Modelling Epidemics

Lecture 6: Heterogeneous deterministic epidemiological models with different levels of susceptibility and infectivity

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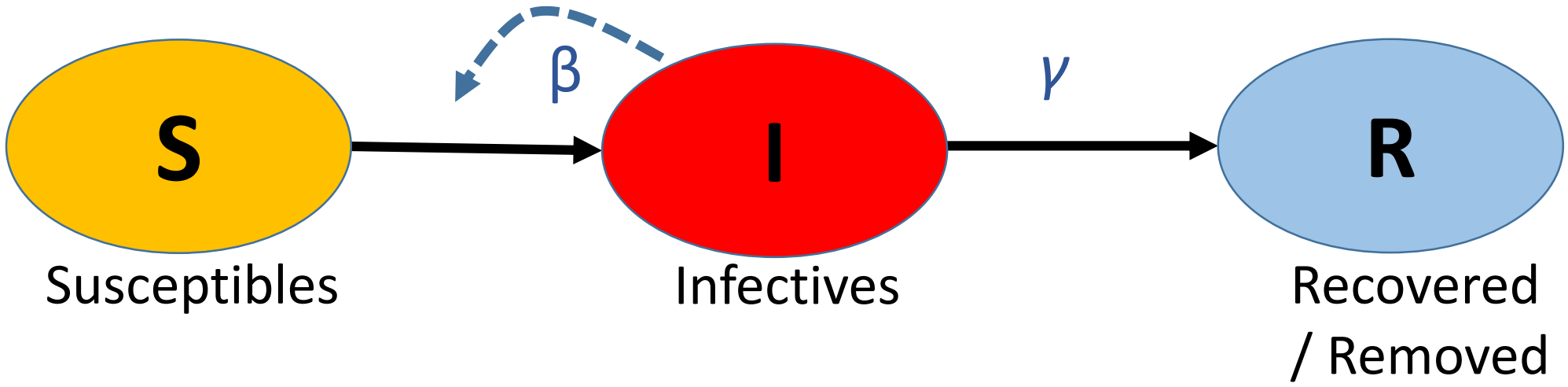
Overview

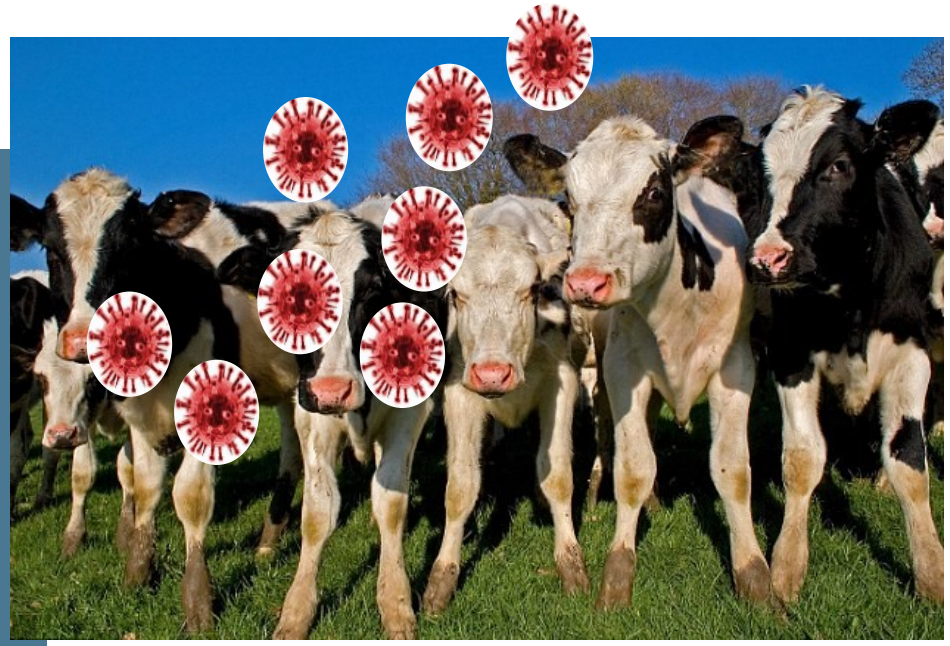
- Implicit assumptions in basic SIR models
- Sources of heterogeneity
- Incorporating genetic heterogeneity
- Case 1: The SIR model for two levels for susceptibility
- Case 2: Difference in susceptibility confers difference in infectivity
- More complex cases of (genetic) heterogeneity

Recap: the basic SIR model



- Assumes that all individuals have the same
  - Risk of becoming infected (susceptibility)
  - Risk of transmitting the infection (infectivity)
  - Duration of infectious period
- Dynamics is fully described by 2 model parameters β and γ and initial proportions of individuals in each compartment

But: not all individuals are the same!



Do these individuals have the same risk of becoming infected or transmitting infections?

Potential sources of host heterogeneity

1. Differences in host environment

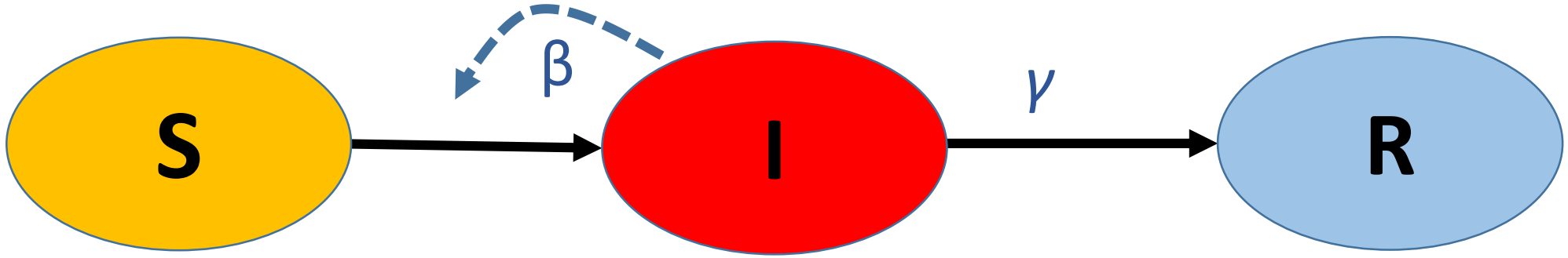
- Rearing system
  - Different rearing systems associated with e.g. different space, nutrition or other environmental factors may affect epidemiological parameters
- Climatic conditions
  - E.g. higher infection pressure for liverfluke or footrot in wet and mild conditions
- Pathogen diversity
  - E.g. exposure to different pathogen strains
  - Co-infections

Potential sources of host heterogeneity (cont.)

2. Differences in host characteristics

- Age
  - Age dependent immunity or contact behaviour may affect transmission and recovery rate
    - e.g. maternal antibodies provide temporal immunity after birth
  - Large body of literature for age-structured epidemiological models
- Immune status
  - E.g. vaccinated / non-vaccinated; previously exposed / not exposed
  - Large body of literature on impact of vaccination on epidemiology
- Host genetics
  - Relatively few studies despite much evidence for genetic heterogeneity
  - Focus in this lecture

How does the host genetics affect the epidemiology?



- Host genetics may affect the
  - Risk of becoming infected (susceptibility): impact on β
  - Risk of transmitting the infection (infectivity): impact on β
  - Ability to interfere with the pathogen life-cycle within the host: impact on duration of infectious period 1/γ

How to incorporate genetic heterogeneity into epidemiological models

- Which host trait is most likely under genetic influence?
  - (e.g. susceptibility, infectivity, time to death / recovery)
- What is the genetic architecture of this trait?
  - Trait primarily controlled by single gene or locus (Major gene model)
    - E.g. gene affecting binding protein
    - Discrete genotypes
  - Trait controlled by many genes, each with a small effect (Polygenic model)
    - Majority of cases
    - Continuous genotypes
  - Different genetic architectures lend themselves to different modelling approaches

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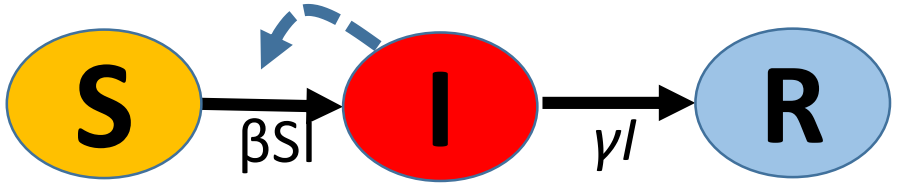
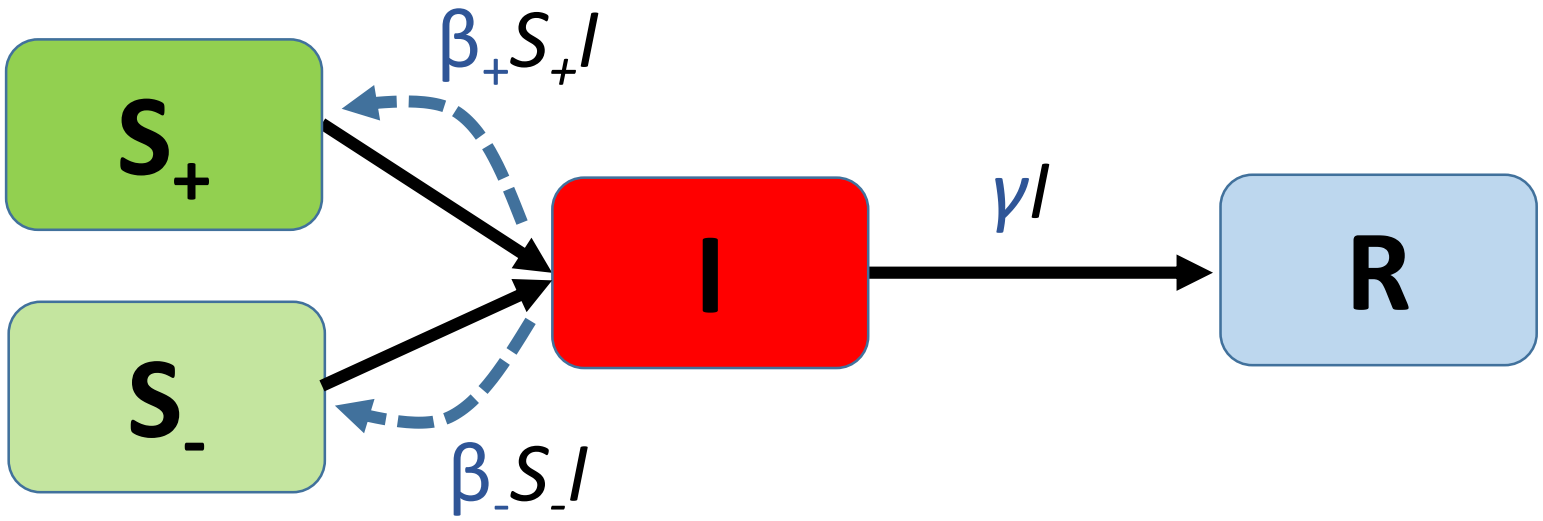
A (very) simple genetic epidemiological model



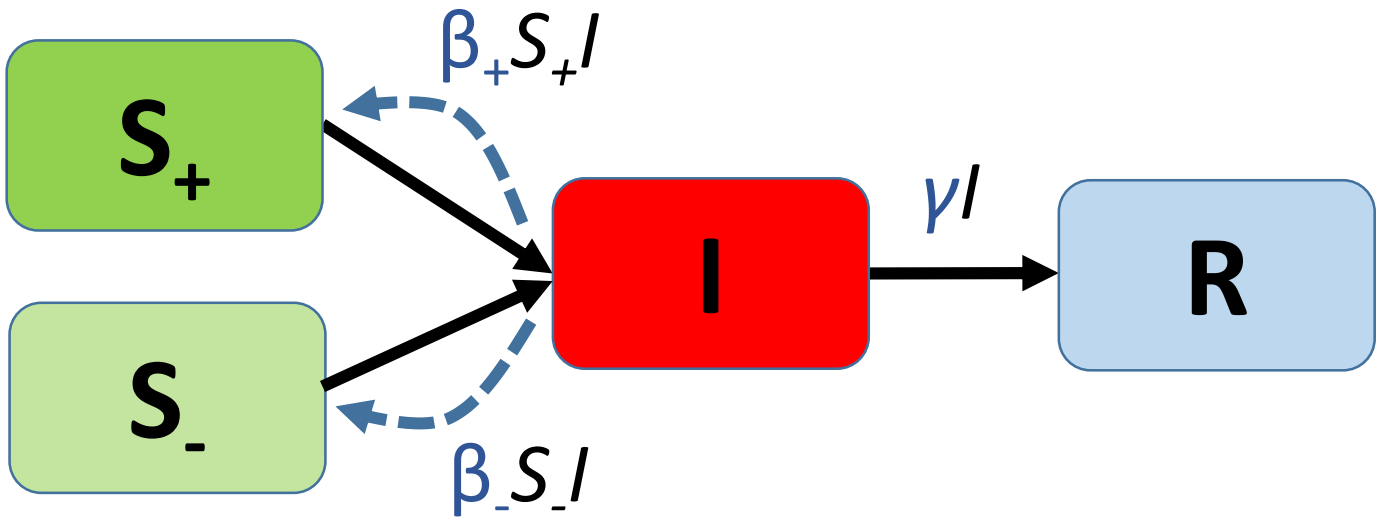
- Assume SIR epidemiological model in a closed population with homogeneous contact structure
- Assume differences in susceptibility only
- For simplicity assume major gene affects susceptibility in a dominant manner, i.e. one copy of the unfavourable allele is sufficient to increase susceptibility (**AA, Aa, aa**)
  - 2 genotypes: **S+** and **S-** representing groups with high and low susceptibility, respectively

A (most) simple genetic epidemiological model

- 2 genotypes: **S+** and **S-** representing high and low susceptibility
- 2 transmission rates: $\beta_+ > \beta_-$



Model equations



ODEs describing the dynamics:

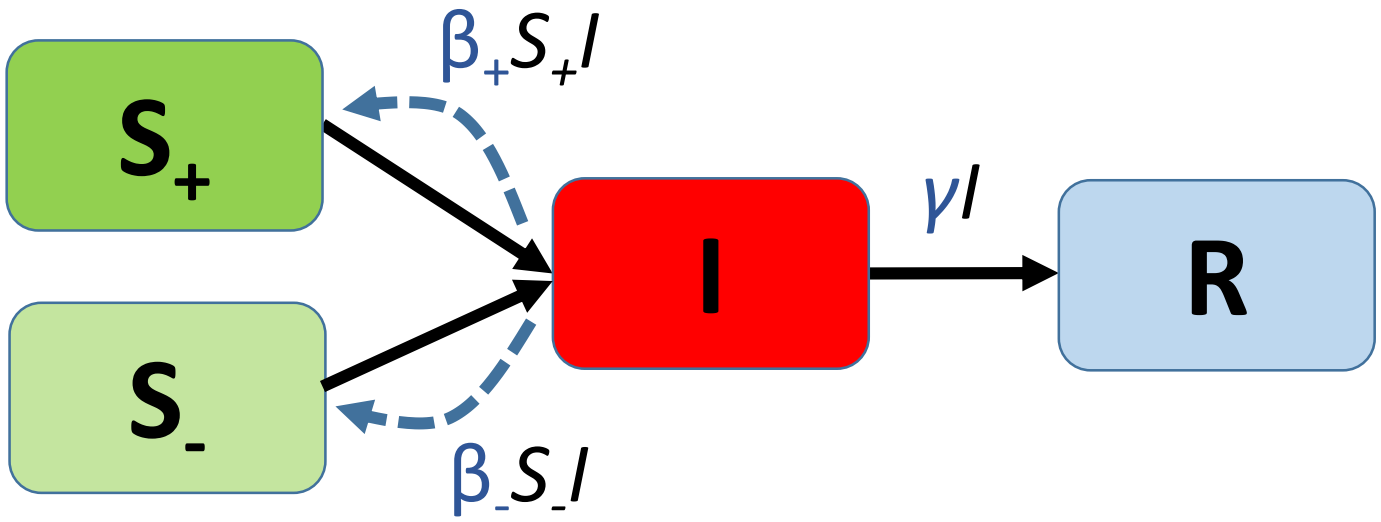
$$\frac{dS_+}{dt} = -\beta_+ S_+ I$$

$$\frac{dS_-}{dt} = -\beta_- S_- I$$

$$\frac{dI}{dt} = (\beta_- S_- + \beta_+ S_+) I - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

Model equations



Initial conditions:

Specify $S_+(0)$, $S_-(0)$, I(0) and R(0) such that:

- Prop. of individuals with low susceptibility = **p**
- $S_+(0) + S_-(0) + I(0) + R(0) = 1$

e.g. $S_-(0) = \frac{p(N-1)}{N}$; $S_+(0) = \frac{(1-p)(N-1)}{N}$; $\mathrm{I}(0) = \frac{1}{N}$; $\mathrm{R}(0) = 0$

ODEs describing the dynamics:

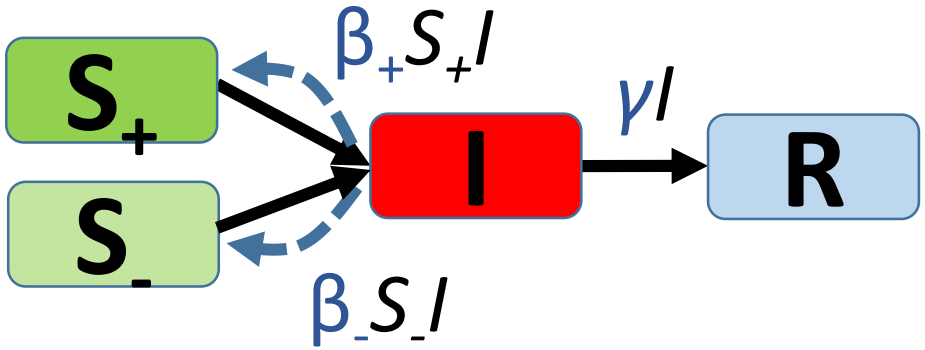
$$\frac{\mathrm{d}S_+}{dt} = -\beta_+ S_+ \mathrm{I}$$

$$\frac{\mathrm{d}S_-}{dt} = -\beta_- S_- \mathrm{I}$$

$$\frac{\mathrm{d}I}{dt} = (\beta_- S_- + \beta_+ S_+)\mathrm{I} - \gamma \mathrm{I}$$

$$\frac{\mathrm{d}R}{dt} = \gamma \mathrm{I}$$

The basic reproductive ratio R_0

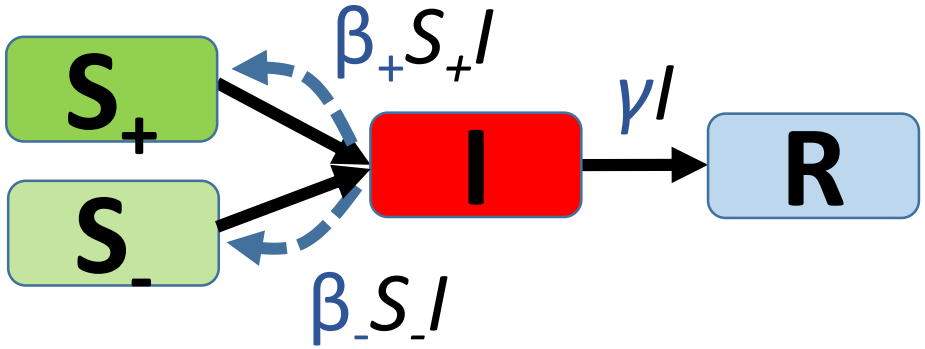


Definition: Basic reproductive ratio R_0 (same as for homogeneous populations)
The average number of individuals an infectious individual will infect, assuming that the rest of the population is susceptible

- **Assume $\beta_+ = \beta$; $\beta_- = \varepsilon\beta, with\ 0 \leq \varepsilon \leq 1$**
- An average infected individual
  - infects $\beta_- S_- + \beta_+ S_+ = \varepsilon\beta p + \beta(1-p)$ susceptible individuals per day
  - is infectious for a period of 1/γ days
  - will thus generate $(p\varepsilon\beta + (1-p)\beta)$ x 1/γ new infections over its lifetime

➢ $$R_0 = \frac{p\,\varepsilon\beta + (1-p)\beta}{\gamma}$$

The Threshold Phenomenon



Imagine a scenario where I_0 infectives are introduced into a susceptible population.

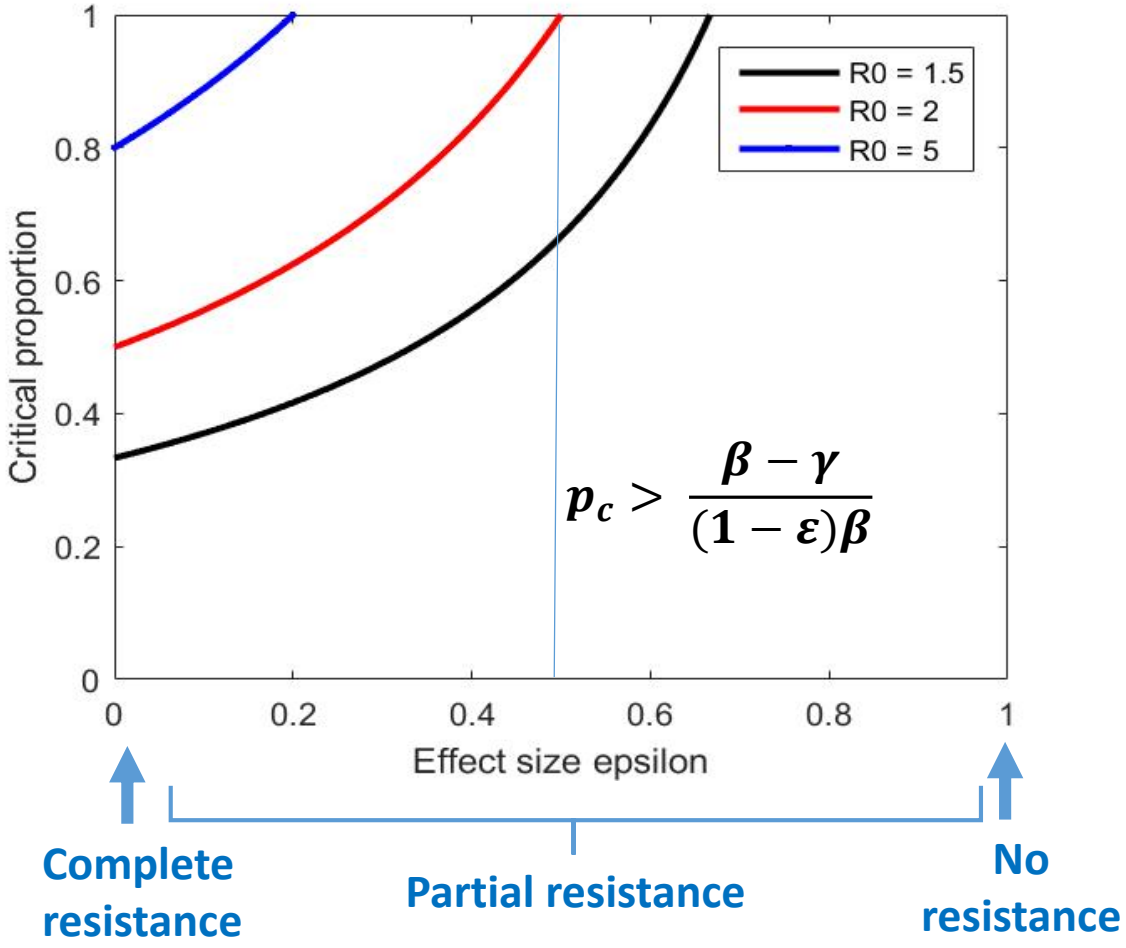
Will there be an epidemic?

- Similar approach as for the homogeneous SIR model:
- Epidemic will not occur if $R_0 < 1$ (or $\frac{dI}{dt} \leq 0$)
- One can show (see tutorial!) that this is the case iff:

the critical proportion $\boldsymbol{p_c}$ of individuals with low susceptibility exceeds the threshold

$$\boldsymbol{p_c > \frac{\beta - \gamma}{(1-\varepsilon)\beta}}$$

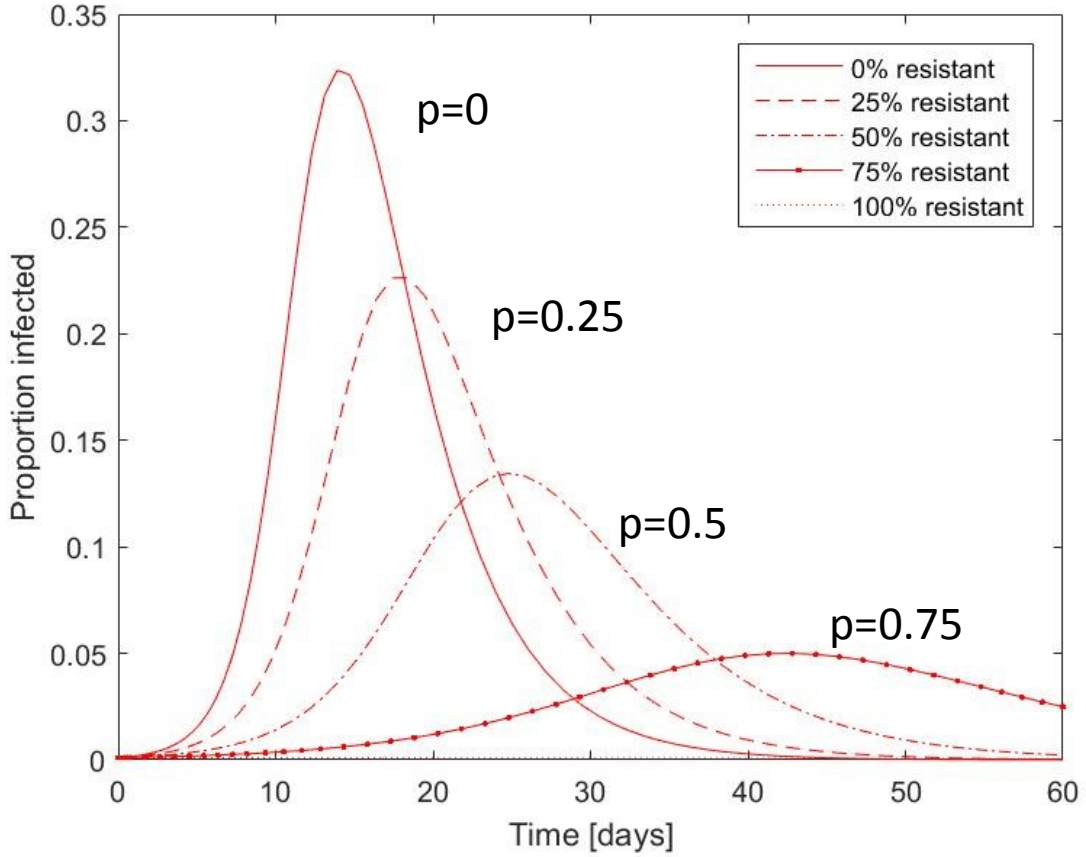
Critical proportion to achieve R_0<1 depends on the level of resistance ε as well as on epidemiological parameters



- More virulent diseases (higher R_0*) require higher proportion of individuals with partial resistance
- The critical proportion increases non-linearly with effect size ε
- Partial resistance may not be sufficient to eliminate the infection
- How does this inform strategies for disease control (e.g. vaccination or genetic selection)?

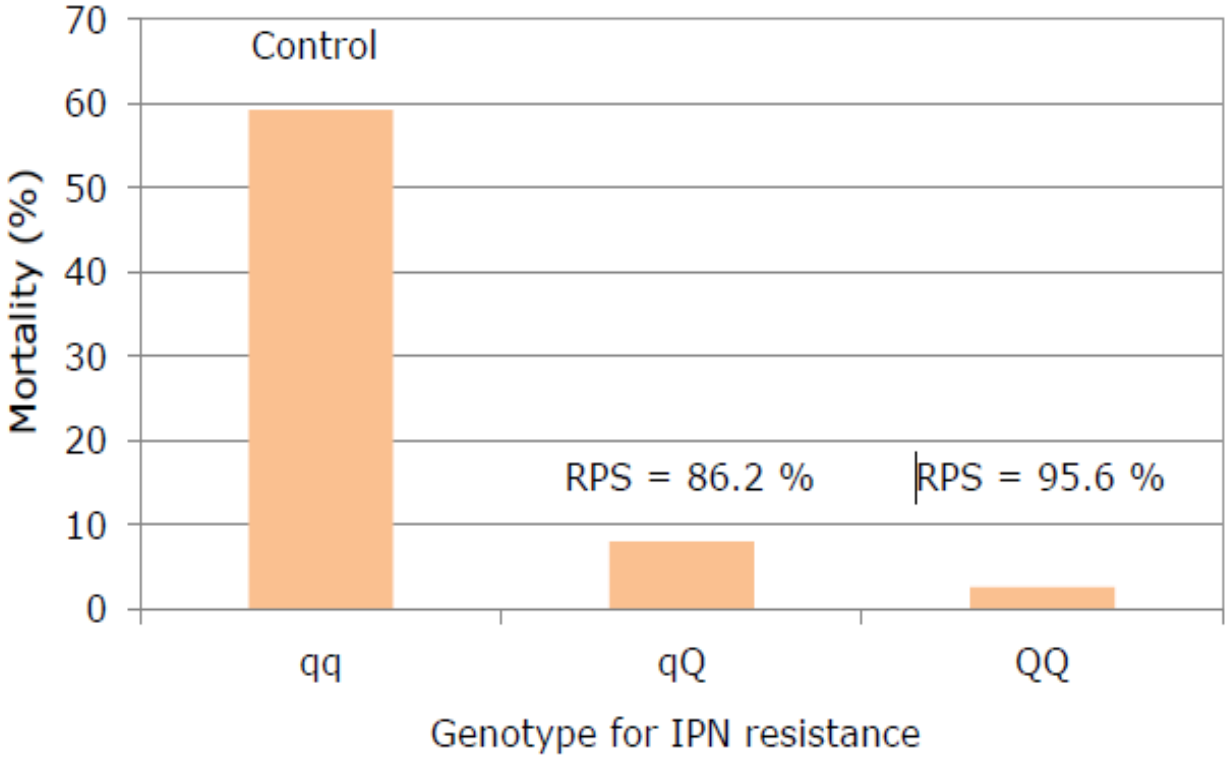
* R_0 in homogeneous population with $R_0 = \beta/\gamma$

Impact of population structure on epidemiological characteristics



- Higher proportion p of individuals with low susceptibility implies weaker, but more prolonged epidemics
- See tutorial for more in depth exploration of dynamic properties of this model

Example: IPN in Atlantic salmon



- Resistance largely controlled by a single gene (Houston et al., 2009; Moen et al. 2009)
- Presence of Q allele confers high resistance
  - Two genotypes:
    S_- (QQ and qQ) and S_+ (qq)
- Disease control through dissemination of salmon eggs with higher resistance in progress

Source: Aquagen newsletter 2014

IPN questions of interest

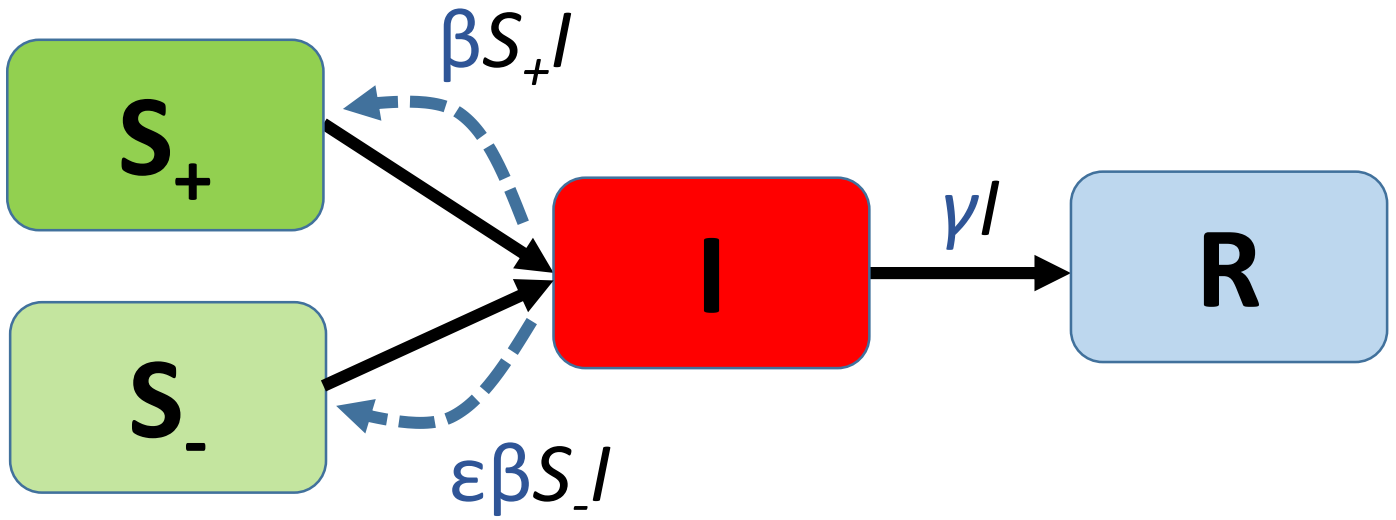
Assuming that the Q allele confers differences in susceptibility only:

What proportion of resistant individuals is required to prevent an IPN outbreak?

Solution: critical proportion of resistant fish for preventing IPN outbreak:

Assuming that the Q allele confers differences in susceptibility only:

What proportion of resistant individuals is required to prevent an IPN outbreak?

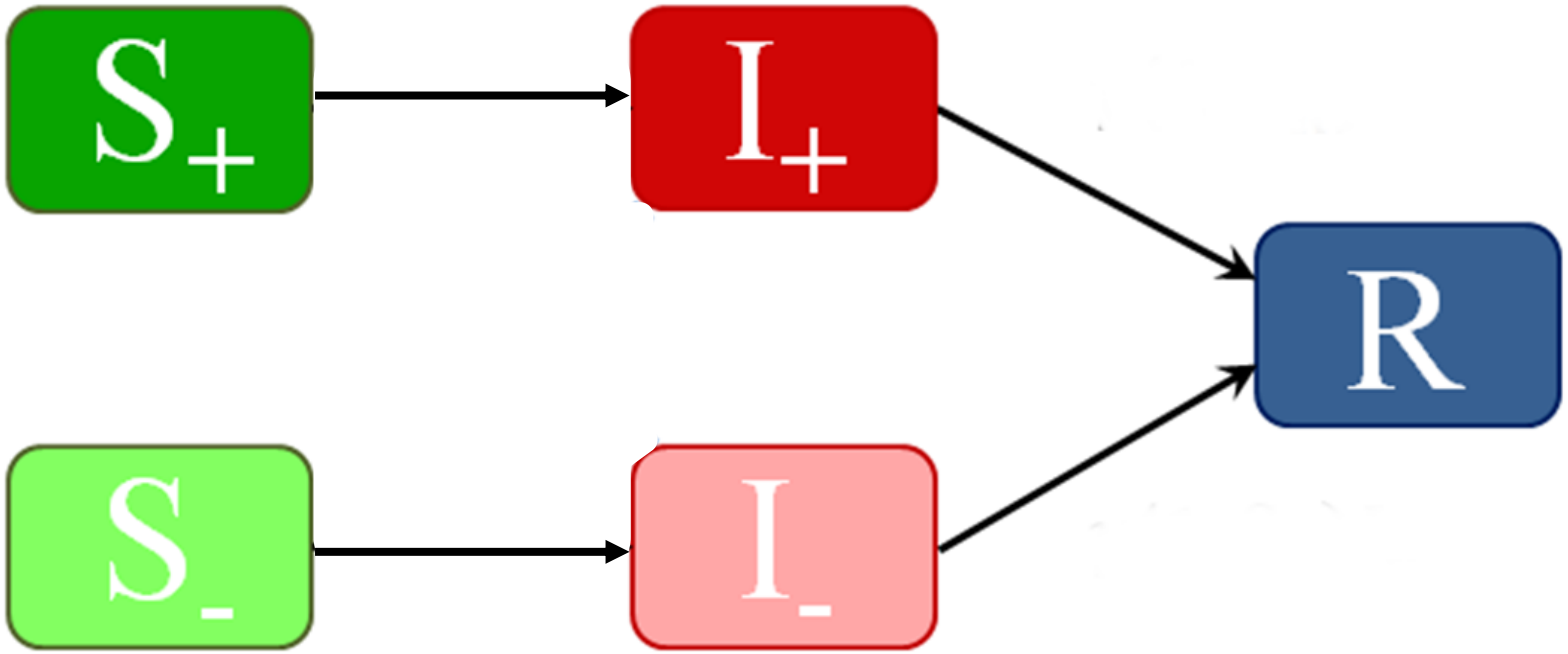


- Infer estimates for ε, β, γ from data
- Apply $p_c > \frac{\beta - \gamma}{(1-\varepsilon)\beta}$

IPN questions of interest

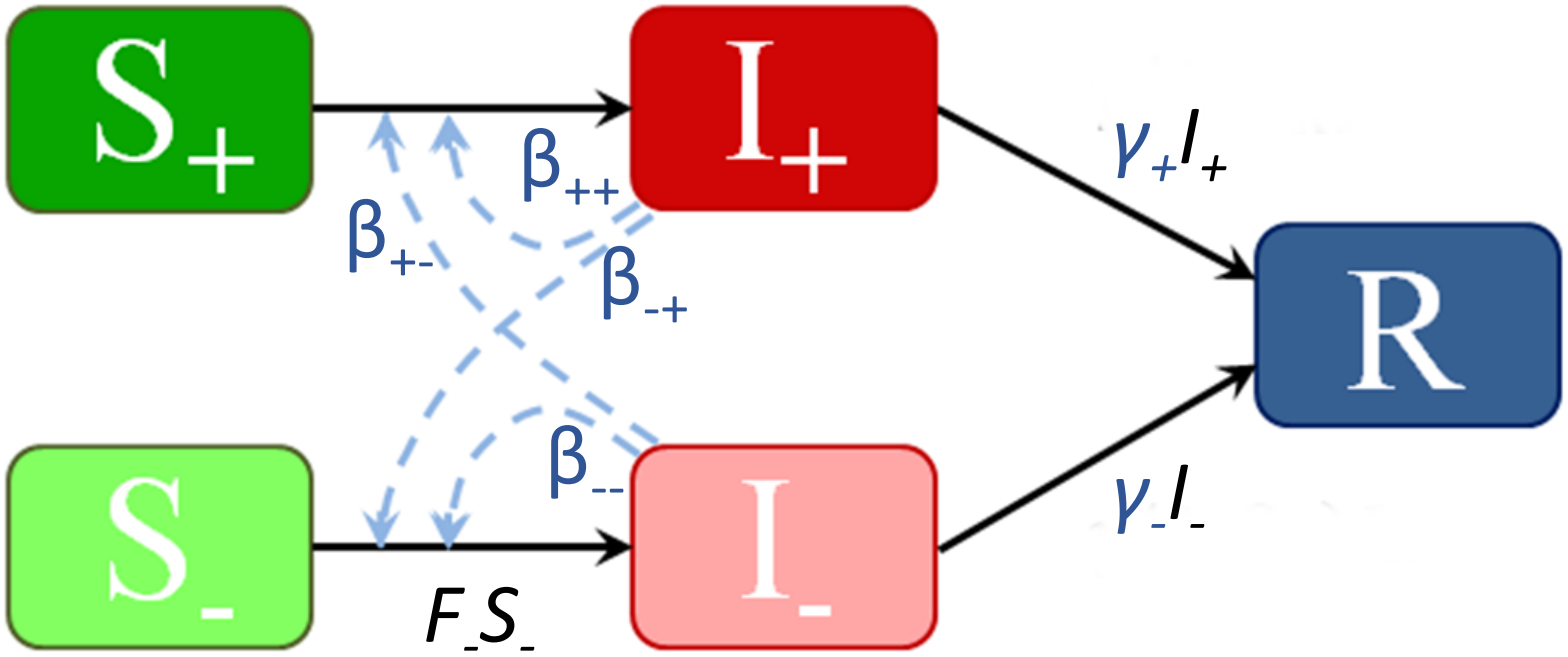
- Are resistant fish also less infectious?
- If so, how does this affect the critical proportion of resistant individuals required to prevent an outbreak?

A more general genetic epidemiological SIR model

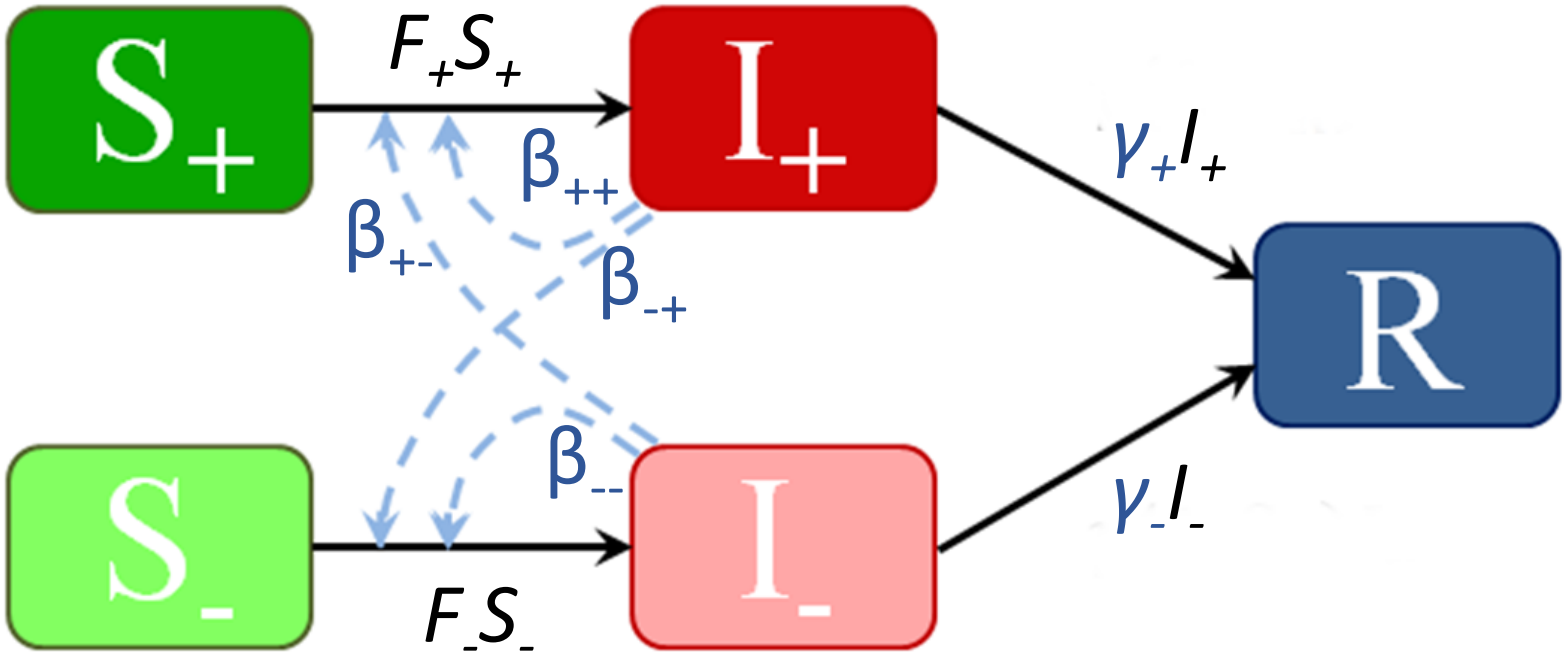


Susceptible Infected Dead

A more general genetic epidemiological SIR model



A more general genetic epidemiological SIR model



Force of infection:

$$F_+ = (\beta_{++} I_+ + \beta_{+-} I_-)/\mathrm{N}$$

$$F_- = (\beta_{-+} I_+ + \beta_{--} I_-)/\mathrm{N}$$

Can you write the model equations?

- See tutorial

The Who Aquires Infection From Whom (WAIFW) matrix

Instead of one transmission parameter β we now get a matrix:

$$\boldsymbol{\beta} = \begin{pmatrix} \beta_{++} & \beta_{+-} \\ \beta_{-+} & \beta_{--} \end{pmatrix}$$

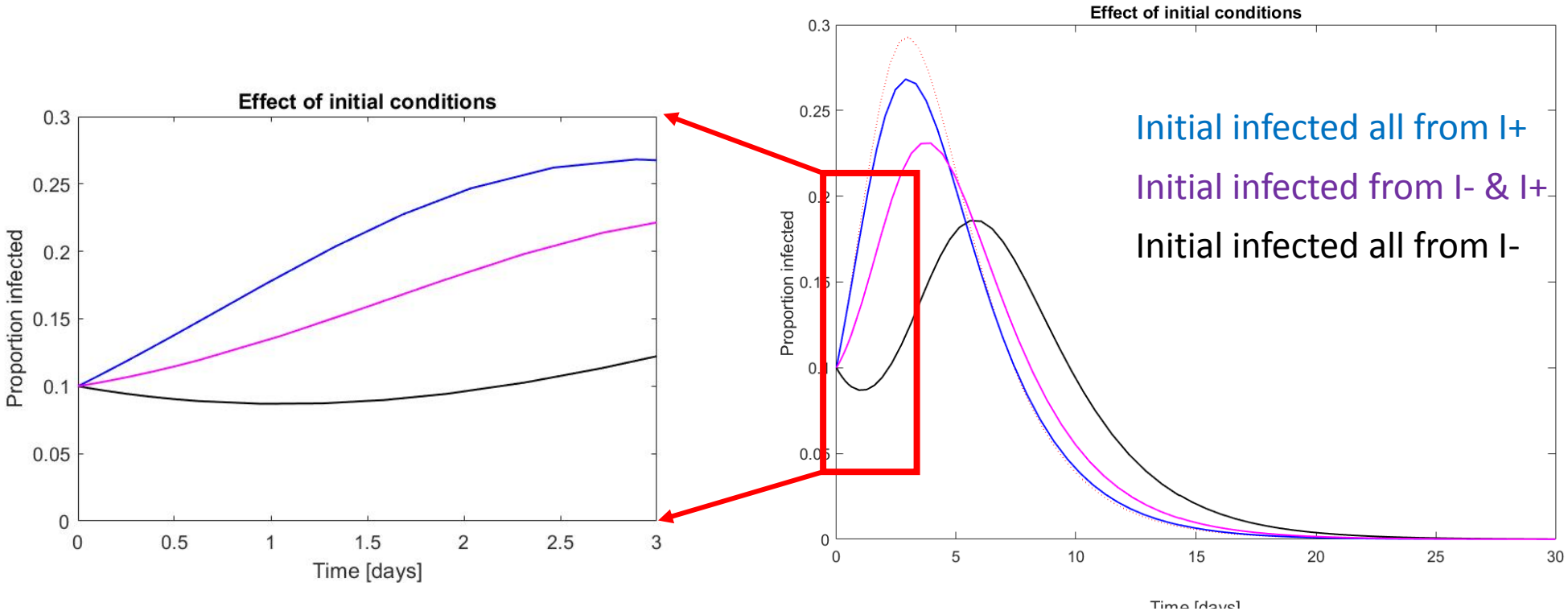
where β_{ij} means infection from individual j to individual i

What do we know about the transmission parameters β in the case of IPN if

- Reduced susceptibility confers no difference in infectivity?
- Reduced susceptibility allele confers higher / lower infectivity?

See tutorial!

Initial dynamics: Effect of initial conditions

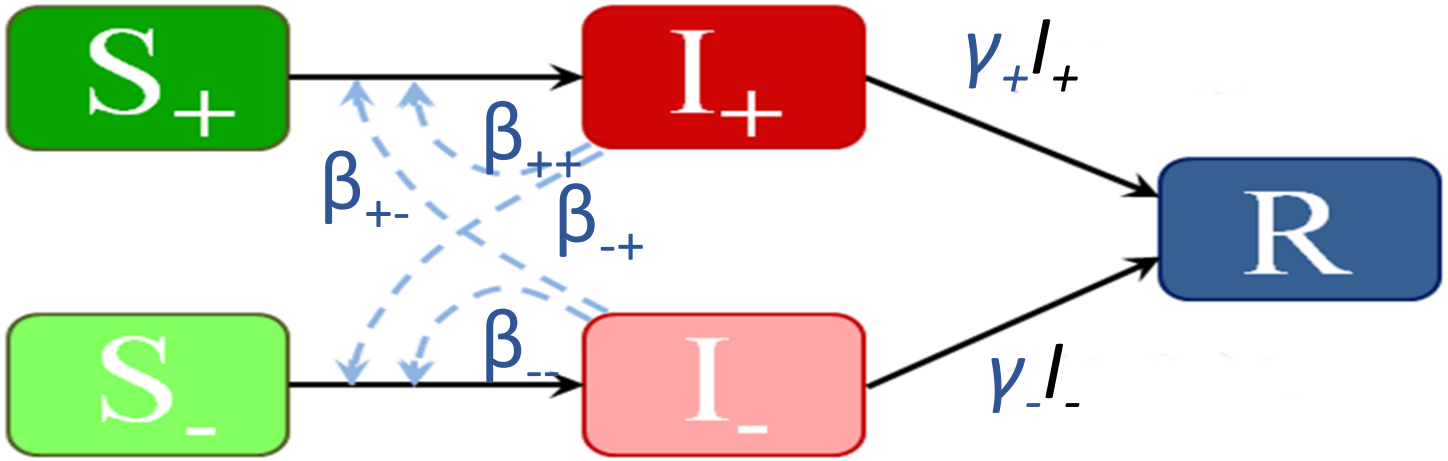


- The early dynamics depend on who is seeding the infection
- The effect of the initial seed fades over time
- R_0 can't be associated with the early stage of the epidemics

The basic reproductive ratio R_0

Definition: Basic reproductive ratio R_0 for heterogeneous populations
*The average number of secondary cases arising from an **average** infected individual in an entirely susceptible population, **once initial transients have decayed**.*

- Threshold characteristics of R_0 still valid, i.e. no epidemic if $R_0<1$
- How to calculate this number?



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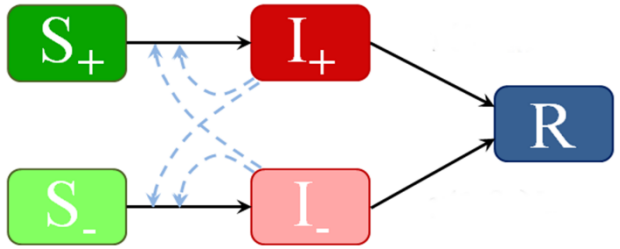


Definition: Basic reproductive ratio R_0 for heterogeneous populations

*The average number of secondary cases arising from an **average** infected individual in an entirely susceptible population, **once initial transients have decayed**.*

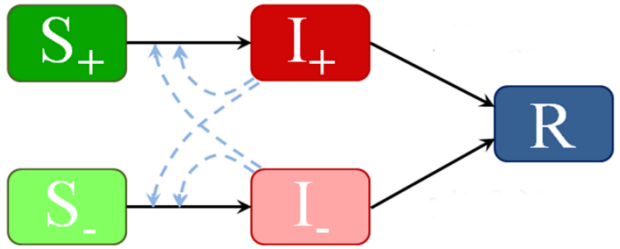
- Assume a susceptible population in which a proportion p is from category S_- and (1-p) from category S_+
- Expected number of secondary cases **arising from from I_+** category:

$$R_0^+ = (\beta_{++}(1-p) + \beta_{-+}\, p)/\gamma_+$$

- Expected number of secondary cases **arising from I_-** category:

$$R_0^- = (\beta_{+-}(1-p) + \beta_{--}\, p)/\gamma_-$$

The next generation matrix M and R_0



Definition: Basic reproductive ratio R_0 for heterogeneous populations

*The average number of secondary cases arising from an **average** infected individual in an entirely susceptible population, **once initial transients have decayed**.*

- The entries of the **Next Generation Matrix M**, i.e. m_{ij} refer to the number of secondary type i cases produced by an infected individual of type j

$$\begin{array}{c} \\ S_+ \\ S_- \end{array} \begin{array}{c} \begin{array}{cc} I_+ & I_- \end{array} \\ \begin{pmatrix} \frac{\beta_{++}(1-p)}{\gamma_+} & \frac{\beta_{+-}(1-p)}{\gamma_-} \\ \frac{\beta_{-+}p}{\gamma_+} & \frac{\beta_{--}p}{\gamma_-} \end{pmatrix} \end{array}$$

- R_0 is the largest eigenvalue of M
- R_0 is bounded by R_0^+ and R_0^-

Calculating Eigenvalues

For a 2×2 matrix: $\begin{bmatrix} a & b \\ c & d \end{bmatrix}$:

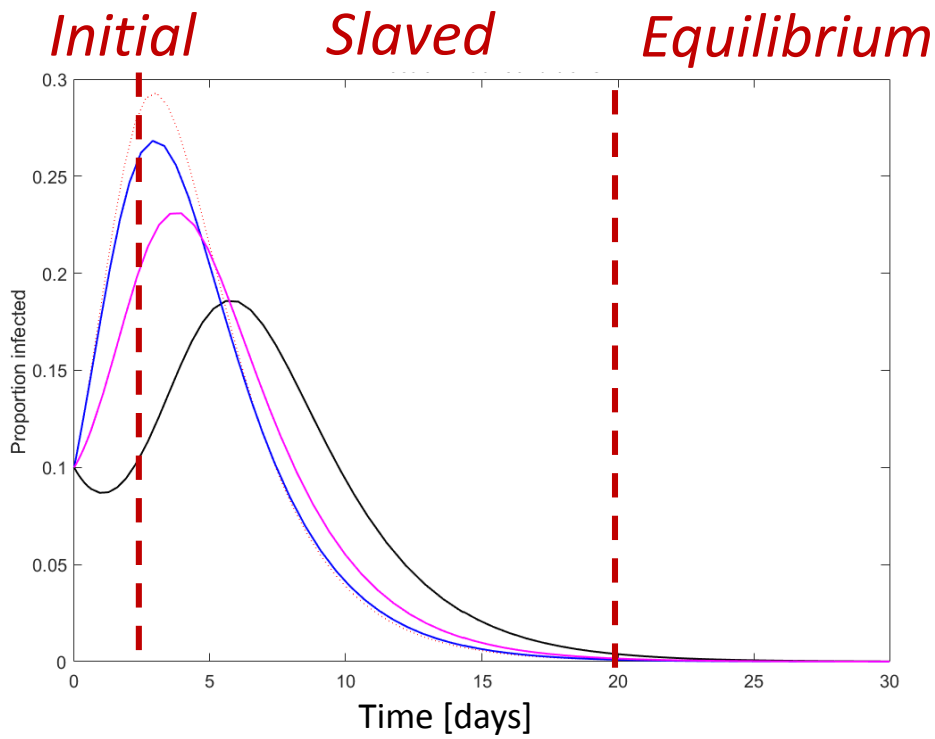
The largest eigenvalue is

$$R_0 = \frac{a + d + \sqrt{(a+d)^2 - 4(ad - bc)}}{2a}$$

It can be calculated in R using *eigen(M)*

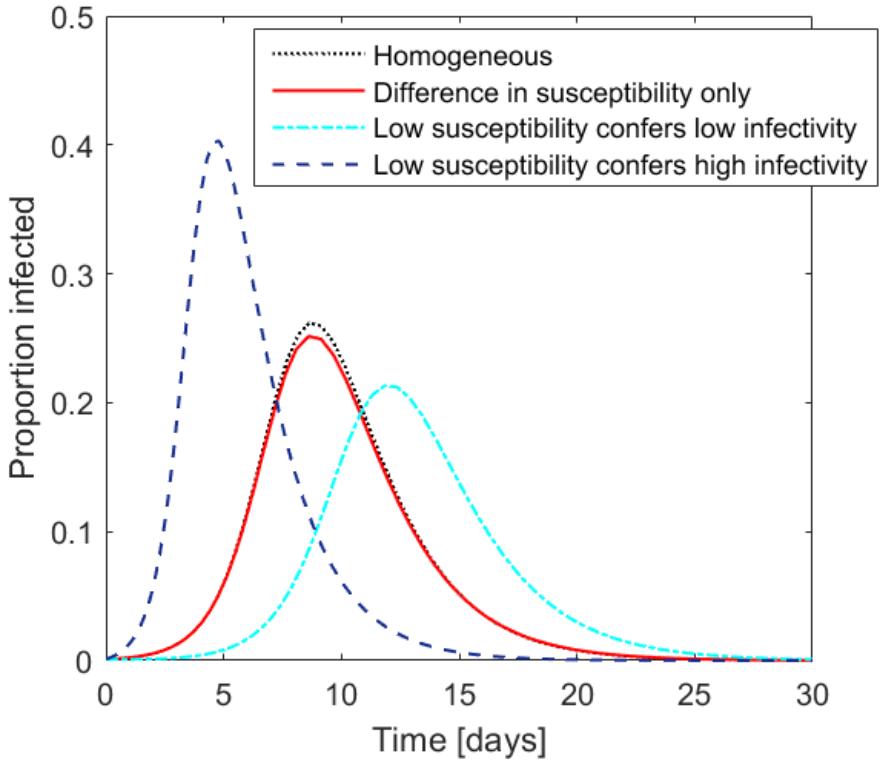
Dynamic properties

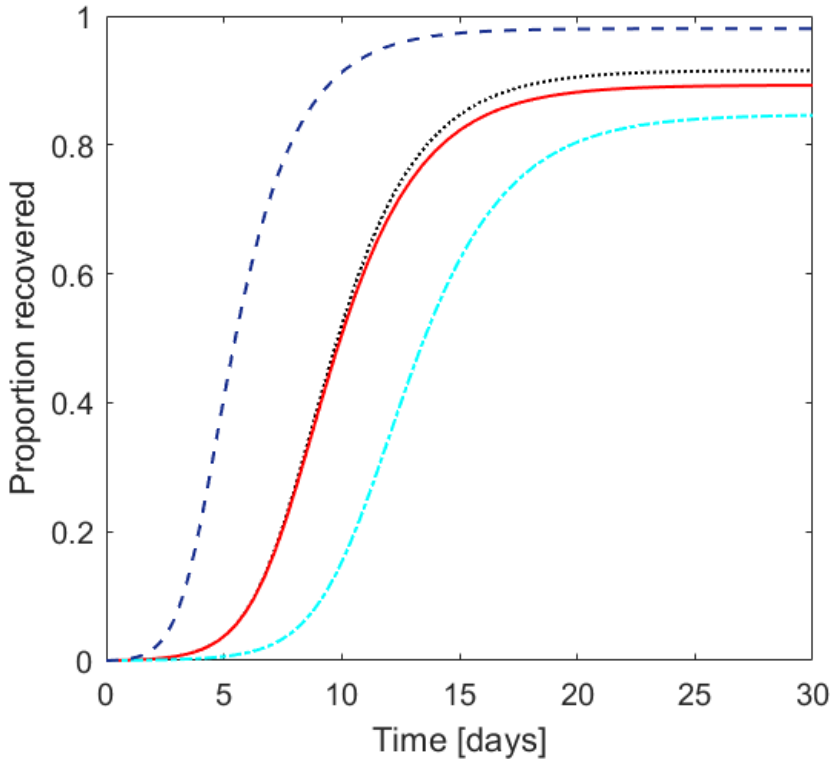
- Epidemics characterised by 3 phases:
  1. Initial phase: depends on who seeds the epidemic
  2. ‘Slaved’ phase: depends on R_0
  3. Equilibrium phase: Infection always dies out, but prop. of infected varies



Dynamic properties

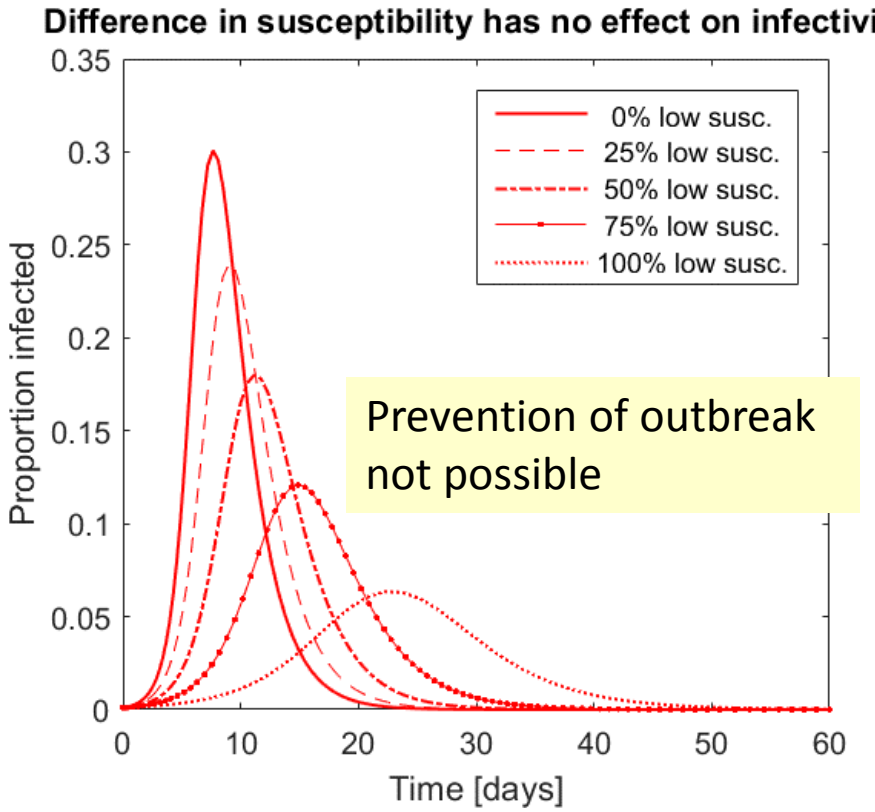
- Similar profile shapes as for homogeneous populations
- But different epidemiological characteristics (peak prevalence, total prop. infected etc.)
  - See tutorial for in depth analysis

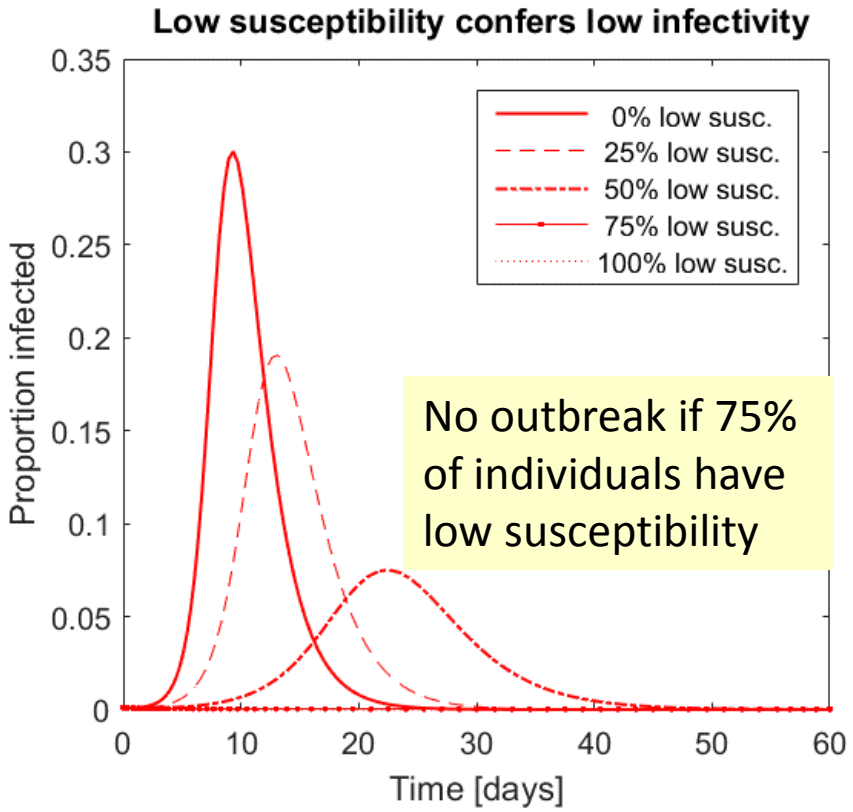




Critical proportion of individuals required to achieve $R_0<1$

- Depends on the relationship between susceptibility & infectivity
  - See tutorial for in depth analysis





Adding complexity

- The model can be easily extended to more discrete classes, e.g.
  - more genotypes (AA, aA, aa) (See Doeschl-Wilson et al. 2018)
  - Susceptibility and infectivity controlled by different genes (see e.g. Anche et al. 2015, Biemans et al. 2017)
  - More sources of heterogeneity (recovery rate)
- For discrete classes the theory is well established, although the analysis (e.g. calculating R_0, equilibria, etc.) becomes more difficult with increasing complexity

General properties of epidemiological models in heterogeneous populations with discrete structures (e.g. genoytpes)

- The single transmission parameter β is replaced by a WAIFW matrix
- R_0 is the largest Eigenvalue of the next generation matrix
  - Derived in Diekmann et al. 1990; Hesterbeek 2002
- R_0 in heterogeneous populations is often larger than if the structures were ignored (i.e. all individuals have same average transmission rate)
  - Harder to eliminate the epidemic in highly heterogeneous populations!

But what if epidemiological parameters follow a continuous distribution?

- **Trait primarily controlled by single gene or locus (Major gene model)**
  - E.g. gene affecting binding protein
  - **Discrete genotypes**
- Trait controlled by many genes, each with a small effect (Polygenic model)
  - Majority of cases
  - Continuous genotypes
- Different genetic architectures lend themselves to different modelling approaches

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- **Trait controlled by many genes, each with a small effect (Polygenic model)**
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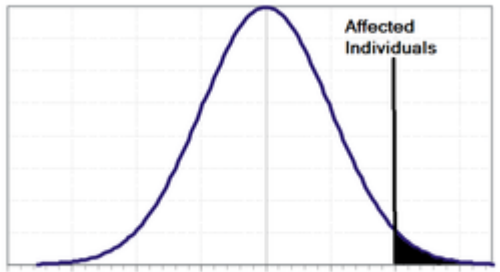
  - **Different modelling approach required!**
    - **See next lecture**



Summary

- Epidemic models including heterogeneity are more realistic
  - Ignoring heterogeneity can produce wrong predictions
- Heterogeneity is relatively easy to implement if represented by discrete classes
  - Individual parameters are replaced by matrices
- The basic reproductive number R_0 is differently defined and calculated for models of heterogeneous populations
  - R_0 found by an eigenvalue approach
- Heterogeneity can be harnessed by control strategies
  - E.g. mixing different types of individuals, targeted treatment, genetic selection, …

References

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