Trends in Parasitology

CellPress REVIEWS

Opinion

Novel Approaches to Control Malaria in Forested Areas of Southeast Asia

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The emergence and spread of drug resistance in the Greater Mekong Subregion (GMS) have added urgency to accelerate malaria elimination while reducing the treatment options. The remaining foci of malaria transmission are often in forests, where vectors tend to bite during daytime and outdoors, thus reducing the effectiveness of insecticide-treated bed nets. Limited periods of exposure suggest that chemoprophylaxis could be a promising strategy to protect forest workers against malaria. Here we discuss three major questions in optimizing malaria chemoprophylaxis for forest workers: which antimalarial drug regimens are most appropriate, how frequently the chemoprophylaxis should be delivered, and how to motivate forest workers to use, and adhere to, malaria prophylaxis.

Highlights

Much progress has been made in the control of falciparum malaria in the GMS, but transmission persists in forested areas.

The programmatic use of chemoprevention for malaria control has been controversial in the past but is increasingly accepted. For example, seasonal malaria chemoprevention is successfully rolled out to prevent malaria in children living in the Sahel.

Forest workers are another population exposed to malaria transmission for limited periods who could benefit from antimalarial prophylaxis.

Research is ongoing to explore and optimize antimalarial regimens to protect forest workers against malaria.

Spreading Multidrug Resistance Adds Urgency to Elimination

Between 2000 and 2017 the malaria burden in the **Greater Mekong Subregion** (**GMS**; see Glossary) has decreased in a heterogeneous fashion (Figure 1). China succeeded in interrupting endogenous malaria transmission by 2017 [1]. Close monitoring, rapid case investigation, reporting, and response played critical roles in this success [2]. In Myanmar, the country with the highest malaria burden, the number of reported malaria cases dropped below 100 000 only in 2017. Two studies published in 2018 demonstrated that the provision of early diagnosis and appropriate treatment of malaria through malaria posts or community health workers can achieve a rapid reduction in malaria incidence in Myanmar [3,4]. In the four other countries in the GMS – Vietnam, Cambodia, Lao PDR, and Thailand – access to early diagnosis and appropriate treatment with **artemisinin combination therapy** (**ACT**) and access to bed nets have contributed to substantial reductions in malaria incidence. Yet by 2018 the decline in malaria incidence has stalled, and in some locations reversed. This has coincided with, and may have been partly caused by, the emergence and spread of *Plasmodium falciparum* multidrug resistance[i]. Decision makers in the GMS have pledged to eliminate malaria by 2030. This will be possible only if all foci sustaining malaria transmission are attacked, including forest-acquired infections.

Concentration of Malaria Transmission in Forested Areas of the GMS

The importance of forests in malaria transmission in Indochina was well established in the 20th century [5]. With better malaria control in residential areas the relative importance of the still poorly controlled transmission of malaria in forested areas has increased. By 2019 malaria transmission is concentrated in the forested areas of Cambodia, Myanmar, Laos, and Vietnam. As shown in multiple studies, the population at highest risk for malaria in the GMS are adults who work in forested areas [6–9]. The malaria risk is lower in children than in adults, but children are exposed when they accompany their parents during forest work or when infected household members returning from forest work transmit malaria in and around their home. Erhart and

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coworkers reported in 2005 that 79% (3412/4306) of their randomly selected study population in central Vietnam were **forest workers**, and even occasional forest work was a significant risk-factor for malaria [10]. Women and children participate in farming activities around forest fringes while logging is predominantly a male domain [11]. Forests remain an important source of residual malaria transmission in the GMS.

How Long Do Forest Visitors Stay in Forested Areas?

During the enrolment in an ongoing malaria trial in Siem Pang, Stung Treng, Cambodia, 58 of 75 confirmed malaria patients reported their occupation as forest-related work, and 29/58 (50%) respondents spent 2 weeks or less in the forest. A recent study from Oddar Meanchey, Cambodia, found high variability in duration ranging from repeated short stays to more extended stays of up to 2 weeks in forested areas [12].

Why Do Forest Visitors Go to the Forest?

The same 58 study respondents were asked about their activities in the forest; 40 (69%) were engaged in some form of logging activities, 15 (26%) were harvesting (collecting fruit, mushrooms, etc.), and the rest were hunting or fishing. There are a range of reasons why people work in the forest, and the character and purpose of forest visits change with season and location. Yet logging is the single most lucrative work in forested areas throughout the GMS. A team of six men can fell a substantial tree, cut it into planks, and transport the planks out of the forest in 3–6 days. The planks are sold to a middle man in the village, and profit is divided among the team members. Timber exports are a major source of income in the forested areas of the GMS, with far-reaching environmental consequences[ii]. Between 1990 and 2015 the forest cover in Myanmar has been reduced by 26%, and in Cambodia by 27% [13]. From 2011 to 2014, Myanmar reported US$2.83 billion in hardwood exports, whereas trading partners reported imports of US$5.57 billion [14]. Illegal logging is likely to account for the US$2.74 billion discrepancy. After the Lao government's 2016–2017 moratorium on the export of logs and timber a noticeable drop in malaria cases was reported[iii]. The 2018 murders of three Cambodian activists who were patrolling a forest in Mondulkiri were linked to retaliation for seizing equipment from illegal loggers [15]. The illegal character of many aspects of forest work is a major reason why so little information about it is available. Where researchers have been able to accompany forest workers there remains a suspicion that the presence of observers modifies the character of their activities.

Where Do People Stay in the Forest?

The anecdotal information available suggests that the accommodation used by forest workers is highly variable, ranging from the makeshift lean-to shelters to housing not different to what is seen in villages. A high proportion of forest workers sleep in improvised ground-level shelters, often in hammocks, where they have greater exposure to malaria vectors than those in raised habitations [16]. This contrasts with the permanent, better constructed housing used by plantation personnel. Forest work is demanding, and the people who work in forests are often socioeconomically disadvantaged, frequently migrants with limited alternative sources of income [6,9,10,17,18].

Vector Ecology

There are several reasons why forests are a favourable ecosystem for mosquitoes and predispose to malaria transmission: tree canopy assures shade even during the hottest hours, humidity protects mosquitoes from estivation and death, there are protected breeding pools rich in nutrients, and importantly, there is an absence of infrastructure and human vector-control measures [19]. The remoteness prevents malaria patients in forests from accessing

Glossary

Artemisinin combination therapy (ACT): is the combination of an artemisinin derivative with a partner drug. The artemisinin component reduces the number of susceptible parasites during the first 3 days of treatment (reduction of parasite biomass), while the role of the partner drug is to eliminate the remaining parasites, including artemisinin-tolerant parasites. ACTs fail when both partner drugs no longer clear the parasites. The spread of parasites resistant to artemisinin derivatives and partner drugs currently ongoing in the GMS has the potential to evolve into an international public health emergency.

Causal prophylaxis: a term chemoprophylaxis which clears the liver stages of *Plasmodium* and thus removes the need for terminal prophylaxis.

Chemoprevention: interchangeably used with chemoprophylaxis, prevention, or prophylaxis.

DEET: diethyltoluamide, the most common active ingredient in insect repellents.

Exophagic: refers to outdoor-feeding mosquitoes.

Exophilic: refers to outdoor-living mosquitoes.

Forest workers: or forest goers or forest visitors are people who supplement their income by working in forested areas.

G6PD: glucose-6-phosphate dehydrogenase, a cytosolic enzyme in the pentose phosphate pathway critical for the metabolism of red blood cells. People deficient in G6PD enzyme activity are at increased risk for haemolysis when exposed to a range of factors, including 8-aminoquinolines.

GMS: the Greater Mekong Subregion comprises Cambodia, Lao PDR, Myanmar, Thailand, Vietnam, and the People's Republic of China (Yunnan Province and Guangxi Zhuang Autonomous Region). It is home to more than 300 million people.

Hypnozoite: a stage in the life cycle of *Plasmodium vivax*. Clearing hypnozoites requires 8-aminoquinoline, for example primaquine, a class of drugs which

health care quickly, which prolongs disease and augments transmission. The malaria vectors associated with forests in the GMS are incredibly diverse, including *Anopheles dirus* complex, *An. minimus* complex, *An. maculatus* complex, *An. kochi, An. jeyporiensis, An. barbirostris* [20]. A critical feature of these mosquitoes is their predominantly **exophilic** and **exophagic** lifestyle [21]. Vector-control strategies based on insecticide-treated bed nets and indoor residual spraying thus provide limited protection against *Plasmodium* infections in forests. As there is no transovarian transmission of *Plasmodium*, and vectors stay within a few kilometres of their breeding sites, the maintenance of malaria transmission depends on the ongoing presence of hosts within the limited range of these mosquitoes. This suggests that forest workers share the same work spaces or congregate around fixed 'campsites'. Forest work is not a solitary occupation – most workers enter forests in groups [12].

Current Malaria Prevention Methods Used by Forest Workers

Forest workers use a range of malaria prevention strategies [22]. Wearing long-sleeved shirts, trousers and socks can reduce mosquito bites but can be unbearably hot in tropical forests [23–25]. Forest workers rely on mosquitoes avoiding smoke by starting fires around their work and campsites [26–28]. Smouldering **mosquito coils** releasing spatial repellents such as **pyrethrins** can kill or at least knock down mosquitoes and are worn by forest workers in a portable coil holder or attached to head- or waist-bands [22]. There is no evidence that clothing, smoke, or mosquito coils protect against malaria but there is evidence that smoke inhalation has detrimental effects on health [29]. Also, smoke may attract unwanted attention from rangers [12]. Mosquito repellents such as **DEET** or **picaridin** are a popular protection against mosquito bites amongst tourists and travellers. Forest workers are reluctant to use such repellents because their frequent use is unaffordable and thought to be harmful to the skin [23,24]. A large cluster randomized study in Ratanakiri, Cambodia, showed that adding a picaridin-based repellent did not add benefit to treated bed nets [30]. Insecticide-treated bed nets provide only limited protection for forest workers first and foremost due to the feeding behaviour of the relevant vectors. Second, poor families may not have a bed net to spare to be taken into the forest without leaving the family at home unprotected [17,18]. Third, despite being lightweight, carrying a bed net and setting it up every night represents a burden which not all forest workers are willing to accept [23]. Because many forest workers sleep in hammocks it has been suggested that insecticide-treated nets be added to robust hammocks to make them impenetrable to mosquitoes [31,32]. However, hammock nets have limited popularity because they limit airflow, are perceived as uncomfortable in humid climates, and are cumbersome [32]. In Cambodia, pilot projects have distributed 'forest packages' containing an impregnated net and a large canister of insect repellent spray containing at least 25% DEET with instructions; however, the impact of this intervention has yet to be evaluated. Stand-by treatment, self-medication based on rapid diagnostic tests, benefits the individual with acute malaria but has no effect on asymptomatic infections and may have little impact on malaria transmission in areas with an extensive asymptomatic *Plasmodium* reservoir [33]. An alternative strategy is the screening of forest workers with highly sensitive rapid diagnostic tests [34] and treatment when found infected [11]. While well accepted, a limitation of this strategy could be the sensitivity of the diagnostic test and large-scale implementation.

Chemoprophylaxis for Forest Workers

Antimalarial prophylaxis is accepted for tourists[iv] and military personnel[v] but prophylaxis in indigenous populations in malaria-endemic regions has faced opposition [35–37]. One reservation is the increase in drug-pressure from imperfect use, another that prophylaxis could suppress antimalarial immunity among people living in endemic regions. Intermittent preventive therapies (IPTs) in which there are inter-dose periods without suppression can be considered

can trigger haemolysis in G6PD-deficient individuals.

IPTp: intermittent preventive treatment in pregnancy; women should receive at least three doses of sulfadoxine/pyrimethamine (SP) 1 month apart during pregnancy.

Mosquito coil: a mosquito-repelling incense, made of the dried paste of pyrethrum powder shaped into a spiral.

Picaridin: a mixture of the four stereoisomers of icaridin which are used as an insect repellent.

Pyrethrins: spatial mosquito repellents released from smouldering mosquito coils.

Simian malarias: a group of malarias which predominantly infect monkeys. *Plasmodium knowlesi* and *Plasmodium cynomolgi* are examples of species which have been shown to infect humans in the GMS.

SMC: seasonal malaria chemoprevention consists of the administration of a minimum of three rounds of a full course of sulfadoxine–pyrimethamine + amodiaquine in areas with highly seasonal malaria transmission in the Sahel subregion of sub-Saharan Africa. The primary target group are children under 5 years, but older children and more rounds of antimalarials are increasingly included in SMC.

Suppressive prophylaxis: refers to chemoprophylaxis with antimalarial drugs which do not clear the liver stages of *P. falciparum*, thus necessitating a need for terminal prophylaxis.

Terminal half-life ($t_{1/2}$): the terminal plasma half-life of a drug is the time required to divide the plasma concentration by two after reaching pseudoequilibrium.

Terminal prophylaxis: following suppressive chemoprophylaxis there remains a need to continue prophylaxis for at least 2 weeks after the last forest visit.

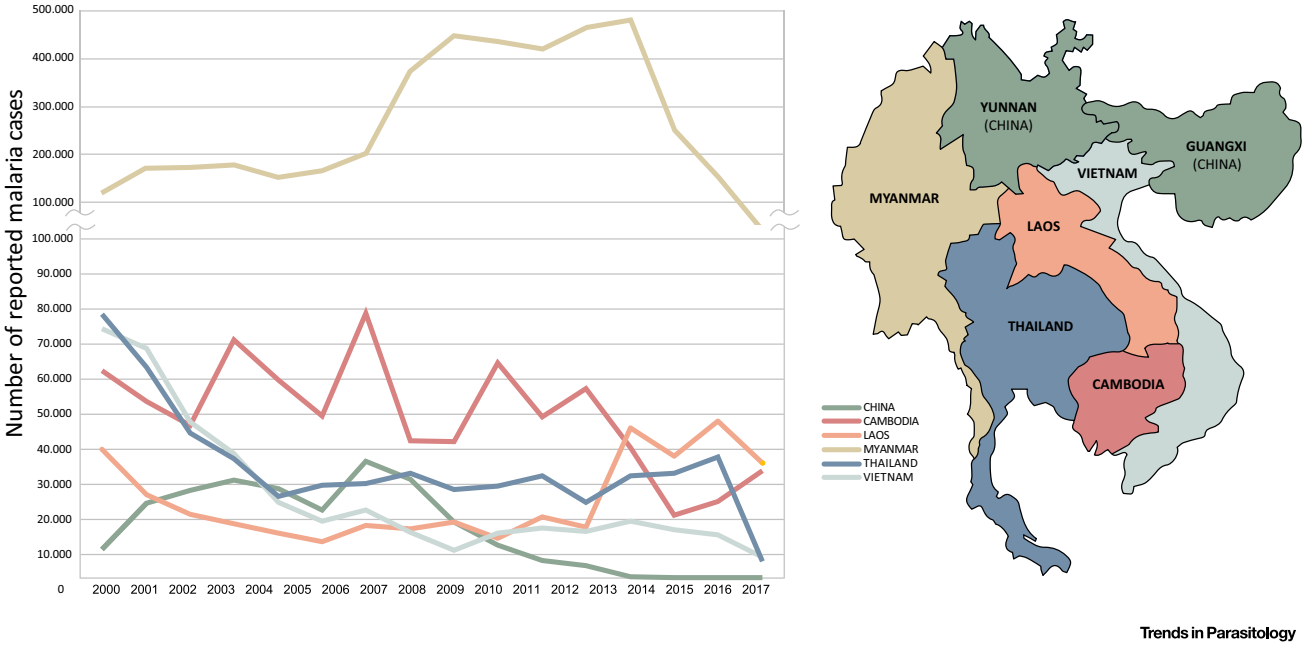

Figure 1. The Greater Mekong Subregion and Its Malaria Burden. The number of reported malaria cases, all species in the Greater Mekong Subregion (GMS) 2000–2017 [65][ix], and a map of the countries included in the regions.

an imperfect form of chemoprophylaxis. Using sulfadoxine–pyrimethamine (S/P) (**IPTp**) to prevent malaria in pregnancy is now generally accepted but is losing efficacy due to the spread and intensification of S/P resistance in Africa [38]. **Seasonal malaria chemoprevention** (**SMC**) in which there should be no inter-dose periods without suppression has been introduced successfully in 12 countries in the Sahel, a region marked by short but intense malaria transmission seasons [39]. In sub-Saharan Africa – in contrast to the GMS – children are at highest risk for malaria; consequently, SMC targets children aged 3–59 months [40]. Like children in the Sahel, forest workers in the GMS are exposed to malaria for limited periods, making chemoprophylaxis an approach worth consideration.

One of the major challenges to implementation of such a strategy is the choice of an appropriate antimalarial drug regimen (Table 1). To assure high uptake, the drugs must be available, affordable, and well tolerated as they are taken by healthy people. The majority of antimalarials are probably not appropriate for chemoprophylaxis of forest workers in the GMS, as discussed in Box 1. Very few drug regimens currently hold promise for chemoprophylaxis in the GMS (Figure 2, Key Figure). Causal regimens with the 8-aminoquinolines primaquine and tafenoquine could be particularly appropriate for forest workers as the drug administration can be stopped on the last day of the forest visit and there is no need for **terminal prophylaxis** as explained in Box 2. The sporadic character of forest work makes it necessary to tailor chemoprophylaxis around the period of exposure. Causal chemoprophylaxis may be more suitable for chemoprophylaxis in forest workers than suppressive chemoprophylaxis because there is no need for continued administration after leaving forested areas. The major challenge for use of primaquine and tafenoquine in chemoprophylaxis is the risk of haemolysis in **G6PD**-deficient individuals. This risk can be mitigated by careful testing. More robust qualitative and

Table 1. Advantages and Disadvantages of Potential Candidate Drugs for Forest Worker *Plasmodium falciparum* Prophylaxis[a]

	$t_{1/2}$	Pros	Cons
Primaquine	3.5–8 hours	Causal prophylaxis. No need for terminal prophylaxis. Radical cure of *Plasmodium vivax* infections.	Can trigger haemolysis in G6PD-deficient individuals.
Tafenoquine	14–28 days		
Atovaquone–proguanil	A: 29–134 h P: 8.0–17.6 h	Not used as a first- line antimalarial. Causal prophylaxis.	Rapid emergence of resistant *Plasmodium falciparum* strains. High cost.
Chloroquine	CQ: 108–291 h	Safe, extensive experience, low cost.	Very few areas remain globally where *P. falciparum* remains susceptible to chloroquine. High chloroquine resistance in the GMS.
Doxycycline	9.8 h	Universal prophylaxis.	Has to be given daily; sunlight hypersensitivity.
S/P	S: 4.1–8.9 days P: 2.8–3.4 days	Single dose.	High resistance in the GMS.
S/P–amodiaquine	S: 4.1–8.9 days P: 2.8–3.4 days A[b]: 4.3–9.0 days	Safe and well tolerated in Africa.	
DHA–piperaquine	D: 0.64–2.5 h P: 12–28 days	Safe, well tolerated and, due to the extended $t_{1/2}$ of piperaquine, confers extended protection.	Until recently the first-line treatment in many places in the GMS. Recent reports of multidrug resistance have resulted in a reluctance to use DHA piperaquine for prophylaxis in GMS countries east of Bangkok.
Artesunate–mefloquine	A: 0.64–2.5 hours M: 8.5–19.3 days	Mefloquine has a relatively long $t_{1/2}$.	Mefloquine resistance in the GMS and poor tolerability.
Artesunate– amodiaquine	A: 0.64–2.5 h A[b]: 4.3–9.0 days	Safe and available.	Amodiaquine has a relatively short $t_{1/2}$. Amodiaquine resistance in the GMS.
Pyronaridine–artesunate	P: 12–14 days [61] A: 0.64–2.5 hours	New drug, still efficacious. Relatively short $t_{1/2}$.	New drug with uncertainty regarding safety and tolerability.
Artemether– lumefantrine	A: 0.5–2.13 h L: 32.7–275 h	Well tolerated, relatively short half-life of lumefantrine.	Six doses, first-line treatment – some low-grade lumefantrine resistance in the GMS.

[a]Abbreviations: S/P, sulfadoxine/pyrimethamine; DHA, dihydroartemisinin; $t_{1/2}$, **terminal half-life**. [The terminal half-lives ($t_{1/2}$) are extracted from *WHO Guidelines for the Treatment of Malaria* (3rd edn)[vii] and *Methods and Techniques for Assessing Exposure to Antimalarial Drugs in Clinical Field Studies*[viii]].
[b]Desethylamodiaquine.

quantitative G6PD tests are becoming available [41]. Second, travellers, tourists, and soldiers relying on chemoprophylaxis tend to come from nonmalarious areas and are unlikely to be infected on entering the area. The situation is different in forest workers who may already carry asymptomatic *Plasmodium* infections when entering malarious forests. The 8-aminoquinolines have excellent activity against the liver stages of *Plasmodium vivax* and *P. falciparum*, but primaquine has very weak activity against the asexual blood stages of *P. falciparum* [42]. Tafenoquine has cleared clinical episodes of vivax malaria but has also less activity against *P. falciparum* infections [43]. Considering that parasite densities in pre-existing subclinical *Plasmodium* infections are orders of magnitude lower than parasite densities seen in clinical malaria episodes, and the host has demonstrated immunity, it is possible that chemoprophylaxis with tafenoquine will clear pre-existing, asymptomatic *Plasmodium* infections; however, empirical confirmation of this assumption is needed. Finally, the efficacy of primaquine may depend on the prevalence of cytochrome P-450 2D6 isotypes in the target population. Whether tafenoquine shares this liability with primaquine needs to be explored further [44].

Box 1. Why Some Drugs Are Not Appropriate for Chemoprophylaxis for Forest Workers in the Greater Mekong Subregion (GMS)

Chloroquine has been widely used as treatment and chemoprophylaxis. Pailin in western Cambodia has been one of the earliest centres of chloroquine-resistant *Plasmodium falciparum* strains. There are still areas in Asia where *Plasmodium vivax* strains remain susceptible to chloroquine but chloroquine-resistant *P. falciparum* strains have spread throughout the GMS [64]. *Sulfadoxine pyrimethamine* (S/P) is administered as a single dose and has a $t_{1/2}$ of about 8 days [65]. Resistance emerged within years of introduction and has rendered S/P inefficacious in the GMS [64,66–68]. Combining S/P with amodiaquine for malaria prophylaxis in the GMS therefore holds little promise. *Mefloquine* is another drug which can no longer be used as monotherapy in the GMS due to high-level resistance. Perhaps more important, mefloquine is poorly tolerated in a substantial proportion of healthy people [69,70]. *Doxycycline* remains an effective malaria prophylactic and protects against a range of bacterial infections [71]. Malaria prophylaxis with doxycycline remains popular with military personnel [72–74], but the need for daily administration could cause adherence issues by less well-regimented populations. A common side-effect, increased sunlight sensitivity, is a distinct disadvantage in the tropics. *Atovaquone–proguanil* is the preferred antimalarial prophylaxis for many affluent tourists and travellers despite the need for daily administration. But the rapid emergence of atovaquone-resistant *P. falciparum* strains on a background of long-standing proguanil resistance limits its usefulness in the GMS [75]. Furthermore, the high production cost of the medically active trans-isomer of atovaquone probably renders this drug unaffordable for public health purposes even as cheaper, generic versions of atovaquone–proguanil become available since the patent expired in 2013 [76]. *Pyronaridine* was developed in China as an antimalarial drug and was shown to be efficacious against *P. falciparum* in Cameroon in 1996 [77]. The coformulated combination pyronaridine/artesunate was found to be safe and effective in the treatment of *P. falciparum* infections in western Cambodia, the epicentre of antimalarial resistance [78]. In a multicentre study in West Africa, 13 (1%) of 996 patients had elevated transaminases following first treatment, 2 (1%) of 311 patients on retreatment [79]. Pyronaridine has an estimated $t_{1/2}$ of 13.2 days in adults, and when coformulated with the short-acting artesunate is a potential candidate for prophylaxis but has not yet been evaluated and approved for use for this purpose [80]. *Pyronaridine/artesunate* has received regulatory approval from the European Medicines Agency but at the time of writing an internal review of its safety by the World Health Organization has not yet been reported. Given that this is possibly the last remaining effective drug for the treatment of multidrug-resistant *P. falciparum* in the eastern GMS, there has been no evaluation nor regulatory approval for its use in prevention, and as there remain unresolved concerns regarding its safety, artesunate–pyronaridine should not be used for chemoprophylaxis at this time.

Dihydroartemisinin (DHA)–piperaquine has been the first-line treatment for uncomplicated malaria in much of the GMS for the last decade; it is remarkably safe and well tolerated. DHA–piperaquine has been used successfully for chemoprophylaxis along the Thailand–Myanmar border areas [45]. Due to the extended half-life of piperaquine it would be well-suited as chemoprophylaxis of forest workers if it were not for the recent emergence of *P. falciparum* strains resistant to both artemisinin and piperaquine [46]. While DHA–piperaquine can no longer clear all symptomatic malaria cases in north-eastern Thailand, Cambodia, and southern Vietnam, in 2016 DHA–piperaquine could still clear asymptomatic *P. falciparum* infections, even infections with genetic markers suggesting multidrug resistance [47]. Further studies are required to determine whether DHA–piperaquine is still effective in **chemoprevention** in the Eastern GMS. Elsewhere, it would seem an ideal candidate. Weekly dosing may be particularly appropriate as it avoids potentially unsafe peak drug concentrations and elevates troughs below the minimal elimination concentration [48,49]. *Artemether/lumefantrine* (A/L) is the single most widely used first-line treatment of uncomplicated falciparum malaria globally. Developed at the end of the last century in China, A/L is licensed in more than 50 malaria-endemic countries, and hundreds of millions of doses have been administered[vi]. The combination A/L is remarkably safe and has retained efficacy in parts of the GMS as recently as 2012 [81–83]. A/L is a potential candidate for forest worker malaria prophylaxis, but since A/L is also an important first-line drug for the treatment of *P. falciparum*, policy makers may be reluctant to recommend a strategy that would add drug pressure to this ACT in the GMS. The six-dose regimen employed for malaria treatment may be inconvenient for prophylaxis and lead to poor adherence. Alternative regimens may be preferable for chemoprevention.

Key Figure

Chemoprophylaxis Regimens for Forest Workers in the Greater Mekong Subregion (GMS)

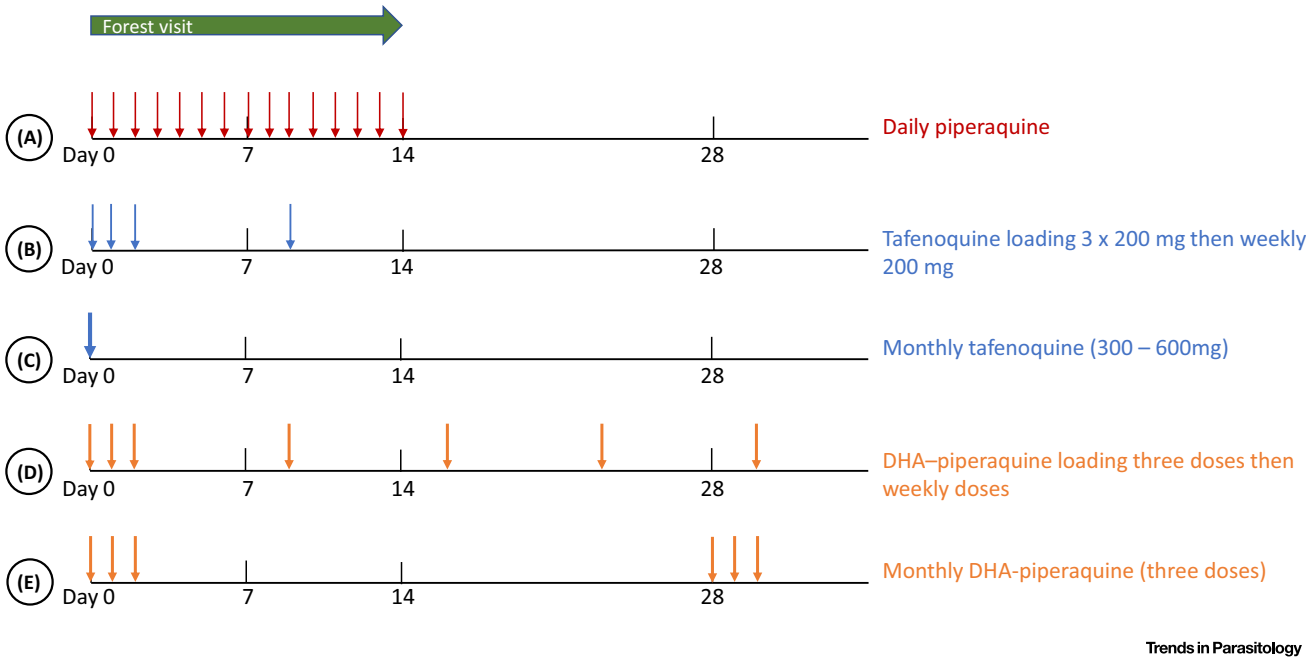

Figure 2. Five prophylaxis regimens to cover a 14-day forest visit. (A) Daily primaquine for the duration of the forest visit. The prophylaxis can be stopped on the last day of the visit as primaquine kills the liver stages of all *Plasmodium* species. A daily 30 mg primaquine regimen has been found to be well tolerated and efficacious in Papua, Indonesia [62]. Primaquine and tafenoquine can only be safely administered to G6PD-normal forest workers. G6PD testing is obligatory if G6PD status is unknown. Primaquine regimens clear pre-existing vivax **hypnozoites**, thus preventing vivax relapse, but have little activity against pre-existing *Plasmodium falciparum* infections [42]. (B) Tafenoquine loading dose followed by weekly tafenoquine. A loading dose (3x daily 200 mg tafenoquine) is followed by weekly 200 mg tafenoquine. This regimen was found to be protective in a recent human challenge study [53]. (C) Monthly tafenoquine for up to five consecutive doses was found to be safe, well tolerated, and highly effective in Thai soldiers [54]. (D) DHA–piperaquine loading dose followed by weekly doses. Weekly DHA–piperaquine doses have been found to be effective in models [48,49]. Weekly doses avoid the potentially unsafe high peak doses and low troughs which allow the escape of *Plasmodium*. This DHA–piperaquine clears pre-existing *P. falciparum* infections but has no effect on *Plasmodium vivax* hypnozoites. (E) Monthly DHA–piperaquine has been found to be safe and effective in clearing *Plasmodium* infections in the GMS in the presence of multidrug-resistant *P. falciparum* strains. Three consecutive monthly rounds were well tolerated [47]. This regimen is conceptually similar to the seasonal malaria chemoprevention providing limited prophylaxis followed by monthly doses sufficient to clear emerging infections [63].

Box 2. Causal versus Suppressive Chemoprophylaxis

Causal prophylaxis clears liver-stage infections but has little or no effect on blood stages. It is therefore not necessary to continue causal prophylaxis once exposure has stopped. The 8-aminoquinolines primaquine and tafenoquine are used for prophylaxis but can trigger haemolysis in G6PD-deficient individuals; hence, testing with a reliable G6PD test is critical prior to administration. A full course of primaquine or tafenoquine clears the liver stages of *Plasmodium* parasites, including *P. vivax*, and prevents future relapse. Other causal prophylactic drugs are atovaquone and proguanil (Box 1). Doxycycline, a synthetically derived tetracycline, is a partially efficacious causal prophylactic drug and a slow-acting blood schizontocidal agent highly effective for the prevention of malaria [84].

By contrast, suppressive chemoprophylactic agents clear exclusively the blood stages of *Plasmodium* infections and have no effect on liver stages. Following exposure, it is essential to continue **suppressive prophylaxis** until emerging liver stages have been cleared (terminal prophylaxis). ACTs provide suppressive chemoprophylaxis.

Considering the permanent threat of emerging and spreading of *P. falciparum* strains resistant to ACT, several triple therapies including ACT are currently under evaluation for treatment of uncomplicated malaria, for example, artemether–lumefantrine–amodiaquine [50]. Triple therapies for prophylaxis may be a strategy to consider in the future, especially once they are coformulated.

Delivery

Maximizing uptake of a malaria prophylaxis is likely to be an iterative process requiring continuous feedback between forest workers and program coordinators. Top-down approaches are unacceptable in the GMS today; active engagement and communication with the target population are more important. It is critical that forest workers understand that they are at risk for malaria, that malaria carries high direct and indirect costs, and that malaria prophylaxis provides potential benefits to themselves and their communities. Establishing an efficient and reliable distribution channel of antimalarial prophylaxis will be critical and may rely heavily on well-functioning village health worker systems to identify forest workers and address their health needs. The large-scale implementation of malaria prophylaxis will be challenging as a large proportion of the rural population in the GMS is at risk for malaria. In villages where private practitioners provide health care, collaboration with these practitioners is essential in order to access all patients [51]. To ensure adherence, groups of forest workers should be encouraged to observe or supervise each other. Delivery strategies need to be adapted to each setting. A 'one size fits all' strategy cannot work: centralized strategies must leave room for decentralized decision making.

Number of Rounds

Forest stays exceeding 2 weeks may require multiple rounds of chemoprophylaxis depending on the drugs used. Data on the optimal dosing interval in terms of efficacy and safety are not yet available for many drug regimens. A 1-month interval between repeated rounds of S/P–amodiaquine was found to be safe and well tolerated in SMC [52]. In G6PD-normal people, 200 mg tafenoquine can be safely administered for extended periods [53,54]. Similarly, three repeated rounds, 1 month apart, of DHA/piperaquine were found to be safe and well tolerated in recent mass drug administrations in the GMS [47]. How often the drugs are best delivered requires further research.

Efficacy, Effectiveness, and Impact on Transmission

It is critical to evaluate the impact of forest worker malaria prophylaxis on malaria transmission in controlled trials. This is a challenging undertaking; not only does the force of infection vary between locations, the duration of exposure of forest workers is variable [55]. A universal study design, as used in treatment efficacy studies, may neither be appropriate nor feasible for the evaluation of forest worker malaria prophylaxis. Instead, a series of sequential trials in diverse settings will be needed, with future trial strategies being optimized by findings from preceding trials.

Risk of Resistance

The distribution of antimalarial drugs for the purpose of prophylaxis will increase the antimalarial drug exposure. Such an increase in drug pressure triggers a reflexive concern that widespread use of antimalarial prophylaxis will increase the risk of emerging resistant *P. falciparum* strains and the loss in efficacy of yet another antimalarial drug. While there are valid reasons for such apprehensions, the actual risk is probably small considering the low parasite density and curative effect of drug regimens. Symptomatic infections with high parasite numbers are the more likely source of resistant *P. falciparum* strains [56]. Still, policy makers may not want antimalarials that are used as a first-line treatment to be used also for prophylaxis.

Political Issues

Considering that many forms of forest work are considered illegal in the GMS, and many forest workers are migrants without political representation, protecting forest workers from malaria may not be a priority for governments. On the other hand, the urgency to eliminate malaria may lead to efforts by national malaria-control programs to engage with forest workers. Discussions with policy makers have to include the importance of forest workers as a continued source of malaria transmission and the need to eliminate this source of transmission in order to eliminate malaria.

Simian Malarias

P. vivax and *P. falciparum* are by far the most important *Plasmodium* species in the GMS. *Plasmodium knowlesi* and *Plasmodium cynomolgi* are also present (see **Simian Malarias** in the Glossary), and, although only responsible for a relatively small fraction of the malaria burden in the region, are important in the prevention of forest malaria as these organisms infect macaques (*Macaca fascicularis* and *Macaca nemestrina*) and are transmitted to forest workers [57–59]. Since their primary hosts are monkeys, *P. knowlesi* and *P. cynomolgi* have little or no survival advantage from drug resistance and remain susceptible to all tested antimalarials [60]. Any antimalarial prophylaxis appropriate for *P. falciparum* in the GMS should also protect against *P. knowlesi* and *P. cynomolgi* infections.

Concluding Remarks

In the GMS, malaria is predominantly a disease in adults who become infected during outdoor work in forested areas. The currently available vector-control measures, including insecticide spraying and treated bed nets, have little effect on mosquitoes that preferentially bite outdoors and during daytime. To eliminate malaria from the GMS it is essential to stop malaria transmission in forested areas in addition to already ongoing malaria-elimination efforts. Antimalarial prophylaxis for forest workers could become a promising concept, but several questions must be addressed before it can be widely used (see Outstanding Questions).

Outstanding Questions

Which drugs should be used to prevent malaria in forest workers in the Greater Mekong Subregion?

How many rounds of antimalarials are appropriate for forest worker malaria prophylaxis?

How is antimalarial prophylaxis best delivered to forest workers to assure high uptake and adherence?

How should trials be designed to evaluate the efficacy, effectiveness, and impact on transmission forest worker malaria prophylaxis?

How should the ongoing effectiveness of malaria prophylaxis be monitored?

Will prophylaxis increase the proportion of antimalarial drug-resistant parasites?

Forest workers are an under-represented population; how can the importance of preventing malaria in this population be advocated for at a policy level?

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Resources

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