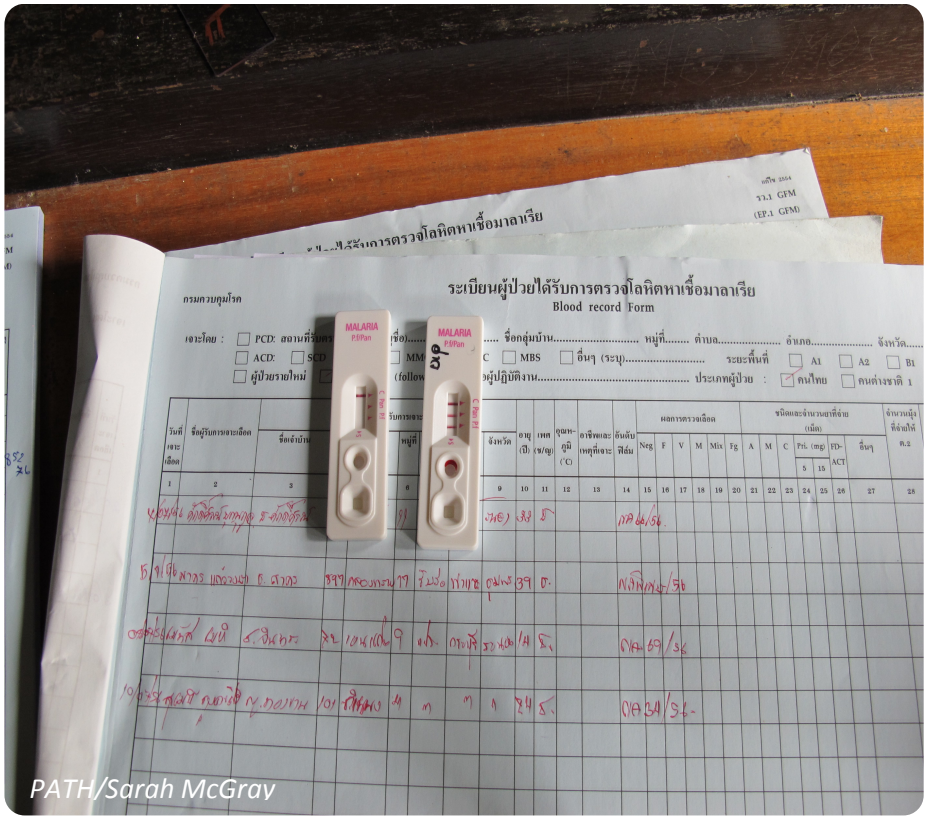

PATH/Sarah McGray

Thailand Trip Report

Project DIAMETER (Diagnostics for Malaria Elimination Toward Eradication)

Submitted to:
The Bill & Melinda Gates Foundation

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Abbreviations

ACD	active case detection
AEIOU	Activity, Environment, Interaction, Object, and User
BVBD	Bureau of Vector Borne Diseases
DOT	directly-observed therapy
DIAMETER	Diagnostics for Malaria Elimination Toward Eradication
FSAT	focal screening and treatment
JOC	Jobs-Outcomes-Constraints
MCs	malaria clinics
MoPH	Ministry of Public Health
MPs	malaria posts
PCD	passive case detection
PCR	polymerase chain reaction
Pf	*Plasmodium falciparum*
Pv	*Plasmodium vivax*
QA	quality assurance
QC	quality control
RACD	reactive case detection
RDT	rapid diagnostic test
WHO	World Health Organization

Thailand Trip Report

Introduction

Project DIAMETER

The goal of Project DIAMETER (Diagnostics for Malaria Elimination Toward Eradication) is to define the diagnostic needs unique to malaria elimination settings with sufficient clarity so that all stakeholders can act with confidence to develop, commercialize, and efficiently implement the most promising, cost-effective, and impactful technologies for malaria elimination.

Recent progress in malaria control has enabled countries to reduce malaria transmission rates. Existing diagnostic technologies—microscopy and rapid diagnostic tests (RDTs)—have played a critical role in this success by enabling many regions to achieve transmission rates near the threshold that defines the elimination phase. However, it is not clear whether these same tests are the most efficient and cost-effective tools to achieve accurate infection detection at low levels of parasitemia which is critical to achieving elimination goals. Furthermore, there is a lack of clarity and agreement on the use scenarios, target product profiles, standardized methods of assay validation, and market potential for the malaria diagnostic tools best suited for cost-effective detection in elimination settings. The resulting ambiguity hinders the development of new infection detection technologies as well as strategic application of existing and nearly ready tools.

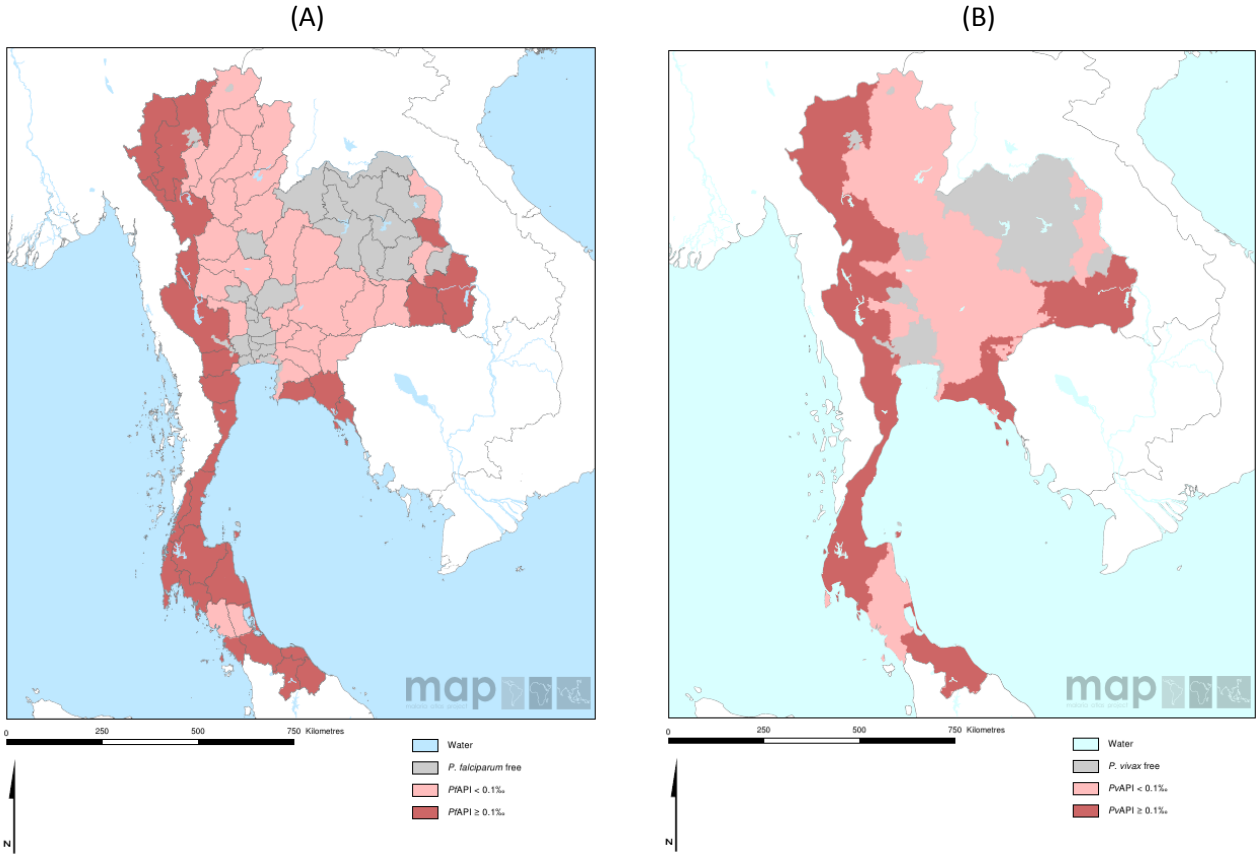
PATH has developed a rigorous approach to identifying the most promising solutions to diagnostic challenges in low-resource settings. This involves aggregating and analyzing user needs, market needs, and technical requirements to generate the comprehensive evidence base necessary to inform program development, commercialization, and strategic program operations. Thus, through extensive field research and collaboration with malaria elimination experts, the DIAMETER team will evaluate and hone the use scenarios and target product profiles for infection detection in elimination scenarios. To this end, stakeholder interviews will be conducted in a selection of countries in Asia, Africa, and South America that are nearing malaria elimination. Information gathered will be collated to inform product development of new diagnostics and areas where further research is required. This report presents findings from stakeholder interviews conducted in Thailand in July 2013.

Malaria in Thailand

Thailand is one of six countries in the World Health Organization (WHO) Greater Mekong Subregion and shares borders with Laos, Cambodia, and Myanmar. Thailand's goal is to achieve malaria elimination in 80% of the country by 2020, with annual parasite incidence reduced to 0.2/1,000 by 2016, malaria mortality reduced to 0.5/1,000 population by 2016, and 60% of the country achieving interrupted transmission (no indigenous transmission) by 2016.

The 2012 population of Thailand was 66.79 million, and of this, approximately 50% live in areas with *Plasmodium falciparum* (*P. falciparum; Pf*) or *Plasmodium vivax* (*P. vivax; Pv*) transmission largely along the borders, while the central region is without malaria endemicity (see maps).[1,2] In 2011, there were 24,897 malaria cases confirmed by microscopy. [3] Although ratios vary by locality, *Pv* prevalence is proportionally higher than *Pf* prevalence, with *Pv* composing 58% of cases.[4]

Figure 1. The spatial limits of *Plasmodium falciparum* (A) and *Plasmodium vivax* (B) malaria transmission in 2010 in Thailand[5,6]



Thailand's porous borders contribute to a high incidence of imported cases, particularly among migrants, who compose an estimated 4.8% of the total population in the 22 provinces that border Myanmar and Cambodia but account for 57% of total malaria burden in those provinces. As artemisinin resistance has cropped up in neighboring countries; population exchange across the borders has contributed to a rise in resistance in Thailand. Among migrants along the Thai-Myanmar border, day 3 *P. falciparum* positivity rate has risen from 0% to 28% in the past decade.[7] The national guidance for *Pf* treatment and follow-up reflects the prioritization of artemisinin resistance containment (see section Thailand's malaria control and elimination program). [8,9,10]

Methods

In order to capture a complete picture of the current state of malaria elimination in each country, Project DIAMETER combines a thorough desk research on malaria control and elimination efforts with theory-driven qualitative research targeting the opinions and actions of key players within the country's malaria program.

Desk research

Prior to initiating in-country research, a literature review of relevant documents was undertaken. This desk research helped the team define priority areas for further research as well as provide context around Thailand's existing malaria program strategies and goals. The preliminary literature review also informed the development of the in-country research tools and key informant list.

Qualitative research

A total of 18 interviews and observational visits were completed. Interview guides and observation checklists were developed in advance to encourage systematic and uniform data collection techniques within the tenets of Contextual Inquiry methodology and using a hybrid of two frameworks—Jobs-Outcomes-Constraints (JOC) and Activity, Environment, Interaction, Object, and User (AEIOU)—to organize concepts.[11,12] Contextual Inquiry approaches qualitative data collection with the objective of describing how actors, objects, and rules influence and are influenced by the larger system in which they exist. This method exposes tacit knowledge that informants may not be aware of and encourages the informant (rather than the reviewer) to prioritize concepts.

Interview guides and observational checklists were used for each category of key informant: program manager, thought leader, Bureau of Vector Borne Diseases (BVBD) staff, public health clinician, and researcher. The data collection tools were developed using a hybrid JOC-AEIOU framework, prompting the interviewees to describe the main elements of the system (AEIOU) within which they work, and then define the barriers to successfully achieving the intended objectives (JOC).

Following data collection, key concepts from each interview and observation visit were summarized by the research team, mapped to the corresponding use scenarios and settings, and aggregated across 18 data sets (12 interviews and 6 observational visits). A spreadsheet mapping key concepts to use scenarios and settings is included as Appendix A.

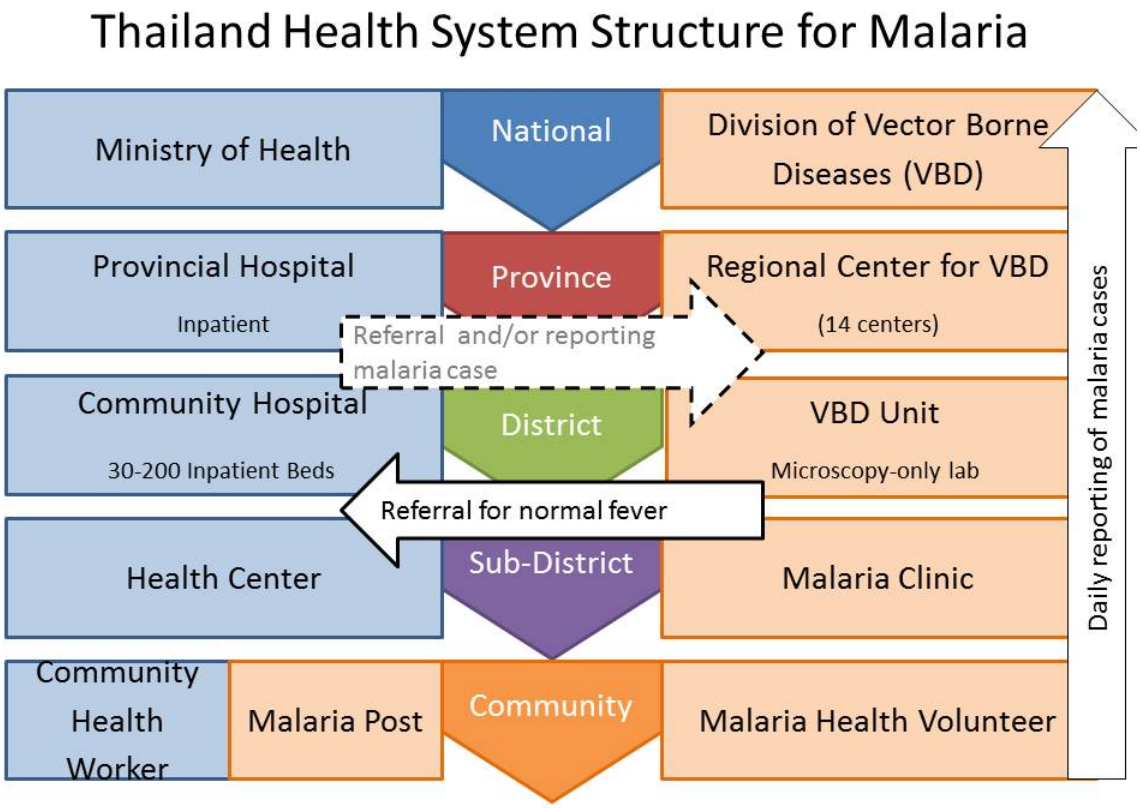
Results

Thailand's malaria control and elimination program

To achieve the national malaria elimination goal, the Thai Ministry of Public Health (MoPH) works in partnership with the BVBD, which is the primary administrative authority for malaria control and

elimination efforts in Thailand. The BVBD has a five-tier structure covering all areas of Thailand with malaria transmission (Figure 2). At each level, dedicated staff oversee and implement all aspects of malaria control for their catchment population, including community education, bed net distribution, household spraying, case detection, and surveillance activities. Each level is also responsible for quality assurance (QA) activities for those facilities underneath it within the BVBD administrative structure. The BVBD is divided into 14 regional centers, each with a reference laboratory where WHO-certified microscopists conduct a quality-check on all slides from the malaria units, clinics, and malaria posts (MPs) in their region before sending all positives and 10% of negatives on to the national lab for final data aggregation and quality-check.

Figure 2. Thailand's Health System Structure for Malaria.



Malaria diagnosis can happen at any level of the Thai public health system or BVBD, but it most commonly occurs within a malaria clinic at any of the BVBD levels. Each level—Center, Unit, Clinic—is equipped with malaria microscopy capacity, while MPs, which are administratively housed under the MoPH are equipped with RDTs (Appendix B). When a malaria case is seen at a MoPH facility, initial diagnosis and treatment may happen at the facility, but patients are encouraged to go to the nearest BVBD facility for follow-up. Similarly, when a non-malaria fever case is seen at a BVBD facility, that person is referred to the nearest MoPH for follow-up. Open lines of communication between MoPH facilities and their BVBD counterparts is a critical component to the proper referral and reporting of malaria cases

within the MoPH system and tracking and treatment of non-malaria cases seen at BVBD facilities. Emailed status reports (excel documents) and phone calls from one local facility to another are used to track patients.

Breakdown of Bureau of Vector Borne Diseases settings

(Further detail is included in Appendix A)

- National Reference Laboratory: The national reference laboratory is a fully-equipped laboratory with full research capabilities. Microscopy quality control (QC) is conducted here for 100% of positive slides and 10% of all negative slides across Thailand. QC is done by a team of microscopists with three-year laboratory technician degrees and WHO microscopist certification.

- BVBD Regional Centers: Regional reference laboratories are responsible for QC and reporting of all positive slides and 10% of negative slides from all malaria facilities within each region. Laboratories are well equipped and staffed with WHO-certified microscopists with three-year laboratory technician degrees. Aside from QC, no other diagnostic scenarios are employed at this level.

- BVBD Units: Units are responsible for planning and oversight of control and elimination strategies within their catchments, as well as QC of slides sent by malaria clinics (MCs). BVBD units also have a MC attached to the unit's administrative offices. While mains power and water are readily available, no back-up generators are provided, and intermittent power outages can interrupt work. Microscopists at this level have three-year laboratory technician degrees plus basic malaria microscopy training.

- Malaria Clinics: Staff at MCs are responsible for implementation of malaria control and elimination strategies and read the majority of slides generated by passive case detection (PCD) and active case detection (ACD) scenarios. Malaria clinics have running water and power from the central grid, but no back-up generator. Power outages can occur with some frequency, interrupting microscopy workflow until power is restored. Microscopists at the clinic level have basic training in malaria microscopy but no degree.

- Malaria Posts: Malaria posts are under the administration of the MoPH and do not participate in malaria control or elimination strategies, aside from PCD. Malaria diagnosis at a MP is done by RDT, with a confirmation slide prepared on site and sent to the nearest MC to be read. MP workers receive a two-week training in RDT use and malaria diagnosis and treatment. No other training is provided.

Population classification and treatment protocols

The mobile nature of patients along the borders of Myanmar and Cambodia generates unique challenges, particularly in the prevention of the spread of artemisinin resistance. Legal status among migrants seen at

Thai malaria clinics is not an issue, as patients are classified by duration of their stay in Thailand, rather than immigration status: Thai citizens, M1 migrants who have lived in Thailand greater than six months, and M2 migrants who have lived in Thailand for fewer than six months. The Thai and Cambodia governments share the burden of free diagnosis and treatment, though, because Thailand has traditionally had a more robust and accessible public (free) health system, Thai BVBD staff at several levels assert that Thailand assumes a greater burden of migrant patient diagnosis and treatment.

Thai treatment guidelines for *Pf* for all cases dictate directly observed therapy **(**DOT) of artemisinin-based combination therapy on days 0, 1, 3, 7, 14, and 21. Days 0, 1, and 3 follow-up may be done at the patient's home if the patient is too ill to travel to the MC or at the MC if the patient is able to travel. In circumstances where the patient may be mobile during the duration of treatment, follow-up becomes increasingly difficult.

Malaria diagnostic tests used in Thailand

The primary mode of malaria diagnosis in Thailand is microscopy. In all but the lowest level of both the BVBD and the public health system, microscopy (thin and thick smear) is used almost exclusively. The exception to this is at malaria posts, where immediate diagnosis is done with RDTs and confirmed with microscopy, and during power outages or heavy rain when microscopy is impossible and RDTs are at hand. RDTs are not routinely supplied to facilities other than malaria posts and, therefore, are used sparingly.

Polymerase chain reaction (PCR) is used for QC and research purposes at the national level only.

Rapid diagnostic tests

RDTs are supplied to all malaria posts for immediate diagnosis and treatment, with a microscopy slide taken and sent to the nearest malaria clinic for confirmation. RDTs are used routinely at MPs only; however MCs keep a small supply for use during power outages or during outreach when it is raining. The RDT that is currently in use is the SD Bioline *Pf*/Pan, which is the current RDT for all MPs. Other RDTs observed are SD Bioline *Pf/Pv*, Para GPO, and Parascreen *Pf*. Supply of RDTs occurs via two distinct mechanisms, the provincial health department supplies MPs with RDTs with stock financed by a Global Fund grant. The BVBD supplies limited volumes of RDTs to its facilities down to the MC level. These supplies are financed by the general BVBD budget allocated from national funds. These multiple supply streams result in several types of RDTs in use in the country at one time.

RDT diagnosis is always confirmed with microscopy, except if, in the course of mobile case detection, it is impossible to prepare a blood slide (heavy rain). Once an RDT is used, it is discarded in batches that are sent to be incinerated at the nearest provincial/district hospital.

Constraints

In general, BVBD staff at the MPs and MCs (including those working at the clinics at the malaria unit level and those based at the MC who do mobile case detection) felt that RDTs are limited in their use, since in almost every case RDT diagnosis is confirmed by microscopy. “RDT is good for going out into the [surrounding] area, but since you need to do a slide anyway I’m not sure what is the point.” (Staff at MC 3.5.3 Bon Pong Nomrang). Users of RDTs felt that they offered sufficient-to-perfect accuracy (depending on the respondent), but felt that confirmation by microscopy is necessary because it offers a quantified result, implying less trust of a non-quantified result from a RDT. They made no comments on drawbacks or constraints to RDTs. Given that RDTs are used almost exclusively at MPs, where only 5–15 patients per week may be seen during the rainy season, and given that brand turnover has been frequent due to Global Fund procurement requirements, the overall exposure to RDTs on a per-user basis may not be high enough for users to notice constraints or problems with RDT use.

Microscopy

Microscopy is used for all case detection, except when it is impossible to prepare slides due to heavy rain during mobile case detection. In cases where immediate microscopy is not possible, such as at the MPs or during power outages, a RDT is used for immediate diagnosis and a microscopy slide is taken for later confirmation.

Microscopy is considered by all users to be the best method of detection currently available in Thailand, due largely to the ability to measure parasitemia in addition to speciation. Parasitemia measurement is specifically required during follow-up on days 1, 3, and 7 of *Pf* cases to track potential drug resistance. Microscopists felt that microscopy is more trustworthy than RDTs because it provides more information for diagnosis and follow-up and because the parasites are visible. “When you can see something, you trust it” (Director, BVBD Area 3). There is an implied lack of trust of a non-quantified result.

There is a structured system for QC of microscopy that is adhered to at each level of BVBD, including MPs. One-hundred percent of positive blood slides and a random selection of 10% negative blood slides are mailed each month (via the Thai postal service) to the next level facility for quality check by the microscopist at that level. Any discrepancies identified at any level of the QC system are reported back down the chain to the originating microscopist. Although follow-up on misdiagnosis is possible, the delay between QC and reporting discordant results may create a barrier to appropriate follow-up. If a QC microscopist notes a particularly high frequency of misdiagnosis by a lower-level microscopist, that individual will be referred for refresher training. With each facility level in the system following this QC structure, the national-level BVBD lab receives all positives and 10% of negatives for the entire country. The lab employs four microscopists for QC at this level.

Constraints

Program directors and managers at the national and regional levels have expressed concerns about maintaining microscopists’ skill levels as malaria rates continue to decline. However, microscopists at

malaria centers do not share this concern, although they acknowledge that they see fewer positive cases than previously.

Microscopists take measures to decrease the time to diagnosis, as patients wait while the slides are prepared. In all facilities where microscopy was performed, either a hair dryer or rack above a light bulb or kerosene wick were used to speed the drying process for both the blood smear and the staining stages. In addition, microscopists may rush reading the slides. During several observations of slide readings the microscopist took 2–3 minutes on average to read 100 fields, 50% less time than the WHO-estimated 6 minutes for a negative slide (10 minutes for a positive slide).[13]

Microscopy also has limitations for use in outreach/mobile settings. When conducting focal screening and treatment (FSAT), reactive case detection (RACD), or mobile PCD, slides are taken in the field but read later that day or the following day at the MC. This creates a lag between sample collection and diagnosis that may lead to loss to follow-up. In addition, lower levels of training for mobile staff, combined with challenging field conditions, can create substandard slide preparation, which may in turn affect microscopy accuracy.

Polymerase chain reaction

Although most regional medical centers in Thailand have PCR capability, currently, malaria PCR is only available at the national level BVBD lab. PCR is also available through select research laboratories but not for population-level research.

Quantitative PCR is currently implemented nationally only as part of the Treatment Efficacy Survey where select sites take dried blood spots in addition to microscopy slides for *Pf* follow-up on days 0, 3, 7, and 14. The dried blood spots are then sent to the national lab where they are read by real-time PCR. The purpose of the Treatment Efficacy Survey is to track drug resistance by capturing those cases that may have parasitemia lower than can be detected by microscopy. The PCR also identifies plasmodium species, and genotyping is done with the amplicon product in *Pf*-positive cases to differentiate between recrudescence and a new infection.

Constraints

PCR results are not reported back to MCs for patient follow-up as the time lag between sample collection and PCR result is too long. In addition, with no reliable biomarkers for resistance, the only way to determine a drug-resistant infection is by comparing the genotype of the parasite at the time of diagnosis with the parasite genotype again at follow-up.

Malaria diagnostic scenarios in Thailand

Passive case detection

PCD is the primary method of malaria diagnosis in Thailand, and is done either by microscopy (majority) or RDT, depending on the setting. PCD occurs at all levels and facilities of the BVBD system and the public health system, but the majority of cases are detected at malaria clinics or at a MP with confirmation at a MC. Skill level of the person making diagnosis varies by facility and setting. In higher-level labs and clinics, microscopists may have a three-year laboratory technician degree as well as a three-month basic malaria microscopy course, and in the regional reference laboratory the microscopists also obtained WHO microscopy certification. At lower-level facilities, microscopists may only have a three-month basic malaria microscopy certificate, while staff members at MPs have a two-week training in malaria diagnosis and treatment, which includes use and interpretation of RDTs.

When a patient presents with symptoms at any facility, axillary temperature is taken and patient demographics are recorded. Demographics include migrant status (resident, migrant living in Thailand > six months, migrant living in Thailand < six months), location of residence, age, and gender). Following this initial intake procedure, a blood slide is taken, either alone or in combination with a finger stick for RDT.

At all facilities, microscopy is done with a combination thick/thin smear slide.

Constraints

With a variety of skill levels performing microscopy and preparing slides, the quality of microscopy may vary. For example, time to read a slide varied significantly by microscopist, with many taking 2–3 minutes to read a slide, rather than the recommended 5–6 minutes. When asked about the amount of time taken to read a slide, responses indicated that some microscopists feel they need less time to read a negative slide because no counting is needed or that their level of experience reading malaria slides helped them read the slide quickly. Insufficient training and supervision may contribute to microscopists' perceptions of sufficient time allocated for reading a single slide, and a heavy workload may increase the pressure to read slides quickly.

In addition to reading slides made at the clinic, each level above MP also reads all positives and 10% of negatives from the facilities below it in its region. This, combined with varying surveillance throughput generated by RACD and ACD scenarios that vary depending on catchment population size and area designation, can dramatically increase total work burden for a microscopist. At the BVBD unit level, this can result in 300–700 slides to read per month, or 20–30 slides per microscopist per day (3–4 hours). Although this may seem like a reasonable throughput, workload is increased when lab setup, record keeping, reporting, and other job duties are factored into the workload of a single microscopist.

Microscopy is dependent on the availability of power to operate microscopes, clean water for performing staining and washes, a clean and dry setup for drying slides, and sufficient supplies of stain (Giemsa stain

is used). While water and stain were always available in sufficient quantities, power outages can interrupt ability to read slides once prepared. Power is also needed to dry the slides, as they generally take too long to dry during the humid rainy season. To speed up the drying process, microscopists use a number of homemade tools, such as hair dryers or light bulbs fixed beneath drying racks. When power is unavailable, slides may take a very long time to dry, or the microscopist may use another method such as a lighter held beneath the slide, or a kerosene lantern fixed beneath the drying rack, to dry the slides. This practice may negatively impact slide quality and subsequent accuracy. WHO recommends that slides be dried at room temperature and not heated to expedite the drying process, as heat drying may prevent the breakdown of red blood cells and inhibit uptake of the stain.[14]

At the MP level, only RDTs are used for initial diagnosis and treatment decisions for febrile patients with a fever above 37°C. Patients with a temperature below 37°C are given a slide only. Although patients are advised to wait for slide confirmation, this process may take several hours. Confirmation by microscopy off site at the nearest MC means there is the potential for loss to follow-up if a patient whose RDT is in fact positive decides to go home before the slide confirmation results are reported back to the MP later that day. In addition, there is the potential for loss to follow-up during DOT because after the Day 0 treatment is provided at the MP, the patient is either instructed to go to the MC for the remainder of his/her course, or the mobile staff from the MC visit the patient at his/her home to continue DOT—the disconnect between where the patient initially seeks care and where s/he completes care leaves several opportunities for missed DOT visits. This is particularly concerning in light of artemisinin resistance in the region.

Similar to the disconnect between where malaria diagnosis is made and treatment is given (for MP patients only), the physical segregation of malaria diagnosis and treatment facilities from the rest of the public health system means that a patient with non-malaria fever must visit two separate facilities before diagnosis, at minimum. In some cases, malaria fever may not be diagnosed as such on the first visit, and the patient may need to return several times to public health and BVBD facilities before the correct diagnosis is made. This can create patient dissatisfaction and distrust of malaria diagnostics and malaria services, particularly if initial diagnosis and final diagnosis differ by test (RDT vs microscopy) or facility (MC vs. district hospital).

Finally, intrinsic to PCD is the absence of detection of asymptomatic cases.

Focal screening and treatment

> *"It is ok to do it this way (stationary slide prep) because the sick people will be home and so we will catch them at the village when they don't come to the clinic."—Malaria Clinic Director*

The objective of FSAT is population screening for active detection of symptomatic and asymptomatic infection. FSAT is a proactive approach, with screening frequency and target coverage rates dictated by area definition (Table 1). A1 areas (stable transmission) are screened every week and target coverage of the community is 100% of households, although actual coverage may be lower, around 80%. A2 areas

(seasonal transmission) are screened every two weeks and target coverage is also 100% of households, but actual coverage may be closer to 60%–70%. B1 areas (high-receptivity area, but no transmission in past three years) are screened once per month, with target coverage at 80%; actual coverage in B1 areas is unknown. B2 areas are without malaria transmission in the past three years and low receptivity; detection is by PCD only.

Table 1. FSAT area designation and coverage rates.

Area designation	Definition	Screening rate	Target coverage	Actual coverage under ideal circumstances
A1	Stable malaria transmission	Every week	100%	80%
A2	Seasonal transmission	Every two weeks during peak transmission	100%	60%–70%
B1	High receptivity, no transmission in last 3 years	Once per month during peak transmission	80%	Unknown
B2	No transmission in last 3 years	Passive case detection	NA	NA

FSAT is implemented in three stages: 1) microscopy slides are prepared and sent back to the malaria clinic for analysis, 2) diagnosis is made by microscopist at the clinic, 3) BVBD staff contact the patient (by phone or by traveling to household) to inform of diagnosis and initiate treatment. The mobile unit is dispatched either in accordance with the surveillance schedule or in response to a trigger such as elevation in cases occurring in a particular area. On occasion, the mobile team will set up an evening visit in advance in order to target a specific population who would otherwise be unavailable. Staff carry finger-stick and slide preparation supplies in a backpack and travel to the village by motorbike or car (depending on the size of the team). Generally, water and electricity are not readily available at this level, and slide prep is done on whatever surface is available, which may be the floor. The delay between slide preparation and final diagnosis can lead to loss to follow-up and leaves a potentially infectious case untreated in the community.

In some circumstances, the standard house-to-house FSAT scenario is modified such that the mobile malaria staff set up a static location for sample preparation, usually in a central location within the village,

and spread the word via colleagues and word of mouth among villagers. Volunteers who wish to be screened will present at the slide preparation station. Although the intended outcomes of this modified FSAT strategy is to conduct focal screening in target areas or respond to flare-ups in a specific hotspot (area or household with elevated incidence) or hotpop (specific population with elevated incidence), the true outcome of this stationary, somewhat passive approach to sampling is to screen a population biased by age, occupation, and illness. This is due to the time during which the mobile malaria team visits villages to conduct FSAT, which are peak working hours for many of the villagers. As a result, villagers who are available to participate in malaria screening are only those who are home due to illness or because they have childcare or household duties, are of advanced age and no longer work, or work at non-peak hours. In addition, not all those who are home at the time the malaria staff are in the village will volunteer to be screened. The result can be a significantly diminished sample size. When asked, one mobile malaria staff estimated he samples 20–25 individuals on an average day, from a village of roughly 150 households of 4–6 people each.

As with PCD, the skill of the person preparing the slide, and of the person reading the slide, varies by individual. It is not necessary for the BVBD staff who are part of the mobile team to have microscopy training, so staff may not have experience reading the slides they prepare. This can impact staff knowledge and practices of proper slide preparation.

Constraints

Because FSAT happens at the village level, infrastructure is limited. While electricity and running water may be available in some communities, not all will have ready or reliable access. FSAT mobile teams may be limited by available space to conduct slide preparation away from the elements—one mobile staff commented that during the rainy season they will also bring along a box of RDTs for use when the rain and lack of shelter makes it impossible to prepare a quality blood slide.

Frequently, mobile malaria teams set up a single slide preparation station in a central location and recruit community members to come to this place for screening, instead of traveling with slide preparation supplies to each household in the area. This does not capture all individuals in a household or area and may result in significantly reduced population coverage for the screening activity and/or sampling bias favoring symptomatic patients who seek out testing.

Sampling bias could be due to a number of perceived limitations from the individual community member's perspective (no community members were interviewed in this data collection activity). Possible perceived barriers to participating in FSAT activity may include:

- Delayed time to diagnosis—since the individual sees no immediate result, the incentive to give blood for screening is low.
- Absence of symptoms—without feeling ill, an individual may not perceive any benefit to participating in screening.

- Inconvenience—time to travel away from the home or workplace to participate in a screening activity and the five minutes taken to participate may be too inconvenient, particularly for women with small children.
- Perceived pain—the individual may fear the pain caused by finger stick.

Successful diagnosis in a FSAT scenario relies on quality slide preparation at the point of contact with the target population. The quality of slide preparation may be compromised due to insufficient training, haste, environmental factors such as rain, or damaged slides.

Slide preparation, access to remote areas, and ability to perform immediate diagnosis are limited by infrastructural barriers at the community level. These include the absence or inconsistent supply of electricity and water, reliable roads during the rainy season, shelter from weather, and surface area for laying out tools and tests.

Finally, the absence of diagnosis at the point of contact imposes a delay between when the patient is first contacted by the system, diagnosis is made, and the patient is followed up to initiate treatment. This delay leaves the infected carrier untreated in the community with the potential to spread infection to other community members.

Reactive case detection

RACD occurs at the community level in response to identification of a hotspot or hotpop or in response to an individual case as part of control measures at the household level. Once triggered, RACD involves a mobile team sent from the malaria clinic to the community to capture as many within the target population or target area as possible. Generally, the mobile team will arrive unannounced, although when targeting a specific population they may call ahead to arrange a time when the majority of the target population will be in the area (e.g., in the evening at a rubber plantation).

As with FSAT, RACD diagnosis happens in three steps, with slide preparation at the household or village level, diagnosis by microscopy at the clinic, and treatment follow-up happening either at the village or clinic. Like FSAT, RACD may happen at a stationary location, when targeting a hotspot or hotpop, or it may happen at a household or household cluster, when responding to individual cases. Although many communities have electricity and running water, the assumption is that these will not be available to the mobile team. As with FSAT, the mobile team implementing RACD may vary in skill level and training, and the mobile staff preparing the slide may not have experience with microscopy beyond slide preparation. Although RACD and FSAT share similar implementation methods and setting characteristics, in a RACD scenario the objective of total or majority coverage of the target population (whether at a community or household scale) is achieved through the intersection of timing, location of specimen collection, and community engagement in recruiting participants to be screened.

Constraints

RACD shares many of the same setting-specific constraints of FSAT, such as absence of unreliable water and electricity, limited road access, and limited indoor space for setting up diagnostic tools. In addition, RACD is one element of a reactive case control effort that includes spraying of homes, distribution of bed nets, and general education on minimizing transmission risk. This multipronged intervention is managed entirely by the 2–3 person mobile team. Time is therefore limited; if not all individuals are available at the moment the team arrives, they may be missed when taking slides for screening, and the time it takes to capture each individual, record complete data in the case register, and prepare a quality blood slide can be burdensome when other tasks must also be completed.

Quality assurance/quality control

The objective of Thailand's QA/QC system is to monitor microscopists' skill levels while maintaining accurate data on all positive malaria cases that are sent to the national level. In the QA/QC scenario, once the malaria clinic-based microscopist has made his diagnosis, all positive slides and 10% of negative slides are forwarded to the microscopists at the next level of the BVBD system. At each level, 100% of positives and 10% of negatives are forwarded on, so that eventually all slides sent up the BVBD chain are read by the WHO-certified microscopists at the regional and national reference labs.

Constraints

Generally, facilities send their slides up to the next level once per month, so it may take up to a month for a microscopist to receive feedback on the quality of his or her performance. Moreover, a missed diagnosis may not be caught for some time, leaving that individual in the community as an infected reservoir. In addition, while a microscopist will be alerted of a misdiagnosis so that s/he may follow up with the patient, the data generated through the QA/QC system are only systematically reported up the chain of the BVBD; facility staff members at the lower levels do not receive QC data.

Confirmation

At MPs, RDTs are used to diagnose symptomatic cases (those with fever over 37°C) and provide immediate treatment. However, for all individuals who seek care at a MP, a slide is also prepared and sent to the nearest MC to be read by a microscopist. This mechanism enables confirmation of RDT diagnosis or the initial diagnosis of patients who did not receive a RDT diagnosis (those with fever under 37°C are generally not given a RDT and instead are tested with the slide only).

Slides are prepared at the MP by a MP staff person who has received a two-week training in malaria diagnosis and treatment. At the MP, running water and electricity are generally present. Once a slide is prepared, the MP staff person will either transport the slide to the nearest MC or will call to the MC for the clinic's mobile unit to retrieve the slide for reading at the clinic level. The results of the slide are then generally read and reported back to the MP staff on the same day.

Constraints

At minimum, there is a several-hour lag between when a patient is diagnosed by RDT and when confirmation by microscopy is reported back to the MP. This delay may result in loss to follow-up if a patient does not stay at the MP to wait for final confirmation and there is discordance between the RDT diagnosis at the MP and the slide confirmation at the MC. As a result, a patient who may not be currently infected may receive unnecessary treatment for a day or two until the revised diagnosis is reported back to the patient and his or her caregiver at the MP or MC. Similarly, a patient with infection who is incorrectly diagnosed by RDT may not receive treatment for several days until a MC or MP staff person can track him/her down (if s/he has not migrated elsewhere) or until the patient re-presents at a MP or MC for the persistent fever.

Summary

Thailand's infrastructure for malaria control and elimination is robust, and it implements several aggressive strategies for case detection, including rigorous and highly structured FSAT and RACD, and strategies for infection detection at the population level. RDTs are used only at the most peripheral level, the MPs, and always confirmed by microscopy. PCR is used in a very limited capacity for research purposes and is only available in the national reference laboratories. Microscopy is the primary form of diagnosis and is integrated into every level of the Thai MoPH and BVBD systems. Even in use scenarios in which microscopy is not feasible, such as population-level screening, slides are prepared and transported back to a facility with microscopy capability for diagnosis or confirmation. This reliance on microscopy has the advantage of providing universal data on speciation and parasitemia for each case detected, which has helped inform national data on parasite trends, including the recent shift from *Pf* to *Pv* dominance and an increase in *Pf* infections with slow clearance rates, pointing to growing artemisinin-resistant infections.

Constraints to achieving its elimination goal are mainly associated with the challenges of microscopy. Slide preparation in field settings can be a challenge, and imperfectly prepared slides can be difficult to read, high throughput workload can result in rushed results, and microscopists' skill levels vary. All of these can contribute to reduced sensitivity of the test. Migrant populations and segregation between where diagnosis is made (at a MC) and where patients are treated and followed up can result in loss to follow-up. These barriers will need to be overcome for Thailand to successfully eliminate malaria along its borders.

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Appendix A: Use scenarios for malaria diagnostic tests in Thailand

Use Scenario	Setting	Inputs				Outcomes	Constraints	Other Notes/Comments
		Diagnostics	Process	Human Resources	Infrastructure/Supplies			
Passive Case Detection (PCD)	Malaria Post (MP) & Border Malaria Post	Rapid diagnostic test (RDT) (Pf/Pan) SD Bioline,	• Patient presents with fever, malaria post worker takes temperature, demographics, does RDT, takes slide for confirmation, administers therapy for RDT-positive patient • Confirmation results returned later that day	• Minimally trained malaria post worker (two week training)	• Cooler for RDT storage, • Phlebotomy & slide supplies • Paper reporting form • Cell phone to initiate slide transfer (unclear if provided by program or personal phone) • Sink & inconsistent power (main) • Rural, proximal to village	• Detect and treat patients with fever • Document patient demographic & travel history • Take slide for confirmation	• Confirmation off-site means loss to follow-up for continued treatment & RDT- patients • No detection of asymptomatic cases • Spacial segregation of Dx and treat for non-malaria fever could create patient disatisfaction when no Tx provided to RDT patient • Alternative drying methods: drying slide is burdensome, esp. during rainy season (use hair dryer, bunsen burner, lightbulb) • Quality of microscopy confirmation is reliant on quality of slide prep, which may be impacted by lower levels of trained staff and less supportive conditions.	• Used RDTs go to district hospital/nearest MOPH facility with incinerator
	Malaria Center (MC)	Microscopy with RDT for back-up (SD Bioline)	• Patient presents with fever, microscopist takes temperature, demographics (includes migrant classification), and makes slide (thin & thick smear) • Patient waits for result • Microscopist administers therapy for positive patient • Instructs on follow-up for directly-observed therapy (DOT) (Days 1,3,7,14, 21)	• Microscopist with three month basic training	• Inconsistent power • Sink • No back-up generator • Computer for daily and weekly reporting • Paper-based case detection books	• Detect and treat patients with fever • Document patient demographic • Document species & parasitemia • DOT for *Plasmodium falciparum* (*Pf*) patients	• Microscopy dependent on electricity, which is not always available • Time taken for microscopy may be rushed (2-3 min/100 fields) • Alternative drying methods: drying slide is burdensome, esp. during rainy season (use hair dryer, bunsen burner, lightbulb) • Limited by microscopist skill level, which seems to vary greatly • Deviation from best practices (not refreshing stain often enough, speeding through field reading, heating slide to dry, etc) • Microscopist skills rusty as prevalence decreases • Inconsistent power--power outages stop work	• All positive slides and random selection of 10% of negative slides are sent to VBD Unit • Monitors treatment efficacy with microscopy
	Vector Borne Diseases (VBD) Unit	Microscopy	• Patient presents with fever, microscopist takes temperature, demographics (includes migrant classification), and makes slide (thin & thick smear) • Patient waits for result • Microscopist administers therapy for positive patient • Instructs on follow-up for DOT (Days 1,3,7,14, 21)	• Microscopist with three year laboratory technician course and microscopy certification	• Sink • Inconsistent power • No back-up generator • Computer for daily and weekly reporting • Paper-based case detection books	• Detect and treat patients with fever • Document patient demographic • Document species & parasitemia • DOT for *Pf* patients	• Microscopy dependent on electricity, which is not always available • Time taken for microscopy may be rushed (2-3 min/100 fields) • Alternative drying methods: drying slide is burdensome, esp. during rainy season (use hair dryer, bunsen burner, lightbulb) • Limited by microscopist skill level, which seems to vary greatly • Deviation from best practices (not refreshing stain often enough, speeding through field reading, heating slide to dry, etc) • Microscopist skills rusty as prevalence decreases • Inconsistent power--power outages stop work	• All positive slides and random selection of 10% of negative slides are sent to VBD Unit • Monitors treatment efficacy with microscopy
	Bureau of Vector Borne Diseases (BVBD) Regional Referal Lab	Microscopy	• Quality Control (QC) for MCs/MPs and clinical cases	• Microscopist with three year laboratory technician degree, basic microscopy training, and WHO levels 1-4 certificate	• Sink • Inconsistent power • No back-up generator • Computer for daily and weekly reporting • Paper-based report forms	• Confirm Dx from MC level • Report results up to national lab	• Inconsistent power--power outages stop work • High throughput can be straining for microscopist	
	Provincial/District Hospital	Microscopy	• Test all patients presenting with fever	• Laboratory technician with three year degree, on-the-job microscopy training	• Power from mains w/ back-up generator • Microscope/Reagents • Fresh stock of Giemsa stain daily • May have automated analyser pipettes in calibration centrifuge • Flow cytometer • RDTs for dengue, HIV,	• Detect and treat patients with fever, then refer to MC for follow-up DOT • Report case to VBD Unit	• Laboratory technician may not have formal malaria microscopy training	• Stark variation between infrastructure/resources available at different district hospitals. A well-resourced hospital had: Automated pieces of equipment must be multi-fuctional--must support multiple core functions, not just one test If they were to get an instrument for malaria detection, need to be random access, time to result in less than three hours Ideally, would like to know if it is PF or PK or anything else (Pv, PO, PM all get same Tx)
	Army	RDT (Parascreen)	• Test soldiers presenting with fever in field	• Army medic (training?)	• Varies • In camp, may have power/water • In field, no power/water • Supplies carried in an anti-malaria rescue pack	• Test & treat	• Soldiers may be far away from nearest medic • Soldiers may be more likely to go to MP or MC for test & treat when symptomatic	

Use Scenario	Setting	Inputs				Outcomes	Constraints	Other Notes/Comments
		Diagnostics	Process	Human Resources	Infrastructure/Supplies			
Treatment Effectiveness Monitoring	Village	Microscopy	• Patients who are unable to travel to the MC for treatment follow-up may be visited at home • Slide is taken at village and brought back to MC to be read by microscopist	• MC microscopists conduct microscopy • Mobile MC staff prepare slide	• No readily available water or electricity • May not have table or bench for setup (use floor) • Supplies carried in backpack on motorbike or car	• Compare parasite levels against prior measurement	• Delay between follow-up visit and microscopy read results in lag in appropriate treatment follow-up/ opportunity for loss to follow-up • Quality of microscopy is reliant on quality of slide prep, which may be impacted by lower levels of trained staff and less supportive conditions • Excessive humidity may make slide prep difficult or impossible • Alternative drying methods: drying slide is burdensome, esp. during rainy season (use hair dryer, bunsen burner, lightbulb)	
	Malaria Post (MP)	Microscopy	• Patient is requested to go from the MP to the MC for follow-up, if able • If patient is unable to travel to MC for follow-up, MP staff can prepare a slide • Slide is read at MC	• MC microscopists conduct microscopy • MP staff or mobile MC staff prepare slide	• Phlebotomy & slide supplies • Paper reporting form • Cell phone to initiate slide transfer (unclear if provided by program or personal phone) • Sink & power (main) • Rural, proximal to village	• Compare parasite levels against prior measurement	• Delay between follow-up visit and microscopy read results in lag in appropriate treatment follow-up/ opportunity for loss to follow-up • Quality of microscopy is reliant on quality of slide prep, which may be impacted by lower levels of trained staff and less supportive conditions • Alternative drying methods: drying slide is burdensome, esp. during rainy season (use hair dryer, bunsen burner, lightbulb)	
	Malaria Clinic (MC)	Microscopy	• Patient is requested to return to the MC for follow-up, where microscopy is performed	• MC microscopists prepare slide and conduct microscopy	• Inconsistent power • Sink • No back-up generator • Computer for daily and weekly reporting • Paper-based case detection books	• Compare parasite levels against prior measurement	• Delay between follow-up visit and microscopy read results in lag in appropriate treatment follow-up/ opportunity for loss to follow-up • Quality of microscopy is reliant on quality of slide prep at the MP or village • Inconsistent power--power outages stop work • Alternative drying methods: drying slide is burdensome, esp. during rainy season (use hair dryer, bunsen burner, lightbulb)	
Focal Screen and Treat (FSAT)	Village	Slides taken to MC May use RDT when rain makes slide prep too difficult	• Mobile malaria unit (based out of MC) selects village for "active" surveillance based on routine surveillance schedule for hotspots (every week for A1 hotspot, every 2 weeks for A2 transmission) , or in response to spike in case detection in PCD setting at MCs and MP • Response is at village level • Mobile malaria unit staff brings slide prep supplies to village center (where villagers can approach for testing), spreads word and asks villagers to come to him for testing • Average day 20-25 slides/village (the village we visited had 150 households [hh]) • May call in advance to target key times when hotpop is available, eg. in the evenings.	• Mobile malaria unit staff (training ??)	• No readily available water or electricity • May have table or bench to set up on, or work on floor • Supplies carried in backpack on motorbike or car • Gloves changed after every 10 patients (even if taken off, reused for next patient)	• Rapid-response test and treat for hotpop/hotspot • DOT for *Pf* patients • Routine screening test & treat, identify flares in hotspots/hotpops	• If team does not always go door-to-door, coverage may be very low • Time constraints, weather, supportive supervision may contribute to modified approach to focal screening and treatment (FSAT) with stationary difficulty drying slides during rainy season (use RDT instead) • Does not capture all members of hh or all members of village • Delay between slide prep and treatment follow-up • Quality of microscopy is reliant on quality of slide prep, which may be impacted by lower levels of trained staff and less supportive conditions • Alternative drying methods: drying slide is burdensome, esp. during rainy season (use hair dryer, bunsen burner, lightbulb)	• Only tests those people who happen to be around at time of visit: during day this is old women and small children • Under represents porportion of asymptomatic cases as these individuals are not around when mobile unit comes through village • May also skew representation of categories of positives (complicated/uncomplicated) than is representative of population because "sick people stay home" • No specific effort to identify asymptomatic cases, and limited understanding of the reason for active case detection as evidenced by statement "it is ok to do it this way --stationary slide prep--because the sick people will be home and so we will catch them at the village when they don't come to the clinic"
Reactive Case Detection (RACD)	Village	Slides taken to MC May use RDT when rain makes slide prep too difficult	• Mobile staff may conduct hh-level screening during RACD visit (with indoor residual spraying (IRS) and DOT) for *Pf* patient in home on days 1 and 3 of infection • IRS conducted within 0.5k of home	• Mobile malaria unit staff (training ??)	• No readily available water or electricity • May have table or bench to set up on, or work on floor • Supplies carried in backpack on motorbike or car • Gloves changed after every 10 patients (even if taken off, reused for next patient)	• Rapid-response test and treat for hotpop/hotspot • DOT for *Pf* patients	• If team does not always go door-to-door, coverage may be very low • Time constraints, weather, supportive supervision may contribute to modified approach to focal screening and treatment (FSAT) with stationary difficulty drying slides during rainy season (use RDT instead) • Does not capture all members of hh or all members of village • Delay between slide prep and treatment follow-up • Quality of microscopy is reliant on quality of slide prep, which may be impacted by lower levels of trained staff and less supportive conditions • Alternative drying methods: drying slide is burdensome, esp. during rainy season (use hair dryer, bunsen burner, lightbulb)	• Only tests those people who happen to be around at time of visit: during day this is old women and small children • Under represents porportion of asymptomatic cases as these individuals are not around when mobile unit comes through village • May also skew representation of categories of positives (complicated/uncomplicated) than is representative of population because "sick people stay home" • No specific effort to identify asymptomatic cases, and limited understanding of the reason for active case detection as evidenced by statement "it is ok to do it this way --stationary slide prep--because the sick people will be home and so we will catch them at the village when they don't come to the clinic"

Use Scenario	Setting	Inputs				Outcomes	Constraints	Other Notes/Comments
		Diagnostics	Process	Human Resources	Infrastructure/Supplies			
Surveys	Research institutes	Microscopy Polymerase chain reaction (PCR) Genotyping RDT	• Varies by institution • Mahidol has fully equipped lab with enormous PCR capacity • Other labs also have PCR capacity	• Highly trained laboratory technicians and microscopists	• Cars/vans for transport • Supplies carried by vehicle • Massive sample collection teams cover entire survey population with >95% coverage	• Prevalence • Speciation • Artemisinin resistance • Genotyping for origin and to distinguish new infection from recrudescence	• None recorded	• Isolated from national malaria program
	National level (Treatment Efficacy Survey)	Microscopy Dried blood spot (DBS) for PCR (probably some RDT use in some areas as well)	• Sample taken from *Pf* and in BVBD clinics--though unclear which clinics, and in what contexts (observed at national level, not regional level)	• Malaria cinic staff--unclear in what context or special training	• Inconsistent power • Sink • No back-up generator • Computer for daily and weekly reporting • Paper-based case detection books	• QC for microscopy • Detect artemisinin resistance (specifically subpatent infection in treated *Pf* patient) • Genotyping from amplicon product to distinguish recrudescence from reinfection	• In specific pilot clinics only • Tests for subpatent infection only--not testing for any AR biomarkers • Includes monoinfection of *Pf* only (no multiple infection) • Delay between DBS collection and delivery to national-level PCR makes reporting back to MCs impractical	
	Army	RDTs & slides prepped in field	• Routine screening among troops every two months; near 100% coverage • Slides reviewed at static mobile unit (hotel) and results reported back to unit for follow-up with medic for treatment	• Armed Forces Research Institute of Medical Sciences (AFRIMS) surveillance team	• Well-equipped mobile microscopy with power/water at hotel • Bring in all supplies	• Prevalence among troops • Test & treat microscopy + patients	• High throughput means heavy time burden (3-4 hours for 100 samples) • May be missing subpatent infections • Surveys not frequent enough to capture each new case	• Twenty-six percent of PCD cases are military, so not all test & treat is captured through surveillance system or existing military PCD structure
Quality Control (QC)	All levels of national malaria program (MP-BVBD Unit)	Microscopy	• Hundred percent positives and 10% negatives at each clinic are sent to the next level BVBD facility for oversight • Cumulates in all positives and 10% negatives at the national reference lab	• Microscopist	• Depends on facility level • At national level, fully equipped lab with WHO certified microscopists	• Supportive supervision of microscopists at each level of BVBD • Quality check against data reported from each level		

Appendix B: Malaria diagnostic setting structure