

An Introduction to Modelling Vector-borne Diseases

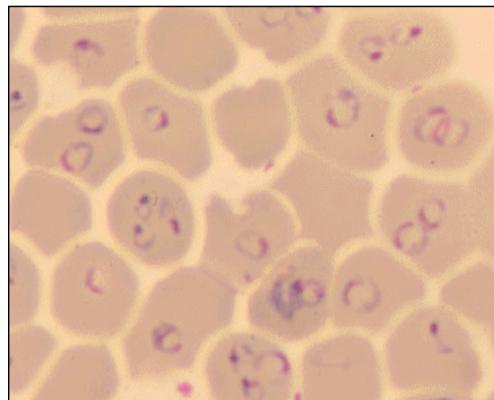
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Human malaria *Plasmodium* species

Plasmodium falciparum



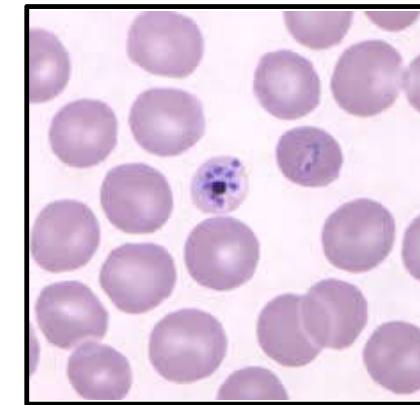
(original image provided by Steve Aley)

Africa
SE Asia
Latin America

P. malariae



P. knowlesi



(mcdinternational.org)

Southeast Asia

P. vivax

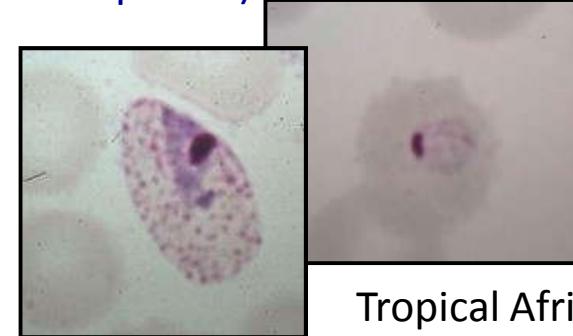


(original image by Mark Lontie)

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



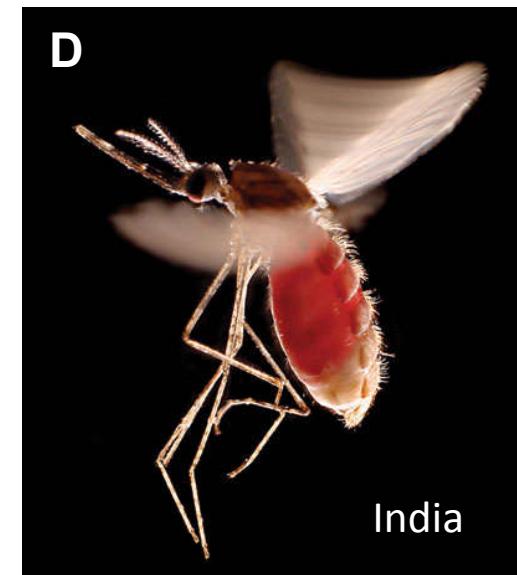
Anopheles albimanus



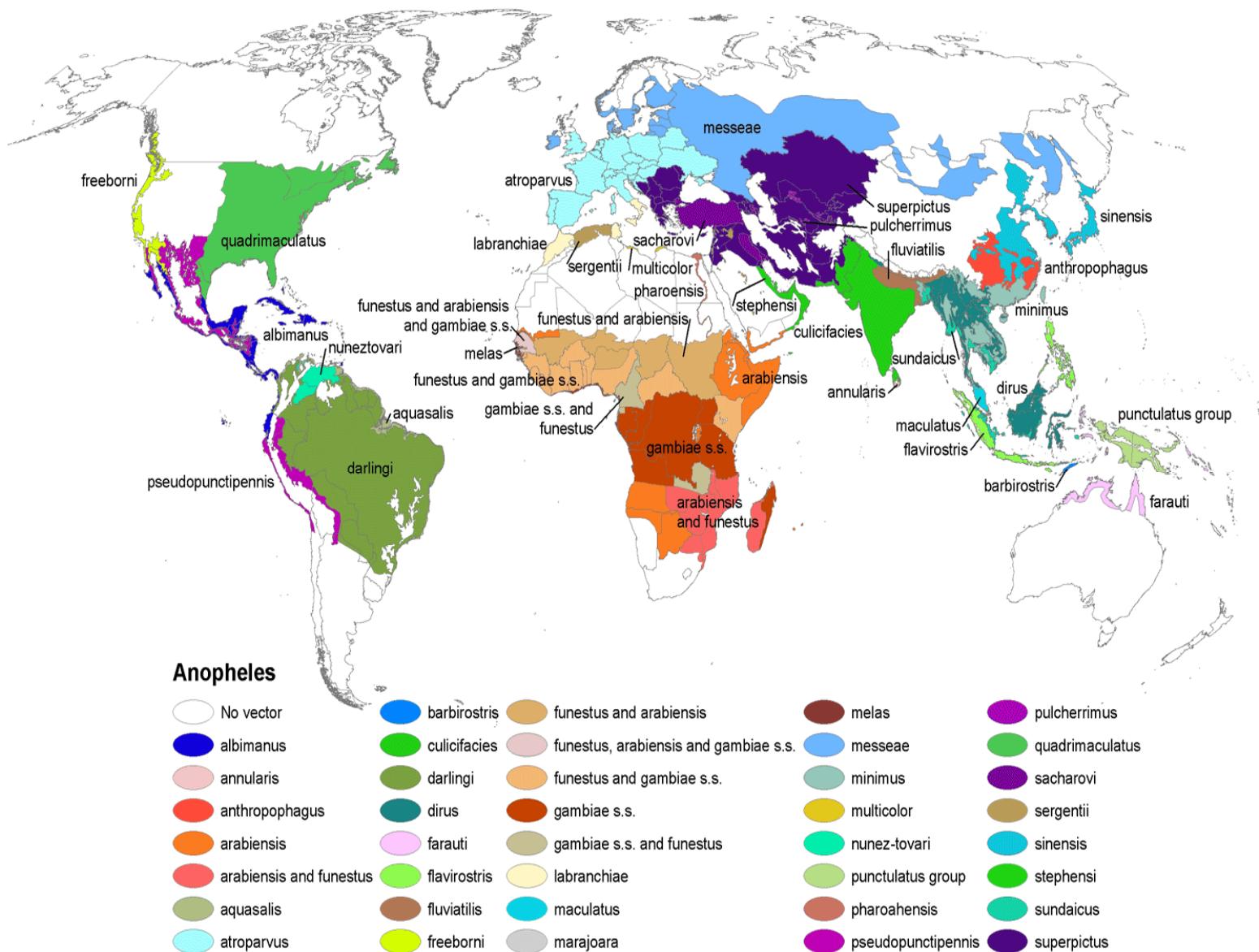
Anopheles stephensi

A, B, C = CDC
Image Library

D = The
Wellcome Trust

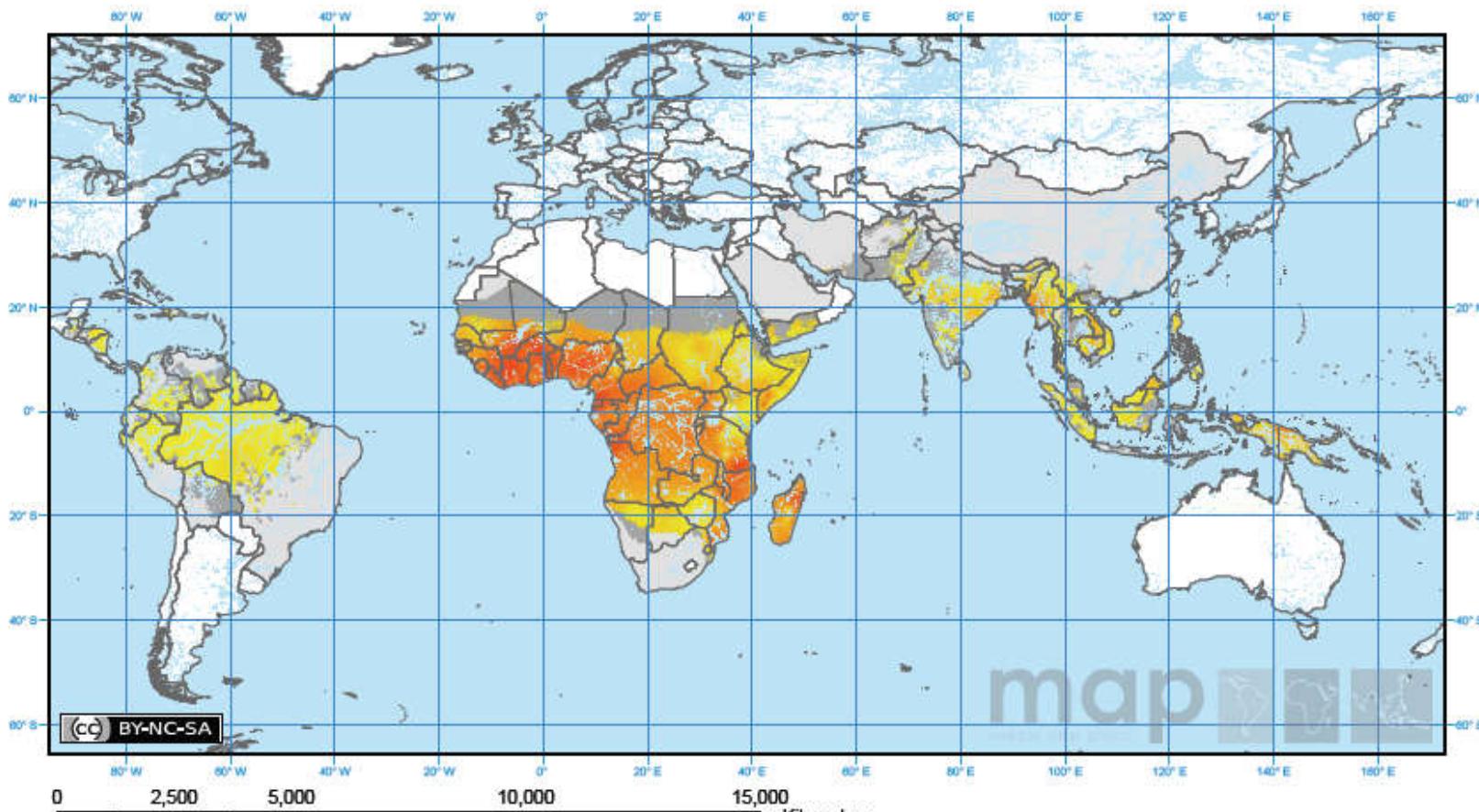


Distribution of *Anopheles* vectors



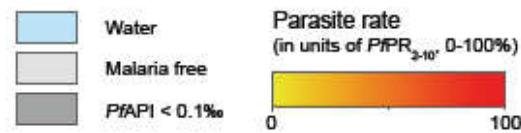
Prevalence of *P. falciparum* in 2007

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



Copyright: Licensed to the Malaria Atlas Project (MAP; www.map.ox.ac.uk) under a Creative Commons Attribution 3.0 License (<http://creativecommons.org/>)

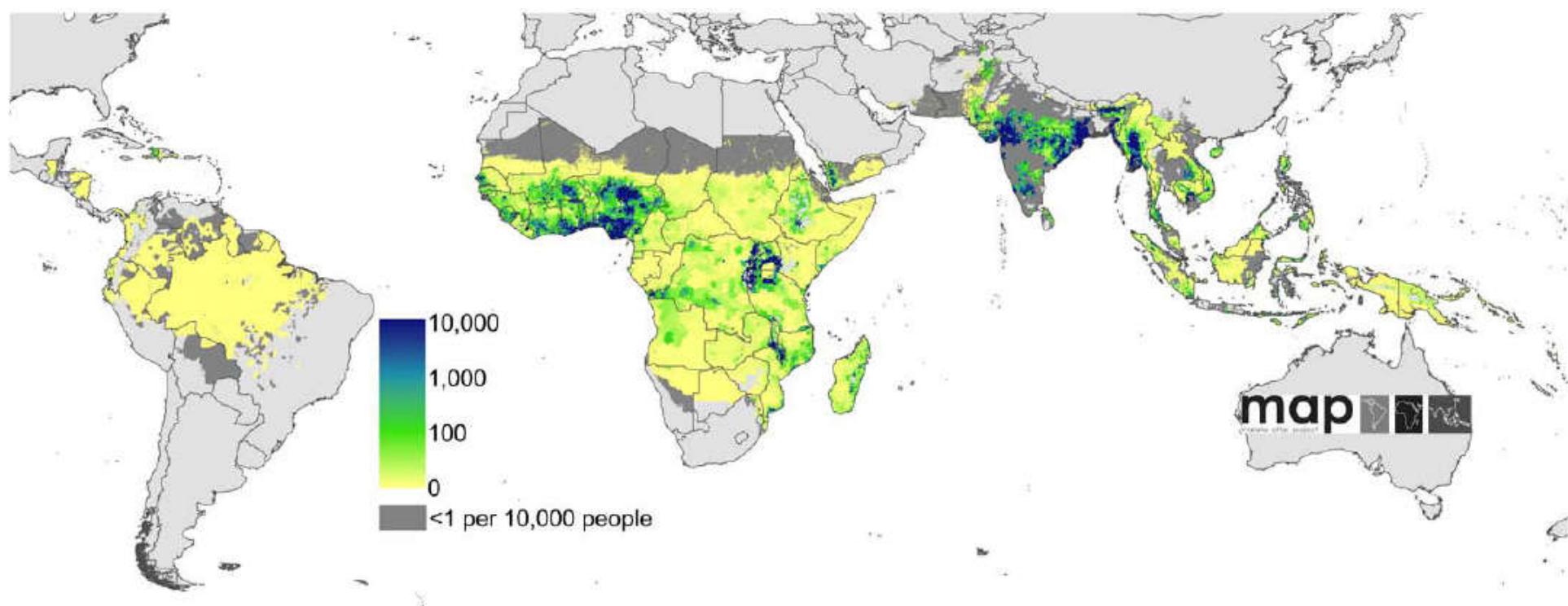
Citation: Hay, S.J. et al. (2009). A world malaria map: *Plasmodium falciparum* endemicity in 2007. PLoS Medicine 6(3): e1000048.
Note: The scalebar is a guide and accurate only at the equator. Projection: Plate carree.



Source: www.map.ox.ac.uk

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

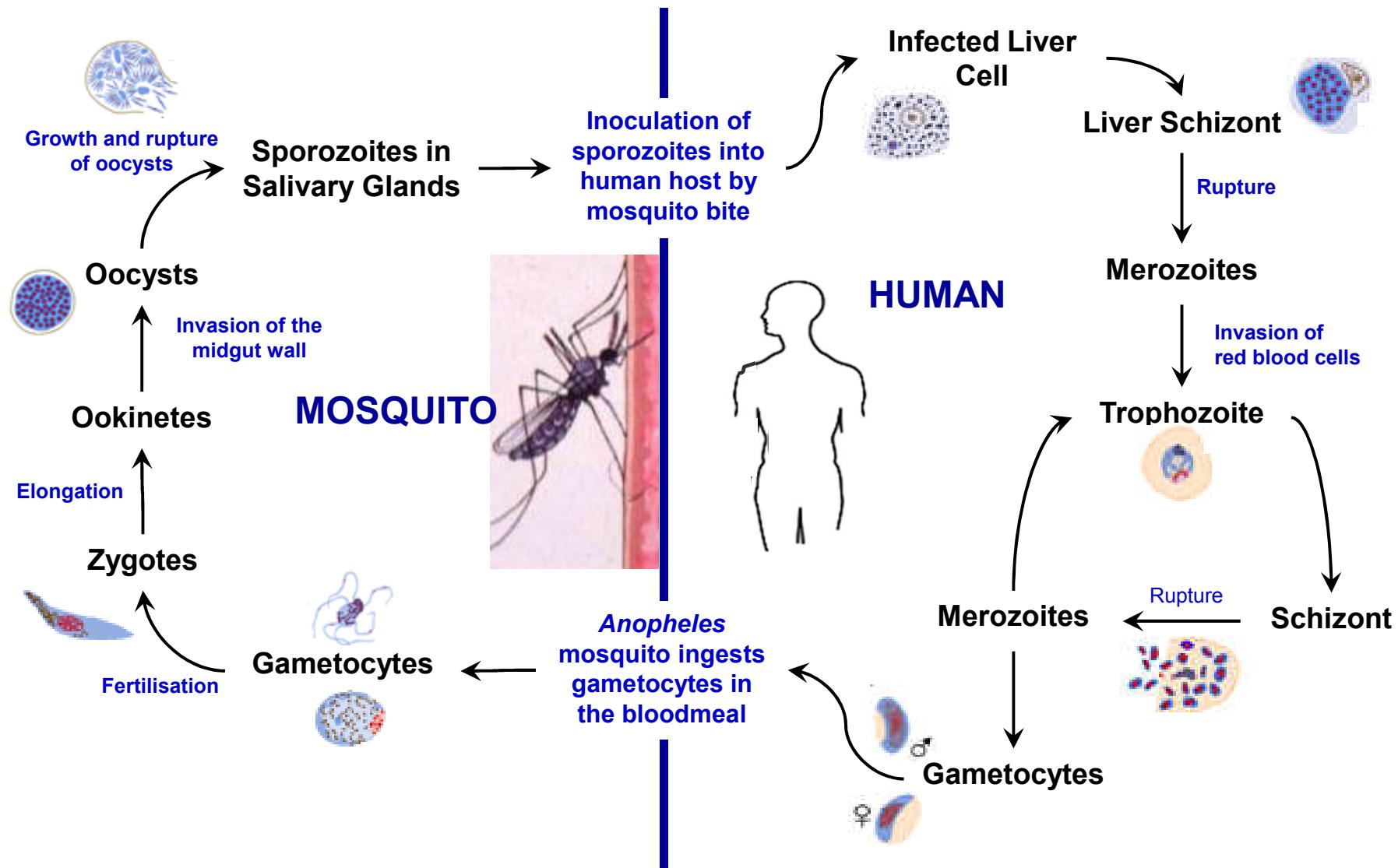
GLOBAL AND REGIONAL MALARIA BURDEN

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

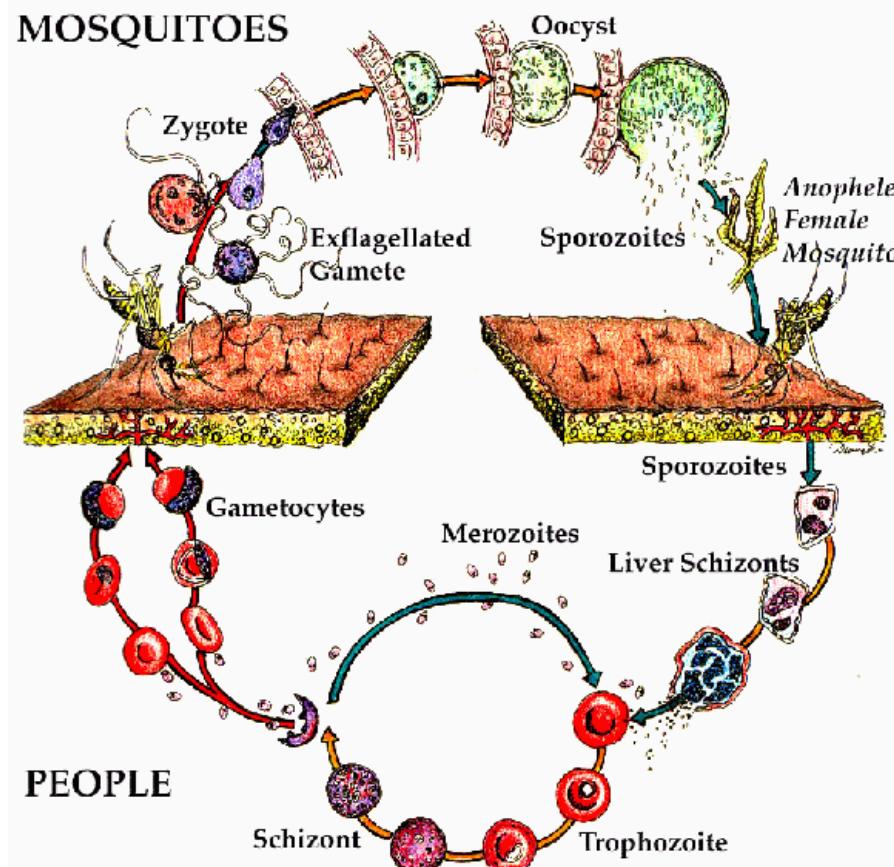
$$\text{Vector population (V)} = X_V + Y_V$$

Susceptible
Mosquitoes

X_V

Infected
Humans

Y_H



Infected
Mosquitoes

Y_V

Susceptible
Humans

X_H

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

The building blocks of our first vector-borne pathogen model

- $m = (V / H)$ 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

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)

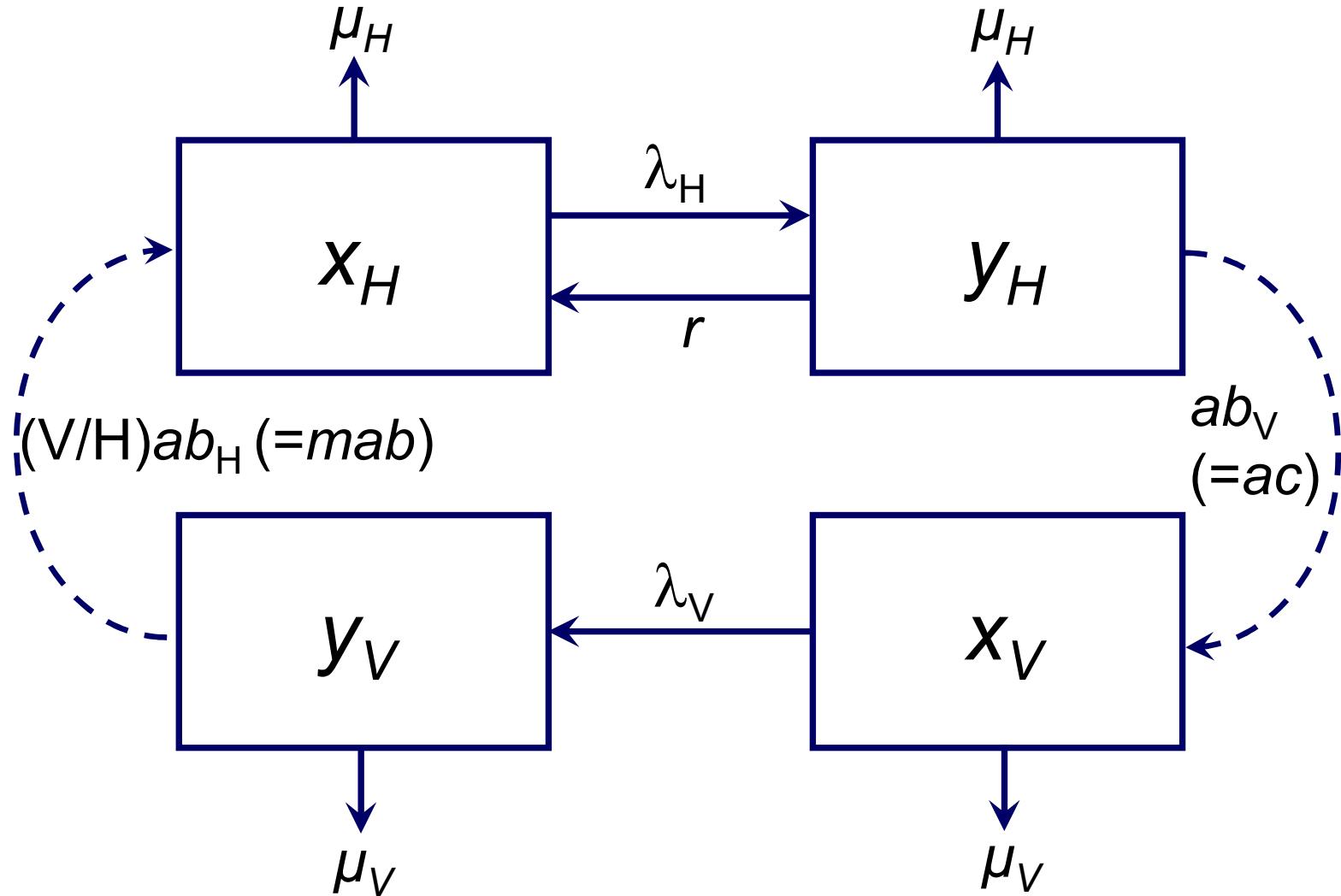
Probability of transmission from human to vector, per bite b_V (c)

Per capita mortality rate of humans μ_H

Per capita mortality rate of vectors μ_V

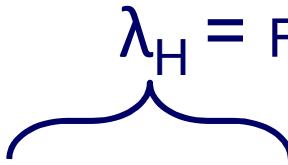
Per capita recovery rate of humans r

Flow diagram



Equations

λ_H = FOI from vectors to humans



EIR

Humans:

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

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

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

Vectors:

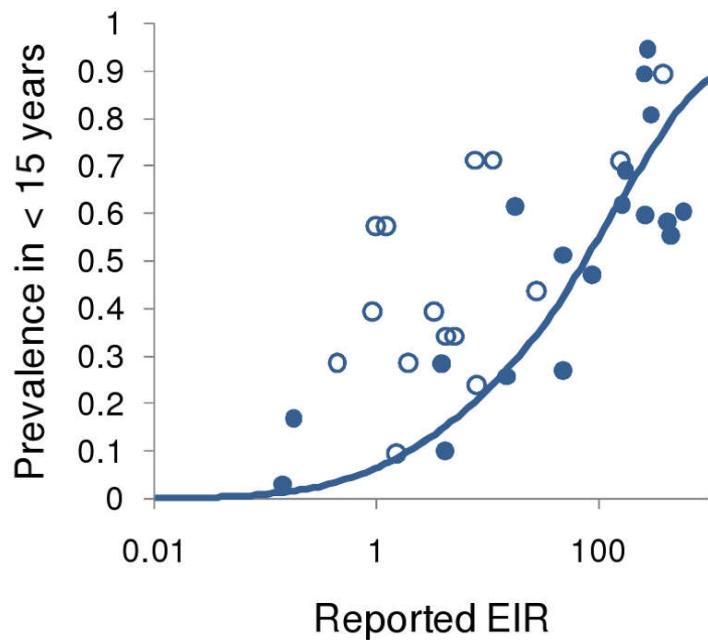
λ_V = FOI from human to vectors

$$\frac{dy_V}{dt} = a y_H b_V (1 - y_V) - \mu_V y_V$$

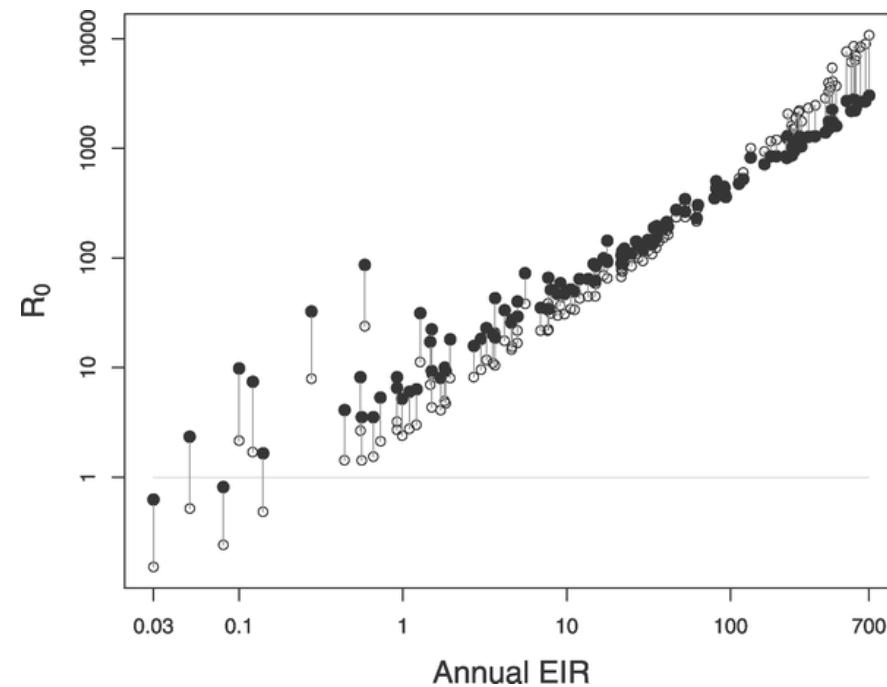
Mosquitoes assumed not to recover from infection and remain infected/infectious for life

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



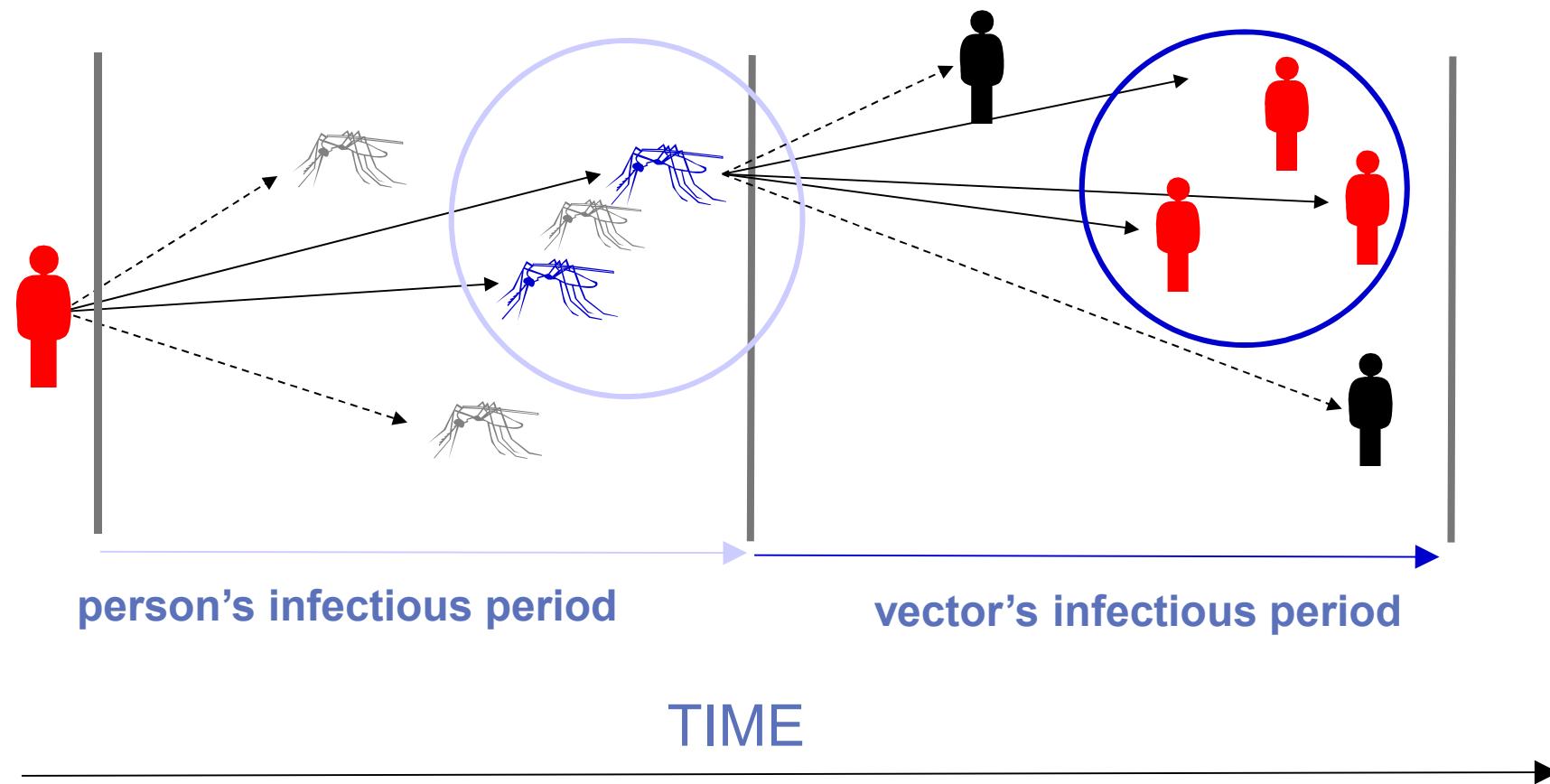
Griffin et al. (2010) PLoS Med 7(8)



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



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



R_0 of Vector-borne Diseases

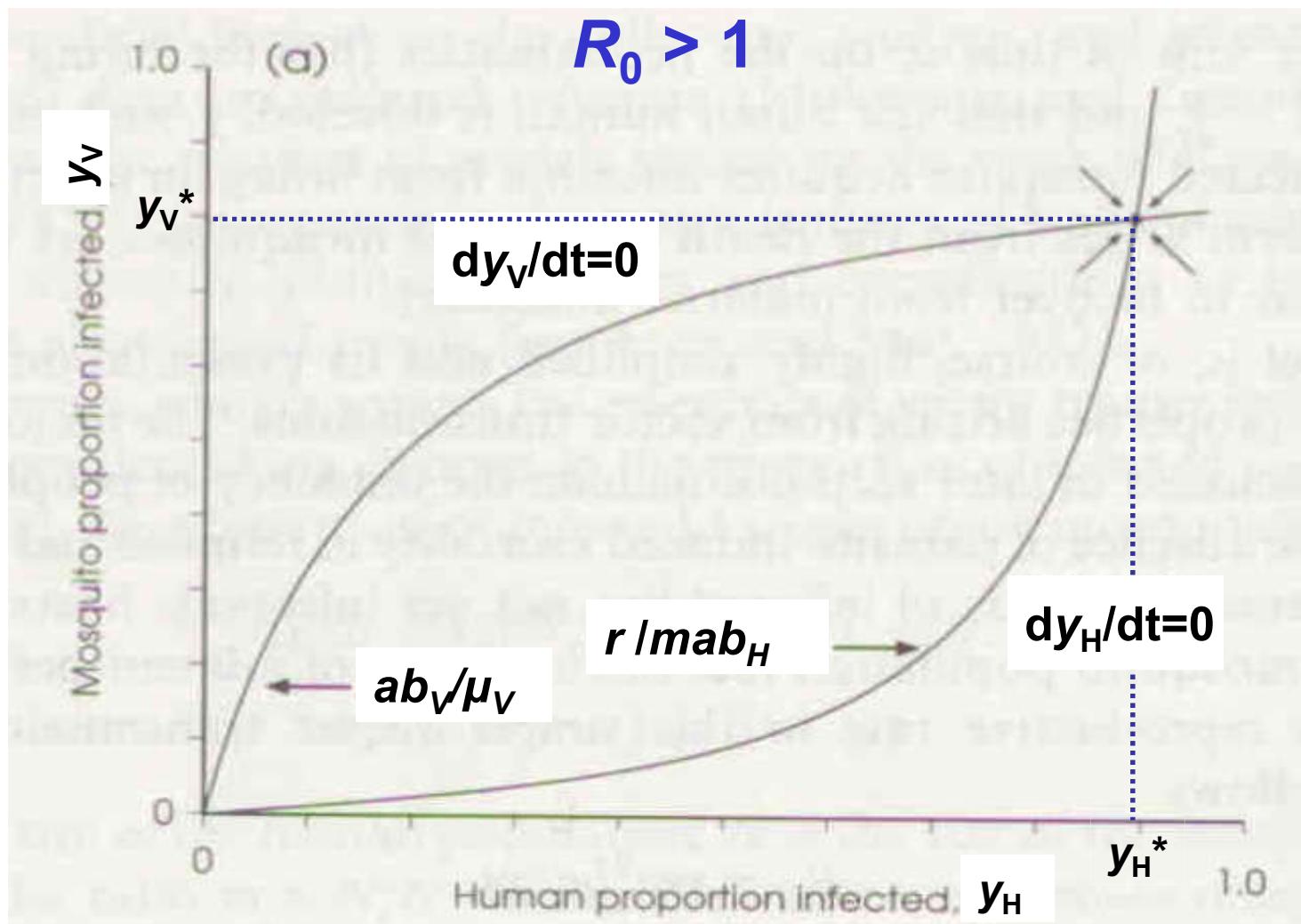
Ignoring the extrinsic incubation period

$$R_0 = \frac{(V/H) a^2 b_H b_V}{r \mu_V}$$

Diagram illustrating the components of the basic reproduction number R_0 :

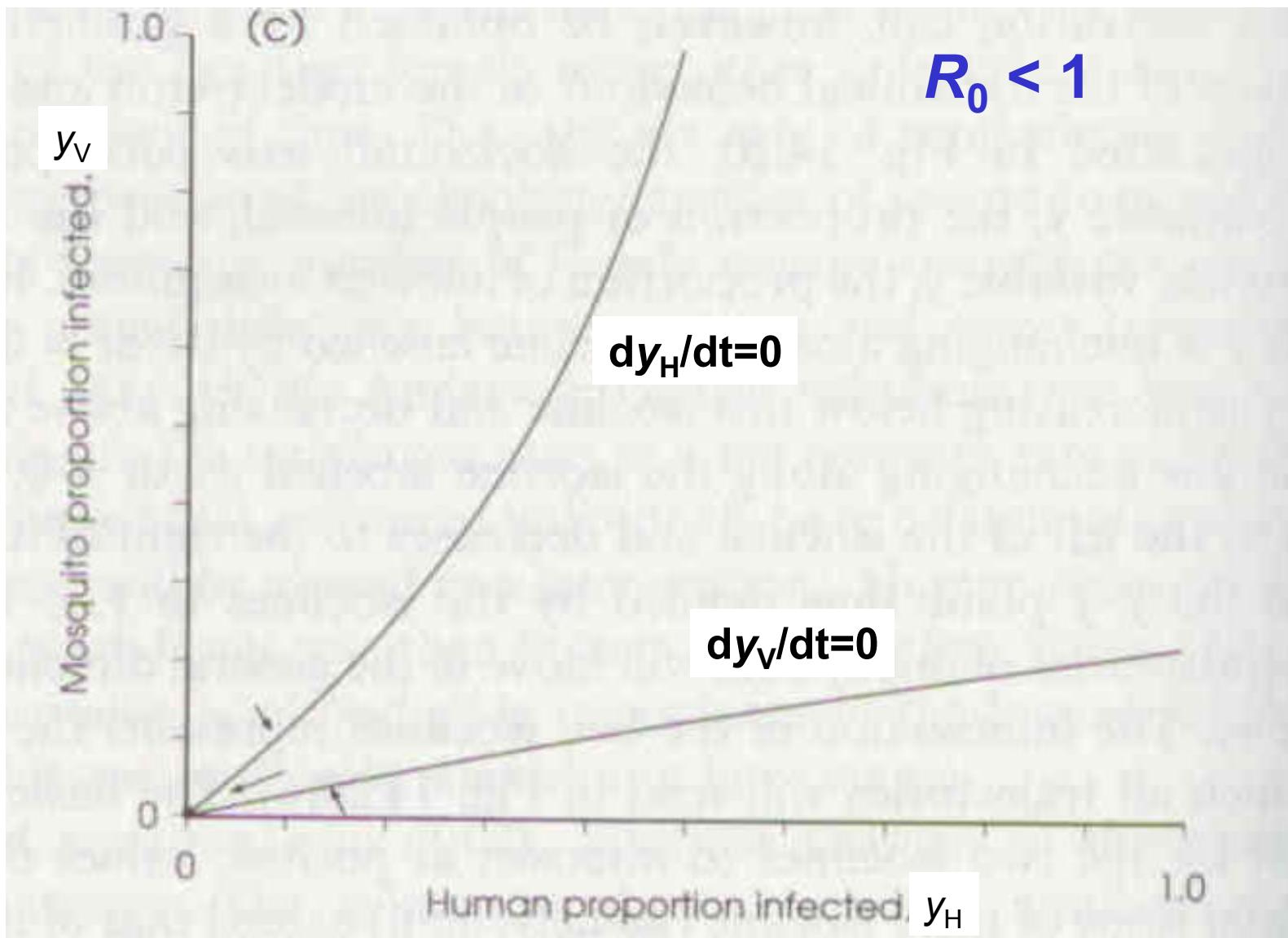
- Biting rate per vector on humans: a^2 (needs to bite twice – to pick up and then to transmit the infection)
- Human population size: V (Transmission probability from vector to host)
- Vector population size: H (Transmission probability from host to vector)
- Recovery rate of the host (loss of infectiousness): r (Per capita vector mortality rate, $1/\mu_V$ = life expectancy)
- Per capita vector mortality rate: μ_V

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

Proportion of individuals in compartment, z



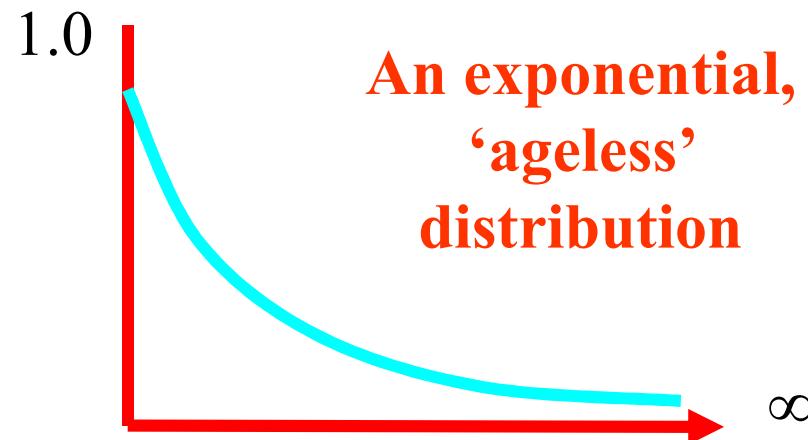
leaving rate is constant, γ

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

Leaving rate = $\gamma = 1/D_Z$ time units $^{-1}$

$$dz/dt = -\gamma z$$

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



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



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

Examples:

μ_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

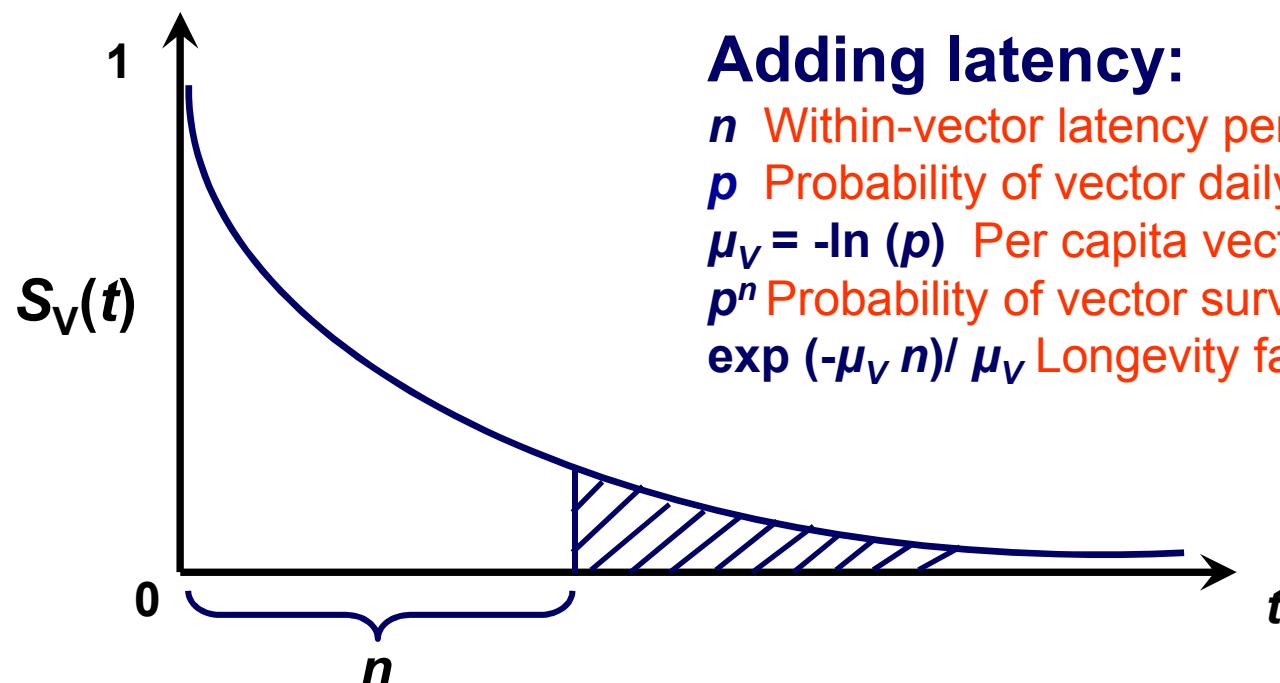
Vector Survival

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?

The diagram illustrates the components of the R_0 formula for vector-borne diseases. A central circle contains the formula $R_0 = \frac{ma^2bc}{r(-\ln p)}p^n$. Surrounding the circle are seven variables, each associated with a colored arrow pointing to its corresponding term in the formula:

- $1/r$: Top left, green circle.
- ma : Top middle, green triangle.
- c : Top right, green square.
- p^n : Bottom right, green square.
- $a/-\ln p$: Bottom middle, green triangle.
- b : Bottom left, green circle.

From Smith, Smith & Hay (2009)

Equations Including Latency

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

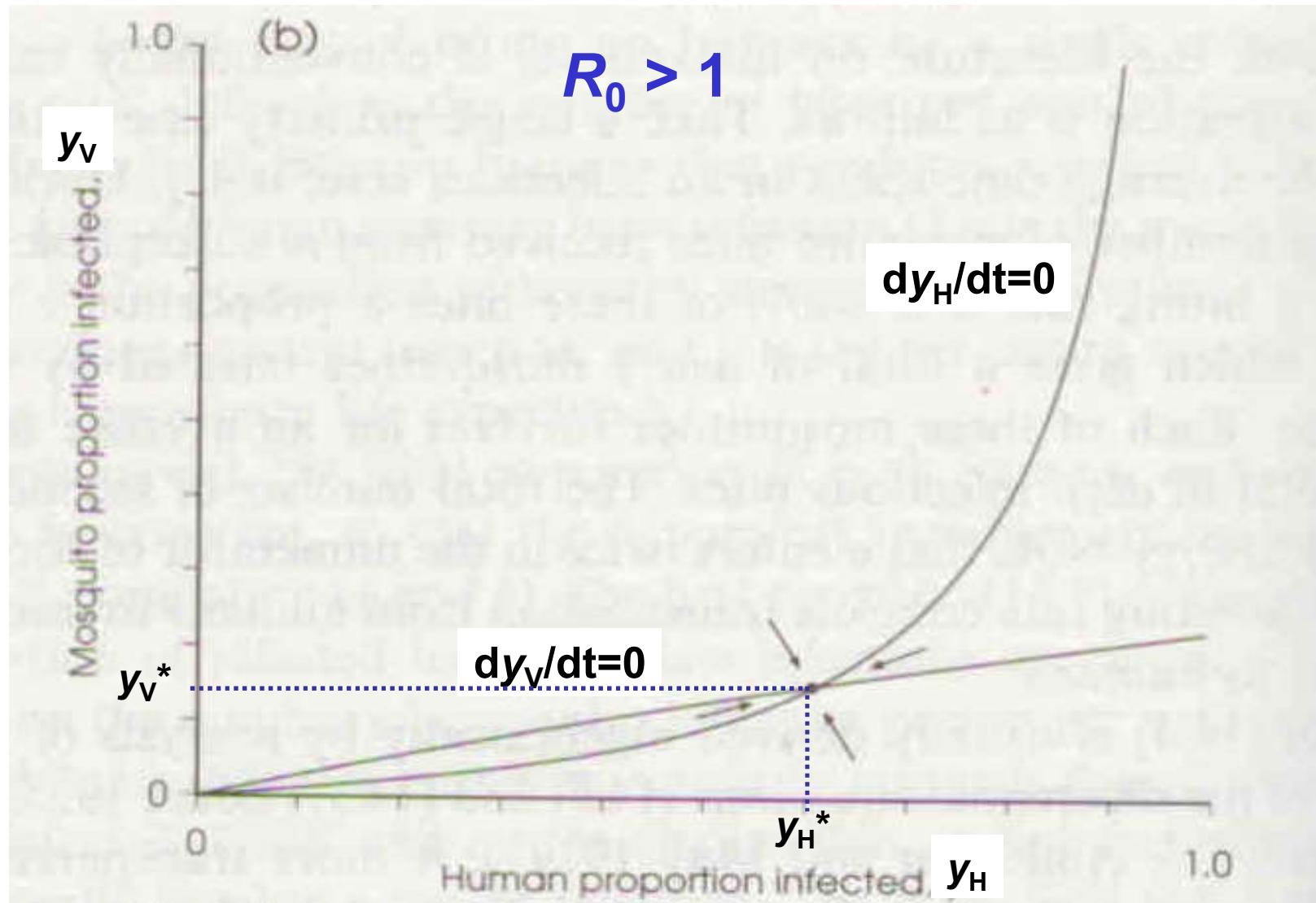
Table 1. The average life expectancy (in the field) of malaria vectors in Africa

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

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

$$\text{ABR} = (\text{V}/\text{H}) \text{ } a = m \text{ } a$$

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

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

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



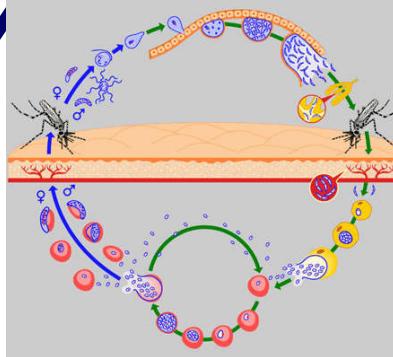
Oocysts in mosquito abdomen

Anopheles



ITNs,
LLINs, IRS

Plasmodium



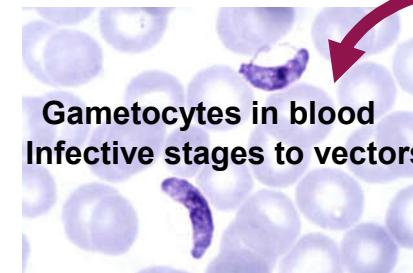
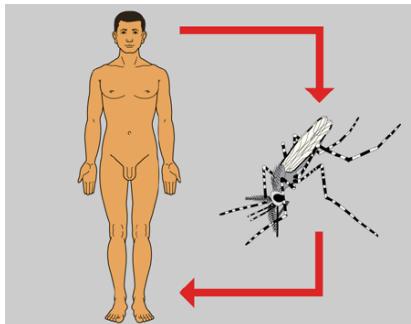
Vaccines against pre-erythrocytic stages, RTS,S



Infective stages to humans

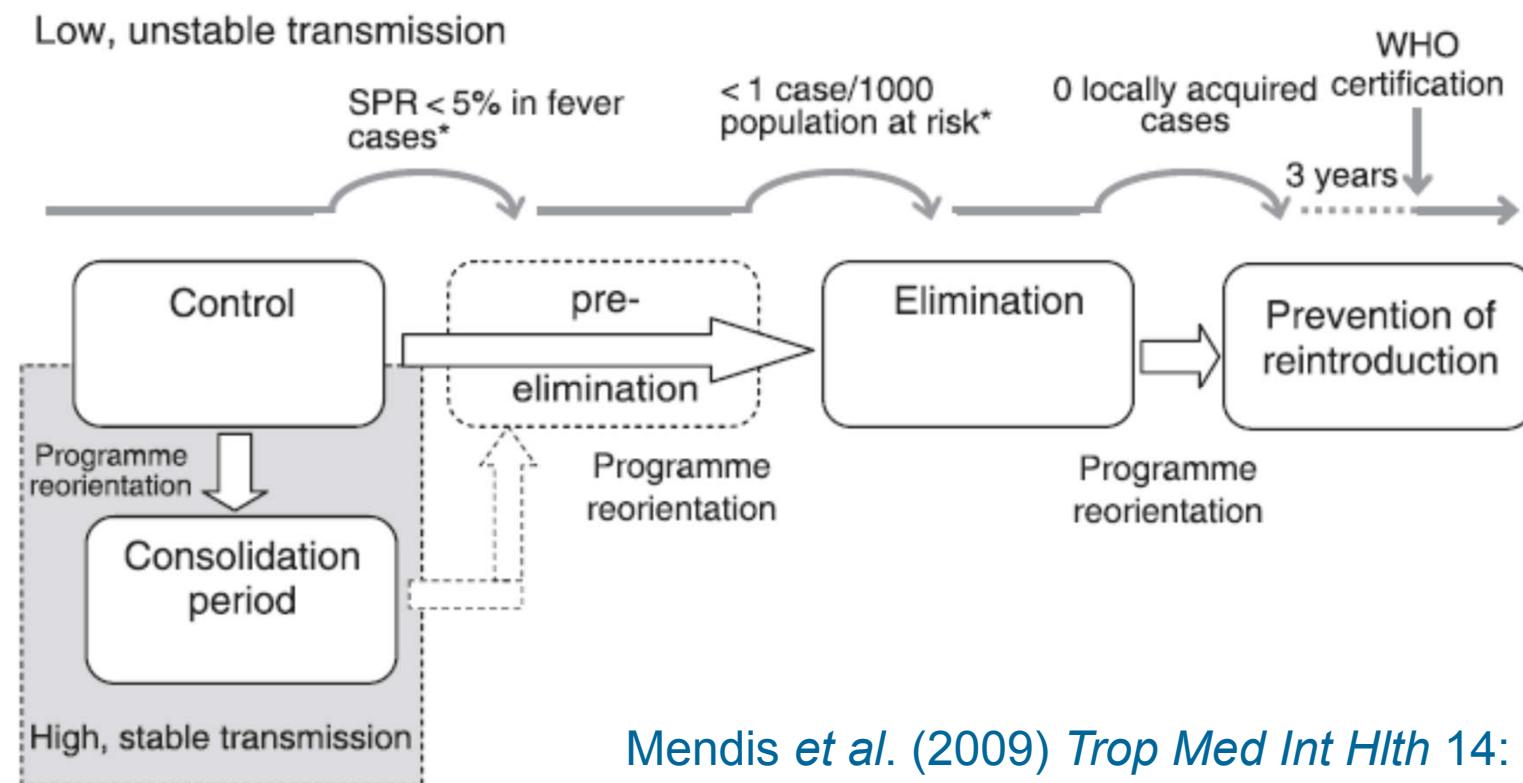
Gametocytocidal treatment
(e.g. ACT, Primaquine)

Human



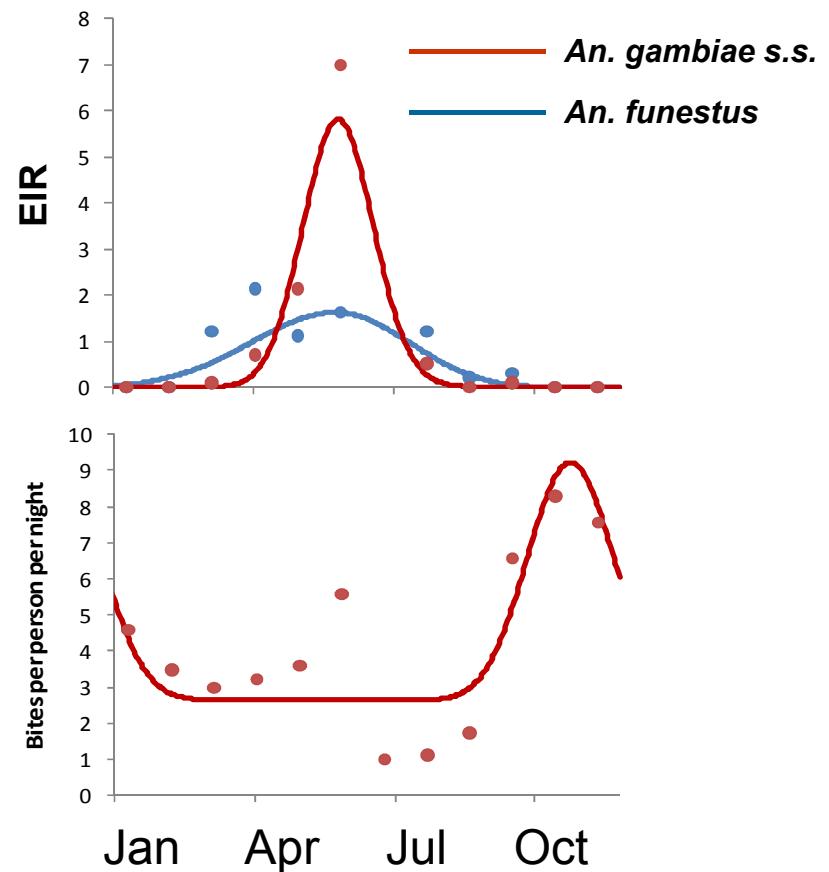
Elimination Strategies

- 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?



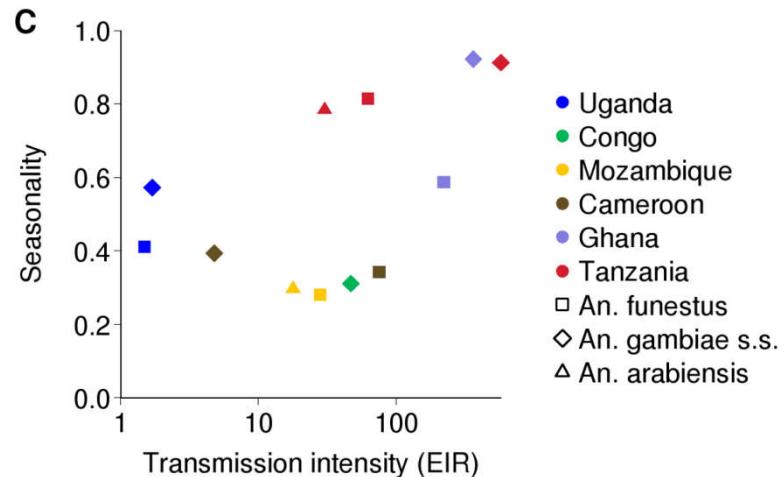
Biological features : Vector bionomics

- Key aspects of mosquito behaviour:
 - Endophagy /Exophagy: propensity to bite indoors / outdoors
 - Endophilic / Exophilic: 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 endophilicity, 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



Transmission Settings

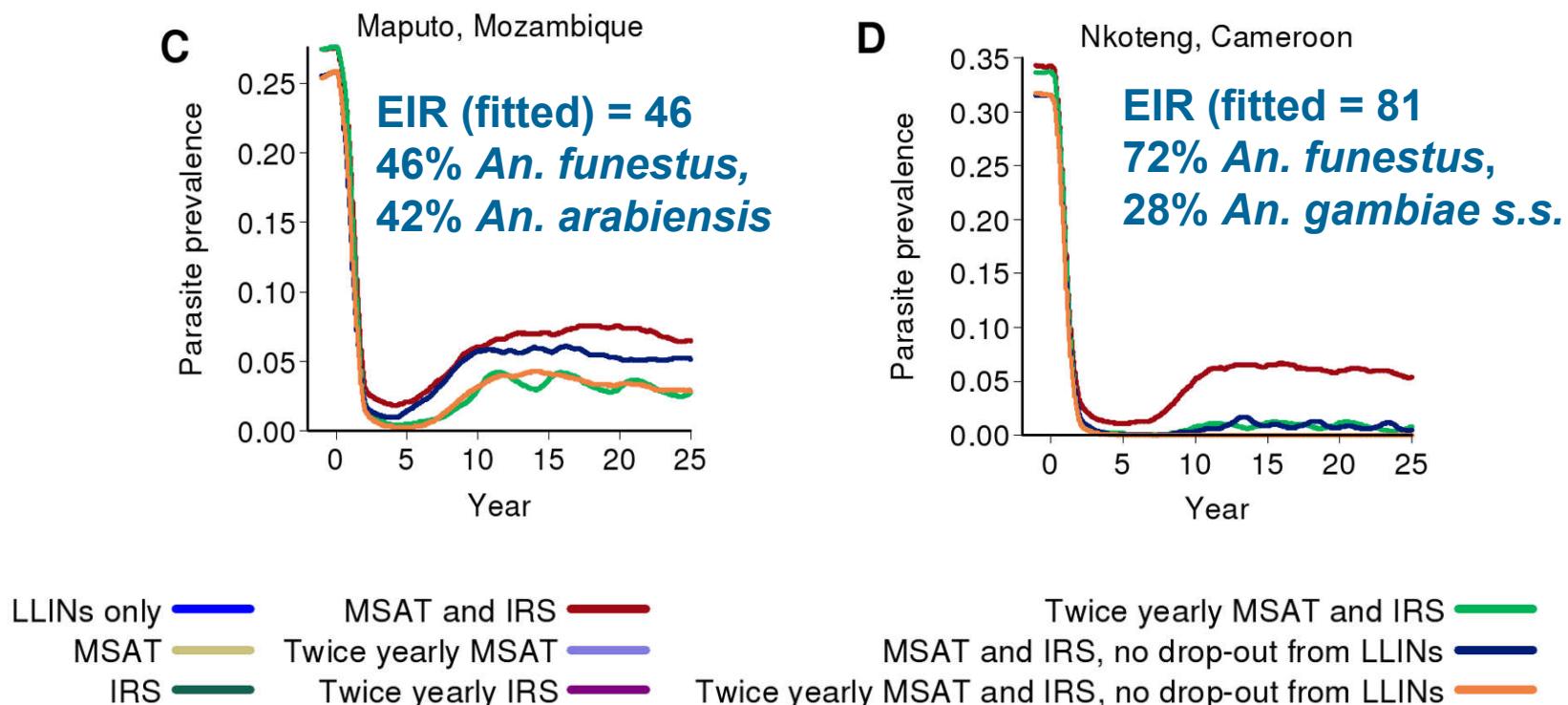
- Consider different settings characterising across Africa:
 - Transmission intensity (EIR)
 - Seasonality Index (proportion of EIR occurring within the peak 3 months of transmission)
 - Vector species combinations



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

IRS and Vector behaviour, Moderate Transmission

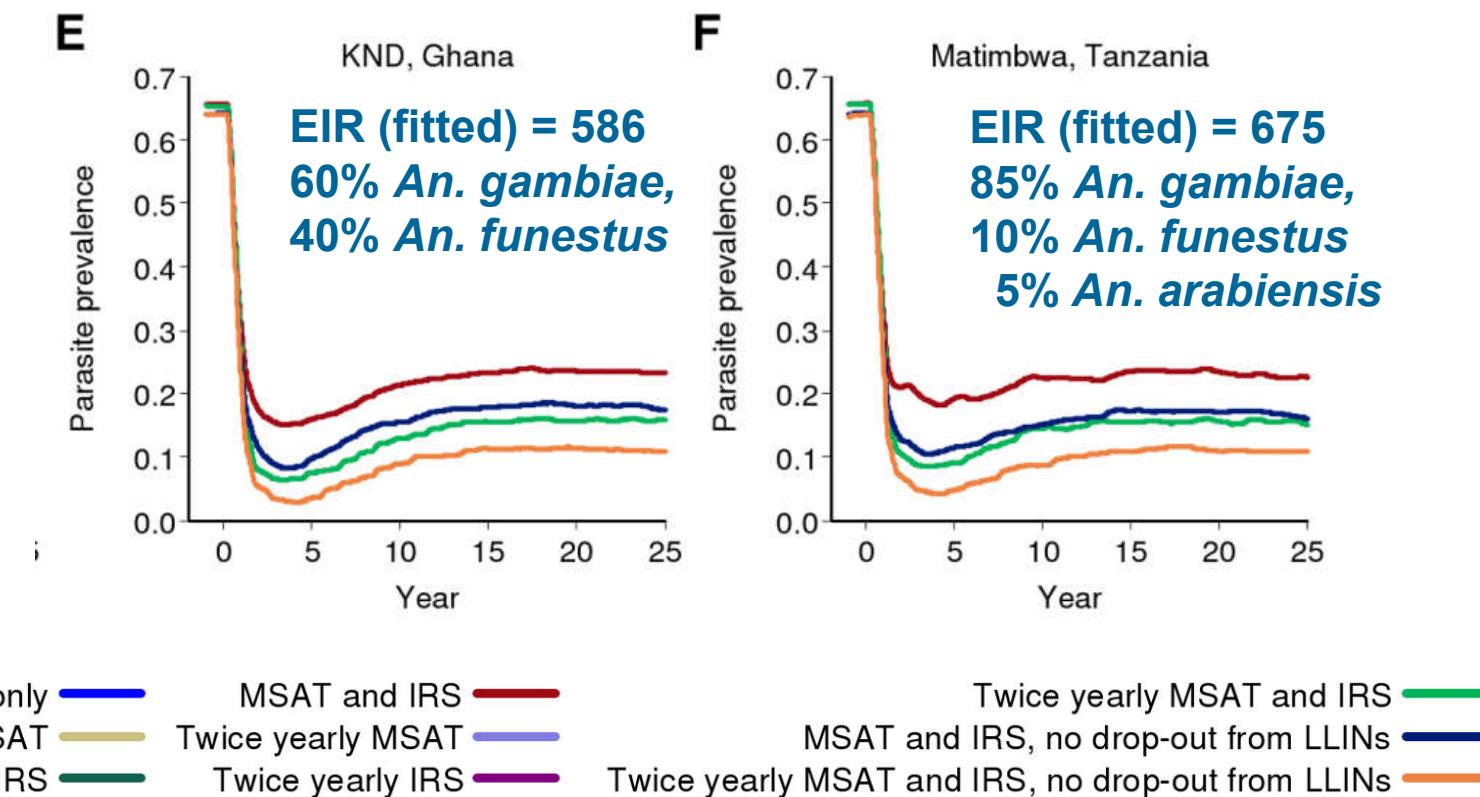
- Interventions will have different impact in settings with similar EIR (e.g. moderate transmission) but different vector species
- IRS and ITNs unlikely to have sufficient impact if outdoor-resting mosquitoes are common (*An. arabiensis*)



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

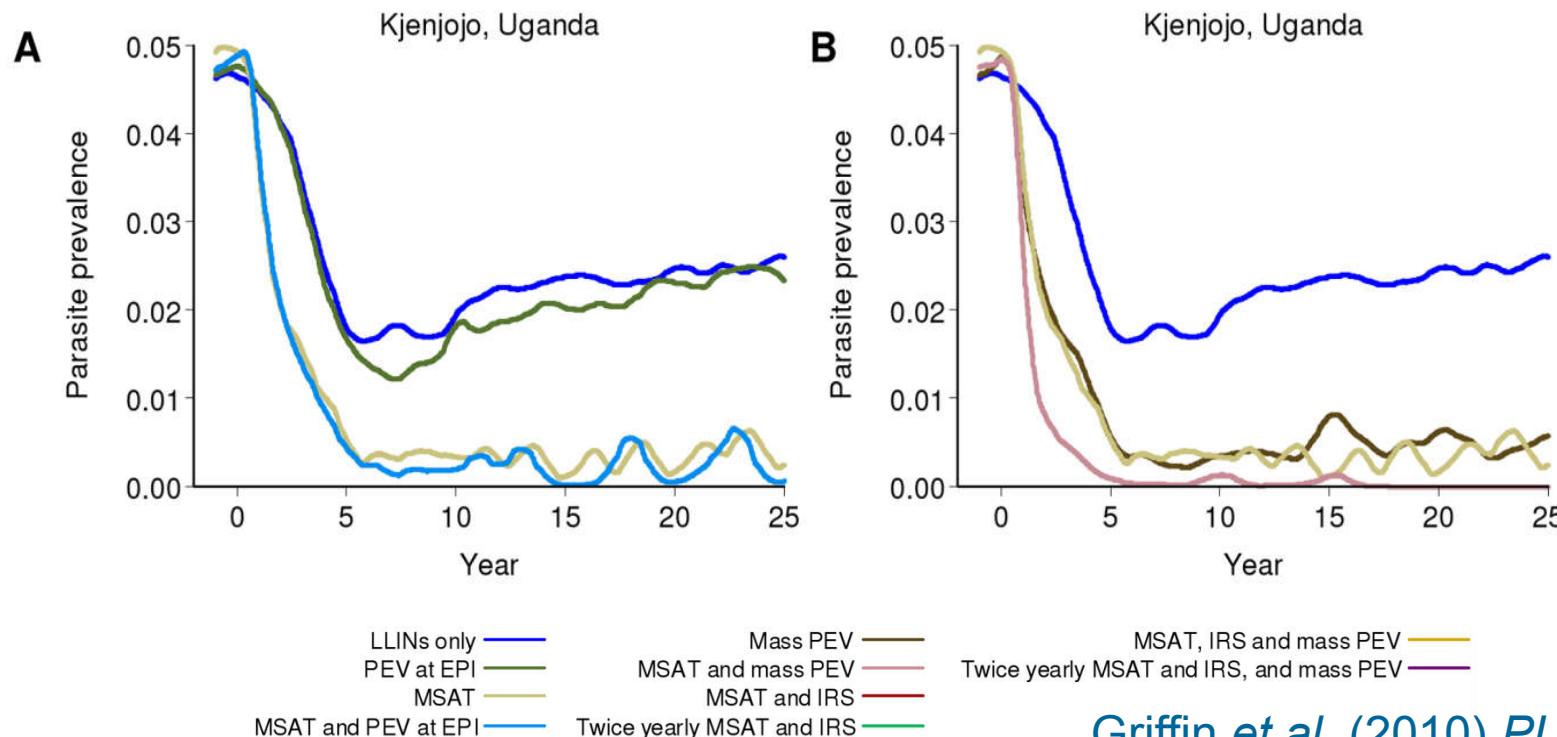
High Transmission Settings

- 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



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

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.)

- 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.)

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