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

Potential conflicts of interest. J. B. P. reports nonfinancial support from Abbott Diagnostics, outside the submitted work. All other authors have no potential conflicts to disclose. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Jessica T. Lin,[1] Jonathan B. Parr,[1] and Billy Ngasala[2]

[1]Institute of Global Health and Infectious Diseases, University of North Carolina, Chapel Hill; and [2]Department of Parasitology and Medical Entomology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

References

1. Groger M, Veletzky L, Lalremruata A, et al. Prospective clinical and molecular evaluation of potential *Plasmodium ovale curtisi* and *wallikeri* relapses in a high-transmission setting. Clin Infect Dis **2019**; Available at: http://dx.doi.org/10.1093/cid/ciz131. Accessed 25 June 2019.
2. Yman V, Wandell G, Mutemi DD, et al. Persistent transmission of *Plasmodium malariae* and *Plasmodium ovale* species in an area of declining *Plasmodium falciparum* transmission in eastern Tanzania. PLoS Negl Trop Dis **2019**; 13:e0007414. Available at: http://dx.doi.org/10.1371/journal.pntd.0007414. Accessed 25 June 2019.
3. Taylor SM, Messina JP, Hand CC, et al. Spatial and molecular epidemiology of malaria in the Democratic Republic of Congo, 2007. PLoS Med **2011**; 6:e16420.
4. Doctor SM, Liu Y, Anderson OG, et al. Low prevalence of *Plasmodium malariae* and *Plasmodium ovale* mono-infections among children in the Democratic Republic of the Congo: a population-based, cross-sectional study. Malar J **2016**; 15:350.
5. Cook J, Xu W, Msellem M, et al. Mass screening and treatment on the basis of results of a *Plasmodium falciparum*-specific rapid diagnostic test did not reduce malaria incidence in Zanzibar. J Infect Dis **2015**; 211:1476–83.
6. Betson M, Clifford S, Stanton M, Kabatereine NB, Stothard JR. Emergence of non-*falciparum Plasmodium* infection despite regular artemisinin combination therapy in an 18-month longitudinal study of Ugandan children and their mothers. J Infect Dis **2018**; 217:1099–109.
7. Imwong M, Snounou G, Pukrittayakamee S, et al. Relapses of *Plasmodium vivax* infection usually result from activation of heterologous hypnozoites. J Infect Dis **2007**; 195:927–33.
8. Popovici J, Friedrich LR, Kim S, et al. Genomic analyses reveal the common occurrence and complexity of *Plasmodium vivax* relapses in Cambodia. MBio **2018**; 9. Available at: http://dx.doi.org/10.1128/mBio.01888-17. Accessed 25 June 2019.
9. Lin JT, Hathaway NJ, Saunders DL, et al. Using amplicon deep sequencing to detect genetic signatures of *Plasmodium vivax* relapse. J Infect Dis **2015**; 212:999–1008.
10. Mueller I, Galinski MR, Tsuboi T, Arevalo-Herrera M, Collins WE, King CL. Natural acquisition of immunity to *Plasmodium vivax*: epidemiological observations and potential targets. Adv Parasitol **2013**; 81:77–131.

Correspondence: J. T. Lin, University of North Carolina (jessica_lin@med.unc.edu).

Reply to Lin et al

To the Editor—We thank Lin and colleagues [1] for their interest in our work and welcome the opportunity to exchange further thoughts about this interesting topic. Indeed, in light of the data published so far characterizing latency periods of *Plasmodium ovale* spp. in returning travelers [2–4], our findings give rise to questions.

We wholeheartedly agree that the absence of *P. ovale wallikeri* relapse in our study is surprising, given the documentation of reappearing *P. ovale wallikeri* parasitemia in returning travelers. The possible explanations for this finding include differences in populations and treatment observation. Although data in our study [5] are from participants residing and being followed up in a highly malaria-endemic country, data in the literature come mostly from individuals residing in a malaria-nonendemic country with a travel history to a malaria-endemic country [2–4].

Thus, though our study reliably captured baseline and recurring infections, and treatment was administered under supervision, the diagnosis of precedent or so called primary infections of travel returnees, as reported in the above-mentioned studies, was neither well defined nor supported by polymerase chain reaction results. Furthermore, travelers may not have adhered to

unsupervised treatment regimens. Some cases could thus reflect prolonged latency or recrudescence of the baseline infection rather than true relapse. However, we need to consider the possibility that the absence of detected homologous relapses of *P. ovale wallikeri* was a chance finding in an overall limited number of patients—a fact we tried to convey in our publication.

Lin et al [1] also rightly question whether our conservative definition of relapse may underestimate the true incidence of relapse events because of the exclusion of heterologous relapses, which may play a particularly important role owing to preferential suppression of homologous relapses by acquired immunity. Although we can only agree with this thoughtful comment, a conservative approach is the only way to exclude the possibility of classifying recrudescences and reinfections as relapse in a long-term follow-up study performed in a region with active transmission. Ultimately, a placebo-controlled randomized clinical trial with a hypnozoitocidal drug is required to adequately address this question.

Note

Mirjam Groger[1,2,3] and Michael Ramharter[1,3,4]

[1]Department of Tropical Medicine, Bernhard Nocht Institute for Tropical Medicine and I. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]Institut für Tropenmedizin, Universität Tübingen, Tübingen, Germany; [3]Centre de Recherches Médicales de Lambaréné, Lambaréné, Gabon; and [4]German Center for Infection Research (DZIF), partner site Hamburg-Luebeck-Borstel, Hamburg, Germany

References

1. Lin JT, Parr JB, Ngasala B, Non-falciparum malaria in Africa and learning from P. vivax in Asia. Clin Infect Dis. **2019**. pii: ciz780. PMID: 31408098. doi:10.1093/cid/ciz780
2. Nolder D, OguikeMC, Maxwell-Scott H, et al. An observational study of malaria in British travellers: *Plasmodium ovale wallikeri* and *Plasmodium ovale curtisi* differ significantly in the duration of latency. BMJ Open **2013**; 3.
3. Rojo-Marcos G, Rubio-Muñoz JM, Ramírez-Olivencia G, et al. Comparison of imported *Plasmodium ovale curtisi* and *P. ovale wallikeri* infections among patients in Spain, 2005-2011. Emerg Infect Dis **2014**; 20:409–16.
4. Zhou R, Li S, Zhao Y, et al. Characterization of *Plasmodium ovale* spp. imported from Africa to Henan Province, China. Sci Rep **2019**; 9:2191.
5. Groger M, Veletzky L, Lalremruata A, et al. Prospective clinical and molecular evaluation of potential *Plasmodium ovale curtisi* and *wallikeri* relapses in a high-transmission setting. Clin Infect Dis **2019**;69:2119–26.

Correspondence: M. Ramharter, Department of Tropical Medicine, Bernhard Nocht Institute for Tropical Medicine & I Dep. of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany (ramharter@bnitm.de).

Are Echinocandins Superior in Efficacy to Azoles?

To the Editor—Dr. Andes provided a very thoughtful editorial commentary on the latest of 10 published, randomized controlled trials (RCTs) comparing drug regimens for the treatment of disseminated candidiasis [1]. These 10 RCTs, published between 1994 and 2019, have compared polyene, azole, and echinocandin regimens. Nine of the 10 RCTs concluded noninferiority of the regimens; the latest trial is the first to achieve a "superiority" conclusion [2]. Dr. Andes summarized the conclusions of the societal guidelines on this disease, based on meta-analyses of prior RCTs, which is that echinocandins are superior in efficacy to azole-based therapy. Although I understand why this may be believed, I remain confused about 3 related questions on this topic.

First is the importance of the superior rate of clinical cure for echinocandins at the end-of-therapy time point mitigated by the lack of difference 2 weeks later [2]? In an era of crushing healthcare costs, does a difference in "cure" (which is hard to define objectively) at end of therapy but not shortly thereafter justify thousands of dollars of additional healthcare expenditures per patient for an echinocandin versus fluconazole?

Second, is there a mortality difference between echinocandin and azole therapy for disseminated candidiasis? Mortality was not different between the 2 arms in the most recent trial [2]. Dr. Andes indicated a nonsignificant trend to reduced mortality in the echinocandin arms in meta-analysis of the prior RCTs, driven primarily by 1 study comparing anidulafungin to fluconazole, in which there was a clear center effect [3]. Because there was no mortality difference in the new RCT, it would be interesting to know how adding it to the meta-analysis would alter the conclusion. Would it make that trend dissipate, particularly at later time points, or reinforce it?

Third, what is the biological basis of echinocandin superiority? One may be tempted to think it is superior microbiological killing of the cidal echinocandin versus static azoles, despite the recent debunking of the very concept of static versus cidal therapies [4]. Consistent with that debunking, in the current and all prior RCTs, there was no difference in rate of clearance of fungemia between any of the arms, so that cannot be the biological basis of clinical superiority. I worry about biological plausibility of a superiority conclusion given virtually identical rates of microbiological clearance, particularly in light of the fact that all RCTs to date have failed to conclude superiority on the most important objective endpoint, mortality.

Overall, I understand and potentially even agree with the belief that echinocandins may be superior. But I wonder if the fact that clinical cure does not differ at later time points, mortality does not differ, and clearance of fungemia does not differ might give pause to a mandate that echinocandins are superior in efficacy and must be used first-line for all patients. Perhaps a more nuanced