Malaria and the heritability of being infectious

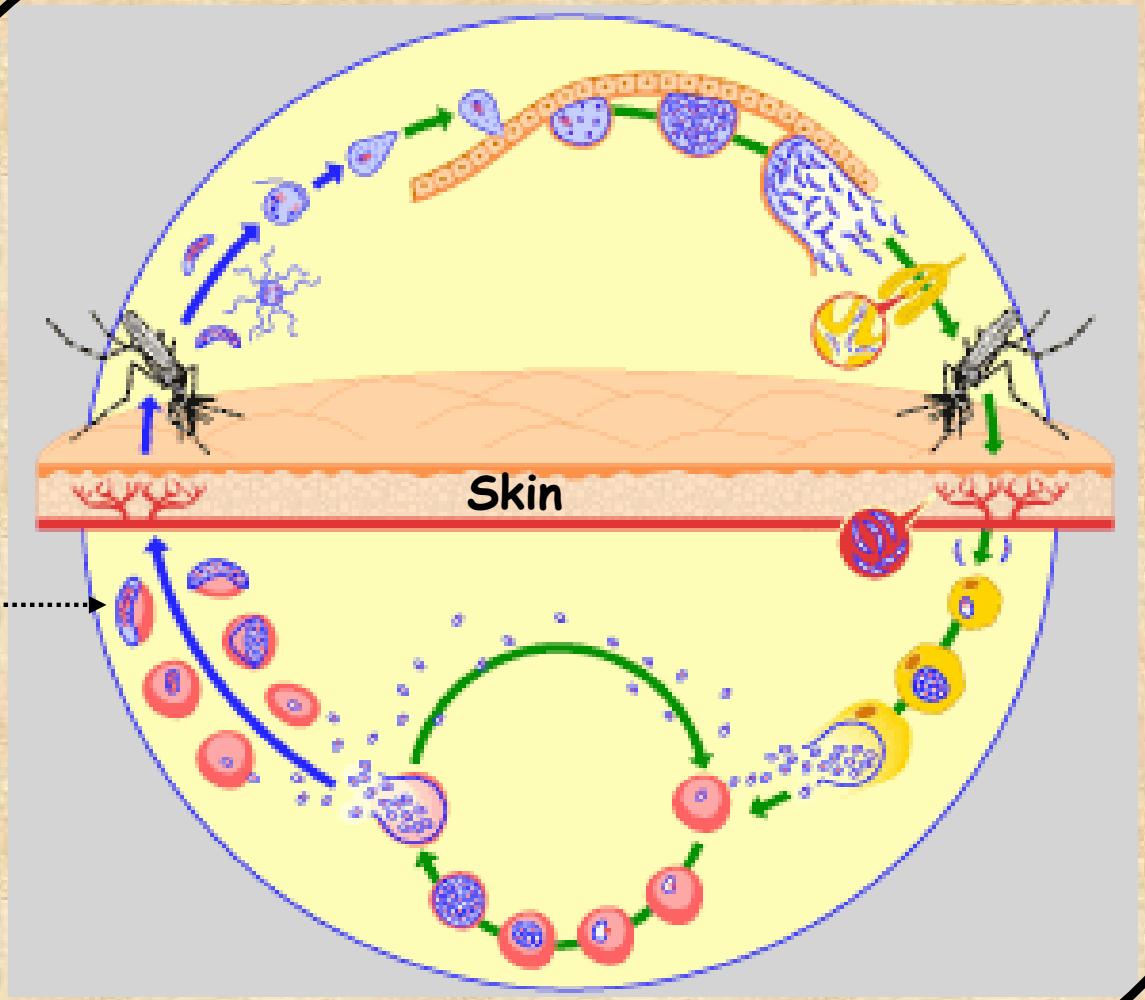
Whose fault is it anyway?

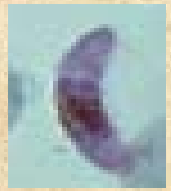
Rick Paul & Anavaj Sakuntabhai
Laboratory of the Genetics of the Human Response to Infection

INSTITUT PASTEUR

Transmission to

Mosquito





Male & Female Gametocytes (falciforme) *Plasmodium falciparum*

Man

Transmission to

INSTITUT PASTEUR

Why gametocytes?

Identification of the reservoir of infection

Who & how many?

- Feasibility of targeted intervention
- Re-evaluation of vaccine strategy using Integrated Control Program

INSTITUT PASTEUR

Why gametocytes?

Identification of the reservoir of infection

Who & how many?

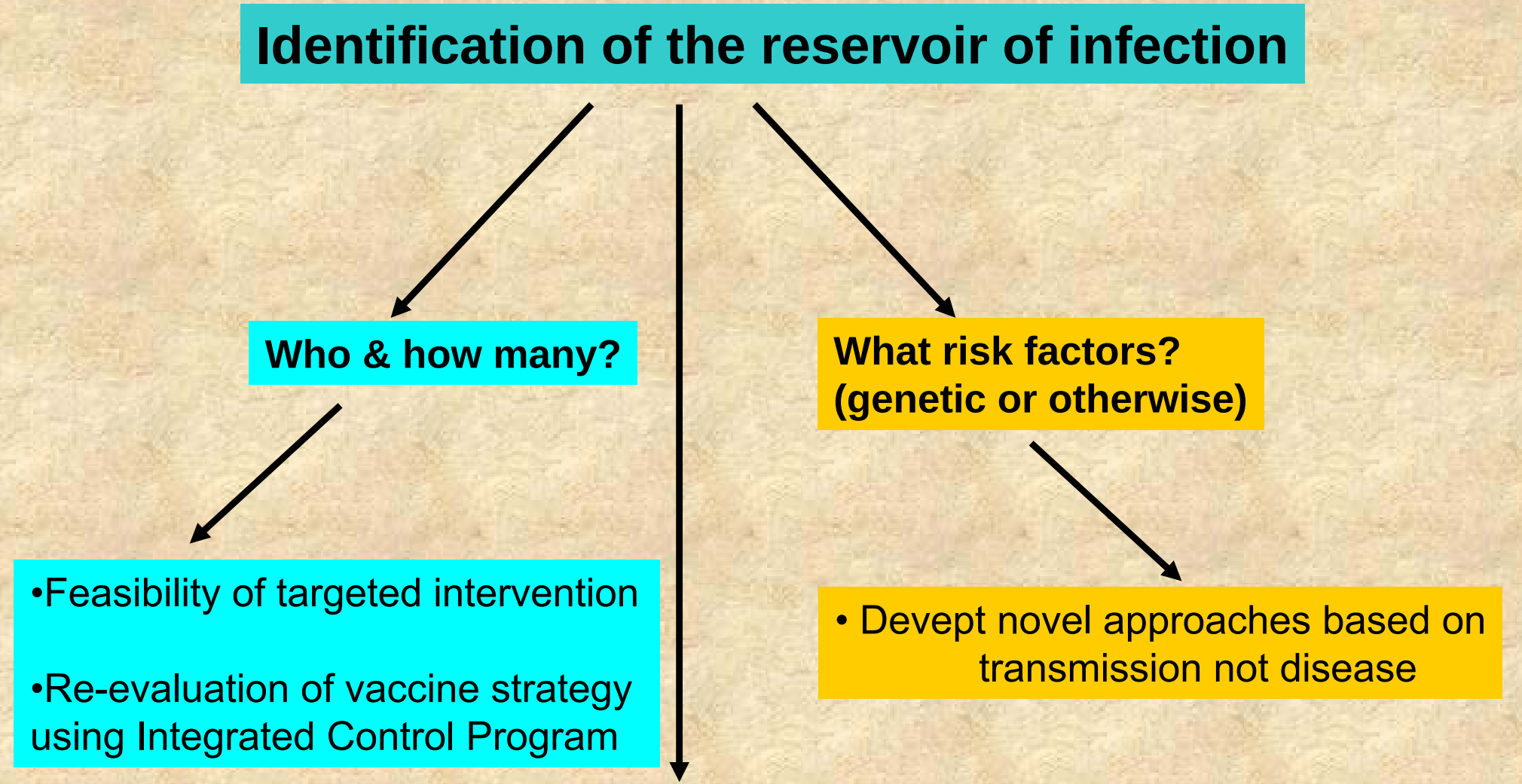
- Feasibility of targeted intervention
- Re-evaluation of vaccine strategy using Integrated Control Program

What risk factors? (genetic or otherwise)

- Devept novel approaches based on transmission not disease

INSTITUT PASTEUR

Why gametocytes?



Ross-Macdonald model of malaria (simplified form)

$$R_0 = \frac{ma^2bc}{\mu\gamma}$$

R_0 : the number of secondary cases arising from a single primary case in a naive population.

INSTITUT PASTEUR

Ross-Macdonald model of malaria

$$R_0 = \frac{ma^2bc}{\mu\gamma}$$

R_0 : the number of secondary cases arising from a single primary case in a naive population.

The primary case remains infected for a period of *$1/\gamma$ days.*

INSTITUT PASTEUR

Ross-Macdonald model of malaria

$$R_0 = \frac{ma^2bc}{\mu\gamma}$$

R_0 : the number of secondary cases arising from a single primary case in a naive population.

The primary case remains infected for a period of $1/\gamma$ *days.*

During this time, this 1° case will be bitten (am/γ) times and a proportion *c* will infect the biting mosquitoes

giving (amc/γ) infected mosquitoes.

INSTITUT PASTEUR

Ross-Macdonald model of malaria

$$R_0 = \frac{ma^2bc}{\mu\gamma}$$

R_0 : the number of secondary cases arising from a single primary case in a naive population.

The primary case remains infected for a period of $1/\gamma$ *days.*

During this time, this 1° case will be bitten (am/γ) times and a proportion *c* will infect the biting mosquitoes

giving (amc/γ) infected mosquitoes.

Each of these mosquitoes lives ($1/\mu$) days and makes a total number (abl/μ) infectious bites in her lifetime.

INSTITUT PASTEUR

Ross-Macdonald model of malaria

$$R_0 = \frac{ma^2bc}{\mu\gamma}$$

R_0 : the number of secondary cases arising from a single primary case in a naive population.

The primary case remains infected for a period of $1/\gamma$ *days.*

During this time, this 1° case will be bitten (am/γ) times and a proportion c will infect the biting mosquitoes

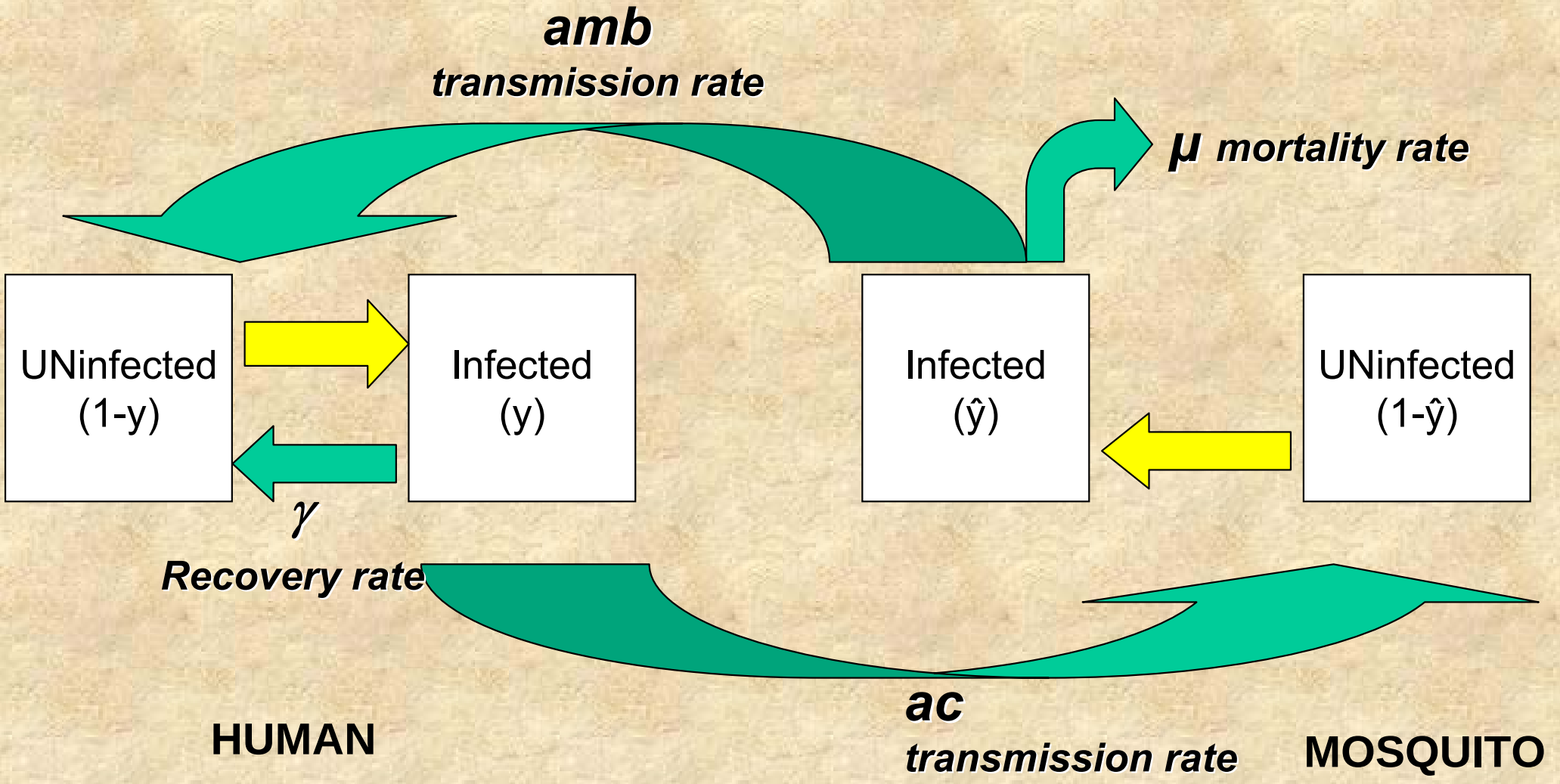
giving (amc/γ) infected mosquitoes.

Each of these mosquitoes lives ($1/\mu$) days and makes a total number (ab/μ) infectious bites in her lifetime.

The number of secondary cases is thus (abl/μ) ($amcl/\gamma$)

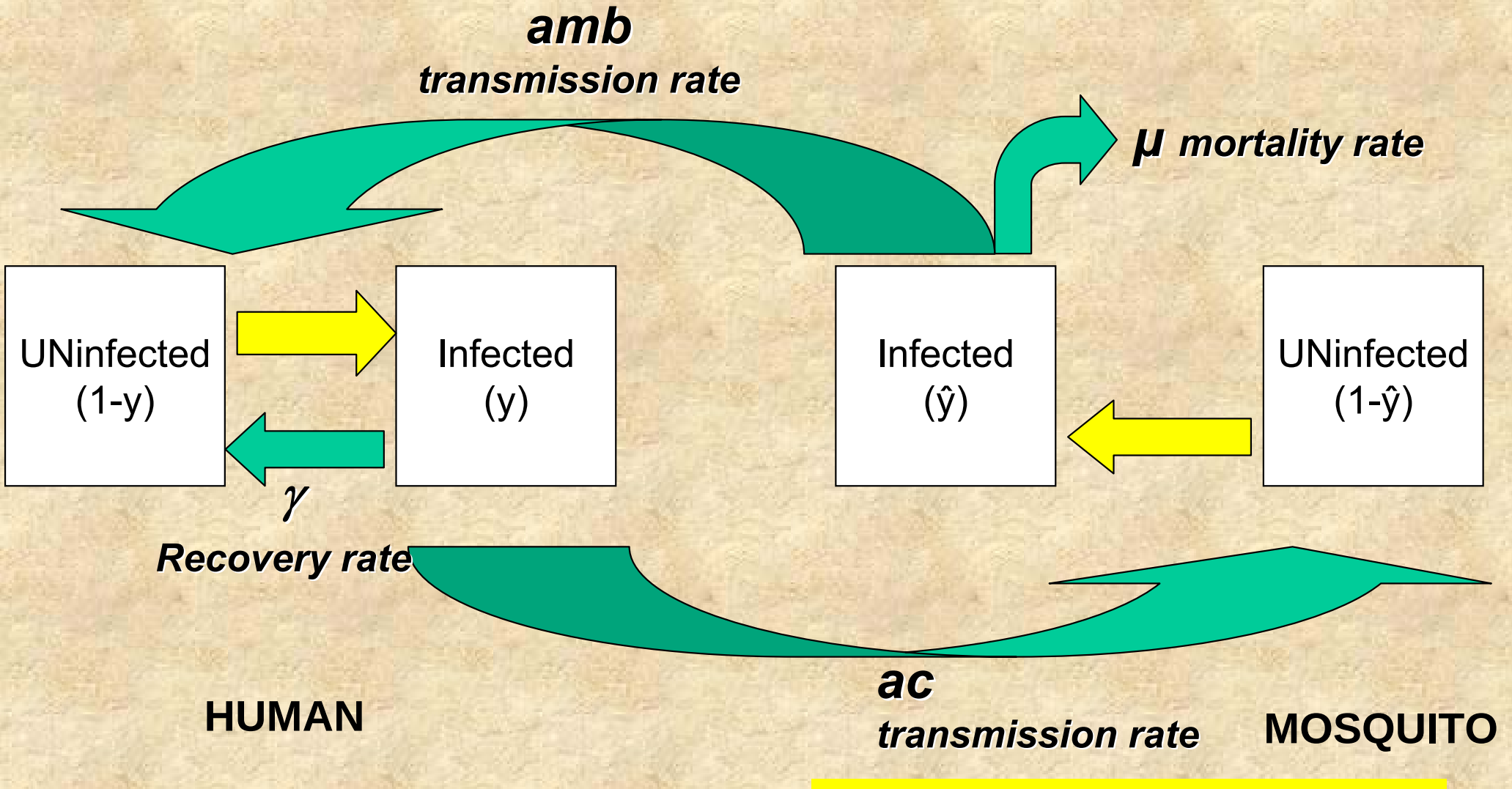
INSTITUT PASTEUR

Transmission and infection is dynamic



INSTITUT PASTEUR

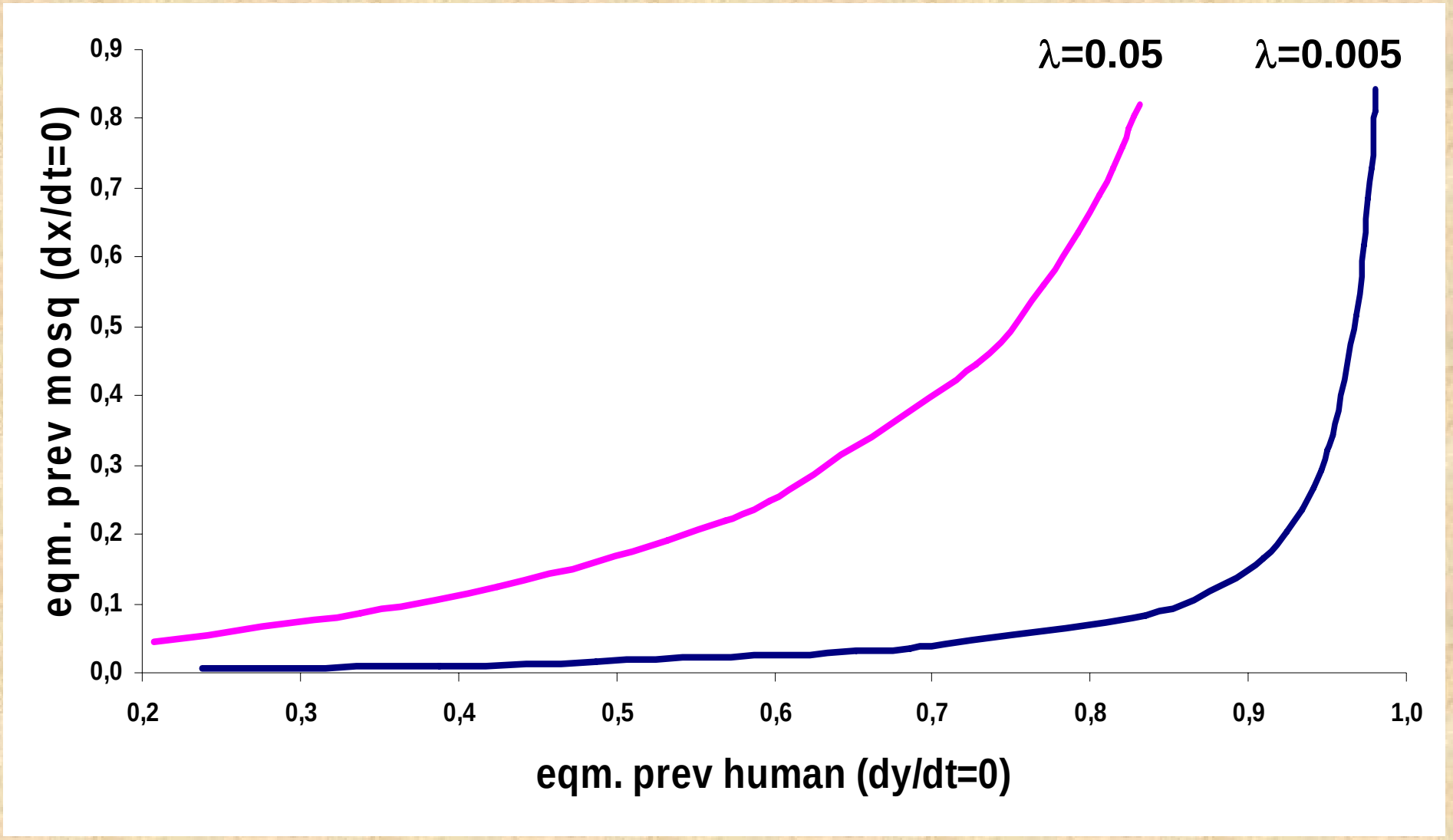
Transmission and infection is dynamic



$$\frac{dy}{dt} = (abm)\hat{y}(1-y) - \gamma y$$

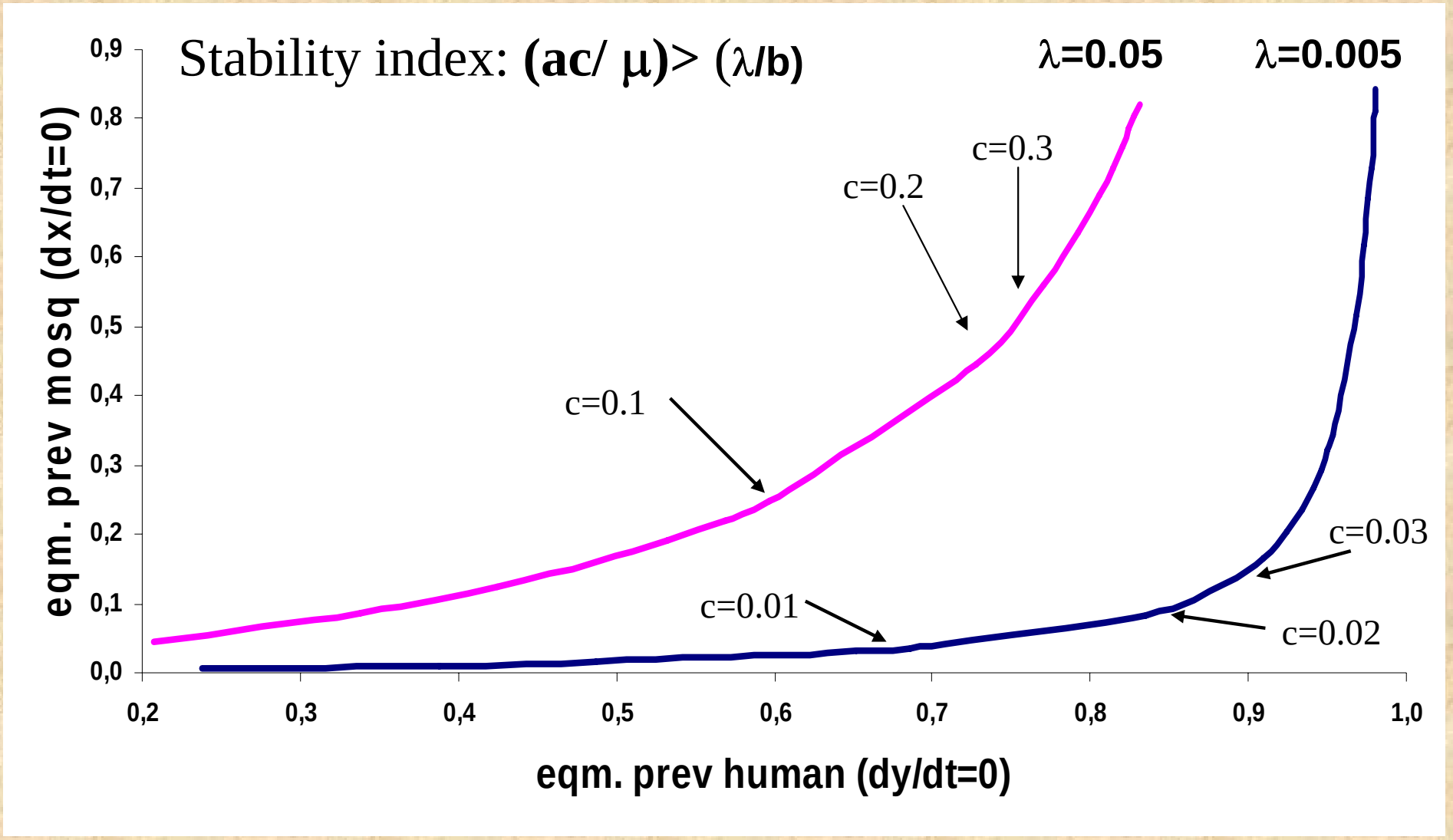
$$\frac{d\hat{y}}{dt} = acy(1-\hat{y}) - \mu\hat{y}$$

The effect of « c » on the prevalence of infection



INSTITUT PASTEUR

The effect of « c » on the prevalence of infection



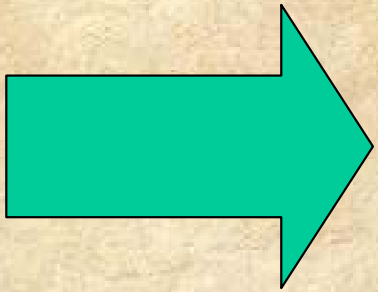
INSTITUT PASTEUR

Risk factors for gametocyte carriage

1. Anaemia

2. Hyperparasitaemia

3. Reaction to antimalarial drug treatment



All in symptomatic infections

INSTITUT PASTEUR

Gametocytes in asymptomatic infections

1. No acquired immunity to gametocytes
   (only to gametes – transmission-blocking vaccines)

2. No real decrease with age and exposure

3. Seasonal variations

INSTITUT PASTEUR

Genetic predisposition to carry gametocytes?

Perry (1914) Madras

Dombo people vs. Pojoras

- Dombo are recent immigrants
- Dombo suffer more clinically
- Dombo have increased spleen rates

<16yr old

	Prev Rate (%)	%infections with gametocytes
Dombos	51	5
Pojoras	78	41

INSTITUT PASTEUR

Genetic effect: estimation of heritability

Variance components

H_0: Vp = Ve
H_1: Vp = Ve + Vg

statistic χ^2 ,df 1 = 2Ln (L1/L0)

Vp = variation of phenotype
Ve = variation due to environment
Vg = variation due to genetics (additive)

Heritability = Vg/Vp

INSTITUT PASTEUR

Family-based longitudinal cohort studies

INSTITUT PASTEUR

Dielmo & Ndiop, Senegal

INSTITUT PASTEUR

Suanpung, Thailand

Study Populations

Population	N	Nuclear families
Dielmo, Senegal	589	190
Ndiop, Senegal	644	208
Suanpung, Thailand	3484	603

INSTITUT PASTEUR

Collection of phenotypes

Intensive survey period

Blood smear regardless of symptoms

Dielmo:	twice weekly from June-September (1990)
Ndiop:	once-twice weekly for 1 year (1992)
Suanpung, Thailand:	once a month for 2 years (1994-1996)

Follow up period

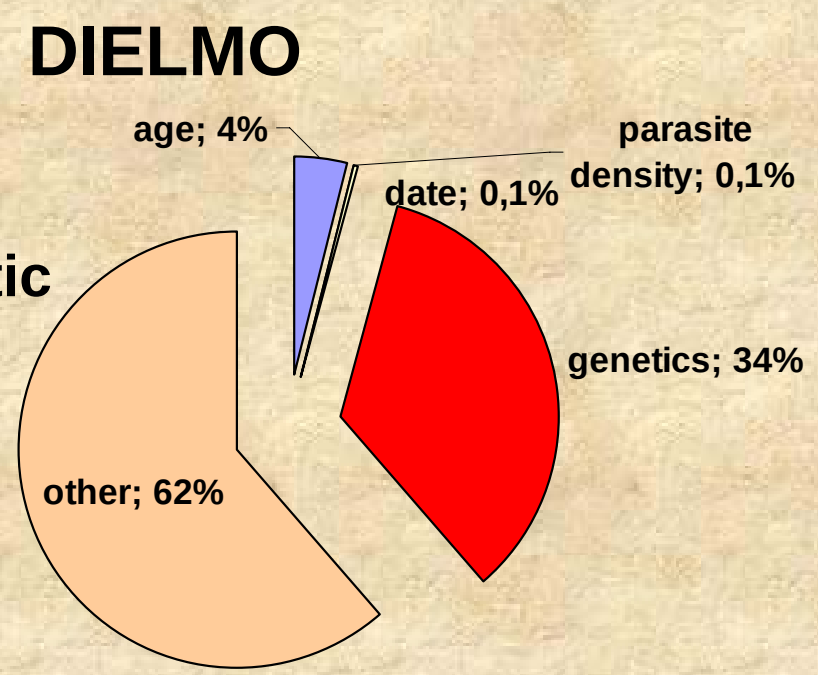
Record clinical malaria attacks

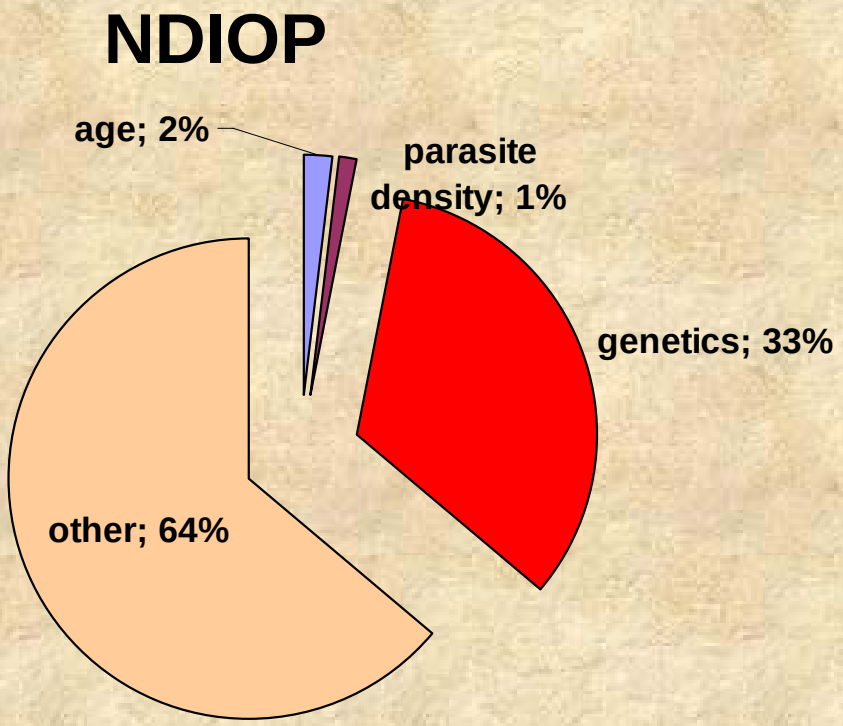
Dielmo:	1990-1999
Ndiop:	1992-2000
Suanpung, Thailand:	1998-2005

INSTITUT PASTEUR

% variability in the proportion of infections that have gametocytes explained by « environmental » and genetic (heritability) factors (1)

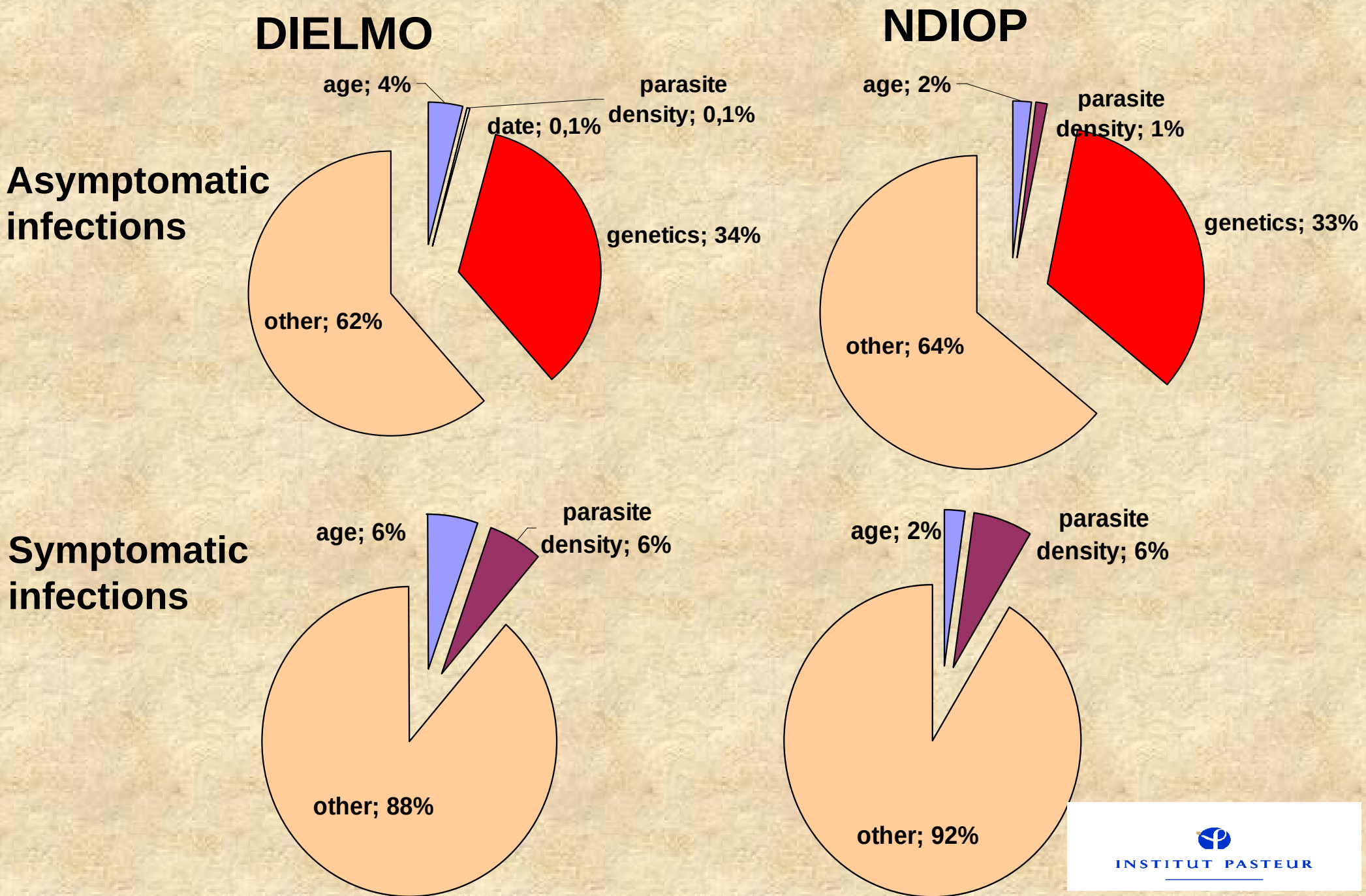
Asymptomatic infections





INSTITUT PASTEUR

% variability in the proportion of infections that have gametocytes explained by « environmental » and genetic (heritability) factors (2)

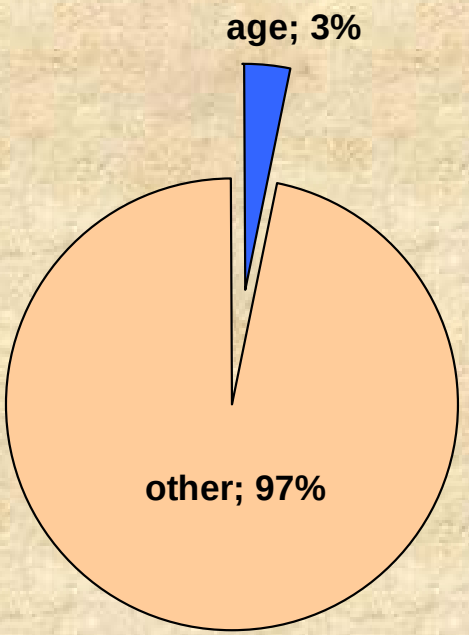


INSTITUT PASTEUR

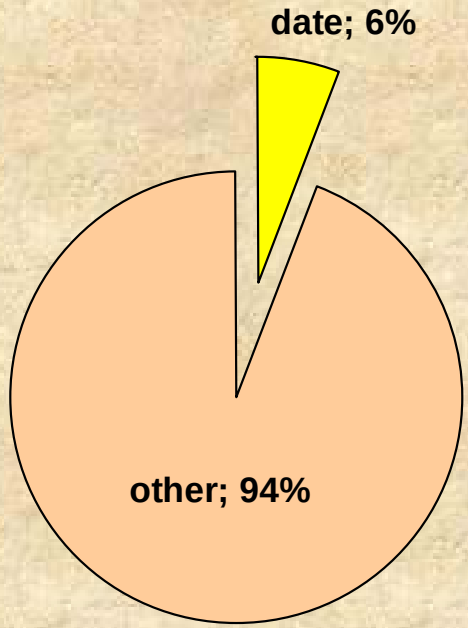
% variability in the proportion of infections that have gametocytes explained by « environmental » and genetic (heritability) factors (3)

Thailand: (virtually) all infections lead to symptomatic episodes

P. falciparum



P. vivax



INSTITUT PASTEUR

Correlation of asymptomatic gametocyte prevalence & other parasite phenotypes

Strong positive correlation with asymptomatic asexual parasite density

$r^2=0.51$ $p<0.0001$ Ndiop and $r^2=0.3$ $p<0.0001$ Dielmo

But heritability greater for gametocyte phenotypes (prevalence or density) than for asexual parasite density (heritability 30-40% vs. ~20%)

& asexual parasite density explain only 0.1% variation in gametocyte prev.

INSTITUT PASTEUR

Conclusions

- Very high heritability for gametocyte carriage
  - biology behind correlation with other phenotypes
  - genome scan & candidate gene selection
- Absence in symptomatic
  - short duration of infection?....
  - differing biological (human) stimuli

INSTITUT PASTEUR

Acknowledgement

Our collaborators:

- P. Singhasivanon,

Faculty of Tropical Medicine, Mahidol University, Thailand

- A. Tall,

Institut Pasteur de Dakar, Senegal

& the participants of the study cohorts in Thailand and Senegal

INSTITUT PASTEUR DE DAKAR

INSTITUT PASTEUR