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Re-emergence of malaria in Karen State, Myanmar: has the battle of Burma been lost?

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Abstract

Background Historically malaria has been a major cause of morbidity and mortality in the Greater Mekong Subregion. In recent years, significant progress towards malaria elimination has been made. Myanmar harbours most of the region's malaria burden, however after initial progress during peace time, the civil war and the COVID-19 pandemic have coincided with a resurgence of malaria. This observational study examines the resurgence of malaria in Eastern Myanmar and its contributory factors.

Methods and results Malariometric and genomic data from a long-established network of malaria clinics and village health workers in eastern Karen State serving an estimated population of 350,000 were reviewed and analysed in the context of the COVID-19 pandemic and the military coup that followed. Data from 2020 and 2024 show that the number of cases of *P. falciparum* malaria increased 12-fold and those of *P. vivax* malaria increased threefold. This resurgence was greatest in the northern parts of Karen State and coincided with reduced access to timely diagnosis and treatment. This was associated with increased malaria transmission of *P. falciparum* (RR = 1.72, 95% CI 1.68–1.76) and *P. vivax* (RR = 1.82, 95% CI 1.80–1.84). Reported malaria-related deaths remained low during the study period though underreporting cannot be excluded.

Conclusion Our study provides evidence that the disruption of services (early diagnosis and treatment) caused by the COVID-19 pandemic followed by insecurity, explains the resurgence of malaria in Karen State in Myanmar. Population movements and the clonal expansion of a specific parasite lineage were likely contributing factors. However, the decline recorded in 2024 in the number of cases and the near absence of malaria mortality showed that despite the difficulties, the malaria control system has been successful in containing the crisis. The battle for malaria control in Burma has not been lost, but the future remains uncertain.

Keywords Malaria, Karen State, Myanmar, Burma, *P. falciparum*, *P. vivax*

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Background

Malaria is endemic in the forested areas of the Greater Mekong Sub-region (GMS). *P. falciparum* is highly drug resistant, but with recent progress towards elimination in several countries, its incidence has declined and *P. vivax* is now the dominant species [1].

The emergence of resistance to artemisinin derivatives in *P. falciparum,* first documented in 2007 [2, 3] and the subsequent loss of efficacy of some of the artemisinin-based combination therapies (ACT) [4–6], provided momentum for attempts at elimination.

The most malaria-affected country in the Greater Mekong Sub-region is Myanmar (Burma), which has suffered decades of instability and conflict [7]. In 2014, a large-scale program was initiated to eliminate multidrug-resistant *P. falciparum* from Karen State in the east of the country, bordering Thailand. The general idea was to eliminate the parasite and thereby reduce the risk that resistant parasites would spread westward to India and Bangladesh, as resistance to chloroquine and pyrimethamine had done decades earlier. The strategy employed to control and eliminate malaria was based on the success of the Tak Malaria Initiative (TMI), conducted nearly 15 years earlier in Thailand. The TMI was a pilot project based upon village-based malaria posts (MPs) where febrile patients could be diagnosed and treated rapidly [8]. The main difference between the TMI and this new campaign (named the Malaria Elimination Task Force [METF]) was the additional use of mass drug administration (MDA) to eliminate sub-microscopic reservoirs of malaria parasites in endemic foci (malaria "hot-spots") [9]. Initially, this elimination campaign in Karen State was very successful. *P. falciparum* was eliminated from a majority (90%) of communities, while the impact on *P. vivax* was much less [10]. This was attributed to relapses. Over the following five years (2014–2019), the MP network continued to function well [11], was used extensively by the population [12] and was not compromised by worsening artemisinin resistance or declining malaria incidence [13]. In 2020, the COVID-19 pandemic began and this was followed in 2021 by a military coup in Myanmar that resulted in extensive violence and civil disruption in most parts of the country.

The military coup in Myanmar further complicated malaria elimination efforts. Initially, it led to a period of relative calm, marked by demonstrations in large cities such as Yangon and Mandalay, before escalating violence disrupted health services and increased operational challenges. However, violence and the onset of an armed rebellion in eastern Burma began later in the same year [14]. The presence of military training activities and camps brought more individuals into the area, potentially increasing the risk of malaria transmission due to greater population density and mobility. Therefore, this study aims to provide an overview of the increase in malaria transmission in Eastern Myanmar and to identify factors that may be linked to this rise.

Methods

Study setting

The Malaria Elimination Task Force is centrally administered by the Shoklo Malaria Research Unit (SMRU) now based in Mae Ramat on the Thailand-Myanmar border. SMRU is a branch of the Mahidol Oxford Tropical Medicine Research Unit (MORU) and operates in collaboration with local health organizations from Karen State [9]. Following the initial set-up phase (2014) of detailed mapping, a network of malaria posts was deployed in 1283 villages in 4 townships (Hpapun, Hlaingbwe, Kawkareik, and Myawaddy) in Karen State. The project region is divided into three areas, each subdivided into zones; one zone contains between 6 and 51 functioning malaria posts. The terrain is difficult, mountainous and forested, villages are isolated and mostly without roads, electricity or mobile phone networks. In each zone, transport routes were mapped and the reporting (surveillance) channels were established through the most appropriate means: mobile phone networks (SMS) when available, radio communication, or runners (Fig. 1).

The central role of these MPs is to provide early detection and treatment (EDT) of malaria cases. Cross-sectional surveys using ultra-sensitive high-volume polymerase chain reaction (PCR) were conducted to identify reservoirs of sub-microscopic infections ("hot-spots"), where MDA-using dihydro-artemisinin-piperaquine and a single low-dose of primaquine was deployed. Detailed entomological studies were conducted to understand vector behaviour and define appropriate vector control measures [15]. Supplies of long-lasting insecticidal nets (LLINs) and rapid diagnostic tests (RDTs), as well as antimalarials, were provided to the MP workers. *P. falciparum* infections were treated with artemether-lumefantrine with a single low-dose of primaquine, while *P. vivax* episodes were treated with chloroquine and primaquine, when G6PD testing was available.

Data collection

MP workers send malaria data on a standardized form on a weekly basis. These data consist of a summary of malaria cases by parasite species, age and sex as well as the total number of febrile cases (prior to testing with a malaria RDT). A daily logbook, containing details of each individual case, including the day of fever (DOF, i.e., the number of days a patient had experienced fever before being tested) is maintained and the data entered into a

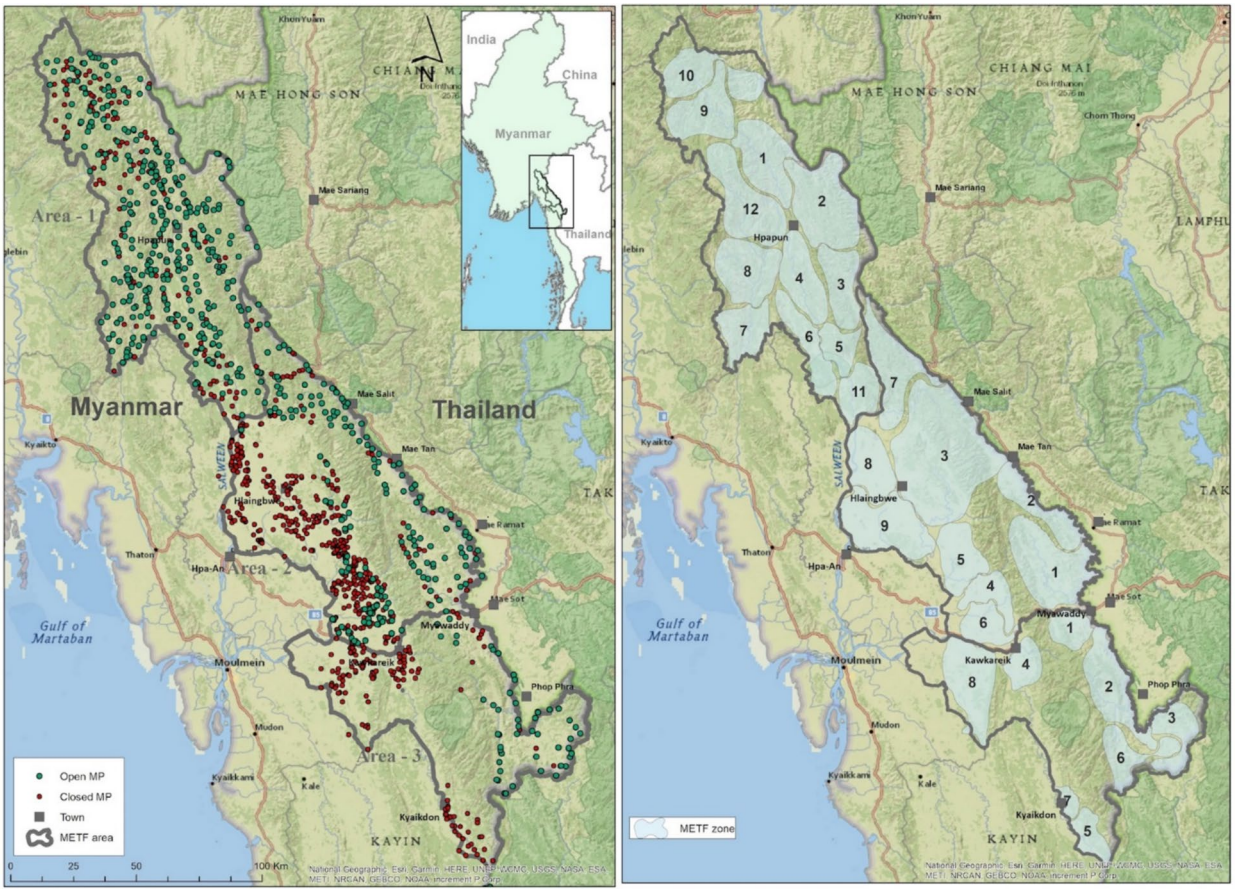

Fig. 1 METF Program coverage. The red MPs were closed over time and the green ones were active in 2024

computer monthly [9]. Used RDTs are sent the SMRU laboratory for quality control. An additional blood sample using dried blood spot (DBS) is collected from the finger prick for parasites genotyping. The *P. falciparum* positive individuals are provided with an explanation of the purpose of the DBS collection and the procedure in the local Kayin language or in Burmese. Additional blood collection is performed only after individuals provided informed consent. All data are centralized and a report is produced weekly and summarized monthly. Given the remoteness of some villages the time taken for the reports to reach the METF varied from 1 day to 2 weeks.

Population

The size of the population living in the project area has always been difficult to estimate due to the remoteness of the area and the geopolitical situation. At the start of the malaria elimination project, the population was estimated to be approximately 350,000. The population in Karen State has been affected by armed conflict with the Burmese military government for decades [7]. Following the military coup in 2021, the violence intensified resulting in extensive population displacements. To estimate the size of the displaced population within the program area, surveys were conducted to obtain more accurate figures from household and population counts and from village authorities (see Supplementary text). Armed clashes and violence events, as well as their locations were reported by the Armed Conflict Location and Event Data (ACLED) [16]. The highest number of battles and airstrikes was reported in 2022 in Karen State, with 35% (380/1067) occurring in the elimination program area [16]. A total of 35,173 people in the program coverage area were estimated to have been directly affected by the armed conflict between 2020 and 2024, resulting in temporary displacement. Fluctuations of population within villages included both increases and decreases, as people moved in search of safety or work in addition to seasonal migration patterns.

Once the population displacement and service disruption had been identified and verified within the METF program area, the EDT services were promptly re-established. Based on epidemiological observations and security assessment, additional interventions including

malaria surveys and LLINS distribution were implemented. LLINS distribution was prioritized for temporary settlements of Internal Displaced People (IDPs) and the mobile and migrant populations between 2021 and 2023. In 2024, mass LLINS distribution campaign was implemented across the four townships.

During this period, groups of fighters moved from place to place and the malaria cases in these groups were not counted in this analysis. These military-related population movements and the uncertainty regarding population size, made malaria surveillance more complicated. For this analysis the civilian population was categorized into the following age groups: children under 5 years (young children), 5–15 years (children), and over 15 years (adults). Villages were further classified based on the sex ratio of malaria cases into four groups; "more males" (male-to-female ratio > 1), "more females" (ratio < 1), "equal M/F" (ratio = 1), or "no females" if no female malaria cases were reported.

Malaria post

Due to the logistical challenges and conflict-related instability, some malaria posts became temporarily non-functioning, limiting access to timely diagnosis and treatment. Malaria posts were considered non-functioning if they were closed due to abandonment, destruction, lack of staff, no malaria cases, or population displacement caused by conflict. Such disruptions also affected the availability of essential supplies, particularly antimalarials and RDTs.

Days of fever

The number of days of fever (DOF) before diagnosis and treatment has been shown to be a very sensitive marker of transmission of *P. falciparum* in this setting [17]. Therefore, individuals with malaria who had fever for more than two days before testing were defined as having delayed detection and treatment. Groups of villages were based arbitrarily on the number of febrile patients (prior to malaria diagnosis) who had been ill for > 2 days (delayed cases, DC): villages with no delayed cases defined the 'No DC' group; those with one to three delayed cases were classified as "Low DC", and those with four or more delayed cases were classified as "High DC".

Genomic data

Genomic analysis of *P. falciparum* parasites collected on DBS by MP workers has played a key role in understanding and monitoring the dynamics of transmission and the impacts of the elimination efforts on drug resistance. For most of the *P. falciparum* cases (and more recently *P. vivax* cases) a DBS was collected, dried, stored in a sealed plastic bag with silica gel and sent to the SMRU central laboratory. These samples were used to monitor the prevalence of *Pf*Kelch gene mutations, a molecular marker of artemisinin resistance and for whole-genome sequencing [9, 13]. DNA was extracted from dried blood spots using the QIAamp Blood Mini Kit. Nested PCR was performed to amplify the *P. falciparum kelch* gene, spanning residues N87K to the stop codon following previously described protocols [3]. The amplified products were visualized by gel electrophoresis and subsequently subjected to direct sequencing (Macrogen, Seoul, South Korea). Sequence data were analysed using the BioEdit software, with the *P. falciparum* 3D7 kelch gene (PF13_0238), NCBI Reference Sequence: XM_001350122.1, used as the reference sequence.

Statistical analysis

Descriptive statistics were used to summarize the data. Categorical variables were presented as numbers and percentages, while continuous variables were summarized using the median and interquartile range (IQR). A negative binomial mixed-effects model was used to examine the association between various factors and the number of *P. falciparum* and *P. vivax* cases. Because malaria cases were clustered within villages, the village was included as a random effect in the model. Additionally, temporal factors such as seasonality were incorporated as fixed effects. Due to geographical differences the analysis was stratified by area. The effect of fever duration before diagnosis (DOF) on malaria infection risk was quantified using relative risk (RR) estimates for each parasite species. The detail statistical method of DOF analysis is described in supplementary text. All analyses were conducted using R (version 4.4.1). A p-value of < 0.05 was considered statistically significant.

Results

Between 2020 to 2024, the METF program operated a network of MPs across part of Karen State. The number of MPs was reduced from 1215 in 2020 to 421 in 2022 because of the absence of transmission for over 12 months (local elimination), then gradually increased again to 553 MPs in 2024 as malaria returned (Table 1). The estimated population living in villages equipped with an MP declined from 384,917 in 2020 to 140,745 in 2022 and increased to 225,848 in 2024. These variations are related to the number of MPs operated annually (Table 1) and the details on the population projection are described in the supplementary file (Tables T1 and T2).

Alongside these structural changes, preventive measures such as LLIN distributions were implemented primarily among mobile and migrant populations between 2021 to 2024. Over the five-year period, MP workers in the METF program tested 564,217 individuals

Table 1 Descriptive data from 2020 to 2024

Variables	Years				
	2020	2021	2022	2023	2024
Malaria posts, n	1215	940	421	539	553
Population	384,917	284,350	140,745	199,025	225,848
Interventions					
LLINS/Hammock nets distribution	–	5188	8190	23,549	121,601
Malaria surveys in village level (using either RDT or PCR), n	18	7	14	–	7
Consultations					
RDT tested, n	96,549	88,933	113,816	136,233	128,686
Malaria positive (RDT results)					
Total positive, n	8756	15,657	36,862	43,667	31,830
P. falciparum, n	609	1095	4615	8700	7030
P. vivax, n	8147	14,562	32,247	34,967	24,800
Malaria related death, n	–	1	–	3	2
Population characteristics					
Days of fever, median (IQR)	1 (1–2)	2 (1–2)	2 (1–3)	2 (1–3)	2 (1–3)
Ratio of Males to Females	1.0	1.1	1.2	1.2	1.2
Age (years), median (IQR)	16 (6–32)	16 (7–30)	12 (5–23)	12 (5–24)	13 (6–26)
Details by *Plasmodium* Species					
P. falciparum					
Case number by area, n					
Area 1	600	1070	4478	8005	6289
Area 2	8	9	122	286	335
Area 3	1	16	15	409	406
Age group, n (%)					
< 5 years	39 (6.4)	108 (9.9)	592 (12.8)	1154 (13.3)	1064 (15.1)
5–15 years	214 (35.1)	484 (44.2)	2191 (47.5)	4038 (46.4)	3257 (46.3)
> 15 years	356 (58.5)	503 (45.9)	1832 (39.7)	3508 (40.3)	2709 (38.5)
Ratio of Males to Females	2.1	1.6	1.3	1.3	1.3
P. vivax					
Case number by area, n					
Area 1	5768	10,649	22,135	24,139	15,976
Area 2	1343	2050	6847	6325	4381
Area 3	1036	1863	3265	4503	4443
Age group, n (%)					
< 5 years	1527 (18.7)	2662 (18.3)	6657 (20.6)	7899 (22.6)	5323 (21.5)
5–15 years	3671 (45.1)	6515 (44.7)	14,773 (45.8)	15,555 (44.5)	9825 (39.6)
> 15 years	2949 (36.2)	5385 (37)	10,815 (33.5)	11,513 (32.9)	9652 (38.9)
Ratio of males to females	1.5	1.5	1.3	1.3	1.4

IQR: interquartile range, RDT: rapid diagnostic test, PCR: polymerase chain reaction, LLINS: long-lasting insecticidal nets

suspected of malaria with RDTs and diagnosed 22,049 *P. falciparum* and 114,723 *P. vivax* cases. Notably, the number of *P. falciparum* cases increased approximately 12-fold in 2024 compared to 2020, while the number of *P. vivax* cases tripled (Table 1).

Geographical distribution of malaria cases

In the project area, the distribution of *P. falciparum* and *P. vivax* cases varied geographically. *P. falciparum* cases in the northern part of the area (Area 1) accounted for the majority of all falciparum cases while *P. vivax* remained

the dominant species in all three areas (Table 1). By the end of 2024, the number of *P. falciparum* cases had increased in both Area 2 and Area 3, rising from single-digit numbers in 2020 to several hundred cases (335 and 406, respectively) in 2024 (Table 1). For *P. vivax*, Area 2 and Area 3 consistently reported fewer cases than Area 1 with case numbers reaching a peak in 2023 across all three areas. The total number of malaria cases declined in all areas in 2024 (Table 1).

Age and sex distribution

The median age of infected individuals decreased from 16 years (IQR: 6–32) in 2020 to 13 years (IQR: 6–26) in 2024 while the male-to-female ratio did not change significantly. *P. falciparum* infections showed a notable increase in young children (< 5 years), rising from 6.4% (39 of 600 cases) in 2020 to 15.1% (1,064 of 6,289 cases) in 2024. Infections in children (5–15 years) also increased over time (Table 1). In 2020, adults were the most affected age group in 55.1% (87 of 158) of villages reporting *P. falciparum* cases. However, by 2024, there was a noticeable shift: young children and adolescents (< 15 years) became the majority of patients in 53.1% (213 of 401) of villages, suggesting increasing local transmission in villages (Fig. 2A). Males remained the dominant group across villages, accounting for the majority of *P. falciparum* cases in 64.6% (102/158) of affected villages in 2020 and 65.8% (264/401) in 2024 (Fig. 2B).

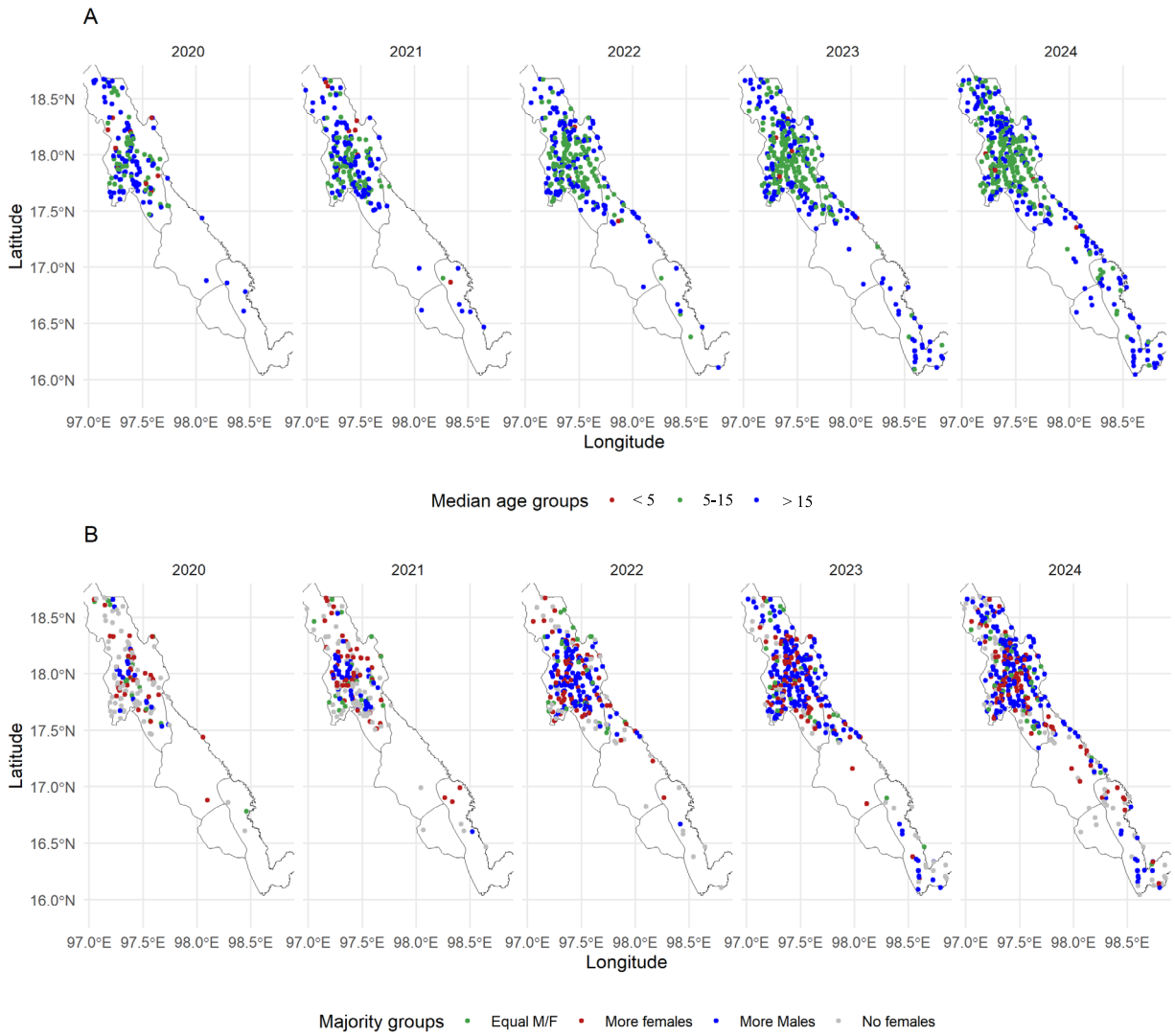

Fig. 2 Median of age group (**A**) and gender group (**B**) distribution among *P. falciparum* patients in METF areas, Kayin State, Myanmar from 2020 to 2024

P. vivax infections were predominantly found in children aged 5–15 years throughout the study period (Table 1). Villages where the median age of *P. vivax* cases fell within this age group accounted for 53.5% (308 of 576 villages with *P. vivax* cases) in 2020 and 54.7% (289 of 528 villages) in 2024 (Fig. 3A). A higher number of *P. vivax* cases was observed among males (as for *P. falciparum*) in the study villages: 62.3% (359/576) of the villages in 2020 and 66.1% (349/528) in 2024. Villages with more female than male cases accounted for only 28.0% (161/576) in 2020 and 24.6% (130/528) in 2024 (Fig. 3B). Overall, the higher number of male patients was observed for both malaria species across all age groups (Table T3).

Species composition

From 2020 to 2022, the ratio of *P. falciparum* to *P. vivax* cases across all areas remained below 0.2 but began to increase toward the end of 2022, reaching 0.5 by 2024 (Fig. 4). This indicates that by 2024 for every two *P. vivax* cases there was approximately one *P. falciparum* case. When examined at the village level, substantial heterogeneity was observed. In the two most recent years (2023 to 2024) an increasing number of villages reported a *P. falciparum* to *P. vivax* ratio exceeding 0.5, with the highest ratios observed in the northern area (Figure S1). Overall, *P. vivax* remained the dominant malaria species in Karen State, however the relative contribution of *P. falciparum* increased steadily over time.

Genomic analysis

A total of 739 *P. falciparum* specimens collected between 2020 to 2023 were genotyped to detect *Pf*Kelch gene mutations associated with artemisinin resistance. The R561H mutation was the most prevalent, found in 630

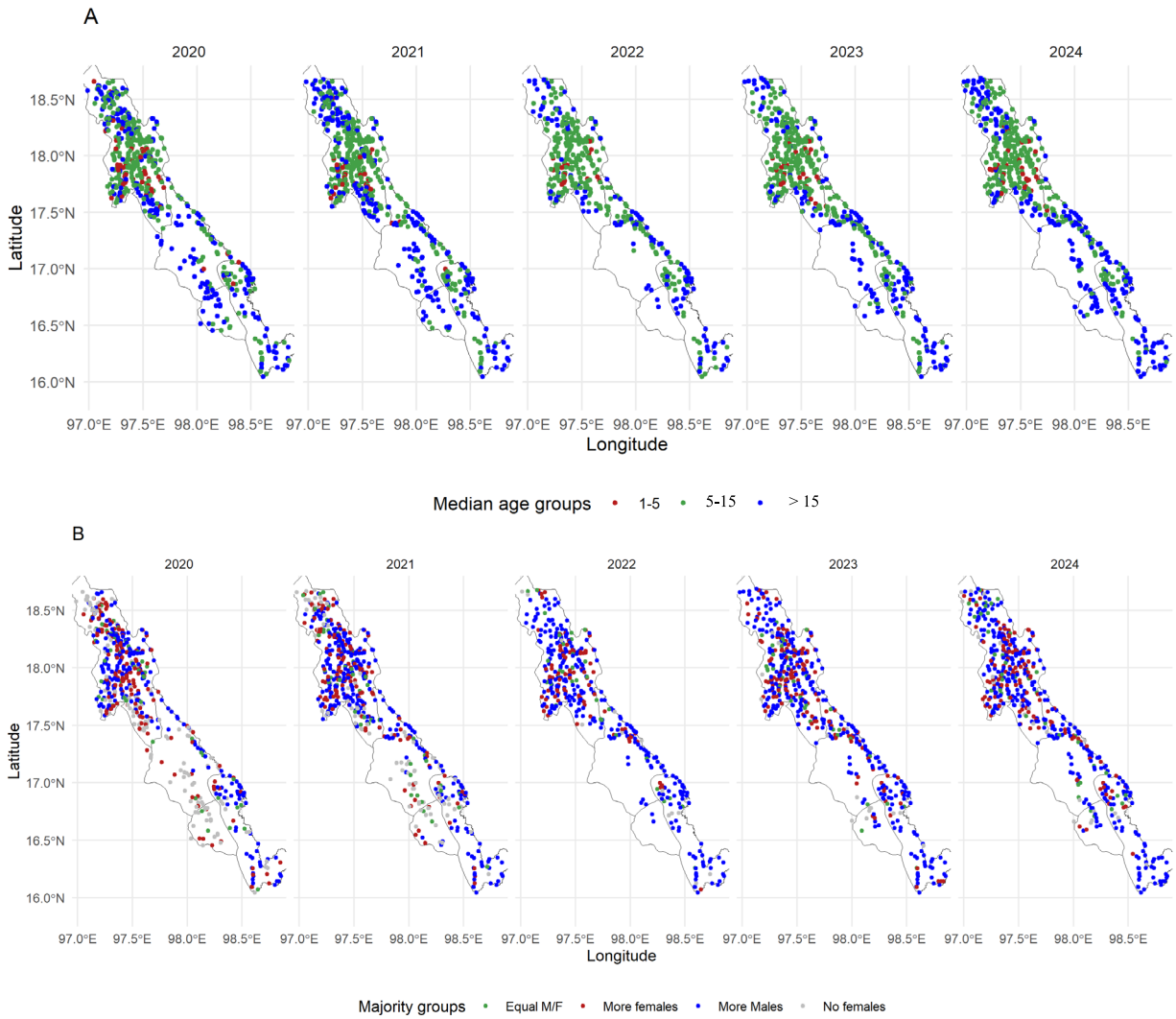

Fig. 3 Median age (**A**) and gender group (**B**) distribution among *P. vivax* patients in METF areas, Kayin State, Myanmar from 2020 to 2024

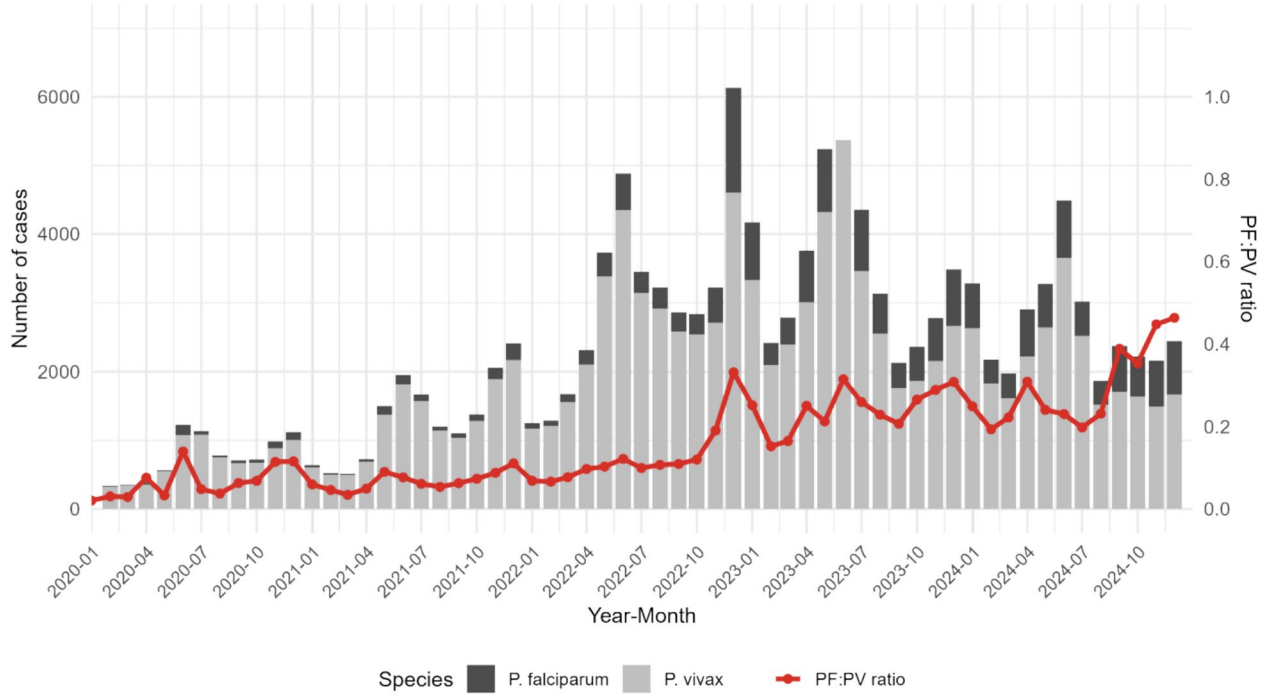

Fig. 4 Monthly *P. falciparum*, *P. vivax* cases and PF:PV ratio trend between 2020 to 2024

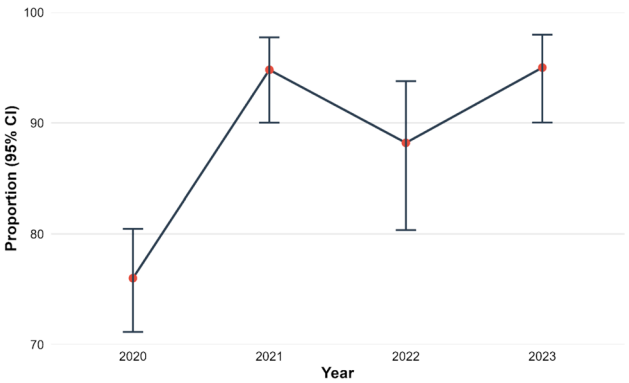

Fig. 5 R561H allele proportion (95% CI) between 2020 to 2023

of 739 genotyped samples (85%), followed by the wild-type (WT) allele in 97 samples (13%). Other mutations were rare and included C580Y (0.8%, n = 6), P441L (0.4%, n = 3) and single allele of E605K, F446I, and I640T. The proportion of the R561H mutant increased remarkably from 76% (260/342; 95% CI 71.14–80.45) in 2020 to 95% (134/141; 95% CI 90.01–97.98) in 2023 (Fig. 5). This increase coincided with the replacement of other alleles, such as C580Y and F446I, which had previously been dominant in this region before 2020 [13, 18, 19]. The proportion of *P. falciparum* cases undergoing genotyping increased substantially from June 2020 onward. As illustrated in Figure S2, the R561H mutation was detected in 29 cases originating from a single village (MP2662) during an outbreak in June 2020, accounting for approximately 83% of the 35 total cases detected across multiple villages (Figure S3).

Conflict and population displacement

Conflict intensity and population displacements were assessed using records of conflict events across the study area. These events are illustrated in the appendix and were primarily concentrated in the northern (Area 1) and the southern (Area 3) regions, as shown in Figure S4. Overall, the civil war that erupted following the 2021 military coup caused the displacement of an estimated 249,000 people in Karen State [20]. This spatial distribution demonstrates that substantial portions of the study area were affected by conflict throughout the study period.

Delayed diagnosis, seasonality and transmission

The number of febrile individuals (before malaria diagnosis) with fever lasting more than two days as well as seasonality, were both significantly associated with *P. falciparum* and *P. vivax* case numbers (Tables 2 and 3). Among febrile individuals living in the "High DC" villages, the incidence risk ratio (IRR) for *P. falciparum* was 14.0 (95% confidence interval [CI]: 13.0–15.1) in Area 1, 15.6 (95% CI 11.1–21.9) in Area 2, and 25.8 (95% CI

Table 2 Mixed-effects model results for the association between the number of people with fever over 2 days and season with *P. falciparum* infections

Variables	IRR	95% CI	P-value
Area 1			
Intercept	0.04	0.03–0.04	
Number of people with fever over 2 days			
No DC	Reference group		
Low DC (1–3 persons)	3.57	3.37–3.77	**< 0.001**
High DC (≥ 4 persons)	13.99	12.96–15.10	**< 0.001**
Season			
Hot	Reference group		
Cold	1.73	1.63–1.84	**< 0.001**
Rainy	1.47	1.39–1.56	**< 0.001**
Random effect: Village	3.32	3.00–3.71	
Area 2			
Intercept	0.0004	0.0002–0.0006	
Number of people with fever over 2 days			
No DC	Reference group		
Low DC (1–3 persons)	5.53	4.20–7.29	**< 0.001**
High DC (≥ 4 persons)	15.62	11.14–21.91	**< 0.001**
Season			
Hot	Reference group		
Cold	3.23	2.29–4.56	**< 0.001**
Rainy	3.21	2.29–4.50	**< 0.001**
Random effect: Village	8.64	5.99–13.44	
Area 3			
Intercept	0.001	0.001–0.003	
Number of people with fever over 2 days			
No DC	Reference group		
Low DC (1–3 persons)	7.77	5.73–10.54	**< 0.001**
High DC (≥ 4 persons)	25.76	17.45–38.01	**< 0.001**
Season			
Hot	Reference group		
Cold	2.36	1.65–3.39	**< 0.001**
Rainy	3.05	2.18–4.27	**< 0.001**
Random effect: Village	7.13	4.47–13.16	

This model estimates incidence rate ratio (IRR) as the outcome, with the number of people with prolong fever > 2 days categorized into 3 groups and season as fixed effects and villages included as a random effect

IRR: incidence risk ratio, CI: confidence interval

17.5–38.0) in Area 3. For *P. vivax*, the corresponding IRR was 7.6 (95% CI 7.3–7.9) in Area 1, 18.5 (95% CI 17.3–19.8) in Area 2, and 14.1 (95% CI 12.9–15.4) in Area 3. When comparing *P. falciparum* febrile cases and malaria-negative febrile cases, individuals with a longer duration of fever were consistently more likely to be infected with *P. falciparum* (Table 4). For *P. vivax*, the relative risk was highest at the two-day fever cut-off and gradually declined with increasing fever duration.

Malaria in the region is seasonal and for *P. falciparum*, case numbers were slightly higher during the cold season (November to January) than during the rainy season, with both seasonal peaks exceeding those observed in the hot season in Areas 1 and 2, but not in Area 3. In contrast, *P. vivax* case numbers were consistently higher in the rainy season than in the cold season, with both seasons showing higher case numbers than the hot season across all areas. These temporal and spatial patterns are illustrated in the animated maps (Figures S5A and S5B).

Table 3 Mixed-effects model results for the association between the number of people with fever over 2 days and season with *P. vivax* infections

Variables	IRR	95% CI	P-value
Area 1			
Intercept	0.26	0.24–0.29	
Number of people in the village with fever over 2 days			
No DC	Reference group		
Low DC (1–3 persons)	2.87	2.79–2.94	**< 0.001**
High DC (≥ 4 persons)	7.60	7.32–7.89	**< 0.001**
Season			
Hot	Reference group		
Cold	1.13	1.10–1.16	**< 0.001**
Rainy	1.25	1.22–1.28	**< 0.001**
Random effect: Village	2.63	2.44–2.86	
Area 2			
Intercept	0.06	0.05–0.07	
Number of people in the village with fever over 2 days			
No DC	Reference group		
Low DC (1–3 persons)	5.06	4.78–5.36	**< 0.001**
High DC (≥ 4 persons)	18.53	17.33–19.81	**< 0.001**
Season			
Hot	Reference group		
Cold	1.08	1.02–1.14	**0.01**
Rainy	1.30	1.24–1.37	**< 0.001**
Random effect: Village	3.42	2.92–4.10	
Area 3			
Intercept	0.22	0.16–0.29	
Number of people in the village with fever over 2 days			
No DC	Reference group		
Low DC (1–3 persons)	3.91	3.64–4.20	**< 0.001**
High DC (≥ 4 persons)	14.06	12.86–15.37	**< 0.001**
Season			
Hot	Reference group		
Cold	1.14	1.06–1.23	**< 0.001**
Rainy	1.48	1.37–1.58	**< 0.001**
Random effect: Village	2.59	2.14–3.30	

IRR: incidence risk ratio, CI: confidence interval

Discussion

In Eastern Myanmar, the number of *P. falciparum* and *P. vivax* cases increased following the COVID-19 pandemic in 2020 and the military coup in 2021, although a recent decline was observed in 2024. A major concern is that the ongoing civil war in Burma could derail the efforts to eliminate drug-resistant *P. falciparum* and facilitate the spread of resistance to artemether-lumefantrine, the main ACT used in the country and globally. ACTs are the cornerstone of treatment for *P. falciparum* malaria worldwide. The emergence of resistance to the artemisinin derivatives in Southeast Asia two decades ago [2, 3] raised fear that progress in malaria control and elimination could be reversed. Monitoring the spread of artemisinin resistance became more feasible following the discovery of the causal molecular markers, mutations in the "propeller" region of the *Pf*Kelch gene [21]. This enabled field studies demonstrating that drug-resistant parasites were spreading widely and also emerging *de-novo* in settings where ACTs were used. The reduced efficacy of the artemisinin component increases selective pressure on the partner drug, ultimately risking treatment failure. This process has been well documented for piperaquine and mefloquine [5, 22] but to date, has fortunately not been observed for lumefantrine, the partner drug to artemether.

Table 4 Relative risk of *P. falciparum* or *P. vivax* infections in the community (by MP) compared to negative cases by fever duration cut-offs

P. falciparum			***P. vivax***		
Variables	**RR**	**95% CI**	**Variables**	**RR**	**95% CI**
2 days cut-offs			2 days cut-offs		
Fever ≤ 2 days	Reference group		Fever ≤ 2 days	Reference group	
Fever > 2 days	1.72	1.68–1.76	Fever > 2 days	1.82	1.80–1.84
5 days cut-offs			5 days cut-offs		
Fever ≤ 5 days	Reference group		Fever ≤ 5 days	Reference group	
Fever > 5 days	2.09	2.00–2.19	Fever > 5 days	1.51	1.47–1.55
7 days cut-offs			7 days cut-offs		
Fever ≤ 7 days	Reference group		Fever ≤ 7 days	Reference group	
Fever > 7 days	2.28	2.07–2.52	Fever > 7 days	1.38	1.30–1.46
10 days cut-offs			10 days cut-offs		
Fever ≤ 10 days	Reference group		Fever ≤ 10 days	Reference group	
Fever > 10 days	2.69	2.30–3.14	Fever > 10 days	1.23	1.10–1.37
14 days cut-offs			14 days cut-offs		
Fever ≤ 14 days	Reference group		Fever ≤ 14 days	Reference group	
Fever > 14 days	2.77	2.12–3.62	Fever > 14 days	1.32	1.10–1.59
			28 days cut-offs		
			Fever ≤ 28 days	Reference group	
			Fever > 28 days	1.04	0.59–1.84

RR: relative risk, CI: confidence interval

In many of the malaria endemic countries, declining malaria transmission has been accompanied by a redistribution of malaria burden toward older age groups, as predicted by previous studies [23]. However, a reversed shift in age-pattern was observed in Kayin State during this resurgence period, an indication of an increase in local malaria transmission in the villages themselves. Young children are at increased risk of severe *P. falciparum* malaria and during early life with potential long-term neurodevelopment consequences [24]. In contrast, recurrent *P. vivax* infections were less associated with severe diseases, while repeated illnesses can cumulatively reduce the quality of life in children [25]. This highlights the importance of uninterrupted access to EDT for both malaria species and a safe radical cure for *P. vivax* with G6PD testing to reduce the malaria associated mortality and morbidity in Kayin and similar settings elsewhere.

Malaria incidence in this area exhibits clear seasonal variation, with peaks occurring during or shortly after the rainy season and a second seasonal peak during the winter months. Studies conducted along the Thailand–Myanmar and China–Myanmar borders have reported distinct seasonal transmission peaks, including bimodal patterns in some localities, reflecting the influence of climatic and environmental factors on vector dynamics and human exposure [26]. In conflict-affected Kayin State, population displacement during the peak transmission seasons can amplify malaria transmission. When affected populations shelter in forest fringe areas or temporary sites, they are often exposed to the outdoors and early mosquito biting and have reduced access to timely diagnosis and treatment and vector control measures. In these circumstances, even a single imported malaria infection can ignite onward transmission and lead to localized outbreaks within closely connected, crowded displacement clusters. Therefore, the interventions must specifically target these high-risk populations, with an effective surveillance and a rapid robust response to prevent outbreaks. This program demonstrated that this can be achieved with appropriate resource allocation and sustained engagement with locally led communities and frontline health workers.

Faced once again with the prospect of nearly untreatable *P. falciparum* malaria, the strategy adopted was to pursue the elimination of *P. falciparum* in regions where the incidence was already low. In 2014 a large-scale program was launched in Karen State, Burma (Myanmar), bordering Thailand, with the aim of eliminating *P. falciparum* parasites and create a "firewall" to prevent the westward spread of resistance to India and Bangladesh. The strategy involved deploying a MP in all villages, each equipped with RDT and ACT (artemether-lumefantrine), to ensure access to early diagnosis and treatment (EDT) for villagers. In addition, submicroscopic parasites

reservoirs identified using ultra-sensitive high-volume PCR were targeted through MDA. The impact of this approach was substantial, with *P. falciparum* eliminated from the majority of villages in this area [10]. In contrast, the impact on *P. vivax* transmission was minimal.

The main obstacle to the elimination of *P. vivax* is the dormant liver stage, which is treatable only with 8-aminoquinoline drugs (primaquine, or tafenoquine), both of which can cause haemolysis in individuals with G6PD deficiency. In addition, adherence to the radical primaquine regimen is poor in this population [27]. In other parts of the GMS, the impact of similar elimination efforts was substantial and the number of *P. falciparum* cases continued to decline in Vietnam, Cambodia and Lao PDR. Although there is a chronic lack of reliable data from Myanmar, it is generally accepted that nearly 90% of all *P. falciparum* cases in Southeast Asia occur in this country, where significant progress was made during peacetime prior to 2020 but was reversed following the onset of civil war. This reversal is likely explained by multiple factors, including political instability, deterioration of health services and large-scale population displacements. The most recent data available are therefore likely to represent a substantial underestimate of the true malaria burden [1, 28].

The resurgence of malaria observed in Karen State since 2020 is likely attributable to several interacting factors. The COVID-19 pandemic disrupted malaria control programs and essential supply chains, interrupting routine diagnosis, treatment, and surveillance activities which have been linked to increased malaria incidence in endemic regions [29]. Political instability, ongoing conflict and population displacements along the Thailand–Myanmar border may have further constrained access to health services and exacerbated malaria transmission risks [30]. Furthermore, the political instability following the 2021 military coup has weakened health system infrastructure, increased population displacements into endemic forested areas and reduced the capacity for malaria control, contributing to heightened transmission [31]. Despite these challenges, efforts to eliminate malaria must continue. In particular for *P. vivax*, significant uncertainties remain, as elimination strategies must address latent liver stages and operational challenges in areas with high G6PD deficiency to safely administer radical cure regimens [32].

Our findings indicate that the longer patients remain febrile before malaria diagnosis, the higher the number of malaria cases observed in that community. This supports the observation that delays in testing and treatment are associated with increased transmission [17, 33]. These finding confirms the central role of early detection and treatment of malaria cases. Any delay beyond 48 h in testing febrile cases and treating the positive cases causes an increase in transmission and in the number of new cases. Reducing the time between fever onset and diagnosis is essential for effective malaria control and elimination.

The genomic surveillance in this program is important to monitor the evolution of resistance to antimalarials and to understand the dynamics of transmission. There was no evidence that the elimination program, including mass drug administration (MDA), contributed to the worsening artemisinin resistance [13, 18]. Further genomic analysis between 2015 and 2020 showed a substantial reduction in the size of the parasite population during the elimination phase, without any indication of positive selection for increased drug resistance. Instead, the parasite population exhibited extreme clonal expansion and inbreeding, characterized by stable localized transmission of specific genotypes [34]. The R561H mutation has been the dominant genotype since 2020, while other previously circulating genotypes have been eliminated. This persistence might be explained either by the lower fitness cost associated with R561H compared to C580Y as demonstrated in the laboratory [19] or by chance.

Although we aimed to collect comprehensive data, several limitations remain. First, there were data gaps due to delays in rolling out updated data collection forms in the field. These revised forms were intended to capture additional variables such as stock balances and supply receipt records, which could have improved our understanding of program performance and resource availability. As a result, some potentially important explanatory factors were not systematically recorded especially during the early phase of the resurgence. Second, the main limitation of this analysis lies in the uncertainty around the population size in the catchment area. Because the population is highly mobile and includes many undocumented such as military personnel or displaced individuals, it is difficult to determine accurate denominators for calculating incidence or coverage metrics. This uncertainty complicates the interpretation of trends and may lead to under- or overestimation of disease burden and the impact of intervention. Third, other potentially relevant data were not included in this analysis because we have limited access to conflict-related information near malaria posts. To better understand potential causal pathways such as how insecurity, displacement or care-seeking delays contribute to malaria transmission, more detailed information would be needed.

The recent turmoil in global health financing has jeopardized the disease control programs in developing countries [35]. The situation in Myanmar has markedly worsened because of an unstable government, the ongoing

armed conflicts around the country. In Myanmar, funding reductions and cuts to malaria control and elimination initiatives threaten to derail the hard-earned control of drug-resistant *P. falciparum* and *P. vivax*. Whereas the battle of Burma has not been lost, the future remains uncertain.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12936-026-05808-0.

Supplementary material 1.

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Author contributions
FN conceptualized the study design. CP and AMT performed the data analysis and contributed to the writing and reviewing. SBN, SWT, AK, WLA, KK and SD contributed to the program data collection and data cleaning. FN, ND and NJW reviewed and edited the manuscript.

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Availability of data and materials
The data utilized for this study are available upon request to the Mahidol-Oxford Tropical Medicine Research Unit data access committee, datasharing@tropmedres.ac.

Declarations

Ethics approval and consent to participate
Ethical approval for this study was obtained from the Ethics Review Committee on Medical Research Involving Human Subjects, Department of Medical Research (Lower Myanmar), Ministry of Health and Sports, Myanmar (Reference No: 73/Ethics 2014).

Competing interests
The authors declare no competing interests.

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