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**Two cases of recurring ovale malaria in Sarawak, Malaysia after successful treatment of imported *P. falciparum* infection**

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1 **Two cases of recurring ovale malaria in Sarawak, Malaysia after successful**  
2 **treatment of imported *P. falciparum* infection**

3 **Running head:** Recurrent ovale malaria after falciparum malaria

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## 26 **Abstract**

27 Here are two cases of recurring ovale malaria in Sarawak, Malaysia, that are likely  
28 relapses which occurred 1 – 2 months after successful treatment of the initial  
29 imported falciparum malaria with artemisinin-based combined therapy (ACT). The  
30 patients have no history or recollection of previous malaria episodes. These cases  
31 add to the little evidence of the relapsing nature of *Plasmodium ovale*, after a febrile  
32 episode. In regions where *P. ovale* is not known to be autochthonous, active follow-  
33 up of treated imported malaria patients is highly recommended following their return,  
34 particularly to areas nearing or having achieved elimination.

35

## 36 **Case Report**

37 A 51-year-old Chinese male presented with fever, headache, rigor and  
38 nausea 3 days after returning to Sarawak, Malaysia from Liberia in June 2017 (Case  
39 1). He had been working in the timber industry for one and a half years in Liberia.  
40 Blood films for malaria parasites (BFMP) indicated falciparum infection with 1294  
41 asexual parasites/ $\mu$ L of blood. Riamet<sup>®</sup> (artemether/lumefantrine) was prescribed for  
42 3 days followed by a dose of primaquine for one day. Treatment with ACT reduced  
43 the parasite density to 80 parasites/ $\mu$ L of blood one day later. Parasites were not  
44 found during follow-ups until he experienced fever on Day 26 after ACT. On Day 28  
45 of follow-up, BFMP was positive for *P. ovale* with 5822 asexual parasites/ $\mu$ L and 118  
46 gametocytes/ $\mu$ L of blood. He was subsequently treated with Riamet<sup>®</sup> for 3 days and  
47 primaquine for 14 days. The patient was cured, with no parasites observed in the  
48 blood films for up to 5 months after treatment. During his stay in Sarawak, he had  
49 only travelled to non-receptive areas.

50 Another case (Case 2) was recorded on November 29, 2017 as an imported  
51 falciparum malaria in a patient returning from Equatorial Guinea with parasite density  
52 of 4123 asexual parasites/ $\mu$ L of blood. The patient was treated as above in Case 1.  
53 On January 24, 2018, approximately 2 months after the first malaria episode, *P.*  
54 *ovale* was detected in the blood smears of this patient. The parasite density was 515  
55 asexual parasites/ and 68 gametocytes/ $\mu$ L of blood. Treatment with Riamet® and  
56 primaquine was similarly given as in Case 1. Within this period of time, the patient  
57 resided in a non-receptive area in Sarawak and had no travel history to any receptive  
58 area.

59 Microscopic examination of Giemsa-stained blood smears, yielded a  
60 diagnosis of imported *Plasmodium falciparum* infection and relapse of *P. ovale* for  
61 both cases. A retrospective nested polymerase chain reaction (PCR) assay targeting  
62 the malaria parasites' 18S small-subunit rRNA gene,<sup>1, 2</sup> were performed on DNA  
63 extracted from bloodspots collected on admission (on the day following ACT  
64 administration) and recurrence episodes for both cases. These confirmed falciparum  
65 malaria on admission and infection with *P. ovale wallikeri* in the recurrence episode  
66 for Case 1, though that of Case 2 was negative. This is the second report of an  
67 imported *P. ovale wallikeri* infection in Malaysia.<sup>3</sup>

68

## 69 Discussion

70 There are increasing reports of ovale malaria, caused by *P. ovale wallikeri*  
71 and *P. ovale curtisi*, among travellers to sub-Saharan Africa, Indonesia, Papua New  
72 Guinea and India.<sup>4</sup> *Plasmodium ovale* is believed to be capable of causing relapses  
73 (due to liver hypnozoites) months to years after the primary infection.<sup>5</sup> Furthermore,  
74 co-infections of *P. ovale* with other malaria species, especially *P. falciparum* are

75 frequent in malaria endemic areas.<sup>6</sup> Two cases similar to those presented here were  
76 recently reported.<sup>7, 8</sup> The patients were admitted in Brazil and Canada, respectively,  
77 where there is no ovale malaria transmission. Recurrent ovale infections following  
78 successful treatment of falciparum malaria, could be a new infection, a  
79 recrudescence, a relapse or a delayed primary attack (the last two derived from  
80 hypnozoites).

81 A new infection of *P. ovale* is highly unlikely in the two cases reported here  
82 because *P. ovale* is not known to be autochthonous in Malaysia, including Sarawak.<sup>3</sup>  
83 Furthermore, a retrospective PCR screening of 44 bloodspots collected between  
84 2015 – 2017 from microscopically determined *Plasmodium vivax*-infected patients in  
85 Sarawak (a parasite species that is morphologically similar to *P. ovale*), showed only  
86 1 misdiagnosed imported ovale malaria case from Gabon (Y.L. Lau, unpublished  
87 data). Therefore, the possibility of misdiagnosing ovale malaria as vivax malaria in  
88 Sarawak is low.

89 Co-infections are frequent in endemic areas though *Plasmodium malariae* and  
90 *P. ovale* whose, parasitemias are often very low or below the detection limit are  
91 easily overlooked microscopically,<sup>6, 9, 10</sup> and are often found with *P. falciparum*  
92 following PCR detection.<sup>11, 12</sup> For Case 1, a patent co-infection on admission is  
93 unlikely because only *P. falciparum* was detected by the PCR assay, and only *P.*  
94 *ovale wallikeri* in the recurrent episode sample. It is unfortunate that the sample from  
95 Case 2 failed to amplify, most likely due to degradation of the DNA or maybe  
96 because of sequence polymorphism at specific primer binding site. A co-infection on  
97 admission would imply that ACT administration, which has effectively eliminated *P.*  
98 *falciparum*, failed to clear *P. ovale*. This is unlikely as ACT is considered highly

99 efficacious for non-falciparum malaria,<sup>13</sup> moreover the recurrent *P. ovale* episodes in  
100 the two cases presented here were rapidly cleared by the ACT administered.

101 Thus, the recurring ovale malaria in both cases are most likely relapses from  
102 hypnozoites even though the patients did not recall any previous clinical malaria  
103 episodes. The timing of these relapses is consistent with previously observed  
104 median times between a primary attack of *P. ovale* and first relapse of 17 weeks  
105 (range 2 – 60 weeks).<sup>4</sup> Our observations are also consistent with the suggestion that  
106 hypnozoite activation to cause relapse may be induced by fever due to a bacterial,  
107 viral or malarial infection.<sup>7, 14, 15</sup> Despite the paucity of observations, as compared to  
108 those of *P. vivax* malaria, suggestions that *P. ovale* does not produce hypnozoites  
109 are likely to be incorrect.<sup>4, 16</sup> In a recent report, convincing evidence for relapse in *P.*  
110 *ovale* infection showed that the re-appearing *P. ovale* parasites following supervised  
111 treatment of a patient in a non-endemic region were of the same genotype as that of  
112 the parasites found in the primary episode.<sup>17</sup> A delayed primary attack originating  
113 from hypnozoites, as described for some *P. vivax* malaria strains from temperate  
114 regions cannot be formally discounted.<sup>14</sup> However, in previous reports of such  
115 delayed attacks, anti-malarial prophylaxis during initial exposure was noted, and a  
116 clinically mild primary episode could not be excluded.

117 Clinical, parasitological and biological investigations on hypnozoites and  
118 relapses are restricted by logistical and ethical considerations, yet this phenomenon  
119 is of importance in the context of malaria control and elimination strategies. The two  
120 cases reported here add to the small number of such observations on *P. ovale* and  
121 provide evidence to support the relapsing nature of this parasite species. For  
122 patients returning from ovale endemic areas, and in particular to regions where  
123 malaria transmission is possible, clinicians should keep in mind the possibilities of

124 co-infection or pre-patent infection with *P. ovale*, especially as prophylactic  
125 medications have little effect on the hypnozoite.<sup>18</sup> Provided adequate screening for  
126 glucose-6-phosphate dehydrogenase, primaquine could be considered for routine  
127 administration to those presenting with malaria on their return from endemic areas,  
128 though cases of primaquine failure to prevent ovale relapses have been reported.<sup>4</sup>  
129 Ultimately, it will be important to maintain an active follow-up for at least three  
130 months for patients returning from areas endemic for relapsing malaria species.<sup>8</sup>

131

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138

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