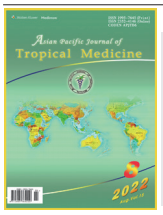

Perspective

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The rise of *Plasmodium knowlesi* cases: Implication to Malaysia's malaria−free status

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Malaria remains a major public health challenge globally. It is one of the world's deadliest diseases, responsible for 627 000 deaths worldwide in 2020 alone[1]. In Malaysia, the Malaria Eradication Programme in Peninsular Malaysia and Malaysia Borneo in 1969 and 1967, respectively, drastically reduced the number of malaria cases in the country[2]. Subsequently, the programme was further reinforced and improved, resulting in zero indigenous human malaria species in 2018[1]. Currently, Malaysia has been identified as one of the World Health Organization (WHO) Western Pacific Region countries with zero indigenous cases for three consecutive years[1], thus eligible for the WHO certification of a malaria-free status country.

Even though the number of human malaria cases has reduced markedly, Malaysia is facing increasing cases of zoonotic malaria due to *Plasmodium (P.) knowlesi*. A significant increase in the number of *P. knowlesi* cases from 376 in 2008 to 4 130 cases was reported in 2018 (Figure 1). Although *P. knowlesi* cases declined slightly in 2019 and 2021 (*i.e.* to 3 222 and 3 575 cases, respectively), *P. knowlesi* malaria resulted in six and 13 deaths in 2019 and 2021, respectively (Figure 1). Most cases of *P. knowlesi* infection and death were recorded in the states of Malaysian Borneo (*i.e.* Sabah and Sarawak). Researchers checked the effect of climatic variables on the malaria incidence[3]. The geographical topography of Sabah and Sarawak, which have vast forested areas, consists of primary and secondary forests that are habitats for the natural reservoir hosts (*i.e.* macaques) and the mosquito vector *Anopheles*[2,4]. It was found that there is a significant positive correlation between forest density and the number of *P. knowlesi* cases[5]. The density of the forest is important as it increases contact between the human hosts and the habitats of *Anopheles* mosquitoes, thus increasing the chance for *P. knowlesi* malaria transmission.

Furthermore, communities living in the forest and on the edges of forests or those engaged in forest-related activities such as hunting and camping are at a higher risk of contracting simian malaria due to their proximity to reservoir macaque hosts and mosquito vectors[6]. In Malaysia, previous studies have also included indigenous and tribal communities, cultivators, and forest workers among the high-risk populations of contracting *P. knowlesi*[4,7]. In addition, the increasing number of naturally acquired zoonotic malaria infections in humans happens in regions where the natural hosts and vectors coexist. This factor is mainly attributed to the increased interconnectivity between humans, the reservoir macaque host, and the competent mosquito vector associated with local ecological changes such as deforestation and biodiversity loss, which eventually modify the dynamics of zoonotic malaria infection transmission[8]. Thus, understanding the effects and causes of biodiversity loss in a changing ecosystem on the risks of contracting infectious diseases, particularly zoonotic malaria, is a multi-factorial issue that must be addressed collectively.

Massive deforestation of tropical rainforests in Malaysia is also a major environmental issue in the country. The rapid expansion of the timber industries and large-scale plantations on agricultural commodities such as palm oil, rubber, and durian can result in an ecosystem imbalance, which is predicted to continue. Diversity and biological imbalance from deforestation may influence the functioning and stability of the natural ecological system (*e.g.* changes in mosquito oviposition sites and wildlife habitat), thus potentially increasing the threat of *P. knowlesi* malaria transmission and other zoonotic disease outbreaks[9]. Furthermore, deforestation results in the loss of habitat diversity, increasing forest fragmentation and decimation, which may affect the dynamics of *P. knowlesi* malaria transmission between macaques, vectors, and people and lead to an increase in the number of *P. knowlesi* cases in the deforested regions[4,9]. Also, forest areas in Malaysia are being cleared and permanently converted into industrial land to cater to the growing demand for socio-economic reasons[10]. The modification of local forested landscapes for anthropogenic land use, such as for economic, residential and recreational use, has been proven to provide the ideal settings for mosquito populations harbouring *P. knowlesi* malaria parasites[11]. Finally, forest fragmentation from human activities can alter macaque population distributions and

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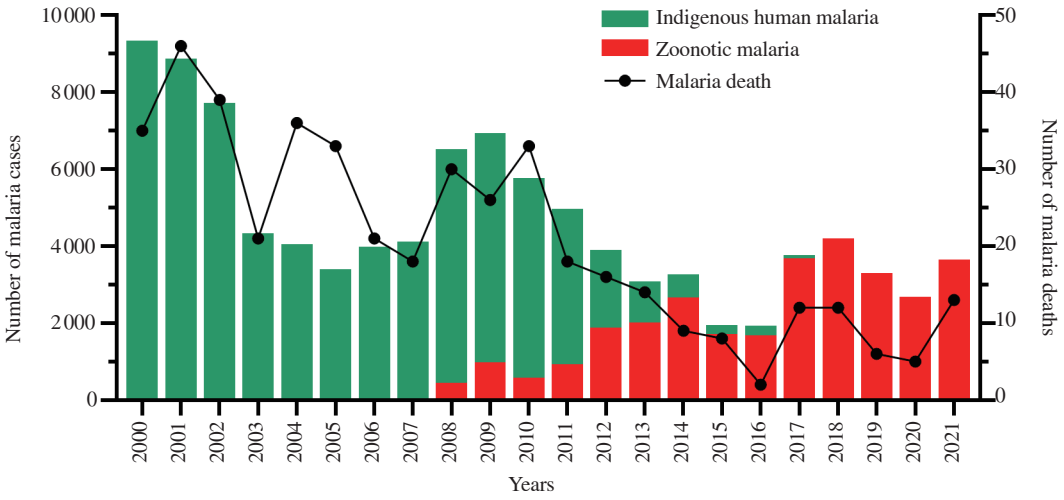

Figure 1. Reported cases of indigenous human malaria, zoonotic malaria and malaria death in Malaysia from 2000 to 2021 (Vector Borne Disease Sector, Disease Control Division, Ministry of Health Malaysia, unpublished data).

behaviours, leading to their invasion and increased proximity to human settlements.

For Malaysia's National Malaria Elimination Strategic Plan to succeed and eventually achieve malaria-free status, Malaysia should aim to further improve the health care system and strengthen case-based surveillance in *P. knowlesi* affected areas. While field epidemiology remains relevant and important for the country, genomic epidemiology is likely to play a critical role in the surveillance. It may eventually help clarify issues related to transmission pathways and the most effective forms of *P. knowlesi* malaria control. Furthermore, with tailor-made strategies, the transmission of *P. knowlesi* in humans may be blocked without severely compromising the welfare of the macaque natural hosts, wildlife biodiversity and economic development of *P. knowlesi* malaria endemic area of the country.

Conflict of interest statement

We declare that there is no conflict of interest.

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Authors' contributions

The conceptualization was done by ZMI. The literature and drafting of the manuscript were conducted by ABM, ENA, NAE, NIA and VCTY. The editing and supervision were performed by ZMI. All authors have read and agreed to the final version of the manuscript.

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