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Predicting Factors for Malaria Reintroduction and A Multi-factorial Approach to Prevent Malaria Outbreaks in the Malaria-free Areas

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Abstract

Thailand's National Malaria Elimination Strategy, 2017–2026, aims to reach zero indigenous transmission by 2024. During 2016–2021, Thailand had successfully reduced its malaria burden by more than 80%. However, a resurgence of malaria in 2022 saw an increase in the incidence in 33 provinces. To identify the predictors of malaria epidemic re-occurring in malaria-free areas, secondary data of malaria-reintroduced villages in 2022 were obtained from the Malaria Information System. A descriptive cross-sectional study was conducted to compare characteristics, prevention, and response measures between villages with and without sustained local transmission after malaria reintroduction. A retrospective cohort study was conducted to determine the associations between sustained local transmission and potential predictors. Among the transmission foci in 2022, 336 villages had previously been malaria-free, of which 73 (21.7%) reported sustained local transmission. A multi-level logistic regression model, considering villages clustered within provinces, found that villages located in a district which contained active foci (adjusted odds ratio (AOR) 1.03, 95% confidence interval (CI) 1.01–1.05) and having a higher proportion of non-Thai cases (AOR 12.3, 95% CI 5.69–26.6) were significantly associated with sustained local transmission whereas coverage of malaria control within 7 days was protective (AOR 0.20, 95% CI 0.09–0.44). Areas with high migrant populations were associated with a higher risk of malaria reintroduction. Proactive case search should target these populations to quickly detect reintroduced cases and conduct timely control to prevent further local transmission.

Keywords: malaria, reintroduction, sustained local transmission, elimination, Thailand

Introduction

Malaria is one of the world's deadliest infectious diseases. The estimated number of malaria deaths globally in 2021 was 619,000.[1] To reduce morbidity and mortality related to malaria, the World Health Organization advocated member states to jointly eliminate the disease by 2030 and the global technical strategy for malaria 2016–2030 was adopted by the World Health Assembly in May 2015.[2] To comply with this global mission, Thailand introduced the malaria elimination program in 2016 and established the National Malaria Elimination Strategy (NMES) 2017–2026 which was approved by the Thai cabinet. The goal of NMES is to reach zero indigenous malaria cases throughout the country by 2024 and eliminate malaria by 2026. The strategy includes four steps: 1) Scaling up malaria elimination in Thailand, 2) Developing technologies, innovations, measures, and models that are appropriate for malaria elimination, 3) Developing partnerships among stakeholders at the national and international levels to enable malaria elimination, and 4) Promoting and empowering communities to protect themselves from malaria.[3]

During the first-half of NMES, Thailand successfully reduced the burden of malaria by more than 80% with the number of cases declining from 19,080 in 2016 to 3,266 in 2021. Additionally, malaria transmission foci (villages) have been contained from 1,084 to 495 foci and are concentrated in the border areas with Myanmar, Cambodia, and Malaysia resulting in an increase of malaria free areas from 42 provinces in 2016 to 48 provinces in 2021.[4] However, a resurgence of malaria in 2022, particularly along Thai-Myanmar border, increased the annual incidence to 10,155 cases

across 675 transmission foci in 33 provinces.[4] This increasing number of malaria cases has raised concerns and awareness among Thailand's Department of Disease Control (DDC), Ministry of Public Health and its stakeholders. Therefore, several efforts have been implemented such as strengthening surveillance with active case detection in malaria-affected communities, building up the capacity of case investigation, laboratory testing, and case management, accelerating transmission foci investigations, close monitoring and evaluation of vector control measures, and engaging stakeholders at all levels to integrate malaria elimination into the public health system and local administrations.[5,6] With these efforts, most of the malaria-reintroduced villages reported no further malaria local transmissions within four weeks after the first introduced case was detected. However, some villages continued to report additional indigenous cases and became epidemic areas again.[4]

To describe the malaria situation and identify predictors of malaria in previously malaria-free areas, we identified malaria-reintroduced villages in 2022 and compared epidemiological characteristics, prevention measures, and malaria response activities between villages with and without sustained local transmission for more than four weeks after malaria reintroduction. It is hoped that the findings of this study can help in the prevention of re-establishment of local malaria transmission, particularly in malaria-free areas, and provide recommendations to revise the operational plans of NMES in 2024–2026.

Methods

A descriptive cross-sectional study was conducted to describe the malaria situation in Thailand between 2016–2022 using malaria case report data obtained from the Malaria Information System (MIS). In 2022, malaria-reintroduced villages were identified. Epidemiological characteristics, prevention measures, and malaria response activities including case management were compared between villages with and without local transmission after malaria was reintroduced to their areas.

A retrospective cohort study was conducted to determine predictors for sustained local transmission. Malaria-reintroduced villages in 2022 were the cohort of interest.

Data Sources and Data Collection

Secondary data were obtained from the MIS, a web-based program for reporting malaria cases under the Division of Vector-borne Diseases, Department of Disease Control. The descriptive study included malaria cases between 2016–2022. For malaria resurgence in 2022, 336 malaria-reintroduced villages were identified. We used data of those villages including malaria prevention activities prior to the reintroduction, characteristics of cases, case investigation, and control measures.

Study Population and Definitions

Malaria cases reported to the MIS during 2016–2022; the reporting case definition was defined as any person with or without symptoms of malaria who had the malaria parasite in their blood smear, either thick or thin blood film, or had a positive result of malaria rapid diagnostic test.

Malaria areas according to Thailand NMES were classified as follows; A1—active foci, a village with reported indigenous cases in the current year, A2—residual foci, a village without local malaria transmission within the current year but not yet malaria-free for three consecutive years, B1—high and moderate receptivity, a village in which malaria transmission was not reported within the last three years, but vectors present, and B2—low and no receptivity, a village in which transmission was not reported within the last three years and vectors absent.

Malaria-reintroduced villages identified in 2022 were defined as those being malaria-free for at least one year (malaria area A2, B1, or B2) but found a new malaria case regardless of the source of infection.

Proactive case detection referred to malaria active case search with blood testing in high-risk areas for malaria reintroduction before a malaria case was detected.

A 1-3-7 approach referred to malaria response activities including case notification to the MIS within one day, case investigation to identify the source of infection within three days, and malaria control in the affected area within seven days after malaria diagnosis.[7]

Complete case follow-up, according to the NMES, referred to all malaria cases being followed up at least four times after treatment to ensure clinical and parasitological cure.

Data Analyses and Statistics

Descriptive study

The annual malaria incidence from 2016–2022 was calculated per 100,000 population. Each year, the number of Thai and non-Thai cases were determined. Malaria reintroduction and further sustained local transmission were calculated in 2021 and 2022 to demonstrate the resurgence of malaria in Thailand. Of the 336 malaria-reintroduced villages in 2022, epidemiological characteristics, prevention and control

measures were described as a proportion, mean, or median. Characteristics were described among villages with and without sustained local transmission using a t-test or Mann-Whitney test for continuous variables and Chi-square or Fisher's exact test for categorical variables.

Analytical study

Dependent variable: A dichotomous outcome of interest was considered from 336 malaria-reintroduced villages in 2022. The outcome was divided into two groups, 1) malaria was controlled within four weeks with no further local transmission, and 2) sustained local transmission for more than four weeks after a reintroduced case was reported.

Independent variables: Data of epidemiological characteristics, coverage of malaria preventive measures, and malaria response activities were aggregated to correspond with the unit of analysis (a village) as shown in Table 1.

Data analyses

A multi-level logistic regression model was used to measure the associations between sustained local transmission and potential predictors. This model incorporates a random intercept with the province as a higher-level variable, considering the hierarchical structure of the data (i.e., villages clustered within the province). Potential predictors were identified from the independent variables that had a *p*-value <0.10 from the descriptive study. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) were reported. Epi-info™ version 7, Centers for Disease Control and Prevention, Atlanta, USA and R were the data analytic tools.[8,9]

Table 1. Management of independent variables for data analysis

Independent variables	Variable types		
	From MIS	For descriptive study	For analytical study
Classified malaria area (NMES)	Categorical (A2, B1, B2)	Categorical (A2, B1, B2)	Categorical (A2, B1, B2)
Located in districts with A1 area	Yes / No	Yes / No	Yes / No
Nationality	Categorical (Thai / non-Thai)	Proportion of non-Thai cases in each village	Categorical (≤10%, >10%)
Age (years)	Ordinal	Proportion of cases aged under 15 years in each village	Categorical (≤25%, >25%–50%, >50%)
Insecticidal net provided ≥1 net per 2 persons in last 3 years	Number of nets and population in each village	Yes / No (ratio of nets per population in each village >1:2)	NA
Proactive case detection	Yes / No	Yes / No	Yes / No
Proportion of cases notified within 1 day	Continuous (Proportion (%))	Mean proportion of the villages	NA
Proportion of cases investigated within 3 days	Continuous (Proportion (%))	Mean proportion of the villages	NA
Proportion of cases controlled within 7 days	Continuous (Proportion (%))	Mean proportion of the villages	Categorical (≤50%, >50%–80%, >80%)
4-time follow up of *P. vivax*	Continuous (Proportion (%))	Median proportion of the villages	NA
Complete follow up of *P. falciparum* or *P. knowlesi*	Continuous (Proportion (%))	Median proportion of the villages	NA
Insecticide-treated net or spraying	Yes / No	Yes / No	Yes / No

MIS: malaria information system. NMES: National Malaria Elimination Strategy. NA: not applicable.

Results

During 2016–2021, the annual malaria incidence declined from 11,595 cases (8.3 per 100,000 population) to 3,266 cases (2.0 per 100,000 population). However, in 2022, the incidence increased to 10,155 cases (8.7 per 100,000 population) and both Thai and non-Thai populations were affected. Additionally, as shown in Figure 1, most cases in 2022 were non-Thai, in contrast to the previous periods where Thais predominated.

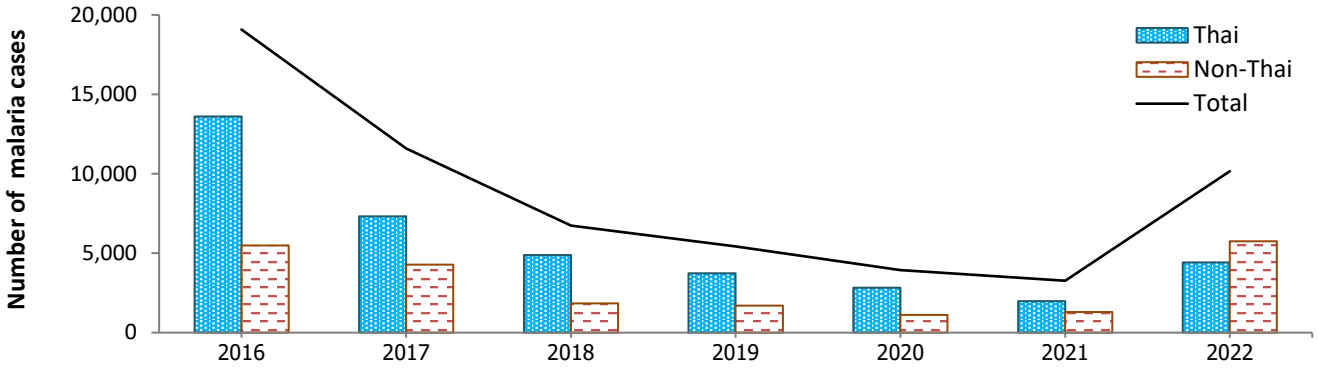

Figure 1. Annual malaria cases (black line) stratified by nationality (vertical bars), Thailand, 2016–2022

The distribution of transmission foci by district in 2021 compared to 2022 is shown in Figure 2. Malaria transmission foci reduced from 1,084 villages in 120 districts (35 provinces) in 2016 to 495 villages in 76 districts (29 provinces) in 2021. However, the number of transmission foci increased in 2022 to 675 villages in 90 districts (33 provinces).

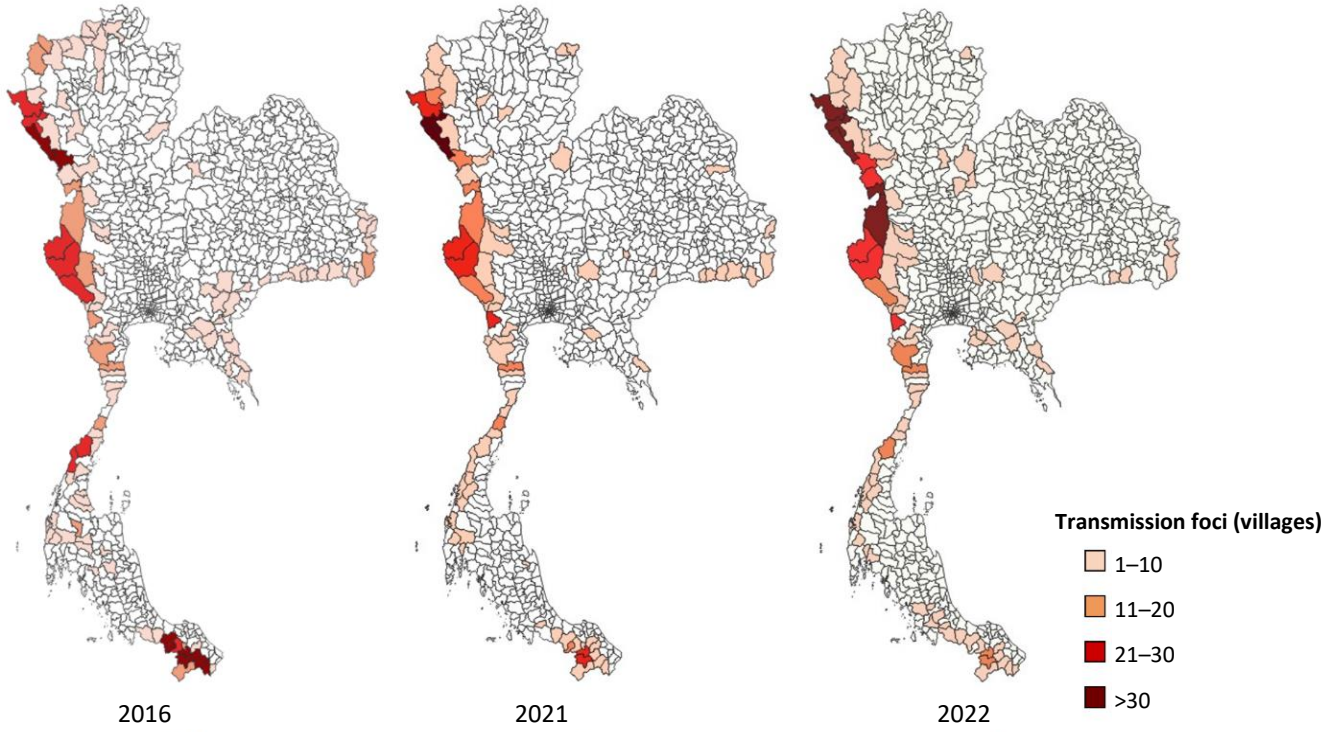

Figure 2. Distribution of malaria transmission foci by district, Thailand, 2016, 2021 and 2022

According to the NMES, the Division of Vector-Borne Diseases, DDC annually classified all villages in Thailand to be A1, A2, B1, or B2 areas to prescribe malaria prevention and elimination measures. Malaria elimination resources and commodities were also mobilized specifically to each area. At the beginning of 2021 and 2022, there were 92,222 and 92,368 malaria-free villages, respectively. In 2021, 132 malaria-free villages reported reintroduction of malaria cases. Of those, 11 (8.3%) could not control the transmission. In 2022, 336 malaria-free villages reported reintroduction, which resulted in 73 (21.7%) having sustained local transmission, as shown in Table 2.

Table 2. Number of malaria-free and malaria reintroduced areas in Thailand, 2021–2022

Year	Number of villages		
	Malaria-free at beginning of the year (A2, B1, and B2 areas)	Malaria reintroduced during the year (%)	Sustained local transmission (%)*
2021	92,222	132 (0.14)	11 (8.3)
2022	92,368	336 (0.36)	73 (21.7)

**Sustained local transmission was defined as villages continuously reporting indigenous cases for more than 4 weeks after a malaria case was reported.*

Considering that the number of malaria-reintroduced villages in 2022 was 2.6 times higher than in 2021, and the proportion of villages with sustained local transmission after the reintroduction in 2022 increased to 21.7%, the risk of a malaria epidemic reoccurring among those reintroduced areas should be determined. Therefore, we compared characteristics of malaria-reintroduced villages in 2022 between the villages with and without sustained local transmission after the reintroduction. NMES classified areas, the proportion of non-Thai cases, proportion of child cases, prevention measures, malaria responses, and control activities are compared between villages with and without sustained local transmission in Table 3. Of the 336 villages compared, 263 (78.3%) could control malaria and stop transmission within four weeks whereas 73 (21.7%) had sustained local transmission. NMES classified areas, Proactive case detection as a malaria preventive measure, and the coverage of insecticide-treated bed nets or spraying when a malaria case was detected had significantly different proportions between the two types of villages. Additionally, villages with sustained local transmission had higher proportions of non-Thai and child cases than villages without sustained local transmission. For 1-3-7 activities, only malaria control within seven days showed a significant lower coverage in the villages with sustained local transmission. Complete follow up of *P. vivax* cases was also lower in villages with sustained local transmission.

Table 3. Characteristics of malaria-reintroduced villages in 2022 compared to villages with and without sustained local transmission after the reintroduction

Characteristics	Malaria reintroduced villages in 2022 n (%)			*P*-value‡
	Total (336 villages)	Without sustained local transmission* (263 villages)	With sustained local transmission† (73 villages)	
Characteristics of malaria-reintroduced villages				
NMES classified area				0.04
A2	132 (39.3)	94 (35.7)	38 (52.1)	
B1	168 (50.0)	140 (53.3)	28 (38.4)	
B2	36 10.7)	29 (11.0)	7 (9.6)	
Located in A1 districts	262 (78.0)	194 (73.8)	68 (93.2)	<0.005
Proportion of non-Thai cases§	55.5%	35.7%	61.6%	<0.005
Proportion of cases <15 years old§	26.8%	24.0%	27.6%	0.06
Coverage of malaria preventive measures				
Insecticidal net provided ≥1 net per 2 persons in last 3 years	63 (18.8)	48 (18.3)	15 (20.6)	0.73
Proactive case detection	75 (22.3)	64 (24.3)	11 (15.1)	0.06
Coverage of malaria response and control activities				
Case notification within 1 day¶	71.5% (38.2)	71.4% (39.2)	71.6% (34.8)	0.97
Case investigation within 3 days¶	76.8% (34.8)	77.0% (35.8)	75.8% (31.3)	0.79
Malaria control within 7 days¶	56.0% (42.4)	58.9% (43.8)	45.7% (35.2)	0.02
Complete follow up of *P. vivax*#	100% (66.7–100)	100% (66.7–100)	90.3% (75.0–100)	0.03
Complete follow up of *P. falciparum* or *P. knowlesi*#	100% (100–100)	100% (100–100)	100% (75.0–100)	0.51
Insecticide-treated net or spraying	128 (38.1)	109 (41.4)	19 (26.0)	0.02

**Malaria was controlled within 4 weeks and no further local transmission. †Having sustained local transmission for more than 4 weeks after reintroduced case was reported. ‡Chi-square or fisher's exact test for categorical variables. T-test or Mann-Whitney test for mean or median respectively. §Calculated from a total number of malaria cases in each group (664 cases in the village without sustained local transmission and 2,179 cases in the village with sustained local transmission). ¶Mean (standard deviation) coverage of cases. #Median (interquartile range) coverage of cases. NMES: National Malaria Elimination Strategy.*

Table 4 presents the results of the multi-level logistic regression model to measure the associations between sustained local transmission and potential predictors identified from descriptive study. Considering villages clustering within provinces, villages located in an A1 district were more likely to have sustained local transmission after malaria reintroduction (AOR 1.03, 95% CI 1.01–1.05) compared to other villages. Villages having a higher proportion of non-Thai cases was strongly associated with sustained local transmission (AOR 12.3, 95% CI 5.69–26.6) and having a coverage of malaria control within seven days higher than 80% of cases was significantly associated with a reduced risk (AOR 0.20, 95% CI 0.09–0.44).

Table 4. Associations of sustained local transmission with characteristics of malaria-reintroduced villages, malaria preventive measures, and malaria response and control activities from the random effect model considering villages clustered within province*

Predicting factors†	Adjusted odds ratio	95% confidence interval
NMES classified as an A2 area	1.66	0.82–3.36
Locating in districts with A1 area	1.03	1.01–1.05
Proportion of non-Thai >10% of cases	12.3	5.69–26.6
Proportion of child cases (%)		
>25–50	0.94	0.38–2.31
>50	0.40	0.13–1.24
Proactive case detection	1.06	0.42–2.65
Insecticide-treated net or spraying	0.54	0.26–1.13
Coverage of malaria control within 7 days (%)		
>50–80 of cases	0.70	0.29–1.68
>80 of cases	0.20	0.09–0.44

**ICC (Intraclass correlation coefficient) = 5 x 10^{-34}. †Independent variables that have a p-value <0.10 from the descriptive analyses were included in the model. NMES: National Malaria Elimination Strategy.*

Discussion

Despite the nationwide implementation of the malaria elimination strategy and efforts, Thailand was not able to achieve the goal of its NMES to stop local transmission by 2024. Our study findings indicate that disease incidence and transmission foci were increasing, particularly in villages located near the Myanmar border. Additionally, the change of epidemiology shows that most malaria cases in Thailand shifted from Thai to non-Thai. After a political crisis broke out in Myanmar in 2021, it was estimated that 4–5 million migrants were living in Thailand.[10,11] Therefore, managing the influx of migrant populations is critical and a serious obstacle to the elimination of malaria.

Among transmission foci in 2022, 336 villages were malaria-free for at least one year, of which 204 were malaria-free for at least three years. Moreover, 73 (21.7%) of these villages could not control the transmission, leading to sustained local transmission. Villages classified as either A2 or located in a district having a village classified as A1 had a higher proportion of sustained local transmission. A1- and A2-classified areas reflect an ecological environment in which Anopheles mosquitoes exist and transmit malaria to humans.[12] We also found that non-Thai cases play a significant role in sustaining transmission and present challenges for the prevention of malaria reintroduction.[13–15] For malaria prevention and response measures, coverage of insecticidal bed net according to NMES (at least one net/two persons/household) was not a significant predictor. This finding is supported by the results of Thailand's malaria survey in 2017 in which only 37% of those surveyed used an insecticidal bed net while sleeping. Therefore, higher coverage of bed net use may not help prevent malaria transmission because the proportion of residents using this protective measure is low. However, malaria response, i.e., malaria control within seven days after index case detection and complete follow-up, particularly for *P. vivax* cases, is important for halting malaria transmission. Similar to another study, imported *P. vivax* infection is a sustained risk for secondary infections among local populations so that timely malaria response, including radical elimination of parasites, is essential.[16]

We found a significant positive association between sustained local transmission of malaria in reintroduced villages and those located in districts classified as A1. The implication is that these areas are receptive and vulnerable for malaria re-establishment.[17,18] Therefore, prevention of malaria reintroduction and effective malaria control should still be in place and targeted to all villages, including those reporting no malaria cases for more than three years. We also found that villages with at least 80% coverage of malaria control within seven days was protective for sustained local transmission. This NMES indicator should be closely monitored and emphasized to all reintroduced cases. Another interesting finding from our analysis is the small intra-class correlation coefficient, which suggests that while the risk of sustained local transmission was associated with several village-level factors, the impact of provincial characteristics on the baseline risk of sustained local transmission was not evident in this study.

Limitations

Similar to other studies that use secondary data, some information of cases and response activities were missing from the MIS, such as complete follow up of

cases and could not be included in the analytical model. Other factors that might affect malaria transmission, e.g., vector profiles in the villages and anti-malaria drug compliance of malaria cases were also not available in the MIS. Their omission could therefore introduce omitted variable bias.

Conclusion and Recommendations

This study demonstrates multiple factors associated with sustained local transmission after malaria reintroduction. Although most villages in Thailand are free from malaria, the increasing influx of migrant populations throughout the country increases the risk of malaria reintroduction. Since resources for malaria control are limited, and requires well-trained vector control staff to handle disease outbreaks, reintroduced cases must be detected as early as possible and preventative measures of local transmission should be strictly implemented. To proactively detect an imported case, all malaria-free areas in Thailand should be assessed for their receptivity and vulnerability for malaria reintroduction. Villages which have ecological environments that support vector breeding should be considered as receptive areas whereas villages with migrant populations should be considered as vulnerable areas. Malaria screening among migrants should be integrated through an existing public health program, e.g. migrant workers health checkup when applying for a work permit. Coverage of proactive case searches among migrant populations should be an additional indicator of the malaria operational plan. Radical cure with complete follow up of *P. vivax* is usually difficult among migrant population and causes *P. vivax* carriers to remain in the population. The DDC should consider alternative or innovative treatment such as short-course of primaquine or long-acting single dose aminoquinoline providing them with an on-site glucose-6-phosphate dehydrogenase (G6PD) testing to ensure G6PD normal status.[19–22] Indicators of complete anti-malaria treatment and radical cure with complete follow up should also be separately evaluated among non-Thais to clearly understand the situation and can be targeted to areas with low completeness. Finally, a multisectoral approach targeting migrant populations in receptive and vulnerable areas needs good collaboration between public health and other sectors to reach the target populations. An action plan for the prevention of malaria re-establishment at local levels should be developed by all stakeholders.

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Conflict of Interest

The author declares that there are no conflicts of interest regarding the publication of this article.

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