Age-specific mortality and immunity patterns of SARS-CoV-2

Megan O’Driscoll

Introduction: IFR

- Infection fatality ratio (IFR) - the proportion of infected individuals that die from their infection

- This can translate the number of deaths to the total number of underlying infections (very helpful for viruses with lots of undetected infections!)
    - Total infections = Total deaths / IFR

- Used in epidemiological modelling to estimate mortality burdens, inform healthcare planning, etc.,.

Introduction: IFR of SARS-CoV-2

- Very clear trend of increasing severity with age

- Complicated by large burdens of SARS-CoV-2 in nursing homes, with very different dynamics than general population
    - Greater frailty
    - Potential for much higher attack rates

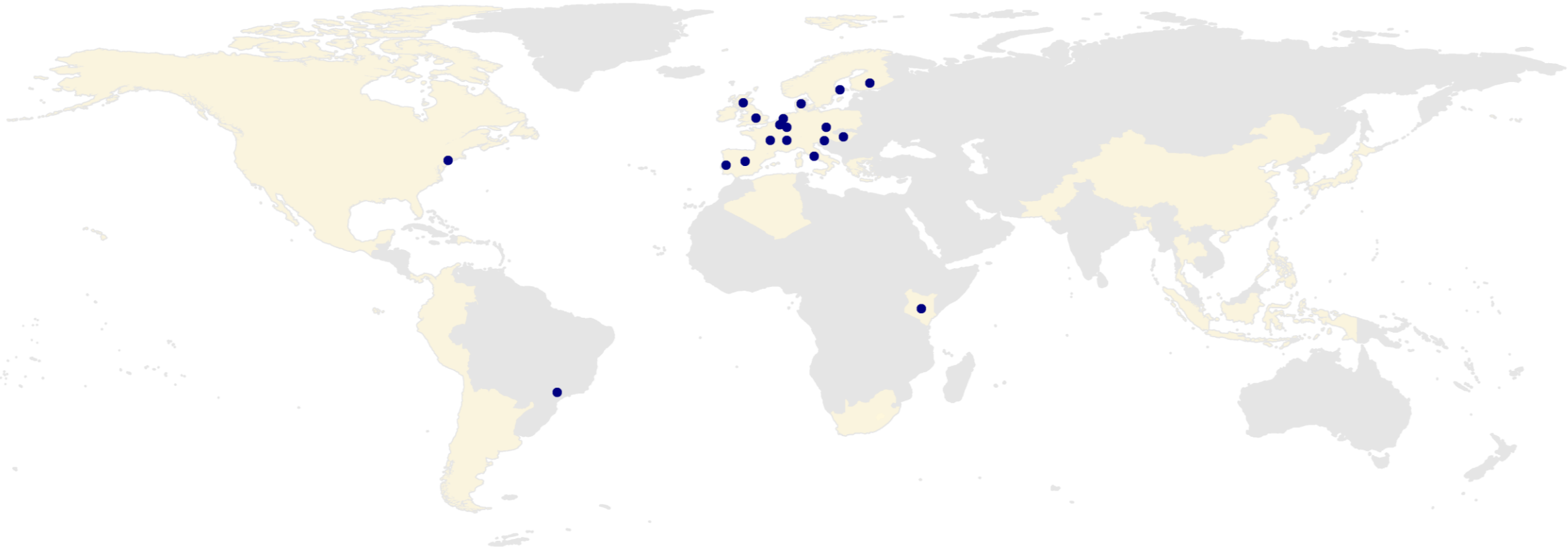
- Other factors to consider when assessing the IFR:
    - Accurate reporting of deaths
    - Prevalence of comorbidities
    - Access to healthcare
    - Quality of healthcare

Key Questions

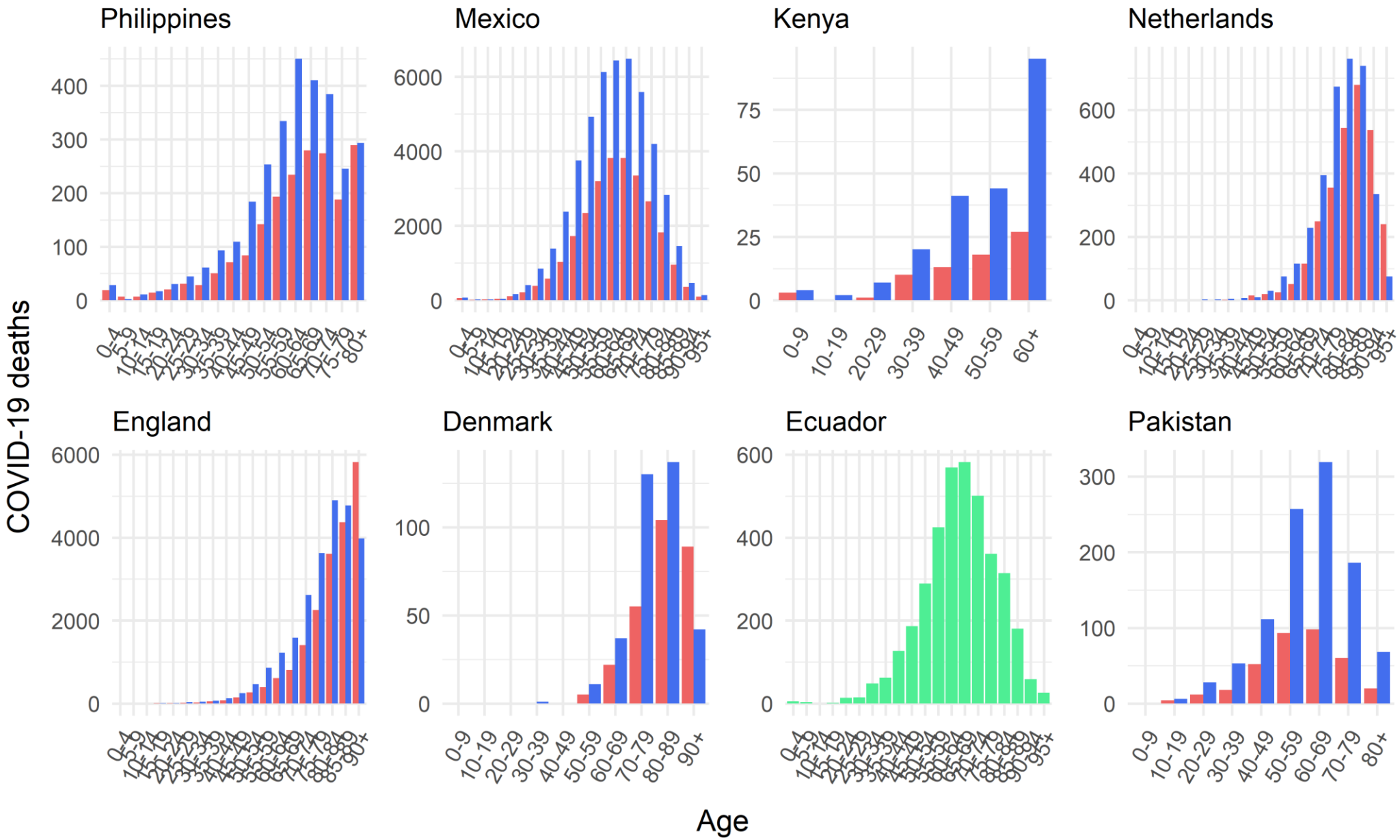
- How consistent is the age-distribution of COVID-19 deaths across countries?
- What does seroprevalence data suggest about the IFR of SARS-CoV-2?
  - Is this consistent across different studies or settings?
- How many people are likely to have been infected?

Data

- Age-specific COVID-19 death data from 45 countries
- 22 national-level seroprevalence surveys from 16 countries



Age Distributions



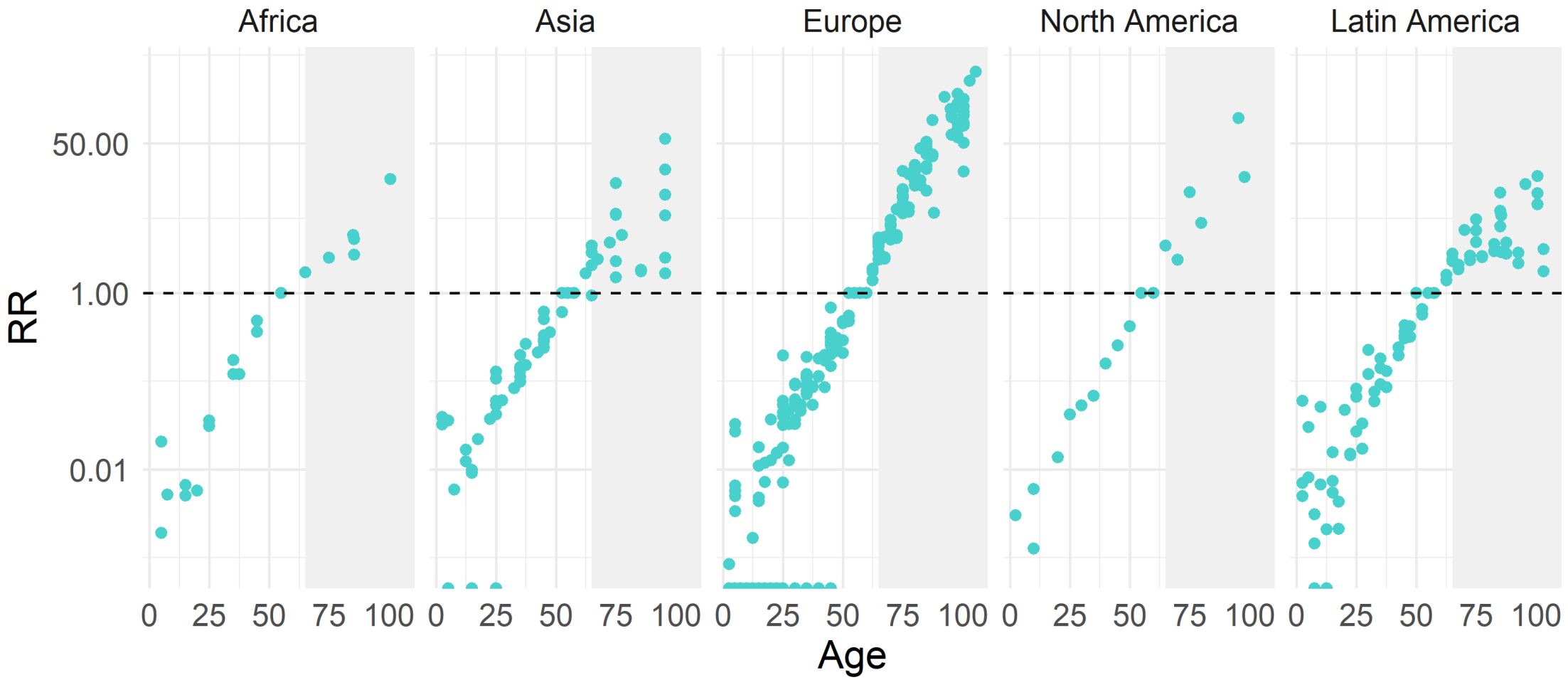
Relative Risks of death by age

To compare the age distribution of deaths across countries accounting for different population demographics we calculate a relative risk (RR) of death by age:

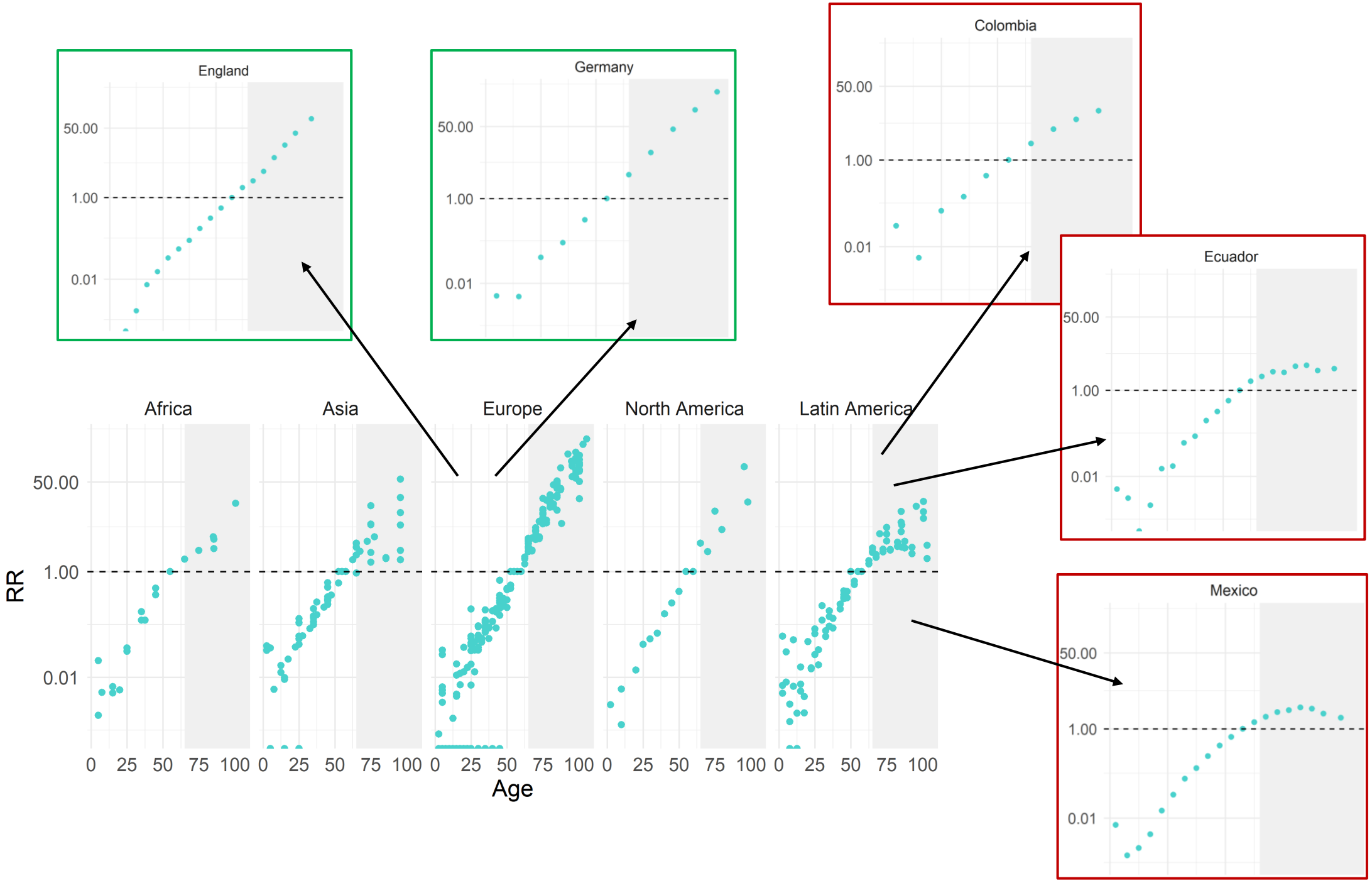
- Risk of death in age group *a,* relative to the risk of death in a reference age group

$$RR = \frac{deaths_a / population_a}{deaths_{ref} / population_{ref}}$$

Relative Risks of death by age



*note the log scale


England
Germany
Colombia
Ecuador
Mexico
Africa
Asia
Europe
North America
Latin America
RR
Age
50.00
1.00
0.01
0
25
50
75
100

Modelling methods

We developed a modelling framework to combine all the results of the available seroprevalence studies and the age-specific death data from all countries

- Fit exclusively to deaths <65 years
- Derived IFRs >65 using non-nursing home data from England
- Bayesian framework

Modelling methods

Inputs:

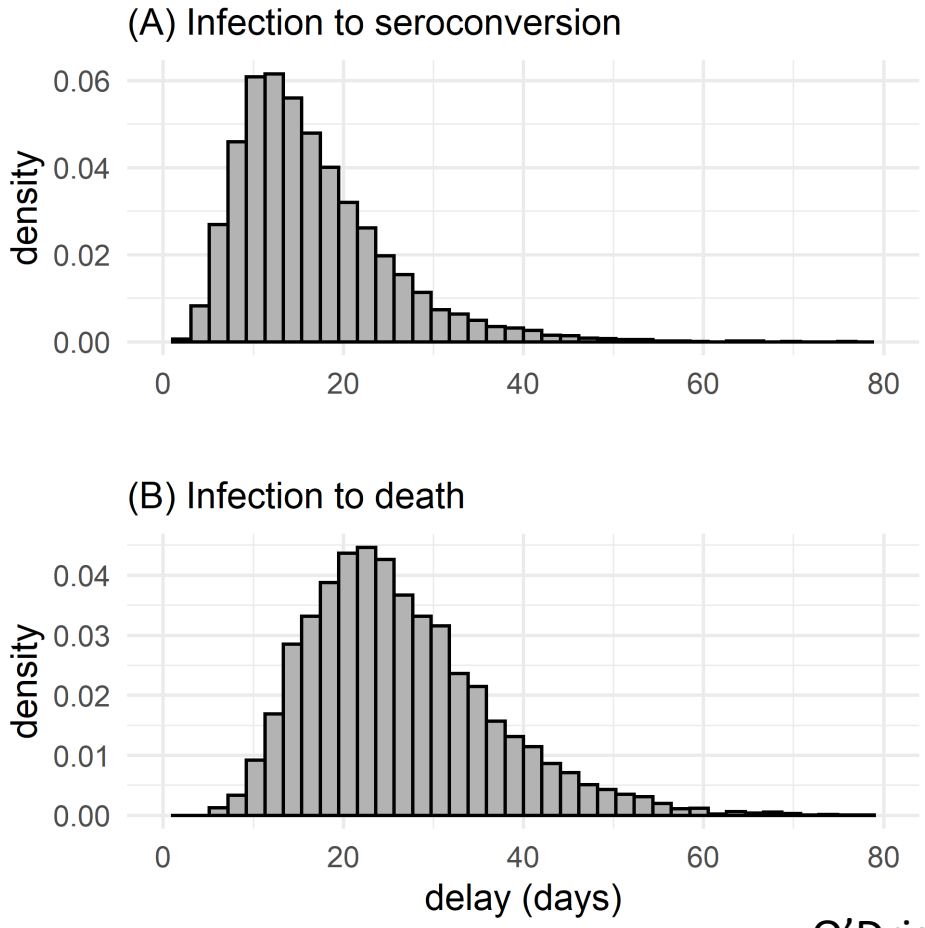
- 22 Seroprevalence studies
- Age-specific death data from 45 countries
- Time series of COVID-19 deaths from 45 countries

Outputs:

- Age-specific IFR estimates (global)
- Population IFR estimates for each country
- Estimates of the proportion infected in each country

Modelling methods

Used delay distributions to link the timing of death data and seroprevalence data



$$D_{c,a,s} = N_{c,a,s} \cdot \Lambda_c \cdot \delta_a \cdot IFR_{a,s}$$

$$\lambda_{c,t} = \Lambda_c \cdot \sum_{i=1}^{t} S_{c,i} \Big/ \sum_{i=1}^{T_c} D_{c,i}$$

O'Driscoll et al., *Nature* https://www.nature.com/articles/s41586-020-2918-0

Modelling methods

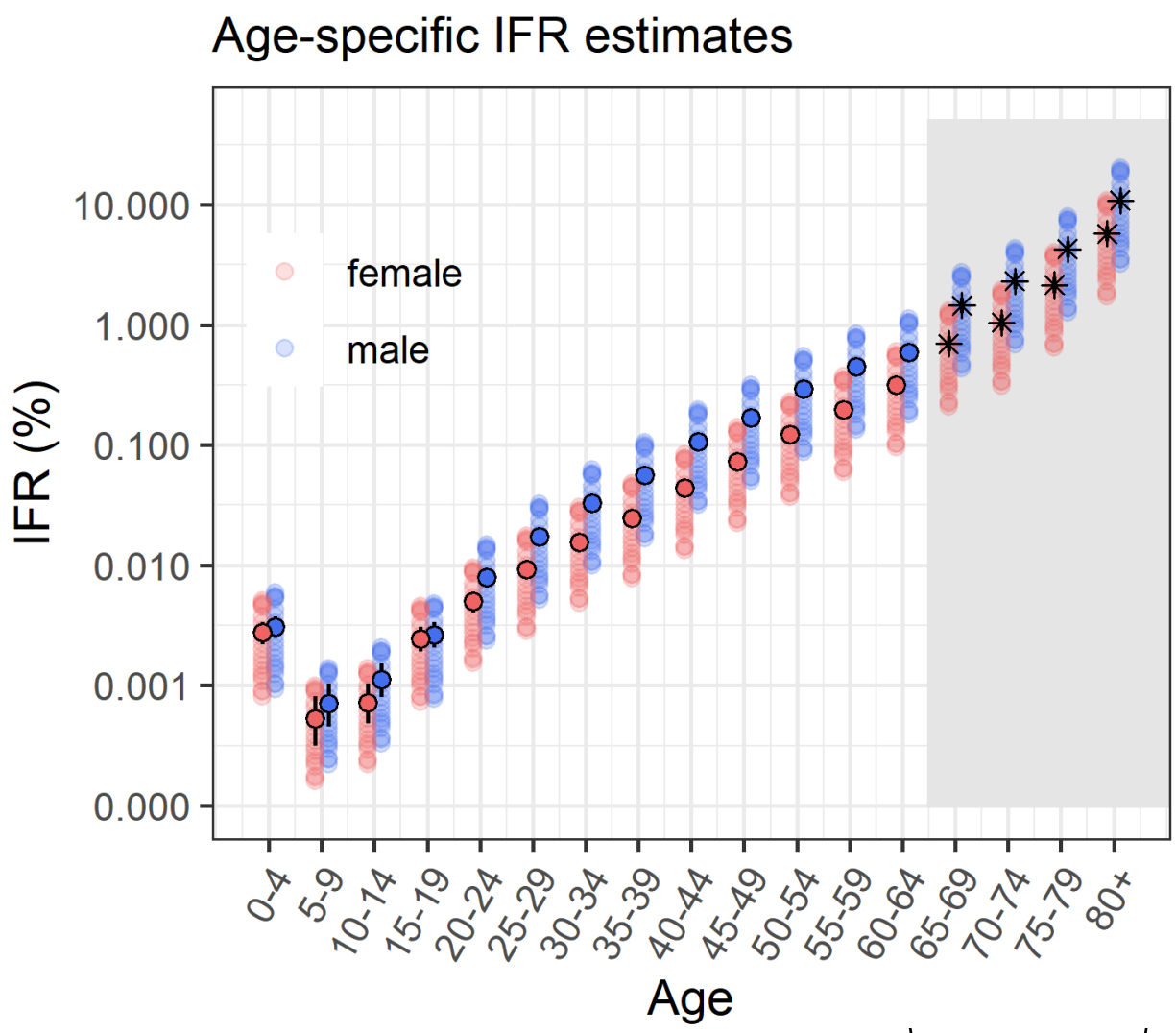
Additional Assumptions:

- Equal infection attack rates by age <65 years
- Relative infection attack rate of 0.7 in those >65 years
- Age distribution of deaths is constant in time

Modelling methods

- **Ensemble Model:**
  - Included all national-level death data & seroprevalence studies

- Individual country/seroprevalence study models

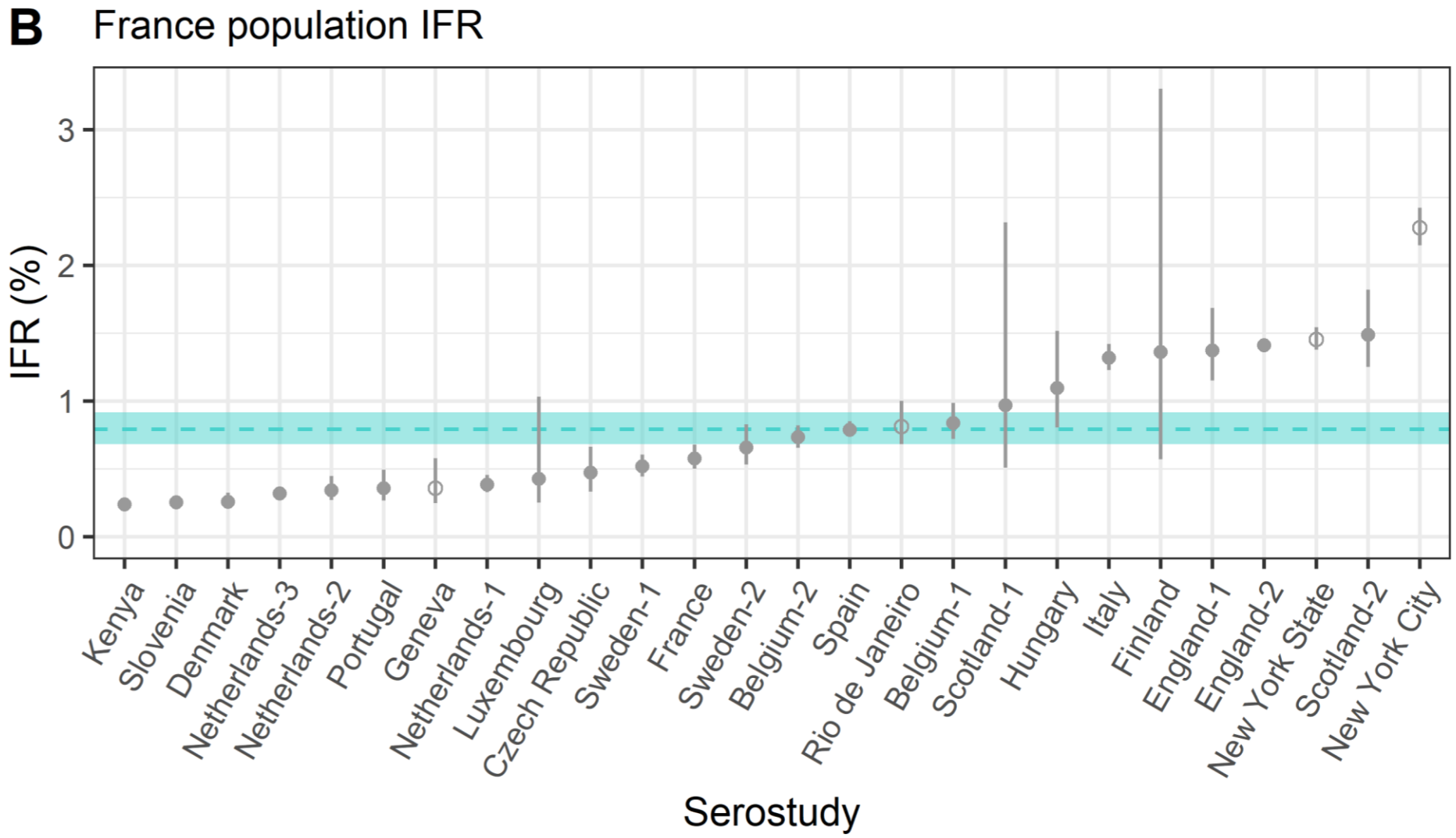


- Lowest IFR in 5-9 year olds:
  - 0.001% (0.000-0.001%)
- Highest IFR in 80+:
  - 8.29% (7.11-9.59%)
- Differences by sex increase with age

**Excluded from model fitting*

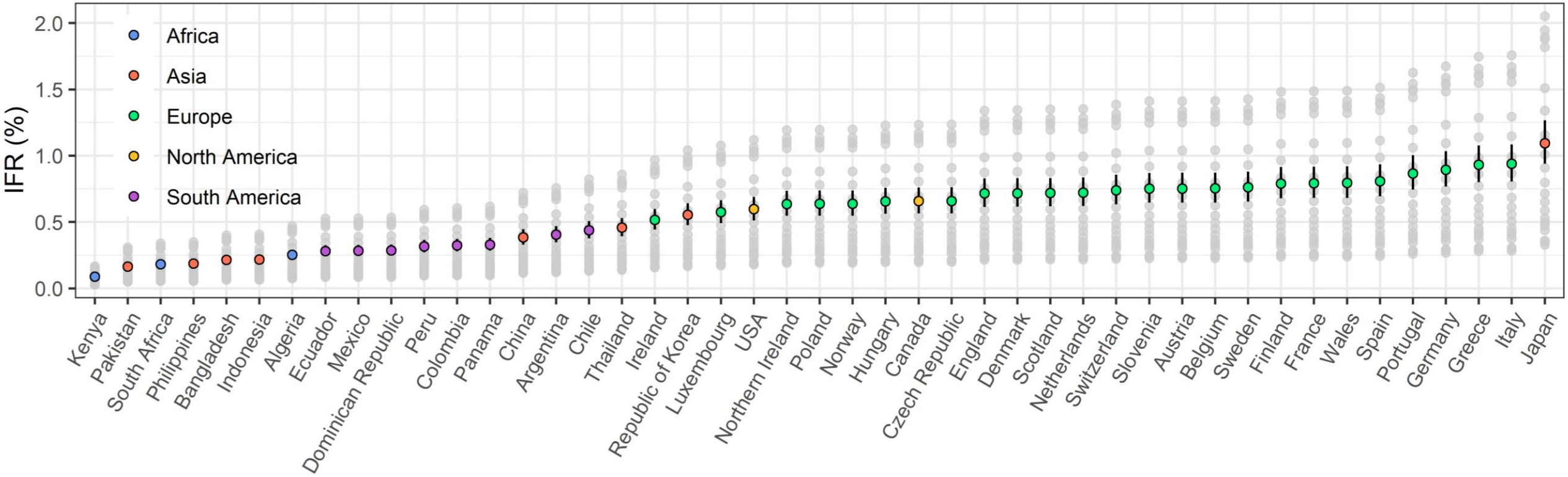
IFRs derived from the relative risk of non-nursing home COVID-19 deaths in England

Consistency of IFR across studies & countries



Demography and IFR

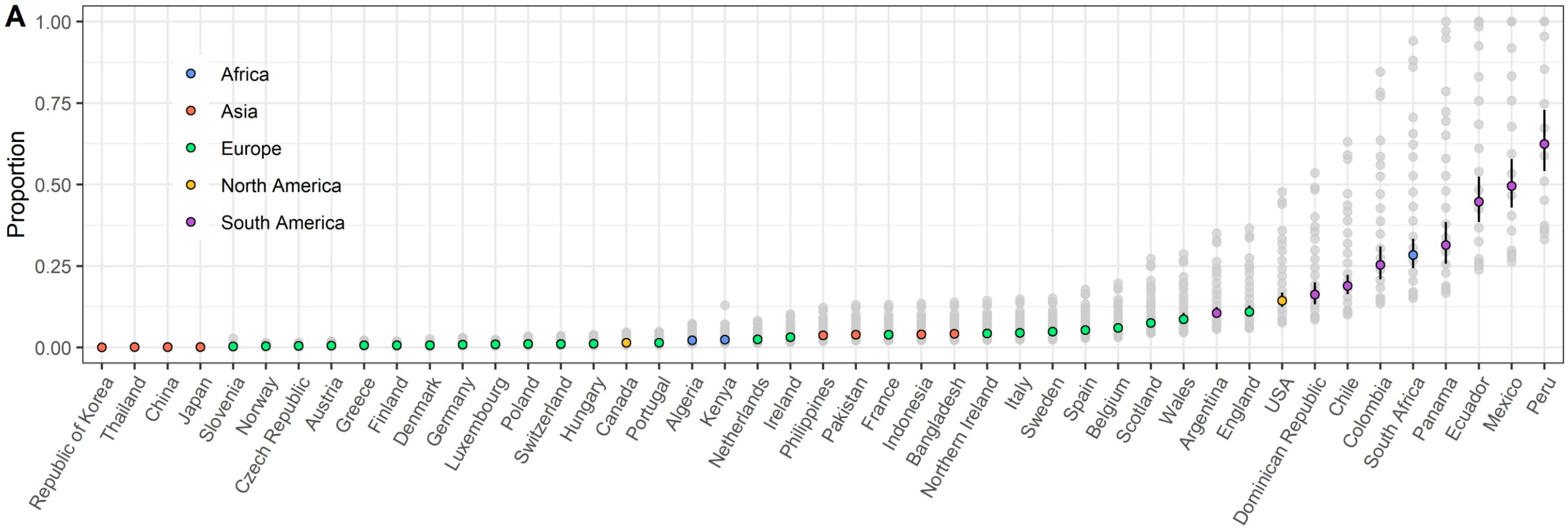
General population IFR



**Assumes that nursing home residents experience the same rates of infection and infection fatality as the general population*

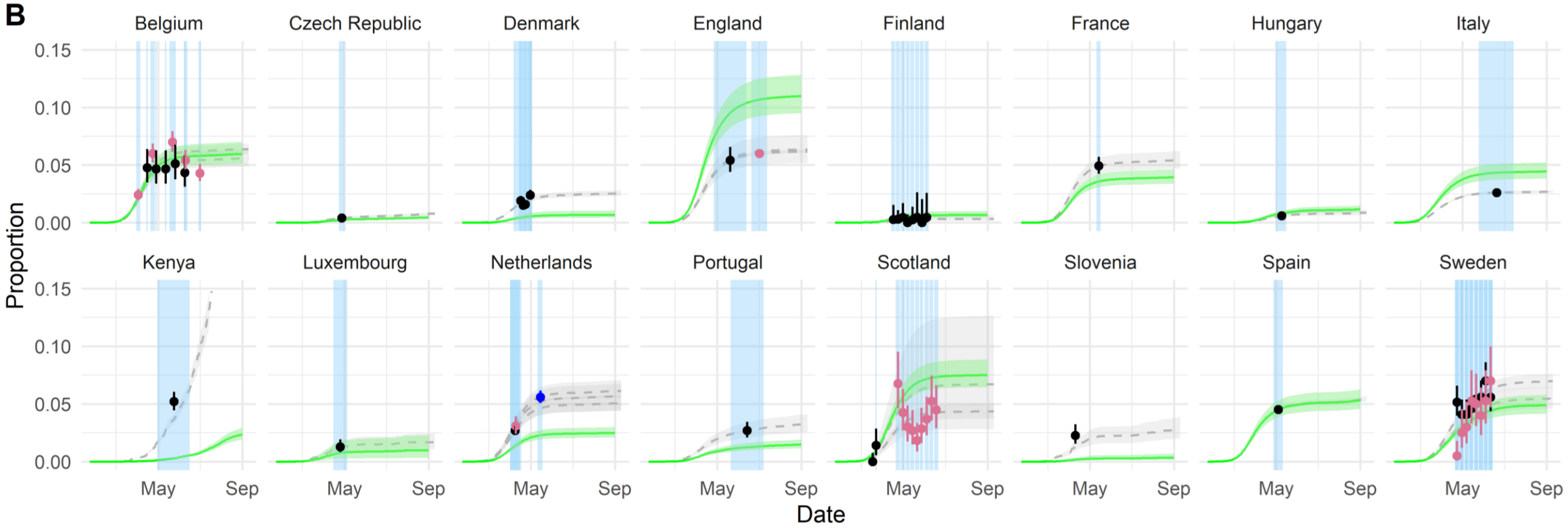
(Now very outdated!)

Proportion Infected by 1st September 2020

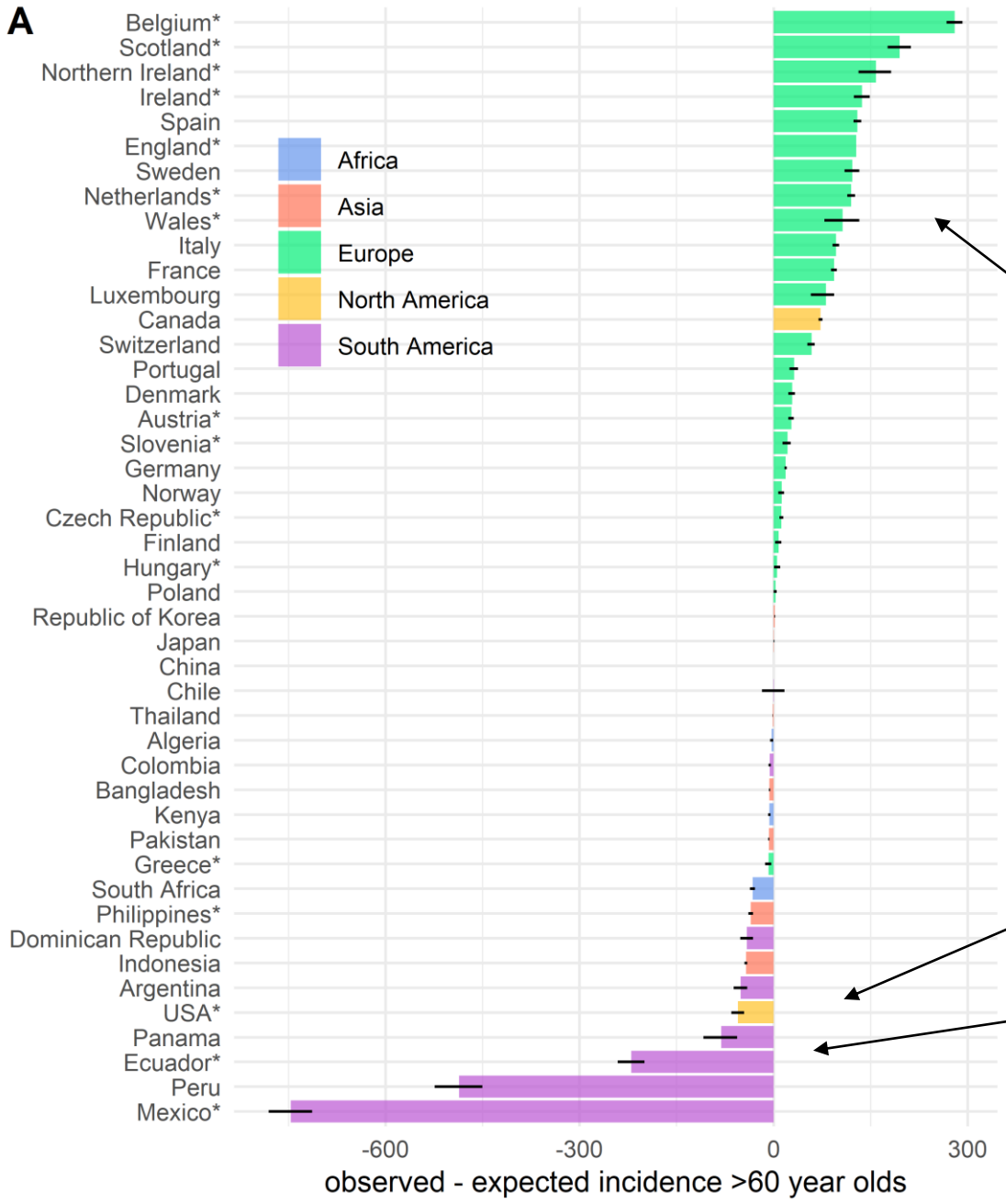


Important to consider full range of uncertainty in these estimates (grey dots)

Fits to seroprevalence data



Mortality rates in older individuals

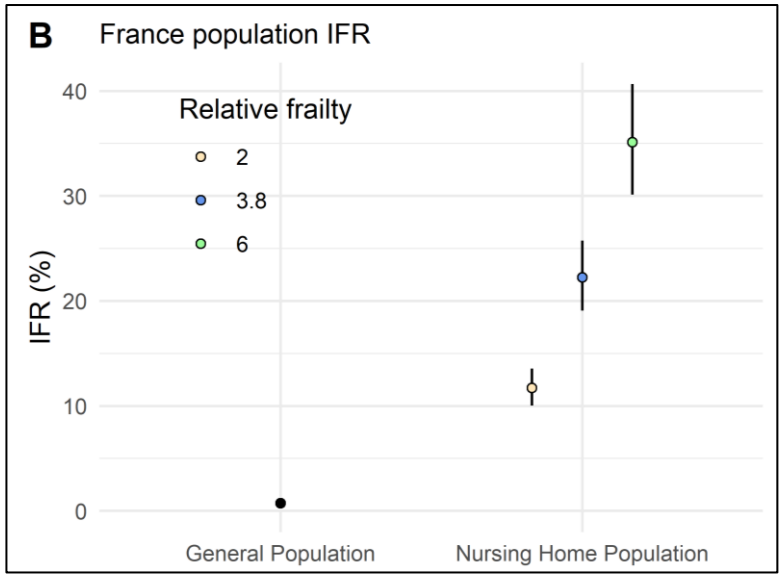


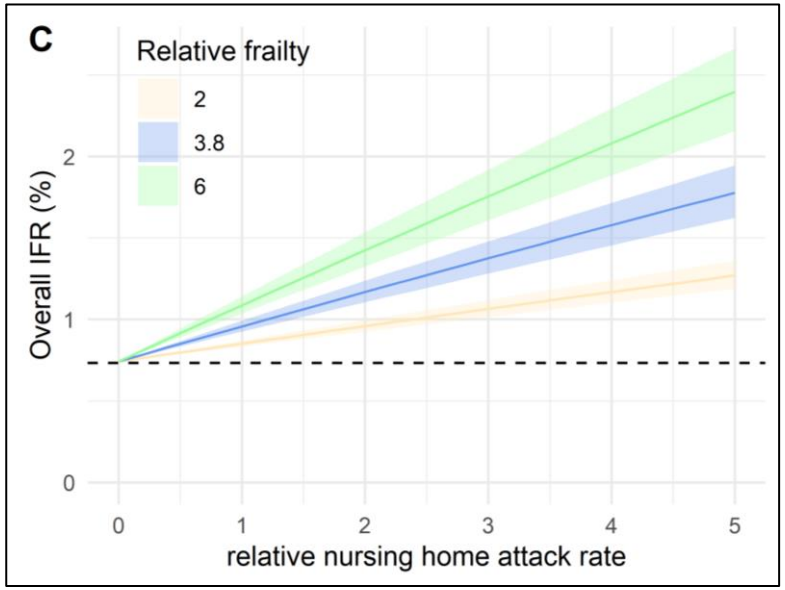
Nursing home outbreaks

Under-reporting of deaths?

Successful shielding programmes?

Nursing Homes and IFR



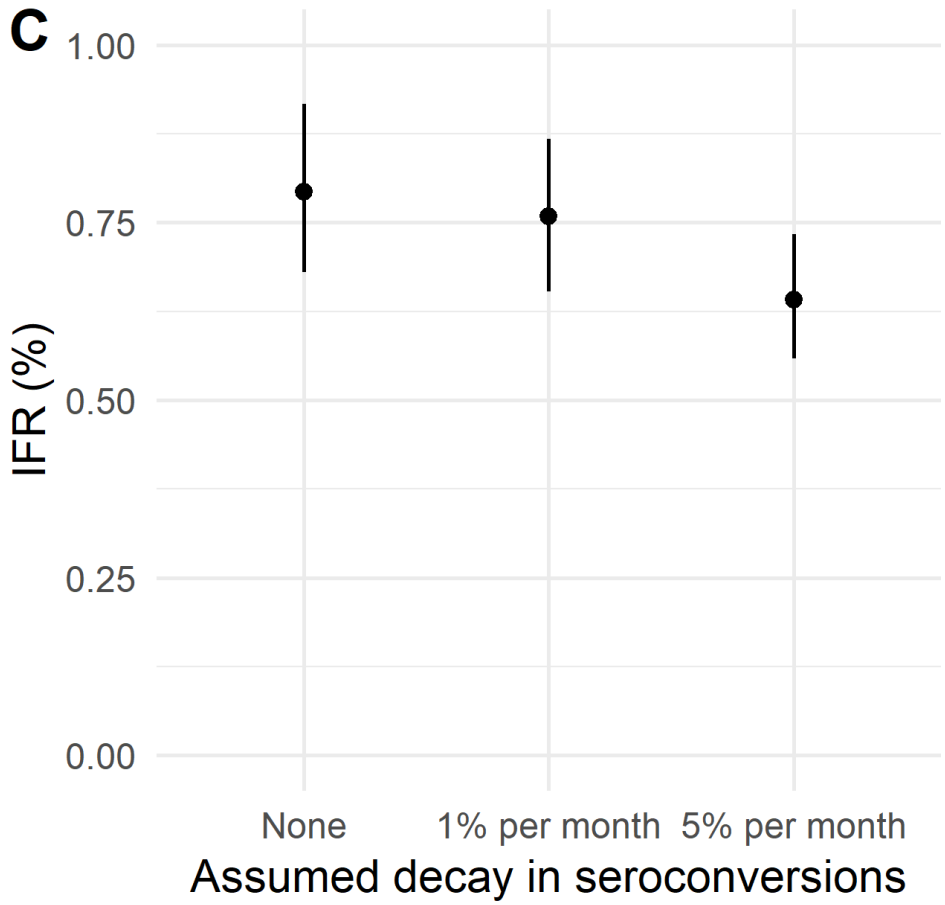


- General Population IFR:
  0.74% (0.64-0.86%)
- Nursing Home Population IFR:
  22.25% (19.06-25.74%)
- Overall IFR:
  1.10% (0.95-1.28%)

Molenberghs et al., *medrxiv*

Some things to consider

- Under-reporting of deaths
- Representativeness of seroprevalence data
- Improvements in severe outcomes over time
- Potential seroreversions
- Different mixing patterns



Acknowledgements

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Juliette Paireau, Institut Pasteur

Arnaud Fontanet, Institut Pasteur

Week 3: Stochasticity

Dr. Rachel Sippy
University of Cambridge

Week 3 Overview

- Monday, August 9:
  - Guest lecture & R session by Megan O'Driscoll
  - Stochastic models
  - Guided practice in R
- Tuesday, August 10:
  - Step-by-step model building
  - Building a COVID-19 model
  - Guided practice in R
- Wednesday, August 11:
  - Comparing models to data & evaluating models
  - Guided practice in R

Post Questions in the Chat!

(or ask over microphone)

Workshop Schedule

Time	Topics
2:00—2:10 pm	~~Greetings~~
2:10—3:00 pm	Guest lecture: COVID-19 with Megan O'Driscoll
3:00—3:10 pm	Break
3:10—4:00 pm	Stochasticity
4:00—4:10 pm	Break
4:00—5:00 pm	R Session

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Stochasticity

Objectives

- Understand the difference between deterministic and stochastic models
- Understand options for adding stochasticity to a model

Modeling Methods

Deterministic

Stochastic

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- Describe what happens “on average” in a population
- Use average (single) value/transition rates in models

Stochastic

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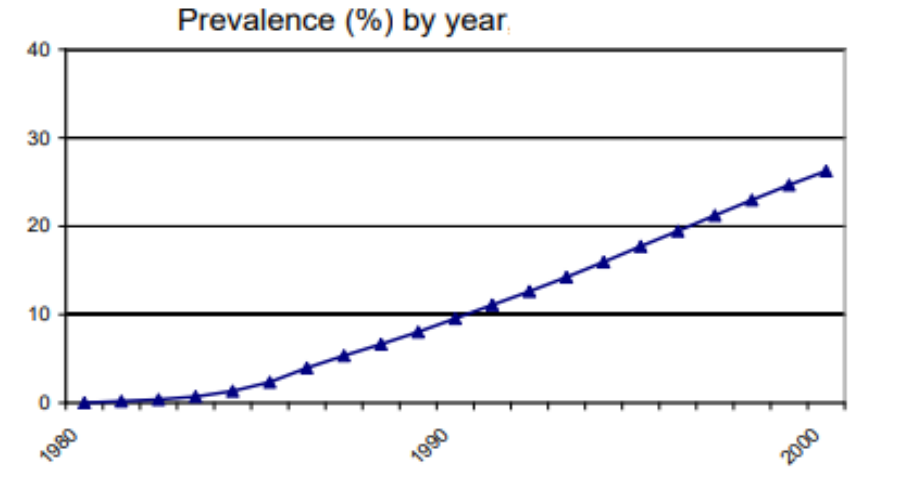

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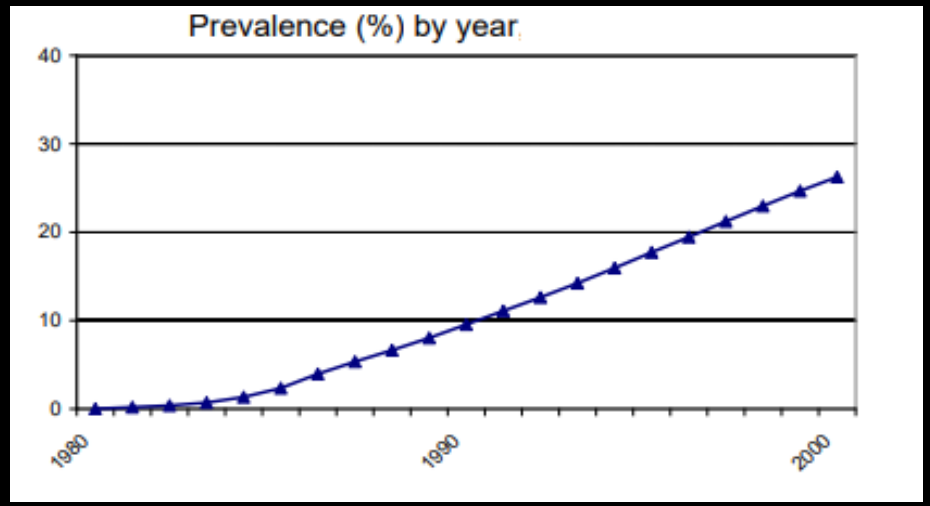

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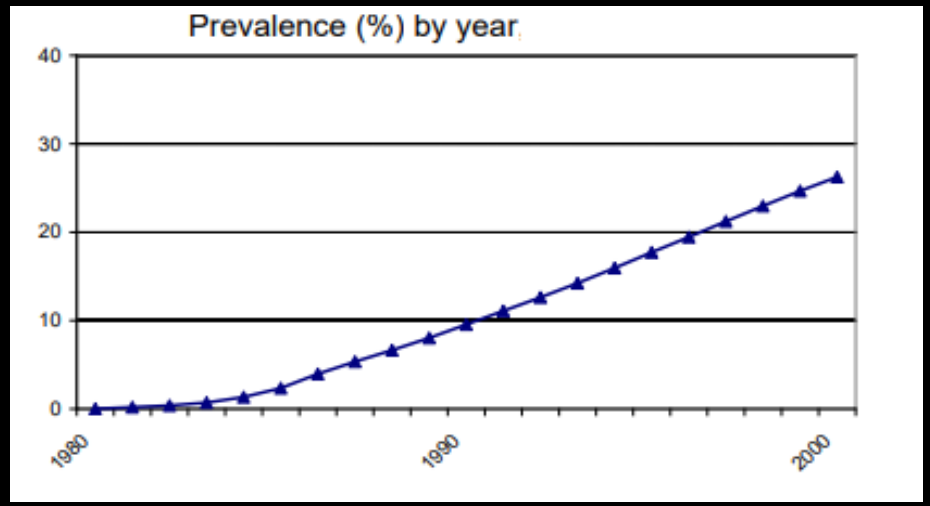

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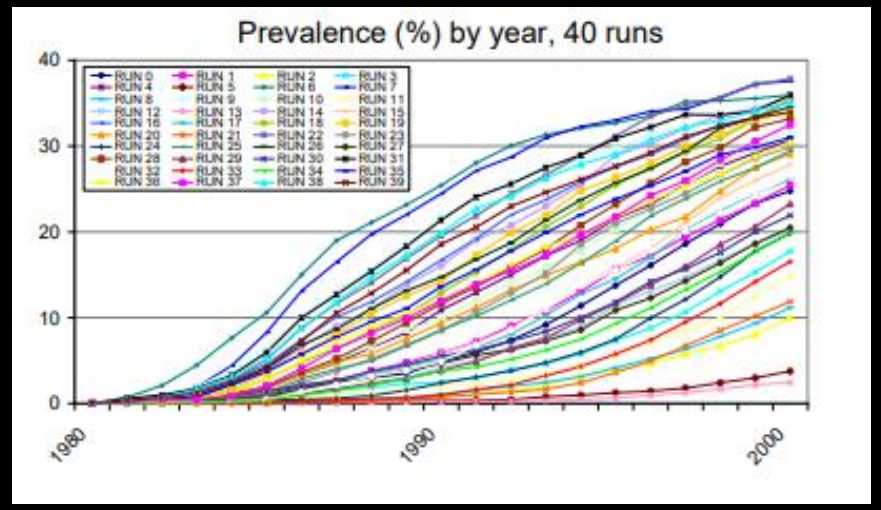

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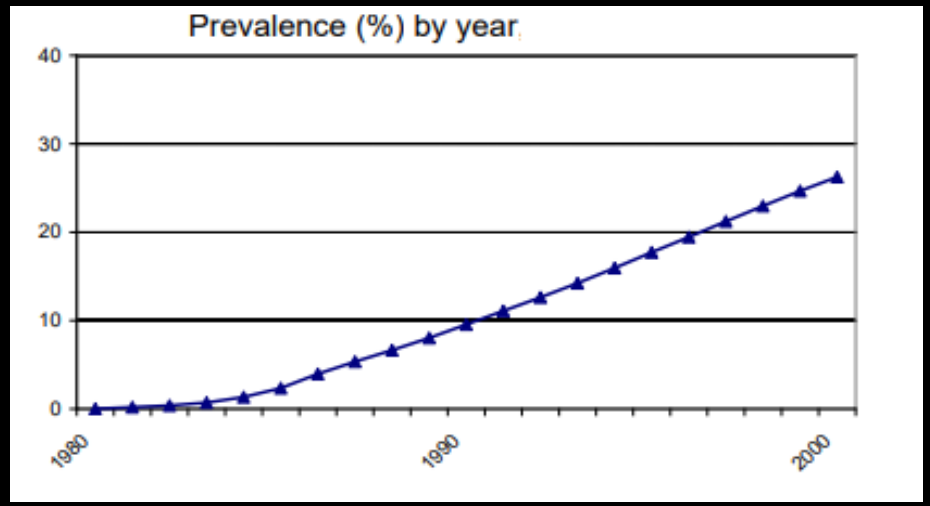

Stochastic – Random!

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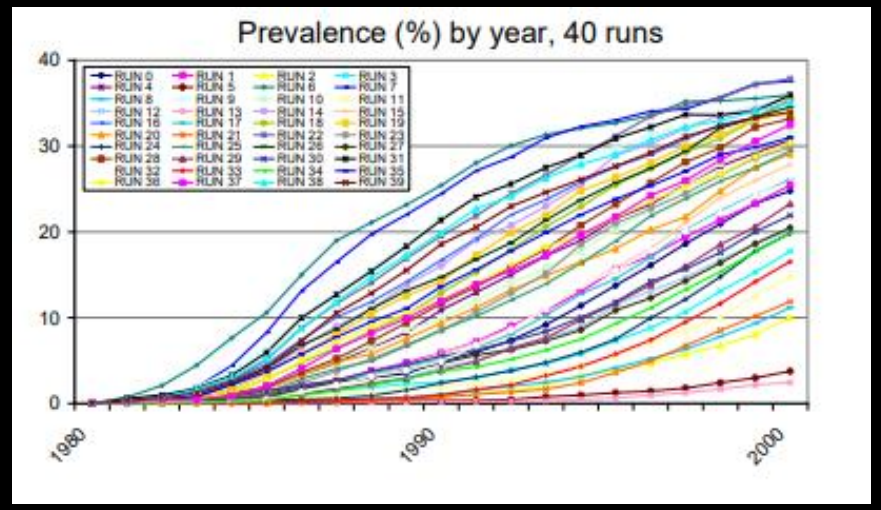

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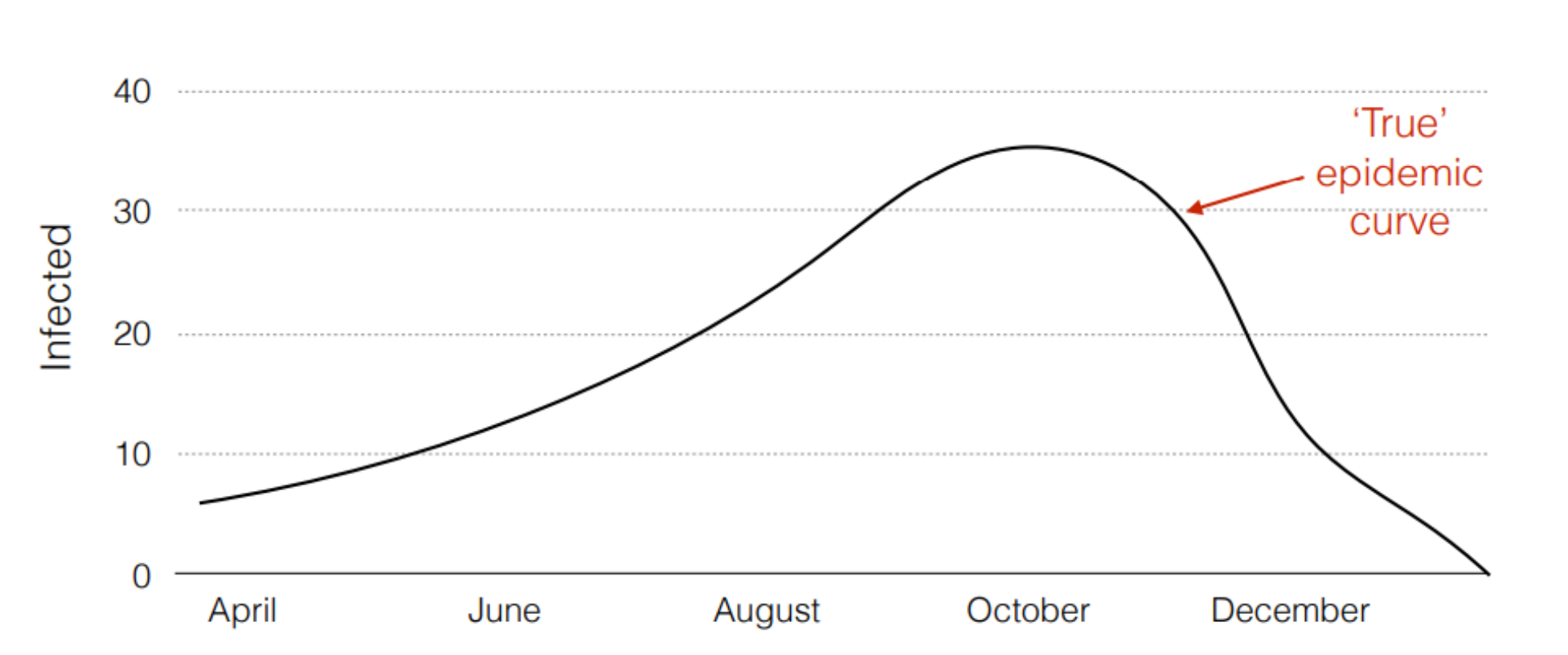
    - will a susceptible contact an infected? will transmission occur?
    - can have profound impact on epidemic dynamics

Observational Stochasticity



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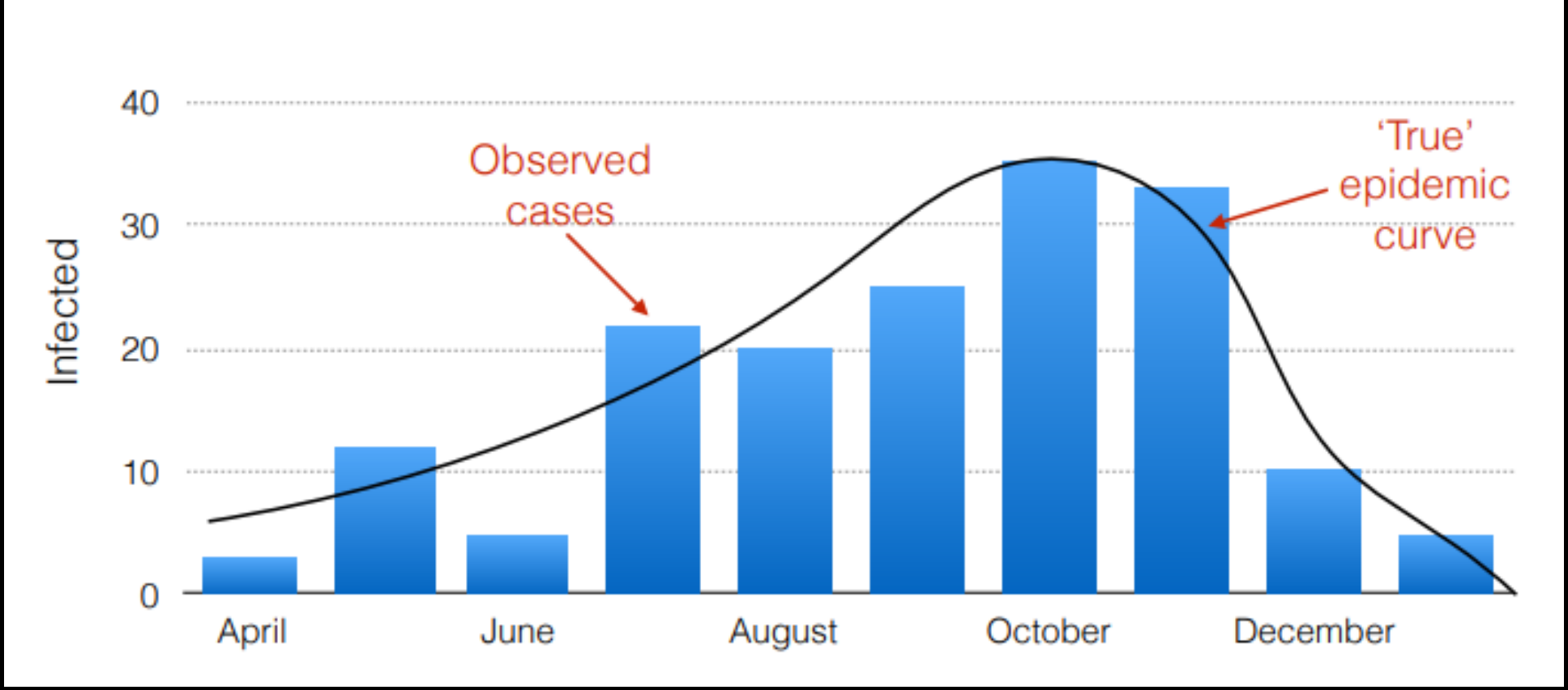

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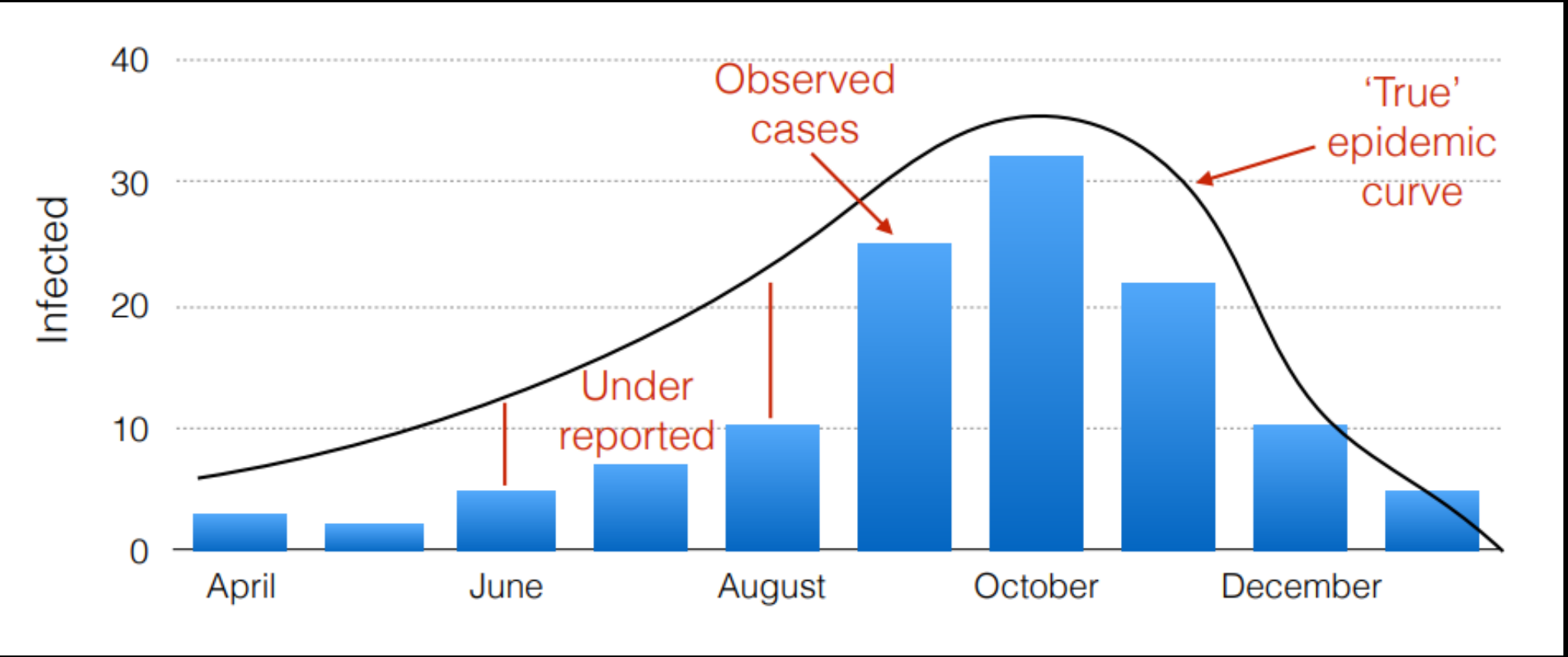
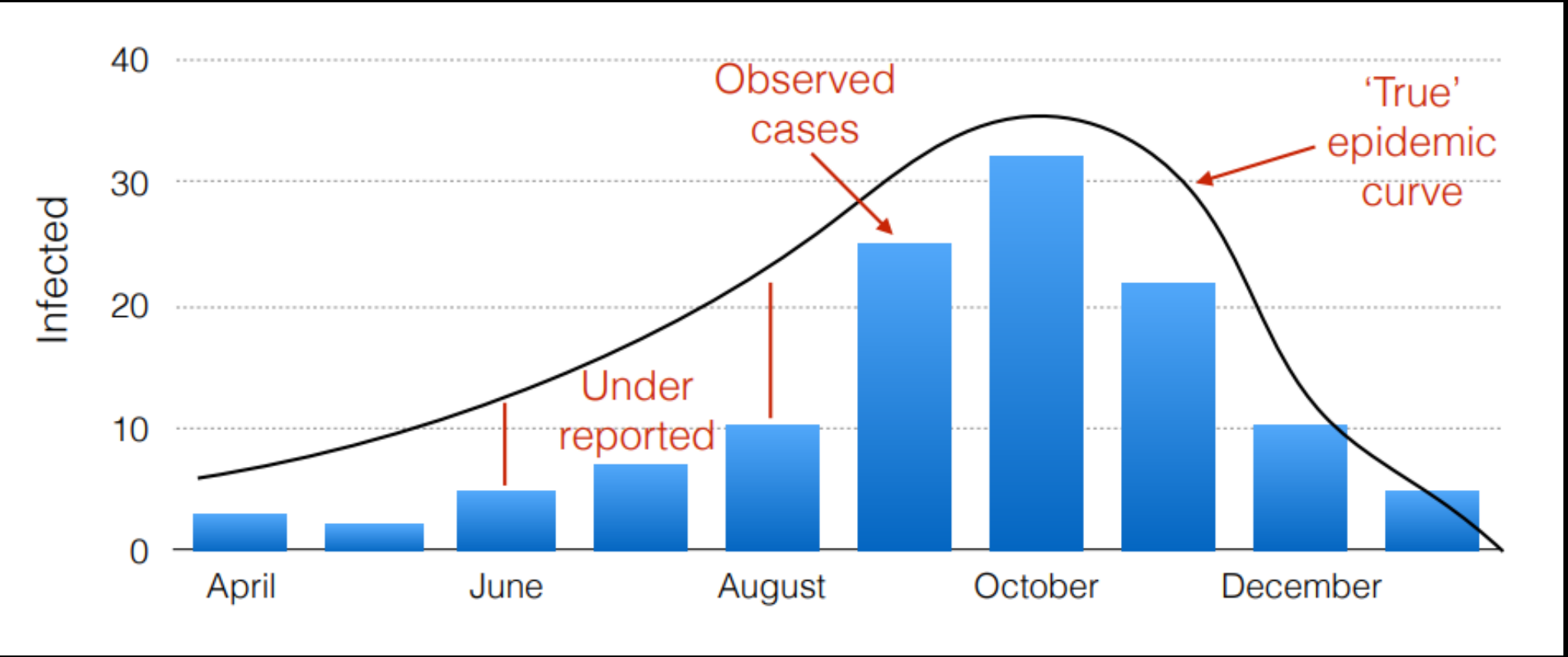


Observational Stochasticity

$$I_t = \rho C_t$$

I_t: number infected
ρ: reporting rate
C_t: case count

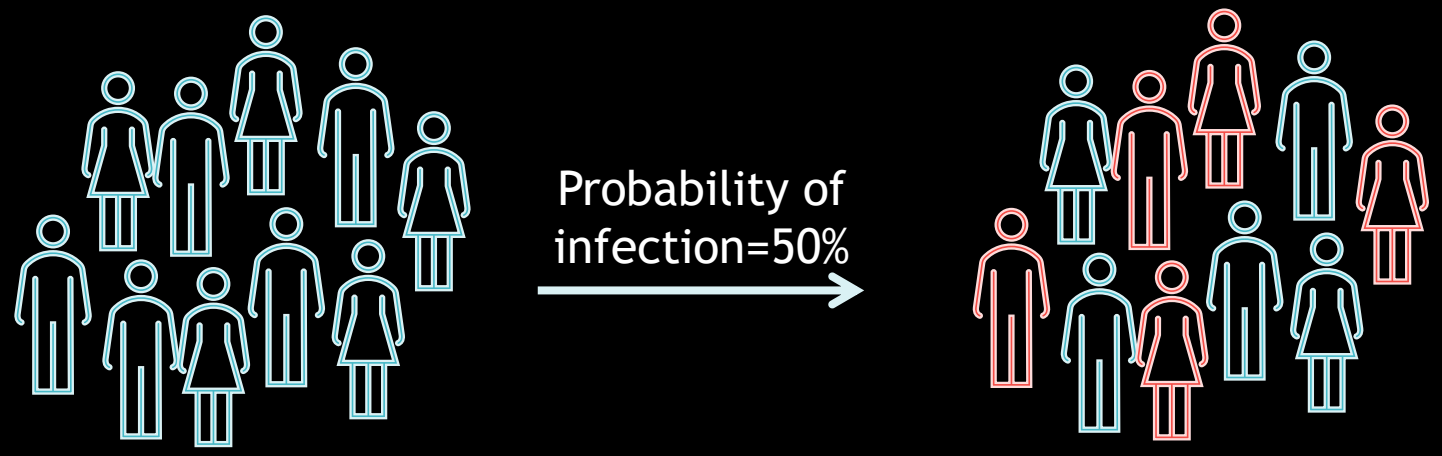


Process Stochasticity

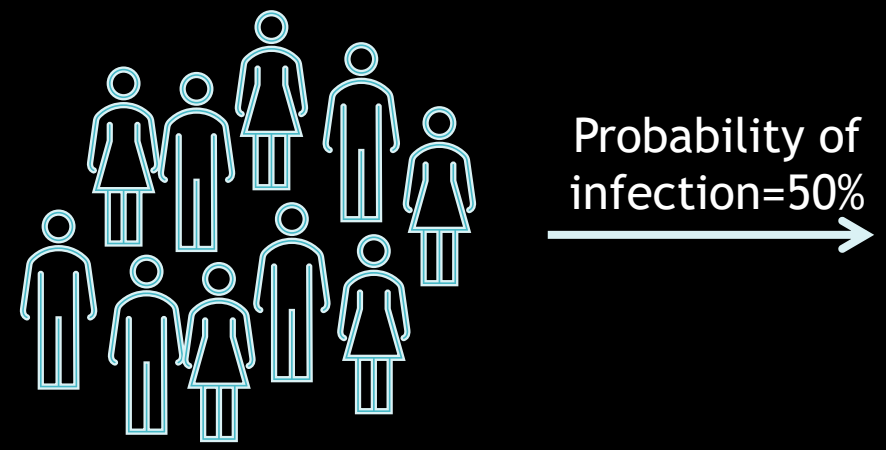
- Infection events are random events!
  - number of individuals you are in contact with
  - whether disease is transmitted during a contact
- These events can have a major impact on an epidemic
  - we want to build this uncertainty into our model

Modeling Results

Deterministic



Stochastic



Starting population

Modeling Results

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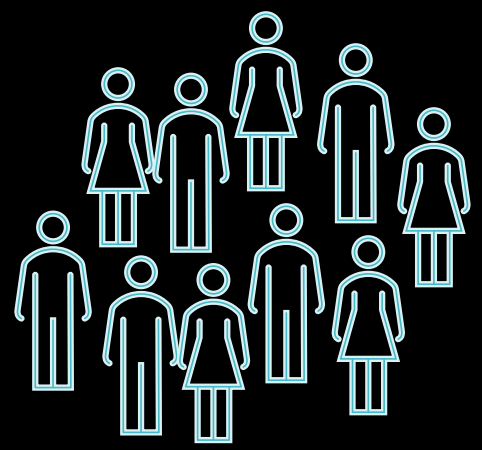
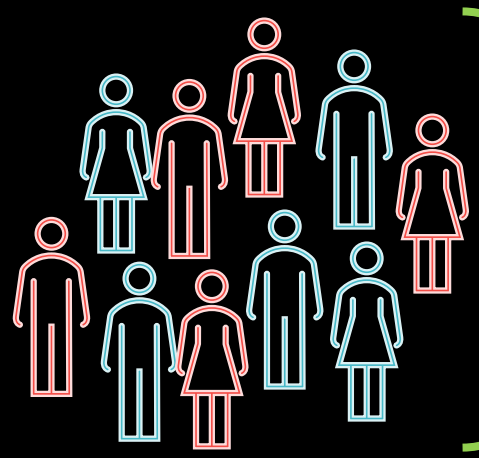
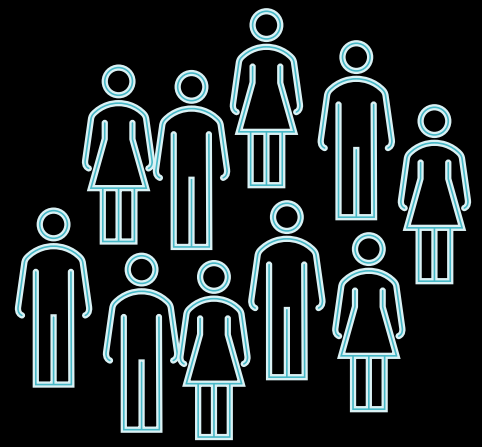


Probability of infection=50%



This is what the outcome will be no matter how many times we run the model!

Stochastic



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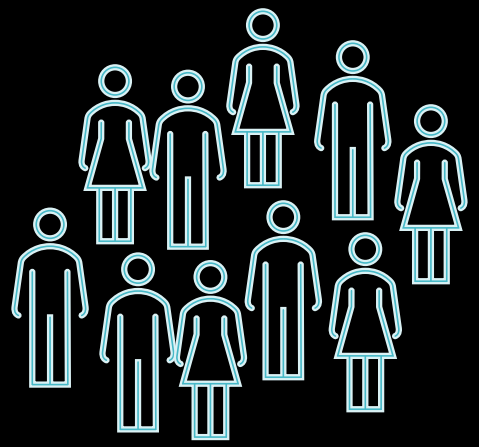

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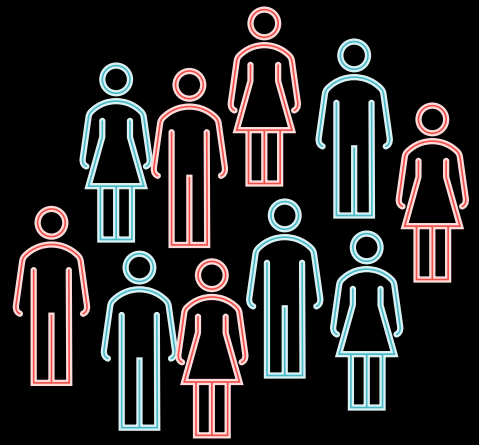

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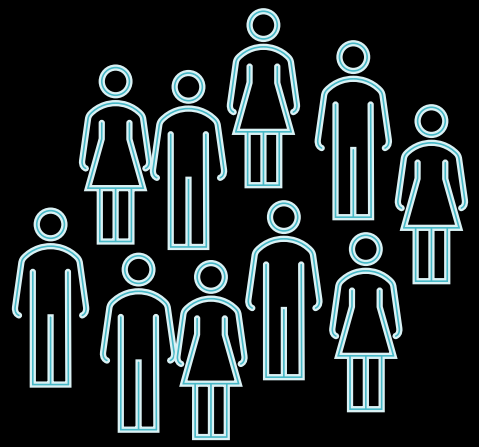

Starting population

Flip a coin for each person
Probability of infection=50%

Modeling Results

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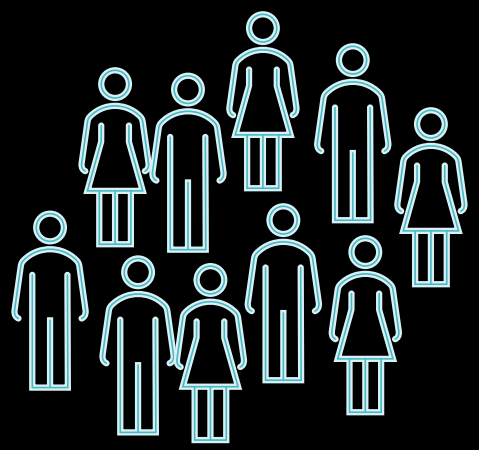

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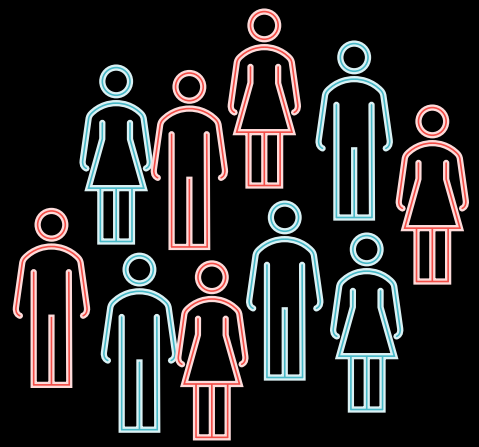

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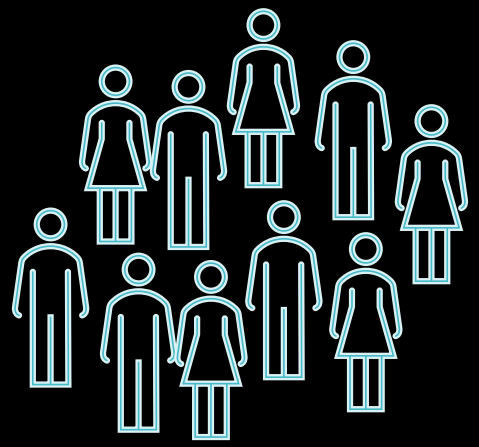

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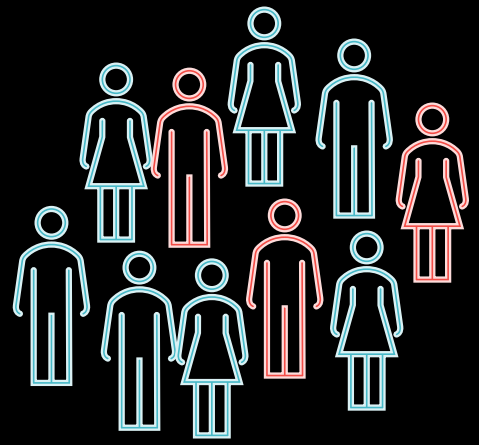

Modeling Results

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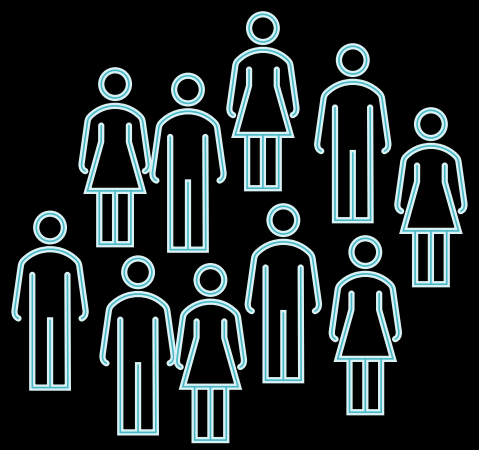

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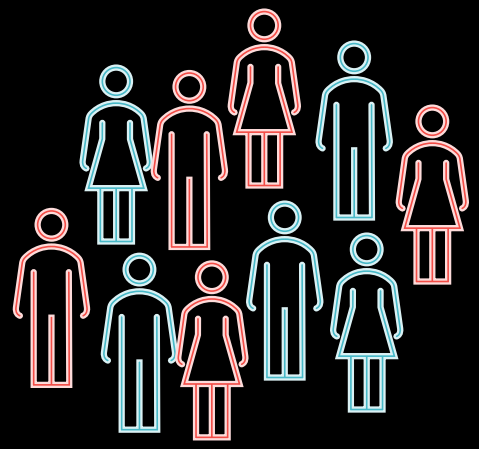
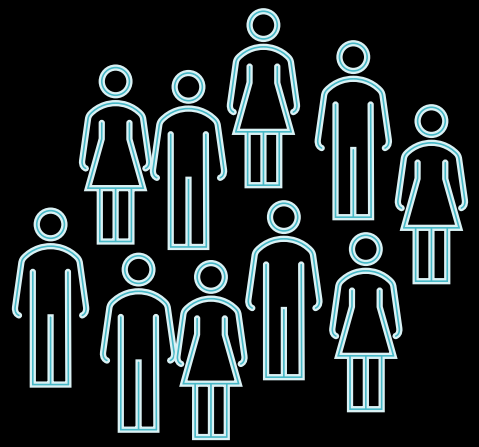


Stochastic



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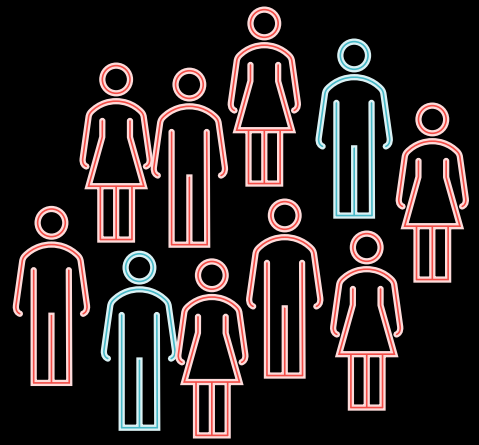

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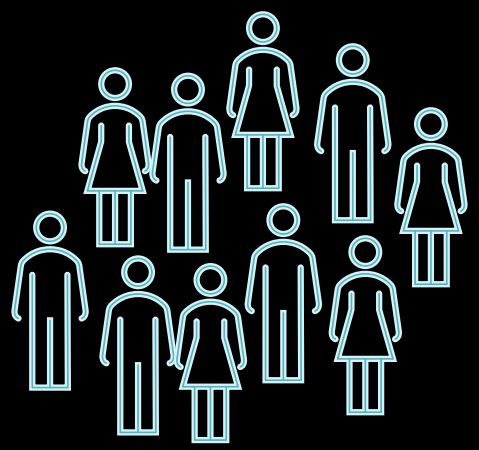

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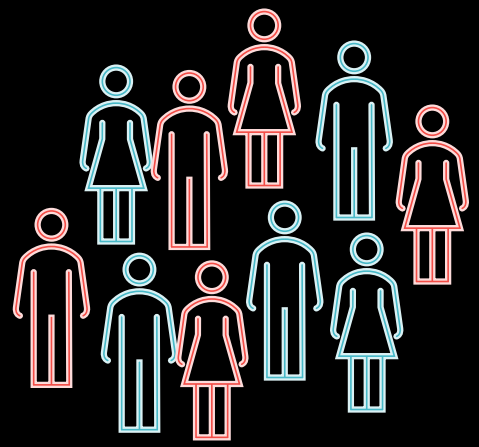

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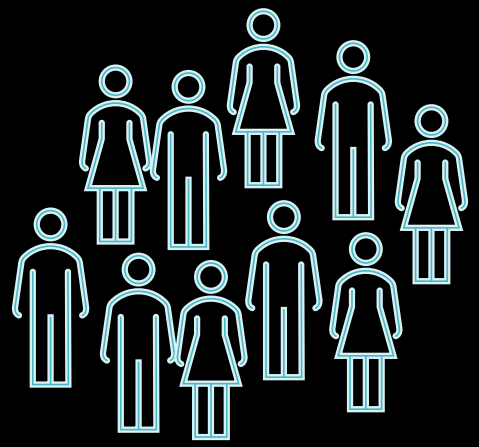

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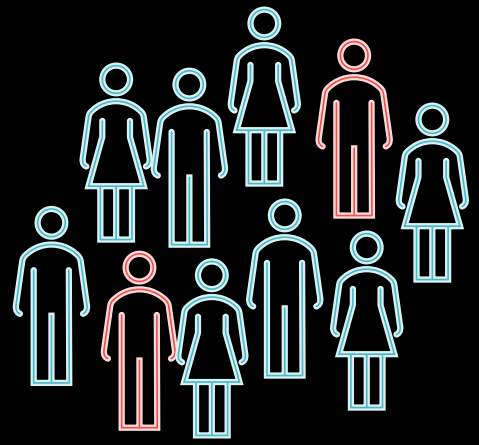

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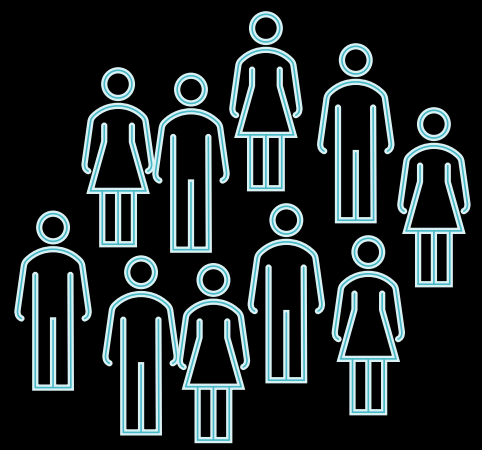

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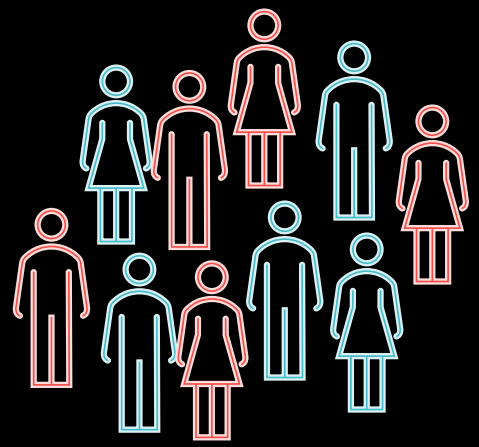

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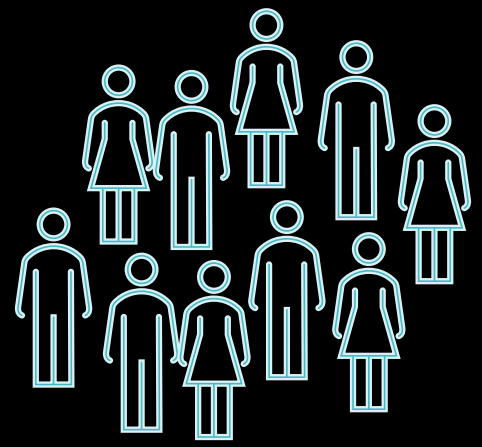

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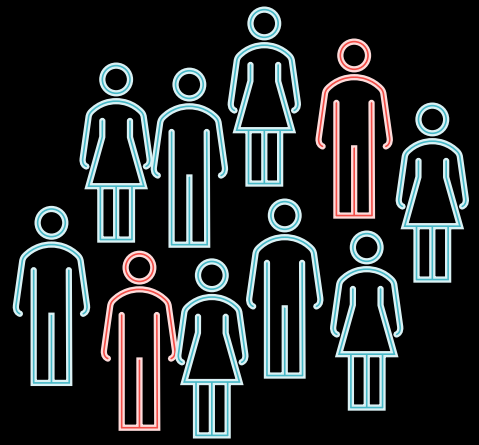

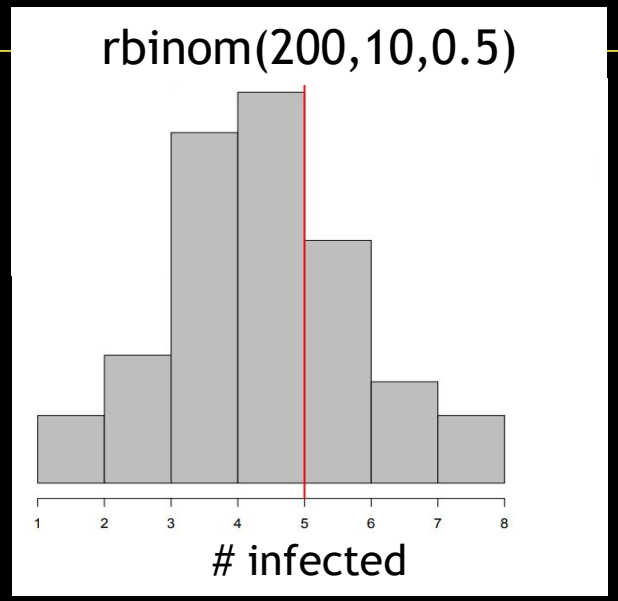

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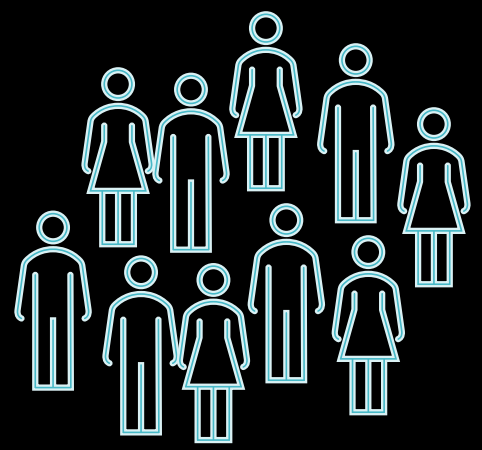

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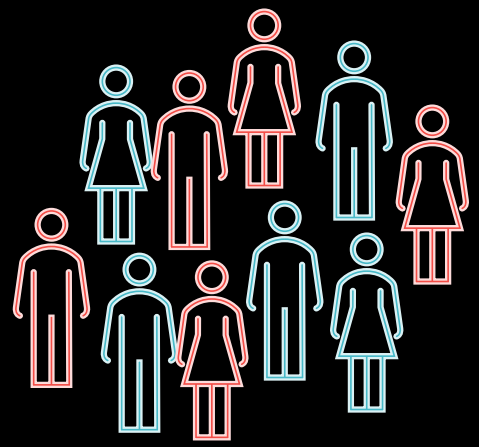
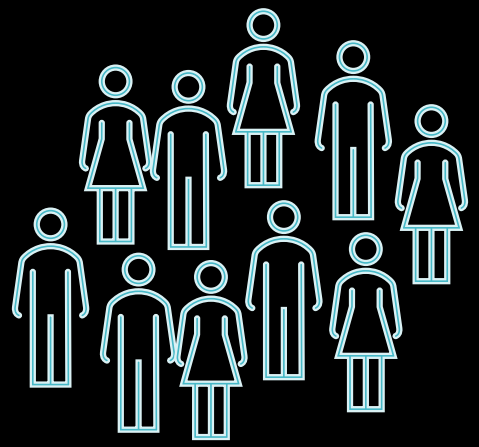


Average # infected will be 5

Stochastic



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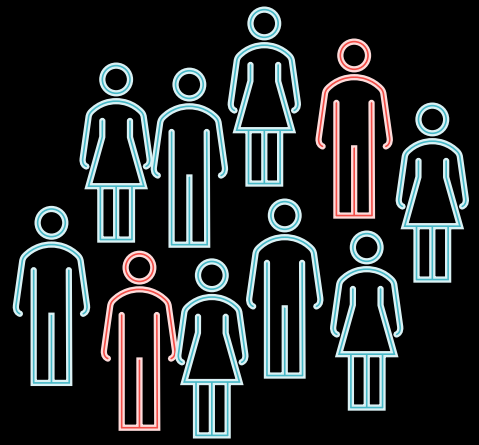

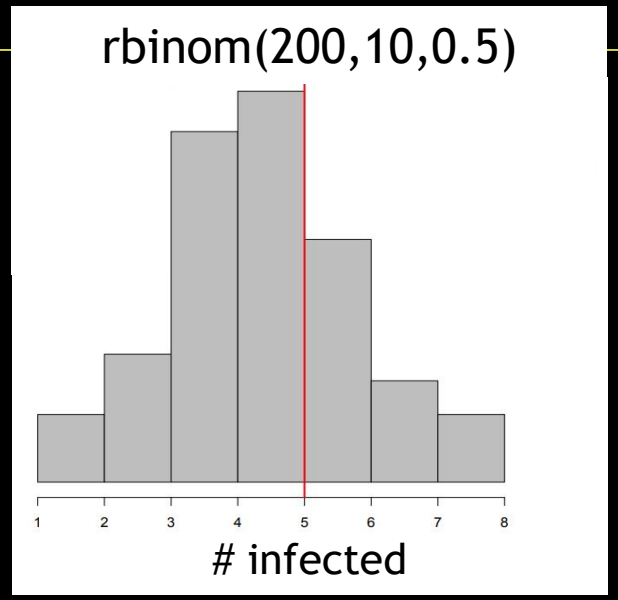

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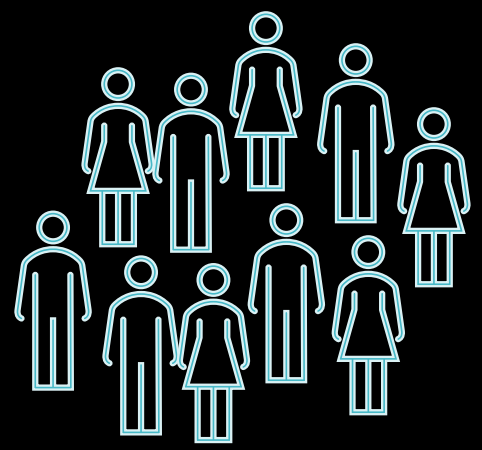

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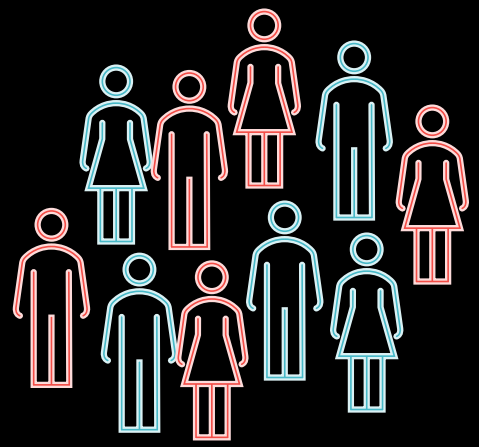

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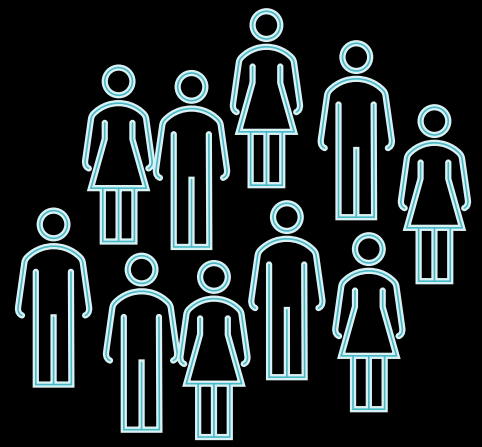

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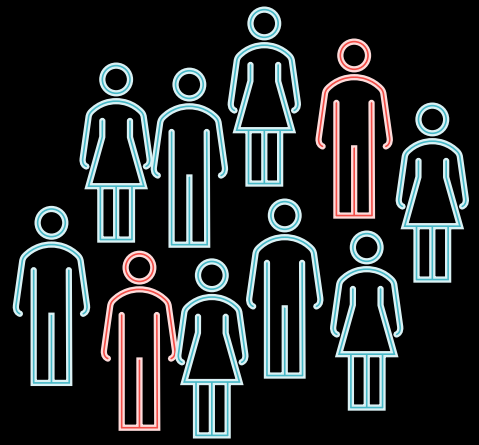

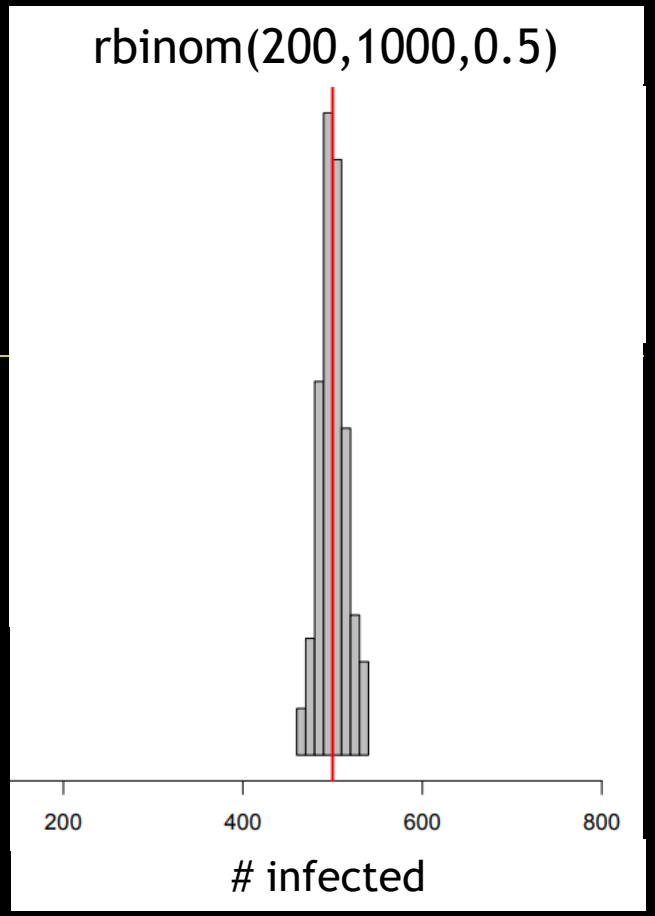

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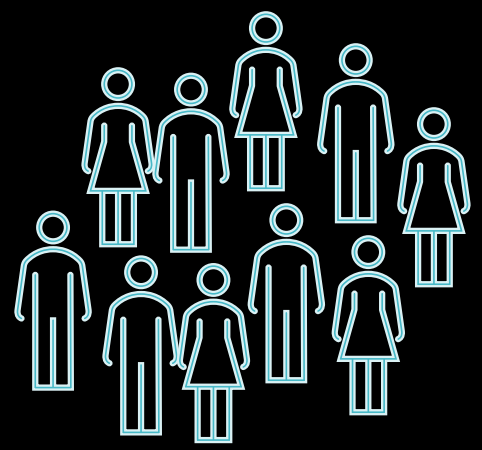

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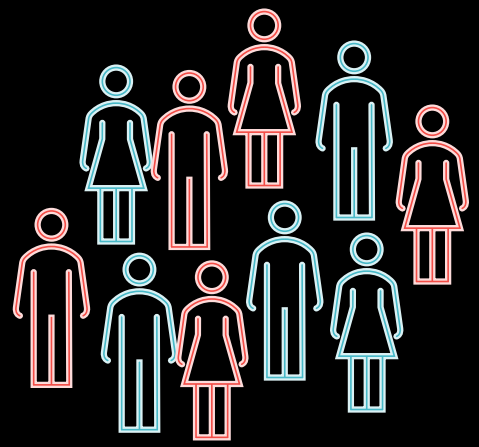

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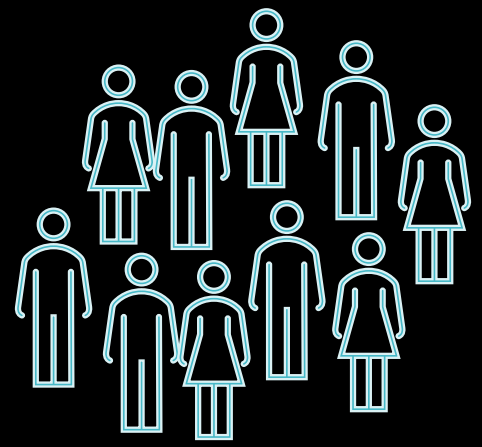

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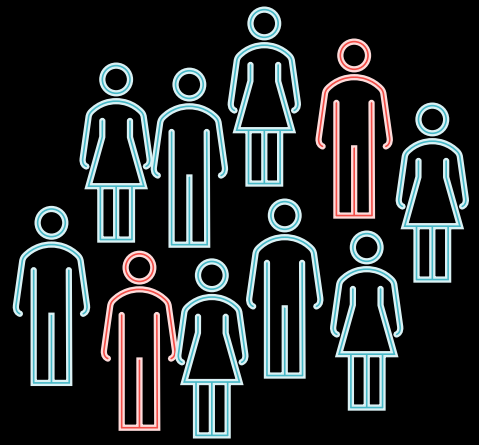
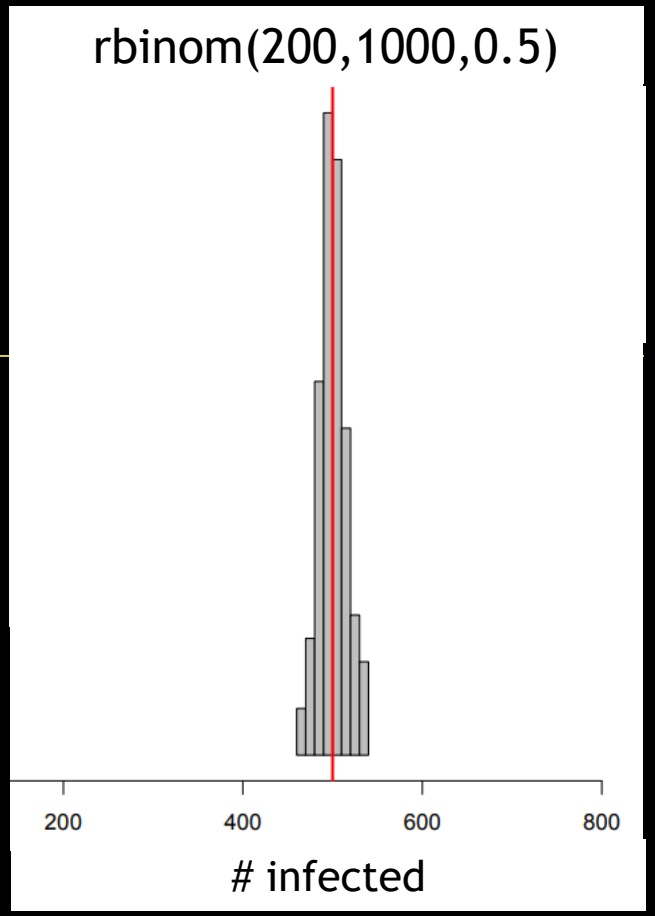


If we have many people, variance will be small – in this case deterministic predictions approximate reality



Process Stochasticity in Models

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Process Stochasticity in Models

- Depends on modeling methods being used, multiple ways to include in models
- Model able to produce different results – even without changing our input values
  - adding stochasticity causes this
- Why do we want to add stochasticity?
  - adds variability to each simulation/modeling run
  - demonstrate extremes of disease dynamics
  - more realistic, more robust

Stochasticity Through Distributions

- Instead of using a single value for our model parameters, we can use a distribution of values

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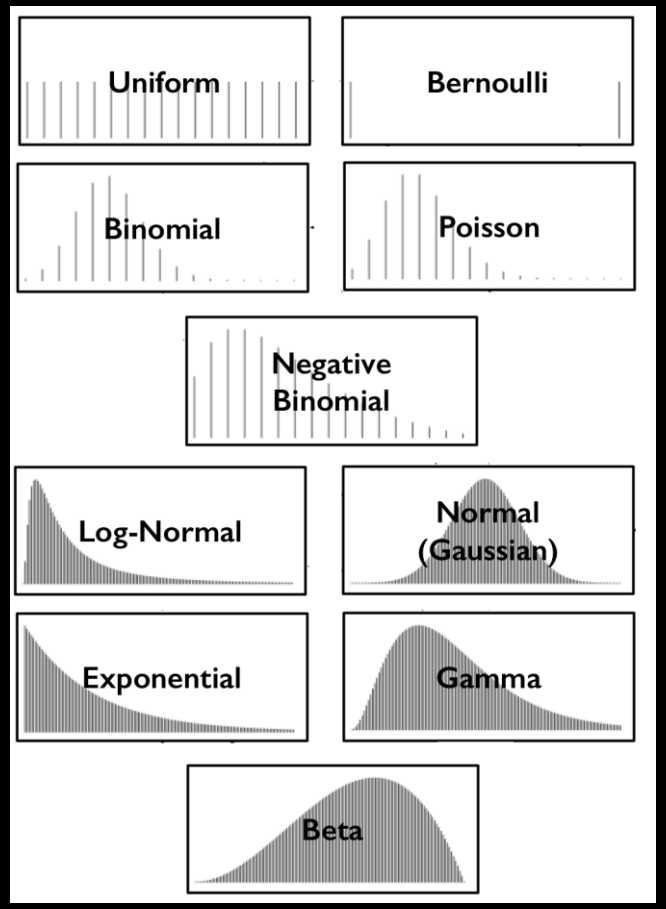
- What are distributions?



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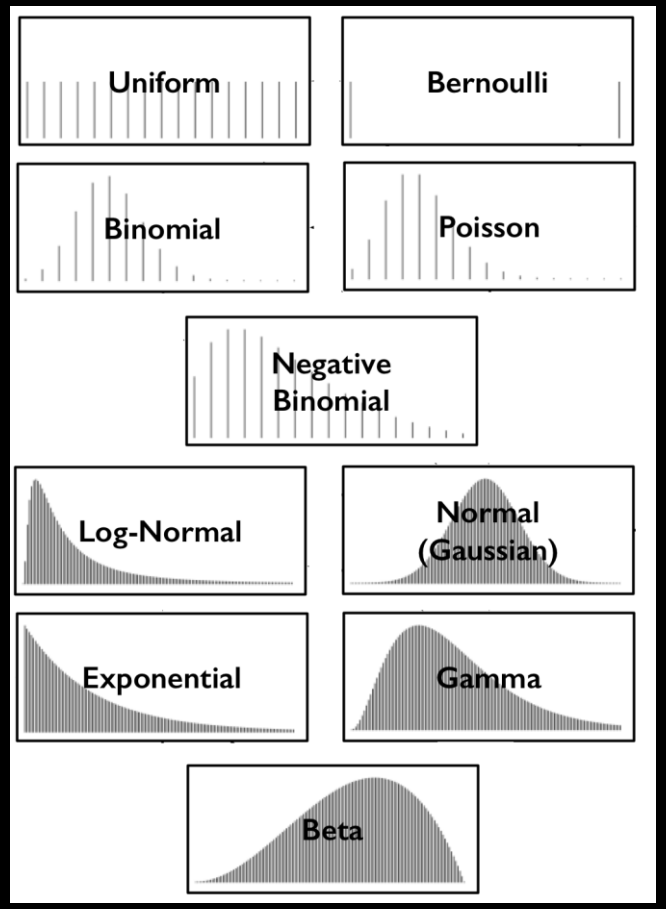
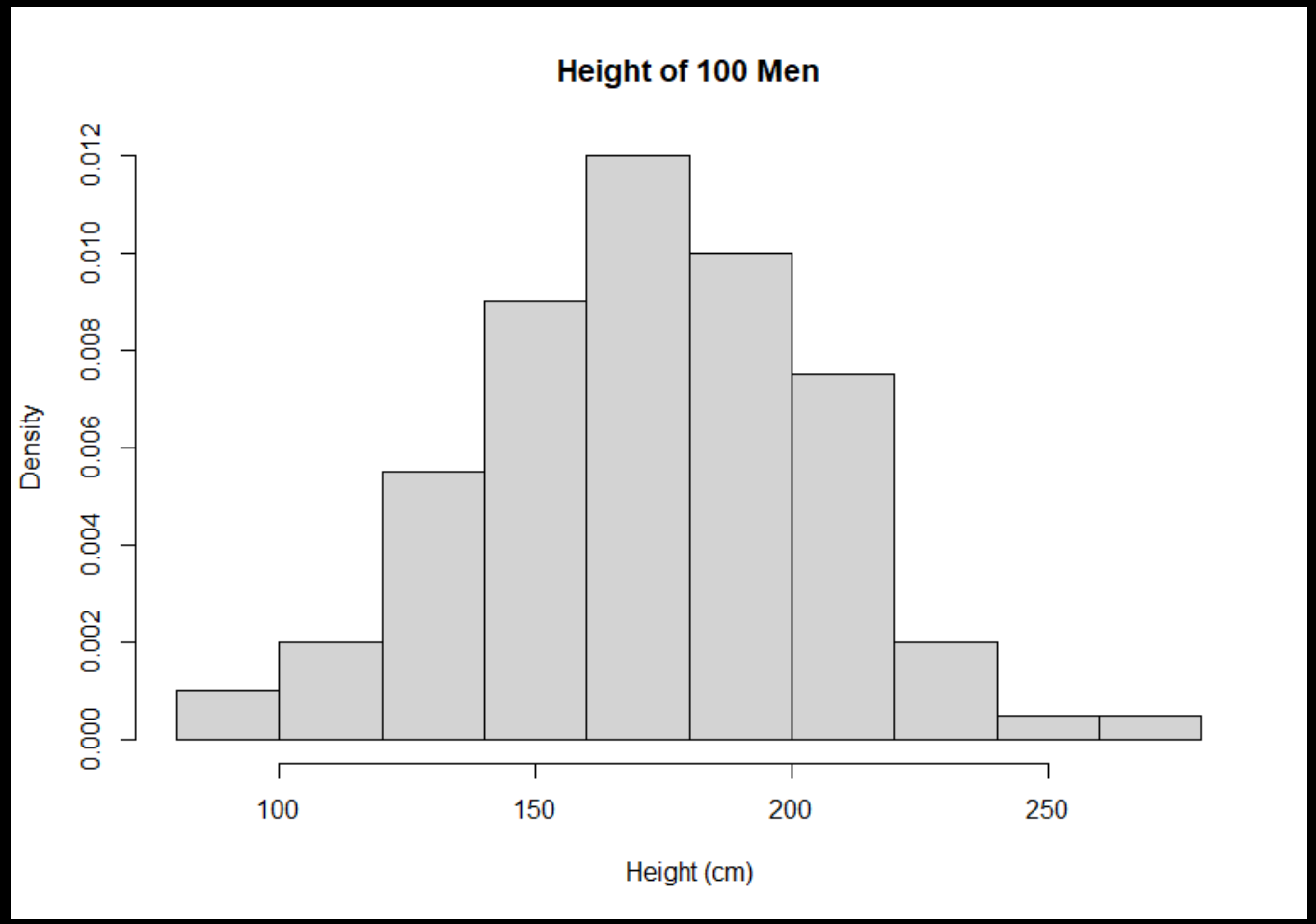
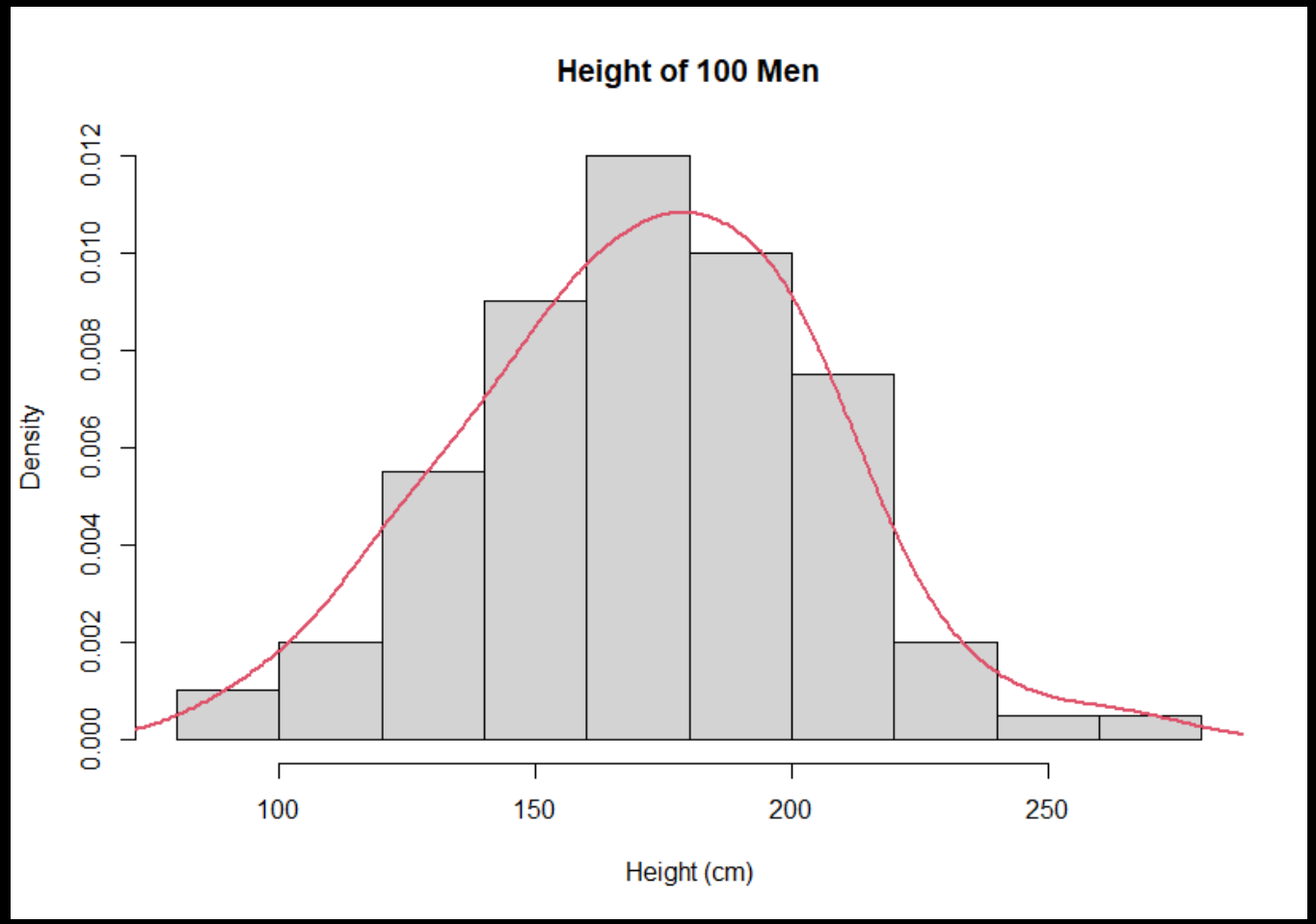




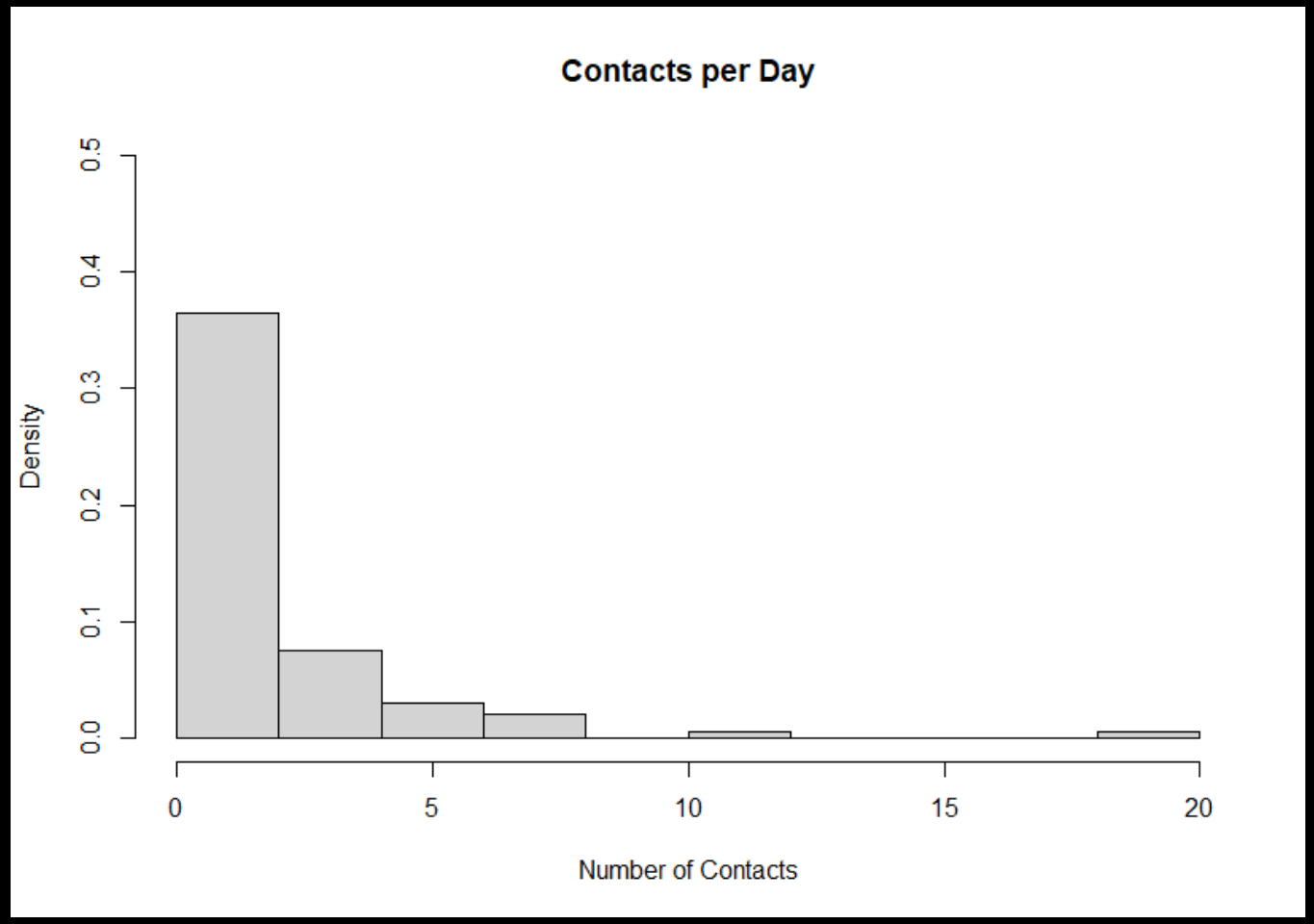
Distributions Can Represent Real-life Phenomena

- Histogram of heights of 100 men



Distributions Can Represent Real-life Phenomena

- Histogram of heights of 100 men
- Approximately normal!
- $Height \sim N(170, 30)$



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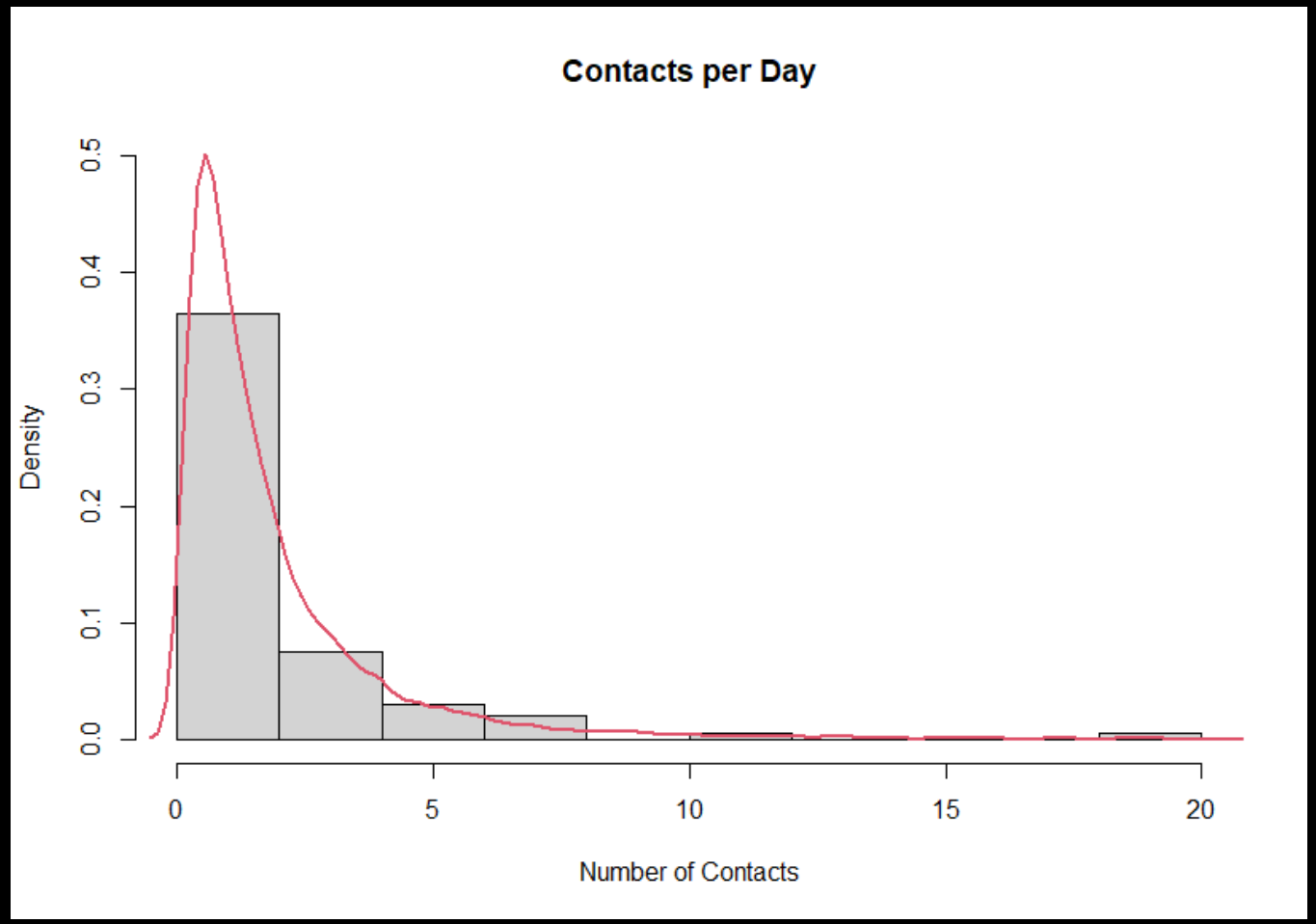
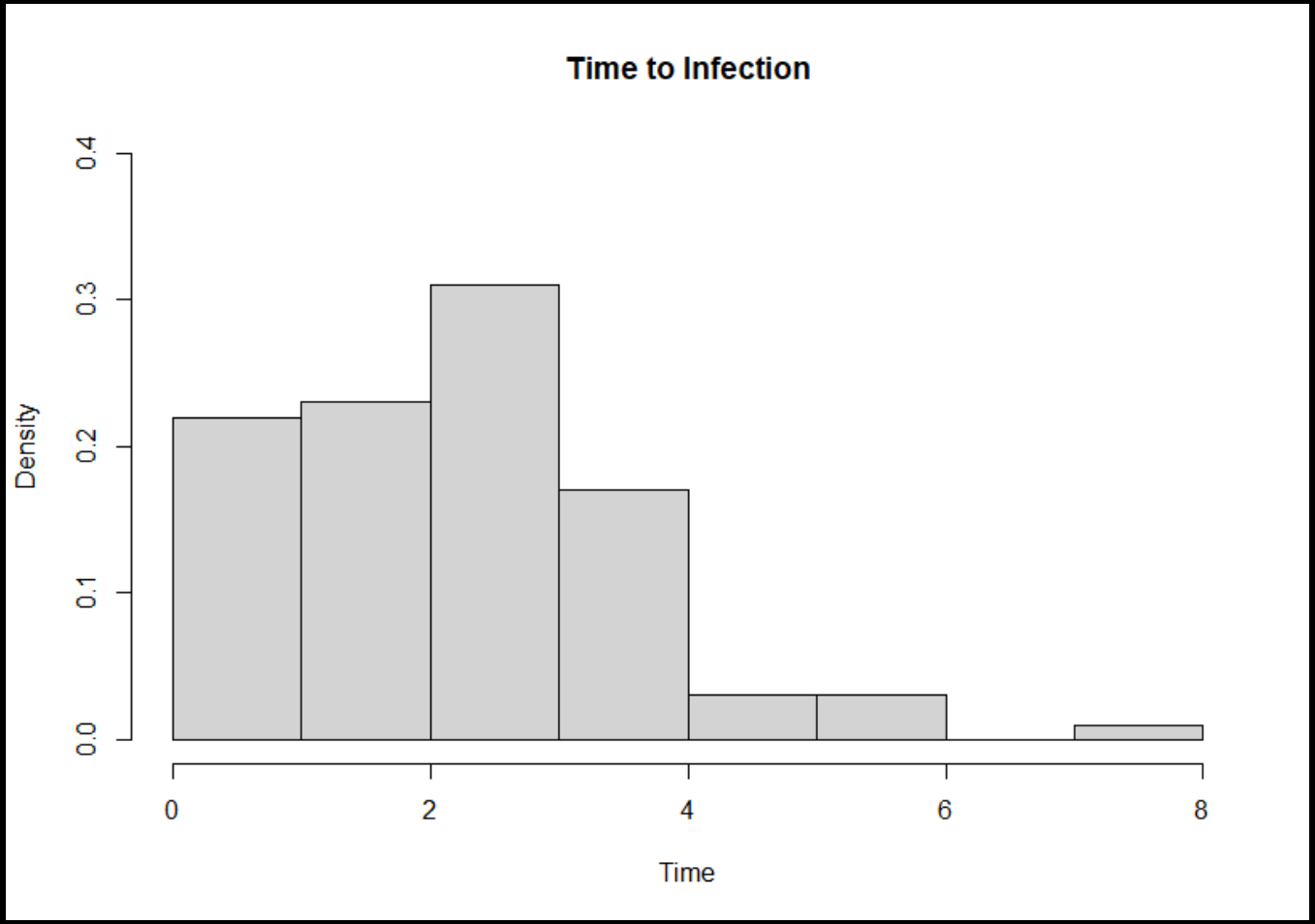
- Histogram of daily number of contacts



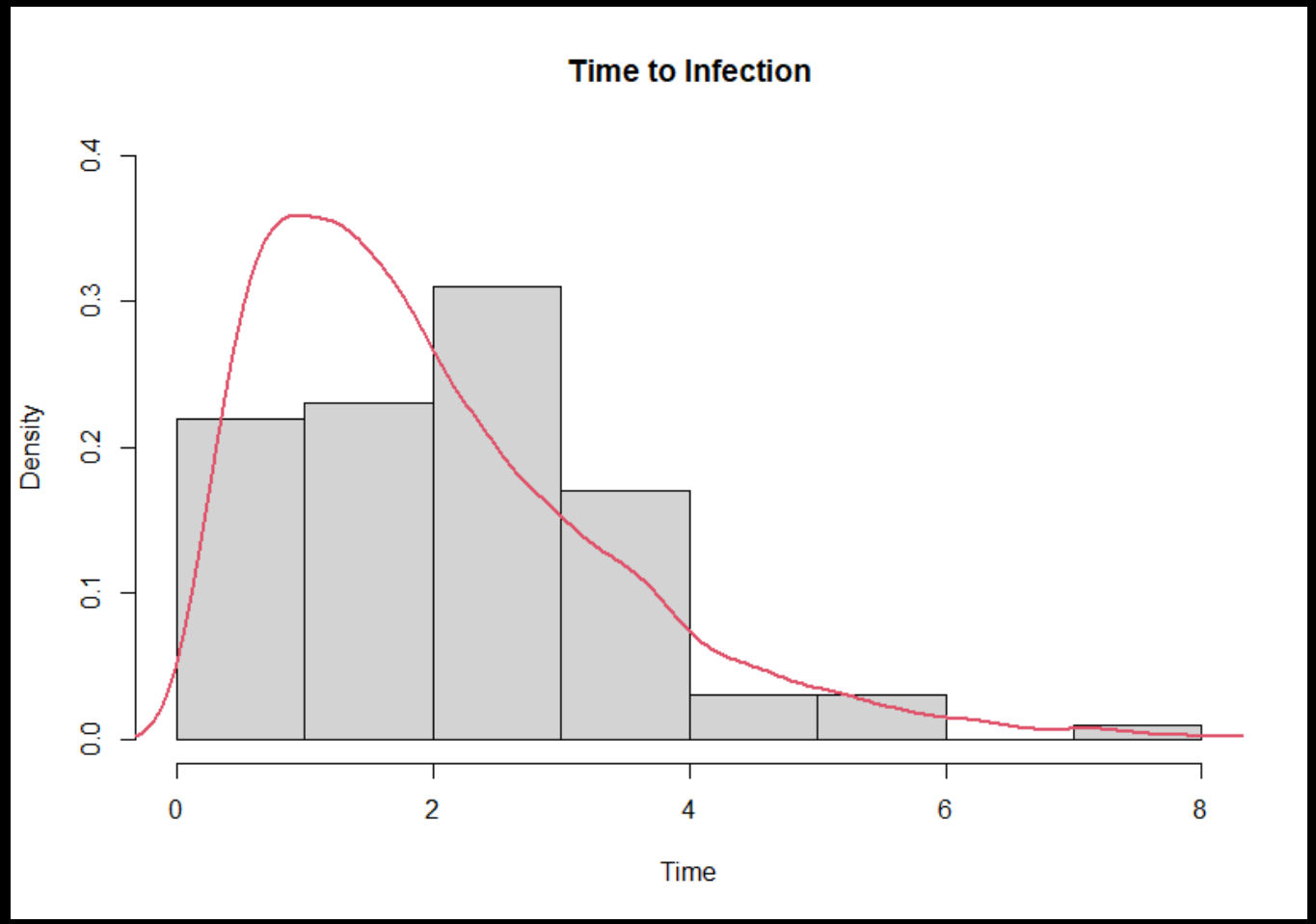
Distributions Can Represent Real-life Phenomena

- Histogram of daily number of contacts
- Lognormal distribution!
- $C \sim LogNormal(0.2)$



Distributions Can Represent Real-life Phenomena

- Histogram of time to infection

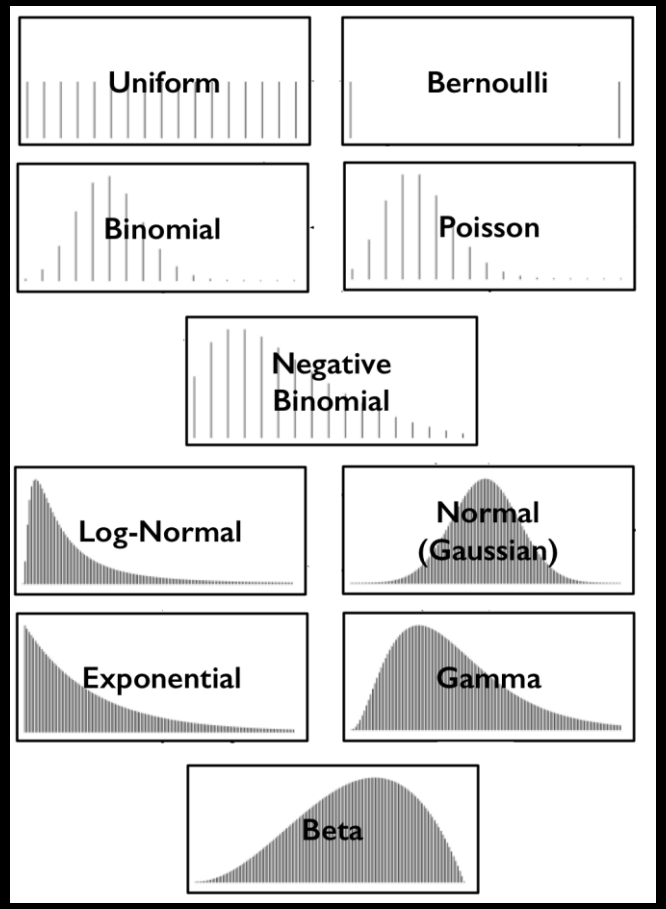


Distributions Can Represent Real-life Phenomena

- Histogram of time to infection
- Gamma distribution!
- $tInf \sim Gamma(2, rate = 1)$

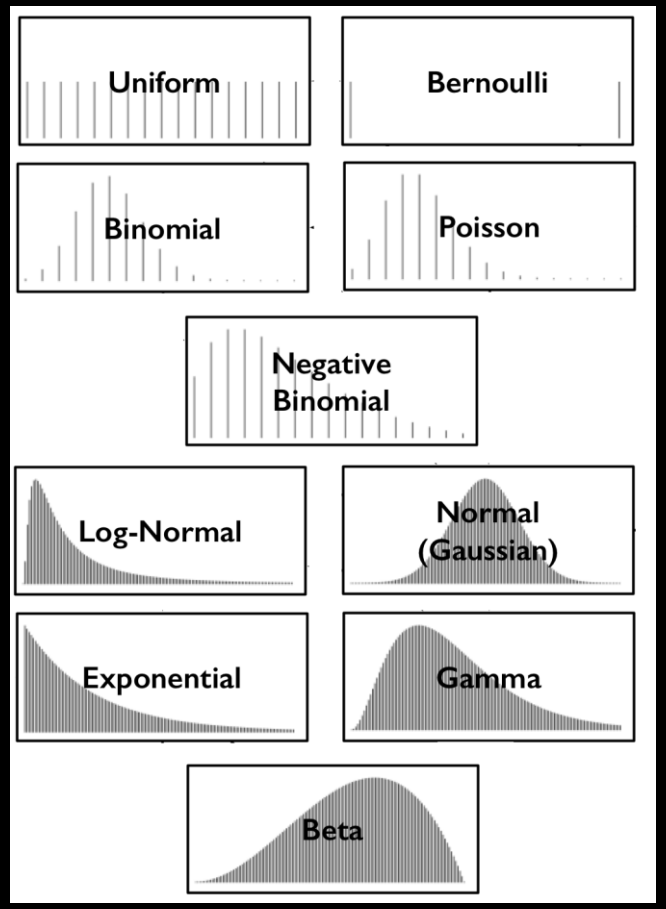
Stochasticity Through Distributions

- Instead of using a single value for our model parameters, we can use a distribution of values
- What are distributions?
  - represents probability that different outcomes will occur
- We can tell the model to select one of the values from the distribution for each run/simulation
- We can include a distribution when making calculations/estimates



Stochasticity Through Distributions

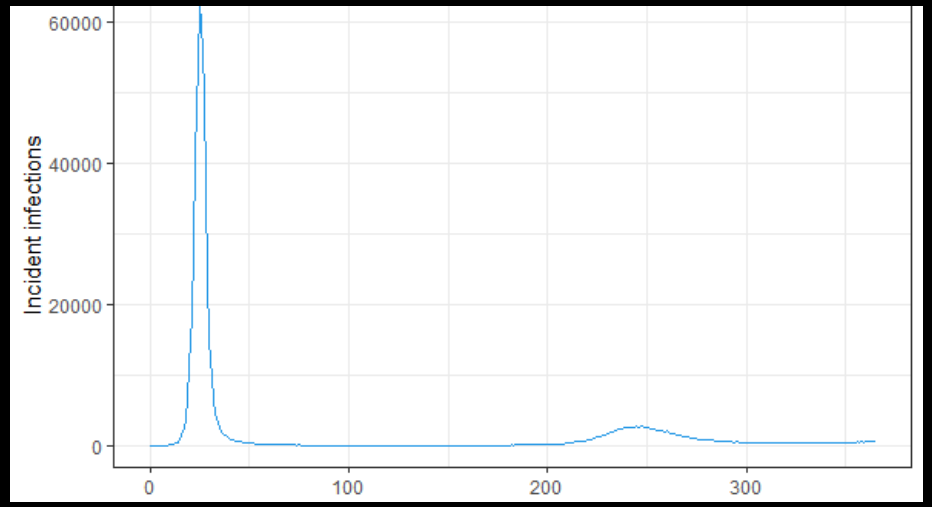
- Example: modeling force of infection (λ)
  - $\lambda(t) = \beta S(t) I(t)$
  - $I(t+1) = \sim NegBin(\lambda(t), S(t))$



Comparison

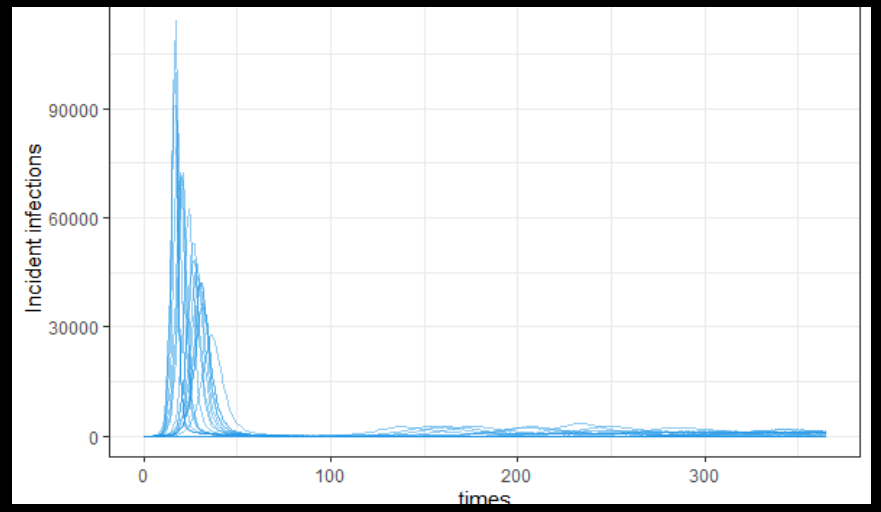
Deterministic

- Use average (single) transition rates in models
  - $\beta = 1$



Stochastic – Random!

- Use many (distribution) transition rates in models
  - $\beta \sim N(1,0.25)$



Modeling with Stochasticity

- Important part of infectious disease dynamics
- Can impact trajectory of disease
- Many ways to integrate stochasticity
  - directly add chance to your equations

Questions?

10 minute break

Workshop Schedule

Time	Topics
2:00—2:10 pm	~~Greetings~~
2:10—3:00 pm	~~Guest lecture: COVID-19 with Megan O'Driscol~~
3:00—3:10 pm	~~Break~~
3:10—4:00 pm	~~Stochasticity~~
4:00—4:10 pm	Break
4:00—5:00 pm	R Session

Week 3: Building & Assessing Models

Dr. Rachel Sippy
University of Cambridge

Week 3 Overview

- Monday, August 9:
  - ~~Guest lecture & R session by Megan O'Driscoll~~
  - ~~Stochastic models~~
  - ~~Guided practice in R~~
- Tuesday, August 10:
  - Step-by-step model building
  - Building a COVID-19 model
  - Guided practice in R
- Wednesday, August 11:
  - Comparing models to data & evaluating models
  - Guided practice in R

Post Questions in the Chat!

(or ask over microphone)

Workshop Schedule

Time	Topics
2:00—2:10 pm	~~Greetings~~
2:10—2:40 pm	R Demonstration
2:40—2:50 pm	Break
2:50—3:30	Steps for Model Building
3:30—3:40 pm	Break
3:40—5:00 pm	Building a COVID-19 Model

Objectives

- Understand the steps involved in developing models
- Practice building a model of COVID-19

Steps for Building a Model

Model Development

- Important to reflect on purpose of model & wider considerations

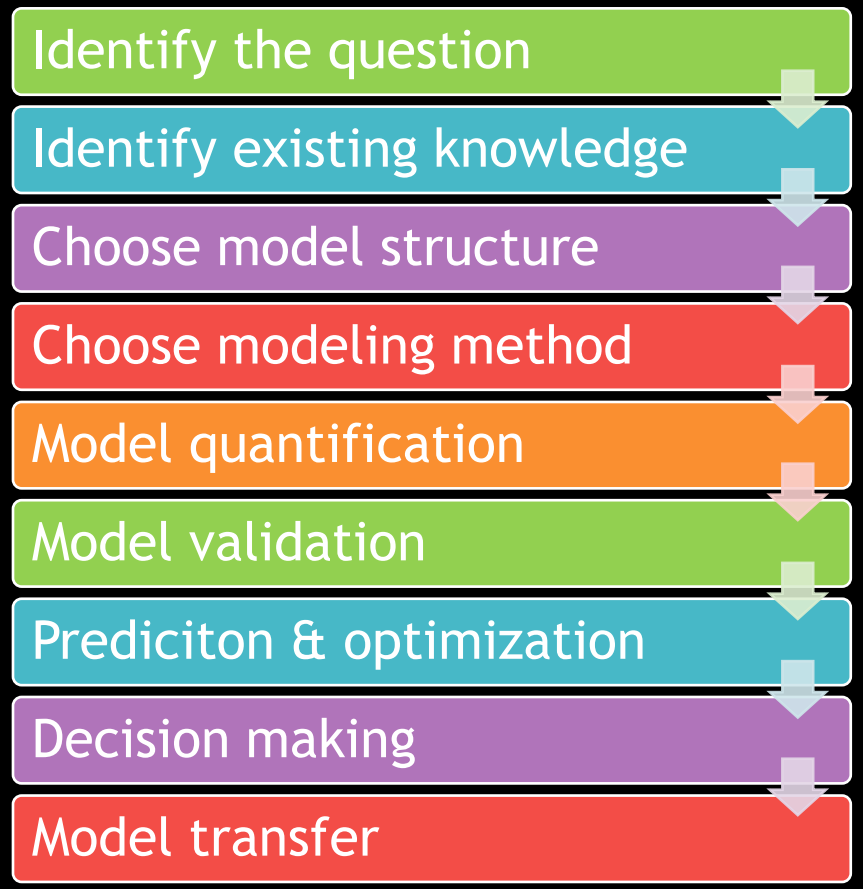
Model Development

- Important to reflect on purpose of model & wider considerations
- 9-step process from Habbema *et al.*, 1996

1. Identify the question
2. Identify existing knowledge
3. Choose model structure
4. Choose modeling method
5. Model quantification
6. Model validation
7. Prediction & optimization
8. Decision making
9. Model transfer

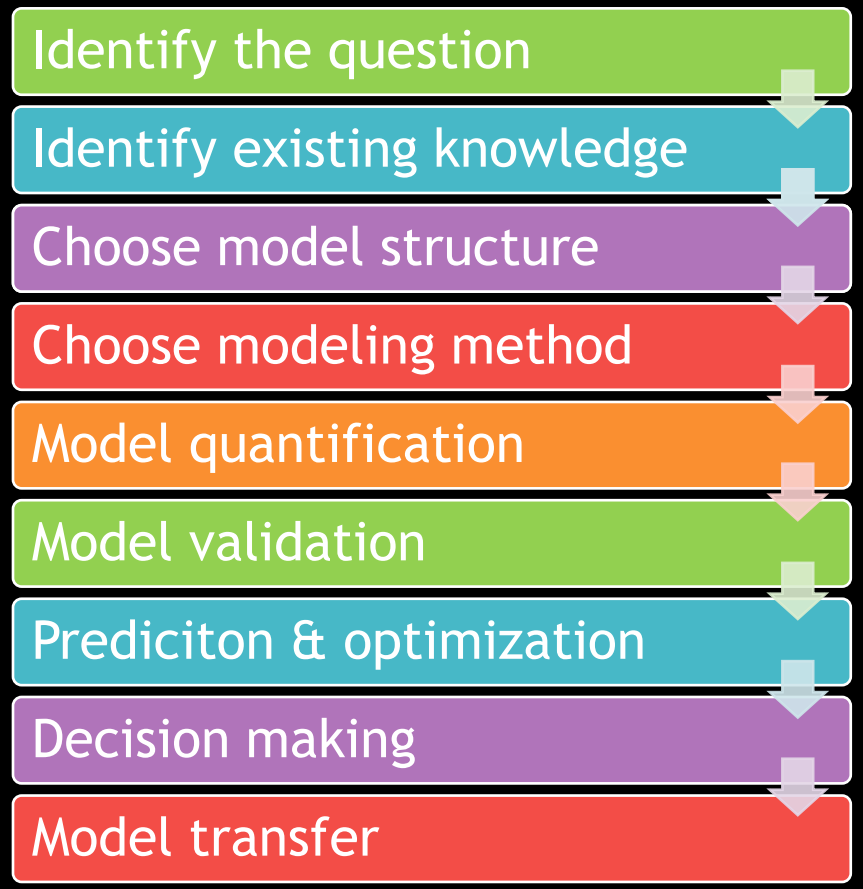
Model Development

- Important to reflect on purpose of model & wider considerations
- 9-step process from Habbema et al., 1996
- Not every model will go through all 9 steps
  - full process likely takes many years



Model Development

- Important to reflect on purpose of model & wider considerations
- 9-step process from Habbema et al., 1996
- Not every model will go through all 9 steps
  - full process likely takes many years
- Use measles as example



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- What is our research question?
  - Inference versus prediction

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  - Epidemiology of infections
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  - Comparison of different controls

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- Common questions/goals
  - Natural history of disease
  - Epidemiology of infections
  - Impact of control or treatment
  - Comparison of different controls
- Measles Scenario
  - closed population of 100,000 susceptibles
  - How will number of susceptible, infected, recovered change over time?

Identify Existing Knowledge

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Identify Existing Knowledge

- What data are available?
  - What inputs do we know?
  - Demographic rates
  - Natural history parameters
  - Control options & impact

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  - Similar disease?
  - Similar scenario?
  - Distributions/values for parameters?

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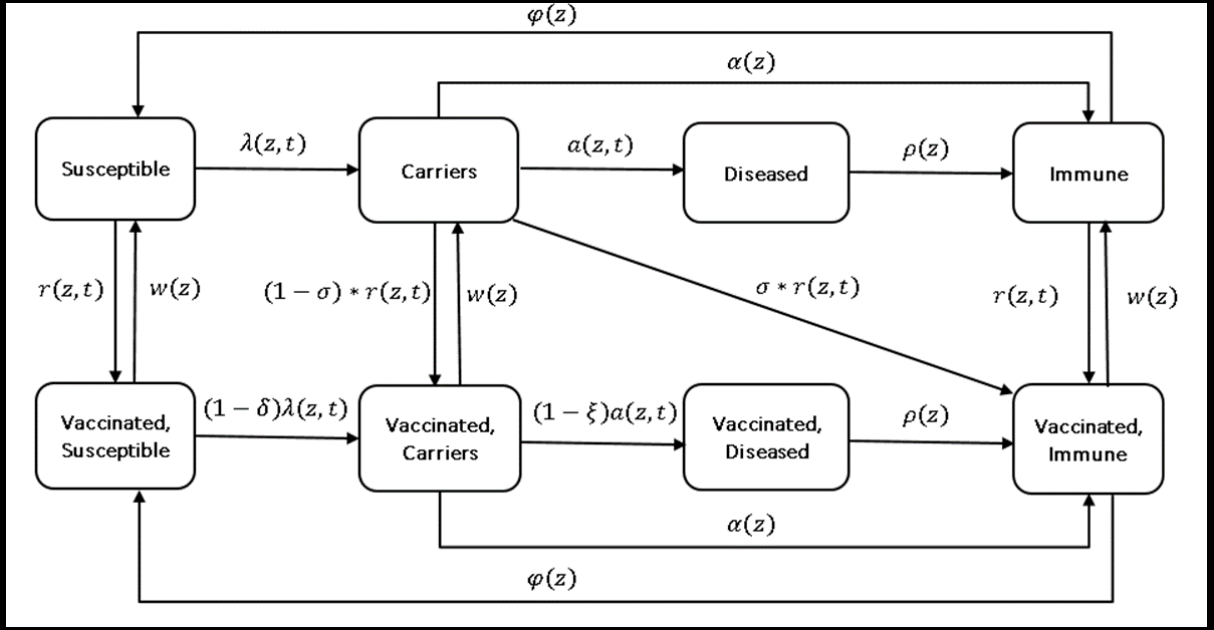

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Identify Existing Knowledge

- What data are available?
  - What inputs do we know?
  - Demographic rates
  - Natural history parameters
  - Control options & impact
- Do other models exist?
  - Similar disease?
  - Similar scenario?

- Measles Scenario
  - near-permanent immunity
  - contact: 1.5 other people/day
  - latent period: 8 days
  - duration of infection: 7 days

Choose Model Structure

- Identify the question
- Identify existing knowledge
- **Choose model structure**

Choose Model Structure

- What compartments are important?
  - Infection categories
  - Population categories/subgroups
- *"Models should be as simple as possible and no simpler."*
  - What compartments are necessary to answer our research question?

Identify the question

Identify existing knowledge

Choose model structure

Choose Model Structure

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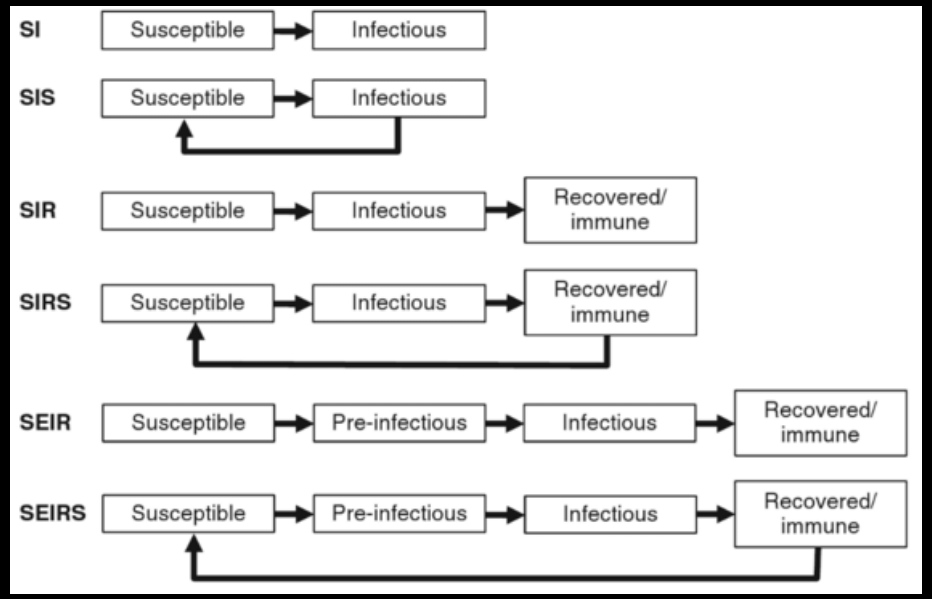

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- Measles Scenario
  - short term question
  - closed SEIR structure

Choose Modeling Method

- Identify the question
- Identify existing knowledge
- Choose model structure
- **Choose modeling method**

Choose Modeling Method

- Deterministic?
  - Describes average outcome
  - Uses average transition rates

Identify the question

Identify existing knowledge

Choose model structure

Choose modeling method

Choose Modeling Method

- Deterministic?
  - Describes average outcome
  - Uses average transition rates
- Stochastic?
  - Incorporate chance variation
  - Range of possible outcomes

Identify the question

Identify existing knowledge

Choose model structure

Choose modeling method

Choose Modeling Method

- Deterministic?
  - Describes average outcome
  - Uses average transition rates
- Stochastic?
  - Incorporate chance variation
  - Range of possible outcomes
- Combination?
  - Deterministic models can include stochastic elements and vice versa

Identify the question

Identify existing knowledge

Choose model structure

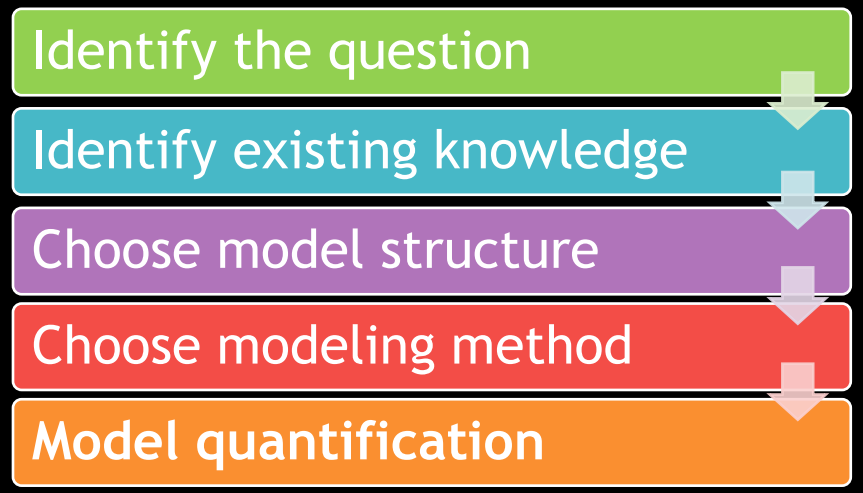
Choose modeling method

Model Quantification

- Identify the question
- Identify existing knowledge
- Choose model structure
- Choose modeling method
- **Model quantification**

Model Quantification

- Specify your inputs
  - Range of possible values from review step
  - Make sure time units are correct!



Model Quantification

- Specify your inputs
  - Range of possible values from review step
  - Make sure time units are correct!

Example: mortality rate (μ)

- $\mu = 1/L$
- L: average life expectancy

Identify the question

Identify existing knowledge

Choose model structure

Choose modeling method

Model quantification

Model Quantification

- Specify your inputs
  - Range of possible values from review step
  - Make sure time units are correct!

Example: mortality rate (μ)

- $\mu = 1/L$
- L: average life expectancy
- L=60 years
- μ=1/60 per year
- μ=1/(60*365) per day

Identify the question

Identify existing knowledge

Choose model structure

Choose modeling method

Model quantification

Model Quantification

- Specify your inputs
  - Range of possible values from review step
  - Make sure time units are correct!
- Estimate from data
  - Collect new data?
  - Statistical model
  - Parameter estimation

Identify the question

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Identify the question

Identify existing knowledge

Choose model structure

Choose modeling method

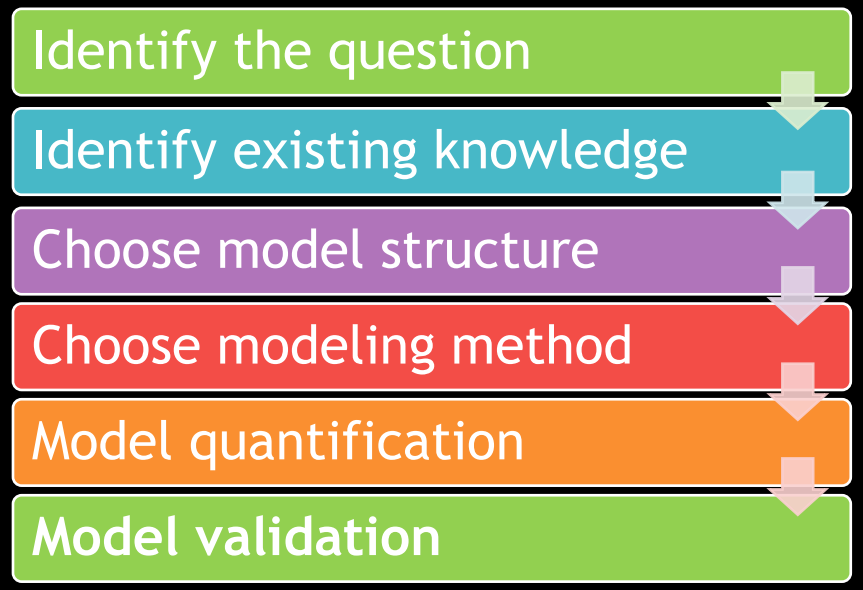
Model quantification

Model Validation

- Identify the question
- Identify existing knowledge
- Choose model structure
- Choose modeling method
- Model quantification
- **Model validation**

Model Validation

- Compare model results with real data
  - Ideally with independent datasets
  - Is the behavior you model consistent with reality?
  - Model fitting
- Share with other experts

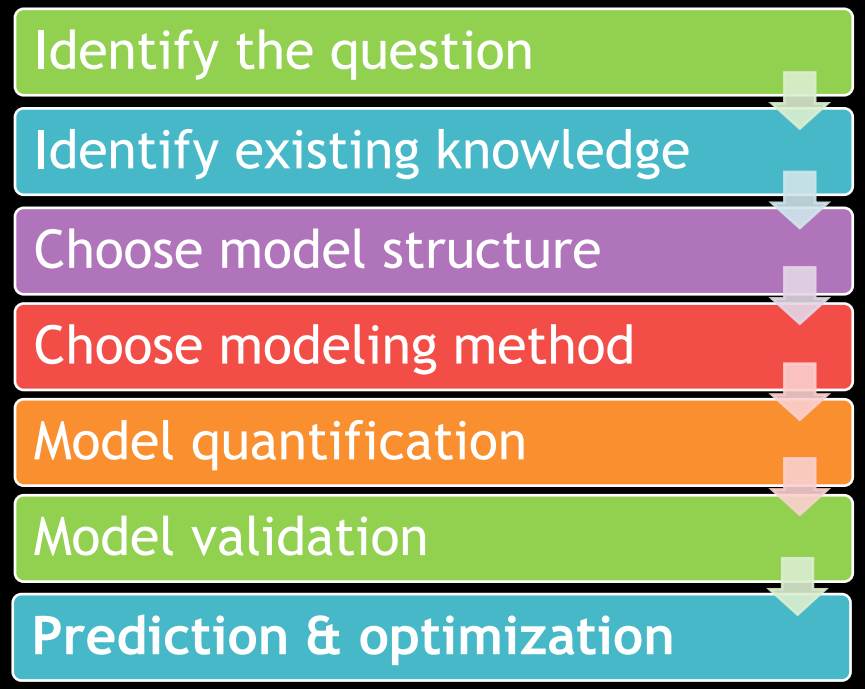


Prediction & Optimization

- Identify the question
- Identify existing knowledge
- Choose model structure
- Choose modeling method
- Model quantification
- Model validation
- **Prediction & optimization**

Prediction & Optimization

- Run your model and make predictions
- Sensitivity analysis
  - Imagine that assumptions are flawed
  - Test boundaries of the model
  - “Try to break the model”
- Report any model limitations

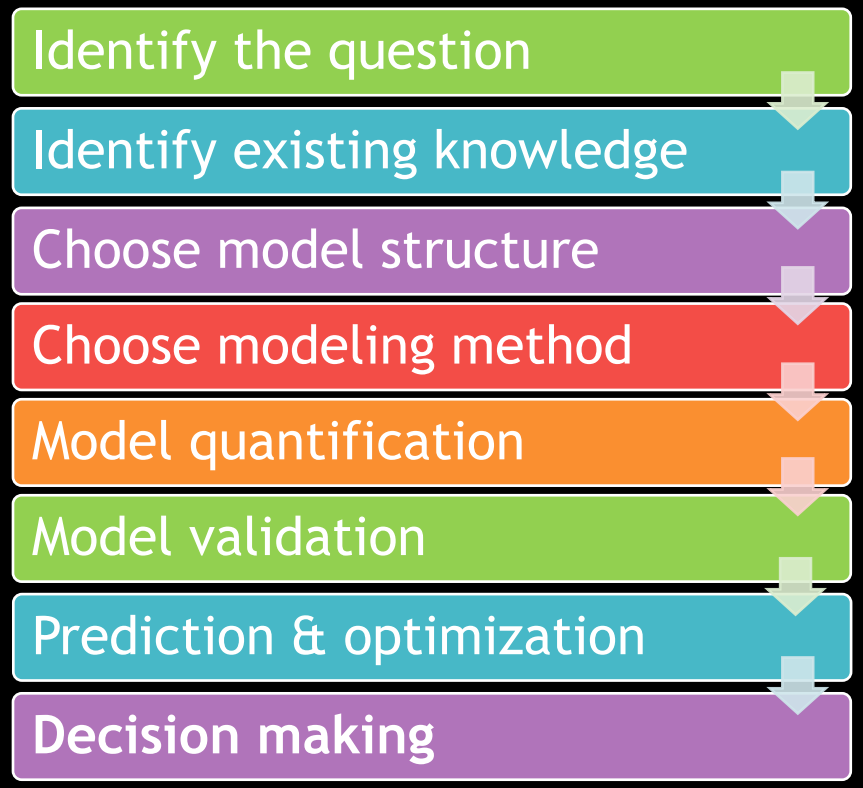


Decision Making

- Identify the question
- Identify existing knowledge
- Choose model structure
- Choose modeling method
- Model quantification
- Model validation
- Prediction & optimization
- **Decision making**

Decision Making

- Public health policy decisions require many experts & stakeholders
  - Make sure the model can be explained to broad audiences
  - Be able to explain model limitations

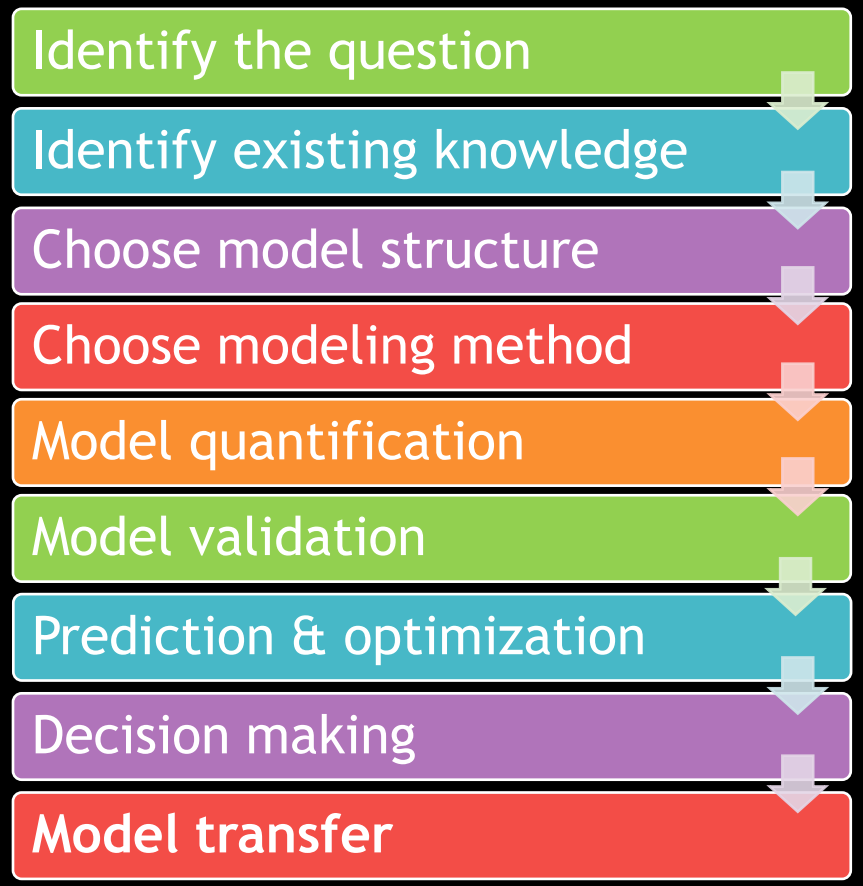


Model Transfer

- Identify the question
- Identify existing knowledge
- Choose model structure
- Choose modeling method
- Model quantification
- Model validation
- Prediction & optimization
- Decision making
- **Model transfer**

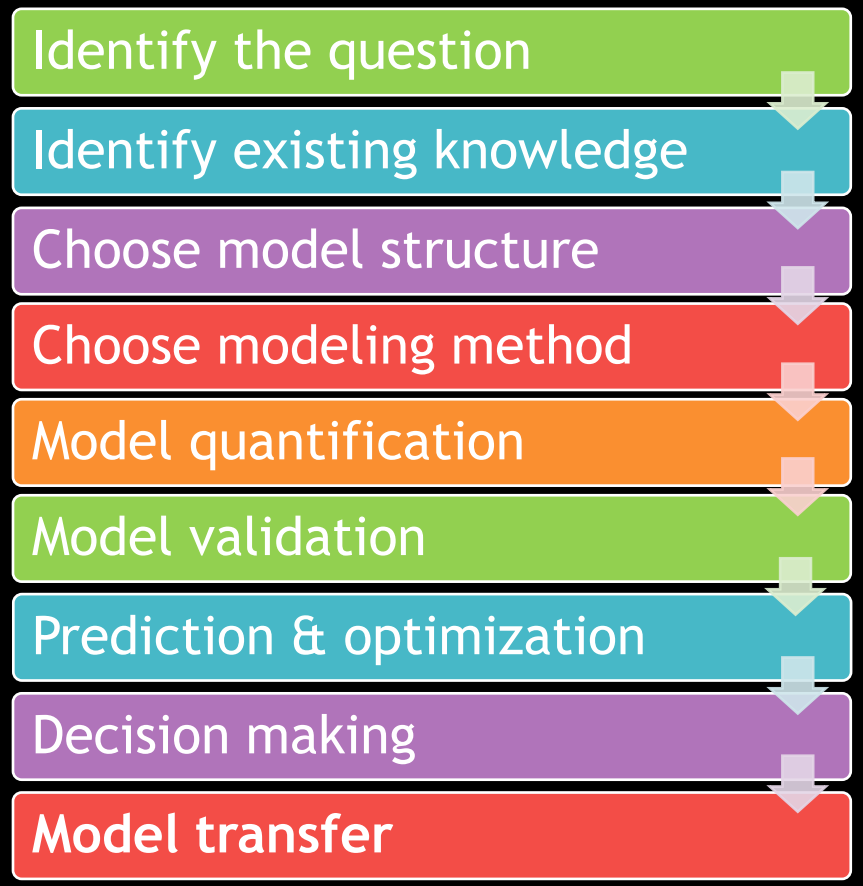
Model Transfer

- Ideally model can be used by ministries of health/public health
  - Only if model design and parameters are unlikely to change



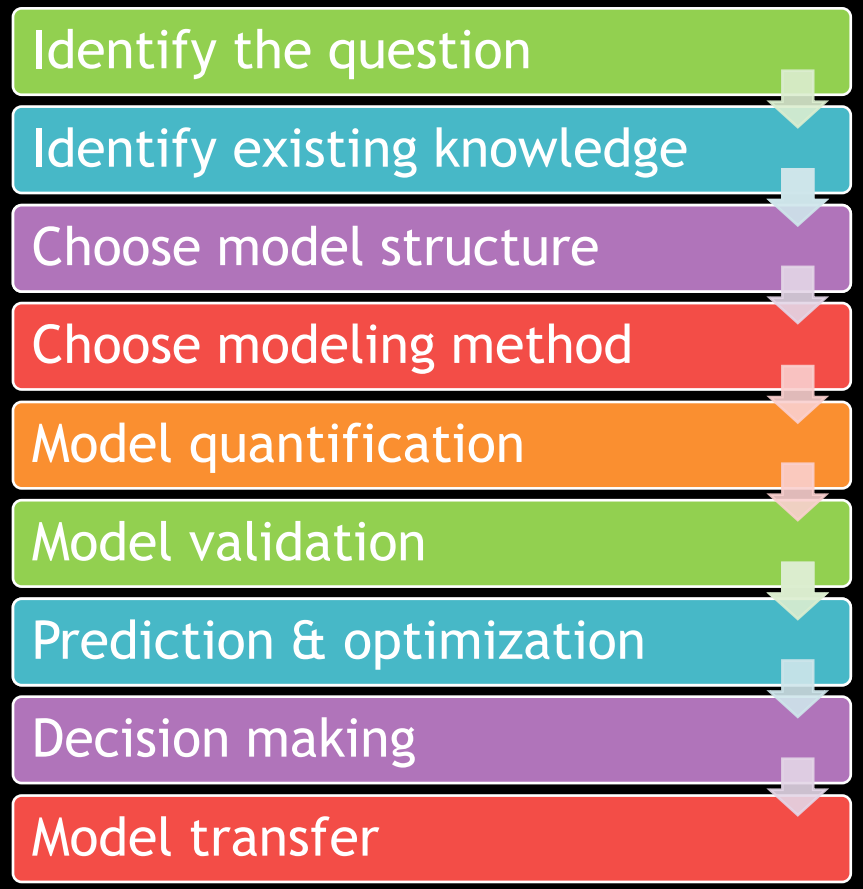
Model Transfer

- Ideally model can be used by ministries of health/public health
  - Only if model design and parameters are unlikely to change
- User-friendly models
  - user's manual
  - user-friendly interface



Model Development is Non-Linear

- Iterative process



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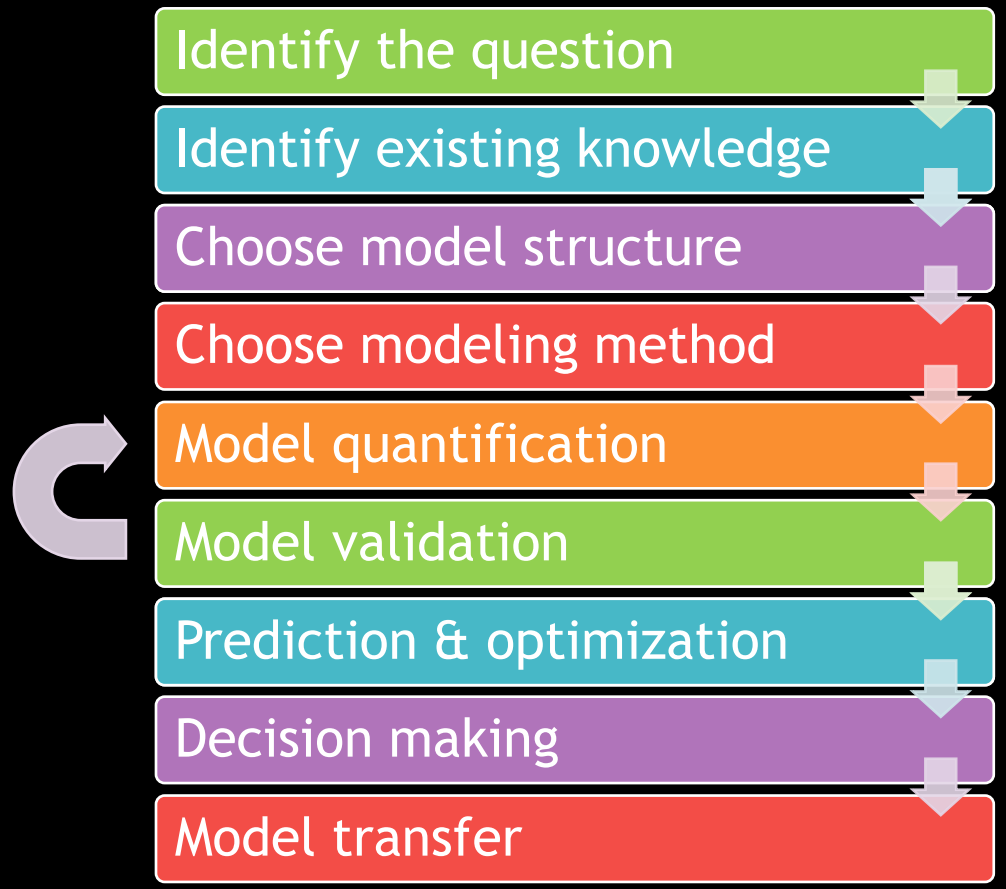

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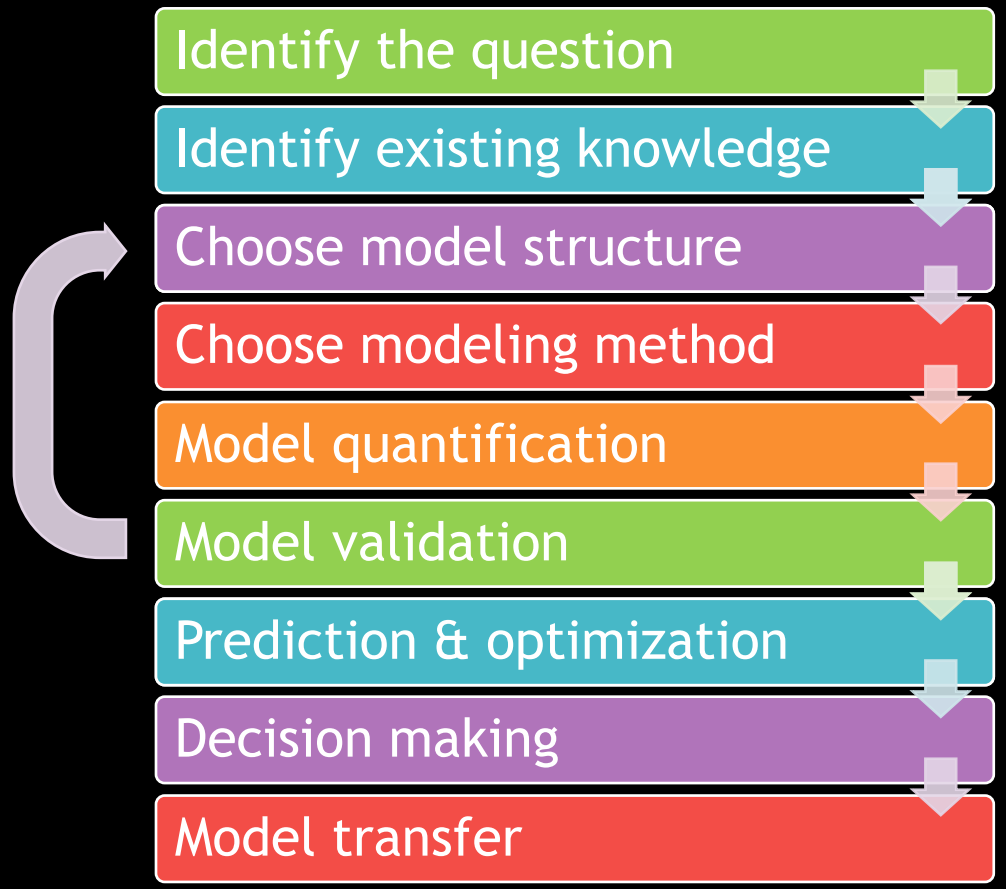

Questions?

10 minute break

Workshop Schedule

Time	Topics
2:00—2:10 pm	~~Greetings~~
2:10—2:40 pm	~~R Demonstration~~
2:40—2:50 pm	~~Break~~
2:50—3:30	~~Steps for Model Building~~
3:30—3:40 pm	Break
3:40—5:00 pm	Building a COVID-19 Model

Week 3: Evaluating Models

Dr. Rachel Sippy
University of Cambridge

Week 3 Overview

- Monday, August 9:
  - ~~Guest lecture & R session by Megan O'Driscoll~~
  - ~~Stochastic models~~
  - ~~Guided practice in R~~
- ~~Tuesday, August 10:~~
  - ~~Step-by-step model building~~
  - ~~Building a COVID-19 model~~
  - ~~Guided practice in R~~
- Wednesday, August 11:
  - Guest lecture: COVID-19 in Bangladesh by Kate Hampson
  - Comparing models to data & evaluating models
  - Guided practice in R

Post Questions in the Chat!

(or ask over microphone)

Workshop Schedule

Time	Topics
2:00—2:10 pm	~~Greetings~~
2:10—3:00 pm	COVID-19 in Bangladesh – Dr. Kate Hampson
3:00—3:10 pm	Break
3:10—3:20 pm	Sensitivity Analysis
3:20—3:50 pm	Assessing Models
3:50—4:00 pm	Break
4:00—5:00 pm	Review & Questions

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Sensitivity Analysis

Terminology

Parameterization	Selecting values for the parameters in the model (taking from literature, best guess, fitting to data)
Fitting (calibration)	Parameterizing the model by finding a model with the “best” fit to some data (using a statistical goodness of fit metric)
Validation	Comparing the results of a parameterized model to data to see if the results are “valid” (are the results reasonable or using some statistical test)
Sensitivity analysis	Changing the values of parameters to see how this affects the results (one-way or multi-way)

Sensitivity Analysis

- Purpose
  - test the “extremes”: best- and worst-case scenarios
  - see how the model performs under range of conditions
  - especially useful when we are uncertain about parameter values!

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- How does parameter uncertainty affect results?
  - how big is the uncertainty around each parameter
  - how important is the parameter

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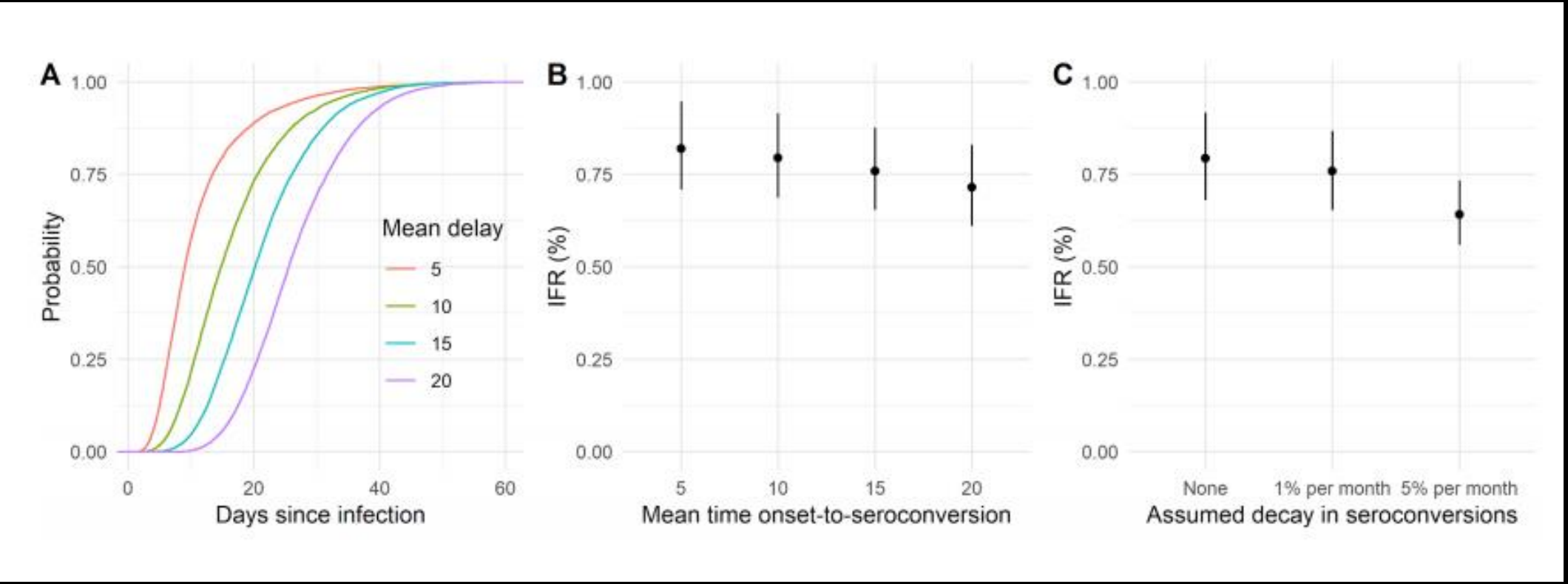
these allow you to calculate confidence intervals

Sensitivity Analysis



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Model Evaluation & Assessment

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     - Models are only one source of information!
     - We cannot make models for every question

What are the Characteristics of a Good Model?

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   - Does the model add to what we already know?
   - Does the model incorporate new information?

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   - Does the model incorporate new information?

- Reasonable, useful & relevant!

Assessing Models

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  - consider the model assumptions and if they are appropriate for the question
- How is uncertainty incorporated into the model?
  - has uncertainty been added to any model parameters?
  - look for confidence/prediction intervals for model estimates
  - was a sensitivity analysis performed?

Assessing Models

- Are there multiple models to consider?

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  - multiple models or models combining models (ensembles)
  - more than one model can help with decision-making
- How wide are the confidence intervals surrounding the estimates?
  - do not be over-confident when interpreting models
  - uncertainty will increase for long-term projections

Assessing Models

- Does the model represent your population/scenario of interest?
  - similar population? similar geopolitical setting?
  - similar stage/timing of epidemic?

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  - if there are differences, consider if the model estimates are applicable to your scenario
  - is the model intended to be generalizable?

comment

Check for updates

The importance of local context in COVID-19 models

COVID-19 models have been extensively used to inform public health officials about potential interventions. Nevertheless, careful attention must be taken when extrapolating projections and parameters across different regions, as there is no one-size-fits-all model for the pandemic.

Rosalind M. Eggo, Jeanette Dawa, Adam J. Kucharski and Zulma M. Cucunuba

Infectious disease models are an integral part of public health decision making, and have been crucial tools throughout the COVID-19 pandemic. In early 2020, models estimated the extent of COVID-19 in Wuhan and regional patterns of importations, made projections of potential epidemics and healthcare needs, and provided short-term predictions of case numbers in newly unfolding outbreaks. As countries considered control and mitigation measures, models helped assess likely effects of proposed interventions and determine 'counterfactuals', that is, expected epidemic trajectories if an intervention was not implemented. However, it is important to stress that the quality of such projections depends on within- and between-country variation in transmission, control and burden.

Transmission

The dynamics of directly transmitted respiratory infections depend on multiple factors, including population demography: variation in age and spatial distribution; size and composition of households, schools, and workplaces; and population behavior, often measured as contact rates between

that each sub-community has a separate epidemic[3], caused by structure within a city[4], geographics[5] or other factors. National or regional differences in extent or type of community structure may impact projections, and multi-peaked epidemics can also result from interventions. These effects are especially difficult to predict for new pathogens.

Another factor is the frequency and characteristics of different settings that drive transmission[6]. For COVID-19, information has emerged about high-risk settings, such as households, hospitals, congregate settings including long-term care facilities, and overcrowded communities. However, incorporating this level of complexity into transmission models before this information becomes available is challenging. As a result, the dynamics of very detailed models are likely to reflect strong underlying assumptions rather than genuine patterns in (as yet unknown) data.

Severity and impact

To project the extent and impact of COVID-19 in other countries, estimates of severity (for example, age-specific hospitalization and mortality rates) were

Excess mortality data can be useful to better understand deaths and pandemic impacts[10]. However, when using excess or all-cause mortality data, care is needed to understand the context, because interventions such as social distancing and stay-at-home orders could have decreased prevalence of other infectious diseases and thus decreased mortality, and could also have reduced deaths due to other causes (for example, road traffic accidents). Conversely, large epidemics or intensive interventions can disrupt care for non-COVID-19 causes, leading to increased morbidity and mortality that can lag the epidemic or interventions by a considerable period of time, as with deaths from diseases like cancer.

Control

Early responses to SARS-CoV-2 outbreaks varied globally, with many countries implementing lockdown-type interventions, including varying levels of school, work and business closures, stay-at-home orders, curfews and quarantines. In addition, test–trace–isolate strategies and individual-level measures like hand-washing and mask-wearing were promoted to varying

?

cable to your

Eggo 2021

Assessing Models

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  - limitations can come from the data being used and the model

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  - if there are differences, consider if the model estimates are applicable to your scenario
  - is the model intended to be generalizable?
- What are the limitations?
  - limitations can come from the data being used and the model
  - are the limitations well-articulated?
  - be realistic about what models can and cannot do!

Wrong but Useful — What Covid-19 Epidemiologic Models Can and Cannot Tell Us

Inga Holmdahl, S.M., and Caroline Buckee, D.Phil.

Amid enormous uncertainty about the future of the Covid-19 pandemic, epidemiologic models are critical planning tools for policymakers, clinicians, and public health practitioners. Some models with apparently conflicting conclusions have received substantial press coverage, giving the impression that mathematical models are in general unreliable or inherently flawed. But infectious disease modeling is an expansive field with a long history, encompassing a range of methods and assumptions that are not necessarily directly comparable, or even designed for the same purpose (see box).

Covid-19 modeling studies generally follow one of two general approaches that we will refer to here as forecasting models and mechanistic models. Although there are hybrid approaches, these two model types tend to address different questions on different time scales, and they deal differently with uncertainty.

Forecasting models are often statistical in nature, fitting a line or curve to data and extrapolating from there — like seeing a pattern in a sequence of numbers

These models yield quantitative projections that policymakers may need in the short term to allocate resources or plan interventions.

The original versions of the controversial model from the Institute for Health Metrics and Evaluation (IHME) fell into this category, approximating the shape of the epidemic curve from outbreaks in China and Italy and applying it elsewhere (see table). Since purely statistical approaches don't account for how transmission occurs, they are generally not well suited for long-term predictions about epidemiologic dynamics (such as when the peak will occur and whether resurgence will happen) or for inference about intervention efficacy.[1] Several forecasting models therefore limit their projections to one week or a few weeks ahead.

Mechanistic models, like the Susceptible–Exposed–Infectious–Recovered frameworks, mimic the way SARS-CoV-2 spreads and can be used to forecast or simulate future transmission scenarios under various assumptions about parameters governing transmission, disease, and immunity. Unlike purely statistical models, mechanistic approaches include important nonlinear feedback — the more people become infected, the faster disease spreads. Because these models reflect the underlying transmission process, the disease-specific parameters driving it can be modified to test how the pandemic may change under various assumptions about the disease and implementation of control measures.

Mechanistic modeling is one of the only ways to explore possible long-term epidemiologic outcomes. For example, the model

Five Questions to Ask about Model Results.

1. What is the purpose and time frame of this model? For example, is it a purely statistical model intended to provide short-term forecasts or a mechanistic model investigating future scenarios? These two types of models have different limitations.
2. What are the basic model assumptions? What is being assumed about immunity and asymptomatic transmission, for example? How are contact parameters included?
3. How is uncertainty being displayed? For statistical models, how are confidence intervals calculated and displayed? Uncertainty should increase as we move into

nterest?

re applicable to your

odel

Holmdahl 2020

Assessing Models

- Is more information needed from the model?
  - model results may lead to additional questions!
  - could the model be improved or expanded?

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Assessing Models

- Is more information needed from the model?
  - model results may lead to additional questions!
  - could the model be improved or expanded?
- Has the model been validated?
  - comparison of model predictions/projections to real-life data
  - fitting the model to these data and assessing model error

Assessing a Model

1. Does the model address the question of interest?
2. How is uncertainty incorporated into the model?
3. Are there multiple models to consider?
4. How wide are the confidence intervals?
5. Does the model represent your population/scenario?
6. What are the limitations?
7. Is more information needed from the model?
8. Has the model been validated?

Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand

Neil M Ferguson, Daniel Laydon, Gemma Nedjati-Gilani, Natsuko Imai, Kylie Ainslie, Marc Baguelin, Sangeeta Bhatia, Adhiratha Boonyasiri, Zulma Cucunubá, Gina Cuomo-Dannenburg, Amy Dighe, Ilaria Dorigatti, Han Fu, Katy Gaythorpe, Will Green, Arran Hamlet, Wes Hinsley, Lucy C Okell, Sabine van Elsland, Hayley Thompson, Robert Verity, Erik Volz, Haowei Wang, Yuanrong Wang, Patrick GT Walker, Caroline Walters, Peter Winskill, Charles Whittaker, Christl A Donnelly, Steven Riley, Azra C Ghani.

On behalf of the Imperial College COVID-19 Response Team

WHO Collaborating Centre for Infectious Disease Modelling
MRC Centre for Global Infectious Disease Analysis
Abdul Latif Jameel Institute for Disease and Emergency Analytics
Imperial College London

Correspondence: neil.ferguson@imperial.ac.uk

Summary

The global impact of COVID-19 has been profound, and the public health threat it represents is the most serious seen in a respiratory virus since the 1918 H1N1 influenza pandemic. Here we present the results of epidemiological modelling which has informed policymaking in the UK and other countries in recent weeks. In the absence of a COVID-19 vaccine, we assess the potential role of a number of public health measures – so-called non-pharmaceutical interventions (NPIs) – aimed at reducing contact rates in the population and thereby reducing transmission of the virus. In the results presented here, we apply a previously published microsimulation model to two countries: the UK (Great Britain specifically) and the US. We conclude that the effectiveness of any one intervention in isolation is likely to be limited, requiring multiple interventions to be combined to have a substantial impact on transmission.

Two fundamental strategies are possible: (a) mitigation, which focuses on slowing but not necessarily

Assessing a Model

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Summary

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Two fundamental strategies are possible: (a) mitigation, which focuses on slowing but not necessarily

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Methods

Transmission Model

We modified an individual-based simulation model developed to support pandemic influenza planning[5,6] to explore scenarios for COVID-19 in GB. The basic structure of the model remains as previously published. In brief, individuals reside in areas defined by high-resolution population density data. Contacts with other individuals in the population are made within the household, at school, in the workplace and in the wider community. Census data were used to define the age and household distribution size. Data on average class sizes and staff-student ratios were used to generate a synthetic population of schools distributed proportional to local population density. Data on the distribution of workplace size was used to generate workplaces with commuting distance data used to locate workplaces appropriately across the population. Individuals are assigned to each of these locations at the start of the simulation.

Transmission events occur through contacts made between susceptible and infectious individuals in either the household, workplace, school or randomly in the community, with the latter depending on spatial distance between contacts. Per-capita contacts within schools were assumed to be double those elsewhere in order to reproduce the attack rates in children observed in past influenza pandemics[7]. With the parameterisation above, approximately one third of transmission occurs in the household, one third in schools and workplaces and the remaining third in the community. These contact patterns reproduce those reported in social mixing surveys[8].

We assumed an incubation period of 5.1 days[9,10]. Infectiousness is assumed to occur from 12 hours prior to the onset of symptoms for those that are symptomatic and from 4.6 days after infection in those that are asymptomatic with an infectiousness profile over time that results in a 6.5-day mean generation time. Based on fits to the early growth-rate of the epidemic in Wuhan[10,11], we make a baseline assumption that R_0=2.4 but examine values between 2.0 and 2.6. We assume that symptomatic individuals are 50% more infectious than asymptomatic individuals. Individual infectiousness is assumed to be variable, described by a gamma distribution with mean 1 and shape parameter α=0.25. On recovery from infection, individuals are assumed to be immune to re-infection in the short term. Evidence from the Flu Watch cohort study suggests that re-infection with the same strain of seasonal circulating coronavirus is highly unlikely in the same or following season (Prof Andrew Hayward, personal communication).

Infection was assumed to be seeded in each country at an exponentially growing rate (with a doubling time of 5 days) from early January 2020, with the rate of seeding being calibrated to give local epidemics which reproduced the observed cumulative number of deaths in GB or the US seen by 14th

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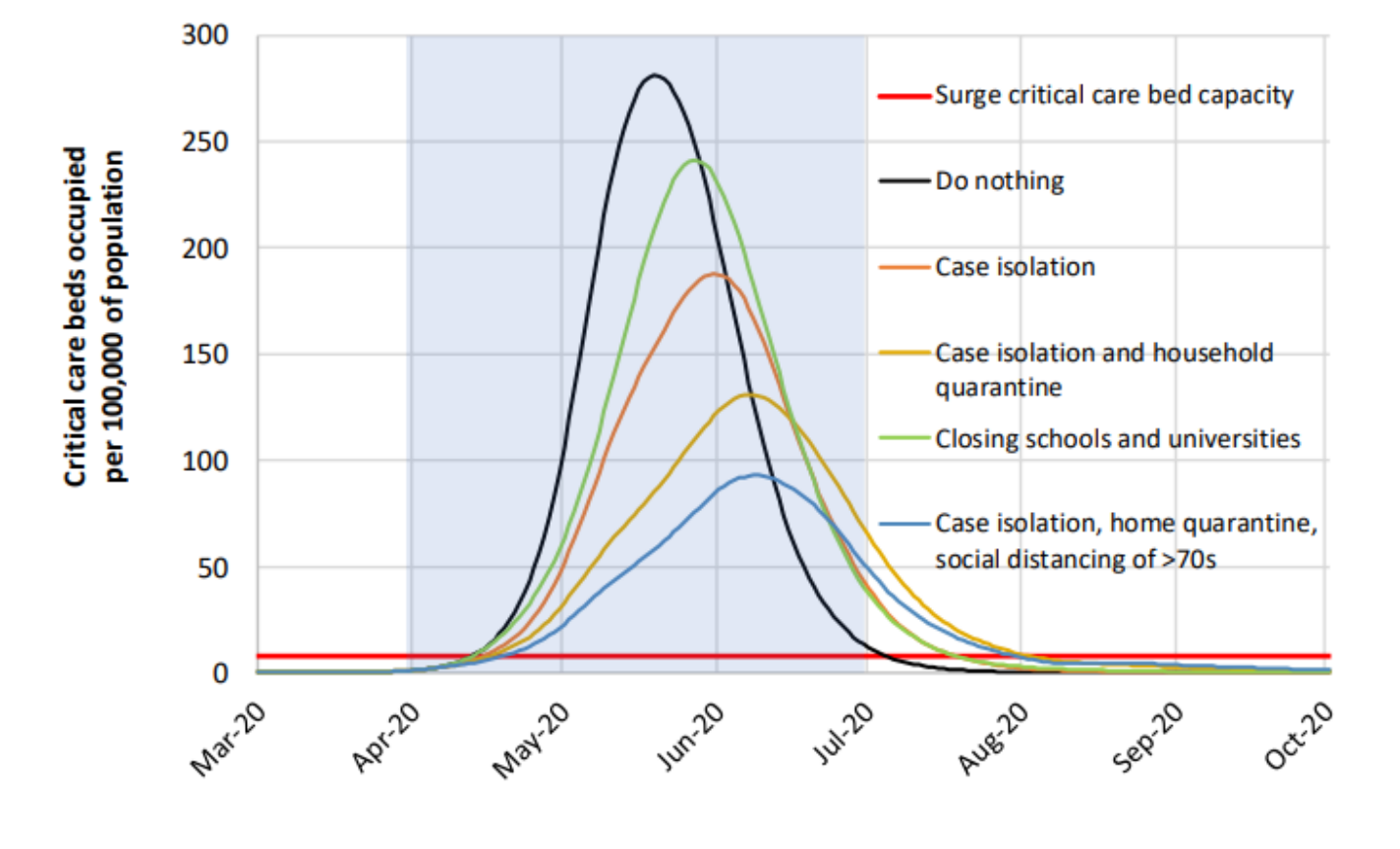

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		Total deaths			
R_0	On Trigger	Do nothing	CI_HQ_SD	PC_CI_SD	PC_CI_HQ_SD
2	60	410,000	47,000	6,400	5,600
	100	410,000	47,000	9,900	8,300
	200	410,000	46,000	17,000	14,000
	300	410,000	45,000	24,000	21,000
	400	410,000	44,000	30,000	26,000
2.2	60	460,000	62,000	9,700	6,900
	100	460,000	61,000	13,000	10,000
	200	460,000	64,000	23,000	17,000
	300	460,000	65,000	32,000	26,000
	400	460,000	68,000	39,000	31,000
2.4	60	510,000	85,000	12,000	8,700
	100	510,000	87,000	19,000	13,000
	200	510,000	90,000	30,000	24,000
	300	510,000	94,000	43,000	34,000
	400	510,000	98,000	53,000	39,000
2.6	60	550,000	110,000	20,000	12,000
	100	550,000	110,000	26,000	16,000
	200	550,000	120,000	39,000	30,000
	300	550,000	120,000	56,000	40,000
	400	550,000	120,000	71,000	48,000

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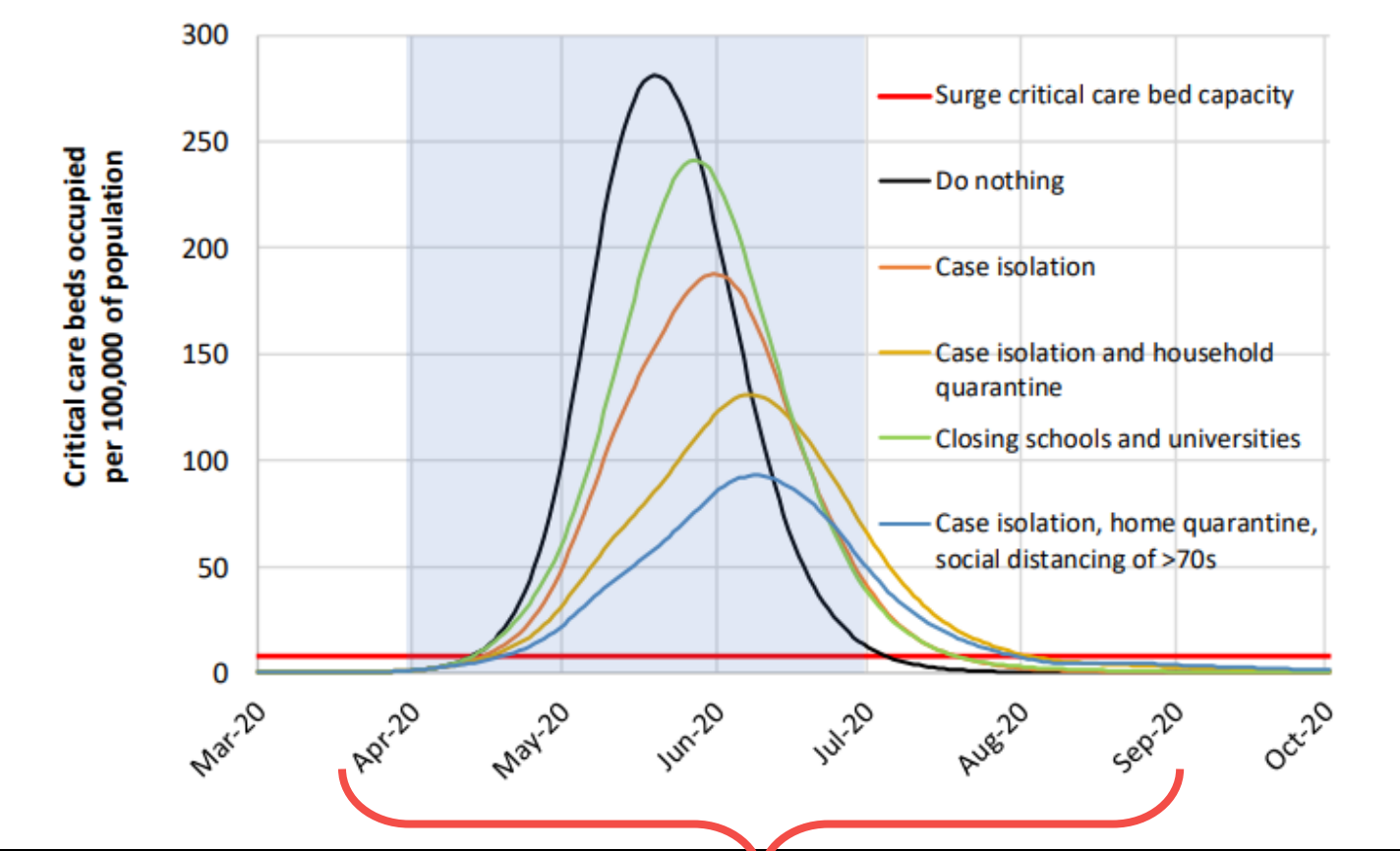

6 months, start of pandemic

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To avoid a rebound in transmission, these policies will need to be maintained until large stocks of vaccine are available to immunise the population – which could be 18 months or more. Adaptive hospital surveillance-based triggers for switching on and off population-wide social distancing and school closure offer greater robustness to uncertainty than fixed duration interventions and can be adapted for regional use (e.g. at the state level in the US). Given local epidemics are not perfectly synchronised, local policies are also more efficient and can achieve comparable levels of suppression to national policies while being in force for a slightly smaller proportion of the time. However, we estimate that for a national GB policy, social distancing would need to be in force for at least 2/3 of the time (for R_0=2.4, see Table 4) until a vaccine was available.

However, there are very large uncertainties around the transmission of this virus, the likely effectiveness of different policies and the extent to which the population spontaneously adopts risk reducing behaviours. This means it is difficult to be definitive about the likely initial duration of measures which will be required, except that it will be several months. Future decisions on when and for how long to relax policies will need to be informed by ongoing surveillance.

The measures used to achieve suppression might also evolve over time. As case numbers fall, it becomes more feasible to adopt intensive testing, contact tracing and quarantine measures akin to the strategies being employed in South Korea today. Technology – such as mobile phone apps that track an individual's interactions with other people in society – might allow such a policy to be more effective and scalable if the associated privacy concerns can be overcome. However, if intensive NPI packages aimed at suppression are not maintained, our analysis suggests that transmission will rapidly rebound, potentially producing an epidemic comparable in scale to what would have been seen had no interventions been adopted.

Long-term suppression may not be a feasible policy option in many countries. Our results show that the alternative relatively short-term (3-month) mitigation policy option might reduce deaths seen in the epidemic by up to half, and peak healthcare demand by two-thirds. The combination of case isolation, household quarantine and social distancing of those at higher risk of severe outcomes (older individuals and those with other underlying health conditions) are the most effective policy combination for epidemic mitigation. Both case isolation and household quarantine are core epidemiological interventions for infectious disease mitigation and act by reducing the potential for onward transmission through reducing the contact rates of those that are known to be infectious (cases) or may be harbouring infection (household contacts). The WHO China Joint Mission Report suggested that 80% of transmission occurred in the household[16], although this was in a context where interpersonal contacts were drastically reduced by the interventions put in place. Social distancing of high-risk groups is predicted to be particularly effective at reducing severe outcomes given the strong

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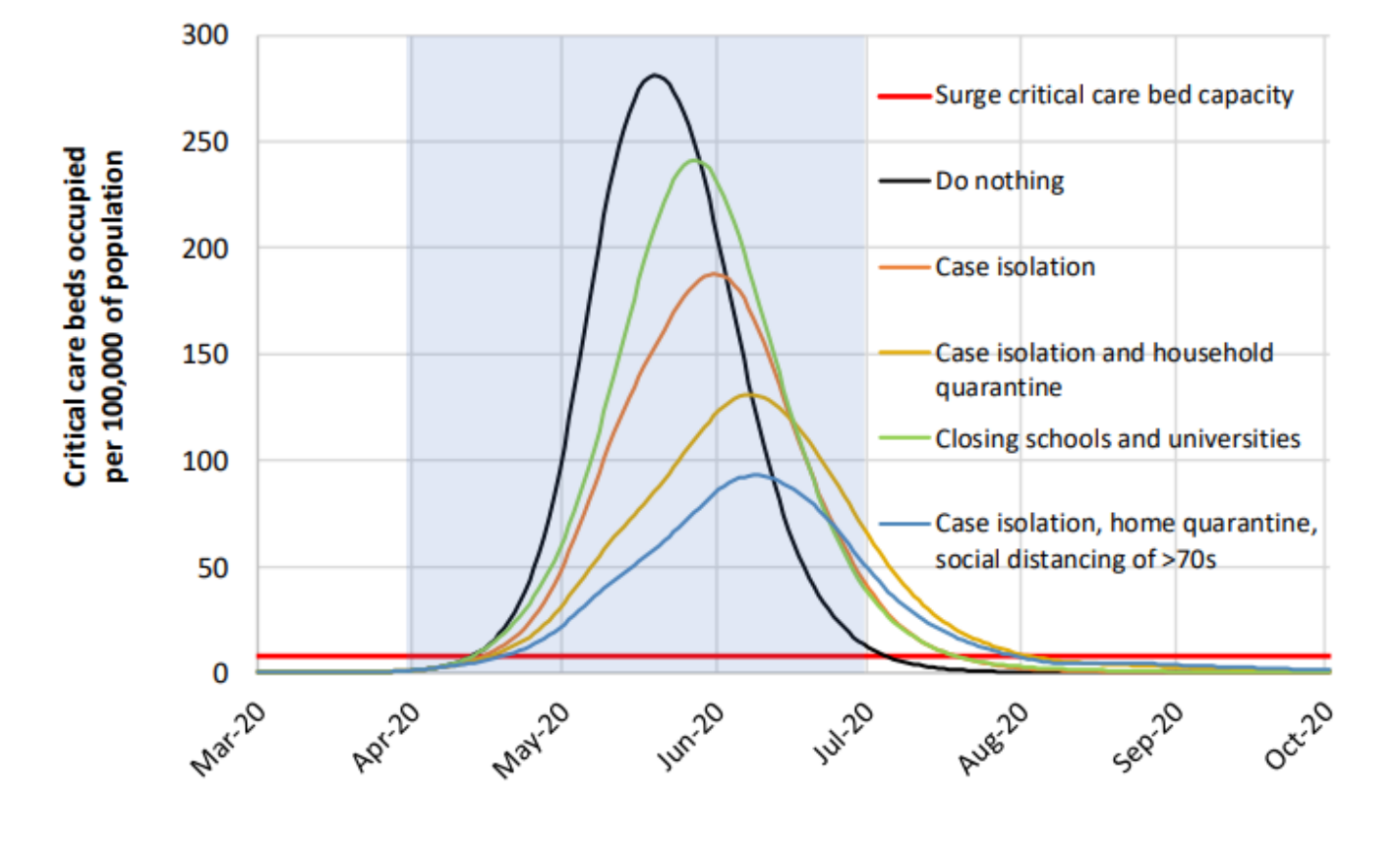

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Questions?

10 minute break

Workshop Schedule

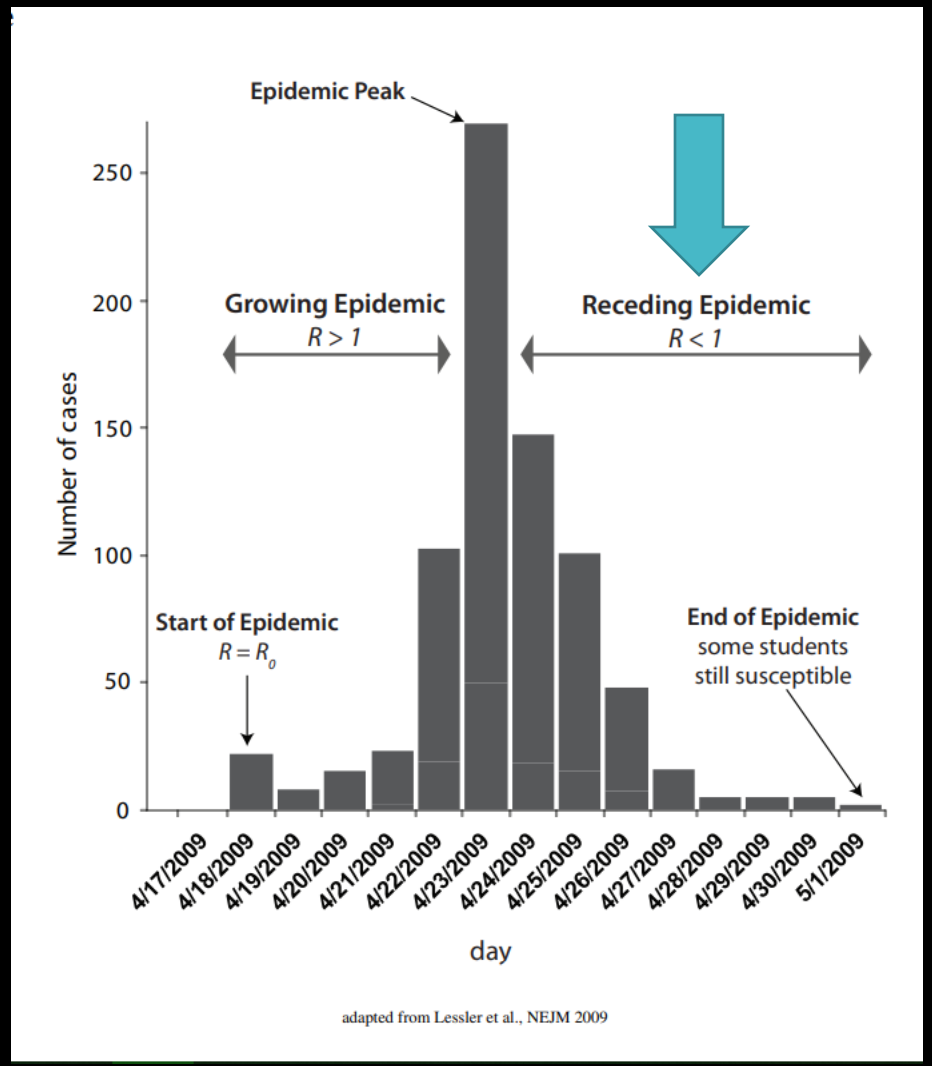
Time	Topics
2:00—2:10 pm	~~Greetings~~
2:10—3:00 pm	~~COVID-19 in Bangladesh - Dr. Kate Hampson~~
3:00—3:10 pm	~~Break~~
3:10—3:20 pm	~~Sensitivity Analysis~~
3:20—3:50 pm	~~Assessing Models~~
3:50—4:00 pm	Break
4:00—5:00 pm	Review & Questions

Review Slides

(& practice questions)

Reproductive Numbers & Epidemic Curve

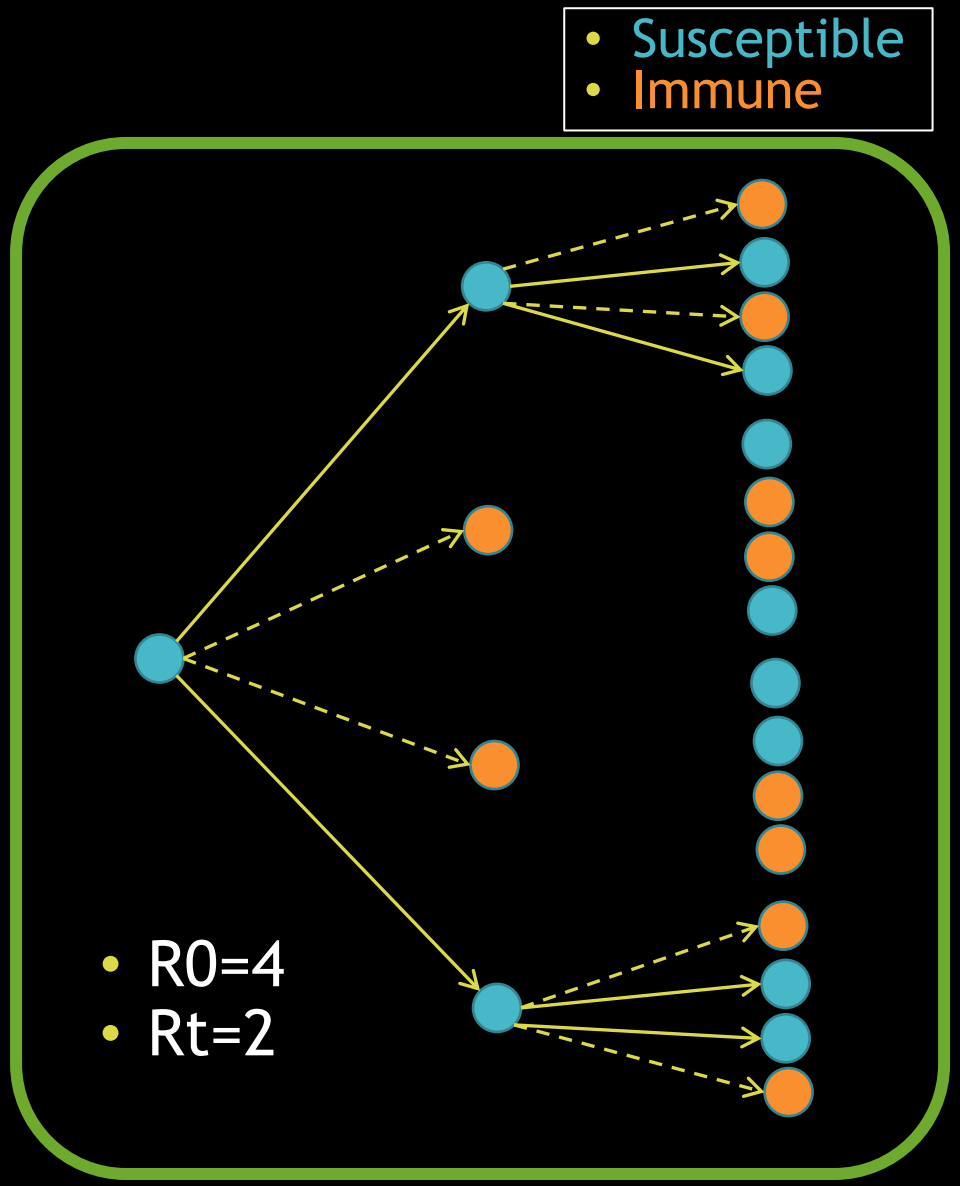
- Reproductive numbers change throughout an epidemic
  - as the epidemic continues, there will be fewer susceptible people and the reproductive number will decrease unless:
    - more susceptibles are added
    - something changes to increase transmission
  - if Rt=1, transmission will be stable
  - as soon as Rt<1, the epidemic will start to fade



adapted from Lessler et al., NEJM 2009

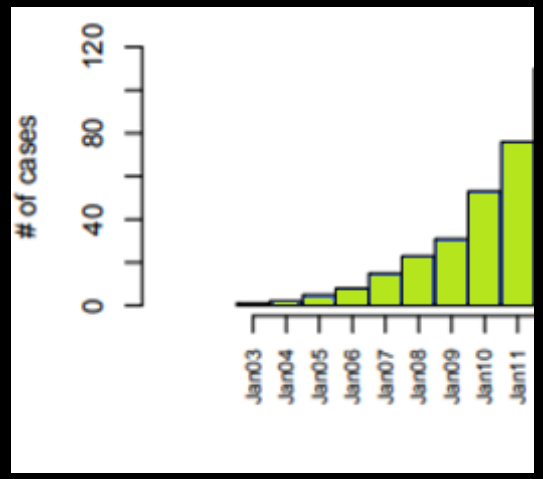
Reproductive Number & Herd Immunity

- Herd immunity
  - recall that the number of new cases depends on the presence of infected persons (to cause infection) but also the presence of susceptible persons (to become infected)
  - $R_t = R_0 s_t$
  - if half of the population is immune, the reproductive number is cut in half
  - if there are enough immunes, we can control transmission

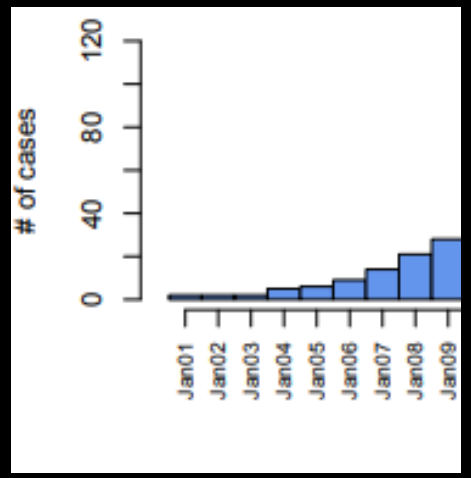


Reproductive Number & Final Size

- We have this equation:
  - $r(\infty) = e^{-R_0 r(\infty)}$
- Which can be arranged as:
  - $R_0 = -\frac{\ln(1-r(\infty))}{r(\infty)}$
- final epidemic size and basic reproductive number can be used to calculate each other if we already know one
- Without going through the derivation, there is another equation for calculating R0 from final size
  - $R_0 = \frac{N}{N-S(0)-R(\infty)} ln \frac{\mathrm{N}-R(\infty)}{S(0)}$



- Epidemic A
  - Y(t)=218
  - t=8
  - γ=1.5
  - R0=2.01
  - Y(t)=31
  - t=4
  - γ=1.5
  - R0=2.29



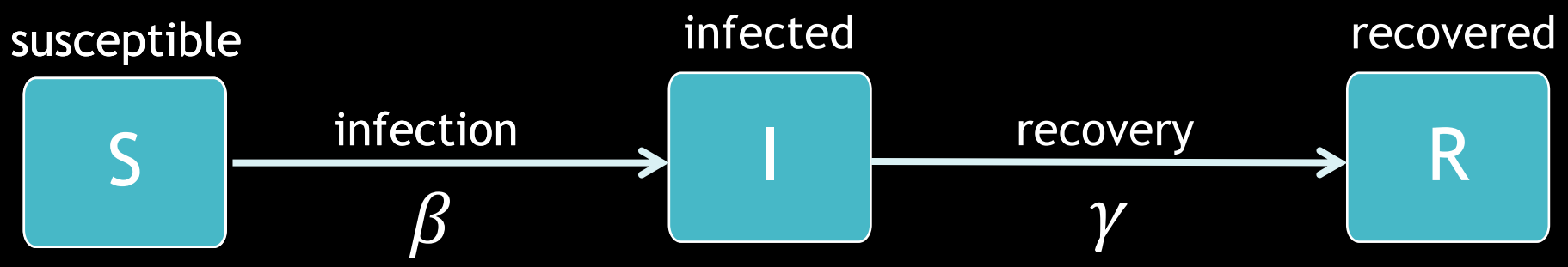
- Epidemic B
  - Y(t)=89
  - t=8
  - γ=1.5
  - R0=1.84
  - Y(t)=17
  - t=4
  - γ=1.5
  - R0=2.06

Method	Epidemic A R0	Epidemic B R0
Final epidemic size	2.04	1.91
Exponential at t=8	2.01	1.84
Exponential at t=4	2.29	2.06

Reproductive Number & Early Size

- We can also use the cumulative number of cases early in an epidemic by fitting an exponential curve to the outbreak
- $R_0 = 1 + \frac{\ln(Y(t))/t}{\gamma}$
- Y(t)=cumulative number of cases at time t

SIR Model: Kermack & McKendrick

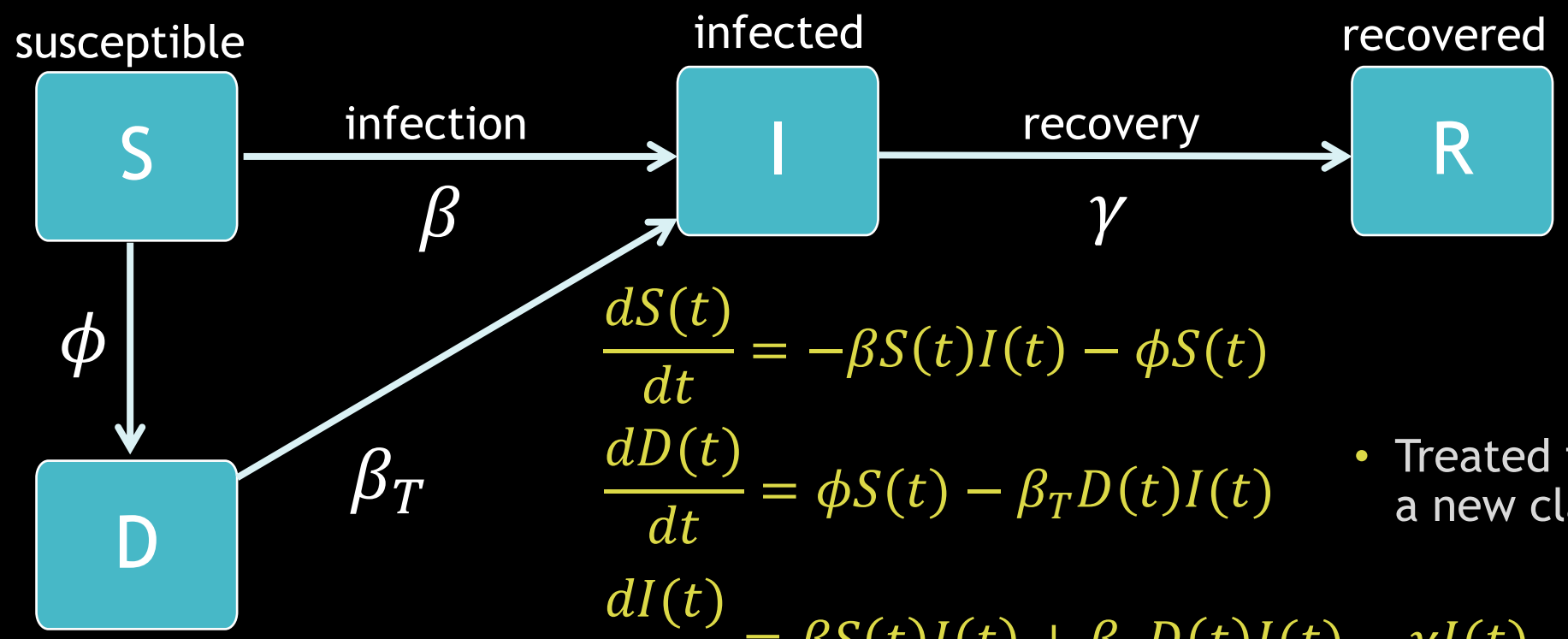


$$\frac{dS(t)}{dt} = -\beta S(t)I(t)$$

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

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

Treatment Provides Partial Protection



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

$$\frac{dD(t)}{dt} = \phi S(t) - \beta_T D(t)I(t)$$

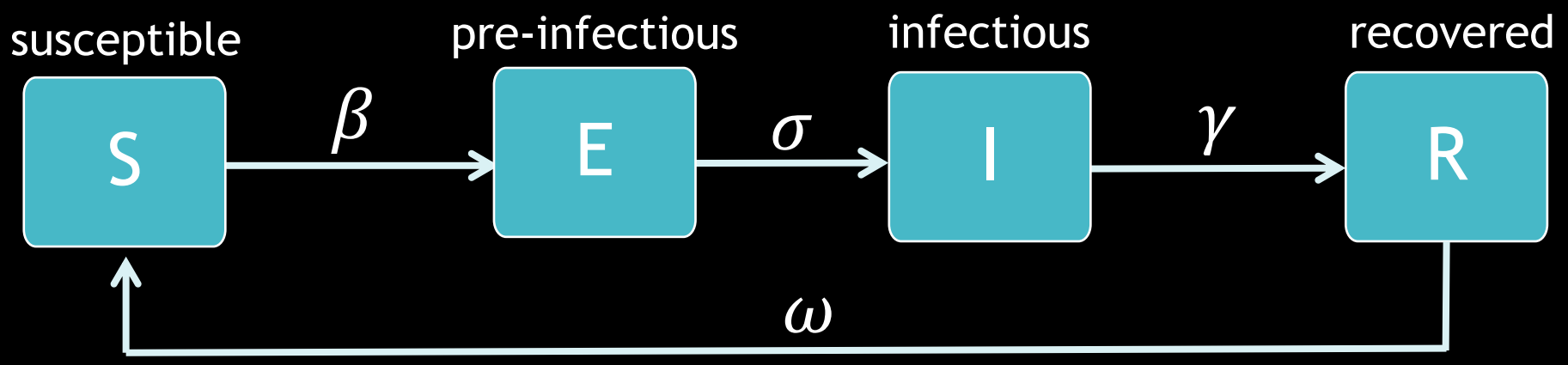
$$\frac{dI(t)}{dt} = \beta S(t)I(t) + \beta_T D(t)I(t) - \gamma I(t)$$

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

- β: transmission coefficient
- γ: recovery rate
- ϕ: rate of providing treatment
- β_T: transmission coefficient for treated individuals

- Treated individuals are in a new class

Knowledge Test



This is a diagram for transmission of *Mycoplasma pneumoniae*. Which of the following statement(s) is/are correct? (may be more than one!)

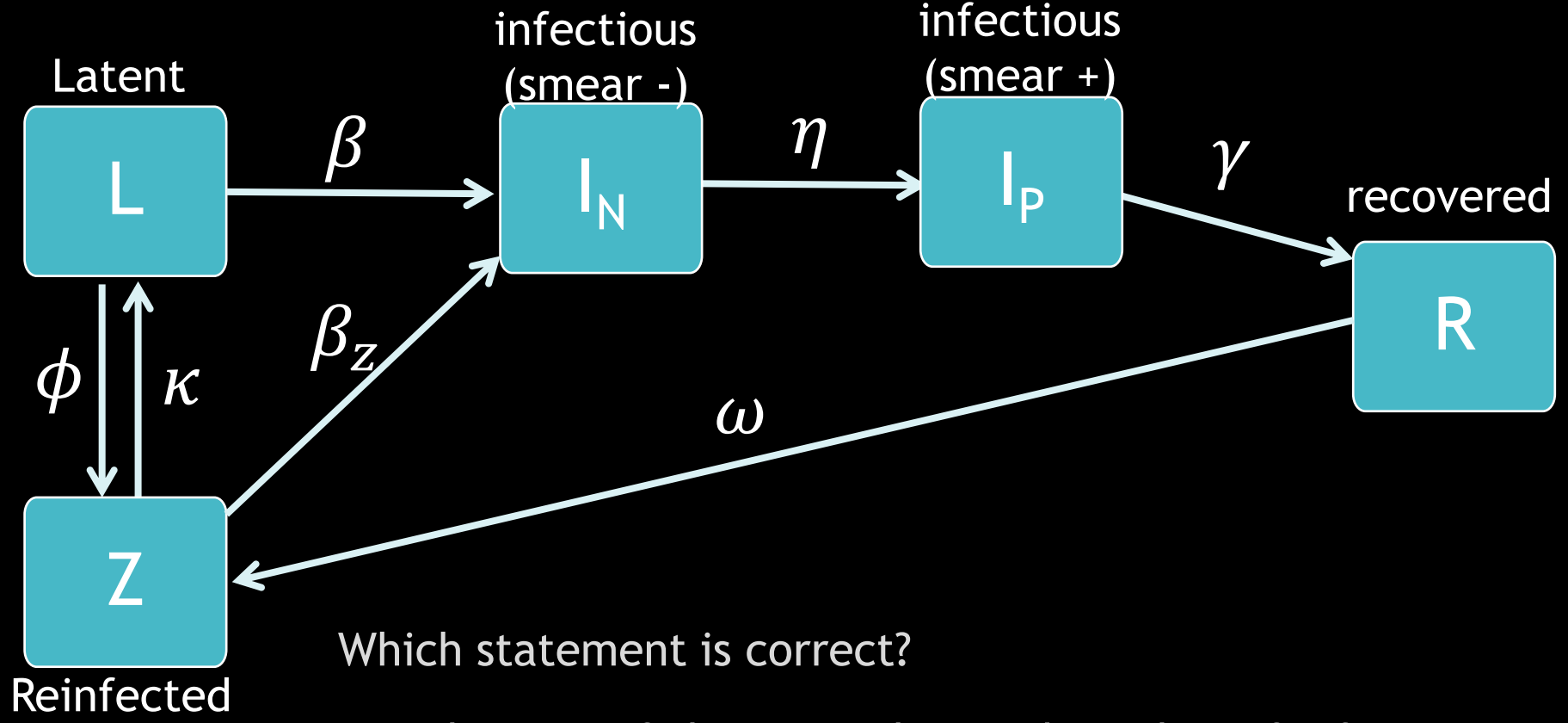
A. The model will predict that the total population will decrease over time

B. The model will predict that the total population will increase over time

C. The model will predict that the total population size will stay the same

D. The rate of change in the number of immune individuals is given by: $\frac{dR(t)}{dt} = \gamma - \omega$

E. The rate of change in the number of immune individuals is given by: $\frac{dR(t)}{dt} = \gamma I(t) - \omega R(t)$



This is a simplified diagram for TB in a high-transmission setting. Smear- and smear+ people are both infectious, but smear- are 25% less infectious

Which statement is correct?

A. The rate of change in the total number of infectious people ($I(t)=I_N(t)+I_P(t)$) is given by:

$$\frac{dI(t)}{dt} = \beta L(t) + \beta_Z Z(t) - \gamma I_P(t)$$

B. The rate of change in the total number of infectious people ($I(t)=I_N(t)+I_P(t)$) is given by:

$$\frac{dI(t)}{dt} = \beta L(t) + \beta_Z Z(t) - \eta I_N(t) - \gamma I_P(t)$$

Questions?