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Plasmodium knowlesi: from macaque monkeys to humans in South-east Asia and the risk of its spread in India

Sarala K. Subbarao

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Abstract The identification of a large focus of *Plasmodium knowlesi* in Malaysian Borneo and subsequent reports from several countries in South-east Asia has led its recognition as the fifth human malaria parasite. The natural preferred hosts of this species still continue to be macaque monkeys that live in broad-leaf rain forests. This review describes the distribution of macaque monkeys, the *Anopheles* species belonging to the Leucosphyrus Group that have been incriminated as vectors, morphological and clinical features of this parasite, and the transmission cycles that have been identified for this parasite. As the North-eastern states of India share their borders with *P. knowlesi* malaria endemic countries and because travelers from countries in South-east Asia visit India and vice versa, risks of this parasite entering India and its spread are also discussed.

Keywords *Plasmodium knowlesi* · Macaque monkeys · Leucosphyrus group · *Anopheles* species · India · South-east Asia

Introduction

Plasmodium knowlesi was described in India in 1931 in a long tailed macaque monkey (*Macaca fascicularis*) imported from Singapore (Knowles and Das Gupta 1932). Though this parasite was identified for the first time in 1931, in 1932 it was named after its discoverer Dr. R. Knowles by Sinton and Mulligan. Knowles and Das Gupta (1932) also succeeded in transmitting this parasite through blood inoculation to a man. At that time the experimental transmission of monkey malaria to humans was important as medical practitioners were looking for alternate treatments to 'human malaria therapy' for neurosyphilis patients. However, *P. knowlesi* infections in humans were soon discontinued as the infections became uncontrollable and life threatening and treatment of neurosyphilis patients was resumed with *P. vivax* infections which were at that time considered totally benign. *P. knowlesi* was found naturally infecting man in 1961 (Chin et al. 1965). With the reporting of a large focus of this infection in humans in Malaysian Borneo (Singh et al. 2004), and subsequent finding of this parasite in several countries in South-east Asia, this parasite was recognized as the fifth human malaria parasite (White 2008). This review describes the distribution of macaque monkeys, the natural hosts of *P. knowlesi* and of other simian malaria parasites, the *Anopheles* species belonging to the Leucosphyrus Group that have been incriminated as vectors of these parasites and their distribution, the wide spread distribution of *P. knowlesi* in humans in South-east Asia and its morphological and clinical features, and the transmission cycles that have been identified. As North-eastern states of India share their borders with *P. knowlesi* malaria endemic countries and because travelers from countries in South-east Asia visit India and vice versa, the risks of this parasite entering India and its spread are also discussed.

Plasmodium knowlesi and other *Plasmodium* species infections in macaque monkeys

Macaque monkeys belong to the Genus *Macaca* and family Cercopithecine. Of the 24 *Plasmodium* species that are found to infect non-human primates, seven *Plasmodium*

S. K. Subbarao (✉)
Division of Epidemiology and Communicable Diseases, Indian Council of Medical Research, New Delhi, India
e-mail: subbaraosk@gmail.com

species are found to infect eight *Macaca* species (Fooden 1994). The *Macaca* species that harbour *Plasmodium* species are *M. sinica*, *M. radiata*, *M. mulatta*, *M. cyclops*, *M. fascicularis*, *M. arctoides*, *M. nemestrina* and *M. nigra*. The seven *Plasmodium* species that are found naturally infecting these *Macaca* monkeys are *P. coatneyi*, *P. cynomolgi*, *P. fieldi*, *P. fragile*, *P. inui*, *P. knowlesi* and *P. simiovale*. Of the seven macaque malaria parasites, *P. inui* is a quartan malaria parasite with a 72 h cycle; five species *P. coatneyi*, *P. cynomolgi*, *P. fieldi*, *P. fragile* and *P. simiovale* are tertian malaria parasites with a 48 h asexual cycle; and *P. knowlesi* is a quotidian parasite with a 24 h asexual parasite cycle.

M. fascicularis and *M. nemestrina* (pig-tailed macaque) are natural hosts of *P. knowlesi* in Peninsular Malaysia (Garnham 1966). *P. cynomolgi*, *P. inui* and *P. knowlesi* in addition to infecting macaque monkeys also naturally infect Asian leaf monkeys, *Presbyits* species. *P. inui*, *P. cynomolgi* and *P. fragile* are found in South western part of India; *P. simiovale* in addition to the above three parasites is found in Sri Lanka; and *P. coatneyi*, *P. cynomolgi*, *P. fieldi*, *P. inui* and *P. knowlesi* are found to the east of Bay of Bengal. Natural infections of *P. knowlesi* have not been reported so far from the west of Bay Bengal either from South-western part of India or Sri Lanka. Even in Greater Nicobar of the Nicobar Islands, Kalra (1980) found natural infections of *P. cynomolgi* in *M. umbrosus* (crab-eating monkeys) but not of *P. knowlesi*. In India, *M. radiata* (bonnet monkey) in the South-western and *M. mulatta* (rhesus monkey) in the remaining parts of the country are reported (Fooden 1994). Ramakrishnan and Mohan (1962) reported natural infections of *P. fragile*, and Choudhury et al. (1963) reported *P. cynomolgi* and *P. inui* in *M. radiata* monkeys. In contrast in a large number of *M. mulatta* monkeys (>24,000) screened in northern India, none were found with any plasmodial parasite infections (Fooden 1994). Macaque malaria is widely distributed east of Bay of Bengal from Bangladesh to Taiwan, south in Java (Indonesia) and east to Philippines, and in the west of Bay of Bengal it extends to South-western India and Sri Lanka. Interestingly the disjunct distribution of macaque malaria parallels similarly the disjunct distribution of broad leaf rain forest where macaque monkeys are found in tropical Asia (Fooden 1994).

P. knowlesi experimental infection was virulent and fatal in Indian rhesus monkey, *M. mulatta*, but was benign in natural hosts, *M. fascicularis* and *M. nemestrina* from South-east Asia (Knowles and DAS Gupta 1932). Experimentally several other non-human primates namely *M. assamensis* (Dutta et al. 1978), the Squirrel monkey, *Saimiri sciureus* (Collins et al. 1978), marmoset monkey, *Presbytis entellus* (Dutta et al. 1981), *M. radiata* (Dutta et al. 1982), two new world monkeys, *Aotus azarae boliviensis* and *Saimiri boliviensis* (Sullivan et al. 1996) and olive baboon from Kenya, *Popio anubis* (Ozwara et al. 2003) were infected with *P. knowlesi* either by mosquitoes or blood to test for their susceptibility and/or suitability as animal models. In most of these experiments *P. knowlesi* infection was either fatal or acute, with animals developing multi-organ and cerebral dysfunctions (Fooden 1994).

Natural *P. knowlesi* infections in humans

The earliest report of a confirmed natural infection of *P. knowlesi* in humans was in 1965 in a US traveler who spent a few weeks in a forest of Pahang, Peninsular Malaysia (Chin et al. 1965). Initially this case was microscopically identified as *P. falciparum* and the next day as *P. malariae*, and later it was confirmed as *P. knowlesi* from the inoculation of infected blood into rhesus monkeys. For several years there were no reports of this parasite in humans. For the first time a large focus of *P. knowlesi* infections in humans was reported by Singh et al. (2004) from Malaysian Borneo. These investigators noted that there had been an unusual increase in the incidence of *P. malariae* cases in the central divisions of Sarawak, Kapit and Miri in 1999. They collected blood spots from 208 cases that were microscopically confirmed for malaria between 2000 and 2002. All the cases that were identified as *P. malariae* microscopically were identified as *P. knowlesi* by the nested polymerase chain reaction (PCR) that was developed by the investigators (Singh et al. 1999, 2004). Identification of more cases in the following years from different hospitals in Sarawak (Cox-Singh et al. 2008), high incidence in the interior divisions of Sabah (Lau et al. 2011) and severe cases from a tertiary hospital in Sabah (Willam et al. 2011) established that the entire Malaysian Borneo has *P. knowlesi* cases. Vythillingam et al. (2008) reported cases from Peninsular Malaysia.

Following the report of Singh et al. (2004), naturally acquired human *P. knowlesi* infections were reported from several South-east Asian countries namely, Thailand (Jongwutiwes et al. 2004), Philippines (Luchavez et al. 2008), Singapore (Ng et al. 2008; Jeslyn et al. 2011), Vietnam (Marchand et al. 2011), and Cambodia (Khim et al. 2011). Naturally acquired cases were also reported in travelers who visited endemic areas and went back to their native countries. Such case reports were from China in 2006 in a traveler returned from Myanmar (quoted from Singh et al. 2004), Sweden in 2006 in a traveler returning from Malaysian Borneo (Bronner et al. 2009), Finland in 2007 in a traveler returning from Peninsular Malaysia (Kantele et al. 2008) and in New York, USA in 2008 in a Philippines woman who has been living in the US for the last 25 years and went to Philippines for a short visit and

returned back to USA (MMWR 2008). There was also a report from the Netherlands in a Malaysian immigrant (van Hellemond et al. 2009). Recently a case of *P. knowlesi* has been identified in Spain in a traveler who spent time in three South-Asian countries, Indonesia, Vietnam and Thailand (Tang et al. 2010), and in Australia in a patient who acquired the infection in Indonesian Borneo (Figtree et al. 2010). All these reports suggest that *P. knowlesi* infections in humans are wide spread in South-east Asia. Retrospective analysis of malaria cases identified by microscopy more than 10–12 years back in Malaysian Borneo ((Lee et al. 2009b) and Tak province in Thailand (Jongwutiwes et al. 2011) found *P. knowlesi* infections among them. These studies suggest that *P. knowlesi* is not a new emergent simian malaria parasite in humans, and it was present in humans prior to Singh et al. (2004) report. These studies also suggest that not finding *P. knowlesi* human infections prior to Singh et al. (2004) report was because *P. knowlesi* specific diagnostic assay/method was not available. Keeping in view the wide spread occurrence of this parasite, White (2008) in his editorial commentary pointed out that despite its simian preference, it is legitimate to claim *P. knowlesi* to be a fifth human malaria parasite.

Morphological characters of *P. knowlesi* parasites and its diagnosis in humans

Almost all the stages that are expected to be seen in a peripheral blood smear of malaria parasite were seen in the *P. Knowlesi* infections (Singh et al. 2004). Table 1 gives salient morphological and clinical characters of *P. knowlesi* parasites, and their distinct resemblances and differences with *P. falciparum*, *P. malariae*, *P. ovale* and *P. vivax*. Misdiagnosis of *P. knowlesi* either as *P. falciparum* or *P. malariae* or mixed infection of *P. falciparum* and *P. malariae* was because late trophozoites and mature schizonts resembled those of *P. malariae* in their morphological characters while the early trophozoites were indistinguishable from rings of *P. falciparum*. Misdiagnosis depended on the stages of the parasite present at the time of microscopic examination. In all the case reports and studies where large foci of this parasite were identified, majority of the infections of *P. knowlesi* were misidentified as *P. malariae* (Lee et al. 2009a). With the development of a nested PCR consisting of *Plasmodium* specific assay (Singh et al. 1999), followed by the use of species specific primers from 18s ribosomal RNA gene (Pmkr8 and Pmk9) in a PCR assay identified *P. knowlesi* with 100% accuracy (Singh et al. 2004). The genus specific primers used in this assay identified all four human malaria parasite species, *falciparum*, *malariae*, *ovale* and *vivax*, and five simian malaria parasites namely, *cynomolgi*, *fragile*, *fieldi*, *inui* and *knowlesi*. Development of this nested PCR assay in 2004, helped in detecting infections of *P. knowlesi* in humans in several countries in the South-east Asia and in travelers as mentioned above.

A rapid diagnostic test using a panel of antibodies developed for human malaria and of *P. knowlesi* in combination with microscopy could identify *P. knowlesi* infections (McCutchun et al. 2008). Another nested PCR using *P. knowlesi* specific primers (Pkf 1140 and Pkr 1550) in the second assay (Imwong et al. 2009) and a real time PCR (Divis et al. 2010) are now available for detection of *P. knowlesi* infections. Using nested or real-time PCR and molecular characterization of CSP or mitochondrial genes, are the diagnostic methods that can be used for the accurate identification of *P. knowlesi* infections.

Clinical symptoms of *P. knowlesi* infections and treatment

Almost all the patients that were diagnosed with *P. knowlesi* infection in Kapit Hospital of Malaysian Borneo exhibited clinical signs and symptoms (Singh et al. 2004). Most of the patients complained of fever with chills and rigors before they approached hospital for the treatment of malaria. The other symptoms that were observed were headache, cough and vomiting. Parasite counts were high with 48–66 640 parasites per µl of blood. About 18% of cases were with about 5,000 parasites per µl of blood. All the patients responded to chloroquine treatment. These patients are those that were diagnosed as *P. malariae* cases based on microscopic examination even though clinical symptoms were different. *P. malariae* cases are generally asymptomatic and chronic with low parasitic levels with mostly less than 5000 parasites per µl of blood. Cox-Singh et al. (2008) reported 4 deaths (1.8%) in Sarawak and William et al. (2011) reported deaths and several patients (39%) with severe malaria having respiratory distress, acute renal failure, and shock from a tertiary hospital in Sabah, Malaysia. But none of the patients went into coma. Both artesunate and artemether-lumifantrine were efficient in clearing the parasites, and treating uncomplicated and severe cases of *P. knowlesi.*

P. knowlesi in humans: a case of malaria zoonoses

Chin et al. (1968) for the first time showed that *P. knowlesi* can be transmitted from monkeys to humans by an infected mosquito. These investigators used *Anopheles balabacensis*, a member of the Leucosphyrus complex placed under the Leucosphyrus Group (Sallum et al. 2005). The proof that *P. knowlesi* in humans is a case of malaria zoonoses came from studies by Vythillingam et al. (2006, 2008). In Sarawak

Table 1 Morphological and clinical characters of *P. knowlesi* and the other four human malaria parasite species

Characters	*P. knowlesi*	*P. falciparum*	*P. malariae*	*P. ovale*	*P. vivax*
Fever pattern/ erythrocytic phase	Quotodian with 24 h cycle	Tertian, sub-tertian with 48 h cycle	Quartan with 72 h cycle	Tertian with 48 h cycle	Tertian with 48 h cycle
Relapse from persistent tissue stages	No	No	No, but blood forms can persist up to 30 years	Yes	Yes
Severe form in	6–10% cases	Up to 24% cases	Very rare	Very rare	Up to 22% cases
Human erythrocyte	Not enlarged, rounded, not distorted	Not enlarged, rounded	Not enlarged, rounded, generally not distorted	Not enlarged, rounded, generally not distorted	Enlarged from trophozoite stage onwards, rounded, not distorted
Stages in peripheral blood	All	Rings and gametocytes	All	All	All
No. of parasites in RBC	Single or multiple (2 or 3)	Single or multiple	Single	Single	Single
Early trophozoite (ring form)	Dense cytoplasm with single or double chromatin, occasionally three chromatins. Chromatin lies inside the ring	Delicate cytoplasm, 1–2 small chromatin dots	Dense cytoplasm with large chromatin	Sturdy cytoplasm; large chromatin	Large cytoplasm with large single chromatin
Late trophozoite	Dense cytoplasm, cytoplasm slightly amoeboid and irregular, band forms, dark brown pigmentation	Rarely seen in peripheral blood. Compact cytoplasm, dark pigment	Compact cytoplasm, rounded large chromatin, occasional band forms, dark brown pigment	Compact cytoplasm with large chromatin, dark brown pigment	Large amoeboid cytoplasm, large chromatin, fine yellowish-brown pigment
Schizont and merozoites	Occupies whole erythrocyte. 10–16 merozoites scattered or grape-like cluster, pigment scattered or collects into a single mass	Seldom seen in peripheral blood. 8–24 small merozoites, dark pigment clumped in a mass	Occupies whole erythrocyte. 6–12 merozoites, usually 8–10 clustered around dark brown pigment forming rosette pattern	Slightly smaller than RBC, round to oval and fimbricated. 6–12 merozoites, usually 8 in a single ring, with large nuclei, clustered around mass of dark-brown pigment	Large may occupy full RBC. 12–24 merozoites, yellowish-brown coalesced pigment
Gametocyte	Occupies whole erythrocyte, round, compact, pigment scattered or collects into a single mass	RBC distorted by parasite, parasite is crescent or sausage shaped, dark pigment mass	Occupies whole erythrocyte, round to oval, scattered brown pigment	Round to oval, compact, may fill RBC, scattered brown pigment	Round to oval, compact, may fill RBC, scattered brown pigment

Source CDC (2011); Lee et al. (2011)

Malaysia, specimens of *An. latens*, another member of the Leucosphyrus complex were incriminated by identifying *P. knowlesi* DNA by nested PCR. This species was found attracted to both monkeys and humans in the forests. In Peninsular Malaysia in 2008, *An. cracens*, a member of the Dirus Complex also belonging to the Leucosphyrus Group was identified as the vector of *P. knowlesi*. In this study Vythillingam et al. (2008) examined blood samples from macaque monkeys, humans residing in the forested villages and mosquitoes collected from human-landing and monkey-baited collections from the same area. *P. knowlesi* infection was found in monkeys and humans, and in *An. cracens* from monkey-baited and human-landing collections.

Anopheline species incriminated as vectors of *P. knowlesi* in humans and monkeys, and of other simian *Plasmodium* parasites found in South-east Asia

As mentioned above both *An. cracens* (a member of the Dirus Complex) and *An. latens* (a member of the Leucosphyrus Complex) were incriminated as vectors of *P. knowlesi* in humans in Malaysian Borneo and Peninsular Malaysia respectively (Vythillingam et al. 2006, 2008). *An. latens* was simultaneously incriminated in the same area as a vector of *P. knowlesi* in monkeys (Vythillingam et al. 2008). In Vietnam, *An. dirus s. s.* was identified with *P. knowlesi* infection and a few specimens were found co-infected with *P. vivax* and one with both *P. vivax* and *P. falciparum* by nested PCR (Marchand et al. 2011). *An. cracens* and *An. elegans* (members of the Dirus complex), and *An. hackeri* (a member of the Hackeri sub-group) have been incriminated as vectors of other simian malaria parasites, *P. inui* and *P. cynomolgi*, and *An.hackeri* has also been incriminated as a vector of *P. knowlesi* and two other simian parasites *P. coatneyi* and *P. fieldi* found in Malaysia (Wharton and Eyles 1961). In India *An. mirans* (as per the revised nomenclature of Sallam et al. 2005) was incriminated as a vector of *P. cynomogi* and *P. inui* (Choudhury et al. 1963 referred the same vector species as *An. elegans*). Baird (2009) considers these two simian species of having biological characters capable of causing zoonoses. All these vector species belong to the Leucosphyrus Group of mosquitoes found in forests. The geographical distribution of this Group of *Anopheles* species extends from the southern islands of Hainan and Taiwan in the east and westward to southern India and Sri Lanka, and it coincides with the distribution of tropical rain forests.

P. knowlesi transmission cycles and its site of transmission to humans

Earlier studies established transmission from macaque monkey-to-macaque monkey. Identification of a large focus of *P. knowlesi* infections in humans in Malaysia and the identification of anopheline vectors that are attracted to both monkeys and humans in the same forest ecosystem and their incrimination by Vythallingam et al. (2008) established the existence of macaque monkey-to-human cycle in the transmission of *P. knowlesi*.

People living in villages that are close to forests and forest fringe areas come in contact with forest dwelling monkeys that are reservoir hosts for *P. knowlesi* and the forest dwelling vectors that have preference to bite both simians and humans. Thus in this ecosystem another mode of transmission for *P. knowlesi* namely from human-to-macaque monkey can be expected. Also in these villages because of the presence of a large number of human infected cases and vector population being in close proximity, human-to-human transmission cycle can be expected**.** In laboratory all four possible transmission cycles mentioned above were demonstrated (Chin et al. 1968). But so far there has been no confirmed evidence for the presence of last two types of transmission cycles mentioned above. Areas endemic for malaria are in close proximity to forests and forest fringe areas, but so far there is no report that human malaria parasites were found in forest dwelling monkeys as seen in Vietnam (Marchand et al. 2011). In Vietnam, *An. dirus s. s.* was found positive for *P. vivax* and *P. falciparum* sporozoite infection along with that of *P. knowlesi*, but none of the macaque monkeys screened were found with human parasites, *P. vivax* and *P. falciparum*. Monkeys were positive with mono-infection of *P. knowlesi.* The prevalence of high incidence of *P. knowlesi* was among the patients in the age group of 21 to 40 years, more in males and in people who spent nights in forested areas for their lively hood (Lau et al. 2011). In Singapore molecular epidemiological studies identified *P. knowlesi* infection in humans who visited forest and in long-tailed monkeys from forests but not in monkeys from national reserve park (Jeslyn et al. 2011). All these studies indicate and support the earlier finding that humans are acquiring the infection in the forest or in the forest fringe areas which are the natural habitats for macaque monkeys and the Leucosphyrus Group of mosquitoes. And that no clustering of cases were found in long house communities in Malaysia also suggests that human to human transmission through mosquitoes may not be occurring (Singh et al. 2004). Absence of human-to-monkey and human-to-human transmissions could be due to parasite specificity or parasite and vector specificity to particular hosts. However, Lee et al. (2011) are of the opinion that because of ongoing ecological changes resulting in deforestation and increase in population, *P. knowlesi* may switch to humans as preferred host.

Risks involved for *P. knowlesi* infections to be found in India and chances for their spread

Of the four countries, Bangladesh, Bhutan, Myanmar and Nepal, that border India, Myanmar is endemic for *P. knowlesi*. Four North-eastern states in India that border Myanmar are Arunachal Pradesh, Manipur, Mizoram and Nagaland. Travelers from Myanmar and other endemic countries visit India and people from India visit many of the endemic countries as tourists. Thus, there will be ample occasions for the *P. knowlesi* infections to come to India. With reference to anopheline vectors, there are three species belonging to the Leucosphyrus Group that are found in India. In forest, forest fringe and foot hill areas of North-eastern states, *An. baimaii* (a major vector of human malaria) and *An. elegans* in hill forest areas of Karnataka and Tamil Nadu in southern India (both are members of the Dirus Complex), and *An. mirans* (a member of the Hackeri sub group) in western-ghats in south-western region are found. *An. baimaii* is also a vector of human malaria parasites in Myanmar. There are no reports available on the role of *An. elegans* as a vector of any type of malaria, and this species has restricted distribution and is found only in India. *An. mirans* also has a restricted distribution, and as mentioned earlier it has been reported as a natural vector of *P. cynomolgi* and *P. inui*. In the Greater Nicobar of the Nicobar Islands Kalra (1980) found *P. cynomolgi* infections in humans and *M. umbrosus* (crab-eating monkeys), and *An. sundaicus* was reported as the vector. In the North-eastern states where *An. baimaii* is found, neither *P. knowles*i nor any other simian malaria parasites have been reported so far. Also there are no natural simian hosts for *P. knowlesi* in India. *M. mulatta* monkeys found in these states were never found with any simian malarial parasites. Thus, chances of monkey–mosquito–monkey, and human–mosquito–monkey transmission cycles to occur are remote in north-eastern states where *An. baimaii* is present. In south-western India, where *An. elegans* and *An. mirans* are found, there can be a risk of *P. knowlesi* establishing a transmission cycle involving *M. radiata* monkeys. But way back in 1932, Knowles and Das Gupta have shown *P. knowlesi* infection was virulent and fatal in *M. radiata* monkeys. As human-to-human cycle has not been reported so far even in the areas where natural infections of *P. knowlesi* are found, transmission of *P. knowlesi* infections among human population in North-eastern states or any other part of India seems a remote possibility.

Conclusions

Finding large number of *P. knowlesi* cases in complete Malaysian Borneo and Pahang region of Peninsular Malaysia, and its occurrence in many other countries in South-east Asia indicates of its Public health importance. Considerable range of severe complications seen in patients emphasizes the need to identify this parasite accurately and early, and treat adequately the positive cases. Both chloroquine and artemisinin derivatives were found effective in treating the patients. Keeping in view that it produces a range of clinical symptoms including severe complications and death, all new anti-malarials that are developed should be tested for their efficacy against this parasite species. Lack of proof for human–mosquito–human transmission so far indicates that *P. knowlesi* malaria continues to be a case of malaria zoonoses, hence control and management strategies are to be planned accordingly. Though there appears to be a strong host and vector specificity for this species, in view of the experimental transmission to a variety of macaque monkeys and other non-human primates were possible, India needs to be vigilant especially in the North-eastern region that is bordering *P. knowlesi* endemic countries. Cox-Singh et al. (2008) suggested that the successful control of human malaria might have allowed *P. knowlesi* infections to surface out. In light of this view, because of intensive efforts that are being carried out to control malaria in India, in Greater Nicobar where *P. cynomolgi* infections were found in humans and monkeys (Kalra 1980) and in the South-western part of mainland India where *P. cynomolgi* infections were found naturally in monkeys (Choudhury et al. 1963), malaria control programme officers and medical practitioners are to be equipped with appropriate diagnostic tools to identify *P. cynomolgi* infections and treat them effectively if the need arises.

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