Modelling drug resistance

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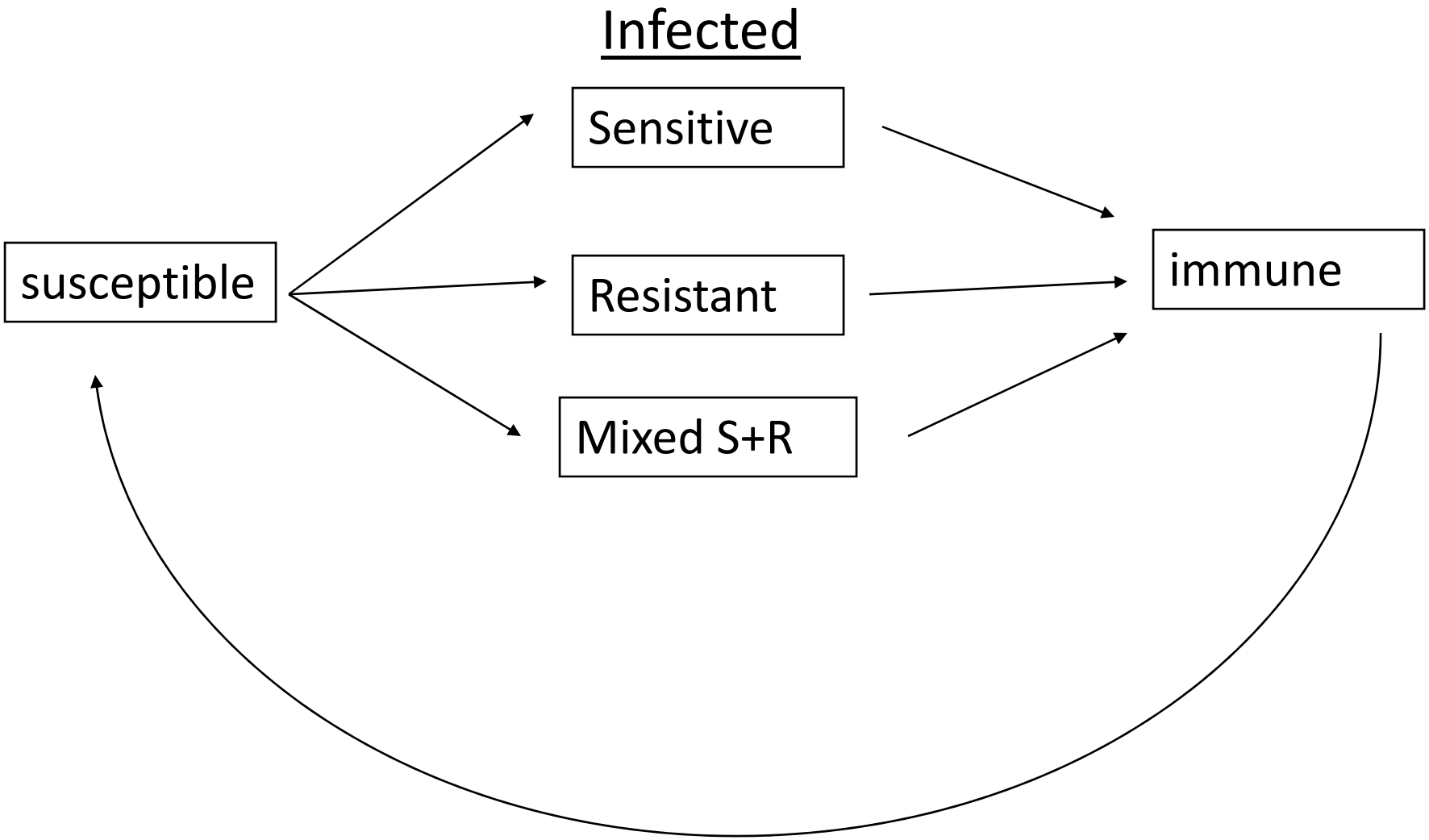
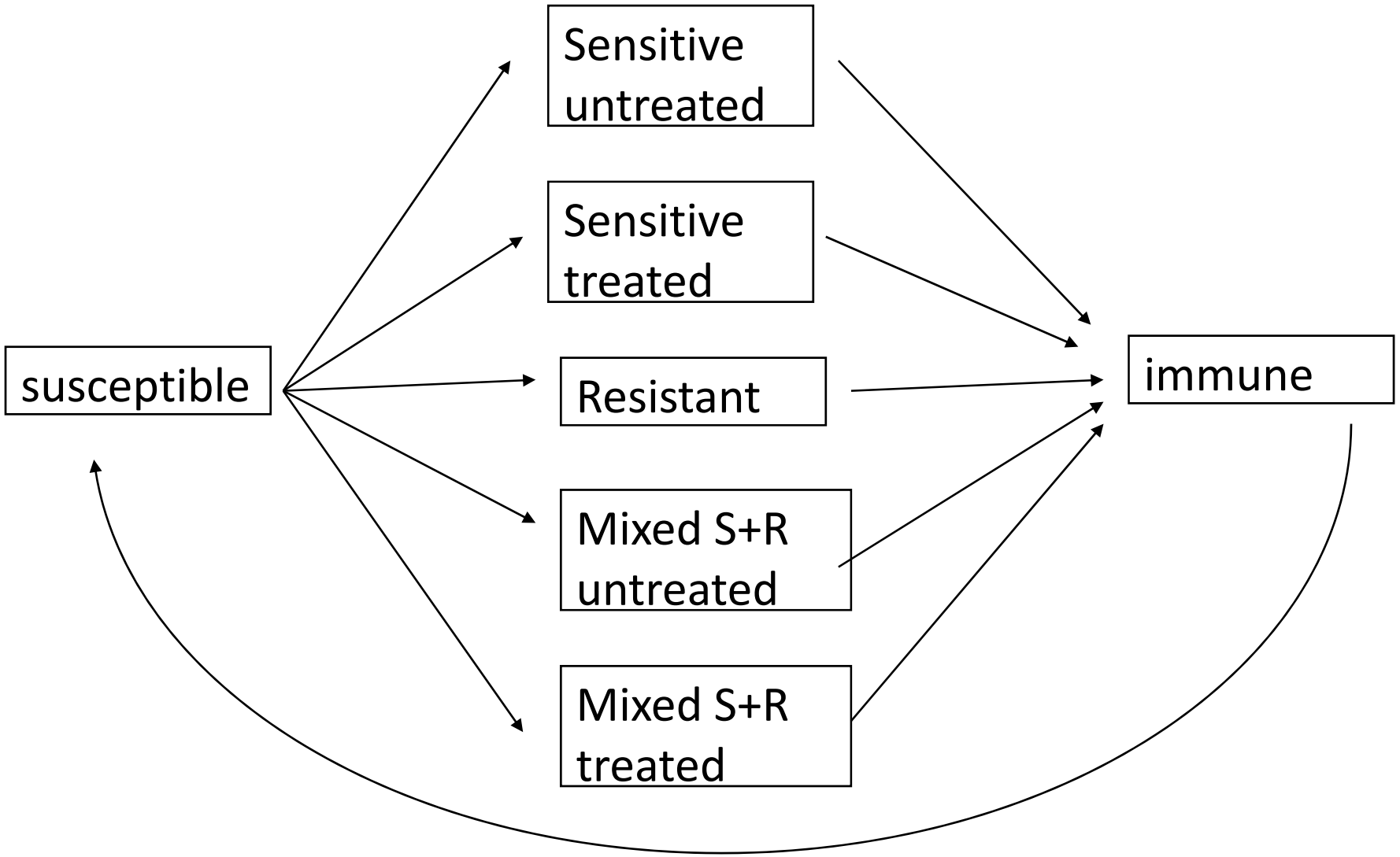
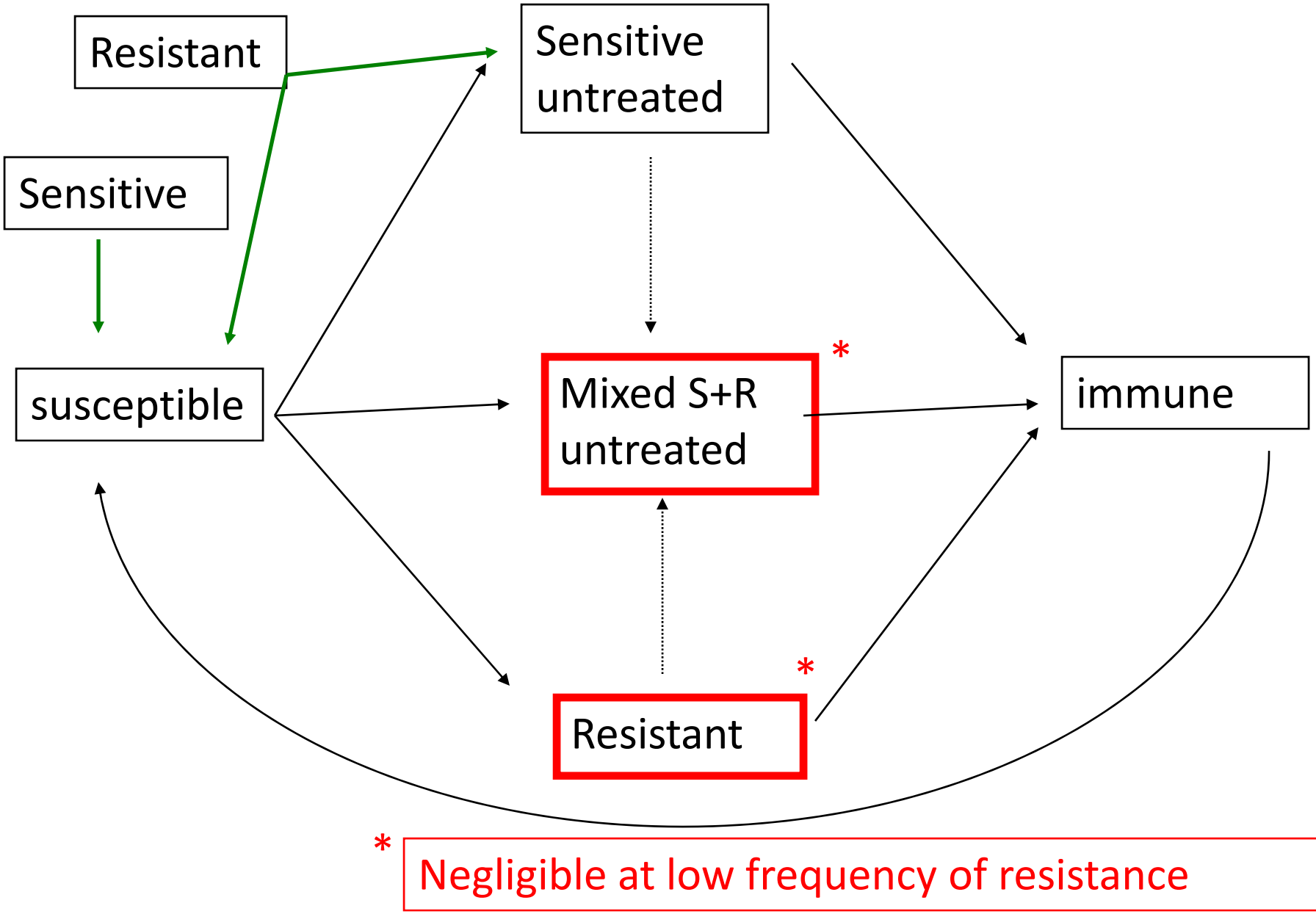
'Epidemiological 'approach



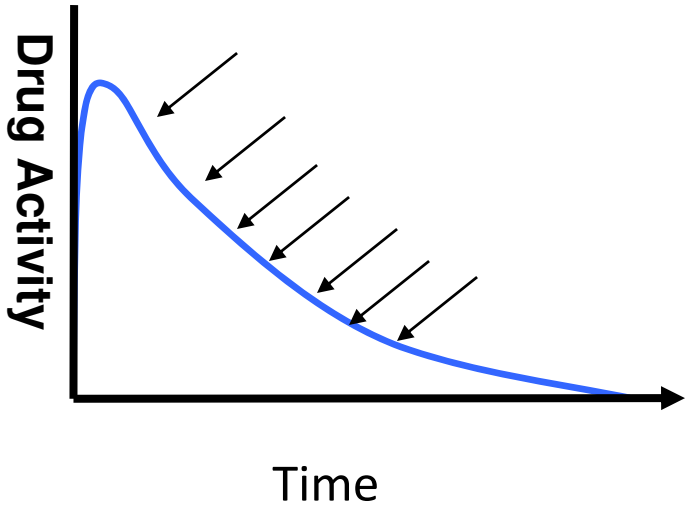
"antimalarial drug resistance can spread in a population, even if no drug is being deployed, and even if there is a metabolic cost of resistance"



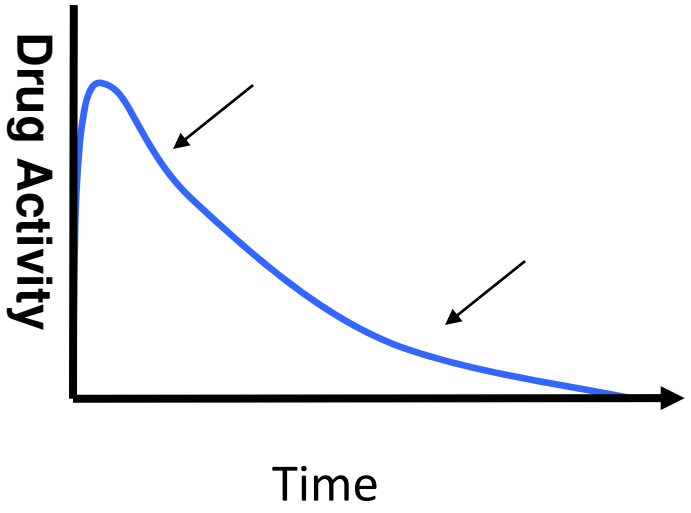

Resistant
Sensitive
Sensitive untreated
susceptible
Mixed S+R untreated
*
immune
Resistant
*
* Negligible at low frequency of resistance

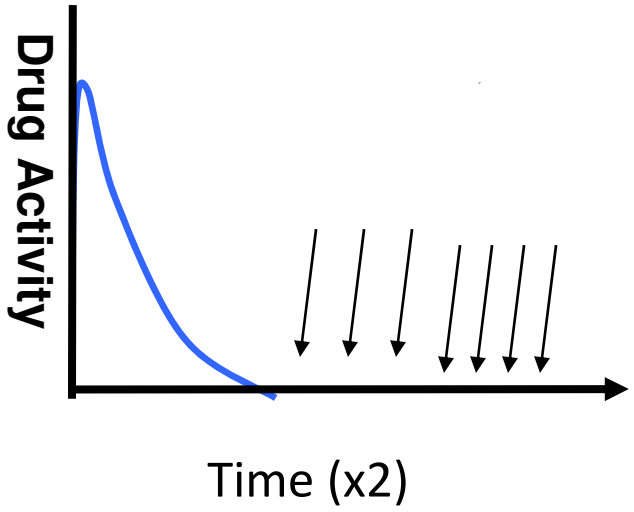
(Algebra Versus Intuition)

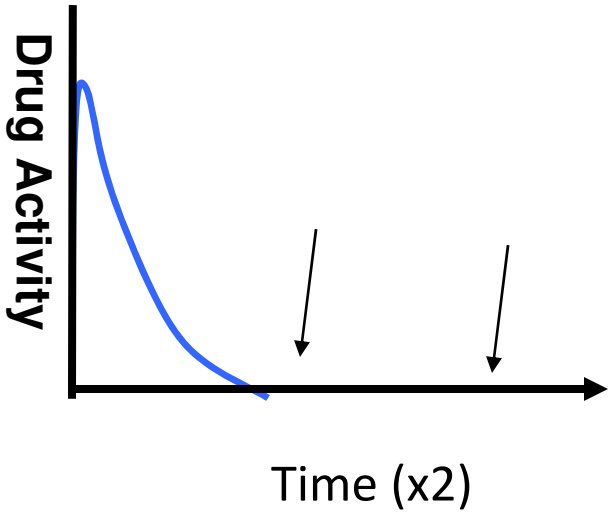
High transmission



Low transmission







$$r' = \frac{rk}{w}$$

$$s' = \frac{sk(1-d)}{w}$$

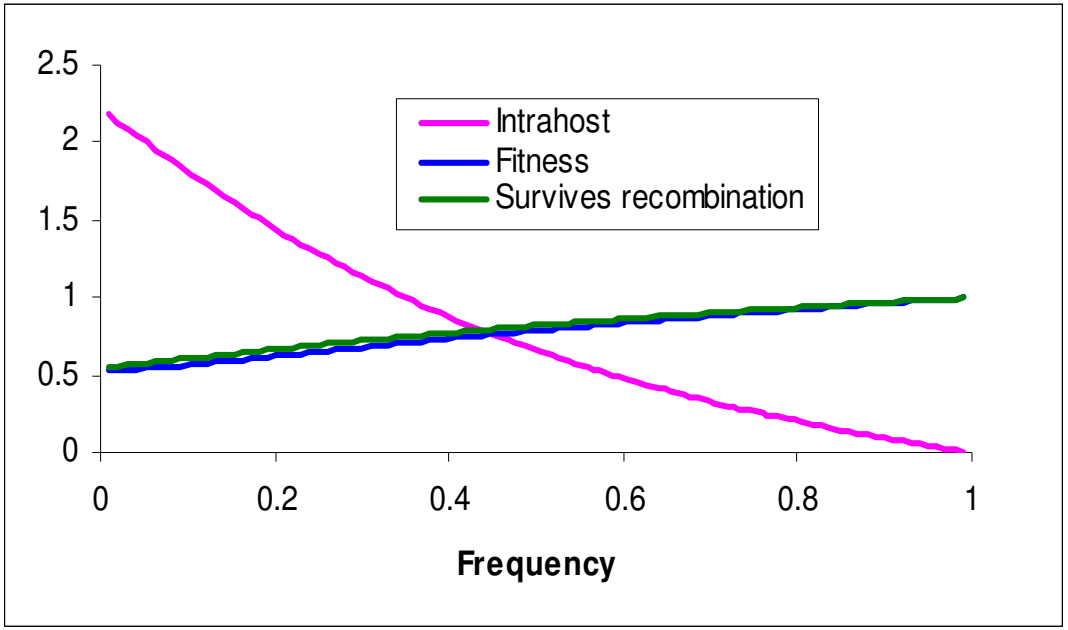
r= freq of resistant form
s= freq. of sensitive
k=no. 'onward' transmissions (discounted by 'impediments' such mosquito deaths, human immunity etc)
d= proportion of humans with decaying drug levels
w = normalising factor

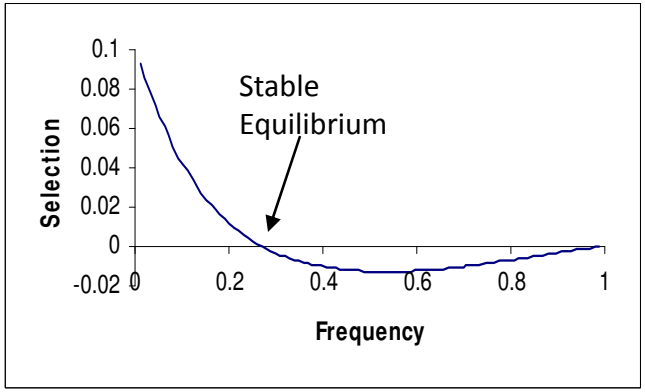
……so intensity of transmission makes no difference

These problems arose because discussion/analysis focussed on humans, not on the parasites and the genes they carry

Analysis of drug resistance must focus on genes and use population genetic methodology that has been developed and refined over century

More complex scenario: resistance requires two genes, and there is a range of clonal multiplicities





20% of human infections are treated by drug-treated; natural selection is mediated by competition between different malaria clones in the same human with a nominal decrease in fitness of drug resistance mutations of 40%, two unlinked genes are required to encode resistance, and human clonal multiplicity follows a truncated Poisson distribution with mean clonal multiplicity of 2.5, and a maximum clonal multiplicity of 7

$$f_h' = \frac{\sum_{c=1}^{c} \sum_{i=0}^{c-i} \sum_{j=0}^{c-i-j} \sum_{k=0}^{1} \sum_{d=0} p(c)\,p(i,j,k,l)\,p(d)\,t(h)}{\overline{W}}$$

where:
f'_h is the frequency of haplotype *h* transmitted to the next malaria generation

c is the number of malaria clones in a human
i is the number of *AB* haplotypes in that host
j is the number of *Ab* haplotypes in that host
k is the number of *aB* haplotypes in that host which
l is the number of *ab* haplotypes in that host (which equals *c-i-j-k)*

d is drug treatment 0=absent, 1=present
p(c) is the proportion of humans with *c* clones; drawn from a (truncated) Poisson distribution
p(i,j,k,l) is the probability of getting this combination of *i,j,k,l* haplotypes, calculated from the multinomial distribution using haplotype frequencies in the current malaria generation
p(d) is the probability of receiving the treatment regimen (i.e. drug-treated or untreated)
t(h) is the proportion of transmissions from this type of host that are of genotype h.

But population genetic analysis ignores changes in host population structure

In essence

Population genetics asks ‘what type ?’

Ecology/epidemiology asks ‘how many ?’

Malaria

Epidemiology extremely complex

e.g. immunity affects:
- Chance of being infected
- Probability of being symptomatic
- Probability of failing drug treatment
- Probability of transmitting infection

'Presumptive' drug use
Level of mixed infection and genetic recombination

Combine population genetics with malaria epidemiology in computer simulations

Insecticide resistance

$$q' = \frac{[q^2(1-F)+qF]+2rq(1-F)(1+hs)+m}{\overline{W}}$$

$$r' = \frac{[r^2(1-F)+rF](1+s)+2rq(1-F)(1+hs)}{\overline{W}}$$

q is freq of sensitive, r is freq of resistant

F is inbreeding (probability of identity by descent)
s is selective advantage of resisting the insecticide
h is dominance
m is immigration

[insects are diploid]

$$r' = \frac{[r^2(1-F)+rF](1-s)+2rq(1-F)(1+hs)}{\overline{W}}$$

$$q' = \frac{[q^2(1-F)+qF]+2rq(1-F)(1+hs)+m}{\overline{W}}$$

Attributable to insecticide deployment

Attributable to insect demography

Conclusions

- Drug (or insecticide) resistance is a genetic property and needs to be addressed using appropriate methodology

- This methodology generally ignores the demographic impact of drug/insecticide deployment

- There is a clear need to develop a methodology to combine population genetics with epidemiology