Guest Editorial

Challenges for *Plasmodium vivax* malaria elimination in the genomics era

Biology largely explains *Plasmodium vivax* resilience to malaria control and elimination strategies. First, low-density blood-stage *P. vivax* infections are common, especially in areas approaching elimination,[1] making laboratory diagnosis particularly difficult.[2] Second, parasites may persist in human hosts for several months as hypnozoites, the dormant liver stages that may eventually cause relapses.[3] Radical cure of vivax malaria thus requires the use of antimalarial drugs that target both blood and liver stages, but the only licensed antimalarial with hypnozoitocidal activity (namely, primaquine) can also cause severe hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a common inborn enzyme deficiency.[4] Compared with *P. falciparum*, *P. vivax* transmission is further facilitated by the early production of infective stages, mature gametocytes. In fact, most vivax malaria patients have gametocytemia detected by microscopy by the time they seek treatment[5] and virtually all *P. vivax* infections, either symptomatic or asymptomatic, comprise gametocyte-specific *pvs25* gene transcripts detectable with sensitive molecular techniques.[6] Finally, *P. vivax* populations are more genetically diverse than sympatric populations of *P. falciparum*[7] and natural infections often comprise several co-existing genetically distinct parasite clones.[8] Reactivation of genetically diverse hypnozoites increases the genetic complexity of blood-stage infections, with more frequent outcrossing during meiotic recombination and faster generation of new parasite strains.

A recent comparative analysis with two closely related species (*P. cynomolgi* and *P. knowlesi*) provided further insights into the patterns of genome-wide variation in *P. vivax*.[9] The authors found that diversity is unevenly distributed across five genomes of *P. vivax*, being increased in subtelomeric regions. The subtelomeric domains are thought to recombine more often than internal regions of chromosomes and harbor gene families coding for proteins involved in host-parasite interactions that may be under strong diversifying selection.[9] Moreover, they characterised almost 2800 genes that are unique to *P. vivax,* possibly as a result of recent duplication events within the *P. vivax* lineage; some of these new genes, however, may have been misannotated in previous analyses.[9] Interestingly, few genes display a significant evidence of positive selection (among them, genes coding for proteins putatively involved in the development of asexual blood stages and gametocytes), while a number of them appear to be under strong negative selection, consistent with a small to moderate effective population size throughout the history of this species.[9] Overall, the extensive genetic diversity of *P. vivax* can translate into parasite's greater adaptability to new challenges, such as better treatments and control measures.

The five review articles published in this special issue of *Pathogens and Global Health* nicely address some major biological obstacles for *P. vivax* control and elimination. J. Kevin Baird focuses on how the lack of practical and reliable point-of-care techniques for G6PD deficiency diagnosis hampers the use of currently available antirelapse drugs (primaquine and tafenoquine), while Campo and colleagues review contemporary strategies for developing new and safer antimalarials with improved activity against hypnozoites. Population genetics and genomics are the main topics of the remaining three articles. Gunawardena and Karunaweera describe a wide range of genetic tools that are currently available to explore malaria parasite biology, while Barry *et al.* and Daniels *et al.* provide illustrative examples of the use of population genetics and genomics, respectively, to monitor and guide current *P. vivax* elimination efforts worldwide.

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References

1 Barbosa S, Gozze AB, Lima NF, Batista CL, Bastos MS, Nicolete VC, Fontoura PS, Gonçalves RM, Viana SA, Menezes MJ, Scopel KK, Cavasini CE, Malafronte RS, Menezes MJ, Scopel KK, Cavasini CE, Malafronte RS, da Silva-Nunes M, Vinetz JM, Castro MC, Ferreira MU. Epidemiology of disappearing *Plasmodium vivax* malaria: a case study in rural Amazonia. PLoS Negl Trop Dis. 2014;8:e3109.
2 Cheng Q, Cunningham J, Gatton ML. Systematic review of sub-microscopic *P. vivax* infections: prevalence and determining factors. PLoS Negl Trop Dis. 2015;9:e3413.
3 White NJ, Imwong M. Relapse. Adv Parasitol. 2012;80:113–50.
4 Howes RE, Battle KE, Satyagraha AW, Baird JK, Hay SI. G6PD deficiency: global distribution, genetic variants and primaquine therapy. Adv Parasitol. 2013;81:133–201.

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5 Douglas NM, Simpson JA, Phyo AP, Siswantoro H, Hasugian AR, Kenangalem E, Poespoprodjo JR, Singhasivanon P, Anstey NM, White NJ, Tjitra E, Nosten F, Price RN. Gametocyte dynamics and the role of drugs in reducing the transmission potential of *Plasmodium vivax*. J Infect Dis. 2013;208:801–12.
6 Lima NF, Bastos MS, Ferreira MU. *Plasmodium vivax*: reverse transcriptase real-time PCR for gametocyte detection and quantitation in clinical samples. Exp Parasitol. 2012;132:348–54.
7 Neafsey DE, Galinsky K, Jiang RH, Young L, Sykes SM, Saif S, Gujja S, Goldberg JM, Young S, Zeng Q, Chapman SB, Dash AP, Anvikar AR, Sutton PL, Birren BW, Escalante AA, Barnwell JW, Carlton JM. The malaria parasite *Plasmodium vivax* exhibits greater genetic diversity than *Plasmodium falciparum*. Nat Genetics. 2012;44:1046–50.
8 Ferreira MU, Karunaweera ND, da Silva-Nunes M, da Silva NS, Wirth DF, Hartl DL. Population structure and transmission dynamics of *Plasmodium vivax* in rural Amazonia. J Infect Dis. 2007;195:1218–26.
9 Cornejo OE, Fisher D, Escalante AA. Genome-wide patterns of genetic polymorphism and signatures of selection in *Plasmodium vivax*. Genome Biol Evol. 2014;7:106–19.