Can we eliminate malaria with current intervention tools?

Lessons from mathematical models for malaria control & elimination

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(with slides from Azra Ghani & Emma Dawes)

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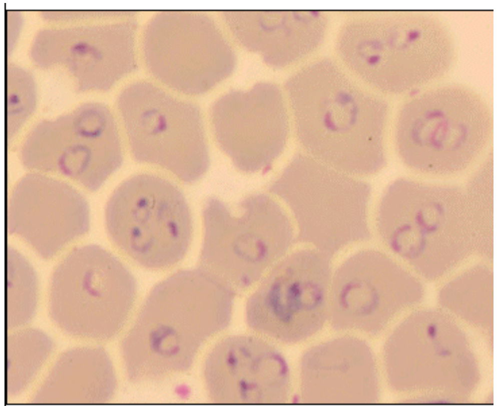
Human malaria *Plasmodium* species

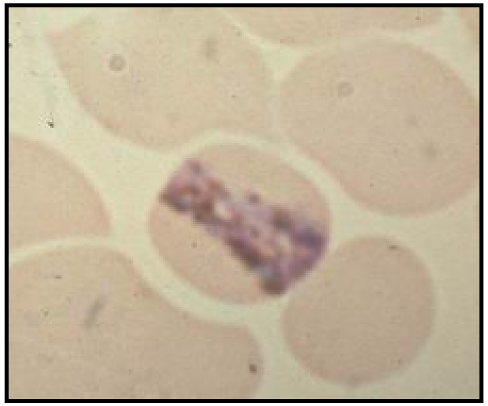
Plasmodium falciparum



(original image provided by Steve Aley)

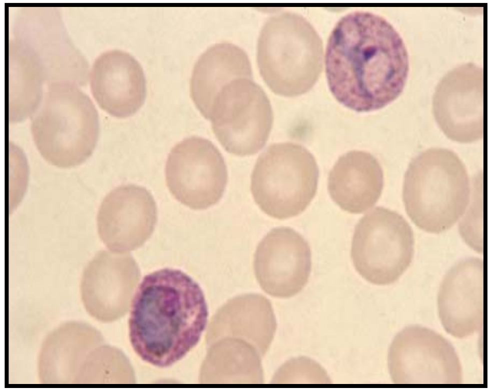
Africa
SE Asia
Latin America

Plasmodium malariae



Africa
SE Asia
Latin America

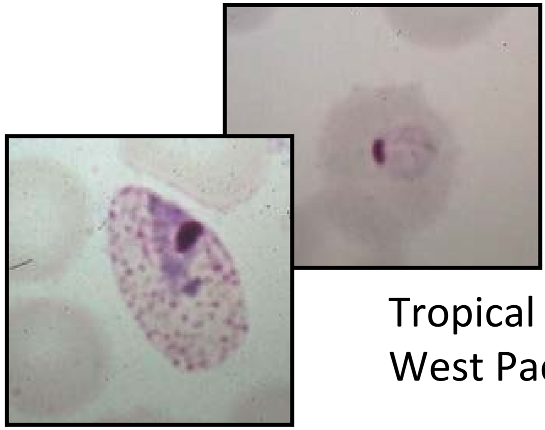
Plasmodium vivax



(original image by Mark Lontie)

Middle East
Asia
Western Pacific
Latin America
Africa

Plasmodium ovale



Tropical Africa
West Pacific

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Life-cycle of *Plasmodium falciparum*

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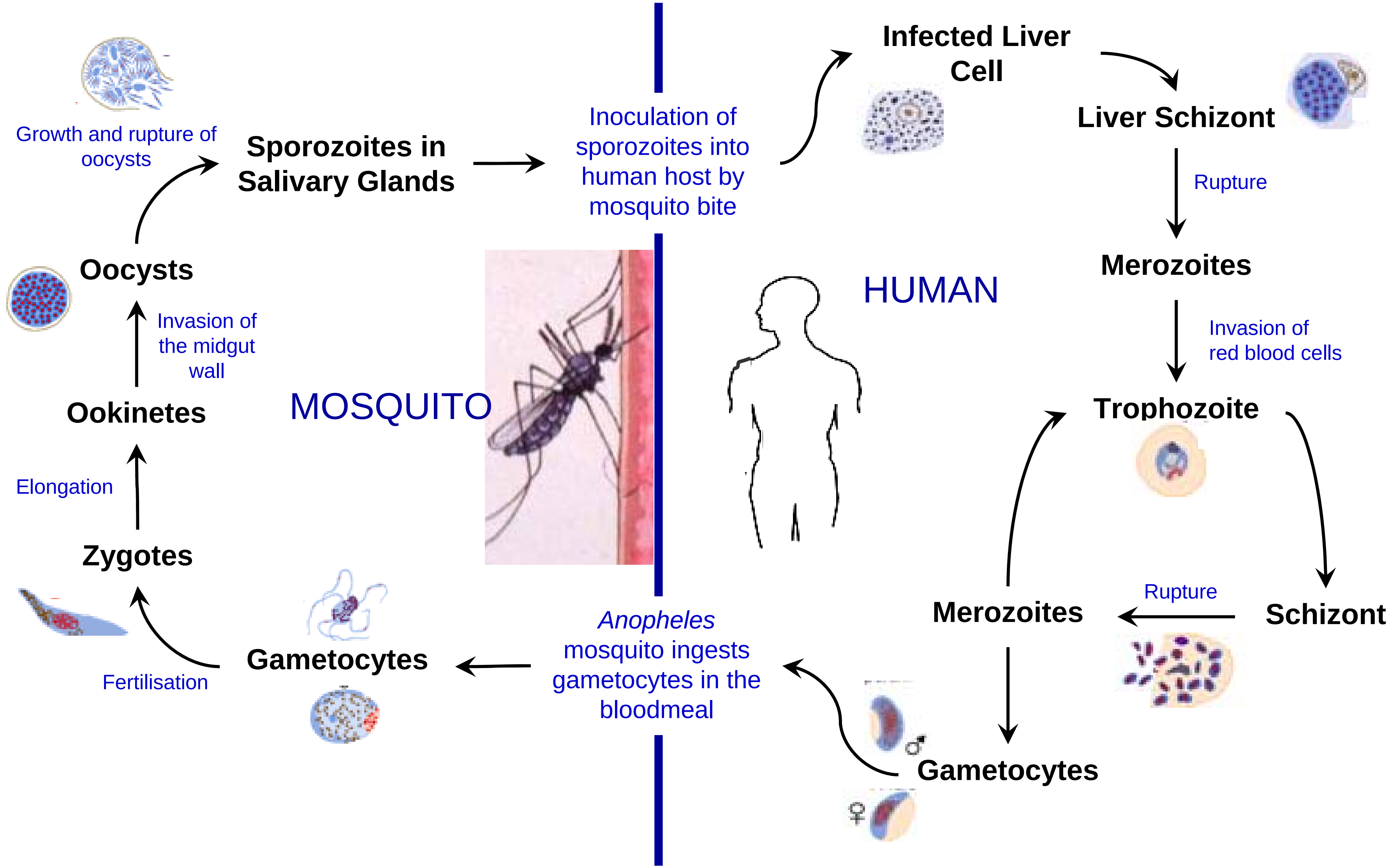

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Human malaria is transmitted by *Anopheles* species mosquitoes

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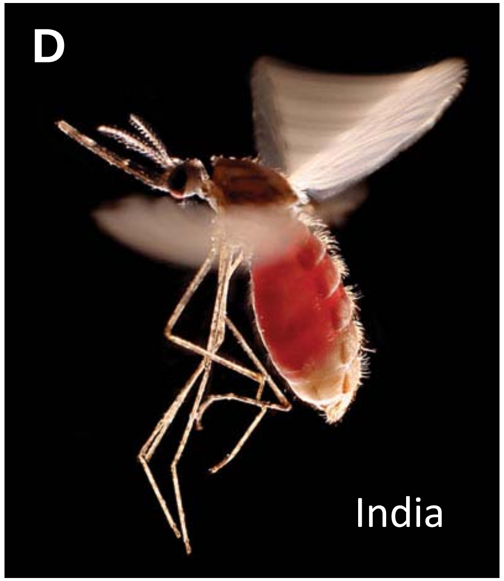
Anopheles gambiae s.l.

Anopheles funestus

Anopheles albimanus

Anopheles stephensi



A, B, C = CDC Image Library

D = The Wellcome Trust

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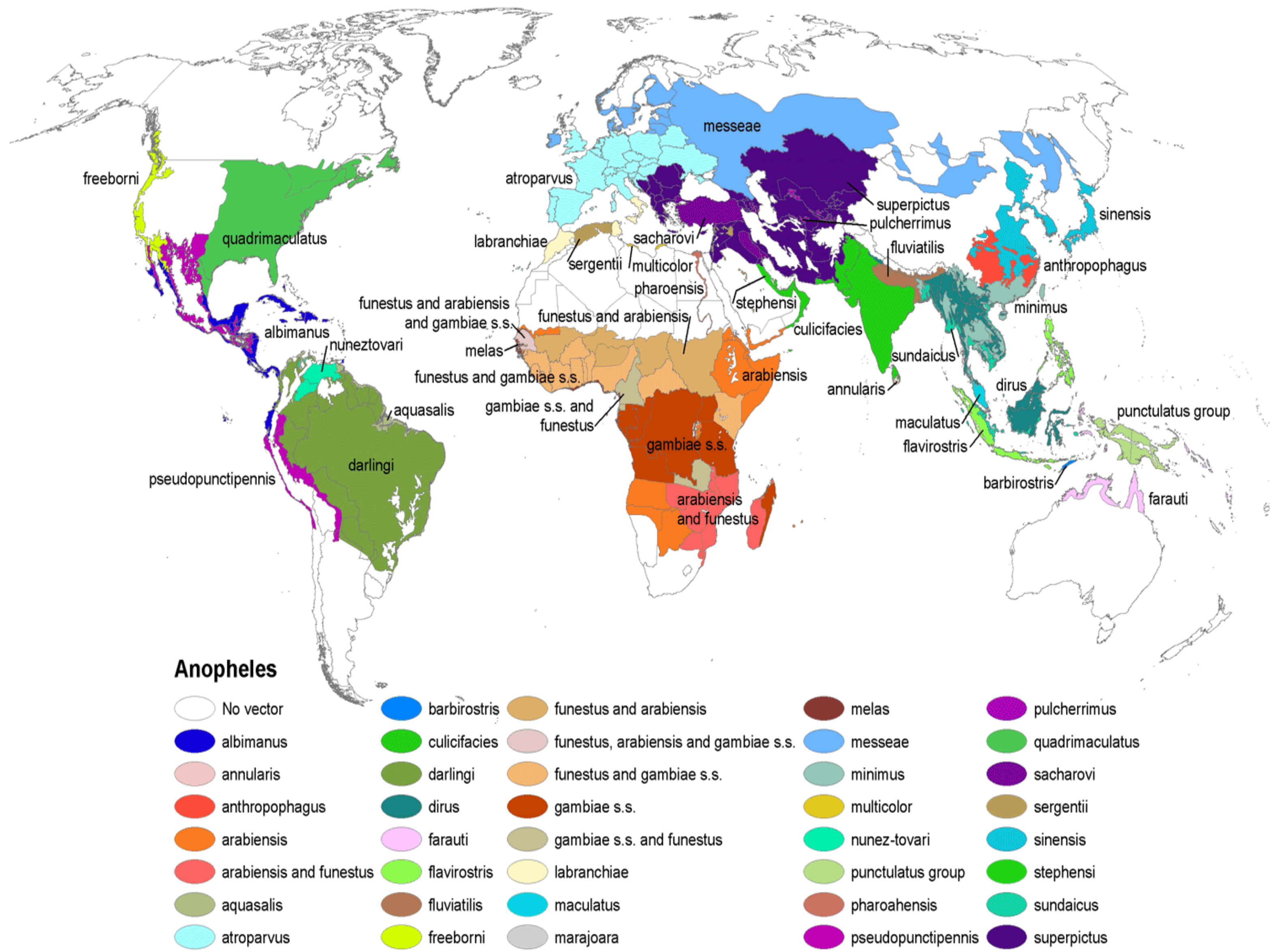
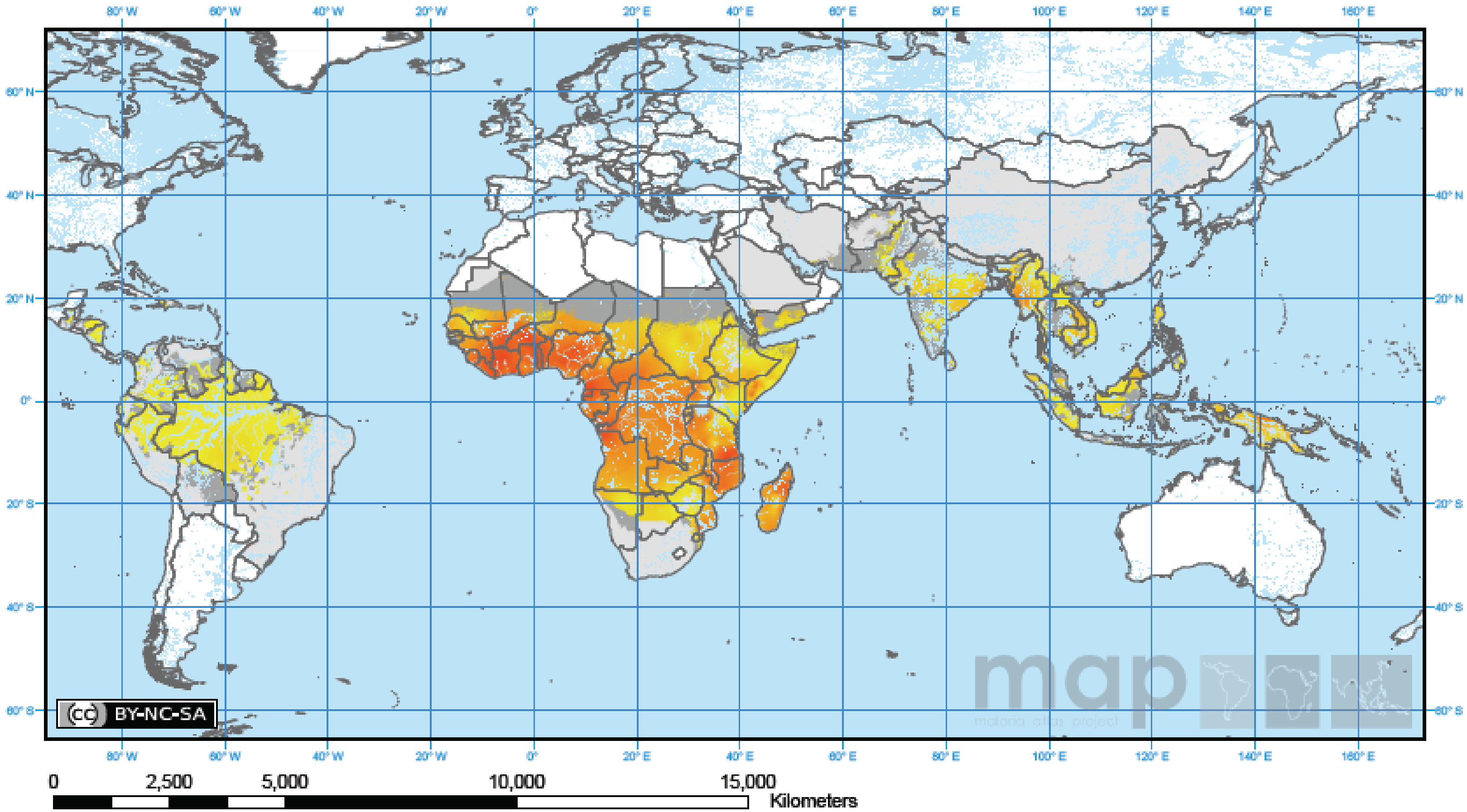
Distribution of *Anopheles* vectors



Prevalence of *P. falciparum* in 2007

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



Citation: Hay, S.I. *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 carrée.

N

Water

Malaria free

*Pf*API < 0.1‰

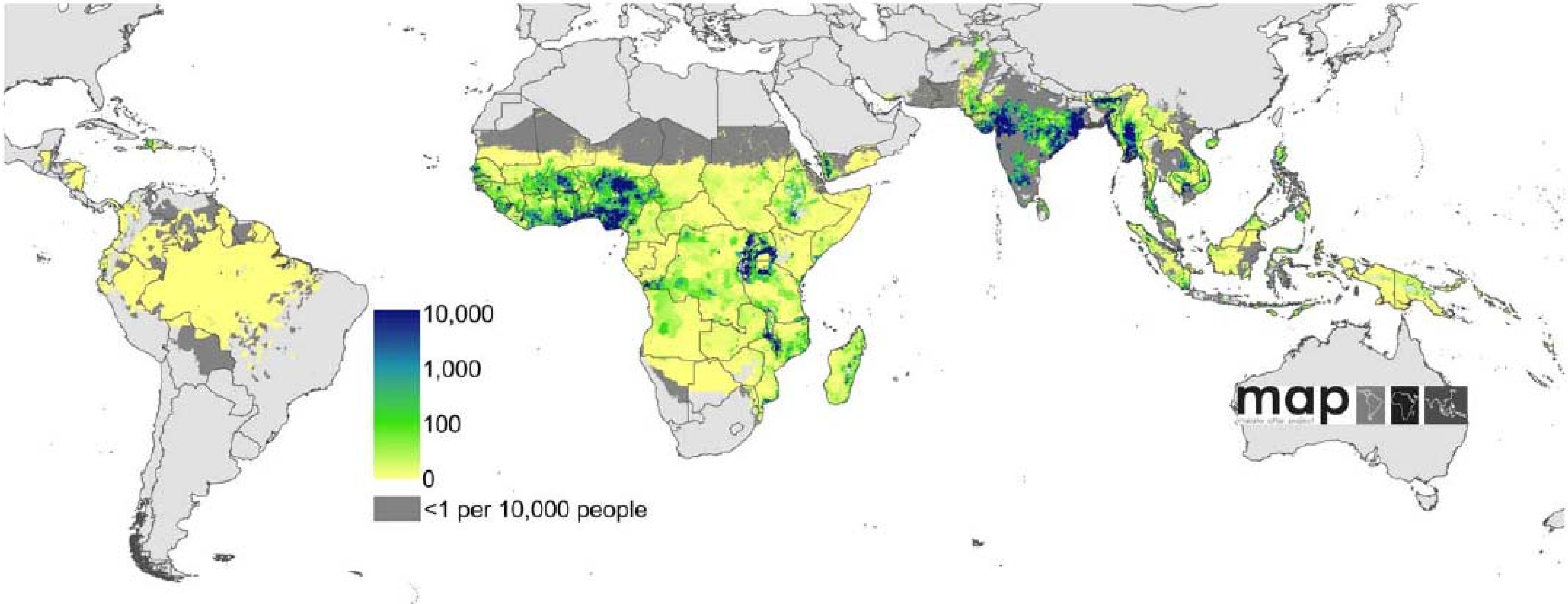
Parasite rate
(in units of $PfPR_{2\text{-}10}$, 0-100%)

0 100

Source: www.map.ox.ac.uk

Burden of Disease 2007

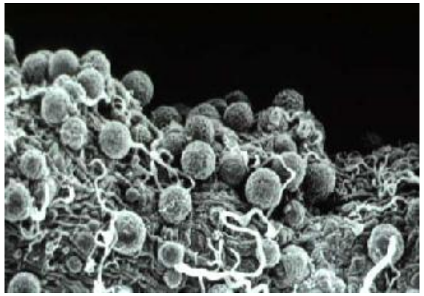
- Estimated 450 million (95% Credible Intervals 349-552 million) cases of malaria
- Majority of cases in population-dense areas e.g. India, Nigeria



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

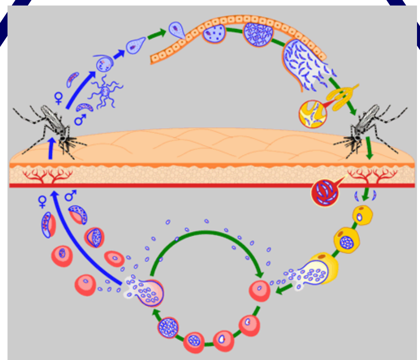
The Triangle of Transmission

Plasmodium



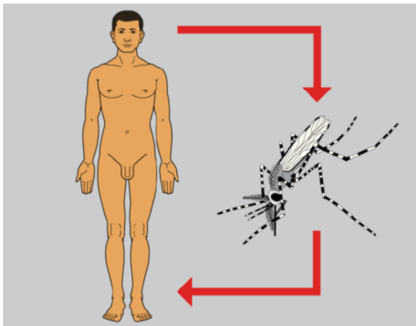
Oocysts in mosquito abdomen

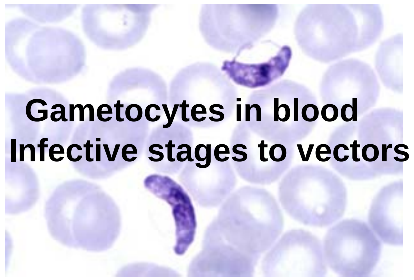
Infective stages to humans



Anopheles

Human





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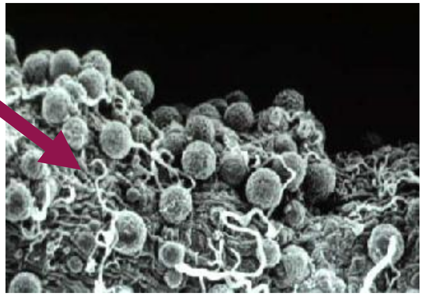
Interrupting the Triangle of Transmission

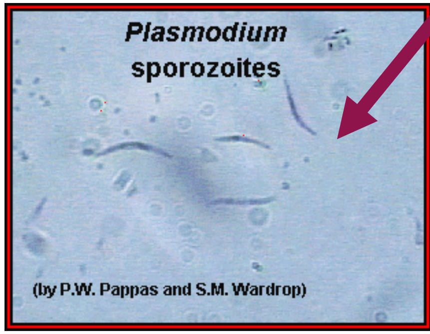
Transmission-blocking vaccines (e.g. preventing oocyst formation).
Refractory, GM mosquitoes



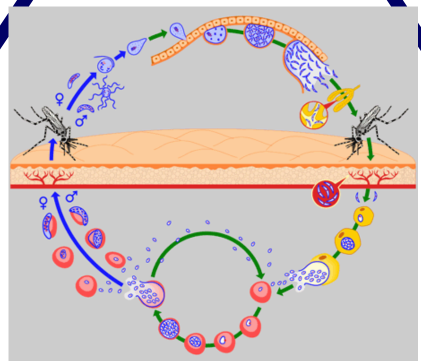
Oocysts in mosquito abdomen

Plasmodium

Vaccines against pre-erythrocytic stages, RTS,S



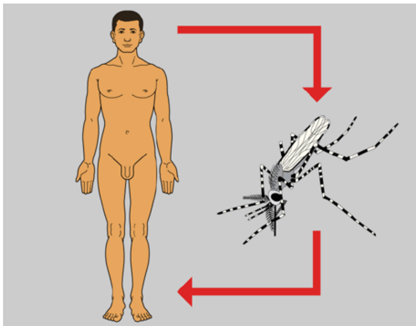
Infective stages to humans



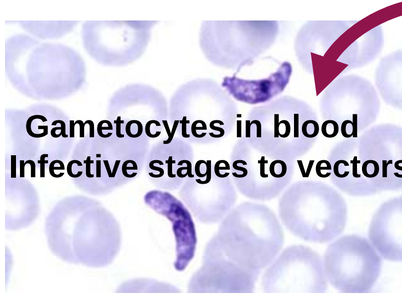
Gametocytocidal treatment (e.g. ACT, Primaquine)

Anopheles

ITNs,
LLINs, IRS



Human



Gametocytes in blood
Infective stages to vectors

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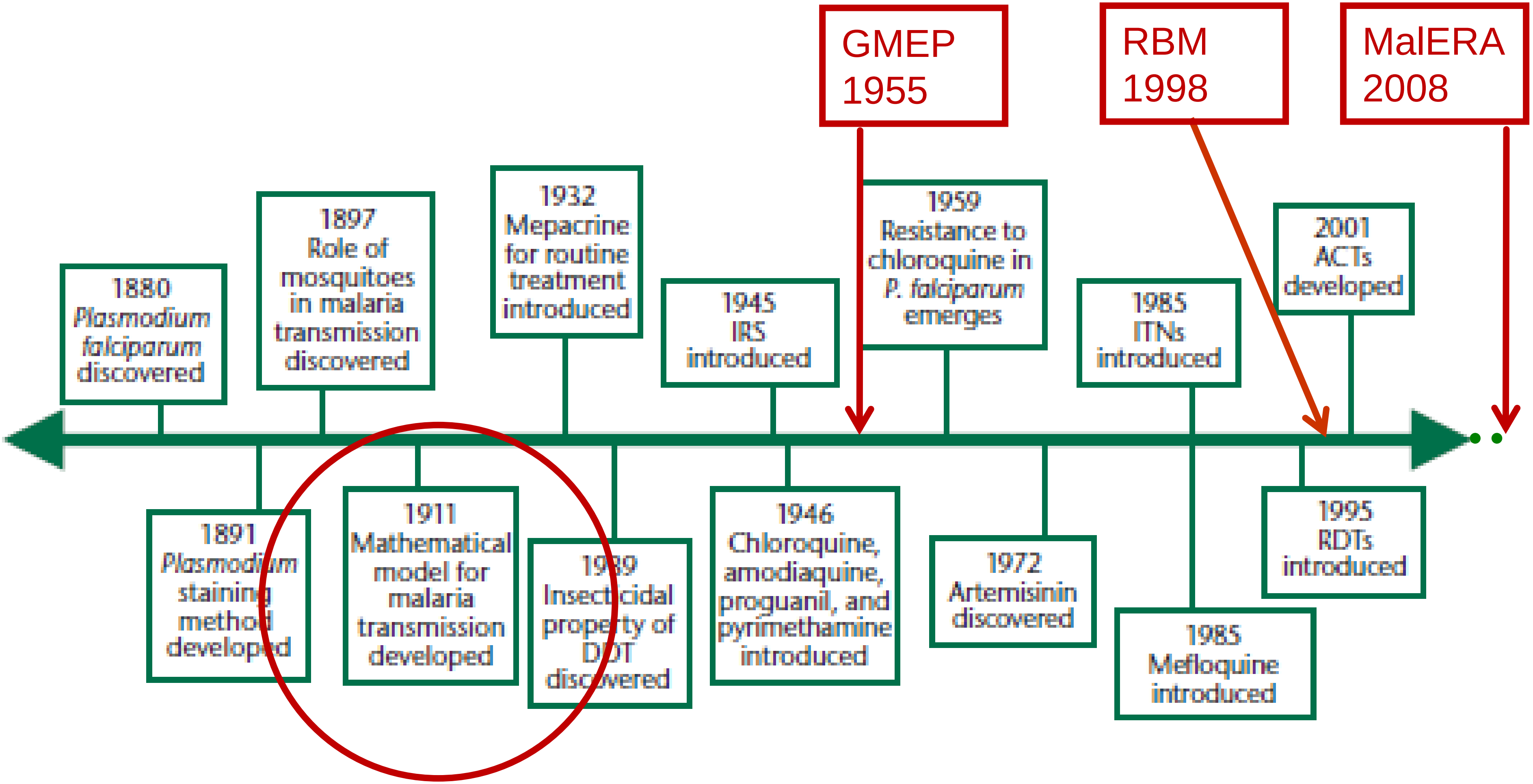
History of Malaria Control



GMEP: Global Malaria Eradication Programme
RBM: Roll Back Malaria (to halve malaria burden by 2010)
MalERA: Malaria Eradication Research Agenda

Wernsdorfer, Hay & Shanks (2009)

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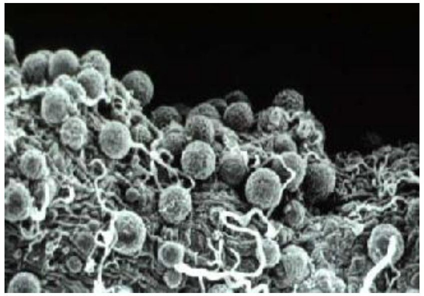
The Components of Transmission

The probability of vectors surviving the *n* days of sporogony and beyond, $p^n/(-\ln(p))$



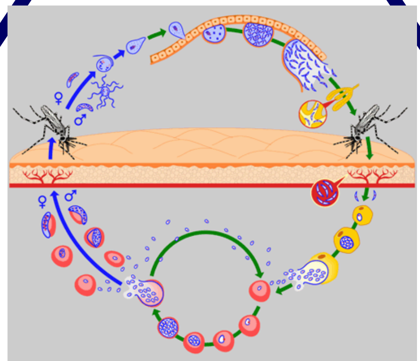
Oocysts in mosquito abdomen

The probability of infection establishing in vectors, *c*

Plasmodium

Infective stages to humans

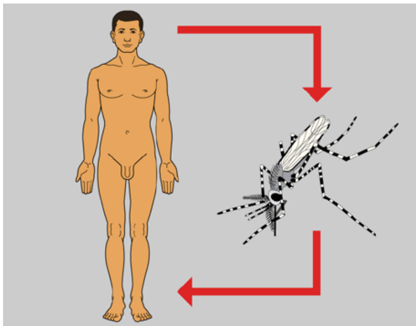
The probability of infection establishing in humans, *b*



Anopheles

The Vector to Human ratio, m = V/H

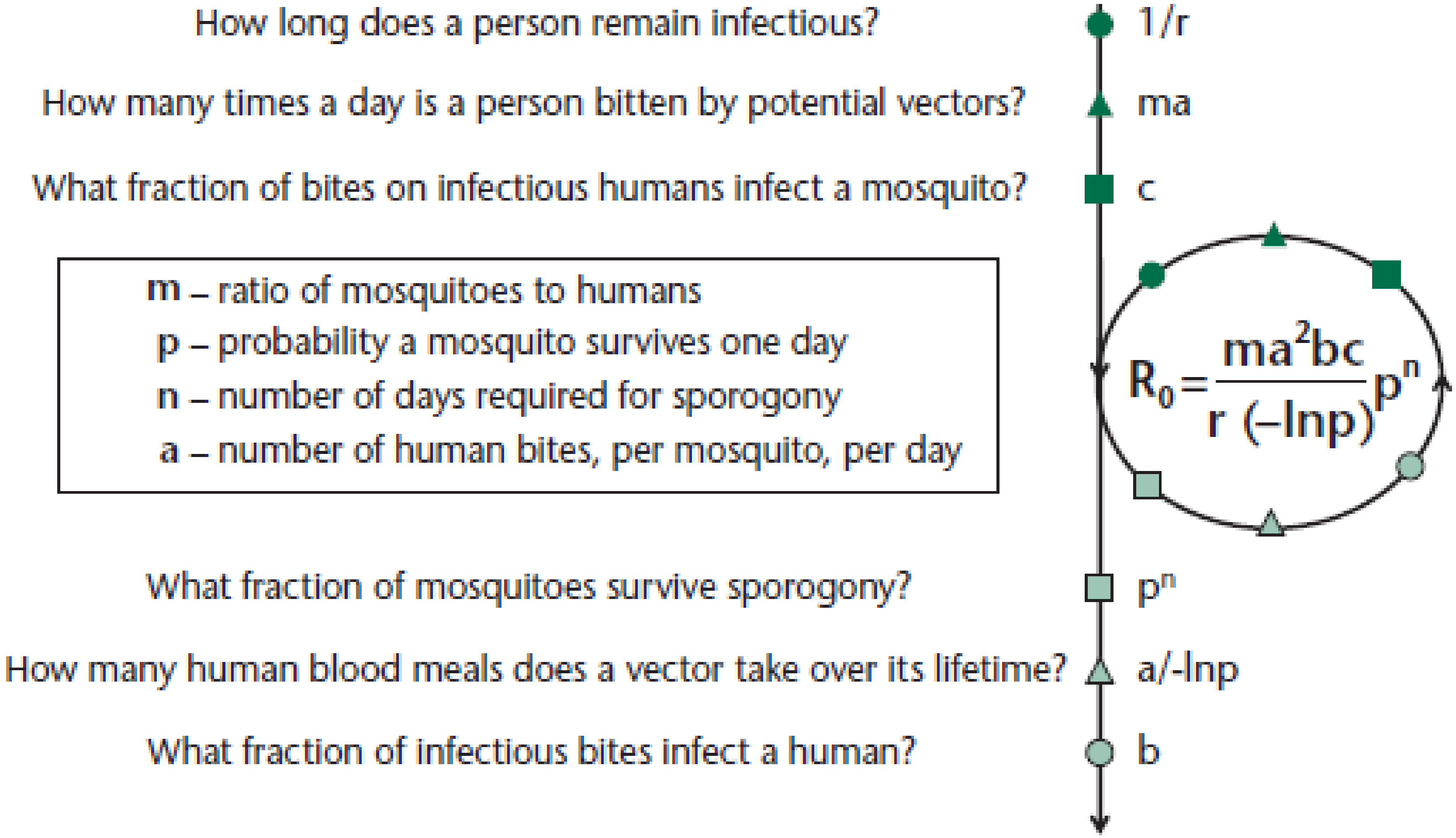
The biting rate per vector on humans, *a*



Human

The duration of infectiousness, $1/r$

The Basic Reproduction Ratio, R_0, for Malaria



From Smith, Smith & Hay **(2009)**

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The Basic Reproduction ratio, R_0, for Malaria

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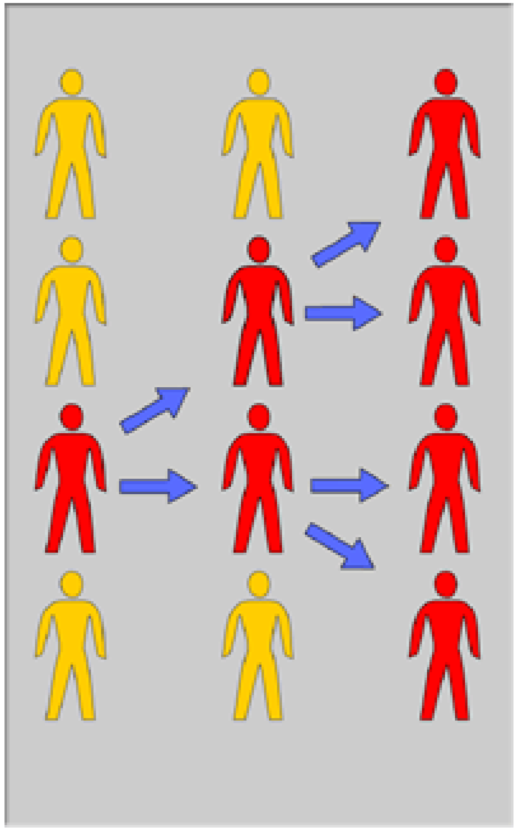
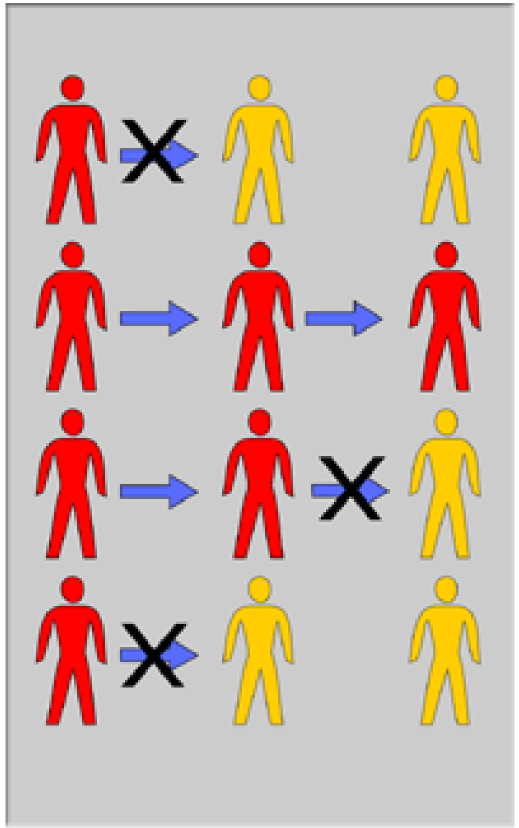
*R*o > 1 (~2)



$$R_0 = \frac{m a^2 b P^n}{r(-\log_e P)}$$

*R*o < 1 (~1/2)



Average number of secondary cases originated during infectiousness by a primary case introduced in a wholly susceptible population

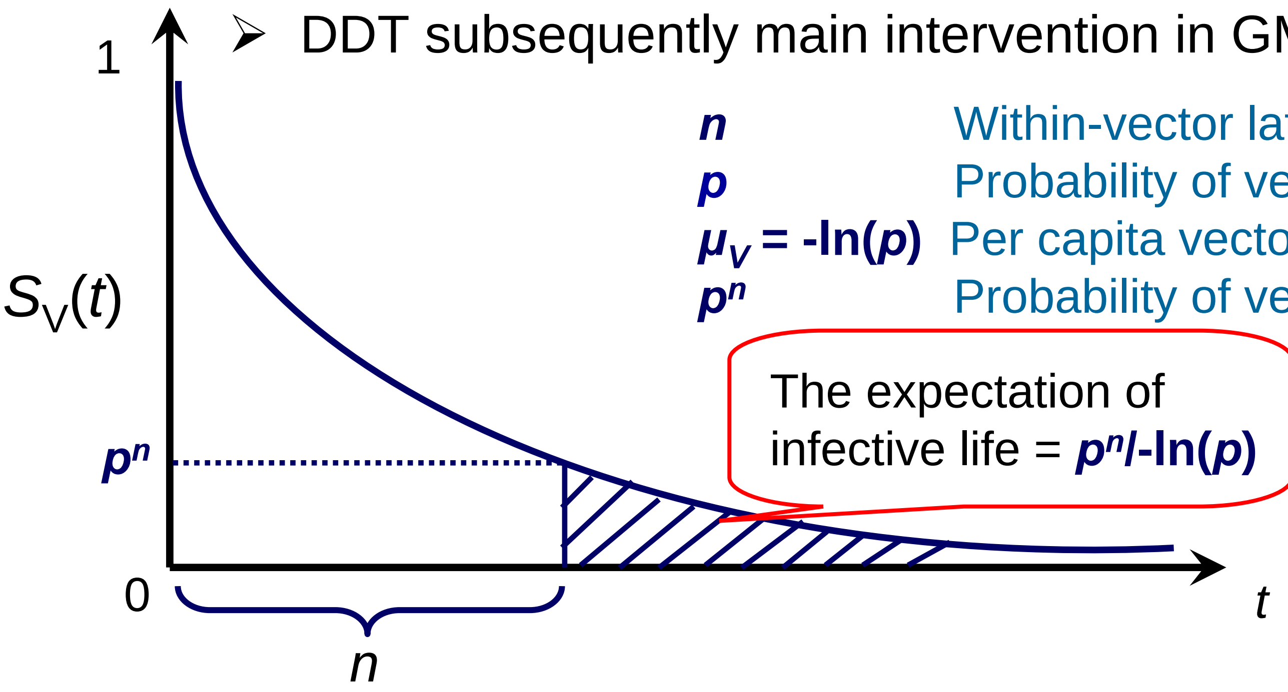
Each case generates on average 2 cases, there will be an epidemic

Each case generates less than 1 case on average, malaria will die down

Macdonald (1950) & Garrett-Jones (1964)

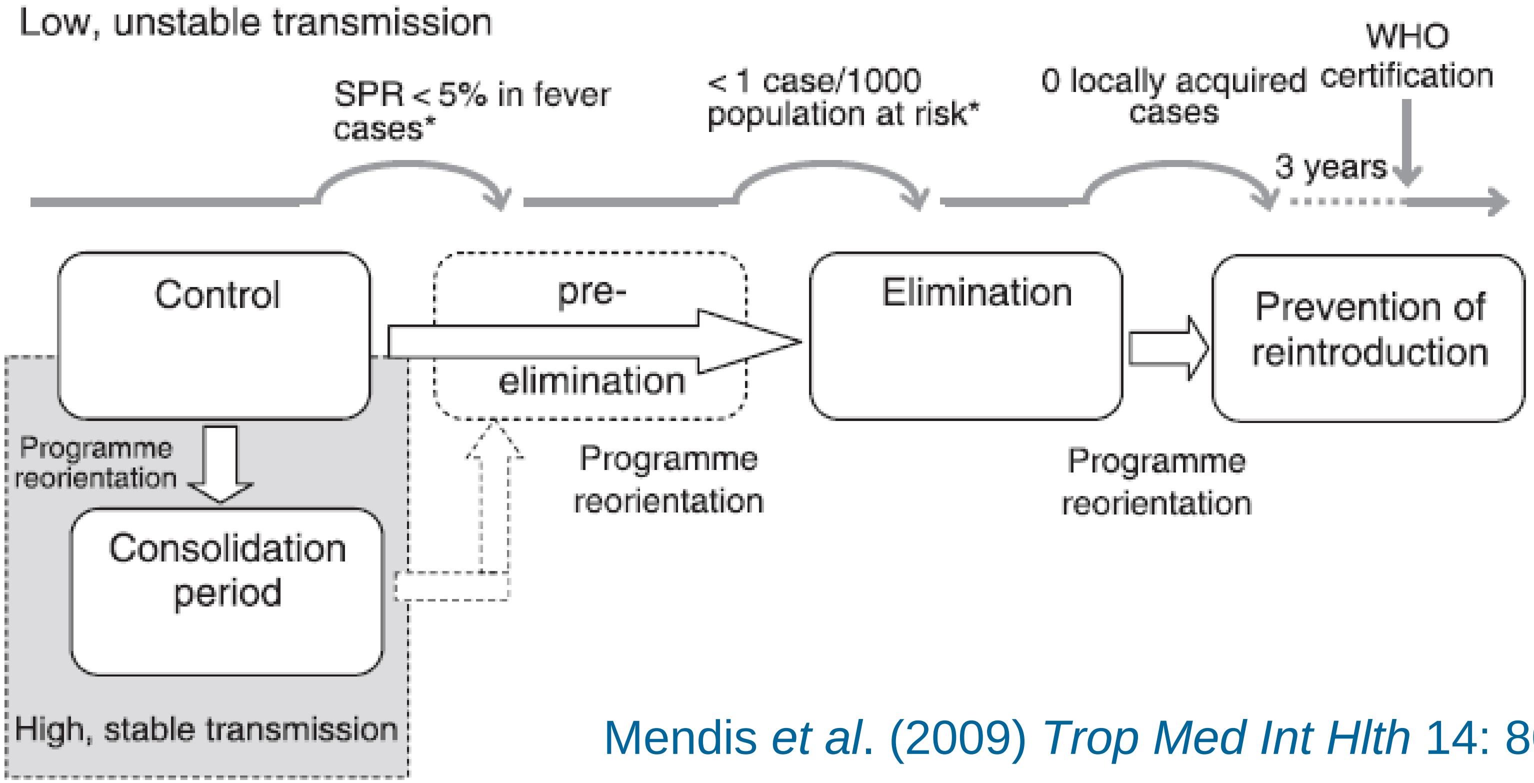
- Delay in the parasite development / multiplication within the mosquito (sporogony) is the “weakest link” in the transmission cycle because sporogony takes an appreciable portion of the vector life-span
- Interventions that reduce adult mosquito life-span (e.g. IRS with DDT) have the greatest potential to reduce R_0 via reducing the probability of daily survival, p (p^n is strongly non-linear)
- DDT subsequently main intervention in GMEP

$\boldsymbol{n}$	Within-vector latency period (sporogony)
$\boldsymbol{p}$	Probability of vector daily survival
$\boldsymbol{\mu_V = -\ln(p)}$	Per capita vector mortality rate
$\boldsymbol{p^n}$	Probability of vector surviving sporogony



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?*



Mendis *et al*. (2009) *Trop Med Int Hlth* 14: 802-809

Control, Elimination, Eradication

Box 1 Definitions (WHO 2006a)

Malaria control is reducing the disease burden to a level at which it is no longer a public health problem.

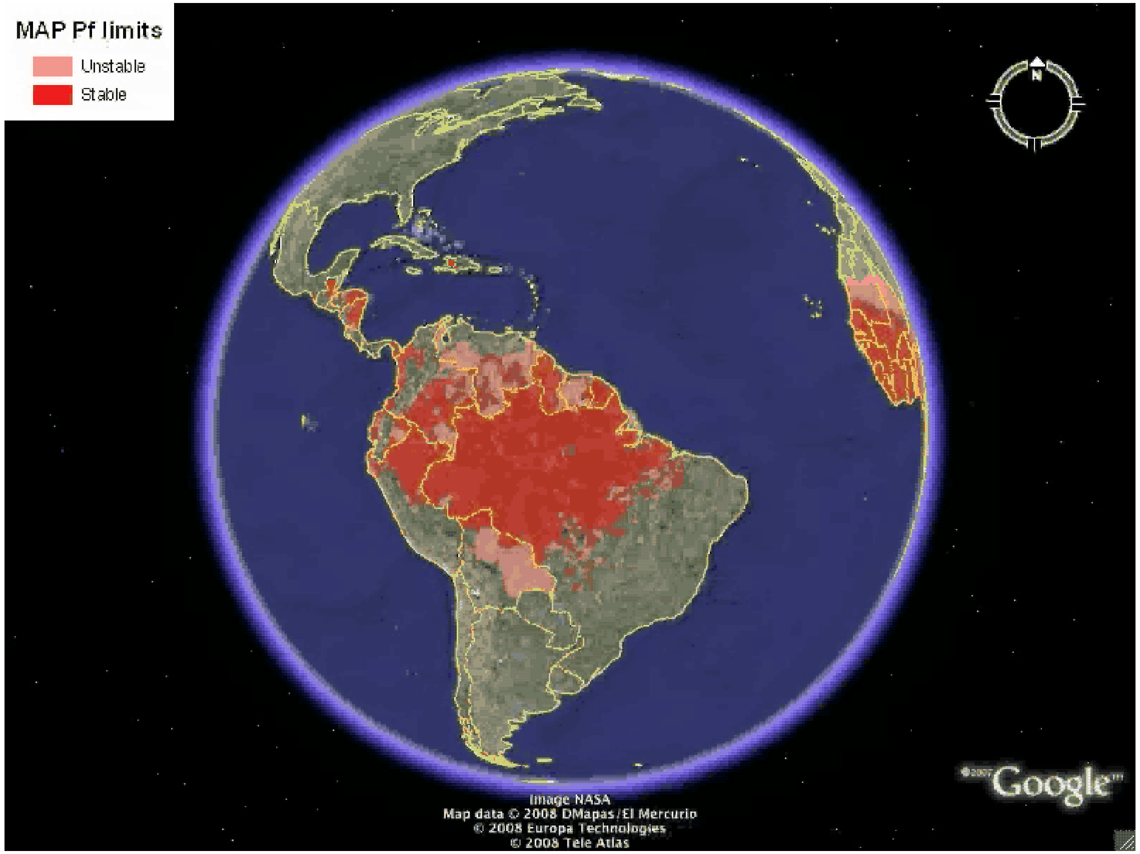
Malaria elimination is interrupting local mosquito-borne malaria transmission in a defined geographical area, i.e. 0 incidence of locally contracted cases.

Malaria eradication is the permanent reduction to 0 of the worldwide incidence of malaria infection caused by a specific agent; i.e. applies to a particular malaria parasite species.

Mendis *et al*. (2009) *Trop Med Int Hlth* 14: 802-809

Elimination – Strategic Questions

- *Where is elimination achievable? Where should initial efforts be focused?*



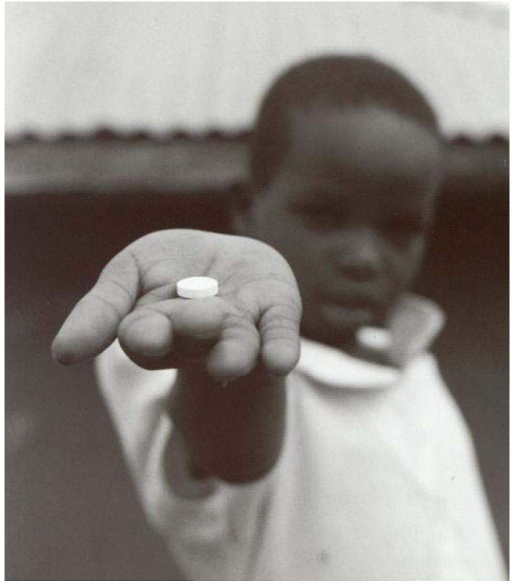
- Shrink the map?
- Focus resources on high transmission foci?

Malaria Atlas Project (www.map.ox.ac.uk)

Current Interventions

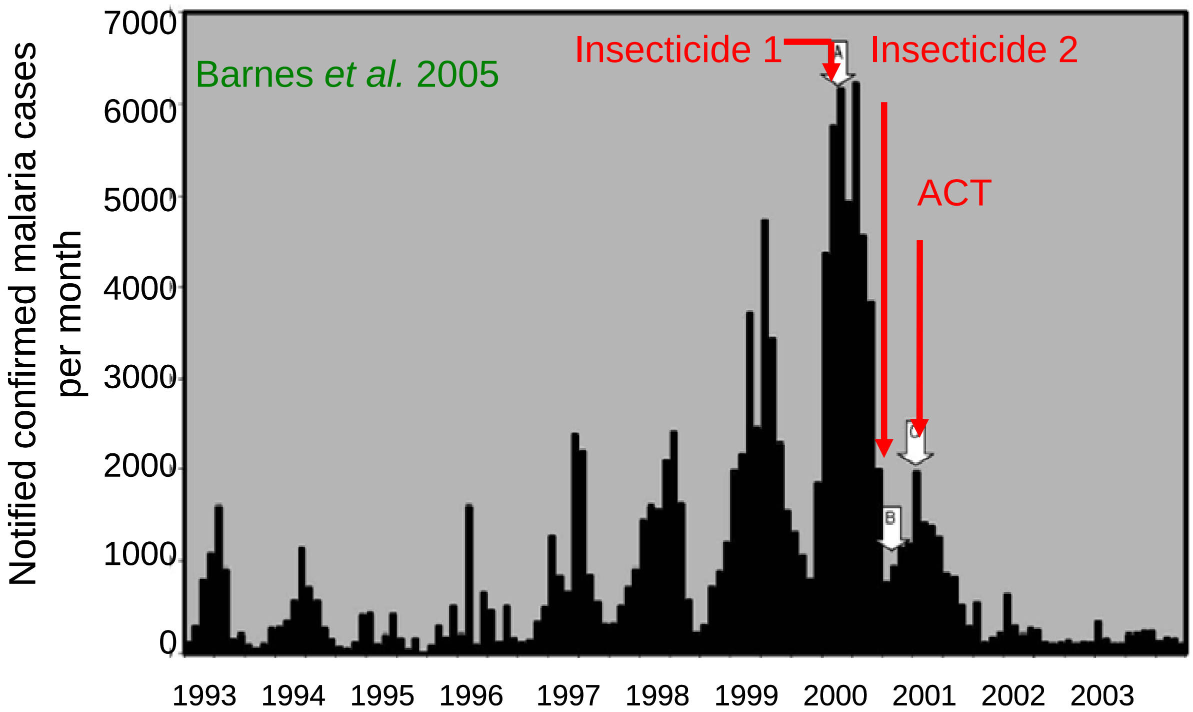
- Vector Targets
  - Long-lasting insecticide-treated nets (LLIN)
  - Indoor Residual Spraying (IRS)
  - Spatial repellents (House screening)
  - Larval control (Source reduction)

- Parasite within Human Targets
  - Switch to ACT regimens as first-line therapy
  - Mass Drug Administration (MDA) or Mass Screening & Treating (MSAT)
  - Pre-erythrocytic vaccine (RTS'S)



Intervention Impact

- Currently observing wide-spread declines in malaria infection prevalence and disease
- Much of the evidence for intervention impact is observational, e.g. Malaria in KwaZulu-Natal, South Africa



Insecticide 1: DDT for IRS in KwaZulu Natal

Insecticide 2: IRS in Mozambique

ACT: Artemether-Lumefantrine for uncomplicated malaria

Barnes *et al*. (2005) *PLoS Med* 2(11):e330

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Questions for Mathematical Models

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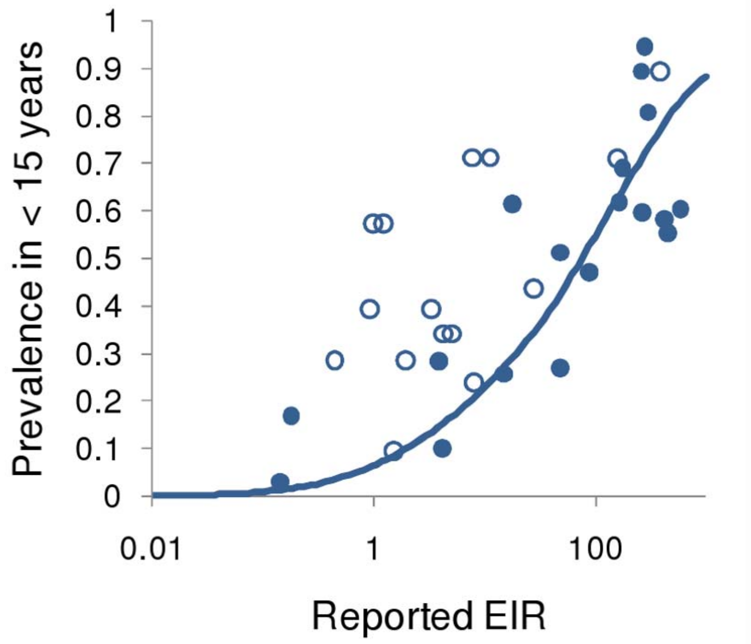
- In which settings are current tool sufficient to reduce prevalence to low levels (PfPR < 1%) ?
- What tools are needed to prevent re-introduction?
- How can we use models to inform strategic planning at a local, national, regional and continental scale?

- Need models which include multiple interventions across different transmission settings

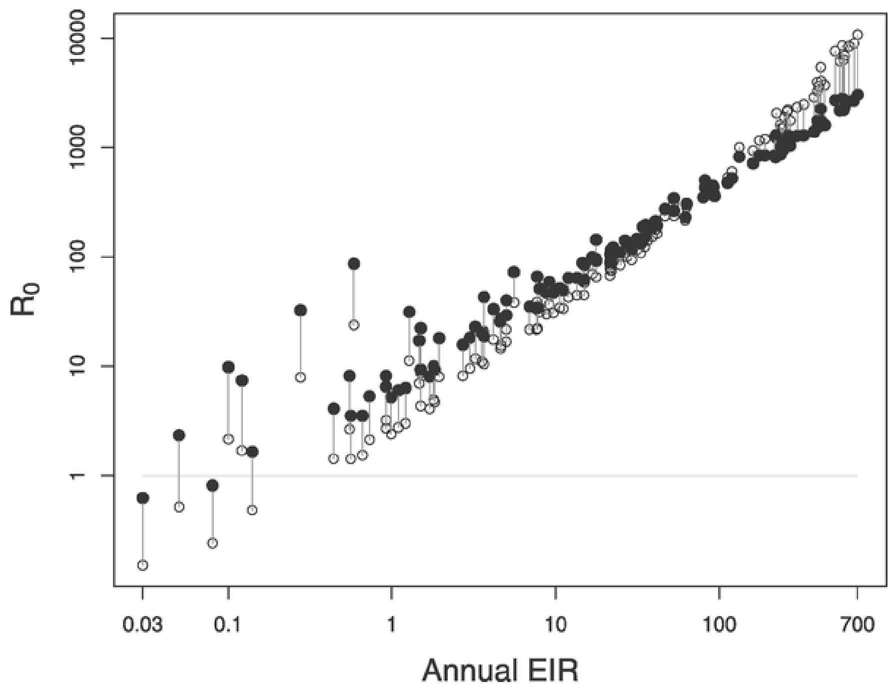
- Transmission measured by the Entomological Inoculation Rate (EIR): The average number of infectious bites received per person per year (if the person is maximally exposed to mosquitoes during the night) = ibppy

Transmission Intensity: EIR and Parasite Prevalence

- Marked variation in the average number of infectious bites individuals are exposed to (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

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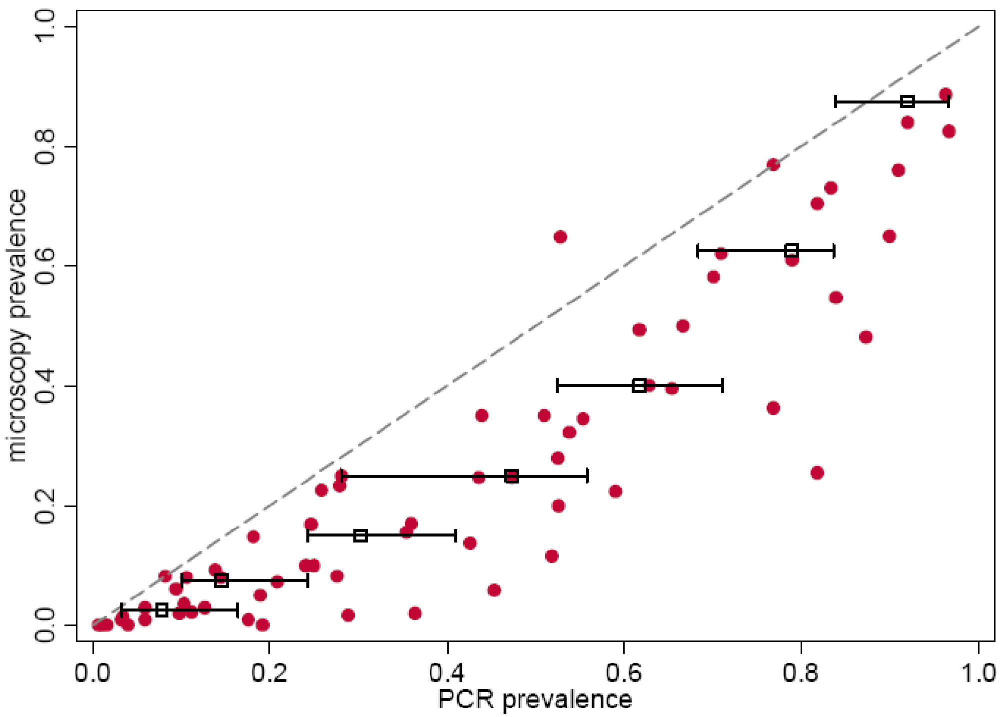
Sub-Microscopic Reservoir

Medical Research Council MRC

- Increasingly apparent that sub-patent infection (not detectable under microscopy) may play a key role in sustaining transmission



Microscopy prevalence	Median PCR prevalence (IQR)
75.0 - 100	92 (84.0-96.5)
50.0 - 74.9	79 (68.4-83.6)
30.0 - 49.9	61.7 (52.4-71.1)
20.0 - 29.9	49.9 (28.0-61.9)
10.0 - 19.9	35.4 (24.3-47.3)
5.0 - 9.9	14.5 (10.0-24.2)
0.0 - 4.9	10.4 (3.4-17.6)

Okell et al. (2009) *J Infect Dis* 200(10):1509-17

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Human Infectious Reservoir

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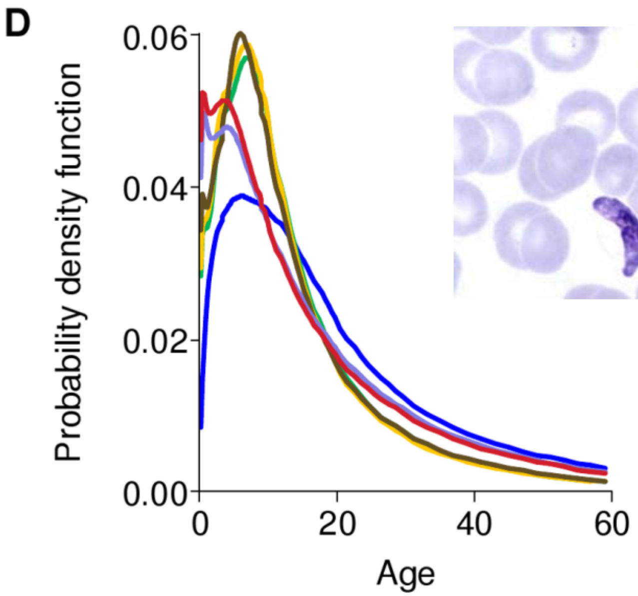
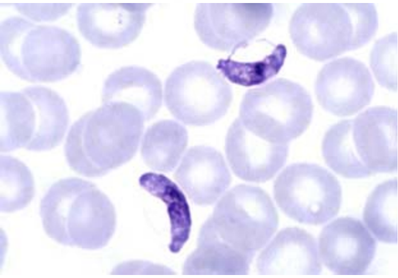
- "Infectious reservoir":
  - Age-specific biting rate x prevalence x infectiousness x population size
- Defines where interventions need to be targeted to reduce transmission rather than control disease
- Depends on:
  - Parasite prevalence by age
  - Gametocytaemia
  - Onward infectiousness
  - Treatment



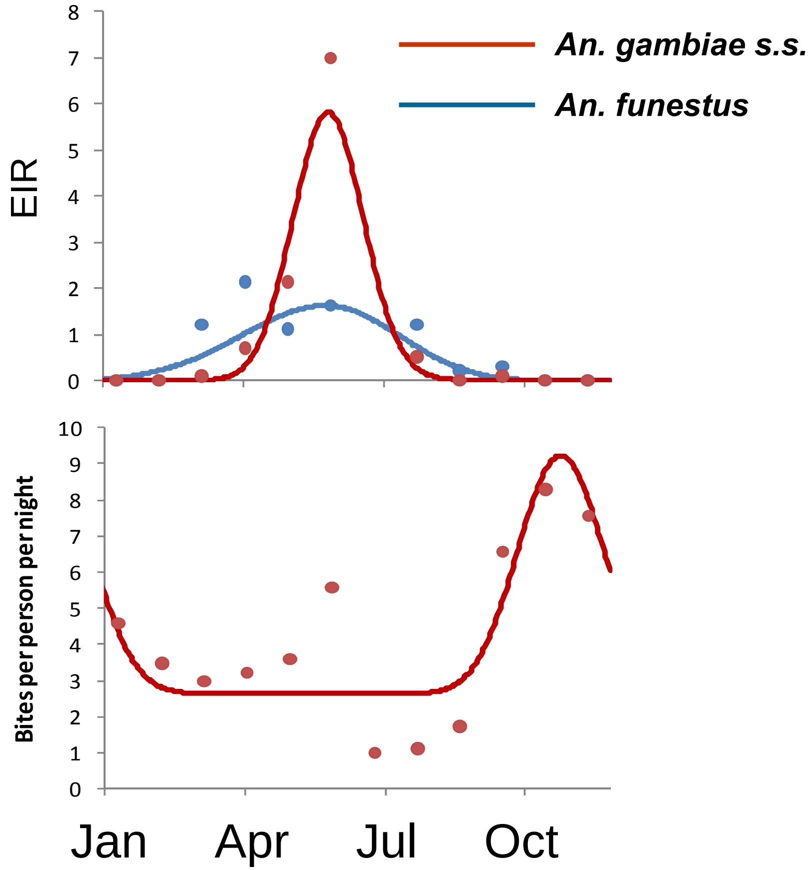


Griffin et al. (2010) *PLoS Med* 7(8)

The Importance of Vector Species

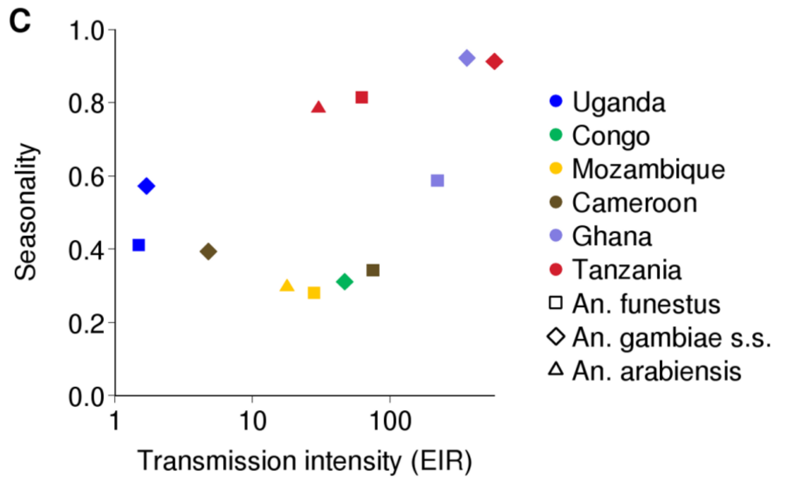
- Key aspects of mosquito behaviour:
  - Endophagy: propensity to bite indoors
  - Endophily: propensity to rest in the house after feeding
  - Human Blood Index (HBI): propensity to bite humans versus e.g. cattle

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



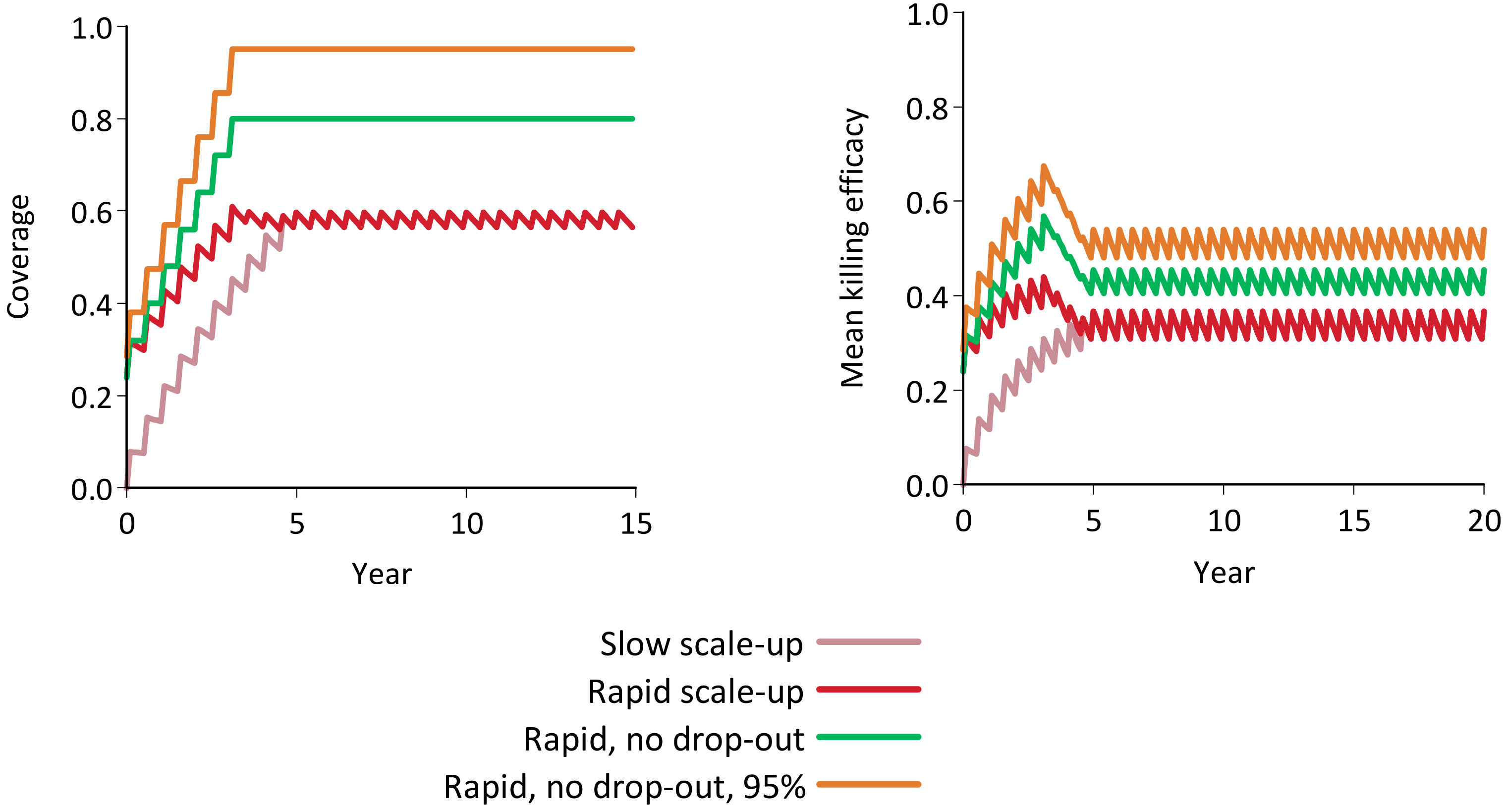
Location	**Population**	**Reported (fitted) annual EIR (ibppy)**	**Type of transmission**		***Anopheles* species composition**
Kjenjojo, Uganda	Rural	7 (3)	Low, perennial	**L**	65% *An. gambiae s.s.*, 35% *An. funestus*
Maputo, Mozambique	Rural	28 (46)	Moderate, perennial	**M**	46% *An. funestus*, 42%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

Scenarios for Intervention Packages

- Prior to 2000:
  - assume the only intervention available was treatment with Sulphadoxine-Pyrimethamine (SP)
- From 2000 to 2010:
  - increase LLIN use from 0% to 20% *(Noor et al.* 2009 *BMC Public Health 9:369)*
  - switch to ACT as first-line therapy
- From 2010:
  - introduce range of intervention packages
- Range of endpoints:
  - change in parasite prevalence
  - change in EIR
  - time to reaching parasite prevalence of <1%

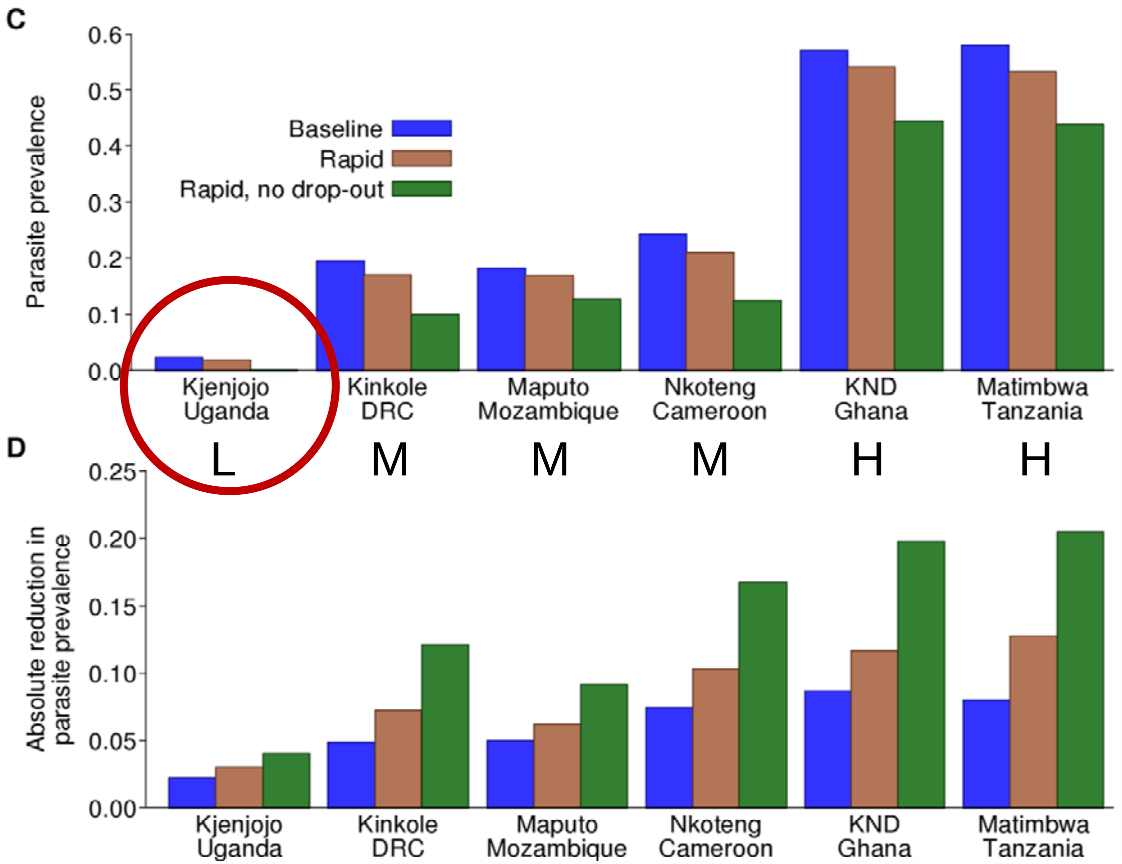
Realistic Coverage

- RBM goals are 80% coverage of ITNs
- Perfect continued usage is unrealistic
- With decaying efficacy, relatively low *effective* coverage



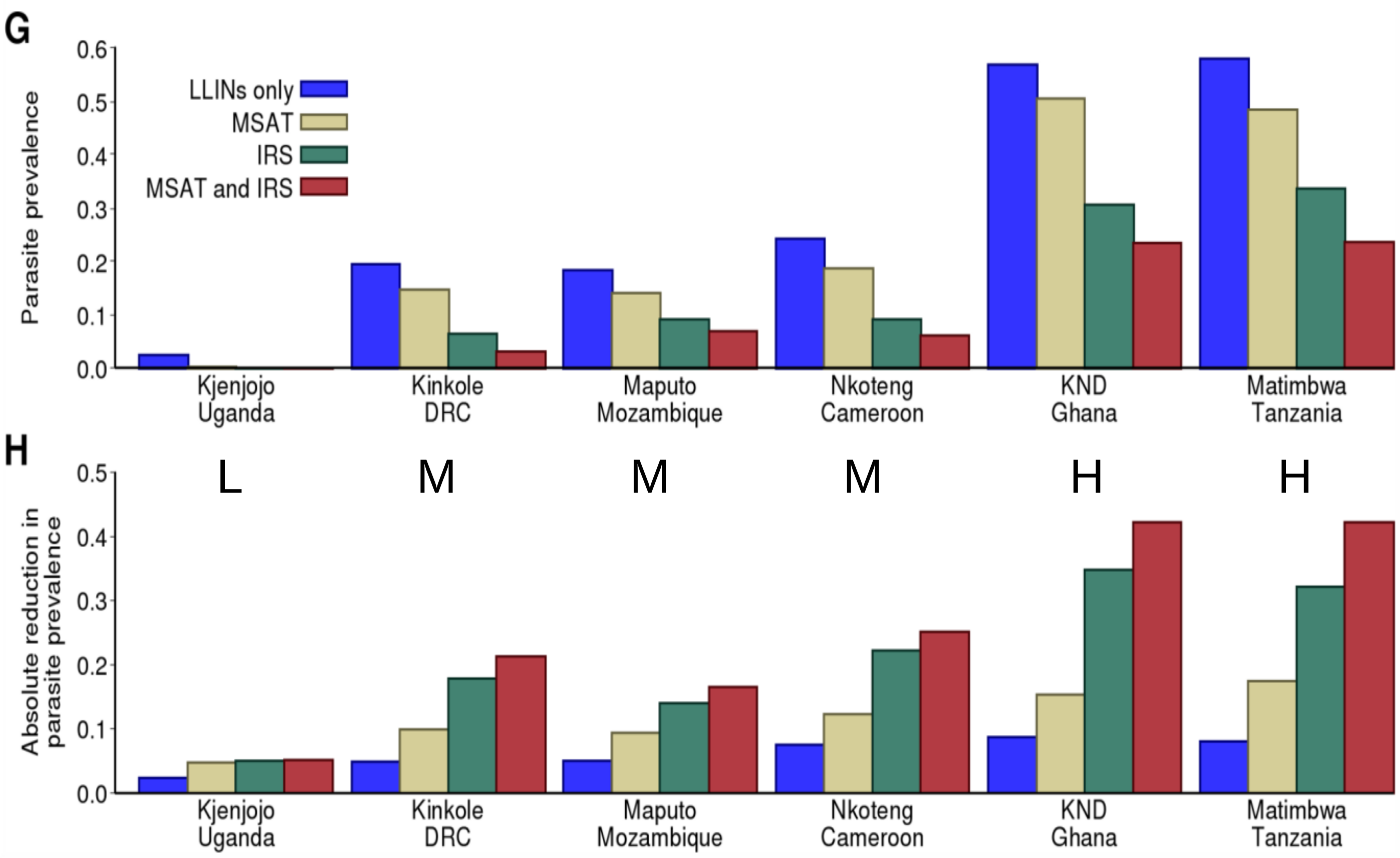
Impact of scale-up of LLINs, Low Transmission

- Increasing coverage to RBM target of 80% can reduce transmission to <1% prevalence in low transmission areas only



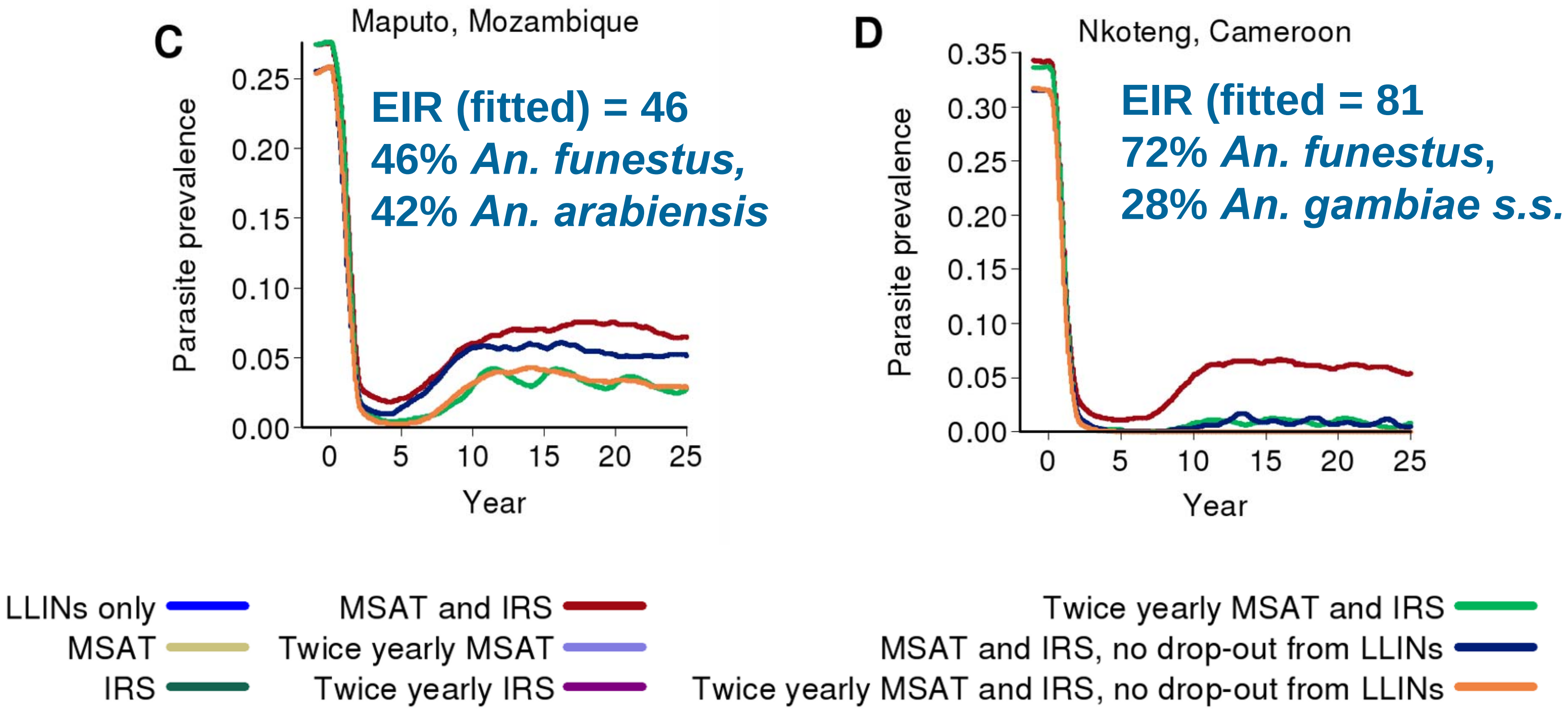
Addition of IRS and MSAT, Moderate Transmission

- Frequent rounds of IRS could reduce prevalence to low levels in areas with moderate transmission
- With additional mass screening and treatment (MSAT) further reductions can be achieved



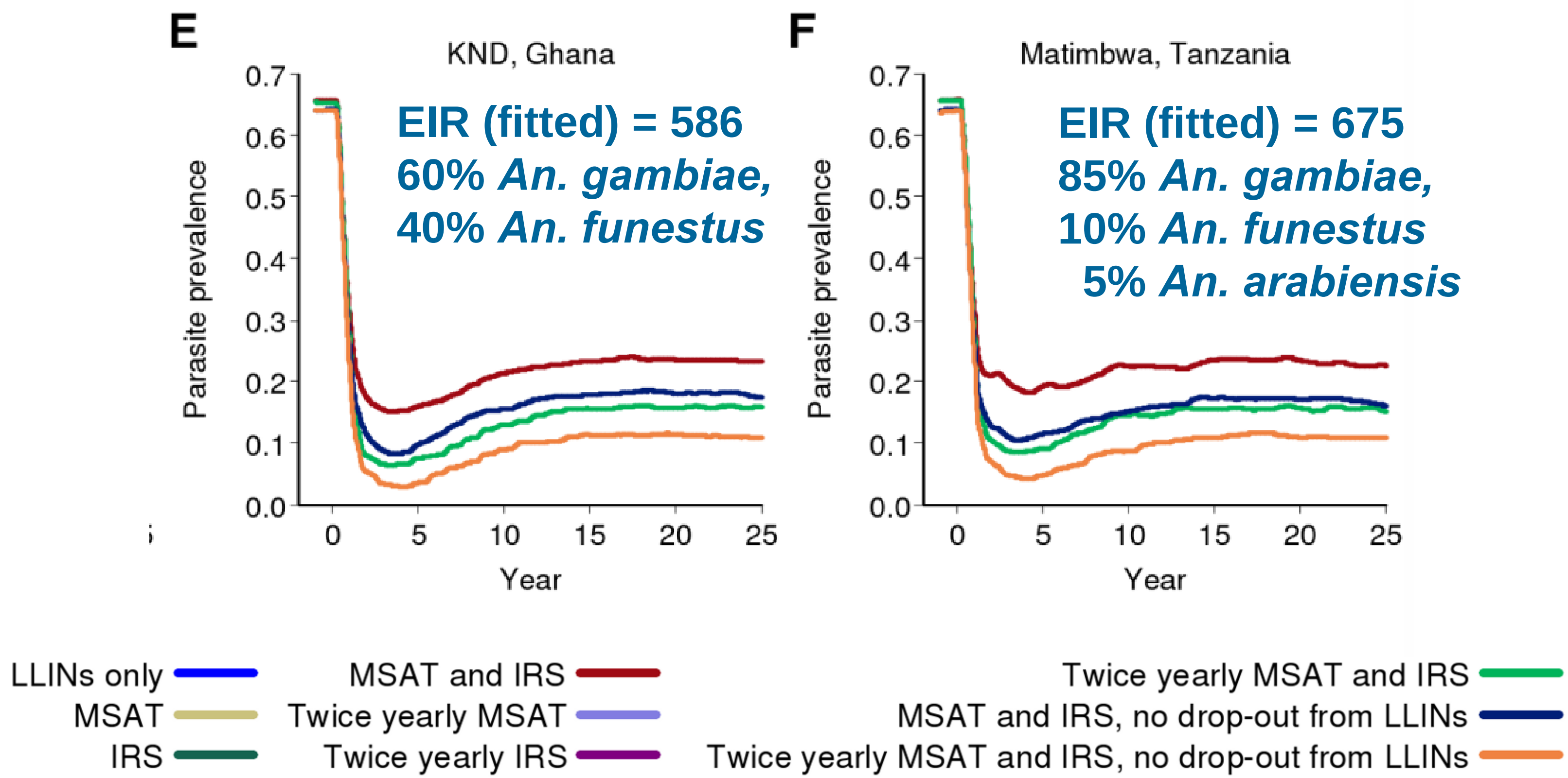
IRS and Vector behaviour, Moderate Transmission

- 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 (Maputo)



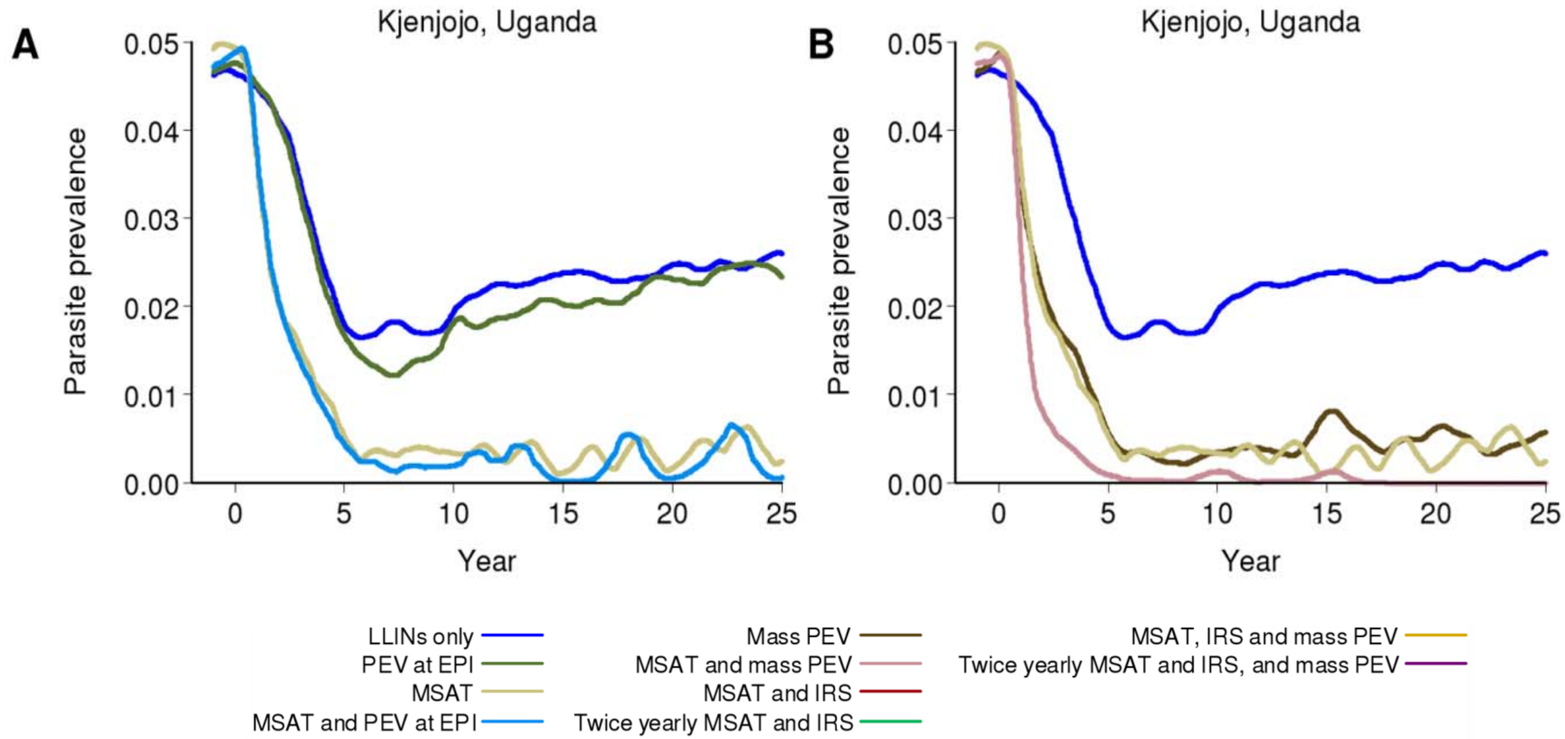
High Transmission Settings

- 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
- Likely to be delivered via Expanded Programme of Immunisation (EPI)
- Additional impact on transmission greatest in low transmission settings



Take Home Messages. I

- 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)
- Elimination programmes aim at reducing R_0 below 1 by implementing interventions that target the above
- 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. II

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

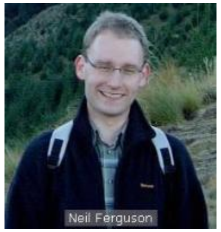
- Planning: Dermining wthat is achievable, with what tools
- Reducing transmission: Identifying optimal combinations and strategies
- Monitoring: Helping design of appropriate surveillance strategies
- Holding the line: Advising on tools needed to prevent re-introduction

- 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 reduce disease / mortality burden)
- So far model assumes no development of insecticide or drug resistance
- Need to combine epidemiological with evolutionary models

Imperial College London

Malaria Research Group

MRC Medical Research Council



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SEVENTH FRAMEWORK PROGRAMME

Blocking Malaria Transmission

MRC Medical Research Council

VMI Vaccine Modeling Initiative

Bill & Melinda Gates foundation

wellcome trust