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Burden of Malaria and Prospective Challenges in South-East Asia Region: A Review

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Malaria caused 350 to 500 million clinical episodes in the year 2000 and remains the fifth most deadly infectious disease worldwide after respiratory infections, HIV/AIDS, diarrhoeal diseases, and tuberculosis. Though malaria remains a global health concern in developing nations, the approximate malaria-infected cases reduced from 227 million cases in 2000 to 198 million cases in 2013 globally. Notably in Africa over the last decades, malaria eradication programmes have received greater international attention leading to reduction of parasite-infected cases by 26%, with a decrease in cases from 173 million in 2000 to 128 million in 2013. Nevertheless malaria remains a global health concern in developing nations. The World Health Organization (WHO) South-East Asia Region (SEAR) comprises of 11 member states (Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste) of which 10 countries are malaria endemic while Maldives has been declared malaria-free nation since 1984. Presently no licensed malaria vaccine is available and vaccine developers are working

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on several novel approaches to make a breakthrough as these vaccines would probably be crucial factor to prevent the transmission and onset of malaria. Further due to excessive dependence on artemisinin-based combination therapy (ACTs), emergence of drug resistant parasites, malaria co-infection in immunocompromised patients and newer *P. knowlesi* strains are fuelling this severe public health problem. Effective measures such as routine surveillance of the antimalarial drug efficacy, newer rapid diagnostic tools (RDTs) and appropriate treatment regimes will help to monitor and limit this deadly disease especially in the malaria-endemic countries. In this review, the various intertwined factors leading to malaria burden – a continuing problem for global health- specially in South-East Asia region are highlighted.

Keywords: Malarial parasite; Plasmodium knowlesi; HIV-malaria coinfection; artemisinin resistance.

1. INTRODUCTION

Malaria is a life-threatening disease caused by *Plasmodium* parasites which is transmitted from one person to another by the bite of infected female mosquitoes of the genus *Anopheles*. The four commonly reported different types of malarial parasites in humans are *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* [1]. Of these, *P. vivax* and *P. falciparum* are the most prevalent malarial parasites while *P. falciparum* is the most lethal of all, with highest number of severe and mortality cases reported. *P. vivax* has a wider geographic distribution than *P. falciparum* since the parasite can grow and survive in the Anopheles mosquito even at lower temperatures such as higher altitudes and cooler climates. Moreover *P. vivax* has a dormant liver stage (called as hypnozoites) completed in human asexual lifecycle, which enables the parasite to survive for long periods in the body and can become activated months later to cause a malarial relapse [1]. There are about 400 different species of Anopheles mosquitoes, of which only 30 are vectors of major importance transmitting malarial parasites. According to the latest World Health Organization report (2014), about 3.2 billion people in 97 countries across the globe are at danger of being infected with malaria disease while 1.2 billion of them are at high risk of developing malaria in a year [2] (Table 1). Globally 198 million cases of malaria occurred in the year 2013 and 584,000 deaths occurred due to it. Across Africa, from the year 2000 due to various malaria eradication programmes, the number of malaria-infected cases have reduced by 26%, that is from 173 million in the year 2000 to 128 million in the year 2013 [2]. Consequently the global malaria mortality rates have also dropped by 47% while 54% in the WHO Africa Region, which reports the maximum number of cases. WHO projects that by the year 2015, with the maintained annual reduction rate over the past 13 years, malaria mortality rates would decline globally and WHO Africa Region by 55% and 62% respectively. Latest report has identified a fifth human malaria parasite, *Plasmodium knowlesi* [3]. Report suggests that *P. knowlesi*, which typically infects macaque monkeys, human infected cases have been identified in Malaysia and Southeast Asian countries. The WHO Global Malaria Programme (GMP) and Roll Back Malaria partnership programmes are globally implemented to coordinate action and measures against malaria control. These partnership programmes comprised of more than 500 partners, which involves, malaria endemic countries, private associations, non-governmental organisations (NGO), community-based foundations, research institutes and academic establishments [1,2].

2. STATUS OF MALARIA IN SOUTH-EAST ASIA REGION

About 80% of estimated malaria-infected cases in the year 2013 were reported from only 18 countries while 80% of mortality due to malaria occurred in 16 of these 18 countries. Majority of *P. vivax* cases, more than 80% of estimated vivax cases, occurs in 03 countries- India, Indonesia and Pakistan [2]. In 2013, approximately 198 million malaria cases were reported globally [2]. Of these, majority of the cases were from WHO African Region (82%), followed by the WHO South-East Asia Region (12%) and the WHO Eastern Mediterranean Region (5%). The WHO South-East Asia Region countries mainly include 10 malaria-endemic countries (Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste. Of the 584, 000 malaria deaths worldwide, about 78% (453,000 malaria deaths) occurred in children aged below 5 years. Malaria mortality mainly occurred in the WHO African Region

(90%) followed by the WHO South-East Asia Region (7%) and the WHO Eastern Mediterranean Region (2%). More than 80% of the *P. vivax* cases were documented from three countries (India, Indonesia and Pakistan). WHO (2014) report estimates suggest that the number of confirmed malaria cases in the South-East Asia region has reduced from 2.9 to 1.5 million between 2000 and 2013 [2]. In 2013, 96% of the cases were accounted from three countries that include India (58%), Myanmar (22%) and Indonesia (16%). In the WHO South-East Asia region, two countries (India and Thailand) are expected to accomplish a decline of 50–75% in malaria-infected cases by the year 2015 mainly because of various National malaria control programmes. On the other side, Sri Lanka reported 124 cases in 2011 and 23 in 2012 but for the first-time it has reported zero locally acquired malaria-incidences in 2013. India reports the maximum number of malaria-infected cases in South-East Asia region while *Plasmodium falciparum* infected-malaria contributes more than 50% of the cases reported annually [4]. The malaria related cases and deaths reported by the Indian Government are mainly from few states in East and North-East India [5,6]. The highly-endemic malaria states mainly include Orissa, Chhattisgarh, Jharkhand, and the north-eastern states of India. The high-malaria states (Orissa, Chhattisgarh, Jharkhand, Northeast states, Madhya Pradesh) include 12% of annual all-India deaths from all diseases and 47% of them due to malaria-related deaths before 70 years of age [6]. In North-Eastern states of India (comprising of eight states which share international borders with China, Bangladesh, Bhutan and Myanmar) only 3.96% of India's population resides but they contributes for more than 10% of total reported malaria cases which includes 11% of *P. falciparum* cases and 20% of malaria mortality annually [7]. Any successful malaria control programmes in rural or urban setting of developing world requires persistent political collaborations, active participation of all levels such as public and private sectors, health and non-health sectors, and supported by technical and management personals. According to WHO report (2009), many countries like Iran, Azerbaijan, Turkmenistan, Oman, Georgia, Turkey, Uzbekistan, Armenia and Kyrgyzstan, have shown severe decline in malaria infection and reported to be in elimination phase [7,8].

2.1 *Plasmodium knowlesi:* The Fifth Human Malaria Parasite

In 1932, R. Knowles and B.M. Das Gupta reported the maintenance of monkey-malaria parasite by serial passage in monkeys and subsequently transmitting this monkey malaria species to human subjects [9]. Natural hosts of the simian malaria parasite *Plasmodium knowlesi*, named after Dr. R. Knowles, are the long-tailed macaques (*Macaca fasicularis)* and pig-tailed macaques (*Macaca nemestrina*) [10,11]. *Anopheles leucosphyrus* mosquitoes are responsible for *P. knowlesi* transmission from human to human or from the macaque monkeys (Old World monkey) to humans. It has become a major cause of human malaria in Southeast Asia widely distributed across Malaysian Borneo and Peninsular Malaysia and the microscopic examination of *P. knowlesi infected-blood was* commonly misidentified with benign *P. malariae parasites* [10]. *P. knowlesi* early blood-trophozoites morphologically resemble those of *P. falciparum intra-erythrocytic trophozoites stages*. While the late and mature trophozoites, schizonts and gametocytes stages appear morphologically similar to those of *P. malariae*. Only careful blood smear examinations revealed that a few morphological differences existed between *P. knowlesi* and *P. malariae such as, P. knowlesi* trophozoites bears double chromatin dots and sometimes with 2 or 3 parasites in each infected RBC while the *P. knowlesi* mature schizonts bears 16 merozoites as compared to 12 in case of *P. malariae* [12]. One of the most effective diagnosis tools for detecting *P. knowlesi* parasite in blood is polymerase chain reaction (PCR) of knowlesi-specific genes, such as small subunit rRNA and mitochondrial cytochrome b [13,14,15].

2.2 The HIV and Malaria Co-Infection

Increasing evidence has shown pathological interactions between Human Immunodeficiency Virus (HIV) infection and Malaria in dually infected individuals; however the exact correlation between the two still remains unclear [16]. Further co-infection might have assisted the geographic spreading out of malaria in highly prevalent HIV-infected areas. HIV infected cases are extensively reported throughout the world and are particularly widespread in sub-Saharan Africa and Asia regions. *P. falciparum*, one of the most common and lethal malaria parasites, is prevalent in sub-Saharan Africa, the Indian

subcontinent, and Southeast Asia. Recent clinical studies have shown that HIV patients are more susceptible to malaria episodes [17]. About 33 million people are HIV infected worldwide, of which 22.5 million cases are from Sub-Saharan Africa only [18]. Together, HIV and malaria cause more than 4 million casualties per year (19). Further, reports suggest that standard antimalarial drugs may be less efficacious in HIV-infected patients [19]. A childhood malaria study in rural Kwazulu-Natal, a province of South Africa, accounted that HIV-infected children are more susceptible to develop severe disease condition [20]. Data from a cohort study reported higher occurrence of malarial parasitaemia in HIV-infected patients that increases with declining CD4-cell count [21]. Antiretroviral HIV protease inhibitors drugs have been shown to augment the antimalarial efficacy of artemisinin against *P. falciparum in vitro* [22]. The burden of HIV/AIDS and malaria requires collective and integrated health services at various levels of communities. These collaborative steps involve strategies to improve drug quality, develop newer rapid diagnostic kits, strict implementation of antimalarial and antiretroviral therapies and accurate drug resistance surveillance plans [19].

2.3 Spread of Artemisinin Resistance in South-East Asia

Artemisinin is isolated from the plant *Artemisia annua also known as* sweet wormwood. Artemisinin and its derivatives are the most potent antimalarial drugs because of its ability to promptly reduce the intra-erythrocytic *Plasmodium* parasites in malaria-infected patient [1,2,7]. Artemisinin-based combination therapies (ACTs) has been strongly recommended by World Health Organisation (WHO) as the first-line drug for treatment of uncomplicated *P. falciparum* malaria [2,7]. ACTs are basically combination of artemisinin derivative along with one or more synergistic or additive partner drug(s). These two or more blood schizontocidal drugs have independent modes of inhibitory action and target different biochemical pathways within the blood stage-parasites. These combinations improve the therapeutic efficacy and delay the drug resistance development against the individual drugs in the combination. Over the years, the number of ACT treatment courses procured by various malaria-endemic countries has grown, which is from 11 million in 2005 to 392 million courses in 2013. WHO guidelines (2014) has further recommended both chloroquine and ACT combined dose with a 14-day course of primaquine so as to prevent relapses in malaria-infected patients, subject to consideration as haemolysis can occur in the glucose-6- phosphate dehydrogenase (G6PD) deficient malaria patients [2]. Primaquine is a vital part of drug regimes as it specifically eliminates the dormant liver stages (hypnozoites) of the parasites. In artemisinin resistant areas, a single dose of primaquine (about 0.25 mg/kg) is recommended to all *P. falciparum* infected patients on the first day of the ACT dosage. In 2013, 79 out of 87 countries recognized as *P. falciparum* endemic countries adopted ACTs in their National Malaria Treatment Policy as the first-line of therapy [2].

Artemisinin-resistant *P. falciparum* has been confirmed from eastern Myanmar, western Cambodia and Thailand, southern Vietnam, southern Laos and north-eastern Cambodia parts of the world (Table 2) [23]. Delayed parasite clearance after Artemisinin Combination Therapies (ACTs), such as artesunate–mefloquine and dihydroartemisinin–piperaquine, is now of supreme concern to World Health Organisation even though ACTs remain the most effective treatment for uncomplicated *P. falciparum* malaria [24,25]. In addition, ACTs treatment failure in Thailand (artesunate–mefloquine) and Cambodia (dihydroartemisinin–piperaquine) has enhanced by a factor of more than 5 [24,25]. Recently, the artemisinin resistance molecular marker in artemisinin-resistant *P. falciparum* parasite line from Africa and clinical isolates from Cambodia region was reported [26]. The whole-genome sequencing showed mutations in the Kelch 13 (K13)-propeller domain responsible for artemisinin resistance *in vitro* and *in vivo* [26]. WHO launched the 'Emergency response to artemisinin resistance (ERAR)' in the Greater Mekong subregion, comprising of six states of the Mekong River basin namely the People's Republic of China (specifically Yunnan Province and Guangxi Zhuang Autonomous Region), Lao People's Democratic Republic, Myanmar, Thailand, and Vietnam and 'WHO Global Plan for Artemisinin Resistance Containment (GPARC)' programme to stop the widespread and emergence of artemisinin-resistant parasites and tackle the declining efficacy of ACTs.

Table 1. Adoption of different policies by various WHO regions (Data compiled from WHO, World malaria report 2014) [2]

Policy	AFR	AMR	EMR	EUR	SEAR	WPR	Total
No. of countries/areas with malaria transmission	45	21	8	3	10	10	97
No. of *P. falciparum* endemic countries/areas	44	17	8	0	9	9	87
No. of *P. vivax* endemic countries/areas	7	19	6	3	10	10	55
ACTs used for treatment of *P. falciparum*	43	9	8	1	9	9	79
Single-dose gametocidal drug primaquine for *P. falciparum* treatment	3	19	4	3	7	3	39
ITNs/LLINs free distribution	41	19	8	4	10	10	92
Insecticide resistance monitoring programmes	41	16	9	5	7	8	86

Abbreviations: ACT, artemisinin-based combination therapy; AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asia Region; WPR, Western Pacific Region; ITN, insecticide-treated mosquito net; LLIN, long-lasting insecticidal net

Table 2. Summary of artemisinin resistance in the Greater Mekong Subregion (Data compiled from WHO, 2014. Status report on artemisinin resistance) [23]

Greater Mekong Subregion	Year of Emergence of Artemisinin Resistance	Year of Detection of Artemisinin Resistance	Year of Start of Control Programmes	AL	AS-MQ	DHA-PPQ
Cambodia	2001	2006	2009	+	+	+
Laos	2013	2013	2014	+	UD	UD
Myanmar	2001	2008	2011	+	+	+
Thailand	2001	2008	2009	+	+	UD
Vietnam	2009	2009	2011	UD	UD	+

Abbreviations: AL: Artemether-Lumefantrine; AS-MQ: Artesunate-Mefloquine; DHA-PPQ: Dihydroartemisinin-Piperaquine; UD: Undetermined

3. CONCLUSION

Malaria caused by *P. falciparum* and *P. vivax* are one of the biggest public health challenges today. WHO report (2014) suggests that the yearly funding on malaria control and elimination programmes has increased in 2013 to US $ 2.7 billion, about three times the sum spent in the year 2005 [2]. Artemisinin-based Combination Therapies (ACTs) have been adopted by most countries with high *P. falciparum* malaria cases as the first-line treatment for intra-erythrocytic malaria parasite. In 2014, revised guidelines on vector control by appropriate administration of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) were issued by WHO. The IRS programmes in several countries use Pyrethroids as the primary class of insecticides. The emergence of artemisinin-resistant parasites, poor quality antimalarials having inadequate or no artemisinin derivatives, HIV-malaria coinfection and development of newer strains have heighten the risk of ACTs treatment failures and high mortality cases across the population specially in infants, young children and pregnant women. In absence of any licensed malaria vaccine, chemoprevention strategies along with vector control programmes are particularly important for malaria eradication programmes. According to WHO report, twenty-five malaria vaccine development projects are in evaluation process. These vaccine candidates are categorised as Pre-erythrocytic, Blood-stages or Transmission-blocking candidates against *P. falciparum* and *P. vivax* malaria. Of all these, 04 candidate vaccines are currently in advance clinical trial stages where 03 candidate vaccines (ChAd63/MVA ME-TRAP, GM22 and MSP3 (181-276)) are in Phase 2B trials and 01 candidate vaccine (RTS,S-AS01) completed its Phase 3 trials [27]. The WHO Global Malaria

Programme along with the WHO regional and country offices, health ministries of malaria-endemic countries and other academic and social partners are working actively to reduce the ongoing malaria transmission and prevent parasite reintroduction across the nations with an aim to eliminate malaria globally.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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