

Opinion

How to Contain Artemisinin- and Multidrug-Resistant *Falciparum* Malaria

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In the Greater Mekong subregion (GMS), artemisinin resistance is increasingly compounded by partner drug resistance, causing high failure rates of artemisinin combination therapies in some areas. For its containment, an accelerated elimination strategy will be needed. This includes high-quality implementation of conventional malaria control measures: early case management with quality artemisinin combination therapies (avoiding artesunate monotherapies) and single gametocytocidal low dose of primaquine, vector control and surveillance. Village health workers (VHWs) play a key role in the provision of community-based services which have to reach even the most remote populations. Additional, more aggressive, approaches will be important to accelerate malaria elimination, which could include mass drug administrations, potentially in combination with ivermectin and vaccination, mass screening and treatment with novel diagnostics, reactive case detection, and other measures.

The Threat of Artemisinin and Partner Drug Resistance

Artemisinin-resistant *falciparum* malaria was first described in Western Cambodia in 2008 [1,2], although the genetic marker for artemisinin can retrospectively be traced back as early as 2001 [3]. Resistance to other antimalarial drugs is generally described in terms of recrudescence infections [4]. Because fast clearance of ring-stage parasites is the hallmark of the artemisinins, artemisinin resistance is best detected as a slowdown of peripheral blood parasite clearance, which can be expressed as an increase in the parasitaemia half-life determined by the log-linear parasite clearance curve [5], or more crudely as a higher proportion of patients remaining parasitaemic by microscopy at day 3 (72 h) after the start of treatment [6,7]. The artemisinins rapidly reduce parasitaemia with a 4-log decrease in parasitaemia every 48 h asexual life cycle in artemisinin-sensitive strains, but this class of drugs has a short plasma half-life of around 1 h. The addition of a slowly eliminated partner drug to the artemisinins is obligatory to clear the remaining parasite load which, in an average adult infection, is usually less than 10^5 parasites. If the partner drug in an artemisinin combination therapy (ACT) is greatly ineffective, for instance in case of high-grade resistance to sulphadoxine-pyrimethamine resistance in several African countries, ACT failure rates are high even in the absence of artemisinin resistance [8,9]. In artemisinin-resistant infections, the remaining parasite load after a 3-day ACT course is over 100 times higher, which thus requires a more potent partner drug, which should be efficacious at curing the infection without dependence on the artemisinin component. This relationship is illustrated with the initially maintained efficacy of artemether-lumefantrine, artesunate-mefloquine, and dihydroartemisinin (DHA)-piperaquine shortly after the arrival of artemisinin resistance. However, a slightly less potent partner drug in an area with artemisinin resistance will result in high failure rates [10].

Trends

Artemisinin resistance in *falciparum* malaria is now widespread in the Greater Mekong subregion (GMS) and has selected for partner drug resistance causing high treatment failure of artemisinin combination therapies (ACTs) in increasing areas of the GMS.

Current containment and malaria elimination projects have substantially reduced the malaria burden in the region, but have not halted expansion of drug resistance.

There is convergence of opinions that quality implementation of malaria-control measures reaching remote populations at risk is essential for malaria elimination, whereas the additional tools needed to accelerate malaria elimination for containment of multidrug-resistant *falciparum* malaria are still a matter of debate.

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More importantly, the presence of artemisinin resistance over time is a prelude to partner drug resistance, because an increased residual parasite biomass after a 3-day ACT regimen is exposed to a single partner drug, which facilitates the selection of parasite strains with emerging resistance towards the partner drug. This has been observed at the Thai–Myanmar border, where soon after artemisinin resistance was established, mefloquine resistance, identifiable by an amplification of the *Pfmdr1* gene, reappeared, and treatment failures increased dramatically [10]. Vice versa, however, introduction of artesunate–mefloquine in the 1990s, did not seem to select for artemisinin resistance. At the time of introduction, substantial mefloquine resistance was present, whereas the combination provided a highly effective treatment for uncomplicated falciparum malaria for over 10 years. Another worrying example of artemisinin resistance enabling partner drug resistance is the rapid expansion of the area in Cambodia with piperaquine-resistant falciparum malaria causing high treatment failure with DHA–piperaquine following its introduction at a time when artemisinin resistance was already firmly established [11–17]. The recently described genetic marker for piperaquine resistance, amplification of *Pfplasmepsin 2* and 3, almost invariably appears on parasites carrying the marker for artemisinin resistance, *Kelch* mutations on chromosome 13 (*PfKelch13*), in particular the C580Y allele [17,18]. Increased treatment failure will increase transmission of drug-resistant falciparum malaria, which will be accelerated by the fact that recrudescence infections have higher gametocyte densities increasing transmissibility [19]. In addition, in some studies, infections with artemisinin-resistant parasites show higher gametocyte densities [20]. We here describe the elements necessary for the containment of the increasing threat of artemisinin and partner drug resistance in the GMS.

Rallying behind a Common Narrative As a Prerequisite

Even now that ACTs are increasingly starting to fail, getting the message across that artemisinin resistance is a health emergency has proven difficult in the absence of an increase in malaria transmission and mortality in areas of artemisinin resistance. Feasibility for containment of artemisinin resistance has been challenged by the observation that the *PfKelch13* molecular marker for artemisinin resistance appeared to have multiple geographical origins, with geographically separate emergence of different mutations in this gene [21,22]. This has motivated endorsement of a regional malaria elimination agenda to address the resistance problems. The urgency of rapid containment of artemisinin resistance, however, becomes more prominent now that recent observations show that, over time, the multiple different *PfKelch13* mutations converge in both Cambodia and the Thai–Myanmar border towards a single *PfKelch13* mutation, C580Y [10], which has a much higher potential to spread. Recent observations from Western Cambodia, Northeastern Thailand, and Southern Lao, show that parasite lineages from this large geographical area carry the same preserved *PfKelch13* C580Y long haplotype, indicating a single origin [23]. These dominant artemisinin-resistant parasite lineages, which have also developed resistance to the ACT partner drug piperaquine, are causing high treatment failure rates of 30% and more [12–16]. Their spread threatens malaria control and elimination throughout the region. If these parasite strains, or the key genetic determinants of resistance which they carry, arrive and settle on the African continent, where most of the world's malaria cases occur, a public health disaster will follow. New, promising, groups of antimalarials are under development, but will only become available if they pass the obligatory safety and efficacy tests, which is expected sometime after 2020 [24], and their combination partners have been determined.

Awareness of the threat of artemisinin resistance is a prerequisite for successful efforts to contain and eliminate artemisinin-resistant falciparum malaria from the GMS. Recognition of this threat led the World Health Organization (WHO) to launch a multi-stakeholder Global Plan for Artemisinin Resistance Containment (GPARC) in 2010 [25], followed by GMS country-specific frameworks for resistance containment. In 2013 the Regional Artemisinin-Resistance

Initiative (RAI), a 3-year 100 million US\$ grant, was launched for this purpose by the Global Fund (GF) (<http://www.raifund.org/>). This was followed by a call for malaria elimination from the GMS, supported by all country governments in 2015 [26]. The call for elimination was linked to the realization that elimination of artemisinin resistance implies elimination of all *Plasmodium falciparum* from areas of resistance, since, with continued drug pressure from ACTs, without current availability of alternative drugs, the last remaining parasite strains will be the most artemisinin resistant [27]. A feasibility assessment concluded that, with the current low number of cases in the region, elimination could be considered a feasible goal. Substantial donor money, around 175 million US\$/year in 2015 alone, has been made available to support efforts for artemisinin resistance containment and malaria elimination from the GMS, including grants from the GF, development partners, and funding organizations such as the Bill and Melinda Gates Foundation. Overall, these efforts have resulted in a substantial reduction in malaria transmission in all participating countries of the GMS [28], but containing artemisinin resistance and partner drug resistance has not been successful, and the problem is spreading over an ever widening geographical area (Figure 1). Outbreaks of falciparum malaria have been observed in areas of artemisinin resistance [29]. The situation is becoming increasingly urgent, and acceleration of falciparum malaria elimination is crucial before the infection becomes close to untreatable, which could cause resurgence of malaria to levels seen at the end of the last

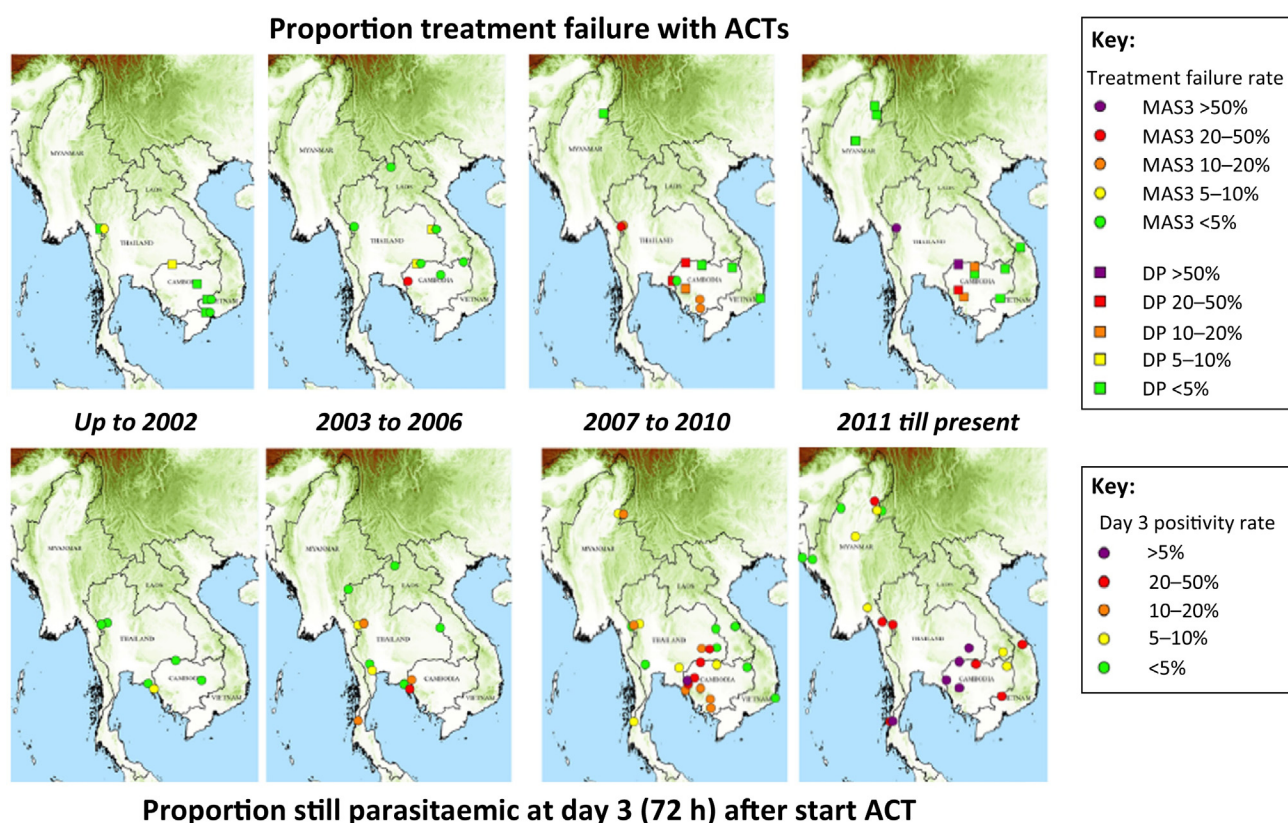


Figure 1. Artemisinin Resistance in the Greater Mekong Subregion. The upper panel shows the proportion of treatment failures after antimalarial therapy with artesunate-mefloquine (MAS3), or dihydroartemisinin-piperaquine (DP). The lower panel shows a current map of artemisinin resistance in *Plasmodium falciparum* malaria, here defined by persistent parasitaemia 3 days after start of artemisinin combination therapy (ACT). Adapted from [82].

century after chloroquine-resistant *Plasmodium falciparum* malaria, with origins in the GMS had become a global problem [30].

How Can We Contain Artemisinin and Partner-Drug Resistance?

Since the elimination of artemisinin resistance requires the elimination of all *falciparum* malaria from the affected areas, the agendas of both efforts largely overlap. The WHO and partners have developed a detailed framework for malaria elimination which is currently being updated [31]. The framework has been adapted to a regional strategy for the GMS [26], and also features in the recent GMS national strategic plans for malaria elimination. The elimination agenda differs in several aspects from the containment agenda. Containment, in contrast to the current elimination agenda, requires shorter timelines and thus fast and rigorous implementation of interventions, greater emphasis on guidance on antimalarial treatment in areas with high ACT failure rates, and outbreak responses to multidrug-resistant *falciparum* malaria. Countries in the GMS must be able to rapidly change drug policies and their implementation.

Several reports have evaluated current initiatives for malaria drug resistance containment and elimination in the GMS [32] (<http://www.raifund.org/> and <https://www.adb.org/sites/default/files/publication/178203/malaria-elimination.pdf>). Recommendations have been made regarding the sense of urgency, governance structures, funding mechanisms, and coordination among the development partners, shared regional intelligence, including data platforms, and technical assistance for micro-level planning and quality control, among others. Building on existing documents, we here describe our views on core elements needed for accelerated elimination of *falciparum* malaria in areas of artemisinin and partner-drug resistance. All elements depend on an infrastructure ensuring the correct implementation of conventional malaria-control measures, which has to reach remote populations at risk. In addition, we discuss additional tools needed to accelerate elimination and indicate where further operational research is needed. None of the interventions will be sufficient on their own to eliminate malaria successfully, and integration will be key.

Community-Based Services

The foundation for any success in controlling and eliminating malaria is a functioning primary health care system. The village malaria worker (VMW) or community health worker (CHW) networks have proven to be a cornerstone for the delivery of all malaria-related interventions and surveillance in the public sector [33–36]. Although the coverage of such networks has increased impressively in many areas of the GMS, it should be universal, and training, supervision, and monitoring of the VMWs should be intensified. Difficult-to-reach areas, such as border areas and conflict zones, can be underserved by the government programs. Here nongovernmental organizations (NGOs) can play an important role in maintaining and expanding CHW networks. Many patients will continue to seek treatment in the private sector, and involving private health care providers in malaria elimination efforts will be crucial. Private corporations could also contribute to increase services to remote populations, including plantation, construction, and mining workers. Public–private partnerships have been set up in this regard in several countries of the GMS and have proven to be an important and effective way to increase the quality of malaria treatment in the private sector, and also provide important supplementary epidemiological data (https://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy11/mekong_mop-fy11.pdf?sfvrsn=6).

Converting networks of VMWs into CHWs with a broader remit will be essential to ensure continued uptake by the villagers when malaria incidence is going down. If patients presenting with nonmalarial fevers are not served, motivation to visit the health worker will rapidly decline. A broader service package can include treatment of malnutrition, respiratory, diarrheal diseases, helminths, and ectoparasites, as well as diagnosis and a referral system for patients with HIV

and suspected tuberculosis. The innovative use of tools such as C-reactive protein, an established biomarker of bacterial infections, may help CHWs to optimise the available antimicrobial treatment for their patient population [37,38].

Networks at the most peripheral level, working with hard-to-reach populations in remote locations, require specific training, supervision, and an uninterrupted supply chain to prevent stock-outs of diagnostics and medication. The sustainability of such community health services requires adequate funding for remuneration, supplies, training, and supervision. Currently, such funding comes mostly from donors. Whether community health insurance or other innovative finance mechanisms can provide a helpful contribution to the sustainability of such structures and services needs further exploration. Community health networks need local adaptation, and their optimal structure will depend on regional differences.

Surveillance

Complete and correct collection and reporting of surveillance data are mandatory to guide a successful elimination program. The VMW/CHW networks are ideally situated for the collection of essential epidemiological data. Near-real-time reporting through mobile phone systems have been piloted successfully in several countries [39,40]. Large-scale implementation will require consideration of the cost implications. With increasingly failing antimalarial therapy, follow-up of patients becomes increasingly important, so that recrudescence infections can be appropriately treated and captured by the routine data-collection systems, which will require a unique identifier code for individual patients. Understanding of the local epidemiology is important to guide interventions, which include distinguishing locally acquired infection versus imported cases. Addition of filter-paper, blood-spot collection for genetic epidemiology can provide a wealth of critical information, such as the nature and cause of resurgent clusters of infections, and routes of spread of artemisinin and partner-drug resistance.

Effective Antimalarial Treatments

Community-level availability of health services will ensure early diagnosis and treatment of malaria with quality-assured ACTs and a gametocytocidal dose of primaquine. The areas with ACT failure are likely to increase over the coming years, and new treatments cannot reasonably be expected within this decade. This necessitates creative use of currently available drugs (Box 1). In Cambodia, a policy of drug rotation between DHA–piperaquine (currently failing) and artesunate–mefloquine (currently effective) has proven to be programmatically difficult. Alternative treatment options, such as the use of triple artemisinin combination therapies instead of double combinations in current ACTs, are being trialled (Trial Registration Number NCT02453308). Additional capacity-building in national malaria programmes and regulatory

Box 1. How to Treat Uncomplicated *Falciparum* Malaria When ACTs Start Failing Using Existing Drugs, Since New Compounds Are Not Expected within This Decade

1. Drug rotation using existing ACTs. Recent observations show that the molecular markers for mefloquine resistance (PfMDR1 amplification) and piperaquine resistance (Pfplasmepsis2 and 3 amplification) are in counter balance, and in areas in Cambodia with resistance to piperaquine, *Plasmodium falciparum* has regained susceptibility to mefloquine. Alternative existing ACTs, such as artesunate–pyronaridine, could also play a role, although the latter had suboptimal efficacy (<90%) in Western Cambodia [81].
2. Triple combinations, combining an artemisinin with two matching partner drugs. The combinations dihydroartemisinin–piperaquine–mefloquine and artemether–lumefantrine–amodiaquine are currently being trialled (trial registration number NCT02453308).
3. Extending the duration of current 3-day ACT regimens to 5 or 7 days, or sequential treatment with two different ACTs. Adherence issues will need to be addressed, and for some partner drugs with long plasma half-lives, potential adverse effects related to drug accumulation need to be studied.
4. Arterolane–piperaquine, registered in India and several other countries. The synthetic trioxolane arterolane needs assessment of its efficacy in areas with artemisinin resistance.

authorities, and increased communication and cooperation between them, will be critical to facilitate rapid implementation of new drug policies.

Vector Control

Insecticide treated bednets (ITNs) have been found to be highly effective, especially in sub-Saharan Africa where malaria vectors tend to bite indoors and at night. ITNs are less effective in the GMS, a region with much more complex vector biology [41–43] and where vectors tend to bite outdoors, and around 60% of infected bites occur before bed time [44]. There has been massive funding of ITNs in the GMS, and ITN coverage has reached saturation in many areas, whereas national malaria plans aim for additional coverage in unserved areas. Each resident in malaria-endemic settings in the GMS should have access to an intact ITN, but, with an estimated maximum efficacy of around 30% to prevent malaria episodes [45,46], it has not been and will not suffice for interruption of malaria transmission.

Indoor residual insecticide spraying (IRS) has found to be highly effective in malaria control, especially in Southern Africa [47]. The impact of IRS has been dampened by the emergence and spread of insecticide-resistant mosquitoes. Originally there were only some islands of resistance, but the problem has increased substantially, especially in Africa [48]. In Southeast Asia the impact of IRS was always limited by the outdoor biting character of the relevant malaria vectors [43]. The traditional architecture of rural homes in Southeast Asia, characterised by elevation and airflow optimisation, help to minimise indoor biting but are less appropriate for indoor spraying compared to traditional sub-Saharan dwellings [49]. It seems unlikely that scaling up IRS will make an important additional impact on malaria transmission in the GMS. Integrated vector control is important as outlined in the WHO guidelines (http://apps.who.int/iris/bitstream/10665/44768/1/9789241502801_eng.pdf). Additional strategies, including long-lasting insecticidal garments, spatial outdoor repellents, and novel attractive toxic traps, need urgent further evaluation. Novel approaches under investigation to identify at-risk groups for exposure to malaria vector bites in areas of low entomological inoculation rates (in the GMS typically <10 persons/year) include assessment of serological salivary biomarkers [50], which could facilitate the targeting of interventions.

Additional Tools Needed to Accelerate Malaria Elimination

Rigorous implementation of conventional malaria-control measures described above will reduce the malaria burden substantially. Once transmission has come down, additional tools will be needed to accelerate elimination, which includes targeting the asymptomatic parasite reservoir.

In high-transmission areas, where immunity against falciparum malaria is slowly acquired during childhood, asymptomatic malaria infections are very common. More recently it has become apparent that, also in low-transmission areas in Southeast Asia, the proportion of healthy asymptomatic individuals carrying both *Plasmodium falciparum* and *Plasmodium vivax* parasites is substantial, often between 5% and 20% of the population [51,52]. Their quantitative contribution to malaria transmission in the region needs further study, but is likely to be significant [53,54]. Since asymptomatic parasite carriers will not seek treatment, alternative approaches are needed to eliminate this parasite reservoir. These include targeted mass drug administration, mass screening and treatment, and reactive case detection. In addition, we discuss the potential of adding vaccination to a malaria elimination effort, and chemoprophylactic antimalarial treatment for high-risk groups.

Targeted Mass Drug Administration

Treating all people in targeted communities through mass drug administration (MDA) should eliminate the parasite reservoir and interrupt transmission at an accelerated rate. The targeted

use of MDA for elimination purposes has been endorsed by the WHO (<http://www.who.int/malaria/publications/atoz/role-of-mda-for-malaria.pdf?ua=1>). Detailed mapping of villages and their population is often not available but is an important first requirement for successful MDAs. Well-functioning village-level malaria posts are needed for surveillance, diagnosis and treatment, and intensive community engagement is essential to ensure high uptake of the intervention. The appropriate targeting of an MDA requires in-depth knowledge of the local malaria epidemiology, specifically the asymptomatic parasite reservoir [55]. MDAs have to target sources of transmission rather than 'sinks', where cases are imported [56], which requires an understanding of population movements. After local interruption of malaria transmission, continued close surveillance will be essential to prevent reintroduction. An MDA-based approach has successfully eliminated malaria in Aneityum, Vanuatu [57]. More recently, a Malaria Elimination Task Force is integrating MDAs with other interventions such as the roll out of village health workers in a demonstration project on the Myanmar–Thai border. This has close to eliminated falciparum malaria from that area. A major determinant of the impact of MDA is coverage. Recent experiences in MDA suggest that community engagement needs to be adapted to the local context, yet the need for trust in the staff managing the campaign seems universal [58,59]. Considering the importance of high coverage, more research to understand the dynamics determining coverage is important. Although the approach has been successfully implemented on the Myanmar–Thai border, scaling up has to address important issues, including scalable methods for prevalence surveys with sufficient sensitivity to detect the asymptomatic reservoir, and alternative ACT regimens in case the currently used DHA–piperaquine combination succumbs to resistance.

Ivermectin, which has been used extensively in MDAs in Africa for the elimination of lymphatic filariasis, has a potential role in malaria elimination, since the life-span of mosquitoes which have ingested a blood meal from a person treated with ivermectin is drastically reduced [60,61]. There is hope that the integration of ivermectin in MDAs could make an impact on vector populations, and could improve the acceptability of MDAs, because of its additional effect on ectoparasites. This approach is promising in theory but has yet to be evaluated in field studies. Combining MDAs with malaria vaccination campaigns is discussed below.

Mass Screening and Treatment (MSAT) Using Novel Diagnostics

Several projects have piloted the use of mass screening of village populations followed by treatment of parasite carriers, who will be predominantly asymptomatic [62–64]. Since conventional rapid diagnostic tests (RDTs) or microscopy lack the sensitivity to detect the majority of asymptomatic carriers, most projects relied on PCR diagnosis in blood spots sent to a central laboratory. The logistics and delays encountered using this approach, and its modest effects on malaria transmission, have tempered enthusiasm [65]. Small-scale projects using loop-amplified isothermal amplification (LAMP) as a field-adapted molecular approach to detect low-level parasitaemia are being trialled. Modelling studies describe the time delay between diagnosis and treatment as an important culprit reducing efficacy [66]. However, a novel RDT based on the histidine-rich protein 2 of *P. falciparum* (PfHRP2) is currently being developed with a sensitivity comparable to PCR from a filter-paper blood spot. This opens new opportunities using MSAT as an approach to support falciparum malaria elimination. The new highly sensitive RDT has yet to arrive on the market, and currently there are no studies available evaluating this novel approach. However, theoretical advantages supported by modelling exercises include the much easier logistics of immediately available test results and much faster coverage of large contiguous areas [66]. Also, if only proven parasite carriers will be treated with antimalarial drugs, community acceptance is likely easier to achieve than with MDA. This strategy will also decrease drug pressure on the parasite population. A disadvantage is that, with a sensitivity of the new RDT of around 5 to 10 parasites per μL , about half of the asymptomatic carriers are likely to be missed [53]. These very low parasitaemias, including gametocytaemias, will unlikely

contribute to mosquito transmission around the moment of sampling [67]. However, the proportion of individuals carrying a very low burden of parasites that will subsequently develop higher and transmissible gametocytaemia is the subject of current studies.

Case and Focus Investigation and Response

Many of the current national strategic plans for malaria elimination in the GMS emphasize reactive case detection as a potential tool for malaria elimination. This involves an active response to an index case, including screening of the household of the case and households within a certain radius. Screening can be performed with conventional RDTs, which provide a fast result, or PCR techniques, which will take longer. Alternatively, all household members within a certain radius of the index case can be treated irrespective of *Plasmodium* infection. An implicit assumption of the approach is that the risk of transmission is inversely proportional to the distance from the index household. It is therefore important to understand local epidemiology and entomology before this approach is implemented. If transmission is in the forest, rather than in the village, or if transmission is by outdoor-biting mosquitoes away from the household, the approach is unlikely to treat an important proportion of the asymptomatic parasite carriers; a recent project in Cambodia showed little additional yield from this approach [68]. Mathematical modelling using micro-epidemiological data from the Thai–Myanmar border shows that the perimeter around the index case household has to be very large in order to capture a significant proportion of the asymptomatic carriers, which is then coming close to screening the whole village [69]. An alternative approach is to target individuals coexposed with the index case to a transmission area, which seems more appropriate in areas of mainly forest-transmitted malaria.

Vaccination

The vaccine candidate RTS,S/AS01 has recently received the stamp of approval of the European Medical Authority, although relevant expert committees were not convinced that with the currently available evidence the vaccine benefits are sufficiently proven for large scale roll-out in malaria-endemic regions in Africa [70]. The limited duration of protection was a major argument against such a recommendation [71]. Limited periods of protection, however, may help to interrupt malaria transmission if, during the vaccine protected period, sources for reimportation can be eliminated using the tools described earlier, including vector control, case management, and MDA [72]. The approach needs further evaluation.

Chemoprophylaxis of High-Risk Groups

In the GMS the highest observed risk for reimportation of parasitaemia into the village is through people who work in forested areas [73–76]. If this is the main risk group for reimportation, it is important to define strategies to prevent malaria infections in such high-risk groups [77]. Forest workers are insufficiently protected against mosquito bites by impregnated bednets or hammocks because vectors in the GMS frequently bite outdoors and before bed-time [78]. There may be an important role for preventive prophylactic treatment for forest goers.

Combining and Integrating Interventions

Optimizing the chances to interrupt malaria transmission requires a combination of interventions. The most basic set of interventions, which should be universally available, are quality VHW/CHW networks equipped with sufficient supplies to provide adequate case management and ITNs. The emergence and spread of *P. falciparum* strains resistant to first-line antimalarial drugs will necessitate rapid replacement with novel drug combinations when needed, which will require considerable flexibility and cooperation among WHO, researchers and policymakers. These universal minimum interventions will likely not be sufficient to eliminate malaria sufficiently fast and will need to be supplemented by more aggressive approaches which also target the asymptomatic parasite reservoir. Of these, targeted MDA in hot spots of transmission has been

studied most in the region and has proven efficacy if deployed within the right context and coverage is high. Ivermectin can be added to the MDA regimen. However, scaling up issues for MDA remain. Reactive case detection has proven successful in the African setting, but its implementation in the GMS will need to be carefully monitored for effectiveness. Chemoprophylaxis of high-risk groups, such as forest goers, could be evaluated and implemented right away. Other tools, including MSAT using hypersensitive RDTs and vaccination with RTS,S, will need further testing. For all interventions discussed, high quality implementation and high coverage will be critical.

Implementation, Evaluation, and Governance

All implementation of new activities will require bottom-up planning, preparation of the health system, and adequate community engagement and participation. Operational and implementation research is important, but since the problem of rapidly increasing multidrug-resistant malaria is an emergency, some tools for elimination will need implementation before they have been fully field-tested. Mathematical modelling can help to prioritize context-specific implementation [79,80]. Near-real-time evaluation of new and more aggressive interventions for elimination will be important to either further scale-up or replace specific interventions. This will require a regional approach, so that the different countries can learn from each other. Although country ownership will obviously remain essential, there is additional value in a regional governance structure that has a broader perspective, access to regional intelligence, and can steer interventions and implementation as needed. Such a regional governance structure will need collaboration of all stakeholders, including national malaria programs and their ministries, WHO, NGOs, and representatives of civil society, private sector providers, academia, development partners, funders, and others.

Concluding Remarks

Increasing artemisinin and partner-drug resistance in the GMS is a public health emergency. Falciparum malaria has to be eliminated from the GMS before it becomes close to untreatable. This requires a sense of urgency, a common spirit, good coordination, locally adapted integrated strategies, impact evaluation, good surveillance, community-based approaches, collaboration between public sector, private sector and civil society organizations, targeting difficult-to-reach populations, targeting the asymptomatic parasite reservoir, adequate funding, and persistence till the end goal is reached (see Outstanding Questions). We cannot afford to lose ACTs as a frontline weapon against malaria, since this will have dramatic consequences for malaria control globally.

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Outstanding Questions

How can the impact of VHWs be optimized? How can the package of services be best defined? How to make the system sustainable? VMWs will have to be converted to CHWs addressing additional health issues to sustain uptake when malaria incidence is going down. This is an important area of research.

How can MDA best be implemented to eliminate the asymptomatic parasite reservoir, in the context of high-quality community-based malaria control? This approach has proven successful for eliminating malaria in a demonstration project. Additional research is needed on scalable methods for prevalence studies to identify sources of transmission, on defining target areas for MDA, on the additional value of ivermectin in MDA, on methods for community engagement essential for reaching high coverage, and on alternative drug regimens in areas of failing DHA–piperaquine.

How can mass vaccination, in particular with the RTS,S/AS01 vaccine, best be implemented as an additional tool in malaria elimination?

What will be the new safe antimalarial compounds, when will they become available, and in which combinations will they be deployed? Increasing treatment failure with current ACTs requires urgent testing of novel treatment approaches using currently available antimalarials, such as in triple combinations, as well continued research on novel compounds.

How can the new, much more sensitive, rapid diagnostic tests be leveraged for malaria elimination? As these become available, mass screening and treatment as a tool for malaria elimination will need renewed evaluation.

How does the local setting and epidemiology influence strategies for malaria elimination? Mathematical modelling can help to define which combination of interventions should be applied to each setting.

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