

Men, Primates, and Germs: An Ongoing Affair

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Abstract Humans and nonhuman primates are phylogenetically (i.e., genetically) related and share pathogens that can jump from one species to another. The specific strategies of three groups of pathogens for crossing the species barrier among primates will be discussed. In Africa, gorillas and chimpanzees have succumbed for years to simultaneous epizootics (i.e., “multi-emergence”) of Ebola virus in places where they are in contact with Chiropters, which could be animal reservoirs of these viruses. Human epidemics often follow these major outbreaks. Simian immunodeficiency viruses (SIVs) have an ancient history of coevolution and many interspecific exchanges with their natural hosts. Chimpanzee and gorilla SIVs have crossed the species barrier at different times and places, leading to the emergence of HIV-1 and HIV-2. Other retroviruses, such as the Simian T-Lymphotropic Viruses and Foamiviruses, have also a unique ancient or recent history of crossing the species barrier. The identification of gorilla *Plasmodium* parasites that are genetically close to *P. falciparum* suggests that gorillas were the source of the

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deadly human *P. falciparum*. Nonhuman plasmodium species that can infect humans represent an underestimated risk.

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1 Introduction

Exchanges of parasite species among vertebrate hosts can be intraspecific or interspecific. Interspecific exchanges occur when a pathogen crosses the species barrier, and the risk of interspecies transmission appears to be naturally high among hosts that are taxonomically closely related or sympatric. Crossing the species barrier is a multifactorial phenomenon that occurs only when a certain number of requirements are met, such as a specific environment, an infected natural “donor” host, a sensitive and permissive recipient host and, sometimes, a vector with trophic preferences for both species.

Microorganisms can *cross the species barrier* in natural and in human environments. Many infectious diseases, including most of the arthropod-borne viral infections, rabies, Lyme disease, hantavirus infections, and arenavirus hemorrhagic fevers (Wolfe et al. 2007), are the outcome of cross-species transmission (CST) of a germ from one species to another. Human infections due to CST of a pathogen are by definition zoonotic diseases as each microorganism’s natural host is a nonhuman vertebrate. Currently, 73 % of emerging human pathogens are zoonotic and many of them have their source in wildlife (Daszak et al. 2000). CST occurs either when humans come into contact (via direct interaction with the infected animal or its excreta, or indirectly via transmission by an insect vector) with an animal pathogen that can also infect humans, or when an alteration occurs in the pathogen’s natural host range that renders the microorganism pathogenic for humans (Klempner and Shapiro 2004). Infectious diseases that occur as a result of CST may lead to pandemics (e.g., primate-to-primate CST: Influenza A virus, HIV, human metapneumovirus, which cause the common cold; nonprimate-to-human CST: SARS, H5N1) possibly due to the immune naivety of the new hosts. Nevertheless, most emerging infectious diseases (EID) are initially considered as transient “spillovers” from a natural animal reservoir and frequently they occur as

“dead-end” infections because effective human-to-human transmission cannot be established (Riedel 2006; Davies and Pedersen 2008).

Humans and nonhuman primates (NHPs) belong to the order *Primates* (Linnaeus, 1758). Although there are many primate families with more than 200 species, the Hominoidea super-family includes only three families: Hylobatidae, Pongidae, and Hominidae. This last family comprises the Gorillinae, Paninae, and Homininae subfamilies that show a genetic difference of only 2 % or less. Moreover, members of the Hominidae subfamily share many morphological, physiological, and ecological features that may have a direct role in the transmission of infectious diseases.

Why do primates share diseases? Although not formally proved, it is generally thought that, due to the very high genetic identity (about 98 %) between NHPs and humans, primate pathogens may easily jump from one to the other. Several studies carried out by the World Conservation Society showed that humans share most of their microbes with primates (rodents and bats come second) and that CST is common. Moreover, studies in closely related bat species found that innate similarities in the immune system defenses favor virus exchanges and the ability to infect new hosts, demonstrating that the most important factor for CST is the species genetic closeness, whereas virus mutations and contact rates are less critical (Wallis and Lee 1999). In zoonotic diseases, NHP-to-human transmissions are abundant, but also human-to-NHP transmission is frequently observed, particularly for viral diseases (Table 1). Therefore, besides pathogen mutations or selection, CST could be considered a major way to support disease/parasite spreading and survival (evolution). More than a step in the evolution of an infectious disease, CST appears to be a sudden event that leads to disease emergence, epidemics and/or pandemics via the introduction of a microorganism into naive human populations that can be efficiently transmitted from person-to-person and consequently each new case will result in multiple new human infections. How does a pathogen step across the species barrier and become capable of efficient transmission? Each germ and host system have their own strategies to persist and spread, as the few examples described below will attest.

2 A Time and a Place for Germ-Primate Affairs

The emergence or reemergence of primate-to-human transmission of a pathogen occurs at a precise time and in a specific environment, and from time to time this local phenomenon will give rise to an “epidemic” and, ultimately, if favorable conditions are present, to an endemic situation in a given territory (i.e., population).

NHPs, humans and germs constitute a biological complex in terms of biodiversity, host genetic plasticity and phenotypes in which environmental factors (temperature, seasons, migrations, ecosystem fragmentation, urbanization, etc.) play a major role in the transmission of pathogens. Therefore, a multidisciplinary approach appears necessary for understanding the complex phenomenon of pathogen transmission

Table 1 Some pathogens that might step across the species barrier between Primates and Humans

Pathogen ^a	Primate host	Human Infection or threat ^b	Transmission ^c
<i>Viruses</i>			
Adenovirus	Chimpanzee	?	P → H
Baboon reovirus	Baboon	?	P → H
Baboon polyoma type 2	Baboon	?	P → H
Callitrichid lymphocrypto v.	Callitrich	?	P → H
Cercopithecine herpes 1	Cercopithecus	+	P → H: direct contact
Ebola	Gorilla, chimpanzee	+	P → H: body fluids
<i>Encephalomyocarditis picorna</i>	NHPs	+	Env → H&P
<i>Herpesvirus simiae</i>	Mac. cynomolgus and <i>M. radiata</i>	+	P → H: bites and aerosol
Marmoset rhabdovirus	Marmoset	?	P → H
Influenza	Monkeys, NHPs	+	H → P → H: direct contact
Hepatitis A	Chimpanzee, patas, woolly monkey, gorilla, Cebus, Aotus, tamarins	+	H → P
Marburg	Vervet	+	P → H
Molluscum contagiosum	Chimpanzee	+	P → H
Monkeypox	Macaca sp.	+	P → H: contact, aerosol
Paramyxovirus, Measles	Apes, marmoset, tamarins, owl	+	H → P
Poliomyelitis	Monkeys	+	H → P
Rabies	Apes	+	P → H
Tana pox	Benign epidermal monkey pox	+	P → H: contact and aerosol
Simian hepatitis G virus	Experimental	+	H → P
Simian Herpes B	Macaca rhesus	+	P → H: bites and aerosol
Simian Immunodeficiency V.	Monkeys and NHPs	+	P → H
<i>Simian parvovirus</i>	Cynomolgus, <i>M. rhesus</i> , macaques	?	P → H
Simian Type D retroviruses	Monkeys	+	P → H
Simian T-lymphotropic virus	Monkeys and NHPs	?	P → H

(continued)

Table 1 (continued)

Pathogen ^a	Primate host	Human Infection or threat ^b	Transmission ^c
<i>Simian rhadinovirus</i> (~HHV8)	Ateles and monkeys	?	P → H
SV40	Monkeys	?	P → H
Yabapox	Macaca, patas, baboon	+	P → H: contact and aerosol
Yellow fever	Monkeys	+	P → H → P: mosquitoes
<i>Bacteria</i>			
Alpha hemolytic streptococci	Laboratory, pet primates	?	
<i>Balantidium coli</i>	Laboratory, pet primates	?	P → H: saliva
<i>Campylobacter jejuni</i>	Laboratory, pet primates	+	P → H: feces
<i>Campylobacter coli</i>	Laboratory, pet primates	+	H → P → H
<i>Enterocytozoon bieneusi</i>	Laboratory, pet primates	?	H → P → H
Enteropathogenic <i>Escherichia coli</i> (EPEC)	Laboratory, pet primates	+	
<i>Haemophilus parainfluenza</i>	Laboratory, pet primates	+	P → H → P
<i>Mycobacterium avium</i>	Laboratory, pet primates	+	P → H: saliva/wound
<i>Mycobacterium kansasii</i> and <i>M. scrofulaceum</i>	Laboratory, pet primates	?	P → H
<i>Mycobacterium bovis</i>	Laboratory, pet primates	+	P → H
<i>Mycobacterium tuberculosis</i>	Rhesus monkeys	+	H → P
<i>Neisseria</i> species	Rhesus monkeys	+	H → P
Pneumocystis jiroveci/carinii	Laboratory, pet primates	+	P → H: saliva/wound
<i>Salmonella typhimurium</i>	Laboratory, pet primates	+	H → P → H
<i>Shigella flexneri</i>	Laboratory, pet primates	+	P → H: fecal/oral route
<i>Shigella sonnei</i>	Laboratory, pet primates	+	P → H: feces
<i>Streptococcus pneumoniae</i>	Laboratory, pet primates	+	P → H: feces
Klebsiella	Laboratory, pet primates	+	P → H: lung or sputum
Pseudomonas	Laboratory, pet primates	+	P → H: fecal/oral route, water
			P → H: fecal/oral route

(continued)

Table 1 (continued)

Pathogen ^a	Primate host	Human Infection or threat ^b	Transmission ^c
<i>Fungi</i>			
<i>Candida albicans</i>	Laboratory, pet primates	+	
<i>Dermatophytus congolensis</i> ,	Aotus, Lagothrix	?	H → P → H
<i>Trichophyton mentagrophytes</i>	All primates	+	P → H
<i>Cryptosporidium parvum</i>	Laboratory, pet primates	+	P → H
<i>Enterocytozoon bieneusi</i>	Laboratory, pet primates	?	P → H: fecal/oral route
Nocardia, coccidiomycetes, cryptococcus	Laboratory, pet primates	+	P → H
<i>Yersinia pseudotuberculosis</i>	Macaca sp.	?	P → H
<i>Protozoan parasites</i>			
<i>Acanthamoeba</i> sp.,	Laboratory, pet primates	+immunodep	H → P
<i>Balamuthia mandrillaris</i>	Laboratory, pet primates	+immunodep	H → P
<i>Balamuthia</i> sp.	Laboratory, pet primates	+	
<i>Blastocystis</i> spp.	Laboratory, pet primates	+	H → P → H
<i>Chilomastix mesnili</i>	Laboratory, pet primates	+	P → H:
<i>Cryptosporidium parvum</i>	Laboratory, pet primates	+	P → H: fecal/oral route
<i>Dientamoeba fragilis</i>	Laboratory, pet primates	+	
<i>Entamoeba histolytica</i> /dispar	Laboratory, pet primates	+	
<i>Entamoeba coli</i>	Laboratory, pet primates	+	P → H
<i>Endolimax nana</i>	Laboratory, pet primates	+	H → P
<i>Entamoeba hartmanni</i> ,	Laboratory, pet primates	+	H → P → H
<i>Giardia duodenalis</i>	Laboratory, pet primates	+	H → P → H: feces
<i>Giardia</i> sp.	Laboratory, pet primates	+	H → P → H
<i>Iodamoeba bueschei</i>	Laboratory, pet primates	+	H → P → H
<i>Isospora</i> sp.	Laboratory, pet primates	+	H → P → H
<i>Naegleria fowleri</i>	Laboratory, pet primates	+	H → P → H
<i>Plasmodium</i> sp. (~20 spp.)	Laboratory, pet primates	+immunodef.	P → H: feces
<i>Helminth parasites</i>	NHPs, Monkeys	+	H → P → H

(continued)

Table 1 (continued)

Pathogen ^a	Primate host	Human Infection or threat ^b	Transmission ^c
<i>Bertiella studeri</i>	Laboratory, pet primates	+	H → P → H
<i>Bertiella mucronata</i>	Laboratory, pet primates	+	H → P → H: anopheline
<i>Hymenolepis nana</i>	Laboratory, pet primates	+	
<i>Oesophagostomum</i> spp.	Laboratory, pet primates	+	
<i>Schistosomia mansoni</i>	Baboon	+	P → H: intermed.host
<i>Schistosomia mekongi</i>	Monkeys	+	P → H: intermed.host
<i>Taenia saginata taiwensis</i>	Monkeys	+	H → P → H
<i>Spirimetra</i> spp.	Monkeys	+	NH → H&P:: larvae
<i>Strongyloides fuelleborni</i>	Laboratory, pet primates	+	P → H
<i>Strongyloides cebus</i>	Laboratory, pet primates	?	P → H
<i>Strongyloides stercoralis</i>	Laboratory, pet primates	+	Undercooked meat
<i>Toxoplasma gondii</i>	Laboratory, pet primates	+	P → H: infected cyclops
<i>Trichuris trichiura</i>	Laboratory, pet primates	+	H → P → H: infective larvae H → P → H: infective larvae H → P → H: infective larvae H → P, indirect H → P, infective larvae

^a Multiple sources Bronson et al. (1972), Renquist and Whitney (1987); Wachtman and Keith (2008), Wolfe et al. (1998), Ruch (1959), Brack (1987)

^b Documented human infection (+), potential threat for humans (?)

^c P → H, H → P → H: = transmission from Primates to Humans or, Humans to Primates to Humans

within and between different primate families. This is in accordance also with the One Health concept that acknowledges the links and therefore the necessity of considering at the same time the health (i.e., diseases) of humans, animals, and of the ecosystem.

2.1 *The Ebola Virus from Africa to Asia*

Ebola virus biodiversity. The Ebola and Marburg viruses are the only members of the *Filoviridae* family and are among the most virulent pathogens for humans and great apes. The five known Ebola virus species are characterized by different geographic locations and case fatality rates and show between 32 and 41 % of sequence differences. The *Reston ebola virus* species (REBOV) was first isolated from Asian cynomolgus monkeys in the Philippines (Jahrling et al. 1990); it is pathogenic for NHPs and apparently nonpathogenic for humans. Recently, REBOV was also isolated from domestic Philippine swine with severe respiratory syndrome (Barrette et al. 2009). *Côte d'Ivoire ebola virus* (CIEBOV) has been associated with a single, nonfatal human infection, in Ivory Coast in 1994, but caused an outbreak in a group of wild chimpanzees in the Taï forest, Côte d'Ivoire (Formenty et al. 1999). *Sudan ebola virus* (SEBOV) has caused four known human outbreaks (three in Sudan and one in Uganda) with a reported case fatality rate of about 50 % (Leroy et al. 2011). The latest species to be discovered, *Bundibugyo ebola virus* (BEBOV), was isolated in Uganda in 2007, where it caused a large human outbreak with 116 confirmed cases and 30 deaths (case fatality rate 26 %) (Towner et al. 2008). Finally, *Zaire ebola virus* (ZEBOV) is the most pathogenic species, with reported case fatality rates up to 90 %. ZEBOV has caused several outbreaks in Central Africa, Democratic Republic of Congo (DRC), Republic of Congo (RC) and Gabon (Leroy et al. 2011).

Origin of the Ebola viruses. Recently, significant advances have been made in our understanding of filovirus ecology. Positivity for anti-ZEBOV antibodies and ZEBOV-specific nucleotide sequences were detected in the liver and spleen of three fruit bat species in Gabon and RC (*Hypsignathus monstrosus*, *Epomops franqueti*, and *Myonycteris torquata*), raising the possibility that they might be reservoirs of ZEBOV (Leroy et al. 2005). Furthermore, a recent study showed that the 2007 Luebo outbreak in DRC was linked to a massive migration of fruit bats, strongly suggesting that humans could be infected directly by bats (Leroy et al. 2009).

The Ebola virus affair. The mechanism of primary transmission of ZEBOV to humans, potentially leading to outbreaks, remains unclear in most cases. However, several outbreaks were clearly linked to the presence of/contact with great ape carcasses. For instance, a Swiss ethnologist became infected by CIEBOV in 1994 while autopsying a chimpanzee. The animal and the ethnologist were found to have been infected by the same strain. Another study conducted in the Taï forest (Côte d'Ivoire) showed that the disappearance of 11 members (26 %) of a group of 43 chimpanzees during November 1994 could have been due to CIEBOV

(Formenty et al. 1999). Similarly, the 1996 Mayibout outbreak in Gabon started among children who had found and butchered a chimpanzee carcass in the forest (Georges et al. 1999). Finally, the Ebola hemorrhagic fever (EHF) outbreaks that occurred in Gabon and RC between 2001 and 2003 were associated with the major outbreaks among chimpanzees and gorillas that have killed thousands of animals during the last decade in parts of Gabon and RC, devastating the local animal populations (Walsh et al. 2003; Leroy et al. 2004a; Bermejo et al. 2006). Primary human transmission has been reported in hunters who became infected after handling animal carcasses found in the forest. Similar sources of infection have been described for the Marburg virus, the other member of the *Filoviridae* family. Indeed, the 1967 outbreak in Marburg and Belgrade was linked to the handling of organs and tissues from vervet monkeys imported from Uganda.

A complex emerging pattern. The chronological and geographic characteristics of the different outbreaks in Gabon and DRC between 1995 and 2003 suggest a drift from north-east Gabon toward DRC. This raises the possibility that gorillas and chimpanzees are succumbing to a single outbreak that has been devastating these animal populations for about 10 years and is spreading along a north-west/south-east axis (Walsh et al. 2005). However, the identification of multiple strains during the 2001–2005 Gabon/RC outbreaks, the diversity of viral sequences found in dead great apes and the recent identification of two phylogenetically divergent lineages suggest independent introductions into great ape and human populations following multiple viral spillovers from a reservoir host (Wittmann et al. 2007). Therefore the great ape outbreaks might be the result of simultaneous, but independent transmission events from the reservoir species. According to this “multi-emergence” hypothesis, Ebola outbreaks in great apes are not due to the propagation of a single infection from one individual to another, but rather to massive, simultaneous infections by the animal reservoir in particular environmental conditions. Indeed, outbreaks always occur at the same time of the year, during the transition period between the dry and rainy season. Human infection occurs secondarily and is generally linked to the handling of animal corpses. Although the idea of multi-emergence makes no reference to a particular time scale, this theory also implicitly assumes that ZEBOV was present in Equatorial Africa long before the first documented outbreak in 1976, as supported by various serological data. For instance, a serologic survey based on 790 samples collected from about 20 primate species in Cameroon, Gabon, and RC over a 15-year period showed that 12.9 % of wild chimpanzees in these countries have Ebola virus-specific IgGs (Leroy et al. 2004b) and that some positive samples largely predated the first human outbreaks in these regions. The results suggest that (i) these animals are in regular contact with the Ebola virus reservoir, (ii) some of them survive the infection, and (iii) Ebola virus has probably been present for a very long time in the forest region of Central African. Ebola virus-specific antibodies were also found in other monkey species (five drills, one baboon, one mandrill and one *Cercopithecus* monkey), suggesting that the Ebola virus circulation may be very complex, involving far more than the simple direct passage from the reservoir to gorillas and chimpanzees.

2.2 *Retroviruses and Primates*

The old family affair with lentiviruses (see for review: Locatelli and Peeters 2012; Sharp and Hahn 2011). Lentiviruses of the *Retroviridae* family infect many mammalian species, including bovines, horses, felines, goats, sheep, and primates. The great majority of lentiviruses are exogenous (i.e., transmitted horizontally), but they can also be integrated in the host genome (one of the main characteristics of retroviruses) and transmitted vertically through the germline, as reported in rabbits (RELK) and lemurs (pSIV), in which the lentivirus became endogenous about 12 and 4 million years ago, respectively (Katzourakis et al. 2007; Gifford et al. 2008; Sharp and Hahn 2011). As stated by Sharp and Hahn (2011) and from the estimated phylogenetic tree by Guindon and Gascuel (2003), such embedded viruses can be considered as “viral fossils” that demonstrate the ancient origin of retroviral infections in vertebrates and provide a direct evidence of the long coevolution of lentiviruses with their hosts. Indeed, although molecular clock calculations based on Simian immunodeficiency virus (SIV) genomic sequences suggest that ancestral SIVs originated only few hundred years ago, the timescale of their evolution appears to be much longer (Holmes 2003). For instance, a study on SIV on Bioko Island, Equatorial Guinea, established that SIV is at least 32,000-year/old (Worobey et al. 2010). Although intraspecific transmission occurs more frequently, interspecific transmissions (i.e., crossing the barrier species) happen as well and they favor two types of SIV evolution: a long-term one, and a more recent diversification, possibly associated with recombination events between different lentiviruses (Souquiere et al. 2001). During both types of evolution, SIV might have jumped the species barrier between humans and NHPs.

The circulation of primate immunodeficiency viruses. Altogether, SIVs seem to have an ancient relationship with their hosts in Africa. Indeed, more than 62 % of the known 73 African primate species harbor a specific SIV. Moreover, CST among African primates has been documented in sympatric species (e.g., CST of SIVagm from African green monkeys to Patas monkeys) (Bibollet-Ruche et al. 2004) along with coinfection and recombination (for instance, SIVmus2 is a recombinant lineage that includes SIVgsn and SIVmus sequences). In addition, exposure to blood or biological products from infected animals (through hunting, bushmeat butchering, bites, and scratches inflicted to humans by NHPs) might be the source of human infection by SIV, simian T cell lymphotropic virus (STLV) or simian foamy virus (SFV).

African chimpanzees and gorillas are both infected by SIVs (SIVcpz and SIVgor, respectively) that have crossed the species barrier at least on four occasions, leading to the emergence of the human immunodeficiency virus type 1 (HIV-1) groups M, N, O, and P (Gao et al. 1999; Plantier et al. 2009). The HIV-2 groups A to H resulted from at least eight independent CSTs of SIVs that infect sooty mangabeys (Hirsch et al. 1989; Hahn et al. 2000; Damond et al. 2004). However, not all CSTs did have the same epidemic outcome.

In only one case (HIV-1 group M) these CSTs gave rise to a pandemic with almost 60 million human infections worldwide. The HIV-1 group M epidemic illustrates the extraordinary social impact and consequences of a single zoonotic transmission. HIV-1 group N appears to be derived from chimpanzee SIV and HIV-1 groups P and O from western lowland gorillas (Locatelli and Peeters 2012). Other retroviruses that infect several NHP species, particularly STLVs and SFV, are also of concern to humans.

Simian T cell lymphotropic viruses STLVs and Human T cell lymphotropic viruses (HTLVs). STLVs (type 1–5) could have been the progenitors of HTLVs (type 1–4) (Mahieux and Gessain 2011) and might have crossed the species barrier on multiple occasions causing HTLV infections that affect between 10 and 20 million people worldwide. However, only 5 % of the HTLV-infected human population develops serious health problems (Gessain 2011). The simian counterparts have been identified only for HTLV-1, HTLV-2, and HTLV-3, but not for the recently discovered HTLV-4 and also, no human counterpart has been found for the Asian STLV-5 from macaques. Unlike the host-specific SIVs, STLVs present phylogenetic geographical clusters, suggesting that multiple CSTs occurred among NHPs and also from NHPs to humans (Locatelli and Peeters 2012).

The simian foamy virus (SFV) is ubiquitous and highly prevalent among NHPs, including New World and Old World monkeys and apes, as well as prosimians. It seems to have coevolved with its hosts for more than 30 million years (Switzer et al. 2005). SFV infects humans more likely through primate bites; however, infected humans do not present any clinical manifestation (Heneine et al. 2003). No human foamy virus has been identified to date.

Human exposure to simian retroviruses appears heterogeneous across the surveyed African countries (Locatelli and Peeters 2012), probably due to the complexity of establishing infection after CTS between NHPs and humans, because the virus has to be “humanized” and, several requirements have to be met following exposure (“first encounter”), such as viral and host molecular characteristics and compatibility, host competency for viral replication and interspecies transmission.

2.3 *Plasmodium Parasites and Primates*

Plasmodium parasites and host biodiversity. Malaria is caused by protozoan parasites that belong mainly to the genus *Plasmodium*. More than 200 *Plasmodium* species have been identified that can infect mammals (more than 50 species), birds, or reptiles. Among mammals, primates are by far the most common intermediate host for *Plasmodium* parasites.

From an evolutionary point of view, primate *Plasmodium* species form a paraphyletic clade (Martinsen et al. 2008) subdivided in two subgenera: the subgenus *Plasmodium* that includes species infecting a large variety of primates in Africa, Asia (catarrhines), and South America (platyrrhines), and the subgenus *Laverania* with species that naturally infect only catarrhines (gorillas, chimpanzees, cercopithecidae

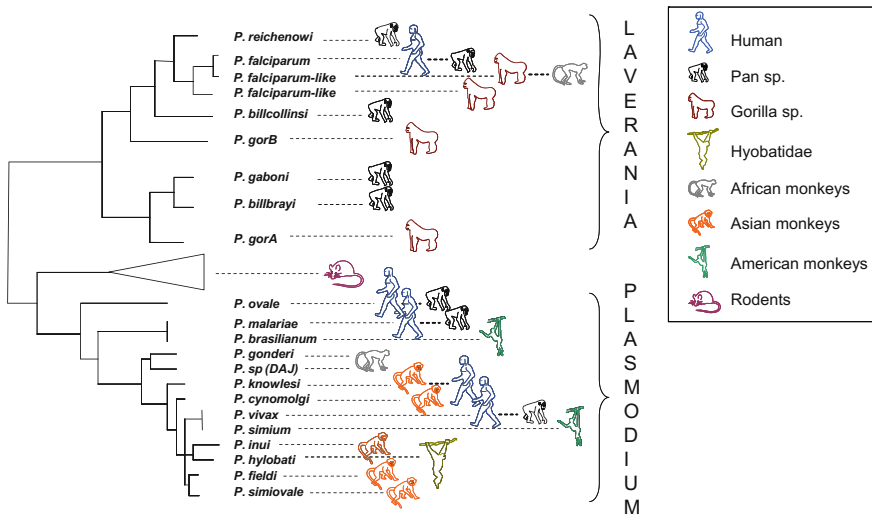


Fig. 1 Schematic representation of the phylogeny of the primate *Plasmodium* with the currently known categories of hosts. Primate *Plasmodium* are subdivided in two subgenus: *Laverania* and *Plasmodium*

and humans). Among these species, five infect humans: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and the most recently identified *P. knowlesi*. As shown in Fig. 1, these five species are only remotely related to each other: four belong to the *Plasmodium* subgenus, but nevertheless constitute divergent lineages, and one is part of the *Laverania* subgenus. This distribution suggests that adaptation to humans has occurred several times independently during the genus history. In addition, the close relationships observed between human parasites and some phylogenetically distant nonhuman primates suggest that some of these species adopted humans as hosts following a lateral transfer. This seems to be the case for the most virulent species of all: *P. falciparum*.

Plasmodium falciparum: the quest for its origin. Currently, *P. falciparum* represents one of the biggest scourges of humanity. Almost half a billion people are infected by this parasite and, despite the medical progress, one million of them still die every year, especially in Sub-Saharan Africa.

The origin of this disease has been the focus of much debate during the past 20 years. Briefly, it was first hypothesized that *P. falciparum* derived from a lateral transfer from birds (Waters et al. 1991, 1993) or rodents, or coevolved with humans (Escalante and Ayala 1994). More recently a jump from chimpanzees (Rich et al. 2009) or bonobos (Krief et al. 2010) to humans (see, Prugnolle et al. 2011b for review) was proposed. Another hypothesis suggested a recent CST from gorillas (Liu et al. 2010) based on the discovery of *P. falciparum*-like pathogens that circulate naturally in wild populations of western gorillas (Liu et al. 2010; Prugnolle et al. 2010).

The NHP origin. The diversity of *Laverania* species infecting great apes in Africa was described for the first time at the beginning of the twentieth century (Coatney et al. 1971). At that time, it was considered that only one sister lineage of *P. falciparum* existed: *P. reichenowi*, a chimpanzee parasite. This notion persisted until the very recent development of non-invasive methods (Prugnolle et al. 2010) and the use of molecular tools that allowed a complete reevaluation of the species diversity of African ape *Plasmodium* parasites (Kaiser et al. 2010; Ollomo et al. 2009; Rich et al. 2009; Duval et al. 2010; Krief et al. 2010; Liu et al. 2010; Prugnolle et al. 2010). This led to the discovery that great apes in Africa are the hosts of a much larger number of *Laverania* species than previously thought. In particular, these studies identified parasites that are very closely related to *P. falciparum* and that infect only gorillas among all the wild populations of great apes (Liu et al. 2010; Prugnolle et al. 2010). Other *P. falciparum*-like parasites were also identified in captive chimpanzees (Duval et al. 2010) and bonobos (Krief et al. 2010), but it was rapidly demonstrated that these parasites resulted from human-to-primate direct transfers.

The discovery of the culprit. The discovery, in gorillas, of parasites that are genetically very close to *P. falciparum* led to the hypothesis that gorillas could be the source of the human malaria parasite *P. falciparum* (Liu et al. 2010). The finding that the *P. falciparum*-like parasites from gorillas display a large mitochondrial genetic diversity compared to the human *P. falciparum* isolates, which form a monophyletic clade within the gorilla diversity, suggests that *P. falciparum* appeared in humans following one single and recent CST event from gorillas (Liu et al. 2010).

Is this the final word on the origin of *P. falciparum* in humans? Nothing is less sure. Indeed, alternative scenarios could explain the genetic diversity profiles of *P. falciparum* from humans and gorillas (e.g., multiple human to gorilla host switches during the history of the lineage) (Prugnolle et al. 2011b). Moreover, it was recently discovered that *P. falciparum*-like pathogens (the ones that infect gorillas in Central Africa) can also naturally infect monkeys in Africa (Prugnolle et al. 2011c). This means that there might be other sylvatic reservoirs of *P. falciparum*-like pathogens and all of them are as likely candidate sources of human *P. falciparum* as the western gorillas (Prugnolle et al. 2011a).

Other human Plasmodium species. The case of *P. falciparum* is not isolated and the tight links between human and NHP *Plasmodium* parasites are numerous. Several examples of transfer from primates to humans or vice versa are now well documented. The case of *P. knowlesi* is certainly the clearest. It was considered to be exclusively a parasite of Asian macaques until it was recently identified as the cause of almost 70 % of human cases of malaria in some areas of South-East Asia. It is now considered to be the “fifth human malaria parasite” (White 2008). It is still unclear whether *P. knowlesi* infections are only due to primate-to-human CST or whether human-to-human transmission may occur as well; however, since 2004, reports on the incidence of this parasite among humans in various countries in South East Asia have been increasing. *P. vivax* has a similar history, but possibly much older. This parasite belongs to a group of *Plasmodium* species that infect

monkeys in Asia (see Fig. 1) and it might have emerged in humans following a transfer from macaques (Mu et al. 2005). Some South American *Plasmodium* species that infect New World monkeys are also very closely related to human *Plasmodium* parasites. For instance, *P. simium* is very close genetically to *P. vivax* and the closest relative of *P. brasilianum* is *P. malariae* (Tazi and Ayala 2010). If the hypothesis of an Asian origin of *P. vivax* is true, the close phylogenetic relationship of *P. simium* with *P. vivax* could be interpreted as the result of an anthroponosis (i.e., host switching from humans to other animals). Concerning *P. brasilianum*, while its close relationship with *P. malariae* is suggestive of a host switch, the question of whether platyrrhines acquired it from or transferred it to humans remains unanswered (Tazi and Ayala 2010).

The risk of emergence of new Plasmodium species in humans. Should we fear the emergence of new zoonoses due to primate *Plasmodium* species? The answer is very likely yes. Human populations are growing very rapidly and they are progressively colonizing areas where NHPs live, thus increasing the possibility that new species of *Plasmodium* might switch to humans. This is all the more likely as some of these NHP pathogens are known to be able to infect humans. For instance, *P. cynomolgi* and *P. inui*, two *Plasmodium* species that infect Asian macaques, have been implicated in symptomatic malaria in humans following experimental or accidental infection (Coatney et al. 1971).

3 The Future of Pathogen Circulation in a Changing world

Environment. Humans, NHPs and their microorganisms appear as a pathogenic complex that varies according to the population territories (environments) and their domain overlaps (not very clear). At any time and space, several pathogens are circulating among human and NHP populations, coinfecting them, spilling over from a species to another and expanding their endemic pattern.

Cross-Species Transmission appears as one of the major factor of evolution at the population level. A successful species jump is achieved when the pathogen becomes transmissible between individuals of the new host population. A successfully masterminded epidemic and the endemic maintenance of the pathogen in the new population require several human and non-human environmental factors (e.g., host receptiveness, proximity, population density, multiple passages, behavior, etc.).

Zoonotic Risk. Given the increasing exposure of humans to NHP pathogens through hunting and bushmeat butchering, it is likely that simian viruses are actually and constantly transmitted to human populations often without “success” and that only exceptionally they will give rise to EIDs. Germ and host biodiversity appear to be the main EID and CST drivers by favoring the fittest “first encounter” between a parasite and a new host. Host, parasite and environmental factors are all required for the optimal success of pathogen transmission; understanding the complexity of their interactions will lead to understanding infectious disease emergence and fulfill the One Health mission.

Sizing the risk. Given that monkeys and apes often share parasites with humans, understanding the ecology of infectious diseases in NHPs is of paramount importance. The zoonotic risk also depends on how environmental changes may promote contacts between primates and increase the possibility of sharing infectious diseases that are detrimental to humans and/or NHPs. Indeed, 244 primate species have a genome that is genetically related to the human genome and could thus exchange parasites. The “first encounter” of NHPs, humans and germs is driven by behavioral and environmental factors. NHP-human transmission may occur both in domestic environments (pets, laboratory animals) and in the wild (Wolfe et al. 2007). Protected areas, ecotourism, exotic pets, and animal farming may thus favor cross-species transmission, leading to pathogen emergence and future plagues.

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