Plasmodium simium

A Brazilian focus of anthropozoonotic vivax malaria?

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See Articles page e1038

Around 25 malaria parasite species have been described in non-human primates. By the 1970s, human beings were shown to be susceptible to experimental infection by eight of these, in addition to a naturally acquired infection reported with *Plasmodium knowlesi*, a parasite of southeast Asian macaques.[1] A large focus of zoonotic *P knowlesi* human infections (historically misdiagnosed as *Plasmodium malariae* by microscopy) was reported in Malaysia in 2004,[2] where it is now the predominant cause of malaria. Cases have subsequently been reported throughout southeast Asia where the natural monkey hosts are distributed.[3] This discovery was only made possible through molecular diagnosis.

The only two parasite species described in South American primates are *Plasmodium brasilianum* and *P simium*. *P brasilianum* is almost morphologically and genetically indistinguishable from *P malariae*, whereas *Plasmodium simium* is nearly indistinguishable from *Plasmodium vivax*. Moreover, human beings have been shown to be susceptible to *P brasilianum*, and most probably to *P simium* also.[4] *P brasilianum* is found throughout South America, whereas *P simium* appears restricted to the Atlantic Forest region in southeastern Brazil, with natural hosts including arboreal howler monkeys (*Alouatta* spp), woolly spider monkeys (*Brachyteles arachnoides*),[5] and capuchin monkeys (genera *Cebus* and *Sapajus*).[6] The *P simium* vector, *Anopheles* (*Kerteszia*) *cruzi*, which is also a known human malaria vector, is found almost exclusively in this area, with the ability to feed on both monkeys in the canopy and human beings at ground level.[4]

In *The Lancet Global Health,* Patrícia Brasil and colleagues[7] explore whether a relatively recent series of rigorously defined autochthonous cases of malaria from the Atlantic Forest coastal region of Brazil (Rio de Janiero state) arose from a zoonotic focus, given that routine microscopy and standard PCR assays are unable to differentiate between *P vivax* and *P simium,* and that malaria in this area was considered to have been eliminated by the late 1970s. Blood samples were taken from 28 human cases and three *Alouatta guariba clamitans* monkeys and were subjected to amplification of *Plasmodium* mitochondrial DNA fragments; all were found to contain the two single-nucleotide polymorphisms considered diagnostic for *P simium*. Three additional human parasite isolates had successful full-length mitochondrial DNA sequencing done, with identical alignment to a *P simium* reference monkey strain, and specificity verified against a large number of homologous *P vivax* reference sequences from around the world.

Some, if not most, of the autochthonous cases previously diagnosed as *P vivax* in the Atlantic Forest region are likely to have been *P simium* acquired via mosquitoes infected from monkeys, thereby making this part of Brazil the site of a second global focus of zoonotic malaria. *P simium* is thought to ancestrally derive from more than one recent *P vivax* host switch from human beings to monkeys.[8] It is plausible that the vacant ecological niche in this area increased the vulnerability of a further host switch for *P simium* back to humans. Contributing factors might include recent human land-use change and encroachment into previously undisturbed enzootic transmission cycles, with subsequent vector or monkey host behavioural adaptation. However, whether zoonotic *P simium* transmission is an emerging phenomenon or more consistent with long-standing occasional spillover events is not clear.

The problem facing Brazil, however, is potentially far more intractable than that posed by *P knowlesi* in southeast Asia, where human-to-human transmission has yet to be observed. Based on the limited molecular evidence, these infections are more likely to be *P vivax* behaving as a true anthropozoonosis, with minimal changes since being introduced to South America by the migration of European populations.[9] Classification of genetically similar *Plasmodium* species as separate entities is difficult when there is no host specificity. Human infections reported in 2015, denoted as *P brasilianum* in Venezuela, were found to be genetically identical to *P brasilianum* in monkeys hosts and *P malariae* in human beings, and were used to argue (on firmer molecular grounds) for a nomenclatorial revision of *P malariae*.[10] However, a genuine absence of host preference might require evidence of equally viable

onward human-to-human transmission, or human-to-monkey transmission. The epidemiological data presented by Brasil and colleagues[7] are most consistent with zoonotic-only transmission, including an absence of sequential case-clustering, and predominantly urban-residing older males with a history of recent travel to forest areas.

This important study raises a number of remaining questions. Firstly, it becomes imperative to obtain the full genome of *P simium* to confirm or reject synonymy with *P vivax*. An anthropozoonotic *P vivax* reservoir in Brazilian monkeys would pose a substantial threat to malaria elimination throughout the continent and possibly beyond, including potential onwards transmission from hypnozoite relapses. One priority should be to investigate the natural history and biology of these two parasites in their non-human primate hosts. Evaluation of the geographical distribution and prevalence of *P simium* in both monkey hosts and mosquito vectors will also assist in accurately defining the population at risk. The clinical features and pathogenesis of *P simium* also remain poorly defined.

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We declare no competing interests.

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