Chapter 3

Preparing for the Next Global Threat: A Call for Targeted, Immediate Decisive Action in Southeast Asia to Prevent the Next Pandemic in Africa

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Additional information is available at the end of the chapter

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Abstract

Global investments have had great impact on malaria—these are now at risk of being reversed. Cambodia is where drug resistance historically emerges and spreads globally to drive resulting pandemics—we are currently watching history repeat itself. Despite large investments and recent success in driving down overall rates of malaria, high levels of resistance to nearly all antimalarial drugs are now widespread in Cambodia. Malaria cases are again rising in both Cambodia and Vietnam. Nearly incurable malaria in this region is a real and present threat. Critical actions to prevent further spread of the emerging incurable parasites are: (1) Commitment and real sense of urgency through declaration of a "Public Health Emergency of International Concern" or a similar set of directives; (2) Establish leadership with sufficient authority, respect, expertise and operational funding; (3) Engage affected security forces to stop disease transmission and support elimination operations; (4) Utilize surveillance as a core intervention with result-based funding targeting malaria transmission foci with rapid and effective action. Immediate decisive action is needed in Southeast Asia to prevent the next malaria pandemic. This chapter highlights persistent gaps in the region with methods to address them. In 2015–2016, our collaboration with NIMPE pilot tested tools to intervene in actual forest transmission foci. Our study district saw a 96% decrease in malaria from 2014 to 2017, with the entire province seeing the largest decrease in Central Vietnam in this same timeframe. We describe methods to tackle transmission foci, with both an integrated prevention and treatment package. We call on all stakeholders to make changes to current investments to address this critical challenge.

Keywords: malaria elimination, multidrug-resistance, surveillance, information systems, public health emergency of international concern (PHEIC), Cambodia, Vietnam, Greater Mekong Subregion (GMS)

1. Introduction

Considerable global and domestic investments have averted millions of malaria-attributable deaths since 2000 [1, 2]. Nevertheless, one person (usually a child) still dies every 1.2 minutes from this disease, with no reduction in mortality between 2015 and 2016 [1]. Progress is further threatened by failure to contain artemisinin resistance, as confirmed by the Regional Artemisinin Initiative (RAI) mid-term review [3]. In Cambodia, between mid-2014 and mid-2015, *Plasmodium falciparum* (Pf) malaria increased by 65%, with further substantial rise in 2017, especially along the border with Vietnam [4]. High rates of clinical treatment failures to nearly all antimalarial drugs—including artemisinin derivatives—are now widespread in the country [3] and there is evidence of its spread into southern Vietnam (from western Cambodia) [5]. Multidrug-resistant malaria parasites could cause a global health catastrophe if they were to spread to other countries, particularly malaria-endemic nations in Africa [4, 6–9]. Spread may be facilitated by international peacekeeping missions and migration for work [10–13]. Given available evidence of this current threat, urgent and decisive action is essential.

We are currently watching history repeat itself. In the late 1950s, resistance to the antimalarial chloroquine emerged in Cambodia. It eventually spread to and throughout Africa during the 1980s [14, 15], resulting in a two- to six-fold increase in malaria-related mortality [14]. Subsequent waves of resistance to two other antimalarial drugs followed the same pattern of spread [6]. It was not until the early 2000s, when international bodies finally took affirmed action against malaria, that mortality rates began to decrease globally. But as the World Malaria Report 2017 states: "*although malaria case incidence has fallen globally since 2010, the rate of decline has stalled and even reversed in some regions since 2014; mortality rates have followed a similar pattern*" [1].

Today, a two-fold increase in mortality [14] would cause in the order of 7 million malaria deaths over a decade. The threat will also be magnified by widespread resistance to insecticides already reported in Africa [16] (again history is repeating itself, in the "malaria eradication" era of 1955–1972, it was DDT resistance [17]). The concomitant threat of insecticide resistance, particularly as it affects the efficacy of insecticide-treated bed nets (ITNs) and household spraying, is widely recognized.

Drug-resistant strains of malaria will likely spread to Africa much faster in the current era. Some security forces in Southeast Asia (SEA) are a reservoir of multidrug-resistant (MDR) malaria parasites due to their occupational risk. In 2010, 5% of Cambodian army personnel, screened for research purposes, tested positive for Pf [18] using DNA (PCR) screening. Additional testing revealed failure to the latest artemisinin-based combination therapy (ACT) used at that time [18]. Despite investment by the Bill and Melinda Gates (BMGF) to stop malaria transmission in these troops, the positive cases for Pf malaria had doubled to 10% by 2016 [19, 20]. During this same time frame, more than 3300 Cambodian soldiers were deployed on UN peacekeeping missions—without prior adequate (PCR) screening for malaria—to eight countries, including five in sub-Saharan Africa [10, 21]. Such missions could lead to

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rapid spread of resistance across the endemic areas of the world. Despite being an obvious conduit for the spread of multidrug-resistant (MDR) malaria, the use of standard malaria prevention measures has not yet been put into practice by most militaries in SEA. This is due, in part, to the fact that they are a neglected population receiving little aid [22].

The spread of disease by peacekeepers is well documented. For example, following the 2010 earthquake in Haiti, United Nations troops from Nepal were the source of a cholera epidemic with over 730,000 cases and 8700 deaths, and an estimated economic cost of US$2.2 billion [10]. A single infected peacekeeper could potentially serve as the source for the next malaria pandemic [10].

A similar threat is posed by migration of workers from SEA to sub-Saharan Africa. For example, nearly 20,000 Vietnamese are legally working in Angola [23], and an unknown number are there illegally. These migrants are importing malaria from Angola into Vietnam [13]; the converse could also happen. Chinese workers are employed in mining and construction industries in the forests of Cambodia. They are hard to access, and malaria prevention and treatment practices are of uncertain quality (CO, personal communications). It is quite probable that some workers will move on to the African continent, where there is huge Chinese investment in these industries. Due to the high burden of malaria in Africa, it is likely that malaria strains originating from Asia would go undetected until the next pandemic is underway.

With immediate decisive action, we believe the transmission of the MDR strains can be interrupted approaching the 2020 target (see box, **Table 1**) [24]. The World Health Organization (WHO)'s declaration of a Public health emergency of international concern (PHEIC) led to impressive increases in resources for both Ebola and Zika epidemics, and may be essential to address the current MDR malaria threat. Together, Ebola and Zika claimed fewer than 12,000 lives [25]. Yet, with MDR malaria, millions of lives are at stake. In 2015, WHO published a document warning that MDR malaria "…*has reached alarming levels in several areas of the GMS"* and that malaria "…*could become untreatable with currently available drugs within a few years*" [24]. In 2014, Bill Gates commented: "*There's the potential for a real nightmare scenario here. If a strain of malaria that's resistant to artemisinin were to spread to Africa*"… "*it would be the worst ever disaster in malaria control*" [7]. Chris Plowe, former president of American Society of Tropical Medicine and Hygiene, argues that, "*The danger of untreatable malaria is real and*

Recommendations for rapid elimination of emerging incurable malaria

The world needs to focus efforts to eliminate incurable malaria strains by 2020. The critical remaining actions are:

1. Commitment and real sense of urgency through declaration of multidrug-resistant malaria as a "Public health emergency of international concern" or similar set of directives;
2. Establish response leadership with sufficient authority, respect, expertise and operational funding;
3. Engage affected security forces to stop disease transmission and support elimination operations;
4. Utilize surveillance as a core intervention with result-based funding to drive the targeting malaria transmission foci with rapid, localized and effective action.

Table 1. Critical actions to eliminate emerging incurable malaria strains.

present" [6]. If the WHO's call for "urgent action" is to be answered, a PHEIC or similar set of directives would be hugely important. The definition of PHEIC is "an extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease and potentially require a coordinated international response" [26–28]. We argue that almost incurable malaria in Cambodia, and now Vietnam, with the threat to other countries and regions, undoubtedly fits this definition. WHO contends the regulations were designed to address acute public health conditions and the public health community has known of the emergence and spread of multidrug resistance for a number of years [29]. We claim that if a PHEIC had been declared in 2014, when WHO first learned of high ACT treatment failure rates crossing into Vietnam, malaria would be nearly eliminated now in these countries. The new "extraordinary event" is a marked increase in malaria in eight provinces of Cambodia in 2017, which is continuing in five provinces in early 2018 (CO, personal communication) despite substantial Global Fund resources in the region. Furthermore, in the province where parasites crossed into Vietnam, malaria was up 2.5 fold in 2017, with an extraordinary annual parasite index of about 55. It is not too late to call a PHEIC. If a PHEIC declaration is politically not achievable, a set of similar instructions could generate both commitment and urgency. One example would be a US Department of Defense (DoD) directive [30]—this should be achievable, as malaria is the number one infectious disease threat for US troops [31] and the US DoD continues to invest large sums of money in new antimalarial drug and vaccine development. We are currently at risk of losing all drugs for both malaria prophylaxis and treatment, which should prompt a major investment in direct support of elimination of these strains. The current Defense Malaria Elimination Program [32] was intended by the lead author to be modeled after the DoD Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome Prevention Program (DHAPP) to Support Foreign Militaries directive [30]; instead it turned out to be just more research funding (CO, unpublished observations).

In the SEA context, the artemisinin-based drugs are only one of several classes of previously effective drugs. Over time, malaria parasites in Cambodia have accumulated multiple resistance mechanisms against all of these drug classes. Global health stakeholders and donors must learn from past experience, and urgently recognize the continually evolving malaria parasites in Cambodia as an emergency that must be halted.

A short-term solution to the challenge is the return of malaria sensitivity to the prior artemisinin combination treatment (ACT) partner drug mefloquine (Lariam®) following its reintroduction in Cambodia. One expert predicts that continued mefloquine efficacy will be short-lived [33]. When used as a monotherapy, mefloquine remained efficacious for <5 years in the Thailand–Cambodia border areas [34]; now, two years after its reintroduction in Cambodia as part of drug combinations, it fortunately appears to remain efficacious (CO, unpublished observations). It is currently being paired with artesunate, to which resistance has emerged, essentially leaving mefloquine again as monotherapy. Moreover, mefloquine is a drug greatly challenged because of both gastrointestinal and neuropsychiatric side-effects, which will undoubtedly affect compliance (adherence, or people completing the recommended three-day regimen), as effective monitoring of adherence is lacking (CO, unpublished observations in northern and eastern Cambodia). Additional solutions are currently undergoing research, including one with a combination of three drugs that are or were failing in other combinations [35]. In addition, molecular marker evidence reveals that the theory of reciprocal cross-resistance is probably not a factor [36]. Another proposed solution is to return to the use of drug combinations that previously

proved inefficacious in initial clinical trials in Cambodia [37]. However, these are unlikely to be more than very temporarily solutions. When international leaders and policy-makers, ministries of health, donors and the philanthropic and scientific communities understand the gravity of this situation, only then can there be a concerted, effective push to finally eliminate malaria in SEA.

Under the late Alan Magill's previous leadership, the BMGF made great strides in its ambitious goal to eradicate malaria; tragically, Dr. Magill passed away before his plan was fully implemented [38, 39]. Two of his key concepts are presented in **Figures 1** and **2**.

In 2014, Bill & Melinda Gates, Alan Magill and a team visited the epicenter of MDR malaria in western Cambodia. In Gates' notes from that trip, they reported the threat as outlined above [7].

Recently, Mr. Gates has proposed a global strategy to prepare for "the next epidemic" [41]. We developed "Recommendations for rapid elimination of emerging incurable malaria" (**Table 1**) based on his article. A key recommendation of Mr. Gates is that it should be "*coordinated by a global institution given enough authority and funding to be effective…*". He also noted that cooperation among various nations' militaries should be a priority. In 2014, SEA military

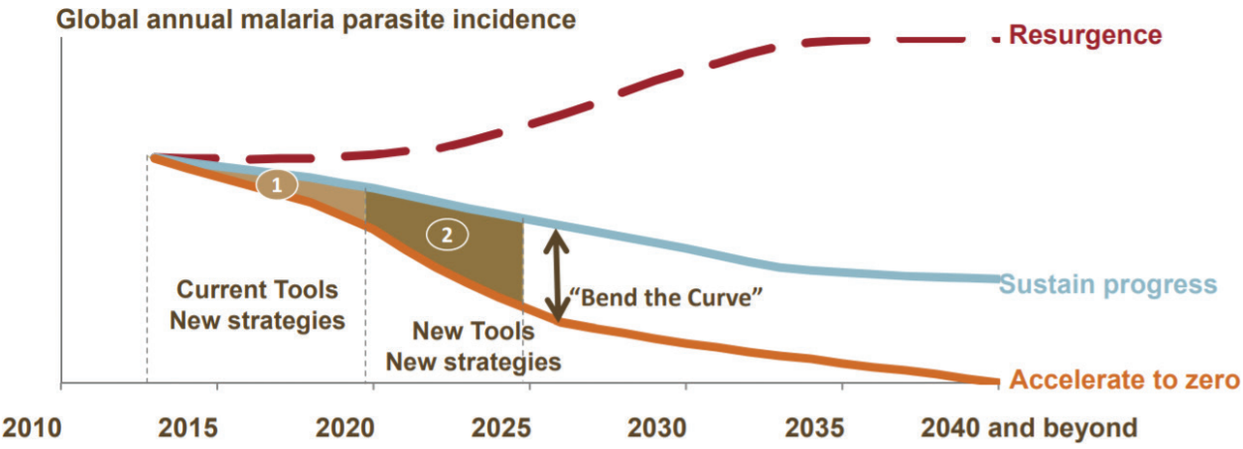

Figure 1. Three potential future trajectories for malaria as per the late Alan Magill from his "Accelerate to Zero" presentation [40]. He recommended to "bend the curve." One of his specific goals was Pf elimination "East of Bangkok" by 2020. 1 and 2 in circles represent additional reduction of malaria cases in the timeframe represented (reproduced with permission from the Bill & Melinda Gates Foundation). We are currently on the resurgence curve in Cambodia and may soon be worldwide if effective action is not taken.

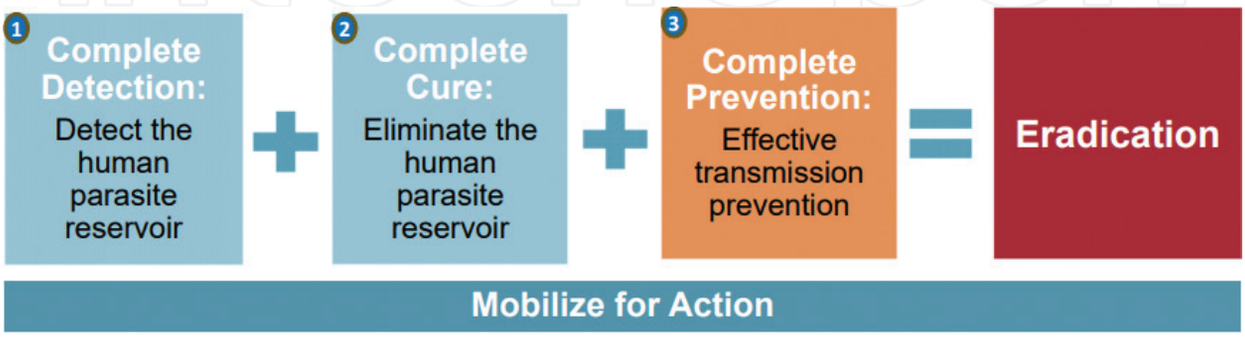

Figure 2. Mobilize for action. How to accelerate the trajectory to malaria eradication by concurrently achieving three goals: (1) identifying the human reservoir of infection in asymptomatic persons + (2) eliminating the human parasite reservoir + (3) combined with geographically and temporally targeted transmission prevention and strengthened surveillance and response [40] (reproduced with permission from the Bill & Melinda Gates Foundation).

leaders met twice and indicated their willingness to support malaria elimination efforts [42], but there has not been effective funding forthcoming to protect troops from malaria nor for them to assist with the much needed effective response. Another meeting was held in 2016, but the only available funding was for research (P. Smith, personal communication), not for an effective treatment and prevention package at scale, nor the needed direct support for malaria elimination operations that militaries can provide. A well-led military response to the MDR malaria crisis would be a large part of the solution to achieve WHO goals.

Gates also called for a warning and response system to enable fast decision-making. A surveillance/information system of the sort envisioned in a recent background paper [43] should be rapidly implemented across the SEA region. This is not an untested assertion, as a simple smart phone-based system has already been successfully pilot tested in central Vietnam [44]. A key 2016 finding was that each household had received an average of 4.3 treated bed nets; despite very high coverage at the household level (where there is little or no transmission), only 16% reported using a treated net when traveling to areas of elevated risk [9]. Similarly, low rates of treated net usage have been anecdotally observed by authors in four provinces in Cambodia recently and in other SEA countries [45, 46]. A smart phone-based system can provide quality monitoring including picture and video evidence to help leadership ensure that those in need of treated bed nets are actually using them and that treatments are being completed [44].

The mechanisms underlying emergence of drug resistance are not fully understood and are believed to be multifactorial [47]. A key factor leading to resistance may be incomplete treatment—effective adherence monitoring is still not in place and must be a priority. Until recently, Vietnam made standby ACT-treatment available to forest-goers, during which partial treatment may frequently occur. The same problem arises when people with symptoms of fever are provided antimalarial drugs by individuals who do not stress the need for complete treatment (e.g., private drug sellers and others). As artemisinin-derivative components have decreased efficacy in the GMS, a greater selection pressure is placed on the partner drugs. Whenever possible, all combination therapies should include a fully curative dose of each component, which, for short half-life drugs, requires seven days of therapy. Seven days of monitored treatment is feasible in the region if patients are renumerated for lost work time.

The role of mosquito vectors in the spread of drug-resistant malaria is also not fully understood. In the GMS, it is clear that malaria transmission is closely associated with the forest and forest-fringe vectors, i.e., *An. dirus* s.l. and *An. minimus* s.l. Fortunately, extensive insecticide resistance has not yet emerged to these vectors. Humans are likely the main transmission reservoir as they can infect mosquitoes for months if not cured of their malaria infection, while mosquitoes are relatively short-lived (lifespan of *Anopheles* female: three to four weeks) [48].

Lastly, no child should currently die from malaria in Africa, as all strains there are fully curable with ACT treatments. The high death rates are due to ineffective prevention and/or delayed/inappropriate treatment as a result of weak health infrastructure. Targeted and decisive action should be taken in Africa to reduce the overall public health impact of malaria while the most commonly used antimalarial drugs remain effective. This can be done using modifications of the same approaches outlined in this chapter. Because of the threat to Africa, where the

combination of both ineffective drugs and weak health infrastructure will lead to another public health emergency, decisive actions must be taken immediately in Asia.

2. Achieve both local and international commitment and a real sense of urgency—a "Public Health Emergency of International Concern (PHEIC) or similar set of directives"

In the 1980s, nearly incurable malaria parasites emerged on the Thailand-Cambodia border. Mefloquine failed four years after introduction in 1985 [34]. The only treatment option at the time was quinine-tetracycline [49]. Quinine is a very poorly tolerated drug requiring three daily doses for seven days—meaning almost no one completes it (e.g., poor adherence or compliance) unless every dose is monitored. Fortunately, artemisinin derivatives and other drugs became available—all of which either did not work at the time of their introduction (e.g., lumefantrine, pyronaridine [50–52]) or have lost therapeutic efficacy (e.g., piperaquine [53]). Presently, the pipeline of new antimalarial drugs is not keeping pace with the emergence of drug resistant strains [37]. Now in Cambodia, mefloquine sensitivity has returned, but is likely to be short-lived (e.g., two more years or less), by which time we may be back to quinine-doxycycline (a tetracycline derivative). We have recently learned that the Vietnam Border Guard Forces have provided doxycycline prophylaxis to more than ½ million people over the last decade (CO, personal communication)—which means this drug might as well be rendered ineffective by now. Identification of the combination partner drugs or the new seven-day regimens must be a priority. Ineffective or incomplete treatment will result in people carrying malaria parasites, an increased transmission reservoir, cases and deaths. The US Center for Disease Control and Prevention (CDC) reported the direct costs for malaria (e.g., illness, treatment, premature death) to be at least $12 billion per year. The cost in lost economic growth is many times more than that [54]. If key leadership does not act rapidly and effectively now, these costs will be much higher. If a PHEIC was declared, these emerging incurable parasites can be rapidly eliminated using the approaches presented here. If not, we will likely have a slight upgrade of "business as usual" with this critical window of opportunity lost.

As advocated early in this chapter and by others [4, 55] (Rear Admiral C. Chinn, personal communication), we believe that the best way to handle this threat is to declare a PHEIC or similar directives. The failure of nearly all drugs in Cambodia, the crossing of these parasites into Vietnam and current increasing Pf malaria in Cambodia arguably constitute such an "extraordinary event" based on the three prongs identified by the International Health Regulations (IHRs). First, the failure of standard treatment options for deadly communicable disease constitutes a public health threat. While all forms of malaria are still currently treatable, the imminent failure of last ACT poses a public health risk, especially for sub-Saharan Africa. This situation would make the deadliest form of malaria untreatable, which would at least be comparable to the "events" that have triggered previous PHEIC declarations [56, 57]. Second, drug-resistant malaria is at risk of spreading internationally as a result of the substantial presence of security personnel from the GMS in sub-Saharan Africa such as Cambodian and military personnel and workers traveling to Africa. There is greater risk that these challenging new parasites will reach both India and Bangladesh soon. These countries have substantial

numbers of their troops in Northeast India and Eastern Bangladesh, where these parasites will first arrive, and are currently the 2nd and 3rd largest contributors to international peacekeeping missions [58]. Third, a coordinated international response is absolutely required to manage this risk. In SEA, there are now fortunately few deaths from malaria. Leadership here has other pressing health issues to address, with malaria now becoming a low priority. Both international leadership and assistance for the countries involved, especially with security forces, is needed to ensure proper response to this peril most directly threatening Africa.

3. Establish mission leadership with enough authority, respect, expertise and functional funding

We urge Bill & Melinda Gates Foundation, the US government and the Asian Development Bank to fill the leadership vaccuum at the operational level, as the newly resistant parasites, if they reach Africa, will make the goal of malaria eradication very much more challenging. We believe these are the only organizations with the authority, resources, and respect to make this happen. Local governmental personnel with the responsibility for the mission must be empowered. Future, on-the-ground non-govermental leadership must be carefully selected to ensure they have the needed commitment, authority, respect, and expertise to be effective [41]. The WHO Emergency Response to Artemisinin Resistance (ERAR) in the GMS hub was established in 2013 [59] to strengthen the response to artemisinin resistant malaria by coordinating action, technical leadership and catalyzing resource mobilization. The ERAR hub was "transitioned" to the Mekong Malaria Elimination program in 2016 [60]. Why containment failed must be objectively evaluated to insure that the new leadership is effective. Public Health Emergency Operations Centers could be a good solution [61].

The elimination of malaria is not as difficult as it appears on the surface. It boils down to prevention and effective treatment of malaria patients in or traveling from the actual transmission foci. GMS original forest areas are now shrinking, which is making the mission easier. Bill Gates himself and others have effectively outlined the actions needed [41, 55]. Cambodia is the epicenter of emerging incurable malaria; the needed policies and guidelines are now in place in this country [24, 62]. What is needed now is quality implementation of relatively straightforward interventions in the field. In 2013, the RAI, a three-year $100 million grant, was launched by the Global Fund (GF) to contain artemisinin-resistant malaria (http://www.raifund.org/). Many of the key impediments were clearly outlined in the 2015 RAI mid-term report [3]. Unfortunately, we were denied permission by Global Fund leadership to publish the conclusions and recommendations from their report in this chapter (A Joubert, personal communication). We were allowed to publish only the map, which revealed Pf was going up at that time (**Figure 3**).

With a new leadership team, given a passion for the mission, along with authority, expertise and sufficient/effective funding, we strongly believe that Pf elimination goals can be achieved near to the WHO targets in the GMS [24]. Determining if the RAI mid-term review results have been effectively addressed should be top priority [3]. The results of routine, truly independent quality monitoring from the field must be a key component. Quality monitoring must focus on what is most important (e.g., effective prevention and treatment in actual transmission foci). Targeted supportive supervision for partners experiencing implementation challenges is also

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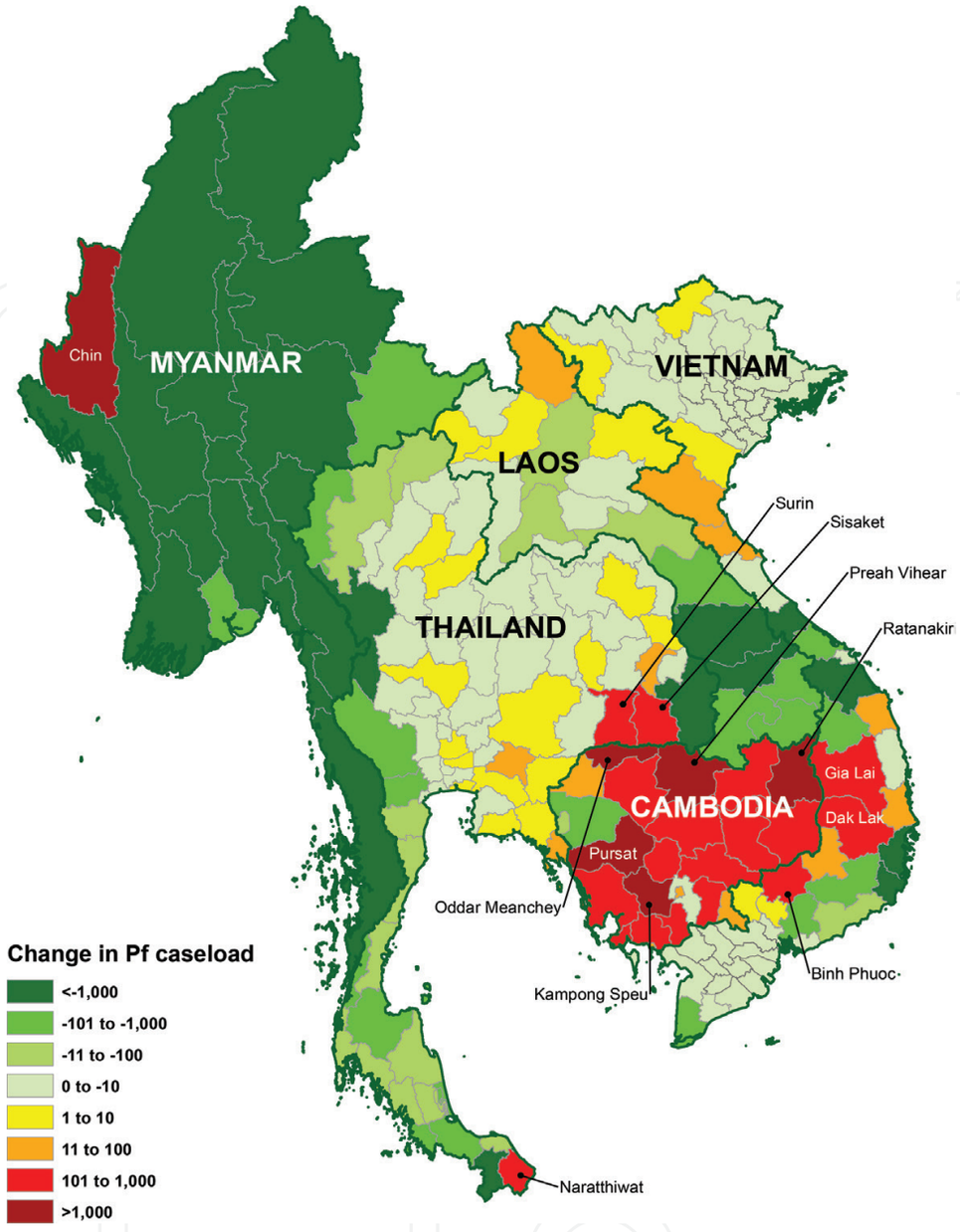

Figure 3. Pf caseload increase between July 2014–June 2015 [3]. Malaria was again rising in 2017–2018 in several provinces of Cambodia.

essential to achieve elimination targets. Our new "Red-to-Green, Keep-It-Green" Information System is an example of the ability to provide near real-time feedback to leadership with image and video documentation of what is really happening in the field (see Section 5.1.1) for both independent quality monitoring and supportive supervision.

GF is by far the largest investor in malaria in the region; their funding, however, is not nearly as effective as it could be for malaria in the GMS, especially in Cambodia. GF has evolved to be a mega-donor. As with all large organizations, this brings bureaucracy; in addition, it has the added challenge of accountabilty for very large sums of money. Malaria in the GMS represents only a small part of the overall portofolio, but has the same rules that apply to all funding, impacting timely and effective intervention implementation. For example, a sub-contractor receiving Presidential Malaria Initiative (PMI) funding reports PMI funds are hard to use, but

GF funds are 10 times worse (CO, person communication). GF funding is focused on process and financial accountability, not on timely, effective and quality implementation of interventions in transmission foci despite WHO's call for "urgent action" [24]. For example, in a province in Eastern Cambodia where malaria increased 2.5 fold in 2017, nets were first delivered to the lower risk villagers in early 2018 and the high risk mobile and migrant populations will not receive nets until at least mid-2018 following the set process. Furthermore, in the villages, a fixed number of treated nets are being provided, resulting in households with more than one forest-goer often not having enough nets. Response to new cases is in the village, which does not make sense with transmission being in the forest. Malaria in the region is an occupational disease for those working in the forest, while most programs have been designed around presumed household exposure. Lastly, Cambodia returned more GF funds unused than any other country in the region in the cycle that ended in December, 2017 (CO, unpublished observation).

Available financial resources must be used much more effectively. Despite large amounts of funding in the region, basic intervention coverage in forest transmission foci is poor. There is markedly disproportionate financial support provided for partner organizations in the region. Each international support staff often costs hundreds of thousands of dollars per person per year, including overhead and allowances. Yet, incentives for good performance are not allowed for malaria-endemic country government staff who have salaries that are not enough for subsistence. For example, district-level health staff typically make $200–$300/month, while salaries for NMCEP staff at the national level are in the range of $300–$1200/month. While GF guidelines do allow for incentives to government employees [63], we have been informed that this policy does not apply in the GMS (CO, personal communications). Undoubtedly, this leads to resentment by those expected to execute malaria elimination operations, which are often beyond their normal duties and may put their own job security at risk. A main argument against incentives is "sustainability in the context of decreasing external financing for malaria" (The RAI-Regional Steering Committee, personal communication), despite 7+ million lives being at risk. Malaria "East of Bangkok" can be rapidly eliminated, making long-term sustainability a non-issue if the recommendations in this chapter are followed.

Leadership must also address many conflicts of interest, which are often subtle in this setting, especially with research. As per the former Pacific Command Surgeon, "[elimination of malaria] is an action problem, not a research problem" (Rear Admiral C. Chinn, personal communication), yet the US Army continues to do only research with substantial increases in funding for malaria. Researchers, to be successful, must enhance their own *curriculum vitae* and malaria research usually requires substantial disease transmission, resulting in disincentives to facilitate elimination. The lead author is most familiar with the malaria research being conducted by the US military, which is expensive, frequently wasteful, often duplicative, many times not impactful and sometimes actually counterproductive (CO, unpublished observations). A mechanism must be in place for research prioritization, independent review by experts who understand the needs and challenges, and for timely action based on important findings [20].

The lead author of this chapter helped to identify funding to protect security forces in the GMS from malaria. His intent was for this to be modeled after the DoD directive to prevent and treat HIV-AIDS [30]. Following the realization that new funding was more for research, the following feedback was received … "I am aware that you're in disagreement… want to see us more

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aggressively target malaria elimination. As we've discussed, we see this ultimately as a host country responsibility…" (M. Fukuda, personal communication). Many in the region are being misled that researchers are actually helping to protect host country militaries from malaria, when in practice, only small research studies are being conducted to fund research staff and to generate publications, with no action being taken based on the results. Leadership must take corrective action as militaries are both a key malaria transmission reservoir and can direclty support elimination operations (see Section 4). Malaria is the largest infectious disease threat for the US DoD and action can be taken as exemplified by an HIV prevention program to support foreign militaries and a DoD directive [30]. The US Army should engage with an institution that is not research-focused to rapidly help eliminate the emerging incurable parasites and ensure than any malaria research funding in the region is focused on rapidly stopping falciparum malaria transmission.

Vietnam can serve as an example for effective leadership and health system strengthening leading to rapid reduction and preparation for elimination of malaria. With intensive implementation of malaria control measures over the past decades, the burden of malaria is decreasing rapidly, and the disease is becoming increasingly focal. Between 2000 and 2016, the number of malaria cases was reduced by 94.4% (74,316 down to 4161) and number of deaths reduced by 97.9% (142 down to 3) [64] (**Figure 4**).

Key factors leading to the success of the program are as follows: (1) strong commitment and substantial investments by the Government of Vietnam and its international development partners, (2) a strong and comprehensive health network from central to community levels, (3) a vertical, well organized and functional program (e.g., health staff specialized in malaria control activities are working effectively at all levels down to village), (4) extensive vector control measures with high coverage of ITNs and indoor residual spraying (IRS), (5) availability of highly effective medicines for malaria treatment at all levels, (6) engagement of multisectoral partners (see Section 4.2).

Although great success towards malaria elimination has been made, Vietnam is now faced with a critical window of opportunity to achieve the elimination of malaria as mandated in

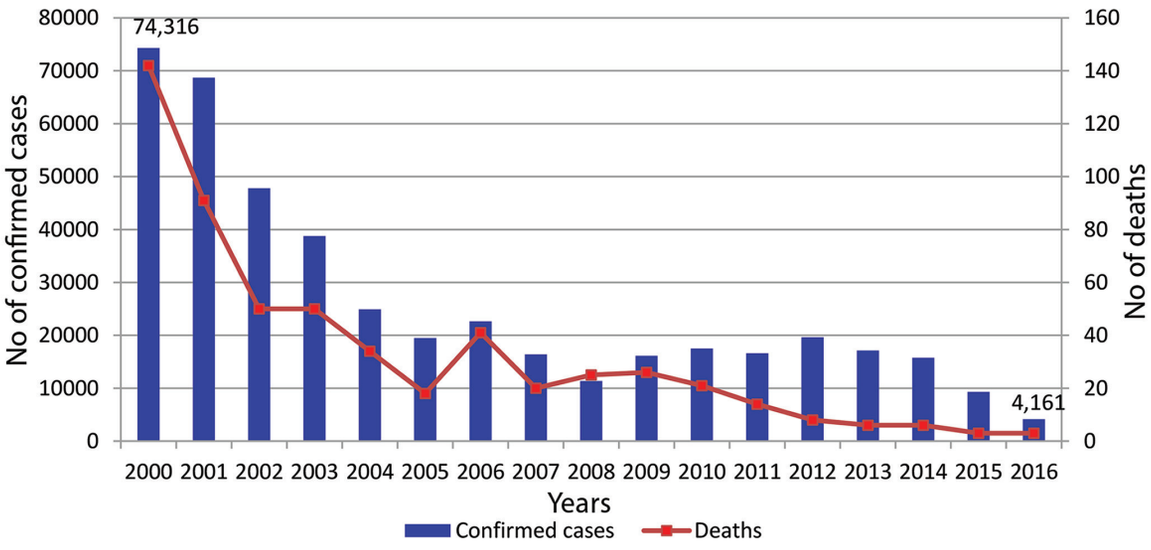

Figure 4. Decreasing malaria transmission trends in Vietnam between 2000 and 2016.

the "National Strategy for Malaria Control and Elimination 2011-2020 and Vision for 2030" [65]. This critical window includes the following factors: (1) efficacious antimalarial combinations still exist but are failing fast; (2) potent tools for vector control are available but could be undermined quickly by the development of insecticide resistance; and (3) financial support from external funding partners continues to flow but is likely time bound. The Government of Vietnam will also need to take bold steps and intensify national malaria elimination efforts to ensure that malaria is eliminated from Vietnam for good before this window of opportunity closes.

In summary, with a new leadership team, given a passion for the mission, along with authority, expertise and sufficient/effective funding, we believe WHO's Pf elimination goals can be achieved near the set target date of 2020. Vietnam is an example of a success story, which can serve as a model for other country programs. However, Vietnam cannot eliminate malaria until neighboring countries also do so. We urge BMGF, Asian Development Bank (ADB), PMI, the US military and other philanthropists to take action to address the challenges presented here in order to drive malaria elimination in the region.

4. Engage security forces to prevent disease spread and support elimination operations

4.1. Security forces as a neglected population contributing to the malaria transmission reservoir and spread of drug-resistant parasites

The GMS security forces are a neglected population group that are at greater risk of contracting malaria, [22, 63] and serving as a transmission reservoir [20, 66]. They are certainly spreading the disease in the region and are the most obvious direct conduit of the current parasites to Africa [10]. In Africa, peacekeeping forces, deployed from many malaria endemic countries, work together, which could cause rapid spread of the new drug-resistant parasites. PCR-based screening of UN peacekeeping troops from Cambodia was initiated in 2015 (PCR is the only method sensitive enough to detect asymptomatic parasite carriers). In 2017, it was learnt that this practice had been discontinued at some point, but with inputs from key leaders to WHO, this was fortunately re-initiated. This process must be monitored so that lapses in screening do not recur. It must also be extended to include other militaries in the region that soon will also be at risk of spreading these parasites.

We have evidence that the Cambodian army has high malaria infection rates, and not been receiving optimal malaria prevention or treatment, and are serving as the primary malaria transmission reservoir in an area of Northwestern Cambodia [67, 68]. In 2010, 5% of troops were reported positive for Pf by PCR during a malaria screening [68]. The study for which the screening was done provided direct evidence, although with small numbers, early warning that dihydroartemisinin-piperaquine was failing as treatment. The lead author urged the US Army to act to stop transmission in these troops, but to no avail. He then contacted BMGF in 2012 to provide funding to stop transmission in these troops; funding was awarded, but not used until 2016, by which time the number positive for Pf had doubled to 10% [20]. It is unclear why the US Army does not act much more quickly given the threat to US troops.

In the 2016 intervention study, Pf transmission was stopped, providing direct evidence that the Cambodian army was the primary Pf transmission reservoir in the area of the study [20]. We believe there is sufficient evidence to scale the interventions that were proven to be effective (e.g., permethrin-treated uniforms, see **Table 2**). The impressive results from the study, however, have unfortunately not yet been acted upon.

Additional evidence of security forces being a transmission reservoir comes from the area where the most resistant parasites cross-border into Vietnam. Forest rangers in the Bu Gia Map National Park screened positive for Pf malaria at about ~11% for Pf (very similar to the Cambodian army in Northwestern Cambodia, see above) [66]. This population is probably a significant malaria transmission reservoir in this area. From the publication, the rangers appear neither to be receiving effective prevention measures nor routine screening and treatment. No funding in the GF 2018–2020 budget was allocated for such activities in this population. The only way it will be possible is to request unused GF year-end funding be reallocated, which is not an easy process (CO, personal communication). Furthermore, since permethrin-treated uniforms are not yet WHO-prequalified (despite standard of care in Western militaries and recent impressive evidence in the Cambodian army), GF funding may not be able to be used for this intervention (CO, personal communications).

Permethrin is very inexpensive, well-tolerated, and widely used for uniform treatment by Western militaries for malaria prevention [69]. The evidence for efficacy of treated uniforms/clothing is summarized in **Table 2**. Based on available evidence, and in light of emerging incurable parasites and pyrethroid sensitivity of the main transmitting mosquitoes (M. Macdonald, personal communication), we believe treated uniforms should be rapidly scaled up for all security forces in the GMS as one component of an integrated vector control package.

In Cambodia, there are three types of government security personnel working in the forest—army, forest rangers, and border police; each falling under different ministries. We are aware of a pilot project in Northwestern Cambodia where an ADB-funded project is working with all of these groups for malaria prevention and treatment (CO, personal communications). We believe this initiative should be taken to scale as quickly as possible in the region.

4.2. GMS security forces can provide direct support if given a mission and properly resourced

The Vietnam People's Army, including the Vietnam Border Defense Force, provides an excellent model for security personnel supporting health interventions. From 2005 to 2015, the Combined Military Medical Program contributed to improve health, hunger elimination and poverty reduction [75]. Example accomplishments for health include: (1) vaccination of 5.1 million children with Ministry of Health-recommended vaccines, (2) family planning for more than 3.7 million people, (3) malaria prevention education for more than 1.8 million people, and (4) IRS of nearly 26 million square meters of housing with National Malaria Control Program with provided pyrethroids.

More than 1300 health stations were strengthened with military staffing, including 1044 health stations in remote and isolated areas (>10% of all nationwide; in locations where it is hard to recruit civilian staff). The system includes 152 border clinics, which also serves as a border surveillance system for early detection of epidemics.

First author and study location	Level of evidence[a]	Study population	Study Design[b]	Intervention groups (n)	Control group (n)	% Failure intervention[c]	% Failure control	Protective efficacy (95% CI)[d]	Reference/ notes[e]
Moore (2019), Tanzania	1	Public Service Corps	CR	Permethrin-treated uniforms (n~500), DEET (N~250)	Untreated uniforms (n~500), DEET placebo (N~250)	NYA	NYA	NYA	1
Wojnarski (2016), Cambodia	2	Military	CR	Permethrin-treated uniforms (n = 125)	Untreated uniforms (n = 143)	10%	24%	56% (21–76%)	[20] 2
Additional arm in Wojnarski (2016)	‘”	””	””	Permethrin-treated uniforms + partially effective prophylaxis (n = 130)	Untreated uniforms (n = 143)	15%	24%	35% (−7–61%)	[20] 2
Soto (1995), Columbia	3	Military	RDBCT	Permethrin-treated uniforms, socks and hat (n = 86)	Water-treatment of the same (n = 86)	3%	14%	75% (15–93%)	[70] 3
Rowland (1999), Pakistan	4	Afghan refugees	RCT (to household)	Permethrin-impregnated headscarves/top sheets (n = 438, 51 families)	Placebo EC formulation (n = 387, 51 families)	25%	38%	36% (21–48%)	[71] 4
Kimani (2006), Kenya	5	Somali refugees	CR	Permethrin-impregnated clothing & sheets (n = 90)	Plain water-impregnated clothing & sheets (n = 91)	38%	66%	43% (22–58%)	[72]

First author and study location	Level of evidence[a]	Study population	Study Design[b]	Intervention groups (n)	Control group (n)	% Failure intervention[c]	% Failure control	Protective efficacy (95% CI)[d]	Reference/ notes[e]
Eamsila (1994), Thailand	6	Military	Unclear, probably CR	Permethrin-treated uniforms (n = 249)	Placebo-treated uniforms (n = 414)	27%	29%	4% (−23–26%)	[73] 5
Most (2016), French Guiana	7	Military	Unclear "conditions identical"	Long-lasting polymer-coated permethrin-impregnated uniforms (n = 25)	Untreated uniforms (n = 125)	0%	9%	100% (NA)	[74]

[a]1 is strongest, 7 least strong.

[b]CR: Cluster randomized trial, RDBCT: randomized, double blind clinical trial.

[c]NYA: Not yet available.

[d]NA: Not available.

[e]Reference in [], notes by number: (1) Trial planned to execute in 2018, (2) True efficacy higher as estimate is confounded with *Plasmodium vivax* (Pv) relapses; efficacy only for Pv as Pf transmission was interrupted by interventions; final clinical study report pending. (3) Instructed to wear their uniforms day and night; under garments also treated, two adverse events in the permethrin arm requiring topical treatment but able to continue in study, no treatment needed in placebo arm; only trial with adverse events reported, (4) < 20 years had ~64% Pf protective efficacy, pooled efficacy underestimated because of Pv relapses, headscarf's were worn by women outside during waking hours and used by the family as bed sheets at night, noted efficacy almost as good a treated bed nets in a prior trial in the same population. (5) Pv cases despite CQ prophylaxis indicated non-adherence; noted incomplete ability to monitoring uniform use, possible randomization leading to unequal exposure (e.g. permethrin-treated uniforms had more malaria than placebo in one area).

Table 2. Review of protective efficacy of permethrin treated clothing for malaria prevention.

In conclusion, we urge donors and NMCEPs to help supporting security forces take action. This should include first to make sure security forces are using appropriate prevention and treatment packages. GMS security forces absolutely can directly support elimination operations. They best understand the mobile and migrant populations (MMPs) and terrain of the remaining forest in the region, understand military planning and have a structured workforce in many of the challenging areas. We call on donors to provide the leadership and funding by making sure that security forces are not a transmission reservoir and are engaged in the fight against malaria.

5. Utilize surveillance as a core intervention linked to results-based funding (SCI-RBF) to achieve rapid and effective action in actual transmission foci

5.1. Development of an innovative information (surveillance) system to eliminate emerging incurable malaria

In 2015–2016, our research team worked in two provinces in Vietnam (**Figure 5**) to field test a surveillance/information system envisioned in a background paper written for the BMGF [43]. We partnered with National Institute of Malariology, Parasitology and Entomology (NIMPE) and the Phu Yen Provincial Health Department (PHD) to develop and pilot test the information system linked to a pay-for-performance system. We also developed concepts to target forest malaria transmission foci and/or people traveling to these locations with effective integrated prevention and treatment.

5.1.1. 2015 results

We defined transmission locations, intervention usage, risk groups/factors and desired interventions. This was first done with a household survey of the identifiable malaria patients from the most recent 100 cases and a sample of nearby houses (**Table 3**). This table illustrates total cases and risk by work-type and that the reported use of program-provided long lasting insecticidal nets (LLINs) in actual transmission areas was very low [9]. For example, most malaria cases (49%) were coming from paper plantations, but farmers and charcoal producers were at higher risk (75 and 80%, respectively). LLIN and overall treated nets in use were only 6 and 19%, respectively. Households with malaria were ~three-fold less likely to use treated nets, Odds Ratio 3.2; $p < 0.01$) [76]. The actual transmission locations were determined by where people reported sleeping one to two weeks before they developed fever (malaria incubation period). The lack of transmission at the village level was confirmed by the lack of malaria patients who remained in the village during the incubation time for malaria.

These results were next confirmed and extended through geographic reconnaissance of sleeping sites of malaria patients (**Figure 6**) [8, 9, 44]. At each sleeping site, GPS coordinates, with images the sleeping structure and the nets being used (if any), were captured (**Figure 6**). The pictures were used to validate self-reported data (e.g., **Figures 7** and **8**). Interviews revealed forest rangers reported taking partial malaria treatment when ill, malaria infection was common and lack of prevention measures for work in the forest at night. Based on this information, we suspected this population was the primary transmission reservoir in this area, similar to that recently reported from forest rangers in a nearby province [66].

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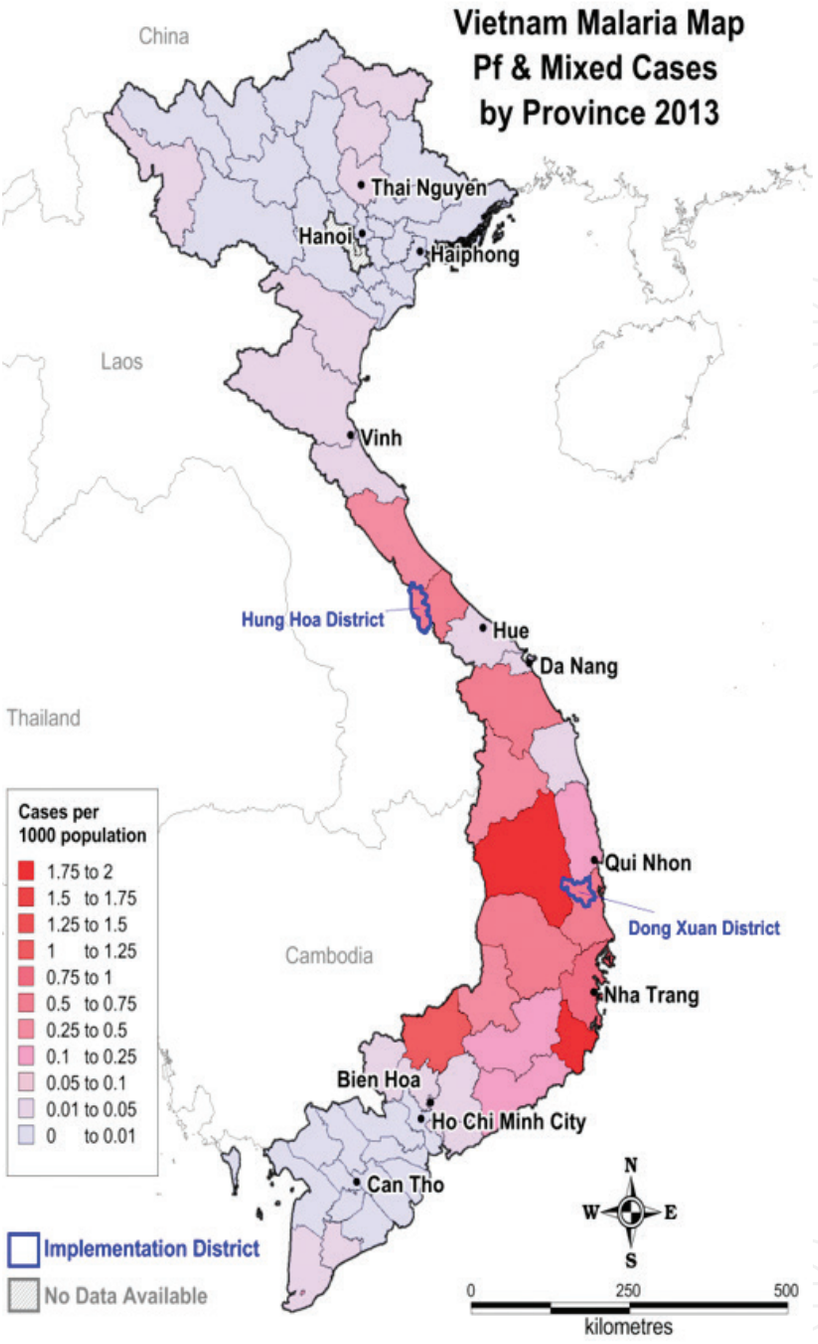

Figure 5. Vietnam study districts in Quang Tri (Hung Hoa District) and Phu Yen Provinces (Dong Xuan District) (blue outlined areas).

Figure 6 illustrates that actual forest transmission locations were readily identifiable; 80% were accessible within one hour by motorcycle. For the remaining 20%, the optimal placement of malaria posts to access those at risk was determined. The primary factors for low treated net use were the fact that 92% desired a hammock net (with few provided) and 83% desired a zip-type hammock net [76]. The hard-type LLINs that were provided were a type that was strongly disliked by 85% of those surveyed. Of the forest-goers surveyed, 89% reported they would be willing to use mosquito repellent and 91% malaria prophylaxis [76]. Based on these results, we believe the provision of nets of a type that people want to use, net retreatment

Main work type	n	Percent interviewed	Number of malaria cases	Percent total malaria (n = 93)	Percent risk malaria[a]	Nets currently used (n = 186)		Net types currently used (n = 189)	
						Any net[b]	At least a treated net type[d]	At least a zip hammock type	At least a LLIN type
Paper plantation	94	49%	44	47%	47%	65%	11%	41%	2%
Agarwood harvesting	39	21%	14	15%	36%	95%	15%	36%	8%
Farmer	16	8%	12	13%	75%	80%	80%	0%	38%
Trapper	16	8%	6	6%	38%	44%	25%	13%	6%
Charcoal production	10	5%	8	9%	80%	70%	0%	50%	0%
Timber harvesting	9	5%	4	4%	44%	33%	11%	11%	0%
Hunter	3	2%	3	3%	100%	0%	0%	0%	0%
Other	3	2%	2	2%	67%	67%	67%	0%	0%
Total or mean	**190**	**100%**	**93**	**100%**	**49%**	**68%**[c]	**19%**	**32%**	**6%**

[a]Cases of malaria/people interviewed.

[b]Number reporting any net reported being used at forest sleeping site/number interviewed in work type.

[c]Number reporting any net reported being used at forest sleeping site/total interviewed.

[d]Program was providing annual net retreatment accounting for the difference between 6% for LLIN.

Table 3. Malaria-risk populations and bed net use in Phu Yen Province, Vietnam in 2015.

for self-purchased products, repellent availability, along with on-going education and use monitoring will enable high usage of an integrated prevention package.

Figure 6 also illustrates the smart-phone based information system, which greatly improved our ability to conduct near-real time data capture and quality control from Hanoi, while the team was working in the field. Information was captured using a smartphone app with the data fed into an on-line server when Internet access was available to the field staff. Ona.io server, KoboToolbox (http://www.kobotoolbox.org/) and other systems are inexpensive, easy-to-program/use, powerful new tools for the fight against malaria.

In **Table 4**, we outline the interventions we believe are needed for rapid malaria elimination. We illustrate linking of successful execution of the interventions to incentive pay, which was successfully pilot tested. Data captured from each intervention can constitute "surveillance as core intervention (SCI)." Incentive payments can be linked to the smartphone-captured data following quality checks. We believe surveillance as an intervention with results-based funding (SCI-RBF) will motivate staff to make sure patients complete antimalarial treatment and effectively intervene in transmission foci (both of which are still largely lacking).

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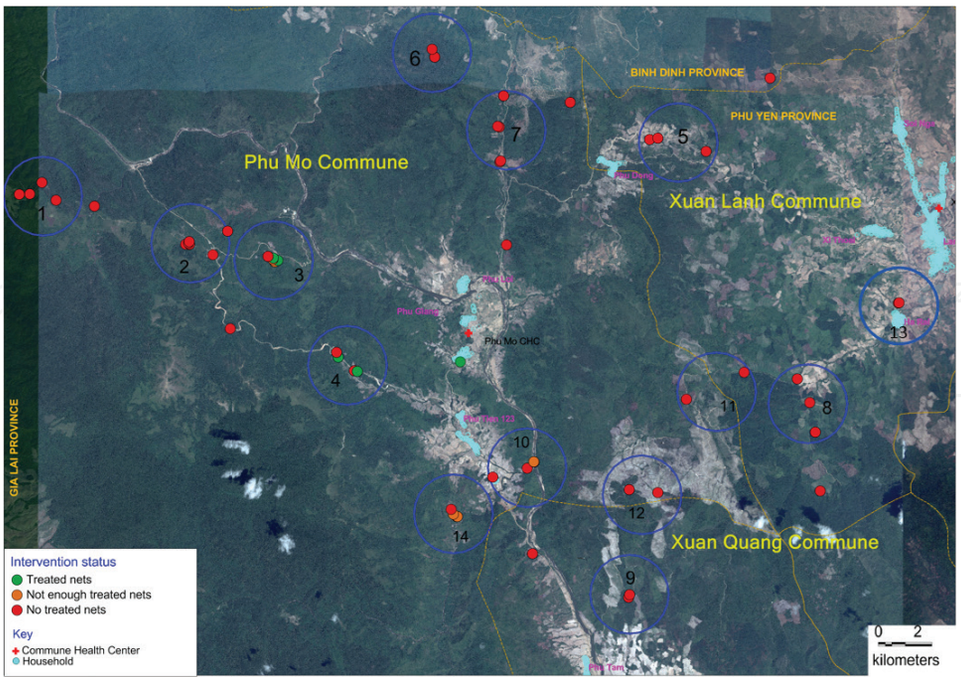


Figure 6. Baseline malaria transmission location map with insecticide treated net (ITN) usage in Phu Yen Province, 2015. The turquoise color represents 4700 households. In 2016, provincial health records showed 4.3 treated nets per household. Dots are the forest sleeping locations 1–2 weeks earlier, including 95% of 2015 cases. The color of the dots reveals very low use of nets in actual transmission areas, despite very high coverage in the village (where there was no transmission). The light purple circles are transmission foci, defined here as two cases within a 1 km radius, which captured 80% of all cases.

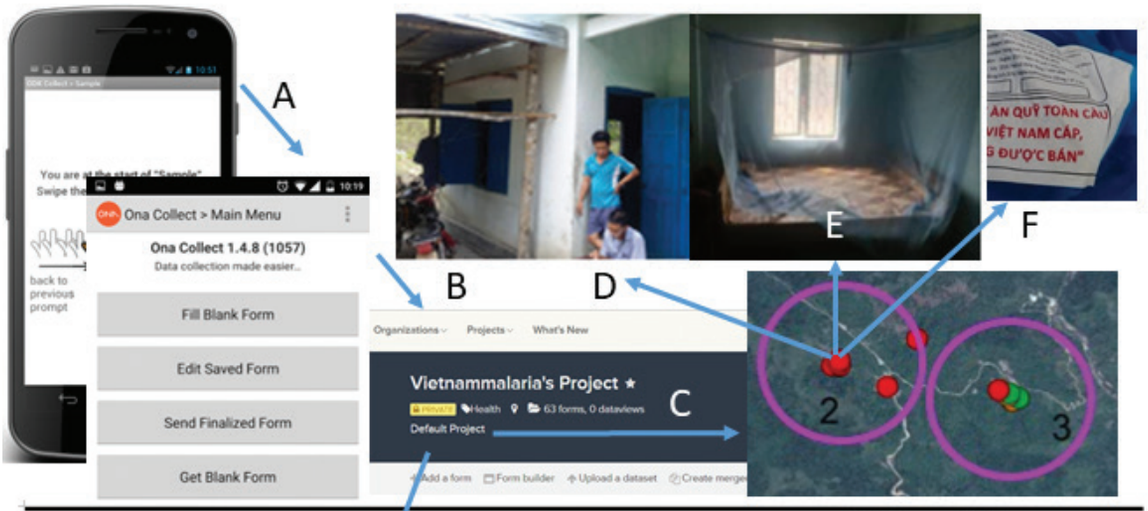
Lastly, a concept was developed for a malaria elimination task force (METF) led and implemented by PHD staff, implemented by mobile malaria workers (MMWs). The METF should routinely have challenge-solving workshops with NMCEP staff to improve the quality of data and responses.

5.1.2. Conclusions

Despite very high household insecticide-treated net coverage, their use in risk areas is very low. Forest transmission sites are identifiable and targetable directly and/or at forest pathway points. The described transformative smart-phone based information technology will facilitate rapid malaria elimination allowing near real-time monitoring to improve the quality and targeting of interventions. Urgent action must be taken to improve the selection of interventions of products benefitting people at risk and for those working in actual transmission areas.

5.1.3. Broader impact

Based in part on our work in 2015–2017, Phu Yen Province saw the largest drop (89%) in malaria of any province in the region of the south-central coast and central highlands in this time frame. In 2016, as cases decreased, the cases spatially clustered into two areas to prioritize (pink dots in **Figure 9**). In our study district, malaria reduction is striking. In 2017, only 13 cases were reported, compared to 52 (**Figure 9**), 133, 292, and 291 in the years 2016–2013, respectively, a



	n	Work type (%)	Net Type (%)		
			No net	Any net	Any treated net
Transmission site survey (119 malaria case)					
Paper Planation Workers	28	24%	79%	29%	14%
Agarwood harvesters	26	22%	77%	8%	4%
Trappers	12	10%	67%	33%	17%
Timber harvesters	12	10%	67%	33%	17%
Charcoal	2	3%	67%	0%	0%
Farmers	28	24%	29%	57%	29%
Other	10	8%	40%	40%	20%
Total or Mean	**119**	**100%**	**61%**	**32%**	**16%**

Figure 7. Example use of smart phone technology to capture information, images and video linked to GPS coordinates. A. Smart phones with good data coverage are becoming ubiquitous, Ona.oi smartphone data capture; B. Ona.io internet interface; C. Transmission focus map with global positioning system (GPS) coordinates of sleeping locations of malaria patients; D-F. Pictures linked to GPS coordinates for quality control, D. Forest ranger station, E. How the net should look not how did it look, F. Tag on the net to confirm if it is an LLIN or not; G. Example of key data. All will allow for near-real time monitoring of intervention quality with regularly updated maps to allow malaria elimination staff, donors, and key leaders to understand what is happening where and when, from anywhere with internet access for the first time—this technology "changes the game".

96% reduction from baseline. The malaria lead for Phu Yen Province reported our contribution, noting the health staff "operated more effectively" during and following our project.

5.2. New approaches to "leap forward" to achieve more rapid malaria elimination

5.2.1. Development of a "Red-to-Green, Keep-it-Green" information system to achieve high adherence with both integrated vector control and treatment interventions

Based on what we learned in 2015, an information system using the "Red light-Green light" approach, as envisioned by Alan Magill, was developed. Based on 2015 case mapping (**Figure 6**), a simple system was developed to prioritize actual transmission areas for targeting interventions (**Figure 10**). The dot in each circle represents prevention status and the triangle treatment status in each focus. Those presented are treated net usage (dots) and time to ACT treatment (triangles), but must be enhanced to include both an integrated prevention and treatment package (**Table 5**).

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Figure 8. Image evidence of LLIN usage. A–C represent probable use and D-F, non-use. Note in E, chickens inside.

One can visualize the low usage of treated bed nets (red dots). In addition, all but two sites are within one hour by motorcycle of a health center for ACT treatment (green triangles). The green triangles also reflect that most of the forest transmission sites are directly accessible for both responses to new cases and for on-going monitoring. The sites with an orange and a red triangle need proper placement of malaria posts or mobile malaria workers to capture people going deeper into the forest.

The map on the bottom of **Figure 10** illustrates perfect, 100% "Green" status. We believe 60–70% "Green" targets will be sufficient to rapidly eliminate malaria. These maps can be

No.	Intervention/item	Description[a]	Cost/form[b]	Cost/intervention/case[b]	Results-based funding (cost/year)[b]
1	Rapid case report, initial investigations and initial response	Full interview and interventions at initial patient encounter	$ 4.15	$ 4.15	$ 4149
2	Treatment plan and follow-up	Document adherence and late treatment success	$ 20.47	$ 51	$ 51,182
3.1	Foci response (Village)	Screen & treat, treat nets, new nets, BCC	$ 3.75	$ 113	$ 67,500
3.2	Foci response (Forest)	Screen & treat, treat nets, new nets, BCC, IT-ASSBA	$ 15.26	$ 305	$ 122,054
3.3	Foci response (Cross-border)	Screen & treat, treat nets, new nets, BCC, IT-ASSBA	$ 30.51	$ 610	$ 61,027
4	Foci monitoring	Screen & treat, treat nets, new nets, BCC, IT-ASSBA	$ 7.63	$ 76	$ 76,284
5	Forest entry point/ work place monitoring	Screen & treat, treat nets, new nets, BCC, IT-ASSBA	$ 3.75	$ 38	$ 37,500
6	On-going provider quality monitoring	Routine visits to document diagnosis, treatment, prevention and reporting	$ 16.00	$ 2500	$ 30,000
	Total				$ 449,696

[a]Screen: screening with new highly sensitive rapid diagnostic tests (hsRDTs); BCC: behavior change communication; IT-ASSBA: insecticide treatment around sleeping, sitting, sleeping and bathing areas (most sleeping structures are huts without walls).

[b]These are example costs; true costs will be estimated in the field in Cambodia from May–August 2018. Some of these costs are currently provided as travel incentives and monthly stipends for field staff which are not focused on results; the estimates do not include commodities.

Table 4. Example of surveillance as an intervention with results-based funding (SCI-RBF) for the first year of implementation.

regularly updated in an on-line information system for donors, national programs and implementers to monitor progress near real-time.

5.2.2. Mitigation of forest malaria transmission with more effective and complete prevention/ treatment packages

We believe a more comprehensive prevention and treatment package targeting malaria transmission foci, and the people working or traveling there, will have rapid impact, especially when those constituting the primary transmission reservoir are targeted. Pf must be the priority as this species is causing the public health emergency. Both Pf and Pv are transmitted by the same vector species. Pv remains a challenge for cure because of the dormant liver stage (hypnozoites). All of the prevention interventions will also be efficacious for control of Pv, and will drive down transmission in parallel. Pv residual transmission will often remain when Pf has been eliminated. The same resources can be used to mop up residual Pv transmission, which will also ensure that Pf has been truly eliminated.

ITNs are the cornerstone for malaria prevention worldwide, but have inadequate efficacy (e.g., in areas of unstable malaria transmission, 62 and 43% efficacy is reported with no or untreated nets for Pf prevention, respectively [77]). ITNs lack effect when not in use as illustrated by

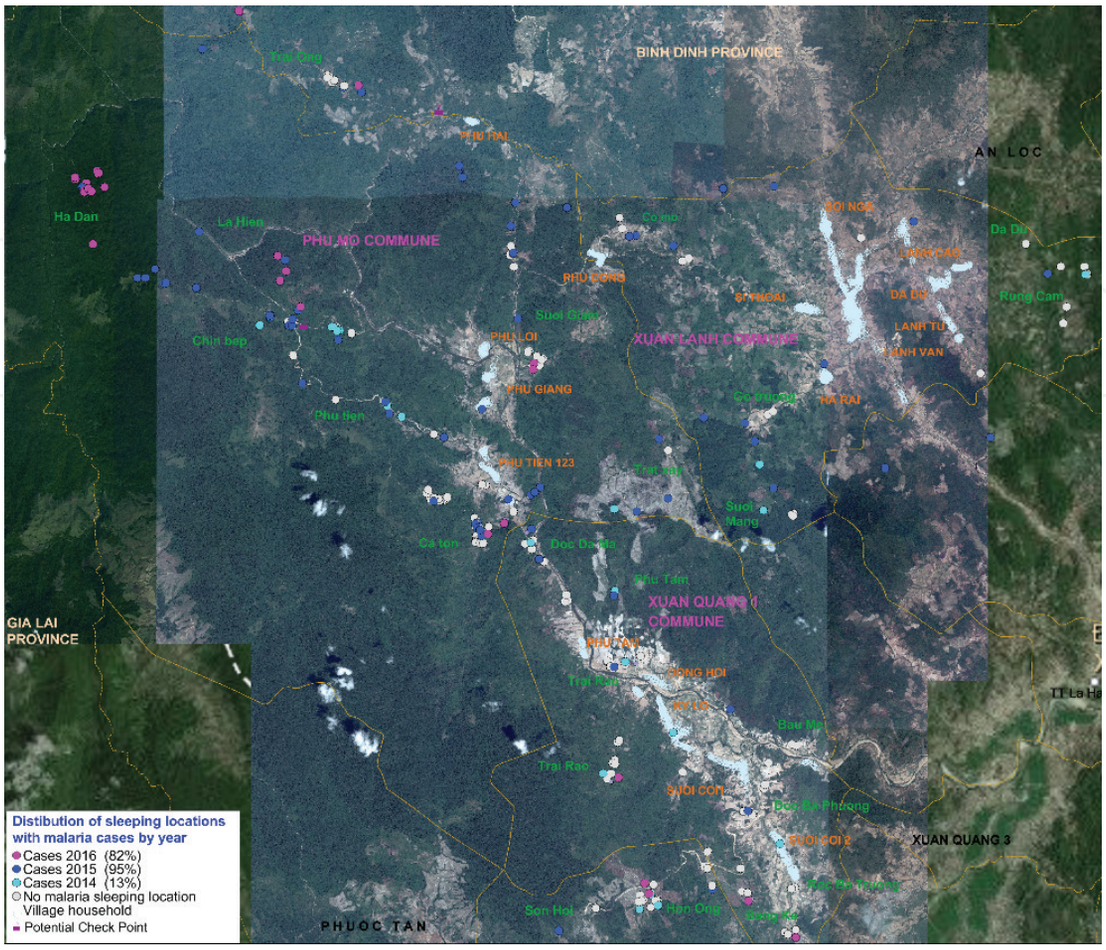


Figure 9. Actual malaria transmission locations by year in Dong Xuan District, Phu Yen Province, Vietnam. Please note the marked clustering of the pink dots as malaria transmission decreased in 2016 to 52 cases from 133 in 2015. Based in part on our effort to demonstrate actual transmission locations and lack of treated nets at these sites, malaria cases continued to decrease to 13 cases in 2017 (a 96% reduction from baseline in 2013-2014).

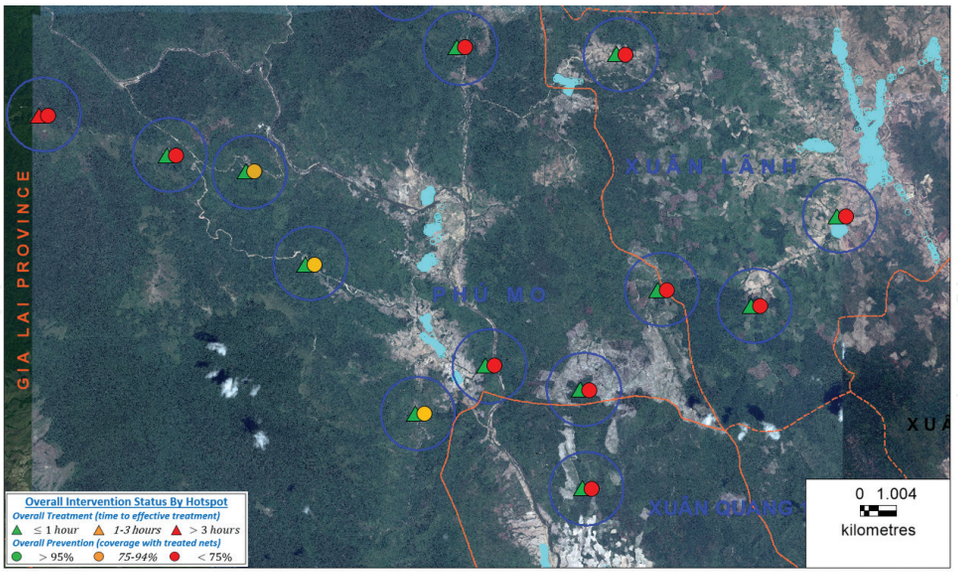
Prevention	Treatment
>90% using a treated net	Complete treatment and follow-up
Treated clothing	Targeted malaria posts to forest entry points
Mosquito repellent	Mobile malaria workers to access hot-spots
Safer sleeping, sitting and bathing areas	Screening with highly sensitive RDTs

Each of these measures has partial efficacy—they must be used in combination with adherence monitoring to achieve high effectiveness. With all drugs soon to be lost, a focus must be placed on use of an integrated vector control package. New vector control products are also in the pipeline, which should be added when effectiveness is demonstrated.

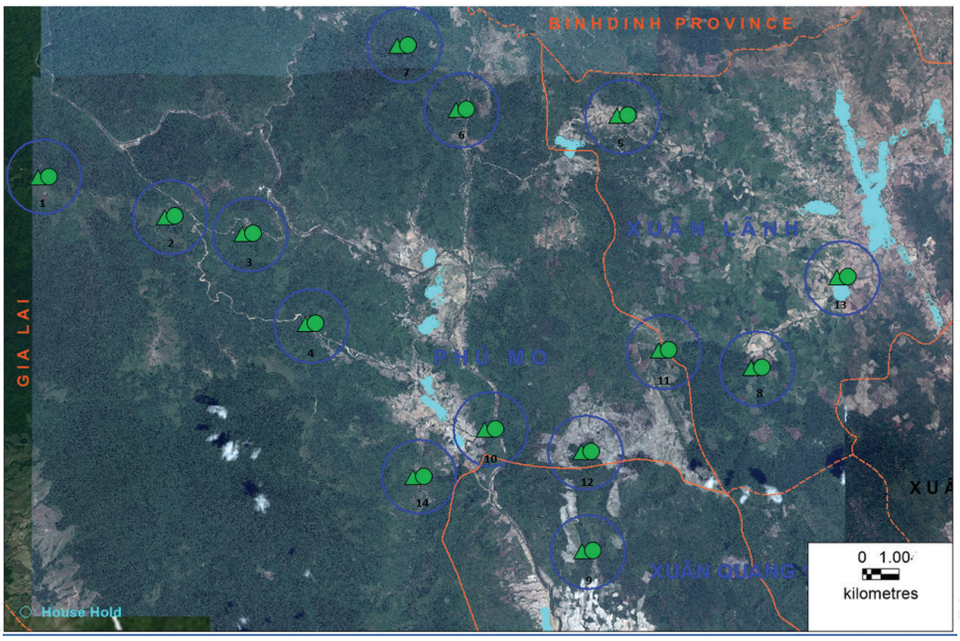
Table 5. Immediately available interventions for integrated prevention and treatment in transmission foci.

Durnez and Coosemans [78] (**Figure 11**). Additional tools are available—achieving adherence with all prevention tools is the critical challenge, which we believe can be addressed with SCI-RBF (see Section 5.1.1).

In **Table 5**, immediately available prevention and treatment measures are outlined. We believe the use of treated nets can be greatly increased in actual transmission areas with smart phone



(a)



(b)

Figure 10. "Red-to-Green, Keep-it-Green" information system (see https://ConsortiumHA.org); (a) the blue circles are transmission areas to prioritize; here classified as 2 cases within a 1 km radius, which captured 80% of cases. Within the blue circles, a small circle represents the prevention package and a triangle represents the treatment package. The top of this figure represents the actual status of Dong Xuan District, Phu Yen Province, Vietnam in 2015. The prevention package was only the use of a treated net or not, and the treatment package was only time to access effective malaria treatment. As you can see, treated net use is poor, but all but two triangles are green, illustrating that all but two transmission foci are within one hour of a health center by motorcycle. This also means they are directly accessible for interventions, both when a new case occurs and for on-going monitoring of use of malaria elimination tools. (b) the theoretical desired 100% green status. 100% will never by achieved – we believe perhaps 60-70% usage of an integrated prevention and treatment package will be enough to rapidly reduce transmission.

monitoring. The SCI-RBF will also allow iterative testing and improvement of methods until high usage is achieved, both with ITNs and an integrated vector control package. There is now direct evidence of substantial efficacy of permethrin-treated uniforms in the Cambodian

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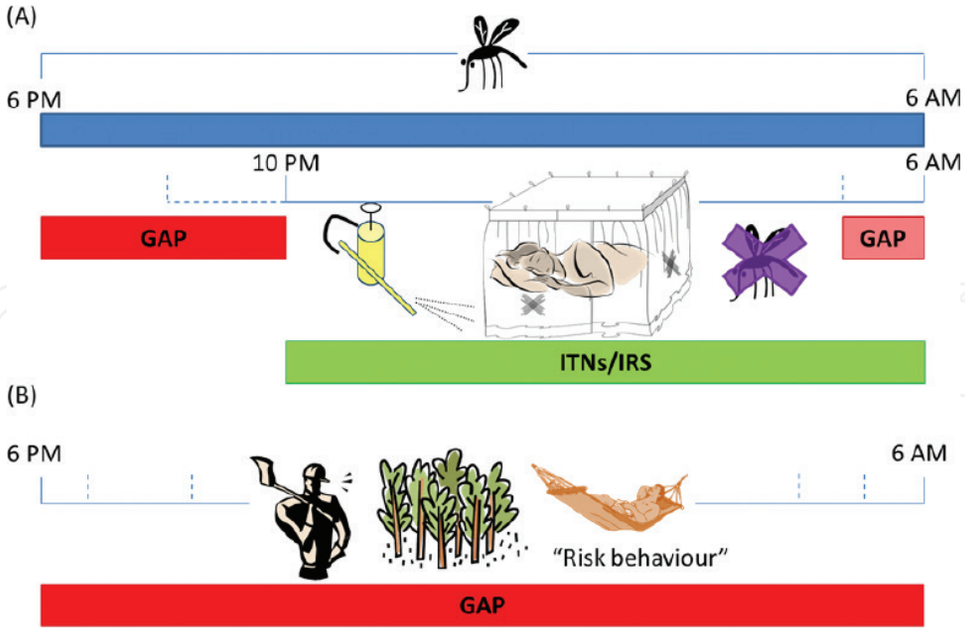

Figure 11. Protection "gap" when only indoor insecticide-based vector control measures are applied. *Anopheles* mosquitoes bite between 6 PM and 6 AM. A "gap" exists while people are not sleeping (A) and for people conducting night-time outdoor activities (B) (courtesy of Durnez and Coosemans [78]). Additional note: even the green part of the figure is also often red in the GMS because of lack of use of ITNs in risk areas (see **Figures 6** and **10**).

military, including contributing to the interruption of Pf transmission [20]. The literature-based evidence of efficacy of permethrin-treated clothing is presented in **Table 2**. Based on the available data and the growing body of evidence that those working in the forest at night in the GMS are a significant transmission reservoir, we believe treated uniforms/clothing should be scaled up as rapidly as possible. We believe retreatment of clothing, self-purchased nets and insecticide treatment around sleeping, sitting and bathing areas (IT-ASSBA) should be routine in hot-spots. Re-treatment will also allow for on-going education and monitoring. Treated netting when used with partial coverage in sleeping areas has been shown to reduce *An. dirus* (the main forest vector in the GMS) bites by 50% in Eastern Vietnam (Marchand R, unpublished data). Some efficacy has also been seen for other insecticide-treated products [79, 80].

Topical insect repellent clearly prevents mosquito bites when used correctly, especially for outdoor biting mosquitoes such as *An. dirus* that are otherwise hard to control with traditional indoor methods (ITN, IRS); however, getting people to regularly use the product in risk areas (be adherent or compliant) is the challenge, probably being the primary factor leading to a lack of efficacy in recent trials in the GMS [81]. Locally available DEET-containing repellent was well accepted and prevented *An. dirus* bites in forest transmission areas all night in a single application in Eastern Vietnam (Marchand R, unpublished data).

Prompt, complete and correct treatment is the cornerstone for malaria therapy. The effective ACT regimen should be used for both Pf and Pv blood stages. Primaquine in standard dosages should be used for Pf gametocytes and Pv hypnozoites in countries where these doses are already being used as standard of care (e.g., Vietnam) or low-dose [82] for Pf gametocytes in areas where there are safety concerns. We believe that all patients in the GMS should have visits on days 28 and 42 to detect late-treatment failure, as well as to have malaria patients and their work groups be transmission-stopping ambassadors. In addition, improved tools are just becoming available to

identify asymptomatic malaria carriers through active case detection (ACD). The BMGF funded the development of a highly sensitive rapid diagnostics test (hsRDT), which is specific for Pf [83]. It is much more sensitive than standard rapid diagnostic tests (RDT), but not as sensitive as PCR (which is probably not necessary) [84, 85]. Alere (www.alere.com, now Abbott) has made these hsRDTs commercially available for $0.95/each; approvals in GMS are in process. The same company also markets a malaria antibody-based RDT for both Pf and Pv [86]. The usefulness of these new tools can be rapidly demonstrated during scale-up; the hsRDT will hopefully obviate the need for mass drug administration [87]. Both of these new RDTs should facilitate defining risk populations.

If the package of available tools does not rapidly stop malaria transmission, other more aggressive tools can be added as they become available [85]. Currently available drugs are problematic for prophylaxis—primaquine and doxycycline require daily dosing; doxycycline has already been widely used along the Vietnam border—its current efficacy is unknown. Mefloquine is poorly tolerated and its use for prophylaxis may accelerate its demise. Tafenoquine [88, 89] and RTS,S malaria vaccine [90] should be accelerated to play a role for prevention in the region.

The last remaining parasites will be the most drug-resistant—alternative regimens are urgently needed. Tafenoquine [91] (unpublished observations for Pf), azithromycin and methylene blue [92–95] are currently under recognized, but could also play a role in combination treatment when no alternatives remain, which may be very soon. New regimens should be urgently evaluated; all should be seven days, as some or all of the drugs will have short half-lives. With seven-day regimens, adherence will be very challenging. Hospitalization with appropriate incentives should become the norm to achieve very high treatment adherence in the near future, including the current three-day regimens in areas where outpatient treatment monitoring is not successful.

6. Conclusion/call to action

Emerging incurable malaria in the GMS is a grave public health threat. We call for targeted, immediate decisive action by international and host country governments to establish mission leadership, enough authority, respect, and expertise at each operational level. Security forces must be engaged. Commitment and a real sense of urgency will be most effectively achieved with a PHEIC. We call on the major donors (BMGF, United States Agency for International Development, ADB, the US military) and other philanthropists/donors to fulfill the need for efficient funding. In this chapter, we have proposed the methodology to achieve elimination of the nearly incurable malaria parasites "East of Bangkok" near the WHO target of 2020 [24]. With the currently available tools, each partially effective, but when used together with smart phone-based quality monitoring of appropriate use in the actual transmission areas—we believe the mission can be accomplished near the target date. We call for the critical actions, focusing resources to where they will have most impact to help prevent the next pandemic.

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Acronyms

ACD	active case detection
ACT	artemisinin-based combination therapy
ADB	Asian Development Bank
BCC	behavior change communication
BMGF	Bill & Melinda Gates Foundation
CDC	US Center for Disease Control and Prevention
ConsortiumHA	Consortium for Health Action
CR	cluster randomized trial
DHAPP	Defense HIV/AIDS Prevention Program
DoD	Department of Defense
ERAR	emergency response to artemisinin resistance
GF	Global Fund
GIS	Geographic Information System
GMS	Greater Mekong Subregion
GPS	global positioning system
hsRDT	highly sensitive rapid diagnostic test
IHRs	International Health Regulations
IRS	indoor residual spraying
IT-ASSBA	insecticide treatment around sleeping, sitting and bathing areas
ITN	insecticide treated nets
LLIN	long lasting insecticidal nets
MDR	multidrug-resistant

METF	malaria elimination task force
MMPs	mobile and migrant populations
MMW	mobile malaria worker
NIMPE	National Institute of Malariology, Parasitology and Entomology
NMC(E)P	National Malaria Control (and Elimination) Program
PCR	polymerase chain reaction
PHEIC	Public Health Emergency of International Concern
Pf	*Plasmodium falciparum*
PHD	Provincial Health Department
PMI	presidential malaria initiative
PPS	pay-for-performance system
Pv	*Plasmodium vivax*
RAI	Regional Artemisinin Initiative
RBF	results-based funding
RDT	rapid diagnostic test
SCI	surveillance as a core intervention
SCI-RBF	surveillance as a core intervention linked to results-based funding
SEA	Southeast Asia
WHO	World Health Organization

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References

[1] WHO. World Health Organization World Malaria Report 2017. Geneva: World Health Organization; 2017

[2] Alonso P, Noor AM. The global fight against malaria is at crossroads. The Lancet. 2017;**390**:2532-2534. DOI: 10.1016/S0140-6736(17)33080-5

[3] Garcia R, Hewitt S, Tulloch J. Report of the Mid-Term Review of the Global Fund Regional Artemisinin Initiative (RAI). Geneva: Global Fund; 2015

[4] Ives M, McNeil D. As malaria resists treatment, experts warn of global crisis. In: The New York Times. 2017

[5] Imwong M, Hien TT, Thuy-Nhien NT, Dondorp AM, White NJ. Spread of a single multidrug resistant malaria parasite lineage (PfPailin) to Vietnam. The Lancet Infectious Diseases. 2017;**17**:1022-1023. DOI: 10.1016/S1473-3099(17)30524-8

[6] Plowe CV. The Danger of Untreatable Malaria Is Real and Present. In: CfSaI S, editor. Washington, DC: Center for Strategic and International Studies; 2014

[7] Gates B. What it takes to wipe out malaria. In: Gatesnotes. 2014

[8] Ohrt C, Ngo TD, Bui PQ, Bertrand W, Pham HQ, Nguyen ND, et al. Emerging incurable malaria in Southeast Asia–A call for targeted, decisive action in the region. American Society of Tropical Medicine and Hygiene Annual Meeting, Abstract 1561. 2016

[9] Ohrt C. Preparing for the next global threat–A call for targeted, decisive action now in Southeast Asia to prevent the next pandemic in Africa. Joint International Tropical Medicine Meeting, Bangkok, Thailand; 2016

[10] Houston S, Houston A. Screening and treating UN peacekeepers to prevent the introduction of artemisinin-resistant malaria into Africa. PLoS Medicine. 2015;**12**:e1001822. DOI: 10.1371/journal.pmed.1001822

[11] Cambodia marks 10th anniversary of peacekeeper deployment Royal Embassy of Cambodia to UK, Denmark, Finland, Ireland, Norway, Sweden, Ethiopia and African Union; 2016

[12] Sovuthy K. Peacekeeper dies from malaria in Mali. In: Cambodia Daily. 2015

[13] Van Hong N, Amambua-Ngwa A, Tuan NQ, Cuong Do D, Giang NT, Van Dung N, et al. Severe malaria not responsive to artemisinin derivatives in man returning from Angola to Vietnam. Emerging Infectious Diseases. 2014;**20**:1199-1202. DOI: 10.3201/eid2007.140155

[14] Trape JF. The public health impact of chloroquine resistance in Africa. The American Journal of Tropical Medicine and Hygiene. 2001;**64**:12-17

[15] Verdrager J. Localized permanent epidemics: The genesis of chloroquine resistance in *Plasmodium falciparum*. The Southeast Asian Journal of Tropical Medicine and Public Health. 1995;**26**:23-28

[16] malERA refresh consultative panel on insecticide and drug resistance. malERA: An updated research agenda for insecticide and drug resistance in malaria elimination and eradication. PLoS Medicine. 2017;**14**:e1002450. DOI: 10.1371/journal.pmed.1002450

[17] Greenwood BM, Fidock DA, Kyle DE, Kappe SH, Alonso PL, Collins FH, et al. Malaria: Progress, perils, and prospects for eradication. The Journal of Clinical Investigation. 2008;**118**:1266-1276. DOI: 10.1172/JCI33996

[18] Lon C, Manning JE, Vanachayangkul P, So M, Sea D, Se Y, et al. Efficacy of two versus three-day regimens of dihydroartemisinin-piperaquine for uncomplicated malaria in military personnel in northern Cambodia: An open-label randomized trial. PLoS One. 2014;**9**:e93138. DOI: 10.1371/journal.pone.0093138

[19] Sok S, Wojnarski M, Prom S, Chann S, Spring M, Gosi P, et al. Comparison of mass drug administration vs. mass screening and treatment high-risk, military mobile populations to support malaria elimination in Cambodia. American Society of Tropical Medicine and Hygiene, Annual Meeting, Abstract 1216. 2016

[20] Wojnarski M, Sok S, Prom S, et al: Review of comparative efficacy and acceptance of interventions of monthly prophylaxis vs. screening and treatment in high-risk, military mobile populations to support malaria elimination in Cambodia. Joint International Tropical Medicine Meeting 2016. Bangkok, Thailand, Poster 93. 2016

[21] Prashanth Parameswaran TD: Cambodia Marks Milestone in UN Peacekeeping Contributions. 2017

[22] Manning JE, Satharath P, Gaywee J, Lopez MN, Lon C, Saunders DL. Fighting the good fight: The role of militaries in malaria elimination in Southeast Asia. Trends in Parasitology. 2014;**30**:571-581. DOI: 10.1016/j.pt.2014.10.002

[23] Angola and Vietnam to Jointly Combat Illegal Immigration. 2016-08-30 Ed. Luanda, Angola: Angola Press Agency; 2016

[24] WHO: Strategy for Malaria Elimination in the Greater Mekong Subregion (2015-2030). 2015

[25] WHO Ebola Response Team. After Ebola in West Africa–Unpredictable risks, preventable epidemics. The New England Journal of Medicine. 2016;**375**:587-596. DOI: 10.1056/NEJMsr1513109

[26] WHO: International Health Regulations and Emergency Committees. 2016

[27] WHO. International Health Regulations (2005). 3rd ed. Geneva; 2016

[28] WHO. Implementation of the International Health Regulations. 2005 Report of the Review Committee on Second Extensions for Establishing National Public Health Capacities and on IHR Implementation. 2015

[29] WHO. Antimalarial Drug Resistance in the Greater Mekong Subregion: How Concerned should we Be? Q&A with Dr Pedro Alonso, Director of the Global Malaria Programme. 2017

[30] Department of Defense Directive 6485. 02E: DoD Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) Prevention Program (DHAPP) to Support Foreign Militaries. US Department of Defense; 2013

[31] Department of Defense Names WRAIR Scientist "Lab Scientist of the Quarter". 2018

[32] President's Malaria Initiative, Thailand, Lao PDR and Regional Malaria Operational Plan FY2018. 2017

[33] Roberts L. Drug resistance triggers war to wipe out malaria in the Mekong region. Science American Association for the Advancement of Science; 2016

[34] Boudreau EF, Fleckenstein L, Pang LW, Childs GE, Schroeder AC, Ratnaratorn B, et al. Mefloquine kinetics in cured and recrudescent patients with acute falciparum malaria and in healthy volunteers. Clinical Pharmacology and Therapeutics. 1990;**48**:399-409

[35] Maxmen A. Back on TRAC: New trial launched in bid to outpace multidrug-resistant malaria. Nature Medicine. 2016;**22**:220-221. DOI: 10.1038/nm0316-220

[36] Rossi G, De Smet M, Khim N, Kindermans JM, Menard D. Emergence of *Plasmodium falciparum* triple mutant in Cambodia. The Lancet Infectious Diseases. 2017;**17**:1233. DOI: 10.1016/S1473-3099(17)30635-7

[37] Phyo AP, von Seidlein L. Challenges to replace ACT as first-line drug. Malaria Journal. 2017;**16**:296. DOI: 10.1186/s12936-017-1942-5

[38] Remembering Alan Magill. The American Journal of Tropical Medicine and Hygiene. 2015;**93**:893. DOI: 10.4269/ajtmh.935mem

[39] Kirby T. Obituary—Alan Magill. The Lancet Infectious Diseases. 2015;**15**:1266. DOI: 10.1016/S1473-3099(15)00365-5

[40] Magill A. Accelerate to zero: Strategies to eliminate malaria. In: MMV Stakeholders Meeting, Medicines for Malaria Venture; 2015

[41] Gates B. The next epidemic–Lessons from Ebola. The New England Journal of Medicine. 2015;**372**:1381-1384. DOI: 10.1056/NEJMp1502918

[42] US PACOM Regional Forum on Drug Resistant Malaria among Military Populations. PACOM Regional Military Meeting Forum. 2014

[43] Ohrt C, Roberts KW, Sturrock HJ, Wegbreit J, Lee BY, Gosling RD. Information systems to support surveillance for malaria elimination. The American Journal of Tropical Medicine and Hygiene. 2015;**93**:145-152. DOI: 10.4269/ajtmh.14-0257

[44] Ngo T, Tran D, Martin N, Nguyen P, Pham H, Dang D, et al. An innovative information system to eliminate emerging incurable malaria. American Society of Tropical Medicine and Hygiene, Annual Meeting, Abstract 1565; 2016

[45] Grietens KP, Xuan XN, Ribera J, Duc TN, Bortel W, Ba NT, et al. Social determinants of long lasting insecticidal hammock use among the Ra-glai ethnic minority in Vietnam: Implications for forest malaria control. PLoS One. 2012;**7**:e29991. DOI: 10.1371/journal.pone.0029991

[46] Aung T, Wei C, McFarland W, Aung YK, Khin HS. Ownership and use of insecticide-treated nets among people living in malaria endemic areas of eastern Myanmar. PLoS One. 2016;**11**:e0162292. DOI: 10.1371/journal.pone.0162292

[47] Menard D, Dondorp A. Antimalarial drug resistance: A threat to malaria elimination. Cold Spring Harbor Perspectives in Medicine. 2017;**7**:1-24. DOI: 10.1101/cshperspect.a025619.

http://publicationslist.org/data/didier.menard/ref-216/Menard%20and%20Dondorp,%20Cold%20Spring%20Harb%20Perspect%20Med_2017.pdf

[48] Manguin S, Carnevale P, Mouchet J, Coosemans M, Julvez J, Richard-Lenoble D, et al. Biodiversity of Malaria in the World. Montrouge, France: John Libbey Eurotext; 2008

[49] Achan J, Talisuna AO, Erhart A, Yeka A, Tibenderana JK, Baliraine FN, et al. Quinine, an old anti-malarial drug in a modern world: Role in the treatment of malaria. Malaria Journal. 2011;**10**:144. DOI: 10.1186/1475-2875-10-144

[50] Leang R, Canavati SE, Khim N, Vestergaard LS, Borghini Fuhrer I, Kim S, et al. Efficacy and safety of pyronaridine-artesunate for the treatment of uncomplicated *Plasmodium falciparum* malaria in western Cambodia. Antimicrobial Agents and Chemotherapy. 2016; **60**:3884-3890. DOI: 10.1128/AAC.00039-16. http://aac.asm.org/content/60/7/3884 . short

[51] Denis MB, Tsuyuoka R, Lim P, Lindegardh N, Yi P, Top SN, et al. Efficacy of artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in Northwest Cambodia. Tropical Medicine & International Health. 2006;**11**:1800-1807. DOI: 10.1111/j.1365-3156.2006.01739.x

[52] Song J, Socheat D, Tan B, Seila S, Xu Y, Ou F, et al. Randomized trials of artemisinin-piperaquine, dihydroartemisinin-piperaquine phosphate and artemether-lumefantrine for the treatment of multi-drug resistant falciparum malaria in Cambodia-Thailand border area. Malaria Journal. 2011;**10**:231. DOI: 10.1186/1475-2875-10-231

[53] Thanh NV, Thuy-Nhien N, Tuyen NT, Tong NT, Nha-Ca NT, Dong LT, et al. Rapid decline in the susceptibility of *Plasmodium falciparum* to dihydroartemisinin-piperaquine in the south of Vietnam. Malaria Journal. 2017;**16**:27. DOI: 10.1186/s12936-017-1680-8

[54] US CDC. Impact of malaria. In: Malaria GHDoPDa, editor. US Centers for Disease Control; 2017

[55] Lover AA, Gosling R, Feachem R, Tulloch J. Eliminate now: Seven critical actions required to accelerate elimination of *Plasmodium falciparum* malaria in the greater Mekong subregion. Malaria Journal. 2016;**15**:518. DOI: 10.1186/s12936-016-1564-3

[56] Heymann DL, Hodgson A, Sall AA, Freedman DO, Staples JE, Althabe F, et al. Zika virus and microcephaly: Why is this situation a PHEIC? Lancet. 2016;**387**:719-721. DOI: 10.1016/S0140-6736(16)00320-2

[57] Siedner MJ, Gostin LO, Cranmer HH, Kraemer JD. Strengthening the detection of and early response to public health emergencies: Lessons from the west African Ebola epidemic. PLoS Medicine. 2015;**12**:e1001804. DOI: 10.1371/journal.pmed.1001804

[58] Troop and police contributors. United Nations Peacekeeping. 2017

[59] WHO. All systems "go" for ERAR hub in Phnom Penh, Cambodia. World Health Organization (WHO); 2014

[60] WHO. Countries of the Greater Mekong Making Inroads in the Race Towards Elimination. World Health Organization (WHO); 2017

[61] Brencic DJ, Pinto M, Gill A, Kinzer MH, Hernandez L, Pasi OG. CDC support for global public health emergency management. Emerging Infectious Diseases. 2017;**23**. DOI: 10.3201/eid2313.170542

[62] Cambodia Malaria Elimination Action Framework (2016-2020). MESA; 2016

[63] The Global Fund. Guidelines for Grant Budgeting; 2017

[64] Vietnam National Malaria Control Program Annual Reports. Hanoi, Vietnam: National Institute of Malariology, Parasitology and Entomology; 2000-2016

[65] National Strategy for Malaria Control and Elimination in the Period 2011-2020 and Orientation to 2030. Issued with Decision No. 1920/QĐ-TTg. Government Socialist Republic of Vietnam; 2011

[66] Son DH, Thuy-Nhien N, von Seidlein L, Le Phuc-Nhi L, Phu NT, NTK T, et al. The prevalence, incidence and prevention of *Plasmodium falciparum* infections in forest rangers in Bu Gia map National Park, Binh Phuoc province, Vietnam: A pilot study. Malaria Journal. 2017;**16**:444. DOI: 10.1186/s12936-017-2091-6

[67] Edwards HM, Canavati SE, Rang C, Ly P, Sovannaroth S, Canier L, et al. Novel cross-border approaches to optimise identification of asymptomatic and artemisinin-resistant *Plasmodium* infection in mobile populations crossing Cambodian borders. PLoS One. 2015;**10**:e0124300. DOI: 10.1371/journal.pone.0124300

[68] Manning J, Vanachayangkul P, Lon C, Spring M, So M, Sea D, et al. Randomized, double-blind, placebo-controlled clinical trial of a two-day regimen of dihydroartemisinin-piperaquine for malaria prevention halted for concern over prolonged corrected QT interval. Antimicrobial Agents and Chemotherapy. 2014;**58**:6056-6067. DOI: 10.1128/AAC.02667-14

[69] Banks SD, Murray N, Wilder-Smith A, Logan JG. Insecticide-treated clothes for the control of vector-borne diseases: A review on effectiveness and safety. Medical and Veterinary Entomology. 2014;**28**(Suppl 1):14-25. DOI: 10.1111/mve.12068

[70] Soto J, Medina F, Dember N, Berman J. Efficacy of permethrin-impregnated uniforms in the prevention of malaria and leishmaniasis in Colombian soldiers. Clinical Infectious Diseases. 1995;**21**:599-602

[71] Rowland M, Durrani N, Hewitt S, Mohammed N, Bouma M, Carneiro I, et al. Permethrin-treated chaddars and top-sheets: Appropriate technology for protection against malaria in Afghanistan and other complex emergencies. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1999;**93**:465-472

[72] Kimani EW, Vulule JM, Kuria IW, Mugisha F. Use of insecticide-treated clothes for personal protection against malaria: A community trial. Malaria Journal. 2006;**5**:63. DOI: 10.1186/1475-2875-5-63

[73] Eamsila C, Frances SP, Strickman D. Evaluation of permethrin-treated military uniforms for personal protection against malaria in northeastern Thailand. Journal of the American Mosquito Control Association. 1994;**10**:515-521

[74] Most B, Pommier de Santi V, Pages F, Mura M, Uedelhoven WM, Faulde MK. Long-lasting permethrin-impregnated clothing: Protective efficacy against malaria in hyperendemic foci, and laundering, wearing, and weathering effects on residual bioactivity after worst-case use in the rain forests of French Guiana. Parasitology Research. 2017;**116**:677-684. DOI: 10.1007/s00436-016-5333-6

[75] Huỳnh QH: The Military Combined Medical Contributed Much to the Success of the Health Sector. 2016

[76] Martin N, Ngo T, Tran D, Dang D, Pham H, Bui T, et al.: U.S navy-NIMPE collaborations and operations research support of the malaria elimination program in Vietnam. American Society of Tropical Medicine and Hygiene Annual Meeting, Abstract 1564 [Internet]; 2016. Available from: https://consortiumhaorg/wp-content/uploads/2016/12/2016_10_31_NMAr_V03_ASTMH-Posterpdf [Accessed: 2017-12-28]

[77] Lengeler C. Insecticide-treated bednets and curtains for preventing malaria. Cochrane Database of Systematic Reviews. 2000:Cd000363. DOI: 10.1002/14651858.cd000363

[78] Durnez L, Coosemans M. Residual transmission of malaria: An old issue for new approaches. In: Manguin S, editor. *Anopheles* Mosquitoes–New Insights into Malaria Vectors. Rijeka, Croatia: InTech; 2013. pp. 672-704

[79] Mittal PK, Sreehari U, Razdan RK, Dash AP. Evaluation of the impact of ZeroFly(R), an insecticide incorporated plastic sheeting on malaria incidence in two temporary labour shelters in India. Journal of Vector Borne Diseases. 2011;**48**:138-143

[80] Burns M, Rowland M, N'Guessan R, Carneiro I, Beeche A, Ruiz SS, et al. Insecticide-treated plastic sheeting for emergency malaria prevention and shelter among displaced populations: An observational cohort study in a refugee setting in Sierra Leone. The American Journal of Tropical Medicine and Hygiene. 2012;**87**:242-250. DOI: 10.4269/ajtmh.2012.11-0744

[81] Sluydts V, Durnez L, Heng S, Gryseels C, Canier L, Kim S, et al. Efficacy of topical mosquito repellent (picaridin) plus long-lasting insecticidal nets versus long-lasting insecticidal nets alone for control of malaria: A cluster randomised controlled trial. The Lancet Infectious Diseases. 2016;**16**:1169-1177. DOI: 10.1016/S1473-3099(16)30148-7

[82] Leang R, Khu NH, Mukaka M, Debackere M, Tripura R, Kheang ST, et al. An optimised age-based dosing regimen for single low-dose primaquine for blocking malaria transmission in Cambodia. BMC Medicine. 2016;**14**:171. DOI: 10.1186/s12916-016-0701-8

[83] Das S, Jang IK, Barney B, Peck R, Rek JC, Arinaitwe E, et al. Performance of a high-sensitivity rapid diagnostic test for *Plasmodium falciparum* malaria in asymptomatic individuals from Uganda and Myanmar and naive human challenge infections. The American Journal of Tropical Medicine and Hygiene. 2017;**97**:1540-1550. DOI: 10.4269/ajtmh.17-0245

[84] Tripura R, Peto TJ, Chalk J, Lee SJ, Sirithiranont P, Nguon C, et al. Persistent *Plasmodium falciparum* and *Plasmodium vivax* infections in a western Cambodian population: Implications for prevention, treatment and elimination strategies. Malaria Journal. 2016;**15**:181. DOI: 10.1186/s12936-016-1224-7

[85] Lin JT, Ubalee R, Lon C, Balasubramanian S, Kuntawunginn W, Rahman R, et al. Microscopic *Plasmodium falciparum* Gametocytemia and infectivity to mosquitoes in Cambodia. The Journal of Infectious Diseases. 2016;**213**:1491-1494. DOI: 10.1093/infdis/jiv599

[86] Cho SJ, Lee J, Lee HJ, Jo HY, Sinniah M, Kim HY, et al. A novel malaria Pf/Pv Ab rapid diagnostic test using a differential diagnostic marker identified by network biology. International Journal of Biological Sciences. 2016;**12**:824-835. DOI: 10.7150/ijbs.14408

[87] Dondorp AM, Smithuis FM, Woodrow C, Seidlein LV. How to contain artemisinin- and multidrug-resistant falciparum malaria. Trends in Parasitology. 2017;**33**:353-363. DOI: 10.1016/j.pt.2017.01.004

[88] Walsh DS, Eamsila C, Sasiprapha T, Sangkharomya S, Khaewsathien P, Supakalin P, et al. Efficacy of monthly tafenoquine for prophylaxis of *Plasmodium vivax* and multi-drug-resistant *P. falciparum* malaria. The Journal of Infectious Diseases. 2004;**190**:1456-1463. DOI: 10.1086/424468

[89] Edstein MD, Walsh DS, Eamsila C, Sasiprapha T, Nasveld PE, Kitchener S, et al. Malaria prophylaxis/radical cure: Recent experiences of the Australian Defence force. Médecine Tropicale (Mars). 2001;**61**:56-58

[90] Gosling R, von Seidlein L. The future of the RTS,S/AS01 malaria vaccine: An alternative development plan. PLoS Medicine. 2016;**13**:e1001994. DOI: 10.1371/journal.pmed.1001994

[91] Fukuda MM, Krudsood S, Mohamed K, Green JA, Warrasak S, Noedl H, et al. A randomized, double-blind, active-control trial to evaluate the efficacy and safety of a three day course of tafenoquine monotherapy for the treatment of *Plasmodium vivax* malaria. PLoS One. 2017;**12**:e0187376. DOI: 10.1371/journal.pone.0187376

[92] Noedl H, Krudsood S, Chalermratana K, Silachamroon U, Leowattana W, Tangpukdee N, et al. Azithromycin combination therapy with artesunate or quinine for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults: A randomized, phase 2 clinical trial in Thailand. Clinical Infectious Diseases. 2006;**43**:1264-1271. DOI: 10.1086/508175

[93] Miller RS, Wongsrichanalai C, Buathong N, McDaniel P, Walsh DS, Knirsch C, et al. Effective treatment of uncomplicated *Plasmodium falciparum* malaria with azithromycin-quinine combinations: A randomized, dose-ranging study. The American Journal of Tropical Medicine and Hygiene. 2006;**74**:401-406

[94] Bhagavathula AS, Elnour AA, Shehab A. Alternatives to currently used antimalarial drugs: In search of a magic bullet. Infectious Diseases of Poverty. 2016;**5**:103. DOI: 10.1186/s40249-016-0196-8

[95] Ohrt C, Li Q, Obaldia N, Im-Erbsin R, Xie L, Berman J. Efficacy of intravenous methylene blue, intravenous artesunate, and their combination in preclinical models of malaria. Malaria Journal. 2014;**13**:415. DOI: 10.1186/1475-2875-13-415

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