Models of Infectious Disease
Formal Demography
Stanford Summer Short Course

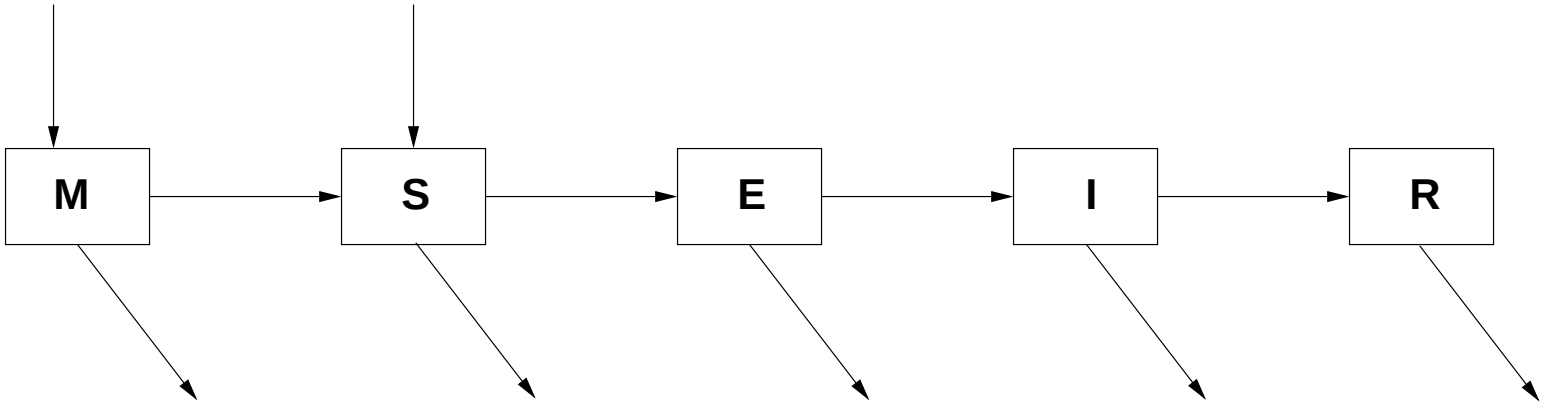
James Holland Jones, Instructor

August 15, 2005

Outline

1. Compartmental Thinking
2. Simple Epidemic
   (a) Epidemic Curve 1: Cumulative Prevalence
   (b) Epidemic Curve 2: Incidence
   (c) Reality Check: Real Epidemic Curves Are Messy
3. General Epidemic
   (a) Epidemic Threshold
   (b) Final Size of the Epidemic
   (c) Analyzing the Effective Contact Rate
   (d) Theory in Public Health
4. Why Do We Care So Much About $\mathcal{R}_0$?
5. Equilibria and Stability
6. $\mathcal{R}_0$ in Structured Epidemic Models

Compartments



A Simple Model of An Infectious Disease

Consider a closed population population of N individuals

There are two states:

- Susceptible
- Infected

Initially I_0 are infected

$N - I_0$ are therefore susceptible

We assume the population is **well mixed**

The probability that a susceptible and infectious individual meet is proportional to their abundances, with **effective transmission rate** β

Simple Epidemic Continued

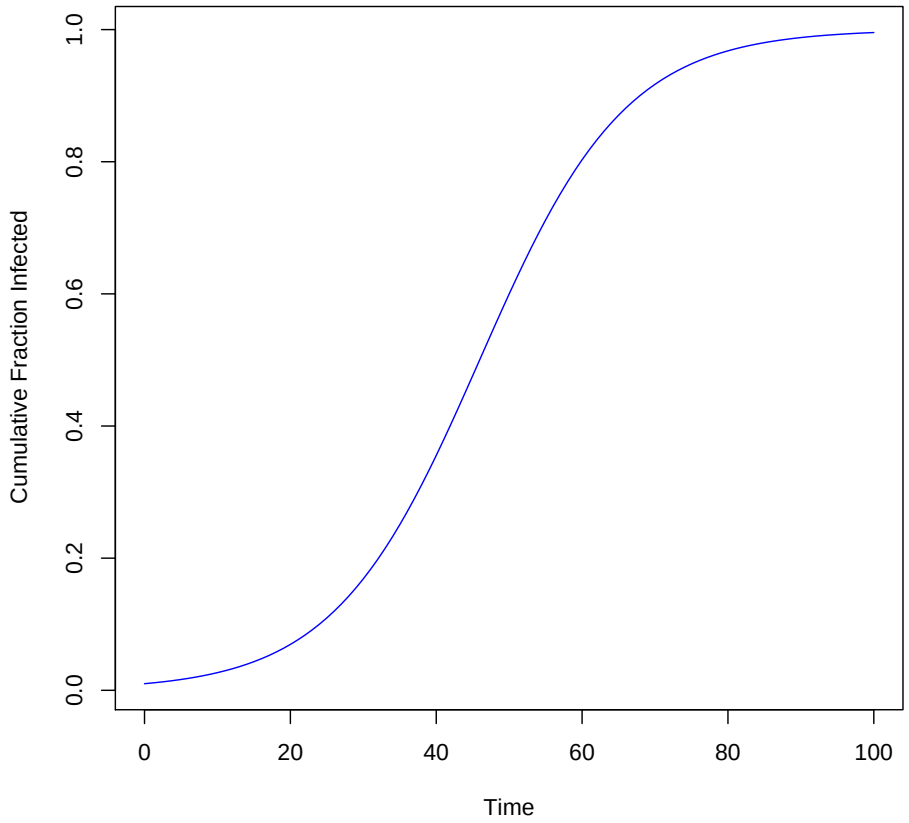
Write $s = S/N$ and $i = I/N$

$$\frac{di}{dt} = \beta i(1 - i). \tag{1}$$

To calculate the number infected at time t, $i(t)$, integrate this equation from time zero to time t, yielding:

$$i(t) = \frac{1}{1 + \frac{1-i_0}{i_0} e^{-\beta t}} \tag{2}$$

This equation yields what is known as the **epidemic curve**



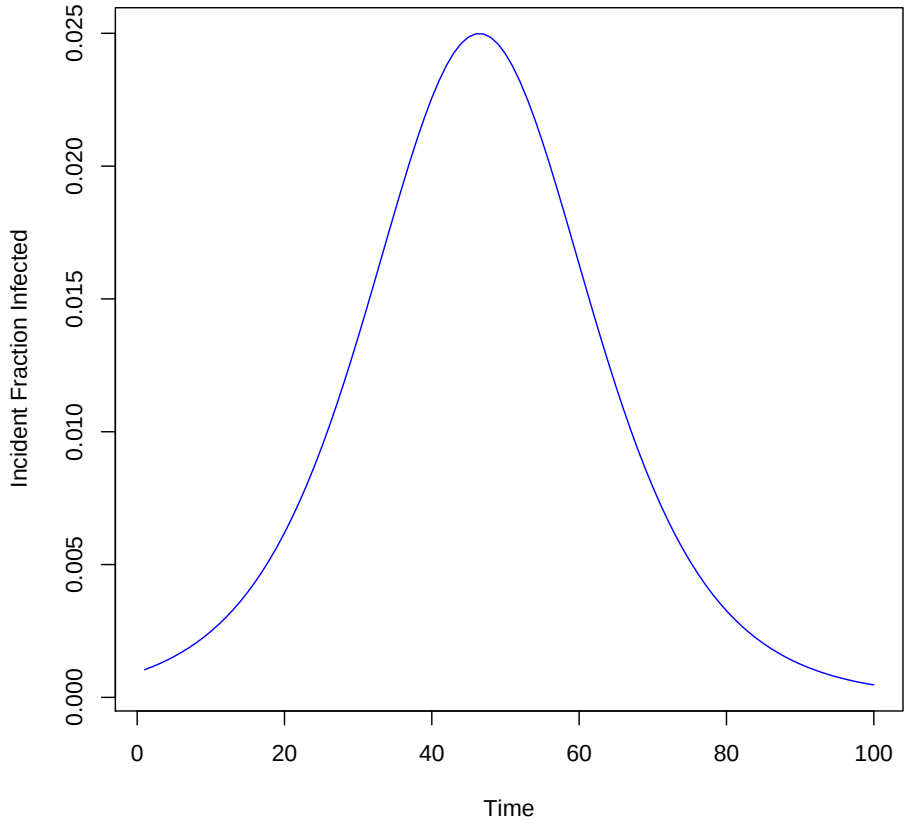

```
epi.curve <- expression(1/(1+ (exp(-beta*t)*(1-a0)/a0)))
a0 <- .01
beta <- 0.1
t <- seq(0,100,1)
plot(t,eval(epi.curve),type="l",col="blue",
     xlab="Time", ylab="Cumulative Fraction Infected")
```

Interpreting the Epidemic Curve

This figure plots the cumulative **prevalence** of the infection

We might also want to know about the shape of the **incidence** of infection, that is, the number of new cases per unit time

```
a <- eval(epi.curve)
b <- diff(a)
plot(1:100,b,type="l",col="blue",
     xlab="Time", ylab="Incident Fraction Infected")
```


Incident Fraction Infected
0.000
0.005
0.010
0.015
0.020
0.025
0
20
40
60
80
100
Time

More Interpretations of the Epidemic Curve

This is the classic **epidemic curve**

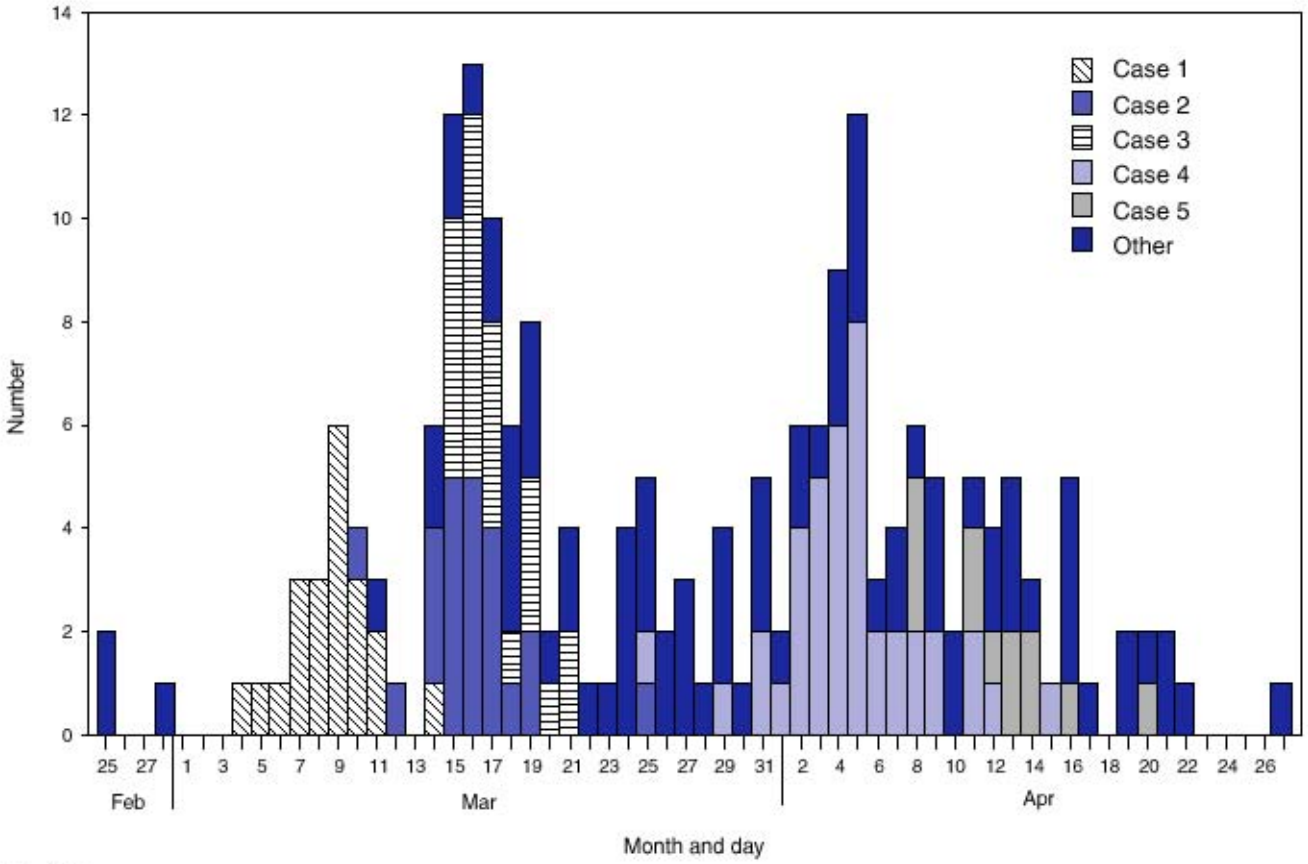
The epidemic curve is "bell-shaped", but not completely symmetric

There is a greater force of infection early on

Note that in the limit $t \to \infty$, **everyone in the population becomes infected**

Real Curves Are a Bit More Messy

FIGURE 1. Number of probable cases of severe acute respiratory syndrome,* by date of fever onset and reported source of infection — Singapore, February 25–April 30, 2003



*n = 201.

General Epidemic: The Basic SIR Model

A population is comprised of three compartments:

Susceptible Segment not yet infected, disease-free (S)
Infected Segment infected and infectious (I)
Removed Recovered (usually) with lifelong immunity (R)

Model Assumptions:

1. Constant (closed) population size
2. Constant rates (e.g., transmission, removal rates)
3. No demography (i.e., births and deaths)
4. Well-mixed population

SIR Continued

Write $s = S/N$, $i = I/N$, $r = R/N$

$$\frac{ds}{dt} = -\beta si \tag{3}$$

$$\frac{di}{dt} = \beta si - \nu i \tag{4}$$

$$\frac{dr}{dt} = \nu i \tag{5}$$

where,

β effective contact rate
ν removal rate

Conditions for an Epidemic

An epidemic occurs if the number of infecteds increases, i.e., $di/dt > 0$

$$\beta si - \nu i > 0$$

$$\frac{\beta si}{\nu} > i$$

At the outset of an epidemic, $s \approx 1$

$$\frac{\beta}{\nu} = \mathcal{R}_0 > 1$$

Basic Reproduction Number

$\mathcal{R}_0$ is the **basic reproduction number** of the epidemic

- **Basic Reproduction Number** ($\mathcal{R}_0$): the expected number of secondary infections generated by a single, typical infection in a completely susceptible population

Note that Hethcote (2000) refers to the quantity β/ν as σ, the "contact rate"

In general

$$\mathcal{R}_0 \geq \sigma \geq \mathcal{R}$$

where $\mathcal{R}$ is the reproduction number at some time other than the outset of the epidemic

When we model fractions of infected individuals in a closed population (i.e., $i = I/N$ instead of I) $\mathcal{R}_0 = \sigma$

When we model I, $\mathcal{R}_0 = \frac{\beta N}{\nu}$

Numerical Solution of the SIR Model

Use R library `odesolve`

write a function that we will call `sir`

function takes three arguments `y`, `t`, and `p`, for the initial conditions, time scope, and parameter values respectively

Create list of parameters `pars`, which contains the two parameters of the model β and ν

```
library(odesolve)
pars <- c("beta"=0.05,"nu"=0.075)
times <- seq(0,10,0.1)
y0 <- c(100,1,0)

sir <- function(t,y,p) {
       yd1 <- -p["beta"] * y[1]*y[2]
       yd2 <-  p["beta"] * y[1]* y[2] - p["nu"]*y[2]
       yd3 <-   p["nu"]*y[2]
       list(c(yd1,yd2,yd3),c(N=sum(y)))
     }
```

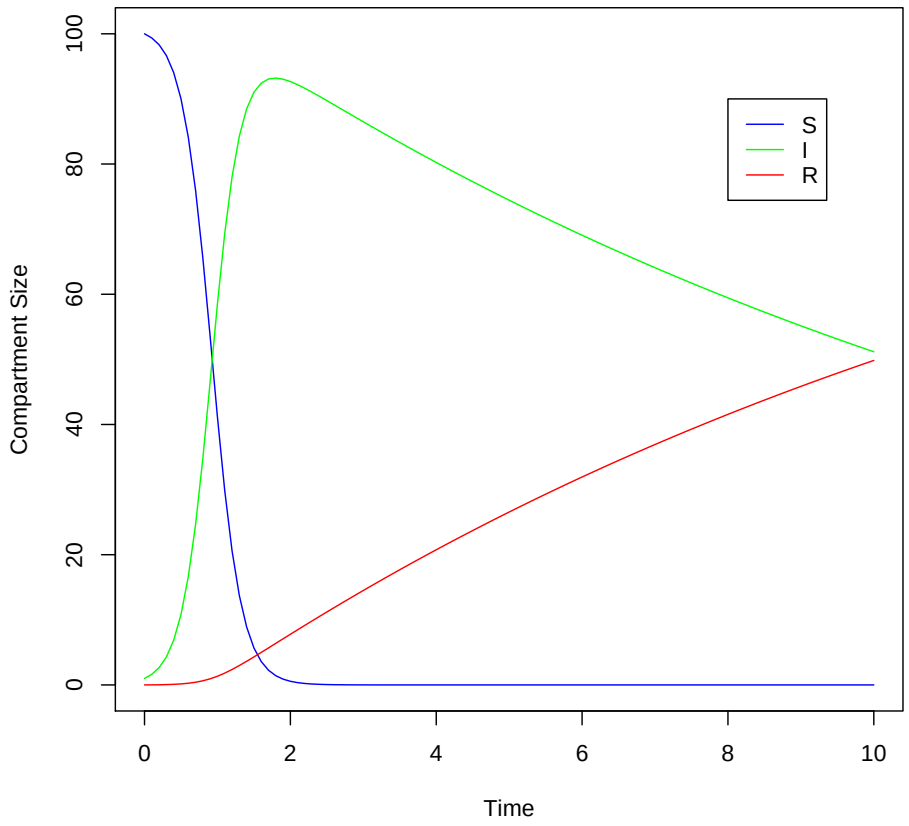
```
sir.out <- lsoda(y0,times,sir,pars)

sir.out
       time             1         2            3   N
  [1,]  0.0  1.000000e+02  1.000000  0.000000000 101
  [2,]  0.1  9.935633e+01  1.633984  0.009686266 101
  [3,]  0.2  9.831563e+01  2.658889  0.025480797 101
  [4,]  0.3  9.665093e+01  4.297969  0.051096592 101
  [5,]  0.4  9.403313e+01  6.874588  0.092284864 101
  [6,]  0.5  9.002495e+01 10.817430  0.157625403 101

...
```

plot the results of this solution

```
plot(sir.out[,1],sir.out[,2],type="l",col="blue",xlab="Time",
    ylab="Compartment Size")
lines(sir.out[,1],sir.out[,3],col="green")
lines(sir.out[,1],sir.out[,4],col="red")
legend(8,90,c("S","I","R"),col=c("blue","green","red"),lty=c(1,1,1))
```


Compartment Size
0
20
40
60
80
100
0
2
4
6
8
10
Time
S
I
R

Simplifying the System (a bit)

Anderson & May (1991) note that the above system of equations can be re-written in terms of the force of infection

Since $S + I + R = N$, the equation 5 is again redundant

Anderson & May (1991) also note that it is frequently convenient to think about epidemics in terms of proportions of the population susceptible, infected, etc.

Write $x = S/N$ and $y = I/N$

Now, A&M show that we can re-write equations 4 and 5 as:

$$\frac{dx}{dt} = \mu - (\mu + \lambda(t))x(t) \tag{6}$$

$$\frac{d\lambda}{dt} = (\nu + \mu)\ \lambda(t)\ (R_0 x(t) - 1) \tag{7}$$

where we write the combination of parameters

$$\frac{\beta N}{\nu + \mu} = R_0$$

This, of course, is the basic reproduction number again

Early Growth of the Epidemic

We'd like to know what happens to an epidemic following the introduction of a pathogen

We assume that the innoculum for the epidemic was very small (usually a single infected individual)

therefore, $x(t) \approx 1$ for small t

In addition, it is almost always the case that $\nu \gg \mu$

for the early part of the epidemic, we can assume $\mu \approx 0$

Substitute these values into the dynamical equation for the force of infection, λ

$$\frac{d\lambda}{dt} \approx \nu(R_0 - 1)\lambda$$

This is (once again) an equation for exponential growth, the solution of which is:

$$\lambda(t) = \lambda(0)e^{\Lambda t}$$

where $\Lambda = \nu(R_0 - 1)$, and the $\lambda(0)$ is the initial seed value of the force of infection $\lambda(0) = \beta I(0)$

Endemic Equilibria

Since we now care about longer time scales, we can consider things like equilibria of the model

To find the equilibria, set our dynamical equations equal to zero

First, we'll do x^* (**Note that to get x^*, we solve the equation for λ and vice-versa**)

$$\frac{d\lambda}{dt} = (\nu + \mu)\ \lambda(t)\ (R_0 x(t) - 1) = 0$$

$$\lambda\ \mathcal{R}_0 x - \lambda = 0$$

$$x^* = \frac{1}{\mathcal{R}_0}$$

Solving for λ^* is only slightly trickier

$$\mu - (\mu + \lambda(t))x(t) = 0$$

$$\lambda = \mu(\frac{1}{x} - 1)$$

Since we already solved for the equilibrium value for x, we substitute this back in

$$\lambda^* = \mu(R_0 - 1)$$

Will the Epidemic Infect Everyone?

Re-write the SIR equations:

$$\begin{aligned} \frac{ds}{dt} &= -\beta si \\ \frac{di}{dt} &= \beta si - \nu i \\ \frac{dr}{dt} &= \nu i \end{aligned} \tag{8}$$

Divide equation 5 by equation 4

$$\frac{di}{ds} = -1 + \frac{\nu}{\beta s}$$

Final Size of the Epidemic

Multiply both sides by ds

$$di = (-1 + \frac{\nu}{\beta s})ds$$

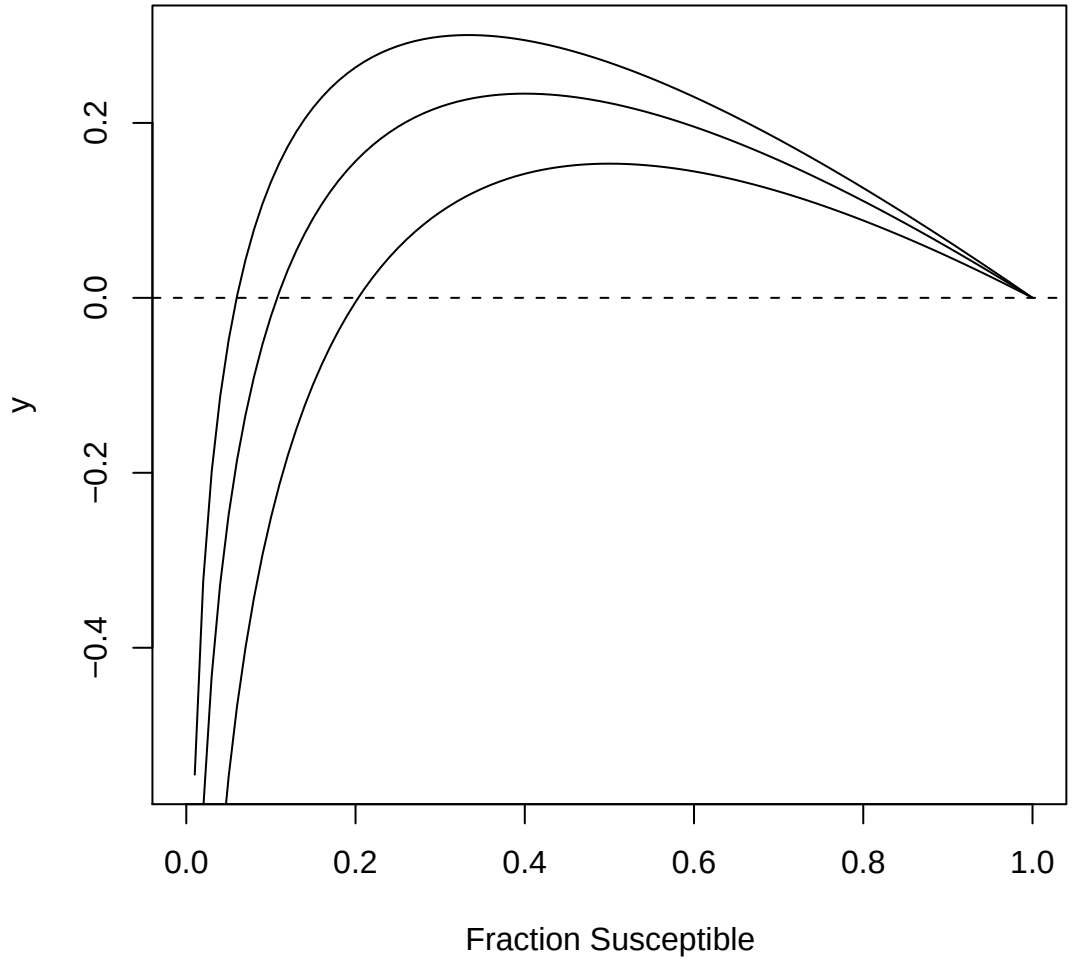
Integrating this (and doing a little algebra) yields

$$\log(s_\infty) = \mathcal{R}_0(s_\infty - 1)$$

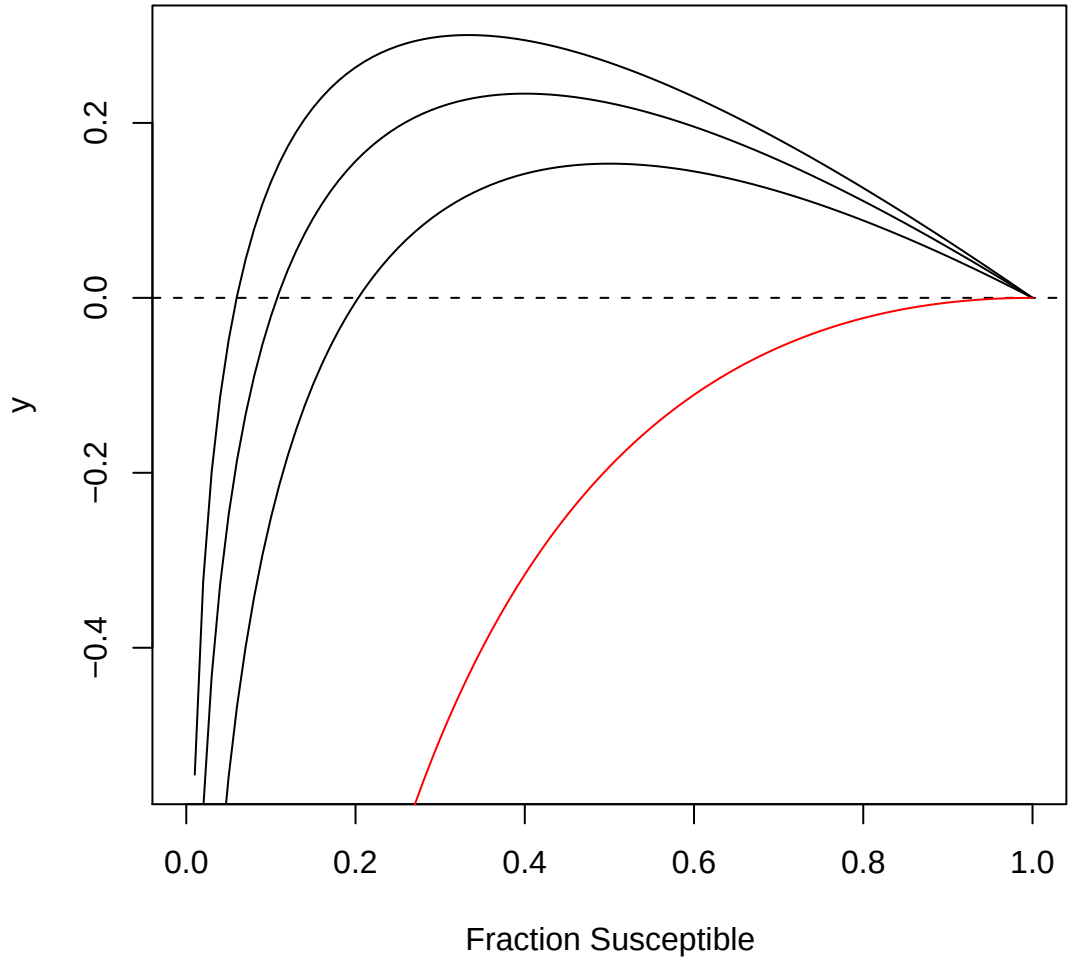
which is an implicit equation for s_∞, the number of susceptibles at the end of the epidemic

When $\mathcal{R}_0 > 1$, this equation has exactly two roots, only one of which lies in the interval $(0, 1)$

$\mathcal{R}_0 > 1$



$\mathcal{R}_0 \leq 1$



Analyzing the Effective Contact Rate, β

Effective contact rate is the per capita rate of infection given contact

- ▷ This is like a rate constant in a thermodynamic equation

Mechanistically, this will involve

- The transmissibility of the pathogen (τ)
- The frequency of contact ($\bar{c}$)

We assumed removal rate was constant $\Rightarrow$ Exponentially distributed

Expected time to removal (δ) is therefore $1/\nu$

$$\mathcal{R}_0 = \tau \bar{c} \delta \tag{9}$$

$\mathcal{R}_0$ is simply the product of the transmissibility, mean contact rate, and the duration of infection

Interpretation: Expected number of secondary infections in a rarefied population produced by a single typical infection

This is a very important result because it tells us how to control epidemics

Reduce Transmissibility, τ Develop vaccines, get people to use barrier contraceptives, use anti-retrovirals (e.g., acyclovir for HSV-2, or HAART for HIV)

Decrease Mean Contact,$\bar{c}$ Isolation/Quarantine, health education programs

Reduce Length of Infectious Period, δ therapeutics, antibiotic treatment of bacterial infections, care of ulcerations, boost innate immune response

This is essentially the entire theoretical basis of public health interventions for infectious diseases!

How Many People Should We Vaccinate?

Say that we can successfully immunize a fraction $0 < p \leq 1$ of the population

How big does p need to be?

Define $\mathcal{R}^*$ to be the reproduction number of the immunized population

$$\mathcal{R}^* \leq \mathcal{R}_0(1-p)$$

Since our threshold criterion is for $\mathcal{R}^* < 1$, we can easily solve this inequality for p

Denote the critical fraction successfully immunized as p_c

$$p_c = 1 - (1/\mathcal{R}_0)$$

Not surprisingly, as $\mathcal{R}_0$ increases, so does the critical vaccination fraction

Critical Values of p for Selected Infections

Infection	$\mathcal{R}_0$	p
Measles	18.8	0.95
Pertusis	3.8-5.6	0.74-0.82
Smallpox	4-10	0.75-0.90
Chancroid	1.1	0.10

Why Do We Care So Much About $\mathcal{R}_0$ Anyway?

$\mathcal{R}_0$ Provides **five** fundamental insights into the dynamics of an infectious disease:

1. $\mathcal{R}_0$ is the **threshold parameter**, determining whether or not there will be an epidemic
2. $\mathcal{R}_0$ determines the **initial rate of increase** of an epidemic (i.e., during its exponential growth phase)
3. $\mathcal{R}_0$ determines the **final size** of the epidemic (i.e., what fraction of susceptibles will ultimately be infected over the course of the outbreak)
4. $\mathcal{R}_0$ determines the **endemic equilibrium** fraction of susceptibles in the population $(= 1/\mathcal{R}_0)$
5. $\mathcal{R}_0$ determines the **critical vaccination threshold** $(= 1/\mathcal{R}_0)$

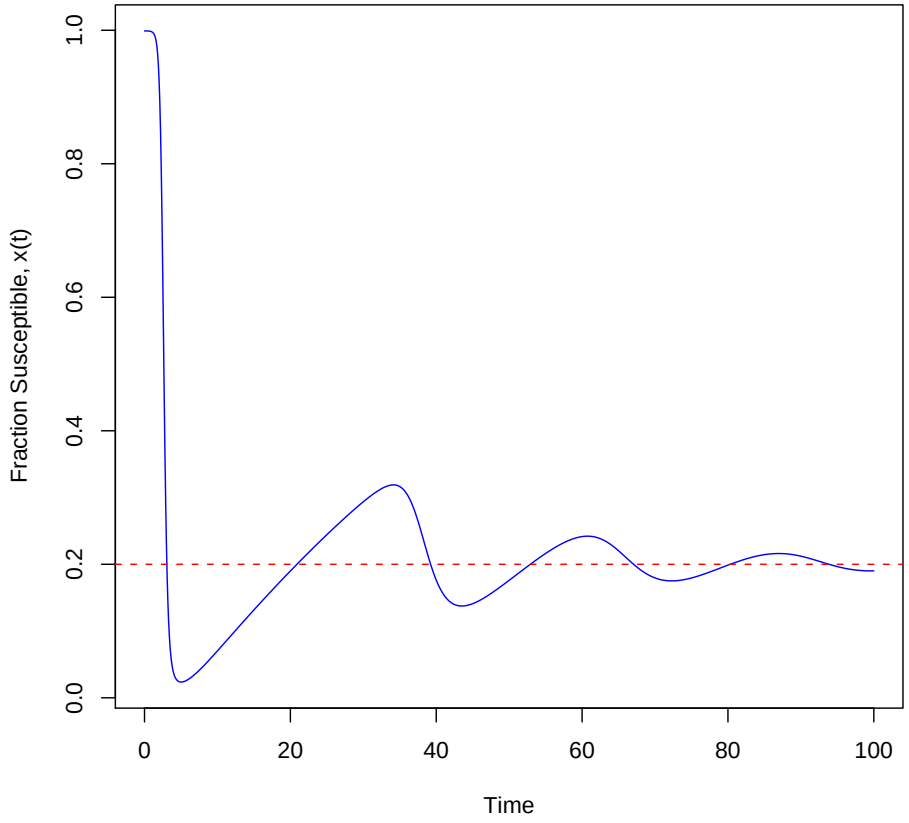
An Example of an Endemic/Epidemic Model

Plot of a hypothetical (and unlikely!) disease's dynamics reproduced from Anderson & May (1991)

The parameters are $\mu = 1/70$, $\nu = 1$, and $R_0 = 5$,

```
lambda.dyn <- function(t,y,p){
yd1 <- p["mu"] - (p["mu"]+y[2])*y[1]
yd2 <- (p["mu"] + p["nu"]) * y[2] * (p["R0"]*y[1] - 1)
list(c(yd1,yd2))
}

pars <- c("R0"=5,"nu"=1.0,"mu"=0.014)
times <- seq(0,100,.1)
y0 <- c(.999,1e-4)
lambda.out <- lsoda(y0,times,lambda.dyn,pars)
plot(lambda.out[,1],lambda.out[,2],type="l",col="blue",
xlab="Time",ylab="Fraction Susceptible, x(t)")
abline(h=.2,lty=2,col="red")
```


Fraction Susceptible, x(t)
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
100
Time

Is the Equilibrium Stable?

How do we calculate the stability of a model that has more than one dimension?

For the one-dimensional models (e.g., the density-dependent population growth models), the process was:

- Calculate the equilibria
- Linearize the model around the equilibrium using a Taylor series approximation
- If the solution to the linearized equilibrium was less than zero, the equilibrium was stable

There is a straightforward extension of this procedure to the multivariate case

A model with multiple variables is stable if and only if the real part of the eigenvalues of the model's **Jacobian Matrix** are less than zero

Great. What's a Jacobian matrix?

write

$$F(x,\lambda) = \frac{dx}{dt} = \mu - (\mu + \lambda(t))x(t),$$

and

$$G(x,\lambda) = \frac{d\lambda}{dt} = (\nu + \mu)\ \lambda(t)\ (R_0 x(t) - 1)$$

The Jacobian is:

$$\mathbf{J} = \begin{pmatrix} \partial F/\partial x & \partial F/\partial \lambda \\ \partial G/\partial x & \partial G/\partial \lambda \end{pmatrix}$$

- While this material is not in Hastings under the SIR model, it is discussed in chapter 8 (especially pp. 151-160) on predator-prey dynamics (of which infectious diseases are essentially a special case)
- In this section, he also discusses quite lucidly why complex eigenvalues lead to oscillations

For the SIR model variant of equations 6 and 7, the Jacobian is:

$$\mathbf{J} = \begin{pmatrix} -\lambda - \mu & -x \\ R_0\,\lambda\,(\mu+\nu) & (-1+R_0\,x)\,(\mu+\nu) \end{pmatrix} \tag{10}$$

Using the equilibrium values of x and λ

$$x^* = 1/\mathcal{R}_0,$$

and

$$\lambda^* = \mu(R_0 - 1)$$

along with the parameter values given before ($\mu = 1/70$, $\nu = 1$, and $R_0 = 5$)

The Jacobian is

$$\mathbf{J} = \begin{pmatrix} -0.07142857 & -0.2 \\ 0.28979592 & 0 \end{pmatrix}$$

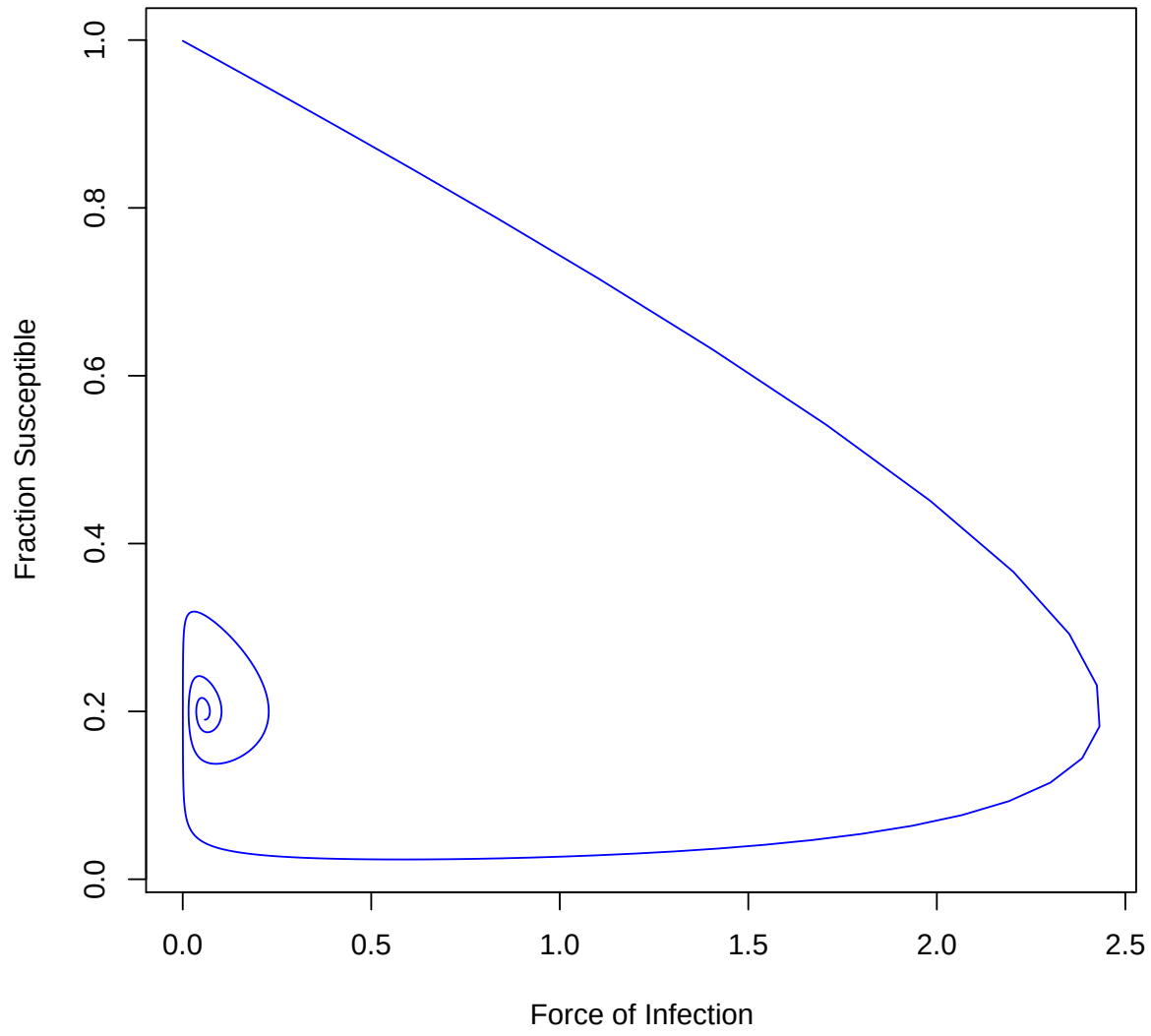
And the eigenvalues of this matrix are

$$\{-0.0357143 - 0.238083\ i, -0.0357143 + 0.238083\ i\}$$

The real parts of both eigenvalues are negative so the equilibrium $\{x^*,\ \lambda^*\}$ is asymptotically stable

```
plot(lambda.out[,3],lambda.out[,2],type="l",col="blue",
  xlab="Force of Infection", ylab="Fraction Susceptible")
```

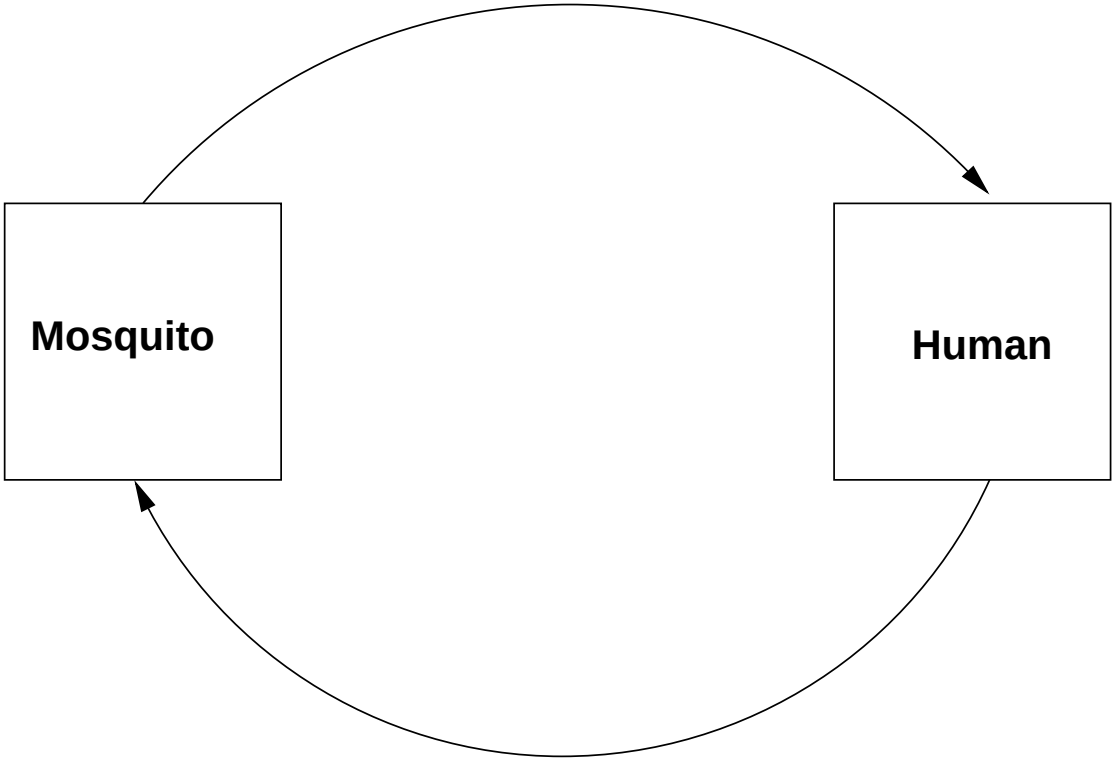
We can see this graphically by plotting the $phase\ plane$ of the model


Fraction Susceptible
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.5
1.0
1.5
2.0
2.5
Force of Infection

Structured Epidemic Models

How do you define $\mathcal{R}_0$ when you have a structured epidemic model?

Consider malaria transmission:



$\mathcal{R}_0$ Generalizes Easily to Structured Epidemic Models

Define a **next generation matrix**, Θ

The elements of this matrix θ_{ij} represent the expected number of type i infections generated by type j infections...

... At the disease-free equilibrium: That is, everyone (everymosquito?) is susceptible

$\mathcal{R}_0$ is the dominant eigenvalue of the next-generation matrix, Θ

For the simple malaria model

$$\Theta = \begin{bmatrix} 0 & \frac{\beta_{12} N_1}{\nu_2} \\ \frac{\beta_{21} N_2}{\nu_1} & 0 \end{bmatrix}$$

$$\mathcal{R}_0 = \rho(\Theta)$$

A Concrete Example

What is the average number of cases produced by a single case of malaria when an infected person infects 10 mosquitos and each mosquito infects 100 people?

$$\Theta = \begin{bmatrix} 0 & 10 \\ 100 & 0 \end{bmatrix}$$

$$\mathcal{R}_0 = \rho(\Theta) = \sqrt{1000} = 31.6$$