Modelling non-pharmaceutical interventions

Luca Ferretti (Big Data Institute, University of Oxford)

What is a NPI?

- Number of forwards transmissions per infected individuals (*Rt*) =
  number of contacts x *risk of transmission per contact*

- Two approaches to reducing *Rt*:
    - Limit number of contacts
    - Reduce risk of transmission

What is a NPI?

- Number of forwards transmissions per infected individuals (*Rt*) =
  number of contacts x *risk of transmission per contact*

- Two approaches to reducing *Rt*:
  - Limit number of contacts*… of whom?*
  - Reduce risk of transmissions*… of whom?*

Person	Random member of population	Known contact of case	Known case
Example measures	General distancing, face masks	Please stay at home	No really, please stay at home

Greater confidence they are infectious (higher specificity)

Can take stronger measures

Tends to happen later in the infection

What is a NPI?

- Number of forwards transmissions per infected individuals (*Rt*) =
  number of contacts x *risk of transmission per contact*

- Two approaches to reducing *Rt*:
  - Limit number of contacts*… of whom? Which contacts? How?*
  - Reduce risk of transmission*… of whom? Which contacts? How?*

COVID-19

Non-pharmaceutical interventions (NPI) are actions that people and communities can take to help slowing down the spread of viruses such as SARS-CoV-2. Such community mitigation strategies, ranging from individual actions such as regularly practising good hand hygiene to more restrictive measures like limiting size of gatherings, should ideally be implemented in combination and applied at the same time.

The mix of chosen NPI should differ based on the local transmission situation.

It can take several weeks before any implemented NPI might show an effect.

More on NPI and how to apply them: http://bit.ly/COVID19_NPIs

1 WHAT EVERYONE OF US CAN DO

- Physical distancing
- Strict hand hygiene
- Respiratory etiquette
- Appropriate use of face masks, in areas where physical distancing is not possible
- Stay at home if you have COVID-19 compatible symptoms

2 POSSIBLE ACTIONS WHEN THERE IS COMMUNITY SPREAD

- If you had direct contact with a COVID-19 case, stay at home and self monitor
- Ideally, meet with the same people, whether family friends or co-workers
- Limit the size of gatherings, eventually close selected businesses
- Work from home where possible
- Regular cleaning of frequently touched surfaces and objects
- Ensure appropriate ventilation of indoor spaces

3 CONSIDERATIONS IN THE EVENT OF WIDESPREAD TRANSMISSION

- STAY HOME — Stay-at-home policy
- Population-wide testing strategies in local settings with high incidence
- Considering closure of schools and educational settings

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

#COVID19

Role of NPIs in controlling infectious diseases

- Timing: can be deployed immediately
- Scalability: some actions taken by individuals, some by public health systems
- Less vulnerable to evolutionary changes (immune escape)

Specificity/sensitivity of NPIs

- Lockdowns/stay-at-home orders or generalised physical distancing
- Closure of high-risk activities
- Quarantine of contacts
- Isolation of cases

Specificity/sensitivity of spatial NPIs

- National closures
- Red zones
- Local closures
- Border controls

Generalised NPIs

- Physical/social distancing
- Masks
- Hygiene, ventilation
- Lockdowns/stay-at-home orders

Basic SIR model

$$\frac{dI}{dt} = \beta \; S \; I - \gamma \; I$$

$$\frac{dS}{dt} = -\beta \; S \; I$$

More targeted NPIs

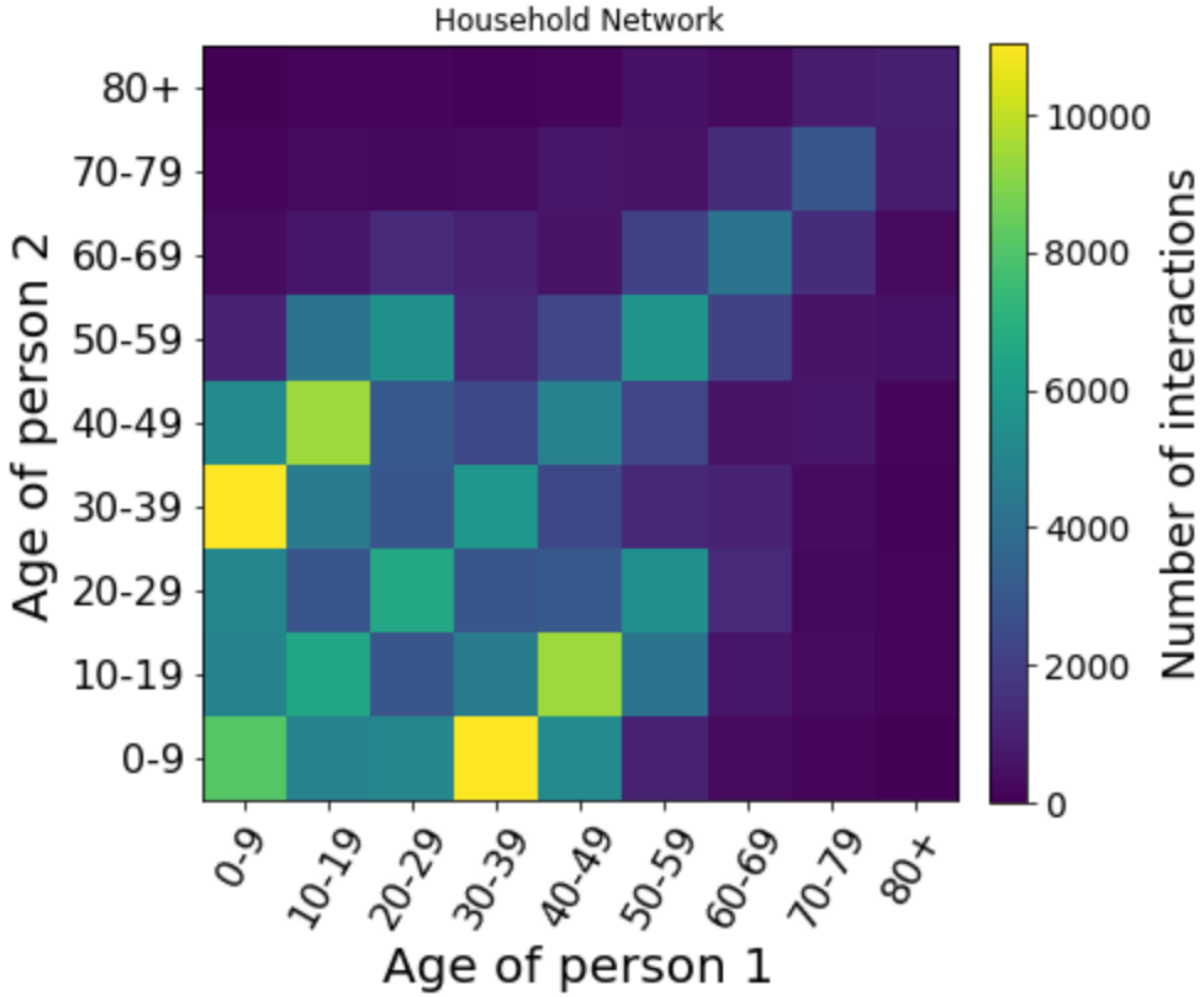
- School closures
- Shielding of fragile/elderly individuals
- Work from home
- Closure of venues, limits on aggregations

Compartmentalised SIR models

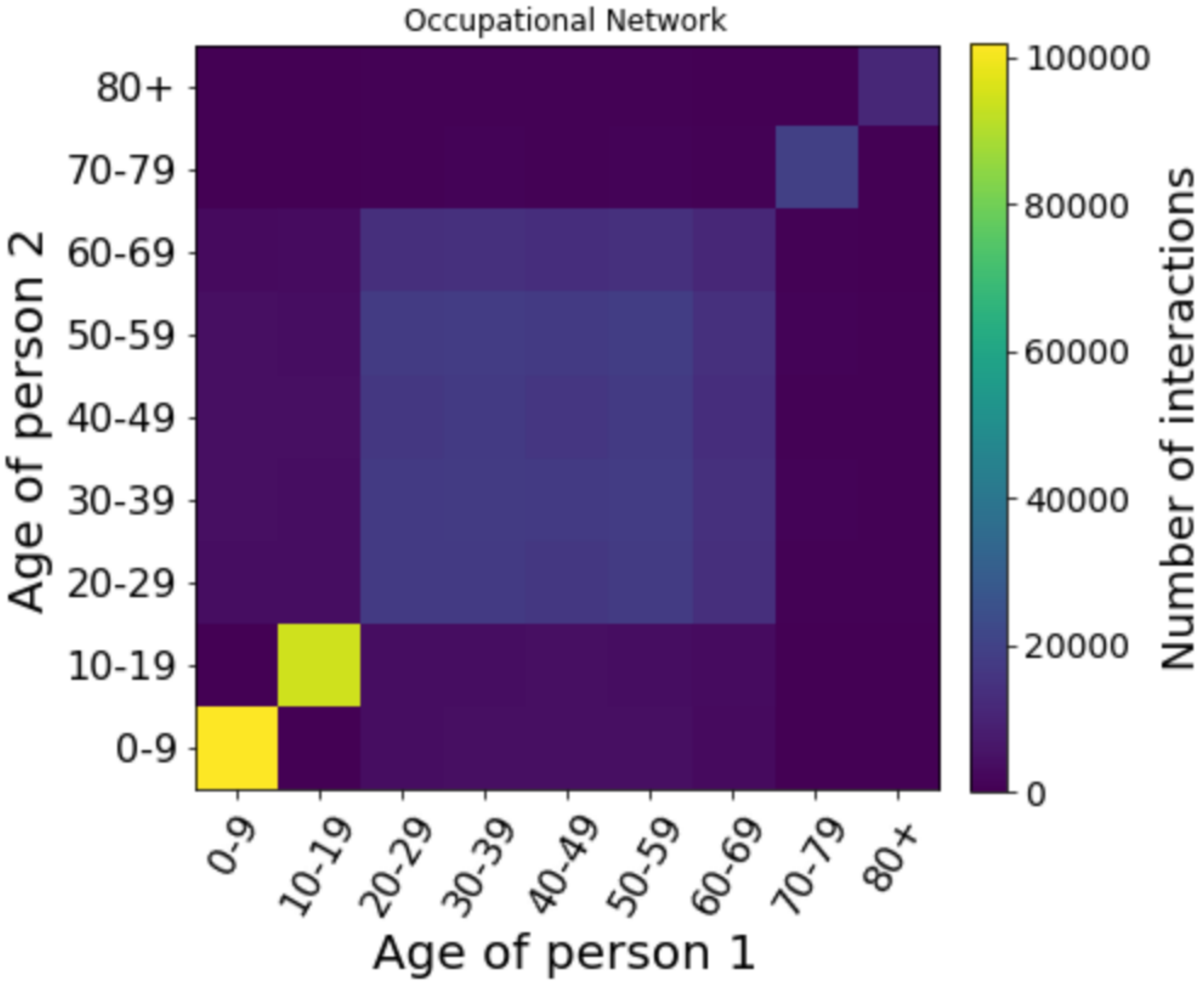
$$\frac{dI_k}{dt} = \sum_j \beta_{j\to k}\, S_k\, I_j - \gamma_k\, I_k$$

$$\frac{dS_k}{dt} = -\sum_j \beta_{j\to k}\, S_k\, I_j$$

Age- and context-specific contact matrices



Age- and context-specific contact matrices



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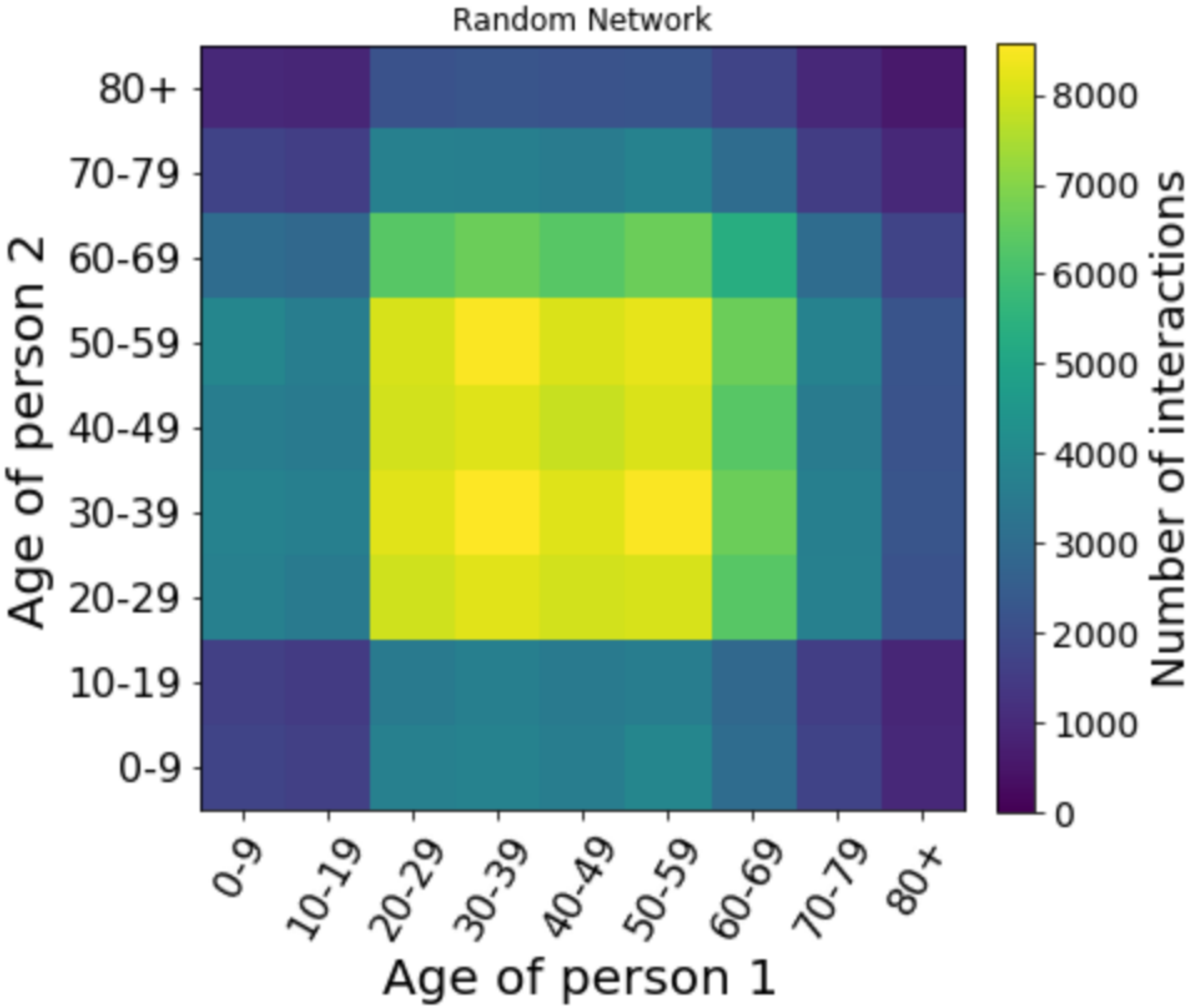
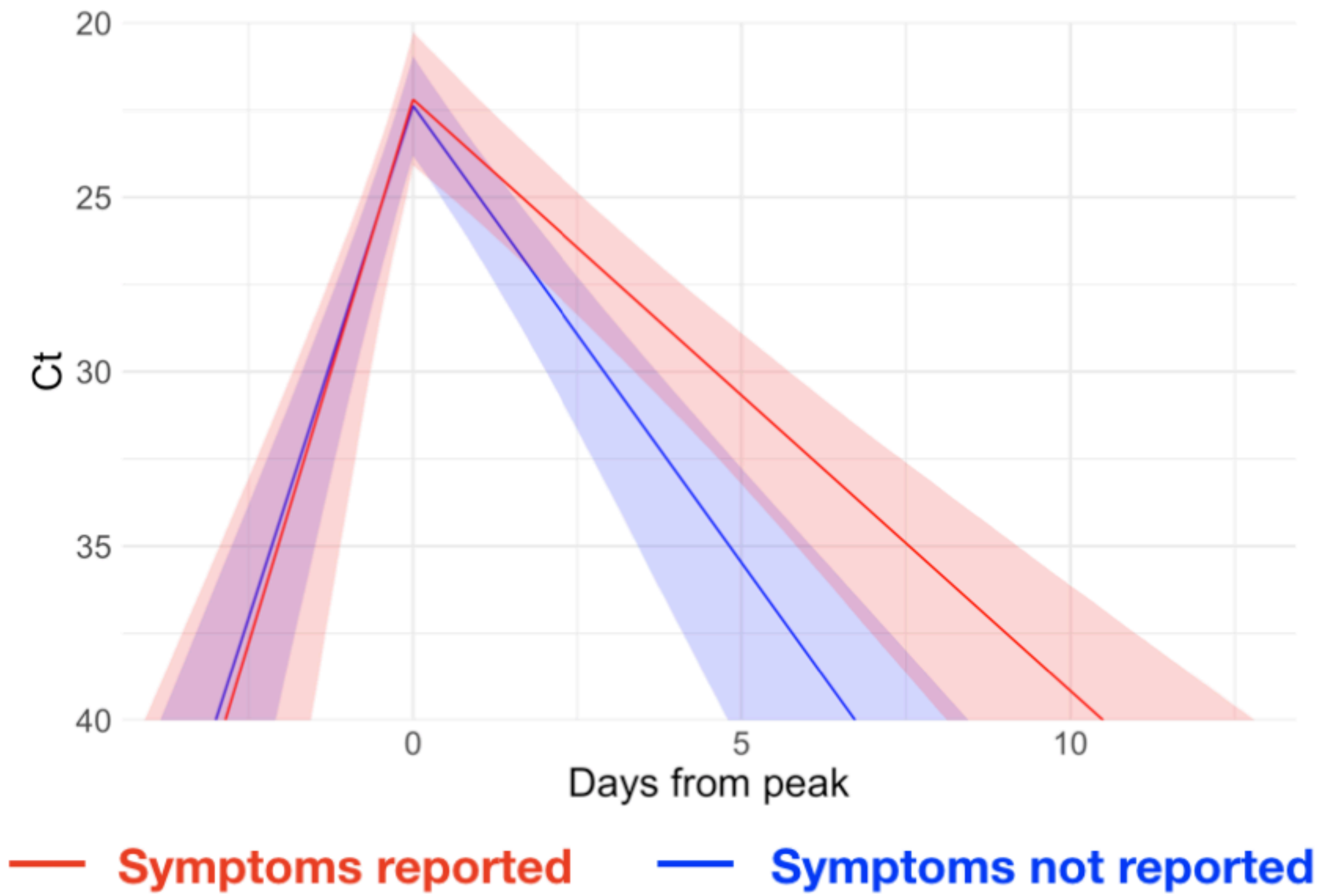


Age- and context-specific contact matrices

Detecting and isolating infected individuals

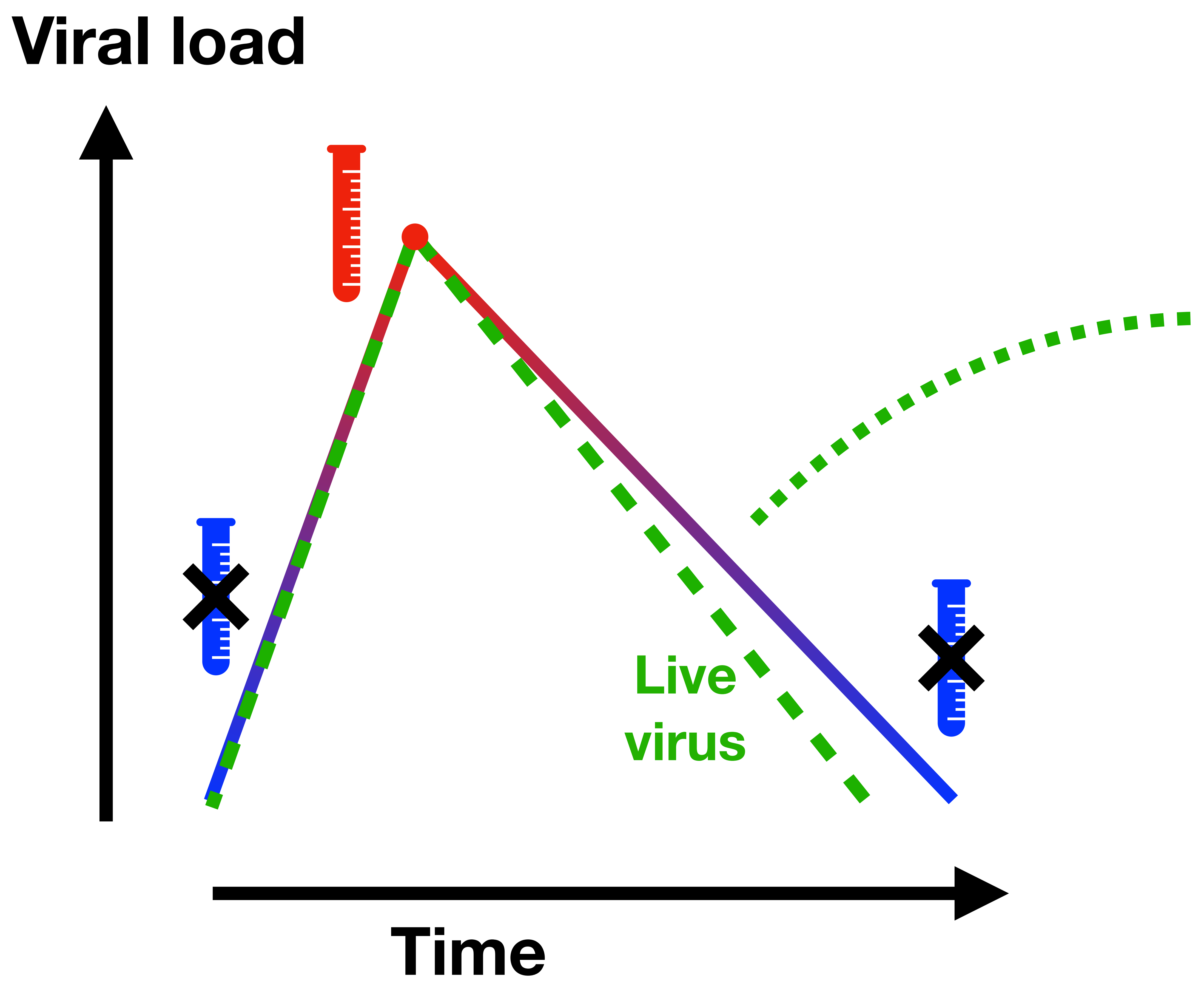
- Random testing
- Syndromic surveillance
  - Symptom-based detection
  - Testing symptomatic individuals
- Mass testing

Viral load dynamics

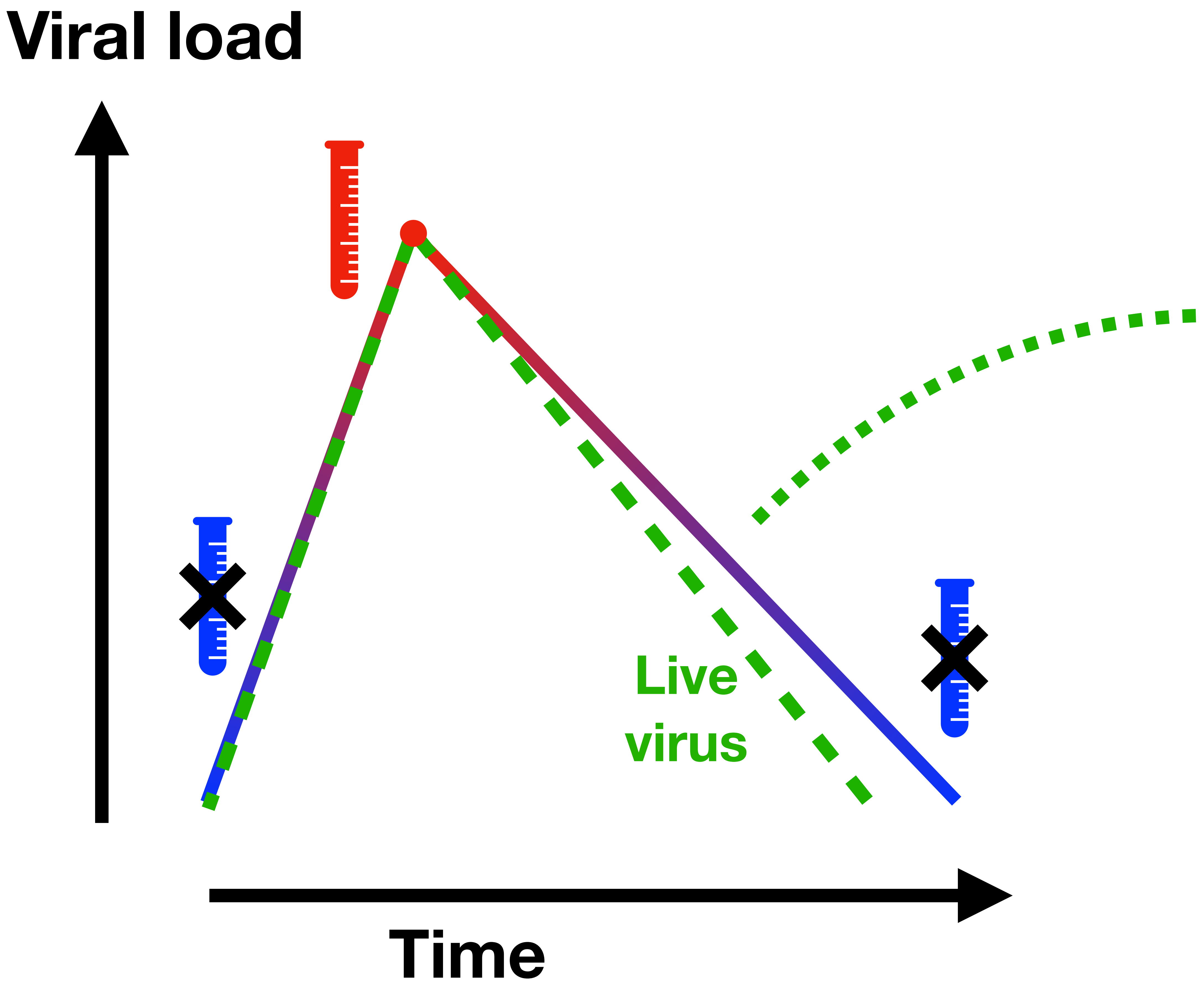


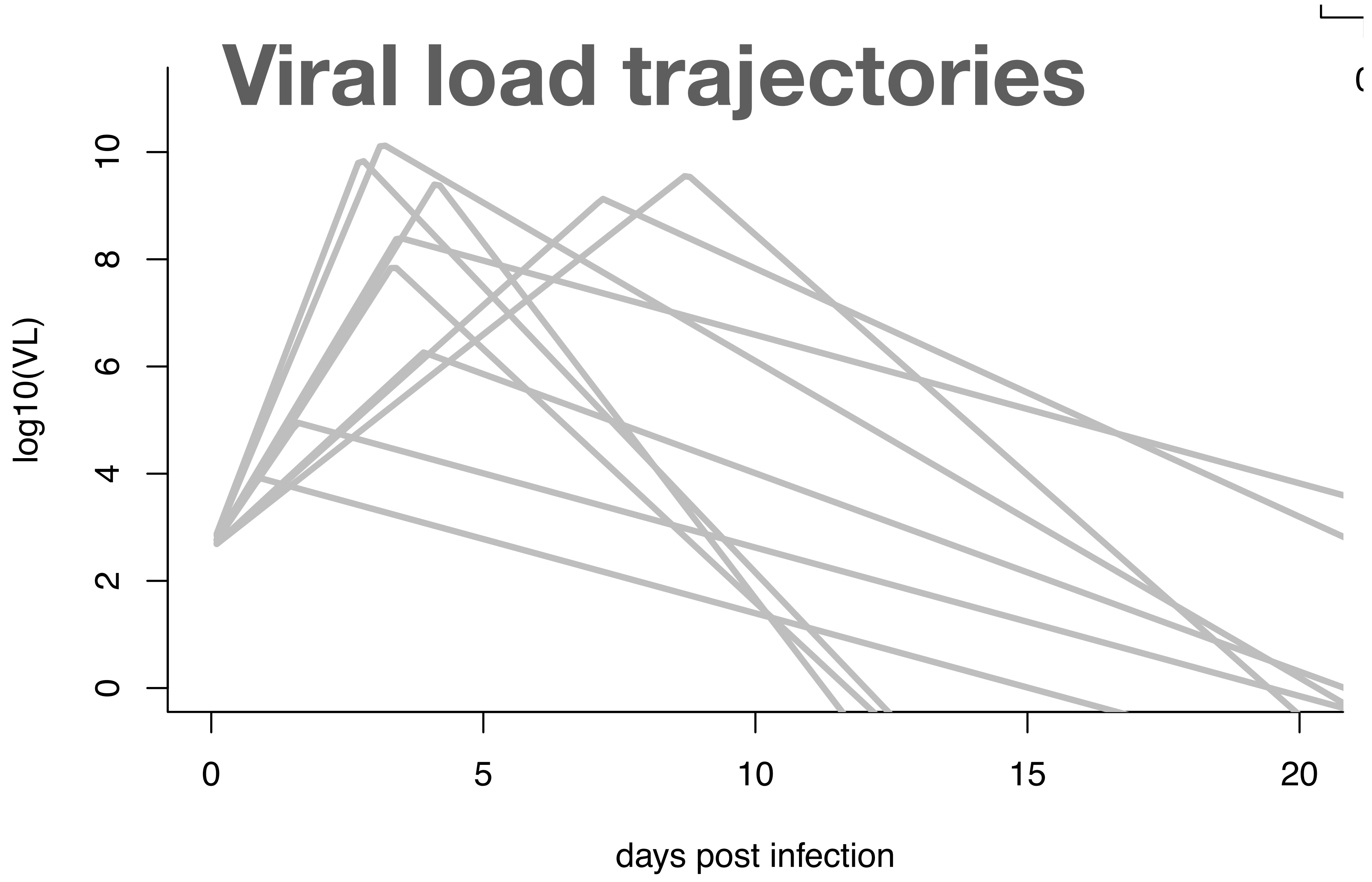
Kissler et al Plos Biology 2021

Modelling testing sensitivity



Modelling testing sensitivity



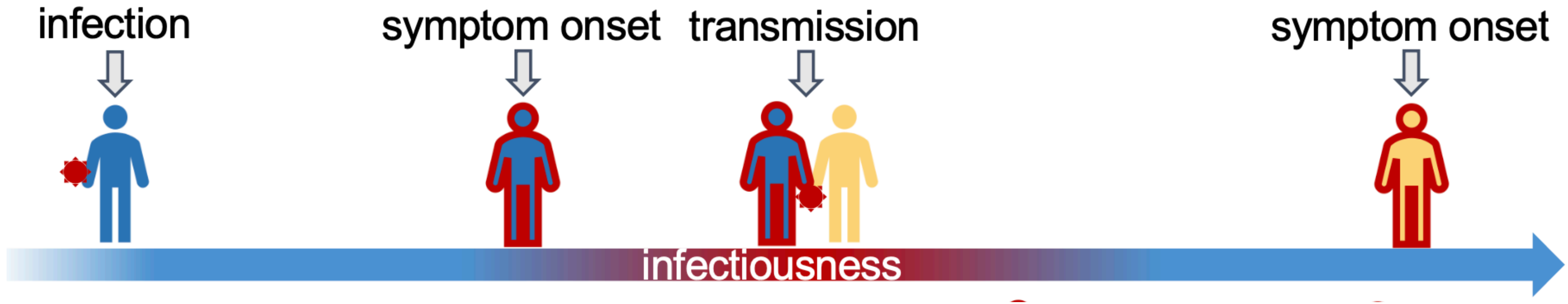


Isolation of infected cases

The effectiveness of isolation in reducing transmissions depends on

- delays
- adherence to isolation
- transmission within households
- policy for other members of the same household

Infectiousness in time



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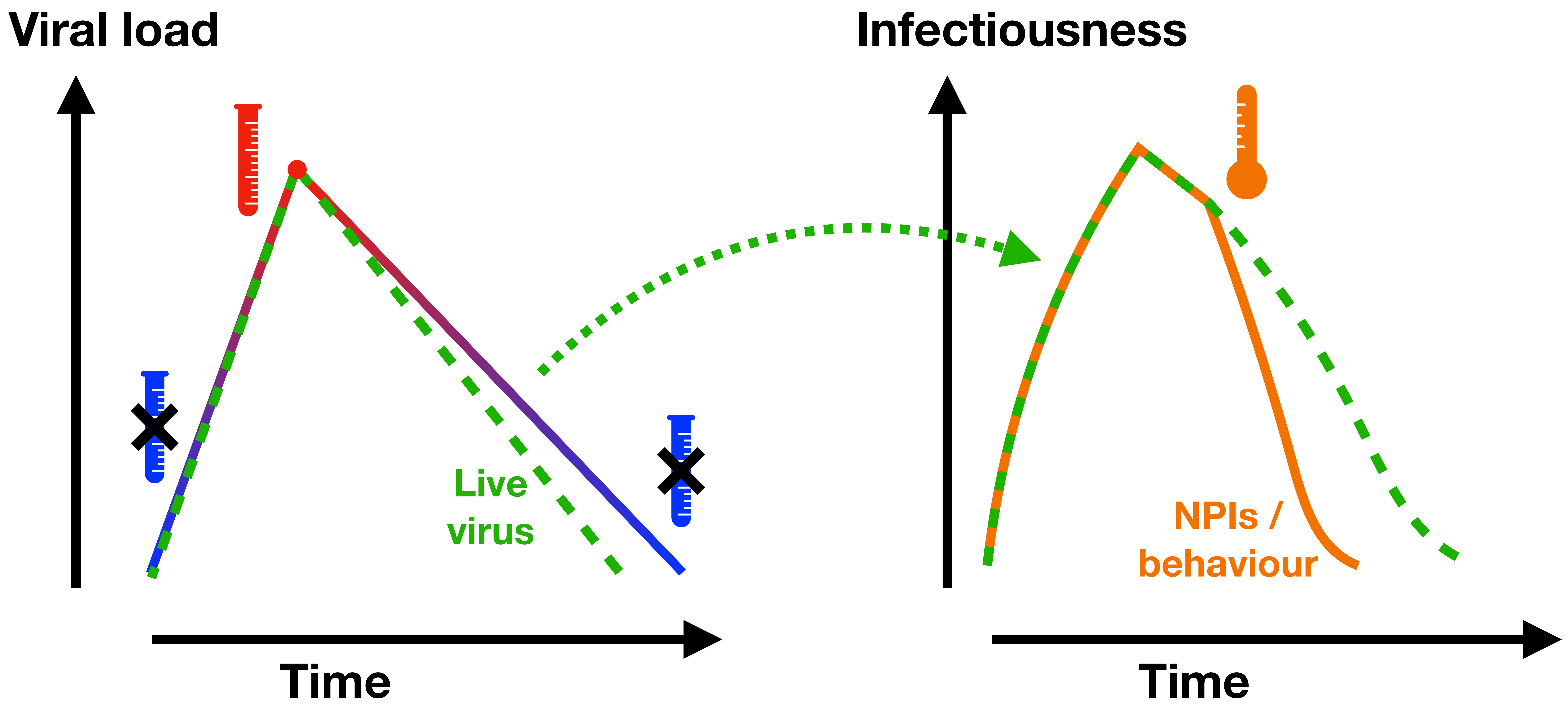
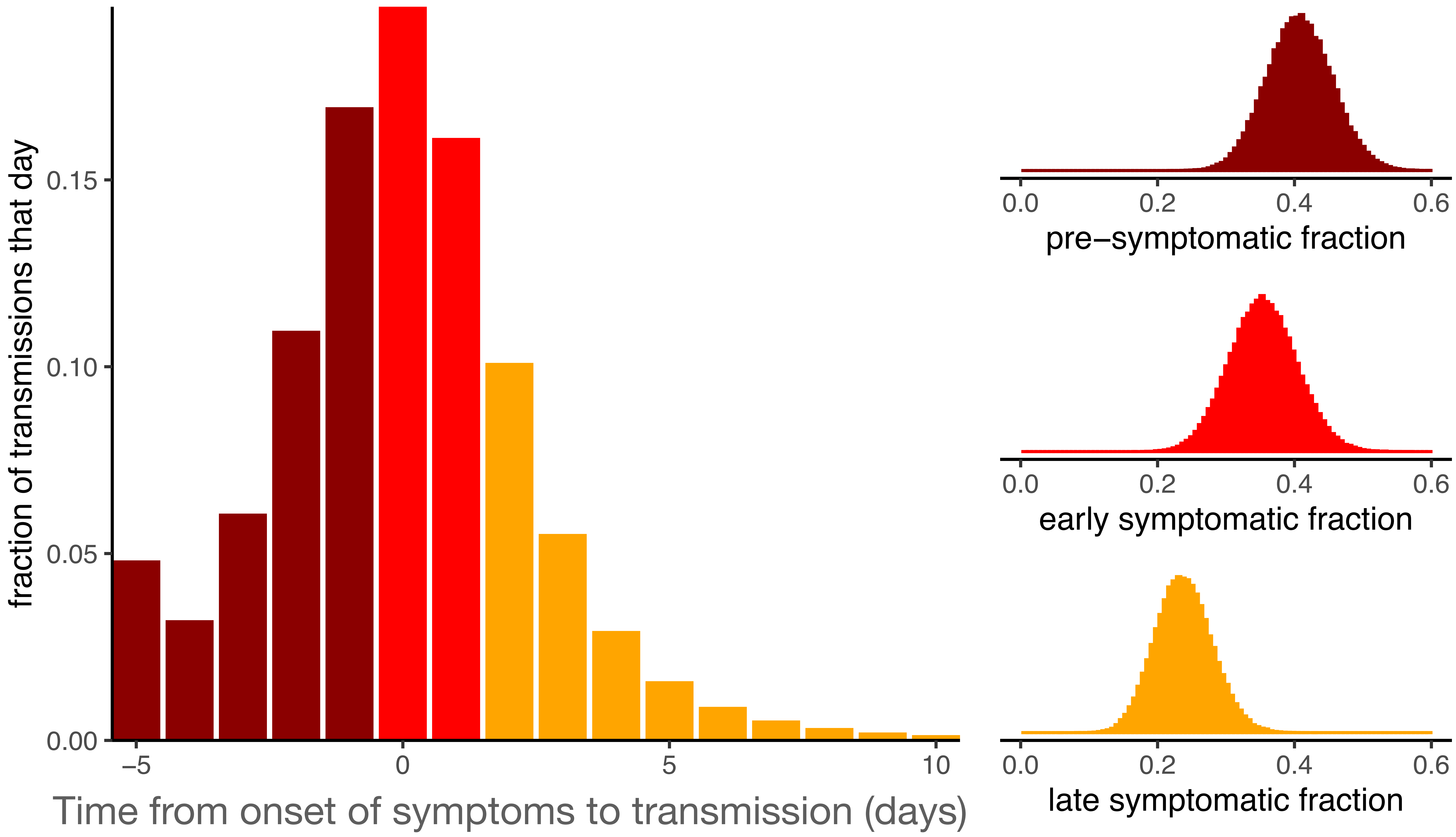
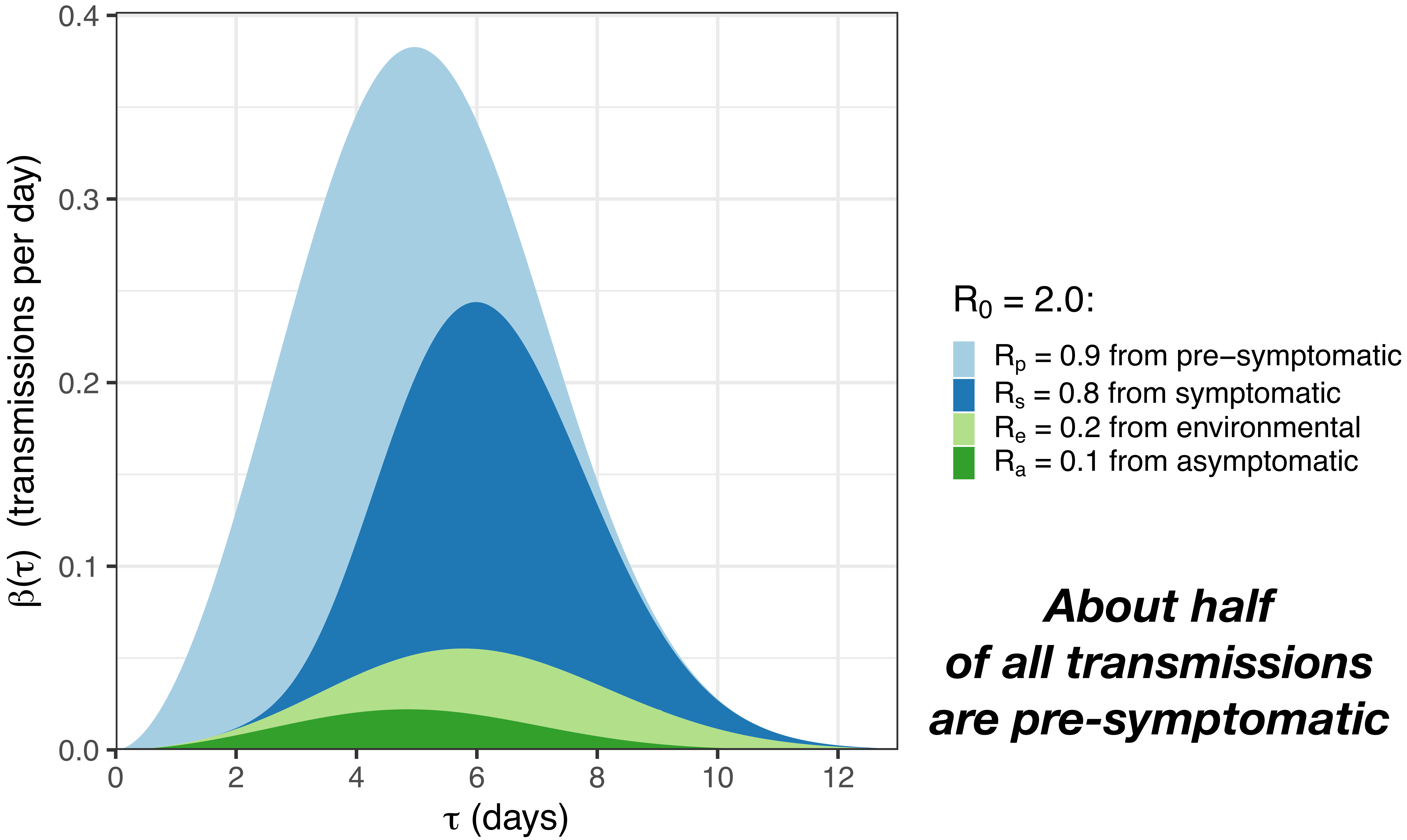


Infectiousness in time

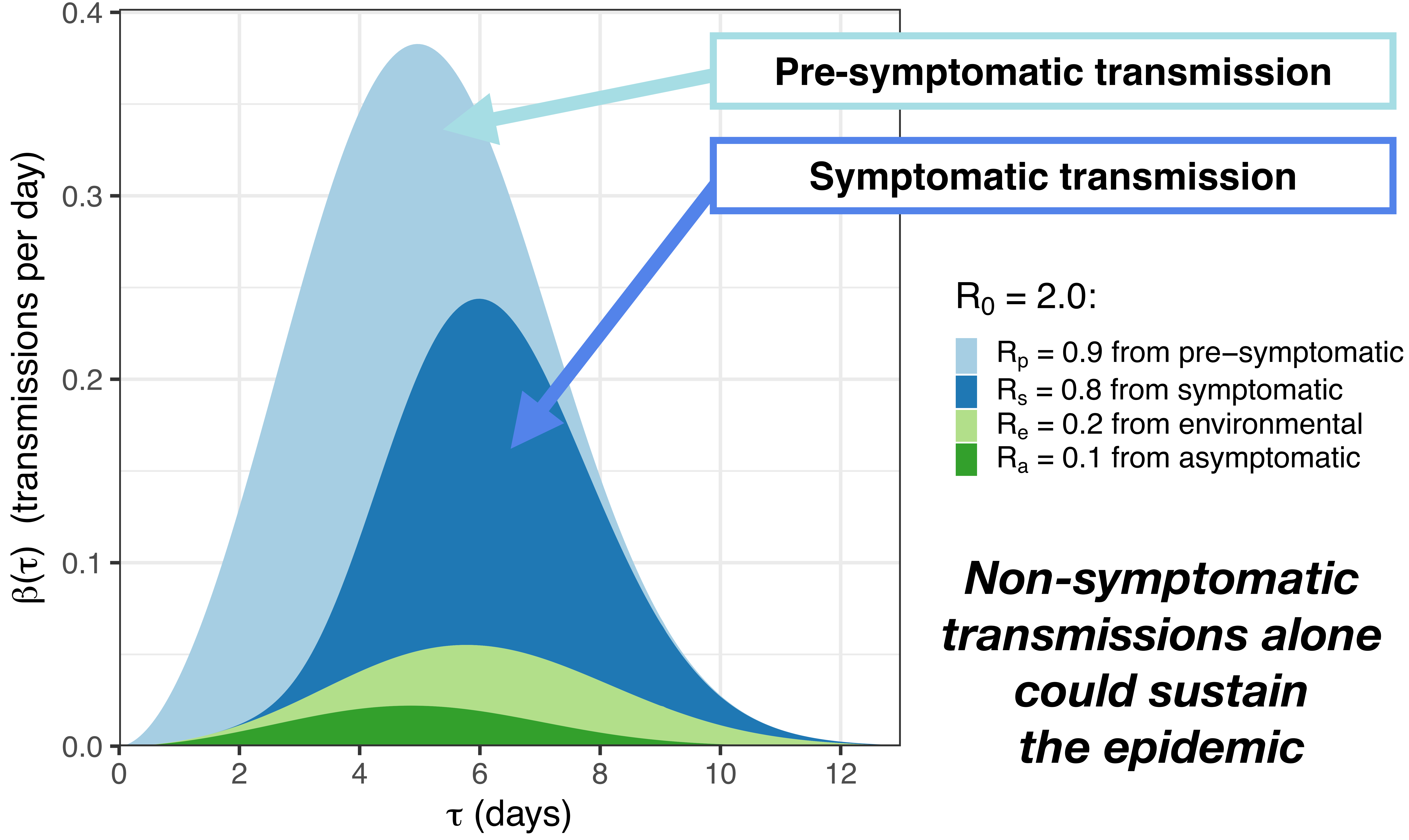


Decomposition of infectiousness



About half of all transmissions are pre-symptomatic

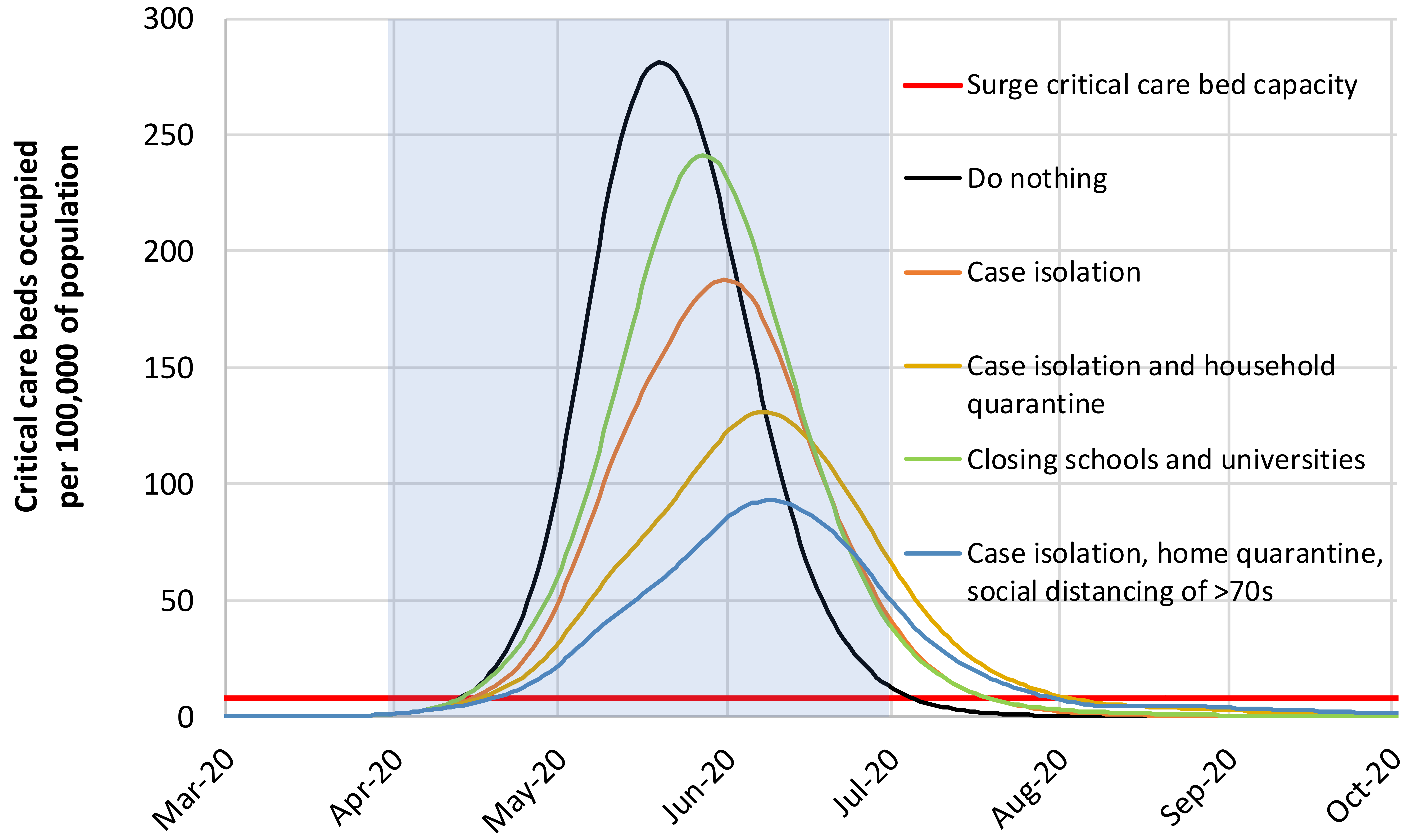
Decomposition of infectiousness



Non-symptomatic transmissions alone could sustain the epidemic

COVID-19 impact on ICUs

(Imperial College report 9, Ferguson et al)



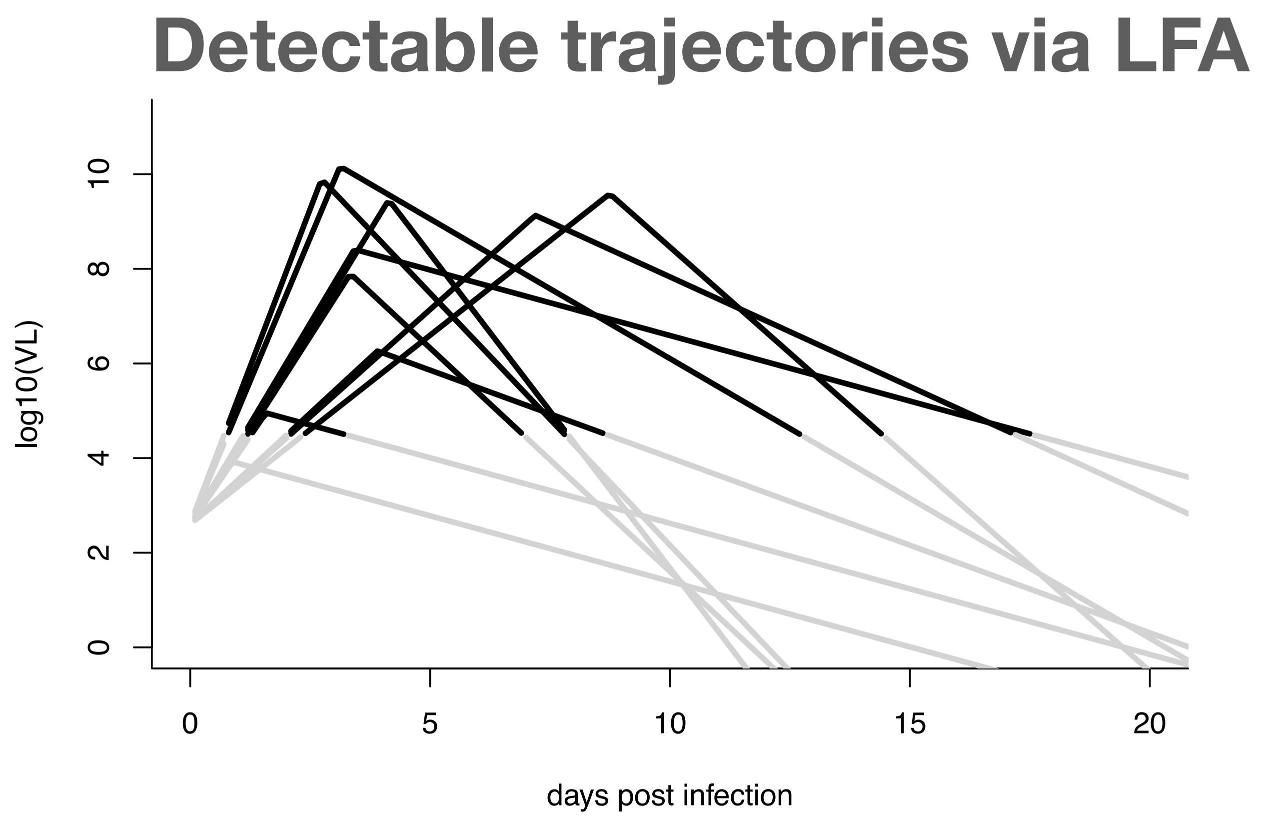
When SIR models are not enough

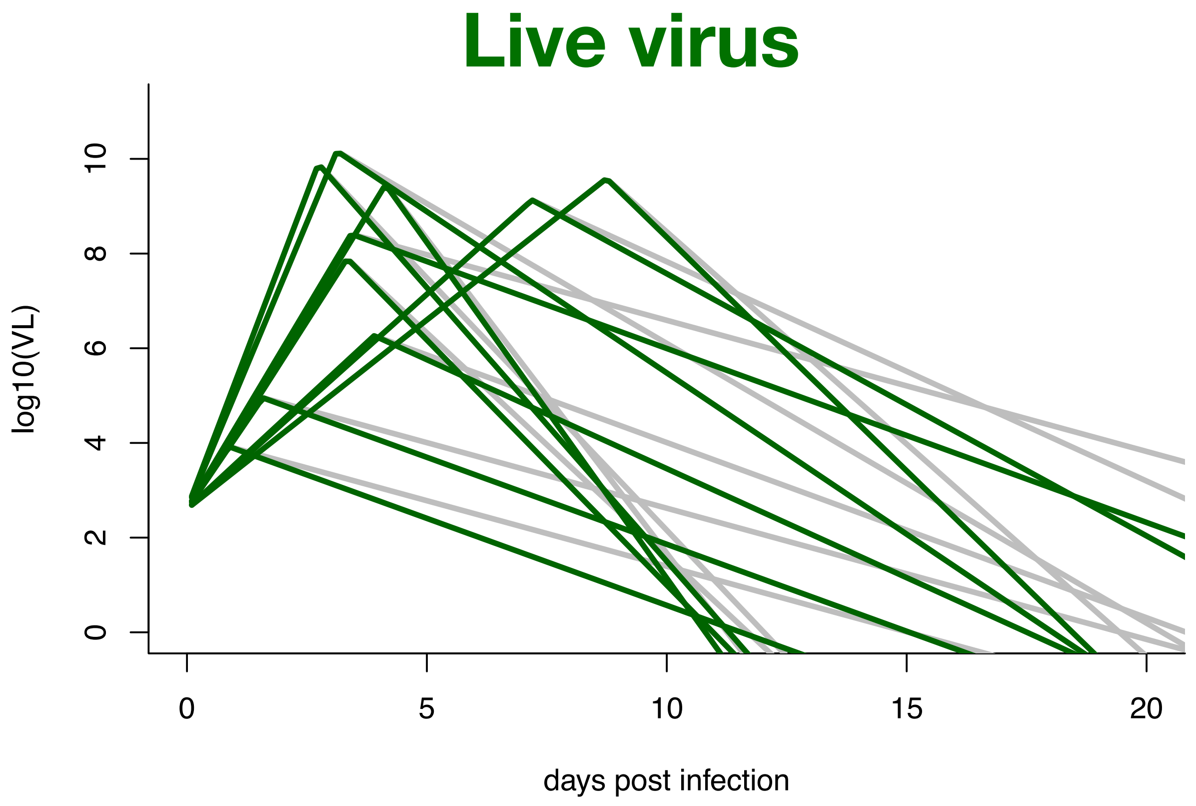
- Realistic delays
    - SIR models limited to Erlang distributions
- Many compartments
    - e.g. multiple factorised classes of individuals
- Correlated heterogeneities among individuals
- Measures focused on contacts
    - e.g. contact tracing

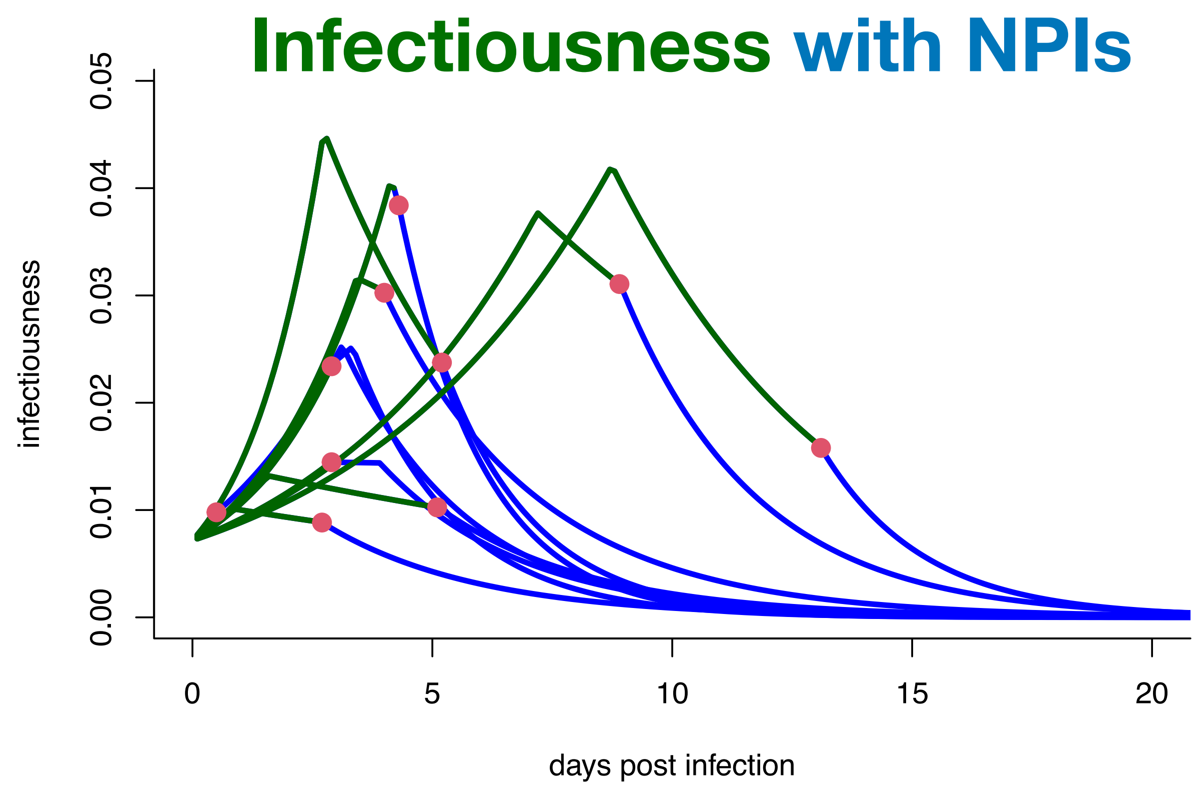
e.g. individual-level modelling

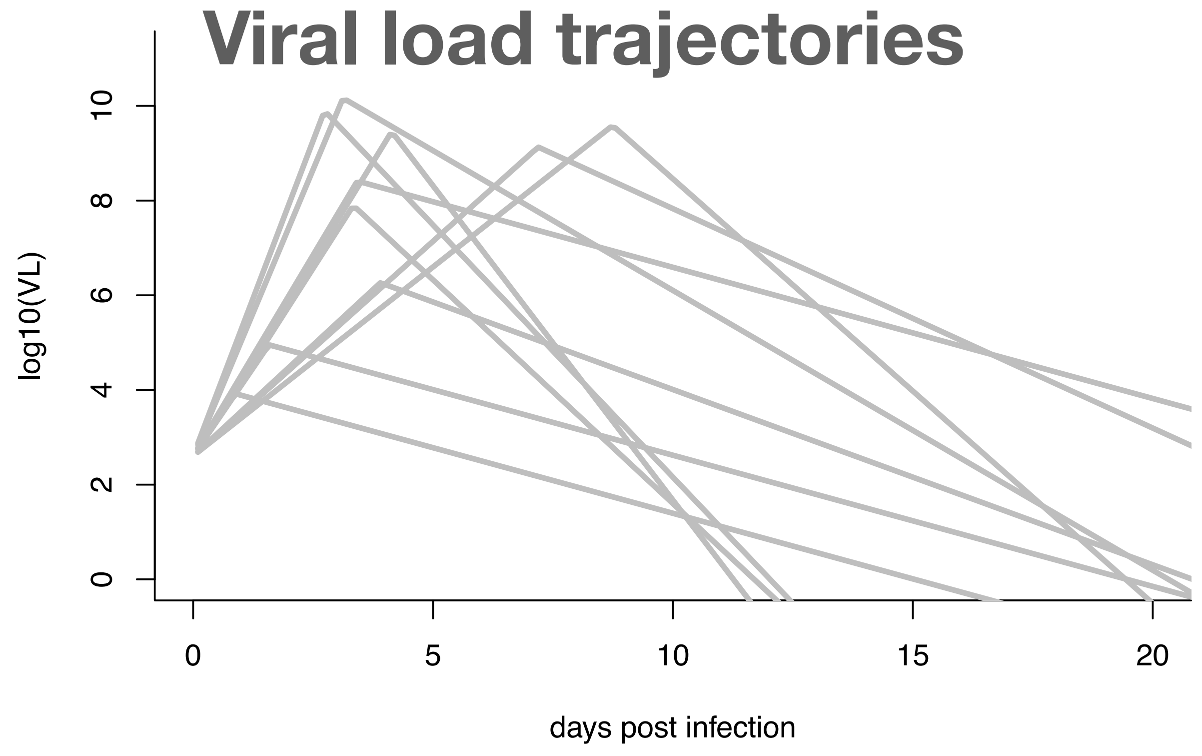
individual-level dynamics

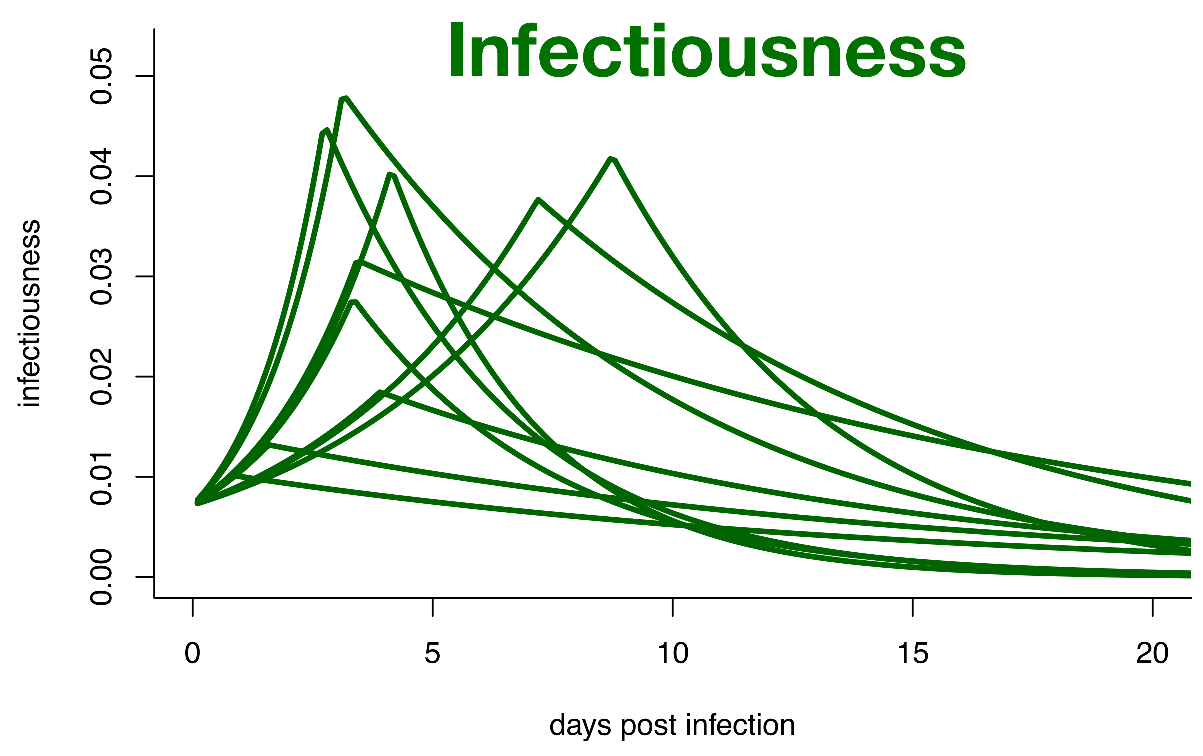
e.g. relation between symptoms, infectiousness and test sensitivity











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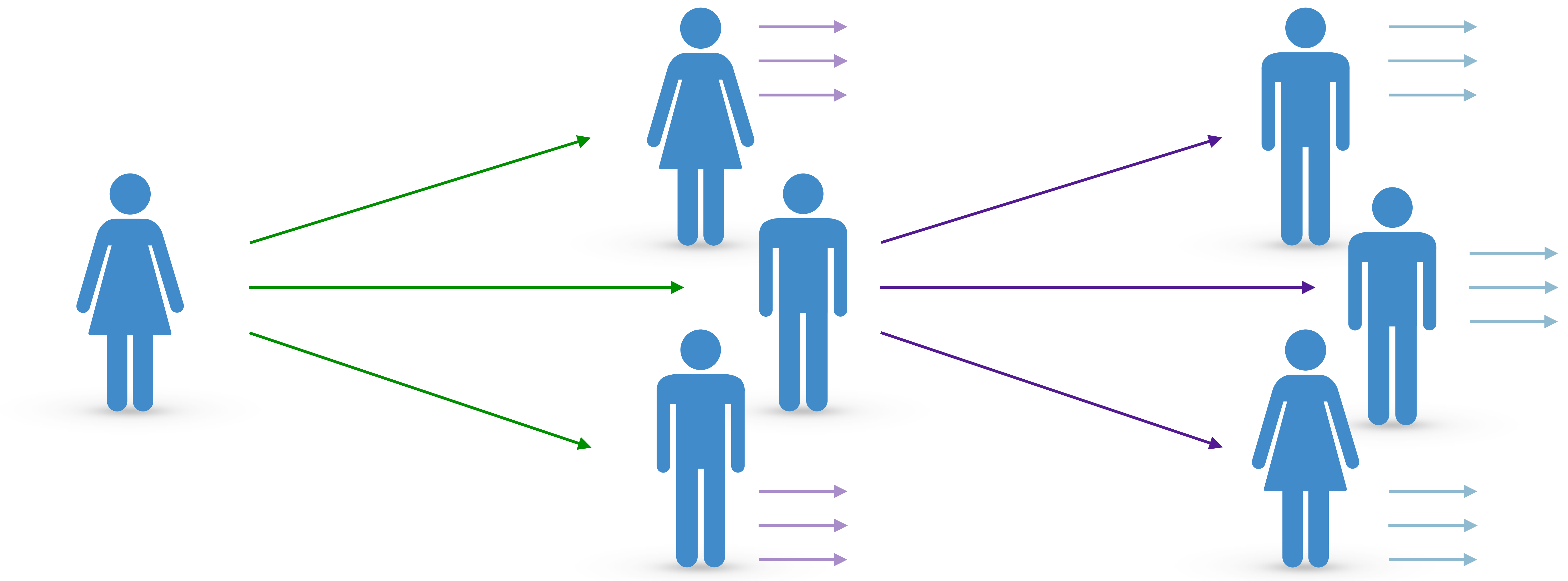
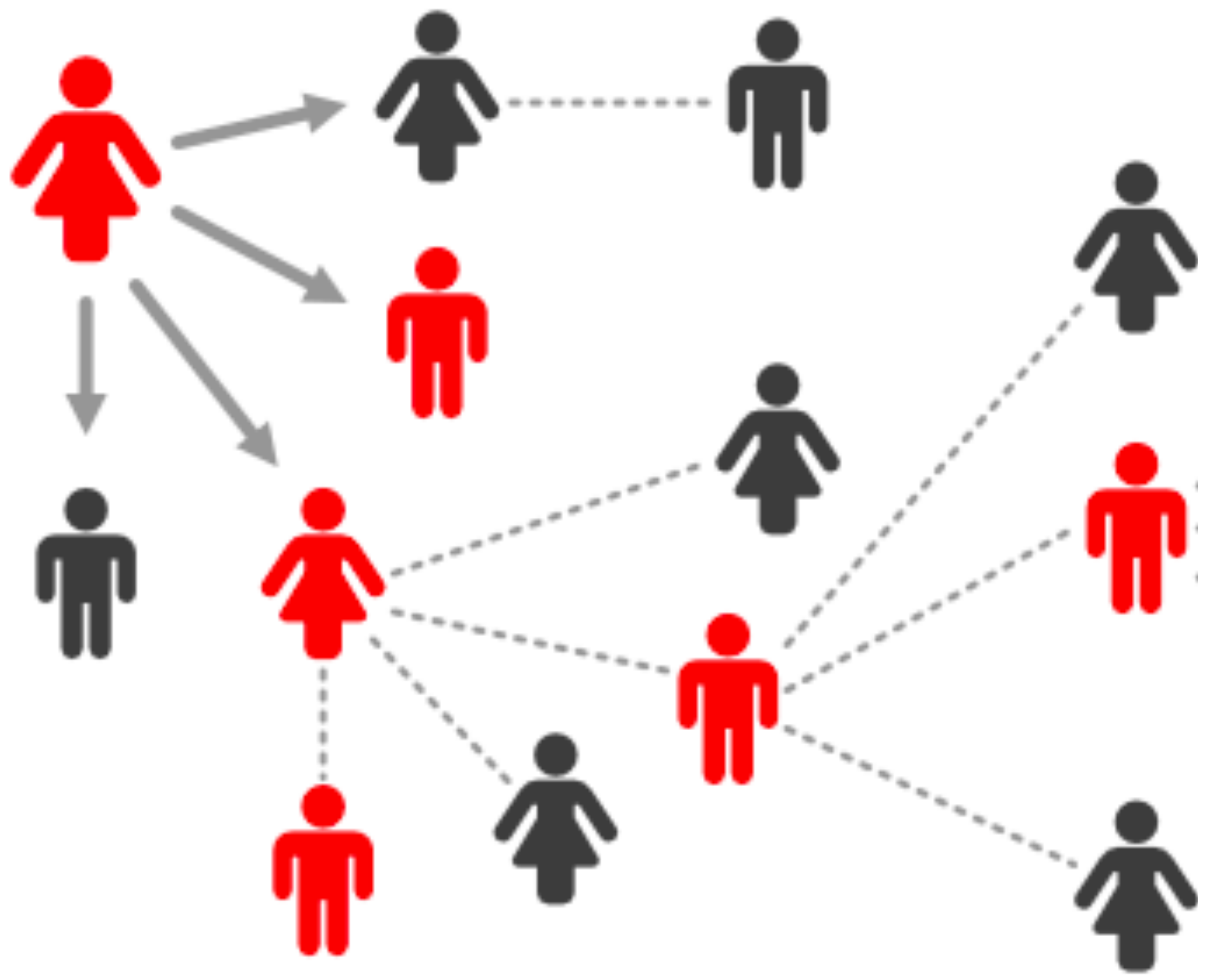
Contact tracing



Contact tracing

Epidemic spread:



Contact tracing

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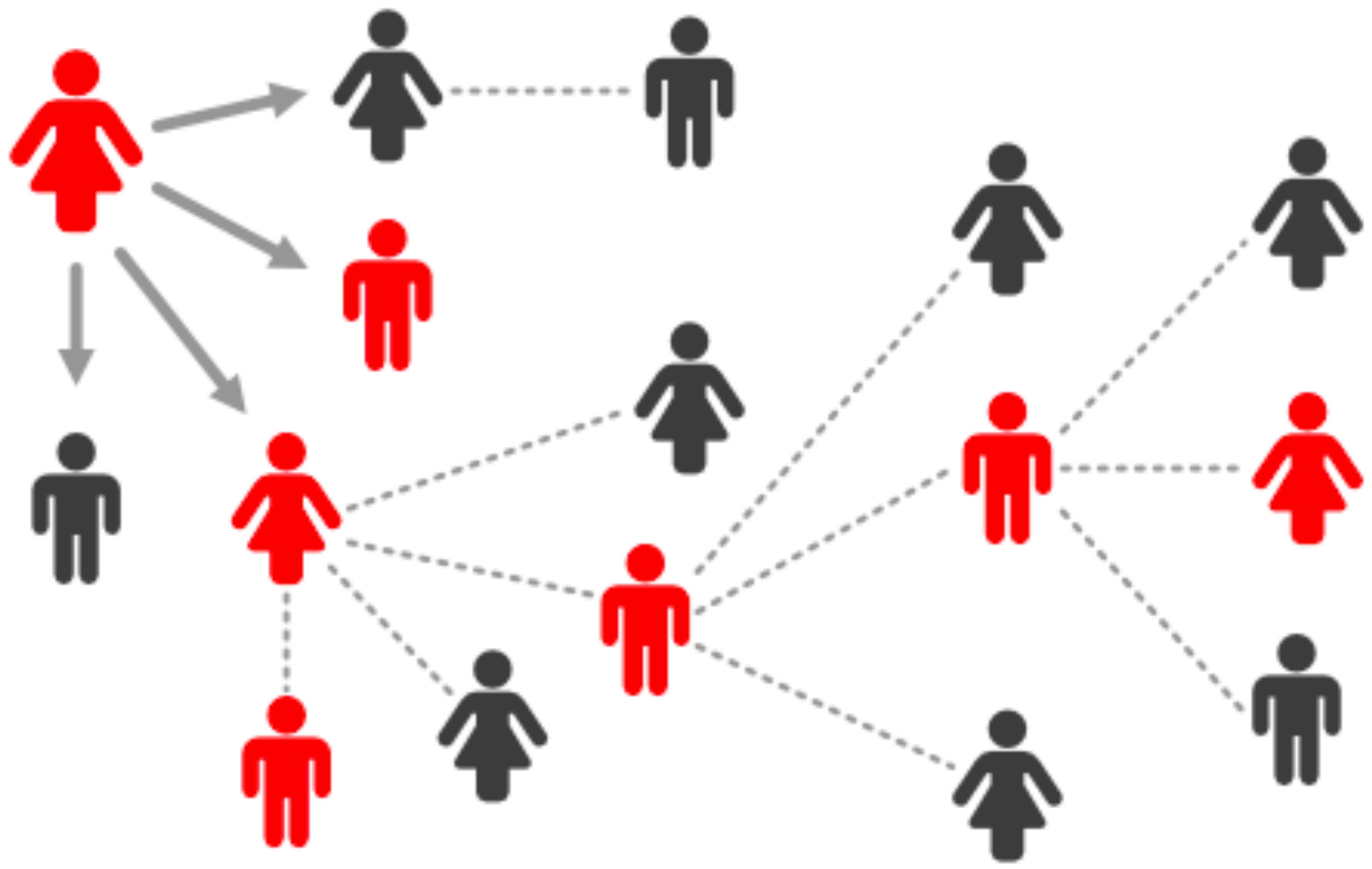

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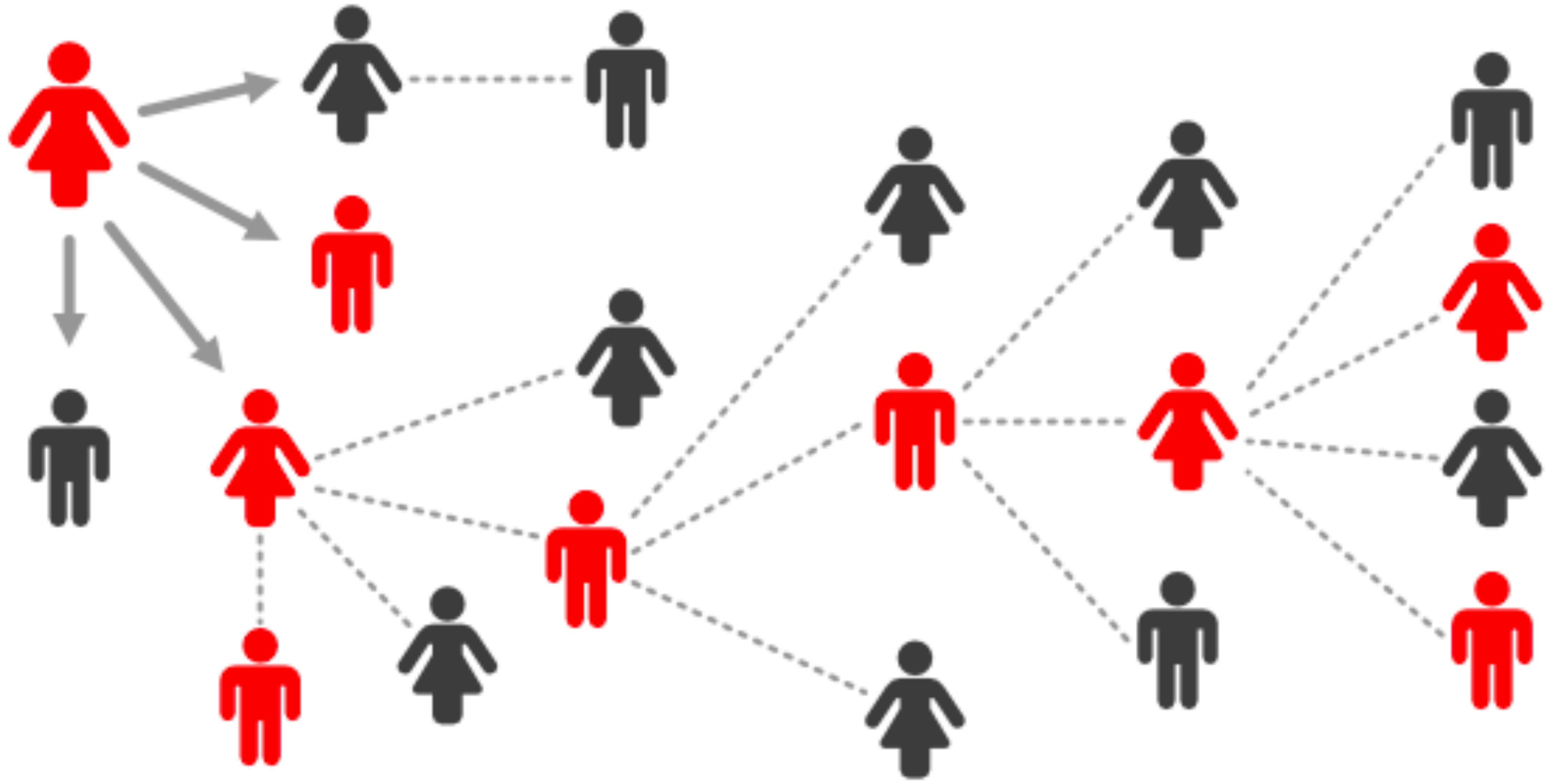

Contact tracing

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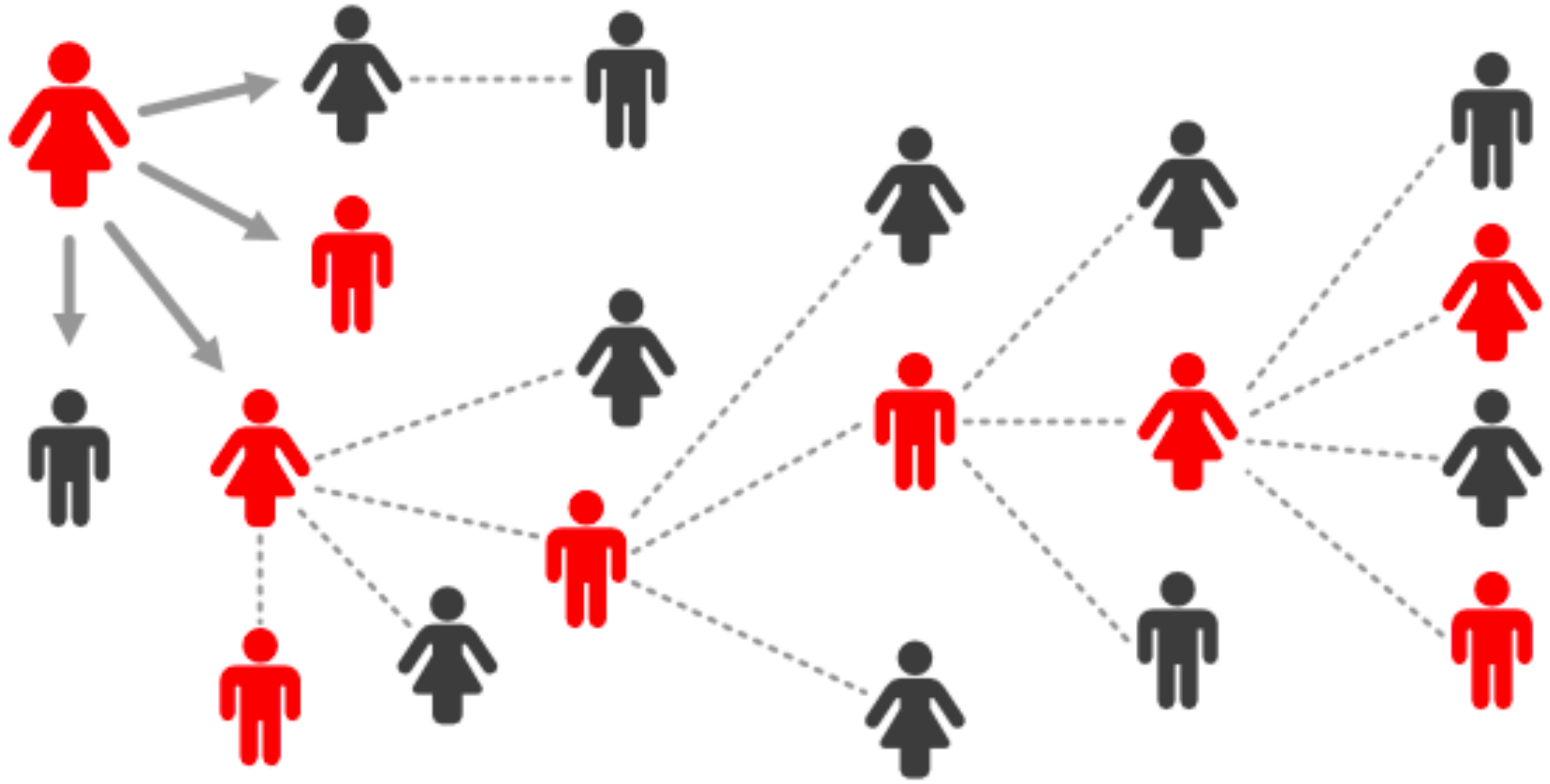

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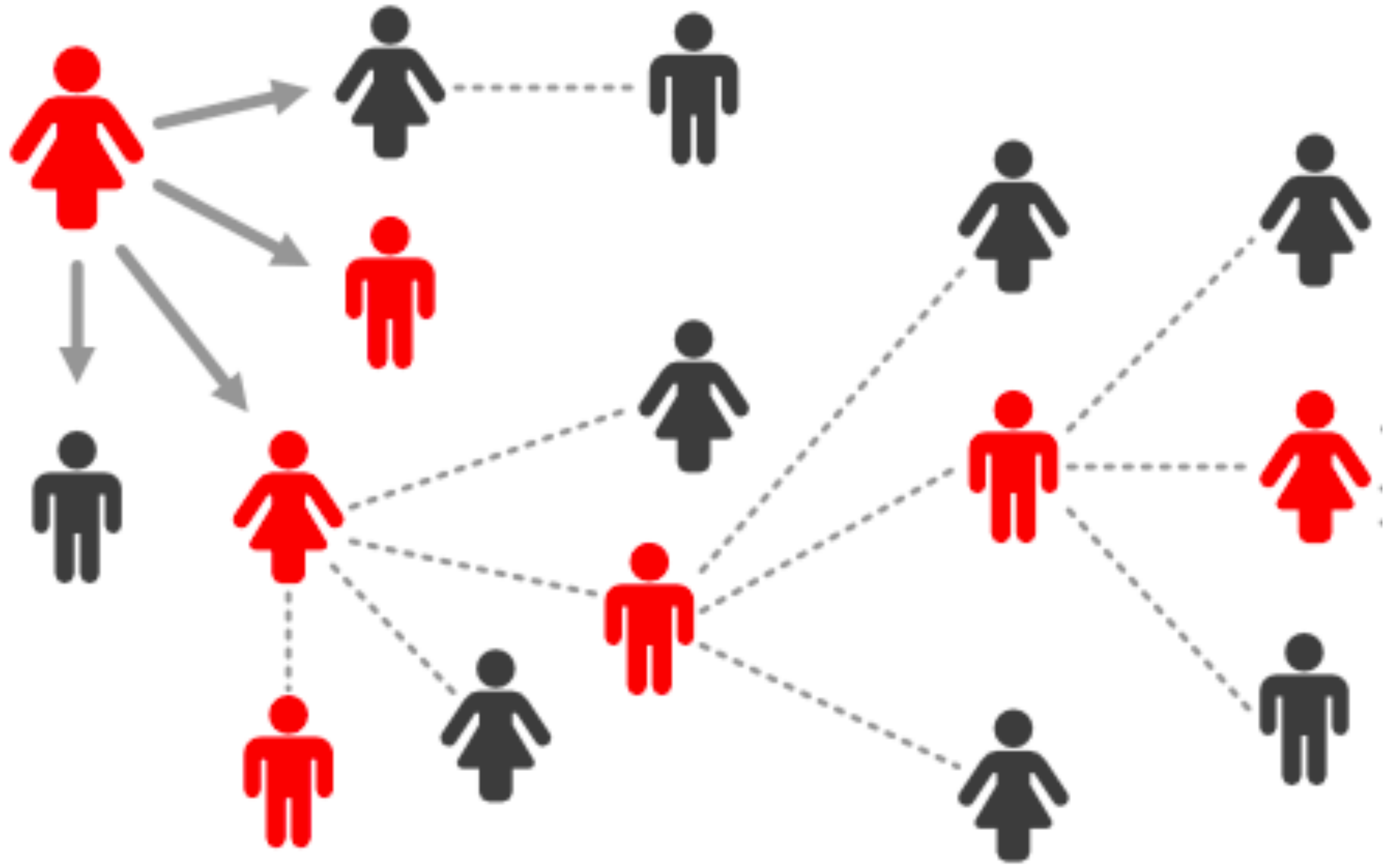

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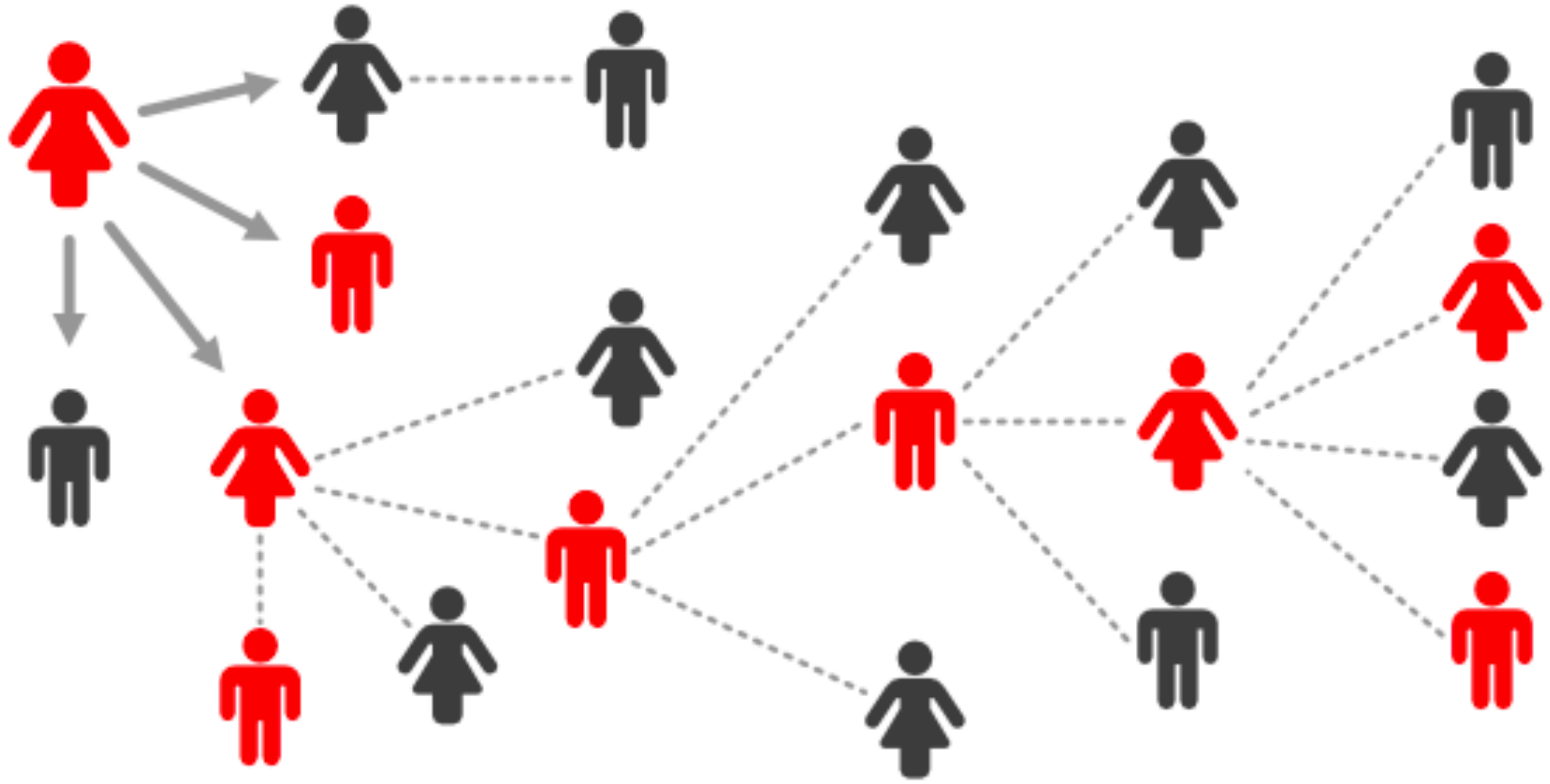

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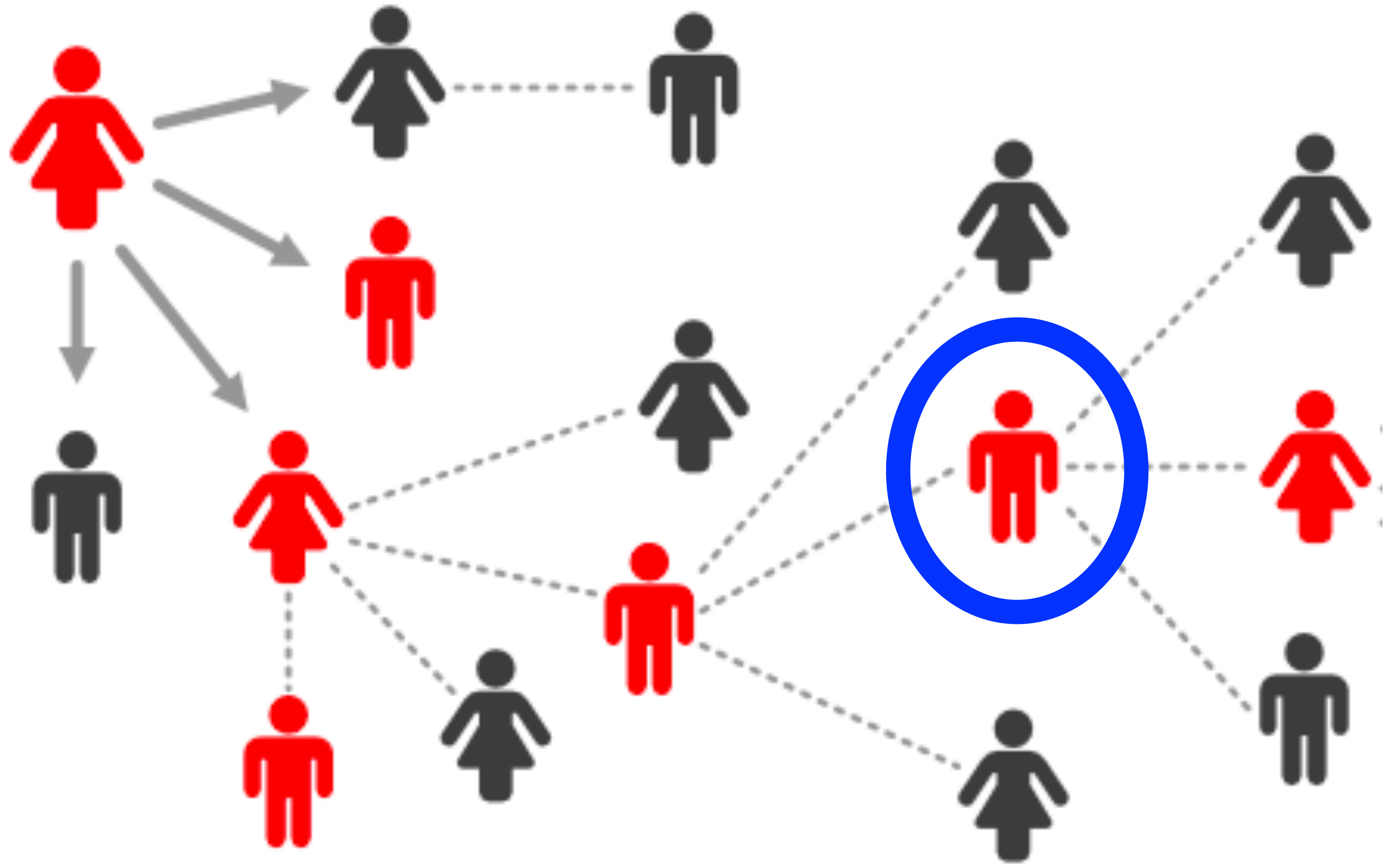

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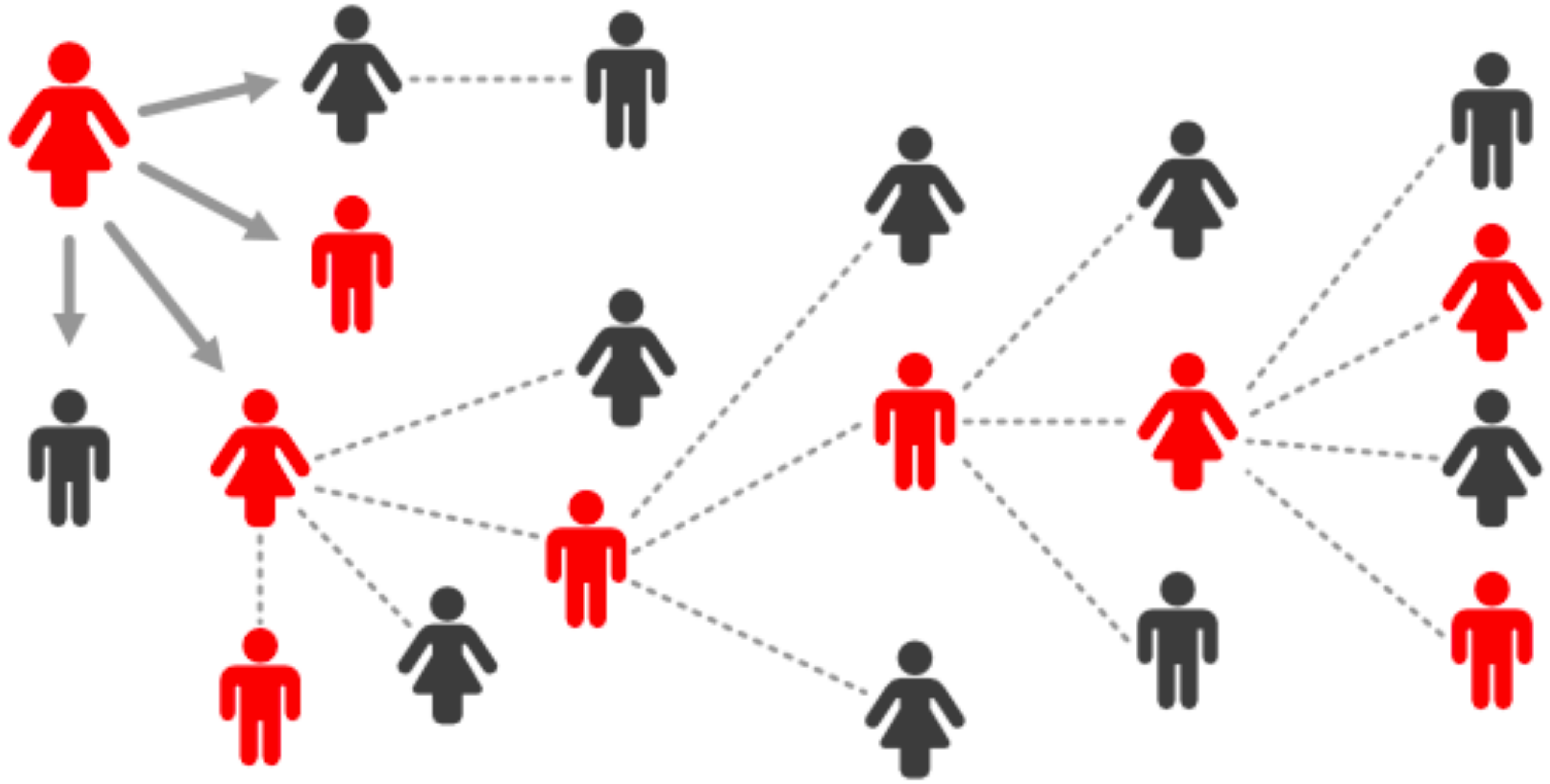

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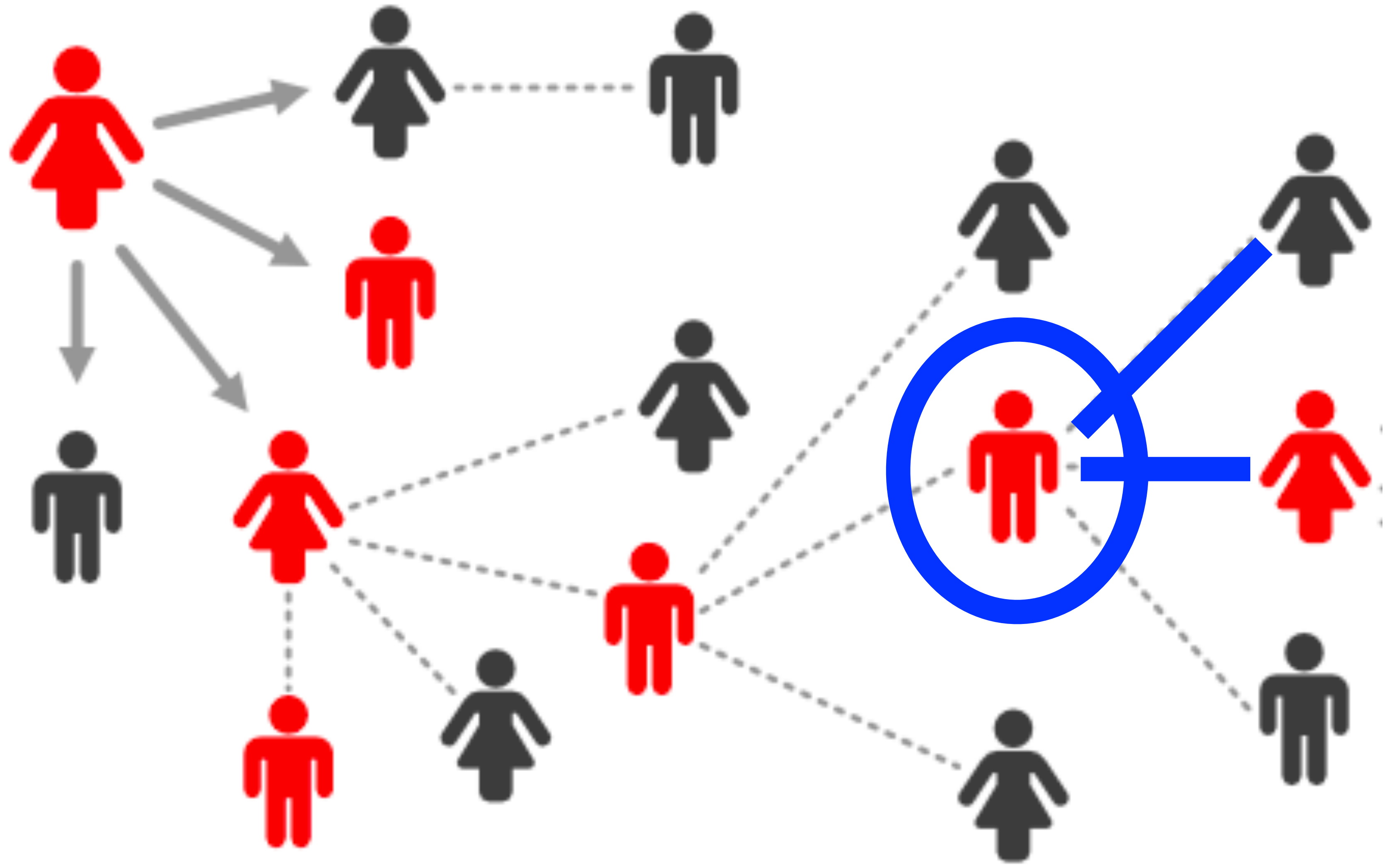

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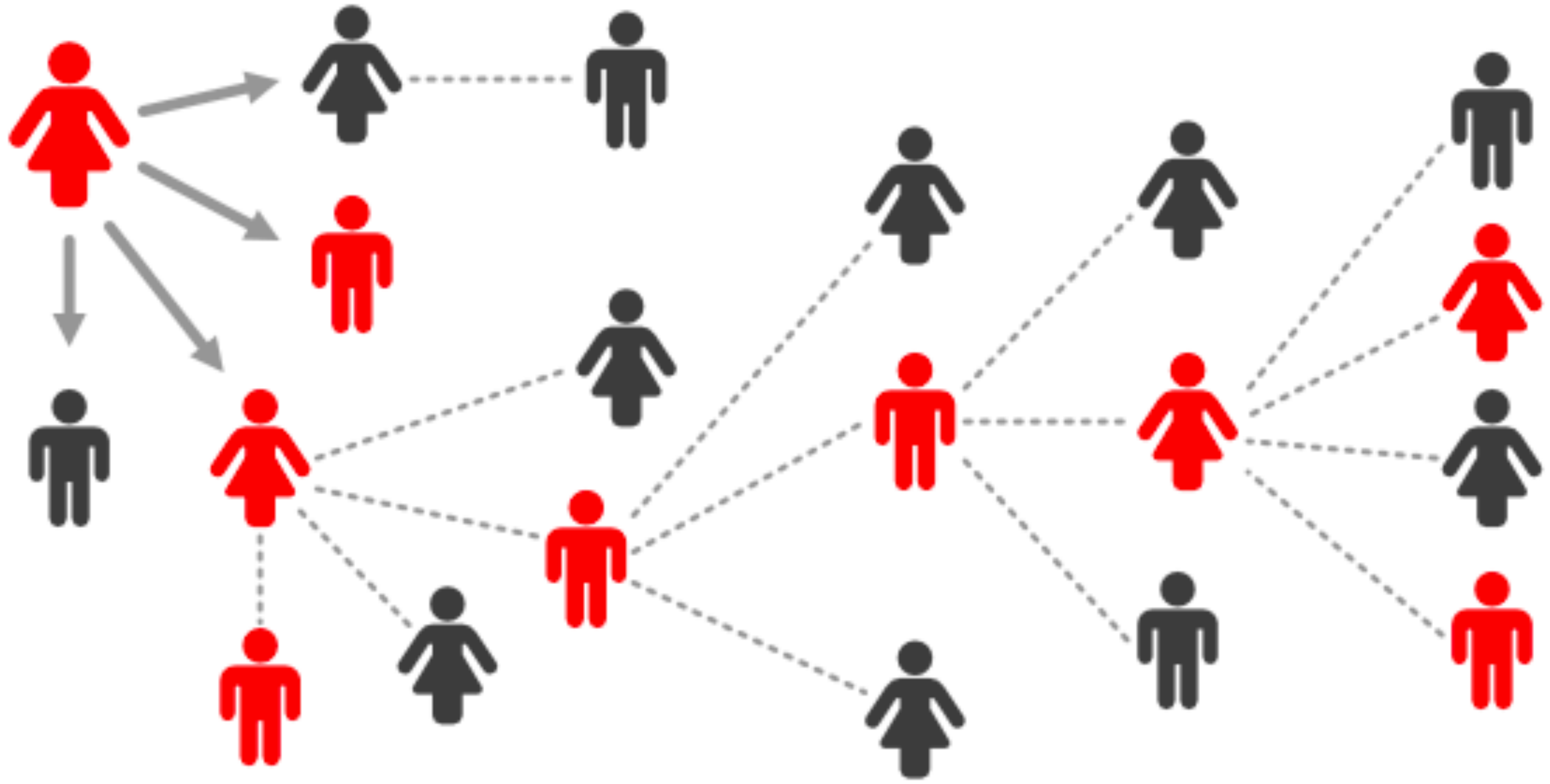

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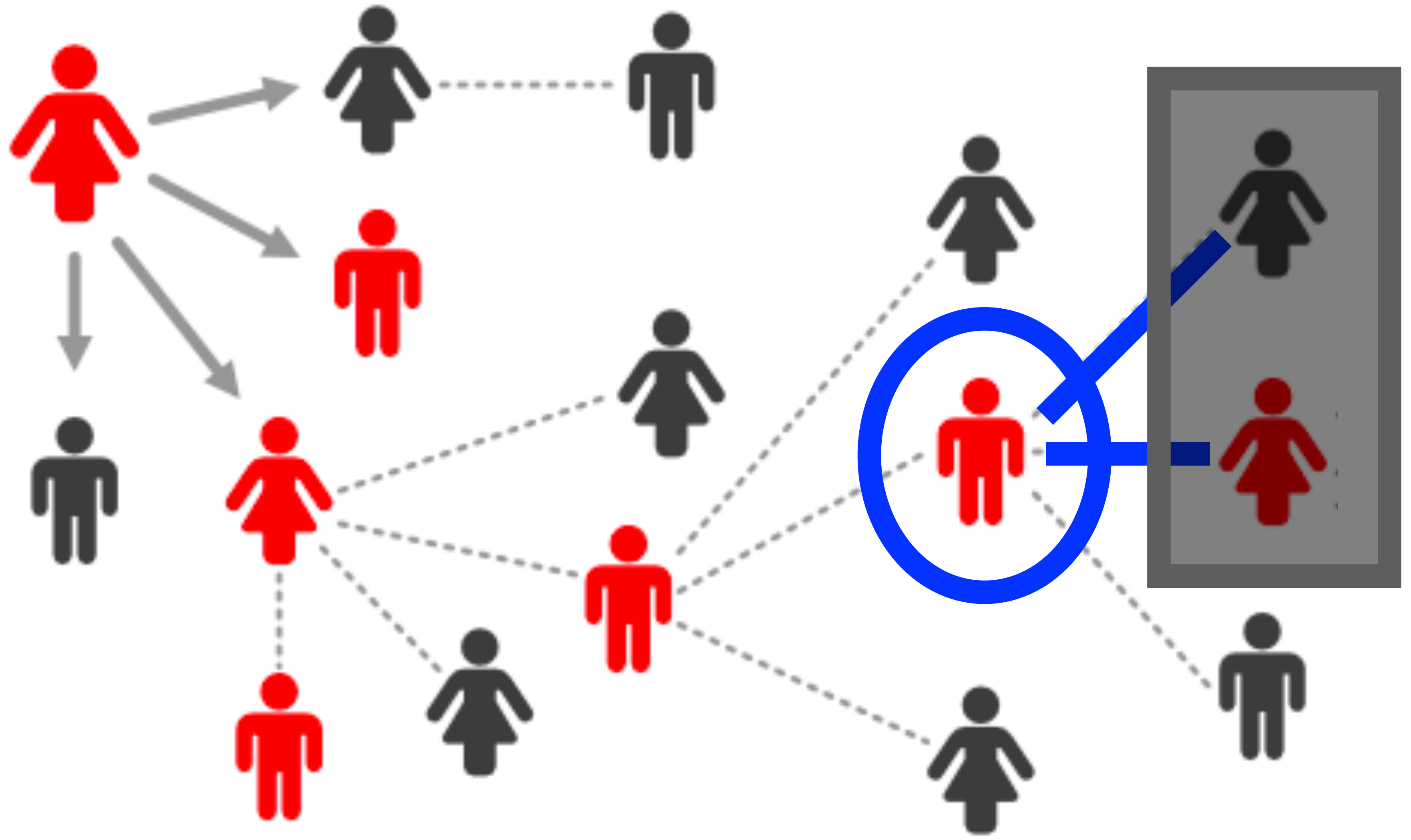
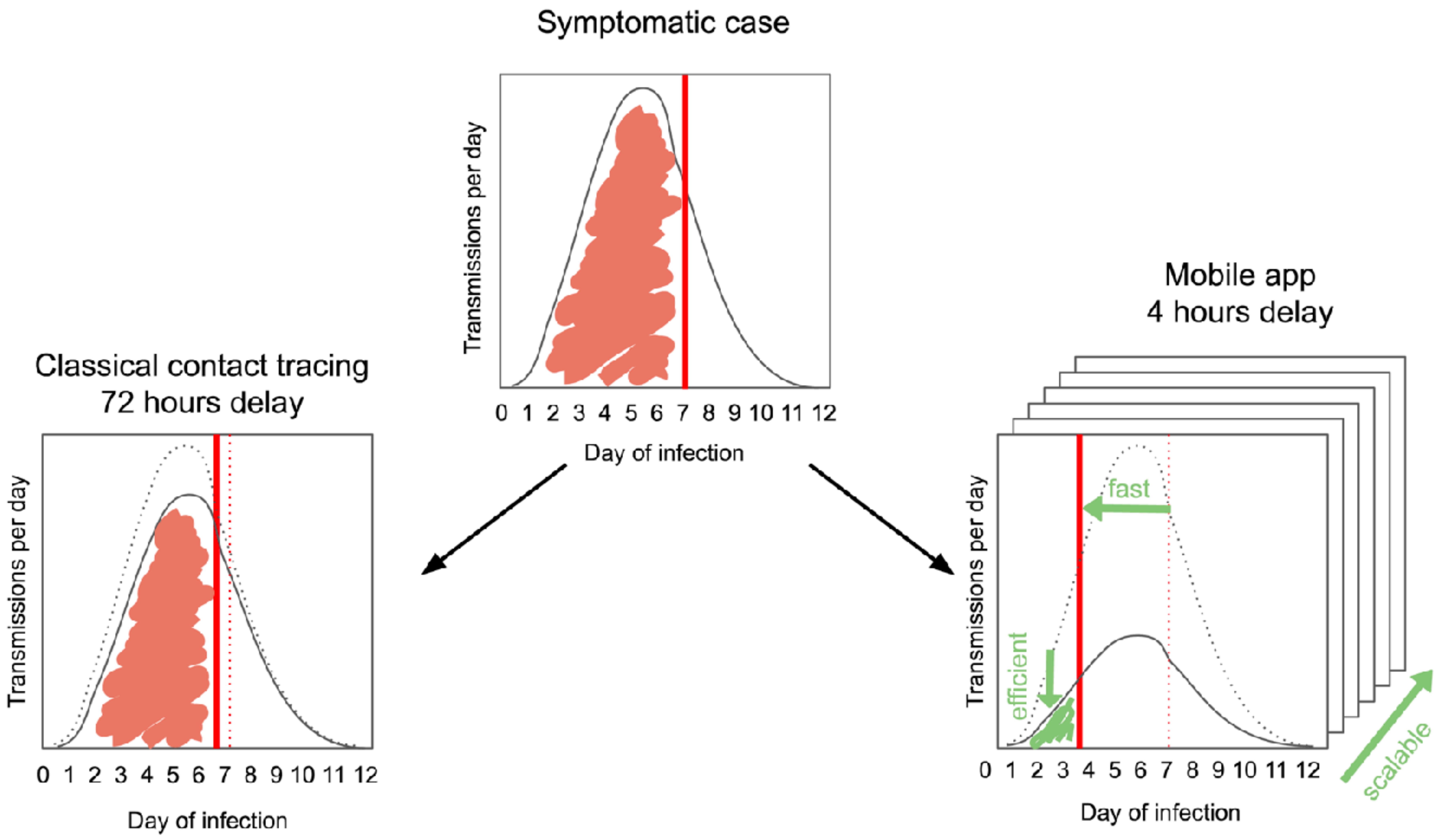


Why rapid contact tracing matters?



Post-tracing measures on contacts are what matters

- Isolate
- Isolate upon symptoms
- Distancing, facemask usage etc
- Test once
- Test repeatedly (e.g. daily contact testing with rapid tests)

- Treat/vaccinate (e.g. ring vaccination)…

Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts

Joel Hellewell, PhD • Sam Abbott, PhD * • Amy Gimma, MSc * • Nikos I Bosse, BSc • Christopher I Jarvis, PhD •
Timothy W Russell, PhD • et al. Show all authors • Show footnotes

Open Access • Published: February 28, 2020 • DOI: https://doi.org/10.1016/S2214-109X(20)30074-7 •

Background

Isolation of cases and contact tracing is used to control outbreaks of infectious diseases, and has been used for coronavirus disease 2019 (COVID-19). Whether this strategy will achieve control depends on characteristics of both the pathogen and the response. Here we use a mathematical model to assess if isolation and contact tracing are able to control onwards transmission from imported cases of COVID-19.

Methods

We developed a stochastic transmission model, parameterised to the COVID-19 outbreak. We used the model to quantify the potential effectiveness of contact tracing and isolation of cases at controlling a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-like pathogen. We considered scenarios that varied in the number of initial cases, the basic reproduction number (R_0), the delay from symptom onset to isolation, the probability that contacts were traced, the proportion of transmission that occurred before symptom onset, and the proportion of subclinical infections. We assumed isolation prevented all further transmission in the model. Outbreaks were deemed controlled if transmission ended within 12 weeks or before 5000 cases in total. We measured the success of controlling outbreaks using isolation and contact tracing, and quantified the weekly maximum number of cases traced to measure feasibility of public health effort.

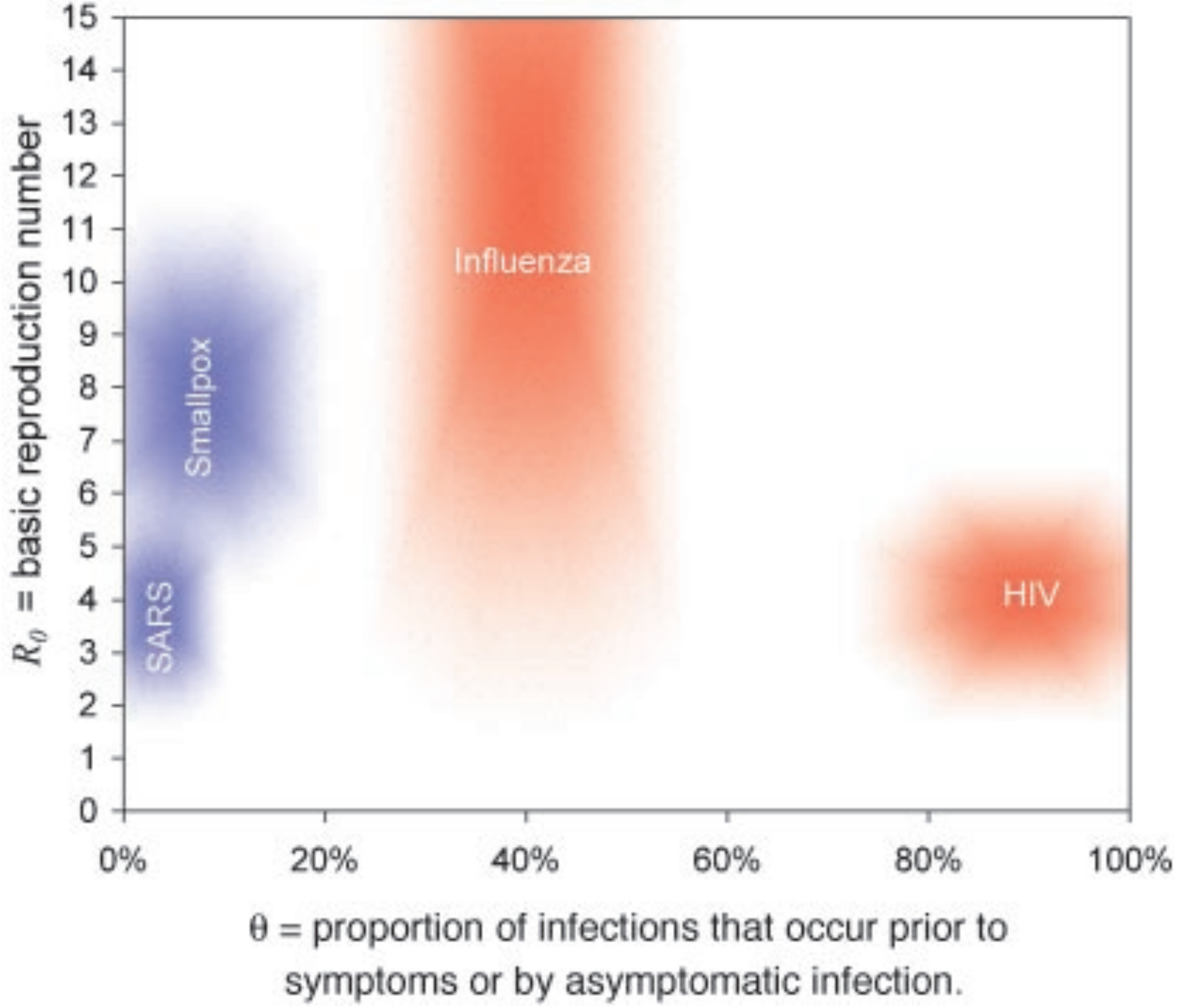
Findings

Simulated outbreaks starting with five initial cases, an R_0 of 1·5, and 0% transmission before symptom onset could be controlled even with low contact tracing probability; however, the probability of controlling an outbreak decreased with the number of initial cases, when R_0 was 2·5 or 3·5 and with more transmission before symptom onset. Across different initial numbers of cases, the majority of scenarios with an R_0 of 1·5 were controllable with less than 50% of contacts successfully traced. To control the majority of outbreaks, for R_0 of 2·5 more than 70% of contacts had to be traced, and for an R_0 of 3·5 more than 90% of contacts had to be traced. The delay between symptom onset and isolation had the largest role in determining whether an outbreak was controllable when R_0 was 1·5. For R_0 values of 2·5 or 3·5, if there were 40 initial cases, contact tracing and isolation were only potentially feasible when less than 1% of transmission occurred before symptom onset.

Factors that make an infectious disease outbreak controllable

Christophe Fraser*†, Steven Riley*, Roy M. Anderson, and Neil M. Ferguson

PNAS 2004



Generalised Euler-Lotka equation for contact tracing

Kermack-McKendrick equations for chains of infections with contact tracing:

(Fraser el al PNAS 2004)

Time-shift invariance:

$$\frac{\partial Y(t,\tau,\tau')}{\partial t} + \frac{\partial Y(t,\tau,\tau')}{\partial \tau} + \frac{\partial Y(t,\tau,\tau')}{\partial \tau'} = 0$$

Renewal equation or
next generation equation:

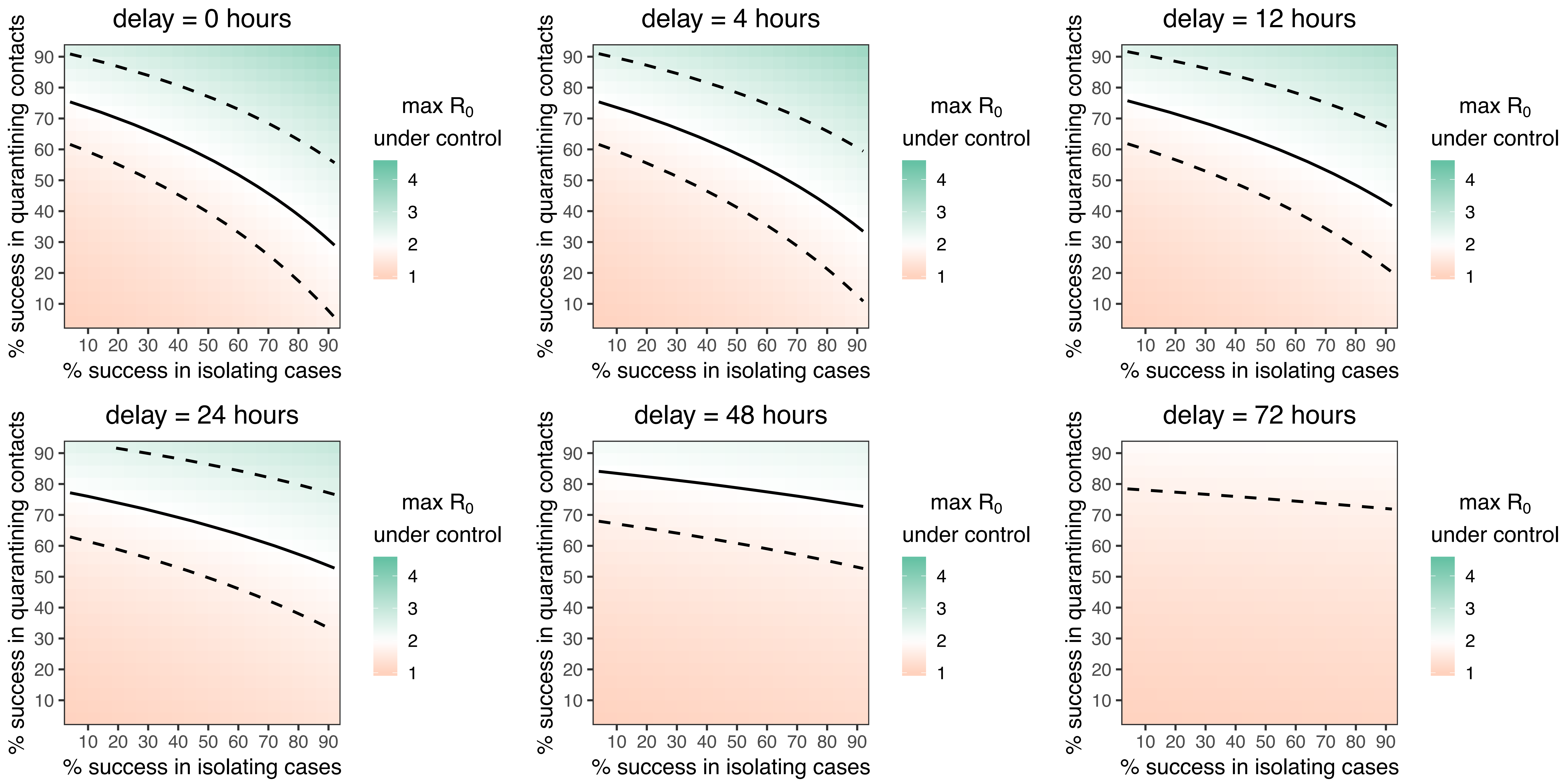
$$Y(t,0,\tau) = \beta(\tau)\left(1 - \epsilon_I s(\tau)\right) \int_\tau^\infty \left(1 - \epsilon_T + \epsilon_T \frac{1 - s(\tau')}{1 - s(\tau' - \tau)}\right) Y(t,\tau,\tau') d\tau'$$

efficiency of isolation *efficiency of contact tracing & quarantine*

The generalised (functional) Euler-Lotka equation
corresponds to the eigenvalue equation (with eigenvalue 1)
for this operator:

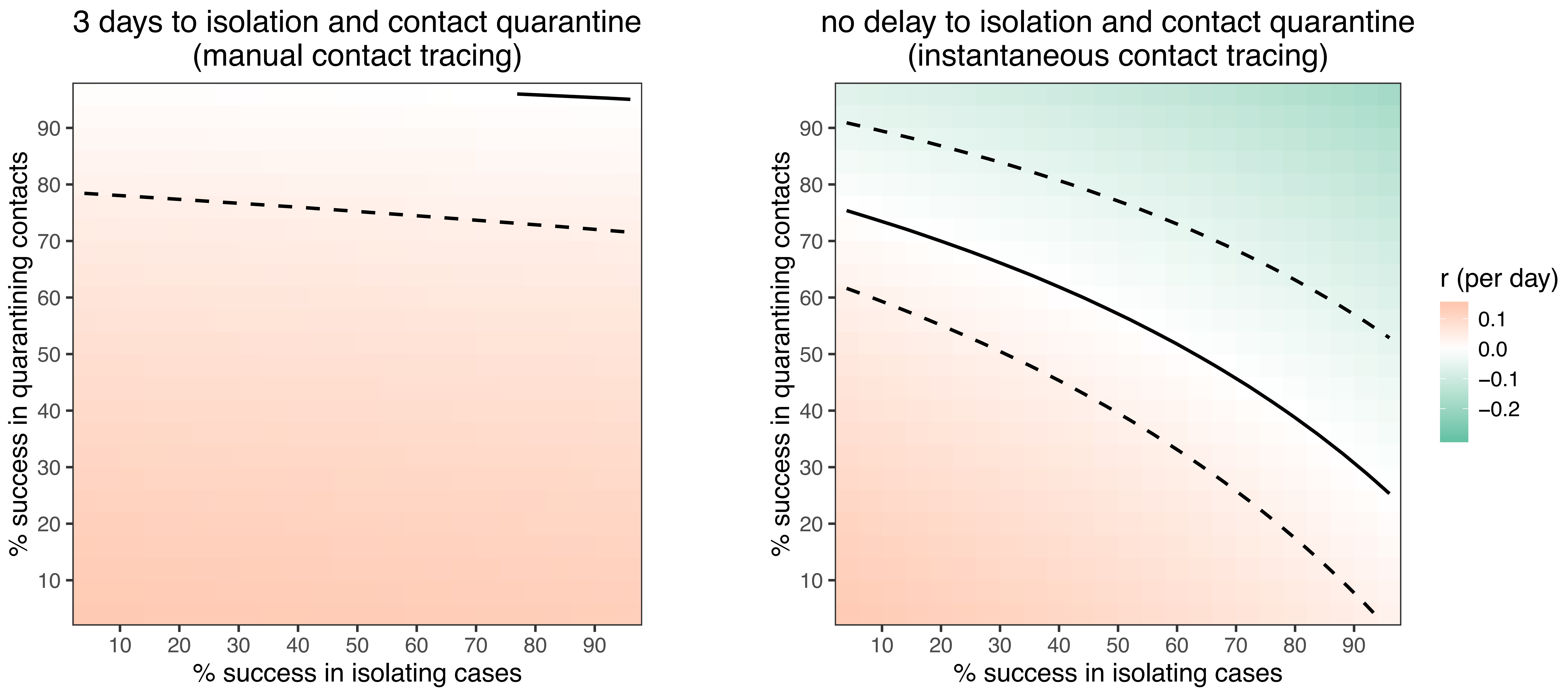
$$\mathcal{N}_r y = e^{-r\tau}\beta(\tau)\left(1 - \epsilon_I s(\tau)\right) \int_0^\infty \left(1 - \epsilon_T \frac{s(\rho+\tau) - s(\rho)}{1 - s(\rho)}\right) y(\rho) d\rho$$

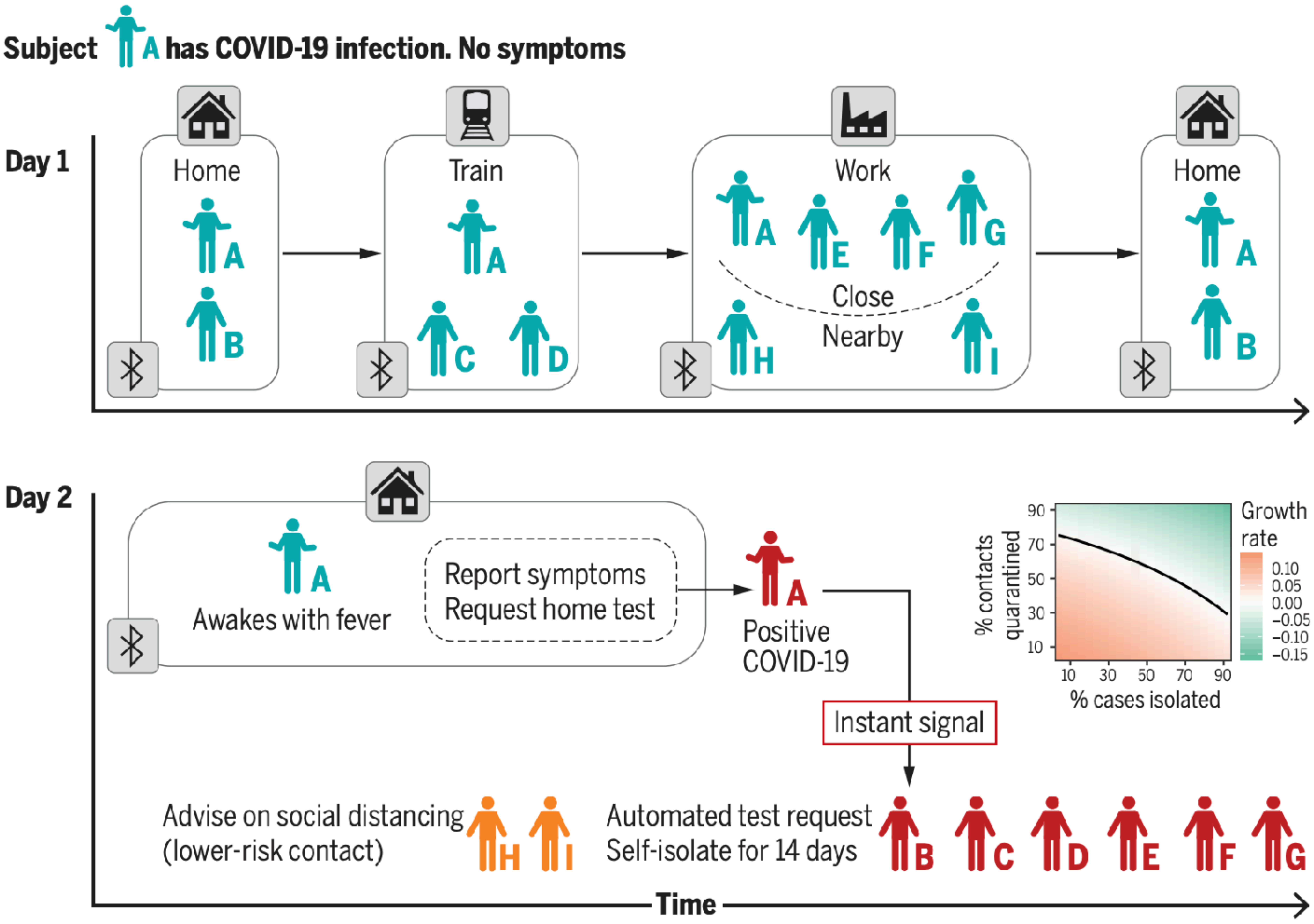
Is the COVID-19 epidemic controllable via realistic contact tracing?



Is the COVID-19 epidemic controllable via realistic contact tracing?

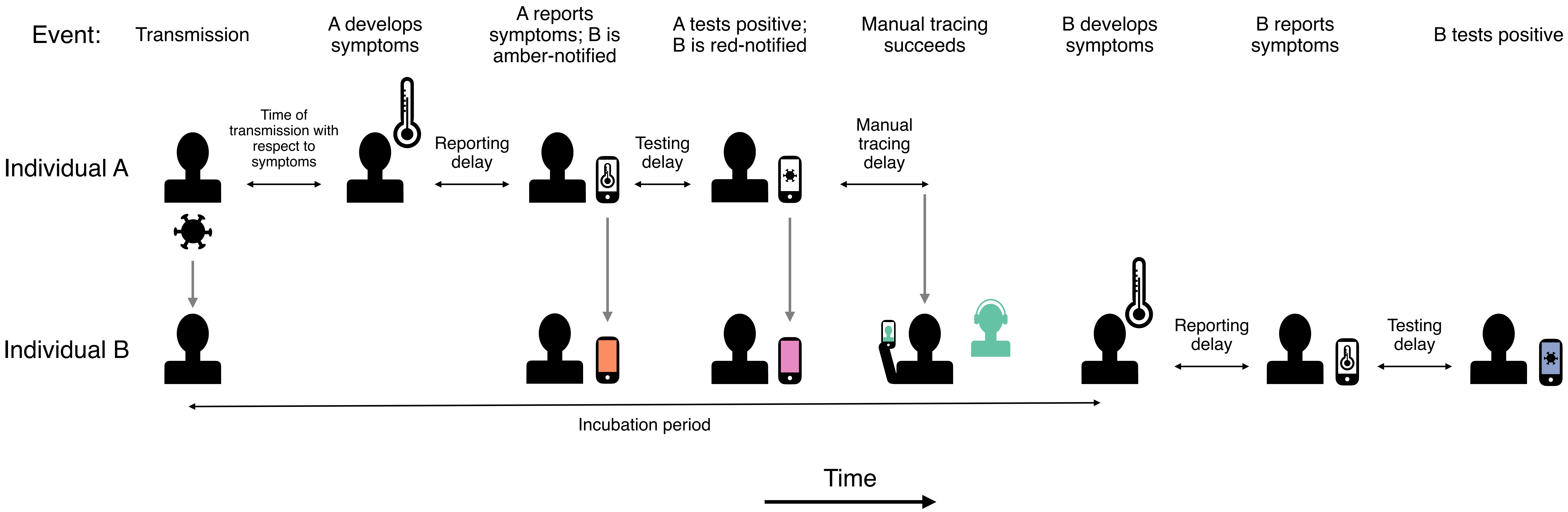
Isolation and contact tracing can stop the epidemic only with high efficiency and short response times





Ferretti & Wymant et al, Science 2020

Realistic picture of delays in manual+digital contact tracing



Agent/individual-based models (ABMs or IBMs)

Step towards more realistic numerical results

- Simulations of interacting individuals
- In case of infectious diseases, both individuals and interactions can be modelled in a relatively simple way
- Very flexible in terms of complexity of the individuals and their behaviour, the details of the interactions, delays, geography etc
- Many parameters, may be computationally intensive
- Require calibration

Purposes of ABMs

1. Optimisation of interventions
2. Building scenarios
3. Parameter inference
4. Epidemiological understanding
5. Short-term prediction
6. Post-hoc evaluation

"The success of app-based contact tracing depends on many factors"
- *vox populi*

"To say that a disease['s control via an app] depends upon certain factors is not to say much, until we can also form an estimate as to how largely each factor influences the whole result."
- *Ronald Ross [kind of]*

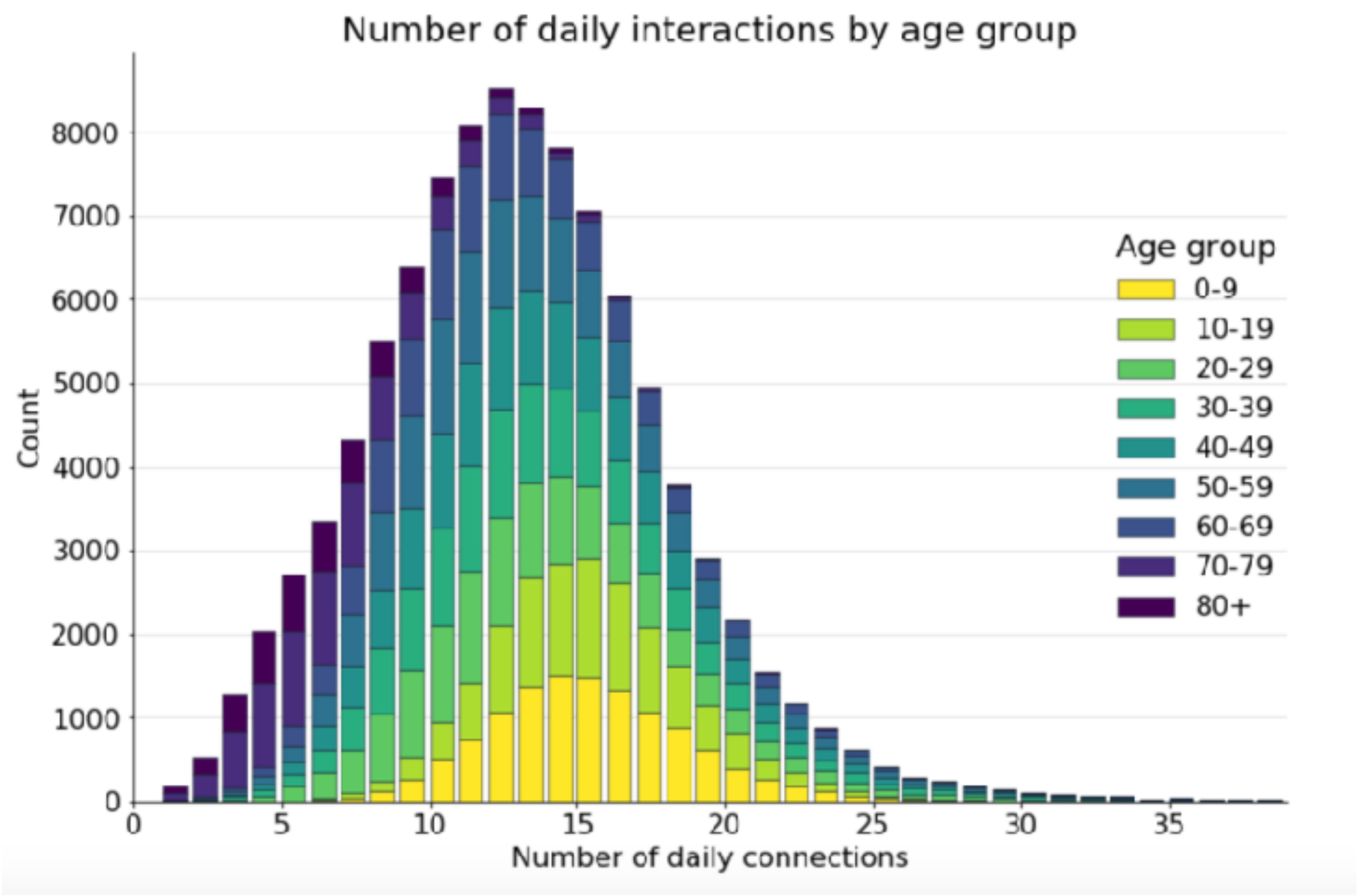
OpenABM-Covid19
Hinch, Probert et al
GitHub.com/BDI-pathogens

OpenABM-Covid19:
Agent-Based Model to evaluate interventions

- Motivation
  - large pre-symptomatic transmission + short generation time ⇒ very quick contract-tracing required
  - modelling for NHSx on app design, NHSE forecasting
  - open-source codebase
- Epidemiological model (ABM)
  - demographics
  - network structure
  - infection model
  - disease model
- Contact-tracing model
  - triggers, compliance, recursion, amber-red messages
  - effectiveness by uptake

Demographics

- Decadal age-bands
- Household reference panel from ONS (age and size distribution)
- Households generated by rejection sampling from reference
- Mean daily interactions: 7-15 based on age

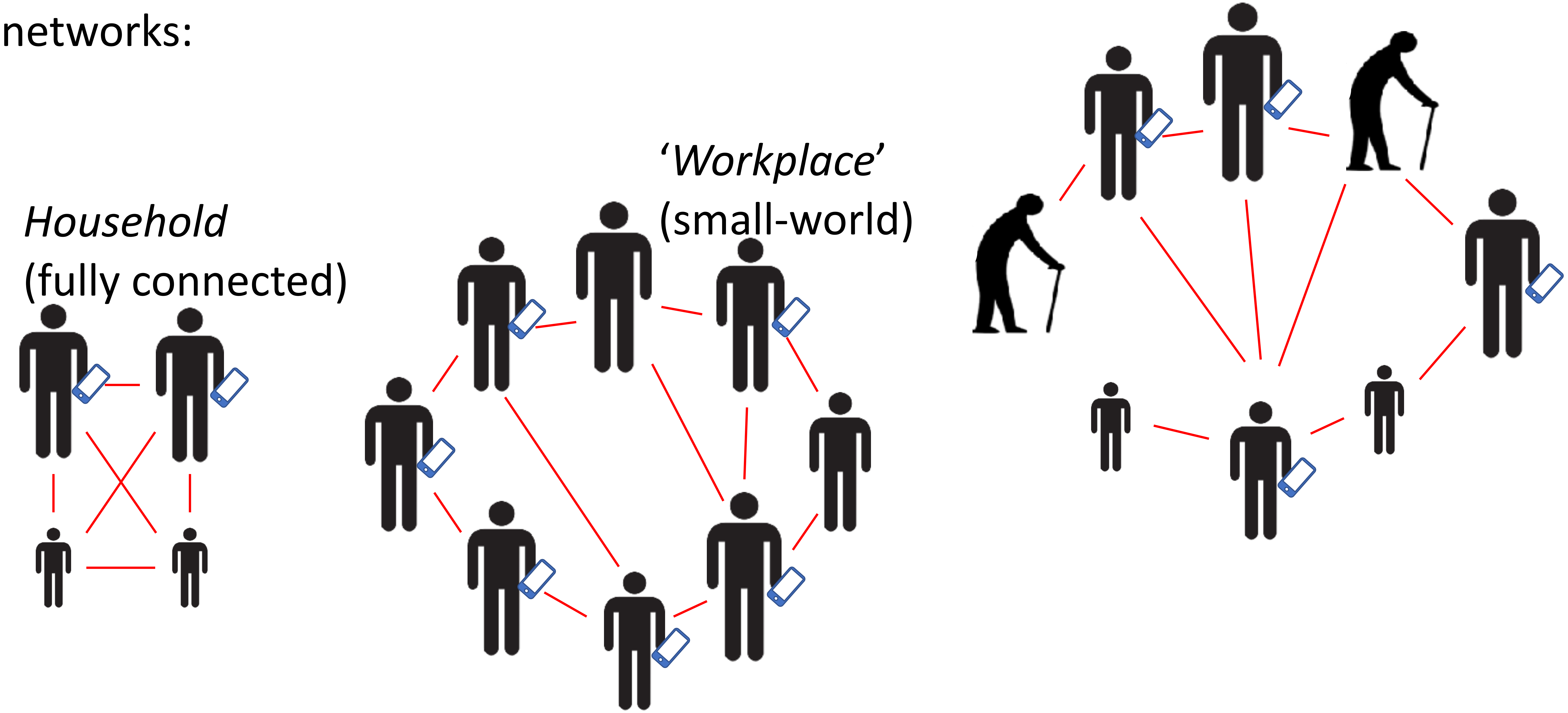


Demographics & networks

age $\in$ {0-9 years, 10-19, … 80+}

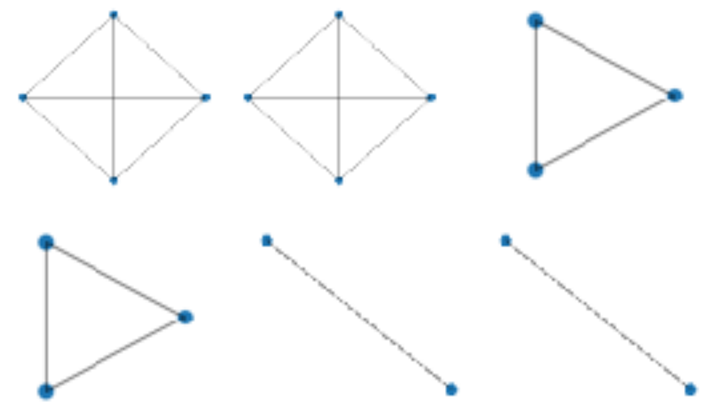
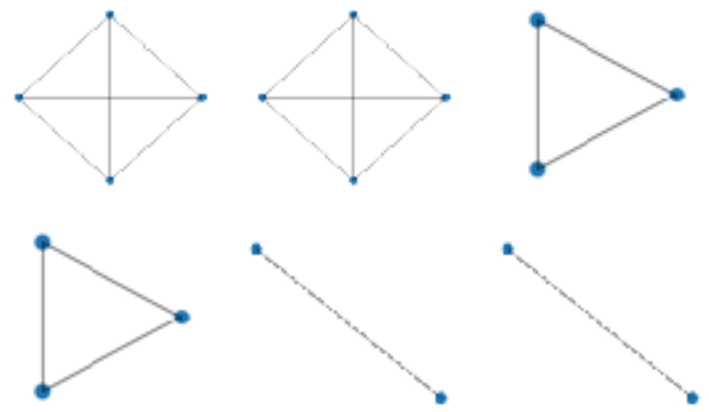
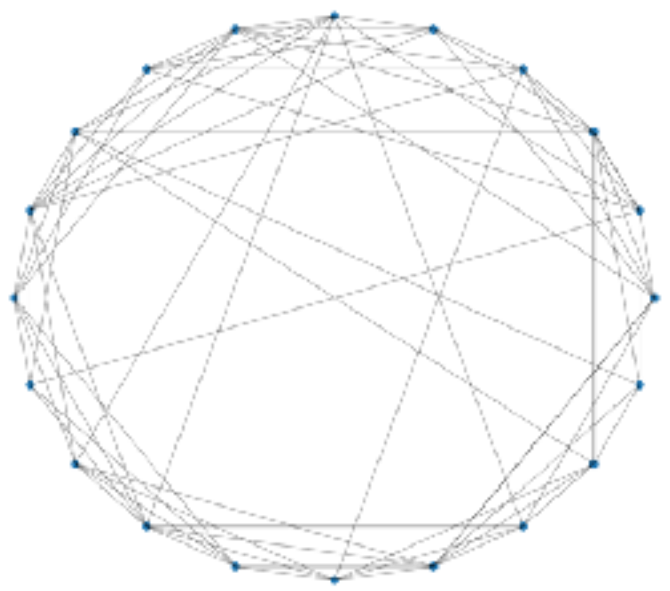
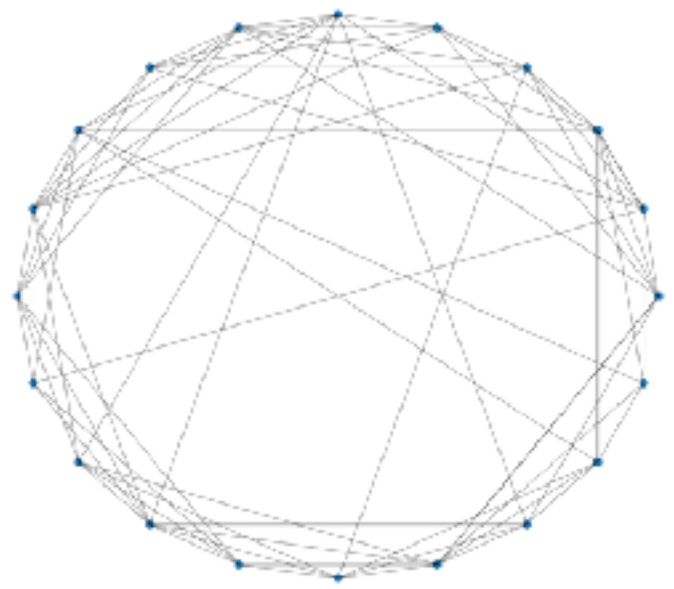
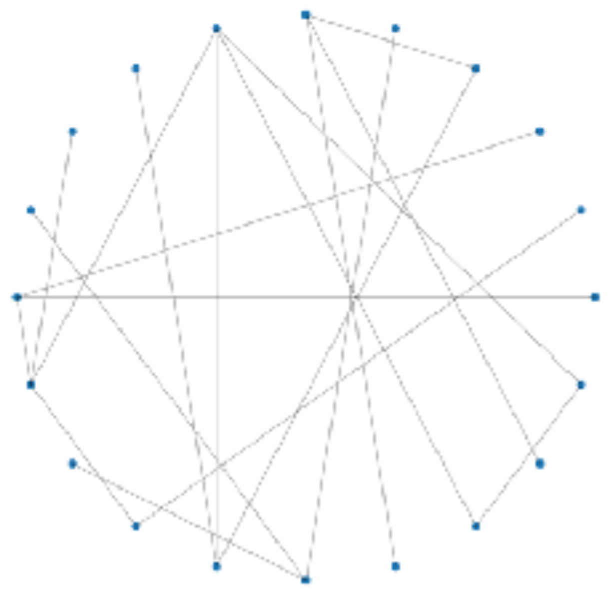
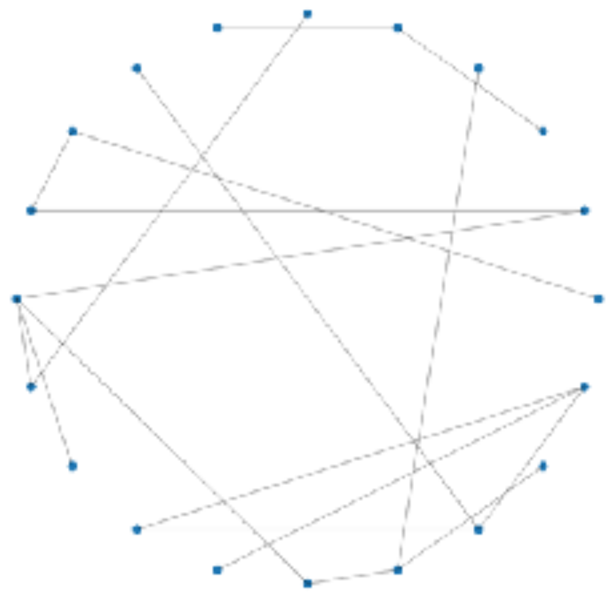
Age-specific smartphone ownership

Three daily, age-stratified, static or dynamic contact networks:



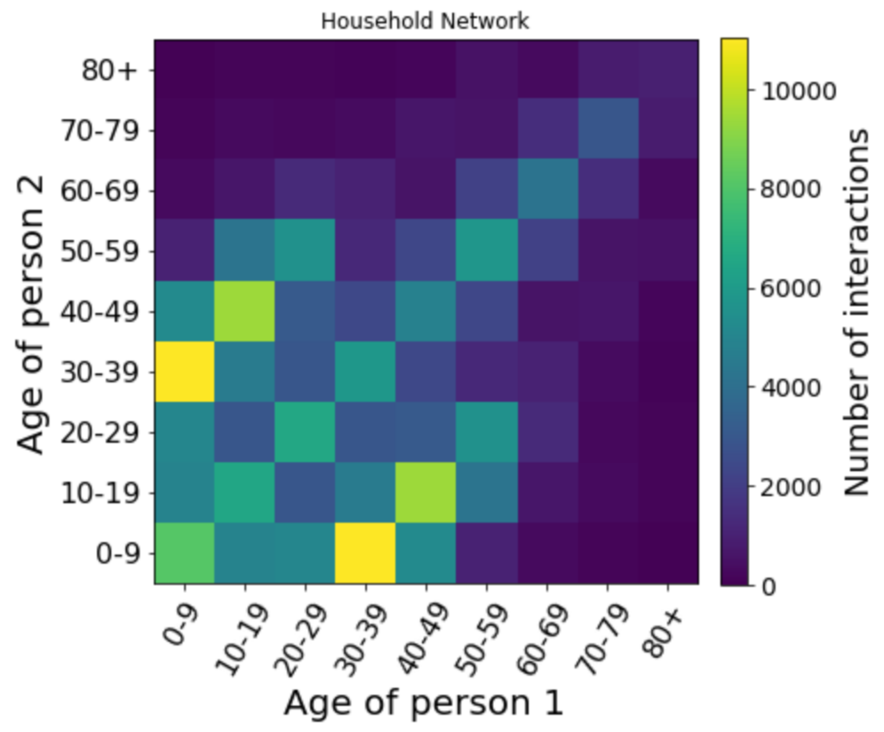
Households & ages: Office of National Statistics
Mixing: Mossong et al *PLoS Med* 2008
Silhouettes: clipart-library.com

Networks -Definitions

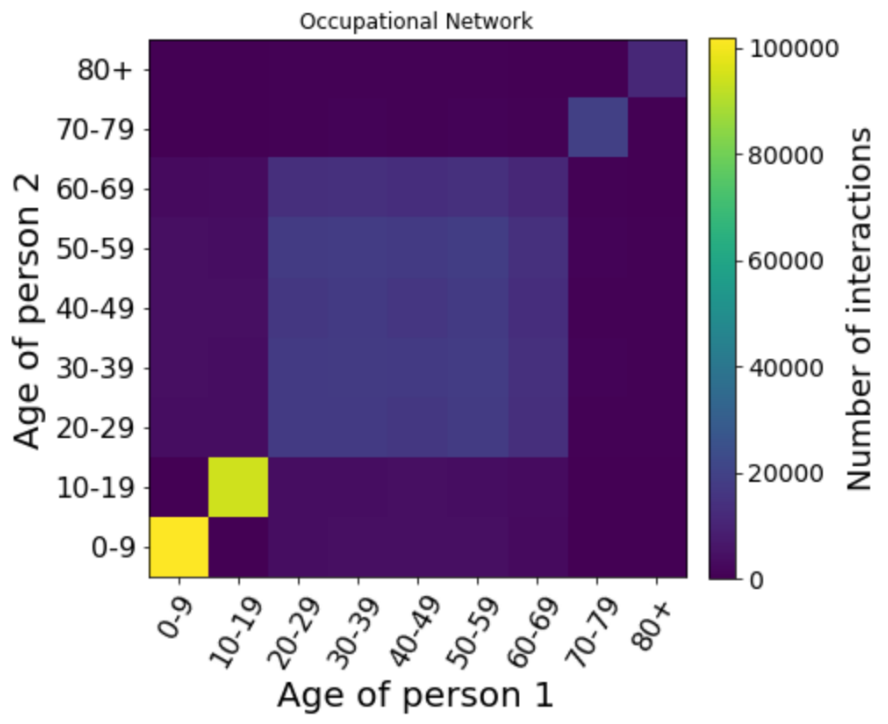
	Day1	Day2
• **Household** - recurrent		
• **Occupation**- small world recurrent (primary, secondary, work, retired, elderly)		
• **Random** - transient		

Networks - age structure

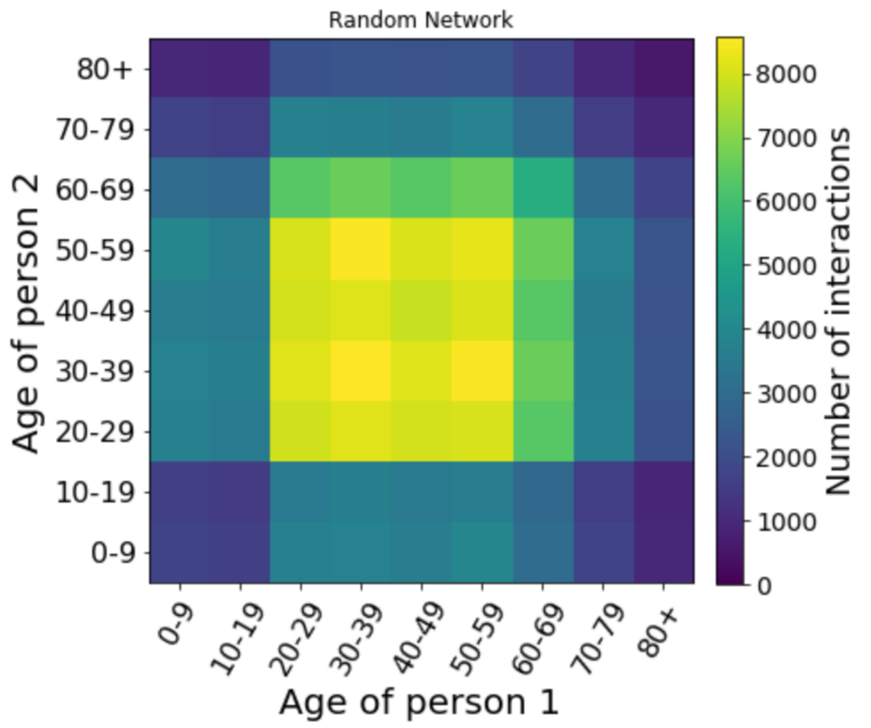
- **Household** - recurrent



- **Occupation** - recurrent, small-world

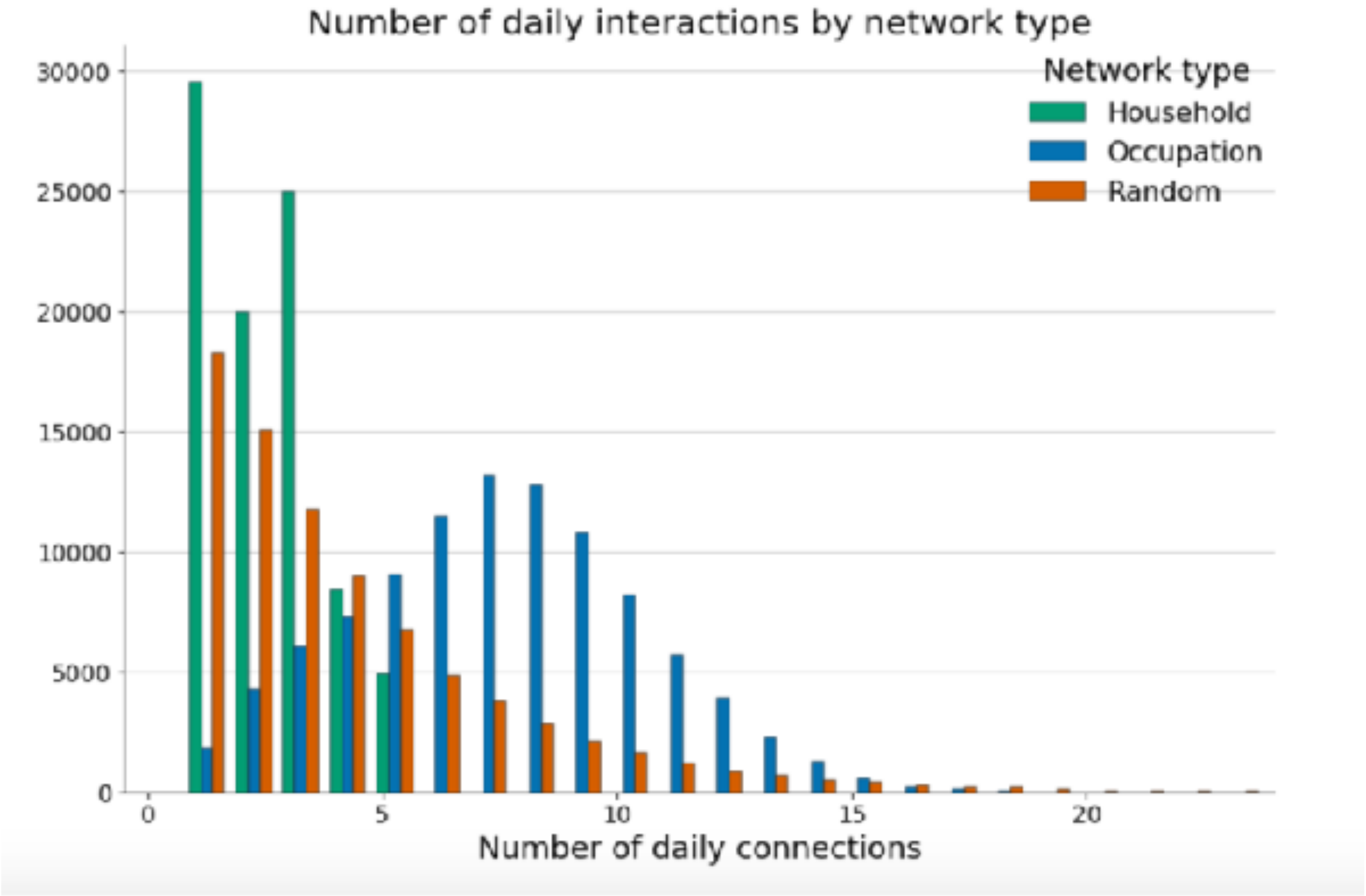


- **Random** - transient

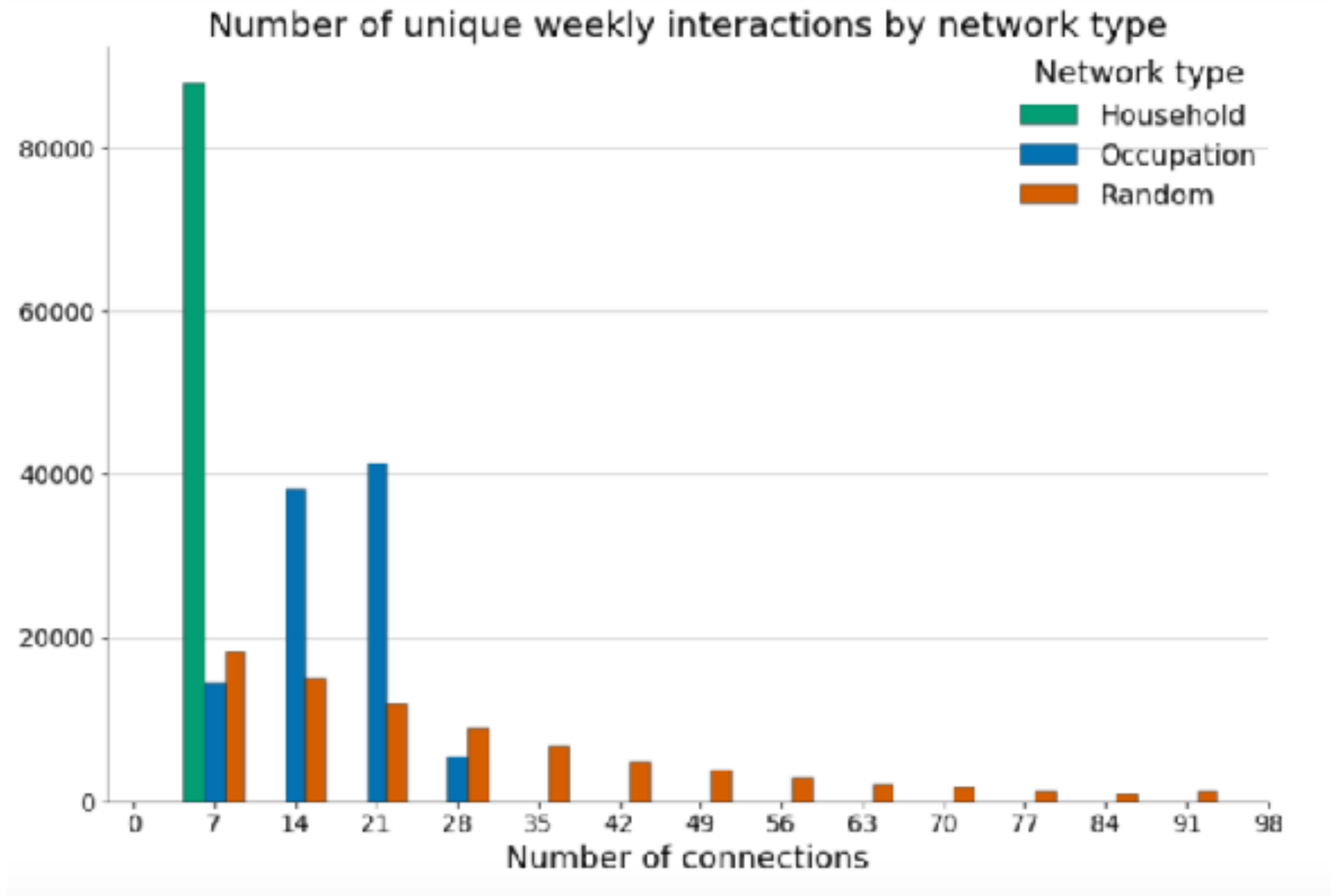


Networks - count

- **Daily** - occupational dominate

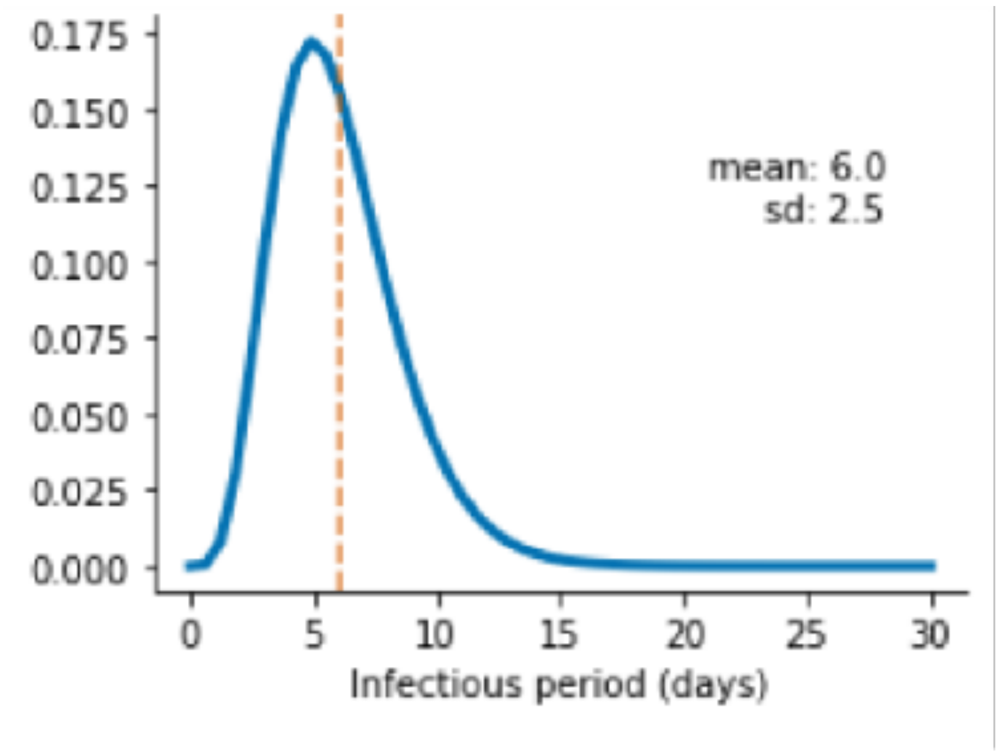


- **Weekly (unique)** - random dominate

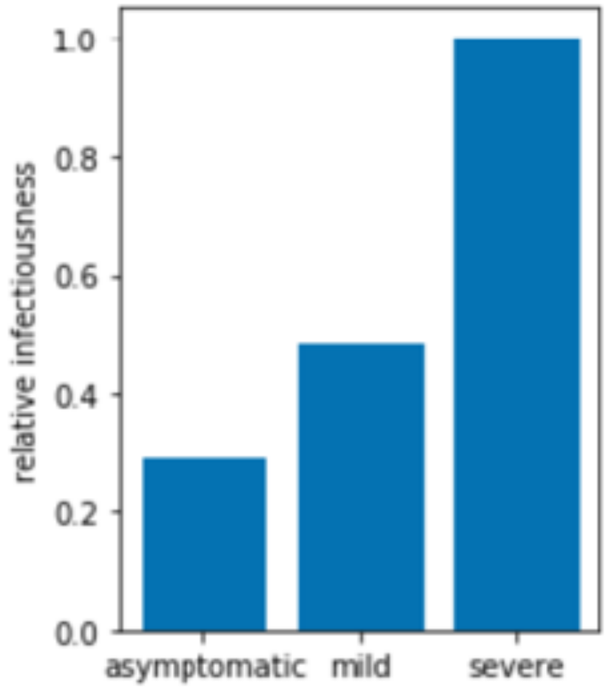


Infection Model

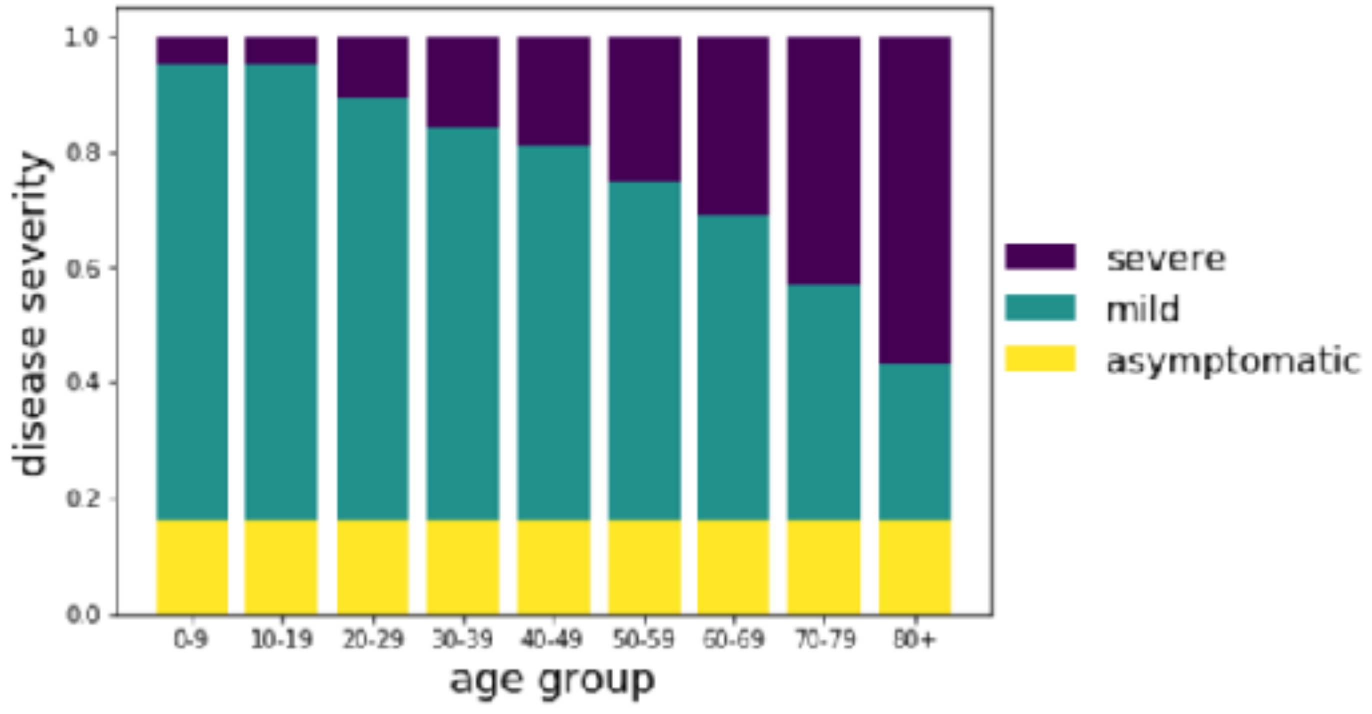
- Infectiousness peaks at 6 days post infection (gamma function)



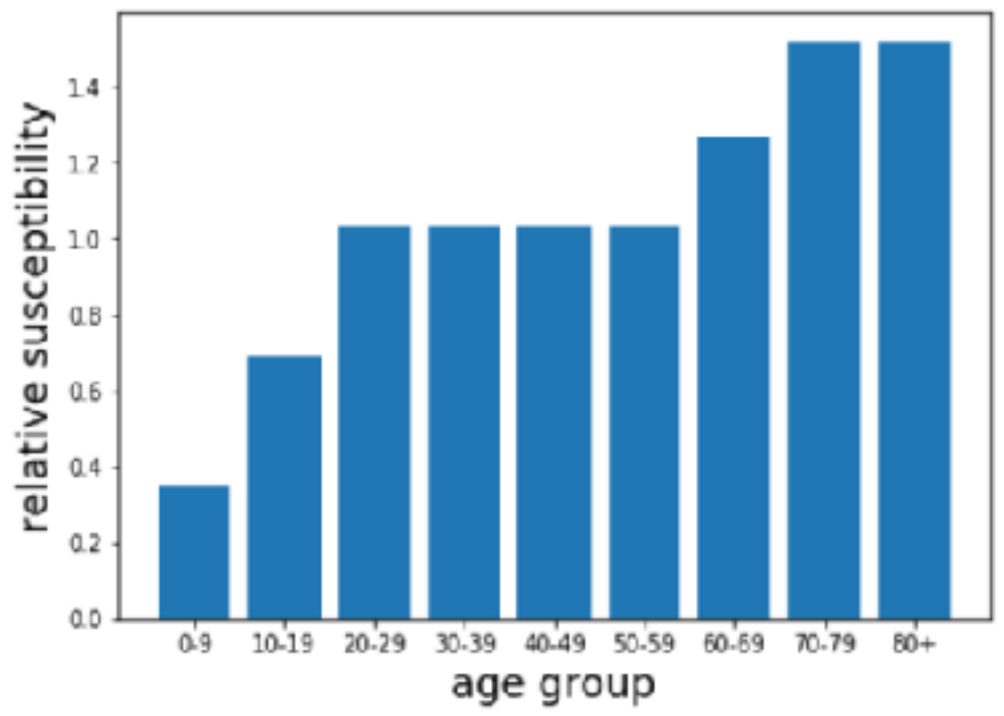
- Infectiousness depends on severity



- Severity depends on age

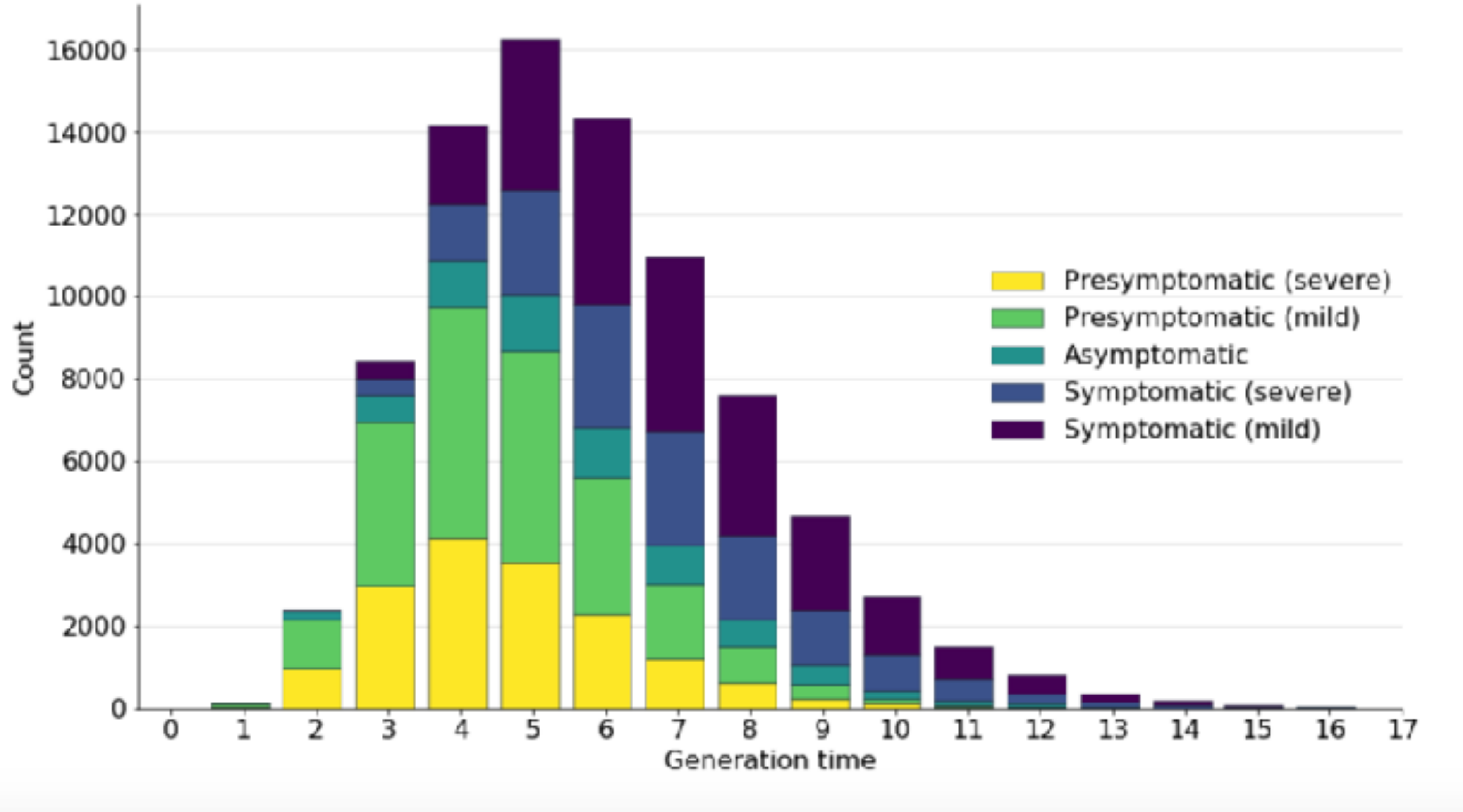


- Susceptibility depends on age

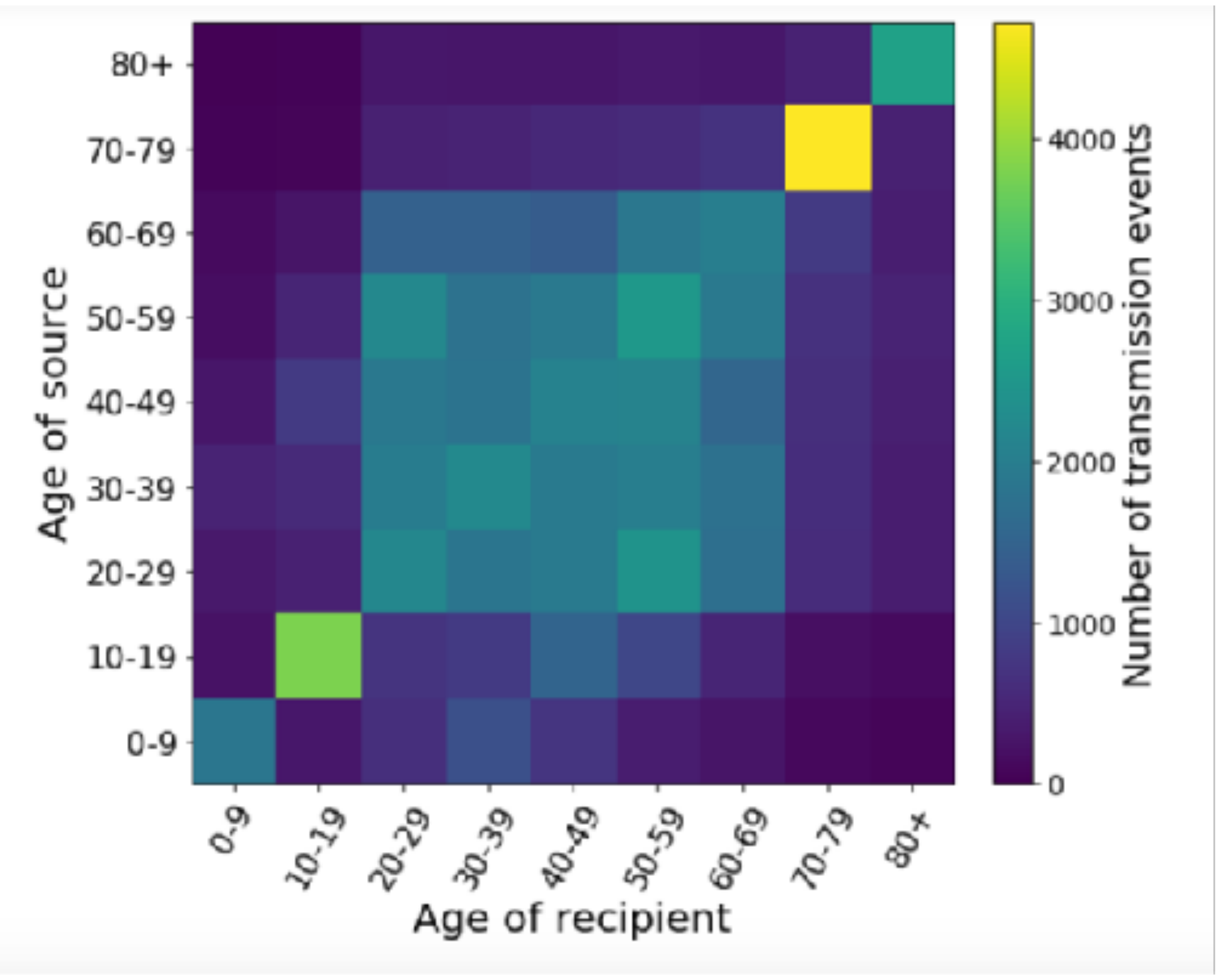


Transmission

- Generation time by infection status of source

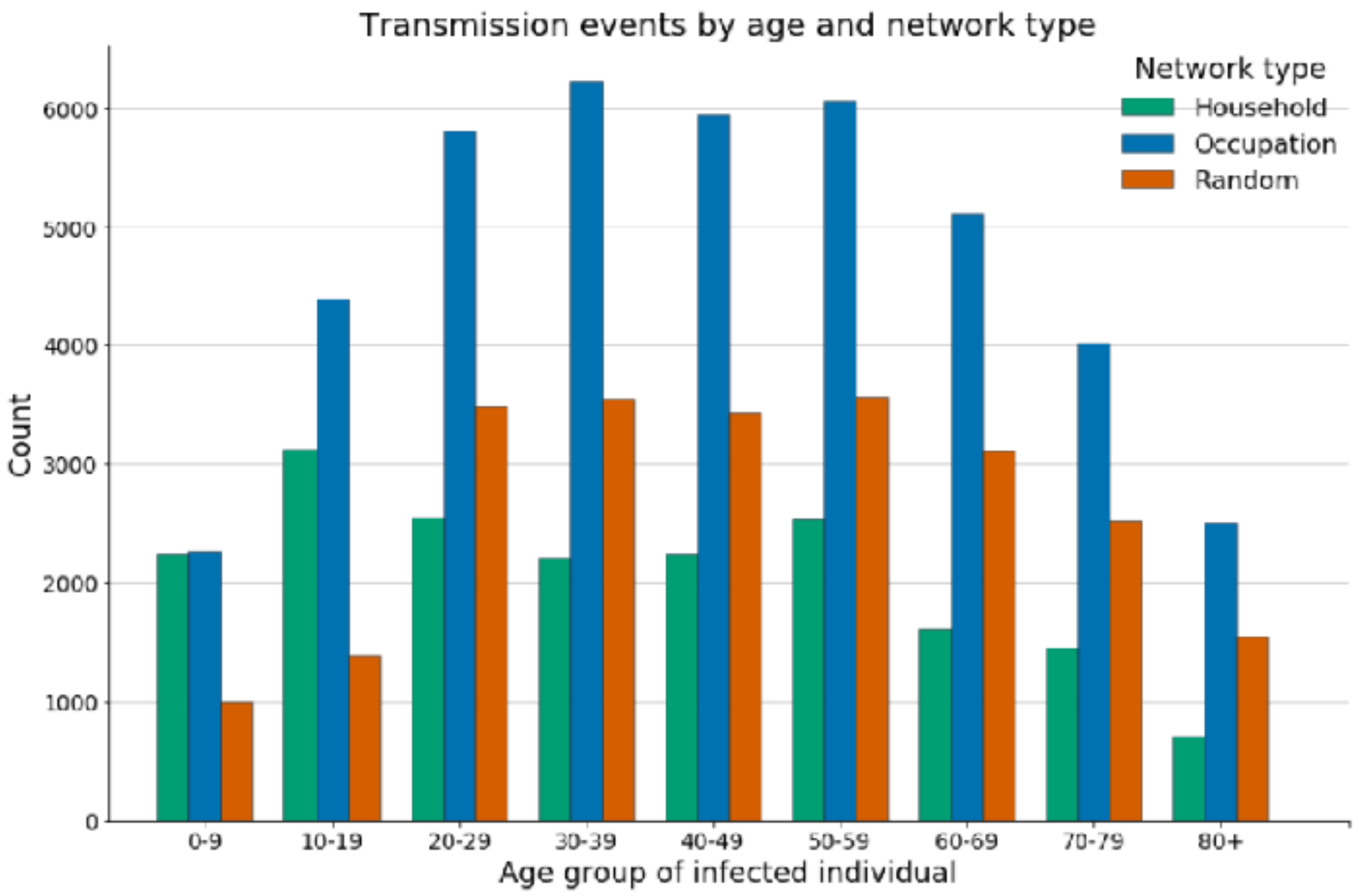


- Transmission by age



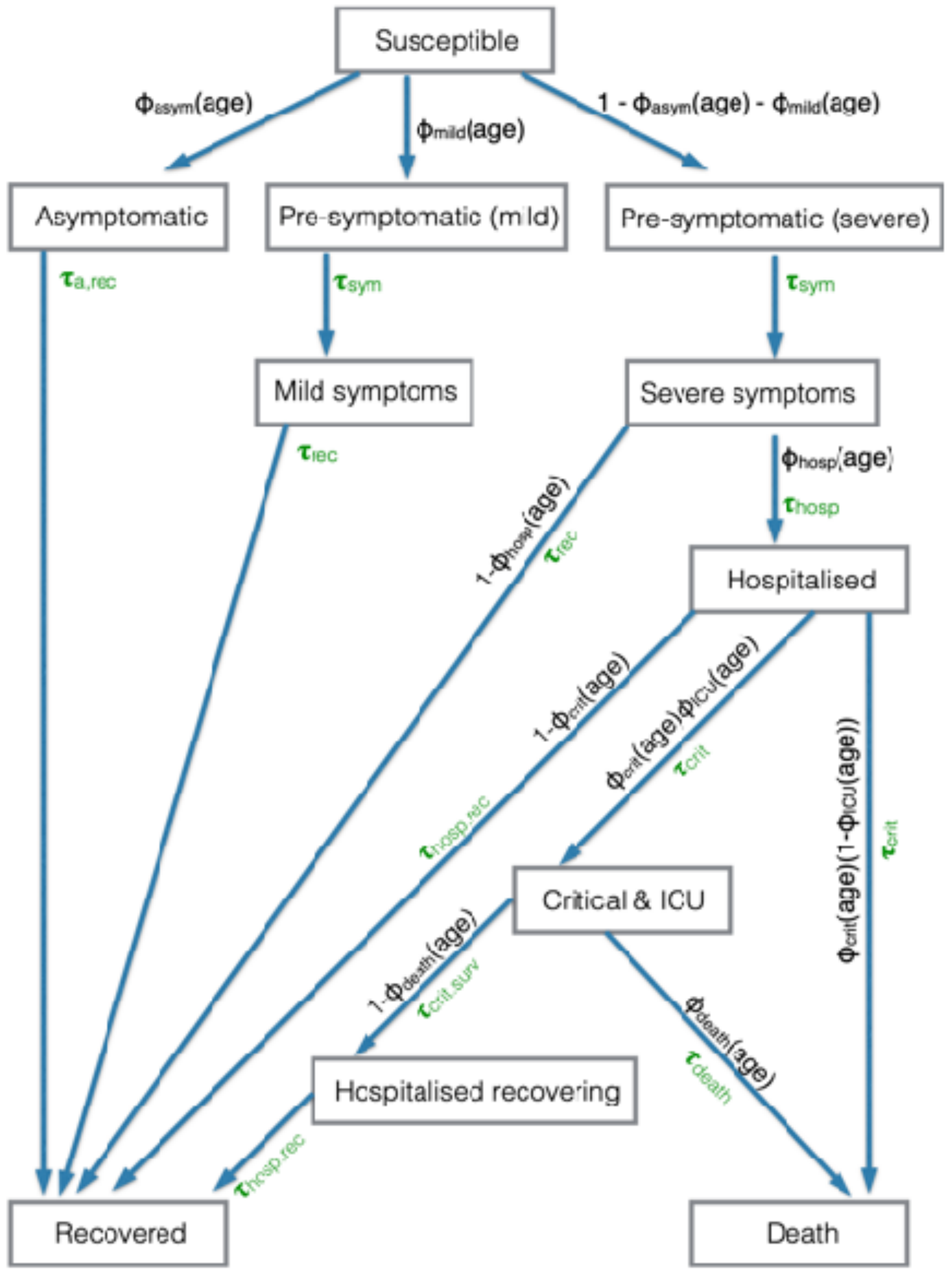
Transmission

- Transmissions on all networks
- Most on occupational networks
  (in absence of controls)



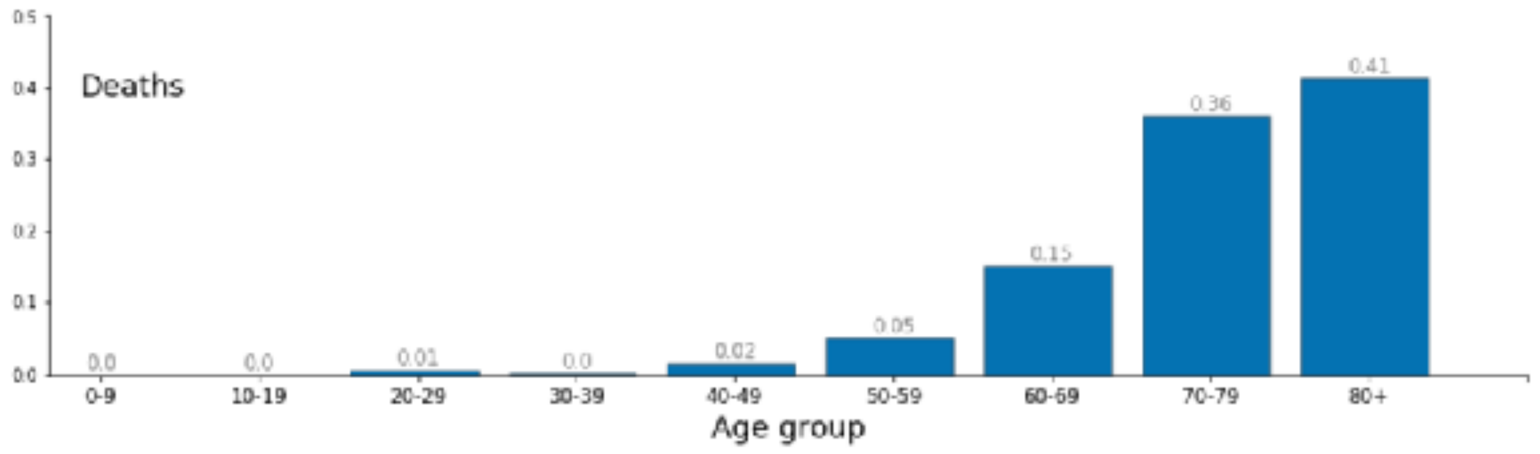
Disease Dynamics

- Disease progression is age dependent



- Severity split between asymptomatic, mild and severe

- Deaths are highly skewed to the elderly

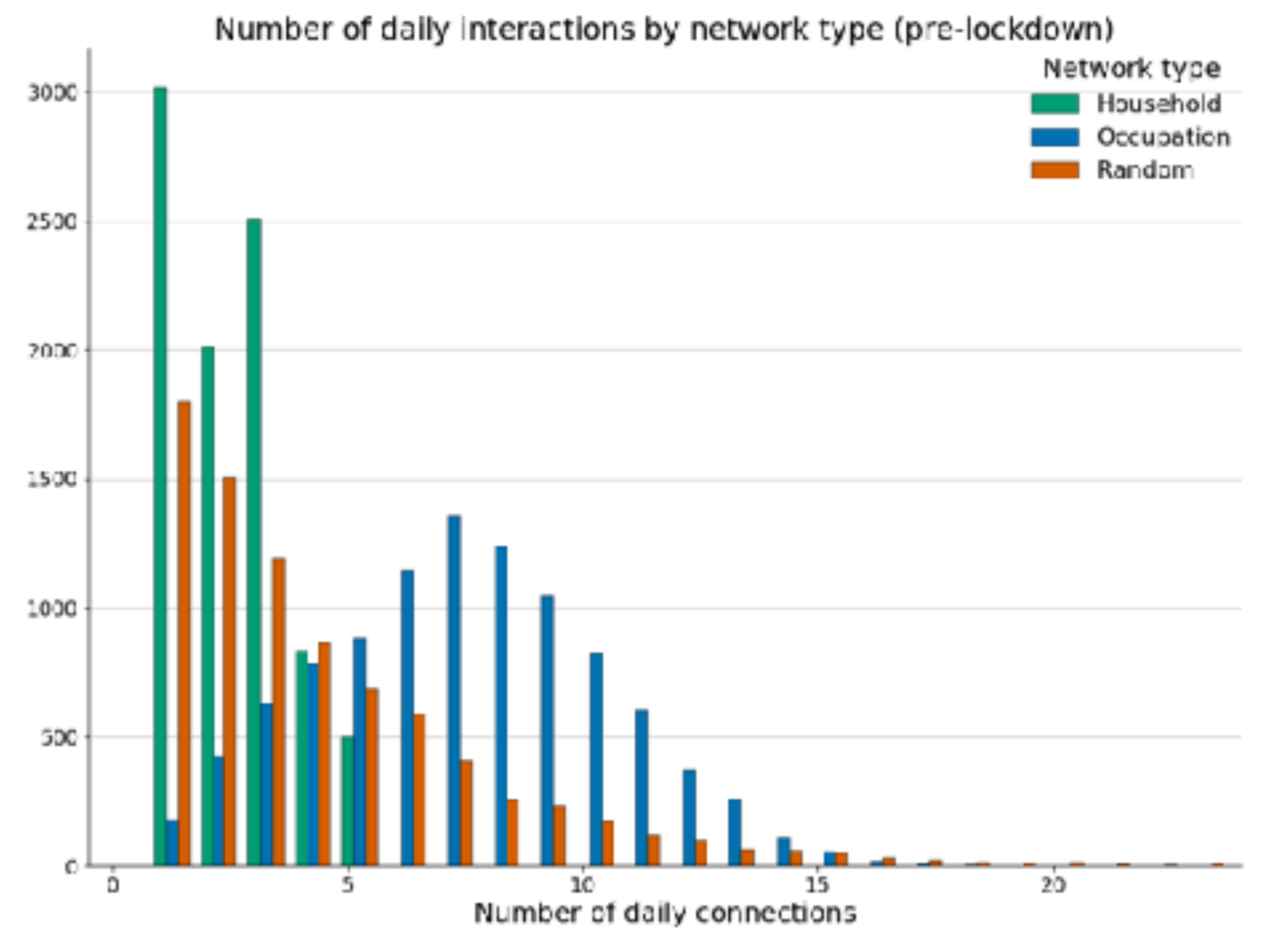


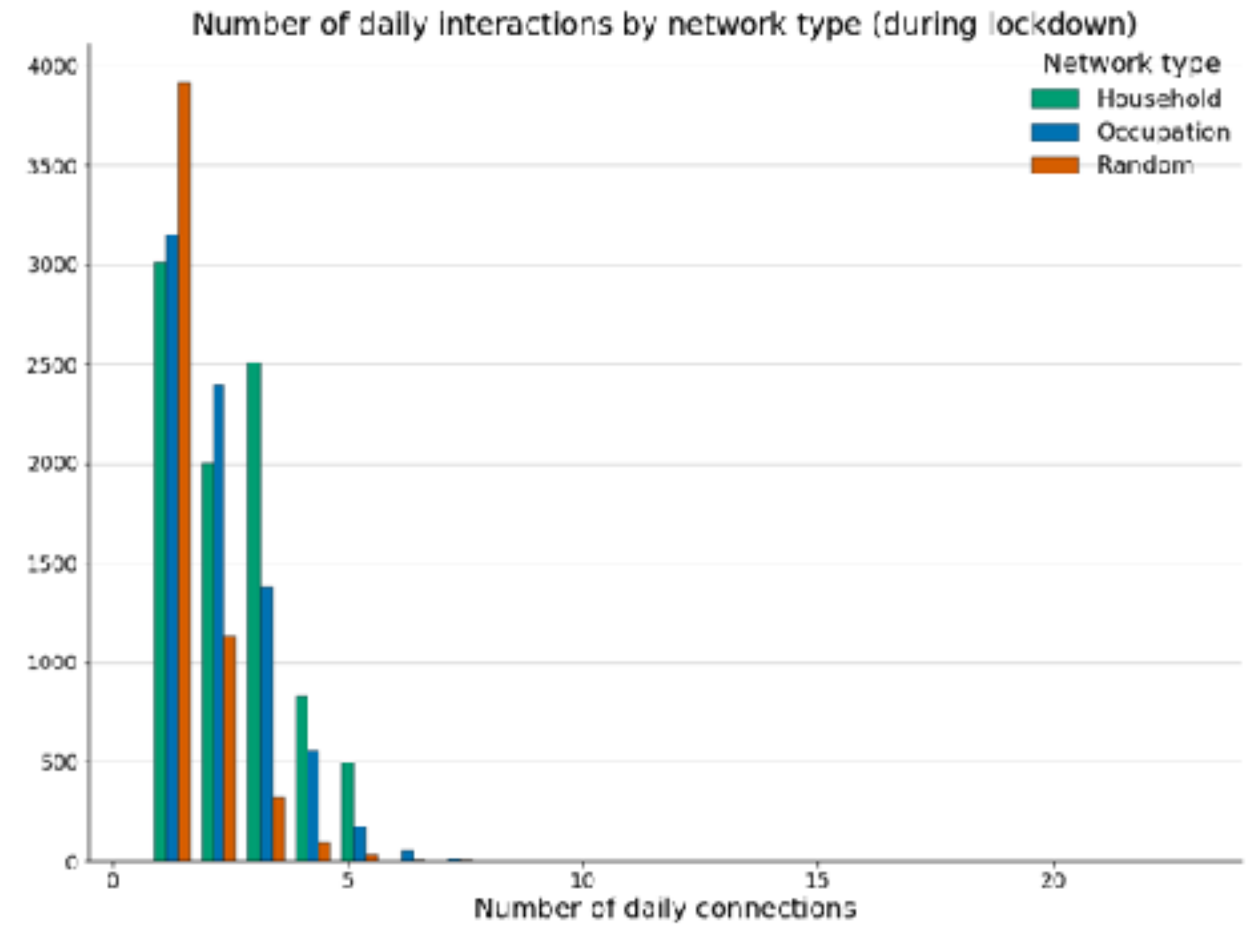
Interventions - Lockdown

- Reduce interactions on occupation and random networks

- Same interaction on household network

- Social distancing - reduction in transmission rates in interactions



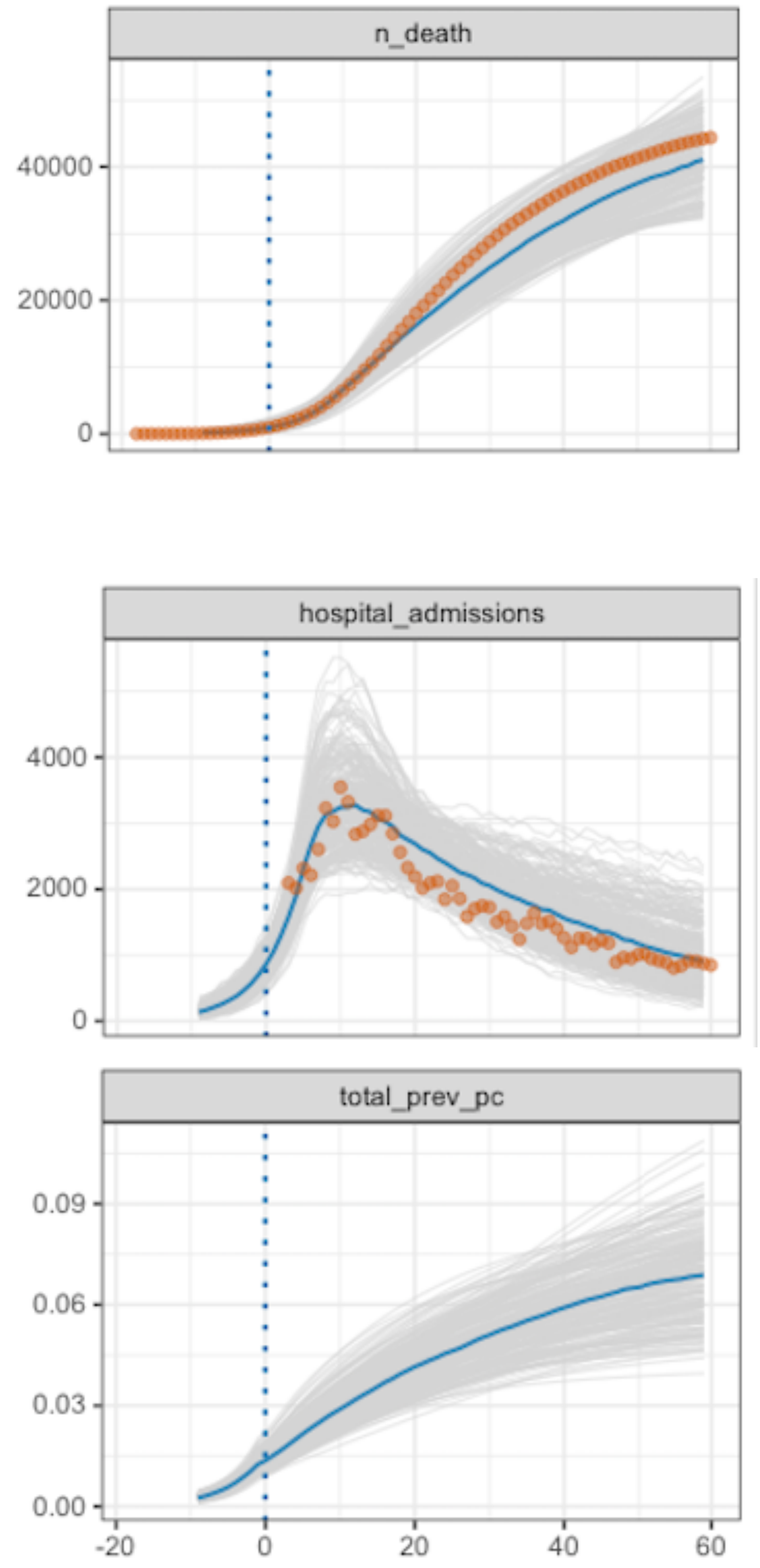


Model Calibration - ABC

- Fit to UK deaths data - calibrate 7 key parameters

- Approximate Bayesian Computation (simple rejection ABC)

- Posterior distribution of prevalence and hospitalisation (lockdown is at day 0)

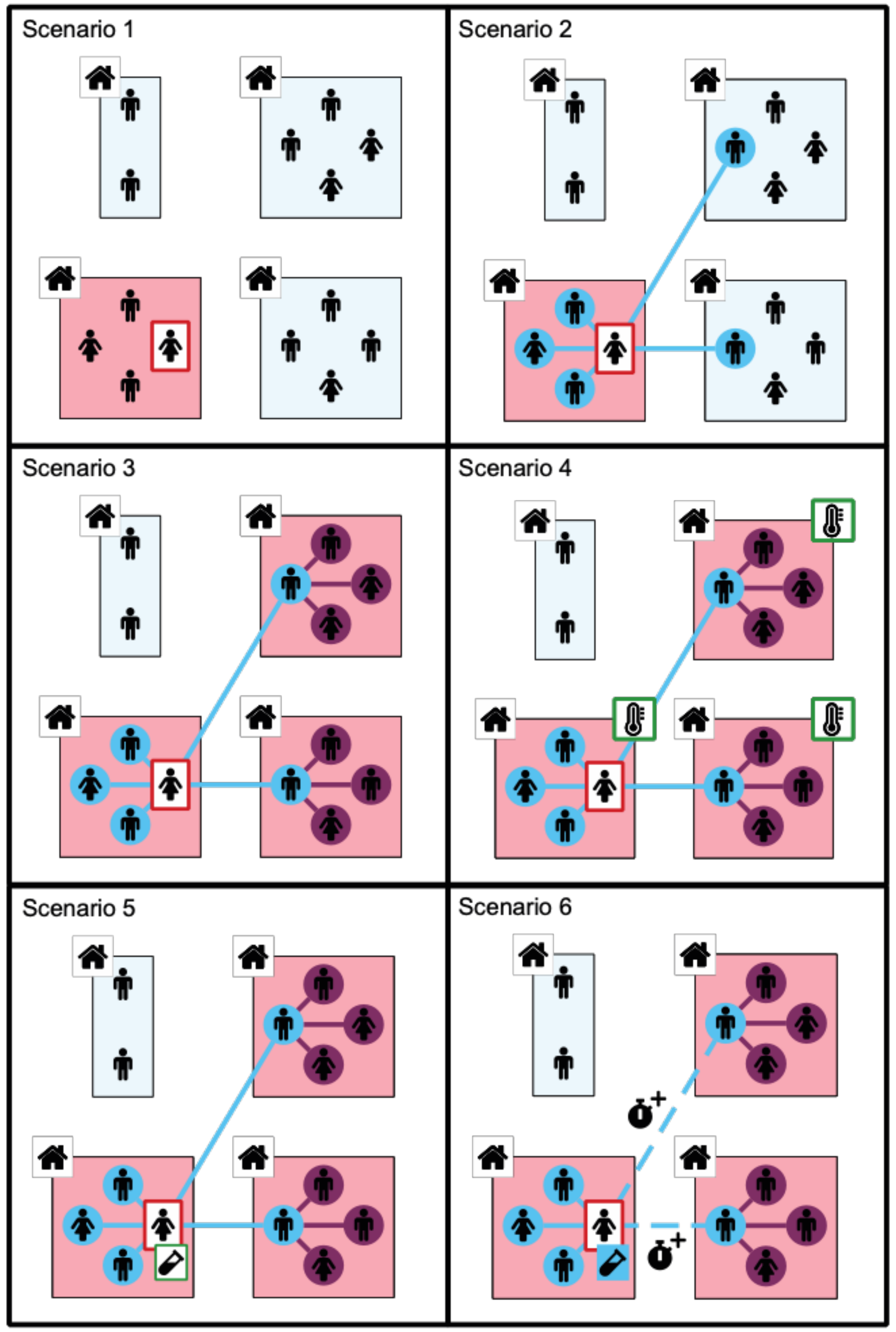


Intervention model

Lockdowns,
age-specific lockdown ('shielding'),
generic reduction in contacts,
+ symptom-based household quarantines, regardless of app.

+ suite of different app-based configurations for quarantining contacts:

- Who is quarantined (recursion)?
- When (symptoms, test)?
- Early cluster release (for confirmed false negatives)?
- Risk scoring (contacts close to symptom onset time upweighted)?



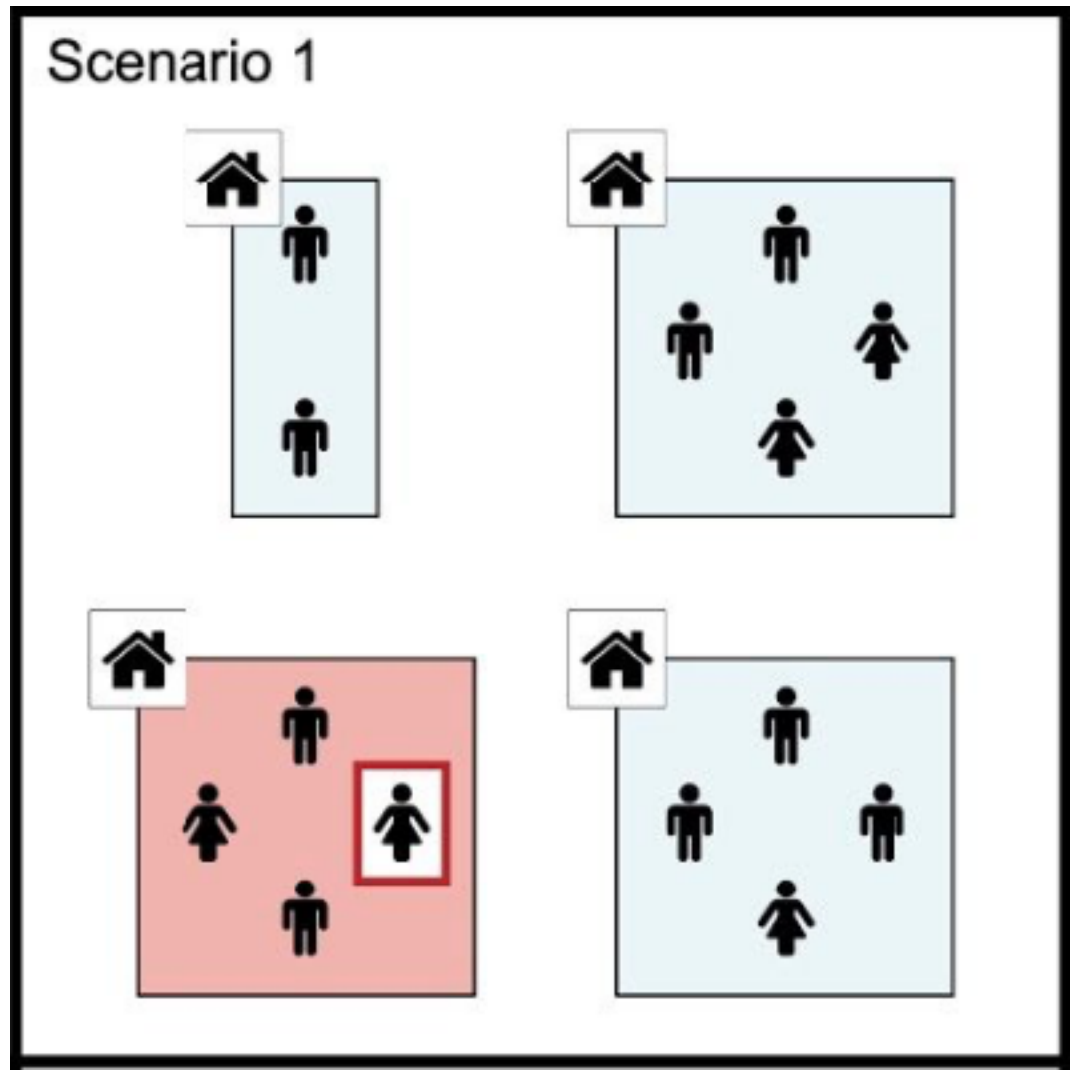
Modelled:

- False positive symptoms
- Imperfect contact detection
- Imperfect adherence to quarantine
- Imperfect testing, delays
- …

Interventions -Isolation

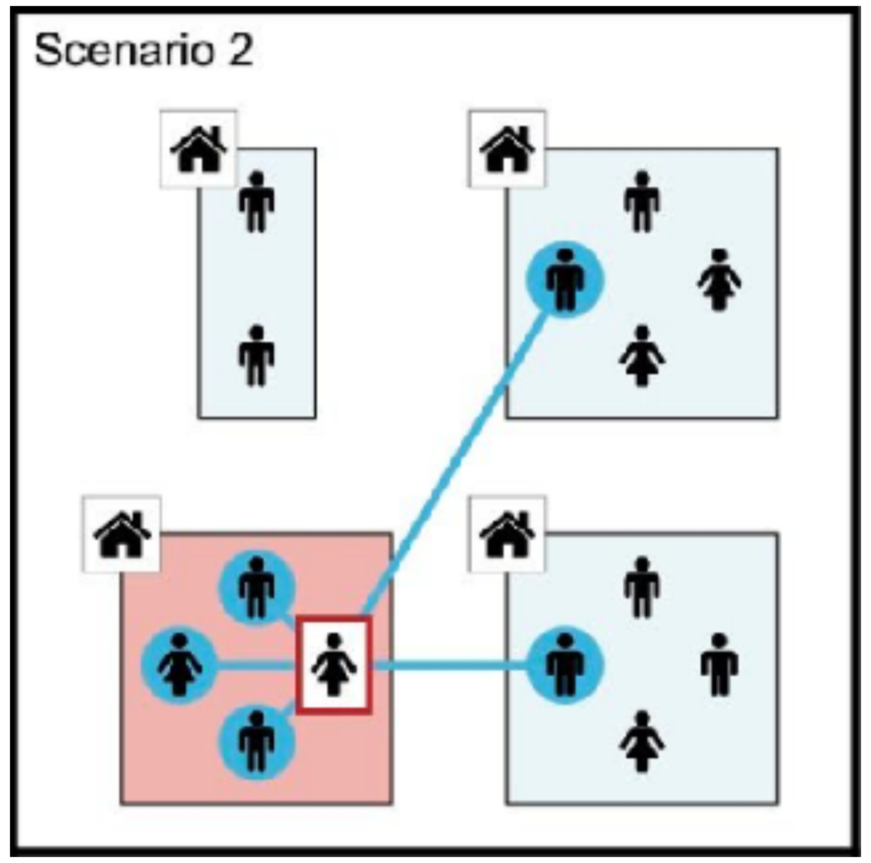
- Self-isolation only occurs after symptoms develop
  - fidelity
  - dropout
  - household members

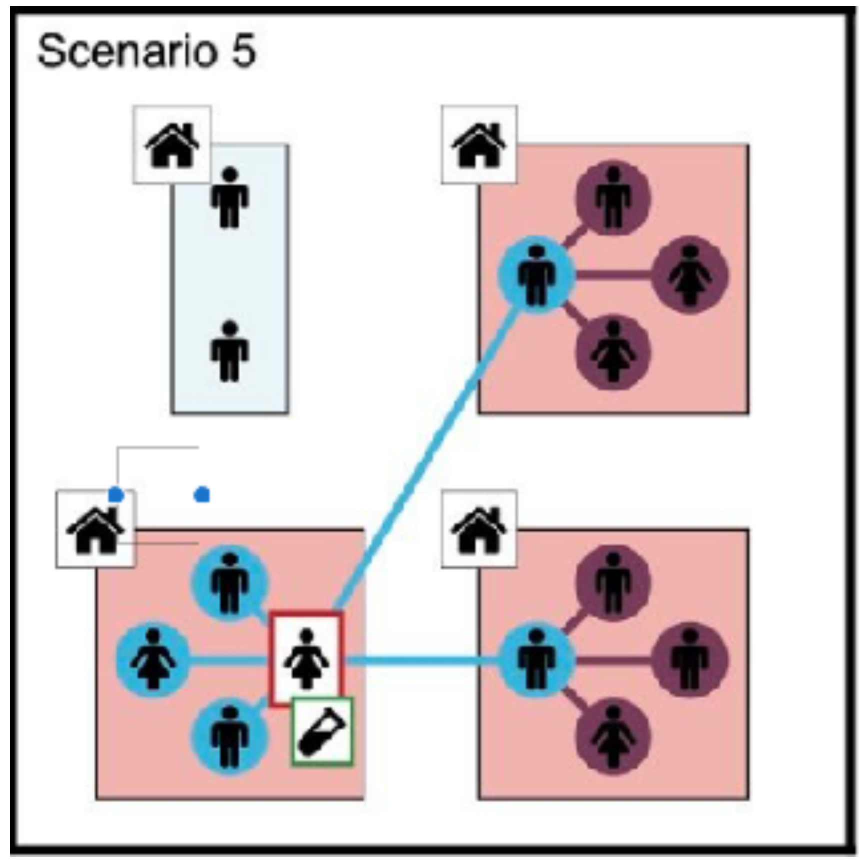
- Trigger point for other interventions
  - testing
  - contact-tracing



(Digital) Contact Tracing

- Smart-phones record interactions via Bluetooth
- Contract-trace on interaction network if both parties have the phone app
- Fidelity of recording contacts
- Compliance with quarantine requests
- Wait for confirmed test result?
- Quarantine household of contacts?
- Test contact-traced?
- Recursive contact-tracing?
- Risk-scoring of contacts
- Prioritise testing based on contacts

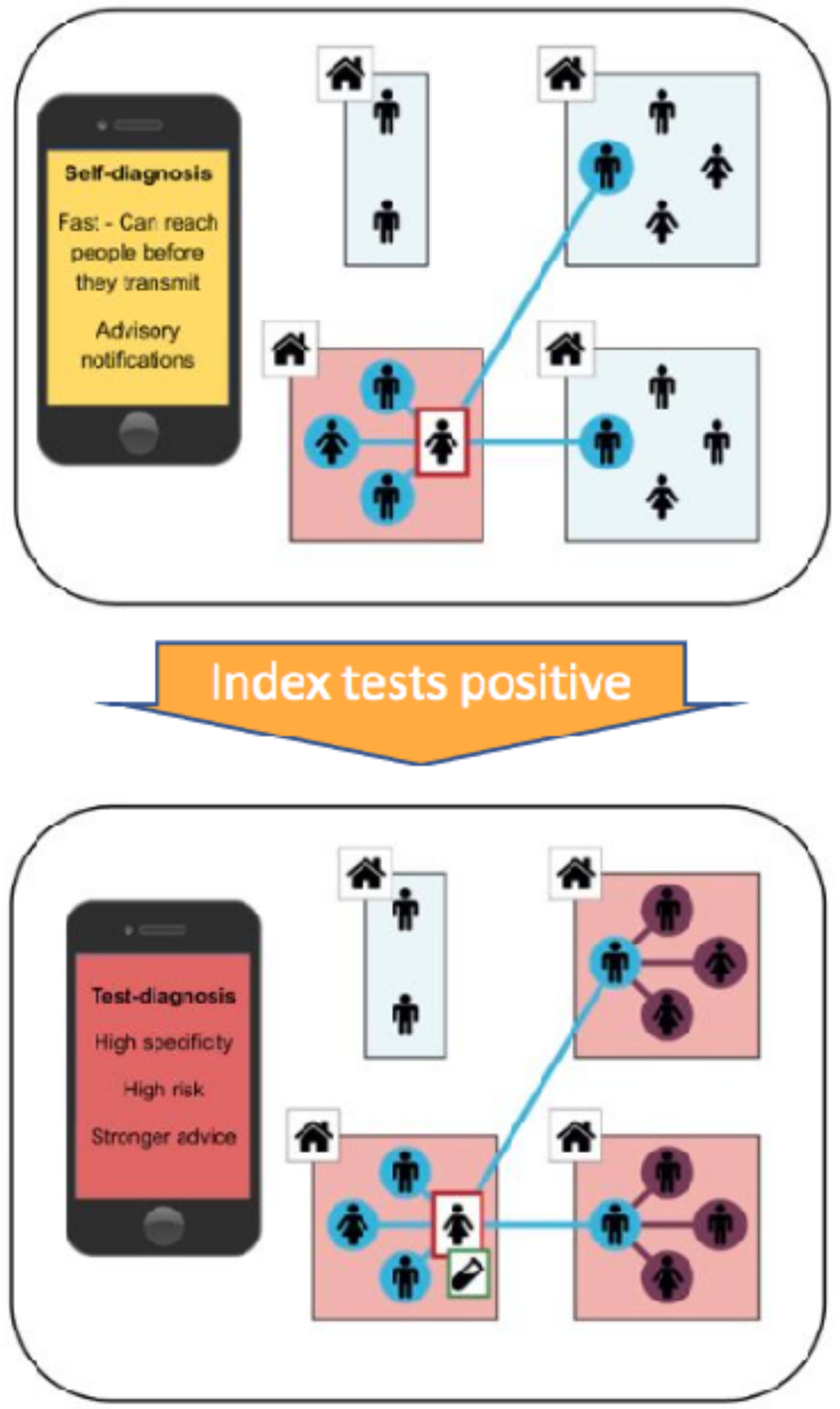




Digital Contact Tracing

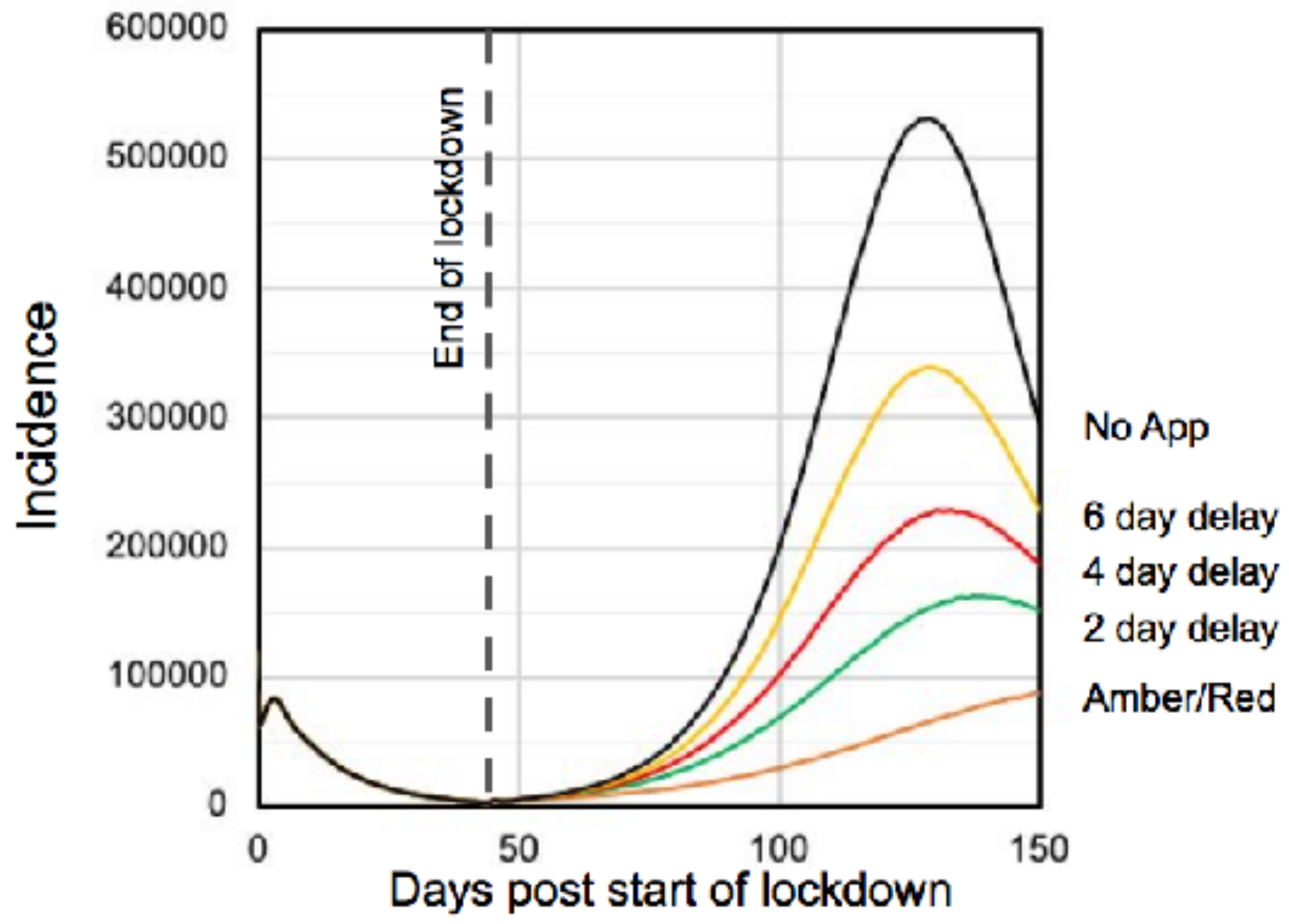
- Amber warning on symptoms
  - request to social-distance and quarantine if possible

- Test index case
  - negative test - remove amber warning message
  - positive test - red request to quarantine and household



Digital Contact Tracing

- Speed is important - large delays in testing renders tracing pointless



- Benefits even at lower levels of coverage