



Mathematical
Institute

MSc mathematical modelling (weeks 7-8)

Mathematical modelling of infectious disease outbreaks

Robin Thompson

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University of Oxford

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)

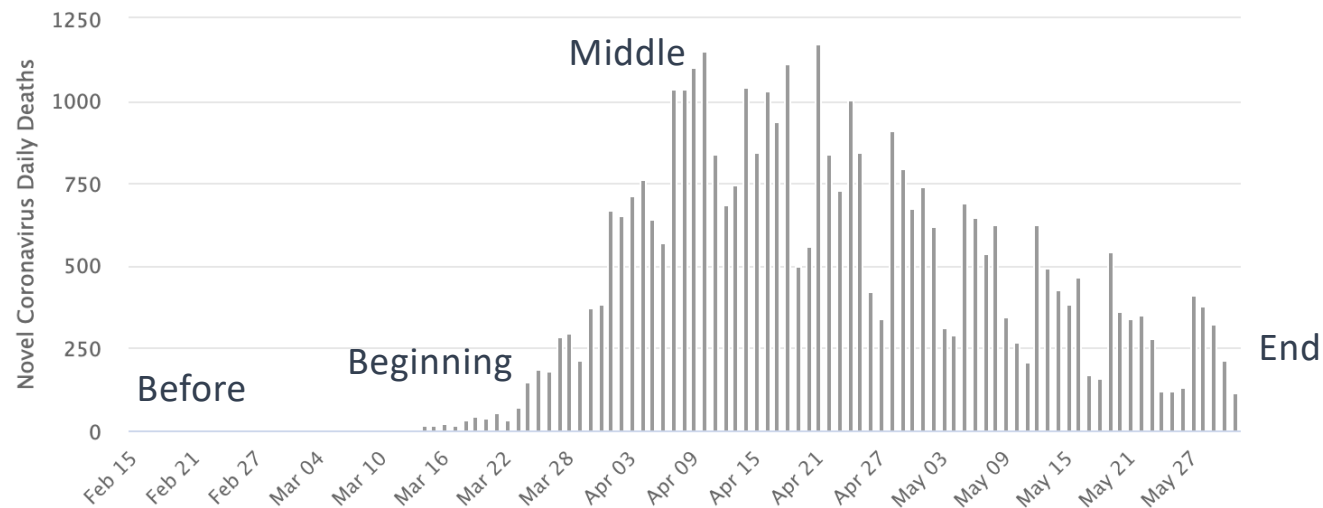
Now!

- Today: 2-hour introduction to infectious disease modelling
- Tomorrow: Assign groups and start infectious disease modelling “mini project”
- Main aim: As a group, put together 2-3 slides about an infectious disease modelling topic (either one of the exercises I will suggest today, or a summary of one of the topics I will explain today)

Now!

- Between tomorrow and next Monday: Please work on your group mini project
- Next Monday 2-4: Extra time to work on group mini project, prepare slides
- Next Tuesday 3-4: Report back on your mini project (2-3 slides per group; please email slides to me by 10am next Tuesday – robin.thompson@maths.ox.ac.uk)
- **This is an opportunity to practise group work (not assessed)**
- **Have fun and enjoy working together to create some slides!!!**

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

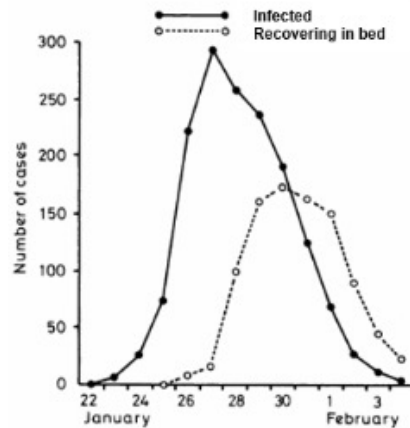
- Inferring current transmissibility [renewal equation model]
- Possible mini project

4. At the end of an epidemic: Assessing when the epidemic is over

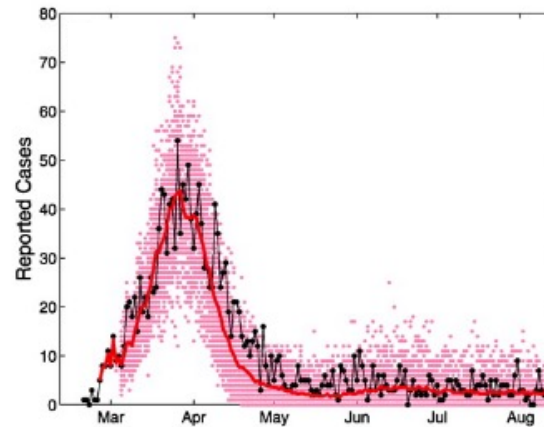
- End-of-outbreak probability estimation [compartmental model and renewal equation model]
- Possible mini project

Outbreak waves have a characteristic “shape”

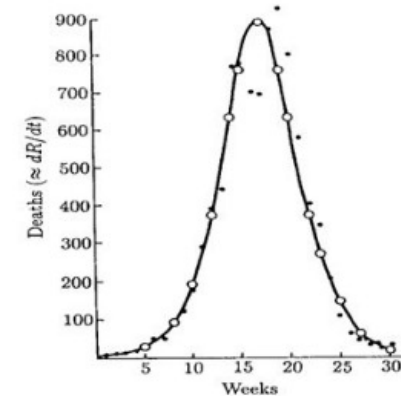
Flu in a school in 1978



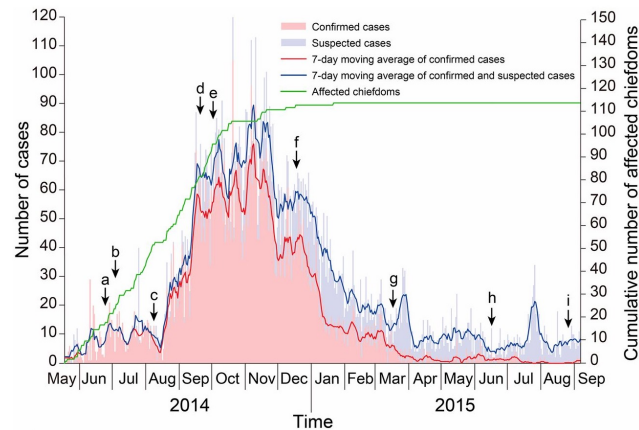
Foot and mouth in the UK 2001



Plague in Mumbai in 1906

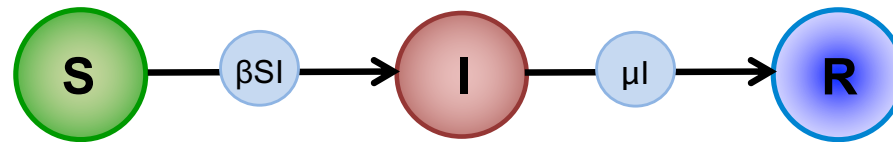


Ebola in West Africa in 2014-15

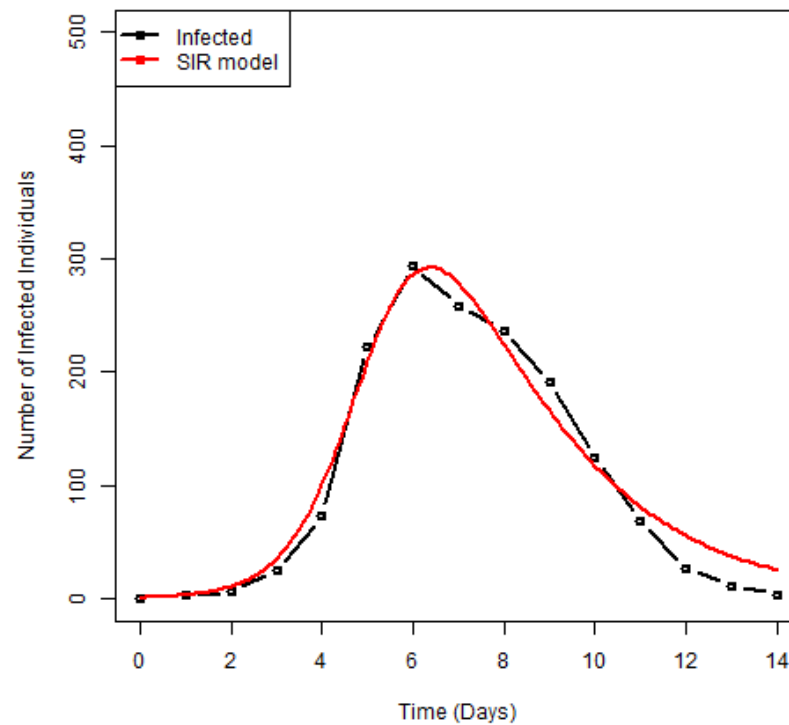


**First compartmental models
(early 20th century)
aimed to capture this shape**

Compartmental models: SIR model



Boarding school flu epidemic

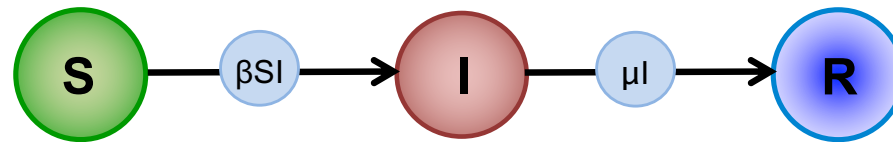


$$\frac{dS}{dt} = -\beta SI$$

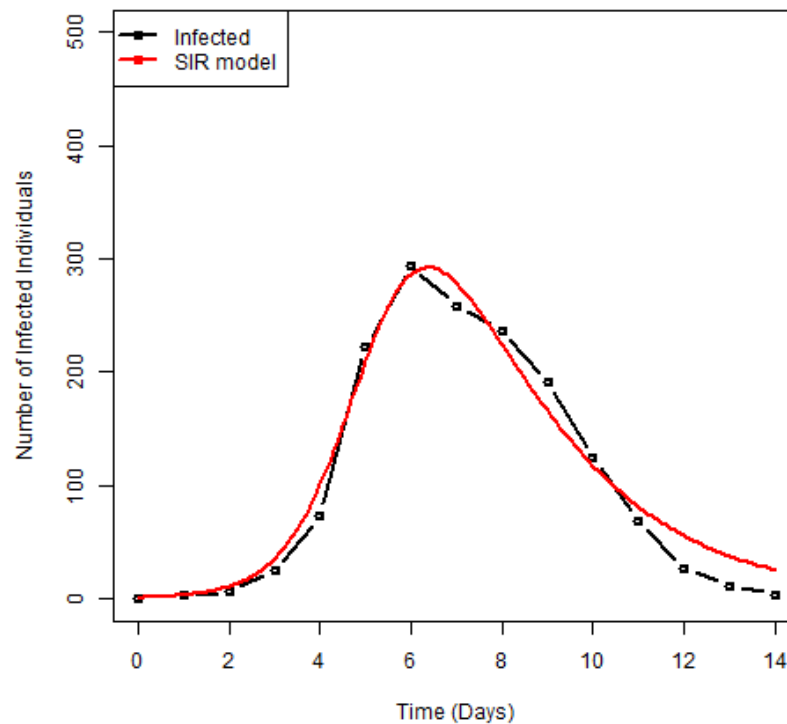
$$\frac{dI}{dt} = \beta SI - \mu I$$

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

Compartmental models: SIR model



Boarding school flu epidemic



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

But... not bad for a two-parameter model

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

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

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

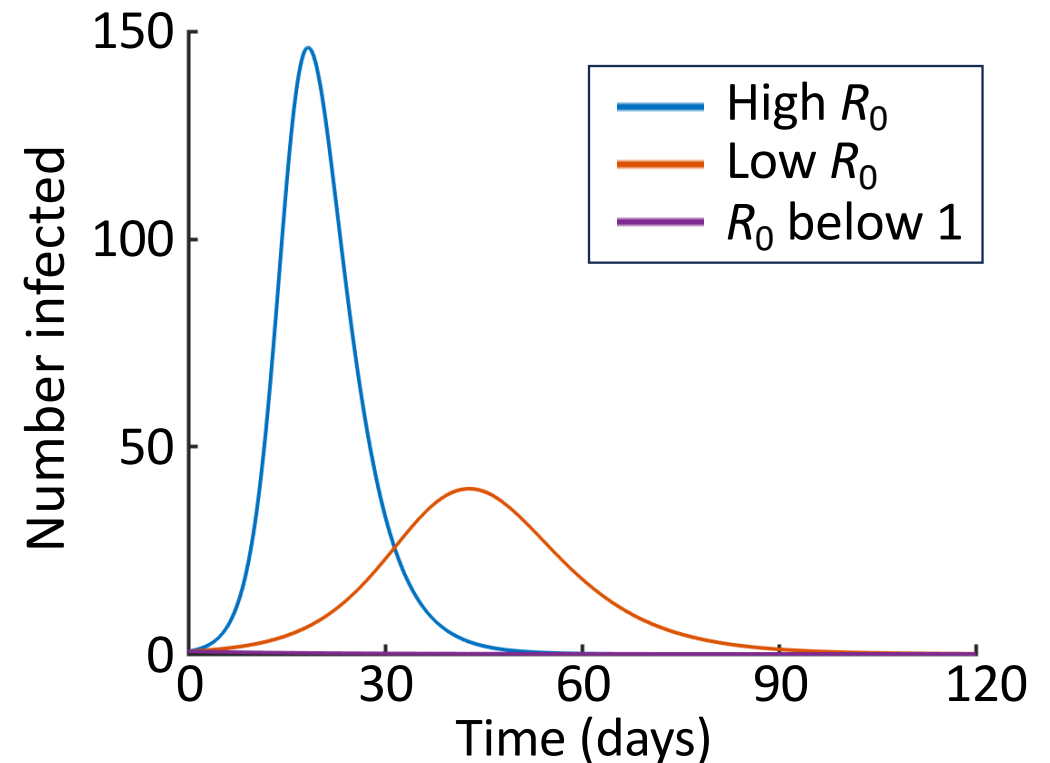
Compartmental models: SIR model

Basic reproduction number, R_0

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

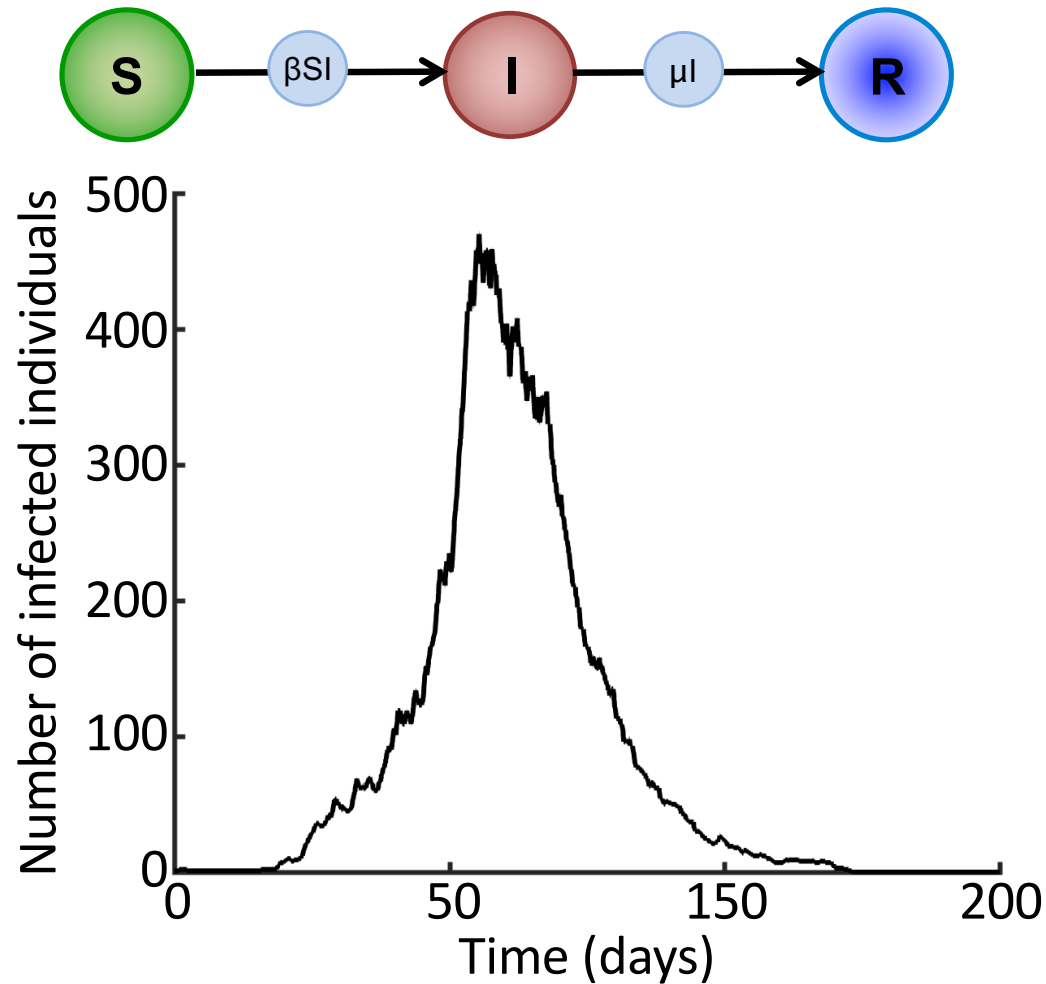
$R_0 = \text{Infection rate} \times \text{Duration of infection}$

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



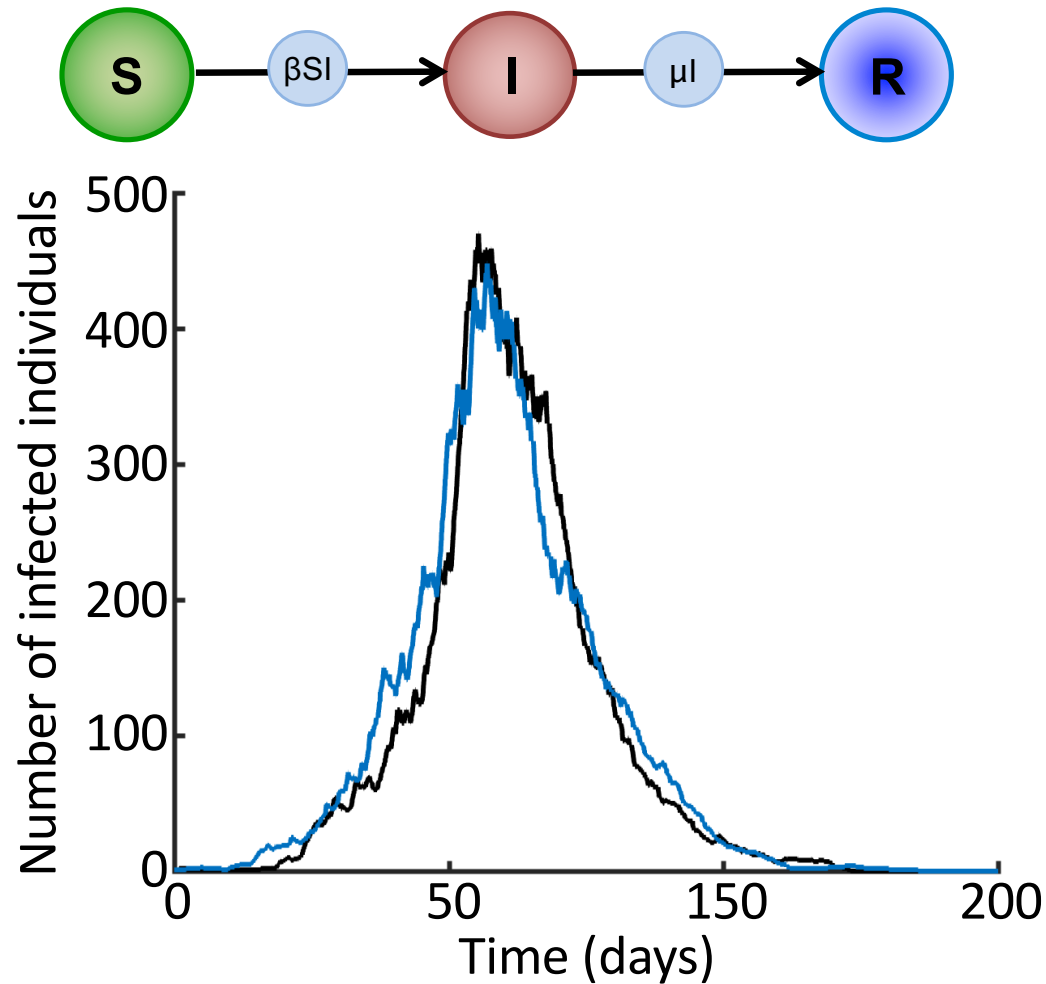
Compartmental models: Extensions to SIR model

1. Infectious disease outbreaks are inherently random



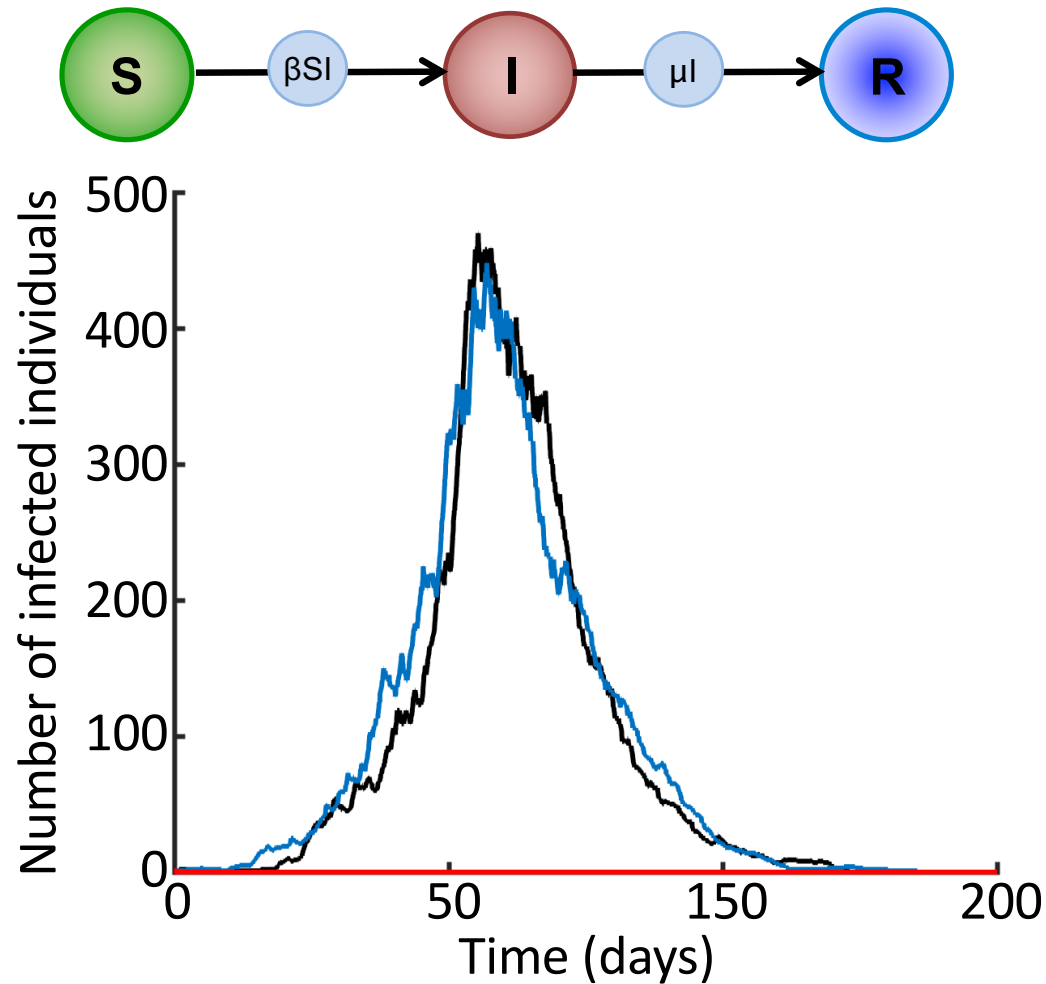
Compartmental models: Extensions to SIR model

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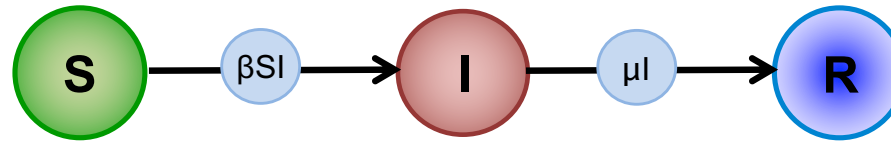
Compartmental models: Extensions to SIR model

1. Infectious disease outbreaks are inherently random



Compartmental models: Extensions to SIR model

1. Infectious disease outbreaks are inherently random



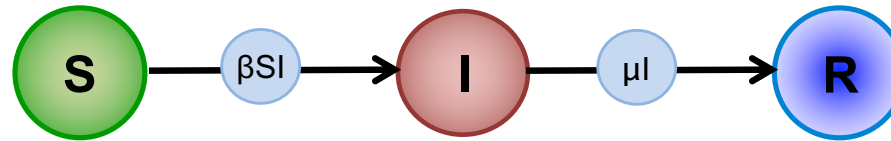
How to run one simulation of stochastic SIR model (using Gillespie direct method):

- 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:

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

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

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

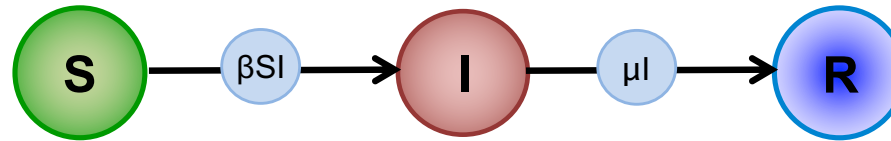
4. Choose whether the next event is an infection event or removal event. If

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

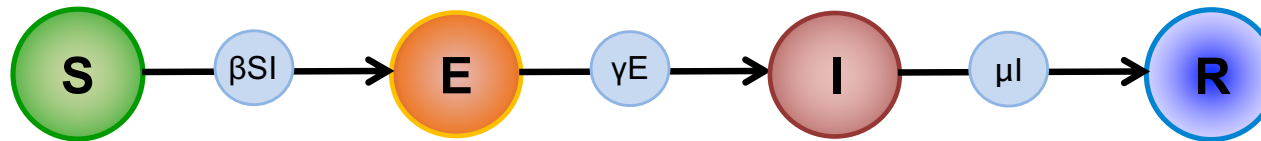
then the next event is an infection event, and so set $S = S - 1$ and $I = I + 1$. Otherwise set $I = I - 1$ and $R = R + 1$.

Compartmental models: Extensions to SIR model

2. Different epidemiology

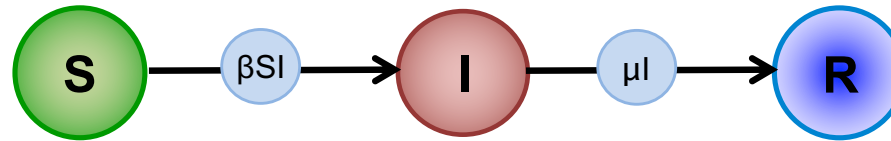


Delay between infection and becoming infectious:

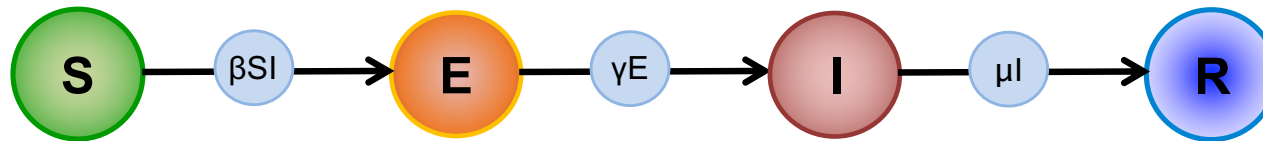


Compartmental models: Extensions to SIR model

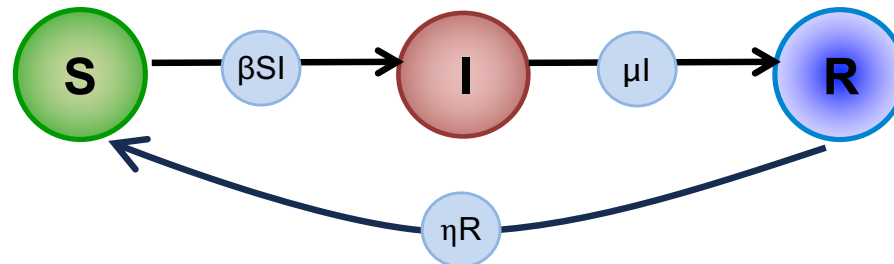
2. Different epidemiology



Delay between infection and becoming infectious:

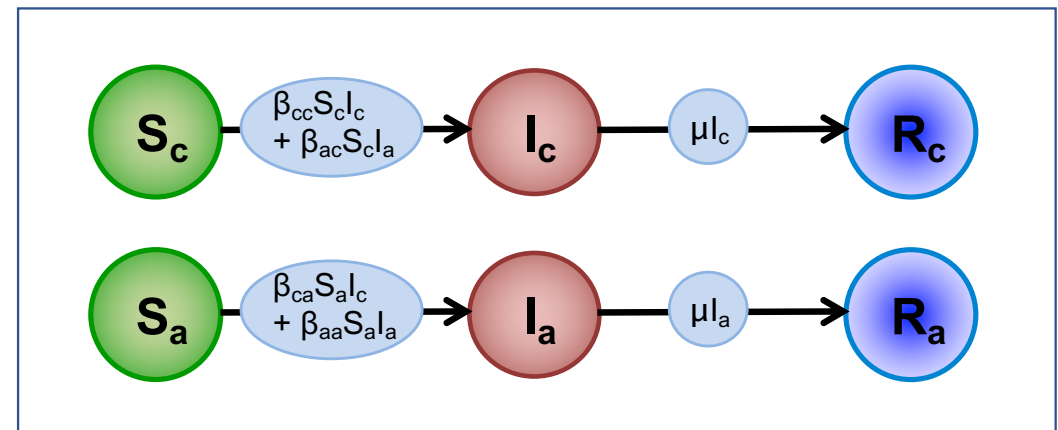
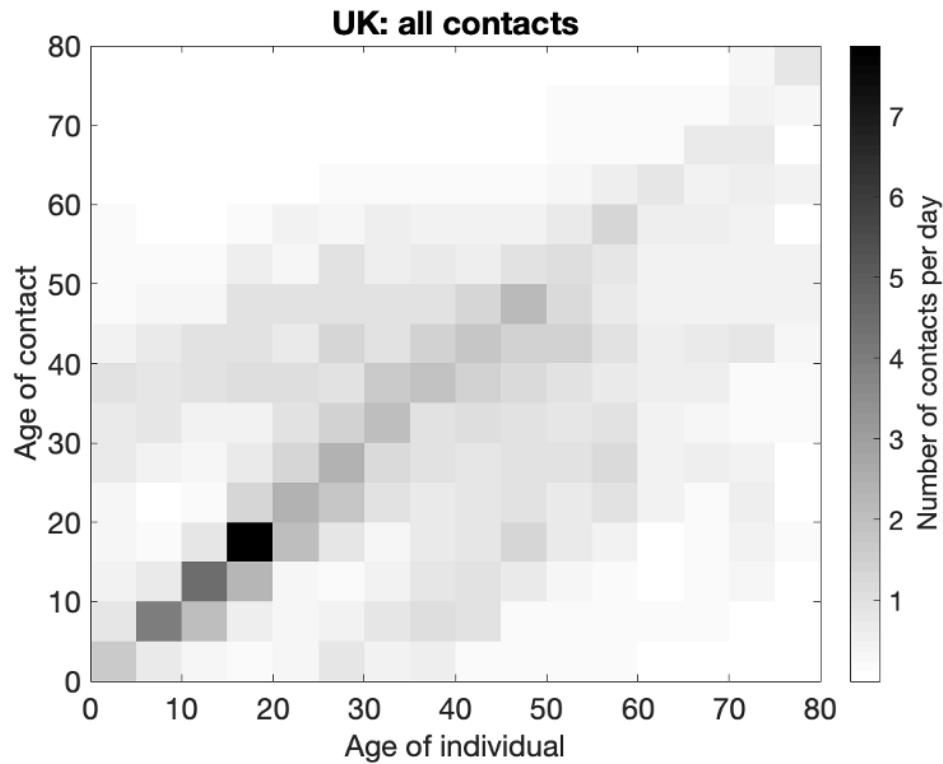


Waning immunity:



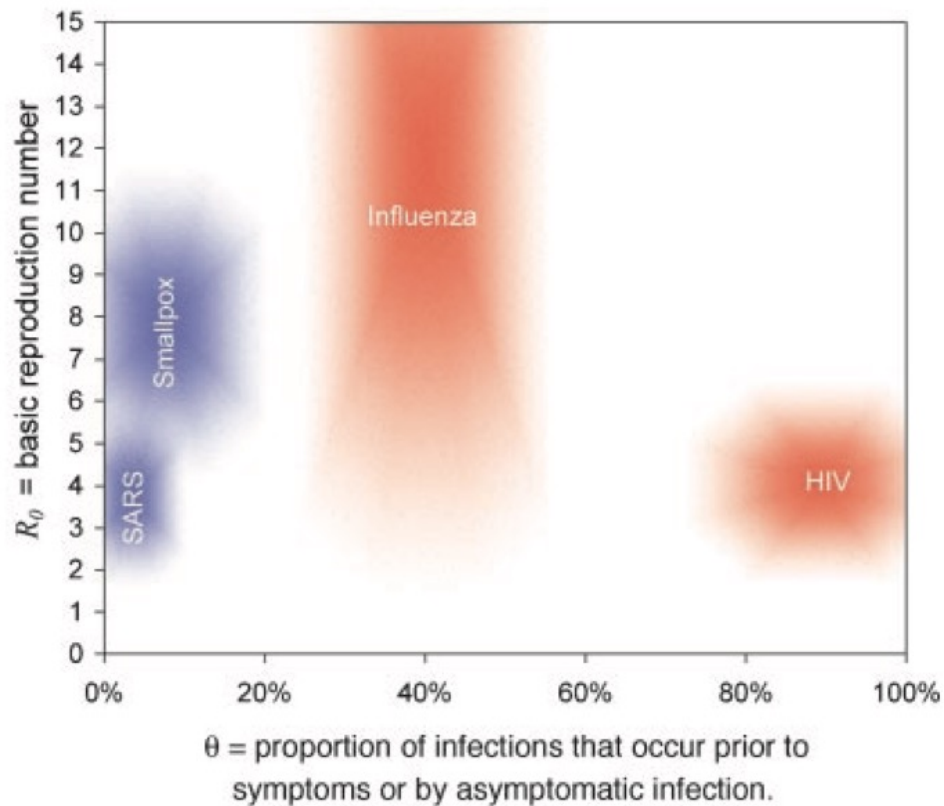
Compartmental models: Extensions to SIR model

3. Age structure

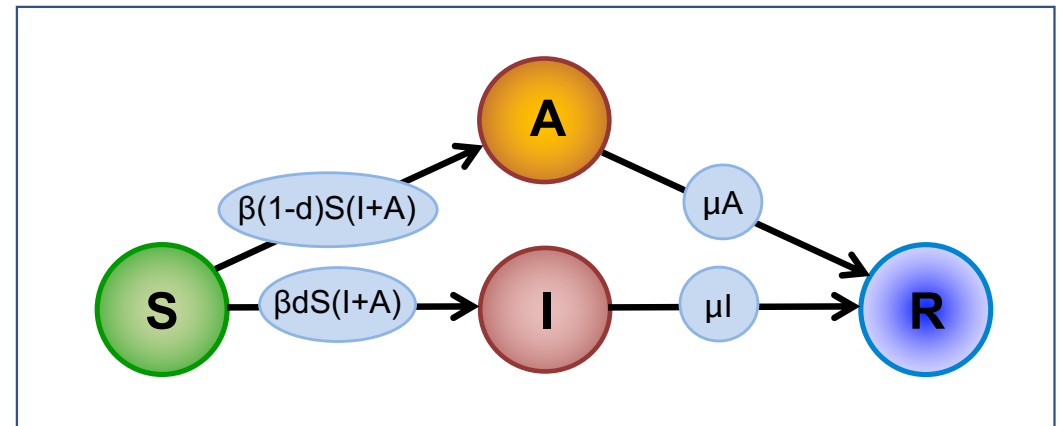


Compartmental models: Extensions to SIR model

4. Asymptomatic transmission



Fraser *et al.* (PNAS, 2004)



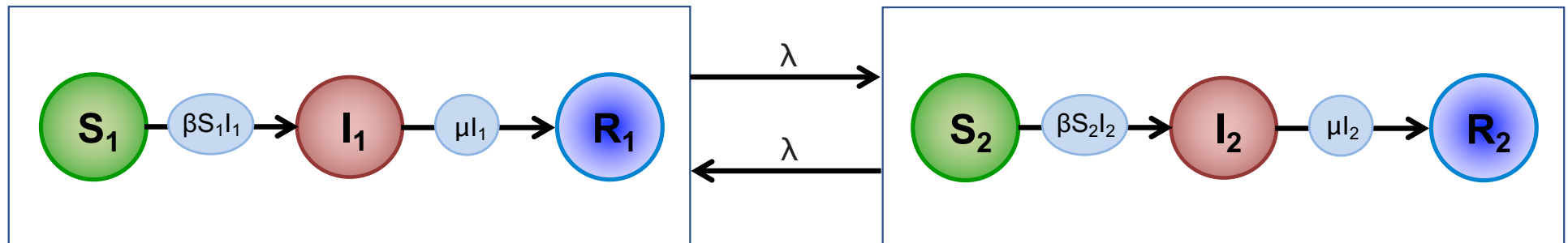
Compartmental models: Extensions to SIR model

5. Spatial structure



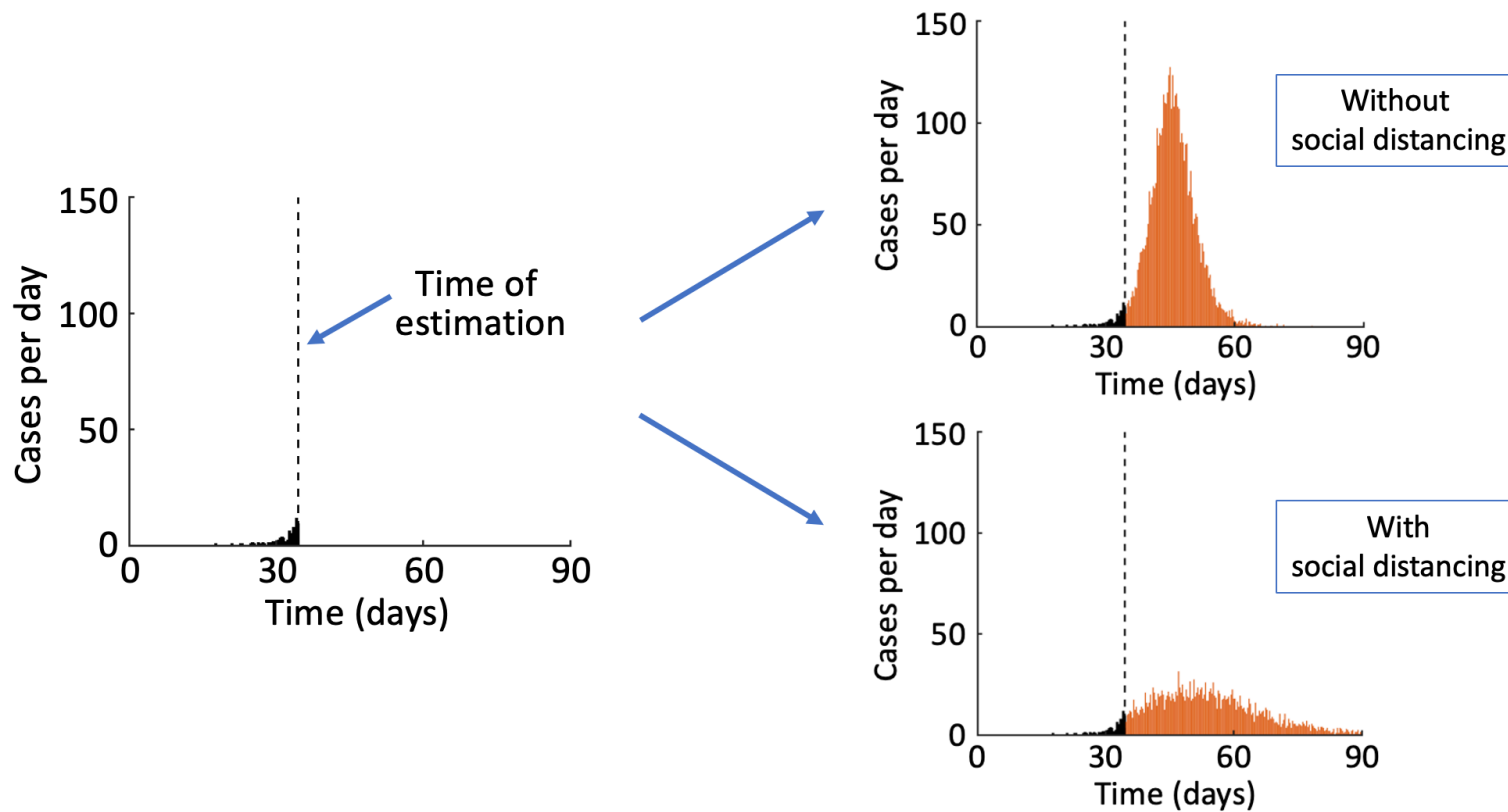
Region 1

Region 2



Compartmental models: Testing interventions

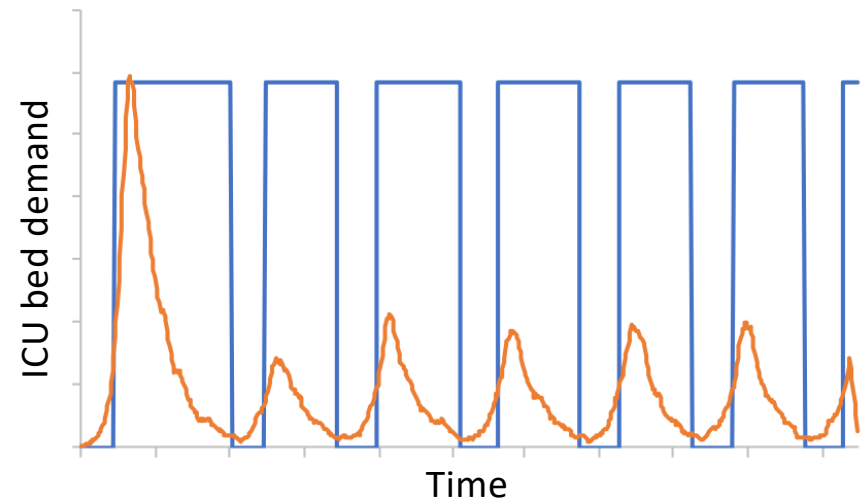
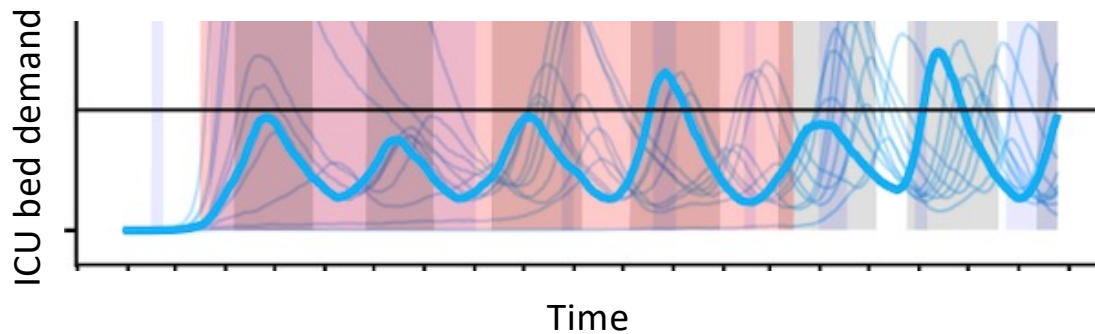
Models can be used to test counterfactual (“what if”) interventions



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

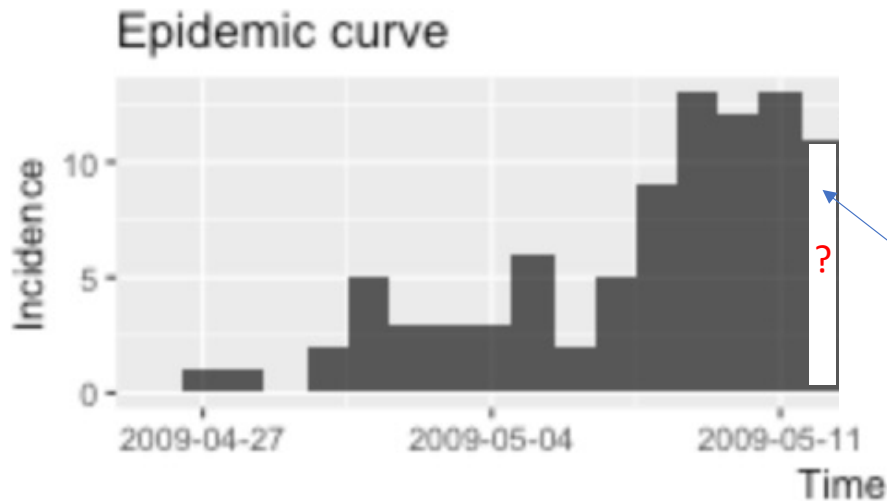
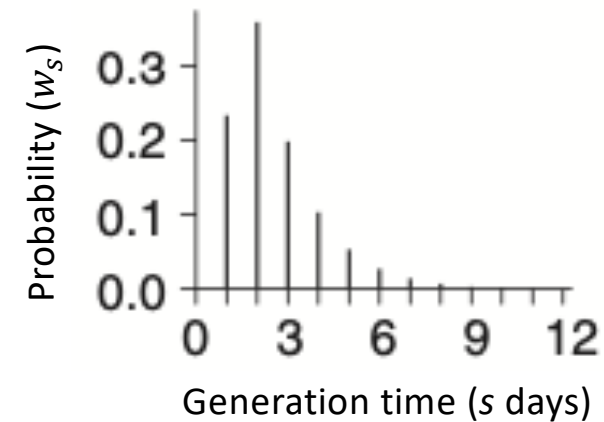
**Avoid need to divide hosts
into compartments; simply
count infections**

Renewal equation models

Avoid need to divide hosts into compartments; simply count infections

Know

R_t &



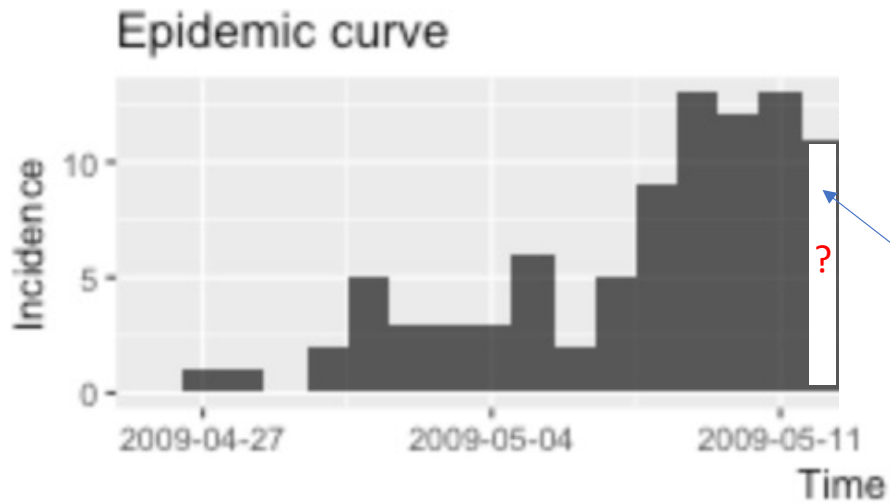
$$E(I_t | R_t, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\}) = R_t \sum_{s=1}^t I_{t-s} w_s$$

I_t cases

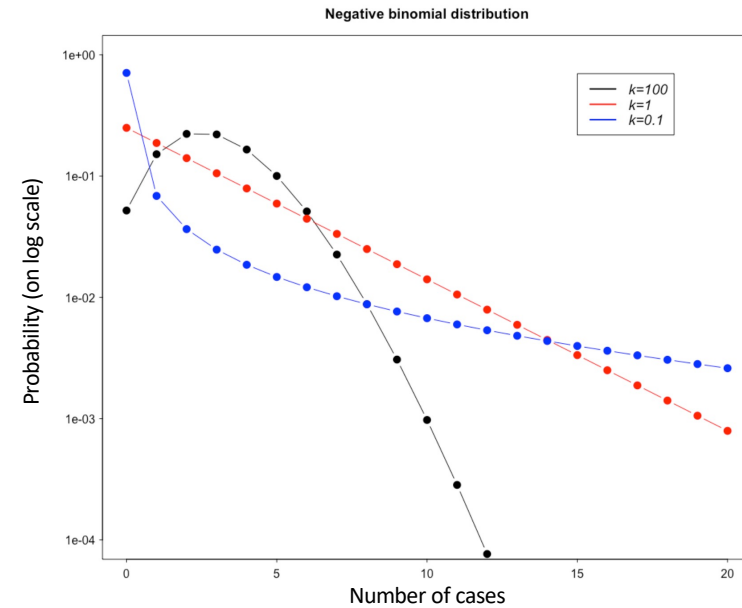
Draw from Poisson distribution or NB distribution

Renewal equation models

Can account for super-spreading events



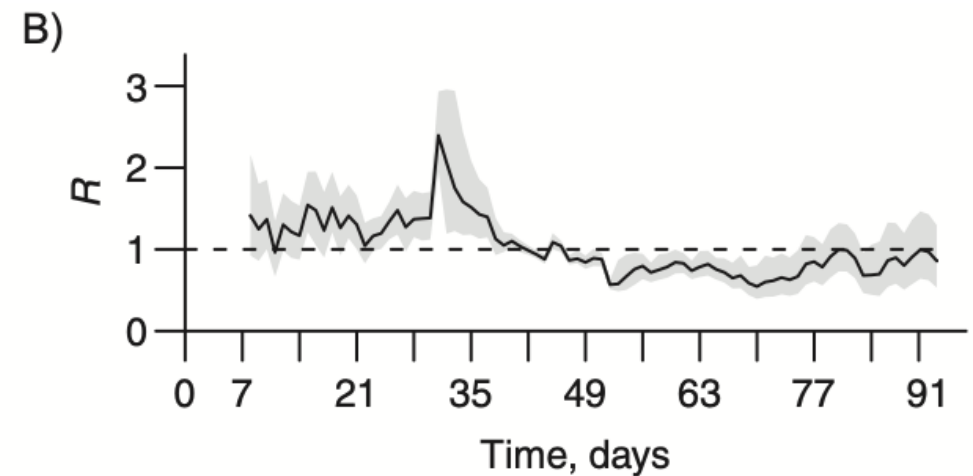
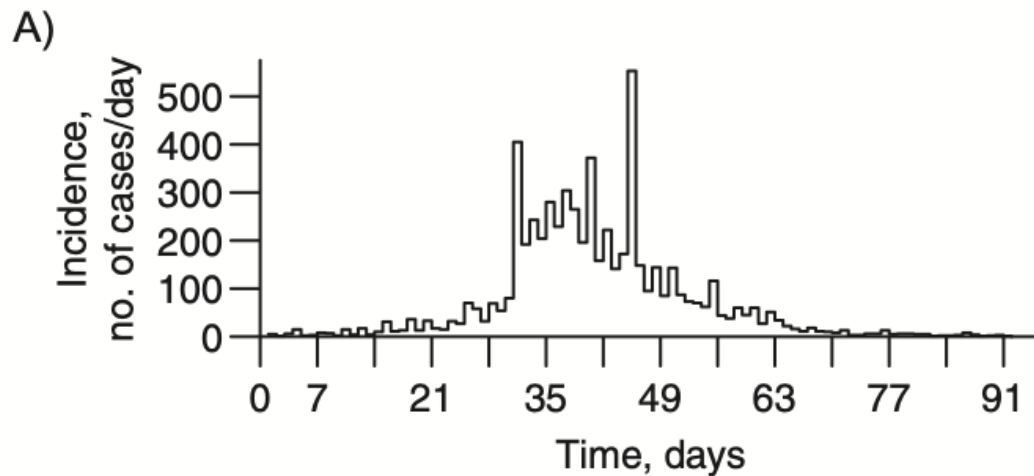
I_t cases



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

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

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- Possible mini project

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

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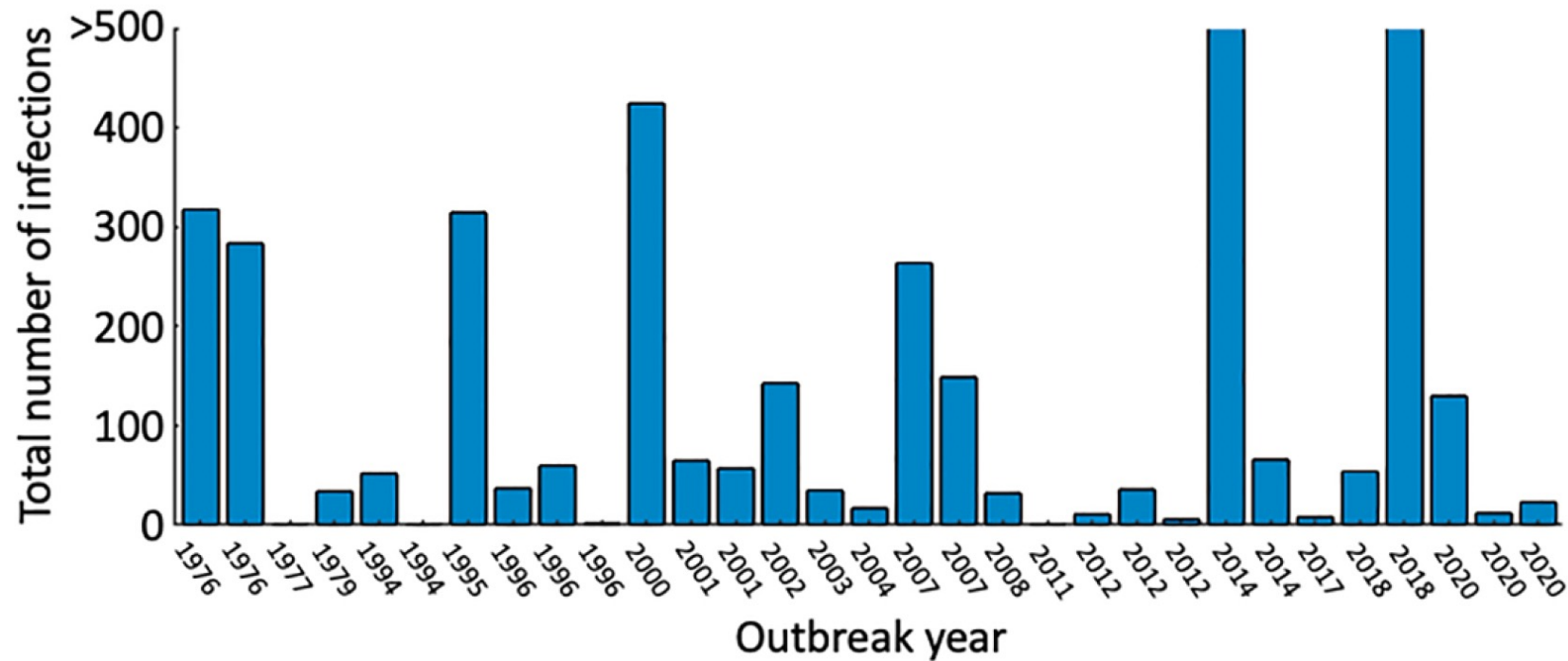
4. At the end of an epidemic: Assessing when the epidemic is over

- 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



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Journal of Theoretical Biology

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

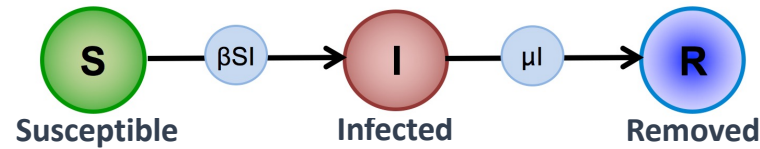


A practical guide to mathematical methods for estimating infectious disease outbreak risks

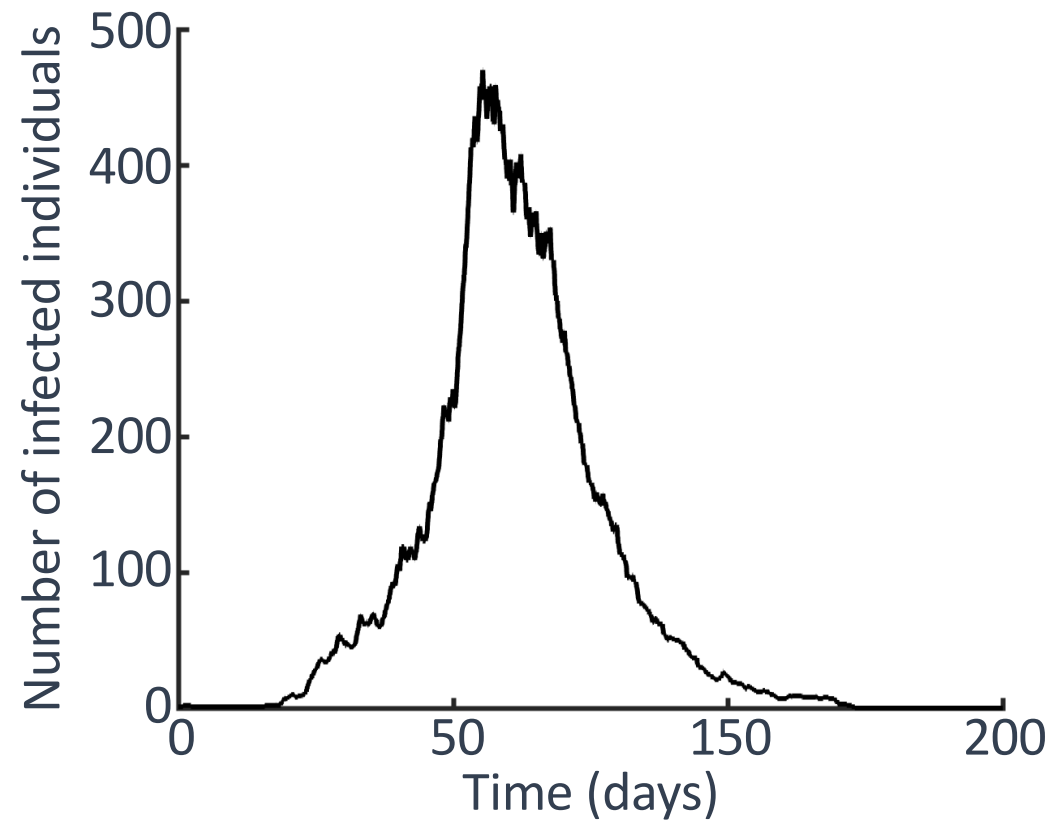
E. Southall^{a,b}, Z. Ogi-Gittins^{a,b}, A.R. Kaye^{a,b}, W.S. Hart^c, F.A. Lovell-Read^c, R.N. Thompson^{a,b,c}



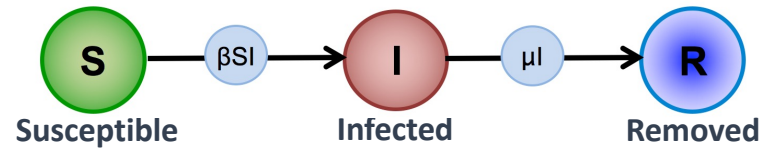
Assessing the risk of a major epidemic



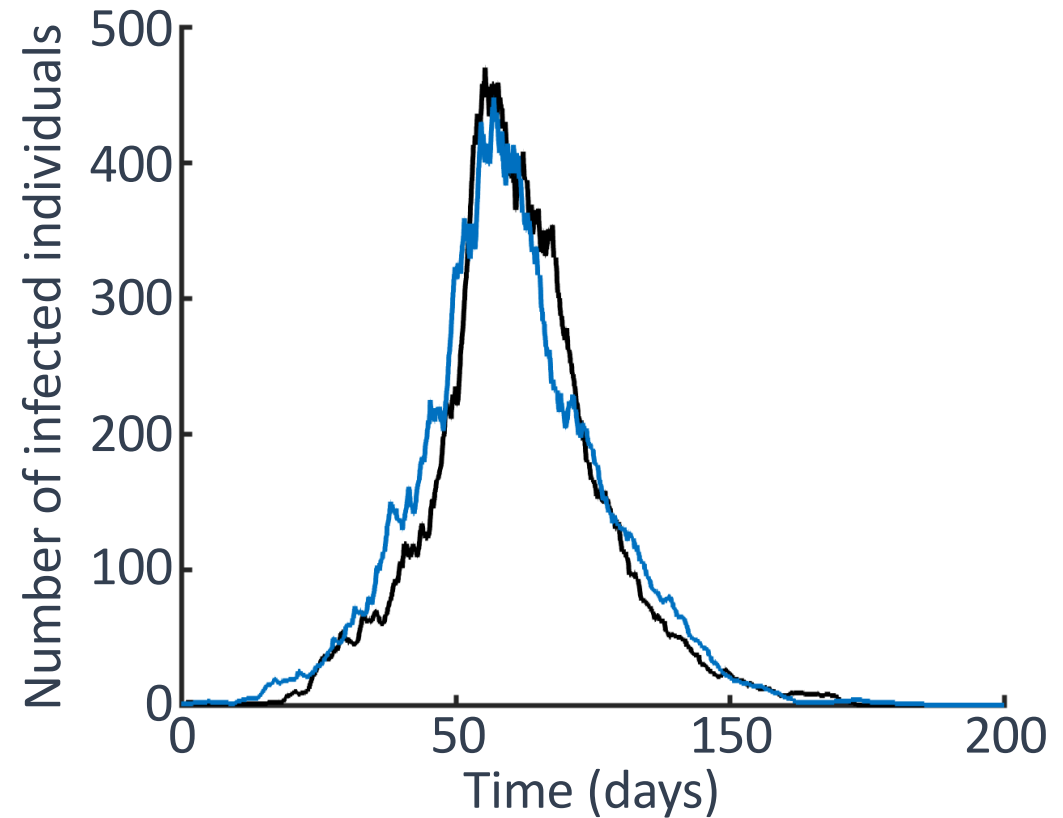
When a pathogen first arrives
in a new population, there are
two possibilities for what
happens next



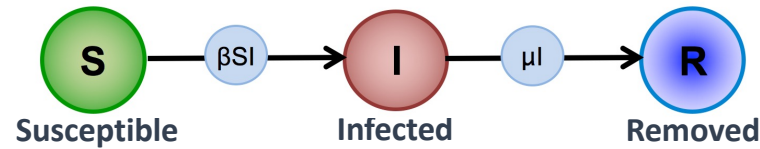
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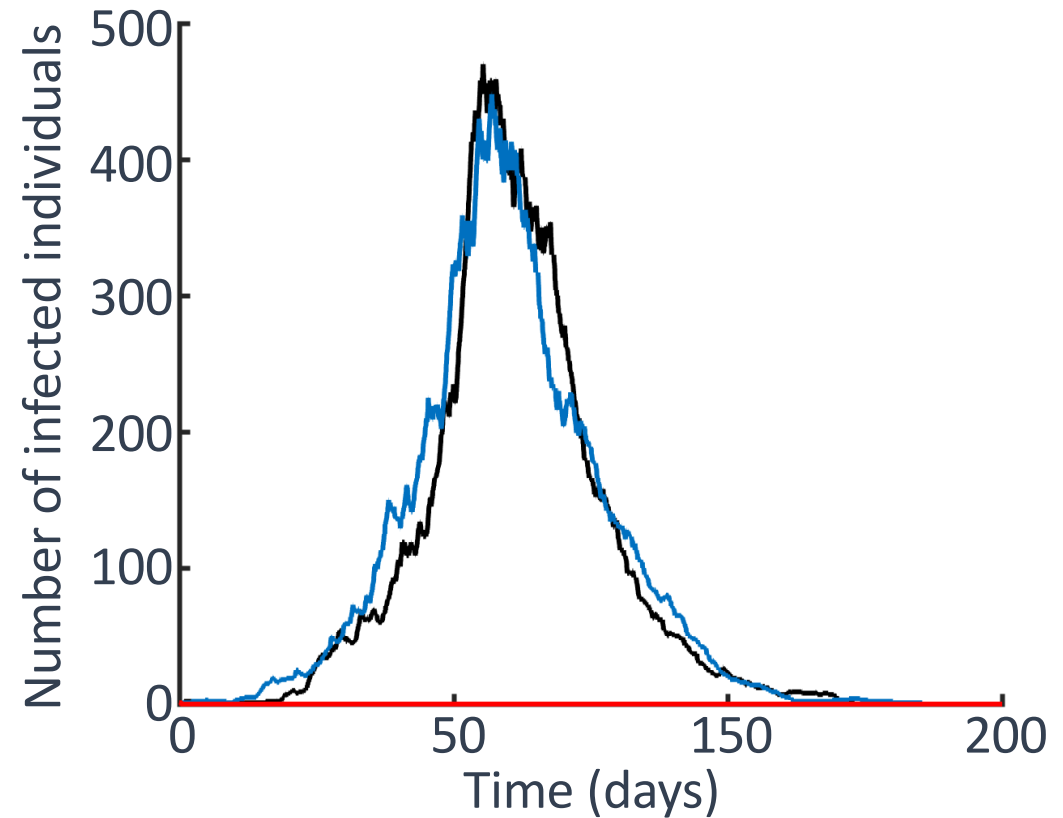
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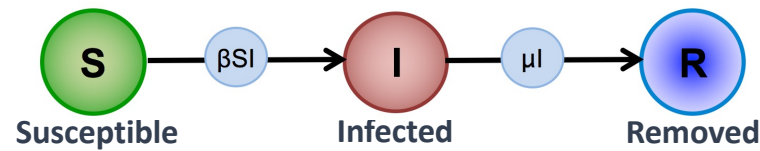
Assessing the risk of a major epidemic



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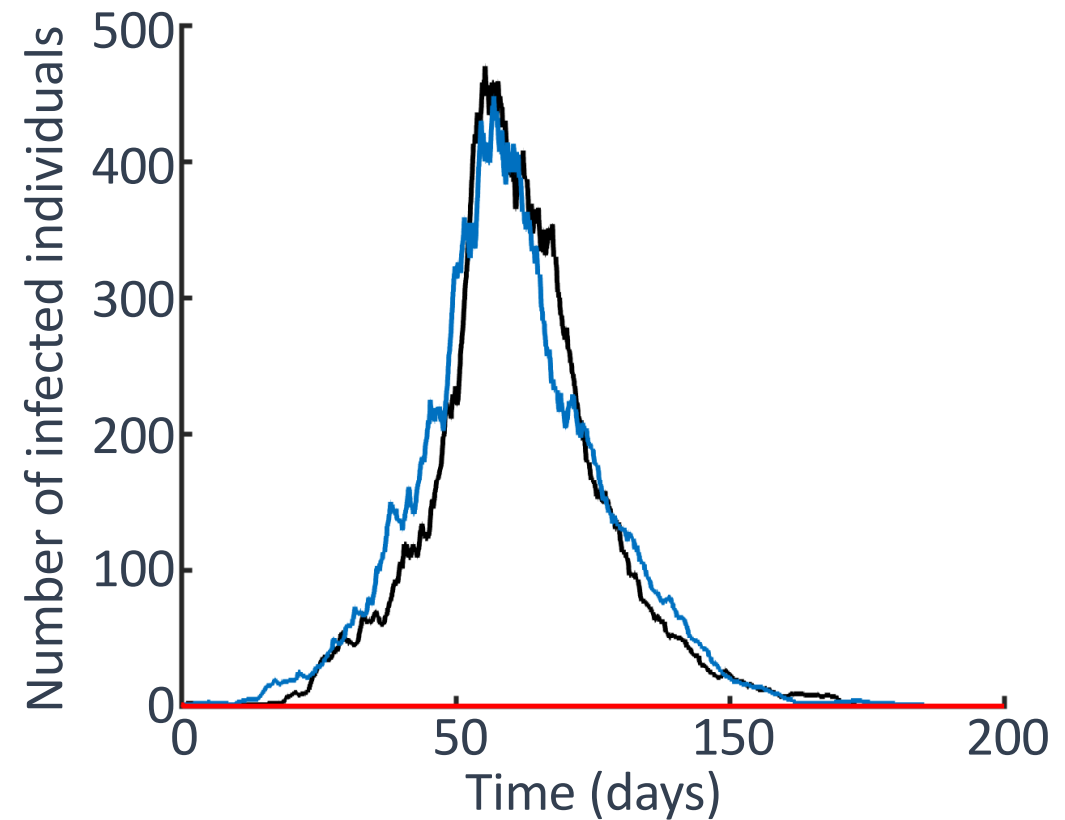
Assessing the risk of a major epidemic



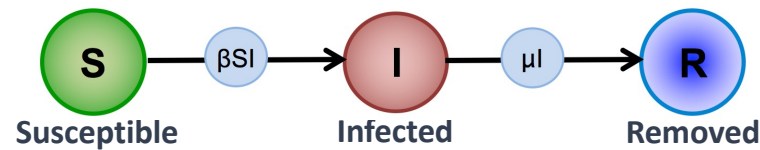
Epidemic Risk: the probability that an imported case leads to a major epidemic

If $ER = 0$; a major epidemic will not occur

If $ER = 1$; a major epidemic will definitely occur

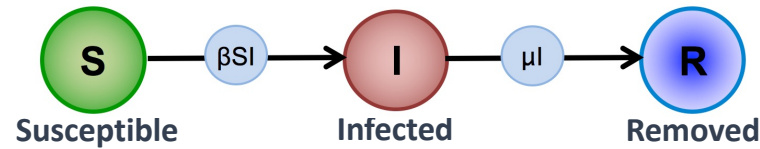


Assessing the risk of a major epidemic



- Assume we start with one infected individual
- Denote $q_i = \text{Prob}(\text{no major epidemic starting from } i \text{ infected individuals})$
- Want to find $1 - q_1$

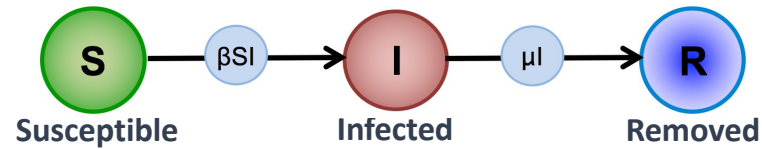
Assessing the risk of a major epidemic



Two possibilities for the next event: infection or recovery

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

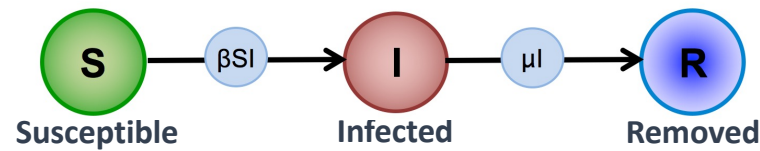
Assessing the risk of a major epidemic



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

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

$$q_1 = \frac{1}{R_e} \text{ or } 1$$

$$ER = 1 - q_1 = 1 - \frac{1}{R_e}$$

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. Gilligan³ and N. J. Cuniffe³



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

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Research



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

Francesca A. Lovell-Read^{1,2}, Sebastian Funk³, Uri Obolski^{4,5}, Christl A. Donnelly^{2,6} and Robin N. Thompson^{1,3,7,8}



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^{a,*}, Christopher A. Gilligan, Nik J. Cuniffe

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

THE LANCET Infectious Diseases

Robin N Thompson, Katri Jalava, *Uri Obolski

INTERFACE

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Research



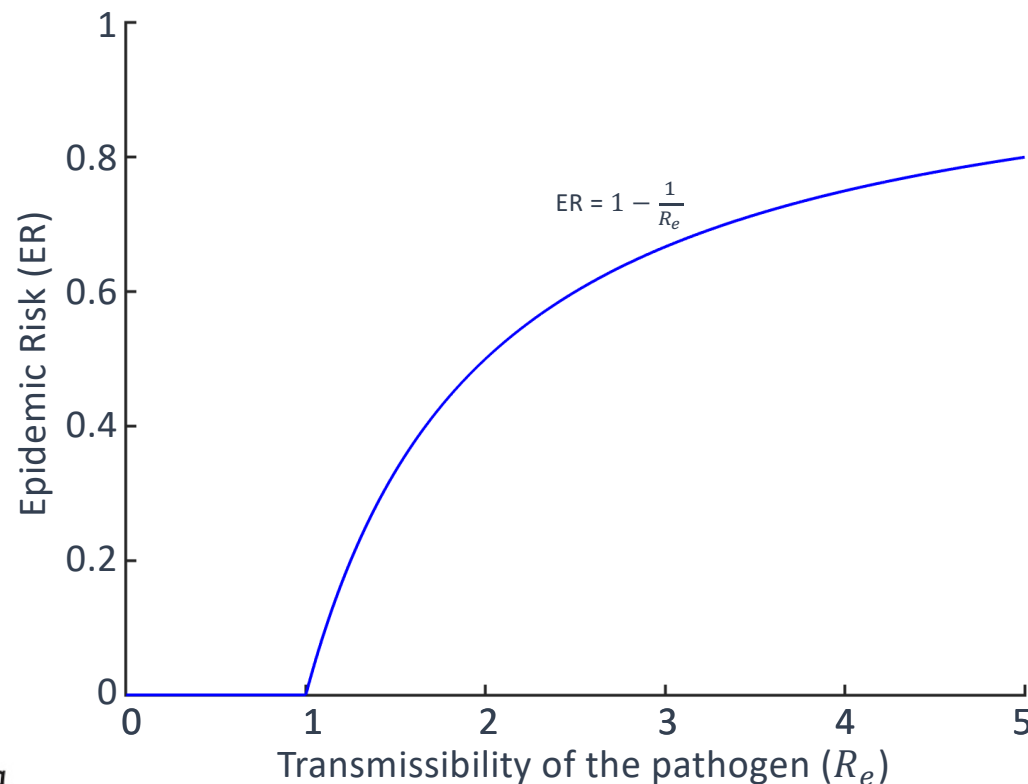
Reducing transmission in multiple settings is required to eliminate the risk of major Ebola outbreaks: a mathematical modelling study

Abbie Evans¹, William Hart¹, Stefano Longobardi², Rajat Desikan³, Anna Sher⁴ and Robin Thompson¹

PLOS COMPUTATIONAL BIOLOGY

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

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



Heterogeneity in reporting rates

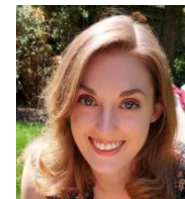
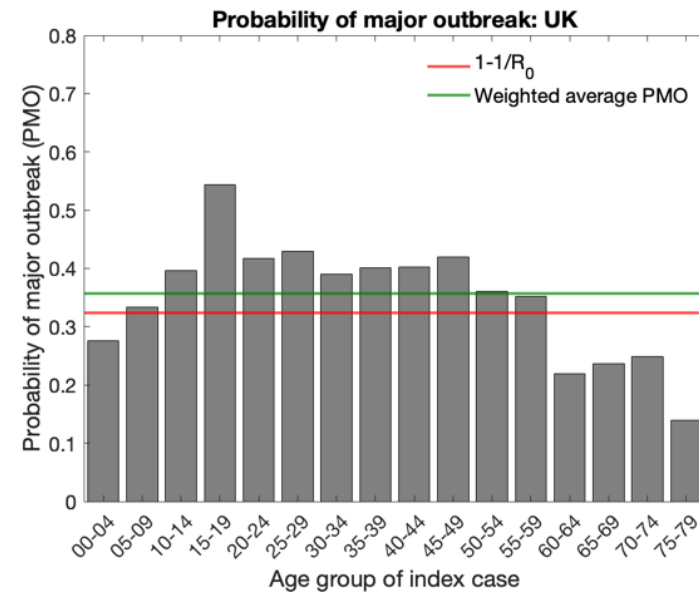
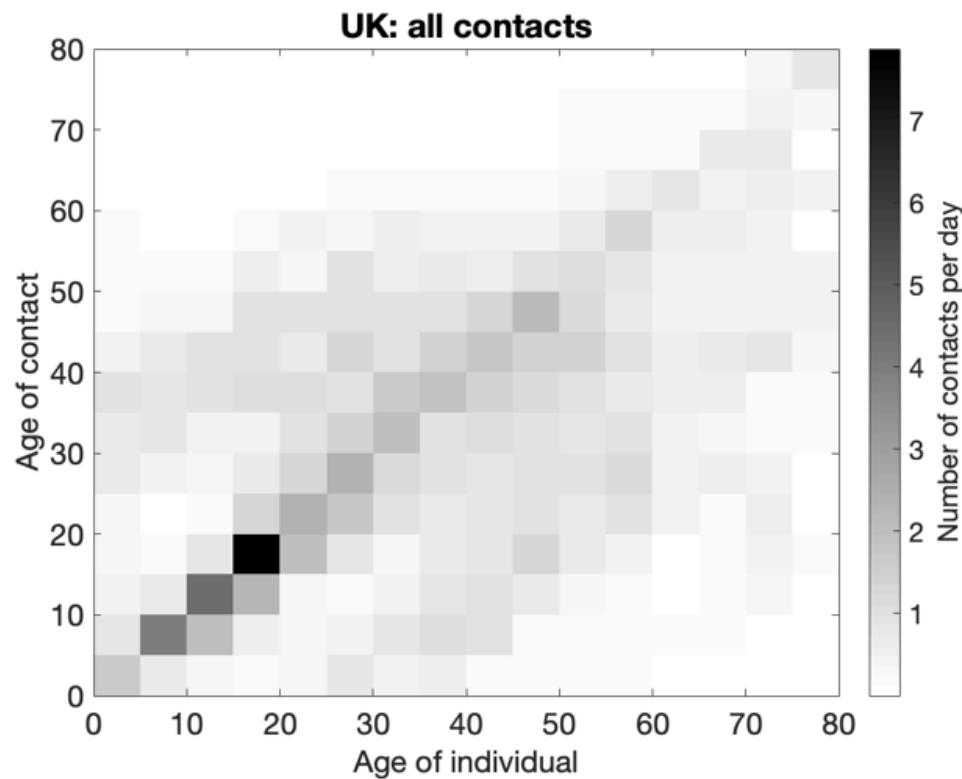
$q_{i,j}$ = Prob(no major epidemic | i fast reporters, j slow reporters)

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

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

Age structure

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



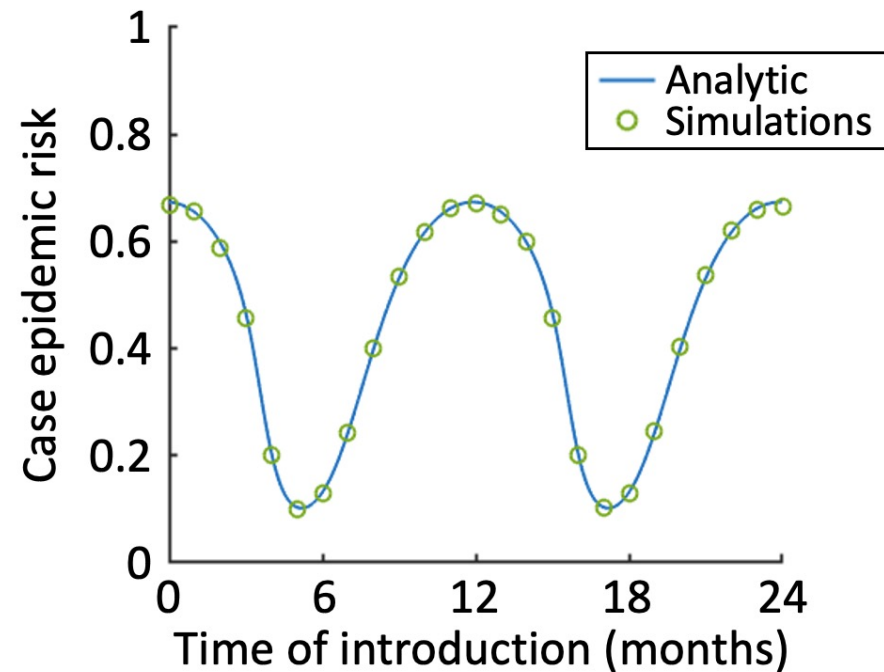
Estimating local outbreak risks and the effects of non-pharmaceutical interventions in age-structured populations: SARS-CoV-2 as a case study

Francesca A. Lovell-Read ^{a,*}, Silvia Shen ^{a,b}, Robin N. Thompson ^{c,d}



Time-dependence

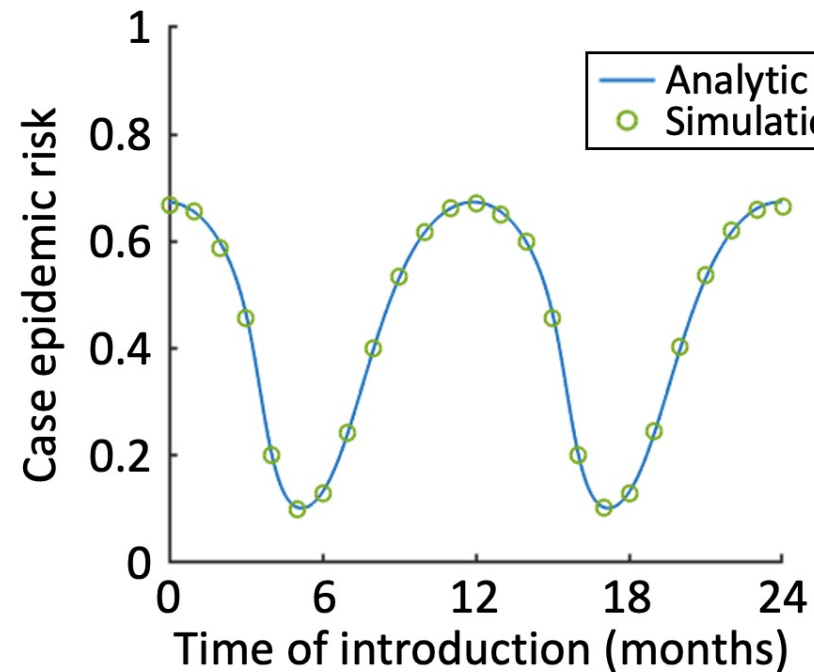
$$q(1, t) = q(2, t + \Delta t)\beta(t)N\Delta t + q(0, t + \Delta t)\mu\Delta t + q(1, t + \Delta t)(1 - \beta(t)N\Delta t - \mu\Delta t).$$



Time-dependence

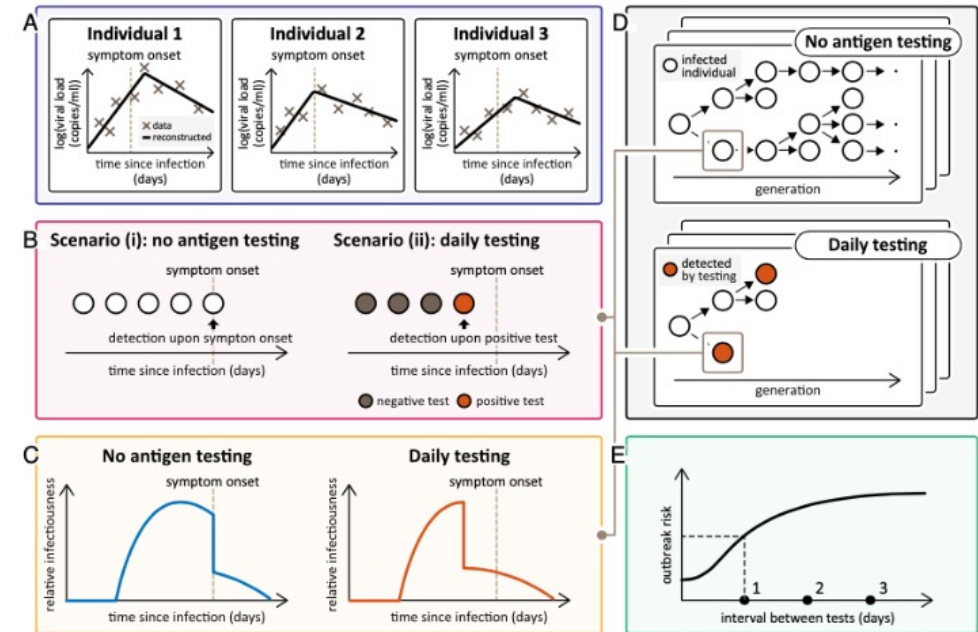
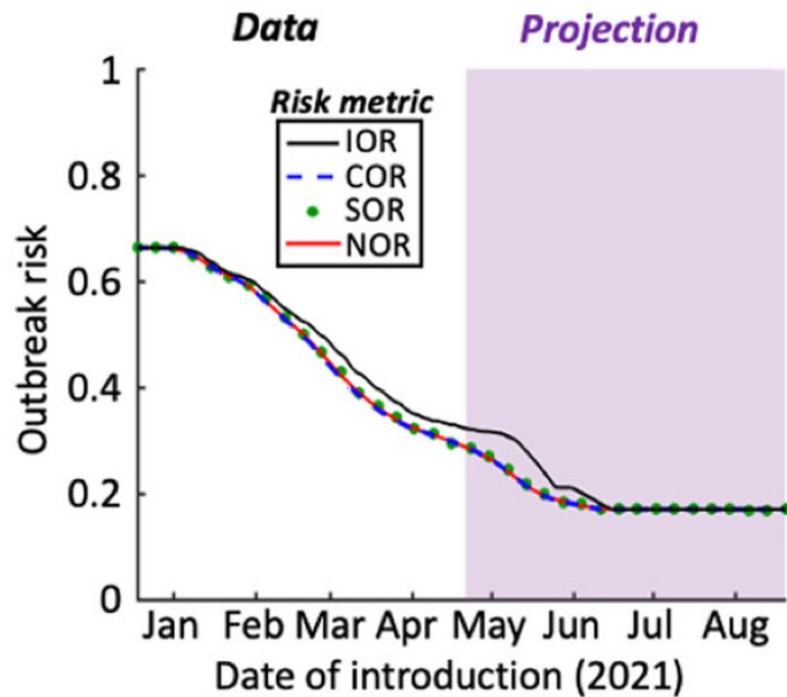
$$q(1, t) = q(2, t + \Delta t)\beta(t)N\Delta t + q(0, t + \Delta t)\mu\Delta t + q(1, t + \Delta t)(1 - \beta(t)N\Delta t - \mu\Delta t).$$

$$\frac{dq_1(t)}{dt} = -\beta(t)q_1(t)^2 + (\beta(t) + \mu(t))q_1(t) - \mu(t).$$



A direct comparison of methods for assessing the threat from emerging infectious diseases in seasonally varying environments
A.R. Kaye^{a,*}, W.S. Hart^a, J. Bromiley^a, S. Iwami^b, 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-Patwa¹, Helen M. Byrne¹, 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^{1,2}, Hyeonki Park³, Yong Dam Jeong^{3,4}, Kwang Su Kim^{5,6}, Raiki Yoshimura⁷, Robin N. Thompson^{1,2,3} and Shingo Iwami^{8,9,10,11,12}

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

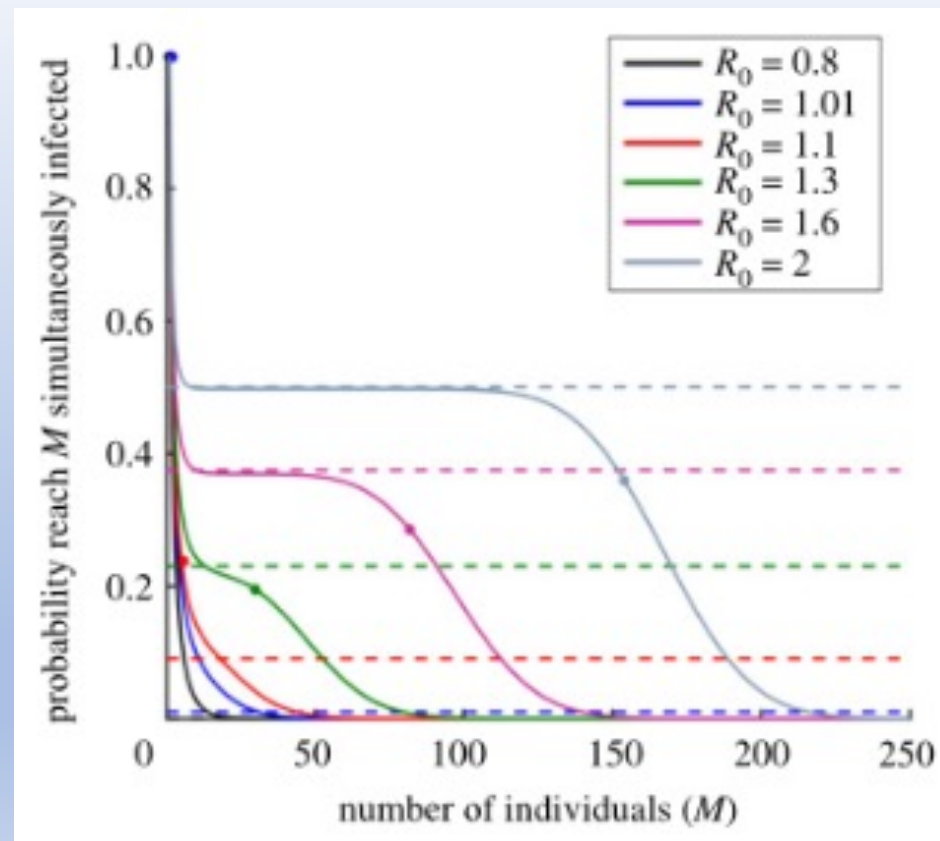
1. Using mathematical models to estimate outbreak risks

- 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

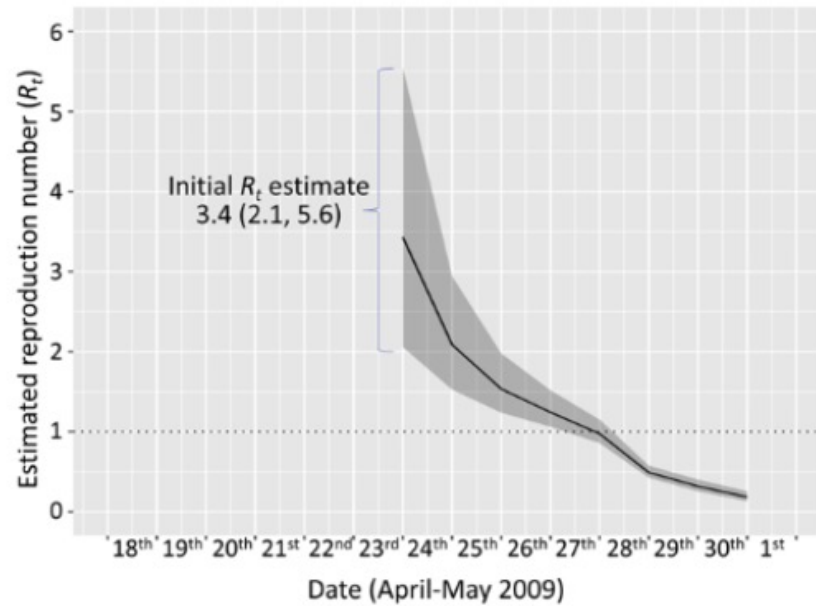
- Inferring current transmissibility [renewal equation model]
- Possible mini project

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?



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

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

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

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

Ready

Step 1 of at most 9. View the [interactive documentation](#) for this state.

Incidence Data

Do you want to use pre-loaded incidence time series data or upload your own?

☒ Pre-loaded

☐ Own data

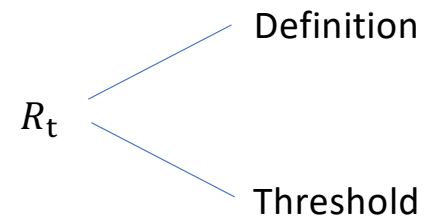
Previous

Next

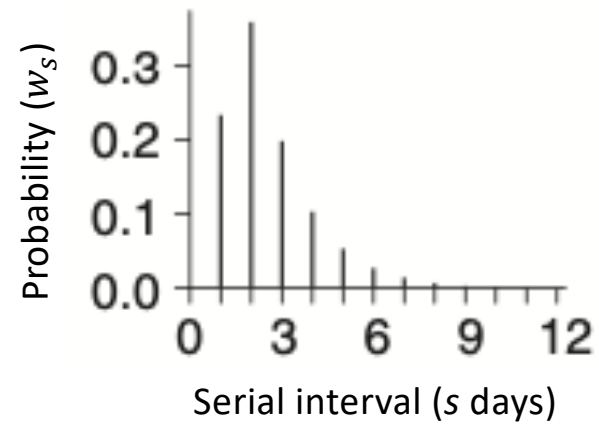
Thompson *et al.*, Epidemics, 2019

Two important quantities

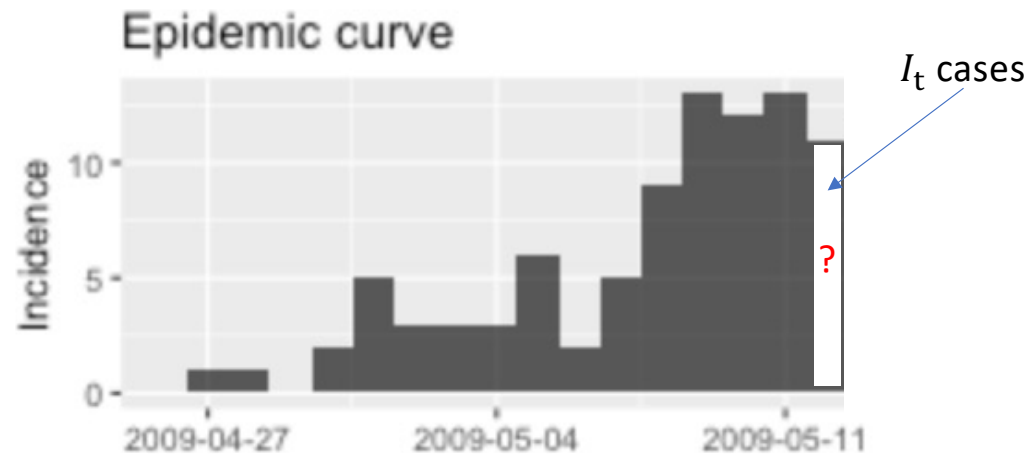
Time dependent
reproduction number



Generation time/
serial interval



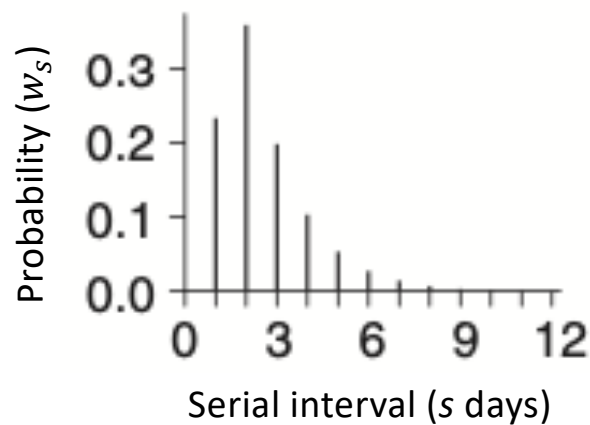
Renewal equation model



Know

R_t

&

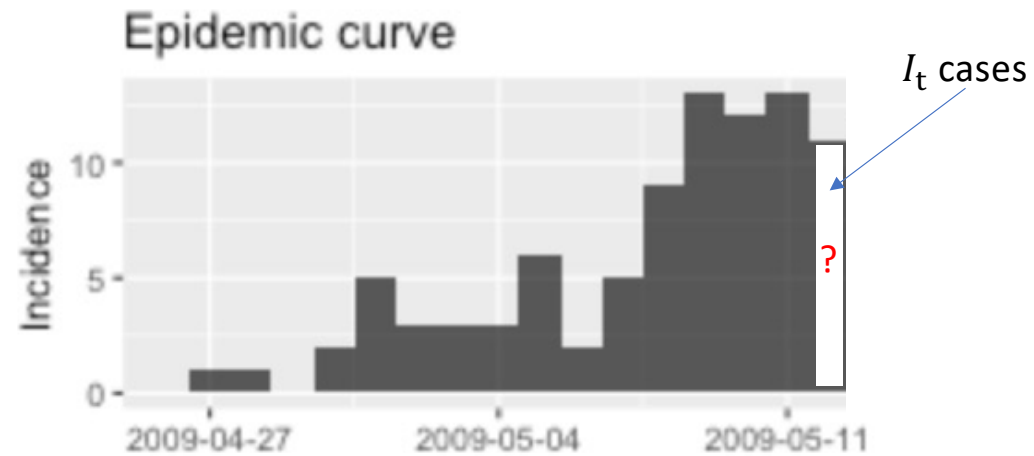


Basic model

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

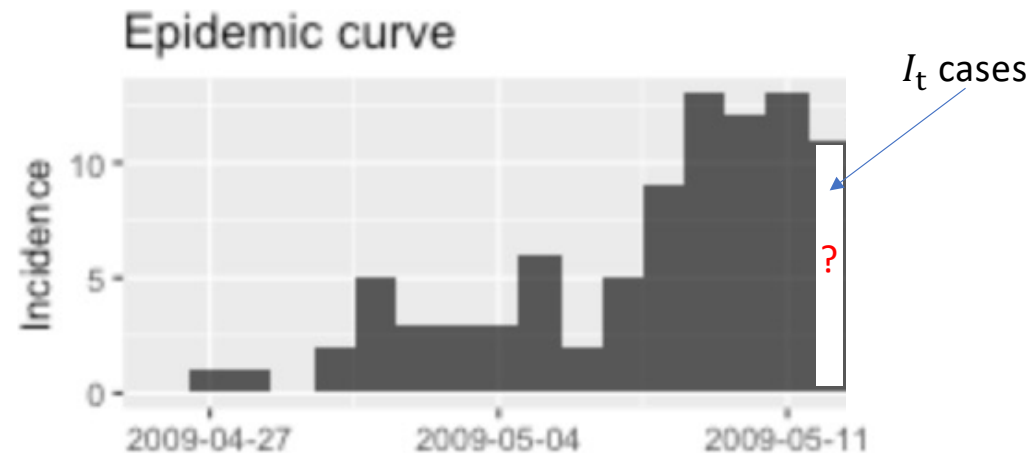
$$P(I_t = x | R_t, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\}) = \frac{(E(I_t))^x \exp(-E(I_t))}{x!}$$

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



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

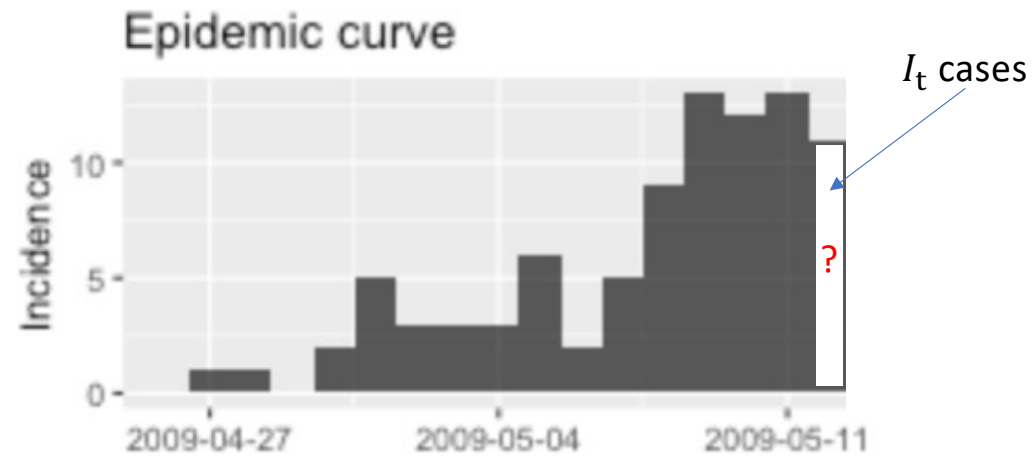
$$P(I_t = x | R_t, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\}) \quad \longrightarrow \quad P(R_t | I_t = x, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\})$$



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

$$P(I_t = x | R_t, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\}) \quad \longrightarrow \quad P(R_t | I_t = x, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-1}\})$$

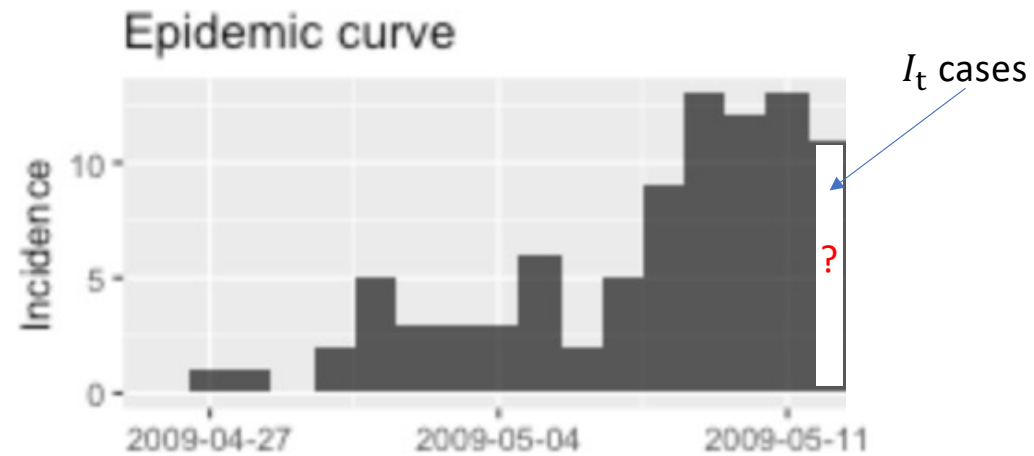
Generates estimates of R_t that are highly sensitive to randomness in I_t
 Solution: Consider constant R_t over a window $\{t - \tau, t - \tau + 1, \dots, t\}$



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

$$P(I_{t-\tau} = x_{t-\tau}, \dots, I_t = x_t | R_t, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-\tau-1}\}) \quad \longrightarrow \quad P(R_t | I_{t-\tau} = x_{t-\tau}, \dots, I_t = x_t, \{w_s\}, \{I_0, I_1, I_2, \dots, I_{t-\tau-1}\})$$

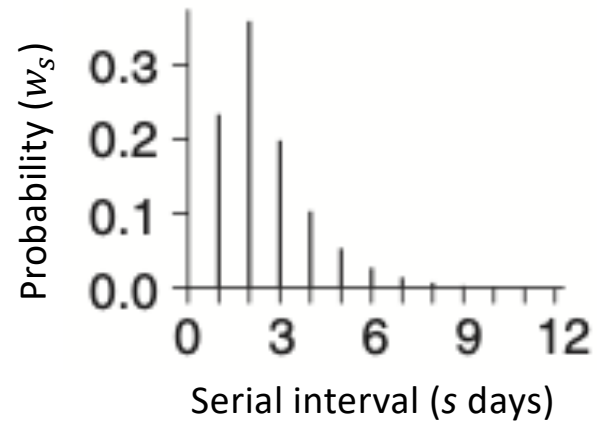
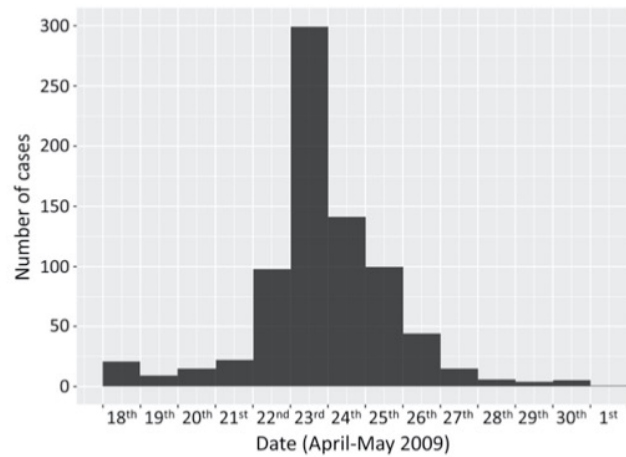
Solution: Consider constant R_t over a window $\{t - \tau, t - \tau + 1, \dots, t\}$



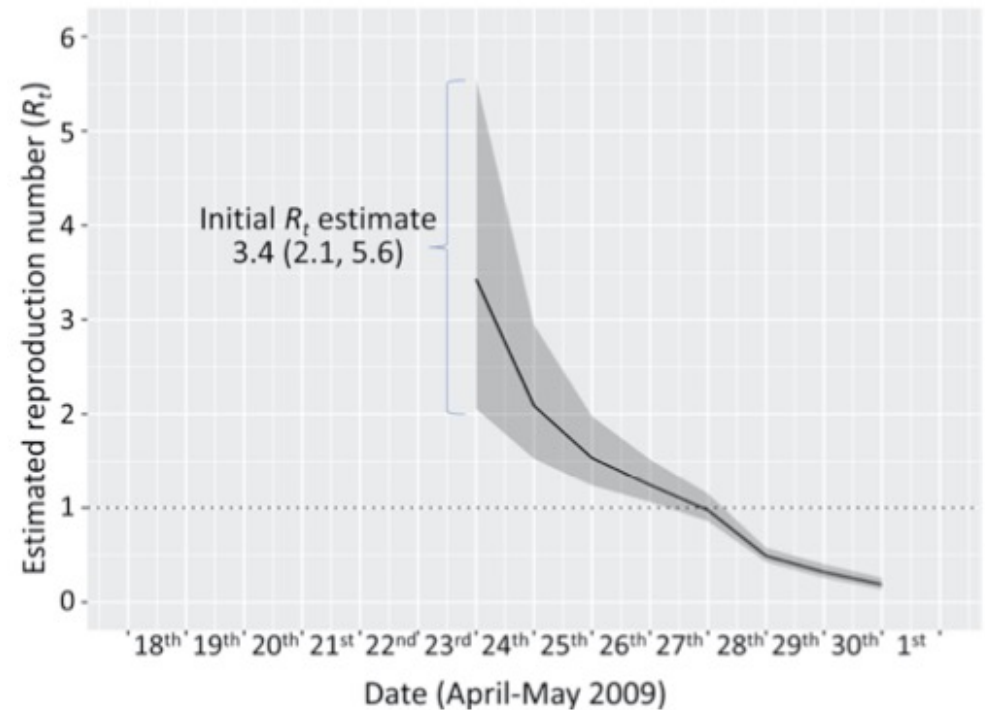
Special case: If the prior for R_t is a gamma distribution with shape parameter α and rate parameter β , then the posterior for R_t is also a gamma distribution with

Shape parameter: $\alpha + \sum_{k=0}^{\tau} I_{t-k}$

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

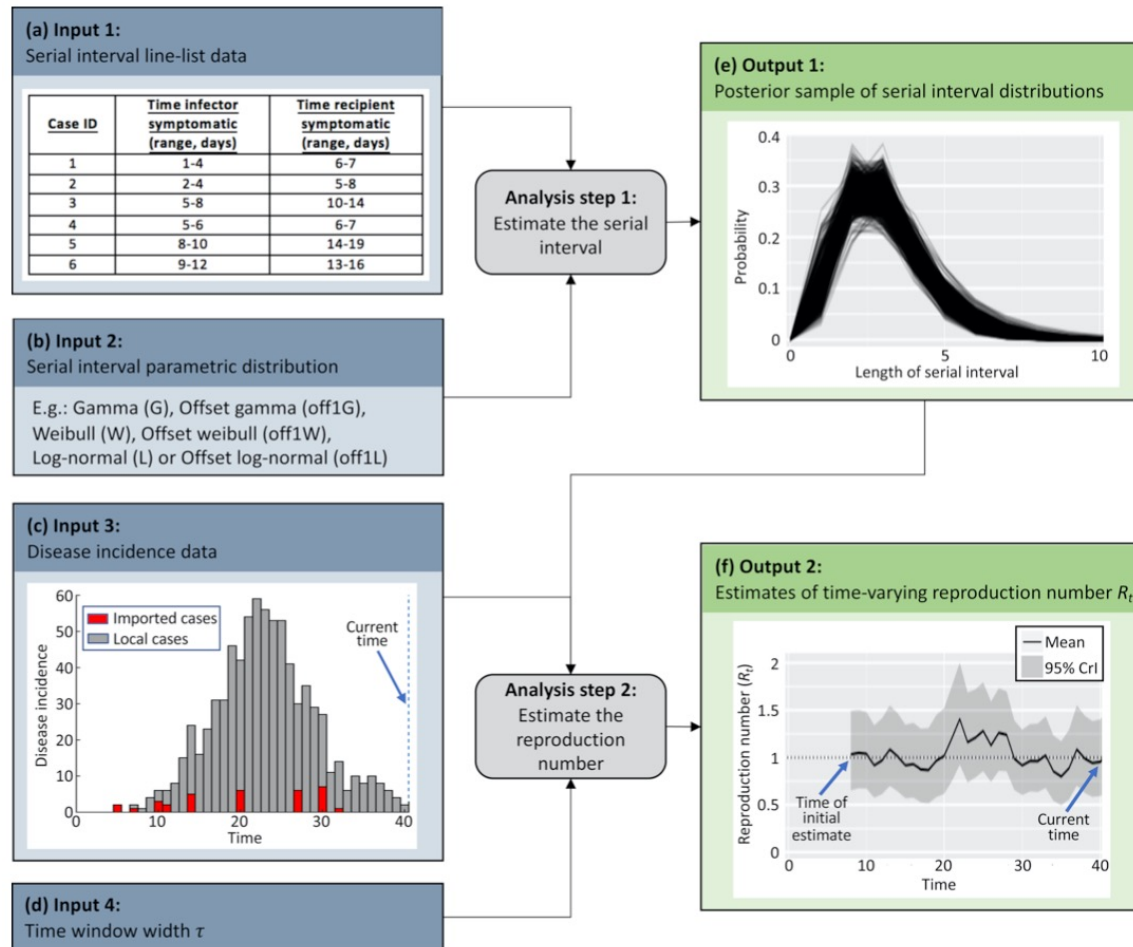


Window length: τ days



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

Uncertainty in the serial interval, imported cases



Ready

Step 1 of at most 9. View the [interactive documentation](#) for this state.

Incidence Data

Do you want to use pre-loaded incidence time series data or upload your own?

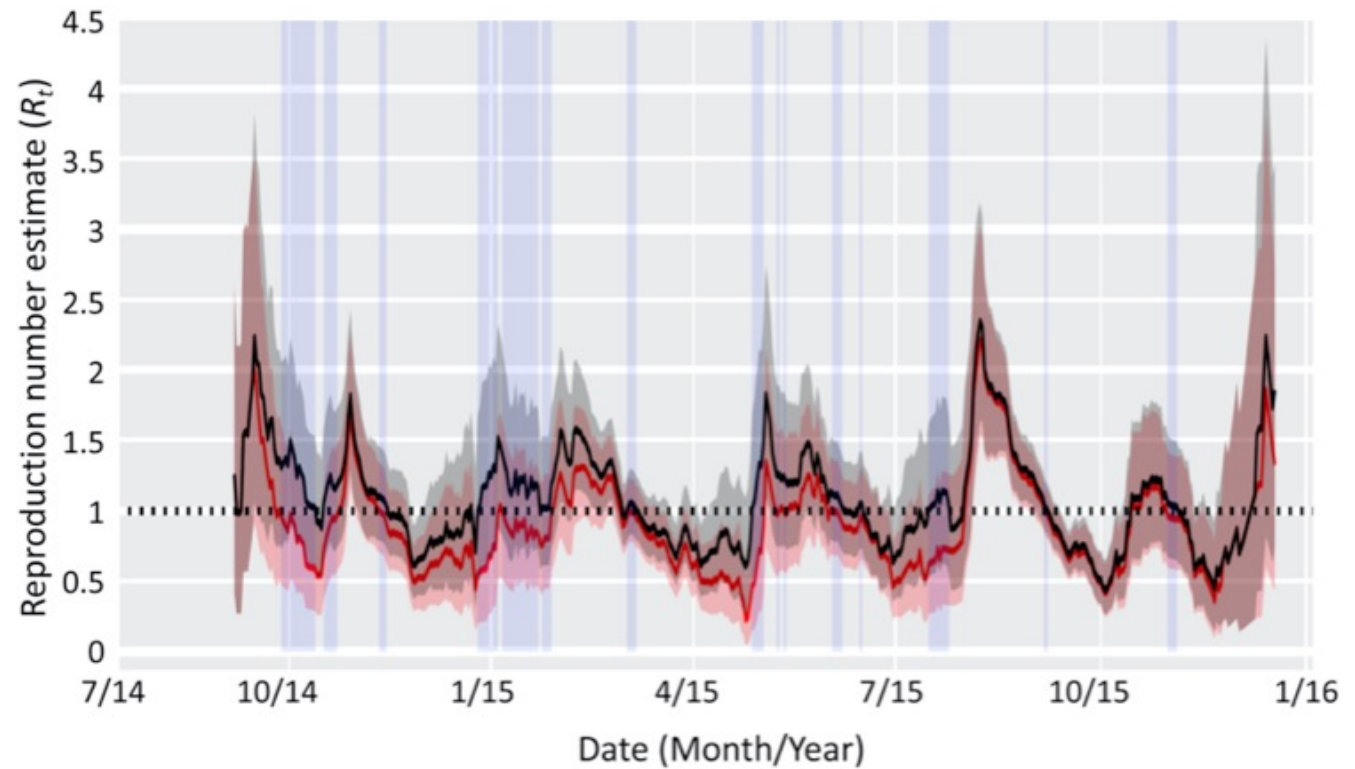
☒ Pre-loaded

☐ Own data

Previous Next

Imported cases

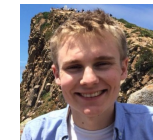
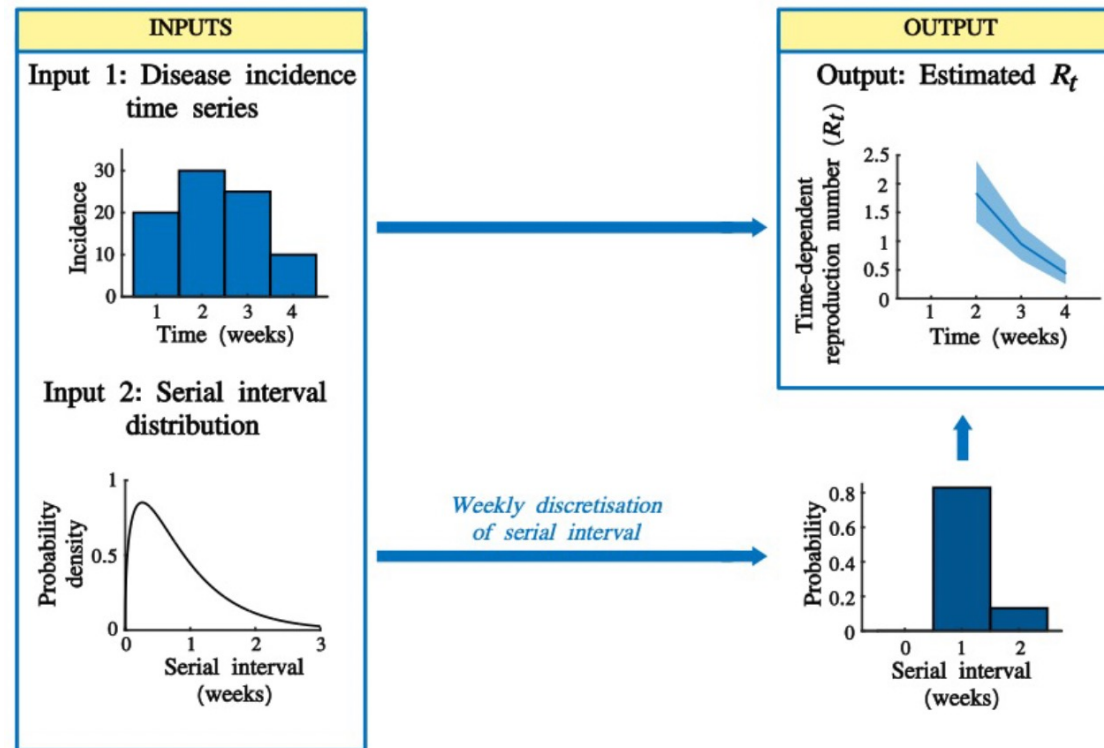
Imported cases have
not been infected
locally



Temporally aggregated data

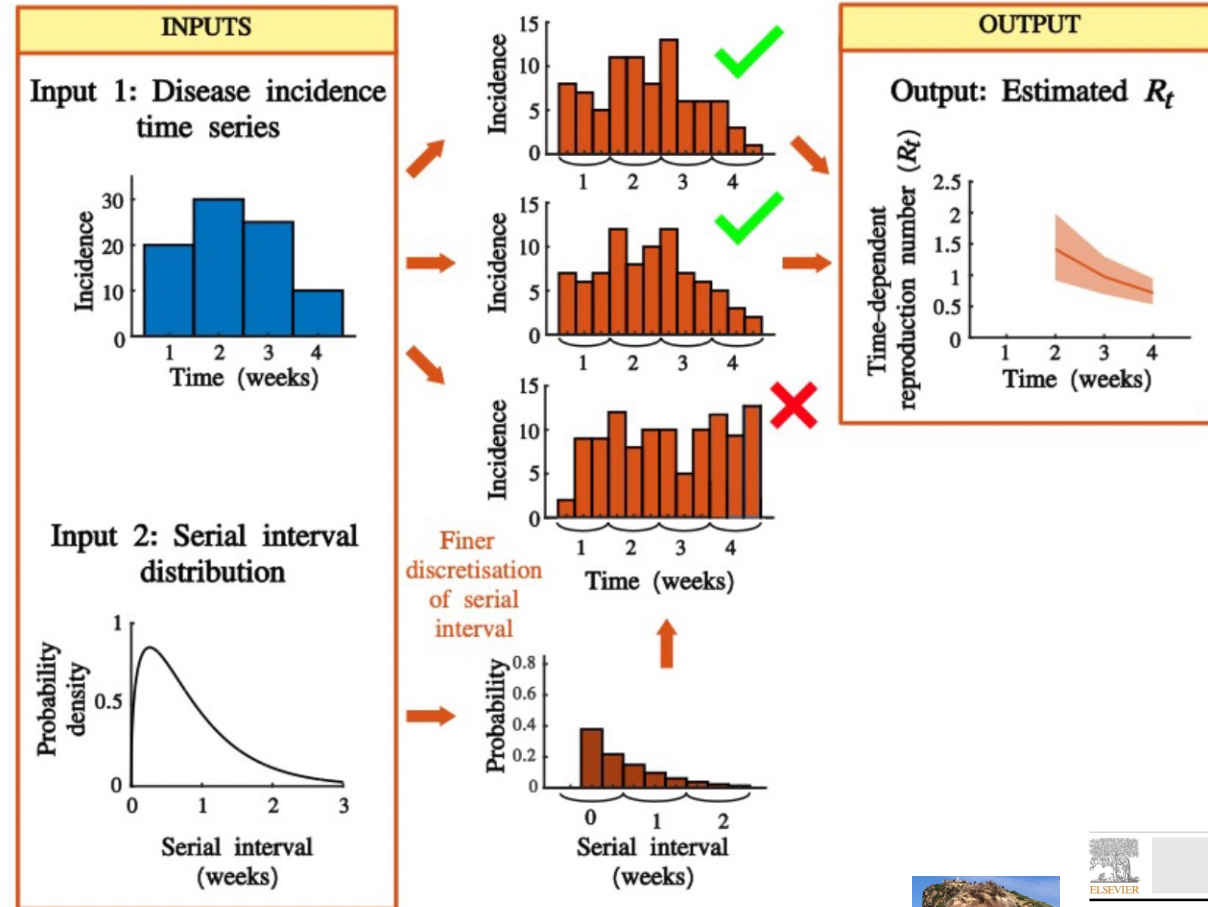
Data are often not reported daily

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

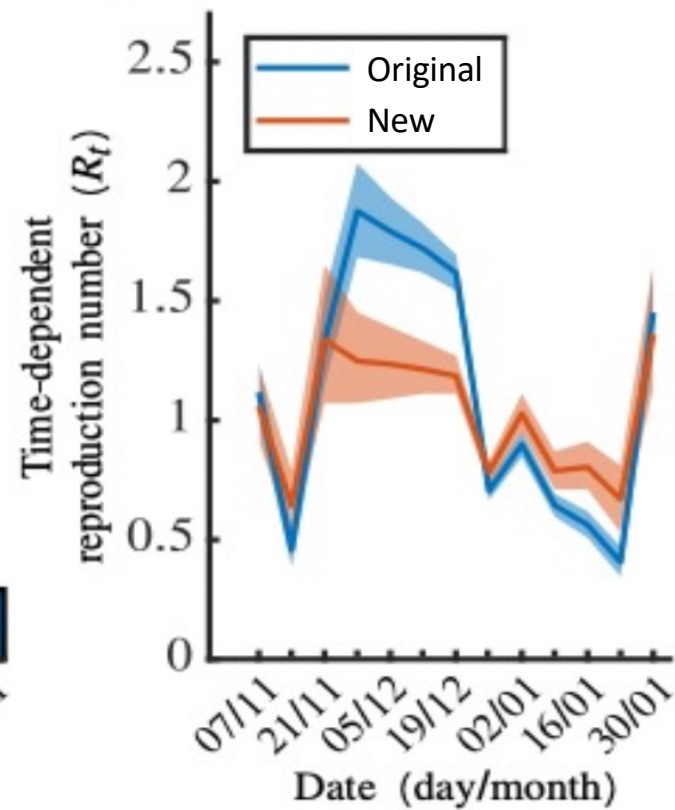
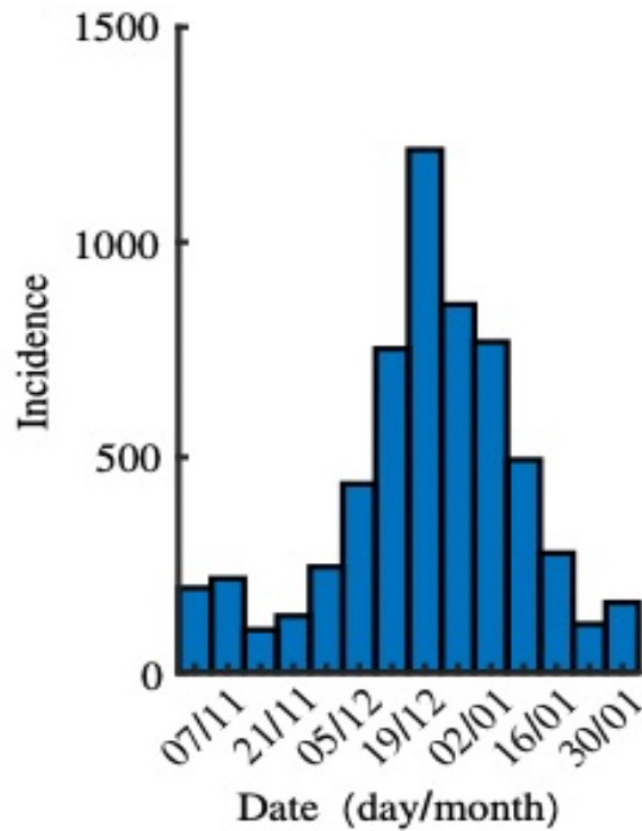


Temporally aggregated data

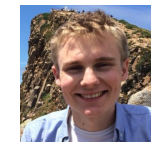
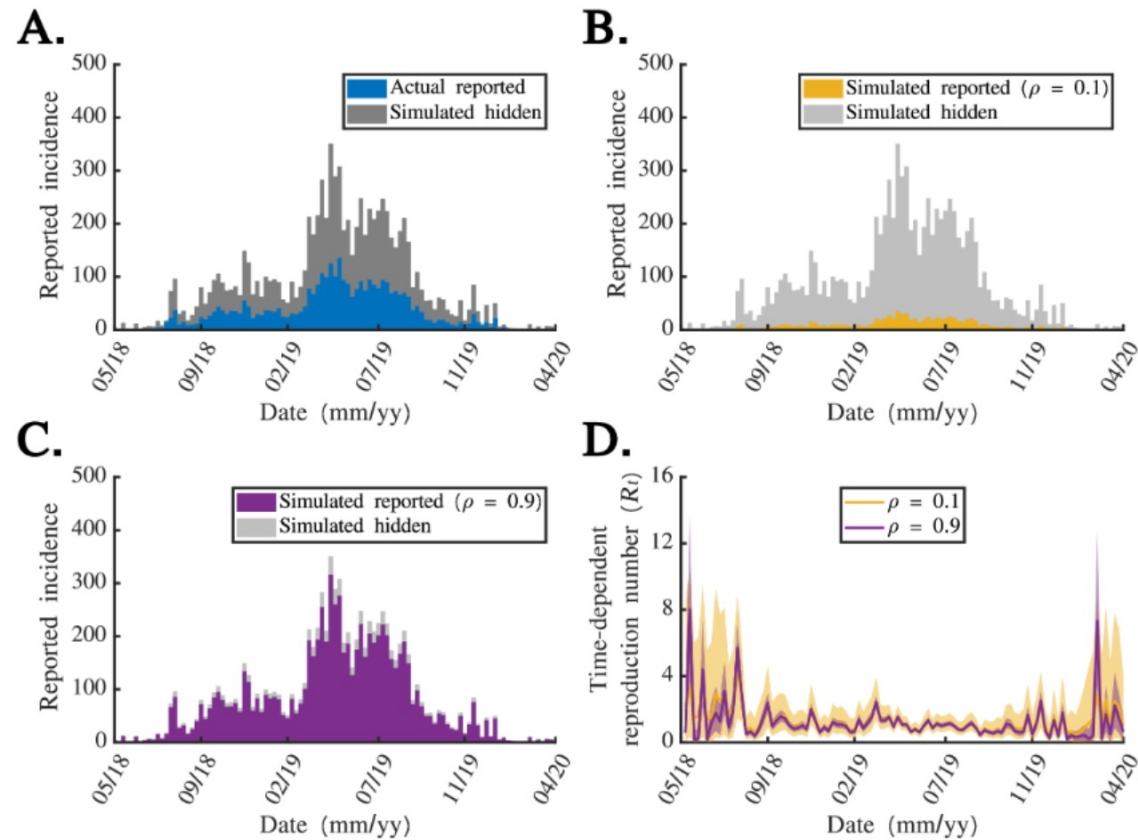
Data are often not reported daily



Temporally aggregated data



Stochastic under-reporting

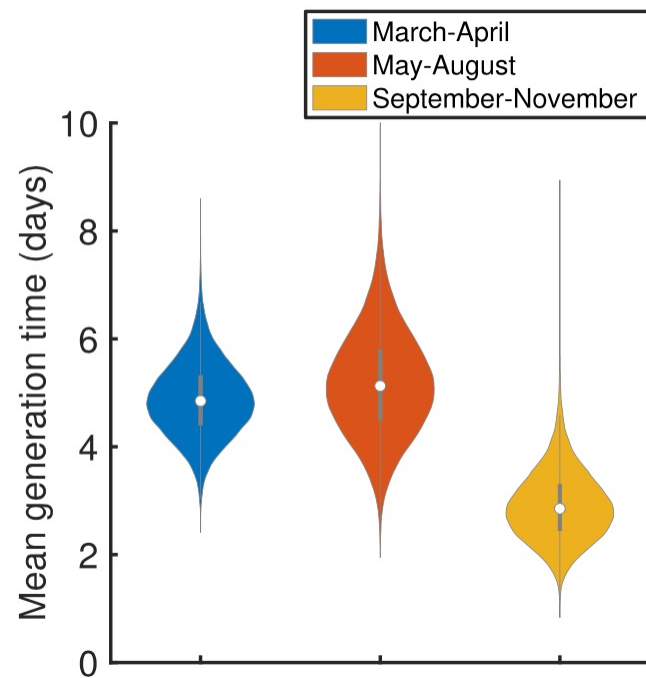


PHILOSOPHICAL
TRANSACTIONS A
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Research
Cite this article: Ogi-Gittins I, Steyn N, Polonsky J, Hart WS, Keita M, Ahuka-Mundike S, Hill EM, Thompson RN. 2020 Simulation-based inference of the time-dependent reproduction number from temporally aggregated and under-reported disease incidence time series data. *Phil. Trans. R. Soc. A* **388**: 20200412.

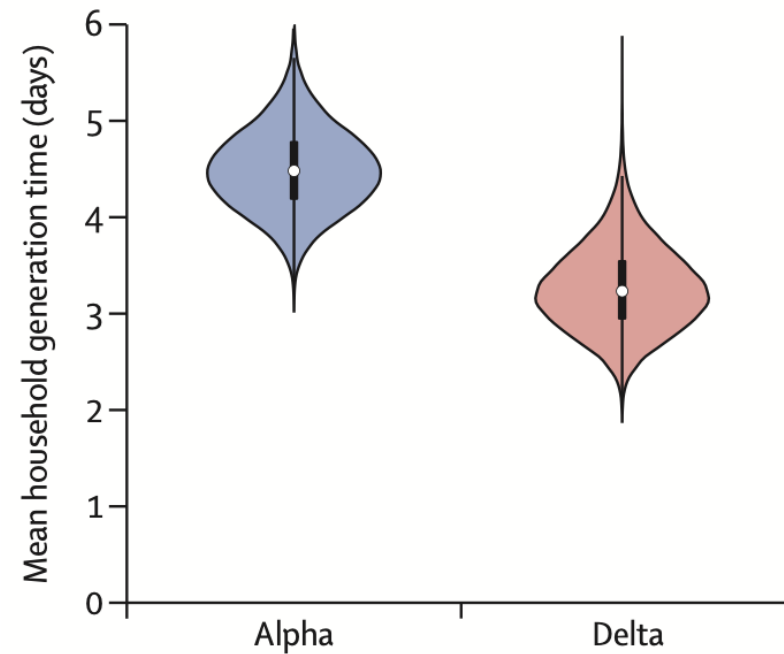
Simulation-based inference of the time-dependent reproduction number from temporally aggregated and under-reported disease incidence time series data

Isaac Ogi-Gittins^{1,2}, Nicholas Steyn³, Jonathan Polonsky³, William S. Hart⁴, Mory Keita^{1,5}, Steve Ahuka-Mundike⁶, Edward M. Hill¹⁰ and Robin N. Thompson⁷

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.*

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- 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'Unienville/Associated Press

Uganda declares end to latest ebola outbreak

By Elias Biryabarema

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

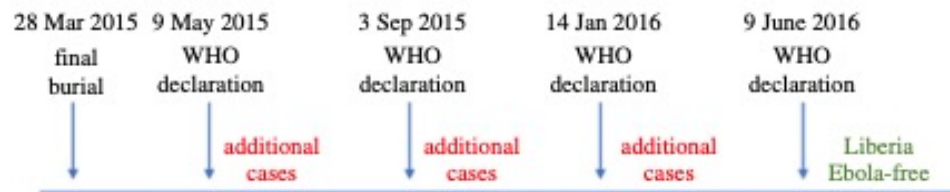


WHO recommended criteria for declaring the end of the Ebola virus disease outbreak

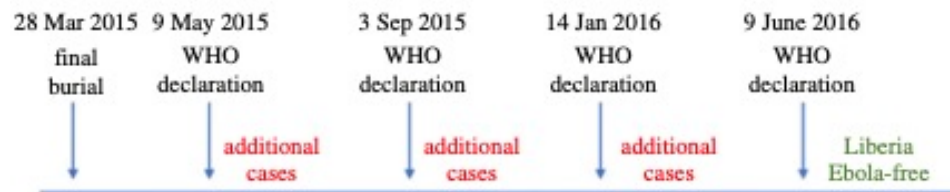
Technical information note - updated 4 March 2020

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?



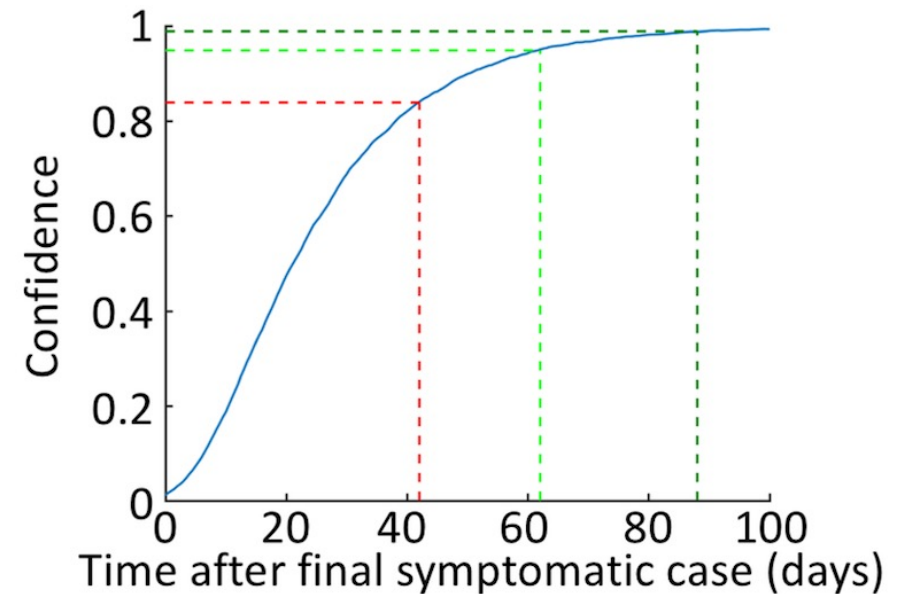
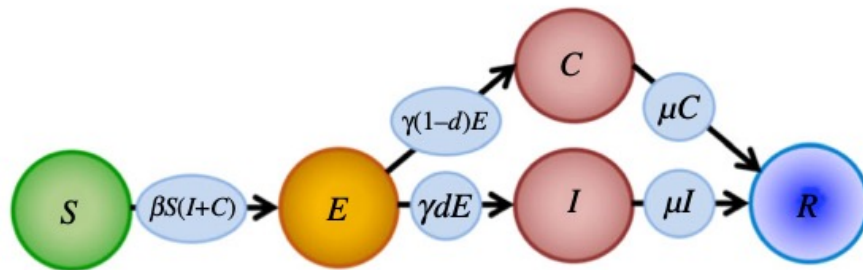
When can outbreaks be declared over?



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

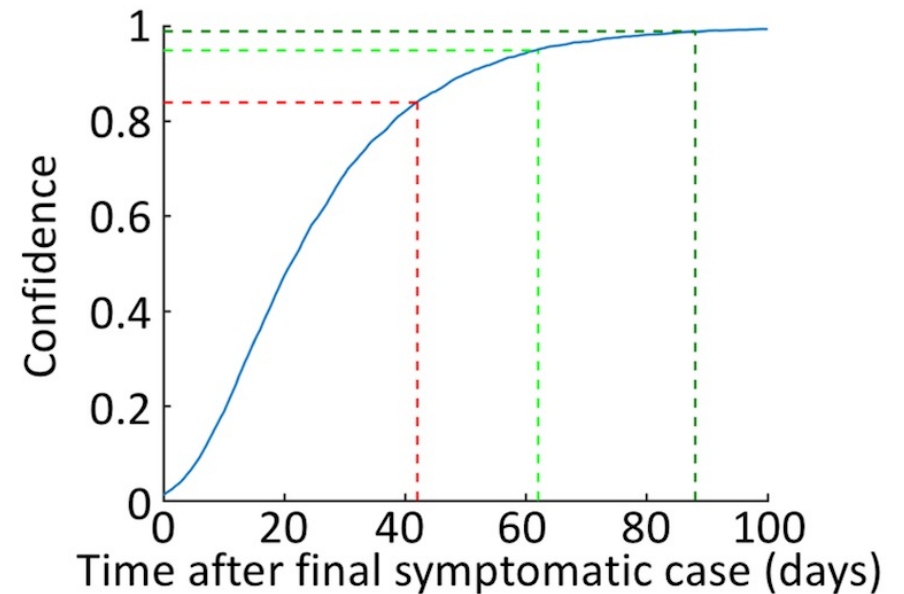
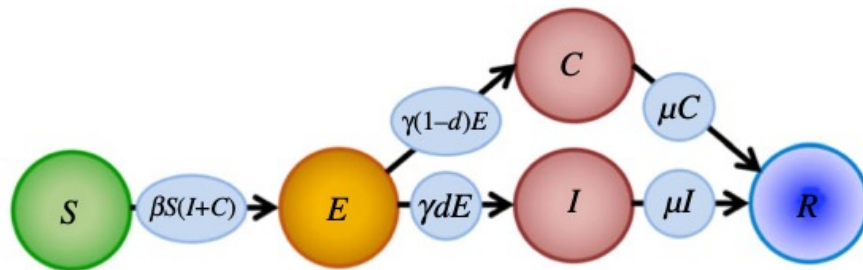
When can outbreaks be declared over?

Initial analysis:

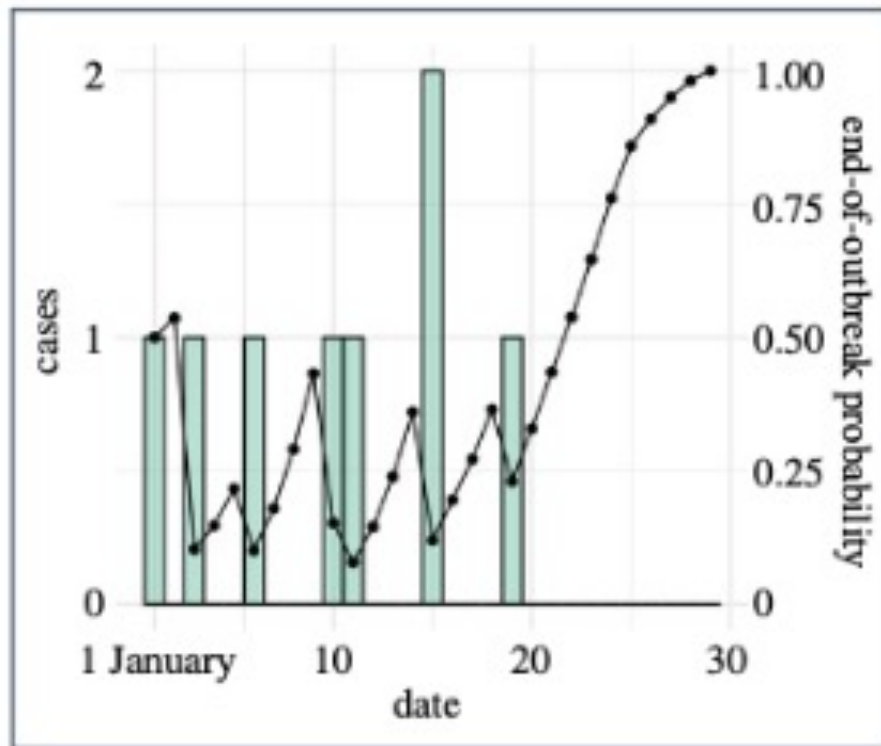


When can outbreaks be declared over?

Initial analysis:

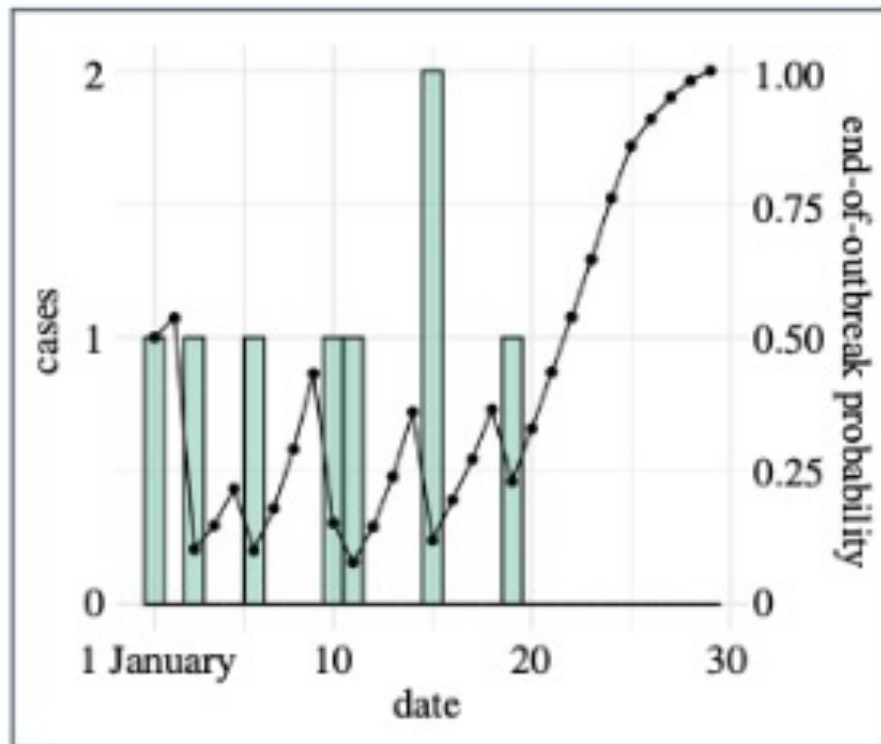


When can outbreaks be declared over?



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:
 $P(\text{no future cases})$

When can outbreaks be declared over?



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)

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



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journal homepage: www.elsevier.com/locate/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

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



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 105 (2021) 286–292



Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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



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

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

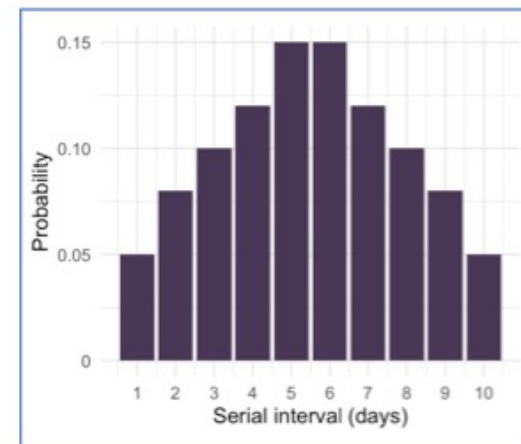
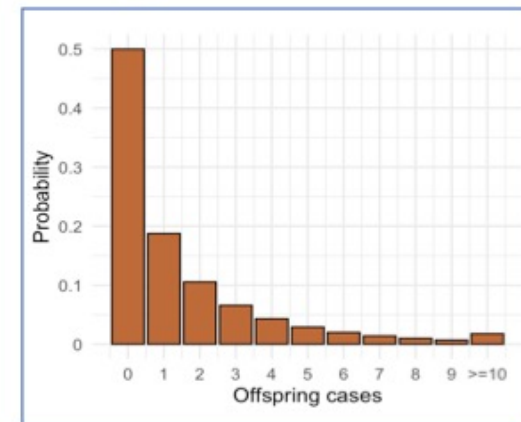
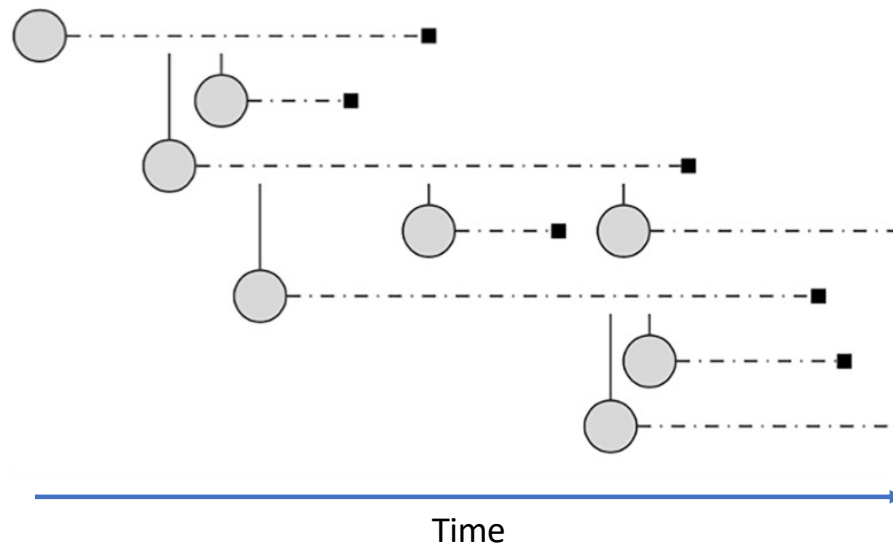
^b Kyoto University School of Public Health, Yoshidakonocho, Sakyo-ku, Kyoto, 606-8501, Japan

^c College of Public Health, National Taiwan University, 17 Xu-Zhou Road, Taipei, 10055, Taiwan

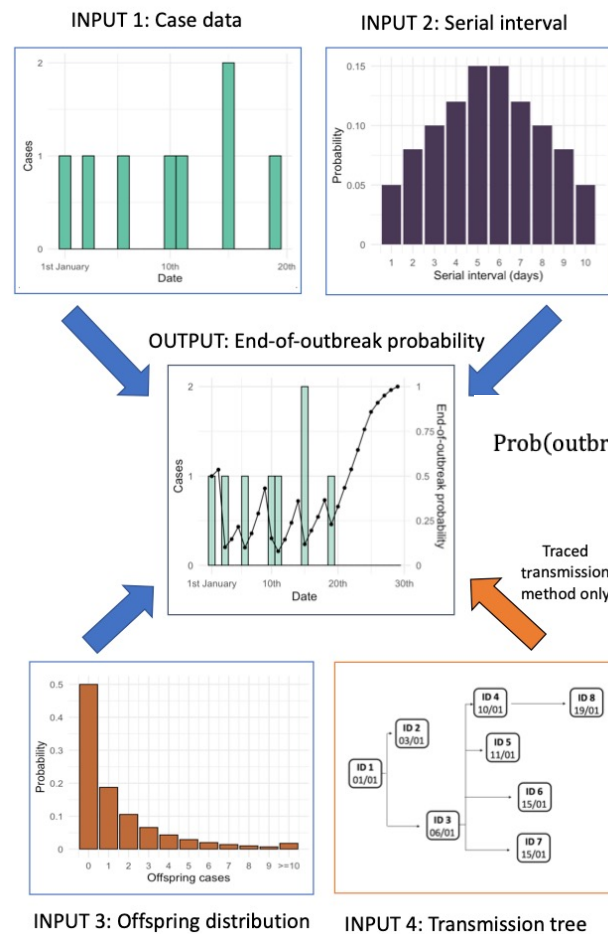


When can outbreaks be declared over?

Transmission
model



When can outbreaks be declared over?



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

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

INTERFACE

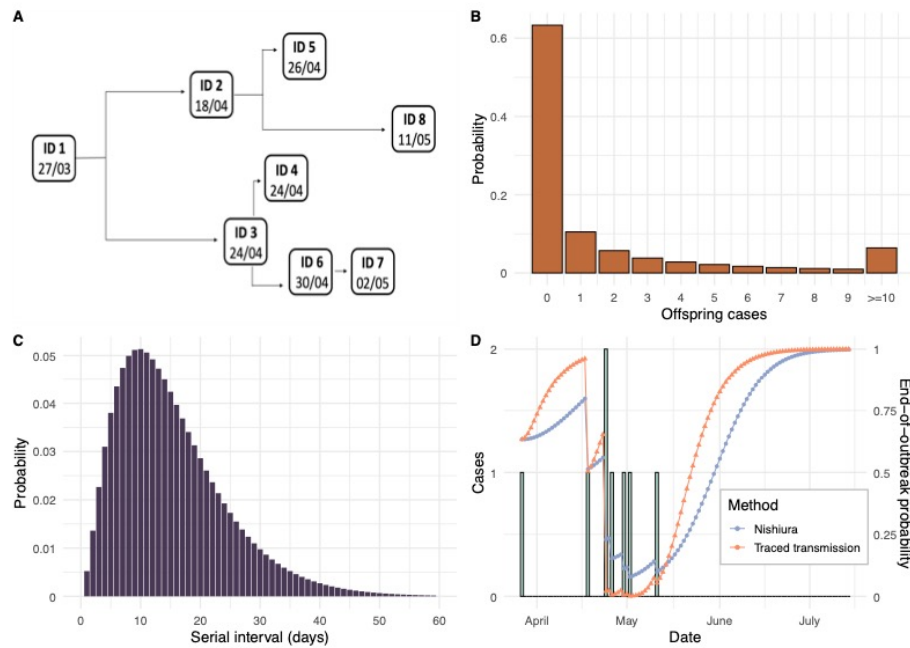
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Exact calculation of end-of-outbreak probabilities using contact tracing data

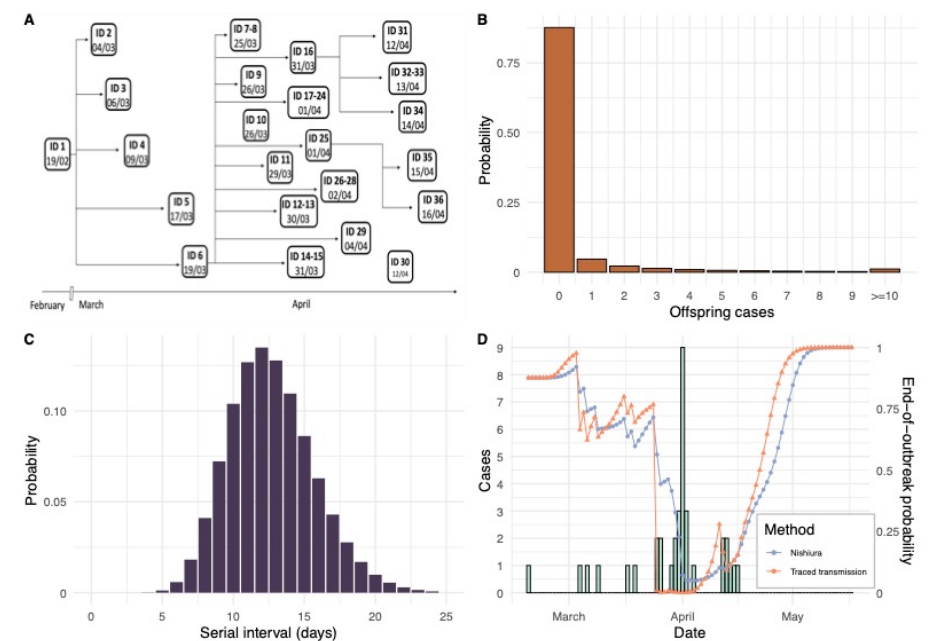
N. V. Bradbury^{1,2,†}, W. S. Hart^{3,†}, F. A. Lovell-Read³, J. A. Polonsky⁴ and R. N. Thompson³

When can outbreaks be declared over?

Ebola in DRC (2017)



Nipah in Bangladesh (2004)



INTERFACE

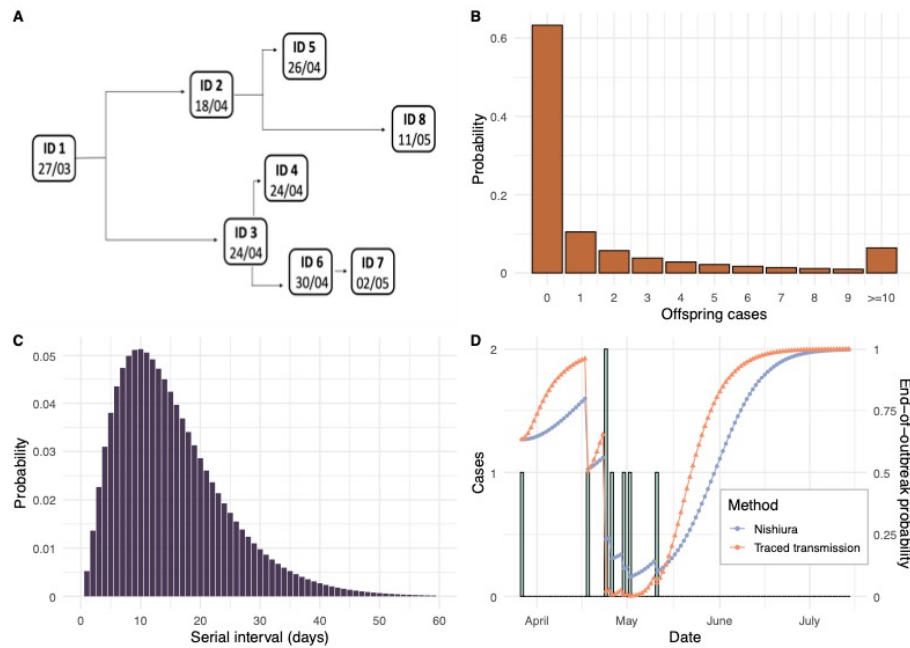
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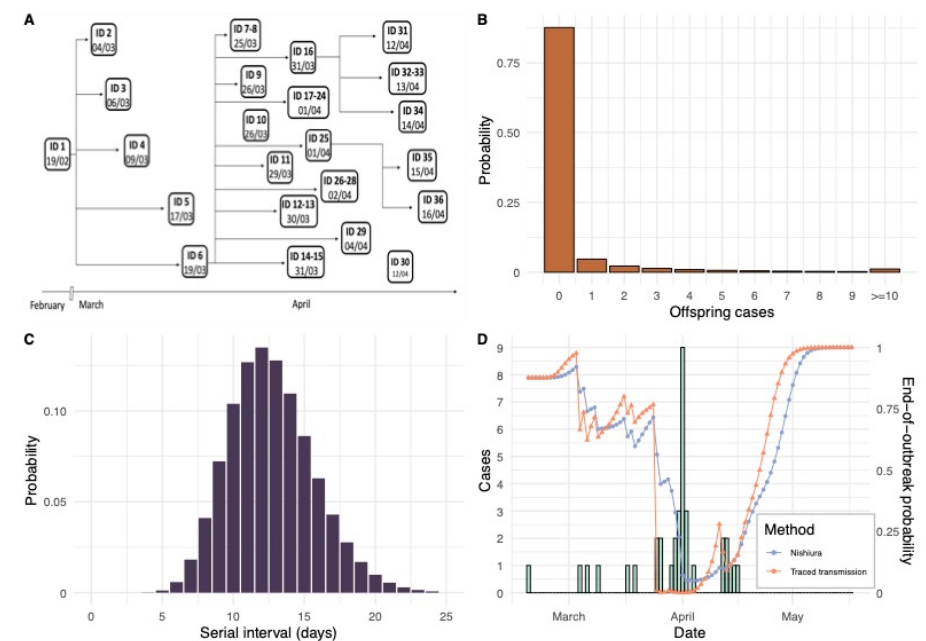
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INTERFACE

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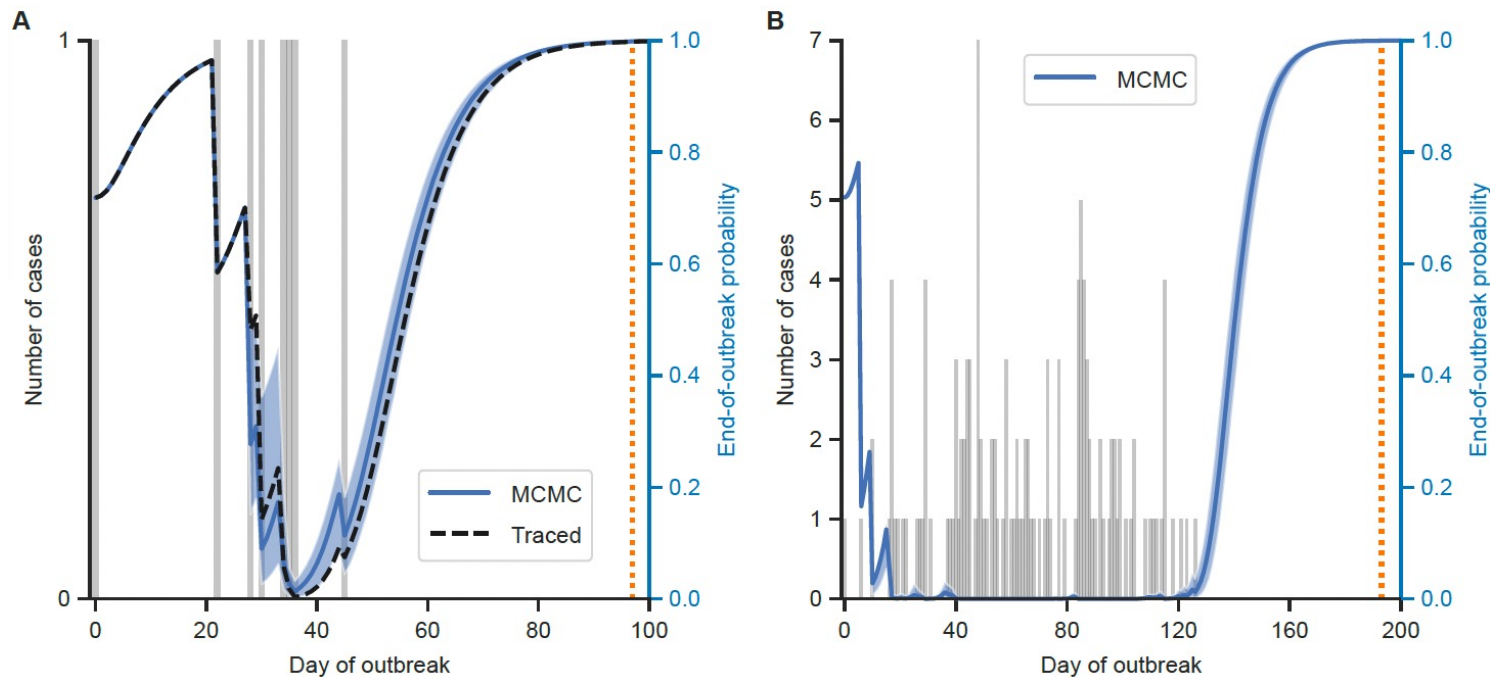
N. V. Bradbury^{1,2,†}, W. S. Hart^{3,†}, F. A. Lovell-Read³, J. A. Polonsky⁴ and R. N. Thompson³

Problem: Transmission tree is often unknown...

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.*)

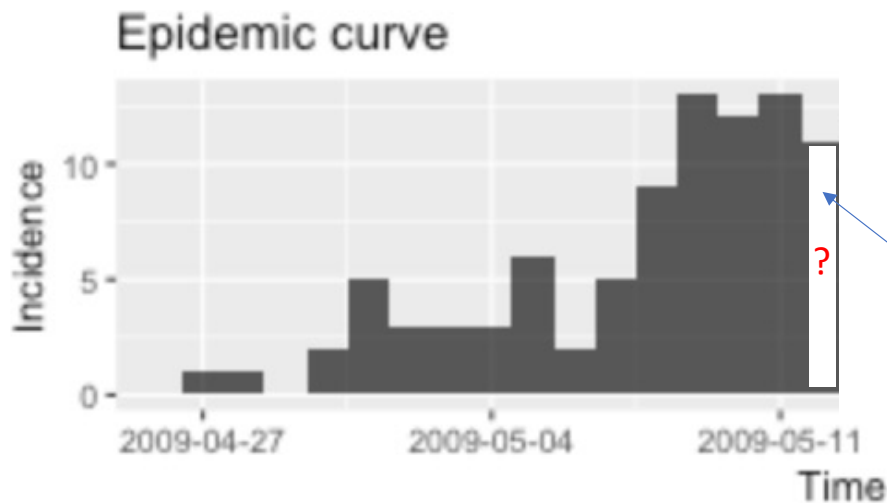
An alternative (easier) modelling framework

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]

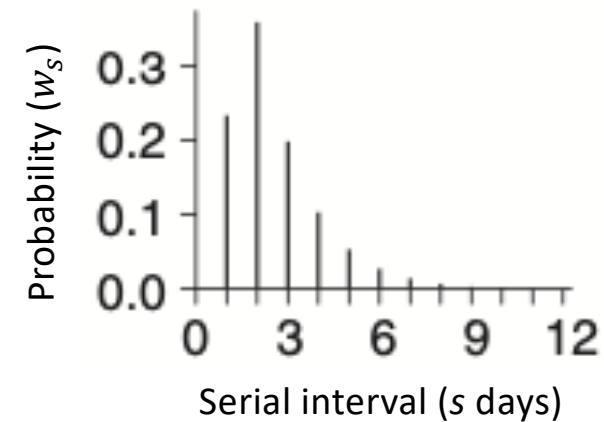
An alternative (easier) modelling framework

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



Know

R &



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

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

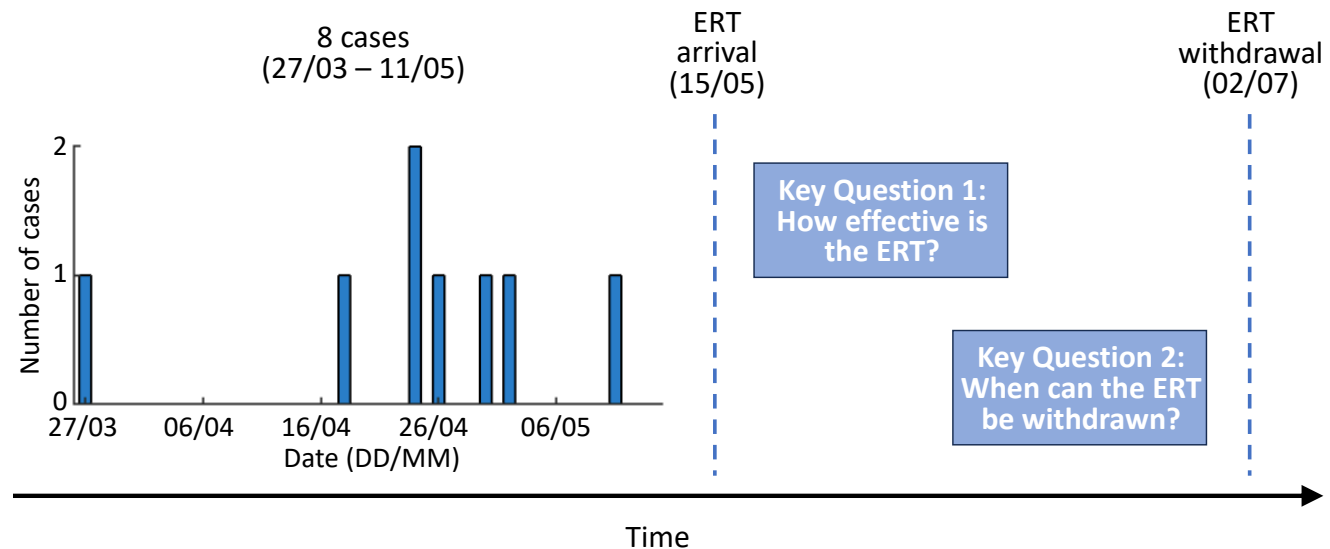
1. Estimate R (and k) pre-ERT

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

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

Risk of withdrawing ERT on day t

$$= 1 - \int_0^\infty \text{Prob (no cases from day } t \text{ onwards} | R) L(R) dR,$$



nature communications



Article

<https://doi.org/10.1038/s41467-024-48885-5>

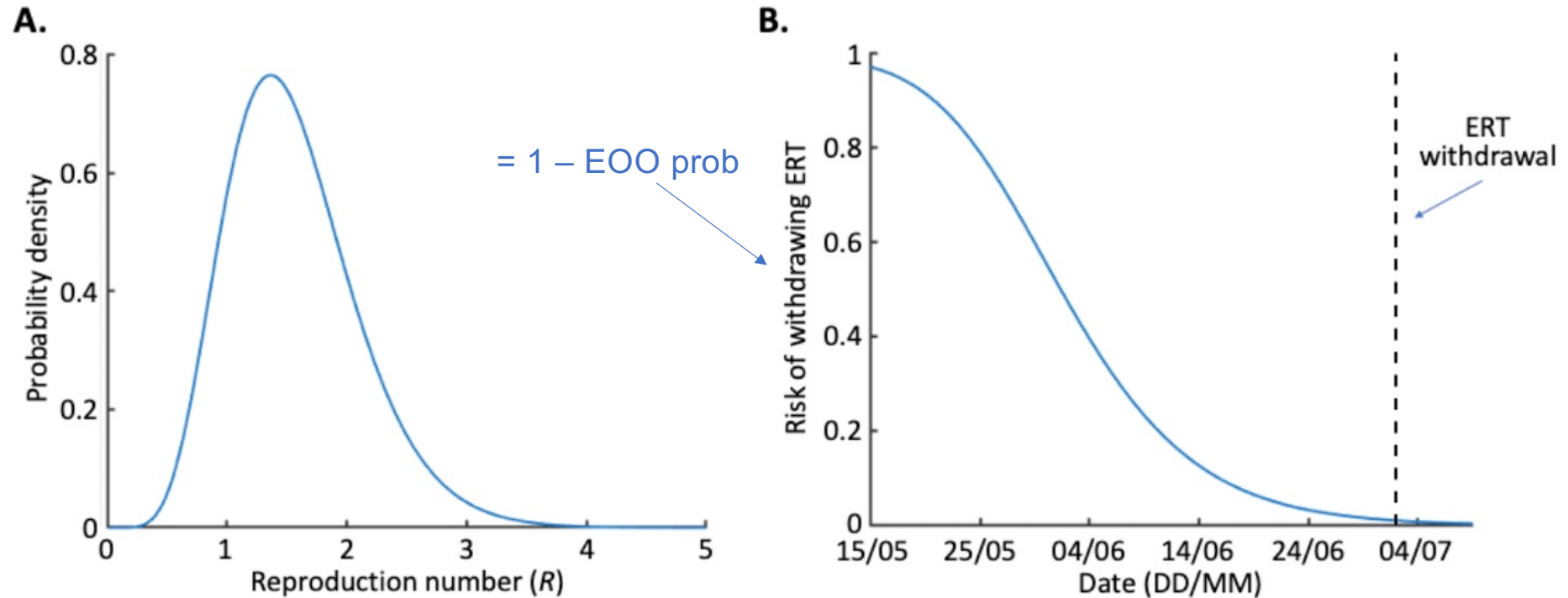
Using real-time modelling to inform the 2017 Ebola outbreak response in DR Congo

Received: 12 February 2024

Accepted: 19 June 2024

R. Thompson¹, W. Hart¹, M. Kaka^{2,3}, I. Fall⁴, A. Guéye², D. Chamla², M. Mossoko⁵, S. Ahuka-Mundele⁶, J. Nkoko-Mbete⁶, T. Jombart⁷ & J. Polonsky⁸

Case study: Ebola virus disease in DRC



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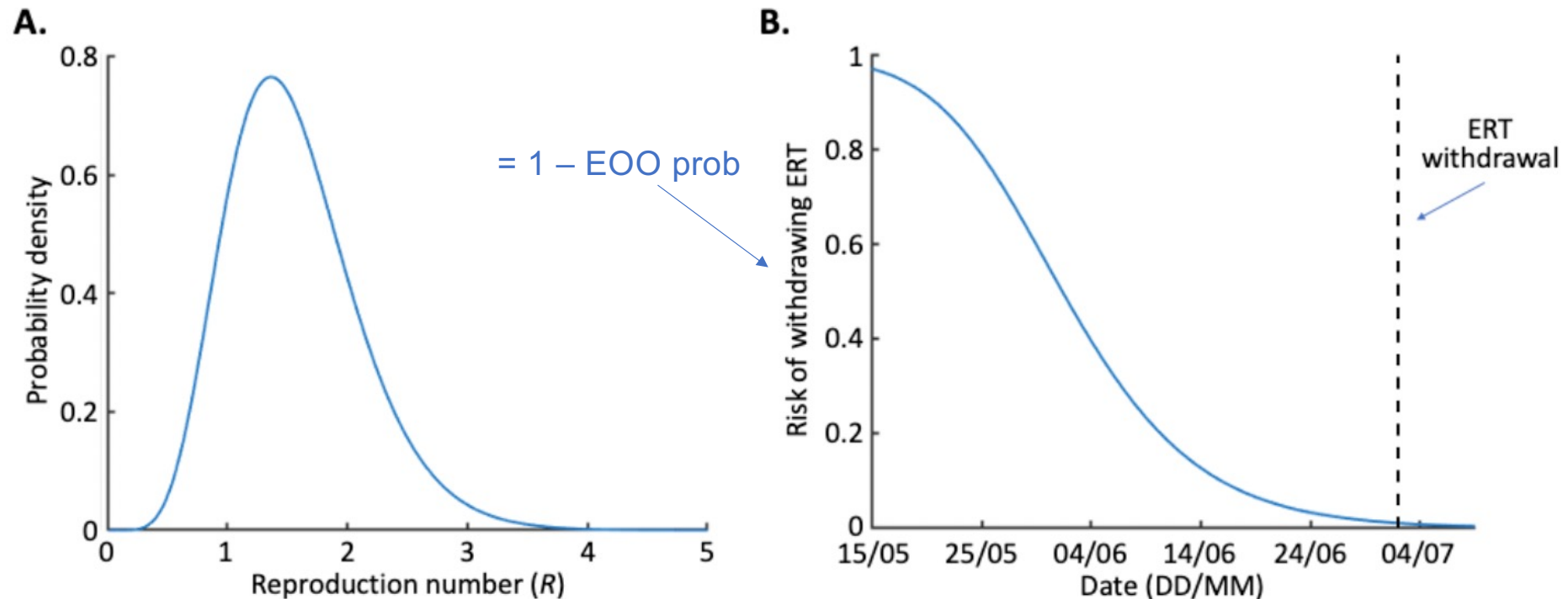
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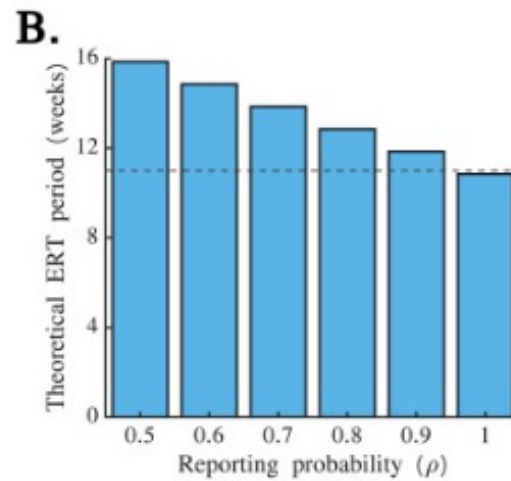
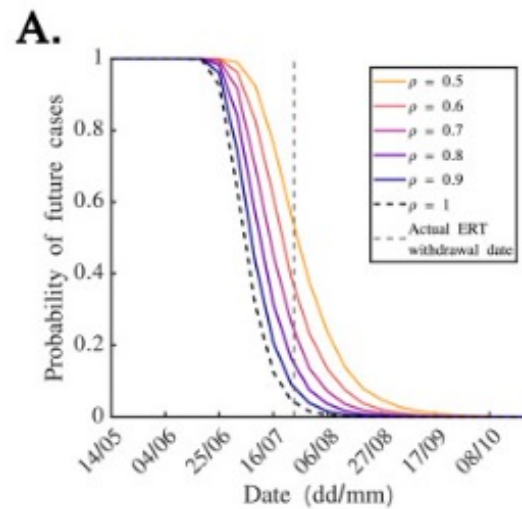
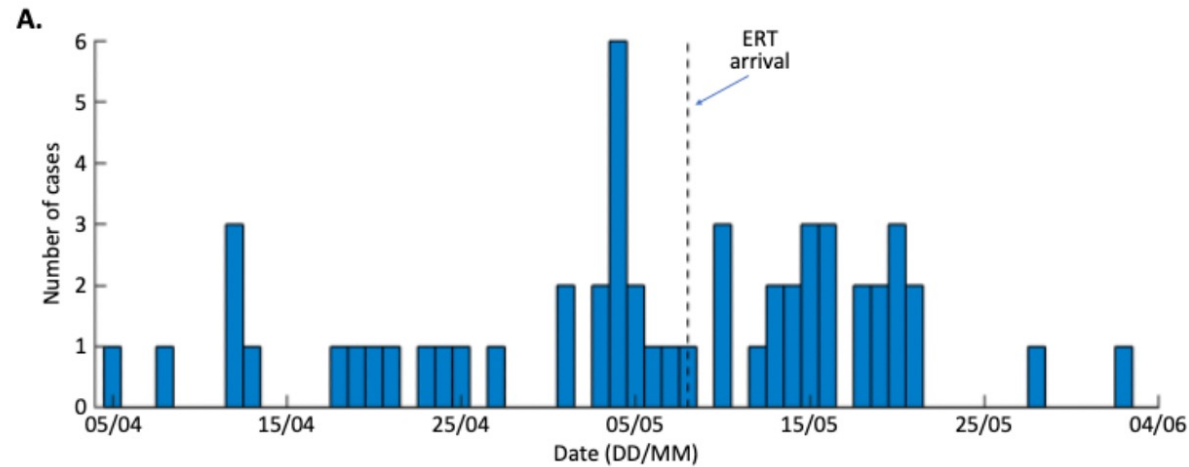
R. Thompson¹, W. Hart¹, M. Kaka^{2,3}, I. Fall⁴, A. Guéye², D. Chamla²,
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Case study: Ebola virus disease in DRC



- ERT effective at limiting transmission
- ERT was only withdrawn when it was safe to do so

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. Polonsky³, M. Keita^{4,5}, S. Ahuka-Mundeke⁶, W.S. Hart⁷, M.J. Plank⁸, B. Lambert⁹, E.M. Hill^{10,11}, R.N. Thompson⁷ 

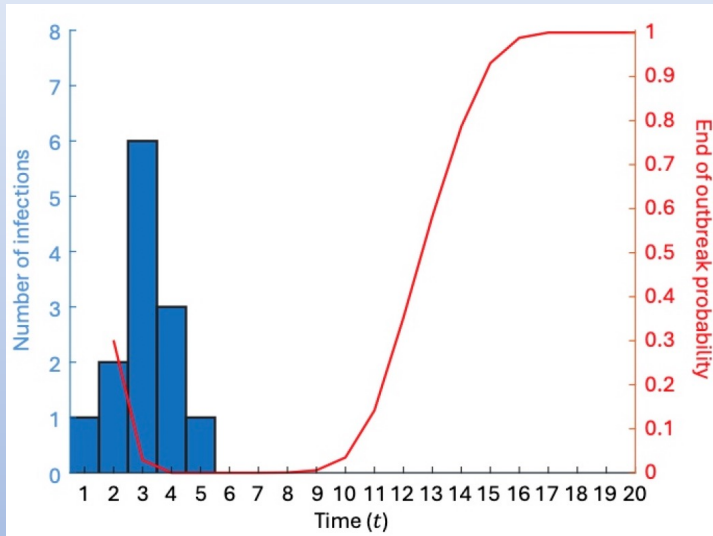
When can outbreaks be declared over?

- 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).



- 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?

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 $s \geq 11$.

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 2-3 slides) next Monday
 - Report back on Tuesday

Can each group please send 2-3 slides to me by 10am next Tuesday?

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