Determining optimal insecticide events to control malaria

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Control

Malaria control primarily consists of

- chemoprophylaxis
  - drugs, vaccines, etc
- vector control
  - insecticides, larvacides, etc
  - aim is to reduce vector population density and survival.

Indoor Residual Spraying

- Malaria vectors are endophilic, resting inside houses after feeding

- Indoor Residual Spraying (IRS) involves spraying houses or dwellings on the inside and under eaves on the outside
- Kills mosquitos after they've fed
- Duration of effective action is 2-6 months.

Effectiveness of IRS

- When implemented well, it can be effective
- IRS has been responsible for suppression of at least one vector of malaria transmission, *An. funestus*
- However, in recent years it has received relatively little attention.

Limitations of a spraying program

- Spraying too frequently:
  - toxicity in individuals and the environment
  - waste of limited resources
- Spraying infrequently:
  - unchecked mosquito reproduction
- Further constraint:
  - Due to resource limitations and logistics, spraying may not occur at regular intervals.

Crucial questions

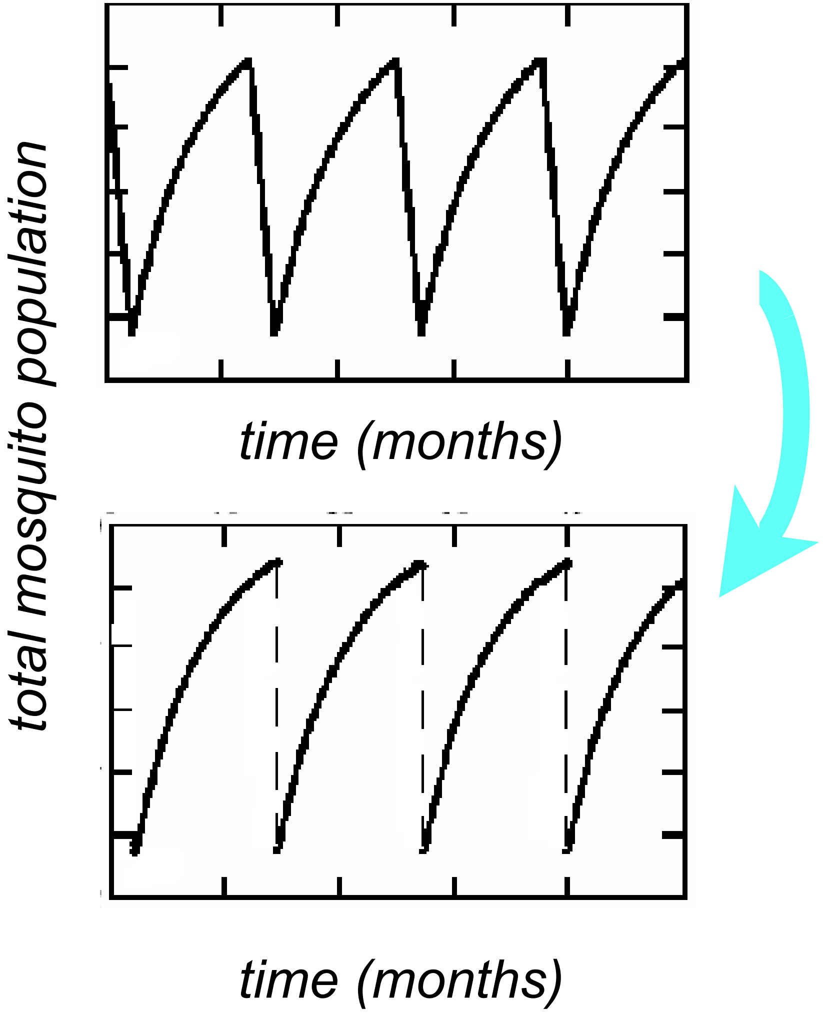
How effective does an insecticide have to be for overall mosquito reduction?

Can we determine the optimal spraying frequency for a given insecticide?

If spraying occurs at non-fixed times, and we know only the times of the previous two spraying events, can we determine the "next best" spraying time?

Impulsive differential equations

- Assume spraying is instantaneous
- That is, the delay in mosquito reduction is assumed to be negligible
- This results in a system of *impulsive differential equations*.



Impulsive effect

- According to impulsive theory, we can describe the nature of the impulse at time r_k via the difference equation

$$\Delta y \equiv y(r_k^+) - y(r_k^-) = f(r_k, y(r_k^-))$$

Difference equation

Depends on the time of impulse and the state immediately beforehand.

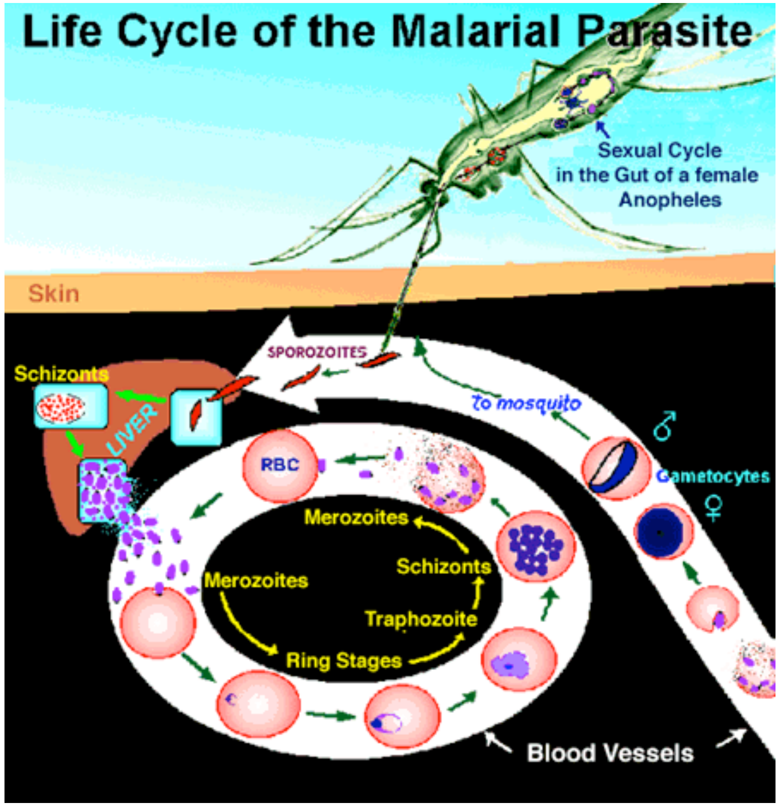
Impulsive DEs

- Solutions are continuous for $t \neq r_k$
- Solutions undergo an instantaneous change in state when $t = r_k$.

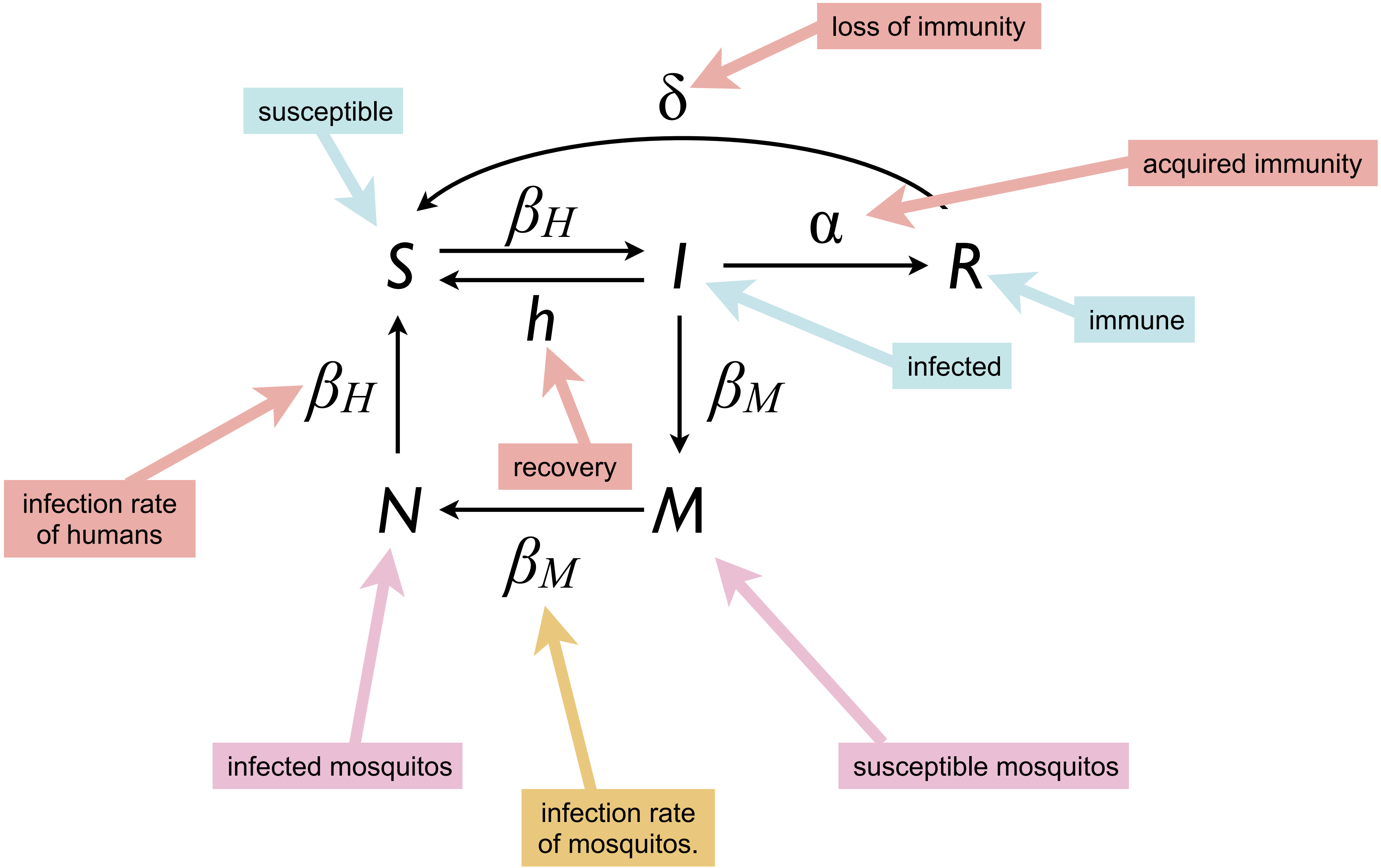
r_k=*impulse time*

Putting it together

- The model thus consists of a system of ODEs (humans), together with ODEs and difference equations (mosquitos).



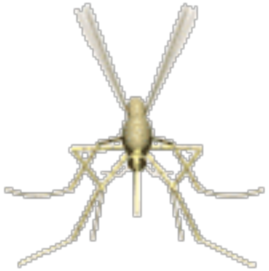
The model


loss of immunity
δ
susceptible
acquired immunity
β_H
α
S
I
R
h
immune
infected
β_H
β_M
recovery
infection rate of humans
N
M
β_M
infected mosquitos
infection rate of mosquitos.
susceptible mosquitos

The differential equations

- At non-spraying times, the ODEs are

$$\begin{aligned}
\frac{dS}{dt} &= \pi - \beta_H S N + hI + \delta R - \mu_H S \\
\frac{dI}{dt} &= \beta_H S N - hI - \alpha I - (\mu_H + \gamma) I \\
\frac{dR}{dt} &= \alpha I - \delta R - \mu_H R \\
\frac{dM}{dt} &= \Lambda - \mu M - \beta_M M I \\
\frac{dN}{dt} &= \beta_M M I - \mu N
\end{aligned}$$



for $t \neq t_k$.

S=Susceptible humans
I=Infected humans
R=Recovered humans
M=Susceptible mosq.
N=Infected mosq.
π,Λ=birth rates
μ,μ_H=death rates
β_H,β_M=transmissibility
γ=malaria death rate
h=recovery rate
α=immunity rate
δ=loss of immunity

Spraying impulse

- At spraying times t_k, the impulsive effect is

$$\begin{aligned}\Delta M &= -rM^- \\ \Delta N &= -rN^-\end{aligned}$$

  for $t = t_k$

- Here, r is the effectiveness of the insecticide.

M=Susceptible mosq.
N=Infected mosq.

The nonimpulsive system

- Without spraying, we have two equilibria:

$$(\bar{S}, \bar{I}, \bar{R}, \bar{M}, \bar{N}) = \left(\frac{\pi}{\mu_H}, 0, 0, \frac{\Lambda}{\mu}, 0\right), (S^*, I^*, R^*, M^*, N^*)$$

  (disease-free and endemic)
- The basic reproductive ratio is

$$R_0 = \frac{\beta_H \beta_M \Lambda \pi}{\mu^2 \mu_H (\mu_H + \alpha + \gamma + h)}$$

- The endemic equilibrium is positive iff $R_0 > 1$.

S=Susceptible humans I=Infected humans
R=Recovered humans M=Susceptible mosq.
N=Infected mosq. π, Λ*=birth rates* α*=immunity rate*
μ, μ_H*=death rates* β_H, β_M*=transmissibility*
γ*=malaria death rate h=recovery rate*

Analysis of the impulsive system

- If we define the total mosquito population by

$$\Psi = M + N\,,$$

then we have the decoupled impulsive differential equation

$$\begin{array}{rclcrcl} \dfrac{d\Psi}{dt} & = & \Lambda - \mu\Psi & \qquad & t & \neq & t_k \\ \Delta\Psi & = & -r\Psi & & t & = & t_k \end{array}$$

- Thus

$$\begin{array}{rcl} \Psi^+ - \Psi^- & = & -r\Psi^- \\ \Psi^+ & = & (1-r)\Psi^-\,. \end{array}$$

Λ=mosq. birth rate
μ=mosq. death rate
r=spraying effectiveness
t_k=spraying times

Solution of the decoupled system

- For $t_k<t<t_{k+1}$, the solution is

$$\Psi(t) \quad = \quad \frac{\Lambda}{\mu}\left(1-e^{-\mu(t-t_k)}\right)+\Psi_k^+ e^{-\mu(t-t_k)}$$

- It follows that the endpoints satisfy the recursion relation

$$\Psi_{k+1}^- \quad = \quad \frac{\Lambda}{\mu}\left(1-e^{-\mu(t_{k+1}-t_k)}\right)+\Psi_k^+ e^{-\mu(t_{k+1}-t_k)}$$

Ψ=*total mosq. population*
Λ=*mosq. birth rate*
μ=*mosq. death rate*
r=spraying effectiveness
t_k=*spraying times*

Regular spraying

- We have the following result:

Theorem: If spraying occurs at fixed times, satisfying $\tau = t_{k+1} - t_k$, then

$$\tilde{\Psi}^-(r) \quad = \quad \frac{\Lambda}{\mu} \cdot \frac{1 - e^{-\mu\tau}}{1 + (r-1)e^{-\mu\tau}}$$

is a globally asymptotically stable fixed point of the recurrence relation

$$\Psi^-_{k+1} \quad = \quad \frac{\Lambda}{\mu}\left(1 - e^{-\mu\tau}\right) + (1-r)\Psi^-_k e^{-\mu\tau}$$

- Furthermore,

$$\lim_{\substack{\tau \to 0 \\ n \to \infty}} \Psi^-_n \quad = \quad 0\,.$$

Ψ=*total mosq. population*
Λ=*mosq. birth rate*
μ=*mosq. death rate*
r=spraying effectiveness
t_k=*spraying times*

Optimal spraying

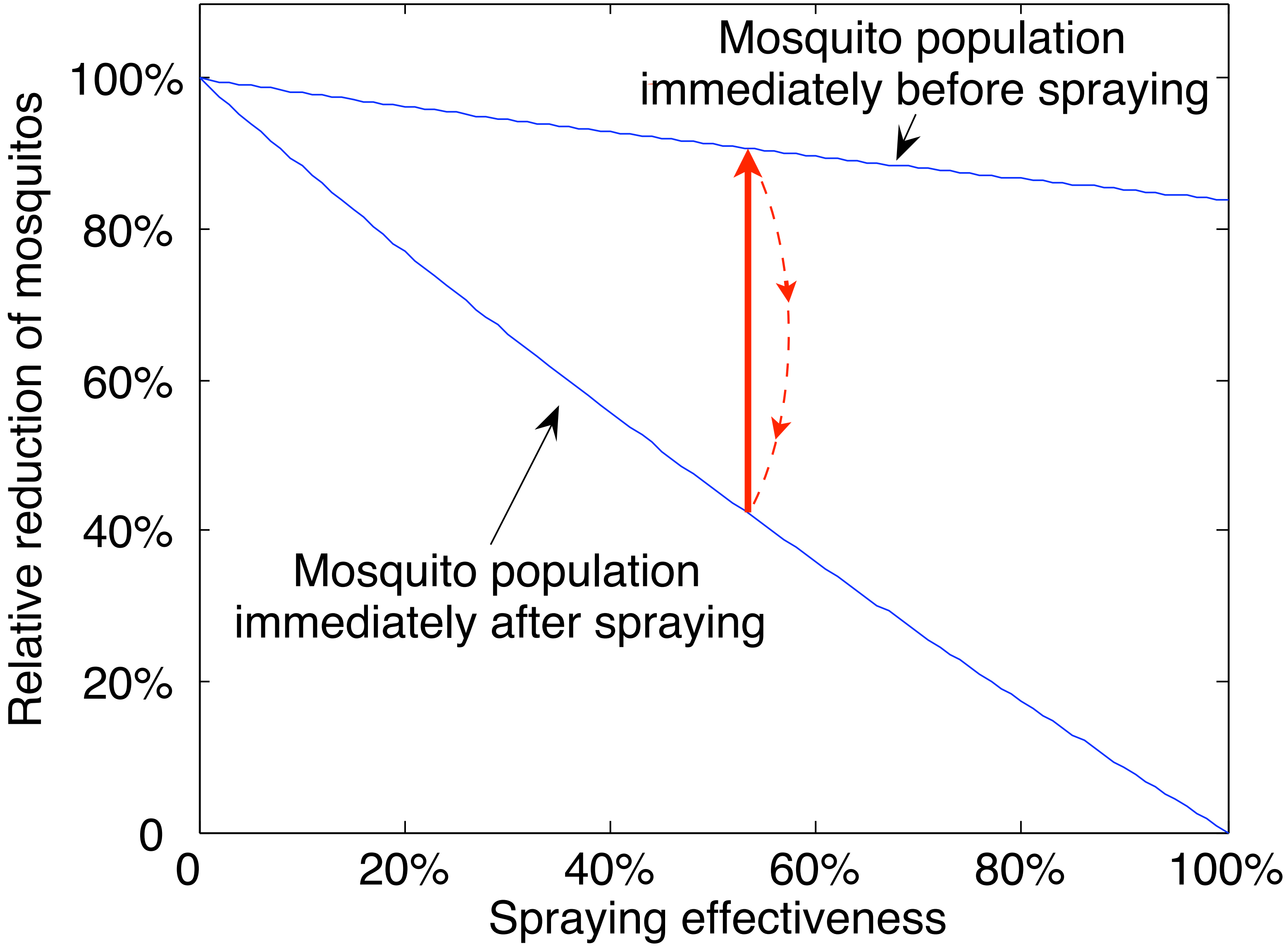
- This has the following implications:

Corollary 1: To reduce the total mosquito population below a desired threshold $\tilde{\Psi}$, the minimum insecticide effectiveness satisfies

$$\tilde{r} \quad = \quad 1 - \left[1 - \frac{\Lambda}{\mu\tilde{\Psi}}(1 - e^{-\mu\tau})\right] e^{\mu\tau}$$

Ψ=total mosq. population
Λ=mosq. birth rate
μ=mosq. death rate
r=spraying effectiveness
τ=spraying period

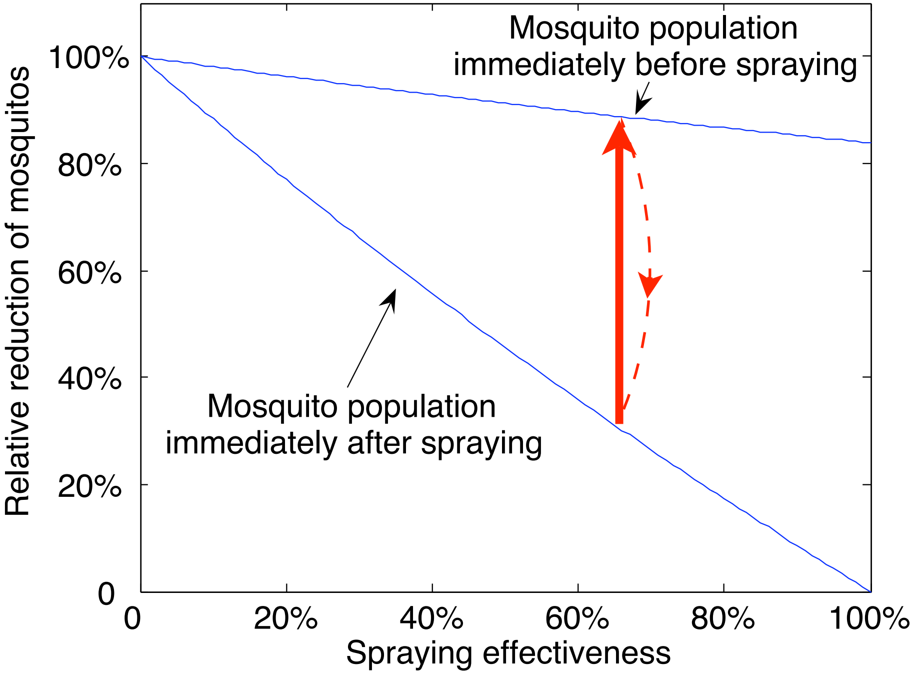
Dependence upon the spraying effectiveness



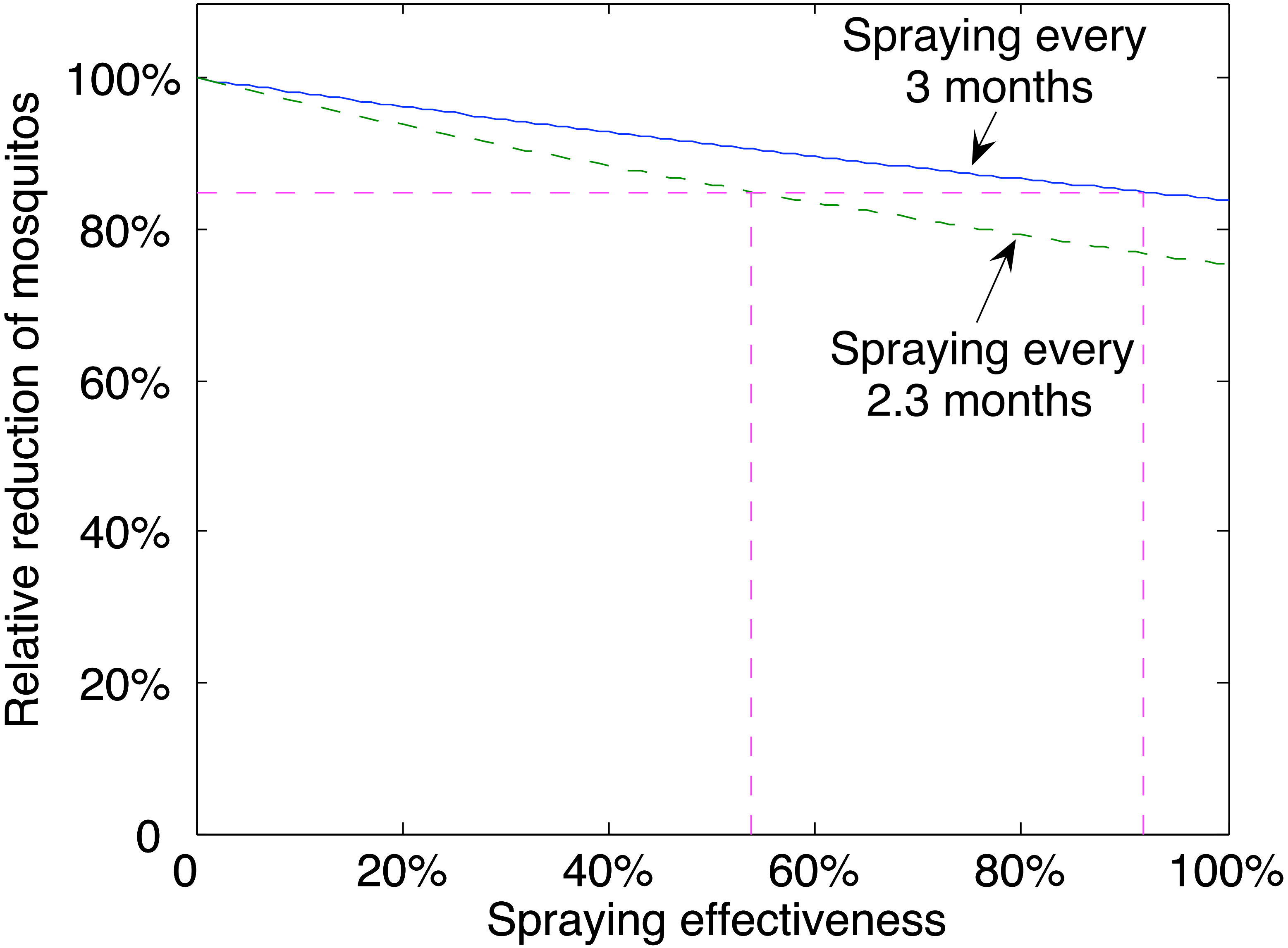
Crucial question #1

How effective does an insecticide have to be for overall mosquito reduction?

- While the maximum may only be reduced slightly, the average mosquito population can be significantly reduced even for moderately effective insecticides.

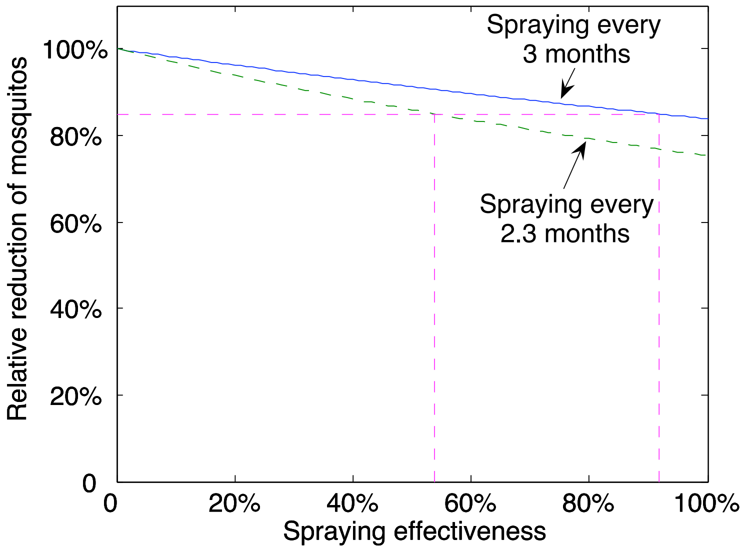


Varying the spraying frequency



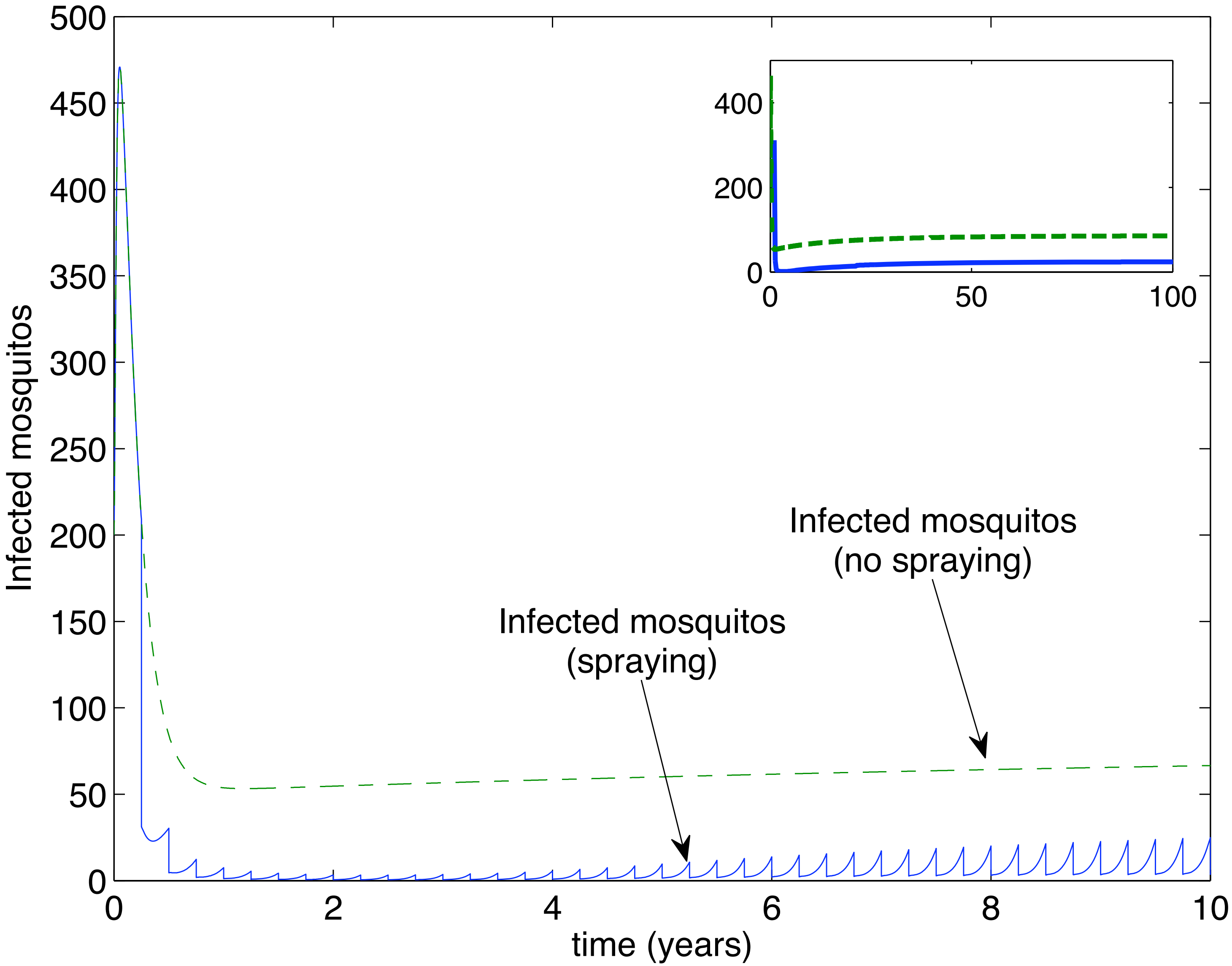
Crucial question #2

Can we determine the optimal spraying frequency for a given insecticide?

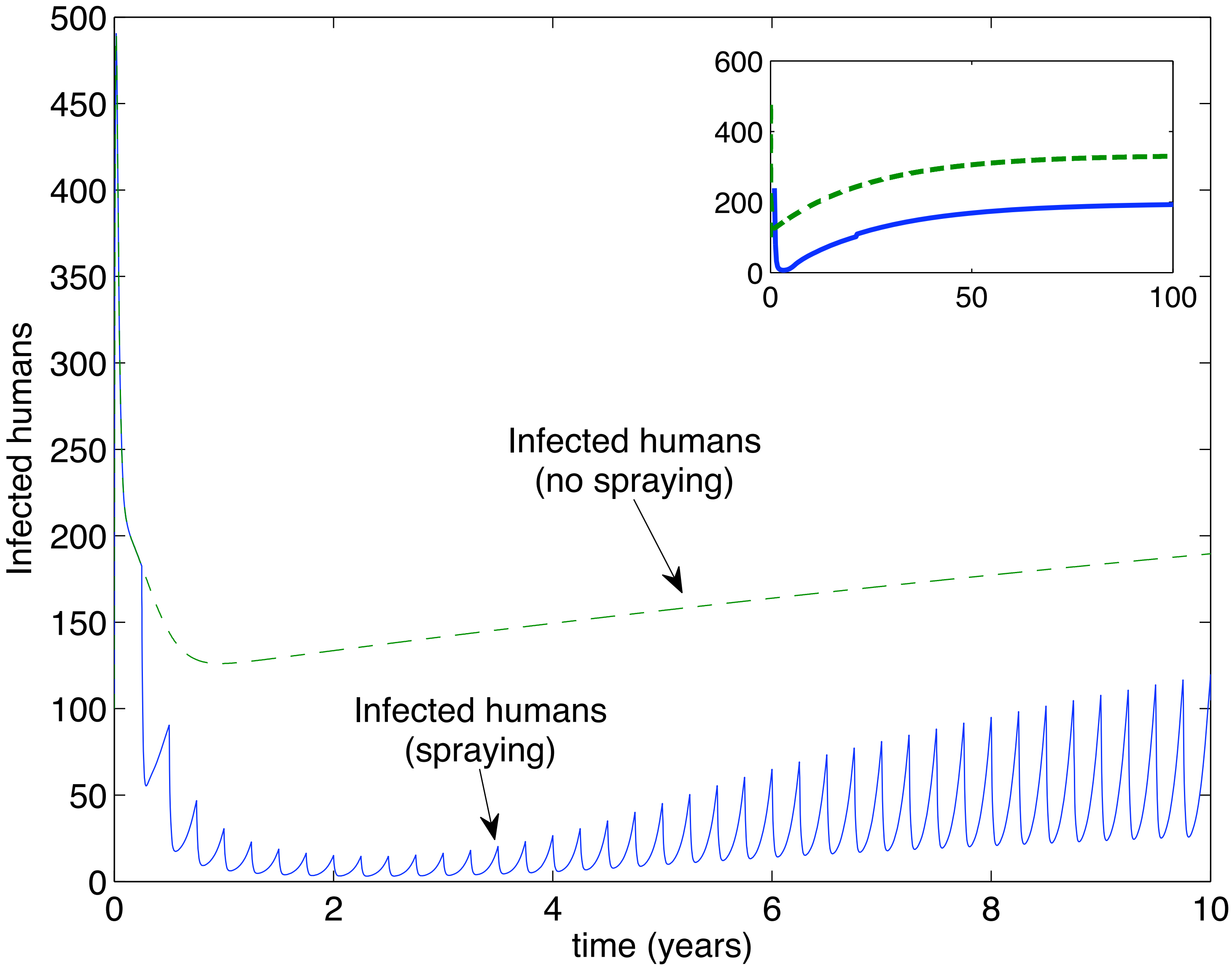


- An insecticide which reduces mosquitos by 90% at each spraying will ultimately result in a 15% reduction in the maximum mosquito numbers if sprayed every three months
- The same maximum reduction can be achieved by an insecticide with 55% effectiveness, if sprayed at 2.3 month intervals.

Spraying every 3 months: mosquitos



Spraying every 3 months: humans



Non-fixed spraying

- If spraying times are not fixed, the optimal solution for the next spraying time depends upon the entire history of spraying
- This is unlikely to be known
- Instead, we determined the “next best” spraying event, assuming that only the two most recent spraying events are known.

The “next best” spraying event

- We thus have the following result:

Theorem: If spraying occurs at non-fixed times, then, assuming the two previous spraying events are known, the population of mosquitos can be reduced below the threshold $\tilde{\Psi}$ if the next spraying event satisfies

$$t_{n+1} \quad \leq \quad t_n - \frac{1}{\mu} \ln \left[\frac{2 - r - \mu \tilde{\Psi} / \Lambda}{1 + r(1-r) e^{-\mu (t_n - t_{n-1})}} \right]$$

Ψ=total mosq. population
Λ=mosq. birth rate
μ=mosq. death rate
r=spraying effectiveness
t_n=spraying times

Crucial question #3

If spraying occurs at non-fixed times, and we know only the times of the previous two spraying events, can we determine the "next best" spraying time?

- The "next best" spraying depends upon
  - the birth and death rates of mosquitos (Λ, μ)
  - the time of the last two sprayings
  - the effectiveness of the insecticide (*r*).

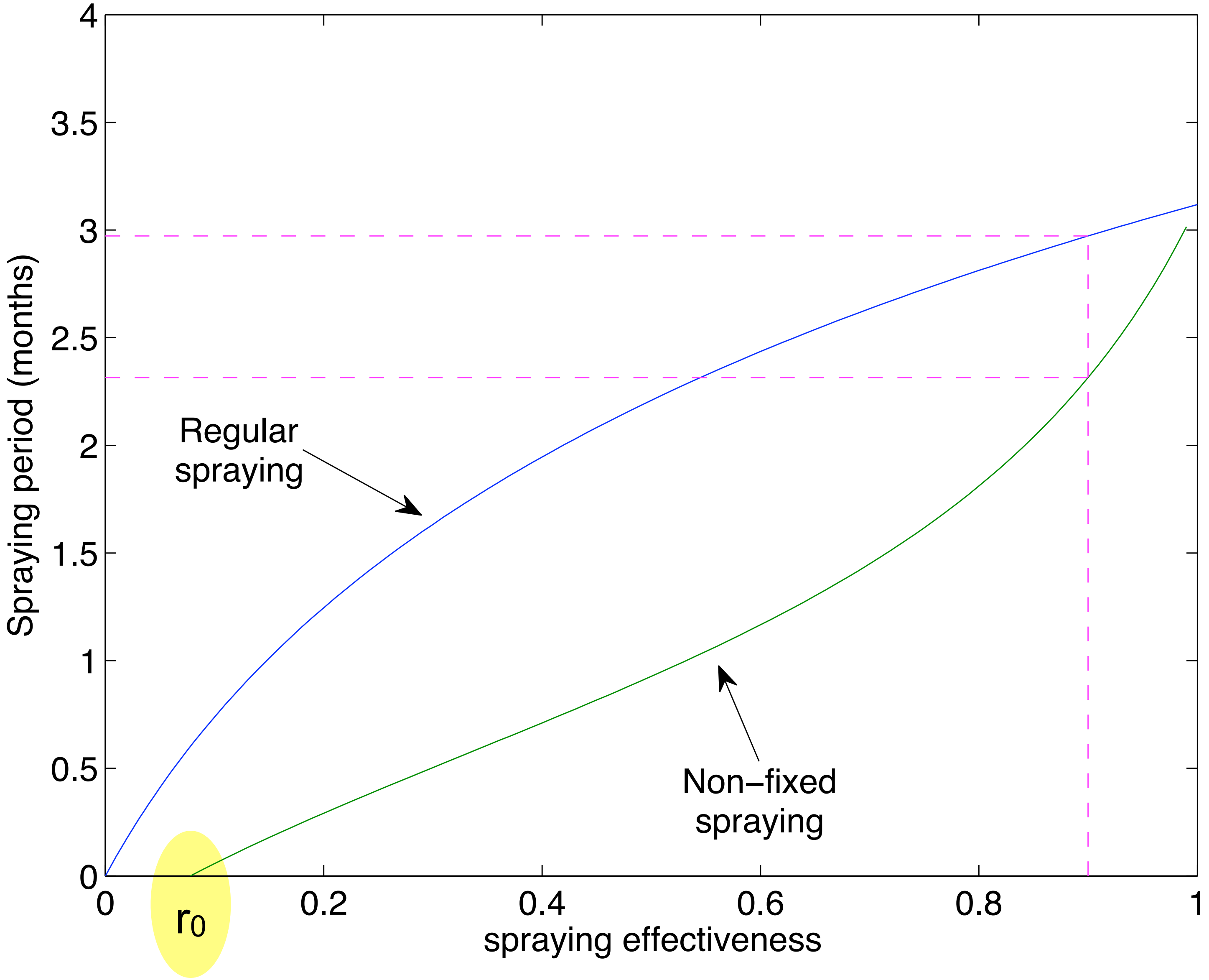
$$t_{n+1} \leq t_n - \frac{1}{\mu} \ln \left[\frac{2 - r - \mu \tilde{\Psi} / \Lambda}{1 + r(1-r) e^{-\mu(t_n - t_{n-1})}} \right]$$

Minimum spraying effectiveness

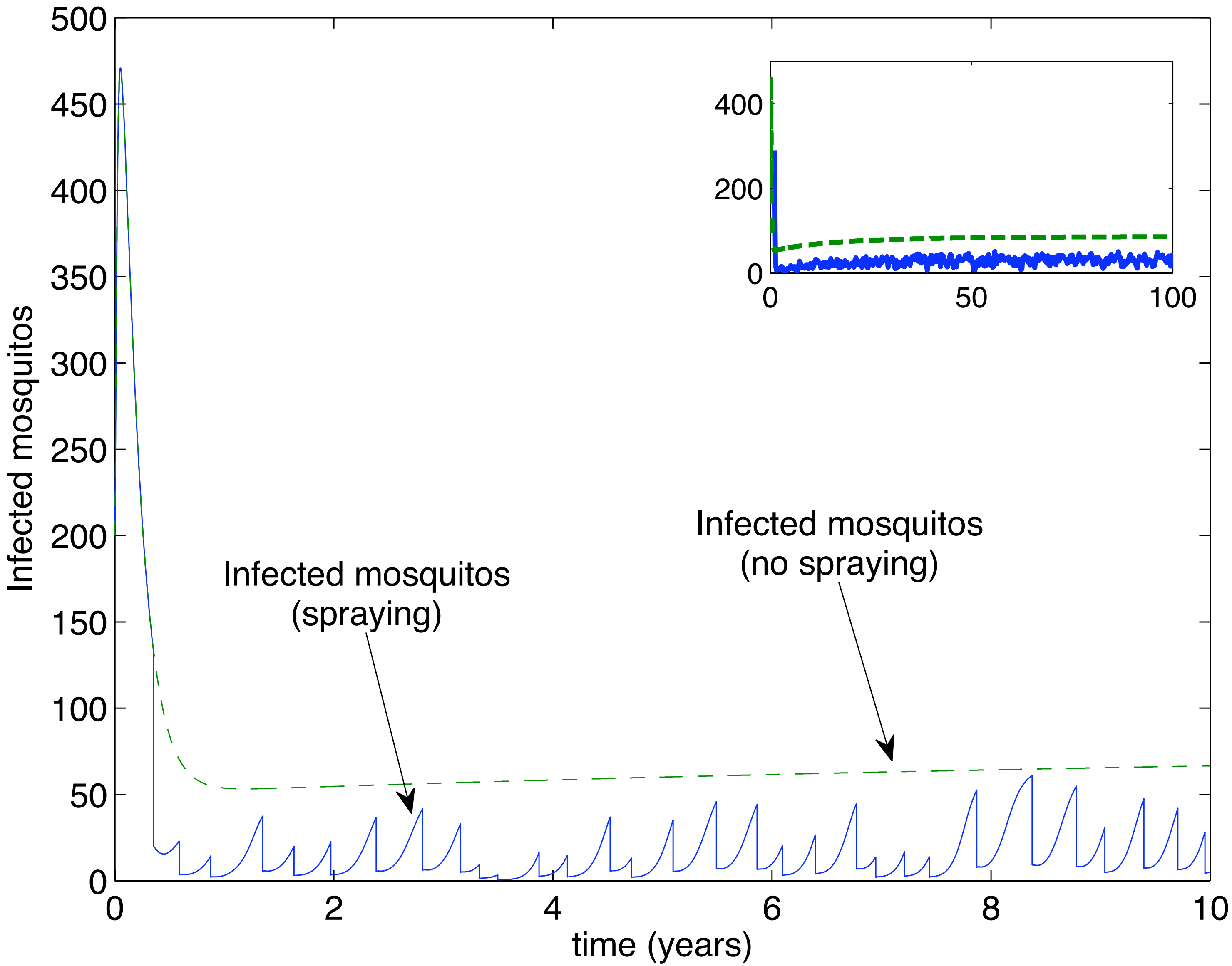
- If non-fixed spraying occurs indefinitely, then there exists a minimum spraying effectiveness, r_0, satisfying $0<r_0<1$
- Non-fixed spraying is only effective for $r_0 \leq r \leq 1$
- Furthermore, on this interval, the minimum spraying interval for indefinite non-fixed spraying is always less than the minimum spraying interval for regular spraying.

r=spraying effectiveness

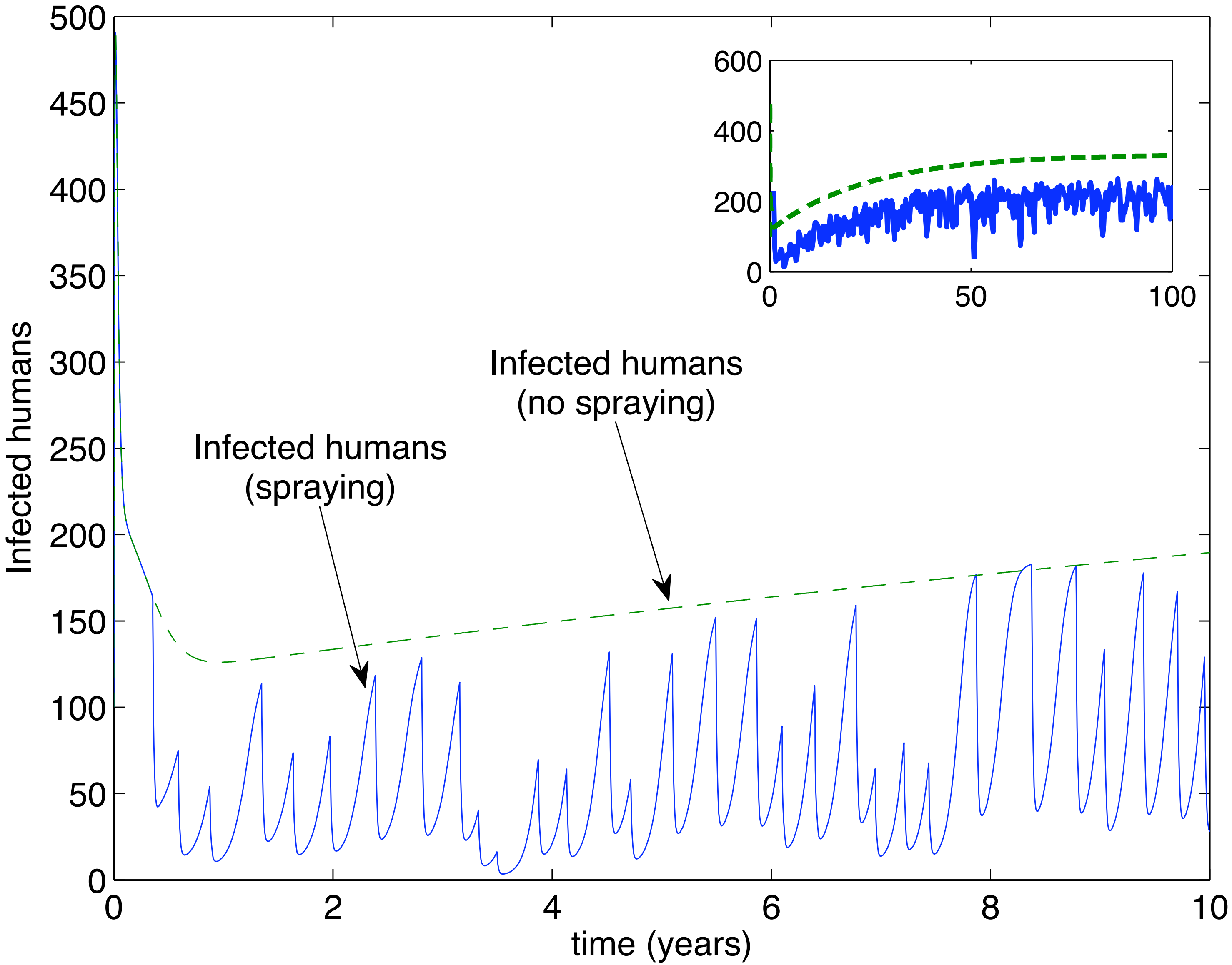
Regular spraying is always better



Non-fixed spraying: mosquitos



Non-fixed spraying: humans



Impact of climate change

- Climate change is likely to increase the mosquito birth rate from Λ to $\Lambda+\Lambda_1$
- To keep the same mosquito thresholds for regular spraying, we can calculate the revised spraying periods.

Spraying in light of climate change

- Our new threshold is

$$\tilde{\Psi} = \frac{\Lambda + \Lambda_1}{\mu} \, \frac{1 - e^{-\mu\tau}}{1 - (1 - r)e^{-\mu\tau}}$$

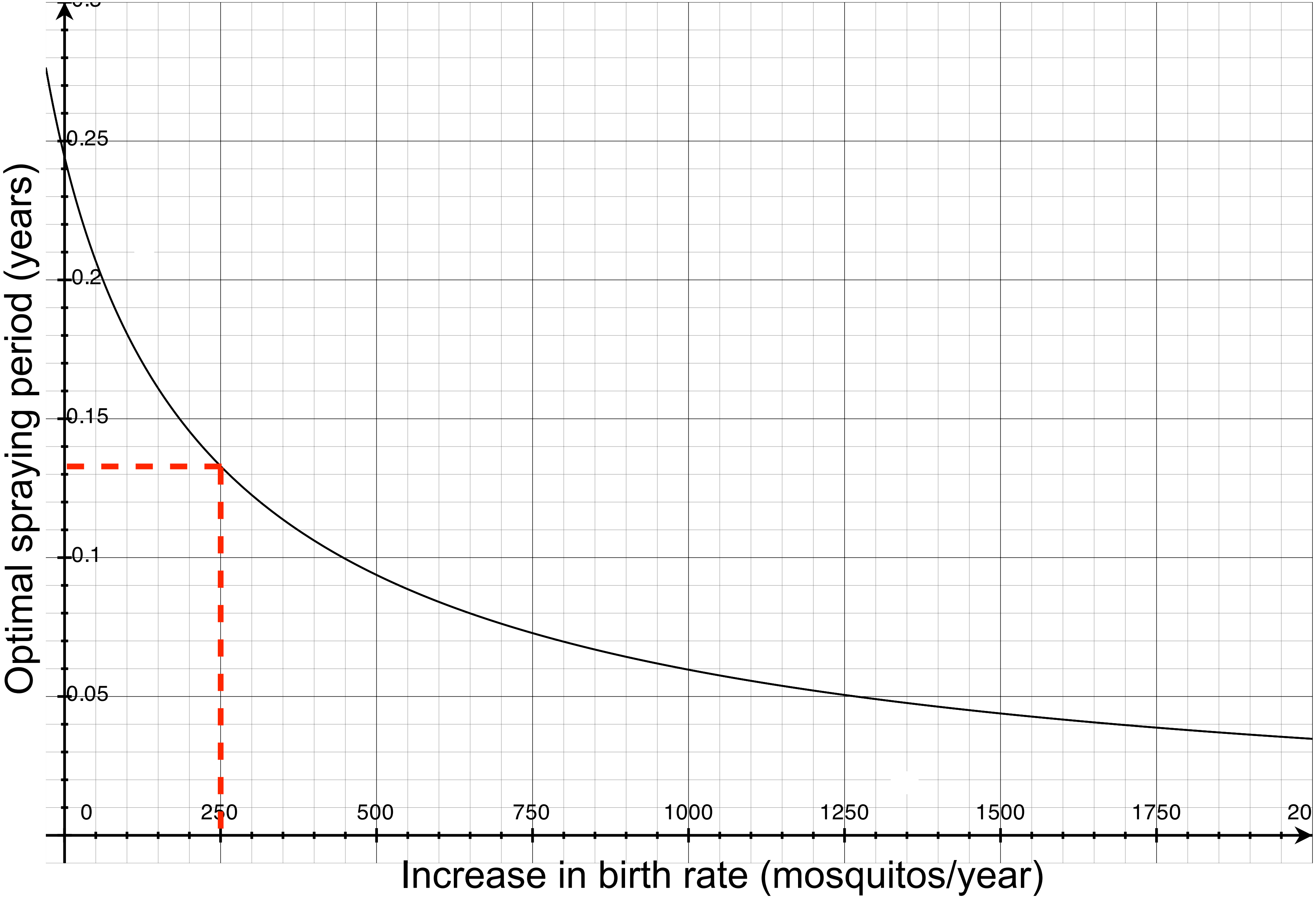
- Rearranging, we find

$$\tau = \frac{1}{\mu} \ln\left(1 + \frac{r\mu\tilde{\Psi}}{\Lambda + \Lambda_1 - \mu\tilde{\Psi}}\right)$$

- Note in particular that

$$\lim_{\Lambda_1 \to \infty} \tau = 0 \, .$$

Effect of increased birth rate on spraying frequency



Results (summary)

- The optimal insecticide effectiveness for regular spraying can be derived
- If only the previous two spraying events are known, the next-best spraying can be determined for non-fixed spraying
- Non-fixed spraying is always suboptimal
- Insecticides must be sufficiently effective
- If climate change increases mosquito birth rates, the resulting spraying period for regular spraying will be lowered.

Generalisation

- The outcome does not depend on the form of the infection dynamics in humans
- These results can be extended to any model where the total mosquito population satisfies

$$\begin{array}{rclcrcl} \Psi' & = & \Lambda - \mu\Psi & \qquad & t & \neq & t_k \\ \Delta\Psi & = & -r\Psi & \qquad & t & = & t_k. \end{array}$$

Ψ=*total mosq. population*
Λ=*mosq. birth rate*
μ=*mosq. death rate*
r=spraying effectiveness
t_k=*spraying times*

Future work

Future work will examine

- the impact of spatial variation on the implementation of IRS
- the re-emergence of disease from point sources missed from the previous spraying
- more complex criteria for non-fixed spraying.

Conclusion

- Regular spraying is superior to non-fixed spraying
- Either can result in a significant reduction in the overall number of mosquitos, as well as the number of malaria cases in humans
- We thus recommend that the use of indoor residual spraying be re-examined for widespread application in malaria-endemic areas.