Non-falciparum Malaria in Africa and Learning From *Plasmodium vivax* in Asia

To the Editor—We read with interest Groger and colleagues' prospective study of *Plasmodium ovale* relapses in Gabon [1]. Their work is timely given non-falciparum malaria's increasing prominence in Africa and the potential role of hypnozoite-induced relapses in this trend. Despite declines in *Plasmodium falciparum* transmission, molecular surveys have shown a 6-fold increase in the odds of *P. ovale* infection in Tanzania from 2010 to 2016 [2], and a similar trend in the Democratic Republic of Congo, where the species' prevalence increased from 0.4 to 8.3% in national surveys conducted in 2007 and 2013 [3, 4]. Successful interventions against *P. falciparum* in Zanzibar [5] and Uganda [6] have not had the same effect on non-falciparum species. Clearly, *P. ovale* is becoming an increasingly important malaria in Africa.

P. vivax studies have taught us that characterizing malaria relapse epidemiology is essential to elimination efforts yet supremely challenging. In this paper, the authors used real-time polymerase chain reaction (PCR) and Sanger sequencing to distinguish between *P. ovale curtisi* and *wallikeri* species. They defined relapses in their cohort as homologous genotypes detected after at least 1 PCR-negative sample between episodes in the setting of adequate drug levels. In contrast to *P. ovale curtisi*, they found no *P. ovale wallikeri* relapses.

This finding is unexpected in the context of studies of travelers returning from Africa. Across studies, *P. ovale wallikeri*-infected travelers presented with presumptive relapse sooner after return to nonendemic areas than those with *P. ovale curtisi*, on the order of 1 versus 3 months, respectively (Table 1). What could explain the difference?

Lessons learned from *P. vivax* studies may explain this discordance. First, although Groger et al's conservative definition of relapse increases confidence

Table 1. *Plasmodium ovale wallikeri* and *Plasmodium ovale curtisi* Exhibit Different Relapse Latencies in Cases of Imported Malaria from Africa.

Region Reporting Imported Cases	*P. ovale* Cases (no.)	Median Latency Period (no. of days with IQR)		Reference
		P. ovale wallikeri	*P. ovale curtisi*	
United Kingdom (2003–2011)	134	41 (29–57)	86 (66–111)	Nolder D, et al. BMJ Open 2013.
Spain (2005–2011)	35	10 (3–58)	95 (13–297)	Rojo-Marcos G, et al. Mal J 2018.
China (2010–2017)	120	31 (14–99)	98 (8–199)	Zhou R, et al. Sci Rep 2019.

Abbreviation: IQR, interquartile range; *P. ovale, Plasmodium ovale.*

in their calls, it also excludes relapses from heterologous hypnozoites. These hypnozoites account for the majority of relapses in Asia; they may arise from previously acquired infections and/or minority genotypes within a polyclonal infection, which are often missed by common genotyping approaches [7–9]. Thus, it is plausible that some or all of the 4 nonhomologous *P. ovale wallikeri* reappearances that Groger et al detected represent heterologous hypnozoite-induced relapse.

Second, acquired immunity likely plays a role in suppressing or masking relapses. Acquired strain-specific immunity during a febrile illness may prevent hypnozoites of the same genotype from achieving blood-stage breakthrough during a subsequent relapse. If *P. ovale wallikeri* is a frequently relapsing strain similar to Asian strains of *P. vivax*, early acquisition of immunity in endemic populations [10] could obscure the short-latency relapses observed in nonimmune travelers. This possibility provides an alternative explanation for the differing *P. ovale wallikeri* relapse frequencies reported by Groger et al compared to others.

Much remains unknown, as *P. ovale* in Africa has long existed in the shadow of *P. falciparum*. It is clear that additional research is needed to build upon the work by Groger et al.[1] We commend the authors on an intriguing first look into *P. ovale* relapses in Africa and an epidemiology that has yet to be defined.

Note

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