Malaria Elimination Task Force
Activity Report Update
May 2014 – December 2019

Foreword

The Malaria Elimination Task Force (METF) was launched in 2014 to respond to the threat of drug resistant malaria, to reduce the burden of malaria, and to ultimately eliminate malaria from the communities in Karen/Kayin State, Myanmar.

As the Chairman of the Executive Committee of the METF I am proud to present you this status report which describes the activities and results of this programme from the 1st May 2014 to the 31st of December 2019.

Under the supervision of the Karen Ethnic Health Organization (Karen Department of Health and Welfare) and in collaboration with the Myanmar National Malaria Control Program (MNMCP) the dense METF network of over 1,200 malaria posts (MPs), operated by 1,500 health workers has provided malaria testing to over 500,000 fever cases and treatment to over 50,000 malaria positive cases.

Since the start of the elimination programme, there has been significant reductions in the burden of malaria, with the majority of the Karen State free from *Plasmodium falciparum* malaria at the end of 2019. This is a result of the dedication of the METF health workers to freeing their communities from the burden of malaria, and the Karen people's continued acceptance and uptake of services provided by these MPs.

I would like to mention here the gratitude of the Karen people to the Global Fund, the Bill & Melinda Gates Foundation and the Wellcome Trust for their great support in eliminating malaria in our communities.

Saw Diamond Khin,
Chairman
Malaria Elimination Task Force Executive Committee

Contents

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

This report in an update to the previous METF report (March 2018).

I. SUMMARY ACHIEVEMENTS: 1st May 2014 – 31st December 2019

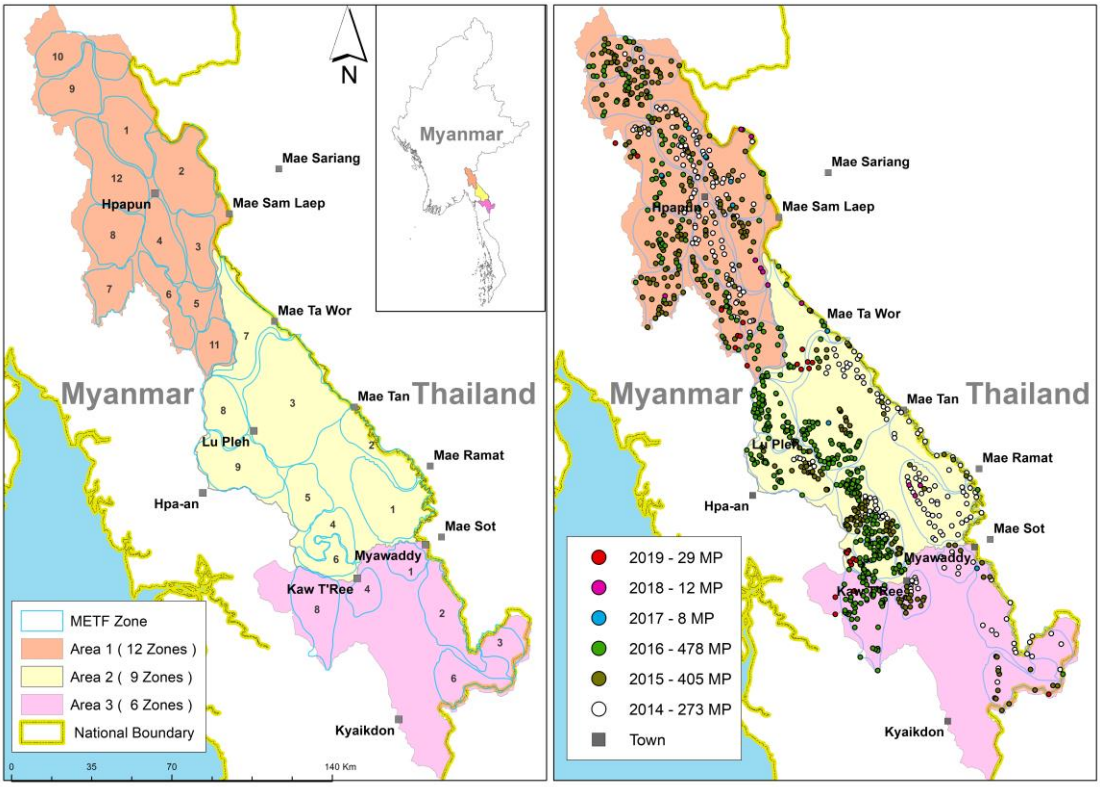

Figure 1. METF malaria posts operating as of December 2019 (n=1205).

Mapping and Geographic Information System (page 10):

The Geographic Information System and subsequent maps contain data from over 1,262 villages, spanning a geographic area of approximately 18002 km^2, divided into 3 areas (Area 1 = 6747 km^2; Area 2 = 6405 km^2; Area 3 = 4850 km^2) (FIG 1), with an estimated coverage population of 365,303 (95% CI: 352381.4 – 378223.2). There are important differences between the areas in terms of population density, settlement patterns, transportation capabilities, communication infrastructure and access to electricity and water. Over 95% of mapped villages in the area currently have an METF operated malaria post (MP) providing services to the community (FIG 1).

Community Engagement (page 10):
Despite decreases in malaria cases, the community engagement (CE) team continues to focus on the importance of early access to diagnosis and treatment and providing primary care to the population through existing MPs in the areas where the METF operates. The CE team organizes continuous training and supervision of malaria post workers (MPWs) to ensure effective functioning of MPs, as well as organizing community meetings. These meetings are important in developing implementation plans, as well as health events and exhibitions to disseminate health information to the public, provide health screenings, public health awareness campaigns, and allow the CE team to learn about community needs. In addition, the CE team has adopted a dialogue drama to convey messages, with the aim of delivering information and explaining the purpose of the METF, particularly where populations are predominantly illiterate and where conventional Information, Education and Communication (IEC) materials are less effective.

Malaria Posts (page 12):
As of 31st December 2019, more than 95% of the mapped villages in Hpapun, Myawaddy, Hlaingbwe and Kawkareik townships have a MP (FIG 1), with a total of 1,205 MPs in operation and a workforce of 1,436 MPWs, 133 MP supervisors and 24 Zone coordinators. Since the start of the programme there has been 68 months of activity from the 1st May 2014 to the 31st of December 2019. Over this period 517,206 fever cases presented to a METF MP, from which 517,111 were tested using a rapid diagnostic test (RDT).

Monitoring and Evaluation (page 13):
Since August 2016, the monitoring and evaluation (M&E) team has conducted 1,267 visits, with 991 individual MPs visited, and 276 MPs receiving more than one visit, not including those visited for case investigation. Out of the 991 MPs visited, 378 MPs were in Area 1, 463 in Area 2, and 150 in Area 3. MPWs who have received formal METF-training (92.8%) constitute the majority of MPWs. From the MPWs who have not received formal training, on the job training is provided by their MP supervisor or the previous MPW in the case of hand-over.

A total of 111 (9.2%) MPs reported no consultations for 3 or more consecutive weeks in 2019, resulting in a targeted investigation to identify possible underlying problems. From those MPs investigated in Area 2 (51 MPs) and Area 3 (22 MPs) the most common issue found was a reduction in community usage of the MPs as a result of MPs providing only malaria diagnosis, with non-malaria fever presentations only receiving paracetamol. However, in Area 1 (38 MPs), no fever testing was most commonly linked to poorly functioning MPs. In response to the identified problems, an appropriate correction plan for each MP has been implemented involving either CE, upgrading of the MP to a village heath posts, or closure of the MP in the case of overlapping medical structures with relocation of resources to other areas.

Real Time Data Collection and Reporting (page 15):
Since 2014, 847 (67.1%) MPs have had no reporting gaps, 311 (24.6%) had at least one gap of one week, and 104 (8.2%) MPs have ever had a gap of longer than one

week between reports. Malaria epidemiological reports are generated monthly and circulated to METF partners, donors and stake holders.

Impact on Malaria (page 16):

The overall malaria incidence has continued to decrease in the period of March 2018 to December 2019 (FIG 2). The total RDT-positivity across the METF network over the 68 months of operation was 11.7% with 16,982 *P. falciparum* cases and 43,835 *P. vivax* cases diagnosed. In 2019 alone the RDT-positivity rate was 9.3% with an annual blood examination rate (ABER) of 21.7%, which remains above the WHO recommended ABER of >10%. Overall, MPs reported eight malaria related deaths: 2 in 2014, 3 in 2015, 1 in 2016, 1 in 2017, 1 in 2018 and no malaria death reported in 2019. MPs also reported 52 severe cases, most of which also occurred in 2014 (54%), followed by a steep decline with only two severe cases reported for 2019. From all females with a positive RDT result, 3.2% were pregnant, with 1.8% of *P. falciparum* and 3.7% of *P. vivax* diagnosed in pregnant women.

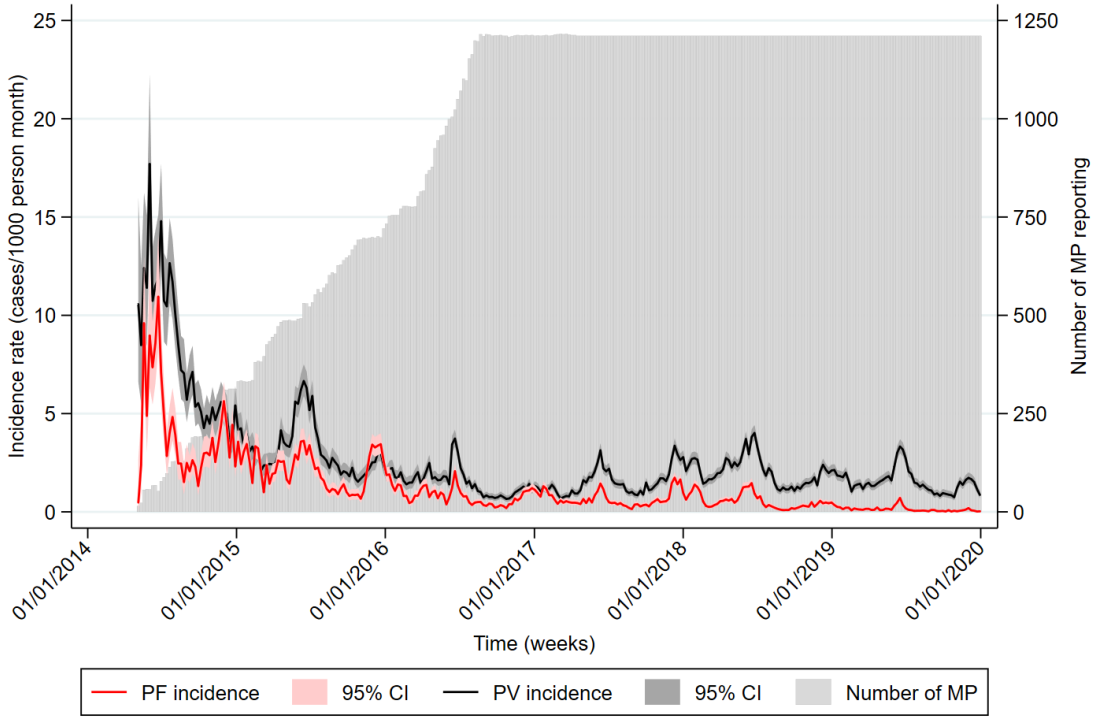

Figure 2. Number of reporting malaria posts, and incidence of *P. falciparum* and *P. vivax* malaria from 2014 to 2019.

The yearly *P. falciparum* incidence across all areas has seen dramatic decreases since 2014. From 2014 to 2019 the yearly *P. falciparum* incidence in Area 1 has decreased by 93.8% (from 106.8 to 6.6 cases per 1,000-person years), and in Areas 2 and 3 has decreased by more than 99%, reaching the WHO defined elimination threshold (<1 case/1,000-person years) after just 2 years of the programme in 2016 with continual decreases thereafter. As of December 2019, 83.6% of the villages in METF target region are under or have reached the WHO threshold of elimination for *P. falciparum*. In addition, 83.5% of all villages reported no *P. falciparum* cases in 2019.

These decreases in incidence are specific to *P. falciparum,* with less significant decreases in *P. vivax* incidence over the same period (FIG 2). This is explained by the low usage of primaquine for radical cure due to the high proportion of G6PD deficiency in the region. However, a key activity for 2020 is the deployment of G6PD point of care testing in villages, allowing for safe radical cure with primaquine.

Aside from providing early diagnosis and treatment, there have been two additional targeted interventions deployed by the METF programme: mass drug administration (MDA) and mass screen and treat (MSAT). MDA was first used with success in 2015, and then in 2016 and 2017 in 73 MPs selected for their high prevalence in sub-microscopic carriers (hotspots). The total number of clinical *P. falciparum* episodes originating from hotspots was reduced 5-fold after MDA with no observed rebound. MDA, in combination with MP services, had a rapid and sustained impact on the reservoir of *P. falciparum* and on the incidence of clinical cases in hotspot villages. Following a ban on MDA by the National Malaria Program in Myanmar, in December 2018, METF implemented a MSAT programme in response to higher incidence peaks in a number of MPs in the previous year. MSAT was limited to 17 MPs based on previous incidence, however, due to low asymptomatic carriage detected by ultrasensitive RDT (uRDT) in these villages, a limited sample of the population received treatment, and thus MSAT provided little impact on the incidence of clinical *P. falciparum* episodes in these villages

Drug resistance (page 21):
Successful genotyping of 2,806 *P. falciparum* samples from 2014 to 2018 was conducted to determine the prevalence of Kelch 13 mutant (K13) parasites. No increase in Kelch13 has been observed in METF across the 4 townships of operation with accelerated malaria elimination interventions. There was no piperaquine resistance (plasmepsin2) detected in 2,621 samples analysed and multiple copies of the Pfmdr1 gene (a marker of resistance to mefloquine) was detected in only 2% (8/485) of samples in 2018.

Entomology (page 22):
Between January 2015 and July 2018, 121,190 *Anopheles* mosquitoes were collected over 3,272 person-nights and 378 cow-nights of collection. All specimens were identified by morphology. Of these, 12,033 mosquitoes were analysed by PCR in order to identify closely related *Anopheles* species and 26,883 were processed to detect *Plasmodium*-infected vectors. The abundance and species distribution were 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 (i.e. “residual” malaria transmission) probably accounts for the majority of transmission. These results also confirm the low infection and high biting rates of malaria vectors in the area. The mean entomological inoculation rate was 0.71 (95%CI= 0.48 – 1.00) and 0.84 (95%CI= 0.59 – 1.16) infective bites /person /month for *P. falciparum* and *P. vivax* respectively.

The impact of outdoor residual spraying (ORS) was evaluated in a trial conducted in 12 villages followed-up for 9 months (3 months of baseline and 6 months of post-intervention follow-up). To date, ORS has shown promising results with a significant decrease in human biting rate compared to the non-intervention villages.

Conclusion

Over the past five and a half years, the METF programme has been implemented with success in five townships of Karen/Kayin State in Eastern Myanmar. Given the rate of decline of *P. falciparum* cases, the programme is on track to achieve its target of *P. falciparum* elimination by the end of 2020. This success is attributed to the fact that the project is imbedded within the communities it serves, it is evidence-based, reactive, adaptable and responsive. In addition to the results in the field, the programme has generated important evidence that should be used elsewhere: the crucial role of functioning MPs and effective CE, the importance of the sub-microscopic reservoir in the transmission of malaria, key data on vector bionomics, and the role of targeted MDA in accelerating elimination. Importantly, the elimination of *P. falciparum* has not resulted in the worsening of drug resistance. The results of the METF project provide clear evidence that the rapid elimination of *P. falciparum* is possible in Eastern Myanmar.

II. BACKGROUND

The METF was set up in 2014 to conduct a large-scale project for *P. falciparum* elimination in 4 townships (Hpapun, Myawaddy, Hlaingbwe, and Kawkareik) of Eastern Myanmar (Karen/Kayin state). The executive committee composed of one representative of local NGOs/CBOs (KDHW, MTC, BPHWT, BMA, KBGF, KPC, KKO, SMRU)[1].

A structure has been developed by the Executive Committee to facilitate communications, logistics, reporting, supervision and management (FIG 3).

- The project region is large and is divided into three '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.
- 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, an epidemiologist, a mapper, and a medical coordinator.
- This central coordination team is headed by the SMRU director and is based in Mae Sot (Thailand). SMRU provides logistical support, data management, grant management and laboratory support.

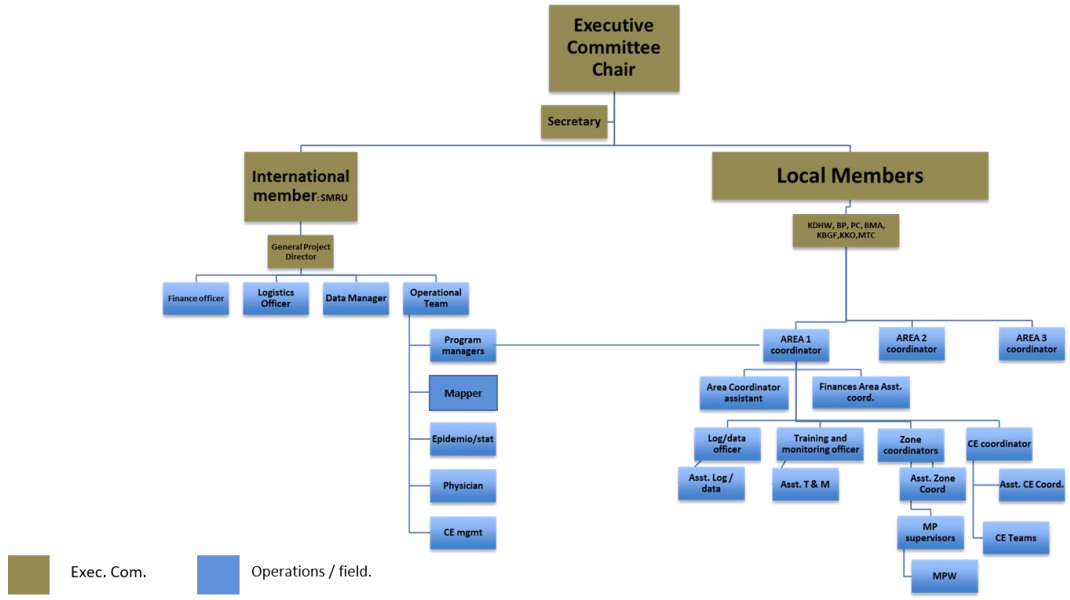

Figure 3. The METF organogram.

[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.

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 METF is to assess the feasibility of eliminating *P. falciparum* rapidly in the context of increasing and spreading artemisinin resistance, and the subsequent failures of ACTs in the region (1–3). It is endorsed by the Ministry of Health of Myanmar and the Karen Department of Health and Welfare (KDHW) and is approved by the Ethics Committee of the Myanmar Department of Medical Research. This report presents an update on the components of the elimination strategy and the results after 68 months of operation.

III. RESULTS

A. Mapping and Geographic Information System

Logistics results

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

Geography, settlement demography and rough development indicators

Overall 1,262 villages and hamlets have been mapped in the target area, spanning approximately 18002 km^2 divided into 3 areas (Area 1 = 6747 km^2; Area 2 = 6405 km^2; Area 3 = 4850 km^2). A GIS database clean-up process was started through a systematic review of all points corresponding to villages visited by the M&E team and 1,262 villages were remapped during monitoring visits between 2018 and 2019.

Figure 4. Programme map showing METF Areas and Zones.

B. Community Engagement

Despite the decreasing number of malaria cases the CE team continues to ensure that MPs are providing early access to diagnosis and treatment in the areas where the METF operates. The CE strategy utilized by METF was developed in collaboration with social scientists (4).

As a good relationship between project implementers and communities is crucial to the programme's success, the CE team works collaboratively with the local authorities, community members and partner organizations on malaria and other aspects of health services. The CE activities include training workshops, community meetings, health-related events, and exhibitions to promote and enhance the understanding of the METF programme.

Training workshops

Continuous training and supervision are given to the MPWs to ensure effective functioning of the MPs. The training workshops equip the MPWs with knowledge of correct malaria treatment, the use and interpretation of RDTs, as well as stock management of antimalarial drugs and medical supplies.
These sessions also allow the CE trainers to gain insight into the challenges encountered by the MPWs regarding their individual capacity and factors affecting their performance. This enables the CE trainers to identify where individuals need support in terms of strengthening their confidence, motivation and competence.

Community meeting and consultations

Misconceptions about the implemented activities can hinder participation in the programme, therefore, greater understanding of the METF activities is provided through community meetings and consultations with local authorities, leaders and community members. In the beginning and throughout the intervention periods, the CE team seeks consultation with community members in the development of implementation plans for proposed activities to ensure the approach is appropriate for the communities.

Health events and exhibitions

Collaboration and partnership are also fostered through health events and exhibitions where the METF team and partner organizations disseminate health information to the public, provide health screenings, raise awareness and learn about community needs.

Translating health messages to the community remains challenging, particularly in communities where the population is predominantly illiterate. In early 2019, the CE team developed a dialogue drama, aiming to deliver information and the purpose of the METF activities to the communities, separate from the usual IEC materials.

The dialogue drama was very well received by the communities. It was not only able to attract community attention as the audiences find it clear, entertaining and informative, but also created a sense of programme ownership and community involvement resulting in high participation in the events.

C. Malaria Posts

Over the course of the programme, 1,262 MPs have provided services to the villages in the METF area and have reported information on consultation numbers, number of *P. falciparum* and *P. vivax* cases, number of cases treated (by age and gender), number of malaria related deaths, severe cases, and number of malaria cases in pregnant women. As of the 31st December 2019, the METF MP

network is comprised of 1,205 MPs covering 95% of mapped villages in Hpapun, Myawaddy, Hlaingbwe and Kawkareik townships (FIG 1). Over the 68 months of operation from May 2014 to December 2019, 517,206 fever cases have presented to a METF MP, from which 517,111 fevers were tested using an RDT.

Overall, 81% of consultations occurred within 48h of fever onset, 13% of consultations occurred between two and three days and less than 6% after three days. This means that the majority of *P. falciparum* clinical cases received treatment prior to becoming infectious (before gametocyte production), therefore contributing to the reduction in malaria transmission.

Refresher and upgrade training

As of 2019, a total of 1,436 MPWs, 133 MP supervisors, and 24 Zone coordinators provide METF services. An annual refresher training course on malaria case management and reporting is provided to MPWs in METF to maintain a high quality of MP services. In 2019, 42% (511/1,205) of the MPs received the refresher training.

In order to maintain community attendance to MPs in the face of decreasing malaria transmission, a community integrated malaria volunteer (ICMV) upgrade training programme was provided to 572 MPWs in 2019. The integrated package included training in screening and referral of TB, HIV, leprosy, and filariasis, as well as a first aid kit, ferrous and vitamin supplements. However, the impact of this integrated package on MP attendance requires further assessment.

Mass LLINs distribution campaign

Between 2015 and 2017, 60,000 long-lasting insecticidal nets (LLINs) were distributed across all METF areas. Additionally, between March and December 2019 a mass LLINs distribution campaign was completed in Area 1 as part of national mass LLIN campaign which distributed 56,195 insecticide treated nets to a population of 126,171 residing in 486 villages.

D. Monitoring and Evaluation

A dedicated field team has performed routine M&E of MP performance since August 2016, with the aim of obtaining information on MP activity and functioning (5). These M&E visits are essential in monitoring service uptake, diagnosis and treatment availability, and MPW performance and knowledge. Selecting MPs for M&E visit is either random or based on suspected issues found in routinely collected data. In 2019, targeted visits focused on monitoring stock distribution of ACT medicines and RDTs to MPs in the METF area as well as other suspected issues detected in routine weekly surveillance.

The M&E team collects information on MP stock management, training, supervisor visits, regularity of salary received, MP closure, and whether another medical structure operates in the area (see survey form in Appendix 1). Additionally, from 2017 the M&E team has used a treatment questionnaire (see questionnaire in Appendix 2) to collect information on MPW knowledge of correct malaria

treatment guidelines. This questionnaire has also been used at training sessions and meetings to capture information on Zone coordinator and MP supervisor knowledge.

Since August 2016, the M&E team has conducted 1,267 visits, with 991 individual MPs visited, and 276 MPs receiving more than one visit, not including those visited for case investigation. Out of the 991 MPs visited, 378 MPs were in Area 1, 463 in Area 2, and 150 in Area 3. MPWs who have received formal METF-training (92.8%) constitute the majority of MPWs operating MPs. The MPWs who have not received formal training, receive on the job training from their MP supervisor or the previous MPW in the case of MP hand-over.

Table 1. Monitoring and Evaluation indicators collected between August 2016 and December 2019.

Indicator	Proportion*	Percentage
MP operated by at least 1 trained MP worker	1,150/1,239	92.8%
Supervisor visit frequency in past 2 months		
0	426/1,245	34.2%
1	148/1,245	11.9%
2-3	241/1,245	19.4%
≥4	430/1,245	34.5%
Reporting Forms on site	1232/1,266	97.3%
MPW Manual on site	1238/1,266	97.8%
Regular salary received	1215/1,254	96.9%
Observed stock outs		
ACT or RDT	122/1,267	9.6%
ACT and RDT	12/1,267	0.9%
Reported stock out of >2 days in past month	83/1,227	6.8%
MP closure for >24 hours in past 2 months	276/1,239	22.3%

*Not all MPWs responded to all questions, resulting in varying denominators for indicator calculations.

Overall, 6.8% of MPW reported a stock out of ACT medicines or RDTs for more than 2 days in the month prior to survey. At the time of survey, there were more stock outs of ACT medicines (6.6%) than of RDTs (4%), and only 0.9% of visited MPs had no stock of both ACT medicines and RDT. An added benefit of M&E visits is that the M&E team carry with them supplies of ACT medicines and RDTs, which allows for on-the-spot stock replenishment when needed.

Between January 2017 and May 2019, MPWs and Area and Zone Coordinators completed 1,492 questionnaires to assess their knowledge of treatment protocols. From them, 635 METF staff completed the questionnaire once, and the remaining 857 METF staff repeated the questionnaire at least once.

On average MPWs responded correctly to 61.8% of the questions related to malaria treatment. Zone and Area coordinators performed slightly better than MPWs, with the average correct response percentage of 71.8%.

Targeted investigations

In September 2019 the METF team conducted an in-depth analysis of routinely collected data to identify MPs that had reported no consultations for three or more consecutive weeks. This analysis identified 111 (9.2%) MPs that the M&E team subsequently investigated to collect information on MP performance and possible reasons for the absence of reported consultations.

The main reason found in Area 2 (51 MPs) and Area 3 (22 MPs) was that MPs provide only malaria diagnosis and treatment, and non-malaria fevers only received paracetamol resulting in reduced attendance due to lack of non-malaria services provided. Whereas in Area 1 (38 MPs), the main reason for no consultations was functionality problems including new MPW with no training, delayed supply shipment and absence of MPW.

In response to this investigation, the METF programme managers have been in consultation with zone-coordinators to propose a tailored plan for each MP that involves either enhanced CE, upgrading of the MP to a village heath post, or closure of the MP in the case of overlapping medical structures.

This investigation highlights the community's demand for non-malaria fever interventions. Integration of other services delivered by the MPWs needs to be prioritized in the coming years to make efficient use of MPs as well to maintain the malaria surveillance network.

E. Real Time Data Collection and Reporting

One of the main contributing factors to the success of the METF programme is the data collection system, allowing for continual tracking of malaria cases, fast reactive case investigation and targeted M&E.

Of the total 1,262 MPs that have ever reported data, 524 (41.5%) reported by SMS and 738 (58.5%) reported by paper datasheets. From the 1,205 MPs reporting data in 2019, 686 (56.9 %) reported by SMS, and 519 (43.1%) reported by paper datasheets. The SMS system enables fast transmission of data from the field to the central office, typically within 1 week. However, paper reporting is still utilised mainly in Area 1 due to the lack of mobile network coverage and results in an additional 1-week lag in the receiving of data at the METF office.

To assess the effectiveness of the reporting system used, METF routinely monitors the number and duration of gaps between reports. Since 2014, 847 (67.1%) MPs have had no reporting gaps, 311 (24.6%) had at least one gap of one week, and only 104 (8.2%) MPs had a gap of longer than one week between reports.
Another measure of reporting system functioning is the time delay in receiving data. Across all available data, the median reporting delay was 4 days (interquartile range (IQR) = 1-8 days), with strong heterogeneity based on sending method. Reports sent via SMS had a median delay of 1 day (IQR = 0-2 days), and paper reports had a median delay of 8 days (IQR = 8-10 days).

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 4,076 records (14% of all records) for 27 variables and 110,052 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 (111/4,076 2.7%). In the remaining 3,965 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 687 MPs for the period of December 2015 and September 2019, corresponding to 10,742 RDTs. The median time between RDT performed by an MPW and quality control was 84 days. This 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 (~34% of tests affected for the *P. vivax* line only and ~29% of tests affected for both *P. vivax* and *P. falciparum* lines) and fading of control lines (~12%). From the 10,742 RDTs, 9,074 were read by an MPW as negative, 487 as *P. falciparum* positive, 8 as mixed infection (*P. falciparum + P. vivax)*, 1,023 as *P. vivax* positive, 19 as invalid, and 131 with unknown result. Of the 495 *P. falciparum* RDTs, 446 (90.1%) were confirmed by the QC as *P. falciparum* positive, and 17 (3.4%) were rechecked as *P. falciparum* negative. Of 1,031 *P. vivax* RDTs, 643 (62.4%) were confirmed by control as *P. vivax* positive, and 66 (6.4%) were rechecked as *P. vivax* negative. Overall the RDTs that could be rechecked, with no blood back flow or fading of the control line, correspond to a Kappa score of 0.88 indicating a good agreement of RDT results.

F. Impact on Malaria

Over the 68 months of operation, MPs diagnosed 16,982 *P. falciparum* cases and 43,835 *P. vivax* cases, resulting in a malaria RDT positivity of 11.7% with large seasonal and geographical variations. In 2019 alone, the RDT-positivity rate as 9.3% with an annual blood examination rate (ABER) of 21.7%, which remains above the WHO recommended ABER of >10%. The age of those diagnosed with *P. falciparum* was slightly higher than those diagnosed with *P. vivax* (see further results in Appendix 3). Moreover, the gender distribution was similar between *P. falciparum* and *P. vivax* with 42% and 41% females for each diagnosis respectively. Out of all females diagnosed with malaria a total of 3.2% were pregnant. Of those pregnant women 1.8% were diagnosed with *P. falciparum* and 3.7% were diagnosed with *P. vivax* (Table 2).

Table 2. Distribution of age and gender by malaria diagnosis over 68 months.

		Diagnosis; % (proportion)		
		P. falciparum	***P. vivax***	**Total**
RDT positivity		3.3 (16,982/518,860)	8.5 (43,835/518,860)	11.7 (60,817/518,860)
Age group	Child (<5 years)	17.3 (2,928/16,982)	26.4 (11,563/43,835)	23.8 (14,491/60,817)
	Adolescent (5-15 years)	38.4 (6,527/16,982)	40.1 (17,549/43,835)	39.6 (24,076/60,817)
	Adult (>15 years)	44.3 (7,527/16,982)	33.6 (14,723/43,835)	36.6 (22,250/60,817)
Gender*	Female	41.9 (7,054/16,854)	41.2 (17,654/42,841)	41.4 (24,708/59,695)
	Male	58.2 (9,800/16,854)	58.8 (25,187/42,841)	58.6 (34,987/59,695)
Pregnant women		1.8 (125/7,054)	3.7 (654/17,654)	3.2 (779/24,708)

*not all cases have information on gender.

Over the whole programme, there were eight malaria related deaths: 2 in 2014, 3 in 2015, 1 in 2016, 1 in 2017, 1 in 2018 and no malaria deaths reported in 2019. MPs also reported 52 severe cases, most of which also occurred in 2014 (54%), followed by a steep decline with only two severe cases reported for 2019.

Malaria clinical case incidence follow-up

Since the start of the programme, Area 1 has seen the majority (71.3%) of clinical cases with high seasonal variability with typically one incidence peak at the start of wet season (June-July) and one in the cold season (December). On the other hand, Areas 2 and 3 have lower incidence rates and a higher proportion of *P. vivax* cases with one dominant malaria peak at the start of wet season (FIG 5).

MP impact on malaria incidence

The significant decrease in *P. falciparum* incidence at village and regional levels is a result of MPs providing access to early diagnosis and treatment (EDT).

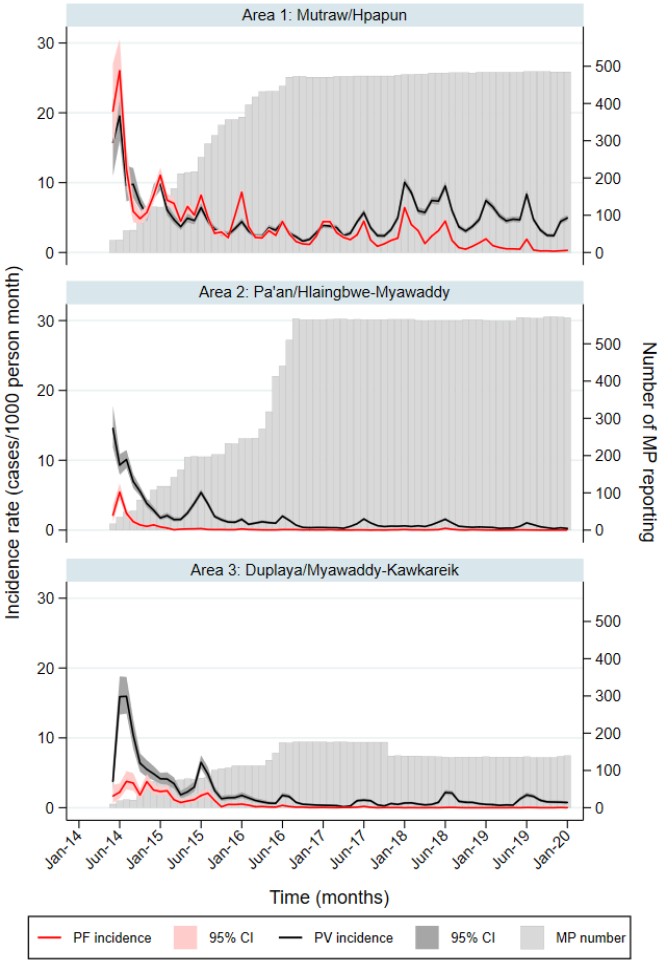

Figure 5. Incidence of *P. falciparum* and *P. vivax* malaria and number of reporting MPs from 2014-2019.

Generally, the number of *P. falciparum* positive cases has been highest during the first weeks of MP operation (FIG 6) and during the first malaria season. Across all MPs, the mean monthly incidence of *P. falciparum* was 5.4 cases per 1,000 persons in the first month of opening, with a much higher initial incidence in Area 1 with 13.5 per 1000 persons per month compared to Areas 2 and 3 which had an initial mean monthly incidence of 0.44 and 1.2 cases per 1,000 persons respectively. The overall yearly incidence by area has seen dramatic decreases. After 2 years of METF activities, Areas 2 and 3 achieved incidence below the WHO defined elimination threshold (<1 case/1,000-persons per year). Moreover, in Area 1 from 2014 to 2019, *P. falciparum* incidence has decreased by 93.8% from 106.8 to 6.6 cases per 1,000 persons per year (Table 3).

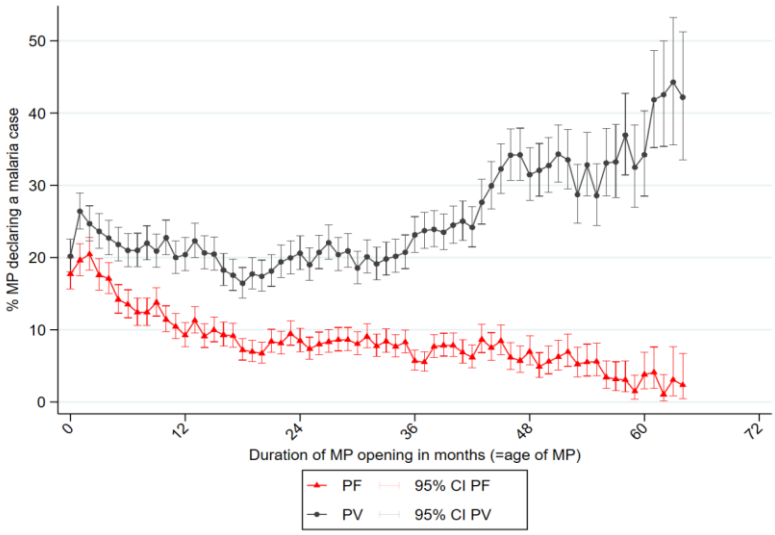

Figure 6. Percent malaria posts declaring *P. falciparum* or *P. vivax* cases according to their age.

Table 3. Decreasing yearly *P. falciparum* incidence across programme areas and year of operation.

	Yearly incidence (per 1,000 persons per year)					
	2014	2015	2016	2017	2018	2019
Area 1	106.8	65.0	31.3	33.2	26.0	6.6
Area 2	14.0	1.5	0.56	0.33	0.72	0.10
Area 3	31.3	6.5	0.76	0.15	0.11	0.08

These decreases in incidence are specific to *P. falciparum,* with less significant decreases in *P. vivax* incidence over the same period due to the inability to provide radical cure safely in a population where the prevalence of G6PD deficiency is high (6). However, a key activity for 2020 is the deployment of G6PD point of care testing in villages, allowing for radical cure with primaquine for those eligible based on G6PD status.

Progress towards elimination

Over the duration of the METF programme, an increasing proportion of MP equipped villages have reported yearly incidence rates under the WHO elimination threshold (FIG 7) from 35% in 2014 to 83.6% in 2019. Moreover, due

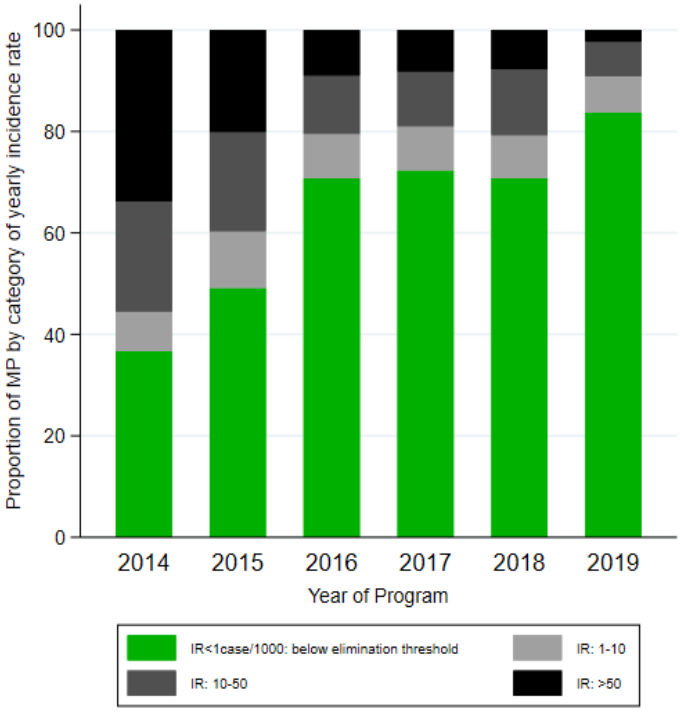

Figure 7. Proportion of malaria posts under the WHO elimination threshold (<1 case/1,000-person years).

to the small village size in the region, typically even small case numbers each year result in a yearly incidence greater than one case per 1000 persons per year, meaning the majority of those villages with an incidence rate below the elimination threshold in fact have **zero *P. falciparum* cases** over the year (FIG 8). The proportion of MPs reporting zero *P. falciparum* malaria cases has increased from 36% in 2014, 48.1% in 2015, 69.4% in 2016, 71% in 2017, 70% in 2018, and 83.5% in 2019.

The majority of MPs with no *P. falciparum* are located in Area 2 and Area 3 which have observed *P. falciparum* cases in only 3.3% (19/578) and 3.5% (5/141) of their respective MPs in 2019 while maintaining an annual blood examination rate of 15.6% and 14.4% in those MPs with zero PF cases in Area 2 and 3 respectively. As the villages in the METF network reach elimination targets it is essential to maintain ongoing M&E as well as reactive case investigation to determine case origin to prevent further transmission.

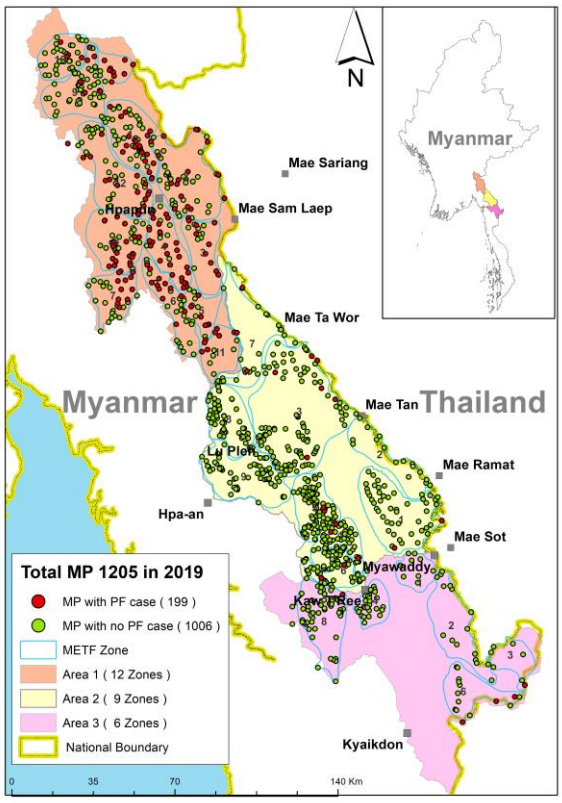

Figure 8. Map of MPs based on presence of *P. falciparum* cases in 2019. Malaria posts with *P. falciparum* cases (n=199) are shown in red, and without (n=1006) are shown in green.

Update on integrated interventions

Aside from providing early diagnosis and treatment, there have been two additional targeted interventions deployed by the METF programme. Mass drug administration (MDA) was first done with success in 2015, and then in 2016 and 2017 in 73 MPs selected for the high proportions of sub-microscopic carriers (hotspots). In this programme, targeted MDA has accelerated the decline in *P. falciparum* incidence (FIG 9). Prevalence surveys conducted 12 months post MDA and the entomological data showed that this is likely a result of reducing the

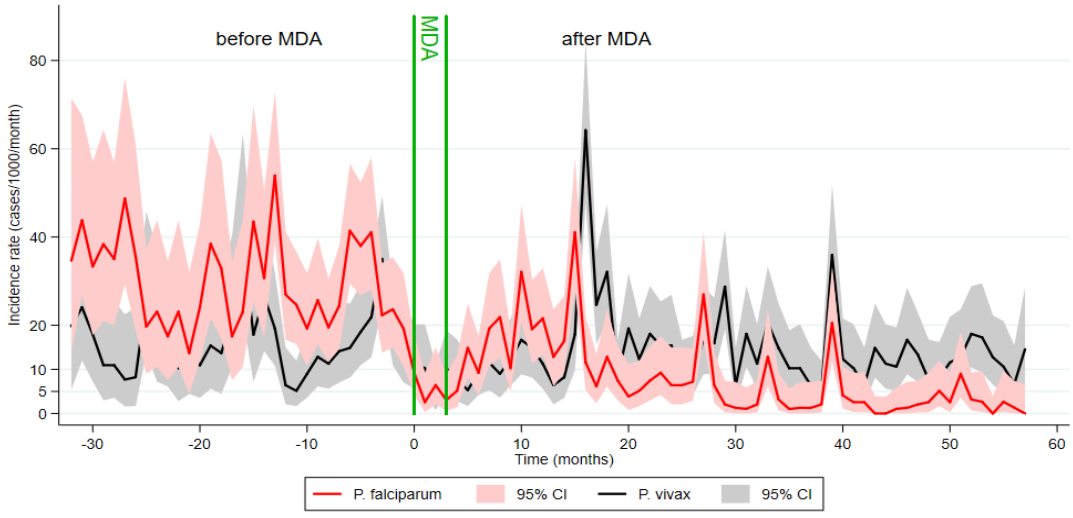

Figure 9. The mean monthly incidence of *P. falciparum* and *P. vivax* in MDA villages before and after intervention.

asymptomatic carriage and the sub-microscopic reservoir (7). The total number of clinical *P. falciparum* episodes originating from hotspots was reduced 5-fold after MDA and no rebound was observed.

In December 2018, METF implemented a mass screen and treat (MSAT) programme in response to higher incidence peaks in the selected MPs in the previous year, and following a ban on MDA by the National Malaria Control Programme. MSAT was limited to 17 MPs reporting a high incidence, however, due to low asymptomatic carriage detected by ultrasensitive RDT (uRDT) in these villages at time of survey, a limited number of people received treatment, and thus MSAT provided little impact on the ongoing incidence of *P. falciparum* in these villages (FIG 10). These villages remain continually monitored as part of the routine weekly data analysis.

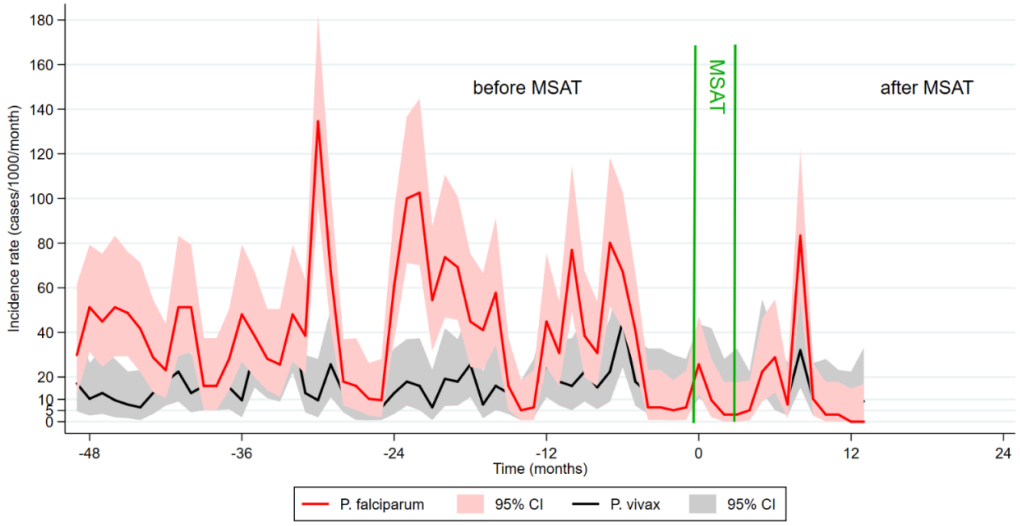

Figure 10. The mean monthly incidence of *P. falciparum* and *P. vivax* in MSAT villages before and after intervention.

Malaria case investigation and response

Malaria case investigation is carried out in villages that have reached the *P. falciparum* elimination threshold (in Area 2 and 3) with the aim of preventing importation of *P. falciparum* using case information found in the routine weekly analysis. Additional measures to enhance elimination efforts include reactive screening and treatment, bed nets distribution, continuous alerts from MPs on cases detected and stock management.

In 2019, a total of 30 *P. falciparum* cases were reported in Areas 2 and 3, with investigation carried out in 90% (27/30) of cases (20 in Area 2 and 7 cases in Area 3). Results from these investigations showed that 86% (n=23) of the cases were imported (either a resident from another village, travelling out of village, or forest going activity), 7% (n=2) were indigenous case, and another 7% (n=2) could not be classified. In Area 1, 32 cases were investigated from 19 outbreak alerts triggered by the weekly surveillance system. Outbreak investigations provide an assessment of reported malaria cases, functionality of MPs, village related information including accessibility, transportation, movement of populations, and the political situation such as conflicts in the area. However, due to the subsequent

decline in malaria incidence in all villages, no additional interventions were required except for 1 village where the MPW had reported false positive RDT results. This MPW was retrained in malaria diagnostics and case management. Timely investigation of cases and appropriate response reduce the risk of reintroduction and outbreaks of *P. falciparum* in those villages. This highlights the important of a robust surveillance system and quick response to maintain the elimination status of the village during the malaria elimination period.

G. Drug resistance

Molecular marker of artemisinin resistance: Kelch 13 alleles distribution

From 2014 to 2018, 2,806 *P. falciparum* samples were successful genotyped to assess the prevalence of Kelch 13 mutant parasite prevalence (FIG 11). The proportion of all analysed samples that were K13 mutants in the 3 METF areas was 61% (157/258) in 2014, 63% (52/82) in 2015, 57% (295/517) in 2016, 60% (870/1446) in 2017 and 58% (291/503) in 2018 (FIG 12). Therefore, no increase in the proportion of Kelch 13 mutant parasites between 2014-2018 was observed (see Table S1 in Appendix 3).

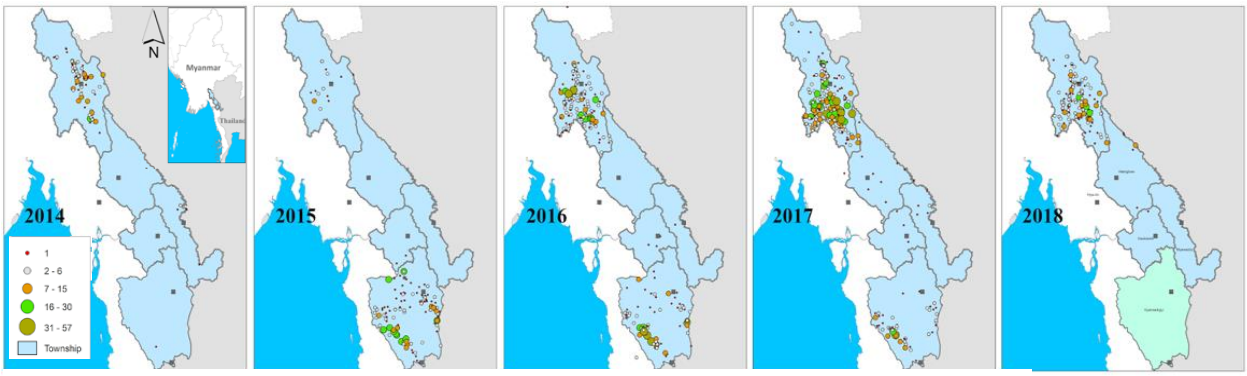

Figure 11. Genotyped samples distribution map (2014-2018).

In the MDA villages, 338 samples were collected before and 478 samples were collected after MDA. In these samples, the proportion of K13 mutants decreased from 62% before MDA to 54% after MDA. These figures indicate that MDA did not result in a worsening of artemisinin resistance. Interestingly, the most common allele is F446I and not C580Y like in western Cambodia or on the Thai Myanmar border before 2014 (see Table S2 in Appendix 3).

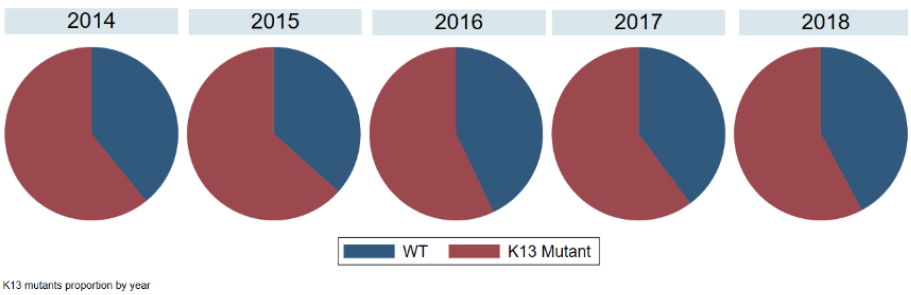

Figure 12. Proportion of K13 mutants (2014-2018).

Molecular markers of partner drug resistance: Pfmdr1 (associated with mefloquine resistance) and plasmepsin 2 (associated with piperaquine resistance) amplification

In the METF area, there has been a very low proportion of isolates with Pfmdr1 multiple copy number: 3% (24/666) in 2016, 4% (57/1389) in 2017 and 2% (8/485) in 2018 (FIG 13). There was no piperaquine resistance molecular marker (plasmepsin2) detected out of 2,621 samples analysed in 2018. This indicates that the intensive use of DHA-piperaquine (for MDA) and of artemether-lumefantrine (first line treatment of clinical cases) has not worsen the resistance to these ACTs.

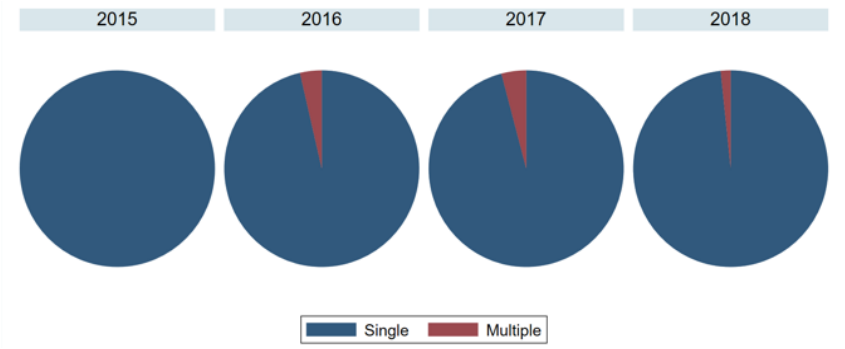

Figure 13. Proportion of pfmdr1 mutants by year (2015-2018).

H. Entomology

Entomological intelligence

Entomological investigations were carried out in 43 hotspots between January 2015 and July 2018 in order to document the diversity, vectorial status and host seeking behaviour of *Anopheles* mosquitoes. We report the occurrence of 35 *Anopheles* species of which 9 were identified as a vector of *P. falciparum* and/or *P. vivax* (Table S3). The mean human-biting rate was 572 bites /person /month (95%CI= 567 – 578). The mean infection rate in the mosquito populations was 0.12% (95%CI= 0.08 – 0.17) and 0.15% (95%CI= 0.10 – 0.20). Unlike previously thought, co-infection with *P. falciparum* and *P. vivax* was relatively frequent: 5/63 *Plasmodium*-infected mosquito specimens carried both malaria parasite species. The mean number of parasites per infected mosquito was less than 100, suggesting that most infections came from a single oocyst. The mean entomological inoculation rate was 0.71 (95%CI= 0.48 – 1.00) and 0.84 (95%CI= 0.59 – 1.16) infective bites /person /month for *P. falciparum* and *P. vivax* respectively. A high prevalence of submicroscopic malaria and human-biting rates were associated with an increase in *P. falciparum* and *P. vivax* entomological inoculation rate (7). There was no association between the incidence of clinical cases and the entomological inoculation rate (Tables S4 and S5). Using mosquito biting profiles determined during the surveys and simulated data on human behaviour, we estimated that the median predictive efficacy of mosquito bed-nets against the bites of malaria mosquitoes happening at night inside the villages was 53% (IQR= 37 – 61). The median predictive efficacy of mosquito bed nets ranged between 5% against the bites of *An. sawadwongporni* and 62% against the bites of *An. minimus*. The median predictive efficacy of mosquito bed-nets varied between

10% and 68% according to the village. Zoophagy, and not only outdoor and early human-biting, were also identified as an important limiting factors of mosquito bed net impact on the total blood resource available to mosquitoes (FIG 14).

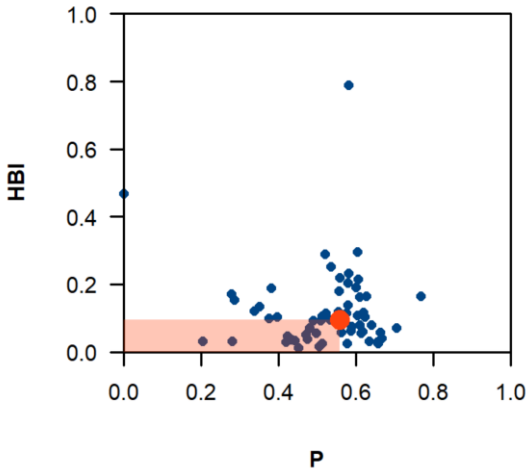

Figure 14. Impact of universal coverage with mosquito bed nets on the total blood resource available to malaria mosquitoes in Kayin state, Myanmar. The orange point represents the median predictive efficacy of mosquito bed nets (P) and human-biting index (HBI) of the mosquito populations collated by survey. P was defined as the proportion of blood meals taken on humans that is prevented by universal coverage with mosquito bed-nets. The HBI was defined as the human-biting rate divided by the sum of the human biting rate and cow-biting rate estimated during the surveys. Orange-shaded area shows the combined contribution of both parameters to overall blood source coverage provided by mosquito bed nets.

Phase development of outdoor residual spraying (ORS)

Laboratory experiments were then conducted in order to characterize the duration and magnitude of residual insecticidal effects of insecticide mists applied to outdoor vegetation (Figures S1 and S2). We observed long-lasting residual effects up to 42 and 90 days during the rainy and dry season respectively. The impact of outdoor residual spraying (ORS) was further evaluated in an entomological trial conducted in 12 villages followed-up for 9 months (3 months of baseline and 6 months of post-intervention follow-up). ORS with lambda-cyhalothrin was carried out in 6 villages in October 2019 and 6 villages were used as controls. Malaria mosquitoes were captured at one-month intervals in each village in order to document the biting-rate, blood seeking behaviour and insecticide resistances. Using model output, we estimated that the human-biting rate of malaria mosquitoes was divided by 9.6 immediately after the intervention (95% CI= 3.91 – 9.8) and remained lower in the sprayed villages than in the controls for the entire follow-up (FIG 15A). ORS was associated with a transient decrease in mortality rate of wild malaria mosquitoes against lambda-cyhalothrin (FIG 15B). The incidence of falciparum malaria was zero hence precluding the estimation for ORS impact on falciparum malaria. The incidence of vivax malaria was zero in the sprayed villages for 2 months after the intervention but not in the control villages, suggesting an impact of the intervention on the transmission of vivax malaria (FIG 15C). ORS was deployed for malaria elimination operations in 12 hotspots of falciparum malaria during June 2019. Intervention impact on the mosquitoes was monitored by carrying out mosquito captures before and immediately after the intervention using animal-baited traps. The median

reduction in mosquito biting rate observed immediately after the intervention was 67% (IQR= 56 – 76, range= 0 – 98) (Figure S3).

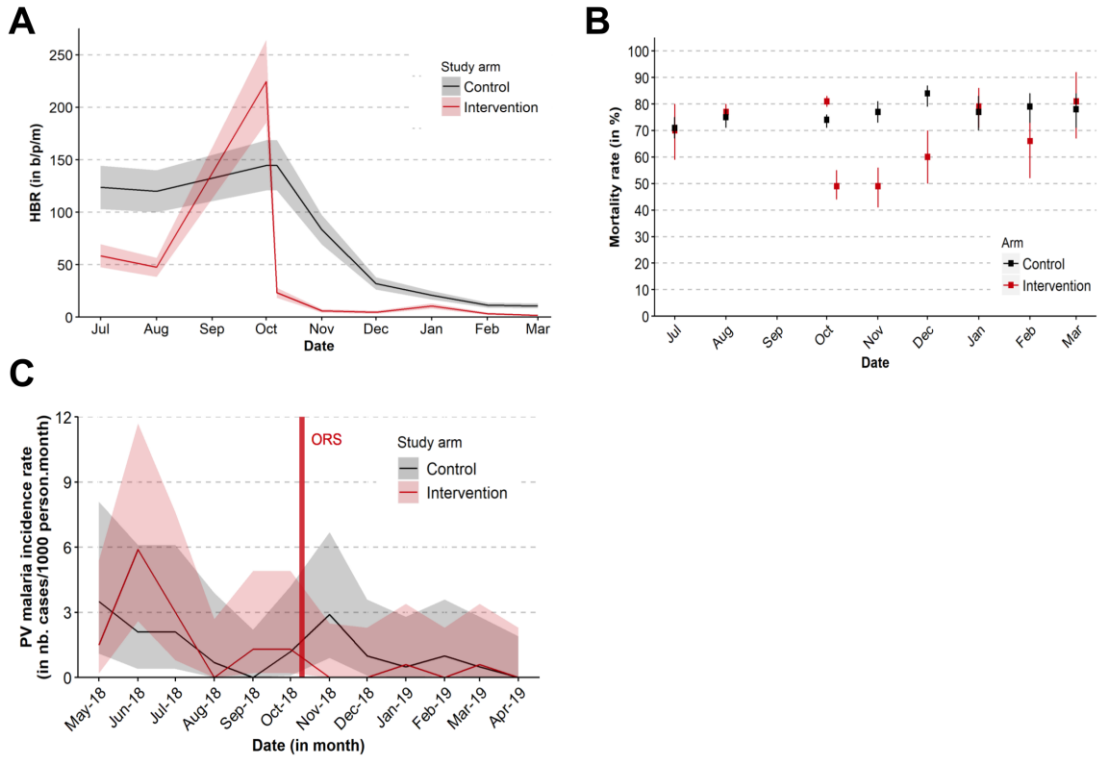

Figure 15. Preliminary analysis of the entomological trial on outdoor residual spraying entomological trial conducted in 12 villages in 2018-2019. (A) Evolution of the human-biting rate of malaria mosquito vectors in the control and sprayed villages (predicated with model output). Solid lines show the mean predicted human-biting rate of malaria mosquito vectors and shaded areas represent 95% confidence interval. (B) Evolution of mortality rate to lambda-cyhalothrin in mosquito populations in the control and sprayed villages determined with standard susceptibility test. Points show mortality rate estimated from pooled mosquito species and error bars indicate 95% confidence intervals. (C) Evolution of vivax malaria incidence in the control and sprayed villages. Solid lines show the mean incidence of vivax malaria and shaded areas represent 95% confidence interval.

IV. DISCUSSION

This report presents an update of the results of the METF programme from May 2014 to December 2019. The project's objective is to eliminate multi-drug resistant *P. falciparum* from five townships in the Karen/Kayin State of Eastern Myanmar bordering Thailand. This is a response to the threat presented by the emergence and spread of artemisinin resistance in *P. falciparum* and subsequent ACT failures (1–3). The results have been spectacular and as of to date, 83.6% of the 1,205 villages included in the programme in 2019, are below the elimination threshold as defined by the WHO and 83.5% of the villages reported zero *P. falciparum* clinical case in 2019. In Area 1, the most remote part of Karen State, the yearly incidence of *P. falciparum* has reduced by 93.8% between 2014 and 2019. Given the rate of decline in *P. falciparum* cases, the programme is on track to achieve elimination by December 2020. This is explained by the high community participation, the commitment of the partners (CBOs and EHOs), the impact of the MPs, the elimination of sub-microscopic reservoirs by MDA and perhaps to a certain extend by the mass distribution of LLINs. The real time reporting system has enabled rapid case investigations as well as the detection of non-functioning MPs and difficulties in the supply chain of RDTs and ACT medicines to MPs, allowing for a fast response to problems encountered. During the course of this programme, some essential evidence has been gathered, analysed and shared with the partners and the National Programme. The most important findings were published so they can be used by others. These findings relate to several key components of the elimination strategy: the impact of Early Detection and Treatment, the accelerating impact of MDA (8), the importance of MP monitoring (5), and the crucial role of CE (9). Precious data on the bionomics of the local malaria vectors and alternative vector-control measures (7,10–14) were also collected and analysed. It is therefore disappointing to see that none of these results are incorporated in the latest WHO supported National Malaria Control Strategic Plan of Myanmar. Importantly, the rapid elimination of *P. falciparum* from this area, has not translated so far into a worsening of drug resistance or into malaria resurgence or epidemics.

In 2020 we will have to complete the elimination of *P. falciparum* in the residual foci of transmission (mostly in the Hpapun Township) and develop a method to prove elimination. The absence of clinical cases does not demonstrate elimination, because some parasites can persist without symptoms for months or even years. METF will also concentrate on the elimination of *P. vivax* in this region. The strategy is likely to be different from that of *P. falciparum* elimination, due to the dormant liver stages of *P. vivax*. For this reason, the two species should not be pooled when reporting malaria cases, in the context of elimination. The elimination of *P. vivax* will involve the use of amino-8-quinoline drugs such as primaquine and/or tafenoquine. However, the use of these drugs implies the detection of G6PD deficiency as recommended by the WHO, to avoid potentially severe haemolysis in G6PD deficient individuals. In practice, METF will conduct Operational Research on the use of point of care testing of G6PD using rapid tests and biosensors, in order to administer these medicines safely. Another on-going project is looking at the usefulness of remote sensing imaging to localize areas at risk of malaria transmission and re-introduction. This work is conducted in

collaboration with the French development agency, Institut de Recherche pour le développement (IRD). Finally, METF will integrate other health projects in the same areas, related to maternal and child health, tuberculosis and non-malaria fevers, in order to diversify and strengthen the already existed MP network.

References

1. Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, et al. Artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med. 2009;
2. Imwong M, Suwannasin K, Kunasol C, Sutawong K, Mayxay M, Rekol H, et al. The spread of artemisinin-resistant Plasmodium falciparum in the Greater Mekong subregion: a molecular epidemiology observational study. Lancet Infect Dis. 2017;
3. Phyo AP, Ashley EA, Anderson TJC, Bozdech Z, Carrara VI, Sriprawat K, et al. Declining Efficacy of Artemisinin Combination Therapy Against P. Falciparum Malaria on the Thai-Myanmar Border (2003-2013): The Role of Parasite Genetic Factors. Clin Infect Dis. 2016;63(6):784–91.
4. Tangseefa D, Monthathip K, Tuenpakdee N, König A, Kajeechiwa L, Thwin MM, et al. "Nine Dimensions": A multidisciplinary approach for community engagement in a complex postwar border region as part of the targeted malaria elimination in Karen/Kayin State, Myanmar [version 2; referees: 2 approved]. Wellcome Open Res. 2019;3.
5. Rae JD, Nosten S, Proux S, Myint Thu A, Cho WC, Paw K, et al. The role of monitoring and evaluation to ensure functional access to community-based early diagnosis and treatment in a malaria elimination programme in Eastern Myanmar. Malar J [Internet]. 2019 Dec 22 [cited 2019 May 25];18(1):50. Available from: https://malariajournal.biomedcentral.com/articles/10.1186/s12936-019-2677-2
6. Bancone G, Chu CS, Somsakchaicharoen R, Chowwiwat N, Parker DM, Charunwatthana P, et al. Characterization of G6PD Genotypes and Phenotypes on the Northwestern Thailand-Myanmar Border. Rénia L, editor. PLoS One [Internet]. 2014 Dec 23 [cited 2019 Apr 21];9(12):e116063. Available from: https://dx.plos.org/10.1371/journal.pone.0116063
7. Chaumeau V, Kajeechiwa L, Fustec B, Landier J, Naw Nyo S, Nay Hsel S, et al. Contribution of Asymptomatic Plasmodium Infections to the Transmission of Malaria in Kayin State, Myanmar. J Infect Dis. 2019;
8. Landier J, Parker DM, Thu AM, Lwin KM, Delmas G, Nosten FH, et al. Effect of generalised access to early diagnosis and treatment and targeted mass drug administration on Plasmodium falciparum malaria in Eastern Myanmar: an observational study of a regional elimination programme. Lancet. 2018;
9. Kajeechiwa L, Thwin MM, Nosten S, Tun SW, Parker D, Von Seidlein L, et al. Community engagement for the rapid elimination of malaria: the case of Kayin State, Myanmar. Wellcome Open Res. 2017;2.
10. Chaumeau V, Andolina C, Fustec B, Ndam NT, Brengues C, Herder S, et al. Comparison of the Performances of Five Primer Sets for the Detection and Quantification of Plasmodium in Anopheline Vectors by Real-Time PCR. PLoS One. 2016;
11. Chaumeau V, Cerqueira D, Zadrozny J, Kittiphanakun P, Andolina C, Chareonviriyaphap T, et al. Insecticide resistance in malaria vectors along the Thailand-Myanmar border. Parasites and Vectors. 2017;

12. Kwansomboon N, Chaumeau V, Kittiphanakun P, Cerqueira D, Corbel V, Chareonviriyaphap T. Vector bionomics and malaria transmission along the Thailand-Myanmar border: a baseline entomological survey. J Vector Ecol. 2017;
13. Chaumeau V, Fustec B, Hsel SN, Montazeau C, Nyo SN, Metaane S, et al. Entomological determinants of malaria transmission in kayin state, eastern myanmar: A 24-month longitudinal study in four villages [version 3; peer review: 2 approved]. Wellcome Open Res. 2019;
14. Sawasdichai S, Chaumeau V, Dah T, Kulabkeeree T, Kajeechiwa L, Phanaphadungtham M, et al. Detection of diverse Wolbachia 16S rRNA sequences at low titers from malaria vectors in Kayin state, Myanmar. Wellcome Open Res [Internet]. 2019 [cited 2019 Dec 27];4:11. Available from: https://wellcomeopenresearch.org/articles/4-11/v4
15. Chaumeau V, Fustec B, Nay Hsel S, Montazeau C, Naw Nyo S, Metaane S, et al. Entomological determinants of malaria transmission in Kayin state, Eastern Myanmar: A 24-month longitudinal study in four villages. Wellcome Open Res. 2019 Jun 17;3:109.

V. APPENDIXES

***Appendix 1*. Malaria Post Assessment Sheet.**

Malaria Post Assessment

Village Name_____ Township_____ District _____State_____

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

Village GPS coordinates : LAT : _____ LONG : _____

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

TRAINING: Yes □ No□

RETRAINING: Yes □ No□

Name of MP Supervisor _____

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)

1	Was the MP closed for > 24 hours in last 2 months? 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?	□YES □NO	
3	Are there valid RDTs in the MP?	□YES □NO	
4	Were there >2 days out of stocks (RDTs or ACTs) in the past 4 weeks? --- Adequate or sufficient medication and supplies (observe and check carefully) SD biolines = tests ACT= tabs CQ = tabs PMQ = tabs Clindamycin	□YES □NO	If no, ask why
5	How are the results reported? □ SMS □ Paper □ Other (……..)		
6	Does the MPW receive regular financial incentive?	□YES □NO	
7	Is there another MP in the village?	□YES □NO	
8	If YES, specify the supporting organization		
8b	If Yes, do you receive malaria data from them?	□ YES □ NO	

[1] Malaria Post

[2] House that are inhabited

[3] Malaria Post Worker

9	How often did you receive the visit of your MP supervisor in the last 2 months? …… time(s)	□1 Per Month □<1 Per Month □>1 Per Month	

Assessment by Evaluator (Check - List)

1	Is there a Malaria Post Manual in the MP?	□ YES □NO
2	Are there reporting forms in the MP?	□ YES □NO
3	Is there a logbook (daily recording of individual patients) in the MP?	□ YES □NO
4	Are the "Days of fever" recorded for each patient? (Review the daily record sheets)	□ YES □NO
5	Are there more than 5 consecutive days without activity[1] in the logbook?	□ YES □NO

1. Comment or suggestions from malaria post worker.
   _____
   _____
   _____
   _____

2. Comments or suggestion from the observer.
   _____
   _____
   _____
   _____

Name: _____

Signature: _____

Date: _____

[1] Activity = (case of fever)

***Appendix 2*. Treatment questionnaire administered to malaria post workers, malaria post supervisors, and zone and assistant zone coordinators.**

1.	What is the correct treatment for pregnant patient diagnosed with *P. falciparum* during 1st trimester of pregnancy? a) Quinine + Clindamycin x 7 days (Q7C7) b) Co-artem + Primaquine (COA3 + PQ 1 time) c) Co-artem + Primaquine (COA3 + PQ 3 time) d) Chloroquine (CQ3)
2.	What to do if a patient vomits the drug more than 1 hour after taking it? a) Repeat the 1st dose again. b) Don't need to repeat the 1st dose c) Stop the treatment d) Change the treatment
3.	What is the correct treatment for pregnant patient diagnosed with *P. falciparum* during and 3rd trimester of pregnancy (between 3 — 9 months)? a) Co-artem + Primaquine (COA3 + PQ 1 time) b) Co-artem only (COA3) c) Chloroquine (CQ3) d) Quinine + Clindamycin x 7 days (Q7C7)
4.	Primaquine should be given to a) f trimester of pregnancy b) 2nd trimester of pregnancy c) Breastfeeding mother with child less than 6 months. d) None of above is true
5.	Treatment of *P. falciparum* in a patient who is allergic to coartem? a) Quinine + Clindamycin x 7 days (Q7C7) b) Chloroquine c) Primaquine d) No treatment
6.	What are anti-malaria drug dosage calculations based on a) Weight (kilogram — kg) b) Weight (pounds — lbs) c) Age (months) d) Age (years)
7.	What is the correct treatment for a non-pregnant patient (age > 5 months) diagnosed with mixed infection (*P. falciparum* & *P. vivax*). a) Co-artem + Primaquine (COA3 + PQ 3 time) b) Chloroquine (CQ3) c) Quinine + Clindamycin x 7 days (Q7C7) d) Co-artem + Primaquine (COA3 + PQ 1 time)
8.	What is the correct treatment for breast-feeding mother with 5 months old child diagnosed with *P. falciparum*? a) Quinine + Clindamycin x 7 days (Q7C7) b) Co-artem + Primaquine (COA3 + PQ 1 time) c) Co-artem + Primaquine (COA3 + PQ 3 time) d) Co-artem only

9.	Treatment of *P. falciparum* in a child under 5 years (but > 6 months old) a) Co-artem + Primaquine (COA3 + PQ 1 time) b) Chloroquine (CQ3) c) Quinine + Clindamycin x 7 days (Q7C7) d) Co-artem only
10.	How will you treat a non-pregnant adult patient with no fever and *P. falciparum* RDT positive? a) Quinine + Clindamycin x 7 days (Q7C7) b) Chloroquine c) Co-artem + Primaquine (COA3 + PQ 1 time) d) No treatment till fever develops
11.	Treatment of *P. falciparum* in a patient that cannot eat or drink a) Refer the patient to nearest hospital or health centre b) Try to give 1st dose of Co-artem and refer quickly to nearest hospital or health centre c) Give Co-artem and primaquine (COA3 + PQ) and send back home d) No treatment
12.	Treatment of *P. falciparum* in child with fever who just wake up from a convulsion a) Cool the child and try to give 1st dose of Co-artem and refer b) No treatment c) Refer the patient to hospital or health centre without treatment d) Give Co-artem and primaquine (COA3 + PQ) and send back home
13.	Treatment of patient with a positive *P. falciparum* RDT 1 week after a <u>complete</u> treatment for malaria? a) Quinine + Clindamycin x 7 days (Q7C7) b) Chloroquine c) Repeat Co-artem d) Give paracetamol and ask to come back if fever continues
14.	Treatment of *P. vivax* in a child who was treated 1 month ago for *P. vivax*? a) Chloroquine b) Co-artem c) Primaquine d) No treatment
15.	Why do we need to treat *P. falciparum* within 48 hours of fever? a) To stop the transmission of *P. falciparum* from one person to another b) To stop the spread of malaria drug resistance in the area c) To prevent the patient to become severe. d) All of the above is true
16.	What to do if a patient vomits the drug less than 30 min after taking it? a) Repeat the 1st dose again. b) Don't need to repeat the 1st dose c) Stop the treatment d) Change the ACTs

17.	How do we administer Coartem for better absorption? a) Water b) Some fat (Milk or after meal) c) Tea d) Coffee
18.	What is the correct treatment for pregnant patient diagnosed with *P. vivax* in first trimester? a) Co-artem b) Chloroquine (CQ3) c) Chloroquine + Primaquine (CQ3 + PQ) d) Quinine + Clindamycin x 7 days (Q7C7)
19.	Treatment of *P. falciparum* in adult a) Chloroquine (CQ3) b) Quinine + Clindamycin x 7 days (Q7C7) c) Co-artem only d) Co-artem + Primaquine (COA3 + PQ 1 time)
20.	What is the correct treatment for pregnant patient diagnosed with Mixed infection (*P. falciparum* & *P. vivax)* during 1st trimester of pregnancy (within first 3 months)? a) Co-artem + Primaquine (COA3 + PQ 3 time) b) Chloroquine (CQ3) c) Quinine + Clindamycin x 7 days (Q7C7) d) Co-artem + Primaquine (COA3 + PQ 1 time)

Appendix 3. Additional PV and PF graphs

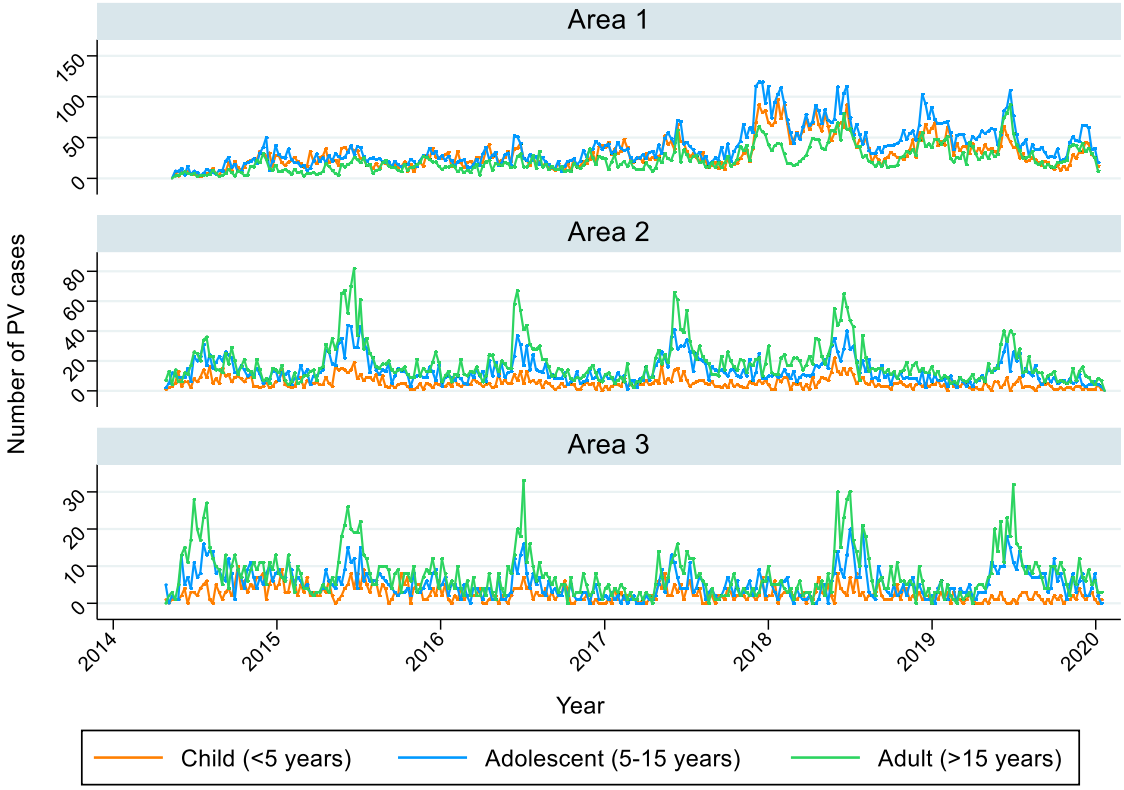

Figure S1. Number of PV cases by age group and area across the METF programme (please note different y-axis scales).

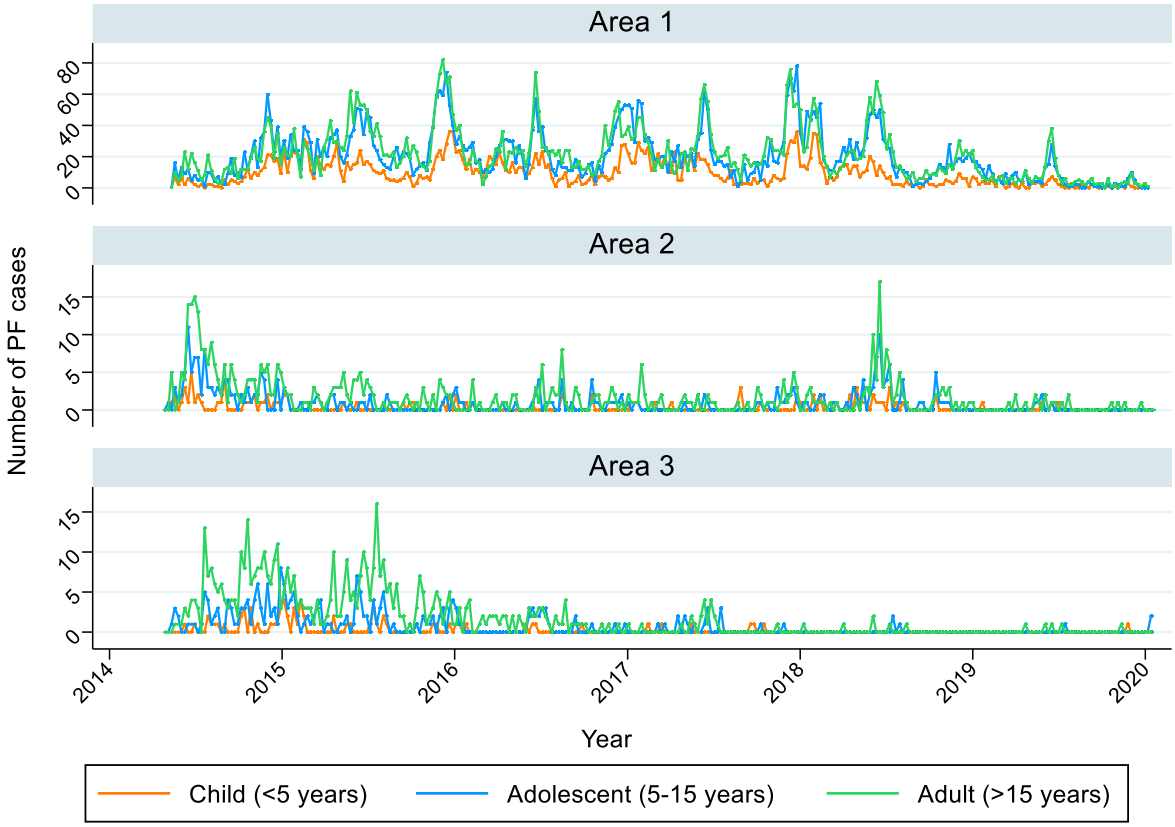

Figure S2. Number of PF cases by age group and area across the METF programme (please note different y-axis scales).

Appendix 4. Additional drug resistance results

Table S1. Kelch 13 Alleles (2014 - 2018)

Alleles, n (%)	Year of collection				
	2014	**2015**	**2016**	**2017**	**2018**
WT	101 (39)	30(37)	222(43)	576(40)	212(42)
K189T	2 (1)	2(2)	-	25(2)	18(4)
V193E	-	-	-	1(0.1)	-
S213G	-	-	-	-	1(0.2)
E252Q	26 (10)	-	-	1(0.1)	3(1)
R265P	1 (0.4)	-	-	-	-
P441L	6 (2)	8(10)	65(13)	270(19)	56(11)
F446I/F	27 (10)	-	64(12)	225(16)	81(16)
G449A	9(3)	-	36(7)	120(8)	60(12)
N458Y	-	-	-	1(0.1)	-
C469F/Y	2(1)	4(5)	5(1)	6(0.4)	-
M476I	16(6)	1(1)	21(4)	32(2)	1(0.2)
N525Y	-	1(1)	-	-	-
G533S	22(9)	8(10)	6(1)	4(0.3)	7(1)
T535M	-	-	-	1(0.1)	-
N537I	-	11(13)	-	-	-
G538V	1(0.4)	-	4(1)	5(0.3)	-
R539T	1(0.4)	-	-	-	-
C542Y	1(0.4)	-	-	-	-
P553S	-	-	1(0.2)	-	-
R561H/R	24(9)	2(2)	35(7)	131(9)	58(12)
M562I	-	-	41(8)	13(1)	2(0.4)
P574L	4(2)	6(7)	-	3(0.2)	2(0.4)
C580Y	14(5)	9(11)	17(3)	30(2)	2(0.4)
A626S/A	1(0.4)	-	-	-	-
P667T	-	-	-	2(0.1)	-
Total	258	82	517	1,446	503

Table S2. Kelch 13 Alleles before and after MDA

Alleles, n (%)	Pre-MDA	Post-MDA
WT	127 (38)	220 (46)
K189T/K	2 (1)	14 (3)
E252Q	9 (3)	3 (1)
R265P	1 (1)	-
P441L	27 (8)	76 (16)
F446I/F	39 (12)	97 (20)
G449A	15 (4)	33 (7)
M476I	9 (3)	6 (1)
G533S	10 (3)	1 (0.2)
G538V	1 (0.3)	1 (0.2)
R561H/R	42 (12)	18 (4)
M562I	40 (12)	4 (1)
P574L	2 (1)	-
C580Y	14 (4)	3 (1)
P667T	-	2 (0.4)
Total	338	478

Appendix 5. Additional entomolgy results

Table S3. Diversity and malaria vector status of human-biting *Anopheles* species in Kayin state, Myanmar.

Group	**No. collected**	**qPCR *Plasmodium***	**PCR sibling species**	**PF** [a]	**PV** [a]	**Species diversity** [a.b,c,d]
Annularis	33442	5471	82	x	x	*An. annularis s.l.*, *An. nivipes*, *An. pallidus* and *An. philippinensis* [d]
Asiaticus	4	2	0			*An. asiaticus s.l.*
Barbirostris	3625	276	2		(x)	*An. barbirostris s.l.* and *An. koreicus* [d]
Funestus	23616	9426	5420	x	x	*An. minimus* [b,c], *An. harrisoni, An. aconitus* [(c)], *An. varuna, An culicifacies* A, *An. culicifacies* B, *An. culicifacies* C, *An. jeyporiensis* [c] (and *An. pampanai*)
Hyrcanus	3784	184	3			*An. peditaeniatus*, *An. sinensis*
Jamesii	7827	978	52	x		*An. jamesii* and *An. splendidus* [b]
Kochi	5449	375	18			*An. kochi*
Leucosphyrus	1176	699	979	(x)	x	*An. introlatus, An. dirus* [(b),c] and *An. baimaii* [c], (*An. cracens* and *An. balabacensis*)
Maculatus	38229	9299	5407	x	x	*An. maculatus* [b,c], *An. dravidicus, An. sawadwongporni* [(b,c)], *An. rampae* [c], *An. dispar* and *An. pseudowillmori* [c]
Tessellatus	624	26	16			*An. tessellatus*
Subpictus	3285	120	50			*An. vagus*
Unclassified	129	27	4			*An. karwari*

[a] Brackets indicate data from previous entomological studies in Kayin state (15);
[b] Identification of *Plasmodium falciparum* infected specimens confirmed by PCR;
[c] Identification of *Plasmodium vivax* infected specimens confirmed by PCR;
[d] Molecular identification of *Plasmodium*-infected specimens not available.

Table S4. Generalized estimating equations model output for the multivariable analysis of *P. falciparum* entomological inoculation rate including season, malaria vectors human-biting rate, prevalence determined by high volume ultra-sensitive PCR and incidence predictors.

Variable	**Category**	**IRR**	**95%CI**	**p-value**
Season	Dry	1	reference	-
	Rainy	3.35	0.44 - 25.24	0.241
Prevalence (%)	0 - 10	1	reference	-
	10 - 100	8.6	1.6 - 46.23	0.012
Incidence (cases /household / month)	0 - 1	1	reference	-
	1-20	0.85	0.15 - 4.97	0.858
HBR (bites / person /month)	0 - 300	1	reference	-
	300 - 4000	10.65	3.92 - 28.92	<0.001

CI: confidence interval; **HBR**: human-biting rate; **IRR**: incidence rate ratio.

Table S5. Generalized estimating equations model output for the multivariable analysis of *P. vivax* entomological inoculation rate including season, malaria vectors human-biting rate, prevalence determined by high volume ultra-sensitive PCR and incidence predictors.

Variable	Category	IRR	95%CI	p-value
Season	Dry	1	reference	-
	Rainy	1.76	0.61 - 5.08	0.299
Prevalence (%)	0 - 15	1	reference	-
	15 - 100	3.85	0.48 - 30.74	0.204
Incidence (cases /household / month)	0 – 0.1	1	reference	-
	0.1-20	0.75	0.24 - 2.36	0.619
HBR (bites / person /month)	0 - 300	1	reference	-
	300 - 4000	3.99	1.52 - 10.52	0.005

CI: confidence interval; **HBR**: human-biting rate; **IRR**: incidence rate ratio.

Table S6. Model output showing predictive efficacy estimates of bed nets against malaria mosquito bites collated by *Anopheles* taxa.

Taxa	No. of estimates	Median	IQR	Range
An. aconitus	29	0.68	0.58-0.78	0-0.8
An. annularis (*s.l.*)	143	0.48	0-0.6	0-0.8
An. asiaticus (*s.l.*)	3	0.66	0.33-0.67	0-0.68
An. baimaii	176	0.61	0.33-0.74	0-0.8
An. barbirostris (*s.l.*)	144	0.36	0-0.59	0-0.8
An. culicifacies A	38	0.66	0.43-0.8	0-0.8
An. culicifacies B	54	0.68	0.15-0.74	0-0.8
An. culicifacies C	14	0.75	0.6-0.8	0-0.8
An. dirus	22	0.66	0-0.8	0-0.8
An. dispar	22	0.51	0-0.71	0-0.8
An. dravidicus	20	0.16	0-0.58	0-0.8
An. harrisoni	30	0.31	0-0.7	0-0.8
An. hyrcanus (*s.l.*)	92	0.48	0-0.67	0-0.8
An. introlatus	5	0.44	0-0.69	0-0.8
An. jamesii (*s.l.*)	163	0.47	0-0.65	0-0.8
An. jeyporiensis	81	0.2	0-0.59	0-0.8
An. karwari	15	0.1	0-0.66	0-0.8
An. kochi	108	0.43	0-0.6	0-0.8
An. maculatus	270	0.37	0-0.53	0-0.8
An. minimus	285	0.62	0.45-0.71	0-0.8
An. pseudowillmori	136	0.59	0.17-0.69	0-0.8
An. rampae	24	0.63	0.17-0.69	0-0.8
An. sawadwongporni	128	0.05	0-0.47	0-0.8
An. subpictus (*s.l.*)	38	0.4	0-0.63	0-0.8
An. tessellatus	58	0.43	0-0.7	0-0.8
An. varuna	16	0	0-0.58	0-0.8
Pooled vector species	343	0.53	0.37-0.61	0-0.8

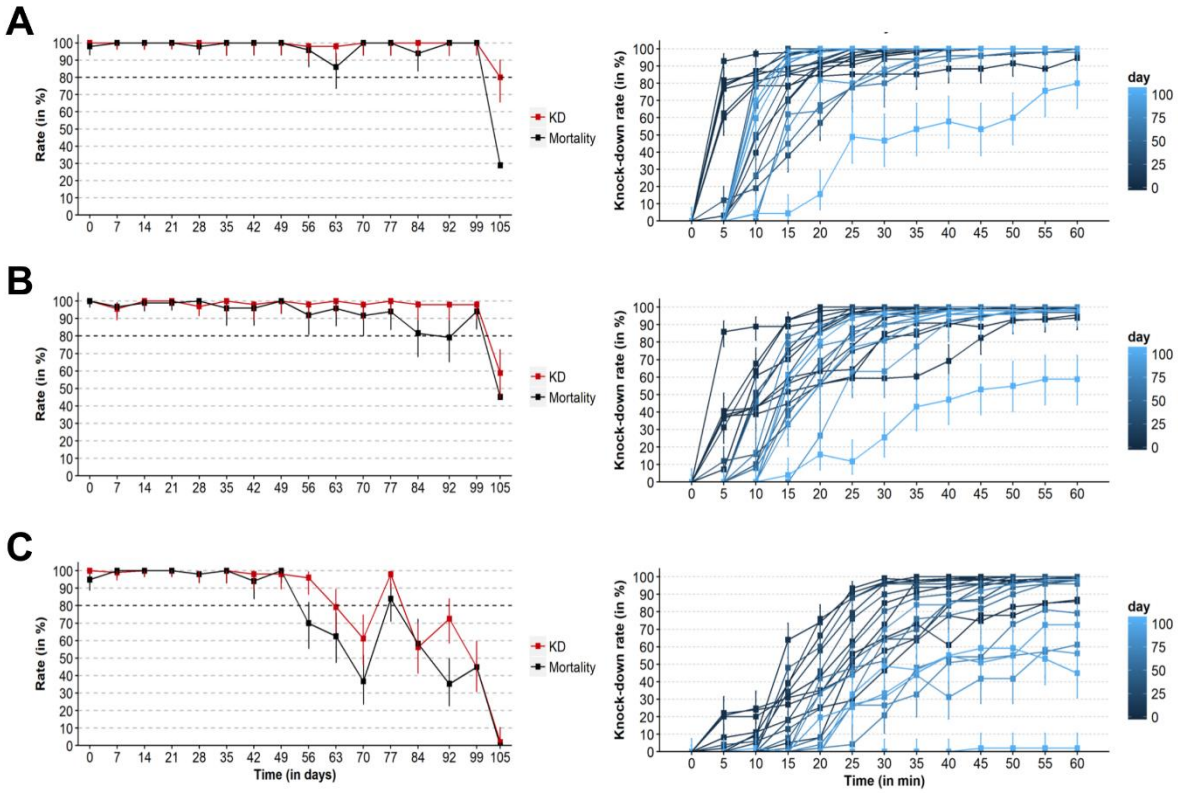

Figure S3. Longevity of the residual insecticidal effects of deltamethrin EC (A), lambda-cyhalothrin CS (B) and bifenthrin WP (C) applied to outdoor vegetation during the dry season. Left panel shows the mortality and KD rates and right panel shows the kinetic of KD rate (right panel). Error bars show 95% binomial confidence intervals calculated with an exact method.

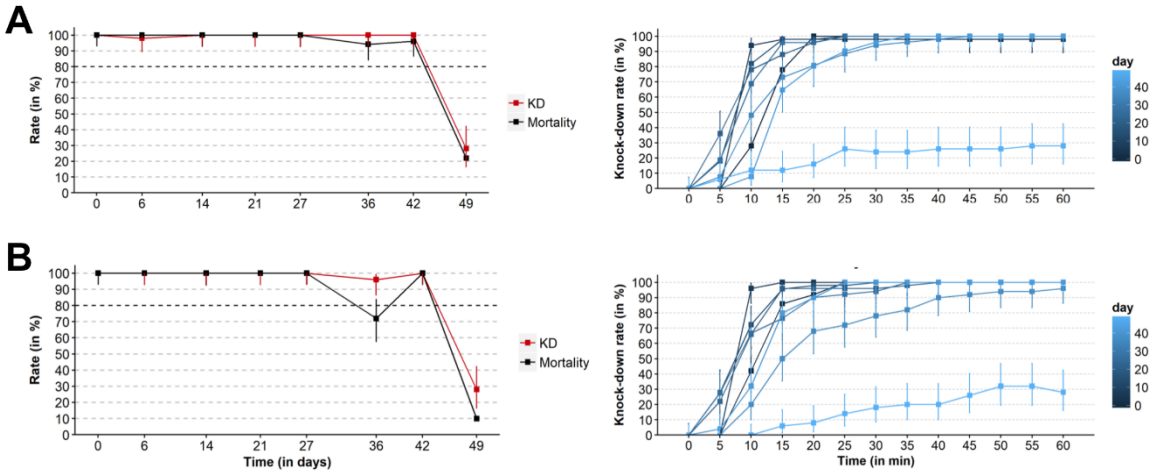

Figure S4. Longevity of the residual insecticidal effects of lambda-cyhalothrin CS applied to outdoor vegetation during the rainy season either without (A) or with (B) artificial washing with 10L of tap water before performing the tests. Left panel shows the mortality and KD rates and right panel shows the kinetic of KD rate (right panel). Error bars show 95% binomial confidence intervals calculated with an exact method.

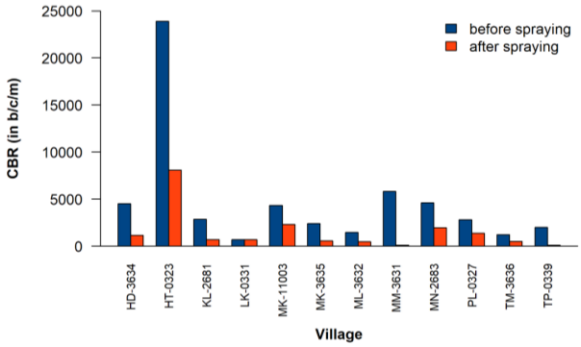

Figure S5. Evolution of village-collated cow-biting rate estimates determined before and after operational deployment of outdoor residual spraying for falciparum malaria elimination in 12 hotspot villages in July 2019.

Glossary

AE: Adverse event

BMA: Burma Medical Association

BMGF: Bill and Melinda Gates Foundation

BPHWT: Back Pack Health Workers Team

CE: Community engagement

CPI: Community Partners International

EC: Executive Committee of the METF

EDT: Early Diagnostic and Treatment

EI: Exophagy index

EIR: entomological inoculation rate

G6PD: glucose-6-phosphate dehydrogenase

GFATM: Global Fund against Aids, Tuberculosis and Malaria

GIS: Geographic information system

GPS: Global positioning system. For our purposes this includes the use of GLONASS (global navigation satellite system). This is a system of recording geographic coordinates (such as latitude and longitude) using satellite technology.

HBR: human biting rate (bites per person per month)

HLC: human landing catch

Hotspot: Our operational definition of a hotspot comes from the results of village-level malaria surveys. Villages are classified as "hotspots" 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%

Incidence: cases per unit of population per unit of time (a rate)

Karen: Former name of Kayin State up to 1989.

Kayin: State of the Union of Myanmar (also referred to until 1989 as Karen State)

KBGF: Karen Border Guard Force

KDHW: Karen Department of Health and Welfare

KKO: Klohtoobaw Karen Organization

KPC: Karen Peace Council

K13: Kelch 13 mutations

Malaria survey: Blood screenings using an ultrasensitive high-volume qPCR assay (uPCR) to identify infections among survey participants, including those with low-density (submicroscopic) parasitaemia which that would be undetectable by conventional methods (microscopy or RDT)

Mapping: for our purposes, mapping includes physically going to a location, taking a recording with a satellite enabled GPS unit and recording some basic information on a survey form.

MAM: Medical Action Myanmar

Mass drug administration: treatment of an entire community/population regardless of symptoms

MDA: Mass drug administration

METF: Malaria Elimination Task Force

MP: Malaria post

MPW: Malaria Post Worker

MTC: Mae Tao Clinic

NMCP: National Malaria Control Program

Pfmdr1 : Plasmodium falciparum multidrug resistance gene

Prevalence: proportion of people carrying an infection at a specific point in time

qrtPCR: quantitative real-time polymerase chain reaction

RDT: Rapid Diagnostic Test

SI: Sporozoite index

SMRU: Shoklo Malaria Research Unit

SMS: short message service or “text messages” sent via mobile telephone system

uPCR: ultrasensitive high-volume quantitative polymerase chain reaction

WHO: World Health Organization

ZI: Zoophagy index