Addressing the threat of antimalarial drug resistance to malaria elimination in Southeast Asia

Workshop report

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Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Academy of Medical Sciences, or its Fellows.

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Contents

Preface

Enormous progress has been made in the control of malaria in the Greater Mekong Subregion of Southeast Asia. As a result, the goal of malaria elimination is a realistic possibility, and a regional policy objective.

Much of this progress has been down to the use of artemisinin-based combination therapies (ACTs) – artemisinin derivatives paired with a second antimalarial drug. However, growing rates of drug resistance are threatening to undermine elimination efforts. Furthermore, there is a real risk that drug-resistant strains of the malaria parasite will spread from the Greater Mekong Subregion to other parts of Asia and to Africa, where the majority of malaria deaths occur.

In October 2020, the UK Academy of Medical Sciences (AMS), the Thai Academy of Science and Technology (TAST) and the National Center for Genetic Engineering and Biotechnology (BIOTEC, a member of the Thailand National Science and Technology Development Agency in the Ministry of Higher Education, Science, Research and Innovation) organised a joint virtual meeting to discuss the current state of malaria drug resistance and the role that research could play in addressing the challenge it poses to malaria elimination. The meeting was funded by the AMS, through the Global Challenges Research Fund.

The workshop programme was developed by the organisers and a steering committee chaired by **Professor Yongyuth Yuthavong**, Professor Emeritus, Mahidol University, and Research Fellow at BIOTEC, Thailand, and **Professor Nick Day FMedSci**, Director of the Mahidol Oxford Tropical Medicine Research Unit, Thailand (Annex 1). This report provides a summary of the key themes to emerge at the workshop. It reflects the views expressed by participants at the workshop and does not necessarily represent the views of all participants, all members of the steering committee, the AMS or the TAST.

Executive summary

Over the past decade, the burden of malaria in the Greater Mekong Subregion has declined substantially. Between 2012 and 2018, the number of deaths from malaria fell by 95%. This progress has been underpinned by a regional commitment to malaria elimination.

Much of the progress in malaria control has come from the use of highly efficacious artemisinin-based combination therapies (ACTs), consisting of an artemisinin derivative such as artesunate and a partner antimalarial drug. Artesunate acts rapidly, clearing most of the parasites, while the longer-lasting partner drug kills any that survive.

Drug use inevitably selects for less susceptible parasite variants. Over the past decade, new parasite strains resistant to artemisinin derivatives and their partner drugs have emerged and spread widely in Southeast Asia. These new strains compromise the ability to treat malaria and undermine the drive towards elimination.

In October 2020, a joint virtual meeting organised by the UK Academy of Medical Sciences (AMS), the Thai Academy of Science and Technology (TAST) and the National Center for Genetic Engineering and Biotechnology (BIOTEC, a member of the National Science and Technology Development Agency in the Ministry of Higher Education, Science, Research and Innovation) took stock of the current state of drug resistance in the Greater Mekong Subregion and how research could address the challenges identified. Through breakout groups and discussions, the following key issues were identified:

- **Drug development:** The number of new antimalarial drugs in the pipeline is low and there is a high attrition rate. Although at least two promising new drugs – cipargamin and ganaplacide – have a realistic prospect of being licensed, their routine use is still some years away. In the meantime, the efficacy of existing drugs must be preserved through approaches such as triple combination therapy, sequential use of drugs and drug rotation.

- **Genomic epidemiology:** The characterisation of genetic markers associated with drug resistance is enabling drug-resistant infections to be identified and mapped. This provides insight into the evolution and spread of drug-resistant strains, and also provides critical information to national malaria control programmes.

- **Malaria control:** As cases of malaria have declined, community-based detection and treatment of infections, through the mobilisation of community health workers, has been shown to be highly effective at reducing the incidence of disease. However, currently recommended strategies to detect and investigate new cases may not be appropriate in remote, hard-to-reach regions. Mass drug administration and/or mass screening and treatment may be valuable alternative or complementary approaches.

- **Communities:** As malaria becomes less common, it is important to maintain community commitment to elimination, support for control measures and adherence to treatment. Elimination-based activities may be particularly challenging in geographically remote communities and among groups such as migrants who are often reluctant to engage with public healthcare systems.

- **Integration:** Malaria control has primarily been a standalone activity. As case numbers decline, it is increasingly important to integrate malaria control and other health services. This will contribute to the development of more patient-centred and sustainable services.

  Participants also identified a range of areas, in addition to current priorities such as drug development and genomic epidemiology, where additional research is needed:

- **Genetic markers of resistance:** Further research is needed to identify emerging mutations associated with drug resistance, for currently used drugs as well as newly developed drugs as they are evaluated in clinical trials.

- **'Final mile':** More research is needed to identify the most effective strategies for malaria control and elimination in areas of low transmission, particularly in environmentally challenging locations. This includes the effectiveness of mass drug administration and mass screening and treatment.

- **Integration:** With integration likely to be key to sustainability, there is a need to identify and evaluate suitable integrated models of care, potentially building upon the community health worker infrastructure established for malaria control. There may also be opportunities for synergies between COVID-19 responses and malaria control.

- **Cost-effectiveness:** For drug introductions, there is the need for additional health economic analyses that include a wider range of factors, such as the long-term benefits of maintaining the efficacy of drugs.

- **Community engagement:** It is essential to maintain public support for malaria elimination and for control measures. There needs to be an emphasis on close engagement with communities to maintain awareness of malaria as a health threat, the mobilisation of support for control activities, and gathering community input into the design of control activities.

Participants concluded that rising levels of antimalarial drug resistance needed to be dealt with as a matter of urgency. Genomic surveillance is providing the tools to understand the nature of the threat, and it was seen as vital that this information was communicated effectively to national malaria control programmes and policymakers, to inform practical control efforts and to mobilise political commitment to malaria elimination. The sharing of data and samples between research and control programmes, and across borders, was identified as essential to provide a comprehensive view of drug resistance and to identify the most effective responses.

A failure to control drug-resistant malaria in the Greater Mekong Subregion could undo years of progress, have a devastating impact on health and economic development, and increase the risk of a potentially catastrophic spread to regions such as sub-Saharan Africa.

Introduction

Between 2012 and 2018, the number of cases of malaria in the Greater Mekong Subregion of Southeast Asia fell by 74% and deaths declined by 95%.[1] These successes have encouraged countries in the region to adopt a goal of malaria elimination, as a stepping stone to full eradication.

A major contribution to malaria control has been the extensive use of artemisinin-based combination therapies (ACTs) – artemisinin derivatives such as artesunate paired with a second antimalarial drug. Drugs such as artesunate are fast-acting and rapidly cleared from the body, while partner drugs persist for longer and kill any surviving parasites. Between 2010 and 2018, around 3 billion ACT treatment courses were procured globally.[2]

This combined use of drugs is important for delaying the emergence of resistance, as parasites need to acquire resistance to both drugs to fully compromise treatment effectiveness. However, over the past decade, levels of resistance to artemisinin derivatives and partner drugs have begun to rise, posing a major threat to elimination efforts.

By itself, resistance to artemisinin derivatives rarely leads to treatment failure. However, it slows the clearance of parasites and increases the risk that resistance will develop to partner drugs. Multiple factors have led to the emergence of drug-resistant parasites, including the use of artemisinin drugs as monotherapies and substandard drug quality.[3]

Resistance to artemisinin derivatives has been found to be associated with a range of malaria parasite mutations, particularly in a gene known as *Pfkelch*. Similar genetic markers of resistance have been identified for other commonly used antimalarial drugs. Genetic approaches therefore provide a way to identify and track the spread of resistant strains of parasite.

Historically, the Greater Mekong Subregion has been a hotspot for the emergence of drug-resistant malaria parasites, which have subsequently spread globally. Although ACT-resistant strains have not yet spread widely beyond the Subregion, there are concerns that they could push westwards into South Asia and to Africa, where the bulk of the 400,000 deaths from malaria occur each year.

Countries in the Subregion have identified malaria elimination as a public health priority, and a regional malaria elimination strategy has been developed.[4] The Global Fund to Fight AIDS, Tuberculosis and Malaria is providing major funding to support elimination campaigns within countries, with financial commitments extending to at least 2023.

In October 2020, the UK Academy of Medical Sciences, the Thai Academy of Science and Technology and the National Center for Genetic Engineering and Biotechnology organised a joint virtual meeting to discuss the current state of play of antimalarial drug resistance in Southeast Asia and to identify priority areas for research and programmatic innovation. As well as presentations, breakout groups explored three key issues – resistance research, ways to address resistance and operational challenges (summarised in Annex 2).

1. WHO (2019). *Countries of the Greater Mekong zero in on falciparum malaria.* Geneva: WHO. https://www.who.int/publications/i/item/countries-of-the-greater-mekong-zero-in-on-falciparum-malaria
2. WHO (2019). *World malaria report 2019.* Geneva: WHO. https://www.who.int/publications/i/item/world-malaria-report-2019
3. Dondorp AM, *et al.* (2010). *Artemisinin resistance: current status and scenarios for containment.* Nat Rev Microbiol **8**:272–280.
4. WHO (2015). *Strategy for malaria elimination in the Greater Mekong Subregion: 2015-2030.* Manila: WHO Regional Office for the Western Pacific. https://apps.who.int/iris/handle/10665/208203

Key issues identified

Drug development

New drugs are needed to replace those that are no longer effective. However, interest in malaria drug discovery in high-income countries and in the pharmaceutical industry has waned in recent decades. New drug development is now heavily dependent on non-profit public-private partnerships such as the Medicines for Malaria Venture (MMV).

Unfortunately, as is typical in drug development, many candidate drugs have failed during clinical evaluation, because of lack of efficacy or safety concerns. While the MMV pipeline includes a range of candidate drugs, it is likely that most will fall by the wayside.

Among the most promising new antimalarials are **cipargamin** and KAF156 **(ganaplacide)**. Of note, cipargamin has a novel mechanism of action (the mechanism of action of ganaplacide is unclear). Importantly, both are not only highly efficacious but also very fast-acting, clearing parasites even more rapidly than artesunate. However, it is likely to be several years until either cipargamin or ganaplacide are licensed, and their use in Southeast Asia may require additional regional data.

Given this gap until new products become available, there is an even greater need to protect existing drugs. One solution may be **triple artemisinin-based therapy (TACT)**, in which existing ACTs are combined with a third drug. The eight-country TRAC II study, comparing conventional ACT and two novel TACTs, recently found that the TACTs tested were safe, efficacious and well-tolerated.[5]

A follow-up study, DeTACT, is currently exploring a wider range of issues associated with the use of TACT. As well as a clinical trial involving nearly 5,000 patients in 13 countries, eight in Africa, the study is also exploring options for co-packaging and co-formulation of drugs. Co-packaging is more straightforward, but raises questions about patient compliance. Co-formulation provides a single pill containing all active ingredients, but is technically more challenging and has regulatory implications. The DeTACT project is also carrying out mathematical modelling, bioethics studies and considering the pathways to introduction in individual countries.

Other approaches include the **sequential use of drugs** – replacing compromised drugs with alternatives in areas affected by resistance – and **drug rotation**, alternating the use of drugs with similar efficacy to reduce selection pressures for resistance. Encouragingly, the withdrawal of a drug can on occasion lead to resensitisation of parasites to that drug. Another possible stopgap solution is to modify **drug formulations** to improve bioavailability. For example, one of the most commonly used antimalarials, lumefantrine, shows low levels of bioavailability. Improved formulations could therefore lead to higher effective drug concentrations in the body and greater efficacy.

ACTs are typically given in one or two doses daily for three days, and much recent effort in antimalarial drug development has been devoted to advancing **single-dose treatments**. Although single-dose treatments would be a major advantage, particularly in areas where follow-up of patients is difficult, participants at the meeting expressed concern that valuable compounds might be at risk of being neglected because they do not fulfill the single-dose criterion.

5. van der Pluijm RW, *et al.* (2020). *Triple artemisinin-based combination therapies versus artemisinin-based combination therapies for uncomplicated Plasmodium falciparum malaria: a multicentre, open-label, randomised clinical trial.* Lancet **395(10233)**:1345-1360. doi: 10.1016/S0140-6736(20)30552-3.

Epidemiology of drug resistant malaria

Multiple mutations associated with reduced sensitivity to artemisinin derivatives have been identified. Analysis of the genes affected can provide clues to the mechanisms of drug resistance, which could inform future drug development efforts. Of more immediate benefit, this knowledge can underpin genomic surveillance programmes that provide insight into the distribution, spread and evolution of resistant strains of parasite, to inform the work of national malaria control programmes.

The GenRe-Mekong project, for example, has established a platform for monitoring resistant genes across a swathe of Greater Mekong Subregion countries. Simple blood spot samples are collected from patients and sent to country or regional laboratories for analysis. Laboratories screen for well-described genetic markers of resistance for a range of antimalarials, and also genetically 'barcode' isolates so that their family relationships can be mapped.

The project's work is closely aligned with that of national malaria control programmes. Raw genetic results are processed into simple reports that provide national policymakers with at-a-glance information on the prevalence and distribution of drug-resistant strains in their country.

Such work provides valuable information on multiple levels. For example, it has revealed insight into the distribution of resistant strains across the region as a whole. One striking finding is that strains appear to segregate into eastern and western groups, with central Thailand appearing to act as a barrier preventing the westward spread of highly drug-resistant strains.[6]

In addition, more granular analyses can provide near real-time data on the spread of resistant strains both within and between countries.[7] Integration with national malaria control programmes means that this information can be immediately acted upon, for instance by adapting local treatment recommendations. In Vietnam and Laos, for example, GenRe-Mekong surveillance data revealed the presence of resistant strains in provinces thought to be unaffected.

The genetic barcoding of isolates enables family trees of parasite strains to be constructed. As well as providing information on the distribution of resistant genes at highly granular levels, this can offer insight into how strains evolve and spread. For example, data from the GenRe-Mekong and TRAC II projects revealed that a multidrug-resistant form of P. falciparum spent several years circulating in Cambodia before acquiring additional mutations conferring resistance to the partner drug piperaquine, generating a family of substrains that spread to neighbouring countries.[8] These offspring continue to accrue new mutations.

Genetic surveillance has the advantage that it can detect reduced sensitivity to, say, artemisinin derivatives before treatment failures begin to emerge. However, genetic studies are of most value when they are linked to clinical data and to biological studies of parasites. Although treatment failure is the most important clinical consequence of resistant mutations, it is often a late consequence of an accumulation of mutations causing resistance to both ACT drug components; laboratory studies on parasite isolates are necessary to determine the links between mutations and resistance to specific drugs.

Combining all three types of data – clinical, parasite biology and genetic – is extremely powerful, but collecting, storing and analysing parasite isolates is logistically and technically complex. There are hopes that rapid cryopreservation and the shipping of isolates to central laboratories could provide a way to generate additional biological data.

Participants noted that the impact of genomic surveillance work is greatly increased by the sharing of data and isolates across countries. It was suggested that wider partnerships could be considered, particularly given the apparent spread of drug-resistant parasites to other parts of Southeast Asia.

6. Hamilton WL, *et al.* (2019). *Evolution and expansion of multidrug-resistant malaria in southeast Asia: a genomic epidemiology study.* Lancet Infect Dis **19(9)**:943-951. doi: 10.1016/S1473-3099(19)30392-5.

7. Jacob CG, et al. (2020). Genetic surveillance in the Greater Mekong Subregion and South Asia to support malaria control and elimination. medRxiv. doi: https://doi.org/10.1101/2020.07.23.20159624

8. Hamilton WL, *et al.* (2019). *Evolution and expansion of multidrug-resistant malaria in southeast Asia: a genomic epidemiology study.* Lancet Infect Dis **19(9)**:943-951. doi: 10.1016/S1473-3099(19)30392-5.

Control strategies and elimination

In 2014, WHO put forward a proposal to eliminate malaria in the Greater Mekong Subregion, which was followed a year later by a strategic plan from the WHO Regional Office for the Western Pacific. In turn, countries in the Subregion have developed national strategies to accelerate malaria control and elimination. Substantial financial support for these efforts – US$230.5m for 2021–24 and nearly US$700m in total – has been provided by the Global Fund to Fight AIDS, Tuberculosis and Malaria. This accounts for around 60–80% of national funding on malaria drug resistance initiatives.

As well as the distribution of insecticide-impregnated bed nets, control has focused on community-based diagnosis and treatment, through the mobilisation of large numbers of community health workers. In areas of Myanmar, this approach has had a dramatic impact, reducing infection levels to near zero within five years.[9] An additional strategy is carrying out targeted mass drug administration in malaria hotspots, which has also been shown to be highly effective.[10]

WHO guidance on malaria control outlines different approaches depending on transmission levels. In areas of high transmission, for example, passive case detection is recommended, as the numbers of cases are relatively high. In areas of low transmission, active case detection is encouraged, based on a '1–3–7' approach – notification of case on day 1, case investigation by day 3, and investigation and response by day 7.

However, recent studies have raised questions about these approaches. For example, the lack of active case detection means that many asymptomatic cases are missed, even though they can be a source of new infections. Furthermore, the rapid reduction of malaria cases in Myanmar9 was achieved through the work of community health workers rather than by using the 1–3–7 approach. Active case detection was also found to provide no additional benefit in low-transmission areas. By contrast, in high-transmission areas, active case detection has been found to improve the identification of malaria cases.

The 1–3–7 approach has been highlighted as central to the successful control of malaria in China. However, participants suggested that there was little published evidence to back this up. Furthermore, the highest prevalence of malaria is now typically found in mountainous, forested and inaccessible areas, with little infrastructure and limited access to mobile phones, making the 1–3–7 approach hard to implement.

It was suggested that control strategies may therefore need to be revisited. In high-transmission areas, it may be necessary to build on passive case detection to accelerate malaria control. There is good evidence on the effectiveness of **mass drug administration**,[11] but it is seldom used by national malaria control programmes. **Mass screening and treatment** ('test and treat') has also been proposed as an alternative to mass drug administration, but there is limited evidence of its effectiveness.

Discussions also identified the need for **high-sensitivity rapid diagnostics** in areas of low transmission when it becomes increasingly important to identify all cases of malaria. A growing shortage of skilled microscopists was also noted. The use of machine learning technologies may facilitate automated analysis of blood films by trained artificial intelligence (AI) systems.[12]

9. McLean ARD, *et al.* (2018). *Malaria elimination in remote communities requires integration of malaria control activities into general health care: an observational study and interrupted time series analysis in Myanmar.* BMC Med **16(1)**:183. doi: 10.1186/s12916-018-1172-x.

10. Landier J, *et al.* (2018). *Effect of generalised access to early diagnosis and treatment and targeted mass drug administration on Plasmodium falciparum malaria in Eastern Myanmar: an observational study of a regional elimination programme.* Lancet **391(10133)**:1916-1926. doi: 10.1016/S0140-6736(18)30792-X

11. von Seidlein L, *et al.* (2019). *The impact of targeted malaria elimination with mass drug administrations on falciparum malaria in Southeast Asia: A cluster randomised trial.* PLoS Med **16(2)**:e1002745. doi: 10.1371/journal.pmed.1002745.

12. Poostchi M, *et al.* (2018). *Image analysis and machine learning for detecting malaria.* Transl Res **194**:36-55. doi: 10.1016/j.trsl.2017.12.004.

Communities

As the prevalence of malaria continues to fall, the attitudes and behaviours of communities are critical to elimination efforts. With malaria becoming less common, memories of its impact may begin to fade. Even so, it is essential that populations remain supportive of elimination in general and of specific control measures, such as mass drug administration and test-and-treat campaigns, which also impact on those without symptoms of malaria.13 Adherence to malaria medication is also vital to reduce the risk of resistance.

National malaria control programmes also face the challenge of accessing hard-to-reach populations, often in remote and inaccessible locations. It was also suggested that some populations, such as migrants, may be reluctant to engage with public health systems.

Integration of health services

A further important consideration is the long-term sustainability of malaria elimination activities. To date, these have typically been organised as standalone ('vertical') programmes. Community health workers, for example, initially dealt only with the diagnosis and care of malaria. With malaria rare, community health workers focused solely on malaria do not meet communities' most important needs, leading to loss of confidence and a reduced use of malaria diagnostic testing.

Conversely, equipping community health workers with the ability to deliver a basic package of healthcare services has been found to increase the use of malaria testing. More integrated approaches therefore offer the prospect of more effective, people-centred and sustainable approaches.

There are also other opportunities for integration. As well as broader service delivery, integrated approaches for infectious disease surveillance and for outbreak detection and response could also be developed. For surveillance, coordination across borders is essential.

13. Pell CL, *et al.* (2019). *Community engagement, social context and coverage of mass anti-malarial administration: Comparative findings from multi-site research in the Greater Mekong sub-Region.* PLoS One **14(3)**:e0214280. doi: 10.1371/journal.pone.0214280.

Research gaps and programmatic innovation

Breakout groups and discussion sessions identified a range of priority areas for research and programmatic innovation. In several of these areas, such as new drug development and genomic surveillance, extensive research efforts are already underway and were recognised as critical. As well as these activities, participants also identified a range of areas where future research efforts could be targeted.

Genetic markers of resistance: New mutations that reduce susceptibility to antimalarial drugs will continue to arise. It is important to identify new mutations and to determine their contributions to resistance and treatment failure, as well as to identify appropriate markers for resistance to currently used drugs, such as lumefantrine, which are currently lacking.

Drug development includes laboratory stages designed to probe the potential for resistance development in laboratory strains of parasites. It was argued that clinical studies should also include screens for mutations conferring reduced sensitivity to new drugs, to identify those that are not generated in laboratory settings.

The 'final mile': Participants recognised that the final push towards elimination requires specific malaria control strategies, often in difficult environmental settings. It was suggested that questions surround the appropriateness of current recommendations, including the 1–3–7 approach, and that further research is needed on elimination-stage malaria control activities to inform global, regional and national policymaking.

Integration: With malaria levels now low in most areas, the appropriateness and sustainability of vertical approaches is open to question; although the infrastructure developed for malaria control provides a foundation for the integration of health services, helping to strengthen primary healthcare systems and advance universal health coverage. Research has the potential to identify and evaluate integrated models of service delivery, and to support the implementation of evidence-based approaches.

Cost-effectiveness: National decision-making on antimalarial drug use necessarily involves a financial dimension. With the need to consider the protection of drugs to preserve their long-term efficacy, and with new drug choices on the horizon, decision-making is increasingly complex. There is an important role for research in developing health economic analyses and models that consider a wide range of factors, including the protection of drug efficacy.

Community engagement: Public support for malaria elimination and for control measures is essential, even as the experience of malaria declines and other health issues come to be seen as higher priorities. Participants identified a need for close engagement with communities to maintain awareness of malaria as a health threat, and to mobilise support for and to gather input into the design of control activities.

Communication and coordination: It was argued that close collaboration between key stakeholders, including the research community, national malaria control programmes, regional stakeholders such as WHO and communities was needed to ensure more rapid progress. Timely sharing of information, allowing the integration of multiple sources of data (such as molecular, clinical and epidemiological data), could facilitate additional analyses and provide new insights to inform control efforts and limit the spread of drug resistance. Such collaboration was felt to depend on open communication and the development of trust.

Conclusions

The Greater Mekong Subregion has made enormous progress towards malaria elimination over the past decade. That progress is now threatened by rising levels of resistance to ACTs, the mainstay of malaria treatment. With new drugs still some way off, it is essential that the focus on malaria elimination remains, even as the malaria disease burdens fall and other health priorities, including COVID-19, capture political and public health attention. With the possibility that global funders prioritise other regions, it is essential that the region and individual countries maintain momentum towards elimination and eradication, through effective and sustainable control programmes.

Resistance is an inevitability of antimalarial drug use. New tools are providing detailed insight into the evolution and spread of resistance, and close links with policymaking are ensuring that this new intelligence shapes responses on the ground. Maintaining and strengthening these links, and ensuring close collaboration and open sharing of samples and data across national borders, will be essential to consolidate and extend current gains and to reduce the risk of resurgence of drug-resistant malaria in the region.

ACTs have saved hundreds of thousands of lives. Their importance has been recognised in the award of a Nobel Prize. Yet there is a real risk that their effectiveness will be compromised – with potentially devastating consequences. Urgent action is needed across multiple domains to prevent an epidemic of drug-resistant malaria that could undo years of progress in Southeast Asia and threaten the health of millions globally.

Box: Target identification

Malaria drug development has traditionally relied on the screening of compound libraries to identify those with activity against malaria parasites. An alternative approach is to identify genes that are essential to parasite survival and which represent targets for the development of new drugs.

Such approaches are facilitated by the increasing ability to manipulate the Plasmodium genome. This allows genes of interest to be 'silenced' and the impact on different aspects of parasite biology to be determined.

For example, glmS riboswitch technology enables a specific DNA fragment to be inserted at the end of a gene of interest. When transcribed into RNA, this fragment adopts a distinct three-dimensional structure which, in the presence of a simple activator molecule (glucosamine), becomes a catalytic enzyme that degrades its associated messenger RNA, leading to loss of gene function.[14]

In proof-of-principle studies, this approach was used to confirm the detrimental impact of the loss of dihydrofolate reductase, a known target of antimalarial drugs.[15]

One use of the technology is to test possible mechanisms of action of antimalarial drugs discovered by phenotypic screening. If a drug has no additional impact on parasite viability when a gene is silenced, that gene can be assumed to be the target of the drug. Such an approach has been used on MMV compound libraries.[16]

The technology can also be used to validate new targets. Silencing of the deoxyhypusine synthase gene, for example, suggested as a possible target for new drug development, led to markedly reduced parasite growth.[17]

The new approach has been widely adopted globally. It has been used to shed light on the functions of dozens of potential new Plasmodium targets, and has illuminated the mechanisms of action of several candidate antimalarials.

14. Shaw PJ & Aroonsri A (2017). *Tools for attenuation of gene expression in malaria parasites.* Int J Parasitol **47(7)**:385-398. doi: 10.1016/j.ijpara.2016.11.006.

15. Prommana P, *et al.* (2013). *Inducible knockdown of Plasmodium gene expression using the glmS ribozyme.* PLoS One **8(8)**:e73783. doi: 10.1371/journal.pone.0073783.

16. Aroonsri A, *et al.* (2016). *Identifying antimalarial compounds targeting dihydrofolate reductase-thymidylate synthase (DHFR-TS) by chemogenomic profiling.* Int J Parasitol **46(8)**:527-35. doi: 10.1016/j.ijpara.2016.04.002.

17. Aroonsri A, *et al.* (2019). *Validation of Plasmodium falciparum deoxyhypusine synthase as an antimalarial target.* Peer J **7**:e6713. doi: 10.7717/peerj.6713.

Box: Vivax malaria

Globally, most cases of malaria are caused by *Plasmodium falciparum*. However, at least four species of *Plasmodium* infect humans, and as the number of cases of falciparum malaria has declined in Southeast Asia so the proportion of disease attributable to *P. vivax* has increased. *P. vivax* now accounts for more than 90% of cases of malaria in the region.

Although similar in many respects to falciparum malaria, vivax malaria has its own distinctive features, including a high rate of relapse. This reflects a vivax-specific stage of the life cycle in the liver, when the parasite lies dormant, periodically reactivating and causing disease. Unfortunately, this liver stage is not sensitive to ACTs.

The mainstay of vivax treatment is primaquine. However, resistance is a growing problem and treatments are also potentially harmful for patients with a relatively common inherited condition, glucose-6-phosphate dehydrogenase (G6PD) deficiency. A new drug, tafenoquine,[18] was approved by the US Food and Drug Administration (FDA) in 2018 and provides a highly effective single-dose cure, but is also unsuitable for people with G6PD deficiency. Other drugs in development, such as bulaquine, do not have such a drawback.

For a variety of reasons, the elimination of vivax malaria will be more challenging. While global attention has focused primarily on falciparum malaria, control efforts have also contributed to a significant decline in the vivax malaria disease burden.[19] Tafenoquine may provide a major step forwards towards vivax malaria elimination, but at some point, a concerted effort towards vivax elimination may also become necessary.

Box: COVID-19 and malaria control

Countries in Southeast Asia have been among the most successful at preventing the spread of COVID-19. Rapid initial responses to the pandemic and effective test, trace and isolate systems have prevented widespread community transmission in most countries.

Nevertheless, managing the impact of COVID-19 has absorbed political and public health resources. In many settings, the pandemic has both disrupted the delivery of health services and influenced healthcare-seeking behaviour, which is likely to have longer-term health consequences. WHO has published guidance on maintaining services during the pandemic, and there is no evidence yet that the pandemic is affecting the incidence of malaria infections.

While continued vigilance is needed to ensure that malaria control is not neglected during the pandemic, the response may provide an opportunity to consider how COVID-19 and malaria-related activities could be coordinated at the community level.

18. Llanos-Cuentas A, *et al.* (2019). *Tafenoquine versus Primaquine to Prevent Relapse of Plasmodium vivax Malaria.* N Engl J Med **380(3)**:229-241. doi: 10.1056/NEJMoa1802537.

19. Battle KE, *et al.* (2019). *Mapping the global endemicity and clinical burden of Plasmodium vivax, 2000-17: a spatial and temporal modelling study.* Lancet **394(10195)**:332-343. doi: 10.1016/S0140-6736(19)31096-7.

Annex 1: Participants list

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