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Ending Malaria Transmission in the Asia Pacific Malaria Elimination Network (APMEN) Countries: Challenges and the Way Forward

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Abstract

Member countries in the Asia Pacific Malaria Elimination Network (APMEN) are pursuing the global goal of malaria elimination by 2030. Different countries are in various phases of malaria elimination and this review aims to present a compilation of available evidence on the challenges and way forward for malaria elimination in APMEN countries. Malaria transmission in these States is complex. APMEN member countries include the largest populations living in areas of malaria transmission risk outside Africa. They are a global source for spread of artemisinin-based combination therapy (ACT) resistance, include the biggest burden of *Plasmodium vivax* and zoonotic malaria, and face many geopolitical and socio-economic factors that will challenge malaria elimination efforts. These challenges can be addressed in part through operational research to identify country-specific solutions, making better use of operational data such as through spatial decision support system (SDSS) approaches, strengthening surveillance, and cross-border initiative for coordinated action.

Keywords: *Plasmodium falciparum*, *P. vivax*, drug-resistance, malaria elimination, APMEN, challenges

1. Background

Malaria imposes great health and socio-economic burden on humanity, with an estimated 3.2 billion people at risk of being infected with malaria [1]. In 2016, there were approximately 216 million cases with 445,000 deaths, most of which were in children aged under 5 years in Africa [2, 3]. However, substantial progress has been made in fighting malaria, with global



Figure 1. Member countries of the Asia Pacific Malaria Elimination Network countries (APMEN).

incidence reducing by 41% and mortality rates by 62% between 2000 and 2015 [1]. In 2016, malaria remained endemic in 91 countries and territories as compared to 108 in 2000 [2]. It is estimated that most (90%) of total malaria cases were in the World Health Organisation (WHO) African Region, followed by the South-East Asian Region (SEAR) (7%) and the Eastern Mediterranean Region (2%) [4]. A number of factors have been attributed for this reduction, including wide-scale deployment of malaria control interventions, economic development in endemic countries, urbanisation, and unprecedented financial support for malaria control interventions [5–8]. In 2016, an estimated US\$ 2.7 billion was invested in malaria control and elimination efforts globally by governments of malaria endemic countries and international partners [1, 9].

Recognising the need to hasten progress in reducing the burden of malaria, WHO developed the *Global Technical Strategy for Malaria 2016–2030* (GTS) [5], which sets out a vision for accelerating progress towards malaria elimination. The WHO strategy is complemented by the Roll Back Malaria advocacy plan, *Action and Investment to Defeat Malaria 2016–2030* (AIM) [10]. GTS and AIM set an ambitious global target of eliminating malaria in at least 21 countries by 2020, identified as E-2020 countries by WHO and 35 countries by 2030 [1, 2, 10].

In line with the global efforts to eliminate malaria, the Asia Pacific Malaria Elimination Network (APMEN) was established in 2009, initially including 10 countries (Bhutan, China,

| No. of cases/year | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
|-------------------|------------|------------|------------|------------|------------|------------|------------|
| Country | | | | | | | |
| Bangladesh | 79,300 | 69,700 | 13,750 | 5000 | 12,990 | 8000 | 6000 |
| Bhutan | 400 | 190 | ≤100 | ≤100 | ≤100 | ≤100 | ≤100 |
| Cambodia | 175,000 | 203,600 | 146,000 | 76,500 | 89,700 | 120,300 | 83,300 |
| China | 5000 | 3000 | 240 | ≤100 | ≤100 | ≤100 | ≤10 |
| DPR Korea | 13,520 | 16,760 | 21,850 | 14,410 | 10,540 | 800 | 2700 |
| India | 21,090,000 | 17,930,000 | 14,640,000 | 11,540,000 | 11,850,000 | 12,670,000 | 13,170,000 |
| Indonesia | 2,715,000 | 2,469,000 | 2,453,000 | 2,017,000 | 1,479,000 | 1,274,000 | 1,281,000 |
| Lao PDR | 51,000 | 42,800 | 112,700 | 93,500 | 117,300 | 87,900 | 27,390 |
| Malaysia | 5000 | 4000 | 4000 | 2900 | 3100 | 240 | 270 |
| Nepal | 43,400 | 32,700 | 20,520 | 16,230 | 8000 | 7000 | 4000 |
| Philippines | 53,200 | 25,970 | 18,630 | 16,290 | 12,210 | 20,580 | 16,630 |
| PNG* | 1,342,000 | 1,130,000 | 1,452,000 | 1,617,000 | 1,260,000 | 1,014,000 | 1,407,000 |
| Republic of Korea | 1300 | 500 | 400 | 400 | 600 | 600 | 600 |
| Solomon Islands | 95,900 | 66,200 | 55,000 | 56,400 | 30,780 | 39,400 | 86,000 |
| Sri Lanka | — | — | — | — | — | — | — |
| Thailand | 32,500 | 24,900 | 32,600 | 33,300 | 37,900 | 8000 | 11,520 |
| Vanuatu | 13,780 | 10,000 | 7000 | 5000 | 1900 | 600 | 4000 |
| Vietnam | 25,460 | 22,630 | 26,610 | 23,140 | 21,200 | 12,560 | 6000 |

Source: World malaria report 2017 (WHO [1, 16])*PNG, Papua New Guinea.

Table 1. Malaria transmission trends in the Asia Pacific Malaria Elimination Network (APMEN) countries based on the estimated malaria cases during 2010–2016.

Democratic People's Republic of Korea (DPR Korea), Indonesia, Malaysia, the Philippines, Republic of Korea, Solomon Islands, Sri Lanka, and Vanuatu) that now have expanded to 18 countries (adding Bangladesh, Cambodia, Lao People's Democratic Republic (Lao PDR), India, Nepal, Papua New Guinea, Thailand, and Vietnam) [11] (**Figure 1**). APMEN countries encompass the largest malaria reporting area outside the African region. APMEN serves the country partners and together with regional partners from the academic, development, non-governmental and private sectors, and global agencies including the WHO, collaboratively address the unique challenges of malaria elimination in the region through leadership, advocacy, capacity building, knowledge exchange and building evidence to support more effective, sustained malaria elimination programmes across the region [12].

Each member State has defined elimination goals based on malaria transmission trends (**Table 1**). Countries with low incidence of malaria are targeting elimination at the national level, while countries with higher incidence are planning to eliminate malaria at the sub-national level before pursuing elimination at the national level. However, all countries are committed to eliminating malaria in the Asia Pacific region by 2030 [13]. Sri Lanka eliminated malaria in 2012 and WHO certified Sri Lanka malaria free nation in 2016 [14]. Bhutan and the Republic of Korea have targeted to eliminate malaria in 2018 and 2019 respectively [15, 16]. Bangladesh, China, Malaysia, Philippines, and Vanuatu plan to eliminate malaria by 2020; DPR Korea, Cambodia, Lao People's Demographic Republic (Lao PDR), and Papua New Guinea (PNG) are planning to eliminate by 2025, and Nepal by 2026; finally India, Indonesia, Thailand, and Vietnam plan to eliminate malaria by 2030 [15]. The success of malaria elimination in APMEN States will greatly enhance the global drive towards malaria elimination. Therefore, the aim of this review is to present a compilation of available evidence on the challenges and way forward for malaria elimination in APMEN countries.

2. Epidemiological drivers of malaria in APMEN countries

Malaria elimination in APMEN countries faces many challenges. The challenges include large numbers of people living in malaria risk areas; presence of all forms of human malaria: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*; the high incidence of *P. vivax* malaria, which is particularly difficult to control due to the dormant stages of its life cycle within the human host, and zoonotic malaria caused by *P. knowlesi*, which has animal reservoirs; anti-malarial drug resistance in *P. falciparum* and *P. vivax* parasites; diverse vectors with different feeding behaviour and insecticide resistance; forest malaria; human migration across porous international borders and cross-border malaria; and inadequacies in health systems in the region.

2.1. *Plasmodium vivax* Malaria

Plasmodium vivax is an important but relatively neglected malaria parasite globally [17]. This form of malaria is more widespread than *P. falciparum* malaria with 2.9 billion people at risk of infection, of which 90% live in the Asia Pacific region [18–22]. *P. vivax* is more difficult to treat than *P. falciparum* due to dormant liver stages (hypnozoites) [23–25], and the development of transmissible blood stages (gametocytes) before clinical symptoms [26]. These characteristics enable the parasite to adapt to environmental challenges and evade control interventions in place and time.

In many countries embarking on malaria elimination, *P. falciparum* incidence declines more rapidly than *P. vivax* incidence, due to the greater effectiveness of interventions for the former. Treating all stages of the parasite (radical cure) is a critical strategy for the successful control and ultimate elimination of *P. vivax*. In order to achieve radical cure of *P. vivax*, blood stage parasites, as well as the hypnozoites, need to be cleared. The only current widely available drug against hypnozoites is the 8-aminoquinoline compound, primaquine [27]. Unfortunately, individuals who have a genetic deficiency for glucose-6-phosphate dehydrogenase (G6PD) enzyme are at risk of severe haemolysis when treated with the drug [28–30]. In addition, primaquine requires prolonged daily administration over seven to 14 days. The complexities of prescribing reliable, safe and effective radical cure of *P. vivax* highlights the urgent need for innovative new approaches to assure schizonticidal and hypnozoiticidal treatment; without which, *P. vivax* elimination is unlikely in most settings.

2.2. Zoonotic malaria

Plasmodium knowlesi infections have been reported in a number of Asian Pacific countries [31–34]. This zoonotic species of malaria, which also infects macaque monkeys that form the main animal reservoir, was probably present in humans but was undiagnosed until molecular detection methods were developed that could distinguish *P. knowlesi* from the morphologically similar human malaria parasite *Plasmodium malariae* [35, 36]. Recently, the first case of human infection with *Plasmodium cynomolgi* was reported in Peninsular Malaysia that resembles *P. vivax* morphologically [37]. The role of animal reservoirs of malaria transmissible to humans is an almost wholly neglected question in the elimination agenda in the Asia-Pacific region [38].

2.3. Characteristics of populations at risk

Nearly 2.1 billion people in the Asia-Pacific region live in areas where there is risk of malaria transmission of which 16.8% live in high-risk areas [2, 39] (**Figure 2**). These high-risk areas include settlements located in remote parts of endemic countries including border areas. Many of these high-risk areas are characterised by forest and forest fringe environment with high malaria transmission, poor geographical accessibility, high population mobility, and low human density. In addition, most of these areas are inhabited by ethnic minorities, refugees and displaced people who are difficult to access and often experience high degree of poverty [40, 41]. Furthermore, these areas are frequented by people engaged in activities with increased risk of malaria exposure, such as tourism and pilgrimages, forest-related work such as logging, gem-mining, latex harvesting, fishing, road construction and other industrial occupations [41–45].

2.4. Antimalarial drug-resistance

Historically, countries in the Mekong Region including Cambodia and Thailand are global epicentres of emerging antimalarial drug resistance [46]. Chloroquine resistance was first reported in this area in the 1970s, followed by resistance to other anti-malarial drugs [47]. Over the past decade, artemisinin-based combination therapy (ACT) became the first-line protocol for the management of *P. falciparum* infections world over. However, parasites that

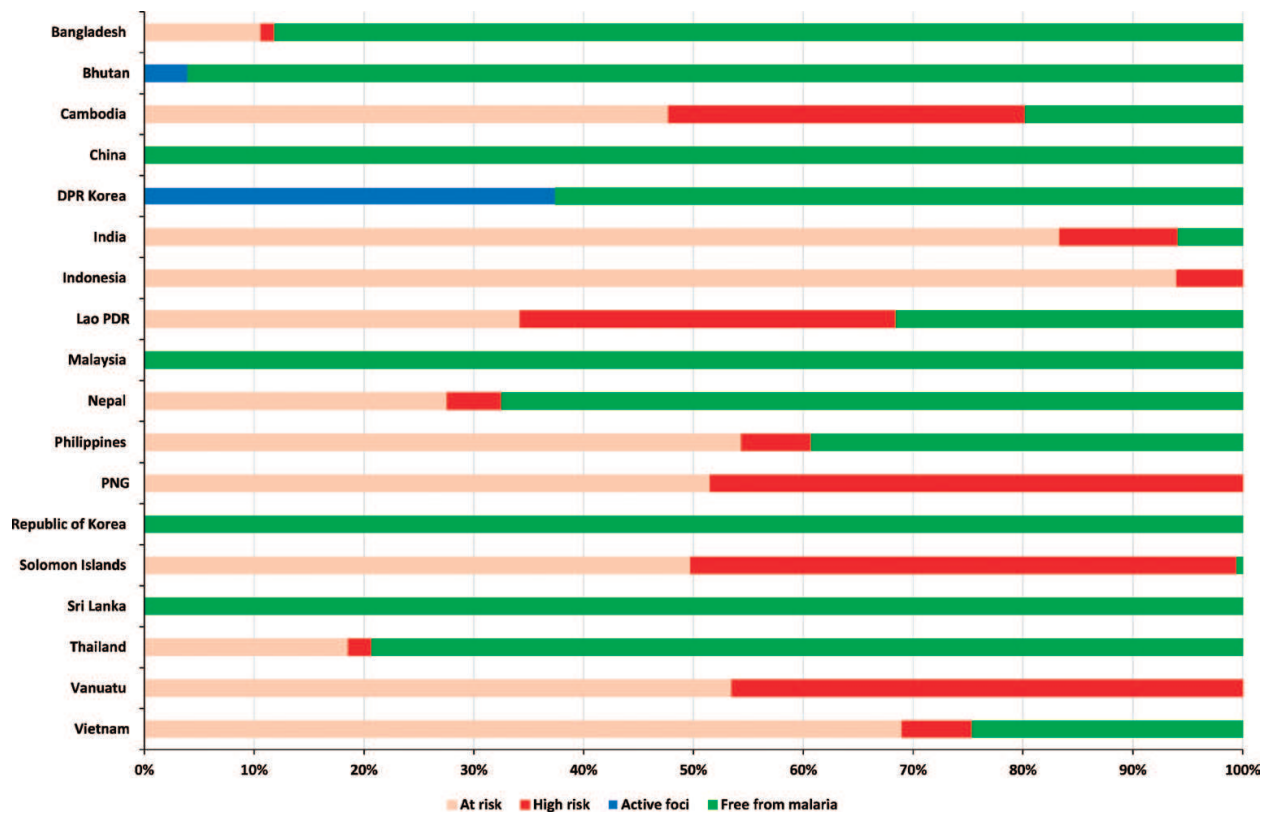


Figure 2. Population at risk of malaria in Asia Pacific Malaria Elimination Network (APMEN) countries for data based on 2016. (at risk- low risk + high risk). Source: World malaria report 2017 [1].

are drug-resistant to artemisinin and its derivatives have recently emerged in various parts of Southeast Asia challenging all control strategies for treatment and elimination efforts [48–51]. Presently, resistance to mefloquine continues to be a concern in Thailand and Cambodia, where artesunate-mefloquine is used as first line treatment [47]. Artemether-lumefantrine remains highly effective in most parts of the world, with the exception of Cambodia [52, 53]. There are evidences of resistance to ACT in Vietnam [2, 54]. In India, ACT is used universally across the country yet declining efficacy to artesunate plus sulphadoxine-pyrimethamine has already been reported in its northeastern region [55–57] however, there have been no reports of ACT resistance in other APMEN member States (**Figure 3**).

Chloroquine has remained the main choice of treatment for *P. vivax* blood stage infections, however, this policy is under threat from emerging drug resistant *P. vivax* strains [58]. A number of APMEN countries have reported *P. vivax* resistance to chloroquine. There are reports of resistance in some States of India [59–62], central Vietnam [63], and Thai-Myanmar border [64]. However, *P. vivax* is still sensitive to chloroquine in Cambodia [65], border area of Yunnan Province of China and Myanmar [66], central China [67], and Nepal [68, 69].

2.5. Vector control

Vector control remains one of the main preventive strategies of containing malaria transmission in APMEN countries. However, a lack of technical capacity in entomology and vector control represents a key gap in elimination programmes. In addition, the diversity of malaria vectors in the

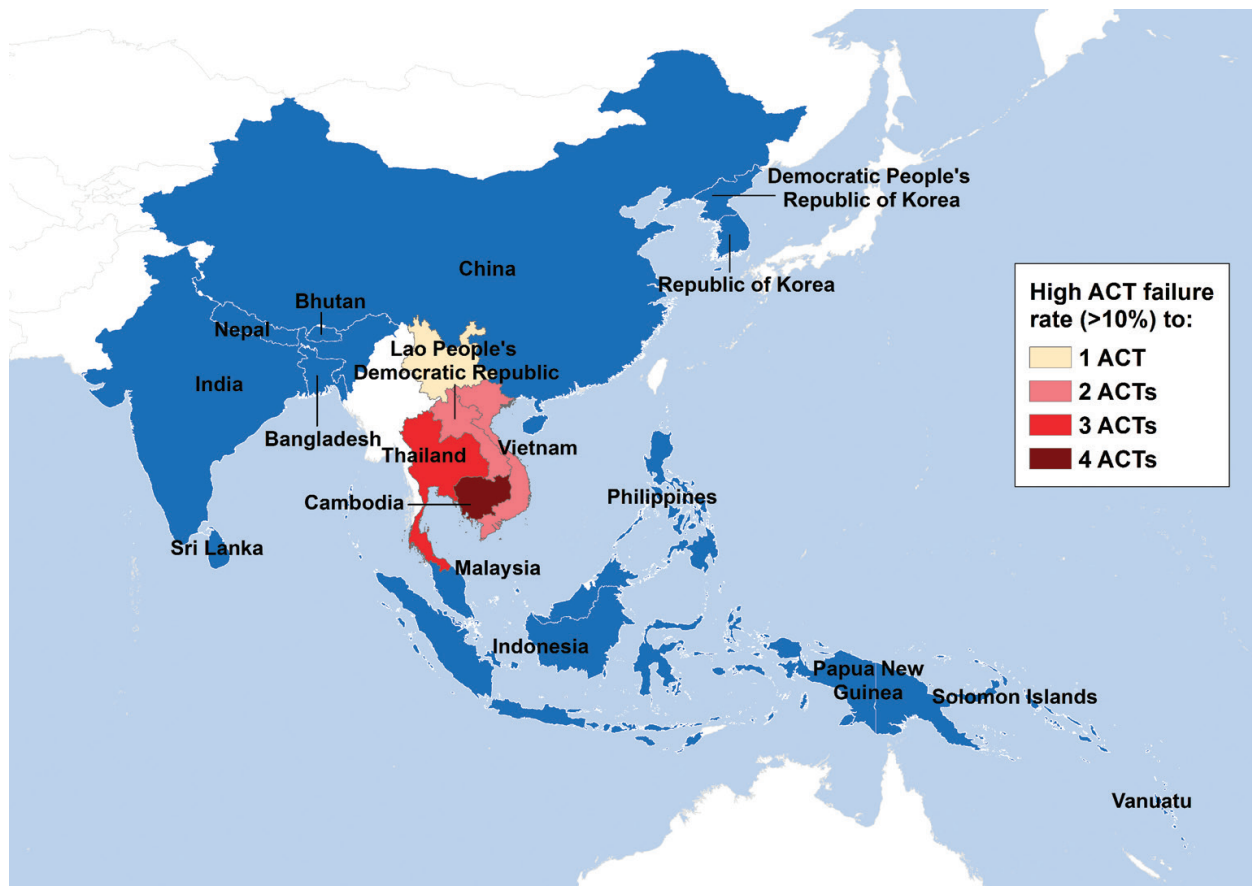


Figure 3. Distribution of malarial multidrug resistance for data based on 2016. ACT- artemisinin-based combination therapy; 1 ACT- resistance to one ACT; 2 ACT- resistance to two ACTs; 3 ACTs- resistance to three ACTs; 4 ACTs- resistance to four ACTs. Source: World malaria report 2017 [1].

Asia-Pacific region (19 different species) poses unique challenges for elimination [70, 71] (**Table 2**). There is considerable variation in biological characteristics of mosquito vectors making control efforts difficult. The commonest malaria vector species in the region, including *Anopheles dirus*, *An. baimaii*, and *An. minimus* [72, 73], are able to avoid indoor sprayed surfaces because of their exophilic and exophagic characteristics [70, 74, 75] rendering most domicile-based interventions, like long-lasting insecticidal nets (LLIN) and indoor residual spraying (IRS), less effective [74, 76]. Other challenges include insecticide resistance [77] and absence of local vector surveillance [78]. To address these challenges, APMEN instituted the APMEN Vector Control Working Group (VcWG) in 2010 [79]. The working group fosters information exchange between vector control experts and national programme managers of APMEN countries to formulate strategies to counter the challenges faced in the region. The Working Group has supported a range of activities to build vector control capacity in the region, including providing training fellowships to vector control officers in priority areas, supporting community efficacy studies of interventions, and consolidating information on vector management practices in the region [78].

2.6. Forest malaria

Forest malaria constitutes bulk of transmission in APMEN countries [42, 43, 80–83]. Many species of *Anopheles* mosquitoes that transmit malaria agents are abundant in natural forests

| Country ^o | Main vectors* |
|-------------------------|---|
| Bangladesh [210] | <i>An. dirus</i> , <i>An. minimus</i> , <i>An. aconitus</i> , <i>An. philippinensis</i> , <i>An. sundaicus</i> , <i>An. barbirostris</i> , <i>An. subpictus</i> , <i>An. culicifacies</i> , <i>An. fluviatilis</i> , <i>An. maculatus</i> |
| Bhutan [210] | <i>An. minimus</i> |
| Cambodia [211] | <i>An. dirus</i> , <i>An. minimus</i> , <i>An. maculatus</i> , <i>An. epiroticus</i> |
| China [73, 212] | <i>An. sinensis</i> , <i>An. lesteri</i> , <i>An. dirus</i> , <i>An. minimus</i> , <i>An. maculatus</i> |
| DPR Korea [210] | <i>An. lesteri</i> , <i>An. sinensis</i> , <i>An. sineroides</i> , <i>An. kleini</i> , <i>An. yatsus hiroensis</i> , <i>An. lindesayi japonicas</i> , <i>An. koreicus</i> |
| India [213] | <i>An. culicifacies</i> , <i>An. baimaii</i> , <i>An. fluviatilis</i> , <i>An. minimus</i> , <i>An. stephensi</i> , <i>An. maculatus</i> , <i>An. sundaicus</i> |
| Indonesia [214] | <i>An. aconitus</i> , <i>An. balabacensis</i> , <i>An. bancrofti</i> , <i>An. barbirostris</i> , <i>An. barbumbrosus</i> , <i>An. farauti</i> , <i>An. flavirostris</i> , <i>An. karwari</i> , <i>An. kochi</i> , <i>An. koliensis</i> , <i>An. leucosphyrus</i> , <i>An. maculatus</i> , <i>An. nigerrimus</i> , <i>An. parangensis</i> , <i>An. punctulatus</i> , <i>An. sinensis</i> , <i>An. subpictus</i> , <i>An. sundaicus</i> , <i>An. tessellatus</i> , <i>An. vagus</i> |
| Lao PDR [211] | <i>An. dirus</i> , <i>An. minimus</i> , <i>An. maculatus</i> , <i>An. jeyporiensis</i> |
| Malaysia [211] | <i>An. balabacensis</i> , <i>An. campestris</i> , <i>An. cracens</i> , <i>An. donaldi</i> , <i>An. flavirostris</i> , <i>An. latens</i> , <i>An. letifer</i> , <i>An. maculatus</i> , <i>An. sundaicus</i> |
| Nepal [210] | <i>An. fluviatilis</i> , <i>An. annularis</i> , <i>An. maculatus</i> |
| Philippines [215] | <i>An. flavirostris</i> , <i>An. balabacensis</i> , <i>An. maculatus</i> , <i>An. litoralis</i> , <i>An. mangyanus</i> |
| PNG [216, 217] | <i>An. farauti</i> , <i>An. koliensis</i> , <i>An. punctulatus</i> , <i>An. bancroftii</i> , <i>An. karwari</i> |
| Republic of Korea [218] | <i>An. kleini</i> , <i>An. pullus</i> , <i>An. belenrae</i> , <i>An. sineroides</i> , <i>An. sinensis</i> , <i>An. lesteri</i> |
| Solomon Islands [217] | <i>An. punctulatus</i> , <i>An. koliensis</i> , <i>An. farauti</i> |
| Sri Lanka [210, 219] | <i>An. culicifacies</i> , <i>An. annularis</i> , <i>An. subpictus</i> , <i>An. tessellatus</i> , <i>An. stephensi</i> |
| Thailand [210] | <i>An. dirus</i> , <i>An. minimus</i> , <i>An. maculatus</i> , <i>An. aconitus</i> , <i>An. epiroticus</i> |
| Vanuatu [217] | <i>An. farauti</i> |
| Vietnam [211] | <i>An. dirus</i> , <i>An. minimus</i> , <i>An. maculatus</i> , <i>An. aconitus</i> , <i>An. jeyporiensis</i> , <i>An. subpictus</i> , <i>An. sinensis</i> , <i>An. pampanai</i> , <i>An. epiroticus</i> |

*An., *Anopheles* names refer either to the group, complex or species when specific identifications have been done.

^oCorresponding references are in brackets.

Table 2. List of the main malaria vectors in the Asia Pacific Malaria Elimination Network (APMEN) countries.

and forested plantations. Both the forests and occurrence of deforestation impact increasing malaria risk and transmission, particularly in border areas. Forested areas provide conducive environment for vector proliferation and survival [84, 85]. Forest vectors usually prefer tree canopy coverage and are known to take shelter in tree holes [86–88]. Forest flora and sugar availability have also been shown to be crucial determinants of vectorial capacity [89]. In addition, leaves falling into larval habitats assure sustainable micro-climatic conditions for larvae of vectors like *An. dirus*, which is a dominant vector in Southeast Asia [90]. Further, there are usually abundant bodies of water including ponds, streams, and rivers in forested areas supporting vector multiplication and survival thereby sustaining malaria transmission

in the region [80, 90–93]. Deforestation increases the risk of malaria through a number of favourable conditions for the *Anopheles* mosquito by creating mosquito-breeding sites in the stumps of trees, ditches and puddles on the ground. The direct sunlight on the pools of water increases temperatures promoting mosquito breeding. Increased human activities in deforested areas such as logging, increased large-scale agricultural activities, mining, building of hydropower projects, and the collection of wood for fuel, all enhance contact with mosquitoes and thereby increased malaria transmission [94–96].

Populations in border areas are at greater risk of malaria infections because they frequently visit forests, forest fringe areas, or forested plantations at or near the border [42, 75, 97, 98]. Occupational exposures affect malarial receptivity by age group—for example, in forest fringe villages, adult infections are more prevalent due to forest-related activities such as logging, rubber tapping, bamboo cutting, charcoaling, foraging, and overnight stays in the forests [99]. Migration of the population working in the forest and forest fringe results in spread via carriers to new areas previously free from malaria transmission [100]. Despite high coverage of preventive measures such as LLIN or insecticide-treated nets (ITNs) and IRS in the member States of APMEN, populations working and staying overnight in the forest are not protected [43, 82, 101]. A lack of infrastructure such as roads and healthcare facilities hinder malaria control activities and delayed treatment.

2.7. Migration and cross-border malaria

One of the main challenges that continues thwart malaria elimination is cross-border malaria [94, 102]. People migrate across international borders for a number of reasons including work opportunities, visiting friends and relatives, and displacement as a result of natural and manmade calamities (such as ethnic conflicts) and major development projects. Malaria control in border areas is often difficult for being heavily forested, mountainous and inaccessible terrain, and unregulated population movements across the borders [103, 104]. Open porous international borders allow unchecked movement of people [105–111]. Such cross-border migration is likely to derail the malaria control activities of the neighbouring countries and risk introduction of drug-resistant parasites [112]. Mobile populations along the border areas often live in poverty and have poor access to healthcare services. Movement of people across international borders has contributed to maintaining high transmission hotspots adjacent to border points [73, 105, 113].

2.8. Misalignment of programmatic approaches

There are differences in programmatic approaches among neighbouring countries in the APMEN region making the coordination of control and preventive measures challenging [114, 115]. For example, there are differences in malaria control activities across Laos-Vietnam border. In Laos, the mainstay of malaria control is distribution of LLINs but on the Vietnamese side there is a stronger focus on IRS [114, 115]. Even where the approaches are similar, the specific antimalarial drugs or insecticides used can influence effectiveness due to parasite or vector resistance. Deltamethrin (synthetic pyrethroid) is used for IRS in Bhutan, however, DDT is used in the neighbouring State of Assam in India [116–118]. Effective control or elimination requires coordinated efforts for control interventions.

3. Way forward

In light of the aforementioned challenges in the APMEN member States, some of the possible solutions for way forward include carrying out operational research (OR) to understand the micro-epidemiology of malaria in each country, the use of technologically-assisted solutions for managing operational data (including spatial decision support systems (SDSS)), strengthening surveillance and initiating cross-border initiative.

3.1. Operational research (OR)

As countries move forward with malaria elimination, this effort requires adjustments on the way national malaria programmes operate. For example, the strategies for case detection and surveillance are radically different in control and elimination programmes. Countries may face constraints or bottlenecks as they make the transition from control to elimination for which OR can help to remove these bottlenecks, thereby enabling countries to make the transition from control to elimination phases more rapidly [119, 120]. OR in health is defined as search for knowledge on interventions, strategies, or tools that can enhance the quality, effectiveness, or coverage of programmes [121], and results in improved policy-making, better design and implementation of health systems, and more efficient methods of service delivery [122–125]. The goal is to strengthen health services and improve healthcare delivery in disease-endemic countries and it has an additional critical role to play in helping solve major implementation problems [121, 126–128]. The key elements of OR are that the research questions are generated by identifying the constraints and challenges encountered during the implementation of programme activities, thus can be imbedded into routine programmatic activities [129]. The WHO and Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) have been encouraging programmes to conduct OR as part of their donor-funded activities [119, 130].

A significant limitation of national programmes has been the poor ability, even inability, to manage operational data collected through surveillance and other health information systems [131]. OR can be used to address these knowledge gaps and provide solutions to this limitation. OR has been under-utilised in APMEN member States [132, 133]. However, some countries including China [134], Bhutan [108], India [135, 136], Nepal [137], Solomon Islands [138], and countries in the Greater Mekong Sub-region (GMS) [120] are starting to address the challenges in malaria elimination efforts through OR in areas such as artemisinin resistance.

A key challenge is a lack of operational research capacity of member States [133]. One of the ways to overcome this shortcoming is to develop research capacity through the Structured Operational Research and Training Initiative (SORT IT), a global partnership-based initiative led by the Special Programme for Research and Training in Tropical Diseases (TDR) of WHO [131, 139, 140].

3.2. Role of geospatial data analysis

Malaria has a focal spatial distribution in pre-elimination and elimination phases, with hotspots of transmission in which the risk of malaria (including asymptomatic parasitaemias) and number of cases are higher than in surrounding areas [141, 142]. The scale at which spatial

heterogeneity occurs ranges from micro-geographical setting beginning with household or village level [143–149] to municipalities [150], sub-districts [111], district [151–153], subnational [105, 154–156], national [40], regional [157], and global scales [70]. These spatial clusters of malaria have the potential to be sources of spread into neighbouring regions and countries if there is no focused intervention in the hotspot areas. Given the spatial heterogeneity of the disease, focused interventions in areas with higher incidence of disease are likely to have greater impact than uniform resource allocation [158]. Therefore, the spatial distribution of malaria and its interventions should be taken into account in national malaria elimination plans.

Risk mapping and temporal forecasting of malaria using environmental and climatic factors as spatial and/or temporal risk predictors has been routinely undertaken [107, 159, 160]. Environmental data for geospatial and temporal analysis can be collected through satellite sensors or meteorological stations [159–162]. Image analysis techniques can be applied to satellite data to derive useful variables for the investigation of environmental drivers of malaria, such as land surface temperature, cloud duration (an indirect measure of rainfall), land use or land cover class, and normalised difference vegetation index (NDVI) [85, 161]. The NDVI can be used as proxy for rainfall through the measure of the greenness of the earth's surface and hence vegetation cover [163]. Meteorological data can be interpolated with statistical techniques to estimate values of climatic variables, such as rainfall, temperature, and humidity, for locations where meteorological data are not available [164]. Currently these approaches have mainly been used in research context, and more research including OR needs to be conducted to establish how these approaches can be of practical benefit to malaria control and elimination programmes.

3.3. Spatial decision support systems

In recent years, spatial decision support systems (SDSSs) have been increasingly used in malaria elimination programmes in some countries of Asia-Pacific region to support planning, monitoring and evaluation, including Vanuatu, Solomon Islands and Bhutan [110, 165]. SDSSs have also been employed for other vector-borne disease control programmes such as dengue in Thailand and Singapore [166–168].

SDSSs are technology-driven systems for the collection, mapping, displaying and dissemination of disease data. They provide computerised support for decision making that helps spatially-explicit resource allocation decisions [107, 169]. Key elements of SDSS include: (i) data inputs from a variety of sources (including geospatial data layers), (ii) automated outputs to guide informed and strategic decision making for designated applications, (iii) enabling application/intervention outcomes re-entered back into the SDSS as a cyclical input, and (iv) expert knowledge integrated throughout all stages of the spatial decision support process [170] (**Figure 4**). In most recent examples, data are fed into the SDSS in the field using personal digital assistants (PDAs). The SDSS contains modules for planning, monitoring and evaluating coverage of target populations with IRS and LLINs, and for mapping malaria surveillance data. A mechanism is provided to link routinely collected data with associated spatial information. Spatial queries and analyses can be conducted and cartographic maps and reports of the areas of interest can be produced. Summary statistics of key indicators and maps are fed back to field teams to enhance implementation of interventions.

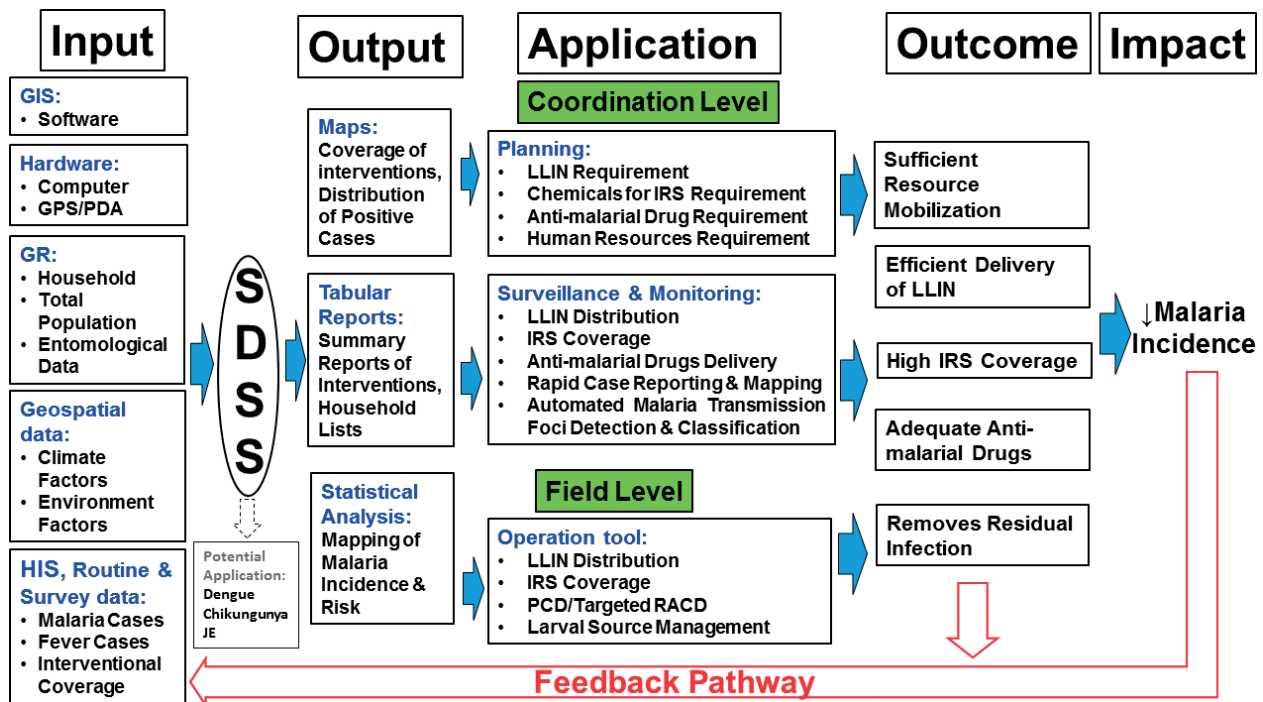


Figure 4. Framework of spatial decision support system for malaria control and prevention with potential use in other vector borne diseases. (GIS geographical information system, PDA personnel digital assistant, GPS global positioning system, SDSS spatial decision support system, GR geographic reconnaissance, LLIN long-lasting insecticidal net, IRS indoor residual spraying, PCD passive case detection, RACD active case detection, JE Japanese encephalitis) (Wangdi et al. [110]).

Limited evaluation to date suggests that these systems support health programmes with a powerful and user-friendly operational tool for evidence-based decision making. Maps are an important SDSS output that provide a visual aid for decision making [170]. An example of map used to monitor LLIN coverage during a mass LLIN distribution in Bhutan is shown in **Figure 5**. This map can inform programme officials of the progress of the campaign and more importantly identifies areas that require catch up activities to achieve target coverage. Malaria incidence maps provide important inputs to policy makers to implement targeted interventions aimed at disease prevention and management. Spatial targeting of malaria interventions, supported by SDSS, will result in more efficient and effective allocation of intervention resources in transmission hotspots helping achieve substantial transmission reduction [135, 156, 158, 171].

3.4. Strengthening surveillance-response and cross-border initiatives

For countries embarking on malaria elimination, malaria surveillance systems need revamping. The main objectives of surveillance in malaria elimination are to detect infections (both symptomatic and asymptomatic), and ensure radical cure. This is in contrast to the malaria control phase in which the main objectives of surveillance is to quantify the level of malaria transmission and to support preventive action at the population level [172, 173]. In most countries, malaria surveillance is based on passive case detection. Passive surveillance involves reporting malaria cases by a health facility, which can be limited by incomplete reporting, healthcare seeking in the private sector (not captured by government systems), and poor diagnostic capacity, particularly in low transmission settings [174]. Prompt detection and radical treatment of

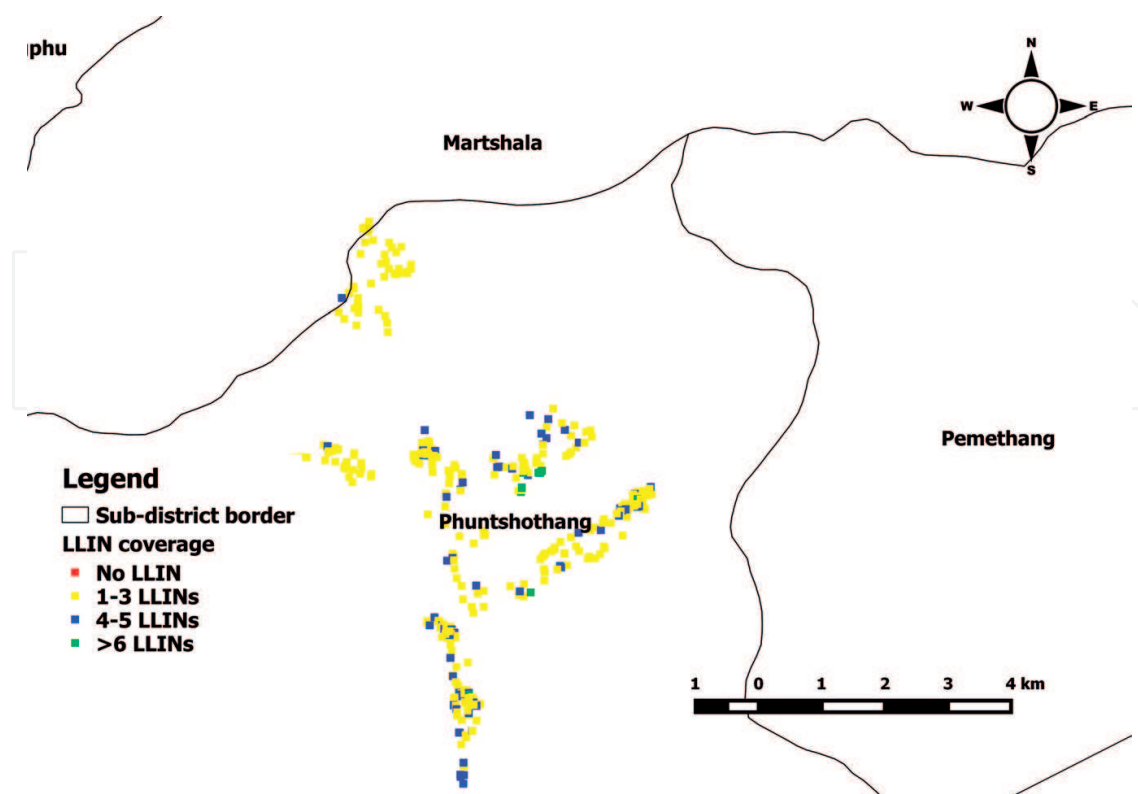


Figure 5. Sample output map for monitoring the coverage of long-lasting insecticidal net in Bhutan (Samdrup Jongkhar) (in this map there was no households without LLIN) (Wangdi et al. [110]).

imported malaria cases is critical for malaria elimination for sustaining the malaria elimination efforts. However, importation of malaria is inevitable, even in countries that have eliminated malaria. Passive case detection (PCD) could capture imported cases and allow interventions that would prevent resurgence in the presence of robust health system [175]. However, in areas with high transmission intensities in APMEN countries [70, 176], and unchecked migration across borders [103–111], there is likely to be significant transmission even in low transmission settings. Therefore, imported infections must be prevented through border screening, regional and cross-border initiatives and dialogue, proactive case detection, and treatment in high-risk population groups and travellers preventing resurgence of the disease [177].

Active surveillance addresses some of the limitations of PCD and generally involves cross-sectional surveys of defined sample populations, where the primary malaria indicator is the proportion of persons infected with malaria parasites (parasite prevalence) [178]. These surveys enable detection of asymptomatic infections that perpetuate transmission [179], and provide an opportunity to concurrently assess coverage of malaria interventions [180], but they are expensive and difficult to implement, and are not efficient in low-transmission settings.

One of the most efficient ways to enhance passive surveillance is through reactive case detection (RACD). When an index case of clinical malaria is detected in a community, RACD is carried out in all the households located within a certain distance of the index case. During the RACD, follow-up activities differ widely and can include testing of fever using RDTs or microscopy for any residual malaria infection and treating those who test positive. In addition, vector control activities including IRS and LLINs are intensified. RACD has been implemented in Africa and

Asia with mixed results [110, 181–186]. Nevertheless, RACD provides an opportunity for public health workers to concurrently assess coverage of malaria interventions including LLINs, and should be advocated and practised. Another efficient way to evaluate the efficacy of vector control methods, also applied in Africa and Asia, is to estimate the human antibody response to *Anopheles* saliva in human populations [187–189].

Diagnostic techniques used for testing blood during RACD will significantly impact the programme effectiveness. Estimating parasite prevalence using microscopy is time and labour intensive, and often inaccurate in operational settings [190]. Newly available rapid diagnostic tests (RDTs) offer on-the-spot results, but have limitations in specificity, sensitivity, quality, and cost [190–193]. Both methods (microscopy and RDTs) may fail to detect a substantial proportion of low-density parasitaemias [186, 194, 195]. Polymerase chain reaction (PCR) provides enhanced sensitivity but results are not available immediately [196], instead Real-time PCR may present a consistent, accurate, and efficient tool for surveillance to assist malaria elimination in the future [196].

Cross-border movement of populations impacts the maintenance of ‘hotspots’ of high transmission along international borders [77, 94, 97, 108, 137, 197–200], and spread of drug-resistance seen along the international border of Thailand and Cambodia [201]. Then, cross-border initiatives should be initiated through sharing of programme data including insecticide resistance, blood testing at the border areas, and treatment of symptomatic cases [177, 202–208]. Such successful cross-border case studies in the region have led to significant reduction in malaria burden in the study areas [209].

4. Conclusions

Successful malaria elimination in the APMEN member States will greatly enhance the global drive to eliminate malaria. Malaria transmission in these States is complex. APMEN member States include the largest populations living in areas of malaria transmission risk outside Africa. They are a global source of ACT resistance, highest burden of *P. vivax* and zoonotic malaria, and face many geopolitical and socioeconomic factors that will challenge malaria elimination efforts. These challenges can be addressed in part through operational research to identify country specific solutions, making better use of operational data such as through implementing SDSS approaches, and strengthening surveillance and cross-border collaborations.

Abbreviations

| | |
|-------|---|
| ACT | artemisinin-based combination therapy |
| AIM | action and investment to defeat malaria 2016–2030 |
| APMEN | Asia Pacific Malaria Elimination Network |
| DDT | dichlorodiphenyltrichloroethane |

| | |
|-----------|---|
| DPR Korea | Democratic People's Republic of Korea |
| G6PD | glucose-6-phosphate dehydrogenase |
| GFATM | Global Fund to Fight AIDS, Tuberculosis and Malaria |
| GIS | geographic information systems |
| GMS | Greater Mekong Sub-region |
| GST | Global Technical Strategy for Malaria |
| IRS | indoor residual spraying |
| ITN | insecticide-treated nets |
| Lao PDR | Lao People's Democratic Republic |
| LLIN | long-lasting insecticidal nets |
| MIS | malaria indicator survey |
| NDVI | normalised difference vegetation index |
| OR | operational research |
| PCD | passive case detection |
| PCR | polymerase chain reaction |
| RACD | reactive case detection |
| RDT | rapid diagnostic test |
| PNG | Papua New Guinea |
| SDSS | spatial decision support systems |
| SEAR | South-East Asian Region |
| SORT IT | Structured Operational Research and Training Initiative |
| TDR | Research and Training in Tropical Diseases |
| VcWG | Vector Control Working Group |
| WHO | World Health Organisation |

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