



Sciences Economiques et Sociales de la Santé  
& Traitement de l'Information Médicale

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**Resolving the cause of recurrent vivax malaria probabilistically**

**January 2020**



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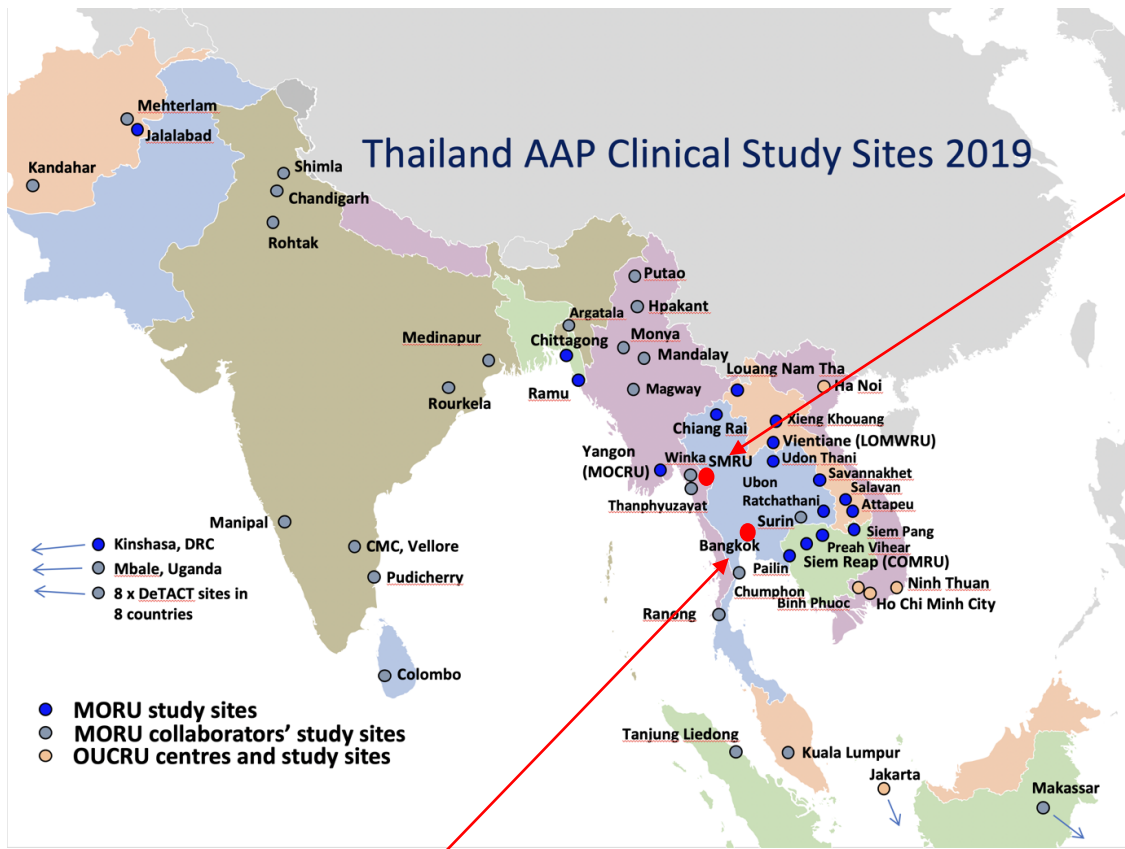
# Resolving the cause of recurrent vivax malaria probabilistically

James Watson

Mahidol Oxford Tropical Medicine Research Unit

Bangkok, Thailand

## Thailand AAP Clinical Study Sites 2019



### Diseases/research areas:

- Malaria
- Critical illness
- Antimicrobial resistance
- Melioidosis, rickettsia

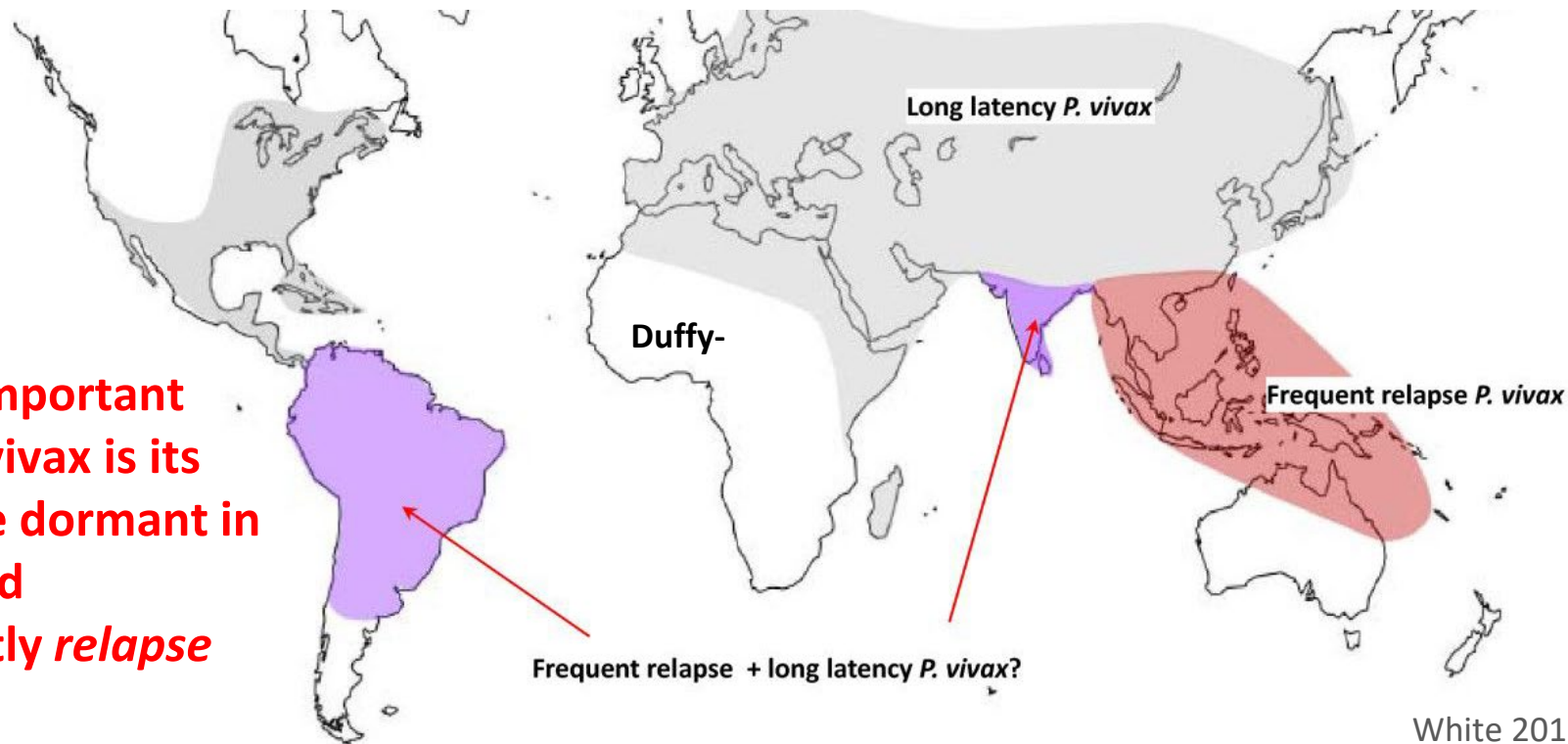
### Focus on:

- Treatment trials
- Pharmacology
- Mathematical modelling
- Epidemiology

# *Plasmodium vivax*: geography

100 years ago, vivax malaria was present across almost all of the inhabited world. Exception sub-Saharan Africa: Duffy- gene

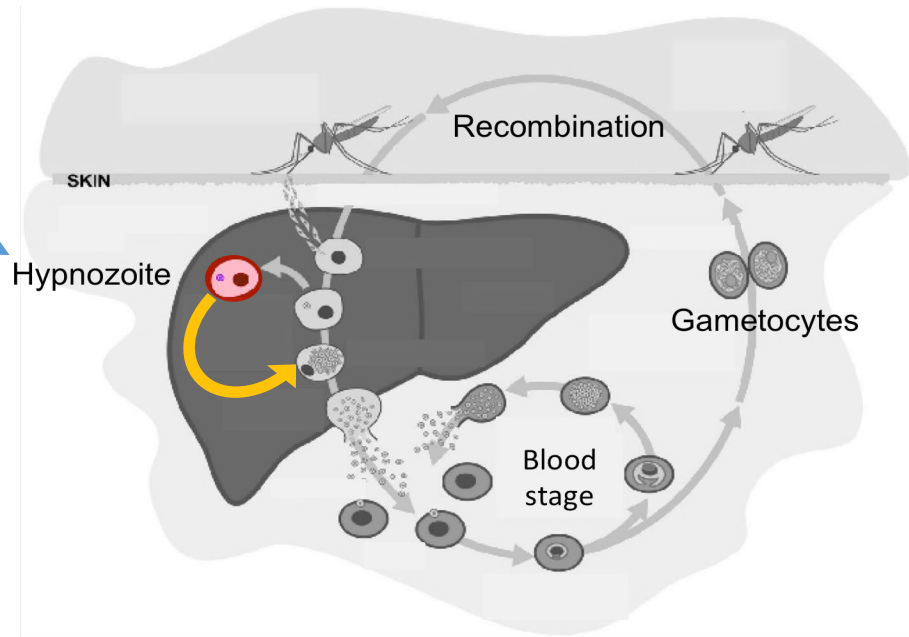
The most important feature of vivax is its ability to lie dormant in the liver and subsequently *relapse*



# *Plasmodium vivax*: biology

*Plasmodium falciparum* has the same life cycle except for the dormant liver stages

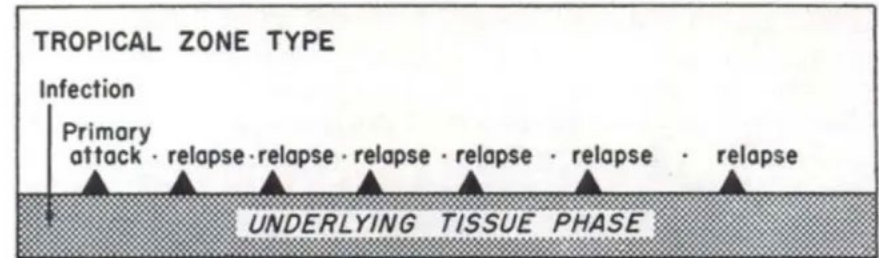
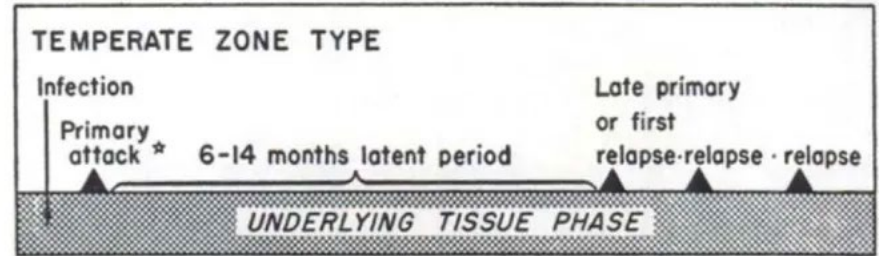
The most important feature of *vivax* is its ability to lie dormant in the liver and subsequently *relapse*



# *Plasmodium vivax*: relapse

Two major hypnozoite phenotypes can be distinguished:

1. Northern/temperate climate: hypnozoites activate after long latency (e.g. *Netherlands, Korea, North America*)
2. Tropical climate: frequent activation of hypnozoites (e.g. *South America, India, South Asia, Oceania*)

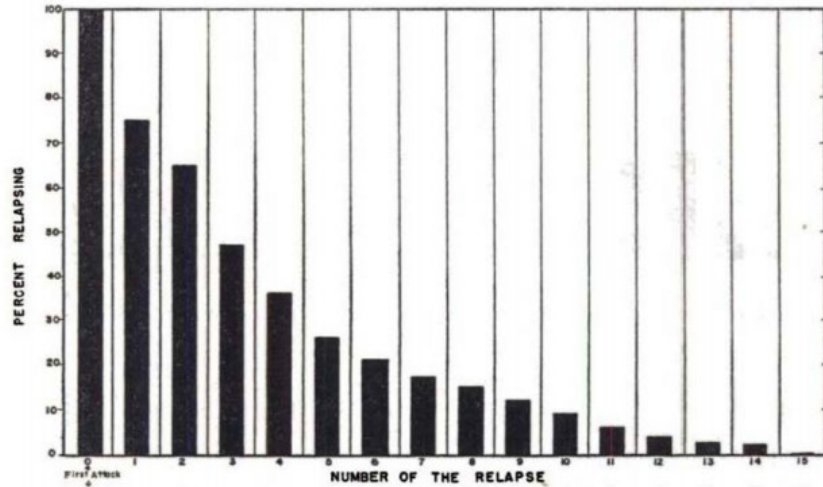


\* Primary attack may be absent

# Plasmodium vivax: relapse

Over time, individuals can build up a liver bank of hypnozoites.  
More exposure = more relapses

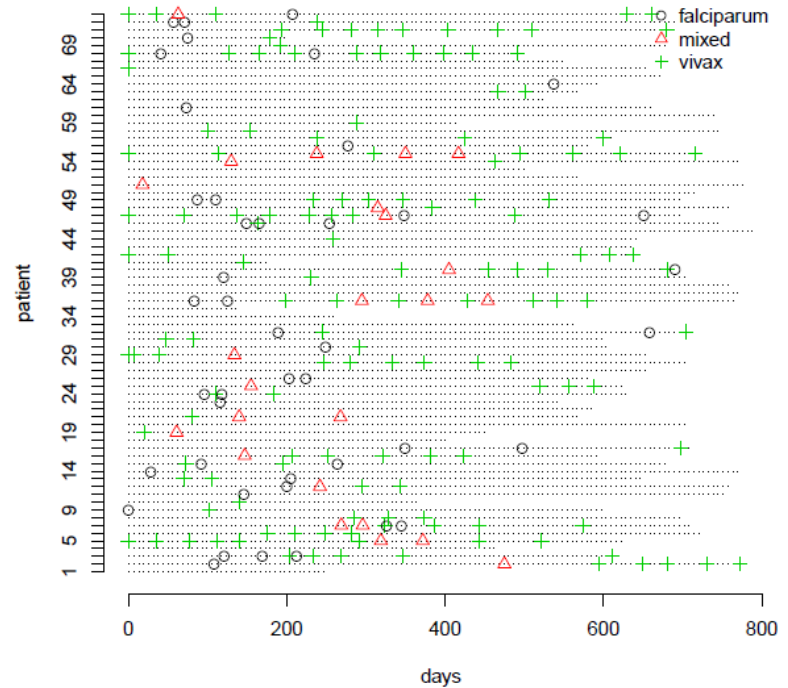
**Soldiers coming back from Pacific: very high exposure**



% of original group	100	75	65	47	36	26	21	17	15	12	9	6	4	2.5	2	0.4
recurring further	75	86	72	76	72	84	81	88	80	75	66	66	62	80		

Figure 15 Proportions of *P. vivax* relapses in 222 US servicemen who had fought in the South Pacific in the Second World War [76].

**2-year olds follow-up on Thai-Myanmar border in the 1990s**



# *Plasmodium vivax*: the 3 Rs

In endemic areas, recurrent infection of vivax malaria could be caused by:

- 1. *Recrudescence*:** previous blood stream infection was not fully eliminated and so the parasites grow back to observable densities
- 2. *Reinfection*:** a new infectious mosquito bite
- 3. *Relapse*:** activation of a liver hypnozoite causing a new blood stream infection

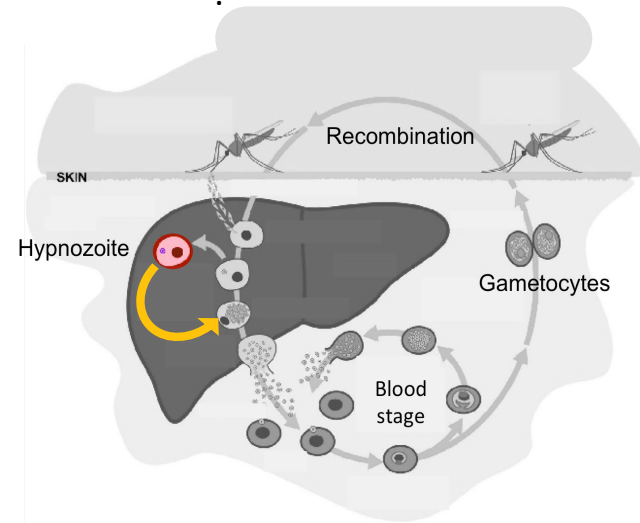


# *Plasmodium vivax*: summary of work

**Relapse:** hypnozoite-derived blood-stage infection

**Problem:** how to distinguish *relapse* from *reinfection*, from *recrudescence*?

**Goal:** estimate the probability that a recurrent *P. vivax* infection is a relapse using *P. vivax* genetic and time-to-recurrence data

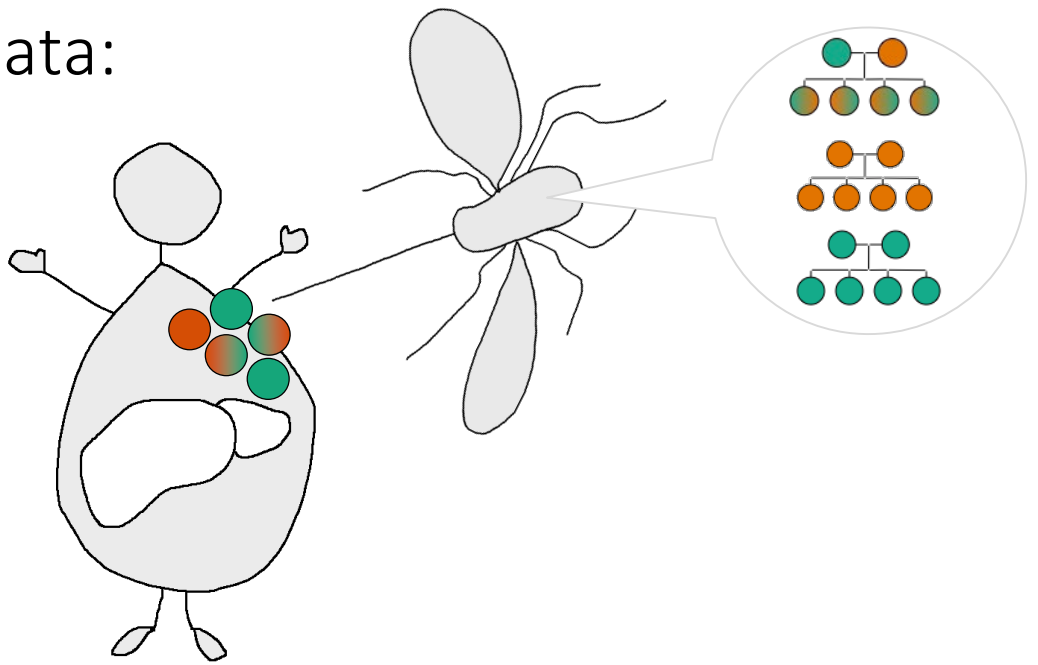


# Information in genetic data

What do relapses look like genetically?

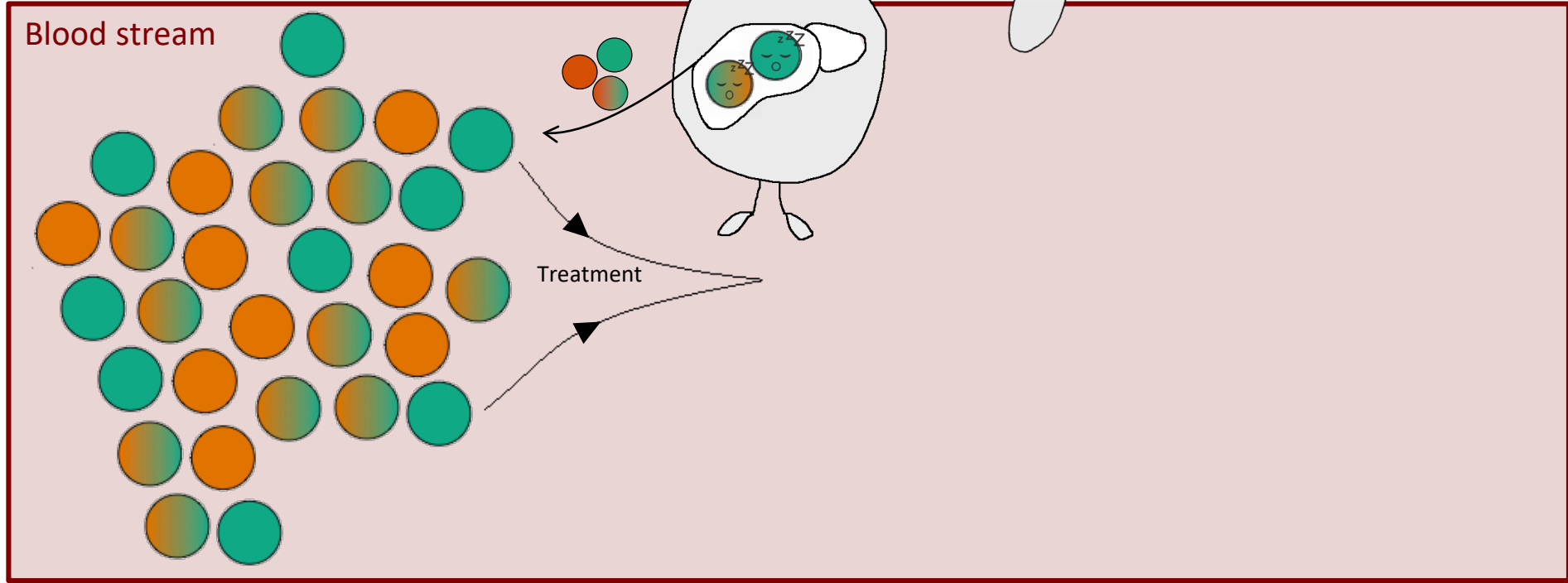
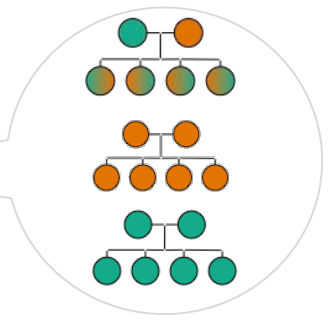
# Information in genetic data:

\*Different colours represent different lineages



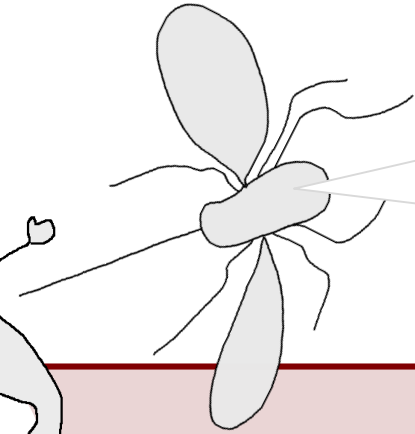
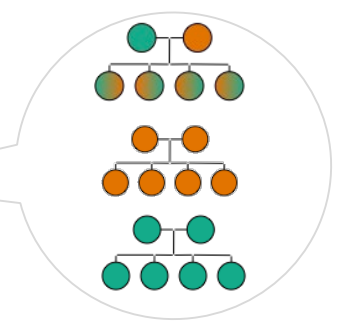
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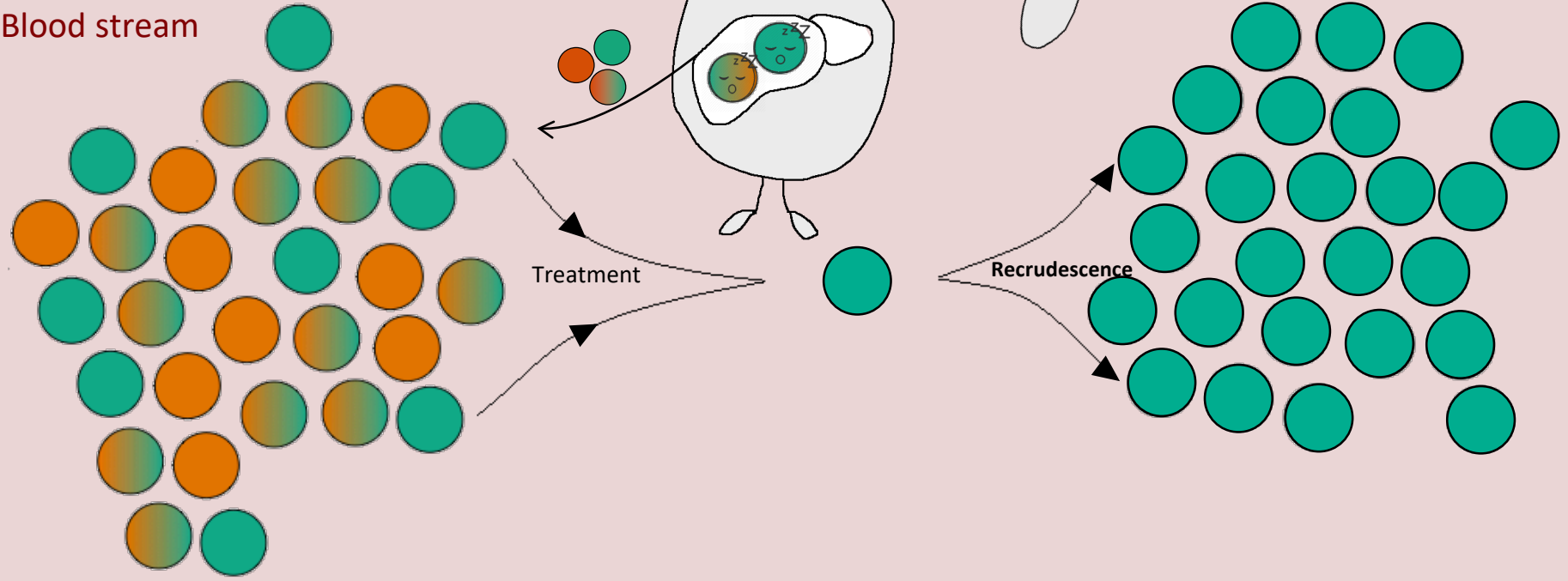


# Information in genetic data: *Recrudescence*

\*Different colours represent different lineages



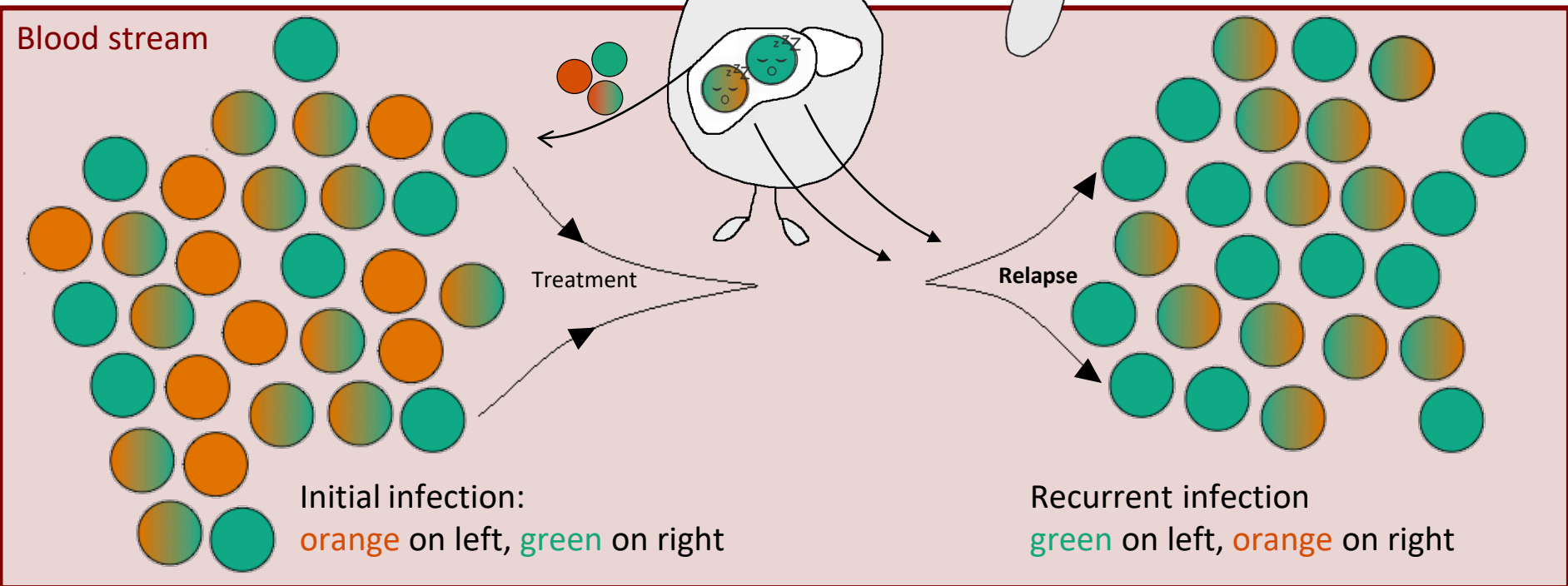
Blood stream



# Information in genetic data:

## *Relapse*

\*Different colours represent different lineages



Blood stream

Treatment

Relapse

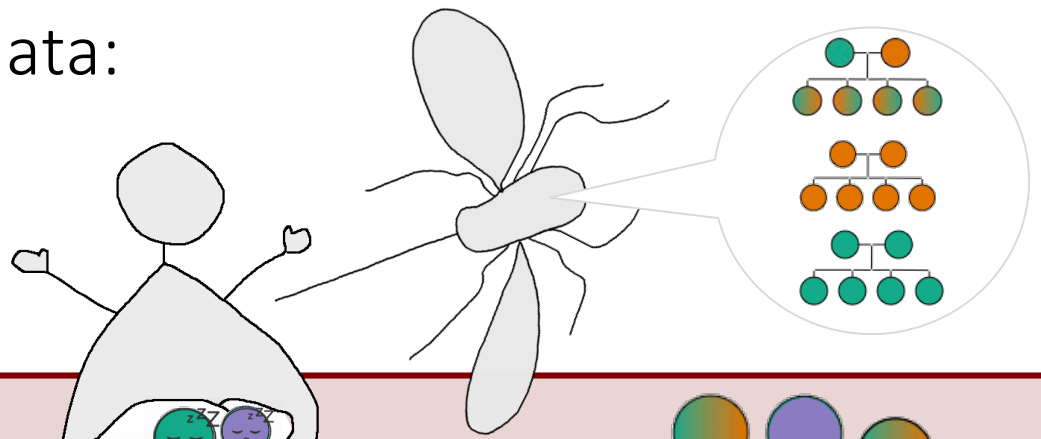
Initial infection:  
orange on left, green on right

Recurrent infection  
green on left, orange on right

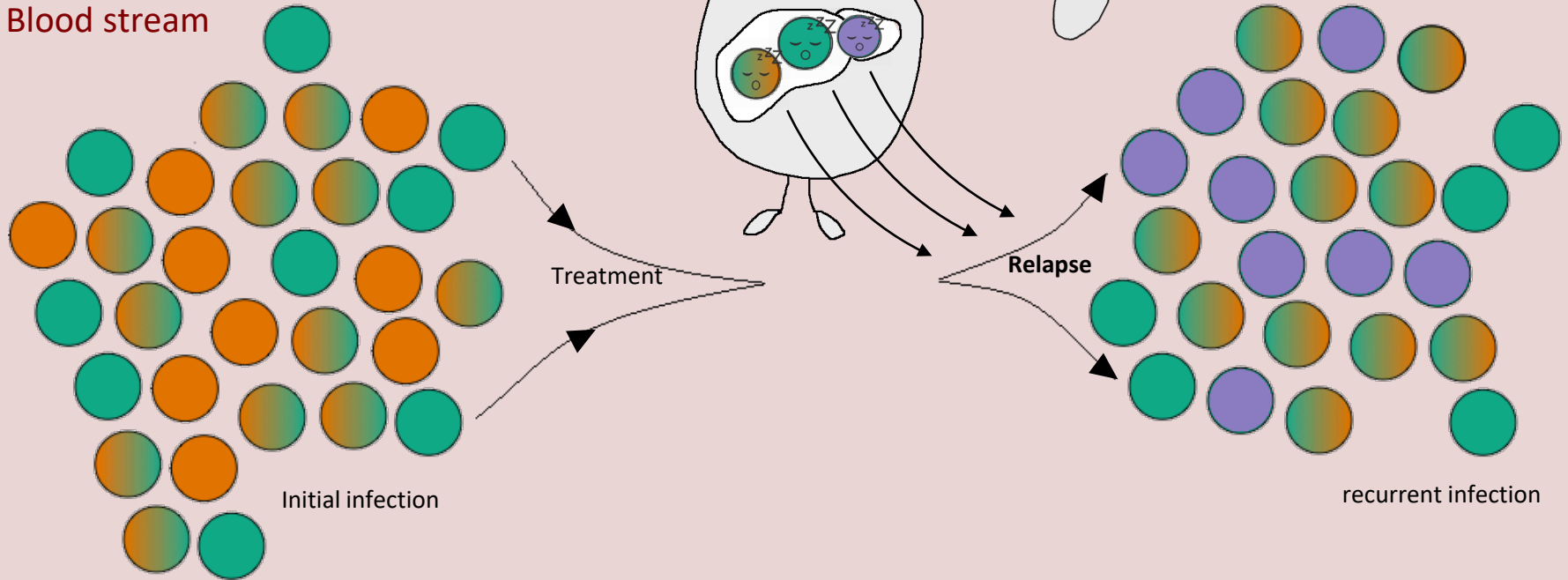
# Information in genetic data:

## *Relapse*

\*Different colours represent different lineages



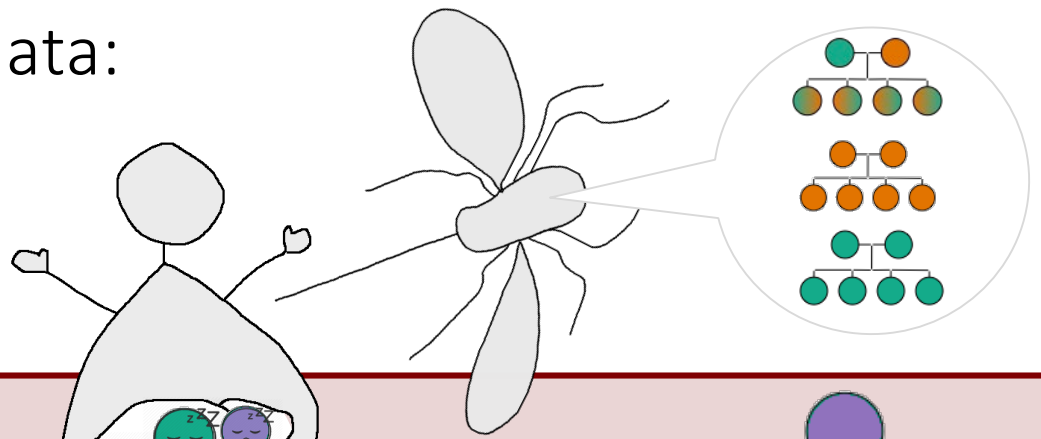
Blood stream



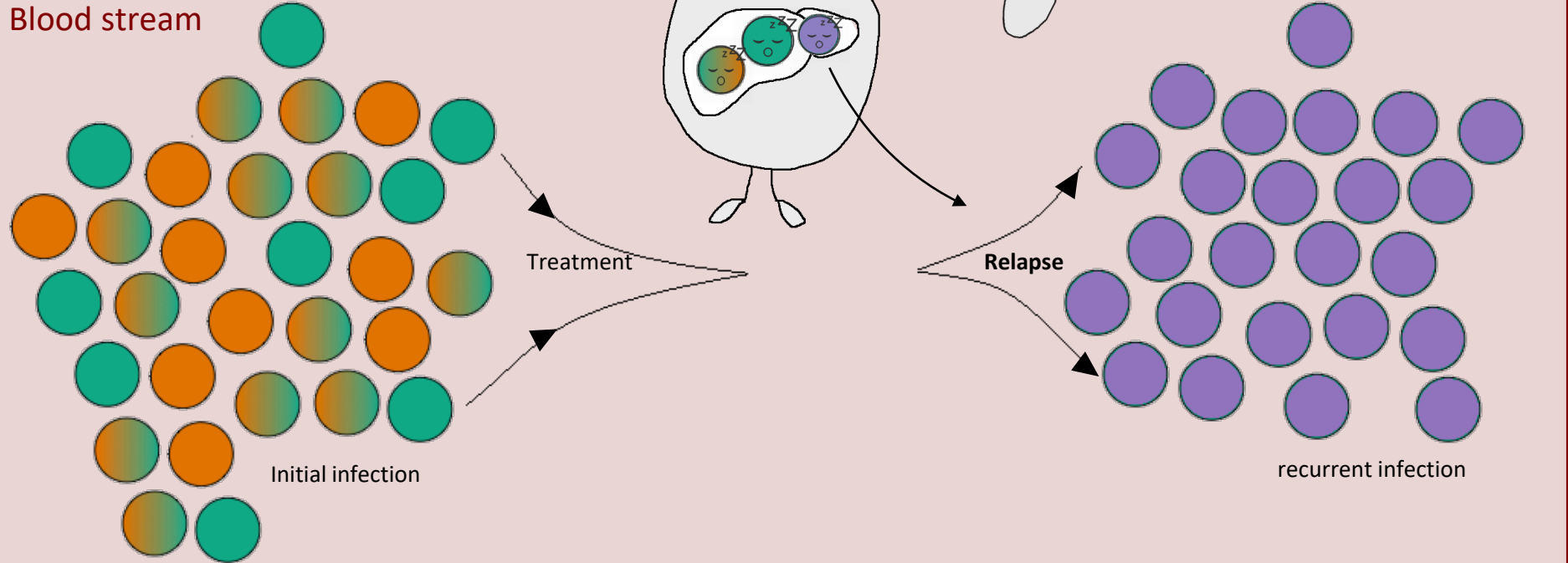
# Information in genetic data:

## *Relapse*

\*Different colours represent different lineages



Blood stream

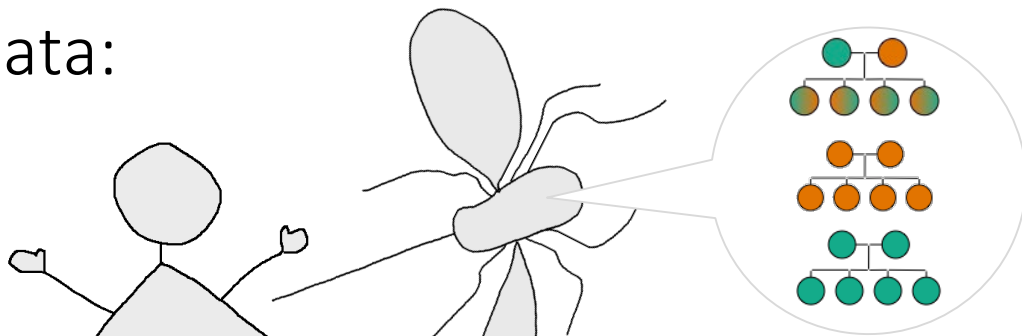




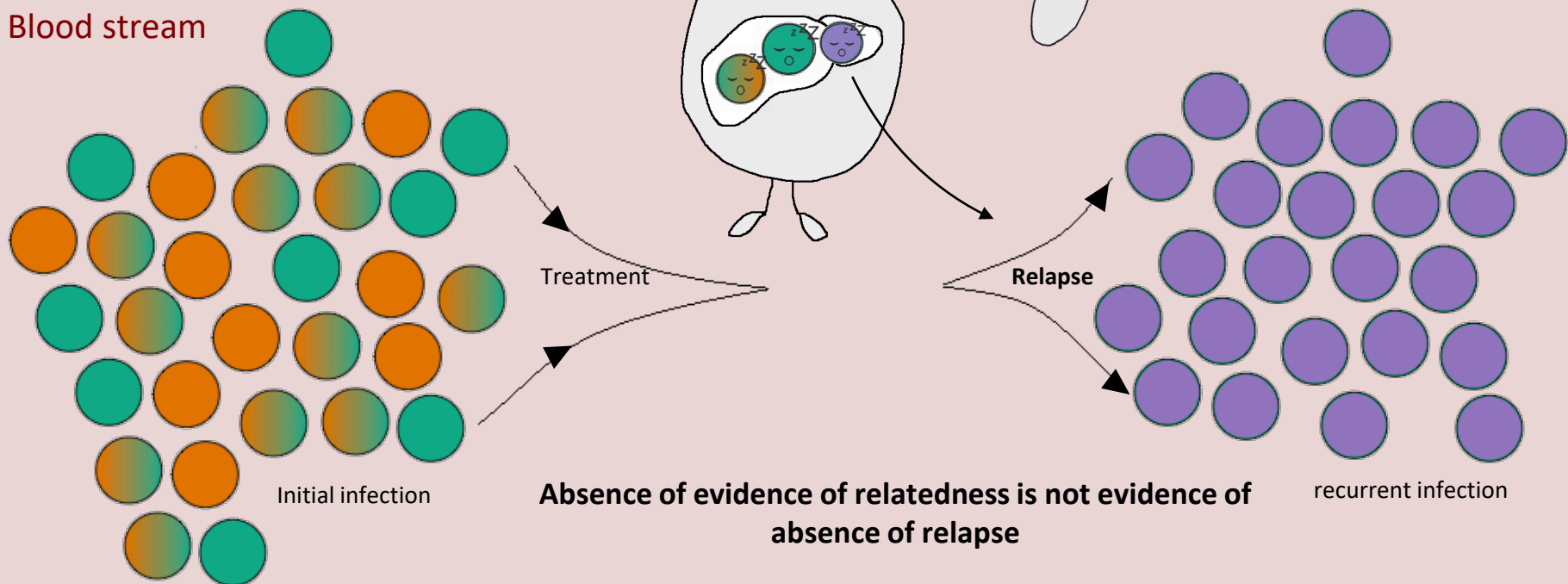
# Information in genetic data:

## *Relapse*

\*Different colours represent different lineages



Blood stream

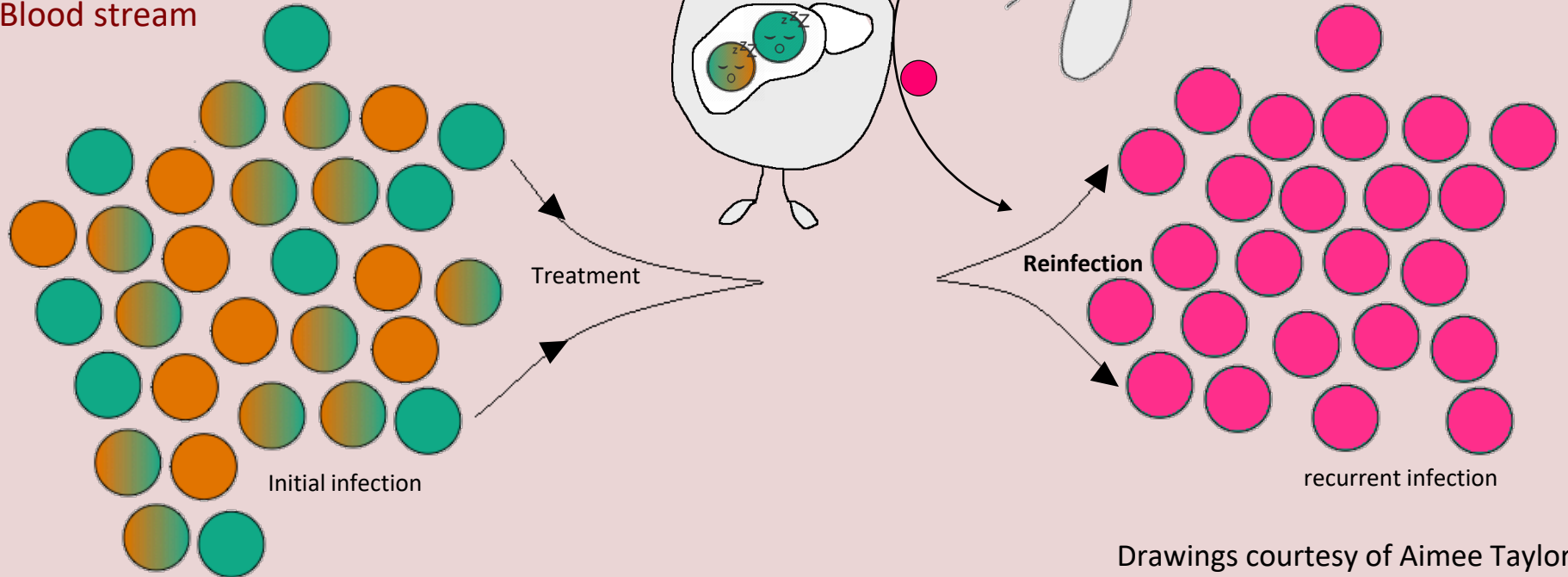


# Information in genetic data: *Reinfection*

New mosquito

\*Different colours represent different lineages

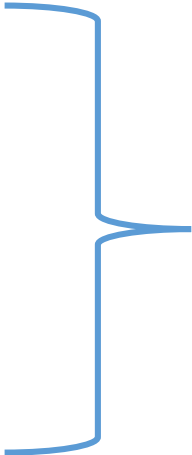
Blood stream



Drawings courtesy of Aimee Taylor

# Summary (conditional on our assumptions)

- Recrudescence: *clonal*
- Relapse: *clonal, sibling* or *stranger*
- Reinfection: *stranger*



Relationships of relatedness between parasite genomes in the initial and recurrent infections

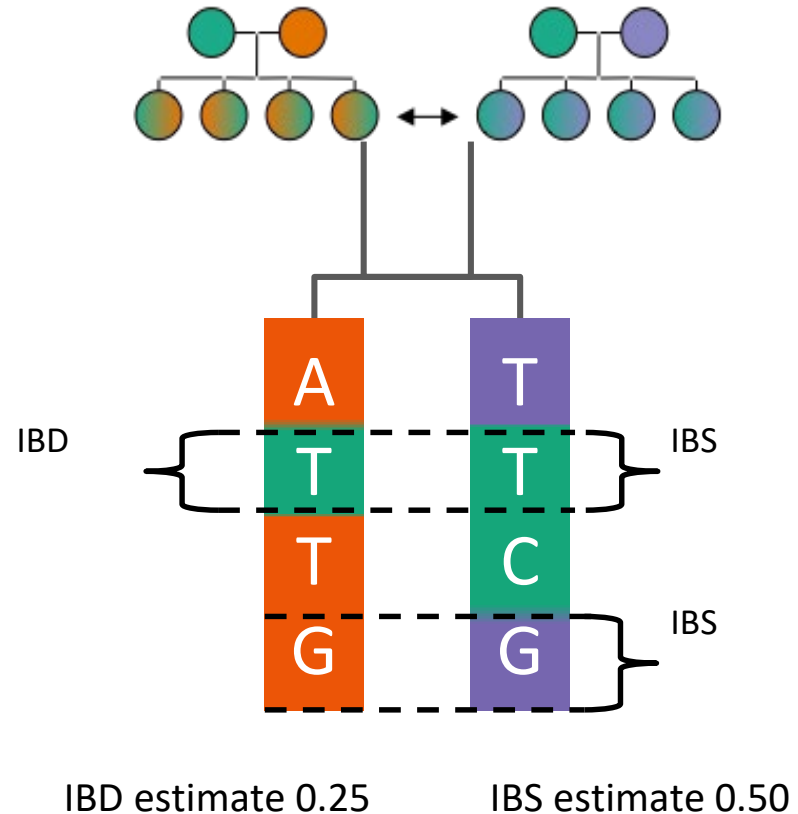
# Relatedness is the probability of identity-by-descent

**IBD Definition:** alleles are identical-by-descent if descended from a common ancestor (hidden)

**IBD** can be estimated using genetic data and a probabilistic model

**IBD** is sometimes approximated by allele sharing (identity-by-state, **IBS**)

**IBS Definition:** alleles are identical-by-state if they are genetically the same (observed)



# Information in time-to-recurrence data

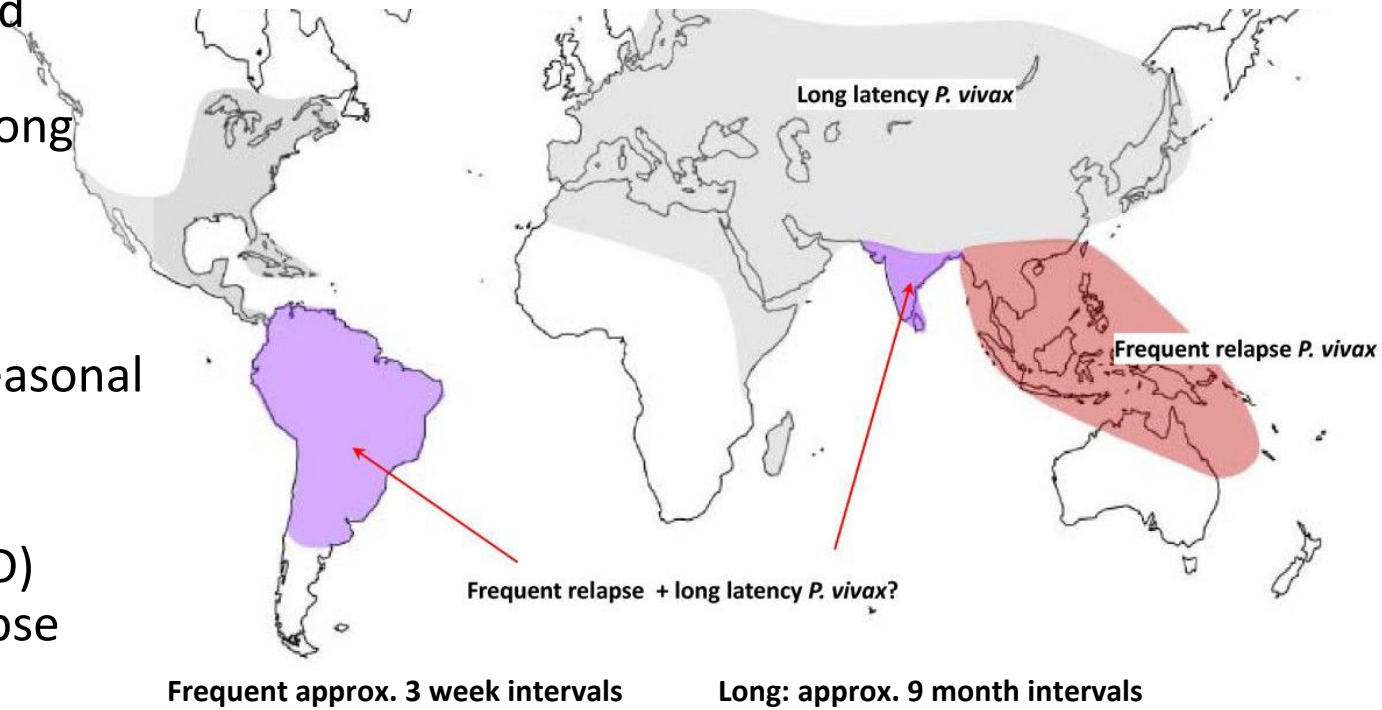
When do relapses happen most often?

# Information in time-to-recurrence data

- Both long-latency and frequent relapsing infections exhibit strong periodicity

- Reinfection rate is seasonal

- Pharmacology (PK-PD) impacts time to relapse and reinfection



# Goal

Estimate the probability that a recurrent *P. vivax* infection is a relapse using *P. vivax* genetic and time-to-recurrence data

# Two trials along Thailand-Myanmar border

Chloroquine resistance not a problem on the Thailand-Myanmar border

Standard of care: chloroquine + primaquine (PMQ)

One year follow up: weekly for 8 weeks then monthly

Every recurrence (malaria positive slide) treated (inc. asymptomatic)

## **Vivax History Trial**

2010 – 2012, 640 patients

Randomization: blood-stage only or radical cure

Each recurrence treated according to the initial randomisation

## **Best Primaquine Dose**

2012 – 2014, 655 patients

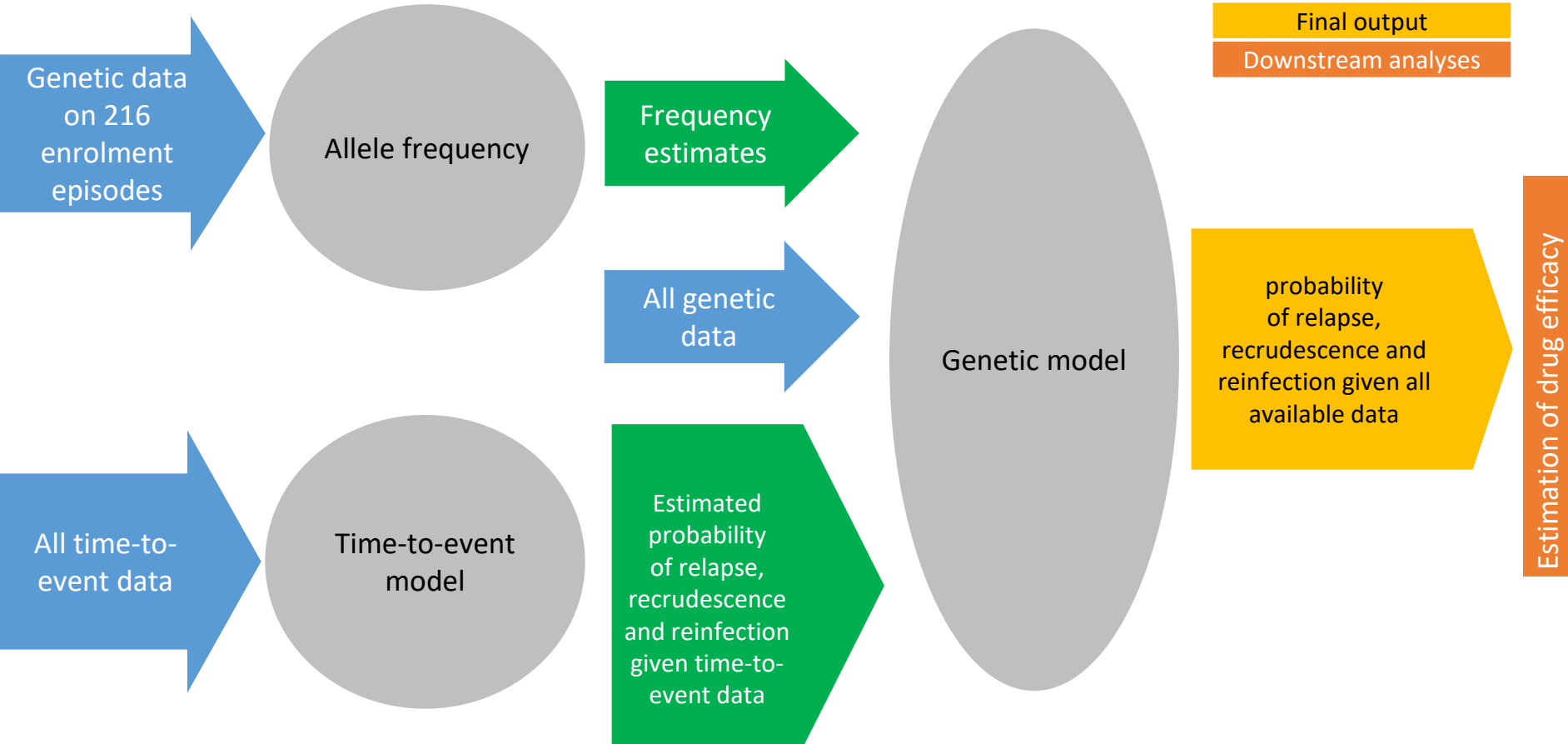
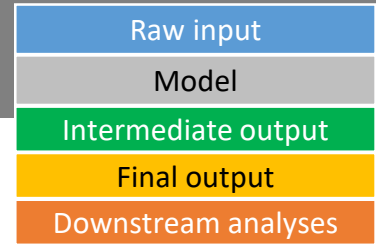
2-way randomisation (inc. 7 or 14 day PMQ); all received 7mg/kg total dose PMQ **radical cure**

Each recurrence treated with standard of care





# Bayesian statistical model framework



# Timing model

Mixture model (deals with censored time intervals, drug dependent model parameters)

$$\text{Time-to-recurrent infection} \sim p_i \text{ Time-to-relapse} + (1-p_i)[ w \text{ Time-to-reinfection} + (1-w) \text{ Time-to-recrudescence} ]$$

$p_i$  is an individual parameter

$$\text{Time-to-relapse} \sim q \text{ Periodic-relapse} + (1-q) \text{ Late/random-relapse}$$

- |                              |                            |   |
|------------------------------|----------------------------|---|
| <i>Periodic-relapse</i>      | = Weibull distribution     | } Strongly informative priors for identifiability |
| <i>Late/random-relapse</i>   | = Exponential distribution |   |
| <i>Time-to-reinfection</i>   | = Exponential distribution |   |
| <i>Time-to-recrudescence</i> | = Exponential distribution |   |

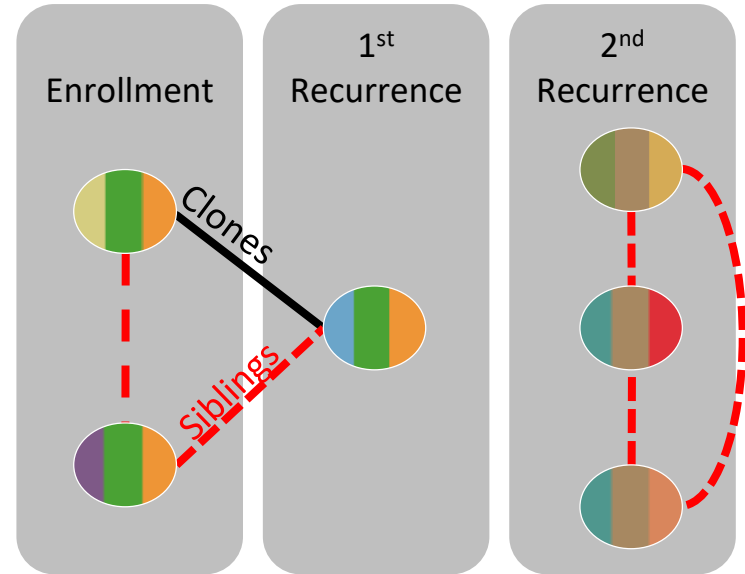
# Genetic model: overview

## Steps of the algorithm:

1. Estimate the complexity of each infection (how many different clones?)
2. Posit a (viable) graph of relationships **within** each infection and **across** infections
3. Calculate how likely the data are conditional on these relationship and the expected relatedness
4. Repeat steps 2-3 for all possible relationship graphs

For each relationship graph, calculate likelihood of phased microsatellite data. Chance sharing of common genetic markers is accounted for by specifying expected relatedness of each relationship in terms of identity-by-descent

Genetic model used to estimate relapse, recrudescence and reinfection for 487 recurrent episodes genotyped at 3-9 microsatellites



### Example graph

Each episode genotyped at 3 microsatellites  
Different colours = different observed alleles

Multiclonal data are phased based on:

- Evidence of two clones at enrolment
- Evidence of one clone in the 1st recurrence
- Evidence of three clones in the 2nd recurrence

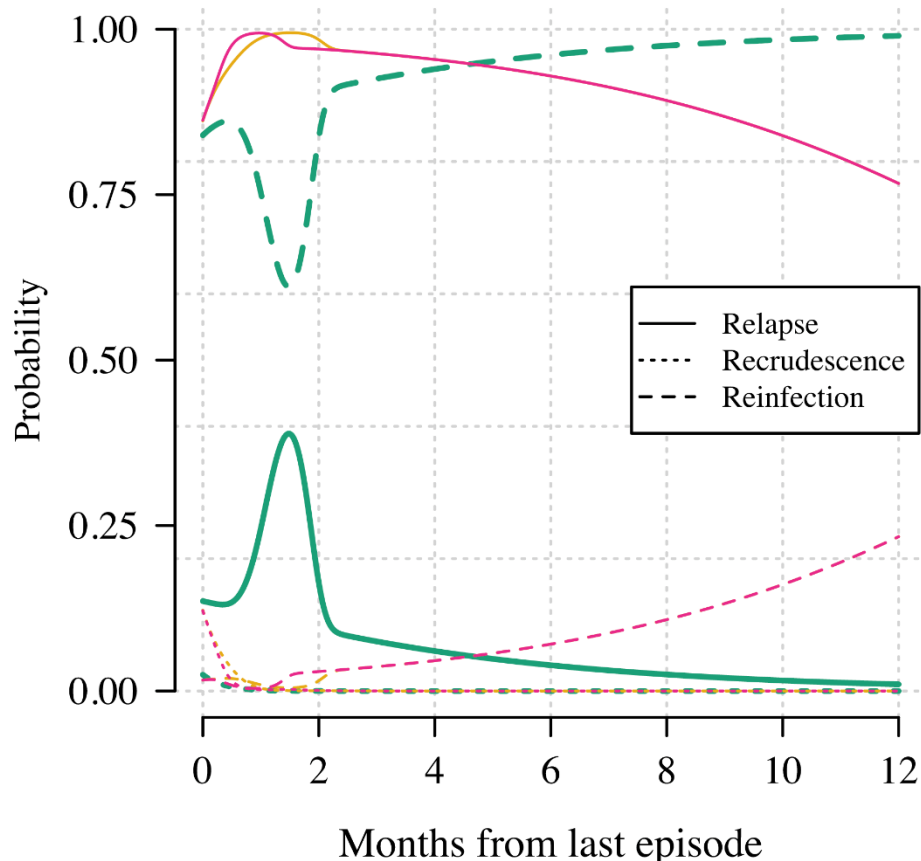
# Results

Joint analysis of all available data

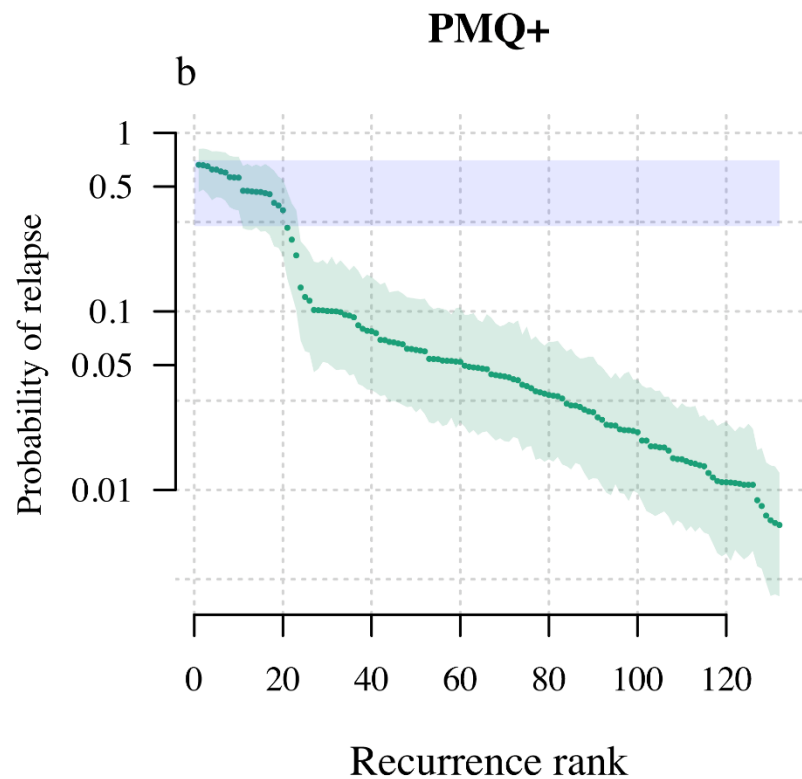
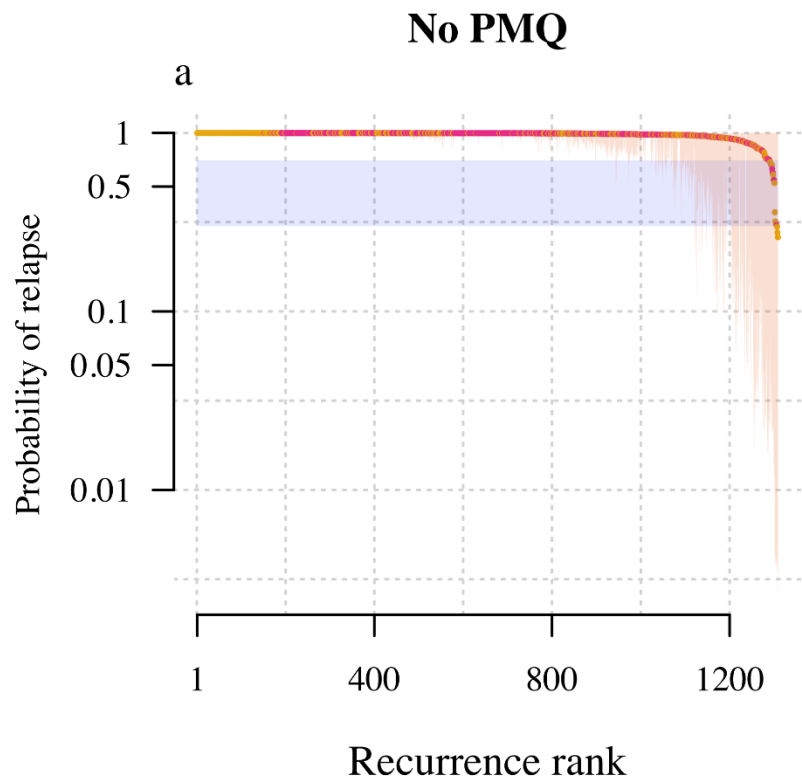
# Results: time-to-event model only

- Artesunate
- Chloroquine
- Primaquine+

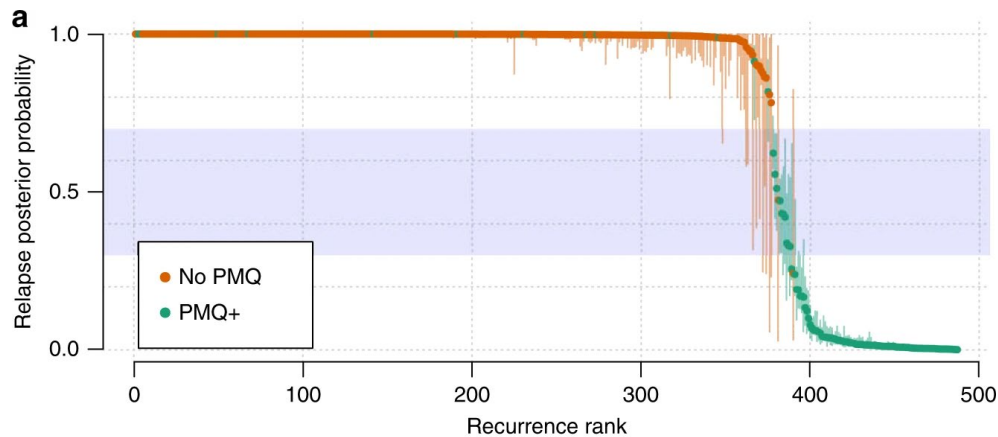
Results based on time-to-event model:  
average probabilities  
of recurrent states as a  
function of months  
from last episode



# Results: time-to-event model only

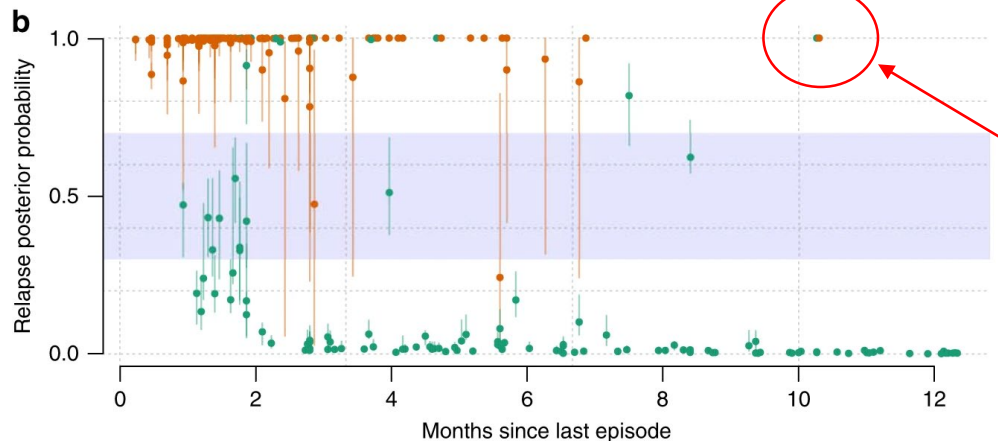


# Results: time-to-event and genetic combined



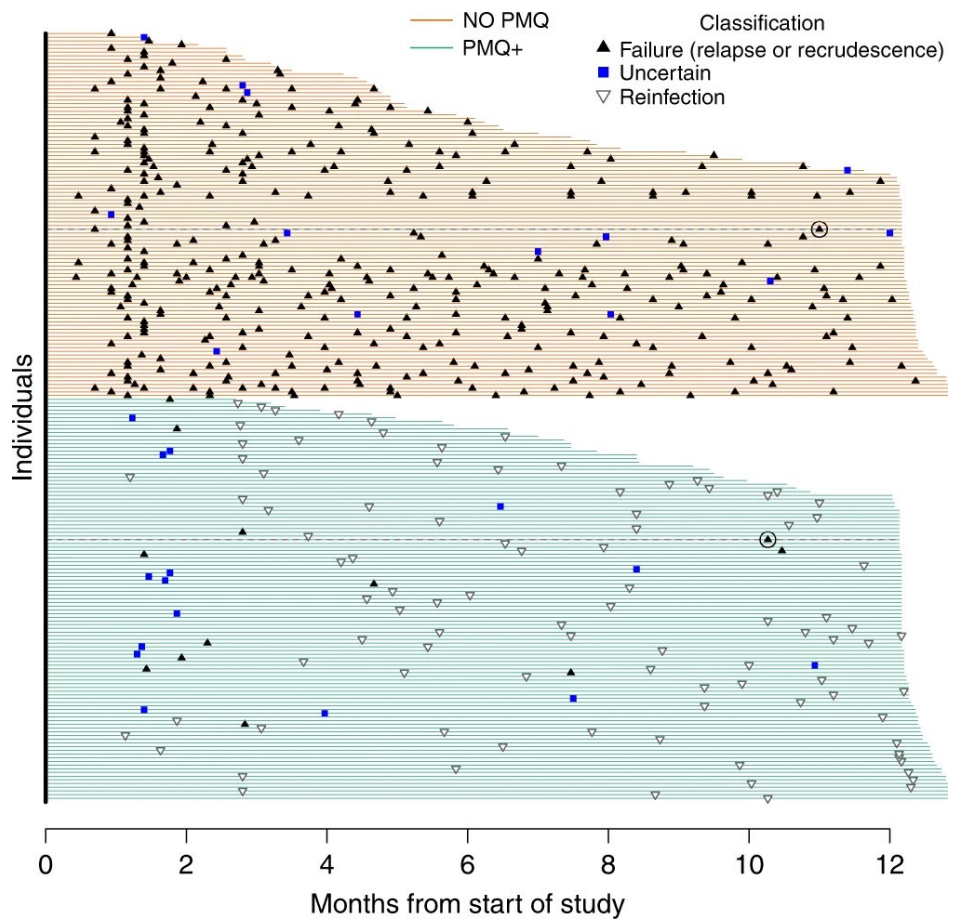
- In individuals not given radical cure (n = 366), on average 99% of the typed recurrences are estimated to be relapses

- In individuals who were given radical cure, on average 15% estimated to be relapses



- Two individuals estimated to have late relapses (>300 days since last episode)

# Results: time-to-event and genetic combined





# Results: revised failure rate estimates

Reinfection-adjusted failure rate estimates of supervised high-dose primaquine:

**2.9%** (2.3-3.8) in all data combined  
(n = 853, follow-up = 677 patient years)

Previous reinfection unadjusted failure rate estimate: **12%** (95% CI: 10-14)

~3 in 4 patients **not given primaquine** had at least one relapse

~1 in 40 patients **given primaquine** had at least one relapse

# Summary

High efficacy of supervised primaquine on Thailand-Myanmar border

Time-to-recurrence and genetic data provide complimentary information.

Joint analysis within a framework that allows amalgamation of different data types in a modular way that is generalisable to future data types.

# Acknowledgements

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Tropical Health Network



Taylor, Watson, *et al.* Resolving the cause of recurrent vivax malaria probabilistically. *Nature Communications* (2019)