Chapter

Origin of Two Most Virulent Agents of Human Malaria: *Plasmodium falciparum* and *Plasmodium vivax*

Boundenga Larson

Abstract

Malaria is a protozoan disease caused by a parasite belonging to *Plasmodium* genus. Five species are known to infect humans: *Plasmodium falciparum, Plasmodium vivax, Plasmodium knowlesi, Plasmodium ovale*, *and Plasmodium malariae*. Among these species, *Plasmodium falciparum* and *Plasmodium vivax* account for more than 95% of all human malaria infections and thus pose a serious public health challenge. *Plasmodium falciparum* is highly prevalent in sub-Saharan Africa, while *Plasmodium vivax* is rare in sub-Saharan Africa but endemic in many parts of Asia. The recent studies using the development of molecular tools have shown that a large diversity of malaria parasites circulate among the nonhuman primates and certainly present a similarity with human parasites. For a long time, the question of the origin of its parasites that infect human population has been the subject of much debate. Today, it would seem that both most virulent agents of human malaria would come from African apes. Thus, this chapter tries to review available data about the origin of these two *Plasmodium* species.

Keywords: *Plasmodium*, nonhuman primate, human, Africa, origin, host switching

1. Introduction

Malaria is a serious infectious disease. It is caused by parasites of the genus *Plasmodium* and transmitted by *Anopheles* mosquitoes to its vertebrate hosts. This disease is an important global health problem, especially in sub-Saharan Africa [1] (**Figure 1**). Indeed, the African region continues to carry a disproportionately high share of the global malaria burden [1, 2]. Among five *Plasmodium* species which infect human, two species *Plasmodium falciparum* and *Plasmodium vivax* pose the greatest threat for human health. For example, *P. falciparum* is the most prevalent malaria parasite on the African continent. It is responsible for most malaria-related deaths globally [3], while *P. vivax* is rare in sub-Saharan Africa, but it is the major malaria parasite in most countries outside of sub-Saharan Africa [4].

The origin of parasites responsible of human malaria has always been at the center of the debate [5, 6]. Understanding the origin of its infectious agents could open a door in the improvement of strategies to fight against the malaria agents which constantly surprise us by their abilities to adapt to the different means of fight put in place. So then, the questions are as follows: *Where do the pathogens*

Figure 1.
Map of world malaria distribution.

responsible for this disease come from in humans? This chapter is a synthesis of the available data on the origin of two most virulent agents of human malaria: *P. falciparum* and *P. vivax*.

2. Nonhuman primate natural hosts of a large *Plasmodium* diversity

Today, the diversity of *Plasmodium* parasites infecting primates is well documented. First studies based in morphological analysis have reported three species which infect African apes (*Plasmodium reichenowi*, *Plasmodium schwetzi*, and *Plasmodium rodhaini*), and some of these were found to resemble human parasites *Plasmodium malariae*, *Plasmodium vivax*, and *Plasmodium ovale* [7]. The development of molecular tools allowed for a re-examination of *Plasmodium* diversity [8–10]. Data collected over the past years have shown that NHPs are infected with large diversity of *Plasmodium* belonging to two subgenera (*Laverania* and *Plasmodium*) [11] (**Figure 2**).

2.1 *Laverania* subgenus

Among species classified into *Laverania* group, four species infect chimpanzees (*P. gaboni*, *P. billcollinsi*, *P. billbrayi*, and *P. reichenowi*), only three infect gorillas (*P. adleri*, *P. blacklocki*, and *P. praefalciparum*), and only one infect bonobo (*P. lomamiensis*) [8, 9, 12]. Therefore, *P. billbrayi* [10] is not accepted as a new species by some authors [6, 13] who reported that these isolates did not seem to be sufficiently distinct from *P. gaboni* to warrant a separate species designation [6]. However, this species was described only in *Pan troglodytes schweinfurthii* and hence is the reason why we believe that could be another species [10] (**Figure 2**). Moreover, Mapua and colleagues reported recently several lineages of these parasites among African apes [14].

To date, all studies on natural populations of apes (based on the analysis of fecal samples) have shown that no *Plasmodium* species from the *Laverania* subgenus is able to infect *in natura* both hosts (gorillas and chimpanzees) [8, 13], thus suggesting the existence of a strong host specificity due to genetic barrier [6, 15]. However, a recent study revealed that this genetic barrier is not completely impermeable [16]; moreover, in this study, authors reported that the exchanges between gorillas

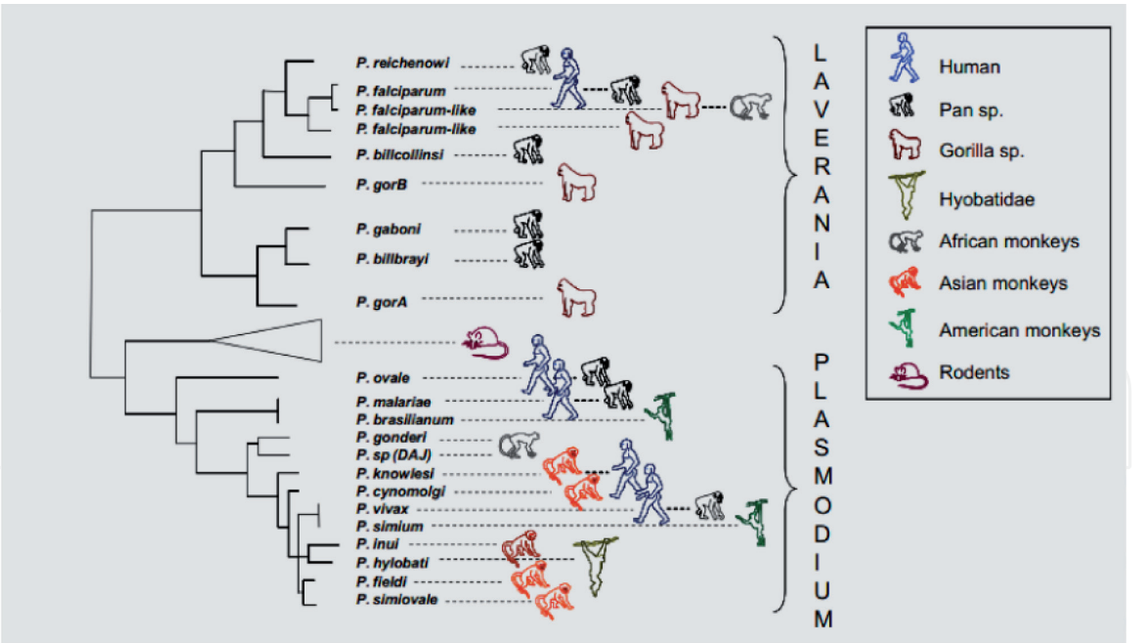
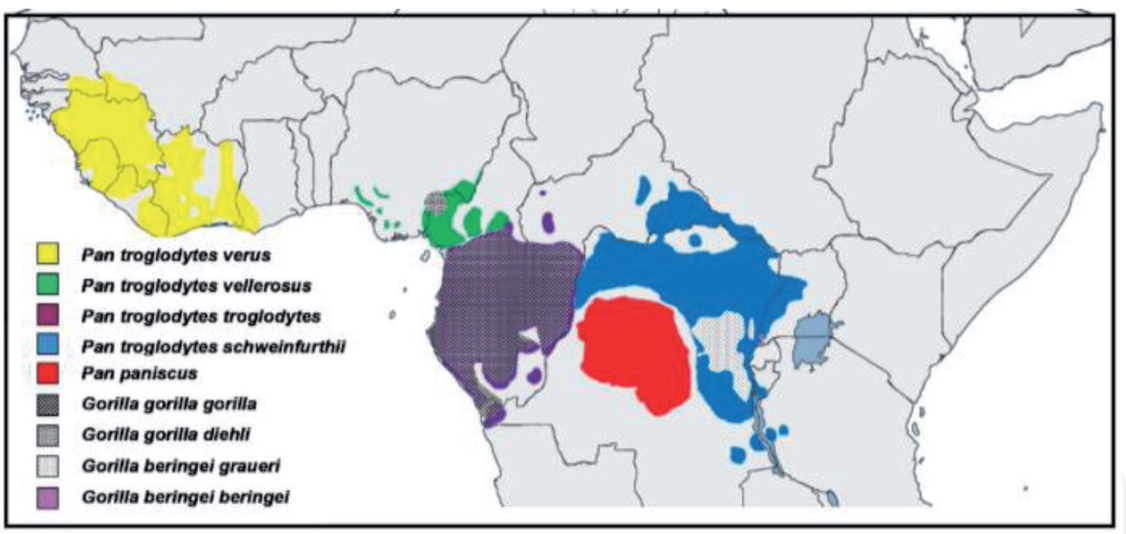


Figure 2.
The tree of relationship of primate Plasmodium with the currently known categories of hosts. Primate ***Plasmodium*** *is subdivided in two subgenera: Laverania and Plasmodium [11].*



Plasmodium sp. / lineage	Host found infected
Plasmodium billbrayi	
Plasmodium gaboni	
Plasmodium GorA	
Plasmodium GorB	
Plasmodium billcollinsi	
Plasmodium reichenowi	
Plasmodium falciparum	
Plasmodium lomamiensis	

Figure 3.
Distribution of the different subspecies of great apes in Africa and representation of the spread of the different Plasmodium species in these species [5].

and chimpanzees were possible in confined environments [16]. Second hypothesis was about the role played by potential vectors [17]. However, this hypothesis was refuted by a study which showed that vectors had no preference for hosts [18]. Thus, other ecological factors could play a potential role in host specificity. Furthermore the simians' species of this group seem to be geographically located in central Africa only (**Figure 3**).

2.2 *Plasmodium* subgenus

Conversely, subgenus *Plasmodium* (non-*Laverania*) includes several species infecting a large variety of primates of varied origins [Africa, Asia (*catarrhines*), South America (*platyrrhines*) and Human] [11]. Two major facts concerning this group were the emergence of *P. knowlesi* in human population [19, 20] and the characterization of *P. vivax*-like in chimpanzees and gorillas [21, 22] which completely changed our consideration of this malaria parasite subgenus [23, 24].

In Africa NHPs, five species of this subgenus circulate among monkeys and great apes, two for monkeys (*P. gonderi* and *P*. sp. DAJ-2004 [called now *Plasmodium mandrilli* [25]]) and three for great apes (*P. vivax*-like, *P. malariae*-like, and *P. ovale*-like) [13, 16]. In African great apes, both hosts (chimpanzee and gorilla) are infected with these parasites (*P. vivax*-like, *P. malariae*-like, and *P. ovale*-like) (**Figures 3** and **4**). Thus, these *Plasmodium* species are not specific hosts, and it would be very interesting to establish the mechanisms which favor host switching for these parasites. Several species were reported as implicate in circulation of malaria parasites in central Africa [17, 18]. In African apes three *Anopheles* species (*An. moucheti*, *An. vinckei*, and *An. marshallii*) are known to allow the circulation of malaria parasites in forest environment [18].

Apart from African apes, Asian monkeys are also infected by many other species of *Plasmodium* (*P. cynomolgi*, *P. hylobati*, *P. knowlesi*, *P. coatneyi*, *P. fragile, P. fieldi*,

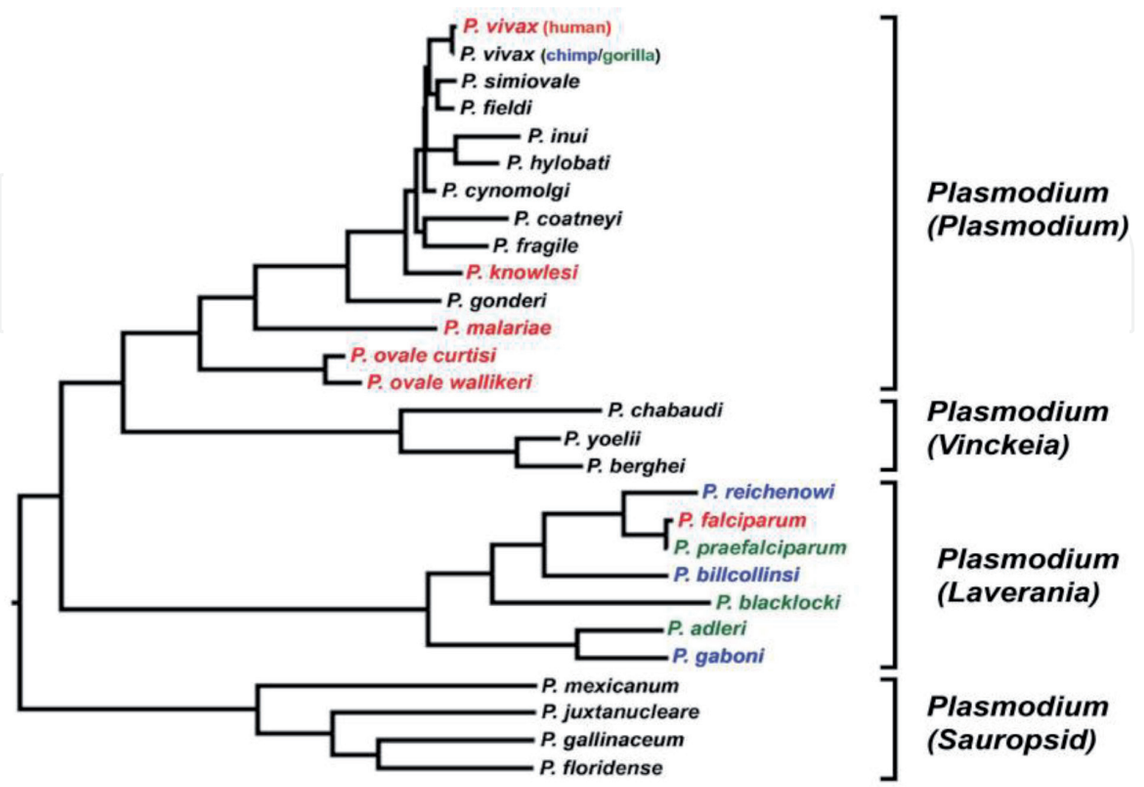


Figure 4.
Phylogenetic tree of some Plasmodium species found in apes.

P. simiovale, and *P inui Plasmodium* spp. [26]) (**Figures 3** and **4**). Several other species of *Plasmodium* were observed among Asian apes by microscopic analyses, but no molecular evidence of the existence of these lineages are available (e.g., *P. pithecia* and *P. sandoshami*). These malaria parasites could infect many apes' hosts. Several studies reported of the different NHP species with same parasites [27] or many parasites which were found in one species of NHP, for example, four species of simian malaria parasites were characterized in the pig-tailed macaques (*Macaca nemestrina*) [28, 29]. In this part of the world, the situation of *P. knowlesi* gives a good example of the risk that these parasites could present to humans. Recently, the probable existence of three divergent subpopulations of *P. knowlesi* with the different origins was reported [30].

Finally, in South America some *Plasmodium* species were described as infecting NHPs. The species found in Southern American primates are *Plasmodium brasilianum* and *Plasmodium simium*, and these parasite species naturally infect monkeys from the Cebidae and Atelidae families [31] (**Figure 3**). However, *P. brasilianum* infects 11 species of monkeys (*Alouatta spp*, *Ateles spp*, *Brachyteles arachnoides*, *Cacajao calvus*, *Callicebus spp*, *Cebus spp, Chiropotes satanas*, *Lagothrix spp*, *Saimiri spp*, *Saguinus midas*, and *Pithecia pithecia*), while *Plasmodium simium* infects only 2 species (*Alouatta spp* and *Brachyteles arachnoides*). In recent studies, *P. simium* was found for the first time in capuchin monkeys from the Brazilian Atlantic Forest [32]. *P. brasilium* and *P. simium* are similar and indistinguishable from human *P. malariae* and *P. vivax.* These similarities occur at the morphological, genetic, and immunological levels [31, 32].

3. Where do the malaria parasites that infect men come from?

The understanding of origin of human malaria parasites has been the subject of numerous studies that have been based on the morphology, biology, and affiliation of parasites to their hosts [33]. However, recent development of molecular tools in diagnosis has made considerable progress in understanding the evolutionary history of malaria parasites. Indeed, the contribution of several new sequences by this new approach will clarify the debate on many theories developed on the subject [34]. Moreover, several of these parasites have been found to be associated with humans by lateral transfer from other vertebrate host species [35, 36]. We will present the probable origin of two most virulent *Plasmodium* species that infect human.

3.1 *Plasmodium falciparum*

The debate on the origin of *P. falciparum* most spread in world (**Figure 5**) was opened with the study of Waters and his collaborators who proposed an avian origin of this parasite that is to say that the man would have recently acquired this parasite of a transfer from birds to humans [37]. Indeed, phylogenetic analyses based on the study of ribosomal RNA subunit (rRNA) sequences showed that *P. falciparum* formed a monophyletic group with *Plasmodium* spp. of birds (see **Figure 6**), hence the conclusion of the authors.

Three years after the first hypothesis on the origin of *P. falciparum*, Escalante and Ayala [38], in their study also based on 18S RNA, take into account for the first time *P. reichenowi*, an isolated parasite in a chimpanzee African (**Figure 7**). They will show that this parasite is the closest parent of *P. falciparum*; therefore, this observation allowed authors to conclude that *Plasmodium falciparum* origin was not a recent lateral transfer of this parasite of birds to humans [38, 39]. In this study, *P. falciparum* and *P. reichenowi* form a large group with primate parasites of the subgenus *Plasmodium* (*non-Laverania*), rodents, and birds [38, 40, 41] (**Figure 7**). This will further fuel the debate on the origin of *P. falciparum*.

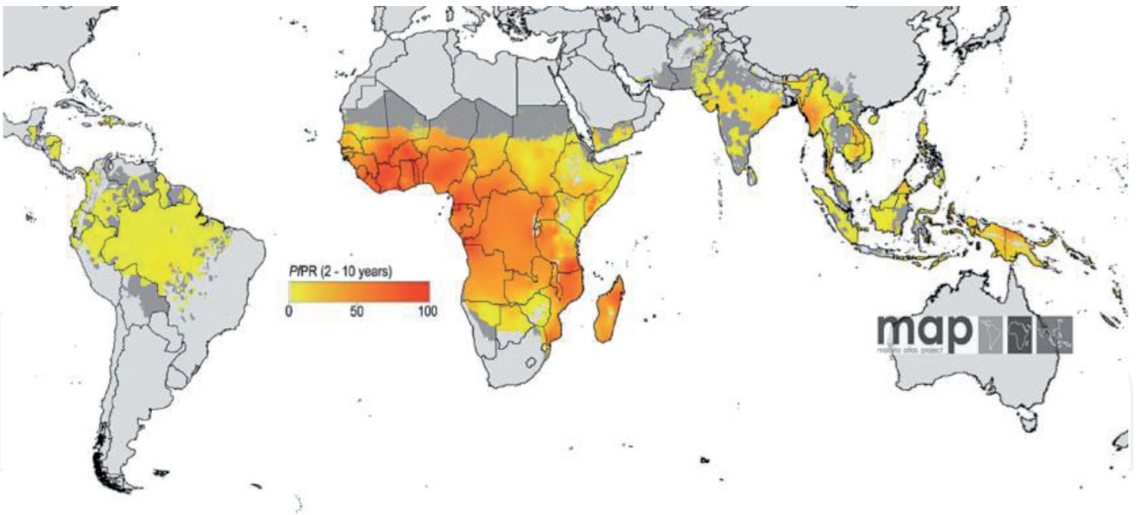


Figure 5.
Distribution of Plasmodium falciparum in the world [42].

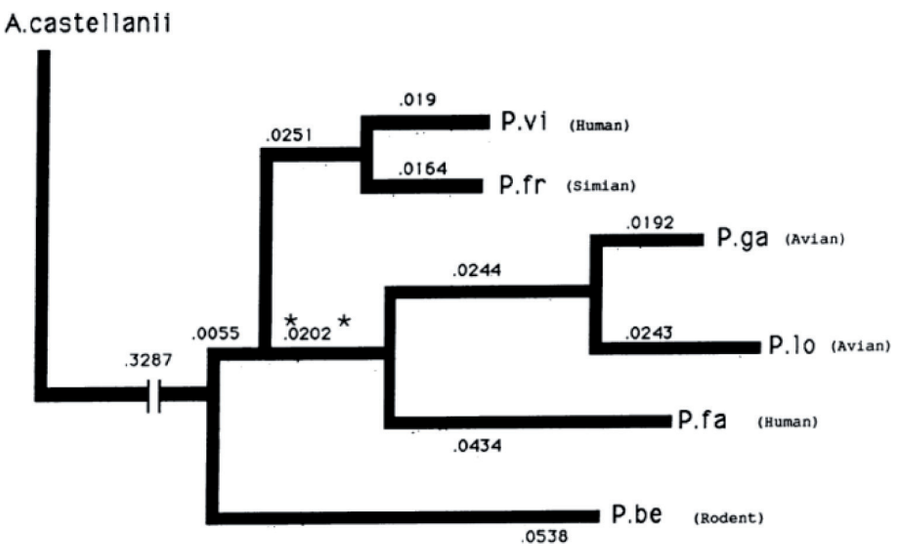


Figure 6.
Phylogenetic tree of malaria parasites obtained by Waters and colleagues [37].

The disputes surround the probable origin of *P. falciparum*, whether it comes from birds or rodents, will be raging. Authors as Prugnolle et al. believe that the problems or weaknesses of many studies were based essentially on two aspects [5]: firstly the low number of plasmodial species and sequences integrated in these analyses and secondly the limited number of molecular markers used for the development of phylogenies. Despite all this controversy, *P. falciparum* will be considered to have an African origin [43–45].

The year 2009 will completely change our understanding of the evolutionary history of *P. falciparum*, because prior to this year, only one species (*P. reichenowi*) was known to be closer to *P. falciparum*. After the discovery of *Plasmodium gaboni* parasite that infects chimpanzees [46], several other sequences from African great apes will definitively bring elements of answers to question on the origin of this parasite.

Indeed, in 2010, Prugnolle and colleagues will highlight for the first time *P. falciparum*-like in gorillas and several other lineages. These studies will prove that the *Laverania* group that includes *P. falciparum* has a great diversity of species that circulate in African primates [9]. This will make it possible to show that the origin

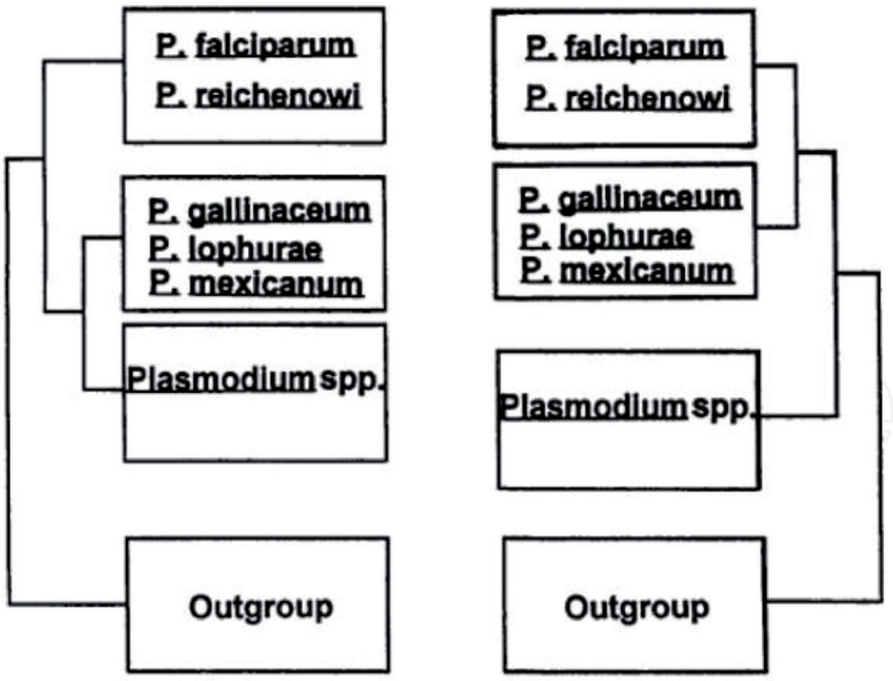


Figure 7.
Two ML phylogenetic trees obtained by grouping 11 Plasmodium species as indicated (the six unlisted species are grouped as Plasmodium spp.) [38].

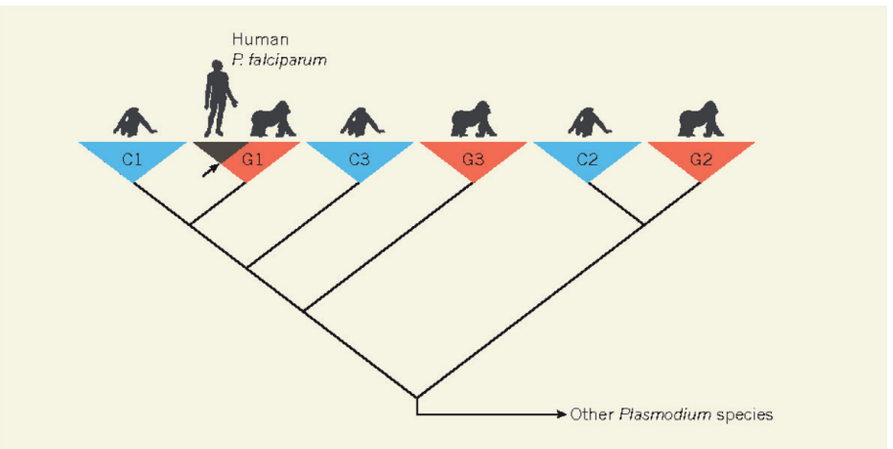


Figure 8.
Origin of human Plasmodium falciparum. This phylogenetic tree illustrates the remarkable diversity of Plasmodium parasites infecting African apes (Holmes 2010).

of *P. falciparum* is not found in birds or rodents but in the gorillas that have recently transmitted it to humans via anophobic zoo-anthropophilic mosquito [17, 18]. *P. falciparum*-like of gorillas will be named *P. praefalciparum* to distinguish it from that which infects humans [11, 13].

In 2011, the hypothesis of a gorilla origin of *P. falciparum* seems to be weakened by the discovery of *P. praefalciparum* in a small African monkey (*Cercopithecus nictitans*) [47]. This study also will reveal the existence of at least two types of *P. praefalciparum*: 1 and 2. *P. praefalciparum*-1 infects gorillas and monkeys (*C. nictitans*), and *P. praefalciparum*-2 infects only gorillas [11]. Other studies will focus on African monkeys, but will not find *P. praefalciparum* [48]. Thus, we believe that the hypothesis of *Plasmodium falciparum* from monkeys is not solid and that *C. nictitans* species is not a natural reservoir for this parasite [48].

Today, after numerous studies that analyzed more than 5000 samples of wild and captives apes [8–10, 12, 13, 16, 21, 22, 47] (**Figure 8**), it appears that gorillas are

the reservoir for the *P. praefalciparum*, even though several hypotheses concerning the origin of *P. falciparum* have been proposed for primates [10, 47].

The hypothesis according to which *Plasmodium falciparum* would come from gorillas seems to be the most plausible at the moment. Indeed, several *P. praefalciparum* sequences had been found from numerous wild-living gorillas in different areas [8, 13]. Loy and colleagues suggested that this parasite strain that was able to cross the host species barrier by carried one or more highly unusual mutations that conferred him an ability to colonize humans [49]. This theory comes to the fact that recent studies in human populations living close to the wild apes did not reveal the presence of parasites of great apes belonging to *Laverania* subgenus in humans [50, 51]. Thus, then it would seem that *P. falciparum* comes from African gorillas according to available data at the moment.

3.2 Origin of *Plasmodium vivax*

Plasmodium vivax is particularly prevalent in Asia, Southeast Asia, South America, and the Western Pacific region [52] (**Figure 9**). Already the first studies on malaria of the great apes had revealed the presence of parasites resembling *P. vivax* [53, 54]. Despite its first observations, the question on the origin of *P. vivax* remained uncertain for several years. Concerning this interesting question of the *P. vivax* origin, several hypotheses have been proposed in recent years.

The first hypotheses about the origin of *P. vivax* had suggested that it originated in Southeast Asia [24, 49]. These hypotheses were based on the fact that *P. vivax* shares morphological and biological traits with several macaque parasites and that *Plasmodium* simian's species are abundant in this Asian region [36]. This hypothesis was supported by the phylogenetic analyses that placed *P. vivax* among the *Plasmodium* spp. of Asian monkeys with like closest parent, *Plasmodium cynomolgi*, which infects macaques in Asia [40, 55]. The consensus view has thus been that *P. vivax* emerged in southeastern Asia following the cross-species transmission of a macaque parasite [23, 56, 57].

In addition to the first hypothesis, another hypothesis will articulate around of the negative Duffy receptor and would suggest African origin of *P. vivax* [58, 59]. Indeed, the presence of negative Duffy blood group in central and West African populations was correlated with the absence of *P. vivax*. This character would confer resistance to *P. vivax* infection, which suggested that this mutation arose in response to prolonged selection pressure from *P. vivax* [60]. Currently, Duffy antigen is the

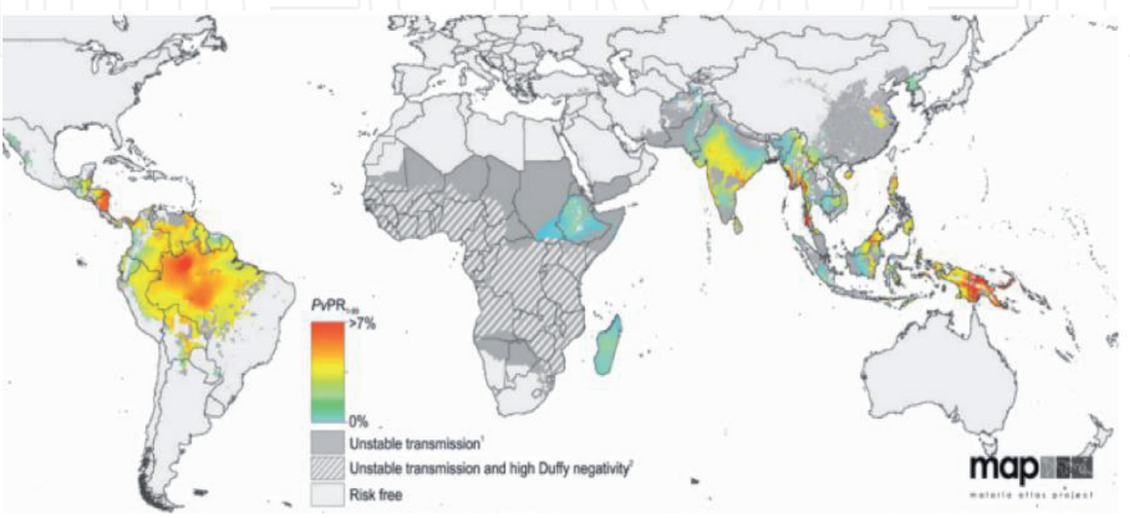


Figure 9.
The spatial distribution of Plasmodium vivax in the world [52].

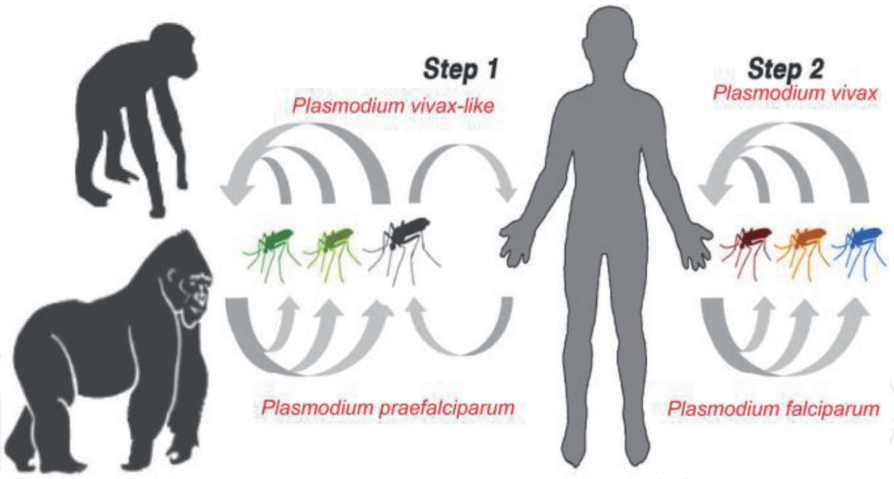


Figure 10.
The diagram presents a possible two-step scenario for the transfer and establishment of ape malarias in humans. Sylvatic anopheline vectors were transmitting malaria between apes; in the first step, one (or more) bridge vector(s) would also transfer infective Plasmodium parasites to humans. In a second step, human-adapted Plasmodium parasites adapted to domesticated mosquito vector species that share the same ecological niche with humans [63].

only receptor known to be used by parasite to invade the red blood cell. Thus, it has been proposed that *P. vivax* co-evolved with African populations for longer than with other human populations [24, 61].

However, the recent studies using the development of molecular tools allow to have a clear view on the origin of this parasite. These studies have shown that chimpanzees and gorillas from central and West Africa harbor a large diversity of *P. vivax*-like parasites [10, 21, 22, 62]. This discovery accentuates the African origin of *Plasmodium vivax* and reveals that African great apes are potential sylvatic reservoir of *P. vivax* [21, 22]. However, elucidation of the origin of *P. vivax* in African apes needed complementary studies of wild-living populations across central Africa [22].

Also, Prugnolle et al. have shown that *P. vivax*-like found among African great apes form a distinct and much more diverse genetic group than that of human parasites [21]. In this study authors revealed also an older origin of the African simian lineages and the fact that these lineages are able to infect the Caucasian population today [21] (**Figure 10**). Thus, the discovery of *P. vivax* in large numbers of chimpanzees and gorillas provides compelling evidence for an African, rather than an Asian, origin of human *P. vivax*.

Today, an interesting question would be to understand how this passage of apes to man had been done. To this question, in view of current data and analyses, we agree to say, instead, it is much more likely that extant human *P. vivax* could represent a lineage that survived after spreading out of Africa [21, 64, 65], because this theory could explain the fact that we observed today a reduced diversity of the human parasites which would result from an out-of-Africa bottleneck, such as observed in *P. falciparum* [45, 66].

4. Malaria like a zoonotic disease: the running toward new environments is a wont for *Plasmodium*

It is true that many *Plasmodium* parasites circulating in African NHPs could produce symptoms of this disease in apes [67]. However, no *Plasmodium* species particularly parasites belonging to *Laverania* subgenus has been found to infect human to date. Studies conducted in rural population in central Africa (Cameroon and Gabon) have shown that *Laverania* parasites were absent of human populations living in villages that are in very close proximity to wild forest [50, 51] and even

those working in very close contact with NHPs [16]. On the other hand, several studies reported that *P. falciparum* is able to infect African apes, for example, Bonobos, chimpanzees [10, 26], and recently the mandrills [16]. The question is *why these transfers are rare or why the ancestral parent of P. falciparum (P. praefalciparum) appear incapable of infecting humans today*. Loy et al. suggest that gorilla parasite strain that was able to cross the host species barrier must have carried one or more highly unusual mutations that enable it to colonize humans [49]. But, supplementary studies would be necessary to support this hypothesis.

In contrast, many parasites of *Plasmodium* subgenus were reported to infect humans. The major case known is *P. knowlesi* that infects NHPs in south Asia and now is considered as the fifth *Plasmodium* species that infects human and cause malaria in southern Asian population [19]. Other cases of natural or accidental infections of humans with simians *Plasmodium* were reported in literature. Indeed, a total of seven species of monkey malaria have been reported via mosquitoes (*P. cynomolgi*, *P. brasilianum*, *P. eylesi*, *P. knowlesi*, *P. inui*, *P. schwetzi*, and *P. simium*) [11, 68, 69]. Recently, ape *P. vivax* has been found to cause clinical malaria in Caucasians who stayed during some days in African forest [21]. Thus, parasites of *Plasmodium* subgenus are apparently able to cross the species barrier to humans. So the emergence of these parasites should be monitored in areas where an influx of contact between humans and NHPs increases with anthropization, which destroys ape habitat and favors contact. In view of the rare faction of monkeys and the increase of the human population, it is feared that human infection of simians *Plasmodium* will become more frequent which could lead to humans becoming simians' major host [70].

5. Prevention

The potential for zoonosis is influenced by human habitation and behavior as well as the adaptive capabilities of parasites and vectors. Indeed, the existence of potential sylvatic reservoirs of *P. vivax* and *P. falciparum* in Africa could compromise malaria control and eradication efforts. Actually, there is lack of knowledge about the real extent of malaria zoonosis. Thus, this aspect of zoonosis malaria parasites must be taken into account by the public health authorities responsible for the fight against malaria. African structures health need to put appropriate strategies of prevention against zoonotic malaria parasites that could be developed. However, they must be based on good data of research on diagnosis and treatment of zoonotic malaria. Moreover, all people living in the locality or monkeys are known to grass a large variety of malaria parasite, which must take their precaution when they venture into forest environment, in order to avoid mosquito bites.

6. Conclusion

The development of the tools of molecular biology allowed us to see clearer in the history of parasite that infects the man, especially *Plasmodium* species. Indeed, these tools allowed us to highlight large diversity of the malaria parasites that circulate to the nonhuman primates, so to understand better the origin of the most virulent parasite responsible for human malaria (*Plasmodium falciparum* and *Plasmodium vivax*). Therefore, on the basis of available data, it is more than likely that its parasites have an African origin and that African gorillas and chimpanzees would constitute potential reservoirs of its parasites. Thus, in this context, it is important to determine or develop appropriate preventive strategies. It is necessary to set up monitoring systems in forest areas and to make sensitization campaigns.

Annex for reader

Diversity: the condition of having or being composed of differing elements (variety). It can also include of different species or genetic lineages.

Gorilla sp.: designs all species belonging to *Gorilla* genus. This genus has three subspecies of *gorilla* (*Gorilla gorilla gorilla; Gorilla gorilla graueri* and *Gorilla gorilla beringei*).

Laverania*:* is a subgenus of the *Plasmodium* genus of parasites. The parasites belonging to this subgenus have a strong host specificity.

Outgroup: outgroup is a more distantly related group of organisms that serves as a reference group when determining the evolutionary relationships of the ingroup, and it is used as a point of comparison for the ingroup and specifically allows for the phylogeny to be rooted.

Phylogenetic tree: a phylogenetic tree is a diagram that represents evolutionary relationships among organisms.

Plasmodium GorA (Prugnolle et al. 2010): *Plasmodium adleri*.

Plasmodium gorB (Prugnolle et al. 2010): *Plasmodium blacklocki*.

Plasmodium (non-*Laverania*): non-Laverania subgenus includes many parasites such as *P. malariae*, *P. vivax*, *P. ovale-curtisi*, and *P. ovale-wallikeri* as well as the monkey parasites *P. inui* and *P. hylobati*.

Pan sp.: *Pan* sp. designs all species belonging to *Pan* genus (the common name of member of this genus chimpanzees and bonobo).

RNA subunit (rRNA): ribosomal ribonucleic acid (rRNA) is the RNA component of the ribosome and is an essential element for protein synthesis in all living organisms.

Author details

Boundenga Larson
Centre International de Recherches Médicales de Franceville (CIRMF), Franceville, Gabon

*Address all correspondence to: boundenga@gmail.com

References

[1] WHO. Malaria Rapid Diagnostic Test Performance: Summary Results of WHO Product Testing of Malaria RDTs: Round 1-8 (2008-2018). 2018

[2] WHO. Malaria Rapid Diagnostic Test Performance: Results of WHO Product Testing of Malaria RDTs: Round 7 (2016-2017). 2017

[3] Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. Nature. 2015;**526**:207-211

[4] WHO. World Malaria Report 2014. World Health Organization; 2015

[5] Prugnolle F, Durand P, Ollomo B, Duval L, Ariey F, Arnathau C, et al. A fresh look at the origin of *Plasmodium falciparum*, the most malignant malaria agent. PLoS Pathogens. 2011;**7**:e1001283

[6] Rayner JC, Liu W, Peeters M, Sharp PM, Hahn BH. A plethora of *Plasmodium* species in wild apes: A source of human infection? Trends in Parasitology. 2011;**27**:222-229

[7] Snounou G, Escalante A, Kasenene J, Rénia L, Grüner AC, Krief S. Le paludisme chez les hominides. Bulletin de l'Académie Nationale de Médecine. 2011;**195**:1945-1954

[8] Boundenga L, Ollomo B, Rougeron V, Mouele LY, Mve-Ondo B, Delicat-Loembet LM, et al. Diversity of malaria parasites in great apes in Gabon. Malaria Journal. 2015;**14**:111

[9] Prugnolle F, Durand P, Neel C, Ollomo B, Ayala FJ, Arnathau C, et al. African great apes are natural hosts of multiple related malaria species, including *Plasmodium falciparum*. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**:1458-1463

[10] Krief S, Escalante AA, Pacheco MA, Mugisha L, Andre C, Halbwax M, et al. On the diversity of malaria parasites in African apes and the origin of *Plasmodium falciparum* from bonobos. PLoS Pathogens. 2010;**6**:e1000765

[11] Gonzalez JP, Prugnolle F, Leroy E. Men, primates, and germs: An ongoing affair. Current Topics in Microbiology and Immunology. 2013;**365**:337-353

[12] Liu W, Sherrill-Mix S, Learn GH, Scully EJ, Li Y, Avitto AN, et al. Wild bonobos host geographically restricted malaria parasites including a putative new Laverania species. Nature Communications. 2017;**8**:1635

[13] Liu W, Li Y, Learn GH, Rudicell RS, Robertson JD, Keele BF, et al. Origin of the human malaria parasite *Plasmodium falciparum* in gorillas. Nature. 2010;**467**:420-425

[14] Mapua MI, Petrzelkova KJ, Burgunder J, Dadakova E, Brozova K, Hrazdilova K, et al. A comparative molecular survey of malaria prevalence among eastern chimpanzee populations in Issa Valley (Tanzania) and Kalinzu (Uganda). Malaria Journal. 2016;**15**:423

[15] Forni D, Pontremoli C, Cagliani R, Pozzoli U, Clerici M, Sironi M. Positive selection underlies the species-specific binding of *Plasmodium falciparum* RH5 to human basigin. Molecular Ecology. 2015;**24**:4711-4722

[16] Ngoubangoye B, Boundenga L, Arnathau C, Mombo IM, Durand P, Tsoumbou TA, et al. The host specificity of ape malaria parasites can be broken in confined environments. International Journal for Parasitology. 2016;**46**:737-744

[17] Paupy C, Makanga B, Ollomo B, Rahola N, Durand P, Magnus J, et al. Anopheles moucheti and Anopheles vinckei are candidate vectors of ape *Plasmodium* parasites, including *Plasmodium praefalciparum* in Gabon. PLoS One. 2013;**8**:e57294

[18] Makanga B, Yangari P, Rahola N, Rougeron V, Elguero E, Boundenga L, et al. Ape malaria transmission and potential for ape-to-human transfers in Africa. Proceedings of the National Academy of Sciences of the United States of America. 2016;**113**:5329-5334

[19] Cox-Singh J, Singh B. Knowlesi malaria: Newly emergent and of public health importance? Trends in Parasitology. 2008;**24**:406-410

[20] White NJ. *Plasmodium knowlesi*: The fifth human malaria parasite. Clinical Infectious Diseases. 2008;**46**:172-173

[21] Prugnolle F, Rougeron V, Becquart P, Berry A, Makanga B, Rahola N, et al. Diversity, host switching and evolution of *Plasmodium vivax* infecting African great apes. Proceedings of the National Academy of Sciences of the United States of America. 2013;**110**:8123-8128

[22] Liu W, Li Y, Shaw KS, Learn GH, Plenderleith LJ, Malenke JA, et al. African origin of the malaria parasite *Plasmodium vivax*. Nature Communications. 2014;**5**:3346

[23] Mu J, Joy DA, Duan J, Huang Y, Carlton J, Walker J, et al. Host switch leads to emergence of *Plasmodium vivax* malaria in humans. Molecular Biology and Evolution. 2005;**22**:1686-1693

[24] Cornejo OE, Escalante AA. The origin and age of *Plasmodium vivax*. Trends in Parasitology. 2006;**22**:558-563

[25] Boundenga L, Ngoubangoye B, Mombo IM, Tsoubmou TA, Renaud F, Rougeron V, et al. Extensive diversity of malaria parasites circulating in central African bats and monkeys. Ecology and Evolution. 2018;**8**:10578-10586

[26] Pacheco MA, Cranfield M, Cameron K, Escalante AA. Malarial parasite diversity in chimpanzees: The value of comparative approaches to ascertain the evolution of *Plasmodium falciparum* antigens. Malaria Journal. 2013;**12**:328

[27] Divis PC, Singh B, Anderios F, Hisam S, Matusop A, Kocken CH, et al. Admixture in humans of two divergent *Plasmodium knowlesi* populations associated with different macaque host species. PLoS Pathogens. 2015;**11**:e1004888

[28] Eyles DE, Fong YL, Warren M, Guinn E, Sandosham A, Wharton R. *Plasmodium coatneyi*, a new species of primate malaria from Malaya. The American Journal of Tropical Medicine and Hygiene. 1962;**11**:597-604

[29] Vythilingam I, Hii J. Simian malaria parasites: Special emphasis on *Plasmodium knowlesi* and their Anopheles vectors in Southeast Asia. In: Anopheles Mosquitoes-New Insights into Malaria Vectors. Rijeka: InTech; 2013

[30] Divis PC, Lin LC, Rovie-Ryan JJ, Kadir KA, Anderios F, Hisam S, et al. Three divergent subpopulations of the malaria parasite *Plasmodium knowlesi*. Emerging Infectious Diseases. 2017;**23**:616-624

[31] de Castro Duarte AMR, dos Santos Malafronte R, Cerutti C Jr, Curado I, de Paiva BR, Maeda AY, et al. Natural Plasmodium infections in Brazilian wild monkeys: Reservoirs for human infections? Acta Tropica. 2008;**107**:179-185

[32] de Alvarenga DA, de Pina-Costa A, de Sousa TN, Pissinatti A, Zalis MG, Suarez-Mutis MC, et al. Simian malaria in the Brazilian Atlantic forest: First description of natural infection of

capuchin monkeys (Cebinae subfamily) by *Plasmodium simium*. Malaria Journal. 2015;**14**:81

[33] Cserti CM, Dzik WH. The ABO blood group system and *Plasmodium falciparum* malaria. Blood. 2007;**110**:2250-2258

[34] Das A, Bajaj R, Mohanty S, Swain V. Genetic diversity and evolutionary history of *Plasmodium falciparum* and *P. vivax*. Current Science. 2007:1516-1524

[35] Garnham P. Immunity against the different stages of malaria parasites. Bulletin de la Societe de pathologie exotique et de ses filiales. 1966;**59**:549-557

[36] Garnham PCC. Malaria Parasites and Other Haemosporidia. Oxford, England: Blackwell; Philadelphia: Davis; 1966. 1132 pp

[37] Waters A, Higgins D, McCutchan T. *Plasmodium falciparum* appears to have arisen as a result of lateral transfer between avian and human hosts. Proceedings of the National Academy of Sciences. 1991;**88**:3140-3144

[38] Escalante AA, Ayala FJ. Phylogeny of the malarial genus *Plasmodium*, derived from rRNA gene sequences. Proceedings of the National Academy of Sciences. 1994;**91**:11373-11377

[39] Escalante AA, Ayala FJ. Evolutionary origin of *Plasmodium* and other Apicomplexa based on rRNA genes. Proceedings of the National Academy of Sciences. 1995;**92**:5793-5797

[40] Perkins SL, Schall J. A molecular phylogeny of malarial parasites recovered from cytochrome b gene sequences. Journal of Parasitology. 2002;**88**:972-978

[41] Escalante AA, Lal AA, Ayala FJ. Genetic polymorphism and natural selection in the malaria parasite *Plasmodium falciparum*. Genetics. 1998;**149**:189-202

[42] Hay SI, Guerra CA, Gething PW, Patil AP, Tatem AJ, Noor AM, et al. A World Malaria Map: Plasmodium falciparum Endemicity in 2007. https://doi.org/10.1371/journal.pmed.1000048

[43] Pearce-Duvet JM. The origin of human pathogens: Evaluating the role of agriculture and domestic animals in the evolution of human disease. Biological Reviews of the Cambridge Philosophical Society. 2006;**81**:369-382

[44] Joy DA, Feng X, Mu J, Furuya T, Chotivanich K, Krettli AU, et al. Early origin and recent expansion of *Plasmodium falciparum*. Science. 2003;**300**:318-321

[45] Conway DJ, Fanello C, Lloyd JM, Al-Joubori BM, Baloch AH, Somanath SD, et al. Origin of *Plasmodium falciparum* malaria is traced by mitochondrial DNA. Molecular and Biochemical Parasitology. 2000;**111**:163-171

[46] Ollomo B, Durand P, Prugnolle F, Douzery E, Arnathau C, Nkoghe D, et al. A new malaria agent in African hominids. PLoS Pathogens. 2009;**5**:e1000446

[47] Prugnolle F, Ollomo B, Durand P, Yalcindag E, Arnathau C, Elguero E, et al. African monkeys are infected by *Plasmodium falciparum* nonhuman primate-specific strains. Proceedings of the National Academy of Sciences of the United States of America. 2011;**108**:11948-11953

[48] Ayouba A, Mouacha F, Learn GH, Mpoudi-Ngole E, Rayner JC, Sharp PM, et al. Ubiquitous Hepatocystis infections, but no evidence of *Plasmodium falciparum*-like malaria parasites in wild greater spot-nosed monkeys (*Cercopithecus nictitans*). International Journal for Parasitology. 2012;**42**:709-713

[49] Loy DE, Liu W, Li Y, Learn GH, Plenderleith LJ, Sundararaman SA, et al. Out of Africa: Origins and evolution of the human malaria parasites *Plasmodium falciparum* and *Plasmodium vivax*. International Journal for Parasitology. 2017;**47**:87-97

[50] Delicat-Loembet L, Rougeron V, Ollomo B, Arnathau C, Roche B, Elguero E, et al. No evidence for ape *Plasmodium* infections in humans in Gabon. PLoS One. 2015;**10**:e0126933

[51] Sundararaman SA, Liu W, Keele BF, Learn GH, Bittinger K, Mouacha F, et al. *Plasmodium falciparum*-like parasites infecting wild apes in southern Cameroon do not represent a recurrent source of human malaria. Proceedings of the National Academy of Sciences of the United States of America. 2013;**110**:7020-7025

[52] Allgower A, Taylor WR, Chappuis F, Eperon G. *Plasmodium vivax*, un parasite qui sort de l'ombre: *Plasmodium vivax*, a parasite coming out of the shadows. Revue Médicale Suisse. 2016;**12**:876-881

[53] Duval L, Fourment M, Nerrienet E, Rousset D, Sadeuh SA, Goodman SM, et al. African apes as reservoirs of *Plasmodium falciparum* and the origin and diversification of the *Laverania subgenus*. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**:10561-10566

[54] Duval L, Nerrienet E, Rousset D, Sadeuh Mba SA, Houze S, Fourment M, et al. Chimpanzee malaria parasites related to *Plasmodium ovale* in Africa. PLoS One. 2009;**4**:e5520

[55] Tachibana S-I, Sullivan SA, Kawai S, Nakamura S, Kim HR, Goto N, et al. *Plasmodium cynomolgi* genome sequences provide insight into *Plasmodium vivax* and the monkey malaria clade. Nature Genetics. 2012;**44**:1051

[56] Escalante AA, Cornejo OE, Freeland DE, Poe AC, Durrego E, Collins WE, et al. A monkey's tale: The origin of *Plasmodium vivax* as a human malaria parasite. Proceedings of the National Academy of Sciences. 2005;**102**:1980-1985

[57] Neafsey DE, Galinsky K, Jiang RH, Young L, Sykes SM, Saif S, et al. The malaria parasite *Plasmodium vivax* exhibits greater genetic diversity than *Plasmodium falciparum*. Nature Genetics. 2012;**44**:1046

[58] Culleton R, Carter R. African *Plasmodium vivax*: Distribution and origins. International Journal for Parasitology. 2012;**42**:1091-1097

[59] Livingstone FB. The Duffy blood groups, vivax malaria, and malaria selection in human populations: A review. Human Biology;**1984**:413-425

[60] Miller LH, Mason SJ, Clyde DF, McGinniss MH. The resistance factor to *Plasmodium vivax* in blacks: The Duffy-blood-group genotype, FyFy. New England Journal of Medicine. 1976;**295**:302-304

[61] Carter R, Mendis KN. Evolutionary and historical aspects of the burden of malaria. Clinical Microbiology Reviews. 2002;**15**:564-594

[62] Kaiser M, Lowa A, Ulrich M, Ellerbrok H, Goffe AS, Blasse A, et al. Wild chimpanzees infected with 5 *Plasmodium* species. Emerging Infectious Diseases. 2010;**16**:1956-1959

[63] Molina-Cruz A, Barillas-Mury C. Mosquito vectors of ape malarias: Another piece of the puzzle. Proceedings of the National Academy of Sciences of the United States of America. 2016;**113**:5153-5154

[64] Gilabert A, Otto TD, Rutledge GG, Franzon B, Ollomo B, Arnathau C, et al. *Plasmodium vivax*-like

genome sequences shed new insights into *Plasmodium vivax* biology and evolution. PLoS Biology. 2018;**16**:e2006035

[65] Loy DE, Plenderleith LJ, Sundararaman SA, Liu W, Gruszczyk J, Chen YJ, et al. Evolutionary history of human *Plasmodium vivax* revealed by genome-wide analyses of related ape parasites. Proceedings of the National Academy of Sciences of the United States of America. 2018;**115**:E8450-e8459

[66] Tanabe K, Mita T, Jombart T, Eriksson A, Horibe S, Palacpac N, et al. *Plasmodium falciparum* accompanied the human expansion out of Africa. Current Biology. 2010;**20**:1283-1289

[67] Herbert A, Boundenga L, Meyer A, Moukodoum DN, Okouga AP, Arnathau C, et al. Malaria-like symptoms associated with a natural *Plasmodium reichenowi* infection in a chimpanzee. Malaria Journal. 2015;**14**:220

[68] Ta TH, Hisam S, Lanza M, Jiram AI, Ismail N, Rubio JM. First case of a naturally acquired human infection with *Plasmodium cynomolgi*. Malaria Journal. 2014;**13**:68

[69] Lalremruata A, Magris M, Vivas-Martínez S, Koehler M, Esen M, Kempaiah P, et al. Natural infection of *Plasmodium brasilianum* in humans: Man and monkey share quartan malaria parasites in the Venezuelan Amazon. eBioMedicine. 2015;**2**:1186-1192

[70] Rodhain F. Is malaria a zoonotic infection? Bulletin de l'Académie Vétérinaire de France. 2012;**165**:335-338