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REVIEW ARTICLE

Threat of zoonotic malaria and strategy to overcome in Kalimantan (Indonesian Borneo) bordering Malaysian Borneo

Diana Natalia[1,2]*, Willy Handoko[2], Sari Rahmayanti[2], Tri Wahyudi[2], Ayu Akida Abdul Rashid[1], and Paul Cliff Simon Divis[1]

[1]Malaria Research Centre, Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, Kota Samarahan, Sarawak, Malaysia

[2]Faculty of Medicine, Universitas Tanjungpura, Pontianak, West Kalimantan, Indonesia

*** Correspondence Author:**

diananatalia@medical.untan.ac.id

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ABSTRACT

Indonesia aims to eradicate malaria by 2030. Indonesia has the second highest disease burden in the WHO South-East Asia region, after India, accounting for 9% of all malaria cases in 2024. Malaria cases have dropped dramatically due to national strategic plans and programs, and the Indonesian Ministry of Health has certified several districts as malaria-free zones. Malaria cases in Kalimantan (Indonesian Borneo), have declined during the last two decades. Nearly all regencies within these provinces have been declared as having low malaria endemic status (API<1 per 1000 people), except for one regency in East Kalimantan Province, which showed a high endemicity level (API>5 per 1000 people). This reduced incidence, however, contrasts sharply with the zoonotic infection caused by the simian parasite *Plasmodium knowlesi*, which is prevalent in Malaysian Borneo. Only a few cases of *P. knowlesi* infection have been reported in South and Central Kalimantan Province since 2010. This difference between Kalimantan, Indonesia and Borneo, Malaysia appears contradictory given that both regions have a similar epidemiological risk of zoonotic malaria infection and share the same natural habitat. The references were tracked using various databases, such as Google Scholar, PubMed (MEDLINE) and other sources (Google engine and manual searching using a reference list). This review's objective was to describe current malaria and zoonotic malaria, mosquito vector prevalence, and the available data from case reports along the Kalimantan border in Indonesia during the malaria elimination phase, compared with malaria distribution in the neighbouring country, Malaysian Borneo.

Keywords: Malaria, simian, *Plasmodium*, Kalimantan border, strategy, threat

INTRODUCTION

Malaria is a mosquito-borne disease caused by *Plasmodium* parasites. There are hundreds of *Plasmodium* species that have been described to infect a wide range of vertebrates, such as primates, rodents, reptiles, and birds.(1) Five *Plasmodium* species, namely *Plasmodium falciparum, P. vivax, P. malariae, P. ovale,* and *P. knowlesi,* are known to infect humans and cause malaria.(2) While *P. vivax* is the most widely distributed species of human malaria, *P. falciparum* is known as the deadliest species.(3) These *Plasmodium* species are transmitted by infected female *Anopheles* mosquitoes that bite humans and infect their red blood cells.(1)

Malaria has been reported to be prevalent in more than 85 endemic countries, with an increase of 5 million cases in 2022 compared with 2021, resulting in 249 million malaria cases.[4] Despite an 11.9% decline in malaria cases between 2021 and 2022 in the WHO South-East Asia region, the disease still accounted for 2% of malaria cases worldwide. Malaria cases and incidence have surged in Bangladesh, Myanmar, and Thailand, with India and Indonesia accounting for 94% of all malaria deaths. The Maldives and Sri Lanka received malaria-free status in 2016 and have maintained that status. [4] Malaysia reported no indigenous infections for the fifth year consecutively and aimed for elimination, despite 2,500 *P. knowlesi* malaria cases being reported in 2022.[4, 5]

Every year, approximately two million cases of malaria are reported in Indonesia.[6, 7] In 2021 throughout the COVID-19 pandemic, a total of 811,636 new malaria cases with 1,412 deaths were reported.[8] The post COVID-19 pandemic situation showed increased malaria cases in 2022 and 2023 (Figure 1), where 98.9% were confirmed by laboratory tests. Of these, 52% of cases were confirmed by standard microscopy and 48% by rapid diagnostic test (RDT).[9] Most malaria cases occur in the eastern part of Indonesia (Papua, East Nusa Tenggara, West Nusa Tenggara, Maluku, part of Sulawesi) accounting for more than 87% of all 3.35 million national cases.[9] In 2021 there were 3 Indonesian provinces with regencies of high endemicity [annual parasite incidence (API) >5 per 1000 people], namely East Nusa Tenggara (3 regencies), East Kalimantan (1 regency), and Papua (17 regencies).[6] Recently, 33 provinces were declared to have malaria elimination status with decreased numbers of malaria cases over the years.[8,10] Overall, *P. falciparum* infections accounted for half of the total malaria cases in 2022, followed by *P. vivax* (33.4%), mixed *P. falciparum* and *P. vivax* (13.2%) and infections by other *Plasmodium* species (2.2%).[11] Infections caused by *P. falciparum* and *P. vivax* were common in Eastern Indonesia (83%), while zoonotic malaria caused by *P. knowlesi* was also found in some regions of Sumatra and Kalimantan, but at low frequency.[12-16]

In Southeast Asia and South America, while some countries reported zero indigenous malaria cases by human *Plasmodium* species, there has been a challenge by the rise of zoonotic malaria infections. Malaysia aimed for malaria elimination with no indigenous cases caused by human *Plasmodium* species since 2018, yet more than 17,000 cases of *P. knowlesi* infection and 48 deaths have been reported since 2017 and also contributing to 90.5% of *P. knowlesi* cases worldwide in 2022.[3- 5] Besides *P. knowlesi*, other zoonotic malaria by non-human primate *Plasmodium* species have been progressively reported. For example, *P. cynomolgi* and *P. inui* infections in Malaysia and Thailand [17-22] and infections with the New World monkey parasites *P. brasilianum* and *P. simium* in Brazil.[23]

Borneo, a hotspot of biodiversity, has already suffered huge deforestation that has endangered many species. Further decreasing biodiversity and bringing more people in closer contact with macaques and mosquitoes may dramatically increase the risk of emerging zoonotic infections, including *P. knowlesi* malaria. Indeed, Malaysian Sabah and Sarawak states, at the northern border of Indonesian Borneo, are among the main areas of *P. knowlesi* transmission to humans, representing more than 9000 cases reported between 2017 and 2019.[24] In 2021, the World Health Organization (WHO) reported 3651 cases globally and 13 deaths from *P. knowlesi* malaria in Malaysia. Meanwhile, the global incidence of *P. knowlesi* has been reported to decrease by 24% in 2022.[4] Given this background, this review aimed to describe the current epidemiology of malaria and zoonotic malaria, mosquito vector prevalence, and the available data from case reports along the Kalimantan border in Indonesia during the malaria elimination phase compared with malaria distribution in the neighbouring country, Malaysian Borneo.

Geographical situation and population

Borneo is the world's third biggest island, covering approximately 287,000 square miles, being located southeast of the Malay Peninsula and southwest of the Philippines. It is divided into four political regions, as shown in Figure 2. Kalimantan is in Indonesia, Sabah and Sarawak are in Malaysia, and the Sultanate of Brunei is situated north of Sabah. Indonesia is the major political component of the island. Borneo island has a tropical climate, often with high temperatures and high humidity. The island is located at the equator and has relatively constant temperatures throughout the year, between 25-35°C. The island is known for its dense rainforests and diverse wildlife.[25]

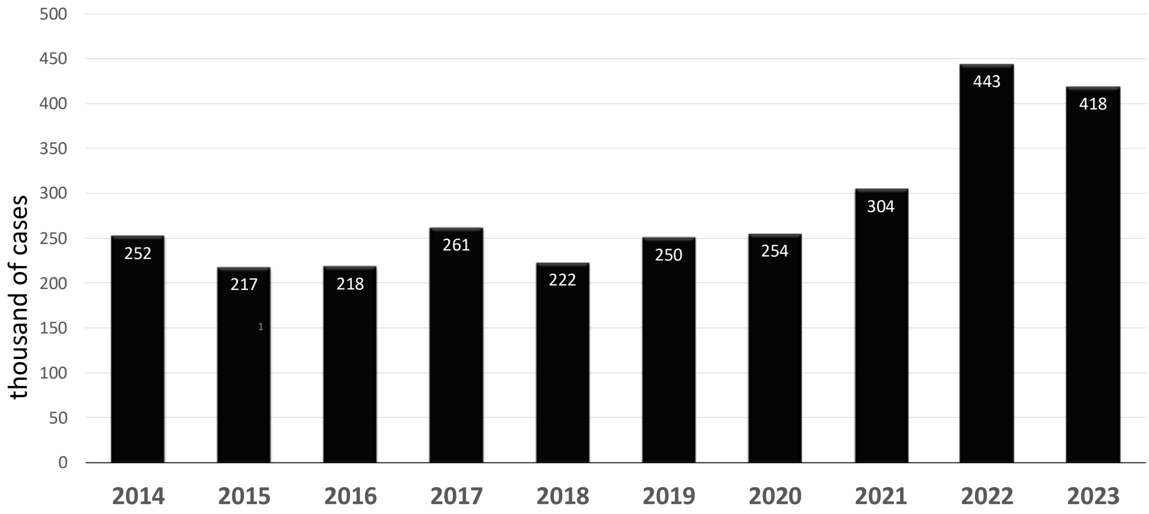

Figure 1. Malaria cases in Indonesia [(11)]

Figure 2. Map of Borneo Island

The map shows three bordering countries: Brunei, Malaysia (Sarawak and Sabah states) and Indonesia (five Kalimantan provinces).

METHODS

The present review on malaria and zoonotic malaria involved an extensive literature search that was performed in PubMed (MEDLINE) and Google Scholar using the keywords "malaria + Kalimantan + Indonesia" and "plasmodium + Kalimantan". Data on malaria were obtained from the provincial Health Department and personal communication with malaria officers in both Indonesia and Malaysia. Publications older than ten years were excluded, as were those published in languages other than English, unless they were the primary source of literature and rare in publication.

Zoonotic malaria

The natural zoonotic malaria infections were initially reported as early as the 1960s and 1970s in Peninsular Malaysia, and were extremely rare until a large focus of *P. knowlesi* infections was reported in Kapit Division in Sarawak, Malaysian Borneo, in 2004.(1,26) Due to this, the causative organism has been recognized as the fifth *Plasmodium* species to affect humans.(1) Since then, similar cases have been documented in all Southeast Asian countries except Timor Leste, as molecular diagnosis has advanced. (24, 27)

Zoonotic infection caused by *P. knowlesi* constitutes the predominant type of malaria in Malaysia, despite the absence of indigenous cases of human *Plasmodium* species infection since 2018. A study conducted in Kapit Division, Sarawak, involving 152 hospitalised patients revealed a 1.8% case fatality rate for knowlesi malaria and 6.5% for severe disease.(28) From 2017 onwards, Malaysia has reported a total of 17,125 cases with 48 deaths attributed to *P. knowlesi* infections. In 2021 alone, 3,575 *P. knowlesi* cases and 13 deaths have been recorded.(3) In comparison, Indonesia, the Philippines, and Thailand collectively reported 435 *P. knowlesi* infections.(3) More recently human natural infections with *P. cynomolgi, P. inui, P. coatneyi* and *P. simiovale* were reported among indigenous communities living near the forest fringe in various locations in Malaysia.(17)

Commonly employed molecular techniques have accurately identified *Plasmodium* species in malaria patients for effective drug therapy.(29) This suggests that simian *Plasmodium* species might regularly infect humans, posing a risk of misdiagnosis as human *Plasmodium* infection when using standard microscopy methods.(30) *P. knowlesi* isolated from humans can be easily misdiagnosed as *P. falciparum* or *P. malariae* due to the morphological similarities with these latter parasites.(27) Similarly, the asexual stage feature of *P. cynomolgi* is indistinguishable from *P. vivax* by microscopy identification.(31) *P. malariae* also has similar morphological features to *P. brasilianum.*(32) The microscopy method is cost-effective and affordable, but its sensitivity is doubtful low parasitemia and a shortage of experienced microscopists.

The natural hosts of simian *Plasmodium* species are very diverse, which include Old World and New World primates as presented in Table 1. (33, 34) The most considered types of simian malaria caused by *P. knowlesi, P. cynomolgi, P. coatneyi,* and *P. inui* were originally harboured by long-tailed macaques (*Macaca fascicularis*), pig-tailed macaques (*Macaca nemestrina*) and banded leaf monkeys (*Presbytis melolophus).*(35) A study in India reported the presence of *P. fragile, P. inui* and *P. cynomolgi* in *Macaca radiata*, as well as the occurrence of *P. falciparum* in *M. mulatta* and *M. radiata.*(36) A molecular analysis of malaria parasites in Malaysian Borneo led to the unexpected discovery of *P. simiovale* in wild macaques.(37) Previously, *P. simiovale* was thought to be restricted to *Macaca sinica* in Sri Lanka.(37) Recent findings revealed its zoonotic potential, with *P. simiovale* infecting humans among indigenous communities living near forest fringes,(17) highlighting the need for enhanced surveillance and understanding of zoonotic malaria dynamics. Entomological surveillance identified most anopheline mosquitoes that transmit simian *Plasmodium* species to humans as belonging to the *Leucosphyrus* group. These include *An. latens* that has been incriminated as the vector of *P. knowlesi* in Sarawak, Malaysia, *An. cracens* in Peninsular Malaysia, and *An. dirus* in Vietnam.(24,38) *An. cracens* and *An. freeborni* have been suspected as vectors of *P. cynomolgi* and *P. inui.*(39) *An. latens, An. balabacensis, An. leucosphyrus, An. introlatus*, and *An. cracens* are the known *P. knowlesi* vectors in Indonesia, while in Kalimantan, *An. balabacensis, An. leucosphyrus,* and *An. latens* are reported as *P. knowlesi* vectors.(40) Recent molecular entomological surveys in Sarawak revealed that more *Anopheles* species are being identified as vectors in areas with low frequencies of zoonotic malaria such as *An. balabacensis* and *An. donaldi* in Lawas district(24) and *An. latens, An. introlatus, An. roperi* and *An. collessi* in Betong district.(38)

The *Leucosphyrus* group of *Anopheles* mosquitoes was previously exclusively known to be found in deep forests in Southeast Asia.[41] The mosquito bites at dusk, when most people return home from the forest or plantations. A recent geospatial analysis revealed that it has followed simian hosts to the edge of forests, farms, and semi-urban regions as a result of deforestation.[42] For example, *An. balabacensis* in Sabah, Malaysia, shifted its habitat from deep forest to fields, naturally shifting its breeding sites and raising its biting rates on humans.[43] Alteration in vector habitats and their behaviour, along with increased proximity to macaques, make humans susceptible to zoonotic malaria infections, particularly forest-dwelling individuals.

Prevalence of malaria in Kalimantan bordering Malaysia

Malaria morbidity and fatality data in the Kalimantan border region have been frequently underreported. Zoonotic infections caused by *P. knowlesi* have been reported in certain regions of Kalimantan, though at very low frequencies. The first documented case involved an Australian traveller returning from South Kalimantan,[12] followed by four additional cases among gold miners in the same region.[45] In 2016, another *P. knowlesi* infection was identified in a traditional gold miner in Central Kalimantan.[15] Despite advancements in diagnostic testing and reporting procedures, accurately determining the burden of zoonosis malaria in Indonesia, particularly *P. knowlesi* infections, remains challenging. *P. knowlesi* is primarily a zoonosis, with human infections occurring among individuals who frequently farm or engage in forested areas near macaque populations. Reported cases of *P. knowlesi* infections in Indonesia are rare, with most detected through PCR in North Sumatra (11.8%) and Aceh Besar (1.27%).[13,14] A limited number of cases have also been reported in Central and South Kalimantan.[12,15,16] There have been no reports of zoonotic malaria in West Kalimantan, despite its proximity to Malaysian Borneo, a region with a high prevalence of *P. knowlesi* infections. However, a study conducted in Kapuas Hulu Regency identified 16 *Plasmodium*-positive individuals using PCR assay targeting the 18S rRNA gene. Among these, five were confirmed as human *Plasmodium* species infections (2 *P. vivax*, 2 *P. ovale*, and 1 *P. malariae*), while 11 infections could not be conclusively identified despite being positive for *Plasmodium* DNA. A BLAST search analysis of short 18S rRNA (174-248 bp) from these samples revealed seven simian *Plasmodium* species including *P. knowlesi, P. coatneyi, P. inui*, and *P. fieldi*. This finding highlights the potential for simian *Plasmodium* infections in West Kalimantan, particularly near the border with Malaysian Borneo.[48]

Table 1. Simian *Plasmodium* species in Southeast Asia [33,44]

***Plasmodium* species**	**Natural host**	**Geographical distribution**
P. knowlesi	Macaques (*M. fascicularis, M. nemestrina*) Leaf monkeys (*Presbytis melalophos)*	Malaysia, Indonesia, Philippines, Vietnam
P. cynomolgi	Macaques (*M. fascicularis, M. nemestrina, M. radiata, M. cyclopis, M. sinica, M. mulatta*) Langur (*Presbytis cristatus, Semnopithecus entellus)*	Malaysia, Indonesia, Taiwan, Cambodia, Sri Lanka
P. inui	Macaques (*M. fascicularis, M. nemestrina, M. radiata, M. cyclopis*) Langur (*Presbytis cristatus, P. obscurus)*	Malaysia, Indonesia, Taiwan
P. coatneyi	Macaques (*M. fascicularis)*	Malaysia, Philippines
P. fragile	Macaques (*M. radiata, M. sinica)*	India, Sri Lanka
P. fieldi	Macaques (*M. fascicularis, M. nemestrina*)	Malaysia
P. simiovale	Macaques (*M. sinica)*	Sri Lanka
P. hylobati	Gibbon (*Hylobates moloch*)	Indonesia
P. youngi	Gibbon (*Hylobates lar*)	Malaysia
P. eylesi	Gibbon (*Hylobates lar*)	Malaysia
P. jefferyi	Gibbon (*Hylobates lar*)	Malaysia
P. sylvaticum	Orangutan (*Pongo pygmaeus*)	Malaysia, Indonesia
P. pitheci	Orangutan (*Pongo pygmaeus*)	Malaysia, Indonesia

Entomological surveys across various regions in Kalimantan have identified various *Anopheles* mosquito species as malaria vectors. In South Kalimantan, *An. subpictus, An. indefinitus, An. leucosphyrus,* and *An. balabacensis* were incriminated as malaria vectors,[47] while *An. vagus*, *An. peditaeniatus* and *An. tessellatus* were specifically associated with *P. vivax* transmission.[48] In Sebatik Island of North Kalimantan bordering the Sabah state of Malaysian Borneo, *An. balabacensis, An. sundaicus, An. maculatus* and *An. peditaeniatus* were identified as vectors.[49] Central Kalimantan was reported to exhibit diverse *Anopheles* species as malaria vectors, including *An. barbumbrosus, An. barbirostris, An. letifer, An. kochi, An. nigerrimus, An. latens, An. umbrosus* and *An. Vagus.*[50]

Prevalence of malaria in Malaysian Borneo

Malaysia has made significant progress in malaria control, achieving zero indigenous cases caused by human *Plasmodium* species since 2018 as shown in Figure 3.[51] However, *P. knowlesi* cases have steadily increased, particularly in Sarawak and Sabah in Malaysian Borneo [5, 42, 52-55] and some regions of Peninsular Malaysia.[56,57] In Sarawak, knowlesi malaria accounts for more than half of malaria admissions in certain hospitals,[42,52] while cases in Sabah have risen more than ten-fold.[55] Since the first large focus of *P. knowlesi* infections in Sarawak in 2004 [26], the importance of diagnosing zoonotic malaria has been widely recognized by clinicians and laboratory microscopists in high-risk areas. This has led to an increase in reported cases of *P. knowlesi* malaria across Malaysia (Figure 3).[55,56,58-61]

Due to the attempts at malaria elimination, molecular testing is increasingly used in surveillance studies to detect low-level illnesses. The effort by the Malaysian Ministry of Health to eliminate malaria has yielded significant success, with a marked reduction in *P. falciparum* and *P. vivax* cases.[3] The use of molecular methods, such as nested PCR assay, revealed *P. knowlesi* infections in humans previously misdiagnosed as '*P. malariae'* in 2001-2006 in Sarawak, indicating that human *P. knowlesi* infections in human are not a "new" emerging disease.[27] A spatiotemporal study in Kapit Division, Sarawak identified two *P. knowlesi* subpopulations associated with long-tailed and pig-tailed macaque hosts (Cluster 1 and Cluster 2, respectively),[62] and linked to human activities and environmental changes.[63] Cluster 1 *P. knowlesi* infections are linked to long-tailed macaques, which live near humans due to food availability and deforestation, whereas Cluster 2 infections are typically associated with activities in deep forest environments.[42] Besides *P. knowlesi*, other simian *Plasmodium* species, including *P. cynomolgi, P. inui*. *P. cynomolgi,* and *P. simiovale* have been reported to infect humans in both Sabah and Sarawak,[17-19] in which both macaque species serve as the primary reservoir host for these parasites.[37]

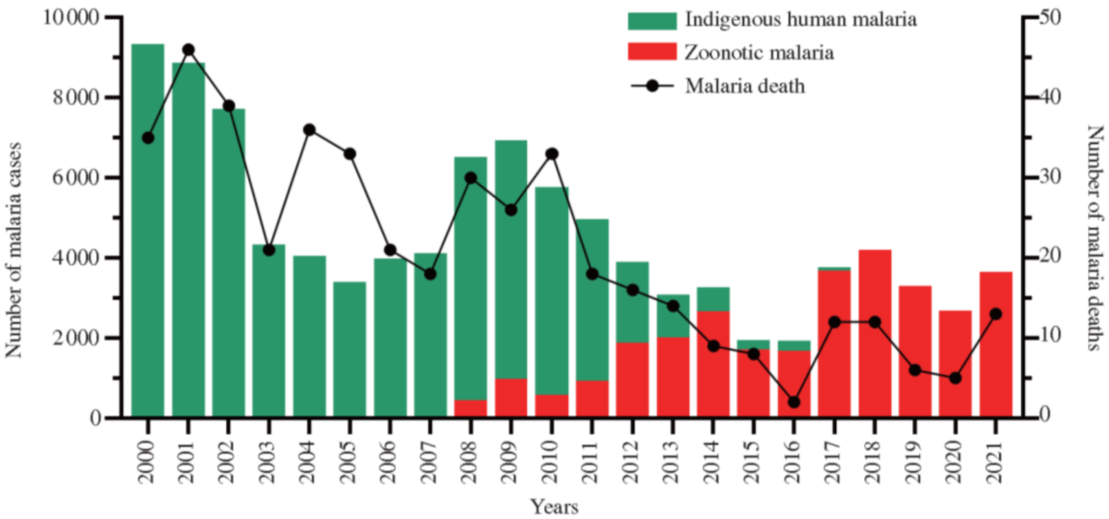

Figure 3. Malaria cases in Malaysia from 2000 to 2021 [65]

Entomological studies in Malaysia have identified nine *Anopheles* species as malaria vectors, including *An. balabacensis, An. maculatus, An. letifer, An. sundaicus, An. campestris, An. donaldi, An. dirus, An. leucosphyrus* and *An. flavirostris.* [64] A recent study in Sarawak indicates that *Anopheles* vectors of simian *Plasmodium* species extend beyond the *Leucosphyrus* Group. Examples include *P. knowlesi* in *An. barbirostris*; *P. coatneyi* in *An. roperi*; and *P. cynomolgi* in *An. latens* and *An. balabacensis.*[38]

Strategies to overcome malaria incidence in Kalimantan-Malaysian Borneo border region

In the Kalimantan-Malaysian Borneo border region, economic disparities between Indonesian provinces and Malaysian states have led to cross-border migration, impacting both trade and infectious disease dynamics. While Indonesians are drawn to Sarawak and Sabah in Malaysia by the economic opportunities and the movement of natural hosts such as wild macaques, these conditions raise concerns about the transmission of malaria between Kalimantan and Malaysian Borneo. Zoonotic malaria caused by *P. knowlesi* is a particularly concerning infectious disease in Malaysian Borneo, posing new challenges for healthcare systems and public health efforts. [65]

Despite the potential risks, there is a lack of systematic epidemiological data on human and zoonotic malaria in Kalimantan, the data coming mostly from presumptive diagnoses based on clinical symptoms. [9] One possible reason for the lack of systematic epidemiological data in Kalimantan is the limited resources allocated to public health activities and surveillance. Additionally, the remote and rural areas in Kalimantan may pose logistical challenges for continuous surveillance, further contributing to the lack of comprehensive data on malaria. This lack of data hinders the understanding and control of malaria transmission in the region.

In Indonesia, malaria surveillance relies on passive case detection by microscopic examination and rapid diagnostic tests (RDTs) at primary health care centers. [66] These tests are sufficient to detect clinical malaria caused by the two major species in Indonesia, *P. falciparum* and *P. vivax*. However, the identification of less common species, particularly at low-density parasitemia, is more challenging, which can lead to underdiagnosis. To pursue malaria elimination in Southeast Asia, molecular assays have increasingly been used to identify low-level infections in surveillance studies. In Malaysian Borneo, successful malaria control has dramatically reduced both *P. falciparum* and *P. vivax* cases but the numbers of *P. knowlesi* cases were increasingly detected by microscopy and initially thought to be the common *P. malariae* infection replacing the former two. Nevertheless, species-specific PCR assay confirmed the presence of *P. knowlesi* infections among these *P. malariae* cases, including cases retrieved from 1996, implying that *P. knowlesi* in humans is not a “new” emerging disease. Malaysia is now moving towards the elimination phase with increased use of molecular tests and a similar pattern with a significant proportion of *P. knowlesi* cases among malaria-infected populations has been observed. Indonesia will also launch sentinel surveillance of *P. knowlesi* that is already in the trial phase with strengthening of microscopy examination in the subdistrict health clinic laboratory, followed by cross-testing in district and provincial laboratories and PCR examination in the national laboratory. [67]

Active case finding through outreach or house-to-house visits by community health workers, distribution of LLINs, training, case and foci analysis, and migration surveillance are all critical and must be doubled to detect, treat, and reduce malaria cases efficiently. Stronger collaboration amongst ministries, particularly the Ministries of Health, Forestry and Environment, and Home Affairs, as well as the WHO, to sustain the malaria eradication programs and to meet the malaria elimination target by 2030, even though *P. knowlesi* malaria in humans is not yet required for malaria-free certification. Even at low transmission rates, it will be difficult to declare a country as malaria-free if there is a risk of *P. knowlesi* malaria. To anticipate the risk of *P. knowlesi* and other simian malarias, more government collaboration across provinces, regencies, and cities is essential throughout Indonesia.

CONCLUSION

The emergence of zoonotic malaria in Indonesia has altered the dynamics of malaria management and control in the pursuit of total eradication among the human population. The growing threat of zoonotic malaria may delay the malaria eradication effort even further. However, with focused efforts, zoonotic malaria transmission in humans can be prevented without jeopardizing the welfare of natural hosts, animal biodiversity, or the economic sector of zoonotic malaria-endemic regions. Before modifying the forest for agricultural use or human resettlement, the native habitat of non-human primates should be carefully considered.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author Contributions

DN, AAAR and PCSD designed the study, supervised the data collection and wrote the manuscript. DN, WH, SR and TW performed the data collection. DN, AAAR and PCSD performed the data analysis. All authors have read and approved the final manuscript.

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Data Availability Statement

Not applicable

Declaration of the Use of AI in Scientific Writing

Nothing to declare

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