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Review Article

Human *Plasmodium knowlesi* infections in South-East Asian countries

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Abstract *Plasmodium knowlesi* is now regarded as the fifth malaria parasite causing human malaria as it is widely distributed in South-East Asian countries especially east Malaysia where two Malaysian states namely Sabah and Sarawak are situated. In 2004, Polymerase Chain Reaction (PCR) was applied for diagnosing knowlesi malaria in the Kapit Division of Sarawak, Malaysia, so that human *P. knowlesi* infections could be detected correctly while blood film microscopy diagnosed incorrectly as *Plasmodium malariae*. This parasite is transmitted from simian hosts to humans via Anopheles vectors. Indonesia is the another country in South East Asia where knowlesi malaria is moderately prevalent. In the last decade, Sarawak and Sabah, the two states of east Malaysia became the target of *P. knowlesi* research due to prevalence of cases with occasional fatal infections. The host species of *P. knowlesi* are three macaque species namely *Macaca fascicularis*, *Macaca nemestrina* and *Macaca leonina* while the vector species are the Leucosphyrus Complex and the Dirus Complex of the Leucophyrus Group of Anopheles mosquitoes. Rapid diagnostic tests (RDT) are non-existent for knowlesi malaria although timely treatment is necessary for preventing complications, fatality and drug resistance. Development of RDT is essential in dealing with *P. knowlesi* infections in poor rural healthcare services. Genetic studies of the parasite on possibility of human-to-human transmission of *P. knowlesi* were recommended for further studies.

Introduction

Plasmodium knowlesi (*P. knowlesi*) is now regarded as the fifth malaria parasite causing human malaria[1] as it is widely distributed in south-east Asian countries especially east Malaysia where two States namely Sabah and Sarawak are situated. A molecular method, Polymerase Chain Reaction (PCR), is preferable to blood film microscopy in detecting *P.*

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knowlesi because late stage trophozoites of *P. knowlesi* and *Plasmodium malariae* are indistinguishable morphologically.[2] PCR was applied in the Kapit Division of Sarawak, Malaysia, so that human *P. knowlesi* infections were detected rather than attributing these infections to *P. malariae*.[3] Existing of simian hosts and Anopheles vectors is an important prerequisite for development of the *P. knowlesi* infections in human. Recent reports indicated that *P. knowlesi* infections are prevalent in Sabah,[4,5] West Malaysia[6,7] and present in south-east Asian countries.[8–11] Three macaque species namely *Macaca fascicularis* (*M. fascicularis*), *Macaca nemestrina* and *Macaca leonina* are the simian hosts whereas the Leucosphyrus Group are the Anopheles vectors.[12] The geographical distribution of *P. knowlesi* infections was proposed to include islands of Indonesia in the southern part while the China–Myanmar border forming the northern limit of this parasite's habitat.[12] In the last decade, Sarawak and Sabah, the two states of east Malaysia became the target of *P. knowlesi* research due to prevalence of cases with occasional fatal infections.[4] Despite the mortality rate being not high, severe and complicated knowlesi malaria may lead to fatality[4] so that healthcare authorities are aware of this simian malaria parasite in south-east Asian countries. *P. knowlesi* is more sensitive to artesunate combination therapy than chloroquine so that correct diagnosis by PCR is vital in obtaining effective treatment.[3]

In this review, human *P. knowlesi* infections in south-east Asia region were discussed with reference to animal hosts and vectors. Furthermore, the disease range of *P. knowlesi* and future research on *P. knowlesi* were described in terms of control of this tropical disease.

P. knowlesi infections in Mainland south-east Asian countries except west Malaysia

In 2008, a study of *P. knowlesi* infection was carried out in China–Myanmar border with the finding of co-infections with *P. knowlesi* and other *Plasmodium* species. Of 150 patients, 26 have coinfections with half of them harbouring both *P. knowlesi* and *Plasmodium falciparum* and the rest having the *P. knowlesi*/*P. vivax* confection.[8] Besides, four monoinfections and two cases of infection with combination of three parasites mentioned above were found.[8] Co-infection by two malaria parasites was common in this region while monoinfection by *P. knowlesi* is rare when compared to other southeast regions. *P. falciparum* and *Plasmodium vivax* infections were also common in this region so that coinfection with these parasites were observed. At the same time, the natural host of *P. knowlesi* exists in the forest. As two parasites have no exclusivity, coinfection was common in the China–Myanmar border.

During 2008 and 2009, 3770 febrile persons from four provinces of Thailand were screened for malaria parasites including *P. knowlesi* by microscopy and nested PCR for 18S-rRNA. *P. knowlesi* was detected in 23 infections including 15 co-infections with other malaria parasite and eight mono-infections by nested PCR.[13] Ten human isolates and five macaque isolates were sequenced for the Complete *Merozoite Surface Protein 1* (*msp1*) gene of *P. knowlesi* which showed considerable genetic diversity[13] However, one isolate of human was identical with that from macaque indicating the naturally infected animal is the source of the human. *Anopheles minimus* (*An. minimus*), *An. maculates*, and *An. dirus* mosquitoes are the Anopheles vectors transmitting human malaria in Thailand.[14] Although *An. dirus* mosquitoes were known as vectors for *P. knowlesi* in this region,[15] this vector has decreased in all malaria endemic areas in Thailand during the previous ten years. Furthermore, *An. dirus* prefers to bite monkeys than human in some areas.[16] Although the presence of *M. fascicularis* and *M. nemestrina* was reported in Thailand, *P. knowlesi* had a prevalence of less than 10% in both simian species.[13] Human *P. knowlesi* infections could be limited in Thailand because of these reasons. Archive blood samples showed that *P. knowlesi* was observed since more than ten years ago in Thailand and in Sarawak.[13] Taken together, these data suggested that *P. knowlesi* was not a newly emerging pathogen.[13] A unique fever pattern of *P. knowlesi* infection has not been diagnostic of such infection because it was not found in early part of infection and mixed infection with *P. vivax* being common, the fever pattern would be atypical. Severe symptoms, complications and fatality were less common than Sarawak, Malaysia in knowlesi malaria cases in Thailand.[13] However, a fatal knowlesi malaria case was observed in a healthy man of middle age with complication of haemorrhage, hepatic failure and renal failure. He had a history of working in the jungle of Thailand–Malaysia border.[17]

A total of about 490 blood samples collected from malaria clinic in Ranong province, Thailand in between 2008 and 2010 were detected by nested PCR of 18S-rRNA genes and confirmed by circumsporozoite protein (*csp*) gene.[18] Two samples, from a Thai worker and a Myanmar worker, only were *P. knowlesi* positive with these assays followed by sequencing.[18] DNA sequences from these two samples and simian hosts were identical. The two patients worked in the same place of Myanmar–Thailand border.[18] In the main land of Myanmar, there was no report on *P. knowlesi* infections up to now.

In 2016, a Laotian boy was diagnosed as knowlesi malaria after 2698 blood samples from patients with malaria in the 5 provinces of Laos during 2015–2016 were tested for human infection with *P. knowlesi* by PCR (Table 1).[9] The detection methods were nested PCR of the *cytochrome b gene* (*cytb*) and *msp1* genes of the parasite and sequencing.[9] The previous malaria episodes in the boy were positive by the rapid diagnostic test as other malaria parasites. The finding indicated that rapid diagnostic test (RDT) kit used in Laos may miss *P. knowlesi*. Because *P. knowlesi* infection may become severe and fatal, patients diagnosed with vivax malaria by RDT need to be treated with caution.[9] Another recent study detected *P. knowlesi* infections in Laos-Vietnam border by PCR amplification of two genes, namely 18S-rRNA and *csp*.[10] Coinfections of *P. knowlesi* and *P. vivax* were observed in all the 9 cases detected in Laos border and 3 cases in Vietnam border.[10] Moreover, all the cases infected with *P. knowlesi* were not more than 15 years of age indicating that there was acquired immunity in older ages.[10] There is no coinfection with *P. knowlesi* and *P. falciparum* observed in Laos-Vietnam border. Although there is prevalence of *P. falciparum* in this region, coinfection of *P. knowlesi* and *P.*

Table 1 Number of *P. knowlesi* cases in south-east Asian countries 2004–2016 (WHO).[27]

Country	Number of *P. knowlesi* cases
Malaysian Borneo	4553
Peninsular Malaysia	204
Indonesia	465
Thailand	37
Myanmar	33
Singapore	6
Philippines	5
Vietnam	33[a] 3 in Laos-Vietnam border[d]
Cambodia	2[b]
Laos	1[c] 9 in Laos-Vietnam border[d]

[a] 2009–2010 cited in Ref. 20.
[b] 2007–2010 cited in Ref. 19.
[c] 2018 cited in Ref. 9.
[d] 2018 cited in Ref. 10.

falciparum was not observed, which do not support no exclusivity theory. However, this finding is not consistent with the observation in China–Myanmar border. There may be reasons other than no exclusivity theory for coinfection. In addition, the clinical manifestation of knowlesi malaria in this study does not include fever with the exception of two cases whereas in Kapit division of Sarawak, most cases of knowlesi malaria present with fever and complication making diagnosis of zoonotic malaria important. This may be due to genetic difference of *P. knowlesi* species in Sarawak and Laos-Vietnam border.

In Cambodia, *P. knowlesi* was detected in 2 patients of Pailin Province during 2007–2010 study (Table 1). Both patients worked in the forests near Pailin, which is the habitat for *M. fascicularis*.[19] Both patients were detected by 18S-rRNA PCR followed by DNA sequencing and confirmation by amplifying and sequencing of *cytochrome oxidase* (*cox*) gene for *P. knowlesi* infection.[19] Extensive study should be done on this parasite to provide further insight into the prevalence and distribution of *P. knowlesi* in Cambodia. There were no coinfections in Cambodia when compared with China–Myanmar border and Thailand, although *P. vivax* and *P. falciparum* infections were highly prevalent in Cambodia. It was well known that artemisinin resistant *P. falciparum* cases had started in Cambodia. RTD could detect neither of these two patients, indicating that RDT has no role in *P. knowlesi* diagnosis while PCR plays a main role in the detection of *P. knowlesi*.[19]

Blood samples were collected by 794 patients during 2009–2010 in south-central Vietnam.[20] *P. knowlesi* was identified in 32 malaria patients who were co-infected with *P. vivax* (Table 1). Co-infection with *P. knowlesi* and *P. falciparum* was found in one case (Table 1) whereas there was monoinfection by *P. knowlesi*.[20] *Anopheles dirus* mosquito could transmit three *Plasmodium* species including *P. knowlesi*.[20] Carriers of *P. knowlesi* were younger than others alluding to the fact that forests harbouring macaques and *An. dirus* mosquitoes remained as a reservoir for the *P. knowlesi* even if human cases were treated.[20]

P. knowlesi infections in Maritime south-east Asian countries

Knowlesi malaria was highly prevalent in Sarawak, east Malaysia while it was common in Sabah, another state of East Malaysia. Regarding West Malaysia, its prevalence is far higher than in other south-east Asian countries except Indonesia.[3] Because knowlesi malaria cases were misdiagnosed as *P. malariae* infections by microscopy, the simian malaria was not realized although human cases are thought to exist in Sarawak in 1996 as shown by studies of archival blood films. Extensive studies in Sarawak since the year 2000 demonstrated that the state appear to have largest number of *P. knowlesi* cases.[3] Only six non indigenous *P. malariae* cases of logging camp workers were observed in the state while over 770 *P. knowlesi* cases were reported (Table 2). *P. knowlesi* is second to *P. vivax* in terms of prevalence in Sarawak contributing to 41% of the total malaria cases. The vector for *P. knowlesi* in Kapit division is *An. latens* which is equally attracted to humans and monkeys. *An. hacker* and *An. cracens*, the vectors for *P. knowlesi* in Selangor and Pahang states respectively in Malaysia, preferentially feed on monkeys (Table 2). This preference is the reason why there is a lower number of *P. knowlesi* infections in west Malaysia including these states when compared with Sarawak.[3]

In Sabah, the percentage of *P. knowlesi* monoinfections among malaria cases notified in 2011 was 35% while it was 1% in 1992.[3] Moreover, *P. knowlesi* cases were 10 times more common in 2011 in comparison to 2004. In Sabah, there was a

Table 2 Significant characteristics of *P. knowlesi* infection.

1. Knowlesi malaria is highly prevalent in east Malaysia.
2. Human contract he infection when they entered the forest and forest fringe where simian hosts and Anopheles vectors were existing.
3. *M. fascicularis*, *M. nemestrina* are the two main macaque hosts whereas Leucosphyrus Complex and Dirus Complex are the two main vectors.
4. PCR of *mtCOI* gene gave rise to high copy number which makes diagnosis of knowlesi malaria detectable in case of low parasitamia.
5. There is no definitive proof of human to mosquito to human transmission of the *P. knowlesi*.
6. *An. Latens* in Sarawak is equally attracted to humans and monkeys whereas *An. hackeri* in Selangor and *An. cracens* in Pahang prefer to feed on monkeys rather than humans in Malaysia.
7. *P. knowlesi* infections range extends beyond habitat of *M. fascicularis*, *M. nemestrina* in the northern part in Myanmar and Myanmar–China border where macaque host is *M. leonina*.
8. *Presbytis melalophus* is the natural host of *P. knowlesi* in Peninsular Malaysia.
9. Social factors include employment, migration, etc whereas environment includes dense forest and forest fringe.

significant increase in knowlesi malaria over the past decade.[3] A significant decrease in *P. vivax* and *P. falciparum* infections has occurred before there was a marked increase in knowlesi malaria. In Sabah, *P. knowlesi* became increasingly dominant (Table 2) while it is the commonest cause of malaria and occurrence of infections has been reported in the districts which are free of *P. knowlesi* before.[3]

In 2007, the first locally acquired knowlesi malaria infection was observed in Singapore, while subsequent five cases were identified in 2007–2008.[21] All the cases were military personnel who took training in forested areas. *P. knowlesi* parasites were seen in the *M. fascicularis* present in the same forest *P. knowlesi* parasites.[21] Analysis of the *P. knowlesi* csp genes showed that the sequences from the human cases and simian hosts were similar. The observations indicated that macaques were the natural hosts of this zoonotic parasite in Singapore.[21] World Health Organization stated that Singapore was free of human malaria. This explains lack of coinfection and the presence of monoinfections in Singapore. *P. knowlesi* was not detected in macaques observed in natural park. Similarly, in Malaysia, in the urban areas where competent vectors were absent, the macaques were not infected by *P. knowlesi* in West Malaysia. In contrast, almost all the macaques from the forest harbour the parasite. The reason that peridomestic monkeys caught in natural park in Singapore did not harbour *P. knowlesi* due to lack of competent vectors.[21] There has been no update information on presence of *An. leucophyrus* group of mosquitoes which can transmit *P. knowlesi* from macaques to human in Singapore. There are *An. sinensis*, *An. kochi*, etc in Singapore and *An. kochi* was observed to carry *P. knowlesi* and has been shown to feed on monkeys.[21] Because *An. kochi* is lesser in population, there were fewer than ten cases of knowlesi malaria while many soldiers took training in the same forest.

In the 2014 study in South Kalimantan, Indonesia, knowlesi malaria was observed in the worker who visited a new mining location in a forest.[11] The infection was detected by nested PCR of 18S-rRNA gene including *P. knowlesi*-specific primers. As the result mitochondrial DNA in this study was high copy number up to 150 copies which made *P. knowlesi* detectable,[11] is negative, PCR and DNA sequencing of *mtCOI* gene of *P. knowlesi* was carried out and observed to be positive.[11] When the parasitaemia level is low, PCR of 18S rRNA gene could not be detected because of low copy number only up to 7 copies.

In the study in 2016, active and passive case detection of *P. knowlesi* infections in North Sumatera province were performed in Indonesia for all *Plasmodium* species.[22] Blood samples were sent to London School of Hygiene and Tropical Medicine and screening for species-specific nested PCR for all *Plasmodium* species infecting human and PCR using *P. knowlesi*-specific primers.[22] One-tenth of the PCR-positive malaria samples were *P. knowlesi* while human malaria infections were caused by all human *Plasmodium* species with the exception of *P. ovale*.[22] The study indicated an increased number of knowlesi malaria in the area where awareness of zoonotic malaria is necessary for the healthcare professionals.

In Sabang, Indonesia, sympatry of *An. leucosphyrus* group of mosquitoes and simian hosts makes the region a habitat for *P. knowlesi*. In 2014–15, there were two clusters of knowlesi infections in Sabang Municipality. One cluster occurred in a construction site in Sabang where workers stayed overnight in the forest.[23] However, the second cluster included the three family members in the same house near the forest with the possibility of transmission around the house.[23] This cluster probably occurred as a zoonotic or human to human transmission of *P. knowlesi*, though there was no definitive proof (Table 2). This report showed that two clusters consisting of 18 locally originated *P. knowlesi* infections were observed in a locality where two common malaria parasites namely *P. vivax* and *P. falciparum* had been eliminated.[23]

Microscopy of the two blood films from two patients showed *P. malariae* in Palawan, Philippines in 2006, in the Malaria Research Centre in Sarawak.[24] When DNA from the two samples were examined by nested PCR assays, one sample was observed to be *P. knowlesi* mono-infection whereas the other sample was a mixed infection of three malarial parasites including *P. knowlesi*.[24] Both of the patients worked for charcoal making in forest at night. The forest was the habitat of *Anopheles flavirostris* mosquitoes and *M. fascicularis*.[24] The additional three of nine samples diagnosed as *P. malariae* infections were checked by nested PCR in the same centre and the results showed were *P. knowlesi* mono-infection.[24] Although *P. knowlesi* was found in local macaques in the Philippines starting from 1961[25] to 1978,[26] knowlesi malaria in human was documented only in the major study undertaken in 2006.[24] Coinfection was not observed in the Philippines with both *P. vivax* and *P. falciparum*.

Disease range of *P. knowlesi* infection and geographical distributions of the host and vector species

The host species of *P. knowlesi* are *M. fascicularis*, *M. nemestrina* and *M. leonina* while the vector species are the Leucosphyrus Complex and the Dirus Complex.[11,28] The disease range of *P. knowlesi* infections was proposed to be islands of Indonesia in the southern part whereas it was up to China–Myanmar border in the northern part.[11] *M. fascicularis* simian hosts are observed across the disease range while habitats of *M. nemestrina* are in the southern part of the *P. knowlesi* disease range.[11] Areas of occurrence by *M. fascicularis* do not extend to the Myanmar/China border in the northern part. Regarding mosquitoes vector, under Leucosphyrus group, there are 3 subgroups namely Leucosphyrus, Hackeri and Riparis subgroups. Leucophyrus Complex and Dirus Complex are under Leucosphyrus Subgroup. Leucophyrus Complex includes *An. latens* and *An. balabacensis* whereas *An. dirus* and *An. cracens* are under Dirus Complex. The distribution of knowlesi malaria depends upon natural or human-made deforested areas. Human *P. knowlesi* infections were detected in the northern side of the habitat of both *M. nemestrina* and *M. fascicularis*. *M. leonina* was assumed to be host species whose habitat extends into northern part of Myanmar and China–Myanmar border where human cases of knowlesi malaria were reported (Table 2)[29] while this species is not found in Malaysia, Brunie and Singapore.[30]

In contrast, a very recent study in 2018 described *M. fascicularis* and *M. nemestrina* as the reservoir whereas the leucosphyrus group of Anopheline mosquitoes as the vector for *P. knowlesi*. *Macaca leonine* was not described in this article while a leaf monkey named *Semnopithecus obscurus*, was proposed to be the natural host of *P. knowlesi* especially in Thailand.[31] In consistent with the above literature, the vectors of *P. knowlesi* are *An. leucophyrus* group of mosquitoes.[31] This group is very diverse and varies with the region. The group transmits *P. vivax*, *P. falciparum* as well as *P. knowlesi*. In east Malaysia, the vector for *P. knowlesi* is *An. balabacensis* whereas it is *An. latens* in Sarawak. In the west Malaysian state Selangor, *An maculatus* contains the oocysts of parasite while *An. cracens* is the predominant malaria vector in Kuala Lupis.[31]

Conclusion

Although *P. knowlesi* malaria was significantly rare until now in other south-east Asian countries, *P. knowlesi* is highly prevalent in Malaysia, mainly east Malaysia, Indonesia and to a limited extent in West Malaysia. Humans contract the infection when they enter the forest which is the habitat of simian host and Anopheline mosquito vectors. PCR based detection assays were critically useful in the diagnosis of knowlesi malaria because late trophozoites of *P. knowlesi* and *P. malariae* in blood film microscopy were similar morphologically[3] while RDT misdiagnosed *P. knowlesi* as other malaria parasite including *P. vivax*.[9] As *P. knowlesi* may give rise to fatality with severe complications as a consequence of high parasitaemia, it is dangerous to misdiagnose it as *Plasmodium vvax*.[4] The three factors including microscopic diagnosis of *P. malariae* with parasite count greater than 5000 per μl of blood, low platelet count and a recent visit to the forest in the history taking indicate *knowlesi* malaria if PCR is not available in the poor rural setting.[3] In case of knowlesi malaria, variable symptoms and signs and complications such as acute respiratory distress syndrome, acute renal failure, hypotension were common whereas cerebral malaria, the common complication of *P. falciparum* was not observed. However, World Health Organisation recommended complicated *P. knowlesi* infections should be treated as severe falciparum malaria.[3] The mosquito vectors which transmitted *P. knowlesi* belong to the Leucosphyrus Complex in the Southern Asia including Malaysia while Dirus Complex is the putative vector in Vietnam, Myanmar, Laos, Cambodia and Thailand in the East Asia.[29] Although there is no proof of human to human transmission via the mosquito vector of *P. knowlesi*, previous experiences in Sabang, Indonesia[23] and Sabah[3] indicate the possibility of this kind of transmission. Control and elimination of knowlesi infections in south-east Asian countries are not successful because it is not feasible to control *P. knowlesi* in macaque populations, which leads to prevalence of knowlesi malaria through zoonotic transmission. Another challenge is the obstacles in the control of vectors in Sarawak, Sabah and Indonesia.

Further recommendations

Rapid diagnostic methods are not available for knowlesi malaria to get the correct treatment in malaria patients to prevent complications, fatality and drug resistance.[32] Therefore, efforts and budget are necessary for innovation of diagnostic tools which can detect *P. knowlesi* within 15–30 min. Currently available RDTs which can distinguish between *P. vivax* and *P. knowlesi* will lead to wrong treatment with consequence of fatality because *P. vivax* infection is mostly a mild one.[32] Simian hosts and vector species should be confirmed by epidemiological and entomological means and disease range of knowlesi malaria should be further studied so that control of infections by this parasite could be successful. Rapid increase in *P. knowlesi* infections in east Malaysia and Indonesia makes the possibility of human to human transmission more concerning. For this reason, genetic studies including tracing of the parasite human cases were clearly required.[32] Drug resistance to antimalarial drugs is not a problem in *P. knowlesi* up to now. If there is human-to-human transmission, drug resistant *P. knowlesi* will appear in the near future because humans are treated by antimalarial drugs while simian hosts are not feasible to be treated by drugs. Despite the assumption that drug resistance is absent in *P. knowlesi*, the feasibility of timely testing of the parasite susceptibility to antimalarials should be investigated. However, *P. knowlesi* has intrinsic tolerance to mefloquine and this drug should be avoided in knowlesi malaria while artesunate-lumefantrine a preferred option in the clinical setting for *P. knowlesi* infections.[33]

Authors' contribution

MTZ, ZL designed and conceived the study; MTZ, ZL wrote the manuscript; both authors read and approved the final manuscript.

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Conflicts of interest

None declared.

Ethical approval

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