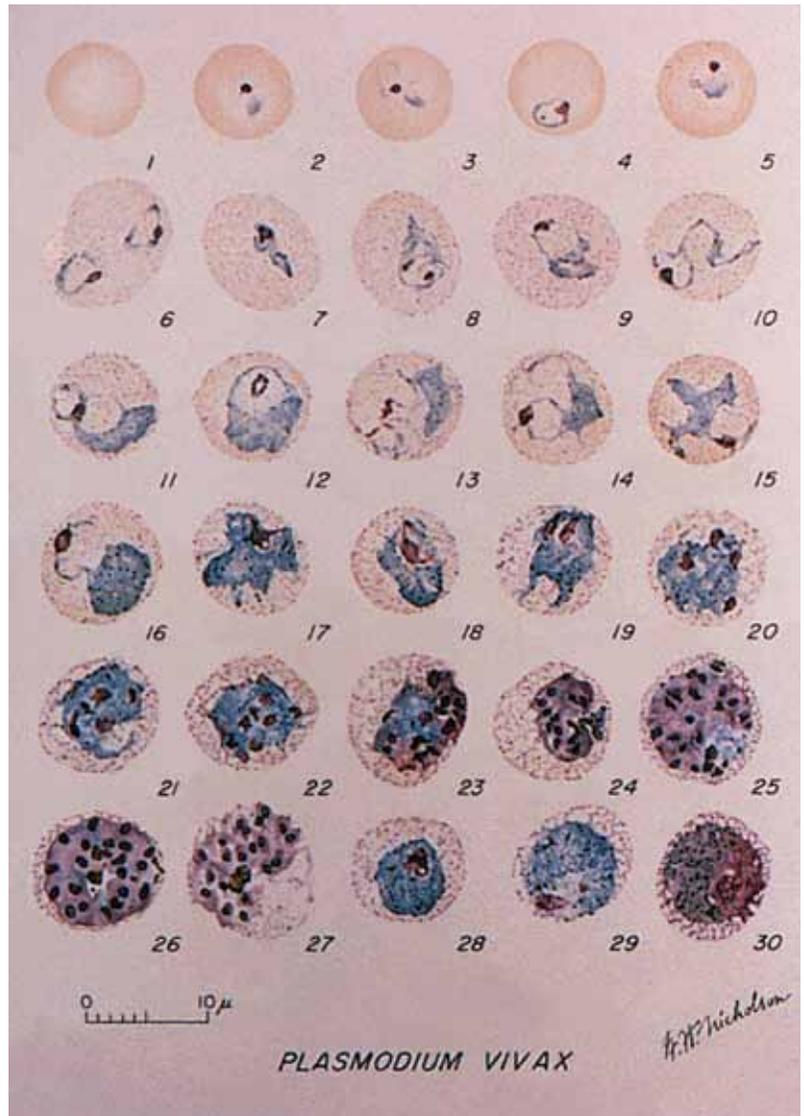


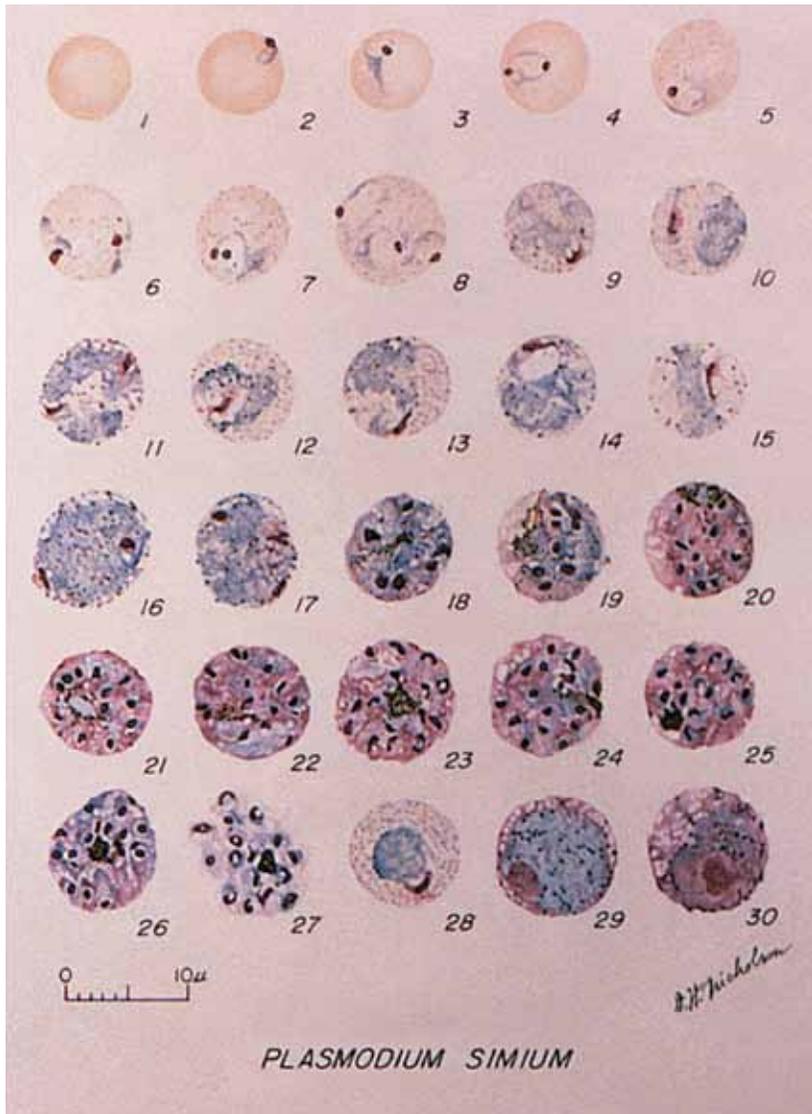
A Fiocruz team suggests a sixth form of malaria that is transmitted by mosquitoes infected after biting wild primates in the Atlantic Forest

Carlos Fioravanti | PUBLISHED IN DECEMBER 2017



# FROM MONKEYS TO PEOPLE

In 1966, Leônidas Deane (1914–1993), a parasitologist from Pará State who at that time was a professor at the University of São Paulo Medical School (FMUSP), described the first known case of human malaria caused by the protozoan *Plasmodium simium*. Previously, this parasite species was thought to cause the disease only in monkeys. The protozoan was found in the blood of a park ranger who collected mosquitoes for researchers from the forest canopy at the Horto Florestal Park in the city of São Paulo, which is a wild area in which no case of malaria had been previously recorded. The possibility that mosquitoes that had bitten infected monkeys could transmit this form of malaria to people



*Plasmodium vivax* in different stages of development in human red blood cells (left) and *P. simium* in monkey red blood cells (right). The first cell in each image is not infected

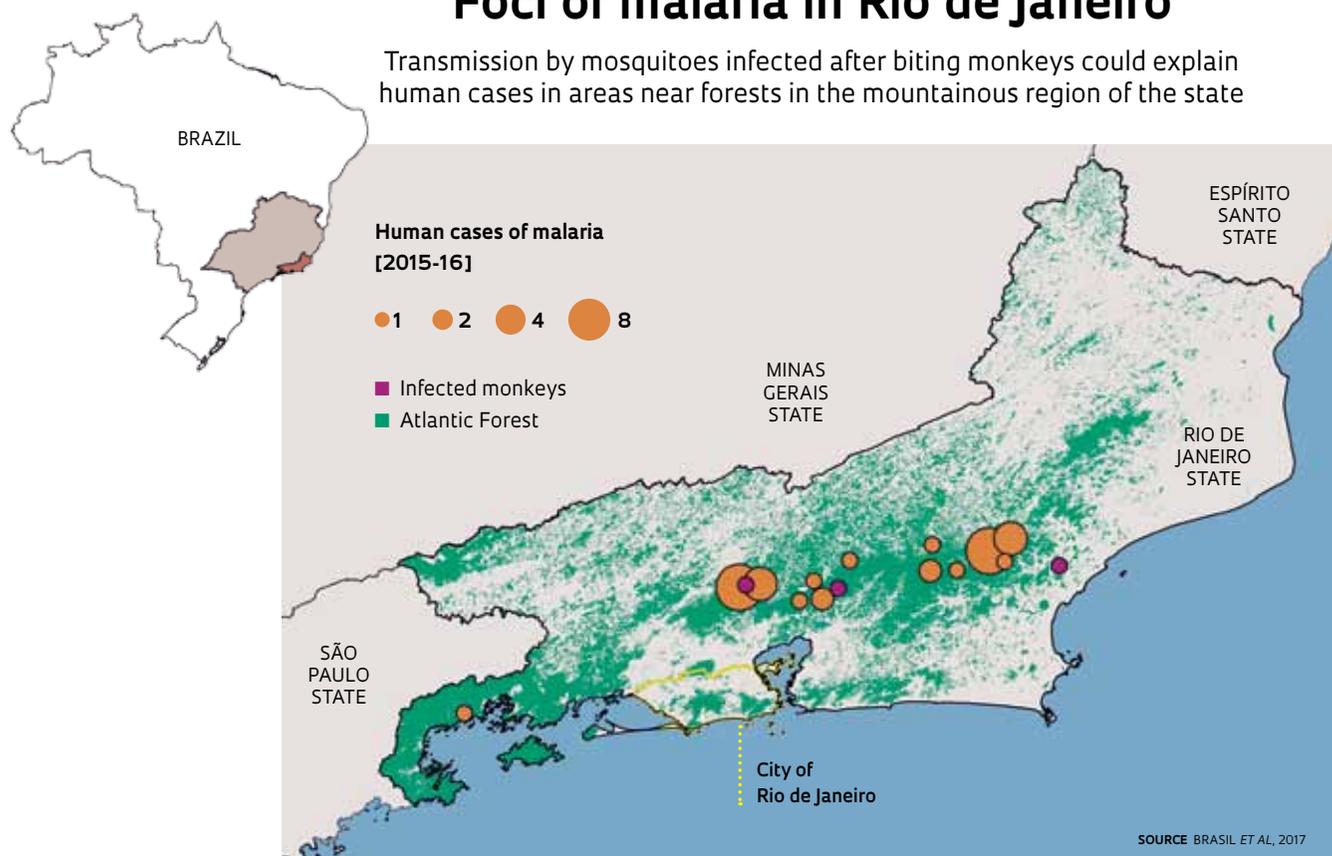
could not be demonstrated at the time when the case appeared. Half a century later, a team from the Oswaldo Cruz Foundation (Fiocruz) returned to Deane's hypothesis and proposed a sixth form of human malaria that was transmitted by mosquitoes infected with *P. simium* after biting contaminated monkeys. This hypothesis has not been confirmed by other studies and recognized by international bodies.

Malaria is transmitted to humans by mosquitoes of genus *Anopheles* contaminated with infectious agents—protozoa of genus *Plasmodium*. The forms of malaria are differentiated by microscopic identification of *Plasmodium* species that multiply in red blood cells. Although the

initial symptoms are similar, including fever, chills, headache, and body aches, progression of the disease depends on its causative agent. For instance, *P. vivax* causes a milder form of malaria, whereas *P. falciparum* infection is more severe (see the table on page 13). One form (caused by *P. knowlesi*) was described in 1965 in Malaysia as the first type of malaria transmitted to humans by mosquitoes infected after biting monkeys; this form is a zoonotic disease involving animals, which function as reservoirs of the infectious agent. *P. knowlesi* was described in 1932 in monkey blood and is easily confused with *P. malariae* and *P. falciparum*. This variant is responsible for a growing number of cases in Malaysia (703

# Foci of malaria in Rio de Janeiro

Transmission by mosquitoes infected after biting monkeys could explain human cases in areas near forests in the mountainous region of the state



in 2011 and 996 in 2013), Thailand, Indonesia, Vietnam, and the Philippines.

The conclusion that monkeys can serve as a reservoir for the protozoa that cause malaria in Brazil was reached after analysis of blood samples from three animals and 28 residents in the mountain region of Rio de Janeiro. “We initially believed they were cases of malaria caused by *P. vivax*, the most common form in Brazil and in the region,” says parasitologist Cláudio Tadeu Daniel-Ribeiro, a Fiocruz researcher in Rio de Janeiro. “Since the symptoms were slightly different, we considered the possibility that it might be the monkey malaria described by Deane.”

*P. vivax* and *P. simium* are very similar in microscopic blood tests. The Fiocruz team distinguished the two types by identifying two different stretches of the mitochondrial DNA from each species and considered the possibility that *P. simium* infection could explain outbreaks in Rio de Janeiro’s Atlantic Forest regions. The researchers identified *P. simium* in 28 of the 49 autochthonous (local) cases of malaria recorded in the region in 2015 and 2016. This work was performed by Fiocruz parasitologist Patrícia Brasil and described in an October article published in *Lancet Global Health* warning of the risk of malaria in areas far from the Amazon, which accounted for 99% of

the 131,000 cases recorded from January to September 2017 according to the Brazilian Ministry of Health. The World Health Organization registered 214 million cases of malaria and 438,000 deaths from the disease in 95 countries in 2015.

**A** Fiocruz team in Minas Gerais state also used molecular analysis to identify *P. simium* in nine of a group of 65 brown howler monkeys (*Alouatta guaririba*) and robust capuchin monkeys (*Sapajus* spp.) living in captivity or in areas of the Atlantic Forest in the city of Indaial, Santa Catarina State, as reported in a 2014 study published in *Memórias do Instituto Oswaldo Cruz*. The miquiqui (*Brachyteles* spp.) is another primate species that can harbor this parasite; the protozoan was identified in 1951 in a monkey from a forest near the city of São Paulo and described for the first time by the parasitologist Flávio Oliveira Ribeiro da Fonseca (1900–1963), who was a native of Rio de Janeiro State and professor at FM-USP. *P. simium* has also been found in the blood of monkeys in the states of São Paulo, Espírito Santo, and Paraná according to biologist Cristiana Ferreira Alves de Brito, who is a researcher at Fiocruz in Belo Horizonte.

“Malaria in humans outside of the Amazon region is much more lethal, because doctors in

# Subtle differences

Malaria is transmitted by mosquitoes; the forms of malaria vary according to the protozoan species that causes the disease

## **PLASMODIUM VIVAX**

Responsible for 90% of cases in Brazil, causes bouts of fever every two days. The fatality rate is low. Dormant forms of the parasite in the liver can cause relapse and are responsible for up to 40% of the malaria crises recorded in the country

## **PLASMODIUM MALARIAE**

Accounts for less than 1% of the total number of cases registered in Brazil, causes fever every 72 hours, which is generally lower than the fever caused by *P. vivax*. May lead to kidney complications

## **PLASMODIUM OVALE**

This mild form of the disease is common in Africa and is not found in Brazil. Relapses may occur after treatment

## **PLASMODIUM FALCIPARUM**

This protozoan is the most common species worldwide, is responsible for approximately 10% of the cases in Brazil and is very deadly. Causes the most serious form of malaria, with intense fever every two days and a risk of brain complications

## **PLASMODIUM KNOWLESI**

This species is not found in Brazil but is responsible for most cases in Malaysia. Fevers appear every day. Severe and lethal disease

## **PLASMODIUM SIMIUM**

Species restricted to the Atlantic Forest in the south and southeast of Brazil. In humans, it is thought to cause symptoms similar to *P. vivax*, but this association has not been proven



SOURCE: FIOCRUZ

cities in the south and southeast of the country do not suspect that the high fever and anemia could be symptoms of malaria,” says Brito. “We need to warn doctors and health centers to make the correct diagnosis, because the treatment is efficient.” In November 2010, one traveler from Nigeria and another from the Ivory Coast died of malaria in São Paulo after seeking care in hospitals where doctors did not diagnose the disease

(see Pesquisa FAPESP, issue No. 186). The São Paulo State Center for Epidemiological Surveillance registered eight autochthonous cases of malaria in humans in 2016 and five as of October 2017, mostly in coastal cities near forested areas.

“Because it is difficult for physicians outside the Amazon region to recognize the disease, the description of malaria cases in Rio de Janeiro as a zoonotic disease is a major challenge for control of this disease,” says biologist Silvia Di Santi, a researcher at the Endemic Diseases Oversight Office (SUCEN) and the Institute of Tropical Medicine at FM-USP. “To better understand this situation, it is essential to broaden the areas of study in regions with the same epidemiological profile and describe the complete transmission cycle with mosquitoes, monkeys, and infected humans.”

The cases of malaria transmitted in areas of the Atlantic Forest along the coast are a benign form of the disease according to Di Santi. Inhabitants of the mountainous region of Rio de Janeiro State infected with *P. simium* exhibit similar but milder symptoms than those caused by *P. vivax* and respond to treatment with a combination of chloroquine and primaquine. Two patients who were unable to take primaquine received only chloroquine and had not relapsed as of 18 months later. According to Ribeiro, the fact that malaria did not reappear in these people is an indication that *P. simium*, unlike *P. vivax*, cannot maintain dormant forms of the parasite in the liver, which are usually eliminated by primaquine.

According to Ribeiro, the infection could be caused by *P. simium* or *P. vivax* that adapted to the monkey and reached humans via mosquitoes, adding, “We will only know when we have sequenced their complete genomes.” There is no expert consensus regarding whether *P. vivax* and *P. simium* are even different species or variations of the same species. In a 2005 article in PNAS, researchers from the University of California at Irvine argued that at least two transfers of *P. vivax* from monkeys to humans or vice versa may have occurred over the past several thousand years. “In Africa,” says Brito, “*vivax* and *falciparum* came from monkeys to humans.” ■

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