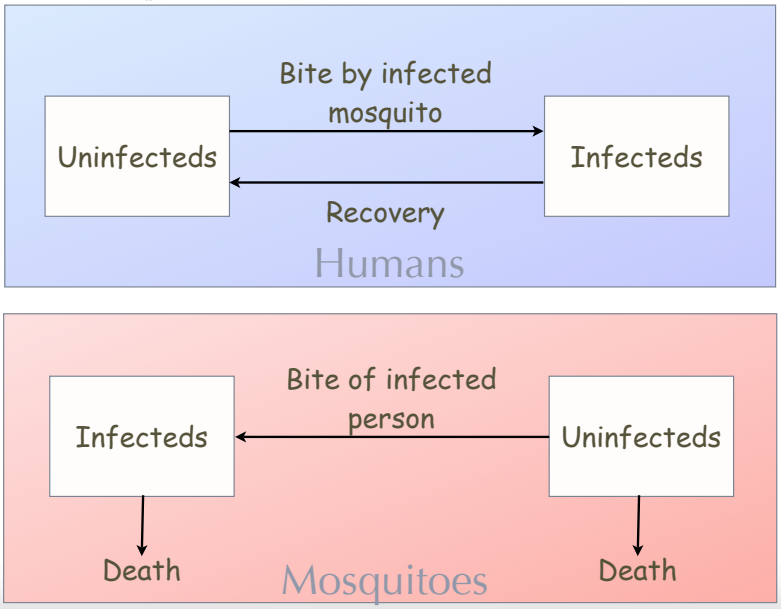
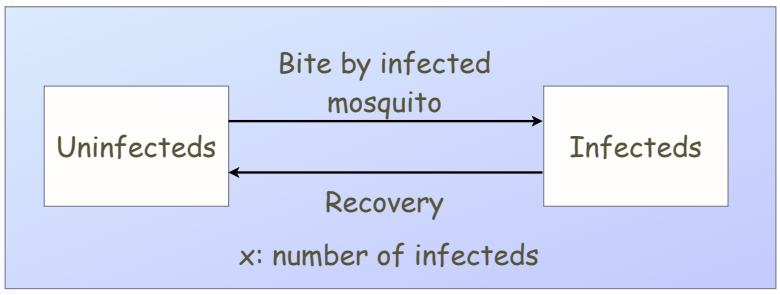
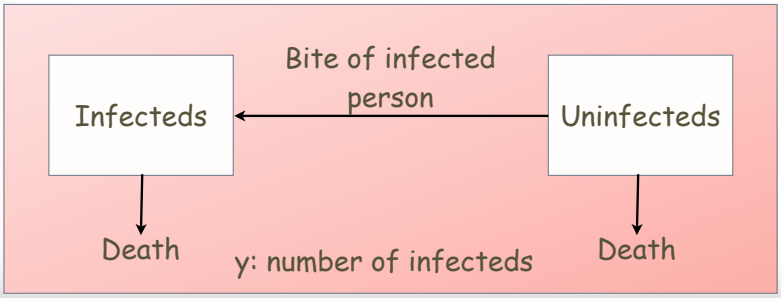
Theory of malaria control



Theory of malaria control



$$\frac{dx}{dt} = \frac{abM}{N} y(1-x) - rx$$



$$\frac{dy}{dt} = ax(1-y) - \mu y$$

Condition for invasion

Can malaria establish itself in a population?
(Is the equilibrium with no disease stable?)

- Equilibrium: x=0, y=0
- What are the dynamics if we introduce (∂x, ∂y)?

$$\frac{dx}{dt} = \frac{abM}{N} y(1-x) - rx \longrightarrow \frac{dx}{dt} \cong \frac{abM}{N} \partial y - r \partial x$$

$$\frac{dy}{dt} = ax(1-y) - \mu y \longrightarrow \frac{dy}{dt} \cong a\delta x - \mu \delta y$$

Note: $\partial x \partial y << \partial x, \partial y$

In matrix form:

$$\begin{bmatrix} \frac{dx}{dt} \\ \frac{dy}{dt} \end{bmatrix} = \begin{bmatrix} -r & \frac{abM}{N} \\ a & -\mu \end{bmatrix} \begin{bmatrix} \partial x \\ \partial y \end{bmatrix}$$

Condition for invasion

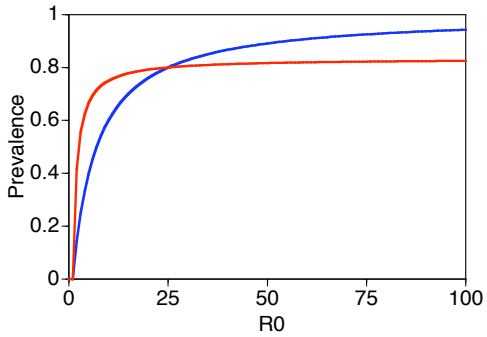
The proportions of infected humans and mosquitoes will increase if the determinant of the matrix is less than 0, i.e. if

$$r\mu - \frac{a^2 bM}{N} < 0$$

$$R_0 = \frac{\frac{M}{N} a^2 b}{r\mu} > 1$$

Equilibrium

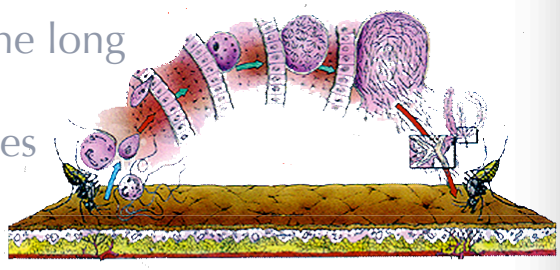
$$\hat{x} = \frac{1 - \frac{1}{R_0}}{1 + \frac{a}{\mu R_0}} \qquad \hat{y} = \frac{1 - \frac{1}{R_0}}{1 + \frac{\mu}{a}}$$



Human prevalence
Mosquito prevalence

Development of parasite in mosquito

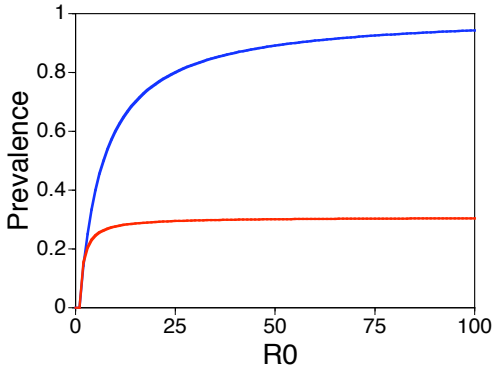
Complication: because of the long development of malaria in mosquitoes, most mosquitoes will have died before the parasite can be transmitted.



T: developmental period in mosquito

$$R_0 = \frac{\frac{M}{N} a^2 b e^{-\mu T}}{r\mu} > 1$$

Development of parasite in mosquito



Malaria control

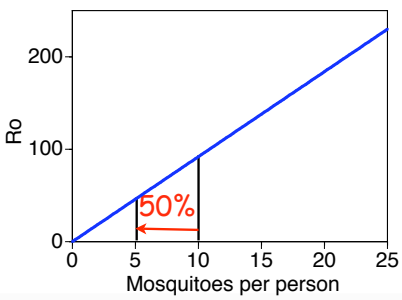
$$R_0 = \frac{\frac{M}{N} a^2 b e^{-\mu T}}{r\mu}$$

How can we achieve most efficient control?
Calculate elasticity of Ro to each parameter

- Number of adults (larval control)

$$\frac{dR_0 / R_0}{dM / M} = 1$$

Elasticity:



Malaria control

$$R_0 = \frac{\frac{M}{N} a^2 b e^{-\mu T}}{r\mu}$$

How can we achieve most efficient control?
Calculate elasticity of Ro to each parameter

- Number of adults (larval control)

$$\frac{dR_0/R_0}{dM/M} = 1$$

- Biting rate (individual protection)

$$\frac{dR_0/R_0}{da/a} = 2$$

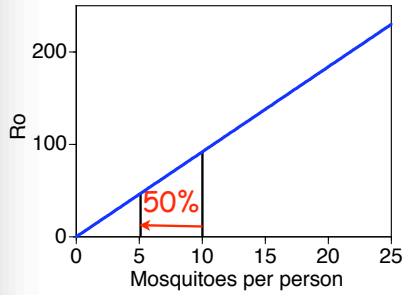
- Recovery (treatment)

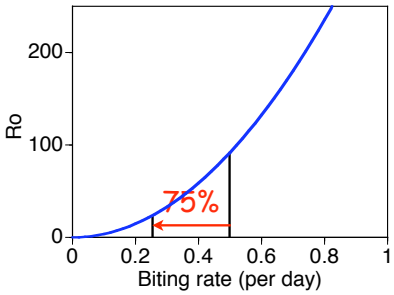
$$\frac{dR_0/R_0}{dr/r} = -1$$

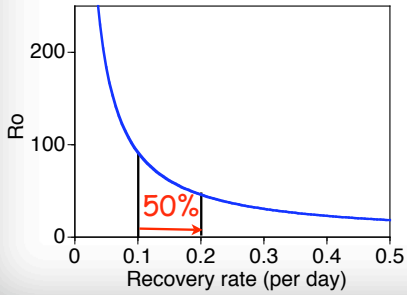
- Mortality (insectides)

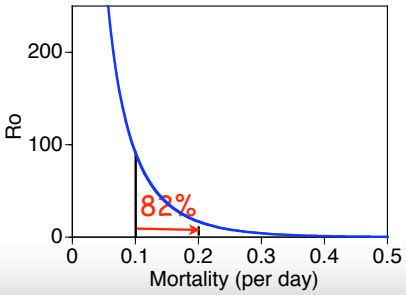
$$\frac{dR_0/R_0}{d\mu/\mu} = -(1+\mu T) \approx 2$$

Elasticity









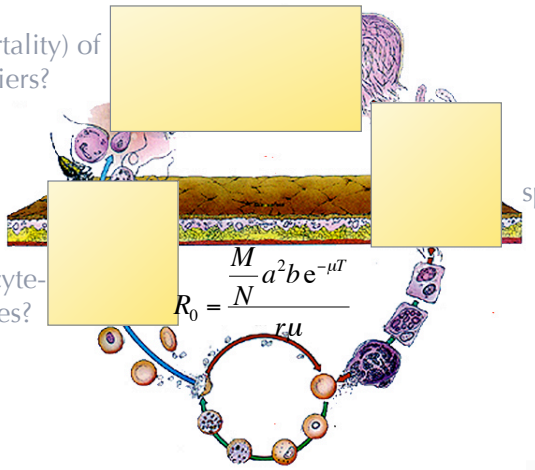
Evolutionary pressure

Can the parasite influence the biting rate and mortality of the mosquito?

Biting-rate (mortality) of oocyst-carriers?

Biting-rate of sporozoite-carriers?

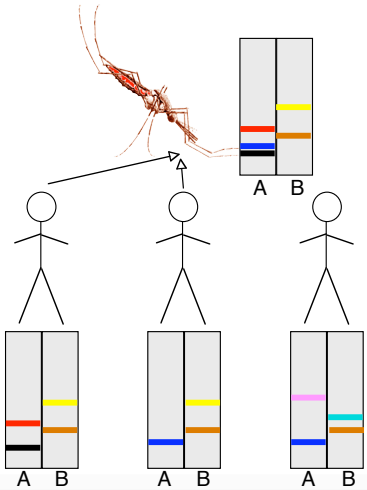
Attraction of gametocyte-carriers to mosquitoes?



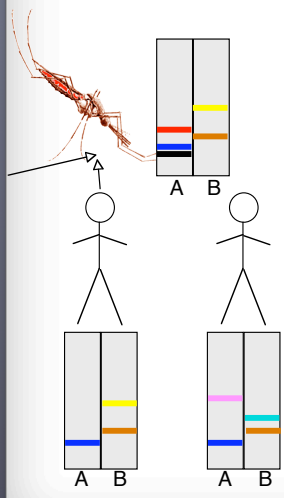
$$R_0 = \frac{\frac{M}{N} a^2 b e^{-\mu T}}{r u}$$

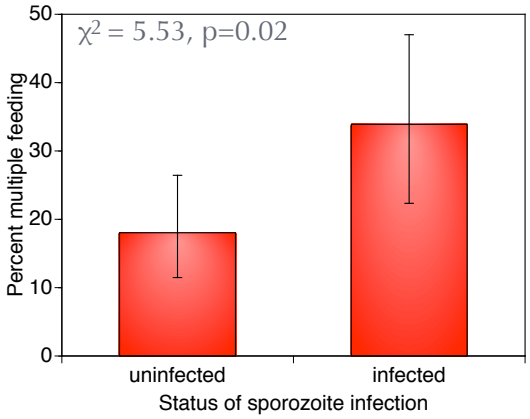
Manipulation of biting-rate

Field-study in Ifakara, Tanzania



Sporozoites increase biting

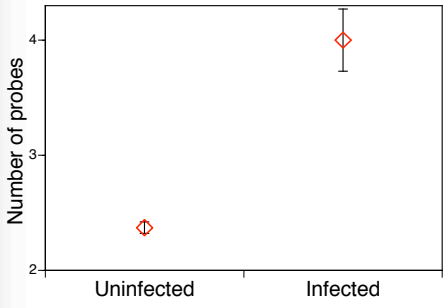


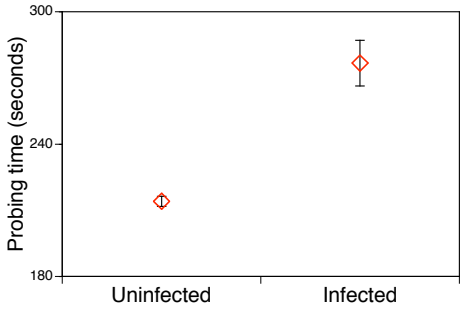


Koella, J.C., Sørensen, F.L. & R.A. Anderson. 1998. Proceedings of the Royal Society of London B 265:763 -768

Mechanism: apyrase

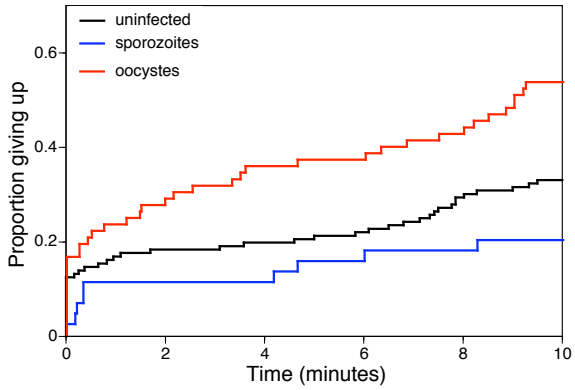
Modification of apyrase makes probing more difficult





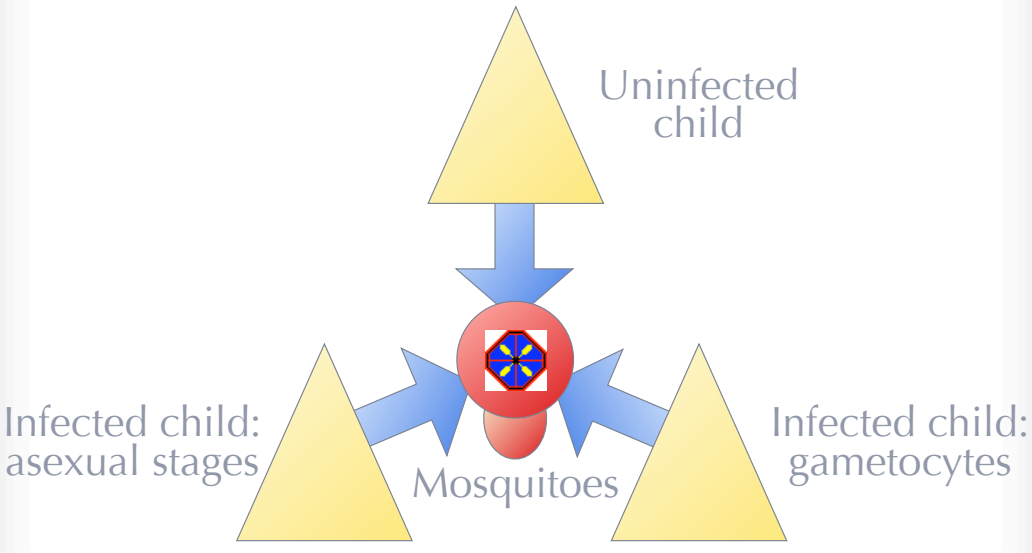
Modification of apyrase makes uptake of blood inefficient

Manipulation of biting rate 2

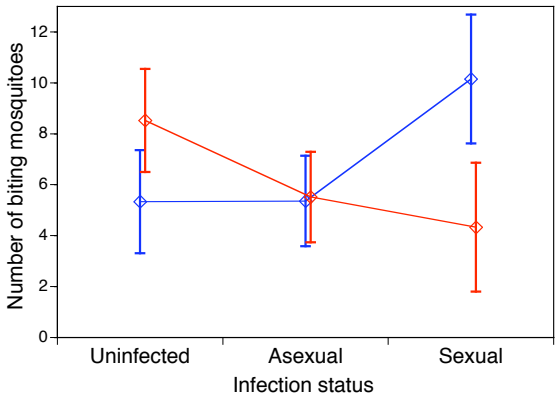


Anderson, R.A. B.J.G. Knols & J.C. Koella 2000. 1998. Parasitology 120:329-333

Manipulation of biting rate 3



Gametocytes enhance attraction



Before treatment

2 weeks after treatment

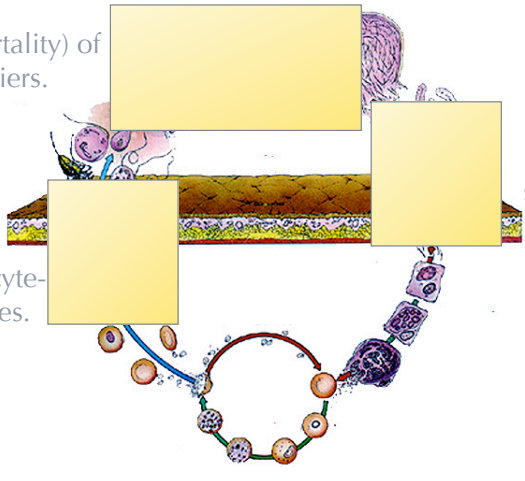
Evolutionary pressure

The parasite manipulates the mosquito, and thus determines its own epidemiology.

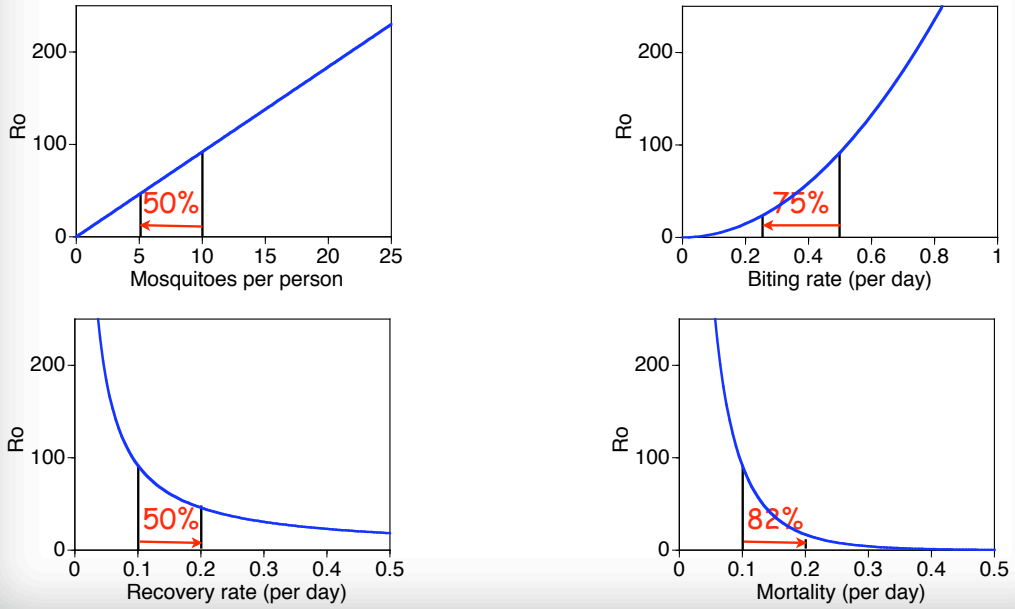
Biting-rate (mortality) of oocyst-carriers.

Biting-rate of sporozoite-carriers.

Attraction of gametocyte-carriers to mosquitoes.



Elasticity



Example: larval control

In India
since 1971: Urban Malaria Scheme in cities with more than 40,000 habitants

In Madras: 'bio-environmental' control
City of 4 million habitants, 150 divisions

- Case study in 6 divisions
(March, 1987: divisions 86-88;
January, 1988: divisions 53-55)

- Untreated area in the city Anna Nagar

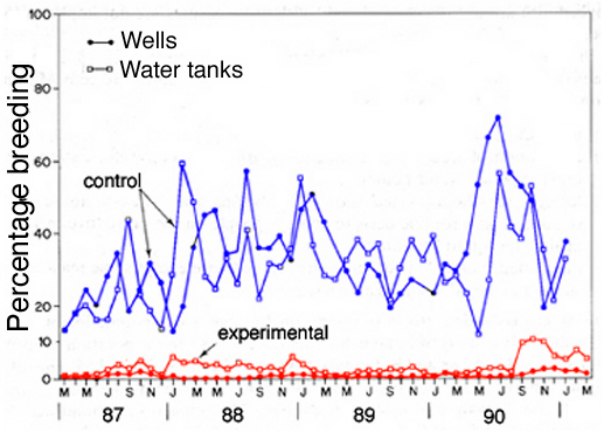
Major malaria vector: *Anopheles stephensi*
Breeds in water tanks and wells

Before mosquito control:

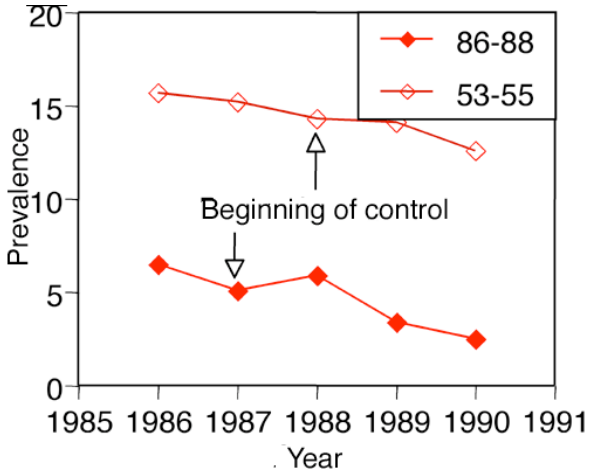
- divisions 86-88: larvae in 25% of tanks & 18% of wells
- divisions 53-55: larvae in 41% of tanks & 27% of wells

- Control of the *A. stephensi* with polystyrene beads
  The beads expand in wells and water tanks.
  Wells thus inaccessible for mosquitoes.
- In addition: education program on mosquito control

Effect of mosquito control



Effect of malaria control

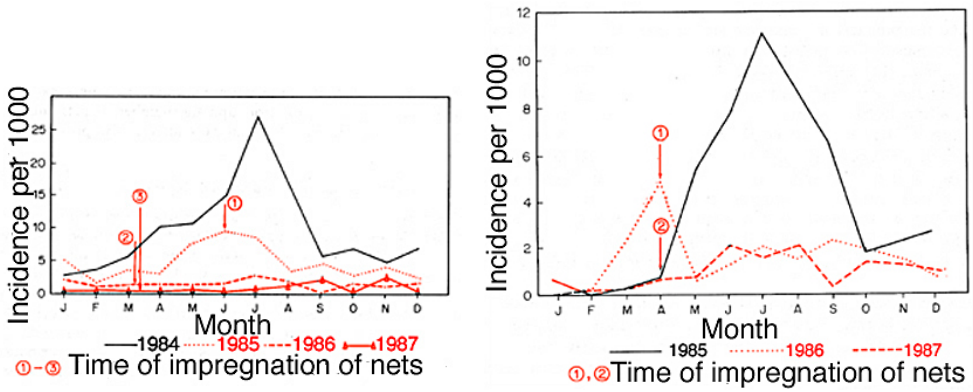


While mosquito control was very successful, there was almost no impact on malaria situation

Example 2: impregnated bed-nets

- Reduce biting rate
- Increase mortality of adult mosquitoes
- Are affordable

Two early studies in China



Later studies in Africa and Asia

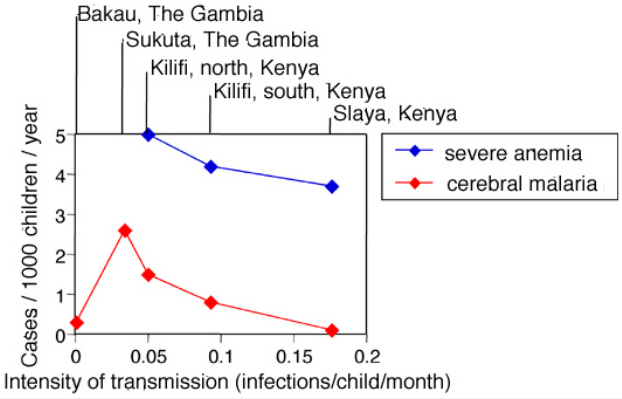
Country	Impact (protective efficacy)			
	Mortality	Mild disease	Parasitemia	Anemia
The Gambia	25-40%			
The Gambia	0%	59%		
Pakistan		78%		
Tanzania			62%	63%
Tanzania	27%			

A potential problem of nets

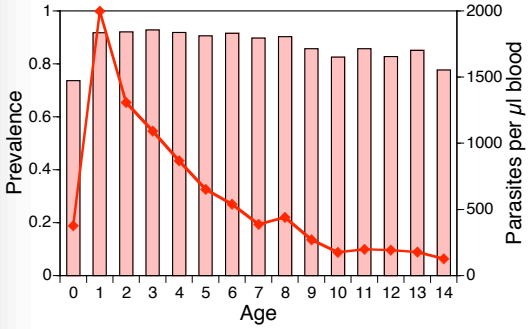
Less transmission means

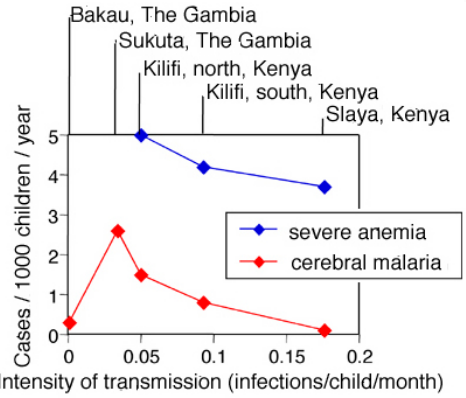
- Loss of immunity
- Infection at an older age

Therefore, more severe disease in the long-run?

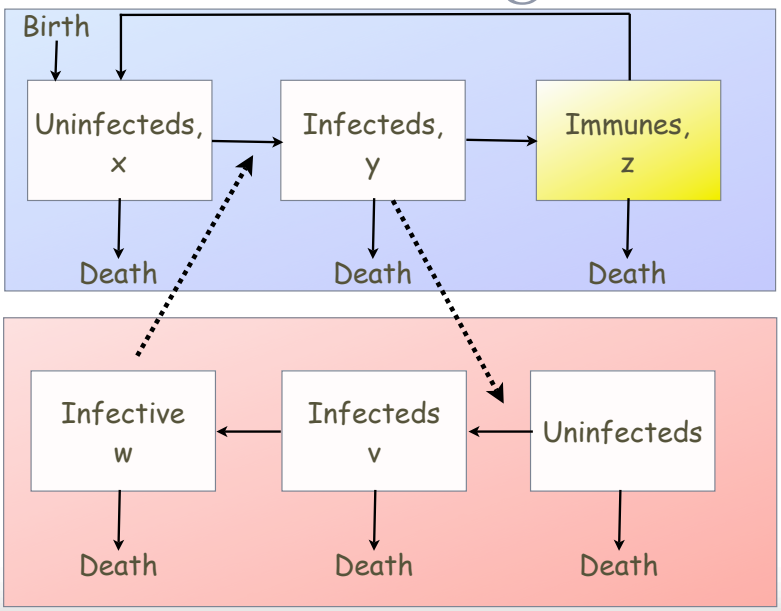


The epidemiological role of partial immunity





A model including immunity



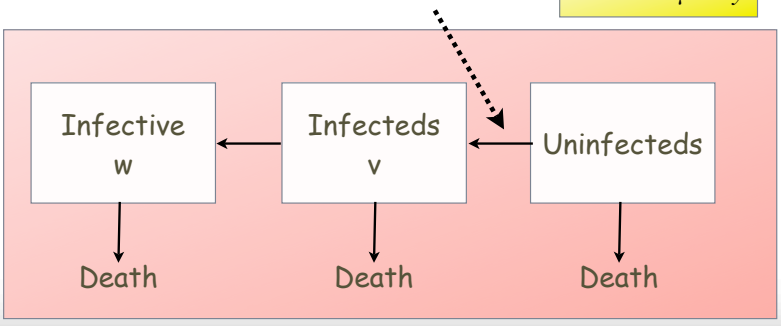
Mosquito dynamics

$$\dot{v} = aby(1-v-w) - ab\hat{y}(1-\hat{v}-\hat{w})e^{-\mu T} - \mu v \qquad \hat{v} = v(t-T)$$

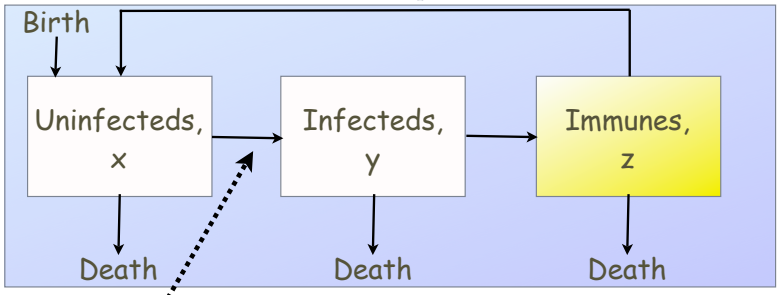
$$\dot{w} = ab\hat{y}(1-\hat{v}-\hat{w})e^{-\mu T} - \mu w \qquad \hat{w} = w(t-T)$$

The mosquito dynamics are rapid, so can be considered to be at equilibrium with respect to the human population

$\dot{v} = \dot{w} = 0$ & $\hat{v} = v;\ \hat{w} = w$ so $w = ae^{-\mu T}\dfrac{y}{\mu + ay}$



Human dynamics



$$h = maw = ma^2 e^{-\mu T} \frac{y}{\mu + ay}$$

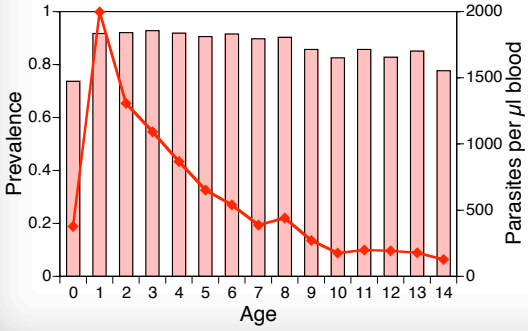
$$\dot{x} = \delta - \delta x - hx + \rho z$$
$$\dot{y} = hx - (r + \delta) y$$
$$\dot{z} = ry - (\rho + \delta) z$$

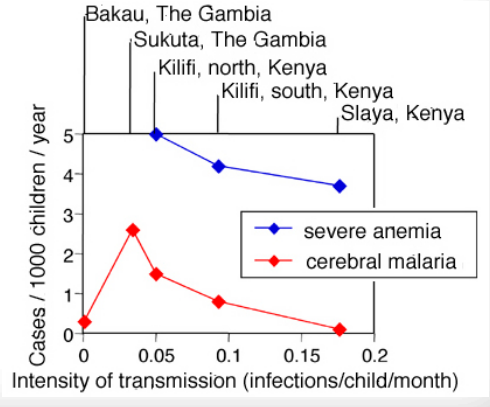
Notes:

- Mortality = birth rate, so that the population size remains constant
- All individuals (uninfected, infected and immune) have same birth rate

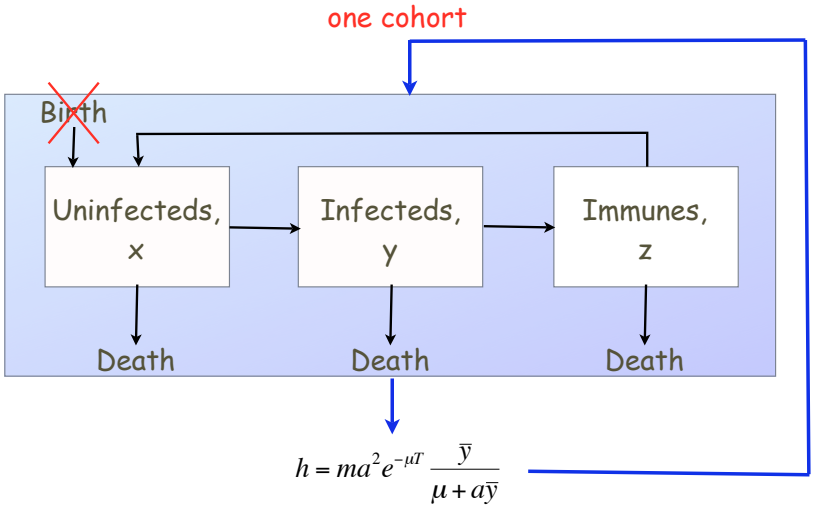
Age-distribution

To relate model to reality:
What we'd really like to know is
age distribution of infection and immunity.



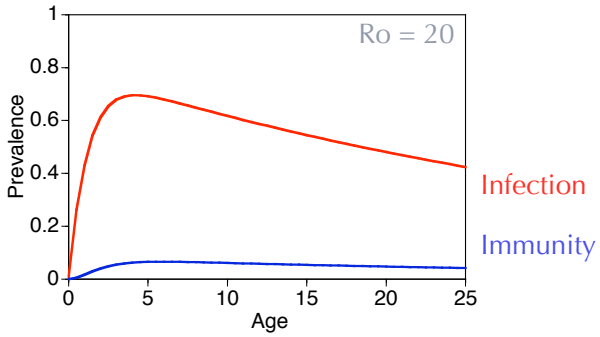


Age distribution



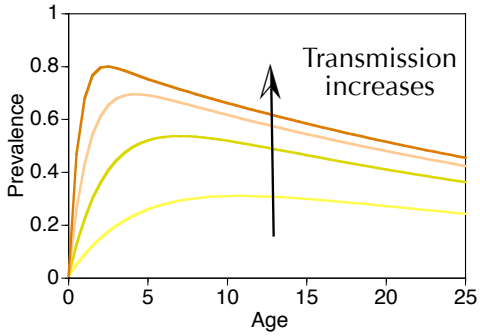
Intermediate transmission

At equilibrium



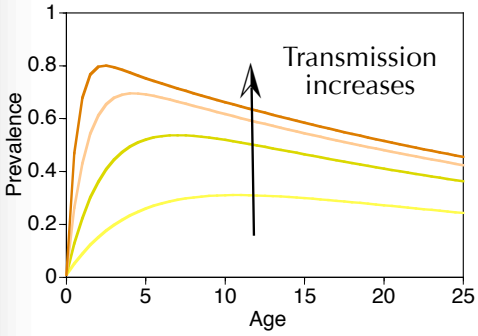
Variation in transmission

At equilibrium

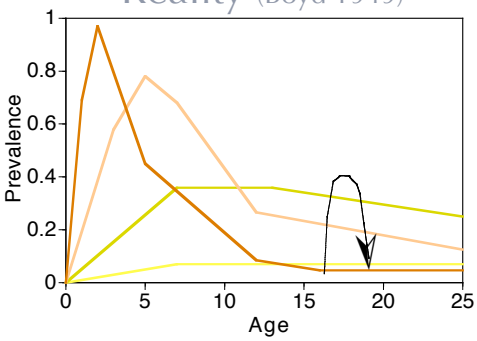


Age-distribution

Predicted



Reality (Boyd 1949)



Boosting of immunity

Immunity is lost after a few years in non-endemic areas, i.e. immunity depends on new infections.

One way of modeling the boosting of immunity:

- Immunity in absence of re-exposure lasts for τ years.
- After re-exposure, immunity lasts for another τ years.

Boosting of immunity

h: inoculation rate

p: p(infection after time τ)

$$p = e^{-h\tau}$$

q: p(infection before time τ)

$$q = 1 - p$$

W: average interval between exposures (if less than τ)

$$W = 1/h - \tau\, p/q$$

N: average number of exposures until susceptible

$$N = q/p$$

T: average time interval in immune state

$$T = WN + \tau = q/ph$$

Boosting of immunity

Rate of losing immunity =
1/average time spent in immune state

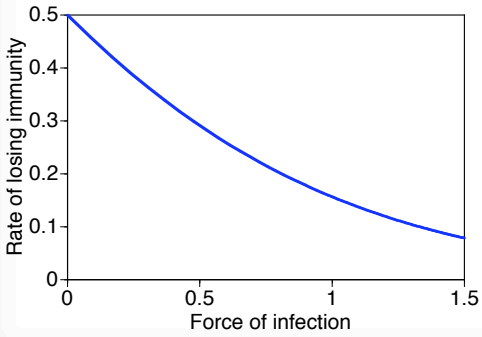
$$\rho = \frac{1}{T} = h\frac{p}{q} = \frac{h}{e^{h\tau} - 1}$$

Boosting of immunity

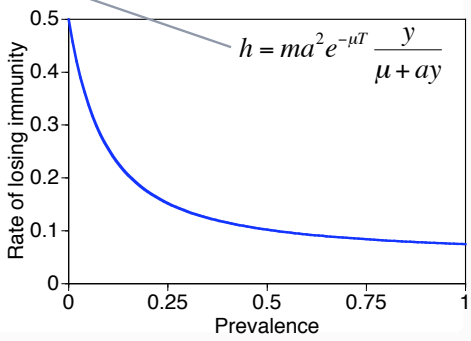
Immunity is lost after a few years in non-endemic areas,
i.e. immunity depends on new infections.

$$\rho = (h+\delta)\frac{e^{-(h+\delta)\tau}}{1-e^{-(h+\delta)\tau}}$$

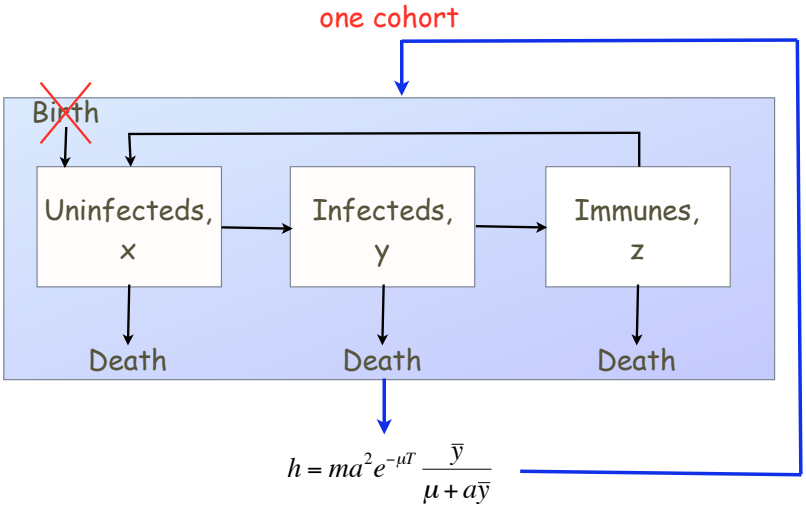
Mortality added



$$h = ma^2 e^{-\mu T}\frac{y}{\mu + ay}$$

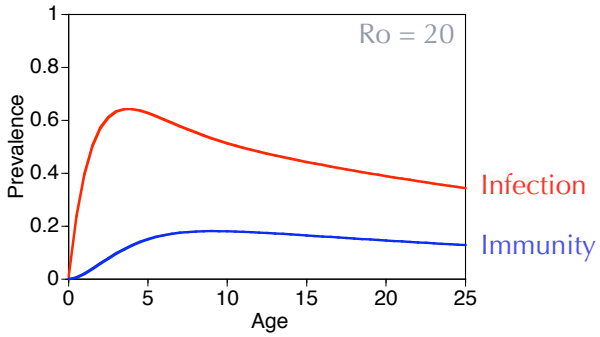


Age-distribution

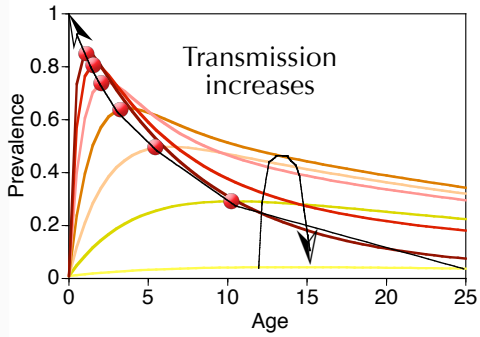


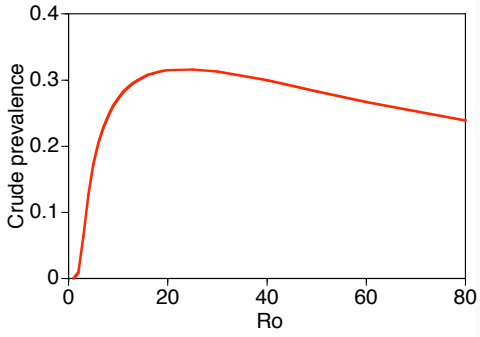
Intermediate transmission

At equilibrium



Variation in transmission



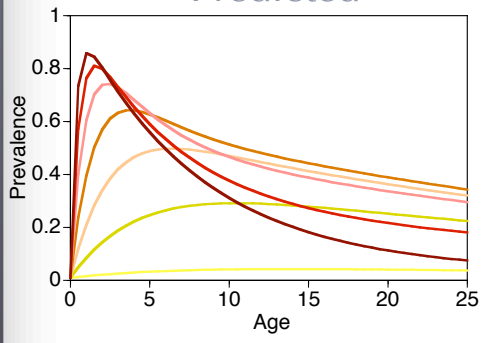


Because immunity must be boosted, a control measure that decreases transmission to intermediate levels can:

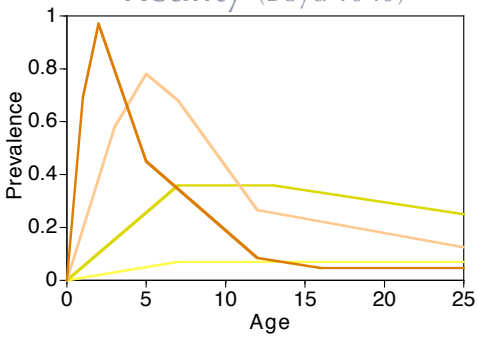
- increase total prevalence
- increase prevalence at critical age

Age-distribution

Predicted



Reality (Boyd 1949)

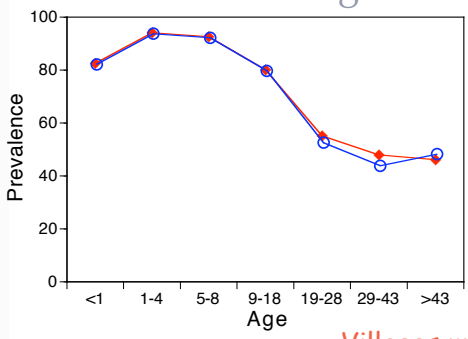


The Garki Project

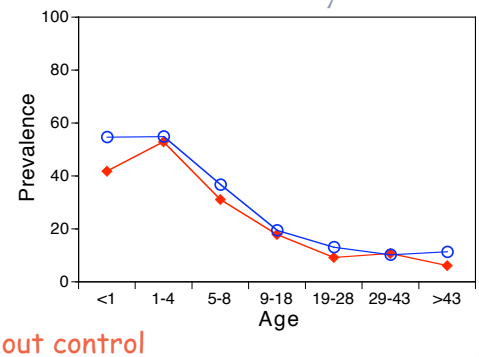
Nigeria, 1970's

Before control

Asexual stages



Gametocytes



Villages without control
Villages with future control

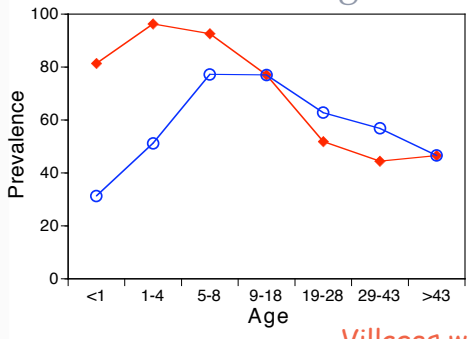
The Garki Project

Nigeria, 1970's

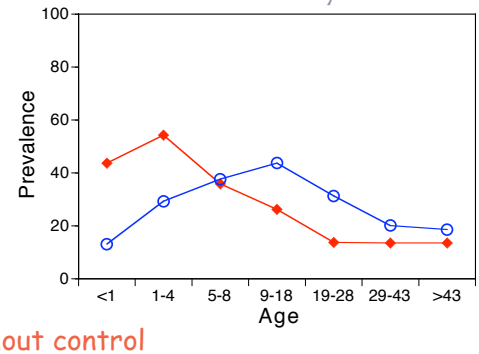
After control

- Residual indoor spraying every 2 months
- Mass drug prophylaxis every 2-10 weeks

Asexual stages



Gametocytes



Villages without control
Villages with control

Molineaux, L. & G. Gramiccia. 1980. the Garki Project. WHO, Geneva