Malaria Elimination Task Force

Activity Report
May 2014-December 2016

METF
malaria elimination

Foreword

In 2014, the Malaria Elimination Task Force (METF) was initiated to carry out an ambitious malaria elimination program in Eastern Karen/Kayin State. As Chairman of the Executive Committee of the Malaria Elimination Task Force, I am proud to present you this report following 32 months of work.
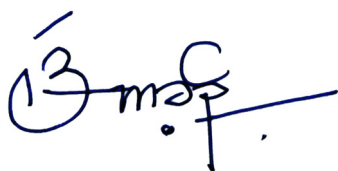
This program is a scale-up from a pilot study initially conducted in 4 Karen villages with high malaria prevalence. The pilot work showed that early detection and treatment of malaria cases, along with targeted mass drug administration, was a safe and potentially effective strategy to eliminate *P. falciparum* malaria.

Beginning in June 2014, under the supervision of the Karen Department of Health and Welfare (KDHW) and in collaboration with the Myanmar National Malaria Control Program (MNMCP), a dense network of more than 1,200 malaria posts (MP) was established. These MPs report numbers of malaria cases and treatments each week. In 32 months the MPs have seen over 200,000 fever cases and have treated over 20,000 malaria patients.

However many people in our communities harbour malaria parasites without showing the normal signs of infection. These people are unlikely to visit an MP for diagnosis and treatment. For elimination to be successful, this hidden reservoir must also be eliminated. The METF team therefore conducted 300 surveys in villages using a highly sensitive detection method to identify these high prevalence villages. Fifty-six hotspot villages were identified, triggering community engagement meetings with the village leaders and community members followed by mass drug administration (MDA). Villagers responded with strong mobilization and support. More than 80% of population participated in each round.

As you will see in this report, the MP system is providing the expected impact: a dramatic decline in the burden of *P. falciparum* malaria with many villages nearing elimination. In areas where the hidden parasite reservoir was high, MDA is clearly accelerating elimination and has been well accepted. Malaria is quickly disappearing from Karen/Kayin State.

I would like to express here the gratitude of the Karen people to the Global Fund, the Bill & Melinda Gates Foundation and the Wellcome Trust for their support in this extraordinary endeavour.

Saw Diamond Khin
Chairman
Malaria Elimination Task Force Executive Committee

Content

EXECUTIVE SUMMARY

The objective of the Malaria Elimination Task Force (METF) is to rapidly eliminate Plasmodium falciparum malaria in Eastern Karen/Kayin State, Myanmar. The specific target is the elimination of artemisinin resistant falciparum malaria. The METF started activities in May of 2014 in four townships of Karen/Kayin State. The task force is supported by the Global Fund Regional Artemisinin Initiative – Inter Country Component (GF-RAI-ICC) and the Bill & Melinda Gates Foundation (BMGF). The METF operates under the governance of an Executive Committee (EC) representing the major health-related organizations in the area.

The strategy of METF rests on seven pillars

Mapping and geographic information system (page 15)

A satellite based cartographic system is the first layer of a comprehensive geographic information system (GIS) that includes village names in all relevant languages (Myanmar, Kayin and English), the presence and nature of communication means, and basic health facilities, demographic and economic information. Maps are used for the planning and monitoring of all subsequent activities and spatial references allow for in-depth analysis of case and prevalence data.

Community engagement (page 16)

In order for populations to appropriate this malaria elimination program, METF works with the communities to facilitate their understanding, to build mutual trust and to identify local partners and relays. METF has benefited from the help of social scientists to formalize the principles of community engagement, but the activities are carried out mainly by people from the affected communities who organize meetings first with the leaders and then with the entire population. Aids such as handbooks, leaflets and posters have also been developed.

Malaria posts (MPs) (page 19)

The functioning and effective malaria post (MP) is key to *P. falciparum* elimination. The MP is a simple structure that provides **free and uninterrupted** access to reliable diagnosis and effective treatment for any clinical malaria cases from the community within 24-48 hours of fever onset. The MP is therefore located close to populations and operated by a worker (MPW) from the village who is trained, monitored and financially supported. MPWs use rapid diagnostic tests (RDTs) and administer artemisinin-based combination therapy (ACT).

Real-time data collection and reporting (page 20)

Weekly data are needed to assess MP activities, responsiveness, supplies and impact. Regular mapping updates identify coverage gaps and changes in communication networks. Extensive use of electronic communication makes this real-time data collection and sharing possible. Intelligence in real-time is crucial to adapt and respond effectively to changes in this rapidly evolving environment.

Malaria prevalence surveys (page 21)

There is now robust evidence that a substantial proportion of the population in endemic areas harbour malaria parasites without apparent illness, many of which would not be detected by microscopy or rapid diagnostic tests (RDT) (Imwong et al. 2015). Identifying and treating these reservoirs is essential for the rapid elimination of *P. falciparum*. Surveys are conducted in both randomly selected villages and in villages close to known reservoirs. A small number of adult villagers are asked to give a blood sample after consent has been obtained. These samples are processed in a central laboratory using a highly sensitive quantitative polymerase chain reaction (uPCR) assay (Imwong et al. 2014). Villages where more than 40% samples are positive for malaria and 20% of the positives are *P. falciparum* are operationally classified as "hotspot" villages.

METF has also participated in improving malaria survey methodology through the evaluation of hypersensitive RDT, as well as pilot testing of on-site sample pre-processing and freezing in the most remote locations.

Mass drug administration (page 23)

Once a "hotspot" is identified, the most effective approach for elimination is mass drug administration (MDA). MDA has two objectives: to eliminate the reservoir of parasites rapidly and to provide protection against new infections for at least a month after each round of MDA. Studies conducted before the start of this programme have shown that the first objective can be achieved if ≥ 80% of the population receives one treatment course. Three months of protection is expected for individuals who receive 3 rounds of treatment at 1-month intervals. This level of participation can only be obtained if the MDA campaign is preceded by comprehensive and effective community engagement (CE) activities.

Entomology (page 25)

Detailed entomological studies that were conducted prior to the start of the METF programme demonstrated that low infectivity rates are compensated by a large number of mosquito vectors and that over 60% of infective bites are unlikely to be prevented by impregnated nets. The studies have also revealed the prevalence of submicroscopic infections closely correlates with the infectivity of the mosquito vectors. As part of the METF programme, mosquito catching is conducted in hotspot villages before and 12 months after the MDA campaign. These surveys guide vector control measures and confirm parasite elimination. Additional studies on the feasibility of innovative vector control strategies are also undertaken to propose relevant additions to impregnated nets.

Mapping and geographic information system (page 26)

The Geographic Information System and subsequent maps contain data from over 1200 villages, spanning an geographic area of approximately 18000 km2, divided into 3 areas (Area 1 = 6747 km2; Area 2 = 6405 km2; Area 3 = 4850 km2) (FIGURE 1). The estimated population covered by MPs is 365303 (95% CI: 352381 – 378223). There are important differences between the areas in terms of population density, settlement patterns, transportation capabilities, communication infrastructure and access to electricity and water. The original geographic survey indicated that only 14% of villages in the project area had functioning MPs. This percentage has increased to >75 % of mapped   villages (FIGURE 2). Geo-spatial analysis of the malaria surveys indicates that hotspot villages tend to occur in clusters, with nearby villages having similar malaria prevalence.
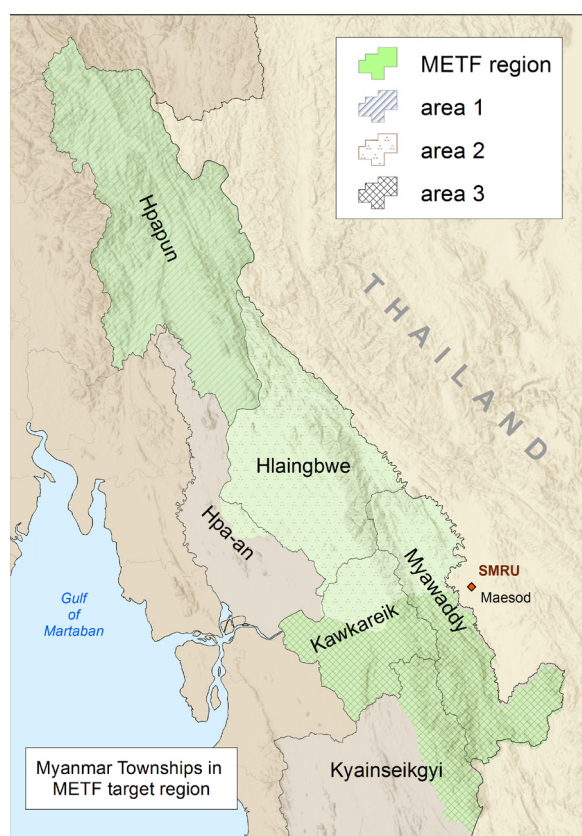

Figure 1: Malaria Elimination Task Force target area and Karen/Kayin State, Myanmar Townships (Myanmar Government designations).

Community engagement (page 27)

The CE team has organized many meetings and workshops. Activities were concentrated particularly in the villages selected for the prevalence surveys and in hotspots treated with MDA. The most important determinant of the effectiveness of MDA in the elimination effort is probably the level of participation in the MDA campaigns. Over 80% of village inhabitants received at least one round of MDA (i.e. one treatment course necessary for reservoir elimination). The proportion of participants who received the full 3 courses (needed for protection) was 62%. Overall the feedback from the population has been very positive.

Malaria posts (page 28)

The METF has trained 1648 MPWs, 109 MP supervisors, 49 Zone coordinators and opened 1220 MPs (FIGURE 2). A total of 210406 fever cases were seen by the MPWs and 211359 RDTs were used.
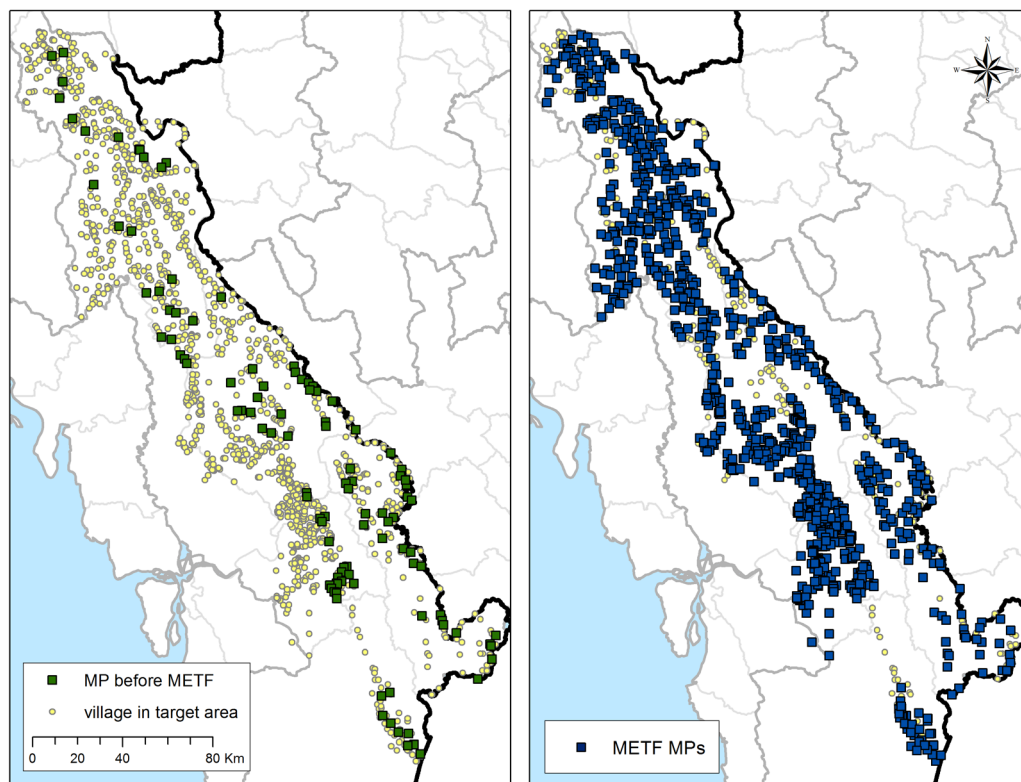
Figure 2: Map of functioning malaria posts before the METF project began (left panel) and current METF MPs (right panel). The baseline geographic survey indicated that only 14% of villages in the program area had functioning malaria posts. This has now increased to over 75%.

Monitoring of MP

Between September and December of 2016, 172 randomly selected malaria posts underwent a monitoring and evaluation visit. 74% of the surveyed MPs reported having never closed for more than 24 hours. At the time of survey, two of the MPs were out of stock of ACT (1%) and 6 (3%) were out of RDTs, indicating that 96% of the MPs are functional. Nine (5%) of the MPs declared that they suffered ACT or RDT stock-outs of more than two consecutive days in the previous month. 85% of MPs had received at least one visit from their supervisor over the previous two months.

Overall, 80% of consultations occurred between zero and 48h of fever onset, less than 15% of consultations occurred between two and three days and less than 5% after three days. These data suggest that most *P. falciparum* clinical cases were treated prior to the parasites becoming infectious (before the start of gametocyte production), and shows a strong mobilization of the community.

Real-time data collection and reporting (page 29)

Of the 1220 MPs, 866 (70%) presented no gap in their data reporting while 331 (29%) had one or several one-week gaps. Only 90 MPs (7%) had reporting gaps of more than one week. Many of these delays resulted from transmission or data entry errors that were subsequently resolved by checking the paper records. Across all available data the median (IQR) delay in data reporting is eight (3-10) days but there is variation by method (i.e. paper versus electronic). Gradual introduction of smartphones resulted in a rapid reduction in delays: data transmitted by SMS were available after a median of one day (IQR=0-2 days), while data relying on porters (Area 1) were available after a median of eight days (IQR=8-9). All data generated by MPs are available on a secured portal that is accessible to all stakeholders: National Malaria Programme, METF partners and donors.

Surveys and mass drug administration (page 31)

During the reporting period 270 surveys were completed and the results are available for 245 surveys. The prevalence of malaria was highly variable: ranging from 0% to 35% for *P. falciparum* and 0% to 64% for *P. vivax.* Out of these 245 surveys, 56 villages meeting hotspot criteria were identified. Most of these villages were located in Area 1. Sub-microscopic malaria hotspots tend to cluster spatially. Most malaria hotspot villages occur within five km of another high prevalence village and this pattern remains when examining at *P. falciparum* or *P. vivax* independently.

MDA was conducted in 50 communities, and 6 hotspots remain to be treated. The proportion of villagers that received at least one round was high (median: 90%; IQR: 85-94). The median proportion of the population receiving the 3 rounds of MDA (complete coverage) was 62% (IQR: 49-72). The difference between these proportions is explained in part by the population mobility which was lower in the communities of METF Area 1 than those from Areas 2 and 3. No severe adverse events were recorded following MDA. On average, 19% of individuals present in a village during a given month of intervention did not receive a curative course. These were grouped in 3 categories: 13% refusing, staying at home, or could not be reached; 4.5% not meeting inclusion criteria; and 1.3% who started the treatment but did not complete it.

Impact on malaria (page 35)

Impact of the MP network

Overall RDT-positivity for malaria was 12%, and 25418 malaria cases were treated (9581 *P. falciparum* and 15837 *P. vivax*). Eighteen deaths related to malaria and 43 severe malaria cases were reported. This translates in a case-fatality rate of 1.8 deaths/1000 *P. falciparum* cases, similar to what was measured in the area before the METF project started. Results indicated that the incidence of *P. falciparum* started declining in the communities as soon as an MP was set up. The decrease in incidence was slower in the communities with the highest malaria burden, warranting specific intervention to speed up the elimination. Similar declines in cases were not seen for *P. vivax* and this resulted in significant changes in the Pf/Pv ratios that correlated with the duration of MP operating (FIGURE 3).
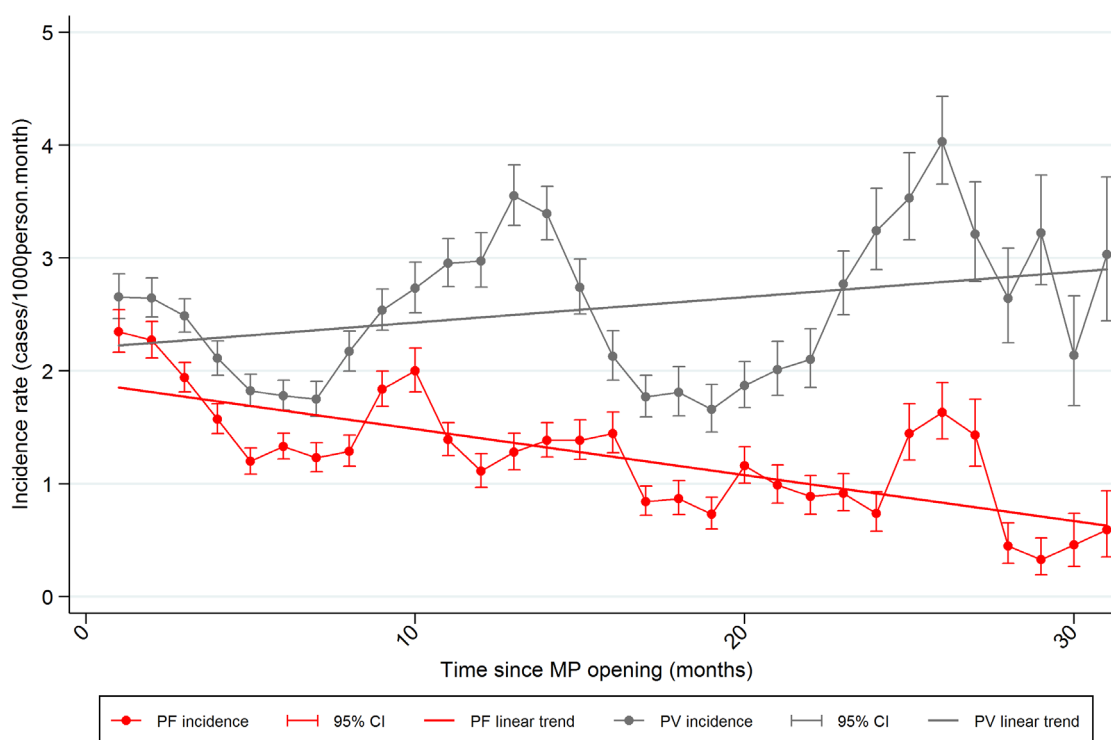

Figure 3: Incidence rate of falciparum and vivax clinical malaria episodes according to the duration of MP functioning, showing a specific decrease in P. falciparum *incidence without significant modifications in* P. vivax *incidence.*

Impact of MDA on hotspots

The prevalence of *P. falciparum* infection was estimated 12 months after MDA in 28 hotspot villages. All villages showed a sustained reduction of prevalence compared to baseline, ranging from a 100% reduction in 13 villages to a 66% reduction in one village. The total number of clinical *P. falciparum* episodes originating from hotspots was reduced by 90% after MDA and no rebound has been observed. MDA, in combination with MPs, had a rapid and sustained impact on the reservoir of *P. falciparum* and on the incidence of clinical cases in hotspot villages.

Approximately 72% of the villages in METF target region are under or have reached the WHO threshold of elimination of < 1 case/1000 person/year.

Impact on molecular markers of antimalarial resistance

No evidence of emergence of piperaquine resistance and no changes in the proportion of the isolates resistant to the artemisinin derivatives were found. Some parasites with an amplified Pfmdr1 gene were detected in the north that could indicate emergence of resistance to lumefantrine.

Entomology results

Forty-four entomological surveys were conducted in 27 villages. A total of 116393 mosquitoes were collected among which 52436 were morphologically identified as Anopheles. Moreover 7644 and 10474 specimens were analyzed by PCR to identify sibling species and by qrtPCR to detect plasmodium respectively, in order to measure malaria vectors biodiversity and infectious rates in the area. The abundance and species distribution was highly variable in time and space, suggesting high heterogeneity in malaria exposure across Karen/Kayin State. Malaria vectors in the region have a strong tendency to feed early and outdoors therefore the transmission that is not prevented by insecticide impregnated bed nets ("residual" malaria transmission) probably accounts for most of the transmission. Our results also confirm the low infection and high biting rates of malaria vectors in the area.

Conclusion

The METF programme provides a comprehensive and effective approach to malaria elimination and is the largest implemented so far in the Greater Mekong Region. The METF is embedded in the community. It is evidence-based, reactive, adaptable and responsive. After 32 months of operation it now covers over 1220 villages, many in hard-to-reach areas of the eastern Karen/Kayin State. The success of the programme derives from a deep knowledge of the population and robust evidence gathered from over 30 years of malaria research in the area. The impact on *P. falciparum* has been spectacular, with a sharp reduction in the number of new clinical cases. The majority of the villages are now below the elimination threshold. This is attributed to the deployment and continued support of effective MPs and the rapid elimination of sub-microscopic infections by MDA. Continued success will depend on coverage of all villages in the area, effective MPs and the sustained efficacy of the drugs used. The objective for 2017 is to maintain a tight early detection and treatment system to prevent re-introduction. Later, elimination of *P. vivax* malaria will provide substantial additional health benefits and critically will sustain the surveillance necessary to maintain elimination of *P. falciparum*. These results should encourage similar programs to be deployed elsewhere in Myanmar and across the Greater Mekong Subregion. As resistance to artemisinin and combination therapies is quickly spreading, we are clearly racing against time. The results of the METF project provide clear evidence that the rapid reduction and elimination of *P. falciparum* is feasible.

Take Home Message:

METF operates a large program: 1220 villages serving approximately 365,000 people.

In 32 months it has recorded a dramatic reduction in the number of clinical P. falciparum *cases.*

72% of the villages with MPs are now under the elimination threshold.

MDA has significantly accelerated the elimination of P. falciparum.

MDA is safe and well accepted and there is no evidence of negative impact.

INTRODUCTION

The Malaria Elimination Task Force (METF) was set up in 2014 to conduct a large-scale project for *P. falciparum* elimination in 4 townships (Kawkareik, Myawaddy, Hlaingbwe, and Hpapun) of Eastern Myanmar (Karen/Kayin State). It is composed of one representative of local NGOs/CBOs (KDHW, MTC, BPHWT, BMA, KBGF, KPC, KKO, SMRU)[1]. Other organisations also involved in malaria elimination in Myanmar (MAM, CPI)[2] are invited as observers to the Executive Committee (EC).

A structure has been developed by the EC to facilitate communications, logistics, reporting, supervision and management (FIGURE 4).
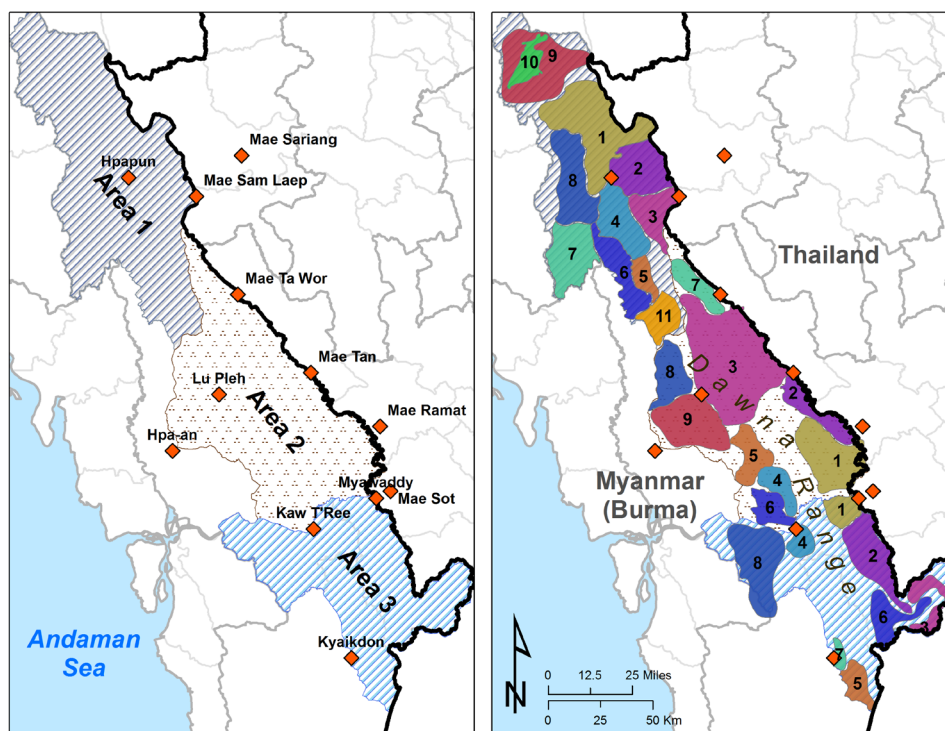

Figure 4: METF Areas (left panel) and Zones (right panel).

- The project area is large and is divided into 3 'Areas' under the responsibility of an area programme manager and a coordinator seconded by a technical team for CE, training/monitoring, data collection and administration (FIGURE4).
- Each area is divided into zones, covering a stretch of land where health services are administered by one of the local NGOs/CBOs.
- Each zone has a number of MPs (depending on the landscape and demographic concentration). An MP supervisor is responsible for 10 to 15 MPs.
- The central coordination team is composed of the area programme managers/coordinators, one epidemiologist/biostatistician, one geographer/spatial epidemiologist and a medical referent.
- This central coordination team is headed by a programme director and is based at SMRU in Mae Sot. SMRU provides support logistics, data management, grant management and laboratory support.

---

[1] KDHW: Karen Department of Health and Welfare; MTC: Mae Tao Clinic; BPHWT: Back Pack Health Workers Team; BMA: Burma Medical Association; KBGF: Karen Border Guard Force; KPC: Karen Peace Council; KKO: Klohtoobaw Karen Organization; SMRU: Shoklo Malaria Research Unit.

[2] MAM; Medical Action Myanmar; CPI: Community Partners International

The METF is supported by the Global Fund Regional Artemisinin Initiative – Inter Country Component (GF-RAI-ICC), the Bill & Melinda Gates Foundation (BMGF) and SMRU is supported by The Wellcome Trust of Great Britain. The aim of this project was to assess the feasibility of eliminating *P. falciparum* rapidly in the context of increasing artemisinin resistance. As such it can be considered as a study or pilot project aimed at answering operational or translational research questions and is endorsed by the Ministry of Health of Myanmar and the Karen Department of Health and Welfare (KDHW). It is approved by the Ethics Committee of the Department of Medical Research (Lower Myanmar). This report presents in detail the components of the elimination strategy and the results after 36 months of operation.

II. BACKGROUND

Malaria is endemic in Myanmar and a major cause of mortality and morbidity. The main plasmodial species involved are *P. falciparum* and *P. vivax*. Transmission is low and seasonal and caused by multiple anopheles vectors (Manguin 2013; Oo 2003; Sinka et al. 2011). Along the border with Thailand, *P. falciparum* has become resistant to almost all available antimalarials including the artemisinin derivatives (Phyo et al. 2012). This problem represents a major threat to the region and the rest of the world. Given the paucity of new drugs, the only alternative is to attempt elimination before the rebound of malaria that inevitably follows the spread of high-level drug resistant parasites. Between 2012 and 2014 a pilot Targeted Chemo-Elimination study (TCE) was conducted in 4 villages on the Thai-Myanmar border (Imwong et al. 2015). These villages were selected because a high proportion of the population was infected with malaria parasites but without symptoms. In each village, malaria posts with RDTs and ACTs were provided as well as long lasting insecticide-treated nets (LLIN). Community engagement (CE) activities were conducted and mass drug administration (MDA) was offered to the populations in this controlled environment. The safety and acceptability of this intervention were carefully evaluated. The impact was measured by detailed surveys using an ultra-sensitive and validated qPCR assay (Imwong et al. 2014). Detailed entomological evaluations were conducted throughout the 24 months of the TCE study (Ya-umphan et al. 2016). The results show that the strategy is safe and effective in rapidly eliminating the sub-microscopic reservoir of malaria parasites, in reducing the transmission to mosquito vectors and is well accepted by the population. It also indicates that new vector control methods are needed because the majority of infections were not preventable by LLINs. These encouraging results motivated the METF project to attempt *P. falciparum* elimination on a larger scale using the same approach.

A. Mapping and geographic information system (GIS)

As Karen/Kayin State has been in civil conflict for over half a century, there was no accurate census or map for most of the target area (South 2011). This information is essential for all further steps in the project (including logistics, sampling and data management). The data generated from field mapping are linked to all other data (survey dates and results, logistics, financial matters, malaria cases at malaria posts, etc.), so that all programme data are spatially referenced in a geographic information system (GIS) and can be analysed in a spatially explicit manner. Maps are useful only if they are accurate, complete and rapidly acquired.

Mapping strategy

- The entire area must be mapped at the smallest geographic unit possible (preferably at least one point per village). Mapping relies on "ground-truth" data as opposed to assuming that existing maps are true or only using remote sensing.
- During mapping basic attributes of a village or other small geographic area are recorded (population estimate, existing health facility capabilities, cell phone service, etc.)
- The area is frequently re-mapped, both as a form of quality control and to capture changes in the geography and demography of the region.
- Unique identification codes are assigned to each of the geographic points (villages or hamlets) and this code is used in all other parts of the program.
- From a logistic and administrative standpoint it is then useful to create aggregate units (e.g. "zones" and "areas") from geographic points.

Mapping logistics

The mapping team is composed of community members familiar with the region, an experienced geographer and several trained staff. Mapping begins with training of these community members, who are recruited via local leaders. The training occurs in a central location and generally lasts one to two days. The training introduces basic map reading concepts, the use of satellite-enabled georeferencing systems (such as GPS and GLONASS), and survey forms. Trainings usually occurred in resource-limited field settings. Marker or chalk boards and maps printed on vinyl were used as instructional aids. Mapping trainings always concluded with a practical exam whereby new mappers are required to visit 3-4 locations near the training site, take a GPS reading at those locations and record the required information about those locations on the survey form. The forms are checked for accuracy on site and if errors are discovered retraining immediately occurs. As soon as field mappers are deemed capable of carrying out the survey, logistic plans are developed through the aid of local community leaders. The plans include which regions will be covered by mapping teams (usually mappers go in groups of two), roughly how long the mapping should take and how to return the GPS units and survey forms to the central location. Once the survey forms and GPS units are collected at the central location they are shipped back to SMRU office.

Geographic surveys

The first surveys focused on whether or not malaria services existed in a community, whether or not they are properly staffed and stocked, names of villages, and the number of houses in a village. A second wave of surveys (conducted in 2014) aimed to correct any missing geographic points that were missing from the first wave, to fill in any gaps in the target area map, and to identify the locations of referral clinics. In 2015-2016 a third wave of mapping and surveys included a small set of economic indicators, including basic questions about agricultural development (whether or not there were tractors in a village), transportation capabilities, electricity and water sources.

Technical aspects of the GIS

Data from the forms are entered into spread sheets that are merged with the geographic data downloaded from each GPS unit. These data form the basic architecture for METF's geographic information system (GIS) and also provide a baseline understanding of the target population.

R statistical software (https://cran.r-project.org/) and Python programming language (https://www.python.org/) are used for data tabulations and merging; mapping of the data has primarily been done using ArcGIS (http://www.esri.com/software/arcgis), especially ArcMap; and QGIS (http://www.qgis.org/) is used for creating and manipulating some spatial shape files. The core GIS data are stored in a file geodatabase (file type .gdb). Each mapped village is assigned an arbitrary identification code and all information relating to a village (blood surveys, weekly malaria post reports, financial reports, etc.) is labelled using this identification code. Such data come in on a continuous basis and are merged to the core data set which can be viewed as a spread sheet (e.g. as a comma separated value file) in a wide variety of software (Access, Excel, LibreOffice, etc.) Python is used to pull new data from various sources and to update the base spread sheet. The geodatabase, spreadsheets and resulting maps are stored on a secure centralized server and shared with METF supervisors and administrators weekly.

B. Community engagement (CE)

Community engagement (CE) is a process by which a dedicated CE team (usually consisting of five – 15 people from the programme team and the community) works with the community to build relations and trust to develop an understanding and to facilitate community ownership of the malaria elimination project. The CE team draws on long-term ties to the target community and uses a modified community-based participatory action research approach (Minkler and Wallerstein 2008). The malaria elimination project relies on widespread participation and cooperation within and between villages. The success (or potential failure) of the project is therefore heavily dependent on the ability to properly interact with the people, making CE a cornerstone of the malaria elimination project.

Preparation with social scientists

The malaria-focused CE work started with four pilot villages as part of the Targeted Malaria Elimination study (TME) in 2013. Through the experiences gained and lessons learned a guiding set of key themes was established, including principles and methods that could be applied across a wide geographic range in the scale-up programme (i.e. METF). Three major themes emerging from this preliminary work were human behaviour, geography, and social structures.

Human behaviour CE workers and other malaria elimination team members must work toward understanding community members' worldviews, the ways that they allocate their time and the motivations and desires that drive their decisions and decision-making processes. For example, CE and other malaria programme tasks must not conflict with villager needs to work at certain times of the year. Most rural villages in the METF area follow a basic calendar revolving around rice paddy farming and several other crops. Harvest seasons (September to December) are typically labour-intensive and require some farmers to spend up to several weeks away to protect the crops and harvest them.

Geography The physical and social geographic attributes of a community have important correlates with regard to CE, public health and ultimately malaria elimination. The relative physical and/or social isolation of a village has a major impact on the knowledge and understanding of the population as well as the logistic constraints of health-related work. For example, people in remote locations are often poor and have had little understanding of malaria or other public health threats. Malaria in such settings may be worse than elsewhere and may also be more difficult to address because of the remoteness.

Social structures It is crucial that CE team members understand and utilize some of the existing social, political and economic power structures in place. Such systems include local village heads, township health officers, important religious and other political and military actors. Furthermore, socio-political dynamics can dictate appropriate means of engaging with community members and rolling out health-focused projects. For example, Karen/Kayin state has many different political actors, some operating simultaneously in the same areas. This political complexity can make implementation of health programs very challenging. The malaria elimination project has been able to work despite these potential obstacles through the incorporation and help of important key contacts. It is often possible to directly go to upper level health officials and obtain permission to set up a malaria programme in an area. Without community acceptance, however, implementation at the ground level may flounder. In at least some places it is much better to work through locally influential people who are capable of drawing on pre-existing strong relationships with villagers and to help navigate complex political hierarchies.

Implementing CE in all aspects of the project

CE training for MPs Malaria posts are typically established in batches. Prior to MPW training, the CE team asks for a meeting with local health workers, village headmen, and other leaders. During this initial meeting the programme, MP function and CE are explained to local leaders. CE training also takes place with the actual MPW during training workshops. MPWs are educated about malaria biology and ecology, how to prevent malaria and what to do in case of malaria symptoms. This training is valuable for the MPWs who will also convey this knowledge to community members. Thus, the MPW effectively becomes an extension of the CE team, an important component, as he/she is already part of the local community.

Malaria prevalence surveys Before embarking on a survey, the project team meets to discuss the detailed planning. Township-level health care leaders and village headmen are then asked to attend a meeting at a central location so that the plan can be proposed and the CE team asks for permission to conduct the surveys. Survey planning relies heavily on village headmen, who notify and gather the participants on the specific day and time(s). The concept of submicroscopic or asymptomatic malaria can be difficult to explain. Several workshops are organised to train local leaders (health care workers and village headmen) who are already trusted by local villagers and can therefore aid in the dispersal of knowledge and information.

MDA preparation Once a village is identified for MDA, plans begin for CE exercises aimed at community preparedness. The Area and Zone coordinators inform the village headmen. The CE team arrives two days prior to the beginning of MDA in order to organize and set up new meetings with leaders and villagers to explain the medication, the potential side effects, and the regimen that will be followed. The MDA team stays in a village for seven days per visit to document any side effects, to address any concerns and to treat other minor illnesses. In villages with MPs already in place feedback from villagers after the seven day period will come via MPW, through MP coordinators, Zone coordinators, and Area coordinators.

CE as an iterative process

CE is not a short-lived process with successes or failures that can easily be measured. The trust and understanding upon which the project is built are based on dynamic relations with the community. Part of this relationship includes providing feedback to the community about the project and reacting to new developments in the community, including rumours that can be detrimental. The CE team must play a central role with regard to such rumours. Rumours act like forest fires, the CE team and other project collaborators must be watchful and catch them early or they will spread far and damage the project.

Tools and activities used for CE

- Workshops, trainings, and group discussions (focus groups)
- Demonstrations and hands-on activities-learning materials including handouts, manuals and posters.
- Capacity building activities aimed at youth, including children's songs and poems, drawing, school activities aimed at teaching scientific methods.
- Participation in monthly village meetings, celebrations, and community work activities (such as farming).
- Household visits.
- Village incentives (water supplies or systems, buildings for community activities, solar panels, some training opportunities for health workers, boosting existing medical capabilities, providing basic out-patient care while the team is in the field).

Picture 1: METF team explaining the submicroscopic parasite carriage during CE.

MPs are set up in all villages in order to provide early malaria diagnosis and tretment for every fever case occurring in the community. MP tasks include:
- *Testing all fever or suspected malaria cases in the village using RDTs within 24 to 48 hours of symptoms.*
- *Administering quality-assured anti-malaria treatment to all confirmed malaria cases: ACT+primaquine for* P. falciparum *and chloroquine for* P. vivax*.*

This activity not only provides treatment for malaria-infected patients but also helps to limit the ongoing transmission of *P. falciparum* since early treatment of symptomatic *P. falciparum* cases prevents the emergence of gametocytes (Eichner et al. 2001). The use of quality-assured antimalarials contributes to fighting drug resistance that may emerge through the use of low quality or substandard drugs.

MP minimal requirements
- A clean place that could be the MPW's household or another location
- Storage room or shelves with proper lock
- Continuous supply of RDTs, ACTs, data forms
- Trained MP worker, available at all times
- Correct diagnosis of malaria
- Correct treatment of malaria
- Timely data return

Choice of antimalarial treatment for uncomplicated malaria
Treatment guideline (FIGURE 23, page 44) follow the Myanmar National Malaria Control Programme, the World Health Organization (WHO) treatment guidelines and the SMRU malaria handbook. For *P. falciparum* infections, a fixed dose formulation of artemether - lumefantrine (AL) is given for three days. Pregnant women are treated with quinine clindamycin for seven days in first trimester and artemether-lumefantrine (AL) in the second and third trimesters of pregnancy. A single low dose of primaquine (0.25 mg/kg) is given to prevent further transmission except in pregnancy, children younger than six months and lactating mothers. Chloroquine 25 mg base/kg over three days is used for the treatment of *P. vivax*. The doses administered are determined by the patient's body weight.

MP worker (MPW) selection and training
MPWs are selected by the village headman and the community. They must have basic literacy skills, interest in health-related activities and they should live in the village. After selection, the MPW undergoes a five-day training covering malaria case management, referral and reporting systems, CE, followed by a course completion test. The training curriculum includes hands-on training on how to use RDTs, dosing-tables to administer weight-based ACT, record patients in logbook and report weekly cases in a standard form. MPWs are provided a MPW manual in a Kayin language (S'gaw), which serves as a reference for their daily activities. Refresher trainings are given annually and include re-trainings on malaria biology, treatment protocols, as well as any programmatic revisions, feedback about technical problems or difficulties encountered in the field. Pre- and post-testing is again conducted to ensure the quality of malaria treatment knowledge of the MPWs.

Real-time data collection

It is essential that all elimination efforts are coordinated at the regional scale in order for the programme to be piloted according to the situation. It is also important that logistics information is available at all times to prevent any stock-outs. Data reports are sent on a weekly basis and reports have to be available to the programme management team in near-real time. Weekly data reports fit on a one-page form (FIGURE 24, page 45) and include:

- All cases of fever by age groups (0-4y, 5-14y and ≥ 15y)
- All RDT results (*P. falciparum* / *P. vivax*/ Negative / Invalid by gender and age groups
- The number of severe malaria cases referred and the number of pregnant women with malaria and the number of deaths attributable to malaria
- Remaining stocks of ACTs and RDTs

The hierarchical organization of the programme allows data to be crosschecked and validated by MP supervisors during transfer from the site to the data centre.

All weekly forms are transmitted from the MPWs to the MP supervisor who controls them and sends them to the nearest data entry point (FIGURE 25, page 46). Data entry mode depends on location and access to a GSM (global system for mobile communications) network.

Paper transmission and online data entry is used for zones where no GSM network is available. Data collection in these zones relies on runners who collect the forms from the MP supervisors and transport them (using any convenient transportation means) to the nearest place where they can be entered in an online data entry form and database developed using VooZaNoo®, an open-source form generator developed by EpiConcept[1].

In areas where access to a GSM network is available, individual weekly data reports are entered using a smartphone application and sent as SMS. Cheap (< $ 100) smartphones (Asus Zenfone 4) are used and are robust and reliable in most field conditions[2]. The data entry form has been developed from DroidDB, an android-based freeware[3] . All generated SMS reports (one per week / MP) are sent to dedicated phone numbers. One reception station is located in Hpa An office for areas relying on Myanmar GSM network and the other station is located in Mae Sot office for areas relying on Thai GSM network. They are extracted into Excel files and imported into the VooZaNoo database. During the week paper forms are collected by MP supervisors, transmitted to Zone coordinators and then to data centres to be filed for future reference.

Data quality and reporting

After aggregation, MP data completion and correctness is assessed regularly by searching for every duplicate and missing week of data in paper records and through integrated weekly GIS routines that link records to spatial references. A double entry is also performed on a subset of records. All errors that are recorded are transmitted to field staff in charge of data to provide key points during MP supervisor meetings and MPW refresher trainings. Regular cleaning of the database in search of duplicates and missing data is performed using paper records or other source data as necessary.

Reports on MP function, data quality and malaria indicators are produced weekly. Feedback information is provided to field teams for programme management and malaria surveillance. All weekly MP data are made available to partners and stakeholders on a secured internet portal and a monthly report on malaria indicators is generated and communicated to partners.

---

[1] http://voozanoo.net

[2] In some places concentrating a lot (sometimes more than 50) malaria posts data for SMS transmission, smartphones have been replaced with 7" phablets (Asus fonepad 7), for more comfort. These phablets are available in Thailand at the price of THB 4,500 ($ 125).

[3] www.droiddb.com

Monitoring of MPs

MPWs have weekly contact with their MP supervisors to aggregate individual patient data into weekly reporting forms. This allows for the follow-up of any event occurring during the previous week. During the initial months of the programme all used RDTs were sent to SMRU for a second reading. The activities of the MPs are continuously monitored via the weekly data reporting system. MPs that cease to transmit data, or report no activity or stock outs are visited by MP supervisors.

A team of six persons (two per area) was recruited for MP monitoring and evaluation (M&E) of the MP network (beginning in 2016). In an initial evaluation phase, 300 MPs (25% of total) were randomly selected to undergo an M&E visit. An M&E visit generally lasts half a day and involves extensive discussion, observation of the MP environment and MPW skills (e.g. to perform RDT). During the visit, a standardised questionnaire is completed by the monitor, including observations of supplies and records, and answers to questions by the person in charge (FIGURE 26) . All data collected are entered in an online database for subsequent analysis.

The M&E team also record geographic coordinates during their MP visits as a further check for concordance between MP identification numbers and the geographic coordinates in the METF data system.

In addition, systematic quality control of RDT is performed at central headquarters in Maesod. 15 MP are randomly selected each month and all RDTs from the selected MPs are assessed by experienced laboratory staff.

Surveys are conducted at the village level to estimate the prevalence of *P. falciparum* and *P. vivax* malaria. An ultrasensitive high-volume qPCR assay (uPCR) is used so that low-density infections that would not be identified using microscopy (sub-microscopic infections) or RDTs are included in the prevalence estimates.

Sample size and randomization
To ensure that the selected villages are representative of the area a grid (with 20km wide by 30km long cells) was superimposed on a map of the target area and each cell of the grid was assigned a number of surveys, sufficient to reach roughly 25% survey coverage (from an original village count of 1000). Villages within each grid cell were then randomly selected. The within-village sample size is calculated taking into account feasibility constraints and the expected precision of estimates. The feasibility constraints are: small village populations, time and conservation of samples (cold chain and processing in Mae Sot within 48h of collection) and access and security of teams (in case of conflict areas or natural disasters). In order to estimate the prevalence of malaria infections of 40% with a precision of +/-10% and a 90% confidence level, the sample size required is between 41 samples for a village of 20 houses (~100 inhabitants) and 65 for larger communities (above 500 houses or 2500 inhabitants).

Surveys were planned in 250 randomly selected villages. As the deployment of the program progressed and more data on prevalence and incidence of malaria was available, it was possible to target an additional 50 surveys towards suspected hotspots: villages located in the vicinity of a hotspot, or villages presenting persisting incident clinical cases in spite of a functional MP for a long period of time.

Survey and laboratory analysis
Three survey teams conduct coordinated survey campaigns in selected villages within a defined sector, which are planned with and agreed by local health and political authorities. These campaigns can include up to 30 villages over several weeks. The logistics are intensive as samples must be shipped to the lab within 48 hours of collection.

Before each survey CE activities are conducted to invite adult villagers to participate. Individuals are randomly selected and willing participants provide 2mL blood by venous puncture, after giving informed consent. Samples are collected on EDTA tubes, stored in an icebox and brought back to SMRU laboratory within 48h of collection. In the laboratory samples are centrifuged to collect packed red blood cells. DNA is extracted from 500µL and analysed by uPCR to detect malaria parasites. This method allows detection of parasitaemias as low as 20 parasites/mL (Imwong et al. 2014). It is estimated that >70% of the total population infected by *P. falciparum* can be detected by this method.

Monitoring of surveys
Monitoring occurs at the planning phase and when teams return since contact with the field is often difficult or impossible (little or no cell phone coverage in many areas). Reports include modifications of the number of samples collected to match the observed number of households in the target village and replacement of selected villages by neighbouring ones when surveys cannot be performed. Sample transportation is closely documented. Upon arrival, the samples, lists and consent forms are checked to ensure proper conservation, labelling and recording. In the laboratory a negative control is included for every 10 samples to detect potential contamination.

Hotspot definition criteria

A village is operationally classified as a "hotspot" when the 90% CI upper limit of the prevalence estimate is ≥ 40% and the corresponding value of the proportion of *P. falciparum* in the positive samples is ≥20%. This is an arbitrary definition and it is reviewed periodically using the data collected. Modelling work has suggested that malaria may more quickly be eliminated if these thresholds are lowered[1]. Surveys where an insufficient number of samples were collected are excluded from analysis.

Developing new tools for field detection of sub-microscopic malaria

In addition to the standard protocol, a specific component has been added to METF surveys to evaluate a new hypersensitive rapid diagnostic test (hsRDT) for *P. falciparum* developed by PATH (formerly Program for Appropriate Technology in Health: http://www.path.org). This hsRDT aims at a 10 times higher sensitivity compared to current RDTs and could be an important alternative to heavily constrained uPCR malaria detection (low number of samples, time-sensitive processing, costly methods). Using already collected samples, our objectives are: to verify the intrinsic properties of this newly developed test (i.e. sensitivity and specificity, limits of detection) compared to currently available RDTs, microscopy and uPCR; and to compare the performance of different methods in the field to measure malaria prevalence

E. Mass drug administration

Choice of drugs for mass administration

In order to limit drug pressure MDA is conducted with different ACTs than those used in MPs. The regimen used in MDA consists of dihydro-artemisinin (7mg/kg) plus piperaquine (55 mg/kg) (DP) with a single low dose of primaquine (0.25mg/kg). DP remains highly efficacious against *P. falciparum* parasites in this region and is associated with a post-treatment prophylactic effect of around 30 days after one complete course. One treatment course (3 days) is sufficient to eliminate the reservoir while three consecutive rounds of DP, one month apart are necessary to maximise the impact on transmission by preventing reinfection from infected mosquitoes.
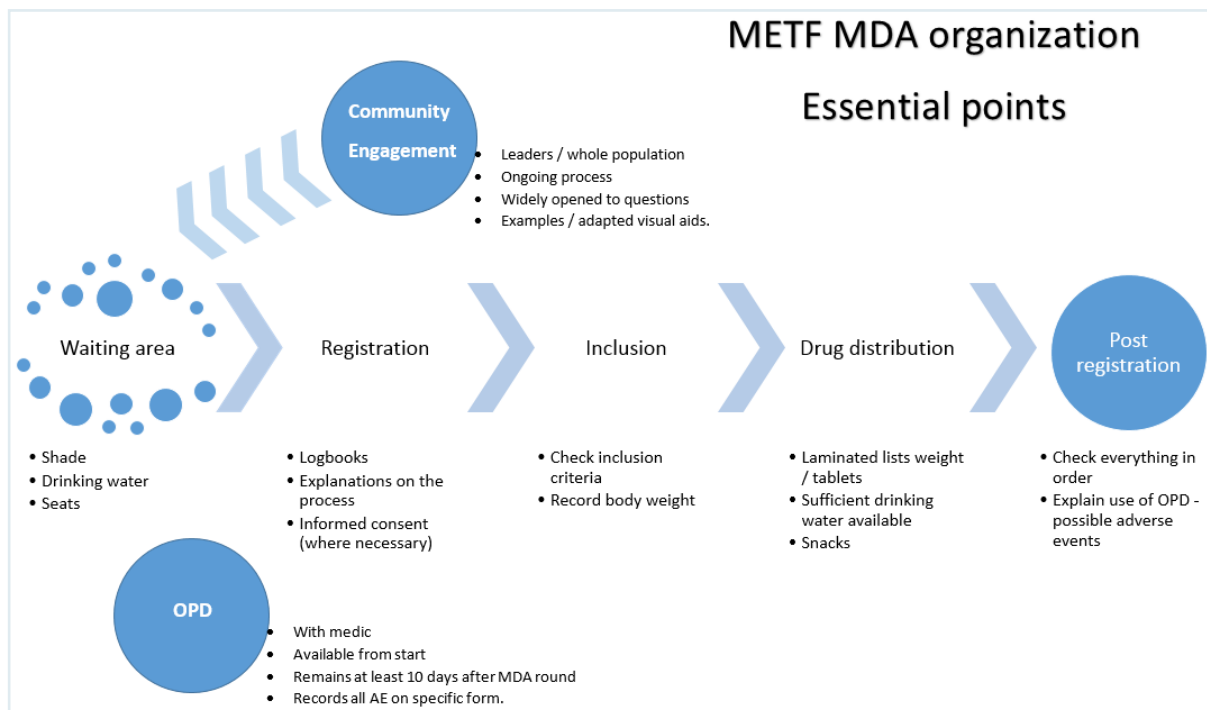
MDA exclusion criteria

Women in the 1st trimester of a pregnancy, children under 1 year of age, individuals with previous drug allergies and villagers who refuse to participate are not included in MDA. Women within reproductive age (roughly 14 – 44 years old) and of unknown pregnancy status are screened with a urinary HCG test kit. Women in the 2nd and 3rd trimester of a pregnancy as well as breastfeeding mothers are eligible for DP treatment but are excluded from the single dose of primaquine.

Treatment administration

After obtaining informed consent, each eligible participant's medical history is briefly reviewed and a clinical examination is conducted. Those who meet the inclusion criteria are provided a 3-day course of DP with a single low dose of primaquine on the first day and this is repeated over 3 consecutive months. Treatment is administered under supervision by the METF team to ensure participant adherence and to monitor the population for adverse events (AE). All AE that are reported by MDA participants within 1 week of taking an MDA course are carefully recorded and treated when necessary.

---

[1]There are practical limitations related to operational design, work load and other expenses associated with surveys and MDA

METF MDA organization

Essential points

Community Engagement
- Leaders / whole population
- Ongoing process
- Widely opened to questions
- Examples / adapted visual aids.

Waiting area → **Registration** → **Inclusion** → **Drug distribution** → **Post registration**

Waiting area
- Shade
- Drinking water
- Seats

Registration
- Logbooks
- Explanations on the process
- Informed consent (where necessary)

Inclusion
- Check inclusion criteria
- Record body weight

Drug distribution
- Laminated lists weight / tablets
- Sufficient drinking water available
- Snacks

Post registration
- Check everything in order
- Explain use of OPD - possible adverse events

OPD
- With medic
- Available from start
- Remains at least 10 days after MDA round
- Records all AE on specific form.

Box MDA : Organization chart of Mass Drug Administration.

Monitoring of MDA

MDA activities are conducted in a stepwise process, with all steps documented and controlled. Teams of health staff are trained before each MDA. Consent forms and MDA logbooks are used daily to record inclusion and to track participant presence and drug uptake. After each day some team members and their supervisor review the logbooks with the team supervisor to check for correctness of inclusion criteria, weight measurement, drug dosage and AEs. After each month of MDA data are transferred to spread sheets for field follow-up. At the end of the 3-month period the logbooks are reviewed again and entered into an Access database. The medical team documents all complaints reported after taking the drug. A medical doctor reviews all symptoms reported to differentiate potential drug-related causes and non-drug related symptoms. The procedure for severe AEs involves alerting a medical doctor to conduct care and assessment of the case.

Assessment of MDA efficacy

MDA efficacy was assessed by prevalence surveys conducted 12 months after the start of MDA. The methods and analysis of these surveys are similar to baseline surveys, however, in order to have a more precise estimates the sample size is increased to roughly 80% of all adult village population for surveys. The sample size is increased so that statistically significant differences (from before and after MDA) can be detected, given that the original prevalence was relatively high. The number of required samples is calculated in order to measure a prevalence representing a 90% decrease of baseline PF prevalence, with a +/-50% precision, at the 95% confidence level.

Entomological surveys

Mosquito collection was performed in 28 hotspot villages before (M0) and 12 months after (M12) the MDA. Mosquitoes were collected individually in 5mL plastic tubes for five consecutive nights from 06.00 pm to 06.00 am using both human landing catch (HLC) and cow bait collection (CBC) methods. A total of 44 surveys were conducted in 27 villages (27 M0 surveys and 17 M12 surveys) yielding a total of 2,200 person-night (1,100 indoor and 1,100 outdoor) and 220 cow-night.

Identification of Anopheles

Anopheles mosquitoes were identified using the morphological key developedfor the identification of anopheline mosquitoes in Thailand (Rattanarithikul 2006). Sibling species among the Minimus and Dirus Complex's and Maculatus Group were identified at the species level using allele specific multiplex PCR   (Garros et al. 2004), (Walton et al. 1999) and (Walton et al. 2007) respectively.

Plasmodium detection

The Plasmodium infection rate of malaria vectors was assessed on whole mosquitoes using a quantitative real-time PCR (qPCR) assay adapted from (Chaumeau et al. 2016). The limit of detection of this assay was estimated at 60 and 36 sporozoites per mosquito for Pf and Pv respectively.

Entomological indexes of malaria transmission

The mean human biting rate (HBR) was calculated as the number of mosquitoes collected on the number of person-nights. The mean sporozoite index (SI) was calculated for Pf and Pv as the number of infected specimens on the total number of mosquitoes passed in qPCR. The mean entomological inoculation rate (EIR) of Pf and Pv was calculated as the product of the SI and the HBR.

G. Drug resistance in METF target area

Antimalarial resistance is monitored through clinical *P. falciparum* cases diagnosed and treated by MPs as well as through resistance markers. During an initial phase, *P. falciparum* positive RDTs were shipped back to the main METF office and stored in a dry, cool location. The RDTs were sorted by MP code (corresponding to the GIS) and sent to the laboratory for subsequent extraction of parasite DNA in order to monitor any major changes in the distribution of important drug resistance markers (markers for artemisinin, mefloquine, or piperaquine resistance) in parasite populations across the area (Ariey et al. 2014; Dondorp 2016; Price et al. 2004). The low amount of parasite genetic material on each RDT meant that this method yielded an interpretable result limited to K13 markers and for only 20% of processed RDTs. Beginning in 2015 MPWs were trained to collect DBS on filter paper from *P. falciparum* infected patients who had presented at an MP and were RDT positive. As of 2015 lab analysis also included mefloquine and piperaquine resistance markers (Pfmdr1 and plasmepsin 2 amplification).

A. Mapping and geographic information system

Logistic results

Villages were aggregated into administrative units including malaria post coordinator areas (usually 5 – 15 MPs), Zones and Areas. There are 3 main Areas each with up to 12 Zones (FIGURE 4). The target area has now been completely re-mapped three times, each time carrying over a few survey questions as a quality control check for the data, and including new questions.

Geography, settlement demography and rough development indicators

Overall 1490 villages and hamlets have been mapped in the target area, spanning approximately 18002 km2 divided into 3 areas (Area 1 = 6747 km2; Area 2 = 6405 km2; Area 3 = 4850 km2). During the 3rd round of mapping some basic economic indicators were recorded. Survey coverage was extensive, though some small areas in the south of Area 1 and north of Area 2 were not covered because of armed conflict (Naing 2016).

Some general patterns have emerged through these geographic surveys. The northernmost area (Area 1) consists mostly of small, rural, evenly distributed villages with 1 major town (Hpapun). Area 1 is the least economically developed, with fewer all-season roads and automobiles and less electricity. Travel and transportation capabilities in Area 1 change drastically by season (TABLE 1). In 54% of the villages in Area 1 the only source of water was a river, there was no electricity, and there were no automobiles (TABLE 1).

Table 1: Economic indicators from geographic survey (proportion (n))

	Area 1	Area 2	Area 3
no automobiles	0.76 (317)	0.04 (29)	0.03 (5)
no electricity	0.96 (399)	0.39 (256)	0.76 (140)
river only source of water	0.65 (272)	0.16 (107)	0.23 (42)
no automobiles, electricity and only river	0.54 (226)	0.01 (9)	0.02 (4)
total villages surveyed	416	664	185

proportion (n)

Area 2 is divided by the Dawna Range. On the eastern side of the Dawna Range consists of more sparsely distributed villages, usually clustering along the Moei River, and several larger population centres. The western side of the Dawna Range in Area 2 also has large population centres and is less sparsely populated, with most of the spaces in-between large towns being inhabited by small farming communities that are evenly distributed across the landscape. The two largest towns on the side of the Dawna Range are Hlaingbwe and Hpa-An and on the Eastern part of the Dawna range the largest town is Koh Ko.

Settlement types in Area 3 are heterogeneous. The southeast is sparsely inhabited, with small villages interspersed with forests and mountains. In the far south and far west of Area 3 are clusters of villages and large towns around the Kaw T'Ree and Kyaikdon areas. A major road network linking Myawaddy to populations on the other side of the Dawna Range divides areas 2 and 3. The largest towns in Area 3 are Myawaddy, Kawkareik and Kyaikdon.

Major developmental changes are occurring throughout the region, including new housing projects (some geared toward repatriation of refugees), new and improved roads and planned dams on the Salween River (which separates Area 1 from Thailand and Area 2).

The CE team has conducted numerous workshops and meetings with community leaders and with the population most related to surveys and MDA.

An overall good rapport between between project implementers and targeted communities is evident through requests from community health leaders for further action to address *P. vivax* infections and by the ability of METF to cover to the target area (with the exception of small ongoing conflict zones) in only 2 years. From the community perspective, there is also a high demand of providing other health- related services at MPs.

MDA participation

Perhaps the best metric for measuring the success of community engagement (CE) efforts is participation in MDA. METF was regularly able to achieve greater than 80% participation in villagers that were present in the village during a round of MDA. In a few cases, there were rumours of side effects or that the medicine could make villagers ill (see next section). For example, after the first round of MDA in one village there were rumours and participation dropped to less than half of the community in the second round. The METF CE team held focus group discussions with the community to uncover and address their concerns. The third round achieved a greater participation.

Rumour control

Rumours can have a major negative impact on any programme. Rumours that have emerged during the malaria project have typically been related to two main factors: 1) blood surveys (dangers or side effects related to sampling, fear of needles, fear of being tested for other conditions or that the blood will be sold, superstitious beliefs related to blood) and 2) MDA (concerns about side effects and fear of being poisoned). Seasonal illnesses sometimes overlap with timing of MDA or blood surveys, and this can result in rumours that the medication is causing illness. The CE team found that if community leaders and local village health workers understand and take ownership of the malaria program, people have more trust in the programme and rumours either do not start or are easily quelled. Focus groups have proven an effective tool to help elucidate potential trust problems, worries, doubts, or misperceptions about the malaria project.

Filling in gaps in MP coverage

Some areas within the target area have been difficult to cover with MPs because of ongoing conflict. These areas have been drastically reduced in both size and number over the life of the project. The ability to open MPs in these areas is directly related to intensive efforts from the CE team to reach agreement with important actors on the ground and at higher levels.

C. Malaria posts

From 1 May 2014 to 31 December 2016, METF has trained 1648 MPWs, 109 MP supervisors, 49 Zone coordinators and opened 1220 MPs covering more than 75% of all villages mapped (FIGURE 2). Of these 1220 MP, 1212 were reporting in December 2016. Out of 8 malaria posts not reporting, 3 are located in an area where conflict sparked in August 2016, disrupting normal MP function.

During the 36 months of activities 210406 fever cases were seen by MPWs and 211359 RDTs were performed. RDT-positivity for malaria was 12.3%, with large seasonal and geographical variations (FIGURE 5). In total, 9,581 *P. falciparum* cases and 15,837 *P. vivax* cases were treated. Eighteen deaths related to malaria and 43 severe malaria cases were reported. This corresponds to a case fatality rate of 1.8 per 1000 as expected in this setting (Luxemburger et al. 1997).
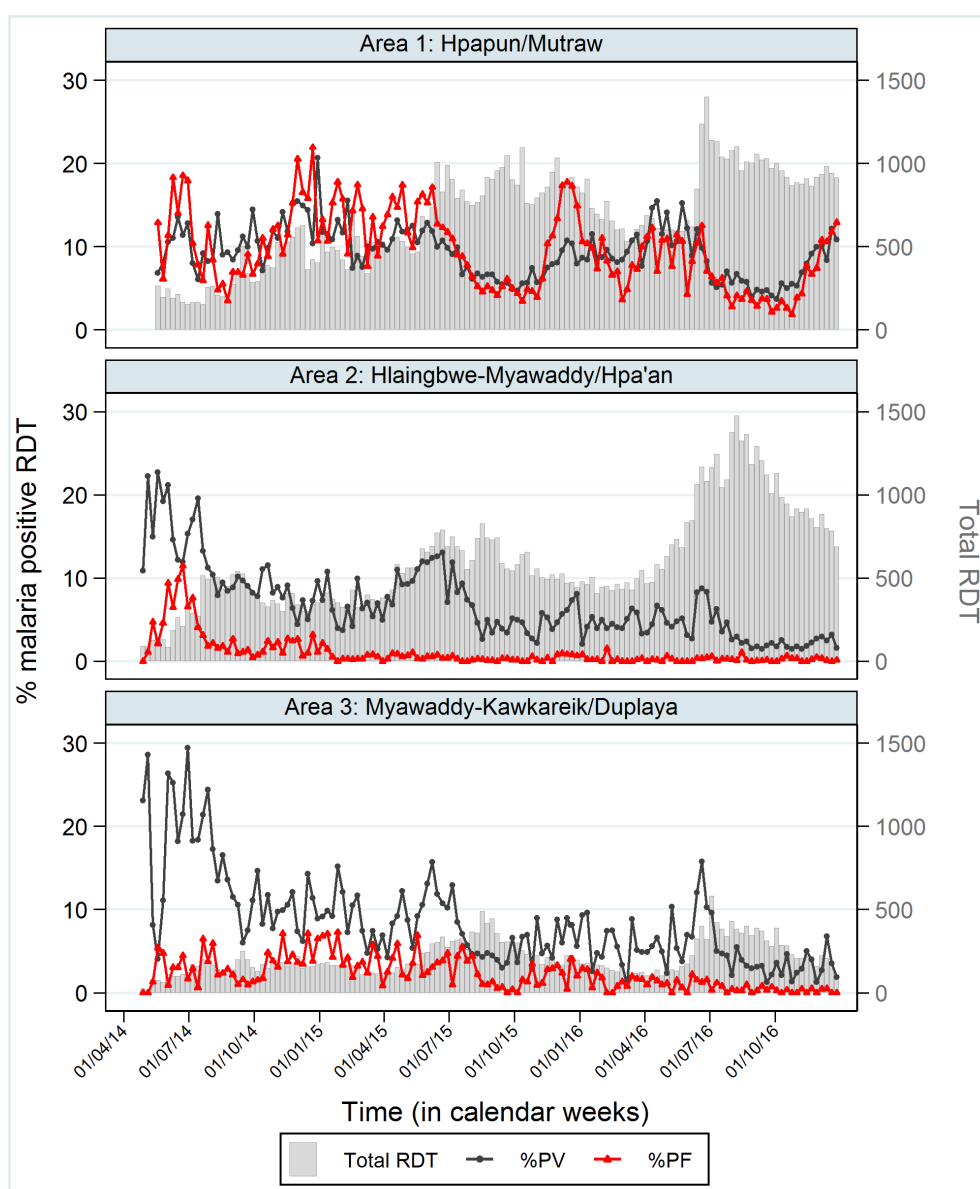

Figure 5 Malaria diagnosis and treatment activity in METF MP: percentage of falciparum and vivax positive RDT and total number of RDT done over time, by area.

Malaria clinical case incidence follow-up

Incidence of RDT-confirmed clinical falciparum and vivax malaria cases was followed through weekly activity reports and showed strong differences between the three project areas. Area 1 had a higher incidence rate with pronounced malaria seasonality with one peak at the start of the rainy season (June-July) and one in the cold season (December). Areas 2 and 3 had generally lower incidence rates, higher proportions of *P. vivax* cases (Pf/Pv ratio<1) and one main malaria peak at the start of the rainy season (FIGURE 6). A strong decrease in malaria incidence was observed over the 30 months since the start of the program (see section E).

Real time data collection

The main indicators for success of real-time data collection are the level of data completion and the delay observed between the end of a reporting week and the availability of data in the database. Out of 1220 MPs opened by 31 December 2016, 686 sent data using smartphones, while paper data sheets were brought to online data entry points for 534. Among MPs transmitting by paper forms, 476 are located in Area 1 where no phone network coverage

Figure 6: Evolution of the incidence of falciparum and vivax clinical malaria episodes since the begining of the METF project as recorded by Malaria Posts, by area.

is available. Of these 1220 MPs, 772 (63%) presented no gap in their series of data, while 352 (29%) had one or several gaps of one week. Only 96 MP (8%) presented gaps of more than one week. Many of these gaps result from transmission or entry errors and can be resolved a posteriori by checking the paper records. Across all available data, the median delay was 7 days (interquartile range (IQR)=1-9 days), but there is strong heterogeneity according to sending method. Gradual introduction of smartphones resulted in a steep decrease in delay where they were implemented: data transmitted by SMS is available after a median of 1 day (IQR=0-2 days), while data relying on porter carriage, mainly in Area 1, is available after a median of 8 days (IQR=8-9).

Quality control of data reporting and RDTs

Early in the project, the quality of the MP weekly data reports was assessed by double entry for 4076 records (14% of all records) for 27 variables and 110052 entries. Overall, the percentage of errors was 1%. Most of these errors (date format error, coding/spelling error, ambiguous handwriting) occurred within the first week of MP activity (111/4076 2.7%). In the remaining 3965 records the proportion of errors was 0.4%.

Systematic checking of reporting quality is now under implementation by comparison of real-time aggregated weekly reports to individual records (transmitted monthly and entered on a quarterly basis).
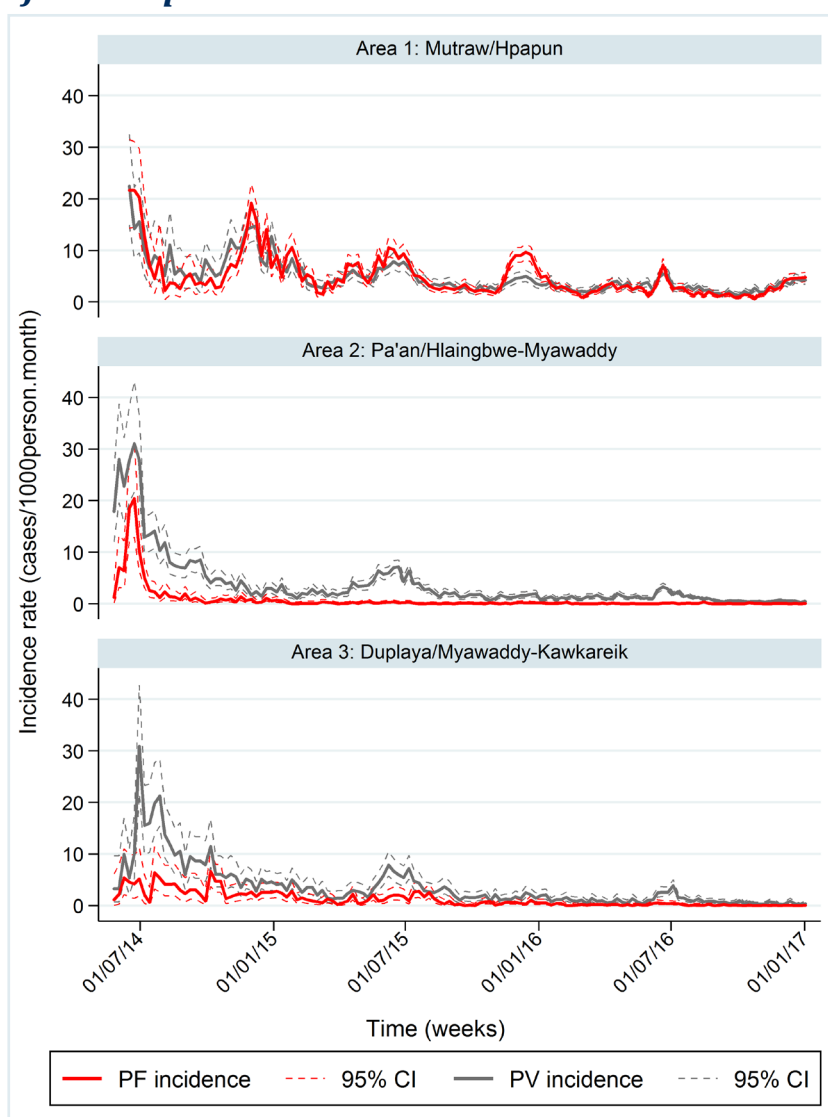
Central quality control (QC) of RDTs was conducted for 130 MPs for the period between January and August 2016, corresponding to 1638 RDTs. RDT quality control performed over 1 month after the test was conducted presents several challenges, especially when the tests are kept in harsh conditions that can alter the result. The most frequent problems are backflow of blood in test units (~30% of tests) and fading of control lines (~10%). Among 1398 negative RDTs, around 50% could not be rechecked properly. Among RDTs that could be rechecked, only one negative RDT was rechecked as positive Pv and 2 were rechecked as doubtful Pv, suggesting there is little false negative readings in the MPs. Of 53 *P. falciparum* positive RDTs that were rechecked, 86.8 % (46/53) were confirmed by QC, while 9% (5/53) were rechecked as negative. Of 151 *P. vivax* positive rechecked, 63% (95/151) were confirmed as P. vivax, 9% (13/151) were rechecked as negative, 17% (26/151) could not be rechecked and 11% (17/151) couldn't be rechecked because of faded control lines.

Monitoring and evaluation visits

After a pilot of 12 visits in August, 162 MPs were visited between September and December 2016. Among these, 130 represented random checks, 30 additional MPs were visited in the vicinity of a randomly targeted MP, and 2 visits were targeted because of suspected problems.

Analysis of the results for the 172 non-targeted visits showed that 87 MPs had only 1 worker, and 85 had 2 MPWs. MPs with 2 workers were located in larger communities (in average 106 households) compared to MPs with a single worker (in average 74 households). MPs with a single MPW were more frequent in Area 1 (90% of MP) compared to Area 2 and 3 (38% of MP). Across 257 MPWs, 225 had received adequate MPW training. This translated to 91% (156/172) of MPs with at least one trained MPW. The MP handbook was available in 171 of 172 MPs.

74% of the surveyed MPs reported having never closed for more than 24 hours in the previous 2 months. There were period(s) of more than 5 consecutive days without consultation in the logbook during the last 2 months for 84% of MPs. At the time of survey, 2 of the MPs were out of stock of ACT (1%) and 6 (3%) were out of RDTs, leading to 96% of functional MP. Nine (5%) of the MPs declared that they experienced ACT or RDT stock-outs of more than 2 consecutive days in the previous month.

The occurrence of supervision visits over the 2 previous months was documented in 160 MPs. In 64% of MPs there had been 2 visits or more, while 21% of MPs reported a unique visit and 15% of MPs reported that they had not been visited by their supervisor. The average number of supervisor visits during the past month was 2.5 (1.01 in area 1, where communications are the most difficult, and 3 in area 2 and 3).

In 30 (17%) of the visited villages, another medical structure (Myanmar government or NGO) was running another MP.

The delay between fever onset and consultation was significantly shorter for village inhabitants (1.7 days [95%CI: 1.7 – 1.8]) than for people not leaving in the village (2.2 days [95%CI: 2.1 – 2.2]). Overall, 80% of consultations occurred between 0 and 48h of fever onset, less than 15% of consultations occurred between 2 and 3 days, and less than 5% after 3 days. This indicates that most *P. falciparum* clinical cases were likely treated before the patient became infectious (before gametocyte production), and indicates the success of MPs.

Survey progress and results

From April 2014 to December 2016, 270 baseline prevalence surveys were completed and the results of 245 surveys were available for analysis. Malaria prevalence was heterogeneous across the target area (FIGURE 7).

The prevalence of falciparum malaria was generally low (median = 2.6%, interquartile range 0-10%) but highly heterogeneous: 30 villages had a prevalence above 20% (maximum prevalence 72%). Vivax malaria prevalence was generally higher (median=15%, IQR=5-15%) and 86 villages had a prevalence above 20% (maximum prevalence 64%).

Detection of hotspots

Out of these 245 surveys, 56 villages meeting hotspot criteria were identified (FIGURE 8). A large majority of these villages was located in Area 1 (FIGURE 9), also characterized by higher incidence of *P. falciparum* clinical episodes.
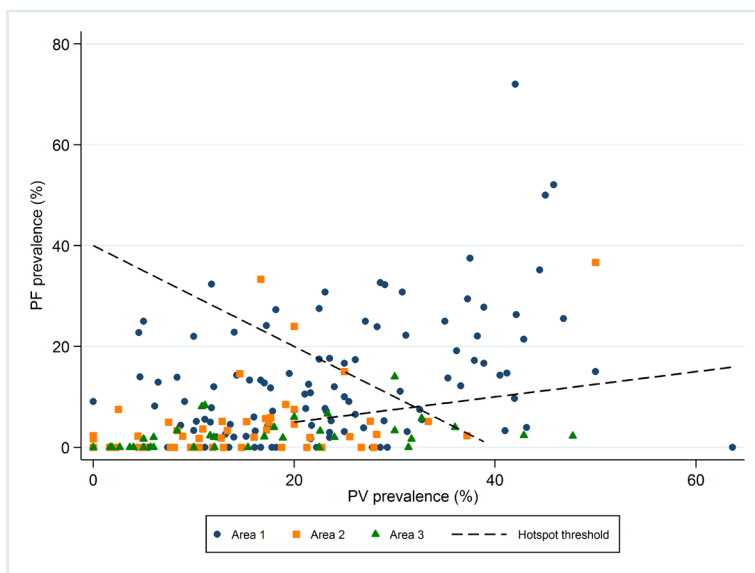

Figure 7: Prevalence of P. falciparum and P. vivax carriage measured by uPCR in 245 surveys conducted between May 2014 and October 2016. Detection of malaria parasites by uPCR allows a precise quantification of the parasite reservoir, including individuals carrying low parasite densities (submicroscopic) who are poorly detected by other methods. Area 1 concentrated most of the villages with high P. falciparum prevalence.

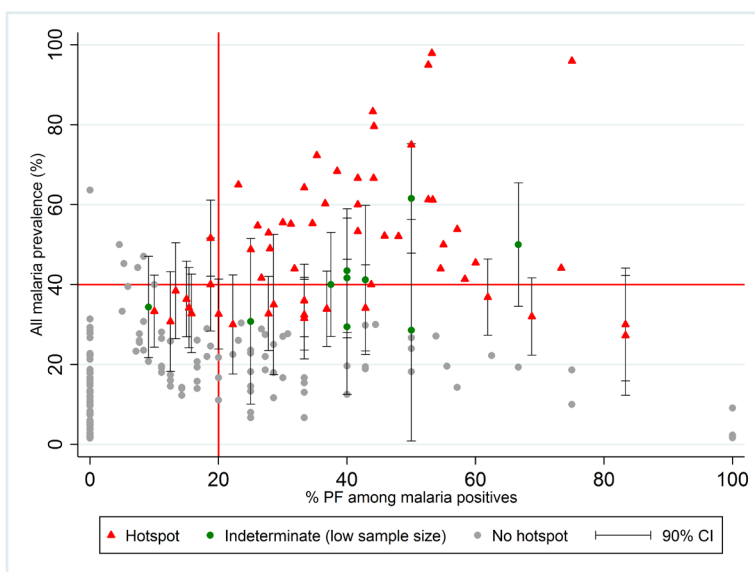*Figure 8: Identification of malaria prevalence hotspots. Horizontal red line indicates the 40% malaria prevalence threshold, while vertical line indicates the 20% of P. falciparum among positive samples. Confidence intervals are shown for villages where the upper limit of the confidence interval was above the threshold. Villages with low sample size had wide confidence intervals and were considered indeterminate.*
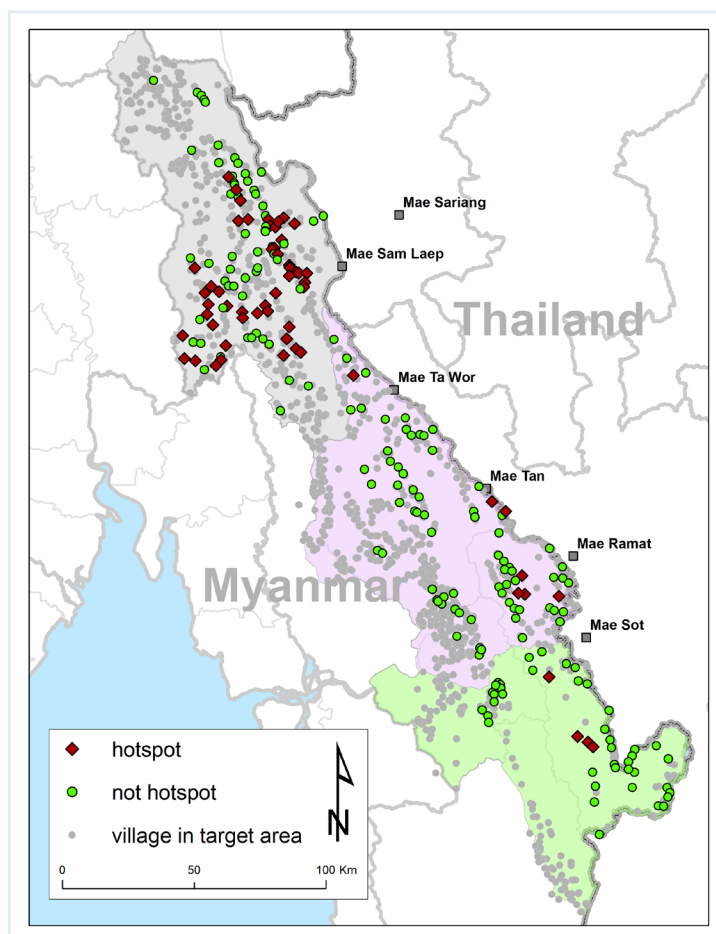
Figure 9: Map indicating survey results in METF target area. Villages that have not been surveyed are in grey, hotspots in red, and non-hotspot villages in green.

Spatial analysis of survey results

Hotspot village tend to spatially cluster across the target area landscape (FIGURE 9). Most hotspots were discovered in the northernmost region despite roughly proportional testing in all three major regions. Out of 154 villages that were randomly selected for malaria surveys, 35 were identified as hotspots, 22 (63%) were less than 5 km from another hotspot and all but 1 were less than 10 km from another hotspot.

Strong clustering of villages by malaria prevalence is also evident when analysing the quantitative prevalence estimates for *P. falciparum* or *P. vivax* rather than the binary hotspot/not data. Spatial clustering was most strong among villages in close proximity and decreased linearly. At 50 km distance there was no correlation between pairs of villages and by 75 km distance there was a significant negative correlation, indicating strong differences between villages that are geographically distal. This pattern of clustering is largely driven by the surveys in Area 1. When the data are stratified by Area the clustering pattern remains in Area 1 (though the overall pattern is less strong) but not in Areas 2 and 3. This suggests that there are no strong spatial patterns in prevalence in Areas 2 and 3, either of high prevalence or low prevalence villages.

These data and analyses suggest that malaria prevalence is the result of ecological patterns that exist on a scale larger than a village. This finding has strong implications with regard to estimating prevalences and their confidence intervals, as well as to mass drug administration, which relies on high proportions of participation among the target community. Well-connected villages or hamlets may behave as a single population unit or community. If only a small portion of a given unit is targeted with MDA, the overall proportion of carriers who participate will necessarily be low (i.e. surrounding villages with high prevalences won't be covered by the MDA).

MDA

MDA was conducted in the 50 out of 56 detected hotspots in five phases over two years. In 2015, 11 villages were treated in the first quarter, two villages in the second quarter and 16 in the third quarter. In 2016, 14 villages were addressed during the first quarter and 7 during the third quarter. The remaining 6 villages have been detected recently and not been addressed yet. Data from participation was available for 43 villages for this report; and M12 prevalence was available for 28 hotspots out of 29 addressed for 1 year or more (1 survey could not be conducted).

Monthly participation and population stability

The population of hotspot villages was generally small (mean=224 inhabitants, range=74-844). Overall, the target population of 43 analyzed hotspot villages was 10485 inhabitants, and 22576 complete curative courses were distributed. The proportion of village population which received at least one 3-day curative course of DP was high (median: 90%; CI: 85-94). In all but one village participation was above 60% (FIGURE 10). Participation dropped in 1 village following rumours, but participation subsequently increased.

MDA coverage was measured by the proportion of the population that received 0, 1, 2 or 3 complete 3-day curative courses, over the 3 months of intervention. In villages with higher magnitudes of population movement, only part of the village population could be reached during each round. Population stability was estimated as the percentage of people present in the village during the 3 months of activity. This stability was lower in Areas 2 and 3 (median 80%) compared to Area 1 (median 87%). At the end of the 3-month intervention the complete coverage (i.e. the proportion of people that received 3 times the treatment course) was 62%, (IQR=49-72) and was significantly correlated with population stability (FIGURE 10).
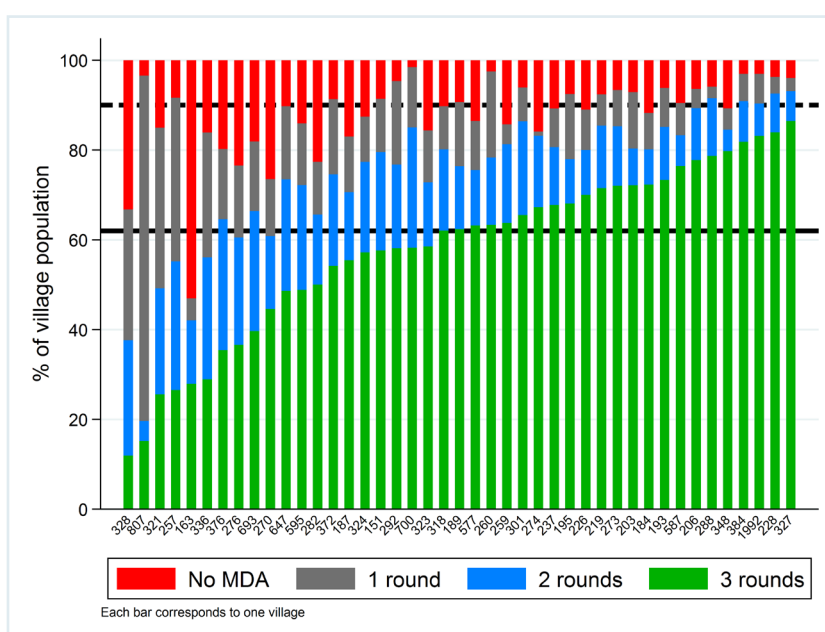

Figure 10: Percentage of the population in hotspot villages covered with 0, 1, 2 or 3 rounds of MDA, at the end of the 3 months of intervention. Across 43 villages, the median percentage of population taking 3 rounds was 62% (solid line), while the median percentage of population taking at least 1 round was 90% (dashed line).

Safety of MDA with DHA-piperaquine and single low-dose primaquine

Reported adverse events were analysed for 15 addressed hotspots. Among 8774 delivered curative course of DP and PQ, the most frequently reported symptoms were dizziness (2%), nausea (2%) and headache (2%), followed by minor gastrointestinal adverse events (1%), anorexia (1%) and sleep problems (1%). Less than 1% reported fatigue and palpitations. One death was reported in a 2-year old boy who was diagnosed with sepsis 2 weeks after the treatment course. No other serious adverse events were reported.

Reasons for non-participation

On average, 19% of individuals present in a village during a given month of intervention did not receive a curative course. These individuals can be grouped into 3 main categories: 13% who refused, stayed at home, or who could not be reached; 4.5% not meeting inclusion criteria; and 1.3% who initiated a treatment but didn't complete it. Among people refusing or staying at home, the main reason given was not wanting to take medicine, mostly because villagers did not feel sick, did not trust "western" medicine, or because they did not see malaria as a problem. Some participants already had other conditions, or felt weak and did not want to take another drug. Overall these results show that MDA intervention is feasible, and well-accepted by the population.
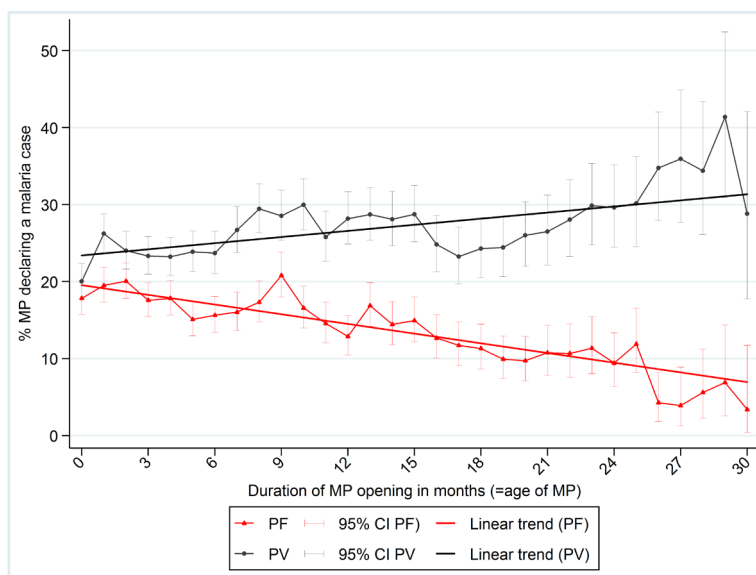
Figure 11: Evolution of the percentage of Malaria posts reporting at least one falciparum or vivax malaria case, according to time since opening. The percentage of MP declaring falciparum cases over time is decreasing while the percentage of MP declaring vivax cases is not. This shows the specific impact of early detection and treatment at MP on P. falciparum transmission.
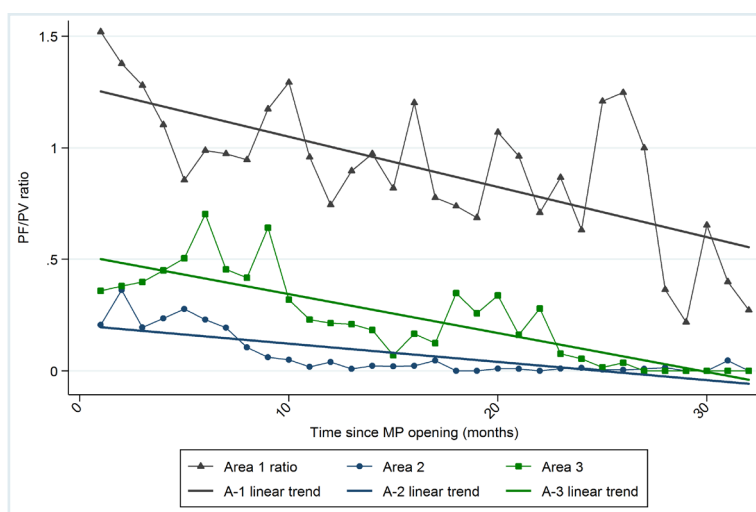

Figure 12: Decrease of PF/PV ratio over time since MP opening in the 3 areas of METF program, illustrating the specific impact on P. falciparum malaria.

MP impact on Malaria incidence

The massive increase in access to early diagnosis and treatment (EDT) via MPs led to significant decreases of *P. falciparum* incidence at the village and the regional level. The number of *P. falciparum* cases recorded was usually highest during the first weeks of opening a MP in a village, and during the first malaria season. On average across all METF villages, the incidence was 2.5 cases per 1000 people per month, during the first month of an MP opening. Afterwards the incidence rate of clinical falciparum malaria followed a decreasing trend, falling below 0.5 cases per 1000 people per month after 2 years of MP activity (FIGURE 3). This decrease was specific to falciparum malaria, with lower reductions in vivax incidence related to MP inability to provide radical cure (requiring 7 – 14 days of primaquine which can be harmful in patients with G6PD deficiency). This decreasing trend was more evident in non-hotspot villages compared to hotspot villages (FIGURE 27, page 49).

The occurrence of *P. falciparum* cases at the village level also decreased. The probability of an MP declaring at least one *P. falciparum* case was 20% during the first months after opening in a village, similar to the probability of declaring one *P. vivax* case. After 24 months the corresponding figure was ≤10% for *P. falciparum* while that of *P. vivax* showed an increasing trend (FIGURE 11).This translated into a decrease in the Pf/Pv ratio according to duration of MP activity (FIGURE 12).

A statistical model was used to quantify the contribution of the different interventions and parameters to the evolution of the incidence rate of *P. falciparum* cases in METF target area. A negative binomial generalised additive multilevel model (GAMM) was used to quantify the impact of MPs, adjusting for seasonality in transmission, the geographic location of villages, elevation, and coverage of neighbouring villages with MP.
Results indicate that, on average, functioning MPs led to a 20% decrease in *P. falciparum* incidence

rate for every 3 months of activity in a village (incidence rate ratio (IRR) for 10 additional weeks of activity=0.80; 95% Confidence interval (95%CI)=0.78-0.83). In addition, an increase of 10% in the proportion of villages equipped with an MP within a village tract resulted in a 5% decrease in incidence rate at the village level, indicating that there is a protective effect of being surrounded by MPs. Finally, this analysis also suggested that MDA had a significant impact on *P. falciparum* incidence in hotspot villages when compared to non-hotspot villages, beyond the effect of the MP itself. Before MDA, hotspot villages had a 3 times higher incidence when compared to non-hotspot villages (IRR [95%CI]=3.5 [2.4-5.3]), and their incidence decreased slower (IRR [95%CI]=0.85 [0.80-0.90] for 10 additional weeks of activity). After MDA there was no difference between hotspot and non-hotspot villages (IRR=0.8 [0.4-1.4]). Further data collection and analysis is warranted to understand if the impact of MP is similar in hotspot and non-hotspot villages.

Progress towards elimination at village level

Throughout the 30 months of the METF program there were an increasing number of villages with incidence rates under the WHO elimination threshold of < 1 case per 1000 people per year. Many villages equipped with MPs reported no falciparum malaria cases (n=693). These posts were mainly located in Area 2 and Area 3, West of the Donna Range near the towns of Kawkareik and Hlaingbwe and opened in 2016. These low malaria prevalence territories are well-connected to high prevalence areas and surveillance is necessary across the entire target region.

Limiting the analysis to villages where MPs declared at least one falciparum malaria case since opening (n=528), the proportion of MPs below the elimination threshold went from 17% in 2014 to 34% in 2016. The contribution of MP activity to falciparum malaria elimination is evident when looking at yearly incidence rate of MP by year of opening (FIGURE 13). For MPs opened in 2014, there was a regular decrease in the proportion of villages with incidence rates above 50 cases /1000 person/years from 43% (104/243) to 22% (53/243) during the first year and to 10% (24/243) during the second year. The proportion of villages below the elimination threshold increased from 17% (42/243) in 2014 to 20% (48/243) in 2015 and to 56% (136/243) in 2016. MPs opened in 2015 appear to follow similar trends, moderate increase in eliminating MP but strong decrease in the number of MP with high incidence over the first year.

Overall, 72% of MP in METF target region had a cumulative incidence rate below the elimination
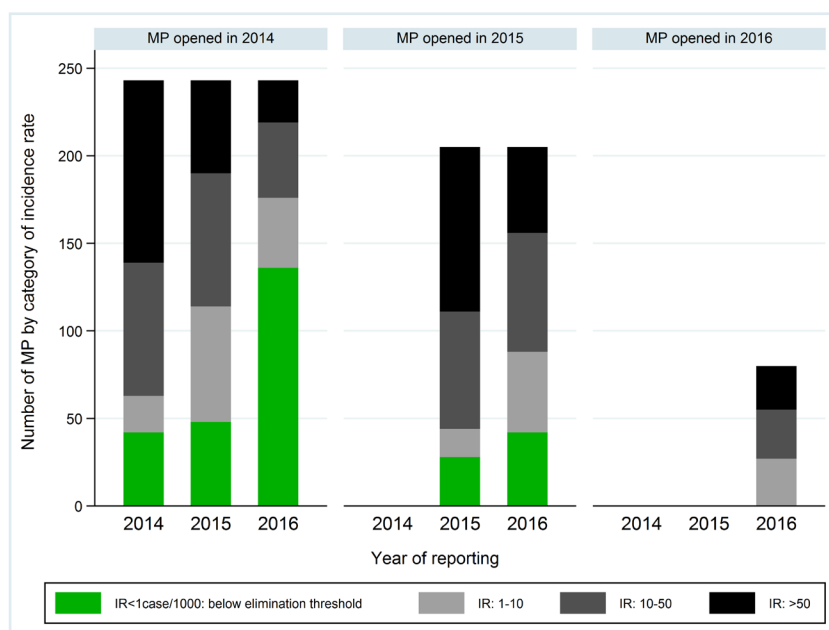

Figure 13: Transition of MP from high incidence to under elimination threshold, by year of opening, limited to 528 MP which declared at least one falciparum malaria case. The number of high incidence villages decreased after the first year but two years seem required in order to see an increase in the number of MP under the elimination threshold (in 2016 for MP opened in 2014).

threshold for 2016. In Area 2, 90% of MPs haven't experienced a single falciparum malaria case for more than one year (since October 2015). Likewise, 40% of MPs in Area 1 and 90% of MPs in Area 3 haven't experienced a falciparum case since last rainy season (April 2016). Overall, only 150 villages declared falciparum cases during the last transmission season (November-December 2016) (FIGURE 14)

MDA efficacy
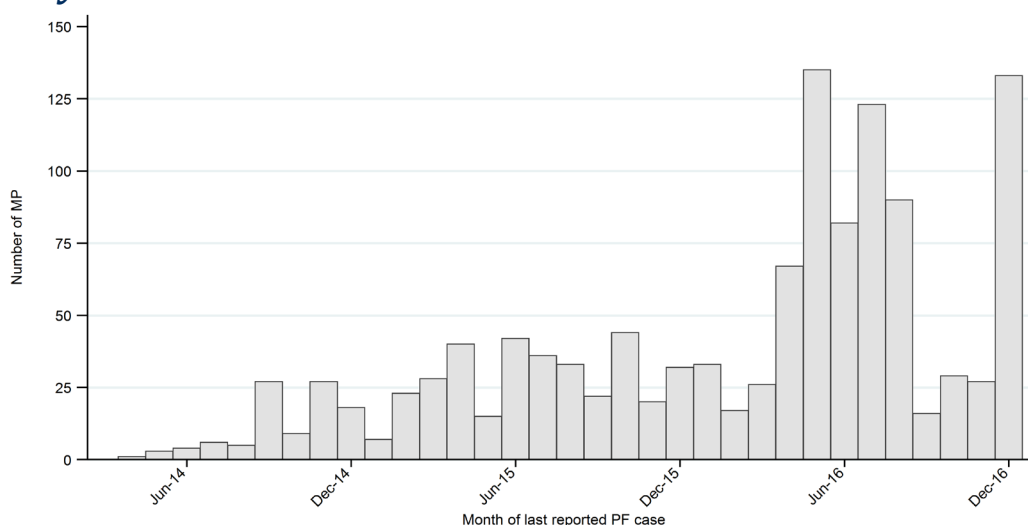
Figure 14: Number of MPs by month of last falciparum malaria case reported. MPs where no falciparum cases were ever reported are represented at their month of opening.

The impact of MDA on the prevalence of *P. falciparum* was strong. The long-term efficacy of MDA at reducing the asymptomatic and submicroscopic reservoir of *P. falciparum* was assessed by a prevalence survey conducted 12 months after the start of MDA. As of the 30th of November 2016, 29 hotspots had completed over 12 months of follow-up and 28 were surveyed. At month 12, the prevalence of *P. falciparum* infection was around 0% in 13 villages and between 0 and 2.5% for another 7 villages, and between 2.5 and 5.3% for the remaining 9 villages. This represented a decrease of 90% or more compared to baseline prevalence for 19 villages, between 80% and 90% for 7 villages, and between 66% and 80% in only 2 villages (FIGURE 15)

The incidence of Pf clinical cases was also reduced during the period after MDA compared to the

Figure 15: Long lasting reduction of P. falciparum reservoir after MDA: comparison of prevalence measured by uPCR in hotspot villages at baseline survey and at follow-up survey 12 months after MDA.

period before MDA (FIGURE 16). In hot-spot villages before MDA, 1997 clinical cases of Pf were diagnosed and treated diagnosed (22% of all cases in METF). Only 234 cases (2.6% of all cases) were recorded in hotspot villages after MDA.

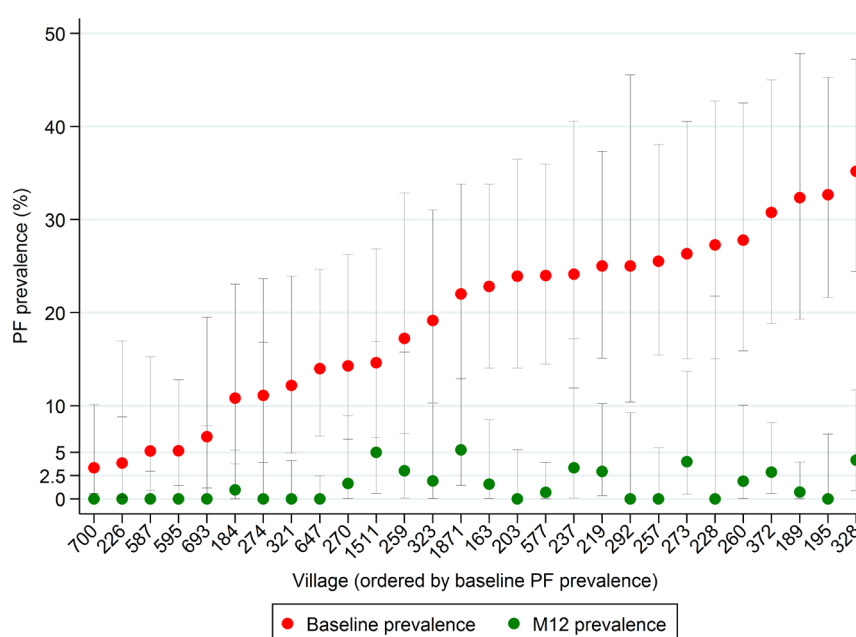Modelling work suggests that MDA alone will not be sufficient to achieve elimination in the target area, but that through pairing MDA with a dense MP network elimination can be achieved. Our results show that in combination with MP activity, MDA proved successful at quickly eliminating the sub-microscopic reservoir of *P. falciparum* and accelerating the decline in incidence of clinical cases.
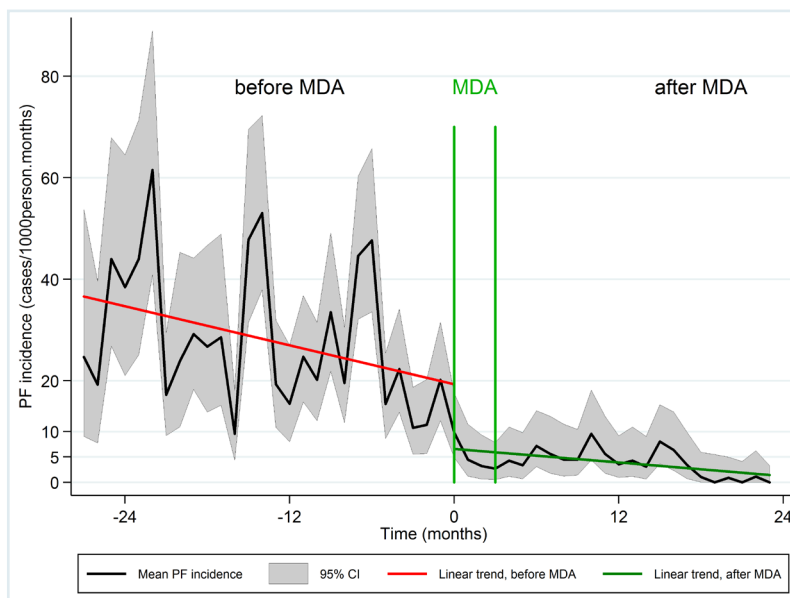
Figure 16: Impact of MDA on incidence of falciparum malaria episodes in hotspots.

Drug resistance in METF target area

The drastic reduction in falciparum cases throughout the target area has made it difficult to collect and analyse samples from a single field site before and after MDA. Resistance markers are here reported by METF Area and year.

Molecular marker of artemisinin resistance: Kelch 13 alleles distribution

The proportion of all analysed samples that were K13 wild-type in Area 1 was 39% (98/254) in 2014, 30% (8/27) in 2015 and 36% (5/14) in 2016. Only 2 samples were analysed from Area 2 (from 2014) and both were wild-type. In Area 3 in 2015 and 2016 the proportions wild-type were 39% (21/54) and 80% (4/5) respectively.

Of the K13 mutants detected in Area 1, 48% (75/156), 58% (11/19), and 22% (2/9) were variants that are associated (validated or implicated) with artemisinin resistance in 2014, 2015 and 2016 respectively (TABLE 3, page 43). In 2015 82% (27/33) of the mutant K13 variants drawn from Area 3 were variants that are associated with artemisinin resistance. Only 1 mutant variant was drawn from Area 3 in 2016 and it was not a variant that is currently associated with artemisinin resistance.

There is evidence of changes in the proportions of certain K13 alleles but not in the overall percentage of parasites with mutations (TABLE 3, page 43).

Molecular markers of partner drug resistance: Pfmdr1 and plasmepsin 2 amplification

From 2015 onwards, samples were analysed for copy number variations in Pfmdr1 and plasmepsin 2, associated with mefloquine and piperaquine resistance respectively.

Figure 17: Distribution and proportion of K13 mutations in samples drawn from Area 1 (Hpapun Township).

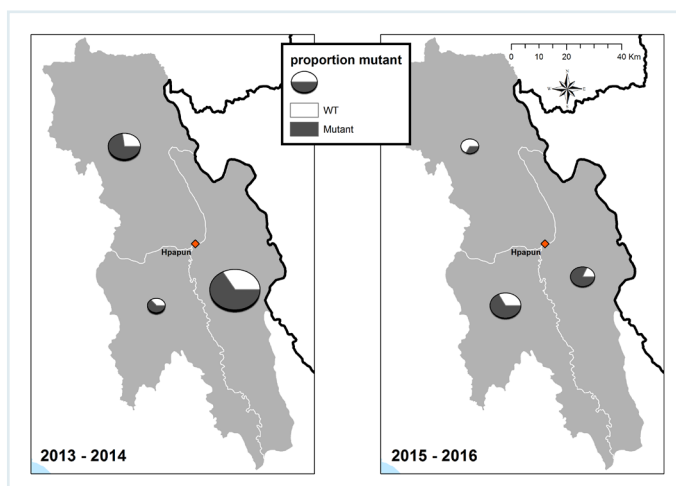Prior to the beginning of METF there were high proportions of Pfmdr1 copy number variants in samples collected from SMRU border clinics. For example, between 1995 and 2003 there were 890 samples with Pfmdr1 multiple copy number out of 2284 total analysed (39%). All samples from 2015 that were analysed for Pfmdr1 copy number repeats (63) were single copy number variants. In 2016 seven samples (out of a total of 303; 2%) had multiple copy number variants. (FIGURE 18). All samples that were analysed for plasmepsin 2 amplification (46 in 2015 and 312 in 2016) were single copy number variants (FIGURE 18).
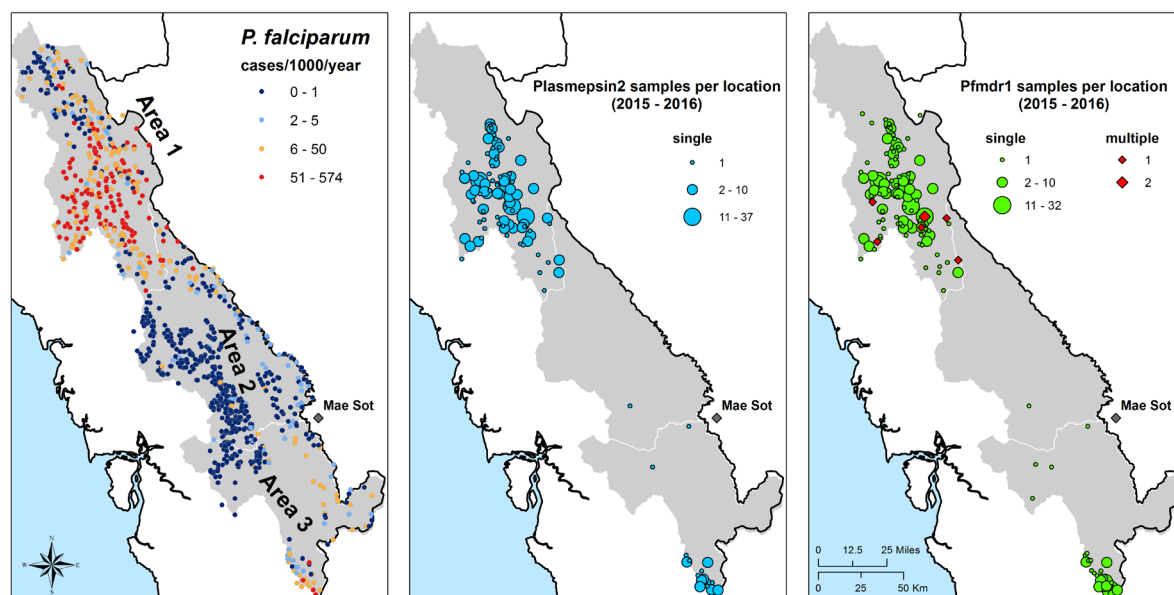
Figure 18: P. falciparum incidence (left panel) and distribution of samples analyzed for piperaquine resistance (middle panel) and for mefloquine resistance (right panel).

F. Entomology

A total of 116393 mosquitoes were collected in 27 villages from January 2015 to September 2016 (27 M0 surveys and 17 M12 surveys). Anopheles accounted for 45% of the mosquitoes collected (52436/116393) and a half of the Anopheles were collected by HLC (25520/52436). The most abundant species were *An. maculatus* s.l (45%, 11415/25520), *An. minimus* s.l. (30%, 7420/25520) and *An. annularis* s.l. (13%, 3434/25520). Malaria vectors represented >90% of the anopheles landing on mosquito collectors.
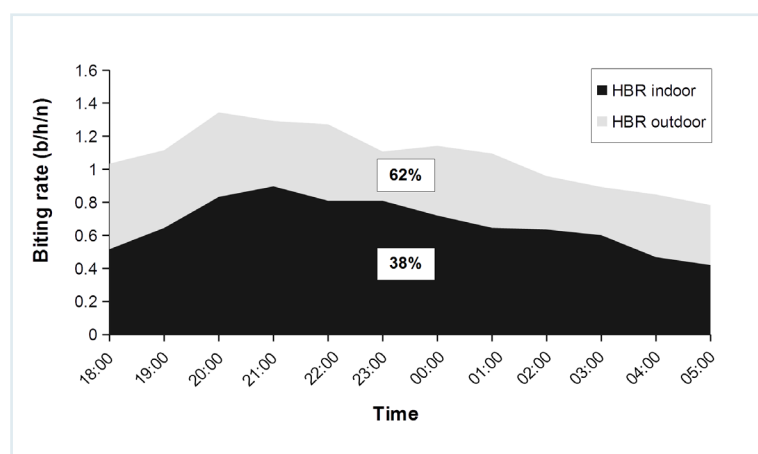
Figure 19: Night biting pattern of malaria vectors collected by indoor and outdoor Human Landing Catch. Most of the vectors are collected outdoor or at a time where people are not protected by insecticide-impregnated bed nets.

Malaria vectors were collected by HLC all throughout the night, but 50% were collected during the early evening and during the early morning (before 10:00 pm and after 04:00 am respectively). The outdoor human biting rate accounted for 62% of the total human biting rate (14177/22975). The cumulative indoor and outdoor HBR of malaria vectors was 8.0 and 12.9 bites/person/night respectively. The proportion of the biting rate that would potentially have been prevented by insecticide impregnated bed nets (indoor biting rate between 10:00 pm and 04:00 am) is 20% (FIGURE 19).

A total of 7644 specimens belonging to Minimus, Maculatus and Dirus Complexes were identified at the species level using PCR (FIGURE 20). J s.s. represented 99.5% of the Minimus Complex; *An. pseudowillmori* and *An. maculatus* were predominant among the Maculatus group (74.5%, 21.3% respectively); and *An. baimai* was the most abundant species among the Dirus Complex (91.2%).
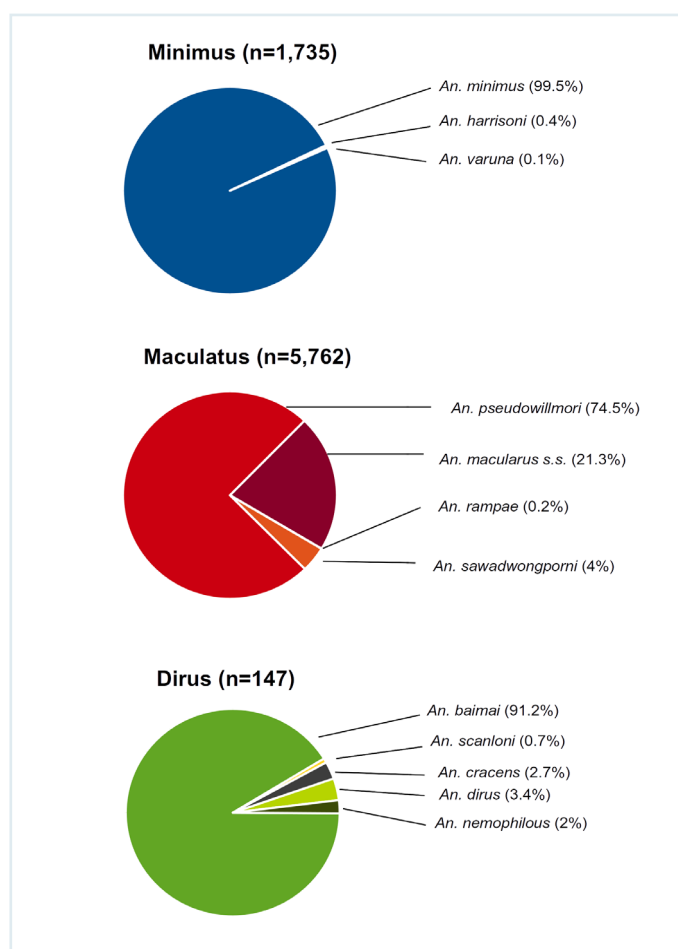
Figure 20: Molecular identification of malaria vectors belonging to the Minimus Complex, Maculatus Group and Dirus Complex.

In addition, 10474 malaria vectors were analysed individually by qPCR to assess the Plasmodium-infection rate. Only two specimens were infected with *P. vivax* (one *An. maculatus* s.s. and one *An. pseudowillmori*), thus Pv-SI was 0.2 per thousand. The mean human biting rate of malaria vectors was 313 bites/person/month which yield an average Pv-EIR of 0.05 infective bites/person/month (or 0.7 Pv-infective bites/person/year). Pf-transmission indexes were below the detection threshold in this study (TABLE 2). Processing of the remaining samples is on-going.

Table 2. Summary of the malaria transmission indexes

Transmission index	Mean value
HBR in bites/person/month (annual value)	313 (3,756)
Pf-SI per thousand	0
Pv-SI per thousand	0.2
Pf-EIR infective bites/person/month (annual value)	0
Pv-EIR infective bites/person/month (annual value)	0.05 (0.7)

DISCUSSION AND PERSPECTIVES

The METF activities have shown considerable progress in the rapid elimination of *P. falciparum*. The strategy used for elimination complements that used for the control of malaria. In a malaria control programme the focus is on the people: preventing infections and treating clinical cases. In the elimination strategy the focus is on the parasite: treating patients before their parasites are transmitted to the vectors, searching and eliminating the sub-microscopic reservoirs because they maintain transmission and preventing new infections by using long acting drugs and adapted vector control measures. The detailed geographic knowledge (mapping), the strict terms of reference of the MPs (detect and treat within 24-48 hours), the real-time data and intelligence gathering and analysis (weekly), the search and treatment of sub-microscopic reservoirs (MDA) are all essential components of this elimination programme. The quality of CE is key to ensure community participation. At a programmatic level the involvement of all health-related Karen organizations (CBO, NGO) is essential to success, within a robust structure to ensure proper management and supervision. The results presented here are all very significant. Participation of the communities has exceeded expectations largely because of the trust built by the CE team, the MPWs have done a fantastic job (even if improvement is possible) and the number of *P. falciparum* cases has been drastically reduced and continues to decline. All operations are going smoothly because of the dedication of the supervisors, coordinators, trainers and surveys and logistic teams, despite operating under difficult circumstances. While the project is going in the right direction, care must be taken in order to not become complacent. Time is of the essence in the elimination of falciparum malaria. Parasite resistance to artemisinin, its derivatives and combination therapies is increasing in the area and new drugs are years away. While we have not detected any decline in the efficacy of piperaquine or the existence of piperaquine resistance markers in the target area, resistance to this drug has emerged in Cambodia and Vietnam [22, 23]. The presence of parasites with multiple copies of Pfmdr1 in the Area1 could signal the emergence of resistance to lumefantrine. In addition there is a growing demand from the population to also tackle *P. vivax* malaria and this is an even greater challenge. Finally, the transition from MP to health post to ensure that the surveillance system remains effective will need to be addressed in the coming months.

A. Budget analysis

The budget allocated for these activities comes from a multi-year commitment from 2 funding sources: the Global Fund RAI-ICC, through the United Nations Office for Project Services (UNOPS) and the B&M Gates Foundation. All funds used in the project are clearly marked to an activity, so that reporting and monitoring are made easier. The main expenses are related to salaries and stipends: although the central coordination team is kept to a minimum (1 project director, 1 geographer/spatial epidemiologist, 1 epidemiologist-biostatistician, 1 medical referent, 1 programme manager per Area (3), 1 grant manager and 1 logistician). All persons working for the project in the field receive monthly monetary compensation, ranging from U.S. $ 50 per month for MPWs to U.S. $ 400 per month for Area coordinators. Other important posts of expense are the procurement and supply of ACT and RDT (11% of the budget), followed by the expenses related to the malaria surveys (10%). Monitoring and data collection consume 10% of the budget. Most of these expenses are related to transportation costs to move from one place where monitoring takes place to the next, as in it an ongoing process. As data collection is concerned, the main expenses relate to the supply of mobile phones or tablets to places relaying the data transmission, top-up of phone subscriptions, and the development of a web portal where data are made available to all stakeholders. The set-up of the MPs (FIGURE 21) represents only 3% of the budget (excluding RDT and ACT supplies). Training and all community engagement activities represent 6% of the budget. Mapping activities and the activities related to entomology represent around 3% each. It is important to note that despite important expenses related to laboratory procedures (i.e. qPCR) are committed at the central level, almost 60% of the funds reach the field.

Activity (%)	SMRU & Partners	Village
1. Salary	18.57	23.26
2. qPCR related	0.28	10.06
3. Anti-malarial drug	1.18	6.52
4. RDT	0.86	2.47
5. MP Set Up & Health Product	-	3.06
6. MP Training, CE & TMT Activity	-	5.98
7. Monitoring & Data Collection	1.93	7.58
8. Mapping	2.99	-
9. Entomology	2.60	-
10. Equipment & Office Running	2.71	-
TOTAL	31.12	58.93

Indirect 9.95%
Sub-contract (KU) 2.01%
SMRU & Partners 31.12%
Village 58.93%
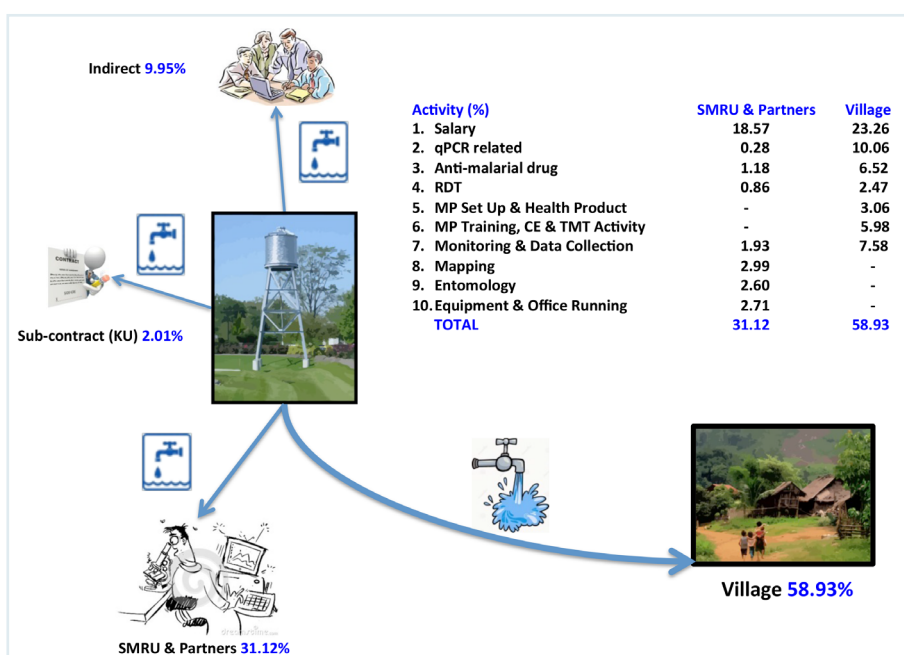
Figure 21: METF program cost analysis

Zoom on the Malaria post.

As MPs are the center piece of the program, it is interesting to follow up on the cost of their maintenance. According to the information gathered from the opening of more than 1,200 MPs over 30months, the expenses related to an MP set up and operation can be evaluated at USD 138 (direct cost) each, distributed as shown in (FIGURE 22).

Equipment, $6.25 5%
Transportation for supervision, referrals…, $15.63, 11%
Non-malaria fevers, $20.00 14%
ACT, $4.00 4%
RDT, $6.00 6%
SIM top up for SMS transmission, $3.13 2%
Smartphones, $10.42 8%
Training, $7.81 6%
Remuneration, $65.00 47%
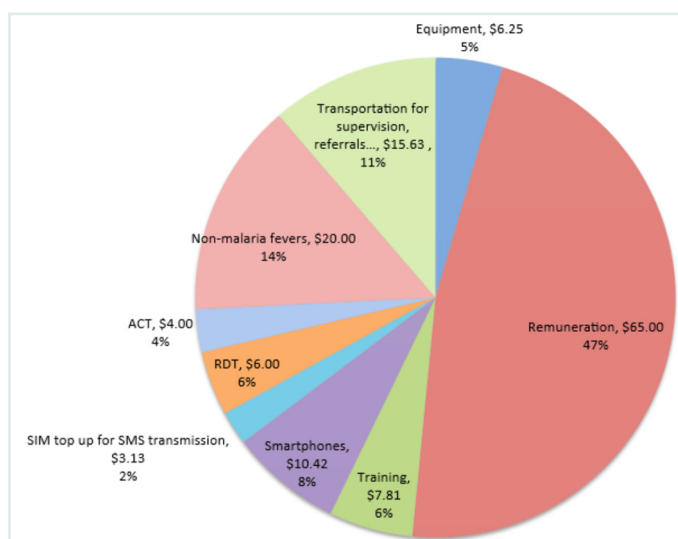
Figure 22: Monthly direct cost of a Malaria Post

B. Supplementary graphs and figures

Table 3: K13 alleles distribution 2014, 2015, 2016

2015		
K13 Alleles	Frequency	Percentage
A626S/A	1	0.4
C469F	1	0.4
C469Y	1	0.4
C542Y	1	0.4
C580Y	13	5.1
E252Q	26	10.2
F446I	27	10.5
G449A	9	3.5
G533S	22	8.6
G538V	1	0.4
K189T	2	0.8
M476I	16	6.3
P441L	6	2.3
P574L	4	1.6
R265P	1	0.4
R539T	1	0.4
R561H	24	9.4
WT	100	39.1
Total	256	100

2015		
K13 Alleles	Frequency	Percentage
C469F	3	3.7
C469Y	1	1.2
C580Y	9	11.1
G533S	8	9.9
K189T	2	2.5
M476I	1	1.2
N525Y	1	1.2
N537I	11	13.6
P441L	8	9.9
P574L	6	7.4
R561H	2	2.5
WT	29	35.8
Total	81	100

2016		
K13 Alleles	Frequency	Percentage
C469F	1	5.3
C469Y	1	5.3
C580Y	1	5.3
F446I	7	36.8
WT	9	47.4
Total	19	100

MP case Management

Patient comes in with fever or history of fever in the last 2 days

↓

Rapid diagnostic test for malaria (SD bioline) OR microscopy

NEG (---)
→ Other diseases
➔ If patient is severe refer to clinic

PF(+)

PV(+)

CQ3

Chloroquine

X 3 days

Pregnant

YES

NO

1st Trimester

1st episode: Qunine / Clindamycine & days

2nd and other episodes: Coartem

2nd and 3rd Trimester Coartem

ACT (Coartem) 3 days + single low dose Primaquine

Supervise the treatment

If reappearance < 2 months

Use an alternative ACT if available

IF SEVERE SIGNS REFER TO CLINIC

- Unconscious, fitting
- Very pale, Severe Jaundice
- Not passing the urine or black urine
- Shortness of breath
- Unable to walk or unable to drink, eat by self
- Spontaneous bleeding from nose, gum etc.

Figure 23: METF algorithm for treatment at the Malaria Post

MP Worker Name:	(Village barcode)
|_____|	Report by: |_____| name

Malaria Elimination Task Force weekly report form (SD BIOLINE)

*From date:\|___\|___\| \|___\|___\| \|___\|___\| to date: :\|___\|___\| \|___\|___\| \|___\|___\|

*Please count from **MONDAY** to **SUNDAY** always:
စၤထီၣ်ဒွၤနွၤလၢမ့ၢ်တနံၤတုၤလၢမ့ၢ်အိၣ်တ့ၤထီဝဲ/း

Table 1: Total fever cases ပုၤဆါတၢ်ကၢ်ထိၣ်(Number of cases of **FEVER** တၢ်ကၢ်ထိၣ်အနီၣ်ဂၢ်)

	Total
<5 years	
5 to 15 years	
Older than 15 years (>15)	
TOTAL	

Table 2: Laboratory results တၢ်မၤကွၢ်အစၢတဖၣ်   **SD BIOLINE**

	Pf	**Pv**	**Neg**	**Invalid**	**Total**
<5 years					
5 to 15 years					
Older than 15 years (>15)					
Total					

Table 3: Number of patients **TREATED** for malaria. ပုၤဆါလၢအဒိးနွၤတၢ်ညၣ်ဂီၢ်ကသံၣ်နီၣ်ဂၢ်

	Pf		**Pv**		**Total**
	Male	Female	Male	Female	
<5 years					
5 to 15 years					
Older than 15 years (>15)					
Total					

A. **Severe cases within reporting week:** ပုၤဆါလၢအနးဖဲတနွၤအံၤတၢ်ဟ်ဖျါ   \|_____\|cases

B. **Death due to Malaria or suspected of Malaria within reporting week:**   \|_____\|cases
ပုၤဆါသံလၢတၢ်ညၣ်ဂီၢ်(မ့)ဆိမိၣ်လၢတၢ်ညါဂီၢ်အယိဖဲတနွၤအံၤတၢ်ဟ်ဖျါ//း

C. **Total pregnant women within reporting week:**   Neg \|____\| Pf \|____\| Pv\|____\|
ပုၤမိၢ်ဒၢနီၣ်ဂၢ်လၢတနွၤအံၤတၢ်ဟ်ဖျါ

Remaining number of SD BIOLINE tests in stock: တၢ်မၤကွၢ် SD BIOLINE လၢအအိၣ်တ့ၢ်   \|_____\|

Remaining number of COARTEM boxes for Pf treatment: ကသံၣ်လၢတၢ်ညၣ်ဂီၢ်ဃၢ် Pf အဂီၢ်အိၣ်တ့ၢ် \|_____\| boxes

တၢ်ဂ့ၢ်တၢ်ကျိၤအဂုၤအဂၤတဖၣ်အဂီၢ်ကွဲးဃီၤလၢအချၢတကပၤ.

| FIGURE 24: MP Weekly reporting form |

Malaria Post

data checking

Village

Weekly report

Logbook
(individual consultations)

Other METF data
from:
- Prevalence surveys
  (field and laboratory)
- Mapping
- MDA (participation)

MP
supervisor

Entry and transmission
- Paper + online database: Voozanoo
- SMS: METF app (developed using DroidDB)

Entry/transmission
- Paper + online
  database: Voozanoo

METF
central office

Data consolidation and data management
- 3 times/week
- METF data management routine (STATA)
- Verification: completion, quality, coherence

Data management
- Verification (STATA)

Data integration and analysis
- Descriptive and analytical statistics (STATA, R...)
- Reporting (files and maps)

Data sharing with
partners
- Online database:
  Voozanoo

Program
management
- MP activity report:
  Excel

Monitoring of
MP
- List of MP with
problems: Excel

Malaria
surveillance
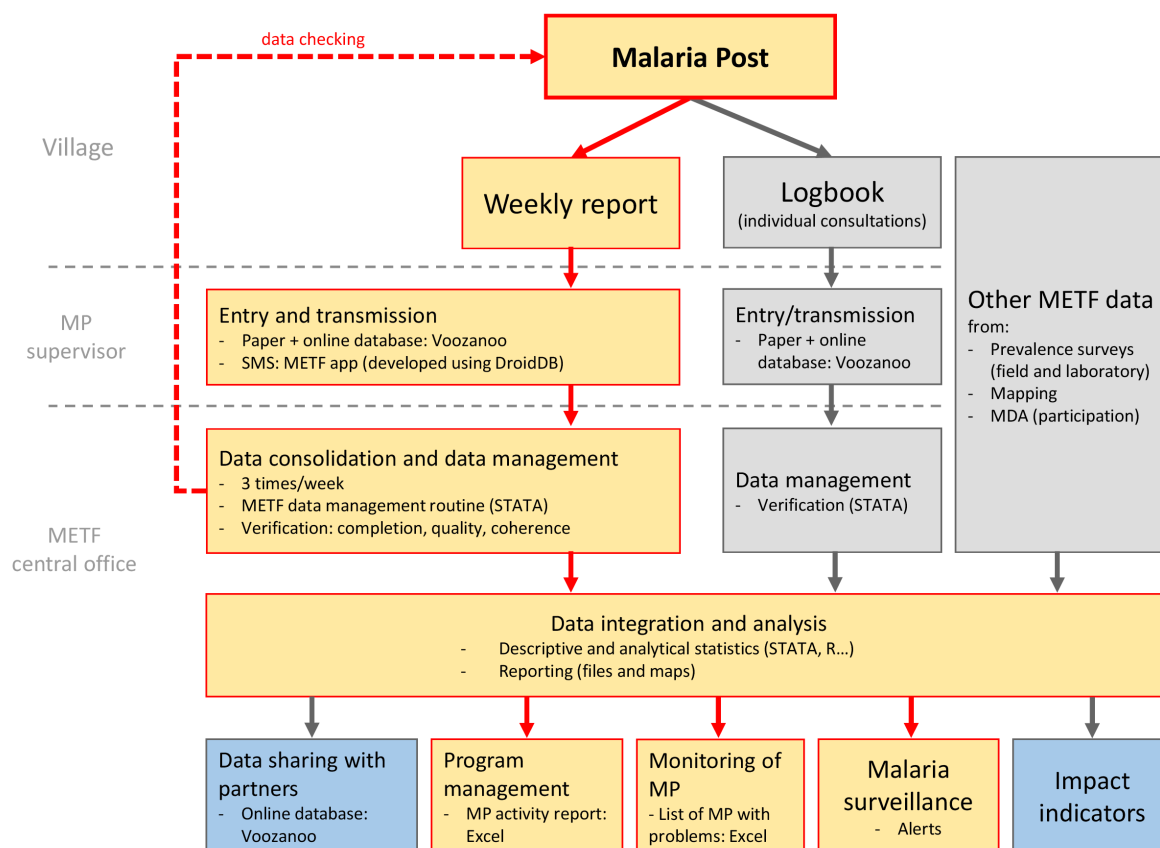- Alerts

Impact
indicators

FIGURE 25: METF Malaria Post data architecture and collection flow. Orange boxes correspond to weekly collected data allowing near real-time surveillance and monitoring of MP activity.

Malaria Post Assessment

Village Name(သဝီမံၢ)_____Township(ကီၢ်ဆၣ်) _____District(ကီၢ်ရ့ၣ်) _____State(ကီၢ်စဲၣ်)_____

[1]Malaria Post Code_____ HH number[2]: _____

Village GPS coordinates: LAT:_____LONG:_____

Name of [3]Malaria post worker   (1) _____ (2) _____
(တၢ်ညၣ်ဂီၢ်ကသံၣ်ဒၢးပှၤမၤတၢ်ဖိအမံၤ)

TRAINING :   Yes ☐   No☐
RETRAINING: Yes ☐   No☐

Name of MP Supervisor (တၢ်ညၣ်ဂီၢ်ကသံၣ်ဒၢးအပှၤဟ့ၣ်ကူၣ်တၢ်အမံၤ) _____

MP worker not present ☐   Number of days since MPW away: ………   Number of days until back: ……….

If not at post, where did the MPW go ? …………………………………………

Assessment questions to MP workers (Ask to malaria workers directly) (တၢ်သံကွၢ်လၢပှၤကွၢ်တၢ်ညၣ်ဂီၢ်ယၢ်အပှၤမၤတၢ်ဖိအဂီၢ်)

1	Was the MP closed for > 24 hours in last 2 months? ဖဲအပူၤကွံာ် ၂ လါနံၣ်မ့ၢ်တၢ်ကွံၢ်တၢ်ညၣ်ဂီၢ်ကသံၣ်ဒၢးပတုာ်ယၢ်အသးအါန့ၢ် ၂၄ နၣ်ရံၣ်ဧါ If MPW was available even if MP was closed, mention in remark	**Condition** ☐ YES ☐NO	**Comment/remark**
2	Are there valid ACTs in the MP? လၢတၢ်ညၣ်ဂီၢ်ကသံၣ်ဒၢးပူၤန့ၣ်ကသံၣ်ယါဘျါတၢ်ညၣ်ဂီၢ်([4]ACTs) လၢအသီတတလၢဘၣ်(အမှံၤ်းတလၢၢ်ဒံး)တဖၣ်အိၣ်ဧါ	☐ YES ☐NO	
3	Are there vaild RDTs in the MP ? လၢတၢ်ကွံၢ်တၢ်ညၣ်ဂီၢ်ကသံၣ်ဒၢးန့ၣ်တၢ်မၤကွၢ်တၢ်ညၣ်ဂီၢ်ယၢ်([5]RDTs) လၢအသီတတလၢဘၣ်(အမှံၤ်းတလၢၢ်ဒံး)တဖၣ်အိၣ်ဧါ	☐ YES ☐NO	
4	Were there >2 days out of stocks (RDTs or ACTs) in the past 4 weeks? ဖဲအပူၤကွံာ် ၄ နံၣ် နံၣ် (RDTs)မ့တမ့ၢ်(ACTs) လၢ်ကွံာ်တအိၣ်လၢၤဘၣ်အါန့ၢ်းဒံး ၂ သီအိၣ်ဧါ --- Adequate or sufficient medication and supplies(observe and check carefully) ကသံၣ်ကသိတၢ်ပီးတၢ်လီအိၣ်လၢအိၣ်ပှဲၤ(ကွၢ်သမံသမိးလီၤတံၢ်လီၤဆဲး) SD biolines = tests ACT= tabs CQ = tabs PMQ = tabs Clindamycin	☐ YES ☐NO	If no, ask why မ့ၢ်တအိၣ်ဘၣ်န့ၣ်သံ ကွၢ်အီၤ "ဘၣ်မနုၤအယိလဲၣ်"
5	How are the results reported? နဆှၢထီၣ်ကွၢ်တၢ်အစၢတဖၣ်လဲၣ် (အကျိုၤအကျဲ) ☐ SMS (ဆှၢဒီဖှိၣ်လီတဲစိ ☐ Paper (လံာ်ကဘျံးပူၤ) ☐ Other (………………)		
6	Does the MPW receive regular financial incentive? တၢ်ညၣ်ဂီၢ်ဒၢးပှၤမၤတၢ်ဖိတဒုဒံးန့ၢ်ဘၣ်ကျိၣ်စ့တၢ်မၤစၢၤထီဘိစ့ၢ်ကီးဧါ	☐ YES ☐NO	
7	Is there another MP in the village? လၢသဝီပူၤအံၤမ့ၢ်တၢ်ကွံၢ်တၢ်ညၣ်ဂီၢ်ဒၢးအဂၤ(လၢအတမ့ၢ်နတၢ်ကရၢကရိ)ဘၣ်န့ၣ်အိၣ်ဧါ	☐ YES ☐NO	

[1] Malaria Post = တၢ်ညၣ်ဂီၢ်ကသံၣ်ဒၢး (တၢ်လီၢ်ဖဲပှၤလဲၤမၤကွၢ်တၢ်ညၣ်ဂီၢ်ယၢ်, ပှၤဖီးစုနာခိၣ်ဒီးမၤကွၢ်တၢ်ညၣ်ဂီၢ်ယၢ်အလီၢ်)
[2] House that are inhabited = ဒၢးလၢပှၤအိၣ်
[3] Malaria Post Worker = တၢ်ညၣ်ဂီၢ်ကသံၣ်ဒၢးအပှၤမၤတၢ်ဖိ (ပှၤမၤတၢ်ဖိလၢအအိၣ်လၢပှၤဖီးစုနာခိၣ်ဒီးမၤကွၢ်တၢ်ညၣ်ဂီၢ်ယၢ်အလီၢ်)
[4] ACT = ကသံၣ်လၢတၢ်ကူစါတၢ်ညၣ်ဂီၢ်ယၢ်
[5] RDT = Rapid Diagnosis Test

FIGURE 26: Monitoring and evaluation form (page 1)

8	If YES, specify the supporting organization တၢ်ညီၢ်ကသံၣ်ဒၢးအဂ့ၢ်အဂၤမ့ၢ်အိၣ်ဘၣ်ဖုးန့ၣ်ကွဲးဖျါထီၣ်တၢ်ကရိလၢအမၤစၢၤအီၤအမံၤ	_____	
8b	: If Yes, do you receive malaria data from them?	☐ YES	☐ NO
9	How often did you receive the visit of your MP supervisor in the last 2 months? ………………… time(s) လၢတလါအတီၢ်ပူၤန့ၣ်,န(supervisor)ဟဲထံၣ်လိာ်အသးဒီးနၤပှဲၤ�’ဘျီလဲၣ်	☐ 1 Per Month ☐ <1 Per Month ☐ > 1 Per Month	

Assessment by Evaluator (Check - List)

1	Is there a Malaria Post Manual in the MP? လံာ်နဲၣ်ကျဲလၢတၢ်ညီၢ်ကသံၣ်ဒၢးအပှၤမၤတၢ်ဖိအိၣ်ဧါ	☐ YES	☐NO
2	Are there reporting forms in the MP? လၢတၢ်ညီၢ်ကသံၣ်ဒၢးန့ၣ်တၢ်ဟ်ဖျါထီၣ်က့ၤအလံာ်တီၤဃ့ၣ်(forms)အိၣ်ဧါ	☐ YES	☐NO
3	Is there a logbook (daily recording of individual patients) in the MP? လၢတၢ်ညီၢ်ကသံၣ်ဒၢးန့ၣ်အလံာ်တၢ်မၤနီၣ်မၤဃါ(တနံၤဘၣ်တနံၤတၢ်ကွဲးနီၣ်ပှၤဆါအစရီ)အိၣ်စ့ၢ်ကီးဧါ	☐ YES	☐NO
4	Are the "Days of fever" recorded for each patient? (Review the daily record sheets) လၢတၢ်ကွဲးနီၣ်အပူၤန့ၣ်မ့ၢ်တၢ်ကွဲးနီၣ်မၤနီၣ်ပှၤဆါတဂၤစုာ်စုာ်အတၢ်ကိၢ်ထိၣ်ယံာ်ပှဲၤသိလဲၣ်အိၣ်စ့ၢ်ကီးဧါ (ကွၢ်လၢတနံၤဘၣ်တနံၤအတၢ်ကွဲးနီၣ်အလံာ်က့ၤပူၤ)	☐ YES	☐NO
5	Are there more than 5 consecutive days without activity[6] in the logbook? လၢတၢ်ကွဲးနီၣ်အလံာ်ပူၤန့ၣ်တၢ်ကွဲးနီၣ်ကွဲးယၢလီၤဟိ(တၢ်ဟူးတၢ်ဂဲၤတအိၣ်)အါန့ၢ်ဒံး ၃ သီ အိၣ်ဧါ	☐ YES	☐NO

1. Comment or suggestions from malaria post worker.
    တၢ်ကွၢ်တၢ်ညီၢ်ကသံၣ်ဒၢးအပှၤမၤတၢ်ဖိတဖၣ်အတၢ်ထံၣ်(မ့တမ့ၢ်)တၢ်ဟ့ၣ်ကူၣ်ဟ့ၣ်ဖး

    _____
    _____
    _____
    _____

2. Comments or suggestion from the observer.

    ပှၤလဲၤလီၤသမံသမိးတၢ်အတၢ်ထံၣ်(မ့တမ့ၢ်)တၢ်ဟ့ၣ်ကူၣ်ဟ့ၣ်ဖး

    _____
    _____
    _____
    _____

    Name (ပှၤသမံသမိးတၢ်အမံၤ) : _____

    Signature (ပှၤသမံသမိးတၢ်ဆဲးလီၤစုမုၢ်ကျၢၢ်) : _____

    Date (မုၢ်နံၤမုၢ်သီ) : _____

---

[6] Activity = (case of fever) တၢ်ဟူးတၢ်ဂဲၤ (ပှၤလီၤကိၢ်ဟဲဒုးနဲၣ်အသးအနီၣ်ဂံၢ်)

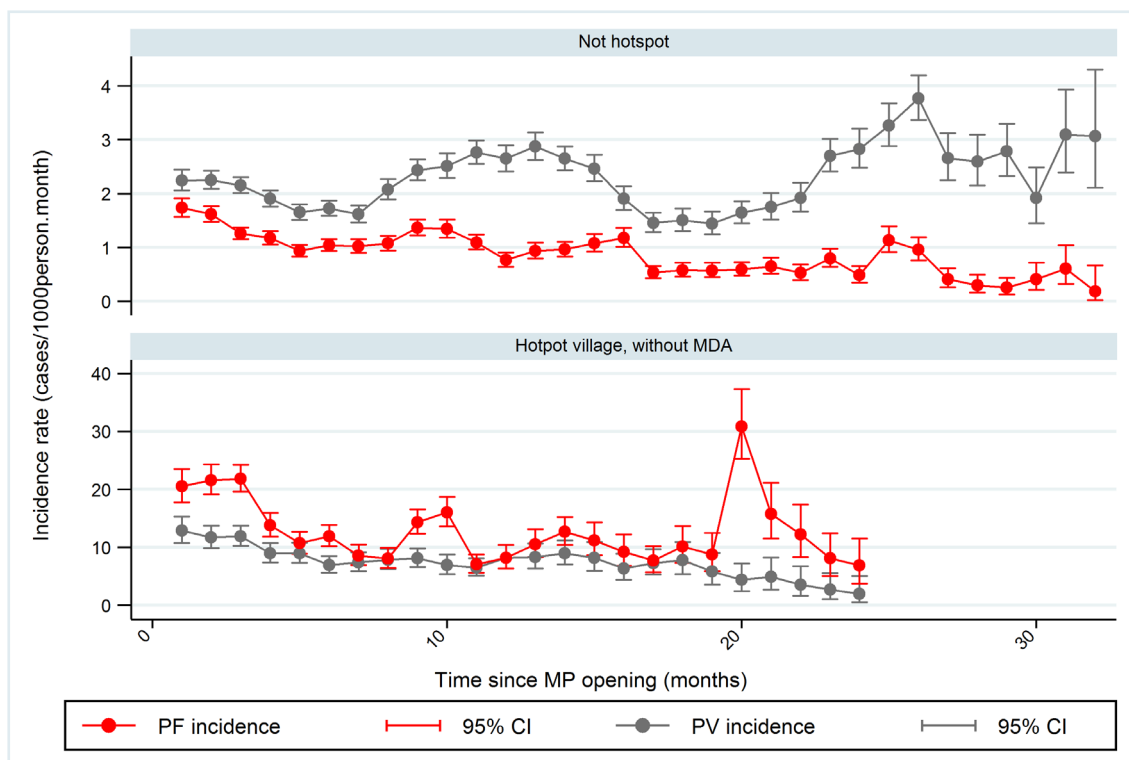*FIGURE 26: Monitoring and evaluation form (page 2)*

Figure 27: Average incidence rate of falciparum and vivax clinical malaria episodes according to the duration of MP functioning for all non-hotspot villages and 56 hotspot villages (before MDA). Range for y-axis is 0-4 for non hotspot villages and 0-40 for hotspots.

REFERENCES

Amaratunga, Chanaki et al. 2016. "Dihydroartemisinin-Piperaquine Resistance in Plasmodium Falciparum Malaria in Cambodia: A Multisite Prospective Cohort Study." The Lancet Infectious Diseases.

Ariey, Frédéric et al. 2014. "A Molecular Marker of Artemisinin- Resistant Plasmodium Falciparum Malaria." Nature 505(7481):50–55.

Chaumeau, V. et al. 2016. "Comparison of the Performances of Five Primer Sets for the Detection and Quantification of Plasmodium in Anopheles Vectors by Real-Time PCR." PLoS One 11(7):e0159160.

Dondorp, Arjen M. 2016. "New Genetic Marker for Piperaquine Resistance in Plasmodium Falciparum." Lancet Infectious Diseases epub ahead.

Eichner, M. et al. 2001. "Genesis, Sequestration and Survival of Plasmodium Falciparum Gametocytes: Parameter Estimates from Fitting a Model to Malariatherapy Data." Transactions of the Royal Society of Tropical Medicine and Hygiene 95(5):497–501.

Garros, C., L. L. Koekemoer, M. Coetzee, M. Coosemans, and S. Manquin. 2004. "A Single Multiplex Assay to Identify Major Malaria Vectors within African Anopheles Funestus and the Oriental An. Minimus Groups." Americal Journal of Tropical Medicine and Hygiene. 70(6):583–90.

Imwong, Mallika et al. 2014. "High-Throughput Ultrasensitive Molecular Techniques for Quantifying Low-Density Malaria Parasitemias." Journal of clinical microbiology 52(9):3303–9.

Imwong, Mallika et al. 2015. "The Epidemiology of Subclinical Malaria Infections in South-East Asia: Findings from Cross-Sectional Surveys in Thailand–Myanmar Border Areas, Cambodia, and Vietnam." Malaria Journal 14(1):381.

Landier, Jordi et al. 2016. "The Role of Early Detection and Treatment in Malaria Elimination." Malaria Journal 1–8.

Luxemburger, C. et al. 1997. "The Epidemiology of Severe Malaria in an Area of Low Transmission in Thailand." Transactions of the Royal Society of Tropical Medicine and Hygiene 91(3):256–62.

Lwin, Khin Maung et al. 2015. "Elimination of Plasmodium Falciparum in an Area of Multi-Drug Resistance." Malaria Journal 14:319.

Manguin, Sylvie, ed. 2013. Anopheles Mosquitoes - New Insights into Malaria Vectors. Rijeka, Croatia: InTech.

Minkler, Meredith and Nina Wallerstein, eds. 2008. Community-Based Participatory Research for Health: From Process to Outcomes. 2nd ed. Jossey-Bass.

Naing, Saw Yan. 2016. "Thousands Flee, Casualties Reported in Karen/Kayin State Conflict." The Irrawaddy, September.

Oo, Thin Thin. 2003. "The Biology and Vector Competence of the Anopheline Mosquitoes of Myanmar with Special Consideration of Anopheles Dirus." Ruperto-Carola University of Heidelberg, Germany.

Phyo, Aung Pyae et al. 2012. "Emergence of Artemisinin-Resistant Malaria on the Western Border of Thailand: A Longitudinal Study." The Lancet 379(9830):1960–66.

Price, Ric N. et al. 2004. "Mefloquine Resistance in Plasmodium Falciparum and Increased pfmdr1 Gene Copy Number." Lancet 364(9432):438–47.

Rattanarithikul, Rampa. 2006. "Illustrated Keys to the Mosquitoes of Thailand- Anopheles." Southeast Asian J Trop Med Public Health 37(Supplement 2):1–128.

Sinka, Marianne E. et al. 2011. "The Dominant Anopheles Vectors of Human Malaria in the Asia-Pacific Region: Occurrence Data, Distribution Maps and Bionomic Précis." Parasites & vectors 4(1):89.

South, Ashley. 2011. Burma's Longest War: Anatomy of the Karen Conflict.

Thanh, Ngo Viet et al. 2017. "Rapid Decline in the Susceptibility of Plasmodium Falciparum to Dihydroartemisinin–piperaquine in the South of Vietnam." Malaria Journal 16(1):27.

Walton, C. et al. 1999. "Identification of Five Species of the Anopheles Dirus Complex from Thailand, Using Allele-Specific Polymerase Chain Reaction." Medical and Veterinary Entomology 13(1):24–32.

Walton, C. et al. 2007. "Genetic Diversity and Molecular Identification of Mosquito Species in the Anopheles Maculatus Group Using the ITS2 Region of rDNA." Infection, Genetics and Evolution 7(1):93–102.

Ya-umphan, P. et al. 2016. "Anopheles Salivary Biomarker to Assess Malaria Transmission Risk along the Thailand-Myanmar Border." Journal of Infectious Diseases first publ.