* Classifying Diseases
  + infectious vs noninfectious
    - Noninfectious
      * epidemiology of noninfectious 🡪 study of risk factors associated w/ chance of developing disease
    - Infectious
      * epidemiology of infectious 🡪 primary risk factor is presence of disease cases in local population
      * Subdivisions:
        + microparasite

(usually single-cell, ie virus, bacteria, protozoa, prions)

in modeling, not worried about # of pathogens, only worried about individuals infection status

* + - * + macro parasite

(larger, flukes or helminthes, etc)

have a complex life cycle, require explicit modeling

# of pathogens in host are important in modeling pathogenicity and disease transmission

* + - * + direct transmission

infection is caught by close contact with an infectious individual

most microparasitic diseases are directly transmitted (ie flue, cold, HIV, etc)

do not survive long outside of host

diseases which require a secondary host (or vector), such as malaria, are considered to be 2 direct transmission events (host1 🡪 insect 🡪 host2)

* + - * + indirect transmission

passed between hosts via the environment (ie cholera is waterborne)

most macroparasitic diseases are indirectly transmitted

* + - * + book will focus on microparasites that are directly transmitted
  + Stats on Diseases
    - 1,414 known human pathogens
      * 53% Microparasites
        + 15% virus or prion, 38% bacteria
      * 61% are zoonotic (can be transferred from animals to humans)
* Characterization of Infectious Diseases
  + Classification of Individuals in an infected population
    - Susceptible = pre-infection
    - Exposed = directly after infection. low levels of pathogen. not contagious. no symptoms.
    - Infectious = sufficient pathogen to transmit disease
    - Recovered = no longer infectious
    - all depend solely on ability to transmit pathogen
  + Models can be SEIR (susceptible, exposed, infectious, recovered) or SIS, or SIR, depending on the characteristics of the specific disease
  + R is a key parameter 🡪 it is the basic reproduction ratio 🡪 defines the average number of secondary cases an average primary case produces in a totally susceptible population
  + Timescale of infection is also a key parameter (is it lifelong like HIV or does it last about a month or less like strep throat?)
* Control of Infectious Diseases
  + we model to control & hopefully eradicate disease from population
  + goal of control methods = reduce avg amount of transmission b/w infectious and susceptible ppl (reduce Ro ? 🡪 not necessarily, can also reduce # of susceptible people.)
  + **Vaccine** = reduce # of susceptible individuals in population
  + **Quarantine** = Reduce # of infected freely mixing with the rest of the population
  + **Culling** = killing potential and identified hosts in the population (mainly for plants and sometimes animals)
  + **Contact Tracing** = questioning infected individuals to identify potential transmission contacts, find others who may be infected and quarantine, or vaccinate, or hospitalize depending on nature of infection
* What Are Mathematical Models?
  + model = conceptual tool that explains how an object (or system of objects) will behave
  + models allow us to predict the population-level epidemic dynamics from an individual-level knowledge of epidemiological factors, the long term behavior from the early invasion dynamics, or the impact of vaccination on the spread of infection
  + all models are “wrong” – all simplify to some extent, none are perfect
  + pick model based on usefulness
  + Forming a model for a particular problem is a trade-off between 3 elements:
    - accuracy
      * def: the ability to reproduce the observed data and reliably predict future dynamics
      * qualitative vs quantitative fit
        + qualitative = sufficient to provide insight to a the dynamics of an infectious disease
        + quantitative = generally necessary if you want to use model to advise future control policies
      * Accuracy improves with increasing model complexity
      * improves w/ inclusion of more heterogeneities and relevant biological detail
      * limited by computational power, the mechanistic understanding of disease natural history, and the availability of necessary parameters.
    - transparency
      * def: being able to understand (either analytically or numerically) how the various model components influence the dynamics and interact
      * achieve by adding or removing components and building upon general intuitions from simpler models
      * transparency decreases with increasing model complexity (direct opposition to accuracy)
    - flexibility
      * def: measures the ease with which the model can be adapted to new situations
      * vital to prediction if environment is changing
      * most mechanistic models are flexible (bc based on well-understood disease transmission principles)
      * “black-box” time series tools (ie neural nets) = less flexible
* What Models Can Do
  + Models have 2 distinct roles:
    - Prediction
      * requires high degree of accuracy
      * guide decision making about control strategies
        + increased complexity of the problem, or lack of understanding or epidemiological parameters, can create issues with prediction of control strats (ie what to do in case of bio terrorist small pox outbreak)
      * also useful as statistical tool
        + if population behavior deviates from predictive model 🡪 indicates certain parameters or behavior may be dif from norm
        + can be used to identify threshold # of cases for which swift action is required
        + use to identify regions that do not respond as well to eradication campaign, use other control measures
        + used to identify early emergence of an epidemic using analysis of reported and hospitalized cases
    - Understanding
      * requires high degree of transparency (in conflict with prediction)
      * understand how disease spreads in the real world, and how various complexities (variables) affect the dynamics
      * ie how does number of sexual partners affect sexually transmitted diseases?
        + effects of increased transmission between children during school terms
      * Helps in turn to develop more advanced predictive models
      * help decide which elements are important, which are negligible
    - Most models in book designed to increase understanding (although some are predictive)
* What Models Cannot Do
  + cannot build 100% accurate model
  + models are not prefect. there are always unknown or unknowable factors at play.
* What Is A Good Model?
  + model should be *suited to its purpose*
    - it should be as simple as possible, but no simpler
    - appropriate balance of accuracy, transparency, and flexibility
    - model built to understand = concentrate on characteristics that are of interest while simplifying all others
    - model built to predict = comprehensive picture of full dynamics, much more complex and inclusive
  + model should be *parameterizable from available data*
    - need to be able to parameterize all variables included in model
    - in some situations, this requirement may make a good predictive model impossible (if more data needs to be gathered, etc)
    - for models built to understand, this is less important (bc understanding is more general)
* Chapter 1 Overview:
  + looking at specifically directly transmitted microparasitic diseases
  + SEIR (or some subset of these) = common way to model
    - all categories relate to the ability of an individual to transmit a disease
    - S = susceptible, E= exposed, I = infectious, R = recovered
  + Important quantities concerning population-level epidemic dynamics:
    - timescale of infection (how long an individual is infectious)
      * measured by the infectious period for SIS and SIR infections
      * measured by a mixture of E & I for SEIR models
    - Ro = basic reproductive ratio
      * avg number of secondary cases resulting from a single primary case in a totally susceptible population
  + Models inform control methods for infectious disease
  + Models are defined by 3 dynamic elements:
    - **accuracy** (being as complex and all-encompassing as possible)
    - **transparency** (being understandable, being able to see how various model components interact & influence dynamics)
    - **flexibility** (able to be applied to different situations)
  + Models are used primarily either to predict or to understand
    - predict = high accuracy
    - understand = high transparency
  + Models are never perfectly accurate.
  + Good models should be:
    - suited to its purpose
      * right mix of accuracy, transparency, and flexibility
    - parameterizable from available data
      * need to be able to parameterize any component you wan to include in model
      * more important for predictive models than understanding models
* Formulating the Deterministic SIR Model
  + Basics:
    - Terminology:
      * Acute vs Chronic
        + Acute = “fast” diseases, rapid immune response removes pathogens after a short period of time (days or weeks)

ie influenza, rabies, chickenpox

* + - * + Chronic = last for longer periods of time (months or years)

ie chlamydia or herpes

* + - Important Parameters:
      * X, Y, Z = number of susceptible, infected, and recovered individuals, respectively
      * S,I,R = proportions
      * λ = strength of infection
      * β = product of contact rates and transmission probability (transmission rate)
      * N = total population size
      * κ = avg number of contacts per unit of time (for a susceptible individual)
    - For this model: look at acute diseases that, after recovery, lead to life-time immunity
    - For SIR model, we have two transitions:
      * S 🡪 I
        + disease transmission
        + determined by 3 factors:

prevalence of infecteds

underlying population contact structure

probability of transmission given contact

* + - * + Force of Infection, λ

Def: the per capita rate at which susceptible individuals contract the infection

therefore, rate at which new infecteds are produced is λX, where X is the number of individuals in class S.

(rate of S 🡪 I = λX, where X is # of S).

proportional to the number of infected individuals

Two ways to parameterize λ, depending on how we expect the contact structure to change with population size:

λ = βY/N (FREQUENCY DEPENDENT or mass-action transmission)

β = product of contact rates and transmission probability

Y = number of infected individuals

N = total population size

reflects a situation where the number of contacts is independent of the population size

considered appropriate for vector-borne pathogens and those with heterogeneous contact structure

λ = βY (DENSITY DEPENDENT or pseudo mass action transmission)

assumes that as the density of individuals (population size..ish) increases, so does the contact rate.

more applicable to plant and animal diseases

Distinction between these two is important when host population size varies (otherwise 1/N term can be absorbed in β in the mass-action term)

S = X/N , and I = Y/N 🡪 proportion of population that are susceptible or infectious

now, Mass-Action (Frequency Dependent): λ = βSI

informs about that rate at which new infectious individuals (as a proportion of the total pop size) are infected

* + - * I 🡪 R
        + happens once infected person fights off infection, stops being contagious
        + typically, time spent in I (the infectious period) is distributed around some mean value (can be parameterized)
        + so, probability of an individual’s transition from I 🡪 R occurring is dependent on how long they have been in the I class.
        + HOWEVER often modelers assume that recovery rate γ (inverse of infectious period) is constant (Makes things simpler)
  + THE SIR MODEL WITHOUT DEMOGRPAHY
    - SIR equations:
      * given:
        + assumption of closed population (no births/deaths/migrations)
        + transmission term = βSI
        + γ = recovery rate and 1/γ = average infectious period
      * dS/dt = -βSI
        + the change in the proportion of susceptible individuals over time
        + rate of S🡪I
      * dI/dt = βSI – γI
        + the change in the proportion of infected individuals over time
        + the rate S🡪I minus the rate of I🡪R
      * dR/dt = γI
        + the change in the proportion of recovered individuals over time
        + rate of I🡪R
      * Initial Conditions: S(0)>0, I(0)>0, R(0)=0
        + at time zero, there must exist some susceptible individuals, and some infected individuals, but no recovered individuals
    - The Threshold Phenomenon
      * Describes initial stages after infectious agent has been introduced
      * If S(0) < γ/β, then dI/dt < 0 and the infection will die out (fail to invade)
        + In other words, S(0) must be greater than γ/β in order for the infection to invade (this is the threshold phenomenon)
        + γ/β 🡪 the relative removal rate
      * Basic Reproductive Ratio Ro: β/γ
        + inverse of relative removal rate
        + definition: the average number of secondary cases arising from an average primary case in an entirely susceptible population
        + measures maximum reproductive potential for an infectious disease
        + Ro depends on both the disease and the host population. So Ro may vary b/w populations for the same disease
        + calculated by multiplying the rate at which new cases are produced by an infectious individual (β) by the average infectious period (1/γ)
      * Another way to write this: Assuming S(0)=1 (everyone is initially susceptible), the pathogen can only invade if Ro>1
        + logical: any disease that does not on average transmit to at least one new host cannot spread.
      * S(0) > 1/Ro in order to invade.
      * Vaccines can reduce the proportion of susceptibles to below 1/Ro, and therefore eradicate the disease.
      * If Ro Is sufficiently large ( approx. greater than 5), essentially everyone in a well-mixed population is likely to contract it
    - Epidemic Burnout
      * Describes the long-term (or “asymptotic”) state of the epidemic
      * The chain of transmission eventually breaks due to the decline in infectives, not do to a complete lack of susceptibles
        + this means there will always be some susceptibles in the population who escape infection
        + Comes from this equation (derives from the 3 SIR equations): S(t)=S(0)e-R(t)Ro

note that S always remains above zero, b/c e-R(t)Ro is always positive.

R(∞) = final proportion of recovered individuals = total proportion of population that gets infected, if it is assumed that the disease is never mortal.

* + - * Epidemic curve = number of new cases per time interval (approximate solution of the SIR model equations)
  + THE SIR MODEL WITH DEMOGRAPHY
    - Introducing demographics:
      * assume there is a natural host lifespan, 1/μ years
      * Rate of natural mortality = μ (NOT DISEASE MORTALITY)
      * assume that μ is also the population’s crude birth rate – therefore, population size is not changing. This won’t work for every population, but it is a simplifying assumption
      * assume all newborns enter the susceptible class
        + if avg age of infection is significantly small (near enough to 6 months), then maternally derived immunity needs to be included in model
    - Generalized SIR Model Equations:
      * dS/dt = μ - βSI - μS
      * dI/dt = βSI – γI – μI
      * dR/dt = γI – μR
      * Ro = β/(γ +μ)
        + note that γ+μ is the infectious period in this model
    - The Equilibrium State
      * inclusion of host demographic dynamics means that an infection may persist long term in a population w/o dying out.
      * Equilibrium occurs when dS/dt = dI/dt = dR/dt = 0
        + find equilibrium by setting each equation =0 and finding the values of the variables

call them S\*, I\*, and R\* for this condition

* + - * Disease-Free Equilibrium:
        + (S\*, I\*, R\*) = (1, 0, 0)
        + infection is extinct. long term, everyone in population is susceptible again.
      * Endemic Equilibrium:
        + the fraction of susceptibles in the population is the inverse of Ro­: S\*= 1/Ro

in other terms, S\*=(γ+μ)/β

(S\*, I\*, R\*) = (1/ Ro, (μ/β)(Ro – 1), 1-1/ Ro - (μ/β)(Ro – 1))

* + - * Stability Properties:
        + In the SIR model with births and deaths, the endemic equilibrium is stable if Ro >1
        + disease-free equilibrium is stable if Ro <= 1.
    - Oscillatory Dynamics
      * SIR System = damped oscillator
        + inherent dynamics contain a strong oscillatory component, but the amplitude of these fluctuations declines over time as the system equilibrates
        + this is the manner in which the stable equilibrium is eventually approached
      * The period of oscillations changes with the transmission rate (β) and the infectious period (1/γ)
        + the period of oscillations becomes longer as the reproductive ratio Ro approaches 1 🡪 slower convergence toward equilibrium
        + The period, T = 2pi(AG)1/2

A= mean age at infection (see next section)

G = 1/(μ+γ) 🡪 determines the typical period of a host’s infectivity

* + - Mean Age at Infection
      * A = mean age of infection
        + (if possible to contract disease multiple times, then we want mean age at first infection)
        + A = 1/(μ(Ro -1))
      * We measure A using age-specific serological data (🡪 presence of antibodies specific to the pathogen)
      * Ro -1 = L/A where L is the host’s life expectancy
      * THE MEAN AGE OF FIRST INFECTION IS EQUAL TO THE AVG LIFE EXPECTANCY OF AN INDIVIDUAL DIVIDED BY RO - 1
* Infection-Induced Morality and SI Models
  + Basics:
    - ρ = the per capita probability of dying from the infection
      * probability of an individual in the I class dying form the infection before either recovering or dying from natural causes
      * takes values from 0 to 1
    - Including ρ, we get this equation:
      * dI/dt = βSI – (γ+μ)/(1-ρ)\*I
    - Mortality rate of infection: m = ρ/(1-ρ) \* (γ + μ)
  + Mortality Throughout Infection
    - Basics:
      * disease-induced mortality could lead to an ever-declining population size
      * To get around this, include a fixed birth rate (v) into the susceptible equation, independent of population size
        + dS/dt = v – βSI – μS
      * since N can vary, need to consider the transmission term βSI in much more detail 🡪 choice between frequency dependent and density dependent really matters now
      * When mortality is very high, the infectious period is substantially reduced. This will also reduce Ro, unless transmission rate compensates by being higher
    - Density-Dependent Transmission (pseudo mass action)
      * This is the case where, as the total population size N decreases, due to disease-induced mortality, there is reduced interaction between hosts.
      * rate at which new cases are produced is βXY
      * v/μ = N (in absence of disease) 🡪 carrying capacity for the population
      * Equilibriums:
        + Disease-Free: (X\*, Y\*, Z\*) = (v/μ, 0, 0)
        + Endemic Equilibrium:

X\* = v/(μ\*Ro)

Y\* = (μ/β) \* (Ro -1)

Z\* = (γ/β) \* (Ro -1)

N\* = X\* [1+(1-ρ)(Ro-1)]

Note that Ro = [β(1-ρ)v] / [μ(μ+γ)]

includes a correction term (1-ρ) to take into account disease mortality (causes reduced period of infectivity)

includes μ/v to take into account population size at disease-free equilibrium

Note that Ro still must be >1 for endemic equilibrium to be possible

Approach to Equilibrium:

damped oscillations

period T = 2pi(AG)1/2

same as period for model w/o disease mortality, but A and G both will contain correction terms to account for disease mortality

EQUILIBRIUM AND STABILITY PROPERTIES SIMPLY REFLECT A CHANGE IN PARAMETERS WHEN DISEASE INDUCED MORTALITY IS ADDED TO A SIR MODEL W/ DENSITY DEPENDENT TRANSMISSION

* + - Frequency-Dependent Transmission (mass action)
      * mass action assumption means that even when the population size is reduced, each individual still has the same average number of contacts
      * When mortality is high, the frequency-dependent assumption leads to the largest drop in the total population size
        + this is bc density-dependent assumes that as population decreases, so does the contact rate, which limits disease spread
      * Overall, when disease-induced mortality is added to the SIR model with frequency-dependent transmission, the equilibrium and stability properties can change substantially, esp if the probability of mortality is high
    - Mortality Late in Infection
      * If mortality occurs late in infection, we want our model to reflect that. We don’t want to see infection period being reduced by mortality rates. Therefore, we choose the following model:
        + dS/dt = v – βSI – μS
        + dI/dt = βSI – (γ+μ)I
        + dR/dt = (1-ρ)γI-μR
      * For Frequency-Dependent Transmission:
        + change in population has no effect on the dynamics, so this model has same properties as the standard SIR model.
      * For Density Dependent Transmission:
        + the reduction in the recovered population will have an effect on the dynamics.
  + Fatal Infections: SI Model
    - SI model (remove recovered class bc all infected die of infection)
      * Frequency Dependent Transmission:
        + dX/dt = v – βXY/N – μX
        + dY/dt = βXY/N – (γ + μ)Y
        + (pretty much the same as mortality late in infection, but instead of recovering, you just die…. so γ becomes rate at which infected individuals die of infection).
      * Density Dependent Transmission:
        + dX/dt = v – βXY – μX
        + βXY – (γ + μ)Y
      * For both, endemic equilibrium is possible so long as Ro=β/(μ+γ)>1.
* Without Immunity: The SIS Model
  + SIS describes a situation where after infection, an individual gains no immunity and becomes susceptible again.
  + This is the basic Model:
    - dS/dt = γI – βIS
    - dI/dt = βIS – γI
    - In this model, demography has been ignored. Note that S+I=1.
  + Equilibrium:
    - Endemic equilibrium will be achieved if Ro=β/γ >1.
    - Convergence to equilibrium is not oscillatory, but rather monotonic in this case.
    - Long term persistence is pretty much guaranteed, as the pool of susceptibles is replenished by nature of the SIS model.
* Waning Immunity: The SIR Model
  + Basics:
    - assumption 🡪 immunity lasts for a limited period before waning such that the individual is once again susceptible.
    - Essentially SIRS model.
    - Three transistions:
      * S🡪I, I🡪R, R🡪S.
    - w = rate at which immunity is lost (rate of R🡪S)
      * when w=0, this is the same as the SIR model
      * when w=∞, we have the SIS model
  + Basic Model:
    - dS/dt = μ + wR – βSI – μS
      * note: why μ? Rate of natural mortality plus number of R🡪S transfers minus number of S🡪I transfers minus natural mortality…. but why start by adding μ?
        + answer: μ also represents crude birth rate. In a stable population, birth rate = natural mortality. Really, it’s new births plus R🡪S transfers minus S🡪I transfers minus natural mortalities.
    - dI/dt = βSI –γI – μI
    - dR/dt = γI – wR – μR
  + Equilibrium:
    - same deal for equilibrium. Ro = β/(γ+μ)> 1.
    - convergence to equilibrium = damped oscillations with a nasty equation for the period that I don’t want to type.
      * period in terms of Ro , A, and G.
      * when the period of immunity (1/w) is reduced 🡪
        + drop in period of damped oscillations
        + dramatic increase in the prevalence of infectious disease
* Adding A Latent Period: The SEIR Model
  + Basics:
    - \*Note that 1/σ = avg duration of latent period, E
    - Model Equations:
      * dS/dt = μ – (βI+μ)S
      * dE/dt = βSI –(μ+σ)E
      * dI/dt = σE – (μ + γ)I
      * dR/dt = γI – μR
    - Note that if σ 🡪 ∞, we have the SIR model.
  + Equilibrium:
    - Disease Free Equilibrium: (1,0,0,0)
    - Endemic Equilibrium:
      * S\* = 1/Ro
      * E\* = μ(μ+γ)/(βσ) \* (Ro-1)
      * I\* = μ/β \* (Ro -1)
      * and R\* = 1 – (S\* + E\* +I\*)
    - SEIR and SIR will behave similarly at equilibrium (when parameters are suitably rescaled)
      * given small death rate
      * so long as Ro  is identical for both models and so long as average infected period is identical for both models
    - SEIR model has a slower growth rate after pathogen invasion
      * due to individuals passing through E phase, which acts as a sort of time delay
* Infections With A Carrier State
  + Basics:
    - S🡪I, but I either goes to R or C.
    - ε = reduced transmission rate from chronic carriers compared to acute infectious individuals
    - q = proportion of acute infections that become carriers (I🡪C)
      * (1-q) = proportion of acute infections that become recovered (I🡪R)
    - Γ = rate at which individuals leave the carrier class (C🡪R)
  + Model Equations:
    - dS/dt = μ – (βI + εβC)S –μS
    - dI/dT = (βI + εβC)S – γI – μI
    - dC/dt = γqI – ΓC – μC
    - dR/dt = γ(1-q)I + ΓC –μR
  + Ro:
    - Ro = β/(γ+μ) + (qγ)/(γ+μ) \* (εβ)/(Γ+μ)
      * (qγ)/(γ+μ) 🡪 accounts for I🡪C individuals
    - Ro is the sum of separate components from the acutely infected and chronic carriers.
  + Equilibrium:
    - Endemic Equilibrium
      * S\* = 1/Ro
      * I\* = μ(1-S\*)/(γ+μ)
      * C\* = γqμ(1-S\*) / [(γ+μ)( Γ+μ)]
    - As q (fraction of infected individuals that become carriers) increases, the number of carriers at equilibrium increases linearly. Often, carriers far outnumber infecteds at equilibrium.
* Discrete Time Models
  + Basics:
    - instead of differential equations, use a discrete time model
    - only works if the latent and infectious periods are relatively constant
    - model based on time increments, in this example, the time increments are exactly one week, which is equal to both the latent and infectious periods
    - We are interested in determining the future changes in the fraction of individuals who are susceptible (St), exposed (Et) or infectious (It) in week t.
  + Model Equations:
    - St+1 = μ – St e-βIt
    - Et+1 = St(1 - e-βIt)
    - It+1 = Et
    - μ = weekly per capita births
  + Differences from Continuous-Time Models
    - exponential term is the per capita probability of not contracting the infection given It infectives with transmission rate β
    - assumes that transmission probability per susceptible follows a Poisson distribution with mean βIt.
    - β is analogous to Ro
    - In order for infection to invade, β>1
    - these models are less stable
    - Endemic equilibria are weakly stable, with perturbations decaying over long periods
* Parameterization
  + Basics:
    - SIR Model Parameters:
      * Birth Rate (v)
      * Natural Death Rate (μ)
      * average infectious period (1/γ)
      * Transmission Rate (β)
        + generally derived from an estimation of Ro
      * Not always enough information to calculate each parameter based on robust statistical inference
        + often use other relevant info to assist us
  + Estimating Ro from Reported Cases
    - difficult due to typically low reporting (only about 60% - not enough)
    - can use the exponential model that predicts the early growth of an epidemic
      * Issues:
        + only works for epidemics, doesn’t give info on endemics
        + in early stages, highly stochastic dynamics will lead to large fluctuations in parameters (including Ro calculations)
        + unlikely that there are no immune individuals in entire population unless disease is entirely new
      * Can get around the last issue by fitting to the entire epidemic, and finding which values of Ro, S(0), and case identification probability lead to a model epidemic that most closely matches recorded profile of cases
      * Usually, we know how many NEW cases are reported in a given time frame, but not the total number of infecteds at a given time
        + so instead of using Y(t), we can introduce K(t), the number of new cases reported at time point T
        + K(t) = the integral from T-1 to T (γI dt)
    - Can use the average age of infection (A = 1/[μ(Ro – 1)]
      * this approximation is most reliable when Ro is large
      * however, may not have the age of patients
      * susceptible to age-related reporting bias.
  + Estimating Ro from Seroprevelance Data
    - Look at presence of antigens to distinguish between people who have not been exposed (S) and those who have (R or I)
    - Pros and Cons:
      * Pros: researcher has full control over sampling of data
      * Cons: data pool will be smaller
    - How to Do it:
      * Use S=1/Ro
        + issues: level of seroprevelance (proportion of exposed individuals) is expected to increase with age
        + need to work in the age-dependent nature of the likelihood of being susceptible

use P(a) = exp(-aμ(Ro -1)

P(a) is the probability that an individual of age “a” is still susceptible

using ages of our sample, we can construct the likelihood that the data comes froma disease with a particular Ro value, and then choose the Ro that maximizes this likelihood

* + - * + Should try to sample individuals with an age close to the estimated average age of infection
  + Estimating Parameters in General
    - For missing parameters, a maximum likelihood approach is often best
      * 1) determine the dynamics predicted by the model
      * 2) calculate likelihood that the observed data came from such dynamics
      * 3) find a set of parameters that maximize likelihood
    - This approach can also allow us to compare & select entire models
* Chapter 2 Overview
  + The Deterministic SIR Model
    - Basics:
      * assumes homogeneous mixing
      * Looks at acute diseases that lead to life-time immunity after recovery
  + Important Parameters:
    - X, Y, Z = number of susceptible, infected, and recovered individuals, respectively
    - S,I,R = proportions
      * S=X/N, I=Y/N, R=Z/N, etc. where N=population size.
    - λ = strength of infection
    - β = product of contact rates and transmission probability
      * rate at which new cases are produced by an infectious individual (when entire population is susceptible)
      * transmission rate
    - N = total population size
    - κ = avg number of contacts per unit of time (for a susceptible individual)
    - γ =recovery rate….. 1/γ=average infectious period
    - μ = rate of natural mortality (not disease-related)… 1/μ = natural host lifespan
    - A = mean age of infection (or avg age of first infection, in SIS or SIRS models)
    - G = average time spent in a given class
      * no subscript = time spent in infectious class
      * GR is time spent in recovered class, etc.
    - ρ = the per capita probability of dying from the infection
    - v = fixed birth rate (independent of population size)
    - w = the rate of transition between R and S in waning immunity models…..1/w = period of immunity
    - 1/σ = average duration of the latent period, E
    - ε = reduced transmission rate from chronic carriers compared to acute infectious individuals (for models with carriers)
    - q = proportion of infected individuals that become carriers (I🡪C)
      * (1-q) = proportion of acute infections that become recovered (I🡪R)
    - Γ = rate at which individuals leave the carrier class (C🡪R)…. 1/Γ = avg ßduration of carrier phase
  + Two transitions
    - S🡪I
      * λ: The force of infection
        + the per-capita probability of acquiring infection (in other words, the transmission rate per susceptible individual)
        + λ=βY/N
        + Transmission rate of the entire susceptible population:

-λX = -βXY/N

* + - * + Transmission rate of entire population (ie rate at which susceptible individuals, as a proportion of total population size, are infected)

dS/dt = -βIS

* + - * Transmission Term:
        + For frequency dependence: βXY/N (of βSI)

looks at proportion of infected individuals

* + - * + For density dependence: βXY

looks at number of infected individuals.

* + - * + Difference between frequency and density dependent transmission become important if the population size changes or we are trying to parameterize disease models across population sizes.
    - I🡪R
    - Threshold Phenomenon:
      * for an infectious disease with an average infectious period 1/γ and a transmission rate β, its basic reproductive ratio Ro is given by β/γ.
      * In a closed population, an infectious disease with a specified Ro can invade only if there is a threshold fraction of susceptibles greater than 1/Ro
        + in other words, S(0)>1/Ro in order to invade.
        + other ways to write this: S(0) > γ/β to invade
      * Vaccination can be used to reduce the proportion of susceptibles below 1/Ro and hence eradicate the disease
    - Epidemic Burnout
      * Describes the long-term (or “asymptotic”) state of the epidemic
      * The chain of transmission eventually breaks due to the decline in infectives, not do to a complete lack of susceptibles
        + this means there will always be some susceptibles in the population who escape infection
        + Comes from this equation (derives from the 3 SIR equations): S(t)=S(0)e-R(t)Ro

note that S always remains above zero, b/c e-R(t)Ro is always positive.

R(∞) = final proportion of recovered individuals = total proportion of population that gets infected, if it is assumed that the disease is never mortal.

* + - * Epidemic curve = number of new cases per time interval (approximate solution of the SIR model equations)
* Looked at multiple model types:
  + SIR
  + SI
  + SIS
  + SIRS (waning immunity)
  + SEIR
  + SIRC (carrier diseases)
* For each model:
  + looked at a set of differential equations that defined the rates of change over time of the proportion of each class of individual
    - defined by a transmission term, which defined the rate at which susceptible individuals were infected
    - defined by an Ro, which defines the average number of secondary cases that arise from a single primary case
  + looked at the equilibrium dynamics. Ro must be greater than 1 for an epidemic to spread. If that happens, the equilibrium will be endemic. If not, it will be disease-free.
    - most of the model types converged on equilibrium in a damped oscillation, so they oscillated over a center and over time the magnitude of the oscillations decreased to zero.