

## *Plasmodium knowlesi* Malaria in Malaysia

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### SUMMARY

*Plasmodium knowlesi*, a simian malaria parasite, is now recognised as the fifth cause of human malaria and can lead to fatal infections in humans. Knowlesi malaria cases are widely distributed in East and West Malaysia and account for more than 50% of admissions for malaria in certain hospitals in the state of Sarawak. This paper will begin with a description of the early studies on *P. knowlesi*, followed by a review of the epidemiology, diagnosis, clinical and laboratory features, and treatment of knowlesi malaria.

### KEY WORDS:

*Plasmodium knowlesi*, Malaria, Clinical and laboratory features, Epidemiology, Treatment

### INTRODUCTION

Malaria in humans was thought to be caused by four species of *Plasmodium* (*P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*)<sup>1</sup> until a large number of human *P. knowlesi* infections were described in the Kapit Division of Sarawak in 2004<sup>2</sup>. Using molecular methods of detection, it was found that that 58% of 201 patients with malaria at Kapit hospital, Sarawak, were infected with the simian malaria parasite, *P. knowlesi*. The infections had been misdiagnosed by microscopy mainly as *P. malariae*. Subsequently, human knowlesi malaria cases have been reported in other parts of East<sup>3,4</sup> and West Malaysia<sup>4,6</sup>, and in other countries in Southeast Asia including Thailand<sup>7,8</sup>, Myanmar<sup>9</sup>, Singapore<sup>10-12</sup>, the Philippines<sup>13</sup>, Vietnam<sup>14</sup> and Indonesia<sup>15,16</sup>. *P. knowlesi* is now considered to be the fifth species of *Plasmodium* that can cause human malaria<sup>17</sup>. Researchers in Malaysia have played a pivotal role in the discovery and descriptions of naturally-acquired human knowlesi malaria and this review will begin with a description of the discovery and early studies on *P. knowlesi* followed by details of the epidemiology, diagnosis, clinical and laboratory features, and treatment of *P. knowlesi* infections.

### HISTORICAL ASPECTS

*P. knowlesi* was first isolated in 1931 from a long-tailed macaque (*Macaca fascicularis*) imported to India from Singapore<sup>18</sup>. The early experiments were mainly conducted by Knowles and Das Gupta, who observed that *P. knowlesi* causes asymptomatic and low level parasitaemia in its natural host, the long-tailed macaque (*M. fascicularis*), but is lethal for Indian rhesus macaques (*M. rhesus*). They further demonstrated that *P. knowlesi* was infectious to three humans by blood passage and that it has the shortest erythrocytic cycle amongst the primate malarias, multiplying in the blood and leading to fever spikes every 24 hours, as compared to 72 hours for *P. malariae* and 48 hours for *P. vivax*, *P. falciparum*

and *P. ovale*. The short erythrocytic cycle prompted the use of *P. knowlesi*, instead of *P. vivax*, as a pyretic agent for the treatment of patients with neurosyphilis, until the mid 1950s when penicillin became the treatment of choice<sup>1,19</sup>.

Although it was known that humans could be infected with *P. knowlesi* by blood passage since 1931, it was not until over thirty years later that the first case of a human infection by mosquito bite under natural conditions was reported<sup>20</sup>. An American army surveyor, who had been working in the forest in Bukit Kertau, near Temerloh in Pahang, became ill upon returning to the United States of America in 1965. His blood sample was sent to a research facility where experiments on *P. malariae* in human volunteers were being conducted. Following inoculation of infected blood into rhesus macaques, it was confirmed that the surveyor was infected with *P. knowlesi*. At that time, studies had already been initiated by a team of American scientists based at the Institute for Medical Research (IMR) in Kuala Lumpur, to determine whether malaria was a zoonosis following accidental infection of humans in two malaria laboratories in the USA with another simian malaria parasite, *P. cynomolgi*, in 1960<sup>1,19</sup>. These studies intensified after the description of the *P. knowlesi* case and involved inoculating rhesus macaques at IMR with pooled blood samples from 1,117 villagers living near the area in Pahang where the American surveyor acquired his infection<sup>21,22</sup>. When none of the rhesus macaques became infected, it was concluded that knowlesi malaria in humans was extremely rare and that zoonotic malaria would not be a major threat to the Malaria Eradication Programme that had been initiated by the World Health Organisation<sup>1</sup>.

### DISCOVERY OF LARGE FOCUS OF P. KNOWLESI MALARIA IN SARAWAK

*P. malariae* malaria is generally accepted as a benign disease, with infected persons having relatively low parasitaemia (seldom above 5,000 parasites per  $\mu$ l blood) and not requiring hospitalisation<sup>1,23</sup>. However, in the Kapit Division of Sarawak, cases identified as *P. malariae* by microscopy had features that were atypical for *P. malariae* malaria. These included the observation that almost all infected persons had clinical signs and sought treatment, approximately a fifth of '*P. malariae* malaria' patients had parasitaemias greater than 5,000 parasites per  $\mu$ l blood, and that the majority of cases occurred in adults<sup>2</sup>. Examination of DNA extracted from 8 patients with '*P. malariae* malaria' by nested PCR assays showed that they had Plasmodium but were negative for *P. malariae*. DNA sequencing and analysis of two genes indicated that these infections were due to *P. knowlesi* and not *P. malariae*<sup>2</sup>. A total of 201 samples from malaria patients at

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