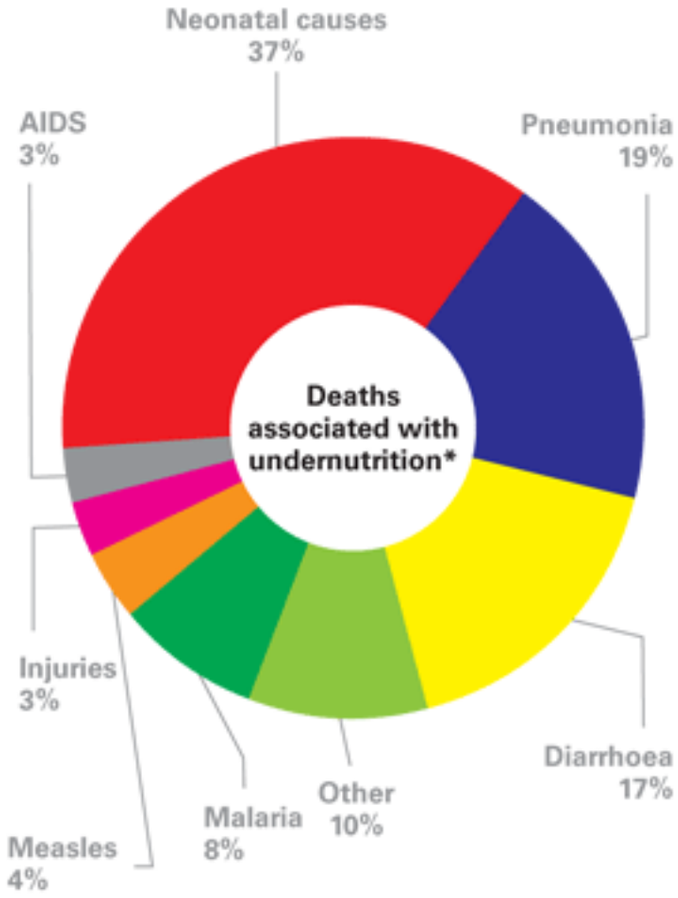
MATHEMATICAL MODELS OF INFECTIOUS DISEASES

Pej Rohani & John Drake

Odum School of Ecology
University of Georgia

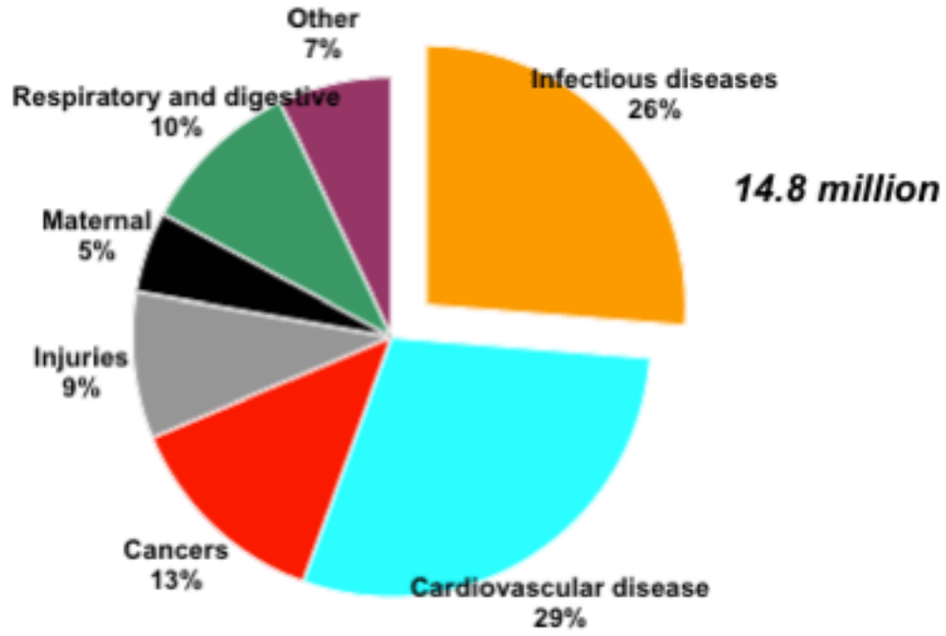
GLOBAL CAUSES OF MORTALITY

World Health Organization



* Undernutrition has been estimated to be an underlying cause in up to half of all under-five deaths. This estimate will be revised in 2008.

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



In low-income countries, 45% of all deaths are from infectious diseases

Total mortality

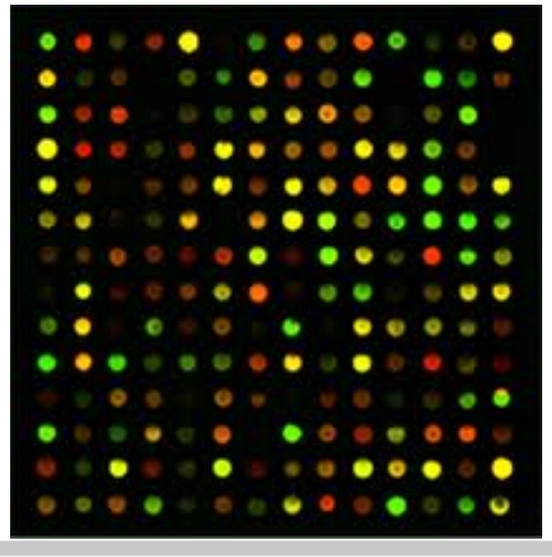
Infant mortality

MULTIFACETED APPROACH TO UNDERSTANDING INFECTIOUS DISEASES

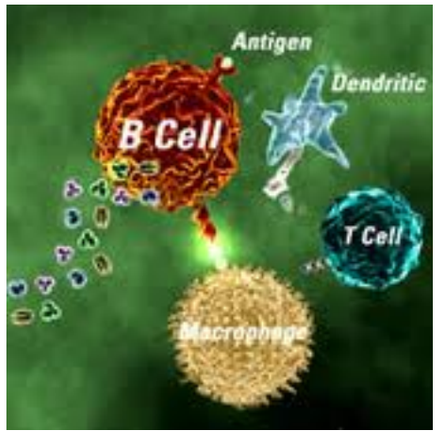
Medicine

Microbiology

Genomics



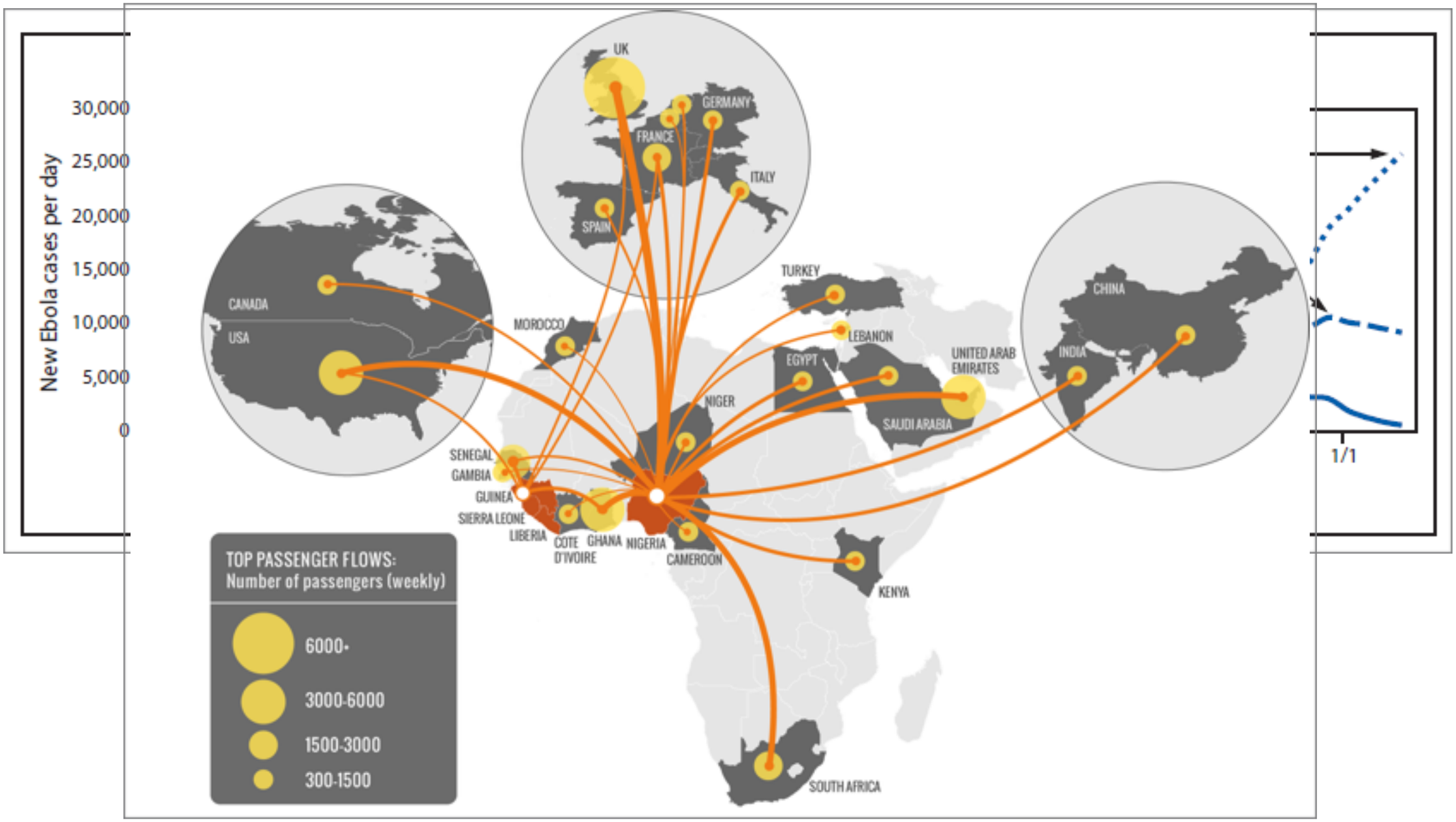
Immunology



Vaccines & Drugs

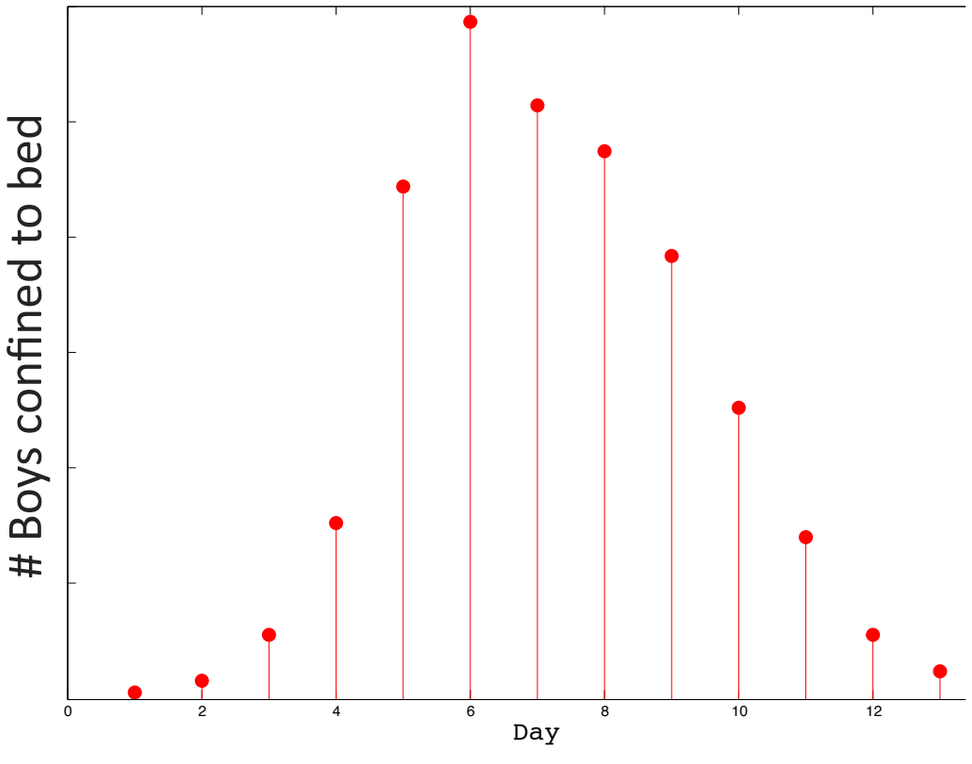
But these approaches don't address important questions at population level ...

EMERGING PATHOGENS



SCHOOL OUTBREAK

Boarding School, England
Jan 1978

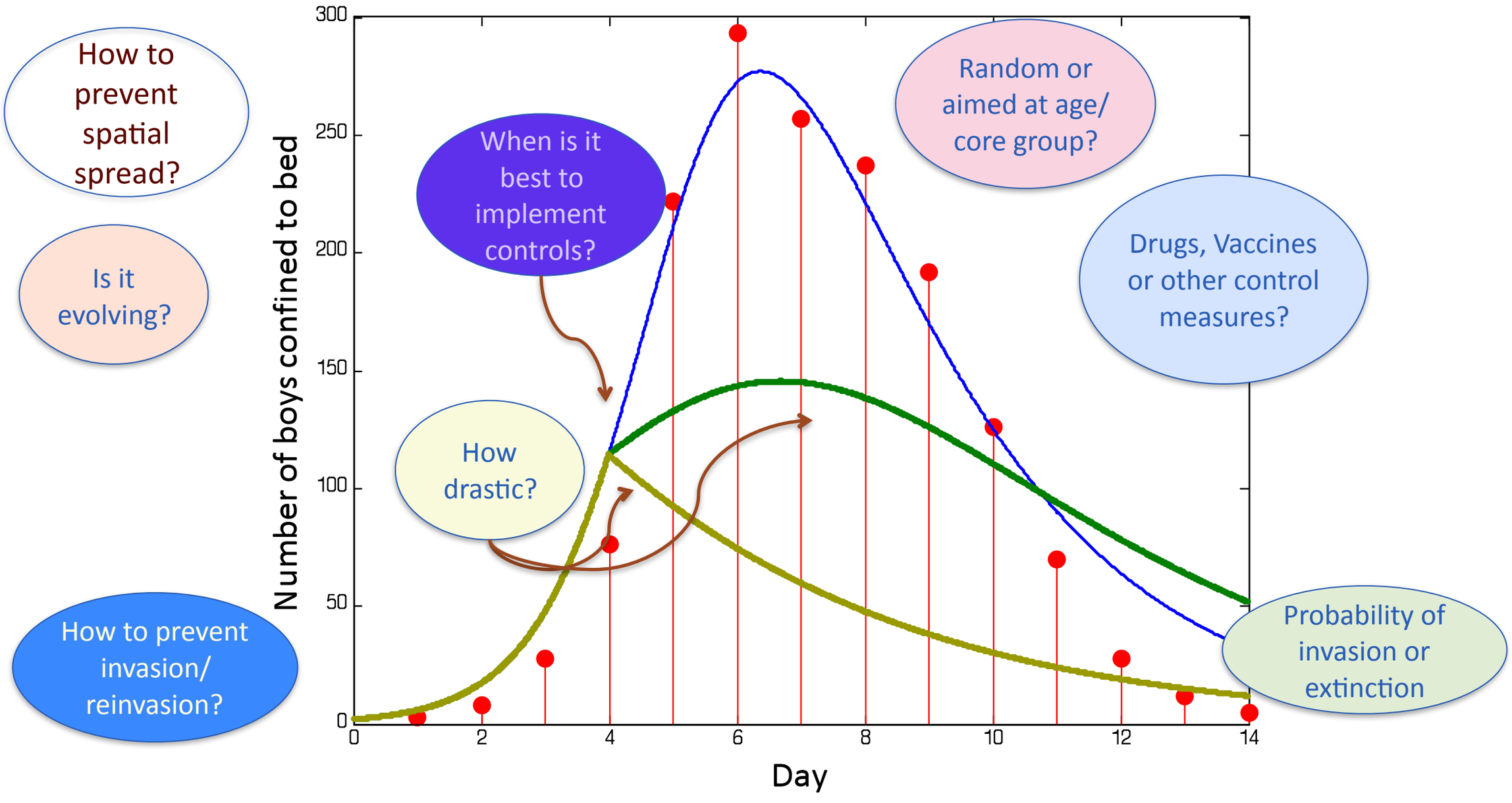


Raises numerous questions:

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

MODELING QUESTIONS I. BASICS

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 mechanistic model is different from statistical analyses of data

ABSTRACTION

Purpose

Components

Reality

Conceptualization

Abstraction

Interpretation

Assumptions

Limitations

Validation

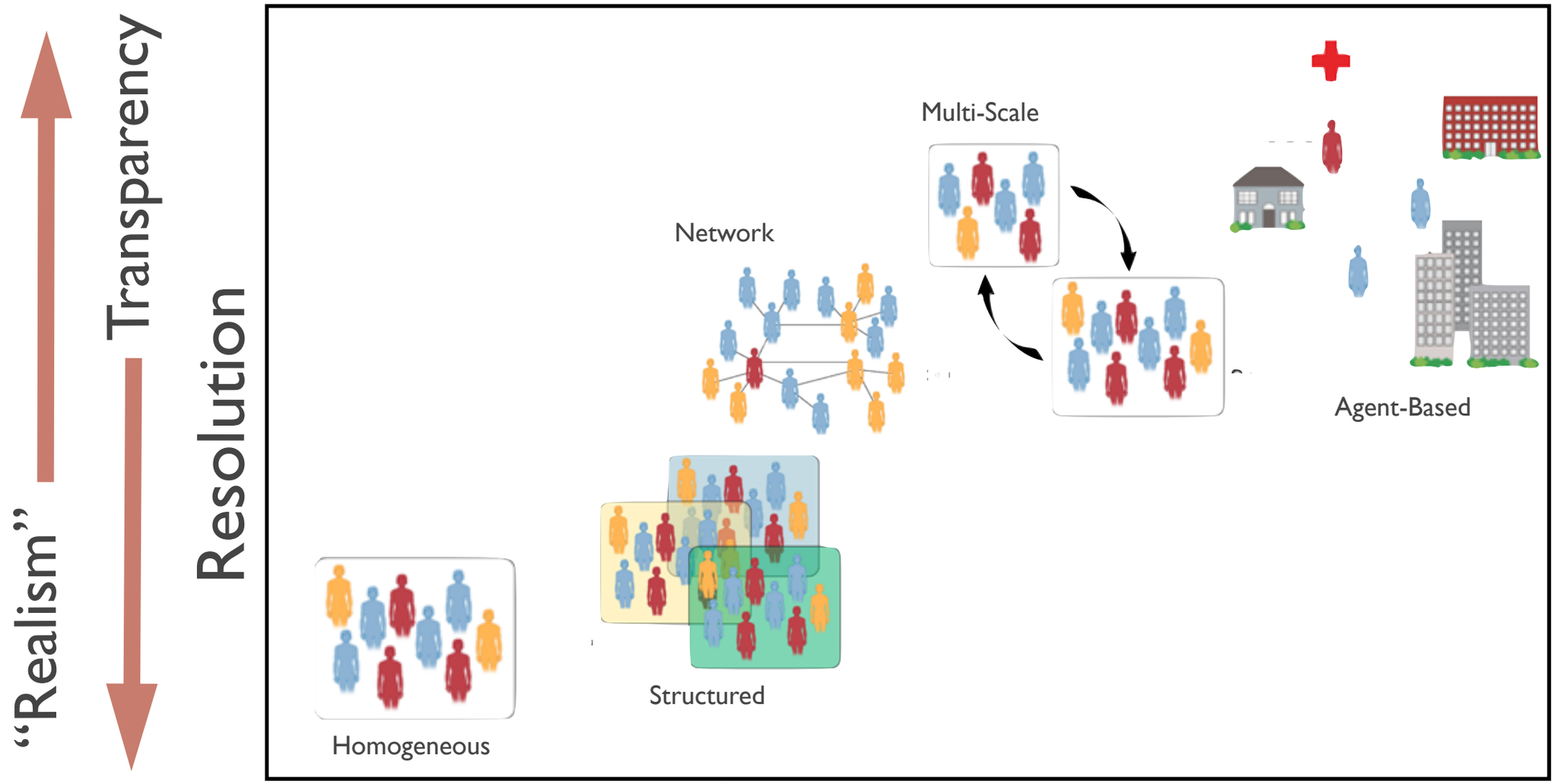
WHAT'S A 'GOOD' MODEL?

- 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

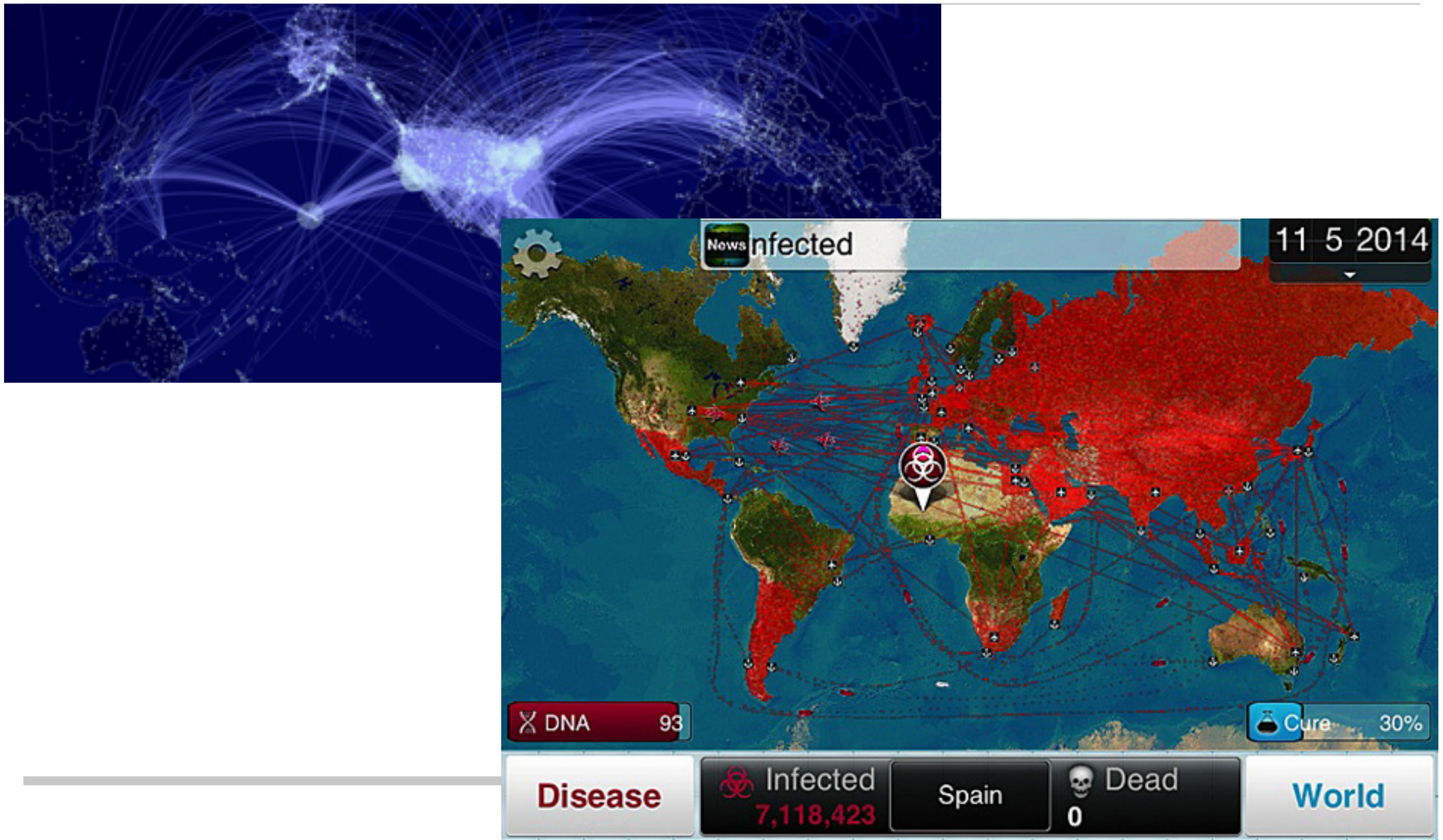
Construct most “appropriate” model and use whatever combination of methods for analysis and prediction.

Ready-Made Software

ModelMaker

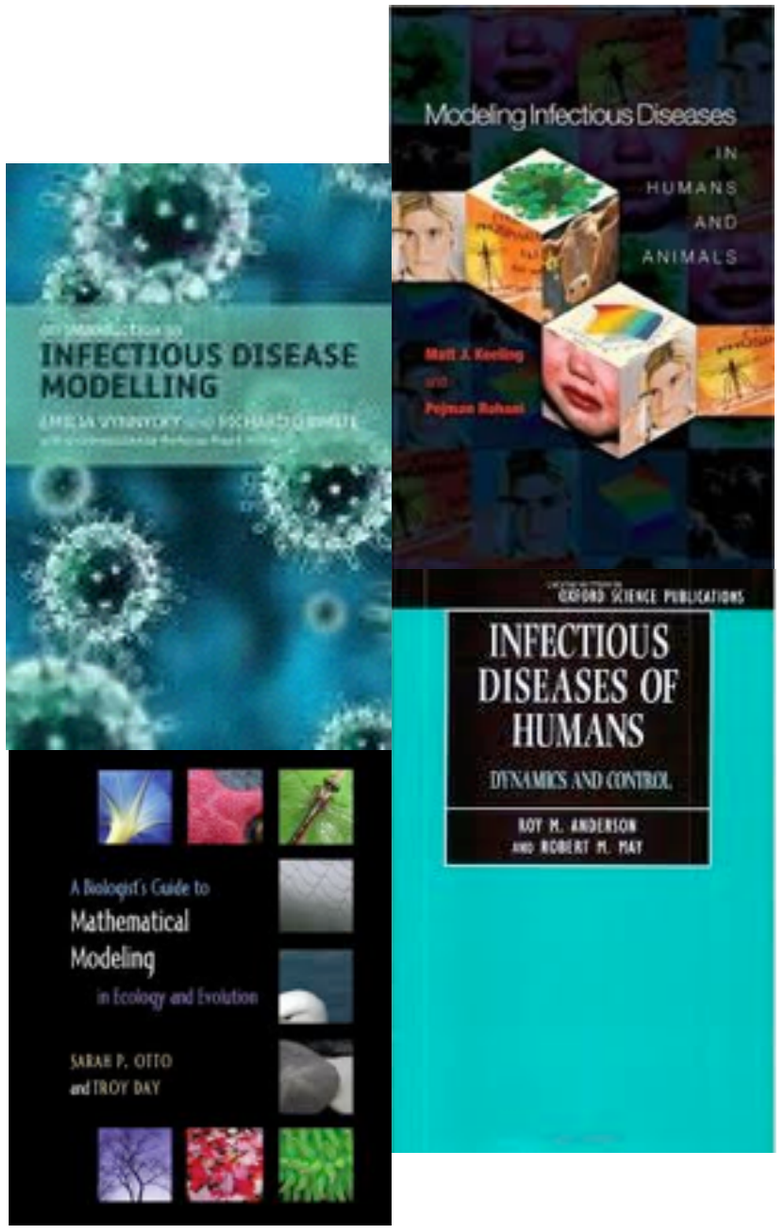
www.modelkinetix.com/modelmaker/modelmaker.html

GLOBAL SIMULATORS



RESOURCE MATERIALS

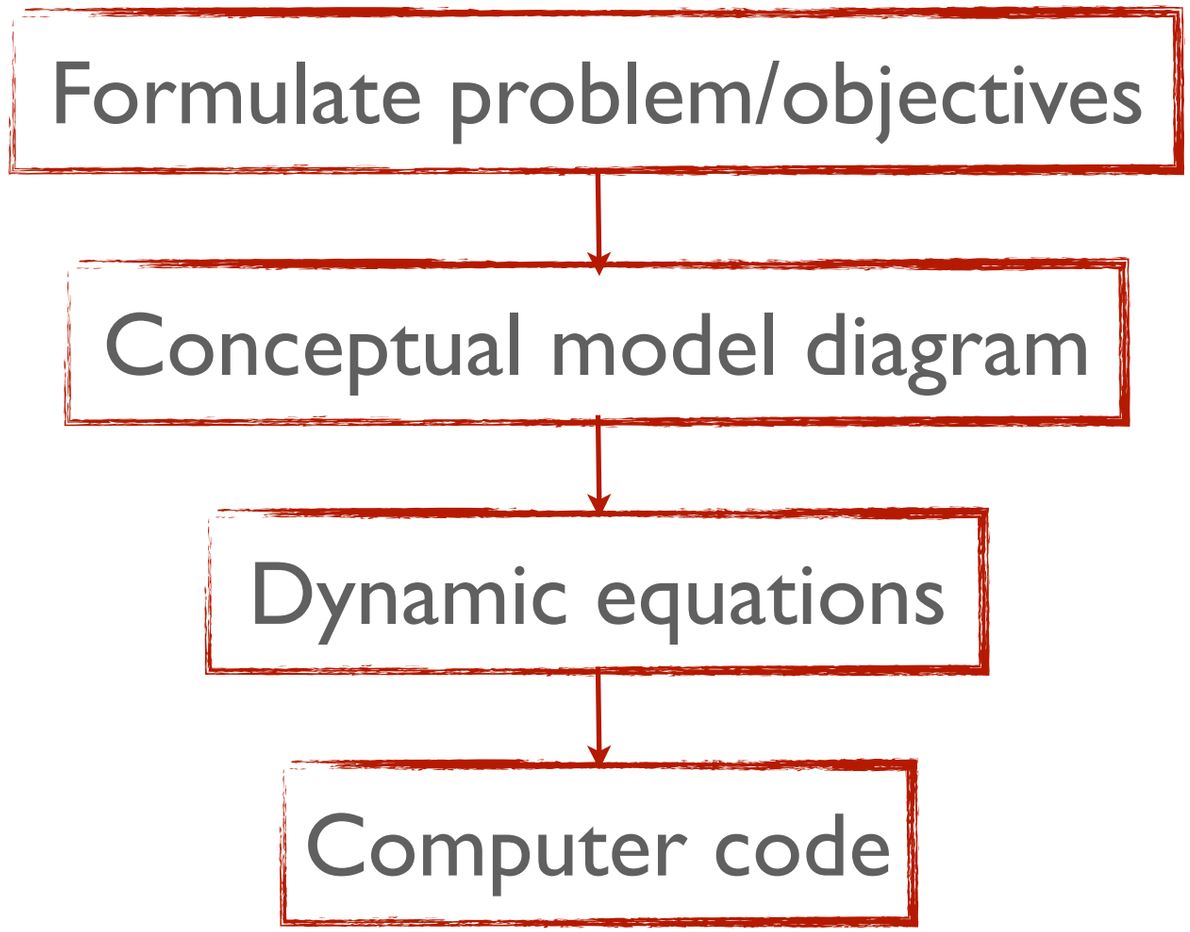
- Keeling & Rohani (2008)
- Vynnycky & White (2010)
- Anderson & May (1991)
- Otto & Day (2007)



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
  - Age-structured transmission
  - Realistic pathogenesis
  - Seasonality
- Objective 5: Sensitivity & Variability
  - Stochastic implementation
  - Parameter uncertainty

STEPS IN DEVELOPING A MODEL



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?

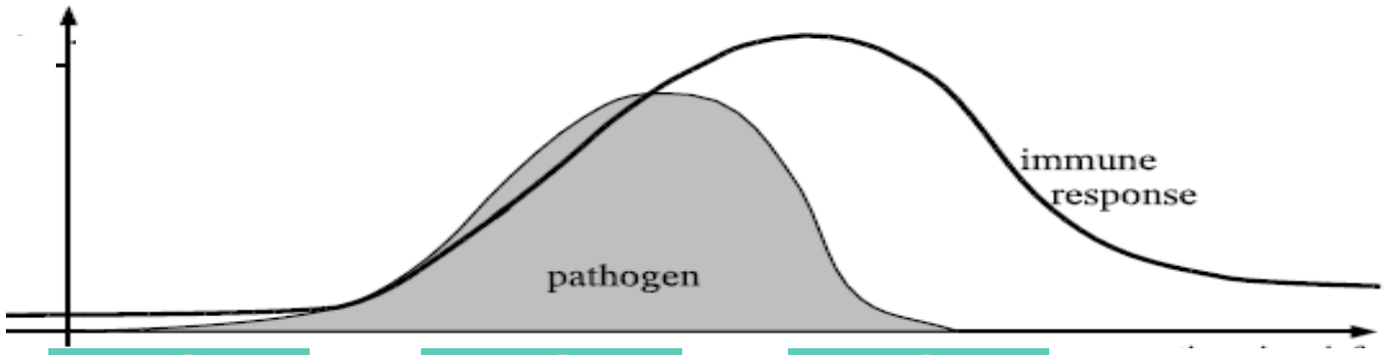
CATEGORISING INDIVIDUALS

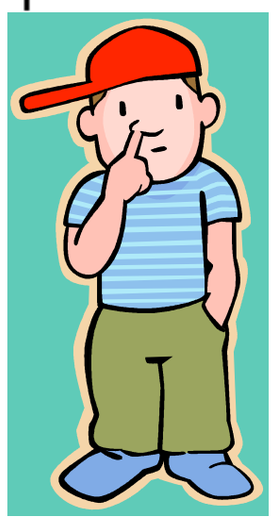
Healthy → Incubating → Diseased

Clinical status

Susceptible → Exposed/latent → Infectious → Recovered/Immune

Infection status

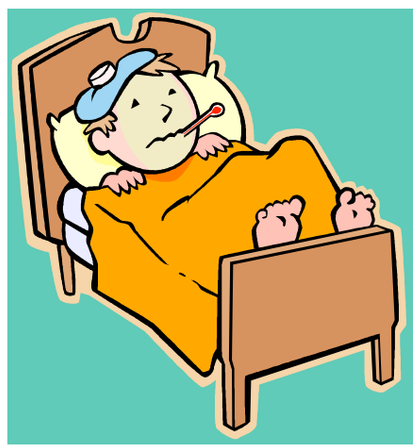




Incubating

Infectious, latent

Infectious, symptomatic



Infectious, quarantined

THE SIMPLEST MODELS

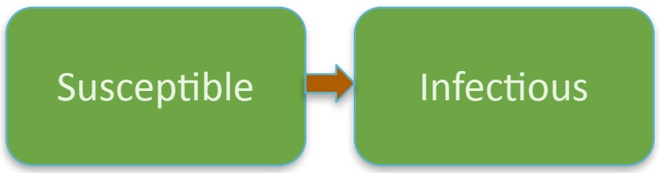
- Pragmatic choice: categorise individuals in population according to their infection status, eg:
  - Susceptible
  - Infectious
  - Recovered/Immune

These are our
"system variables"

THE SIMPLEST MODELS

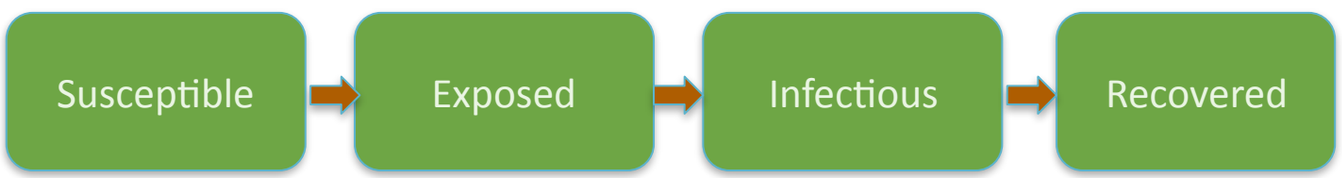
2. **What model structure?**

   -- Determined by pathogen biology

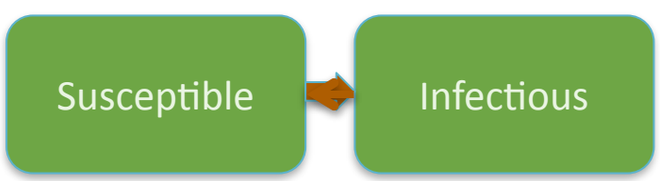


SI – signifies fatal infection

SIR – recovery after infection



SEIR – latency

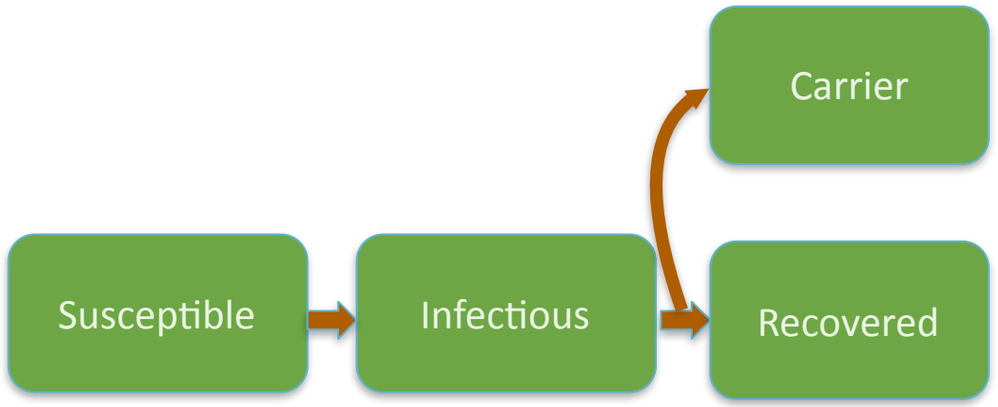


SIS – no immunity elicited

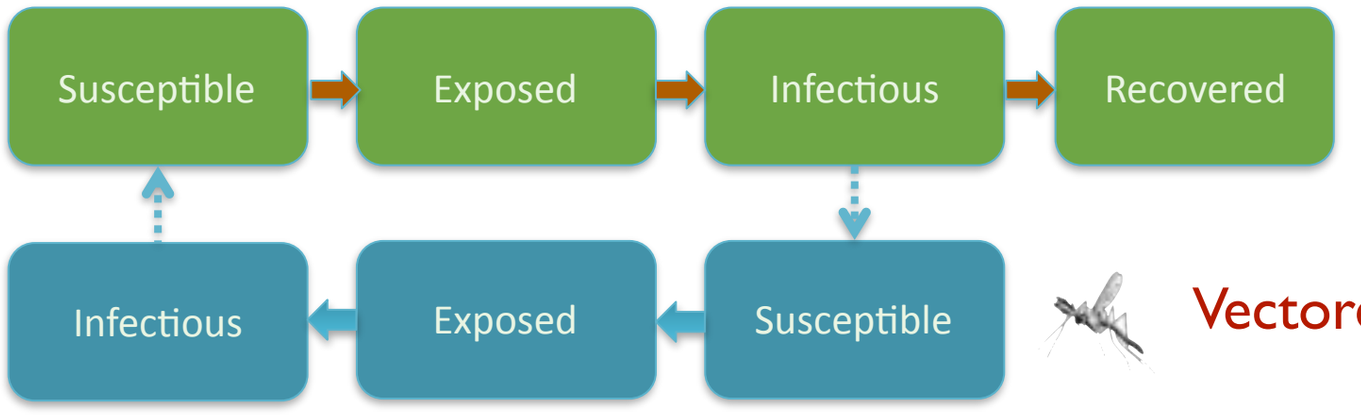
THE SIMPLEST MODELS

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

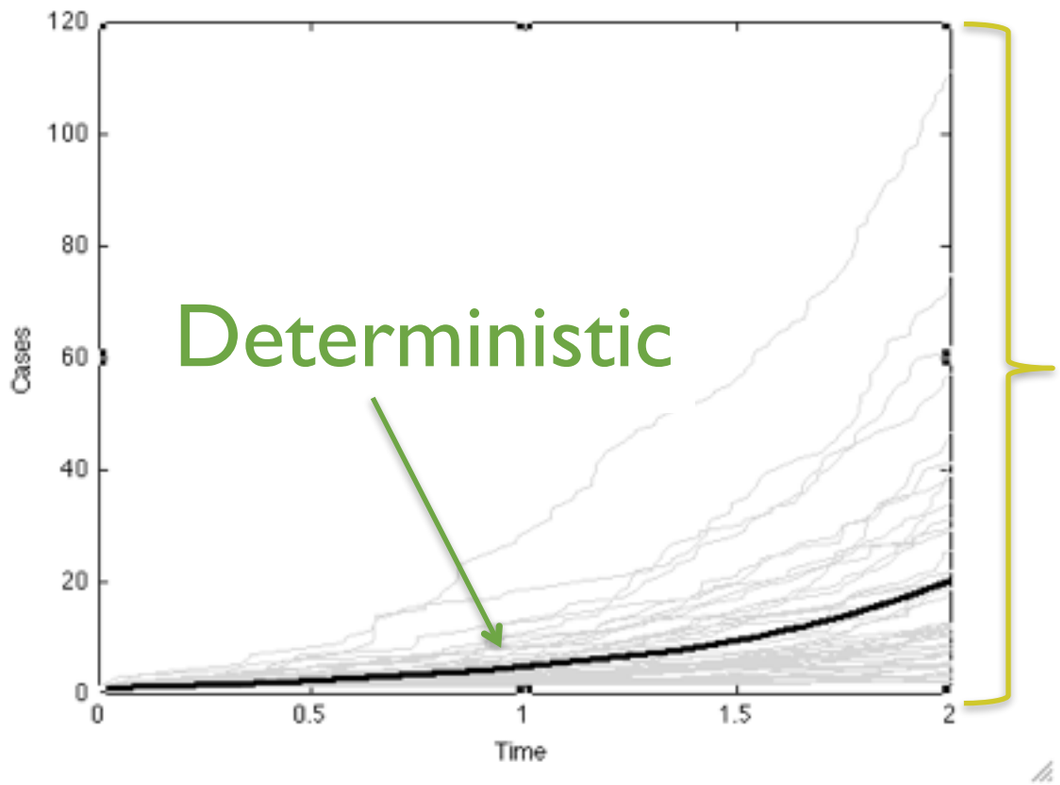
- Flow between classes/compartments determined by details of host population structure and pathogen biology

- Host population size
- Contact rates
- Pathogen infectivity

These are our "parameters"

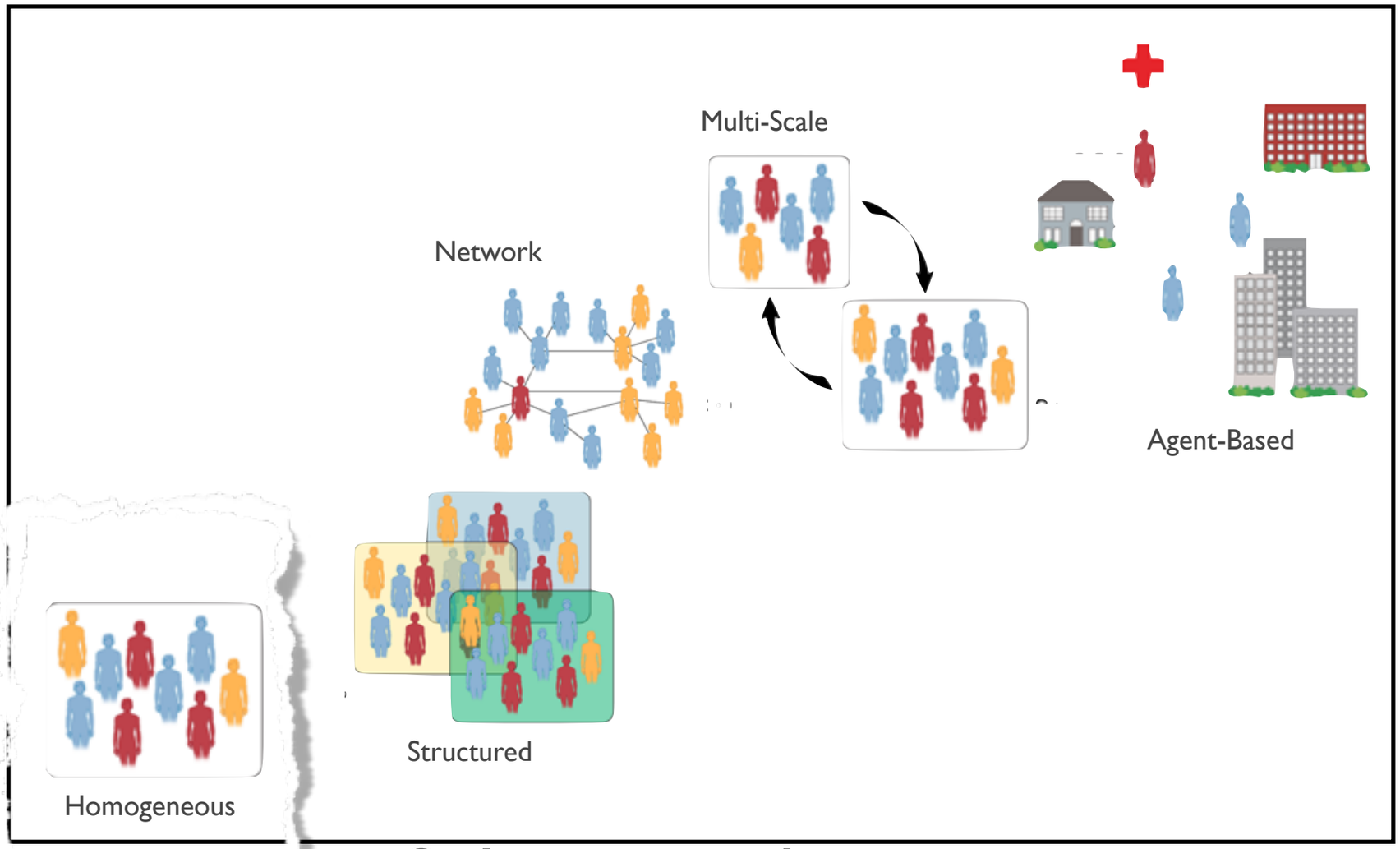
THE SIMPLEST MODELS

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

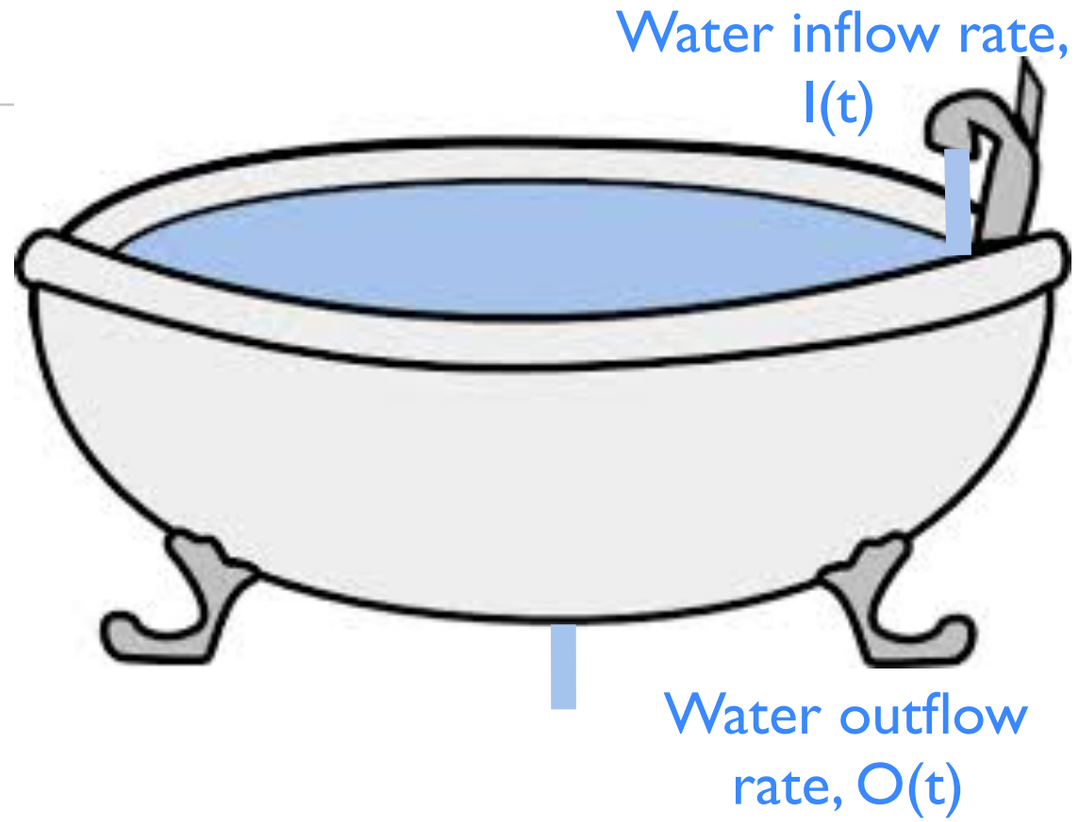
- OTHER AUTHORS MAY USE DIFFERENT LETTERS TO DENOTE SAME VARIABLES OR PARAMETERS.

- 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

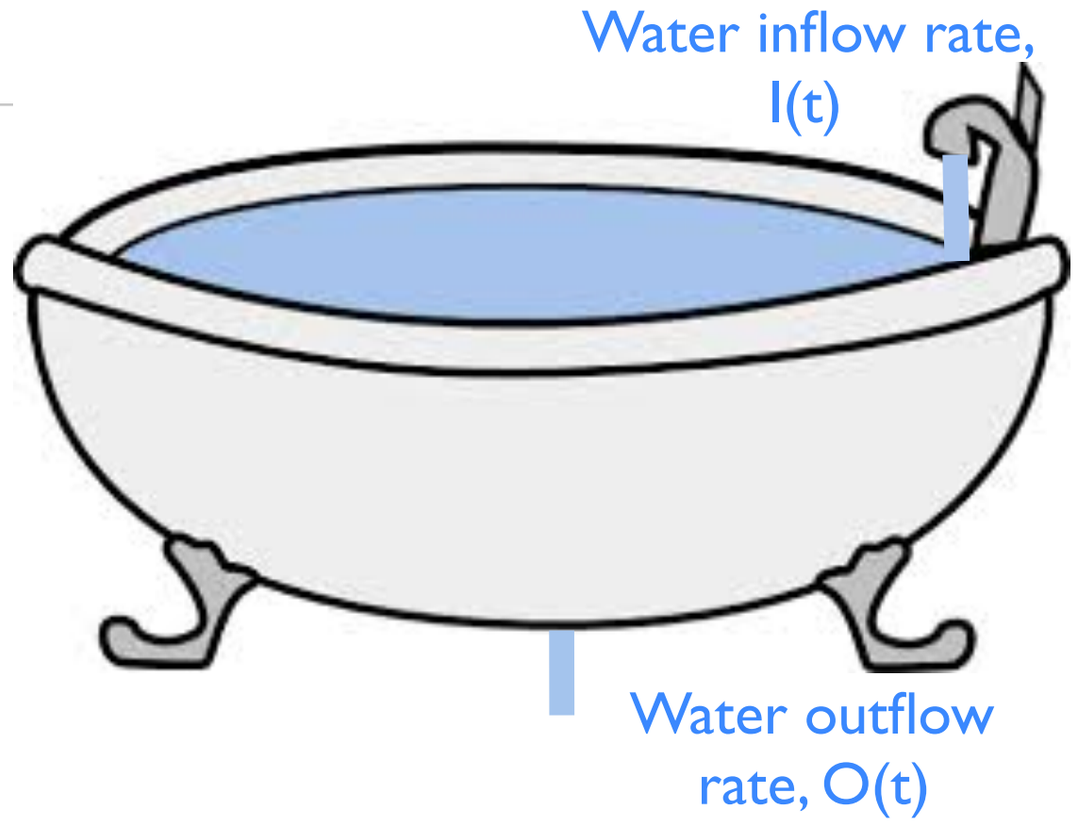


* Consider a small time interval, δt
* Then,

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

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 δt → 0

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

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 $I(t) = e^{-\gamma t}$

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

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 $\int_0^\infty x f(x)dx$

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 $\delta t \rightarrow 0$,

$$dX/dt = -\beta\, XY/N$$

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

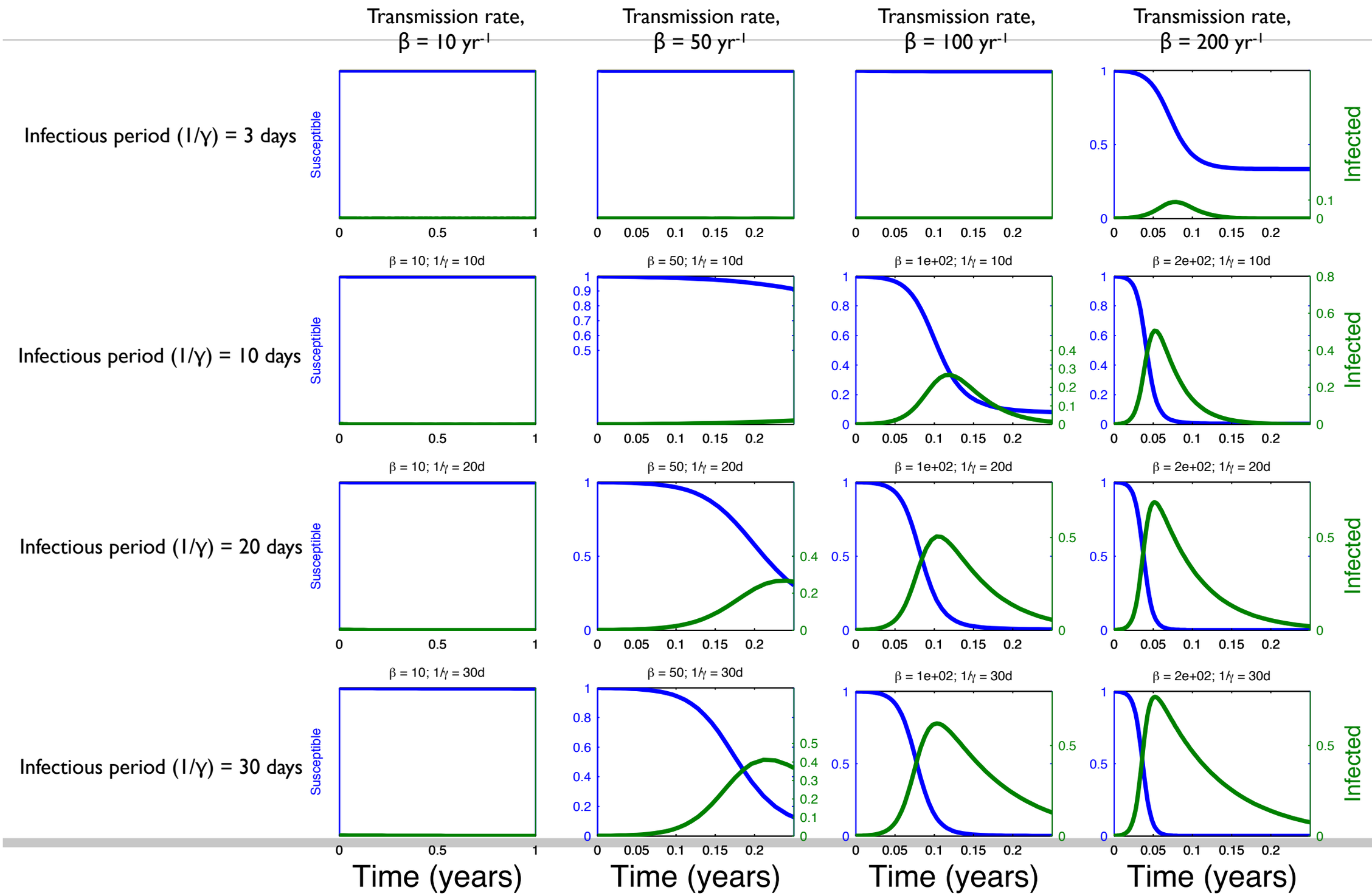
$$\frac{dX}{dt} = -\beta X \frac{Y}{N}$$

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

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

- 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?

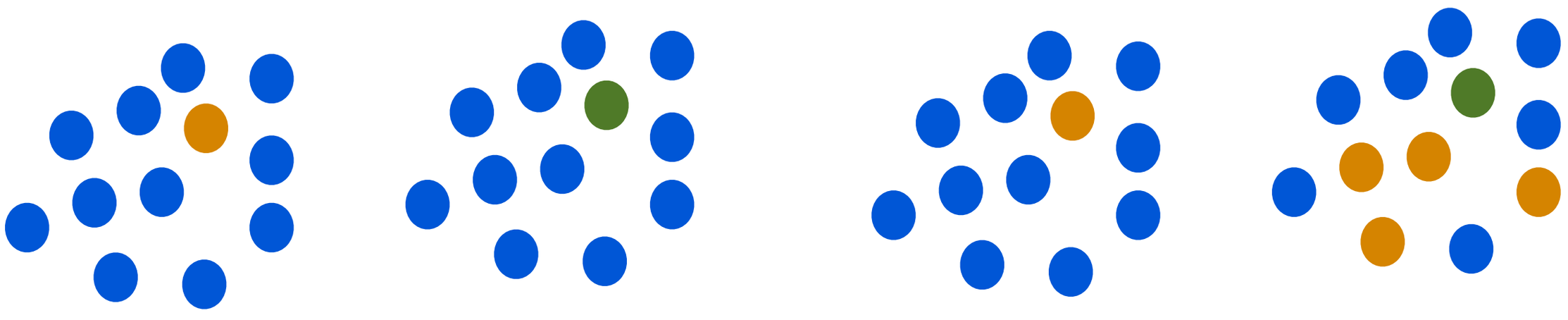
THE INVASION THRESHOLD

- 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_0

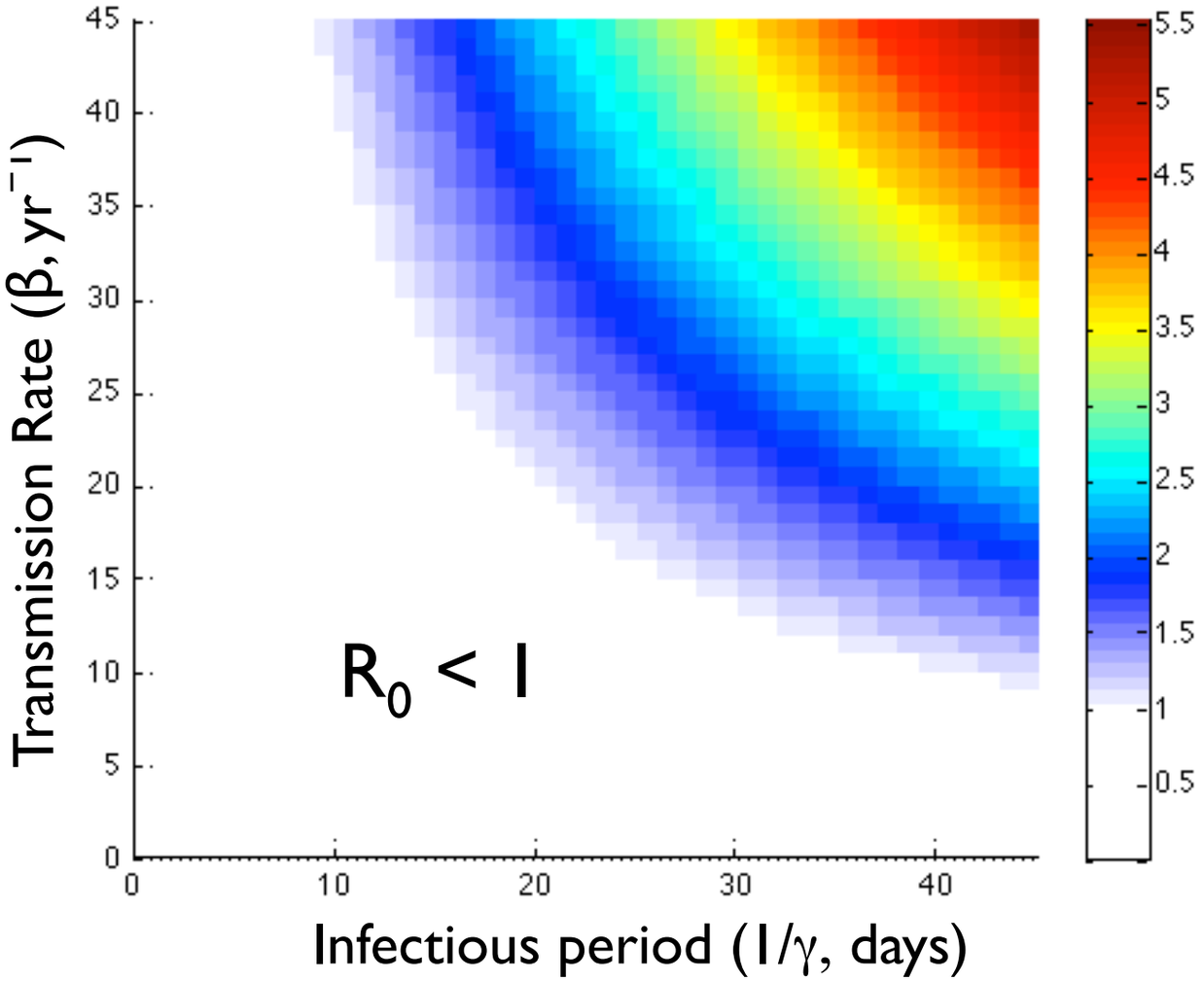
- Ratio β/γ gives number of cases before infected individual recovers
- Universally referred to as R_0 or **Basic Reproductive Ratio**
- Definition: Number of secondary cases generated by a typical infected in an entirely susceptible population



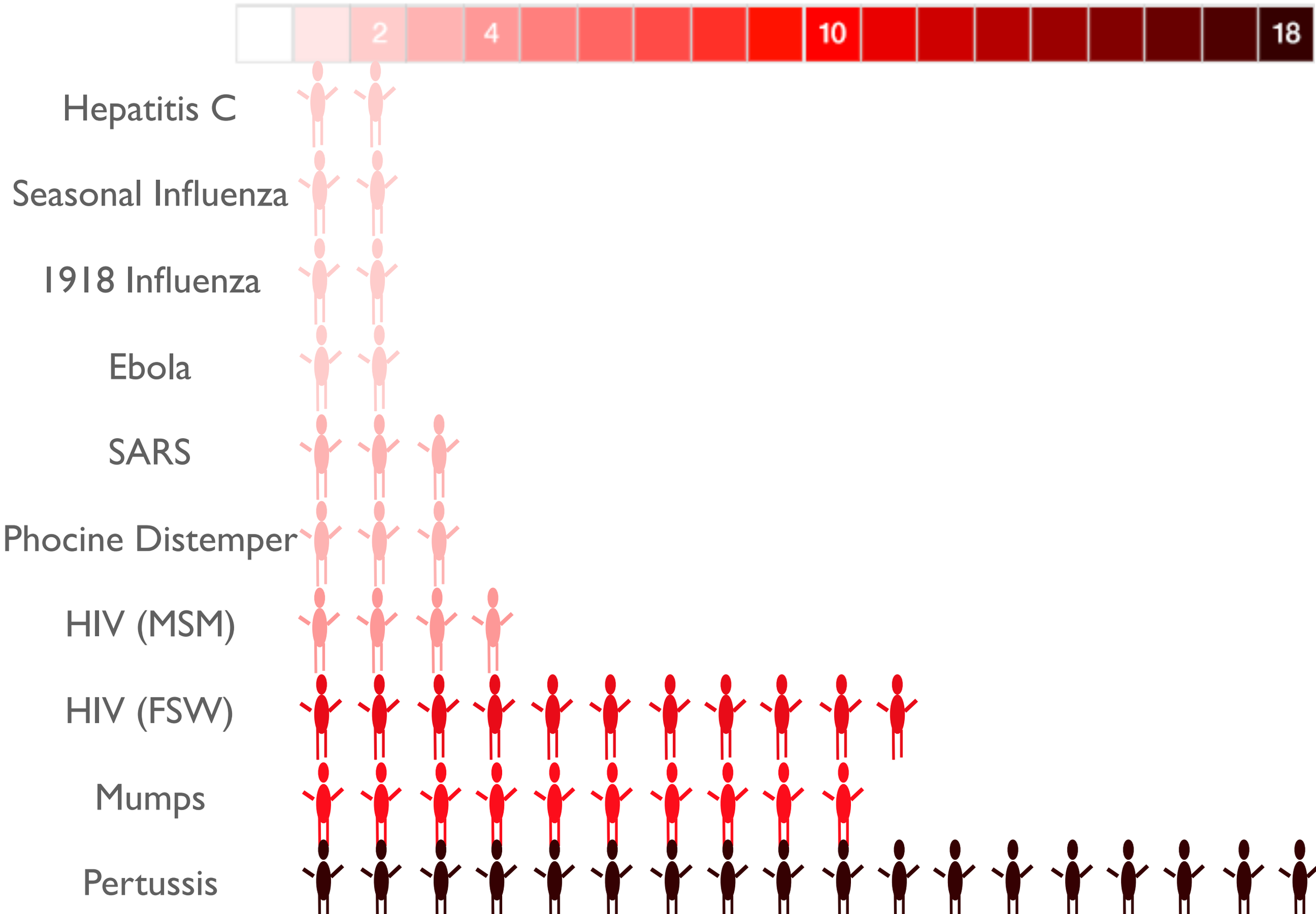
$R_0 < 1$
No invasion

$R_0 = 4$
Successful invasion

R_0 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:
  $dX/dZ = -(\beta X Y/N)/(\gamma Y)$
  $= -R_0 X/N$

- Integrate with respect to Z
  - $X(t) = X(0)\, e^{-Z(t)\, R_0/N}$

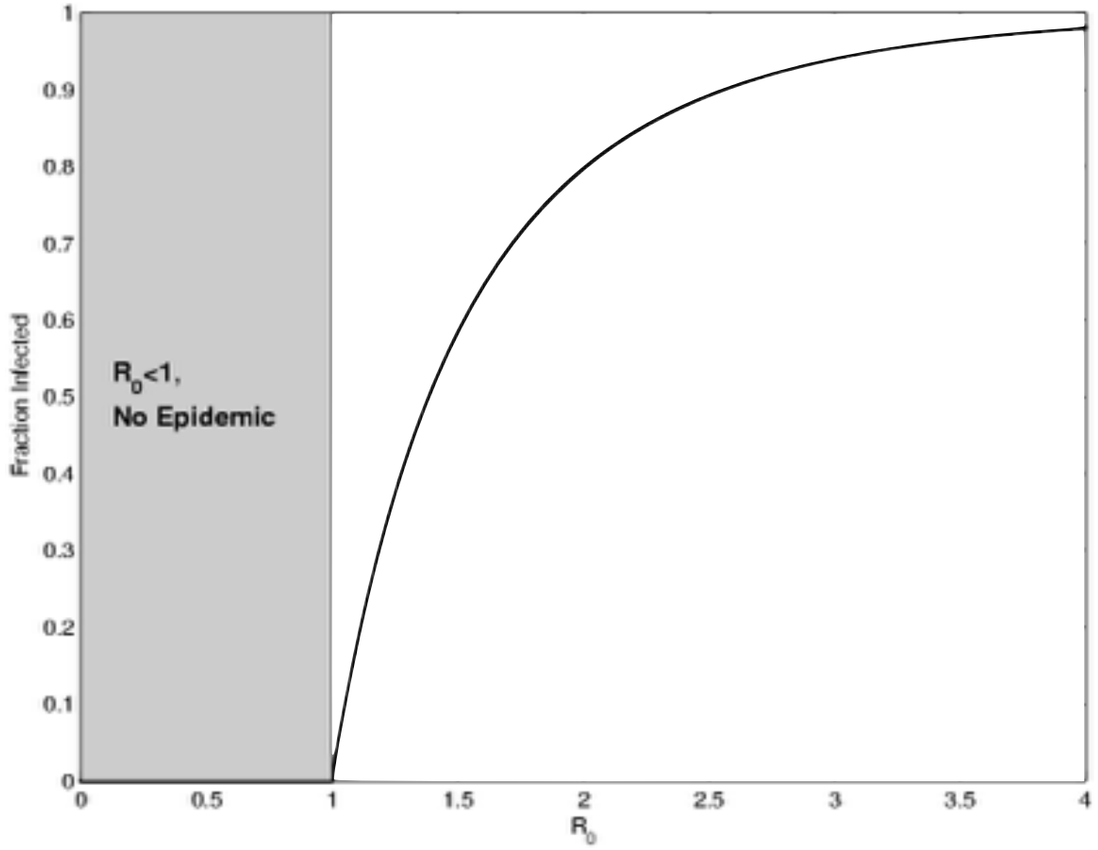
- When epidemic is over, by definition, we have $X(\infty), Y(\infty)$ (=0), and $Z(\infty)$

- $X(\infty) = N - Z(\infty) = X(0)\, e^{-Z(\infty)\, R_0/N}$

THE DEATH OF AN EPIDEMIC

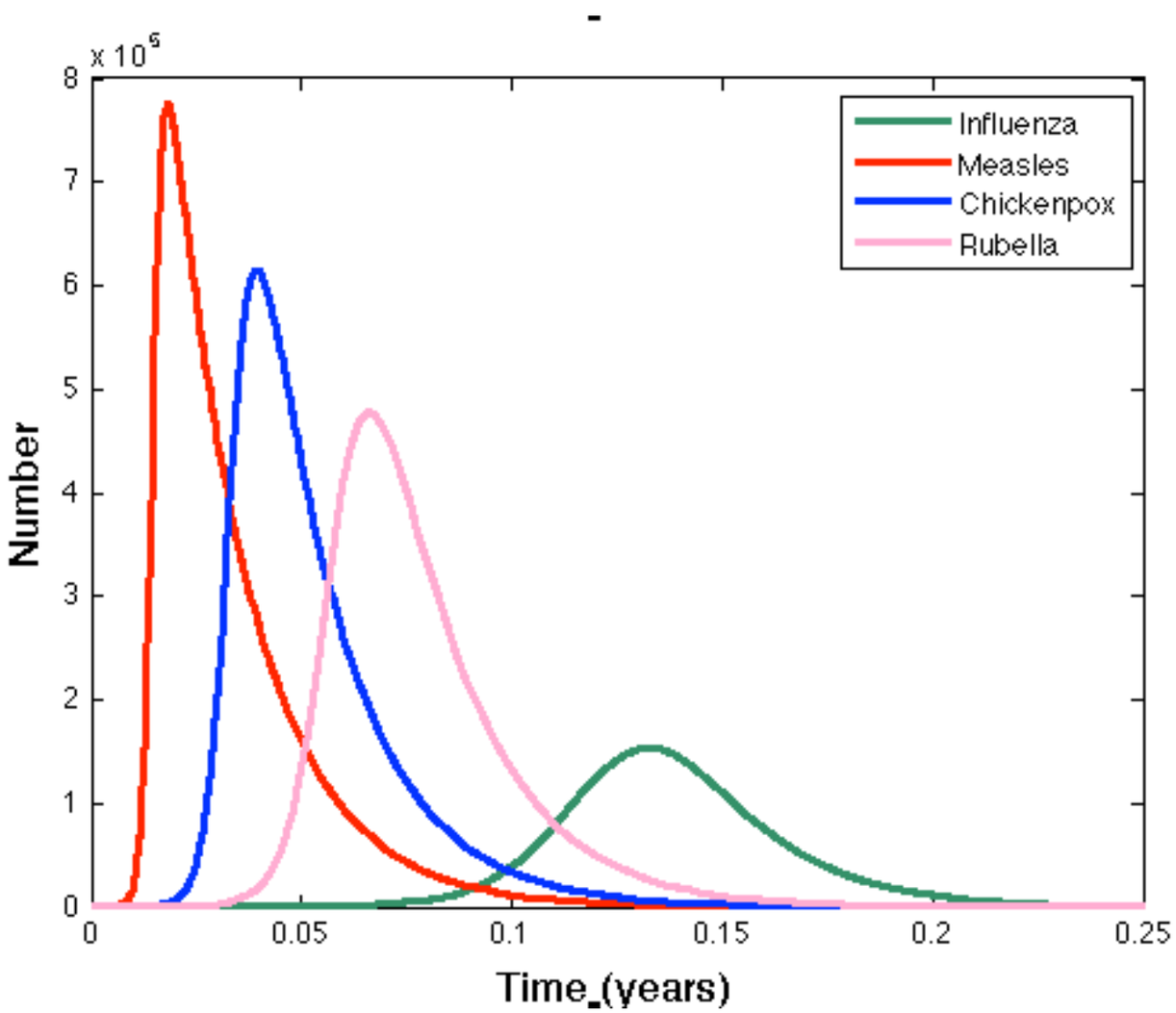
- So, $N - Z(\infty) - X(0)\, e^{-Z(\infty)\, R_0/N} = 0$
- Solve this numerically ('transcendental' equation)

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



Kermack & McKendrick (1927)

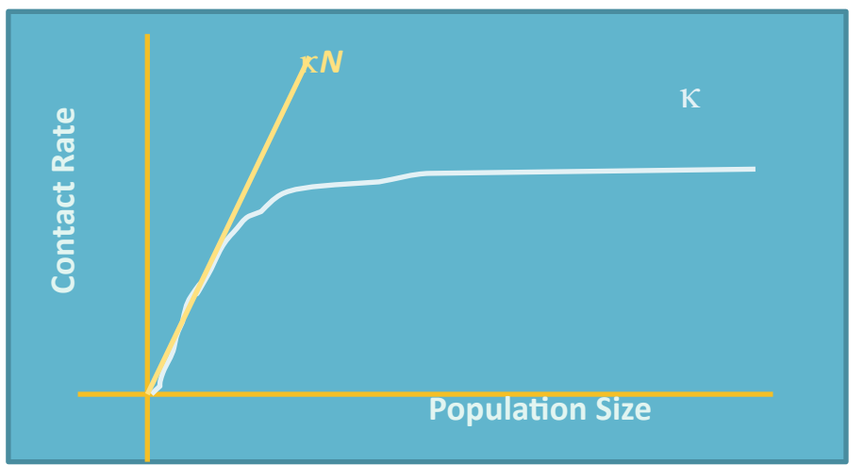
SIMPLE EPIDEMICS



	β	1/γ	R_0
"Measles"	886 /yr	0.019 yr	17
"Influenza"	180 /yr	0.011 yr	2
"Chickenpox"	315 /yr	0.022 yr	7
"Rubella"	200 /yr	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

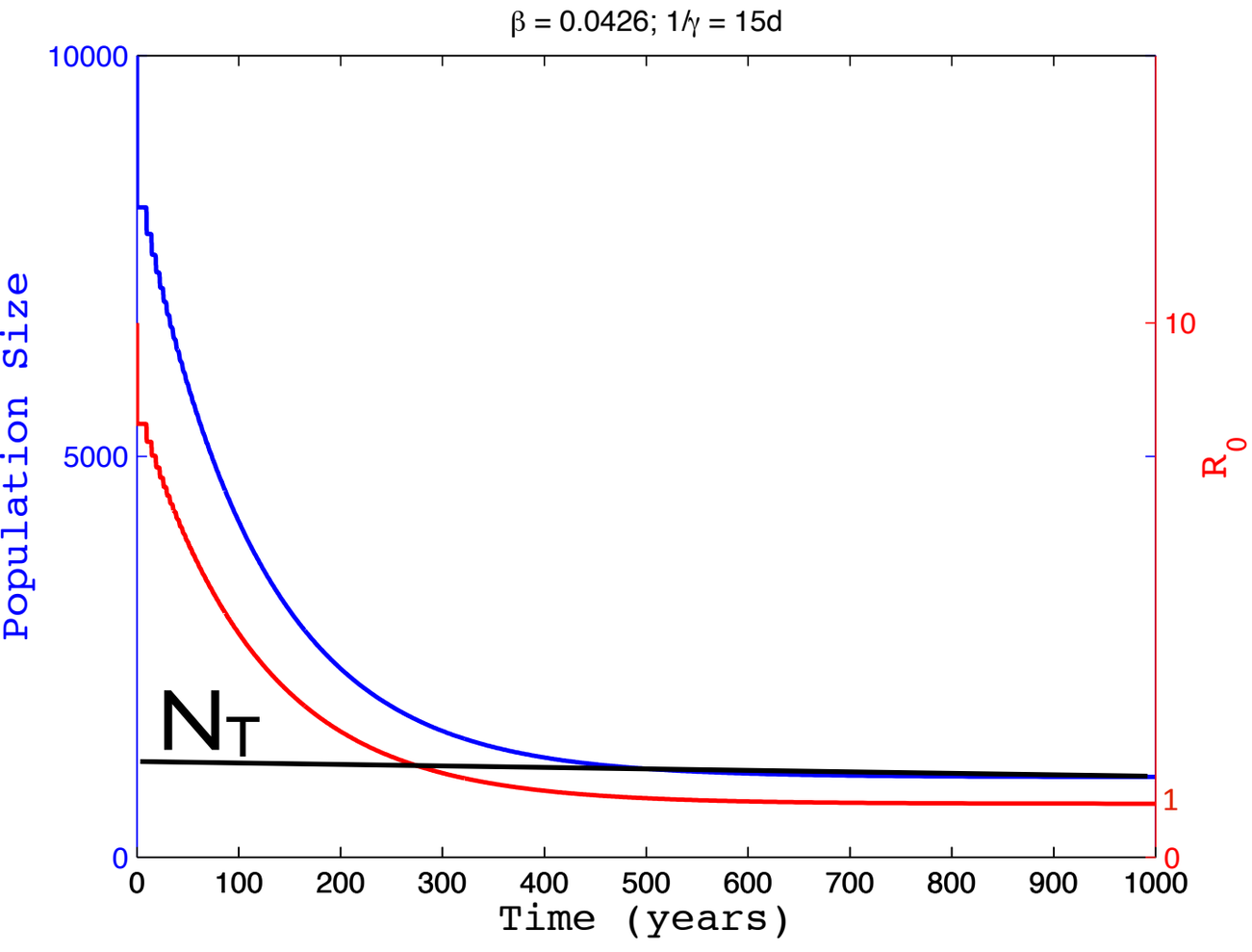
$$\frac{dY}{dt} = \ldots - \gamma Y - \alpha Y$$

TRANSMISSION & R_0

Density Dependent

β=0.0426, γ=24, α=18, μ=0.02

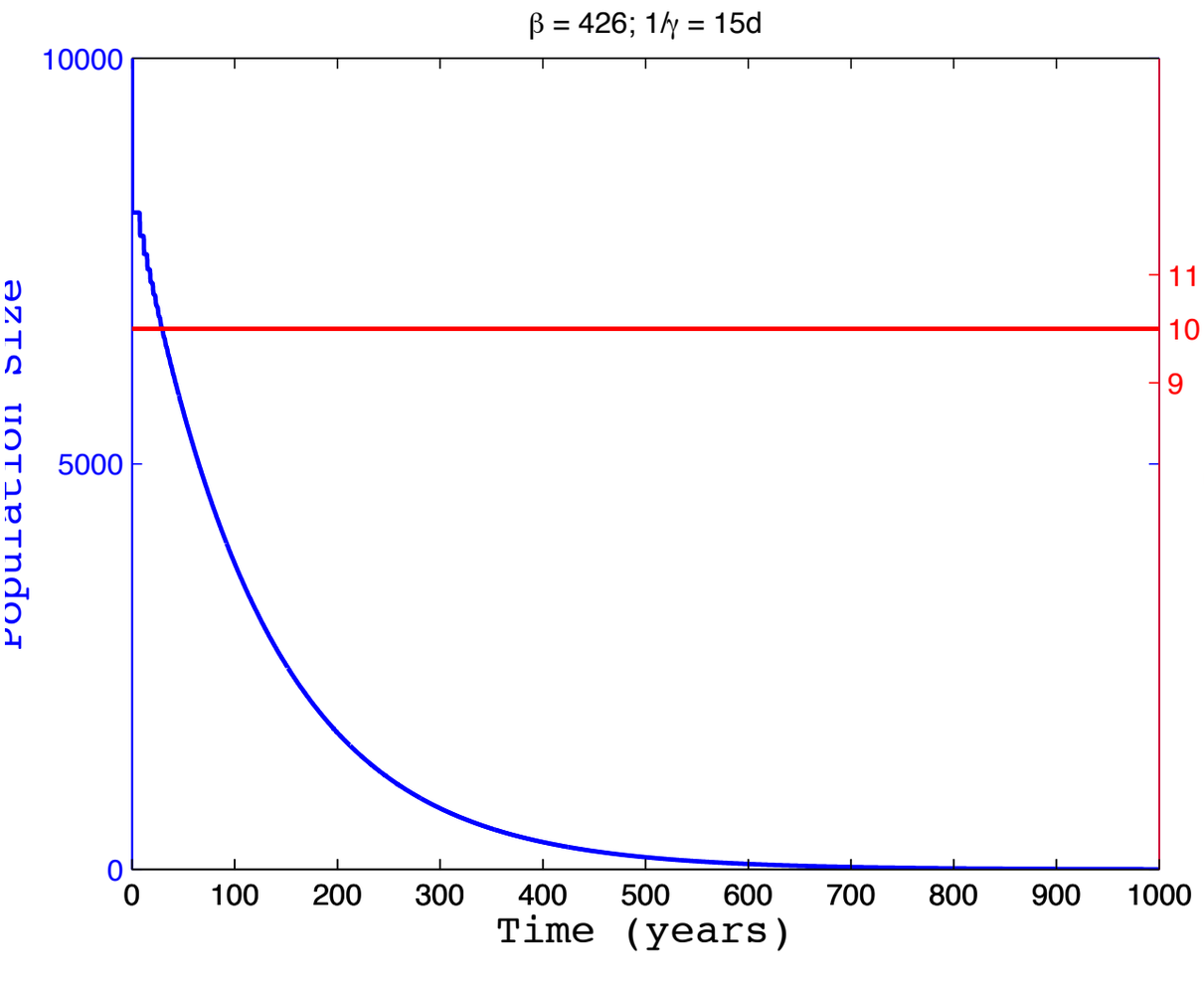
N_T = 1000



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)