

Perspective

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Plasmodium cynomolgi: An emerging threat of zoonotic malaria species in Malaysia?Nor Diyana Dian¹, Mohd Amirul Fitri A Rahim¹, Zulkarnain Md Idris^{1,2}✉¹Department of Parasitology and Medical Entomology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia²Infectious Disease Group, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Malaria remains a public health problem in many parts of the world. It is a disease that can endanger human life if left untreated, especially among young children and pregnant women. In Malaysia, the number of malaria cases has decreased significantly since the introduction of the Malaria Elimination Program in 1961 in Malaysia Borneo, and in 1967 in Peninsular Malaysia. Since 1988, malaria has been on the notifiable disease list under the Communicable Diseases Act of Malaysia that mandates notification within 7 days. The significant progress towards the national elimination programme and effective disease notification on malaria has resulted in zero indigenous human malaria cases in 2018[1]. However, the emergence of zoonotic malaria in recent years has less been tractable to conventional malaria control and elimination programme in the country. Malaria cases shifted from predominantly human malaria to non-human primate malaria species in the early 2000s, and are now responsible for the majority of malaria case in less developed areas of both Peninsular Malaysia and Malaysia Borneo[2]. The main key driver to the apparent emergence of zoonotic malaria infection in Malaysia is the ongoing environmental and ecological changes (*i.e.* deforestation, less biodiversity, migration of macaques to forest fringes) and likely to shape changing risk to the infection. Deforestation and other landscape changes for economic exploitation are known to impact the distribution, susceptibility and behaviour of human populations, wildlife reservoir (*i.e.* macaques) and vector (*i.e.* *Anopheles leucosphyrus*) dynamics, thus exacerbating the risk of zoonotic malaria infections in the country[3].

Although *Plasmodium (P.) knowlesi* is the most widely reported zoonotic malaria species, there is notably increased epidemiological evidence on naturally acquired human infection of *P. cynomolgi* in Malaysia. The first case of naturally acquired human *cynomolgi* malaria infection was recorded in a 39-year-old woman from the east coast of Peninsular Malaysia (*i.e.* Hulu Terengganu) in 2014[4]. Since then, there have been four more published studies (*i.e.* as of

December 2021) reported on *P. cynomolgi* infection, including symptomatic infection of a tourist travelling to Peninsular Malaysia and multiple asymptomatic infection cases in Malaysia Borneo[5–8] (Figure 1). In the first reported case study, the patient's blood sample was diagnosed as *P. vivax* malaria infection microscopically but was confirmed by molecular PCR method as *P. cynomolgi*. Due to morphologic similarities between *P. cynomolgi* and *P. vivax*, it is difficult to identify *P. cynomolgi* parasites correctly by conventional microscopy. Both species have similar biological capabilities including exoerythrocytic dormant stages in the liver with associated hypnozoites and favouring infecting reticulocytes[9]. Therefore, if solely relying on microscopy examination, it is highly likely that there will be more misdiagnosed or undetected sub-microscopic infections of *P. cynomolgi* in the population. A recent study in the state of Sarawak (Malaysia Borneo) also noted that *P. cynomolgi* parasites made a low percentage of the parasites consisted of *P. cynomolgi* in the two individuals whose blood films were analysed, which explains why microscopy analysis detected only single *P. knowlesi* infections in those patients[7]. The difference in the period of development in the liver and the duration of the erythrocytic cycle between *P. knowlesi* and *P. cynomolgi* accounts for *P. knowlesi* dominance over *P. cynomolgi* hence, making it harder to detect *P. cynomolgi* malaria in case of mixed infection[7,9]. Besides that, *P.*

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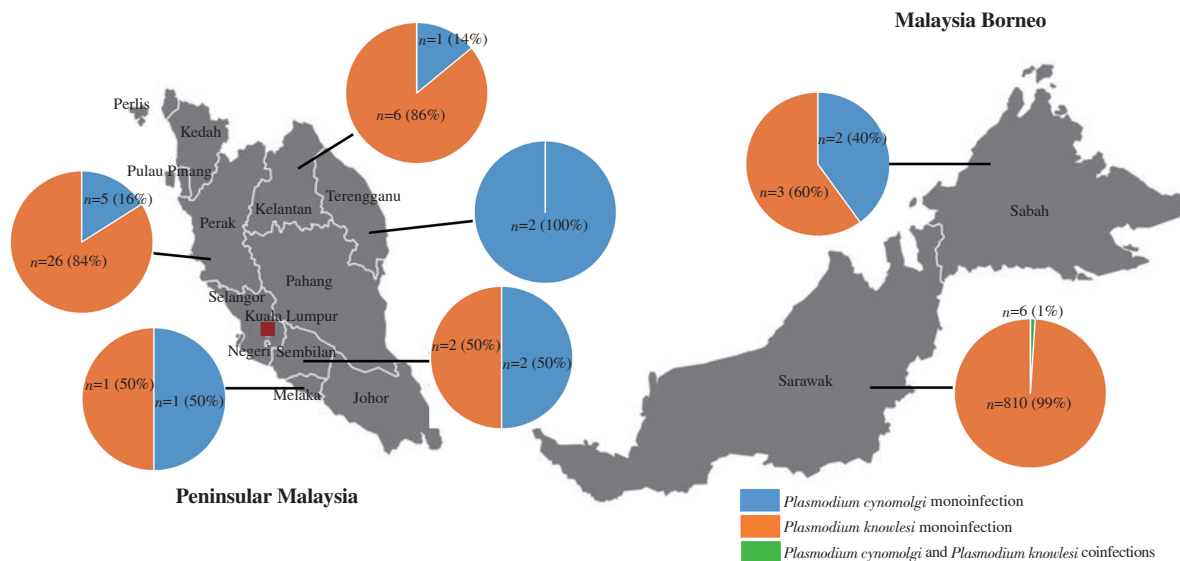


Figure 1. Map of Malaysia showing location of the positive *Plasmodium cynomolgi* areas. Pie charts represent number of cases and percentages of *Plasmodium cynomolgi* and *Plasmodium knowlesi* malaria infections determined by species-specific PCR from five studies [4–8] (2014–2021).

cynomolgi infections in humans are mild or even asymptomatic. In the reported symptomatic natural infection, the patient experienced cyclical fevers, myalgia, general malaise, cephalgia and abdominal pain that were described as generalised non-specific flu-like syndrome [4,5]. This suggests very low parasite densities and the need for improved diagnostic methods to detect these infections. Furthermore, due to the limited disease severity of *P. cynomolgi* and its morphological similarity to *P. vivax*, which makes accurate microscopic speciation difficult, the true incidence rates of *P. cynomolgi* are likely to be significantly higher than what is currently thought.

Although co-infection of *P. cynomolgi* with other zoonotic malaria species has recently been documented from archived blood samples of the indigenous population in Malaysia [7], there is a risk of *P. cynomolgi* being underdiagnosed because the molecular characterization of the *P. cynomolgi* parasite is not commonly performed. Hence, any co-infections would be assigned only to the other malaria species involved. Furthermore, zoonotic malaria cases are widely reported in Malaysian Borneo (*i.e.* Sarawak and Sabah) as many studies are conducted there [2]. In Peninsular Malaysia, fewer epidemiological studies were conducted in regards to zoonotic malaria. There were only 13 malaria epidemiological studies that have been carried out in Peninsular Malaysia over the past 40 years, mostly by using conventional microscopy examination [2]. The low number of malaria epidemiological surveys in Peninsular Malaysia particularly among indigenous communities could lead to an under-report of the real incidence of zoonotic malaria in this hard-to-reach population.

Albeit *P. cynomolgi* infections may not yet pose a significant health

risk, any new infections make it increasingly challenging for public health officials to eliminate zoonotic diseases [10]. The significance of *P. cynomolgi* that is transmissible cannot be ignored given the increasing identification of infection. Further studies and continued surveillance of *P. cynomolgi* and other zoonotic malarias in Malaysia are necessary through the use of sensitive molecular methods such as developing molecular analysis with specific primers for *P. cynomolgi* and abolishing the requirement for genotyping analyses in order to obtain accurate and relevant data for the detection and reporting of these emerging zoonotic malaria. Research involving the mosquito vector is needed to determine the importance of *P. cynomolgi* malaria in mosquitos and its implications for human public health and malaria control. Furthermore, more research into the biology of *P. cynomolgi*, the possibility of relapses/recurrences and asymptomatic infections, all of which have a direct impact on malaria epidemiology is required.

Conflict of interest statement

We declare that there is no conflict of interest.

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Authors' contributions

The conceptualization was done by NDD and ZMI. The literature and drafting of the manuscript were conducted by NDD and MAFAR. The editing and supervision were performed by ZMI. All authors have read and agreed to the final version of the manuscript.

References

- [1] World Health Organization. *World malaria report 2021*. [Online]. Available from: <https://www.who.int/publications/i/item/9789240015791>. [Accessed on 16 November 2021].
- [2] Rahim MAFA, Munajat MB, Idris ZM. Malaria distribution and performance of malaria diagnostic methods in Malaysia (1980-2019): A systematic review. *Malar J* 2020; **19**(1): 395.
- [3] Phang WK, Hamid MHA, Jelip J, Mudin RN, Chuang TW, Lau YL, et al. Spatial and temporal analysis of *Plasmodium knowlesi* infection in Peninsular Malaysia, 2011 to 2018. *Int J Environ Res Public Health* 2020; **17**(24): 9271.
- [4] Ta TH, Hisam S, Lanza M, Jiram AI, Ismail N, Rubio JM. First case of a naturally acquired human infection with *Plasmodium cynomolgi*. *Malar J* 2014; **13**: 68.
- [5] Hartmeyer GN, Stensvold CR, Fabricius T, Marmolin ES, Hoegh SV, Nielsen HV, et al. *Plasmodium cynomolgi* as cause of malaria in tourist to Southeast Asia, 2018. *Emerg Infect Dis* 2019; **25**(10): 1936-1939.
- [6] Grignard L, Shah S, Chua TH, William T, Drakeley CJ, Fornace KM. Natural human infections with *Plasmodium cynomolgi* and other malaria species in an elimination setting in Sabah, Malaysia. *J Infect Dis* 2019; **220**(12): 1946-1949.
- [7] Raja TN, Hu TH, Kadir KA, Mohamad DSA, Rosli N, Wong LL, et al. Naturally acquired human *Plasmodium cynomolgi* and *Plasmodium knowlesi* infections, Malaysian Borneo. *Emerg Infect Dis* 2020; **26**(8): 1801-1809.
- [8] Yap NJ, Hossain H, Nada-Raja T, Ngui R, Muslim A, Hoh BP, et al. Natural human infections with *Plasmodium cynomolgi*, *P. inui*, and 4 other simian malaria parasites, Malaysia. *Emerg Infect Dis* 2021; **27**(8): 2187-2191.
- [9] Kotepui M, Masangkay FR, Kotepui KU, Milanez GDJ. Preliminary review on the prevalence, proportion, geographical distribution, and characteristics of naturally acquired *Plasmodium cynomolgi* infection in mosquitoes, macaques, and humans: A systematic review and meta-analysis. *BMC Infect Dis* 2021; **21**(1): 259.
- [10] Muraina IA. COVID-19 and zoonosis: Control strategy through One Health approach. *Asian Pac J Trop Med* 2020; **13**(9): 381-383.