Lecture 3

Epidemic theory part 2: epidemiological and biological parameters and their interactions with transmission and interventions

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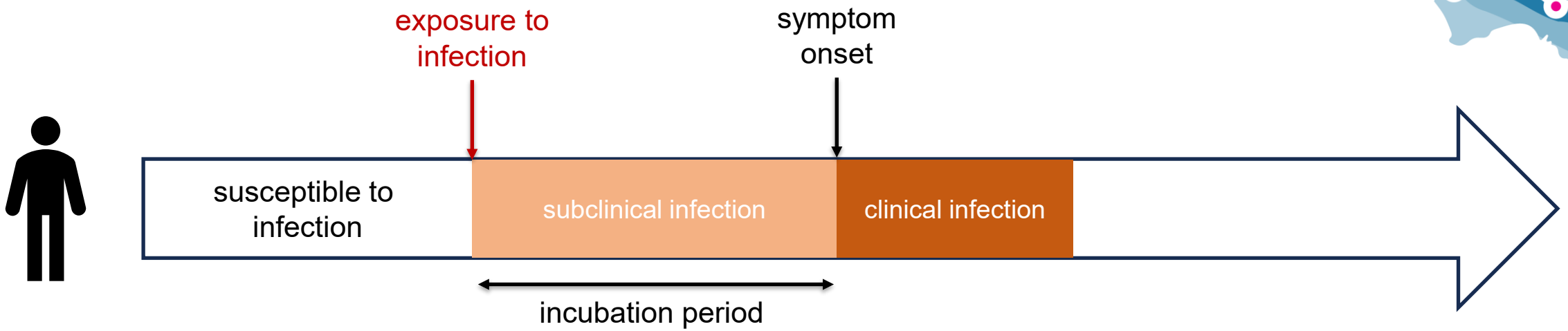
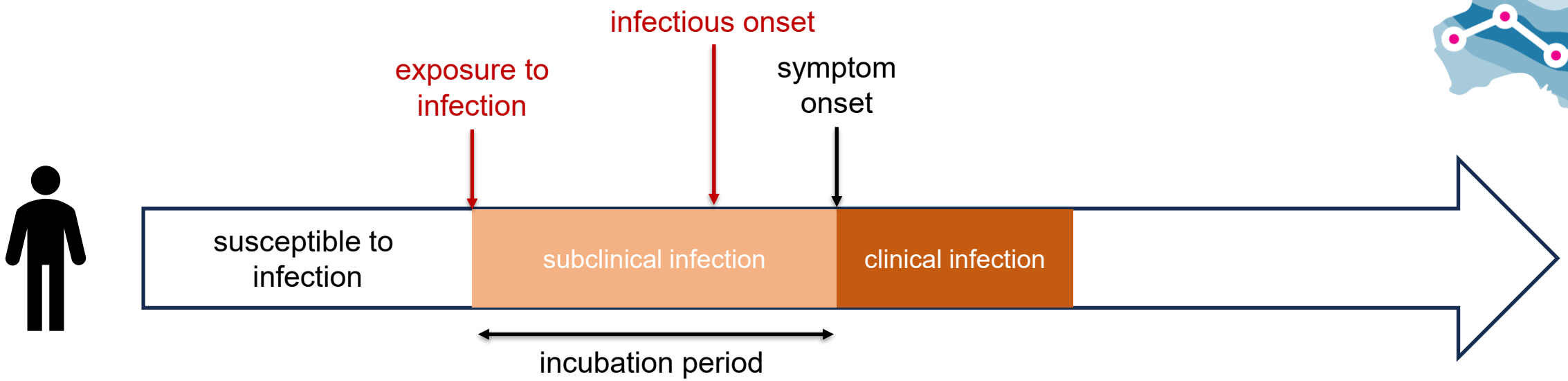
Outline

1. Key epidemiological quantities and interpretation
2. Epidemic dynamics
3. Individual-level and population-level heterogeneity
4. Modelling interventions

Key terms that we will be exploring

- Incubation period
- Latent period
- Infectious period
- Generation interval (or generation time)
- Serial interval


exposure to infection
symptom onset
susceptible to infection
subclinical infection
clinical infection
incubation period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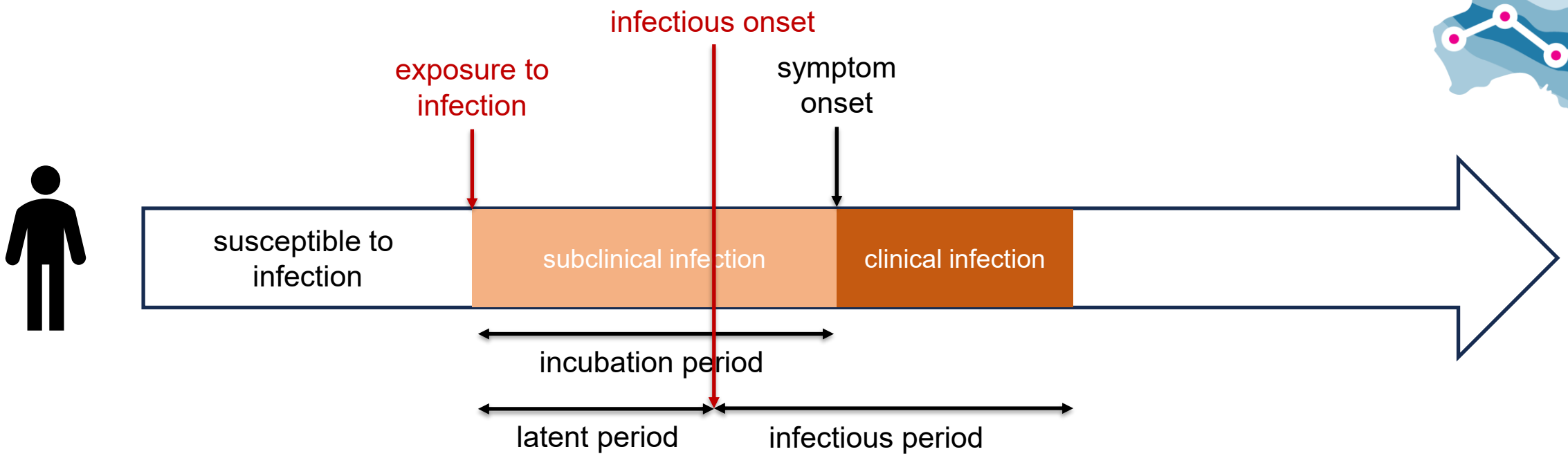
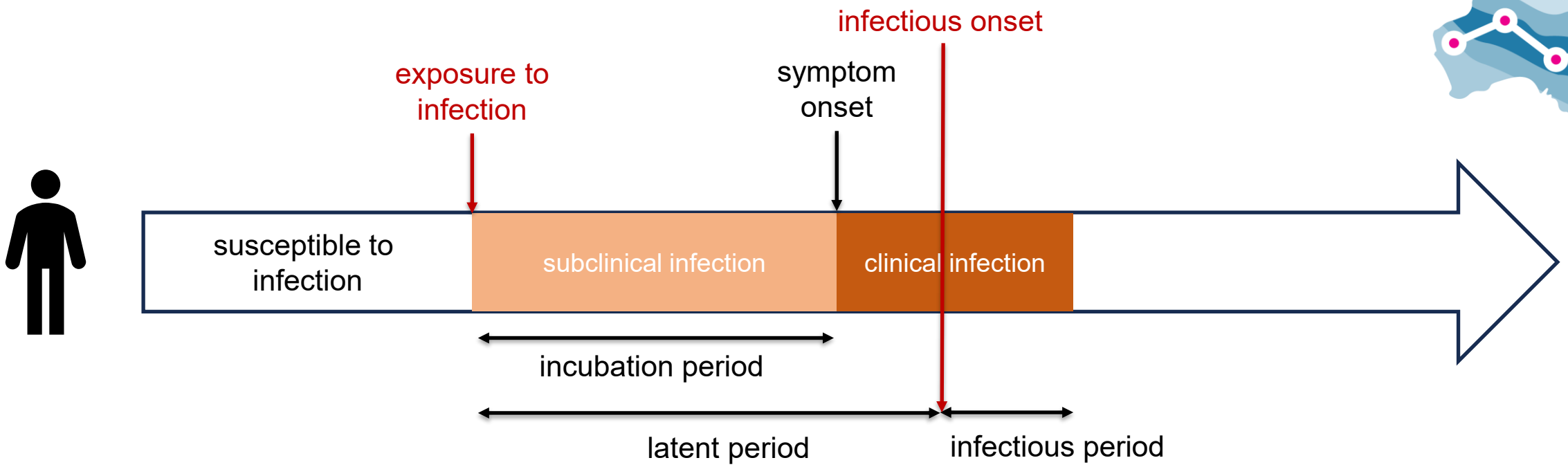
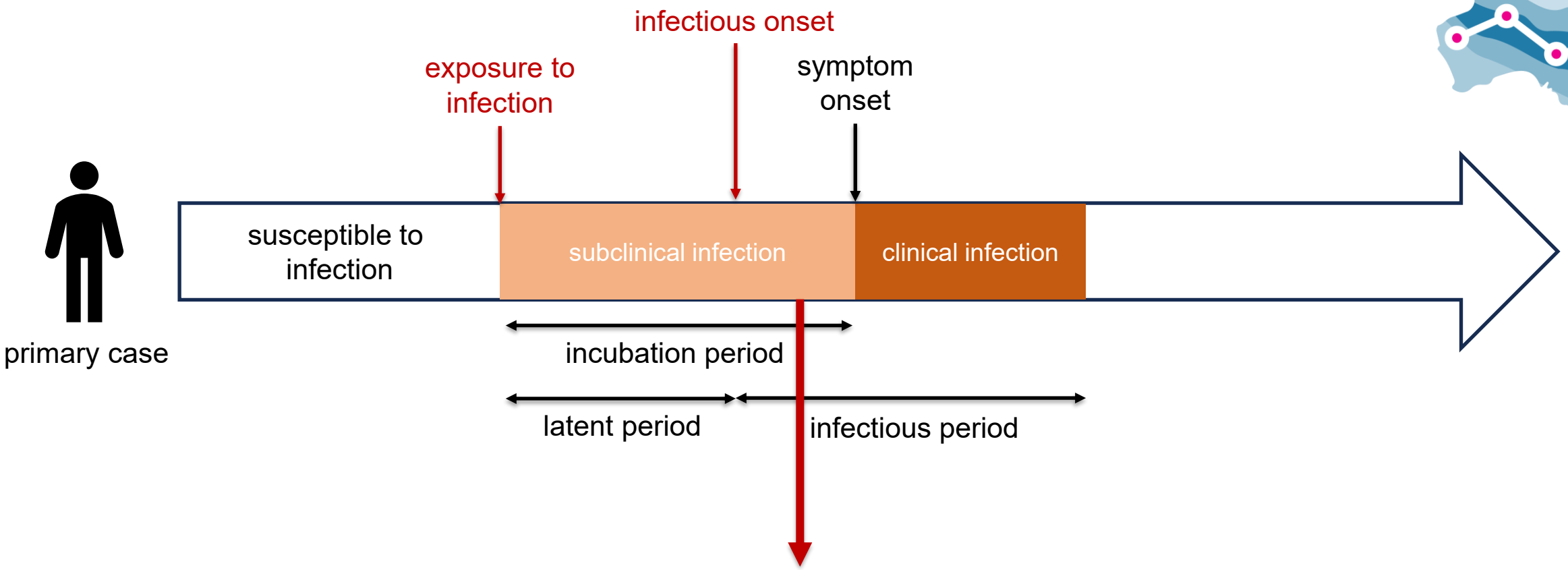
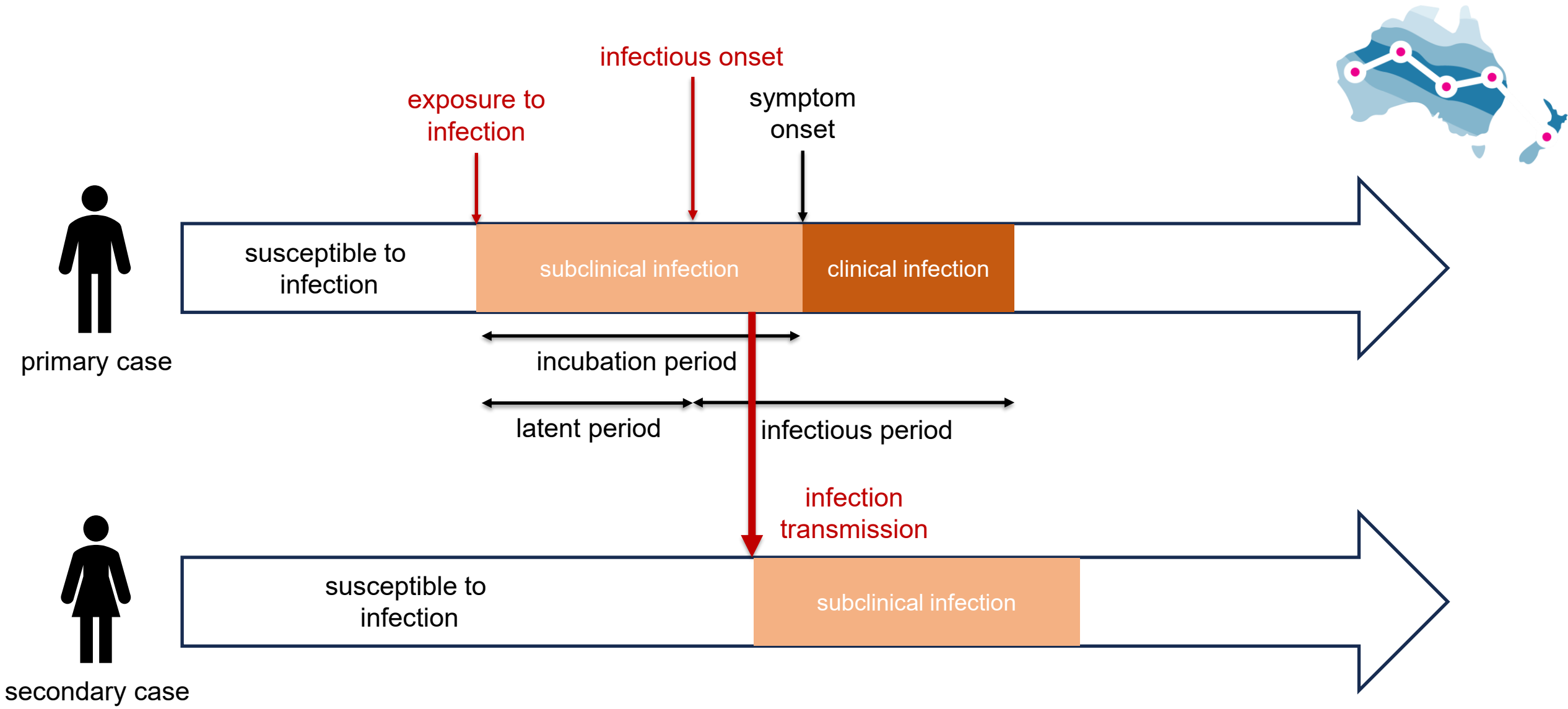


infectious onset **before** symptom onset



infectious onset **after** symptom onset


infectious onset
exposure to infection
symptom onset
susceptible to infection
subclinical infection
clinical infection
primary case
incubation period
latent period
infectious period


infectious onset
exposure to infection
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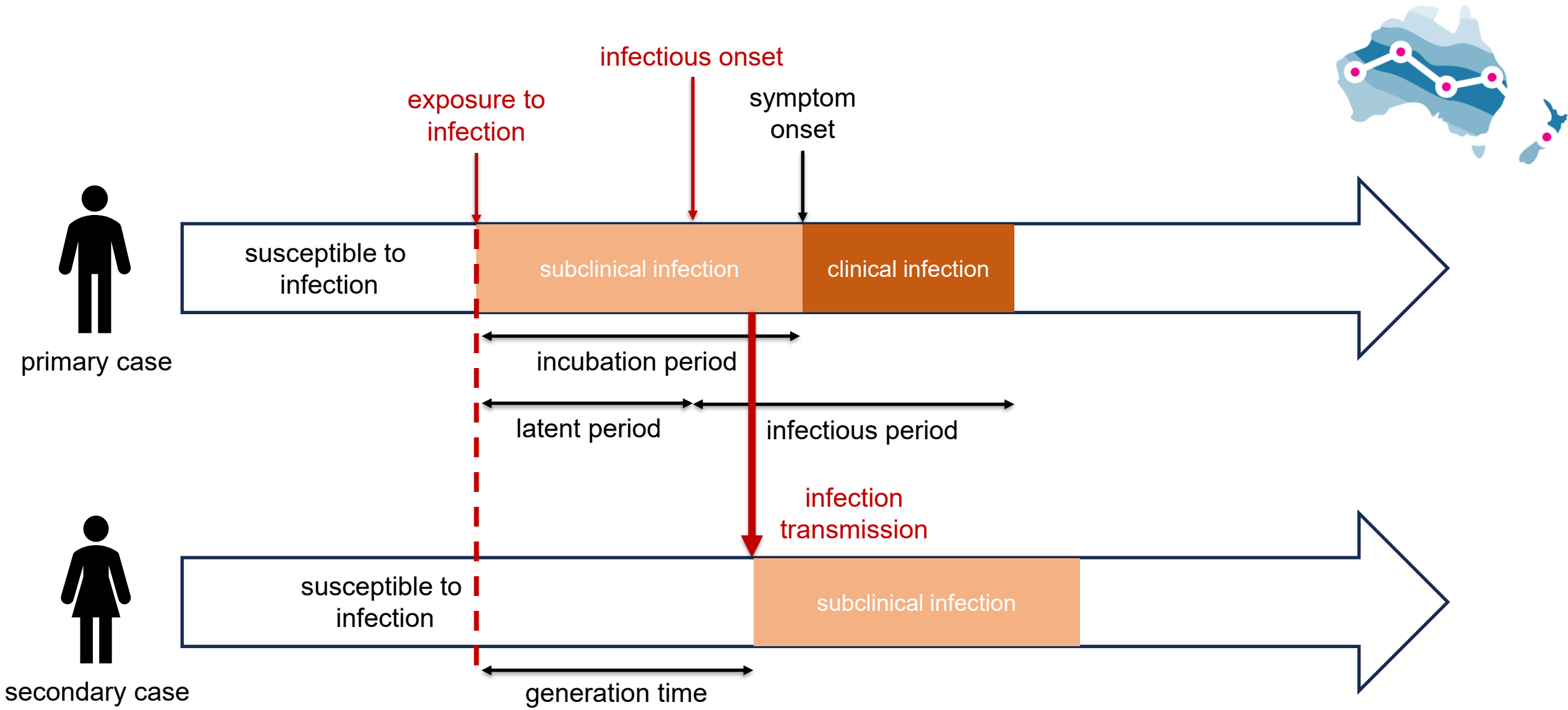
susceptible to infection
subclinical infection
clinical infection
primary case
incubation period
latent period
infectious period
infection transmission
susceptible to infection
subclinical infection
secondary case


infectious onset
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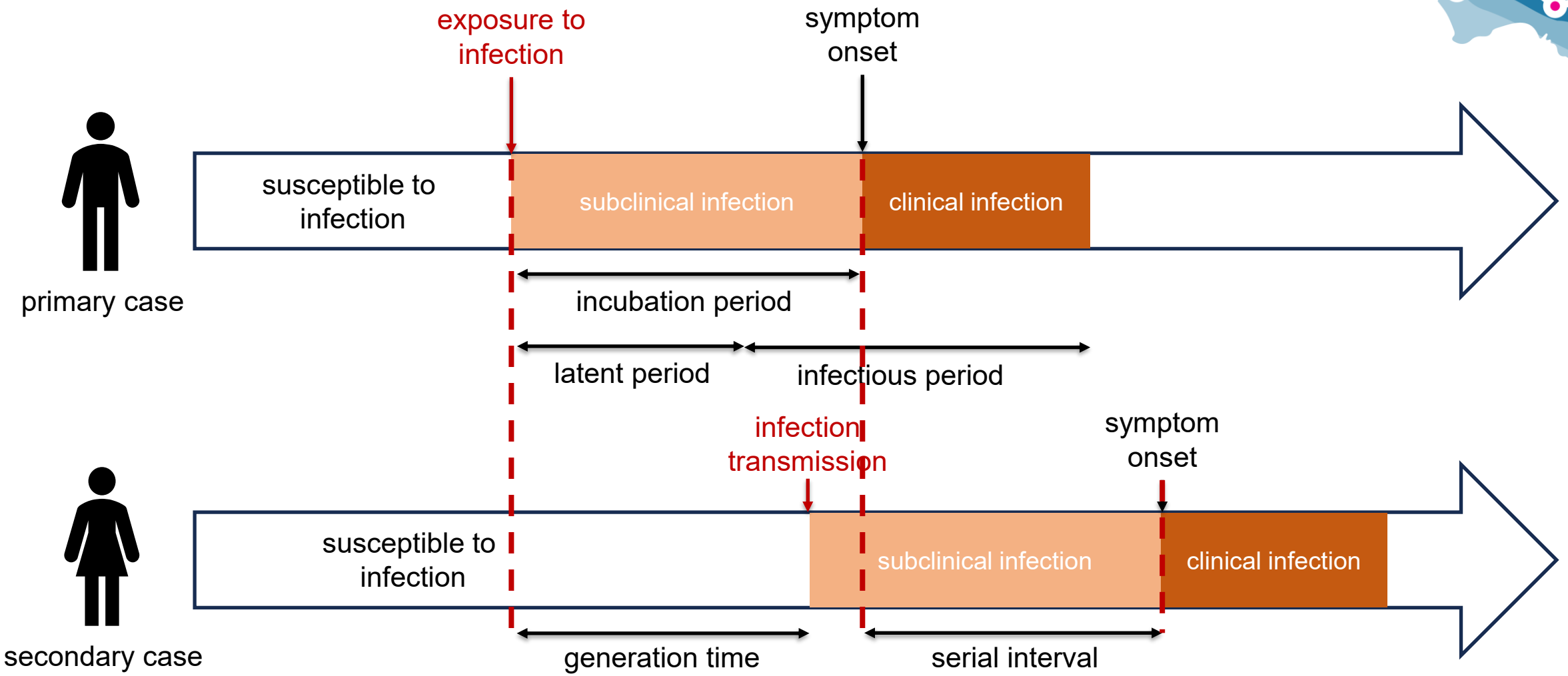
incubation period
latent period
infectious period
infection transmission
susceptible to infection
subclinical infection
secondary case
generation time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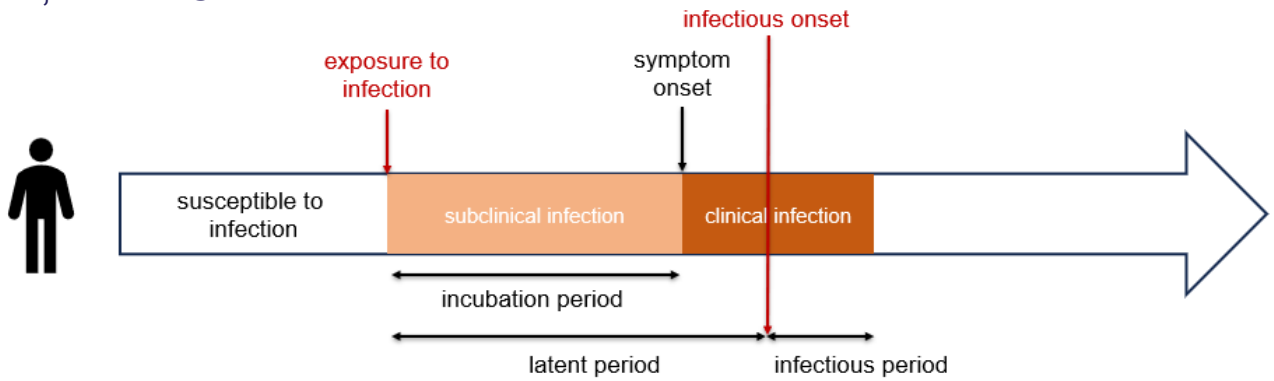
susceptible to infection
subclinical infection
clinical infection
secondary case
generation time
serial interval

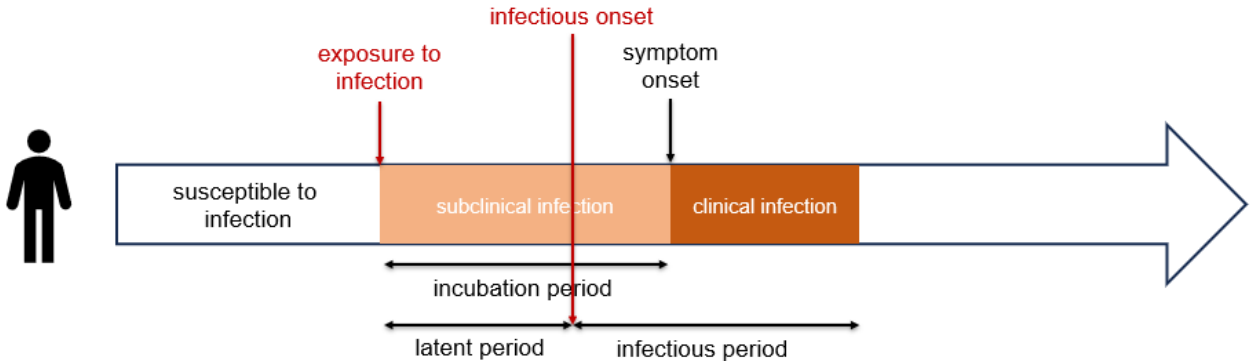
Incubation and latent periods

The relative durations of the **incubation** and **latent** periods have implications for disease surveillance and control

- Latent period ≥ incubation period: transmission is symptomatic
  - E.g. Smallpox, SARS-CoV-1



- Latent period < incubation period: presymptomatic transmission (i.e. individual is infectious before developing symptoms)
  - E.g. SARS-CoV-2, HIV (note different timescales)



Summary of the key terms

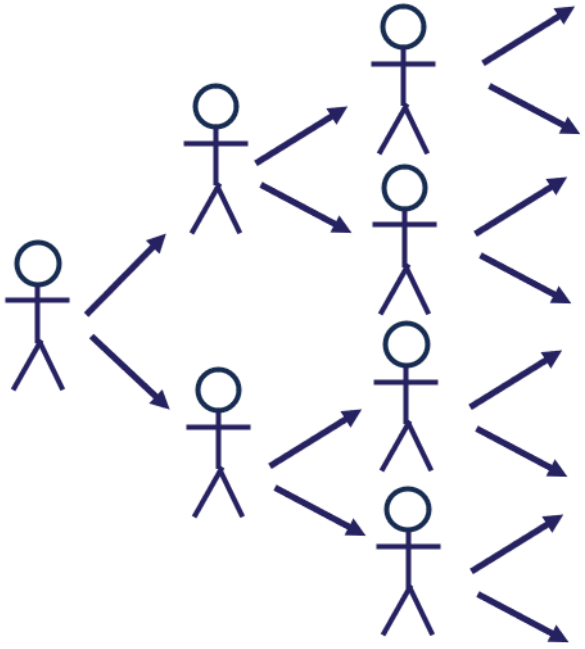
Incubation period. The time between exposure and onset of symptoms (within a single individual)

Latent period. The time between exposure, and becoming infectious (within a single individual)

Infectious period. The duration that an individual is infectious

Implications for R_0

- R_0 is the basic reproduction number – or number of infections generated by a single infectious individual in a fully susceptible population.
- Infectious period is important in terms of transmission dynamics
- Even if a pathogen has low transmissibility, if the infectious period is long, the R_0 can be high



Note that R_0 does not specify the time over which infections occur

transmissibility

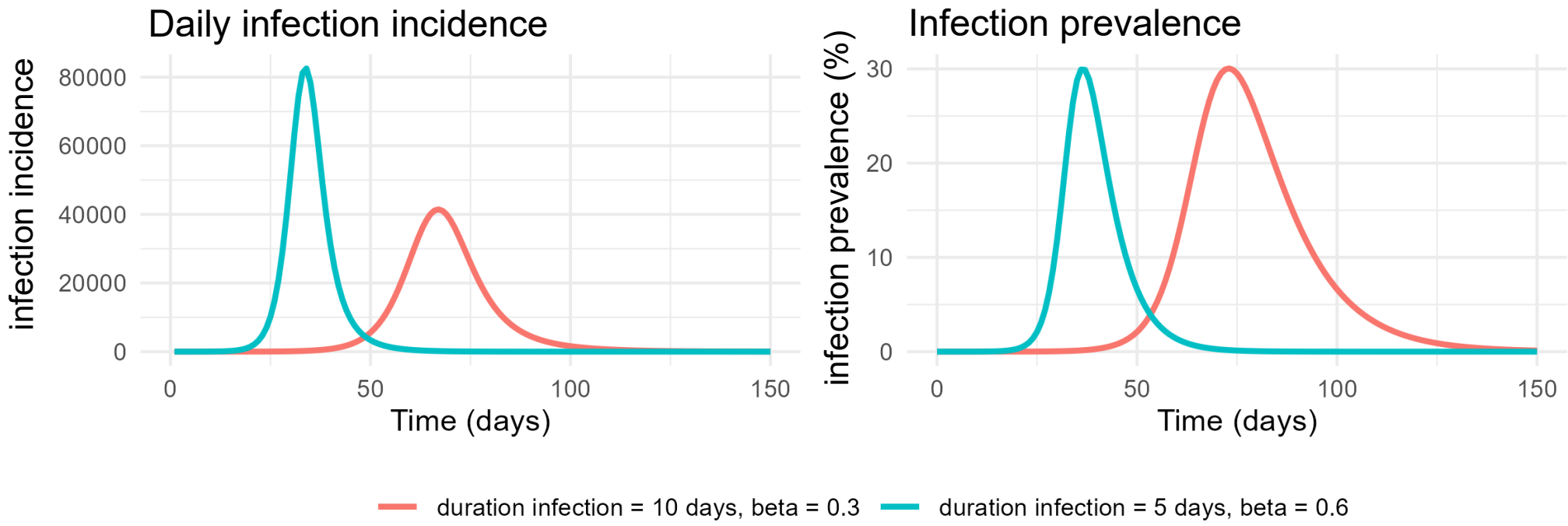
$$R_0 = \beta \times \frac{1}{\gamma}$$

infectious period

Implications for R_0

- Remember that β is the expected amount of people that an infectious person infects each day they are infectious
- The same R_0 can be comprised of a different **beta** and **duration of infection**
- These two epidemics with the same R_0 have different properties – **total incidence is the same**, but distributed over different time windows

Example: SIR model with $R_0 = 3$



R_0 doesn't tell us the time period over which an epidemic occurs

Back to our list of key terms…

- Incubation period
- Latent period
- Infectious period
- **Generation interval (or generation time)**
- **Serial interval**

What about those intervals that tell us something about the timing of events between an infector-infectee pair?

Generation interval

- The generation interval is the delay between acquisition of infections in a primary and secondary case
- Relates to how fast a pathogen is spreading (rather than R_0, which relates to the number of infections) and has implications for containment strategies

$$R_0 = 1 + r\mathrm{T_C}$$

$\mathrm{T_C}$: mean generation interval

r: growth rate, or per capita change in number of new cases per unit of time

- Is a function of different factors:
  - Duration of the latent period, duration of infectiousness
  - Contact patterns, individual behaviour
- Not fixed between different infectious individuals - has a distribution

Favero et al 2022, https://pmc.ncbi.nlm.nih.gov/articles/PMC9198515/

Estimating the generation interval

- Difficult to measure because the time of infection is not usually known
- Can sometimes be approximated by the **serial interval**, as symptom onset is easier to observe than infection (but limitations in this approach)

Chen et al 2022, https://www.nature.com/articles/s41467-022-35496-8

Serial interval

- Time between symptom onsets in an infector–infectee pair
- In practice it is typically used to quantify R_0 at the start of an outbreak
- Ideally, estimated using contact tracing data (pairs of infector-infectee with known dates of symptom onset); household studies
- There are limitations of using the serial interval as an approximation of the generation time, and potential biases to account for (more in this in later lectures)[2]
- Serial intervals can vary widely between pathogens:[1]
  - Ancestral COVID-19 (4–8 days)
  - RSV (~8 days)
  - Pertussis (~20 days)
  - Smallpox (9–45 days)
  - Tuberculosis (months–years)

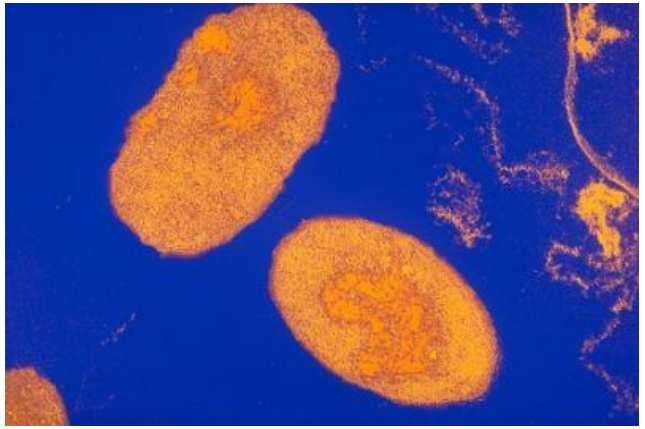


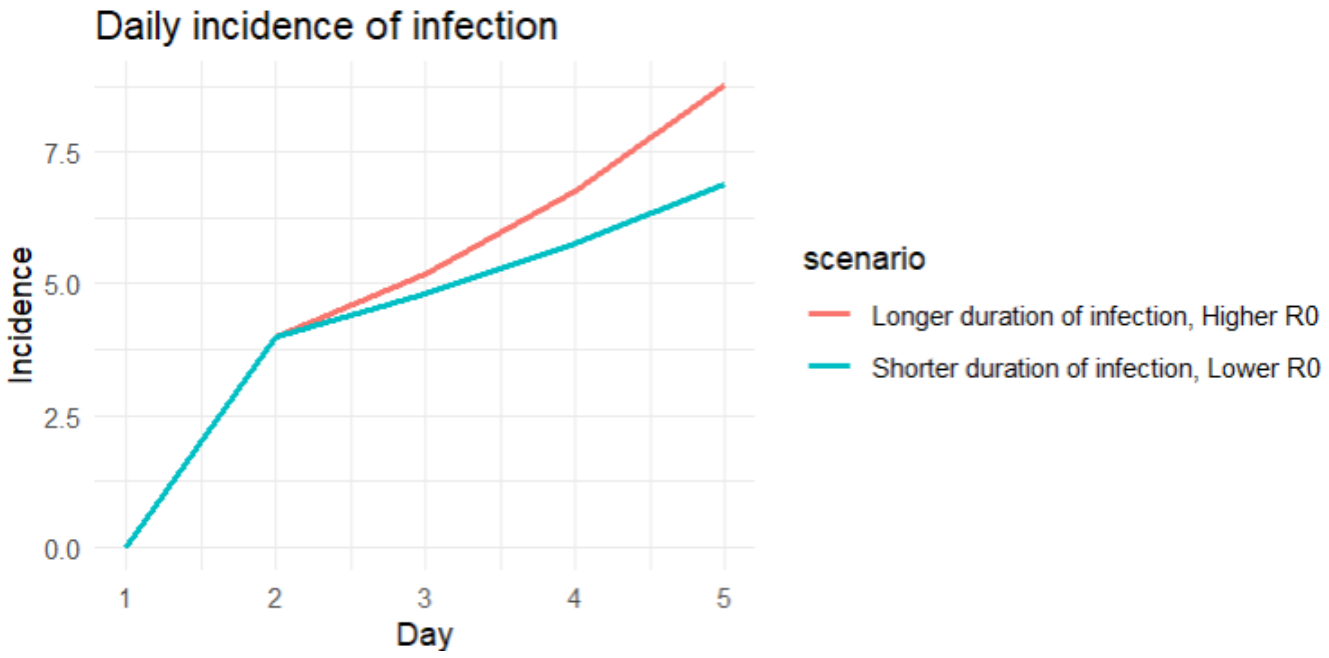
Image: Electron microscope image of the bacteria *Bordetella pertussis*.
Credit: Sanofi Pasteur
Sourced from: https://www.niaid.nih.gov/diseases-conditions/pertussis-whooping-cough

[1] Vink et al 2014, https://doi.org/10.1093/aje/kwu209
[2] Favero et al 2022, https://pmc.ncbi.nlm.nih.gov/articles/PMC9198515/

How do these quantities influence epidemic dynamics?

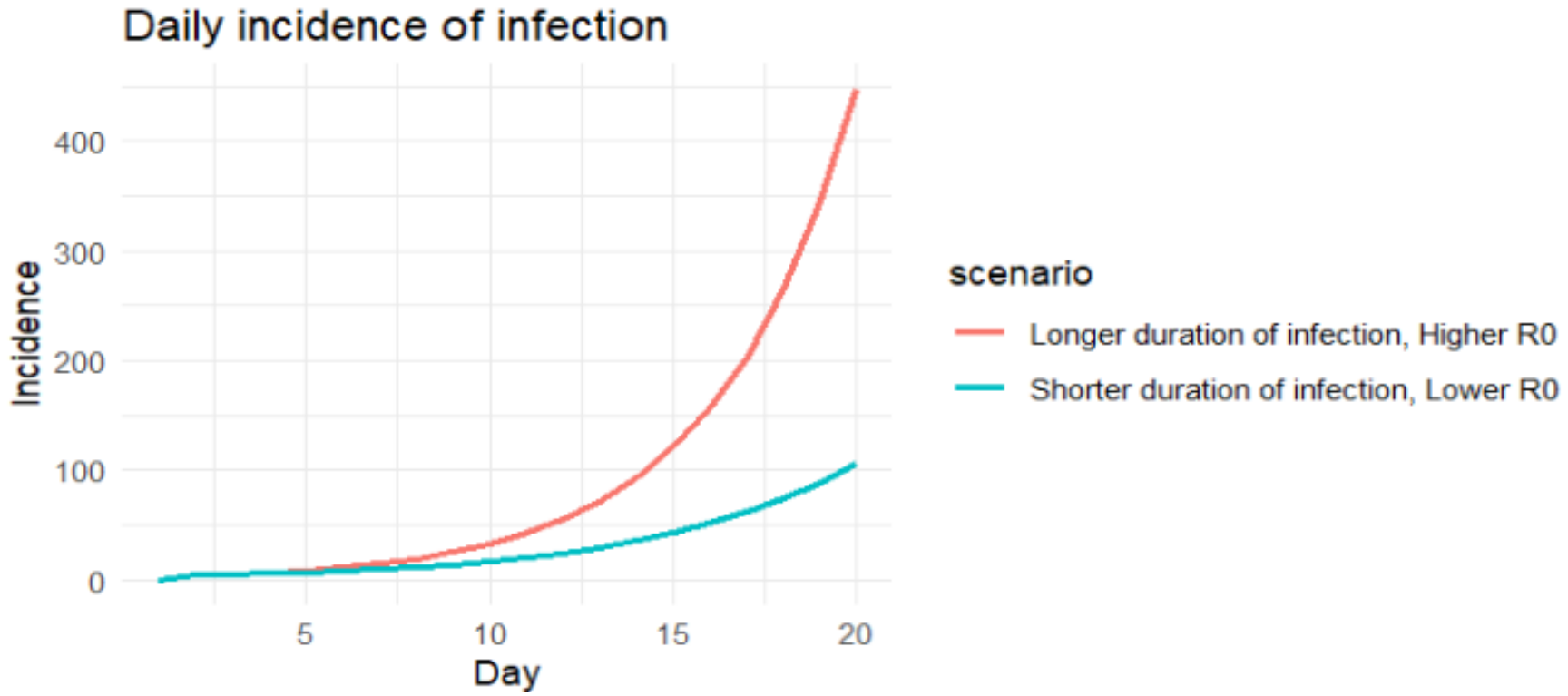
- Consider an SIR model with two different scenarios:
  - beta (the expected amount of people an infected person infects per timestep) is the same between scenarios
  - R_0 and the generation time are different between scenarios

In the early phase, the epidemic trajectories look similar



How do these quantities influence epidemic dynamics?

- However, the epidemics then look very different and have different peak sizes and durations
- The same observed growth rate and initial case numbers can correspond to very different underlying processes (knowing the epi curve is not enough)
- This has implications for control strategies



Individual heterogeneity

In practice, we define these quantities across **distributions**, because

- Different individuals are infectious for different periods, or take shorter or longer times to infect others
  - Individual immune response
  - Demographic risk factors (age, sex, ethnicity)

These distributions can also change over time

- Pathogen strain

Using modelling to explore the impact of interventions

Interventions that are applied to control an infectious disease may be designed to shorten the infectious period (and therefore also shorten the generation time), or to reduce new infections per unit time, or both

How do interventions relate to the quantities we have discussed?

- **Vaccination**: can mitigate transmission by reducing susceptibility and infectiousness (reduces growth rate)
- **Masking and social distancing**: reduces contacts, and the probability of transmission given contact (reduces growth rate)
- **Contact tracing and isolation of infectious individuals**: removes infectious individuals, reduces transmission (reduces growth rate)
- **Early case detection and isolation** (shortens infectious period)
- **Treatment** (reduces infectiousness and shortens infectious period)

Impact of case isolation and/or contact tracing on transmission

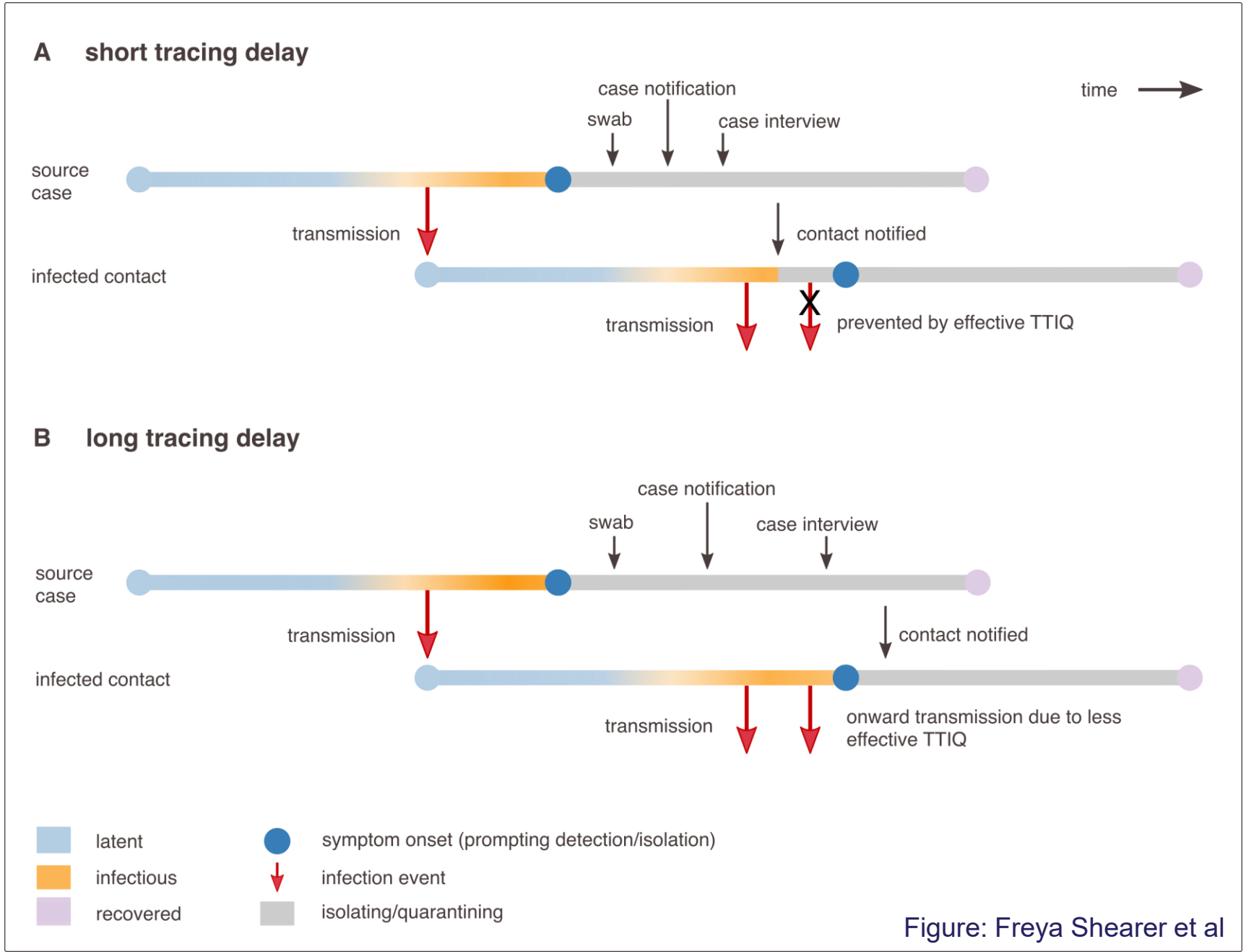
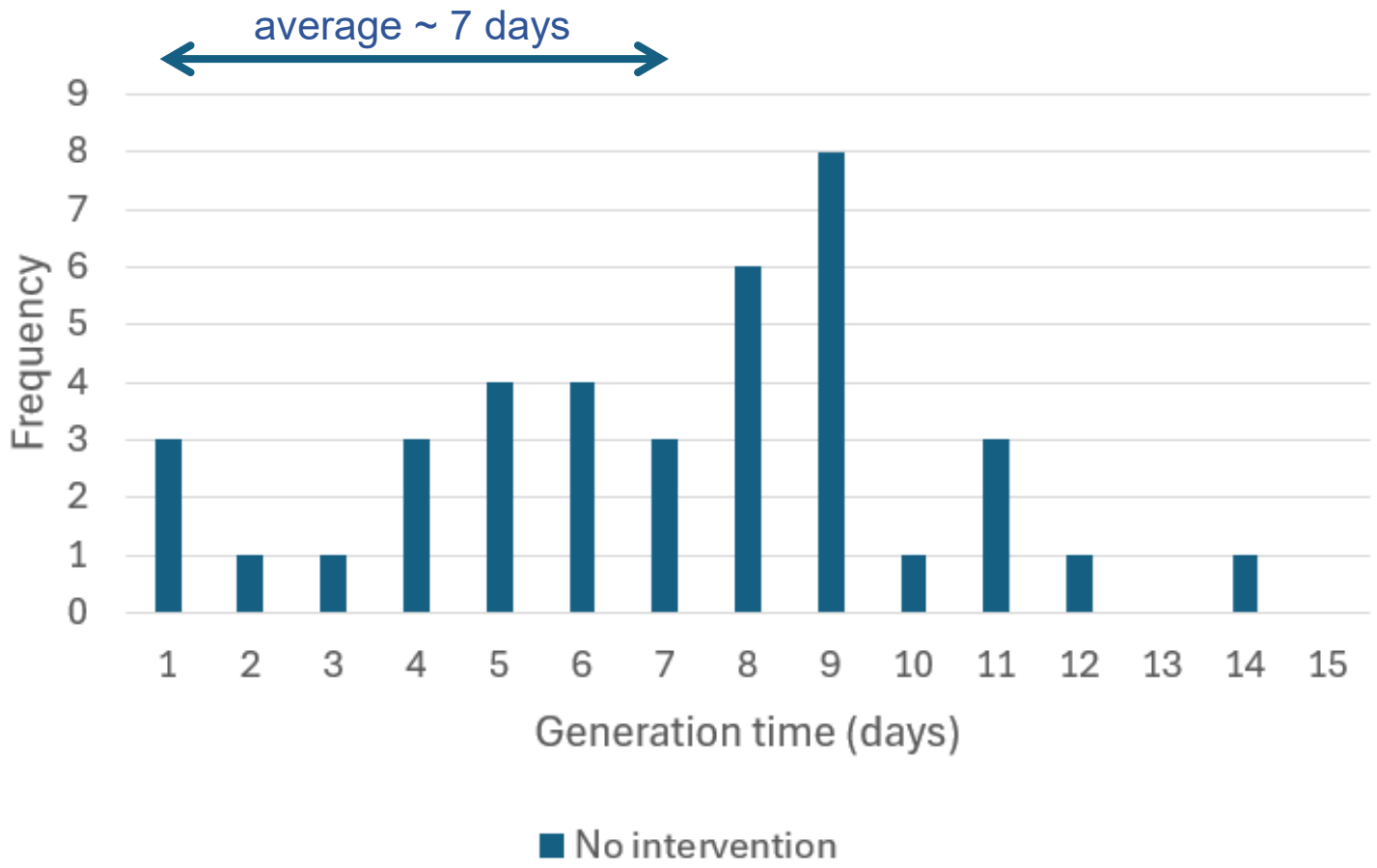


Figure: Freya Shearer et al

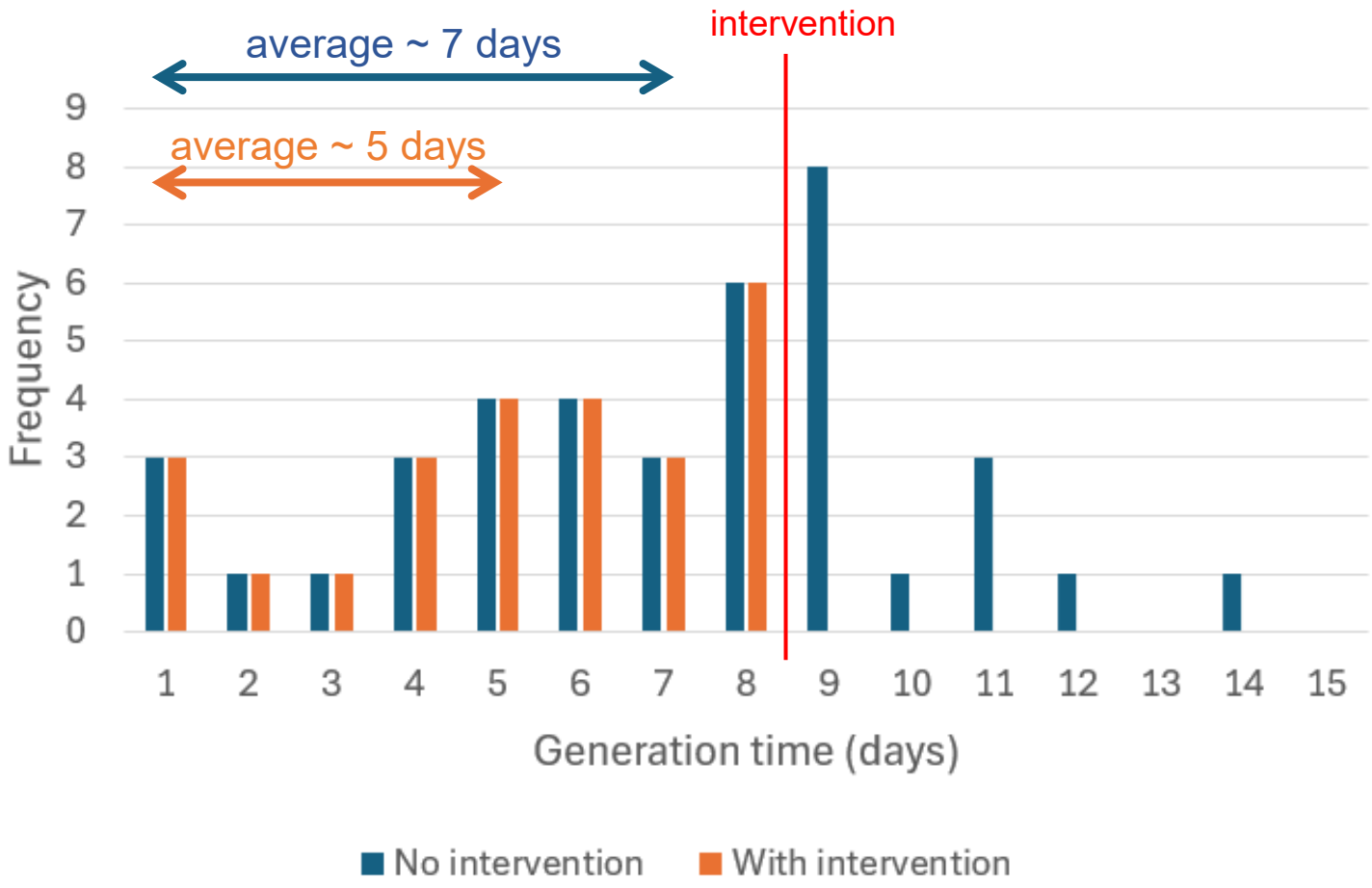
Generation time distribution and interventions

Illustrative example of a distribution of different **generation times** for a pathogen



Generation time distribution and interventions

If an intervention such as contact tracing or case isolation is introduced, the longer generation times are not observed



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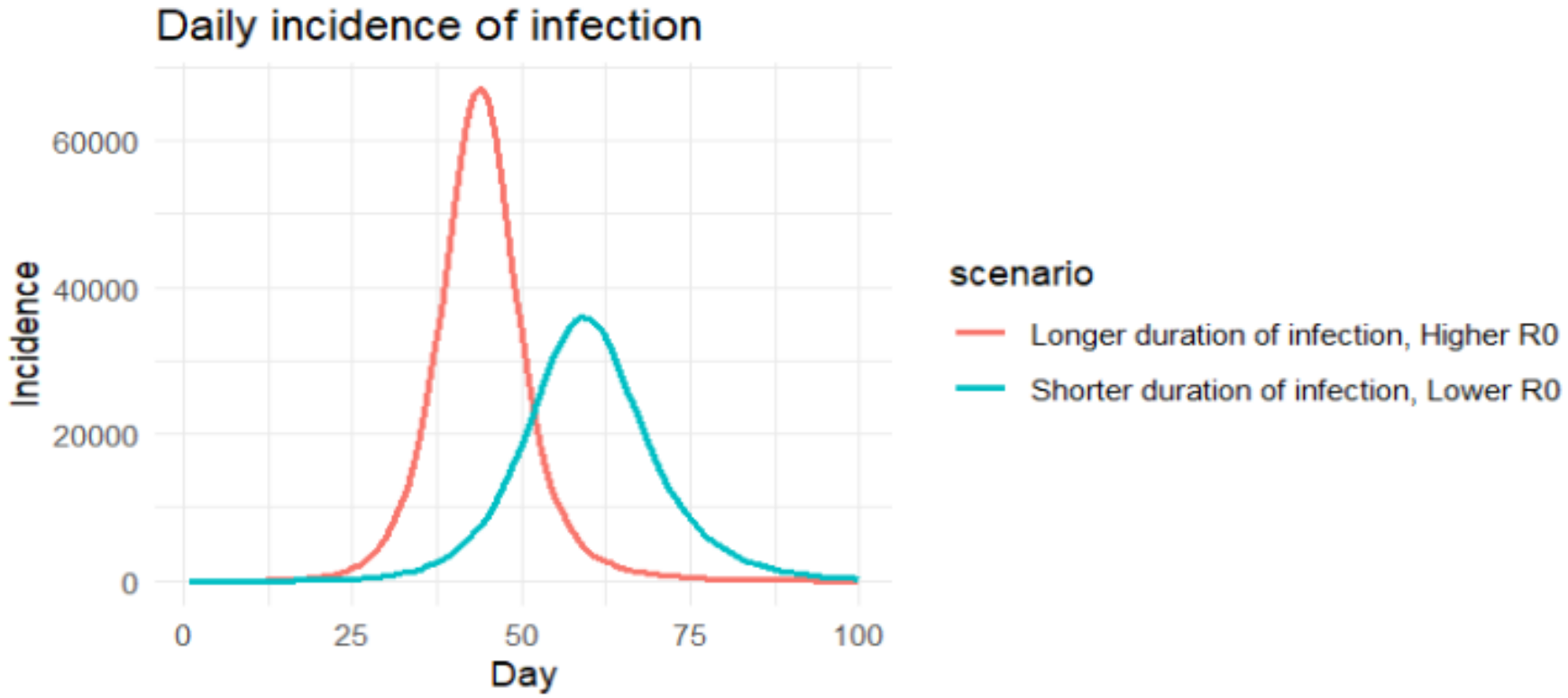


Population heterogeneity

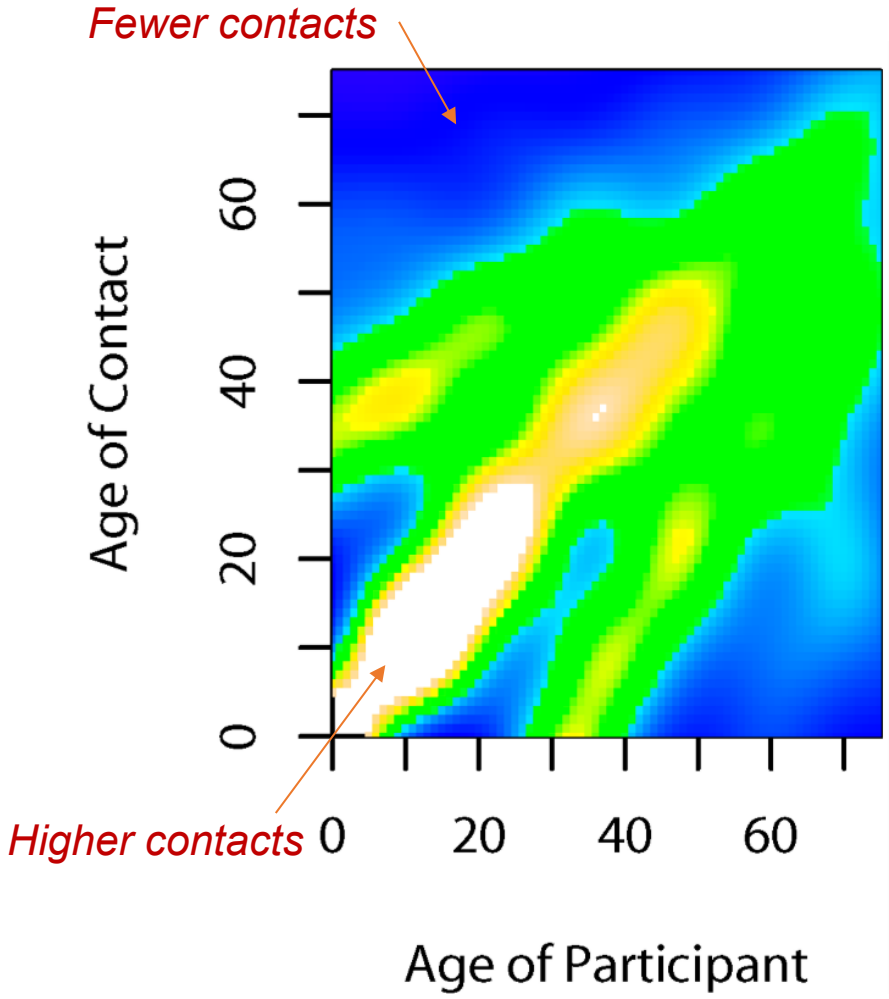
Models can be further adapted to account for different population groups

The important groups might depend on

- Disease being modelled
- Policy question being asked
- Data available to inform parameters

Age the most important factor that is typically included (by additional states in an SIR model)

Social mixing within and between age groups captured by contact matrices[1]



[1] eg Mossong et al 2008, https://doi.org/10.1371/journal.pmed.0050074

Using modelling to explore the impact of interventions

Short-term and long-term horizons

- Prediction: “what do we think is going to happen next?”
- Scenarios: “what will happen if we do X?”

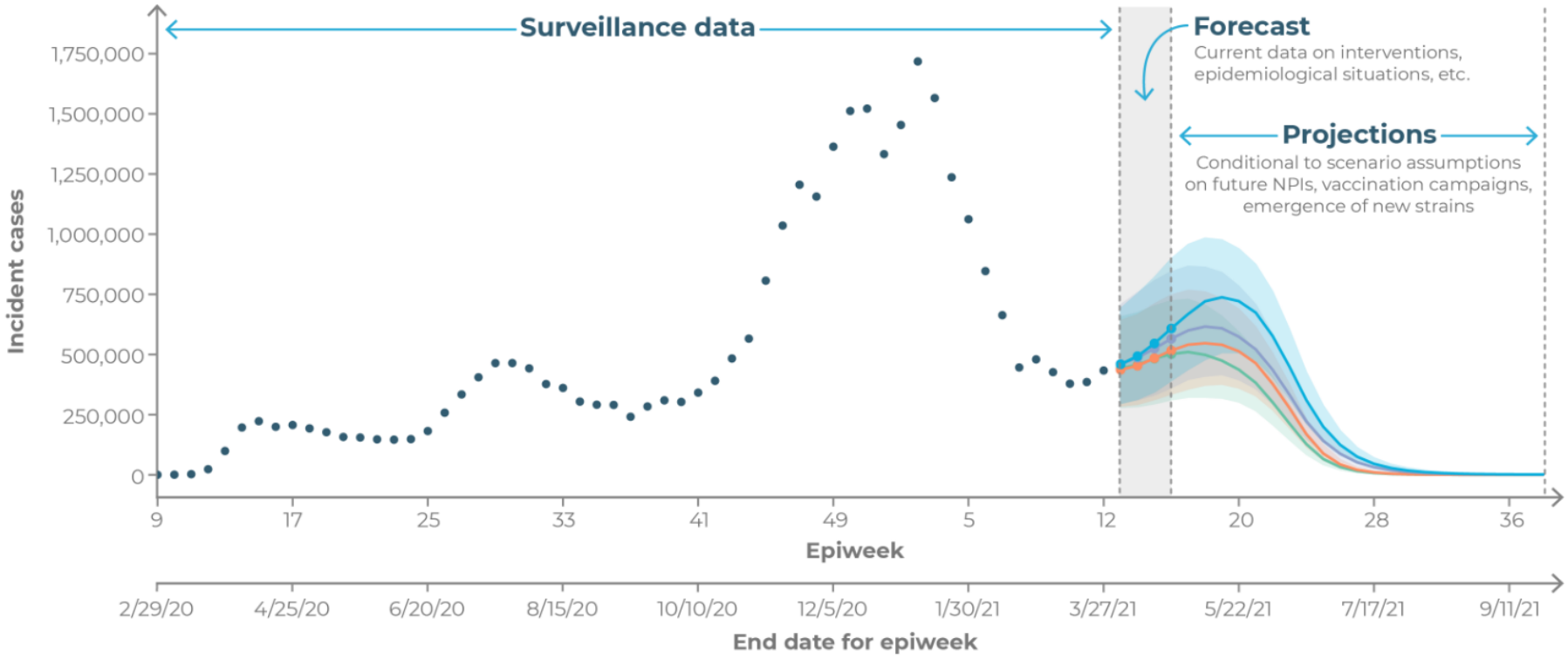


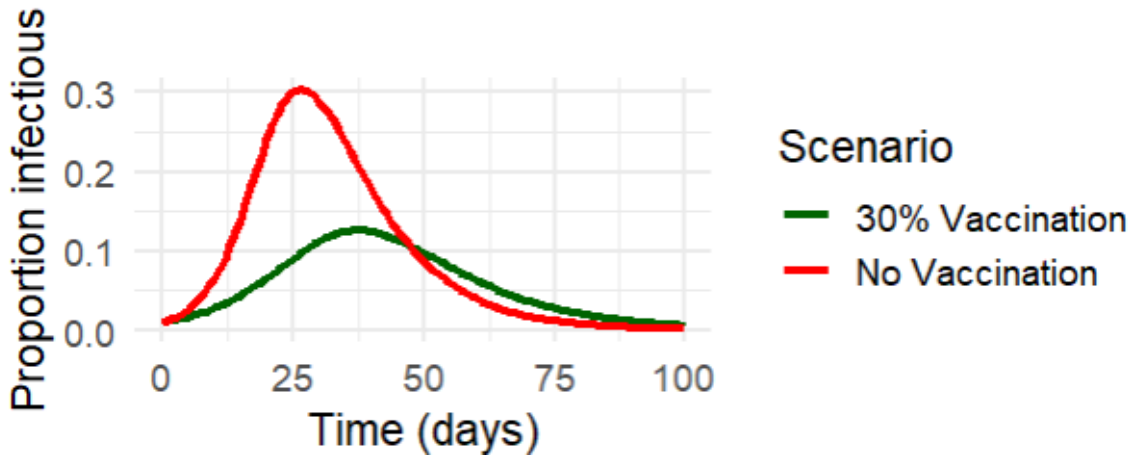
Figure: from the US Scenario Modelling Hub, https://covid19scenariomodelinghub.org/index.html

Using modelling to explore the impact of interventions

- The compartmental SIR model can be expanded to include additional states to capture important epidemiological or population features
- Can also be used to capture interventions – such as vaccination
- Typically an extra compartment is included to represent the vaccinated population
- The specific structure depends on the disease and vaccine being modelled

Using modelling to explore the impact of interventions

Example: a proportion of the population is removed to a Vaccinated (i.e. immune) class with **complete protection**



Using modelling to explore the impact of interventions

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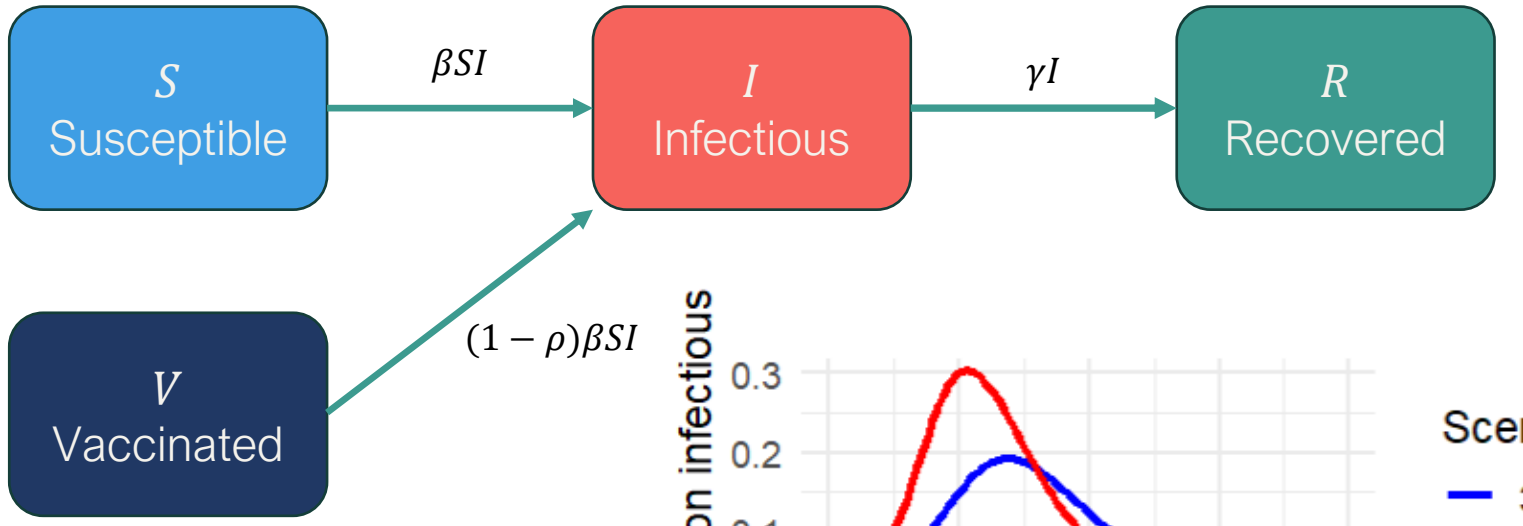
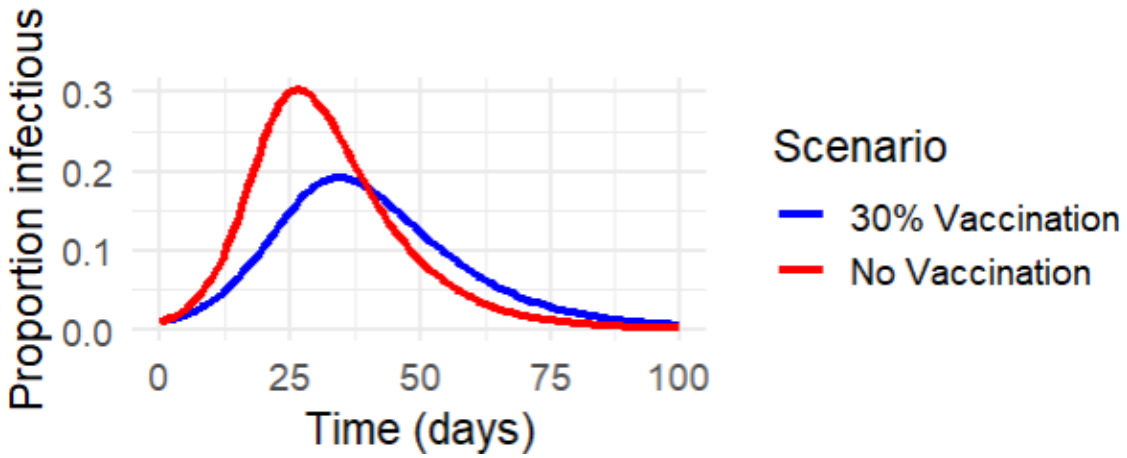
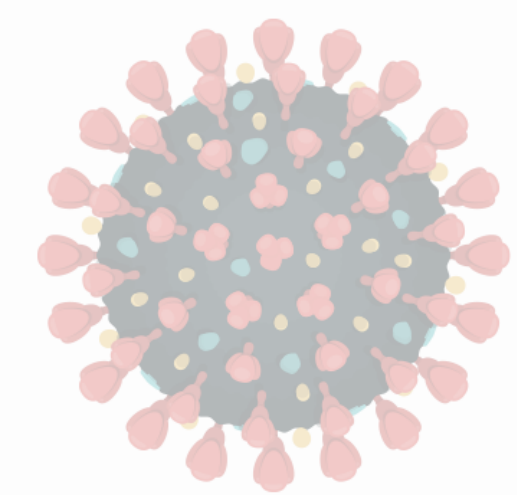


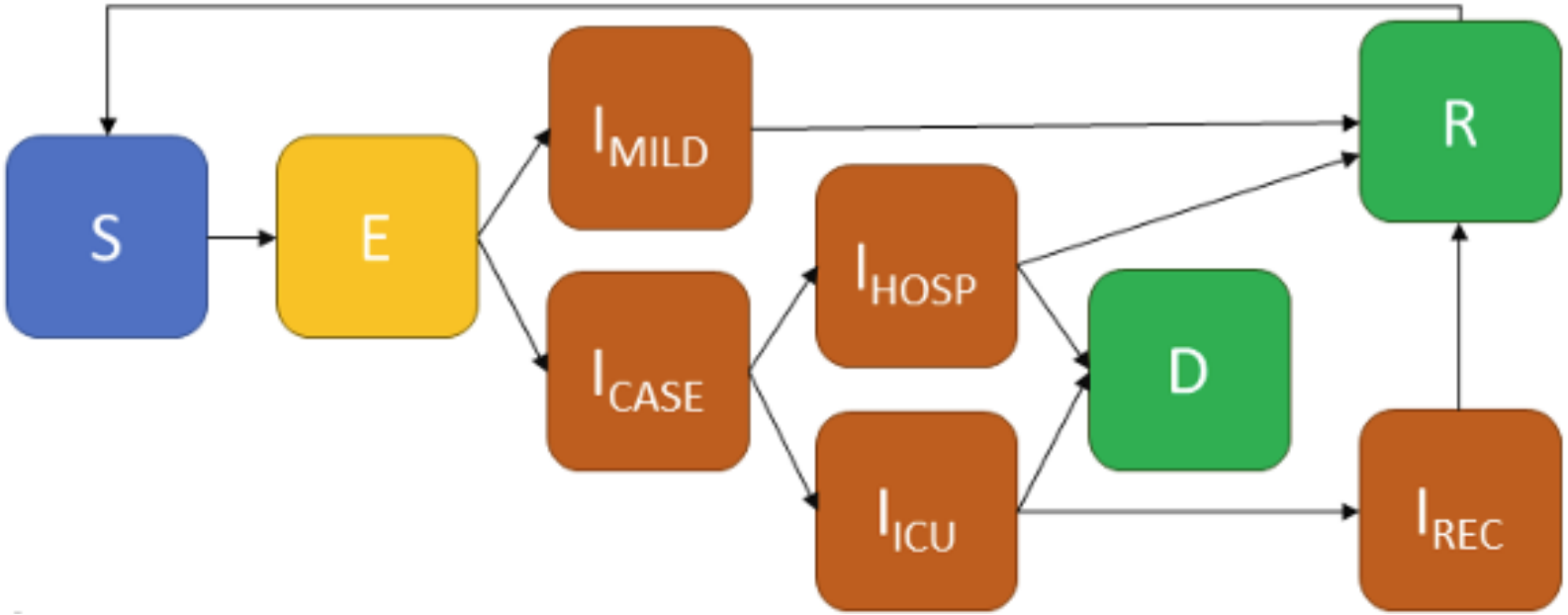


Example: early SARS-CoV-2 modelling



Simple SIR models such as these used early in COVID-19 pandemic to:

- Understand epidemiology
- Forecast
- Predict impact of vaccination



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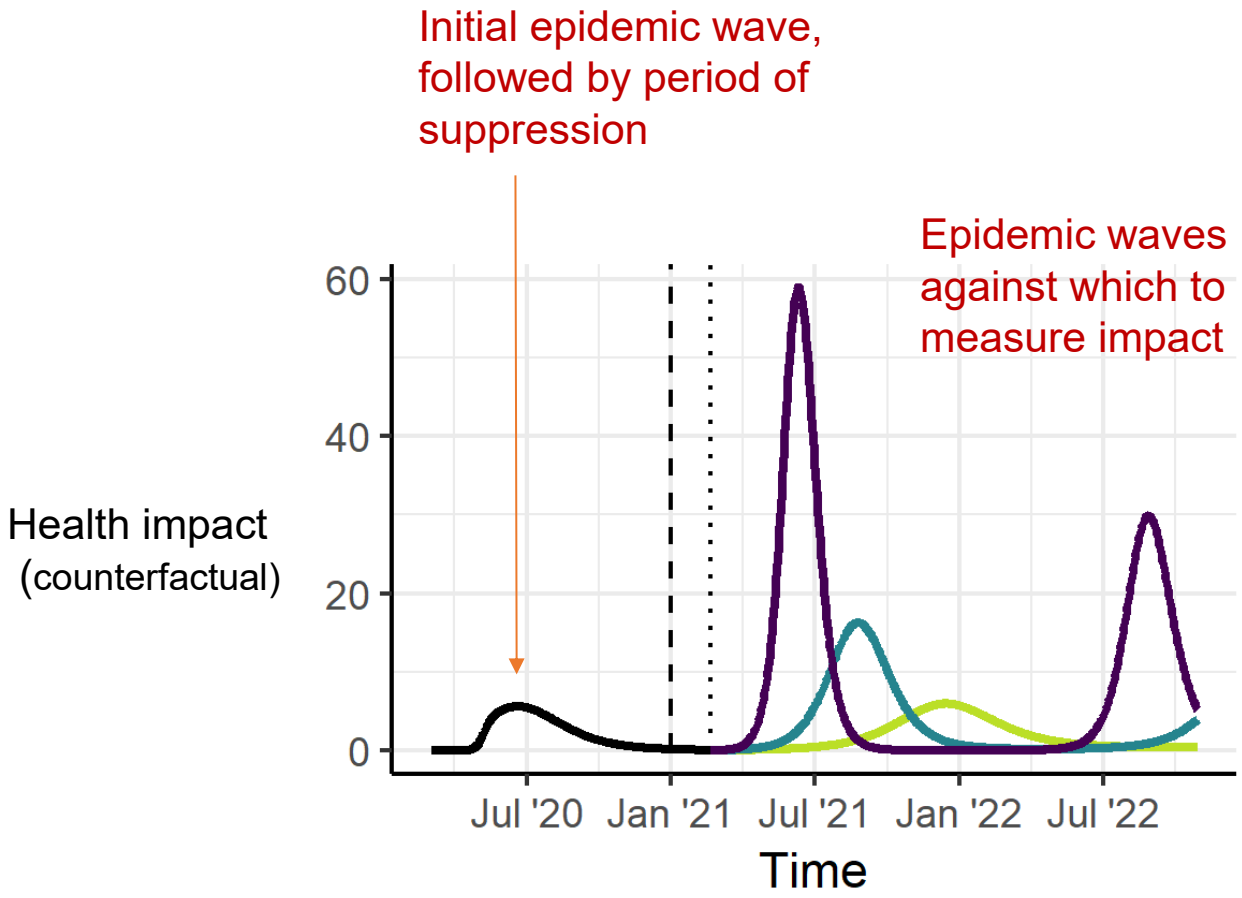
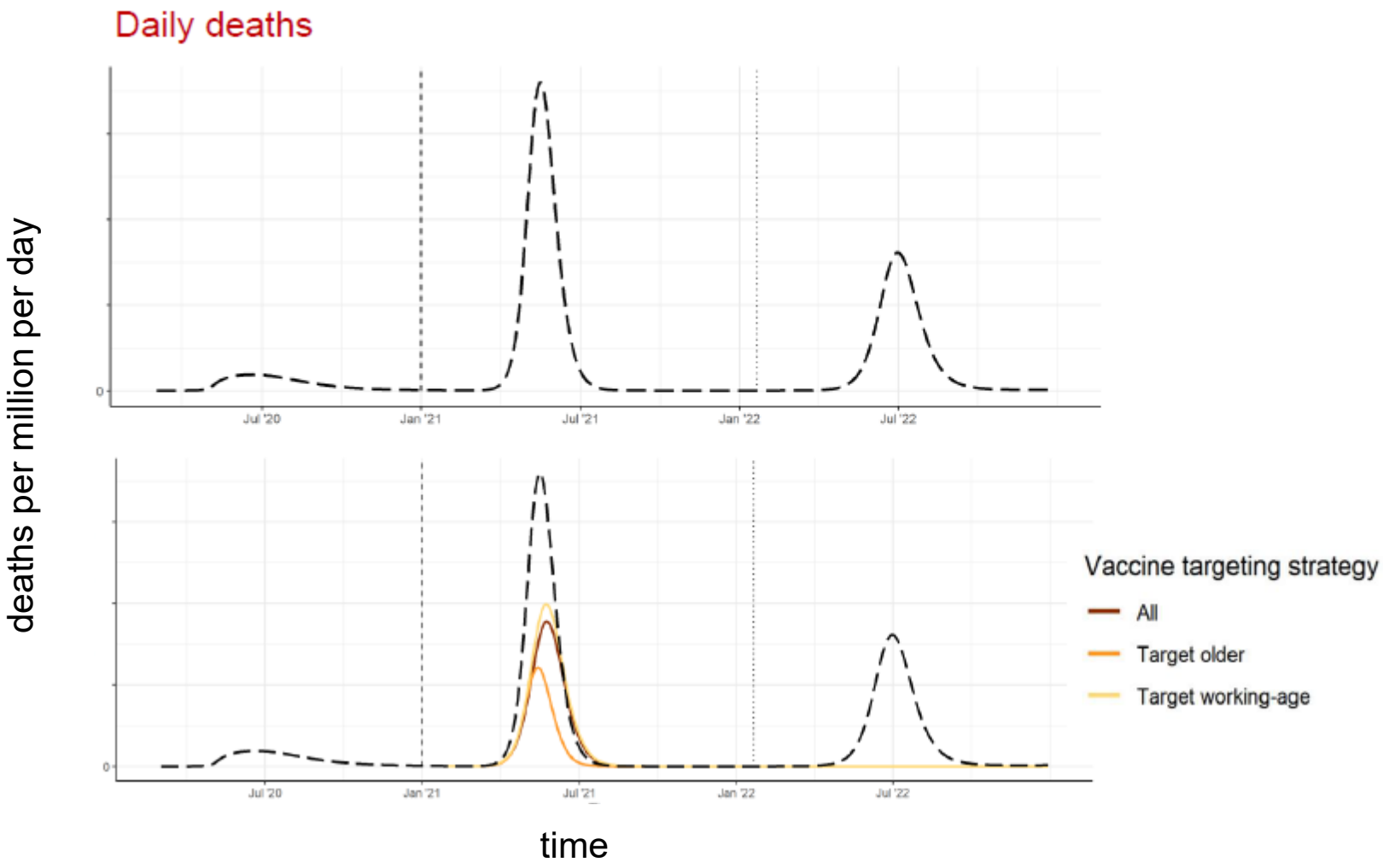


Coloured lines: different scenarios for how R_0 varied over time

Can use these scenarios to quantify impact of vaccination

- How many deaths would a vaccine avert?
- Who to vaccinate?
- Timing of lifting lockdowns?
- Unknown vaccine characteristics and supply?

Example: early SARS-CoV-2 modelling



Hogan & Winskill, Vaccine 2021, https://www.sciencedirect.com/science/article/pii/S0264410X21004278#s0070

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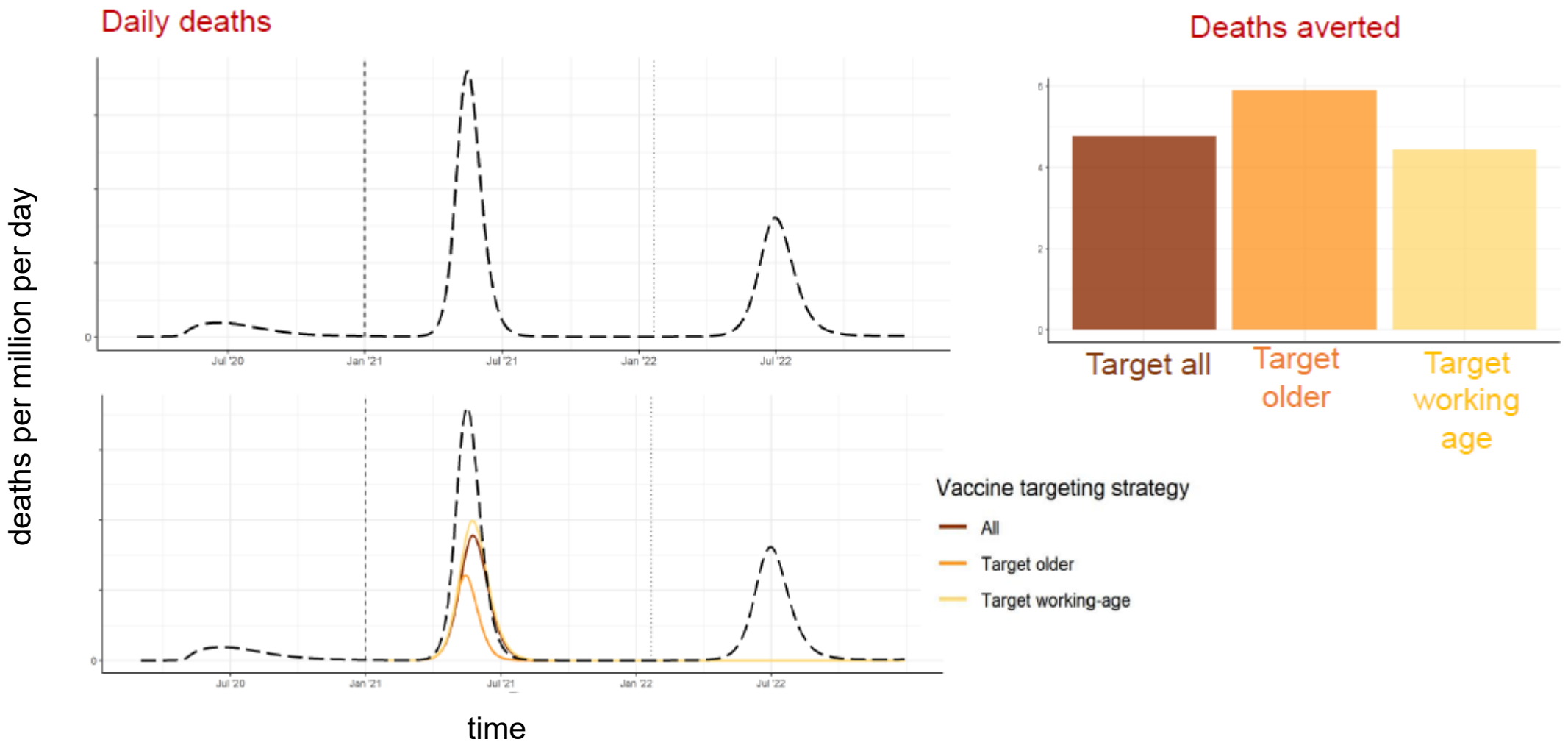


Hogan & Winskill, Vaccine 2021, https://www.sciencedirect.com/science/article/pii/S0264410X21004278#s0070

Herd immunity

- Herd immunity is an important form of indirect protection that applies to infectious diseases
- It occurs when there are enough immune individuals in a population such that each infectious individual can no longer infect more than one person
- This threshold is directly related to the reproduction number R_0

$$p_c = 1 - \frac{1}{R_0}$$

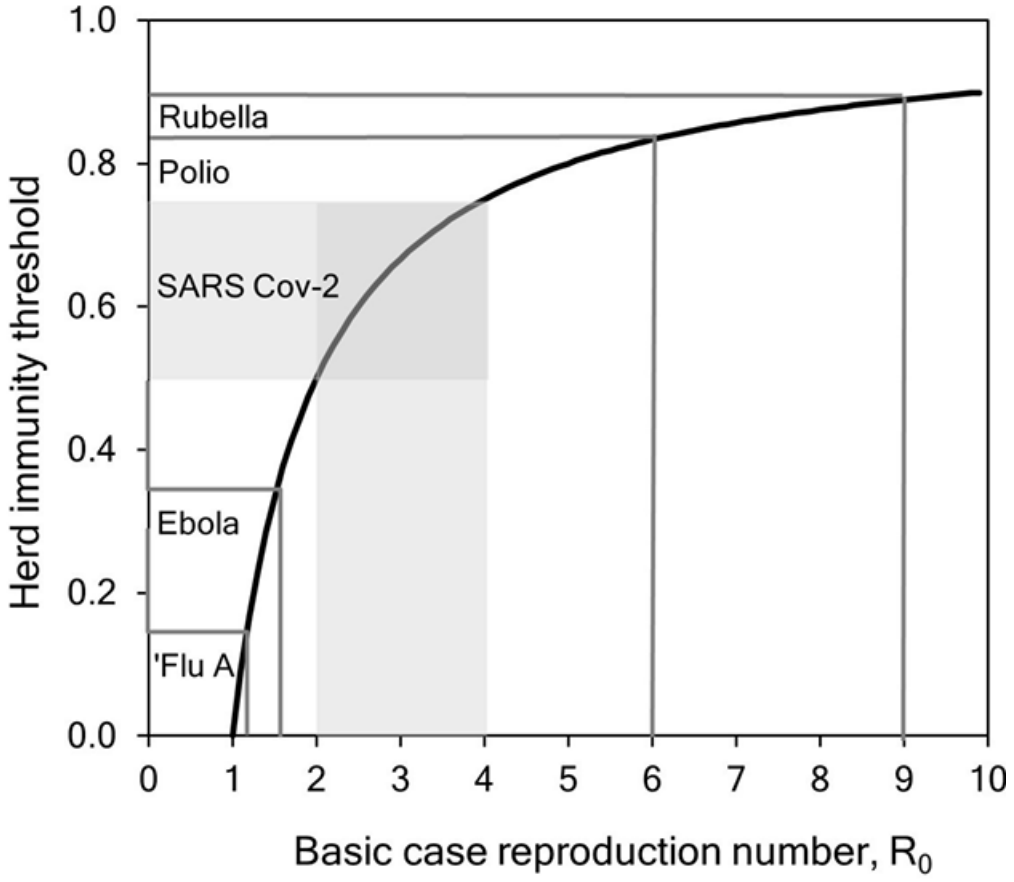


Figure: Herd immunity in the epidemiology and control of SARS-CoV-2 (Royal Society preprint, 2020)

Herd immunity: an illustration using measles

- Before the introduction of vaccination, measles epidemics occurred roughly every two years in England and Wales; the introduction of measles vaccination in 1968 had a dramatic effect on these epidemics.[1]

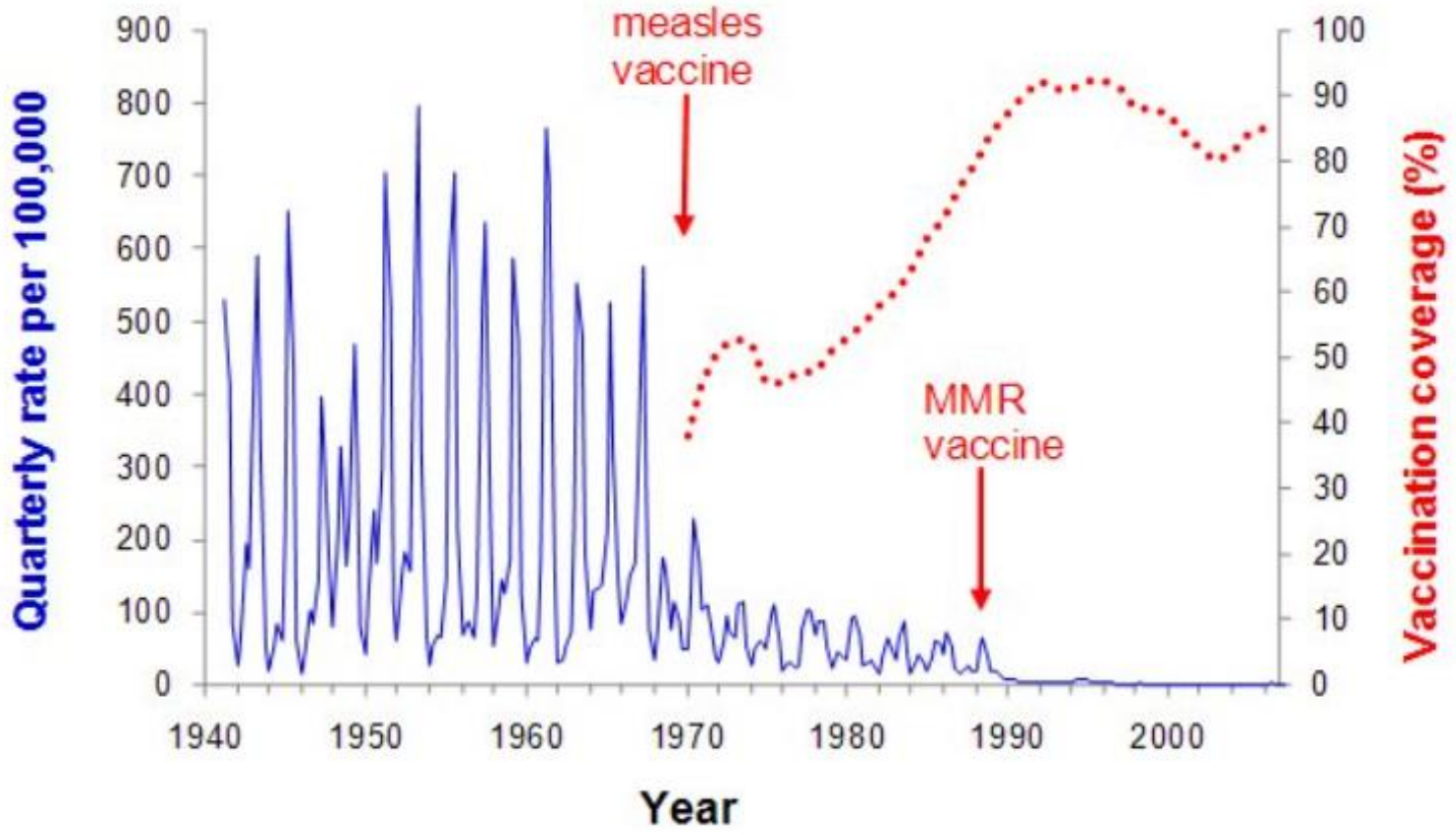
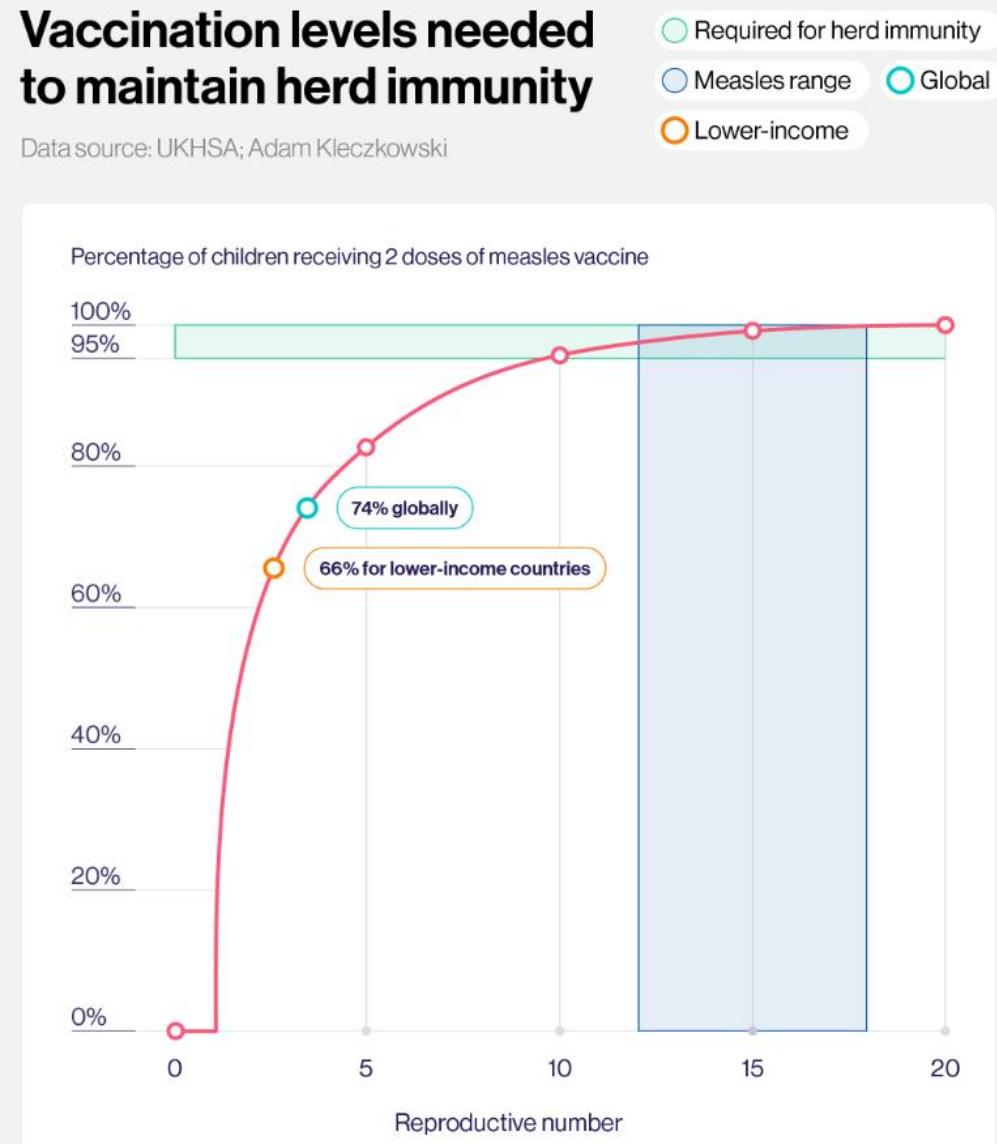
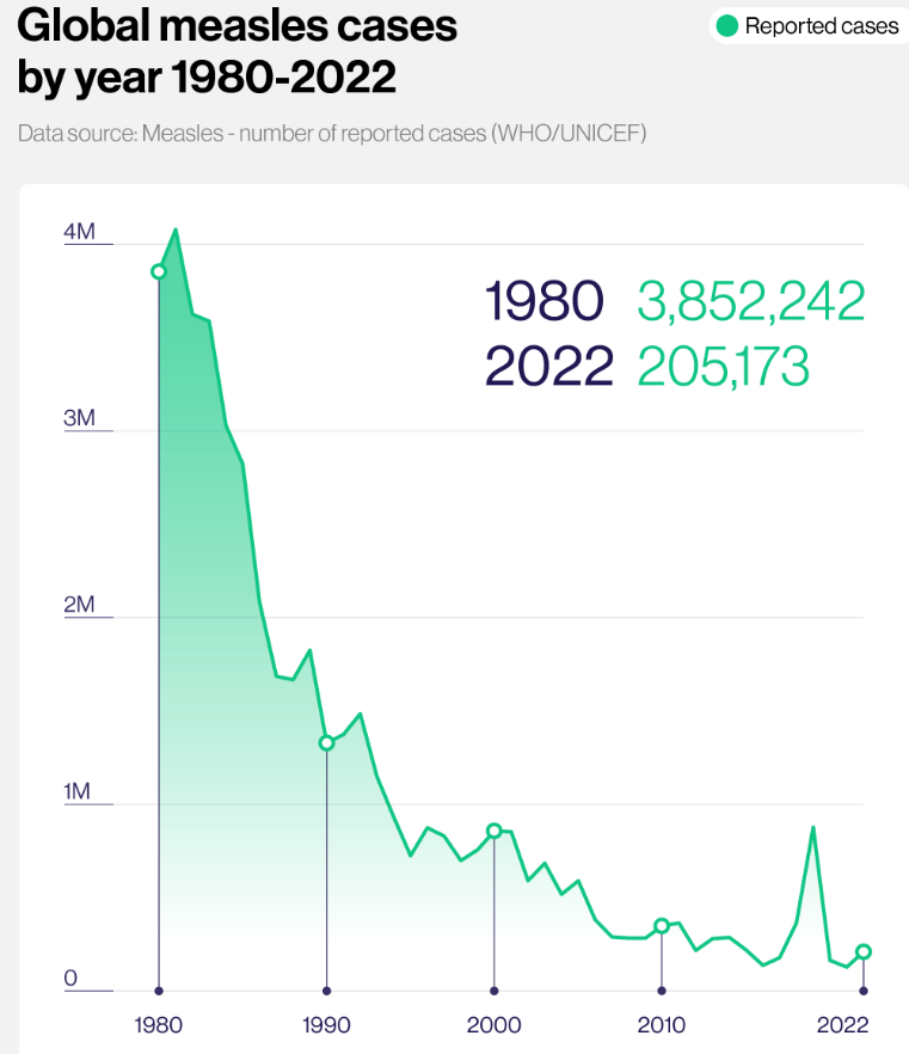


Figure: Quarterly notification rates of measles and measles vaccination coverage in England and Wales (data sources: Health Protection Agency and Office for Population Censuses and Surveys)

1 Vynnycky and White; https://anintroductiontoinfectiousdiseasemodelling.com/chapters/chapter-4/

Herd immunity: an illustration using measles



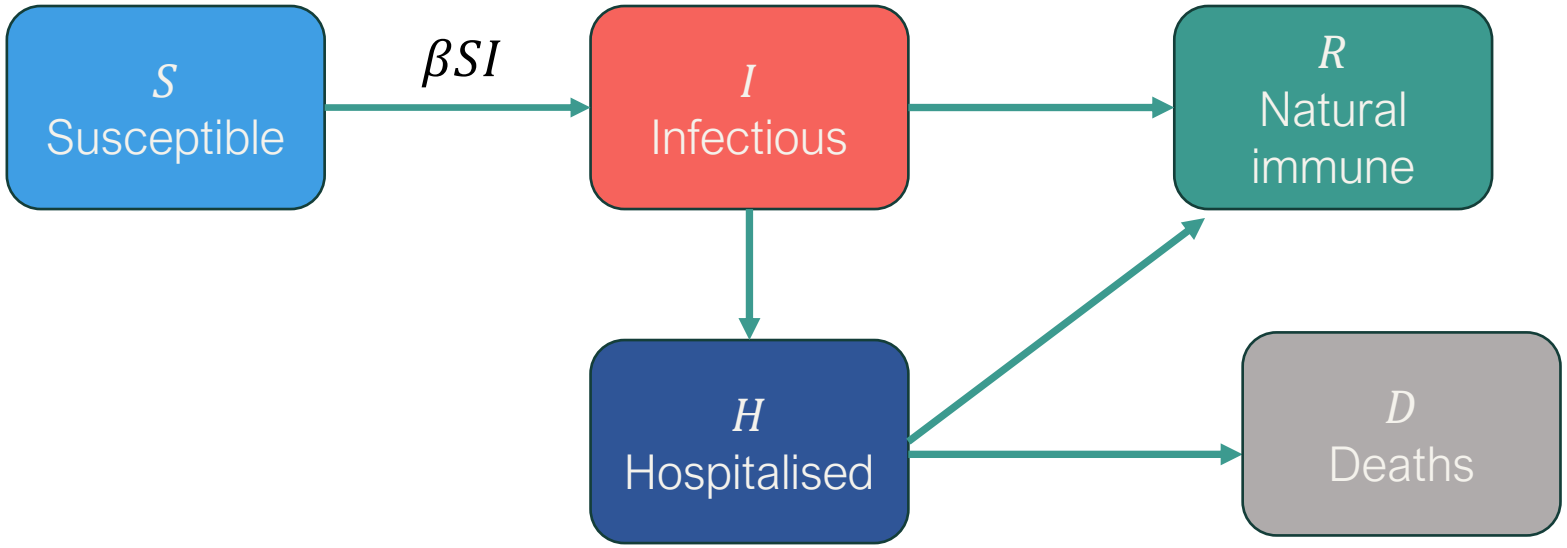


https://www.gavi.org/vaccineswork/story-measles-five-charts

Data considerations

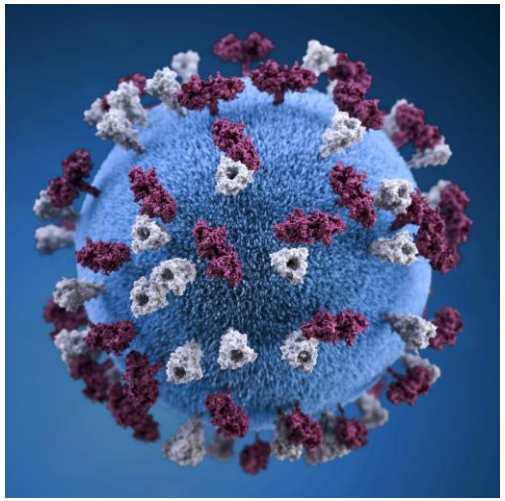
More on this in lecture 5

- While we capture the infection process in our models, we typically only observe some fraction of these in the reported data
- Transmission model may be linked to an observation model to represent changes in hospitalisations or other measurable health burden outcomes
- Can be difficulties in understanding what proportion of infections that burden data represents (and may change over time, and by age)



Wrap-up

- Epidemiological quantities such as the duration of infection, serial interval and generation time have important implications for epidemic outcomes
- The growth rate does not tell us everything – we need to know something about the underlying generation time to help us understand the dynamics and plan interventions
- The serial interval is often used as a proxy for the generation time in practice
- Mathematical models can be used to capture these quantities and simulate epidemics
- Models can then be used to simulate the impact of interventions and plan outbreak response
- Note the models described here assume long-term immunity following infection (have focused on short-term outbreak response)



Figures: https://www.who.int/news-room/spotlight/history-of-vaccination/history-of-measles-vaccination