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Re-Emergence of Malaria in Malaysia: A Review Article

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Abstract

Malaria is a global health problem, affecting millions of people annually. According to the World Malaria Report 2015, there were 214 million new cases of malaria globally (range 149 - 303 million) with an estimated mortality of 438,000 (range 236,000 - 635,000). The vast majority of the cases occur in the WHO African Region (88%), with the rest being in the WHO South East Asian Region (10%) and the WHO Eastern Mediterranean Region (2%). Malaysia is experiencing sporadic outbreaks of malaria due to influx of foreign workers from neighboring countries and failure to take antimalarial prophylaxis amongst travellers. The aim of the review is to increase the awareness among the healthcare professionals on the increasing prevalence of malaria especially among migrant workers. Currently our health screening program for migrant workers does not include screening for malaria.

Subject Areas

Global Health

Keywords

Malaria, South East Asian Region, Foreign Workers, Malaysia

1. Introduction

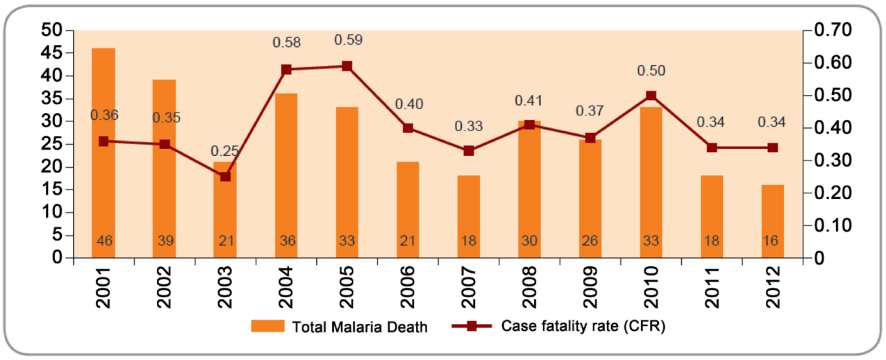
A decade ago, the incidence of malaria was estimated to be 262 million in the year 2000 with 839,000 deaths. With continuous effort from World Health Organization and local government, the annual incidence rate and mortality rate have decreased by 37% and 48% respectively between 2000 and 2015 [1].

Malaysia has made great progress in the control of malaria as shown in the decrease of incidence rate (per 100,000 population) of 37.0 in 2001 to 14.7 in 2006 and a further reduction to 7.1 in 2012. However, **Figure 1** shows the case

fatality rate was fluctuating throughout the years of 2001-2012 between 0.25 to 0.59 with the current rate of 0.34 in the year 2012 [2]. The National Strategic Plan for Malaria Elimination 2011-2020 was initiated with the objective of stopping locally-acquired malaria in Peninsular Malaysia by 2015 and in East Malaysia by 2020 [3]. **Figure 2** shows that Sabah and Sarawak contribute to most of the malaria cases in Malaysia due to the isolated geographic area and high number of migrant workers [3] [4]. According to WHO Malaria Report 2015, Malaysia is in the pre-elimination phase of malaria with an approximation of 1.3 million population living in areas where malaria transmission is active. As of 2010, 24.5% of the population in Sabah is at risk of contracting malaria whereas the risk was 19.7% in Sarawak and 0.4% in West Malaysia [4].

2. Plasmodium Species

The causative agent of malaria is Plasmodium parasites, which are transmitted to human through bites of infected female Anopheles mosquitoes. There are five



X-axis: Year; Y-axis: Right: Total number of deaths; Left: Case fatality rate.

Figure 1. Total malaria deaths and case fatality rate in Malaysia from year 2001 to 2012 [2].

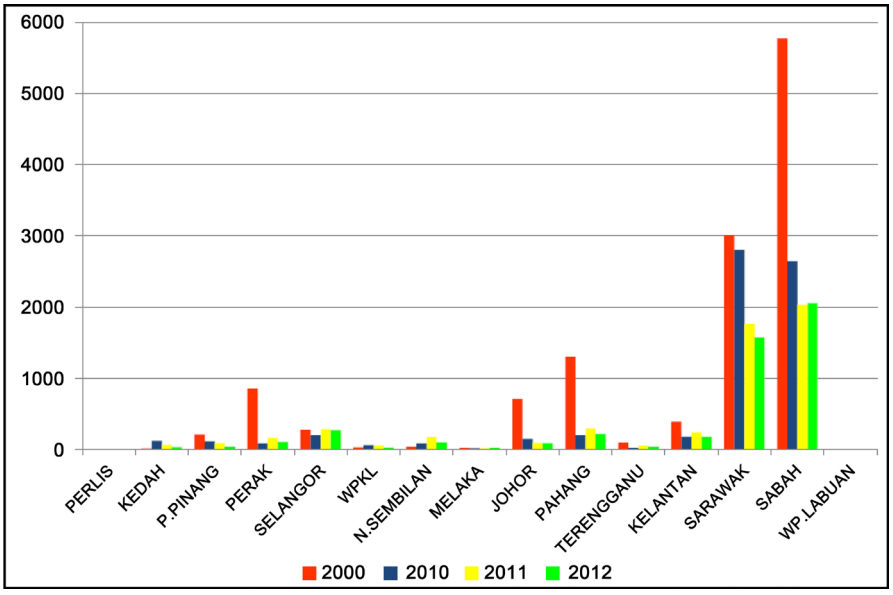


Figure 2. Trend of distribution of malaria cases in Malaysia by states [4].

parasite species that infect human, namely *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. Among them, *P. falciparum* and *P. vivax* are the most common parasites with *P. falciparum* being dominant in Africa and *P. vivax* in most countries outside of sub-Saharan Africa [5]. Before the first naturally acquired *P. knowlesi* infection in humans was reported in 1965, *P. knowlesi* is only found in macaque monkeys [6]. *P. malariae* and *P. knowlesi* are difficult to distinguish microscopically, leading to misdiagnosis and classification as a single group for notification of cases [7] [8].

P. falciparum used to be the most prevalent parasite in Malaysia but there was a declining trend in *P. falciparum* cases from 1997 to 2011. As of 2011, *P. vivax* accounted for almost half of the causative parasite (2 422 cases, 45.6%), followed by *P. falciparum* (973 cases, 18.3%), *P. malariae* (903 cases, 17.0%) and *P. knowlesi* (854 cases, 16.1%) (**Figure 3**) [3]. However, **Figure 4** shows there are concerns of increasing reported cases of *P. knowlesi* in Malaysia since year 2008, making it the country with highest proportion of *P. knowlesi* in WHO Western Pacific Region [1]. According to retrospective review of Sabah Department of Health malaria notification data from 1992-2013, the percentage of malaria cases in Sabah caused by *P. malariae*/*P. knowlesi* was on the increasing trend from 1% in 1992 to 35% in 2011 and to 62% in 2013 [8] [9].

Parasite Life Cycle

Malaria parasite is transmitted by a vector, which is female Anopheles mosquito. The disease-causing vectors vary according to geographical location. In Malaysia, An. maculates, An. balabacensis, An. dirus, An. letifer, An. camperstris, An. sundaicus, An donaldi, An. leucophyrus and An. flavirostris are the common Anopheles species responsible as vector [10]. The basic life cycle of malaria parasites comprises sexual phase in the mosquitoes and asexual phase in human.

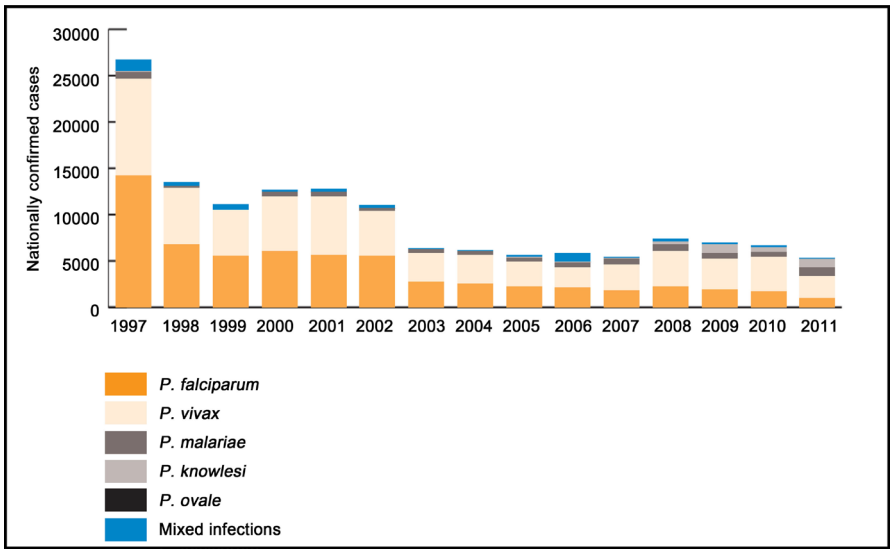


Figure 3. Trend of malaria cases by plasmodium species in Malaysia from year 1997 to 2011 (*P. knowlesi* cases were reported starting in 2008) [3].

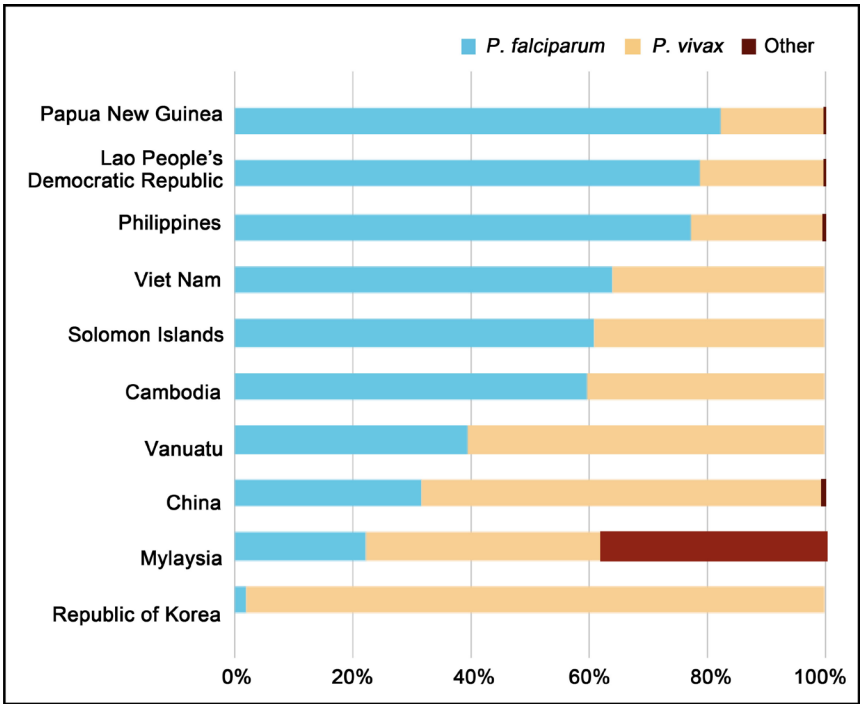


Figure 4. Proportion of malaria cases due to *P. falciparum* and *P. vivax* in WHO Western Pacific Region from year 2010 to 2014 [1].

When an infected vector bites a human, malarial sporoziotes are injected and introduced into human blood stream. Theses sporozoites infect liver cells and mature into schizonts. This exo-erythrocytic cycle which involves asexual fission does not produce any clinical symptoms in patient. When the schizonts rupture, thousands of merozoites are released and they infect erythrocytes. In the erythrocytes, the immature trophozoites develop into schizonts, which release merozoites and toxic products of parasite's metabolism into the blood stream when ruptured. The blood stage of parasites, known as the erythrocytic cycle, is associated with the periodic nature of fever because every time the erythrocytes rupture, the toxins released stimulate cytokine production which causes rise in temperature. The length of erythrocytic cycle varies between different parasites: 24 hours for *P. knowlesi*; 48 hours for *P. falciparum*, *P. ovale* and *P. vivax*; and 72 hours for *P. malariae*. *P. vivax* and *P. ovale* are related to relapses of malaria due to the presence of dormant stage of parasite, the hypnozoite, in the liver for weeks or years before entering exo-erythrocytic cycle. If left untreated, merozoites can mature into gametocytes, which can be taken up by mosquito during a blood meal and undergo sexual reproduction for further transmission of the infection [11] [12] [13]. (**Figure 5**)

3. Risk Factors

The transmission of malaria is affected by a number of environmental, socio-demographic, economic and human factors. For environmental factors, malaria prevalence is positively associated with increased in rainfall and living in areas

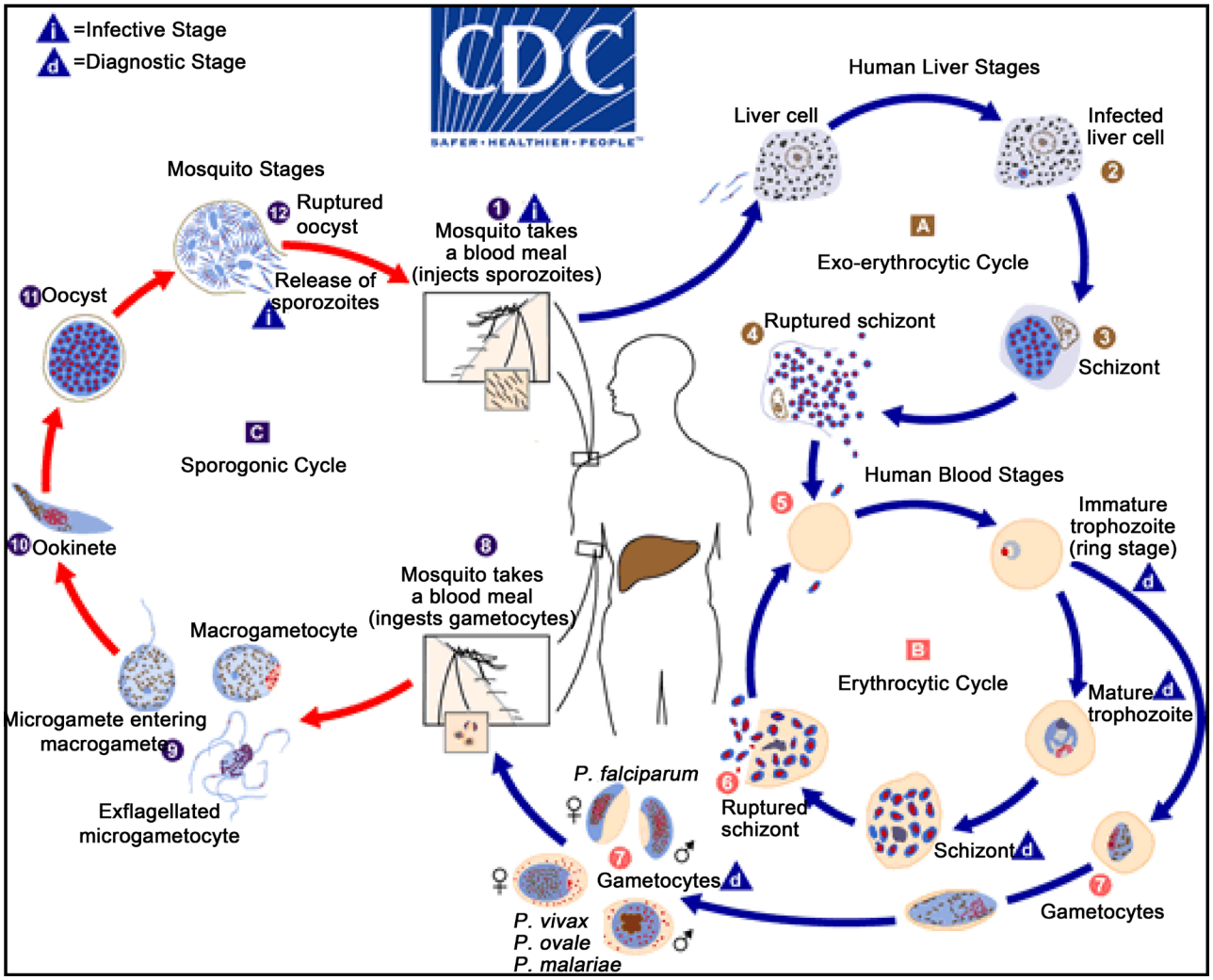


Figure 5 illustrates the life cycle of malaria (No 1 - 12) as described below. The infected female anopheles mosquito takes a blood meal (1) and injects the sporozoites into the human blood stream. The sporozoites, in turn, go on to infect the liver cells and proliferate of which some may become dormant to cause relapse later. After multiplication in the liver cells, schizonts will form and the rupture of the liver cells releases merozoites into the blood stream. Now the erythrocytic stage begins. There are various stages in the red blood cell like the ring form, immature trophozoites, mature trophozoites, schizonts, rupture of red blood cells and further repetition of cycle in new red blood cells. Some of the trophozoites may develop into the male and female gametocytes which the anopheles mosquito takes up during the blood meal beginning the sporogonic life cycle in the mosquito resulting in trophozoite formation to infect more humans. The sporogonic cycle takes place in the mosquito. The male and female gametocytes develop into mature gametes and with fusion, the zygote forms. The zygote elongates into ookinetes which move through the stomach wall. The ookinetes develop into oocyts. The oocyts grow and rupture releasing sporozoites. The sprorozoites migrate into the salivary glands and is ready to begin a new cycle in the human following a mosquito bite.

Figure 5. Life cycle of malaria parasites adopted from Centers for Disease Control and Prevention (2016).

where stream or stagnant water existed because water provides a good breeding ground for the Anopheles mosquitoes [14] [15] [16]. Global warming also has an effect on the spread of malaria as places that are formerly too cold to support malaria are now susceptible to the vectors [17].

Socioeconomic risk factors are involved in transmission of malaria as low household income is often associated to poor housing conditions, overcrowding and living in rural areas [18] [19]. Urbanization also contributes to transmission of malaria due to high rate of construction which leads to improper water drai-

nage and influx of foreign laborers [20]. In Malaysia, malaria transmission is also closely related to occupations such as forest workers (loggers, rattan collectors and forest product gatherers), plantation workers and the aboriginal groups who have intimate contact with jungles [21] [22].

For travelers, malaria infection is associated with season of malaria transmission in country of visit, longer duration of stay, failure to use antimalarial prophylaxis and lack of room air-conditioning [23] [24]. Different personal protection measures (PPM) against mosquito bites are recommended for travelers such as staying in rooms with air-conditioning, using screens, bed nets, repellents, insecticides and wearing clothing that cover exposed parts of the body at dawn or dusk. Among the PPMs, staying in air-conditioned rooms and covering arms and legs were effective while the use of repellants and insecticides did not show significant protection [25]. A meta-analysis proved that chemoprophylaxis with atovaquone-proguanil has prophylaxis efficacy of 95.8% compared to placebo and was well tolerated [26]. A Cochrane review on the effectiveness of insecticide-treated nets (ITNs) in prevention of malaria showed that the use of ITNs reduced the incidence of uncomplicated malarial episodes by 50% and 62% in areas of stable and unstable malaria respectively. On top of that, ITNs also conferred benefits in areas of stable malaria by providing protection against severe malaria, parasitaemia, splenomegaly and anaemia [27].

4. Clinical Presentations

Uncomplicated malaria is usually associated with influenza-like symptoms such as fever, chills, sweats, headaches, nausea and vomiting, body aches and general malaise [28]. The frequencies of the common complaints as investigated in Northeastern Indonesian Papua were as follows: fever (87%), vomiting (55%), nausea (22%), headache (18%), chills (16%), malaise (11%), and vertigo (11%) [29]. Severe malaria often leads to poor clinical outcomes. The case fatality rate in travelers with severe malaria caused by *P. falciparum* can be higher than 20% [30]. The criteria for severe malaria established by WHO (revised in 2000) which are used to assist clinical and epidemiological studies are as follows: impaired consciousness (Glasgow Coma Score < 11 in adults or Blantyre coma score < 3 in children), acidosis (base deficit of >8 meq/l or plasma bicarbonate of <15 mM or lactate > 5 mM), hypoglycaemia (plasma glucose < 2.2 mM), severe malarial anaemia (haemoglobin concentration < 5 g/dl with parasite count > 10,000/μl), renal impairment (serum creatinine > 265 μM or blood urea > 20 mM), jaundice (serum bilirubin > 50 μM), pulmonary oedema (Radiologically confirmed, or oxygen saturation < 92% on room air with a respiratory rate > 30/min), significant bleeding, shock and hyperparasitaemia (*P. falciparum* parasitaemia > 10%) [31]. The manifestations of severe malaria differ according to age of patient: in children under 2 years old, severe anaemia predominates; in older children, seizure and cerebral malaria are more frequent; whereas in adults, acute renal failure, acute pulmonary oedema, liver dysfunction, and cerebral malaria are all possible [32].

Cerebral malaria is characterized by coma at least 1 hour after termination of a seizure or correction of hypoglycemia and presence of asexual forms of the *P. falciparum* parasite on peripheral blood smears. Annually, 575,000 children in Africa develop cerebral malaria and the mortality rate is 15% - 20% even with treatment by parenteral antimalarials. Clinical presentations of cerebral malaria include brain swelling, intracranial hypertension, retinal changes and brainstem signs (abnormalities in posture, pupil size and reaction, ocular movements or abnormal respiratory patterns). Cerebral malaria is caused mainly by parasite sequestration in cerebral microvasculature which leads to changes in surrounding tissues [33].

4.1. Factors Influencing Clinical Outcomes

Several factors contribute to the poor prognosis of severe malaria such as the infecting malaria parasite species, the degree of abnormality, the number of systems affected, coexisting medical conditions, no antimalarial prophylaxis, delay in treatment, age, gender (especially when associated with pregnancy) and background immunity (nonimmune status) [30] [31]. *P. knowlesi* infections lead to the highest mortality rate, followed by those caused by *P. falciparum* [31]. In areas where malaria is endemic, approximately 70% of deaths occur in children age under 5 due to the lack of protective semi-immune status which is likely to be acquired after repeated bouts of infections [34]. Base deficit, impaired consciousness, convulsions, elevated blood urea, and underlying chronic illness were identified as the key prognostic indicators in children [35]. In non-endemic area, population generally lacks protective immunity and case fatality rate is almost 6 times greater among elderly patients [36].

4.2. Diagnosis

Diagnosis of malaria is based on clinical suspicion and parasitological confirmation (detection of parasites in the blood). In countries where malaria is endemic but access to laboratory confirmation is severely limited such as in most of Africa south of the Sahara, probable or suspected cases are defined as diagnosis and treatment of malaria based on clinical presentations. The diagnosis is based on patients' signs and symptoms and physical findings such as fever, headache, weakness, myalgia, chills, dizziness, abdominal pain, diarrhoea, nausea, vomiting and pruritus [37]. However, these clinical presentations are non-specific and overlap with other common diseases, making clinical diagnosis less sensitive and specific. Studies had shown that malaria is overly treated in most malaria endemic areas, where only less than half of patients with suspected malaria infection are truly infected with a malaria parasite.

Different tests are available for parasitological diagnosis of malaria such as Blood Film for Malaria Parasite (BFMP), Polymerase Chain Reaction (PCR) and Rapid Diagnostic Test (RDT) (**Table 1**). BFMP involves microscopic examination of thick film to detect malaria parasite and examination of thin film to differentiate

Table 1. Adapted from Malaria Diagnosis: A Brief Review [37].

	Clinical diagnosis	BFMP	PCR	RDT
Principle of method	Based on presenting signs and symptoms	Visualisation of thick and thin blood smear under light microscope	Specific amplification of malaria DNA	Detection of parasite antigens or enzymes
Detection limit (parasites/μl)	Undetermined	5 - 10 (expert) >50 (routinely)	≥1	50 - 100
Sensitivity and specificity	Depends on malarial endemicity	Depends on technique, reagent and lab technician's skill	Excellent	Moderate if >100 parasite/μl
Time consumed (min)	Depends on physician	30 - 60	45 - 360 (depends on methods)	10 - 15
Expertise required	High	High	High	Low
Instrument cost	-	Low	High	Moderate
Other considerations		- Need considerable expertise - Mixed infection and low parasitaemia might cause misdiagnosis	- Useful for quantifying at low parasitaemia - Useful in indentifying drug resistance	- Unable to differentiate between *P. vivax*, *P. ovale* and *P. malariae* - Unable to quantify parasites

the parasite species. PCR works by detecting parasitic nucleic acid and is highly sensitive and specific. However, its use is only indicated in certain situations such as cases with clinical symptoms but negative microscopy results and in cases with microscopic appearance of *P. malariae* due to its high cost of labour and reagents and long processing time [38]. RDT, also known as immunochromatographic test, functions by detecting parasite antigens in the blood and is useful in patients with negative results from blood films due to incomplete antimalarial treatment [39]. Current RDTs on the market detect antigens namely histidine-rich protein 2 (HRP2), various subtypes of Plasmodium lactate dehydrogenase (pLDH), and aldolase in various combinations. Thus, selection of RDTs will be dependent on the species of parasite present in the particular region [40]. The test can provide results within 2 - 15 minutes but lack sensitivity and ability to quantify the parasites [41]. Besides that, it is sensitive to heat and humidity, making storage and transport inconvenient [42].

4.3. Diagnostic Challenges

In non-endemic regions, diagnosis can be challenging due to low parasite density which might lead to false negative results by RDT, altered parasite morphology due to consumption of chemoprophylaxis and inexperienced lab technicians in differentiating malaria species [42]. In malaria endemic regions such as Africa, fever and septic shock are frequently misdiagnosed as severe malaria, leading to failure to treat the true underlying infections. Even in symptomatic individuals, parasitaemia might not be the definitive diagnosis of malaria because it can be incidental to other concurrent diseases [42] [43]. In these areas, children under 5 years old are always overly-treated for malaria, causing unnecessary ex-

penditure and contributing to the spread of drug resistance [44].

4.4. Co-Infection

Another mosquito-borne infection that causes high morbidity and mortality rate in tropical countries is dengue. Retrospective study involving 1723 febrile patients in French Guiana found that the rate of dengue-malaria co-infection was 0.99% whereas a cross-sectional study in the Brazilian Amazon involving 1578 subjects showed a higher rate of 2.8% [45] [46]. It is interesting to note that despite the high incidence rate of dengue and malaria in South East Asia, concurrent malaria and dengue infections are rarely reported [47]. In a study involving 194 patients with dengue in Thailand, no co-infection with malaria was detected whereas another study involving 1723 consecutive febrile patients in French Guiana found 17 co-infections [48] [49]. A review of dengue-malaria co-infection in Asia by Selvaretnam, Sahu, Sahu, & Ambu (2016) showed that in the past decades, there were 36 reported incidences of dengue-malaria co-infection in Asia, of which majority (26 cases) were from India. In Malaysia, there is only one case report of patient co-infected with malaria, dengue and leptospirosis [50]. No study has been published to investigate the lower rate of dengue malaria co-infection in Asia thus far.

5. Treatment

According to Ministry Of Health Malaysia (2013), the preferred treatment for patient with uncomplicated *P. falciparum*, *P. malariae* and *P. knowlesi* is artemisinin-based combination therapies (ACT), which include regime of artemether and lumefantrine for 3 days or artesunate and doxycycline for 7 days for severe cases. For uncomplicated *P. vivax* and *P. ovale* infection, chloroquine is recommended but ACT should be used in chloroquine-resistant infections. Primaquine is given for 14 days to prevent relapse of the infection.

Of the five species of plasmodium that infect human, *P. falciparum* and *P. vivax* have been reported to be resistant to antimalarial drugs [51]. Researchers found that resistance commonly develops within 10 - 15 years after an antimalarial is introduced [52]. Since 1946, chloroquine (CQ) has been used as the drug of choice for uncomplicated falciparum malaria until 1950s when drug resistance was reported and reduced its usefulness [53]. Depending on geographical location, *P. falciparum* has developed resistance to nearly all anti-malarials in current use such as chloroquine, sulfadoxine-pyrimethamine (SP) and mefloquine (MEF) whereas *P. vivax* is reported to be resistant to CQ and primaquine [51]. Resistance occurs when the parasites undergo spontaneous single or multiple point mutations which makes them less sensitive to anti-malarial drugs. For instance, *P. falciparum* develops resistance towards CQ via its increased capacity to expel chloroquine to prevent it from inhibiting its haem polymerisation process [51]. Cross resistance may occur to the other quinoline antimalarials (amodiaquine, mefloquine, halofantrine, and quinine) but the exact mode of

mechanism is unknown [51] [54]. Drug pressure which arises due to mass drug administration (MDA) or extensive duration of monotherapy treatment has been identified as one of the key factors that leads to emergence of resistant strains of parasite [55]. This was clearly demonstrated during the Global Malaria Eradication campaign launched in 1955 by WHO which implemented MDA by introducing chlorquine and pyrimethamine into cooking salt which later led to rapid development of drug resistance [55] [56].

In general, antimalarial drug resistance can be tested using four methods, namely *in vivo*, *in vitro*, animal model studies, and molecular characterization. *In vivo* test involves treating a group of symptomatic patient and subsequent monitoring of the parasitological or clinical response over time whereas *in vitro* test involves exposure of parasites obtained from patient's blood sample to drug and observed for its effect. Animal model study is similar to *in vivo* test except it is being conducted in non-human animal models.

Artemisinin was discovered in the 1970s and was widely used in South East Asia since 1990s due to its notable pharmacological features of rapid action, broad coverage of different stages of parasites and ability to kill gametocytes. However, its short half life and efficacy invoke concerns over incomplete treatment as patients have the tendency to terminate their 7-day artemisinin monotherapy earlier once they feel better. In order to ensure complete clearance of parasites and reduce therapy duration, another longer acting antimalarial such as lumefantrine, mefloquine, sulfadoxine-pyrimethamine, piperaquine or amodiaquine has been included as fixed dose artemisinin-based combination therapies (ACT). In addition, the 99.99% efficacy of artemisinin in clearing parasites helps reduce the risk of producing parasite resistance to its longer-acting partner drug in ACT. However, artemisinin resistance was recently reported in the Greater Mekong region (which includes Cambodia, Thailand, China's Yunnan province, Lao PDR, Myanmar, and Vietnam) due to the frequent mobilization of gem miners across different countries and other reasons [56] (**Figure 6**). In view of that, the WHO Global Malaria Programme announced a "Global Plan for Artemisinin Resistance Containment" (GPARC) in 2011 to prevent the emergence and spread of artemisinin resistance. The program focuses on five strategies namely: i) stopping the spread of resistant parasites; ii) strengthening surveillance to evaluate the threat of artemisinin resistance; iii) improvement of access to diagnostics and rational treatment with ACTs; iv) investment in artemisinin resistance-related research; and v) motivating action and mobilizing resources [57].

Malaysia is vulnerable to having CQ-resistant *P. vivax* strain due to the frequent of mobilisation of people between neighbouring countries with high grade CQ-resistance such as Indonesia and Papua New Guinea or low grade CQ-resistance in Philippines, Thailand, and Vietnam [52]. Even though there is no systematic clinical evaluation on cases of CQ-resistant malaria in Malaysia, a retrospective study in Klang, Selangor from 2004 to 2006 showed that of the 37 malaria cases recorded, 40.5% (15 cases) developed CQ resistance whereas a

similar study in University Malaya Medical Center over the period of 10 years from 1994-2003 found that 12% (10 out of 86 cases) of the malaria cases were resistant to CQ [58]. A recent randomised trial conducted in Sabah from 2012 to 2014 revealed an alarming 61.1% of treatment failure following CQ treatment in 49 patients with *P. vivax* infection as compared to 0% treatment failure in those who received artesunate-mefloquine.

6. Malaria Outbreaks

A number of factors can contribute to outbreaks such as increase in vector breeding sites, migration of infection people to non-malarious areas but with abundance of vector, introduction of new efficient vector, resistance of parasites to treatment or insecticides and breakdown of vector control measures [59]. There were plenty of recorded outbreaks in the region such as the Bo Rai outbreak (1988-1997) in Thailand near Thailand-Cambodia border due to the daily movement of gem miners across the two countries. The annual incidence of as high as 70,000 cases was also attributed to the decrease in efficacy of mefloquine in treating falciparum malaria [60] [61]. The malaria outbreak in Naxalbari, West Bengal, India in 2005 involving 7303 cases was due to breeding of vectors in abandoned wells, breakdown in vector control and parasite resistance to chloroquine [59].

7. Malaria Surveillance

The majority of malaria cases in Malaysia are found through passive case detection

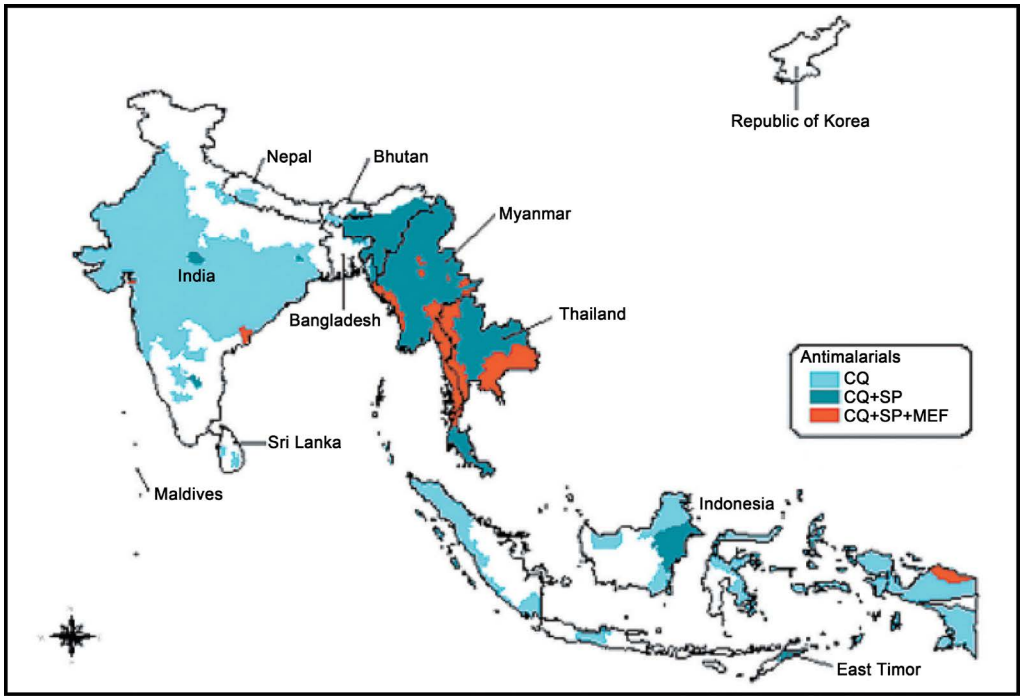


Figure 6. Distribution of confirmed foci and areas of anti-malarial resistant of *P. falciparum* malaria in South East Asia [54].

at a health facility. According to national elimination guidelines, all febrile cases must be screened for malaria upon presentation to a clinic or hospital. Patients returning from highly endemic countries and all pregnant women living in high-risk areas are required to be screened on their first clinic visit. Apart from passive case detection, active case detection is usually employed to screen for febrile individuals during outbreaks or for high risk groups such as military personnel, indigenous people in West Malaysia, mobile ethnic groups in Sarawak, communities in Sabah that are forest-dwelling and migrant workers. Mass blood survey requires at least 80% of populations receiving ITN and indoor residual spray (IRS) to be tested for malaria. It is also done in response to outbreaks and upon arrivals of foreign workers. All malaria cases in Malaysia are documented, investigated and followed-up. District health officers are required to collect blood sample and check symptoms in discharged patients weekly for a month and then monthly for eleven additional months for *P. vivax* and *P. ovale* cases or additional five months for *P. malariae* and *P. knowlesi* cases.

In Malaysia, a number of outbreaks were due to imported cases such as the outbreak in Tanjung Bungah, Penang in April 2006 of which 56 of the 58 positive cases involved foreign workers with majority from Indonesia. Following the outbreak, 187 medicated mosquito nets were distributed, 54 focal spraying and 9118 fogging exercises were conducted along with talks, dialogues and distribution posters and pamphlets to stop further transmission of the outbreak [62]. Another outbreak in April 2007 which affected 61 people from seven villages in Lawin, Gerik, Ipoh was attributed to infected Thai rubber tappers in the area [63]. According to CDC outbreak guideline, measures to prevent further transmission during an outbreak include vector management, health promotion to educate public on protective behaviours, active case finding, identify vulnerable groups using community mapping, provide insecticide treated nets and mosquito repellent, and other control measures [64]. Malaysia has included "preparedness and outbreak response" as one of the seven strategies in the National Strategic Planning for elimination of malaria (2011-2020) with the aim to allow early detection of outbreak and control it within 6 weeks [4]. Malaysia has also been collaborating with private sectors such as plantation companies since 1990s as one of the efforts to eliminate malaria. Such partnerships have brought great success in accessing the high-risk population [4] [65].

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List of Abbreviations

None.

Statement of Competing Interest

None.

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