Theory of malaria control

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

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

Uninfecteds → Bite by infected mosquito → Infecteds

Infecteds → Recovery → Humans

Infecteds → Bite of infected person → Uninfecteds

Uninfecteds → Death

Infecteds → Death

Humans → Death

Mosquitoes

x: number of infecteds

y: number of infecteds
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 $(x, y)$?

\[
\begin{align*}
\frac{dx}{dt} &= \frac{abM}{N} y (1 - x) - rx \\
\frac{dy}{dt} &= ax (1 - y) - \mu y
\end{align*}
\]

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

In matrix form:
\[
\begin{bmatrix}
\frac{dx}{dt} \\
\frac{dy}{dt}
\end{bmatrix} = \begin{bmatrix}
-r & \frac{abM}{N} \\
 a & -\mu
\end{bmatrix} \begin{bmatrix}
x \\
y
\end{bmatrix}
\]

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

\[
r\mu - \frac{a^2 b M}{N} < 0
\]

\[
R_0 = \frac{M \cdot a^2 b}{N \cdot r \mu} > 1
\]
Equilibrium

\[
\hat{x} = \frac{1 - \frac{1}{R_0}}{1 + \frac{a}{\mu R_0}}
\]

\[
\hat{y} = \frac{1 - \frac{1}{R_0}}{1 + \frac{\mu}{a}}
\]

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.

\[T: \text{developmental period in mosquito}\]

\[R_0 = \frac{M}{N} \frac{a^2 e^{-\mu T}}{r \mu} > 1\]
Development of parasite in mosquito

Human prevalence

Mosquito prevalence (sporozoites)

Malaria control

\[ R_0 = \frac{M}{N} \frac{a^2 b e^{\mu r}}{\mu} \]

How can we achieve most efficient control? Calculate elasticity of \( R_0 \) to each parameter

- Number of adults (larval control)

\[ \frac{dR_0}{dM/M} = 1 \]

Elasticity:

\[ R_0 \] vs. Mosquitoes per person

50%
Malaria control

\[ R_0 = \frac{M e^{\frac{a R_0}{\mu}}}{N} \]

How can we achieve most efficient control? Calculate elasticity of \( R_0 \) to each parameter

- **Number of adults** (larval control): \( \frac{dR_0}{dM} = 1 \)
- **Biting rate** (individual protection): \( \frac{dR_0}{da} = 2 \)
- **Recovery** (treatment): \( \frac{dR_0}{dr} = -1 \)
- **Mortality** (insecticides): \( \frac{dR_0}{d\mu} = -(1 + \mu T) \approx 2 \)

**Elasticity**

- Mosquitoes per person
  - 50% elasticity
  - 75% elasticity

- Biting rate (per day)
  - 75% elasticity

- Recovery rate (per day)
  - 82% elasticity

- Mortality (per day)
  - 82% elasticity
Evolutionary pressure
Can the parasite influence the biting rate and mortality of the mosquito?

Attraction of gametocyte-carriers to mosquitoes?
Biting-rate of sporozoite-carriers?
Biting-rate (mortality) of oocyst-carriers?

\[ R_0 = \frac{M a^2 b e^{-\mu t}}{N} \]

Manipulation of biting-rate
Field-study in Ifakara, Tanzania
Sporozoites increase biting

\[ \chi^2 = 5.53, p=0.02 \]

Uninfected
Infected

0
10
20
30
40
50

Percent multiple feeding


Mechanism: apyrase

Modification of apyrase makes probing more difficult

Modification of apyrase makes uptake of blood inefficient
Manipulation of biting rate 2

![Graph showing proportion giving up over time for uninfected and infected sporozoites and oocysts.](image)


Manipulation of biting rate 3

Uninfected child

Infected child: asexual stages

Mosquitoes

Infected child: gametocytes
Gametocytes enhance attraction

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

Effect of malaria control

Example 2: impregnated bed-nets
- Reduce biting rate
- Increase mortality of adult mosquitoes
- Are affordable
Two early studies in China

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

\[
\begin{align*}
\dot{v} &= aby(1 - v - w) - ab\hat{y}(1 - \hat{v} - \hat{w})e^{-\mu T} - \mu v \\
\dot{w} &= ab\hat{y}(1 - \hat{v} - \hat{w})e^{-\mu T} - \mu w
\end{align*}
\]

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

\[
\begin{align*}
\dot{v} &= 0 \\
\dot{w} &= 0 \\
\end{align*}
\]

so

\[
\frac{w}{\mu + ay}
\]
Human dynamics

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

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

Uninfecteds, $x$ → Death

Infecteds, $y$ → Death

Immunes, $z$ → Death

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

Intermediate transmission

At equilibrium

Ro = 20

Prevalence vs Age

Infection

Immunity
Variation in transmission

At equilibrium

Transmission increases

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 $\tau$ years.
- After re-exposure, immunity lasts for another $\tau$ years.

$h$: inoculation rate
$p$: $p(\text{infection after time } \tau)$
$q$: $p(\text{infection before time } \tau)$
$W$: average interval between exposures (if less than $\tau$)
$N$: average number of exposures until susceptible
$T$: average time interval in immune state

\[
p = e^{-h\tau}
\]
\[
q = 1 - p
\]
\[
W = 1/h - \tau p/q
\]
\[
N = q/p
\]
\[
T = WN + \tau = q/\rho h
\]
Boosting of immunity

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

\[ \rho = \frac{1}{T} = h \frac{p}{q} = \frac{h}{e^{ht} - 1} \]

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

\[ h = ma^2 e^{-\mu t} \frac{y}{\mu + a} \]

Intermediate transmission

At equilibrium

\[ \text{Prevalence} \]

\[ \text{Age} \]

\[ \text{Ro} = 20 \]

\[ \text{Infection} \]

\[ \text{Immunity} \]
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

After control

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

Gametocytes