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Malaria Elimination in the Greater Mekong Subregion: Challenges and Prospects

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Abstract

Malaria is a significant public health problem and impediment to socioeconomic development in countries of the Greater Mekong Subregion (GMS), which comprises Cambodia, China's Yunnan Province, Lao People's Democratic Republic, Myanmar, Thailand, and Vietnam. Over the past decade, intensified malaria control has greatly reduced the regional malaria burden. Driven by increasing political commitment, motivated by recent achievements in malaria control, and urged by the imminent threat of emerging artemisinin resistance, the GMS countries have endorsed a regional malaria elimination plan with a goal of eliminating malaria by 2030. However, this ambitious, but laudable, goal faces a daunting array of challenges and requires integrated strategies tailored to the region, which should be based on a mechanistic understanding of the human, parasite, and vector factors sustaining continued malaria transmission along international borders. Malaria epidemiology in the GMS is complex and rapidly evolving. Spatial heterogeneity requires targeted use of the limited resources. Border malaria accounts for continued malaria transmission and represents sources of parasite introduction through porous borders by highly mobile human populations. Asymptomatic infections constitute huge parasite reservoir requiring interventions in time and place to pave the way for malaria elimination. Of the two most predominant malaria parasites, *Plasmodium falciparum* and *P. vivax*, the prevalence of the latter is increasing in most member GMS countries. This parasite requires the use of 8-aminoquinoline drugs to prevent relapses from liver hypnozoites, but high prevalence of glucose-6-phosphate dehydrogenase deficiency in the endemic human populations makes it difficult to adopt this treatment regimen. The recent emergence of resistance to artemisinins and partner drugs in *P. falciparum* has raised both regional and global concerns, and elimination efforts are invariably prioritized against this parasite to avert spread. Moreover, the effectiveness of the two core vector control interventions—insecticide-treated nets and indoor residual spraying—has been declining due to insecticide

resistance and increased outdoor biting activity of mosquito vectors. These technical challenges, though varying from country to country, require integrated approaches and better understanding of the malaria epidemiology enabling targeted control of the parasites and vectors. Understanding the mechanism and distribution of drug-resistant parasites will allow effective drug treatment and prevent, or slow down, the spread of drug resistance. Coordination among the GMS countries is essential to prevent parasite reintroduction across the international borders to achieve regional malaria elimination.

Keywords: malaria elimination, Greater Mekong Subregion, epidemiology, drug resistance, migration, insecticide resistance

1. Introduction

With steady gains in the fight against malaria over the past decade, the international malaria community once again is embracing the global goal of malaria eradication. Meanwhile, the World Health Organization (WHO) has launched a new Global Technical Strategy for Malaria (http://www.who.int/malaria/areas/global_technical_strategy/en/) as the operational framework guiding malarious nations and regions in their pursuit of malaria elimination. In the Greater Mekong Subregion (GMS) of Southeast Asia (SEA), which comprises Cambodia, China's Yunnan Province, Lao People's Democratic Republic (Laos), Myanmar, Thailand, and Vietnam, malaria has been a significant public health problem and impediment to socioeconomic development [1, 2]. Intensified malaria control in recent years, fueled by increased international funding and local bustling economic development, has greatly reduced the regional malaria burden. Compared with confirmed malaria cases in 2010, the number of malaria cases in the GMS was reduced by ~50% in 2014. Driven by increasing political will and financial support and motivated by recent achievements in malaria control, the six GMS nations have endorsed a regional malaria elimination plan with an ultimate goal of eliminating *Plasmodium falciparum* malaria by 2025 and all malaria by 2030 [3]. Emerging artemisinin resistance in this region further escalated urgency for National Malaria Control Programmes (NMCPs) to make such a transition of their aims [4, 5]. However, this ambitious goal faces numerous technical challenges [6] and requires integrated strategies tailored to the whole region and individual countries. In the malaria elimination settings, control strategies need to align with the changing malaria epidemiology. Control measures such as long-lasting insecticide-treated bed nets (LLINs), indoor residual insecticide spraying (IRS), rapid diagnostic tests (RDTs), and artemisinin combined therapies (ACTs) used to effectively reduce malaria burden in hyperendemic regions may not be enough for the malaria elimination task. Additional tools such as mass drug administration (MDA) and innovative vector control programs may be needed. Here, we attempt to provide an updated view of the changing malaria epidemiology, the challenges, and prospect of malaria elimination in the GMS.

2. Border malaria

Malaria epidemiology in the GMS is complex and rapidly evolving. There is immense spatial heterogeneity in both regional and countrywide disease distribution (**Figure 1** and **Table 1**). Within the GMS, Myanmar has the heaviest malaria burden and accounts for more than 53%

of regionally confirmed malaria cases. Within each country, the pattern of malaria distribution remains similar, but transmission is still concentrated along international borders—the so-called border malaria. In border areas, there is poor accessibility to healthcare services, and surveillance for malaria is far less than optimal [8]. Given that these border regions represent probable malaria reservoirs and that importation and dispersal by migratory human populations are extremely difficult to monitor, border malaria constitutes one of the biggest obstacles for malaria elimination. Highly mobile populations crossing porous borders are a major contributor to parasite introduction and continued transmission [9]. Border areas also are home to ethnic minorities, hill tribes, temporary and seasonal migrants, refugees, and internally displaced people; many have poor educational level, limited access to healthcare services, and reduced legal rights. Geographical and cultural isolation leaves these groups at a high risk for infection and poor access to treatment [1, 2, 10, 11]. In Thailand, malaria makes up ~31% of communicable diseases diagnosed in migrants, as compared to 3% in Thai natives [12]. Heavy population flow along the extremely porous borders makes neighboring countries very vulnerable to malaria introduction and reintroduction [13, 14]. As a result, malaria prevalence on both sides of the border is often highly correlated [15]. In Yunnan Province of China, although autochthonous *P. vivax* malaria was still detected, *P. falciparum* infections were mostly associated with travel history to Myanmar [16]. There is also genetic evidence of asymmetric parasite flow from the more endemic to the less endemic side of the border [17, 18]. On a smaller geographical scale in a border village in Western Thailand, malaria incidence was clustered and significantly associated with citizen status indicating recent migration [19]. Moreover, there is a high probability that frequent border crossings by migrants will spread artemisinin-resistant *P. falciparum* [20, 21] beyond the “containment zone” [22, 23]. More sophisticated surveillance



Figure 1. The geographical proximity of countries and reported malaria cases for data based on 2016 in the Greater Mekong Subregion (GMS). *Note:* The majority of malaria cases in Yunnan Province of China were imported.

Country/drug policy ^a	Year	No. of malaria cases	% of confirmed cases ^b			No. of death cases
			Pf	Pv	Others	
China	2011	3000	41.9	56.6	1.5	≤100
Uncomplicated Pf: ART + NQ; AS + AQ; D-P	2012	240	8.2	91.8	—	0
Severe malaria:	2013	≤100	64.1	35.9	—	0
AM; AS; pyronaridine	2014	≤100	10.7	89.3	—	0
<i>P. vivax</i> : CQ + PQ (8d)	2015	≤100	3.0	78.8	18.2	0
	2016	≤10	0.0	100.0	—	0
Cambodia	2011	203,600	62.6	37.4	—	400
Uncomplicated Pf: AS + MQ, D-P	2012	146,000	50.4	49.6	—	220
Severe malaria:	2013	76,500	45.8	54.2	—	110
AM; AS; QN	2014	89,700	58.8	41.2	—	150
<i>P. vivax</i> : D-P + PQ (14d)	2015	120,300	61.3	38.7	—	210
	2016	83,300	58.2	41.8	—	140
Laos	2011	42,800	92.7	7.1	0.2	≤100
Uncomplicated Pf: AL	2012	112,700	83.4	16.6	—	250
Severe malaria:	2013	93,500	67.0	33.0	—	170
AS + AL	2014	117,300	52.9	47.1	—	180
<i>P. vivax</i> : CQ + PQ (14d)	2015	87,900	42.3	57.7	—	120
	2016	27,390	39.5	60.5	—	≤100
Myanmar	2011	1,506,000	68.4	31.6	—	2800
Uncomplicated Pf: AL; AM; AS + MQ; D-P; PQ	2012	1,974,000	71.8	28.2	—	4000
Severe malaria:	2013	585,000	70.4	29.6	—	1100
AM; AS; QN	2014	360,000	69.9	30.1	—	700
<i>P. vivax</i> : CQ + PQ (14d)	2015	236,500	64.1	35.9	—	400
	2016	142,600	60.3	39.7	—	240
Thailand	2011	24,900	40.5	59.5	0.1	≤100
Uncomplicated Pf: D-P	2012	32,600	39.8	60.2	—	≤100
Severe malaria:	2013	33,300	44.0	46.8	9.3	≤100
QN + doxycycline	2014	37,900	37.8	54.1	8.1	≤100
<i>P. vivax</i> : CQ + PQ (14d)	2015	8000	41.7	58.0	0.2	≤100
	2016	11,520	32.5	46.1	21.5	≤100

Country/drug policy ^a	Year	No. of malaria cases	% of confirmed cases ^o			No. of death cases
			Pf	Pv	Others	
Vietnam	2011	22,630	64.3	35.7	—	≤100
Uncomplicated Pf:	2012	26,610	61.3	38.7	—	≤100
D-P	2013	23,140	58.0	42.0	—	≤100
Severe malaria:	2014	21,200	54.2	45.8	—	≤100
AS; QN	2015	12,560	48.9	51.0	0.2	≤100
<i>P. vivax</i> : CQ + PQ (14d)	2016	6000	57.6	42.1	0.4	≤10

^aAL, artemether + lumefantrine; AM, artemether; AQ, amodiaquine; ART, artemisinin; AS, artesunate; CQ, chloroquine; D-P, dihydroartemisinin + piperaquine; MQ, mefloquine; NQ, naphthoquine; PQ, primaquine; QN, quinine.

^oPf: *Plasmodium falciparum*; Pv: *Plasmodium vivax*.

Table 1. Antimalarial drug policy and malaria transmission trends in the Greater Mekong Subregion (GMS) countries during 2011–2016 [7].

tools are needed to provide a clear picture of border malaria transmission so that targeted control measures are implemented to curb the spread of resistance and to prevent the reintroduction of parasites into populations where they have been eliminated. Thus, malaria elimination is a multinational, multipronged issue, with cross-border migration posing one of the largest threats to its success [24]. In recognition of this issue, the GMS countries have initiated bi- and multilateral coordination between the NMCPs. While the healthcare systems in the GMS countries are improving, further bolstering is needed to meet the malaria elimination challenge.

3. Asymptomatic malaria as an important reservoir

It has long been held as conventional wisdom that asymptomatic infections would be much less frequent in low-endemicity settings because the level of exposure-related immunity to malaria in human populations may be low [25]. However, asymptomatic infections represent the vast majority of infections in all endemic settings [26]. The use of molecular tools is essential for identifying submicroscopic infections. For both *P. falciparum* and *P. vivax*, microscopy detects only 1/3–1/2 of the infections detected by regular PCR [27, 28]. As the sensitivity of detection methods increases (e.g., with the use of a larger blood volume or reverse transcriptase-PCR targeting the parasite 18S rRNA), greater proportions of asymptomatic infections are discovered, revealing larger pools of infections [29, 30]. In Western Thailand and other GMS regions, qPCR and large-volume ultrasensitive qPCR could detect as much as 20% of the villagers harboring malaria infections as compared to ~5% detected by microscopy [31, 32]. Although we still do not have a clear picture about how much these asymptomatic infections actually contribute to malaria transmission in these areas [33], studies in Western Thailand have clearly demonstrated mosquito infectivity of submicroscopic *P. falciparum* and *P. vivax* [34], albeit the asymptomatic parasite carriers were found to be much less infective to mosquitoes than acute cases [35]. Since asymptomatic individuals are unlikely to seek treatment, they are missed by passive case detection, and submicroscopic infections also are missed by microscopy-based active case detection. It is highly possible that these asymptomatic infections act as important silent reservoirs of transmission. Even under such

low-endemicity settings, it is estimated that submicroscopic carriers may be the source of 20–50% of all human-to-mosquito transmission [36], underlining the significance of managing this population in the malaria elimination phase. Therefore, information about the prevalence and seasonal dynamics of the asymptomatic infections in the border regions and their contribution to transmission is required to guide the efforts of NMCPs to achieve malaria elimination.

4. The burden of *P. vivax* malaria and G6PD deficiency

Another characteristic of the rapidly evolving malaria epidemiology in the GMS is that the prevalence of *P. vivax* is increasing proportionally to *P. falciparum* [37] (Table 1). The resilience of vivax malaria to control efforts may be attributed to some intrinsic biological features of this parasite. First, *P. vivax* only invades reticulocytes, and thus the resulting parasitemia is normally far lower than that of *P. falciparum* malaria. This makes microscopy-based diagnosis and RDTs not sufficiently sensitive in detecting *P. vivax* infections [38–40]. Second, during blood-stage infections with *P. vivax*, gametocytes are formed before the manifestation of clinical symptoms, which allows transmission of the parasite before treatment. Third, *P. vivax* develops dormant hypnozoites in the liver of the human host, which awaken in the weeks and months following a primary attack and cause relapses. Finally, vivax malaria is often transmitted by outdoor biting mosquitoes, making the current insecticide-based control measures (LLIN and IRS) less effective. Because of these unique features, traditional malaria control efforts often fail to control *P. vivax* transmission. In addition, containment of *P. falciparum* has been prioritized in the GMS, partially because of the emerging artemisinin resistance. As a result, *P. falciparum* prevalence has decreased, while the proportion of *P. vivax* has increased.

In the GMS, the first-line therapy for vivax malaria remains chloroquine (CQ) and primaquine (PQ) (Table 1) [41]. Reports of clinical CQ resistance in many regions of the world and falling efficacy of PQ are of great concern for vivax malaria control [42–45]. Although some studies indicated that *P. vivax* in the GMS remained sensitive to CQ [46–51], others clearly documented CQ-resistant *P. vivax* [52–55]. In Myanmar, sporadic CQ-resistant *P. vivax* cases were first reported more than 20 years ago [52, 53]. A later report of 34% treatment failures in Dawei of Southern Myanmar suggests an increase of CQ resistance [55]. More recent studies identified both early and late treatment failures in Myawaddy of the Kayin State and Kawthaung of the Tanintharyi Region, Myanmar [56]. In northeastern Myanmar bordering China, a recent study showed 5.2% cumulative incidence of recurrent parasitemia during a 28-day follow-up of 587 *P. vivax* treated with CQ/PQ [57], suggesting sensitivity to CQ may also be deteriorating in this region. This reduced sensitivity of *P. vivax* to CQ requires close surveillance and potential implementation of more effective treatment measures such as ACTs [58].

Studies from Papua New Guinea suggest that 80% of the vivax infections may be attributed to relapses. A modeling approach predicts that as much as 96% of clinical attacks by *P. vivax* in Thailand are due to relapses [60]. For radical cure, WHO recommends a dose of 0.25–0.5 mg/kg of PQ daily for 14 days. However, the lower dose (total of 3.5 mg/kg) fails to prevent relapses in many different endemic sites [61]. Because of the potential risk of severe hemolysis that this drug could cause in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, PQ is not widely prescribed [43, 62, 63]. In routine practice, G6PD status is not screened; the GMS

nations still use the lower total dose of PQ in fear of the possible harm to those with G6PD deficiency. Because evaluation of PQ efficacy in preventing relapses requires longer-term follow-up, the clinical efficacy of the current PQ regimen for radical cure of vivax malaria in the GMS is unknown. Even with longer follow-ups, it is still not possible to reliably determine whether a recurrent infection after day 28 is due to relapse or reinfection given that a relapse infection may be from reactivation of a different hypnozoite clone [64, 65]. For PQ efficacy, host factors also need to be considered. Recently, failures of the PQ radical cure have been linked to reduced activity of the hepatic cytochrome P450 (CYP) 2D6 [66], which mediates activation of PQ to its active metabolite(s) [67, 68]. Different CYP2D6 activities have differential effects on the pharmacokinetics of PQ [69]. CYP2D6 is involved in the metabolism of as many as 25% of drugs in clinical use and is also a member of the CYP450 family with the greatest prevalence and genetic polymorphism [70, 71]. About 70 CYP2D6 allelic variants have been found and grouped into 4 phenotypic classes of ultra-rapid, extensive, intermediate, and abolished protein activity [72]. The frequency of alleles with reduced function is as high as 50% in most Asian populations [73]. Thus, it is important to determine the extent by which reduced CYP2D6 activity is responsible for PQ failures in radical cure of vivax malaria [74].

The *G6PD* gene is extraordinarily polymorphic with more than 400 variants discovered based on biochemical diagnosis [75], among which 186 mutations are associated with G6PD deficiency [76]. The prevalence of G6PD deficiency and distribution of G6PD variants vary geographically [77]. In the GMS, G6PD deficiency is often highly prevalent among ethnic groups. Along the Thailand-Myanmar border, the prevalence of G6PD deficiency was above 10% [78–80], whereas in the Kachin ethnicity along the China-Myanmar border, it almost reached 30% [81]. In Thailand and Myanmar, the Mahidol variant (487G>A) is the most predominant and often accounts for ~90% of all mutations [79, 81–83]. According to the WHO classification, the Mahidol variant is a Class III mutation or mild-deficient variant with 60% enzyme activity [76]. However, this classification may not be accurate since patients with the Mahidol variant often had <1% of the normal G6PD activity [79, 84, 85]. Patients having the G6PD Mahidol variant (487G>A) rarely had acute hemolytic anemia after taking the normal dose of PQ [84, 86]. In contrast to the belief that PQ only induces mild hemolysis in patients with the Mahidol variant, there have been case reports showing that the normal dosage of 15 mg/kg/day for 3 days in vivax patients with this G6PD variant could lead to acute hemolytic anemia that required blood transfusion or even cause renal failure [87–89]. It is noteworthy that G6PD activity can vary substantially between individuals with the same variant and even within the same individual over time. Therefore, with the prevalence of vivax malaria in this region and the goal of malaria elimination, the deployment of point-of-care G6PD deficiency diagnostics is urgent [90]. In addition, there is a need to test whether weekly PQ of 0.75 mg/kg for 8 weeks, a dosage considered safe for the G6PD African variant [91], could be prescribed in the GMS without prior testing for G6PD deficiency.

5. Management of drug resistance in *P. falciparum*

ACTs have played an indispensable role in reducing global malaria-associated mortality and morbidity. However, these achievements are threatened by the recent emergence of artemisinin resistance in *P. falciparum* in the GMS [92–94]. Artemisinin resistance is associated with a parasite clearance half-life of >5 h as compared to a normal value of ~2 h [94–96].

Clinical artemisinin resistance was first detected in western Cambodia [92, 93, 96, 97] but is now detected in other GMS regions including Thailand, Laos, Vietnam, Southern Myanmar, and the China-Myanmar border area [94, 95, 98–103]. Out of fear of a catastrophic spread of artemisinin resistance to Africa, WHO deployed an artemisinin resistance containment plan in Cambodia [104]. Later, with the finding that artemisinin resistance has emerged independently in many areas of the GMS [105], the containment plan has been revised to a regional malaria elimination strategy [3, 4].

The principle of ACTs is that the fast-acting artemisinins rapidly reduce the parasite biomass, leaving the slow-eliminating partner drugs to clear the residual parasites. The emergence of artemisinin resistance means that a larger parasite mass is left for the partner drugs to clear after the usual 3-day ACT course, which increases the chance of resistance development to the partner drugs. Indeed, in the short period of time since the deployment of ACTs, clinical resistance to two ACTs, first artesunate/mefloquine [106] and more recently dihydroartemisinin/piperaquine (DHA/PPQ), has emerged in the GMS. These are the two most popular ACTs deployed in the GMS countries (**Table 1**). Since promising new antimalarials are still in the development pipeline, possible solutions to this problem include introduction of new ACTs, rotation of different ACTs, use of longer course of ACT treatment, and introduction of triple ACTs (artemisinin derivatives with two slow-eliminating partner drugs) [112]. To mitigate the threat of spread of artemisinin-resistant *P. falciparum* parasites, heightened surveillance is needed in sentinel sites of the GMS [113].

Tools for monitoring the epidemiology of antimalarial drug resistance include *ex vivo* or *in vitro* drug assays and molecular surveillance, which complement *in vivo* drug efficacy studies. It is noteworthy that the slow-clearance phenotype of clinical artemisinin resistance does not correspond to the 50% inhibitory concentrations of artemisinin drugs estimated from the conventional DNA replication-based *in vitro* assay but is better reflected in the newly developed ring-stage survival assay, which quantifies the number of early ring-stage parasites (0–3 h) that can survive the exposure to 700 nM of DHA for 6 h [114]. The discovery of mutations in the *kelch* domain protein K13 associated with artemisinin resistance provides a convenient molecular marker for a large-scale surveillance purpose [115]. To date, the correlations of K13 mutations with delayed parasite clearance have been established in several studies [95, 105, 115–117] but only a very limited number of K13 mutations were confirmed to confer *in vitro* artemisinin resistance through genetic manipulations [118, 119]. The K13 gene in the world *P. falciparum* populations harbors more than 108 nonsynonymous mutations, which showed marked geographic disparity in frequency and distribution [120]. Similarly, K13 mutations in the GMS also showed highly heterogeneous distribution [103, 121–125], possibly reflecting different drug histories and evolutionary origins of the parasite populations [126]. Clinical failures of DHA/PPQ have been associated with increased *in vitro* PPQ resistance and the molecular markers of PPQ resistance in western Cambodia include amplification of the aspartic protease genes *plasmepsin 2–3* and point mutation E415G in an exonuclease gene (PF3D7_12362500) [127, 128]. Molecular surveillance of artemisinin resistance in western Cambodia, Thailand, and Laos has detected the spread of a parasite clone with a long K13 haplotype carrying the C580Y mutation (the artemisinin-resistant mutation reaching near fixation in western Cambodia) to northeastern Thailand and southern Laos, which indicates a transnational selective sweep [129]. Importantly, this parasite lineage also harbors the *plasmepsin 2* amplification, which may preclude further use of DHA/PPQ in this region. In addition, this situation also necessitates implementation of

stringent follow-ups of malaria cases after ACT treatment to ensure that recrudescence cases are treated with effective antimalarials. Thus, surveillance should be mandatory to delay the spread of the resistant parasites and to accelerate malaria elimination in the GMS.

6. Vectors

LLINs and IRS are the key vector-based malaria interventions that have been found to be highly effective in sub-Saharan Africa. However, these measures are much less efficient in the GMS [130]. The GMS has a complex vector system; most of the malaria vectors belong to species complexes or groups such as *Dirus*, *Minimus*, *Maculatus*, and *Sundaicus*, which vary significantly in terms of geographic distribution, ecology, behavior, and vectorial competence [131–133]. At least 19 species are known malaria vectors, some of which comprise cryptic species complexes [132]. In order to apply the appropriate control approaches in relation to the biology of the vector species, we first need to identify the mosquitoes to their species level and to differentiate the vector from nonvector species, which requires molecular assays [134]. These vector species display significant variations in geographical distribution and seasonal dynamics, and accordingly their roles in malaria transmission also vary in space and time [135]. In many endemic areas of the GMS, perennial malaria transmission is maintained by *Anopheles dirus* during the rainy season and *An. minimus* during the drier periods of the year [132, 136]. Environmental changes such as deforestation have caused changes in the vector species composition [137, 138] and benefited the survivorship of major vectors [40]. Since many of these vector species exhibit early evening and outdoor biting preferences, LLINs alone are not sufficient for interrupting malaria transmission [140]. In addition, the emergence and spread of insecticide resistance further compromise the effectiveness of the mosquito control measures [141–143].

7. Technological innovation for malaria elimination

The technical challenges discussed here suggest that the currently used malaria control tools (RDT, ACT, LLIN, and IRS) that were instrumental for the gains against malaria may not be sufficient for malaria elimination [144]. Additional tools are needed to achieve the final goal of malaria elimination in the GMS. First, residual transmission requires MDA to eliminate asymptomatic and submicroscopic parasite reservoirs. For the success of MDA, better knowledge of malaria epidemiology is needed so that targeted MDA can be implemented. Successful MDA programs also require strong community engagement. MDA has proved successful in eliminating malaria in Asia-Pacific regions such as Vanuatu and central China [145, 146]. In an earlier study conducted in Cambodian villages, MDA of artemisinin-PPQ at 10-day intervals for 6 months drastically reduced *P. falciparum* rates [147]. A recent pilot MDA study conducted in villages of Kayin State, Myanmar, showed that a 3-day supervised course of DHA/PPQ was well tolerated and highly effective in reducing asymptomatic *P. falciparum* carriage, whereas the effect on reducing *P. vivax* was transient presumably due to relapse [148]. Thus, drugs targeting the *P. vivax* hypnozoite reservoir are required for MDA in the GMS, where *P. vivax* is becoming the predominant parasite species [149]. The high prevalence of G6PD deficiency in the target populations demands prescreening using a point-of-care diagnostic for G6PD deficiency. From

a programmatic standpoint, such an operation requires substantial financial commitment. Second, effective management of malaria cases in the face of emergence and spread of drug resistance requires new therapies such as triple ACTs. Third, novel vector control approaches are desperately needed including larval control strategies [150], incorporation of ivermectin in the MDA program to reduce the life span of mosquitoes [151, 152], topical and spatial repellents against outdoor biting vectors [153, 154], genetically manipulated mosquitoes for population replacement [155], and next generation of LLINs and IRS [156]. It is imperative that new interventions are continuously developed and integrated into malaria elimination programs.

8. Conclusions

Malaria elimination in the GMS carries the urgency of eliminating artemisinin-resistant *P. falciparum* parasites before they become untreatable and spread to Africa. The changing malaria epidemiology with increasing proportion of *P. vivax* malaria requires an 8-aminoquinoline drug for radical cure, but it demands deployment of point-of-care diagnostics for G6PD deficiency due to its high prevalence in endemic human populations. In addition, the prevalent asymptomatic parasite reservoirs need to be targeted by a MDA approach. The diversity of *Anopheles* vectors in the GMS and decreasing effectiveness of indoor control measures, such as LLIN and IRS facing the outdoor malaria transmission, also require development and implementation of novel interventions for vector control. To meet the challenge of border malaria, coordinated efforts among the NMCPs targeting the mobile and migrant populations along international borders will prevent cross-border reintroduction of malaria. Altogether, a holistic attack on malaria using integrated approaches is necessary to achieve the goal of regional malaria elimination in the GMS.

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