

# Estimation of the reproduction number of influenza

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# Outline

- General concepts:  $R_0$  and transmission models
- Estimation of the reproduction number of pandemic influenza from daily notification data
  - Fitting SIR model to epidemic curve
  - Estimating initial growth rate
- Conclusion and hands-on!

# Epidemic models

- Epidemic models can help us clarify an epidemic process. In particular:
  - Transmission mechanisms (e.g., close contact, sexual contact, airborne transmission, age groups driving transmission)
  - Immunity (waning or life-long immunity)
- Epidemic models are useful tools for public health to:
  - predict the spread of infectious disease
  - evaluate the impact of different mitigation strategies (e.g., foot-and-mouth disease, SARS, smallpox, pandemic influenza)



Sir Ronald Ross

# The basic reproduction number, $R_0$

- $R_0$  = The number of secondary cases generated by an index case during the infectious period, in an entirely susceptible population

$$R_0 > 1$$

Disease can spread

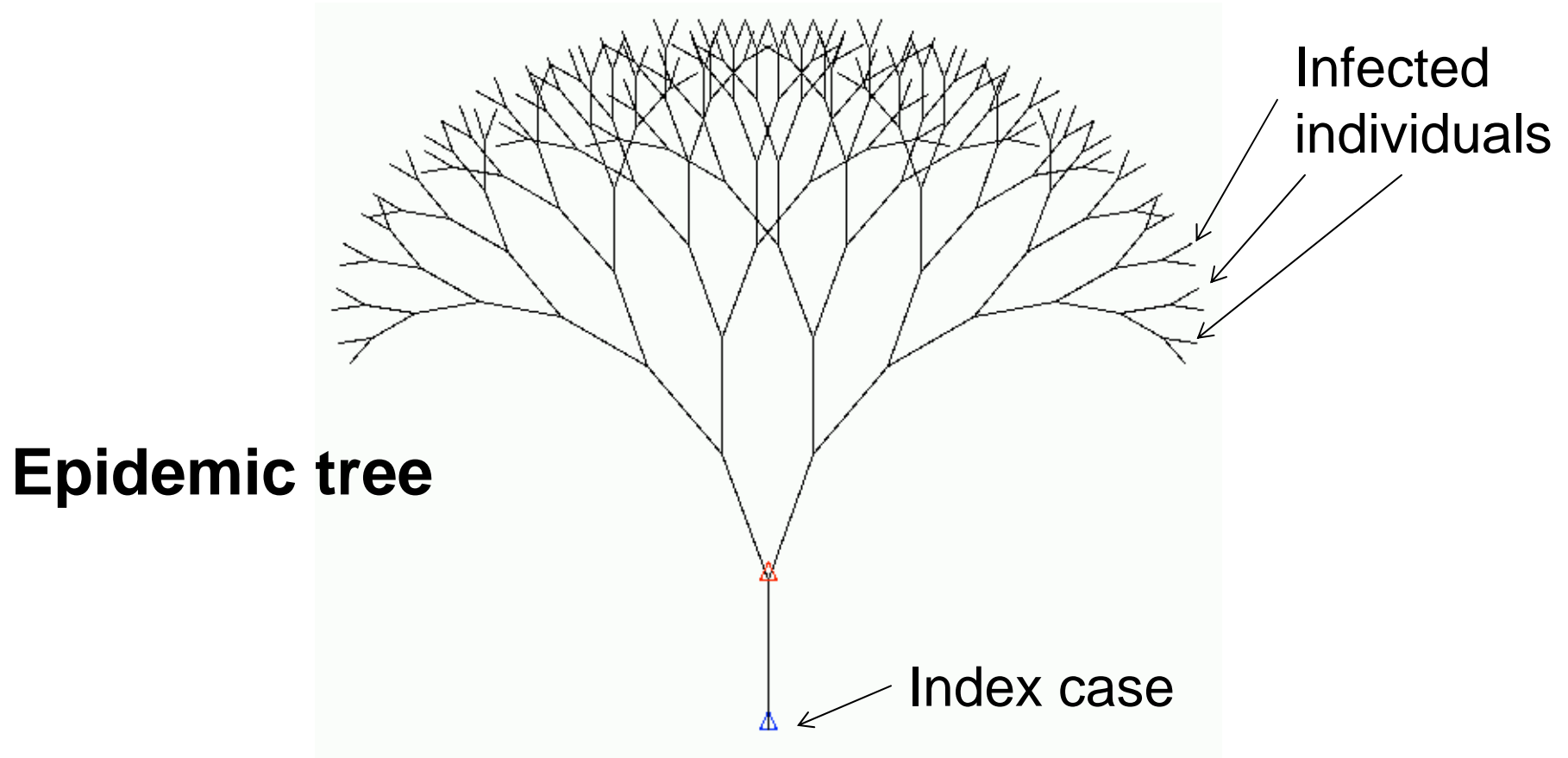
$$R_0 < 1$$

Disease

cannot spread

The goal of public health interventions is to reduce  $R_0$  to a number below 1.

# Outbreaks can go out of control quickly!



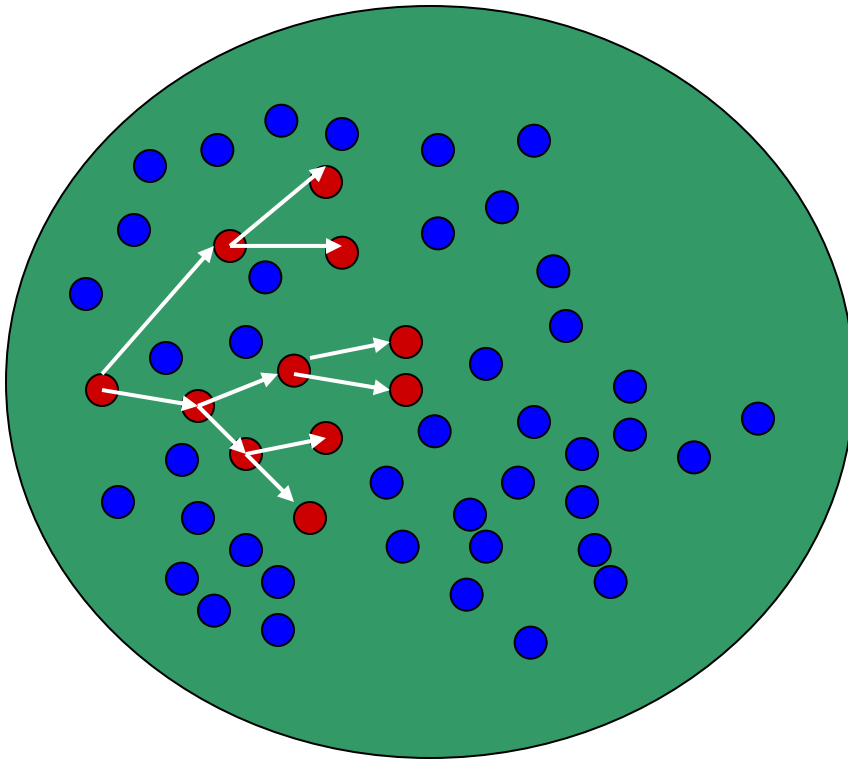
Vertices of the tree are infected individuals. Branches of the tree grow as the epidemic progresses through the population of susceptible hosts.

# The reproduction number

- A more practical quantity is the **reproduction number (R)** which measures the transmissibility in a partially immune population because of previous exposures to the infectious agent or vaccination campaigns.
- In a well-mixed population,
- $p$  is the fraction of the population that is effectively protected (immune)
- $R = (1-p) R_0$  and hence  $R \leq R_0$ .

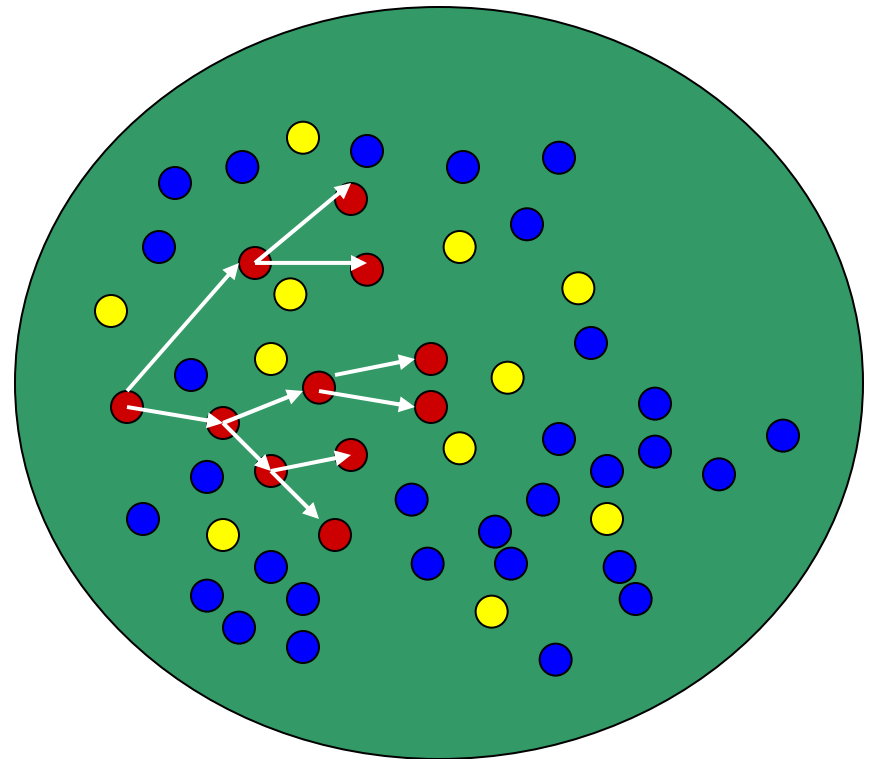
Basic reproduction number

$$R_0 = 2$$



Reproduction number

$$R = 2$$



- Susceptible individual
- Infectious individual
- Immune (e.g., previous exposures or vaccination campaigns)

# Fraction of population to immunize to achieve herd immunity

- $R = (1-p) \cdot R_0 \leq 1$   
 $p \geq 1 - 1/R_0$
- If  $R_0 = 2$ ,  $p = 50\%$ . If a vaccine is available and 100% efficacious then only need to vaccinate 50% of pop to stop transmission
- No need to vaccinate entire population to stop transmission = achieve herd immunity

# Estimated values of $R_0$ for various infections

Estimated Herd Immunity thresholds for vaccine preventable diseases<sup>[2]</sup>

Disease	Transmission	$R_0$	Herd immunity threshold
Diphtheria	Saliva	6-7	85%
Measles	Airborne	12-18	83 - 94%
Mumps	Airborne droplet	4-7	75 - 86%
Pertussis	Airborne droplet	12-17	92 - 94%
Polio	Fecal-oral route	5-7	80 - 86%
Rubella	Airborne droplet	5-7	80 - 85%
Smallpox	Social contact	6-7	83 - 85%

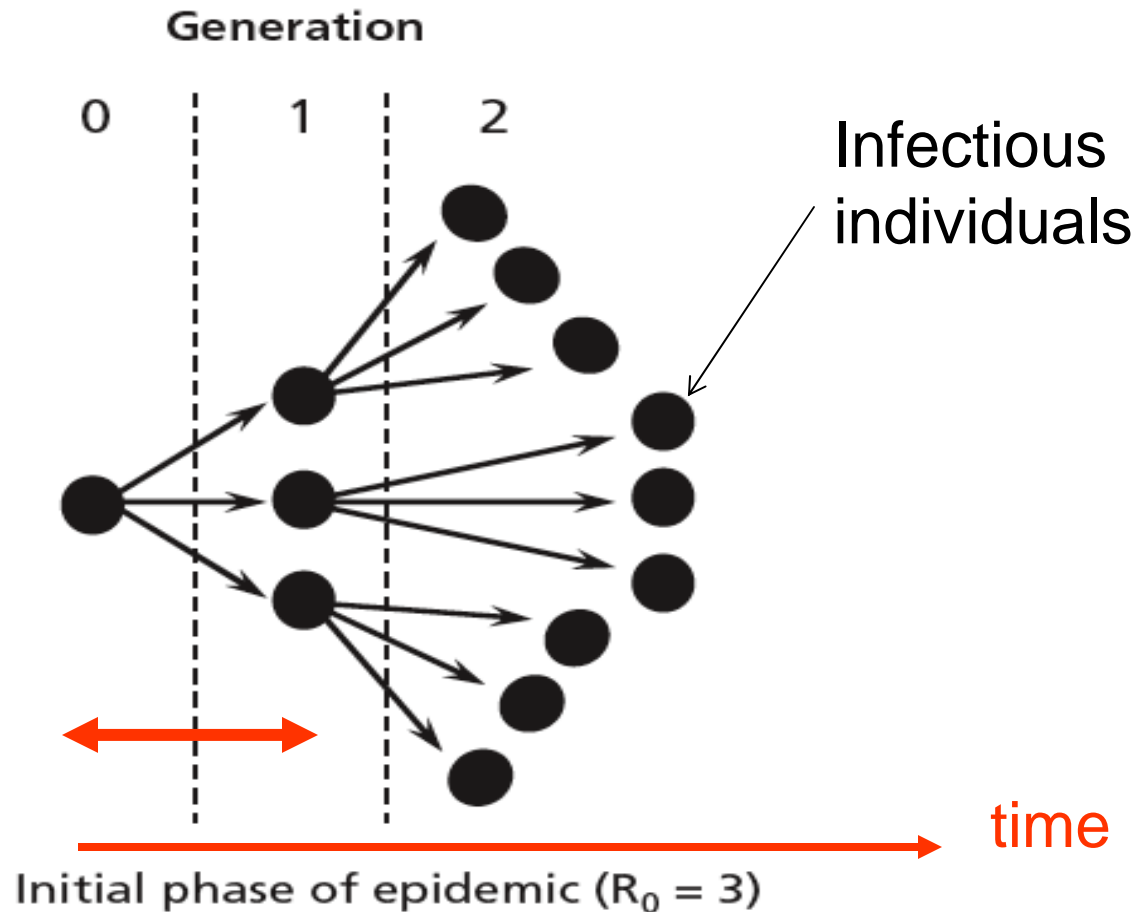
<sup>A</sup> -  $R_0$  is the basic reproduction number, or the average number of secondary infectious cases that are produced by a single index case in completely susceptible population.

Influenza : low  $R_0 \sim 2.0-3.0$

Rotavirus:  $R_0 \sim 30$

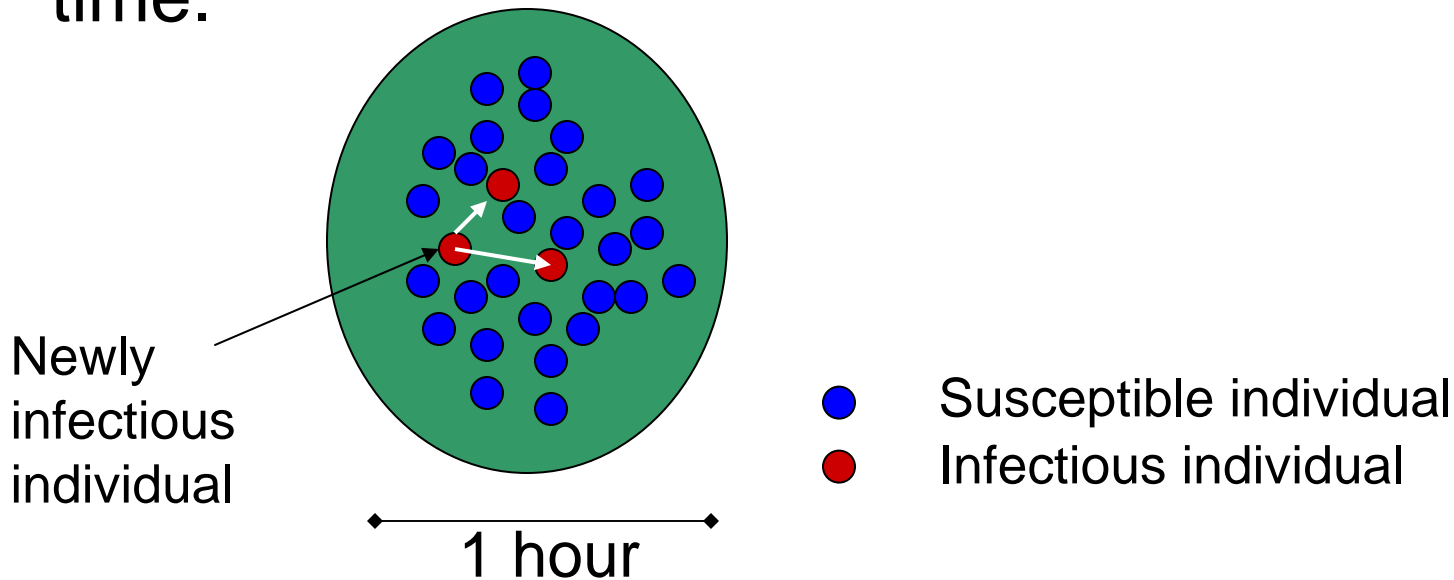
# Generation time

- The time interval between infections in two consecutive cases



# Transmission rate

- It measures how many new infections each infectious individual generates per unit of time.



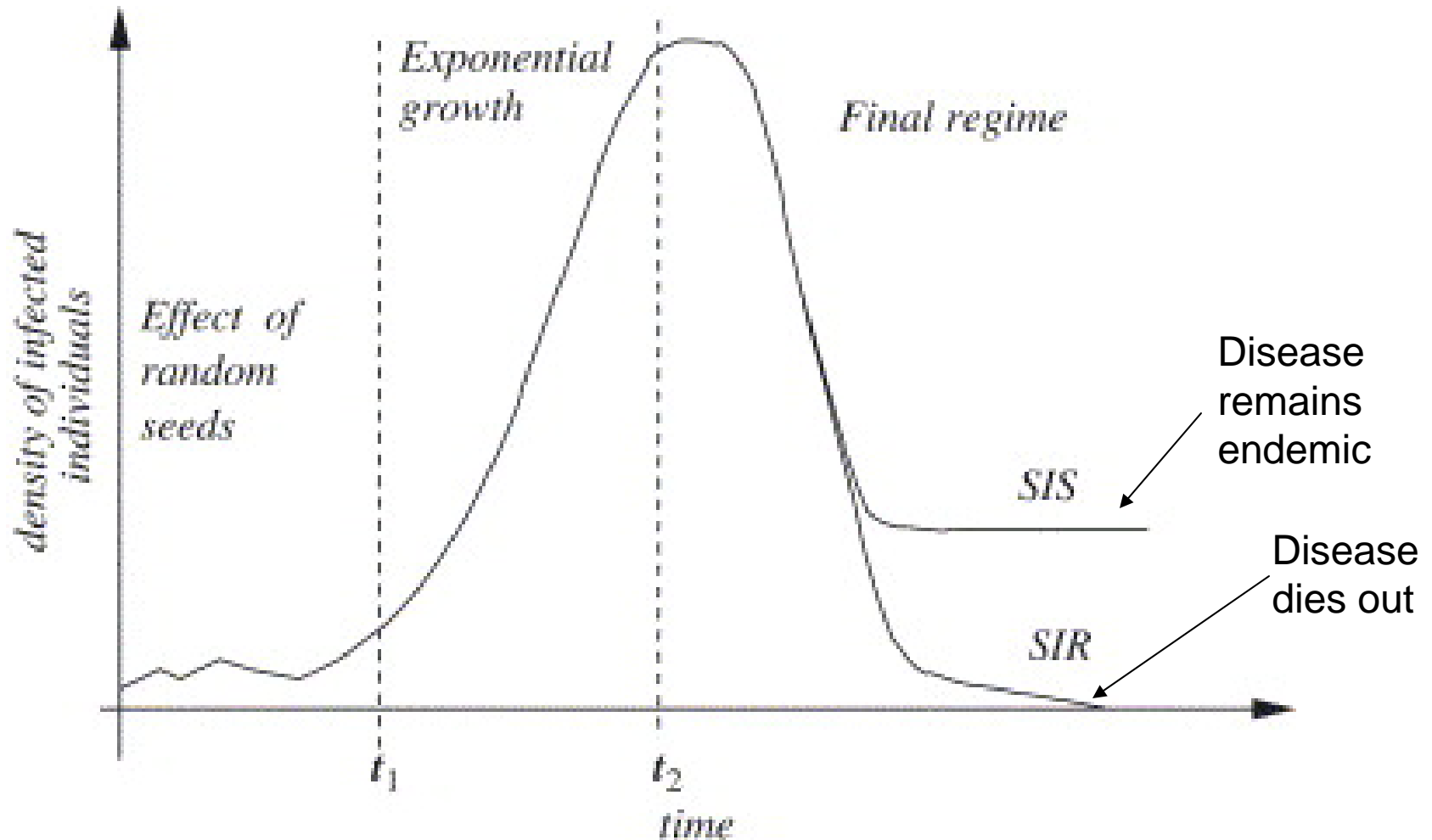
How to calculate the transmission rate?



**Transmission rate =**

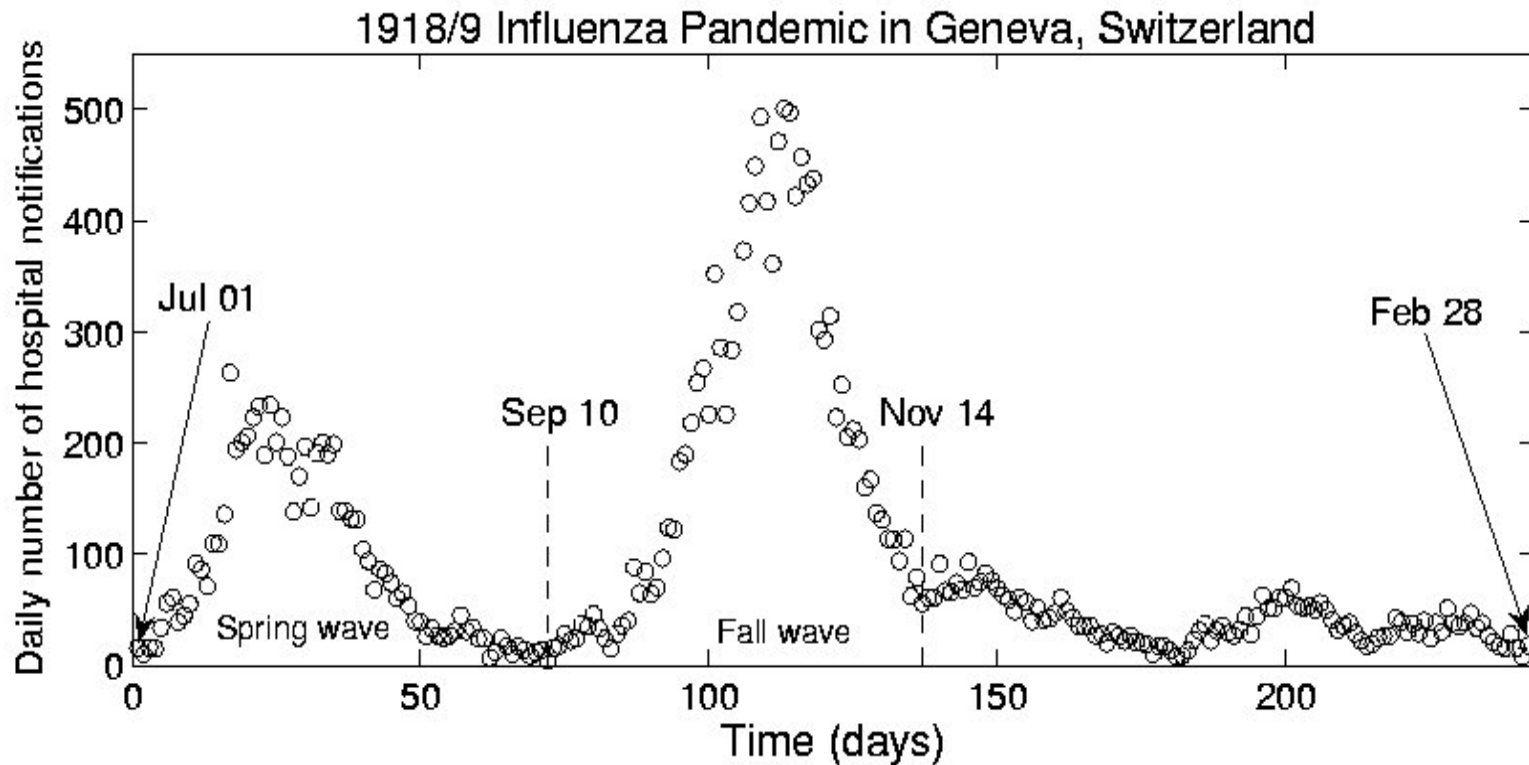
(Number of contacts per person per unit of time) X (Fraction of contacts that lead to infection)

# Typical shapes of epidemic curves

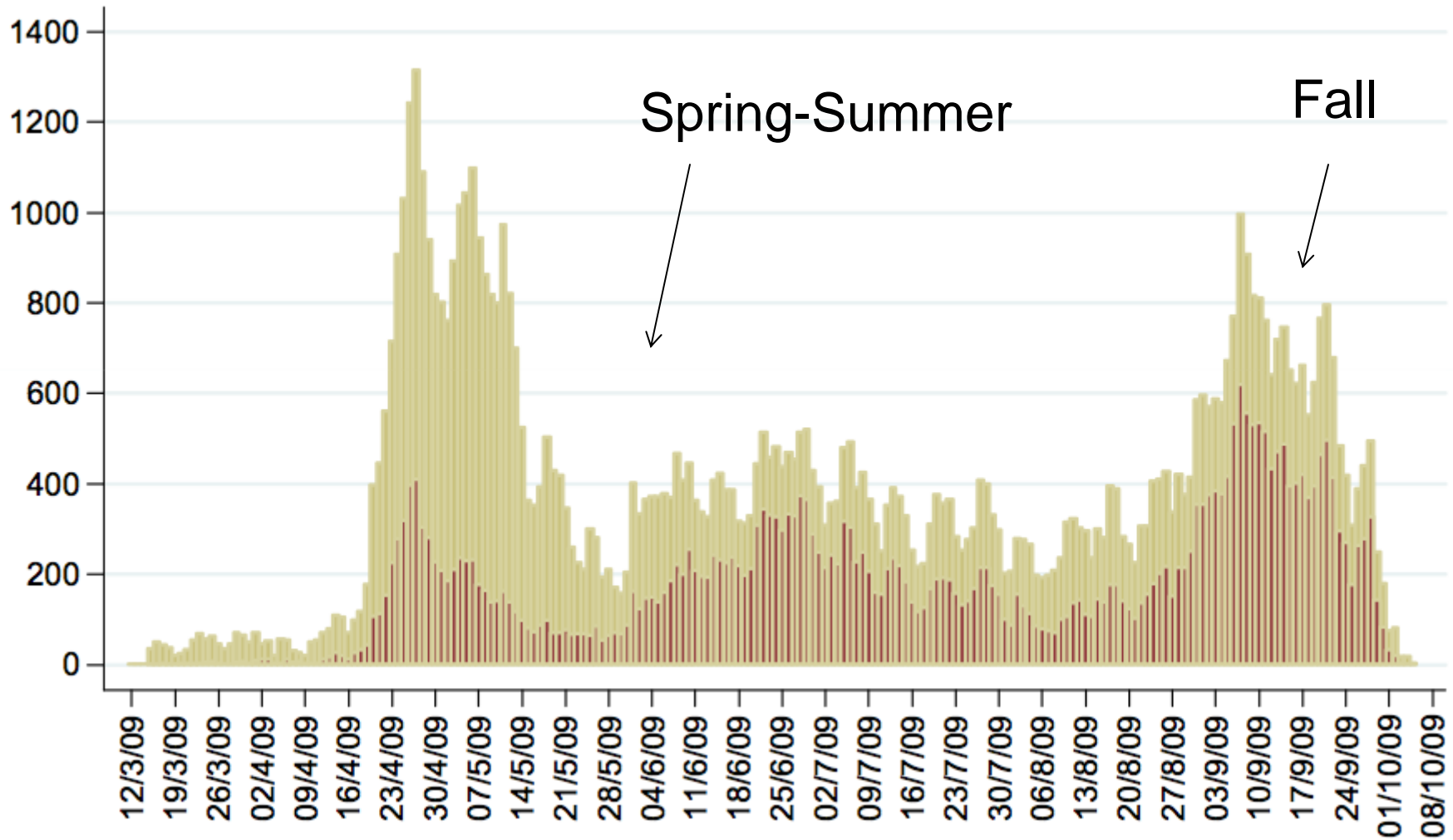


# 1918-19 pandemic in Geneva, Switzerland

- 3 waves: July – October - December
- Start among soldiers
- Spread to civilians



# 2009 influenza pandemic in Mexico



# A simple epidemic model (SIR)



- Homogeneous mixing (individuals mix uniformly in the population)
- The entire population is equally susceptible to infectious agent
- Individuals become infectious instantaneously after exposure to infectious agent.

# $R_0$ for SIR model

## Susceptible-Infectious-Recovered model



$$R_0 = (\text{transmission rate}) \times (\text{infectious period})$$



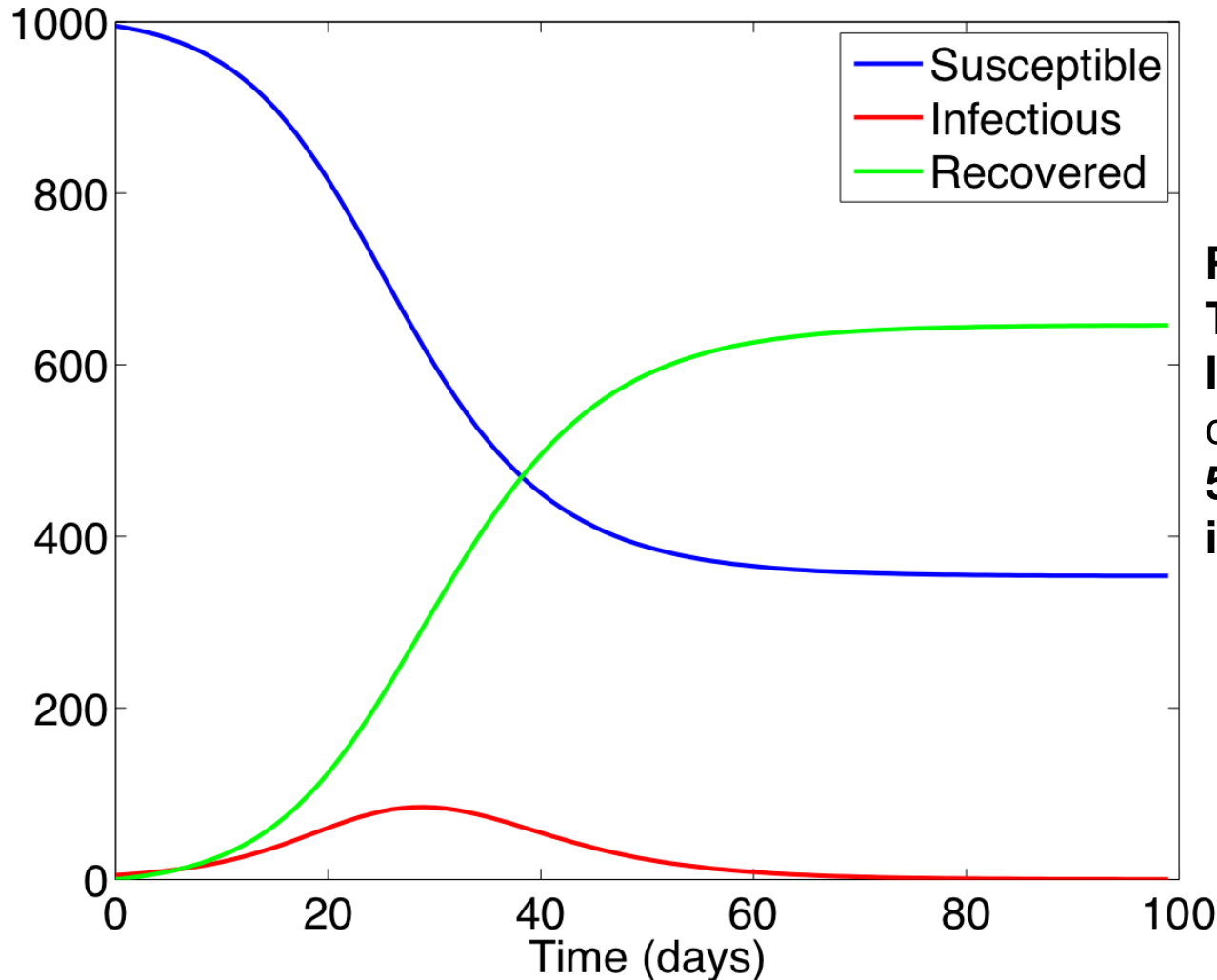
*If the mean infectious period is about 4 days  
and the mean transmission rate is about 0.4  
new infections per day per infected person:*

$$R_0 = 0.4 \times 4 = 1.6$$



# SIR mathematical model results

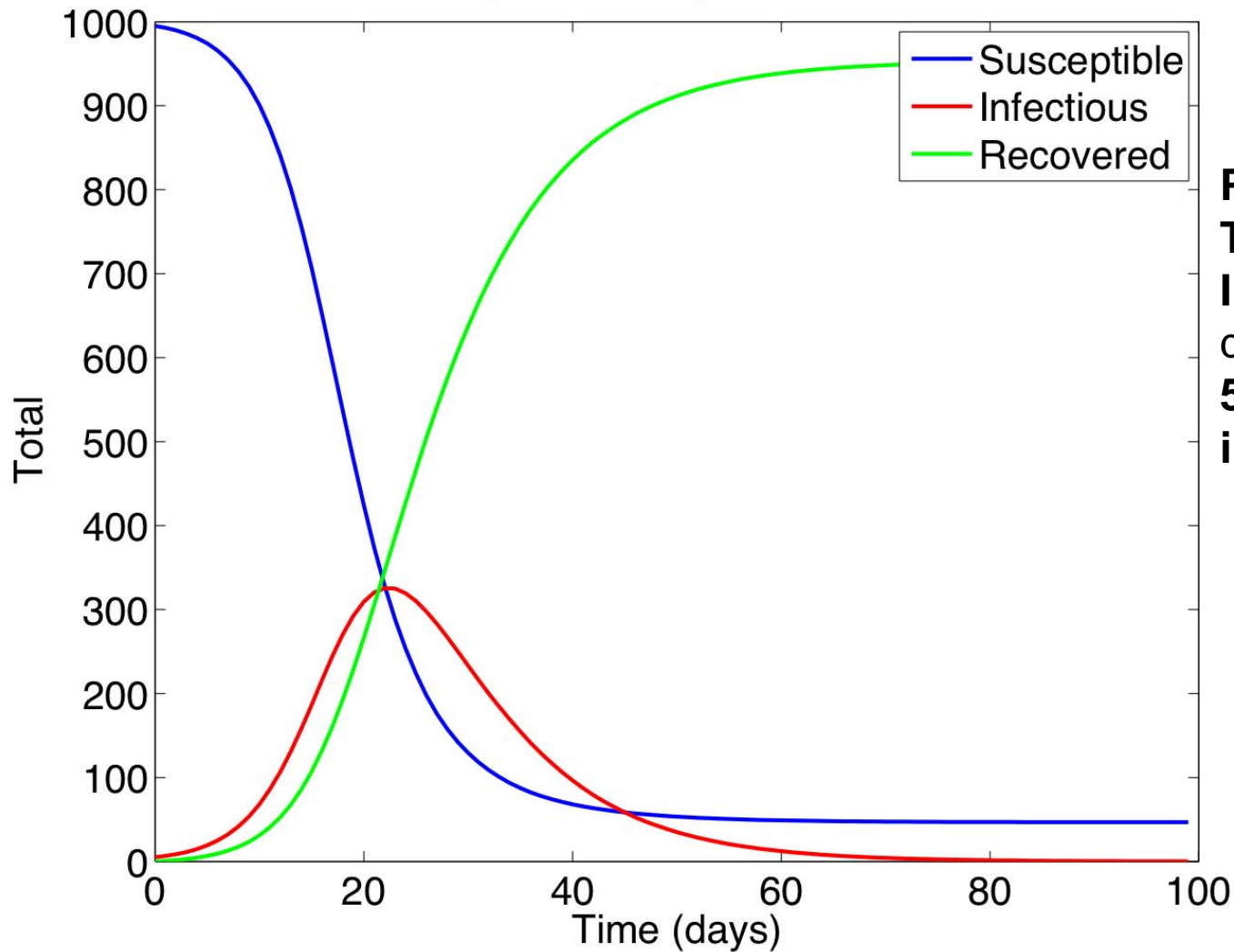
Example of SIR epidemic course



**Population size=1000**  
**Transmission rate=0.4**  
**Infectious period=4**  
**days**  
**5 individuals initially**  
**infectious**

$R_0=1.6$

Example of SIR epidemic course

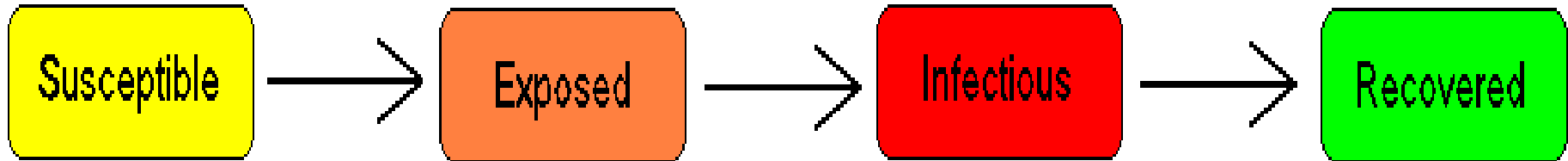


**Population size=1000**  
**Transmission rate=0.4**  
**Infectious period=8**  
**days**  
**5 individuals initially**  
**infectious**

**$R_0=3.2$**

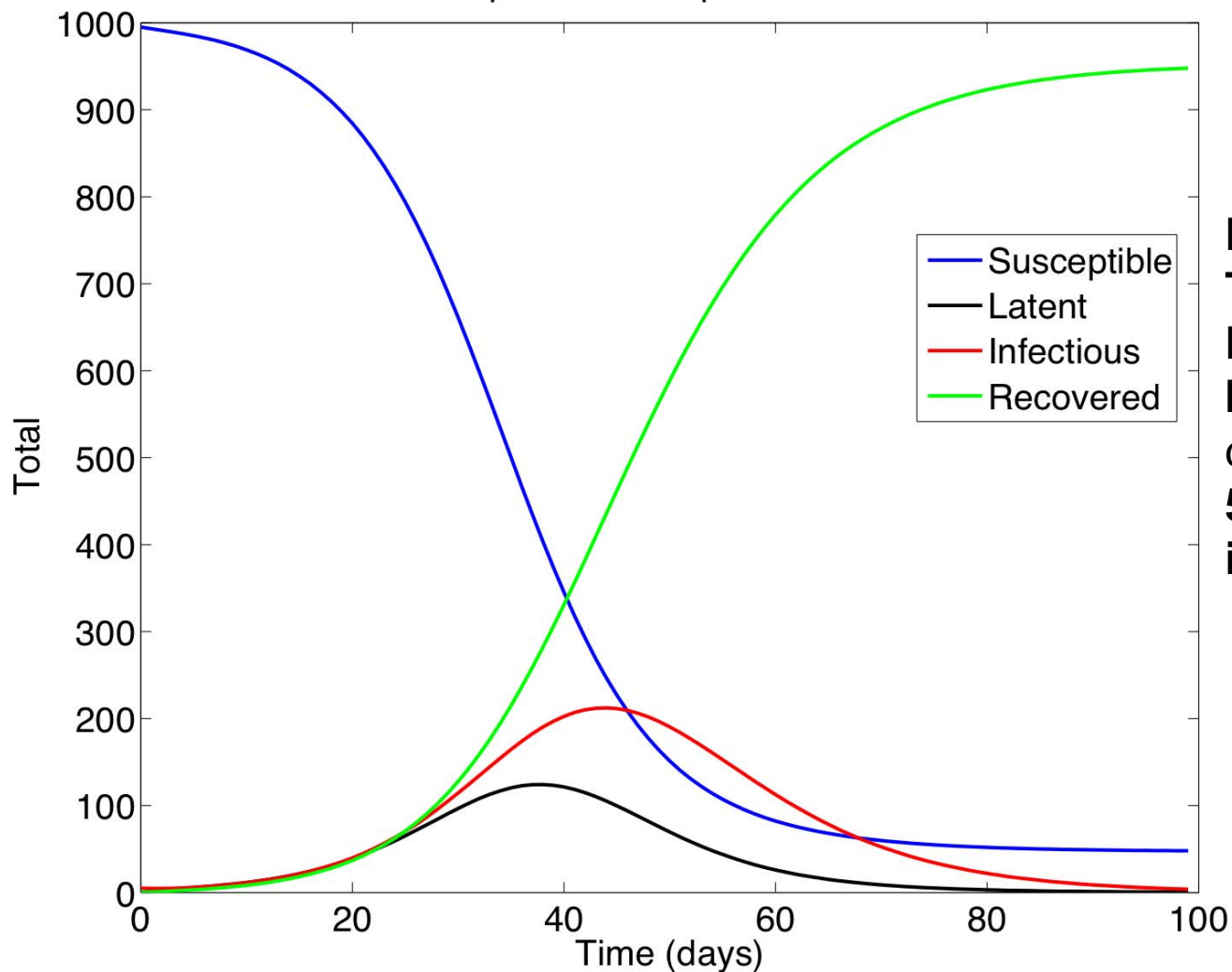
# Susceptible-Exposed- Infectious-Recovered model

**Inclusion of latency period via an exposed class.** Time elapsed from effective exposure to the infectious agent to infectiousness.



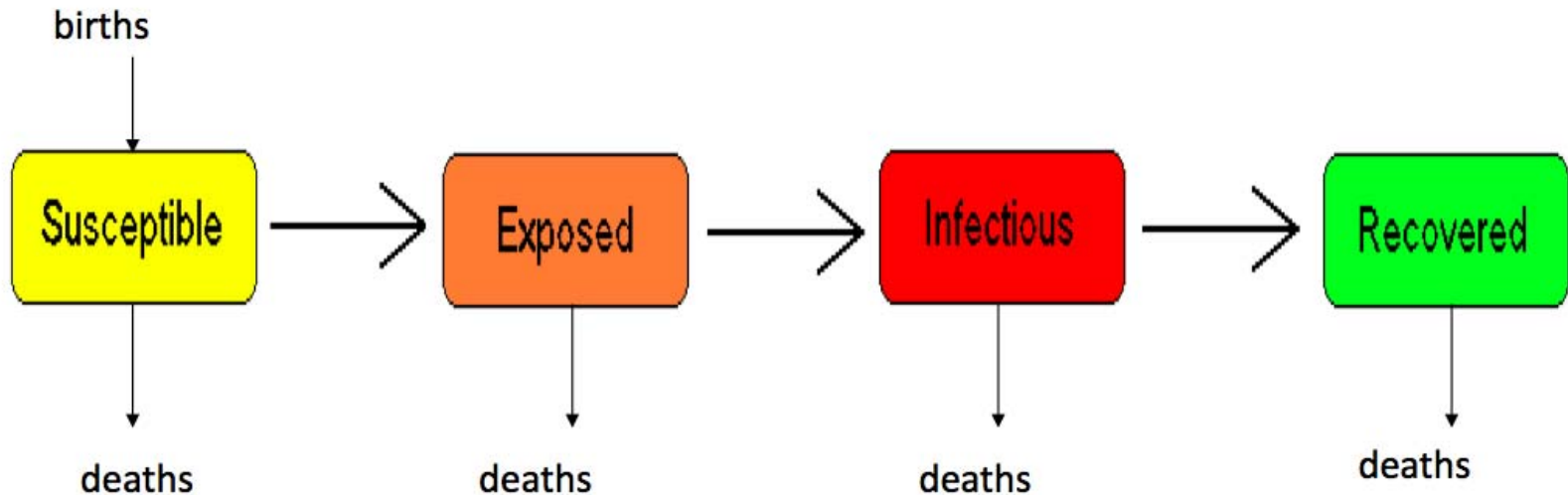
**Note:** The formula for  $R_0$  is the same formula as that of the SIR model.

Example of SEIR epidemic course

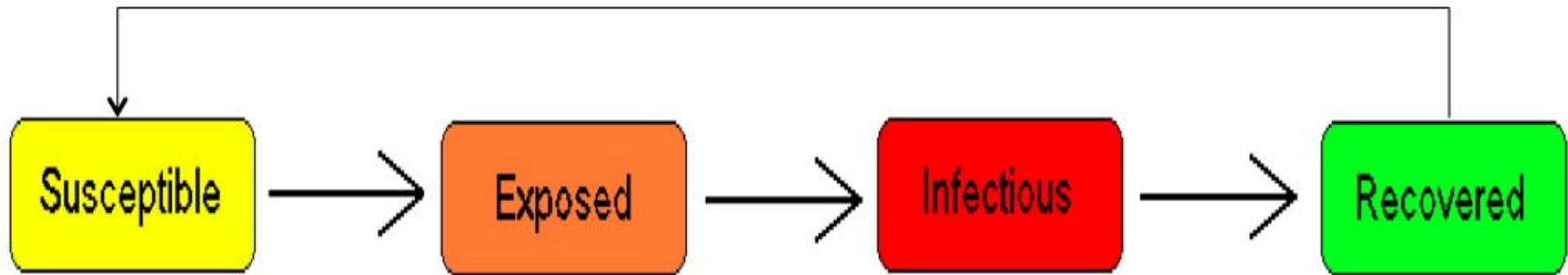


**Population size=1000**  
**Transmission rate=0.4**  
**Latent period=4 days**  
**Infectious period=4 days**  
**5 individuals initially infectious**

# Accounting for demographic processes (births and deaths)



# Modeling temporary immunity for SIR epidemics (SIRS)



**Can you mention a few diseases that would fall into this category?**

$$R_0 = (\text{transmission rate}) \times (\text{infectious period})$$

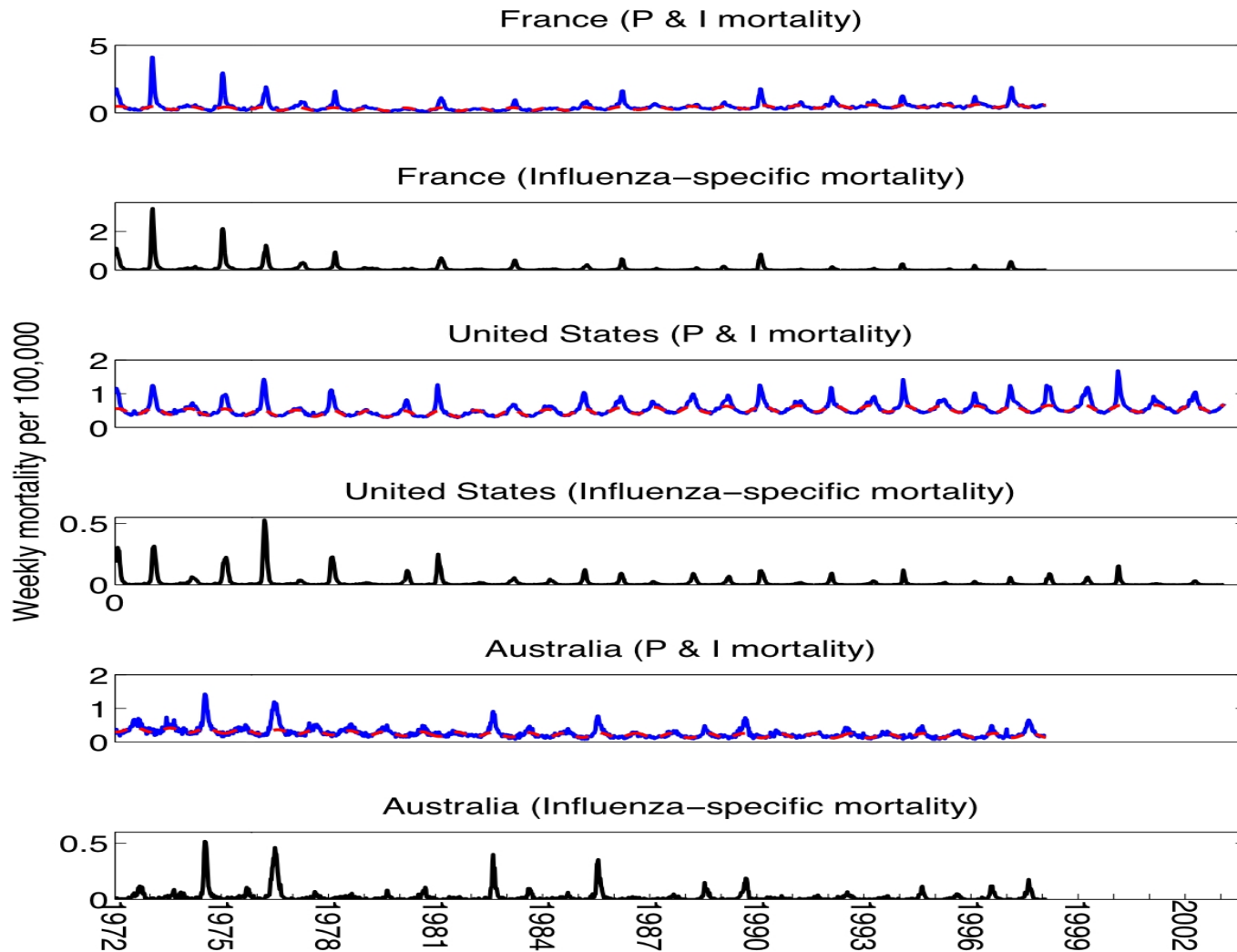


# Methods to estimate the reproduction number

- Contact tracing: observe sequences of index and secondary cases (SARS)
- Use the population-wide epidemic curve
  - To fit a transmission model (SIR and derivatives)
  - Estimate the initial growth rate during the exponential phase of the outbreak

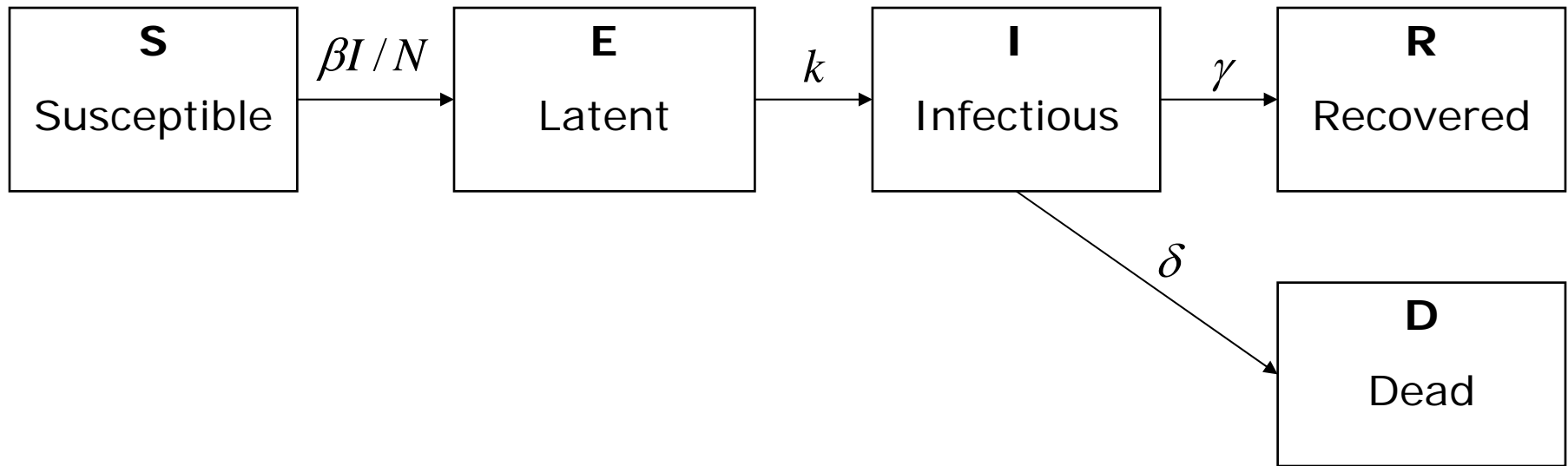
Fitting SIR models to epidemic  
curves to estimate R

# Mortality data for seasonal influenza



# Simple SEIR model

Kermack and Mackendrick, 1927

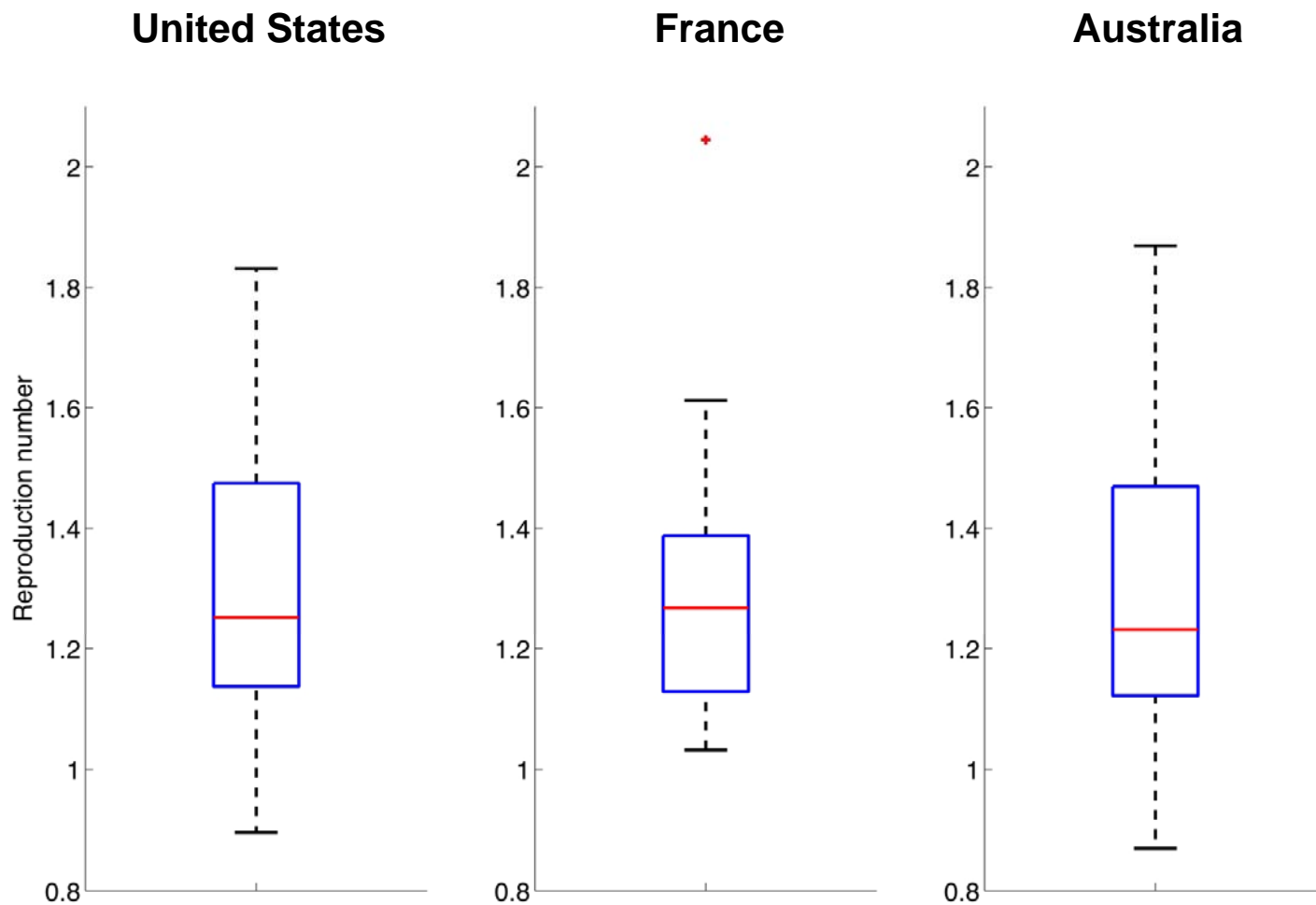


$\beta$  = Transmission rate;  $N$  = total population size;  $1/k$  = Latent period;  $1/\gamma$  = Recovery period;  $\delta$  = Mortality rate.

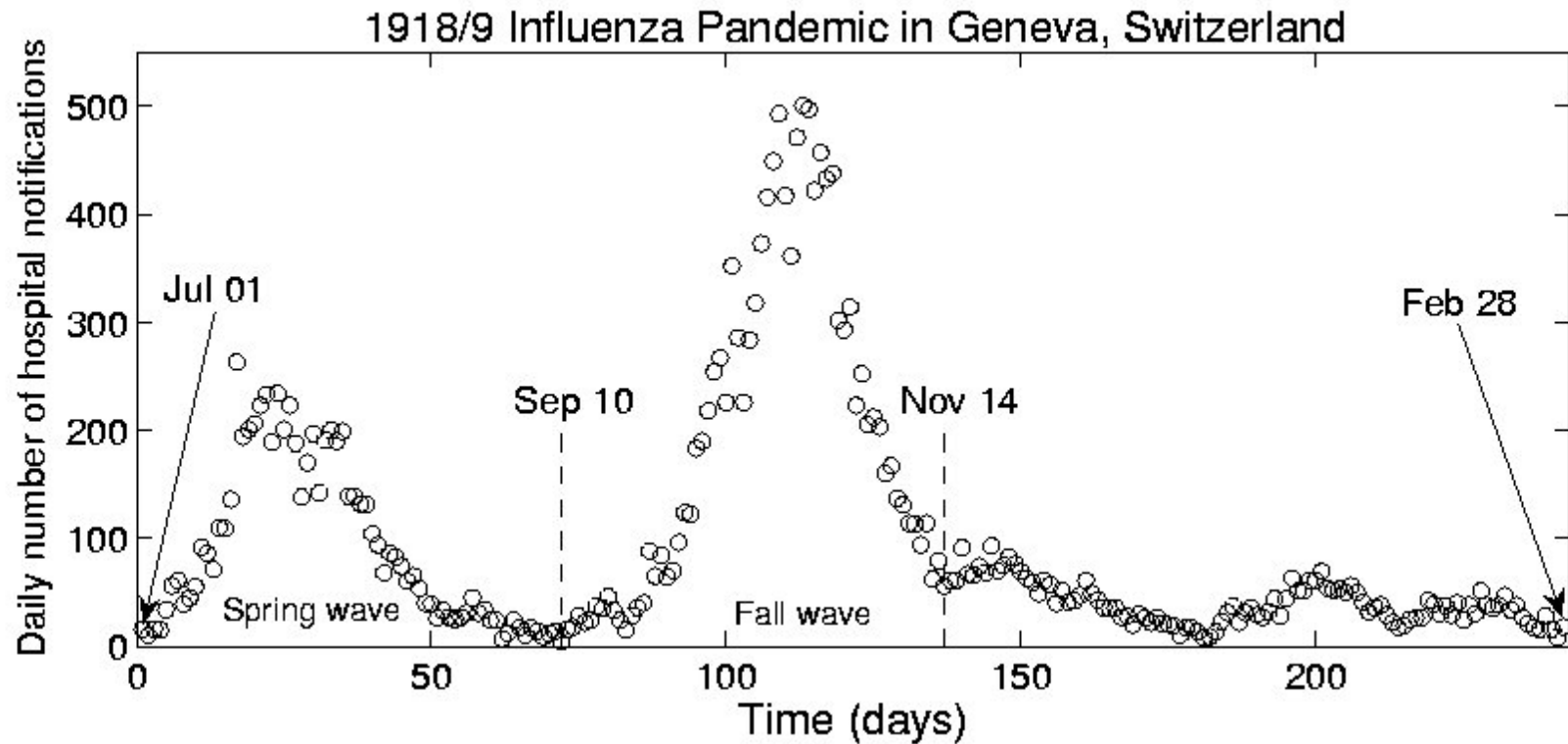
# Model parameters

Parameter	Definition	Source	Estimate	Range
1/k	Latent period	Mills et al., 2004	1.9 days	
1/γ	Recovery period	Mills et al., 2004	4.1 days	
CFP	Case fatality proportion	Weycker et al., 2005; Mills et al., 2004	0.20%	0.1% - 0.4%
δ	Mortality rate	$\gamma$ [CFP/(1-CFP)]	0.0005 per day	0.0002- 0.001
S(0)	Initial number of susceptible individuals	Census data	Entire population size	
β	Transmission rate	Estimated		
E(0)	Initial number of exposed cases	Estimated		
I(0)	Initial number of infectious cases	Estimated		

# Reproduction number, $R$ , derived from P & I mortality data

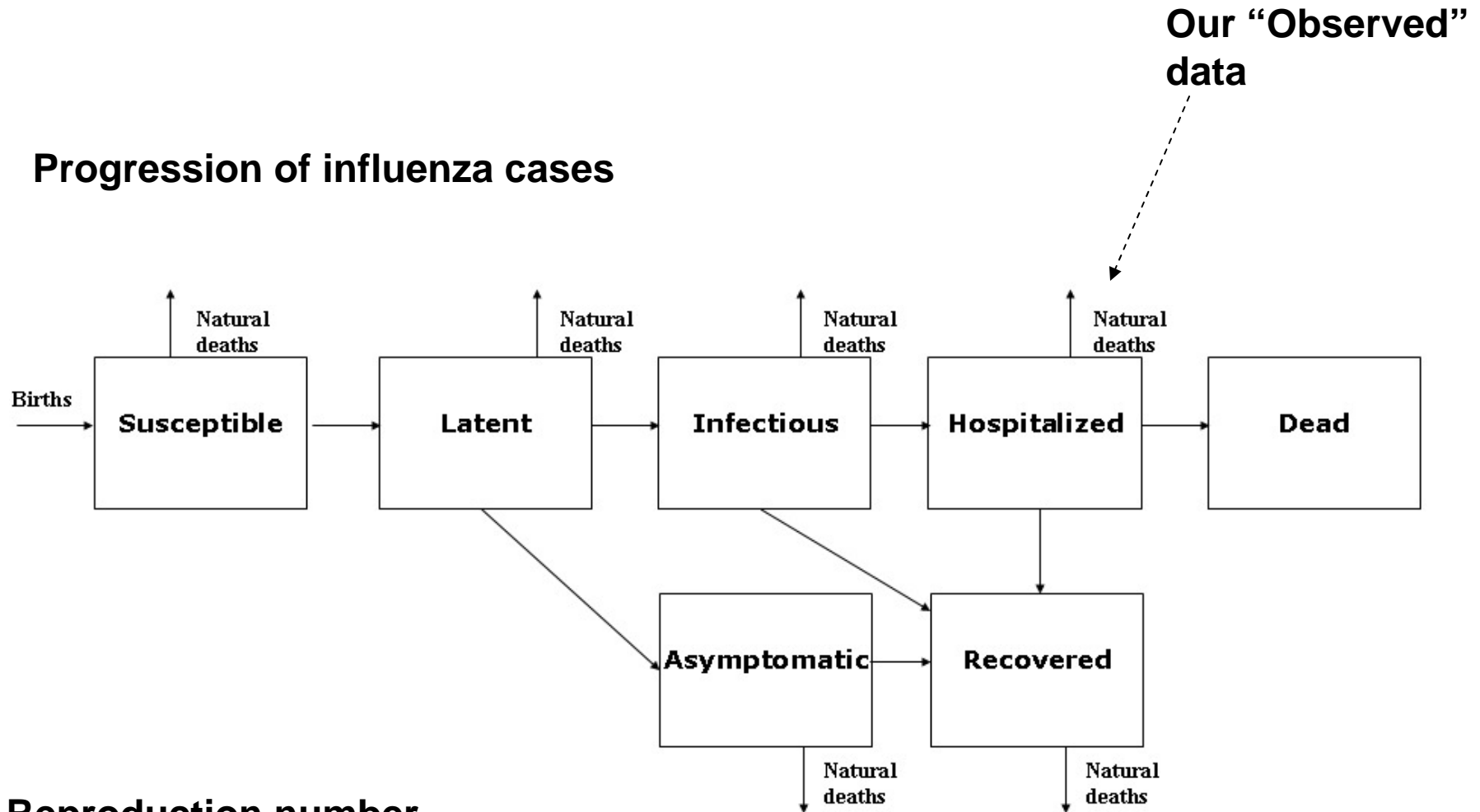


# The 1918-1919 influenza pandemic in Geneva, Switzerland



# Complex SEIR model for pandemic flu

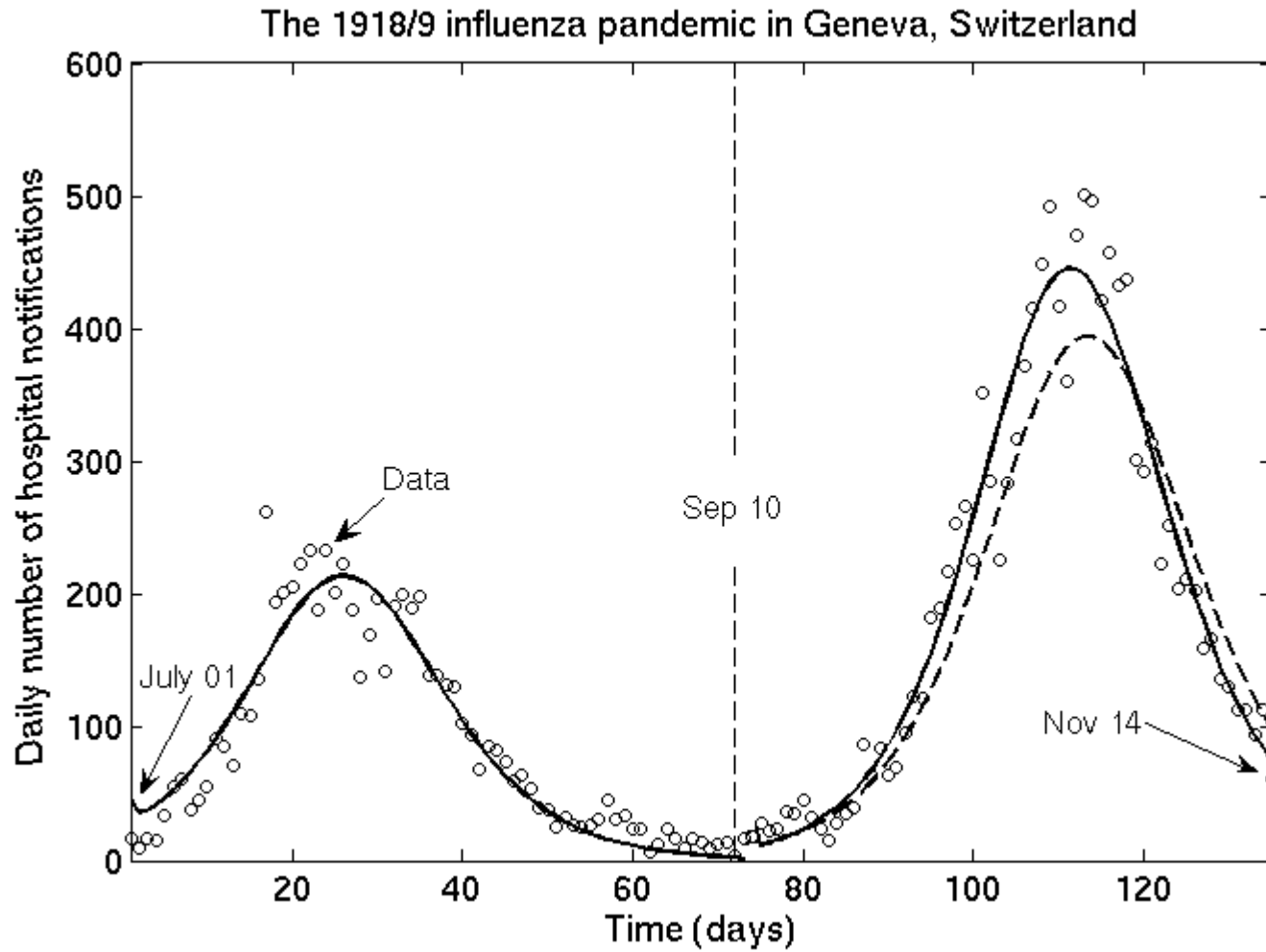
## Progression of influenza cases



## Reproduction number

$$R_i = R_i^{\text{infectious}} + R_i^{\text{hospitalized}} + R_i^{\text{asymptomatic}}$$

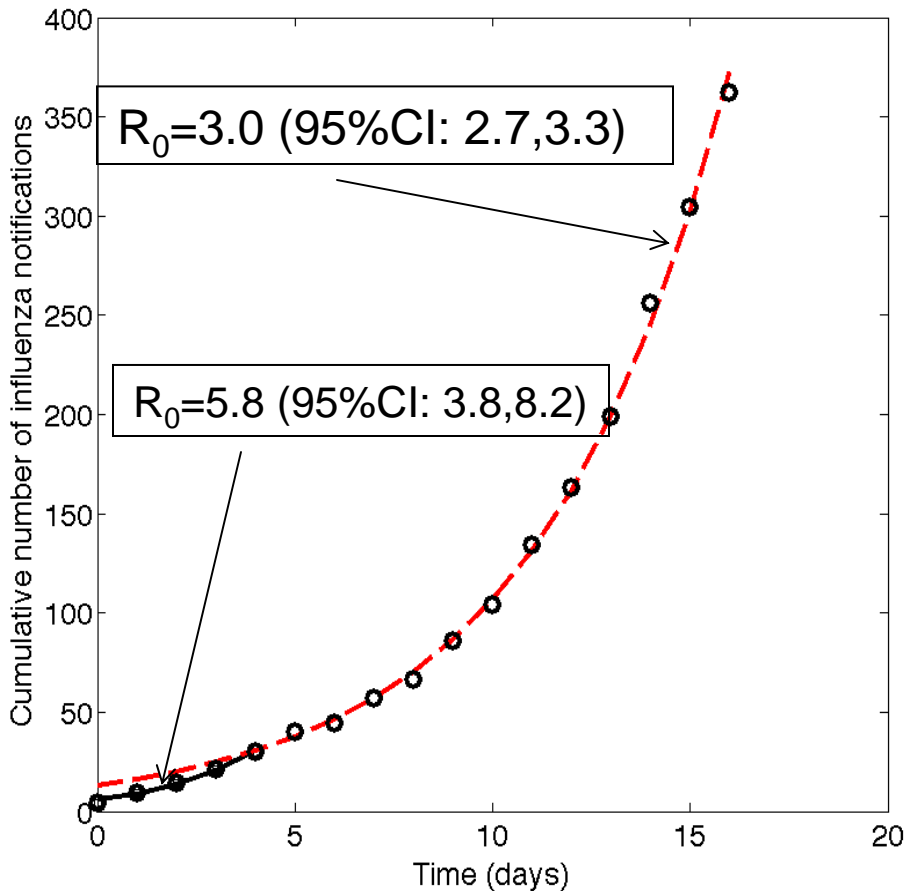
# Model fit



R estimation from the initial  
exponential growth rate

# How generation intervals shape the relationship between growth rates and reproductive numbers

J. Wallinga<sup>1,\*</sup> and M. Lipsitch<sup>2</sup>



SEIR model:

$$R = (1 + r/b_1)(1 + r/b_2),$$

$r$  = Intrinsic growth rate  
(estimated assuming an  
exponential growth phase)

$b_1$  = Mean latent period.

$b_2$  = Mean infectious period

## **How generation intervals shape the relationship between growth rates and reproductive numbers**

J. Wallinga<sup>1,\*</sup> and M. Lipsitch<sup>2</sup>

Upper bound on  $R_0$  based on fixed serial interval

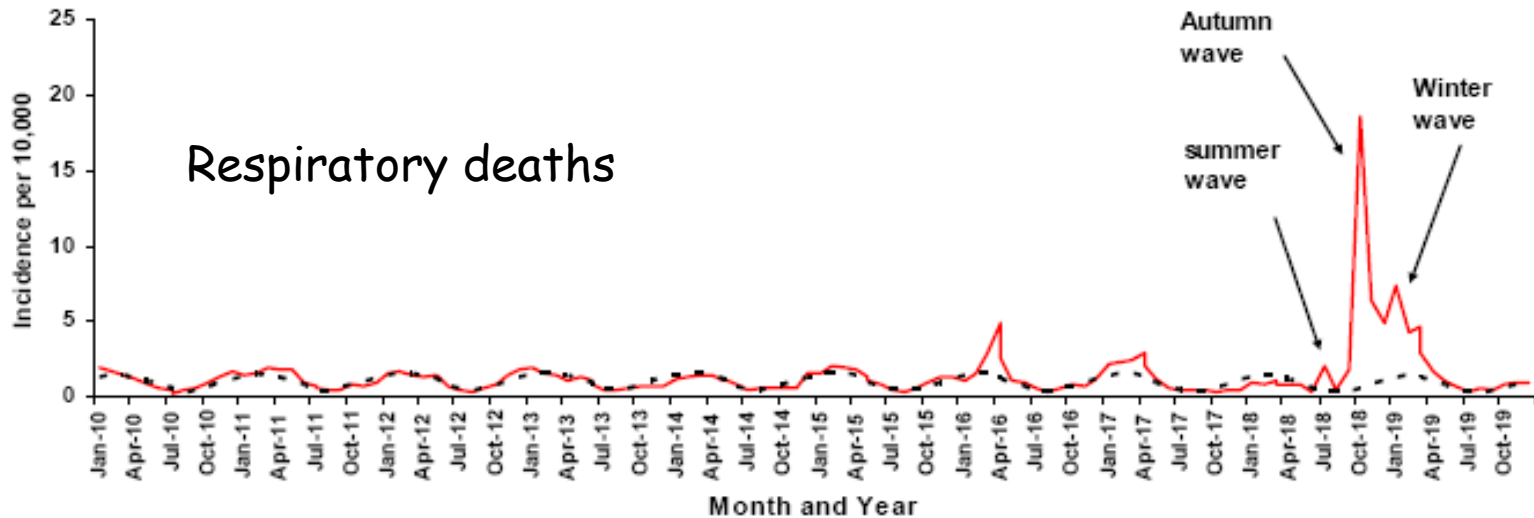
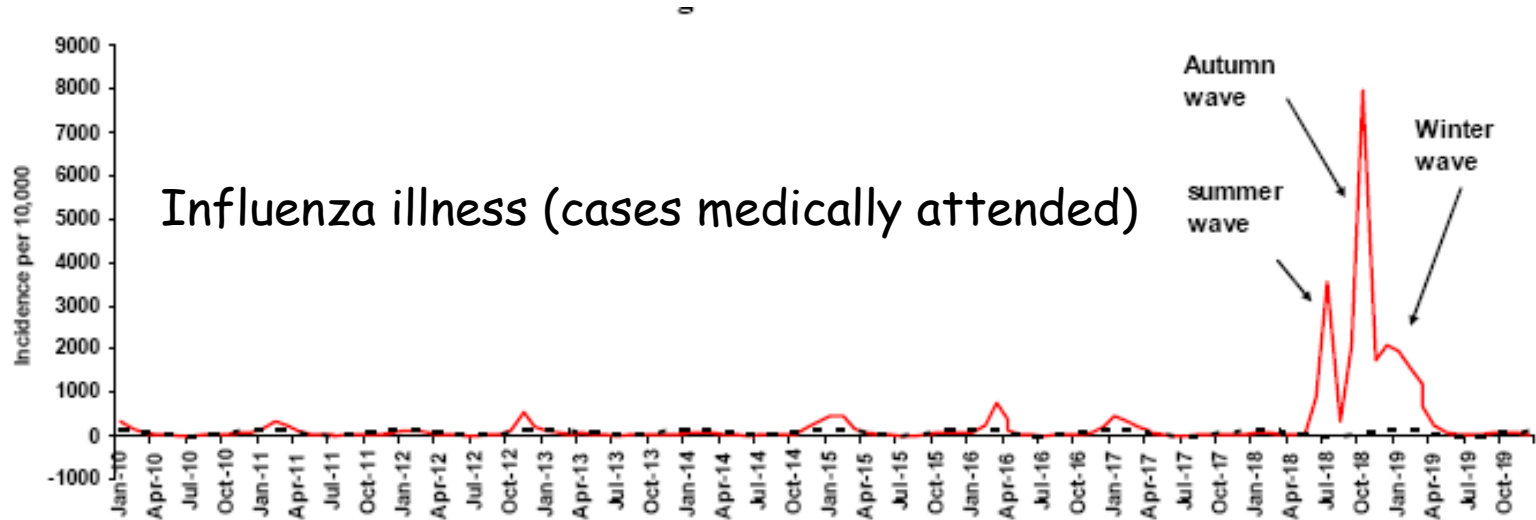
$$R = e^{rT}$$

$r$  = exponential growth rate (1/time)

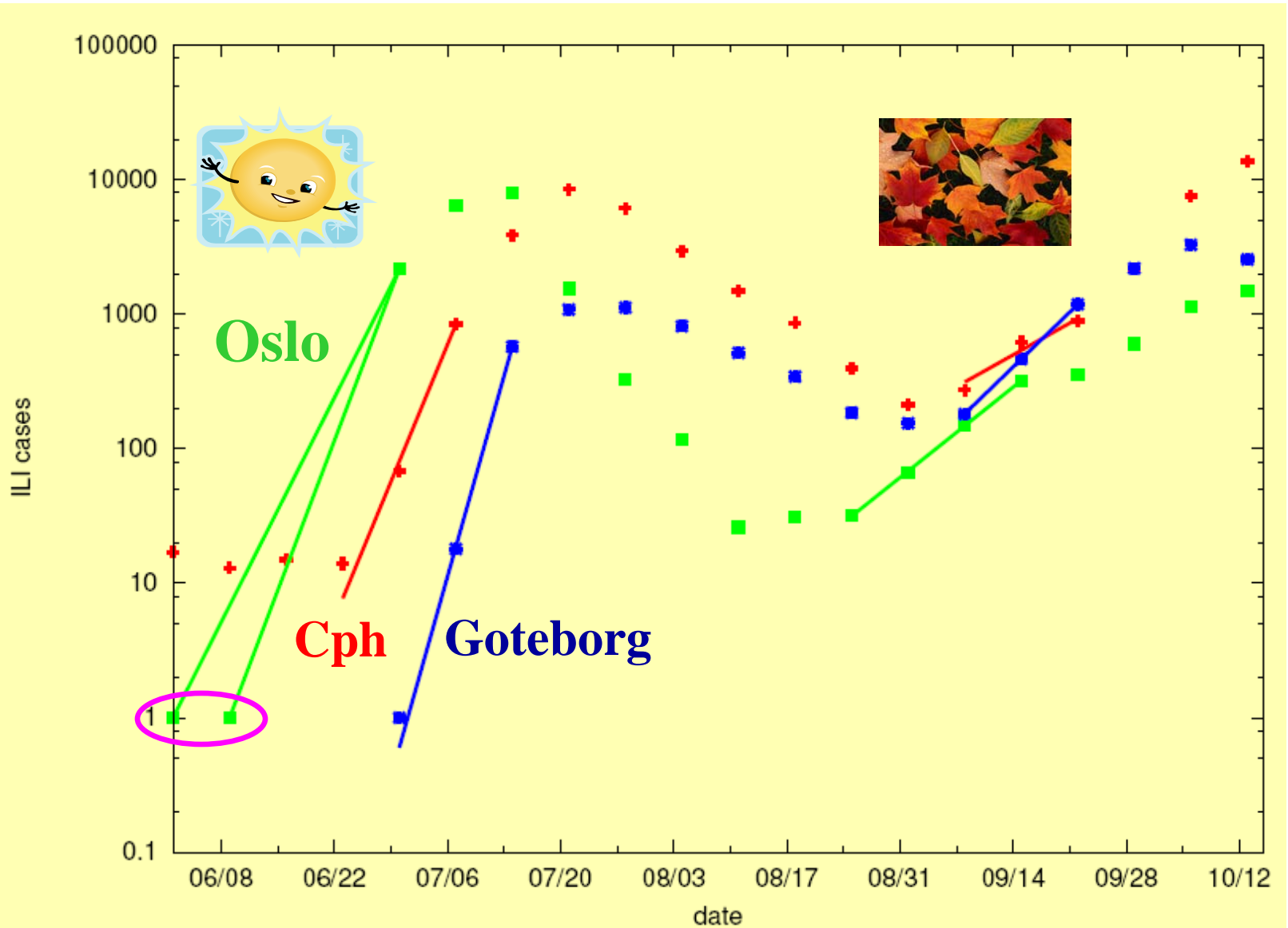
$T$  = serial interval = mean latent period + mean infectious period

*Wallinga et al, 2006; Chowell et al, 2007*

# Influenza surveillance in Copenhagen, 1910-1920

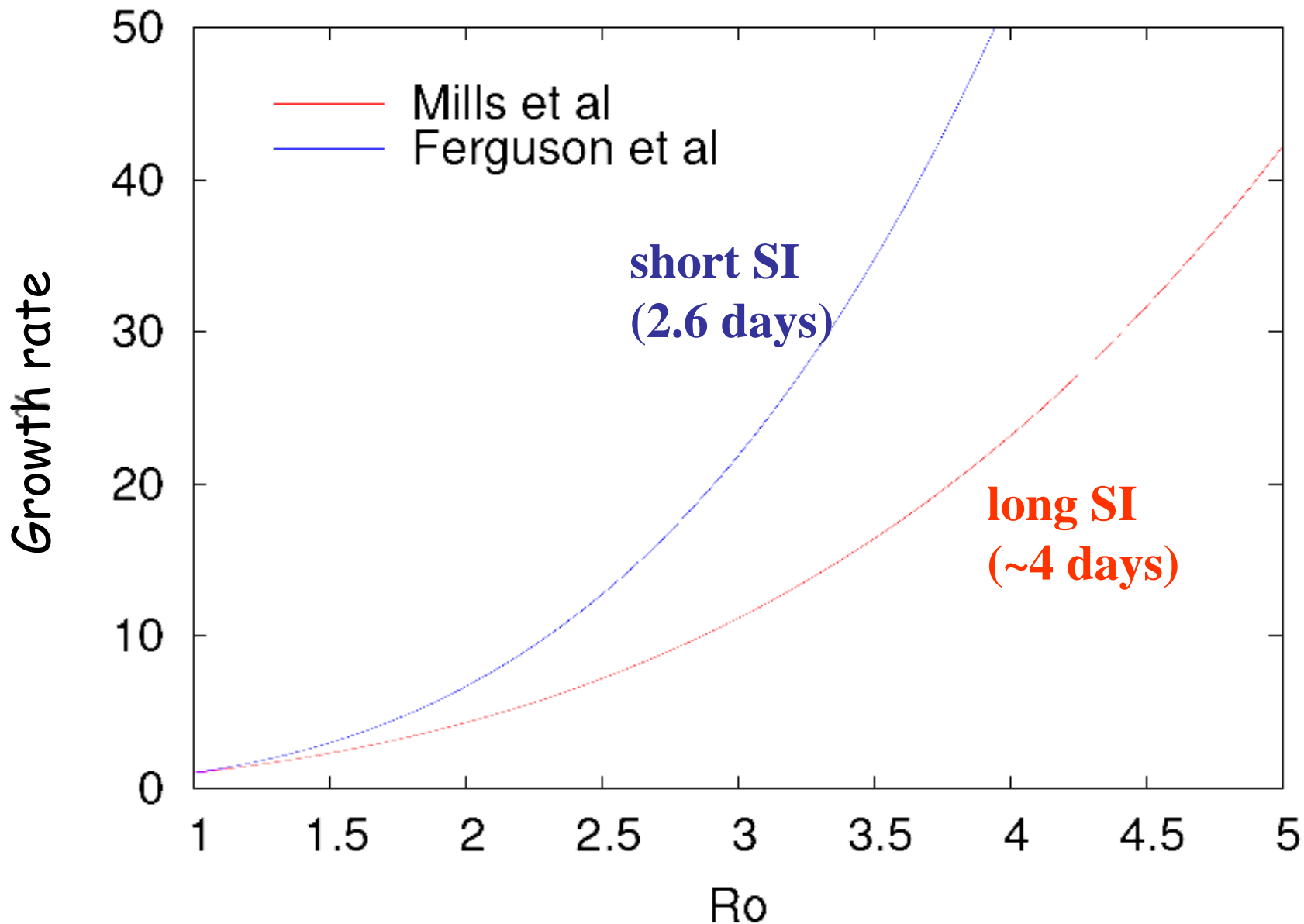


# Measuring pandemic growth rates in weekly influenza cases in 3 Scandinavian Cities

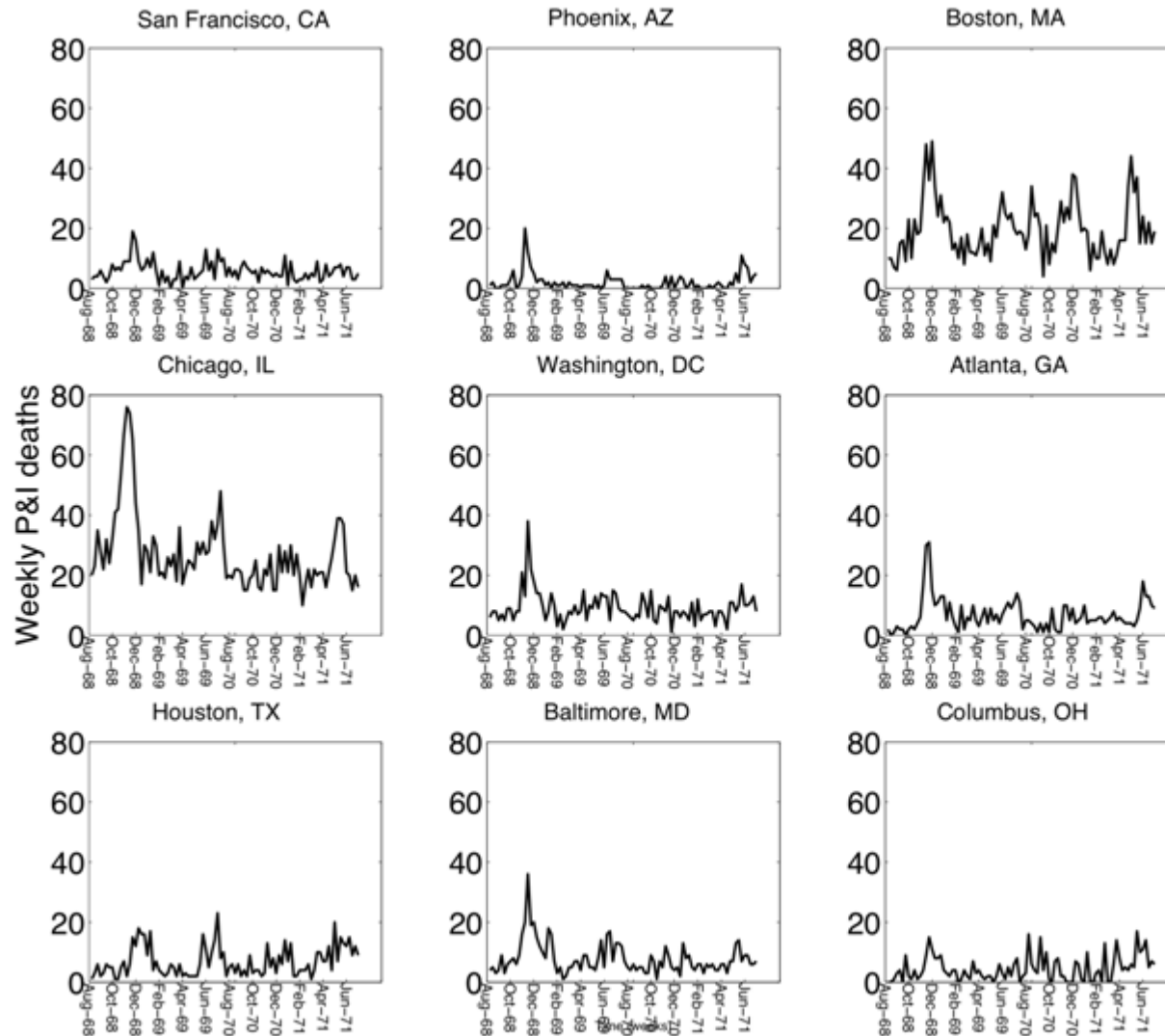


# Translating weekly growth rates into R estimates

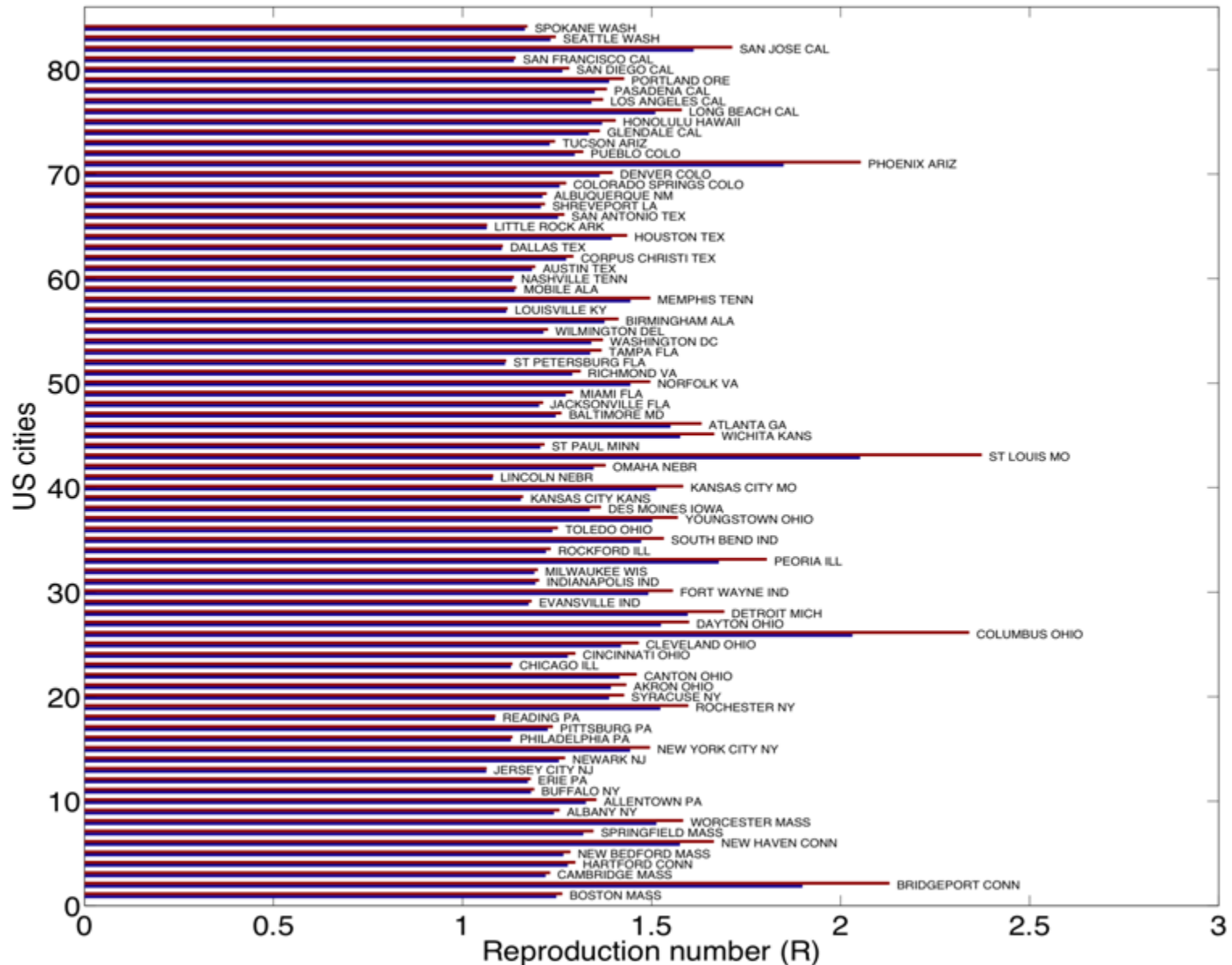
- depends on assumptions about serial interval (SI)



# Weekly P&I deaths for 9 representative US cities (1968 pandemic)



# Estimation of R from the initial growth rate



# Conclusions

- $R_0$  &  $R$  estimates depend on assumptions about
  - the serial interval
  - period of exponential growth
- Estimates useful to assess transmission potential and evaluate impact of control strategies
- Important to have good temporal resolution (daily, weekly)

# Hands on!

- Estimate  $R$  for the fall wave of the 1918 influenza pandemic in military and civilian populations of Kentucky, USA
- R code and time series data provided
- Method: initial growth rate

# Acknowledgements

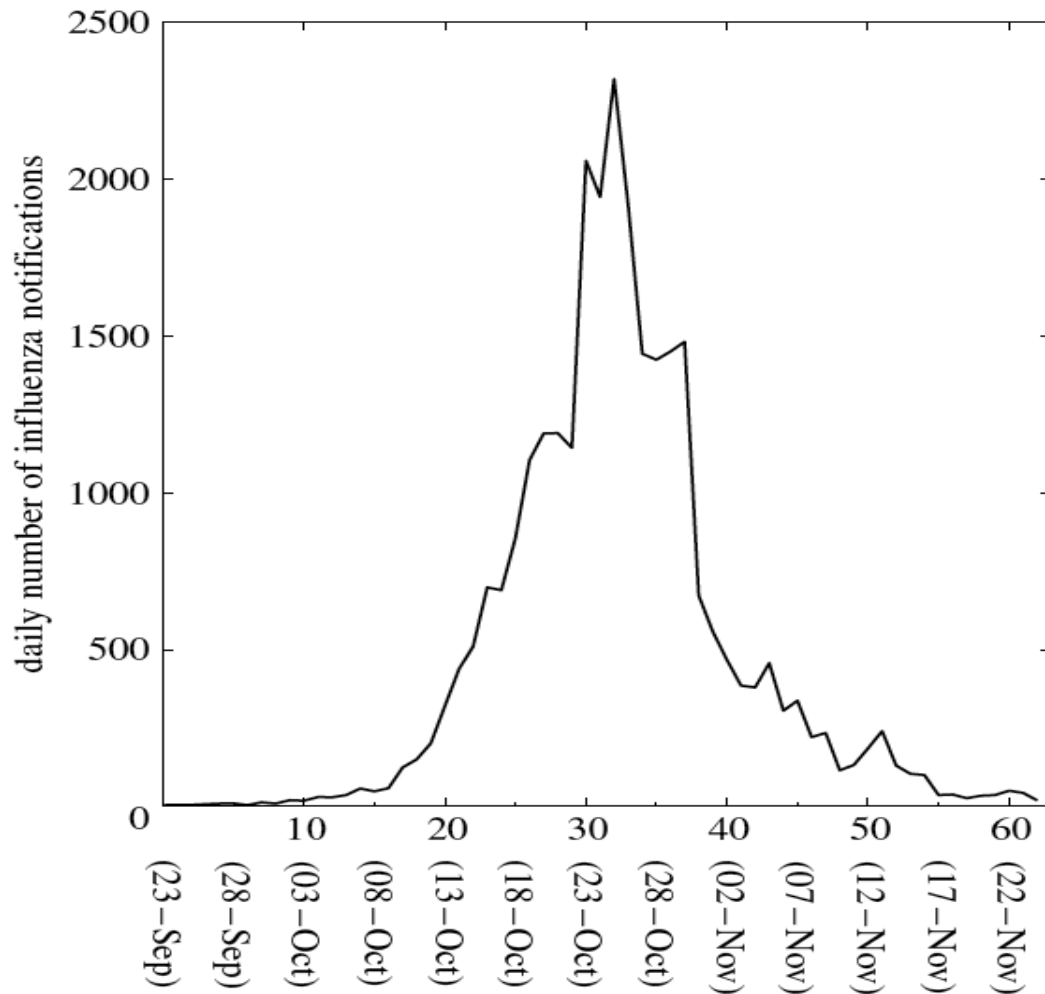
## Epidemiology and mortality studies

- Lone Simonsen (George Washington U., FIC)
- Mark Miller (FIC, NIH)
- Wladimir Alonso (FIC, NIH)
- Multinational Influenza Seasonal Mortality Study collaborators

## Modeling

- Gerardo Chowell (Arizona State & FIC)
- Viggo Andreasen (Roskilde U.)
- Bryan Grenfell (CIDDD, Princeton)
- Ottar Bjornstad (CIDDD, Penn State U.)
- Dave Smith (Hopkins, USA)
- Andreas Handel (Emory, USA)

# 1918 influenza pandemic in San Francisco, California

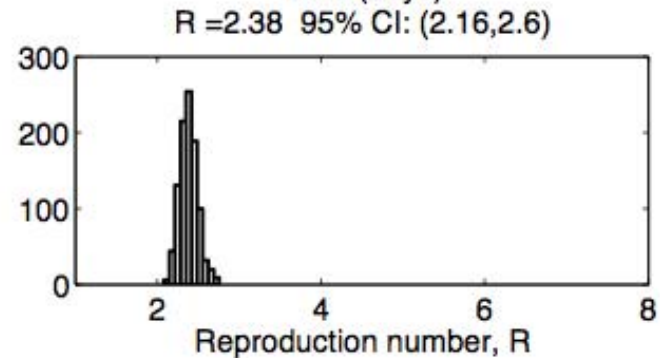
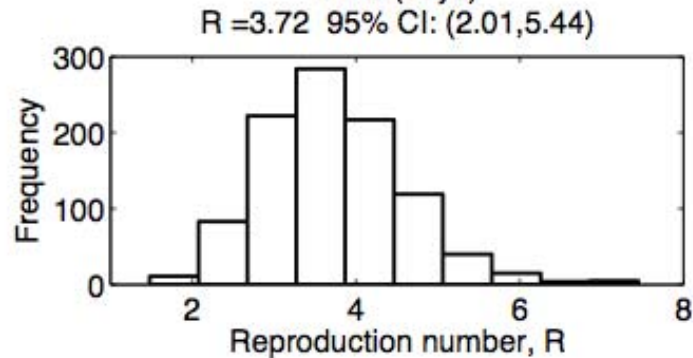
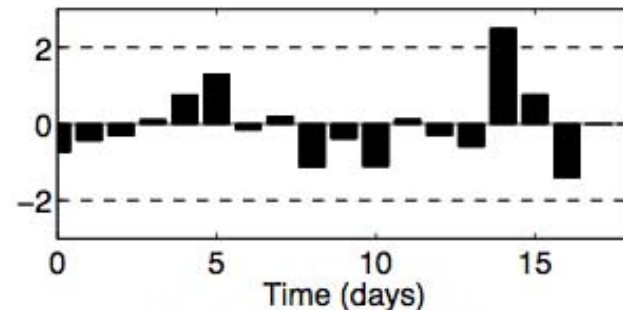
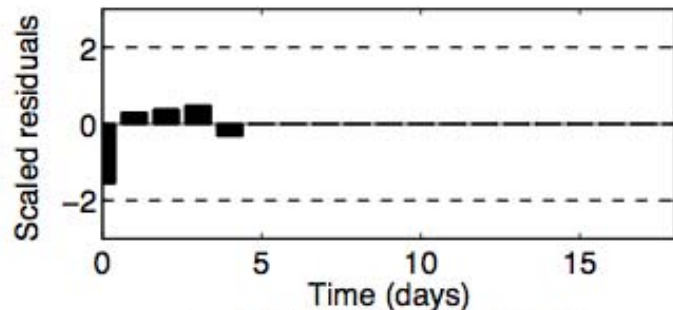
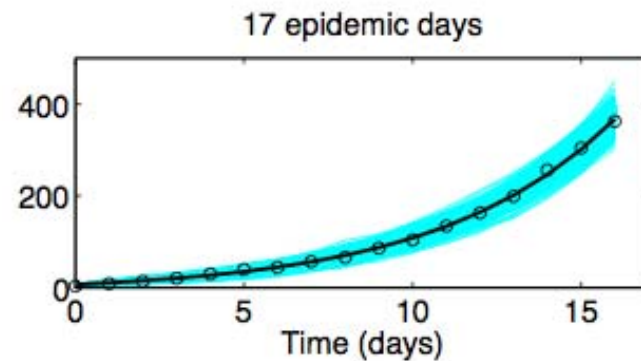
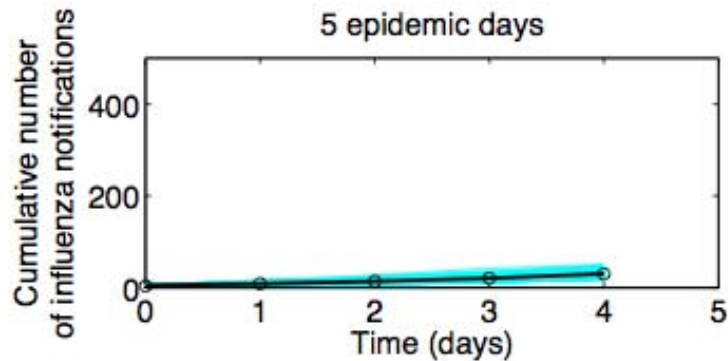


Estimation of R from:

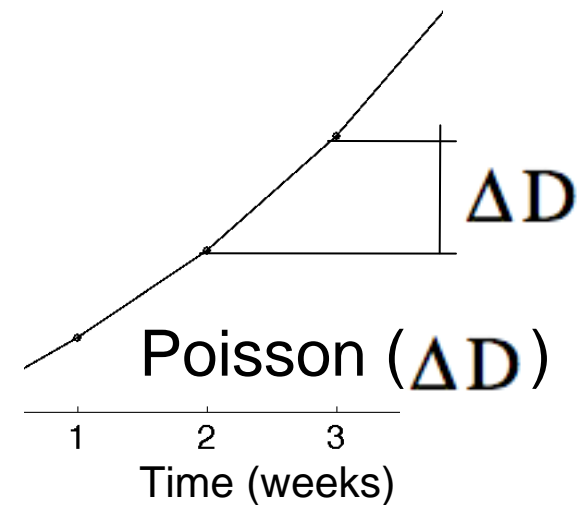
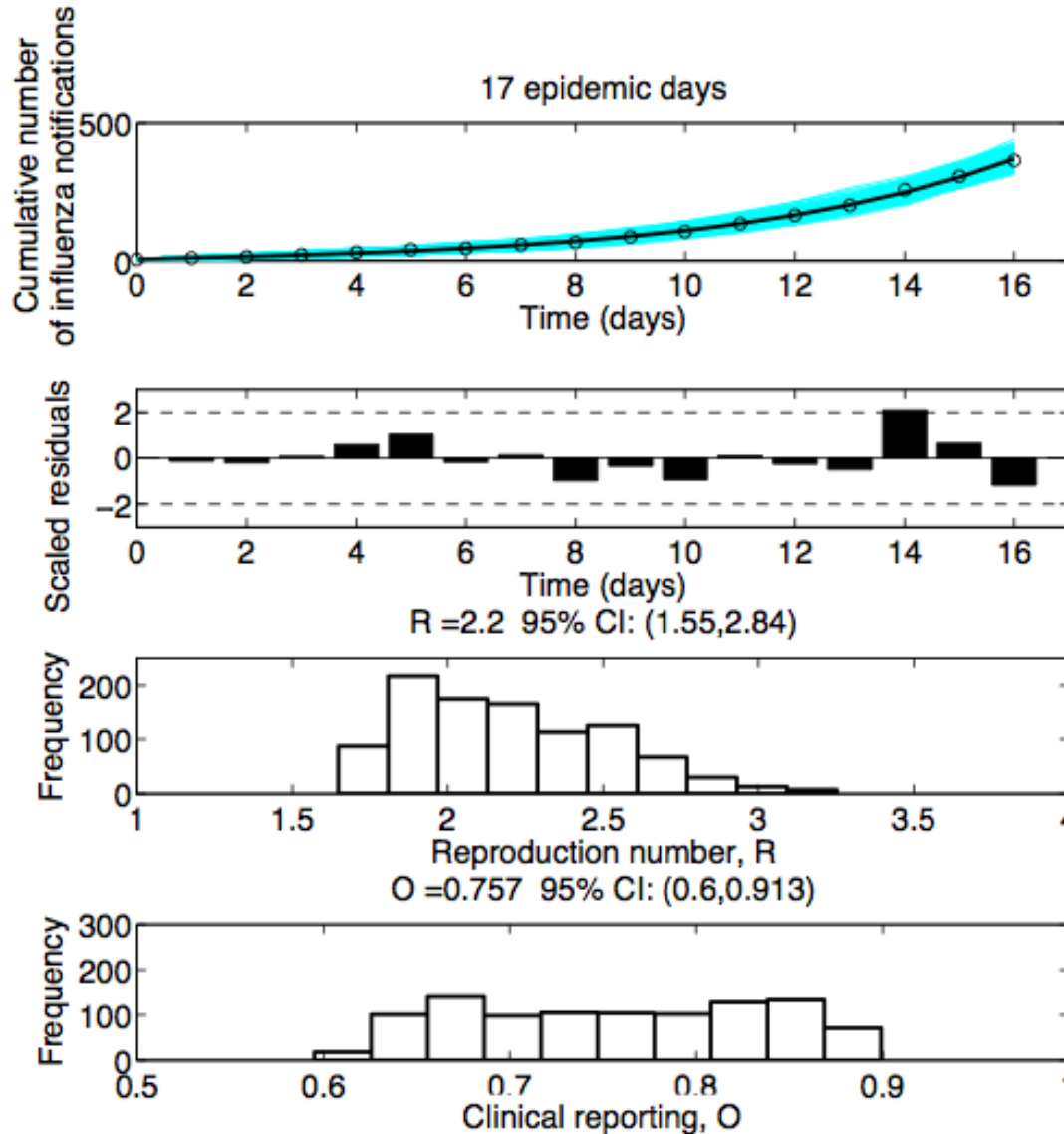
1. Initial growth rate
2. Simple SEIR model
3. Complex SEIR model

San Francisco  
population of about  
550,000 in 1918 (Crosby 2003)

# Simple SEIR – 1918 influenza pandemic in San Francisco



# Complex SEIR – 1918 influenza pandemic in San Francisco



# Goodness of fit

