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A comparison of the clinical, laboratory and epidemiological features of two divergent subpopulations of *Plasmodium knowlesi*

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***Plasmodium knowlesi*, a simian malaria parasite responsible for all recent indigenous cases of malaria in Malaysia, infects humans throughout Southeast Asia. There are two genetically distinct subpopulations of *Plasmodium knowlesi* in Malaysian Borneo, one associated with long-tailed macaques (termed cluster 1) and the other with pig-tailed macaques (cluster 2). A prospective study was conducted to determine whether there were any between-subpopulation differences in clinical and laboratory features, as well as in epidemiological characteristics. Over 2 years, 420 adults admitted to Kapit Hospital, Malaysian Borneo with knowlesi malaria were studied. Infections with each subpopulation resulted in mostly uncomplicated malaria. Severe disease was observed in 35/298 (11.7%) of single cluster 1 and 8/115 (7.0%) of single cluster 2 infections ($p = 0.208$). There was no clinically significant difference in outcome between the two subpopulations. Cluster 1 infections were more likely to be associated with peri-domestic activities while cluster 2 were associated with interior forest activities consistent with the preferred habitats of the respective macaque hosts. Infections with both *P. knowlesi* subpopulations cause a wide spectrum of disease including potentially life-threatening complications, with no implications for differential patient management.**

The simian malaria parasite, *Plasmodium knowlesi* was found to be the commonest cause of human malaria infections in the Kapit Division of Sarawak, Malaysian Borneo in 2004[1]. Subsequent studies have shown that zoonotic malaria cases occur throughout Southeast Asia and in the Andaman and Nicobar islands of India[2–5]. The highest incidence is in Malaysia, where 13,612 knowlesi malaria cases were reported between 2017 to 2020, with 87% from the Malaysian Borneo states of Sabah and Sarawak (B. Singh, unpublished data). All the indigenous malaria cases in Malaysia in 2018 and 2019 were due to *P. knowlesi*[6]. Human knowlesi malaria infections have been increasing in Malaysia since they were first reported in 2004[1]. From the 120 cases detected in Sarawak over a 32-month period at that time[1], the annual number of reported cases in Malaysia has increased to 912 in 2009, and to between 1600 and 4131 since 2012[7]. This increase may reflect improved diagnostic capacity, decrease in cross-species immunity due to decrease in malaria caused by human malaria species, and increased interaction between humans, macaques and mosquito vectors. This latter explanation is based on land-use changes leading to alterations in mosquito abundance and composition, and to greater proximity of the movement of the reservoir macaque hosts to human habitation[7,8]. The increase in zoonotic malaria cases is of public health concern and a threat to the elimination of malaria.

Micro-satellite genotyping of *P. knowlesi* isolates from wild macaques in Kapit, Malaysian Borneo and humans across Malaysia has identified two simian host-associated genetically distinct subpopulations[9]. Two-thirds of human infections were of one subpopulation (termed cluster 1) associated with long-tailed macaques (*Macaca*

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