Malaria Parasite Transfer Among Human and Wild Primates

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2013

Zoonoses and Emergence of New Infectious Diseases:
Biology Meets Anthropology
Collège de France
Paris

Malaria

- Very ancient vector-borne (mosquito) disease caused by *Plasmodium* spp. parasites
- Malaria documented in approximately 150 species of mammals, birds, and reptiles
- Primates are particularly vulnerable
- Documented in 60+ primate species
- Documented in at least 40 species of New World monkeys
- Extensive evolutionary history of “host-switching” of plasmodia among anthropoid primates[1] (i.e., humans, apes, monkeys)

1. Cormier (2011)

Four Plasmodia Responsible for Human Malaria

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium malaraiae*
- *Plasmodium ovale*

All are vector-borne diseases transmitted by anopheline mosquitoes and causing symptoms by plasmodial invasion of red blood cells during life cycle, creating symptoms of cyclical fevers

False Dichotomy

- Distinction between “human” and “nonhuman” malaria inappropriate
- The four types of plasmodia that cause human malaria are far more closely related to wild primate malarias than they are to each other
- Long historical and evolutionary history of “host-switching” among the primate malarias

*note: limiting to anthropoid primates (monkeys, apes, humans); prosimian malaria plasmodia currently little studied

Falciparum Type
"African Ape Malaria"

Humans likely acquired in host-switch from gorillas
(Liu et al. 2010)

- *P. falciparum*
  - *Gorilla gorilla* (western)
  - *Homo sapiens*
  - *Pan troglodytes*
- *P. cf. falciparum*
  - *Pan paniscus*
- *P. reichenowi*
  - *Gorilla gorilla* s.l.
  - *Pan troglodytes*
- *P. billrayi* sp. n.
  - *Pan troglodytes*
- *P. billcollensi* sp. n.
  - *Pan troglodytes*
- *P. GorA* sp. n.
  - *Gorilla gorilla* (western)
- *P. GorB* sp. n.
  - *Gorilla gorilla* (western)

Vivax Type "Macaque Malaria"

P. vivax: humans and chimpanzees
P. knowlesi: 3 macaque spp., one leaf monkey sp.; some consider a fifth human malaria

Asia

- *P. coatneyi:* 2 macaque spp.
- *P. cynomolgi*: 6 macaque spp., 2 leaf monkey spp.
- *P. fieldi*: 2 macaque spp.
- *P. fragile*: 2 macaque spp.
- *P. inui:* 7 macaque sp., 3 leaf monkey spp.
- *P. simiovale*: one macaque sp.
- *P. hylobates*: 2 gibbon spp.

Africa

- *P. gonderi:* 4 mangabey spp. and the mandrill

South America

- *P. simium*: 3 New World Monkey spp.

Other

- A number of other plasmodia that will probably be linked to vivax including those found in orangutans, gibbons, and mangabeys

Malariae Type “New World Monkey” Malaria

Recent and rapid proliferation in New World primates after introduced by humans during colonization

- *P. malariae*
  - Humans, chimpanzees
- *P. rodhaini*
  - Chimpanzees
- *P. brasilianum*:
  - 35+ New World Monkey species including howlers, owl monkeys, spider monkeys, woolly monkeys, muriquis, uakaris, sakis, titi monkeys, capuchins, and squirrel monkeys
  - Not yet identified in callitrichids (tamarins and marmosets)

Ovale Type

Relatively understudied because both a relatively benign form of malaria, and accounts for less than 7% of human malaria cases

- *P. ovale*
  - Humans and chimpanzees
- Primarily found in humans West Africa, but also with significant cases in Southeast Asia and Papua New Guinea
- *P. schwetzi* infection of gorillas and chimpanzees may belong to the ovale group

Implications of “Primate” Malaria Plasmodia: Lessons from Yellow Fever (and Dengue)

- Both are vector-borne viral diseases transmitted *Aedes* spp. mosquitoes
- Hosts: humans and wild primates
- *Aedes* vector introduced from Africa to South America in the 16th century, in the wake of colonization
- Effective yellow fever vaccine developed over 50 years ago
- Nonetheless, remains difficult to eradicate in both Africa and New World (Central and South America) because continuously maintained in wild primate reservoirs

Sylvatic/Enzootic Cycle of *Aedes* mosquito (presumed similar sylvatic cycle for malaria vectors)

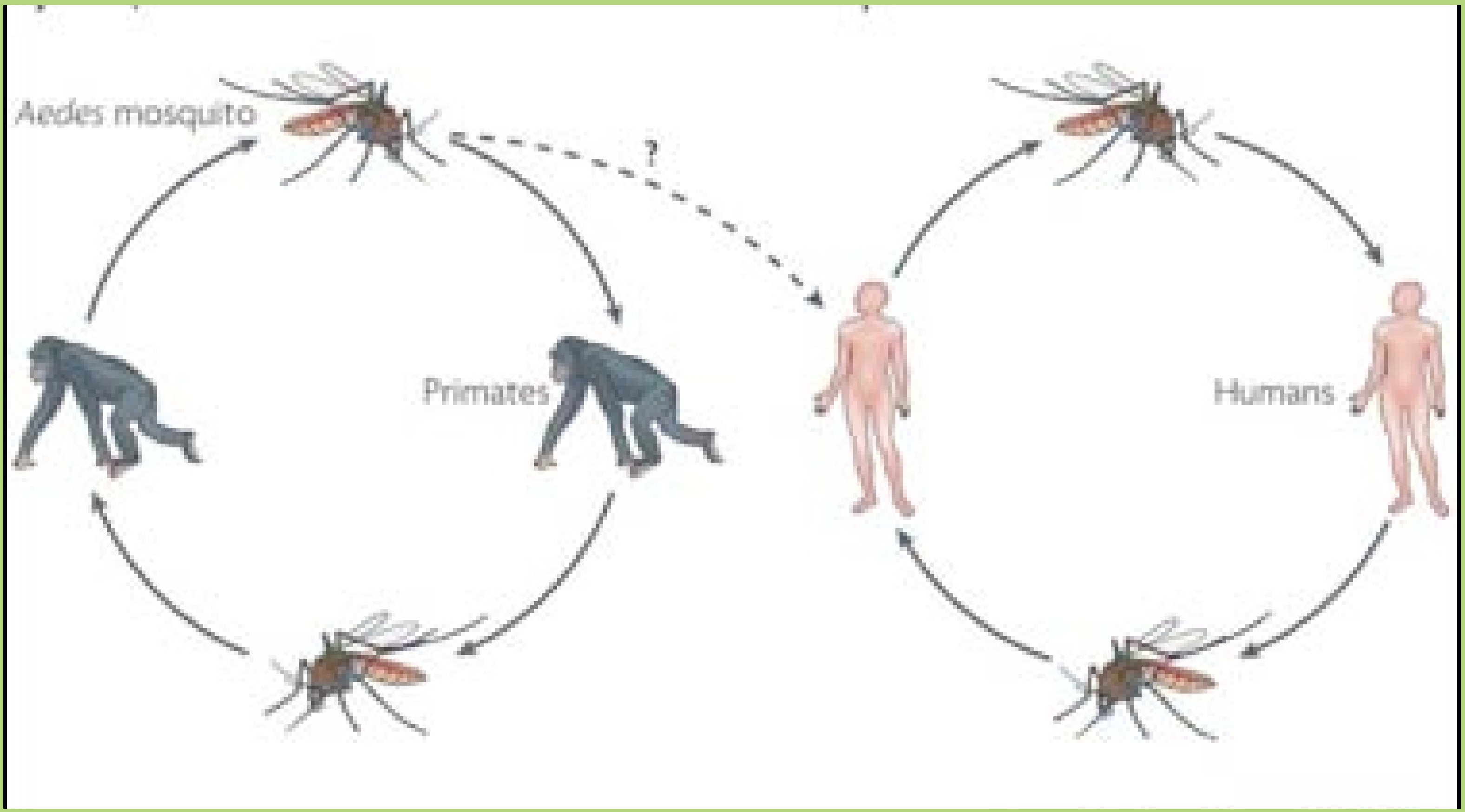


Image: Whitehead et al. (2007)

Urban Effective Enzootic Distance = approx. ½ mile

Most mosquito species travel no further than 1 mile from place of birth during lifetime

Guaja Boy and Pet Capuchin

Effective Indigenous Enzootic Distance

Can be ground zero

Many indigenous peoples hunt wild primate for food and keep as pets

Background: Guaja and Ethnoprimatology

- Close cultural and ecological relationship with wild monkeys
- Guaja consider monkeys to be quasi-human and nurture as pets, yet a key food source
- Wild primates incorporated into kinship system
- Also, complex human-primate relationships in Guaja cosmology and cosmogeny

Original Research Question Related to Malaria:

Do Guaja possess indigenous remedies against malaria?

- By far, the majority of Guaja Medical plants are "ghost repellents"
- Ghosts of the dead eat the souls of the living with the primary symptom being fever
- Bathing Infusions made from numerous plants to repel ghosts
- A number of geographically and linguistically distant Amazonian groups have similar beliefs regarding supernatural effects of medicinal baths
- Debate as to whether malaria existed in New World prior to colonization

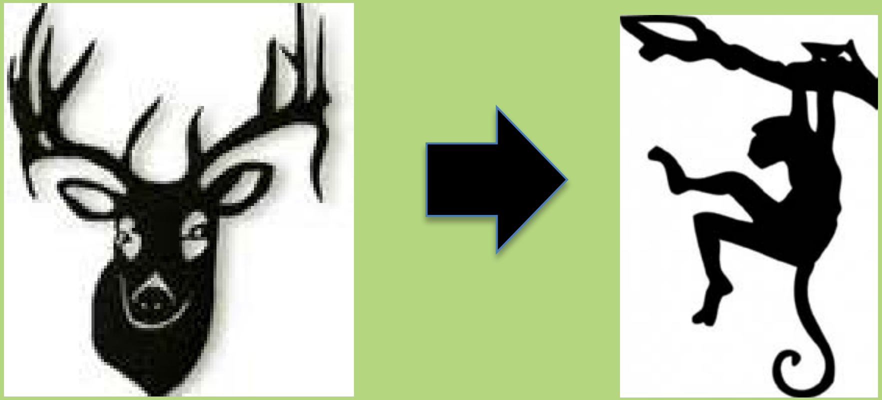
New World Wild Primate Malaria

Close genetic relationship between

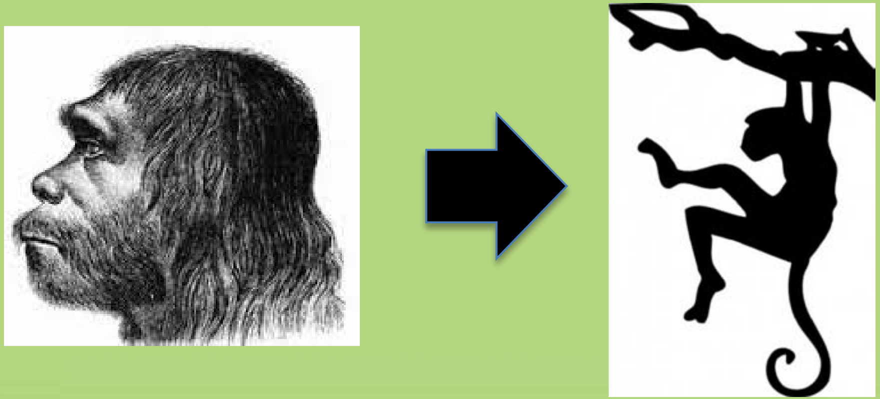
- Human *Plasmodium malariae* and New World Monkey Primate *P. brasilianum* (considered genetically indistinguishable)
- Human *Plasmodium vivax* and New World Monkey *P. simium* (genetically close enough to warrant conclusion of a host switch, in some direction)

New World Malaria Origins:

Disconnect Between Anthropology and Molecular Biology



Anthropology: Origin of NW monkey malaria in cervid deer: virtual impossibility in terms of evolutionary relationships among malaria plasmodia



Molecular Biology: Origin of NW malaria in Neanderthals: virtual impossibility in terms of known hominin migrations

Two Hypotheses for Origin of Vivax and Malariae Types in the New World

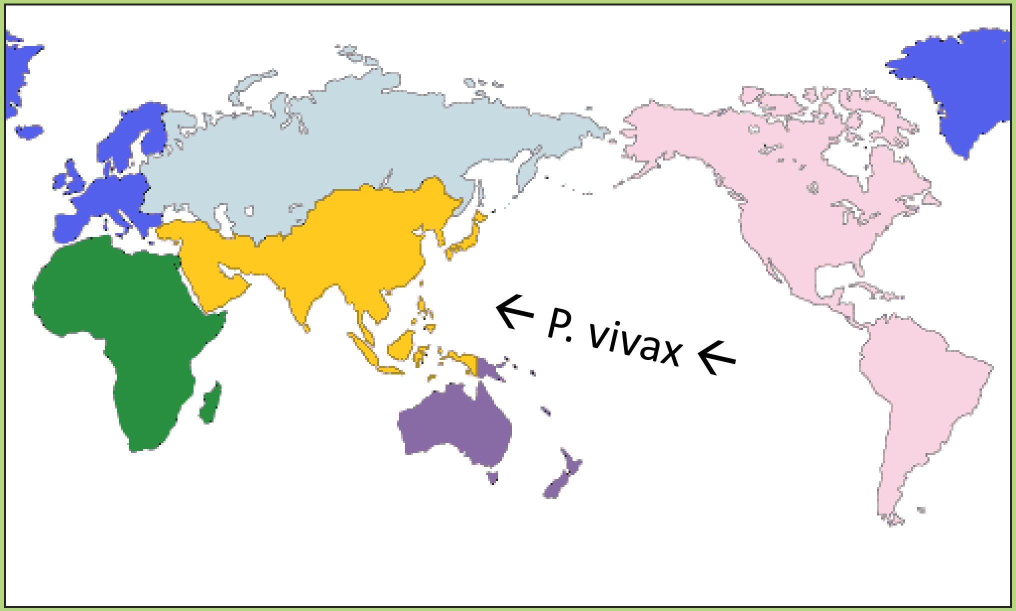
1. Out of Africa: All Malaria Introduced to New World

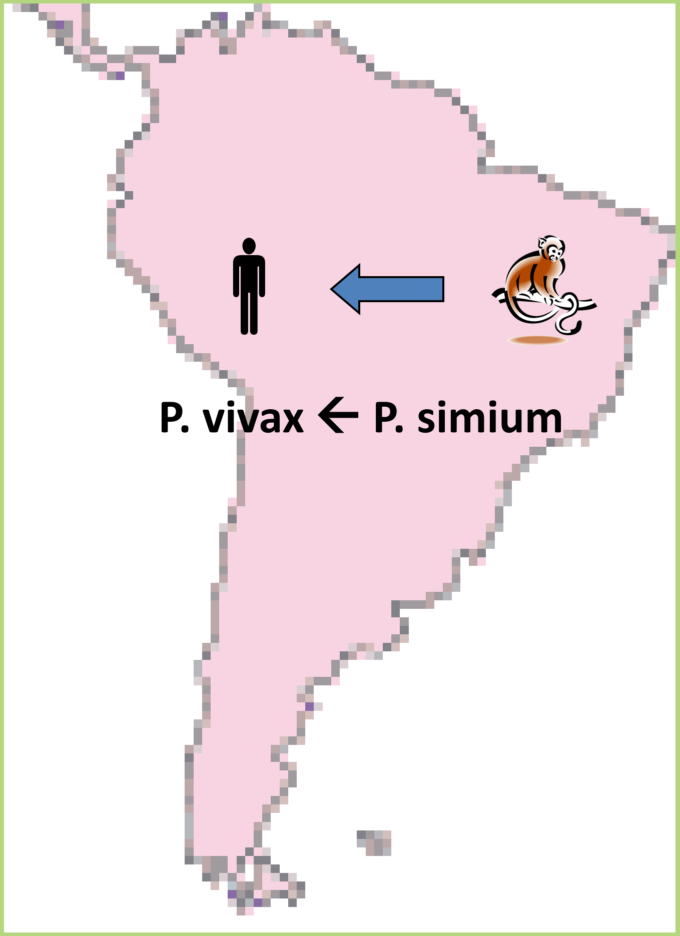
African Slaves/Europeans → Amazonian Peoples →
Neotropical Monkeys

2. Out of Amazonia: Some Malaria Endemic to Neotropics

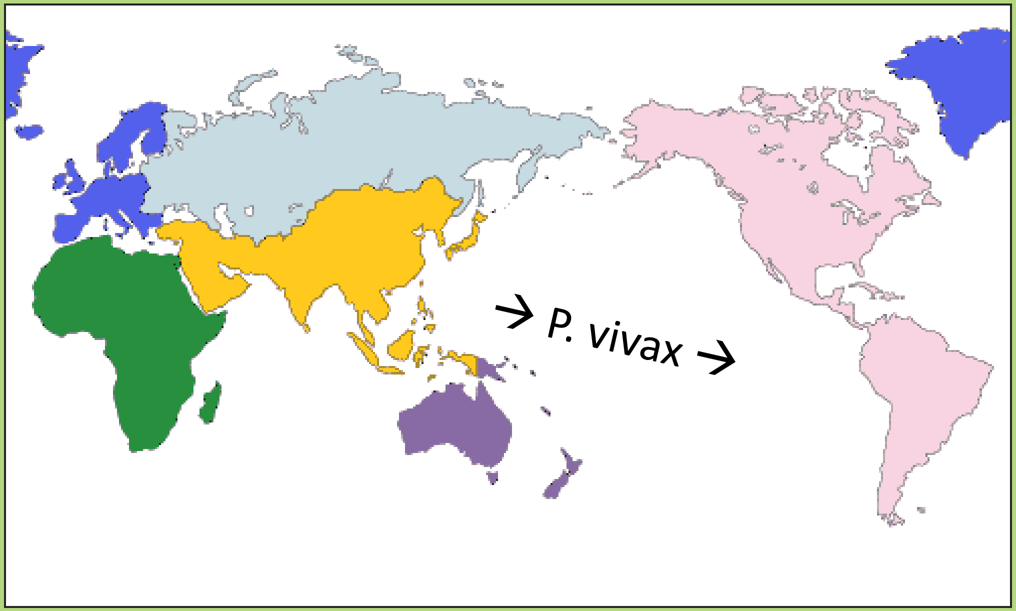
Neotropical Monkeys → Amazonian Peoples→
Old World Peoples and Monkeys

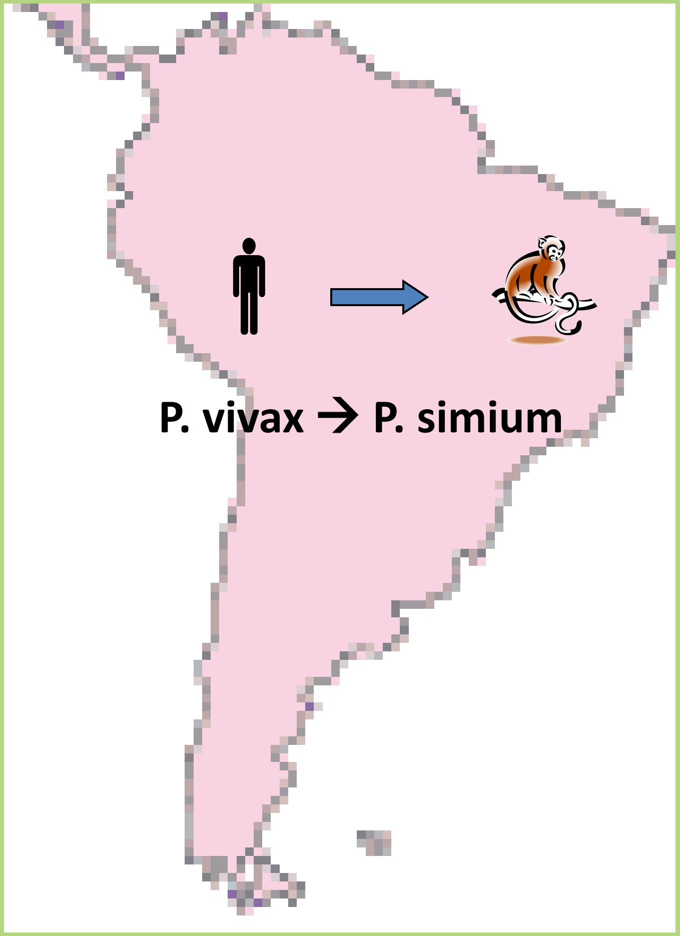
Trans-Pacific South American origin of Pre-Columbian P. vivax in Asia/Polynesia (Kon Tiki Route)





Trans-Pacific Asian → Southeast Asian origin of P. vivax → Polynesia → South America





Two Vivax forms in Amazonia?

- *P. vivax collensi*[1] = human New World vivax (European human origin)
- *P. vivax* = *P. simium* in NW monkeys (Asian human origin)

Genetic evidence that New World Monkey vivax type (*P. simium*) more closely related to human Asian *P. vivax* than Human *P. vivax (collensi variant)* in humans

?NW monkeys have human Asian vivax variant while humans have European vivax variant

1) Li et al. (2001)

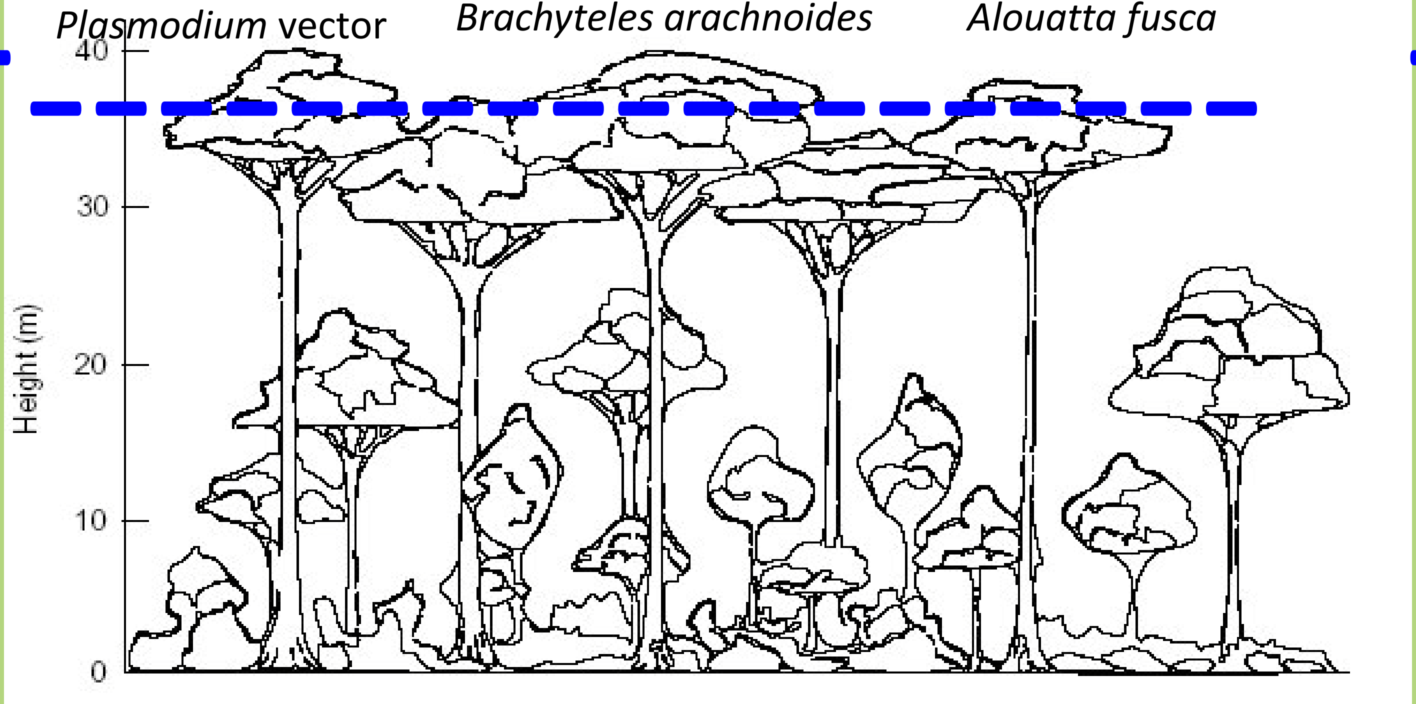
CONTEMPORARY DISTRIBUTION OF ViVAX TYPE (Horizontal problem)

Alouatta fusca	***Brachyteles arachnoides***
Brown howler	Woolly spider monkey

(Emmons and Freer 1990:125,130)

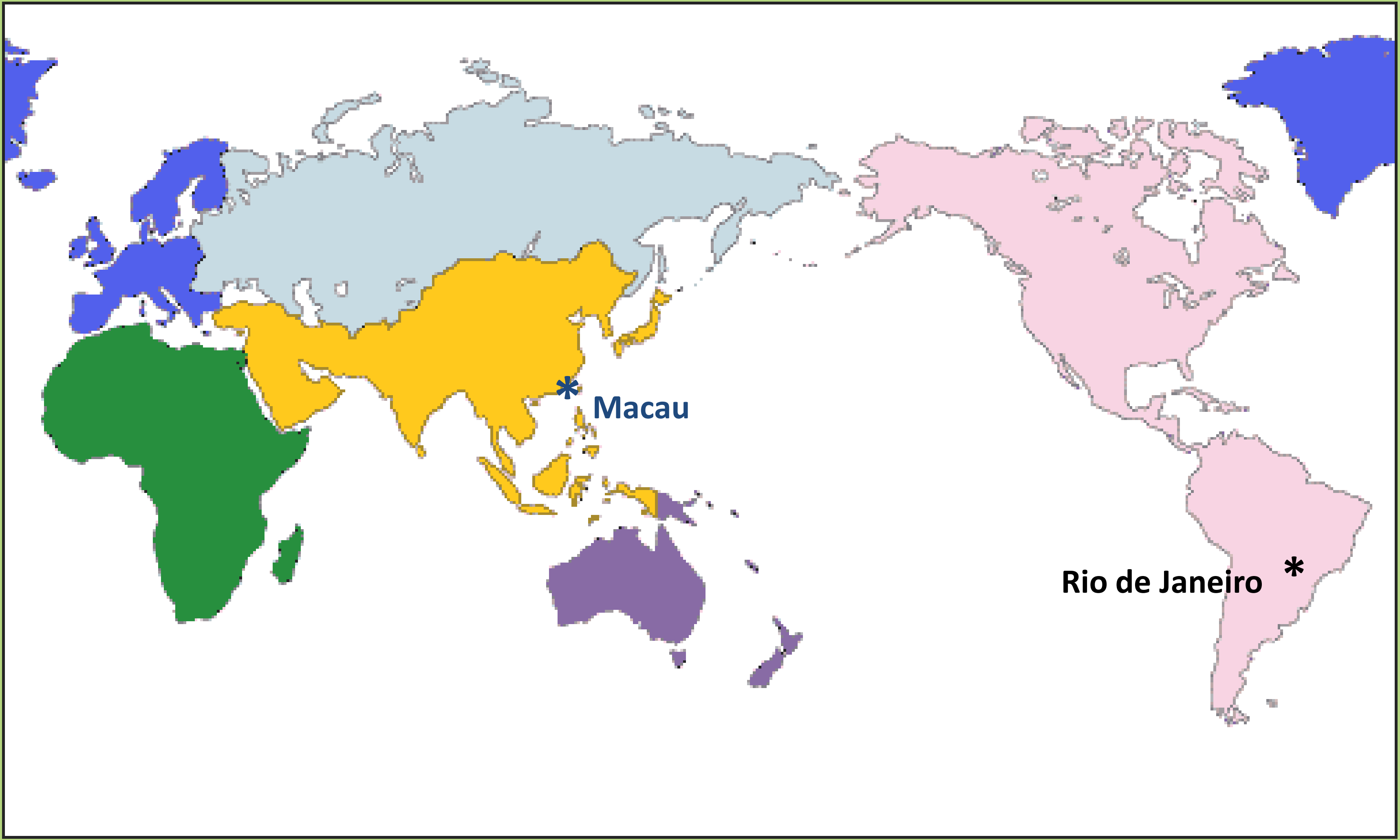
P. simium mosquito vector and monkey hosts in canopy/emergent forest levels
(Vertical Problem)

Anopheles cruzi	**Woolly Spider Monkey**	**Brown Howler**
Plasmodium vector	*Brachyteles arachnoides*	*Alouatta fusca*

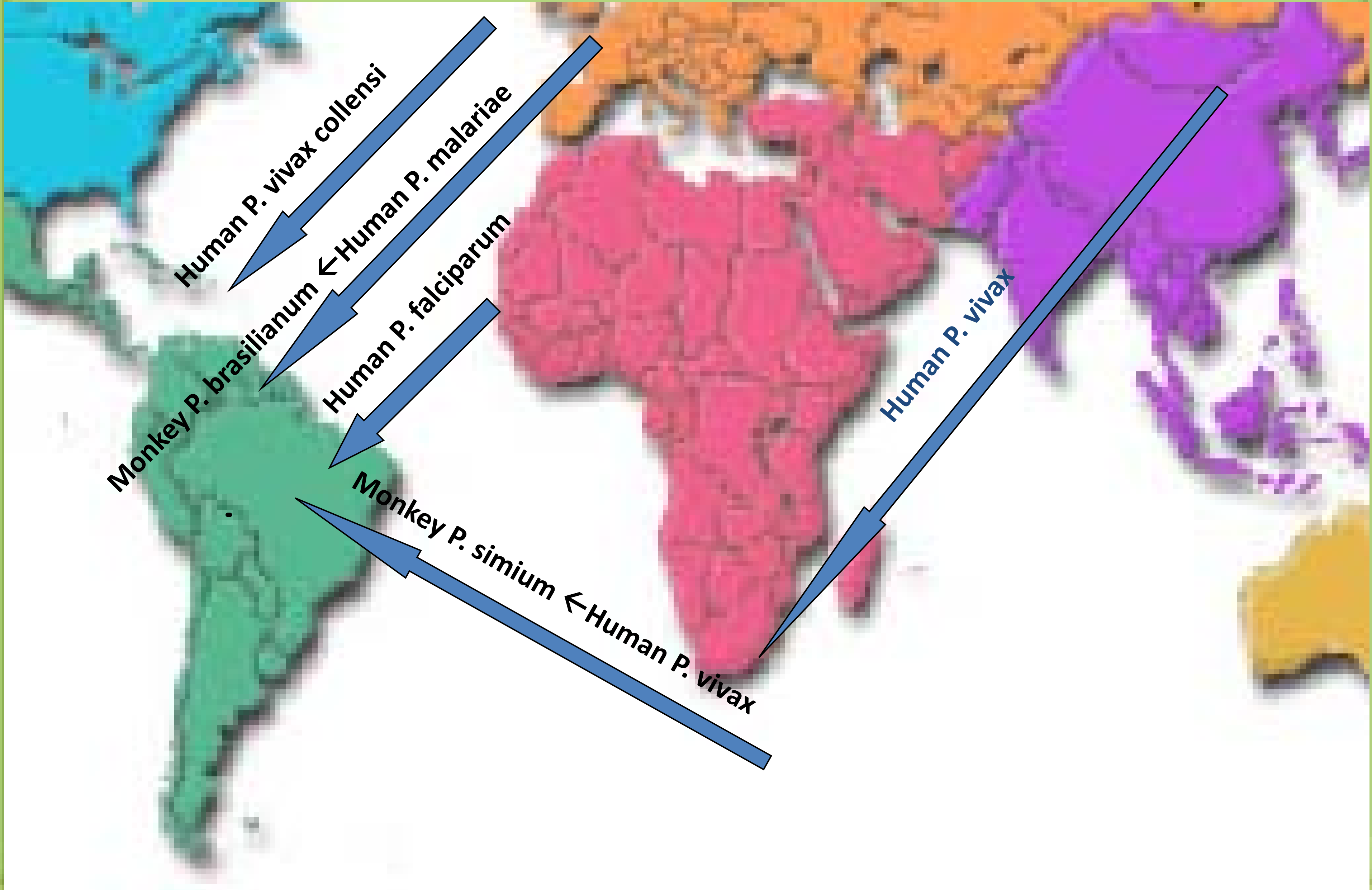


Chinese Immigrant Workers to Brazil in the 19th Century (total ~3000)

Date	# Chinese Workers	Place of Departure	Destination	Source
1810	~500	?	Rio de Janeiro	Conrad 1975, Poppino 1973
1814	200	Macau	Rio de Janeiro	Marchant 1961
1856	360	?	Rio de Janeiro	Conrad 1975
1859 and 1866	612	Singapore	?	Conrad 1975
1874	1000	Macau	?	Conrad 1975, Lesser 1999
~1882	100	?	Minas Gerais	Lesser 1999
1893	375 or 475	Macau	Rio de Janeiro	Conrad 1975, Lesser 1999


* Macau
Rio de Janeiro *

Contemporary Distribution of Macaca mulatta (Rhesus macaque),
a host of *Plasmodium cynomolgi*



Human P. vivax collensi

Monkey P. brasilianum ←Human P. malariae

Human P. falciparum

Human P. vivax

Monkey P. simium ←Human P. vivax

New World Monkey Vivax-Type Malaria

- Perhaps ultimately originating in desire for Brazilian Royalties for tea
- Asian indentured servants felling trees in Atlantic forest
- Introducing Vivax type malaria to wild monkeys
- Subsequent deforestation of Atlantic forest limiting spread of vivax to wild monkey conspecifics and related species

Relative Mirror Image Vivax Type Distribution in New World and African monkeys:

- Distribution appears to be limited to geographic "coastal islands" rather than genetically related species
- Suggests relatively recent human introduction (working hypothesis)

WHO Malaria Statistics for Amazonian South America

- *Plasmodium vivax*   75%
- *Plasmodium falciparum* 25%
- *Plasmodium malariae* < 1%

[indigenous groups disappear in population stats---implications for funding and research]

P. malariae/brasilanum rates may be underestimated for Indigenous Peoples

WHO stats = < 1% in Amazonia (humans), but…

- French Guiana[1]
  - 38.8% of Wayana of French Guiana positive
  - 45.4 % of Wayampi of French Guiana positive
  - 73% of local monkeys positive for *P. malariae/brasilianum*
- Northern Brazil[2]
  - 90% of adult Asurini of Northern Brazil positive
  - 100% of adult Metuktire positive
  - Authors suggest primate pet-keeping may be responsible for high rates

1. Volney et al. (2002)
2. De Arruda et al. (1989)

Falciparum Type: Africa

“African Great Ape” Malaria

- Various falciparum forms (particularly *P. reichenowi*) in chimpanzees, bonobos, and gorillas
- Recent discovery that human falciparum malaria originated in host switch from gorillas in Africa[1]
- “Big bang” in African malaria with advent of agriculture; swidden agricultural creating new habitats for anopheline mosquito vectors
- Mutation of relatively benign African ape *P. reichenowi* malaria into lethal human form
- Falciparum malaria introduced to New World peoples approximately 500 years ago with colonization with Trans-Atlantic slave trade

1. Liu et al. (2010)

“Red Queen” Hypothesis

Hypothesis that organisms must constantly adapt and evolve, not merely to gain reproductive advantage, but also simply to survive pitted against ever-evolving opposing organisms in an ever-changing environment (described by Leigh van Valen)

“It takes all the running you can do to keep in the same place” The Red Queen from *Alice’s Adventures in Wonderland* (Lewis Carroll, 1865)

Red Queen Effect in Falciparum Malaria

- After human/Pan/Gorilla split, an enzyme mutation evolved in humans that provided resistance to Africa ape *P. reichenowi*
- *P. reichenowi* subsequently mutated into *P. falciparum,* which allowed it to more readily infect humans with anti-reichenowi mutation → highly virulent expression of *P. falciparum* in humans

New World Monkeys

- Have same enzyme mutation as humans that makes susceptible to falciparum malaria[1]
- Falciparum arose at some point after the divergence of African and Asian apes
- Earliest possible date would be Middle Miocene, approximately 13 mya
- New World monkeys colonized South America in the early Oligocene, approximately 33 million years ago
- No evidence of any form of falciparum malaria in New World until last 500 years
- The enzyme mutation apparently evolved in New World monkeys independently for reasons unrelated to falciparum malaria
- Why?? Remains unclear (but side issue for this talk)

1. Martin et al. (2005)

Wild New World Monkeys and Falciparum Malaria

- A number of studies in Amazonia in last 20 years finding that several of species of New World monkeys demonstrate evidence of exposure to human falciparum, but no cases with evidence that they are infected (and thus infectious)
- That is, anti-falciparum antibodies detected (indicating exposure), but no evidence that any wild New World monkeys infected with falciparum
- Until…

Duarte et al. (2008) found *P. falciparum* infection two Atlantic Forest Howler species

Alouatta guariba

Alouatta caraya

Howler Images from Primate Info Net (pin.primate.wisc.edu/)

Concern

- Possibility of spread of falciparum among Neotropical primates in pattern similar to *P. malariae/P. brasilianum*
- Wild primates could become significant reservoir for falciparum malaria in Africa
- Potential for sylvatic/enzootic cycle of transmission between wild primates and humans
- Could lead to Africa-like falciparum malaria conditions in humans
- Also…health serious threat to New World monkeys

Conclusions

- Long history of host-switching among plasmodia creating disease of malaria in humans and primates
- Runs gamut of:
  - Ancient host switch of gorilla falciparum to humans
  - Colonial transfer of human malariae/brasilianum and vivax/simium to NW primate
  - Recent epidemic outbreak of of macaque *P. knowlesi* in humans in Southeast Asia
  - Recent (last 5 years) transfer of human falciparum to New World Monkeys
- Deforestation/habitat destruction: creating new ecological zones for malaria and other zoonotic transfer
- Little addressed: effects of human malaria transfer to wild primates

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