection of information to capture travel history, medical history, and other key information from the detected cases in order to classify them by origin of infection. Once a case has been investigated, it is classified into one of the following categories: local, imported, or relapse/recrudescent. The case notification form, which includes case investigation questions and case classification options, will be uploaded directly to the MIS server upon completion.

Objective: Every case is investigated and classified on the same day as diagnosis (D0).

The case investigation and classification are undertaken by the point of care (hospital, HC, VMW, MMW, or HP) where the case is identified. Provision of appropriate training, mentoring, and supervision are critical to ensure consistent, high-quality investigation and classification.

There are four classifications in total based on where transmission is believed to have taken place relative to the village where the patient currently resides:

- **"L1"** for cases that have stayed every night within their current residence in the last two weeks.
- **"LC"** for cases who slept at least one night outside of their village of current residence, but within Cambodia, in the last two weeks.
- **"Imported"** for cases who have slept at least one night outside of the country in the past two weeks.
- **"Relapse/recrudescent"** for cases where the patient is diagnosed with *P. vivax* infection and reported having *P. vivax* in the last 12 months.

For details on the specific questions used to reach these classifications, see Figure 5.

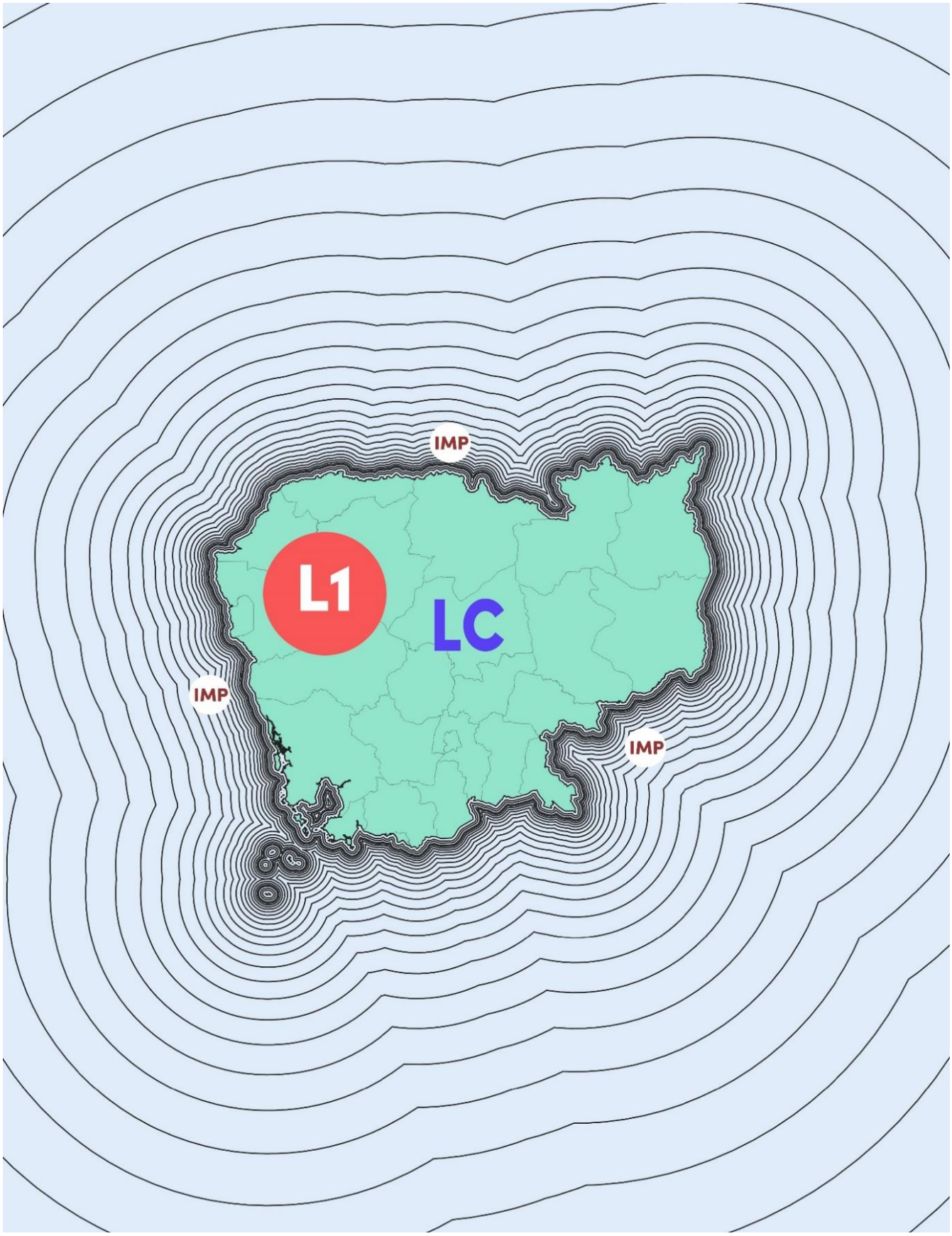

Figure 5: Case classifications by location

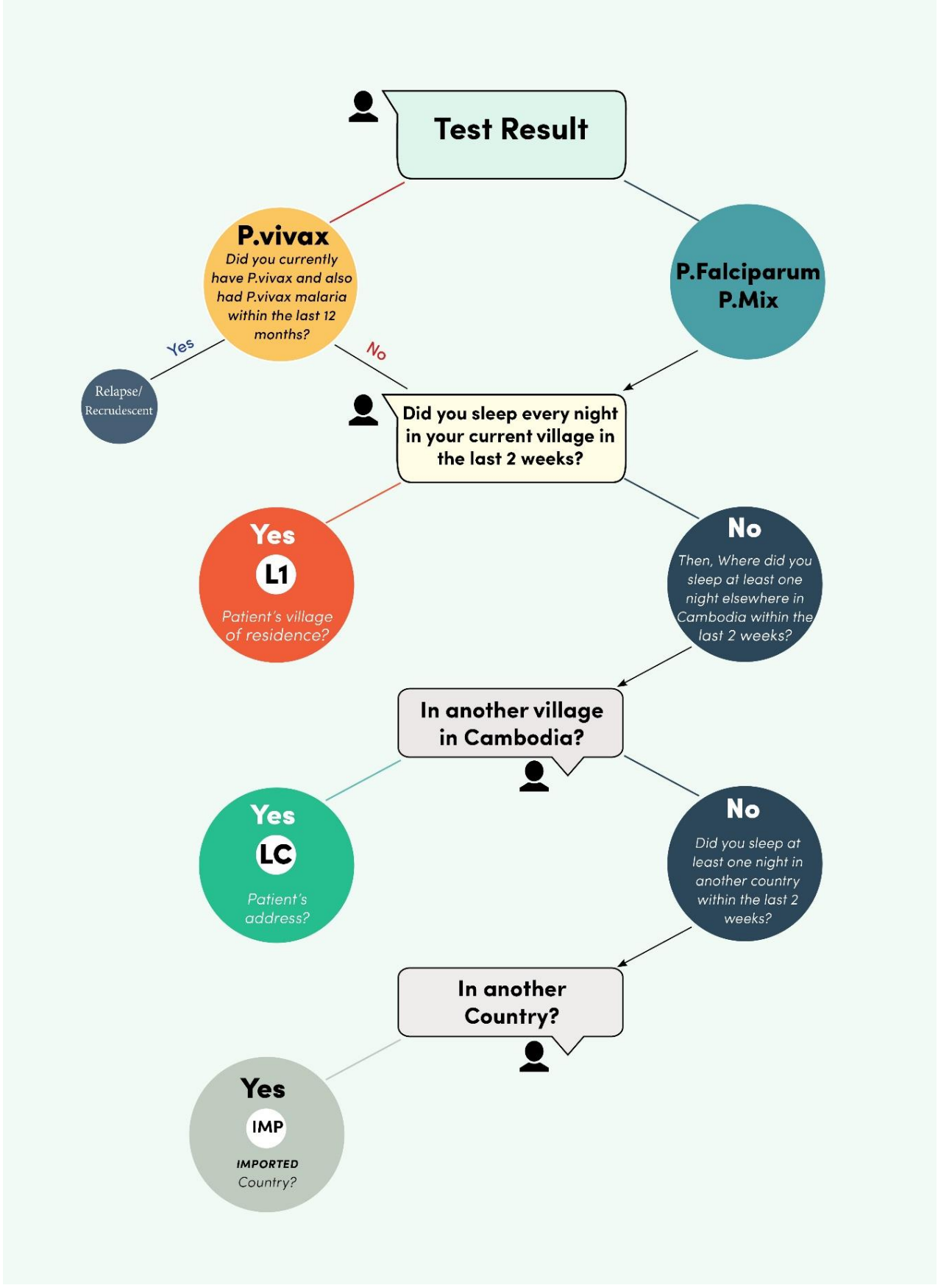

Figure 6: Case classification algorithm

Table 3: Case classification and corresponding case-based response

ABBREVIATION	SUSPECTED ORIGIN	CASE CLASSIFICATION	CRITERIA	CASE-BASED RESPONSE
L1	Local	From the patient's village of residence	Slept every night at village of residence within the last 2 weeks	*P. falciparum* or mix cases: None (focus-based response covered in 2.3.3)
				P. vivax cases: RACD in the patient's village of residence
LC	Local	From elsewhere in Cambodia other than the village of residence	Slept at least one night outside of the village of residence within the last 2 weeks	*P. falciparum* or mix cases: RACD in village where the case was identified
				P. vivax cases: None
IMP	Imported	From another country	Slept at least one night in another country within the last 2 weeks	*P. falciparum* or mix cases: RACD in village where the case was identified.
				P. vivax cases: None
REL / REC	Unknown	From a previous episode of malaria	Has *P. vivax* and had *P. vivax* within the last 12 months	None

2.2.3 Case Registration and Automated Alert

All confirmed cases (regardless of species) which are notified, investigated, and classified are given a serial unique identification number and stored in the module of MIS data platform dedicated to the national case register.

The notification of a confirmed case of any species submitted by the point of care generates an alert to the Health Center, OD, and PHD where the patient's village of residence is situated, as well as to CNM. The objective is to give information to the OD staff to verify that all cases were appropriately investigated and classified and get confirmation on L1 cases to prepare for potential focus investigations and responses. The alert includes the patient's age, sex, village of residence, and phone number, but also includes information on the case travel history, case classification, the point of care, including the type (i.e., VMW/MMW/HC/HP) and location.

Table 4: Points of care and reporting applications required.

TYPE	POINT OF CARE	MIS APP
PUBLIC HEALTH FACILITY	Reference Hospital	PC/Tablet
	Former District Hospital	PC/Tablet
	Health Center	PC/Tablet
	Health Post	PC/Tablet
COMMUNITY HEALTH WORKER	Village Malaria Workers	Smart Phone
	Mobile Malaria Worker	Smart Phone
MILITARY	Military	PC/Tablet
POLICE	Police	PC/Tablet

2.2.4 DOT and Case Follow Up

(Please see detail in "SOP for DOT and Case Follow Up")

D0 Direct-Observed Treatment (DOT). The first dose of ACT is given immediately on D0 and should be observed by the health care provider (HC/VMW/MMW) for all cases (*P. falciparum*, *P. vivax* and mix infections).

Patient Follow up on Treatment Adherence – *P. falciparum* infection. This activity could be implemented only in villages where a VMW/MMW is active. All patients with confirmed *P. falciparum* infection will intake their subsequent doses at D1 and D2, ideally in the presence of a VMW/MMW. If not possible, the VMW/MMW should visit the patient on day 3 to confirm that the treatment was completed.

IDES for *P. falciparum* Patients. All Pf/mix infection will be followed up for 42 days after a treatment supervised by VMW on D1 and D2 to measure the efficacy of the ACT treatment. Initial diagnosis on D0 is performed using standard RDT or microscopy and a dry blood spot on filter paper will be collected for PCR/genotyping. It will be used to confirm diagnosis by PCR, to distinguish between reinfection and recrudescence in case of reappearance of parasitaemia and to look for molecular markers of drug resistance. A blood smear for microscopy examination and a second dry blood spot will be collected 42 days after the treatment or before it if the patient experiences malaria symptoms. The slides will be read within 24h by a quality assured microscopy laboratory. Patient and referent care providers should be immediately informed about the result and those with a positive result be treated with the second line treatment.

Patient Follow up on Treatment Adherence – *P. vivax* or mix infection.
For patients who receive a positive RDT or microscopy result for *P. vivax*, a G6PD test will also be administered by health facility staff to both male and female patients to determine eligibility for safe radical cure. The Primaquine for 14 days for G6PD normal will be administered to the patients and will be followed up for adherence to treatment by either their Health Center or the VMW/MMW. If a VMW/MMW is present in the village of the positive case, the VMW/MMW will follow up with the patient on day 3, 7, and 14. During these visits the VMW will ask and observe the patient's history of side effects and symptoms of hemolysis (AHA) from the date of the first dose or from the last visit by VMW. If the VMW identifies one or more dangerous sign(s), they will either (i) call the HC staff to consult if the patient needs to be referred or (ii) refer the patient to the closest Health Center or provincial hospital if the Health Center staff are not reachable or the case is experiencing severe side effects. At each visit, the VMW will ask the number of tablets taken from the patients, check the number of tablets remaining, monitor the patient's treatment adherence form, and enter the treatment adherence data in the MIS App. If no VMW/MMW is in the village of the patient, the Health Center staff will call the patient on day 3, 7, and 14 to check on treatment adherence. The Health Center will then report this information in the MIS.

2.2.5 Reactive Case Detection for *P. falciparum* or mix LC and Imported Cases and *P. vivax* L1 Cases

(Please see detail in ("SOP FOR REACTIVE CASE DETECTION FOR PF/MIX LC AND IMPORTED CASES AND L1 PV")

When a *P. falciparum* or mixed malaria case is classified as "LC" or "Imported" or a *P. vivax* case is classified as "L1", reactive case detection is conducted to detect concomitant or secondary infections that may have occurred but have not yet captured through the passive system.

The Health Center responsible for the catchment area that includes the patient's village of residence will undertake the reactive case detection within three days (D3) of case notification and classification.

More details on the specifics of how reactive case detection for LC or Imported *P. falciparum* and L1 *P. vivax* cases are to be implemented can be found in the SOPs in Annex 5.

Table 5: Reactive case detection summary

This involves house-to-house visits with:	
01	All members of the index case's household should be tested for malaria and treated if found to be positive
02	20 neighboring households (or all households within a 1km radius if there are less than 20 households nearby) should be visited. They should be tested with an RDT if they have any of the following risk factors: - Fever, chills, or sweats in the last two weeks. - Slept in the forest or at a worksite/farm in the 30 days. - Returned from travel in high-risk malaria area(s) in the last 30 days. - Had malaria previously. - Had someone in the family with malaria in the last month.
03	All co-travelers not covered in the testing of neighboring households should be visited and tested regardless of symptoms or potential risk factors. If co-travelers are in nearby villages with a VMW, those VMWs should be contacted and informed of potential co-travelers to test and treat.
04	Positive individuals found during reactive case detection receive standard treatment and are notified to the MIS using the standard case notification, investigation, and classification form.
05	Data collected during Reactive Case Detection (number of tests conducted, number of positives found, etc.) will be collected on the Reactive Case Detection Form (Annex 6) and will be entered into the MIS by the Health Center

Important note:

- Re-active case detection is conducted with RDTs as the currently available "point of care" diagnosis tool. The use of more sensitive diagnosis tool such as nucleic acid amplification techniques like polymerase chain reaction (PCR), loop-mediated isothermal amplification (LAMP) or high-sensitivity RDTs (hsRDTs) is not recommended as available evidence does not show any clear benefits over microscopy or standard RDTs.

Figure 7: Neighboring households census

2.2.6 Roles and Responsibilities

The priority is ensuring that every case is immediately detected, notified, investigated, and classified. As such, both the Health Center staff and VMW have an expanded role as they are the primary implementers for case detection, investigation, classification, and reactive case detection.

All points of care are responsible for identifying all malaria suspected cases and appropriately diagnosing and treating positive malaria cases. In addition, VMWs selected for outreach are required once per month to test at least 25 individuals within their community during outreach activities. MMWs are required twice a month to conduct outreach activities in nearby hotspots.

All points of care will be responsible for carrying out case investigation and classification activities for cases identified at their facility on the date of diagnosis (D0). Health Centers will be responsible for conducting reactive case detection activities in response to each LC or Imported *P. falciparum* and mix case and L1 *P. vivax* case found within their catchment area within three days of notification (D3). VMWs will assist Health Center staff with reactive case detection if they are present in the village where the activity is to take place.

More detailed roles and responsibilities for each of these activities can be found in the SOPs for each activity in the annexes and additional information on the outreach activities can be found in the Intensification Plan 2 SOP.

Table 6: Roles and responsibilities for reactive case detection (RACD)

TYPE	CATEGORY	RESPONSIBILITIES
PUBLIC HEALTH FACILITY	RH	- Passive case detection - Case notification, investigation, and classification - DOT on day 0
	FDH	- Passive case detection - Case notification, investigation, and classification - DOT on day 0
	HC/HP	- Passive and active case detection - Case notification, investigation, and classification - DOT on day 0, Patient Follow up on Treatment Adherence and/or IDES - Reactive case detection
COMMUNITY HEALTH WORKER	VMWs	- Passive and active case detection - Case notification, investigation, and classification - DOT on day 0, Patient Follow up on Treatment Adherence and/or IDES - Reactive case detection
	MMW	- Passive and active case detection - Case notification, investigation, and classification - DOT on day 0, Patient Follow up on Treatment Adherence and/or IDES
MILITARY	Military	- Passive case detection - Case notification, investigation, and classification - DOT on day 0, Patient Follow up on Treatment Adherence and/or IDES
POLICE	Police	- Passive case detection - Case notification, investigation, and classification - DOT on day 0, Patient Follow up on Treatment Adherence and/or IDES

OD		- Review case classification data - Conduct supervision visits to HCs for case investigation, classification, and RACD
PHD		- Review case classification data - Conduct supervision visits to OD
CNM		- Conduct data management and analysis
		- Conduct supervision visits to PHDs and ODs

2.3 Foci Investigation, Classification, and Management

Interventions during Elimination are based on the concept of a malaria focus, assuming that transmission is focalized and no longer homogeneous across the country. Monitoring the status of foci, with precise identification of their functional status, is a cornerstone for success in interrupting malaria transmission. The objective is to restrict interventions to areas in which the risk of the continuation or resumption of transmission has been once documented and is regularly monitored.

A focus is "a defined, circumscribed locality situated in a currently or former malarious area containing the continuous or intermittent epidemiological and ecological factors necessary for malaria transmission". In Cambodia, a focus is defined as an individual village. A focus would therefore be a village that was identified as the source of infection for a local case. This emphasizes the ecological character of a focus as an integration of the physical environment and the three populations required for malaria transmission (humans, mosquito vectors, and parasites) as well as other biological determinants, especially animals, which may act as alternative sources of blood for local vectors.

To reach Elimination, the foci should be areas where:

- Surveillance and treatment are prompt and rigorous so that any new case is rapidly detected and treated to prevent transmission between humans.
- Interventions required to limit importation of parasites and/or infective vectors are implemented as per official guidance, with full coverage by effective interventions is provided to prevent any forward transmission.

2.3.1 Foci Investigation

Please see detail in ("SOP FOR FOCI INVESTIGATION AND CLASSIFICATION")

Investigation of a new active focus

All newly classified foci are required to be visited for a focus investigation. A new active focus is defined as a village which has been identified as the origin of infection of a local *P. falciparum* or mix case (L1). The investigation of a **new active focus is therefore triggered by a *P. falciparum* or mix L1 case** and should be completed within one week.

Objective: Every new active focus is investigated and classified within one week (D7)

The objective of the focus investigation is to provide the necessary information to:

- Describe the areas where malaria infection occurred.
- Define the population at risk and their behavior.

- Ascertain risk factors.
- Classify the focus.
- Select the optimal strategies for interruption of transmission.

The investigation is expected to last 4 days. The foci investigation is initiated from the OD level with OD malaria supervisor and a technician. They are assisted, if necessary, by staff from the closest Health Center and active VMWs, if in place.

The components of a foci investigation consist of:

1. **Desk review of past reported cases.** Epidemiological information from the last 3 years are reviewed. Case investigation reports from the village recorded over the last 12 months are reviewed to assess the ratio between L1 and other case classes. Seasonal pattern of incidence and sociodemographic information is also examined to better understand the potential receptivity and vulnerability of the focus.
2. **Index case confirmation**. The L1 index case that prompted the focus investigation is visited and questioned to ensure the veracity of the case classification.
3. **Night capture of mosquitoes**. The team conducts the capture of mosquitos over 3 consecutive nights. The objective is to confirm presence and/or absence of vectors. The most sensitive and simple mosquito trapping method will be selected ranging from human landing collection (HLC), cattle baited net collection (CBNC), and human baited double net collection (HDNC). Collected mosquitoes will be identified morphologically and stored in ethanol or other suitable preservative and sent to CNM for identification.
4. **Mobility assessment.** Each household within 1km is administered a standard questionnaire about their occupants' mobility and activity in the forest during the last year. They are classified as mobile, seasonal workers, or forest goers and asked how many nights they spent outside the village over the last 4 weeks.

All additional details about foci investigation are provided in related "SOP for Foci Investigation and Classification" in Annex 7.

Figture 8: Night capture of mosquitoes & household mapping in foci village.

Classification of an active focus

Outcomes of the focus investigation are used to assess level of receptivity (potential transmission) and vulnerability (importation of parasite or infected vector) which in turn determine the classification of the village.

- Areas are **receptive** when the presence of vector anophelines and the prevailing ecological and climatic factors favor malaria transmission. It is a reflection of the vectorial capacity of local anophelines during the season most favorable for malaria transmission.
- Areas are **vulnerable** when they are in proximity to malarious areas or are prone to the frequent influx of infected individuals or groups and/or infective anophelines.

Each of the questions on focus investigation form are weighted for their relative importance. **A focus is considered receptive or vulnerable if the scoring in either of the checklists is greater than six.**

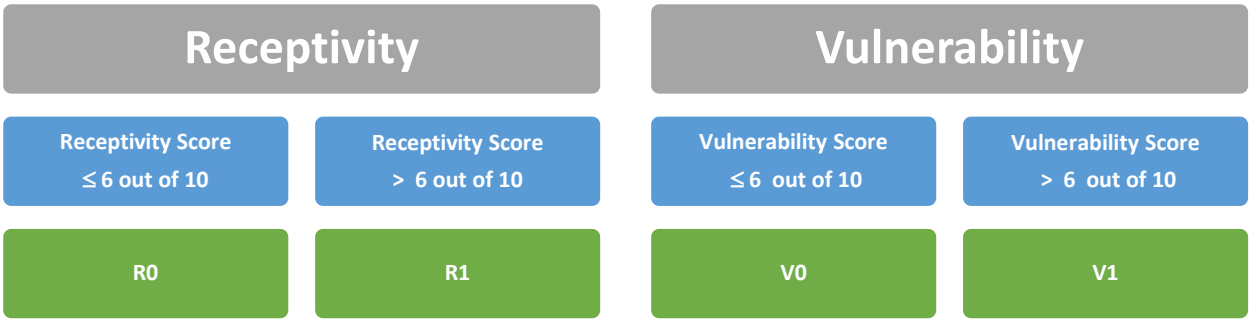

Figure 9: How receptivity and vulnerability scoring feeds into receptivity and vulnerability classifications

Table 7: Receptivity scoring

No	Parameters		Weight
1	Presence of permanent river or stream within 3km from focus boundary	Yes	1
		No	0
2	Capture of Anopheles sp.	Primary	5
		Other *Anopheles*	1
		No	0
3	Distance to forest	< 1 km	2
		< 5 km	1
		> 5 km	0
4	Malaria cases < 5 years old in the last 12 months	Yes	2
		No	0
		Total	10

Table 8: Vulnerability scoring

No	Parameters		Weight
1	Percentage of travelers > 20%	Yes	4
		No	0
2	Percentage of forest goers > 20%	Yes	4
		No	0
3	Presence of worksites with high-risk populations (seasonal workers, security personnel, construction/mine workers) near the village	Yes	2
		No	0
		Total	10

Data collection and reporting

Data from the focus investigation will be entered onto the focus investigation forms (Annexes 8, 9, 10, and 11) by the OD conducting the investigation. Once the OD returns from the investigation, they will be responsible for entering the data from the forms into the MIS as soon as possible to ensure foci response activities can take place in a timely manner. Given that the mosquito species identification by CNM's entomology unit is unlikely to be completed by the time the data is uploaded, all data on the forms except for the entomological data should be entered by the OD or CNM Entomology team. The entomology unit will then be responsible for updating the form on the MIS once species identification has been completed and notifying the OD, PHD, and CNM who will determine if focus response activities are appropriate.

2.3.2 Annual Foci Classification and Monitoring

Based on the case classification and the epidemiological history of locally acquired cases in the foci, a focus can be classified into one of three classifications:

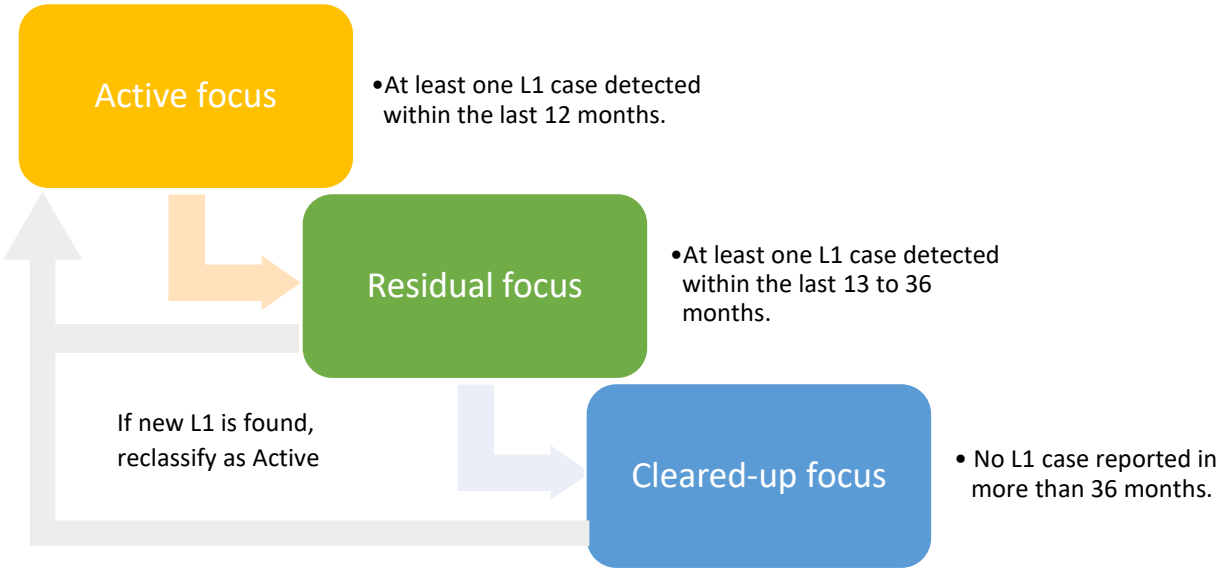

Figure 10: Focus classification algorithm
https://apps.who.int/iris/bitstream/handle/10665/254761/9789241511988-eng.pdf page: 47

- **Active focus** is a village from which at least one positive case has been investigated and classified as L1 within the last 12 months.
- **Residual focus** is a village from which at least one positive case has been investigated and classified as L1 from 13 to 36 months.
- **Cleared-up focus** is a village formerly defined as an active focus in which no cases investigated and classified as L1 have been detected in more than 36 months.

Each new active focus is recorded in the national foci register on the MIS. A new foci investigation is not needed for the reclassification of foci; reclassification will be based solely on the number of L1 cases found within the previous 36 months and the classification of a focus will be automatically updated every 12 months from the date of the last classification. After 12 months, if an Active focus has not recorded a locally acquired case, it should be reclassified as Residual. Residual and Cleared-up foci are immediately reclassified as Active if new L1 cases are identified. Additional foci investigations may be recommended by CNM if an increase in cases warrants further investigation into the drivers of transmission behind the rise (see section 2.3.1 for more details).

2.3.3 Foci Response – Interventions to Interrupt Transmission in Active Foci

Please see detail in ("SOP FOR SELECTION OF INTERVENTIONS FOCI RESPONSE FOR L1 P. FALCIPARUM AND MIX CASES ONLY")

After the classification of the focus the OD malaria focal point, in consultation with PHD and CNM national focal persons, will prepare a response plan according to the results of the focus investigation. Foci response activities will depend on the species of L1 cases found within the focus.

Foci response for L1 P. falciparum and mix cases

Figure 11: Foci response for L1 P. falciparum and mix cases

		RECEPTIVITY	
		R0	R1
VULNERABILITY	V0	VMW/MMW	LLINs + LLHINs TDA AFS – IPT *f*
	V1	LLIN + LLHINs AFS – IPT *f*	LLINs + LLHINs TDA AFS – IPT *f*

If L1 *P. falciparum*/mix cases have been found within the focus, foci response activities will be implemented according to the receptivity and vulnerability scoring of the focus. The possible activities include:

1. **VMW/MMW**: The recruitment and training of a VMW or MMW to provide passive case detection within the focus, if not already existing.
2. **LLINs + LLIHNs**: The top up LLINs and continual distribution of LLIHNs to high-risk populations.
3. **Active Fever Screening (AFS)**: Weekly fever screening to all high-risk populations within the focus.
4. **Targeted Drug Administration (TDA)**: The distribution of ACT which currently ASMQ to males between 15 and 49 years old within the focus for two consecutive months at the beginning of response activities.
5. **Intermittent Preventative Treatment for Forest Goers (IPTf)**: The providing of ACT which currently ASMQ to males between 15 and 49 years old as a preventative measure to focus residents who plan on working in nearby forested areas within the following month.

These activities will be preceded by community engagement and a full focus census for receptive and/or vulnerable foci to ensure the community is involved in the process and that interventions are targeting the most at-risk individuals. Further information on each of these activities and how they are to be implemented can be found in Annexes 12 to 18.

Note that the implementation of these response activities for foci (TDA & IPTf) with *P. falciparum*/mix cases are to be considered as a pilot for the time being. If these strategies later prove ineffective, overburden the delivery of existing health services, or prove too costly to implement, alternative methods will be considered in their place as determined by CNM.

Foci Response for L1 P. vivax cases

Response activities for foci with only L1 *P. vivax* cases will not receive any foci response activities for the time being. CNM will analyze the results of the expansion of case classification to *P. vivax* cases within the first few months of the launch of these updated guidelines to determine the number of foci that would require a response if activities for *P. vivax* only foci were considered.

2.3.4 Foci Management

All foci should be managed and 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.

Table 9: Focus management details by focus classification

FOCI	FOCI DEFINITION	FOCI MANAGEMENT ACTIVITIES
Active	A focus with ongoing transmission. Locally acquired case(s) – L1 – have been detected within the last 12 months	• PCD through Health Centers, VMWs and MMWs Within 14 days of last L1 case: • VMW/MMW • LLIN + LLINHs • Community engagement • Full focus census Month 1-2: • VMWs/MMW • AFS (if R1 or V1) • TDA (if R1) Month 3-12 (once a month): • VMW/MMW • AFS (if R1 or V1) • IPTf (if R1 or V1) *LLIN + LLINHs (if required)*
Residual	Transmission interrupted within the last 3 years. The last locally acquired case(s) was detected 13 to 36 months ago.	• PCD through Health Centers, VMWs and MMWs • Active case detection with VMW outreach activity once a month, and MMW outreach activity twice a month • LLINs/LLIHNs mass and continuous distribution (as required) • Community mobilization through established village and other public networks
Cleared	A focus with no local transmission for more than 3 years. The last locally acquired case was detected more than 36 months ago.	• PCD through Health Centers, VMWs and MMWs • No response (however surveillance must still be sensitive & responsive)

2.3.5 Roles and Responsibilities

The first priority is ensuring that every local case (L1) is immediately reviewed, with identification of the village where the L1 case was infected. The OD staff have an expanded role in Elimination ODs as they are the primary implementers for foci investigation and response activities.

Table 10: Overview of roles and responsibilities for foci management

TYPE	CATEGORY	RESPONSIBILITIES
PUBLIC HEALTH FACILITY	RH	*None*
	FDH	*None*
	HC	Assist OD staff to conduct: - Foci investigation and classification - Foci response
	HP	*None*
COMMUNITY HEALTH WORKER	VMW	Assist OD staff to conduct: - Foci investigation and classification - Foci response
	MMW	Assist OD staff to conduct: - Foci investigation and classification - Foci response
MILITARY	MILITARY	Assist OD staff to conduct: - Foci investigation and classification - Foci interventions
POLICE	POLICE	
OD		Organize and lead: - Foci investigation and classification - Foci response - Foci data management and analysis
PHD		- Supervise ODs for foci investigation, classification, and response - Data management and analysis
CNM		- Conduct supervision visits to PHD and ODs - Identification of captured mosquito - Foci data management and analysis

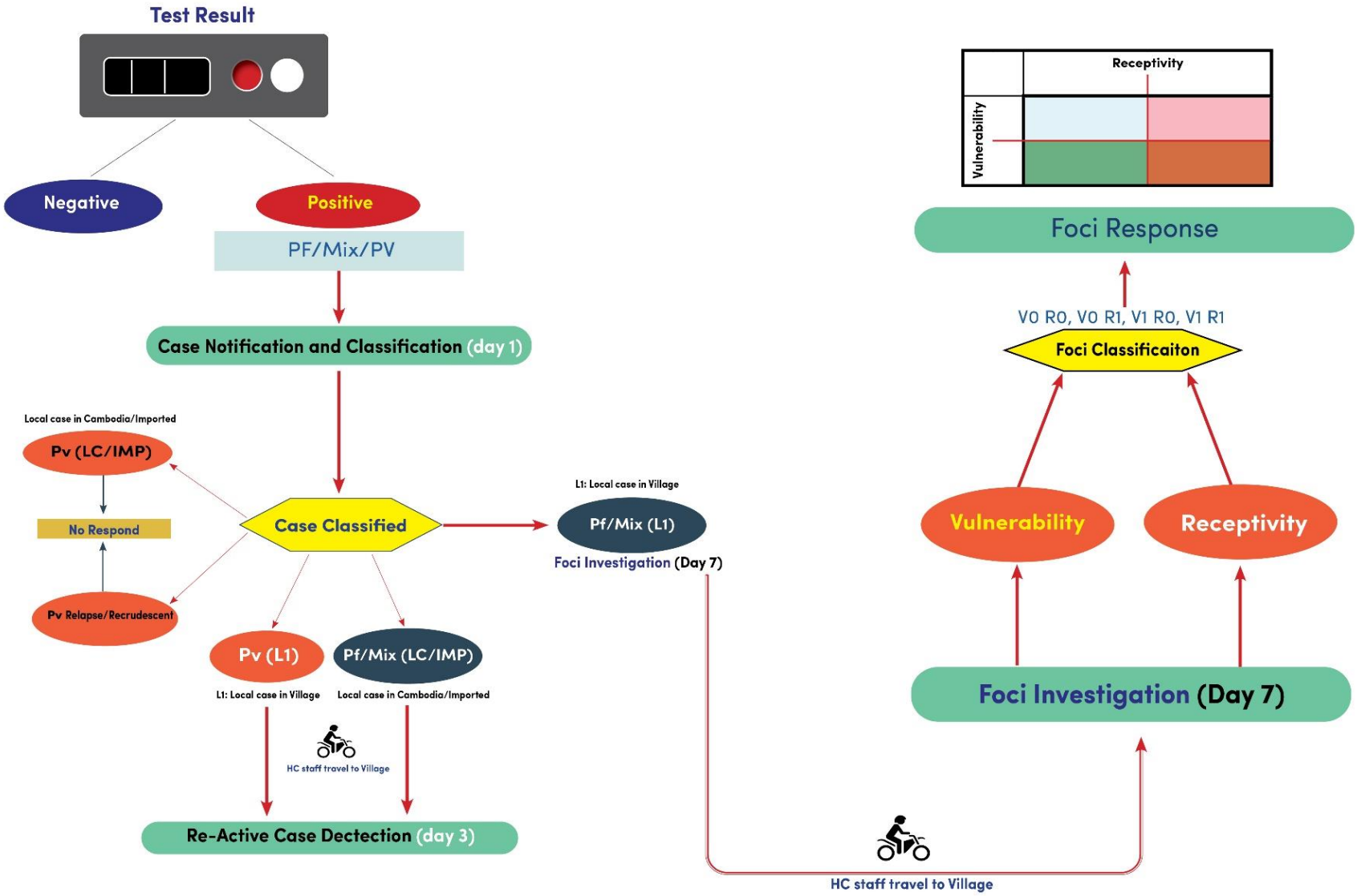

Figure 12: Surveillance decision tree

Chapter 3 – Data Management and Analysis

3.1 MIS Access and Maintenance

Periphery-level users will only be able to enter data for their relevant areas of operation. They may also be able to access and view visualizations for data from operational units in nearby geographical areas, as defined by CNM. For example, a Health Center will only be able to enter data from VMWs and MMWs in their catchment area as needed, while ODs will only be able to see data for points of care within their OD and nearby. Central-level CNM will have complete oversight of all data in MIS.

OD staff will be responsible for the regular updating of census-related information for their OD. This includes data such as names and geographical coordinates of points of care, as well as total population figures of villages. OD staff will coordinate with the relevant stakeholders (i.e., village chiefs, Health Center staff) to update these figures annually within a time frame to be specified by CNM.

Non-endemic ODs will report malaria cases directly to the HIS and that data will be imported monthly into the MIS to ensure the MIS captures all malaria cases within the country.

3.2 Data Management

Validation of completeness and quality of data entry help ensure captured statistics are meaningful. Regular checks are necessary at each step of the reporting process, including for the fully compiled database. Both regular and random assessments should be done to evaluate this properly and identify where operational or quality gaps may exist. At the uppermost level of data validation, automated system checks will be available to aid in the process, highlighting data discrepancies or missing values.

3.2.1 Data entry completeness, timeliness, and feedback

On the 05th of every month, CNM data management staff will check for completion and timeliness of data entered by the VMWs/MMWs, and Heath Facilities (OD, HC, RH, etc.). Specifically, CNM will assess whether data has been entered for all VMWs/MMWs and Health Centers under their OD catchment area, as well as perform a comprehensive system check for data quality. Non-submission by the point of care and a confirmed submission of zero cases for that reporting period will be denoted separately. CNM data management staff will follow-up with OD data entry staff at an operational level individually if data entry is incomplete, of poor quality, or late. OD/PHD staff will then follow-up with points of care on submitting reports.

Completeness and timeliness of data entry into MIS is automatically measured through a built-in algorithm. These measures the completeness and timeliness of reporting by the point of care as well as of the OD's data entry into the MIS.

- **Completeness by field**: Measures the percentage of individual line lists that have data entered for the specified field. Regular system-level M&E indicators will be produced by the MIS after each monthly submission deadline to inform completeness.
- **Completeness by point of care:** Measures the percentage of points of care that have data entered for each month. Points of care that did not submit reports will be marked as "incomplete", while points of care that reported zero tests and cases will be marked as complete.
- **Timeliness by case:** Measures the percentage of individual line listed cases where the difference between date diagnosed and date entered into the MIS is less than or equal to 24 hours to ensure that all cases are notified, investigated, and classified within 24 hours. Separately, also measures the difference between date entered into the MIS and when RACD activities were completed for L1 *P. vivax* or LC/Imported *P. falciparum*/mix cases to ensure RACD is completed within three days of notification.
- **Timeliness by focus:** Measures the time between when an L1 *P. falciparum*/mixed case is entered into the MIS for a focus that has not received a focus investigation and when a focus investigation is completed to ensure that all focus investigations are completed within seven days of notification of an L1 *P. falciparum*/mixed case.

ODs will be able to analyze data entry completeness and timeliness using the built-in MIS visualizations and follow-up with points of care that are not reporting regularly or in a timely manner.

3.2.2 Reporting completeness and feedback

Completeness of the MIS paper-based forms will be assessed in-person through routine mechanisms or supervision visits. In all such cases, verbal feedback will be provided to the point of care to encourage improved reporting completeness.

- HC/OD staff will oversee completeness of VMW and MMW data, reporting routinely at the monthly (VMW, MMW) meetings. At these meetings, HC/OD staff will cross-check the number of used RDTs and drugs against the case data reported on the paper forms.
- Routine visits by OD, PHD, and CNM staff to public health facilities, and community health workers, will include spot-checking for completeness of data reporting. These visits will be informed by the established performance of the points of care and target low performers.

3.3 Data Analysis

Standard adapted methodology for data analysis is a critical component for an efficient MIS but is continues development according to the demand. Once finalized, this section will describe in detail the required operations for the computation of all surveillance-based indicators included in the MEAF performance framework. This will guide the programming of MIS platform for automated outputs adapted to users at different levels of the system.

3.4 Feedback and Reporting

This section will provide a standard template for monthly, quarterly surveillance bulletin disaggregated by OD allowing tabular and graphical trend analysis of a set of core indicators.

Table 11: Core impact indicators

	IMPACT INDICATORS
CM-1a	Annual blood Examination Rate – Passive case detection: Number of parasitological tests carried out per 100 population
CM-1b	Annual blood Examination Rate – Active case detection: Number of parasitological tests carried out per 100 population
IP-3b	Annual Plasmodium *falciparum* Incidence: Number of confirmed Plasmodium *falciparum* malaria cases, including mixed per 1,000 population
	Annual Parasite Incidence: Number of local malaria cases for all species per 1,000 population
	Test positivity rate: Percentage of positive malaria tests for all species
	Number of Operational Districts (ODs) that have malaria API less than 1 per 1,000 population for all species
	Number of Operational Districts (ODs) that have malaria API less than 1 per 1,000 population for *P. falciparum* and mixed
	Percentage of cases that are classified as indigenous (L1-LC)
	Number of active foci
	SURVEILLANCE – COMPLETENESS AND TIMELINESS INDICATORS
SV-1a	Percentage of expected MIS reports submitted from Referral Hospitals
SV-1b	Percentage of expected monthly MIS reports submitted from public HFs
Sv-1c	Percentage of expected monthly MIS reports submitted from VMW/MMWs
	SURVEILLANCE – ELIMINATION INDICATORS
EL-1	Percentage of malaria cases notified, investigated, and classified within 24h after detection
IP-6	Number of investigated Plasmodium *falciparum* cases, including mixed that are classified as local
EL-3	Percentage of patients with Plasmodium *falciparum* malaria (including mixed) with directly observed treatment (DOT) by VMWs
	Percentage of patients with *P. vivax* malaria with adherence to treatment by VMWs or HCs
	Percentage of malaria cases investigated and classified and responded to with reactive case detection out of the total number of cases requiring reactive case detection
EL-4	Proportion of cases investigated who were diagnosed within 24 hours after onset of symptoms
EL-5	Percentage of new active foci investigated according to surveillance manual
EL-6	Percentage of investigated foci in which response was initiated according to surveillance manual
	Percentage of eligible population receiving ACT compared to total eligible population in the village (TDA round 1 and TDA round 2)
	Percentage of the forest goer population receiving ACT before going to the forest in the village
	Test positivity rate of active fever screening

Figure 13: Malaria Information System

Further information on each of these activities and how they are to be implemented (SOP) can be found in a separate SOP document.

Surveillance for Malaria Elimination

Surveillance Guidelines 2021

The guideline is designed as a practical guide to standardize implementation of surveillance strategies at the central, peripheral and commnunity levels.

The surveillance guidelines consist of three chapters:

CHAPTER 01

Overview of the Surveillance Strategy provides an overview of malaria situation and surveillance strategy for malaria elimination in Cambodia.

CHAPTER 02

Surveillance for Elimination serves as a practical guide to implement surveillance activities for malaria elimination.

CHAPTER 03

Data management and analysis serves as a practical guide for CNM staff on routine management and analysis.

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