Mathematical Models of Infectious Diseases

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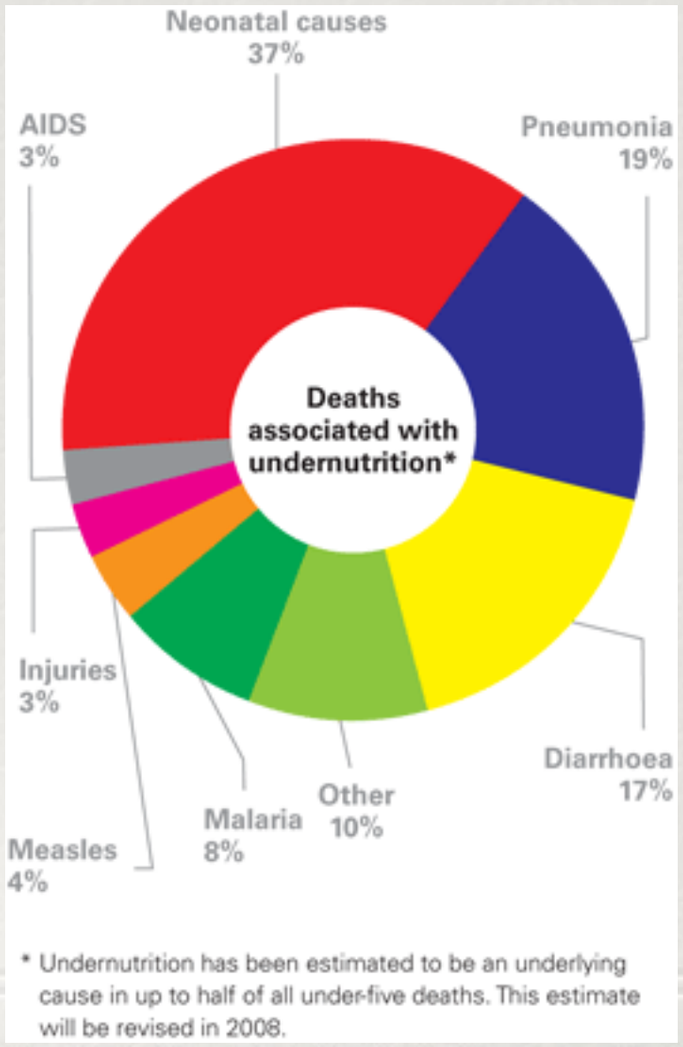
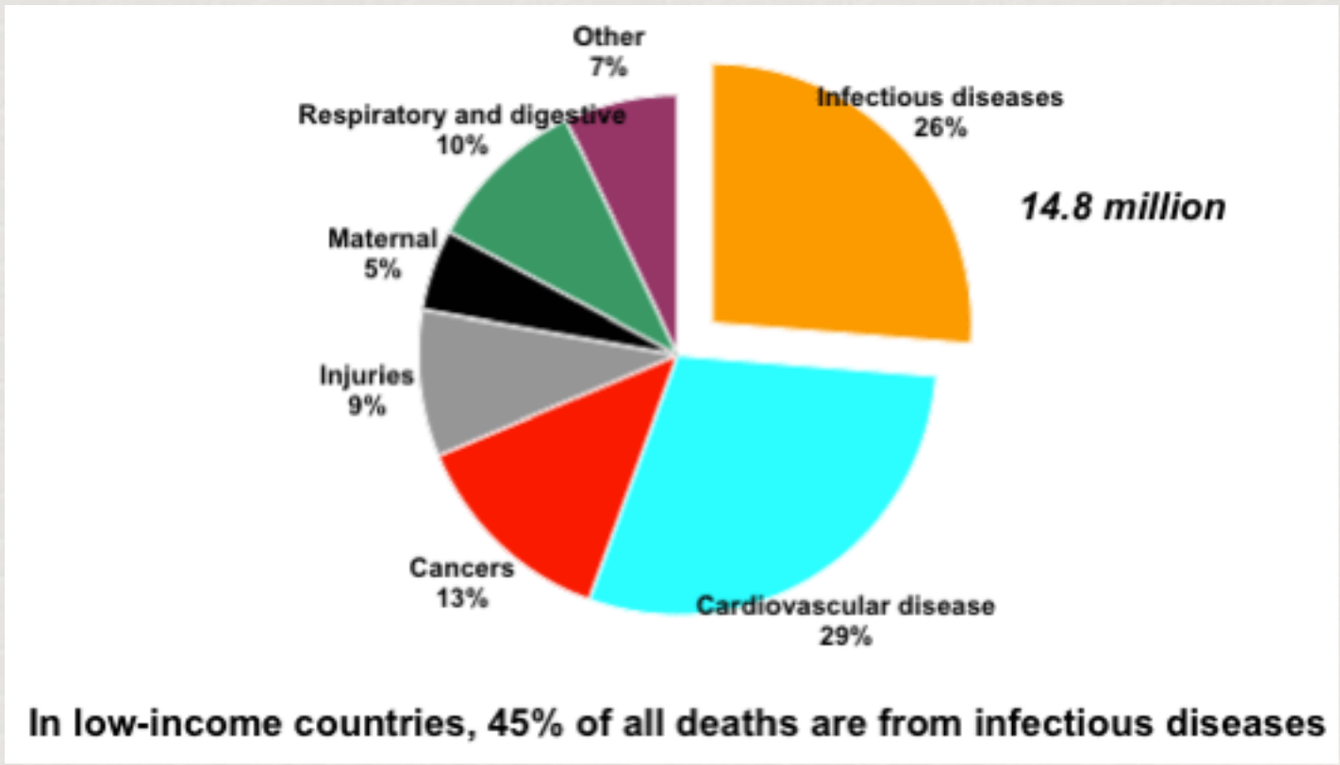
Global causes of mortality

World Health Organization

Measles & pertussis account for ~300,000 and ~200,000 annual deaths





Total mortality

Infant mortality

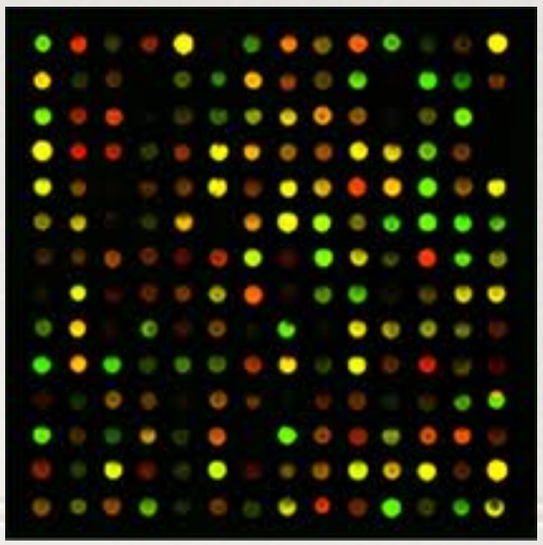
Multifaceted approach to understanding infectious diseases

Medicine

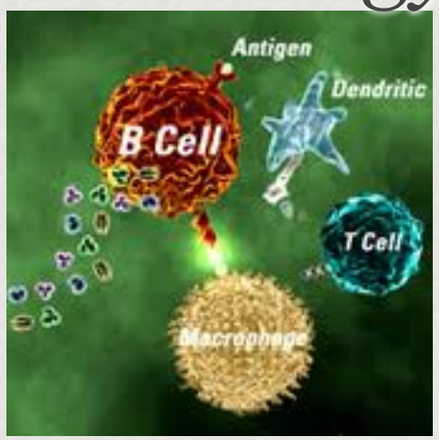
But these approaches don't address important questions at population level ...

Microbiology

Genomics



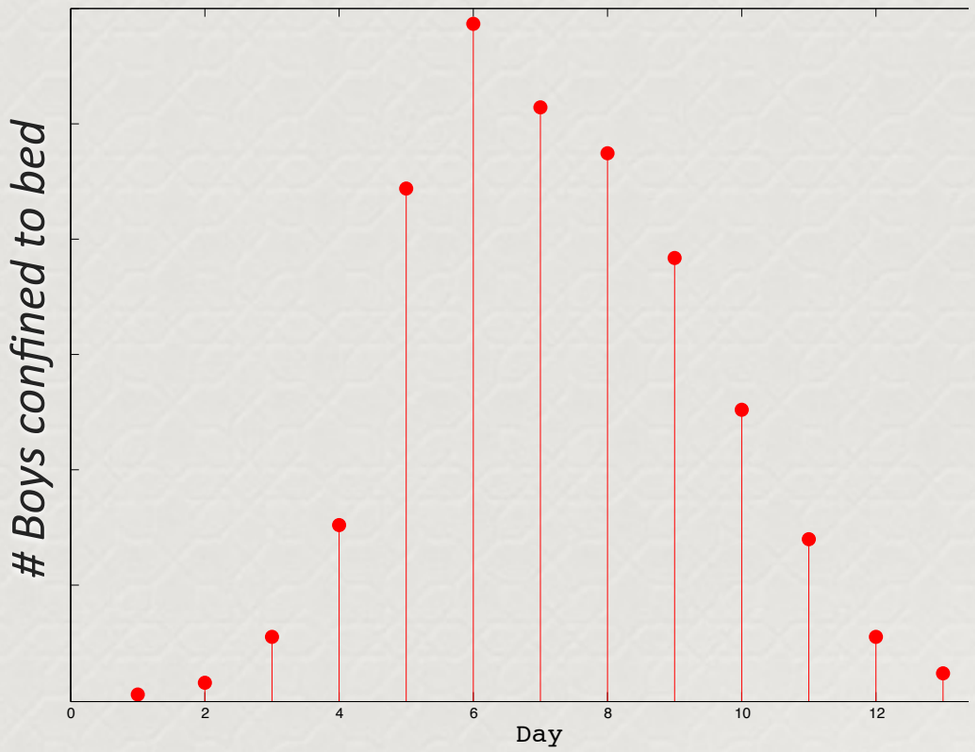
Immunology



Vaccines & Drugs

School outbreak

Boarding School, England
Jan 1978



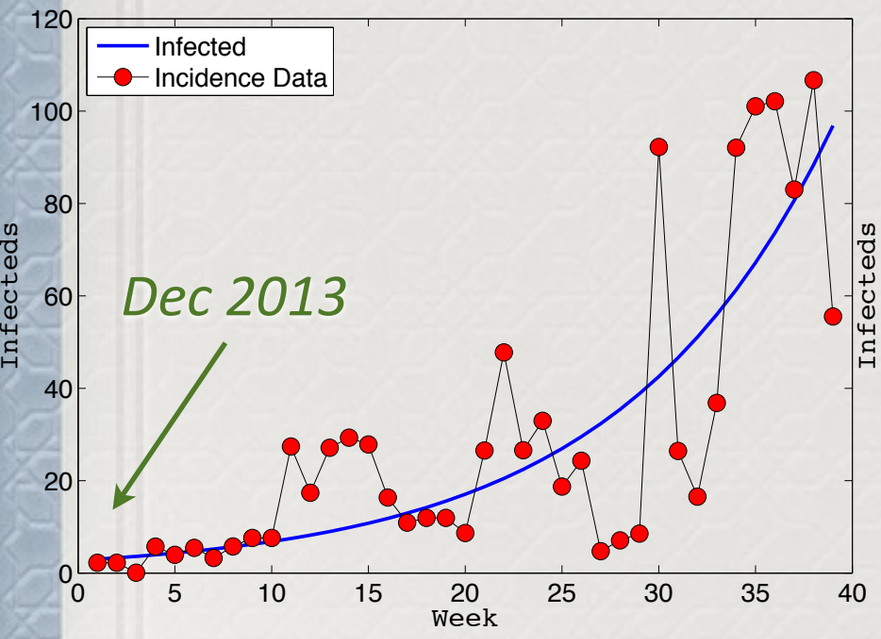
Raises numerous questions:

- *What is etiological agent?*
- *Is it novel?*
- *Is a vaccine available?*

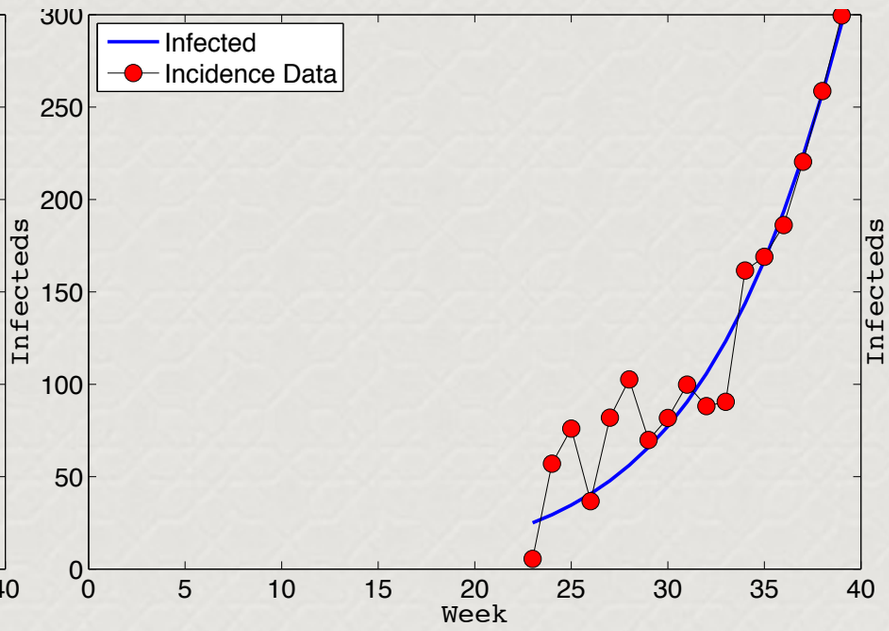
Modeling questions I. Basics

2014 Ebola outbreak in West Africa

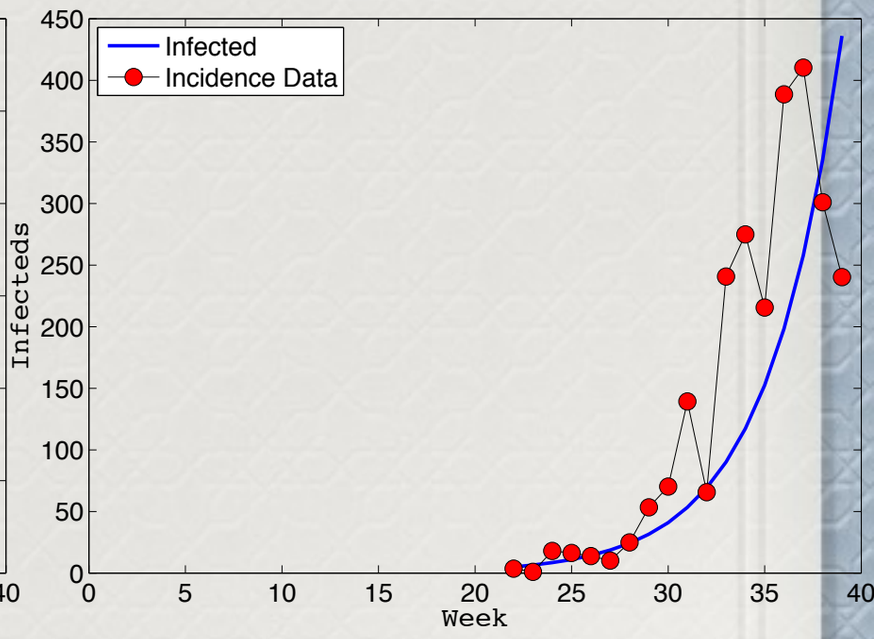
Guinea



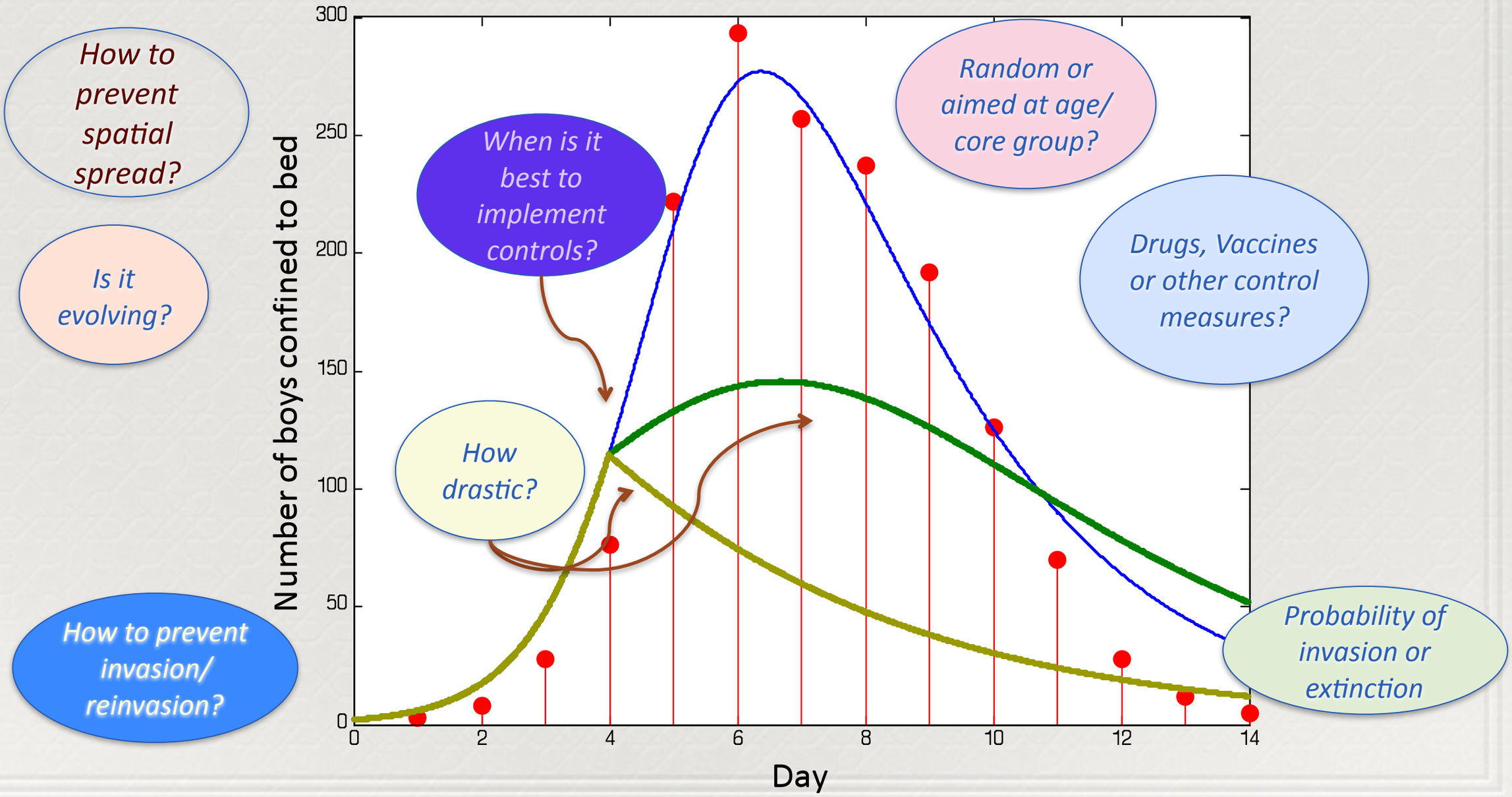
Sierra Leone



Liberia



Modeling questions II. Control Implications



What is a model?

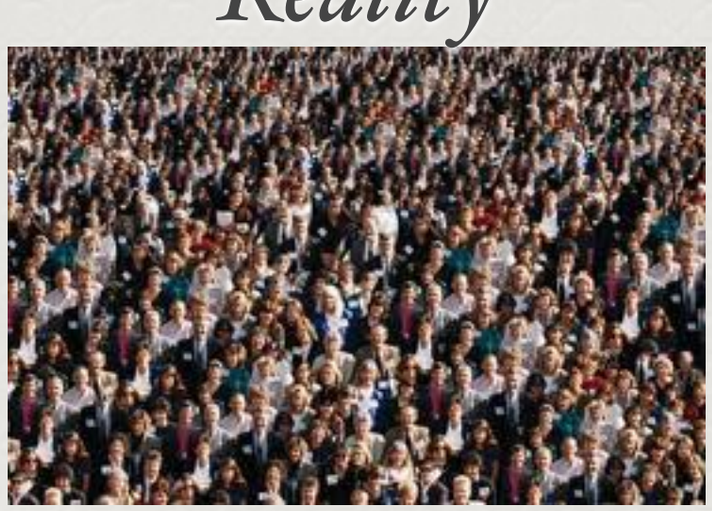
- *Different types of models:*
  - *A **mathematical/computational model** is an abstract model that uses mathematical language to describe the behaviour of a system*
    - *A **Statistical model** attempts to describe relationships between observed quantities and independent variables*
- *Developing a model is different from statistical analyses of data*

Abstraction

Purpose

Components

Reality



Conceptualization

Abstraction

Interpretation

Assumptions

Limitations

Validation

What's a 'Good' Model?

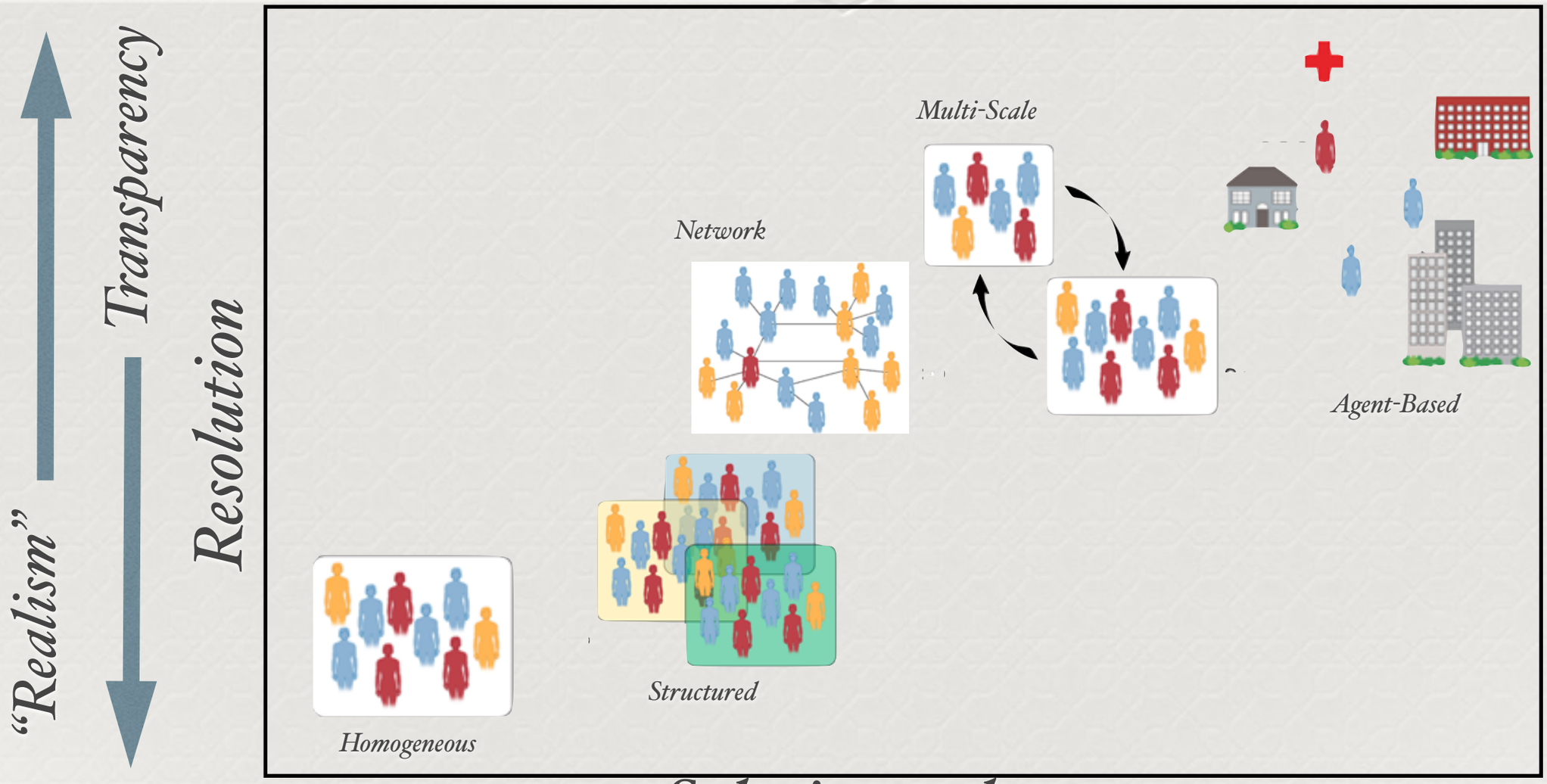
- Choice of model depends crucially on focal question and available data (hammer & chisel or pneumatic drill?)

- Use model principally for
  - understanding nature
  - making predictions

Judging a Model…

- Three fundamental features of models, often opposing forces:
  - ***Accuracy***
    - *Capture observed patterns (qualitative or quantitative?) and make predictions*
    - *Increases with model complexity*
  - ***Transparency***
    - *Ability to understand model components*
    - *Decreases with model complexity*
  - ***Flexibility***
    - *How easily can model be adapted to new scenarios?*
    - *Decreases with model complexity*

Realism Vs Transparency



Solution tools

‘How’ do you Model?

Analytical Models

Concentrate on problems that can be expressed and analysed fully using analytical approaches.

The MathWorks

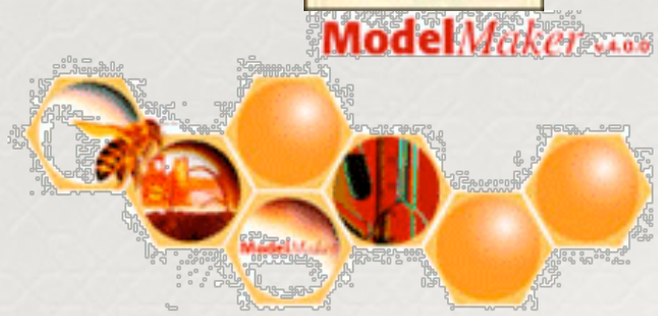
Problem-based Models

Construct most “appropriate” model and use whatever combination of methods for analysis and prediction.

Ready-Made Software

ModelMaker

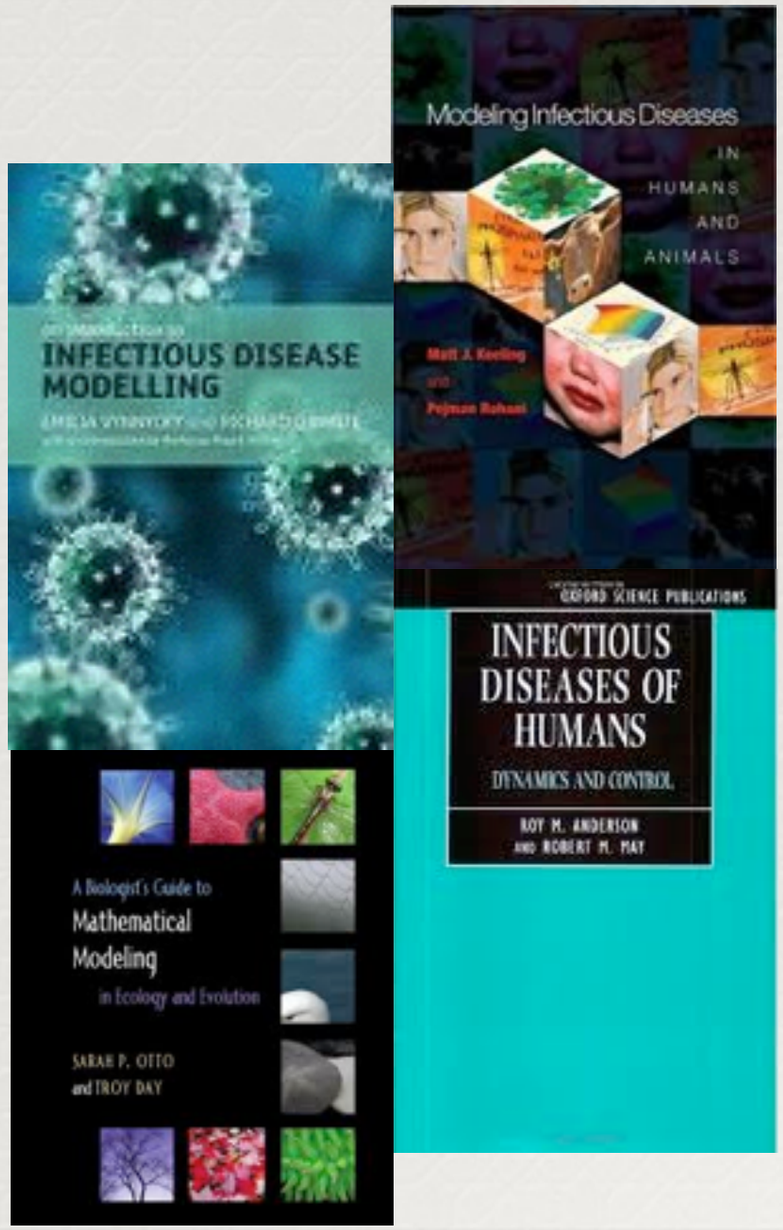
www.modelkinetix.com/modelmaker/modelmaker.html



Global simulators

Resource Materials

- *Keeling & Rohani (2008)*
- *Vynnycky & White (2010)*
- *Anderson & May (1991)*
- *Otto & Day (2007)*



Mathematical Modelling of Infectious Diseases

- Objective 1: Setting up simple models
  - Different transmission modes
    - Basic Reproduction Ratio (R_0), Simple Epidemics, Invasion threshold & extinction
  - Stability analysis
- Objective 2: Control
  - Infection management
- Objective 3: Statistical estimation
  - R_0 and other parameters
- Objective 4: Heterogeneities
  - Risk structure
  - Realistic pathogenesis
  - Seasonality
  - Age-structured transmission effects
- Objective 5: Sensitivity
  - Stochastic implementation
  - Parameter uncertainty

Steps in Developing a Model

Formulate problem/objectives

↓

Conceptual model diagram

↓

Dynamic equations

↓

Computer code

The simplest models

- *Let's develop a model for Boarding School influenza outbreak*
- *Some **important** choices need to be made at outset*

1. ***What do we want to keep track of?***
   - *Amount of virus in population?*
   - *Antibody titre of everyone in population (school)?*
   - *Cities in which infected people have been found?*

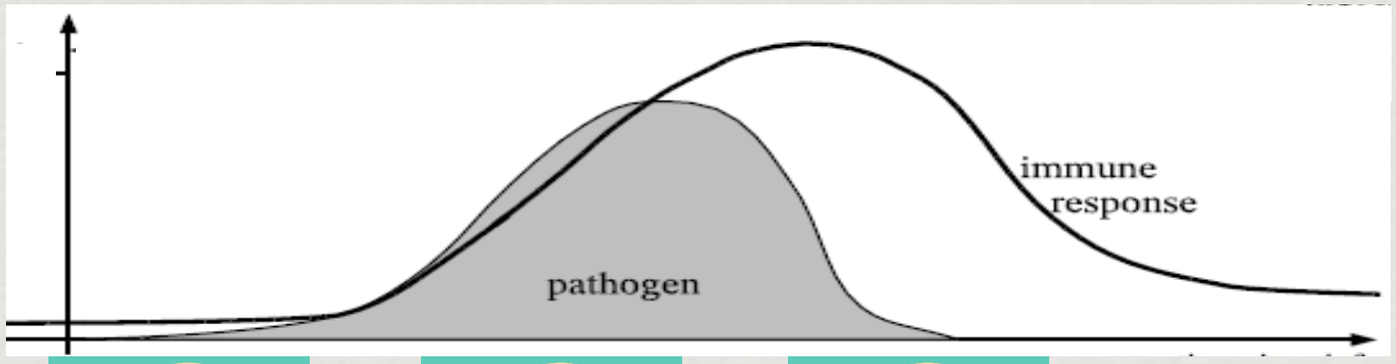
Categorising individuals

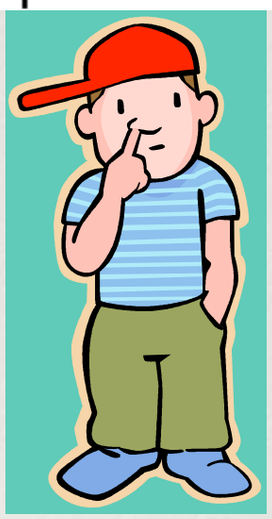
Healthy *Incubating* *Diseased*

Medical status

Susceptible *Exposed/latent* *Infectious* *Recovered/Immune*

Infection status

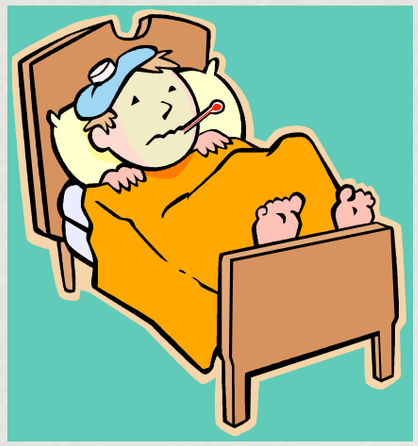




Incubating

Infectious, latent

Infectious, symptomatic



Infectious, quarantined

The simplest models

- Pragmatic choice: categorise individuals in population according to their infection status, eg:

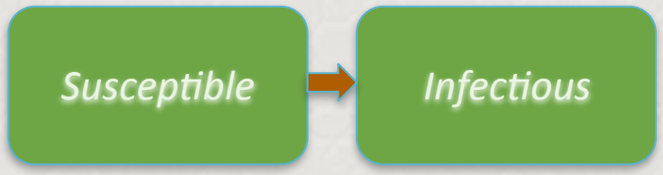
  - Susceptible
  - Infectious
  - Recovered/Immune

These are our "system variables"

The simplest models

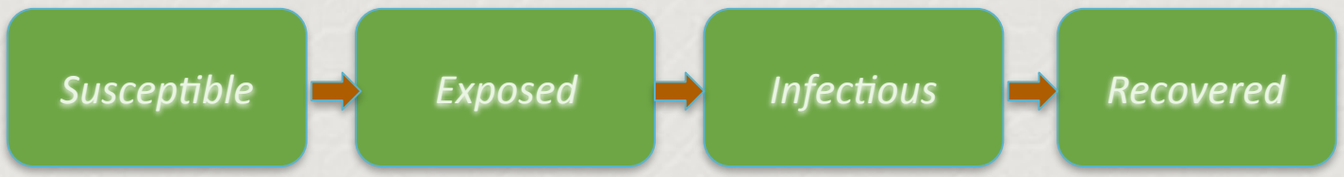
2. **What model structure?**

-- Determined by pathogen biology

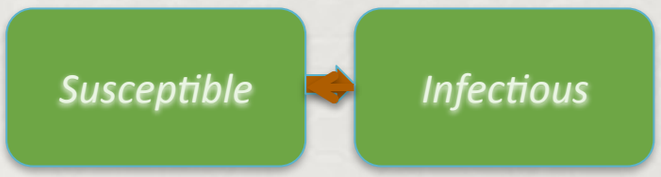


SI – signifies fatal infection

SIR – recovery after infection



SEIR – latency

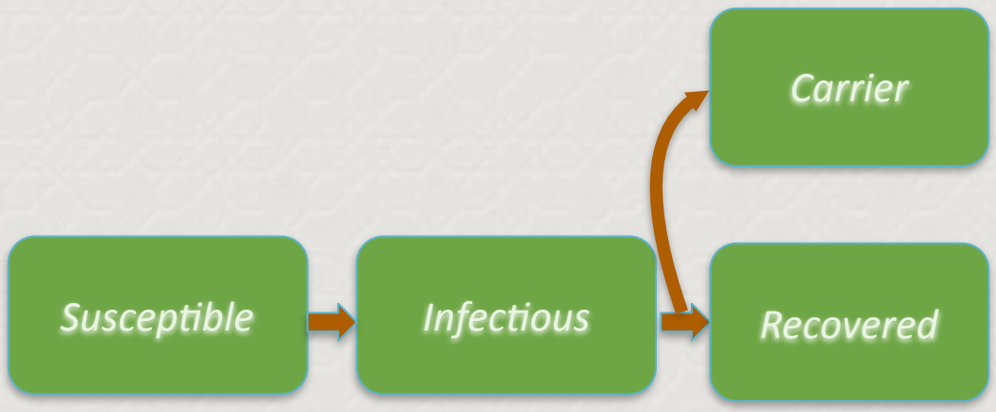


SIS – no immunity elicited

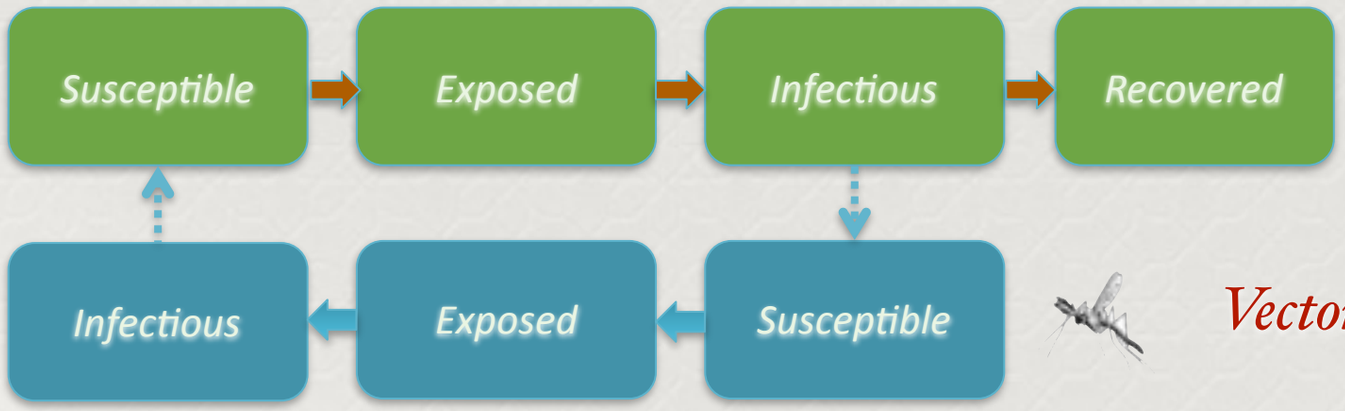
The simplest models

2. **What model structure?**

-- Determined by pathogen biology



SIR – with carriers



Vectored transmission

The simplest models

- **What model structure?**
- Depends on what do we know about the pathogen (eg, influenza)
  - It's directly transmitted (aerosol)
  - An acute infection
  - Lifelong immunity (to that strain)

The simplest models

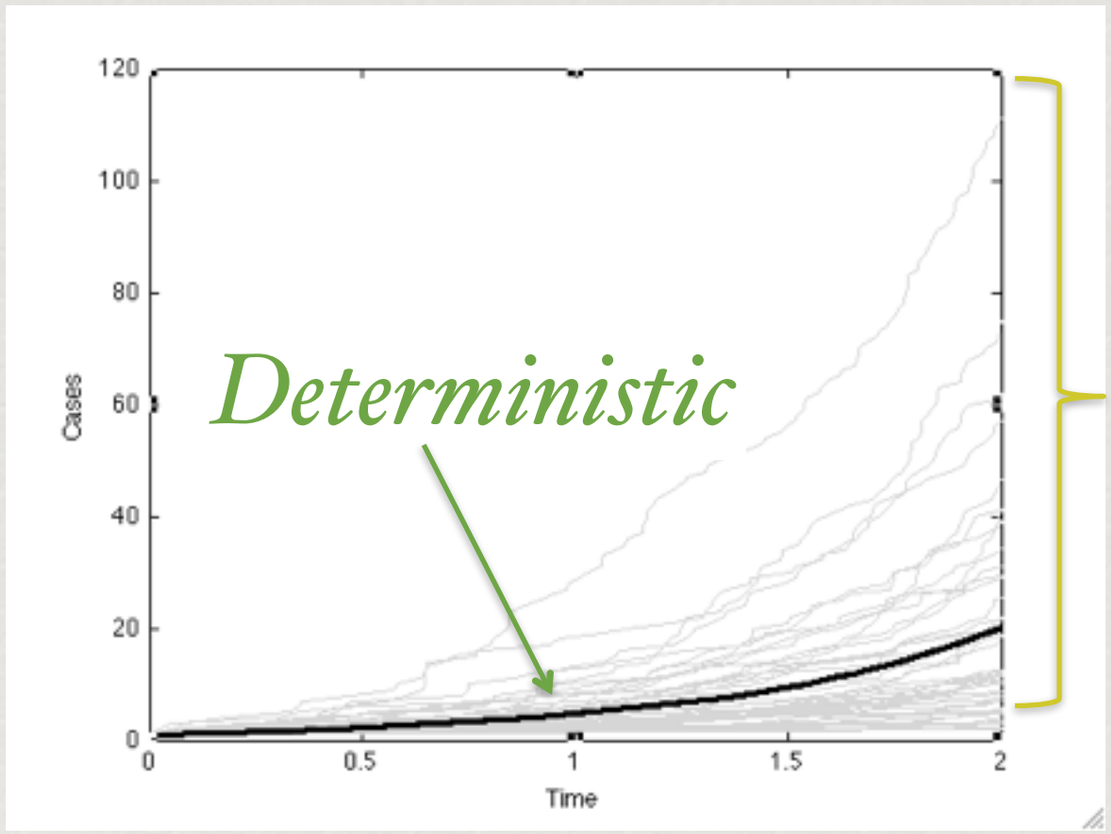
- *Flow between classes/compartments determined by details of host population structure and pathogen biology*

- *Host population size*
- *Contact rates*
- *Pathogen infectivity*

These are our "parameters"

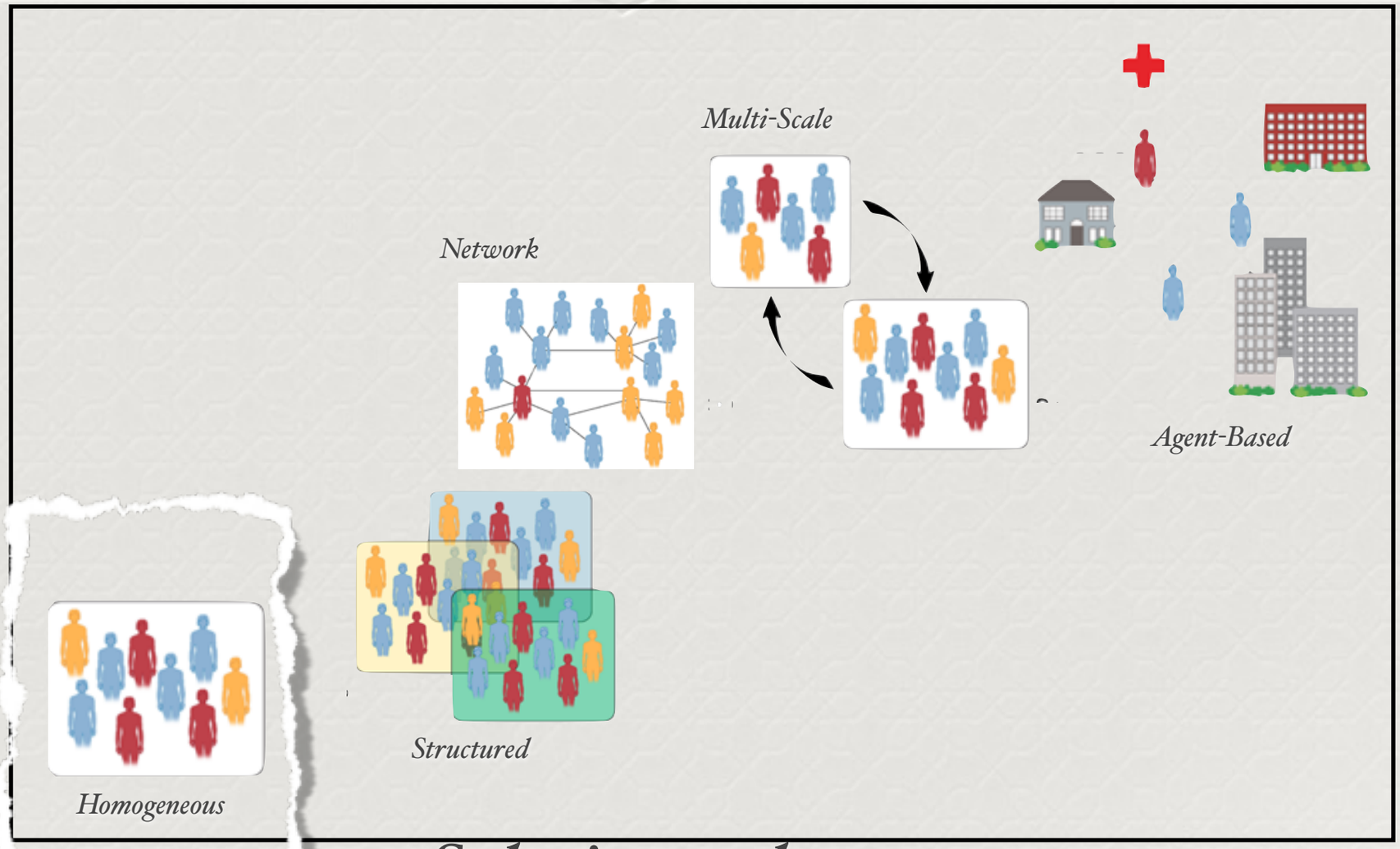
The simplest models

3. **Deterministic or stochastic?**



On average, stochastic simulations identical to deterministic predictions, though individual realizations may be quite different

Realism Vs Transparency



Solution tools

The simplest models

- We've settled on a deterministic SIR model – now what?
- How do we write down some equations to describe spread of 'flu in this population?
  - Assign each system variable a unique Roman letter, eg:
    - Susceptible, S (proportion) or X (number)
    - Infectious, I (proportion) or Y (number)
    - Recovered/Immune, R (proportion) or Z (number)
  - Assign parameters a unique (typically Greek) letter, eg:
    - Contact rate, κ
    - Pathogen infectivity, ν

Very important!

- NOTHING SPECIAL ABOUT MY CHOICE OF NOTATION – USE OF PARTICULAR LETTERS HIGHLY IDIOSYNCRATIC

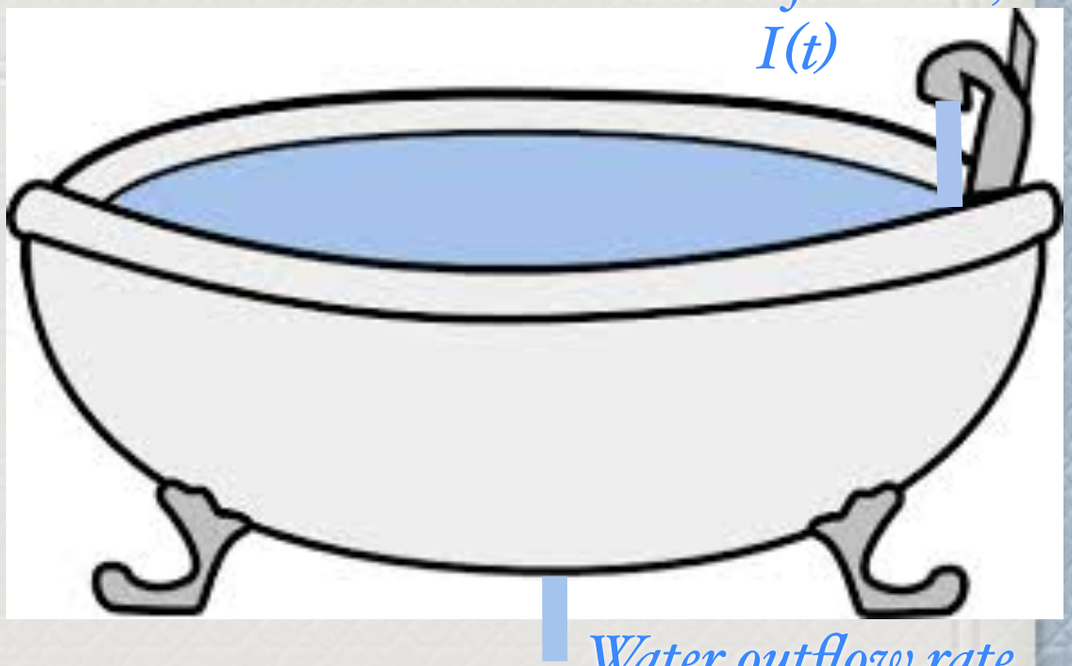
- OTHER AUTHORS MAY USE DIFFERENT LETTERS TO DENOTE SAME VARIABLES OR PARAMETERS.

- YOU CANNOT AUTOMATICALLY ASSUME THAT β IN TWO DIFFERENT PAPERS MEANS THE SAME THING!

3. Model equations

Bath tub example

- *Let W(t) be amount of water in bathtub (ml)*
- *Need a dynamic equation that tells us how W(t) will change through time*

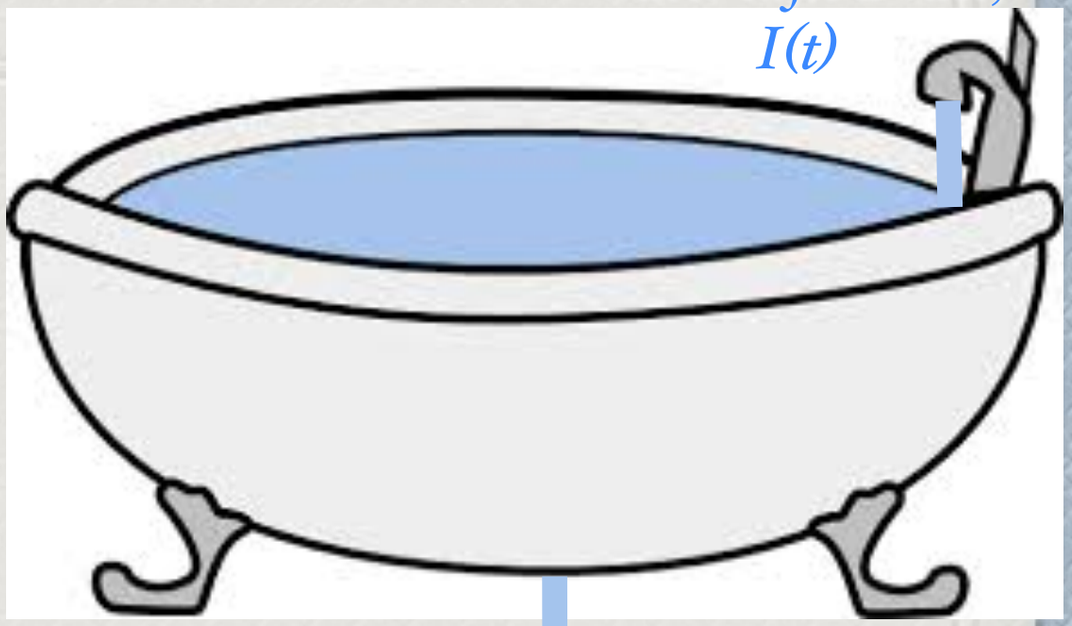


- *Consider a small time interval, δt*
- *Then,*

$$W(t+\delta t) = W(t) + \text{Inflow rate} \times \text{elapsed time} - \text{Outflow rate} \times \text{elapsed time}$$

Bath tub example

$$W(t+\delta t) = W(t) + I \times \delta t - O \times \delta t$$



* *Rearrange*

$$\frac{W(t+\delta t) - W(t)}{\delta t} = I - O$$

* *Left hand side is a difference quotient for derivative of W with respect to time*

* *Let* $\delta t \to o$

$$\frac{dW}{dt} = I - O$$

Many bathtubs = compartment models

Model equations

- If we knew X_t and Y_t, could we predict $X_{t+\delta t}$ and $Y_{t+\delta t}$, where δt is some (very short) time later?

$$X_{t+\delta t} = X_t - (\nu\kappa\ \delta t)\ X_t\ Y_t/N$$

$$Y_{t+\delta t} = Y_t + (\nu\kappa\ \delta t)\ X_t\ Y_t/N - (\gamma\ \delta t)\ Y_t$$

- And

$$Z_{t+\delta t} = Z_t + (\gamma\ \delta t)\ Y_t$$

ν *is probability of transmission given contact*
κ *is contact rate*

Basic questions?

$\beta = \nu\kappa$

$$X_{t+\delta t} = X_t - (\beta\ \delta t)\ X_t\ Y_t/N$$

$$Y_{t+\delta t} = Y_t + (\beta\ \delta t)\ X_t\ Y_t/N - (\gamma\ \delta t)\ Y_t$$

$$Z_{t+\delta t} = Z_t + (\gamma\ \delta t)\ Y_t$$

- Average infectious period given by $1/\gamma$ [why?]

Mean life time calculation

Consider recovery of a single infectious individual $I(t) = e^{-\gamma t}$

$$1 = \int_o^\infty ce^{-\gamma t}dt \qquad = \frac{c}{\gamma}$$

Hence, probability density function is $\gamma e^{-\gamma t}$

$$\tau = \int_0^\infty t\gamma e^{-\gamma t}dt \; = \frac{1}{\gamma}$$

For a random variable x, with probability density function f(x), the mean is given by $\int_0^\infty xf(x)dx$

An ODE model

- Consider the equation describing Susceptible dynamics

$$X_{t+\delta t} = X_t - (\beta\, \delta t)\, X_t\, Y_t/N$$

- Re-write as

$$X_{t+\delta t} - X_t = -(\beta\, \delta t)\, X_t\, Y_t/N$$

$$(X_{t+\delta t} - X_t)/\, \delta t = \beta\, X_t\, Y_t/N$$

By fundamental theorem of calculus, as $\delta t \to 0$,

$$dX/dt = -\beta\, X\, Y/N$$

An ODE SIR model

$$\frac{dX}{dt} = -\beta X \frac{Y}{N}$$

$$\frac{dY}{dt} = \beta X \frac{Y}{N} - \gamma Y$$

$$\frac{dZ}{dt} = \gamma Y$$

- By definition, X+Y+Z = N
- These equations describe rates of change in state variables
- Parameters β, γ represent instantaneous rates

An ODE SIR model

In my lectures (as in K&R 2008), variables X, Y & Z refer to the numbers of individuals in each class. Variables S, I, & R refer to the proportions of the population in each class

- These equations describe rates of change in state variables
- Parameters β, γ represent instantaneous rates

An ODE SIR model

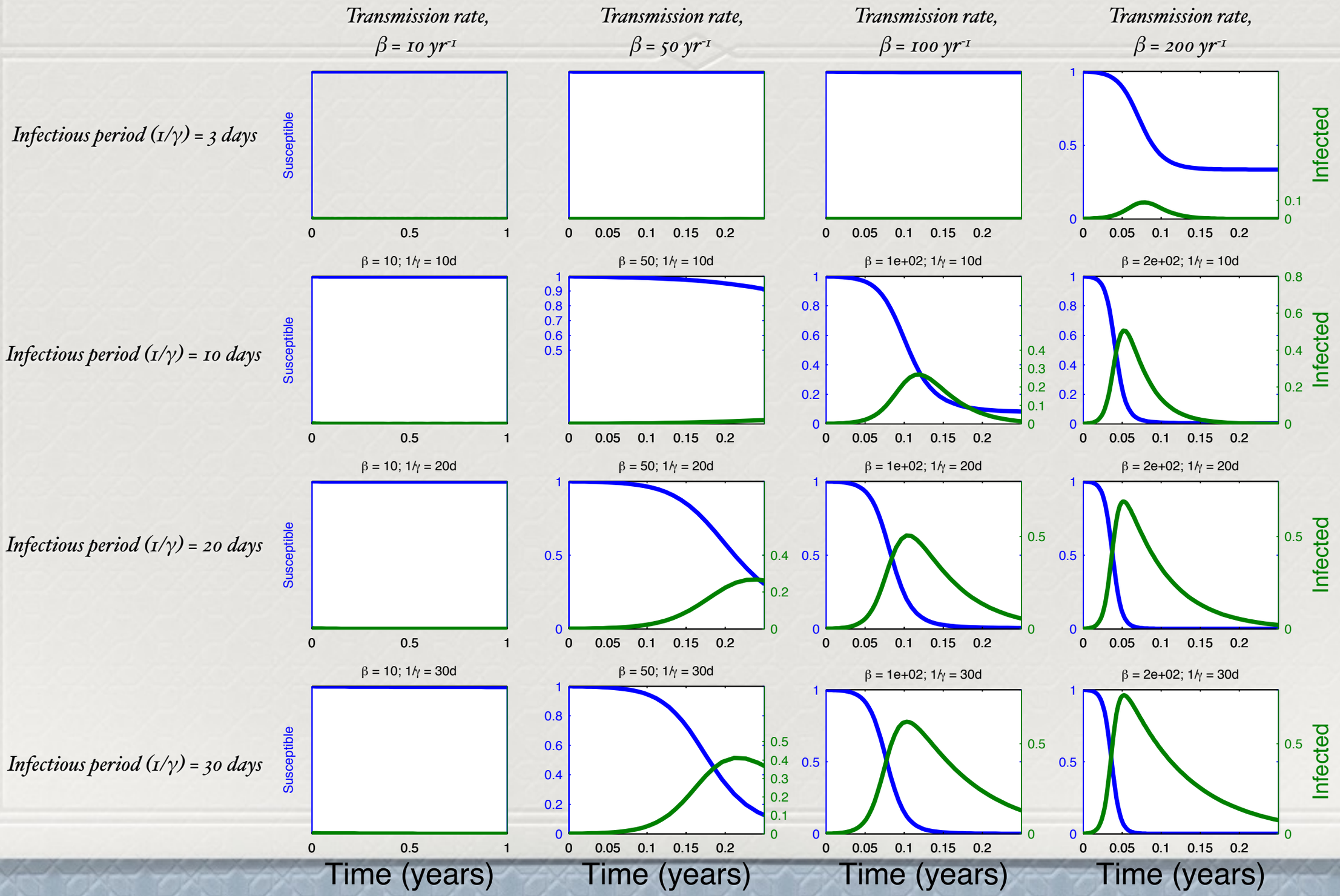
$$\frac{dX}{dt} = -\beta X \frac{Y}{N}$$

$$\frac{dY}{dt} = \beta X \frac{Y}{N} - \gamma Y$$

$$\frac{dZ}{dt} = \gamma Y$$

- Important to notice: transmission rate is assumed to depend on frequency of infecteds in population (Y/N). Hence, this is frequency-dependent transmission

Simulating epidemics



Model dynamics

- *As parameters are varied, model predicts different outcomes*
- *Can we anticipate trajectories without resorting to numerical integration?*
- *Question: under what conditions will an infectious disease invade a system?*

The Invasion Threshold

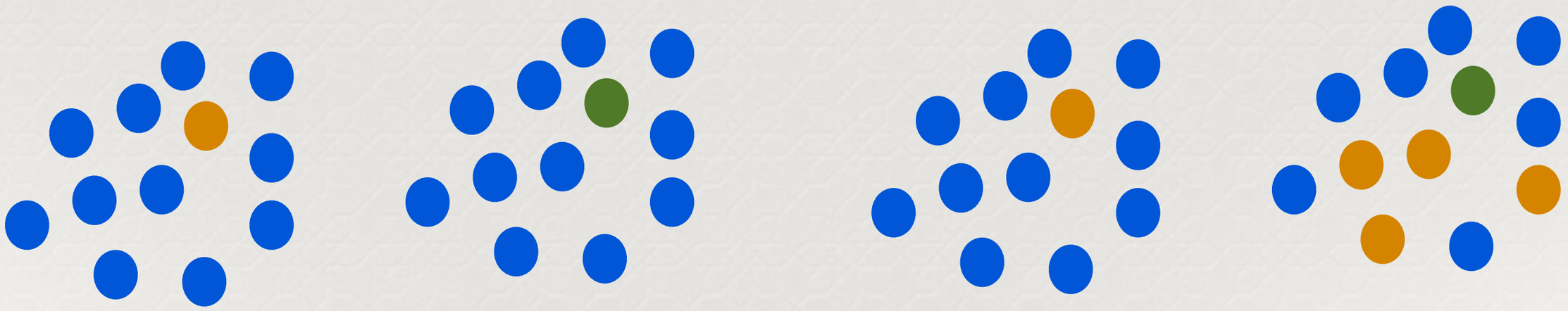
- When can an infectious disease invade a population?
- Initial conditions: $X(0) = N$, $Y(0) = 1$, $Z(0) = 0$
- Invasion only if $dY/dt > 0$
- ie, $\beta XY/N - \gamma Y > 0 \quad \Rightarrow Y(\beta X/N - \gamma) > 0$
  - If and only if $X/N > \gamma/\beta$
  - Since $X=N$, requires $1 > \gamma/\beta$
  - Or $\beta/\gamma > 1$

Kermack & McKendrick (1927)

Basic Reproductive Ratio, R_o

- Ratio β/γ gives number of cases before infected individual recovers
- Universally referred to as R_o or **Basic Reproductive Ratio**

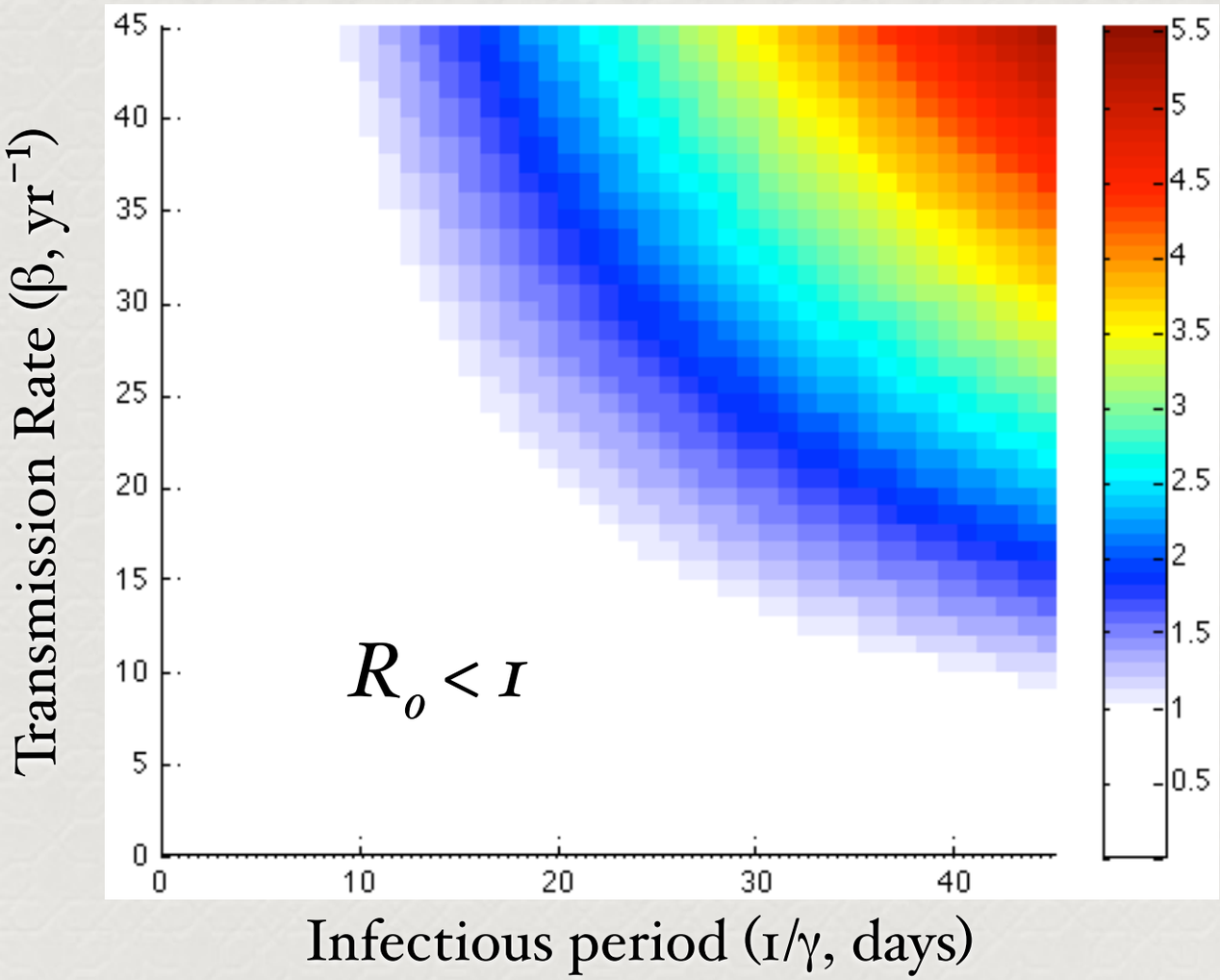
- Definition: Number of secondary cases generated by a typical infected in an entirely susceptible population



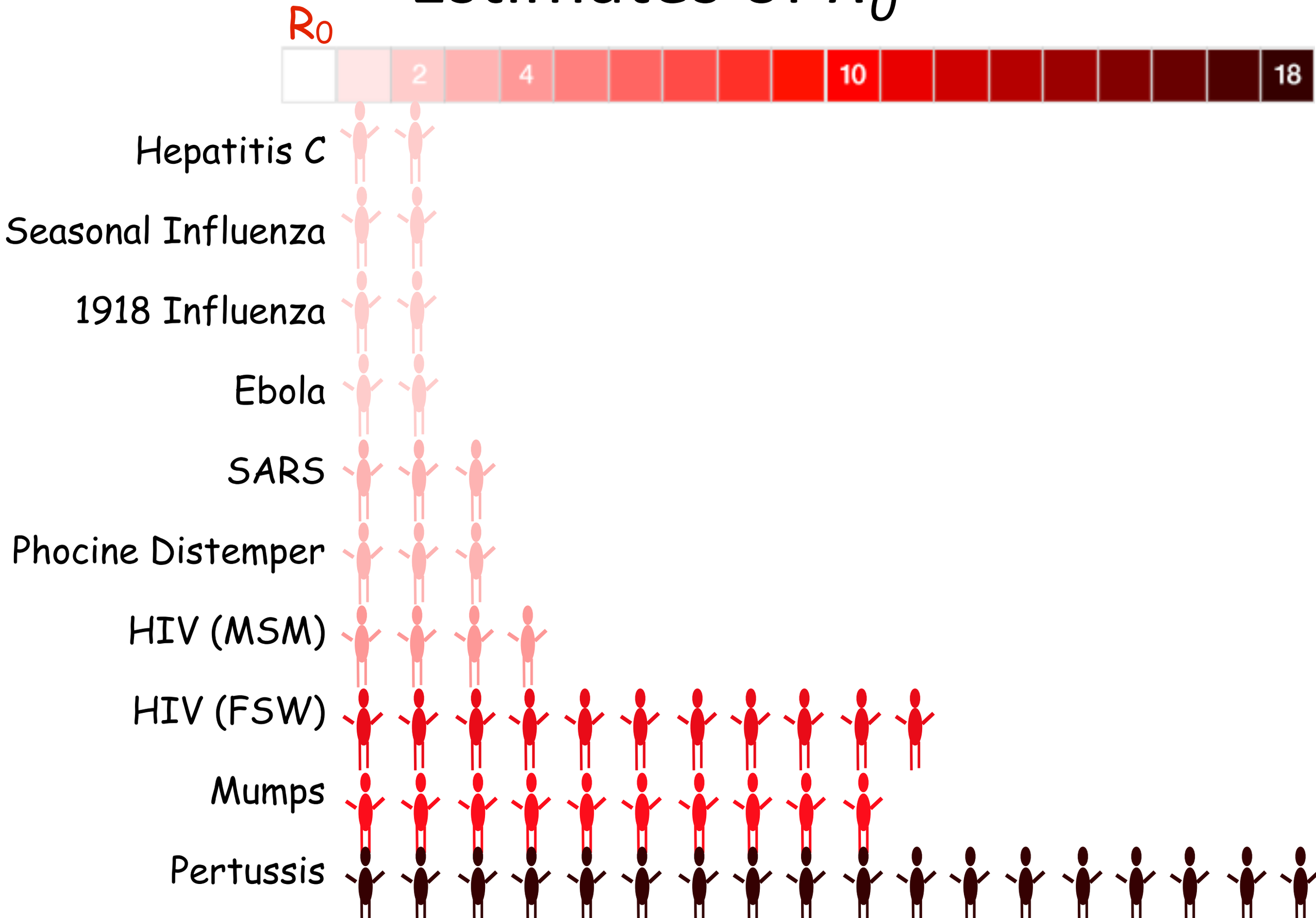
$R_0 < 1$
No invasion

$R_0 = 4$
Successful invasion

R_o and Model parameters



Estimates of R_0



The death of an epidemic

- In SIR equations, let's divide equation for dX/dt by dZ/dt:

  $dX/dZ = -(\beta X Y/N)/(\gamma Y)$

  $= -R_o X/N$

- Integrate with respect to Z
  - $X(t) = X(0)\, e^{-Z(t) R_o/N}$

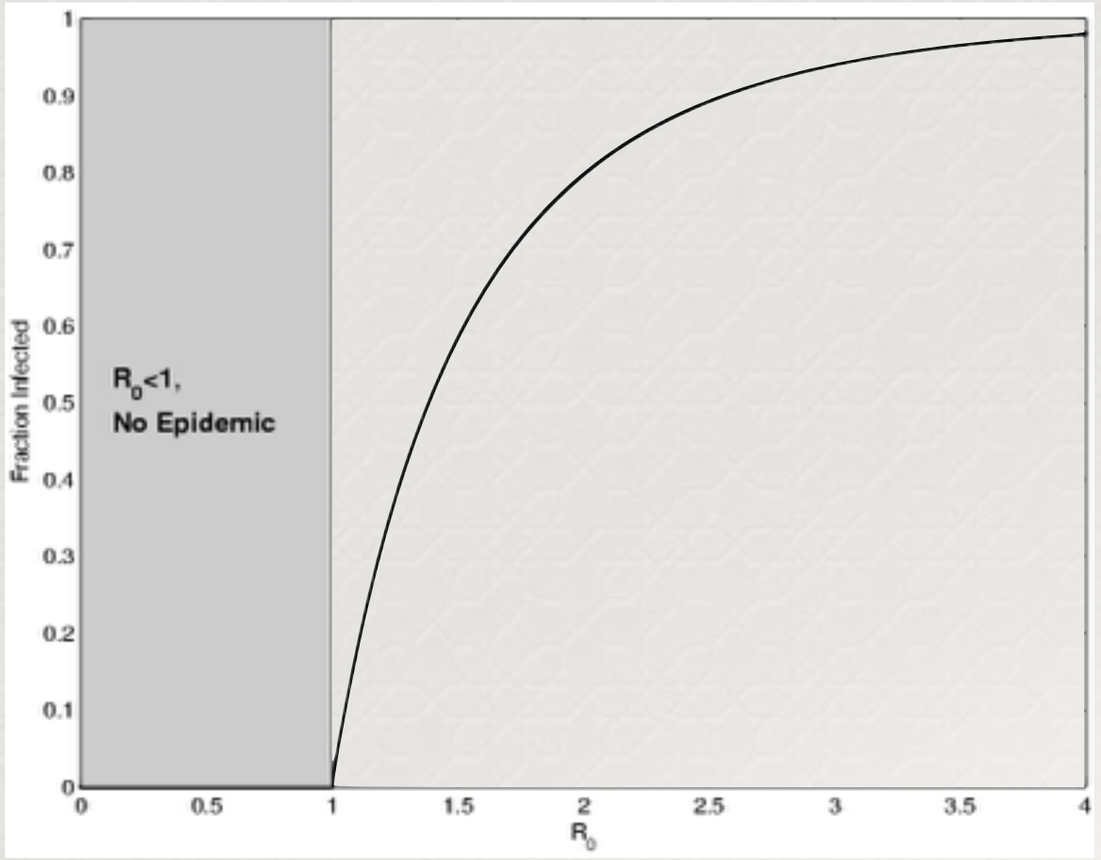
- When epidemic is over, by definition, we have $X(\infty)$, $Y(\infty)$ $(=0)$, and $Z(\infty)$

- $X(\infty) = N - Z(\infty) = X(0)\, e^{-Z(\infty) R_o/N}$

The death of an epidemic

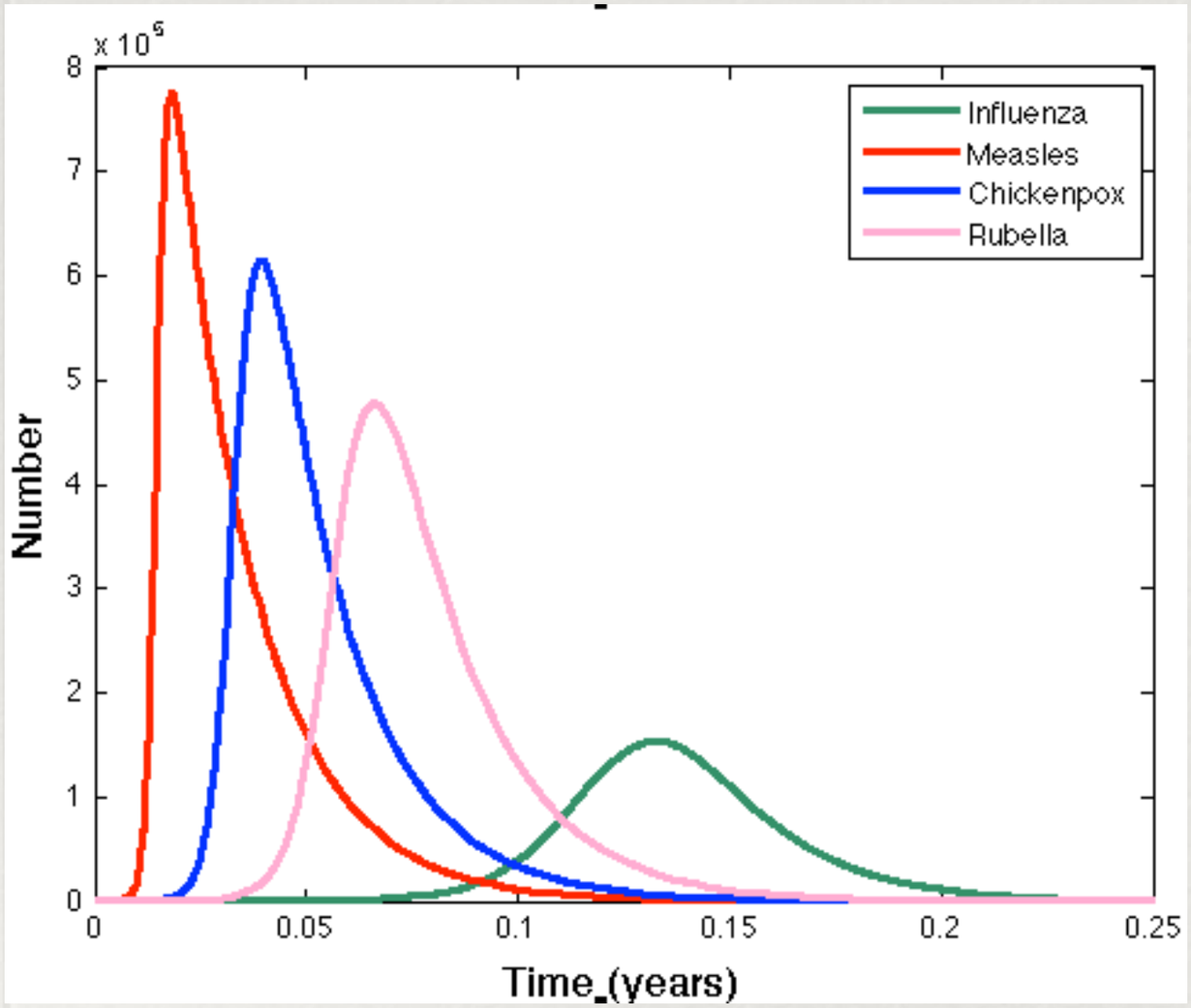
- So, $N - Z(\infty) - X(0)\, e^{-Z(\infty) R_0/N} = 0$
- Solve this numerically ('transcendental' equation)

Epidemic dies out because there are too few infectives, not because of too few susceptibles



Kermack & McKendrick (1927)

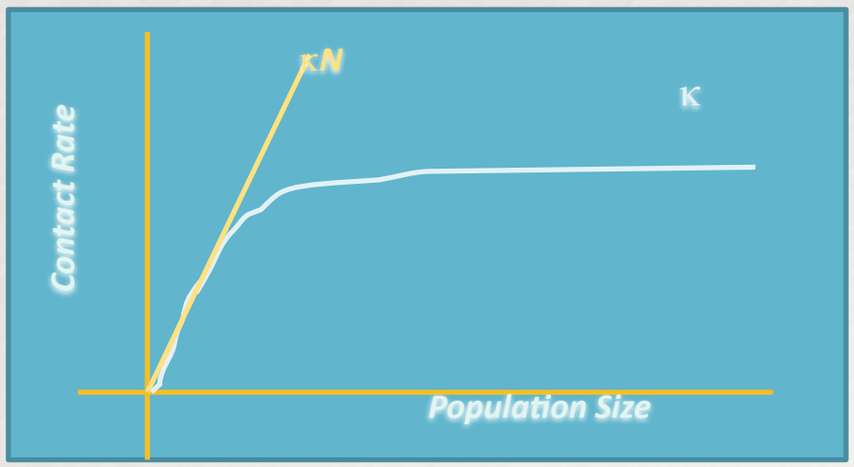
Simple Epidemics



	β	$1/\gamma$	R_0
"Measles"	886 yr^{-1}	0.019 yr	17
"Influenza"	180 yr^{-1}	0.011 yr	2
"Chickenpox"	315 yr^{-1}	0.022 yr	7
"Rubella"	200 yr^{-1}	0.025 yr	5

Frequency- or Density-Dependent Transmission?

- Assumed contact rate, κ, constant: 'mixing' is independent of population size: frequency-dependent transmission. Reasonable?
- If we assume contact rate to be κN (increases with 'crowding'), then transmission rate is
  - $dX/dt = -\beta XY$
- Called density-dependent transmission



Does it Matter?

- Again, pathogen invasion if $dY/dt > 0$
- If initially everyone susceptible ($X=N$),

$$\beta NY - \gamma Y > 0 \Rightarrow Y(\beta N - \gamma) > 0$$

- In this case, we define $R_0 = \beta N/\gamma$, so need $R_0 > 1$

- Hence, for any particular β and γ, there's now a threshold population density required for invasion

Incorporating virulence

- *Assume infectious individuals die at rate* α

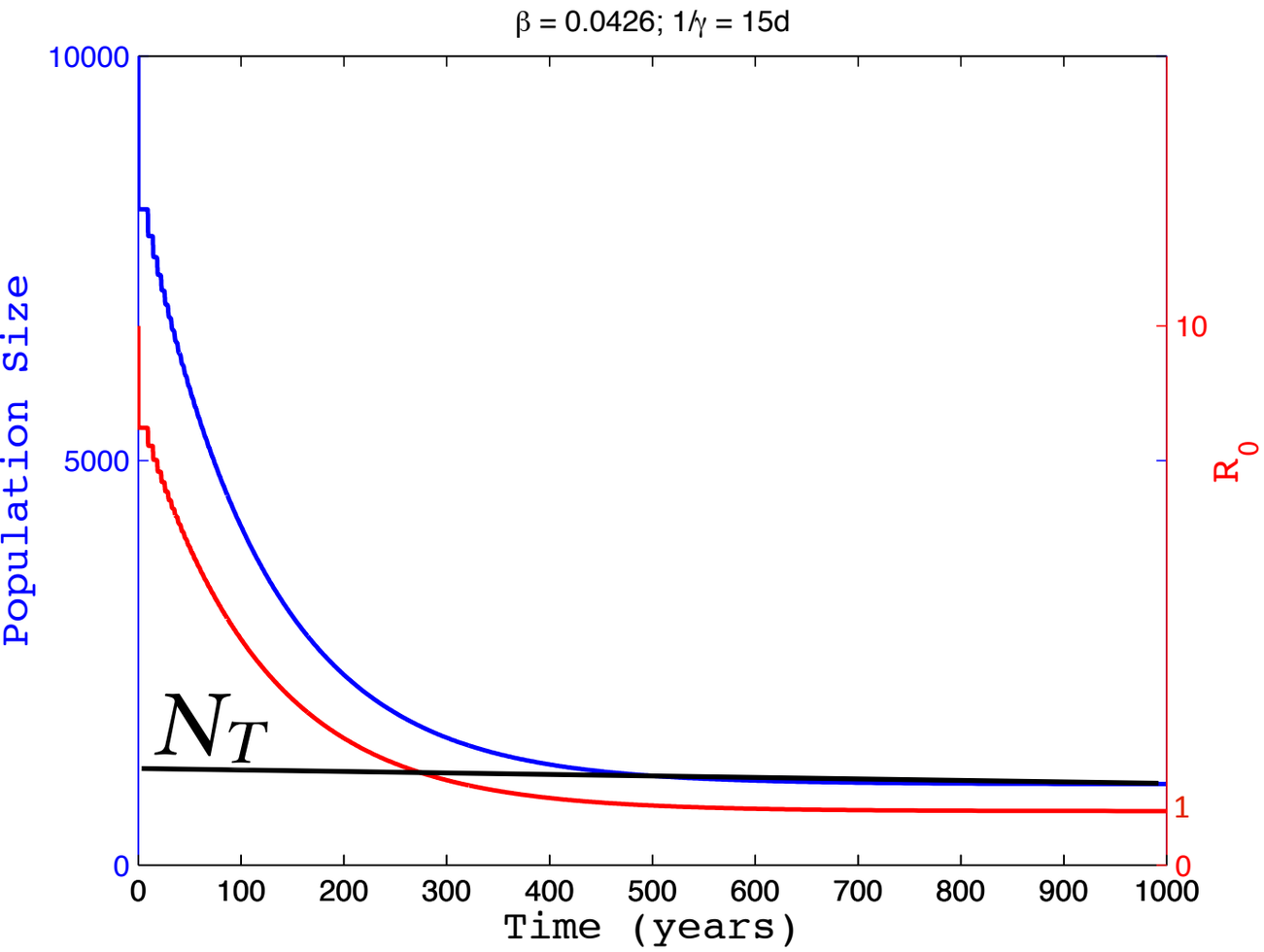
$$\frac{dY}{dt} = \ldots - \gamma Y - \alpha Y$$

Transmission & R_0

Density Dependent

β=0.0426, γ=24, α=18, μ=0.02

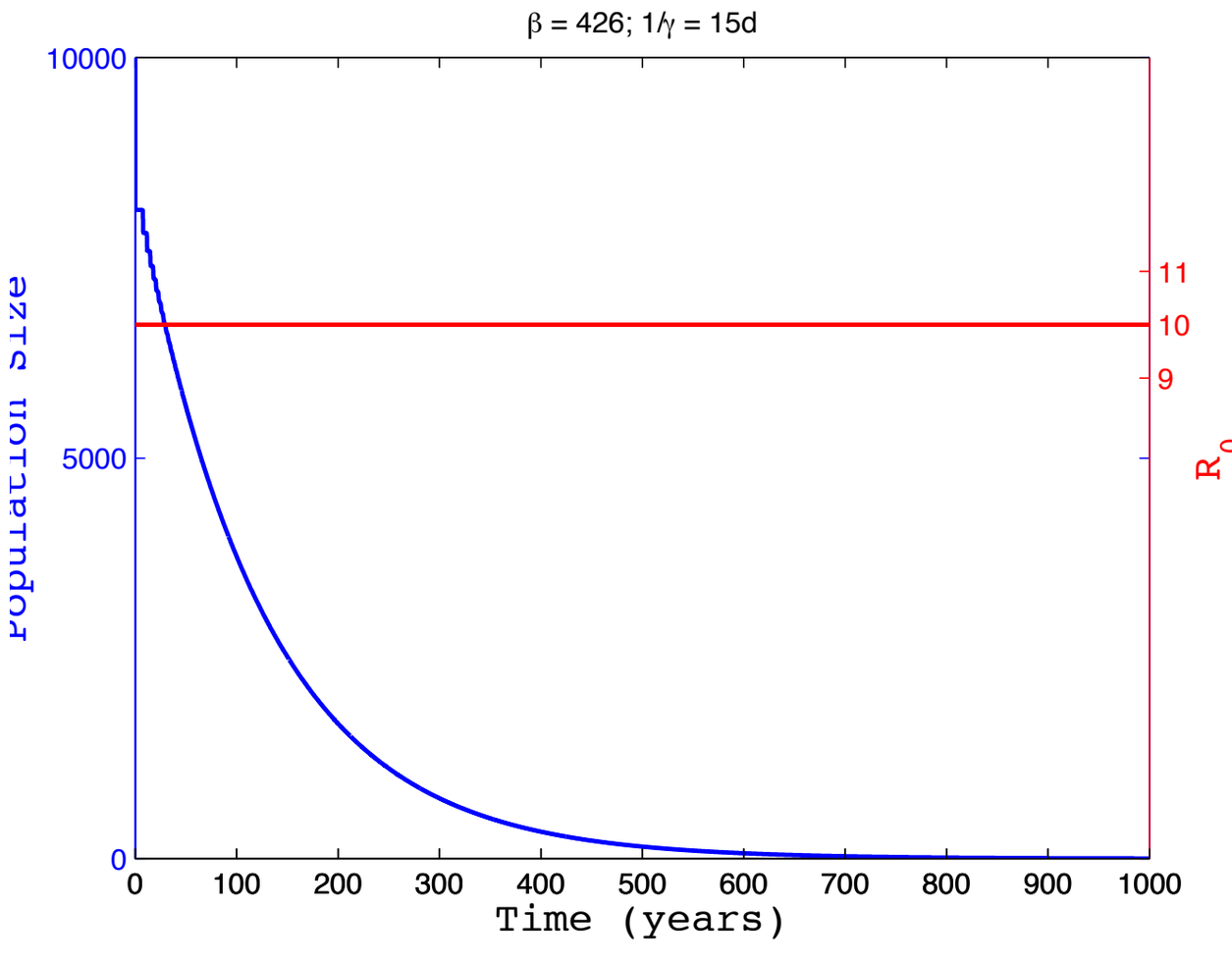
N_T = 1000



Frequency Dependent

β=426, γ=24, α=18, μ=0.02

No invasion threshold



FD transmission → pathogen can wipe out host

What should we do?

- If population size doesn't change, FD & DD equivalent ($\beta_{FD} = N \times \beta_{DD}$)
- Otherwise:
  - Frequency-dependence generally more appropriate in large populations with heterogenous mixing, STDs, vector-borne pathogens
  - Density-dependence representative of wildlife & livestock diseases (especially with smaller population sizes)