Compartmental Disease Models

Model Formulation

Major decisions in designing a model

Even after compartmental framework is chosen, still need to decide:

- Deterministic vs stochastic
- Discrete vs continuous time
- Discrete vs continuous state variables
- Random mixing vs structured population
- Homogeneous vs heterogeneous

  (and which heterogeneities to include?)

Deterministic vs stochastic models

Deterministic models

- Given model structure, parameter values, and initial conditions, there is no variation in output.

Stochastic models incorporate chance.

- Stochastic effects are important when numbers are small, e.g. during invasion of a new disease
- Demographic stochasticity: variation arising because individual outcomes are not certain
- Environmental stochasticity: variation arising from fluctuations in the environment (i.e. factors not explicitly included in the model)

Important classes of stochastic epidemic models

Monte Carlo simulation

- Any model can be made stochastic by using a pseudo-random number generator to “roll the dice” on whether events occur.

Branching process

- Model of invasion in a large susceptible population

- Allows flexibility in distribution of secondary infections, but does not account for depletion of susceptibles.

Important classes of stochastic epidemic models

Chain binomial

- Model of an epidemic in a finite population.
- For each generation of transmission, calculates new infected individuals as a binomial random draw from the remaining susceptible.

Diffusion

- Model of an endemic disease in a large population.
- Number of infectious individuals does a random walk around its equilibrium value → quasi-stationary distribution

Continuous vs discrete time

<u>Continuous-time models (ODEs, PDEs)</u>

$$\frac{dN}{dt} = \lambda N$$

- Well suited for mathematical analysis
- Real events occur in continuous time
- Allow arbitrary flexibility in durations and residence times

<u>Discrete-time models</u>

$$N(t+1) = \lambda N(t)$$

- Data often recorded in discrete time intervals
- Can match natural timescale of system, e.g. generation time or length of a season
- Easy to code (simple loop) and intuitive
- Note: can yield unexpected behaviour which may or may not be biologically relevant (e.g. chaos).

Continuous vs discrete state variables

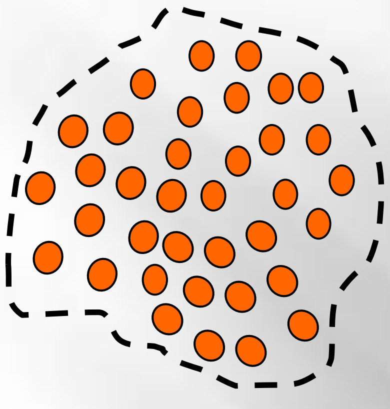
Continuous state variables arise naturally in differential equation models.

- Mathematically tractable, but biological interpretation is vague (sometimes called 'density' to avoid problem of fractional individuals).
- Ignoring discreteness of individuals can yield artefactual model results (e.g. the "atto-fox" problem).
- Quasi-extinction threshold: assume that population goes extinct if continuous variable drops below a small value

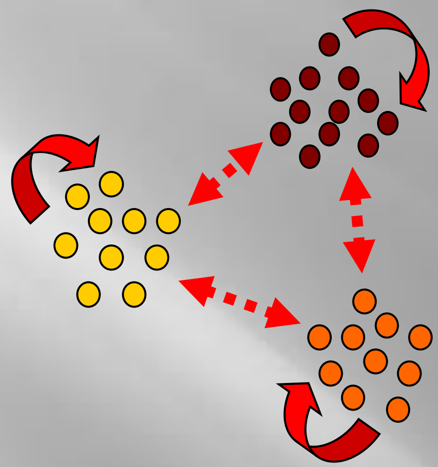
Discrete state variables arise naturally in many stochastic models, which treat individuals (and individual outcomes) explicitly.

Models for population structure

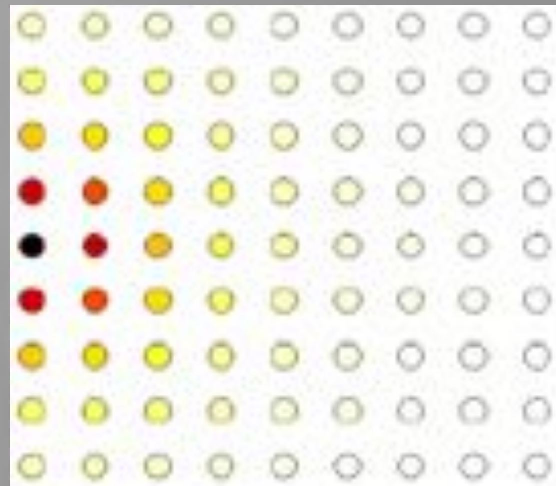
Random mixing



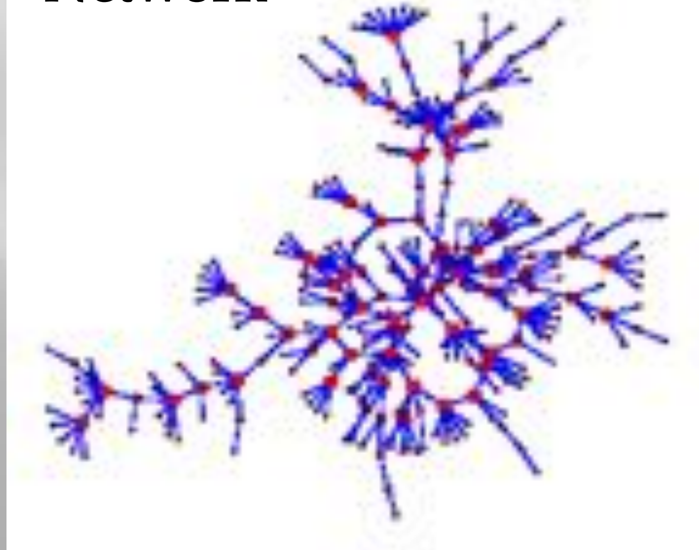
Multi-group



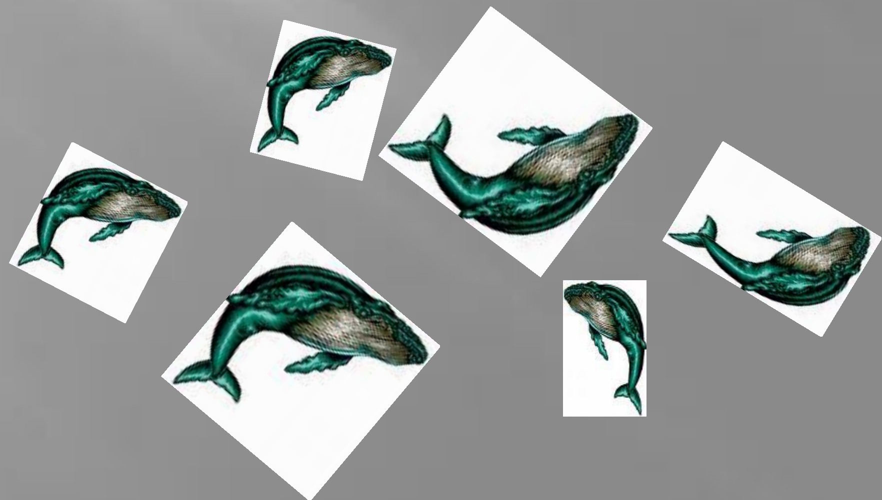
Spatial mixing



Network



Individual-based model



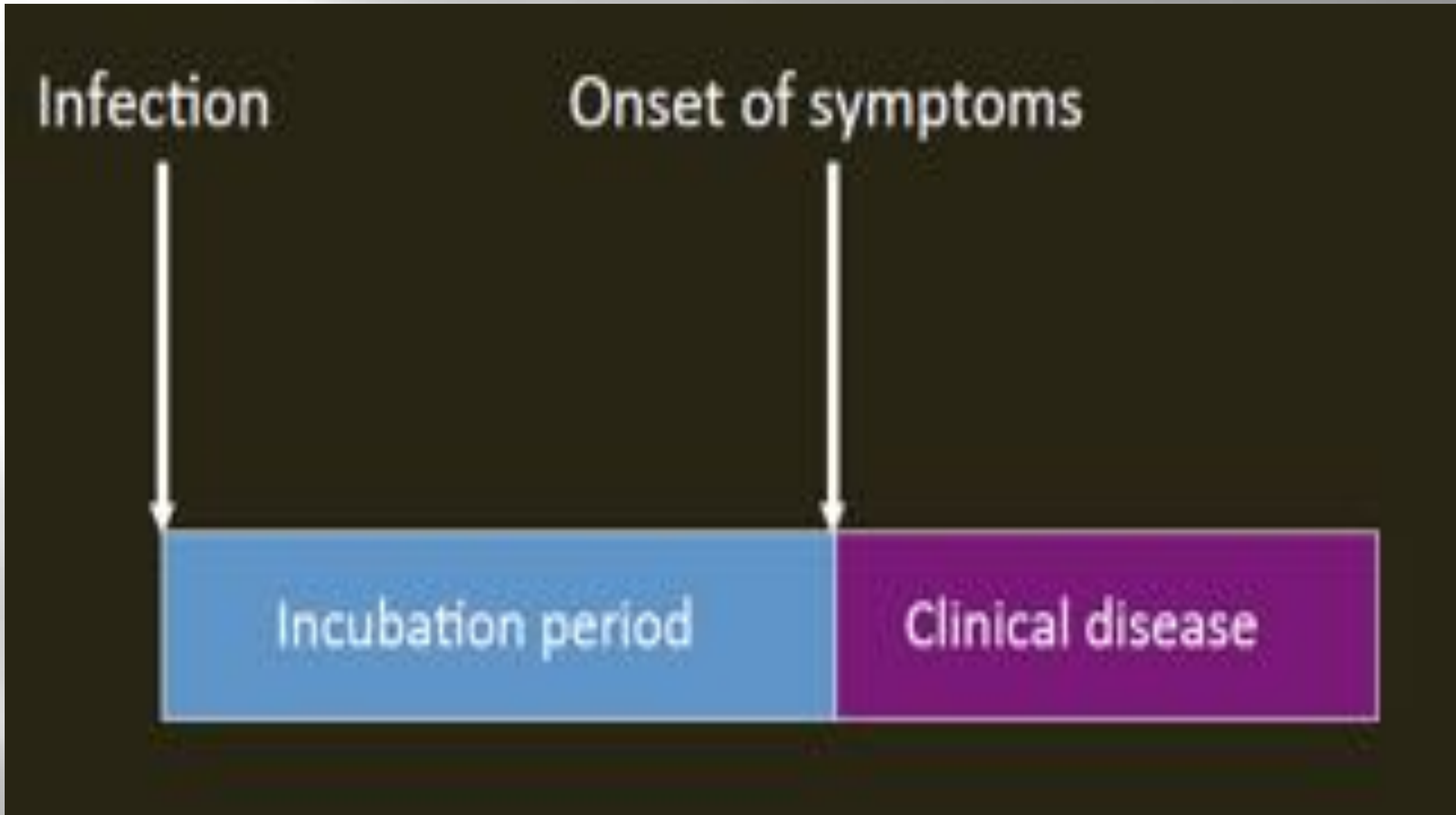
Population heterogeneities

In real populations, almost everything is heterogeneous – no two individuals are completely alike.

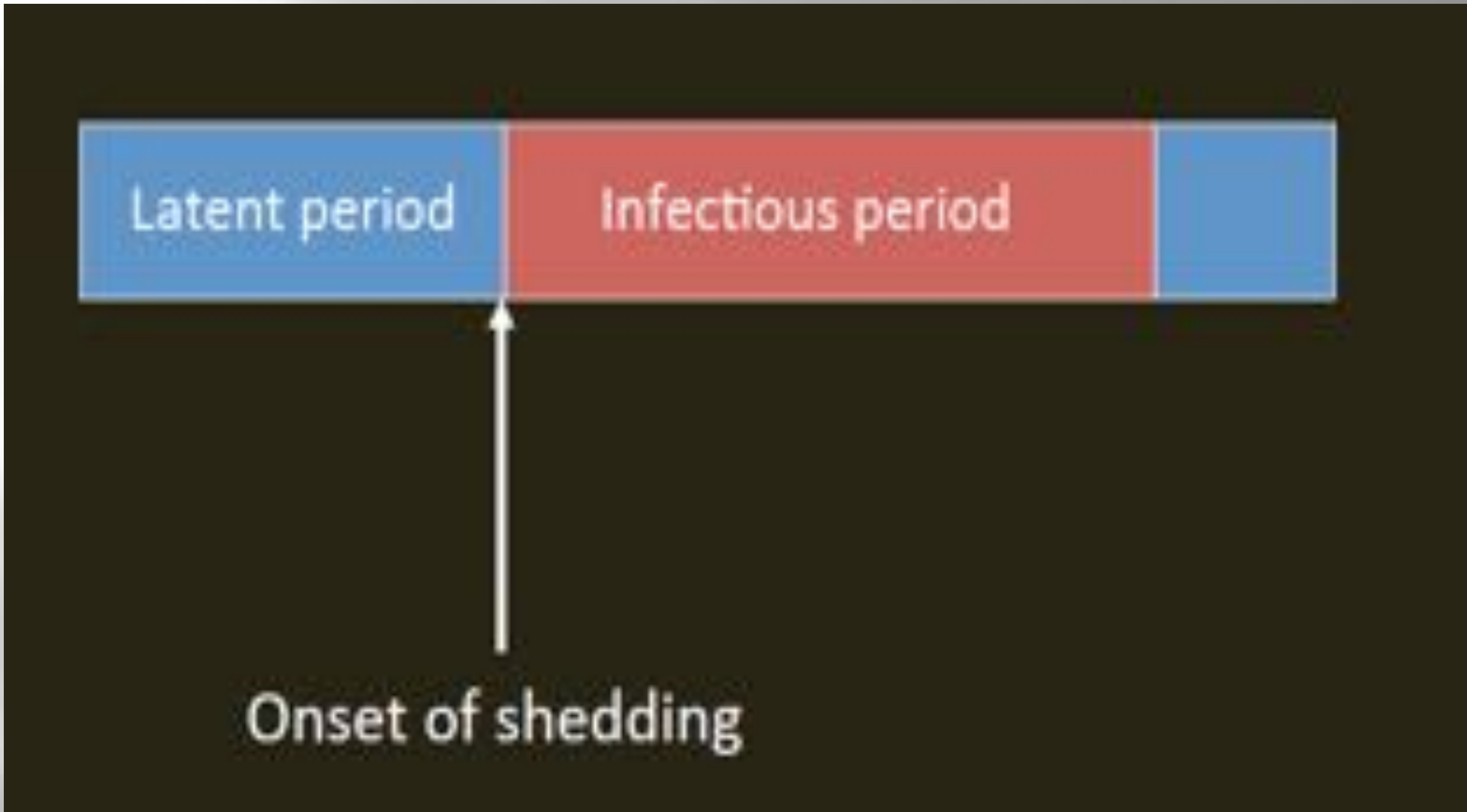
Which heterogeneities are important for the question at hand? Do they affect epidemiological rates or mixing? Can parameters be estimated to describe their effect?

- often modelled using multi-group models, but networks, IBMs, PDEs also useful.

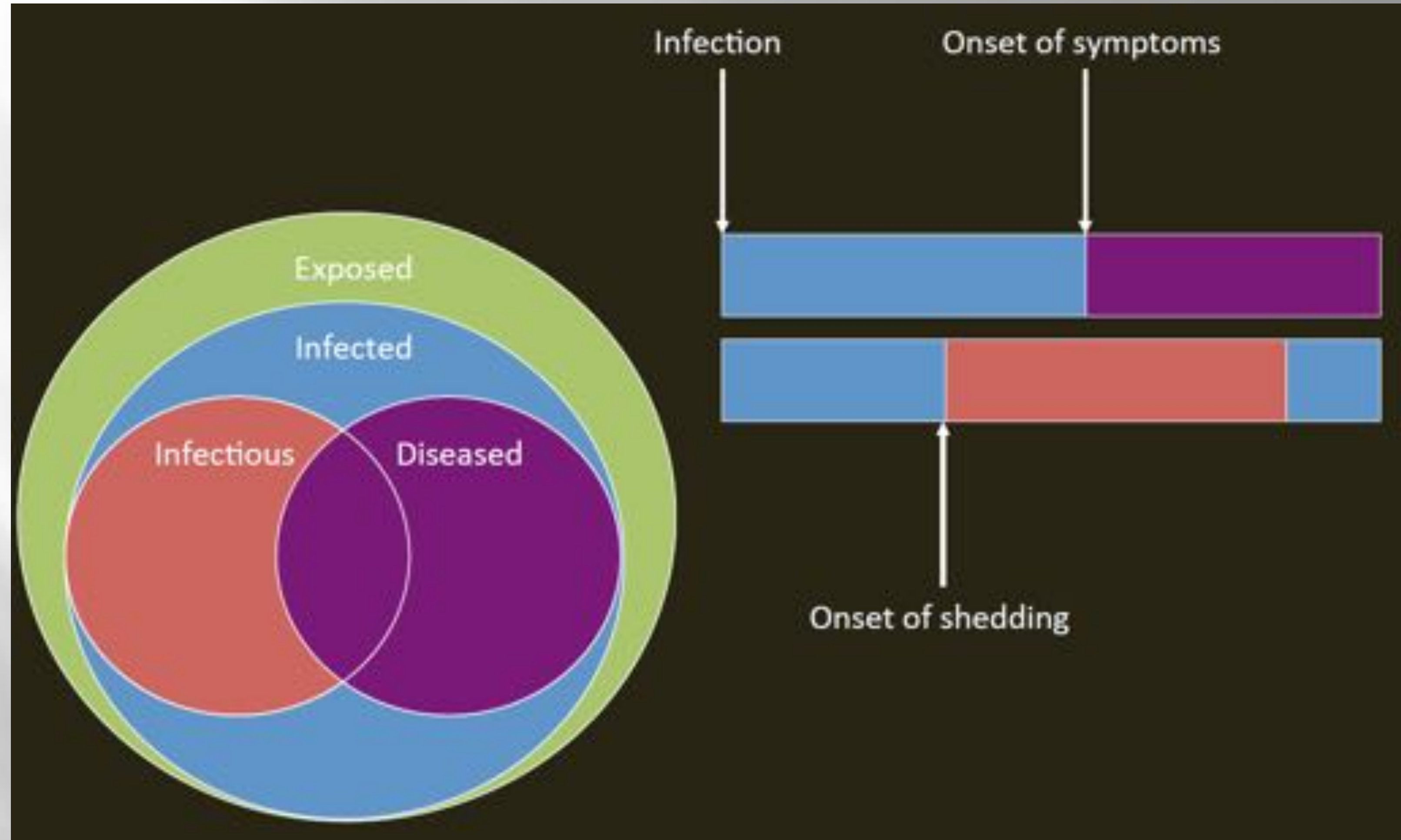
Natural History of Infection



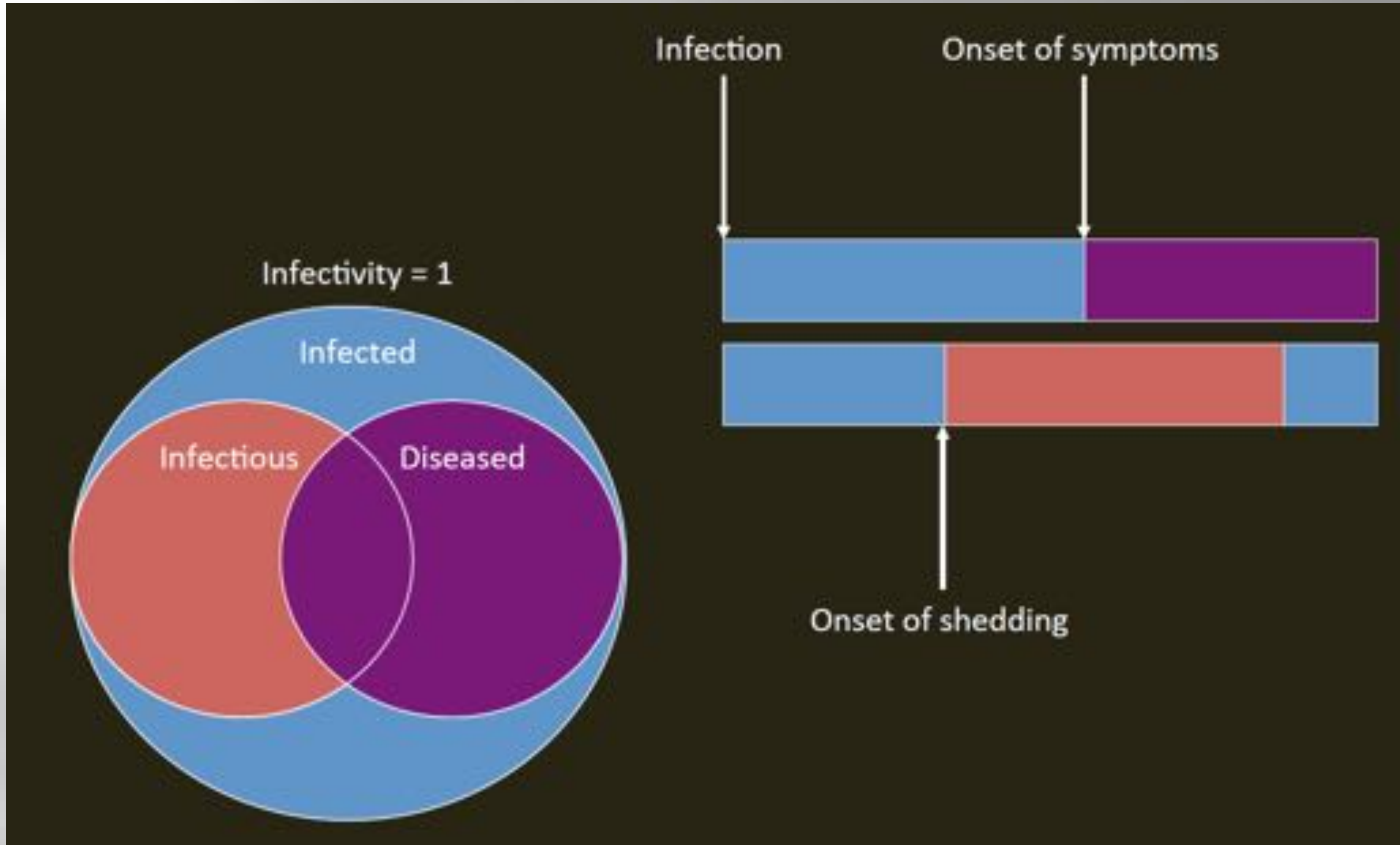
Natural History of Infection



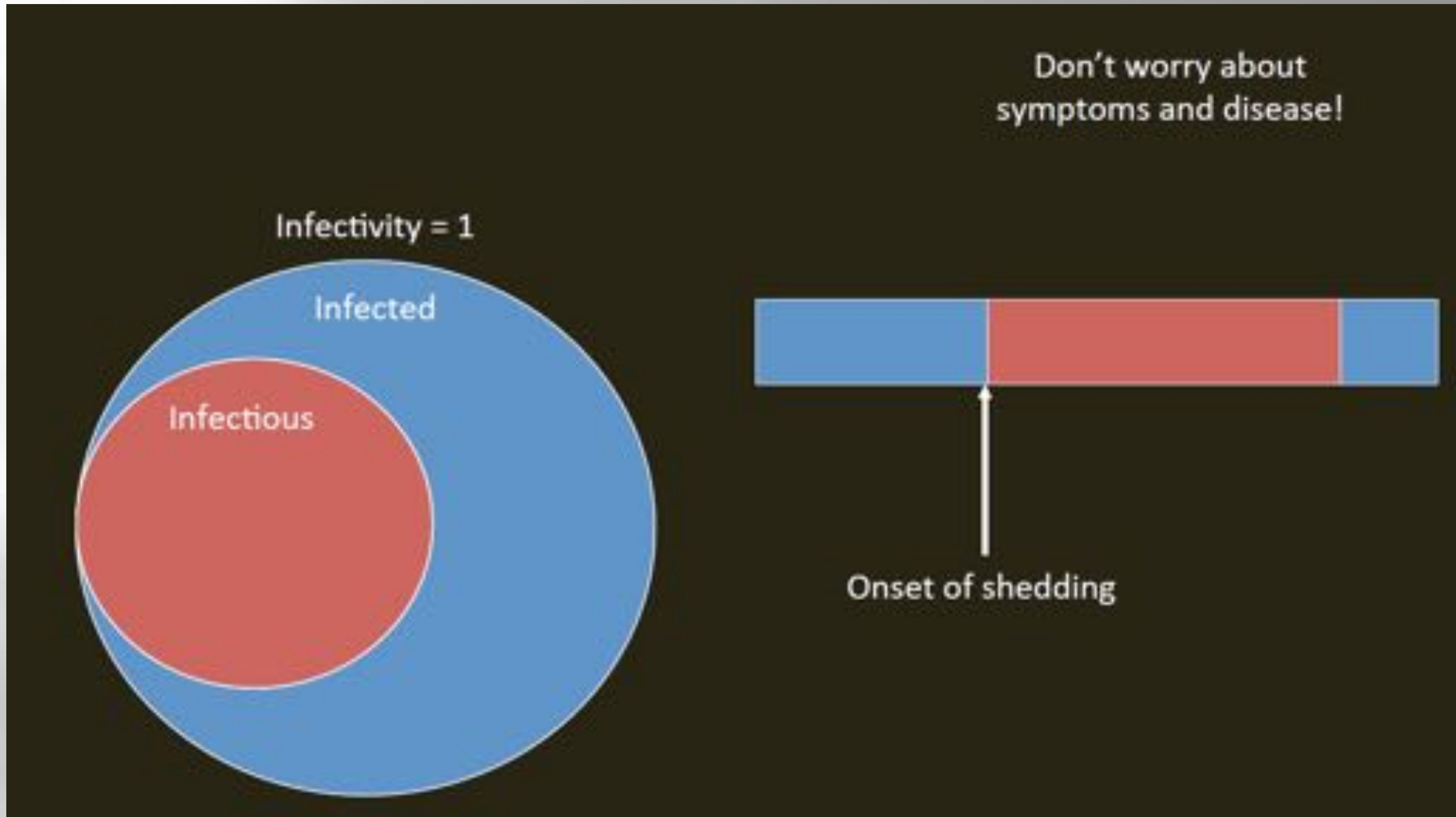
Terminology



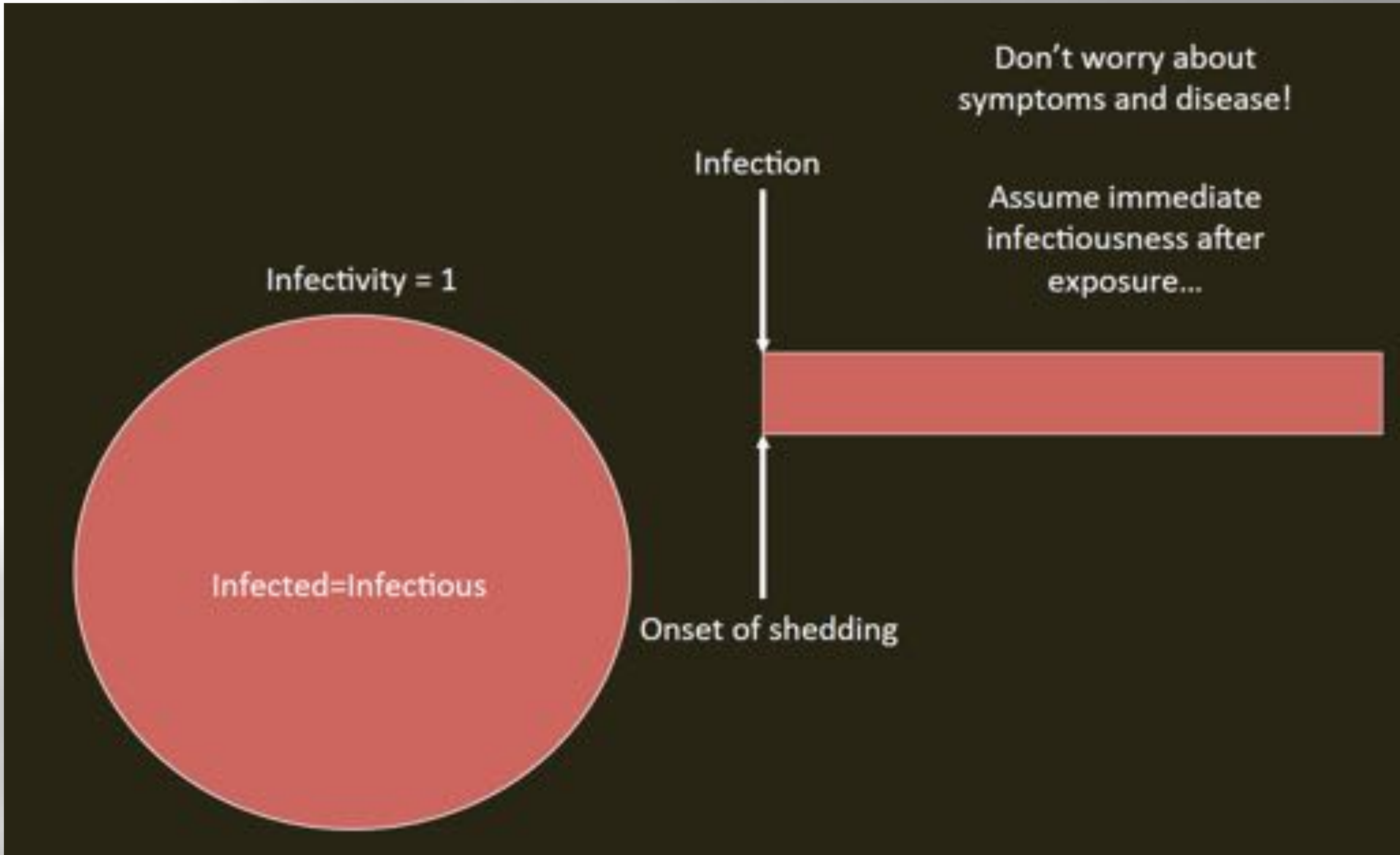
A simple view of the world



A simpler view of the world



An extremely simple view of the world



Formulating Mathematical Models

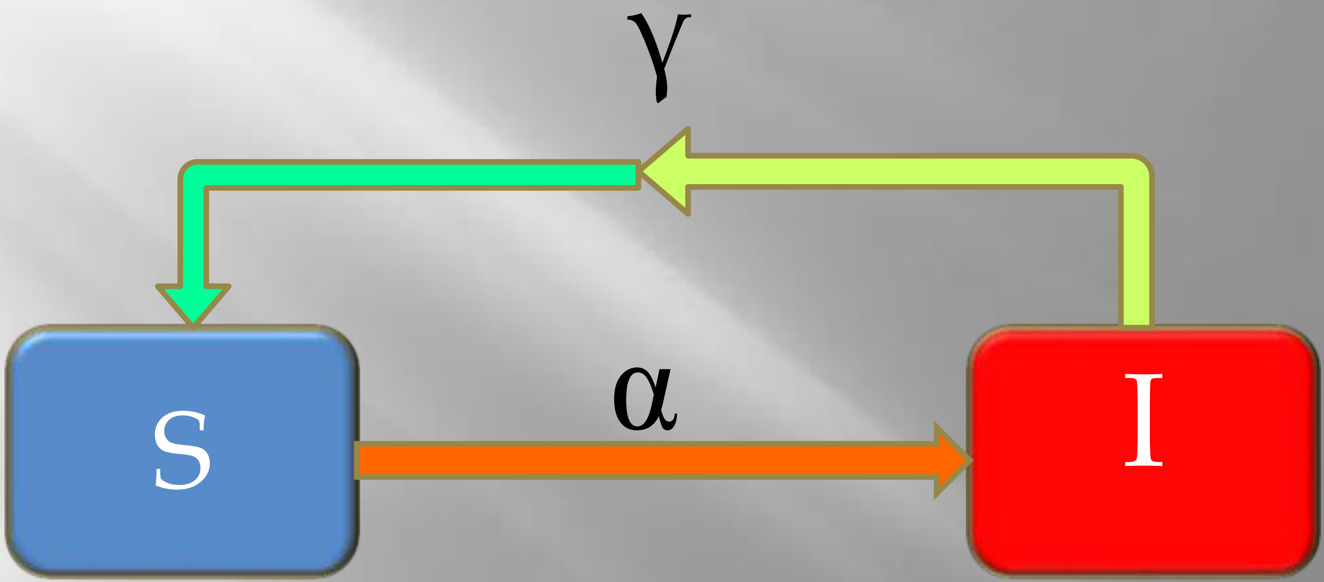
We shall consider two kinds of compartmental models:

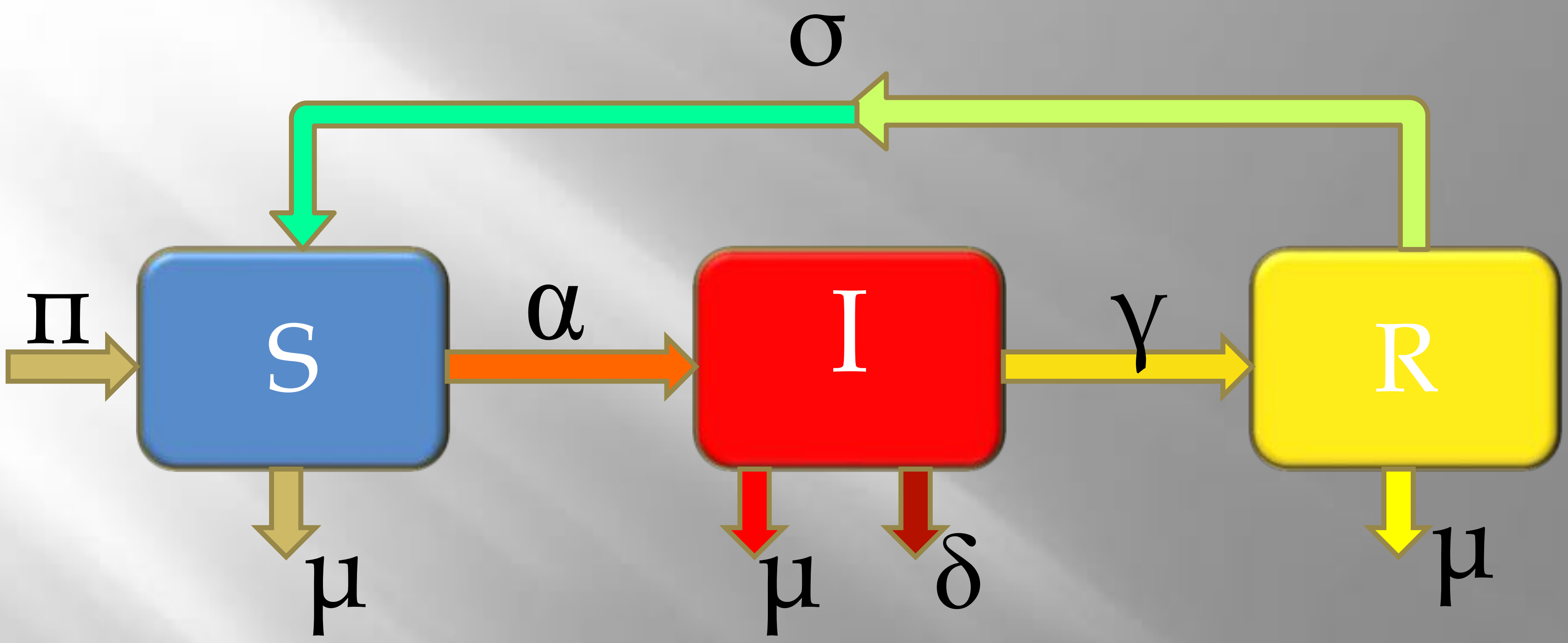
Models without demography:
These models have "closed population" without births, deaths, or migration. Ideal for diseases with short term duration, example seasonal flu.

Models with demography:
These models include births, deaths, or migration and are best for modeling diseases with long term duration like TB. Allows the exploration of long-term persistence and endemic dynamics of the disease.

Compartmental Models

We can use ordinary differential equations (ODE) to describe the rate at which individuals flow between states.

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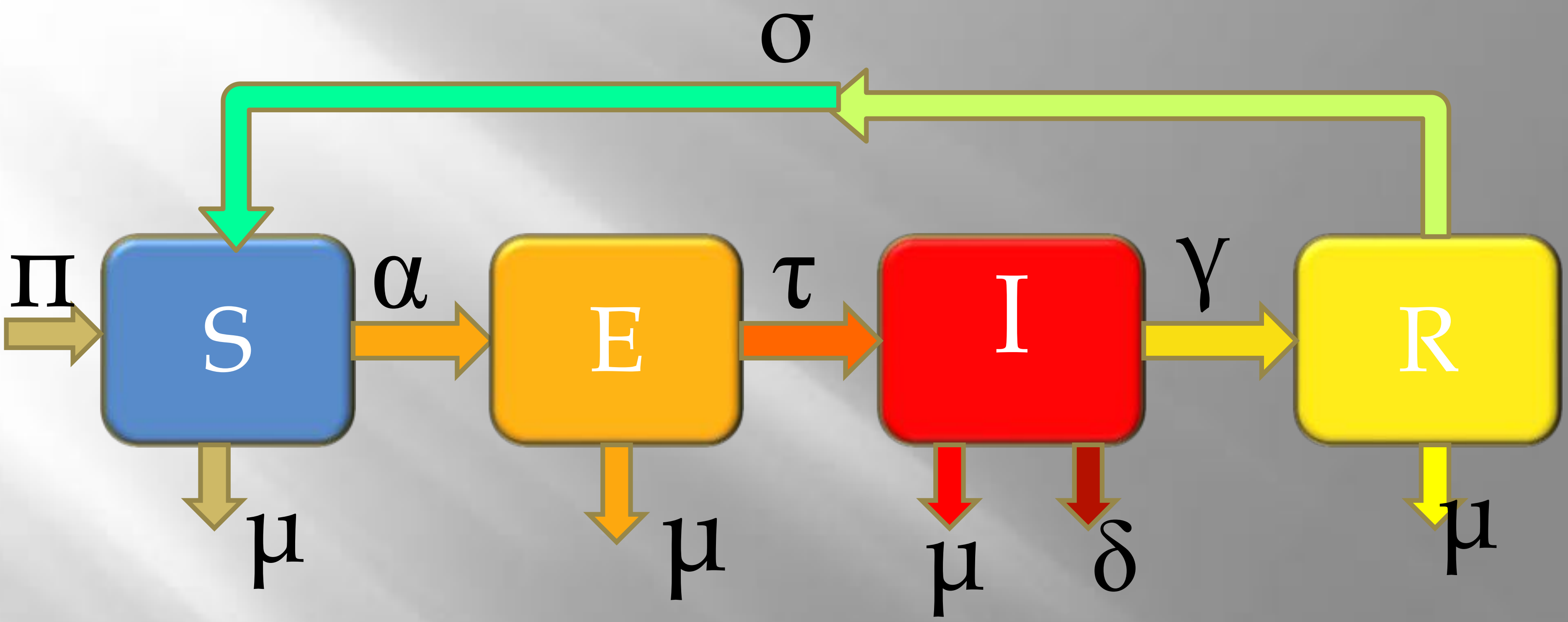
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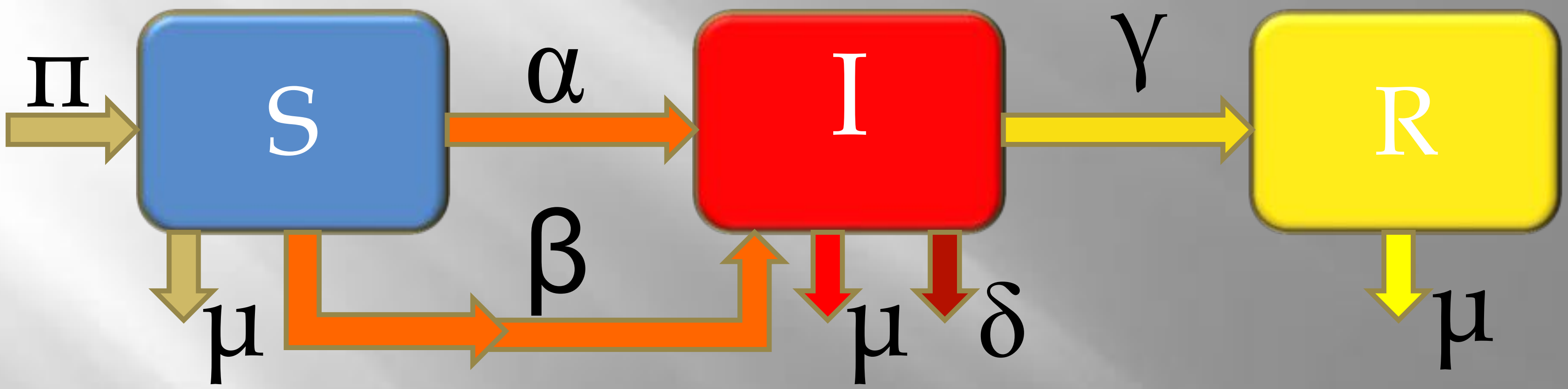
AVIAN INFLUENZA MODEL



Agusto, F. B & Ogunye, O.R.
Avian influenza optimal seasonal vaccination therapy. **AZIAM J. 51 (2010).** pp 394 – 405.

Developing a disease model

From History of Infection to Compartmental Models

Measles

Signs and symptoms

The first sign of measles is usually a high fever, which begins about 10 to 12 days after exposure to the virus, and lasts 4 to 7 days. A runny nose, a cough, red and watery eyes, and small white spots inside the cheeks can develop in the initial stage. After several days, a rash erupts, usually on the face and upper neck. Over about 3 days, the rash spreads, eventually reaching the hands and feet. The rash lasts for 5 to 6 days, and then fades. On average, the rash occurs 14 days after exposure to the virus (within a range of 7 to 18 days).

Most measles-related deaths are caused by complications associated with the disease. Complications are more common in children under the age of 5, or adults over the age of 20. The most serious complications include blindness, encephalitis (an infection that causes brain swelling), severe diarrhoea and related dehydration, ear infections, or severe respiratory infections such as pneumonia. Severe measles is more likely among poorly nourished young children, especially those with insufficient vitamin A, or whose immune systems have been weakened by HIV/AIDS or other diseases.

http://www.who.int/mediacentre/factsheets/fs286/en/

Transmission

The highly contagious virus is spread by coughing and sneezing, close personal contact or direct contact with infected nasal or throat secretions.

The virus remains active and contagious in the air or on infected surfaces for up to 2 hours. It can be transmitted by an infected person from 4 days prior to the onset of the rash to 4 days after the rash erupts.

Measles outbreaks can result in epidemics that cause many deaths, especially among young, malnourished children. In countries where measles has been largely eliminated, cases imported from other countries remain an important source of infection.

Treatment

No specific antiviral treatment exists for measles virus.

Severe complications from measles can be avoided through supportive care that ensures good nutrition, adequate fluid intake and treatment of dehydration with WHO-recommended oral rehydration solution. This solution replaces fluids and other essential elements that are lost through diarrhoea or vomiting. Antibiotics should be prescribed to treat eye and ear infections, and pneumonia.

http://www.who.int/mediacentre/factsheets/fs286/en/

Chlamydia

The Facts

- Chlamydia (cla MI dee a) is a sexually transmitted disease (STD).
- Anyone can get chlamydia. It is very common among teens and young adults.

- Most people who have chlamydia don't know it. Often the disease has no symptoms.

- Chlamydia is easy to treat and cure.

Can I get Chlamydia again after I've been treated?

Yes, you can get chlamydia again. You can get it from an untreated partner or a new partner.

http://www.cdc.gov/std/chlamydia/the-facts/default.htm

Tuberculosis (TB)

Tuberculosis (TB) is caused by bacteria (Mycobacterium tuberculosis) that most often affect the lungs.

Tuberculosis is curable and preventable.

https://www.cdc.gov/tb/topic/basics/risk.htm

http://www.who.int/mediacentre/factsheets/fs104/en/

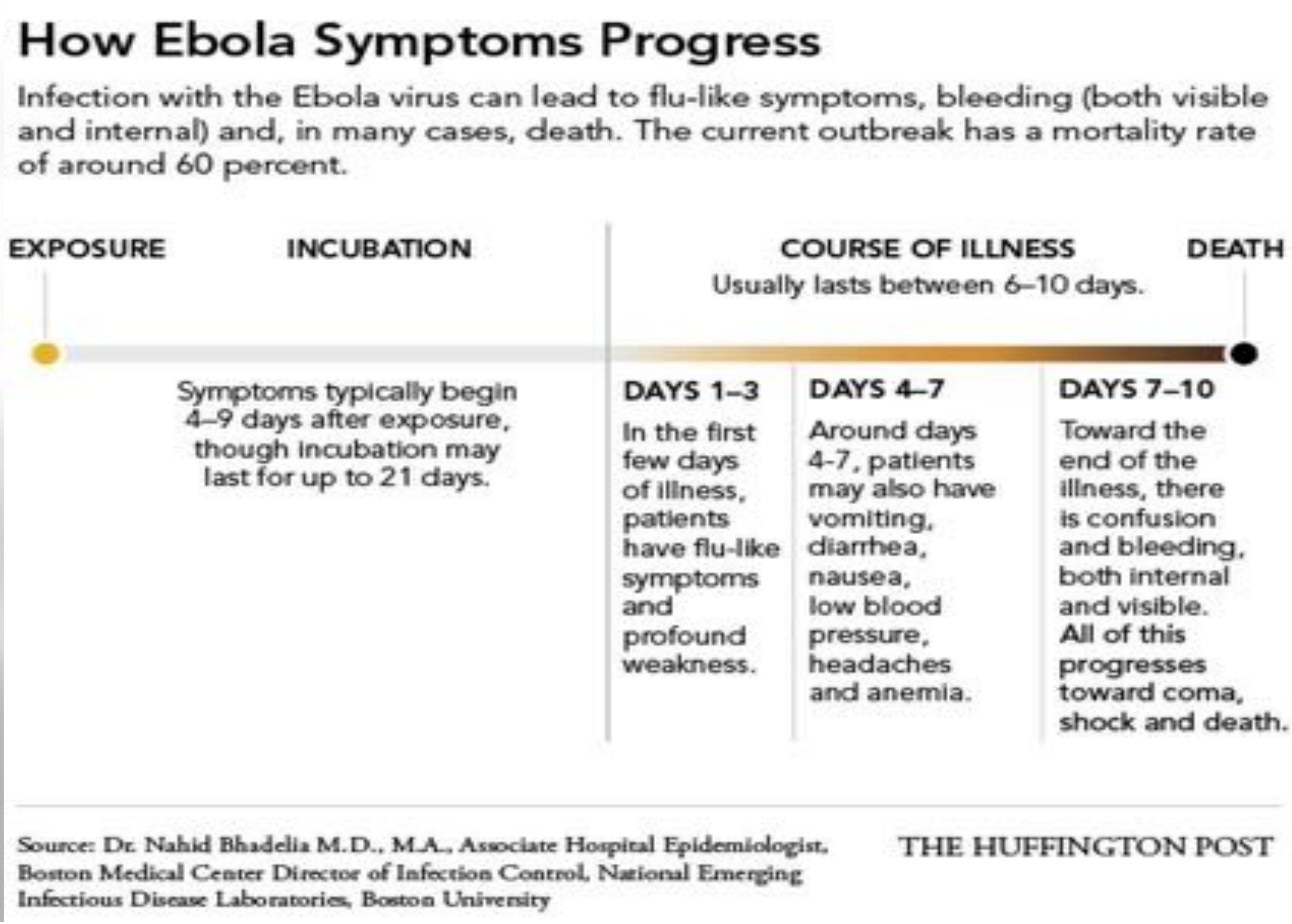
Chikungunya

Chikungunya is a viral disease transmitted to humans by infected mosquitoes.

http://www.who.int/mediacentre/factsheets/fs327/en/

https://www.cdc.gov/chikungunya/

Ebola virus disease



Incidence rate or Force of Infection

The incidence rate

Incidence term in models describes the rate that new infections arise.

$$\alpha = f(S,I) = Force\ of\ infection \times S$$

Force of infection, $\lambda = c(N)\, p\, I/N$

$c\ (N)$ = contact rate (possibly density-dependent)

p = probability of transmission given contact

I/N = prob. that randomly-chosen partner is infectious

So
$$f\ (S,I) = c(N\ )\ p\, \frac{SI}{N}$$

Density-dependent transmission

$$f\,(S,I) = c(N\,)\,p\,\frac{SI}{N}$$

If contact rate is linearly density-dependent: $c(N) = kN$

Then $f(S,I) = kN\,p\,SI/N$

$= \beta_{MA}\,SI$ where $\beta_{MA} = kp$

→ "**Mass action**" transmission. Also known as density-dependent.

Frequency-dependent transmission

$$f\,(S,I) = c(N\,)\,p\frac{SI}{N}$$

If contact rate is linearly density-independent:

$$c(N) = C_0$$

Then $f(S,I) \;=\; C_0 p\, SI/N$

$= \;\beta_{FD}\, SI/N$ where $\beta_{FD} = C_0 p$

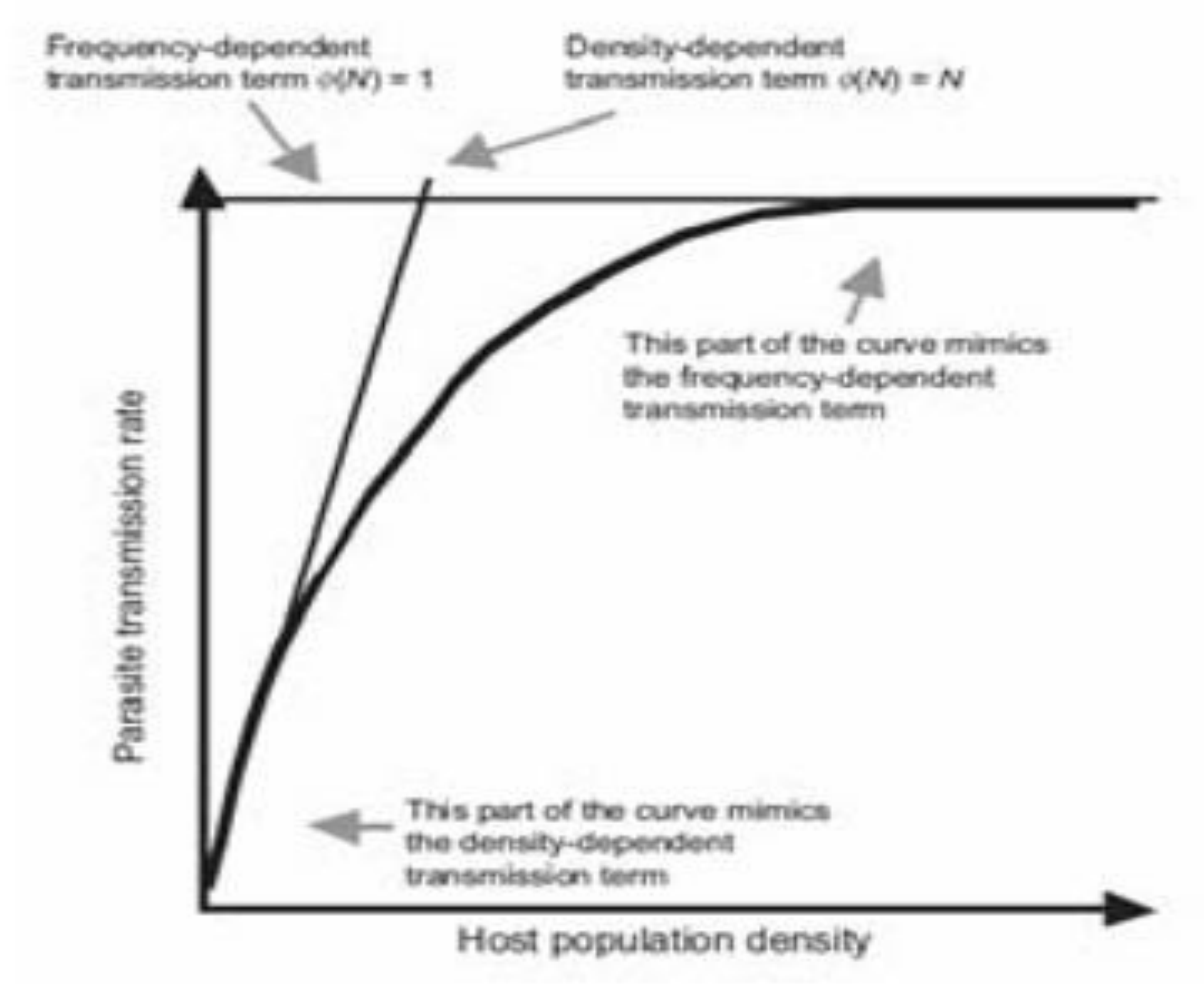
→ "**Frequency-dependent**" transmission. Also known as the standard incidence.

Table 1. Some proposed forms for the transmission function

Number	Function[a]	Comments
1	βSI	Mass action
2	$\beta SI/N$	Frequency-dependent transmission
3	$\beta S^p I^q$	Power relationship; Constants: $0 < p < 1$, $0 < q < 1$. Phenomenological
4	$\beta I(N - I/q)$; $I < qN$ 0; $I \geq qN$	Constant: $0 < q < 1$. Embodies a refuge effect (q = proportion of the population potentially susceptible, because of spatial or other heterogeneities)
5	$kS \ln\left(1 + \frac{\beta I}{k}\right)$	Negative binomial. Small k corresponds to highly aggregated infection. As $k \rightarrow \infty$, expression reduces to βSI (mass action)
6	$\frac{N}{1-\varepsilon+\varepsilon N} \frac{F(S,I)}{N}$	Asymptotic contact function separated from the mixing term $F(S,I)$, which may be any of those above. If constant $\varepsilon = 0$, contacts are proportional to N. If $\varepsilon = 1$, contacts are independent of N
7	$\frac{\beta SI}{c+S+I}$	Asymptotic transmission. c is a constant

McCallum et al (2001) Trends Ecol Evol 16: 295-300.

Saturating transmission



Deredec et al (2003) Ann Zool Fenn 40: 115-130.

Many choices – what to do?

Classically it was assumed that transmission rate increases with population size, because contacts increase with crowding.

→ mass action (βSI) was dominant transmission term

Hethcote and others argued that rates of sexual contact are determined more by behavior and social norms than by density, and favored frequency-dependent transmission for STDs.

Since the 1990s, this has been a topic of active research using experimental epidemics, field systems, and epidemiological data.

Detecting density dependence

How can we test for density dependence in transmission?

• Fit models with different transmission functions to epidemic time series.

• Look at indicators for transmission ∝ N in epidemiological data:

With increased transmission rate, we expect:

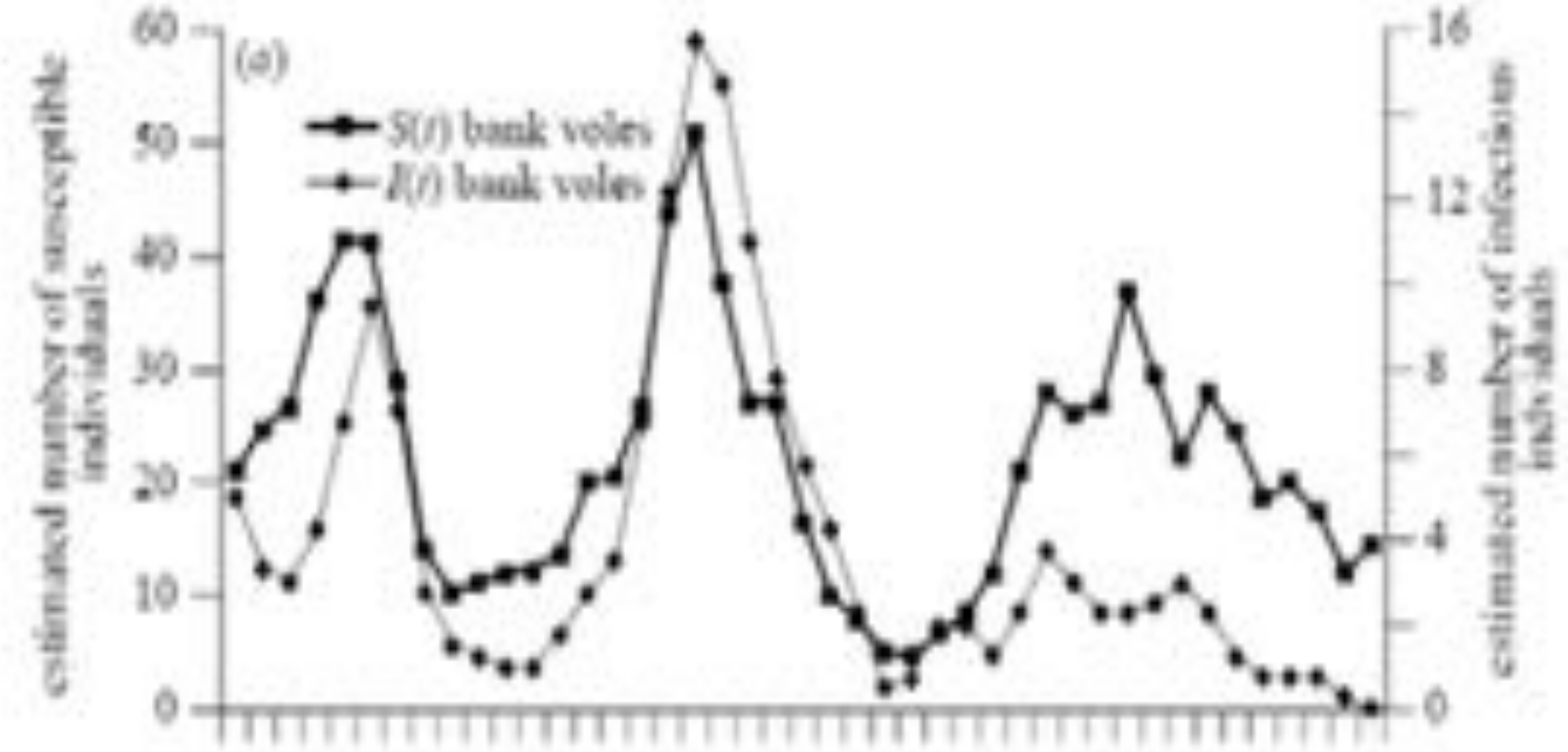
↑ estimates of R_0

↑ exponential growth rate of epidemic, r

↓ proportion susceptible following epidemic, or at steady state

↓ mean age of infection in endemic setting

Evidence for FD vs MA transmission



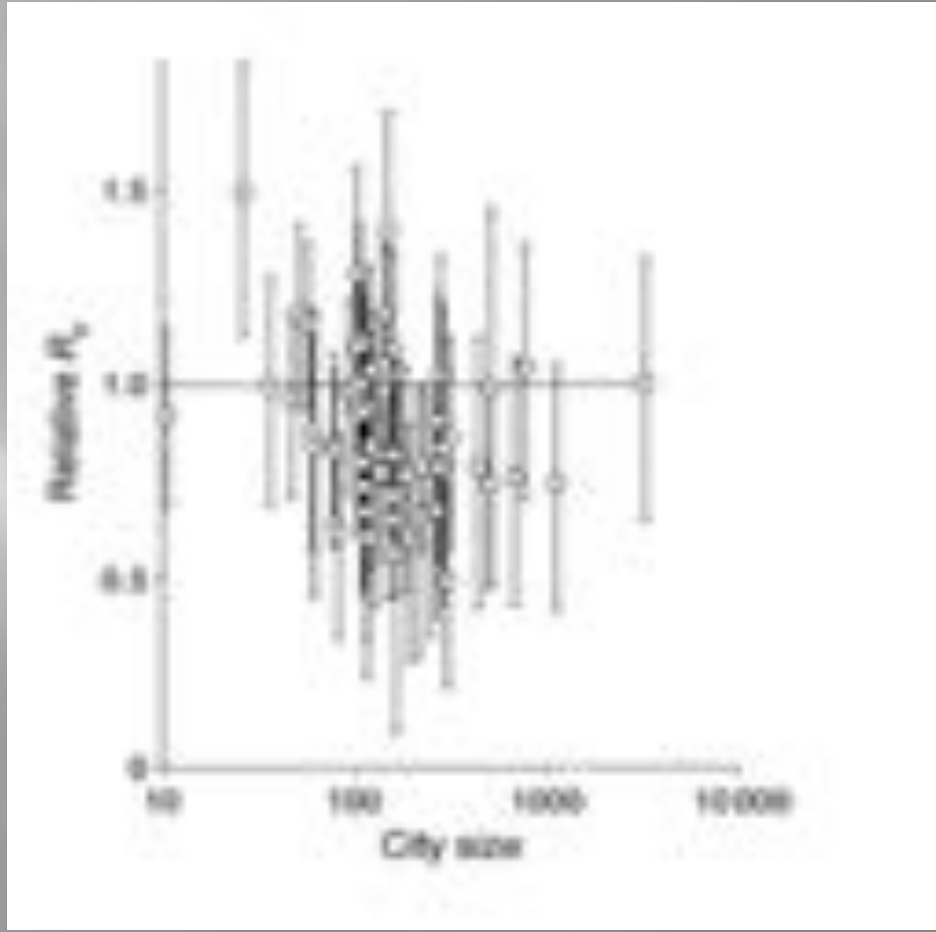
Fitting models to data from **cowpox in bank voles and wood mice.**
→ FD model is better fit than MA (though neither is perfect)

Begon et al (1999) Proc Roy Soc B 266: 1939-1945.

Evidence for FD vs MA transmission

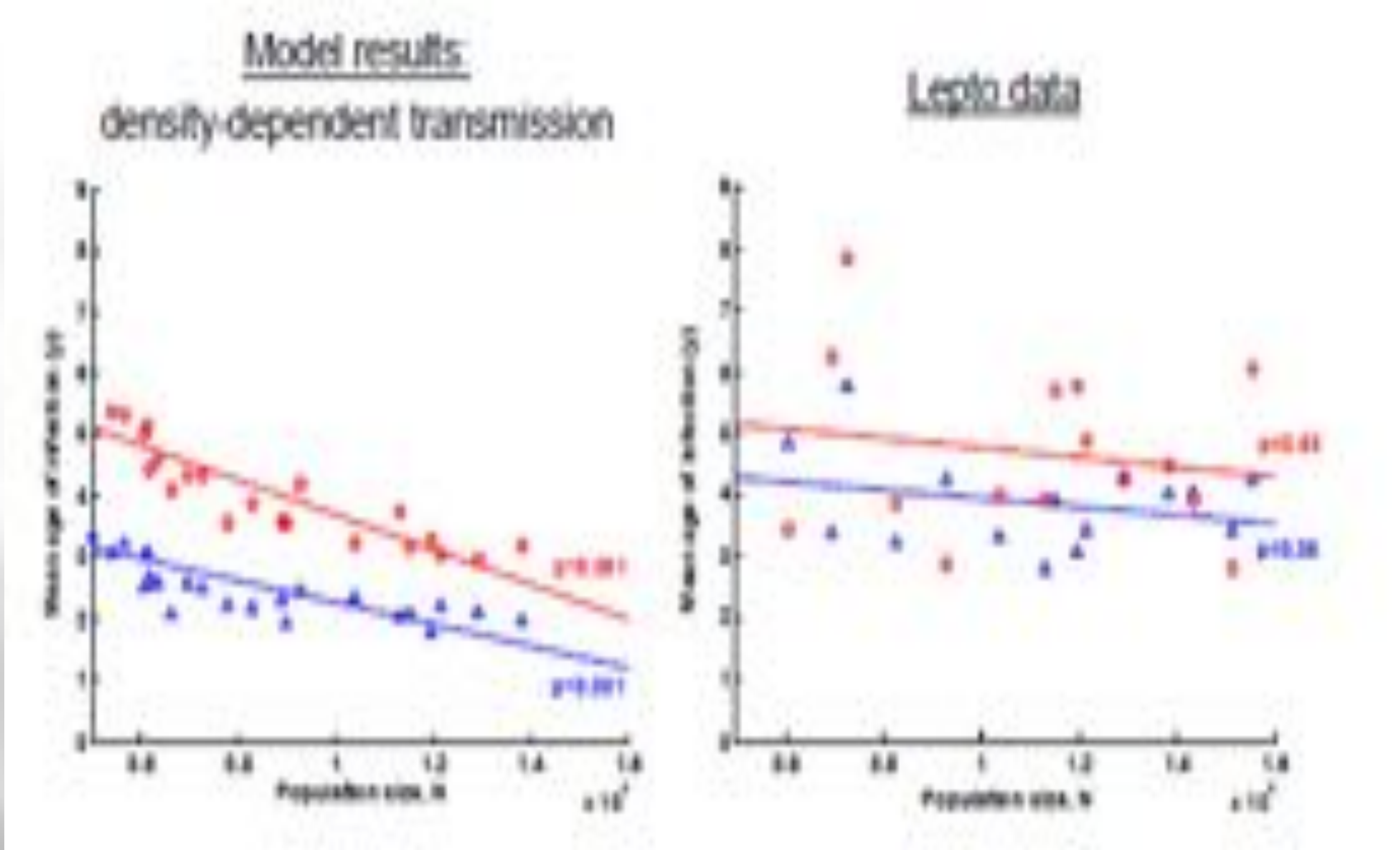
Measles in England and Wales

• R_0 is ~ constant vs population size roughly FD transmission (recall that MA predicts that $R_0 \propto N$)



Bjornstad et al (2002) Ecol Monog. 72: 169-184

Evidence for FD vs MA transmission



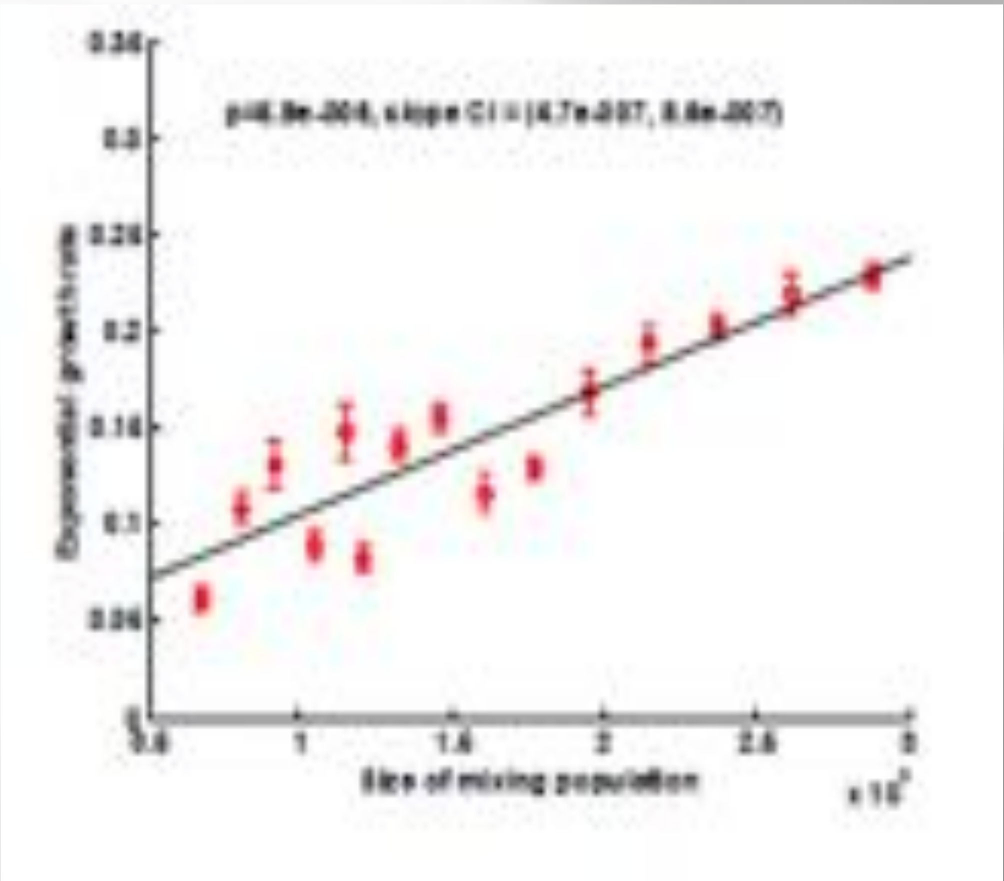
Leptospirosis in California sea lions

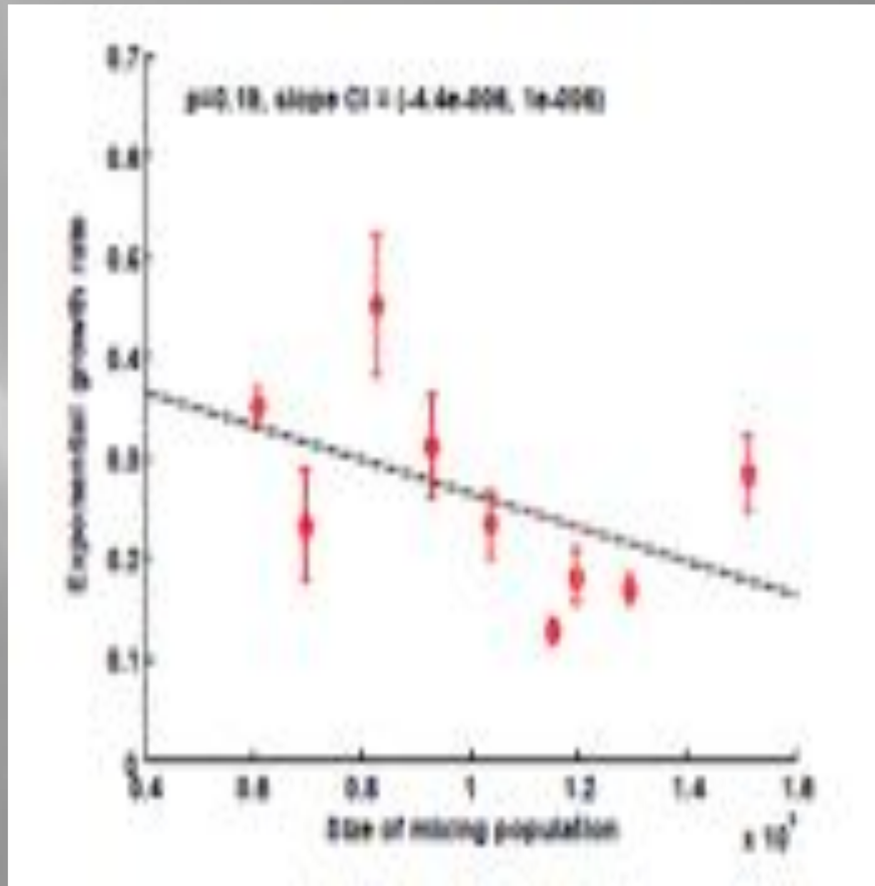
Mean age of infection does not decrease with *N* transmission
→ not density-dependent.

Evidence for FD vs MA transmission

<u>Model results:</u>
density-dependent transmission

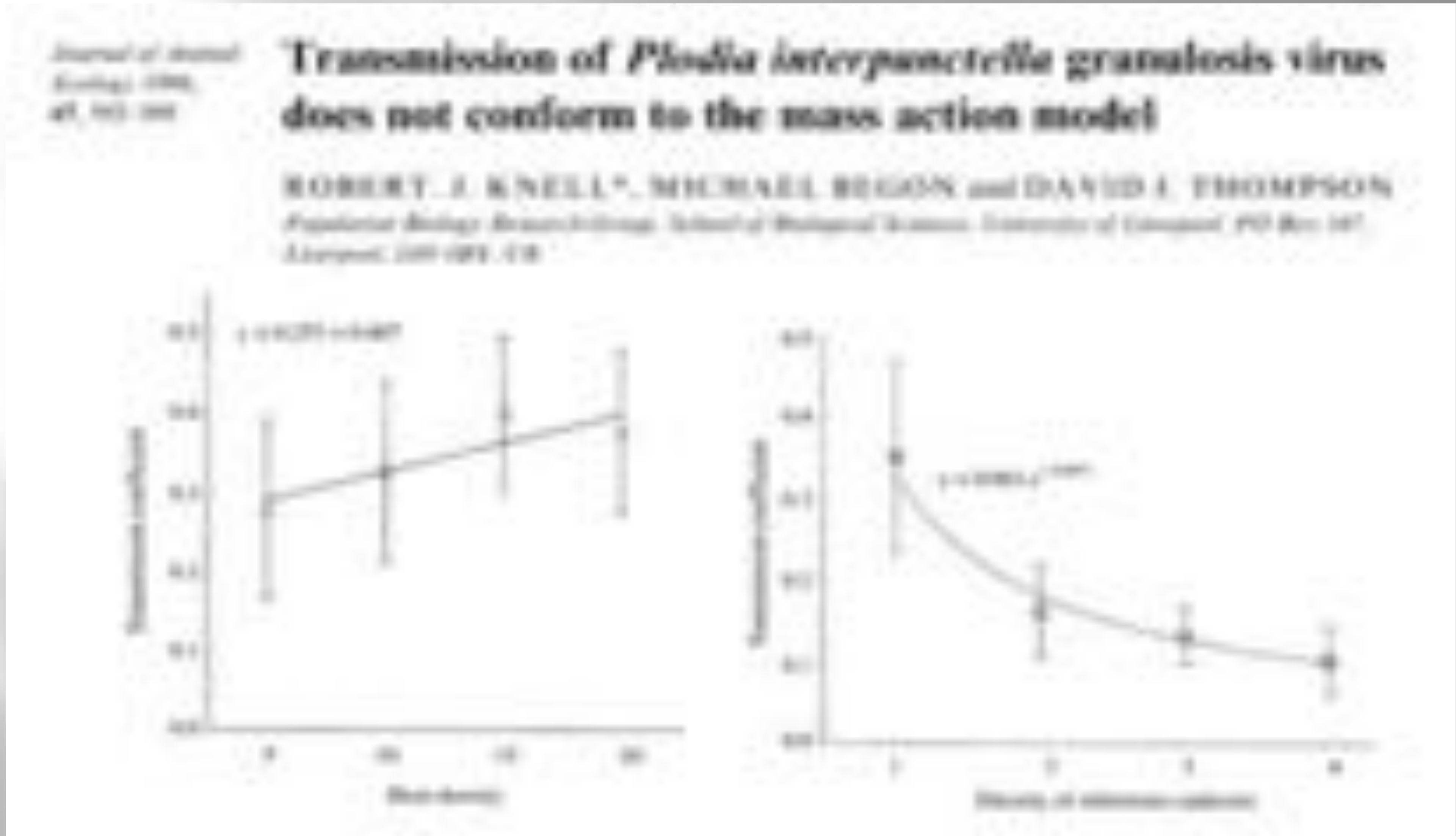
<u>Lepto data</u>





Leptospirosis in California sea lions
Epidemic growth rate does not increase with *N*
→ transmission not density-dependent.

Evidence for FD vs MA transmission → neither?



PiGV in *Plodia* (Indian meal moth)

Transmission rate is not FD or MA – need complex functional forms.

Interpret in terms of host heterogeneity and effects of density on behaviour.

So what should we do?

Despite its fundamental importance, the issue of how to formulate the transmission term in simple models is unresolved. Some pointers:

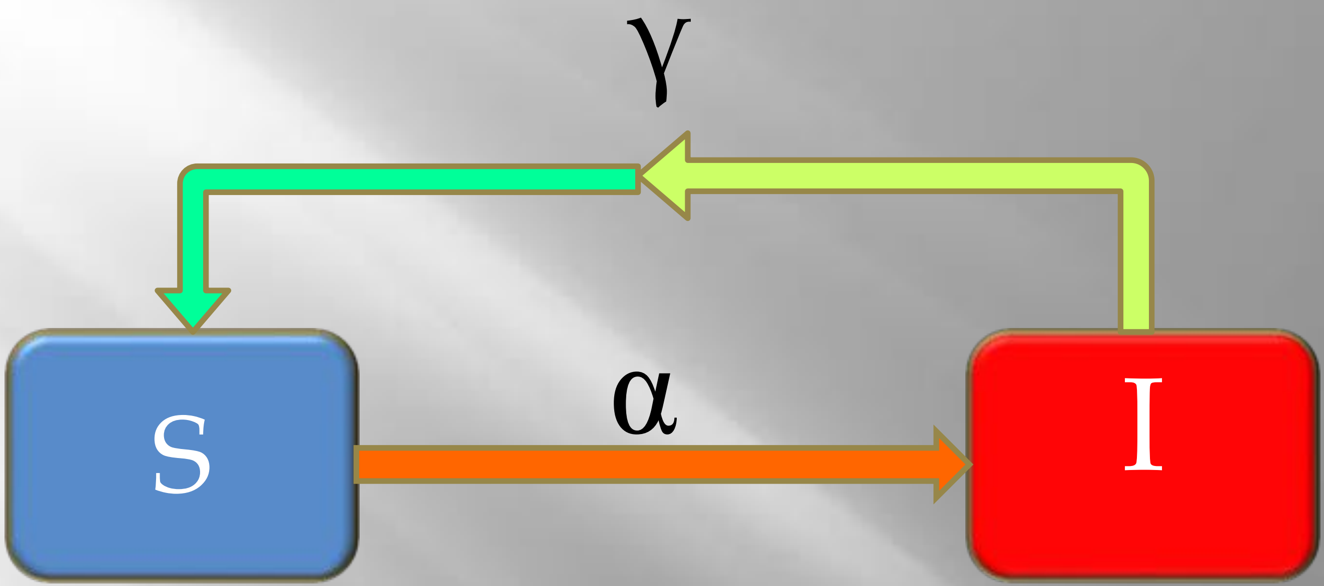
• FD transmission is generally thought to be more appropriate than MA in **large well-mixed populations.**

• In quite **small populations**, transmission is generally thought to exhibit some density dependence and MA is acceptable.

• Think about **population structure** and **mechanisms of mixing** at the scales of space and time you're thinking about. Is a very simple model appropriate?

Converting Compartmental Models
To
System of Differential Equations

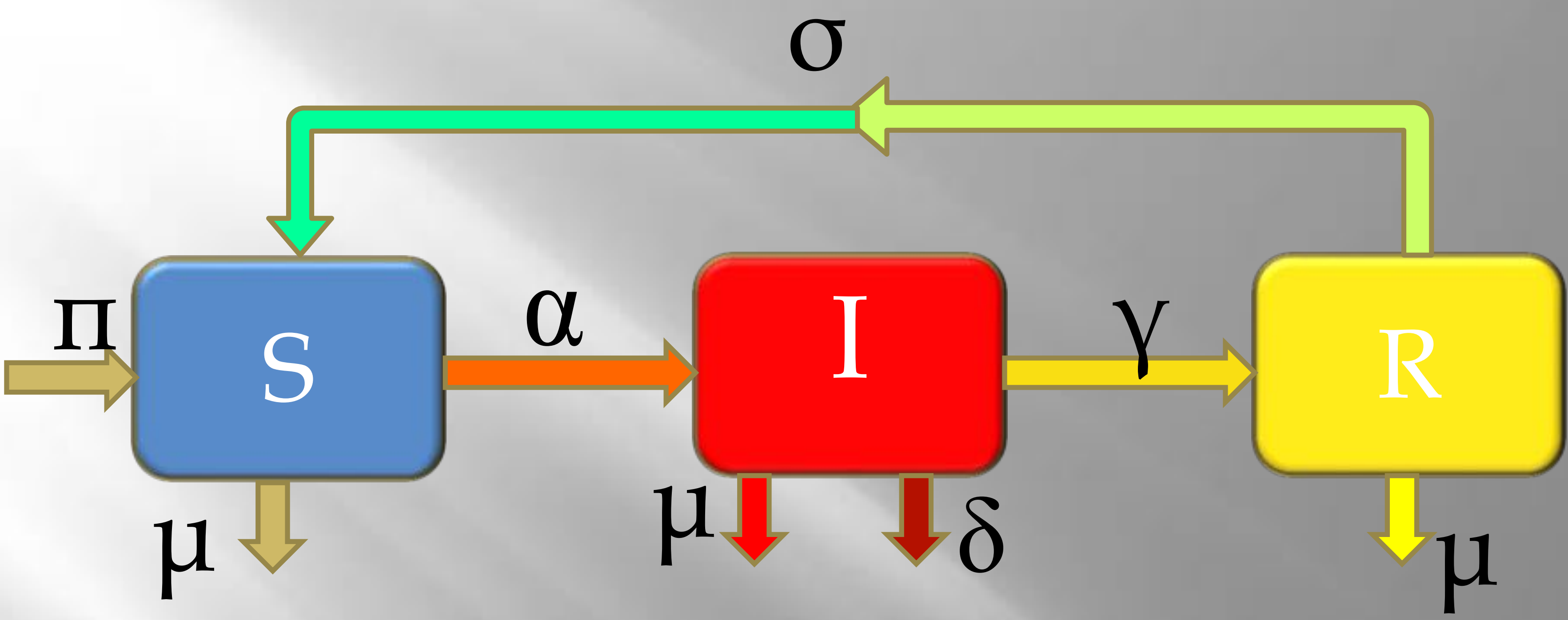
Models without Demography



Model Equations

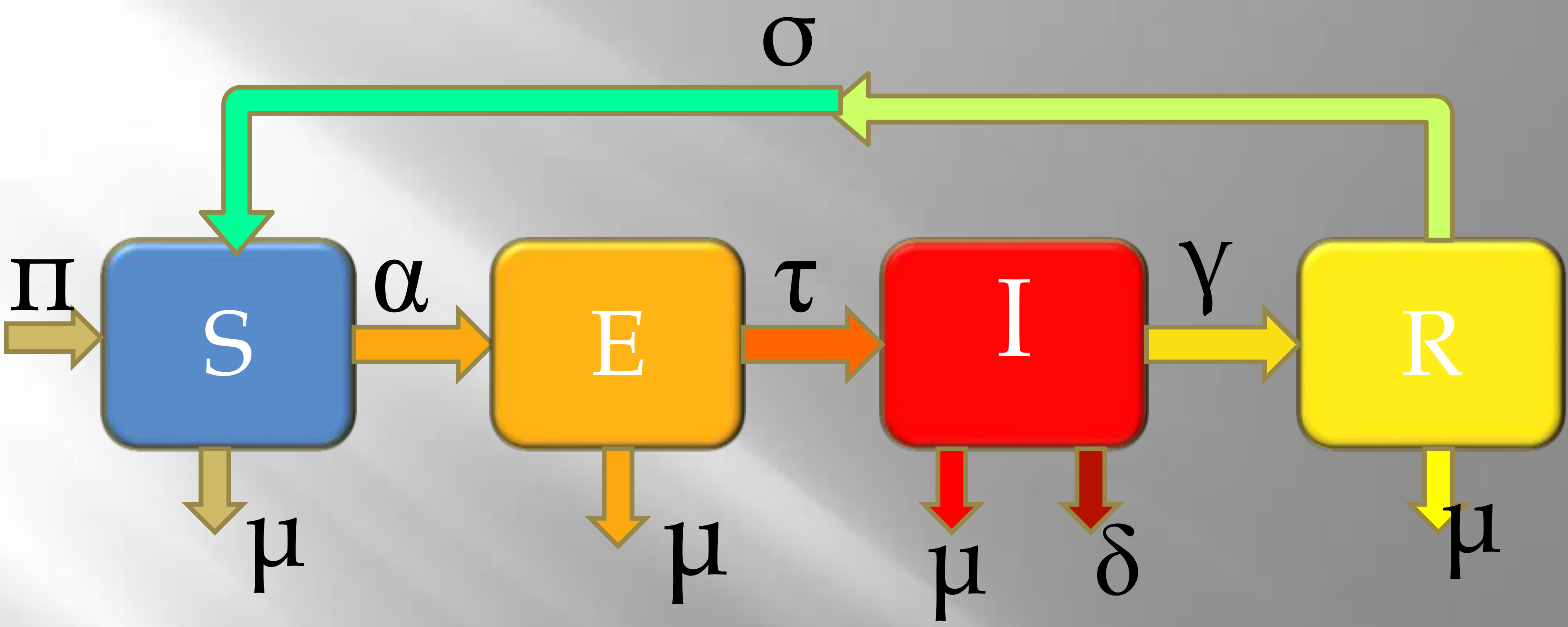
The equations for this model can be expressed as:

Model with Demography



Model Equations

The equations for this model can be expressed as:



Model Equations

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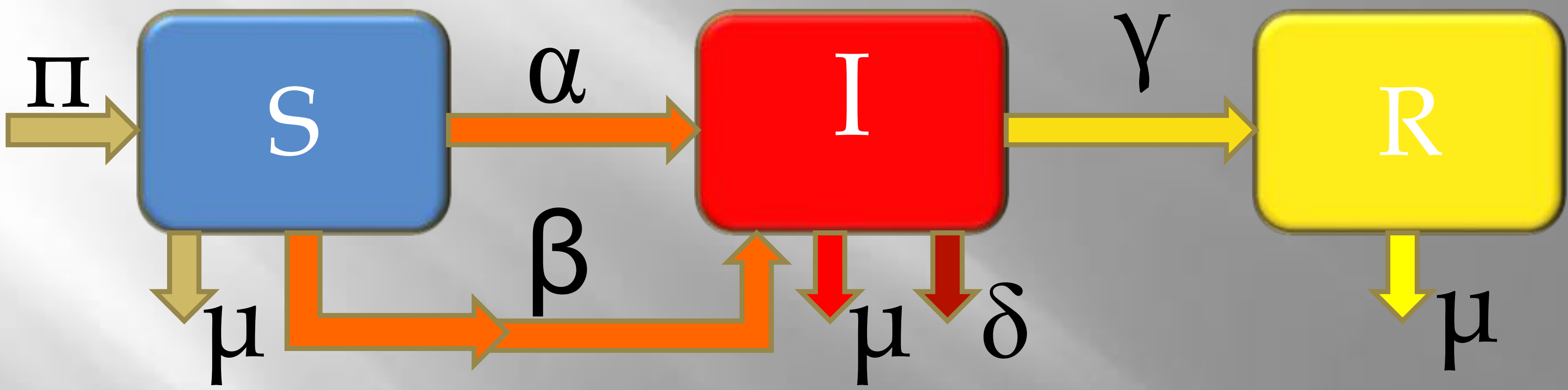
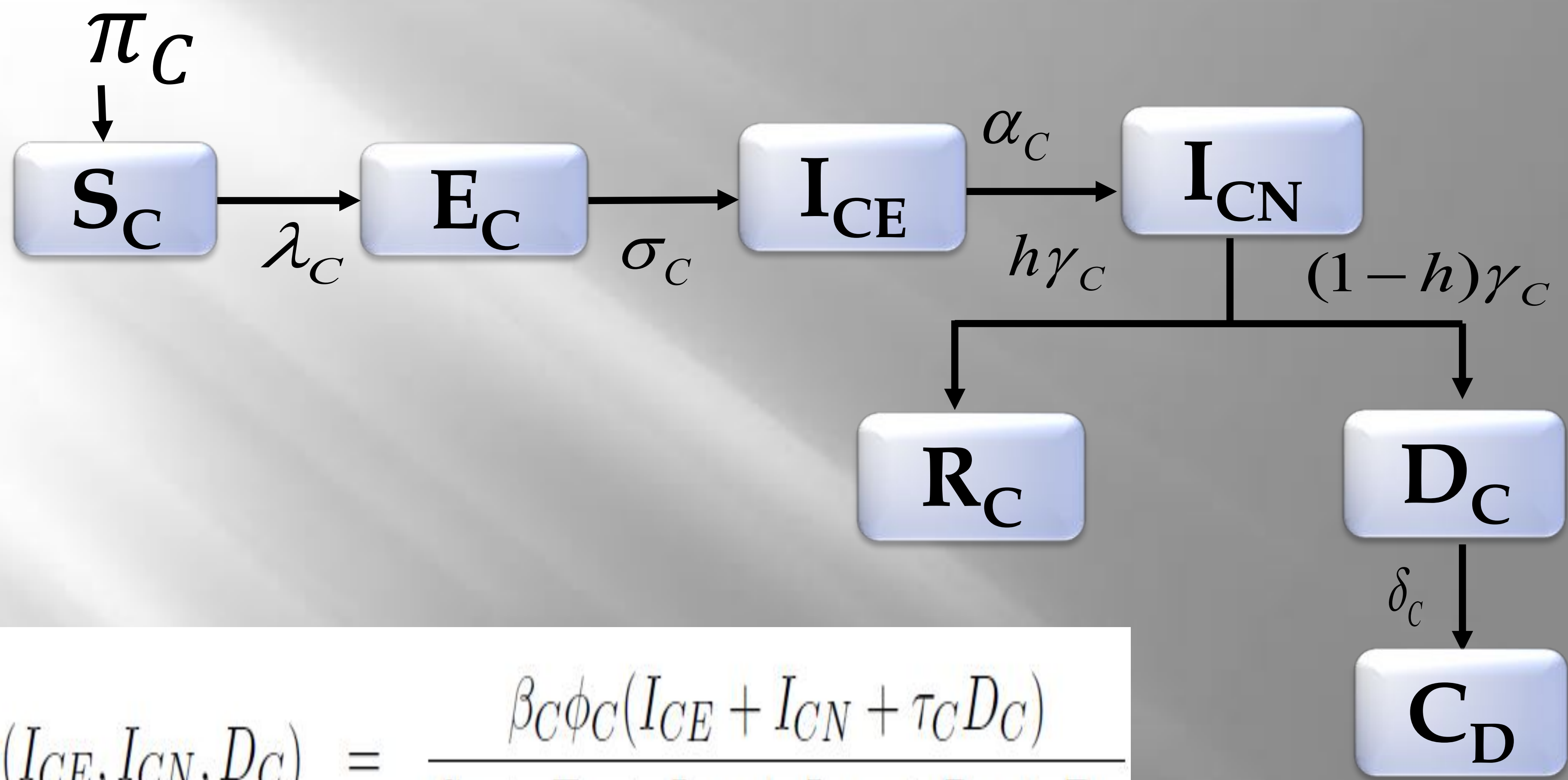
AVIAN INFLUENZA MODEL



Ebola Pre-Intervention Model

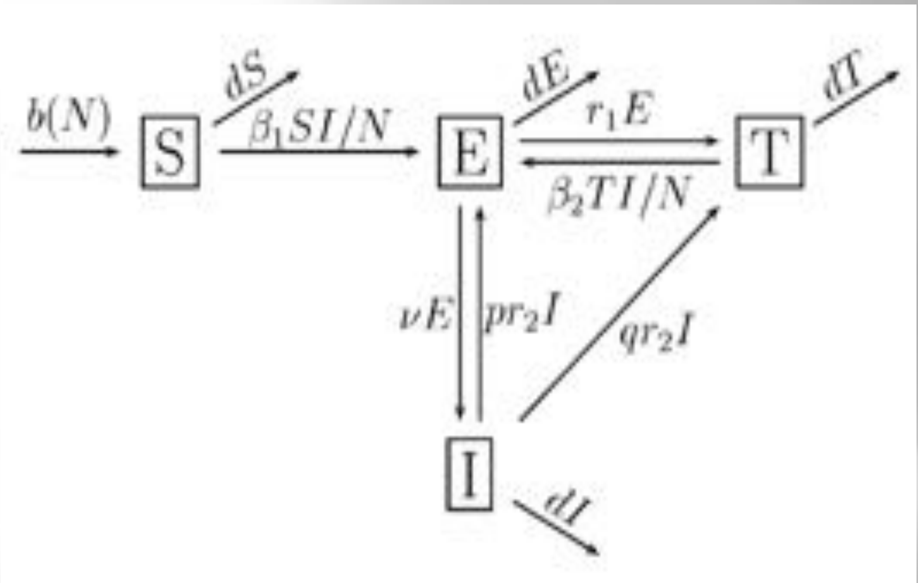


$$\lambda_C(I_{CE}, I_{CN}, D_C) = \frac{\beta_C \phi_C (I_{CE} + I_{CN} + \tau_C D_C)}{S_C + E_C + I_{CE} + I_{CN} + R_C + D_C}$$

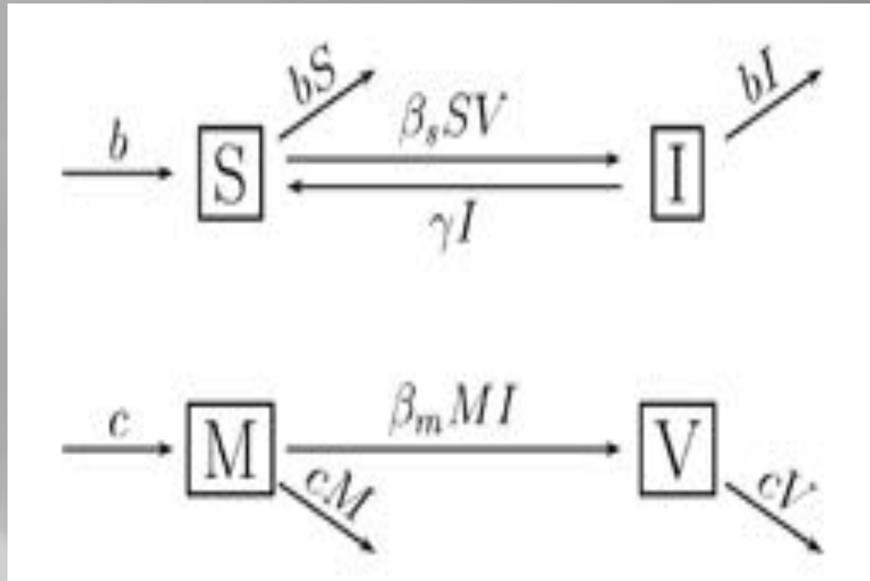
F. B. Agusto, M.I Teboh-Ewungkem and A.B. Gumel
Mathematical assessment of the role of traditional belief systems and customs and health-care settings in the transmission dynamics of the 2014 Ebola outbreaks. ***BMC Medicine*** 2015, **13**:96.

Home Work

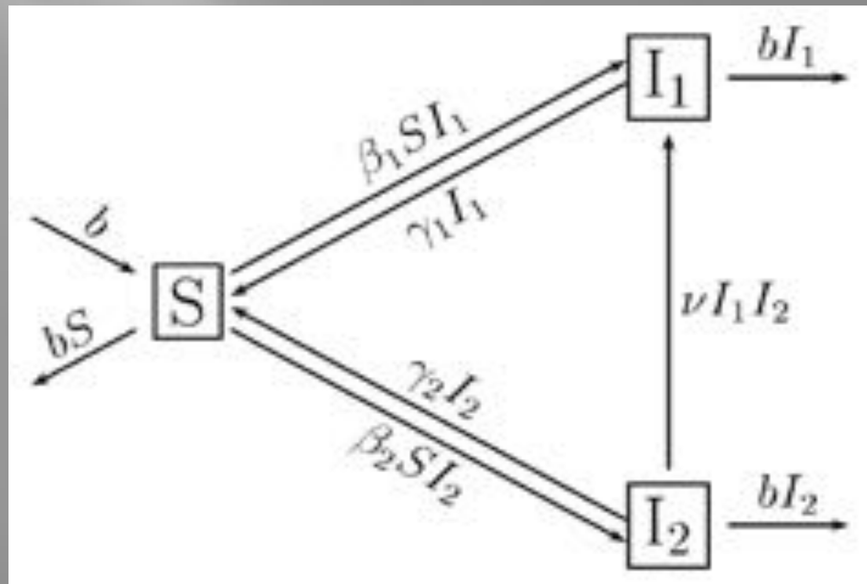
Write the equations of the following systems



Progression of infection from susceptible (S) individuals through the exposed (E), infected (I), and treated (T) compartments for the treatment model



Progression diagram for the vector–host mode



Progression diagram for the multistrain model

Home Work

Develop a compartmental flow diagram for the following infectious diseases

1. Human Papillomavirus (HPV)

2. Zika

3. Typhoid Fever