

# Plasmodium interspecies fertilisation: rare or underexplored



The concomitant presence of the gametes of *Plasmodium falciparum* and *Plasmodium vivax* in the mosquito midgut during a mixed infection might create opportunities for genetic exchange through interspecies fertilisation. Any such events might be further favoured by various factors, including the current accelerated efforts to eliminate malaria; as *P falciparum* and *P vivax* are the main focus of malaria elimination campaigns, it is plausible that the human-driven pressure affecting parasite survival might promote interspecies fertilisation. However, whether such interactions, if they do take place, translate to viable hybrids or genetic introgression is unknown.

For interspecies sexual interactions between *P falciparum* and *P vivax* to occur in natural mixed infections, the gamete surface recognition proteins would need to allow such interactions. Viable hybrids from such events could be a threat to malaria elimination. Potential sexual interactions, with a hybrid as an independent evolutionary entity, could theoretically result in the diversification and persistence of novel parasite genotypes, leading to more complex infections that are difficult to diagnose and treat. Investigation of the complexities of interspecies sexual interactions would help to evaluate whether the current diagnostic and therapeutic approaches should be modified. Hybrids might escape diagnosis under existing protocols for parasite identification, which rely on the independent detection of *P falciparum* and *P vivax*.

Little is known about interspecies sexual interactions during mixed-species *Plasmodium* infections. For *P falciparum*–*P vivax* mixed infections, the absence of literature could be largely due to the preconceived assumption that *P falciparum* and *P vivax* gametes cannot combine because of the distant genetic relatedness of the two parasite species. The understanding of interspecies sexual interactions has been constrained by the dearth of studies reporting fertilisation, hybridisation, or introgression among *Plasmodium* species.

No particular threshold of genetic divergence exists beyond which introgression becomes impossible, as such thresholds are computational constructs that vary among organismal groups, depending on both the source of genetic material used to decipher the phylogenetic distance and the degree of divergence. We believe that phylogeny-based assumptions which deny the possibility of interspecies fertilisation between *P falciparum* and

*P vivax* are not necessarily valid, particularly because of the limited understanding of the pre-zygotic and post-zygotic barriers between these species. However, empirical evidence indicates that such barriers exist in *Plasmodium ovale* sensu lato taxa.<sup>1</sup>

Hybridisation is more common in nature than expected<sup>2,3</sup> and is well-documented for some non-plasmodial parasites.<sup>4</sup> Sexual interaction between two rodent-infecting species, *Plasmodium yoelii* and *Plasmodium berghei*, has been reported.<sup>5</sup> Furthermore, introgression has been described among *Laverania* species, specifically between the gorilla parasite ancestors of *Plasmodium adleri* and *Plasmodium praefalciparum*, chimpanzee parasites *Plasmodium gaboni* and *Plasmodium billcollinsi*, and ancestors of *Plasmodium reichenowi* and *P billcollinsi*.<sup>6–8</sup> Nevertheless, hybridisation, interspecies fertilisation, and introgression remain poorly understood for *Plasmodium*, and laboratory evidence for interspecies hybridisation among human malarial parasites is apparently non-existent.

Direct experimental proof would be first-hand indications of interspecies hybridisation between human plasmodial species. Finding any such evidence non-experimentally presents challenges, as hybridisation, if it occurs, is likely rare, making the presence of hybrids difficult to identify in population-level studies. In this context, the significance of published reports of abnormal erythrocytic parasite morphology is unclear. Moreover, the genetic make-up of hybrids might not be sufficiently predictable to allow the development of molecular tools for their reliable identification. Any hybrids in nature could represent the tip of an iceberg, with many interspecies fertilisation products possibly failing to survive due to insufficient biological fitness. Currently, few approaches exist to recognise plasmodial hybridisation, which limits the understanding of its potential effect on human populations.<sup>4</sup>

Intraspecies cross-fertilisation can occur between cloned lines of *P falciparum*,<sup>9</sup> indicating the theoretical potential for interspecies hybridisation. Research in this area would be facilitated if a robust in-vitro culture system is set up for *P vivax*, similar to that developed for the related species *Plasmodium cynomolgi*.<sup>10</sup> To explore the possibility of interspecies sexual interactions between *P falciparum* and *P vivax*, species-specific male and female gametocytes would have to be separated. However, sex-selective drugs and genetically modified parasite lines are available only

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for *P. falciparum*. Additional technical challenges and the scarcity of appropriate methodologies for studying interspecies fertilisation between *P. falciparum* and *P. vivax* limit the assessment of the likelihood and frequency of occurrence of such hybrids.

Here, we propose a schematic experimental model to test the concept of interspecies fertilisation between *P. falciparum* and *P. vivax* using genetically modified *P. falciparum* parasite lines and aphidicolin (appendix). We believe that this approach can facilitate the genomic characterisation of any resulting hybrids.

We declare no competing interests.

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See Online for appendix