Phylogeny of human malaria parasites and some related parasites of nonhuman primates, and time chart of events relating to their evolution.


Malaria
Changes in continental landmasses, climate and the distributions of primates and their malaria parasites in the Old World from the Eocene to the late Pleistocene.

Key:
- **Black cross-hatching**: arid and desert regions;
- **Black dots**: regions of permafrost;
- **Blue**: ice sheets;
- **Green**: regions of temperate climate;
- **Pink**: regions of warm and humid climate;
- **Red triangles and arrows**: general location and direction of change in the distributions of primates.

Global dispersals of *Plasmodium vivax* malaria from the time of the Ice Ages

Blue arrows represent postulated dispersals of a *Plasmodium vivax* stock isolated in human populations in sub-Saharan Africa until after the beginning of the present interglacial period, 18000 years ago.

Red arrows represent the dispersals of a stock of *P. vivax* that might have become trapped in the Mediterranean Ice Age refuge since before the beginning of the last Ice Age.

Source:

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**Phylogeny of non human primate malaria parasites.**

- The earliest primates probably carried the ancestors of present-day malaria parasites in the Lower Tertiary period.
- The putative ancestor of present-day primate malaria parasites is *Hepatocystis*, an ubiquitous parasite of African monkeys and apes, a well-adapted, rather benign parasite, producing only gametocytes in the circulation.
- The malaria parasites of New World monkeys, however, are thought to have come from Europe and Africa during the slave trade (little evidence of malaria in the pre-Columbian New World).
- The two species of monkey malaria in the New World, *P. brasiliannum* and *P. simium*, are closely related molecularly to the human malaria parasites, *P. malariae* and *P. vivax*.

(Million years ago)
Malaria Infection
Epidemiology

*P. vivax*, *P. simium* – Humans, New World monkeys
*P. cynomolgi, P. knowlesi* – Non-Human Primates, South Asia
*P. schwetzi, P. gonderi* – Apes, monkeys Sub-Saharan Africa

The life cycle includes an obligate sojourn in an *Anopheles* mosquito vector where sexual reproduction takes place. While taking a blood meal, the female Anopheline injects sporozoites, which go directly to the liver. Hepatic stages include schizonts that develop to release merozoites, which then invade red blood cells. Asexual stages seen in blood films are young trophozoites (often called ring forms), mature trophozoites, and the dividing schizonts that yield the merozoites for a new generation. Sexual stages in the blood are the microgametocytes (male) and macrogametocytes (female).
Some species of *Plasmodium* infecting primates (*P. cynomolgi, P. simiovale, P. fieldi*) also produce latent hepatic stages (hypnozoites) which are responsible for malaria relapse.

Relapse is very specifically defined in malaria as a recurrence of parasites in the peripheral blood, after adequate blood schizonticidal therapy, and results from the re-invasion of the peripheral blood by merozoites, produced by the latent liver stages.
Malaria in primates.

- Most primate malaria parasites exhibit tertian periodicity, completing one asexual cycle every 48 hours.

- Exceptions are *P. knowlesi* in Old World monkeys which has a quotidian or 24 hour cycle, as well as *P. inui* and *P. brasilianum* which have a quartan or 72 hour cycle.

Malaria in primates.

- Most primate malarias are subclinical, unless the animal is immunosuppressed or splenectomized.
- Experimental infections of rhesus macaques with *P. knowlesi*, *P. coatneyi*, and less often *P. cynomolgi*, may be characterized by jaundice, anorexia, listlessness, fever, anemia and splenomegaly in spleen-intact animals.
- Clinical signs of chills and fever are in response to toxins (*Plasmodium* GPI) exposed during the release of merozoites from the red cell.
- Pregnant animals may experience more severe anemia, which will have an impact on the health of the fetus.

Malaria icterus in a rhesus macaque following an experimental infection with *Plasmodium cynomolgi*. (Photo courtesy G. Baskin)
Malaria in primates: Zoonotic aspect.

• In general, human malaria caused by plasmodia of simian origin resembles a mild and benign infection caused by human plasmodia. The disease is of short duration, parasitemia are low and relapses are rare.

• Usually cycle of transmission of human malaria and NHP malaria are independent, (since the vectors of human plasmodia feed at ground level, while those of simian plasmodia feed at treetops).

• Man is very rarely infected by nonhuman primates malaria. Only three human infections acquired under natural field conditions are known; two cases caused by *P. knowlesi* in Malaysia and one by *P. simium* in Brazil. *P. cynomolgi*: spontaneous infections in man following accidental laboratory exposure, as a result of bites by infected anopheline mosquitoes. *P. knowlesi* has been transmitted from monkey to man by infected mosquitoes, and from man to monkey.

Malaria Infection

Diagnostics

Diagnosis of malaria is best accomplished with a thick and thin blood smear. The thick smear is more sensitive (20 parasites/ml) while the thin smear is used to confirm morphology.

Other blood stains (Field's, Quickstain) are less than satisfactory, although Wright's stain may be used.

Blood samples can be taken by earstick or tailstick using disposable lancets. It is helpful to shave the tip of the tail or ear before taking a drop of blood in a capillary tube.

The thin smear should be fixed as soon as it is dry; the thick smear must be allowed to dry thoroughly before staining.
**Malaria Infection**

**Diagnostics**

Dipstick tests for circulating antigen (hrp2, ldh) may give positive results for *P. cynomolgi*, *P. coatneyi*, and *P. knowlesi*. Other non-human primate malarias have not been tested.

PCR is not generally useful in a clinical setting unless one is interested in specific molecular sequences. It is not more sensitive than a well-made thick smear and available primer sequences are limited to *Plasmodium* species used in malaria model work, e.g. *P. cynomolgi*, *P. knowlesi*, and *P. coatneyi*.

**Malaria Infection**

**Treatment**

Most primate malarias can be treated with **Chloroquine** at a dosage of 7 mg/kg base for 5 days (total = 35 mg/kg) as an IM injection or per os via nasogastric tube. The bitter taste of 4-aminoquinolines precludes putting it in food. **Chloroquine** is effective against the circulating trophozoite (feeding) stage of the parasite but will not affect hepatic stages nor circulating gametocytes.

**Mefloquine** can be used, especially if an isolate is suspected to be chloroquine-resistant, at a dose of 20 mg/kg, one dose, per os.

Hepatic stages of *Plasmodium* require treatment with an 8-aminoquinoline (primaquine) at a dose of 3 mg base/kg body weight per os for 7 days. This may be necessary in sporozoite-induced (i.e. natural) infections with *P. cynomolgi*, *P. simiovale* and *P. fieldi* where malarial relapse is a consideration.
Chagas' disease (American trypanosomiasis) is a major health problem in areas of Latin America.

The causative agent is the hemoflagellate, *Trypanosoma cruzi*, whose vertebrate hosts, in addition to man, includes several genera of neotropical nonhuman primates. Opossums are the principal sylvatic reservoir.

Triatomid bugs act as intermediate hosts, and infection may be acquired from their bites or feces, or by ingesting them.
Trypanosoma cruzi Infection

In monkeys, clinical signs are usually very discrete and parasitemia are usually low. Latent infections in monkeys that are stressed may produce effects. Lesions are usually incidental finding at necropsy and include foci of *Trypanosoma* in the heart, liver, spleen, brain and intestine. Focal infiltration of monocytes was also seen in the livers of tamarins with heavy trypanosomal infections.

Although *Trypanosoma cruzi* is most commonly spread between monkeys in the wild by reduviid bugs, this infection can also be propagated in open monkey colonies by trauma, blood-to-blood exposure, saliva, sexual activity and transplacental transmission.

Trypanosoma cruzi Infection

• In humans, a local lesion (chagoma, palpebral edema) can appear at the site of inoculation.

• The acute phase is usually asymptomatic, but can present with manifestations that include fever, anorexia, lymphadenopathy, mild hepatosplenomegaly, and myocarditis. Most acute cases resolve over a period of 2 to 3 months into an asymptomatic chronic stage.

• The symptomatic chronic stage may not occur for years or even decades after initial infection. Its manifestations include cardiomyopathy, pathologies of the digestive tract such as megaesophagus and megacolon; and weight loss. Chronic Chagas disease and its complications can be fatal.
**Trypanosoma cruzi Infection**

• A study conducted in squirrel monkeys from the Brazilian Amazon showed that 68% (112/165) were positive for trypanosomes of four different species (*T. rangeli*, *T. minasense*, *T. saimiri* and *T. cruzi*). (Ziccardi and Lourenco-de-Oliveira, 1997).

• More recently, Anti-*T. cruzi* antibodies were observed (by IFA) in 40 monkeys (26.5%) in a breeding in captivity program of neotropical primates for subsequent reintroduction in nature at the Primatology Center of Rio de Janeiro (CPRJ) (Lisboa et al., 2004). Mini-exon gene analysis genotyped all isolates as *T. cruzi* II, which is associated with human disease in Brazil. A wild primate unit such as CPRJ, located inside the forest and near human dwellings and with *T. cruzi* II infected animals, deserves a careful surveillance in order to prevent expansion of the infection.

**Leishmania Infection**

*Leishmania brasiliensis* was isolated from a wild *Saguinus geoffroyi* in Panama. There were no lesions or clinical signs.

If any, the role of monkeys in the transmission of leishmaniasis must be very limited, as they play a marginal role in the life cycles of the American *leishmania* species.

NHP have however been used as animal models for human infection and are susceptible to experimental infection.
Toxoplasma Infection

Toxoplasmosis is a common infection in many mammal species, including man and nonhuman primates.

In nonhuman primates, New World primates are more often infected, but the infection can also affect Old World monkeys, apes and prosimians. This may reflect the feeding behavior of the species affected. New World monkeys have generally much higher protein requirements than Old World species and are known to catch insects, birds and, at least in captivity, small rodents. Baboons, macaques and chimpanzees prey occasionally on other animals or are apt to cannibalism.

Toxoplasma Infection

In nonhuman primates, the symptoms in acute infections consist of fever and anorexia, or depression. Involvement of the respiratory tract is indicated by quick breathing or frictious sounds. Vomitus and intermittent diarrhea occur in the digestive form.

The most common lesions are acute focal pneumonia, hydropericard, or focal necrosis of various organs, especially the liver. Some authors have concluded that Old world monkeys are more resistant than New World monkeys, and that resistance appears to be absent in Callitrichids. Extreme susceptibility of the latter group could account for failure to find seropositive animals in nature.
Toxoplasma Infection

In nonhuman primates, the symptoms in acute infections consist of fever and anorexia, or depression. Involvement of the respiratory tract is indicated by quick breathing or frictious sounds. Vomitus and intermitent diarrhea occur in the digestive form.

Epiphano et al. (2003) reported on the pathology of toxoplasmosis in captive new world primates. The most common clinical findings were malaise (40.6%), dyspnoea (18.7%), hypothermia (15.6%) and a serosanguinous or foamy nasal discharge (12.5%). The most common post-mortem findings were pulmonary congestion (78.8%), pulmonary oedema (75.8%), splenomegaly (57.6%) and mesenteric lymphadenitis (54.6%). The most common histopathological findings were multifocal necrotic hepatitis (97%), lymphadenitis (95.4%), interstitial pneumonia (90.3%) and necrotic splenitis (71.4%).

Toxoplasma Infection

Cunningham et al. (1992), reported a major outbreak in a colony of squirrel monkeys where 30% of the monkeys died of acute infection. In that outbreak which occurred in the spring of 1989 at the London Zoo, the source of infection was not found, but suspicion was consumption of possibly infected horse meat.

In Japan, Asai et al. found a low prevalence of Toxoplasma antibody in 443 breeding monkeys, as only 16 (3.6%) of the monkeys were positive. Similarly, Inoue (1997) reported an outbreak of acute toxoplasmosis in caged squirrel monkeys (Saimiri sciureus). In an experiment, Furuta et al. (2001) were able to show that transmission of T. gondii from infected monkeys to cagemates occurred easily. As tachyzoites were recovered from the broncho-alveolar lavages of the 3 T. gondii-inoculated monkeys, they suggested that aerosol infection plays an important role for transmission of infection in colonies of squirrel monkeys.
Mycotic Zoonoses

Superficial Mycoses:

Black Piedra, caused by *Piedraia hortae*, an Ascomycotina, forms hard, gritty nodules around the hairs, which gave the condition its name (piedra=stone in Spanish).

It has been reported only in tropical and subtropical areas (Africa, Asia, Americas), in man and chimpanzees, marmosets and Saimiri.

In non-human primates, the lesions are found particularly in the ano-genital area. In humans, it affects mainly the scalp hair. It is certainly a saprophyte in nature, probably in soil. Man to man or animal to man transmission is not known.

Mycotic Zoonoses

Cutaneous Mycoses:

*Trychophyton Spp* and *Microsporum Spp* are zoonotic mycoses that can be transmitted from and to monkeys. *Trychophyton mentagrophytes* induce ringworm or tinea in man and several species of nonhuman primates: macaques, cercopithecus.

Transmission of *T. mentagrophytes* from monkey to man has been established in at least two cases. In rhesus monkeys, alopecia, scaly erythematous patches were observed. Lesions are mainly observed on the head, but widespread infection has also been reported.
Mycotic Zoonoses

Cutaneous Mycoses:

Other agents of ringworm in monkeys are *Trichophyton rubrum*, agent of tinea pedum or onychomycosis in man (found in chimpanzees), and *T. simii*. Treatment of choice is oral griseofulvin (microsize 125 to 150 mg orally with mashed feed). The animal(s) should be isolated during the treatment. *Microsporum canis*, is the principal agent of canine and feline ringworm. Nonhuman primate infection has been reported in rhesus monkey, *Ateles* and hominoid primates. Transmission of *M. canis* from non-human primates to man, usually caretakers, has been reported in several instances.

Mycotic Zoonoses

Systemic mycoses: Candidiasis

In nonhuman primates: No host-species preferences, although a higher incidence in New World species has been suggested.

The incidence of *Candida albicans* isolation from the throat of imported *Saguinus* was 30% and 2% from acclimated tamarins. Infection has been reported from various species of nonhuman primates, hominoids or lower primates, but it is usually secondary to nutritional deficiency, other disease, or extensive antibiotic treatment. *C. albicans* is an inhabitant of the upper alimentary tract and of the lower female genital tract. The yeasts become infectious after structural changes of the mucous membranes (gestation); after damage of the competitive bacteria (antibiotic treatment) or immunosuppression.
**Mycotic Zoonoses**

**Systemic mycoses:**
In nonhuman primates, candidiasis is mostly a disease of the upper digestive tract appearing as whitish streaks and plaques or even ulcers of the tongue or other oral mucous membranes. These lesions may be associated with diarrhea, dysphagia or even respiratory difficulty.

Man is susceptible to the infection; however, it usually requires a favorable moist environment or reduced defenses caused by another disease.

Treatment is based on the use of Amphotericin B. Ketoconazole has been found effective in the therapy of mucocutaneous candidiasis.