



## Case Report: Two cases of recurring ovale malaria in Sarawak, Malaysia, after successful treatment of imported *Plasmodium falciparum* infection

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### ► To cite this version:

Jonathan Wee Kent Liew, Choo Huck Ooi, Georges Snounou, Yee Ling Lau. Case Report: Two cases of recurring ovale malaria in Sarawak, Malaysia, after successful treatment of imported *Plasmodium falciparum* infection. American Journal of Tropical Medicine and Hygiene, 2019, 101 (6), pp.1402-1404. 10.4269/ajtmh.19-0305 . hal-03059786

**HAL Id: hal-03059786**

**<https://cnrs.hal.science/hal-03059786>**

Submitted on 4 Sep 2021

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Journal:	<i>American Journal of Tropical Medicine &amp; Hygiene</i>
Manuscript ID	Draft
Manuscript Type:	Clinical Case Report
Date Submitted by the Author:	n/a
Complete List of Authors:	Liew, Jonathan; University of Malaya, Parasitology Ooi, Choo-Huck; Sarawak State Health Department, Sarawak State Health Department Snounou, Georges; INSERM, Immunology of Viral Infections and Autoimmune Diseases (IMVA), IDMIT Department Lau, Yee Ling; University of Malaya, Parasitology
Key Words:	Plasmodium ovale, relapse, recurrence, imported malaria

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

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

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**Key words:** *Plasmodium ovale*, relapse, recurrence, imported malaria

**Word counts**

Abstract: 95

Text: 1102

## Abstract

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

## Case Report

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

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

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

## Discussion

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

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

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

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

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

**Acknowledgements:** We would like to thank the Director General of Health Malaysia for his permission to publish this article.

**Financial Support:** YLL is supported by the Ministry of Education Malaysia (Long term research grant scheme LR002D-2018). GS was supported by a grant from the Agence Nationale de la Recherche, France (ANR-17-CE13-0025-01).

**Disclosures:** The authors declare no conflict of interest.

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151 **References**

152 1. Singh B, Bobogare A, Cox-Singh J, Snounou G, Mohammad Shukri Abdullah,  
153 Hasan Abdul Rahman, 1999. A genus- and species-specific nested  
154 polymerase chain reaction malaria detection assay for epidemiologic studies.  
155 *Am J Trop Med Hyg* 60: 687-692.

156 2. Calderaro A et al., 2007. Genetic polymorphisms influence *Plasmodium ovale*  
157 PCR detection accuracy. *J Clin Microbiol* 45: 1624-1627.

158 3. Liew JWK, Mahmud R, Tan LH, Lau YL, 2016. Diagnosis of an imported  
159 *Plasmodium ovale wallikeri* infection in Malaysia. *Malar J* 15: 8.

160 4. Groger M, Fischer HS, Veletzky L, Lalremruata A, Ramharter M, 2017. A  
161 systematic review of the clinical presentation, treatment and relapse  
162 characteristics of human *Plasmodium ovale* malaria. *Malar J* 16: 112.

163 5. Collins WE, Jeffery GM, 2005. *Plasmodium ovale*: Parasite and Disease. *Clin*  
164 *Microbiol Rev* 18: 570-581.

165 6. Smith A, Denholm J, Shortt J, Spelman D, 2011. *Plasmodium* species co-  
166 infection as a cause of treatment failure. *Travel Med Infect Dis* 9: 306-309.

167 7. Lupi O, Ridolfi F, da Silva S, Zanini GM, Lavigne A, Nogueira RMR, Cruz  
168 MdFFd, Daniel-Ribeiro CT, Brasil P, 2016. Dengue infection as a potential  
169 trigger of an imported *Plasmodium ovale* malaria relapse or a long incubation  
170 period in a non-endemic malaria region. *Int J Infect Dis* 44: 20-24.

- 171 8. Senn H, Alattas N, Boggild AK, Morris SK, 2014. Mixed-species *Plasmodium*  
172 *falciparum* and *Plasmodium ovale* malaria in a paediatric returned traveller.  
173 *Malar J* 13: 78.
- 174 9. Bichara C, Flahaut P, Costa D, Bienvenu A-L, Picot S, Gargala G, 2017.  
175 Cryptic *Plasmodium ovale* concurrent with mixed *Plasmodium falciparum* and  
176 *Plasmodium malariae* infection in two children from Central African Republic.  
177 *Malar J* 16: 339.
- 178 10. Mueller I, Zimmerman PA, Reeder JC, 2007. *Plasmodium malariae* and  
179 *Plasmodium ovale*--the "bashful" malaria parasites. *Trends Parasitol* 23: 278-  
180 283.
- 181 11. Dinko B, Oguike MC, Larbi JA, Bousema T, Sutherland CJ, 2013. Persistent  
182 detection of *Plasmodium falciparum*, *P. malariae*, *P. ovale curtisi* and *P. ovale*  
183 *wallikeri* after ACT treatment of asymptomatic Ghanaian school-children. *Int J*  
184 *Parasitol Drugs Drug Resist* 3: 45-50.
- 185 12. Miller RH, Obuya CO, Wanja EW, Ogutu B, Waitumbi J, Luckhart S, Stewart  
186 VA, 2015. Characterization of *Plasmodium ovale curtisi* and *P. ovale wallikeri*  
187 in Western Kenya utilizing a novel species-specific real-time PCR assay.  
188 *PLoS Negl Trop Dis* 9: e0003469.
- 189 13. Visser BJ, Wieten RW, Kroon D, Nagel IM, B  lard S, van Vugt M, Grobusch  
190 MP, 2014. Efficacy and safety of artemisinin combination therapy (ACT) for  
191 non-falciparum malaria: a systematic review. *Malar J* 13: 463.
- 192 14. White NJ, 2011. Determinants of relapse periodicity in *Plasmodium vivax*  
193 malaria. *Malar J* 10: 297.
- 194 15. Douglas NM, Nosten F, Ashley EA, Phaiphun L, van Vugt M, Singhasivanon  
195 P, White NJ, Price RN, 2011. *Plasmodium vivax* recurrence following

- 196            falciparum and mixed species malaria: risk factors and effect of antimalarial  
197            kinetics. *Clin Infect Dis* 52: 612-620.
- 198    16.    Richter J, Franken G, Mehlhorn H, Labisch A, Häussinger D, 2010. What is  
199            the evidence for the existence of *Plasmodium ovale* hypnozoites? *Parasitol*  
200            *Res* 107: 1285-1290.
- 201    17.    Veletzky L, Groger M, Lagler H, Walochnik J, Auer H, Fuehrer H-P,  
202            Ramharter M, 2018. Molecular evidence for relapse of an imported  
203            *Plasmodium ovale wallikeri* infection. *Malar J* 17: 78.
- 204    18.    Gallien S, Taieb F, Schlemmer F, Lagrange-Xelot M, Atlan A, Sarfati C,  
205            Molina JM, 2008. Failure of atovaquone/proguanil to prevent *Plasmodium*  
206            *ovale* malaria in traveler returning from Cameroon. *Travel Med Infect Dis* 6:  
207            128-129.