Chapter 5

Human and Simian Malaria in the Greater Mekong Subregion and Challenges for Elimination

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Additional information is available at the end of the chapter

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Abstract

In recent years malaria initiatives have increasingly shifted from malaria control to a focus on achieving malaria elimination in the Southeast Asia region. However, this region experiences unique challenges in this transition due to its distinctive malaria ecosystem (mainly related to forests) and high volume of population movement (both within and between countries). These bioenvironmental factors increase the exposure of populations at higher risk due to their close association with forest, and contributes to outdoor and residual transmission. Given that this region has also historically been the source of resistance to anti-malarial drugs, the potential spread of artemisinin resistance via global transportation routes would pose a major threat to malaria control and elimination efforts worldwide. In addition, other factors also hinder the malaria elimination goal such as importation of parasite infection, uncontrolled monkey malaria (*Plasmodium knowlesi*), or the fact that many countries in this region experience mixed infections where *P. vivax* becomes a more predominant species as overall malaria transmission decreases. This chapter addresses these challenges in detail and provide recommendations and key priorities to overcome these obstacles to accelerate efforts for achieving malaria elimination.

Keywords: malaria, elimination, Greater Mekong Subregion, drug-resistance, *Plasmodium knowlesi*, vivax malaria, residual transmission

1. Introduction

In the Greater Mekong Subregion (GMS)[1], malaria is still a substantial public health problem, especially along international borders and forested areas, adversely putting populations such as migrants, refugees, and forest workers most at risk. In 2013, there were 447,800 malaria cases and 342 deaths in the GMS, with close to 700 million people living in risk areas [1]. Between 2012 and 2016, the reported number of malaria cases in the GMS fell by 74% (**Figure 1**) and malaria deaths by 91% in the same period (**Figure 2**).

Mid-year estimates for 2017 point to a further decline in cases [2]. Contributing to these impressive results, all six countries of the Subregion are making significant headway towards a common target: eliminating malaria by the year 2030 at the latest.

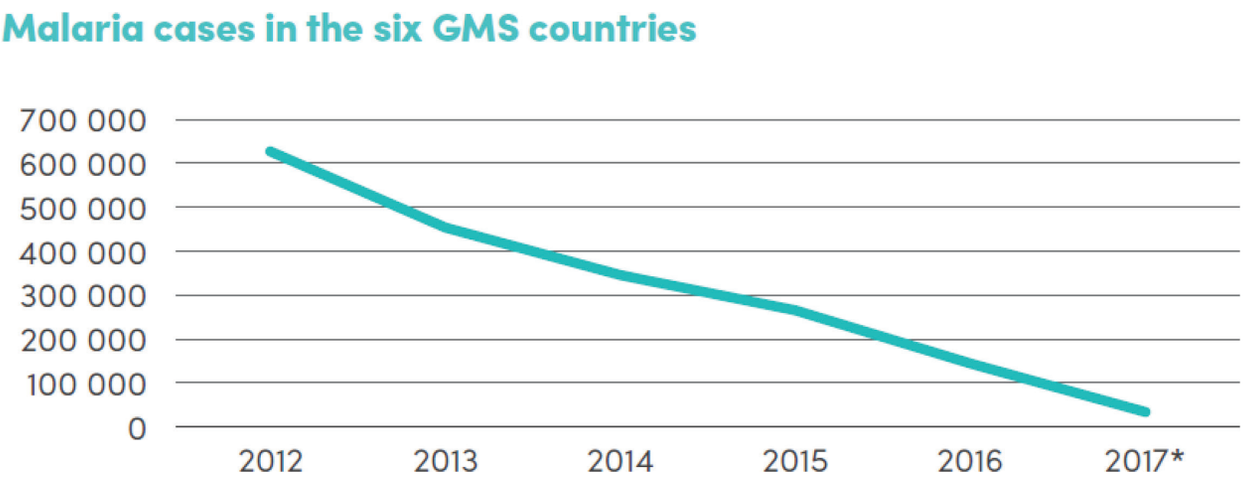

Figure 1. Declining trends of malaria transmission in the Greater Mekong Subregion (GMS) since 2012 (source: [2]).

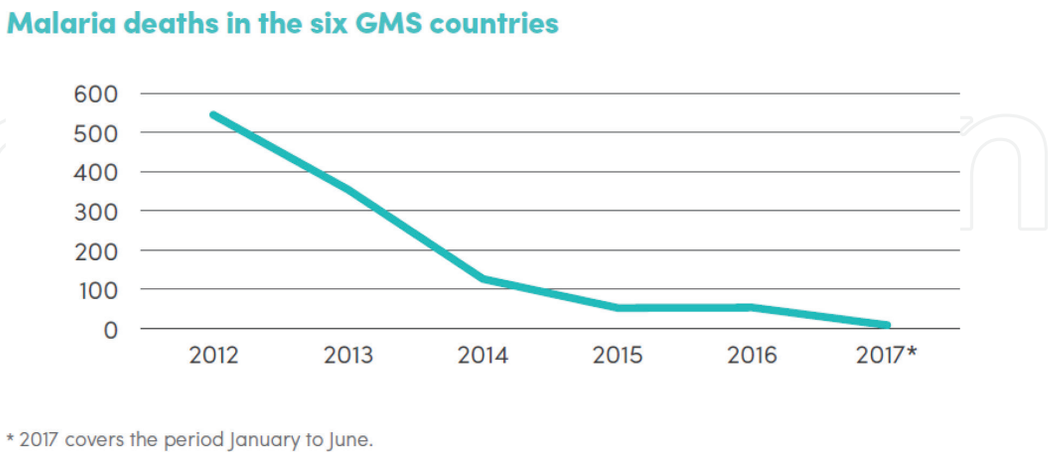

Figure 2. Declining trend of malaria deaths in the Greater Mekong Subregion (GMS) since 2012 (source: [2]).

[1]Cambodia, The People's Republic of China (specifically Yunnan Province), the Lao People's Democratic Republic (Lao PDR), Myanmar, Thailand, and Vietnam.

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These goals will not be easy to achieve. Despite these reductions and the subsequent move towards elimination, malaria remains an important cause of morbidity for an estimated 32 million inhabitants, especially in remote areas with low population densities and limited healthcare services and infrastructure, located in and near forested areas, which often lie close to international borders [3, 4]. In many places, the population groups most affected are ethnic minorities and forest-goers who are rapidly becoming the most important source of transmission in areas where main vectors are present. Within these groups, cultural and linguistic barriers often constrain malaria control efforts due to their high mobility and low access to interventions to prevent, diagnose and treat malaria.

In some areas the malaria situation has deteriorated by armed conflict affecting access to malaria control services. Population movements are a key feature in the GMS and are largely occupationally/economically driven; occur within borders and across borders; involve multiple factors and complex dynamics of movement; and affect different subsets of moving populations [5], thus further complicating the epidemiology and control of the disease [6]. The rapid increase in the number of large infrastructure and agricultural development projects in the region is also having a significant impact on the epidemiology of communicable diseases in general, and malaria in particular [7]. This chapter addresses several key challenges faced by elimination programmes to contain the unacceptably high disease burden against the background of rapidly declining incidence.

2. Resistance to artemisinin and ACT: current and future approaches

Antimalarial drug resistance is not a new biological phenomenon. In the 1970s and 1980s, *Plasmodium falciparum*—the parasite species responsible for the most common and deadliest form of malaria—developed widespread resistance to previous antimalarial medicines, such as chloroquine and sulfadoxine-pyrimethamine (SP) [8]. Artemisinin based combination therapies (ACTs), introduced in the 1990s, are currently the most effective antimalarial drugs [9] and represent the first line-treatment for uncomplicated falciparum malaria in all endemic countries.

Although artemisinin usually kills all malaria parasites, the use of a combination of drugs—as opposed to monotherapy—helps ensure that any remaining parasites will be killed by the partner drug before the resistant parasites can spread. According to the World Health Organisation (WHO), clinical artemisinin (and its derivatives) resistance is defined as delayed parasite clearance and represents a partial/relative resistance that has thus far only affected ring-stage malaria parasites [10]. In Southeast Asia, however, some malaria parasites have already developed resistance to artemisinin-based drugs; a recent report of a single multi-drug resistant malaria parasite lineage (PfPailin) with associated piperaquine resistance in Vietnam and its implications of subsequent transnational spread is of international concern [11]. Artemisinin resistance was first reported along the Thailand-Cambodia border in 2008 [12, 13] and has continued to spread in all Greater Mekong Subregion countries [14–18]. In addition, artemisinin resistance has been involved in selecting for resistance to ACT partner drugs, resulting in high late treatment failure rates with dihydroartemisinin-piperaquine in Cambodia [14, 19–25] and with artesunate-mefloquine on the Thai-Myanmar border [26].

There are many factors that are thought to have contributed to the emergence and spread of artemisinin resistance in the GMS. One important factor is thought to be the use of oral artemisinin monotherapy (AMT) in place of WHO-recommended ACTs (as unregulated artemisinin or artesunate monotherapy has been available since mid-1970s in the region). In Myanmar, private healthcare facilities and healthcare providers who prioritize consumers' demand instead of recommended practices were more likely to stock oral AMT [26, 27]. Malaria elimination strategies should include targeted interventions to effectively reach these outlets. Fortunately, a major achievement during the resistance containment (and more recently elimination) activities has ceased the use of artemisinin monotherapies. ACT watch methods are monitoring displacement of oral AMTs, a major objective of the resistance containment strategy [28], and data will feed into regional score cards such as the Asia Pacific Leaders Malaria Alliance Access to Quality Medicines Task Force and the World Health Organisation (WHO) Emergency Response to Artemisinin Resistance (ERAR), which are vested in supporting national programs in tracking progress towards halting the availability and use of oral AMTs [28]. In Southeast Asia, where malaria transmission is generally low and emergence of resistance has been documented in multiple independent locations [29]; containment programmes have been converted into elimination of *P. falciparum* strategies to ensure halting the spread of resistance entirely.

Other contributing factors are the use of substandard and counterfeit anti-malarial drugs and the difficulty of controlling malaria within migrant and hard-to-reach populations [30]. Given the transnational nature of this problem, the establishment of effective mechanisms for cross-country surveillance, information exchange and coordinated action is also necessary. This includes reinforcing existing institutional frameworks for regional health cooperation, particularly the Association of Southeast Asian Nations, and their potential to support enhanced capacities and cooperation to address this challenge [31]. Lastly, selection pressure—genetic mutations of wild-type genes in the parasite render them insusceptible to antimalarial drug treatment—is also thought to be important. The use of antimalarial drugs in patients with parasites containing mutations can eliminate susceptible parasites but leave resistant mutants to survive and reproduce [32].

More recently another potential contributing factor has been hypothesized. Given that there are parasite isolates that do not infect some *Anopheles* species, it is thought that artemisinin-resistant parasites are spreading so fast in Southeast Asia because they infect most or all native *Anopheles* species (e.g., *Anopheles dirus* and *An. minimus*), including African vector counterparts such as *An. coluzzii* (formerly *Anopheles gambiae* M form) [33]. The ability of artemisinin-resistant parasite clones to infect three highly genetically diverse vectors suggests that these resistant parasites have enhanced their transmission in the region and could effectively spread in sub-Saharan Africa, where most of the world's malaria mortality, morbidity, and transmission occurs [33, 34].

Since there are no equally effective alternative drugs to treat malaria, the spread of artemisinin resistance through India (Asia) to Africa and beyond could be a catastrophic setback to global efforts to control and eliminate the disease. Infection and mortality rates could dramatically increase in both regions, reversing the progress made towards malaria control and elimination efforts. The spread of artemisinin resistance would in turn expose the partner drugs in ACTs to greater selection pressure for the development of resistance and increased failure rates for the treatment of uncomplicated malaria. For severe malaria, the recent change in recommended treatment from quinine to artesunate [35] increased survival by 25%, and

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many endemic countries have adopted (or are adopting) this policy [36, 37]. Reverting back to quinine because of artemisinin resistance would also jeopardise all these gains achieved in the management of severe malaria.

The spread of ACT resistance requires constant and comprehensive monitoring across regions. Continuous monitoring of drug resistance in malaria-endemic countries along with contributing factors is a key and will enable health authorities and practitioners to prevent drug resistance from spreading. WHO issues regular reports about the status of artemisinin resistance in malaria endemic countries [38], provides updates on the status of resistance to artemisinins and ACT, and maintains a network of sentinel sites performing therapeutic efficacy studies of first and second-line antimalarial drugs [38, 39].

3. Targeting interventions in hard-to-reach population groups

Although most of malaria endemic countries in Southeast Asia have incorporated malaria elimination goals in their national strategic plans, yet this region experiences high volume of population movement (both within and between countries) causing a great hindrance in achieving their elimination targets given the increased risk of importation of infection, spread of drug resistance, and challenges in providing healthcare services to mobile populations at higher risk of malaria [40, 41].

It is the movement of populations that results in importation of new infections leading to a source of local transmission [42, 43]. Cross-border movement of populations has contributed to establishment of "hot-spots" of high transmission along international borders [44, 45], and spread of drug resistance [6], because mobile populations often experience delays in receiving diagnosis and treatment, have improper health-seeking behaviour or self-medicate [88], and are subject to lower levels of surveillance [41, 46, 47]. Population mobility in the GMS is strongly associated with shifting land use, including large rural infrastructure projects and agricultural industries that attract migrant labor and influence human-vector contact. With the recent Association of Southeast Asian Nations (ASEAN) Economic Community agreement, allowing free movement of goods, services and labor between ASEAN countries [48]; population movement is expected to rise even more in the coming years [6].

In addition, the epidemiology of malaria in many parts of Southeast Asia is shifting toward migratory labor force that gets exposed to vectors in the forest, construction sites, and has variable access to healthcare services [46, 47, 49–53]. Since forested regions are concentrated along borders and much of the cross-border movement is from the migrant labor population, malaria prevalence in these pockets was hypothesized to represent foci of hotspots. Following this rationale, the increased malaria risk in these groups was recently documented in a cross-border malaria project conducted in the Thai-Cambodian, Lao-Cambodia and Vietnam-Cambodian borders. In this study [45], it was observed that the odds of infection in security/armed forces and forest-goers was 8 and 13 times higher compared to low-risk occupations (e.g., teachers, traders, salesmen, etc.). Mechanisms and risk reduction strategies should be in place to appropriately cover these special occupational high-risk groups.

Therefore, although population mobility is a key factor to take into account when addressing drug resistance, it suffers from a range of challenges that limit countries' capacity to effectively engage and deliver interventions to migrant and mobile populations (MMPs). In addition, outdoor biting mosquitoes represent a major challenge for vector control for MMPs working during the night or sleeping outdoors, as well as forest-fringe communities.

Another challenge is the large proportion of asymptomatic infections within geographical clusters of high malaria transmission (hot-spots), where infections with low and submicroscopic parasite densities are highly prevalent in MMP and other risk groups [54]. Asymptomatic carriers can repeatedly fuel transmission to surrounding areas as the vector population expands during the wet season [55–57]. Whilst groups of homesteads consisting of asymptomatic carriers can act as stable clusters over several years [7], it is likely that the flight range of 800 m for *An. dirus* may account for increased probability of repeated mosquito feeding in the same house and clustering of cases over the dry season in Southeastern Thailand [58]. Recent clusters of malaria infection among the parasite reservoir responsible for preserving malaria over the dry season in Ratanakiri Province (northeastern Cambodia) may also explain recurrent transmission at the onset of the rainy season when the vector populations expand [59]. This reservoir is often not (completely) covered by control strategies [60] and parasite specific approaches are non-existent [61]. Programmatic interventions to interrupt transmission in "hidden" asymptomatic reservoir must focus on individuals with malaria infection at early stage, as asexual parasitemia left untreated will eventually produce gametocytes, and diagnostics for the sexual stage are limited [62].

This represents an important hindrance to malaria elimination as these infections are unlikely to be detected by passive surveillance and conventional diagnostic tools, and therefore require additional approaches to effectively reach all infections [63]. A combination of methods, or new diagnostics, may be required to detect infections in these asymptomatic parasite reservoirs. Also, a cross-sectoral response, involving non-health government agencies and the private sector addressing the links between malaria transmission, mobility and labor, will play an important role in responding to drug resistance and achieving elimination in the Southeast Asia region. Preliminary studies of the use of peer outreach workers to conduct screening of suspected cases, providing health education, and distributing nets in hot-spot areas in or near the forest, suggest that it is feasible to target high-risk populations in a culturally appropriate and evidence-based manner to reach the goal of elimination in Pursat Province, Cambodia [64]. Mobile Malaria Workers or peer outreach activities often face logistic challenges including muddy roads, river crossings, and transportation difficulties that make it hard to quickly respond to all infections. The recent President Malaria Initiative (PMI) studies show this is a potential resource that can be piloted or replicated across GMS countries (John Hustedt, personal communication).

Lastly, persisting low health-care coverage and access in remote locations remains an important challenge for mobile populations and migrant workers in some Southeast Asian countries, limiting the ability of malaria programmes to effectively capture these groups through the routine surveillance system, but most importantly to adequately provide the necessary preventive measures and care needed [65]. It is encouraging, however, to see that malaria infection rates in people who had sought treatment, or blood-smear examined in a previous malaria episode, and/or who knew how to prevent malaria (e.g., sleeping under a mosquito net), tend to be lower than those that did not seek treatment or had inadequate malaria knowledge [45]. This highlights the

importance of scaling up and expanding the reach of point of access care and dissemination of information, such as through border posts or at large development or construction areas that are likely to host high-risk malaria occupational groups. These posts can potentially be used as effective channels to target and deliver specific interventions such as Behavioral Change Communication (BCC) materials, insecticide-treated uniforms or hammock nets.

Therefore, there is an urgent need to develop appropriate and sustainable malaria services for MMPs in different settings, in the context of the spread of artemisinin resistance and malaria elimination in the GMS. Different types of mobility require different malaria control interventions and therefore elimination strategies that should be based on an in-depth understanding of malaria risk in each group [66]. A population movement framework can assist in improved targeting of malaria (and other public health interventions) by going beyond a simple labeling of risk groups to develop a better understanding of risk behaviour and vulnerabilities. The implementation of the framework should be carefully evaluated to identify the changes in coverage, access, and effectiveness of the programme efforts to serve MMPs [67].

4. Residual and outdoor transmission: how much and where?

In 2012, global malaria transmission was reported as mainly attributable to 51 *Anopheles* species, with an average of about 3 major species per country [68]. Biological factors that determine whether a species becomes a major local threat are its competence for transmitting human malaria parasites, its anthropophilic *versus* zoophilic preference, and its abundance in relation to its ability to multiply, survive, and compete for resources with other *Anopheles* species. The third of these factors is regulated by the ecosystem's carrying capacity for potent vectors depending on their ecological niches [69]. Species of several *Anopheles* complexes are either major or secondary malaria vectors depending on their geographical range of distribution [70]. The peculiarity of these sibling species within a complex is that they cannot be distinguished using morphological criteria. However, several Asian malaria vectors within the Dirus, Leucosphyrus, Minimus, Maculatus, Culicifacies, Sundaicus, Subpictus complexes or groups show similar morphological characteristics, different ecological traits and vector competencies and overlapping geographical distribution with other vectors and non-vectors [70, 85, 92]. As some of these sibling species occur sympatrically and differ in their ability to transmit malaria and in their behaviour, the use of molecular tools to differentiate the vectors from the non-vectors is essential to target the correct species in vector control programs.

Malaria vector control relies largely on Long-Lasting Insecticidal Nets (LLINs) and Indoor Residual Spraying (IRS), along with Larval Source Management (LSM) as a supplementary measure appropriate in certain settings. These core interventions are highly efficacious for control of susceptible malaria vectors when implemented at universal coverage; LLINs and IRS contributed to a 48% reduction in malaria infection prevalence and 47% reduction in mortality worldwide between 2000 and 2013 [71]. However, malaria transmission can persist even when LLINs and/or IRS are effectively implemented and malaria vectors are susceptible to the insecticides used. This may be due to a combination of vector and human behaviour and bionomical characteristics, which compromise inadequate control measures against early and/or outdoor biting mosquitoes, and human activity away from protected houses or places

at peak biting times. With current efforts focusing on malaria elimination [72], there is considerable interest in vector behaviour that is not influenced by application of core interventions (i.e., conventional IRS and Insecticide Treated Nets (ITNs)), such as feeding earlier and resting outdoors when humans are not protected. For example, an unprecedented malaria outbreak, related to illegal rosewood logging, occurred in 2014 with a seven-fold increase of cases in 1 year in Ubon Ratchathani Province, Northeastern Thailand [73]. Insecticide-susceptible and exophilic *An. dirus s.l.* were collected from a forested area in Ban Pakla and Chong Ta Ou Thai border control station, including *An. maculatus s.l.* collected remote villages with potentially low insecticide pressure [73]. These susceptible vector species are less amenable to control interventions due to their behaviour and their interactions with humans contribute to persistent residual transmission and represent barrier to success [74, 75].

From a geographical perspective, residual malaria parasite transmission has been reported across numerous transmission settings, even with good access and usage of LLINs or well-implemented IRS [76–80]. From the programmatic perspective, residual malaria transmission (RMT) is defined as the persistent malaria transmission that occurs once universal coverage of LLINs and maximal coverage of IRS have been achieved. Identification and elucidation of RMT requires the following pre-conditions: (a) comprehensive and up-to-date LLIN and IRS coverage data, where coverage is defined as 100% access and usage of ITN/LLIN or IRS [81]; (b) outdoor human activity or behaviour to allow identification of outdoor sites and "gaps" in protection, not only before sleeping time, but also for people that remain outdoors during the night. In many countries of the GMS, LLIN and IRS distribution data are sparse or not readily available. Where these data are available, it is often compiled at a relatively high administrative level, such as district or province. Malaria transmission at the community level can vary considerably within a small area and thus to investigate RMT at this level, LLIN and IRS coverage data by village are necessary. Furthermore, LLIN coverage figures quoted at the province or district level often do not match the actual situation at the community level, perhaps due to inequities in distribution, inaccurate population estimates, and calculation of procurement need, limited replacement of outdated and damaged LLIN; the outcome of which could lead to an underestimation of the magnitude of RMT.

As malaria is becoming more and more restricted to hard-to-reach population groups, alternative or adapted control strategies are required who are somehow marginalised, poor, on the fringes of the public health system, living in dwellings that are either very close to the forest or harbour people who are exposed to the forest through their occupation (e.g., development sites and seasonal labour areas) or mobility behaviour. As shown in **Table 1**, the risk of RMT in the malaria foci is spread over the entire night, from dusk-to-dawn, requiring a combination of complementary vector control measures, such as long-lasting insecticide hammock nets (LLIHN) that can be used during different periods of the night. However, the use of LLIHN, single LLIN/ITN or topical repellents in the field may not be acceptable due to cultural and linguistic barriers of ethnic minorities and MMPs for which specific acceptability studies should be conducted to guide the feasibility of these vector control tools.

Another driver of RMT is mega and micro-development projects impacting the forest or creating new conditions suitable for vector species, and often attracting a substantial workforce from various horizons across borders and cultural boundaries [6]. Their sleeping or residential places can have additional vulnerabilities if they are remote, comprising mainly ethnic

minorities, or in conflict areas, all of which can hinder access to the public health system. Another key concern is to restrict or mitigate the widespread dispersal of parasites by these elusive population groups.

Just as forest workers often stay in the forests for several days and sleep exposed to vectors [84], rubber tappers also work in plantations at night with higher likelihoods of being bitten by *Anopheles* mosquitoes, in particular vector species of the Dirus Complex [3, 85]; they all have poor access to healthcare services [86]. Plantation work is seasonal, and manpower is often composed of highly mobile seasonal migrants, but little is known about their patterns of movement. More malaria infections were observed in people with temporary labour positions and plantation workers at the Thailand-Myanmar border [87], but this was not confirmed due to a very high proportion of the study participants opting to perform forest or field activities, and a very low number opting to work in rubber plantation [59]. Many migrants that arrive for rubber tapping settle beyond the harvest season [87] and go on to work on other cash crops (e.g., rice,

District, province, country	Ecotype	% Access to LLIN	% Use of LLIN	Proportion of *Anopheles* bites or infective bites in relation to sleeping time	Reference
Eastern region: Borkeo & O'Chum districts, Rattanakiri Province; Western region: Pailin & Pursat Provinces; Cambodia	Forest plots & villages	68.4% (Ratanakiri)	70.7% (forest workers)	After 22:00 h 71%	[53, 102]
	Forest plots	69.2% (Pailin); 81.8% (Pursat)	66.3% (forest workers)	Before 22:00 h 29%	
Ma Noi and Phuoc Binh communes, Ninh Thuan Province, south-central Vietnam	Village	NA	85%	Before 22:00 h 45% (bites only)	[83]
	Way to the forest	NA	NA	Before 19:00 h 13% (bites of *An maculatus)*	
	Forest plots	NA	53%	Before 21:00 h 64% (bites only)	
Tha Song Yang, Tak Province, Thailand	Village[a]	78%	80%	Before 21:00 h and 05:00 h	[82]
	Hamlets[b]	100%	75–95%	20.0% Suan Oi	
	Farm huts	NA	NA	33.7% Pha Man	
				37.6% farm huts	
Son Thai commune, Khan Hoa Province, central Vietnam	Village	78%	95%	Before 20:00 and 05:00 h	
	Farm huts	NA	62.7%[c]	26% farm huts	
	Forest	NA	25%[c]	37% forest	

NA: not available.

[a]Suan Oi village.

[b]Pha Man & Komonae hamlets, Thailand [82].

[c]Regular use of LLIN.

Table 1. Overview of residual malaria parasite transmission (RMT) in various ecological settings in Greater Mekong Subregion.

cassava, fruit orchards). On return to their usual settlements, they contribute to the spread of malaria within and across international borders [41, 43]. By creating hot-spots of malaria and disproportionately affecting people with certain high-risk occupations [86, 89], residual transmission under these circumstances has so far hindered progress towards elimination.

5. Correct identification of malaria vectors and *Plasmodium* detection

High levels of malaria transmission occurring in forest-fringe areas of Southeast Asia is explained by movements of people in search of forest products and exposure to many highly efficient vector species that have adapted to forest ecotypes [66, 85, 102, 103]. The wide diversity of both the deep-forest (e.g., Leucosphyrus Group of mosquitoes), forest-fringe and deforested area main vectors (e.g., *An. minimus*, *An. maculatus s.l.*, *An. culicifacies s.l.*, *An. fluviatilis s.l.*, *An. letifer*, *An. donaldi*), as well as their great potential to adapt to habitat changes, means that the consequences of deforestation on malaria transmission in Southeast Asia are difficult to predict and unlikely to be unidirectional [104]. Whilst *An. dirus* and *An. baimaii*, main vectors of the Dirus complex, can find tree-crop plantations suitable for breeding, a close association between malaria and rubber plantations has been demonstrated [4, 105–108], contributing to high larval and pupal density during the rainy season [90, 91] and low numbers during the cool-dry season [92, 109], or provide conditions that are similar to this vector's natural habitat [110]. This ecological adaptation in human settlements and shaded plantations contributes to outdoor transmission among rubber tappers.

The identification of secondary or incidental vector species poses new challenges as shown by mixed results of sporozoite-positivity using nested Polymerase chain reaction (PCR) and routine circumsporozoite enzyme-linked immunosorbent assay (CSP-ELISA) (**Table 2**). Confirmation of all positive CSP-ELISA results by a second CSP-ELISA test on the heated ELISA lysate, especially in zoophilic species showed a relatively high proportion of false positives (40%) [93]. On the other hand, PCR analysis of Deoxyribonucleic acid (DNA) extracted from the head and thorax alone, along with sequence data, revealed five *Anopheles* species (*An. hyrcanus*, *An. barbirostris s.s.*, *An. barbirostris* clade III, *An. nivipes*, and *An. peditaeniatus*) infected with *Plasmodium falciparum,* which are not considered major vectors in the GMS [94]. Similarly, out of 11 *P. falciparum* CSP positive samples from Bangladesh, seven turned out to be positive by PCR suggesting that *An. maculatus*, *An. jeyporiensis* and *An. nivipes* play important roles in malaria transmission in Kuhalong District [95]. In Vietnam, the role of a secondary vector, *An. pampanai* infected with *P. vivax*, was also reported in the Binh Phuoc Province [96]. Morphological misidentification of the closely related sympatric species, such as *An. aconitus*, *An. pampanai* and *An. varuna* are common [99, 100]. Morphological identification of *Anopheles* specimens prior to PCR assays allows them to be sort out at the group or complex level but does not permit species identification [85]. PCR assays must be applied for a reliable identification to the species level, which ensures that data received by malaria vector control programmes are suitable for targeting the correct vector species [101]. Given the low infection rates among many of these species especially in elimination phase, it is important for field entomologists to assess various

Morphological *Anopheles* species*	Nested PCR, Cambodia [93]		Circumsporozoite ELISA, Thailand [97]		Prior heating of eluate and circumsporozoite ELISA, Bangladesh [98]		PCR confirmation of ELISA-positives Bangladesh [95]	
	Total collection (%)	Positive/ total	Total collection (%)	Positive /total	Total collection (%)	Positive /total	Total collection (%)	Positive / total
An. maculatus s.l			21.43	4/640			4.3	2/97
An. annularis s.l.			14.43	3/431	0.78	1/19		
An. kochi					0.93	1/44		
An. barbirostris s.s.	6.6	3/55	3.52	1/105	2.9	1/140	7.4	1/186
An. peditaeniatus					5.08	3/139		
An. hyrcanus	0.09	2/2						
An. nigerrimus	0.87	1/21					4.1	1/104
An. philippinensis		3/219			24.7	25/1169		
An. vagus					41.9	25/1978		
An. nivipes							10.8	1/264
An. jeyporiensis					3.1	1/142	18.9	2/479
An. karwari					5.16	11/244	1.7	

*Molecular identification was specifically conducted on *Anopheles barbirostris* s.s. and *An. barbirostris* clade III; *An. hyrcanus* and *An. hyrcanus* s.s; *An. peditaeniatus* and *An. nivipes*, and morphological identification for the other *Anopheles* species.

Table 2. Sporozoite infectivity rates of less known (secondary) vectors along the Bangladesh-Thailand-Cambodia corridor.

species' role in malaria transmission in the eco-epidemiological context. When changing objectives from control to elimination of malaria in Southeast Asia, the need to focus not only in the so-called main vector species, but also on secondary vectors is increasingly important.

Deforestation may deplete the populations of deep-forest vectors and so initially reduce malaria transmission; in some localities this depletion may be followed by the invasion of other efficient vector species resulting in increased transmission. With the exception of two longitudinal studies examining the effects of progressive land use changes from pre-development forest to oil palm cultivation on the distribution of disease vectors and malaria incidence [111], there is a striking lack of primary research directly measuring the impact of deforestation on malaria in Southeast Asia [104]. Recent studies showed that *An. dirus s.l.* was abundant in rubber plantations in Myanmar [109] and *An. baimaii* (molecularly identified) adults were caught from human landing collections in Wae Kha Mi, Mon State, the site of an acceptability study of permethrin-treated clothing [110]. In Lao PDR, a total of 46 *An. dirus s.l.* were collected, of which 31 were

from immature rubber plantations, nine from mature rubber plantations, five from secondary forests and one from the rural village [105] (Tangena Julie-Ann, personal communication).

6. *Plasmodium knowlesi*: an additional challenge to malaria elimination

Plasmodium knowlesi, a simian malaria parasite, is now considered the 5th parasite affecting humans [112]. All countries in Southeast Asia have reported cases of *P. knowlesi* with the exception of Lao PDR and Timor Leste [113]. Since most countries are now working towards malaria elimination, it is pertinent to pay serious attention to malaria cases especially in areas where malaria has been reduced to very low levels. A good example is Sabah, Malaysian Borneo where large numbers of *P. knowlesi* were diagnosed in areas where *P. falciparum* and *P. vivax* were occurring in very low numbers [114]. Malaysia is working towards malaria elimination by 2020 and currently more than 60% of the malaria cases are due to *P. knowlesi* (MOH personal communication).

Recently, an increasing number of cases of *P. knowlesi* were reported from Kalimantan and Ache in Indonesia [115, 116] where malaria was in process of being eliminated. In Northern Sumatra, Indonesia where they are working towards malaria elimination, they recorded only 614 (16.5%) positive malaria cases by microscopy out of 3731 people examined [117]. However, PCR detected malaria parasites in 1169 (31.3%) individuals. Of these, 74.9% were mono-infection and 25.1% were multiple infection. *P. falciparum* constituted 24.8%, *P. vivax* 33.9%, *P. malariae* 9.3%, and *P. knowlesi* 32% [114] of the cases. It was also found that the primers developed from the SICAvar gene were more sensitive than the SSU rRNA gene [117]. It is obvious that parasite species are being mis-identified and many people who are asymptomatic are also missed by conventional microscopy [117, 118]. Thus, it is important to develop Rapid Diagnostic Tests (RDTs) that can be used by field workers to detect accurately malaria parasite species, especially *P. knowlesi,* and also additional laboratories should be established to conduct molecular assays for malaria diagnosis in the context of malaria elimination.

Deforestation and changes in the environment are the key factors leading to a surge of *P. knowlesi* malaria [119]. This parasite occurs in *Macaca fascicularis* (long-tailed) and *Macaca nemestrina* (pig-tailed) monkeys and its distribution is limited by some species of the Leucosphyrus Group of *Anopheles* mosquitoes [120]. These species are found biting in greater abundance in forest and farms compared to villages [121, 122]. However, in Sabah, Malaysian Borneo, it was found that *An. balabacensis* was abundant in villages as well [123], and sporozoite-positive specimens were reported in addition to farms and forest [123], while infective mosquitoes were found only in the forested sites and farms in Sarawak (Borneo) and Pahang (Peninsular), Malaysia [121, 122]. In addition, vector studies have also been conducted in Vietnam [124, 125] where the species *An. dirus* has been incriminated as the simian malaria vector in Khanh Phu—South Central Vietnam. Studies were conducted in the forest and forest-fringe areas near Nga Hai village where both human malaria parasites, *P. falciparum* and *P. vivax*, were found along with *P. knowlesi* in order to determine the potential role of *An. dirus* as bridge vectors of *Plasmodium* parasites from monkeys to humans [126]. Based on these studies, it was possible for *An. dirus* to pick up infection from humans and macaques during the mosquito's lifespan. However, since there have been no reports of epidemics of *P. knowlesi,* it is believed that humans are infected by mosquitoes

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which acquired infection from the macaques. Perhaps even likely given that confirmed vectors of human plasmodia in Southeast Asia also become naturally infected by the monkey malaria species [127]. A recent case control study conducted in Sabah revealed that the age group >15, predominantly males, working in farms, plantations, forested areas, and with travel history, were independently associated with the risk of acquiring knowlesi malaria [128]. It also highlighted that IRS was associated with decrease of risk [128].

There are only few investigations on record in understanding bionomics of vectors transmitting *P. knowlesi* malaria. In order to implement vector control activities, the bionomics of the vectors must be understood. Based on few studies, it has been shown that the vectors are biting in the early part of the night from 18:00 h to 21:00 h and mostly outdoors [121–123, 129]. In these rural areas, people go to bed by 22:00 h and they are up by 05:00 h. The results showed that only 39.79% of *An. balabacensis* [123], 43.8% of *An. latens* [121] and 12.8% of *An. cracens* [122] were found biting during this sleeping time. Thus, current vector control measures like IRS and ITNs are not appropriate for the exophagic and exophilic vectors. The forests in Southeast Asia is providing a favorable environment with high percentage of macaques being positive for *P. knowlesi* [130–132], and with the presence of the vectors, it is going to be a daunting task to eliminate malaria. On a global scale, malaria has been reduced to low levels due to the scaling up of ITNs, IRS, ACTs, and intermittent preventive treatment to infants and pregnant women [133]. Thus, it is obvious that new tools are urgently required for successful malaria elimination.

It is known that the two human malaria species (*P. falciparum* and *P. vivax*), which infects millions of people actually were of zoonotic origin (from the African apes), which evolved thousands of years ago [134, 135]. Thus, there is always a possibility that in the future *P. knowlesi* and other simian malarias may become established in humans, especially when human malaria is eliminated. However, currently human-to-human transmission of knowlesi malaria by mosquitoes has not been established. This is crucial in the light of malaria elimination and more focused research is needed on this topic if we are to succeed with malaria elimination.

Changing landscape affects *Anopheles* distribution, mosquito density and diversity in Malaysia, and more globally Southeast Asia [105, 111, 136–138]. It has been shown that with loss of forest cover, cases of *P. knowlesi* have increased in Sabah [119]. Land use change has also led to increase of malaria cases due to various factors such as increase of macaques in small forest patches along with the colonization of the main vectors [119, 136]. It is interesting to note that *An. balabacensis*, the predominant vector of human and simian malaria, was found in great abundance in logged forest, followed by thinly logged virgin jungle reserve and was lowest in primary forest [136]. This vector was also found to be biting humans more at ground level compared to canopy level [136]. It is therefore important to include both the public health and agro-forestry sectors in controlling malaria vectors in the country. Studies from Thailand also indicate that if landscape management should be used for malaria control in northern Thailand, large-scale reduction and fragmentation of forest cover would be needed [139, 140]. Such drastic actions, however, do not align with current global objectives concerning forest and biodiversity conservation.

The vectors of simian malaria described to date were *An. hackeri* (Leucosphyrus Group) [141] recorded biting mainly the macaques and large numbers were collected resting on Nipah palm trees in Selangor in 1960s; *An. cracens* (Dirus Complex) [122] biting both macaques and humans and found mainly in the forest and farms; *An. latens* (Leucosphyrus Complex) [121] was the

predominant mosquito in the forest compared to farm and village, and was biting macaques at ground level and at six meters in the canopy compared to three meters. The biting ratio of monkey *versus* human for *An. latens* was 1:1.3 [121]. *An. introlatus* (Leucosphyrus Complex) [142] was biting in the early part of the night from 19:00 h to 21:00 h and was the predominant mosquito in Hulu Selangor where cases of *P. knowlesi* were reported. Most recently, *An. balabacensis* (Leucosphyrus Complex) has been incriminated as vector of *P. knowlesi* in Sabah [123], as well as human malaria and Bancroftian lymphatic filariasis due to *Wuchereria bancrofti* [143–145].

Although an increased number of countries are successfully eliminating human malaria in recent years, no country has yet eliminated non-human malaria, which adds another layer of complexity to be addressed. The complex situation of malaria is Southeast Asia is very unique from the rest of the tropical countries. More effort is needed to study the host switching mechanisms between the parasites in humans, macaques and vectors. A series of review papers have been published over the years and all these have indicated the importance of addressing the problem caused by *P. knowlesi,* if malaria elimination is to be successful in the region [113, 146–151].

7. Targeting vivax malaria: a bottleneck to malaria elimination

As opposed to *P. falciparum* infection, which does not have latency (dormant), *P. vivax* causes two distinct infection syndromes, one that actively proliferates and the other latent due to hypnozoites. Each of these *P. vivax* forms requires distinct therapeutic treatments and the latent form cannot be diagnosed [152]. Most acute attacks of *P. vivax* in endemic areas originate from hypnozoites, and unless that reservoir is aggressively attacked, elimination of transmission may be an unrealistic goal.

Treatment of latent vivax represents an important challenge as the only known therapies are 8-aminoquinoline drugs, which results in acute hemolytic anemia in patients deficient in glucose-6-phosphate dehydrogenase (G6PD)—a highly polymorphic inherited disorder affecting 1–30% of residents of malaria-endemic nations [153]. The single low dose of primaquine against gametocytes of *P. falciparum* does not threaten the G6PD deficient subjects [154]. Another challenge is that the parasitemia of vivax malaria patients is typically an order of magnitude lower than falciparum malaria, causing larger proportions of parasitemia to fall below diagnostics detection thresholds [152]. In addition, vivax malaria patients may exhibit very low parasitemia, and yet become severely ill. These fundamental distinctions between the two dominant human malarias explain why *P. vivax* is relatively unaffected by interventions tailored to control *P. falciparum* calling for new strategies needed for combatting vivax malaria [155].

In addition, *P. vivax* has the ability to develop at lower temperature than *P. falciparum* and has a shorter sporogonic cycle in the vector, which results in *P. vivax* extending beyond tropical climates into temperate regions. This ability, combined with its early-biting, outdoor-feeding and outdoor-resting behavior of vector mosquito species, also makes them less susceptible to vector control measures such as IRS, which have proven effective against transmission of *P. falciparum* [156]. Also having dormant forms in the liver (hypnozoites) mean that one successful infection will generate a number of parasitological and clinical episodes without reinfection. Therefore, recurrent cases cannot be prevented via vector control, though, paradoxically, successful transmission control of

vivax malaria could reduce the disease burden more than that of *P. falciparum*, because avoiding one infection will result in preventing a number of clinical episodes over several years [155].

Vivax malaria is diagnosed late, because infected people get ill with low parasite densities, which cannot be detected with current diagnostics, such as RDTs and microscopy. Delayed diagnosis means not only delayed treatment (hence prolonged morbidity, especially anemia) but also ability to transmit over an extended period. This is further amplified by the fact that mature gametocytes appear simultaneously with asexual forms—hence transmission occurs before diagnosis and treatment [157, 158].

As recently described [156], an effective *P. vivax* control and elimination toolbox should include:

i. Practical point-of-care G6PD deficiency diagnostics allowing wider access to safe primaquine therapy or with tafenoquine—a related single dose hypnozoitocide recently developed by GSK and Medicines for Malaria Venture (MMV); the latter has been submitted to the United States Food and Drug Administration (FDA) seeking approval of single-dose tafenoquine for the radical cure (prevention of relapse) of vivax malaria in patients 16 years of age and older [159];

ii. More sensitive point-of-care diagnostics for detecting intrinsically lower parasitemia, including sub-patent and asymptomatic infections;

iii. Validated strategies for relapse prevention in special population groups, i.e., pregnant women, young infants, G6PD deficient and G6PD unknowns in which 8-aminoquinoline is contraindicated;

iv. Clinical care algorithms acknowledging risk of severe and threatening syndromes despite seemingly non-threatening levels of parasitemia; and

v. Interventions of proven efficacy to minimize human contact with often zoophilic, exophagic and exophilic *Anopheles* species of great diversity.

In conclusion, the malaria community needs to address these challenges and create a viable strategy to achieve vivax elimination goals, providing novel solutions for overcoming critical bottlenecks. This process needs to begin now to enhance treatment practice for 8-aminoquinoline drugs based radical cure. Highlighting the benefits of radical cure for the patient and community will improve prescription practice and patient adherence [160]. Coupling this with improved access to adequate G6PD testing will pave the way for the introduction of tafenoquine, with huge potential to accelerate the elimination of *P. vivax*.

8. Socio-ecological and adaptive management of malaria ecosystem in areas approaching malaria elimination

WHO has recently proposed sustainable prevention and control of diseases emerging within complex, dynamic, adaptive systems, such as malaria, based on interdisciplinary and approaches addressing environmental and social health determinants holistically [161]. More

insights into transmission dynamics and the possibility of intersectoral ecosystem management programs for malaria elimination and control are urgently needed. An ecosystem approach to successful reduction of vector-borne disease burden [162, 163] can lead to considerable health gains [Available at: http://www.maweb.org/documents/document.317.aspx.pdf].

Once local entomological inoculation rates (EIRs) have been reduced to a level of unstable transmission the infectious reservoir can be eliminated via several approaches without a threat of malaria re-emergence from reintroduction of parasites. At this point, use of time-limited mass drug administrations (MDA) campaign at high coverage should be sufficient to effectively clear the majority of remaining *P. falciparum* cases, and may be considered for epidemic control as part of the initial response, along with the urgent introduction of other interventions [164]. This can be supplemented by screening and treatment programmes based on WHO Global Malaria Programme's T3: Test, Treat, Track initiative supporting malaria-endemic countries in their efforts to achieve universal coverage with diagnostic testing and antimalarial treatment, as well as in strengthening their malaria surveillance system [WHO T3: Test, Treat, Track. Scaling up diagnostic testing, treatment and surveillance for malaria. World Health Organisation; 2012. http://www.who.int/malaria/publications/atoz/t3_brochure/en/]. Healthcare workers or locally trained and supervised community volunteer networks can apply this method to effectively limit reintroduction of parasites from other areas to a minimum, and apply additional active case management, e.g., the systematic detection and treatment of parasitemia using highly sensitive RDTs can reduce the risk attributed to any unscreened or asymptomatic cases.

Depending on the local situations, supplementary measures, in addition to LLINs or IRS, such as repellents or treated clothing for high-risk individuals, offer special precautionary preventive protection [1, 110, 165, 166]. Passive case management should suffice for treating any symptomatic infections as they may occur. This, however, assumes at least a periodic provision of health services at all locations, including remote ones. A transdisciplinary approach integrates different scientific perspectives [167, 168] and provides a formal platform for stakeholder participation in the research and development of new information, ideas and strategies, their testing and eventual application.

Participatory approaches that engage local communities in a complex social-ecological mapping process are a vital starting point for identifying community-applicable solutions and leveraging community capacity for local interventions [169, 170] and promoting integrative and equitable collaboration within partnership of researchers and communities [170, 171]. Ownership of continuous surveillance, monitoring, treatment and preventive efforts should be transferred to members of local communities, assuming collective responsibility for their continuous well-being.

9. Conclusions

This review attempts to consolidate the challenges of operational research for innovations in designing interventions [172], according to the current situation and progress made, for achieving malaria elimination in Southeast Asia. As the entry of artemisinin resistant parasites to India could be the first step in their spread to Africa, the current priority must be to

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address this problem in Southeast Asia before it can become a threat in Africa. Continuous monitoring of drug resistance in conjunction with analysis and proper interpretation is critical to guide the appropriate action for effective treatment. While *P. falciparum* elimination in the GMS is realistic, feasible and particularly urgent in the context of drug resistance, the main challenges are to ensure community participation and plan for the preservation of ACT potency so that the dosing regimens and surveillance for resistance are rigorously pursued to sustain their efficacy for as long as possible [172].

We support a priority focus on MMP and other high-risk groups to contain the spread of artemisinin resistance and new hot-spots, however, implementation challenges should be considered when planning future interventions. More efforts are needed in documenting the malaria risk among different types of MMPs, innovative tools and interventions, as well as designing implementation in a way that can be evaluated, lessons learned, and programmes adapted in an on-going process [172]. New ways of evaluating MMP interventions (including highly sensitive RDTs) are needed, as routine health information systems have limitations and might not allow capturing the information and data needed, and existing type of surveys might not be sufficient for monitoring interventions for MMP.

Malaria programmes need to heed the recent revised WHO recommendations for achieving universal coverage with LLINs or IRS for populations at risk [173]. The coverage of key interventions is critically low in some countries and sub-optimal in most others, threatening progress across the region as a whole [174]. Malaria programmes are encouraged to evaluate the magnitude (and drivers) of the residual transmission in their country, regarding both mosquito and human behavior. This information will provide a boost for industry and academic partners to develop new vector control methods and paradigms for outdoor and residual transmission.

The current precarious funding situation could undermine elimination efforts and result in a resurgence of disease. The threat posed to regional and global malaria control and elimination efforts by artemisinin resistant *P. falciparum* parasites is imminent and potentially severe. In many Asian countries, operational feasibility of *P. vivax* elimination is lower than that for *P. falciparum* [27]. Therefore, creating a viable strategy to achieve vivax elimination goals should include improvements in access to safe treatment to 8-aminoquinoline drugs based radical cure together with improved access to adequate G6PD testing in *P. vivax* endemic countries.

Whilst human *P. knowlesi* is still largely a zoonosis, all indications suggest that human-to human transmission can take place, and probably is taking place in some situations [175]. More research is required to substantiate the body of evidence for human-to-human transmission, laboratory diagnosis and clinical management, and mapping vectors of *P. knowlesi* and environmental risk factors.

The challenge for elimination programmes is dealing with dynamic, social-ecological systems for which an entirely different kind of thinking and scientific framework is required. The retooling for this next phase is more challenging this time since it requires malaria experts and managers to understand complex systems, thinking and practices. This thinking and actions are more or less contrary to conventional understandings of disease control, which tend to be top down and not guided by concepts like resilience and adaptive management developed as part of so-called ecosystem approach/management.

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Conflict of interest

All authors declare no conflict of interest related to the writing of this chapter.

List of acronyms

ACT	Artemisinin-based combination therapy
AMT	Artemisinin monotherapy
ASEAN	Association of Southeast Asian nations
BCC	Behavioral change communication
DNA	Deoxyribonucleic acid
CSP	Circumsporozoite
EIR	Entomological inoculation rate
ELISA	Enzyme-linked immunosorbent assay
ERAR	Emergency response to artemisinin resistance
FDA	Food and drug administration
G6PD	Glucose-6-phosphate dehydrogenase
GMS	Greater Mekong Subregion
IRS	Indoor residual spraying
ITN	Insecticide treated nets
LLIN	Long lasting insecticidal nets
LLIHN	Long lasting insecticidal hammock nets
LSM	Larval source management

MDA	Mass drug administration
MMP	Mobile and migrant populations
MMV	Medicines for malaria venture
MOH	Ministry of Health
PCR	Polymerase chain reaction
PMI	President Malaria Initiative
RDT	Rapid diagnostic test
RMT	Residual malaria transmission
SES	Socio-ecological system
SP	Sulfadoxine-pyrimethamine
WHO	World Health Organisation

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