Implementation of One Health Approach for Malaria Zoonotic Control in Indonesia: Past, Present, and Future

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Abstract. Malaria zoonotic, *Plasmodium knowlesi* threatens the global development of malaria elimination. Even though current control efforts have been implemented, the prevalence of malaria zoonotic in Indonesia cannot be ignored. Conventional measures to control malaria in humans ignore the transmission of residual *P. knowlesi* between hosts and natural primate vectors. Attempting to manage *Plasmodium knowlesi* transmission should try applying the One Health approach theme, which focuses on the management of the infectious disease agent to be researched at the man-animal-ecosystem interface. This review will present a brief history of malaria knowlesi in Indonesia, risk factors, and the application of the one health approach that has been carried out in the past until now. Furthermore, the efforts to optimize the one health approach in the future, especially in controlling and eradicating malaria, were presented. This condition suggests an integrative control strategy through improving surveillance methods and understanding the risks associated with disease transmission in line with the One Health approach. It is also recommended that Indonesian policymakers facilitate multidisciplinary collaborative research on incidence rates, clinical spectrum, clusters, and geographical distribution of *Plasmodium knowlesi* transmission. They impose ecological regulations that restrict forest transformation and encourage ecosystem regeneration. Hence, combining solitary protective measures, promoting malaria control strategies that improve health insurance, mosquito-based food traps, and biocontrol strategies in synergy with current control practices are expected to minimize transmission capacity.

1 Introduction

Malaria, a vector-borne disease, is endemic in tropical climates worldwide. World Health Organization (WHO) released that malaria was responsible for approximately 227 million cases in 85 malaria-endemic countries (e.g., the French Guiana region). Furthermore, malaria cases increased by around 14 million (becoming 241 million from 2019 to 2020) due to the COVID-19 pandemic and service disturbances.[1]. Furthermore, in 2020, 1 year after the COVID-19 pandemic and service disruptions, the estimated number of malaria cases rose to 241 million cases, increasing to 14 million cases compared to 2019[1]. Over the past 20 years (2000-2020), the Southeast Asian (SEA) region has declared a reduction in the prevalence of malaria infection in humans by almost 78% [1,2]. However, the lack of consideration of disease-specific management techniques of *Plasmodium knowlesi* precludes prospects for the total elimination of malaria in humans [1]. *P. knowlesi*, a simian-malaria, is a malaria parasite that was first discovered in 1930 in a specimen of *Macaca fascicularis* from Singapore, which leads to mild to chronic infection in Macaque species as natural hosts [3,4,5]. Before molecular-based diagnostics advanced, a human infection caused by *Plasmodium knowlesi* was considered impossible. For the first time in 2004, the Malaysian Borneo Kapit division analyzed the recurrent misidentification of *P. knowlesi* transmission in humans[4,5]. The investigators exposed that >50% of reported cases from 2000 to 2002 that were examined by conventional microscope were misdiagnosed as *Plasmodium malaria* [2,6]. Ever since the prevalence of *P. knowlesi* has increased significantly, and the distribution of the disease is expanding in a number of the Southeast Asian region.

In Indonesia, there were 418 cases of *P. knowlesi* from 2008 to 2015 [7]. The estimated prevalence of *P. knowlesi* infection in Indonesia is around 1%, much lower than the prevalence in Malaysia, which is around 27.7-58% [7,8]. In addition to natural infections, there is also malaria knowlesi data among travellers. An increasing number of malaria knowlesi cases carried from Southeast Asia (Indonesia, Malaysia, Thailand) to Asia, Europe, Oceania, and America [7]. The lower prevalence of malaria knowlesi reported in Indonesia and other countries in Southeast Asia occurred due to a lack of diagnostic instruments and disease information; consequently, misdiagnosis is inevitable [2,3,9]. Furthermore, the reported cases of malaria knowlesi from these countries are like the surface of the iceberg, which means there are many infection cases, but they are not well detectable. This condition emphasized the significance of implementing one health on a multinational basis in

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minimizing, controlling, as well as eliminating malaria knowlesi transmission in the future.

One Health (OH) is an approach that is carried by all experts throughout the world, involving communication, coordination, and collaboration of transdisciplinary sectoral, working at the local, regional, national, and global levels to reach an optimal health outcome by recognizing the interconnectedness of human, plants, animals and their neighbourhood [2,10]. Currently, the One Health approach received more attention as a globally standardized approach to combating emerging and re-emerging infectious diseases as well as zoonotic threats such as malaria knowlesi [2, 10].

This review will present a brief history of malaria knowlesi in Indonesia, risk factors, and the application of the one health approach that has been carried out in the past until now. Furthermore, our review will also highlight possible future strategies in implementing One Health to support malaria elimination by 2030.

2 Materials and Methods

All literature utilized in this review was searched using search engines such as Google Scholar, PubMed as well as Web of Science to discover relevant material involving simian malaria in humans, risk factors associated, and vectors. This review is a conventional review that is synthesized in the form of a narrative review. The following search terms are used singly or in combination: one health, Indonesia, primate malaria, simian malaria, *Plasmodium knowlesi*, non-human primate, zoonotic malaria, and malaria vectors. All up-to-date publications correlated to the current topic are preferred.

3 Results and Discussion

3.1 Zoonotic malaria: Brief History and Current Situation

Plasmodium knowlesi naturally infect non-human primates of Macaca species (monkeys), namely: long-tailed monkeys (*Macaca fascicularis*), short-tailed monkeys (*Macaca nemestrina*), and langurs (*Phylobates melalophos*)[11]. In recent decades, *P. knowlesi* has attracted attention because this zoonotic parasite can infect humans. In addition, *P. knowlesi* has a faster life cycle (24 hours) compared to other malaria parasites (48-72 hours) and infects all ages of erythrocytes so that it quickly causes high parasitemia, which results in complications and even death and a higher risk of serious illness in adults than malaria falciparum [11,12]. The year 2004 was the first known zoonotic endemic malaria caused by *P. knowlesi*. Research in Sarawak, Malaysia, reported the presence of *P. knowlesi,* which infects humans in very large numbers [3]. However, this incident is not an extraordinary event but is associated with a 'misdiagnosis' of an infectious parasite whose morphology is like *P. malariae*. The hyper-parasitemia found is atypical, and the clinical manifestations are much more severe [13]. The molecular analysis found that the majority (58% of 208) of malaria cases in Sarawak were caused by *P knowlesi*. The states of Sarawak and Sabah, Malaysia, were the areas where the *P. knowlesi* infection was highest in Southeast Asia. Since then, WHO has declared that *P. knowlesi* is the fifth species of malaria parasite that can infect humans [14,15].

Several studies have reported that not only established in Malaysia but also, Plasmodium knowlesi transmission has spread to other parts of Southeast Asia such as Thailand [16], Cambodia[17], Myanmar[18], Singapore[19], Indonesia[9], Vietnam[20], and the Philippines. This current situation causes *Plasmodium knowlesi*, the fifth *Plasmodium* species that can infect humans besides *Plasmodium falciparum, Plasmodium malariae, Plasmodium vivax,* and *Plasmodium ovale* [4,5].

3.2 Risk Factors

Plasmodium knowlesi, known as malaria zoonoses, involves the agent-vector-host and the environment in its transmission. *Plasmodium knowlesi* is transmitted to vectors with the help of Anopheles mosquitoes, such as *Anopheles latens* (Sarawak), *Anopheles balabacencis (Sabah), Anopheles cracens* (Peninsular Malaysia), and *Anopheles leucosphyrus* (Indonesia). The natural hosts of *Plasmodium knowlesi* are *Macaca nemestrina, Macaca fascicularis,* and *P. melalophus*[3,4,5].

Several risk factors support the transmission of *Plasmodium knowlesi* from its natural host to humans, including 1). The extinction of wildlife in Indonesia results from logging, land clearing, forest fires, and natural disasters, 2). The conflict between humans and animals, 3). behavior changes in the community, especially the contact between humans and wild animals in the forest, 4). Increasing nature tourism in the forest, 5). Adaptation of parasites and vectors, 6). The existence

Table 1. One Health Approach to Malaria Zoonoses Control in Indonesia: Past, Present, and Future

Indicator	2010-2020	2021	2022-2030
Detection methods for zoonotic malaria	++	+++	++++
Surveillance	+	++	++++
Evaluate risk factors associated with zoonotic malaria transmission	+	++	++++
Communication, Coordination, and Collaboration: government, researchers, society, etc.	+	++	++++
Integrative research: vector identification, vector control, environment, host-pathogen interaction, etc.	-	+	++++
Raising public awareness: health promotion	-	+	++++
Policy: Malaria zoonoses guidelines	-	-	++++

Note: (-) none, (+) lack, (++) not optimize, (+++) optimal, (++++) maximize

of a suitable vector, 7). Identification of malaria primates is still lacking, 8). Lack of proper diagnostic method 9). The system of prevention and control of this disease is still very limited [4,21,22,23]. The above risk factors are the triggers for increasing zoonotic cases in Indonesia.[4,21,22,23]. The above risk factors are the triggers for increasing zoonotic cases in Indonesia.

3.3 One Health Approach for Malaria Zoonoses Control: Past and Present

The prevalence and distribution of *P. knowlesi* infection in humans in Indonesia has not been well studied but continues to be explored until now. In Indonesia, the first *P. knowlesi* case was reported in 2010, namely an Australian citizen who worked in the forest areas of South Kalimantan for 18 months [9]. After returning to his country, he had a high fever with other clinical symptoms of malaria. The morphology of the parasite was similar to that of P. malariae and *P. falciparum*, but the rapid diagnosis (RDT) for HRP-2 was negative. The examination results using the Polymerase Chain Reaction (PCR) technique using a primer specific for *P. knowlesi* were positive. The following three cases were indigenous people in South Kalimantan, reported in 2010 (1 case) and 2012 (2 cases)[6]. The discovery of four cases of *P. knowlesi* malaria in South Kalimantan is the first evidence of the transmission of this type of malaria in Indonesia [6,24,25]. Until 2014, seven malaria knowlesi were reported in humans in Indonesia, and all transmission occurred locally around forests in Kalimantan [6]. In 2015 three (1.05%) *P. knowlesi* positive samples were reported from 287 samples examined. Two of the three cases came from the province of South Kalimantan and one from Central Kalimantan [6]. The following case of malaria knowlesi from Central Kalimantan was a worker in a coal mine [25]. In 2015 in Jambi, from 34 positive malaria cases in humans, 1 case of *Plasmodium knowlesi* was found, and six were positive for *Plasmodium knowlesi* in monkeys from 38 samples [15]. In general, malaria knowlesi cases in Indonesia in 2008-2015 were recorded at 418 cases [7]. The One Health approach in the prevention and control of zoonotic malaria in Indonesia has been carried out since the first case in 2010 and will continue to be carried out until 2021 [2,6,7,9]. However, the implementation of one health is still not optimal.

In the last ten years, the one health approach related to developing appropriate and rapid diagnostic methods has been widely studied and developed, likewise with disease surveillance. However, in its implementation, there are still shortcomings. This is indicated by the fact that there are still many misdiagnoses of *Plasmodium knowlesi* with other types of Plasmodia that usually attack humans due to the researchers not getting comprehensive knowledge regarding the microscopic picture of *Plasmodium knowlesi* [4,21]. There are no guidelines for the management of malaria caused by *Plasmodium knowlesi*. PCR as a standard of examination and confirmation has not been studied much. Passive surveillance in primary health care using microscopic examinations and diagnostic tests is still lacking. Evaluations related to risk factors for the transmission of malaria knowlesi are also considered very lacking. This is related to the lack of an integrated pattern of communication, coordination, and collaboration between the government, researchers, and the community [2,10, 25,26]. However, in 2021, all of the above indicators have been greatly improved by increasing multi-sectoral integrated research and showing positive responses from all sectors.

3.4 Future Challenge: Integrative, Collaborative, and Impactful

Every year worldwide, it is estimated that zoonotic cases (diseases transmitted by animals to humans) cause 2.5 trillion cases of illness and 2.7 million deaths [1,27]. Of course, this is an unavoidable threat. Looking ahead with the development of the epidemiology of zoonotic malaria requires us to move together to do something that impacts society and the world. It is essential to strengthen the one health approach in controlling zoonotic malaria in Indonesia. This condition suggests three main points that can be improved: 1) an integrative control strategy through improving surveillance methods to provide a local evidence base and understanding of the risks associated with disease transmission based on the One Health approach. 2). Suggests that Indonesian policymakers facilitate multidisciplinary collaborative research (regional, national and international) related to incidence rates, clinical spectrum, cluster diversity, and geographical distribution of *P. knowlesi* transmission, impose ecological regulations that restrict forest transformation, and encourage ecosystem regeneration. Next, 3). combining solitary protection measures, promotion of malaria control strategies that improve health insurance, insect trapping, and biocontrol strategies that synergize with current control practices so that they can significantly impact transmission capacity

4 Conclusion

The application of one health in zoonotic malaria cases in Indonesia has been carried out from time to time by applying the simple one health concept of communication, coordination, and collaboration. However, its implementation encountered many challenges. Hence, in the future, the one health approach is expected to be more precisely on three main points, such as integrated control strategy, increasing research collaboration and combining individual protection measures, and promotion of malaria control strategies that increase health insurance so that it can have an impact on efforts to prevent and control malaria zoonotic in Indonesia.

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