MSc mathematical modelling (weeks 7-8)

Mathematical modelling of infectious disease outbreaks

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UNIVERSITY OF OXFORD

Mathematical Institute

Next term…

- Case study in mathematical modelling
- Work in a group of around 5-6 students on a modelling research project

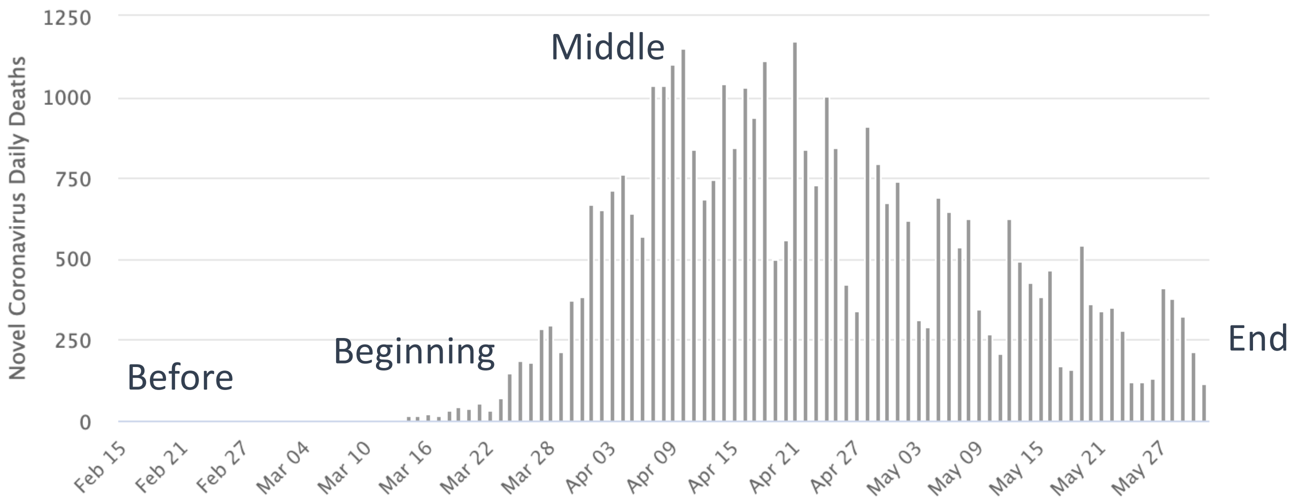
  [last year: cycle races, Alzheimer's modelling etc…]
- Work on project throughout Hilary term
- Deliver group presentation (20% of final mark)
- Write individual project report (80% of final mark)

Now!

- Today: 2-hour introduction to infectious disease modelling
- Tomorrow: Assign groups and start infectious disease modelling “mini project”
- Next Monday 2-4: Work on group mini project, prepare slides
- Next Tuesday 3-4: Report back on your mini project (3-5 slides per group; please email slides to me by noon next Tuesday – robin.thompson@maths.ox.ac.uk)

- **This is an opportunity to practise group work (not assessed)**
- In the next 2 hours, I will give you some suggestions for possible mini projects to do over the next week: your group can do one of these, all of these, or something different!
- **Have fun!!!**

Modelling for real-time outbreak response



Before

- Where is an outbreak most likely to occur?
- Where should surveillance resources be deployed?

Beginning

- Will initial cases lead to a major epidemic?
- Which interventions reduce the epidemic risk?

Middle

- How effective are current interventions?
- Which interventions optimally balance benefits and costs?

End

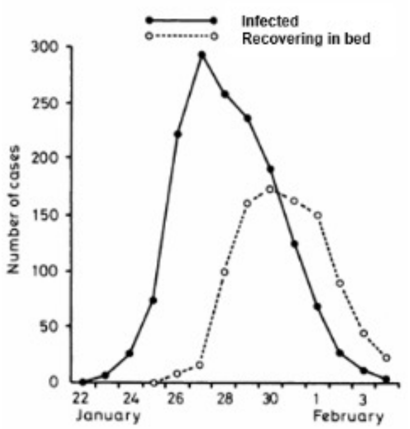
- How should interventions be lifted?
- Is the epidemic over?

Outline

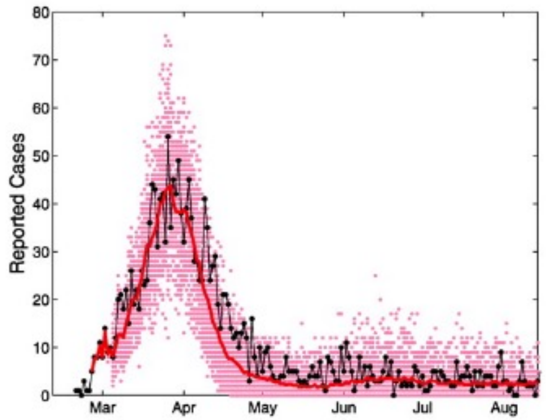
1. Introduction to common infectious disease outbreak models
    - Compartmental models
    - Renewal equation models
2. Early in an outbreak: Assessing the risk of major epidemics
    - Estimating the probability of a major epidemic [stochastic compartmental model]
    - Possible mini project
3. During an epidemic: Assessing the effectiveness of current interventions
    - Inferring current transmissibility [renewal equation model]
    - Possible mini project
4. At the end of an epidemic: Assessing when the epidemic is over
    - End-of-outbreak probability estimation [compartmental model and renewal equation model]
    - Possible mini project

Outbreak waves have a characteristic "shape"

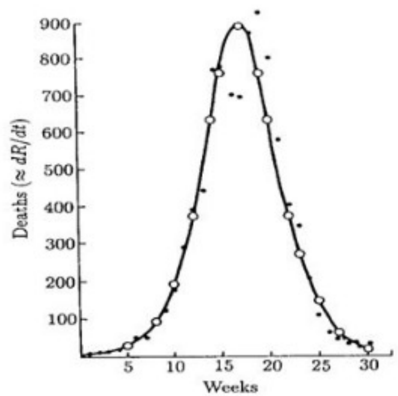
Flu in a school in 1978



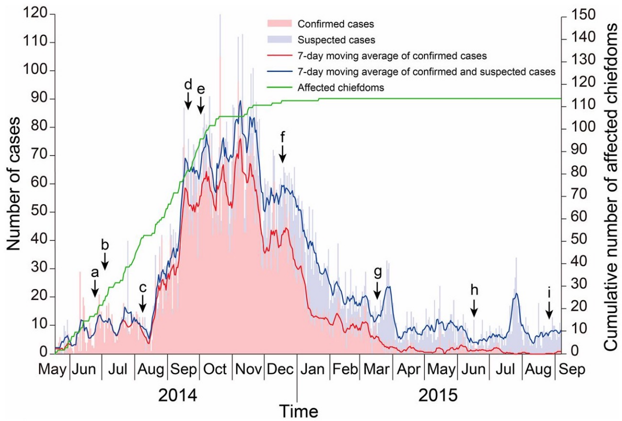
Foot and mouth in the UK 2001



Plague in Mumbai in 1906



Ebola in West Africa in 2014-15

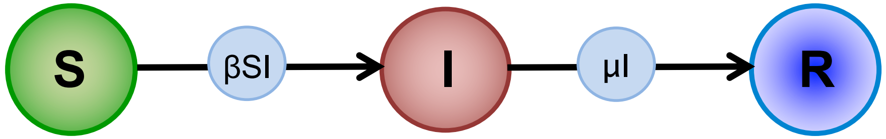


First compartmental models

(early 20th century)

aimed to capture this shape

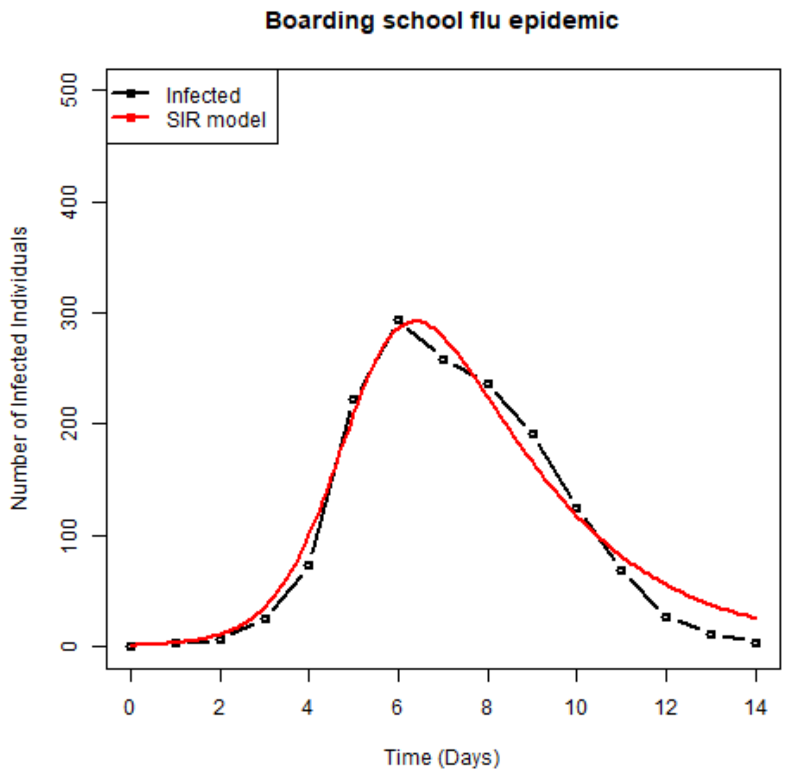
Compartmental models: SIR model



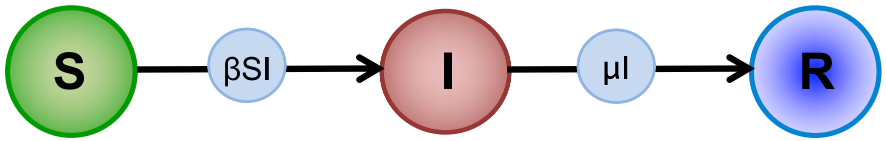
$$\frac{dS}{dt} = -\beta SI$$

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

$$\frac{dR}{dt} = \mu I$$



Compartmental models: SIR model



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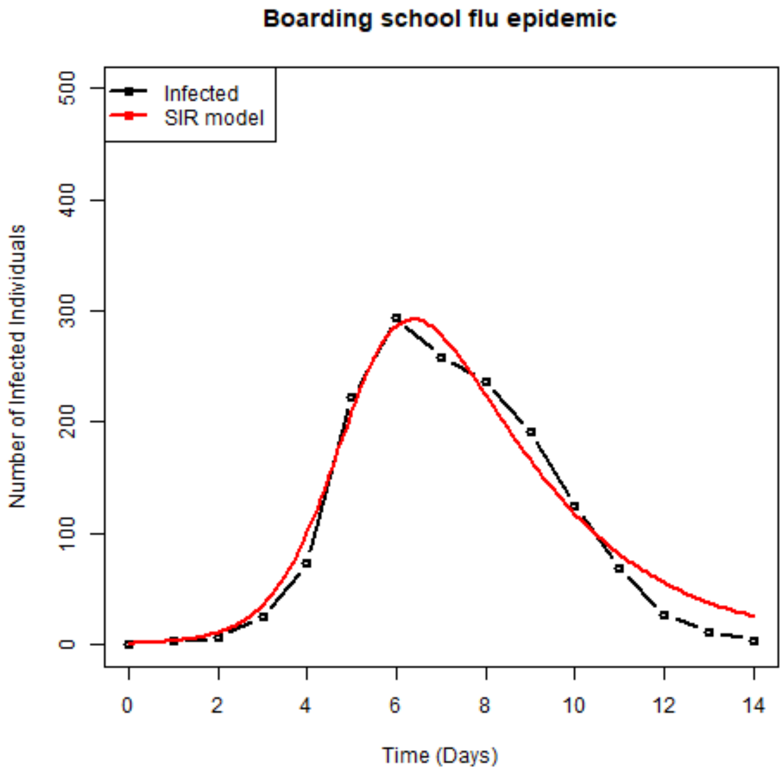


Involves assumptions (homogeneous mixing, infected individuals immediately infectious, etc)

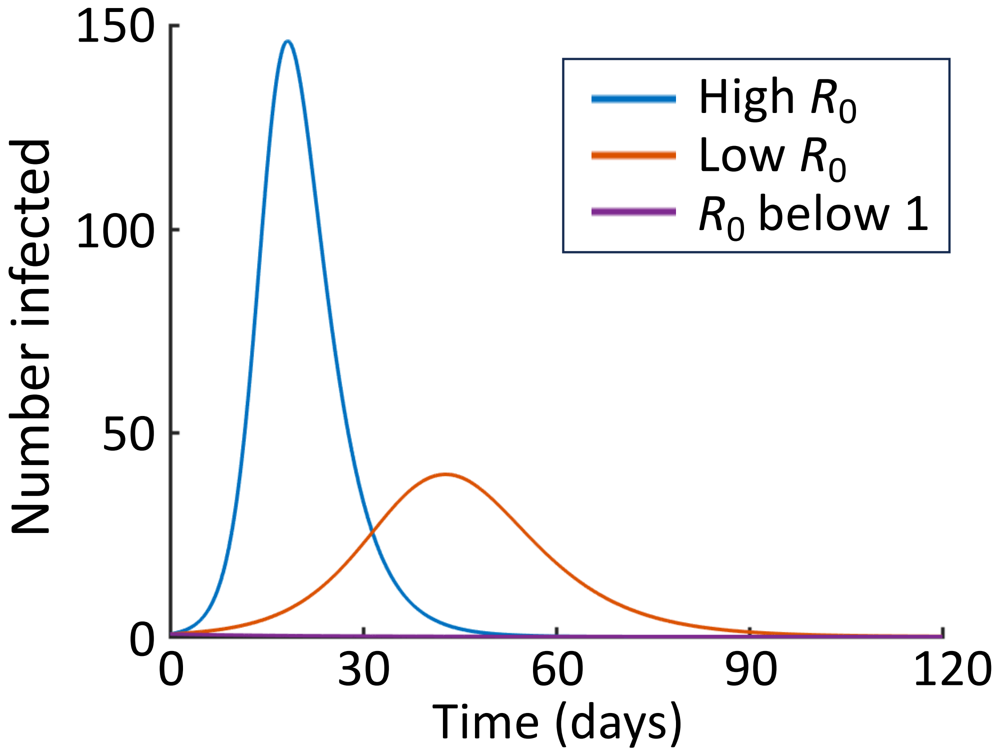
But… not bad for a two-parameter model

Compartmental models: SIR model

- R_0 – Number of cases of disease arising from each primary case (in an entirely susceptible population)

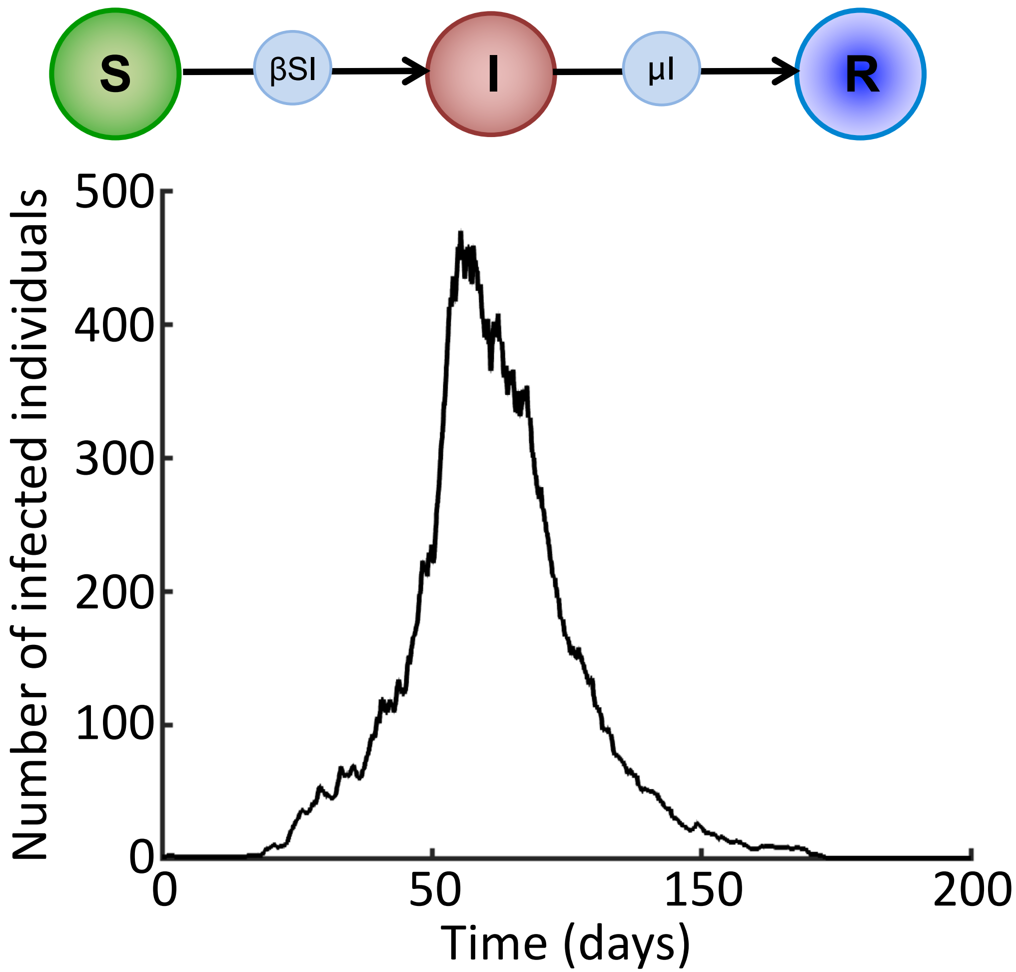
R_0 = Infection rate x Duration of infection

$R_0 = \beta N \times 1/\mu$



Compartmental models: Extensions to SIR model

1. Infectious disease outbreaks are inherently random



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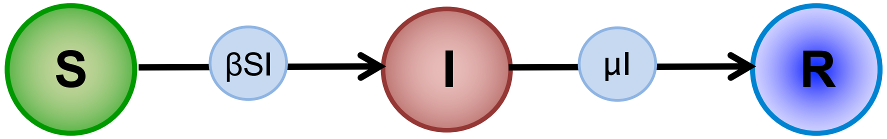

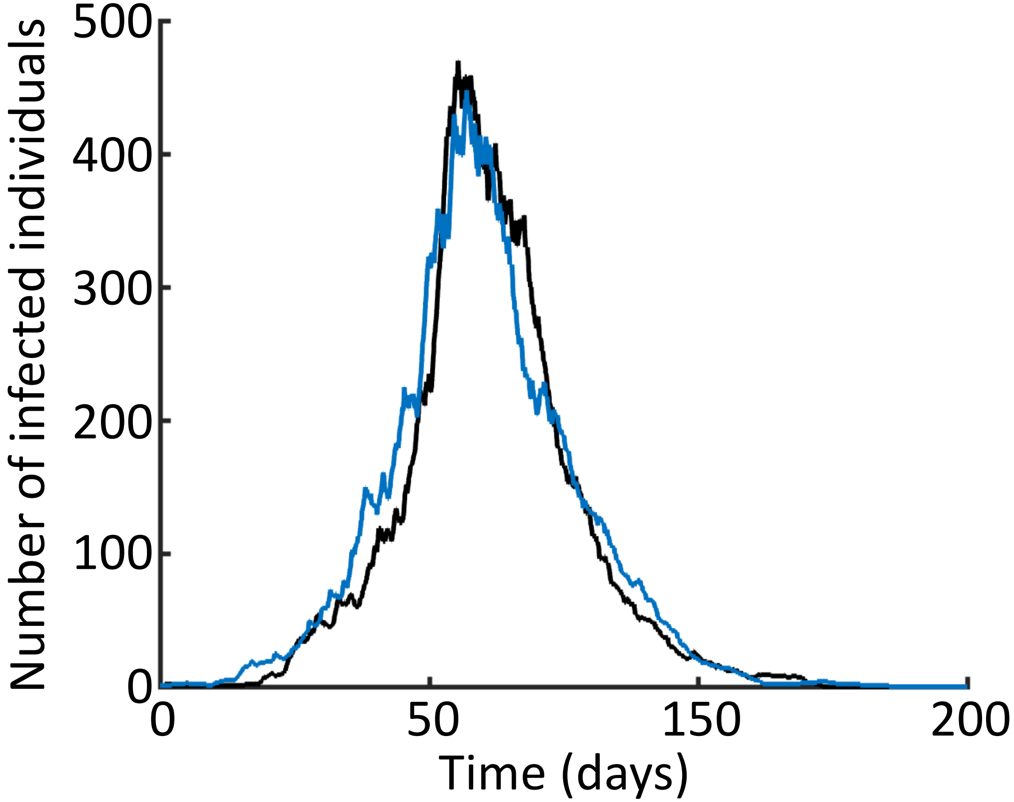

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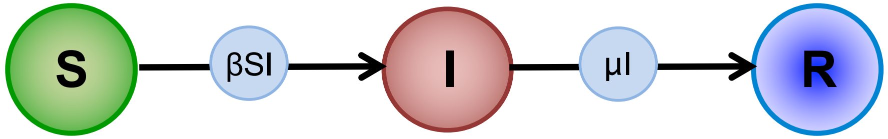

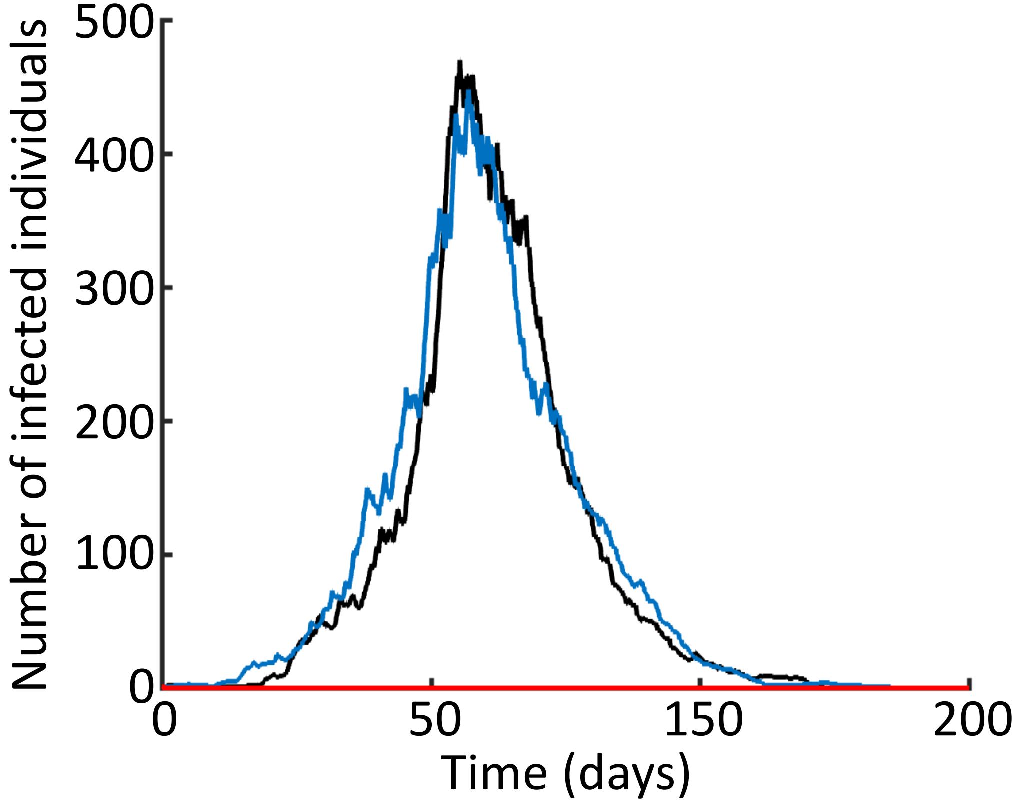

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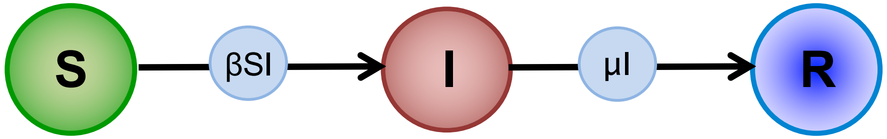


How to run one simulation of stochastic SIR model (using Gillespie direct method):

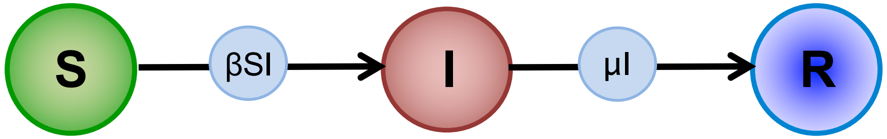
- Assume that events occur at exponentially distributed time intervals. The time until the next event therefore follows an exponential distribution with rate parameter $\beta SI + \mu I$.

- The probability that the next event is an infection is:

$$\text{Prob(infection)} = \frac{\beta SI}{\beta SI + \mu I}. \qquad \text{Similarly,} \ \ \text{Prob(removal)} = \frac{\mu I}{\beta SI + \mu I}$$

Compartmental models: Extensions to SIR model

1. Infectious disease outbreaks are inherently random



How to run one simulation of stochastic SIR model (using Gillespie direct method):

1. Initialise the number of individuals in each of the *S*, *I* and *R* classes in the model, and set the outbreak time *t* = 0.

2. Steps 2-4 should be repeated while the outbreak is still ongoing (i.e. *I* > 0). First calculate two random numbers r_1, r_2 each uniformly distributed in (0,1).

3. Calculate the time of the next event from an exponential distribution. Set

$$t = t + \frac{1}{\beta IS + \mu I} \ln\left(\frac{1}{r_1}\right).$$

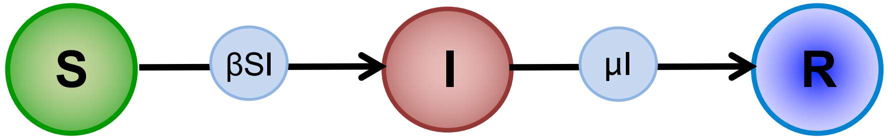
4. Choose whether the next event is an infection event or removal event. If

$$r_2 < \frac{\beta IS}{\beta IS + \mu I},$$

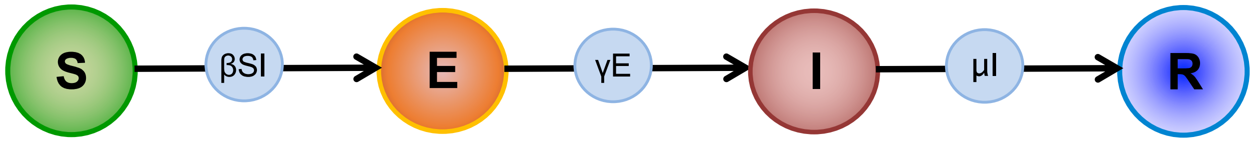
then the next event is an infection event, and so set *S* = *S* – 1 and *I* = *I* + 1. Otherwise set *I* = *I* – 1 and *R* = *R* + 1.

Compartmental models: Extensions to SIR model

2. Different epidemiology

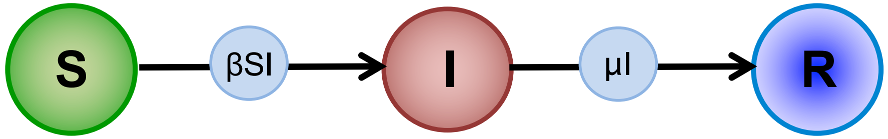


Delay between infection and becoming infectious:



Compartmental models: Extensions to SIR model

2. Different epidemiology



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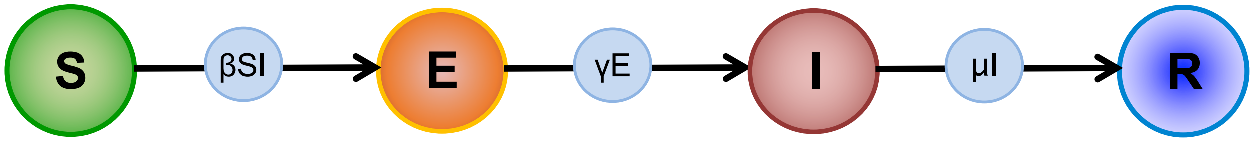
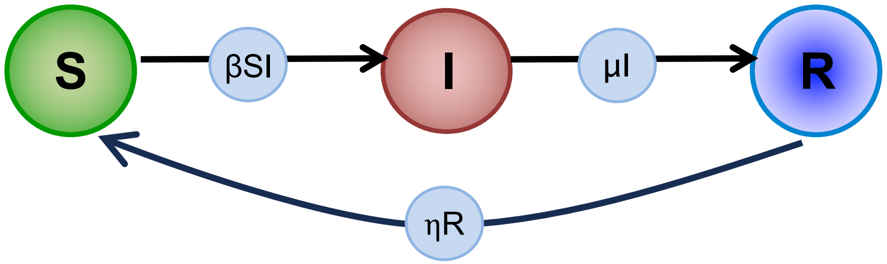
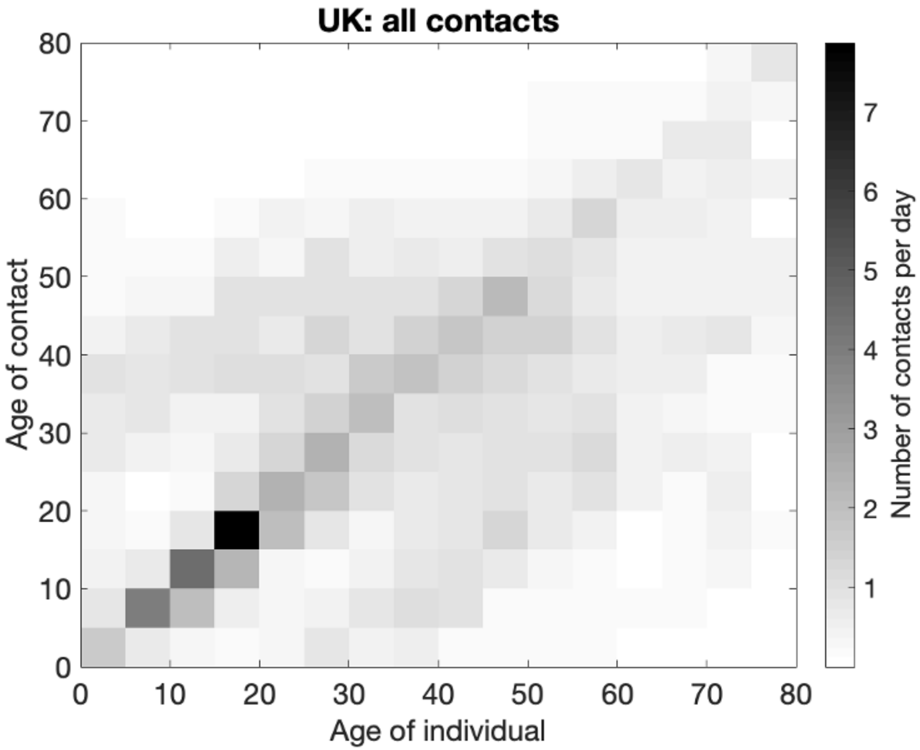


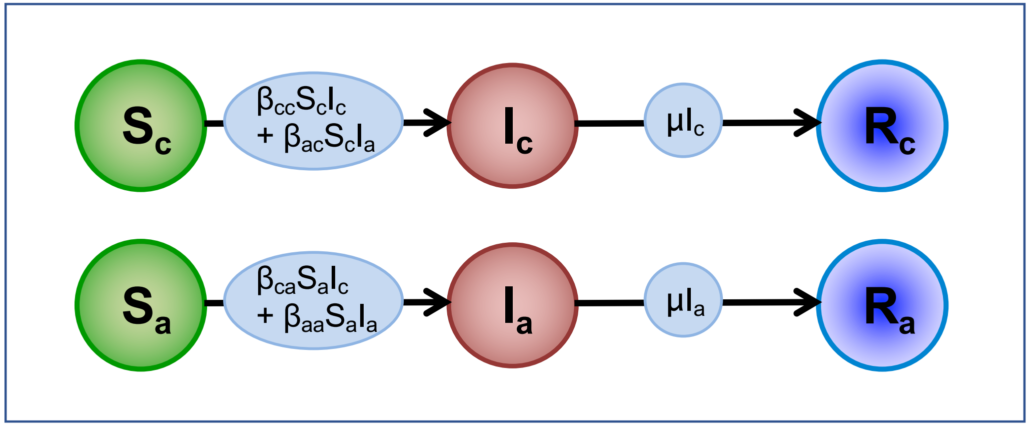
Waning immunity:



Compartmental models: Extensions to SIR model

3. Age structure





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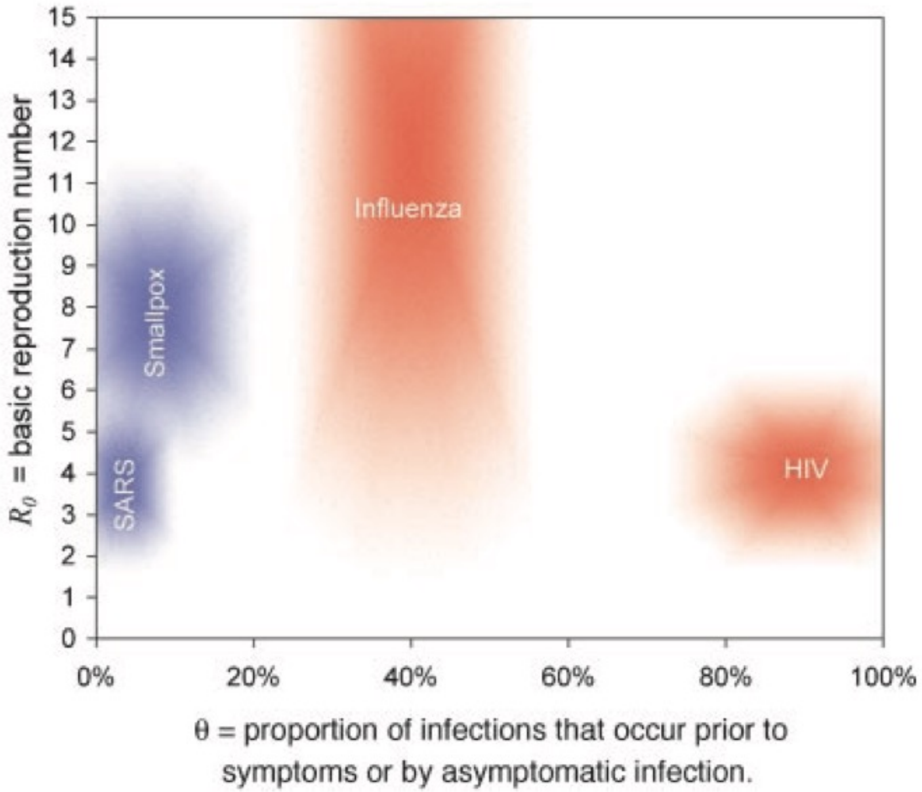
Estimating local outbreak risks and the effects of non-pharmaceutical interventions in age-structured populations: SARS-CoV-2 as a case study

Francesca A. Lovell-Read [a,*], Silvia Shen [a,b], Robin N. Thompson [c,d]

Compartmental models: Extensions to SIR model

4. Asymptomatic transmission



Fraser *et al.* (*PNAS*, 2004)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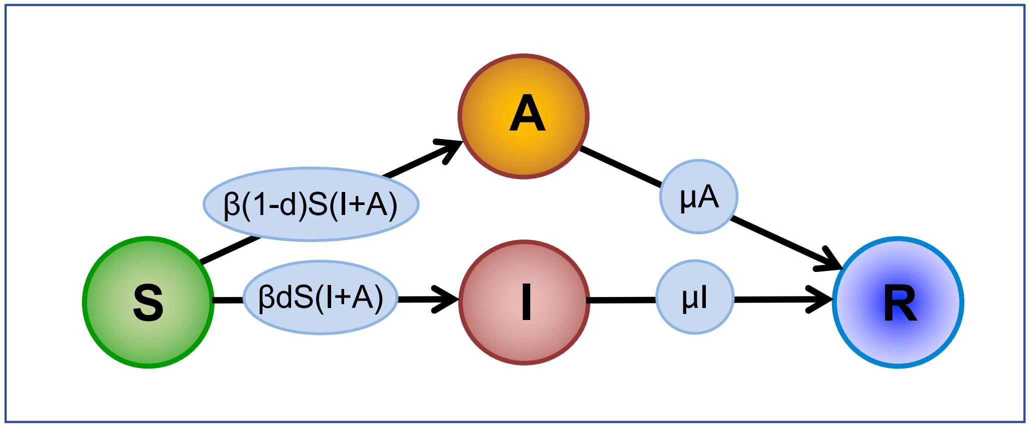
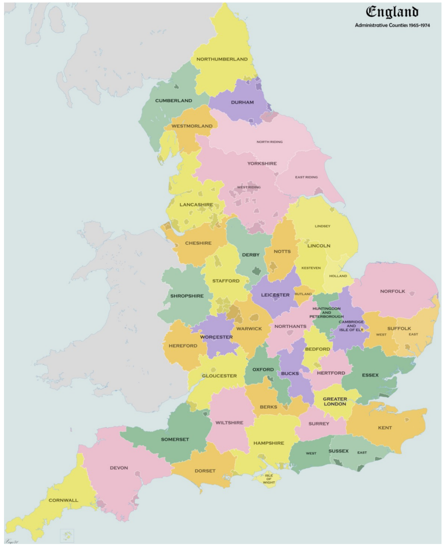
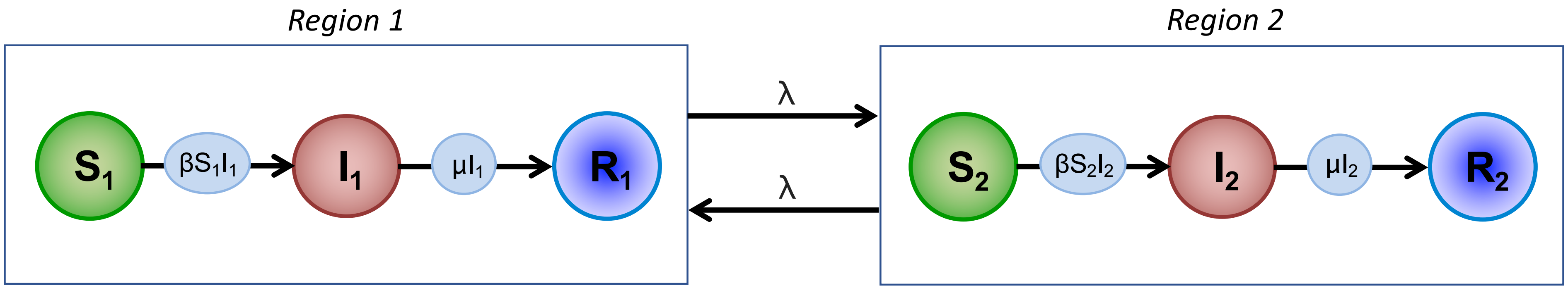


Compartmental models: Extensions to SIR model

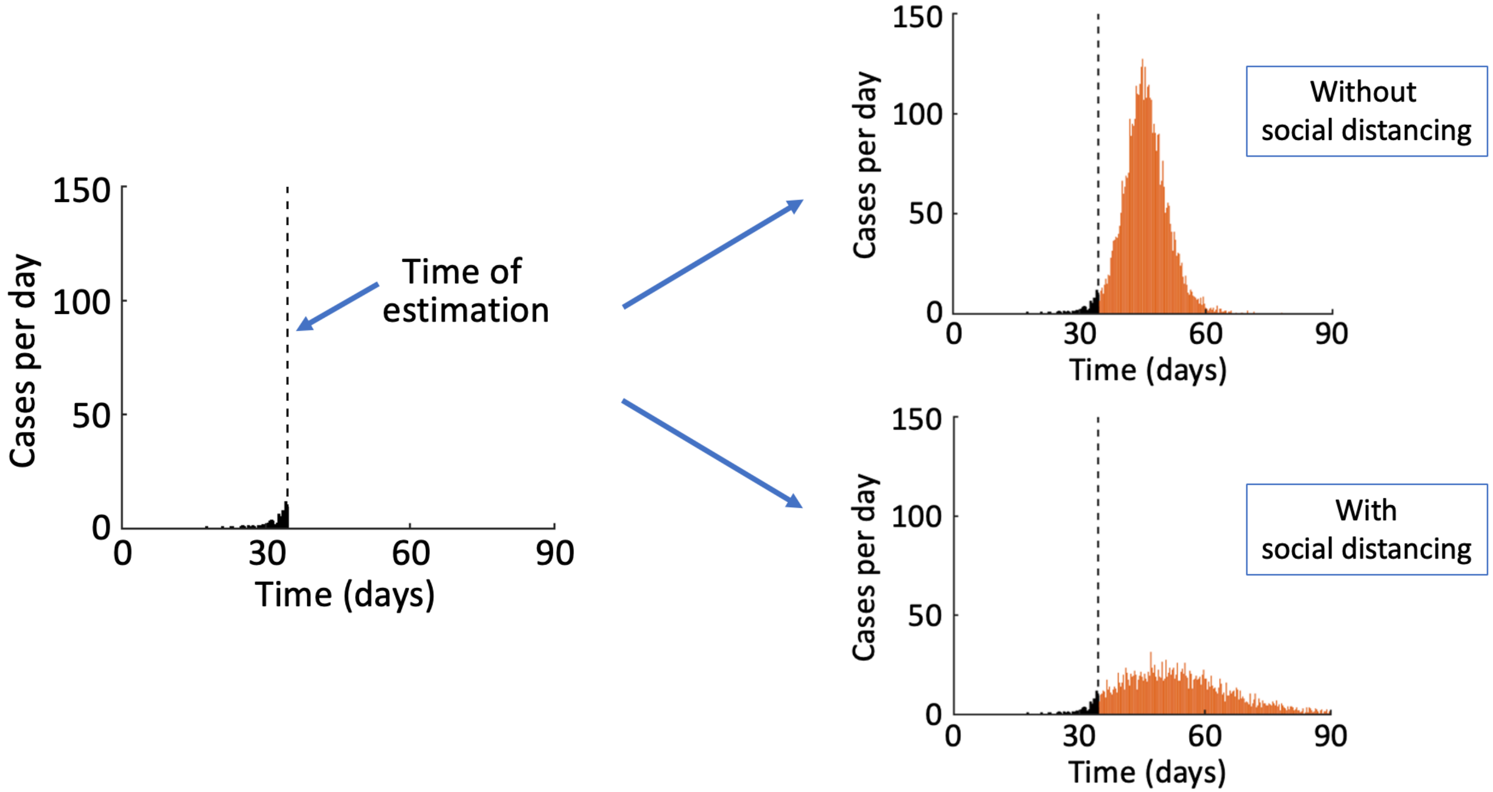
5. Spatial structure





Compartmental models: Testing interventions

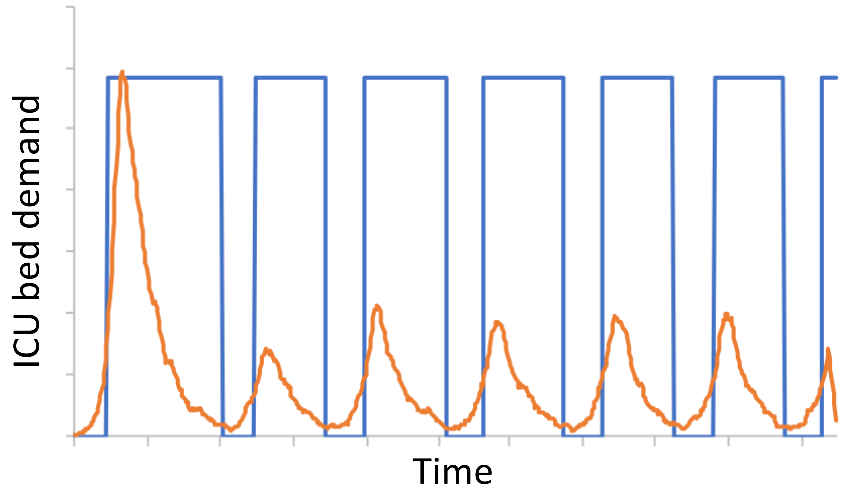
Models can be used to test counterfactual (“what if”) interventions

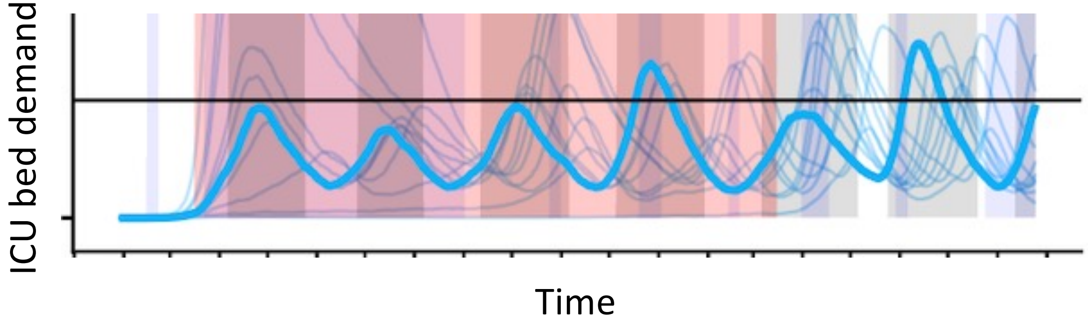


Compartmental models: Testing interventions

Interventions with increasing complexity can be tested

Reduce R_0 periodically via social distancing to keep healthcare demand "manageable"





Adapted from research on COVID-19 by Imperial and LSHTM

Renewal equation models

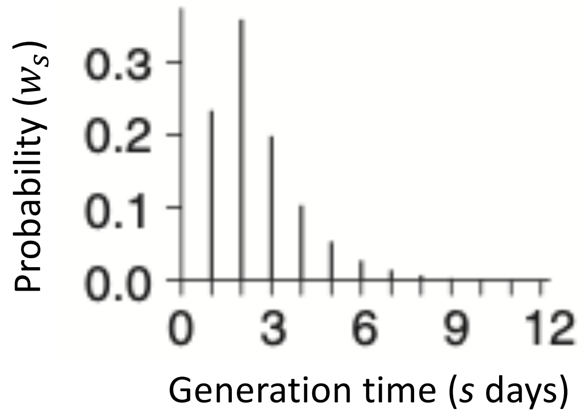
Avoid need to divide hosts into compartments; simply count infections

Renewal equation models

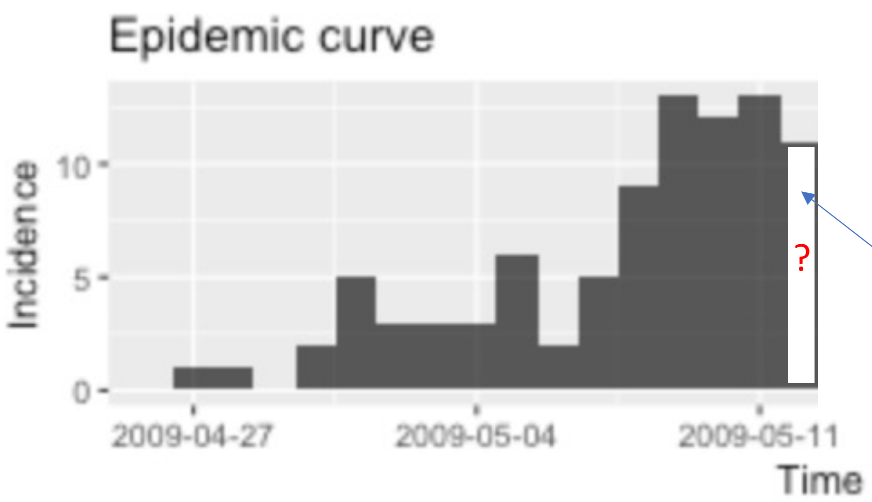
Avoid need to divide hosts into compartments; simply count infections

Know

R_t &



$$E(I_t \mid R_t, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\}) = R_t \sum_{s=1}^{t} I_{t-s} w_s$$

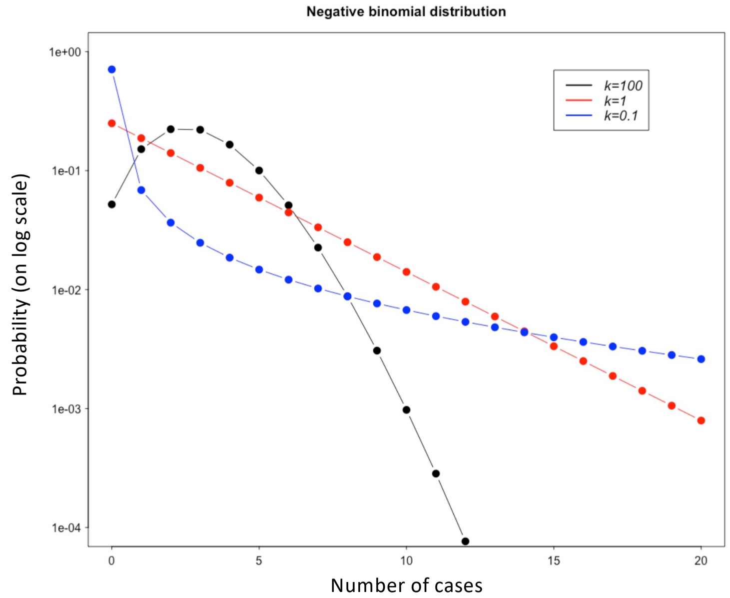


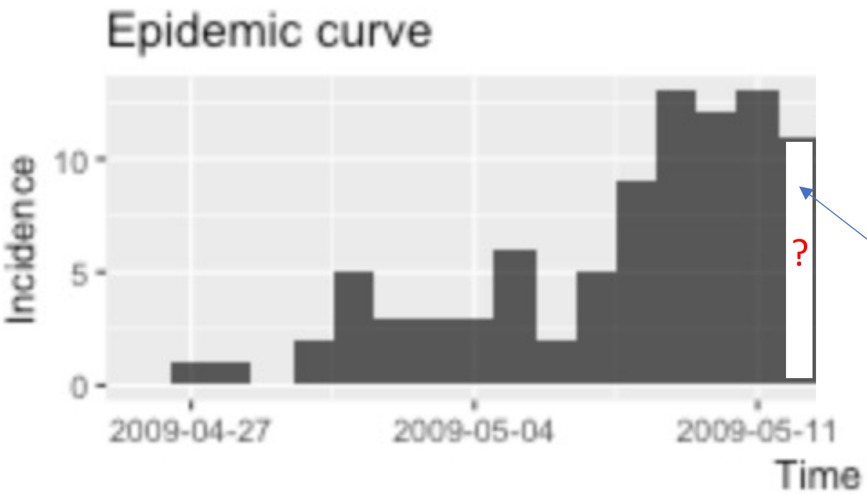
I_t cases

Draw from Poisson distribution or NB distribution

Renewal equation models

Can account for super-spreading events





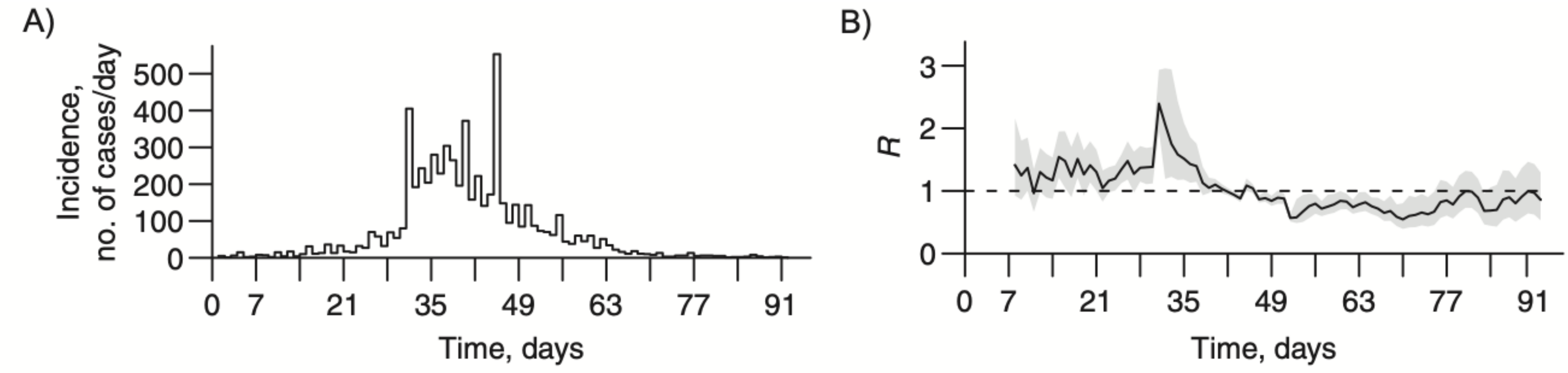
I_t cases

Draw from Poisson distribution or NB distribution

Renewal equation models

Commonly used to infer R_t

(more later in talk)



Outline

1. Introduction to common infectious disease outbreak models

- Compartmental models
- Renewal equation models

2. Early in an outbreak: Assessing the risk of major epidemics

- Estimating the probability of a major epidemic [stochastic compartmental model]
- Possible mini project

3. During an epidemic: Assessing the effectiveness of current interventions

- Inferring current transmissibility [renewal equation model]
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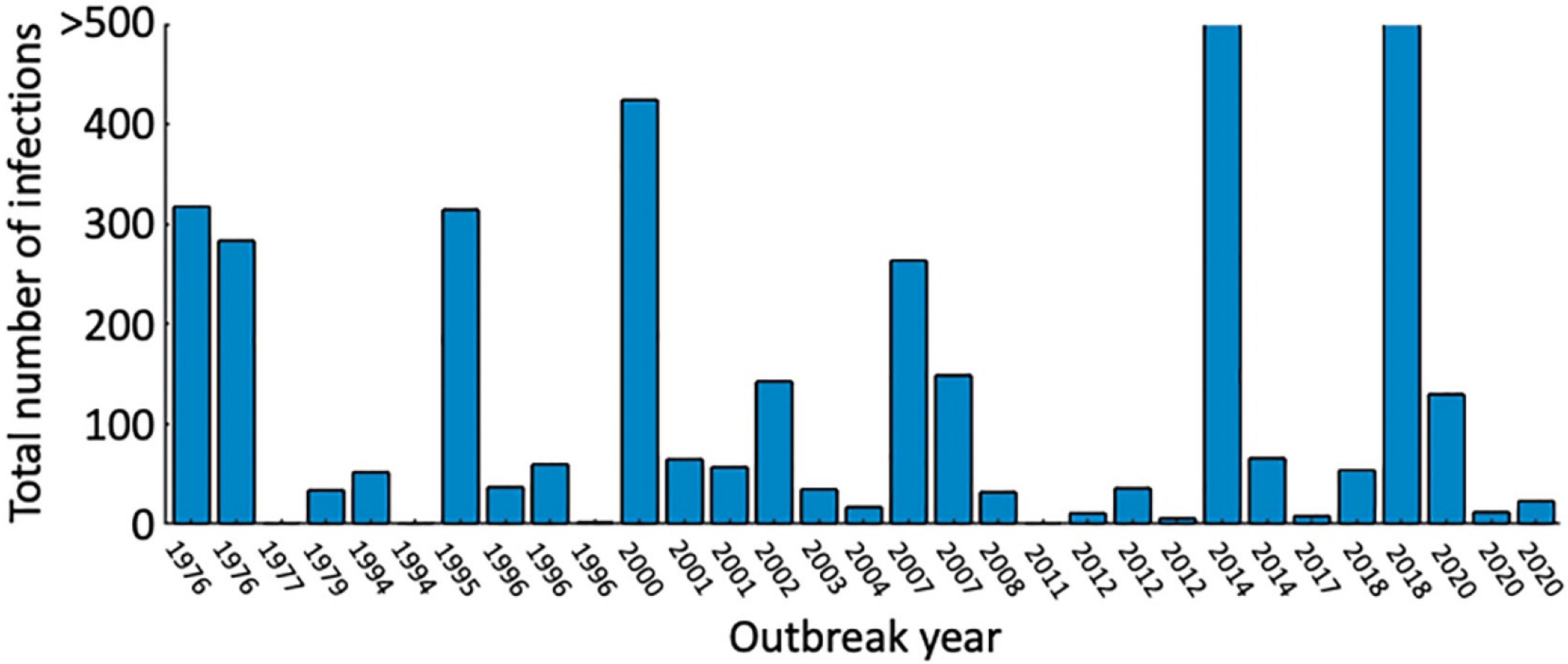
4. At the end of an epidemic: Assessing when the epidemic is over

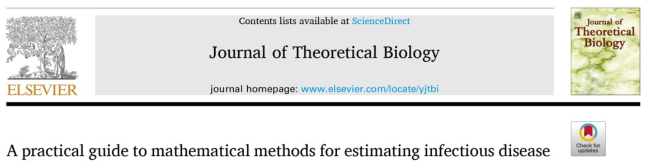
- End-of-outbreak probability estimation [compartmental model and renewal equation model]
- Possible mini project

Early in an outbreak

When a pathogen first arrives in a new host population,
will initial cases fade out, or will they lead to a major epidemic?

Assessing the risk of a major epidemic





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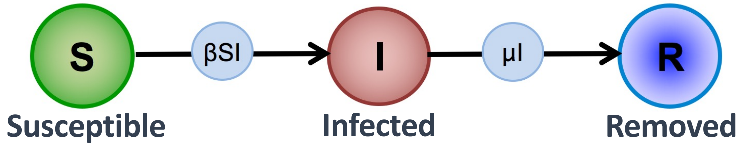
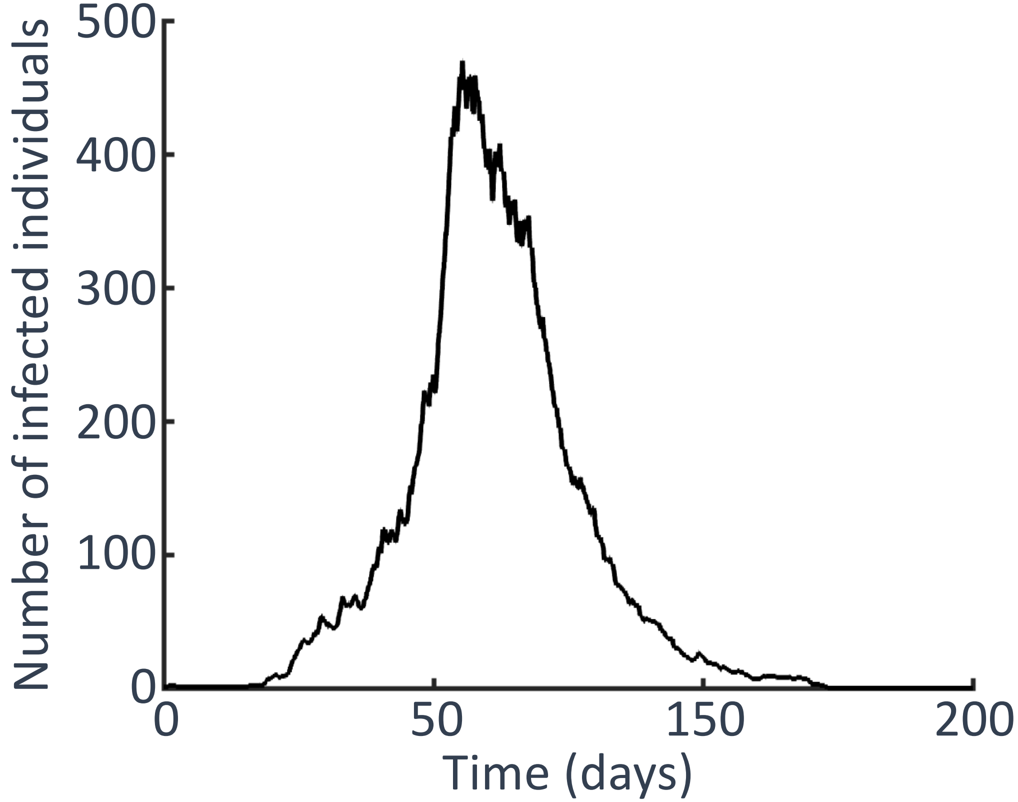
A practical guide to mathematical methods for estimating infectious disease outbreak risks

E. Southall [a,b], Z. Ogi-Gittins [a,b], A.R. Kaye [a,b], W.S. Hart [c], F.A. Lovell-Read [c], R.N. Thompson [a,b,*]

Assessing the risk of a major epidemic



When a pathogen first arrives in a new population, there are two possibilities for what happens next



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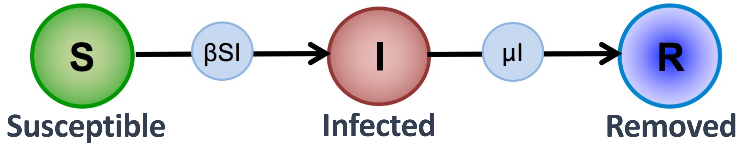

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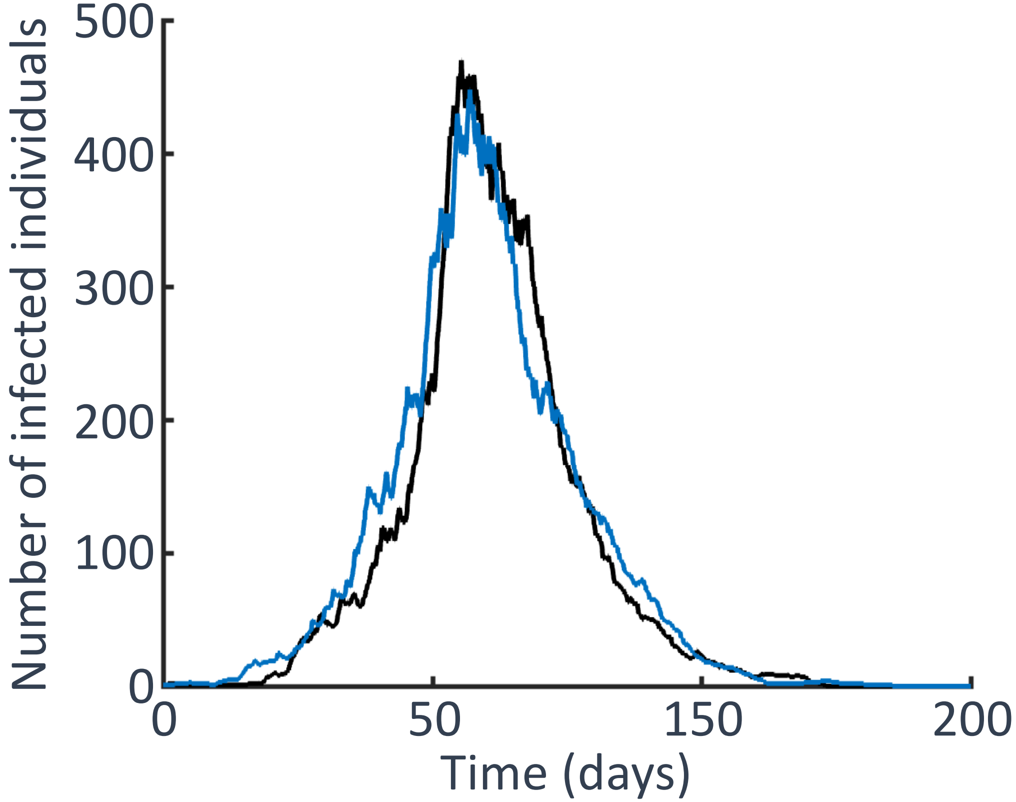

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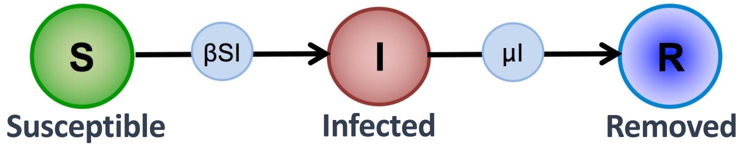

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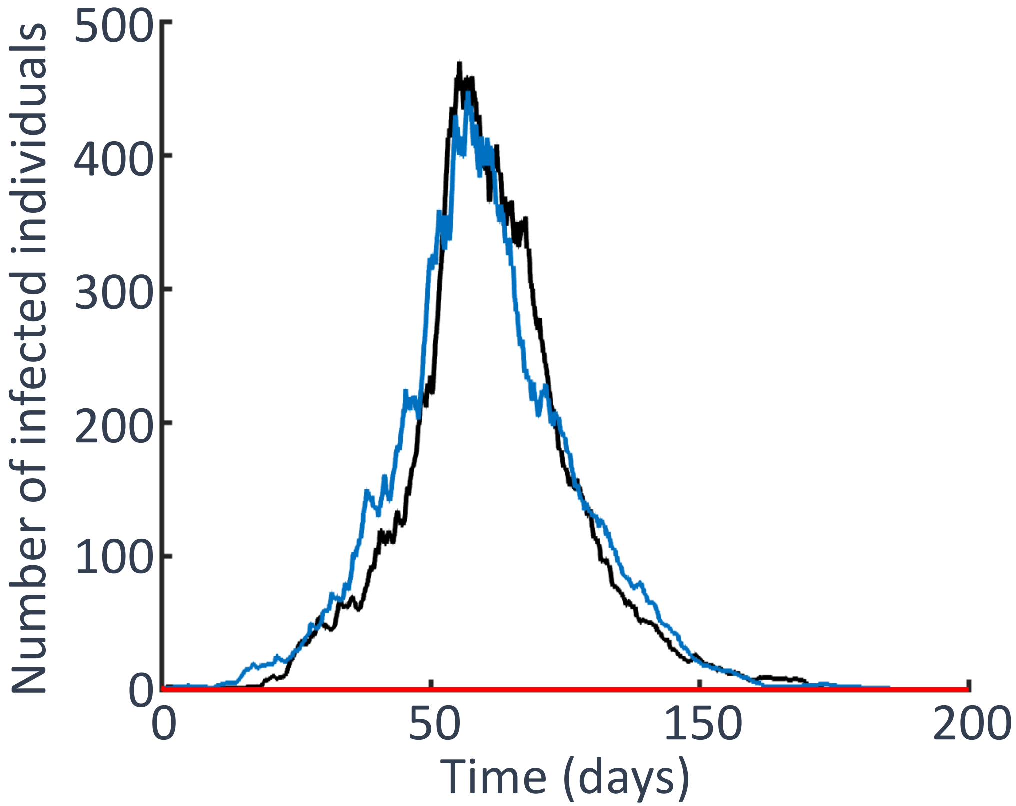

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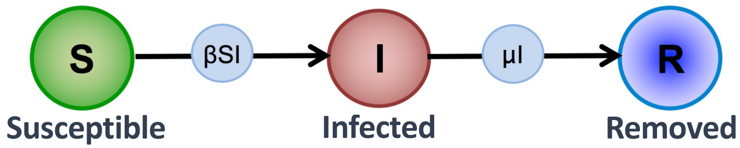
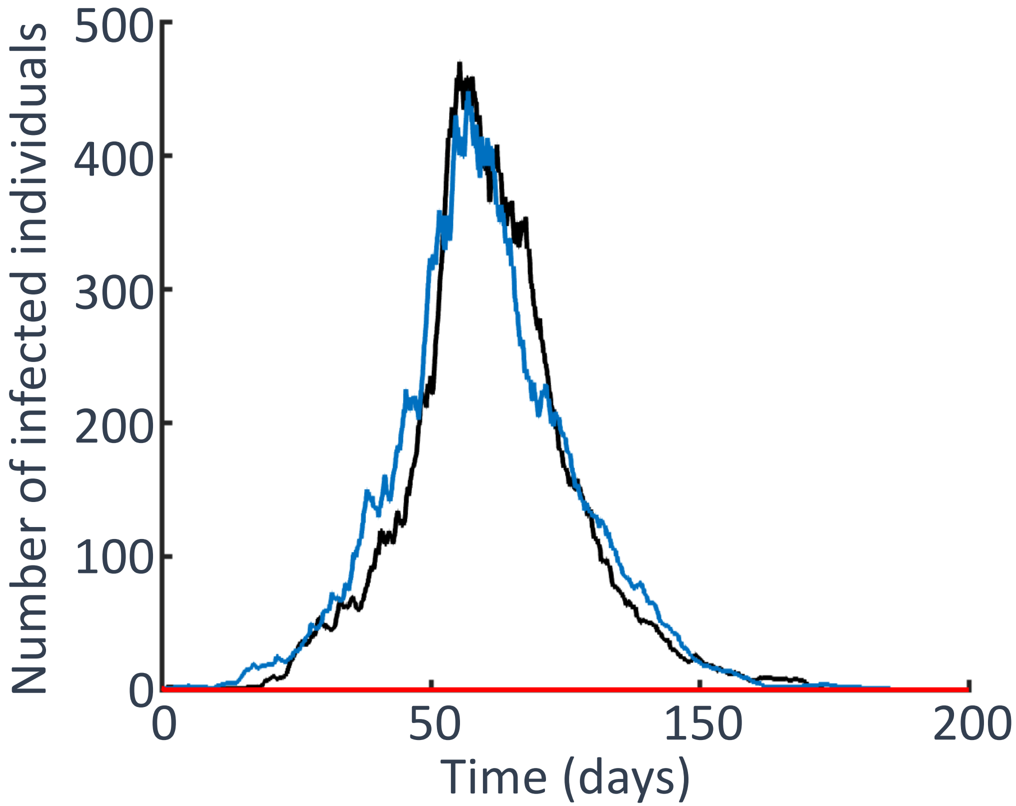
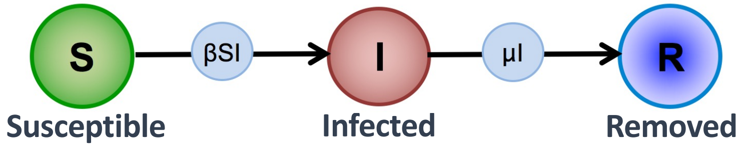




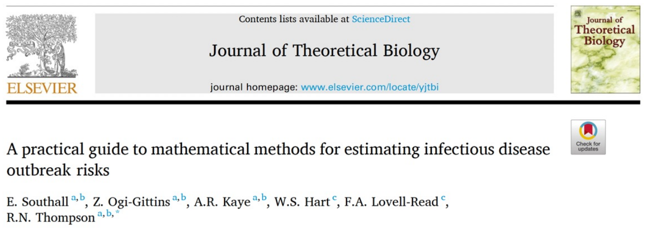
Epidemic Risk: the probability that an imported case leads to a major epidemic

If ER = 0; a major epidemic will not occur
If ER = 1; a major epidemic will definitely occur

Assessing the risk of a major epidemic



- Assume we start with one infected individual
- Denote q_i = Prob(no major epidemic starting from *i* infected individuals)
- Want to find $1 - q_1$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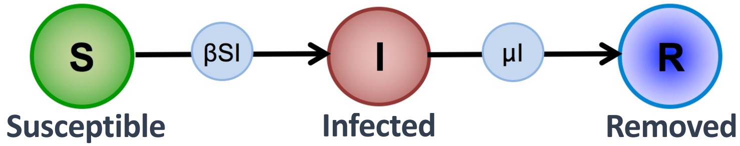
A practical guide to mathematical methods for estimating infectious disease outbreak risks

E. Southall[a,b], Z. Ogi-Gittins[a,b], A.R. Kaye[a,b], W.S. Hart[c], F.A. Lovell-Read[c], R.N. Thompson[a,b,*]

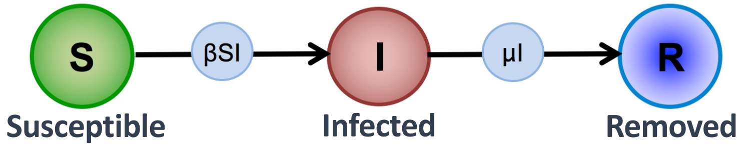
Assessing the risk of a major epidemic



Two possibilities for the next event: infection or recovery

$$q_1 = \mathbb{P}(\text{infection}) \times q_2 + \mathbb{P}(\text{recovery}) \times q_0$$

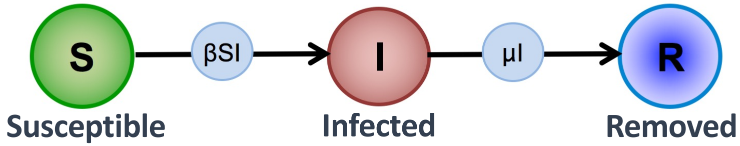
Assessing the risk of a major epidemic



Two possibilities for the next event: infection or recovery

$$q_1 \approx \mathbb{P}(\text{infection}) \times {q_1}^2 + \mathbb{P}(\text{recovery})$$

Assessing the risk of a major epidemic



Two possibilities for the next event: infection or recovery

$$q_1 \approx \mathbb{P}(\text{infection}) \times {q_1}^2 + \mathbb{P}(\text{recovery})$$

$$q_1 = \frac{1}{R_e} \text{ or } 1 \qquad ER = 1 - q_1 = 1 - \frac{1}{R_e}$$

INTERFACE

royalsocietypublishing.org/journal/rsif

Research

Will an outbreak exceed available resources for control? Estimating the risk from invading pathogens using practical definitions of a severe epidemic

R. N. Thompson[1,2], C. A. Gilligan[3] and N. J. Cunniffe[3]

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journal homepage: www.elsevier.com/locate/yjtbi

A practical guide to mathematical methods for estimating infectious disease outbreak risks

E. Southall[a,b], Z. Ogi-Gittins[a,b], A.R. Kaye[a,b], W.S. Hart[c], F.A. Lovell-Read[c], R.N. Thompson[a,b,*]

INTERFACE

royalsocietypublishing.org/journal/rsif

Research

Interventions targeting non-symptomatic cases can be important to prevent local outbreaks: SARS-CoV-2 as a case study

Francesca A. Lovell-Read[1,†], Sebastian Funk[3], Uri Obolski[4,5], Christl A. Donnelly[2,6] and Robin N. Thompson[1,3,7,8]

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Estimating local outbreak risks and the effects of non-pharmaceutical interventions in age-structured populations: SARS-CoV-2 as a case study

Francesca A. Lovell-Read[a,*], Silvia Shen[a,b], Robin N. Thompson[c,d]

PLOS | COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Detecting Presymptomatic Infection Is Necessary to Forecast Major Epidemics in the Earliest Stages of Infectious Disease Outbreaks

Robin N. Thompson*, Christopher A. Gilligan, Nik J. Cunniffe

Sustained transmission of Ebola in new locations: more likely than previously thought

THE LANCET Infectious Diseases

*Robin N Thompson, Katri Jalava, *Uri Obolski*

INTERFACE

royalsocietypublishing.org/journal/rsif

Research

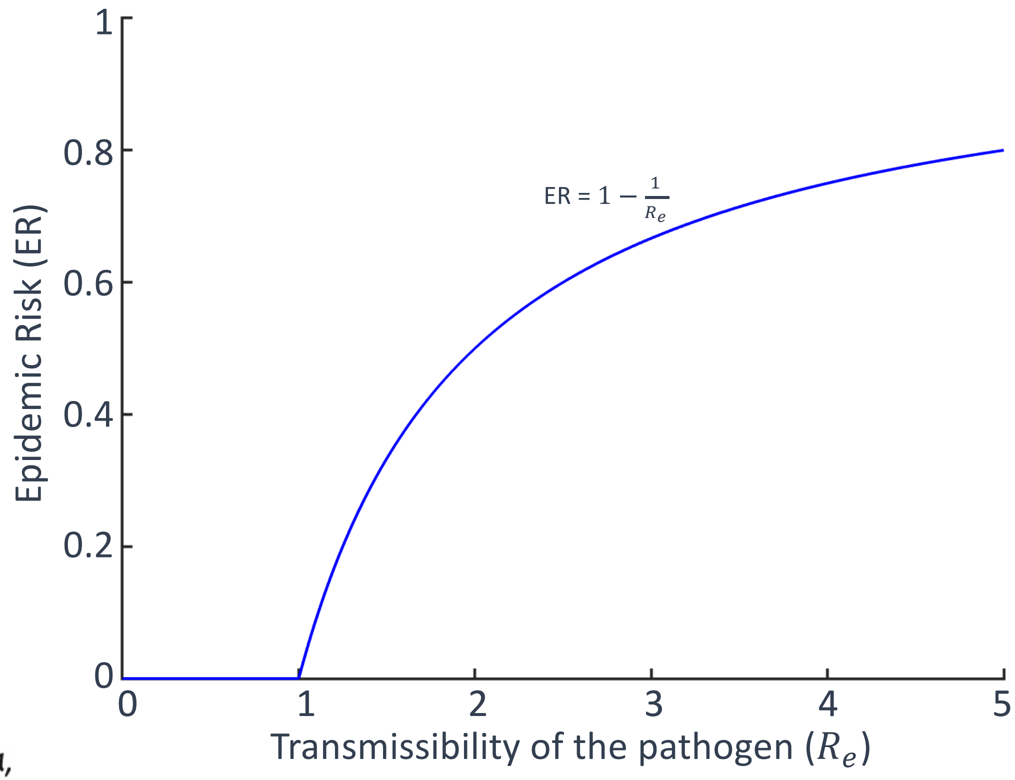
Reducing transmission in multiple settings is required to eliminate the risk of major Ebola outbreaks: a mathematical modelling study

Abbie Evans[1], William Hart[1], Stefano Longobardi[2], Rajat Desikan[3], Anna Sher[4] and Robin Thompson[1]

PLOS | COMPUTATIONAL BIOLOGY

Quantifying infectious disease epidemic risks: A practical approach for seasonal pathogens

Alexander R Kaye, Giorgio Guzzetta, Michael J Tildesley, Robin N Thompson



Heterogeneity in reporting rates

$q_{i,j}$ = Prob(no major epidemic | i fast reporters, j slow reporters)

$$q_{1,0} = \frac{\alpha\beta}{\beta+\gamma^{(1)}} q_{2,0} + \frac{(1-\alpha)\beta}{\beta+\gamma^{(1)}} q_{1,1} + \frac{\gamma^{(1)}}{\beta+\gamma^{(1)}} q_{0,0},$$

$$q_{0,1} = \frac{\alpha\beta}{\beta+\gamma^{(2)}} q_{1,1} + \frac{(1-\alpha)\beta}{\beta+\gamma^{(2)}} q_{0,2} + \frac{\gamma^{(2)}}{\beta+\gamma^{(2)}} q_{0,0}.$$

Journal of *Clinical Medicine*

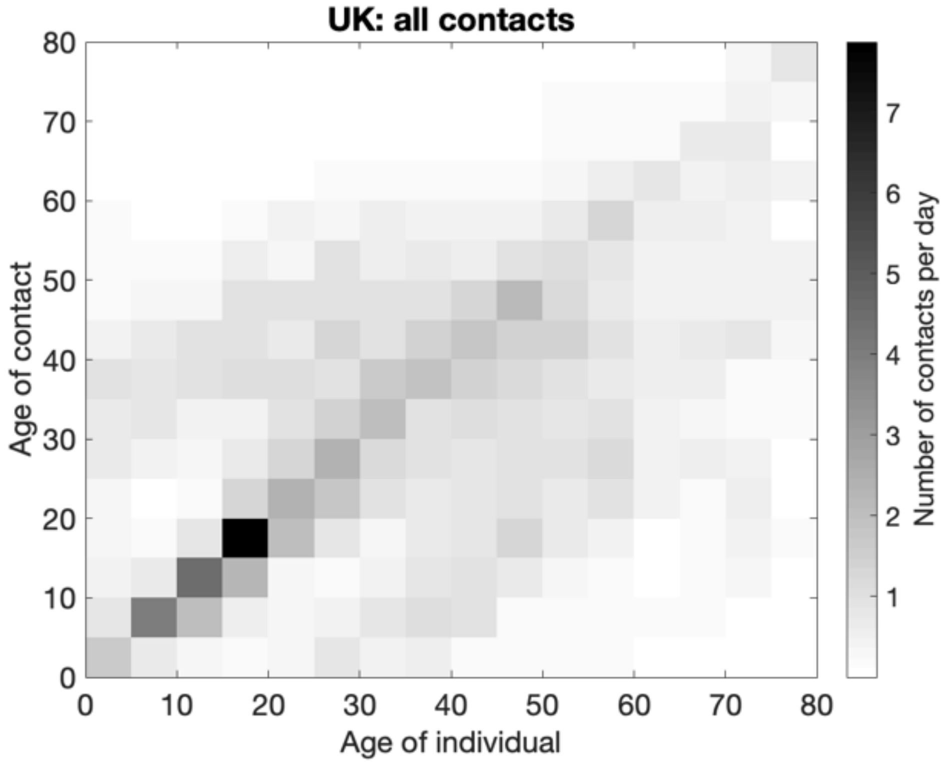
Article

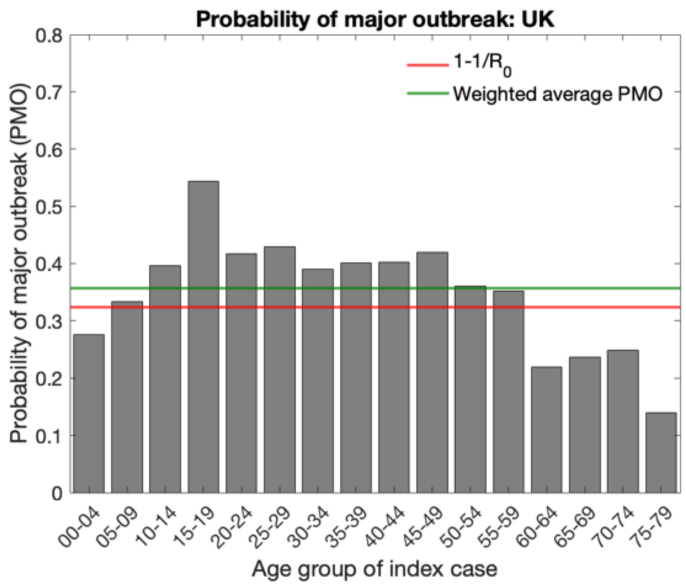
Novel Coronavirus Outbreak in Wuhan, China, 2020: Intense Surveillance Is Vital for Preventing Sustained Transmission in New Locations

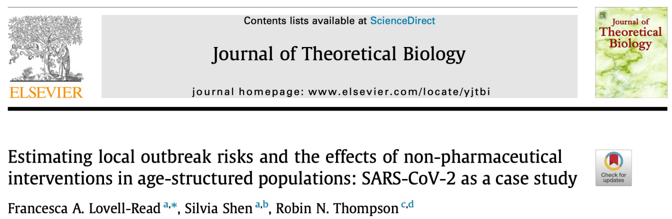
Robin N. Thompson [1,2]

Age structure

$$q_{i,j,k,\ldots} = \text{Prob}(\text{no major epidemic} \mid i \text{ in age group } 1, j \text{ in age group } 2, k \text{ in age group } 3, \ldots.)$$



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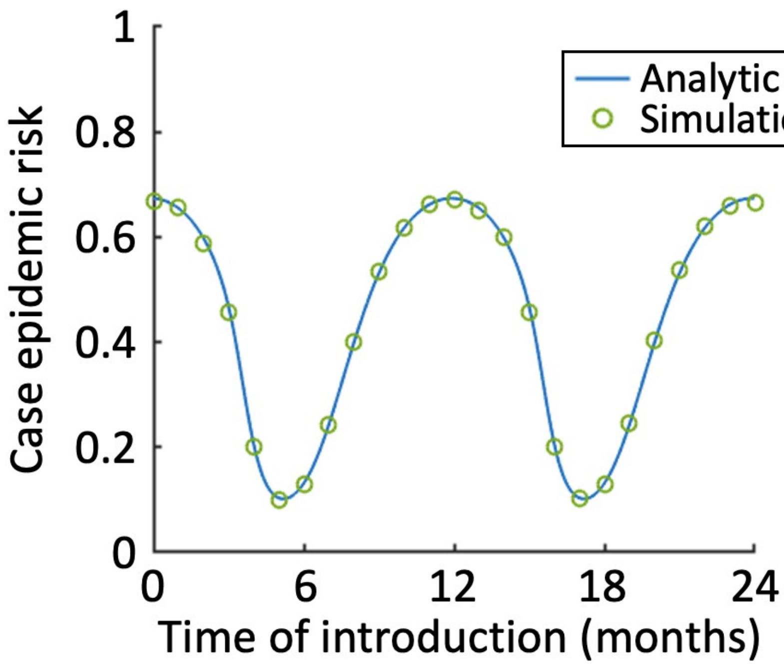
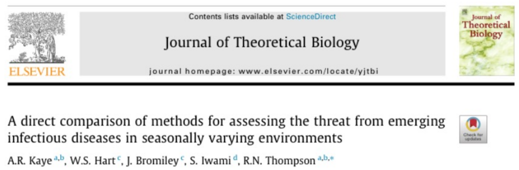
Time-dependence

$$q(1,t) = q(2,t+\Delta t)\beta(t)N\Delta t + q(0,t+\Delta t)\mu\Delta t + q(1,t+\Delta t)(1-\beta(t)N\Delta t - \mu\Delta t).$$

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ELSEVIER

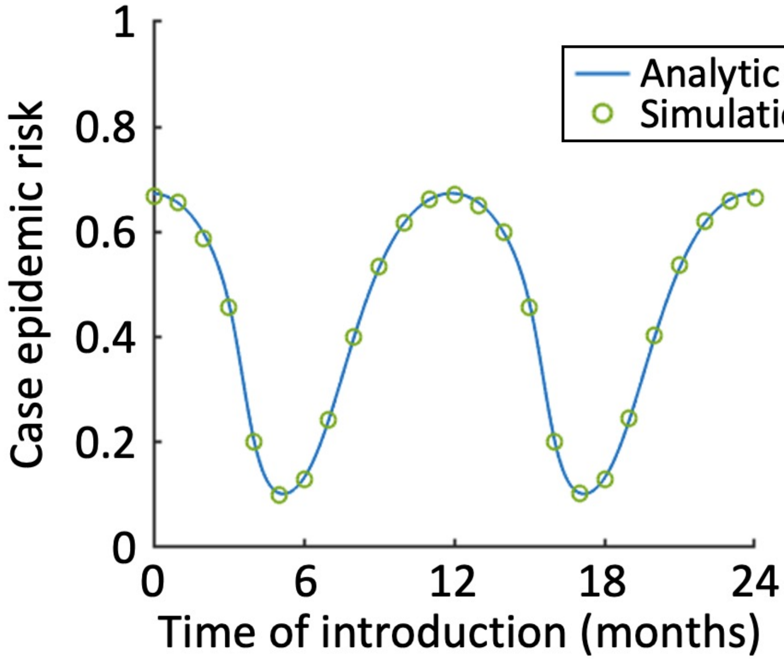
A direct comparison of methods for assessing the threat from emerging infectious diseases in seasonally varying environments

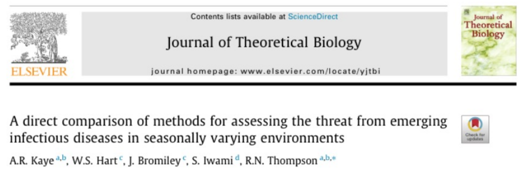
A.R. Kaye [a,b], W.S. Hart [c], J. Bromiley [c], S. Iwami [d], R.N. Thompson [a,b,*]

Time-dependence

$$q(1,t) = q(2,t+\Delta t)\beta(t)N\Delta t + q(0,t+\Delta t)\mu\Delta t + q(1,t+\Delta t)(1-\beta(t)N\Delta t-\mu\Delta t).$$

$$\frac{\mathrm{d}q_1(t)}{\mathrm{d}t} = -\beta(t)q_1(t)^2 + (\beta(t)+\mu(t))q_1(t) - \mu(t).$$





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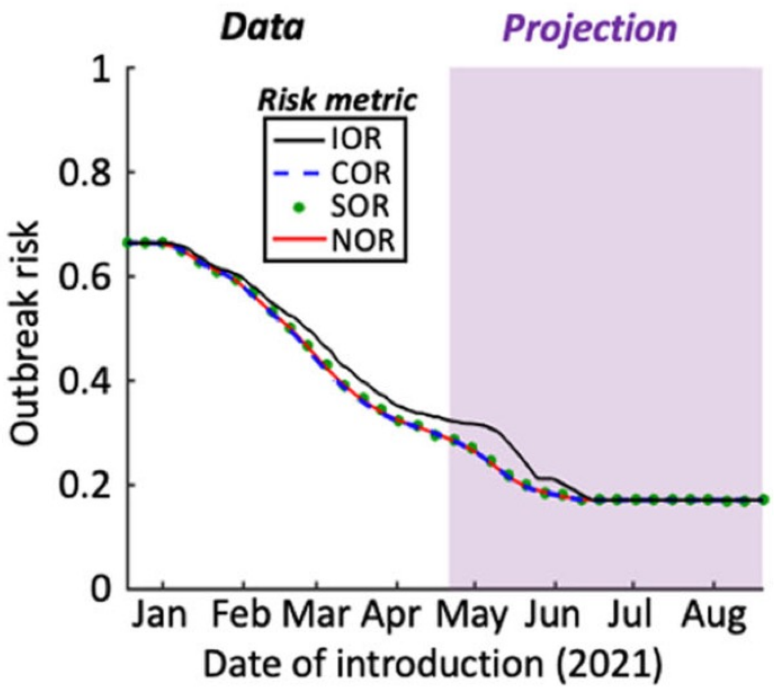
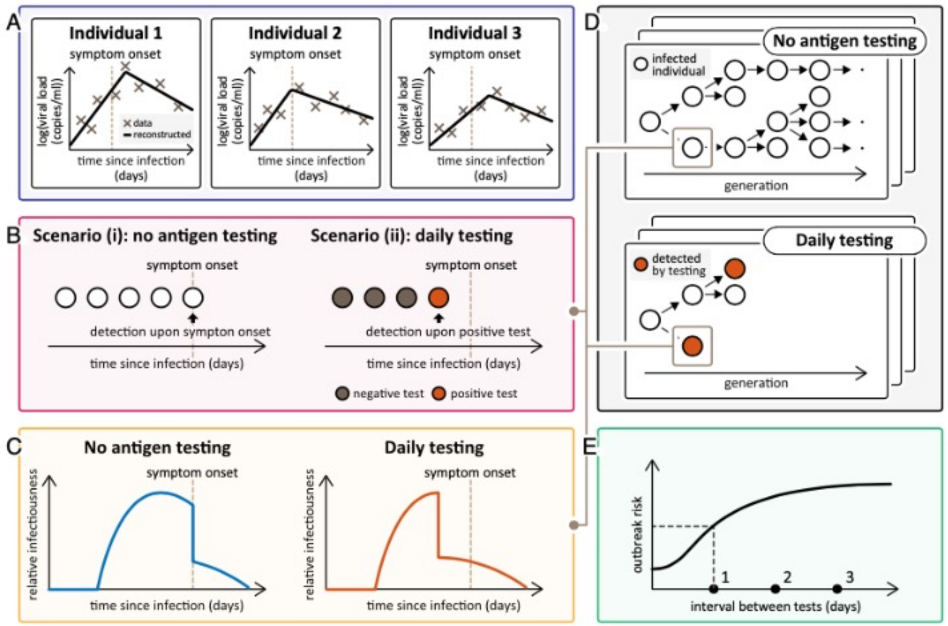
A.R. Kaye [a,b], W.S. Hart [c], J. Bromiley [c], S. Iwami [d], R.N. Thompson [a,b,*]

Other factors (vaccination, within-host dynamics)





communications
medicine

ARTICLE

https://doi.org/10.1038/s43856-021-00038-8 OPEN

The risk of SARS-CoV-2 outbreaks in low prevalence settings following the removal of travel restrictions

Rahil Sachak-Patwa[1], Helen M. Byrne[1], Louise Dyson[2,3] & Robin N. Thompson[2,3]✉

PNAS RESEARCH ARTICLE | BIOPHYSICS AND COMPUTATIONAL BIOLOGY
APPLIED MATHEMATICS
OPEN ACCESS

Analysis of the risk and pre-emptive control of viral outbreaks accounting for within-host dynamics: SARS-CoV-2 as a case study

William S. Hart[a,b,1], Hyeongki Park[b], Yong Dam Jeong[b,c], Kwang Su Kim[b,d], Raiki Yoshimura[b], Robin N. Thompson[a,e,f,2], and Shingo Iwami[b,g,h,i,j,k,2]

Assessing Epidemic Risks – Summary

Stochastic compartmental models can be **used to estimate the Epidemic Risk** (the probability that an imported case leads to a major epidemic)

Epidemic Risk estimates can be **generated analytically**, informed by using outbreak data, and **adjusted in real-time**

Estimates can be extended to include a range of features, **including heterogeneity in reporting rates, age structure and temporal heterogeneity**

Possible mini project

1. Using mathematical models to estimate outbreak risks

- Read “A practical guide to mathematical models for estimating infectious disease outbreak risks” by Southall *et al.*

- Derive the probability of a major outbreak starting from 1 infected individual for the stochastic SIR model (the “theoretical” result).

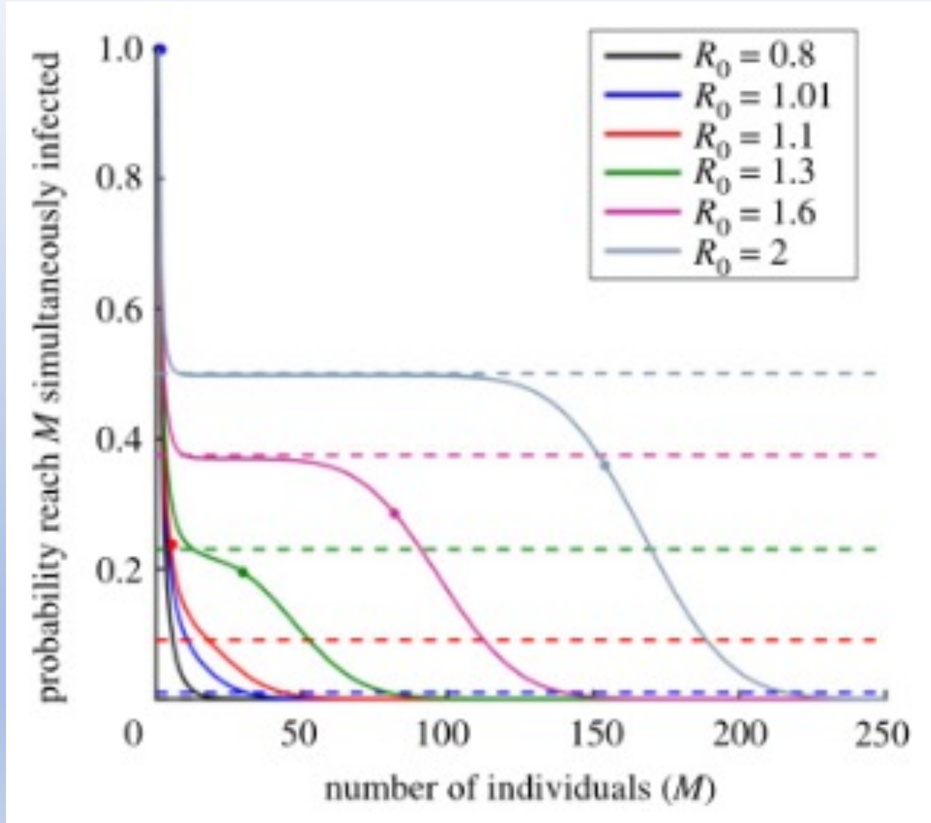
- Simulate the stochastic SIR model lots of times (each time starting from 1 infected individual), and calculate the proportion of simulations that are “major outbreaks” according to a definition of your choice (e.g. total number of infections exceeding 50 before disease dies out and I hits 0).

- Consider different possible definitions of a major outbreak, and investigate when the simulation-based probability of a major outbreak is matched by the theoretical value.

Possible definitions include: total infections exceeding x, maximum concurrent *I* exceeding x, outbreak lasting for more than x days, etc….

Possible mini project

Possible plot:



Possible mini project

2. Using mathematical models to estimate outbreak risks

- Read "A practical guide to mathematical models for estimating infectious disease outbreak risks" by Southall *et al.*

- Derive the probability of a major outbreak starting from 1 infected for the stochastic SIR model. Test against model simulations (proportion of simulations in which at least 50 infections occur, say). Plot the probability of a major outbreak as a function of R_0.

- Derive the probability of a major outbreak for another model of your choice – for example, the children-adults model in Southall *et al.* (section 4.2 of that paper; can you reproduce Fig 4?).

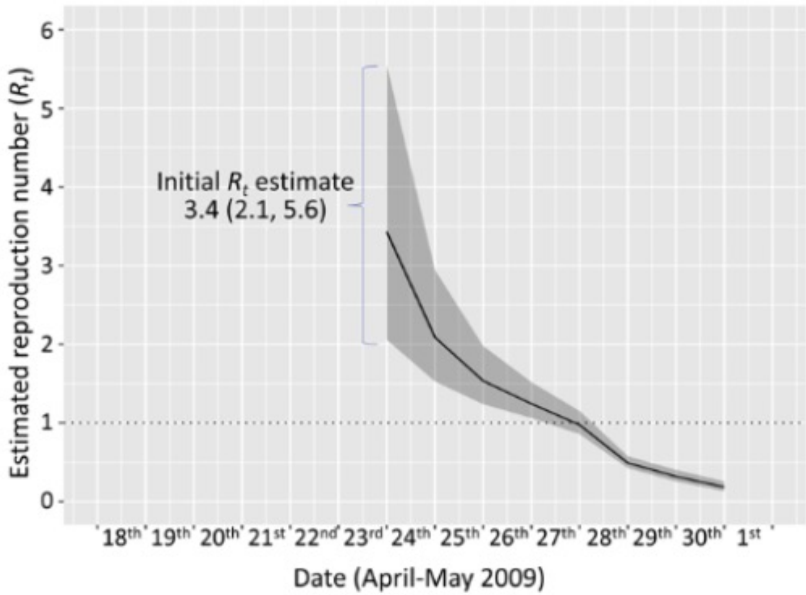
- Longer term extension: Consider the probability of a major outbreak for a model with multiple age groups (derive equations, solve them numerically). Contact matrices that can be used to inform infection rates between ages are available for different countries in the supplementary material of "Projecting social contact matrices in 152 countries using contact surveys and demographic data" by Prem *et al.*

Outline

1. Introduction to common infectious disease outbreak models
   - Compartmental models
   - Renewal equation models
2. Early in an outbreak: Assessing the risk of major epidemics
   - Estimating the probability of a major epidemic [stochastic compartmental model]
   - Possible mini project
3. During an epidemic: Assessing the effectiveness of current interventions
   - Inferring current transmissibility [renewal equation model]
   - Possible mini project
4. At the end of an epidemic: Assessing when the epidemic is over
   - End-of-outbreak probability estimation [compartmental model and renewal equation model]
   - Possible mini project

During an outbreak

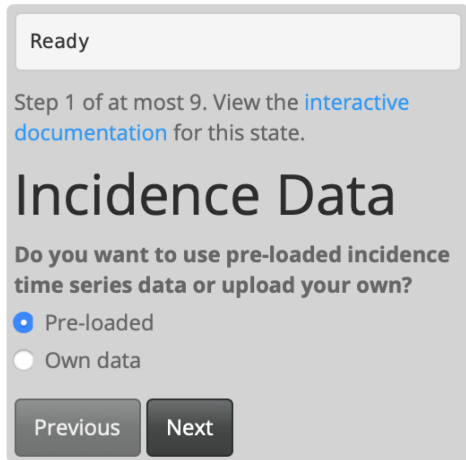
Can we quantify pathogen transmissibility in real-time?



$$\mathbf{P}(I_{t-\tau}^{\mathrm{local}}, I_{t-\tau+1}^{\mathrm{local}}, \ldots, I_t^{\mathrm{local}} \mid I_0, \ldots, I_{t-\tau-1}, w_s, R_t) = \prod_{k=t-\tau}^{t} \frac{(R_t \Lambda_k(w_s))^{I_k^{\mathrm{local}}} \exp(-R_t \Lambda_k(w_s))}{I_k^{\mathrm{local}}!}$$

$$\mathbf{P}(R_t \mid I_0, I_1, I_2, \ldots, I_{t-\tau-1}, I_{t-\tau}^{\mathrm{local}}, I_{t-\tau+1}^{\mathrm{local}}, \ldots, I_t^{\mathrm{local}}, w_s)$$

$$\propto \mathbf{P}(I_{t-\tau}^{\mathrm{local}}, I_{t-\tau+1}^{\mathrm{local}}, \ldots, I_t^{\mathrm{local}} \mid I_0, \ldots, I_{t-\tau-1}, w_s, R_t)\mathbf{P}(R_t)$$



- **Estimating changes in disease transmissibility (to e.g. assess the efficacy of current interventions)**

Thompson *et al.*, Epidemics, 2019

Two important quantities

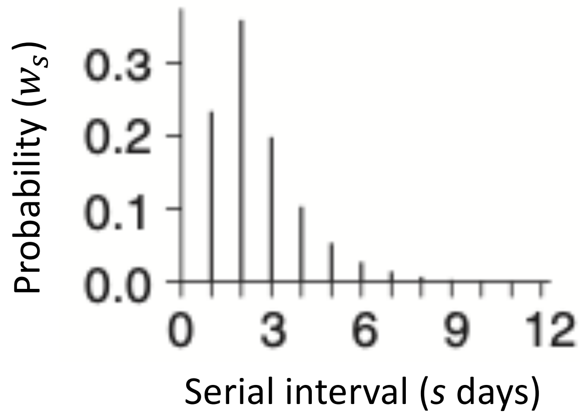
Time dependent reproduction number

R_t

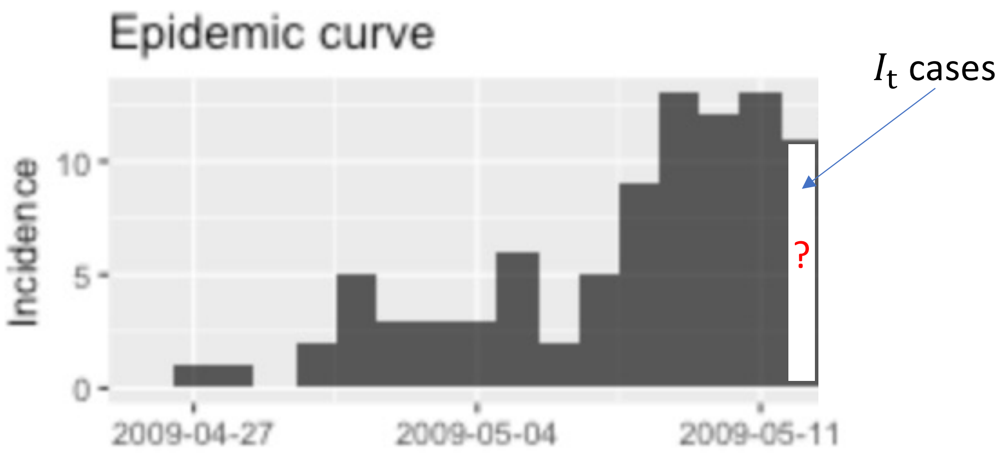
Definition

Threshold

Generation time/ serial interval

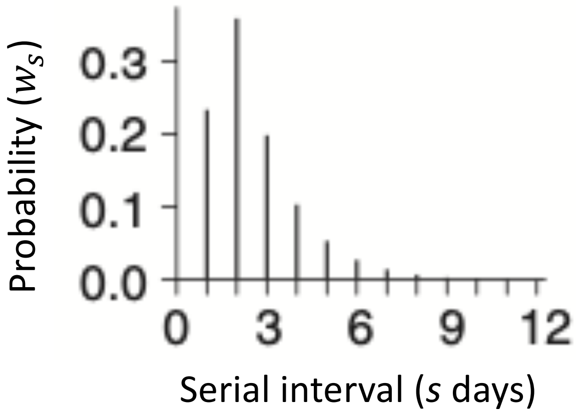


Renewal equation model



Know

R_t &

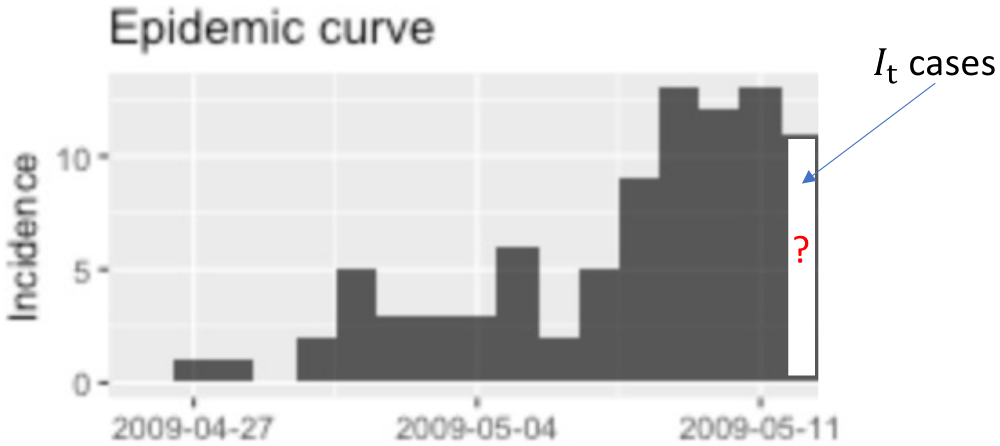


Basic model

$$\mathrm{E}(I_t \mid R_t, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\}) = R_t \sum_{s=1}^{t} I_{t-s} w_s$$

$$\mathrm{P}(I_t = x \mid R_t, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\}) = \frac{(\mathrm{E}(I_t))^x \exp(-\mathrm{E}(I_t))}{x!}$$

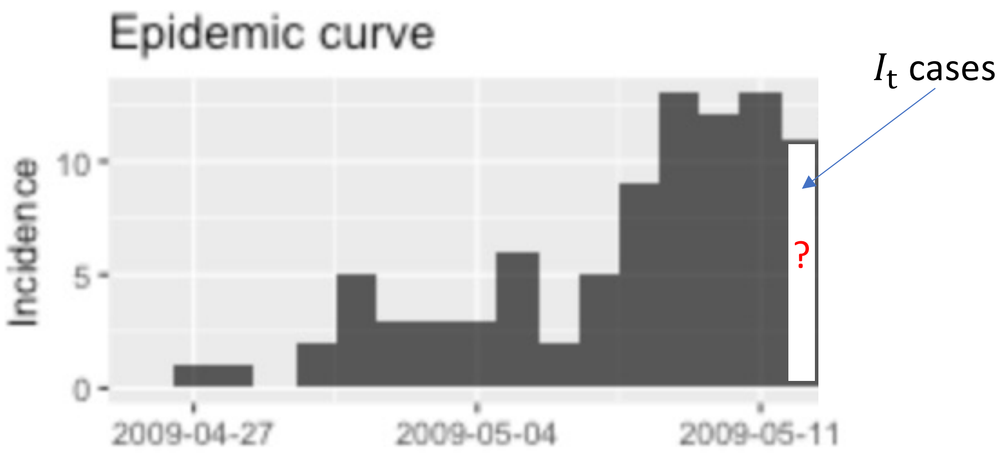
Cori *et al.*, Am. J. Epi., 2013



Bayes'rule: $\mathrm{P}(A \mid B) = \dfrac{\mathrm{P}(B \mid A)P(A)}{P(B)}$

$\mathrm{P}(I_t = x \mid R_t, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\})$ ⇒ $\mathrm{P}(R_t \mid I_t = x, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\})$

Cori *et al.*, Am. J. Epi., 2013

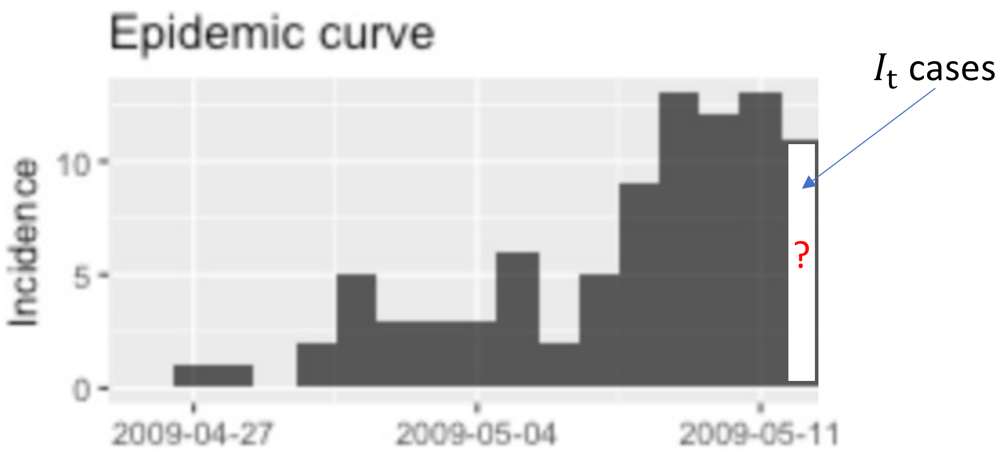


$$\text{Bayes' rule:} \quad \mathrm{P}(A \mid B) = \frac{\mathrm{P}(B \mid A)P(A)}{P(B)}$$

$$\mathrm{P}(I_t = x \mid R_t, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\}) \Rightarrow \mathrm{P}(R_t \mid I_t = x, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\})$$

Generates estimates of R_t that are highly sensitive to randomness in I_t
Solution: Consider constant R_t over a window $\{t-\tau, t-\tau+1, \dots t\}$

Cori *et al.*, Am. J. Epi., 2013

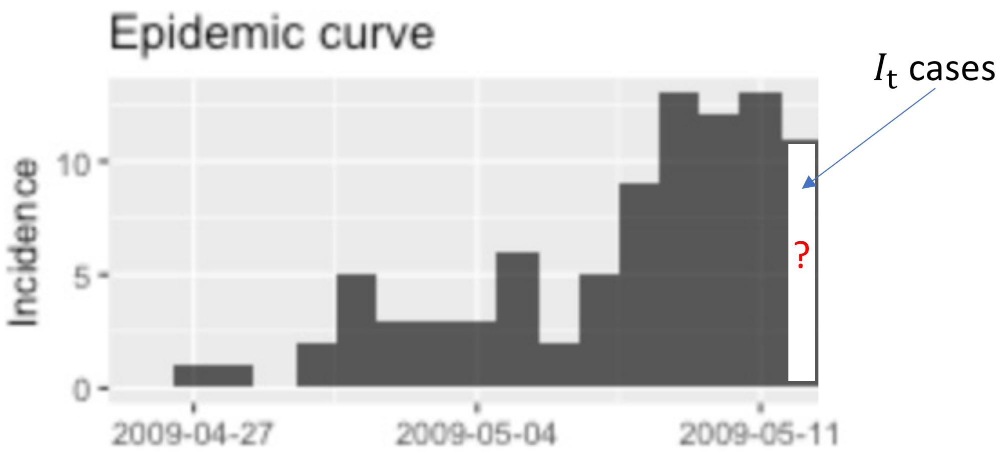


$$\text{Bayes' rule: } P(A \mid B) = \frac{P(B \mid A) P(A)}{P(B)}$$

$$P(I_{t-\tau} = x_{t-\tau}, \ldots, I_t = x_t \mid R_t, \{w_s\}, \{I_0, I_1, I_2, \ldots, I_{t-\tau-1}\}) \Rightarrow P(R_t \mid I_{t-\tau} = x_{t-\tau}, \ldots I_t = x_t, \{w_s\}, \{I_0, I_1, I_2, \ldots, I_{t-\tau-1}\})$$

Solution: Consider constant R_t over a window $\{t-\tau, t-\tau+1, \ldots t\}$

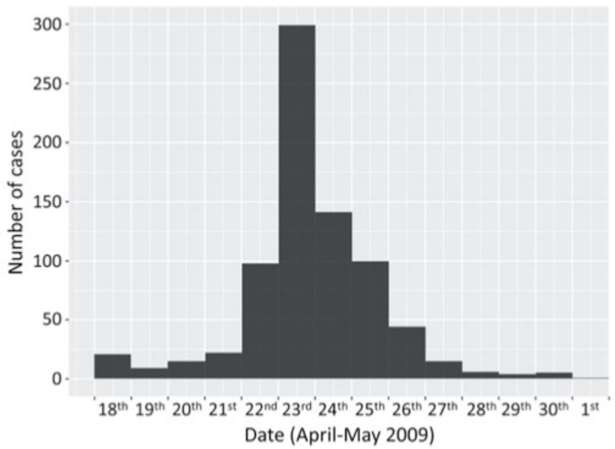
Cori *et al.*, Am. J. Epi., 2013

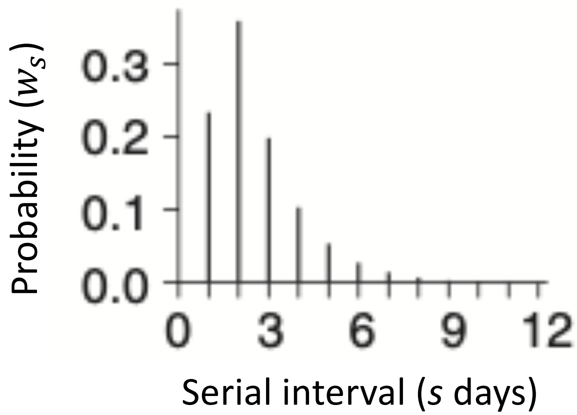


Special case: If the prior for R_t is a gamma distribution with shape parameter α and rate parameter β, then the posterior for R_t is also a gamma distribution with

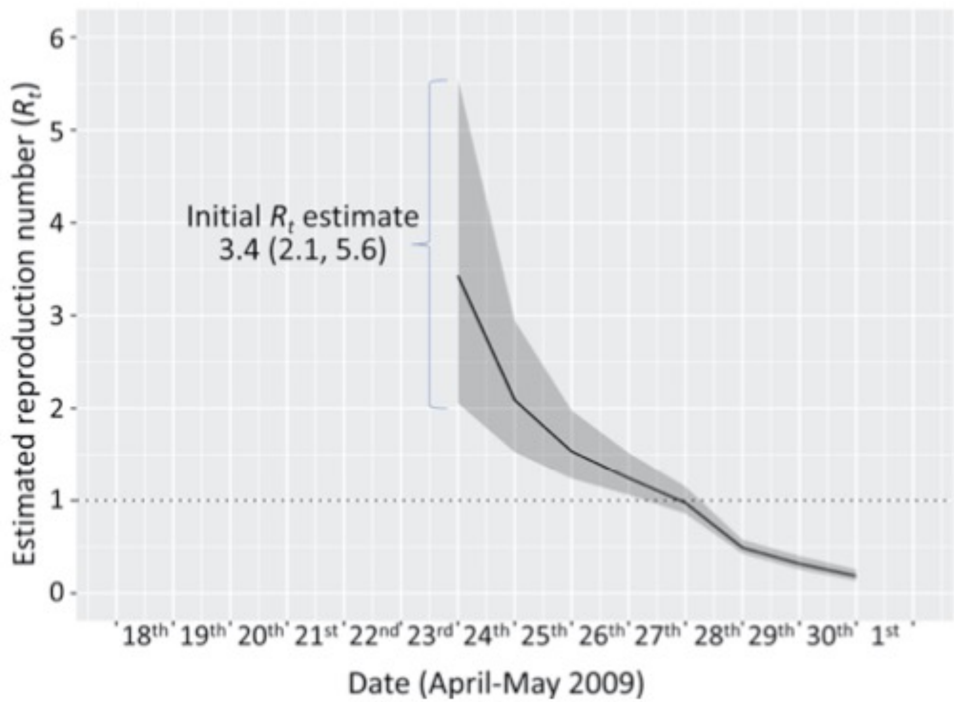
Shape parameter: $\alpha + \sum_{k=0}^{\tau} I_{t-k}$
Rate parameter: $\beta + \sum_{k=0}^{\tau} I_{t-k} \sum_{s=1}^{t-k-1} I_{t-k-s} w_s$

Cori *et al.*, Am. J. Epi., 2013



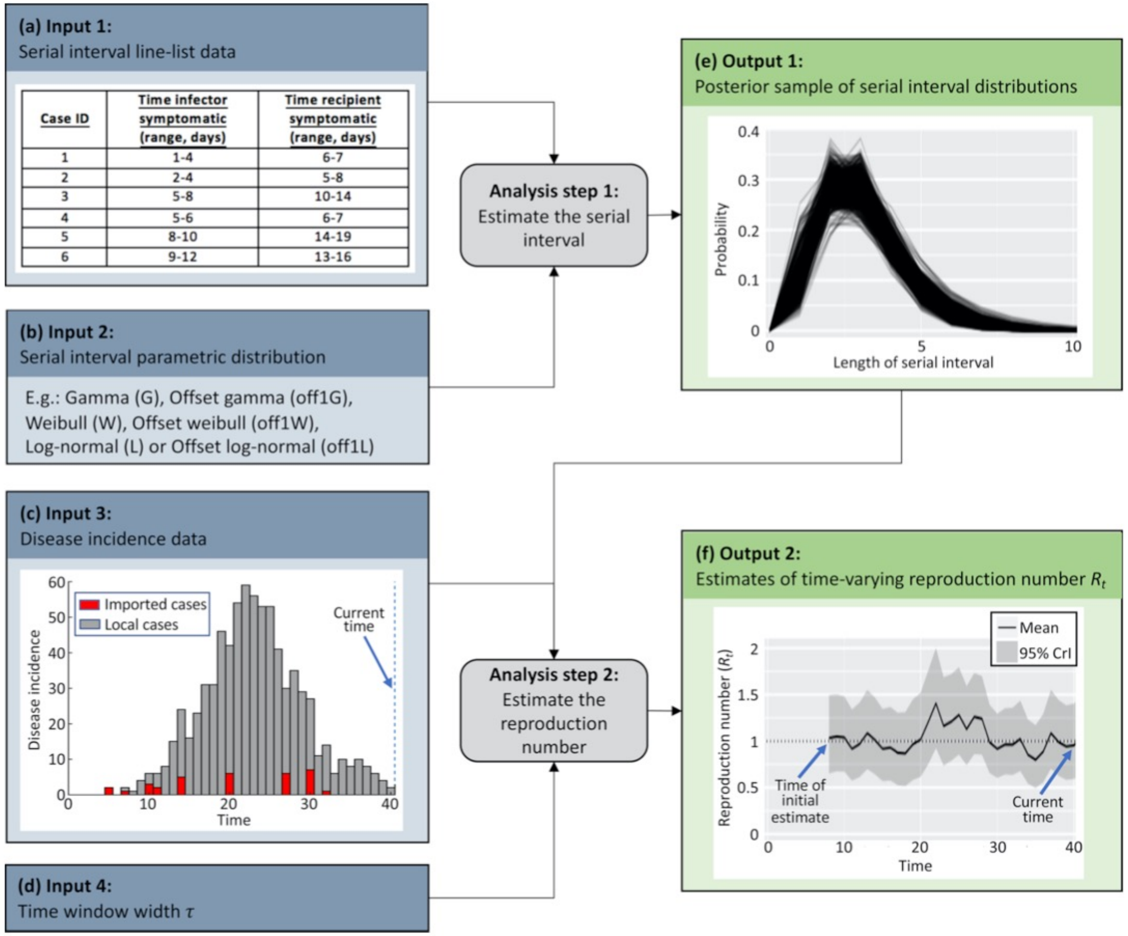


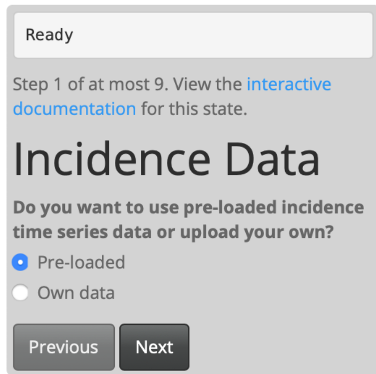
Window length: τ days



Cori *et al.*, Am. J. Epi., 2013
Thompson *et al.*, Epidemics, 2019

Uncertainty in the serial interval, imported cases

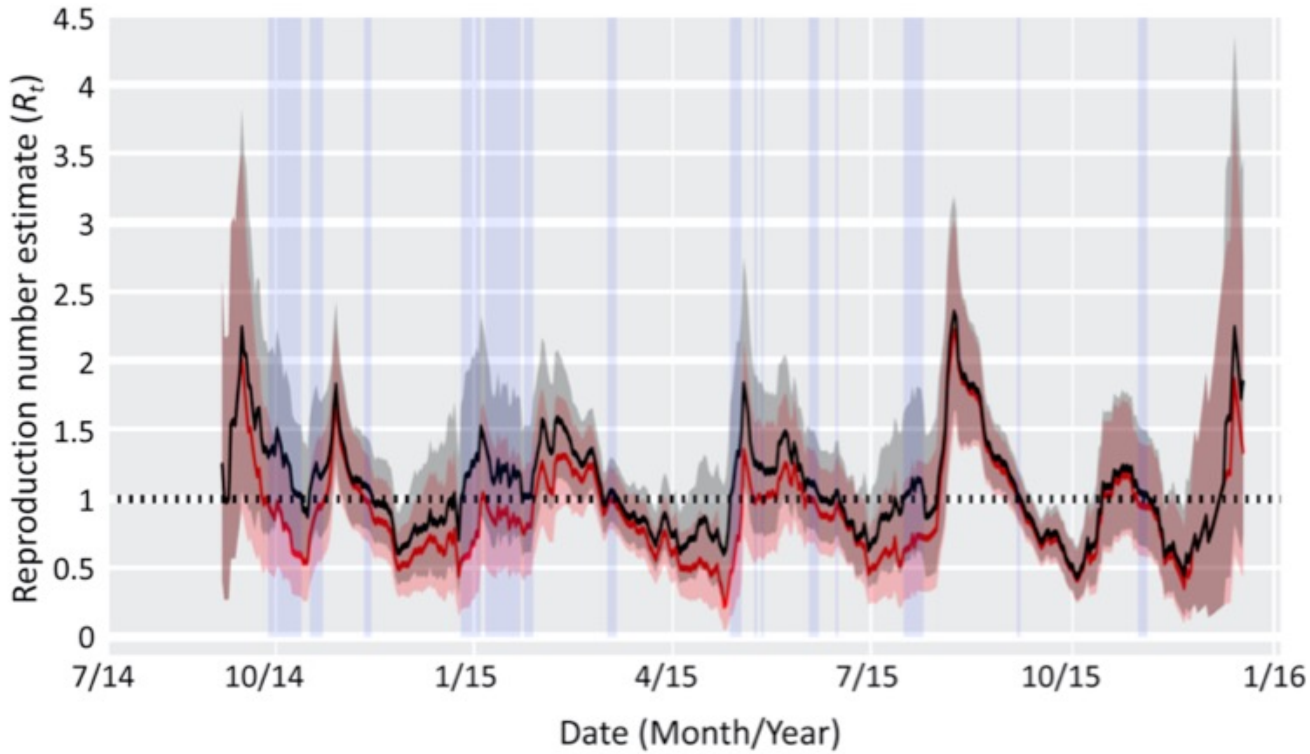




Thompson *et al.*, Epidemics, 2019

Imported cases

Imported cases have not been infected locally

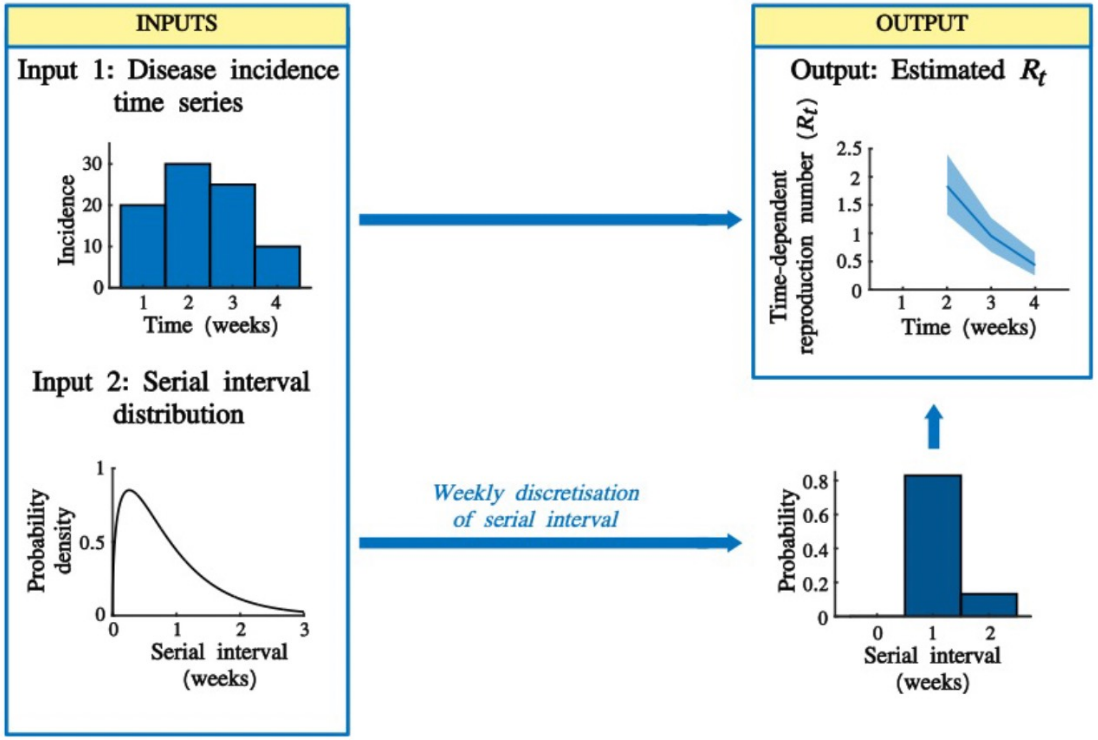


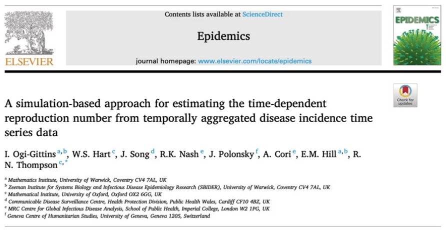
Thompson *et al.*, Epidemics, 2019

Temporally aggregated data

Data are often not reported daily

$$E(I_t \mid R_t, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\}) = R_t \sum_{s=1}^{t} I_{t-s} w_s$$

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Epidemics

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A simulation-based approach for estimating the time-dependent reproduction number from temporally aggregated disease incidence time series data

I. Ogi-Gittins [a,b], W.S. Hart [c], J. Song [d], R.K. Nash [e], J. Polonsky [f], A. Cori [e], E.M. Hill [a,b], R. N. Thompson [c,*]

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[b] Zeeman Institute for Systems Biology and Infectious Disease Epidemiology Research (SBIDER), University of Warwick, Coventry CV4 7AL, UK
[c] Mathematical Institute, University of Oxford, Oxford OX2 6GG, UK
[d] Communicable Disease Surveillance Centre, Health Protection Division, Public Health Wales, Cardiff CF10 4BZ, UK
[e] MRC Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College, London W2 1PG, UK
[f] Geneva Centre of Humanitarian Studies, University of Geneva, Geneva 1205, Switzerland

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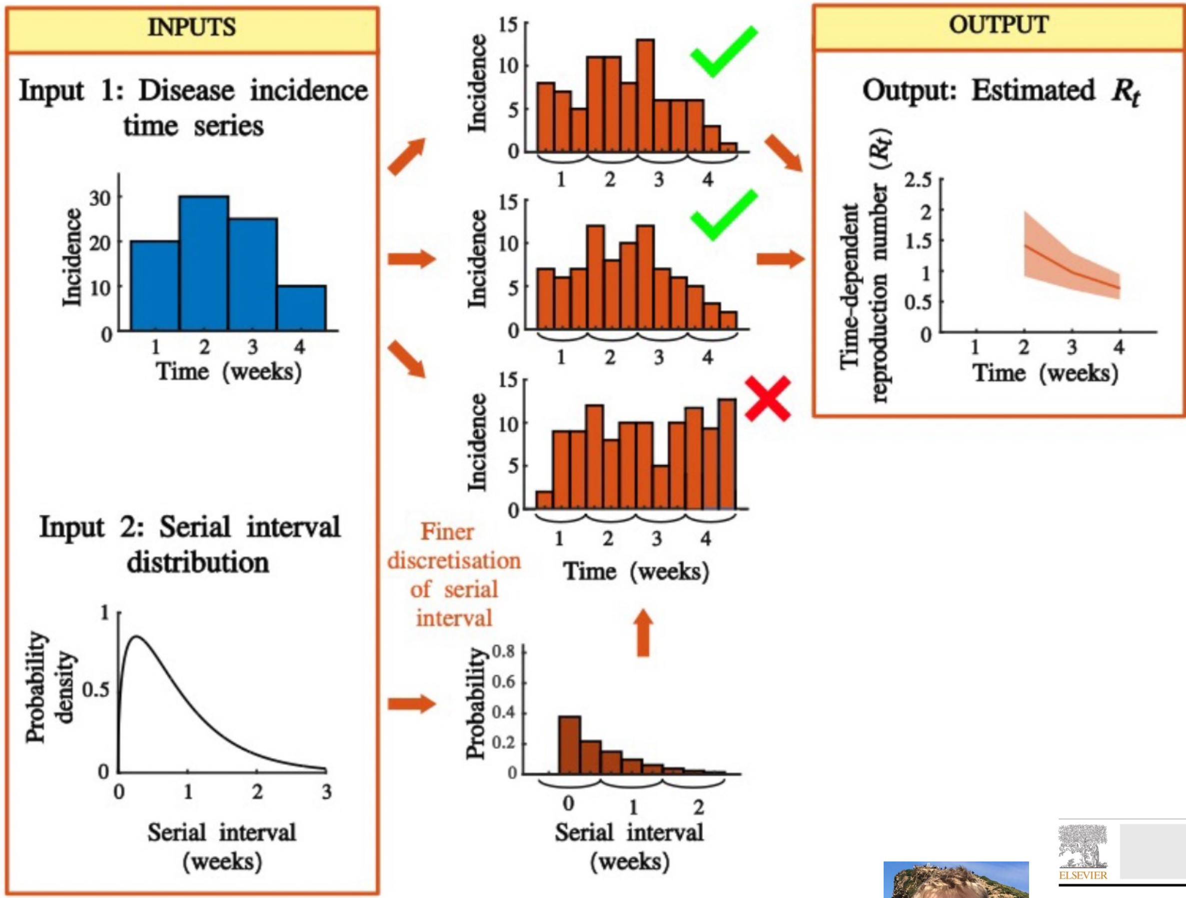

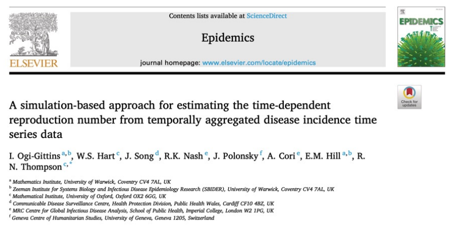
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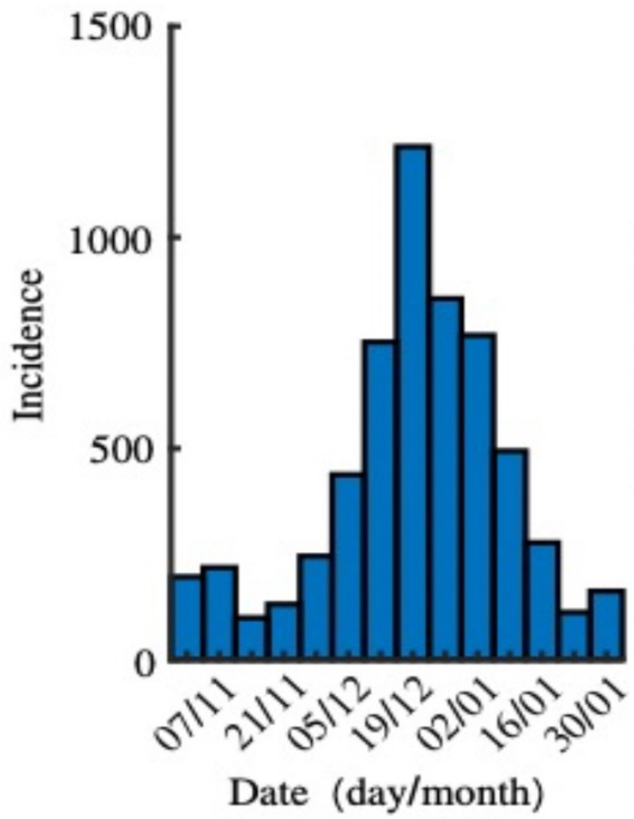

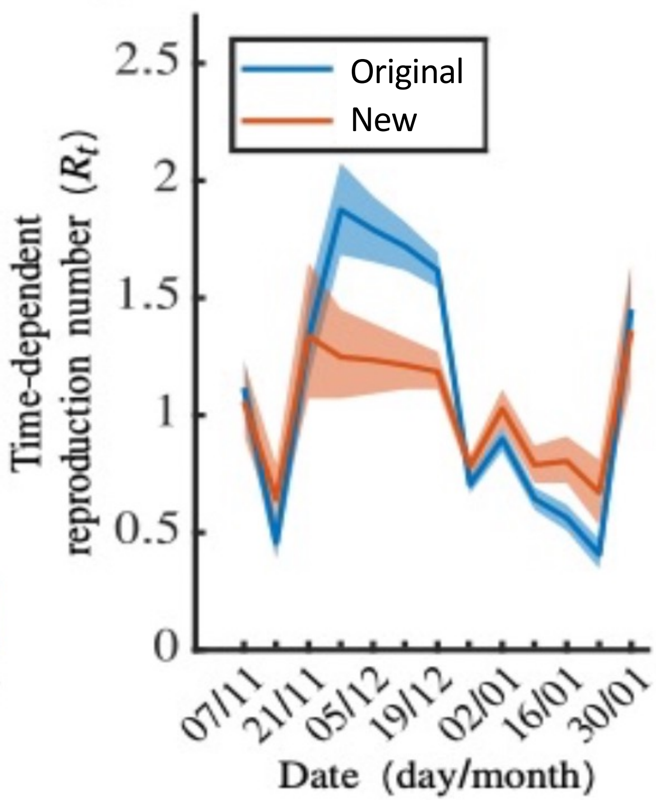

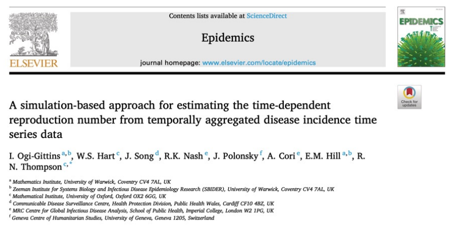
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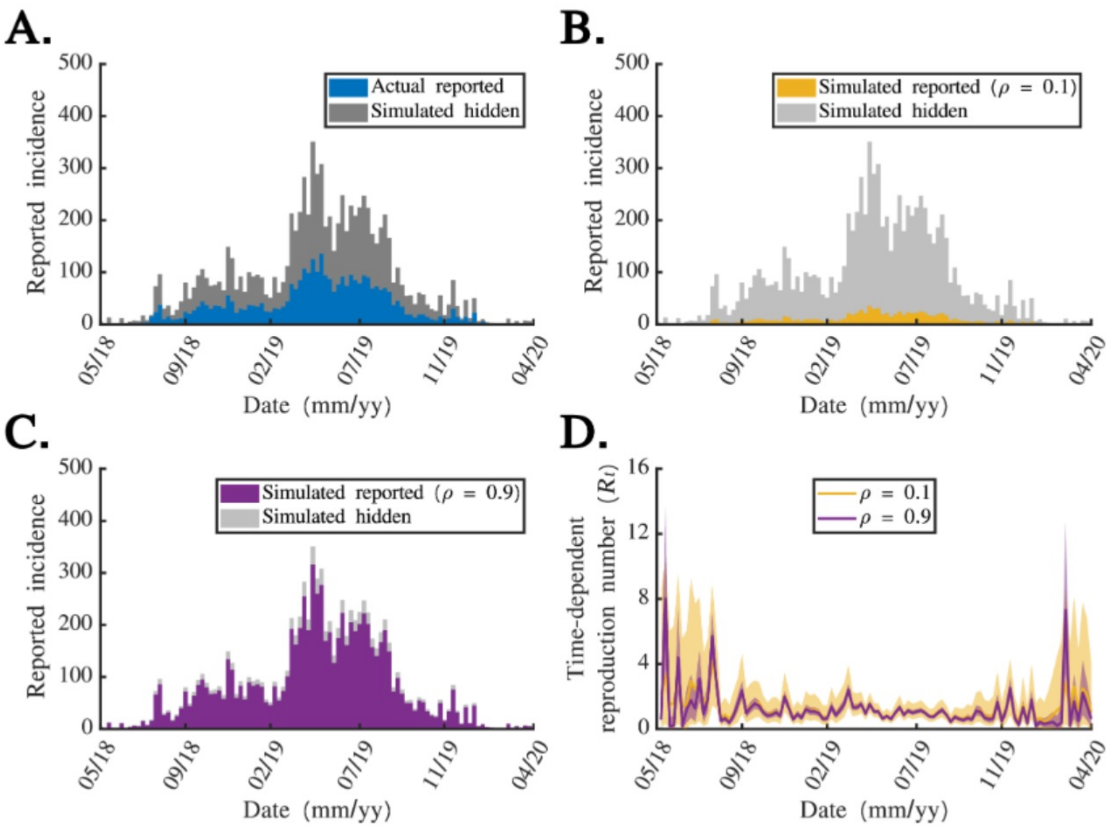
Stochastic under-reporting



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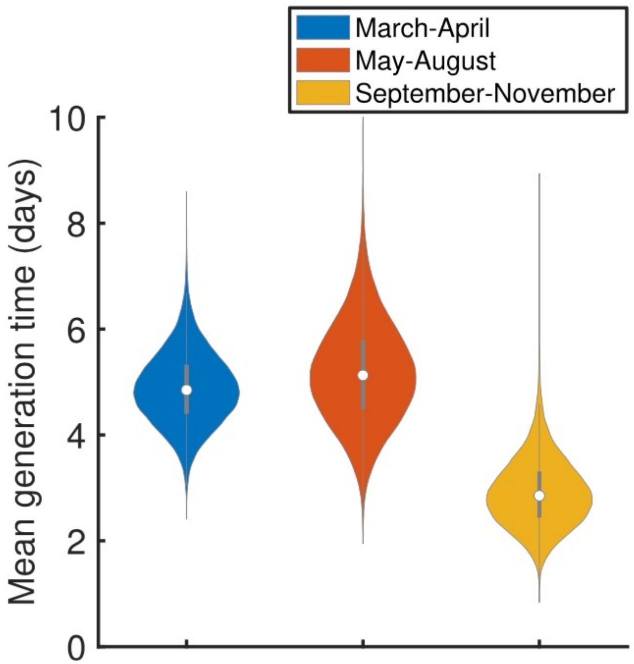
Research

Cite this article: Ogi-Gittins I, Steyn N, Polonsky J, Hart WS, Keita M, Ahuka-Mundeke S, Hill EM, Thompson RN. 2025 Simulation-based inference of the time-dependent reproduction number from temporally aggregated and under-reported disease incidence time series data. *Phil. Trans. R. Soc. A* **383**: 20240412.

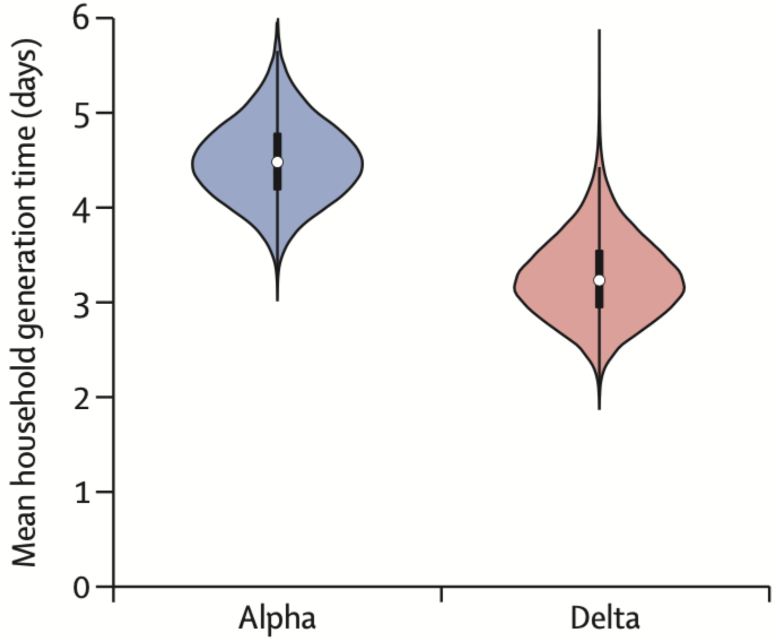
Simulation-based inference of the time-dependent reproduction number from temporally aggregated and under-reported disease incidence time series data

Isaac Ogi-Gittins[1,2], Nicholas Steyn[3], Jonathan Polonsky[5], William S. Hart[4], Mory Keita[7,6], Steve Ahuka-Mundeke[8], Edward M. Hill[9,10] and Robin N. Thompson[4]

Warning: model inputs may change during an epidemic



Hart *et al.* (eLife, 2022)



Hart *et al.* (Lancet Inf Dis, 2022)

Estimating changes in pathogen transmissibility – Summary

Bayesian inference methods can be used to **estimate reproduction numbers** in real-time during epidemics; these approaches were **used worldwide for COVID-19**

Population heterogeneity is important (e.g. imported vs local cases) and methods can be adapted for use with **temporally aggregated data**

Care is needed to ensure that **model inputs are accurate**

Possible mini project

3. Using mathematical models to infer changes in disease transmission during an outbreak

- Write code that takes the following as inputs: i) disease incidence time series; ii) discrete serial interval distribution; iii) parameters of the (gamma distributed) prior for R_t; iv) window length τ; and generates a plot of R_t vs t (for $t > \tau$) including 95% credible intervals.
- Download data for i and ii from EpiEstim App (https://shiny.dide.imperial.ac.uk/epiestim/).
- Compare results generated by your code from results generated using EpiEstim App

(if you prefer, rather than using the app you could use the R software package EpiEstim and use in-built datasets from that package).

- Find a disease dataset online and apply your code to a new dataset.

- Longer term project. Extend the model to differentiate between imported cases and local cases – as described in "Improved inference of time-varying reproduction numbers during infectious disease outbreaks" by Thompson *et al.*

Key references:
- "New framework and software to estimate time-varying reproduction numbers during epidemics" by Cori *et al.*
- "Improved inference of time-varying reproduction numbers during infectious disease outbreaks" by Thompson *et al.*

Outline

1. Introduction to common infectious disease outbreak models
   - Compartmental models
   - Renewal equation models
2. Early in an outbreak: Assessing the risk of major epidemics
   - Estimating the probability of a major epidemic [stochastic compartmental model]
   - Possible mini project
3. During an epidemic: Assessing the effectiveness of current interventions
   - Inferring current transmissibility [renewal equation model]
   - Possible mini project
4. At the end of an epidemic: Assessing when the epidemic is over
   - End-of-outbreak probability estimation [compartmental model and renewal equation model]
   - Possible mini project

At the end of an outbreak

When can an outbreak be declared over?

When can outbreaks be declared over?

The New York Times

Sierra Leone Declared Free of Ebola Transmissions

Share full article

People in Freetown, Sierra Leone, on Saturday, after the country passed 42 days without an Ebola case. Aurelie Marrier D'Unienvil/Associated Press

Uganda declares end to latest ebola outbreak

By **Elias Biryabarema**

April 26, 2025 8:30 AM GMT+1 · Updated 4 days ago

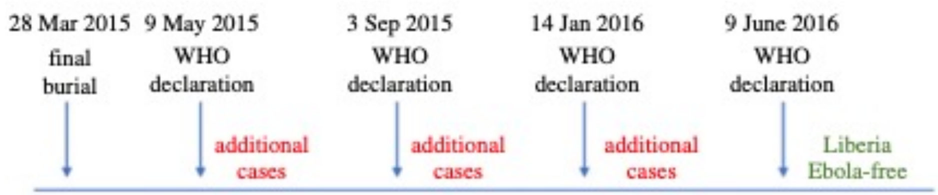
Reuters

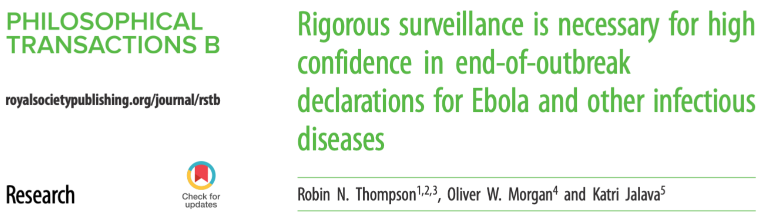
WHO recommended criteria for declaring the end of the Ebola virus disease outbreak

Technical information note - updated 4 March 2020

The acute phase of the outbreak is defined by the propagation of the virus within communities through transmission of the virus from one person to another. This phase will be considered to have been interrupted when **no confirmed or probable Ebola virus disease (EVD) cases are detected for a period of 42 days (i.e. twice the maximum incubation period for Ebola infections) since the last potential exposure to the last case occurred.**

When can outbreaks be declared over?




PHILOSOPHICAL TRANSACTIONS B

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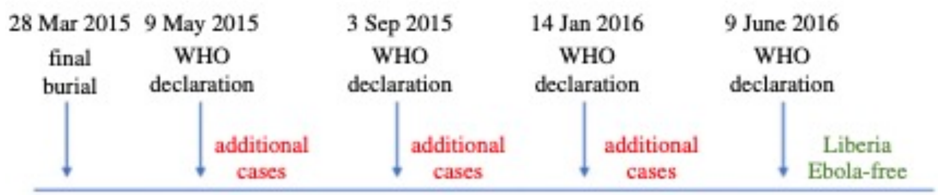
Research

Check for updates

Rigorous surveillance is necessary for high confidence in end-of-outbreak declarations for Ebola and other infectious diseases

Robin N. Thompson[1,2,3], Oliver W. Morgan[4] and Katri Jalava[5]

When can outbreaks be declared over?



How long is it necessary to wait before declaring an outbreak over?

PHILOSOPHICAL TRANSACTIONS B

royalsocietypublishing.org/journal/rstb

Research

Rigorous surveillance is necessary for high confidence in end-of-outbreak declarations for Ebola and other infectious diseases

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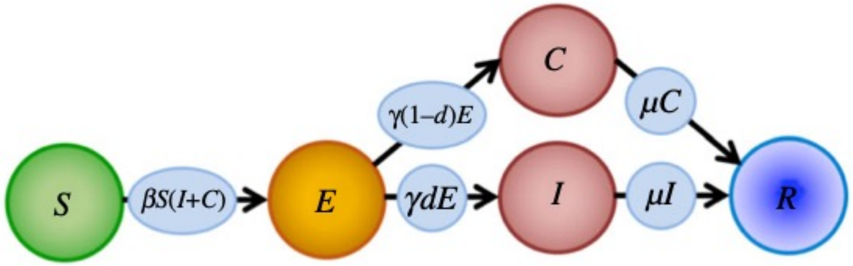
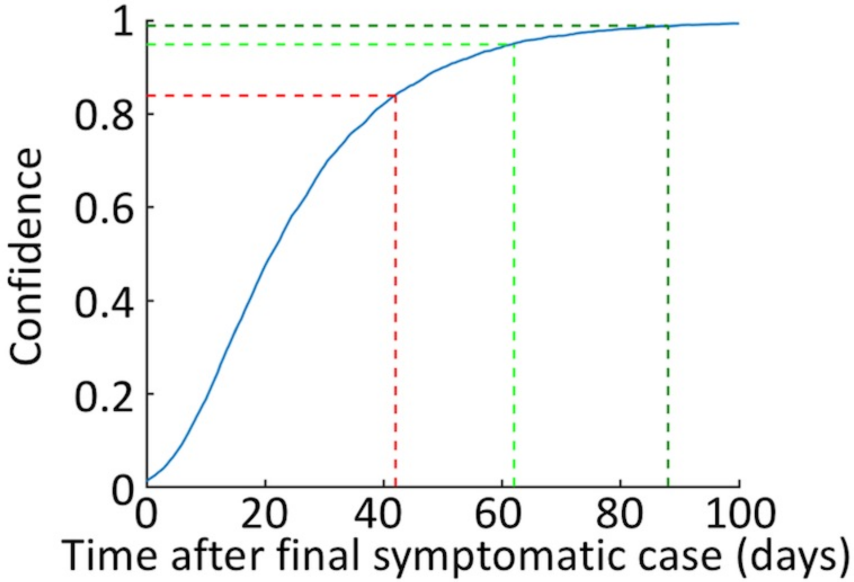
When can outbreaks be declared over?

Initial analysis:





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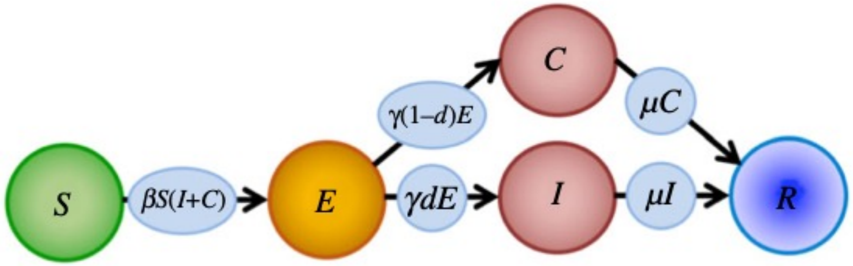

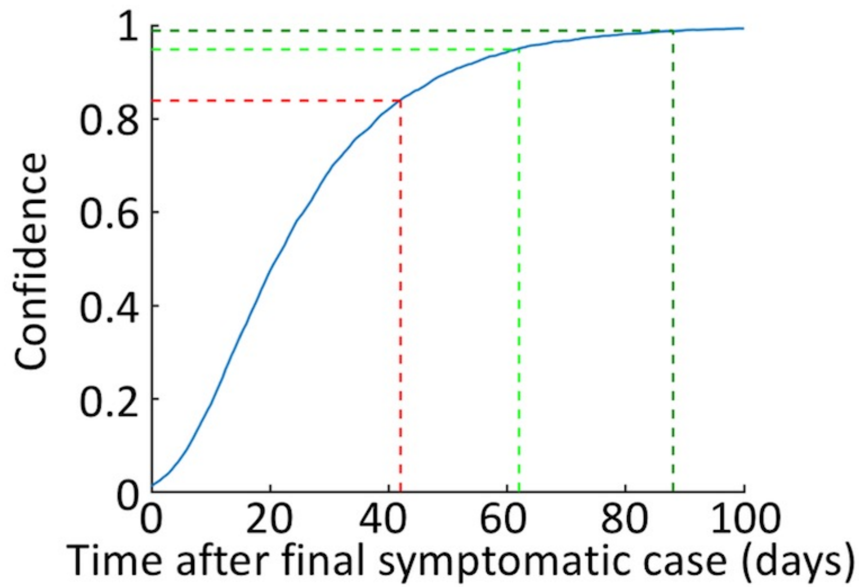

PHILOSOPHICAL TRANSACTIONS B

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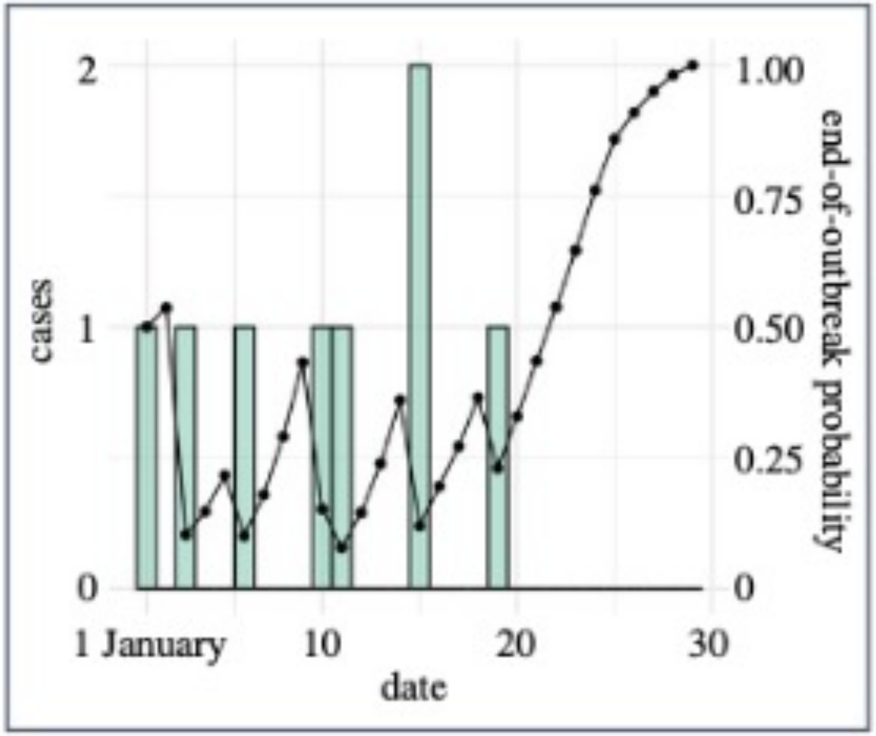
Research

Rigorous surveillance is necessary for high confidence in end-of-outbreak declarations for Ebola and other infectious diseases

Robin N. Thompson[1,2,3], Oliver W. Morgan[4] and Katri Jalava[5]

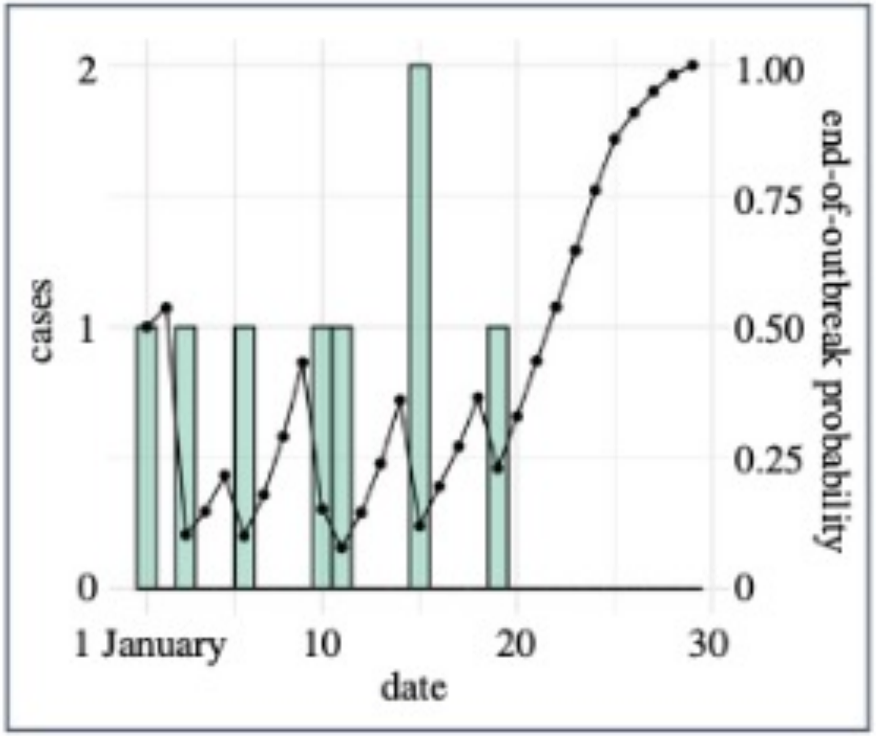
Provides a "general rule" based on the time since the last observed case

When can outbreaks be declared over?



End-of-outbreak declarations based solely on the time since the previous observed case fail to reflect outbreak-specific effects on the end-of-outbreak probability

When can outbreaks be declared over?



End-of-outbreak declarations based solely on the time since the previous observed case fail to reflect outbreak-specific effects on the end-of-outbreak probability

IDEA: Take a specific disease incidence time series and calculate:

P(no future cases)

When can outbreaks be declared over?

EMERGING INFECTIOUS DISEASES

Objective Determination of End of MERS Outbreak, South Korea, 2015

Hiroshi Nishiura, Yuichiro Miyamatsu, Kenji Mizumoto

Author affiliations: The University of Tokyo, Tokyo, Japan (H. Nishiura, Y. Miyamatsu, Kenji Mizumoto); Japan Science and Technology Agency, Kawaguchi Saitama, Japan (H. Nishiura, Y. Miyamatsu, K. Mizumoto)

Nishiura *et al.* derived an outbreak-specific approximation of the end-of-outbreak probability under a branching process transmission model

International Journal of Infectious Diseases 110 (2021) 15–20

Contents lists available at ScienceDirect

ELSEVIER

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

IJID

A hospital-related outbreak of SARS-CoV-2 associated with variant Epsilon (B.1.429) in Taiwan: transmission potential and outbreak containment under intensified contact tracing, January–February 2021

Check for updates

Andrei R. Akhmetzhanov[a,*], Sung-mok Jung[b,c], Hao-Yuan Cheng[d], Robin N. Thompson[e,f]

International Journal of Infectious Diseases 105 (2021) 286–292

Contents lists available at ScienceDirect

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INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

Localized end-of-outbreak determination for coronavirus disease 2019 (COVID-19): examples from clusters in Japan

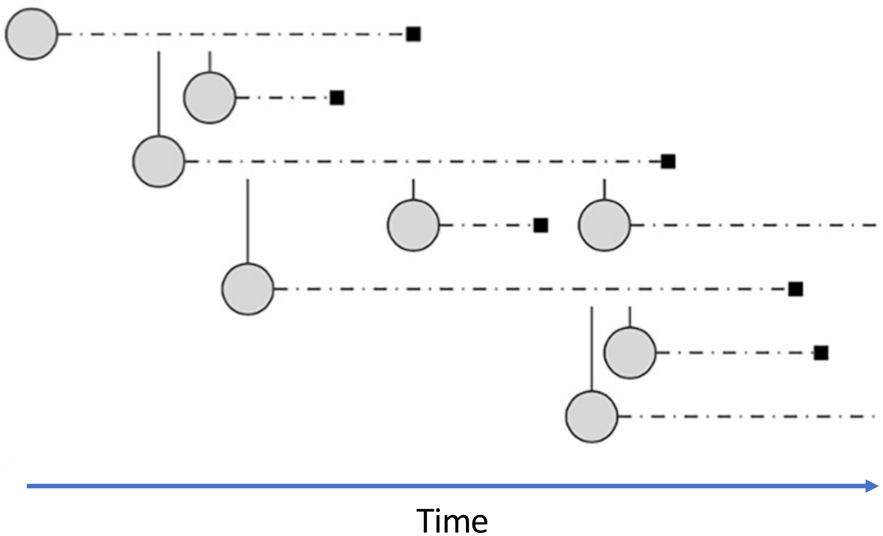
Check for updates

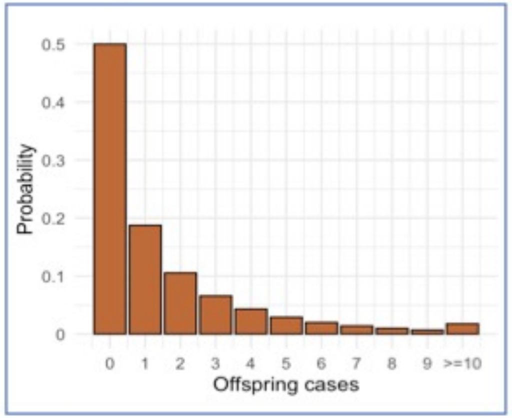
Natalie M. Linton[a,b], Andrei R. Akhmetzhanov[a,c], Hiroshi Nishiura[a,b,*]

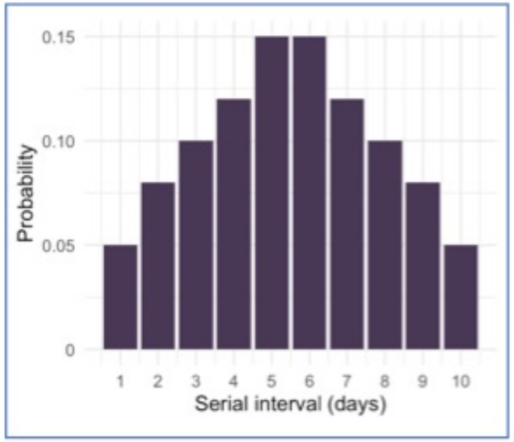
[a] Graduate School of Medicine, Hokkaido University, Kita 15 Jo Nishi 7 Chome, Kita-ku, Sapporo-shi, Hokkaido, 060-8638, Japan
[b] Kyoto University School of Public Health, Yoshidakonoecho, Sakyoku, Kyoto, 606-8501, Japan
[c] College of Public Health, National Taiwan University, 17 Xu-Zhou Road, Taipei, 10055, Taiwan

When can outbreaks be declared over?

Transmission model







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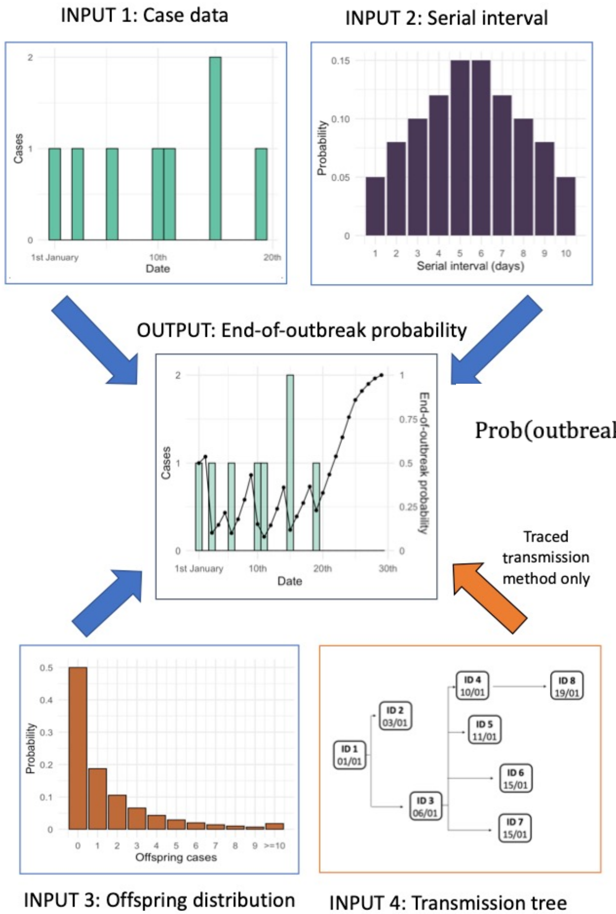


$$\text{Prob(outbreak over on day } t) = \prod_{i=1}^{m} \left(1 - p_0(1 - F(t - t_i))\right)^{(k+a_i)}.$$

Under this transmission model, the end-of-outbreak probability can be calculated exactly if the outbreak transmission tree is known

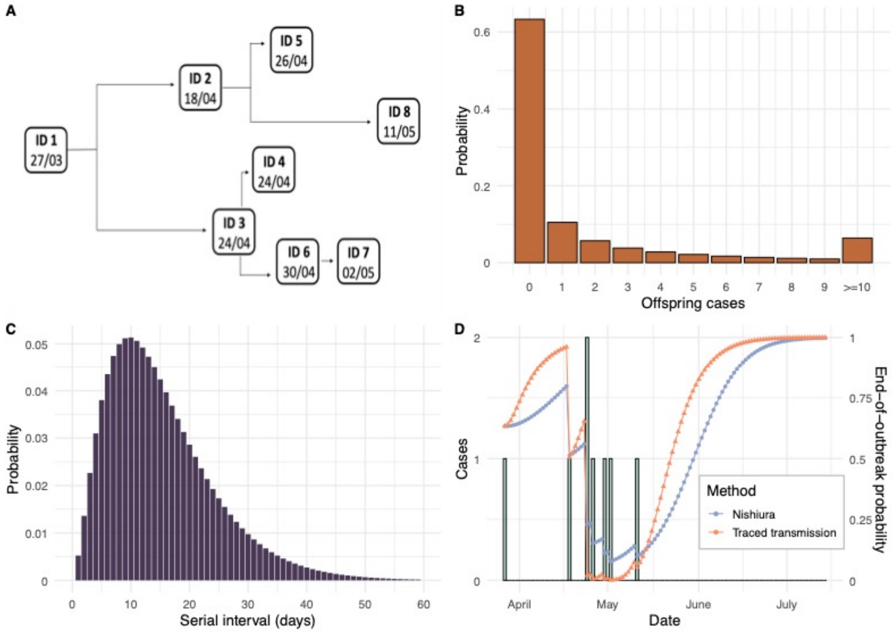
INTERFACE
royalsocietypublishing.org/journal/rsif

Exact calculation of end-of-outbreak probabilities using contact tracing data

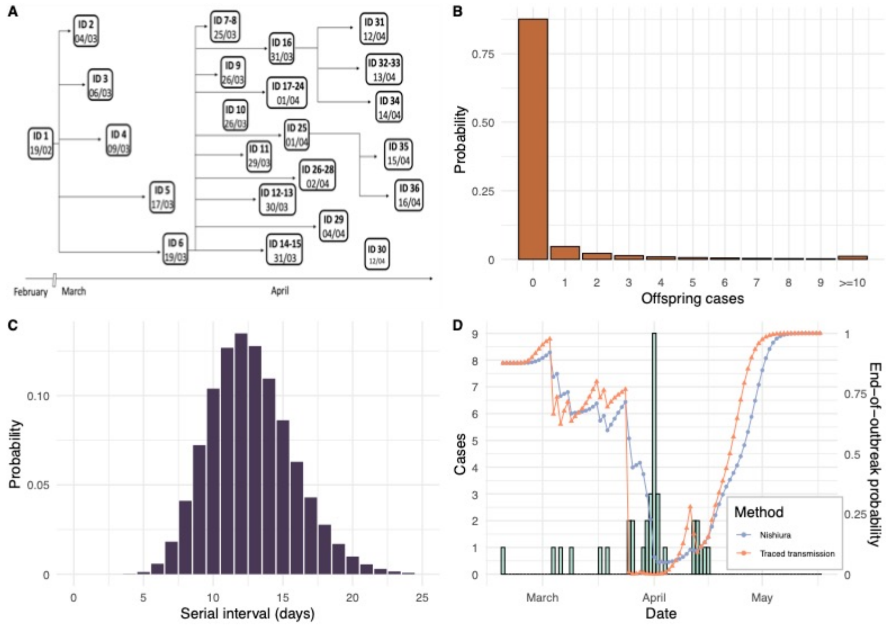
N. V. Bradbury[1,2,†], W. S. Hart[3,†], F. A. Lovell-Read[3], J. A. Polonsky[4] and R. N. Thompson[3]

When can outbreaks be declared over?

Ebola in DRC (2017)



Nipah in Bangladesh (2004)



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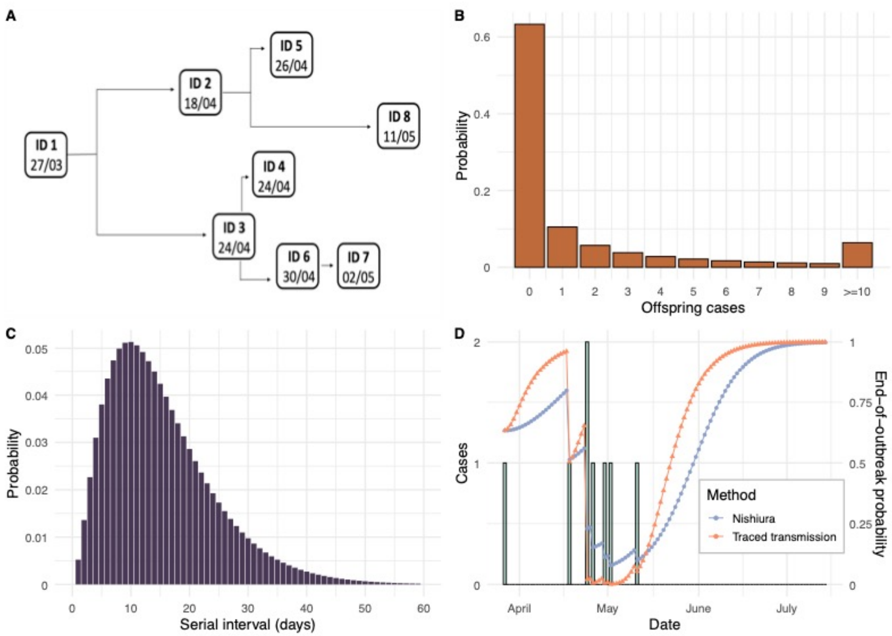

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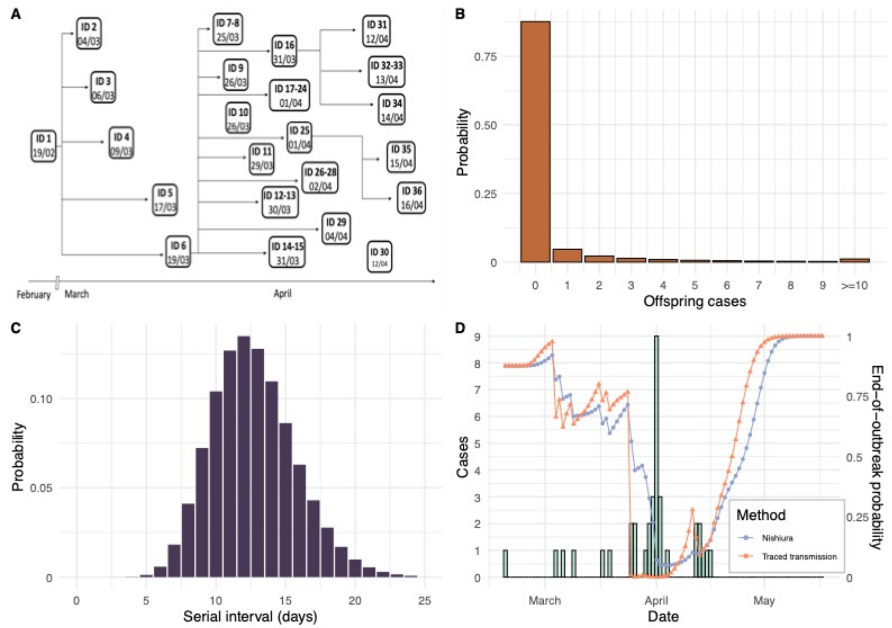

Problem: Transmission tree is often unknown…

INTERFACE

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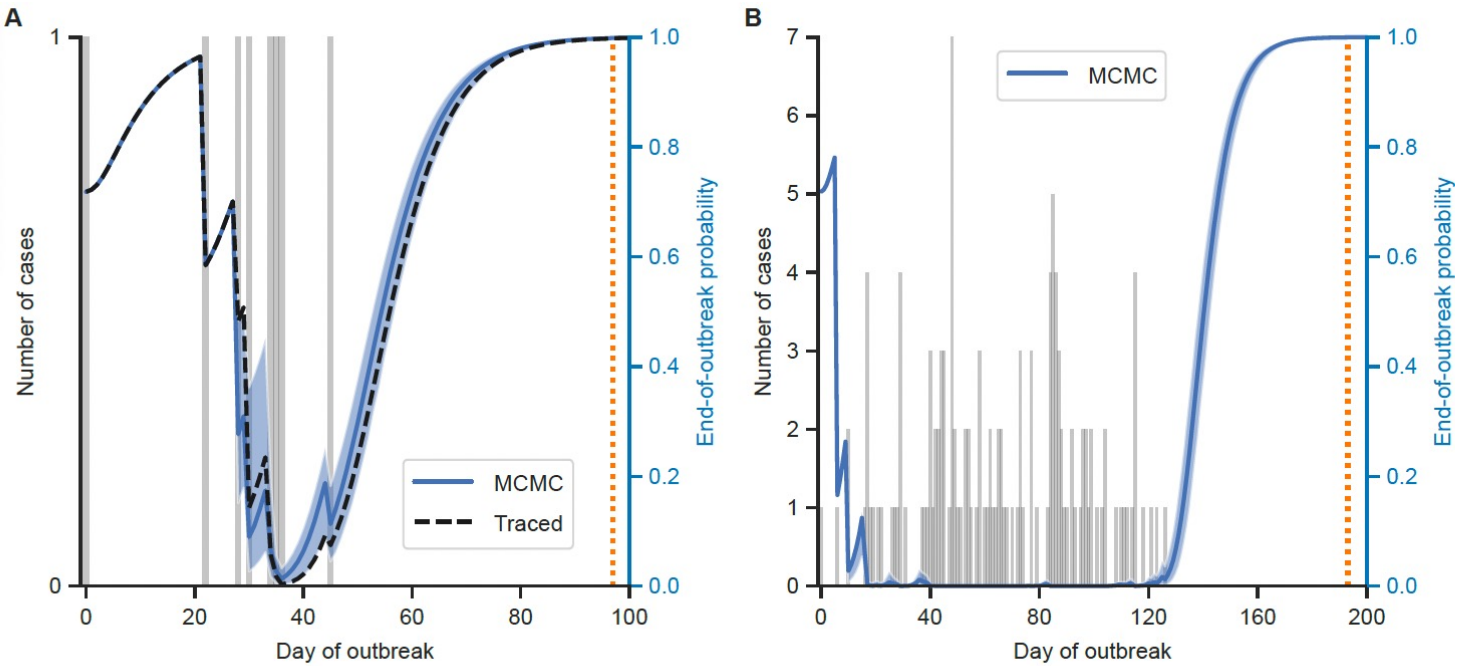
When can outbreaks be declared over?

If the transmission tree is unknown, then the end-of-outbreak probability can be considering "all possible transmission trees":

$$\mathbb{P}(\text{no future cases}) = \sum_i \mathbb{P}(\text{no future cases} \mid \text{transmission tree } i) \times \mathbb{P}(\text{transmission tree } i)$$



SCIENCE ADVANCES | RESEARCH ARTICLE

Optimizing the timing of an end-of-outbreak declaration

Hart *et al.*

When can outbreaks be declared over?

- WHO declares Ebola outbreaks over after 42 “case-free” days
- Simple rules of thumb for end-of-outbreak declarations can be tested using repeated model simulation (of e.g. stochastic compartmental models) – but these are not “outbreak specific”
- Under a branching process model, Nishiura *et al.* derived an approximation to the end-of-outbreak probability
- The end-of-outbreak probability can be calculated exactly under the same model, if the transmission tree is known (Bradbury *et al.*)
- If the transmission tree is not known, an unbiased estimate of the end-of-outbreak probability can be calculated by enumerating over all possible transmission trees (or using MCMC to estimate the transmission tree; Hart *et al.*)

An alternative (easier) modelling framework

Instead of using compartmental models or individual-based branching processes, an alternative modelling framework involves **renewal equations**

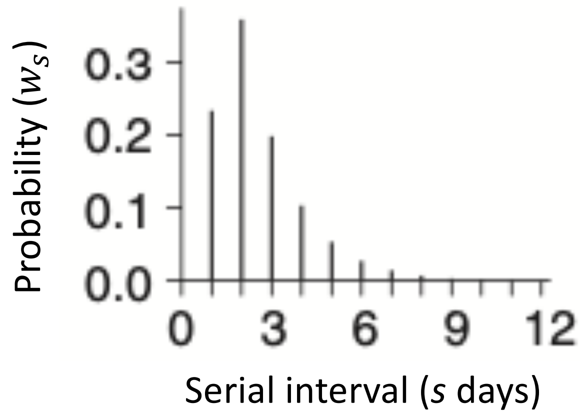
[same model as described earlier, but assuming constant *R*]

An alternative (easier) modelling framework

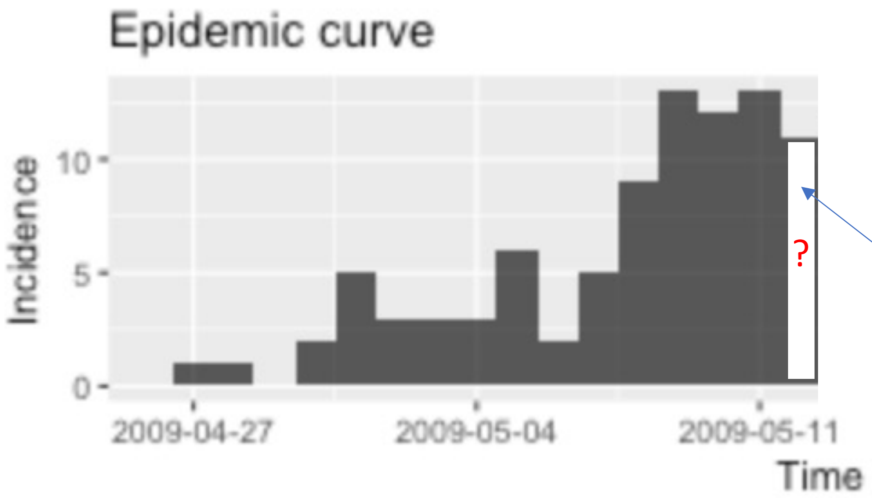
Instead of using compartmental models or individual-based branching processes, an alternative modelling framework involves **renewal equations**

Know

R &



$$\mathrm{E}(I_t \mid R, \{w_s\}, \{I_0, I_1, I_2, \ldots, I_{t-1}\}) = R \sum_{s=1}^{t} I_{t-s} w_s$$



I_t cases ← Draw from Poisson distribution or NB distribution

An alternative (easier) modelling framework

Instead of using compartmental models or individual-based branching processes, an alternative modelling framework involves **renewal equations**

End of outbreak probability:

$$\prod_{j=t}^{\infty} \exp\left(-R \sum_{s=1}^{j-1} I_{j-s} w_s\right)$$

Poisson model

$$\prod_{j=t}^{\infty} \left(\frac{k}{k + R \sum_{s=1}^{j-1} I_{j-s} w_s}\right)^k$$

NB model

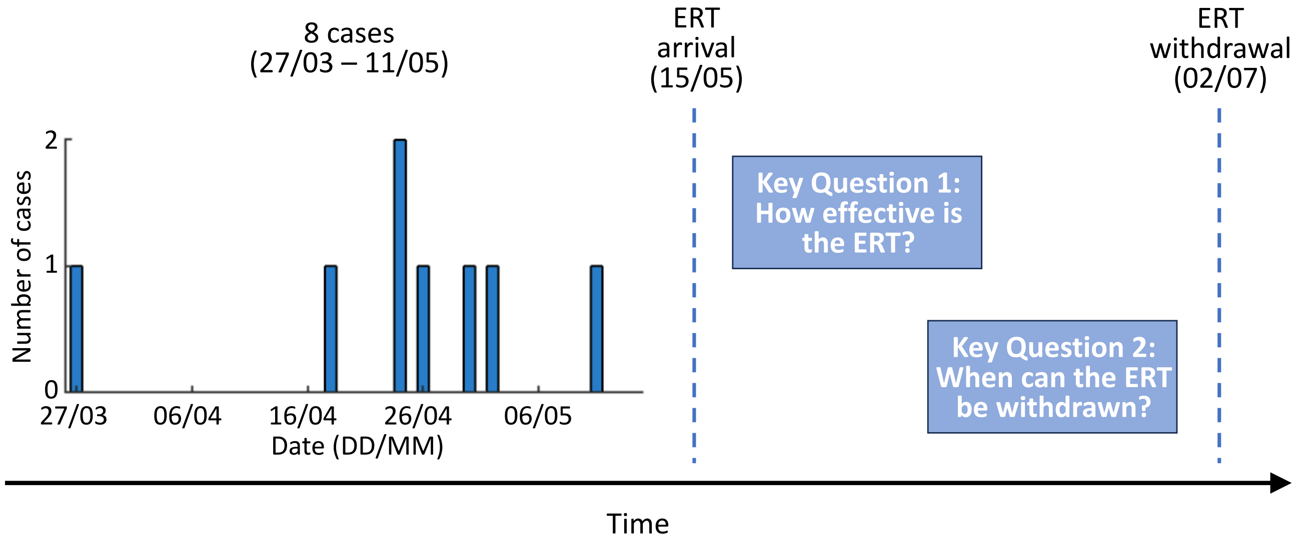
Case study: Ebola virus disease in DRC

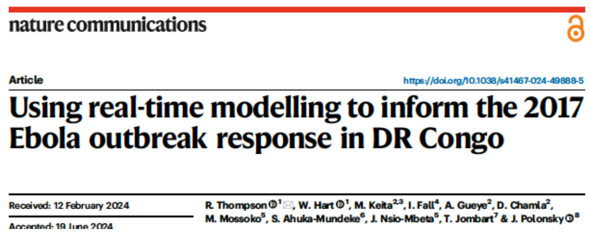
1. Estimate R (and k) pre-ERT

$$L\left(R\right)=\frac{1}{M_1}\prod_{t=2}^{49}\frac{\left(R\sum_{s=1}^{t-1}I_{t-s}w_s\right)^{I_t}\exp\left(-R\sum_{s=1}^{t-1}I_{t-s}w_s\right)}{I_t!}$$

2. Calculate risk of future cases each day if the ERT is withdrawn

$$\text{Risk of withdrawing ERT on day } t$$
$$= 1 - \int_0^\infty \text{Prob (no cases from day } t \text{ onwards} | R)\, L(R) \mathrm{d}R,$$




nature communications

Article

https://doi.org/10.1038/s41467-024-49888-5

Using real-time modelling to inform the 2017 Ebola outbreak response in DR Congo

Received: 12 February 2024

Accepted: 19 June 2024

R. Thompson[1], W. Hart[1], M. Keita[2,3], I. Fall[4], A. Gueye[2], D. Chamla[2], M. Mossoko[5], S. Ahuka-Mundeke[6], J. Nsio-Mbeta[5], T. Jombart[7] & J. Polonsky[8]

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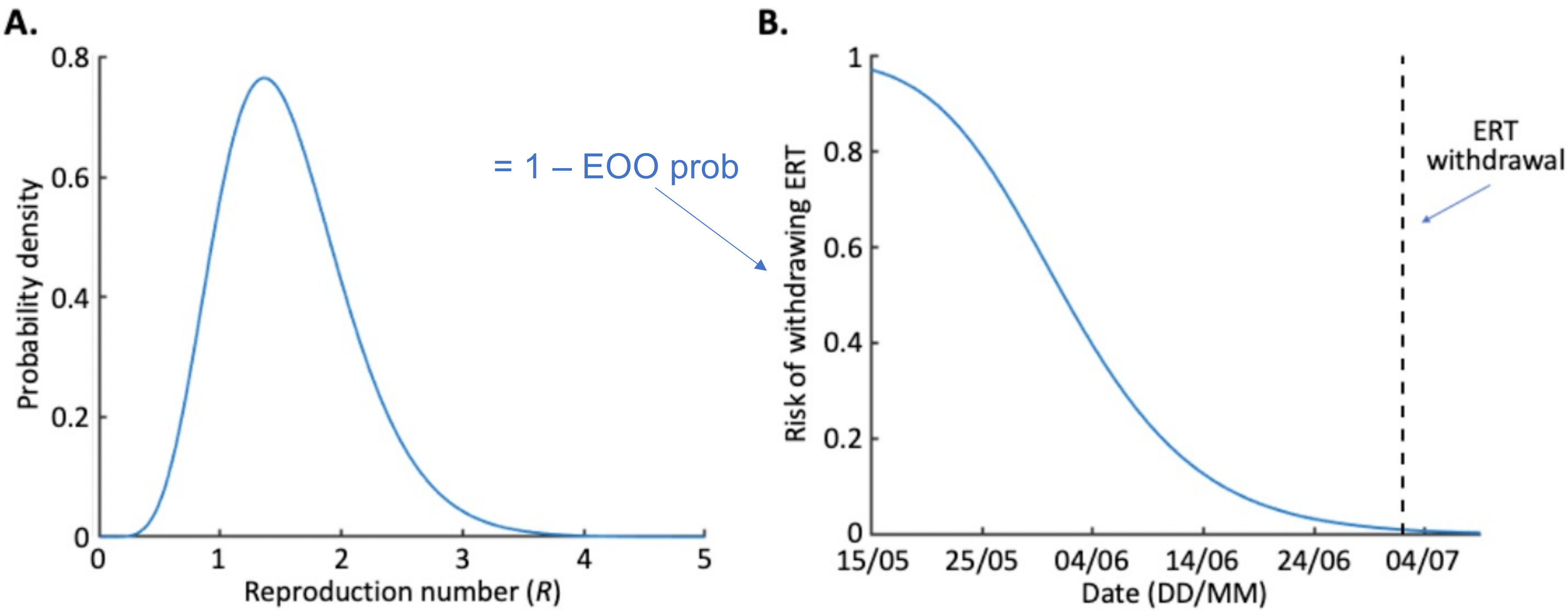

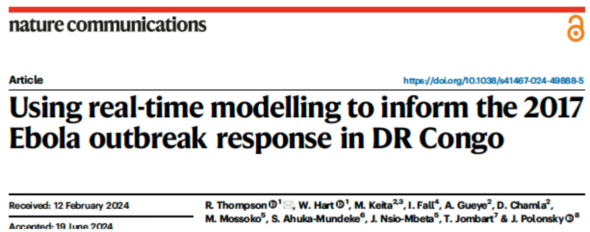
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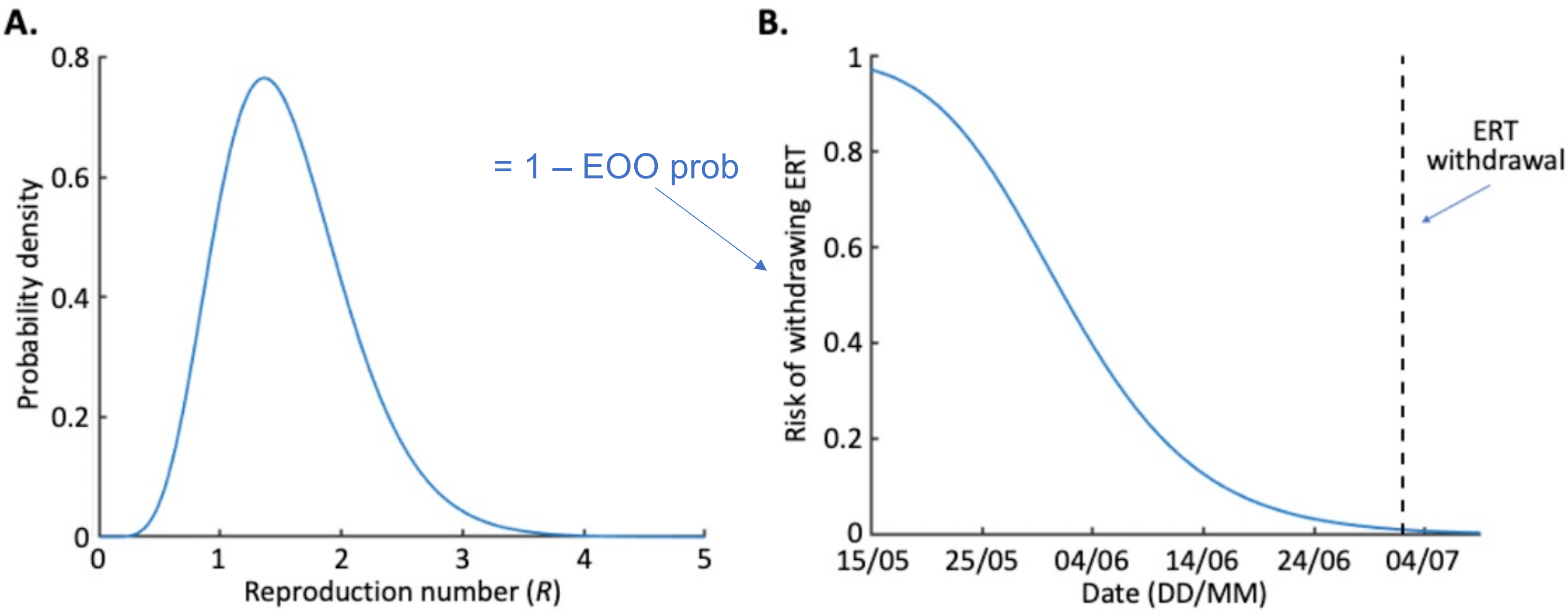
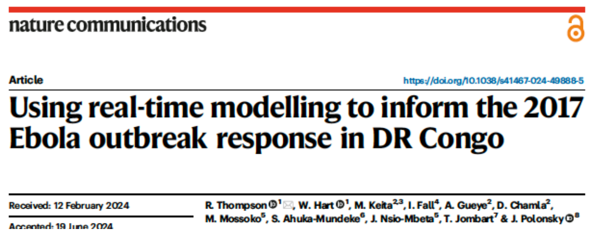


- ERT effective at limiting transmission
- ERT was only withdrawn when it was safe to do so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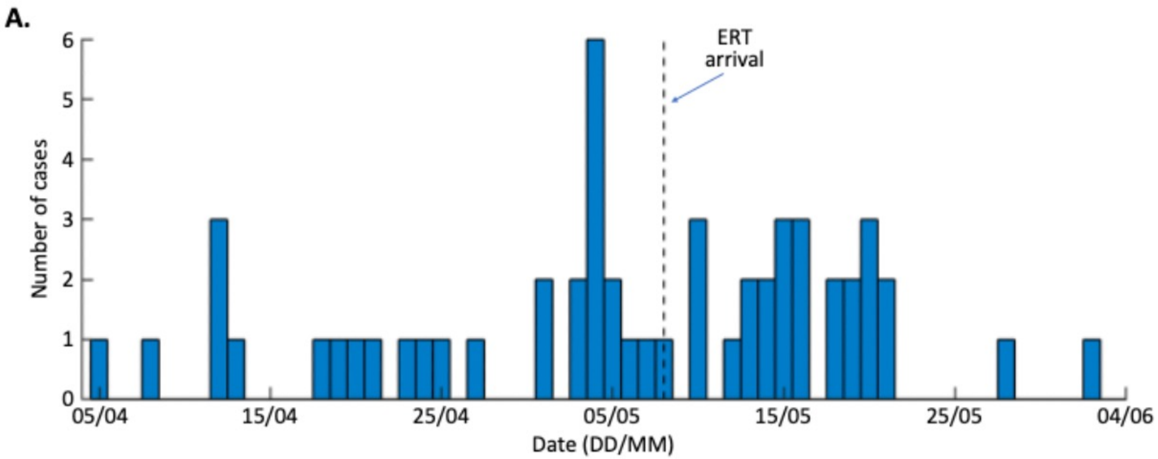
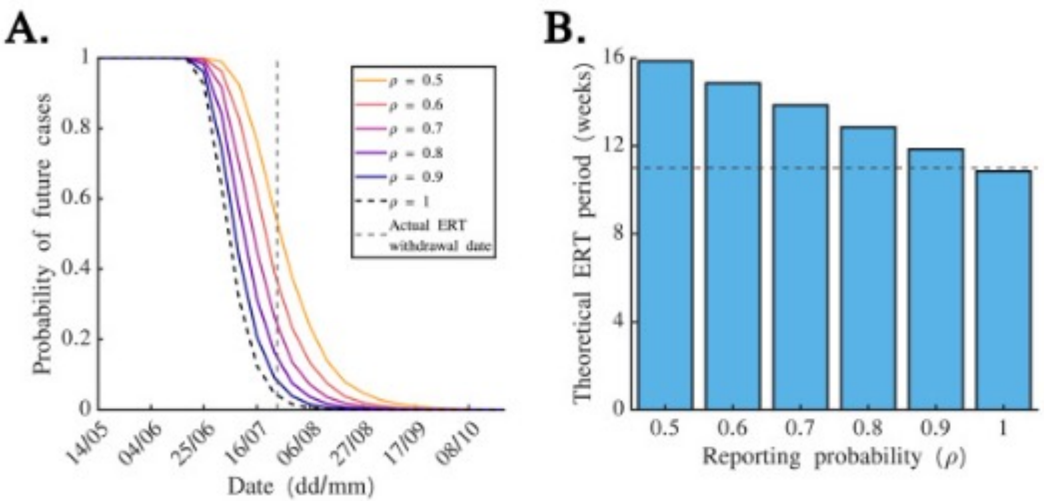
Effect of under-reporting





Infectious Disease Modelling

Real-time inference of the end of an outbreak: Temporally aggregated disease incidence data and under-reporting

I. Ogi-Gittins [1 2], J. Polonsky [3], M. Keita [4 5], S. Ahuka-Mundeke [6], W.S. Hart [7], M.J. Plank [8], B. Lambert [9], E.M. Hill [10 11], R.N. Thompson [7]

When can outbreaks be declared over?

- Renewal equation models provide a framework for inferring the end-of-outbreak probability straightforwardly (obtaining outbreak-specific estimates)
- Estimates can be informed by outbreak data and adjusted as additional data arise
- An outbreak can be declared over when the inferred end-of-outbreak probability falls below a threshold reflecting a policy-makers' appetite for risk
- Superspreading events can be accounted for by assuming a NB distributed number of cases each day
- Effective disease surveillance is essential to declare outbreaks over quickly and accurately following the final case

Possible mini project

4. Using mathematical models to determine when an outbreak is over

- Write code that takes the following as inputs: i) a disease incidence time series; ii) a discrete serial interval distribution; iii) the value of R; iv) (for NB distribution only) the value of *k;* and generates estimates of the probability that no cases will occur in future (using the renewal equation method).

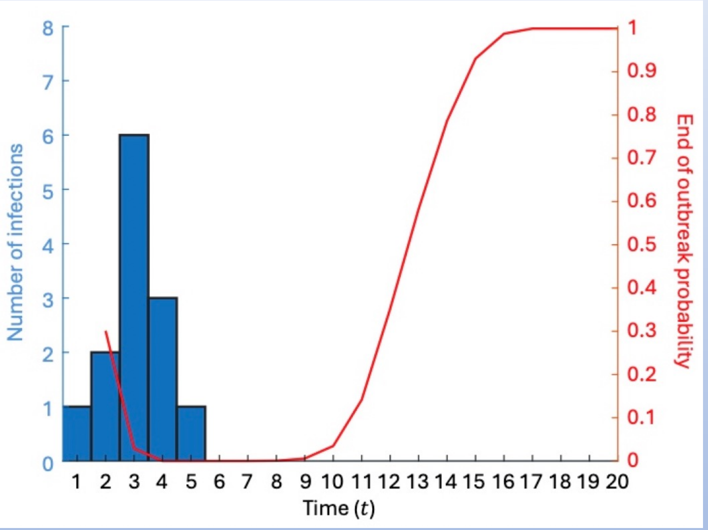


Figure 5.5: Calculation of the end-of-outbreak probability using a renewal equation model. Blue bars represent the number of infections each day, and the red line represents the end-of-outbreak probability estimate based on the infections arising prior to the current day. The end-of-outbreak probability was calculated assuming that $R_t = 1.2$ for all values of t and $\{w_s\}_{s=1}^{11} = \{0.05, 0.1, 0.2, 0.2, 0.15, 0.1, 0.1, 0.05, 0.02, 0.02, 0.01\}$ with $w_s = 0$ for $s \geq 11$.

- Can you reproduce this figure? (for number of cases each day drawn from a Poisson distribution)

- Can you apply your methods to other datasets (e.g. the datasets suggested under project idea 3)? How long is it necessary to wait to be confident that an outbreak is over for different outbreaks/diseases?

Summary

- Infectious disease models exist in a range of forms (here: compartmental models and renewal equations)
- Certain models may be more suitable to answer specific questions
- Compartmental models are flexible and can easily include different epidemiology
- Renewal equations simply track case numbers
- Epidemiological models can be used to answer different questions at different outbreak stages (e.g., early in an outbreak = assess PMO, middle of an outbreak = estimate R_t, late in outbreak = assess when outbreak has finished).

https://www.maths.ox.ac.uk/groups/mathematical-biology/infectious-disease-modelling

- Assign groups
- Get started on an infectious disease modelling mini project (come up with some interesting plots to show next week ☺)
- Finish project (and 3-5 slides) next Monday
- Report back on Tuesday

Can each group please send 3-5 slides to me by noon next Tuesday?

robin.thompson@maths.ox.ac.uk