

# An Introduction to Modelling Vector-borne Diseases

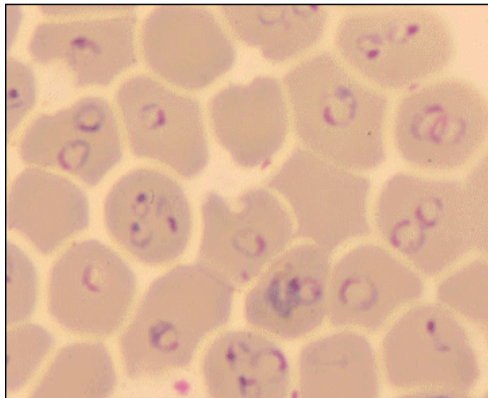
**Prof. María-Gloria Basáñez**

[m.basanez@imperial.ac.uk](mailto:m.basanez@imperial.ac.uk)

Department of Infectious Disease Epidemiology

# Human malaria *Plasmodium* species

## *Plasmodium falciparum*



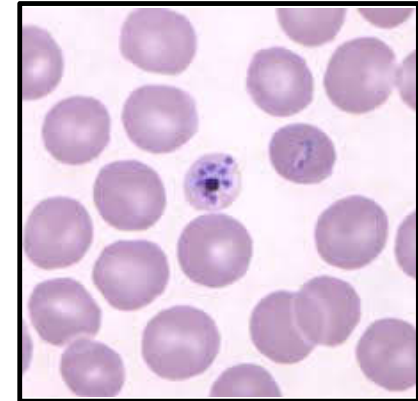
(original image provided by Steve Aley)

Africa  
SE Asia  
Latin America

## *P. malariae*



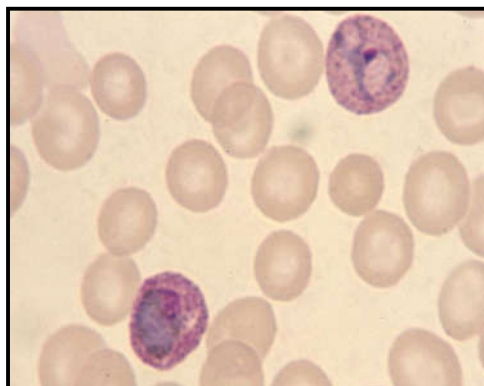
## *P. knowlesi*



(mcdinternational.org)

Southeast Asia

## *P. vivax*

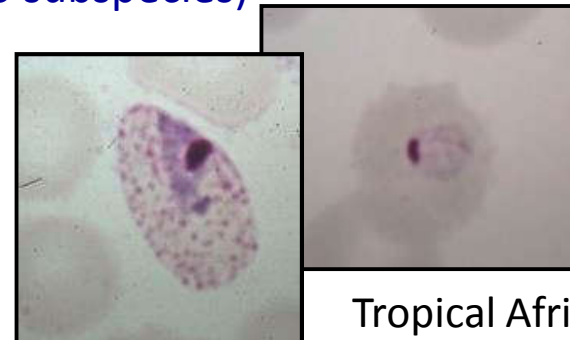


(original image by Mark Lontie)

Middle East  
Asia  
Western Pacific  
Latin America  
Africa

## *P. ovale*

(now two subspecies)



Tropical Africa  
West Pacific

# Human malaria is transmitted by *Anopheles* species mosquitoes

*Anopheles gambiae* s.l.



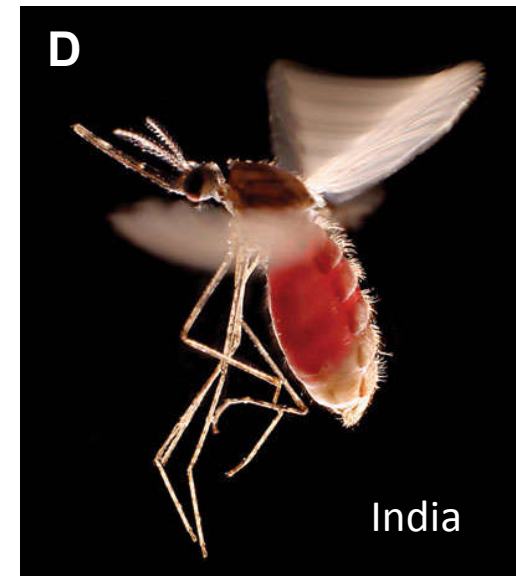
*Anopheles funestus*



*Anopheles albimanus*



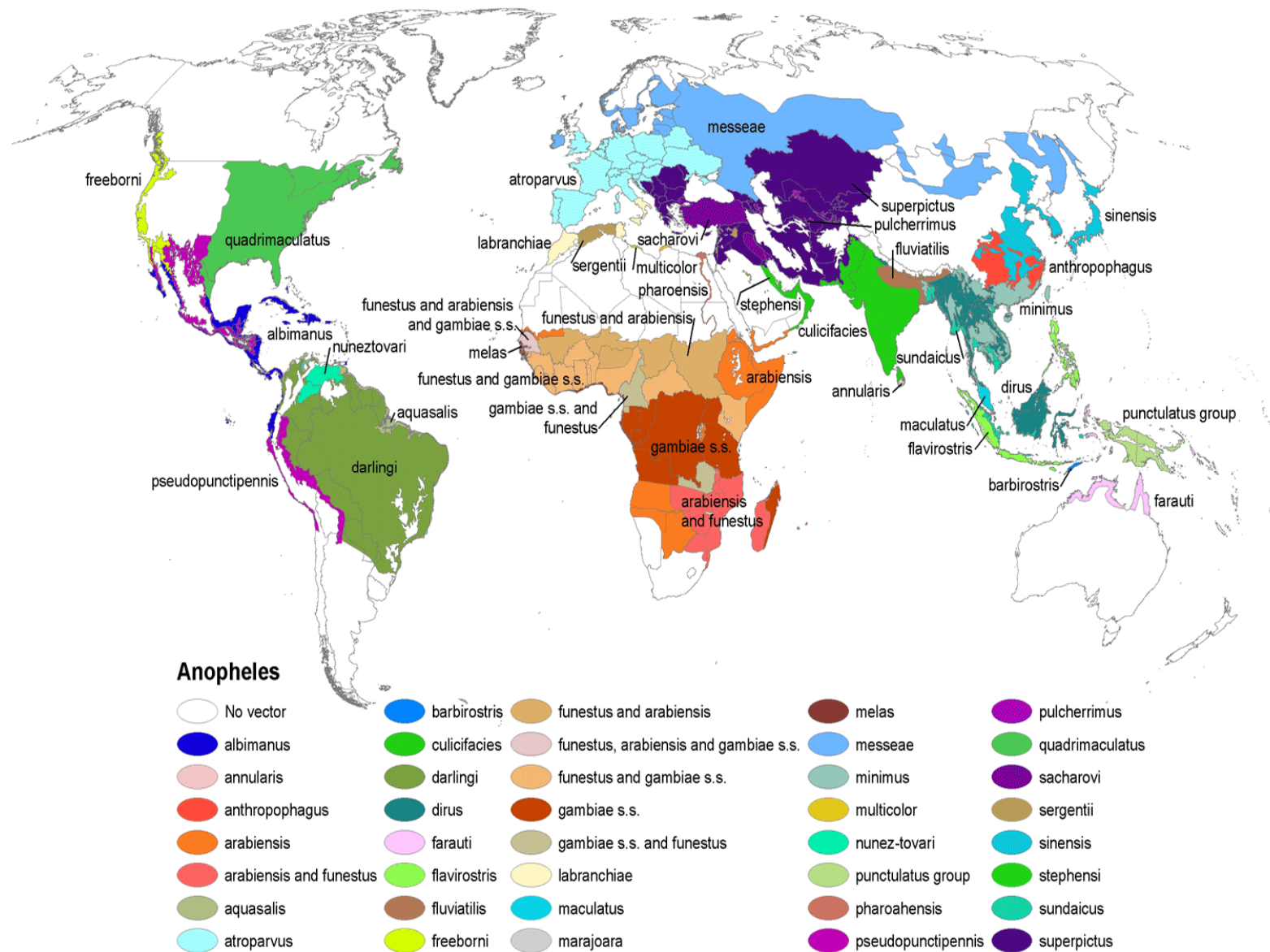
*Anopheles stephensi*



A, B, C = CDC  
Image Library

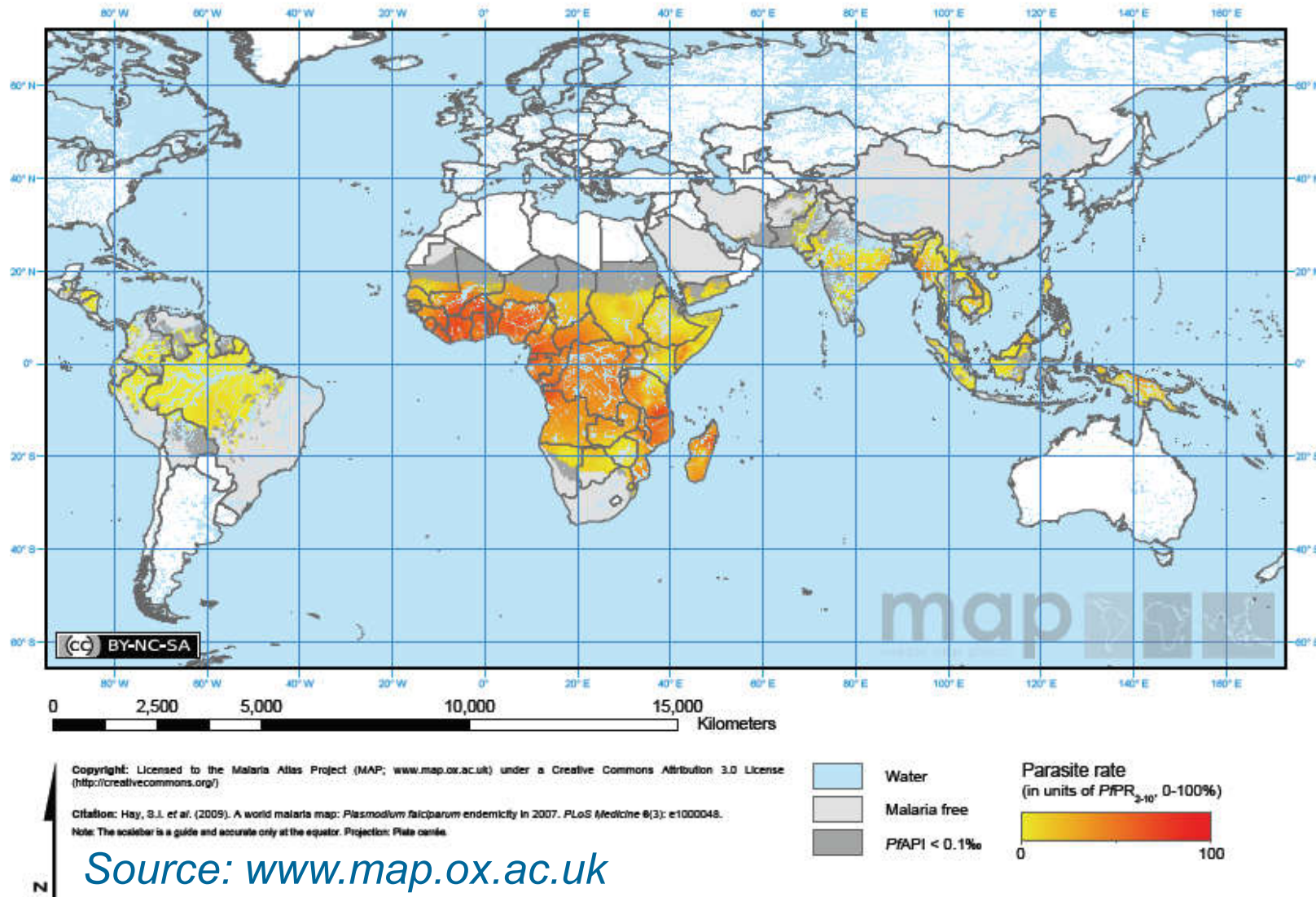
D = The  
Wellcome Trust

# Distribution of *Anopheles* vectors



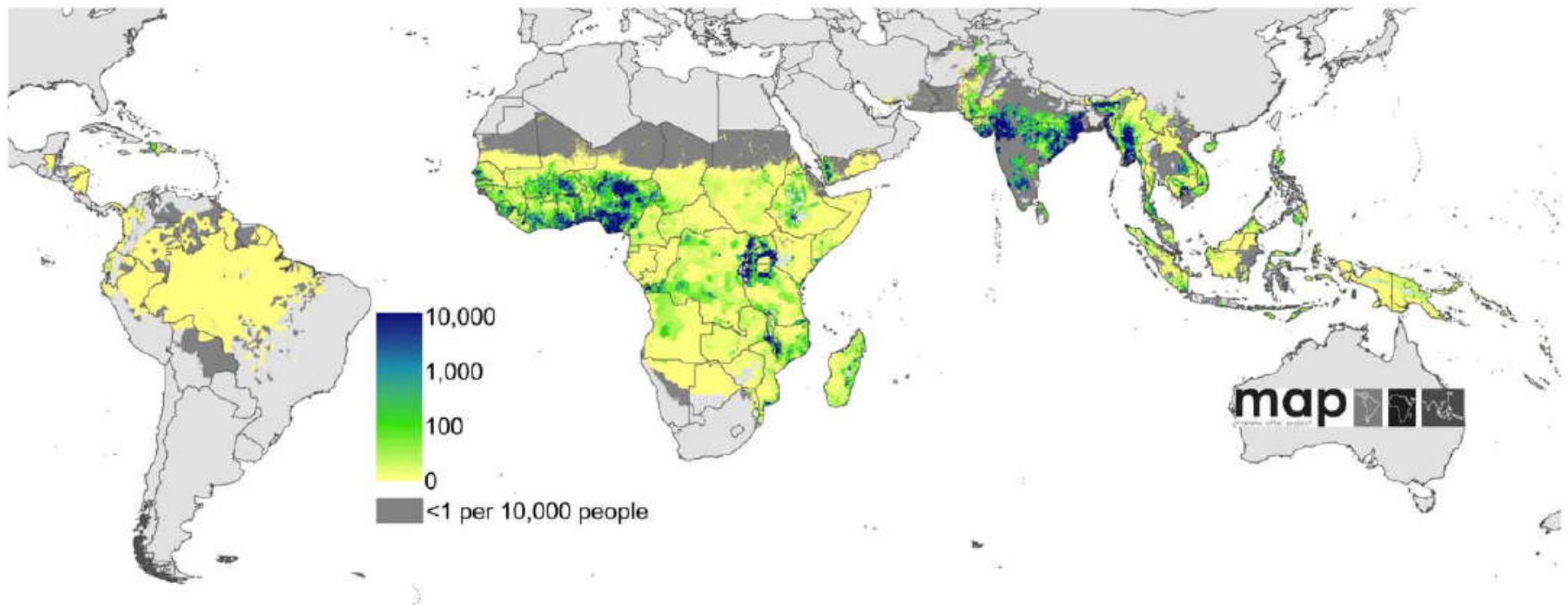
# Prevalence of *P. falciparum* in 2007

The spatial distribution of *Plasmodium falciparum* malaria endemicity in the World



# Burden of Disease in 2007

- Estimated 450 million (95% Credible Intervals 349-552 million) cases of malaria
- Majority of cases in population-dense areas e.g. India, Nigeria



*Hay et al. (2010) PLoS Med 7(6)*

# Malaria Burden in 2017

**Data from 2015–2017 highlight that no significant progress in reducing global malaria cases was made in this period. There were an estimated 219 million cases and 435,000 related deaths in 2017**

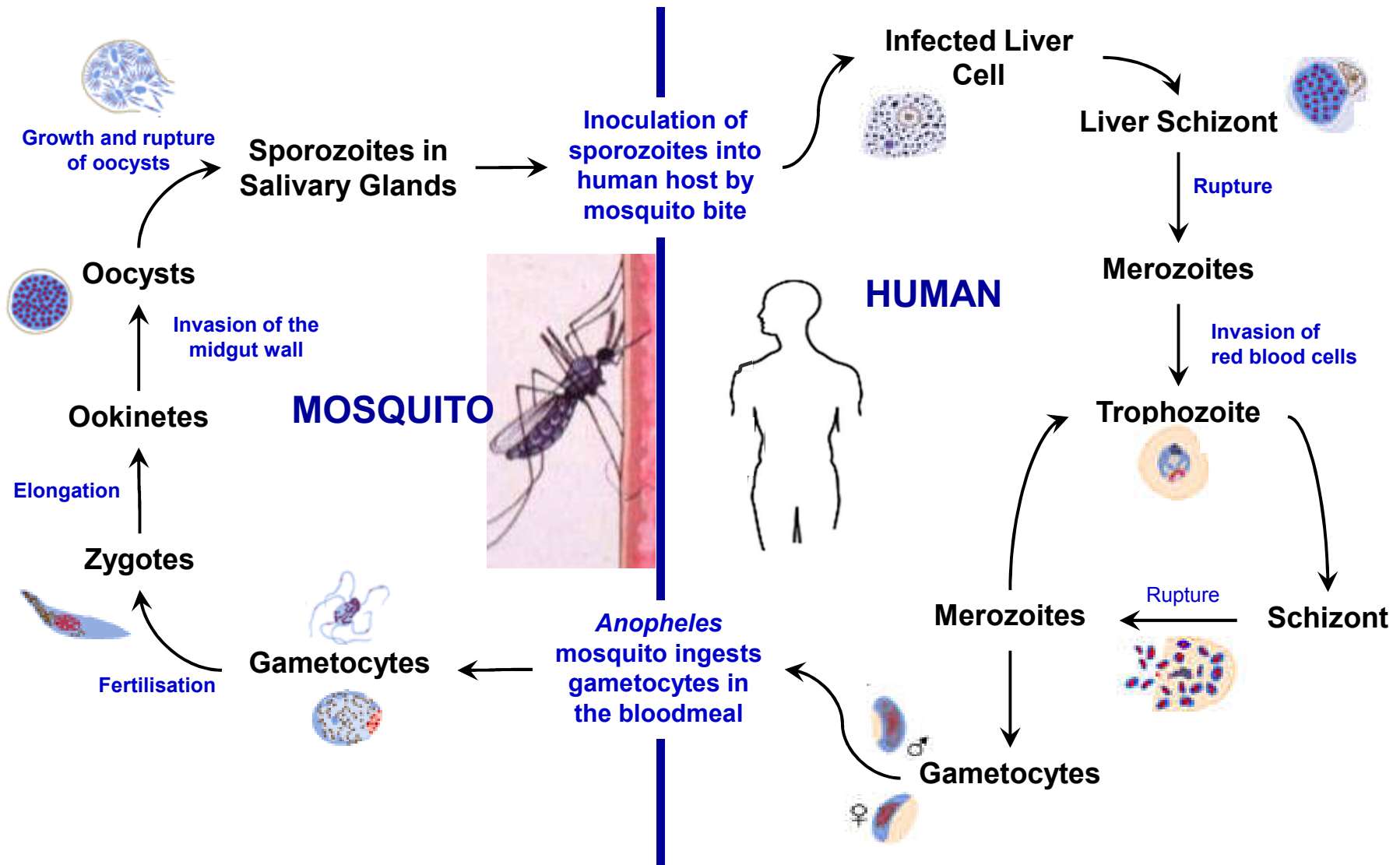
## GLOBAL AND REGIONAL MALARIA BURDEN



### Malaria cases

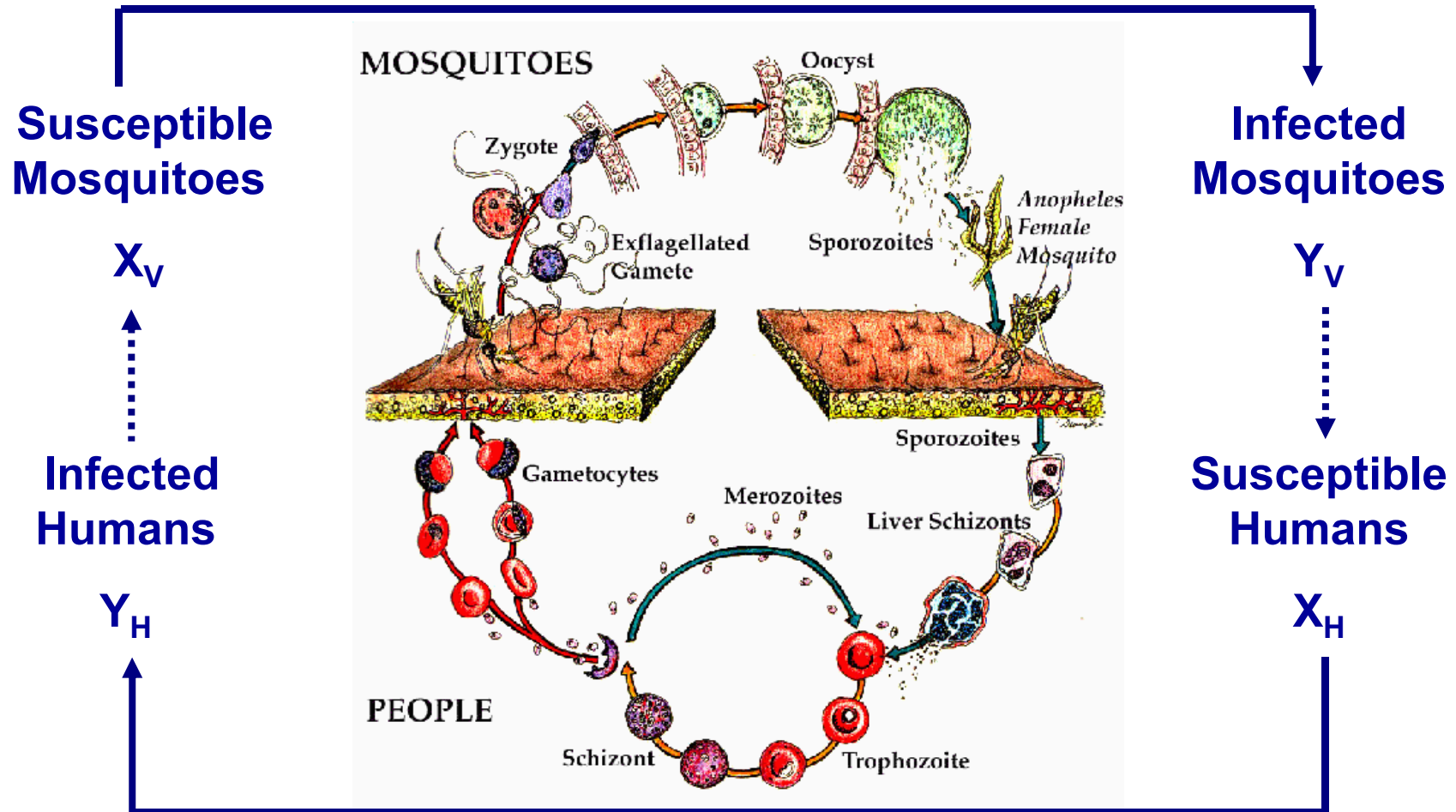
- In 2017, an estimated 219 million cases of malaria occurred worldwide (95% confidence interval [CI]: 203–262 million), compared with 239 million cases in 2010 (95% CI: 219–285 million) and 217 million cases in 2016 (95% CI: 200–259 million).
- Although there were an estimated 20 million fewer malaria cases in 2017 than in 2010, data for the period 2015–2017 highlight that no significant progress in reducing global malaria cases was made in this timeframe.
- Most malaria cases in 2017 were in the WHO African Region (200 million or 92%), followed by the WHO South-East Asia Region with 5% of the cases and the WHO Eastern Mediterranean Region with 2%.
- Fifteen countries in sub-Saharan Africa and India carried almost 80% of the global malaria burden. Five countries accounted for nearly half of all malaria cases worldwide: Nigeria (25%), Democratic Republic of the Congo (11%), Mozambique (5%), India (4%) and Uganda (4%).

# Life-cycle of *Plasmodium falciparum*



# Life-cycle of the Malaria Parasite

$$\text{Vector population (V)} = X_V + Y_V$$



$$\text{Host population (H)} = X_H + Y_H$$

# The building blocks of our first vector-borne pathogen model

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- $m = (V / H)$  Vector to human ratio
- $a = (h / g)$  Biting rate per vector on humans
- $b_V, b_H$  Probabilities of transmission upon contact from human to vector, and from vector to human
- $n$  Within-vector latency: extrinsic incubation period, EIP
- $p$  Daily probability of vector survival
- $\mu_V = -\ln(p)$  Per capita vector mortality rate
- $r$  Per capita rate of host recovery

# Building blocks and notation – Basic malaria model

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$X_H / H$  = Proportion of humans susceptible

$x_H$

$X_V / V$  = Proportion of vectors susceptible

$x_V$

$Y_H / H$  = Proportion of humans infected / infective

$y_H$

$Y_V / V$  = Proportion of vectors infected / infective

$y_V$

$V / H$  = The vector to human ratio

$m$

Biting rate per mosquito on humans

$a$

[Reciprocal of gonotrophic cycle length ( $1/g$ ) \* the proportion of blood meals taken on humans ( $h$ )]

Probability of transmission from vector to human, per bite

$b_H$  (b)

Probability of transmission from human to vector, per bite

$b_V$  (c)

Per capita mortality rate of humans

$\mu_H$

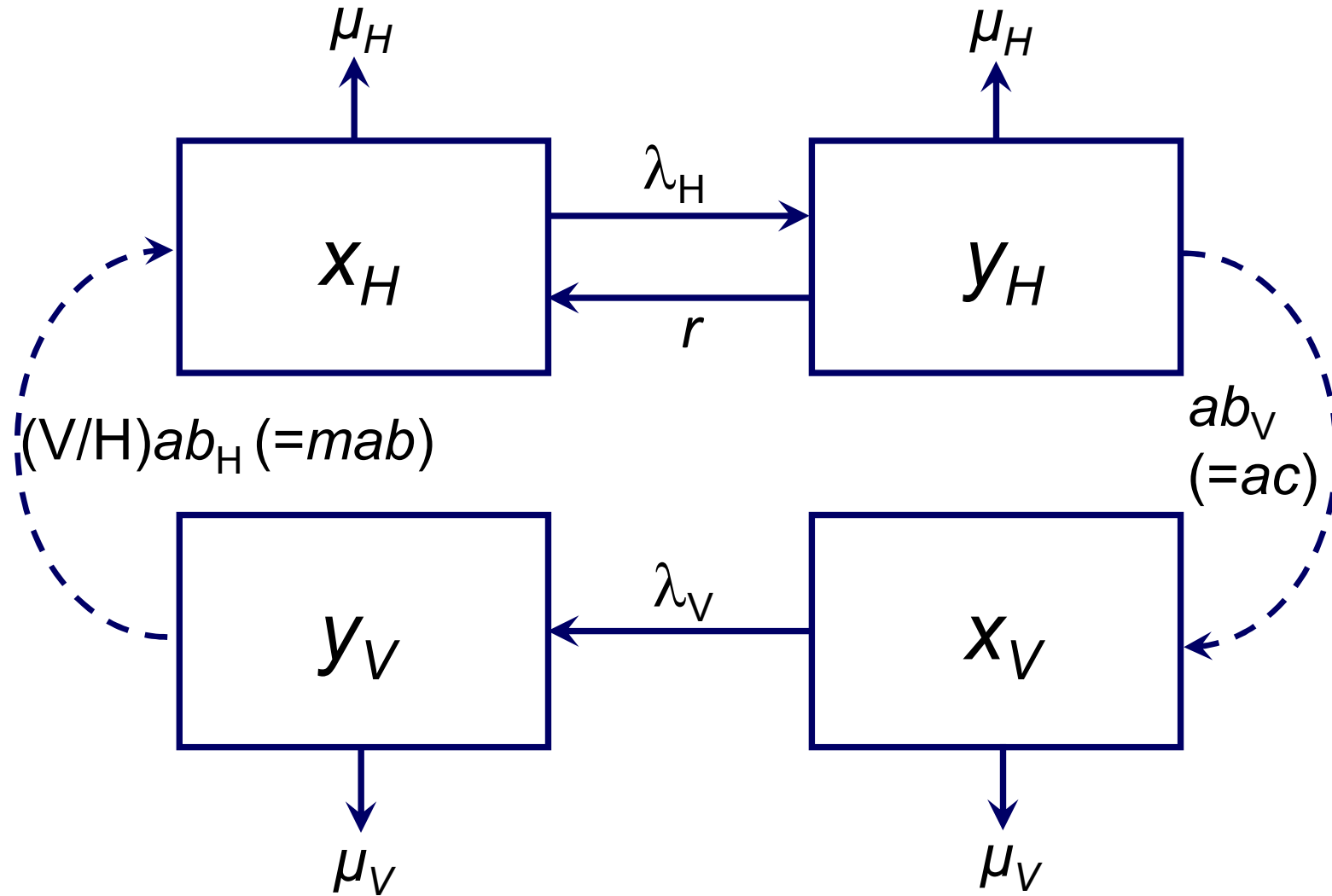
Per capita mortality rate of vectors

$\mu_V$

Per capita recovery rate of humans

$r$

## Flow diagram



# Equations

$$\underbrace{\lambda_H}_{\text{EIR}} = \text{FOI from vectors to humans}$$

Humans:

$$\frac{d y_H}{dt} = \underbrace{\frac{V}{H} a y_V b_H}_{\text{EIR}} (1 - y_H) - (r + \mu_H) y_H$$

*As  $r \gg \mu_H$ , often simplified to:*

$$\frac{d y_H}{dt} = \frac{V}{H} a y_V b_H (1 - y_H) - r y_H$$

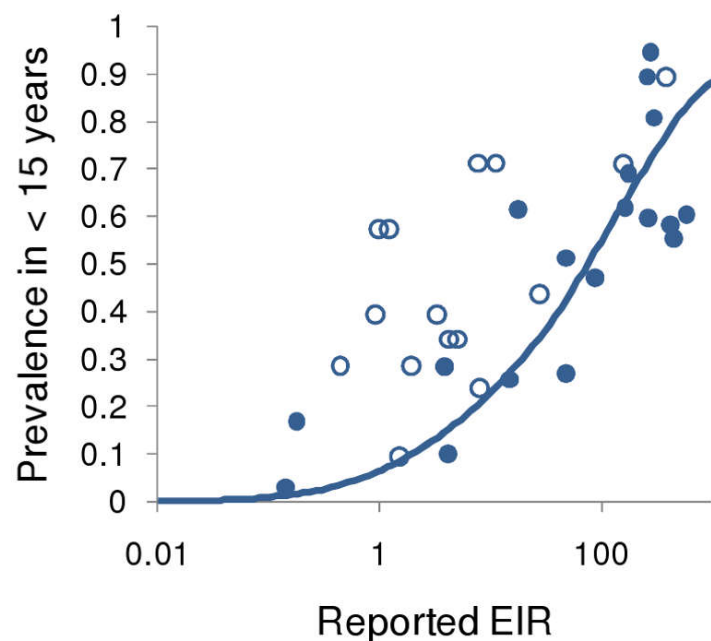
Vectors:

$$\frac{d y_V}{dt} = \underbrace{a y_H b_V}_{\lambda_V = \text{FOI from human to vectors}} (1 - y_V) - \mu_V y_V$$

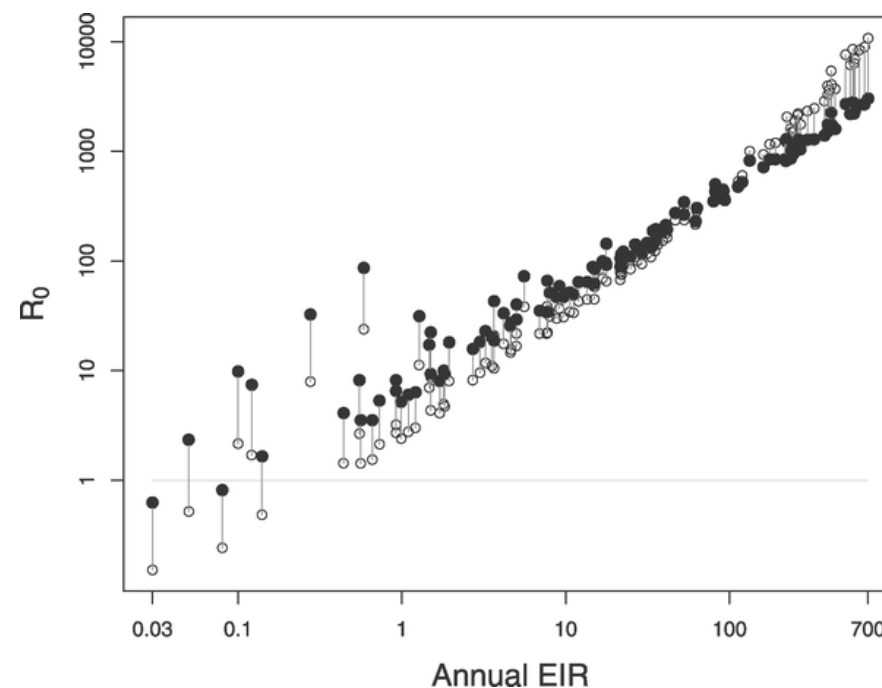
Mosquitoes assumed not to recover from infection and remain infected/infectious for life

# Transmission Intensity (Malaria): EIR, Parasite Prevalence and $R_0$

- Marked variation in the average number of infectious bites to which individuals are exposed (Entomological Inoculation Rate – EIR)
- Determines the reproduction number ( $R_0$ ) in any setting as well as endemic prevalence



*Griffin et al. (2010) PLoS Med 7(8)*



*Smith et al. (2007) PLoS Biol 5(3):e42*

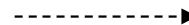
susceptible



infected



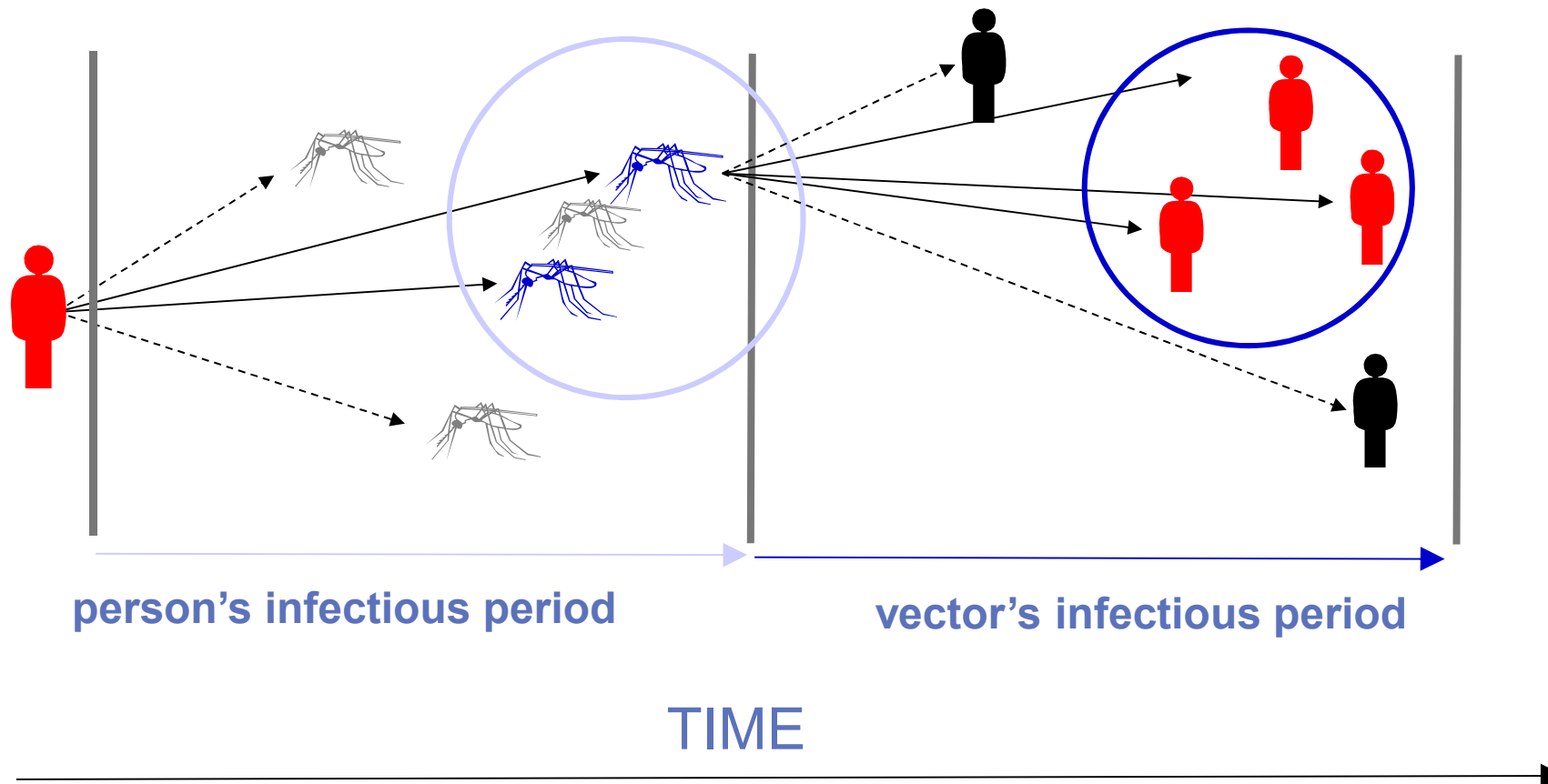
no infection



infection

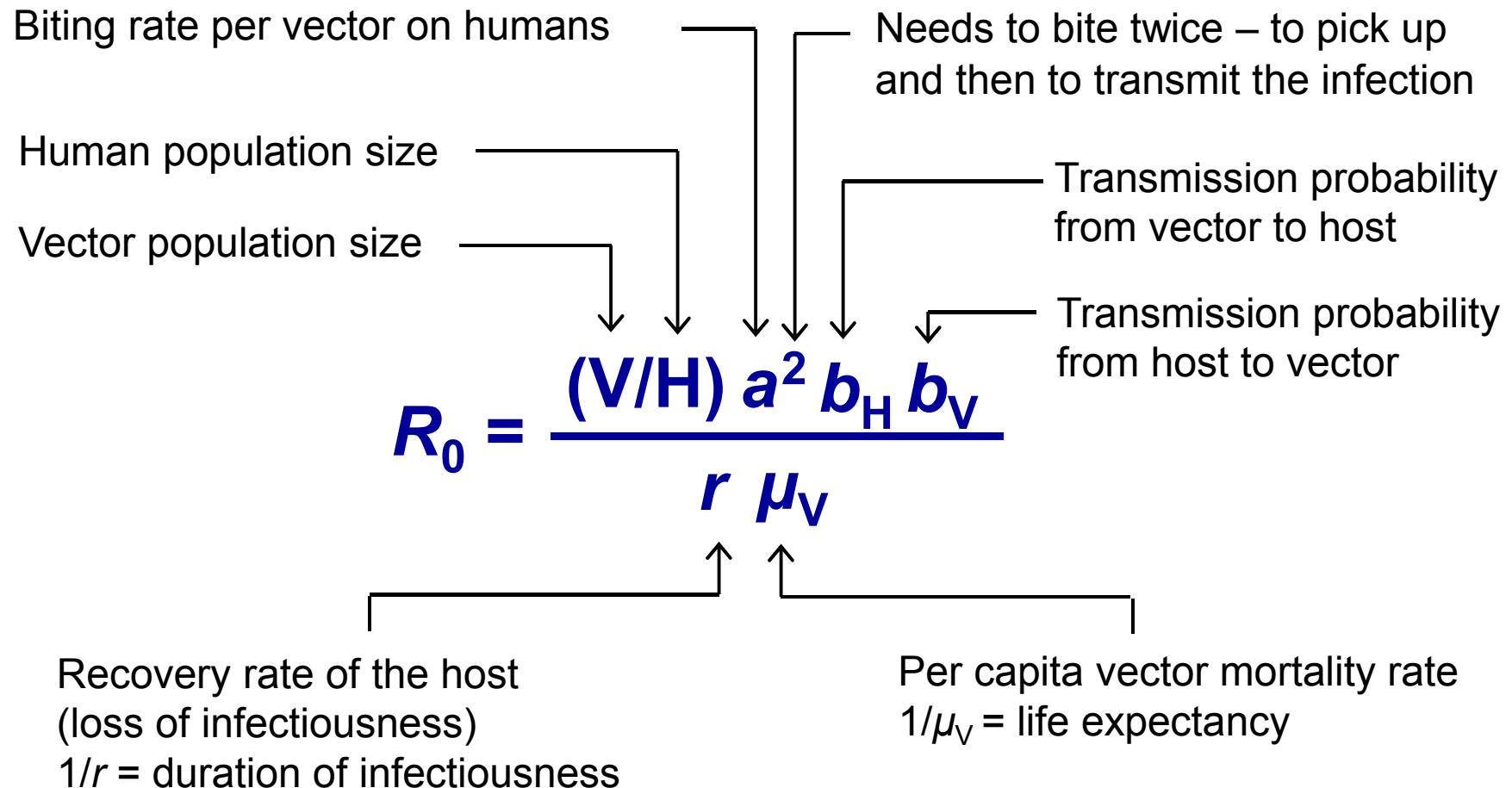


$$R_0 = \underbrace{(\text{no. vectors infected by the person})}_{R_0 H} \times \underbrace{(\text{no. people infected by a vector})}_{R_0 V}$$

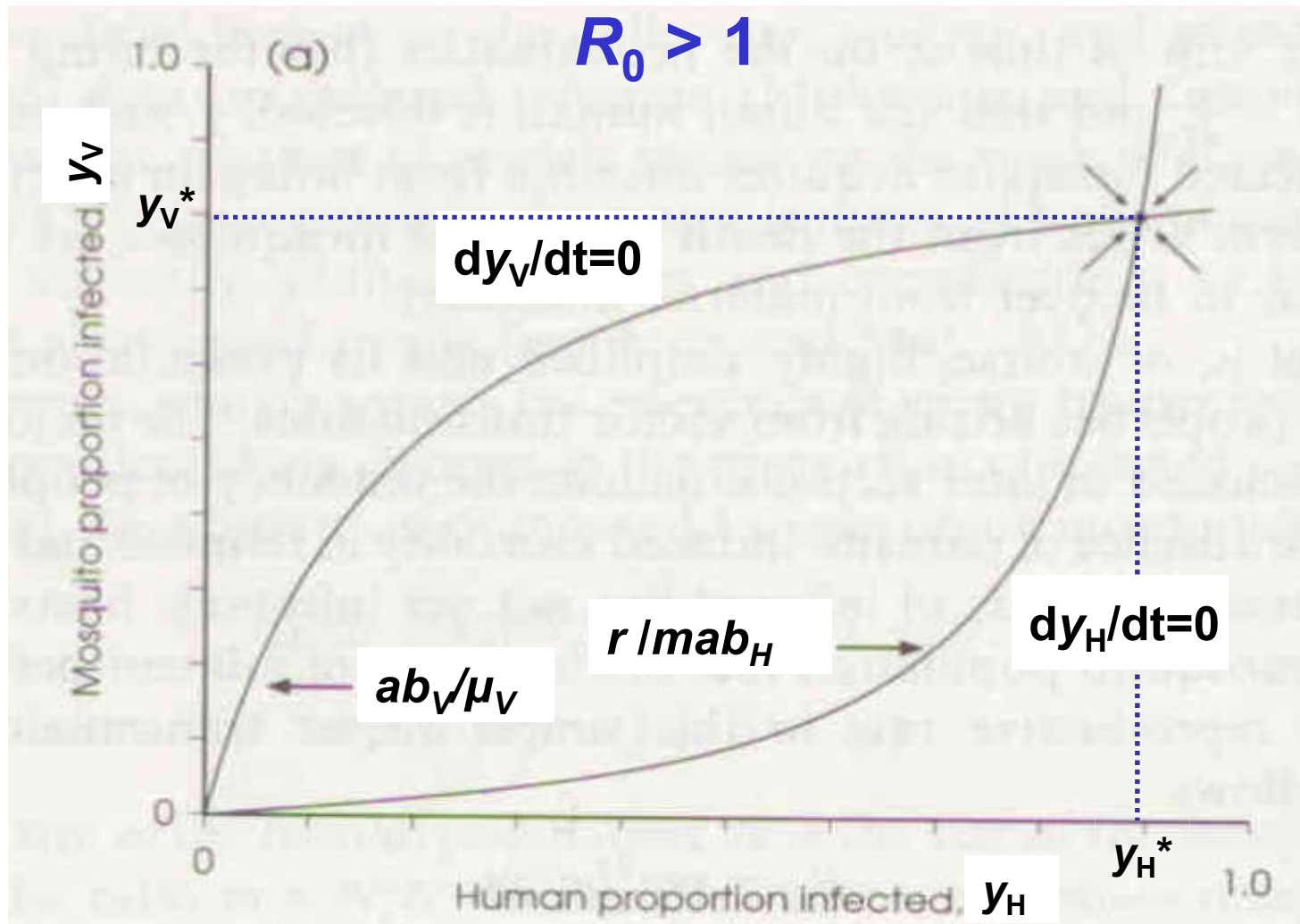


# $R_0$ of Vector-borne Diseases

## Ignoring the extrinsic incubation period

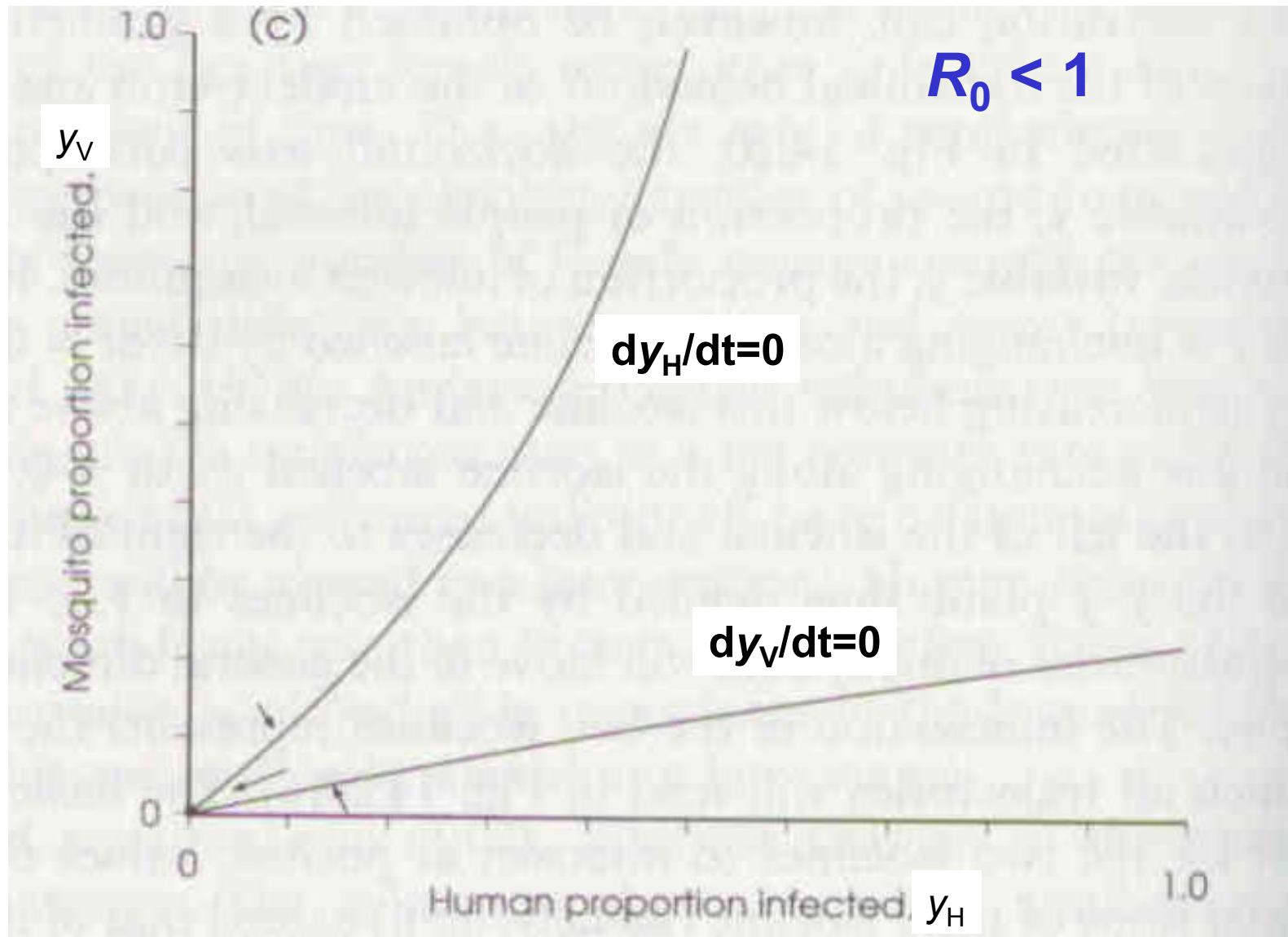


# Stable malaria



*Anderson & May (1991) Infectious Diseases of Humans. OUP*

# Unstable malaria



*Anderson & May (1991) Infectious Diseases of Humans. OUP*

# RELATIONSHIP BETWEEN DURATION IN A COMPARTMENT OF THE MODEL & THE RATE AT WHICH INDIVIDUALS LEAVE THE COMPARTMENT

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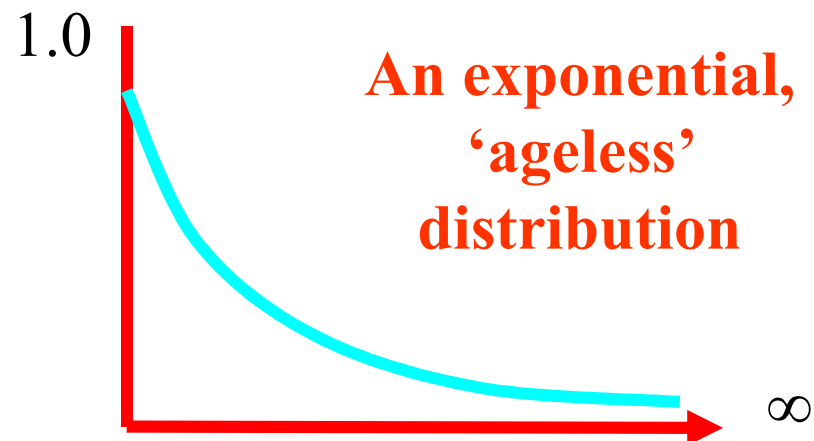
Proportion of individuals in compartment,  $z$

leaving rate is constant,  $\gamma$

Duration in compartment =  $D_Z$  time units ( $= 1/\gamma$ )

Leaving rate =  $\gamma = 1/D_Z$  time units<sup>-1</sup>

$$\frac{dz}{dt} = -\gamma z$$
$$z(t) = z(0) e^{-\gamma t}$$



# RELATIONSHIP BETWEEN DURATION IN A COMPARTMENT OF THE MODEL & THE RATE AT WHICH INDIVIDUALS LEAVE THE COMPARTMENT

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The duration in the compartment = the life expectancy,  $L$ , then the rate of leaving the compartment (dying) =  $1/L$  (and vice versa)

## Examples:

$\mu_v$  = per capita mortality rate of vectors

$1/\mu_v$  = vector life-expectancy

$r$  = per capita recovery rate of humans

$1/r$  = duration of infection in humans

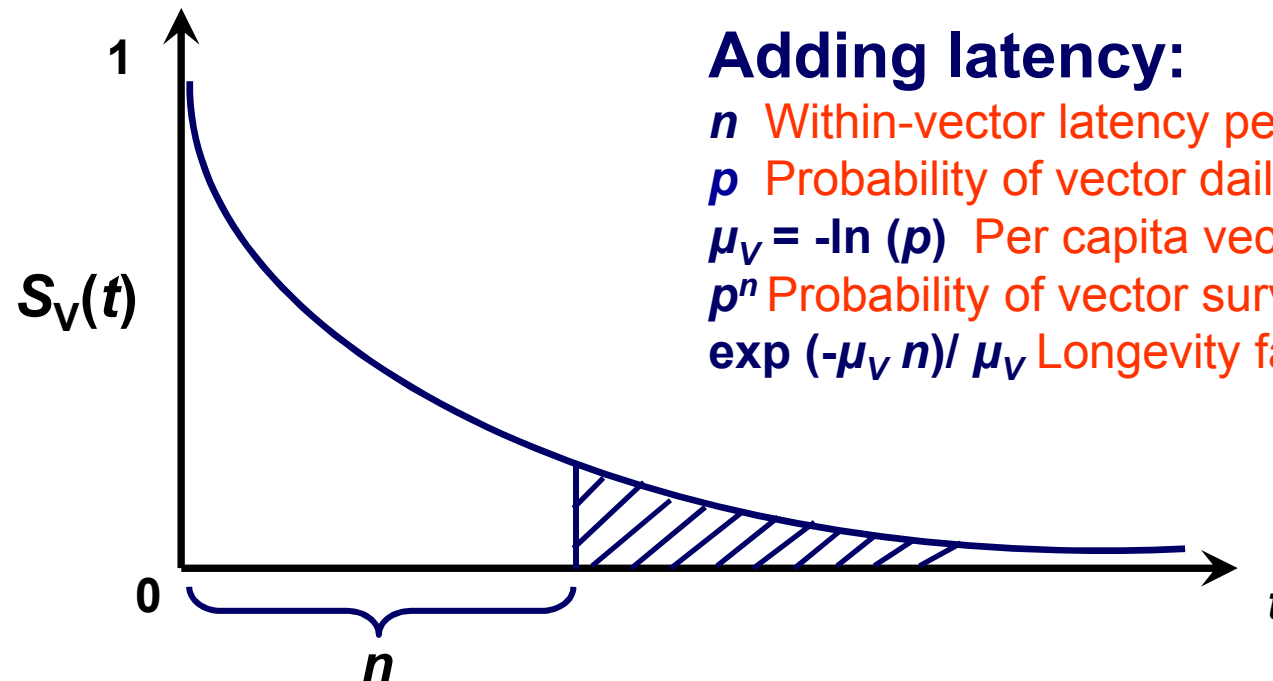
# Vector Survival

With the assumption that the mortality rate does not change with mosquito's age ( $t$ ):

$$\mu_V(t) = \mu_V \quad (\text{i.e. there is constant mortality})$$

survival times will be exponentially distributed:

$$N_V(t) = N_V(0) \exp(-\mu_V t); \quad S_V(t) = \exp(-\mu_V t)$$



## Adding latency:

$n$  Within-vector latency period

$p$  Probability of vector daily survival =  $\exp(-\mu_V)$

$\mu_V = -\ln(p)$  Per capita vector mortality rate

$p^n$  Probability of vector surviving the latency period

$\exp(-\mu_V n) / \mu_V$  Longevity factor

# $R_0$ of Vector-borne Diseases

## Including the extrinsic incubation period

How long does a person remain infectious?

How many times a day is a person bitten by potential vectors?

What fraction of bites on infectious humans infect a mosquito?

$m$  – ratio of mosquitoes to humans

$p$  – probability a mosquito survives one day

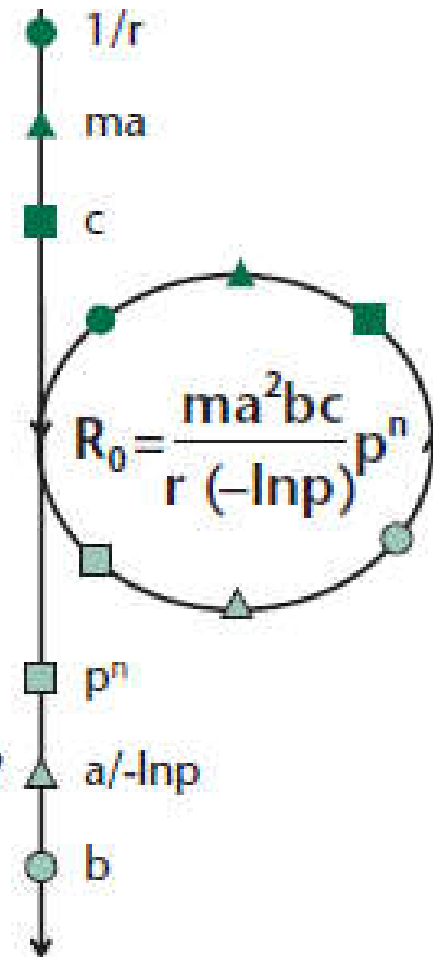
$n$  – number of days required for sporogony

$a$  – number of human bites, per mosquito, per day

What fraction of mosquitoes survive sporogony?

How many human blood meals does a vector take over its lifetime?

What fraction of infectious bites infect a human?



*From Smith, Smith & Hay (2009)*

# Equations Including Latency

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If we incorporate latency in the vector, only a fraction of infected mosquitoes will survive the extrinsic incubation period (EIP) ( $n$  days) and become infective

$$dy_V(t)/dt = a b_V y_H(t-n) [1-y_V(t-n)] \boxed{\exp(-\mu_V n)} - \mu_V y_V(t)$$

(version in Rogers, 1988)

$$dy_V/dt = a b_V y_H (1-y_V) \boxed{p^n} - \mu_V y_V$$

(version in Dye, 1994)

# The Prevalence of Infection in Vectors is Low

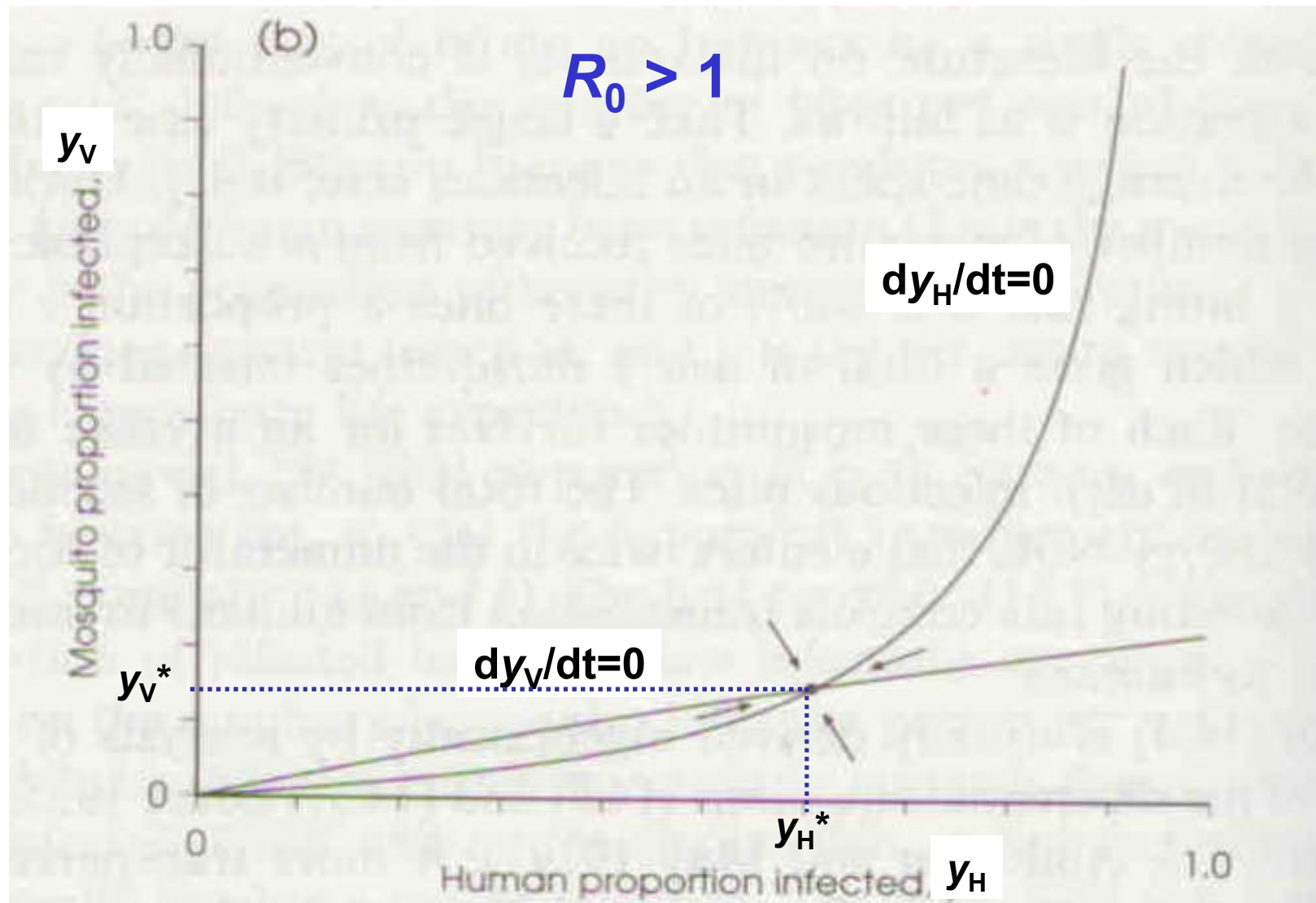
**Table 1. The average life expectancy (in the field) of malaria vectors in Africa**

Vector	Expected life span (days)	Reference
<i>Anopheles funestus</i>	5.6	Krafsur & Garrett-Jones 1977
<i>Anopheles funestus</i>	5.9	Gillies & Wilkes 1963
<i>Anopheles funestus</i>	10.2	Garrett-Jones & Grab 1964
<i>Anopheles gambiae</i>	11.3	Gillies & Wilkes 1965
<i>Anopheles gambiae</i>	15.4	Garrett-Jones & Shidrawi 1969
<i>Anopheles gambiae</i>	8.0	Garrett-Jones & Grab 1964

**Table 2. The prevalence of infection in vector population samples**

Vector	Parasite	Study area	Prevalence (%)	Reference
<i>An. gambiae</i>	<i>P. falciparum</i>	Ethiopia	1.87	Krafsur & Garrett-Jones 1977
<i>An. funestus</i>	<i>P. falciparum</i>	Ethiopia	1.23	Krafsur & Garrett-Jones 1977

## Incorporating latency in the vector



*Anderson & May (1991) Infectious Diseases of Humans. OUP*

# Measures of Transmission Intensity

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- The annual biting rate (ABR): the number of bites received by a person per year

$$ABR = (V/H) a = m a$$

- The infective biting rate (AIBR): the number of infective bites received by a person per year

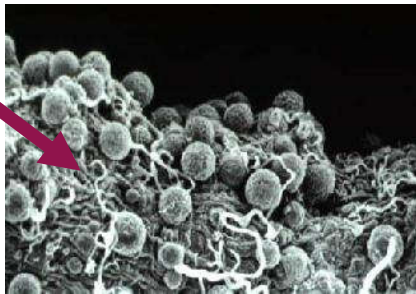
$$AIBR = (V/H) a \times \text{the proportion of infective vectors}$$

This is equivalent to the entomological inoculation rate in malaria (EIR)  $ibppy$

The annual biting rate and the proportion of infectious vectors are estimated by a number of methods depending on the vector species

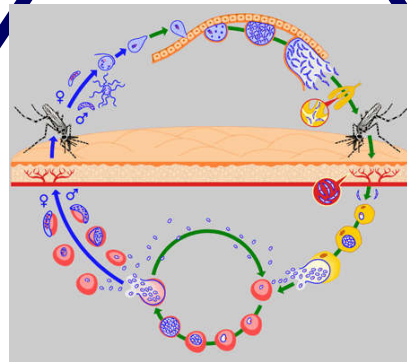
# Interrupting the Triangle of Transmission

Transmission-blocking vaccines (e.g. preventing oocyst formation).  
Refractory, GM mosquitoes

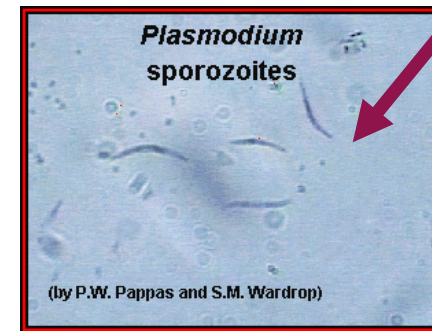


Oocysts in mosquito abdomen

*Plasmodium*



Vaccines against pre-erythrocytic stages, RTS,S



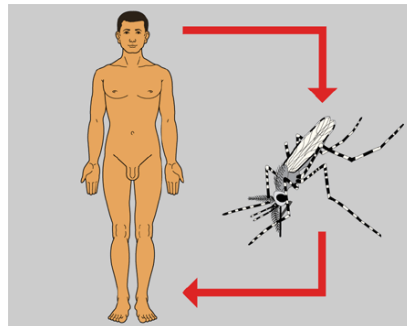
Infective stages to humans

Gametocytocidal treatment (e.g. ACT, Primaquine)

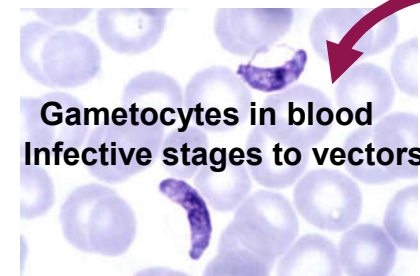
*Anopheles*



ITNs, LLINs, IRS

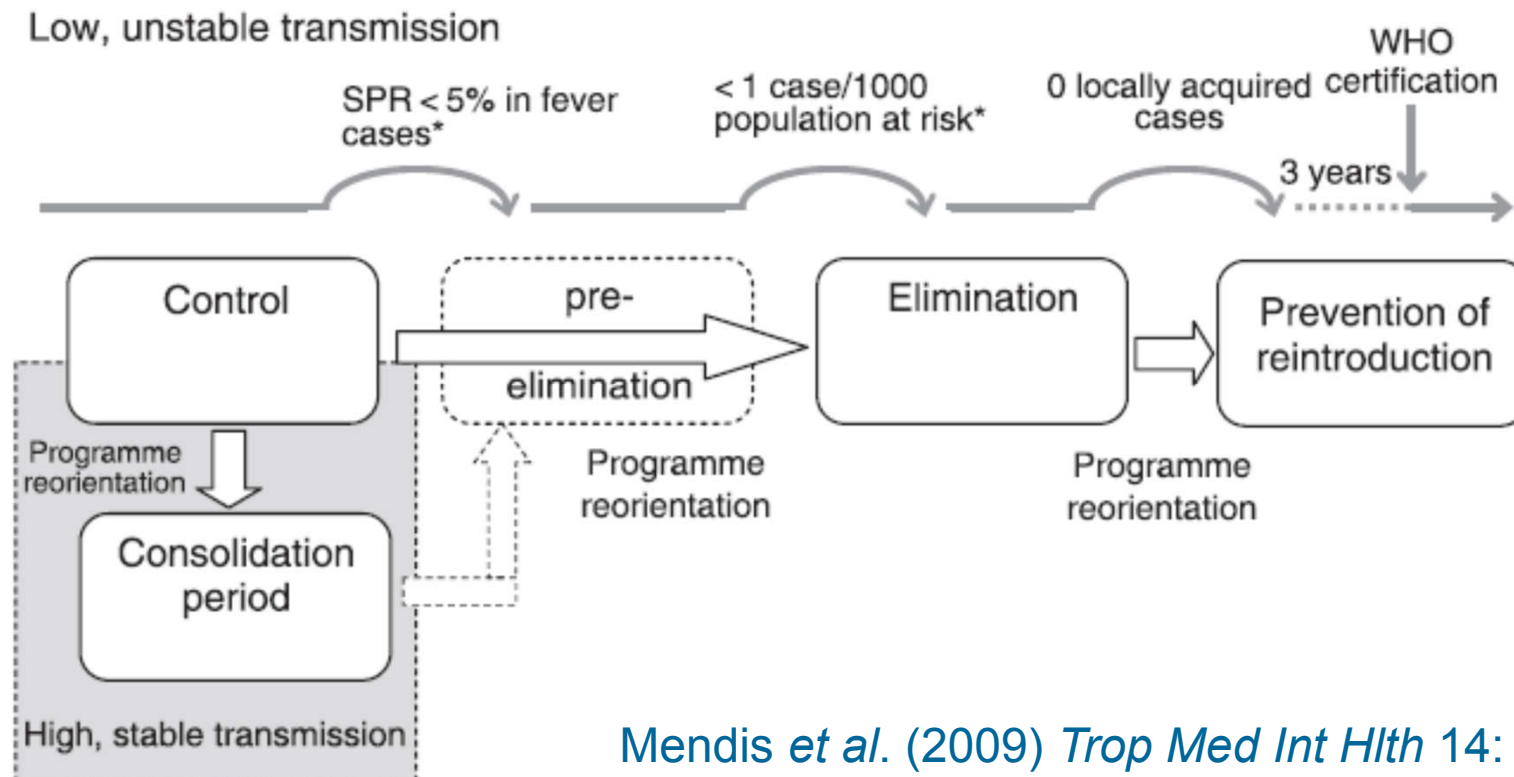


**Human**



# Elimination Strategies

- *Which interventions, alone and/or in combination, have the potential to achieve local elimination and how best to combine such strategies to achieve elimination?*
- *When should interventions be initiated, what effort is needed & how long will it take?*



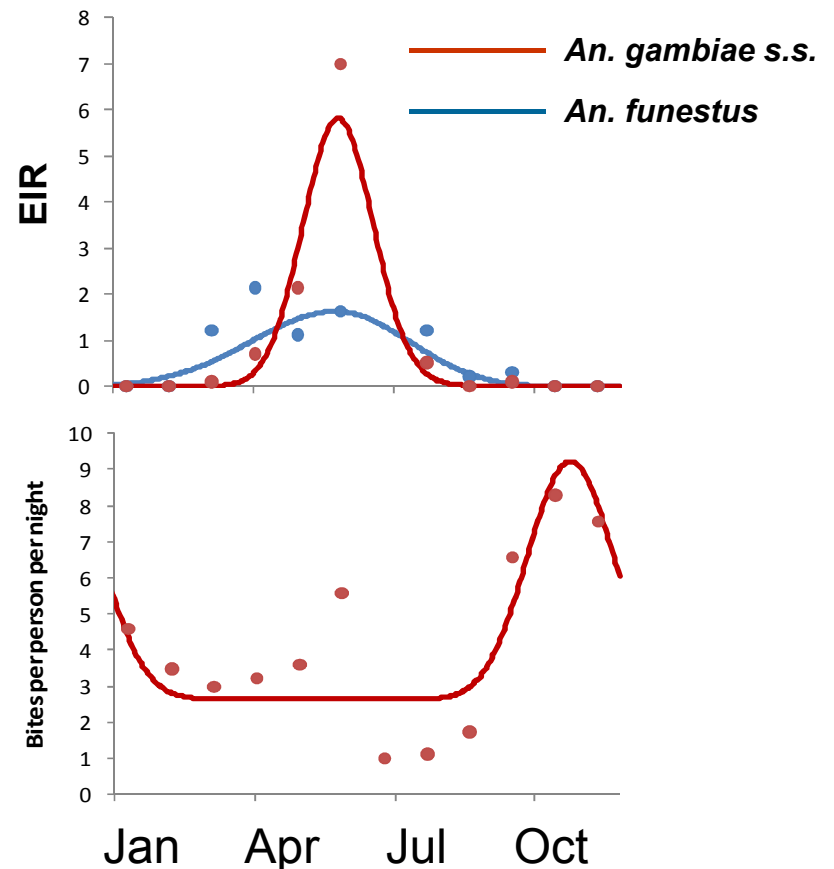
# Biological features : Vector bionomics

- **Key aspects of mosquito behaviour:**

- Endophagy / Exophagy: propensity to bite indoors / outdoors
- Endophily / Exophily: propensity to rest inside / outside the house after feeding
- Human Blood Index (HBI): propensity to bite humans versus e.g. cattle

- Three key malaria vector species in Africa:

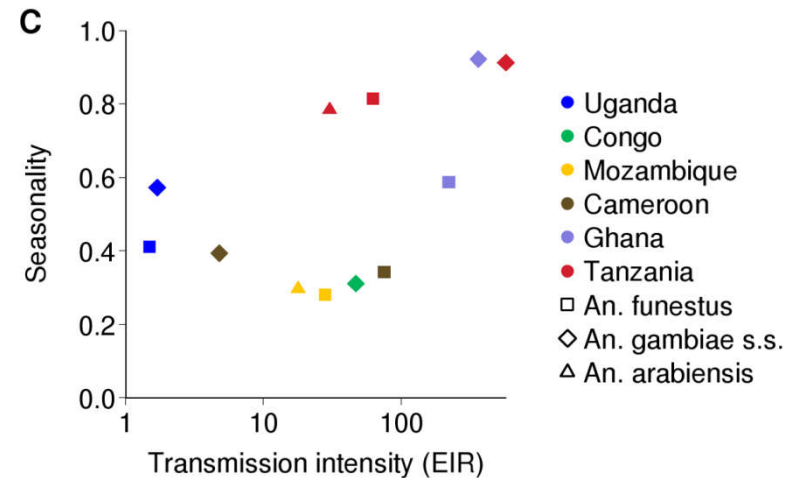
- ***An. gambiae s.s.*** – dominant vector species, high endophagy & high endophily, high HBI
- ***An. arabiensis*** – more common in less humid times of the year, low endophagy & low HBI
- ***An. funestus*** – breeds in swamp areas, high HBI



Griffin et al. (2010) PLoS Med 7(8)

# Transmission Settings

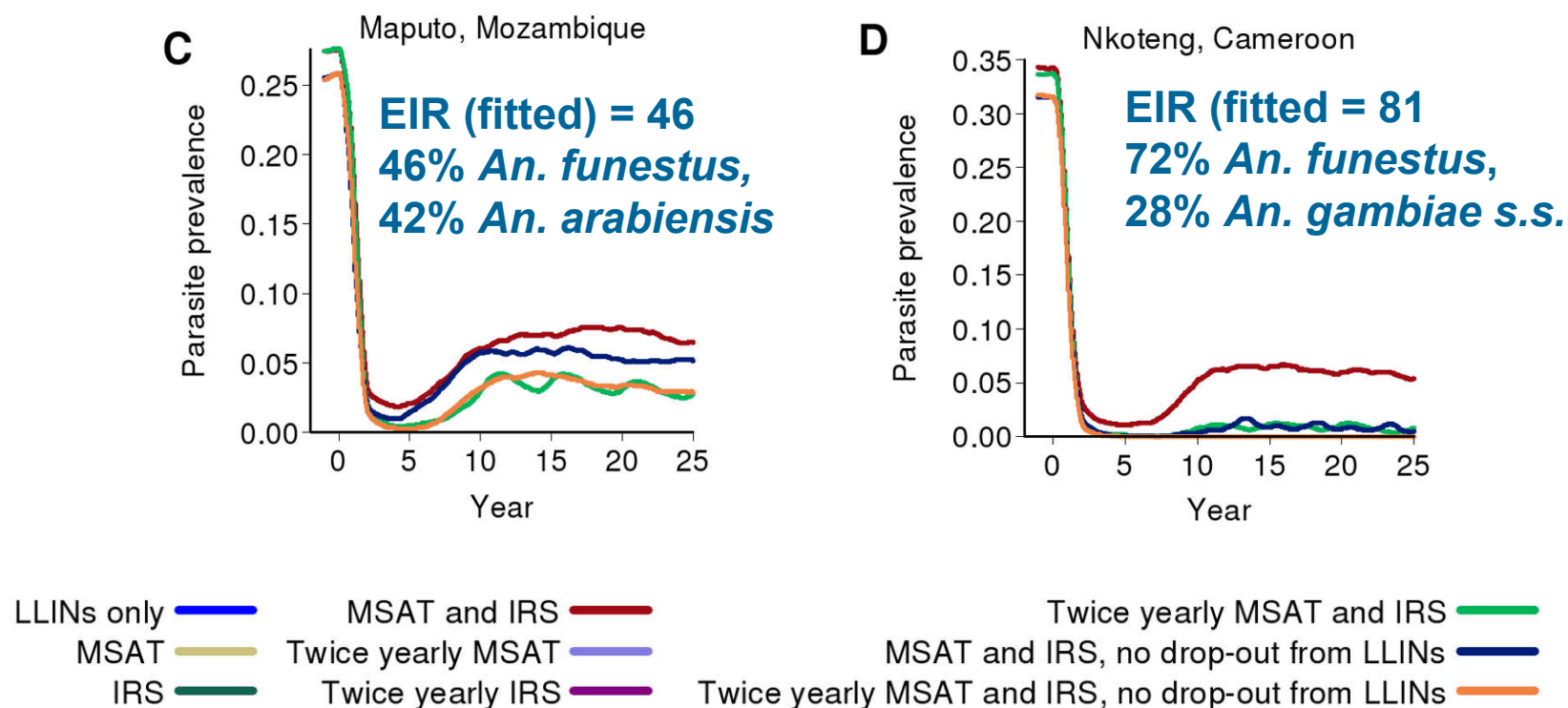
- Consider different settings characterising across Africa:
  - Transmission intensity (EIR)
  - Seasonality Index (proportion of EIR occurring within the peak 3 months of transmission)
  - Vector species combinations



Location	Population	Reported (fitted) annual EIR (ibppy)	Type of transmission	<i>Anopheles</i> species composition
Kjenjojo, Uganda	Rural	7 (3)	Low, perennial <b>L</b>	65% <i>An. gambiae s.s.</i> , 35% <i>An. funestus</i>
Maputo, Mozambique	Rural	28 (46)	Moderate, perennial <b>M</b>	46% <i>An. funestus</i> , 42% <i>An. arabiensis</i>
Kinkole, DRC	Rural	48 (43)	Moderate, perennial <b>M</b>	Nearly 100% <i>An. gambiae s.s.</i>
Nkoteng, Cameroon	Rural	94 (81)	Moderate, perennial <b>M</b>	72% <i>An. funestus</i> , 28% <i>An. gambiae s.s.</i>
KND, Ghana	Rural	630 (586)	High, seasonal <b>H</b>	60% <i>An. gambiae s.s.</i> , 40% <i>An. funestus</i>
Matimbwa, Tanzania	Rural	703 (675)	High, seasonal <b>H</b>	85% <i>An. gambiae s.s.</i> , 10% <i>An. funestus</i> , 5% <i>An. arabiensis</i>

# IRS and Vector behaviour, Moderate Transmission

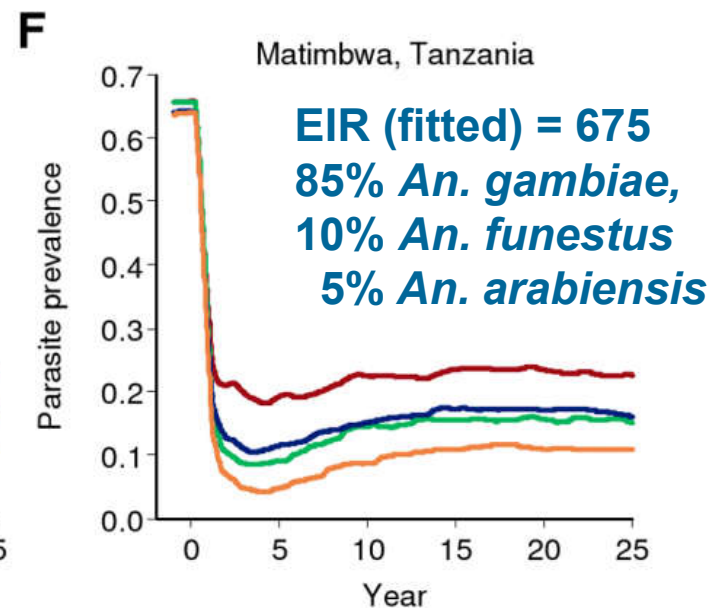
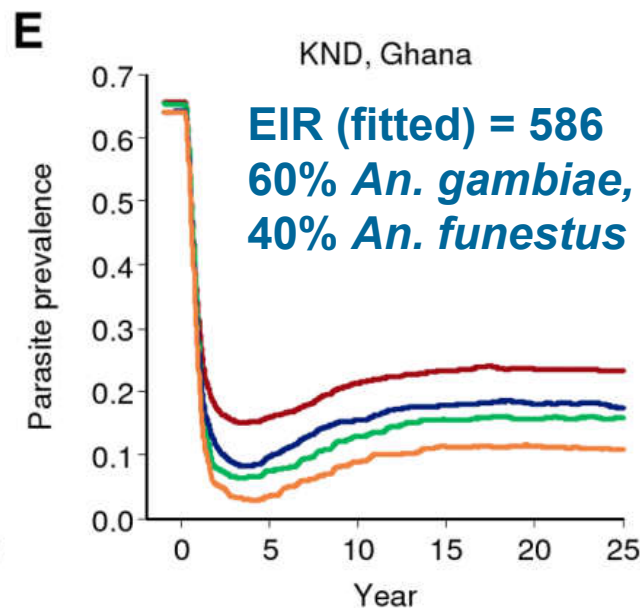
- Interventions will have different impact in settings with similar EIR (e.g. moderate transmission) but different vector species
- IRS and ITNs unlikely to have sufficient impact if outdoor-resting mosquitoes are common (*An. arabiensis*)



Griffin *et al.* (2010) *PLoS Med* 7(8): e1000324

# High Transmission Settings

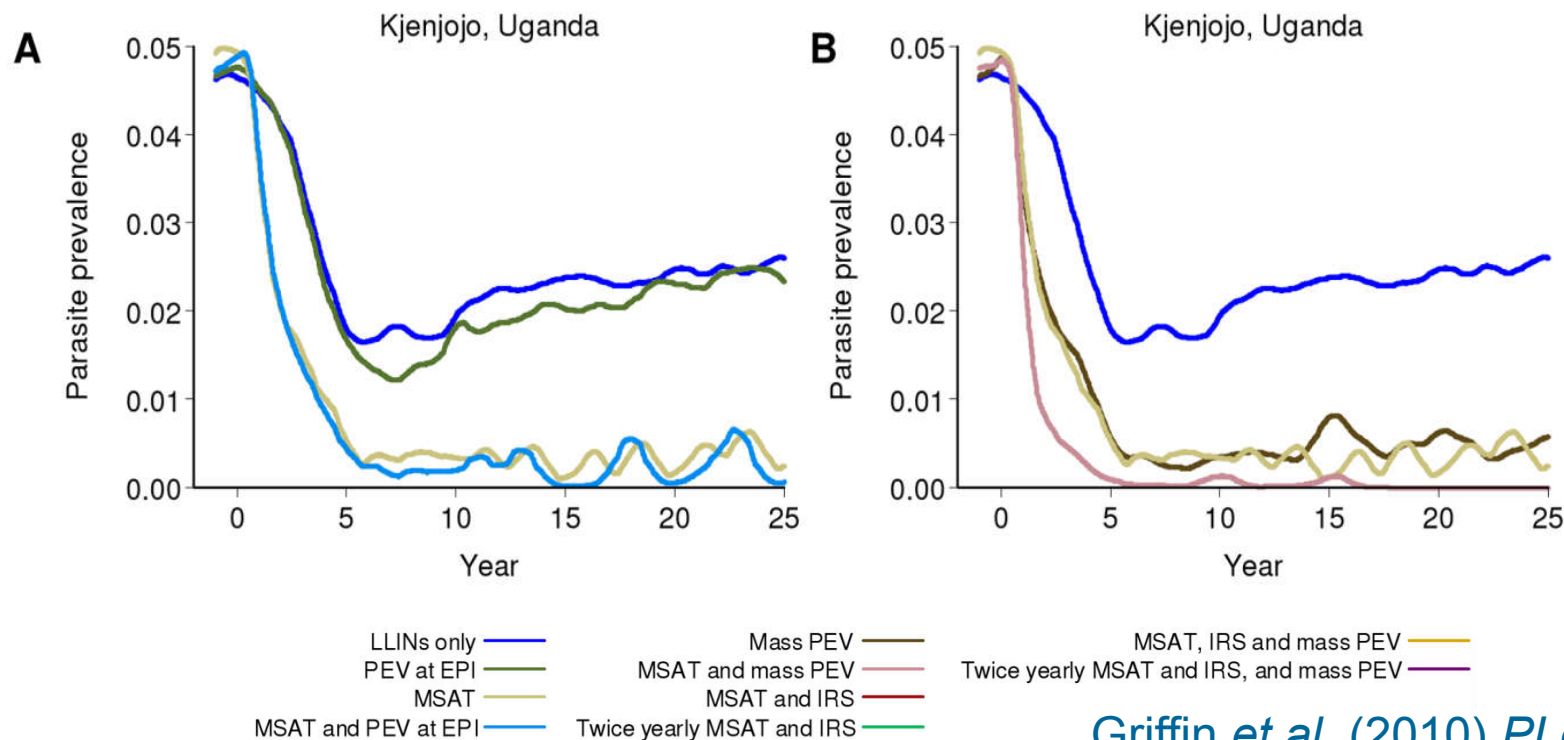
- Current tools are unlikely to be sufficient to reach the pre-elimination threshold of 1% parasite prevalence in areas of high transmission
- However, substantial declines in prevalence can be achieved
- Interventions will greatly reduce incidence of disease / clinical burden



LLINs only	MSAT and IRS	Twice yearly MSAT and IRS
MSAT	Twice yearly MSAT	MSAT and IRS, no drop-out from LLINs
IRS	Twice yearly IRS	Twice yearly MSAT and IRS, no drop-out from LLINs

# Vaccine Impact, Low transmission settings

- RTS,S vaccine in Phase III trials prevents infection (pre-erythrocytic vaccine – PEV)
- Efficacy ~50% from Phase II studies (disappointing Phase III studies)
- Likely to be delivered via Expanded Programme of Immunisation (EPI)
- Additional impact on transmission greatest in low transmission settings



Griffin *et al.* (2010) *PLoS Med*

# **Take Home Messages: Models for Indirectly-transmitted Microparasites, Malaria**

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**Prevalence framework has been customarily used, but the importance of parasite density is starting to be recognized**

**Modelling prevalence of infection in humans and mosquitoes**

**Modifications of the Ross-Macdonald Malaria model**

**Introducing parasite latency in the model improves prevalence outcomes in the vector population**

# Take Home Messages (Cont.)

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- The Basic Reproduction Ratio ( $R_0$ ) of malaria depends on:
  - entomological components (vector density, biting rate on humans, probability of daily survival)
  - components of the vector-parasite interface (probability of successful establishment in the vector, duration of sporogony)
  - components of the human-parasite interface (probability of successful establishment in the human, duration of infectiousness)
- Control & elimination programmes aim at reducing the magnitude of the above components by implementing interventions
- Mathematical models provide useful tools to summarise and update current knowledge on the biology and epidemiology of malaria and its transmission in a quantitative framework, so that impact of interventions can be measured / anticipated

# Take Home Messages (Cont.)

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Mathematical models are important in all stages of malaria elimination programmes:

- **Planning:** Determining what is achievable, with what tools
- **Reducing transmission:** Identifying optimal combinations and strategies
- **Monitoring:** Helping to design appropriate surveillance strategies
- **Holding the line:** Advising on tools needed to prevent re-introduction
- Can also aid in defining properties of new tools needed in areas where current tools are insufficient
- Importance of local vector species composition (feeding / resting behaviour) as well as overall transmission intensity
- Currently available tools insufficient to eliminate malaria in high transmission settings (but can help to reduce disease / mortality burden)
- So far model assumes no development of insecticide or drug resistance
- Need to combine epidemiological with evolutionary models