

# Infectious Disease Modeling Using Dynamic Compartmental Models in R

SMDM Short Course

22 October 2023

Philadelphia, PA

## Conflicts of interest & funding disclaimer

We have no conflicts of interest to declare and no relevant funding to disclose.

# Acknowledgements



Jason Andrew



Jeremy Goldhaber-Fiebert

# Instructors & introductions

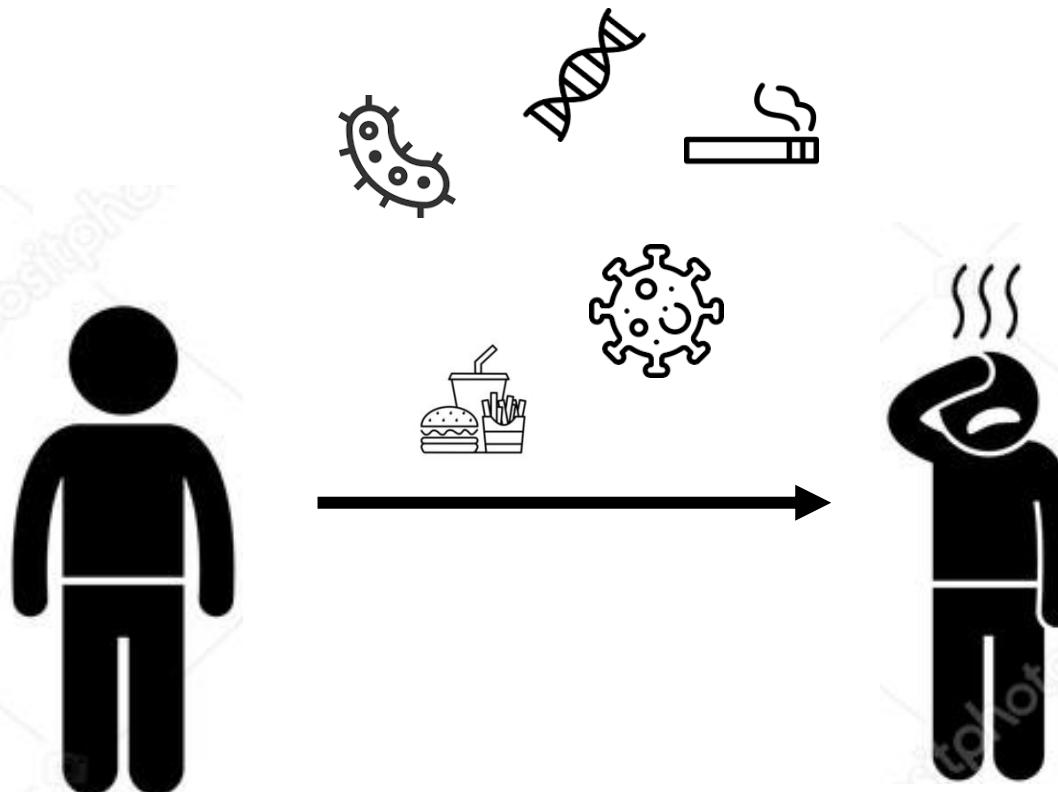


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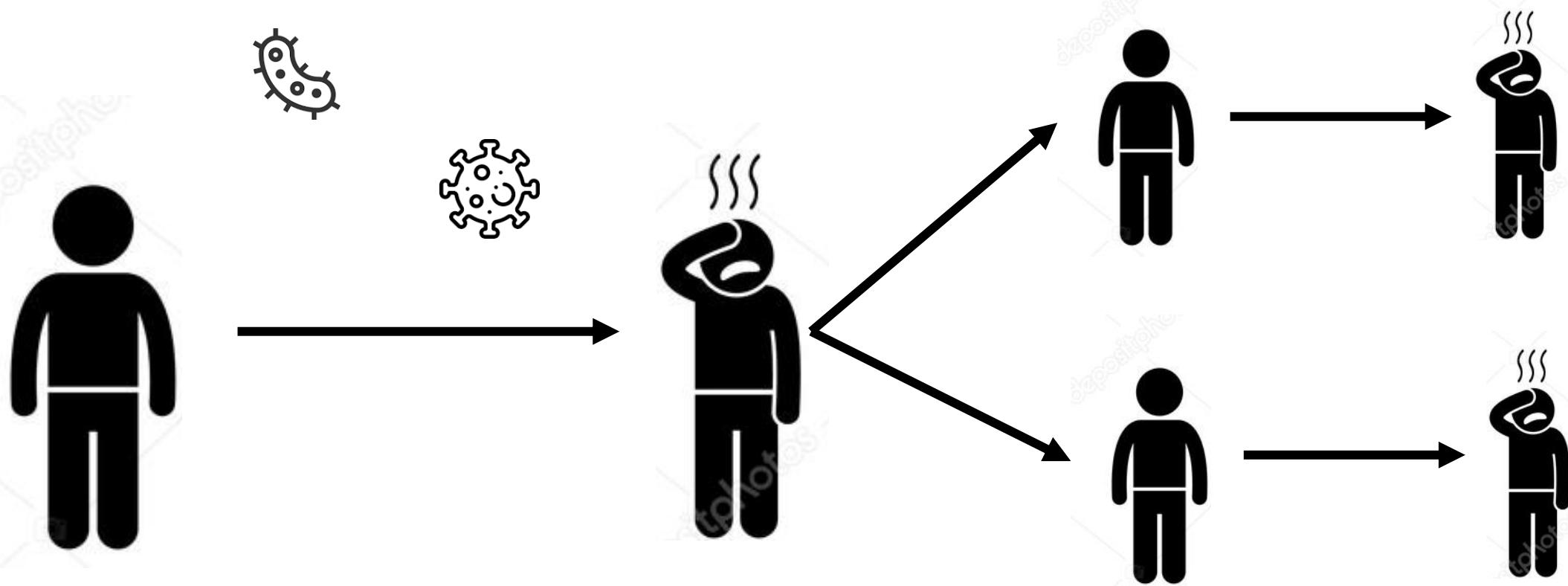


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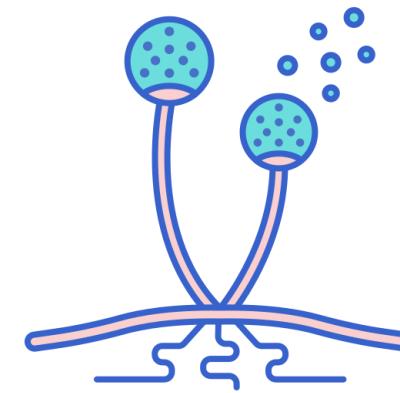
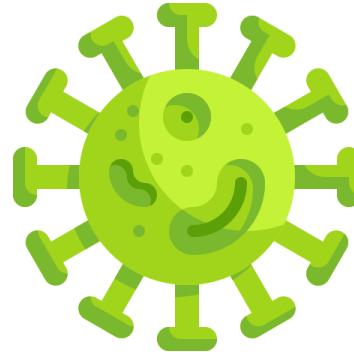
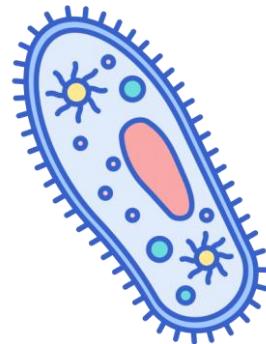
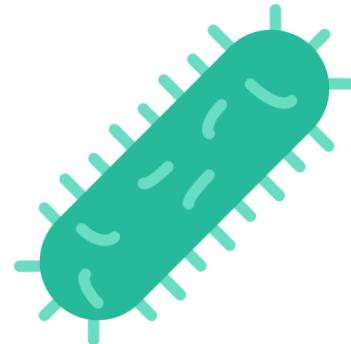
# Communicable vs. non-communicable diseases



# Communicable vs. non-communicable diseases



# Pathogens that can cause human infectious diseases



## Bacteria

- Tuberculosis
- Pneumonia
- Gonorrhea
- Tetanus
- Diphtheria
- Pertussis
- Streptococcal infections

## Protozoa

- Malaria
- Giardia
- Trichomoniasis

## Virus

- AIDS/HIV
- Influenza
- Herpes
- Hepatitis
- Measles
- Mumps
- Rubella

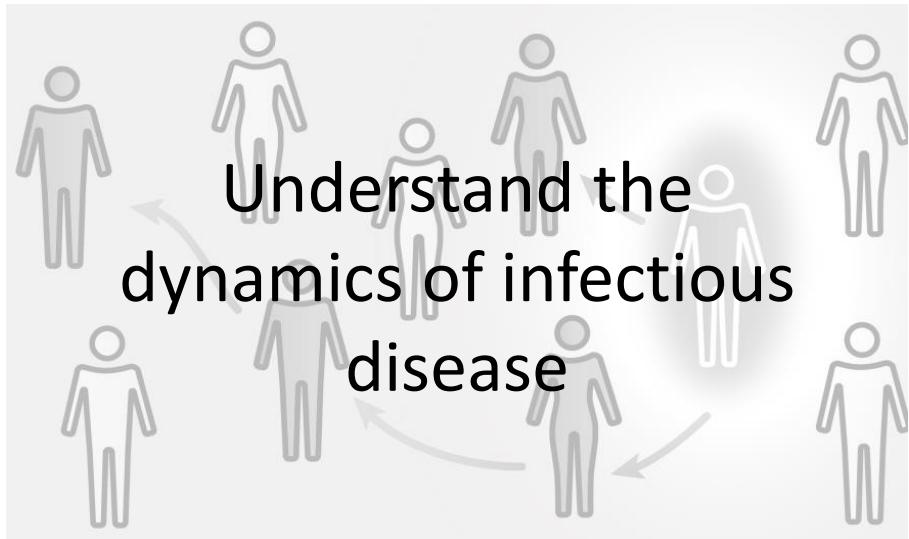
## Fungi

- Ringworm
- Candidiasis

## Helminths

- Ascariasis
- Trichuriasis
- Hookworm
- Schistosomiasis

# Why model infectious diseases?



# Examples of infectious disease modeling for public health

Disease	Modeling study	Scope	Public health impact
2009 A(H1N1)	Fraser C 2009 Garske T 2009 Shaman J 2011	Pandemic	<ul style="list-style-type: none"><li>• Quantify transmission</li><li>• Assess severity</li><li>• Assess potential seasonality</li><li>• Support WHO's decision on timing and targeting of vaccination</li></ul>
Ebola	Chretien JP 2015 Kucharski AJ 2016 Camacho A 2017	Outbreak	<ul style="list-style-type: none"><li>• Assess the impact of case isolation, contact-tracing with quarantine, and sanitary funeral practices on the number of new infections</li><li>• Design ring vaccination strategy</li><li>• WHO guideline on designing vaccine efficacy trials</li></ul>
HIV	Granich RM 2009 Bernard C 2017	Endemic	<ul style="list-style-type: none"><li>• Introduce the test-and-treat strategy</li><li>• Recommend PrEP for a high-risk group</li></ul>

# Multiple ways of modeling infectious diseases

Model type	Time-scale	Feedback allowed	Stochasticity	Modeling unit	Mixing pattern
Discrete-time state transition	Discrete	Yes	No	Population/ subpopulation	Homogeneous
Static compartmental	Continuous	No	No	Population/ subpopulation	Homogeneous
Dynamic compartmental	Continuous	Yes	No	Population/ subpopulation	Homogeneous/ heterogeneous
Microsimulation	Discrete	Yes	Yes	Individual	Homogeneous/ heterogeneous
Network	Discrete	Yes	Yes	Individual/ subpopulation	Homogeneous/ heterogeneous
Agent-based model	Discrete	Yes	Yes	Individual	Homogeneous/ heterogeneous



# Course aim

- To understand the fundamentals of infectious disease epidemiology.
- To learn how to construct and parameterize dynamic compartmental models of infectious disease transmission and simulate disease control interventions using R.
- To choose an appropriate model structure and set of assumptions for a given use case.

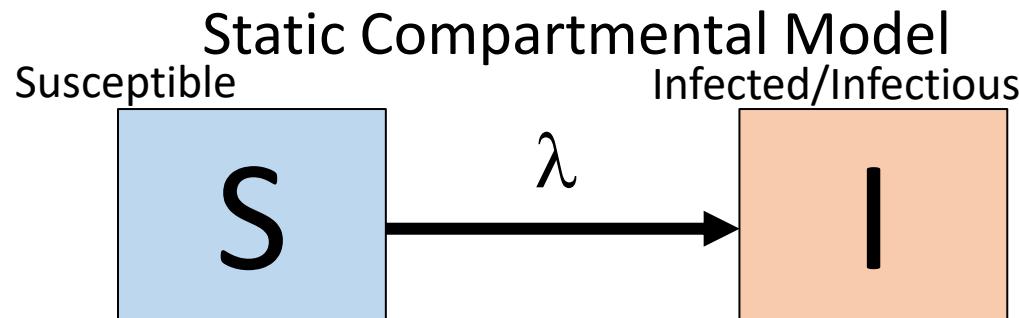
# Outline

Time	Part	Contents
8:30-8:45	Introduction & course aim	
8:40-9:45	Part I: Basics and SIR model	<ul style="list-style-type: none"><li>• Fundamentals of infectious disease epidemiology</li><li>• SIR model as a base model</li><li>• R session #1</li></ul>
	Part 2: Embellishments to the SIR model	<ul style="list-style-type: none"><li>• Adding demography</li><li>• Chronic infection</li><li>• Adding heterogeneity</li><li>• R session #2</li></ul>
9:45-10:00	Break	
10:00-10:40	Part 3: Embellishments to the SIR model	<ul style="list-style-type: none"><li>• Adding waning/no immunity</li><li>• Adding latent period</li><li>• R session #3</li><li>• Interventions: vaccine, quarantine, contact tracing</li><li>• R session #4</li></ul>
10:40-11:30	Exercise (50 mins)	
11:30-11:45	Wrap-up	
11:45-12:00	Q&A	

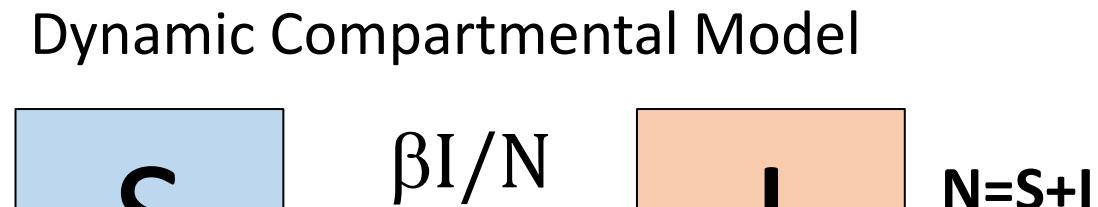
# Part I: Basics & the SIR Model

# Compartmental models

- Population-level models that track individuals according to health states.
- Typically governed by series of ordinary differential equations (ODEs).
- **Dynamic** compartmental models allow for “feedback loops”
  - e.g., Population-level risk of infection increases as more people are infected
  - Critical for many uses of infectious disease models



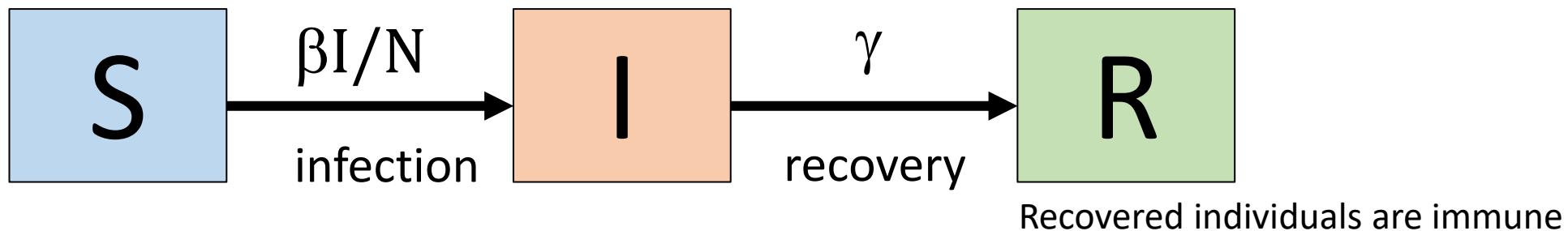
$$\frac{dI(t)}{dt} = \lambda S(t)$$



$$\frac{dI(t)}{dt} = \frac{\beta S(t)I(t)}{N(t)}$$

# SIR: Susceptible-Infected-Recovered

Today's model structures will build on the basic SIR model



$$\frac{dS(t)}{dt} = -\frac{\beta S(t)I(t)}{N(t)}$$

$$\frac{dI(t)}{dt} = \frac{\beta S(t)I(t)}{N(t)} - \gamma I(t)$$

$$\frac{dR(t)}{dt} = \gamma I(t)$$

# Quick differential equations recap

You don't need to remember how to solve these equations.

Rate of change in the size of compartment  $I$  over time  $t$

$$\frac{dI(t)}{dt} = \frac{\beta S(t)I(t)}{N(t)} - \gamma I(t)$$

New infections = product of:  
susceptible population  
% pop infected, and  
parameter beta

Infected individuals exit compartment  $I$  at rate gamma.

$$\frac{dS(t)}{dt} = -\frac{\beta S(t)I(t)}{N(t)}$$

Beta is known as the “effective contact rate” – we'll return to beta later.

$$\frac{dR(t)}{dt} = \gamma I(t)$$

# Quick differential equations recap

Rate of change in the size of compartment  $I$  over time  $t$

$$\frac{dI(t)}{dt} = \frac{\beta S(t)I(t)}{N(t)} - \gamma I(t)$$

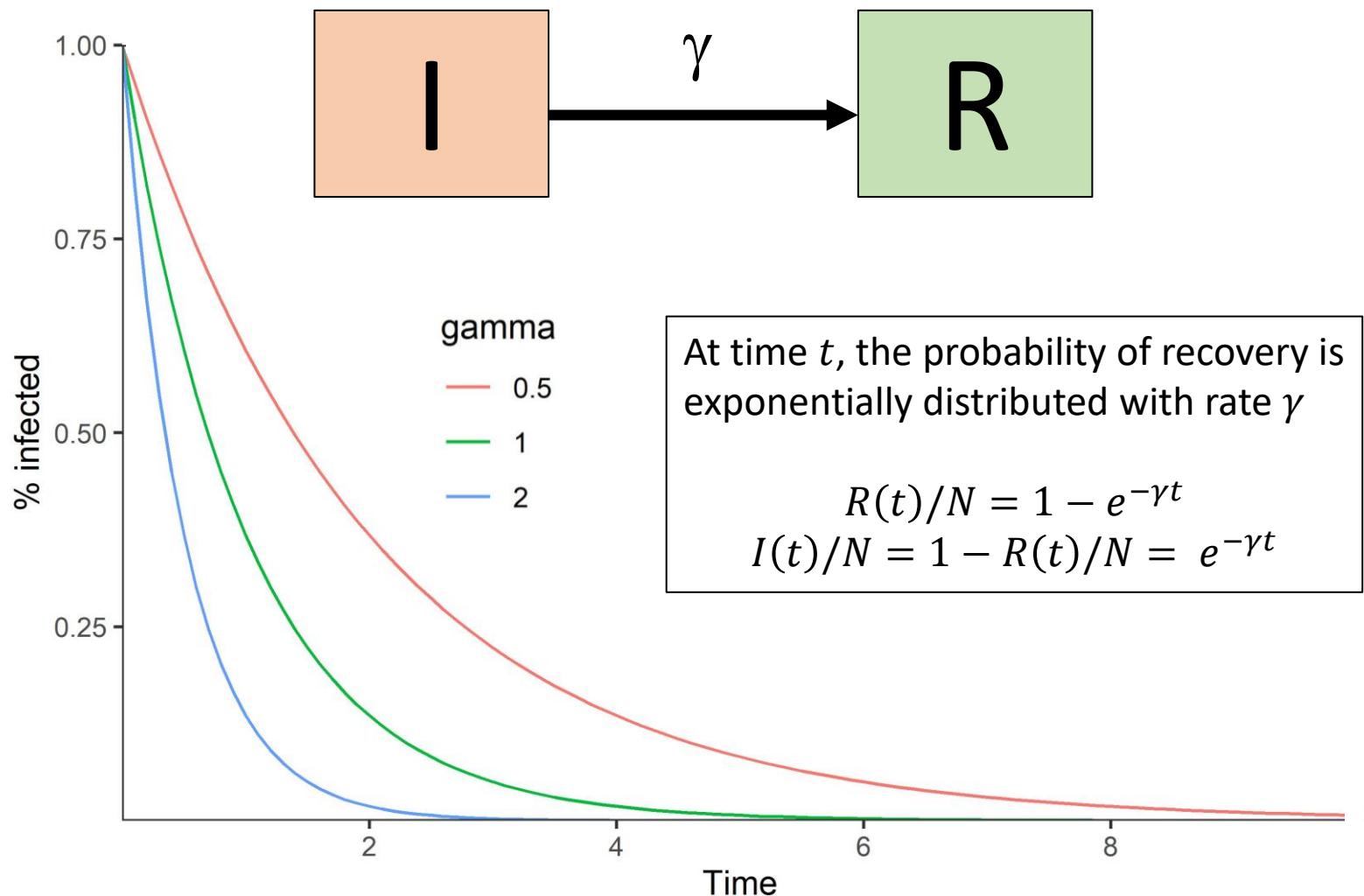
Infected individuals exit compartment  $I$  at rate gamma.

Differential equations use rates, not probabilities

- Recovery rate gamma  $\neq$  probability that someone recovers
- $\gamma$  is related to the recovery probability over a specified time period  $t$ :
  - $p = 1 - e^{-\gamma t}$
  - Assumes time to event is exponentially distributed (implicit in ODEs - unless we specify parameters that vary over time)
- The inverse of a rate is the average time until the event occurs
  - $\frac{1}{\gamma} = \text{average duration of infectiousness}$

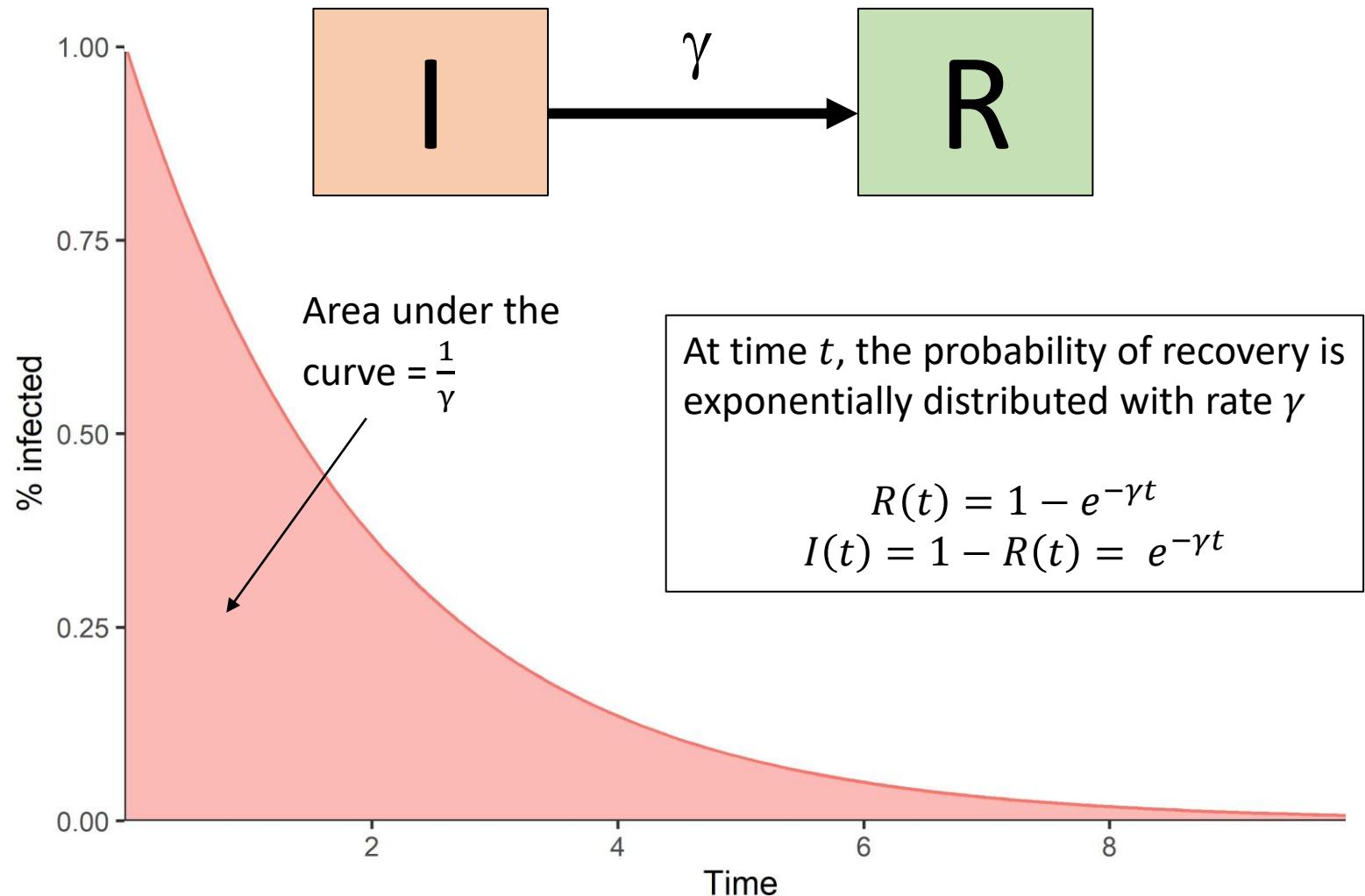
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# Quick differential equations recap

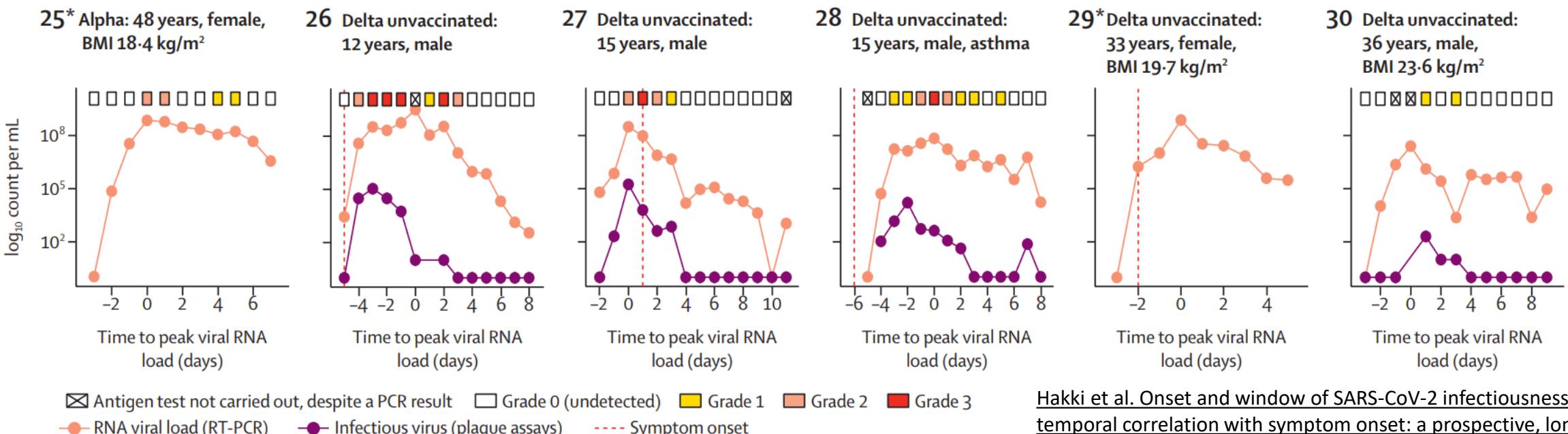
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- The inverse of a rate is the average time until the event occurs
  - $\frac{1}{\gamma} = \text{avg duration of infectiousness}$



# How to estimate the recovery rate

- The inverse of a rate is the average time until the event occurs:  $\frac{1}{\gamma} = \text{avg duration of infectiousness}$
- We can try to estimate **duration of infectiousness** using empirical data
  - Easiest: duration of symptoms**
    - But what about subclinical transmission?
    - Duration of infectiousness may not equal duration of symptoms (return to this later)
  - An alternative: duration of viral or bacterial shedding**
    - Cases must be detected prior to infectiousness – e.g., household/other contacts of cases

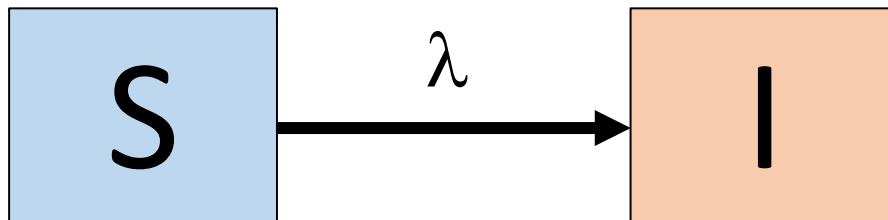
- Median duration of infectiousness: 5 [3-7] days.
- 20% of patients shed infectious virus pre-symptomatically.



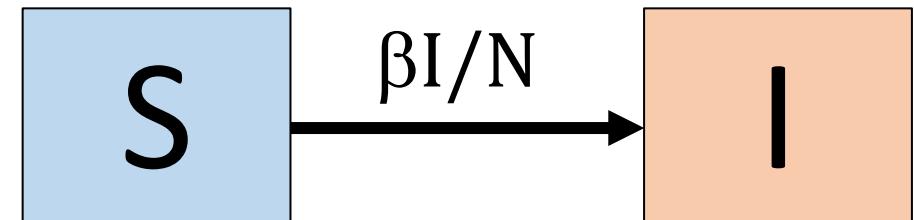
Hakki et al. *Onset and window of SARS-CoV-2 infectiousness and temporal correlation with symptom onset: a prospective, longitudinal, community cohort study*. Lancet Respiratory Medicine 2022.

# Effective contact rate & force of infection

Static Compartmental Model



Dynamic Compartmental Model



**Force of infection ( $\lambda$ ):** rate at which susceptibles are infected. Function of:

- Number of infected individuals  $I$
- **Effective contact rate ( $\beta$ ):** rate at which infected individuals  $I$  infect others. Product of:
  - Number of contacts each infected person has per unit time ( $k$ )
  - Probability of infection per contact ( $p$ )

$$\lambda(t) = \frac{\beta I(t)}{N(t)}$$

$$\beta = k * p$$

# Reproductive numbers

**Basic reproductive number ( $R_0$ ):**

**Effective reproductive number ( $R_t$ ):**

# Reproductive numbers

## Basic reproductive number ( $R_0$ ):

- Also known as: R zero, R naught, R not
- Average number of infections generated by a single infectious individual - *in a fully-susceptible population*
- Fixed characteristic of a disease? (in a given setting?)
- In the SIR model,  $R_0 = \frac{\beta}{\gamma}$
- An epidemic can occur if  $R_0 > 1$  and  $S(0)/N > \frac{1}{R_0}$

## Effective reproductive number ( $R_t$ ):

- Also known as:  $R_e$ ,  $R(t)$
- Average number of infections generated by a single infectious individual - *in the current population*
- Time-varying, based on changing population immunity
- In the SIR model,  $R_e(t) = R_0 S(t)/N$
- Infections grow while  $R_e > 1$  (i.e., while  $\frac{\gamma}{\beta} < \frac{S}{N}$ )

Based on conditions under which  $\frac{dI}{dt} > 0$

# $R_0$ estimates for various diseases

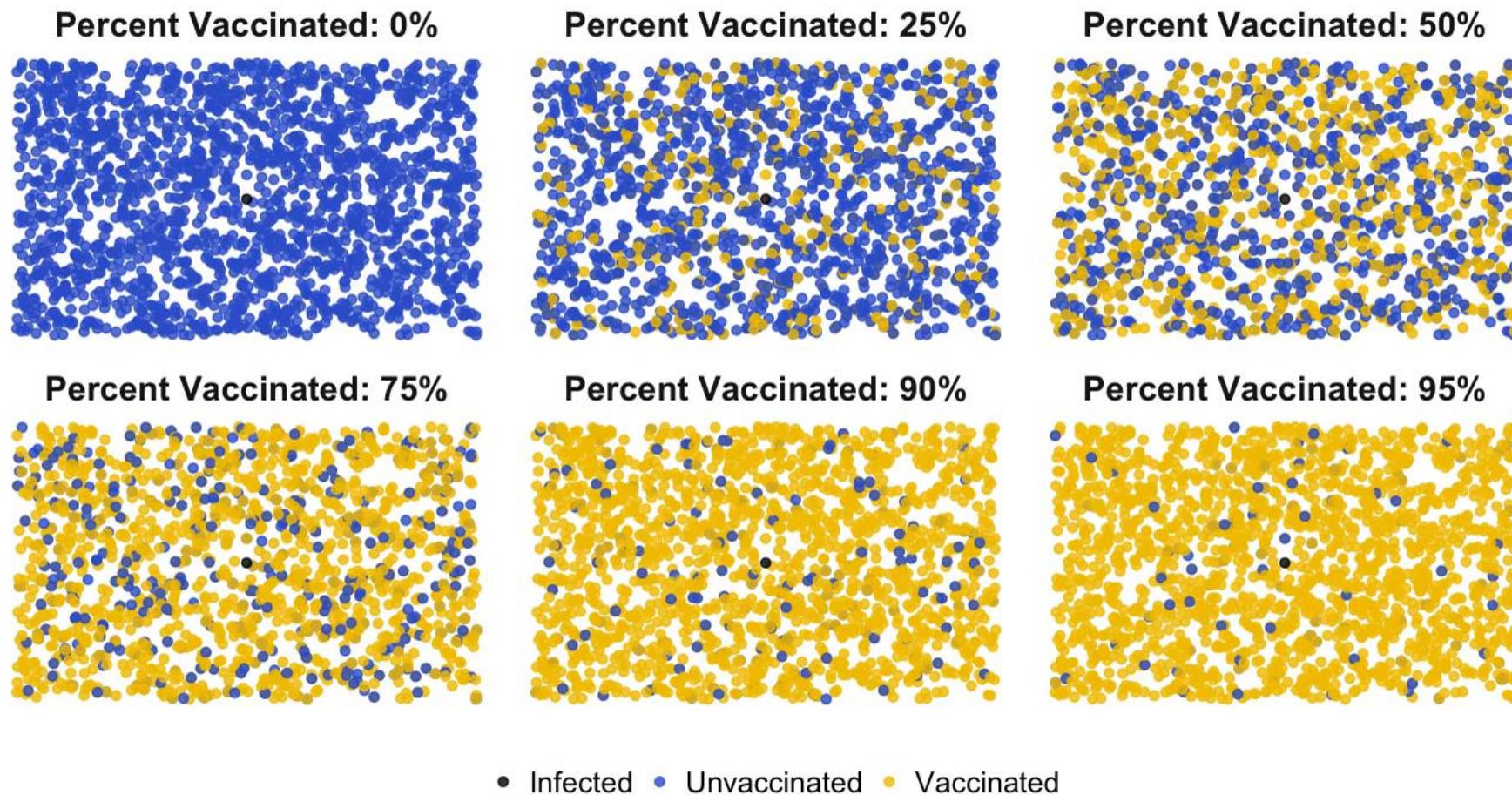
Disease	$R_0$ Estimates/Range	Sources (mostly systematic reviews)
Tuberculosis	< 1 to 4	<a href="#">Ma et al. Epidemiology &amp; Infection 2018</a>
Monkeypox (2022-23)	< 1 to 3	<a href="#">Banuet-Martinez et al. Epidemiology &amp; Infection 2023.</a>
Ebola (2014 outbreak)	1.3-1.8	<a href="#">Wong et al. Epidemiology &amp; Infection 2017.</a>
Seasonal Influenza	1-2	<a href="#">Chowell, Miller, &amp; Viboud, Epidemiology &amp; Infection 2008</a>
COVID-19 (“ancestral”)	2-5	<a href="#">Billah et al. PLOS ONE 2020.</a>
Pertussis	5-6	<a href="#">Kretzschmar et al. PLOS Med. 2010</a>
<i>Mumps, Rubella, Varicella generally in this range</i>		
Measles	12-18	<a href="#">Guerra et al. Lancet ID 2017</a>

Caveats:

- $R_0$  can be setting-specific but still informative
- Methods vary across studies
- Viruses (and bacteria) evolve
- As outbreaks unfold, or for endemic diseases, we might care more about  $R_e$  than  $R_0$

# Herd immunity

Population susceptibility is the limiting factor in epidemics - dictating whether they start & when they end

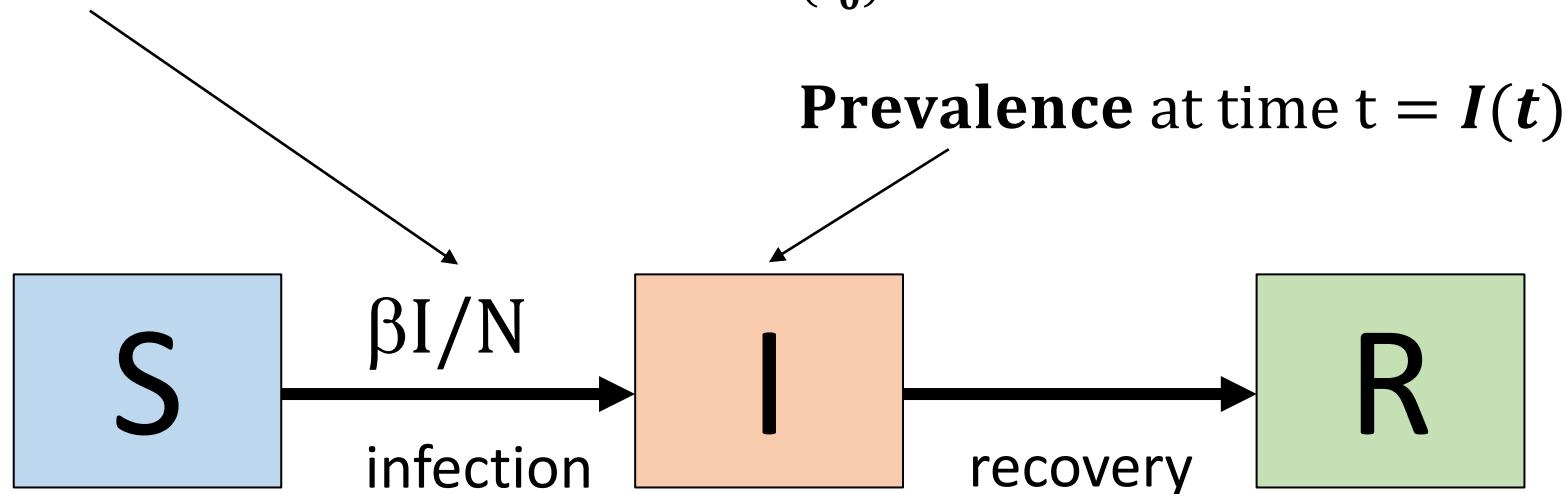


- Infected
- Unvaccinated
- Vaccinated

# Incidence & prevalence

In this diagram, what corresponds to prevalence and/or incidence?

Annual **incidence** from  $t_0$  to  $t_1$  =  $\frac{\beta S(t_0)I(t_0)}{N(t_0)}$  where beta is an annual rate



# R Session #1: Setting up & running an SIR model

## What do we need?

1. Code and packages
  - Main package: **deSolve** (ODE solver in R)
  - Code is provided – we'll walk through it together
2. Parameter values – typically calibrated
  - **Effective contact rate (beta)**: can be informed by empirical data on  $R_0$
  - **Recovery rate (gamma)**: can be informed by empirical data on duration of infectiousness
3. Starting population sizes
  - **New disease/outbreak**: “seed” 1 infected person, everyone starts out susceptible
  - **Endemic disease**: “burn in” model for several timesteps until it reaches a steady state (that should match empirical data, e.g., on prevalence or seroprevalence)
    - We'll return to this in part 2

# R Session #1: Introductory SIR model

## Demo:

- How to set up and run the SIR model in R and visualize model output
- How to calculate  $R_0$  and  $R_t$  from model parameters and output
  - How does  $R_t$  characterize infection dynamics over time?

## On your own:

- Try running the code that we went through together yourself
  - Check that you understand what is happening in the code, ask questions!
- Assess how infection dynamics change as the two parameters in the SIR model – effective contact rate (beta) and recovery rate (gamma) – vary
  - Can you compare these changes in infection dynamics to changes in  $R_0$ ?
  - We've provided some starter code

# Part 2: Embellishments to the SIR Model

# Some limitations of the basic SIR model:

- Epidemic always burns through the population eventually
- Most infectious diseases carry mortality risks (which can alter dynamics)
- Assumes completely homogeneous population
- Immunity isn't usually lifelong
- Infected  $\neq$  infectious (not always)
- Durations are not always exponentially-distributed
- Doesn't always accommodate interventions

# Adding demography: SIR w/ births & deaths

## Motivation:

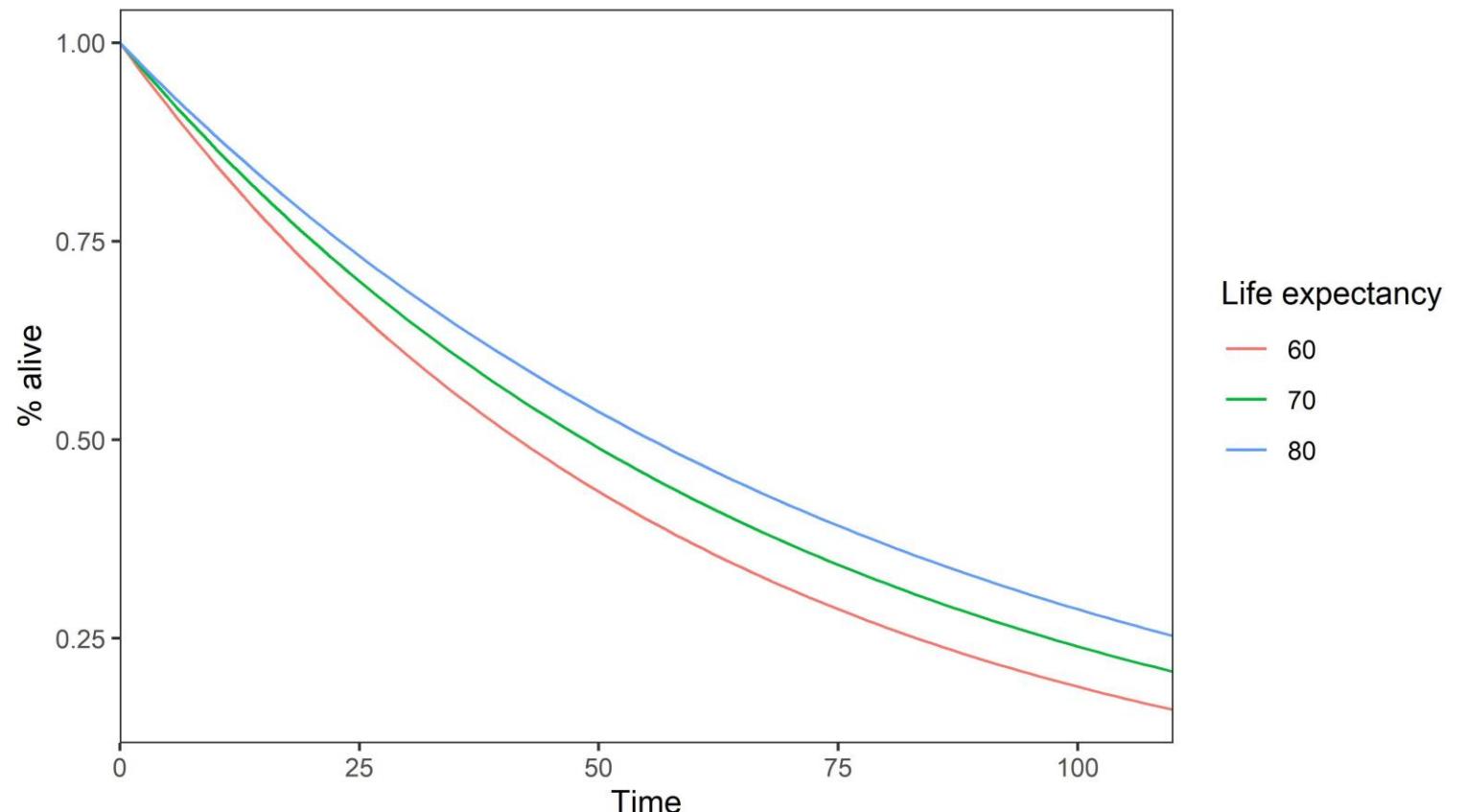
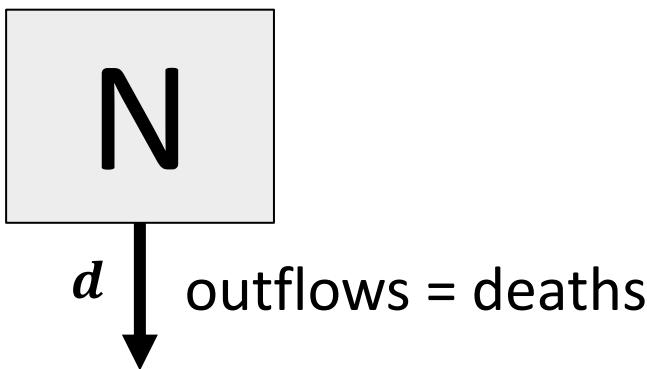
From Part 1: Population susceptibility is the limiting factor in epidemics - dictating whether they start & when they end.

→ models that don't allow for replenishment of susceptibles will always predict that epidemics burn out eventually.

**Incorporating births and deaths allows for more realistic disease dynamics, including endemicity.**

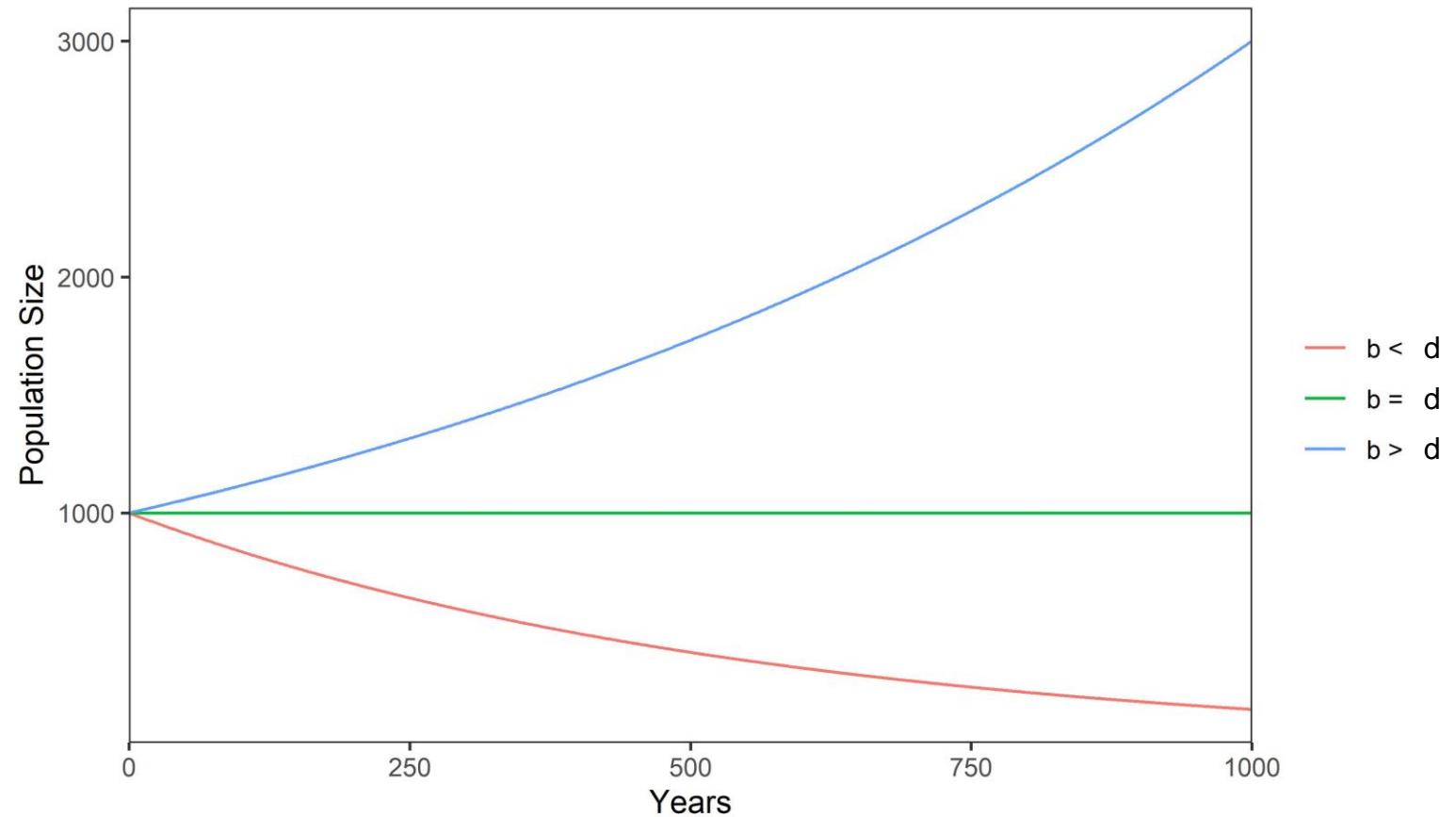
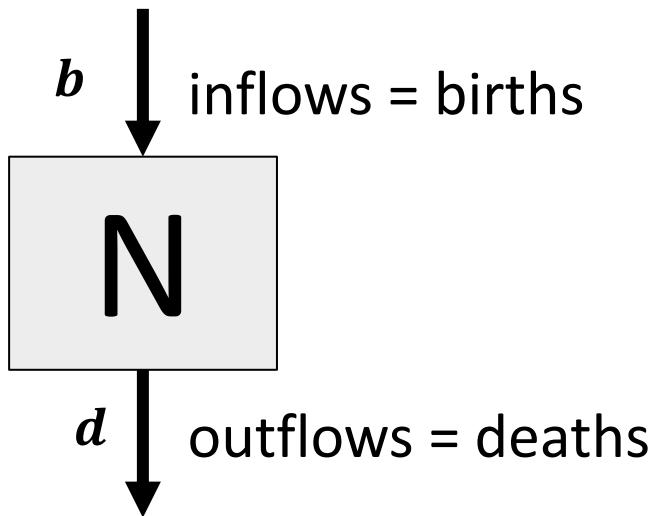
# Adding demography: SIR w/ births & deaths

First consider modeling demography outside of an ID model.



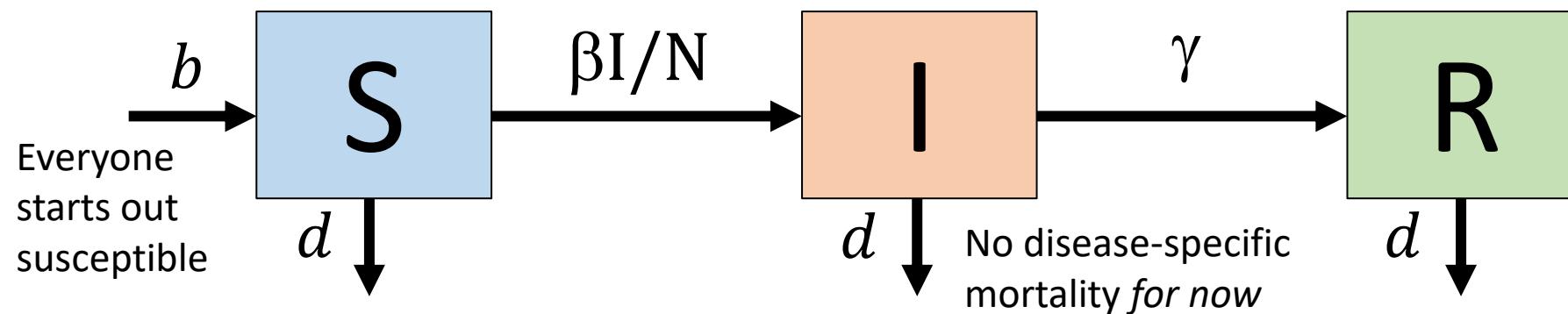
# Adding demography: SIR w/ births & deaths

First consider modeling demography outside of an ID model.



# Adding demography: SIR w/ births & deaths

Now let's consider adding demographics to our SIR model.



$$\frac{dS}{dt} = -\frac{\beta SI}{N} - dS + b(S + I + R)$$

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

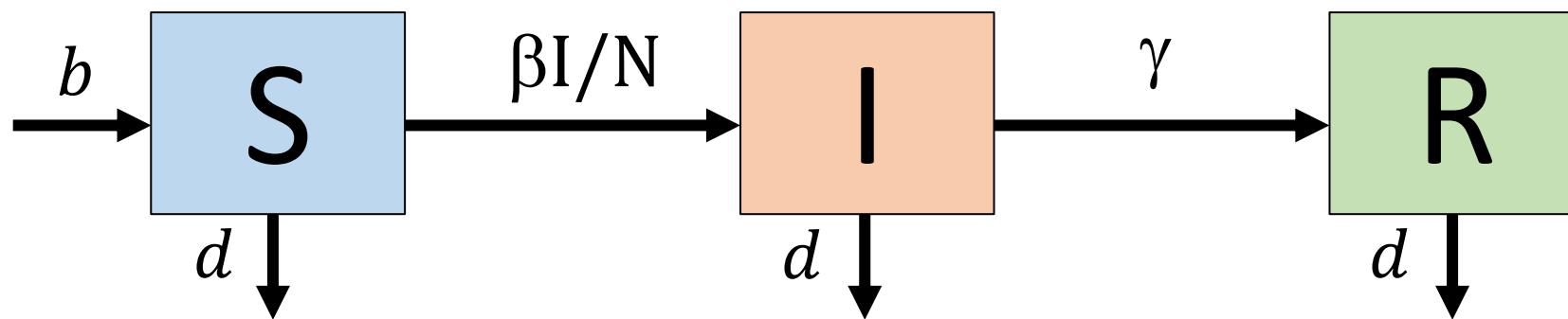
$$\frac{dR}{dt} = \gamma I - dR$$

Often, set  $b = d$  for simplicity

But – incorporating growing/shrinking populations can be more realistic, especially if important age-related factors

# Adding demography: SIR w/ births & deaths

Now let's consider adding demographics to our SIR model.



$$\frac{dS}{dt} = -\frac{\beta SI}{N} - dS + b(S + I + R)$$

Recall - without demography: epidemic takes off when  $\frac{S}{N} > \frac{\gamma}{\beta}$

With demography:  $\frac{dI}{dt} > 0$  when  $\frac{S}{N} > \frac{\gamma+d}{\beta} \rightarrow R_0 = \frac{\beta}{\gamma+d}$

Why? Mortality shortens the duration of infectiousness

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

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

# SIR with demography: R code

## SIR without demography

```
BasicSIR<-function(t, state, parameters) {  
  with(as.list(c(state, parameters)), {  
    N = S + I + R  
  
    #SIR model equations from slides  
    ds <- -beta*S*I/N  
    dI <- beta*S*I/N - gamma*I  
    dR <- gamma*I  
  
    #return the rates of change as a list  
    list(c(ds, dI, dR))  
  })  
}
```

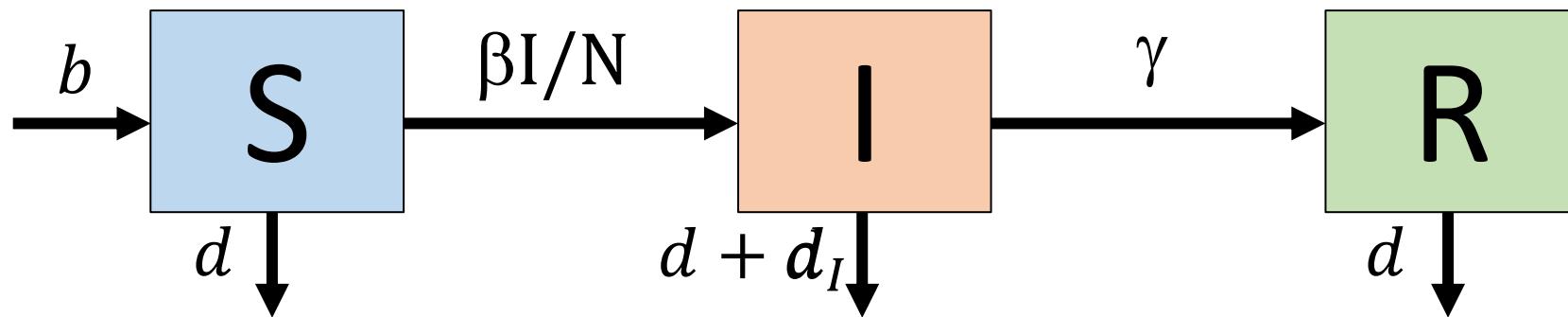
## SIR with demography

```
openSIR<-function(t, state, parameters) {  
  with(as.list(c(state, parameters)), {  
    N = S + I + R  
  
    #SIR w/ demography equations from the slides  
    ds <- -beta*S*I/N + birth*N - death*S  
    dI <- beta*S*I/N - death*I - gamma*I  
    dR <- gamma*I - death*R  
  
    # return the rates of change as a list  
    list(c(ds, dI, dR))  
  })  
}
```

```
parameters <- c(beta = 0.5, #effective contact rate  
                  gamma = 0.3, #recovery rate (1/duration infection)  
                  birth = 0.02, #birth rate (per capita)  
                  death = 0.02 #all-cause mortality rate  
)
```

# Adding demography: SIR w/ births & deaths

Incorporating disease-specific mortality



$$\frac{dS}{dt} = -\frac{\beta SI}{N} - dS + b(S + I + R)$$

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

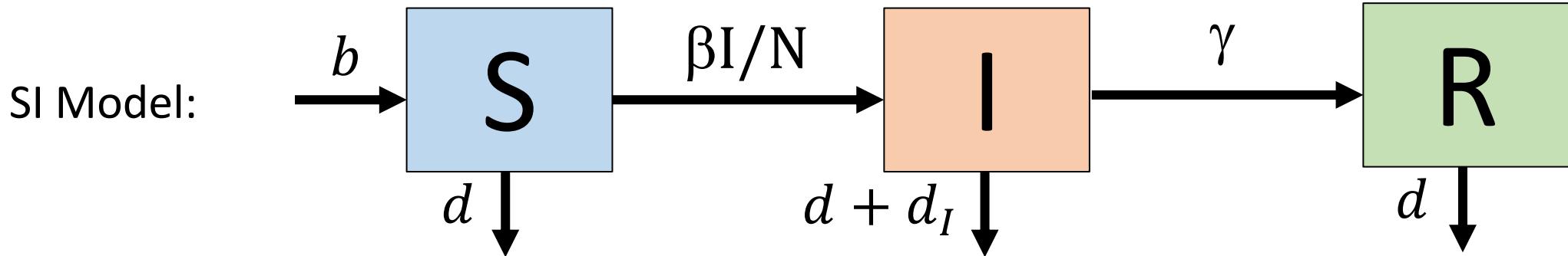
$$\frac{dR}{dt} = \gamma I - dR$$

When is it most important to include disease-specific mortality?

- Want to estimate deaths from a disease
- Long duration of infection
- High case-fatality ratio

# Chronic infections

What changes would you make to the SIR model to model a chronic infectious disease, like HIV or HCV?



$$\frac{dS}{dt} = -\frac{\beta SI}{N} - dS + b(S + I)$$

$$\frac{dI}{dt} = \frac{\beta SI}{N} - dI - d_I I$$

Need to include births/deaths or everyone will eventually become infected.

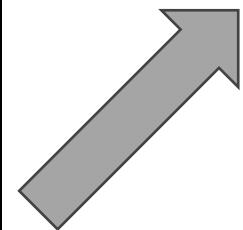
# SI model: R code

## SIR Model

```
openSIR<-function(t, state, parameters) {  
  with(as.list(c(state, parameters)), {  
    N = S + I + R  
  
    #SIR w/ demography equations from the slides  
    ds <- -beta*S*I/N + birth*N - death*S  
    dI <- beta*S*I/N - death*I - gamma*I  
    dR <- gamma*I - death*R  
  
    # return the rates of change as a list  
    list(c(ds, dI, dR))  
  })  
}
```

SI Model: same code, set recovery rate to 0

```
parameters <- c(beta = 0.5,  
                 gamma = 0,  
                 birth = 0.02,  
                 death = 0.02  
)
```



```
parameters <- c(beta = 0.5, #effective contact rate  
                 gamma = 0.3, #recovery rate (1/duration infection)  
                 birth = 0.02, #birth rate (per capita)  
                 death = 0.02 #all-cause mortality rate  
)
```

# Adding heterogeneity: models w/ stratification(s)

Low-risk group



If  $\beta$  remains a scalar, nothing changes.

High-risk group

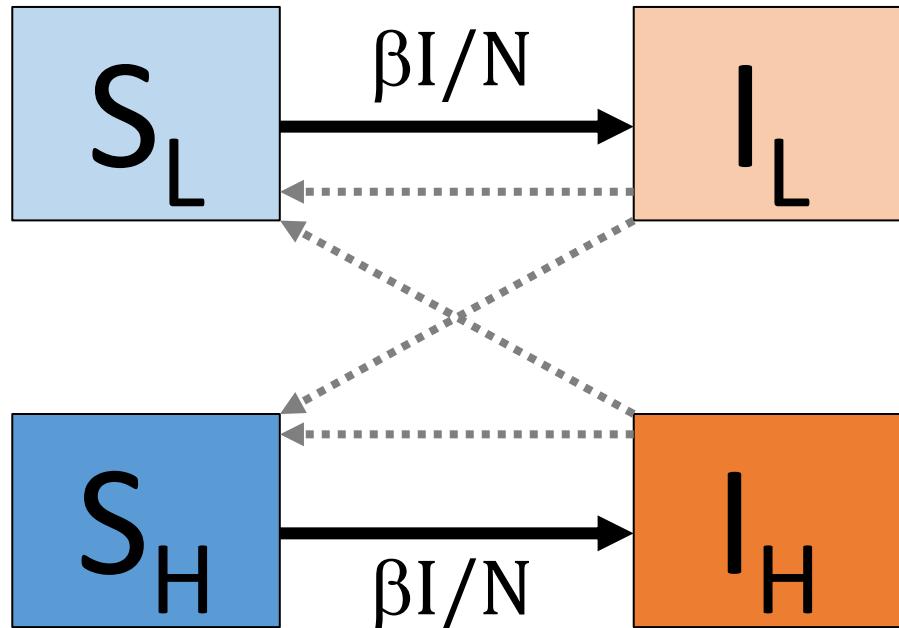


Typically,  $\beta$  now becomes a matrix.

←--- Transmission

Omitting recovery & demography for now – but these can easily be included

# Adding heterogeneity: models w/ stratification(s)



**Who Acquired Infection From Whom  
(WAIFW) or Contact Matrix:**

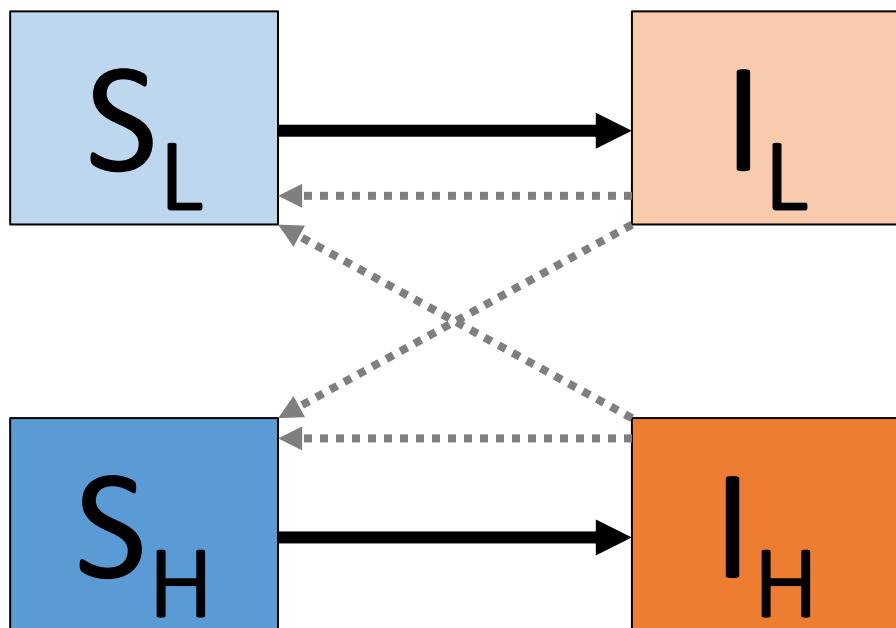
$$\boldsymbol{\beta} = \begin{pmatrix} \beta_{HH} & \beta_{HL} \\ \beta_{LH} & \beta_{LL} \end{pmatrix}$$

Low risk group acquires transmission from high-risk group

$$\frac{dS_L}{dt} = -(\beta_{LL}S_LI_L + \beta_{LH}S_LI_H)/N \quad \frac{dI_L}{dt} = (\beta_{LL}S_LI_L + \beta_{LH}S_LI_H)/N$$

$$\frac{dS_H}{dt} = -(\beta_{HH}S_HI_H + \beta_{HL}S_HI_L)/N \quad \frac{dI_H}{dt} = (\beta_{HH}S_HI_H + \beta_{HL}S_HI_L)/N$$

# Adding heterogeneity: models w/ stratification(s)



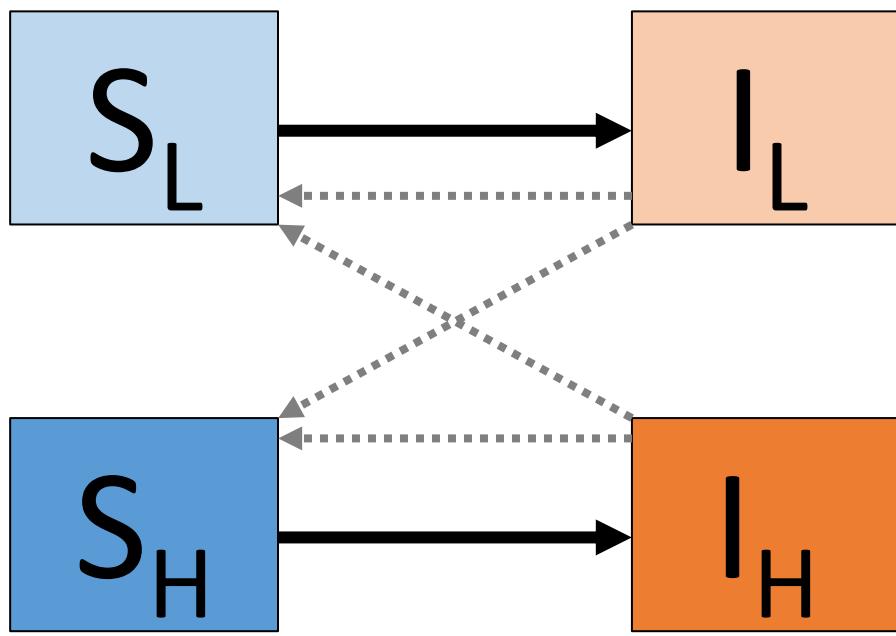
**Who Acquired Infection From Whom  
(WAIFW) or Contact Matrix:**

$$\beta = \begin{pmatrix} \beta_{HH} & \beta_{HL} \\ \beta_{LH} & \beta_{LL} \end{pmatrix}$$

If  $\beta_{HH} = \beta_{HL} = \beta_{LH} = \beta_{LL}$ , then this is the same as the non-stratified model.

If  $\beta_{HL} = \beta_{LH} = 0$ , then this is like having 2 separate models.

# Adding heterogeneity: models w/ stratification(s)



**Who Acquired Infection From Whom  
(WAIFW) or Contact Matrix:**

$$\beta = \begin{pmatrix} \beta_{HH} & \beta_{HL} \\ \beta_{LH} & \beta_{LL} \end{pmatrix}$$

Usually, a group is at **high risk** because:

$$\beta_{HH} + \beta_{HL} > \beta_{LL} + \beta_{LH}$$

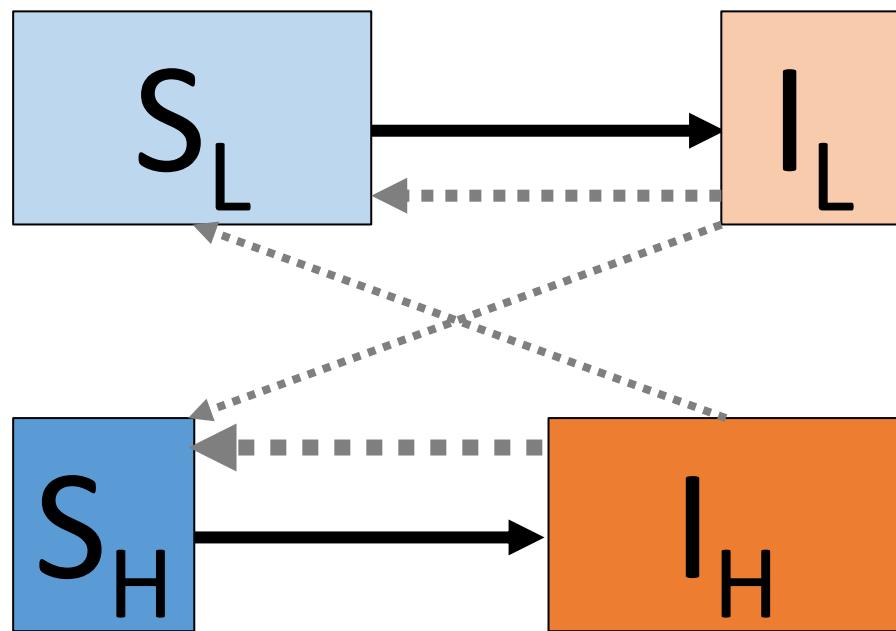
**Assortative** (non-homogenous) mixing:

$$\beta_{HH} > \beta_{HL} \text{ and } \beta_{LL} > \beta_{LH}$$

If risk of infection & contact same – **symmetry**:

$$\beta_{HL} = \beta_{LH}$$

# Adding heterogeneity: models w/ stratification(s)



## Implications:

- Even if the high-risk group doesn't contact the low-risk group much, they can still drive the epidemic among the low-risk group
  - Because most of the infections will be among the high-risk group
- Endemic equilibrium can be sustained with lower prevalence, because stratification increases  $R_0$ .

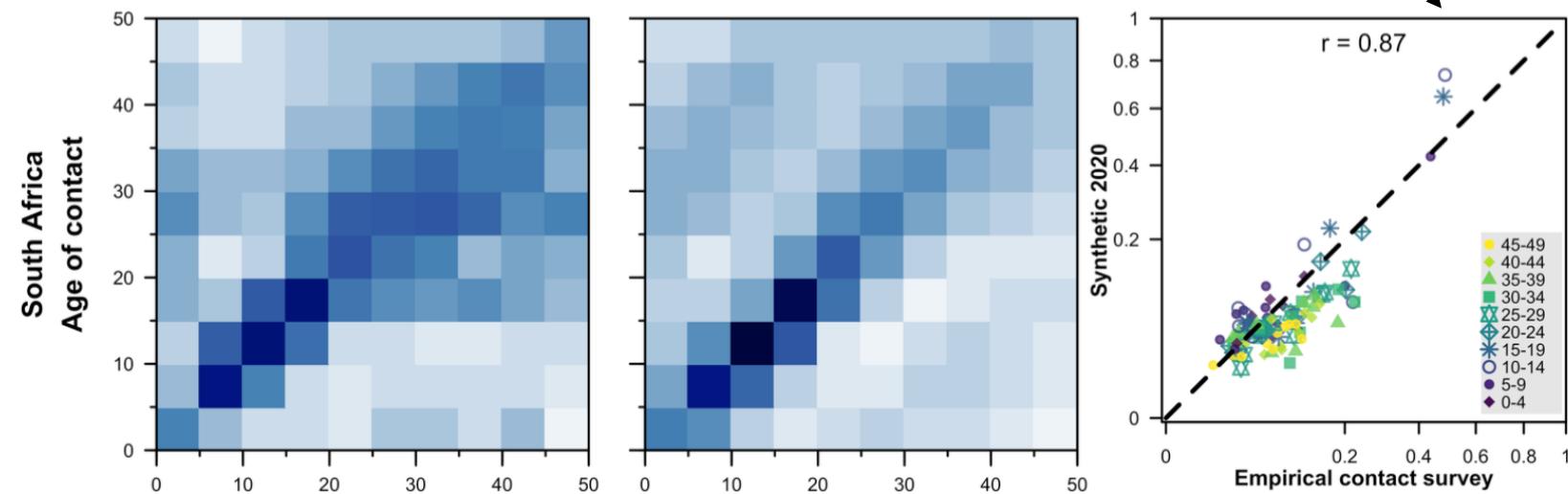
# Adding heterogeneity: models w/ stratification(s)

In addition to high- vs. low-risk groups, stratifications can also represent:

- Age groups
  - Include “aging rate” to transition from 1 age strata to the next
- Geographic locations
- Different types of contacts (e.g., household vs. general)
- Groups with different uptake of interventions (later)
- Different strains of a disease

# How to estimate contact matrices?

- Algorithms: random, proportional restricted/preferred, selective mixing
- Surveys of contact patterns
  - Relevant for respiratory/airborne pathogens
  - Resources
    - [Mossong et al. Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases. PLOS Medicine 2008.](#)
    - [Prem et al. Projecting contact matrices in 177 geographical regions: An update and comparison with empirical data for the COVID-19 era. PLOS Computational Biology 2021.](#)
    - [McCreesh et al. Estimating age-mixing patterns relevant for the transmission of airborne infections. Epidemics 2019.](#)
- Surveys to identify contact networks
  - Relevant for STIs, needle-sharing
  - More at the end of this presentation

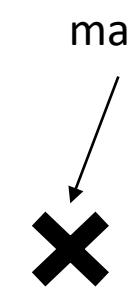


# SIR w/ heterogeneous mixing – R code

```
MixingSIR<-function(t, state, parameters) {  
  
state <- matrix(data=state, nrow=ncol(parameters$contact_matrix))  
colnames(state) <- c("S", "I", "R")  
rownames(state) <- c("h", "l")  
  
with(parameters, {  
  ds <- -1*state[, "S"]*state[, "I"]%*%contact_matrix/sum(state)  
  dI <- state[, "S"]*state[, "I"]%*%contact_matrix/sum(state) -  
    gamma*state[, "I"]  
  dR <- gamma*state[, "I"]  
  
  #return the rates of change as a list  
  list(c(ds, dI, dR))  
})  
}
```

	STATE	S	I	R
MATRIX				
High-Risk	24,999	1	0	
Low-Risk	75,000	0	0	

matrix multiplication



WAIFW Matrix	From High-Risk	From Low-Risk
To High-Risk	2.9	0.1
To Low-Risk	0.1	0.5

# R Session #2: SIR with demography or heterogeneous mixing

## SIR with demography (births & deaths)

1. How do infection dynamics change compared to the Basic SIR model (without demography)?
2. How do observed dynamics correspond to changes in  $R_t$ ?
3. **How do dynamics change as birth/death rates rise or fall?**

## SIR with heterogeneous mixing

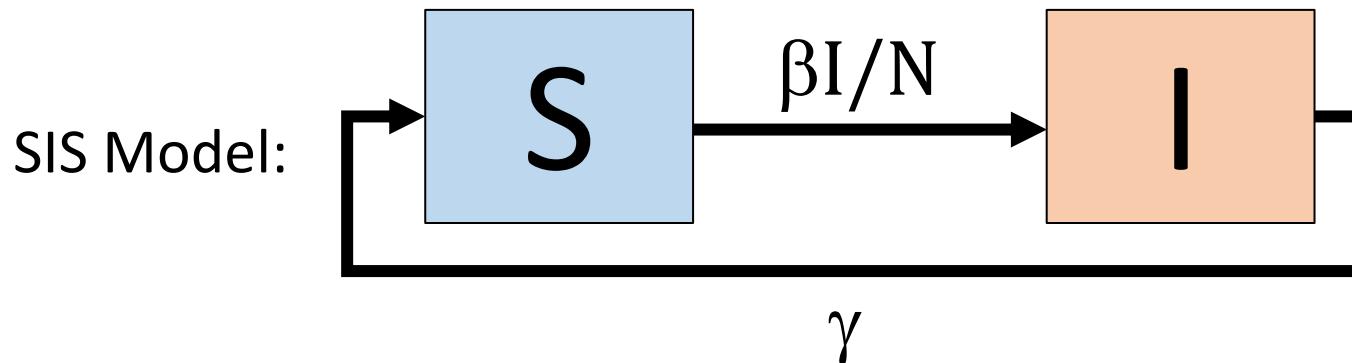
1. How do we define the contact matrix and starting pop. distribution in this model?
2. How do infection dynamics look in the high-risk group vs. the low-risk group?
  - And how does this compare to an SIR model without stratified risk groups?
3. **How do infection dynamics change as the mixing between the 2 groups changes?**

# 15-minute break

# Part 3: Embellishments to the SIR Model

# Infections without immunity

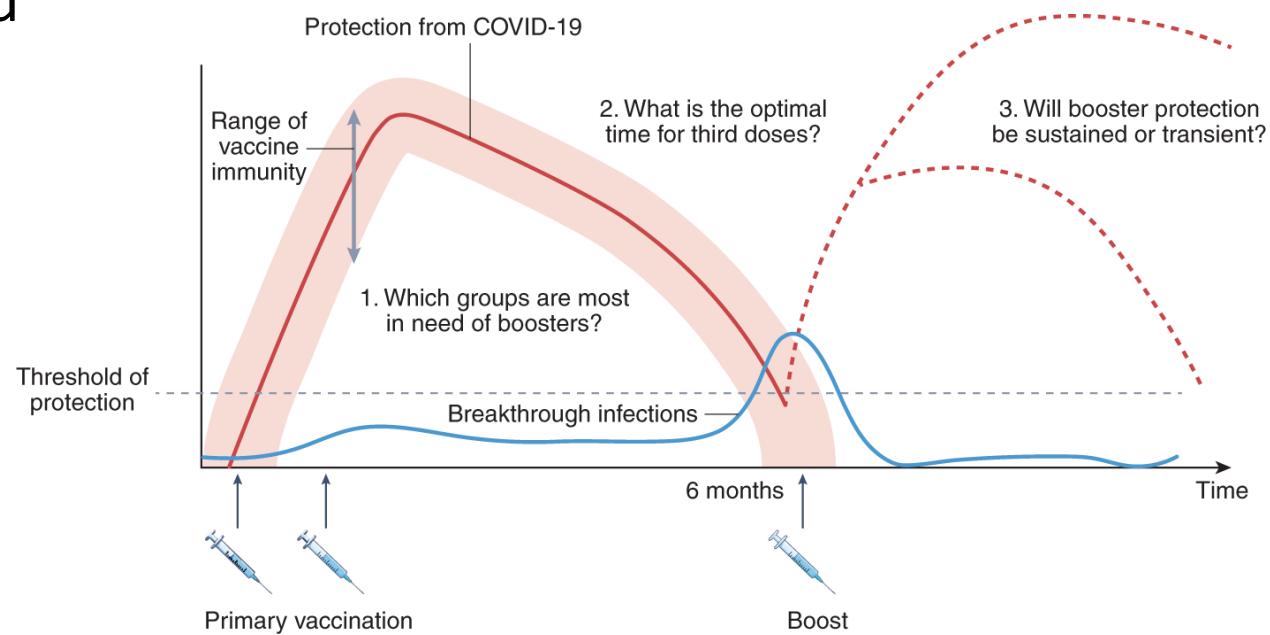
- How would you think about modeling this?



- Diseases this might apply to?
  - Rapidly waning immunity: Gonorrhea, syphilis
  - Many co-circulating strains with little cross-immunity or rapid viral evolution that evades immunity: SARS-CoV-2, Seasonal influenza

# Waning immunity

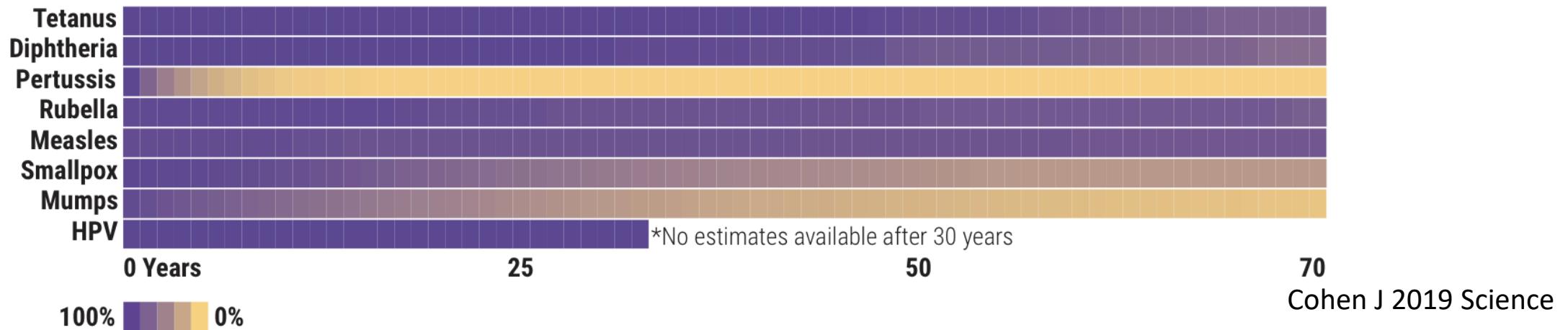
- Immunity elicited by initial infection and vaccination decreases over time
- What determines the rate of waning immunity?
  - Host factors: age, underlying health condition, immunity induced by infection or vaccination
  - Vaccine factors: vaccine type, use of adjuvants, dose of vaccines
  - Pathogen factors: rate of pathogen evolution (rate of immune escape)



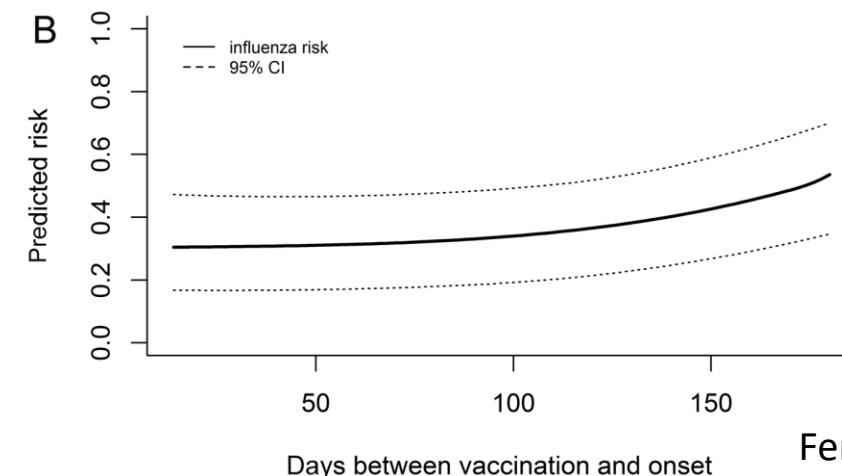
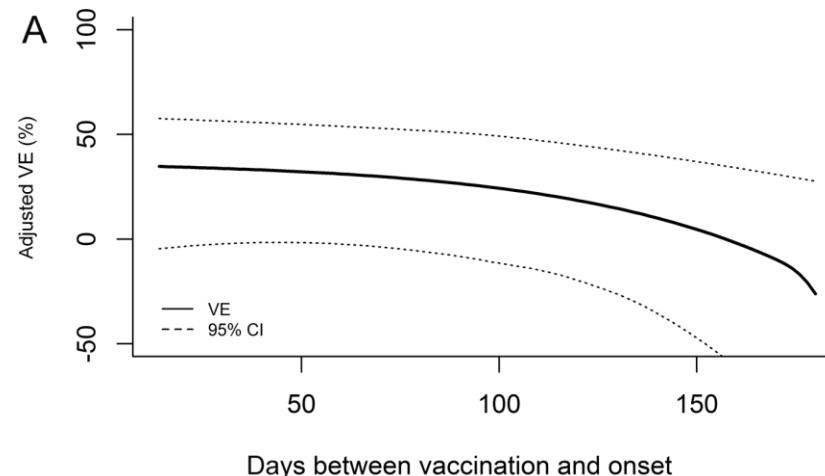
Juno JA Nature 2021

# Waning immunity after vaccination - examples

< Variability in vaccine-induced immunity by disease >

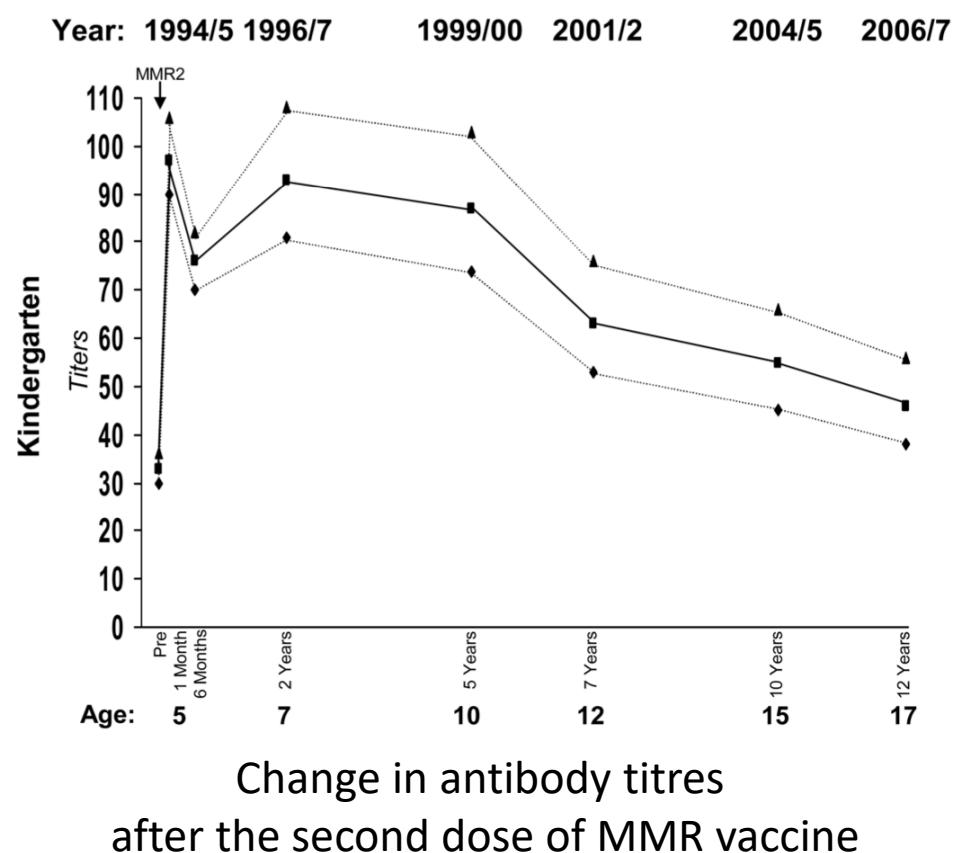


< Intra-seasonal measure of declining VE against influenza A(H3N2) >



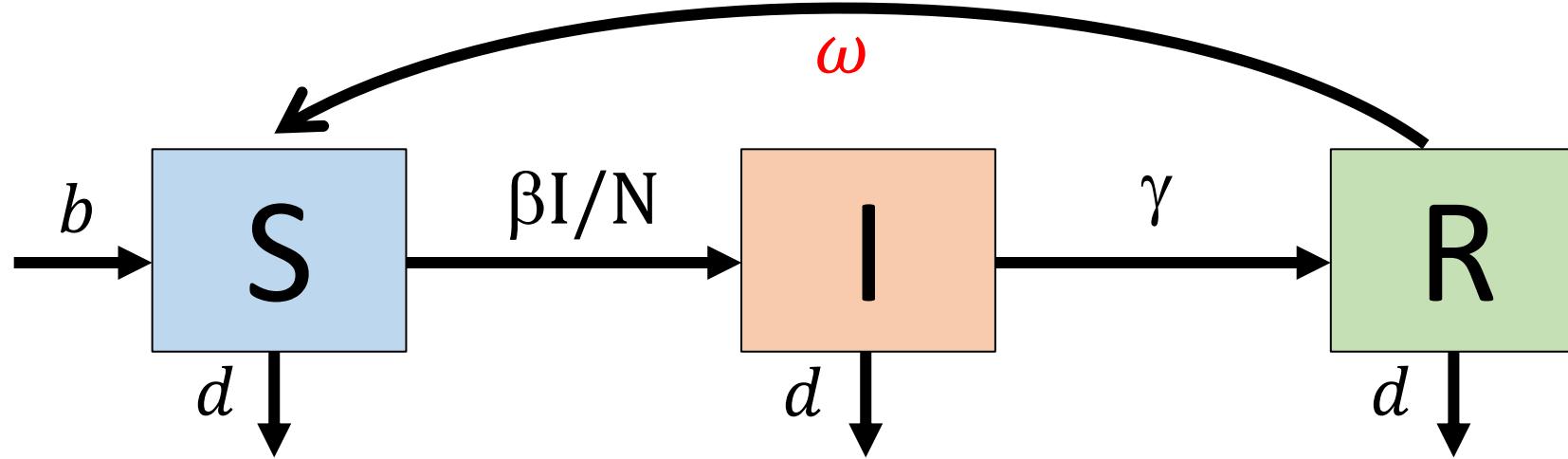
# Estimating rate of waning immunity

- We can estimate the rate of waning immunity based on the duration of immunity
  - How can we define “duration of immunity”?
  - (1) based on the time until next infection
  - (2) based on the duration of viable antibody level
- If constant rate of waning immunity is assumed,  
rate of waning immunity = 1/mean duration of immunity
  - E.g. rate of waning immunity after second dose of MMR vaccine = 1/12 years
  - E.g. rate of waning immunity after flu vaccination = 1/3 months



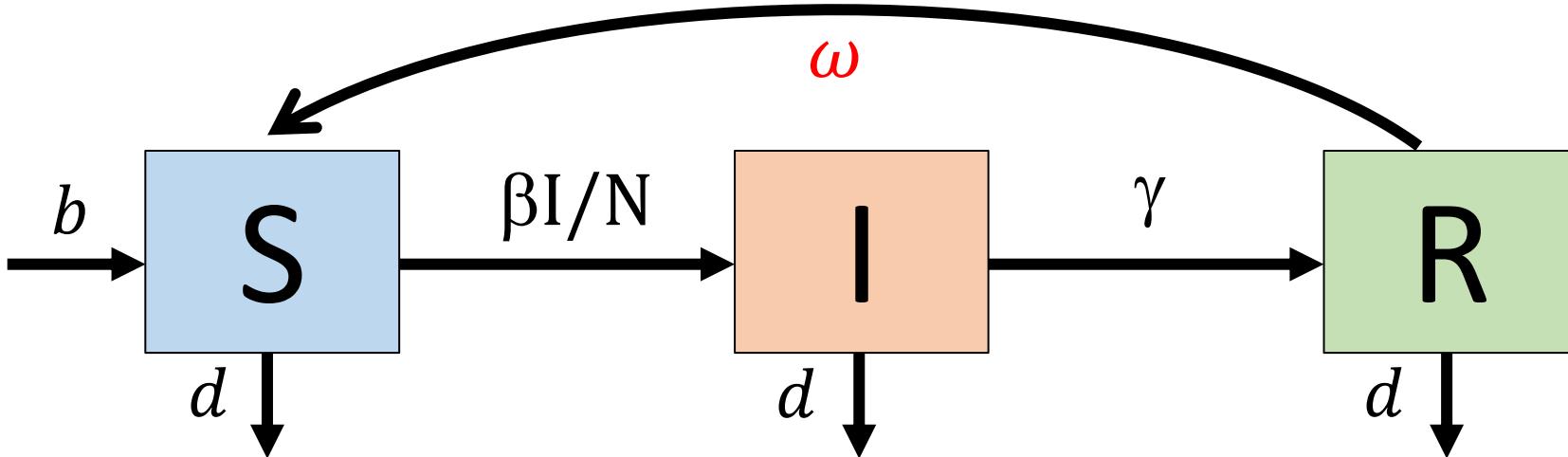
# Adding waning immunity

- Here we brought back the SIR model with demographics.



- Adding a flow  $R \rightarrow S$  to the SIR model allows immunity to wane
  - $\omega$  : rate of waning immunity  
 $= 1/\text{duration of immunity}$

# Adding waning immunity



$$\frac{dS}{dt} = -\frac{\beta SI}{N} - dS + b(S + I + R) + \omega R$$

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

$$\frac{dR}{dt} = \gamma I - dR - \omega R$$

- Epidemic can persist with those who lost immunity over time and became susceptible

# SIRS model: R code

## SIR Model

```
OpenSIR<-function(t, state, parameters) {  
  with(as.list(c(state, parameters)), {  
    N = S + I + R  
  
    #SIR w/ demography equations from the slides  
    dS <- -beta*S*I/N + birth*N - death*S  
    dI <- beta*S*I/N - death*I - gamma*I  
    dR <- gamma*I - death*R  
  
    # return the rates of change as a list  
    list(c(dS, dI, dR))  
  })  
}
```

## SIRS Model

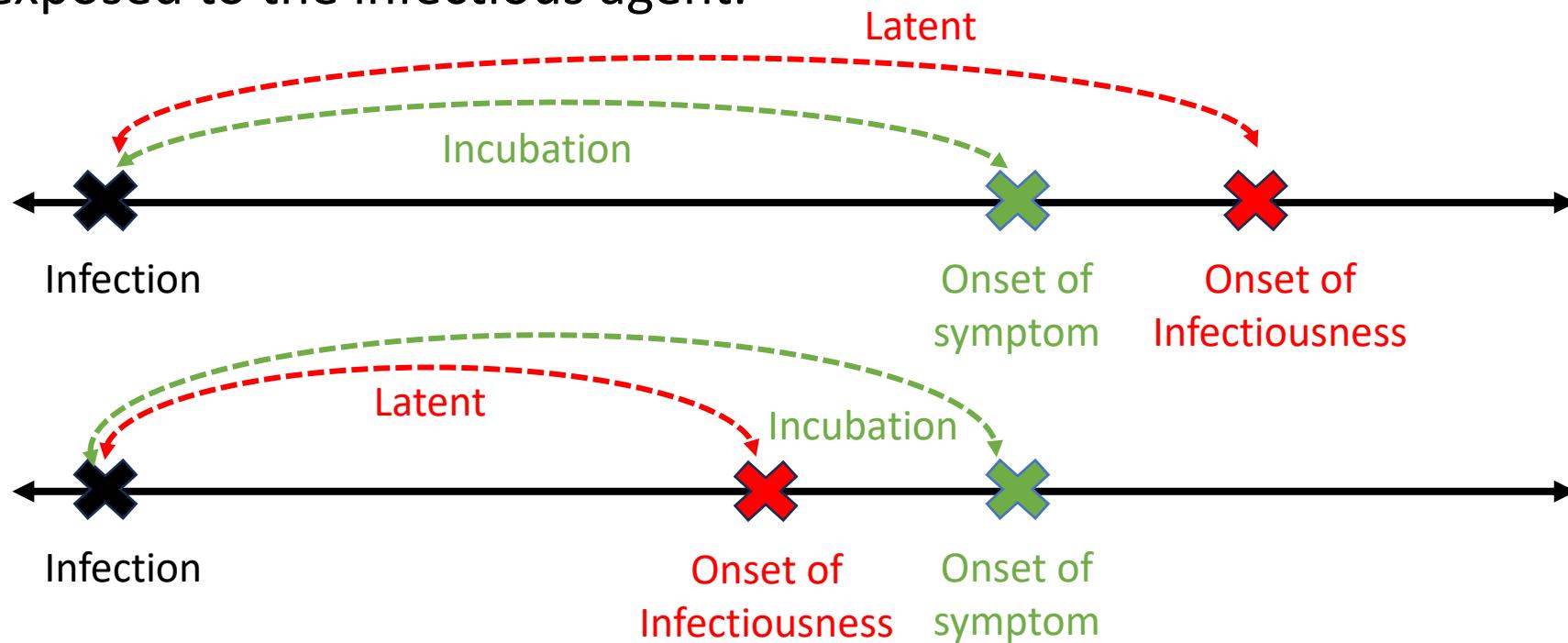
```
OpenSIRS<-function(t, state, parameters) {  
  with(as.list(c(state, parameters)), {  
    N = S + I + R  
  
    #SIR w/ demography equations from lecture  
    dS <- -beta*S*I/N + birth*N - death*S + omega*R  
    dI <- beta*S*I/N - death*I - gamma*I  
    dR <- gamma*I - death*R - omega*R  
  
    # return the rates of change as a list  
    list(c(dS, dI, dR))  
  })  
}
```

```
parameters <- c(beta = 0.5, #  
                  gamma = 0.3, #  
                  birth = 0.03,  
                  death = 0.03,  
                  omega = 0.3 #
```

Omega = 1/duration of immunity

# Incubation and latent period

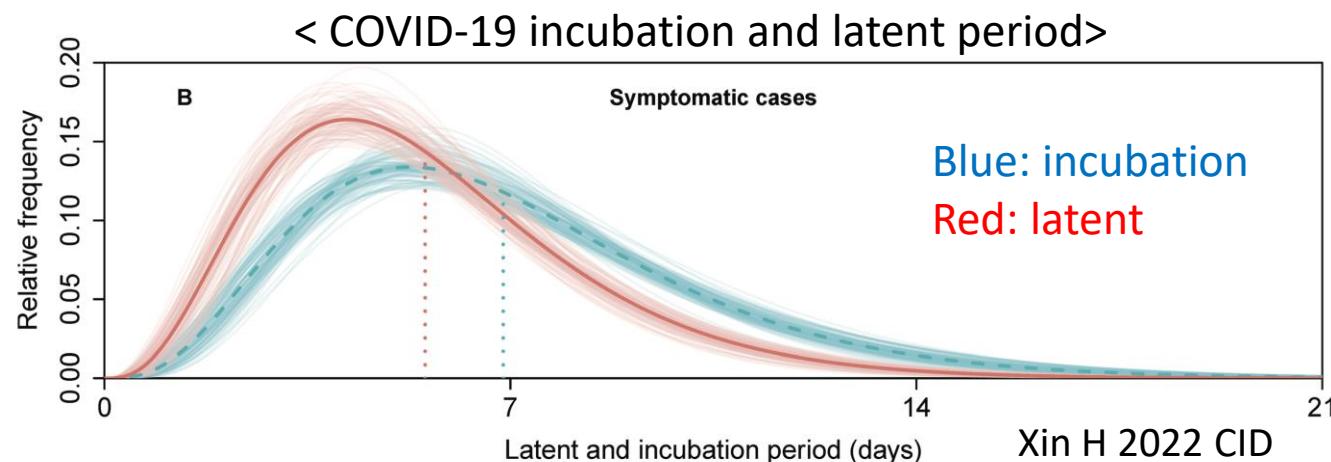
- Individuals usually do not become symptomatic or infectious immediately after being exposed to the infectious agent.



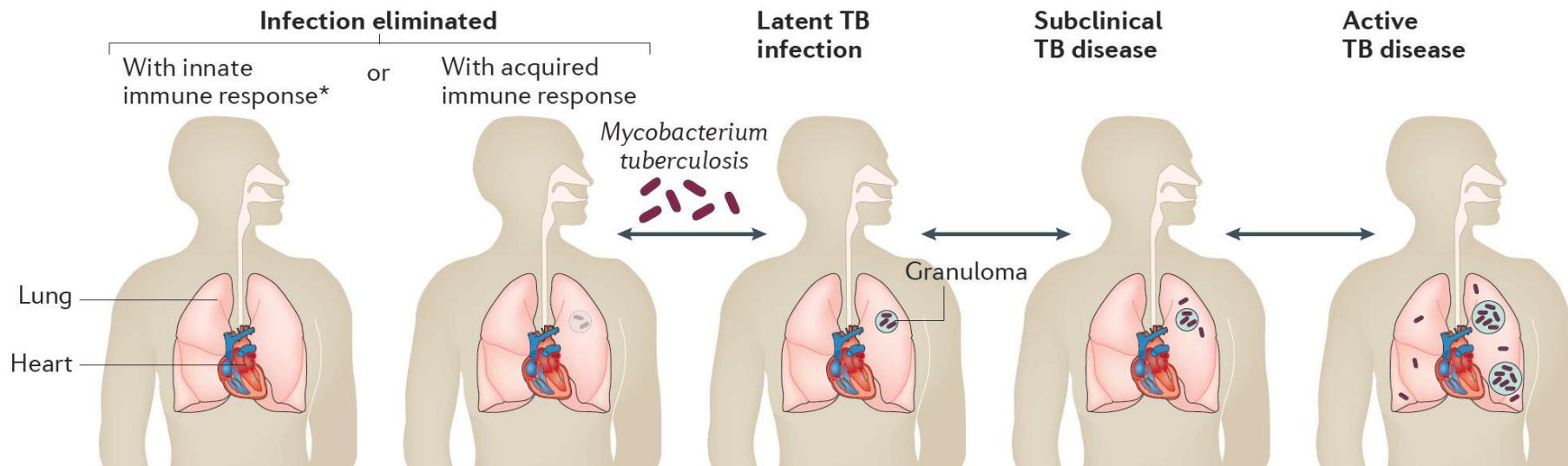
- Incubation period:** time interval between infection and the onset of clinical symptoms
- Latent period:** time interval between infection and becoming infectious

# Incubation and latent period

- Why considering incubation period?
  - Incubation period provides insights on pathogen growth, replication rate, and toxin excretion
- Why considering latent period?
  - Screening and treatment strategy/target can vary depending on if subclinical transmission (latent < incubation) happens
  - In early stage of epidemic, considering latent period leads to more precise prediction on epidemic growth
- Estimating incubation & latent period
  - Data source: contact tracing, lab testing results, clinical data, viral excretion

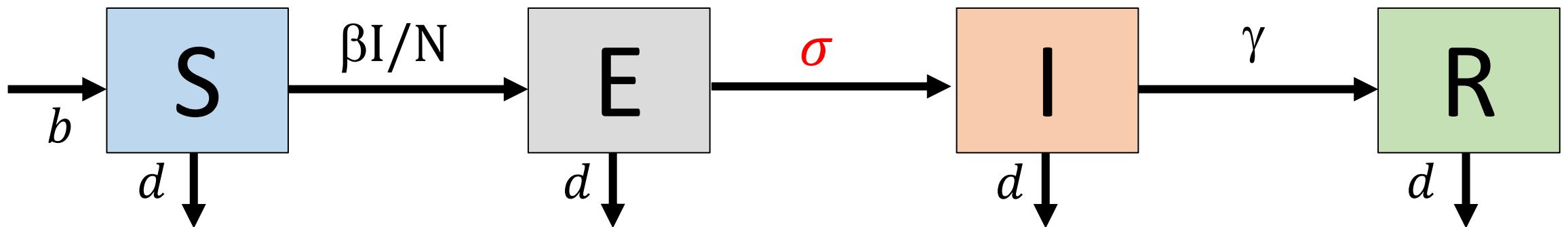


# Latent vs. active TB infection



	Infection eliminated	Latent TB infection	Subclinical TB disease	Active TB disease	
<b>TST</b>	Negative	Positive	Positive	Positive	Usually positive
<b>IGRA</b>	Negative	Positive	Positive	Positive	Usually positive
<b>Culture</b>	Negative	Negative	Negative	Intermittently positive	Positive
<b>Sputum smear</b>	Negative	Negative	Negative	Usually negative	Positive or negative
<b>Infectious</b>	No	No	No	Sporadically	Yes
<b>Symptoms</b>	None	None	None	Mild or none	Mild to severe
<b>Preferred treatment</b>	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

# Adding latent period



$$\frac{dS}{dt} = -\frac{\beta SI}{N} - dS + b(S + I + R)$$

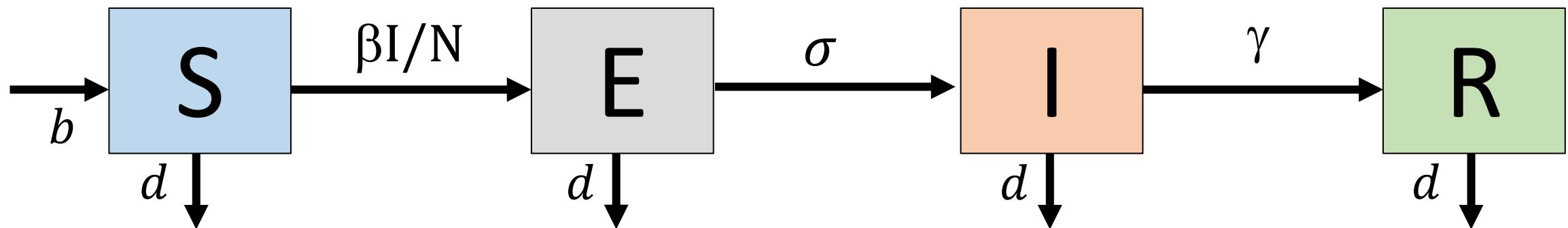
- $\sigma = 1/\text{latent period}$

$$\frac{dE}{dt} = \frac{\beta SI}{N} - \sigma E - dE$$

$$\frac{dI}{dt} = \sigma E - dI - \gamma I$$

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

# Calculating $R_0$ in SEIR model



$$\begin{aligned} R_0 &= \frac{\beta \sigma}{(d + \gamma)(d + \sigma)} \\ &= \beta * \frac{1}{(d+\gamma)} * \frac{\sigma}{(d+\sigma)} \end{aligned}$$

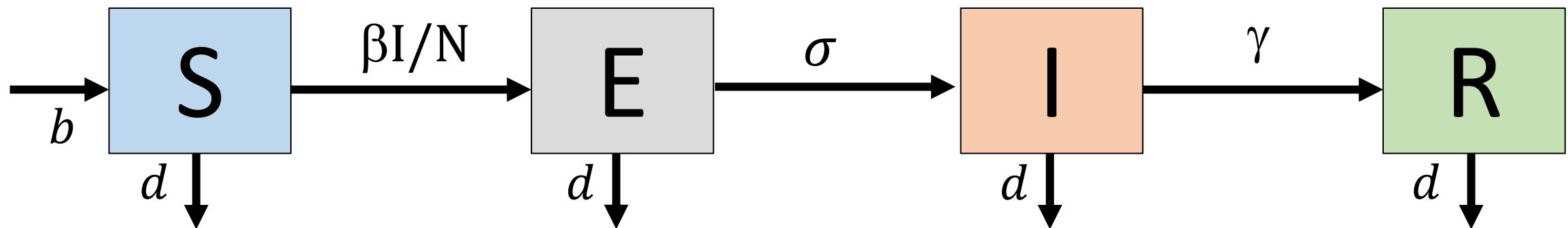
↗    Probability of surviving E

Duration of infectiousness

$$= R_{0,SIR} * \frac{\sigma}{(d+\sigma)}$$

-> If  $\sigma \gg d$ ,  $R_{0,SIR} \sim R_{0,SEIR}$

# Calculating R<sub>0</sub> in SEIR model



- For Tuberculosis: only 10% of infected individuals ever develop active TB
- People with active TB infect 10 people per year and are infectious for 2 years.
- What is the R<sub>0</sub> for TB?
  
- $R_0 = 10 * 2 * 0.1 = 2$

# SEIR model: R code

## SIR Model

```
OpenSIR<-function(t, state, parameters) {  
  with(as.list(c(state, parameters)), {  
    N = S + I + R  
  
    #SIR w/ demography equations from the slides  
    dS <- -beta*S*I/N + birth*N - death*S  
    dI <- beta*S*I/N - death*I - gamma*I  
    dR <- gamma*I - death*R  
  
    # return the rates of change as a list  
    list(c(dS, dI, dR))  
  })  
}
```

```
parameters <- c(beta = 0.5, #  
                  gamma = 0.3,  
                  birth = 0.03,  
                  death = 0.03,  
                  omega = 0, #  
                  t_lat = 3 # l
```

## SEIR Model

```
OpenSEIR<-function(t, state, parameters) {  
  with(as.list(c(state, parameters)), {  
    N = S + E + I + R  
    sigma = 1/t_lat # 1/latent period  
  
    #SIR w/ demography equations from lecture  
    dS <- -beta*S*I/N + birth*N - death*S + omega*R  
    dE <- beta*S*I/N - sigma*E - death*E  
    dI <- sigma*E - death*I - gamma*I  
    dR <- gamma*I - death*R - omega*R  
  
    # return the rates of change as a list  
    list(c(dS, dE, dI, dR))  
  })  
}
```

t\_lat: latent period  
sigma = 1/t\_lat

# Lab #3: SIRS and SEIR model

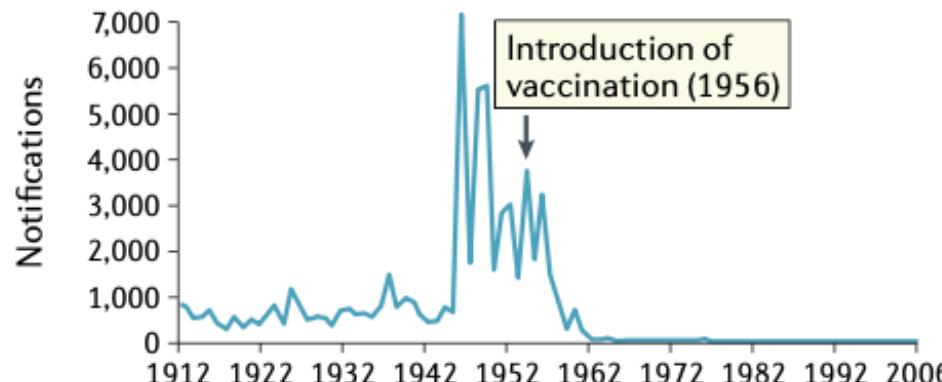
- Run SIRS model in R
  - Q. How does the epidemic change as we change waning immunity?
  - Q. How does the epidemic change as we change both waning immunity and effective contact rate?
- Run SEIR model in R
  - Q. How does the epidemic change as we have longer latent period?

# Controlling Infectious Diseases (1) Vaccines

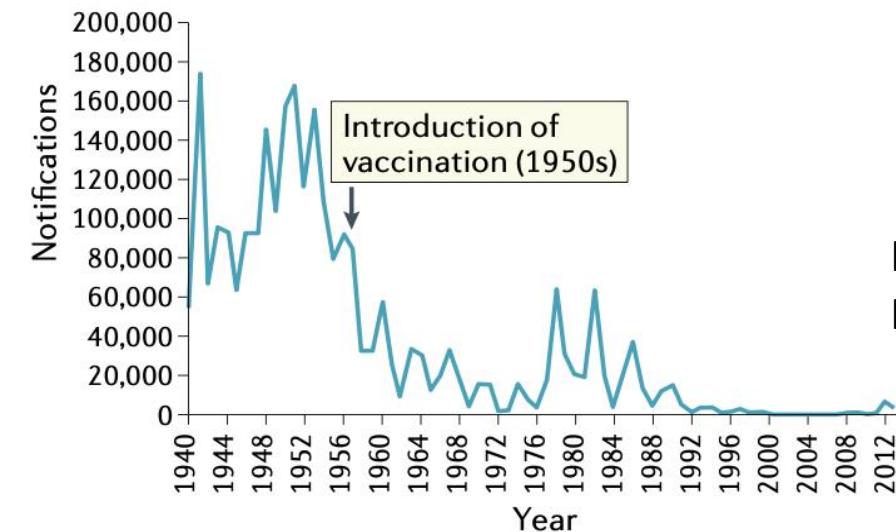
- Vaccination

- Vaccines contain antigens of disease pathogens that can induce the immune responses similar with long-lasting immunity to the infection
- Vaccines can reduce the risk of infection and severe complication after infections
- Vaccines protect both vaccinated and non-vaccinated individuals through herd immunity

c Polio



f Pertussis



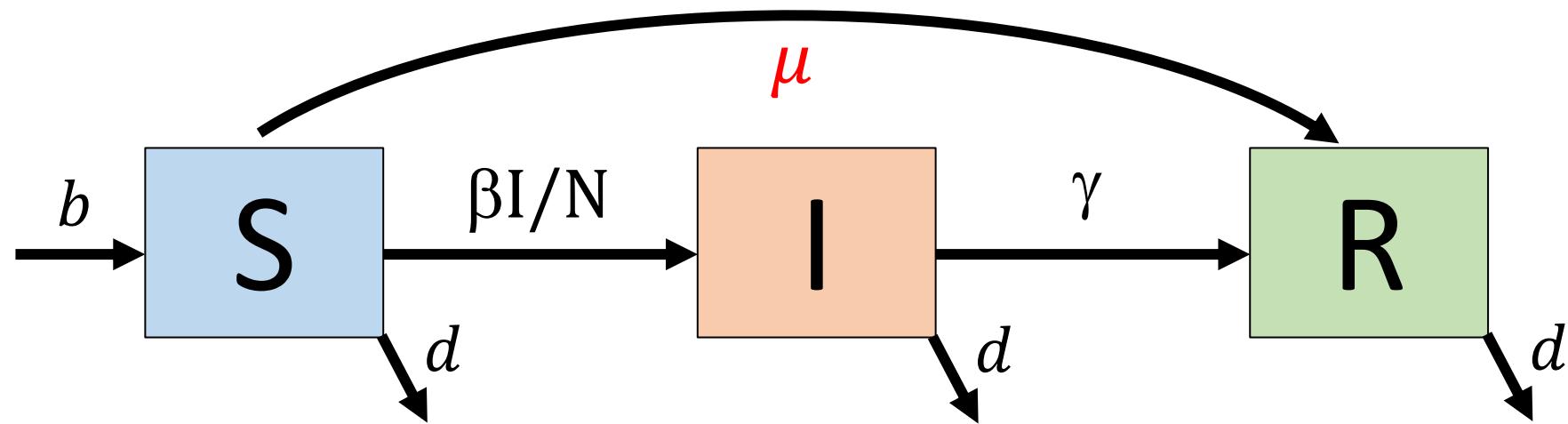
Pollard AJ Nature  
Reviews 2021

# Controlling Infectious Diseases (1) Vaccines

- Types of vaccines
  - Live-attenuated, inactivated, subunit, recombinant/viral vector vaccines, mRNA
- Targets of vaccines
  - Wildlife vaccination (e.g. rabies, distemper)
  - Mass vaccination (e.g. influenza)
  - Pediatric vaccination (e.g. MMR, polio)
  - Age-structured vaccination (HPV, Shingles)
  - Targeted vaccination (e.g. Monkey pox)
- Factors affecting vaccine protection
  - Age
  - Prior infection and vaccination experience
  - Vaccine schedule
  - Vaccine dose

# Controlling Infectious Diseases (1) Vaccines

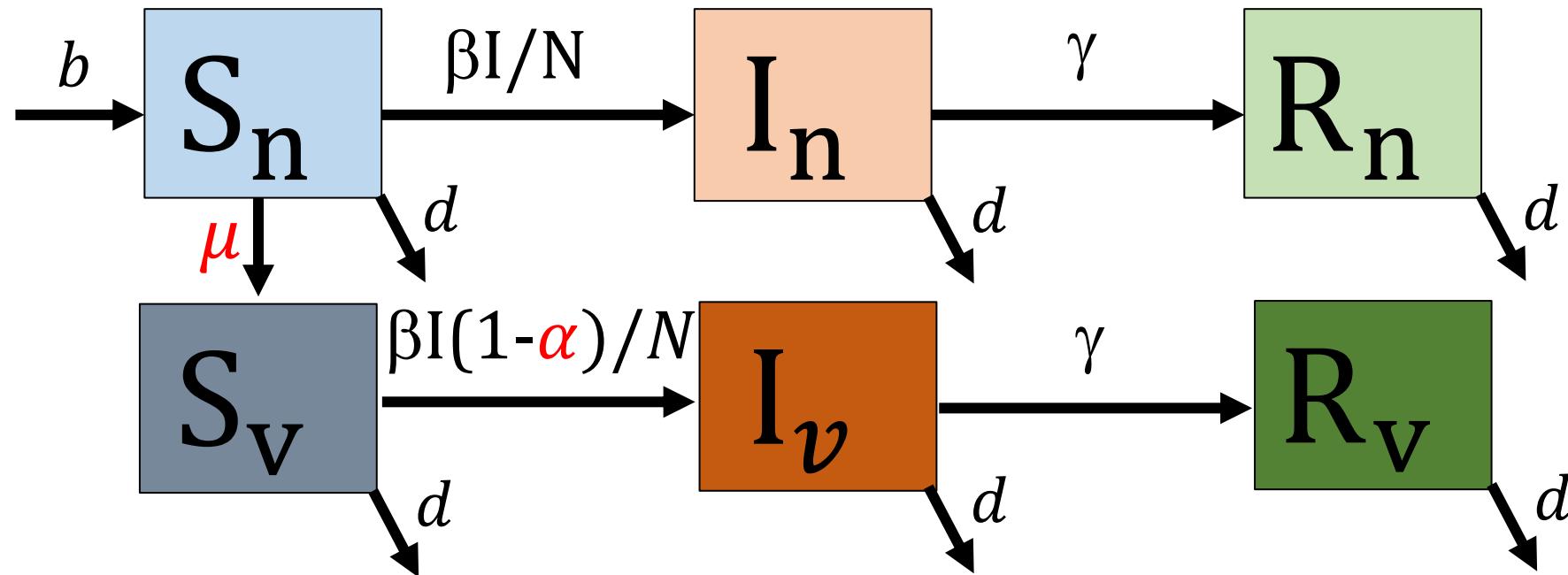
- Modeling vaccine effectiveness in different ways
  - If vaccine provides perfect immunity:



- $\mu$  : rate of vaccination
  - A portion of susceptible population obtain perfect immunity through vaccination  
→ Vaccine effectiveness is 100%

# Controlling Infectious Diseases (1) Vaccines

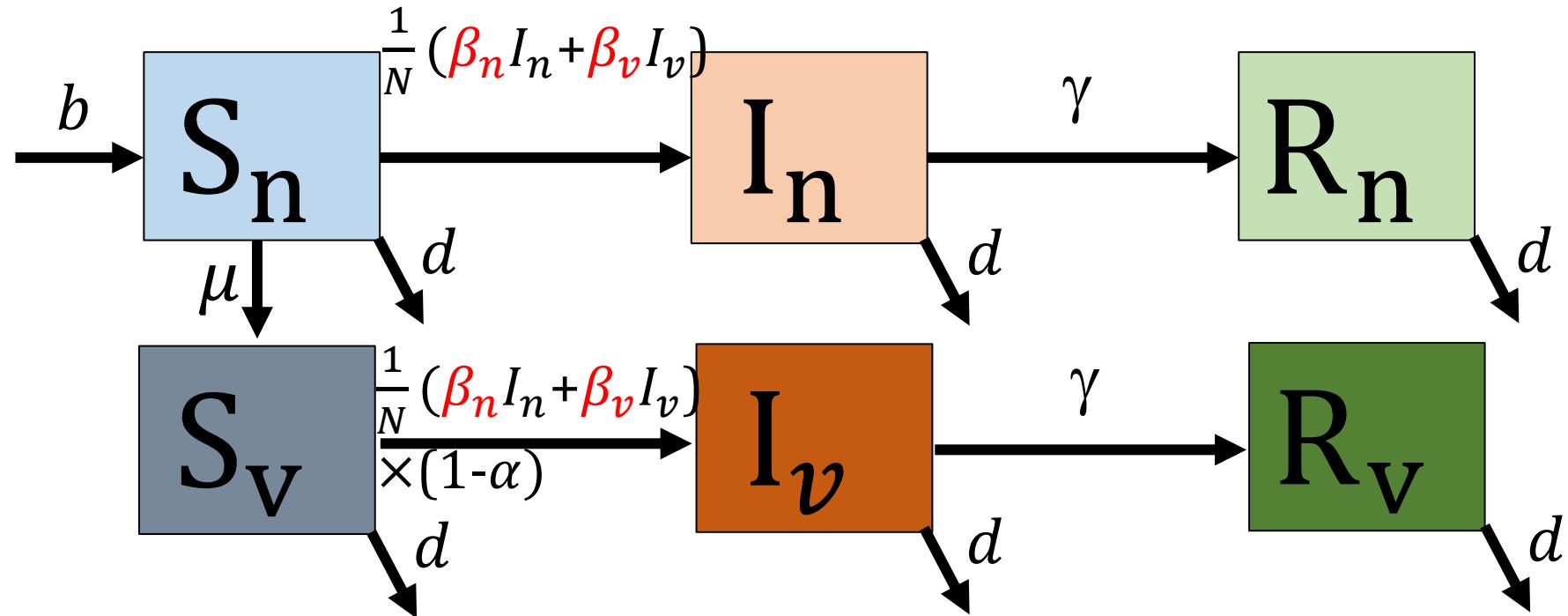
- Modeling vaccine effectiveness in different ways
  - If vaccine provides imperfect immunity for infection w/o change in infectiousness



- $\mu$  : rate of vaccination
- $\alpha$ : vaccine effectiveness against infection
- $I = I_n + I_v$
- $\beta I(1-\alpha)/N$  indicates breakthrough infection

# Controlling Infectious Diseases (1) Vaccines

- Modeling vaccine effectiveness in different ways
  - If vaccine provides imperfect immunity for infection w/ change in infectiousness



- $\beta_{n(v)}$ : transmission rate through interaction with those are infected without (with) vaccination
- Differential transmission rate is assumed based on vaccination status among the infected

# SIR model w/ vaccination, perfect protection: R code

**SIR + vaccine Model** When vaccine provides perfect immunity

```
OpenSIR_Vax_pp<-function(t, state, parameters) {  
  with(as.list(c(state, parameters)), {  
    N = S + I + R  
  
    #SIR w/ demography equations from lecture  
    dS <- -beta*S*I/N + birth*N - death*S - mu*S  
    dI <- beta*S*I/N - death*I - gamma*I  
    dR <- gamma*I + mu*S - death*R  
  
    dC <- beta*S*I/N  
    # return the rates of change as a list  
    list(c(dS, dI, dR, dC))  
  })  
}  
  
parameters <- c(beta = 0.5, #  
  beta.1 = 0.5,  
  mbeta = 0.5, #  
  gamma = 0.3, #  
  birth = 0.03,  
  death = 0.03,  
  omega = 0, # v  
  mu = 0.01, # v  
  alpha = 0.3, #  
  q = 0.02 # quo
```

# SIR model w/ vaccination, imperfect protection: R code

## SIR + vaccine Model When vaccine provides imperfect immunity

```
OpenSIR_Vax_ip<-function(t, state, parameters) {
  with(as.list(c(state, parameters)),{
    N = S_NotV + S_V + I_NotV + I_V + R_NotV + R_V

    #compartments without vaccination
    dS_NotV <- -beta*S_NotV*(I_NotV+I_V)/N + birth*N - death*S_NotV - mu*S_NotV
    dI_NotV <- beta*S_NotV*(I_NotV+I_V)/N - death*I_NotV - gamma*I_NotV
    dR_NotV <- gamma*I_NotV - death*R_NotV
    #compartments with vaccination
    dS_V <- -beta*S_V*(I_NotV+I_V)/N*(1-alpha) + birth*N - death*S_V + mu*S_NotV
    dI_V <- beta*S_V*(I_NotV+I_V)/N*(1-alpha) - death*I_V - gamma*I_V
    dR_V <- gamma*I_V - death*R_V

    #cumulative number of cases
    dC <- beta*S_NotV*(I_NotV+I_V)/N + beta*S_V*(I_NotV+I_V)/N*(1-alpha)

    # return the rates of change as a list
    list(c(dS_NotV,dS_V,dI_NotV,dI_V, dR_NotV,dR_V,dC))
  })
}
```

```
parameters <- c(beta = 0.5, #
                  beta.1 = 0.5,
                  mbeta = 0.5, #
                  gamma = 0.3, #
                  birth = 0.03,
                  death = 0.03,
                  omega = 0, # v
                  mu = 0.01, # v
                  alpha = 0.3, #
                  q = 0.02 # quc
```

# SIR model w/ vaccination, imperfect protection: R code

## SIR + vaccine Model

When vaccine provides imperfect immunity & change infectiousness

```
openSIR_Vax_ip2<-function(t, state, parameters) {  
  with(as.list(c(state, parameters)), {  
    N = S_NotV + S_V + I_NotV + I_V + R_NotV + R_V  
    beta.2 = mbeta*beta.1 # transmission rate given vaccination  
  
    #compartments without vaccination  
    dS_NotV <- -beta.1*S_NotV*I_NotV/N - beta.2*S_NotV*I_V/N + birth*N - death*S_NotV - mu*S_NotV  
    dI_NotV <- beta.1*S_NotV*I_NotV/N + beta.2*S_NotV*I_V/N - death*I_NotV - gamma*I_NotV  
    dR_NotV <- gamma*I_NotV - death*R_NotV  
    #compartments with vaccination  
    dS_V <- -beta.1*S_V*I_NotV/N*(1-alpha) - beta.2*S_V*I_V/N*(1-alpha) + birth*N - death*S_V + mu*S_V  
    dI_V <- beta.1*S_V*I_NotV/N*(1-alpha) + beta.2*S_V*I_V/N*(1-alpha) - death*I_V - gamma*I_V  
    dR_V <- gamma*I_V - death*R_V  
  
    #cumulative number of cases  
    dC <- beta.1*S_NotV*I_NotV/N + beta.1*S_V*I_NotV/N*(1-alpha) + beta.2*S_NotV*I_V/N + beta.2*S_V*I_V/N*(1-alpha)  
  
    # return the rates of change as a list  
    list(c(dS_NotV,dS_V,dI_NotV,dI_V, dR_NotV,dR_V, dC))  
  })  
}
```

```
parameters <- c(beta = 0.5, #  
                  beta.1 = 0.5,  
                  mbeta = 0.5, #  
                  gamma = 0.3, #  
                  birth = 0.03,  
                  death = 0.03,  
                  omega = 0, # v  
                  mu = 0.01, # v  
                  alpha = 0.3, #  
                  q = 0.02 # quick  
)
```

-> Differential beta values (transmission rates) were applied to I\_V and I\_NotV

# Controlling Infectious Diseases (2) Quarantine

- Quarantine separates and restricts the movement of people who were exposed to a contagious disease
- Quarantine is a powerful control method, especially when the knowledge of pathogen is not yet established.

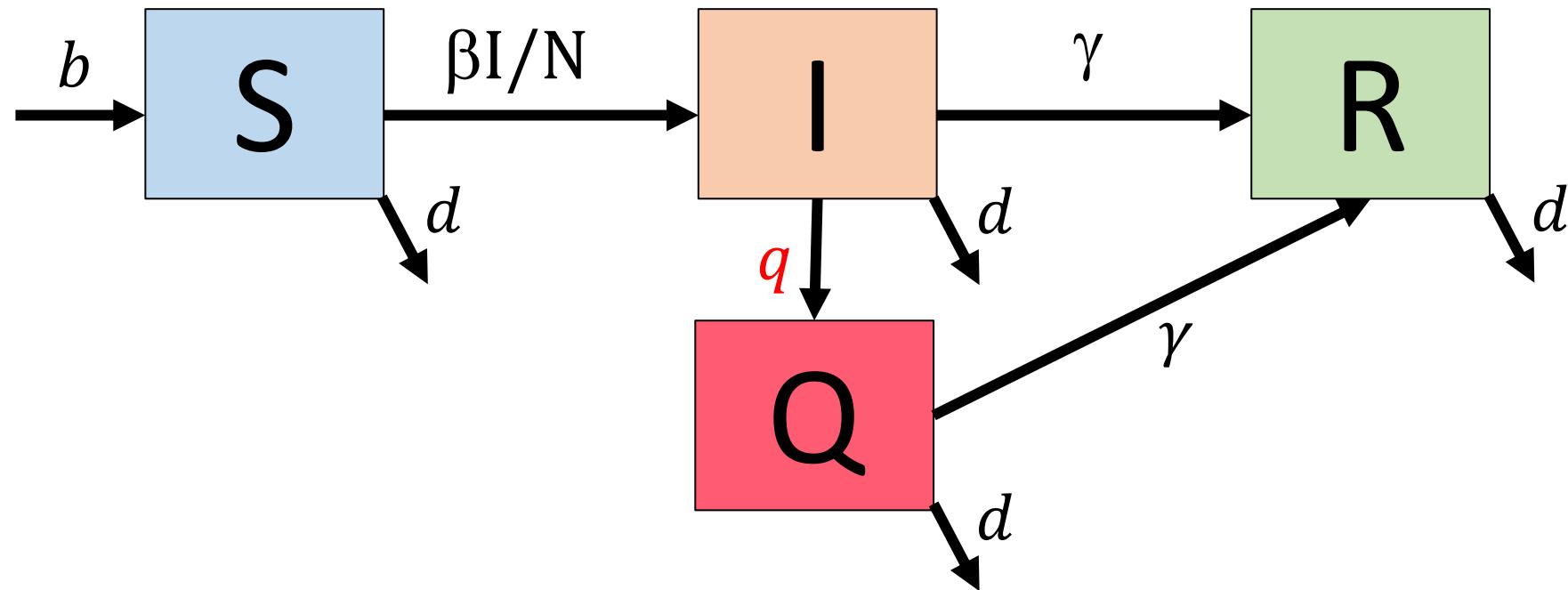


Figure 2. Quarantine. The female dormitory. France–Italy border during the cholera epidemic of 1865–1866. (Photograph in the author's possession).

Tognotti E EID 2013

# Controlling Infectious Diseases (2) Quarantine

- Modeling quarantine as simple isolation

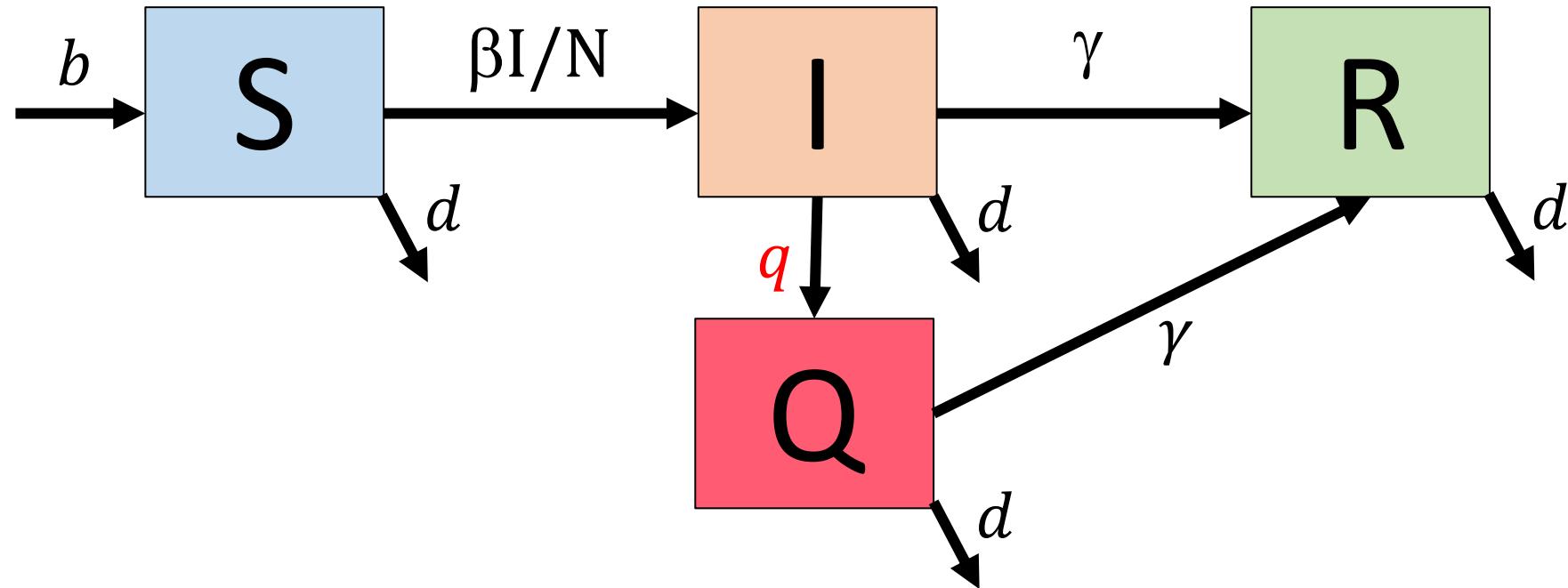


- $q$  : rate of detecting and "removing" infected individuals to quarantine

- Quarantine rate ( $q$ ) can be determined by testing rate/test characteristics
- $Q$  doesn't infect others because no interaction with  $S$

# Controlling Infectious Diseases (2) Quarantine

- Modeling quarantine as simple isolation

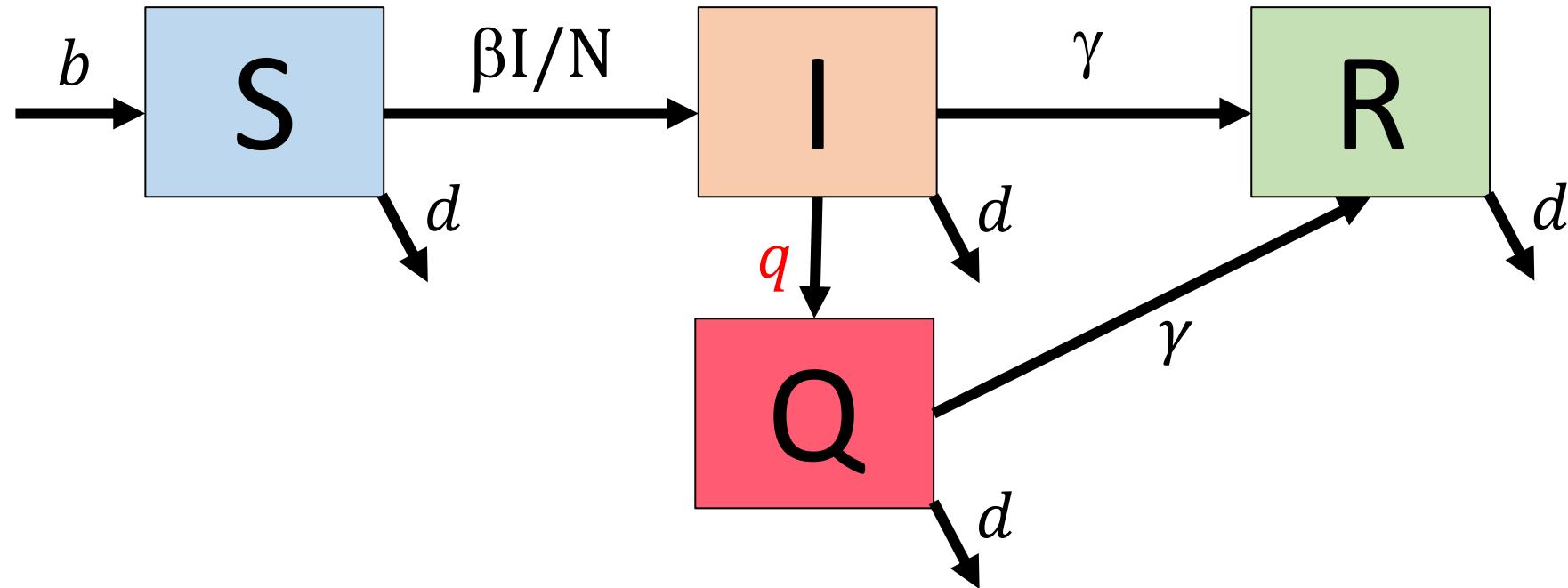


$$\frac{dI}{dt} = \frac{\beta SI}{N} - \gamma I - dI - qI$$

- Quarantine reduces the effective length of the infectious period

# Controlling Infectious Diseases (2) Quarantine

- Modeling quarantine as simple isolation



$$\frac{dI}{dt} = \frac{\beta SI}{N} - \gamma I - dI - qI$$

- Quarantine ends when symptoms are resolved (recovered)
- When is quarantine less effective?

# SIR model w/ quarantine: R code

## SIR + quarantine Model

```
OpenSIR_Qrtn<-function(t, state, parameters) {  
  with(as.list(c(state, parameters)), {  
    N = S + I + Q + R  
  
    #SIR with quarantine  
    dS<- -beta*S*I/N + birth*N - death*S  
    dI <- beta*S*I/N - death*I - q*I - gamma*I  
    dQ <- q*I - death*Q - gamma*Q  
    dR <- gamma*I + gamma*Q - death*R  
    dC <- beta*S*I/N  
  
    # return the rates of change as a list  
    list(c(dS, dI, dQ, dR, dC))  
  })  
}
```

```
parameters <- c(beta = 0.5, #  
                 beta.1 = 0.5,  
                 mbeta = 0.5, #  
                 gamma = 0.3, #  
                 birth = 0.03,  
                 death = 0.03,  
                 omega = 0, # \n  
                 mu = 0.01, # \n  
                 alpha = 0.3, #\n                 q = 0.02 # quo
```

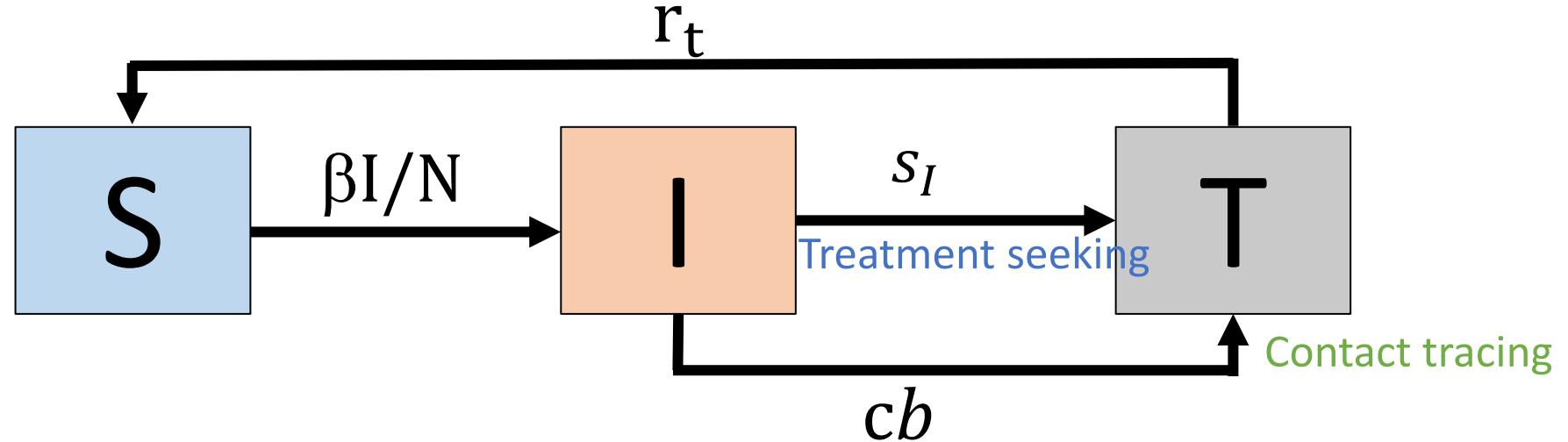
# Controlling Infectious Diseases (3) Contact tracing

- Contact tracing identifies potential exposure to the infectious agent based on the contact history with the diagnosed individuals
- It has been used to control STIs
- A complete model should reflect the social structure of contacts (e.g. network model)



# Controlling Infectious Diseases (3) Contact tracing

Adding to SI Model:



$$\frac{dS}{dt} = -\frac{\beta SI}{N} + r_t T$$

$$\frac{dI}{dt} = \frac{\beta SI}{N} - s_I I - cbT$$

$$\frac{dT}{dt} = s_I I + cbT - r_t T$$

- T: Treatment and tracing class
- $s_I$  : rate of seeking treatment
- c : rate of contact tracing
- b : probability that a traced individual is infectious
- $1/ r_t$  = average time in the treatment and tracing class

# SI model w/ contact tracing: R code

## SIR + vaccine Model

```
# 1. Define model function
SI_CC<-function(t, state, parameters) {
  with(as.list(c(state, parameters)),{
    N = S + I + Tx

    #SI w/o demography equations from lecture
    dS <- -beta*S*I/N + rt*Tx
    dI <- beta*S*I/N - si*I - c*b*Tx
    dTx <- si*I + c*b*Tx - rt*Tx
    # Cumulative incidence
    dC <- beta*S*I/N
    # return the rates of change as a list
    list(c(dS, dI, dTx, dC))
  })
}
```

```
parameters <- c(beta = 0.5, #effective contact rate (aka transmission rate)
                 rt = 0.1, # 1/duration of treatment and tracing
                 si = 0.1, # rate of seeking treatment
                 c = 0.05, # rate of contact tracing
                 b = 0.05# probability that a traced individual is infected
)
```

# Lab #4: Modeling interventions

- Run SIR model with vaccination strategy under varying assumptions on vaccine effectiveness

Q. How did different assumptions on vaccine effectiveness/vaccination rate/reduced infectiousness with vaccination change the predicted epidemics?
- Run SIR model with quarantine strategy

Q. How does the predicted epidemic change as we increase quarantine rate?
- Run SIS model with contact tracing strategy

Q. How does the predicted epidemic change as we increase contact tracing rate?

# Exercise

**Background:** You are the chief health officer in the isolated city-state of SMDMopolis, which has its first ever documented case of **Virus X**. Virus X is an emerging infectious disease. You review the limited literature from past outbreaks in other locations and find:

- People tend to develop symptoms 5 days after being exposed to the virus and feel better 2 weeks after developing symptoms. No evidence of subclinical transmission has been documented.
- In previous outbreaks, contact tracing studies have found that the average infected person infected between 3 and 5 other people. Because of the high population density of SMDMopolis and airborne transmission of Virus X, you expect that transmission could be at least this high, and up to 2x as high, in this outbreak.
- While Virus X is not generally fatal, left untreated, people often experience long-term side effects that can disrupt daily life.
- In previous outbreaks, which tended to last 1-2 months, there were no documented instances of someone acquiring Virus X twice. However, one study found that antibody levels wane substantially 3 months after recovery.
- There are no biomedical interventions to protect someone against Virus X, and treatment does not reduce infectiousness. A vaccine is under development but will not be available for several months at the earliest.

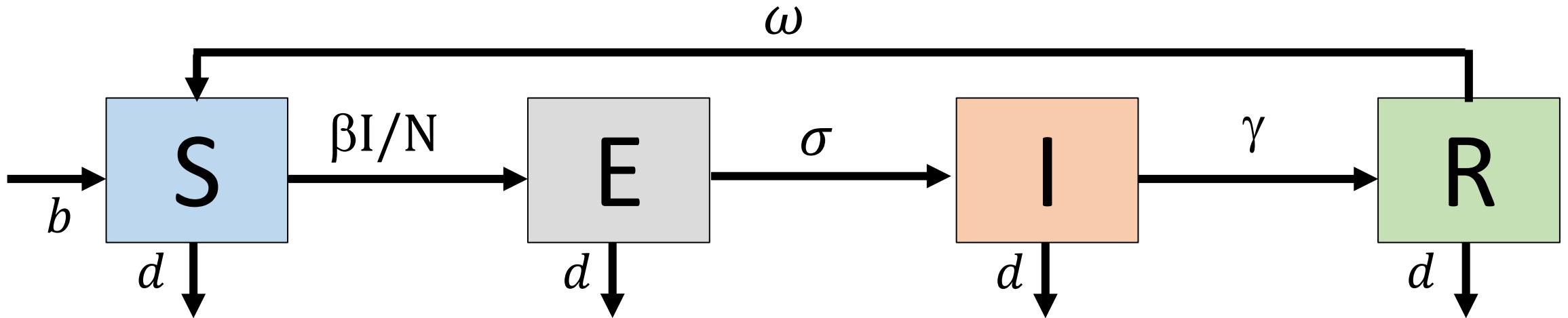
SMDMopolis' chief demographer tells you that there are 10,000 people living in the city-state. Last year, there were around 120 new births and 120 deaths documented in the population.

**Questions:** The head of state in SMDMopolis, President Beate Sander, has asked you to assess the likely spread of Virus X over the next 300 days, until the vaccine might become available. She is particularly interested in best- and worst-case scenarios, given uncertainties about the likely rate of spread in the population, and has asked you to investigate:

1. The cumulative number of infections absent intervention.
  2. The likely size and the timing of the epidemic peak, so she can make appropriate decisions regarding treatment supply.
- President Sander is also considering instituting a policy of isolation for people with symptoms. She is wondering (again, for best- & worse-case scenarios):
3. Whether an immediate, but less effective (daily rate of 0.5) isolation policy will prevent more infections than a delayed response (by 3 weeks) with higher (rate=0.9) coverage?
    - Will either isolation policy effectively control the outbreak?
  4. How the answer to question #3 varies if a vaccine becomes available earlier than anticipated (at day 75)?
    - Hint: Try to think about how you could answer this question without actually modeling vaccination. You can assume that once available, the vaccine effectively controls the epidemic.

# 30-minute exercise

# Solution for exercise



- $b = 3.66/12/30.5 = 0.01$
- $d = 3.66/12/30.5 = 0.01$
- $\sigma = 1/5$
- $\gamma = 1/14$
- $\omega = 1/(30.5*3)$

**$\beta$  calculations:**

$$R_0 = \frac{\beta\sigma}{(d + \gamma)(d + \sigma)} \rightarrow \beta = \frac{R_0(d + \gamma)(d + \sigma)}{\sigma}$$

$R_0 = 3$  (best case) implies  $\beta \approx 0.21$

$R_0 = 10$  (worse case) implies  $\beta \approx 0.71$

# Solution for exercise (R code): #1-2

```
# SEIRS model with births and deaths
openSEIRS<-function(t, state, parameters) {
  with(as.list(c(state, parameters)),{
    N = S + E + I + R
    sigma = 1/t_lat # 1/latent period

    #SIR w/ demography equations from lecture
    dS <- -beta*S*I/N + birth*N - death*S + omega*R
    dE <- beta*S*I/N - sigma*E - death*E
    dI <- sigma*E - death*I - gamma*I
    dR <- gamma*I - death*R - omega*R

    dC <- beta*S*I/N

    # return the rates of change as a list
    list(c(dS, dE, dI, dR, dC))
  })
}
```

```
parameters <- c(gamma = 1/14, #recovery rate (1/duration infection)
                birth = 12/1000/365,#0.0000027, #birth rate (per capita)
                death = 12/1000/365, #all-cause mortality rate
                omega = 1/(30.5^3),#0.01, # waning immunity
                t_lat = 5 # latent period from E
)

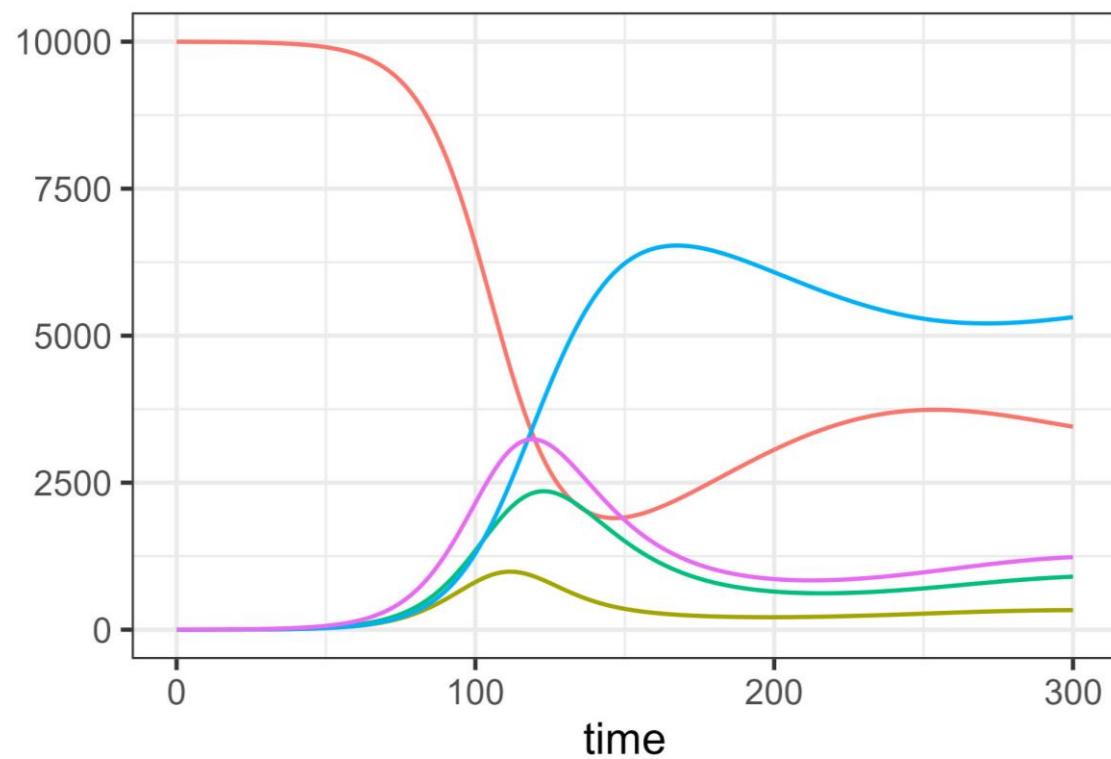
beta_low <- 3*(parameters[["death"]] + parameters[["gamma"]])*
  (parameters[["death"]] + 1/parameters[["t_lat"]])*parameters[["t_lat"]]
beta_high <- 10*(parameters[["death"]] + parameters[["gamma"]])*
  (parameters[["death"]] + 1/parameters[["t_lat"]])*parameters[["t_lat"]]

state <- c(S = 10000-1, #population of 10,000, 1 person starts of infected
            E = 0,
            I = 1,
            R = 0,
            C = 0 #track cumulative number of infections
)

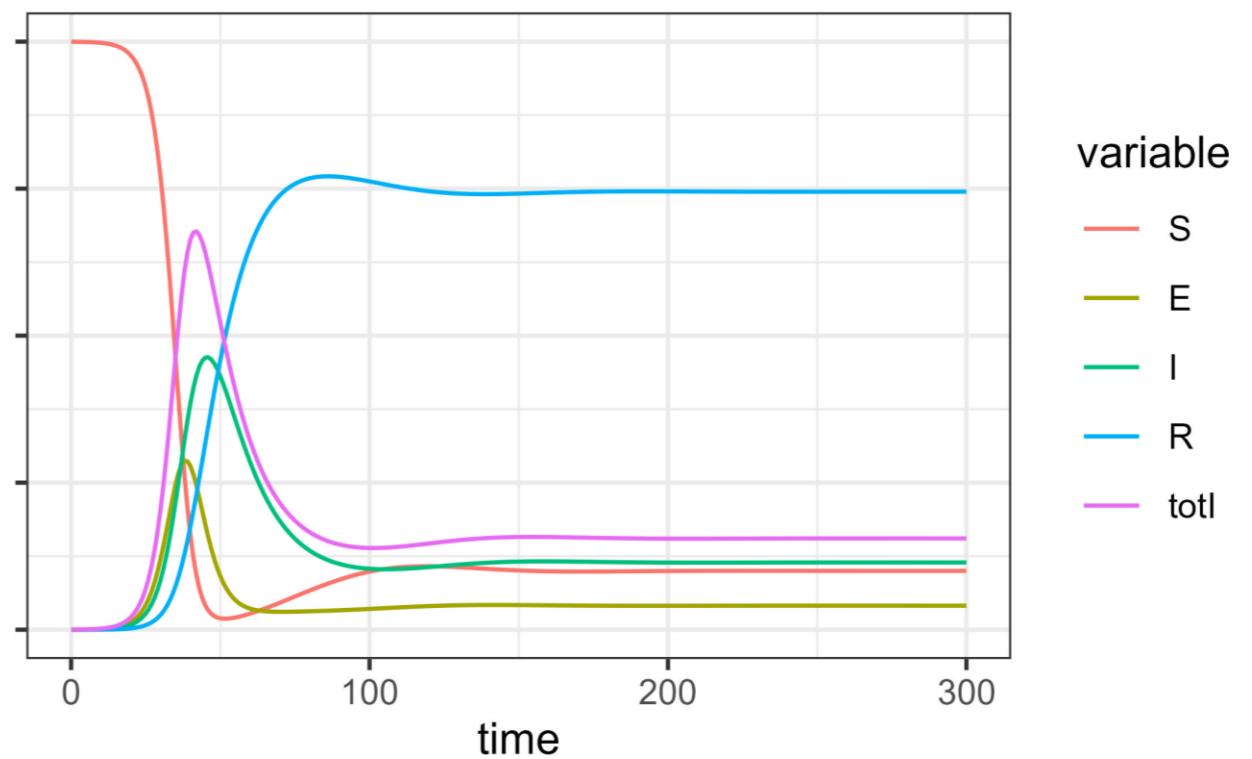
T_end <- 300 #run model for 300 time steps (e.g. days)
times <- seq(0, T_end, by = 1) #runs the model for 300 time steps (e.g. days)
```

# Solution for exercise: dynamics w/out quarantine

$R_0 = 3$

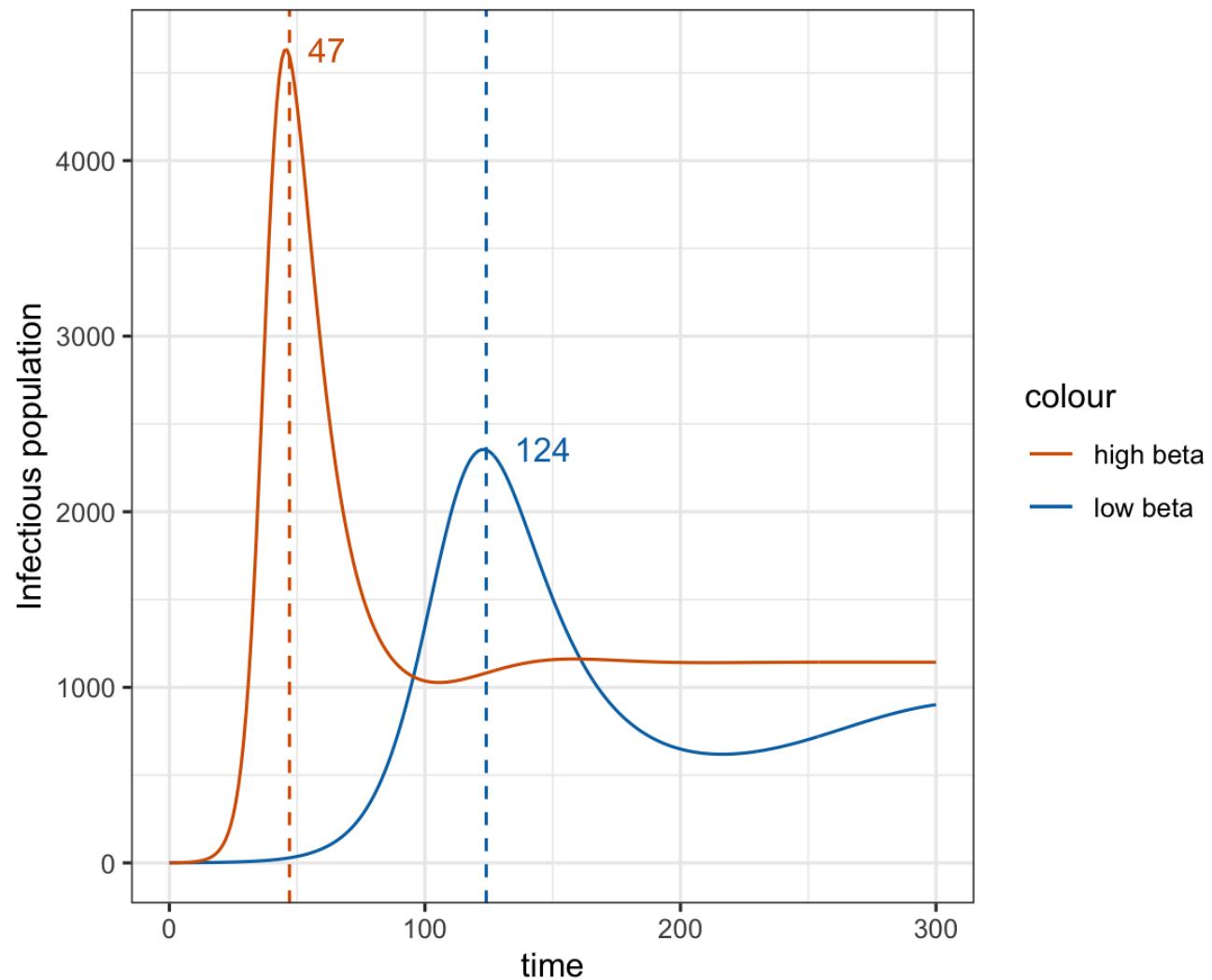


$R_0 = 10$



# Solution for exercise: question #1 and 2

Total number of infectious individuals ( $I$ )



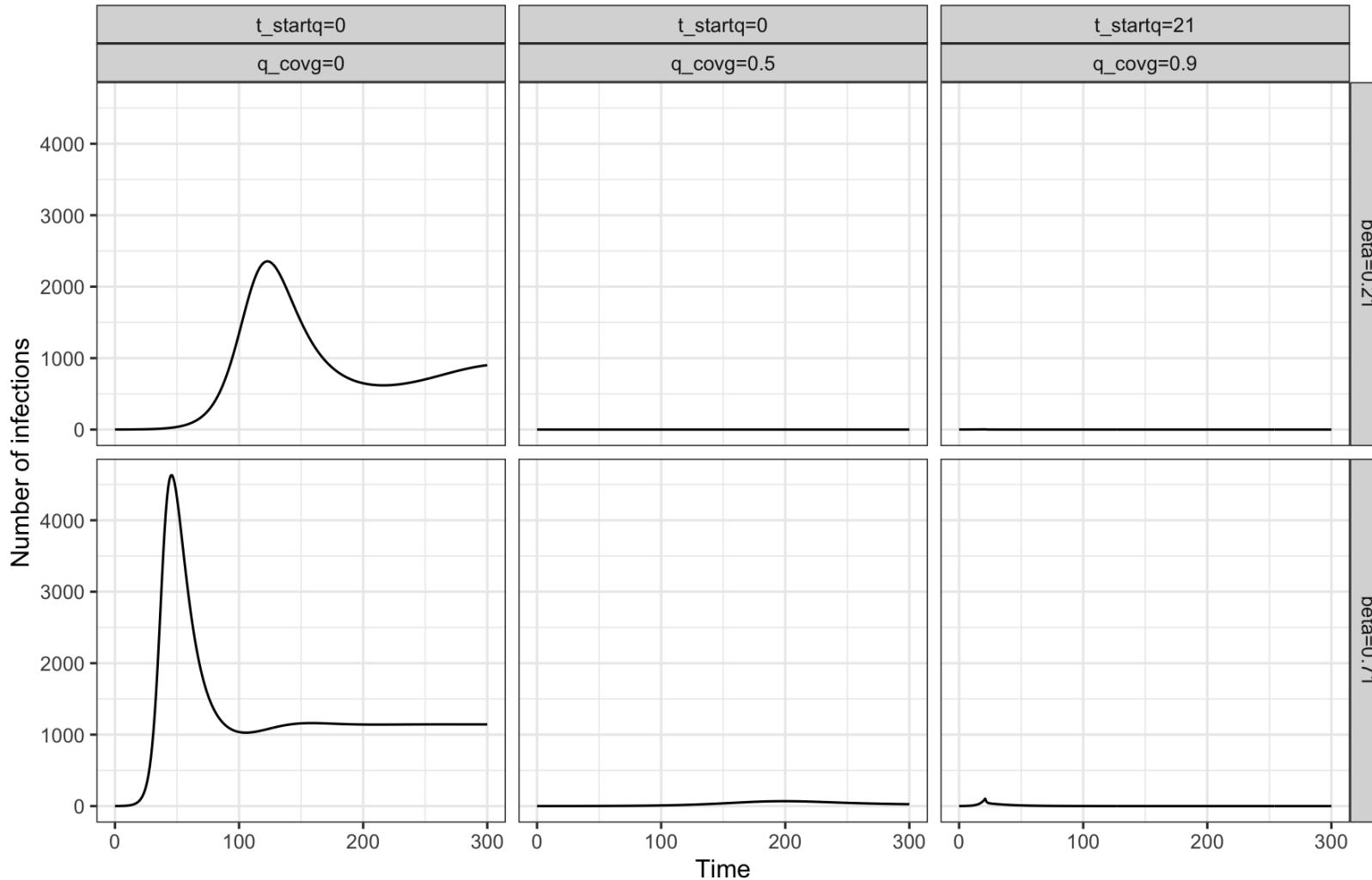
- With a high effective contact rate ( $R_0=10$ ):
  - The epidemic will peak 47 days after the outbreak starts.
  - Cumulative infections: 29,708
- With a low effective contact rate ( $R_0=3$ ):
  - The epidemic will peak 124 days after the outbreak starts.
  - Cumulative infections: 18,412

# Solution for exercise (R code): #3-4

```
# SEIRS model with quarantine
OpenSEIRS_qrtn<-function(t, state, parameters) {
  with(as.list(c(state, parameters)),{
    N = S + E + I + R + Q
    sigma = 1/t_lat # 1/latent period
    q_t = ifelse(t< t_start_q, 0, q) # before implementing quarantine, q(t) = 0
    #SIR w/ demography equations from lecture
    dS <- -beta*S*I/N + birth*N - death*S + omega*R
    dE <- beta*S*I/N - sigma*E - death*E
    dI <- sigma*E - death*I - gamma*I - q_t*I
    dQ <- q_t*I - death*Q - gamma*Q
    dR <- gamma*I + gamma*Q - death*R - omega*R
    # Cumulative number of infection
    dC <- beta*S*I/N
    # return the rates of change as a list
    list(c(dS, dE, dI, dQ, dR, dC))
  })
}
```

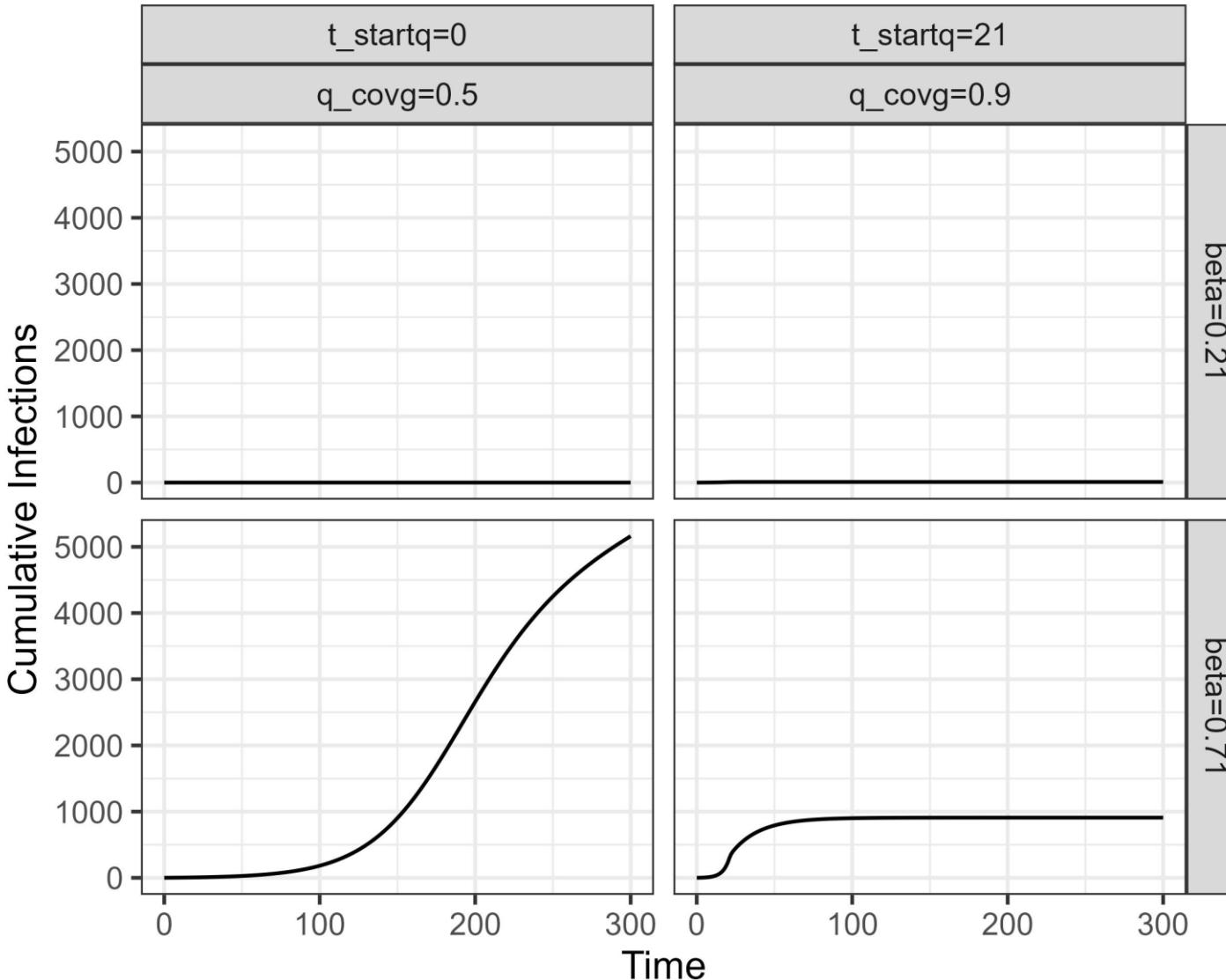
```
# Start quarantine at day = 0/21 with coverage 0.5/0.9 at different R0s
t_start_q_list <- c(0,0,21) # 0 is for absence of intervention
q_covg_list <- c(0,0.5, 0.9) # 0 is for absence of intervention
beta_list <- c(beta_low,beta_high)
twsa_dt <- data.frame() # data to save the ode outcomes|
```

# Solution for exercise: Question #3, #4



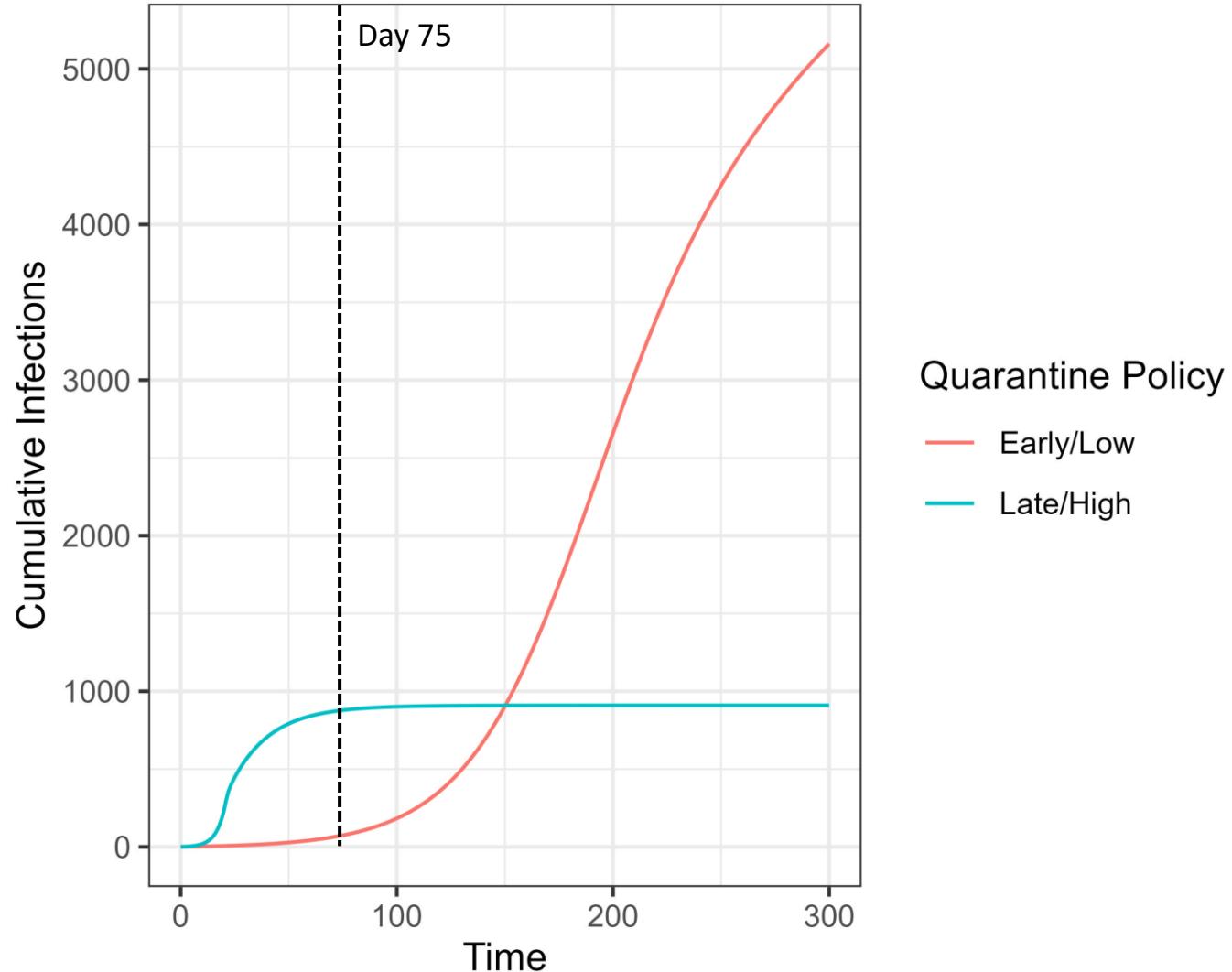
Both quarantine strategies were effective in that they substantially reduce the number of infections under both the “best case” (low  $\beta$ ) and “worst case” (high  $\beta$ ) scenarios

# Solution for exercise: Question #3, #4



- When  $R_0$  is low, both strategies effectively control the epidemic.
- When  $R_0$  is high:
  - Early quarantine delays epidemic growth but does not eliminate the outbreak with low coverage
  - Late quarantine does not prevent early epidemic growth but can effectively control it under high coverage
  - Total number of infections was lower with late quarantine with high coverage than early quarantine with low coverage

# Solution for exercise: Question #3, #4



**With high beta:** Early distribution of new vaccine can benefit from the early implementation of quarantine because it delays epidemic peak

# Part 4: Other Models & Wrap Up

Several additional complexities can be incorporated in dynamic compartmental models

- Additional types of heterogeneities (already discussed)
- Zoonotic transmission
- Vector-borne transmission
- Water- and food-borne pathogens
- Seasonality
- “Density-dependent” infections
- Multiple overlapping diseases
- Multiple competing strains of a single disease (including antimicrobial resistance)

# Multiple ways of modeling infectious diseases

Model Type	Distinct Features	Use Cases
1. Static (compartmental or discrete-time state transition)	Force of infection doesn't vary w/ the size of the infected population	- Interventions not expected to affect transmission OR - Not comparing interventions
2. Dynamic compartmental	Dynamic transmission, population-level, no stochasticity	-Interventions could affect transmission AND -Important heterogeneities can be captured through stratification AND -Low chance of random extinction
3. Microsimulation	Individual-level, includes stochasticity, can include dynamic transmission	-Important to capture many subgroups, heterogeneous contact structure, individual-level variation in transmission, etc. OR
4. Discrete event simulation		-Random extinction likely (e.g., small outbreak)
5. Agent-based model		
6. Branching model	Simple, stochastic transmission model	-Random extinction likely (e.g., small outbreak), other aspects of the disease are fairly simple, short time horizon.
7. Network model	Similar to 3-5, but includes explicit contact network structure	-Very heterogeneous contact network important to replicate (IDU or sexual networks drive transmission)
8. Statistical models	Non-mechanistic projections based on fit to recent trends	-"Nowcasting", or forecasting with a short time horizon AND -Not comparing interventions
9. Within-host models	Models a population of pathogens within an individual	-Within-host evolution (e.g., antimicrobial resistance) -Pharmacokinetic models
10. Gravity/spatial models	Non-mechanistically simulate spatial spread, including of diseases	-Can be used within an SIR model/similar to parameterize mixing across space, geographic regions, etc.

# Best practices

Although they often require a specific set of methods, best practices for ID modeling are similar to best practices for any disease/health policy modeling.

1. Carefully consider which model structure best fits your disease & the goals of your analysis.
  - Simplicity-complexity tradeoffs
  - Be able to explain implications of your modeling assumptions and how they might be affecting results
2. Transparency and reproducibility
  - Parameter estimation strategy
  - Model equations
  - Making your model code available
3. Incorporate uncertainty and recognize limitations
  - Especially early in a new epidemic: <https://www.bmjjournals.org/content/375/bmj.n2365>
  - Parameters AND structural sensitivity analysis
4. Choose a time horizon long enough to capture all benefits
  - Sensitivity analysis on the time horizon and discount rate
5. Involve subject matter experts and local partners
6. Take advantage of disease modeling consortia & other resources

For more on best practices of ID modeling: Pitman 2012 (pre-read)

# Thank You!

Please fill out the post-meeting survey (or give us feedback in some other way)! This is our first time teaching this class and we want to hear what you liked and how we could make it better.

Our contact info:

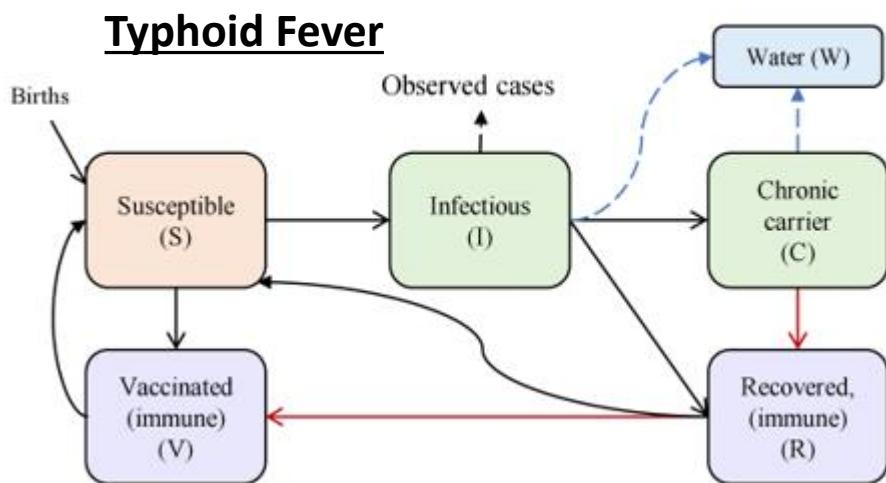
- Kyu: [kyueunl@uw.edu](mailto:kyueunl@uw.edu)
- Tess: [tryckma1@jh.edu](mailto:tryckma1@jh.edu)

# Extra Slides

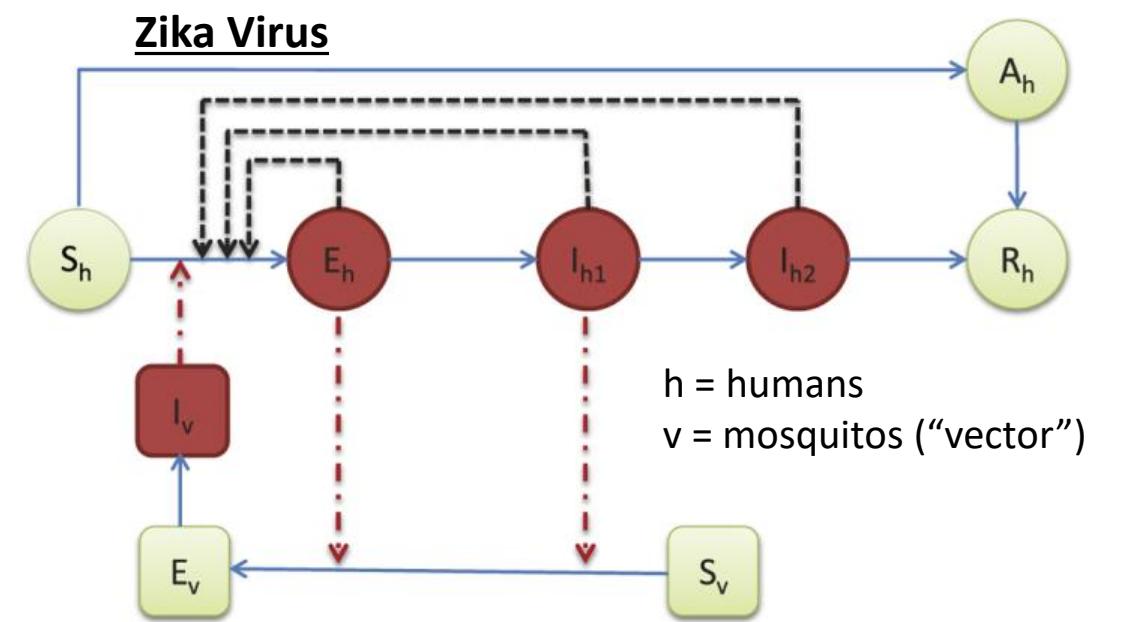
# Vector-borne & environmental pathogens

Typically, add reservoir components to represent vectors, animals, water, food, surfaces, etc.

- Force of infection is often non-linear function of prevalence, with saturation/threshold effects
- Can slow/dampen impact of interventions that focus on humans
- Can more directly simulate environmental interventions (sanitation, insecticides, etc.)
- Disease dynamics dependent on local conditions (can a water or animal reservoir be sustained?)
- Introductory resource: Keeling & Rohani, Ch 4



Burrows et al. Comparison of model predictions of typhoid conjugate vaccine public health impact and cost-effectiveness. Vaccine 2023.



Gao et al. Prevention and Control of Zika as a Mosquito-Borne and Sexually Transmitted Disease: A Mathematical Modeling Analysis. Sci Rep. 2016.

# Seasonality

- Can model immunity and evolution of new strains
  - Andreasen V 1997, Lin J 1999, Gog JR 2002, - influenza, added antigenic drift and cross-immunity
  - Alexander H 2010 – conceptual SIR model with consideration of within-host evolution
  - K Lee 2020 – multi-strain SEIR influenza model with waning/propagated/cross- immunity
- Can allow parameters to vary seasonally (e.g., contacts, vaccination)
  - Ibrahim MA 2023 Measles in Pakistan, beta is time-dependent and in a form of periodic function
  - Zhimin Li 2022 – COVID-19 model, beta is a periodic transmission rate
  - R.Yaari 2013 – Influenza model, estimated time-dependent betas using meteorological data (e.g. temperature, absolute humidity)

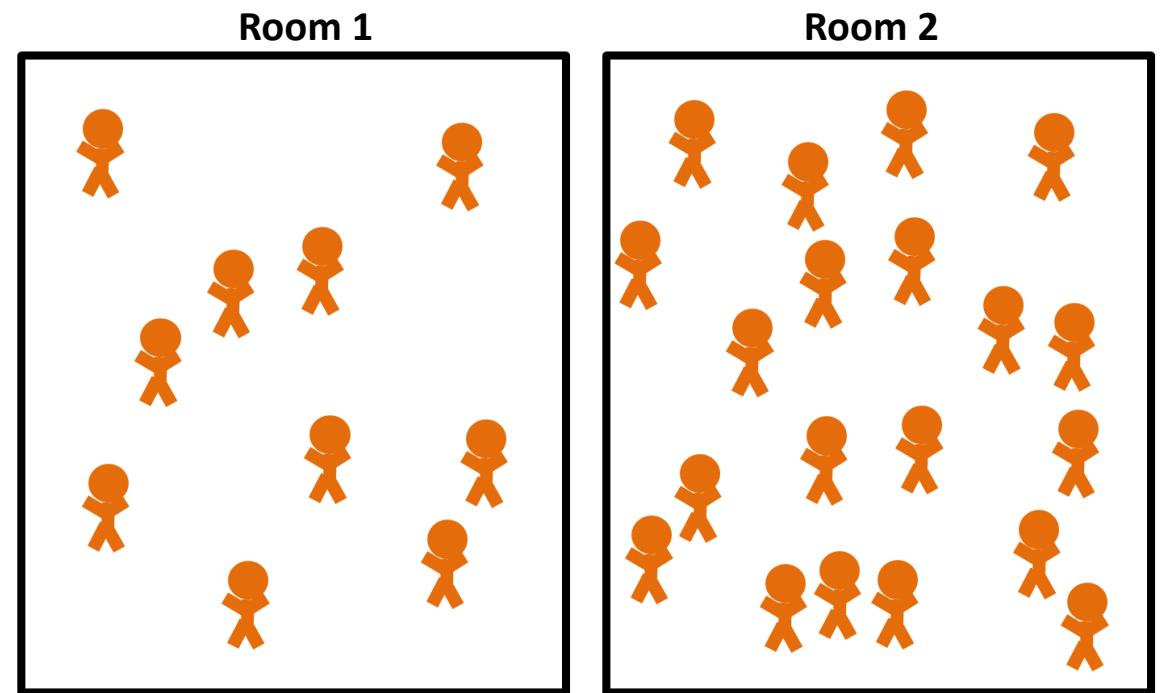
# Frequency-dependency vs. density-dependency

**Frequency dependence** (“true mass action”):  
number of effective contacts is unchanged as  
population grows

- $\lambda = \beta I / N$  : product of beta and the proportion of the population infected
- Most ID models in humans (all of today's models)

**Density dependence** (“pseudo mass action”):  
number of effective contacts scales with  
population density

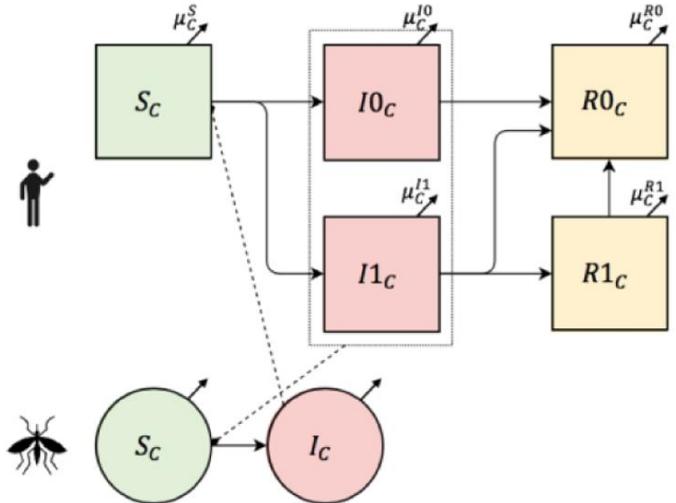
- $\lambda = \beta I$ : product of beta and the number of people infected
- Some animal/plant diseases, modeling small populations



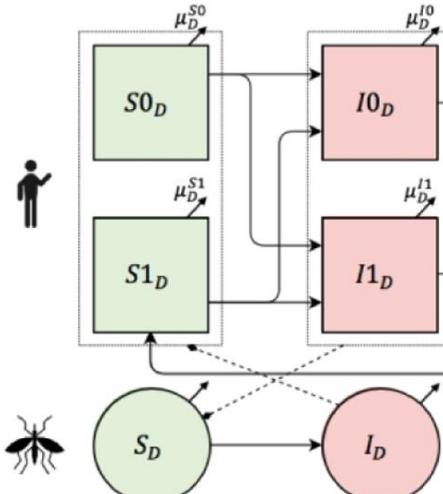
# Multiple diseases

Claypool, Goldhaber-Fiebert, & Brandeau. Assessing Interventions that Prevent Multiple Infectious Diseases: Simple Methods for Multi-Disease Modeling. MDM 2022.

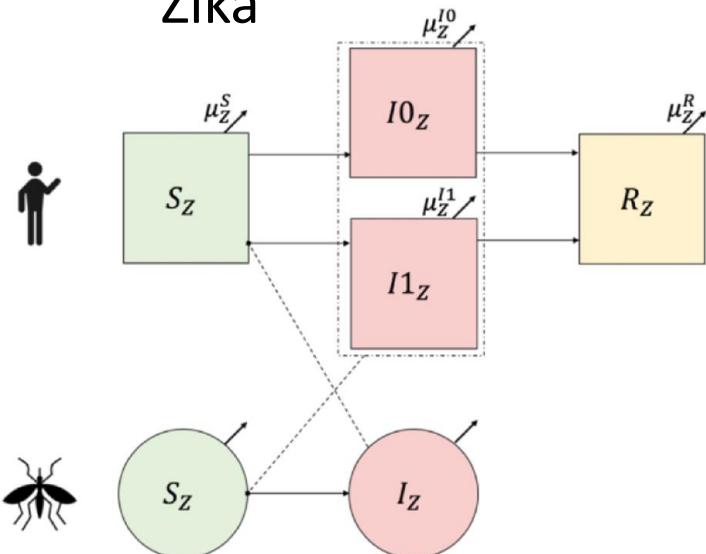
## Chikungunya



## Dengue



## Zika



Adjusting estimated Zika mortality to incorporate competing Chikungunya and Dengue mortality risks

$$\mu_Z^S = \mu S_Z + \mu((HR_C - 1)I_{1C} + (HR_D - 1)I_{1D}) \frac{S_Z}{T_Z}$$

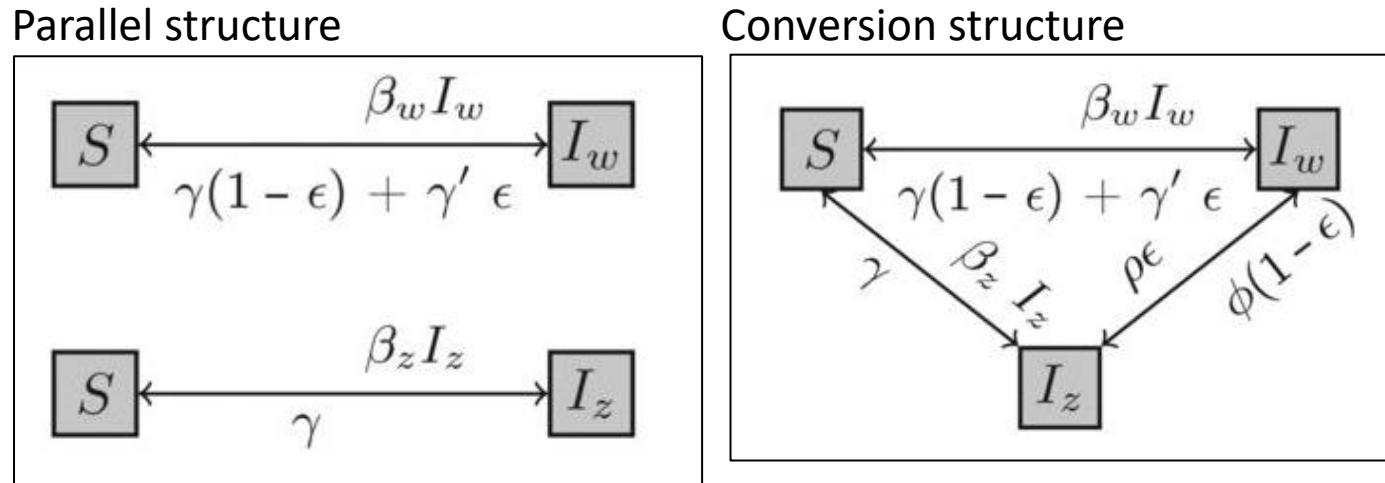
$$\mu_Z^{I0} = \mu I_{0Z} + \mu((HR_C - 1)I_{1C} + (HR_D - 1)I_{1D}) \frac{I_{0Z}}{T_Z}$$

$$\mu_Z^{I1} = \mu I_{0Z} + \mu((HR_C - 1)I_{1C} + (HR_D - 1)I_{1D}) \frac{I_{1Z}}{T_Z}$$

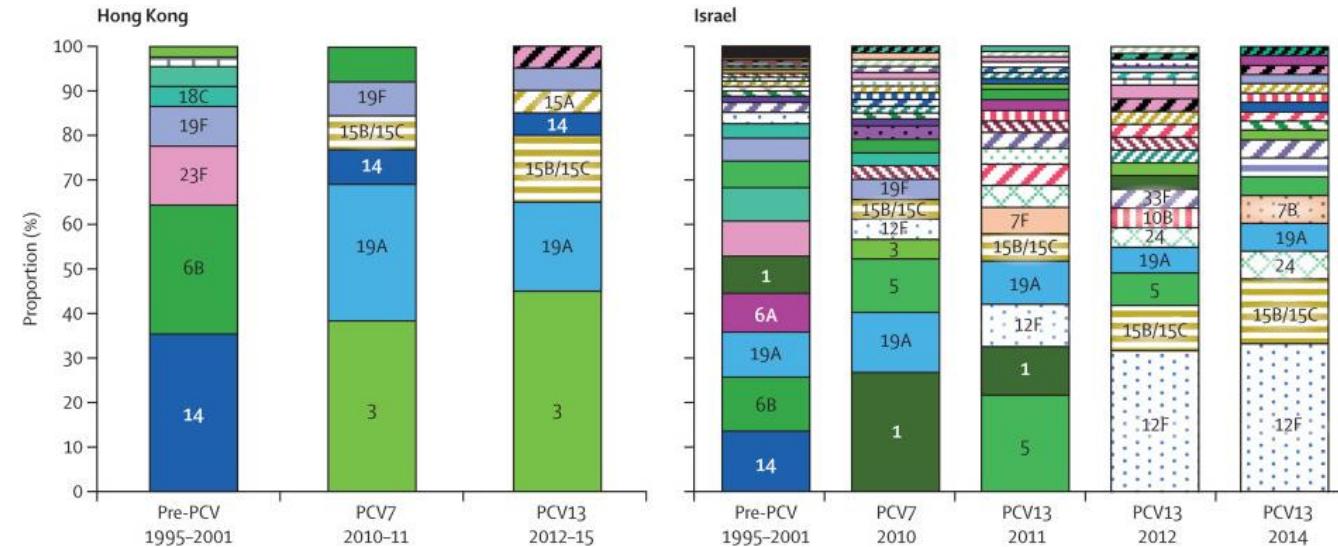
$$\mu_Z^R = \mu R_Z + \mu((HR_C - 1)I_{1C} + (HR_D - 1)I_{1D}) \frac{R_Z}{T_Z}$$

# Multiple competing strains

- Multiple strains of a disease can be accommodated by adding stratifications
- Examples
  - Population-level trends in antimicrobial resistance
  - Vaccines can alter the prevalence of strains in the population
- BUT dynamic compartmental models don't easily allow us to model pathogen evolution



[Spicknall et al. A Modeling Framework for the Evolution and Spread of Antibiotic Resistance: Literature Review and Model Categorization. Am J Epi 2013.](#)

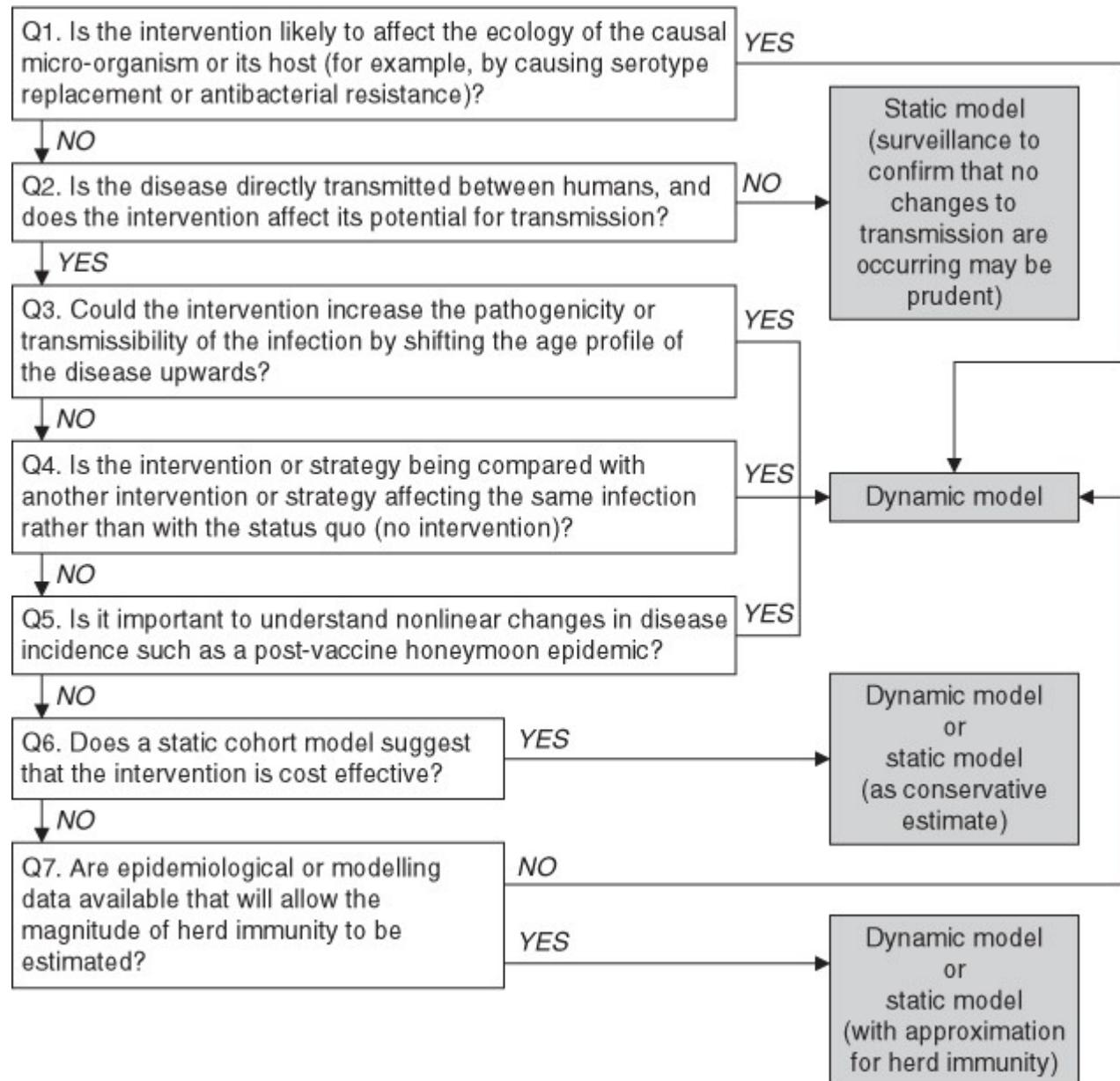


[Lo et al. Pneumococcal lineages associated with serotype replacement and antibiotic resistance in childhood invasive pneumococcal disease in the post-PCV13 era: an international whole-genome sequencing study. Lancet ID 2019.](#)

# Static models

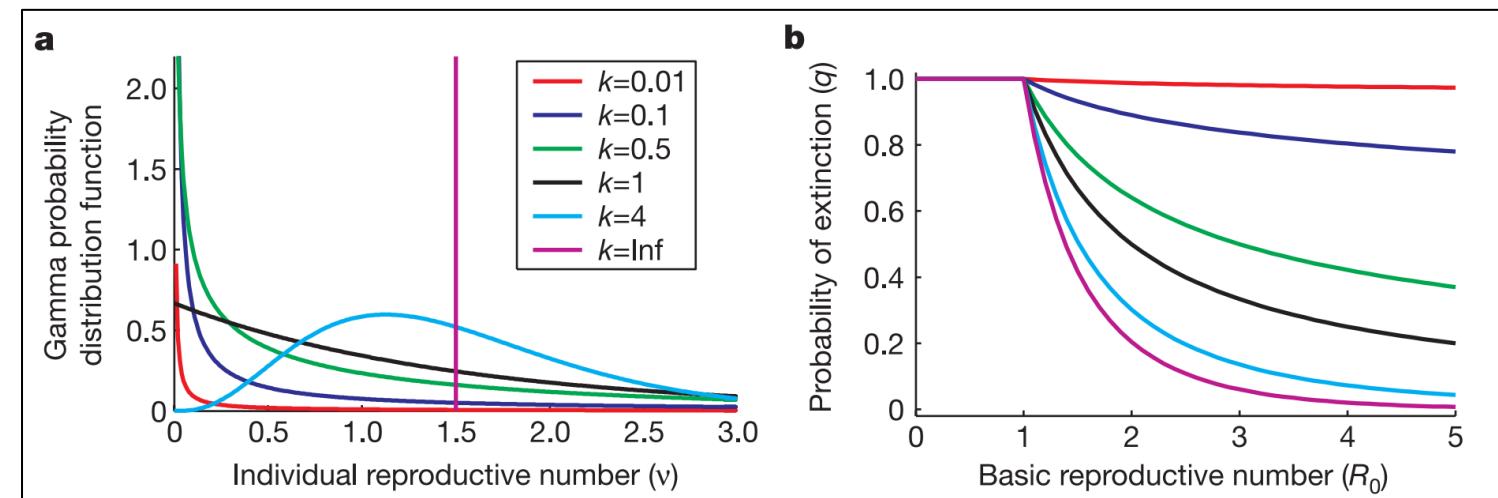
## Static model types:

- Markov model
- Individual-level model, but without dynamic transmission
- Modeling dynamic transmission adds complexity, reduces transparency
- It is often less important to model transmission dynamically when:
  - Interventions are not expected to affect transmission
    - Treating people for diseases with large environmental reservoirs.
    - Interventions that only prevent/treat severe disease, not infection/infectiousness.
    - Intervening on a small subset of the population
  - We are using a model to learn more about disease epidemiology or natural history



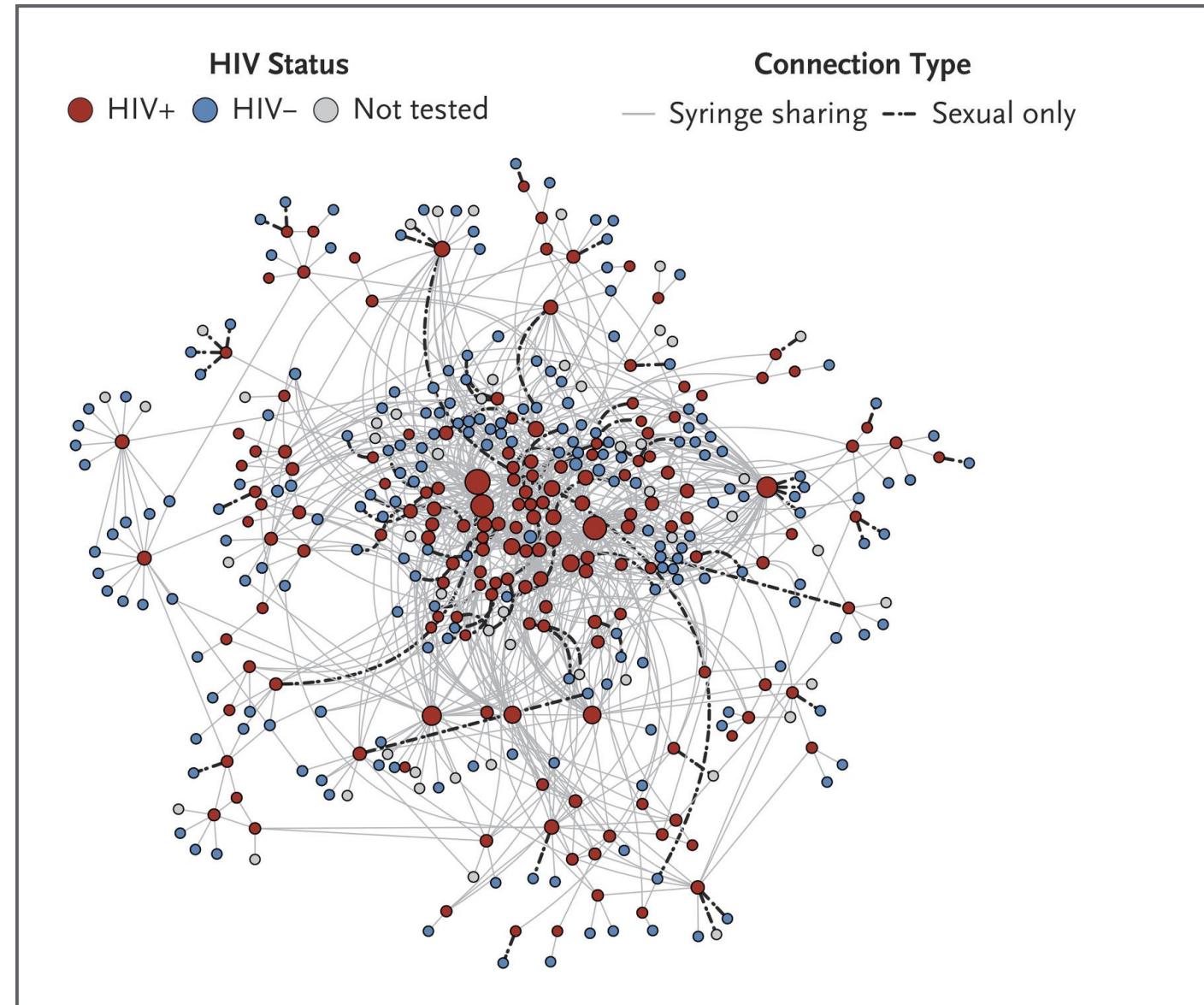
# Individual-level stochastic models

- Motivation
  - Outbreaks have a random chance of dying out (SARS v1 or localized outbreak example)
    - More likely with small populations, diseases w/ low  $R_0$ , seasonal fluctuations in prevalence, early on in an epidemic
  - Variation (across individuals or over time) matters
  - Heterogeneous contact networks are important to disease dynamics (next slide)
- Individual-level stochastic models typically use random numbers to determine whether each modeled individual experiences an event (e.g., infection) each [discrete] time step
- Types of models:
  - Branching process
  - Microsimulation
  - Agent-based models
  - Discrete event simulation
    - models “time to event”
  - Network models (next slide)



# Network models

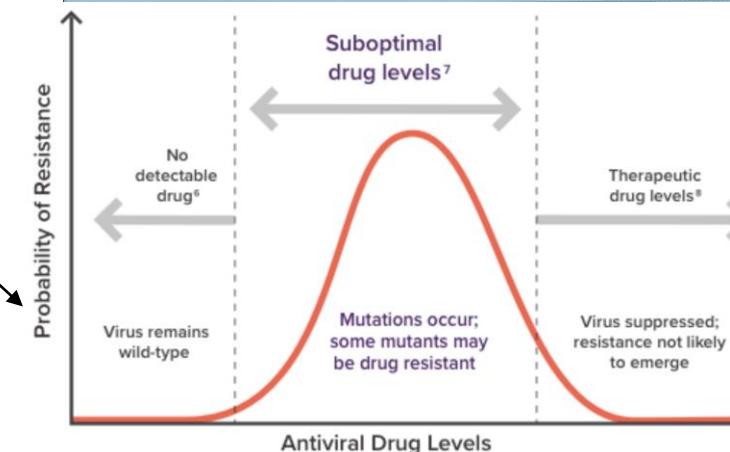
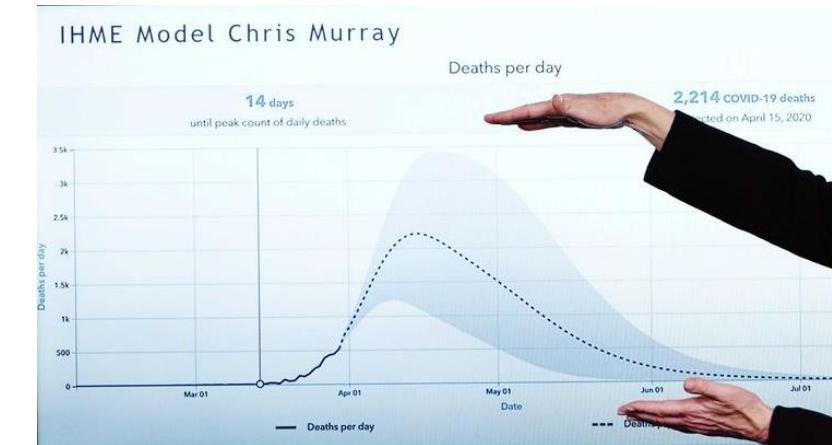
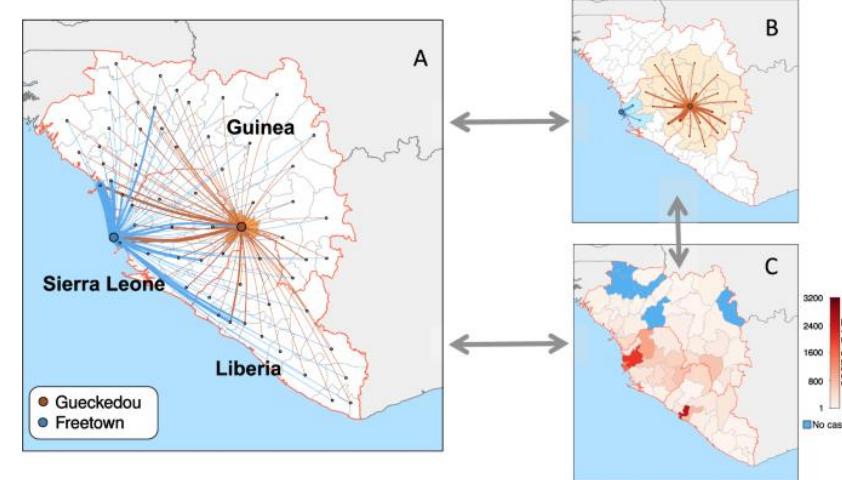
- Motivation
  - Very heterogeneous contact network that cannot be accommodated through a stratified compartmental model
  - Examples: STIs, needle-sharing, fine-scale spatial models
- Introductory resource:  
[Keeling & Eames. Networks and epidemic models. J R Soc Interface. 2005.](#)



Peters et al. HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014–2015. NEJM 2016.

# Other types of models

- **Gravity/similar spatial models**
  - Can be used to describe spread and dynamics of infectious diseases over space
- **Statistical models**
  - Non-mechanistic models that extrapolate based on fitted disease trends
  - Most suitable for nowcasting or projections with a very short timeframe
  - Less useful for projecting longer-term disease trajectories or modeling the impact of interventions
- **Within-host evolutionary/pharmacokinetic models**
  - Evolution (e.g., drug resistance) of a population of pathogens within a host (e.g., infected person)



<https://www.helpstopheviruspro.com/en/barrier-to-resistance>

Kraemer et al.  
Utilizing general  
human  
movement  
models to  
predict the  
spread of  
emerging  
infectious  
diseases in  
resource poor  
settings.  
Scientific  
Reports 2019.

# Model calibration

- Broadly similar to calibrating a non-dynamic model – but some added challenges
  - Burn-in needed to reach a steady state - adds computational time
  - May have very uninformed priors on some parameters, like beta
  - Some combinations of parameters may lead to very odd behavior that “breaks” the *ode* solver (need to exclude these combinations)
  - May need to tweak arguments in the *ode* function (tolerance, etc.)

## Resources (some using ID models):

- [Menzies et al. Bayesian Methods for Calibrating Health Policy Models: A Tutorial. Pharmacoconomics 2017.](#)
- [Vanni et al. Calibrating Models in Economic Evaluation. Pharmacoconomics, 2012.](#)
- [Jackson et al. Calibration of Complex Models through Bayesian Evidence Synthesis: A Demonstration and Tutorial. MDM 2013.](#)
- SMDM courses/workshops

# Why do we need a special set of modeling methods for infectious diseases?

- Start with Markov model example and reasons why it might not always be a good fit for ID modeling
- Transmission rate depends on # ppl infected – in a Markov model it would have to change every second to account for this -> better to use ODEs
- Explain ODEs – allows for use of continuous time scale/continuous transition rates between different states (don't have to keep updating transition matrix as we would in a Markov model)
- Discrete vs. continuous time
- Rates vs. probabilities
- Show comparison (Markov model structure and results vs. ODE)
- Focusing today on dynamic compartmental models like SIR and variations of SIR that use ODEs

# Calculating R<sub>0</sub> in models other than SIR

- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6002118/pdf/main.pdf>