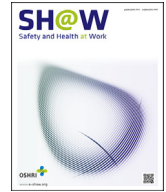




Contents lists available at ScienceDirect

Safety and Health at Work

journal homepage: www.e-shaw.org

Short Communication

Occupationally Acquired *Plasmodium knowlesi* Malaria in Brunei Darussalam

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ARTICLE INFO

Article history:

Received 5 June 2018

Accepted 28 September 2018

Available online 11 October 2018

Keywords:

Brunei

Occupational infections

Plasmodium knowlesi

Zoonosis

ABSTRACT

Simian malaria is a zoonotic disease caused by *Plasmodium knowlesi* infection. The common natural reservoir of the parasite is the macaque monkey and the vector is the *Anopheles* mosquito. Human cases of *P. knowlesi* infection has been reported in all South East Asian countries in the last decade, and it is currently the most common type of malaria seen in Malaysia and Brunei. Between 2007–2017, 73 cases of *P. knowlesi* infection were notified and confirmed to the Ministry of Health in Brunei. Of these, 15 cases (21%) were documented as work-related, and 28 other cases (38%) were classified as probably related to work (due to incomplete history). The occupations of those with probable and confirmed work related infections were border patrol officers, Armed Forces and security personnel, Department of Forestry officers, boatmen and researchers. The remaining cases classified as most likely not related to work were possibly acquired via peri-domestic transmission. The risk of this zoonotic infection extends to tourists and overseas visitors who have to travel to the jungle in the course of their work. It can be minimised with the recommended use of prophylaxis for those going on duty into the jungles, application of mosquito/insect repellants, and use of repellent impregnated uniforms and bed nets in jungle camp sites.

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1. Introduction

In 2016, there were an estimated 216 million cases of malaria globally with 445,000 deaths. Most of the cases (90%) occurred in the World Health Organization African Region with 99% of cases due to *Plasmodium falciparum* (*P. falciparum*) infections. Other parts of the world, such as the World Health Organization South-East Asia Region (which accounted for 7% of all cases), had >30% of cases due to *P. vivax* infections [1].

There are currently several known species of *Plasmodium*, e.g., *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*, that can infect humans in nature. Human *P. knowlesi* infection is largely a zoonotic disease, which occurs in persons who have traveled to, or live around forested areas where the natural animal reservoir and mosquito vector are present [2]. The predominant natural animal hosts for *P. knowlesi* in South East Asia are the long-tailed macaque (*Macaca fascicularis*) and pig-tailed macaques (*Macaca nemestrina*). Besides *P. knowlesi*, several other malaria parasites, such as

P. coatneyi, *P. inui*, *P. fieldi*, and *P. cynomolgi*, can also be found in the macaques [3]. The parasites are transmitted by the *leucosphyrus* group of anopheline mosquitoes e.g., *Anopheles balabacensis*, *An. latens*, *An. cracens*, and *An. maculatus* [4].

The first documented natural infection by *P. knowlesi* in human beings was in a US military surveyor who returned to the USA from the Pahang jungle in Malaysia, where he was working overnight in a forested area [5]. The disease was believed to be rare, until a cluster of more than 100 cases was described in Sarawak in 2004 [6]. Subsequently, human *P. knowlesi* infections have been reported in all countries in Southeast Asia.

The incubation period of *P. knowlesi* is from 9 to 12 days. This infection is known to lead to very high parasitemia compared with *P. malariae* infections. Presenting symptoms are nonspecific including fever and chills, rigors, headache, and malaise. The patient may have fever, tachypnea, tachycardia, hepatomegaly (24%–40% of patients), and splenomegaly (15%–33% of patients) [7,8]. Morphologically, *P. knowlesi* is often mistaken with *P. malariae*

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Table 1
Occupations of persons with *Plasmodium knowlesi* malaria in Brunei Darussalam, 2007–2017

Occupation	Work related, n = 15 (21%)	Probably work, related n = 28 (38%)	Probably not work related, n = 30 (41%)	
			Travel to the jungle for recreational/social activities, n = 19 (26%)	No history of travel to the jungle, n = 11 (15%)
Military	3	7	—	—
Police/security	9	9	1	1
Surveyor	—	1	—	—
Forestry/agriculture	—	6	—	1
Researcher/teacher	1	2	—	—
Fireman	1	—	—	—
Boatman	1	1	—	—
Driver	—	1	2	1
Others	—	Government worker, 1	Odd job, 1 General labor, 1 Housewife, 1 Student, 1 Construction, 1 Mosque worker, 1 Building supervisor, 1 Unknown, 3 Retired, 6	Clerk, 1 Retired, 1 Wood worker, 1 Pensioner, 1 Unknown, 2 Housewife, 2

under microscopy, but its differentiation is made possible by use of PCR-based assays. Infections are usually uncomplicated, but severe *knowlesi* malaria occurs in 9% to 29% of acute admissions, depending on the referral population. Case fatality rates can range from 0 to 2% [7,8]. Unlike *falciparum* malaria, abnormal neurological findings are not a prominent feature of *knowlesi* malaria [9]. The treatment of choice for severe *knowlesi* malaria is intravenous artesunate. For uncomplicated cases, chloroquine or artemisinin combination therapy can be used [10].

Brunei Darussalam is a sultanate situated in the island of Borneo in Southeast Asia. It has a land area of 5,770 square km, of which 80% is covered by tropical rainforest. In 2016, the country had a total population of 423,000, with 78% of the residents being urban dwellers. About 2,700 persons were employed as agricultural, animal husbandry, and forestry workers and as fishermen and hunters in 2014 [11]. Brunei Darussalam was declared “malaria free” in August 1987.

2. Methods

We reviewed the records of all cases of *P. knowlesi* malaria that were notified to the Ministry of Health in Brunei Darussalam for the period 2007–2017. All cases had the diagnosis confirmed by microscopic examination of patients' blood films. Cases were classified as the following:

2.1. Work related

Patients whose occupation required them to travel to, and spend time in forested areas where long-tailed macaques are known to be present; who had a documented history of travel to the jungle in the last month for work purposes; and who had no history of overseas travel in the last month.

2.2. Probably work related

Patients whose occupation required them to travel and spend time in forested areas where long-tailed macaques are known to be present; who had a history of travel to the jungle in the last month, but uncertain if it was for work (owing to omissions in the clinical history); and who had no history of overseas travel in the last month.

2.3. Probably not work related

Patients with documented history of travel to the jungle in the last month for nonwork-related purposes (e.g., on social or recreational purposes) or those with no history of travel to the jungle.

3. Results

Of the 73 cases notified between 2007 and 2017, 15 cases (21%) were clearly documented to be work related. Twenty-eight cases (38%) were classified as probably related to work because of an incomplete history. The occupations of those with probable and confirmed work-related infections were border patrol officers, armed forces and security personnel, department of forestry officers, boatmen, and researchers.

The remaining cases (41%) were classified as most likely not related to work. Nineteen cases (26%) had the infections acquired during recreational or social visits to the jungle, while the remaining 11 cases (15%) had no history of travel to the jungle in the past month and possibly acquired the infection via peridomestic transmission (Table 1).

4. Discussion

Human *knowlesi* malaria cases have been reported in all countries in Southeast Asia. Malaysia has reported the highest number of cases in the region, where *P. knowlesi* infection has been observed as the commonest type of malaria. In a study of 453 blood samples of malaria patients collected from both east and west Malaysia between 2012 and 2013, nested PCR assay targeting 18S rRNA gene was used to determine the infecting *Plasmodium* species. *P. knowlesi* was detected in 56.5%, *P. vivax* in 29.4%, and *P. falciparum* in 10.8% of cases. *P. ovale* and *P. malariae* were noted in <1% of the samples [12].

A country can be declared “malaria free” and still has endemic cases of *P. knowlesi* infection as this infection is not considered in the determination of the malaria status of a country.

4.1. Occupations at risk

Many of the reported cases occur among persons who have to work in, or travel to forested areas. In the Kapit region of Sarawak,

most patients with *knowlesi* malaria are Iban farmers or loggers, with 87% of patients reporting recent activities in the jungle or forest fringes [7]. In Sabah, farming or plantation work accounted for 40% of the occupations of patients. Ninety-two percent had some forest exposure in the preceding 4 weeks [8]. In Singapore, the first locally acquired human *Plasmodium knowlesi* infection in 2007 was in a soldier who had training in a forested area where long-tailed macaques were frequently seen. Subsequent comprehensive disease surveillance and monitoring detected four additional cases in 2007 and one in 2008. All involved military personnel who had undergone training in the forested area [13]. Another group at risk includes tourists and those who have to travel to forested areas as part of their work and account for up to several million persons a year [14].

4.2. Role of peridomestic transmission

However, not all cases of *P. knowlesi* infection are acquired during travel for work or recreational reasons to heavily forested areas. Cases have also been reported in areas of secondary forest, hilly areas, and oil palm and rubber estates, which are habitats for long-tailed macaques and *Anopheles* species, for example, in Kudat, Sabah [15]. This raises the possibility of peridomestic (outdoors but around the household) and domestic transmission. *P. knowlesi* was the most common cause of malaria admissions to Kudat District Hospital, which does not serve a heavily forested region [15]. This was in contrast to the previous reports of *P. knowlesi* infections which occurred in densely forested areas of Borneo. Among the admissions to the Kudat District Hospital were patients with a wide age distribution and two family clusters with PCR-confirmed *knowlesi* malaria—a father with two children aged 10 and 11 years and three brothers aged 1 to 11 years. This patient distribution suggests that transmission may occur close to, or even inside people's homes.

5. Conclusion

Despite being declared “malaria free”, some countries can still have cases of indigenous *P. knowlesi* malaria. In Brunei Darussalam, 73 cases were reported from 2007–2017, of which 21% were definitely work related and another 38% were probably work related. The number of work-related cases is underestimated because of underreporting and inconsistent history taking in notified cases. The nonwork-related cases occur among those who enter the jungle for recreational purposes (26%), while some cases may be due to peridomestic transmission.

There is a need for increased awareness for both the public and the health authorities regarding the risk of *P. knowlesi* malaria despite the “malaria free” status of some countries. Those at risk include residents who are required to work in the jungle, those who enter the jungles for recreational reasons, and overseas travelers or tourists who may go into the jungle for work or leisure. The risk can be adequately managed by the use of standard advisories for malaria control. The potential for its peridomestic transmission has significant implications for malaria control. Finally, it may be timely to heed the call for *P. knowlesi* to be included in the world malaria report [16].

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

The authors would like to thank Dr Jeffrin Yusof of the Ministry of Health, Brunei Darussalam, for his assistance in this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.shaw.2018.09.002>.

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