The challenges of malaria elimination in the Asia–Pacific region

In the Asia–Pacific region, more than 2 billion people are at risk of malaria. The epidemiology of malaria is highly heterogeneous, with *Plasmodium falciparum*, *Plasmodium vivax* and zoonotic *Plasmodium knowlesi* infections being co-endemic and transmitted by 19 major vector species, and focused in hard-to-reach areas and populations.[1] In response to emerging multidrug-resistant malaria in the Greater Mekong Subregion, the World Health Organization (WHO) has prioritised malaria elimination in the Asia–Pacific region by 2030.[1] The Asia Pacific Leaders Malaria Alliance (APLMA) is a coalition of 22 governments in the Asia–Pacific region, including Australia, committed to eliminating malaria by 2030.[2] Australia has made substantial financial and technical contributions to APLMA and its implementing partner, the Asia Pacific Malaria Elimination Network (APMEN), recognising that investment in malaria research is one of the "best buys" in global health security.[2] Malaria elimination will save millions of lives over a generation and deliver regional economic benefits worth billions of dollars, as well as strengthening Australia's biosecurity. Important global investments have been made over the past two decades (around US$60 billion), resulting in significant reductions in malaria cases (a 76% and 48% reduction in WHO Southeast Asia and Western Pacific regions, respectively, to 3.0 and 2.4 malaria cases per 1000 population at risk).[1] Despite these investments, only Sri Lanka and China in the Asia–Pacific region have achieved this goal, with Timor-Leste in the pre-certification phase. Other countries are progressing towards malaria elimination goals. Malaysia has eliminated human malaria parasite species,[1] and Vietnam, Lao People's Democratic Republic and Cambodia had only 316, 785 and 1382 respective locally transmitted (indigenous) cases (mainly *P. vivax*) in 2023.[3] Since 2015, progress in reducing the malaria burden in the Asia–Pacific region has been highly variable within and across countries and *Plasmodium* spp, and recently it has stalled, and even reversed, in many countries, including Papua New Guinea, Myanmar and Pakistan.[1] The reasons behind the slowing progress are multifactorial, but, in recent times, the coronavirus disease 2019 (COVID-19) pandemic, climate change and armed conflict have interrupted health services, affected people migration and movements, and increased malaria transmission risk. Moreover, there are emerging threats in our ability to track, prevent and treat malaria, which impedes progress towards APLMA's 2021 roadmap to malaria elimination.[2]

Challenges in tracking transmission: a lack of sensitive tools to detect malaria

Residual parasite reservoirs need to be detected and eliminated to prevent ongoing transmission. However, the cornerstone of malaria diagnosis, which are rapid diagnostic tests (RDTs) and light microscopy, have suboptimal sensitivity to detect low density asymptomatic infections, which prevail in the Asia–Pacific region.[4] Furthermore, RDTs are beginning to fail due to deletions in the *P. falciparum* target antigen gene (*hrp2/3*), particularly in Africa, but *hrp2/3* deletions have been recently detected in Asia albeit at lower frequencies.[5] In addition, RDTs (nor any other tool) cannot detect hypnozoites, which are a dormant asymptomatic liver stage formed by *P. vivax* that can reactivate weeks to years after the initial infection. Nor do RDTs specifically detect monkey malaria, an emerging zoonotic infection caused by *P. knowlesi*, transmitted from macaques to humans via mosquitoes — current RDTs are insensitive and cannot differentiate between *P. knowlesi* and *P. vivax*. These infections present significant issues for countries such as Malaysia, which has successfully eliminated all human malaria but still harbours zoonotic monkey malaria.[1] RDTs also cannot discriminate between imported or indigenous cases, which can be done with genomics. New highly sensitive tools that can detect and track the diversity of *Plasmodium* spp (and *Anopheles* spp, which transmit them), low density or asymptomatic infections, or *P. vivax* dormant liver stage infections are urgently required.

Detection of malaria by molecular methods such as polymerase chain reaction and loop-mediated isothermal amplification is possible in most Asian–Pacific countries. However, any available facilities tend to be centralised, and, as such, are unable to provide timely diagnosis, but can provide useful data for surveillance and research. Therefore, malaria programs will continue to rely on conventional RDTs and light microscopy where available. Various next-generation RDTs with improved sensitivity and specificity are currently under development and evaluation for WHO pre-qualification status.[6] These next-generation RDTs include detection of parasites with *hrp* deletions as well as *P. knowlesi*, but do not include RDTs for the detection of hypnozoites. If proven to be effective and cost-effective, future procurement of next-generation RDTs would replace conventional RDTs, which in the Asia–Pacific region are primarily performed by front-line malaria providers, such as community health workers, who can access hard-to-reach areas and populations. However, with the recent decline of malaria transmission in some areas in the Asia–Pacific, RDTs administered in the community are often negative and the role and motivation of community workers as well as their malaria annual blood examination rates have also declined. Therefore, it has been proposed to expand the role of community health workers to deliver primary health care services for other common diseases in the community to increase motivation and malaria testing rates in order to detect and eliminate

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all malaria infections and achieve malaria elimination certification by the WHO.[7]

Current malaria prevention tools are not fit-for-purpose

The tools currently available to prevent malaria transmission in our region are also not fit-for-purpose, relying on long-lasting insecticide-treated bed nets and indoor spraying of residual insecticides. Long-lasting insecticide-treated bed nets have been the cornerstone of vector control globally and are attributed to the large reduction in the malaria case burden in Africa. However, these bed nets and indoor residual spraying have limited efficacy against the prevalent mosquito vectors in the Asia–Pacific region because a high proportion of mosquitoes in the area bite outdoors and early in the evening, when people are not protected by nets, and are insufficient for reducing malaria transmission in mobile migrant populations.[8,9] Their effectiveness is further eroded by the substandard bio-efficacy of nets and emerging insecticide resistance.[10,11] Improved insecticide formulations and evidence for complementary strategies (such as spatial repellent emanation devices, as well as personal repellent and longer-lasting insecticide-treated hammocks) tailored to at-risk populations are required to further reduce transmission.

The WHO currently recommends mass drug administration for the interruption of transmission of *P. falciparum* malaria in areas approaching elimination.[12] Mass drug administration is predicted to be highly effective in isolated, population movement-controlled areas where regular health services for malaria are maintained.[13] However, although providing mass drug administration in low transmission areas at the village level, as well as targeting high risk populations with intermittent preventive treatment, can significantly reduce both *P. falciparum* and *P. vivax* infections, the longer term impacts of mass drug administration on infection rates remain unclear.[14,15] Including hypnozoidal drugs, such as primaquine or tafenoquine, in mass drug administration without glucose-6-phosphate dehydrogenase (G6PD) testing is not widely supported due to the risks of drug-induced severe haemolysis in individuals with G6PD enzyme deficiency, an inherited enzymopathy present in 1–30% of individuals. Recently, patented serological tools, which can detect more than 80% of hypnozoite carriers in different populations, have been developed, which will enable diagnosis of hypnozoite infection.[16] Seropositive individuals could then be targeted with efficacious drugs to eliminate hypnozoites. However, it is not yet known how effective serological testing and treating is for reducing *P. vivax* transmission.

In 2021, the WHO recommended implementation of a malaria vaccine in high risk African children,[17] but no vaccine has been endorsed for the Asia–Pacific region. However, RTS,S/AS01 and R21/Matrix-M vaccines only have moderate longer term efficacy in Africa and are only effective against *P. falciparum*.[17] Vaccines with higher efficacy or different indications, including vaccines for *P. vivax*, are in clinical trials. All malaria vaccines evaluated in clinical trials to date have shown strain-specific protection, and parasites expressing polymorphic variants can mediate vaccine escape, which is concerning given the diversity in genetic variants for candidate vaccine antigens circulating globally.[18] These challenges need to be addressed to achieve maximum impact of vaccines in the Asia–Pacific region.

Drug resistance and toxicity challenges the treatment of malaria

Artemisinin-based combination therapies (ACTs) are the current first line treatment for *P. falciparum* infection and hundreds of millions of ACTs are administered annually. ACTs involve co-administering a fast-acting and highly potent artemisinin-derivative with a longer-acting partner drug. The efficacy of ACTs is increasingly compromised by artemisinin resistance, which was first reported in Cambodia in 2008 and is now widespread throughout Southeast Asia, and emerging in Papua New Guinea and some African countries, as is resistance to the partner drugs.[19-21] The emergence and spread of artemisinin resistance undermines current treatment strategies and novel regimens, such as triple ACT, and combinations of current and new therapeutic agents are needed urgently.[22,23]

The treatment of *P. vivax* infection is complicated by dormant hypnozoites. Treatment requires a combination of drugs that kill both the blood and dormant liver stages (known as radical cure), but hypnozoidal drugs (primaquine and tafenoquine) can cause severe drug-induced haemolysis in G6PD-deficient individuals. Primaquine, the most widely used drug, is recommended as a low dose regimen (total dose of 3.5 mg/kg)[24], which has suboptimal efficacy[25] and has poor adherence when given over 14 days.[26] A large multinational trial and further individual patient data meta-analyses have confirmed the improved efficacy with higher dose regimens as well as limited safety concerns.[25,27,28] The current WHO malaria guidelines highlight the need for evidence on the implementation of a high dose seven-day primaquine regimen to guide the public health impact and cost-effectiveness of radical cure.[29] In areas co-endemic for falciparum and vivax malaria, there is a high risk of *P. vivax* recurrences in patients treated for *P. falciparum* infection.[30] Prospective data from a cluster randomised trial[31] and an individually randomised multicentre study[32] demonstrated significant reductions of *P. vivax* recurrences when patients presenting with *P. falciparum* malaria were treated with radical cure (universal radical cure). The acceptability and cost-effectiveness of universal radical cure for areas with varying prevalence of *P. falciparum* and *P. vivax* are needed to comprehensively evaluate the impact of this treatment policy.

Conclusions

Overall, the Asia–Pacific region is progressing towards malaria elimination, but there are significant

roadblocks to overcome, which we summarised in this perspective article. To accelerate towards malaria elimination by 2030, innovative new tools and strategies to map, prevent, test and treat the disease must be developed, evaluated and rapidly deployed. These new strategies must be effective, safe, affordable, accessible and well monitored, and must fit into existing local health care, national planning and procurement systems. With political commitment from stakeholders, national and regional collaboration, evidence generation from researchers, and effective community engagement, malaria elimination in the Asia–Pacific region is both realistic and achievable.

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