Malaria in the Year of the Monkey

Zoonotic infections are increasing as the human population expands and comes into closer contact with reservoir hosts such as macaques. Prof William Brieger assesses the risks for malaria transmission.

As human population expands and people move into once seemingly remote wilderness, there is greater contact between people and various animals, and the greater chance for the spread of zoonotic disease. The devastating example of the West African Ebola outbreak is a case in point. Now as the Luna Year of the Monkey has begun, it is an important time to highlight the potential of shared disease between humans and their primate cousins. This challenge is being added to the already potentially devastating effects of malaria parasite resistance to current medicines and mosquito resistance to insecticides used in insecticide treated nets and indoor residual spraying.

*Plasmodium knowlesi*, the most well known malaria zoonosis

The most widely known form of malaria that people acquire from monkeys occurs in Southeast Asia, *Plasmodium knowlesi*. The blame has been laid squarely on the shoulders of deforestation caused by human expansion into what was previously the primary domain of macaque monkeys. The discovery of the parasite is credited to Giuseppe Franchini in 1927. Published studies in English date back to the late 1930s, and for the next seven decades the primary focus of most research was on the effect on monkeys themselves as well as use of the parasite to model human disease.

In 1957 Garnham and colleagues ‘suggested that *P. knowlesi* is very probably the fifth species that can cause human malaria, and that the infection may be a zoonosis, involving man and monkeys in Malaya and the East Indies’. Finally in 2004, researchers noted a large number of people in Borneo had *P. knowlesi* infection, leading the scientific community to ask whether *P. knowlesi* was the fifth form of human malaria. Then in 2008, a number of publications documented the acquisition of *P. knowlesi* by humans widely across the region from the Philippines to Singapore and Malaysia.

On the clinical side, the US Centres for Disease Control and Prevention (CDC) notes that *P. knowlesi* ‘has recently been shown to be a significant cause of zoonotic malaria in that region, particularly in Malaysia. *P. knowlesi* has a 24-hour replication cycle and so can rapidly progress from an uncomplicated to a severe infection; fatal cases have been reported’. Diagnosis of this malaria species is complicated by the fact that it occurs in areas where another tropical febrile disease, dengue, is common and with microscopy it can initially resemble *P. malariae*. Like *P. falciparum*, *P. knowlesi* requires urgent initiation of appropriate therapy is especially critical. Fortunately ‘there has been no widespread evidence of chloroquine resistance in *P. malariae* and *P. knowlesi* species; therefore, chloroquine (or hydroxychloroquine) may still be used for both of these infections’, but other approved treatment regimens like artemisinin-based combination therapy are also acceptable.

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Malaria in African primates

Researchers working in Gabon found *P. falciparum*, the most common species of malaria in Africa in the greater spot-nosed monkey (*Cercopithecus nictitans*). This primate derived from a line different to that of humans, which suggests that, ‘the origin of the parasite probably predates the origins of the African hominids line’.14

Today wild chimpanzees and gorillas throughout central Africa are endemically infected with parasites that are closely related to human *P. vivax*, with the implication that, ‘All extant human *P. vivax* parasites are derived from a single ancestor that escaped out of Africa’.15 The researchers concluded that further stud-

ies are ‘necessary to inform malaria control and eradica-
tion efforts and to assess future human zoonotic risk’.

Duval and colleagues studied malaria in chimpanzees and gorillas in Cameroon. They found that, ‘One chimpanzee *Plasmodium* strain was ge-
etically identical, on all three markers tested, to variant *P. ovale* type’, found in humans.16 The authors warned of the ‘pos-
sibility of natural cross-species exchange of *P. ovale* between humans and chimpanzees’. Again in Cameroon, Duval and co-researchers identified samples of *Plasmodium* species in gorillas and chimpanzees that related to *P. falciparum*.17

**Implications for control and elimination**

As long as the potential for zoonotic malaria transmission from primates to humans exists along with the potential for adaptation of such parasites to humans, and subsequent trans-

mission among humans, our goals of eliminating malaria as a human disease by 2030 are at risk.18 Ironically, it is human activity that heightens this risk.

As Kim-Sung Lee and col-

leagues observe, ‘… human infections with *P. knowlesi* are not newly emergent in Southeast Asia and that *knowlesi* malaria is (cur-
rently) primarily a zoonosis with wild macaques as the reservoir hosts. However, ongoing ecological changes resulting from deforestation, with an associated increase in the human population, could enable this pathogenic species of *Plasmodium* to switch to humans as the preferred host’.19 According to Fornace and colleagues, ‘Land use changes, such as deforestation and agricultural expan-

sion, have been proposed as the main drivers of this apparent emergence’.20 Specifically, there are reports that villagers in Malaysia are employed in tree clearance and agricultural expansion, bringing them in closer contact with long-tailed and pig-tailed macaques, and the malaria carrying mosquitoes that bite them.21

To date it does not appear that primate to human malaria transmission is occurring in Africa. Sundararaman and colleagues note there is, ‘evidence that *P. falciparum* emerged following a single gorilla-to-human transmis-

**Surveillance and detection of zoonotic malaria between monkeys and humans includes testing through microscopy and rapid diagnostic tests (above)**
sion’, but unlike the P. knowlesi situation Southeast Asia, ‘African apes harboring Laverania parasites do not seem to serve as a recurrent source of human malaria’. This is an important finding and potential reprieve for ongoing control and eradication measures in Africa.22

At the same time this is not a call for complacency, but a call for better surveillance, especially in areas where humans and primates are likely to come into contact. Such centres need to be able to distinguish more than the typical human malaria parasites.

In a broader context Faust and Dobson explain that, ‘The diversity and distribution of primate malaria are an essential prerequisite to understanding the mechanisms and circumstances that allow Plasmodium to jump species barriers, both in the evolution of malaria parasites and current cases of spillover into humans’,21 implying it is not a matter of if humans and primates might share malaria disease in Africa, but when it will happen on the scale seen in Southeast Asia.

References