

Infectious Disease Modeling Using Dynamic Compartmental Models in R

HEOR 533

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Acknowledgements



Jason Andrew
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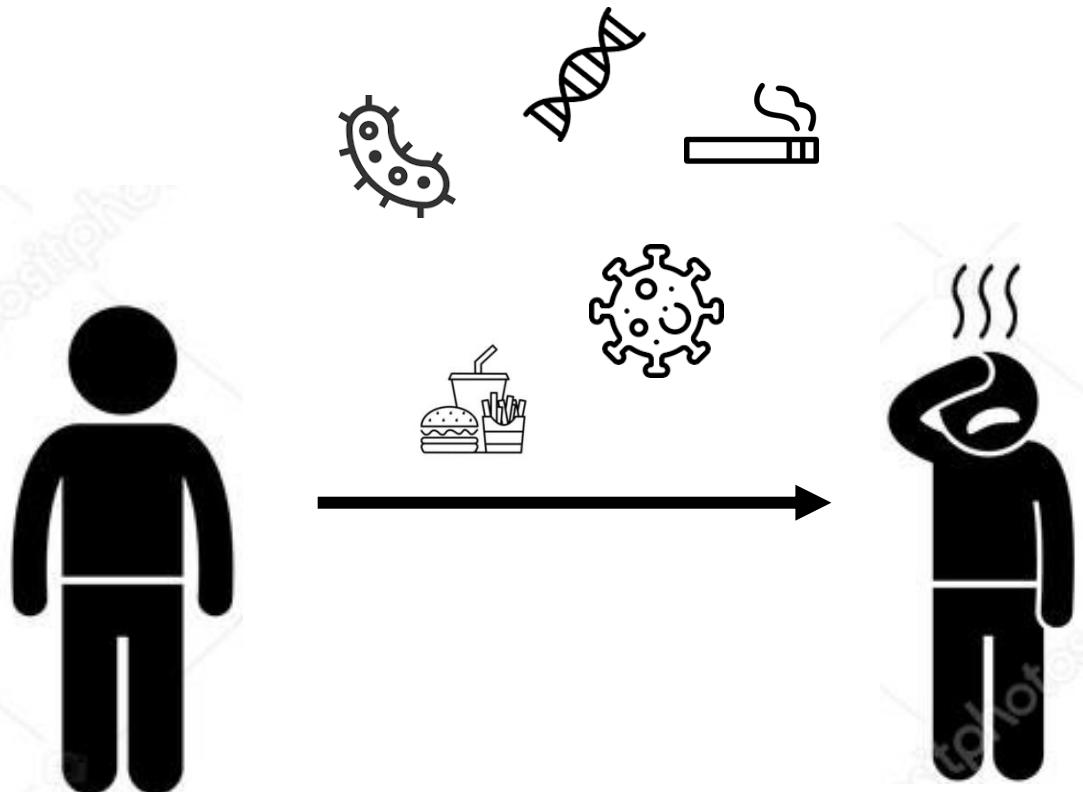


Jeremy Goldhaber-Fiebert
Stanford University

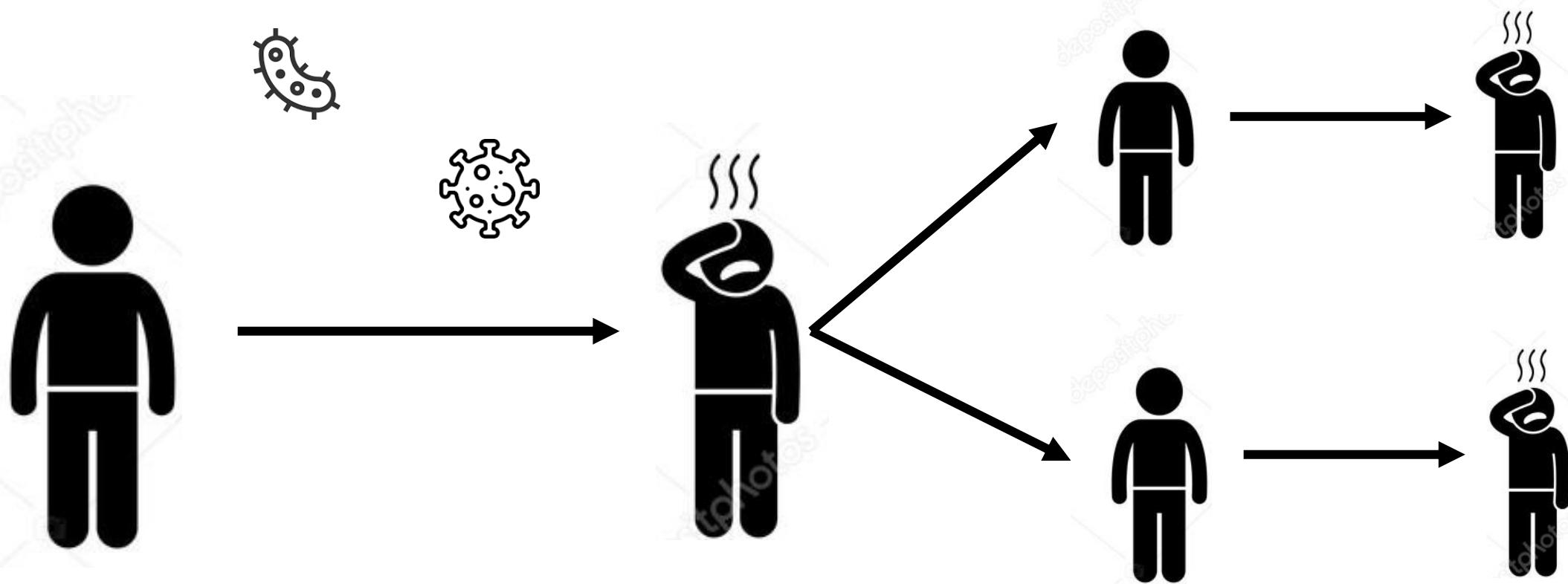


Tess Ryckman, PhD
Johns Hopkins University

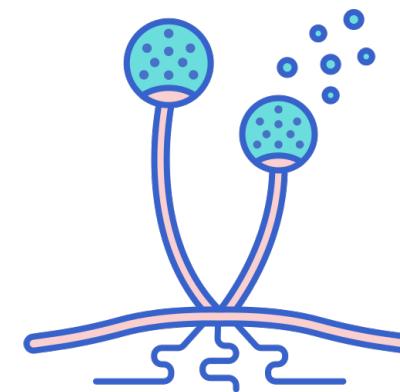
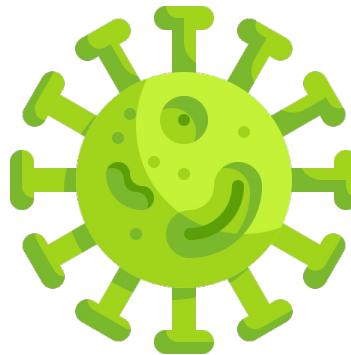
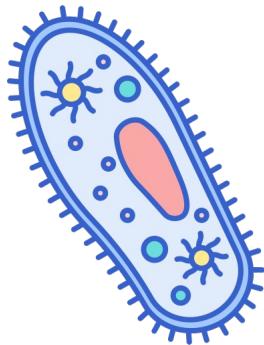
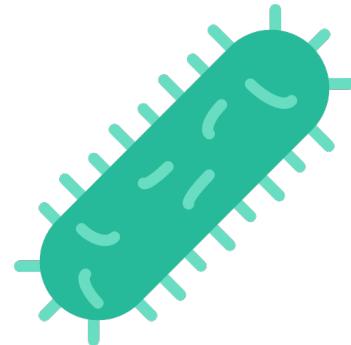
Communicable vs. non-communicable diseases



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

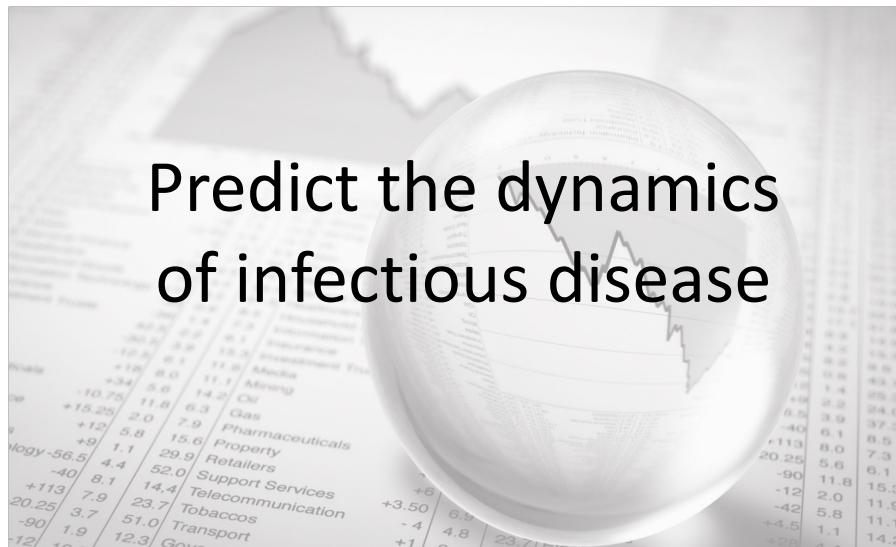
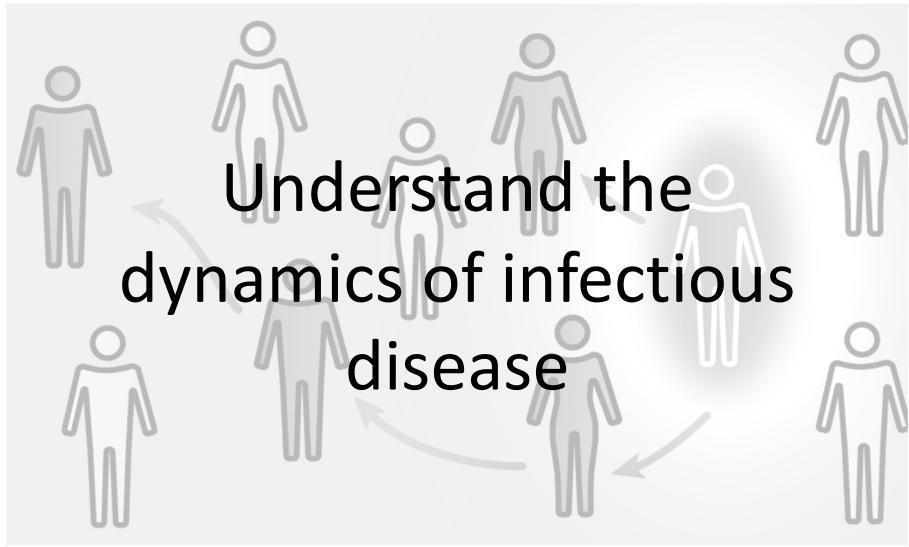
Fungi

- 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">• Quantify transmission• Assess severity• Assess potential seasonality• Support WHO's decision on timing and targeting of vaccination
Ebola	Chretien JP 2015 Kucharski AJ 2016 Camacho A 2017	Outbreak	<ul style="list-style-type: none">• Assess the impact of case isolation, contact-tracing with quarantine, and sanitary funeral practices on the number of new infections• Design ring vaccination strategy• WHO guideline on designing vaccine efficacy trials
HIV	Granich RM 2009 Bernard C 2017	Endemic	<ul style="list-style-type: none">• Introduce the test-and-treat strategy• Recommend PrEP for a high-risk group

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

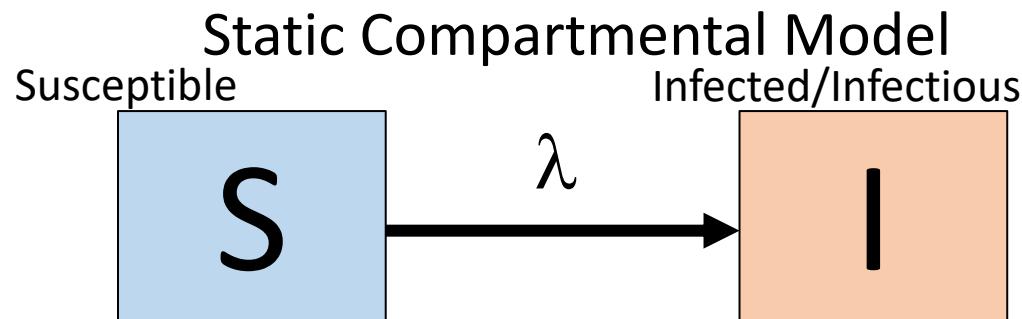
Course aim

- 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.

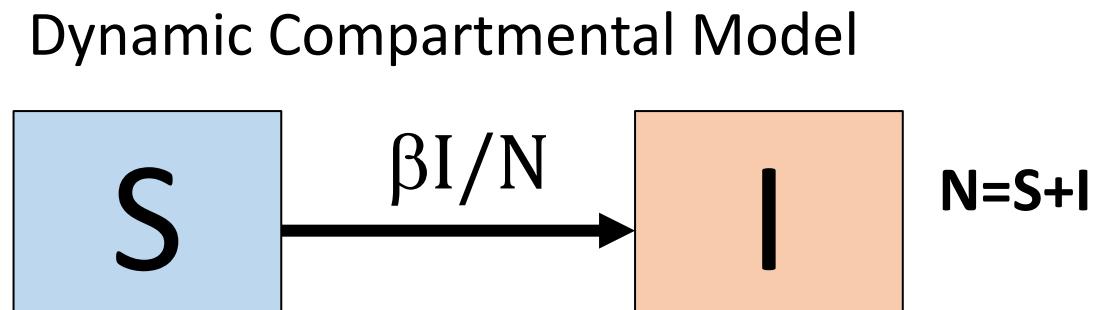
Part I: Basics & the SIR Model

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



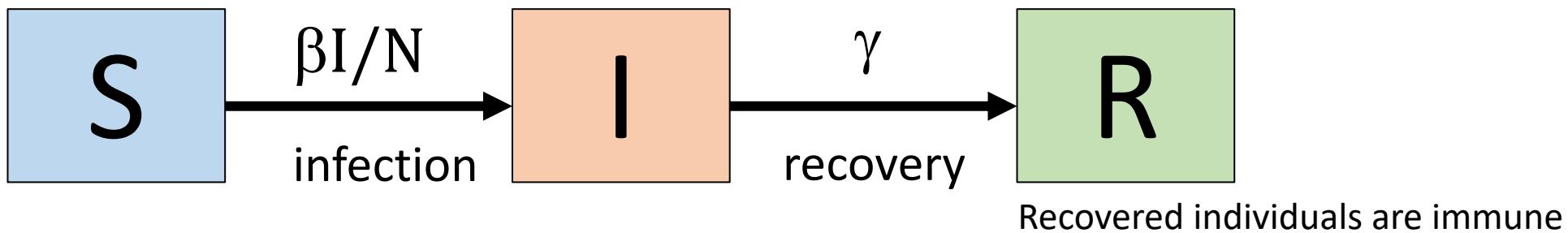
$$\frac{dI(t)}{dt} = \lambda S(t)$$



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

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

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

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

Infected individuals exit compartment I at rate gamma.

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

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

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

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

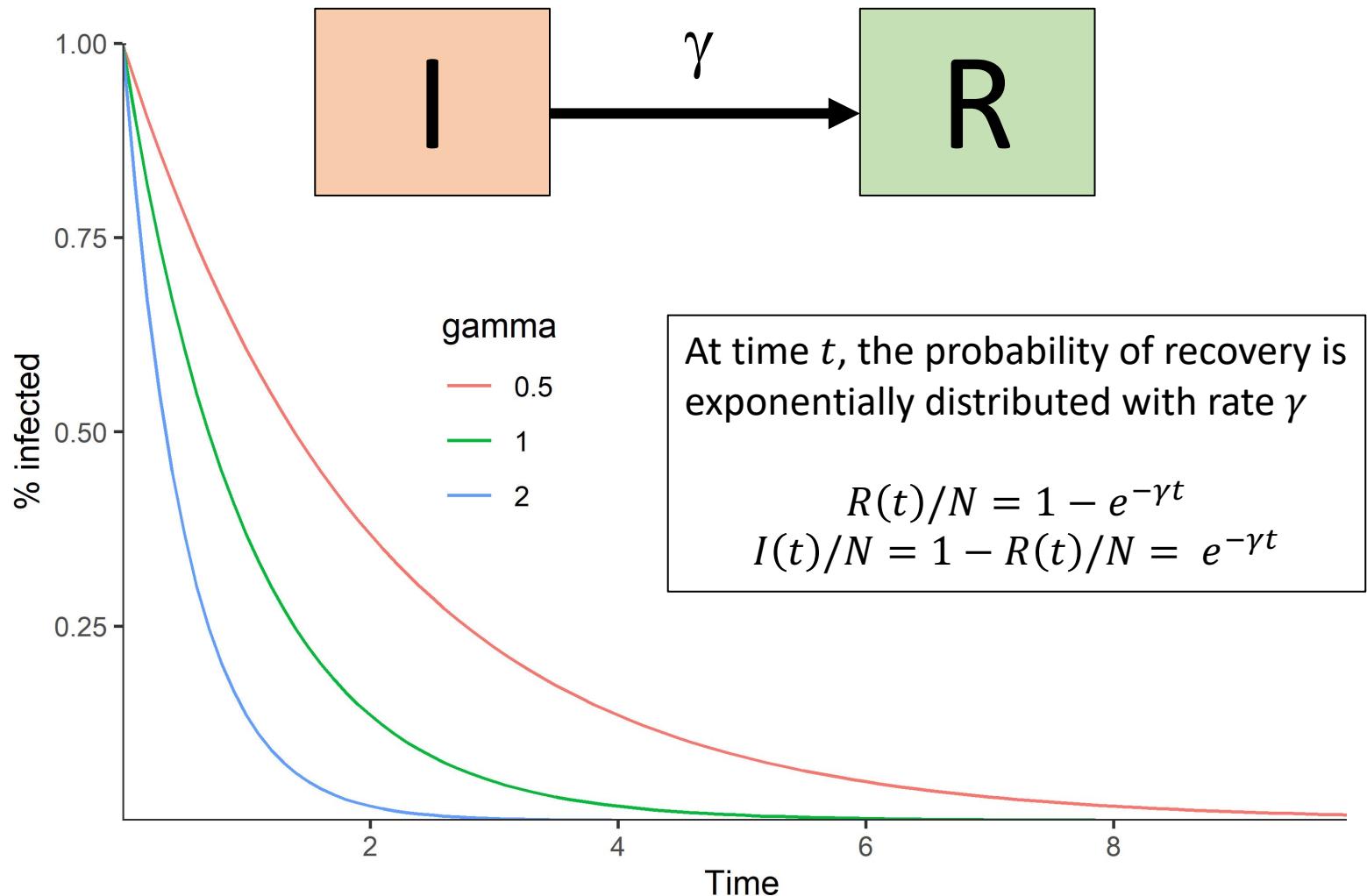
Infected individuals exit compartment I at rate gamma.

Differential equations use rates, not probabilities

- Recovery rate gamma \neq probability that someone recovers
- γ 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
 - $\frac{1}{\gamma} = \text{average duration of infectiousness}$

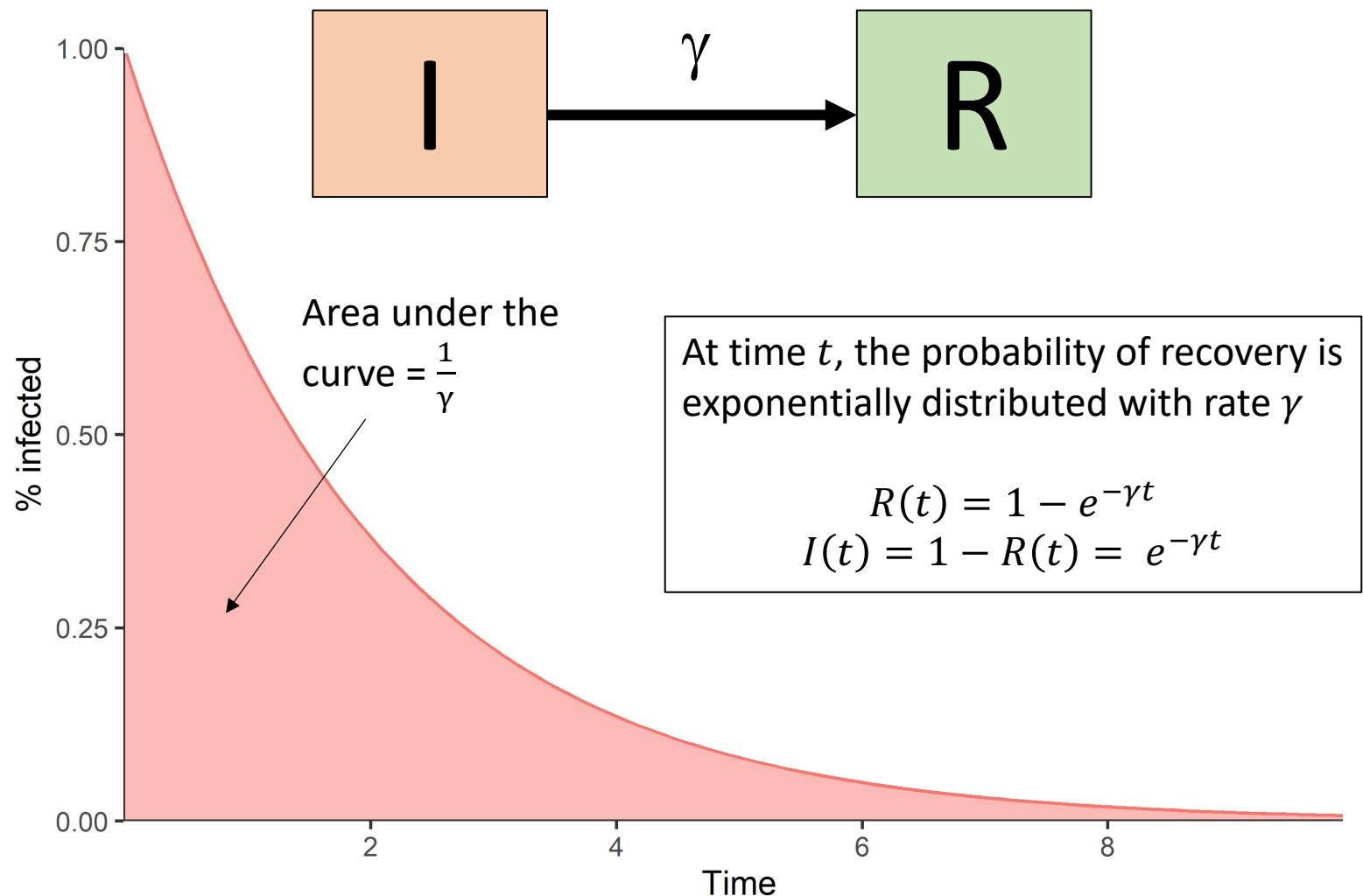
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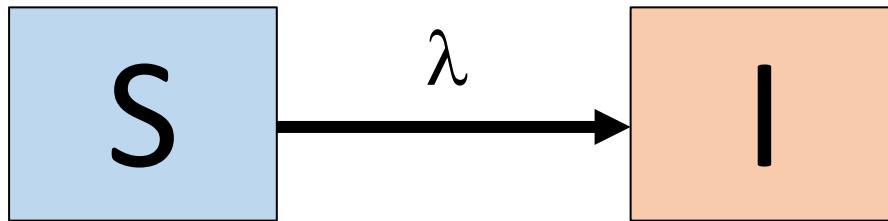
Quick differential equations recap

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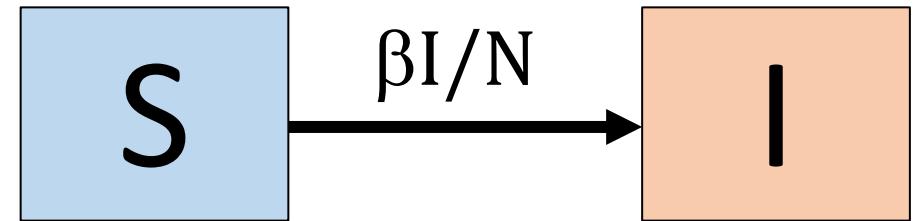


Effective contact rate & force of infection

Static Compartmental Model



Dynamic Compartmental Model



Force of infection (λ): rate at which susceptibles are infected. Function of:

- Number of infected individuals I
- **Effective contact rate (β):** rate at which an infected individual I infects 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

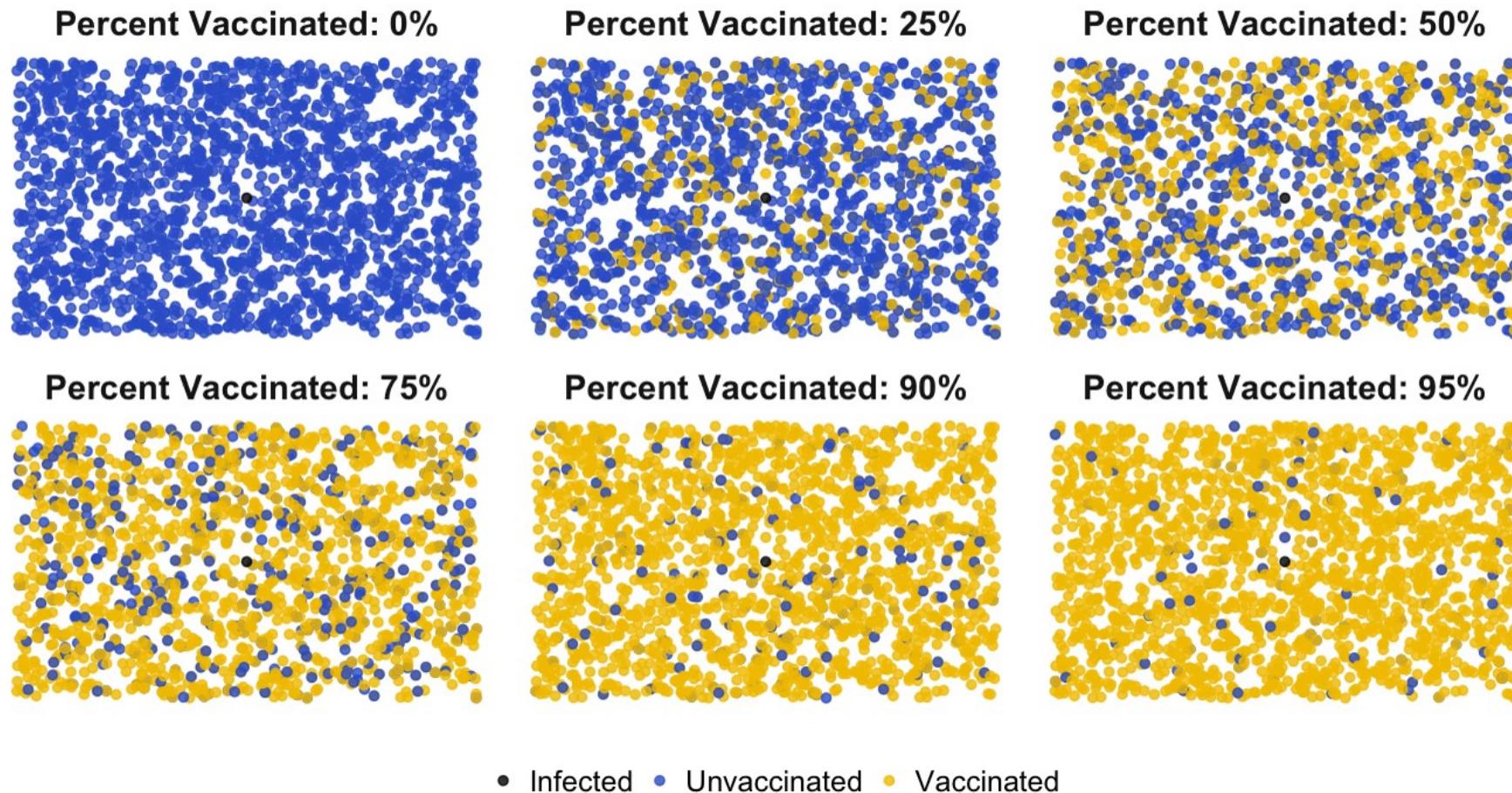
Disease	R_0 Estimates/Range	Sources (mostly systematic reviews)
Tuberculosis	< 1 to 4	Ma et al. Epidemiology & Infection 2018
Monkeypox (2022-23)	< 1 to 3	Banuet-Martinez et al. Epidemiology & Infection 2023.
Ebola (2014 outbreak)	1.3-1.8	Wong et al. Epidemiology & Infection 2017.
Seasonal Influenza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

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

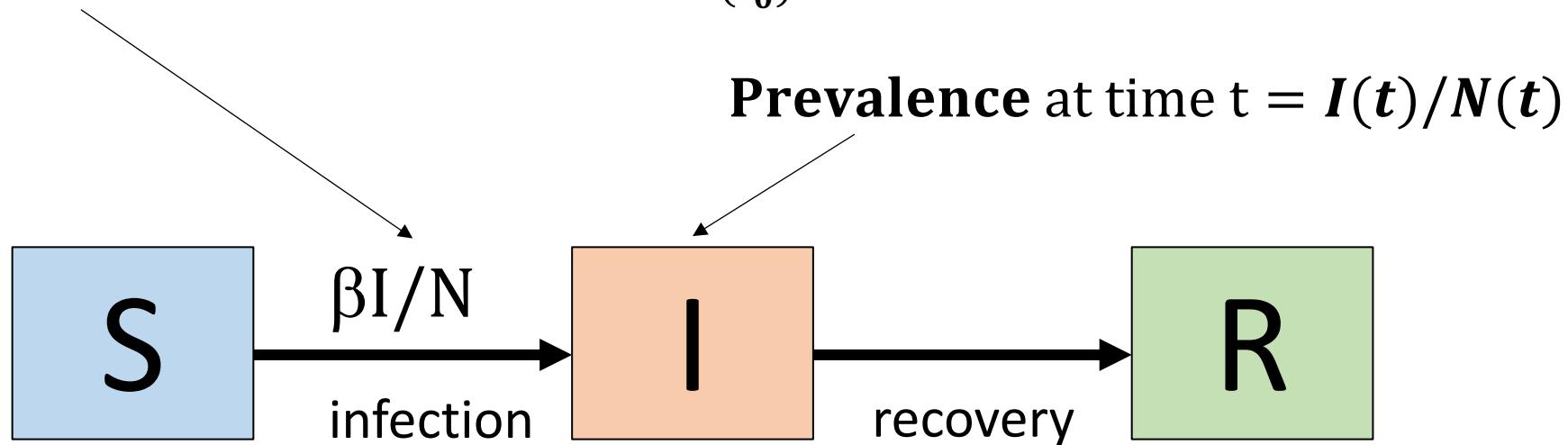
Population susceptibility is the limiting factor in epidemics - dictating whether they start & when they end



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)

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)
- Immunity isn't usually lifelong
- Infected \neq infectious (not always)
- Doesn't always accommodate interventions
- Assumes completely homogeneous population
- Durations are not always exponentially-distributed

Some limitations of the basic SIR model:

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

Adding demography: SIR w/ births & deaths

Motivation:

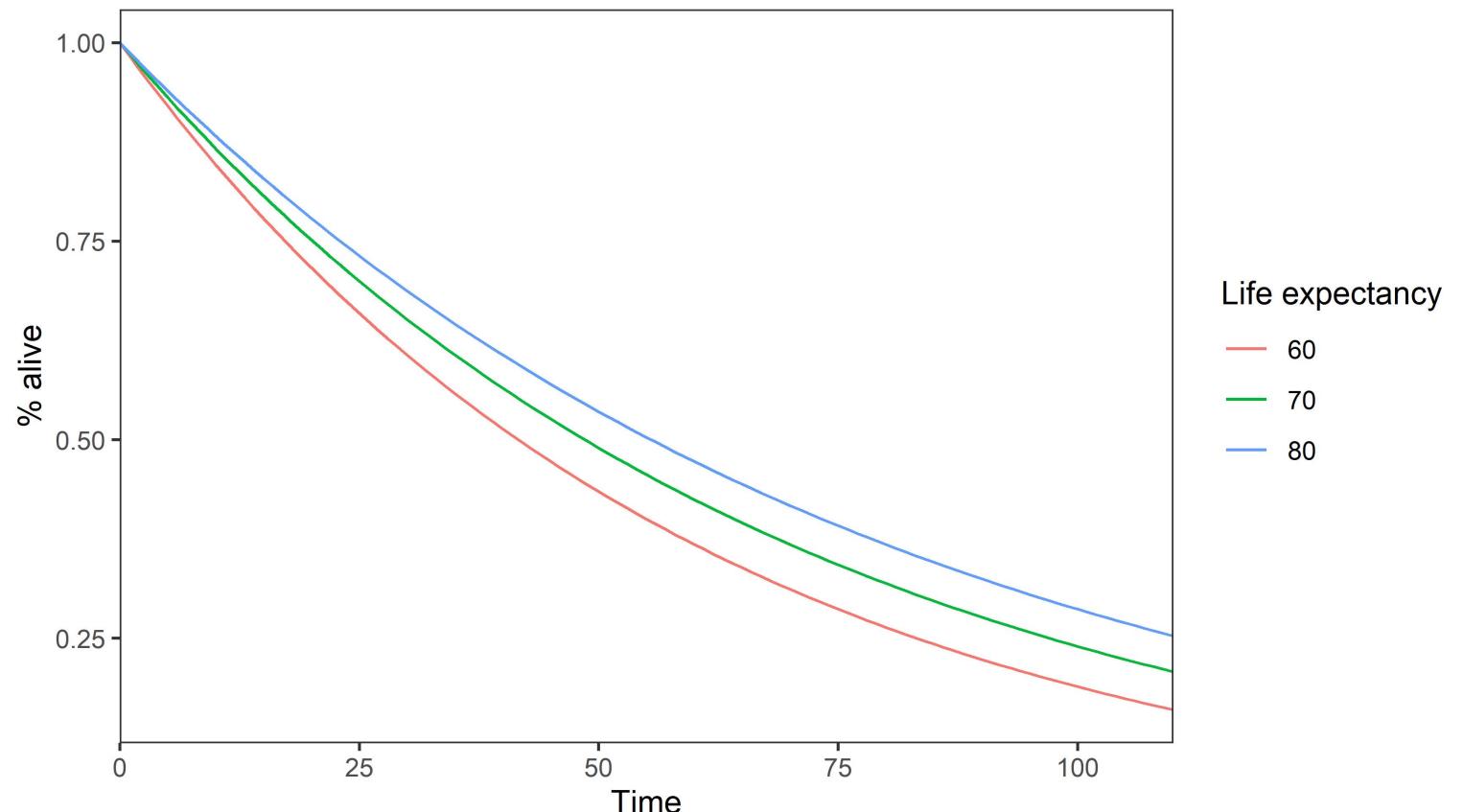
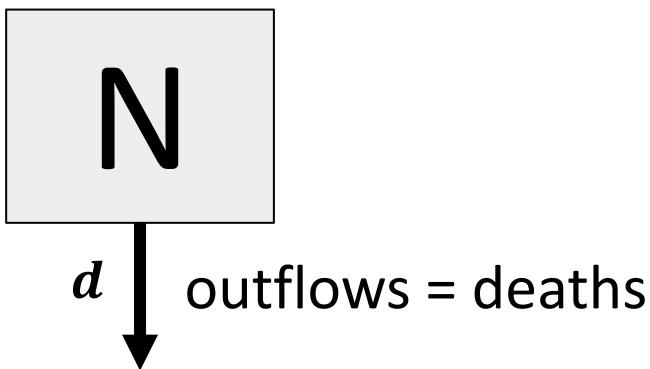
From Part 1: Population susceptibility is the limiting factor in epidemics - dictating whether they start & when they end.

→ 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.

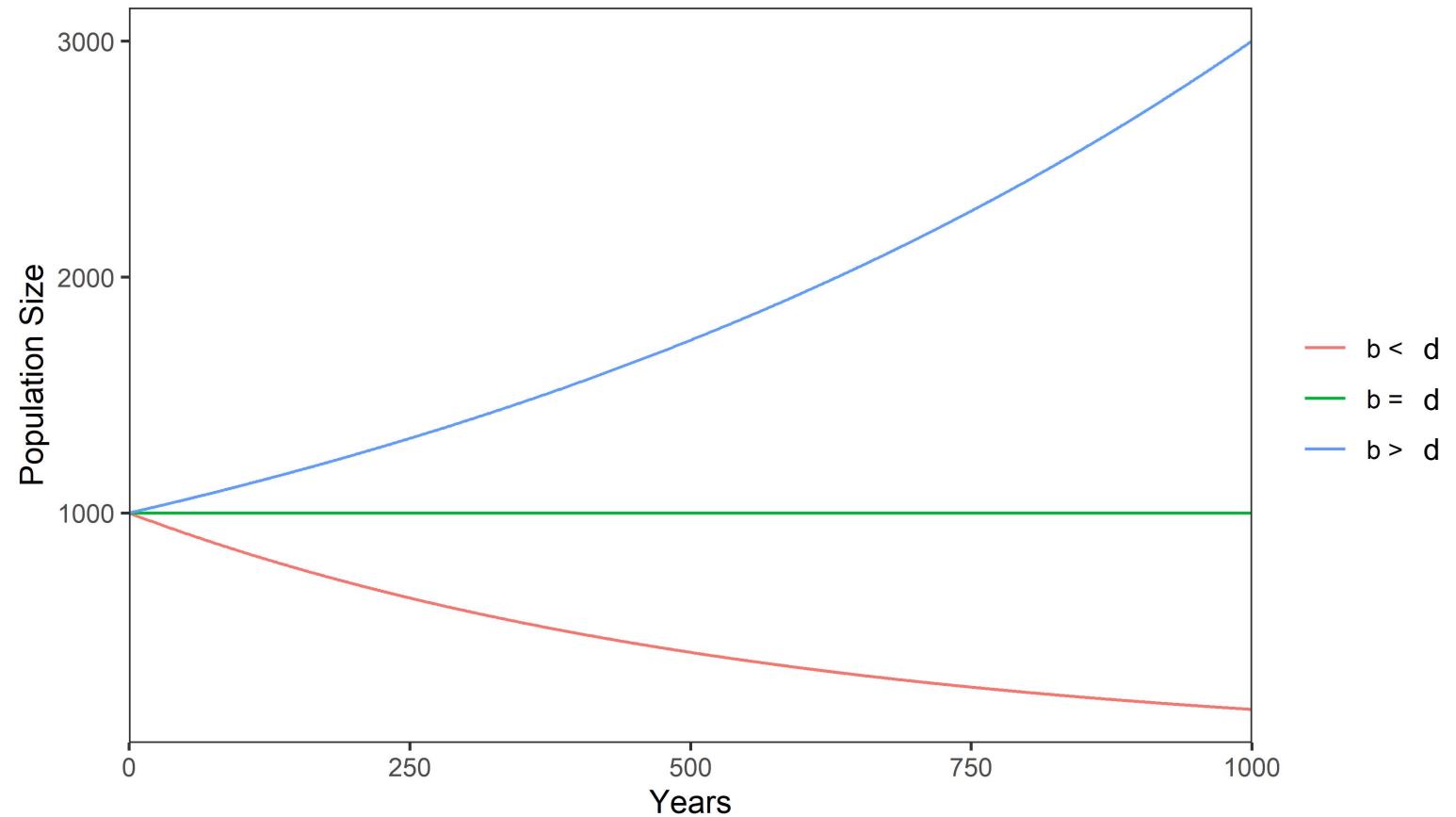
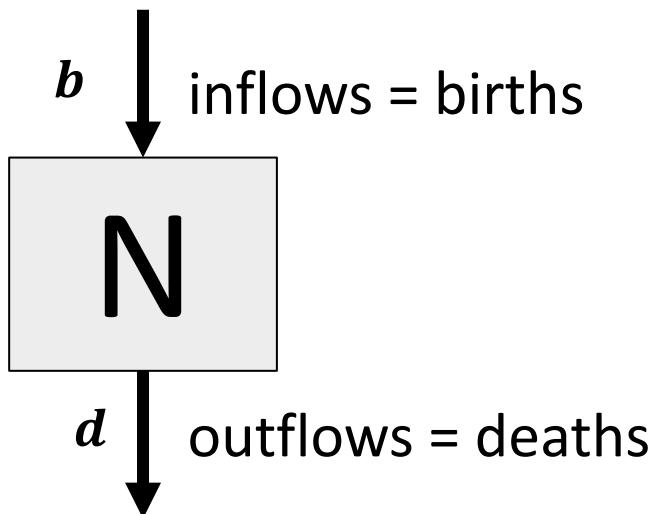
Adding demography: SIR w/ births & deaths

First consider modeling demography outside of an ID model.



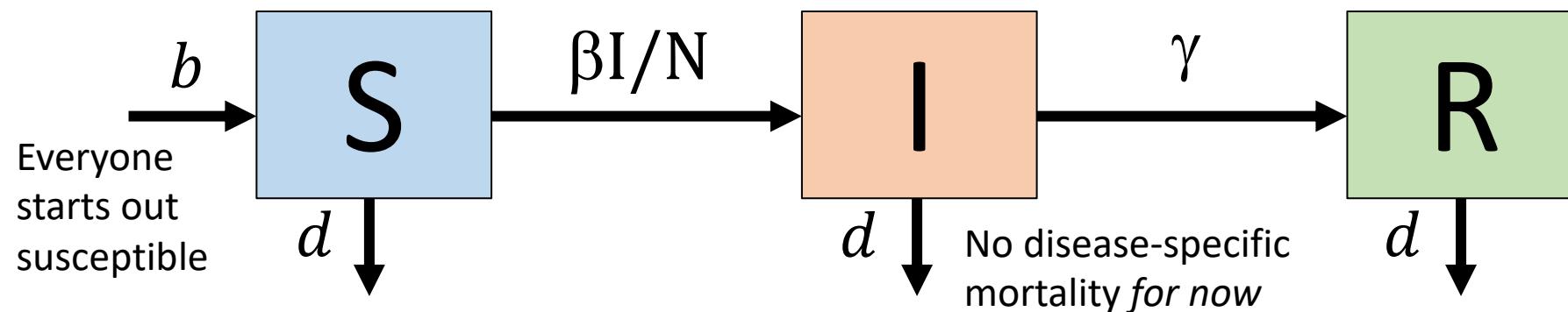
Adding demography: SIR w/ births & deaths

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.



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

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

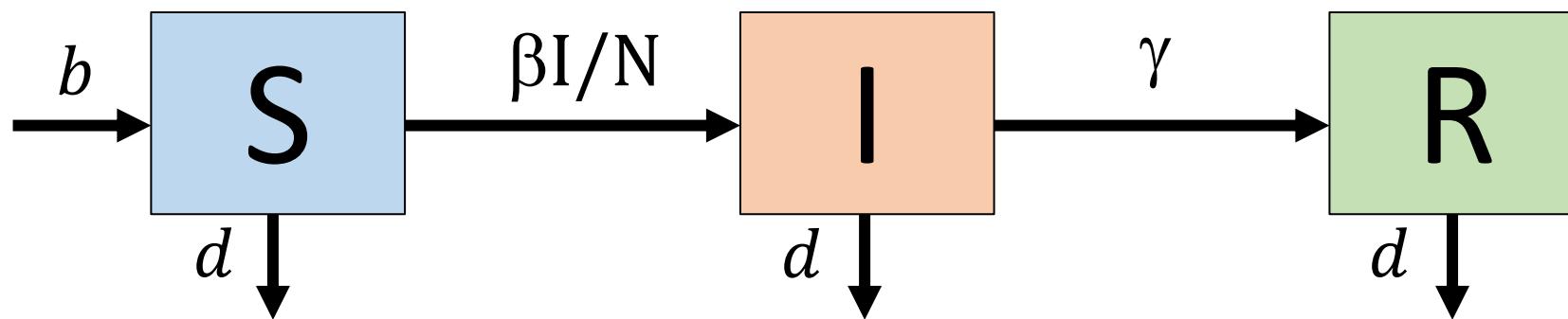
$$\frac{dR}{dt} = \gamma I - dR$$

Often, set $b = d$ for simplicity

But – incorporating growing/shrinking populations can be more realistic

Adding demography: SIR w/ births & deaths

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



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

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

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

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

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))  
  })  
}
```

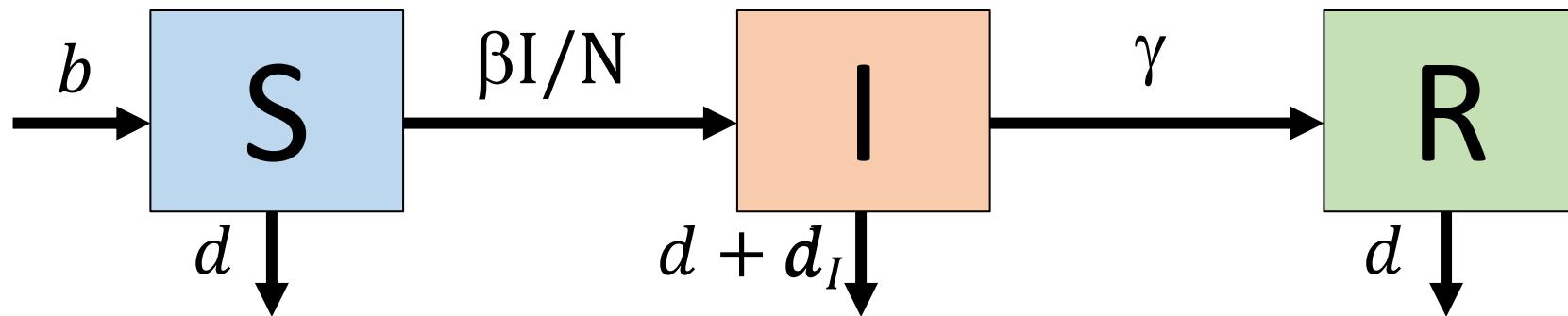
SIR with demography

```
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
- High case-fatality ratio
- Long duration of infection

R Session #2: SIR with demography

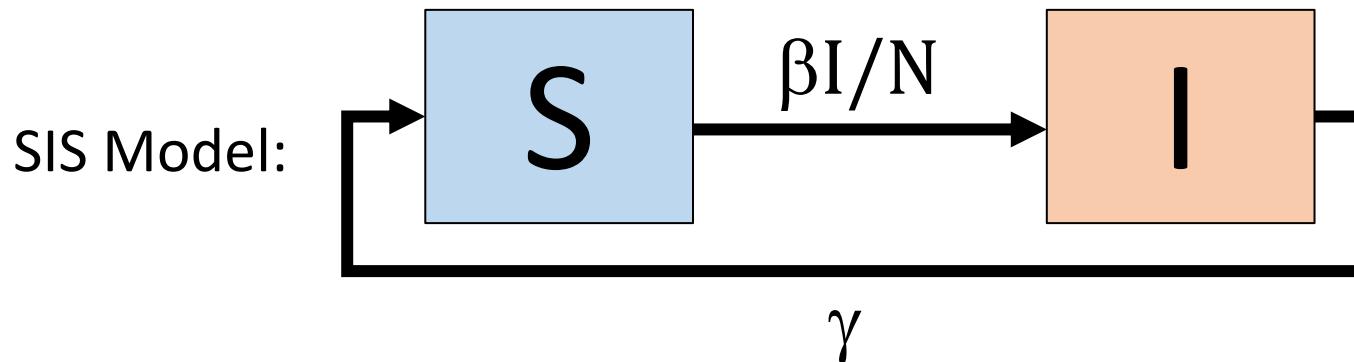
SIR with demography (births & deaths)

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?

Open SIR_demography.R

Infections without immunity

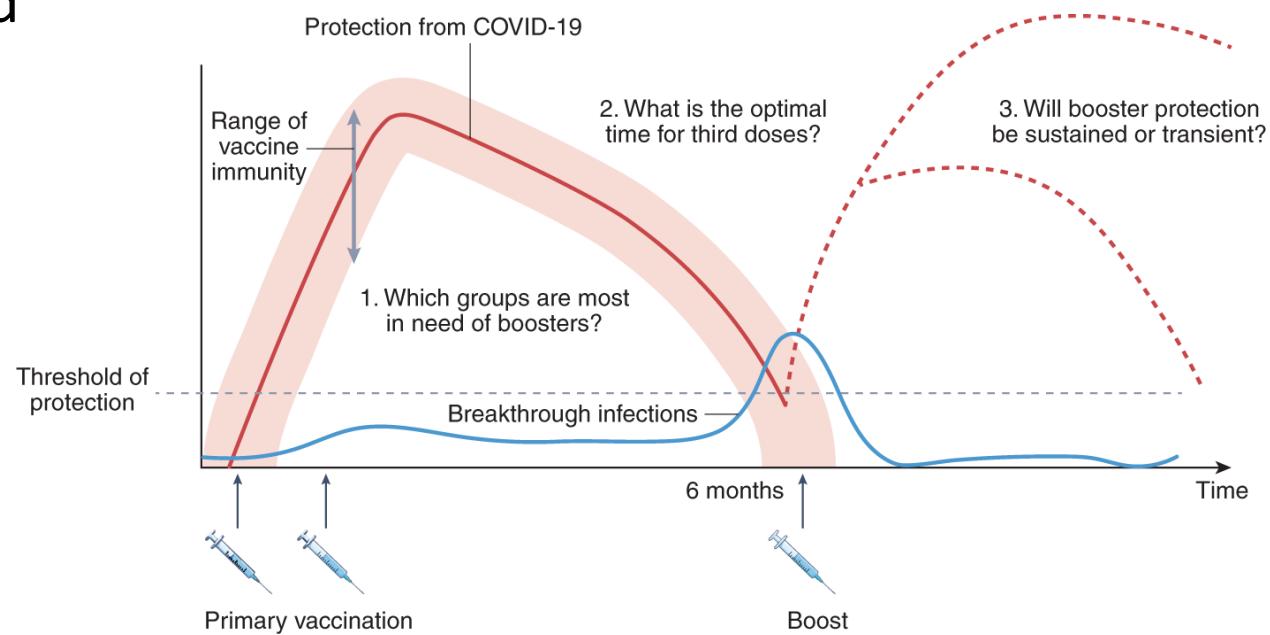
- How would you think about modeling this?



- 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

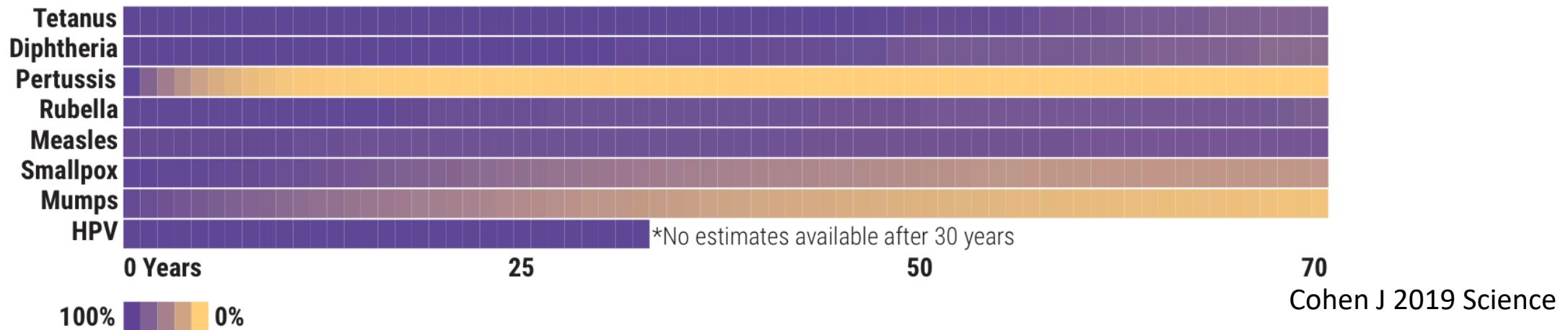
- Immunity elicited by initial infection and vaccination decreases over time
- What determines the rate of waning immunity?
 - Host factors: age, underlying health condition, immunity induced by infection or vaccination
 - Vaccine factors: vaccine type, use of adjuvants, dose of vaccines
 - Pathogen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



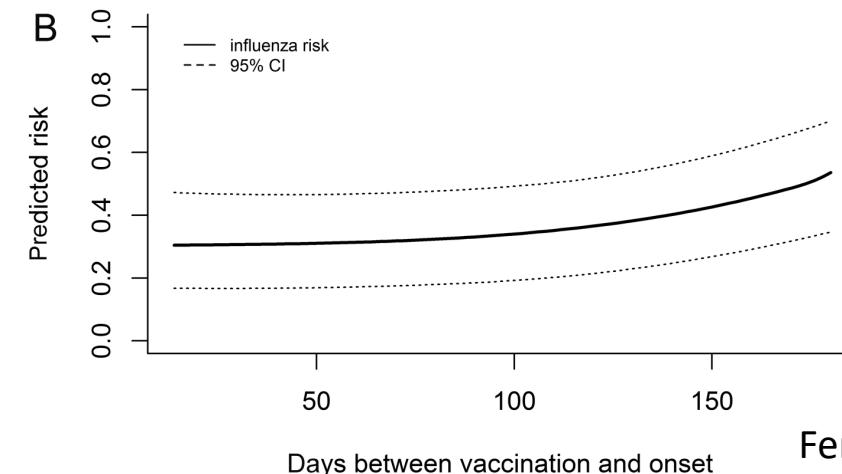
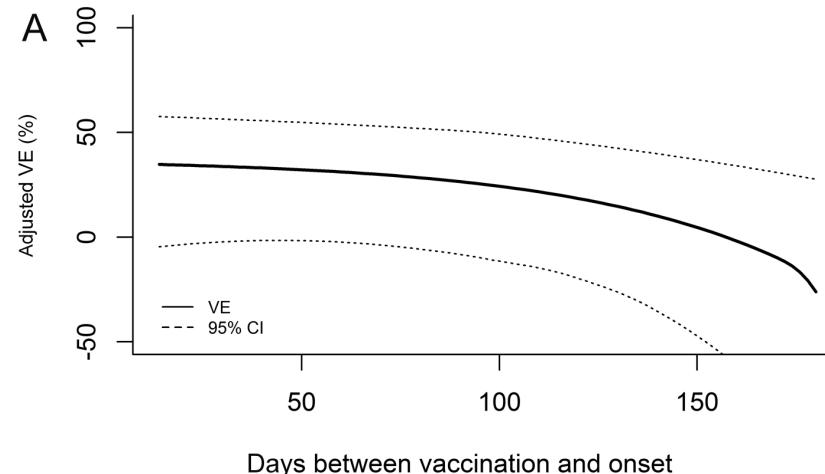
Juno JA Nature 2021

Waning immunity after vaccination - examples

< Variability in vaccine-induced immunity by disease >

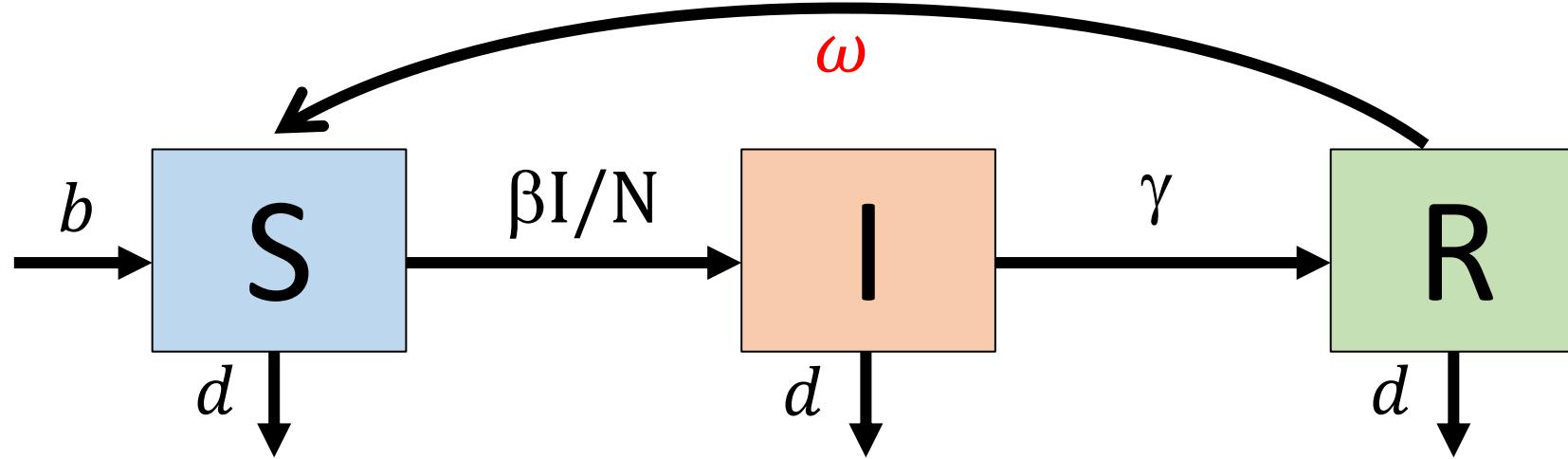


< Intra-seasonal measure of declining VE against influenza A(H3N2) >



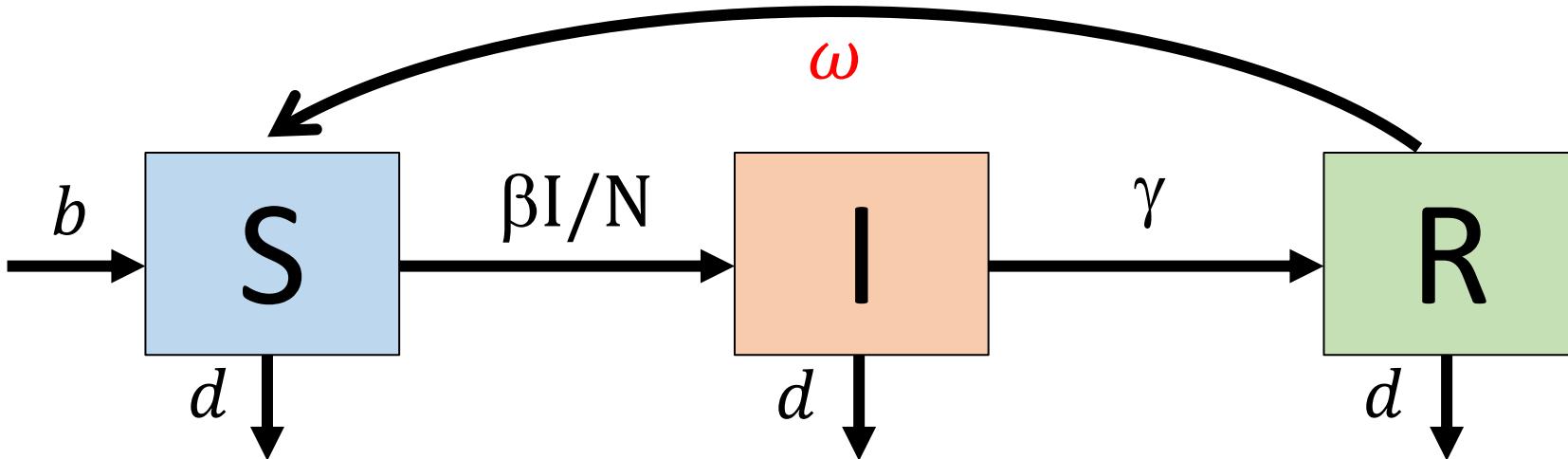
Adding waning immunity

- Here we brought back the SIR model with demographics.



- Adding a flow $R \rightarrow S$ to the SIR model allows immunity to wane
 - ω : 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

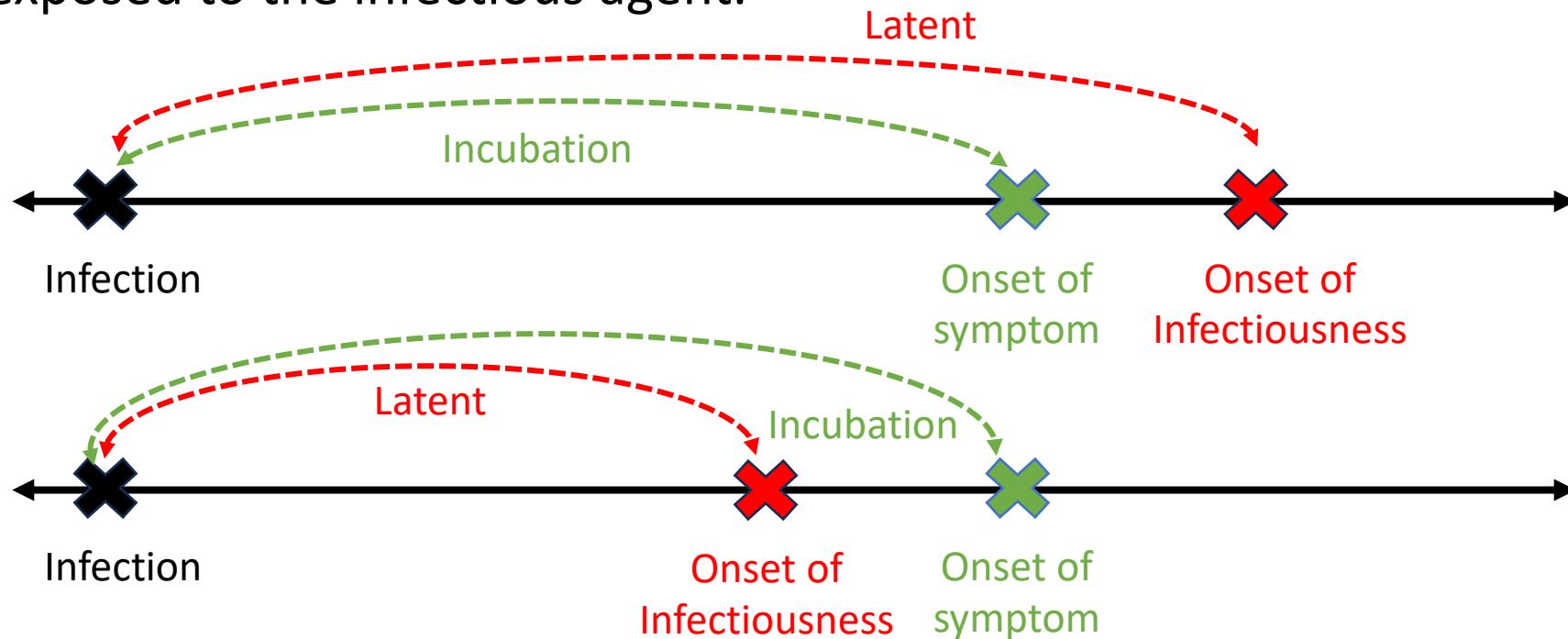
```
OpenSIRS<-function(t, state, parameters) {  
  with(as.list(c(state, parameters)), {  
    N = S + I + R  
  
    #SIR w/ demography equations from lecture  
    dS <- -beta*S*I/N + birth*N - death*S + omega*R  
    dI <- beta*S*I/N - death*I - gamma*I  
    dR <- gamma*I - death*R - omega*R  
 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

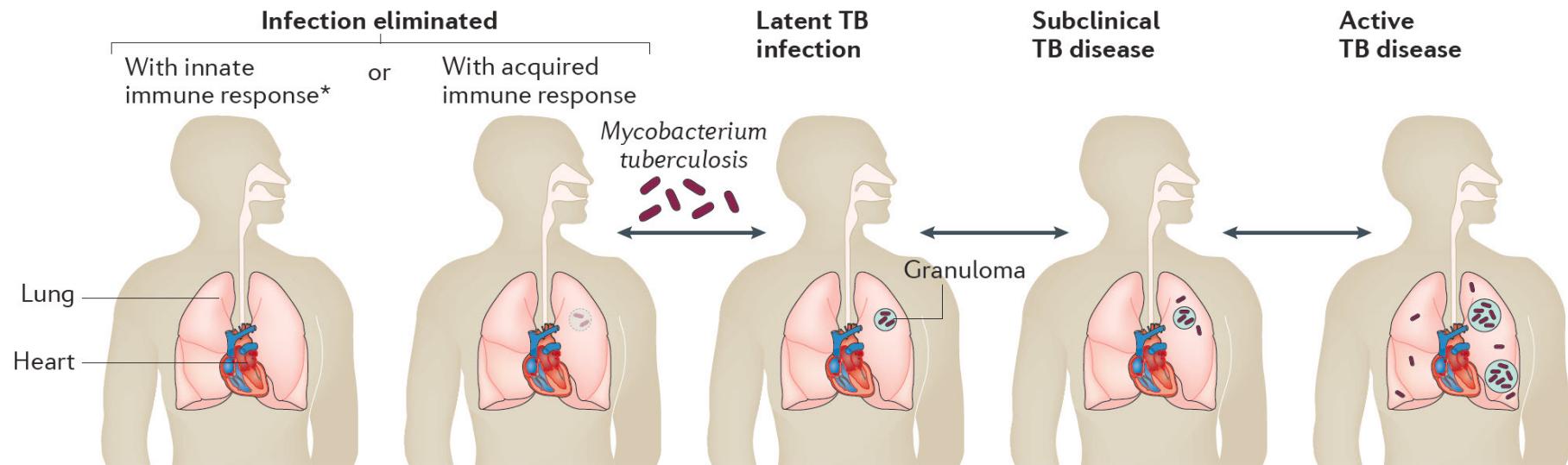
Incubation and latent period

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



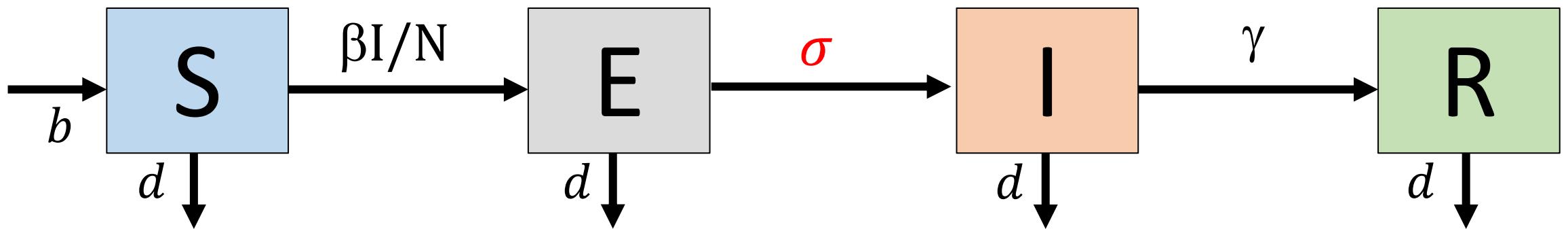
- Incubation period:** time interval between infection and the onset of clinical symptoms
- Latent period:** time interval between infection and becoming infectious

Latent vs. active TB infection



	Infection eliminated With innate immune response*	Infection eliminated With acquired immune response	Latent TB infection	Subclinical TB disease	Active TB disease
TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Adding latent period



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

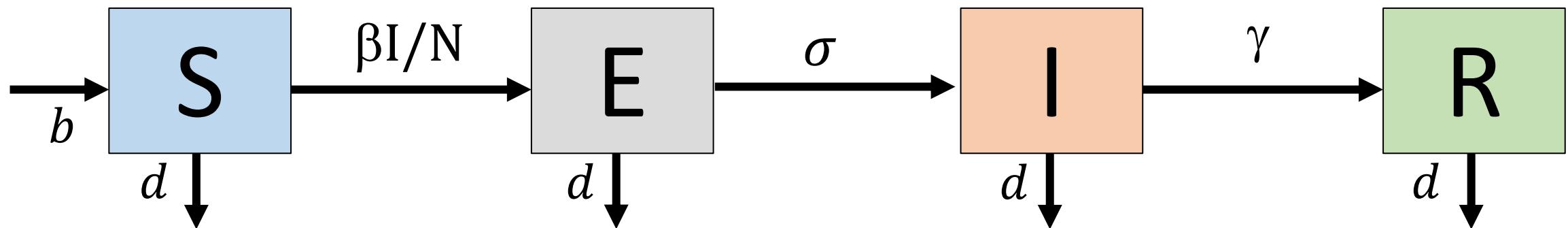
- $\sigma = 1/\text{latent period}$

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

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

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

Calculating R₀ in SEIR model



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

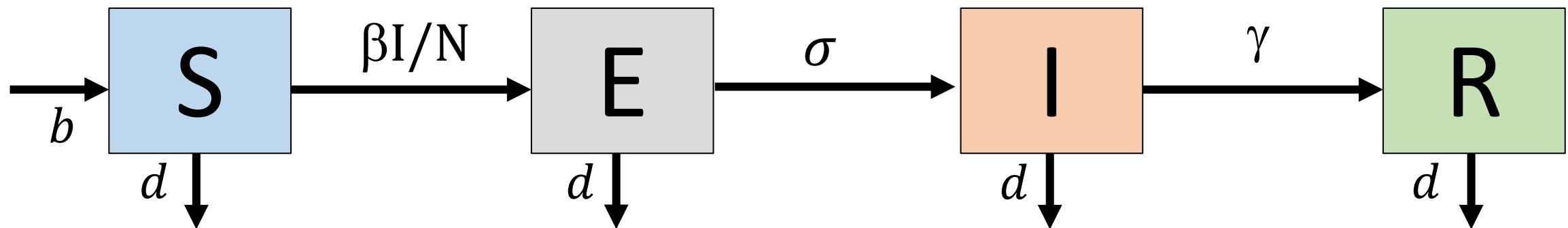
↗ Probability of surviving E

Duration of infectiousness

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

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

Calculating R₀ 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 R₀ 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

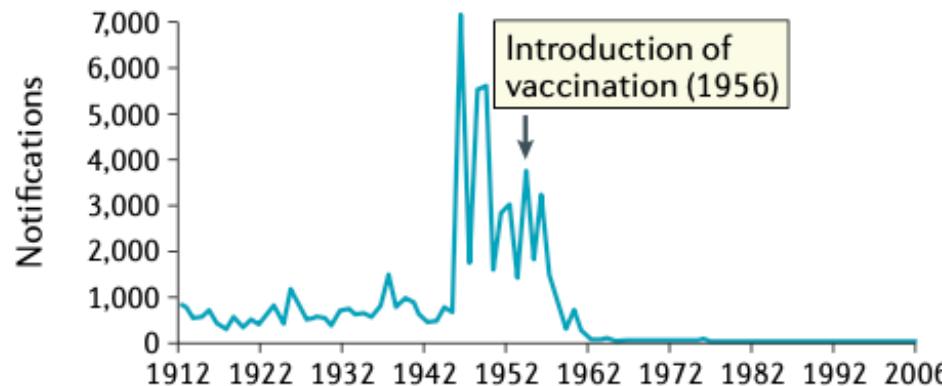
- Run SIRS model in R (waning immunity)
 - Q. How does the epidemic change as we change waning immunity?
 - Q. How does the epidemic change as we change both waning immunity and effective contact rate?
- Run SEIR model in R (latency)
 - Q. How does the epidemic change as we have longer latent period?

Controlling Infectious Diseases (1) Vaccines

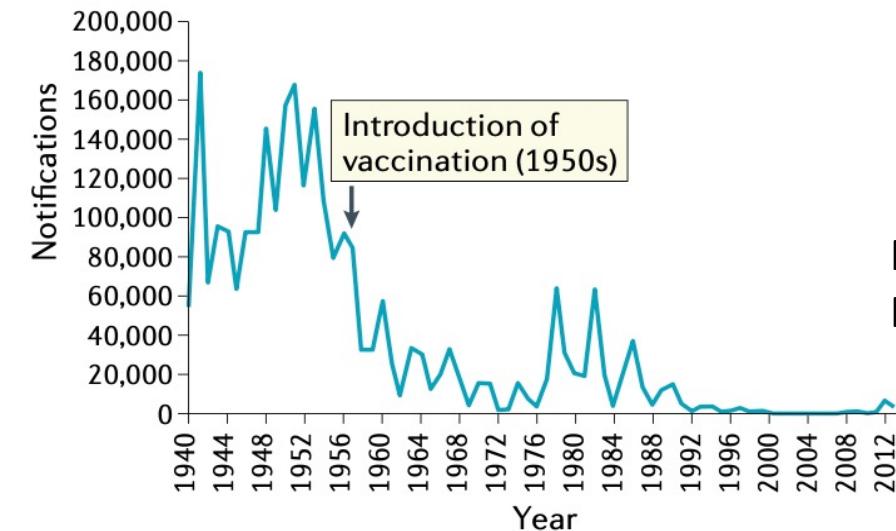
- Vaccination

- 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



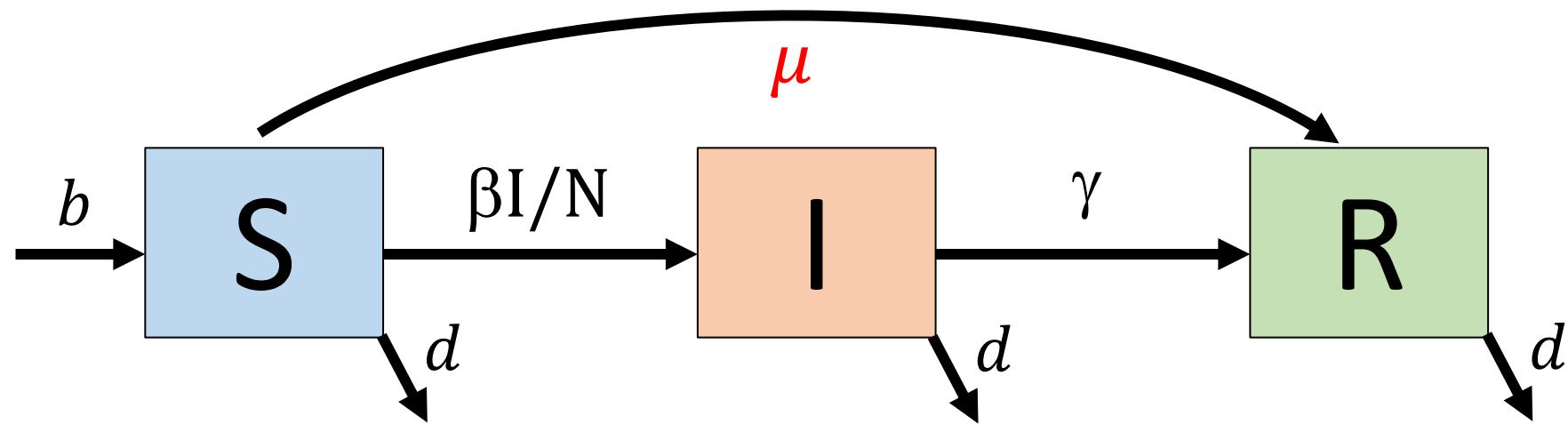
Pollard AJ Nature
Reviews 2021

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

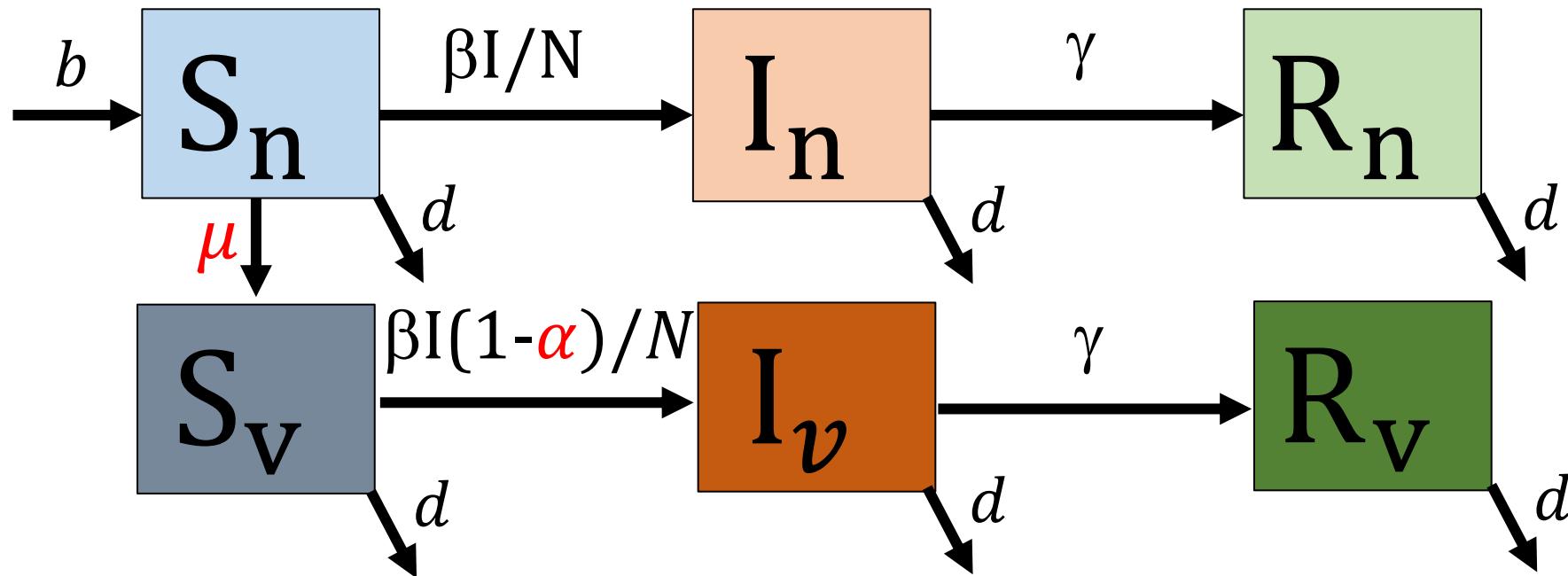
- Modeling vaccine effectiveness in different ways
 - If vaccine provides perfect immunity:



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

Controlling Infectious Diseases (1) Vaccines

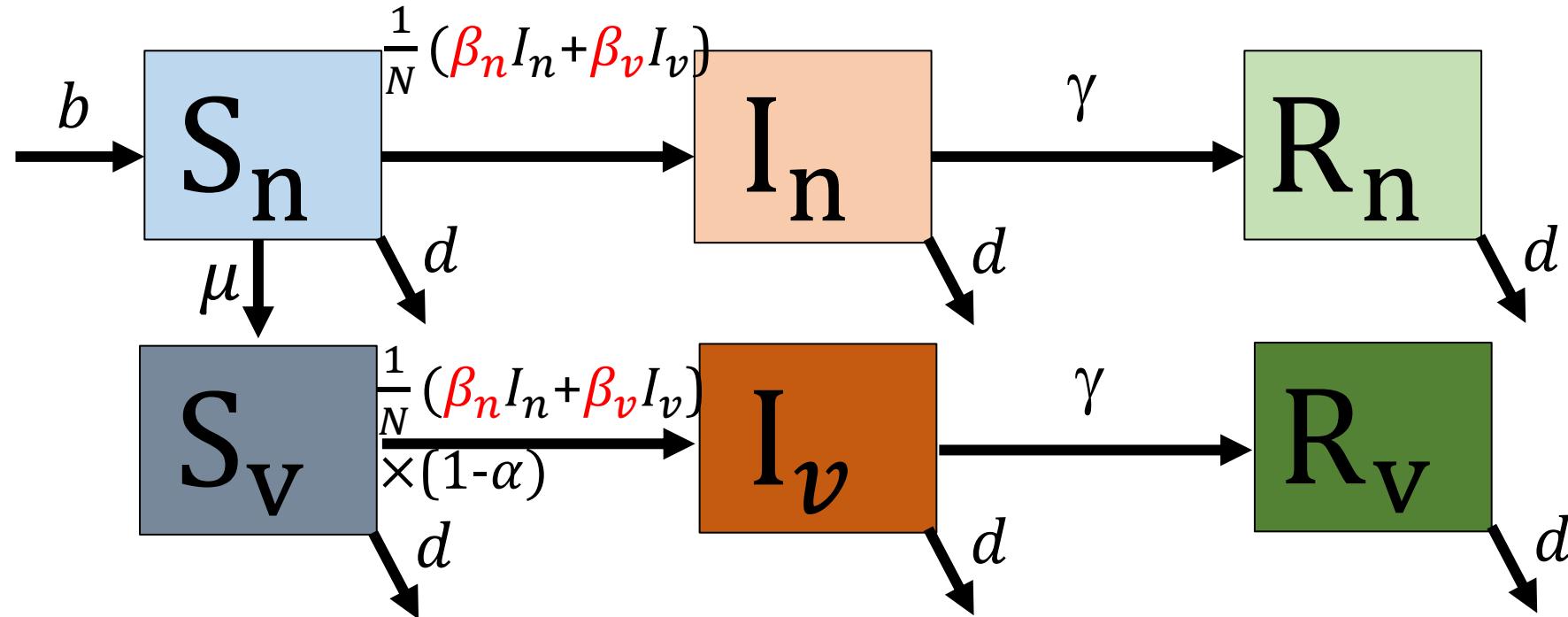
- Modeling vaccine effectiveness in different ways
 - If vaccine provides imperfect immunity for infection w/o change in infectiousness



- μ : rate of vaccination
- α : 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, # \n  
  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, # \
                  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, # \alpha
alpha = 0.3, #
q = 0.02 # quc)

-> Differential beta values (transmission rates) were applied to I_V and I_NotV

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?

Part 3: 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)

Assignment

Background: You are the chief health officer in the isolated city-state of Soundopolis, 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 Soundopolis 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.

Soundopolis' 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 Soundopolis, President Jamie Karlson, 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:

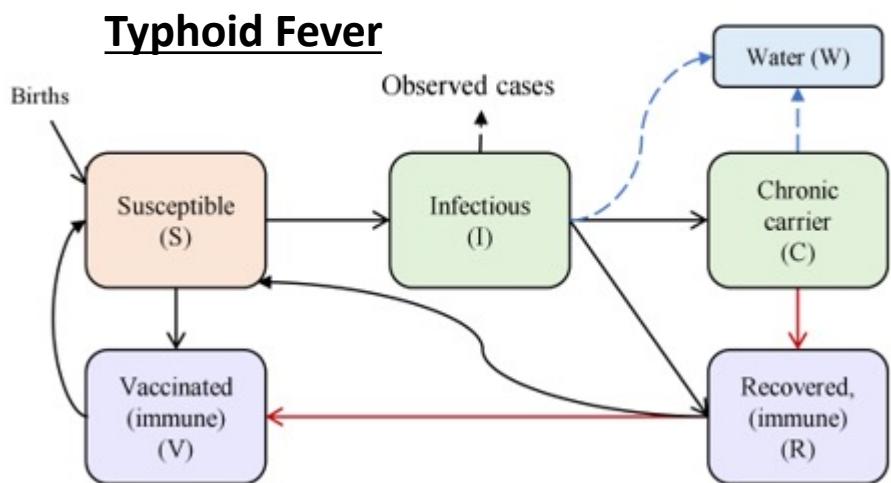
1. The cumulative number of infections absent intervention.
2. The likely size and the timing of the epidemic peak, so she can make appropriate decisions regarding treatment supply.

Extra Slides

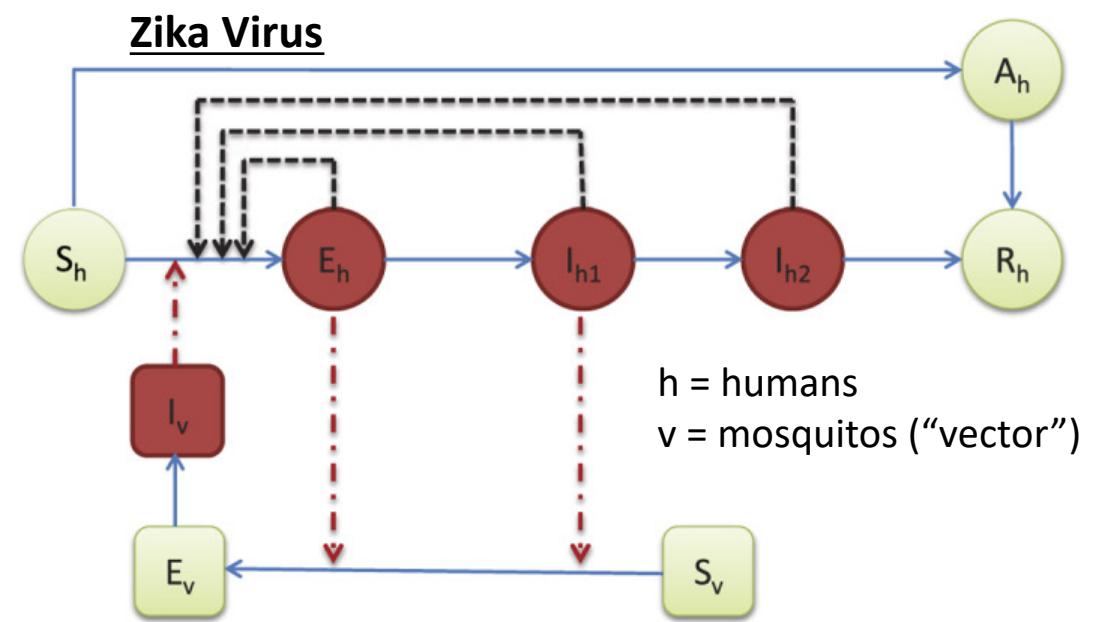
Vector-borne & environmental pathogens

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)

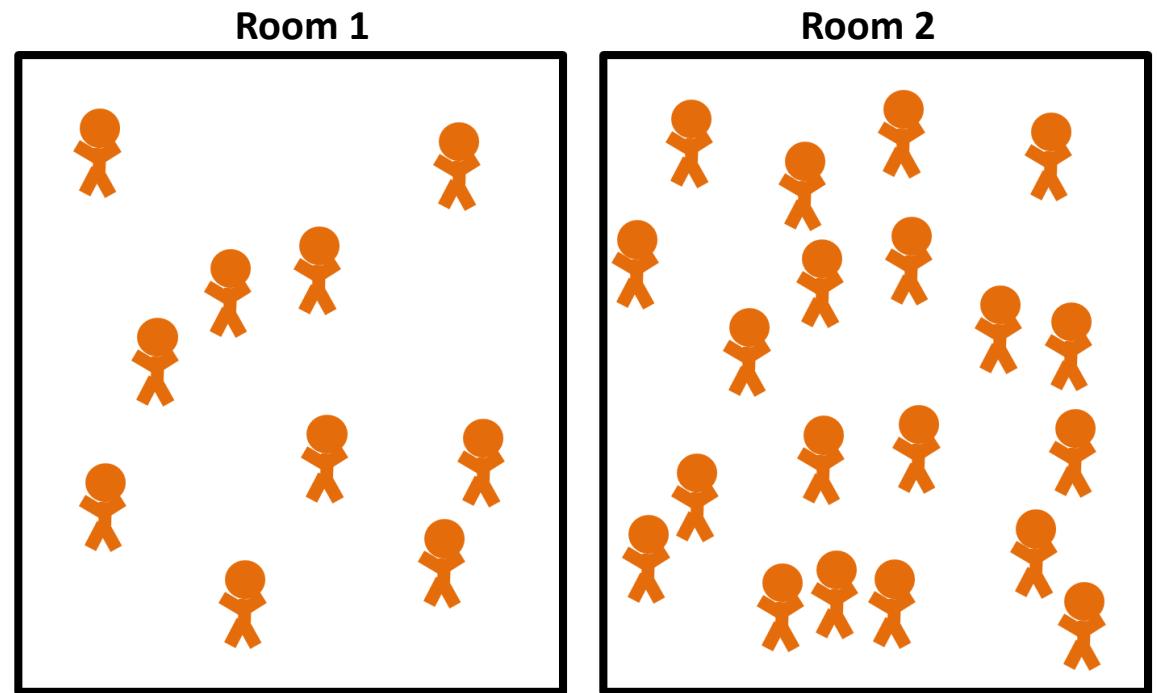
Frequency-dependency vs. density-dependency

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

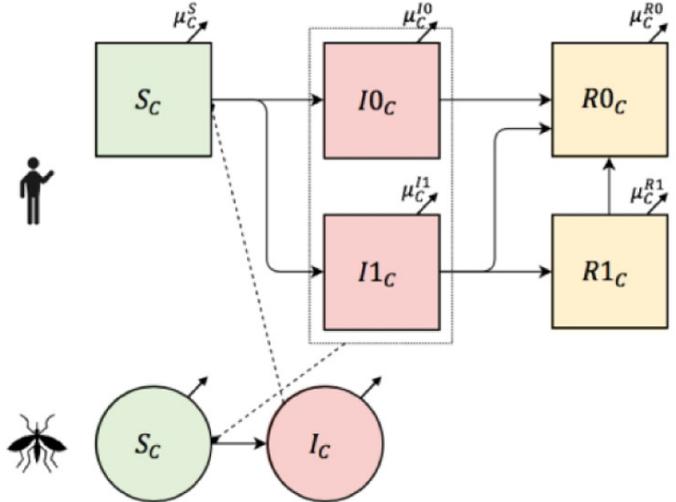
- $\lambda = \beta I$: product of beta and the number of people infected
- Some animal/plant diseases, modeling small populations



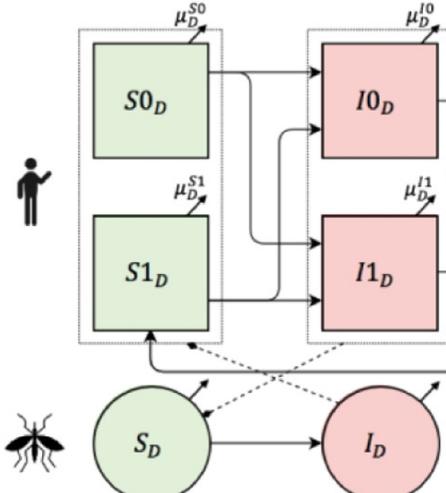
Multiple diseases

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

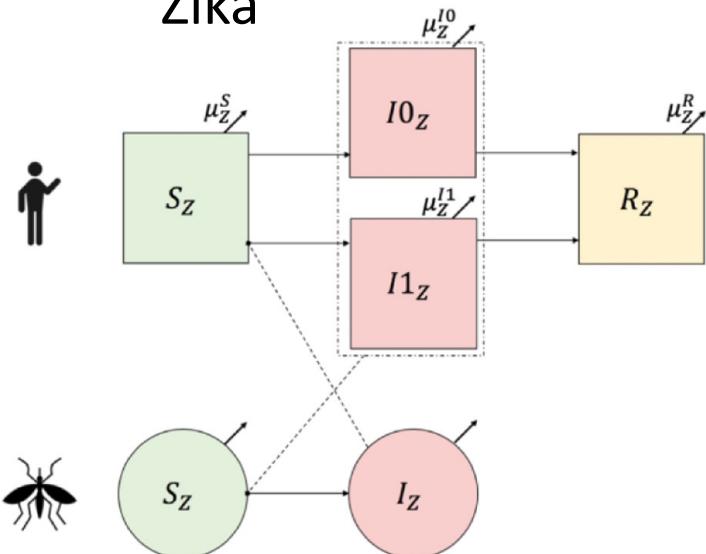
Chikungunya



Dengue



Zika



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

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

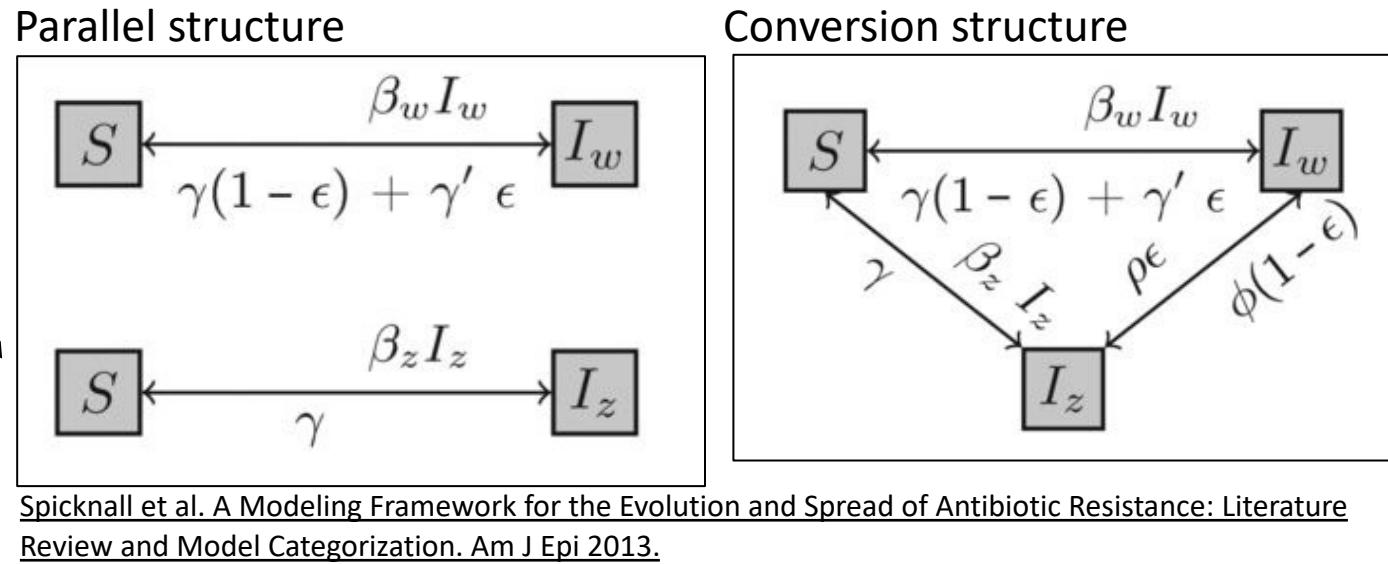
$$\mu_Z^{I0} = \mu I_{0Z} + \mu((HR_C - 1)I_{1C} + (HR_D - 1)I_{1D}) \frac{I_{0Z}}{T_Z}$$

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

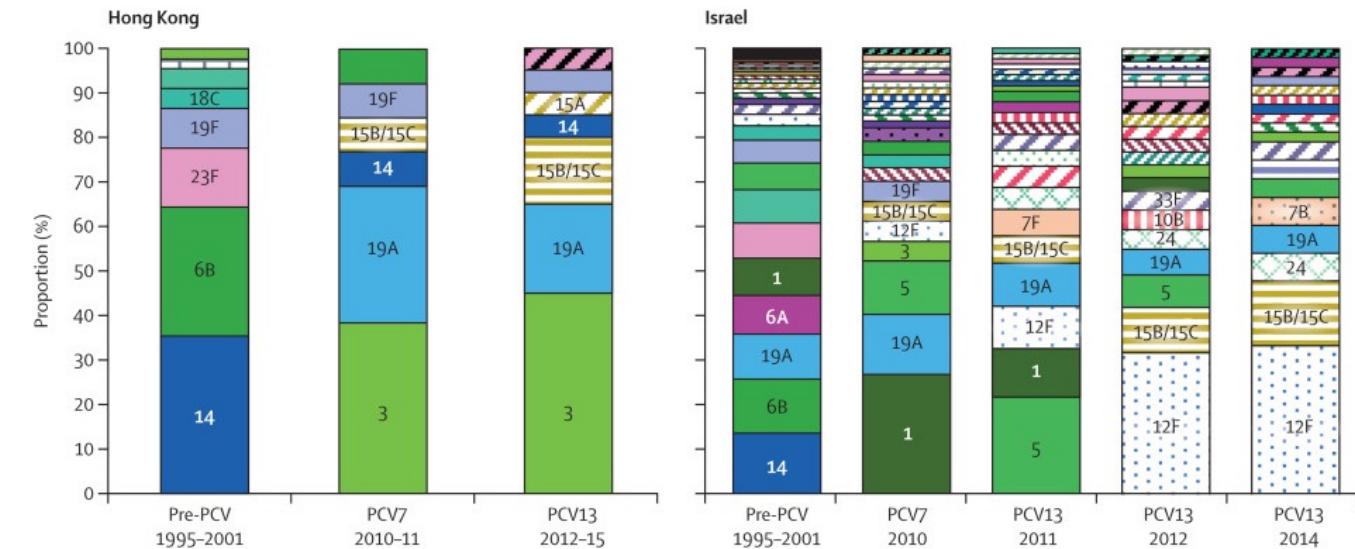
$$\mu_Z^R = \mu R_Z + \mu((HR_C - 1)I_{1C} + (HR_D - 1)I_{1D}) \frac{R_Z}{T_Z}$$

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.](#)

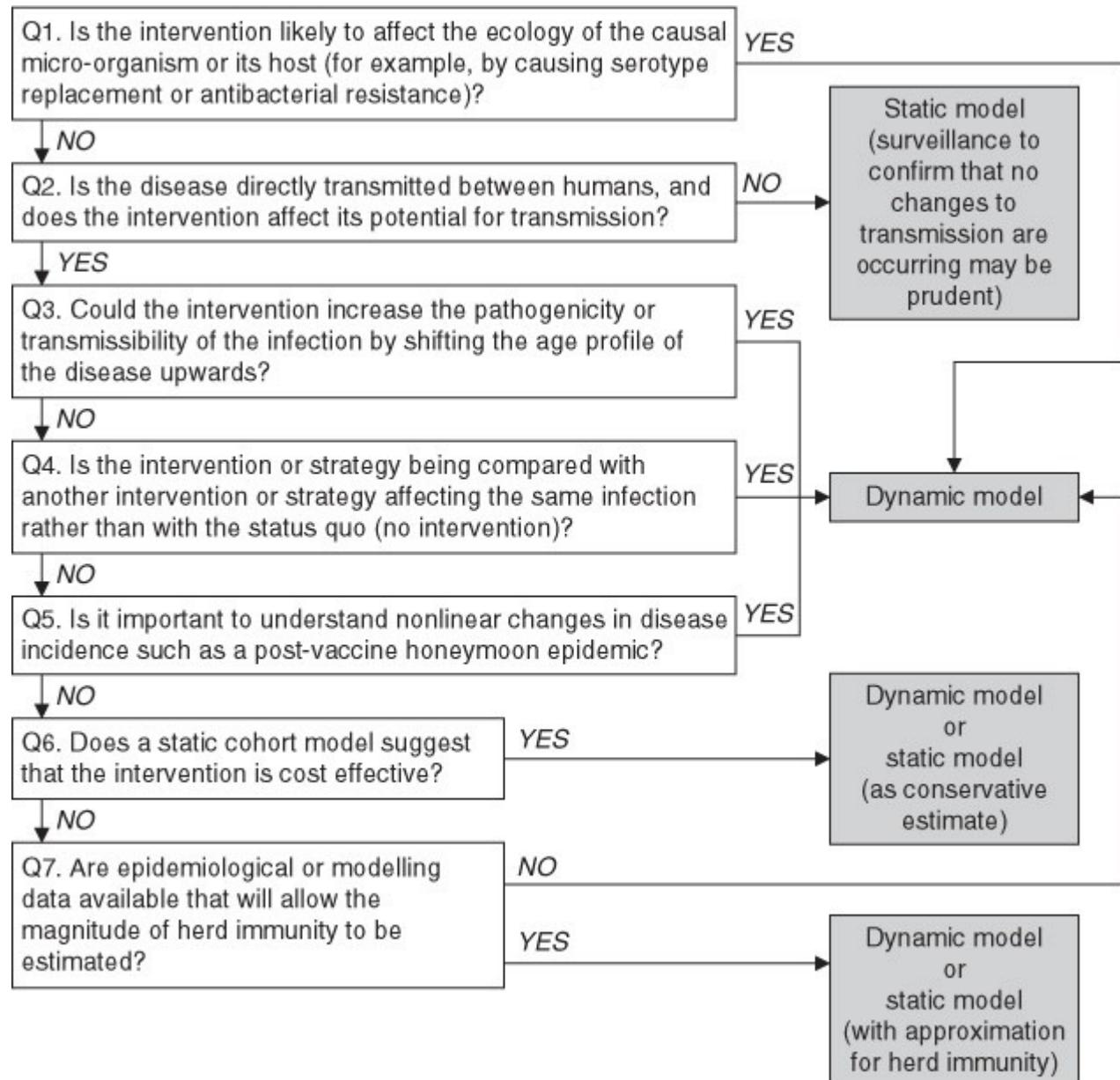


[Lo et al. Pneumococcal lineages associated with serotype replacement and antibiotic resistance in childhood invasive pneumococcal disease in the post-PCV13 era: an international whole-genome sequencing study. Lancet ID 2019.](#)

Static models

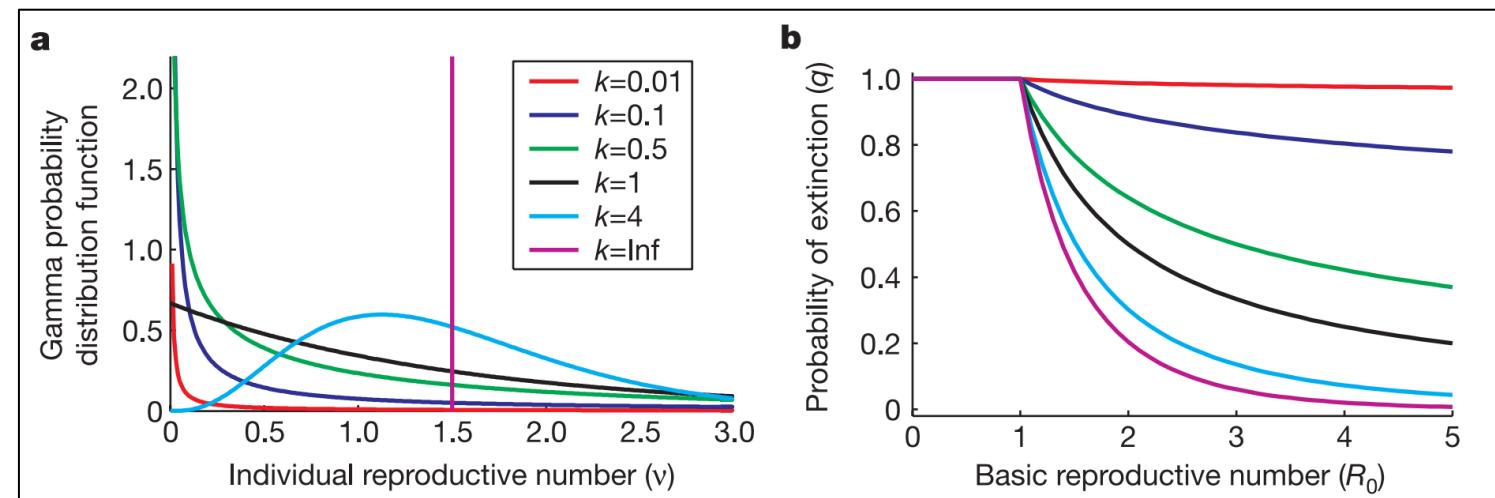
Static model types:

- 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



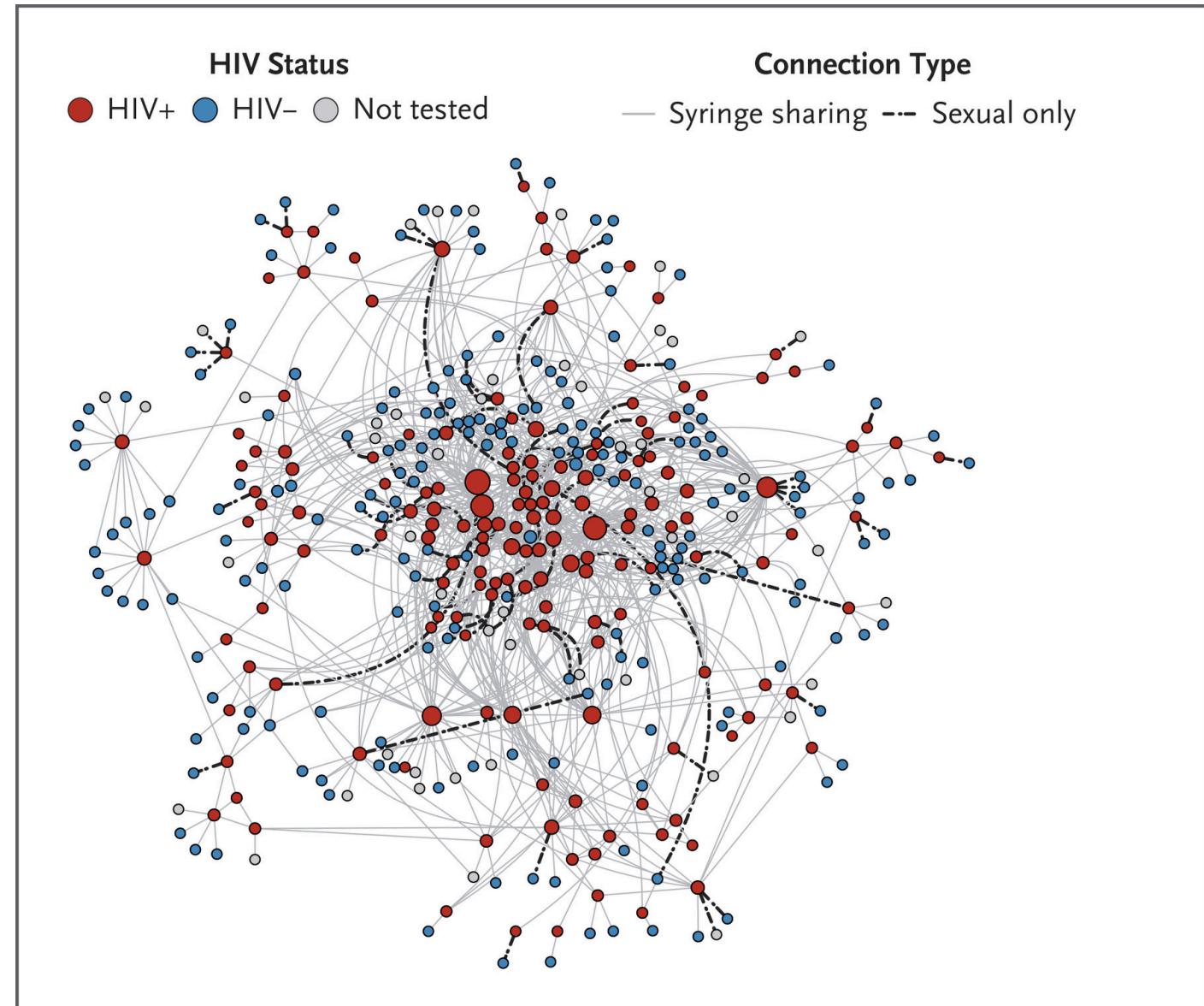
Individual-level stochastic models

- 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

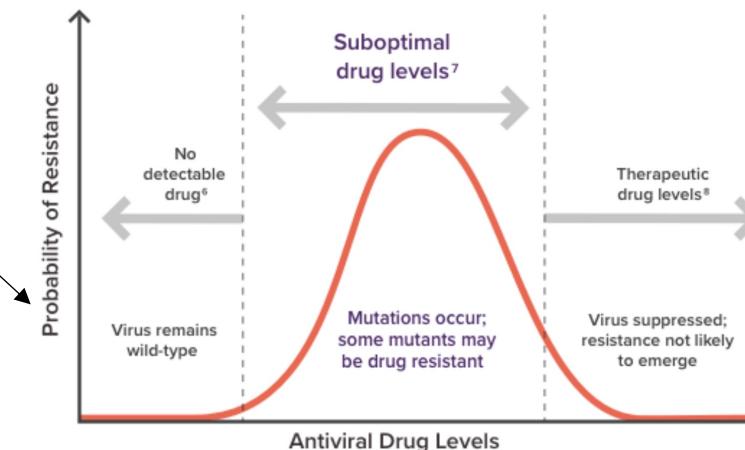
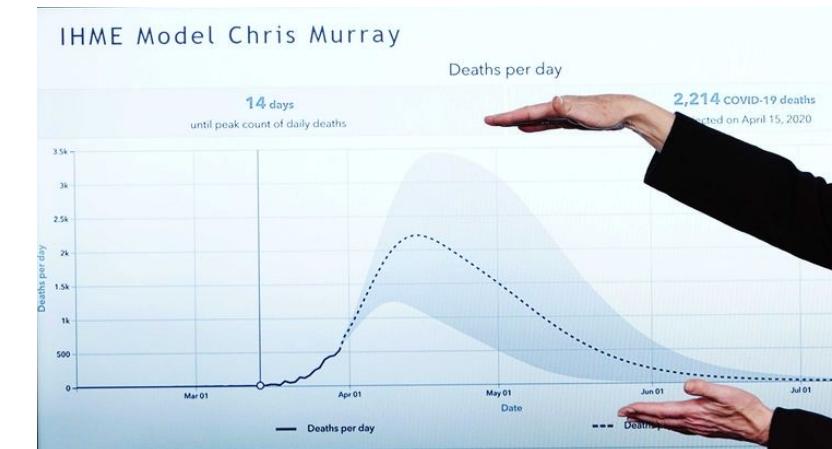
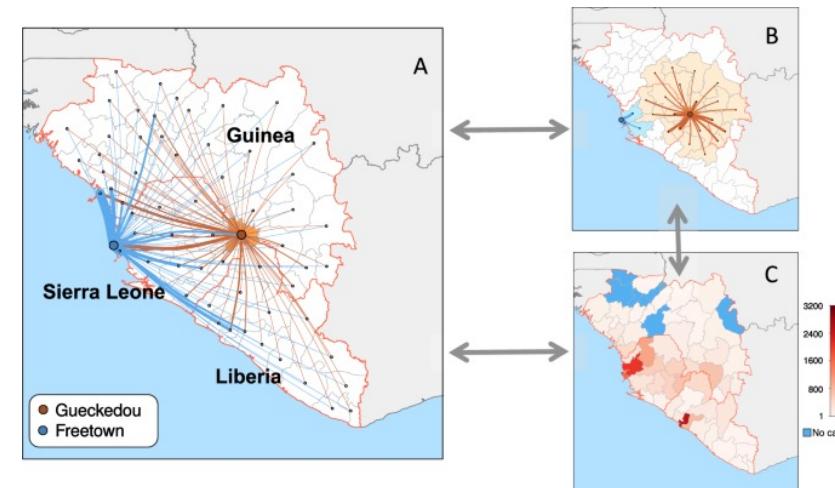
- Motivation
 - Very heterogeneous contact network that cannot be accommodated through a stratified compartmental model
 - Examples: STIs, needle-sharing, fine-scale spatial models
- Introductory resource:
[Keeling & Eames. Networks and epidemic models. J R Soc Interface. 2005.](#)



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):

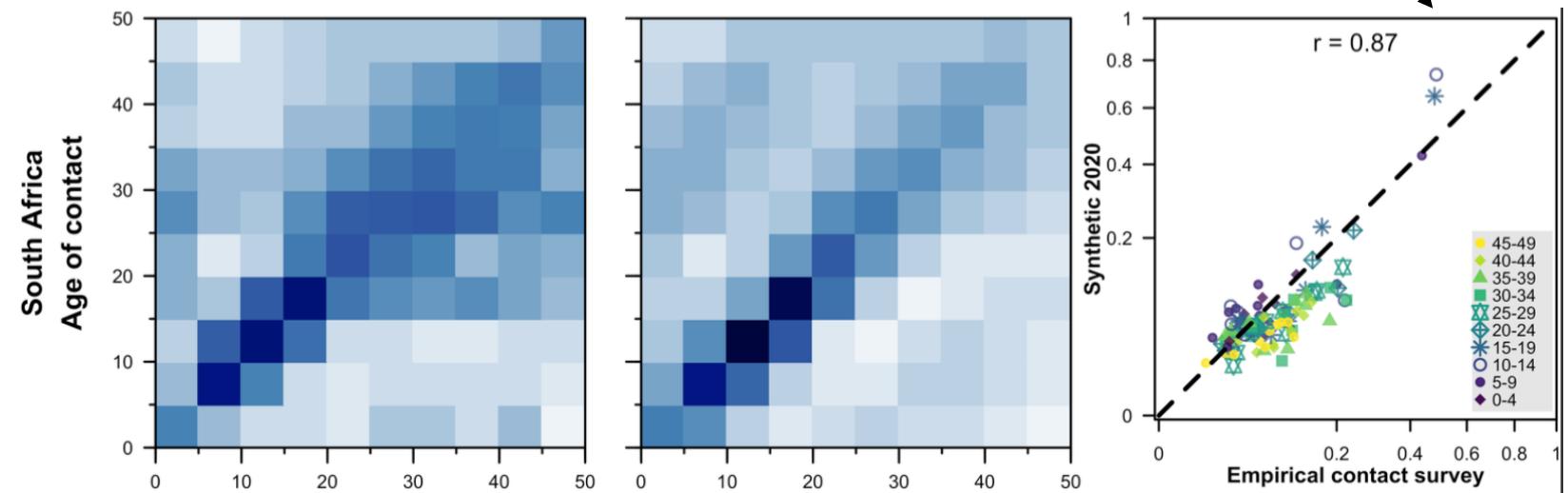
- [Menzies et al. Bayesian Methods for Calibrating Health Policy Models: A Tutorial. Pharmacoconomics 2017.](#)
- [Vanni et al. Calibrating Models in Economic Evaluation. Pharmacoconomics, 2012.](#)
- [Jackson et al. Calibration of Complex Models through Bayesian Evidence Synthesis: A Demonstration and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

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



Calculating R₀ in models other than SIR

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