Lecture 4: Alternative Model Structures

April 16, 2020

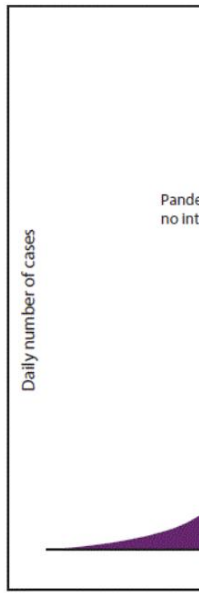
“Flattening the Curve”

The Coronavirus Outbreak | LIVE

Coronav
and will

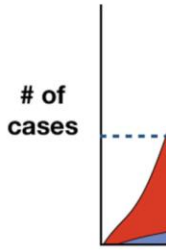
By Brandon Speckt

Many hundre
don't all have



Flatten

One chart e
nearly as im



Adapte

The longer it takes for co
Drew Harris

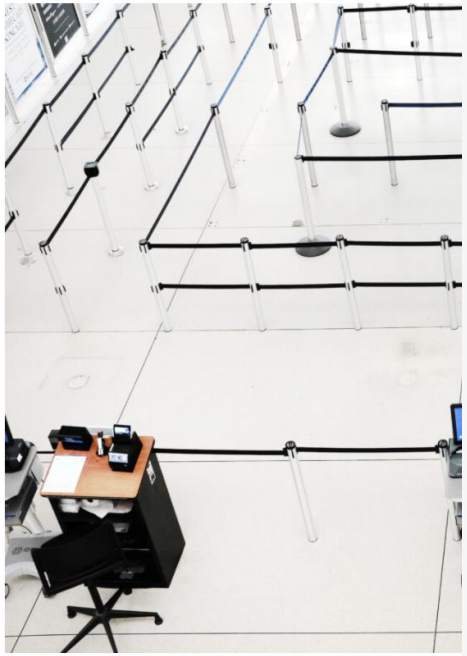
By Siobhan Rob

March 27, 2020

HEALTH

Why ‘flattening
world’s best be
coronavirus

By HELEN BRANSWELL @HelenBranswell /



A person checks in at security at an internat
on March 7.

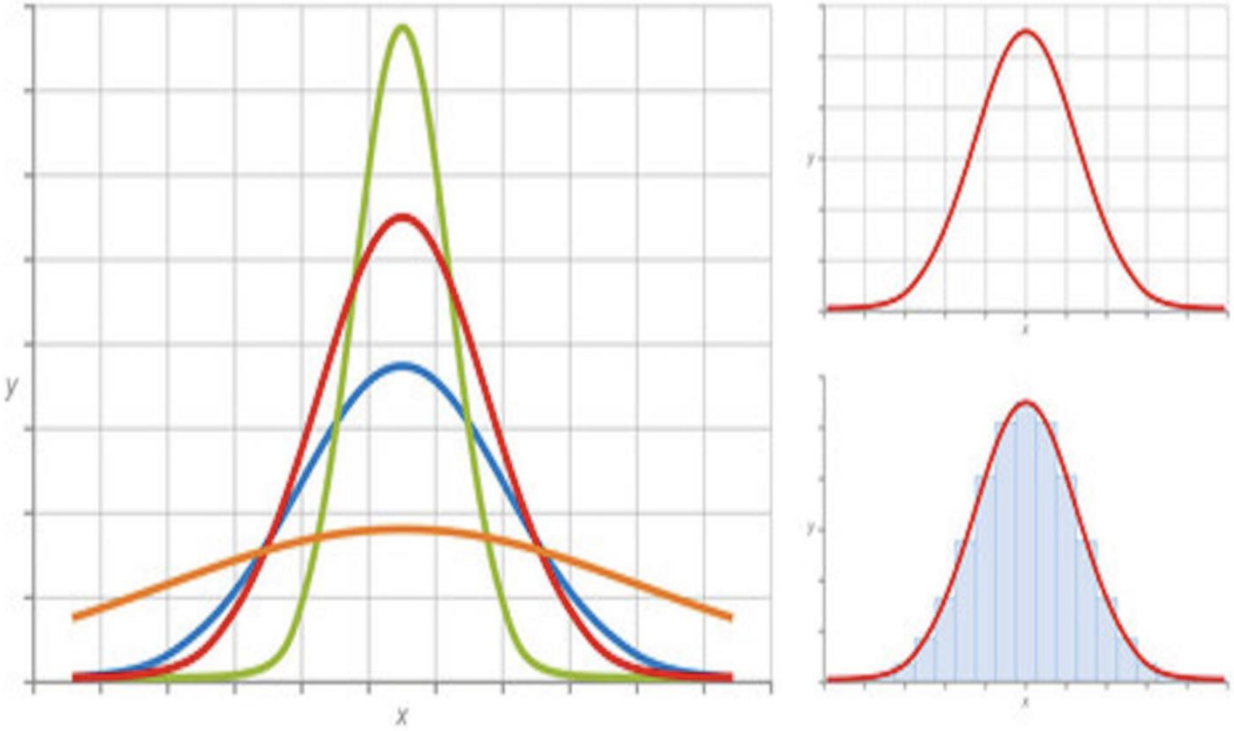
SPENCER PLATT/GETTY IMAGES

Is your state flattening the COVID-19 curve? Here’s the latest data

Bruce Barcott

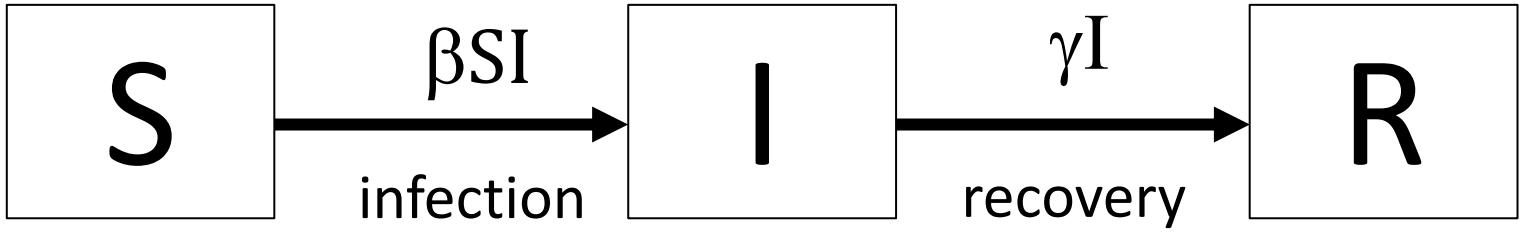
April 5, 2020

Share | Print



Flattening the curve refers to community isolation measu
a manageable level for medical providers.
(Image: © CDC)

SIR Model

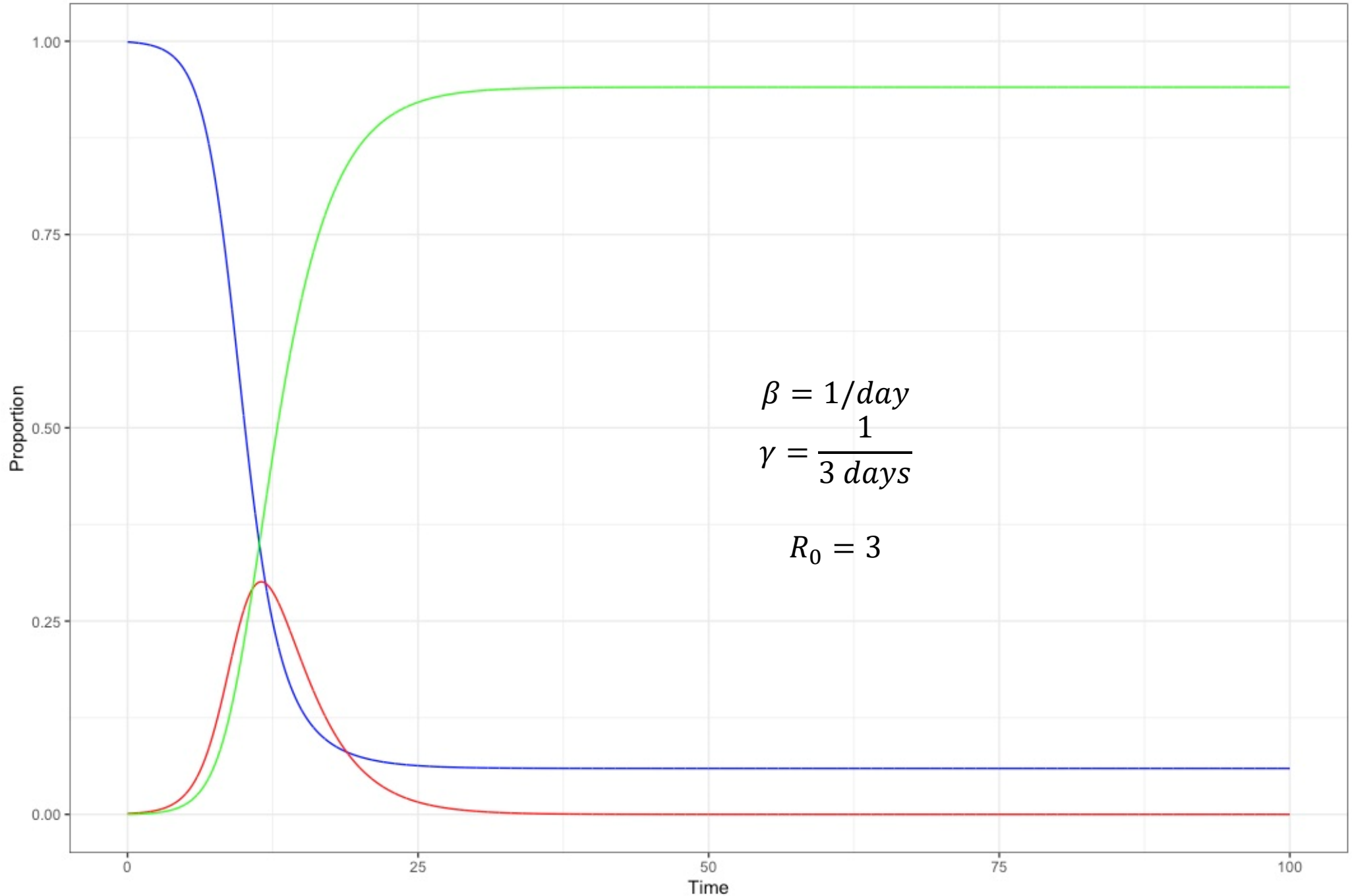


$$\frac{dS}{dt} = -\beta SI$$

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

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

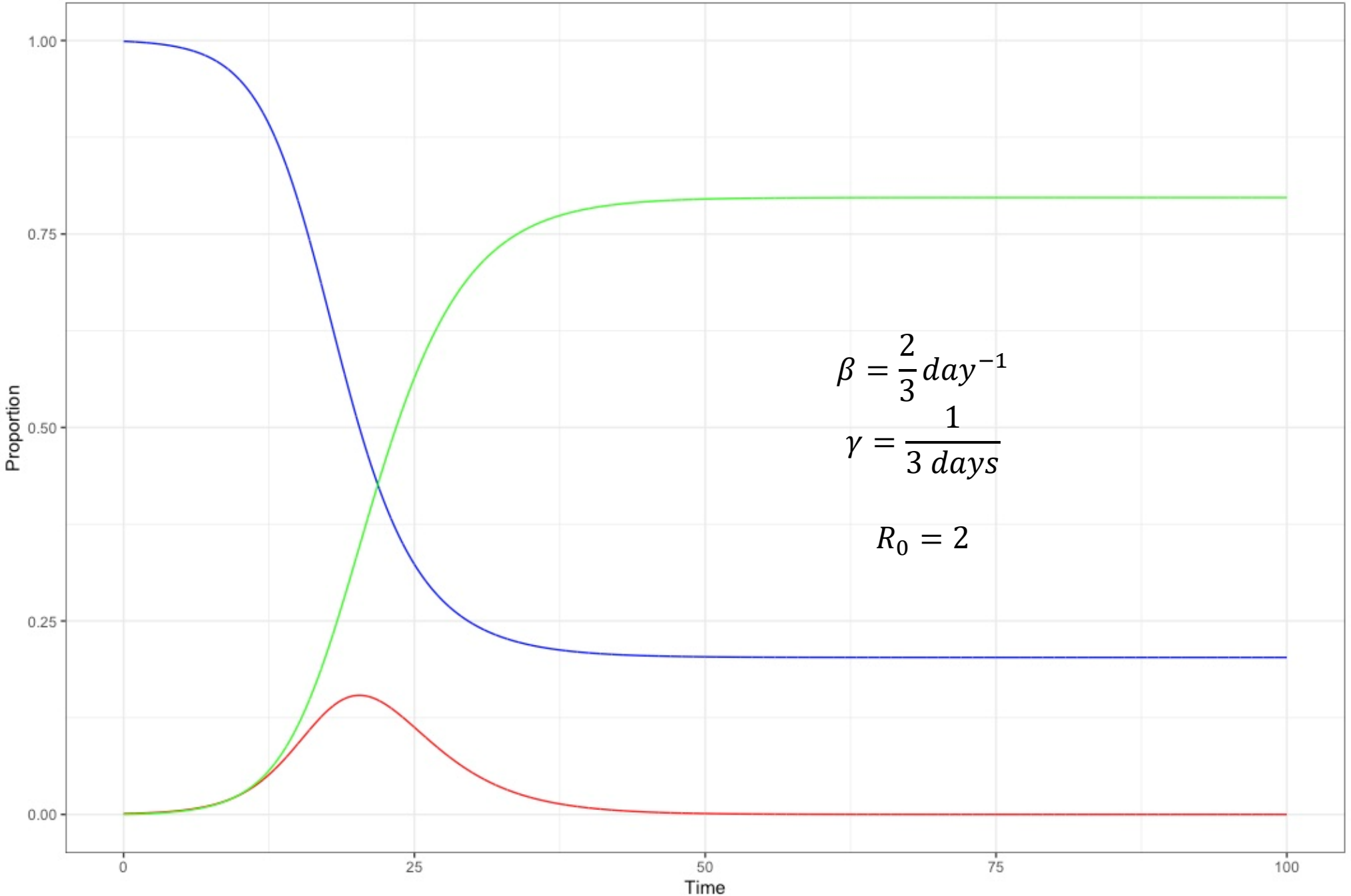
Which component of the model do our physical distancing interventions target?

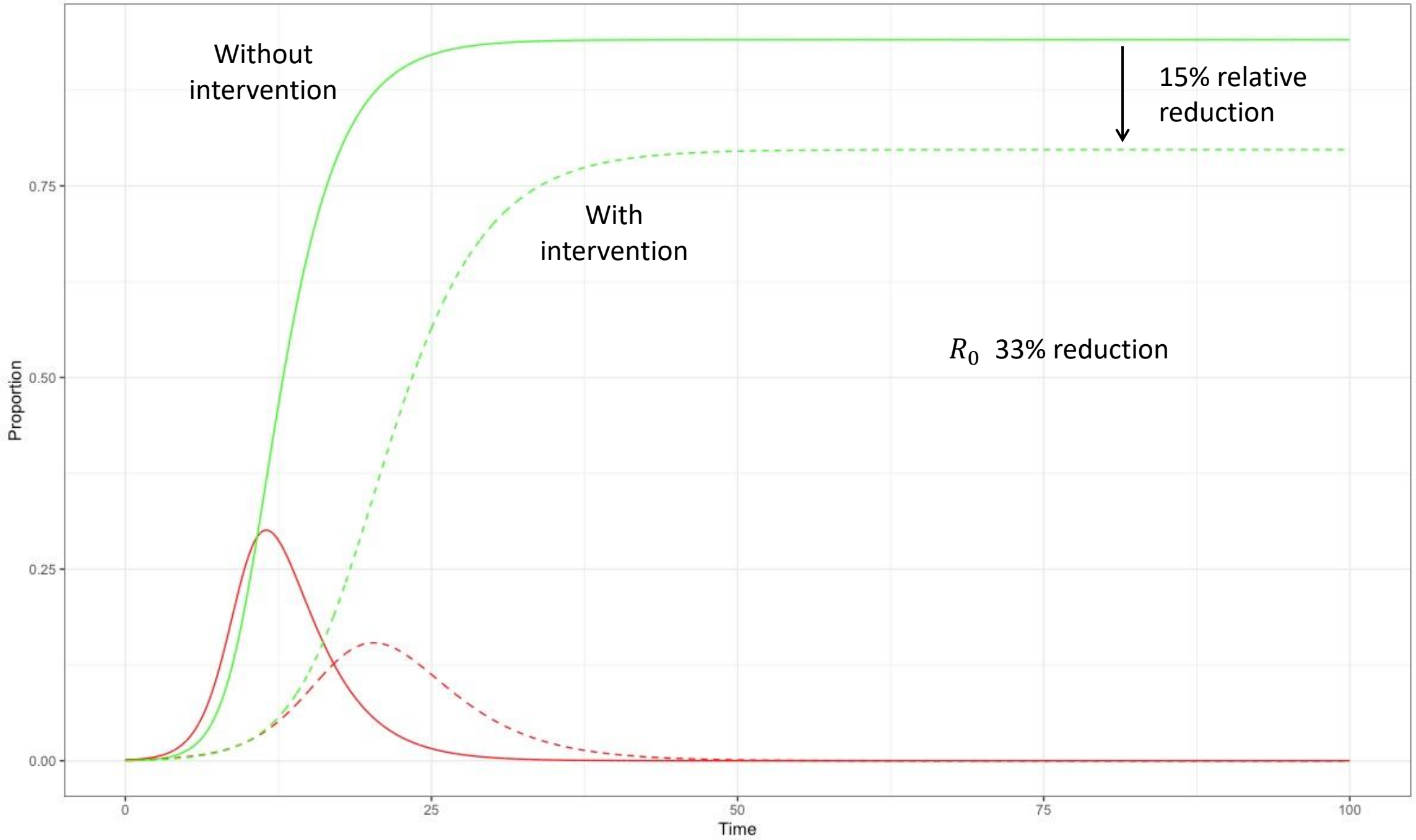


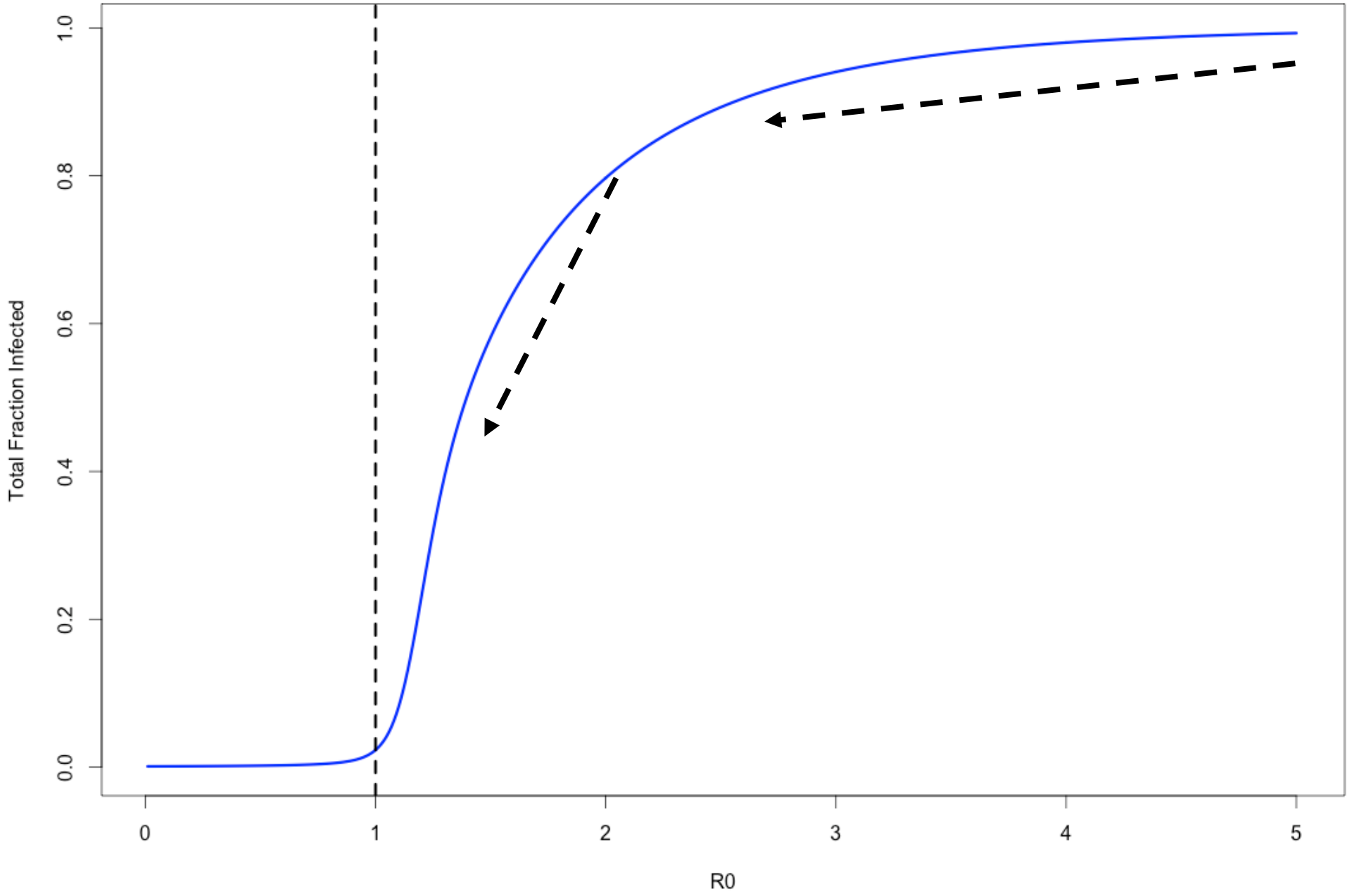
$$\beta = 1/day$$

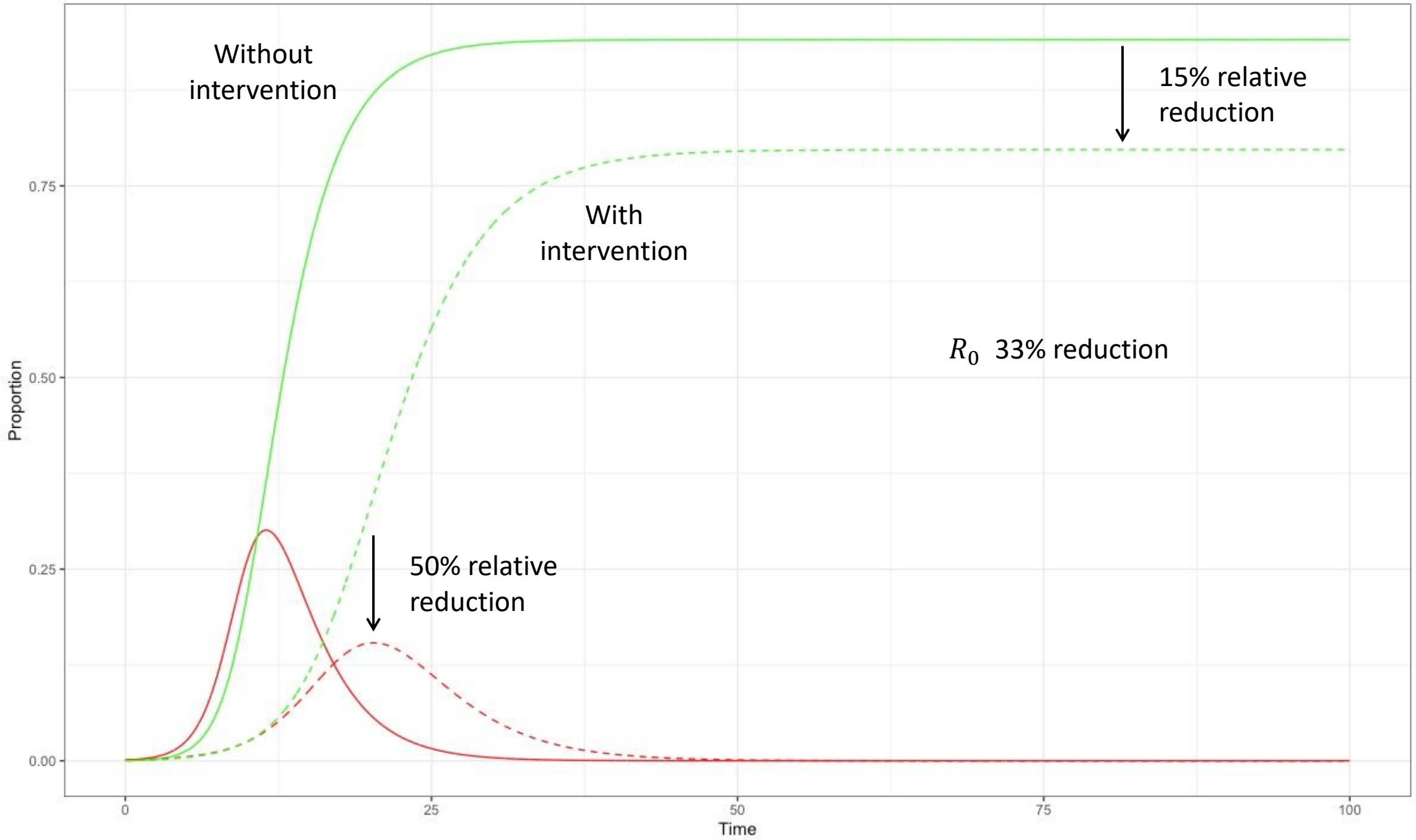
$$\gamma = \frac{1}{3\ days}$$

$$R_0 = 3$$


1.00
0.75
0.50
0.25
0.00
Proportion
0
25
50
75
100
Time
$\beta = \frac{2}{3} day^{-1}$
$\gamma = \frac{1}{3\ days}$
$R_0 = 2$


Without intervention
With intervention
15% relative reduction
R_0 33% reduction
Proportion
0.00
0.25
0.50
0.75
0
25
50
75
100
Time


Total Fraction Infected
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
R0


Without intervention
With intervention
15% relative reduction
R_0 33% reduction
50% relative reduction
Proportion
0.00
0.25
0.50
0.75
0
25
50
75
100
Time

Public health interventions and epidemic intensity during the 1918 influenza pandemic

Richard J. Hatchett*†, Carter E. Mecher‡§, and Marc Lipsitch¶

*Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892; ‡Department of Veterans Affairs, VA Southeast Network, 3700 Crestwood Parkway, Duluth, GA 30096; §Homeland Security Council, Executive Office of the President, EEOB, 1650 Pennsylvania Avenue NW, Washington, DC 20502; and ¶Department of Epidemiology and Department of Immunology and Infectious Diseases, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115

Philadelphia
- First case: Sept 17
- City-wide parade Sept 28
- Social distancing began Oct 3
- (17 days)

St. Louis
- First Case: Oct 5
- Social distancing: Oct 7
- (2 days)

Peak Death Rate
257 / 100,000

Cumulative Excess Death Rate
719/100,000

Peak Death Rate
31 / 100,000

Cumulative Excess Death Rate
347/100,000

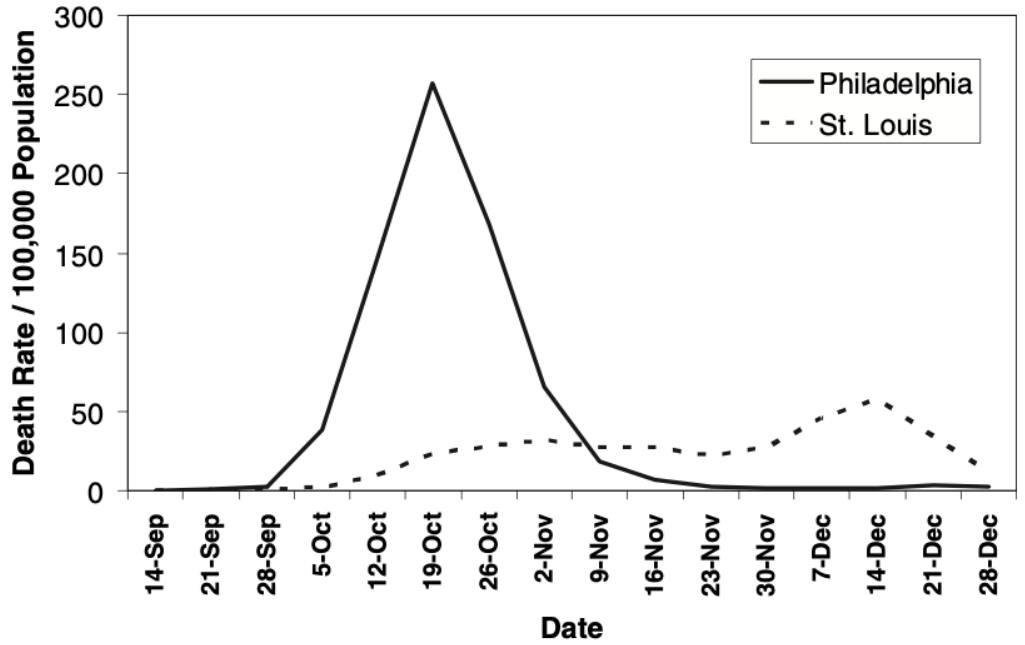
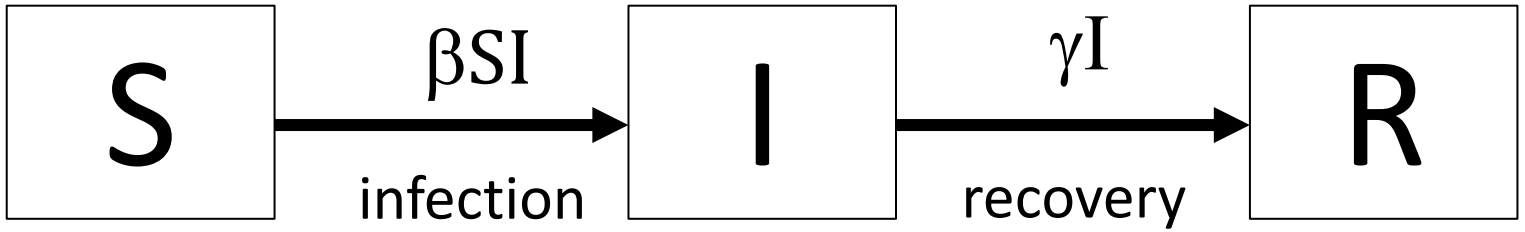


Fig. 1. Excess P&I mortality over 1913–1917 baseline in Philadelphia and Louis, September 8–December 28, 1918. Data are derived from ref. 10.

Learning Objectives

- Understand key components of the natural history and transmission of infectious diseases, including incubation period, latent period, infectious period and serial interval
- Describe approaches to characterizing these intervals
- Understand the differences in behavior of SIR and SEIR models, and when SEIR models may be preferred
- Identify limitations to the common ODE formulation of SIR/SEIR models

SIR Model



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

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

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

Natural History and Transmission Intervals

- Individuals are almost never symptomatic or infectious immediately after being infected
- There are “incubation” and “latent” periods
- SIR model ignores these states

Models with short latent periods

The Epider

Alexander A. Alemi,[1,*] Ma
[1] *Laboratory of Ato*
[2] *Institute*

We use a popular fict
epidemiology modelling,
We consider variants of z
exact stochastic dynamic
the way, we offer a close
and demonstrate that th
lies in the percolation u
outbreak, including the a

PACS numbers: 87.23.Cc,

When zombies attack!: Mathemati

of a

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* To whom correspondence should be addressed

compartments.

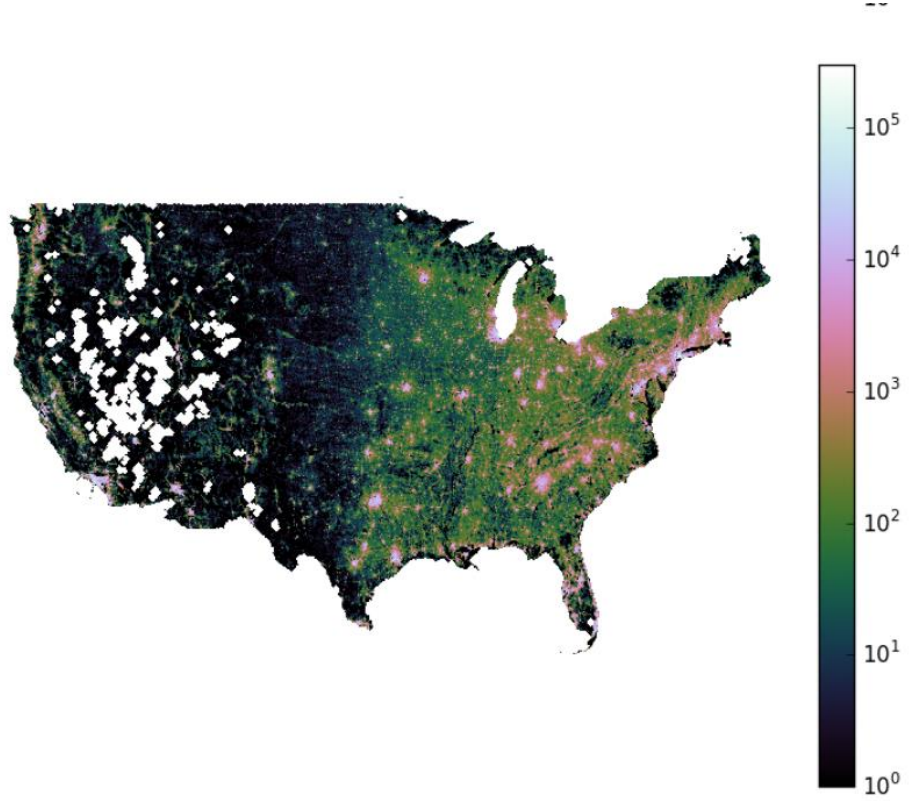
$$F = \begin{bmatrix} 0 & \beta N & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$

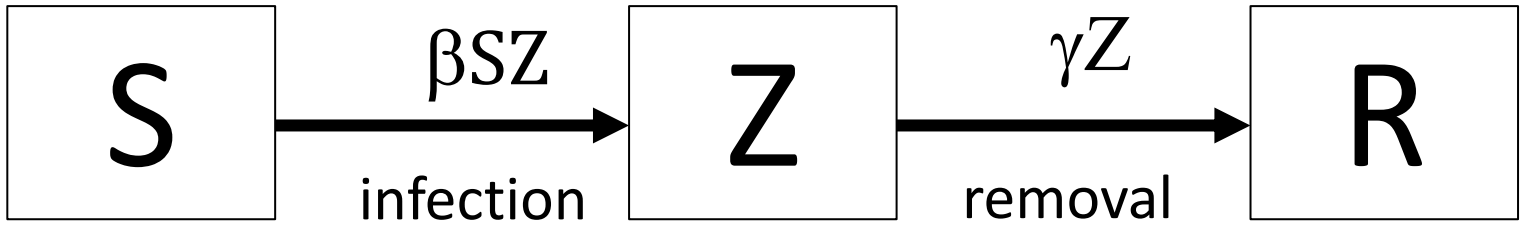
$$V^{-1} = \frac{1}{\gamma(\rho+\kappa)(\alpha N+\sigma)} \begin{bmatrix} \\ \\ \end{bmatrix}$$

$$FV^{-1} = \frac{1}{\gamma(\rho+\kappa)(\alpha N+\sigma)} \begin{bmatrix} \\ \\ \end{bmatrix}$$

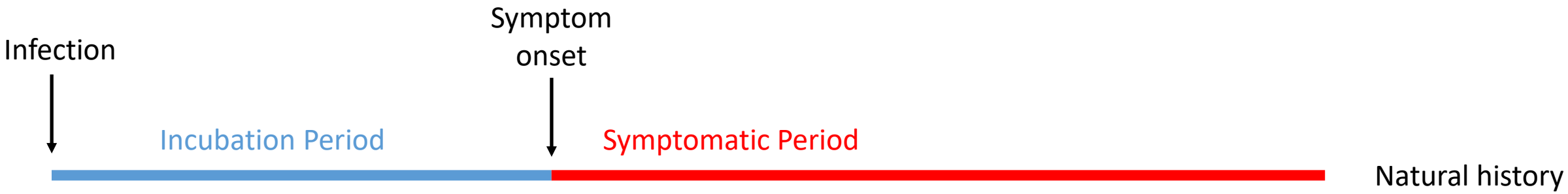
This gives us

$$R_0 =$$

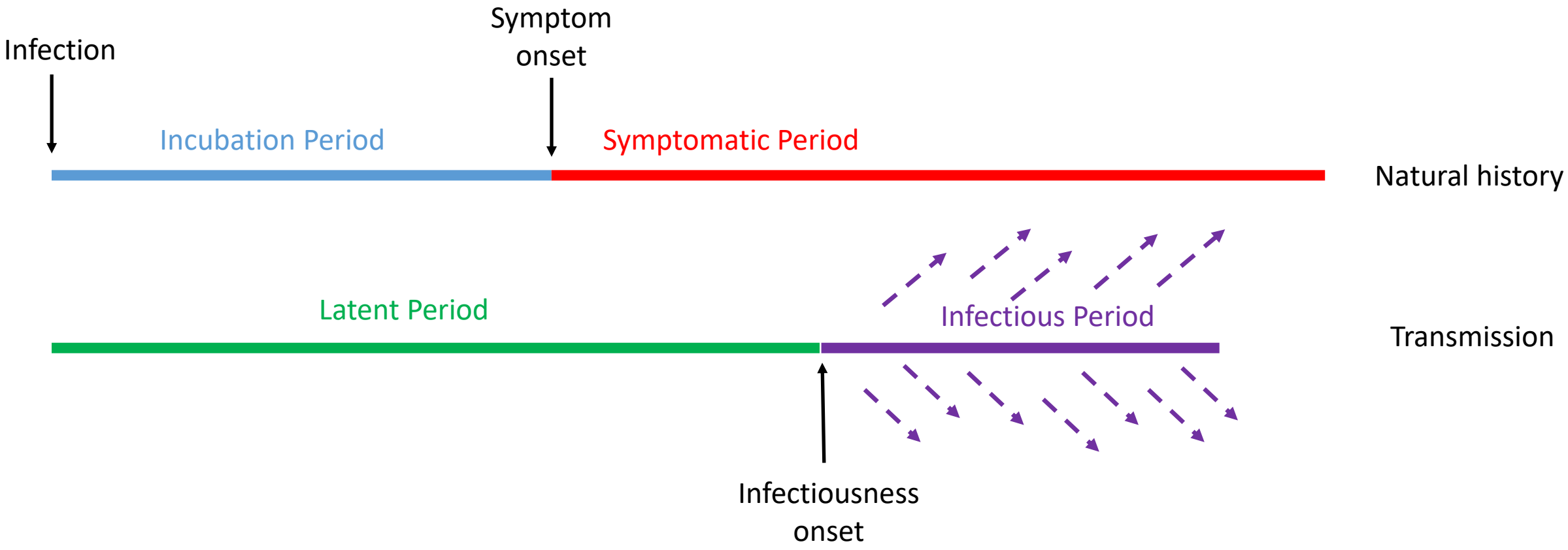




Natural History and Transmission Intervals



Natural History and Transmission Intervals



Natural History and Transmission Intervals

Infectious diseases	Latent period (days)	Infectious period (days)	Incubation period (days)
Measles	6–9	6–7	8–13
Mumps	12–18	4–8	12–26
Whooping cough (pertussis)	21–23	7–10	6–10
Rubella	7–14	11–12	14–21
Diphtheria	14–21	2–5	2–5
Varicella	8–12	10–11	13–17
Hepatitis B	13–17	19–22	50–110
Poliomyelitis	1–3	2–3	7–12
Influenza	1–3	2–3	1–3

http://schoolbag.info/biology/microbiology/33.html

How do we measure these?

How do we measure these intervals?

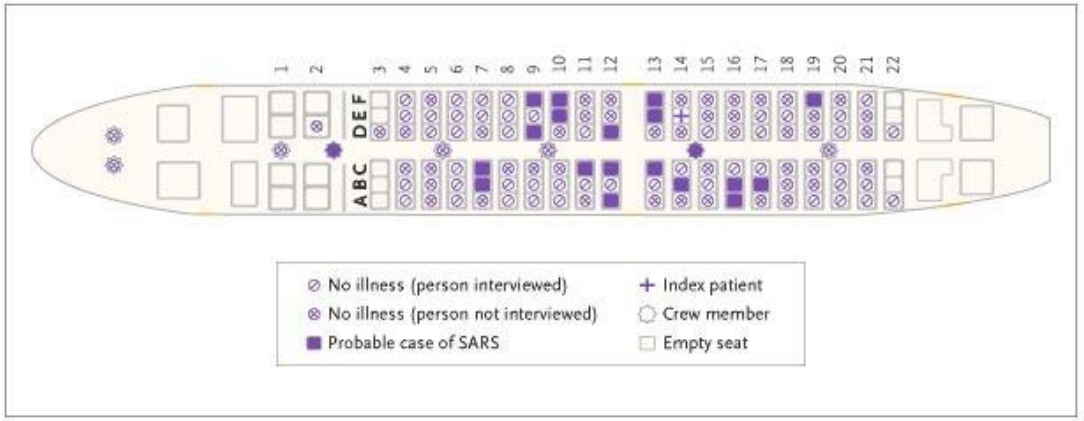
- Difficult with recurrent, household exposures
- Take advantage of specific, single event exposures of a known time and character

The NEW ENGLAND JOURNAL of MEDICINE

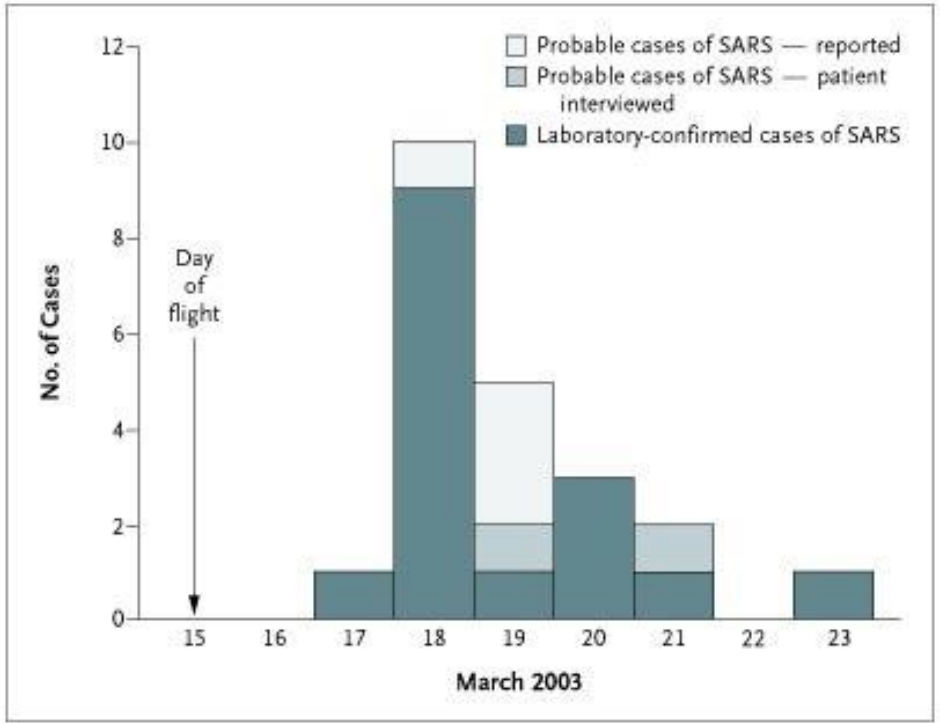
ORIGINAL ARTICLE

Transmission of the Severe Acute Respiratory Syndrome on Aircraft

Sonja J. Olsen, Ph.D., Hsiao-Ling Chang, M.P.H.,
Terence Yung-Yan Cheung, M.B., B.S., Antony Fai-Yu Tang, M.B., B.S., M.P.H.,
Tamara L. Fisk, M.D., Steven Peng-Lim Ooi, M.B., B.S., M.Sc., M.P.H.,
Hung-Wei Kuo, M.P.H., Donald Dah-Shyong Jiang, Ph.D.,
Kow-Tong Chen, M.D., M.P.H., Ph.D., Jim Lando, M.D., M.P.H.,
Kwo-Hsiung Hsu, M.S., Tzay-Jinn Chen, M.D., M.P.H.,
and Scott F. Dowell, M.D., M.P.H.



- 3-hour flight from Hong Kong to Beijing
- Index case was symptomatic man 4 days into illness
- 22 people probable secondary cases



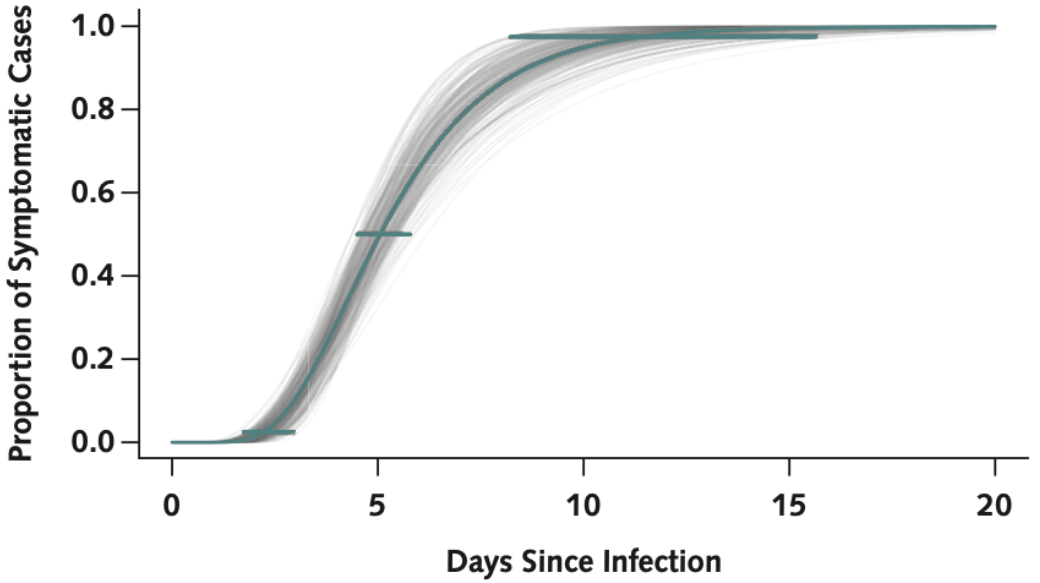
Annals of Internal Medicine ORIGINAL RESEARCH

The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application

Stephen A. Lauer, MS, PhD*; Kyra H. Grantz, BA*; Qifang Bi, MHS; Forrest K. Jones, MPH; Qulu Zheng, MHS; Hannah R. Meredith, PhD; Andrew S. Azman, PhD; Nicholas G. Reich, PhD; and Justin Lessler, PhD

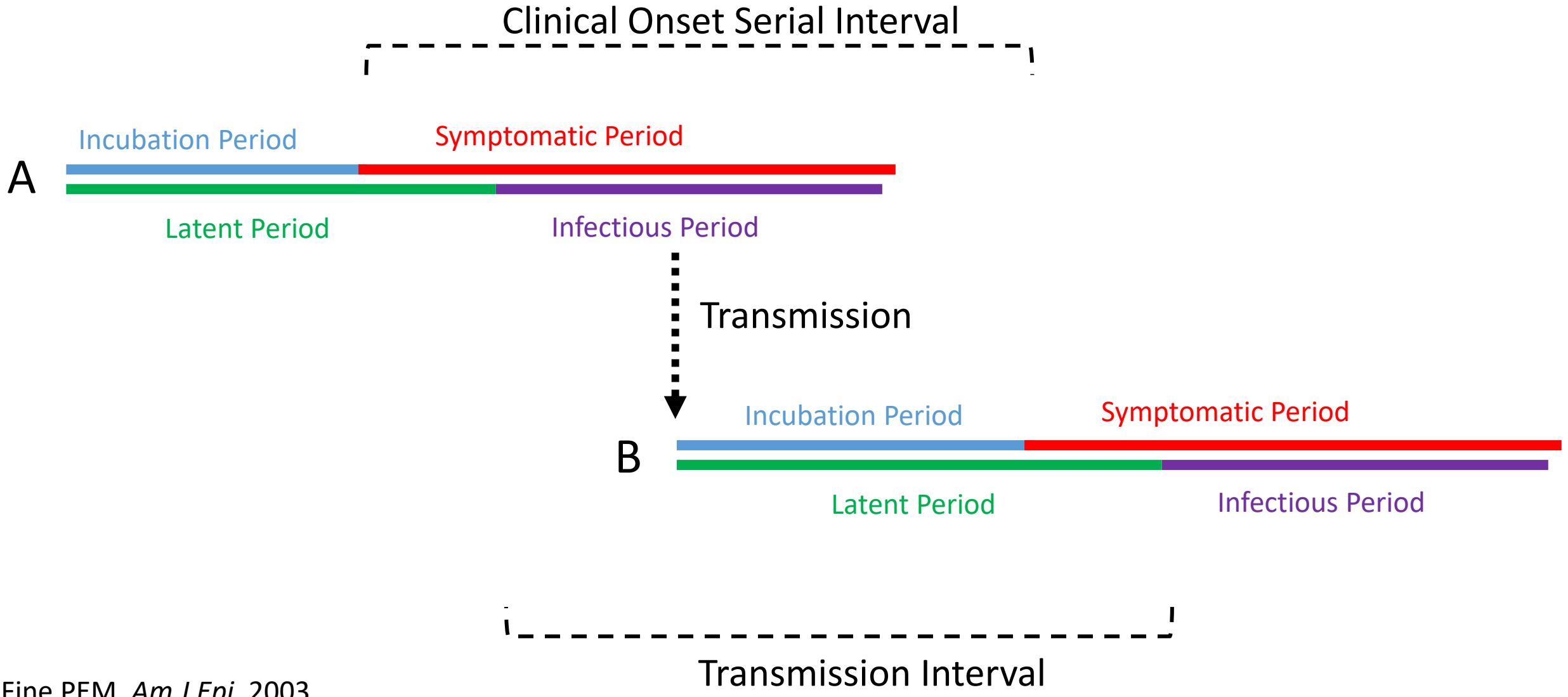
- 181 cases with identifiable exposure and symptom onset windows

Figure 2. Cumulative distribution function of the COVID-19 incubation period estimate from the log-normal model.



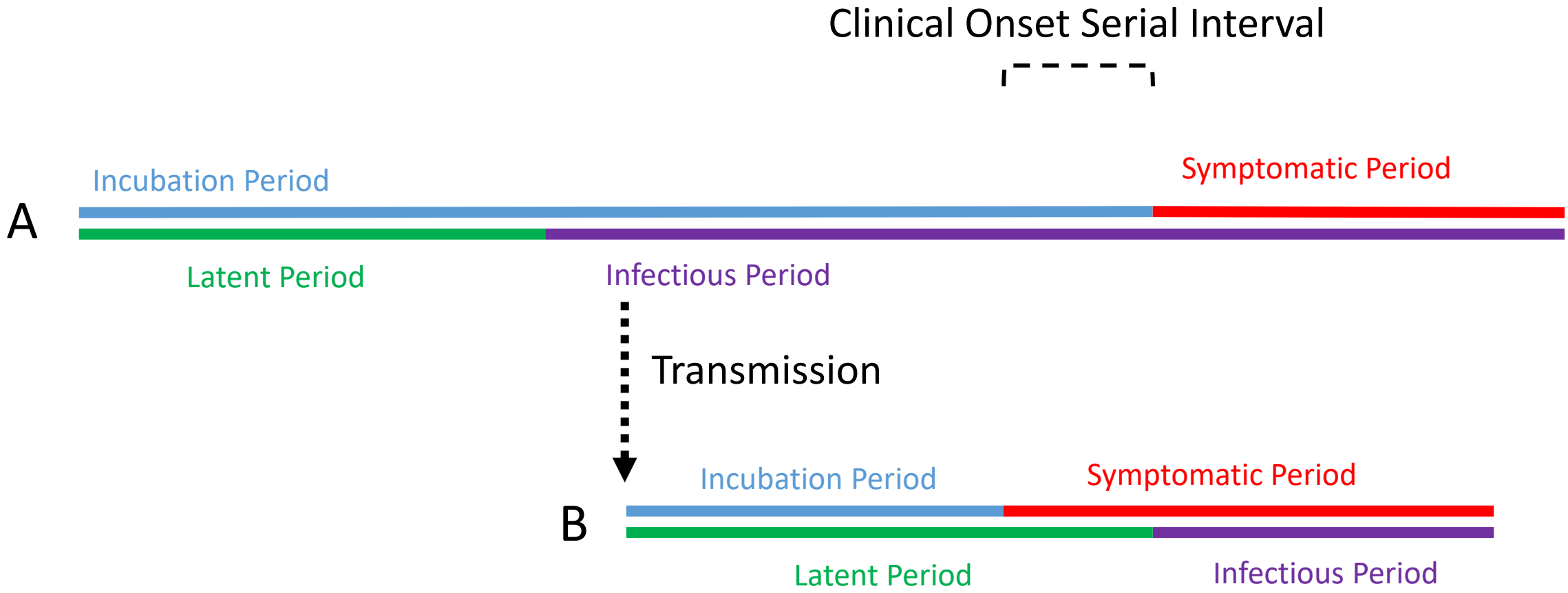
The estimated median incubation period of COVID-19 was 5.1 days (CI, 4.5 to 5.8 days). We estimated that fewer than 2.5% of infected persons will display symptoms within 2.2 days (CI, 1.8 to 2.9 days) of exposure, whereas symptom onset will occur within 11.5 days (CI, 8.2 to 15.6 days) for 97.5% of infected persons. Horizontal bars represent the 95% CIs of the 2.5th, 50th, and 97.5th percentiles of the incubation period distribution. The estimate of the dispersion parameter is 1.52 (CI, 1.32 to 1.72). COVID-19 = coronavirus disease 2019.

Incubation Periods and Serial Intervals



Fine PEM, *Am J Epi,* 2003

Incubation Periods and Serial Intervals



Fine PEM, *Am J Epi,* 2003

Evolutionary Perspective on Serial Intervals

- From pathogen perspective, what are advantages to a short serial interval?
- To a long serial interval?

nature medicine

BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-020-0869-5

Check for updates

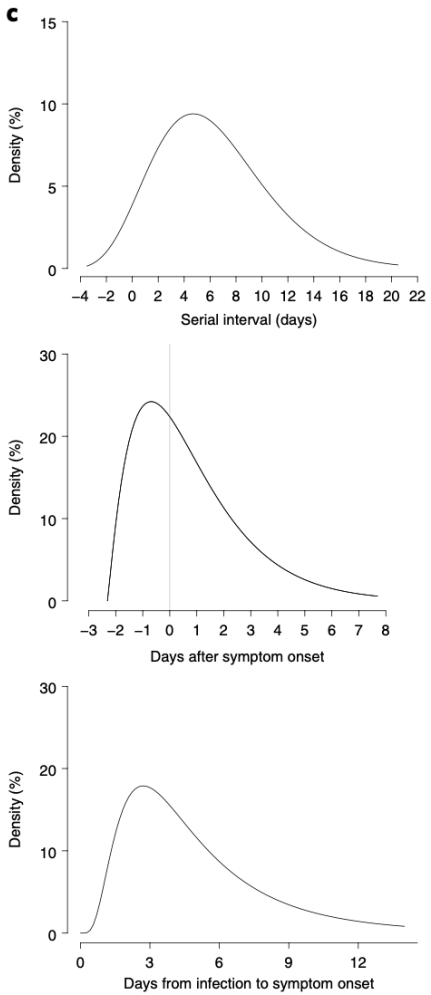
Temporal dynamics in viral shedding and transmissibility of COVID-19

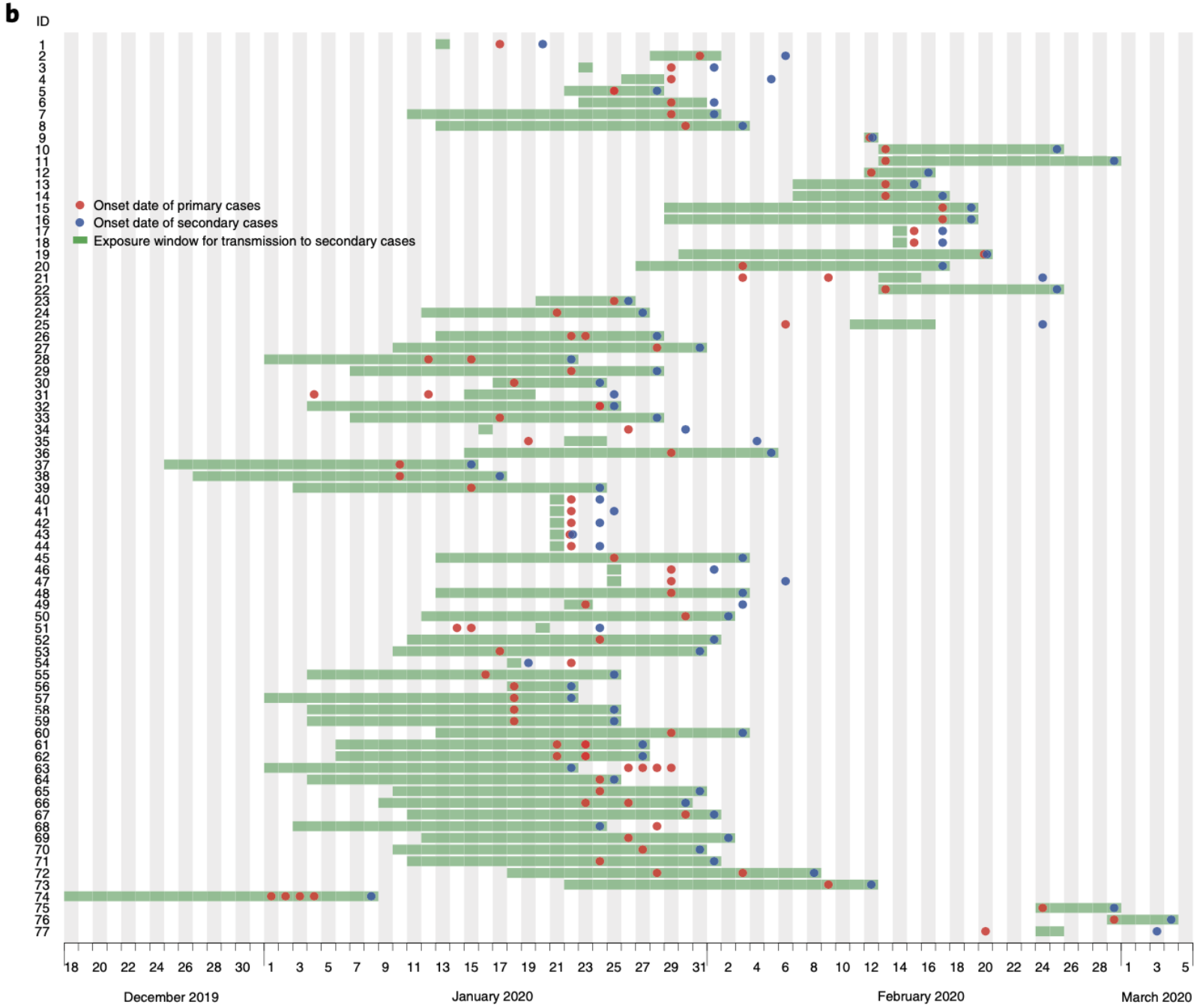
Xi He[1,3], Eric H. Y. Lau[2,3]✉, Peng Wu[2], Xilong Deng[1], Jian Wang[1], Xinxin Hao[2], Yiu Chung Lau[2], Jessica Y. Wong[2], Yujuan Guan[1], Xinghua Tan[1], Xiaoneng Mo[1], Yanqing Chen[1], Baolin Liao[1], Weilie Chen[1], Fengyu Hu[1], Qing Zhang[1], Mingqiu Zhong[1], Yanrong Wu[1], Lingzhai Zhao[1], Fuchun Zhang[1], Benjamin J. Cowling[2,4], Fang Li[1,4] and Gabriel M. Leung[2,4]

Serial interval

Transmission distribution

Incubation period





Estimates

- Serial interval mean: 5.8 days
- Infectiousness began 2.3 days before symptom onset and peaks 0.7 days before symptom onset
- Infectiousness declined quickly within 7 days
- 44% of transmission in pre-symptomatic period

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

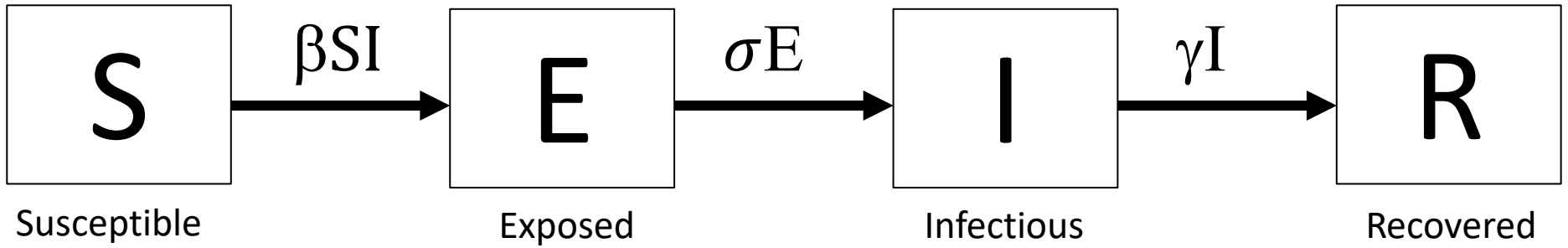
Spread of SARS-CoV-2 in the Icelandic Population

D.F. Gudbjartsson, A. Helgason, H. Jonsson, O.T. Magnusson, P. Melsted, G.L. Norddahl, J. Saemundsdottir, A. Sigurdsson, P. Sulem, A.B. Agustsdottir, B. Eiriksdottir, R. Fridriksdottir, E.E. Gardarsdottir, G. Georgsson, O.S. Gretarsdottir, K.R. Gudmundsson, T.R. Gunnarsdottir, A. Gylfason, H. Holm, B.O. Jensson, A. Jonasdottir, F. Jonsson, K.S. Josefsdottir, T. Kristjansson, D.N. Magnusdottir, L. le Roux, G. Sigmundsdottir, G. Sveinbjornsson, K.E. Sveinsdottir, M. Sveinsdottir, E.A. Thorarensen, B. Thorbjornsson, A. Löve, G. Masson, I. Jonsdottir, A.D. Möller, T. Gudnason, K.G. Kristinsson, U. Thorsteinsdottir, and K. Stefansson

- Population-based screening
- 43% of PCR+, confirmed Covid-19 cases were asymptomatic

SEIR Models

The SEIR Model



Latent period = $1/\sigma$

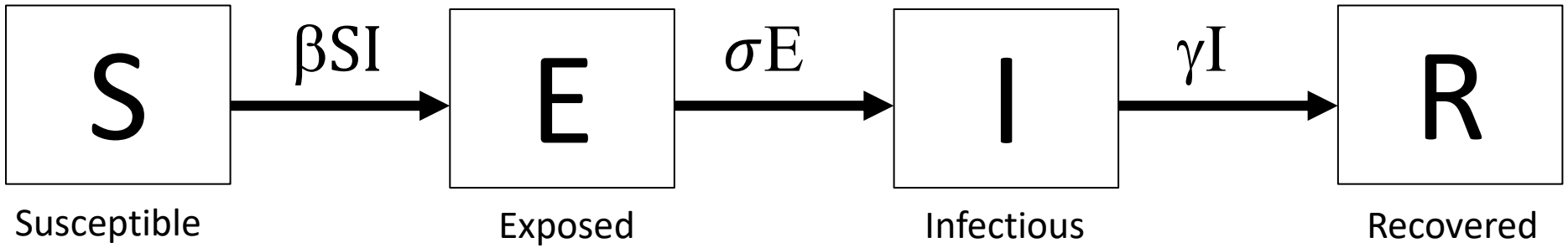
$$\frac{dS}{dt} = \mu - \beta SI - \mu \mathrm{S}$$

$$\frac{dE}{dt} = \beta SI - \sigma E - \mu \mathrm{E}$$

$$\frac{dI}{dt} = \sigma E - \mu \mathrm{I}$$

$$\frac{dR}{dt} = \gamma I - \mu \mathrm{R}$$

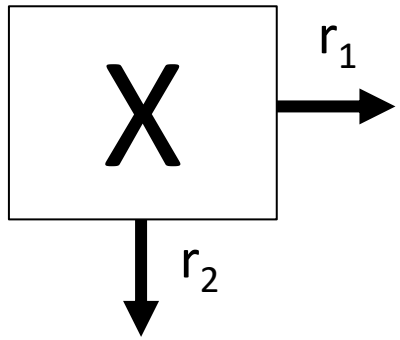
The SEIR Model



$$R_0 = \frac{\beta\sigma}{(\mu+\gamma)(\mu+\sigma)}$$

$$R_0 = \frac{\beta\sigma}{(\mu+\gamma)(\mu+\sigma)}$$

Competing Risks



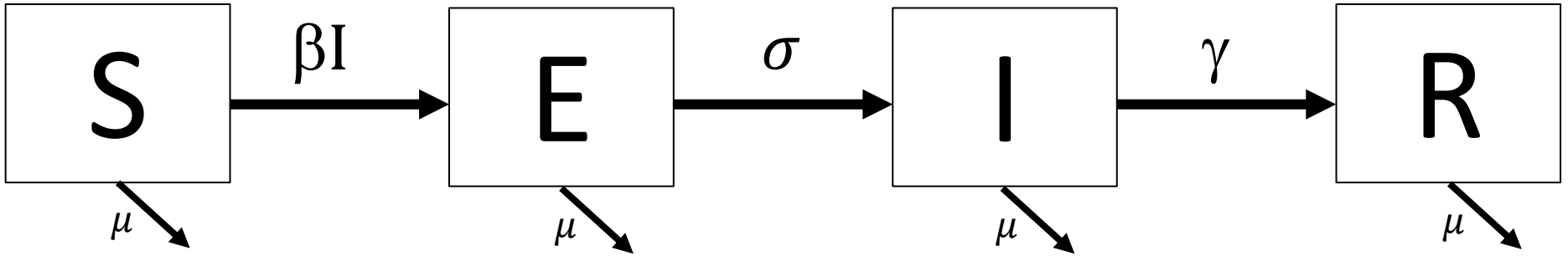
Suppose you arrive a train station at a random time.

The A train comes every 15 minutes

The B train comes every 10 minutes.

What is the probability that the A train arrives first?

Probability r_1 occurs = $\frac{r_1}{r_1+r_2}$



$$R_0 = \frac{\beta\sigma}{(\mu+\gamma)(\mu+\sigma)}$$

$$Duration\ of\ infectiousness = \frac{1}{\mu+\gamma} = D$$

$$R_0\ in\ SIR\ model\ with\ demography = \beta D = \frac{\beta}{\mu+\gamma}$$

$$Probability\ of\ surviving\ E = \frac{\sigma}{\mu+\sigma}$$

$$R_0 = \frac{\beta\sigma}{(\mu+\gamma)(\mu+\sigma)}$$

$$R_0 \; in \; SIR \; model \; with \; demography = \beta D = \frac{\beta}{\mu+\gamma}$$

$$Probability \; of \; surviving \; E = \frac{\sigma}{\mu+\sigma}$$

If $\sigma >> \mu$, $\frac{\sigma}{\mu+\sigma} \approx 1$

Example: Latent period for measles ~ 7 days

σ = (1/7 days) = 1/week = 52/year

$$\frac{52/yr}{(\frac{1}{70\ years})+52/yr} = \frac{52}{0.14+52} = 0.997$$

$$R_0 = \frac{\beta\sigma}{(\mu+\gamma)(\mu+\sigma)}$$

$$R_0\ in\ SIR\ model\ with\ demography = \beta D = \frac{\beta}{\mu+\gamma}$$

$$Probability\ of\ surviving\ E = \frac{\sigma}{\mu+\sigma} = p$$

Tuberculosis: among people who are infected, only 10% ever develop active TB, 90% remain latent (in E).

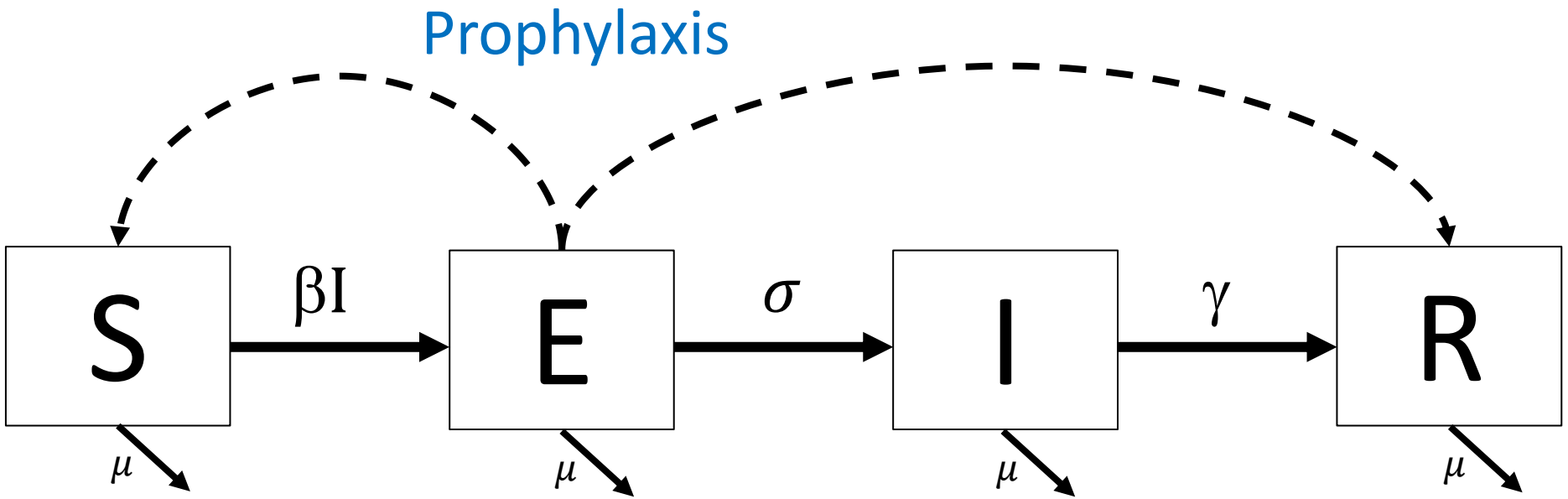
We estimate that without treatment, people with active TB infect 10 people per year and are infections for 2 years

$R_0 = \beta Dp = (10)(2)(0.10) = 2$

Why use SEIR model?

- Long latent period
- Interventions
- Growth Rate

Interventions targeting latent period



- Used widely for TB, HIV, other infections
- Under evaluation now for household contacts of Covid-19 patients

How effective do interventions need to be?

$R_0 = \beta D p$

where $p =$ proportion of latent infections that reach infectious state

Suppose for SARS-CoV-2, R_0 = 2.5. How effective would prophylaxis need to be to avert epidemics?

$R_0 = \beta D p = 2.5 \; when \; p \approx 1$, so $\beta D \approx 2.5$

Need $R_0 < 1$

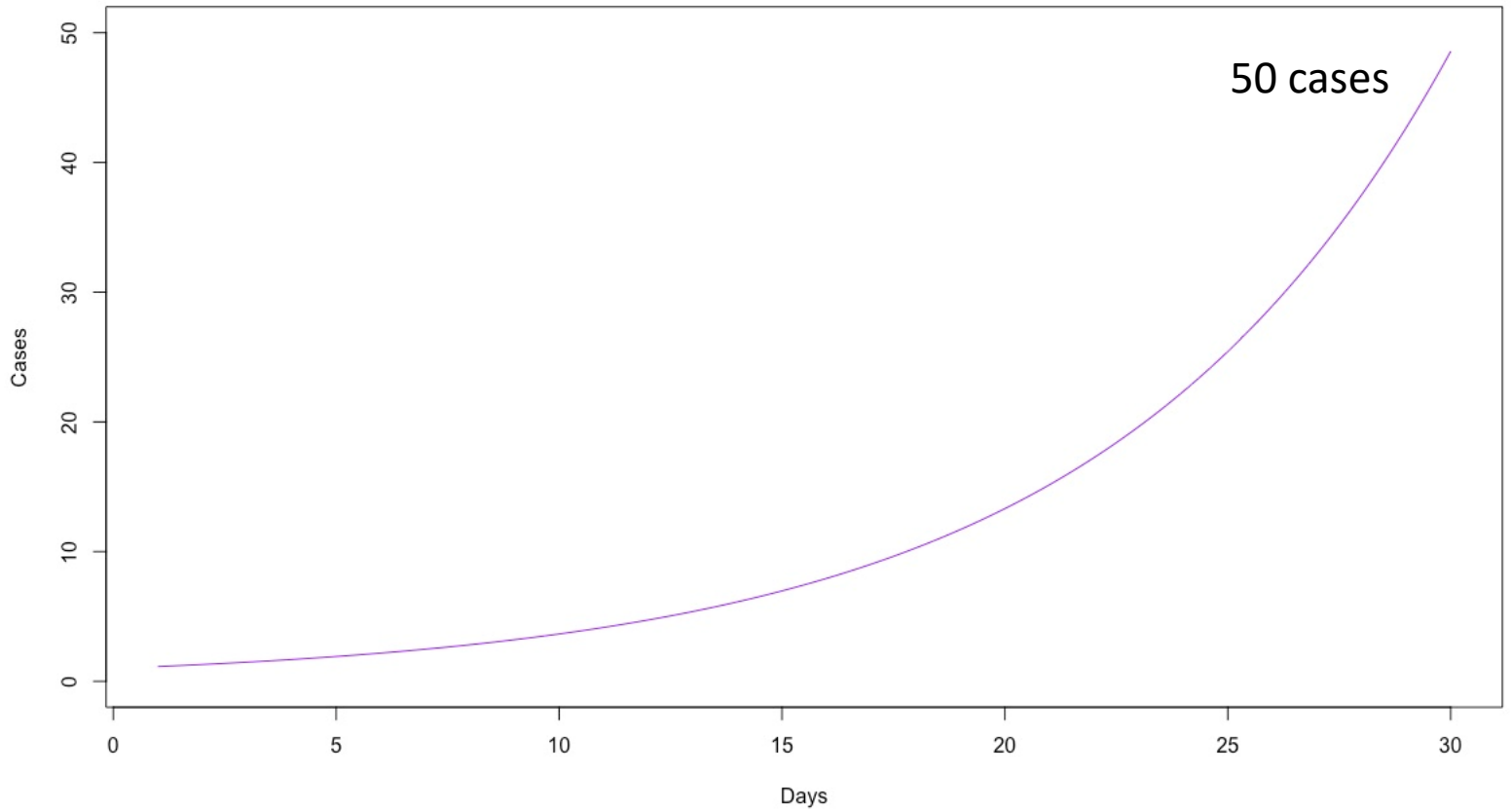
$\beta D p < 1$, so $2.5p < 1$.

$p < \frac{1}{2.5} = 0.40.$

Need intervention to reduce p by 60%

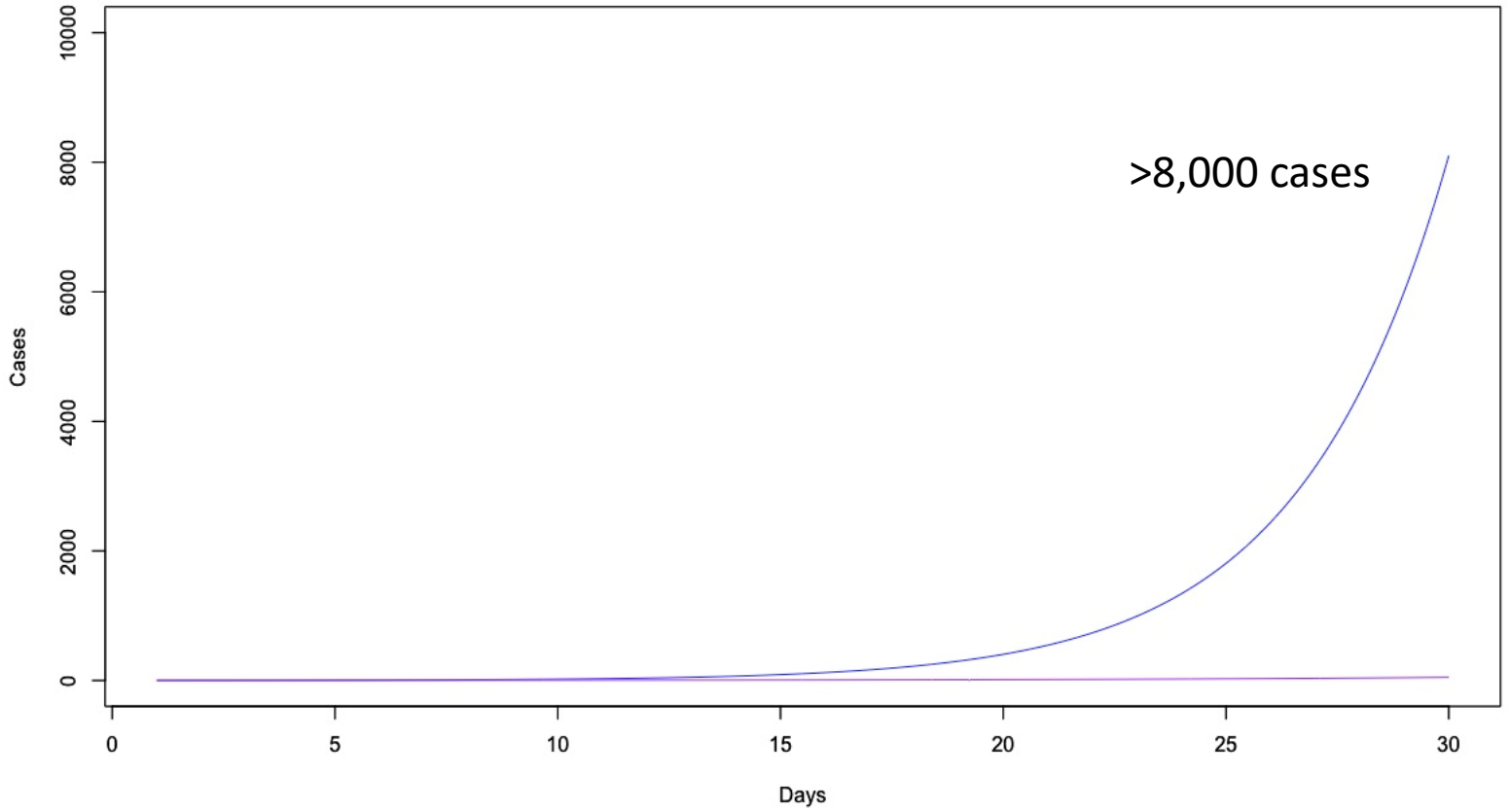
Modeling Growth Rate More Accurately

SEIR Model with R_0 = 2.5, Latent Period = 4, Infectious Period = 5

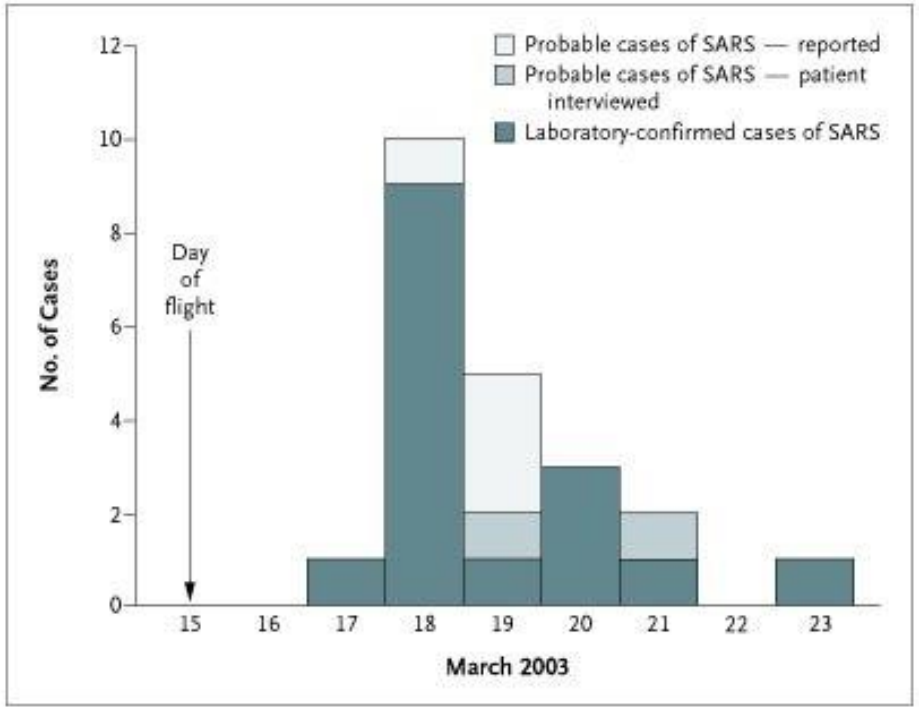


Modeling Growth Rate More Accurately

SEIR Model with $R_0 = 2.5$, Latent Period = 4, Infectious Period = 5
SIR Model with $R_0 = 2.5$, Infectious Period = 5



Distribution times in compartmental models

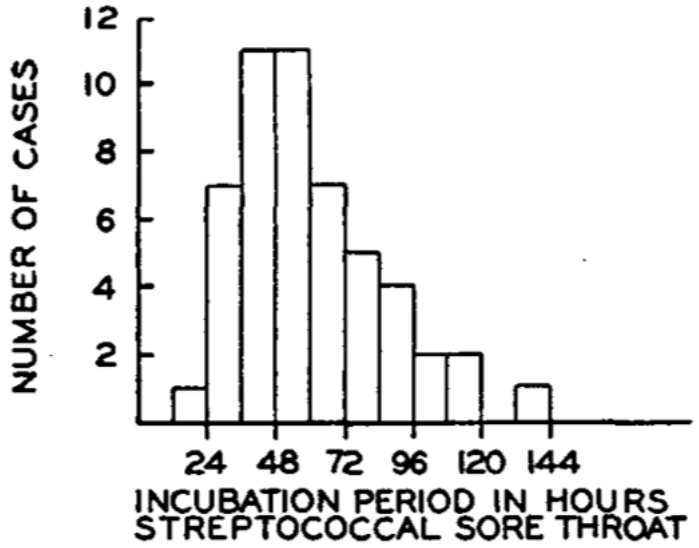


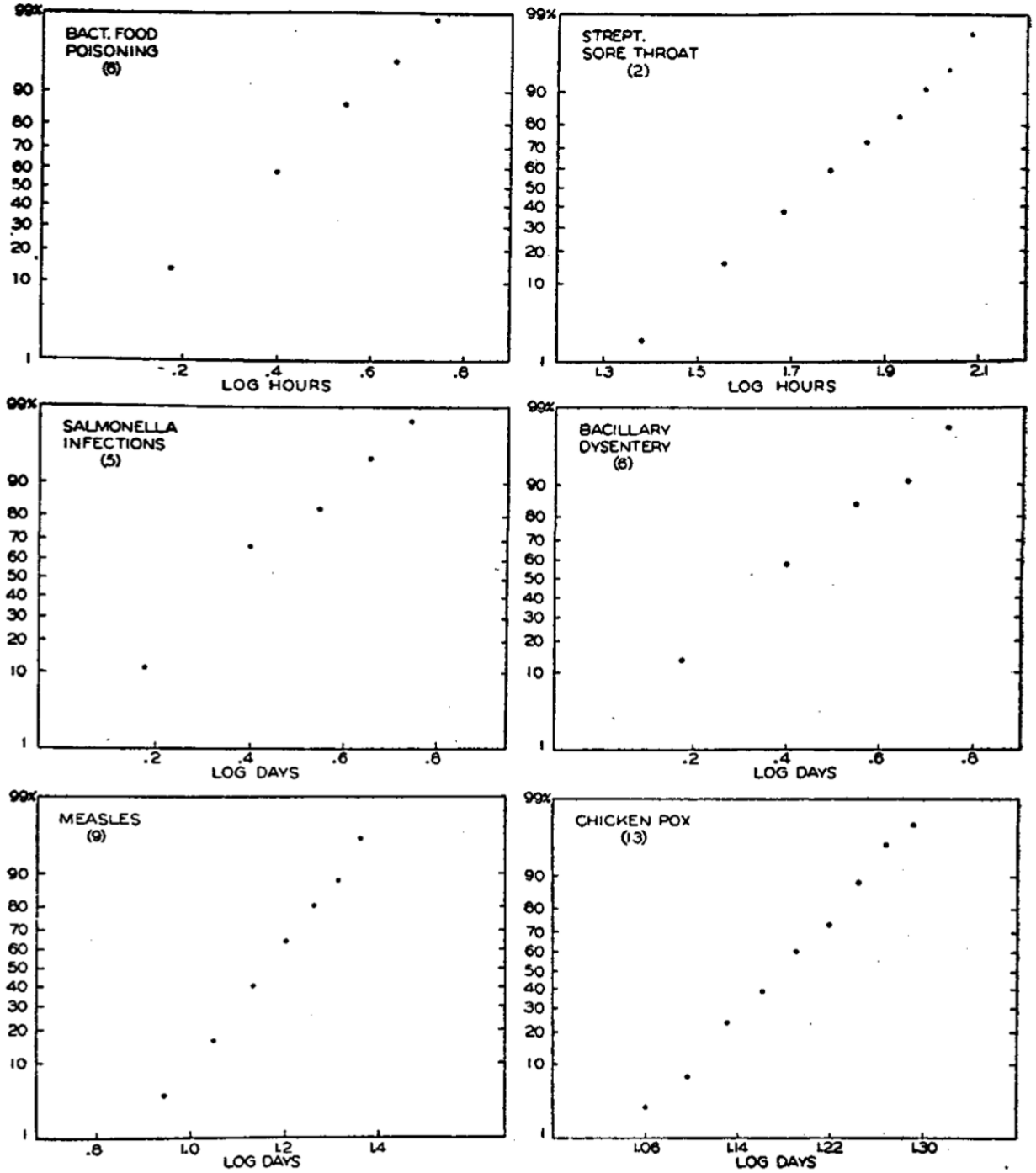
THE DISTRIBUTION OF INCUBATION PERIODS OF INFECTIOUS DISEASE [1]

By

PHILIP E. SARTWELL [2]

(Received for publication November 30th, 1949)





Incubation periods typically follow log-normal distribution

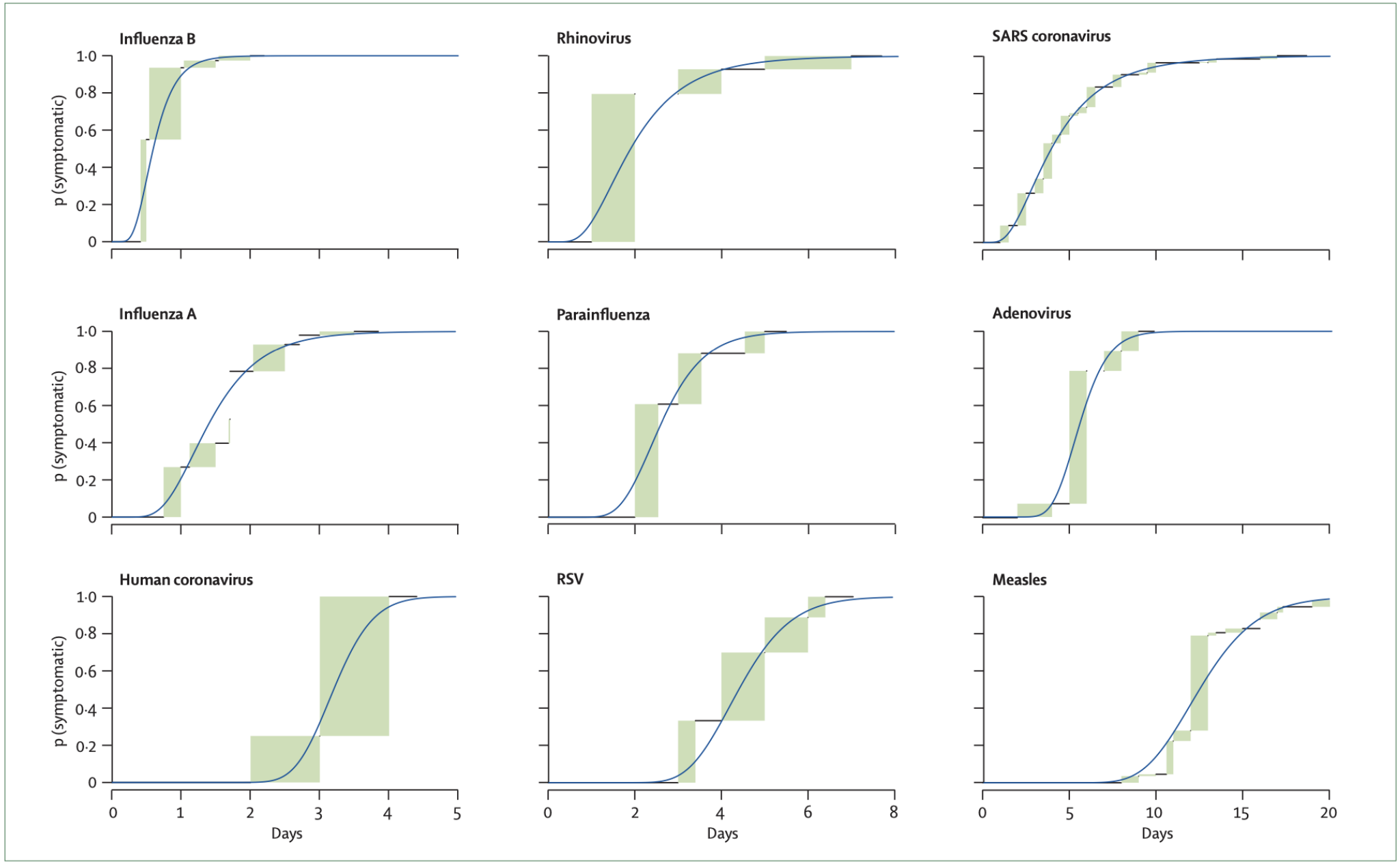
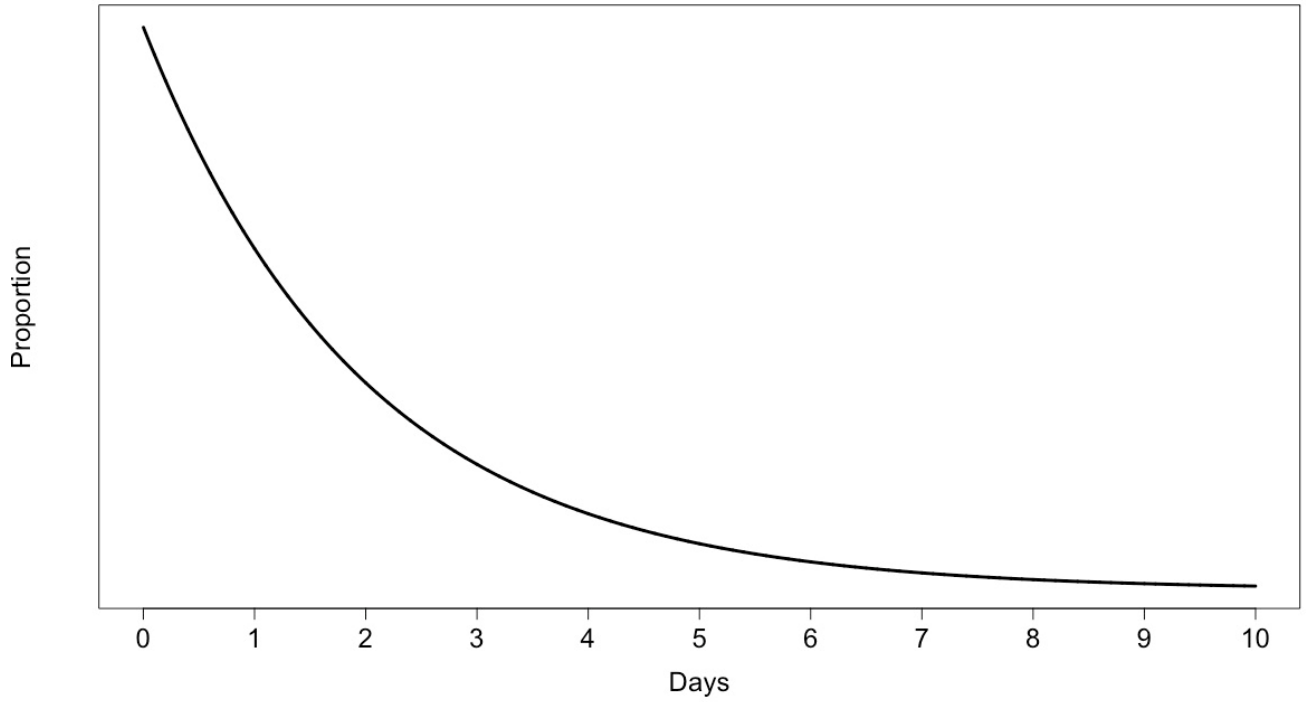
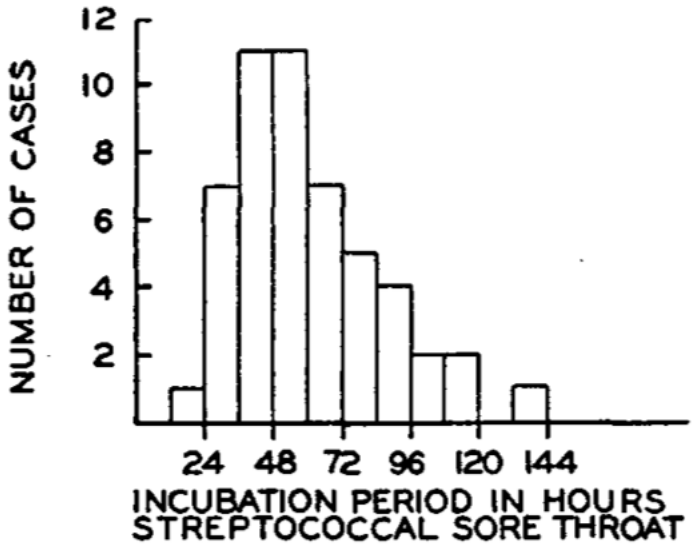


Figure 2: **Parametric and non-parametric estimates of the incubation period**

Cumulative percentage of cases developing symptoms by a given day under the estimates for the log-normal distribution (continuous line) are shown, compared with the non-parametric estimates calculated by the method of Turnbull[62] (rectangles). Rectangular regions represent estimates with equivalent support (ie, not statistically distinguishable). RSV=respiratory syncytial virus. SARS=severe acute respiratory syndrome.

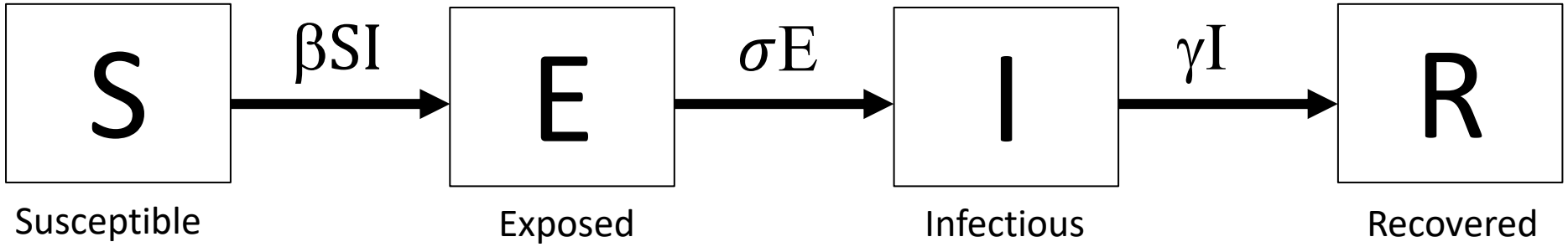
Distribution times in compartmental models

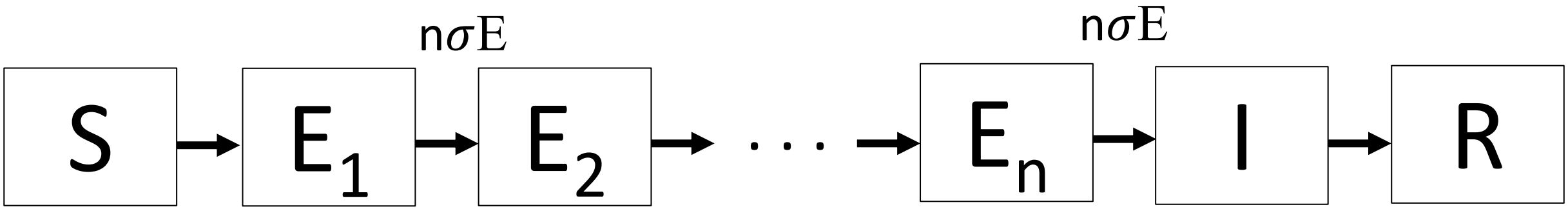




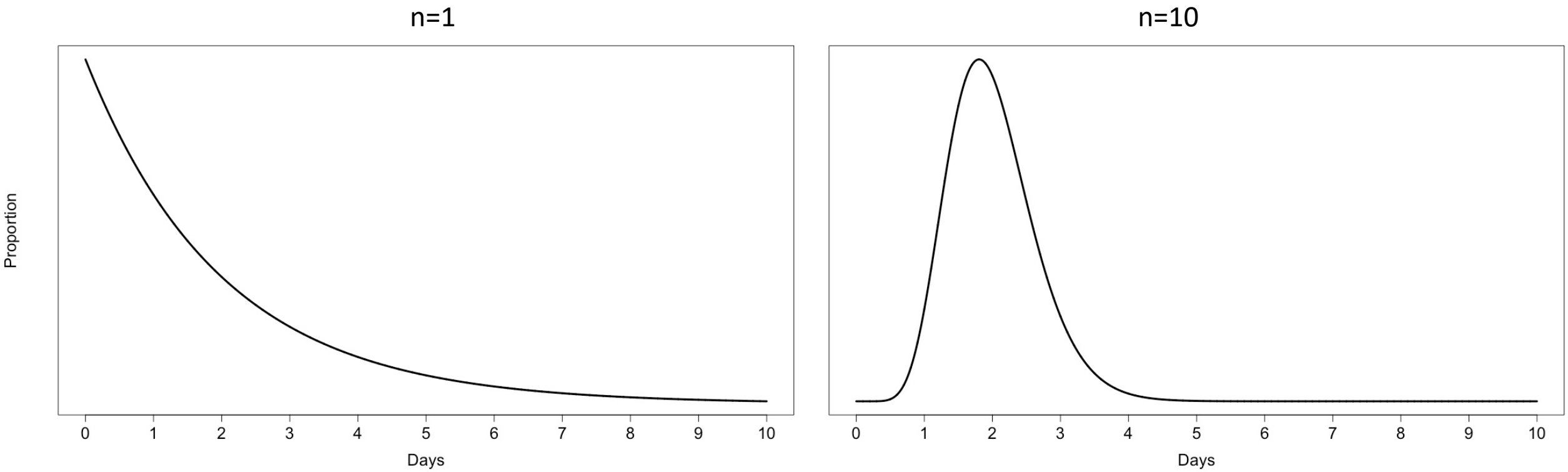
What can be problems with using this distribution?

Distribution times in compartmental models



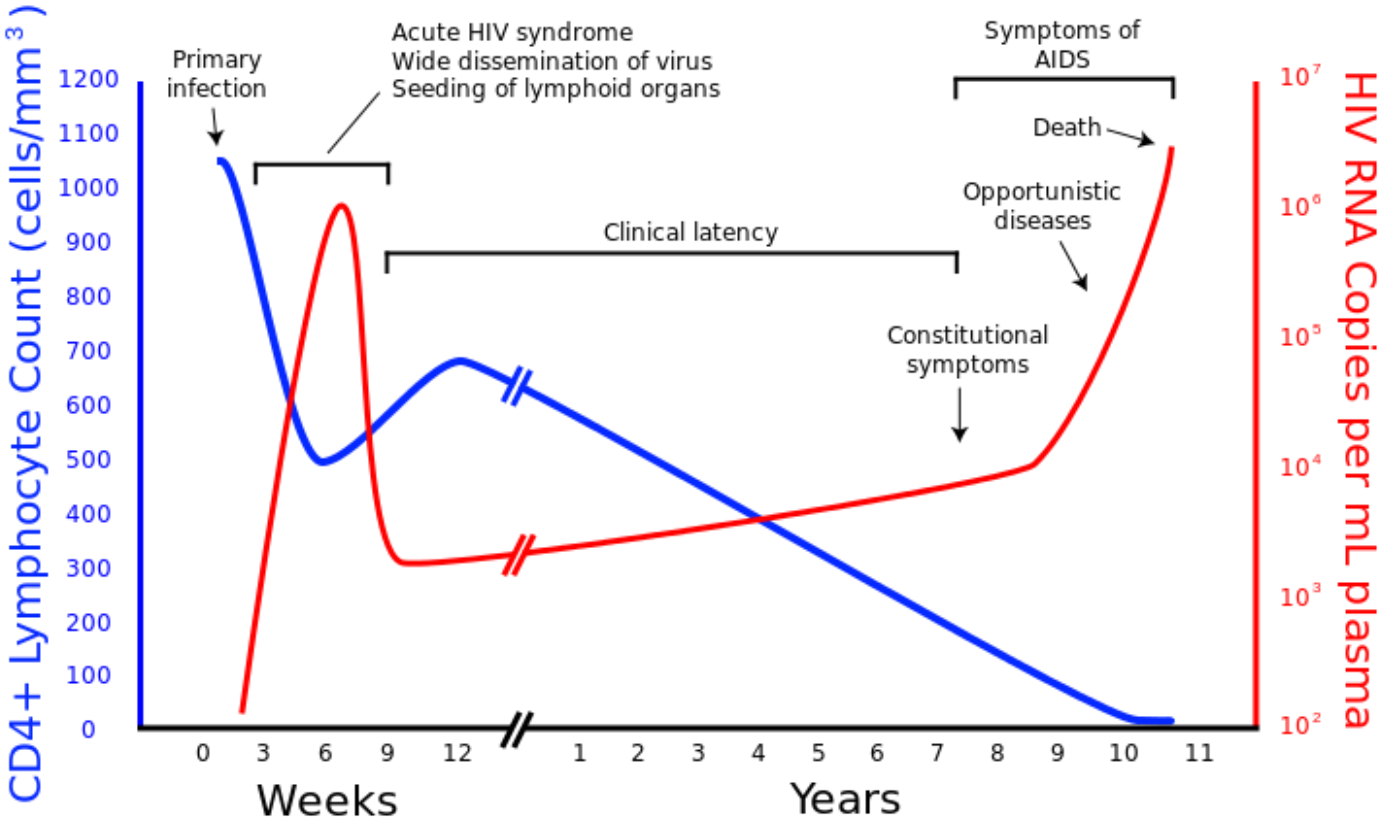


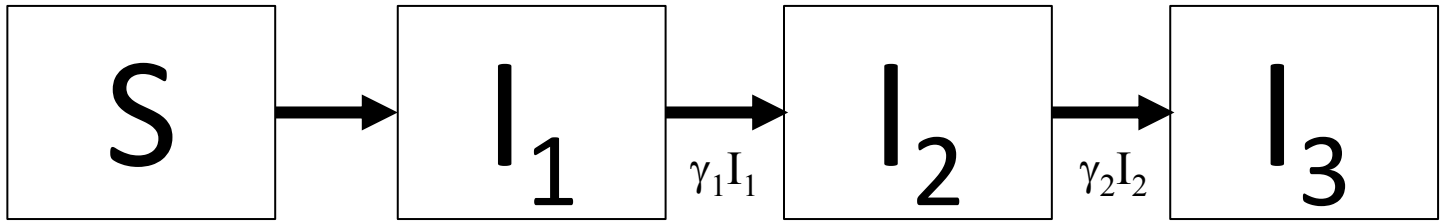
SE_nIR



SEIR Model and Infectiousness

- Infectiousness often changes over the course of an illness





$$S(\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3)$$

What may cause changes in effective contact rate over course of illness?

- Burden of pathogens
- Symptoms
- Contact rates

Concepts Review

- Understanding the incubation period and latent period is important for characterizing transmission of infectious diseases; models typically use a latent period unless explicitly modeling symptoms
- Exposure times and symptom onset can be used to estimate these entities, but are most tractable with discrete exposures
- SEIR models are useful when the latent period is long, epidemic growth rate is of interest, or when modeling interventions during the latent period
- Compartmental ODE models have exponential time distributions which rarely reflect realistic intervals; simple modifications can capture these distributions

Survey

Questions?