Clinically-Immune Hosts as a Refuge for Drug-Sensitive Malaria Parasites

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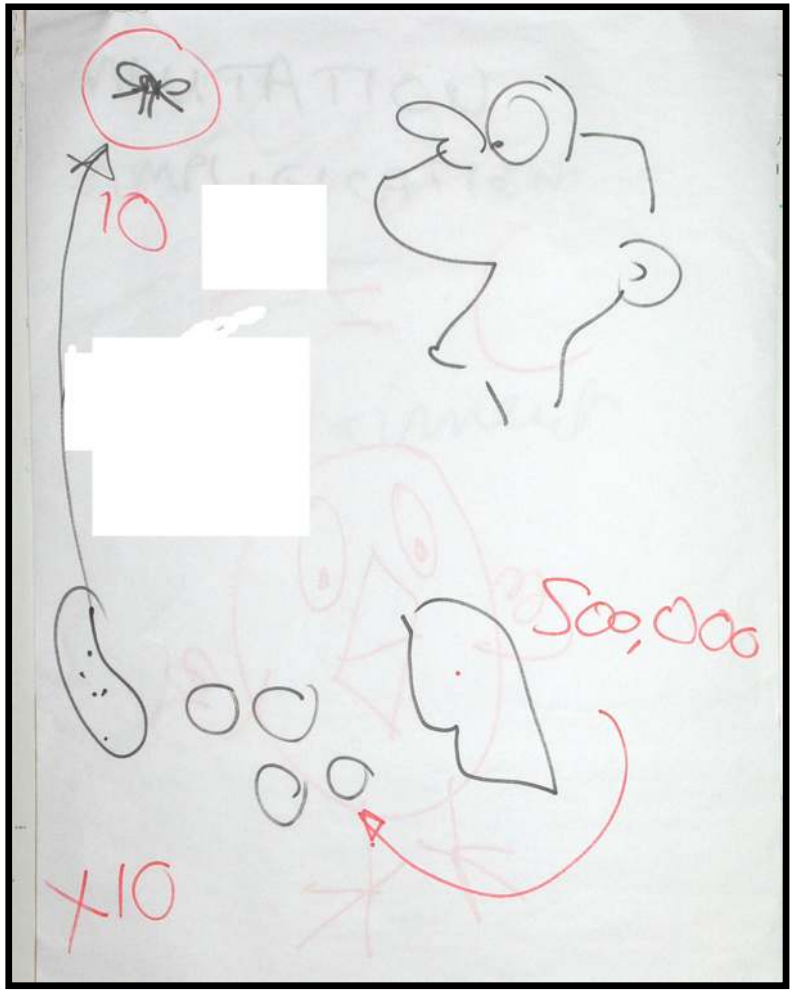
Outline

- Malaria Parasite Life-Cycle
- Evolution of Resistance to Malaria
- Population Genetics Models
- History of Epidemiological Models
- Two-stage model for transmission of drug-resistant malaria parasites

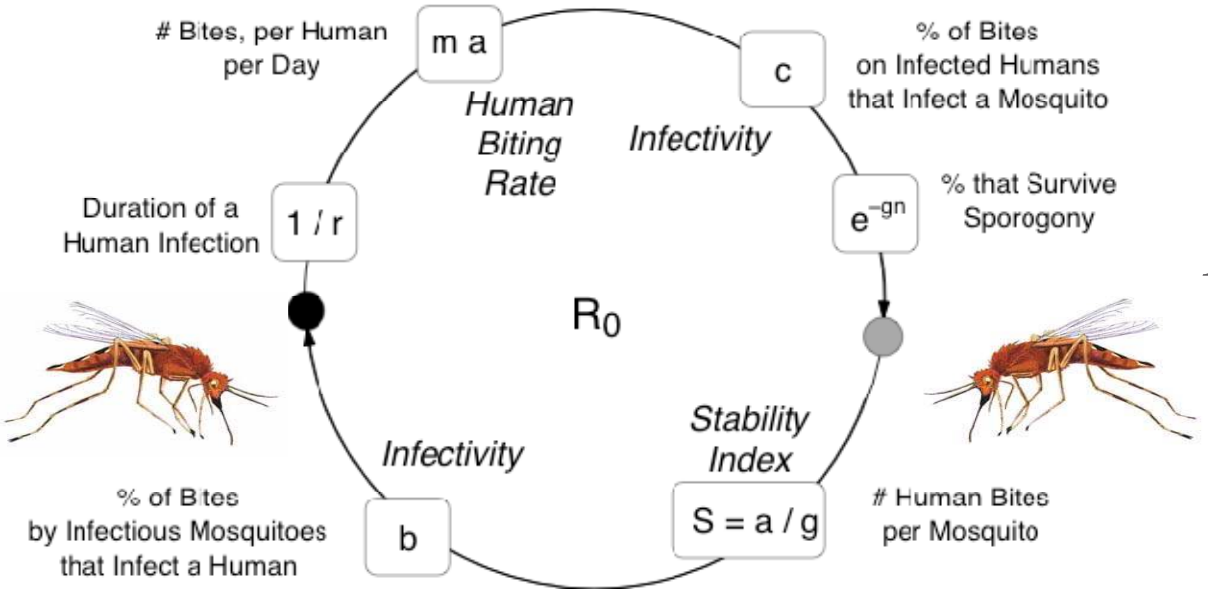
Parasite Life-Cycle



Basic Reproductive Number (R_0)

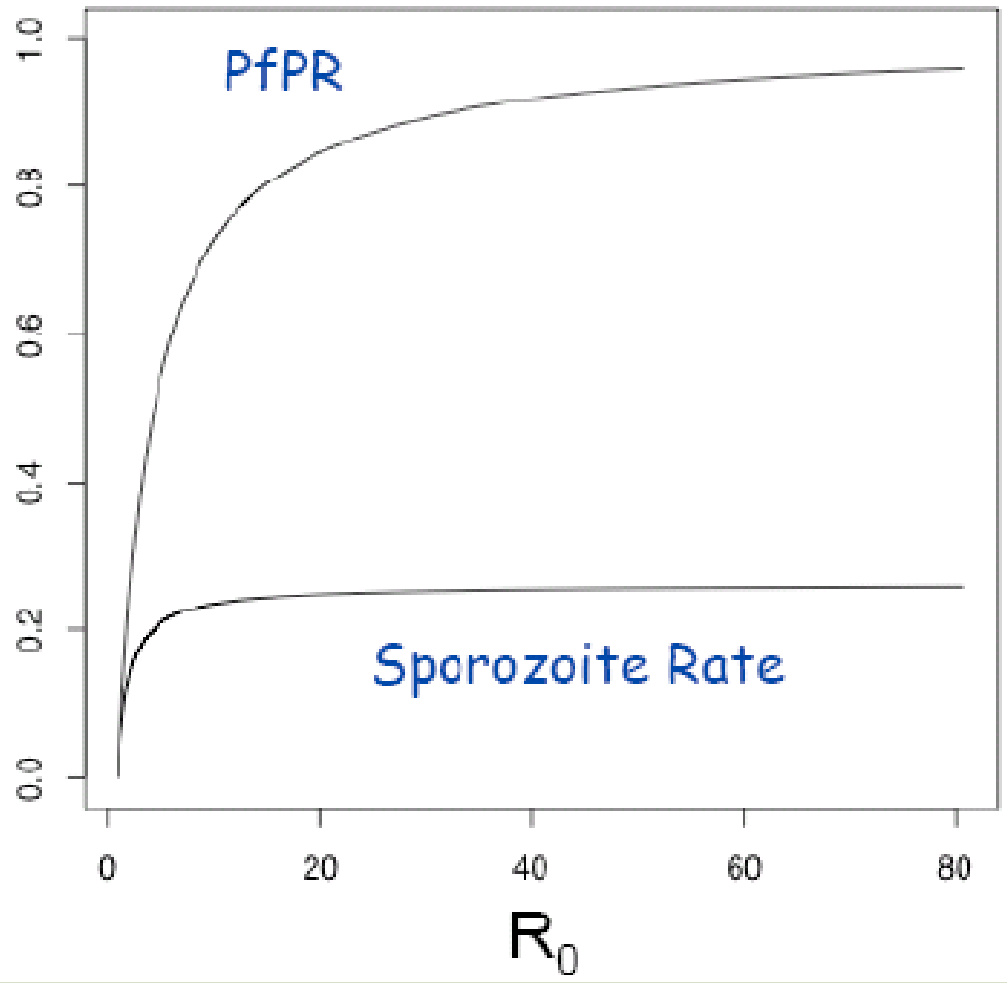
Basic Reproductive Number

The expected number of infected mosquitoes that will eventually arise from one infected mosquito after one complete generation of the parasite.



$$R_0 = \frac{ma^2bce^{-gn}}{rg}$$

Plasmodium falciparum Parasite Rate (PfPR)



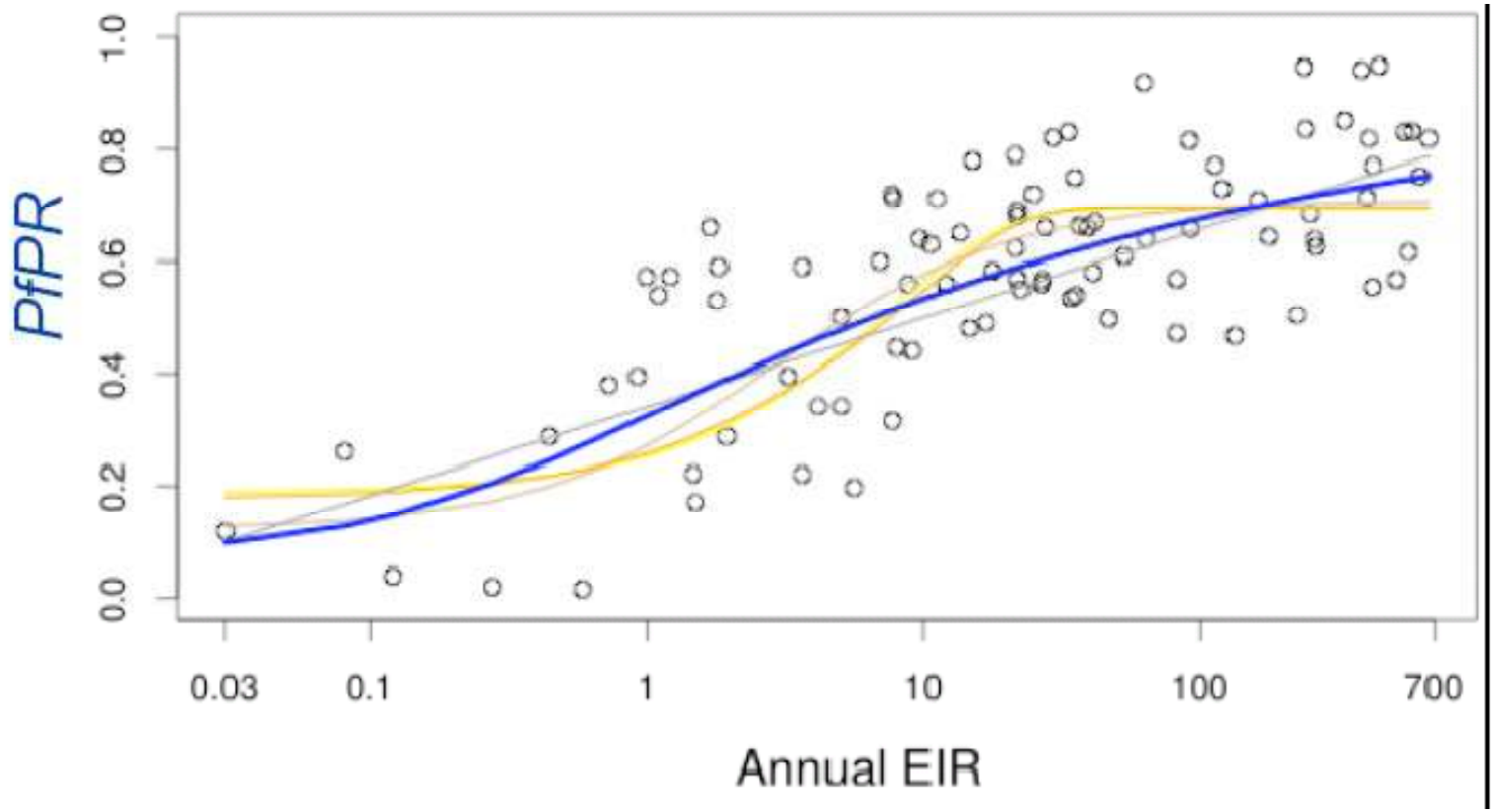
Plasmodium falciparum **Parasite Rate (PfPR)**
Proportion of Humans Infected

Sporozoite Rate
Proportion of Mosquitos that are Infectious

Entomological Inoculation Rate

Entomological Inoculation Rate

The Number of Infectious bites received per day by a human

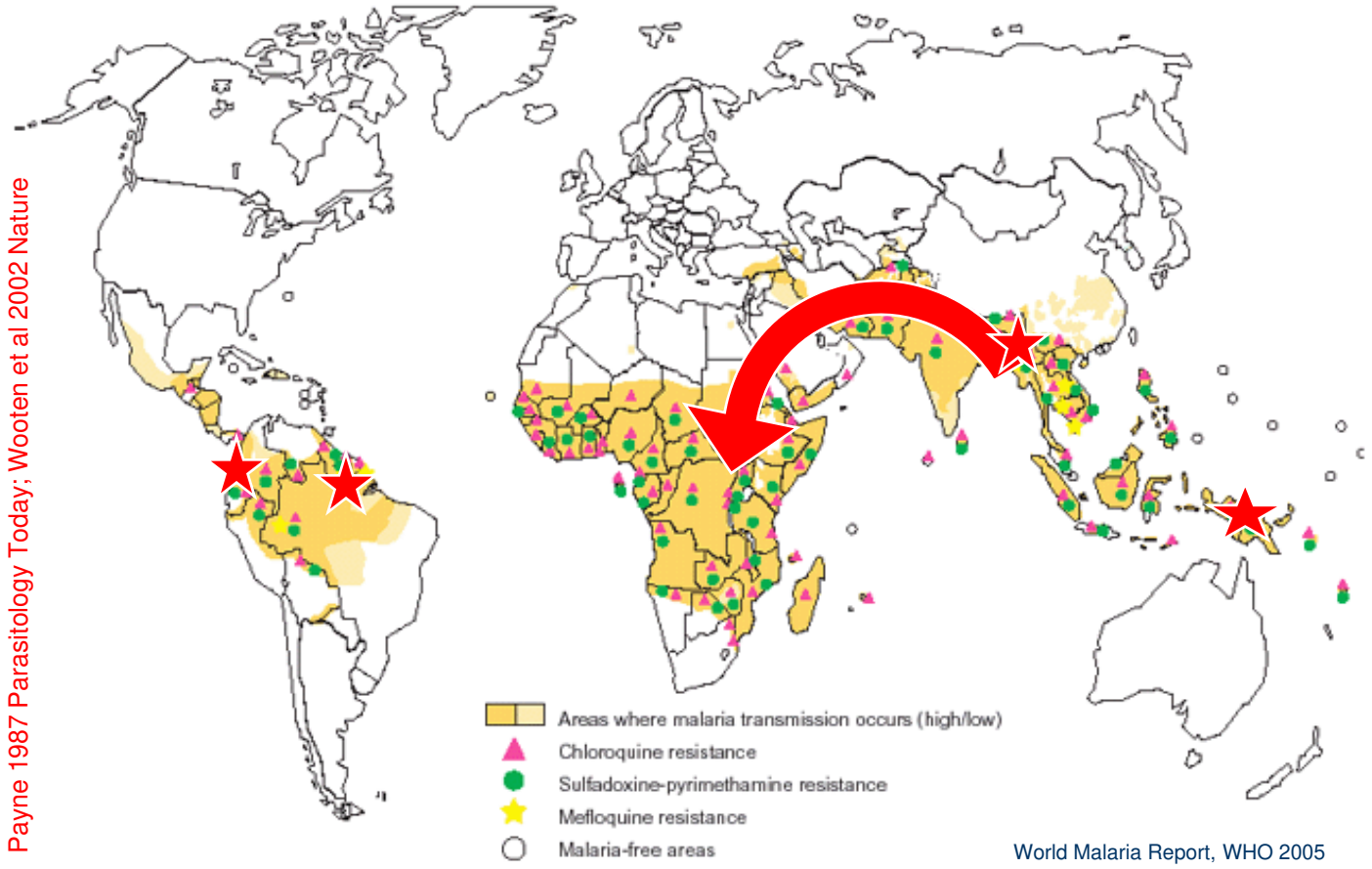


Malaria Immunity

- PREVENTS INFECTION
  - *Infection Blocking:* infection of humans
  - *Transmission Blocking*: infection of mosquitoes
- PROTECTS AGAINST CLINICAL MALARIA
  - *Premunition:* asymptomatic infection
  - *Acute-Phase:* recent clinical episode
  - *Functional Immunity:* age & exposure
  - *Blood Stage Immunity:* age & exposure

Evolution of Resistance

- *De novo* mutation rate
- Spread of resistant parasites



Payne 1987 Parasitology Today; Wooten et al 2002 Nature

Population Genetics Models

Reasons for resistance emergence in low transmission settings

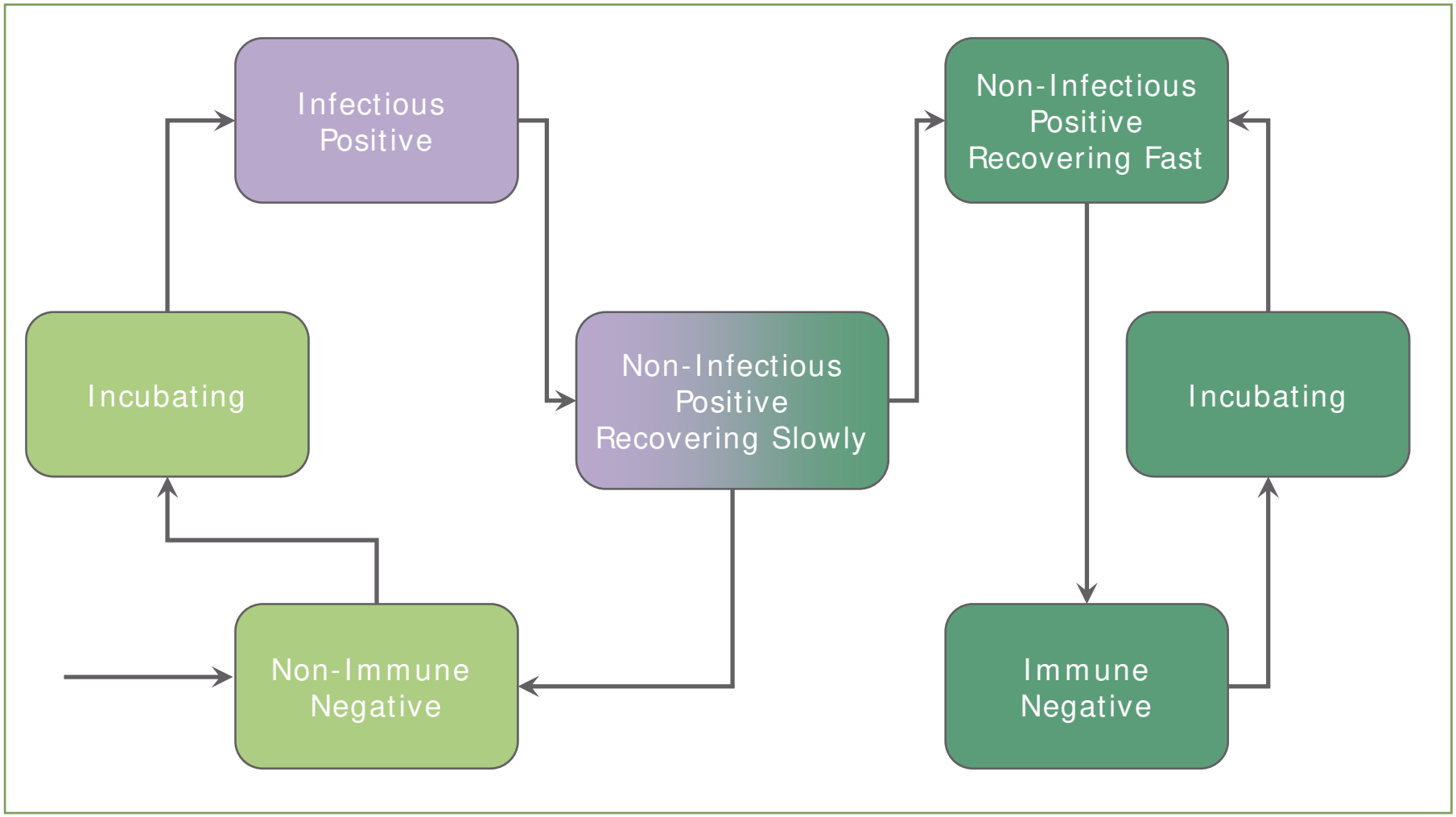
- A higher frequency of resistant alleles (mutation-selection balance)
  - (Hastings *Parasitology* (1997) **115**:133-141)
- More drug treatment (per parasite)
  - (White and Pongatavornpinyo *Proc R Soc Lond B* (2003) **270**:545-554)
- More selfing
  - (Dye and Williams *Proc R Soc Lond B* (1997) 264:61-67; Hastings *Parasitology* (1997) **115**:133-141)
- Mutant parasites are less likely to survive a host immune response when immunity is better developed
  - (Gatton et al Parasitology (2001) **123**:537-46)

Epidemiological models

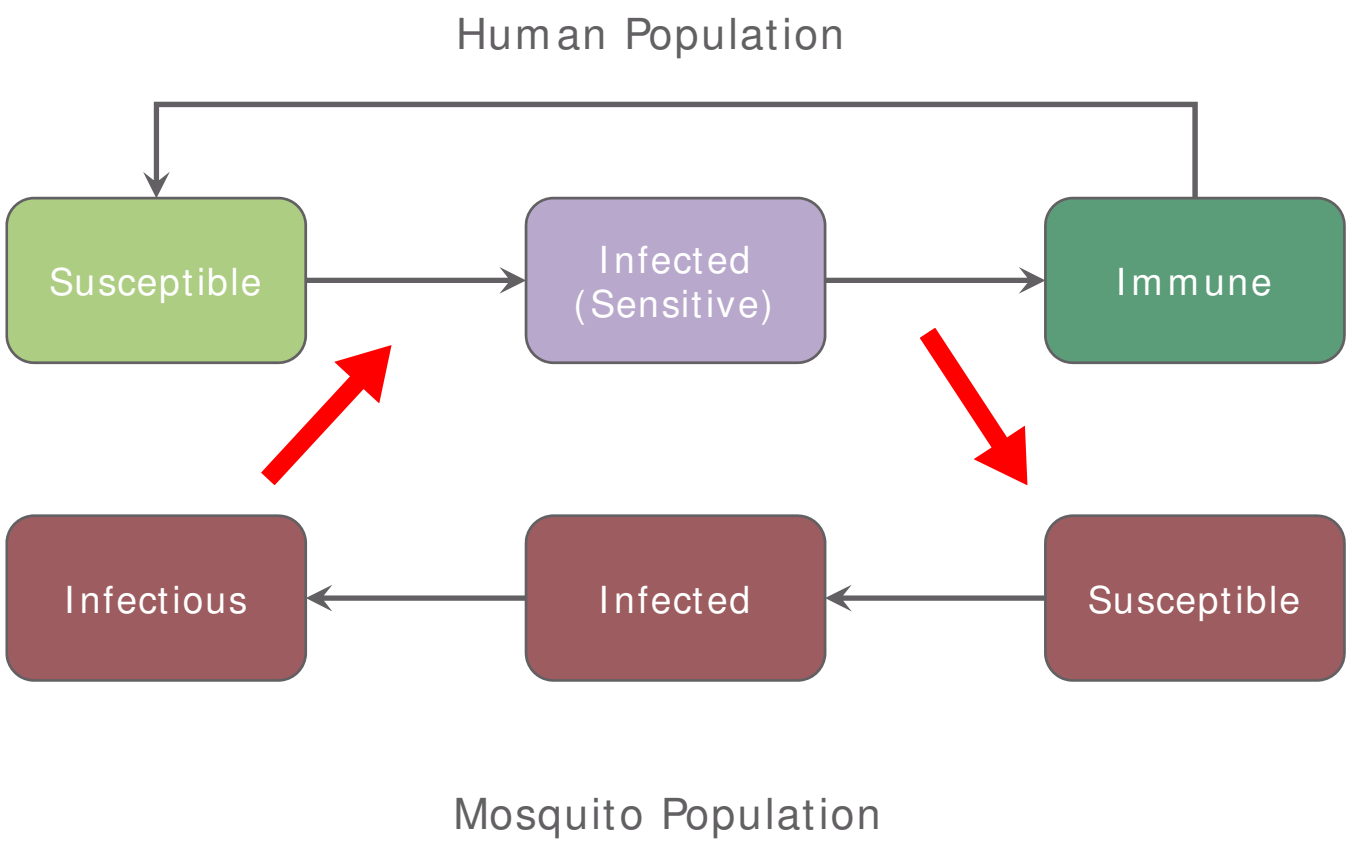
Ross – 1910

Macdonald – 1957

The Garki Model

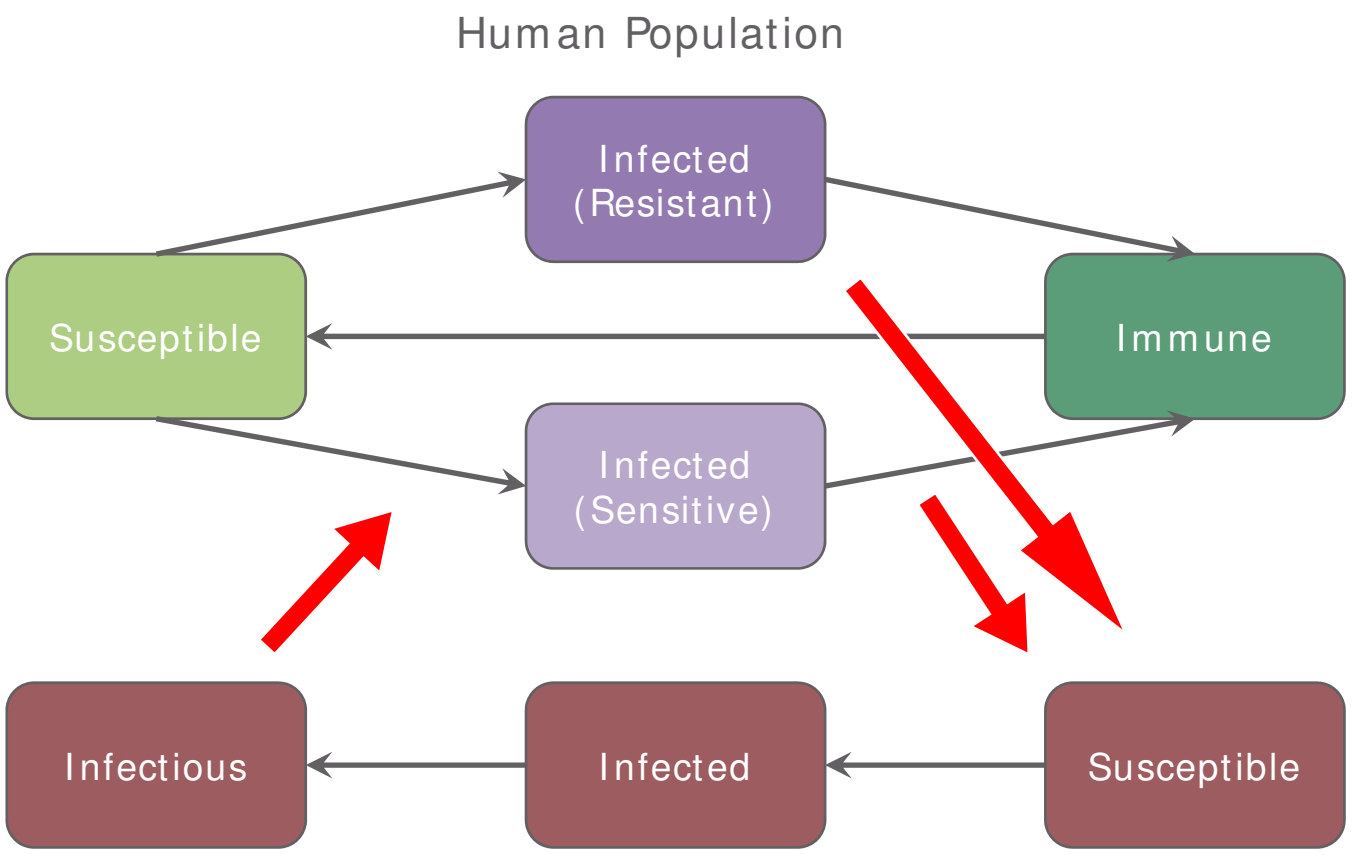


SIR Model



Koella and Antia, Malaria Journal 2003, 2:3

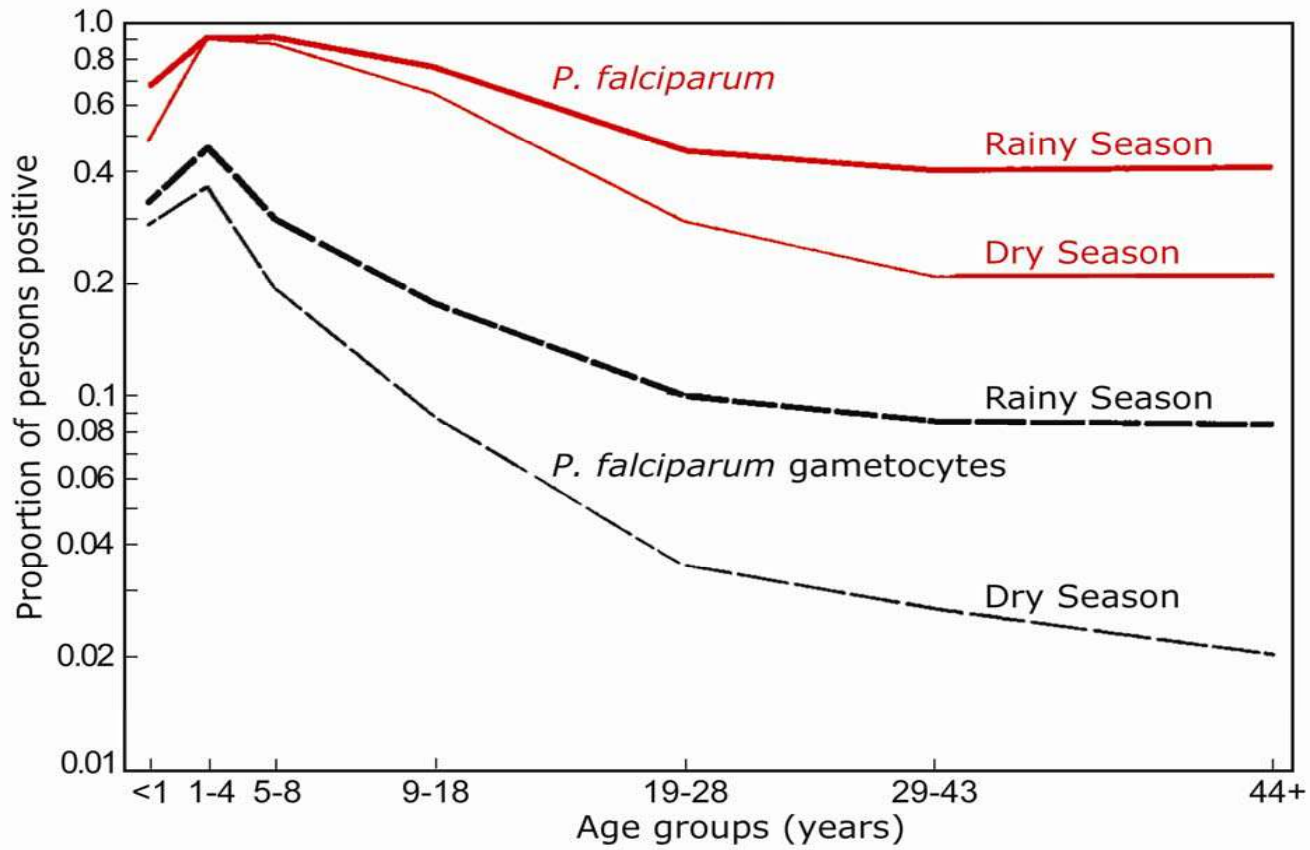
SIR Model with Resistance



Koella and Antia, Malaria Journal 2003, 2:3

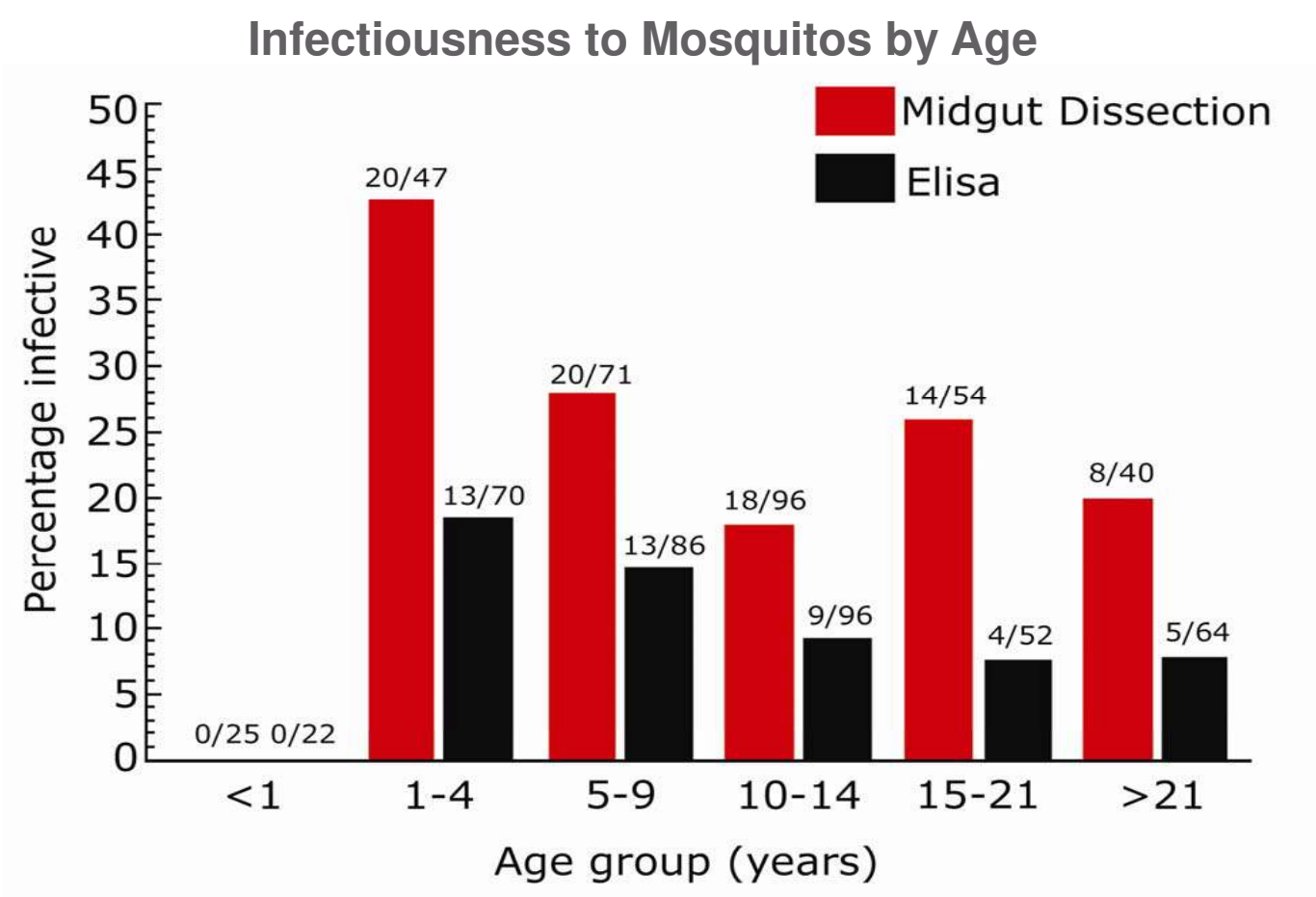
Immune Individuals Are Infected

Prevalence of P. falciparum (trophozoites/gametocytes) by age and season



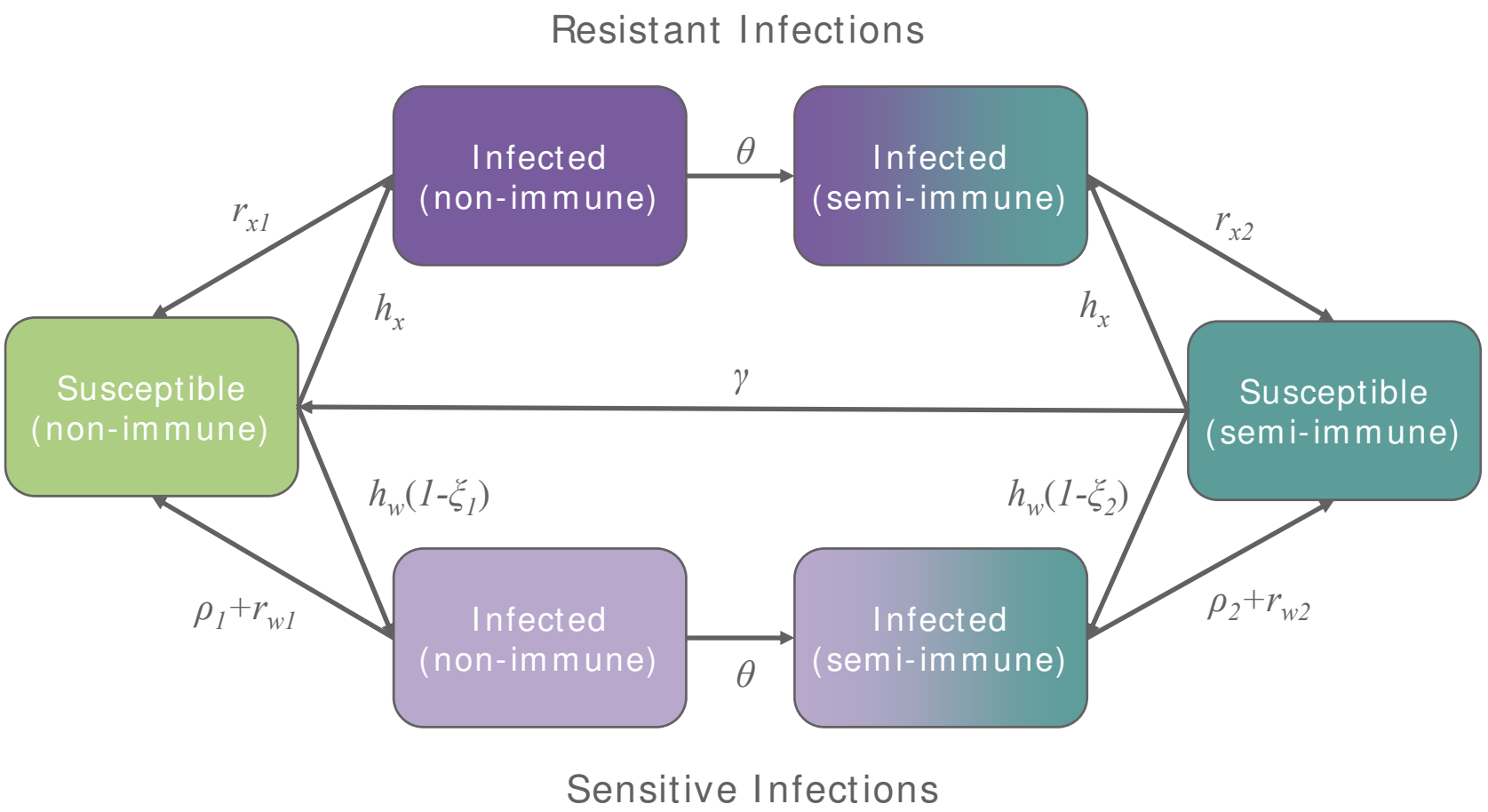
Dietz, K et al. Bull Wld Hlth Org (1974) 50:347-357

Immune Individuals Transmit



Githeko, AK et al Trans R Soc Trop Med Hyg (1992) 86, 355-358

Two-Stage SIS Model



Model Equations

$$\dot{S}_1 = B + \gamma S_2 + I_{w1}(\rho_1 + r_w) + I_{x1} r_x - S_1(h_w(1-\xi_1) + h_x + \mu)$$

$$\dot{I}_{w1} = S_1 h_w (1-\xi_1) - I_{w1}(\rho_1 + r_w + \theta + \mu)$$

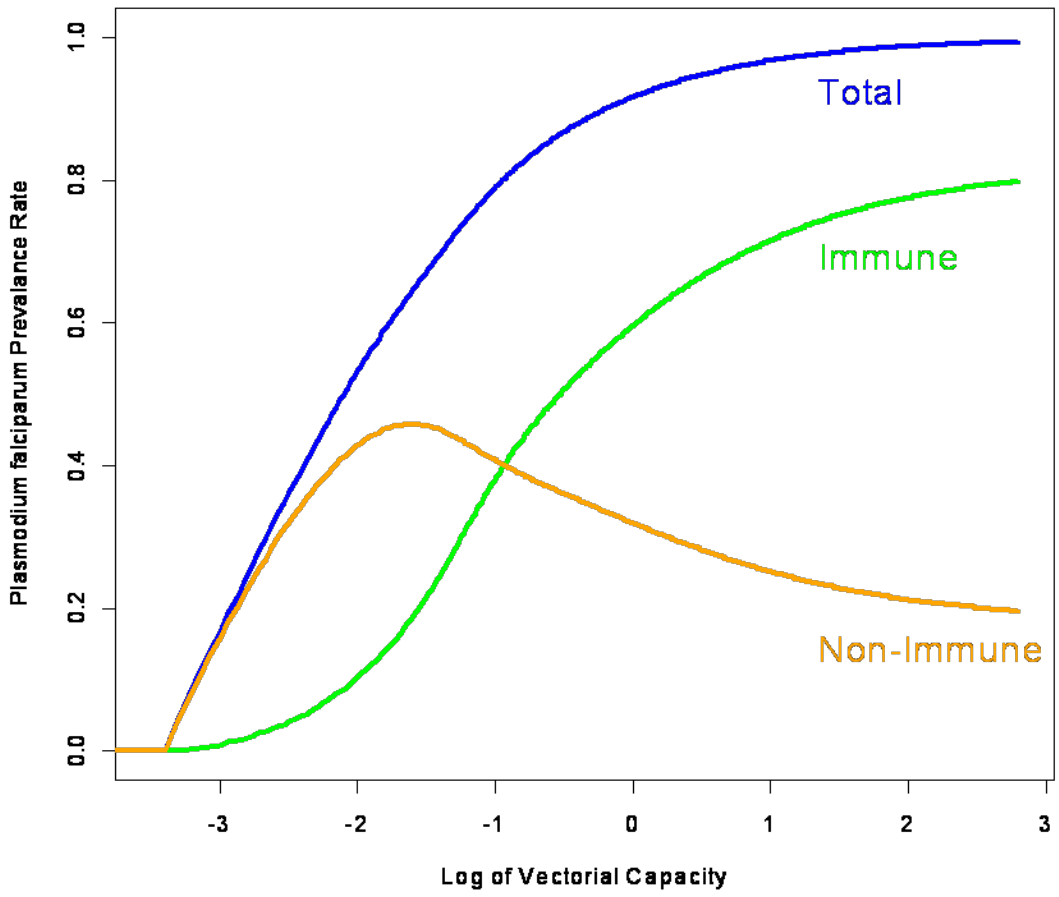
$$\dot{I}_{x1} = S_1 h_x - I_{x1}(r_x + \theta + \mu)$$

$$\dot{S}_2 = I_{w2}(\rho_2 + r_w) + I_{x2} r_x - S_2(h_w(1-\xi_2) + h_x + \gamma + \mu)$$

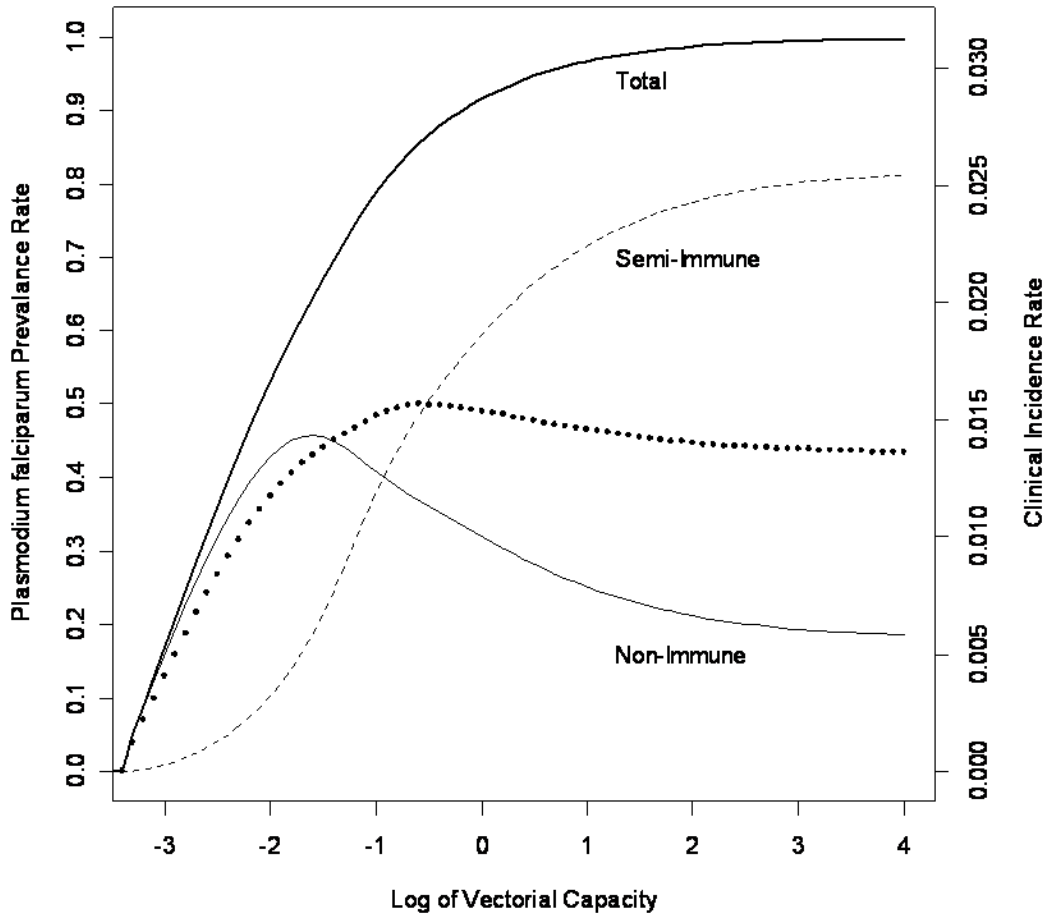
$$\dot{I}_{w2} = S_2 h_w (1-\xi_2) + I_{w1}\theta - I_{w2}(\rho_2 + r_w + \mu)$$

$$\dot{I}_{x2} = S_2 h_x + I_{x1}\theta - I_{x2}(r_x + \mu)$$

Model With No Resistance



Model With No Resistance



R_0 – Again!

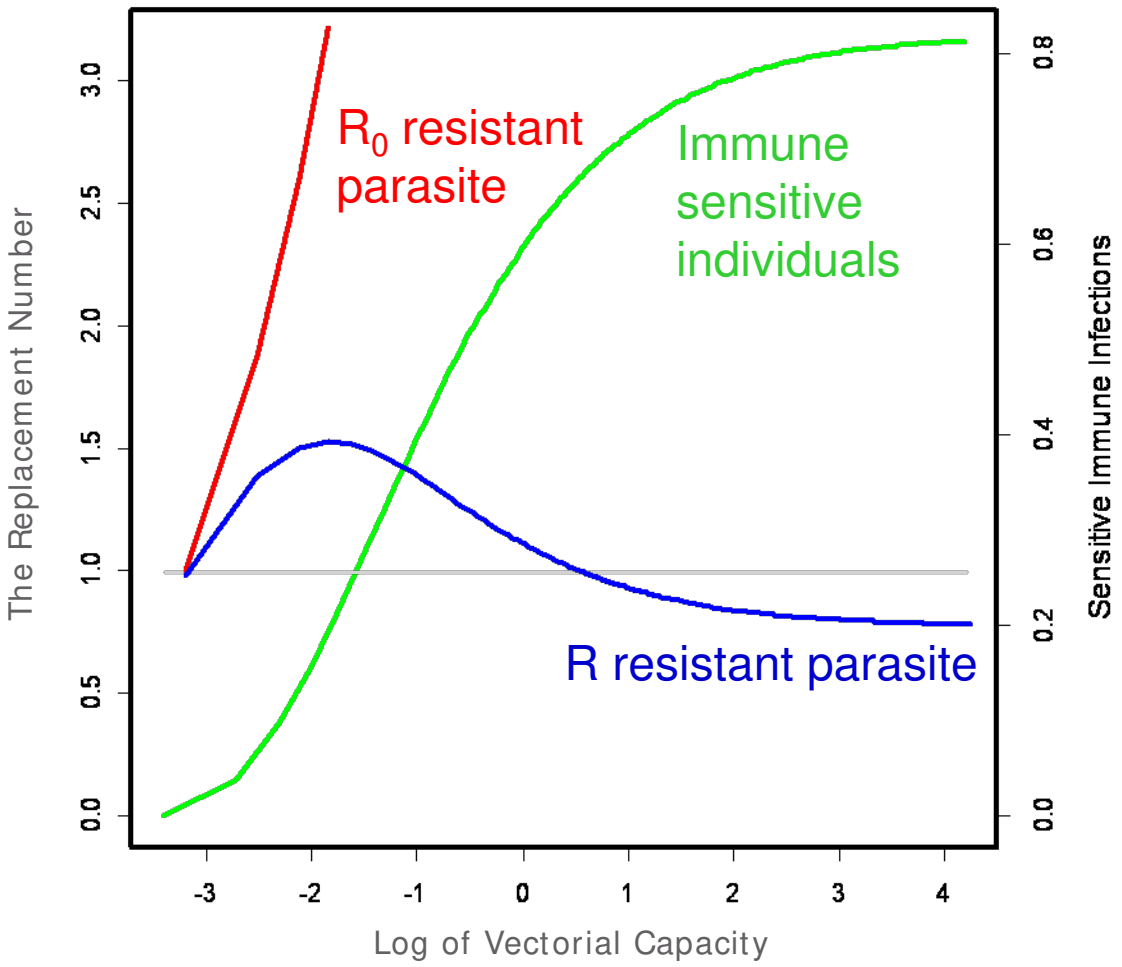
Basic Reproductive Number (R_0)

The expected number of infected humans that will eventually arise from one infected human after one complete generation of the parasite.

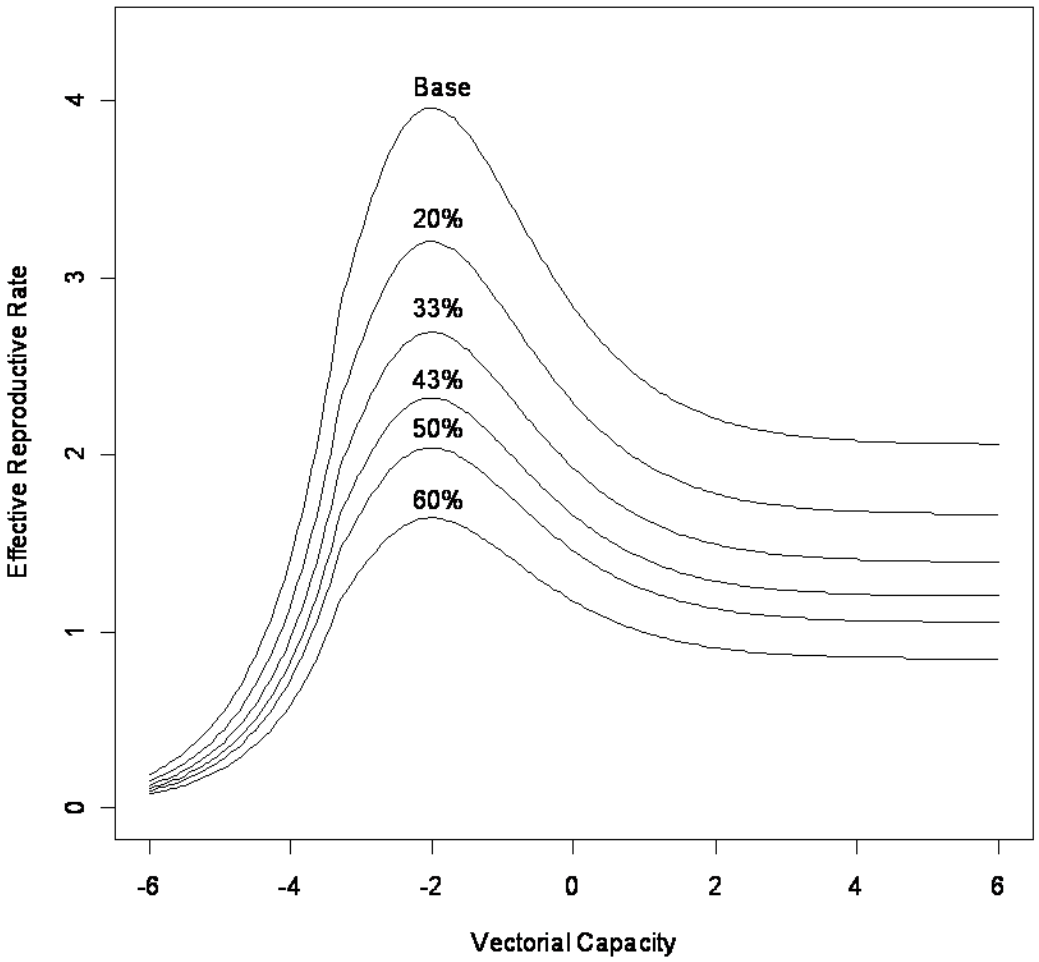
The Replacement Number (R_X)

The expected number of infected humans that will eventually arise from one infected human after one complete generation of the parasite when the prevalence of infection is X.

A Refuge for Sensitive Parasites



Fitness cost of Resistance



Conclusion

- Asymptomatic semi-immune individuals provide a refuge for sensitive parasites and can prevent the spread of resistant parasites at high transmission levels assuming a great enough fitness cost
- Implications for control strategies aimed at reducing the transmission level (ITNs, IRS)
- Unlike models of antibiotic resistance (Bonhoeffer, Lipsitch et al. 1997), the parasite with the highest R_0 may not predominate
- Allows for coexistence of both sensitive and resistant parasites