Humans, macaques, and malaria parasites in a shared and changing landscape

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Plasmodium knowlesi, a simian malaria that naturally infects long-tailed macaques (*Macaca fascicularis*) and pig-tailed macaques (*Macaca nemestrina*), was discovered in a long-tailed macaque from Singapore in 1931.[1] Although simian malarias were known to be capable of experimentally infecting humans, questions remained about their zoonotic potential. The first known natural infection of a human by a simian malaria was documented in 1965, when a surveyor for the US Army Map Service, working deep in the jungles of peninsular Malaysia, was infected by *P knowlesi*.[2] Previous experimental *P knowlesi* infections in humans had revealed the daily fever pattern of this parasite and tests had also shown that rhesus macaques (*Macaca mulatta*) infected with *P knowlesi* developed severe disease and often died. This first known zoonotic infection was confirmed to be *P knowlesi* by experimental inoculation—by use of blood from the infected person—of seven other individuals (who subsequently developed daily fevers) and three rhesus macaques, all of which subsequently died.

The possibility of zoonotic malaria had major implications for ongoing malaria elimination and eradication efforts and sparked a massive research project in the jungles where the zoonosis had likely occurred (central Pahang).[3] Blood was collected from 1117 participants living in the area and *M mulatta* monkeys were subsequently inoculated. None showed signs of illness. Although it was apparent that *P knowlesi* could infect humans, the findings from this investigation led many to believe that this only occurred in rare circumstances.[3]

More than 30 years later, investigations into an abnormally high burden of *Plasmodium malariae* uncovered a large focus of misdiagnosed *P knowlesi* infections in Malaysian Borneo.[4] Since then, human *P knowlesi* infections have been identified in most other nations in southeast Asia, although the heaviest apparent burden continues to exist in northern Borneo.[5] Most cases have been detected through passive case detection, leaving questions about the true burden of the disease in endemic areas.

An impressive cross-sectional study by Kimberley Fornace and colleagues,[6] in *The Lancet Planetary Health*, provides the first detailed description of the overall burden of *P knowlesi* across a wide geographical region that is endemic for the disease (four districts in northern Sabah of Malaysian Borneo). Approximately 5% of the total surveyed population was seropositive for *P knowlesi*. Predictors of exposure included male sex, older age groups, reported contact with macaques, and reported activities in forested areas. Environmental attributes that were positively associated with *P knowlesi* exposure included living near irrigated rice paddy fields and pulpwood plantations, and near fragmented oil palm plantations. Participants living near fragmented forests and at higher geographical elevations were less likely to be seropositive for *P knowlesi*.

Contact patterns between humans, mosquito vectors, and macaques are influenced by movement and land use patterns across heterogeneous environments. The movement ranges of human, macaque, and mosquito populations are likely to span different spatial scales. The most appropriate spatial scale for predicting risk of exposure to *P knowlesi* is therefore unclear. Rather than choosing arbitrary spatial units for use in their model, Fornace and colleagues measured environmental variables at radii ranging from 100 m to 5000 m around participant households and used a data mining approach to choose a best fitting model. This approach could usefully be implemented with many other datasets and with different disease systems.

Some key questions remain unanswered. Although it is clear that humans can acquire this infection from macaques, human-to-human transfer in nature has not been established. Further basic science and ecological research into this disease system is warranted. *P knowlesi* infections appear to be relatively rare and heterogeneously distributed, but it is possible that low-density infections are missed. Methods that are designed to detect low-density infections[7] might be informative for understanding the epidemiology of *P knowlesi*. Serological markers can be useful for measuring historical disease burdens, and are perhaps especially useful in situations where infections are rare. Serological work on *P knowlesi* is promising, but continued work on the longevity and seroreactivity of

antigenic responses to the parasite are needed. In this study, the authors attempted to measure only recent exposure. However, it is not immediately clear why exposure would increase (almost linearly) with age. This might be the result of behavioural differences across age groups, repeated exposure across the lifespan, or a combination of both factors.

Although globally rare, *P knowlesi* malaria will probably continue to have public health significance at least for northern Borneo, where it is the largest overall contributor to malaria[8] and where the landscape is quickly changing. Malaria elimination is being considered by most nations in this region[9] but the primary focus has been on *P falciparum*, with a growing interest in *Plasmodium vivax*. This zoonotic malaria, which exists at extremely high prevalence in some macaque populations,[10] poses unique challenges that will need to be addressed if all forms of malaria are to be eliminated.

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I declare no competing interests.

1 Knowles R, Gupta BMD. A Study of monkey-malaria, and its experimental transmission to man. *Ind Med Gaz* 1932; **67:** 301–20.
2 Chin W, Contacos PG, Coatney GR, Kimball HR. A naturally acquired quotidian-type malaria in man transferable to monkeys. *Science* 1965; **149:** 865–65.
3 Warren M, Cheong WH, Fredericks HK, Coatney GR. Cycles of jungle malaria in west Malaysia. *Am J Trop Med Hyg* 1970; **19:** 383–93.
4 Singh B, Sung LK, Matusop A, et al. A large focus of naturally acquired *Plasmodium knowlesi* infections in human beings. *Lancet* 2004; **363:** 1017–24.
5 Singh B, Daneshvar C. Human infections and detection of *Plasmodium knowlesi*. *Clin Microbiol Rev* 2013; **26:** 165–84.
6 Fornace KM, Brock PM, Abidin TR, et al. Environmental risk factors and exposure to the zoonotic malaria parasite *Plasmodium knowlesi* across northern Sabah, Malaysia: a population-based cross-sectional survey. *Lancet Planet Health* 2019; **3:** e157–8.
7 Imwong M, Hanchana S, Malleret B, et al. High-throughput ultrasensitive molecular techniques for quantifying low-density malaria parasitemias. *J Clin Microbiol* 2014; **52:** 3303–09.
8 WHO Regional Office for Western Pacific. Expert consultation on *Plasmodium knowlesi* malaria to guide malaria elimination strategies, Kota Kinabalu, Malaysia, 1–2 March 2017: meeting report. Manila: WHO Regional Office for the Western Pacific, 2017.
9 WHO. Eliminating malaria in the greater Mekong subregion: united to end a deadly disease. November, 2016. http://www.who.int/malaria/publications/atoz/eliminating-malaria-greater-mekong/en/ (accessed March 19, 2019).
10 Lee K-S, Divis PCS, Zakaria SK, et al. *Plasmodium knowlesi*: reservoir hosts and tracking the emergence in humans and macaques. *PLoS Pathogens* 2011; **7:** e1002015.