Article

The Historical Ecology of Human and Wild Primate Malarias in the New World

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Abstract: The origin and subsequent proliferation of malarias capable of infecting humans in South America remain unclear, particularly with respect to the role of Neotropical monkeys in the infectious chain. The evidence to date will be reviewed for Pre-Columbian human malaria, introduction with colonization, zoonotic transfer from cebid monkeys, and anthroponotic transfer to monkeys. Cultural behaviors (primate hunting and pet-keeping) and ecological changes favorable to proliferation of mosquito vectors are also addressed.

Keywords: Amazonia; malaria; Neotropical monkeys; historical ecology; ethnoprimatology

1. Introduction

The importance of human cultural behaviors in the disease ecology of malaria has been clear at least since Livingstone's 1958 [1] groundbreaking study describing the interrelationships among iron tools, swidden horticulture, vector proliferation, and sickle cell trait in tropical Africa. In brief, he argued that the development of iron tools led to the widespread adoption of swidden ("slash and burn") agriculture. These cleared agricultural fields carved out a new breeding area for mosquito vectors in stagnant pools of water exposed to direct sunlight. The proliferation of mosquito vectors and the subsequent heavier malarial burden in human populations led to the genetic adaptation of increased frequency of sickle cell trait, which confers some resistance to malaria. Although malaria is likely a disease of considerable antiquity in human populations, Livingstone's work suggests its pervasiveness in Africa can be traced to cultural changes occurring in the last 10,000 years.

In tropical South America, little attention has been given to cultural behaviors among indigenous peoples that may affect the disease ecology of malaria. One area of potential significance for malaria involves the relationship between human groups and Neotropical monkeys. Many indigenous

Amazonian peoples not only hunt monkeys for food, but incorporate them into their households as pets [2-3]. Such close interactions set up an environment where diseases can be shared. Neotropical monkeys have been long suspected to play a role as reservoirs for some types of human malarias [4-11]. Under experimental conditions, numerous New World monkeys species have been infected with human *Plasmodium falciparum* and *P. vivax* malarias including howler monkeys (*Alouatta* spp.), owl monkeys *(Aotus* spp.), spider monkeys *(Ateles* spp.), squirrel monkeys (*Saimiri* spp.), and tamarins (*Saguinus* sp.) [4,12-16]. In the 1960s and 1970s, over 100 prisoners were experimentally infected with various forms wild primate malaria [16], some of which included transfer through mosquito vectors[1]. In addition, cases of naturally acquired human infections have been documented with both wild primate *P. cynomolgi* [17,18] and *P. knowlesi* [19-32].

A related question concerns the time depth of malaria in the New World. Introduced Old World diseases literally decimated indigenous Old World populations during the colonial era [33-36] and malaria has generally been considered to have been one of these introduced diseases [see also 37-39]. However, in the past, a few have raised the possibility that endemic malaria may have existed in the Americas prior to colonization [40,41]. Over the last several years, a revitalization of the endemic Pre-Columbian hypothesis has occurred, deriving from studies of the malarial genetics of Neotropical monkeys [42-46]. This review will address the relevance of human-monkey interactions to both the origin of malaria in the New World and contemporary behaviors that may foster cross-species transmission of malaria.

2. Human and Wild Primate Malarias in South America

Malaria is a parasitic infection caused by protozoa of the genus *Plasmodium*, family Plasmodiidae, suborder Haemosporidae, order Coccidia [47]. It is particularly successful in primates, occurring in multiple species of prosimians, New World monkeys, Old World monkeys, African apes, and Asian apes [4]. Sinden and Giles [47] estimate that malaria occurs in approximately 120 species of mammals, reptiles, and birds. That figure may be an underestimate when considering the extent of malaria in wild primate species. A recent review of the literature by this author found documentation of malaria in 63 species of wild primates, with malaria occurring in 38 species of New World monkeys [16]. In Deane's review of over 4500 documented cases of platyrrhine malaria in Brazil, he found rates of 35.6% in Southeastern region, 17.9% in the Southern region, 10.1% in Amazonia, and none in the Northeastern region of Brazil [48].

Most malarias are transmitted through mosquito vectors, and all human malarias are transmitted by anopheline mosquitoes [47]. Approximately 70 species of the *Anopheles* genus are malaria vectors, and of those, about 40 are considered to be of major importance [49].

Malaria in humans is typically caused by one of four plasmodia species: *Plasmodium falciparum, P. vivax, P. malariae,* and *P. ovale* [50]. All but *P. ovale* are present in South America, which occurs primarily in tropical Africa, but occasionally occurs in the West Pacific [4,51]. According to the WHO (World Health Organization) [52], malaria occurs in South America in the nine countries that are contiguous with the Amazonian rain forest: Bolivia, Brazil, Columbia, Ecuador, French Guiana, Guyana, Peru, Suriname, and Venezuela. The WHO 2005 report also indicated that 25% of these cases were caused by *P. falciparum* and 75% were caused by *P. vivax.* Although the WHO report also listed

P. malariae as occurring in the region, it was not documented at a statistically appreciable level. As will be discussed further below, there is reason to believe that indigenous Amazonians experience greater rates of *P. malariae* than has been revealed in aggregate statistics compiled by the WHO.

Of the three human forms of malaria occurring in South America, two are closely linked to endemic malaria in New World primates: *P. vivax* and *P. malariae*. These two forms of malaria are not closely related to one another, but each one is related to a malarial form occurring in Neotropical monkeys. Human *P. vivax* is a close genetic relative of Neotropical primate *P. simium*, which occurs in three species of monkeys (see Table 1). Human *P. malariae* is a close genetic relative of Neotropical primate *P. brasilianum*, which is more widespread, documented in thirty-five species monkeys. The relationship is so close between the human/monkey pairs that some malarial geneticists have argued that they should be considered indistinguishable conspecifics (e.g., [8,9,44,53,54]).

Although human falciparum malaria does not have a close relative genetic relative among Neotropical primates, it is closely related to *P. reichenowi*, a malarial form found in the African great apes, chimpanzees and gorillas (e.g., [43,54,55]). Much debate has surrounded the origin of *P. falciparum* in human populations which is relevant here for two reasons. One, it provides a caveat for reliance on molecular genetics; it should be remembered that this is still a field of science in its infancy. Second, the potential exists for Neotropical primates to become reservoirs of human falciparum malaria.

Some of the early molecular studies seemed to provide evidence that *P. falciparum* and avian malarias were closely related, suggesting that *P. falciparum* was a zoonosis acquired from birds [56,57]. The researchers interpreted the findings to suggest that *P. falciparum* originated within the last 5,000−10,000 years with the domestication of animals, which would have provided a cultural context for close interaction among human populations and bird species. However, because great ape *P. reichenowi* was not included when constructing the phylogenies, a false close relationship was suggested by the data due to a statistical error known as "long branch attraction." In brief, long branch attraction can occur when insufficient taxa are included and distantly related species can appear to share a common ancestor when their resemblances are the result of independent evolution[2] [58,59].

In subsequent studies where great ape *P. reichenowi* was included (and long branch attraction eliminated), the avian hypothesis was discounted [60-65]. However, the studies that immediately followed assumed that because *P. falciparum* and *P. reichenowi* had been demonstrated to be sister taxa, that they co-evolved with humans and great apes. That is to say, the reasoning was that an ancestral form of *P. reichenowi/P. falciparum* existed prior to the divergence of human ancestors and great ape ancestors. By this logic, when humans and great apes diverged, so did their parasites, placing the time frame for the divergence of *P. reichenowi* and *P. falciparum* at somewhere between 6 and 10 million years ago. This presented a radically different date of origin of falciparum from the assumptions of the avian hypothesis, closer to 6−10 *thousand* years ago, rather than 6−10 *million* years ago.

The first challenge to the very ancient date of the origin of human falciparum malaria came with the "Malaria's Eve" hypothesis. Due to very low levels of neutral polymorphisms[3], it was argued that a bottleneck effect had occurred among *P. falciparum* s.l., giving rise to contemporary *P. falciparum* s.s., within at least the last 200,000 years and perhaps within the last few thousand years ([66-68]; see also [69]). Thus, the Malaria's Eve hypothesis suggested that regardless of the ultimate age of *P.*

falciparum, all extant *P. falciparum* may have derived from a common ancestor, relatively recently. Within the last few months of the writing of this article, two studies were published that suggest that *P. falciparum* is a zoonotic disease, acquired from chimpanzees perhaps within the last 10,000 years [70,71]. Here, the evidence derives from the sequencing of eight additional chimpanzee falciparum-like plasmodia and finding far more genetic diversity than previously known. Human *P. falciparum* is argued to fall within the broader range of genetic diversity of *P. reichenowi*, and appears to be derivative.

New World monkeys, unlike Old World monkeys, are susceptible to *P. falciparum*; parallel evolution of a cell surface mutation created a human-like pattern of vulnerability to *P. falciparum* malaria [72]. New World monkeys are not natural hosts of *P. falciparum* and there is little reason to question that it was introduced to the New World from the Old World during the colonial era. However, because New World monkeys are susceptible to human falciparum malaria, they have served as important models for human malaria and drug testing, primarily owl monkeys (*Aotus* spp.) (e.g., [73-75]) and squirrel monkeys (*Saimiri* spp.) (e.g., [76-78], see 16 for a complete literature review). However, very recently, *P. falciparum* was identified in two species of wild howler monkeys [79]. It is not yet known if this is an isolated case, but it presents a very frightening scenario that New World monkeys could potentially serve as reservoirs for *P. falciparum* in the way that they appear to do now for *P. vivax* and *P. malariae*. Next, the relationship between human-NWM *P.vivax-P.simium* and *P. malariae-P. brasilianum* will be examined with attention to the question of the possibility of the existence of a Pre-Columbian form of malaria among New World Monkeys.

Table 1. Plasmodia and their Natural New World Primate Hosts.

Plasmodium brasilianum		
Primate Species	**Common Name**	**References**
Alouatta belzebul	Red-handed howler	5, 48[vi], 80[vi]
Alouatta caraya	Black howler	48, 79, 80
Alouatta guariba	Brown howler	48, 79-81
Alouatta palliata	Mantled howler	80-82
Alouatta seniculus	Red howler	5, 8, 11, 80, 81, 83
Alouatta pigra[i]	Guatemalan black howler	80-82, 84
Alouatta spp.	Howler	81, 85
Aotus vociferans	Spix's night monkey	80, 86
Ateles belzebuth	Long-haired spider monkey	80
Ateles fusciceps	Brown-headed spider monkey	79-82, 84
Ateles geoffroyi	Black-handed spider monkey	80-82, 84
Ateles paniscus	Black spider monkey	5, 48, 80-82, 87
Ateles spp.	Spider monkey	85
Brachyteles arachnoides	Woolly spider monkey, Muriqui	48, 80, 81
Cacajao calvus[ii]	Bald uakari	5, 21, 48, 82, 85, 88
Callicebus brunneus	Brown titi	5, 80
Callicebus moloch	Dusky titi	5, 80, 81
Callicebus moloch complex	Titi monkey	5
Callicebus ornatus	Ornate titi	80

Table 1. *Cont*.

Callicebus torquatus	Collared titi	5, 80, 81
Cebus albifrons	White-fronted capuchin	5, 48, 81, 82
Cebus apella	Tufted capuchin	5, 48, 80-82, 87
Cebus capucinus	White-faced capuchin	80-82, 84
Cebus spp.	Capuchin	85
Chiropotes albinasus	White-nosed saki	5, 48, 80
Chiropotes chiropotes	Red-backed bearded saki	48, 79
Chiropotes satanas	Black-bearded saki	5, 48, 80
Lagothrix cana	Peruvian woolly monkey	48, 81
Lagothrix poeppigii[iii]	Woolly monkey	48, 81, 82, 87
Lagothrix lagotricha[iv]	Common woolly monkey	5, 48, 80-82
Lagothrix sp.	Woolly monkey	85
Pithecia irrorata	Bald-faced saki, Tapajós saki	5, 48, 80
Pithecia monachus	Monk saki	48, 80
Pithecia pithecia	White-faced saki	5, 8, 11, 48, 80, 83
Saguinus geoffroyi	Panamanian tamarin	80, 89
Saguinus midas	Red-handed tamarin	5, 8, 11, 80, 83
Saimiri boliviensis	Bolivian squirrel monkey	5, 48, 80-82, 87
Saimiri sciureus	Common squirrel monkey	5, 48, 80-82, 87
Saimiri ustus	Bare-eared squirrel monkey	5, 48, 80
Saimiri sp.	Squirrel monkey	85, 90
Plasmodium simium		
Alouatta caraya	Black howler	79[vii]
Alouatta guariba[v]	Brown howler	21, 79-82, 85, 88, 90-91
Brachyteles arachnoides	Woolly spider monkey, Muriqui	21, 80, 81

i. *Alouatta pigra = Alouatta villosa*
ii. Including *Cacajao rubicundus*
iii. Described as *Lagothrix infumata*. In the older literature, this designation has been used to refer to both *Lagothrix lagotricha* and *Lagothrix poeppigii* [92]. Dunn and Lambrecht [87] identify the location as Loretto province in eastern Peru, so they are probably referring to *L. poeppigii*. Eyles [82] and Cogswell's [81] use of the term *Lagothrix lagotricha* is apparently following Dunn and Lambrecht's designation.
iv. *Lagothrix lagotricha = Lagothrix lagothricha*
v. *Alouatta guariba = Alouatta fusca*
vi. Also see table of references therein
vii. Duarte *et al*. [79] do not distinguish between *P. simium/P. vivax* or *P. brasilianum/P. malariae* for *Alouatta carya* and *Alouatta guariba*

3. Out of Africa[4]: Introduced Malaria

The most widely accepted scenario is that all malarial forms in the New World are of Old World origin and were introduced to Native American populations by Africans and Europeans during the colonial era. Here, the Neotropical monkey malarias that bear a close genetic relationship to human malarias would be explained through a lateral transmission from humans to monkeys. That is to say, Neotropical monkey malaria is anthroponotic. Three lines of evidence in support of this view are: the evolutionary diversification of malaria, human genetic adaptations to malaria, and the ethnohistorical record.

First, differences in the patterns of malarial diversification in the New World and the Old World support the hypothesis of its introduction during the colonial era. Malaria is found in all major groups of Old World terrestrial vertebrates [41]. Its diversification among varied species suggests a long evolutionary history in the Old World. In South America, malaria is much more restricted. The only mammals infected with malaria are humans and monkeys[5]. Also, although malaria occurs in over thirty species of New World primates, these represent only two forms of malaria, each of which is genetically similar to human forms of malaria. The lack of diversification in South America suggests a much shallower time depth, which would be consistent with a late introduction in the colonial era.

Perhaps the most compelling evidence in favor of a late introduction of malaria into the New World is the lack of genetic polymorphisms that confer some form of resistance to malaria. When higher frequencies of genetic polymorphism occur in a population than would be expected by random mutation, long-term co-evolution of the parasite and its host is strongly indicated. A number of genetic variations have been linked to resistance to malaria, such as sickle cell trait (e.g., [1,93-94]), α and β-thalassemia (e.g., [95,96]), glucose-6-phosphate (G6PD) [97-99], and RBC Duffy negativity [100-102]. None of these disorders have high rates of prevalence among indigenous populations in the Americas, which would be suggestive of selection for resistance against malaria sickle cell trait (e.g., [93,103]), α and β-thalassemia (e.g., [103-105]), glucose-6-phosphate (G6PD) (e.g., [103,106,107]), RBC Duffy negativity (e.g., [108,109]).

Several lines of ethnohistorical evidence also point to an Old World origin of malaria. Despite potential debate regarding the origins of *P. vivax* and *P. malariae*, there is little doubt that *P. falciparum* was introduced to the Americas from the Old World. Thus, it is clear that at least one form of malaria was introduced, which arguably could bolster the case that the other forms were introduced as well. By way of analogy, clearer ethnohistorical evidence exists for the introduction of another arthropod-borne infection, yellow fever, during the colonial era. Wide agreement exists that both the *Flavivirus* disease agent and the *Aedes aegypti* mosquito vector of yellow fever were introduced from Africa to the Americas during the slave trade (e.g., [36,39,110]). The virus that causes yellow fever is identical in monkeys and humans and in Africa and tropical South and Central America; it is entrenched in an enzootic cycle where it passes between unvaccinated humans and wild primates [111]. Historians believe that medical records document yellow fever epidemics in Europe in the 6th and 7th centuries [112,113]. In addition, African populations and Old World primate populations also demonstrate immunological resistance to yellow fever lacking among Native Americans and Neotropical monkeys [110]. Given that an identical virus causes yellow fever in monkeys and humans, some historical evidence for Pre-Columbian existence in the Old World, and the historical evidence for the introduction of a key vector with the slave trade, it strongly suggests that yellow fever was introduced to Neotropical primates by human beings.

The possibility of a European introduction of malaria to the New World has received less attention. Several lines of evidence do suggest that Europeans could have been a source for malarial transmission into the Americas. Malaria was probably endemic in ancient Greece by the 4th century B.C. Frequent references can be found in the works of the Greek physician Hippocrates describing the periodicity of fever, splenomegaly, and the relationship of the malady to inhabitants of low, marshy areas [114]. Similar descriptions of intermittent fevers were recorded in the works of Celsus, Pliny the Elder, and Galen [115] as well as in the works of Classical Roman physicians such as Martialis, Juvenal, Horace,

and Livy [116]. Stannard [116] cautions that such references should be viewed critically for the Classical Roman physicians had no understanding of the plasmodia involved, may have confused febrile diseases, and were interpreting disease according to the cultural beliefs of their time. Nevertheless, the frequency of the references and the consistency of the symptoms leave little doubt of the presence of malaria in ancient Rome. In South Asia, the Ayurvedic Hindu medical text Susruta (by 6−7th century A.D.) also describes a febrile disease with a relationship to mosquitoes that is likely a form of malaria [117]. Portugal and Spain were key colonizing forces of South America, and some evidence suggests that falciparum malaria may have existed on the Iberian peninsula during medieval times. Arab physicians in the 11th and 12th centuries in Islamic Spain describe epidemic pernicious tertian fevers linked to stagnant water sources [114].

In addition, another ethnohistorical argument relates to the timing of the first reports of malaria in the New World. Joralemon [118] describes the absence of reports of malaria among early explorers who visited Amazonian groups in riverine habitats, where malaria is found today. According to Joralemon, it is not documented until after 1650 in the Northeast and Eastern Coasts of South America. He argues that this is compelling evidence for a late introduction.

4. Out of Amazonia: Pre-Columbian Endemic Malaria in the New World

The endemic New World malaria hypothesis argues that some, but not all forms of malaria may have been present in the New World in Pre-Columbian times. This hypothesis also assumes a lateral transfer between humans and New World monkeys. Although the direction of monkey-human transmission is not clear, most taking this position view malaria as most likely a monkey zoonosis transmitted to humans. This scenario entails the spread of some forms of malaria from Amazonia to the Old World during the colonial period, rather than it occurring the other way around. Three lines of evidence lend support to this view: Amazonian ethnomedicine, environmental change, and Neotropical malarial genetics.

My original interest in the possibility of endemic malaria derived from ethnobotanical research among the Guajá people of Eastern Amazonia [119-121]. The Guajá treat malarial fevers through bathing in infusions of aromatic plants. They believe these fevers to be caused by the cannibalization of the soul by the *aiyã* ghosts of the dead. Although introduced viral diseases, such as influenza, are also fever-producing ailments afflicting the Guajá, these are recognized to be introduced diseases of the *karaí* (non-Indians). The use of medicinal baths against malevolent spirits is also found in numerous other Amazonian groups, some of which are linguistically and geographically distant from one another such as the Arawakan-speaking Matsigenka of Peru [122], the Tupi-speaking Kayabi of Brazil [123], the Panoan-speaking Yora of Peru [122], and the Warao of Venezuela whose language is classified as an "isolate" [124].

Given that similar folk beliefs are deeply embedded in the mythico-religious systems of widespread Amazonian peoples, the possibility exists that this may be an indigenous response to a disease of great antiquity, pre-dating European contact. Moreover, given that the Guajá make a distinction between malaria and "non-Indian" diseases, indigenous disease classifications lend further weight to the possibility that malarial forms may have existed in Pre-Columbian Amazonia.

Perhaps better known is the anti-malarial activity of the South American cinchona bark from which the medicine quinine was developed. Honigsbaum and Willcox [125] have reviewed the debate surrounding whether or not cinchona[6] was used as an anti-malarial by indigenous South Americans. Records of Spanish chroniclers trace the origin of cinchona in the 17th century to the Loja region in the Spanish ViceRoyalty of Peru, which is now in southern Ecuador. Jesuit priests brought the bark to Europe, but it has been unclear whether the Jesuits learned of the bark through local Quechua-speaking Indians or whether they discovered its medicinal properties independently. Evidence in support of cinchona as an indigenous remedy stems from its use today among Ecuadorian healers to treat diarrhea, to induce labor, and as a dentrifice. Its use specifically as an indigenous anti-malarial has been questioned for key two reasons according to Honigsbaum and Willcox's review. The first is that no record has been found of cinchona being used as a febrifuge, nor does a record exist of cinchona in Incan hieroglyphics or archaeological remains. The second argument has been the assumption that malaria was not present in the New World prior to colonization.

While insufficient documentary or archaeological evidence currently exists to resolve the question of the discovery of cinchona, several points warrant discussion. First, it is an ethnographic error to generalize from the Inca to all Quechua speakers given that today, there are over 10 million speakers of Quechua in South America [126], who display not only regional dialect differences in the language, but also cultural differences. Environmental differences also exist among Quechua speakers. The Inca were unlikely to have developed a malaria remedy because of the difficulty of survival of the mosquito vector in the cold, dry, high altitude conditions of the Andes. If cinchona was used as a malarial remedy among Quechua-speakers, it is more likely to have been used in the more lowland areas, where preservation of archaeological plant remains would be far more difficult to recover.

A second possible line of evidence in support of endemic malaria lies with environmental change. Malaria presents a more complicated picture than other introduced diseases such as smallpox or the influenzas because it cannot be passed directly from human to human, but requires a mosquito vector. Thus, ecological conditions must also be taken into account. A number of researchers (e.g., [127]) have noted that environmental changes during the colonial period created ideal breeding grounds for *Anopheles* vectors, echoing back to Livingstone's [1] work on the relationship of swidden agriculture to the proliferation of malaria in Central Africa. One the one hand, one might take this as an argument in support of an African introduction. That is to say, development of the tropical forest in the wake of colonization provided the ecological conditions fostering the development of an introduced malaria in the New World, much in the same way that it did under similar conditions in Africa.

These same ecological conditions can also be used make a case for the possibility of an endemic malaria. In Livingstone's [1] original article, he proposed a solution to combat African malaria which was what he called "rejunglization." In other words, if mosquito vectors of malaria thrived in areas of agricultural development, allowing the forest to regrow would lead to the diminishment of mosquito vectors. In Amazonia, such a scenario apparently occurred. Recent work in historical ecology by researchers such as Denevan [128], Heckenberger *et al*. [129], Balée and Erickson [130] have challenged what Denevan refers to as the "pristine myth." In brief, the pristine myth argues that the Amazonian environment documented in 1750 had radically changed from its Pre-Columbian state. The demographic collapse of indigenous peoples from introduced diseases, perhaps as great as more than 90% of the population [34,36], also represented a major ecological event. The sudden, massive

depopulation of indigenous Amazonia created shifts in the ecological pressure on flora and fauna due to the absence of human environmental agents. In essence, Amazonia was "wilder" in 1750 than it was in 1500. A process of reforestation occurred between initial contact and colonization in earnest in the 18th century.

The evidence for the ecological rebound of Amazonia cannot tell us whether or not endemic malaria was present. Nonetheless, it does call into question the weight given to the historical relationship between malaria and colonization. In other words, if Pre-Columbian malaria did exist in Amazonia, it might very well have resurged under conditions of environmental change beginning in the colonial era. What appeared to be a virgin soil epidemic may have been an endemic malaria mimicking a virgin soil epidemic due to environmental changes which allowed malaria to resurge. By way of analogy, it is interesting to note that according to Carmichael [131], mosquito-borne diseases increased in Europe after 1500, which she attributes as due in part to an increase in rice cultivation during this time, which created breeding grounds for mosquitoes.

The strongest evidence for possibly Pre-Columbian endemic malaria rests on the relationship between Neotropical monkey malarias and human malarias. The existence of a genetic relationship alone would not necessarily imply endemic malaria, for it can be argued that the Neotropical monkey malarias are anthroponotic. For *P. vivax* malaria, an African origin should be excluded as feasible due to Duffy RBC negativity in the areas of the European slave trade. Duffy blood group negativity is a homozygous state of RBC antigens that confers complete resistance to *P. vivax* [102]. Over 97% of the indigenous populations in sub-Saharan and West Africa exhibit RBC Duffy negativity [100] with *P. vivax* occurring at a rate of less than 1% [101]. Those cases that occur have been judged to be attributable to either immigrants into the region or from indigenous inhabitants returning from areas where *P. vivax* is common. Moreover, several recent studies in the malarial genetics of Neotropical monkey *P. simium* have pointed to its origination in South America. The *P. vivax/P. simium* relationship presents a complicated and challenging puzzle.

5. Out of Asia: A Closer Look at *Plasmodium vivax* and *Plasmodium simium*

A strong case can be made that human *P. vivax* malaria originated in Southeast Asia. *P. vivax* is closely related to about a half a dozen forms of macaque malaria occurring in the area (e.g., [44,55,64,132,133]). Since human beings and macaques are very distant primate cousins, the relationship between human *P. vivax* and macaque *P. vivax*-like malarias could only be explained through a lateral transfer. This suggests that either *P. vivax* is a zoonosis acquired by humans from macaques or that the macaque vivax-like malarias were anthroponotically acquired.

Malarial geneticists have identified a problem with the hypothesis of a Southeast Asian center of endemicity for the *P. vivax*-like malarias when trying to understand the relationship of Neotropical monkey *P. simium* to the *P. vivax*-like malarias. Asian macaques and South American monkeys do not share a recent common ancestor. Monkeys are first documented in the South American fossil record in the Late Oligocene of Bolivia, approximately 30 million years ago (e.g., [134,135]). With the span of the Pacific Ocean dividing the two continents, there is but minimal possibility of direct lateral transfer between macaques and New World monkeys. The genetic connections between macaque and New World monkey vivax-like malarias could only have occurred through a human intermediary. Even

more puzzling is that human *P. vivax* is actually more closely related to Neotropical monkey *P. simium* than it is to the Southeast Asian cluster of macaque malarias [43-45]. So, in terms of evolutionary history, human and New World monkey plasmodia share a more recent common ancestor than the outlying macaque vivax-like malarias.

If it were not for the seemingly insurmountable issue of the ecology of malarial mosquito vectors, it might be possible to account for the connection through the migrations of Asian peoples across the Bering Strait from North America to South America where malaria could have been introduced to Neotropical monkeys. The protozoa involved in *P. vivax* (as well as *P. malariae*) will not develop in anopheline mosquitoes whose body temperature is less than 15 ℃ (59 ℉) [136]. For that reason, a Beringia route for malaria would seem to be extremely unlikely because it would have been far too cold for any of the known suitable malarial vectors to sustain the disease in a population and there would have been far too little time for a hypothetical malarial-bearing group to live long enough to cross three continents to introduce malaria to monkeys that harbor *P. vivax*-like malaria in Southern Brazil[7].

To account for these relationships, some malarial geneticists have hypothesized that *P. vivax* may have originated in the Neotropics and was transmitted as a zoonosis from New World monkeys to New World humans [42,43]. One might conclude that Thor Heyerdahl's [137] controversial hypothesis of Pre-Columbian travel from South America to Polynesia was right after all, and perhaps New World malaria took a *Kon Tiki* route from the New World to the Pacific Islands. It still leaves a serious problem, because if true, it would mean that *P. vivax* both spread worldwide to human populations and diversified in macaques only within the last several hundred years after colonization. It is also at odds with the historical literature previously described which suggests the existence of a vivax-like malaria in human populations in Europe and the Mediterranean dating back several millennia.

A recent study has refuted the hypothesis of a Neotropical monkey origin of *P. vivax*, but the reason why for its refutation is surprising and also raises further questions. A study by Li *et al.* [45] of the relationship among variant forms of *P. vivax* in human populations found derived differences between Old World and New World forms of *P. vivax*, so a degree of diversification has occurred between these two variants of *P. vivax*. Oddly, Neotropical monkey *P. simium* clusters with Old World *P. vivax* rather than New World *P. vivax*. In other words, this study suggests that there is a closer genetic relationship between Asian human *P. vivax* and Neotropical monkey *P. simium* than either have with the form of *P. vivax*-like malaria occurring in contemporary indigenous New World peoples. On the basis of the genetic distances among these *P. vivax* groups, Li *et al.* [45] have suggested that the *P. vivax*-like form of malaria occurring in South America be reclassified as at least a new subspecies of *P. vivax* called *P. vivax collensi*, and probably warrants a designation as an entirely separate species of plasmodia, *P. collensi*. The difficulty is in explaining the historical events that could account for the relationship between Neotropical monkey malaria and Asian human malaria[8].

Carter [46] has attempted to explain the relationship through a Pre-Columbian Trans-Pacific origin of human Southeast Asian malaria to the New World. Rather than malaria originating in New World monkeys and spreading to the Old World, he reverses the *Kon Tiki* route and suggests that a Southeast Asian human population migrated to the New World and introduced malaria to New World monkeys. He speculates that this early form of malaria must have then disappeared from the original human carriers, perhaps due to some form of environmental or cultural behavior that prevented its

perpetuation. Carter also hypothesizes that the *P. vivax*-like malaria present today in indigenous Amazonians was introduced by Europeans and represents a form that was eradicated from that continent in the mid-20th century.

One possible source of evidence that could support Carter's model lies with the nature of the mosquito vector of *P. simium, Anopheles cruzii. A. cruzii* is a sylvatic mosquito. In one study, it was found to spend 99% of its time in the upper canopy [80, see also138]. Two of the species of monkeys that carry *P. simium*, the woolly spider monkey (*Brachyteles arachnoides*) and the brown howler monkey (*Alouatta guariba*) also spend most of their time in the upper canopy or emergent levels of the forest[9] [139]. So once transmitted, the habitats of the monkeys and the mosquito vector provide a natural barrier, making it difficult to transfer *P. simium* from monkeys to humans in the wild[10]. In fact there has only been one documented case of natural transmission of *P. simium* to a human host, and that occurred in a worker who was up in the canopy collecting *Anopheles cruzii* mosquitoes [80].

Carter's Pre-Columbian Trans-Pacific hypothesis presents a major problem when considering the distribution of the woolly spider monkey and the two howler species that harbor *P. simium* in South America. *They are on the wrong side of the continent.* All three are Atlantic forest species of the East Coast [140]. So, a hypothetical human population would need to sustain malaria long enough to trek at least a thousand miles, including going over the Andes Mountains, to give malaria to the howlers and woolly spider monkeys in the Atlantic Forest. Logically, if *P. vivax* could have been maintained in a human population long enough for them to make such a long and arduous journey, it should have been sustained in them. At the very least it would be expected that the related *P. simium* would occur in some of the intervening monkey populations, particularly the howler species that are closer to the Pacific Coast.

I can propose one possible simpler explanation for how Asian *P. vivax* was introduced to these two monkey species. It could have been introduced much later in the 19th century from the importation of Chinese workers by the Brazilians as agricultural laborers in the vicinity of Rio de Janeiro. A key reason that Chinese workers were brought to Brazil was due to a great interest in tea as an exotic commodity. In 1814, Dom João brought a colony of 200 Chinese to Rio de Janeiro to give instruction on the preparation of tea and for its cultivation in the Royal Botanical garden [141]. Over the course of a century, approximately 3,000 laborers from Macao, a Portuguese colony in southern China, were brought to work in Rio de Janeiro [141-143].

A Chinese origin of Neotropical vivax-like malaria could be one viable alternative scenario due to its potential to explain much of the puzzling data related to the relationships among the vivax-like malarias in humans and monkeys. First, it is a far simpler scenario for malaria to have been brought directly from southern China in the late colonial era rather than Southeast Asians needing to cross the span of the Pacific Ocean in primitive watercraft in Pre-Columbian times.

A 19th century Asian introduction also matches the geographic distribution of the woolly spider monkey and brown howler monkey more closely, because the Chinese were brought directly into the region of the Atlantic forest. It would eliminate the need for malarial-bearing humans to cross the width of the continent of South America to reach the Atlantic forest. A direct Atlantic forest introduction would also explain why *P. simium* does not occur in the intervening primate populations between the Pacific Coast and the Atlantic Forest. And finally, the agricultural laboring activities that the Chinese were involved in would have put them in the vicinity of the sylvatic habitat of the

mosquito vector that transmits *P. simium* in the Atlantic forest. Perhaps even the felling of trees may have made it more likely to have direct contact with the mosquito vectors. It might even be argued that given the rapid development of the area of Rio during the 19th century and the displacement of all indigenous South American peoples from that region, Chinese immigrants may have been more likely to come into habitats of Atlantic Forest monkeys than indigenous peoples. So, in sum, the possibility exists that brown howlers and woolly spider monkeys have malaria because of the desire of Portuguese colonists to drink tea.

6. *Plasmodium malariae* and *Plasmodium brasilianum*

The relationship between human *P. malariae* and *P. brasilianum* poses a different set of circumstances than the *P. vivax/P. simium* relationship. First, a New World origin of *P. malariae* seems very unlikely. *P. malariae* is a natural parasite of both humans and the great apes in Africa [99]. Evolutionary parsimony would suggest that *P. malariae* was introduced in the colonial era from human populations and entered the New World primate population as an anthroponosis. Perhaps the most likely scenario is that it arrived with African slaves, who transmitted it to indigenous Amazonians, who then transmitted it to the local monkey population. It is also possible that *P. malariae* was already extant among European colonists who transmitted it to indigenous peoples. Since the identity of the malaria or malarias present in Europe during the colonial era is unknown, either or both *P. malariae* and *P. vivax* could have been present. In addition, European colonists could have served as an intermediary population that transmitted *P. malariae* to indigenous Amazonians from their slave-raiding and colonization in Africa. In any event, all evidence would seem to point to an Old World origin of *P. malariae*.

Significant differences also exist between Neotropical primate *P. simium* and *P. brasilianum* in terms of their distribution. As previously discussed, *P. simium* is restricted to a circumscribed region of the Atlantic forest in Brazil and occurs in only two primate species. In contrast, *P. brasilianum* has been documented in thirty-four species of monkeys which are widely distributed in Panama, Brazil, Venezuela, Peru, and Columbia (see Table 1). The general question of the extent to which Neotropical monkeys serve as reservoirs (or perhaps more accurately, amplifying hosts) of human malaria would apply best to the widely distributed simian *P. brasilianum*.

The importance of non-human primates in malarial transmission of *P. malariae* might seem to be minor given the previously mentioned WHO [52] statistic that 25% of the cases of malaria in South America are attributable to *P. falciparum* and 75% of the cases were attributable to *P. vivax*. While the WHO report indicates that *P. malariae* is present in South America, it is noteworthy that it is not detected at a statistically appreciable level. The statistical insignificance of *P. malariae* is more likely a reflection of the inability of current surveillance methods to measure adequately the incidence of *P. malariae* among indigenous Amazonians than it is an accurate measure of the status of *P. malariae* in that region.

Several problems exist in accurately measuring the prevalence of malaria among indigenous peoples. One is that malaria is usually diagnosed through passive case detection (PCD) or less commonly, through active case detection (ACD). In passive case detection, when an individual reports symptoms to a health care worker, he or she is tested for malaria. In 2000, nearly 75% of the nearly

five million malaria smears in the Americas were collected passively [144]. Active case detection involves periodic visits to communities and collecting blood samples from individuals who have had a fever since the last visit. In Brazil, a program of aggressive active case detection (AACD) has been implemented in limited areas, such as among the Yanomami, and has met with success in significantly reducing malarial rates [145]. Aggressive active case detection involves taking monthly blood surveys of everyone, whether or not an individual is exhibiting a fever. Despite the success of AACD in selected groups, nearly all malaria cases in Brazil are still identified through either active or passive case detection [145].

Given that nearly 3/4 of malaria cases in the Americas are identified through passive case detection, cases among indigenous peoples are less likely to be diagnosed. A 2006 Pan American Health Organization report [146] estimates that 40% of indigenous peoples in the Americas lack access to conventional health-related services and than 80% rely on a traditional healer. The PAHO report also indicated that even when health care services are available, cultural barriers obtain that may prevent indigenous people from seeking treatment. Such barriers include language differences and distrust or fear of health care workers.

The rates of *P. malariae* may be underestimated because this form of malaria may be harder to detect by microscopy. Cavasini *et al*. [147] found *P. malariae* occurring at a rate of 10% in Western Rondônia, Brazil, using PCR (polymerase chain reaction). They emphasize that this contrasts sharply with national statistics from Brazil as a whole. Two to three million GTS (Giemsa-stained thick smears) are examined every year in Brazil with the *P. malariae* rate at 0.3%. They suggest that the incidence of *P. malariae* may be significantly underestimated by GTS microscopy. A similar study conducted in Mato Grosso, Brazil compared *P. malariae* rates using GTS and PCR simultaneously in the same group [148]. The GTS showed a prevalence of 1.2% while PCR showed a prevalence of 11.9%.

Another problem is identification of cases that are sub-clinical or asymptomatic, which is particularly difficult when passive case detection methods are used. In a review article of studies of asymptomatic malaria in Brazil, the rate of positive results from PCR testing in individuals not exhibiting symptoms ranged from 20.4−49.5% [149]. *Plasmodium malariae*, which often presents as a relatively mild form of malaria [150], may be underrepresented in the statistics if symptoms are not severe. If asymptomatic individuals are not identified and treated, then the reservoir for the disease will be maintained.

Few published studies have been conducted on the prevalence of malaria among indigenous Amazonian groups. The data that are available suggest that substantial differences may exist between those living in urban or settled rural areas (where data are most readily gathered) and Amerindian populations living in the tropical forest habitats. For example, in a recent study of several indigenous groups in French Guiana, 38.8% of the Wayana and Emerillon Indians in the Maroni River basin and 45.4% of the Wayampi and Emerillon Indians in the Oyapock River basin were seropositive for antisporozoite antibodies against *P. malariae/P. brasilianum* [11]. The study also included testing the sera of 113 monkeys in the area, and 73% tested positive for the *P. malariae/P. brasilianum* circumsporozoite peptide.

A similar study by De Arruda *et al*. [6] in Northern Brazil (Xingu River basin) found that almost 90% of adult Asurini[11] Indians and 100% of adult Metuktire Indians tested had antisporozoite

antibodies against *P. malariae/P. brasilianum.* They suspected that pet-keeping of monkeys by the Indians might be an explanation for the high rates of *P. malariae.* It is possible that these groups represent aberrant cases. However, with seropositivity ranging from 40–100%, it at least suggests that *P. malariae* is significant for some Amazonian groups. It seems more probable that the incidence of *P. malariae* has been grossly underestimated.

A sylvatic enzootic cycle involving nonhuman primates in the Neotropics has been identified for both dengue and yellow fever [111,151] and a similar process may be occurring with *P. malariae/ P. brasilianum.* The relative importance of monkey *P. brasilianum* infections in sustaining human *P. malariae* infections may be minimized since the Amerindians in the tropical forests who would be most affected are those who are least likely to be adequately surveyed. An addition implication is that the recent WHO [52] intervention measures for vector control to combat malaria are neither adequate nor appropriate for tropical forest-dwelling people in Amazonia. Larviciding, indoor residual spraying, and insecticide treated mosquito netting can offer little protection for peoples who routinely travel long distances in the forest to hunt and gather. Moreover, if the human/primate cross-infection proves to be significant, these intervention measures cannot address the problem of monkey populations serving as malarial amplifiers.

7. Conclusion

In conclusion, while the evidence does not lend strong support to Pre-Columbian malaria in the New World, it does present a complicated picture of the relationship between human and nonhuman primate malarias in South America. First, it seems clear that falciparum malaria was introduced from the Old World to the New World, probably originating in African slaves during the colonial period. Falciparum malaria is a human malaria without an analog in Neotropical monkeys. The two vivax-like malarias affecting human and non-human primates may derive from different sources. I have hypothesized that the most parsimonious explanation to account for the close genetic relationship between Asian *P. vivax* and Neotropical primate *P. simium* is that monkeys acquired this form of malaria anthroponotically from immigrant Chinese laborers in the Atlantic forest in the late 19th century. Indigenous Amazonian *P. vivax collensi* (following the designation of Li *et al.* [45] may have been introduced directly from European colonists, representing a form of malaria that is no longer in existence on that continent.

The evidence also points to an Old World origin of *P. malariae*, introduced from either African populations, or perhaps Europeans. The closely related Neotropical primate *P. brasilianum* is best explained as anthroponotically transmitted from humans to monkeys.

I have also argued that although the WHO generated statistical analysis of malarial cases reported in South America indicate that *P. malariae* occurs at a rate of less than one percent, that there is reason to suspect this is an underestimate due to passive case detection, unreliability of GTS microscopy, and asymptomatic cases.

The few data available from studies that have directly tested all members of an indigenous group for *P. malariae* demonstrate high levels of infection among some indigenous groups in tropical forest habitats. The enzootic cycle of *P. brasilianum* in monkeys is likely a significant factor in sustaining malaria among some indigenous peoples. Moreover, numerous groups hunt monkeys and keep them as

pets, placing them not only in the same general geographic locale, but in direct contact with humans and human society. In my own fieldwork with the Guajá people [2,120,152], infant monkeys whose mothers were killed for food were incorporated into the kinship system as quasi-human beings who were nurtured as children.

The broader implication for *P. malariae* is that the vulnerability of indigenous peoples presents a very different set of circumstances than the current malarial control measures in South America are designed to address. Chemical vector control is not a viable solution for people who live in the tropical forest. Subsistence strategies that involve hunting, gathering, fishing, and agricultural activities in areas in or near where mosquitoes thrive render local spraying for vectors an ineffective intervention. Residual household spraying has little meaning for people living in thatched housing structures that do not provide an effective barrier between in-doors and out-doors. And ultimately, the enzootic amplification in monkey populations places these human populations at continual risk.

Acknowledgments

Notes

1. In 1960, three researchers at a Memphis malarial research laboratory were naturally infected with a form of monkey malaria, *P. cynomolgi* [17,18]. Prior to this time, it had not been believed that it was possible for a human to contract wild primate malaria. This was followed by a series of studies among prisoners at the Atlanta Penitentiary in the 1960s and 1970s that involved experimental infections with various forms of monkey malaria that are documented in the *Journal of Tropical Medicine and Hygiene* [16].

2. Because the number of nucleotides is limited to four (ACGT), it can be difficult to differentiate between nucleotides that represent common ancestry and mutations that are the result of independent evolution. See Cormier [16] for a more extensive review of the problem of long branch attraction in constructing phylogenies of primate plasmodia.

3. Neutral polymorphisms or "silent mutations" are mutations that do not affect the amino acid sequence coded [100], and presumably are not under selective pressure.

4. I am borrowing here from Carter's [46] terminology contrasting these two views as "Out of Africa" versus "Out of Amazonia."

5. In North America, Caribbean *Anolis* lizards can be infected with *Plasmodium floridense* and *P. azurophilum*[153]. Garnham and Kuttler [154] have hypothesized the presence of *Plasmodium odocoilei* in the North America white-tailed deer (*Odocoileus virginianus*) originates in cervids who brought the plasmodium to the New World in Pliocene times across the Bering Land Bridge based on comparative phylogeny of plasmodia in Old World ungulates. If they are correct, it raises the possibility, however unlikely, of plasmodia parasites entering the New World with humans across the Bering Strait.

6. *Cinchona* is a member of the Rubiaceae family and is not a single plant, but includes from 23-36 different species, depending on the botanical classification [125].

7. Although Ramenofsky [136] mentions a malarial epidemic occurring in Yukon among the Tlingit, citing Marchand 1943 [155], no mention of malaria could be found in Marchand's article.

8. It should be noted that these genetic relationships are still far from settled. A phylogenetic analysis conducted by Mu *et al*. [156] did not determine clear distinctions between Old World and New World forms of *P. vivax* or a closer connection of *P. simium* to Old World *P. vivax*. Nevertheless, Mu *et al*. found support for an Asian origin of *P. vivax*-like malarias, which were transmitted to New World humans and monkeys through a series of host transfers. However, even less is known about the basic biology and genomic diversity of *P. vivax* than *P. falciparum* [157].

9. *Alouatta caraya* is more variable in the canopy strata utilized.

10. However, differences in the vertical forest niches of monkeys and humans do not provide a completely satisfactory explanation; such ecological barriers do not explain why *P. simium* has not spread more widely among monkeys. Here, horizontal barriers may be more at play in the highly developed and fragmented Atlantic forest.

11. More commonly spelled, Assurini.

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