Today's Learning Objectives

- Show how outbreaks can be analyzed to estimate the dynamic properties of diseases using two real world examples.
  - Swine Flu at Fort Dix, 1976
  - Influenza in a Thai Remand Facility, 2006
- Understand how mass action models can be used to represent disease dynamics.
- Understand when the assumptions of mass action models apply, and introduce methods for testing assumptions.
- Learn the basics of estimating R_0 and the serial interval from outbreak data.

Outline

Contents

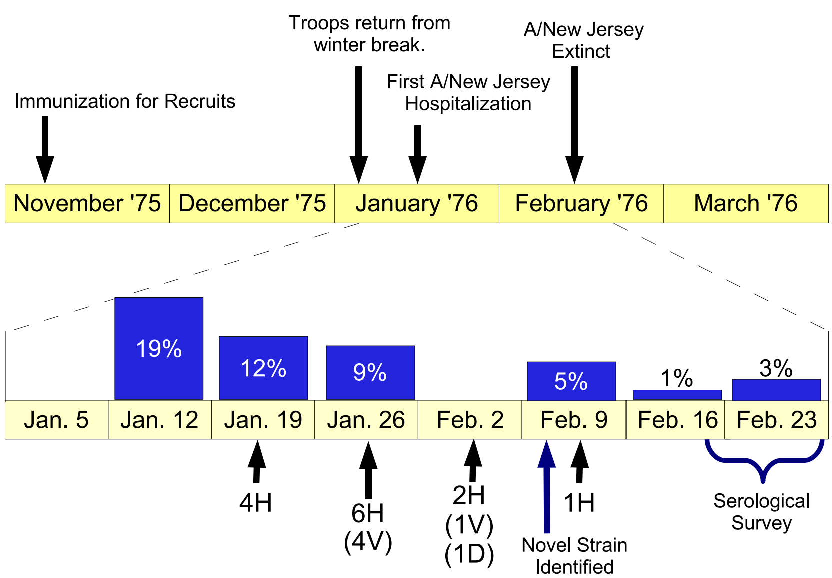
1 Two Institutional Epidemics

1.1 Swine Flu at Fort Dix, 1976

Fort Dix Training Facility

- Fort Dix Served as a training facility for new recruits and advanced infantry training in for the U.S. army in 1976.
- The base was largely deserted over winter break.
- Troops returned and new recruits began arriving at the base on January 5th.

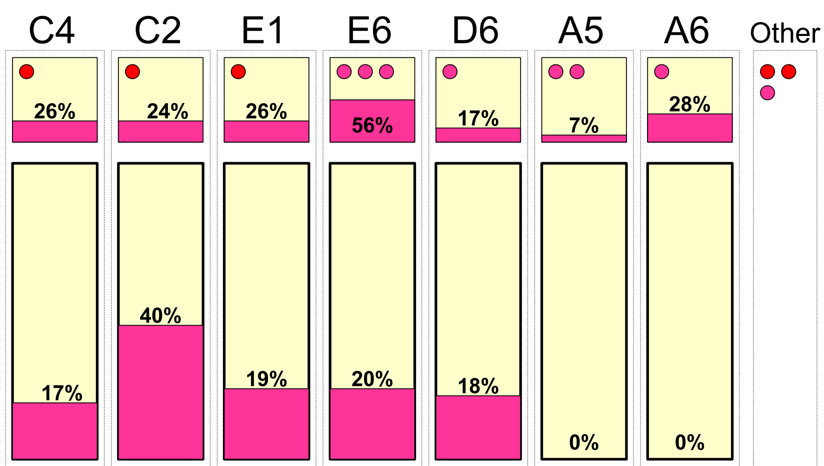
Time Line



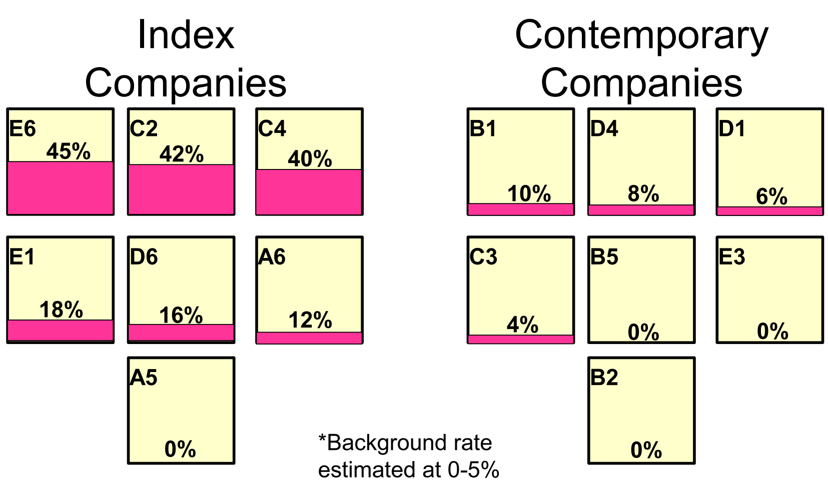
- Immunization for new recruits in October and November.
- First hospitalization on January 19th...on set apparently on the 12th, but likely late.

- By late February transmission has ended...A/New Jersey extinct!?!
- Blue bars show %sero-positive by week of training start.
- 13 hospitalized cases, 5 with virology and one who died.
- Serological survey between February 17 and 26

A/New Jersey Incidence in Platoons



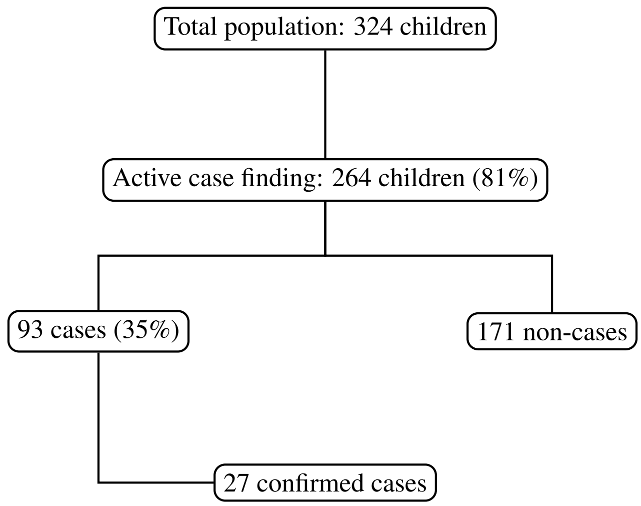
A/New Jersey Incidence in Companies



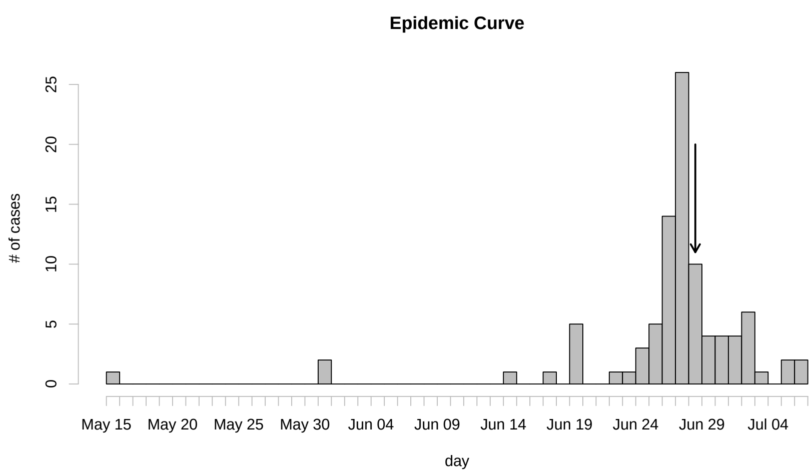
- Based on these incidence rates the original authors estimate a 230 total cases.

1.2 H1N1 in Remand Home, Bangkok 2006

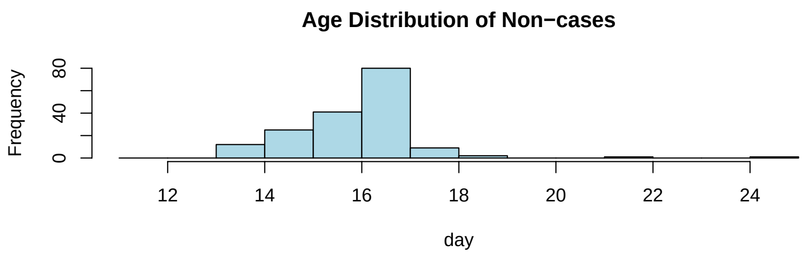
Study Population

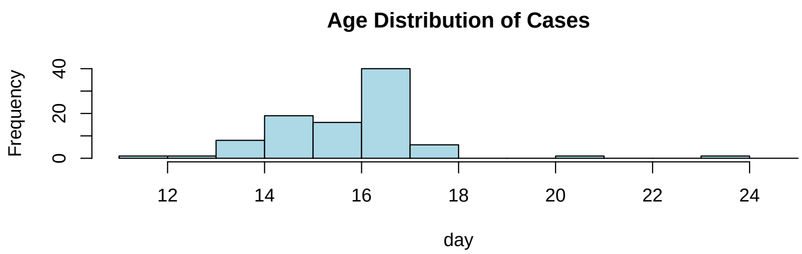


Epidemic Curve

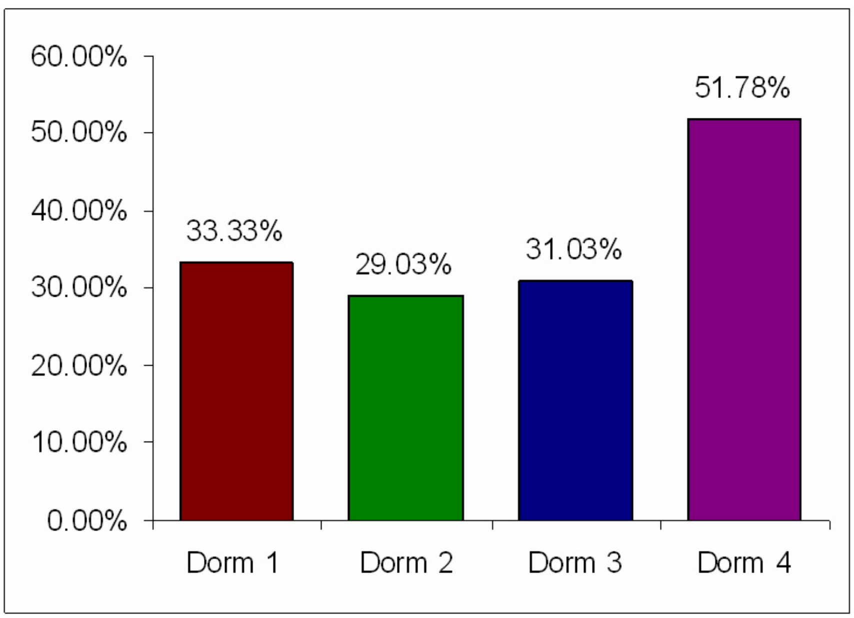


Age Distribution of Cases

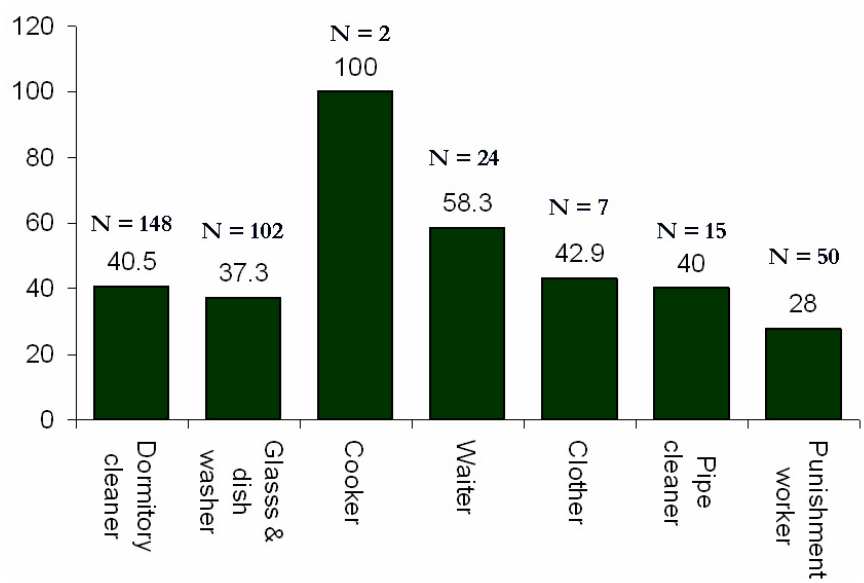




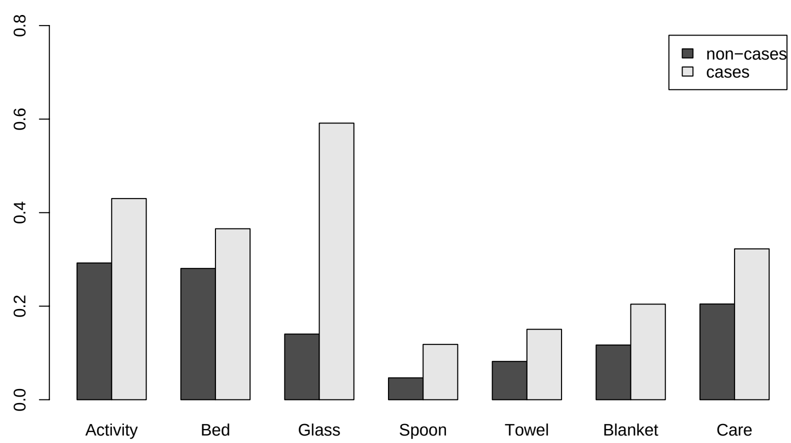
Dormitory Specific Attack Rates



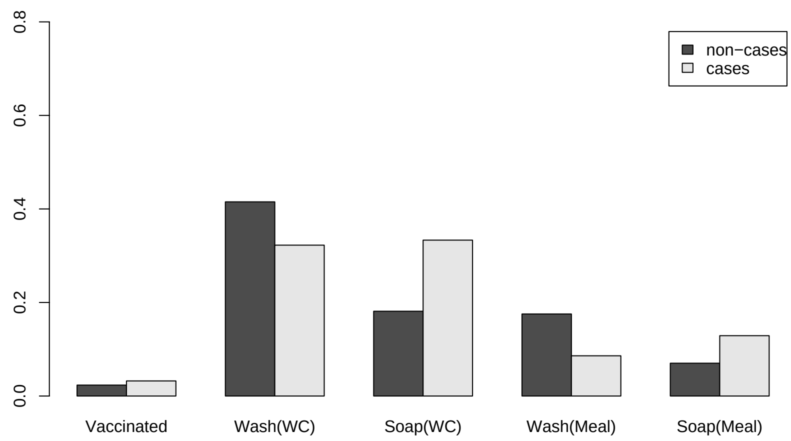
Job Specific Attack Rates



Case Exposure Frequencies in Cases and Non-cases



Health Behaviors is Cases and Non-cases



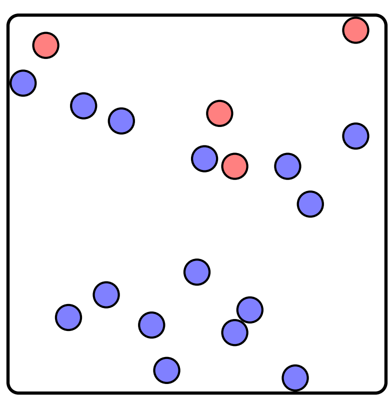
2 Mass Action: Comparmental Models

Two Essential Questions

- How does the disease spread through the population?

- How will our actions or interventions influence this spread?

Mass Action Random mixing as a simple model fo disease spread



Mass action is a description used for a model of disease spread where we assume that individuals contact eachother randomly and with equal probability in a population. This is similar to the way gases interact in a bottle, all the particals (people) move around randomly in the bottle, randomly touching eachother. The speed of a chemical interaction (the dynamics of the epidemic) are dictated by how often paricals of different types bump up against one another.

The Kermack-McKendrick SIR Model

$$\boxed{\mathrm{S}} \xrightarrow{\lambda I} \boxed{\mathrm{I}} \xrightarrow{\gamma} \boxed{\mathrm{R}}$$

As a system of ordinary differential equations:

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

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

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

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

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

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

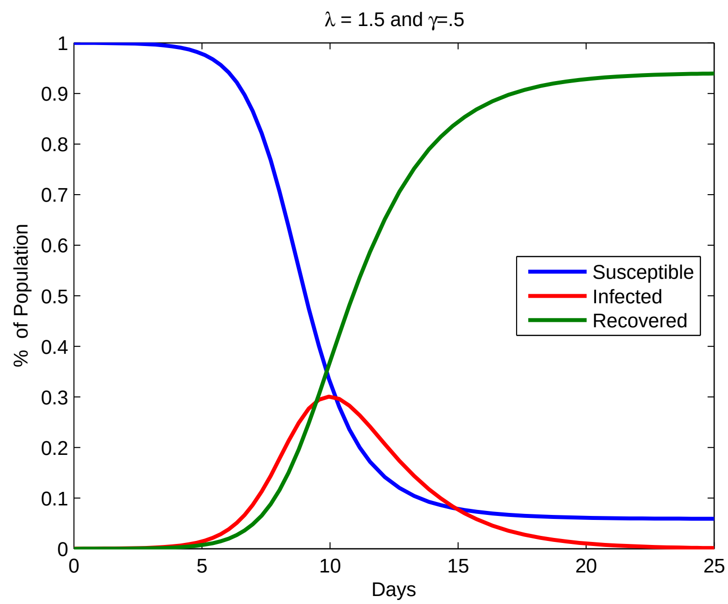
$$\frac{ds}{dt} = -\lambda si$$

$$\frac{di}{dt} = \lambda si - \gamma i$$

$$\frac{dr}{dt} = \gamma i$$

Compartamental models treat people as moving between different compartments corresponding to different states in the natural history of a disease. In the simplest version, the SIR model, individuals are either (S)usceptible to infection, (I)nfected, or (R)emoved from the system due to death or immunity. A system of equations can be created to represent how people move between these compartments.

A Simple Epidemic



By looking at the nuber of individuals in each of these compartments we can track the state of an epidemic.

An Alphabet Soup of Models

SIR:

$$\boxed{S} \longrightarrow \boxed{I} \longrightarrow \boxed{R}$$

SEIR:

$$\boxed{S} \longrightarrow \boxed{E} \longrightarrow \boxed{I} \longrightarrow \boxed{R}$$

SIS:

$$\begin{tikzcd} \boxed{S} \arrow[r] & \boxed{I} \arrow[l, bend right] \end{tikzcd}$$

MSIR:

$$\boxed{M} \longrightarrow \boxed{S} \longrightarrow \boxed{I} \longrightarrow \boxed{R}$$

This is just a sampling of the types of models that are often used. Most often the model has special categories and transitions tailored to the type of problem being addressed. Can you think of other types?

R_0: The Basic Reproductive Number

$$\boxed{\text{S}} \xrightarrow{\lambda I} \boxed{\text{I}} \xrightarrow{\gamma} \boxed{\text{R}}$$

R_0 Combines Force of Infection and Recovery Rate

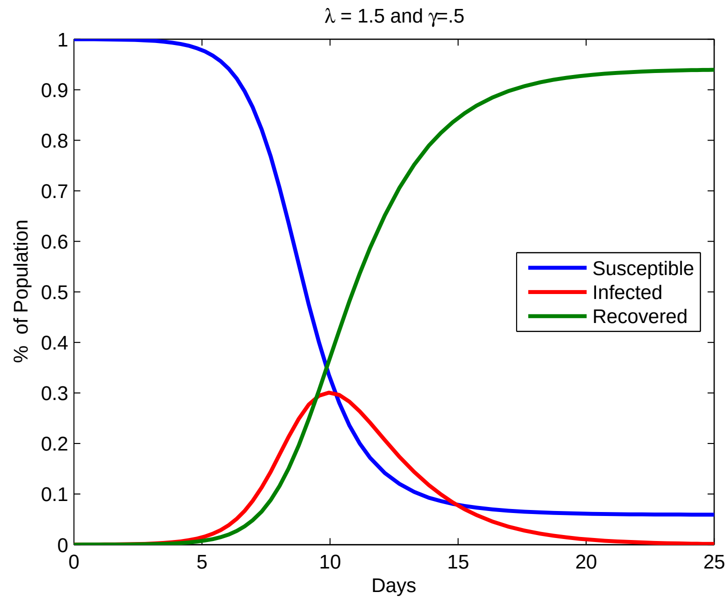
$$R_0 = \frac{\lambda}{\gamma}$$

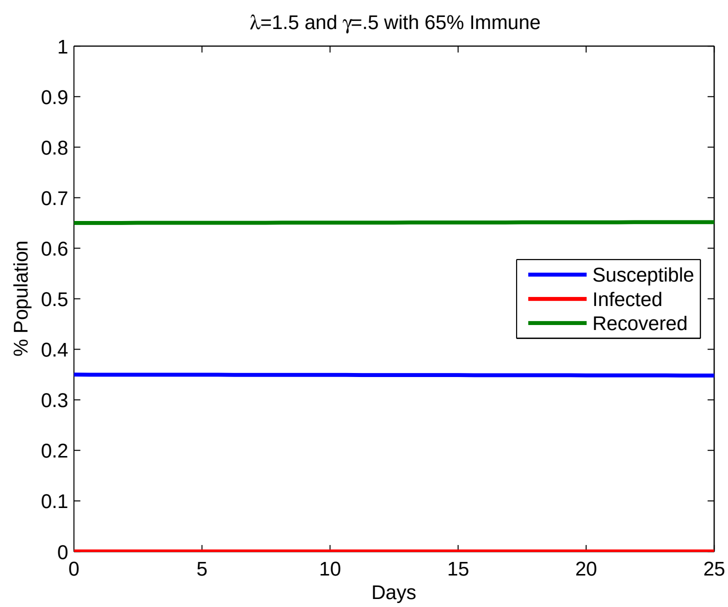
R_0 is offers a summary measure of these two parameters. Using this relationship we can derive some useful results that relate the dynamics mass action epidemics to R_0. These may provide insights into infection control, or derive important parameters of disease transmission from looking at the final population state after an epidemic.

Some Results

- Total number infected.
$$R_0 = -\frac{\ln(1 - i_{tot})}{i_{tot}}$$
- Threshold for "Herd Immunity"
$$V = 1 - \frac{1}{R_0}$$

A Simple Epidemic

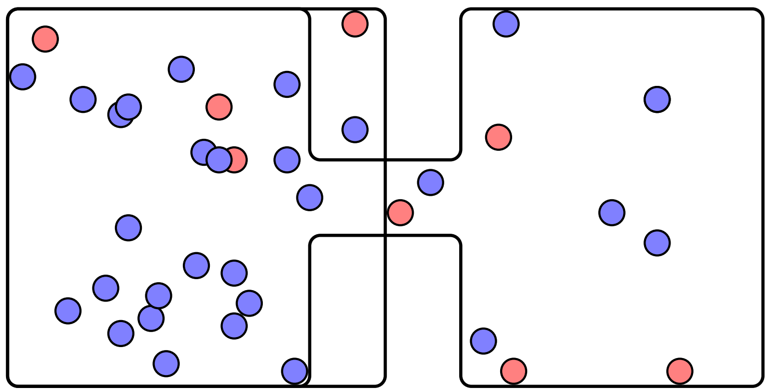




3 Checking for Group Differences

Mass Action Where? At what level is even mixing occurring?

Is mixing happening like this ...or like this?



If we are going to use mass action models and their dervied results we must be looking at units where the assumption (or approximation) of even mixing holds. Sometimes the approximation holds because we are looking at such big populations that local or regional differences are not important, alternately we can be looking at smaller units where the even mixing assumptions holds more directly, such as a dorm, an army platoon, or a elementary school class.

Mass Action Where? At what level is even mixing occurring?
How can we tell what level of mixing we are observing?

- Compare epidemic curves
- Compare attack rates
- Knowledge about the physical and social structure of the populations

By looking at the results of an epidemic we can get some idea of at what level even mixing is occurring. Similar epidemic curves and attack rates suggest a population where there is a single epidemic, differnces suggest linked epidemics.

The Likelihood A tool for comparing hypotheses

- Probabilities are to the chances of seeing an *event* given a *generating process*.

  For example: the chances of seeing four heads given a fair coin.

- Likelihoods represent how much a particular generating *process* is supported by the observed *events*/

  For example: how much more likely is it that the coin being flipped is not fair given that we just saw four flips come up heads.

- Both probabilities and likelihoods have the same formula, but a different "unknown"

$$L(\theta; x_1, x_2, ...) = \Pr(x_1, x_2, ...|\theta) = \Pr(x_1|\theta) \cdot \Pr(x_2|\theta) \cdot \Pr(x_3|\theta) \cdots$$

The Likelihood A tool for comparing hypotheses

Exercise: is Derek drawing from a cup of all green M&Ms or a cup of half green and half yellow M&Ms?

How confident are we about the nature of the cup of M&Ms after each draw?

The Likelihood A tool for comparing hypotheses

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Mass Action Where? At what level is even mixing occurring?

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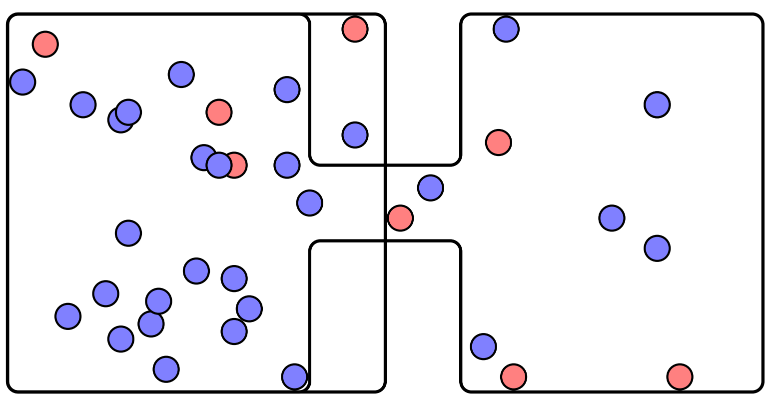


Fort Dix Was there mixing between platoons?

	C4	C2	E1	E6	D6	A5	A6	Total
cases	11	11	12	22	8	2	2	68
non-cases	31	35	34	17	38	26	5	186
$\Pr(case)$	0.26	0.24	0.26	0.56	0.17	0.07	0.28	0.27

- Chances of seeing this distribution of cases with a common chance of infection: $L(\theta_0) = 1.9x10^{-11}$

- Chances of seeing this distribution of cases with independent chances of infection: $L(\theta_1) = 4.4x10^{-6}$
- This does not show very strong evidence for independent epidemics:

$$LR = \frac{\theta_1}{\theta_0} = 231,453.7$$

Here we have relatively strong evidence in favor of different infection rates. In addition, we know that soldiers do not mix much between platoons during basic training. For these reasons we feel that each platoon is having an independent epidemic.

Thai Remand Facility Did ages mix together?

	≤ 14	14-19	≥ 20	total
non-cases	12	157	2	171
cases	10	81	2	93
$\Pr(case)$	0.45	0.34	0.5	0.35

- Chances of seeing this distribution of cases with a common chance of infection: $L(\theta_0) = 0.0016$
- Chances of seeing this distribution of cases with independent chances of infection: $L(\theta_1) = 0.0035$
- This does not show very strong evidence for independent epidemics:

$$LR = \frac{\theta_1}{\theta_0} = 2.1$$

Here the evidence of differences between ages is very weak. Recall what two meant in the example with the green M&Ms

Also, we know that different age groups share dorms and jobs, even if they are in separate classes. Therefore we are willing to treat this as a single epidemic occurring throughout the facility.

Mass Action Where? At what level is even mixing occurring?

- At Fort Dix mass action appears to be occurring in platoons, they should be analyzed independently.
- At the Thai Remand Facility mass action appears to be occurring throughout the facility, it should be analyzed as a single unit.

4 Finding R_0

4.1 Fort Dix, 1976

R_0 for Swine Flu at Fort Dix What do we know?

- Attack rates for individual platoons.
- An upper bound on the maximum length of the epidemic.
- There were no control measures put in place to contain this epidemic.
- Everyone involved was susceptible to infection.

R_0 for Swine Flu at Fort Dix Method 1: Final Epidemic Size

We can use the formula presented earlier and the final sizes of the platoon specific outbreaks to estimate R_0.

$$R_0 = -\frac{\ln(1 - i_{tot})}{i_{tot}}$$

What is this for platoon C4 where 26% were infected?

R_0 for Swine Flu at Fort Dix Method 1: Final Epidemic Size

Platoon	% Infected	R_0 Estimate
C4	26	1.15
C2	24	1.14
E1	26	1.15
E6	56	1.46
D6	17	1.09
A5	7	1.03
$\vdots$	$\vdots$	$\vdots$

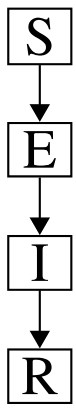
Combining this data using inverse variance weighting gives us an overall estimate for the R_0 of this outbreak of:

$$R_0 = 1.09$$

R_0 for Swine Flu at Fort Dix Method 2: stochastic simulations

- Create a compartmental model based upon our knowledge of the natural history of the disease.
- Run simulations on hypothetical populations using different possible parameterizations of the model.

- By running many simulations determine the probability of various outcomes under the different model assumptions.
- Use these probabilities to determine the likelihood of the parameterizations given the observed data.



Individuals infected remain in S until infected by an $I \in i$.

Individuals infected remain in E for $t \sim$ Weibull(η, β, γ) days.

Individuals infected remain in I for $t \sim$ logNormal(μ, σ) days.

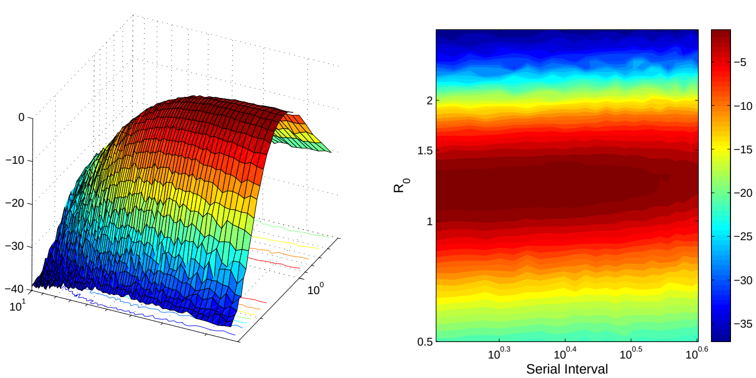
Individuals infected remain in R permanently.

R_0 for Swine Flu at Fort Dix Method 2: stochastic simulations

Simulations Method 2: stochastic simulations

- Ran 10,000 simulations at each parameterization.
- Varied R_0 from .5-3
- Varied $\mathcal{SI}$ from 1.6 to 10.

R_0 for Swine Flu at Fort Dix Method 2: stochastic simulations



R_0: 1.2, Supported Range: 1.1-1.4
Serial Interval: 1.9 days, Supported Range: 1.6-3.8

4.2 Thailand, 2006

R_0 for Influenza at a Thai Remand Facility What do we know?

- Day specific attack rates.
- Attack rates for individual dorms, age groups, job types, etc.
- Control measures were put in place during the epidemic.
- This strain of influenza (H1N1) had circulated in the lifetime of these participants.

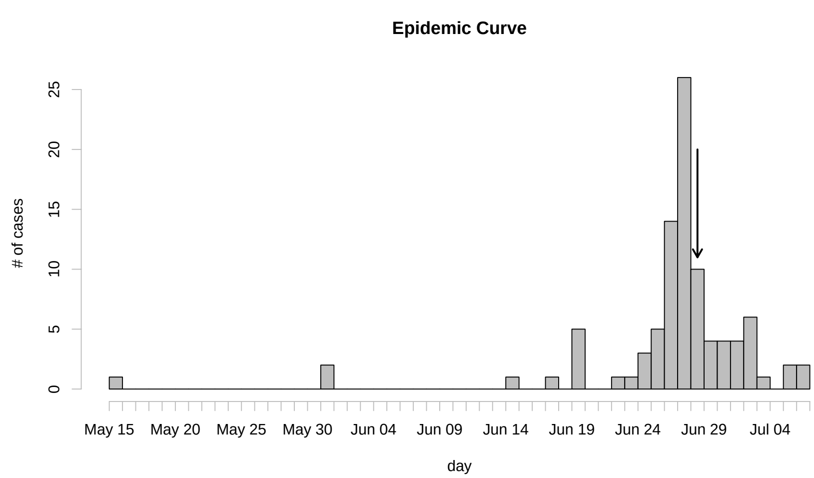
R_0 for Influenza at a Thai Remand Facility Method 1: Final Epidemic Size
Can we do this in this situation?

We probably should not attempt to use this method here because of the presence of an intervention and the existence of background immunity.

R_0 for Influenza at a Thai Remand Facility Method 3: Fitting the initial growth of the epidemic.

- In the early stages of an epidemic we can assume that the impact of loss of susceptibles is small and assume cases are growing exponentially.
- We can solve for R_0 by equating this exponential increase to the dominant eigenvalue of the disease free equilibrium.
- The represents the instantaneous growth rate given by the equations.

R_0 for Influenza at a Thai Remand Facility Method 3: Fitting the initial growth of the epidemic.



- Assume cases are growing exponentially.
- Over 3 days cases grow from 1 to 14.

R_0 for Influenza at a Thai Remand Facility Method 3: Fitting the initial growth of the epidemic.

- The rate of exponential increase can be derived using the log of the number infected divided by the time.
$$\lambda = \frac{\ln Y(t)}{t}$$
- In our case this 14 infected at 3 days:
$$\lambda = \frac{\ln 14\text{cases}}{3\text{days}} = 0.88$$

R_0 for Influenza at a Thai Remand Facility Method 3: Fitting the initial growth of the epidemic.

We need to find the dominant eigenvalue for the model best representing influenza.

- What is this model?

  An SEIR model.
- What properties of the disease do you think will be important in the equations?

  The serial interval, S, the latent period, L, and the exponential rate of increase, λ.

R_0 for Influenza at a Thai Remand Facility Method 3: Fitting the initial growth of the epidemic.

Time for some fancy math!

$$\lambda = \frac{-1 + \sqrt{(1-2f)^2 + 4f(1-f)R}}{2Sf(1-f)}$$

Where $f = \frac{L}{S}$.

Hence:

$$R = 1 + \lambda S + f(1-f)(\lambda S)^2$$

R_0 for Influenza at a Thai Remand Facility Method 3: Fitting the initial growth of the epidemic.

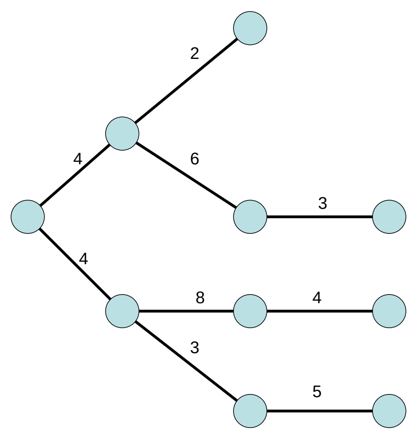
So in this case:

$$\begin{aligned} R_0 &= 1 + \lambda S + f(1-f)(\lambda S)^2 \\ &= 1 + (0.88)(2.6) + (0.62)(1-0.62)(0.88 \cdot 2.6)^2 \\ &= 4.52 \end{aligned}$$

Recall that S is the serial interval, λ is the exponential growth rate, and f is the ratio of mean latent period to serial interval.

R_0 for Influenza at a Thai Remand Facility Method 4: Recreating potential chains of transmission

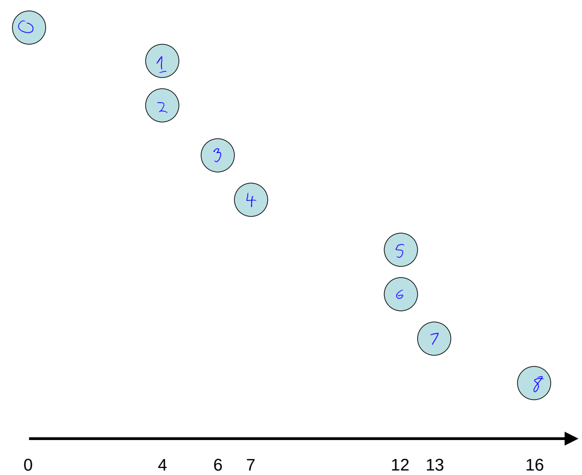
Ideally we would know who infected who and when every individual got sick, and could then calculate $R(t)$ and the serial interval directly:



Lets go through the exercises of figuring this out on the white board.

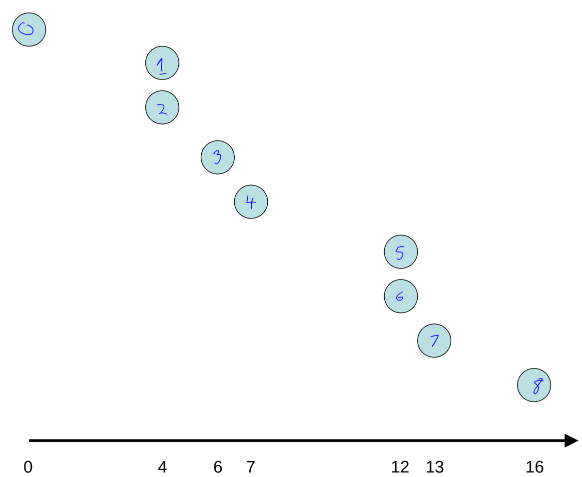
R_0 for Influenza at a Thai Remand Facility Method 4: Recreating potential chains of transmission

But in reality we only get to see the dates of symptom onset like this:



R_0 for Influenza at a Thai Remand Facility Method 4: Recreating potential chains of transmission

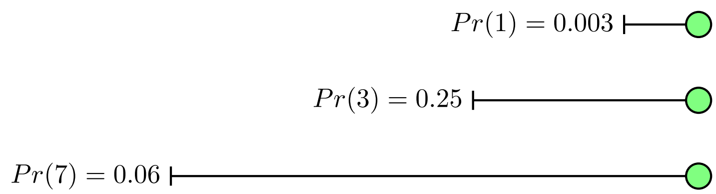
Can we still use this idea to calculate R_0 and/or the serial interval?



R_0 for Influenza at a Thai Remand Facility Method 4: Recreating potential chains of transmission

- Suppose we know the distribution of the serial interval.

- We can then look at the probability of having been infected by a with a given onset date.



- We can use this information to find the probability that this case was infected by a case on a particular day.

$$\text{Pr(Infected by case 0)} = \frac{0.06}{0.06 + 0.025 + 0.003} = 0.19$$

R_0 for Influenza at a Thai Remand Facility Method 4: Recreating potential chains of transmission

We can now use this information to find the probability that a case was infected on a particular day.

- Step one: make a list of the probability of given incubation periods.

Length	Probability
≤ 0	0
1	0.003
2	0.11
3	0.25
4	0.24
⋮	⋮
15	0.0004
16	0.0002

R_0 for Influenza at a Thai Remand Facility Method 4: Recreating potential chains of transmission

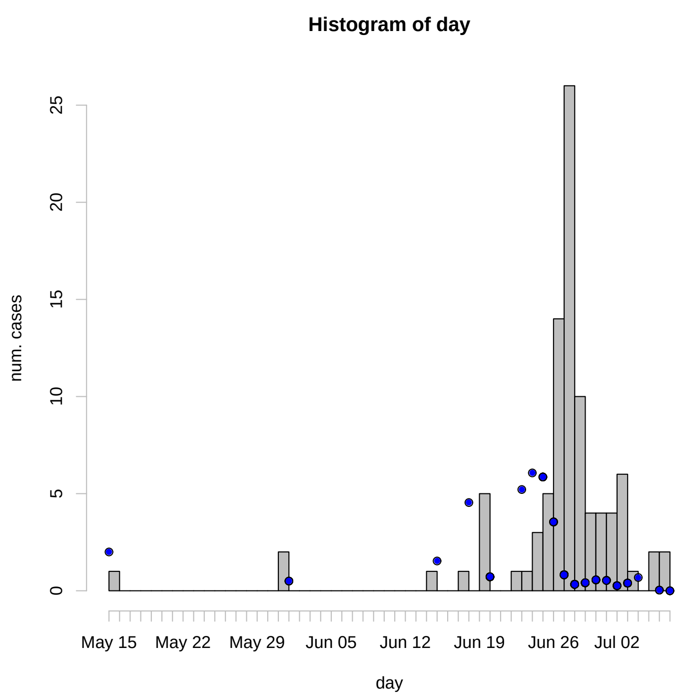
We can now use this information to find the probability that a case was infected on a particular day.

- Step two: use this information to calculate the probability that individual cases were infected on a given day: Step three: sum up the probabilities and divide by the number infectious on that day to get the estimated $R(t)$

Case	Pr(Infected by 3)
0	0.00
1	0.00
2	0.00
3	0.00
4	0.01
5	0.30
6	0.30
7	0.28
8	0.01
	0.90

$$R(6) = \frac{0.9}{1} = 0.9$$

R_0 for Influenza at a Thai Remand Facility Method 4: Recreating potential chains of transmission



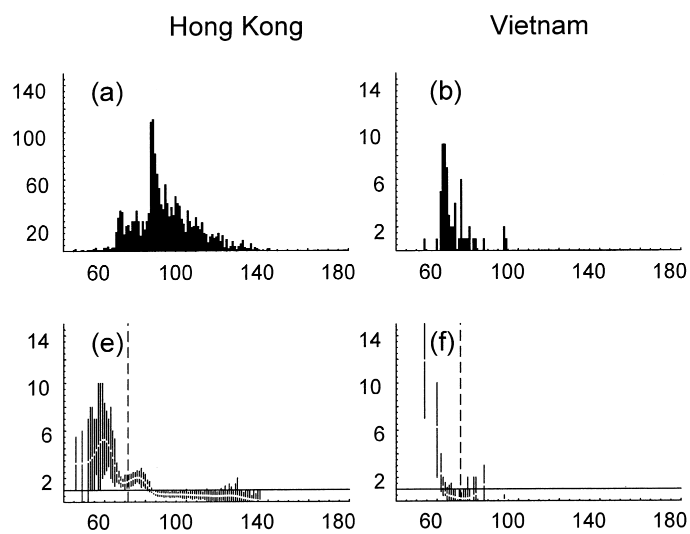
R_0 for Influenza at a Thai Remand Facility Method 4: Recreating potential chains of transmission

- Estimates from early in the epidemic are approximations of R_0.
- In this case R_0 appears to be around 5.

R_0 for Influenza at a Thai Remand Facility

Why is this R_0 higher than what Derek told you the R_0 for influenza should be yesterday?

R_0 for Influenza at a Thai Remand Facility Comparison with SARS



From Wallinga 2004

Today's Learning Objectives

- Show how outbreaks can be analyzed to estimate the dynamic properties of diseases using two real world examples.
  - Swine Flu at Fort Dix, 1976
  - Influenza in a Thai Remand Facility, 2006
- Understand how mass action models can be used to represent disease dynamics.
- Understand when the assumptions of mass action models apply, and introduce methods for testing assumptions.
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More to Do

- Dealing with observational biases in measuring epidemic giving incorrect estimates.

- Alternate and more complex formulations of mass action models.
- Representing the uncertainty in our estimates from outbreak data.
- *Much much more...*