

BURDEN OF MALARIA AND PROSPECTIVE CHALLENGES IN SOUTH-EAST ASIA REGION: A REVIEW

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. Even though over the year 2000 to 2013, malaria eradication programmes has received greater international attention leading to reduction of parasite-infected cases by 26%, from 173 million to 128 million, nevertheless malaria remains a global health concern in developing nations. Of the 11 The WHO South-East Asia Region 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 since the year 1984. Excessive dependence on artemisinin combination therapy, emergence of drug resistant parasites, coinfection in immunocompromised patients and newer *P. knowlesi* strains are fuelling this health concern further. Routine surveillance of the antimalarial therapeutic efficacy, new rapid diagnostic tools and appropriate treatment interventions can certainly monitoring and limit this deadly disease especially in the malaria-endemic countries. In this review, the various intertwined factors leading to high malaria burden and concern globally are highlighted.

Keywords: *Malarial parasite, Plasmodium Knowlesi, HIV-malaria coinfection, Artemisinin resistance*

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31 INTRODUCTION

32 Malaria is a life-threatening disease caused by *Plasmodium* parasites which is transmitted from one
33 person to another by the bite of infected female mosquitoes of the genus *Anopheles*. The four
34 commonly reported different types of malarial parasites in humans are *P. falciparum*, *P. vivax*, *P.*
35 *ovale*, and *P. malariae* [1]. Of these, *P. vivax* and *P. falciparum* are the most prevalent malarial
36 parasites while *P. falciparum* is the most lethal of all, with highest number of severe and mortality
37 cases reported. *P. vivax* has a wider geographic distribution than *P. falciparum* since the parasite can
38 grow and survive in the *Anopheles* mosquito even at lower temperatures such as higher altitudes and
39 cooler climates. Moreover *P. vivax* has a dormant liver stage (called as hypnozoites) completed in
40 human asexual lifecycle, which enables the parasite to survive for long periods in the body and can
41 become activated months later to cause a malarial relapse [1]. There are about 400 different species
42 of *Anopheles* mosquitoes, of which only 30 are vectors of major importance transmitting malarial
43 parasites. According to the latest World Health Organization report (2014), about 3.2 billion people in
44 97 countries across the globe are at danger of being infected with malaria disease while 1.2 billion of
45 them are at high risk of developing malaria in a year [2] (Table 1). In 2013, 198 million cases of
46 malaria occurred worldwide and 5,84,000 deaths occurred due to it. Since the year 2000 due to
47 various malaria eradication programmes, the number of malaria infection cases have reduced by
48 26%, that is from 173 million in the year 2000 to 128 million in the year 2013 [2]. Consequently the
49 global malaria mortality rates have also dropped by 47% while 54% in the WHO Africa Region, which
50 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, who involves, malaria endemic countries, private associations, non-governmental organisations (NGO), community-based foundations, research institutes and academic establishments [1,2].

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 <i>P. falciparum</i> endemic countries/areas	44	17	8	0	9	9	87
No. of <i>P. vivax</i> endemic countries/areas	7	19	6	3	10	10	55
ACTs used for treatment of <i>P. falciparum</i>	43	9	8	1	9	9	79
Single-dose gametocidal drug primaquine for <i>P. falciparum</i> 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.

69 **STATUS OF MALARIA IN SOUTH-EAST ASIA REGION**

70 In 2013, approximately 198 million malaria cases were reported globally [2]. Of these, majority of the
 71 cases were from WHO African Region (82%), followed by the WHO South-East Asia Region (12%)
 72 and the WHO Eastern Mediterranean Region (5%). The WHO South-East Asia Region countries
 73 mainly include 10 malaria-endemic countries (Bangladesh, Bhutan, Democratic People's Republic of
 74 Korea, India, Indonesia, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste. Of the 5, 84, 000 malaria
 75 deaths worldwide, about 78% (4,53,000 malaria deaths) occurred in children aged below 5 years.
 76 Malaria mortality mainly occurred in the WHO African Region (90%) followed by the WHO South-East
 77 Asia Region (7%) and the WHO Eastern Mediterranean Region (2%). More than 80% of the *P. vivax*
 78 cases were documented from three countries (India, Indonesia and Pakistan). WHO (2014) report
 79 estimates suggest that the number of confirmed malaria cases in the South-East Asia region has
 80 reduced from 2.9 to 1.5 million between 2000 and 2013 [2]. In 2013, 96% of the cases were
 81 accounted from three countries that include India (58%), Myanmar (22%) and Indonesia (16%). In the
 82 WHO South-East Asia region, two countries (India and Thailand) are expected to accomplish a
 83 decline of 50–75% in malaria-infected cases by the year 2015 mainly because of various National
 84 malaria control programmes. On the other side, Sri Lanka reported 124 cases in 2011 and 23 in 2012
 85 but for the first-time it has reported zero locally acquired malaria-incidences in 2013. India reports the
 86 maximum number of malaria-infected cases in South-East Asia region while *Plasmodium falciparum*
 87 infected-malaria contributes more than 50% of the cases reported annually [4]. The malaria related
 88 cases and deaths reported by the Indian Government are mainly from few states in East and North-
 89 East India [5,6]. The highly-endemic malaria states mainly include Orissa, Chhattisgarh, Jharkhand,
 90 and the north-eastern states of India. The high-malaria states (Orissa, Chhattisgarh, Jharkhand,
 91 Northeast states, Madhya Pradesh) include 12% of annual all-India deaths from all diseases and 47%
 92 of them due to malaria-related deaths before 70 years of age [6]. In North-Eastern states of India
 93 (comprising of eight states which share international borders with China, Bangladesh, Bhutan and
 94 Myanmar) only 3.96% of India's population resides but they contributes for more than 10% of total
 95 reported malaria cases which includes 11% of *P. falciparum* cases and 20% of malaria mortality
 96 annually [7]. Any successful malaria control programmes in rural or urban setting of developing world
 97 requires persistent political collaborations, active participation of all levels such as public and private

98 sectors, health and non-health sectors, and supported by technical and management personals.
 99 According to WHO report (2009), many countries like Iran, Azerbaijan, Turkmenistan, Oman, Georgia,
 100 Turkey, Uzbekistan, Armenia and Kyrgyzstan, have shown severe decline in malaria infection and
 101 reported to be in elimination phase [7,8].

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103 ***PLASMODIUM KNOWLESI* : THE FIFTH HUMAN MALARIA PARASITE**

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

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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].

SPREAD OF ARTEMISININ RESISTANCE IN SOUTH-EAST ASIA

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 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.

CONCLUSION

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 failure, selecting resistant strains and higher mortality in population subgroups specially in infants, young children and pregnant women. Concerted global efforts and appropriate public health interventions would certainly help to control and eliminate the burden of malaria.

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