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Modelling in Vet Vaccine Response

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Outline

- A brief introduction to mathematical modelling
  - Basic principles
  - What they can / can't do
- Modelling vaccine effectiveness in the field
  - Modelling epidemics in non-vaccinated & vaccinated populations: key concepts & insights
- Case study: Foot & Mouth Disease

What is a mathematical model?

Model (Definition):

- A representation of a system that allows for
  - **investigation** of the properties of the system
  - and, in some cases, **prediction** of future outcomes.
- Always requires **simplification**

Mathematical model:

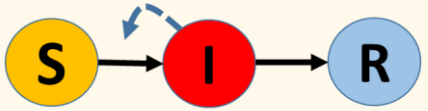
- Uses mathematical equations to describe a system

$$\frac{dS}{dt} = -\beta S I$$

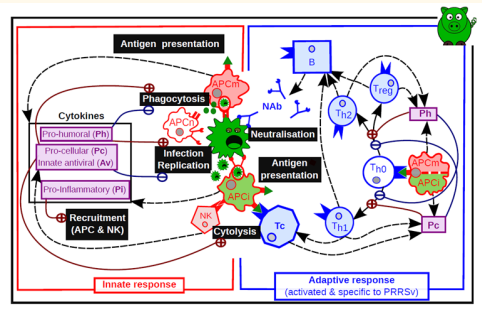
$$\frac{dI}{dt} = \beta S I - \gamma I$$

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

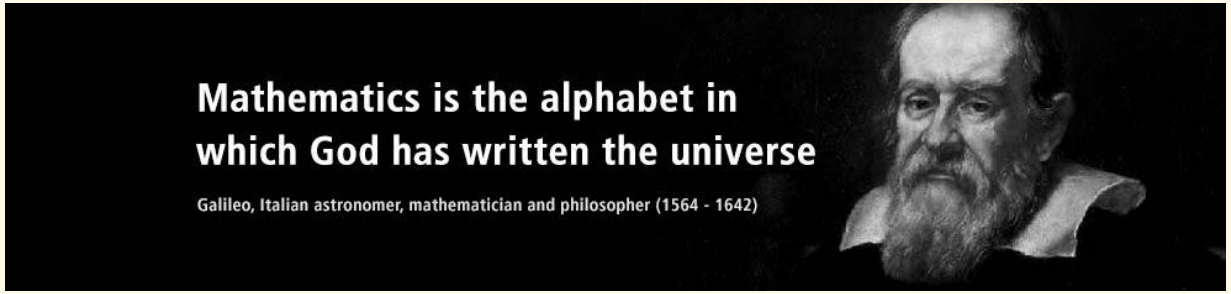
Why do we need (mathematical) models?



- They provide a framework for conceptualizing our ideas about the behaviour of a particular system
- They allow us to find structure in complex systems & to investigate how different components (e.g. host – pathogen) interact
- Models can play an important role in informing policies:
  - By providing understanding about key components and their interactions for a complex phenomenon
  - By predicting the future



Why mathematics?



- Mathematics is a precise language
  - Forces us to formulate concrete ideas and assumptions in an unambiguous way
- Mathematics is a concise language
  - One equation says more than 1000 words
- Mathematics is a universal language
  - Same mathematical techniques can be applied over a range of scales
- Mathematics is an old but still trendy language
  - The rich toolbox created by mathematicians over centuries is available at our disposal
- Mathematics is the language that computers understand best

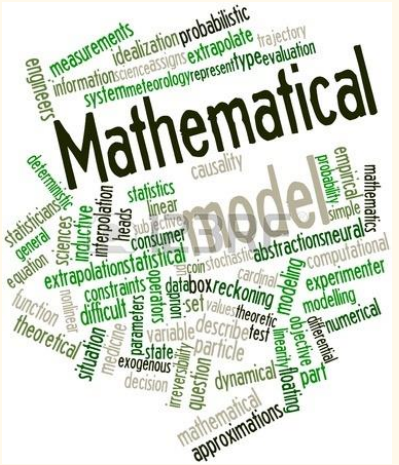
Mathematical models are not bound by physical constraints

- Mathematical equations can handle all types of interactions between different system components
- Powerful tool to explore ‘what if scenarios’
- Extremely useful in the context of infectious disease where experimental constraints are strong

Limitations of mathematical models

1. Lack of quantifiable knowledge
   - Models that encompass mechanisms (e.g. infection process) require quantitative understanding of these mechanisms in order to make reliable predictions
2. Lack of available data / methods for estimating model parameters
   - E.g. how to estimate e.g. transmission rate from field data?
   - Much improvement to be expected over the next years due to recent advances in statistical inference and data explosion
3. Inherent stochasticity of the biological system
   - Infection is a stochastic process
   - It is impossible to make accurate predictions for infection spread on the individual herd level

Classification of mathematical models

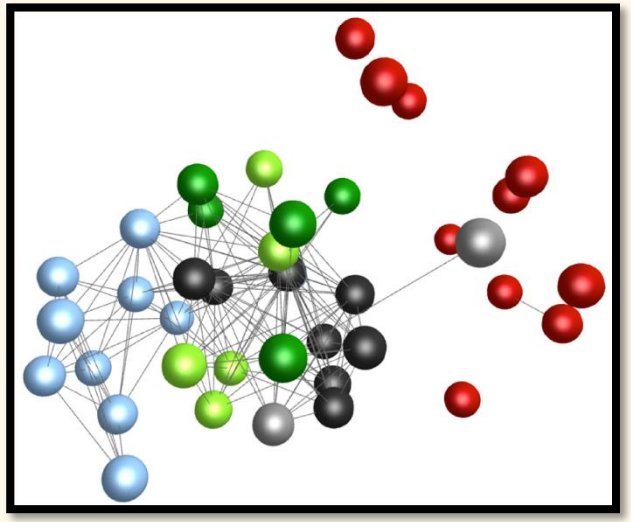


- Mathematical models come in all shapes & sizes
- Classifying them into broad categories can tell you much about their purpose & scope and often require different mathematical techniques
- Typical distinctions:
  - Empirical vs mechanistic
  - Deterministic vs. stochastic
  - Systems vs molecular model
  - Static vs dynamic
  - Linear vs non-linear
  - Discrete vs. continuous

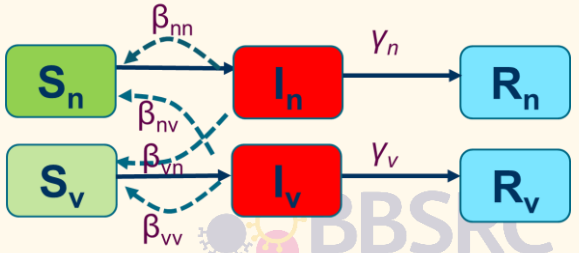
All mathematical models consist of variables and parameters, and a mathematical description of the relationship between them

Empirical vs mechanistic models

- Empirical Models
  - Data driven modelling approach
  - Starting point: data obtained from empirical studies
  - Aim: to determine patterns & relationships between data
  - Require no prior knowledge of the underlying biology
  - Tools: statistics, bio-informatics, machine / deep learning

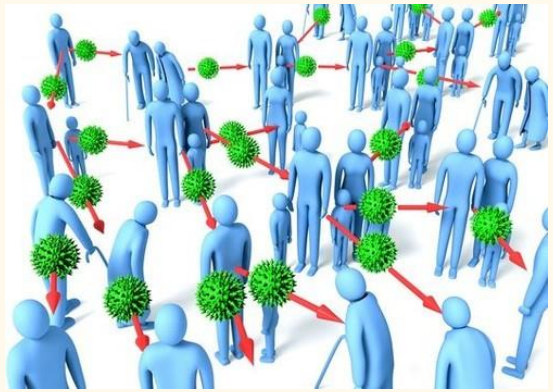


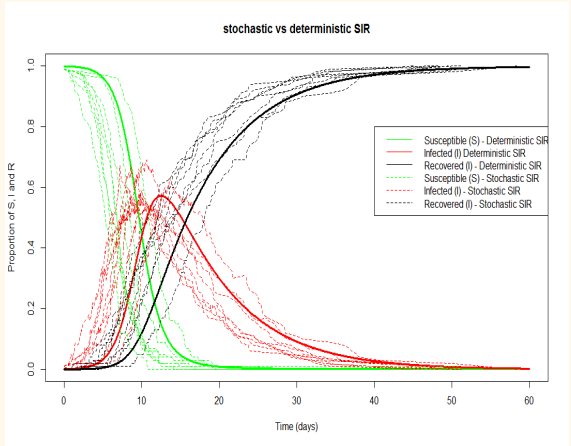
- Mechanistic Models (also called Process Based Models):
  - Hypothesis driven modelling approach
  - Starting point: specific phenomena of interest – observed from data
  - Aim: to provide understanding for underlying mechanisms; to predict
  - Require prior understanding of system
  - Data are used to parameterise / validate the model
  - Tools: mathematical dynamic systems theory, simulations



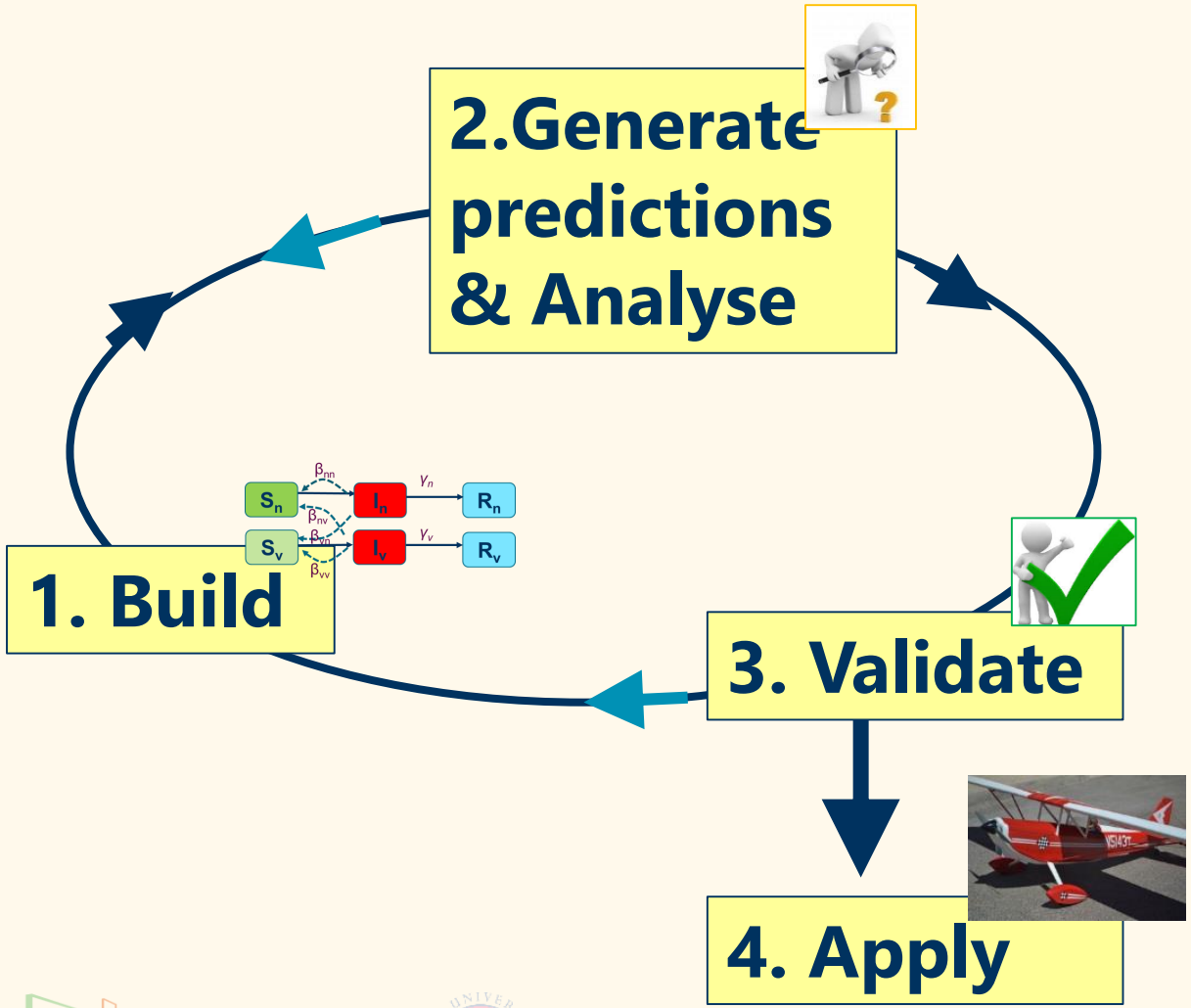
What is a simulation model?

- Simulation models are not specific types of mathematical models
- The term ‘simulation model’ refers to the process of implementing mathematical model, i.e. via computer simulations
- Simulation models usually simulate the process of data generation assuming the model was true
  - E.g. epidemiological simulation models
    - simulate disease spread in a population
    - Generate (simulated) data of disease prevalence over time





The 4 stages of modelling



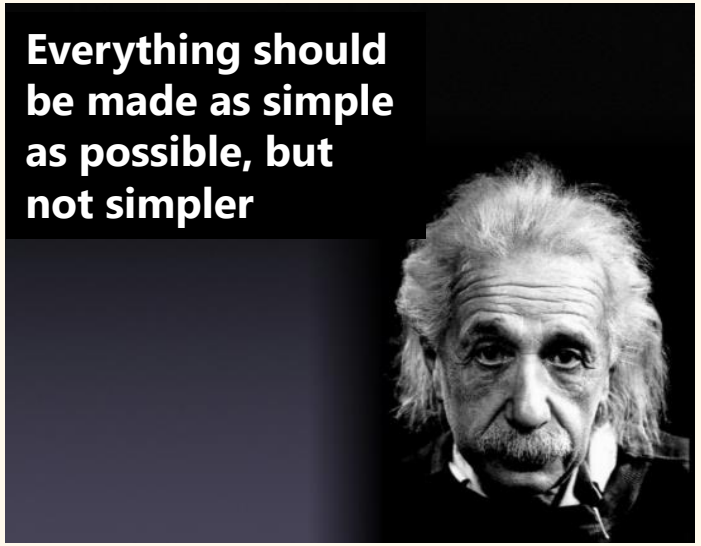
Similar process as for conducting a biological experiment:

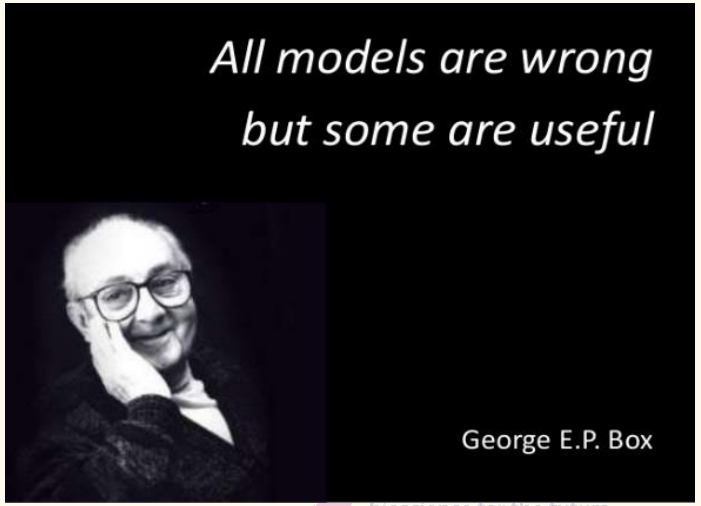
1. Design the experiment
2. Generate & analyse data
3. Validate findings
4. Apply results in practice

Modelling is more flexible but can be much more elaborate

What makes a good mathematical model?

- Fit for purpose
- Verifiable
- As simple as possible, but sufficiently complex to adequately represent the real system without obstructing understanding
- Appropriate balance between accuracy, transparency and flexibility

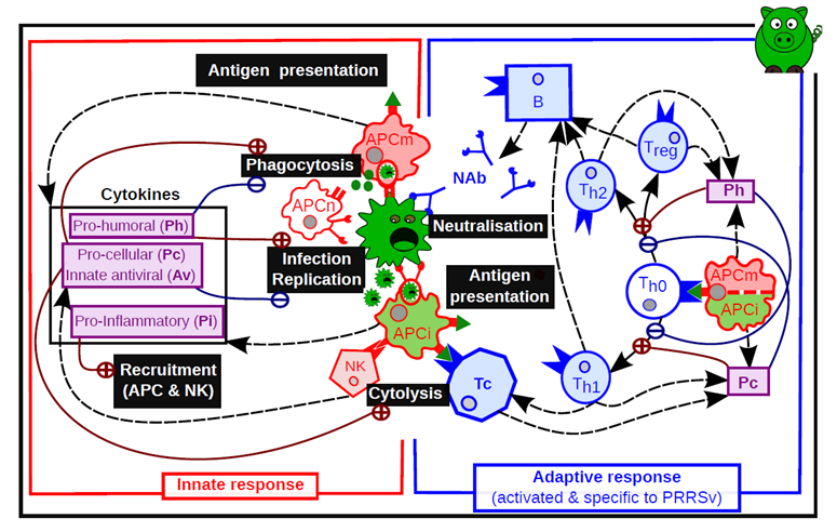




Modelling vaccine response

Modelling vaccine response

- **Host-pathogen interaction models**
  - Within host
  - Models immune response & impact of vaccines on it
  - Useful for identifying vaccine targets



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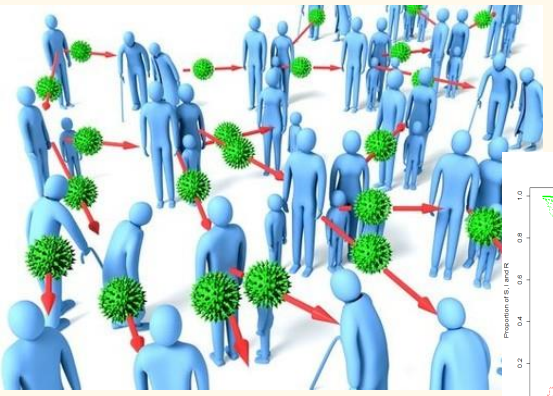
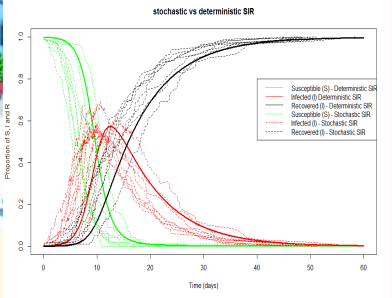
- **Epidemiological models**
  - Between hosts
  - Model spread of infection between individuals / herds & vaccine effectiveness
  - Useful for assessing vaccination strategies





Epidemiological models

What questions should the model answer?

- **What is the risk** of an outbreak to occur?
- **How severe** will it be?
  - What proportion of the population will become infected?
  - What proportion will die?
- **How long** will it last?
- Are **all individuals** at risk of becoming infected?
- **How far** will it spread?
- What **impact** does a particular **intervention** (e.g. vaccine) have on these characteristics?

The basic reproductive ratio R_0

- R_0 is a key epidemiological measure for how "infectious" a disease is

Definition: Basic reproductive ratio R_0
The average number of individuals that an infectious individual is expected to infect, assuming that the rest of the population is susceptible

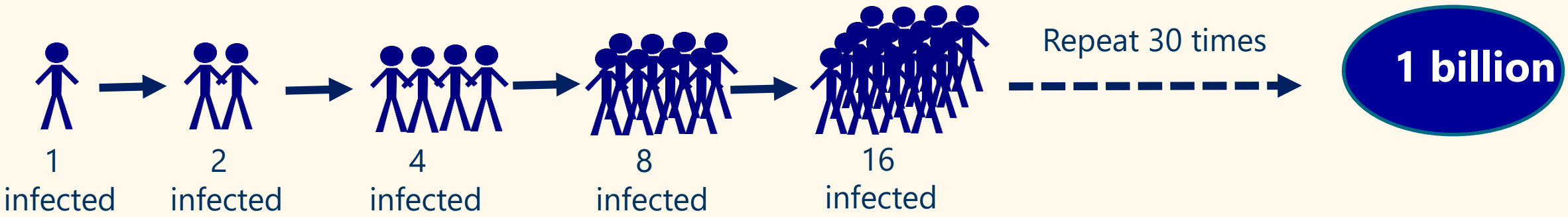
- $R_0 = 1$ is a threshold between epidemic / no epidemic
- $R_0 > 1$: Disease can invade
- $R_0 < 1$: Disease will die out

The basic reproductive ratio R_0

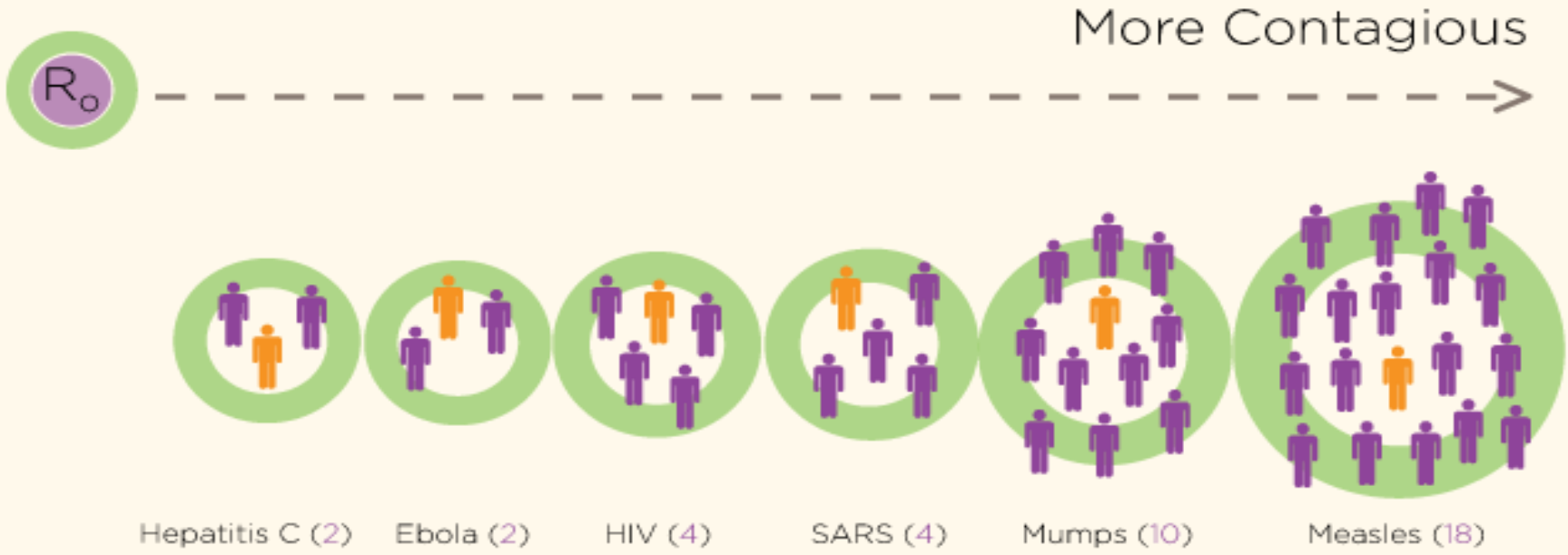
- R_0 is a key epidemiological measure for how "infectious" a disease is

In Contagion, Dr. Erin Mears (Kate Winslet) explains R0

- E.g. R_0 = 2 (Contagion)



Examples for R0 estimates for livestock diseases



BSE $0 \leq R_0 \leq 14$

Scrapie $1.6 \leq R_0 \leq 3.9$

Foot & Mouth Disease $1.6 \leq R_0 \leq 4.6$

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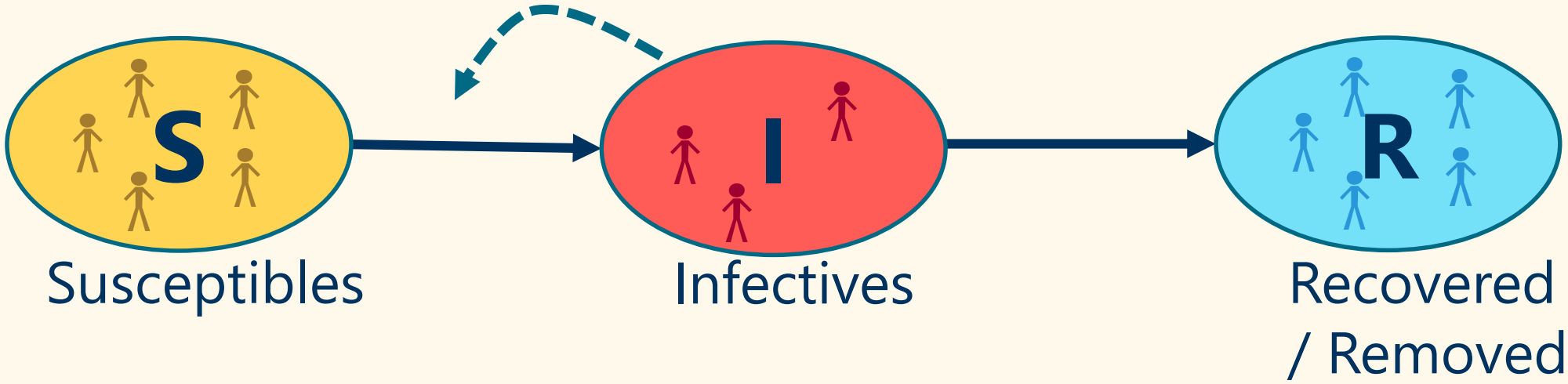
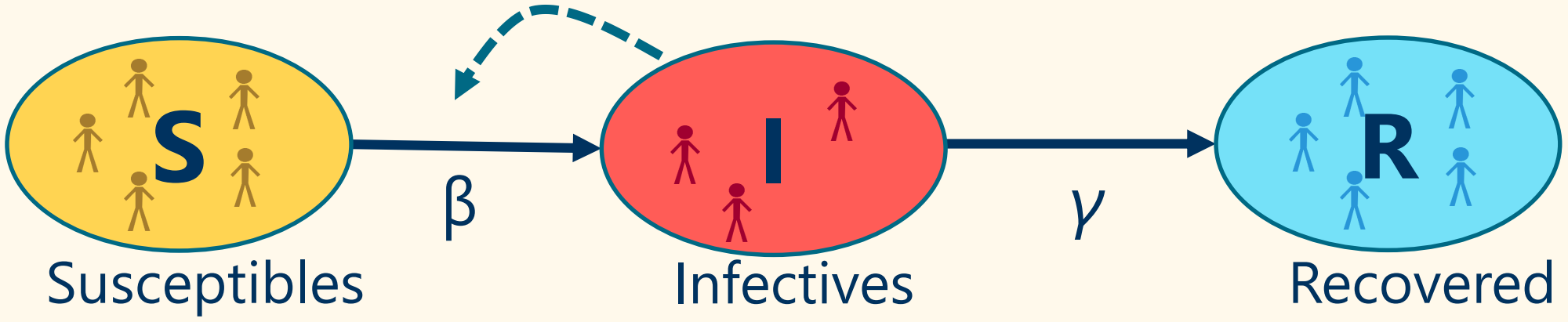
The compartmental SIR epidemic model without demography



- X = nr of susceptibles, Y = nr of infectives, Z = nr of recovered
- Describes acute infections transmitted by infected individuals;
- Pathogen causes illness for a period of time followed by death or life-long immunity

The compartmental SIR epidemic model without demography



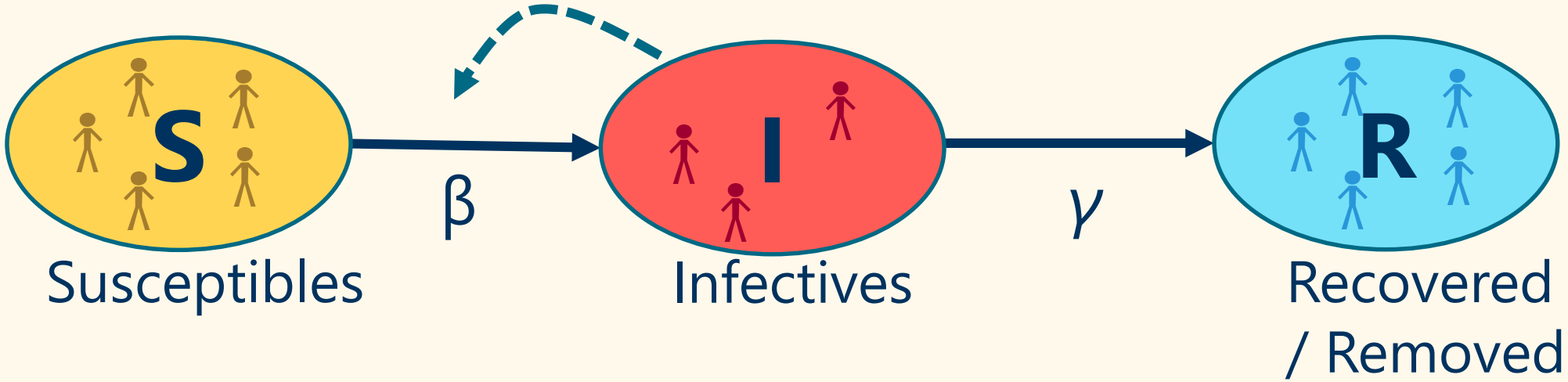
Transition between the states is defined by:

- The rate at which susceptible individuals get infected (S→I)
- The rate at which infected individuals recover (or die) (I→R)

This gives rise to 2 model parameters:

- The transmission term β (= contact rate x transmission probability)
- The recovery rate γ

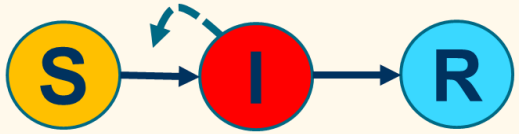
R_0 for the SIR epidemic model



- An average infected individual
  - is infectious for a period of 1/γ days
  - infects β susceptible individuals per day
  - will thus generate β x 1/γ new infections over its lifetime

$$R_0 = \frac{\beta}{\gamma}$$

The SIR model without demography



Model equations → Model inputs: → Model output:

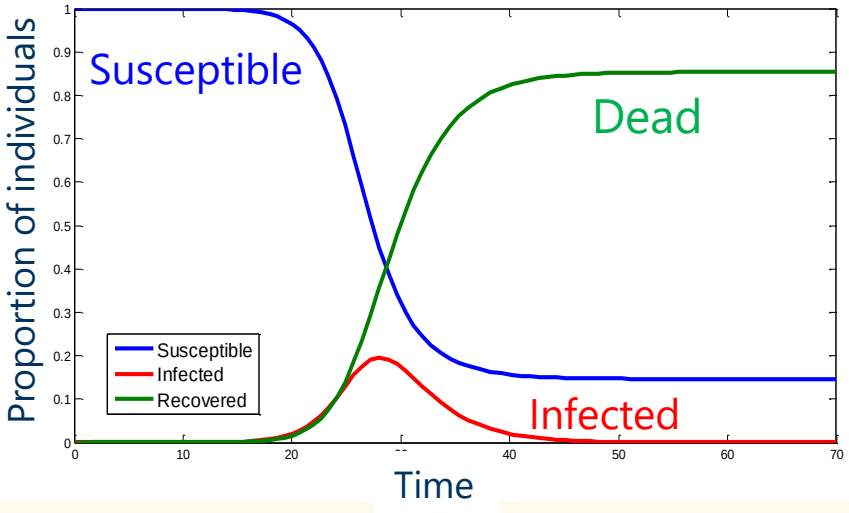
$$\frac{dS}{dt} = -\beta S I$$

$$\frac{dI}{dt} = \beta S I - \gamma I$$

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

- Values for β and γ
- Initial conditions

S(t=0), I(t=0), R(t=0)



The model cannot be solved analytically, i.e. no analytical expression for S(t), I(t), R(t)

- Need computer programme

The threshold phenomenon

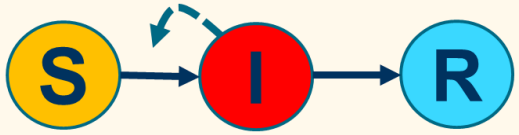
Imagine a scenario where I_0 infectious individuals are introduced into a susceptible population.

Will there be an epidemic?

One can prove mathematically that the infection can only invade if

- $R_0 > 1$
- The initial proportion of susceptibles S_0 exceeds $\gamma/\beta = 1/R_0$
  - Implications for successful vaccination: not everybody needs to be vaccinated

Epidemic burnout



Imagine a scenario where the infection can invade a population

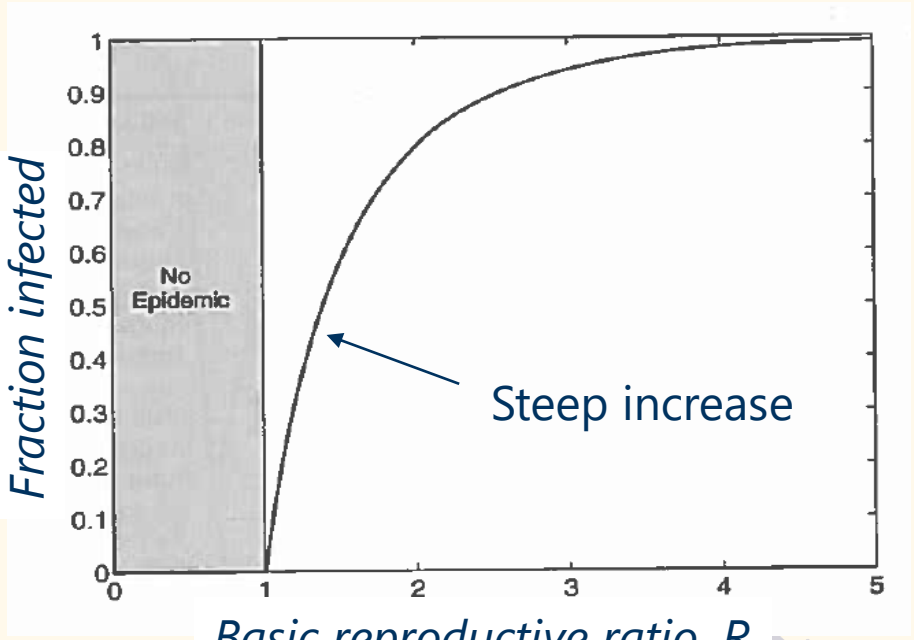
What happens in the long-term?

What proportion of the population will contract the infection?

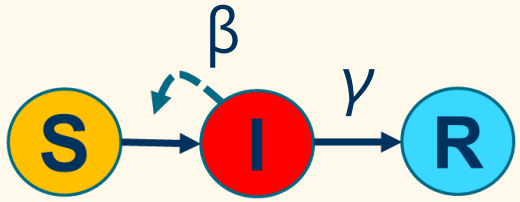
One can show mathematically:

- The epidemic eventually burns out (I = 0)
- Not all susceptibles will become infected
- There is a relationship between the **final size** $S(\infty)$ of the epidemic and R_0:

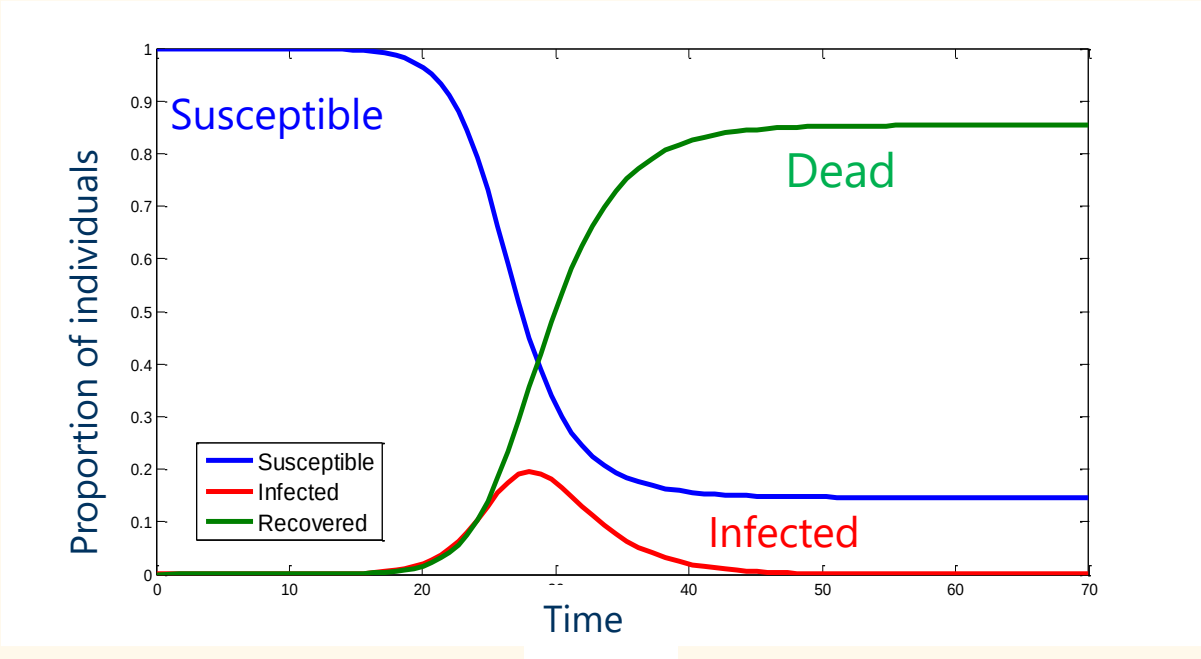
$$S(\infty) = S(0)e^{(S(\infty)-1)R_0}$$



Dynamic behaviour

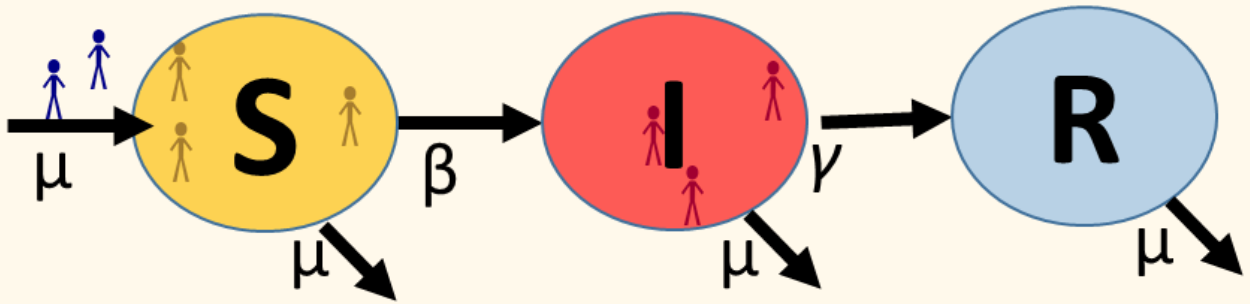


- All epidemic profiles have the same shape characteristics
- The specific profile shape depend on the model parameters and on the initial conditions S(0), I(0), R(0)



The SIR model with demography

- Assume the epidemic progresses at a slower time scale so that the assumption of a closed population is no longer valid
- Assume constant replenishment rate / removal rate = μ

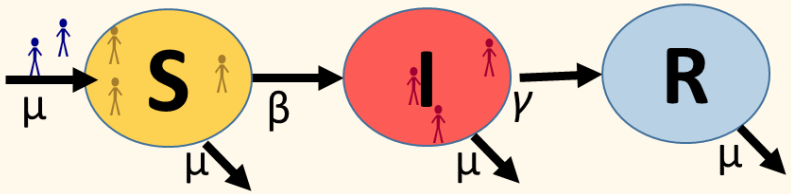


$$R_0 = \frac{\beta}{\gamma + \mu}$$

R_0 is smaller than for a closed population

➢ Epidemics are less likely

What will happen in the long-term?



2 potential outcomes:

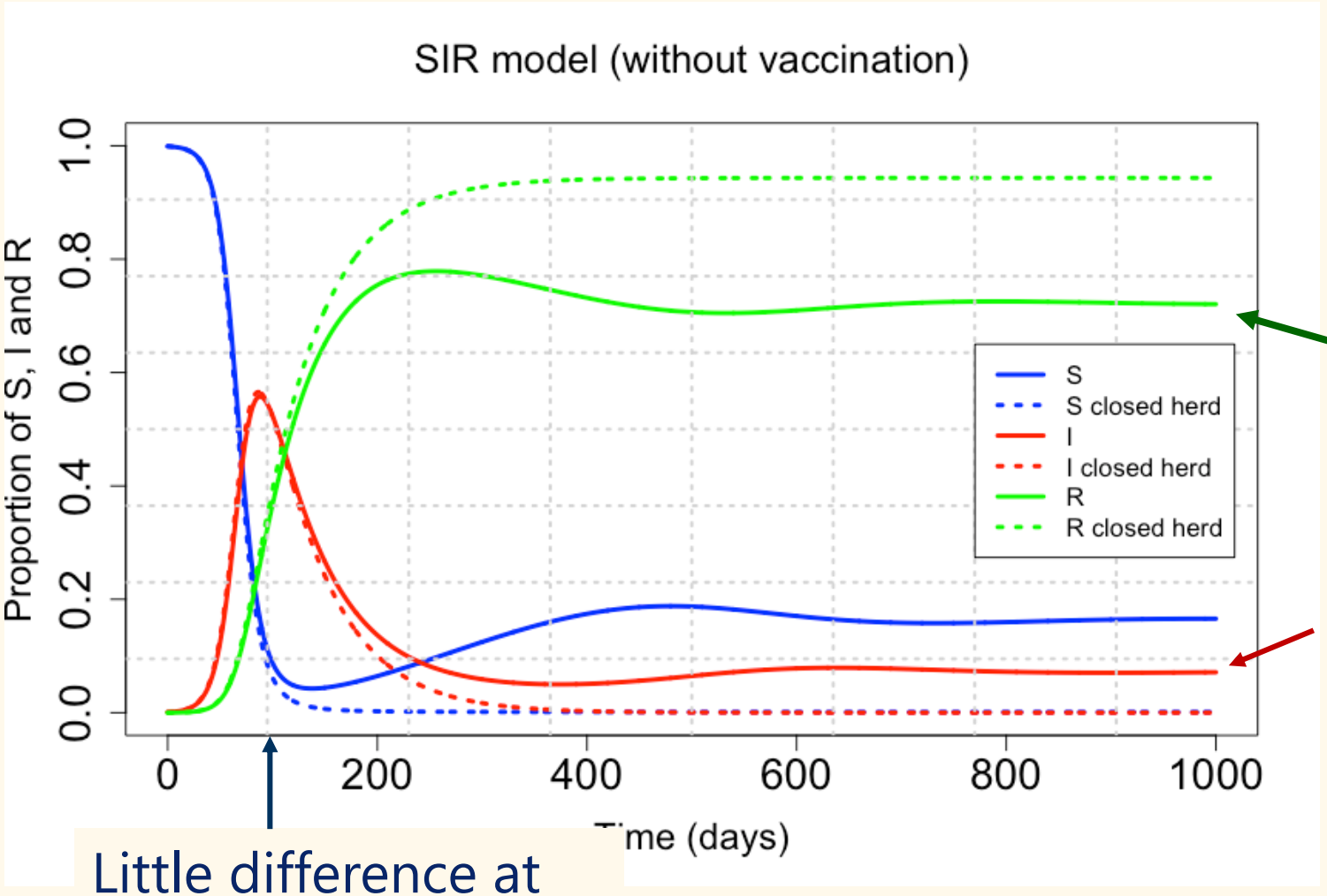
(S*, I*, R*) = (1, 0, 0) *Disease free*

$$(S^*, I^*, R^*) = \left(\frac{1}{R_0}, \frac{\mu}{\beta}(R_0 - 1), 1 - \frac{1}{R_0} - \frac{\mu}{\beta}(R_0 - 1)\right)$$ *Disease persists*

Which outcome will be achieved?

If an infection can invade (i.e. if $R_0 > 1$) , then the topping up of the susceptible pool causes the disease to persist

Dynamic behaviour: open vs closed herds

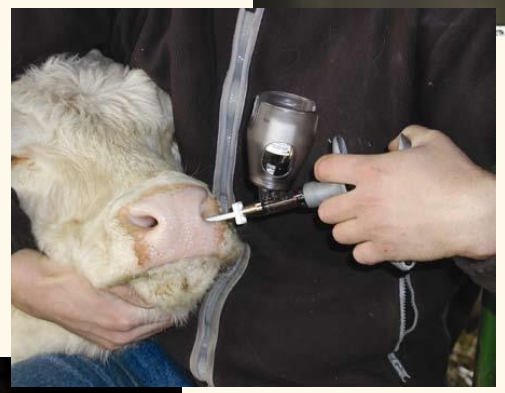


Lower seroprevalence in open herds

Disease persists

Little difference at the early stages of an outbreak

Modelling the impact of vaccination on epidemics



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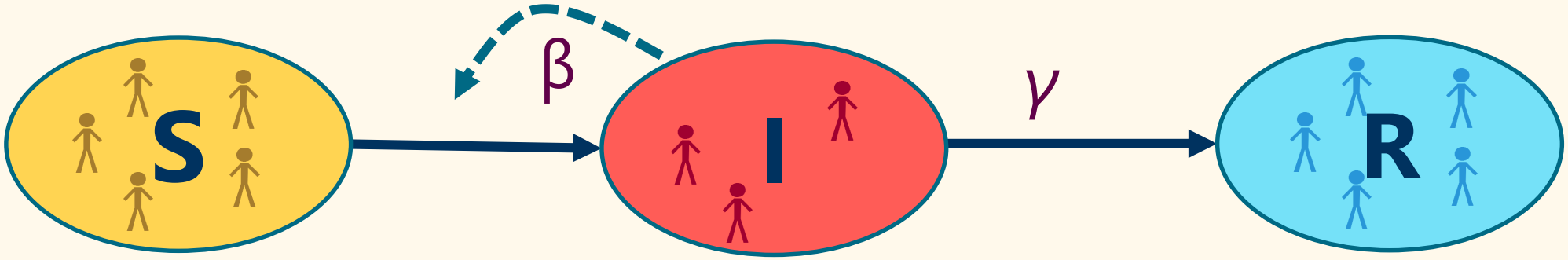
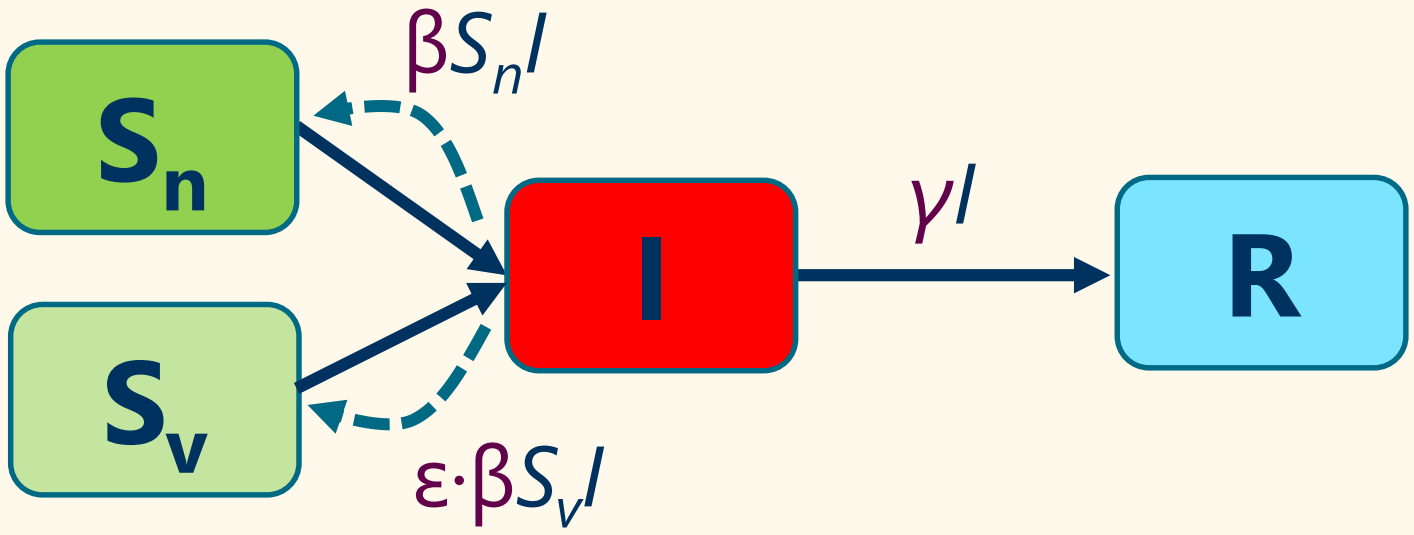
How may vaccines affect the epidemics?



- Vaccines may affect the individual
  - Risk of becoming infected (susceptibility): impact on β
  - Risk of transmitting the infection when infected (infectivity): impact on β
  - Duration of infectious period: 1/γ

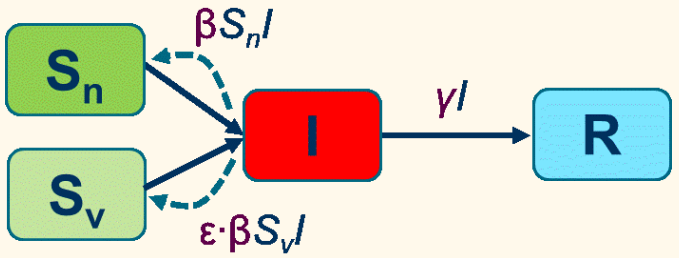
The most simple epidemiological vaccination model

- Assume a closed population
- A proportion **p** are vaccinated with a vaccine with efficacy **ε**



NB: This model could be valid even in the context of mass vaccination (e.g. if some individuals are 'immune' to the vaccine)

The threshold phenomenon in a vaccinated population



Assume I_0 infectives are introduced into this population

Will there be an epidemic?

Effective reproductive ratio in a vaccinated population:

$$R_0^v = p(1-\varepsilon)R_0 + (1-p)R_0 \leq R_0$$

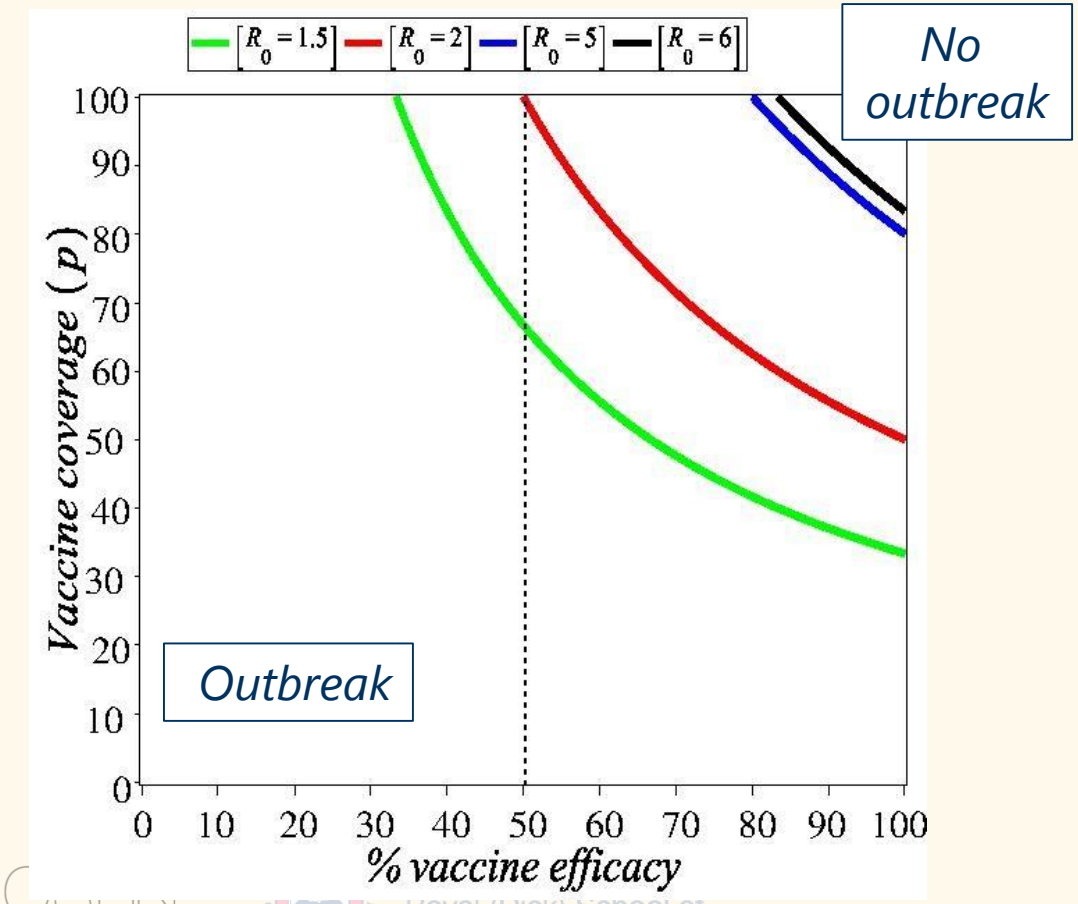
Epidemic will not occur if $R_0^v < 1$

This is the case if the proportion of vaccinated individuals p_c exceeds

$$p_c < \frac{1}{\varepsilon}\left(1 - \frac{1}{R_0}\right)$$

Interdependence between vaccine efficacy & vaccine coverage

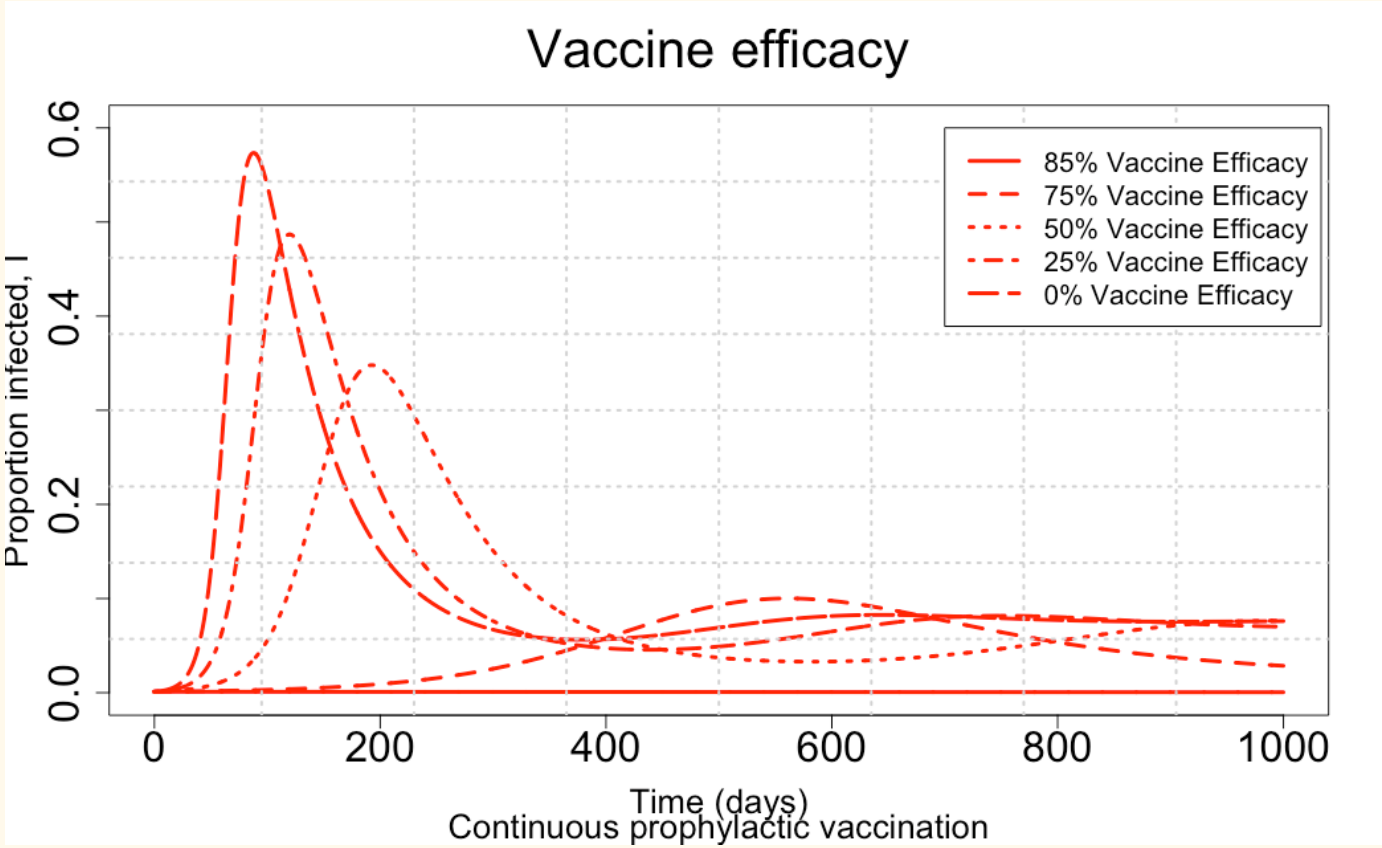
Criteria for preventing an outbreak in a farm where vaccination is applied



- **More virulent diseases (higher R_0) require better vaccines and higher vaccine coverage**
- **The critical proportion of vaccinated decreases non-linearly with vaccine efficacy ε**

Bitsouni et al. 2018

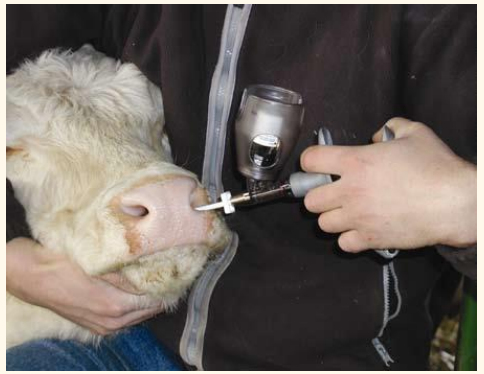
Impact of vaccination on epidemiological characteristics



- **Vaccines with higher efficacy generate less severe outbreaks**
- **Peak prevalence occurs later**

Bitsouni et al. 2018

Moving closer to reality



Factors affecting vaccine effectiveness in the field

Vaccine properties:
- Efficacy
- Immunogenicity
- Safety

Vaccine administration:
- Vaccine coverage
- Timing & frequency
  - Prophylactic or re-active

Vaccine effectiveness:
Reduction in disease prevalence under vaccination vs. non-vaccination

Host / pathogen characteristics
Heterogeneity in host susceptibility due to
- Age
- Genetics
- Spatial structure

Environmental effects
- season

Herd management & demography
- Farm structure
- Replacement rate
- Biosecurity
- Co-infections & treatments

Predicting the duration of vaccine effectiveness

Vaccine properties:
- Efficacy
- Immunogenicity
- **Safety**

Vaccine administration:
- Vaccine coverage
- Timing & frequency
  - Prophylactic or re-active

Vaccine effectiveness
- How much is disease prevalence reduced?
- **For how long?**

Pathogen chara
- Ge
- **Ev**

Demography

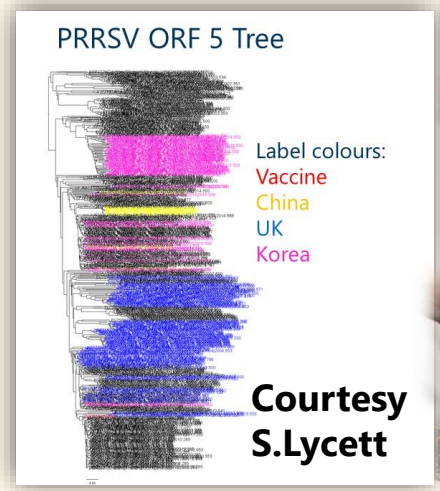
eatments

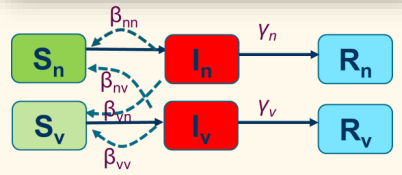
Mathematical models are the only way to determine how different factors together affect the degree & duration of vaccine effectiveness

SAPHIR
Strengthening Animal Production and Health through the Immune Response

WP16: Predicting vaccine effectiveness in the field

1. Establish epidemiological & evolutionary risk factors of SAPHIR vaccines
2. Develop a mathematical model to investigate epidemiological & evolutionary consequences of vaccination
   - Parameterize for attenuated PRRS vaccine
3. Determine vaccination strategies to maximise vaccine effectiveness in short & long-term





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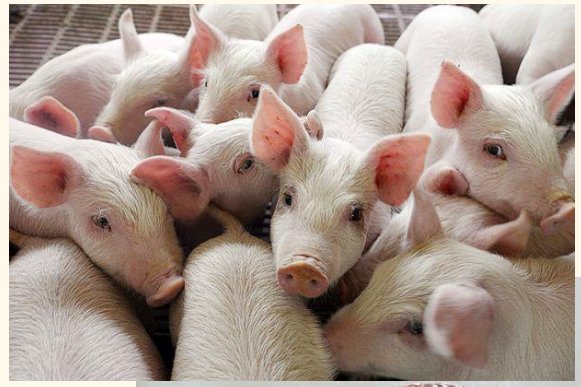
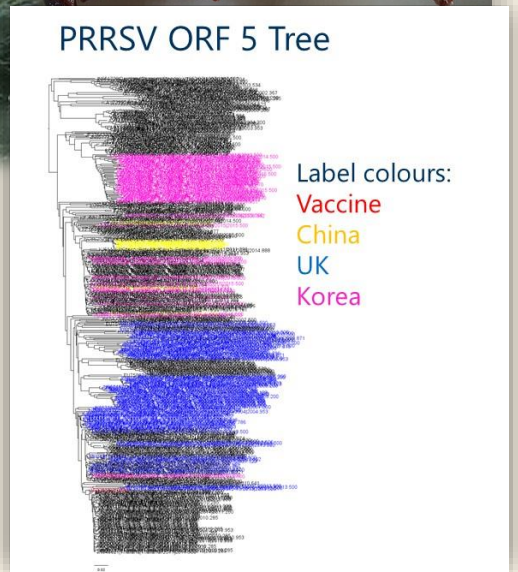
Porcine Reproductive & Respiratory Syndrome - PRRS

- Endemic viral disease, causes dramatic losses to the pig industry worldwide
- Symptoms:
  - Reproductive failure in mature pigs
  - Respiratory problems, fever, weight loss, death in growing pigs
- Arterivirus, 2 broad genotypes
  - High strain diversity within each genotype
  - Evolves incredibly fast





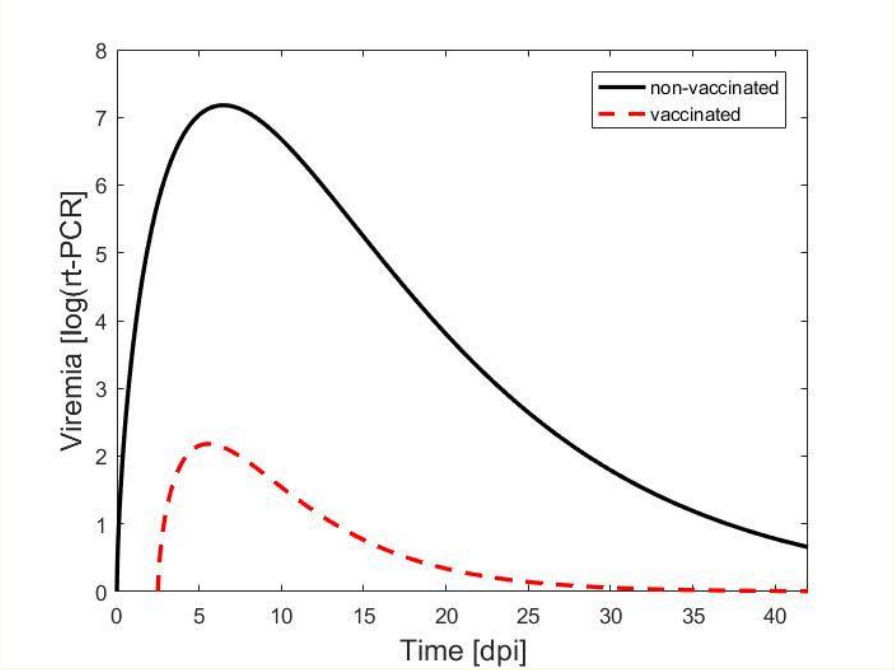
PRRS vaccines

Killed vaccines

- Very poor cross-protection
- Reduce severity of infection
  - Reduced virus load, faster recovery
- Safe

Modified life vaccines

- Better (but not perfect) cross-protection
- Reduce severity of infection
- Safe???



Modelling questions

1. What level of cross-protection & immunogenicity is required for a vaccine to prevent a PRRS outbreak in a herd?

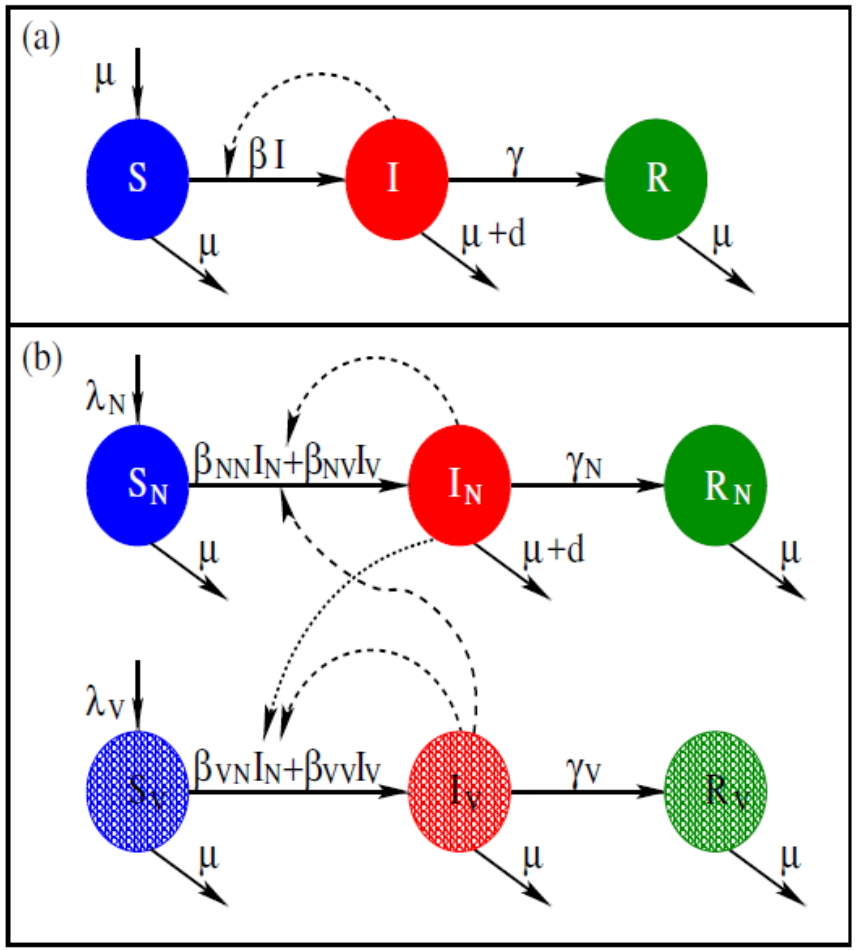
2. How does this depend on the vaccination strategy?

Modelling approach

Deterministic SIR model, adapted to PRRS

- Use parameter values from literature estimates (w.o. vaccination)
- Implement vaccine characteristics
  - Efficacy, immunogenicity
- Model different vaccination strategies
  - Prophylactic vs reactive
  - Continuous vs one-off
  - With / without additional biosecurity

Flow diagrams of the models presented

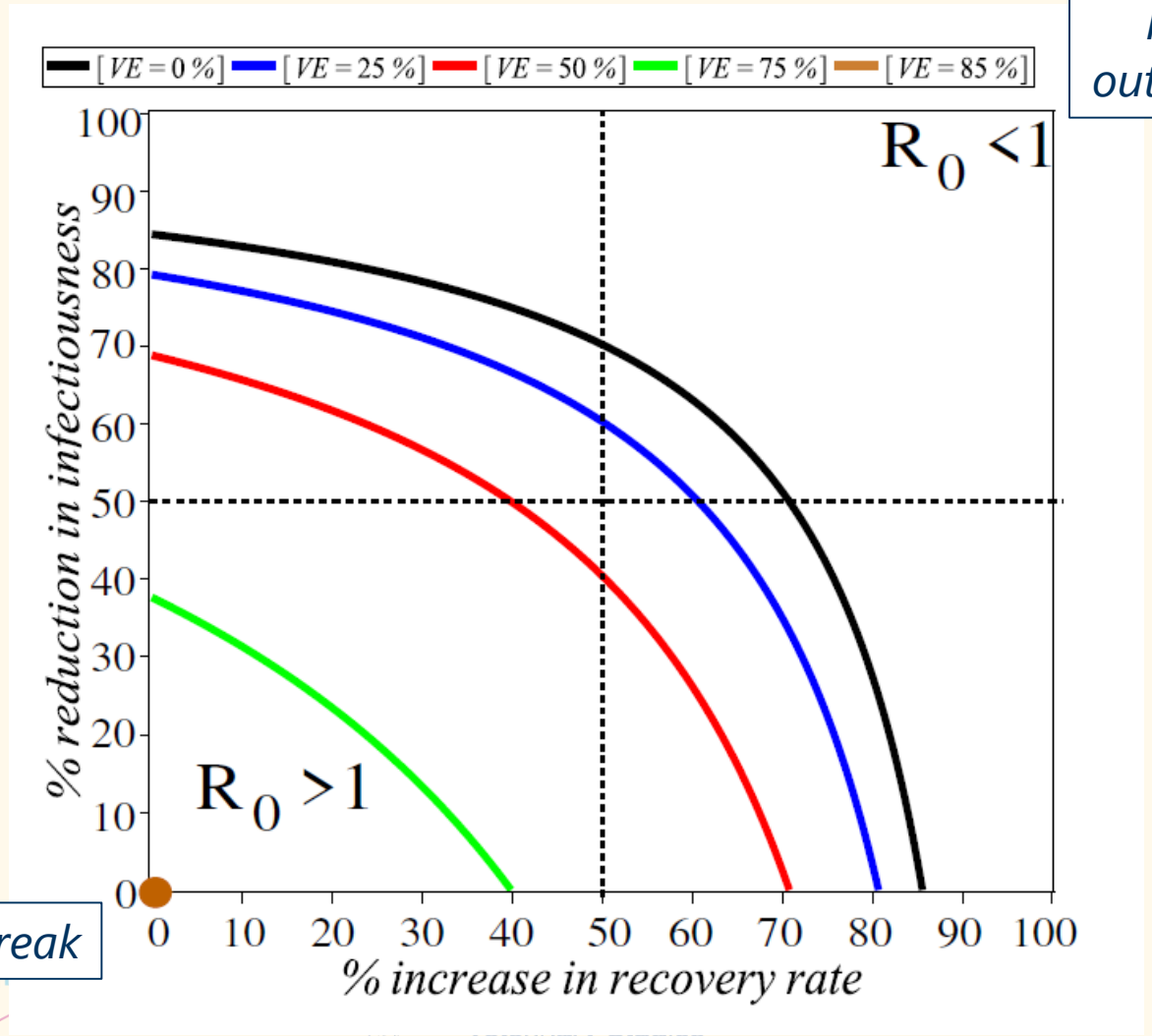


- S_N: Non-vaccinated Susceptible
- S_V: Vaccinated Susceptible
- I_N: Non-vaccinated Infected
- I_V: Vaccinated Infected
- R_N: Non-vaccinated Recovered
- R_V: Vaccinated Recovered

- β_{ij}: Transmission rate from infected j to susceptible i
- γ_j: Recovery rate of $j = N$ or V
- λ_j: Repl./Birth rate of $j = N$ or V
- μ: Remov./Death rate
- d: Death rate due to disease

Bitsouni et al. 2018

What level of efficacy / immunogenicity is required for preventing a PRRS outbreak?



No outbreak

Outbreak

- Even (highly) imperfect vaccines can prevent a PRRS outbreak
- 50% efficacy, when combined with immunogenicity is sufficient

Assumptions:
- continuous prophylactic mass vaccination
- full coverage

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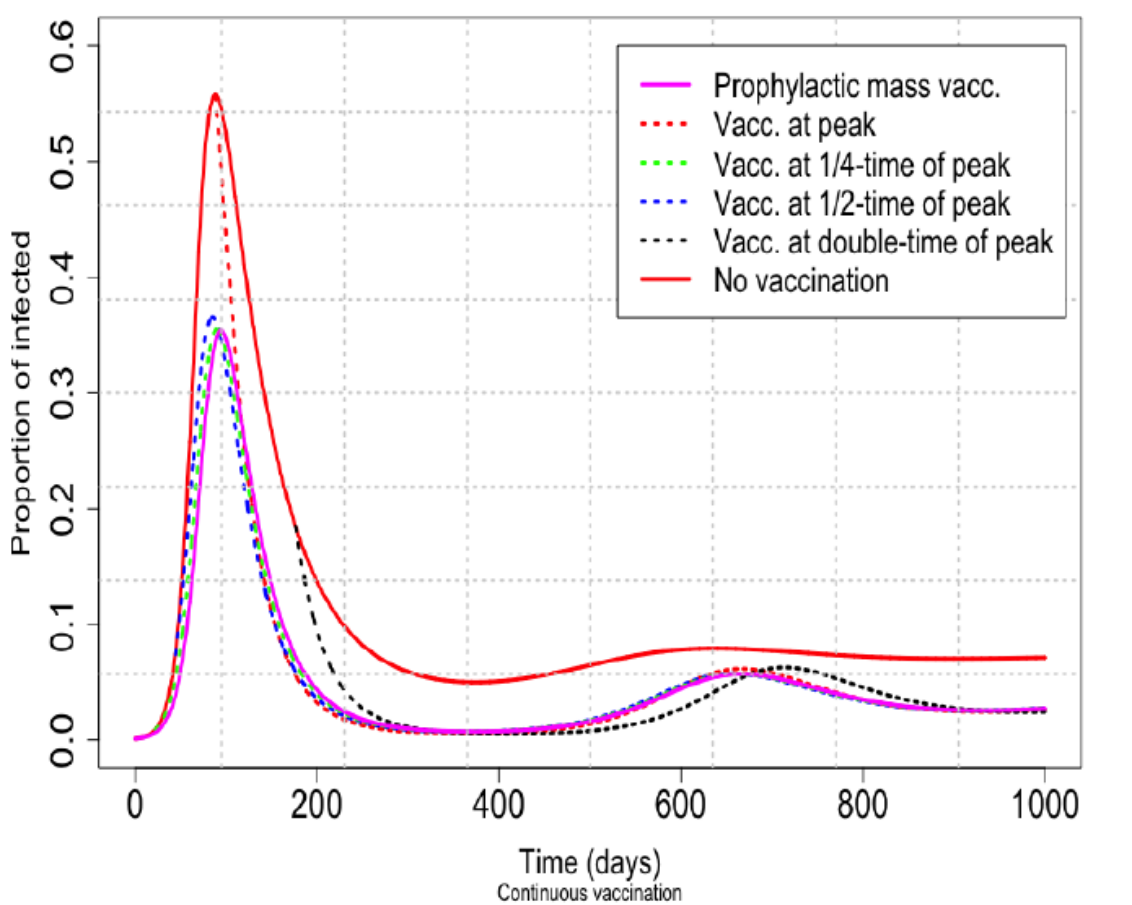
Reactive vaccination – a matter of timing



- Reactive vaccination can substantially reduce PRRS prevalence
- The earlier the better!

Epidemiological models as decision making tools

Case study: Foot & Mouth Disease (FMD)

2001 FMD crisis in UK:

- Led to the killing of over 10 million sheep & cattle
- Cost ~£20bn

- Problem: Rapid transmission between wide range of livestock species
- Infection is rarely fatal, but causes severe reduction in growth rate and in milk production (dairy cattle)
- Strong economic impact: export ban of milk and meat, and movement restrictions in affected farms

Epidemiological models & policy decisions

- Several control options available:
  - Culling, vaccination (prophylactic / reactive / targeted / predicted), prolonged movement & export restrictions …
- Main policy aim: achieve disease-free status asap
- Trade-off: minimize time vs minimize disturbance
  - Difficult to achieve optimal balance without a quantitative predictive framework
- "Scientific policy approach": Appointment of Prof. Roy Anderson, leading epidemiological modeler

➢ 3 epidemiological models for FMD were developed to inform policy decisions

Why 3 FMD models?

- Essential differences between the 3 FMD models
  - Modelling approach (deterministic / stochastic)
  - Complexity (e.g. accurate representation of spatial structure)
  - Scope
  - Purpose
  - Transparency, flexibility, runtime
- Models agreed in their main predictions:
  - Successful control of FMD requires **rigorous** application of **culling** (combined with vaccination) **on a wide scale**

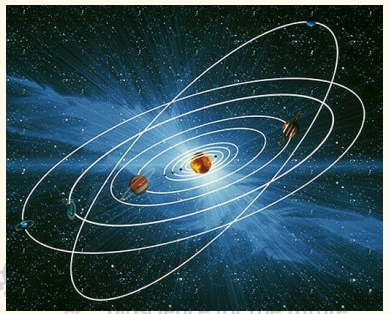
Stakeholder reactions

- Policy makers: application of stringent culling
  - UK reverted to FMD free status within a few months
- Farmers & Veterinarians:

Resolving the conflict (Keeling 2005): The issue of scale

- Optimum approach & control strategy depends on the scale:
- Individual farm level / local scale:
  - Veterinary judgement is most accurate / suitable
  - Less stringent control measure is optimal

- National level / global scale:
  - Mathematical model best suited to weigh pros & cons
  - More stringent control measure is optimal



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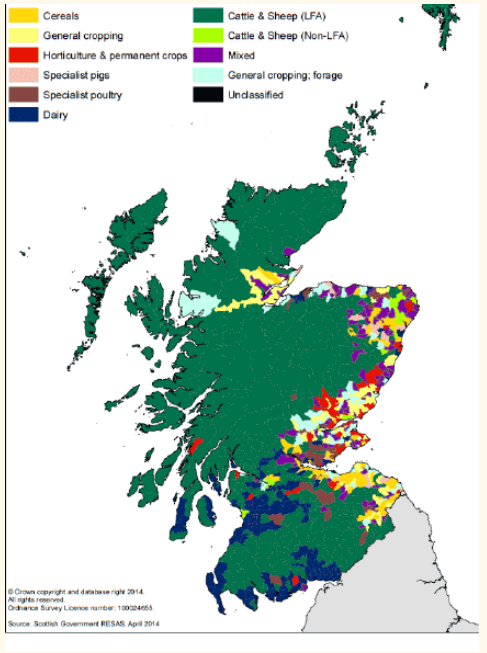
Keeling Proc R Soc B 2005

Conclusions

- Mathematical models can help decision making when faced with complex problems, such as predicting vaccine effectiveness
- There is not one best model: Different models provide different insights
- All models require simplification
- Mathematical models can cause friction between modellers / veterinarians / farmers / experimental scientists
- Effective communication is key for effective modelling

The Cambridge – Edinburgh FMD Model

- Stochastic simulation model
- Takes spatial structure of farms into account
- Less explicit representation of temporal aspects
- Simplified representation of transmission dynamics
  - Farm-level transmission dynamics



Keeling et al., 2001 & 2003;

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Investigation of vaccination strategies with the Cambridge – Edinburgh model

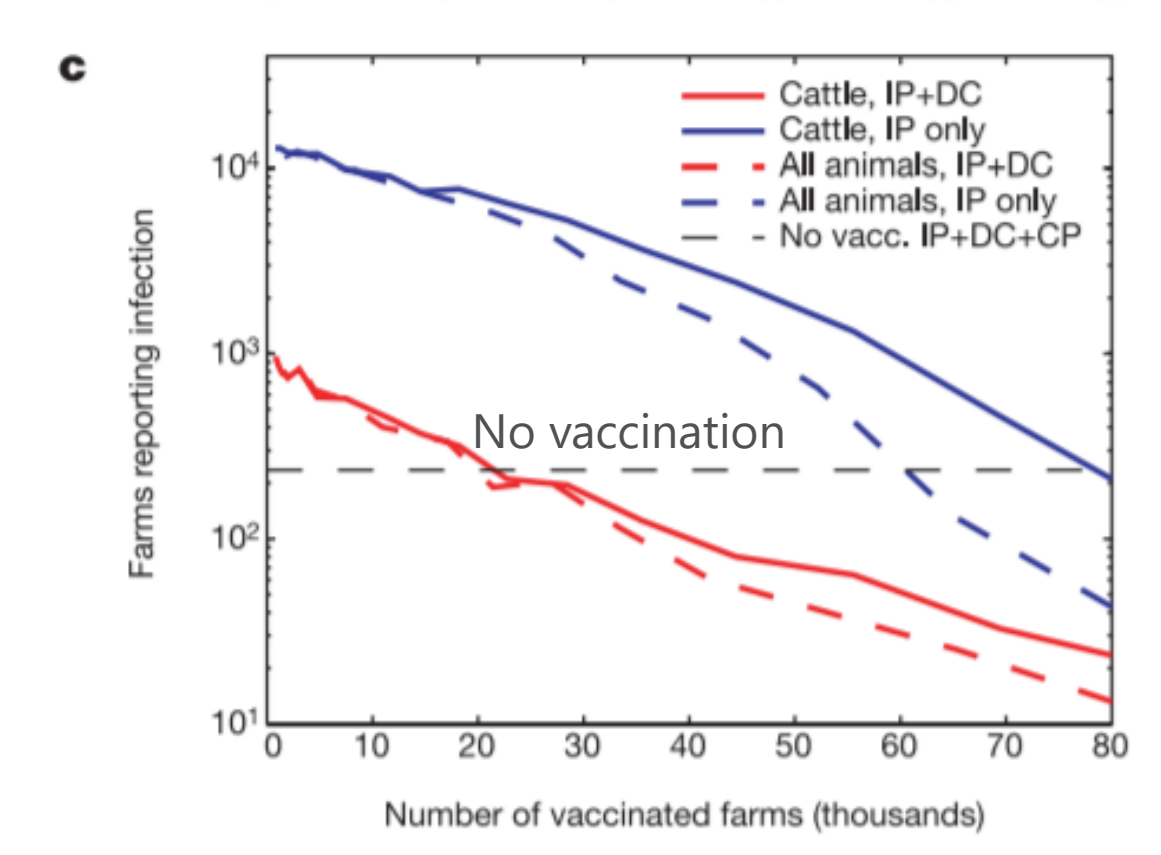
Scenarios considered: Vaccination, combined with diverse culling strategies & movement restrictions

Prophylactic vaccination

- Dependency on coverage, efficacy, random / targeted vaccination

- Reactive vaccination
  - Mass vaccination
  - Ring vaccination
  - Predictive vaccination

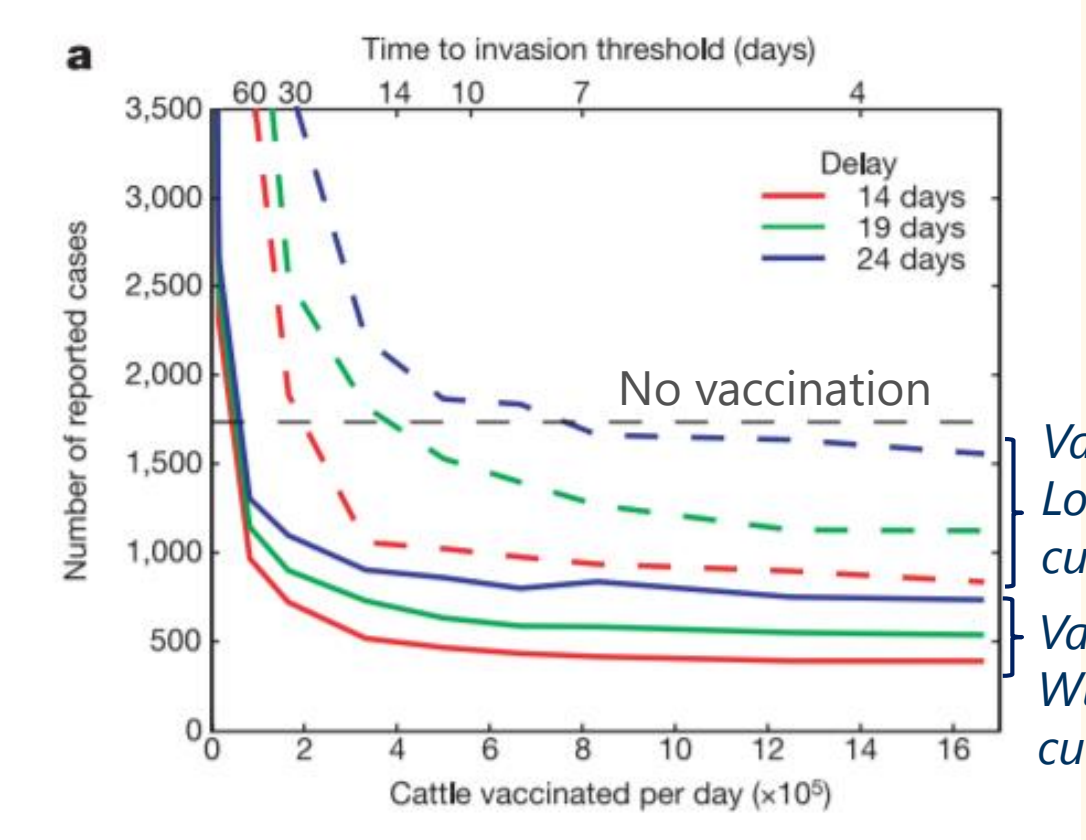
Prophylactic vaccination



1. Prophylactic vaccination can be more effective than extensive culling,
   - but only if vaccine coverage is high
2. Vaccine effectiveness depends on other control strategies applied
3. Vaccination of cattle may be sufficient, if combined with cull
   - Little benefits from vaccinating all animal species

Keeling et al. 2003

Reactive vaccination

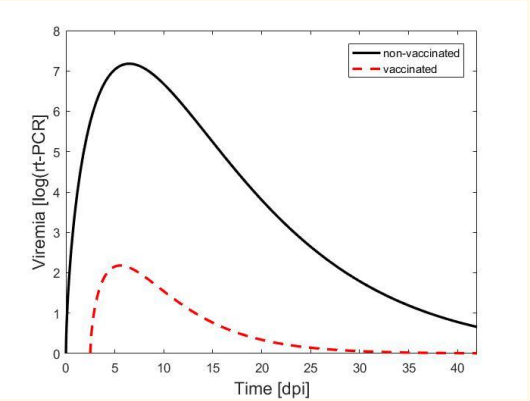


The effectiveness of reactive vaccination depends (non-linearly) on how many cattle can be vaccinated per day

- Low coverage is not enough

Keeling et al., 2003

The vaccine developer's question:
How can we make vaccines to make animals more disease resistant?



The stakeholder's question:
How can vaccines help to reduce infectious disease risk & prevalence?

- **How will vaccination affect the pathogen landscape?**

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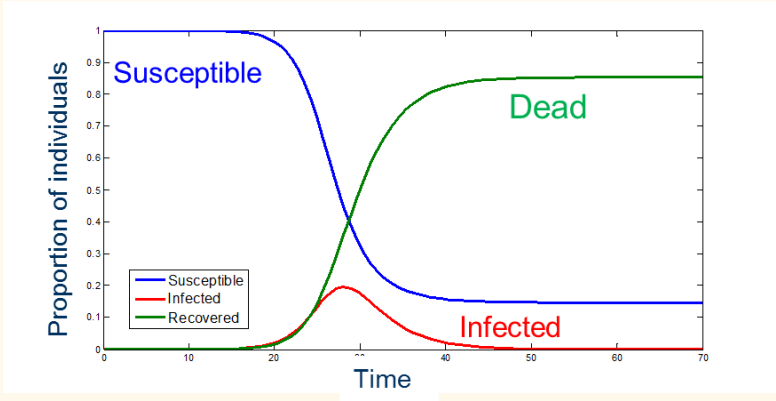
Deterministic vs stochastic models

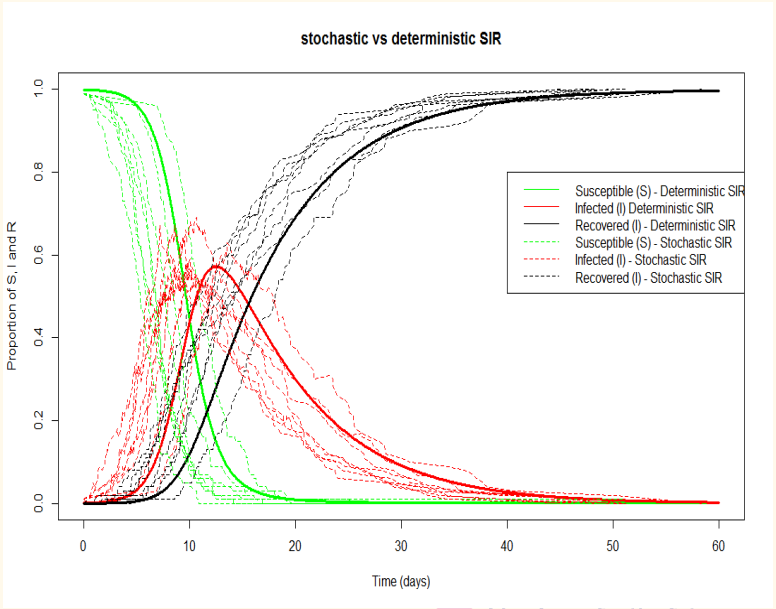
Deterministic models

- Assume that the outcome is precisely determined by the model inputs and relationships
- Ignore all random variation
- A given input always produces the same output



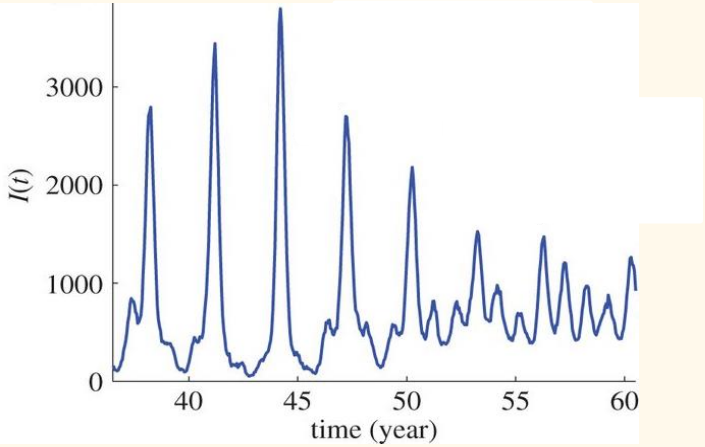
Stochastic models

- Incorporate inherent randomness of system
- E.g. infection is a chance event that occurs at a certain probability
- The same input produces an ensemble of outputs



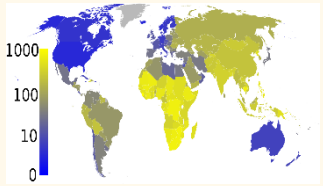
Why & when do we need stochastic models for modelling epidemics

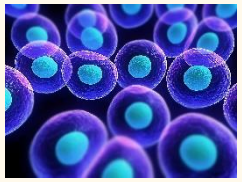
- Stochasticity is particularly important when the number of infectious individuals is small
  1. At the early stage, when disease is invading
     → Probability of an outbreak to occur
  2. During a trough phase of an epidemic cycle
     → Probability of extinction
  3. When population size is small
     →Chance fluctuations cause extinction

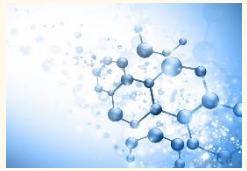


Classification according to the scale of modelling

- National
- Herd
- Individual
- Organ
- Cell
- Molecules
- Genes







Mechanistic models often combine 2 or more adjacent levels of the hierarchy

Systems models combine several levels of the hierarchy

See lecture on within host infection dynamics: (molecules → cell → organ)

The appropriate scale for modelling depends on the model objectives

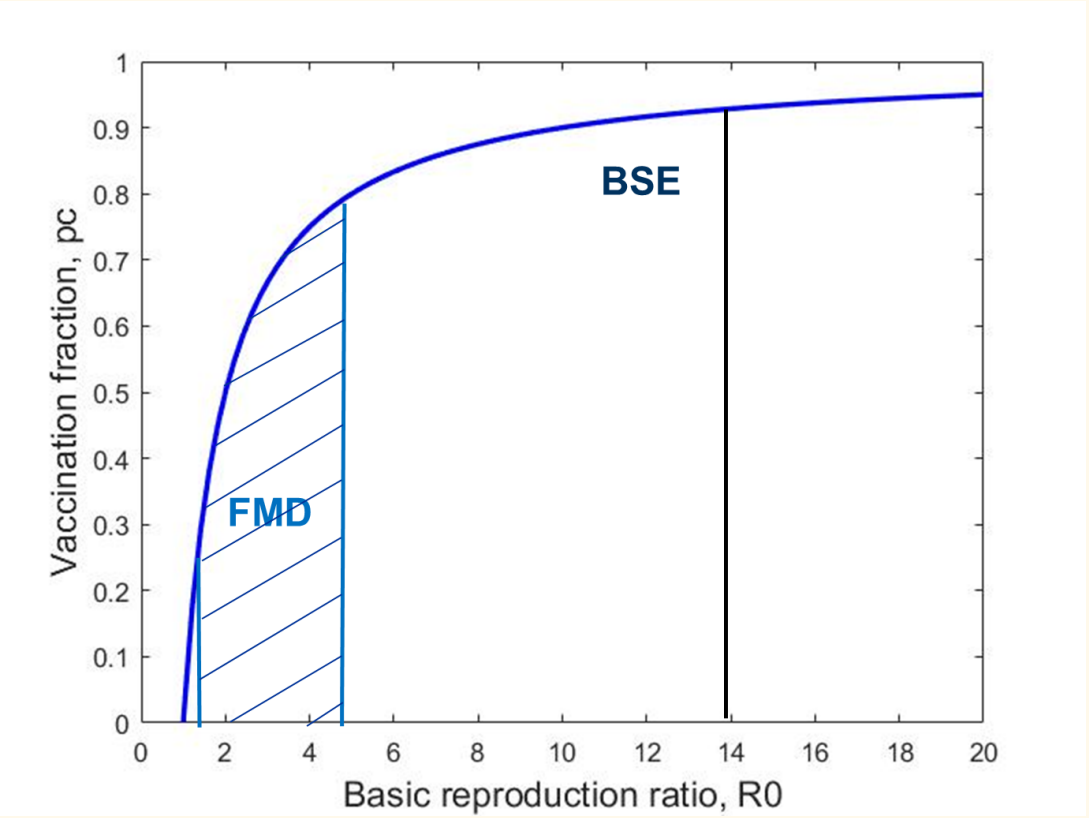
Herd immunity for a fully protective vaccine

$$R_0^{v} = (1 - p)\, R_0$$

Critical proportion of individuals to be vaccinated:

$$p_c = 1 - \frac{1}{R_0}$$

In order to eradicate an infection, not all individuals need to be vaccinated ("Herd immunity")



Insights: Cambridge-Edinburgh FMD model

- Mass prophylactic vaccination can effectively prevent major epidemics
  - More efficient if high-risk farms are targeted
- Reactive vaccination, when combined with wide-spread culling can effectively control ongoing epidemics
  - Can be optimised by targeted / predictive vaccination
- Limitations:
  - ‘Idealized’ conditions (e.g. mass vaccination, high efficacy,…)
  - No consideration of strain diversity & evolutionary risk

Vaccine properties

i) *Vaccine efficacy:* We assume that the vaccine reduces host susceptibility by considering:

$$\beta_{VN} = (1-\epsilon_s)\beta_{NN},\ \beta_{VV} = (1-\epsilon_s)\beta_{NV},\quad 0 \leqslant \epsilon_s < 1,$$

where ϵ_s the vaccine's efficacy (McLean, 1995).

ii) *Vaccine immunogenicity:* We assume that the vaccine
i) reduces the degree of host infectiousness:

$$\beta_{NV} = (1-\epsilon_i)\beta_{NN},\ \beta_{VV} = (1-\epsilon_i)\beta_{VN},\quad 0 \leqslant \epsilon_i < 1,$$

and
ii) reduces the duration of infectiousness:

$$\gamma_V = \frac{\gamma_N}{(1-\epsilon_\gamma)},\quad 0 \leqslant \epsilon_\gamma < 1.$$