Models for Understanding and Controlling Global Infectious Diseases HUMBIO 154D / HRP 204

Session 3

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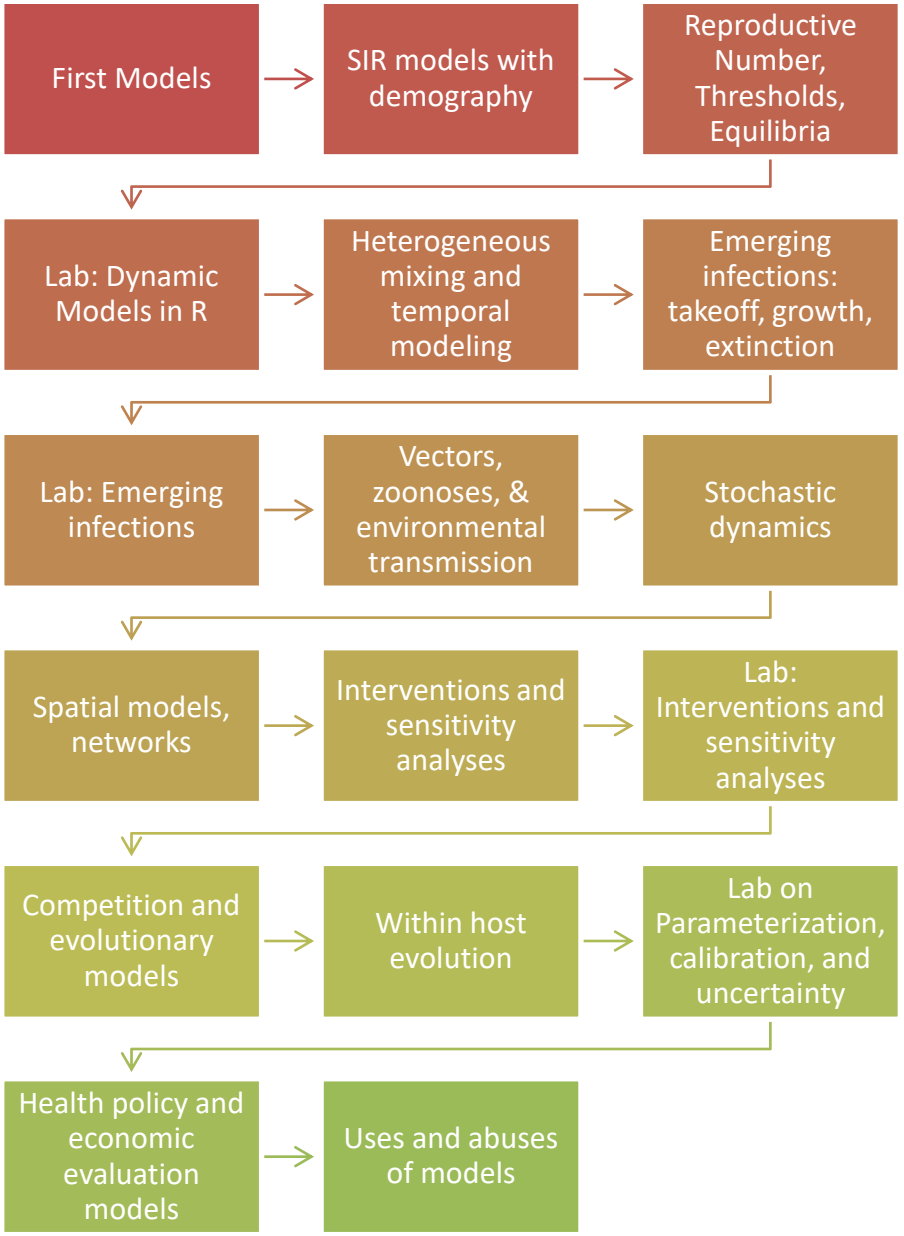
2020

5-10 MINUTES OF LECTURE 2 RECAP: JASON ANDREWS

Course Roadmap



Practical Questions

How do we describe the long-term dynamics of infectious diseases?

Under what conditions will an infectious disease become and remain endemic in a population?

Do declines in an infectious disease's prevalence over relatively long time periods necessarily mean that it is dying out in that population?

Learning Objectives

- Define relevant demographic features for SIR models
- Compare implications for R0 and equilibrium properties for SIR models with and without demography
- Consider endemic equilibria and how SIR models predict that prevalence of infections will move towards those equilibria from various initial conditions. For oscillatory equilibria consider drivers of the periods of oscillation
- Evaluate how average age of infection can be computed from data and from models
- Compare and contrast related models: SIR models with demography and excess mortality, chronic infection models, models with no or waning immunity

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Motivating Example

The New York Times

Opinion

Who Is Immune to the Coronavirus?

About this question, too, decisions with great consequences are being made, as they must be, based on only glimmers of data.

By Marc Lipsitch
Mr. Lipsitch is an epidemiologist and infectious disease specialist.

April 13, 2020

Santi Palacios/Associated Press

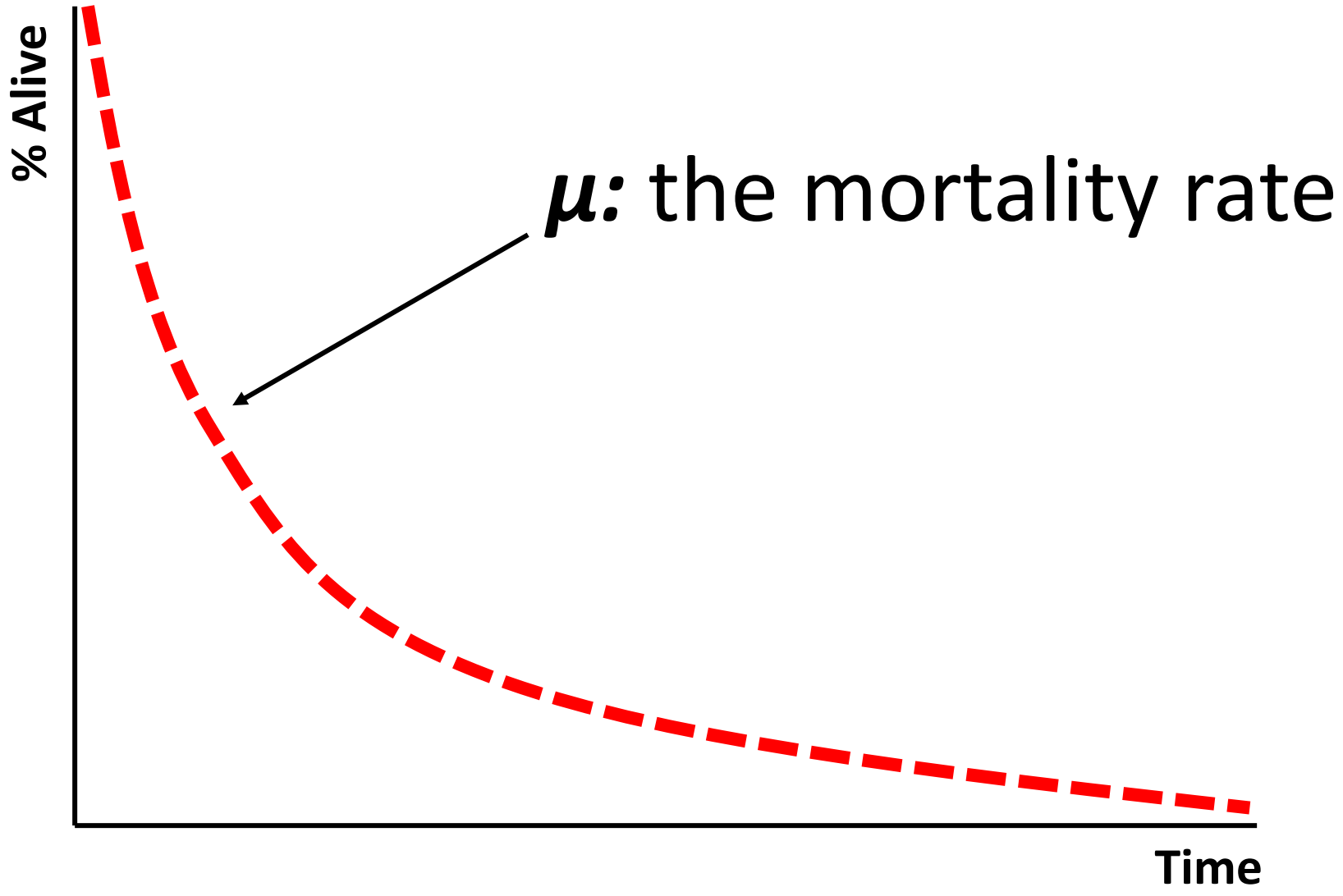
Among the many uncertainties that remain about Covid-19 is how the human immune system responds to infection and what that means for the spread of the disease. Immunity after any infection can range from lifelong and complete to nearly nonexistent. So far, however, only the first glimmers of data are available about immunity to SARS-CoV-2, the coronavirus that causes Covid-19.

What is Demography?

Demography is the study of human populations in terms of their size and structure and how processes of birth, death, migration, and aging unfold within them

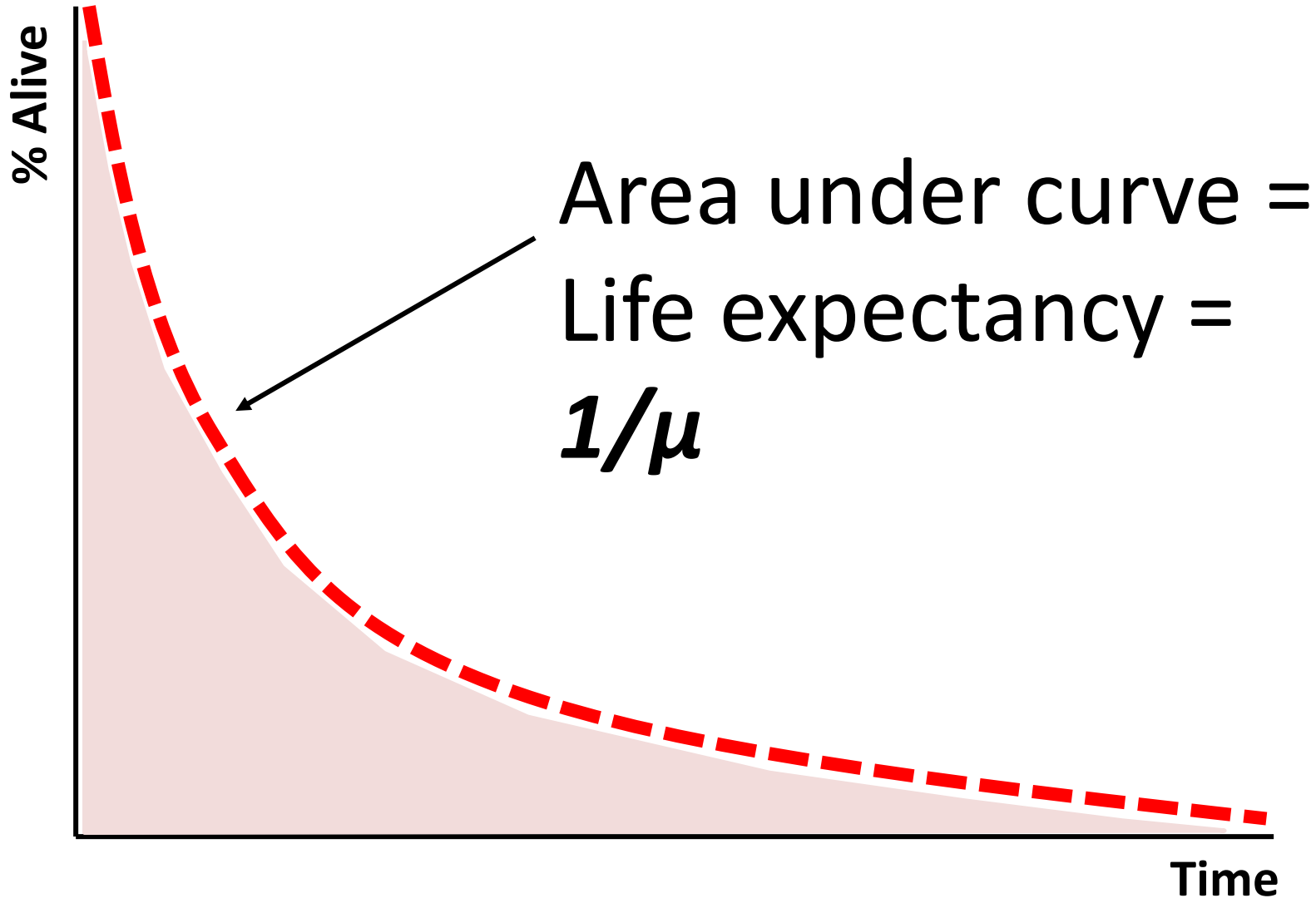
For our purposes today, we are specifically going to focus on birth and death in the human populations our infectious disease models typically focus on

Survival Curves



μ: the mortality rate

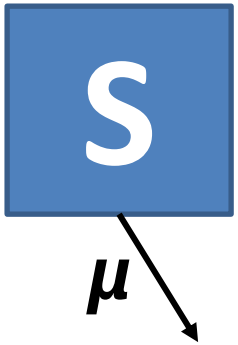
Survival Curves

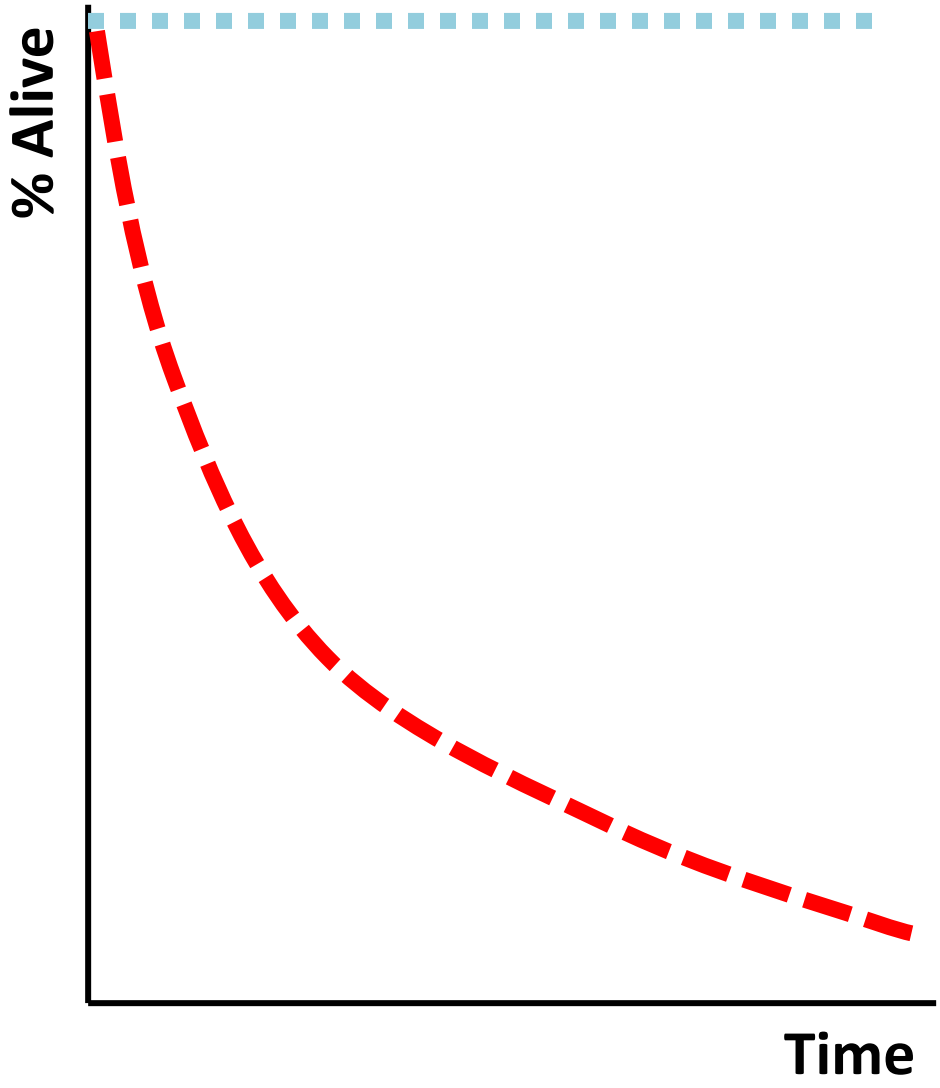


Mortality in a Simple Model

World's Simplest Model

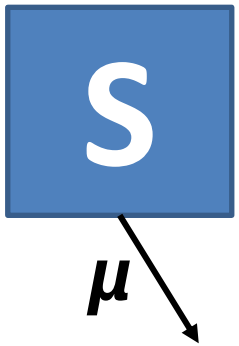
World's Simplest Model with Mortality



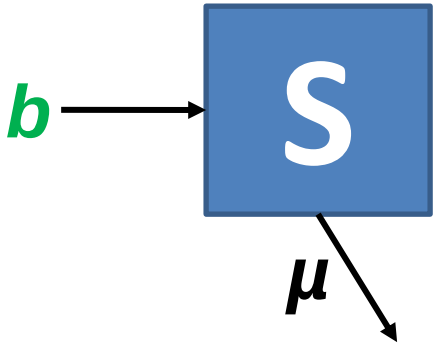


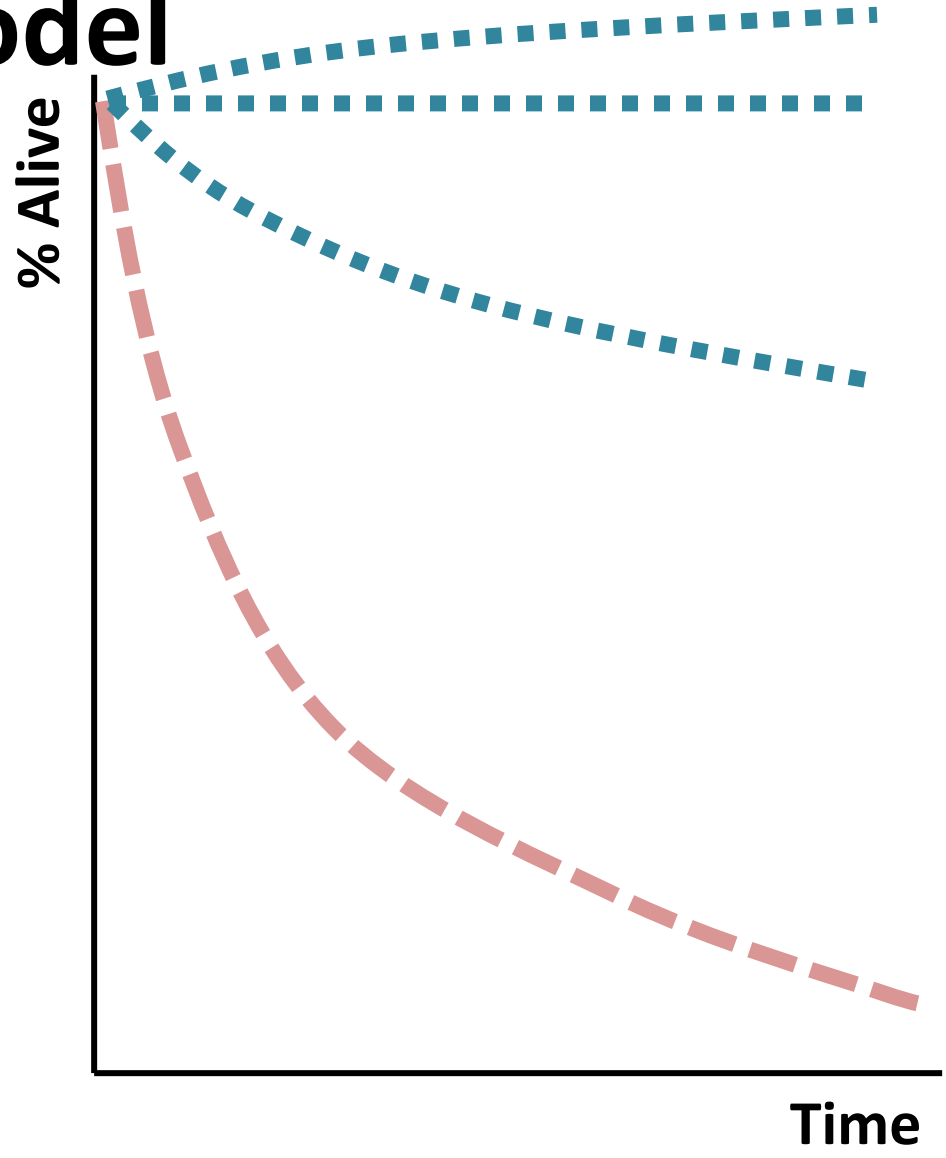
Mortality and *Birth* in a Simple Model

World's Simplest Model with Mortality



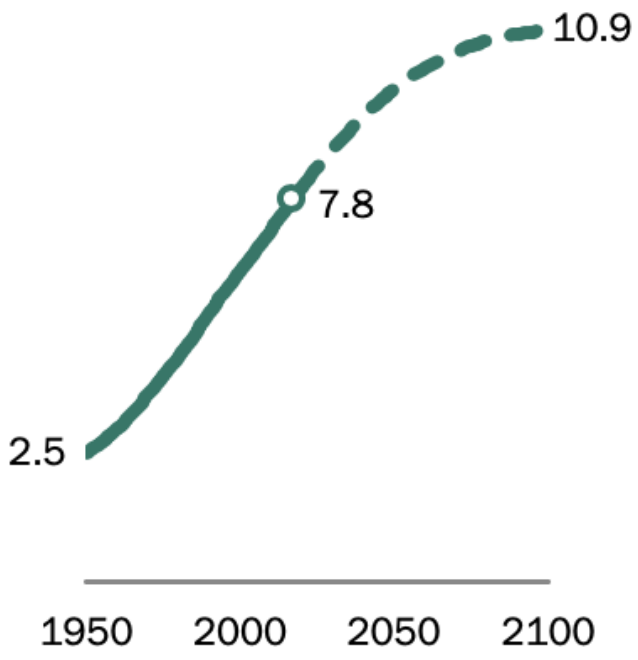
World's Simplest Model with Mortality and Birth





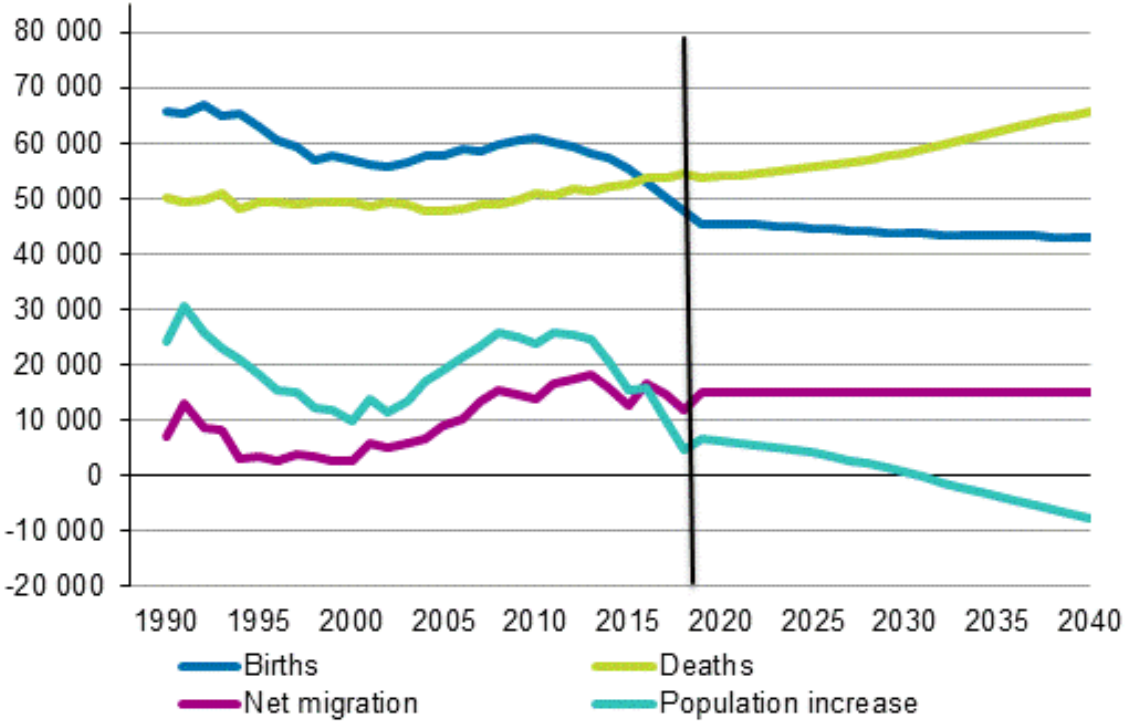
World population growth is projected to flatten in coming decades

World population, in billions

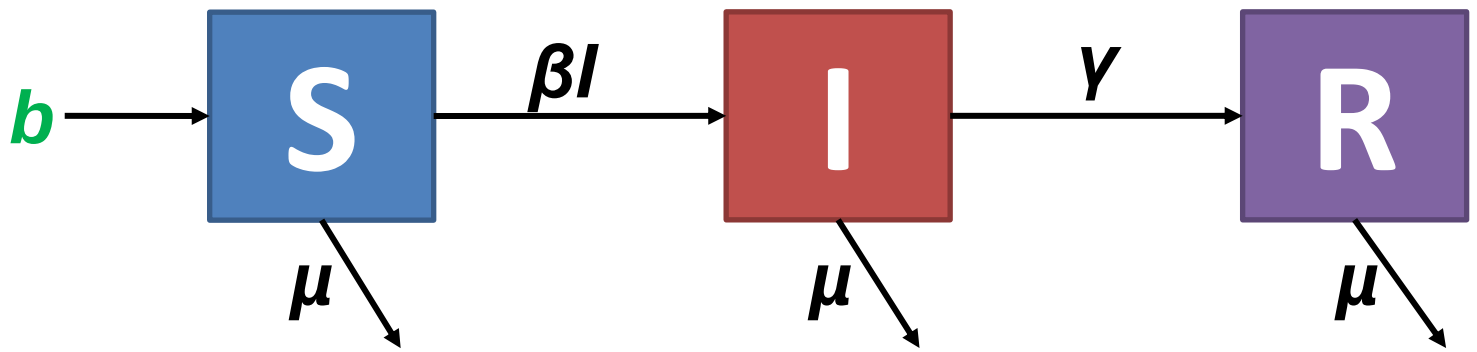


Note: Data labels shown for 1950, 2020 and 2100.
Source: United Nations Department of Economic and Social Affairs, Population Division, "World Population Prospects 2019."

But not everywhere … Finland



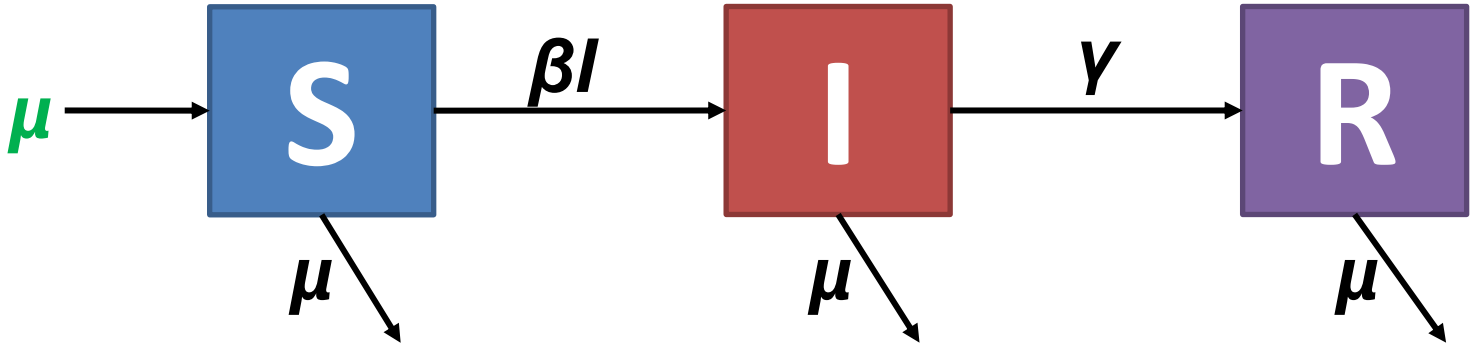
Mortality and *Birth* in SIR Models



Basic, Typical Assumptions:

1) Mortality is the same for all states (not yet incorporating infection-caused excess mortality)
2) Birth equals death (**b = *μ***) => Population size stable

Mortality and *Birth* in SIR Models: Equations

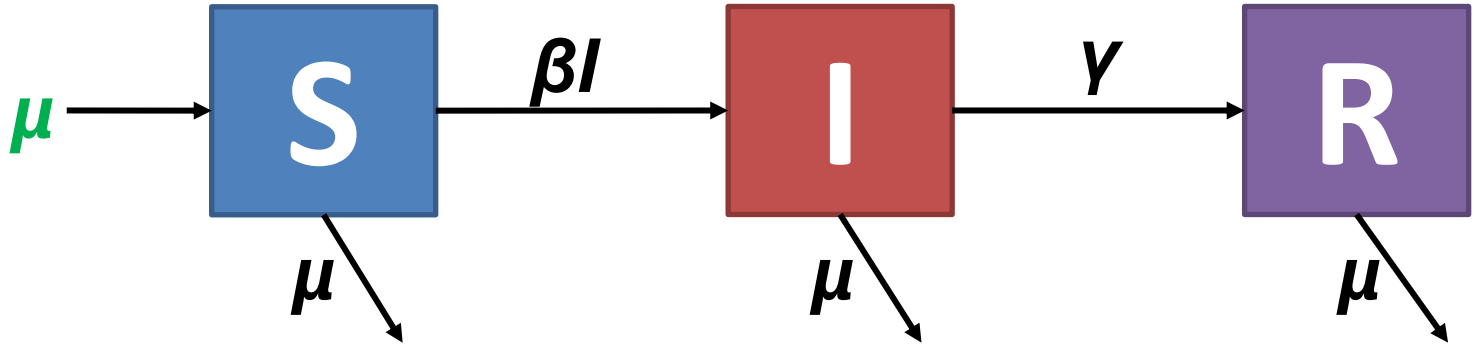


$$\frac{dS}{dt} = \mu - \beta IS - \mu S$$

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

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

R0 in an SIR model with demography: Requirements for "take off"



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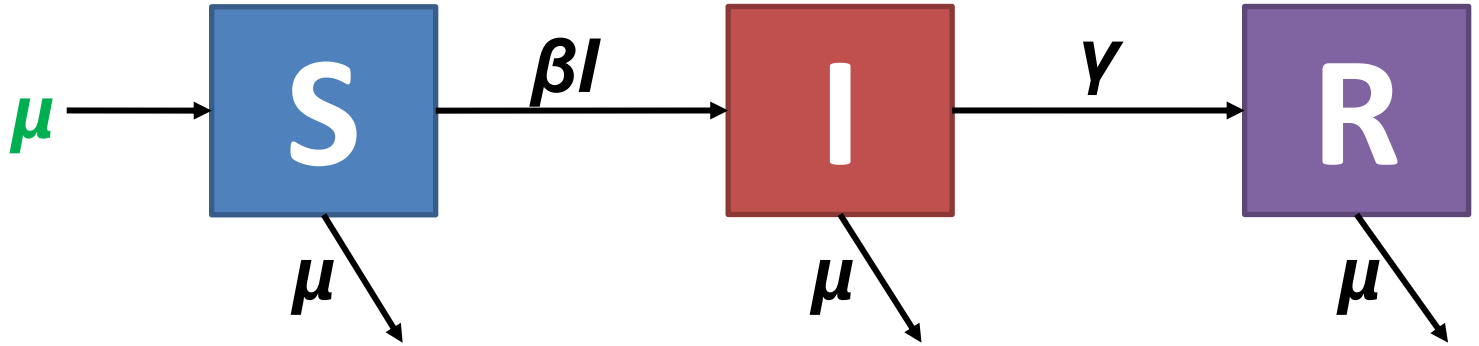
To determine the Basic Reproductive Number (R0), we first focus on a related concept, the threshold (minimum) fraction of Susceptibles required for infection to "take off"

R0 in an SIR model with demography: Requirements for "take off"



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

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Infections "taking off"/invading =>

$$0 \leq \frac{dI}{dt} \Rightarrow 0 \leq \beta IS - \gamma I - \mu I$$

$$\frac{\gamma + \mu}{\beta} \leq S$$

R0 in an SIR model with demography: Requirements for "take off"

With demography

Infections "taking off" =>

$$0 \leq \frac{dI}{dt} \Rightarrow 0 \leq \beta IS - \gamma I - \mu I$$

$$\frac{\boldsymbol{\gamma + \mu}}{\boldsymbol{\beta}} \leq \boldsymbol{S}$$

Without demography

Infections "taking off" =>

$$0 \leq \frac{dI}{dt} \Rightarrow 0 \leq \beta IS - \gamma I$$

$$\frac{\boldsymbol{\gamma}}{\boldsymbol{\beta}} \leq \boldsymbol{S}$$

The number of Susceptibles required is larger for infections to take off w/ demography than w/o demography. Why?

R0 in an SIR model with demography: Requirements for “take off”

With demography

Typical period of infectiousness

$$\frac{1}{\gamma + \mu}$$

Without demography

Typical period of infectiousness

$$\frac{1}{\gamma}$$

Infectious individual are infectious for shorter periods of time (like Life Expectancy but with competing risks). People stop being infectious when they recover OR die

R0 in an SIR model with demography

With demography

R0 is the inverse of the susceptible fraction =>

$$R_0 = \frac{\beta}{\gamma + \mu}$$

Without demography

R0 is the inverse of the susceptible fraction =>

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

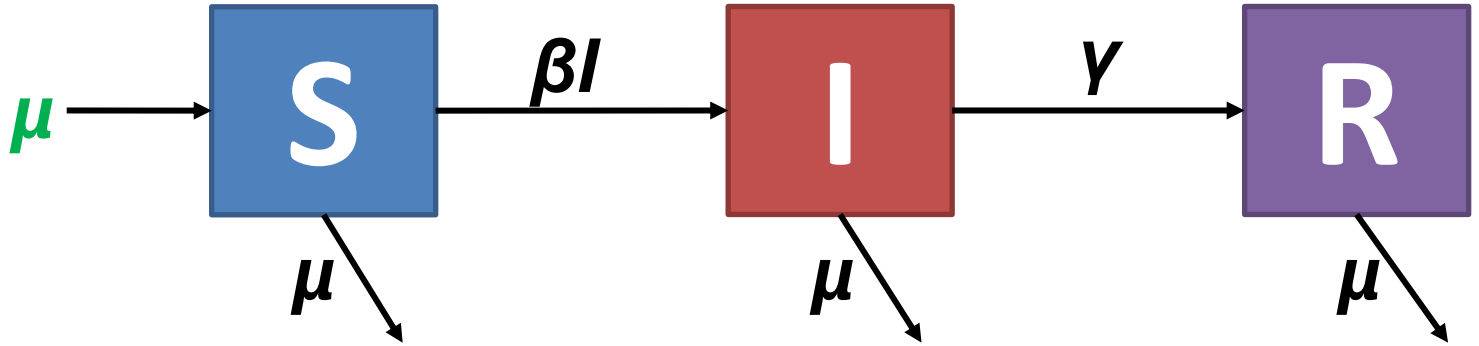
$$R_{0,demography} \leq R_{0,no\_demography}$$

Equilibria and Endemicity

- Equilibrium: Within a population, an infectious disease is in equilibrium when its level remains constant over time

- Endemic: Within a population, an infectious disease is endemic when it is maintained at a non-zero level

SIR model with demography: Equilibria



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

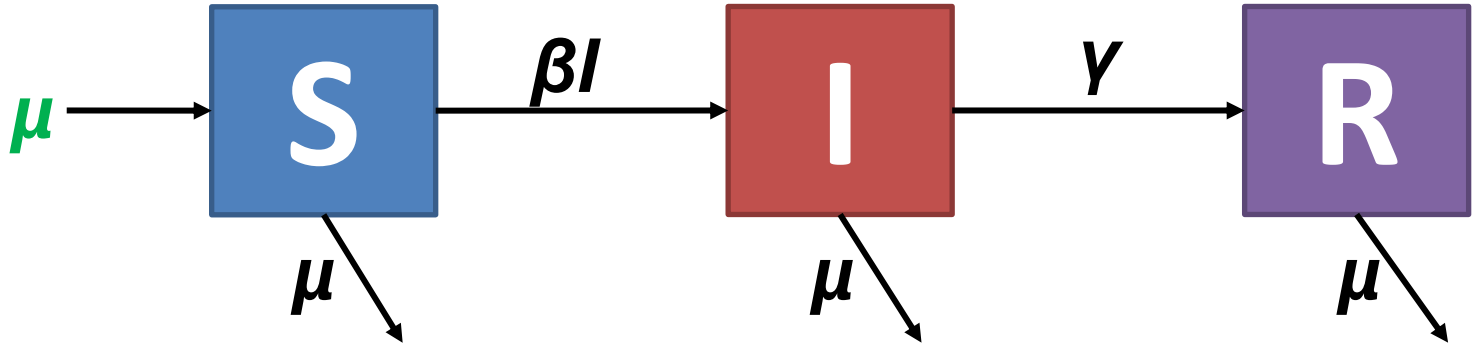
$$\frac{dI}{dt} = \beta IS - \gamma I - \mu I$$

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

(S^*, I^*, R^*), such that:

$\frac{dS}{dt} = 0$, $\frac{dI}{dt} = 0$, and $\frac{dR}{dt} = 0$

SIR model with demography: Disease- Free Equilibrium



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(S^*, I^*, R^*), such that:

$\frac{dS}{dt} = 0$, $\frac{dI}{dt} = 0$, and $\frac{dR}{dt} = 0$

$$(S^*, I^*, R^*) = (1, 0, 0)$$

SIR model with demography: Endemic Equilibrium

(S^*, I^*, R^*), such that:

$$\frac{dS}{dt} = 0, \frac{dI}{dt} = 0, \text{ and } \frac{dR}{dt} = 0 \text{ AND } I^* > 0$$

$$\frac{dI}{dt} = \beta IS - \gamma I - \mu I = 0$$

$$I^*(\beta S^* - \gamma - \mu) = 0$$

$$\boldsymbol{S^* = \frac{1}{R_0}}$$

The larger R_0, the smaller the fraction of Susceptibles in endemic equilibrium (but there will always be some)

SIR model with demography: Endemic Equilibrium

(S^*, I^*, R^*), such that:

$\frac{dS}{dt} = 0$, $\frac{dI}{dt} = 0$, and $\frac{dR}{dt} = 0$ AND $I^* > 0$

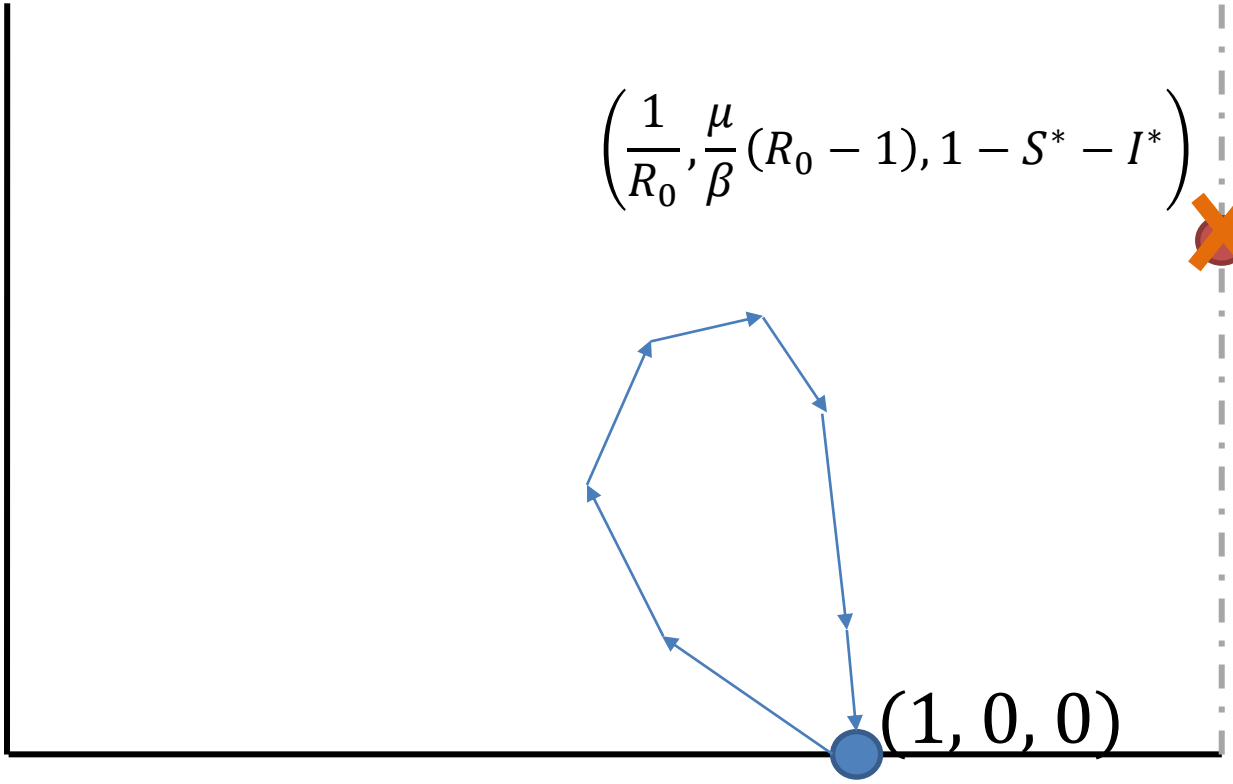
$$\frac{dS}{dt} = \mu - \beta IS - \mu S = 0$$

$$\mu - \beta I^* \frac{1}{R_0} - \mu \frac{1}{R_0} = 0$$

$$\boldsymbol{I^* = \frac{\mu}{\beta}(R_0 - 1)}$$

$R_0 > 1$ for endemic equilibrium because Infection must sustain itself

SIR model with demography: Equilibria and Stability



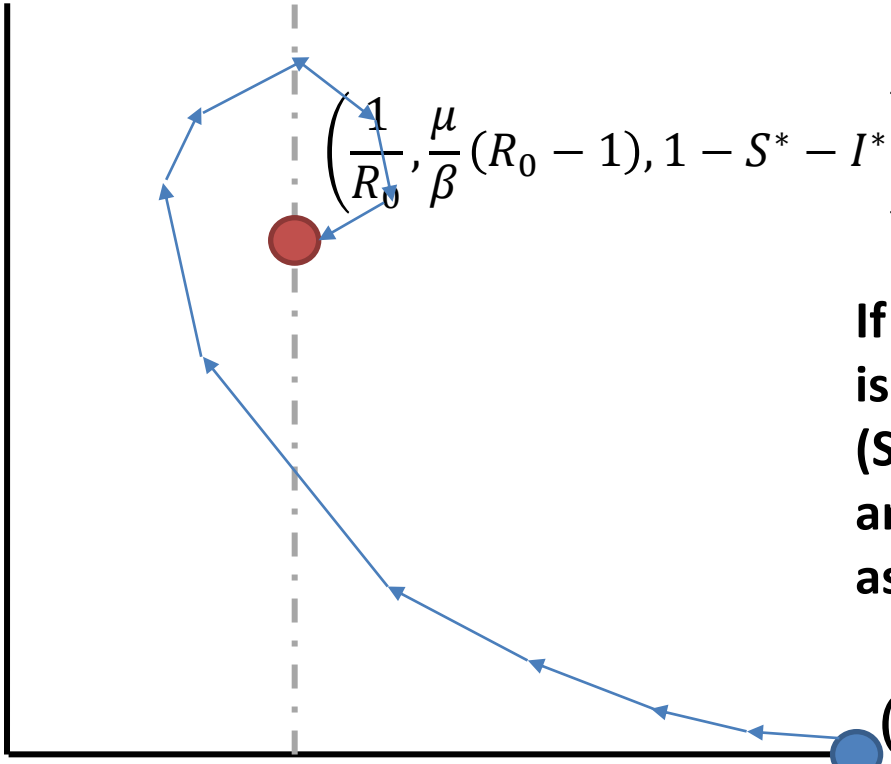
I Prevalence

$R_0 < 1$, Endemic equilibrium is not feasible

$S = \frac{1}{R_0}$

S Prevalence

SIR model with demography: Equilibria and Stability



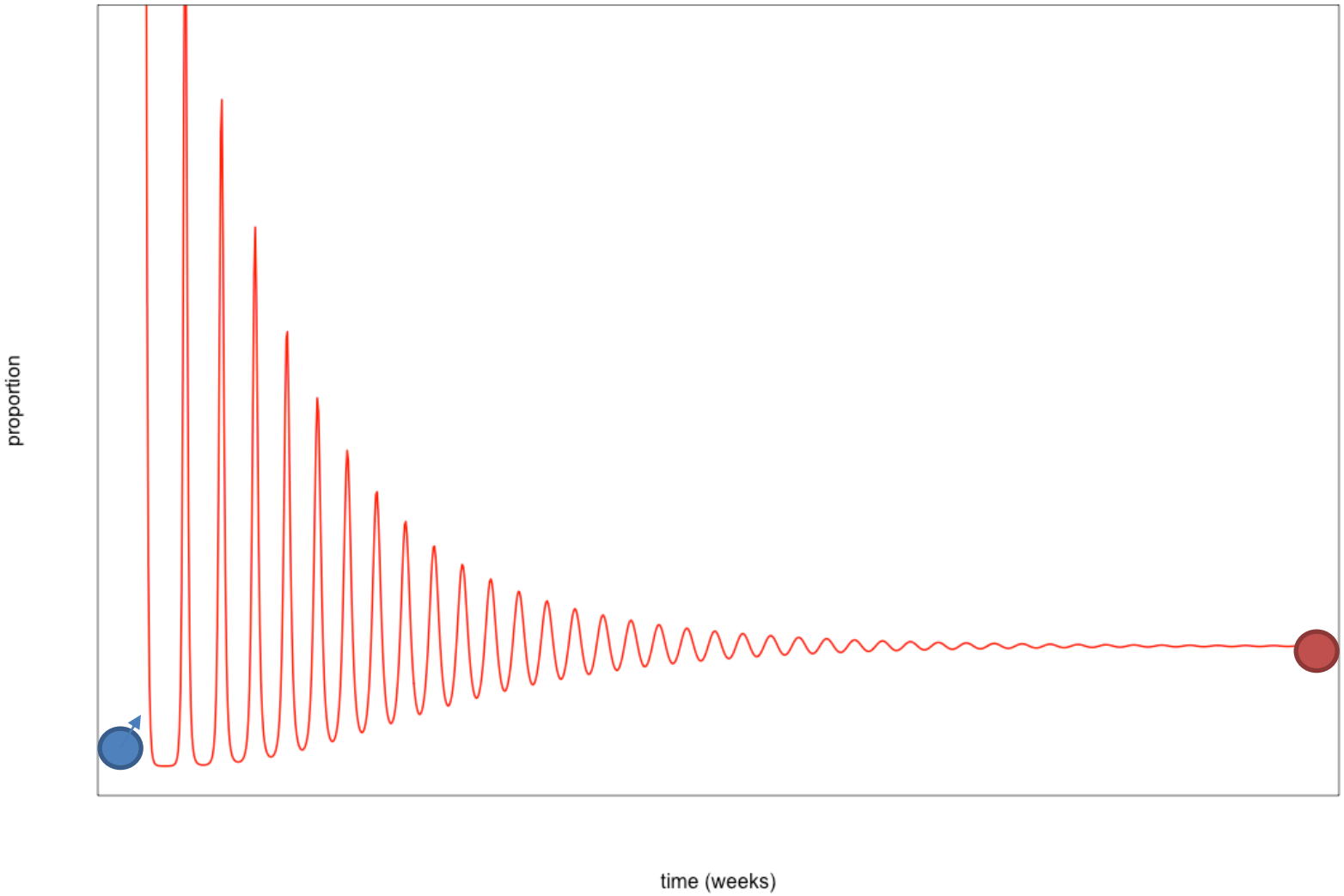
I Prevalence

$S = \frac{1}{R_0}$

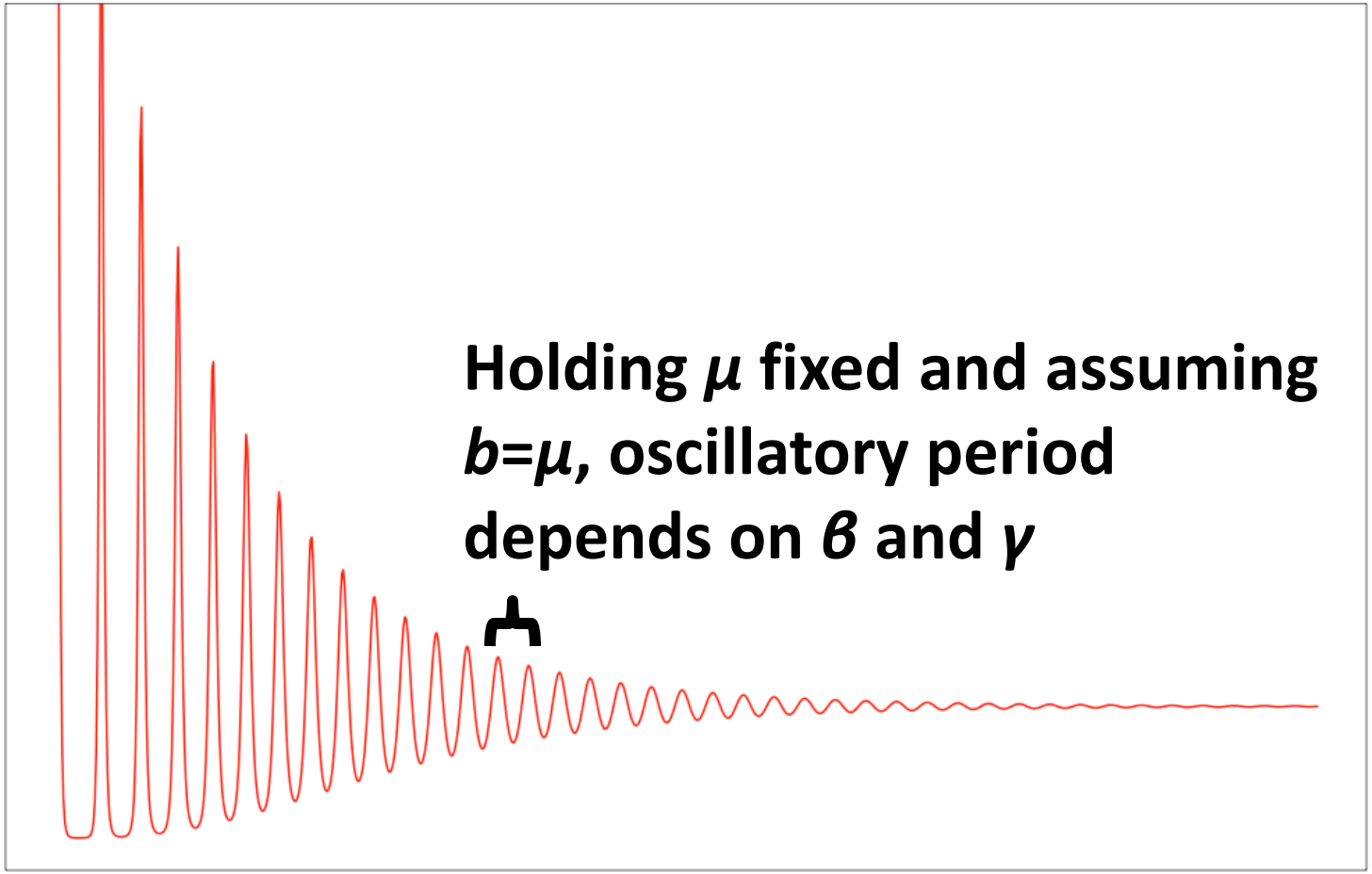
S Prevalence

If R_0 is 1+, Endemic equilibrium is feasible and stable
(See Box 2.4 for formal Jacobian and Eigenvalue approach to assessing stability)

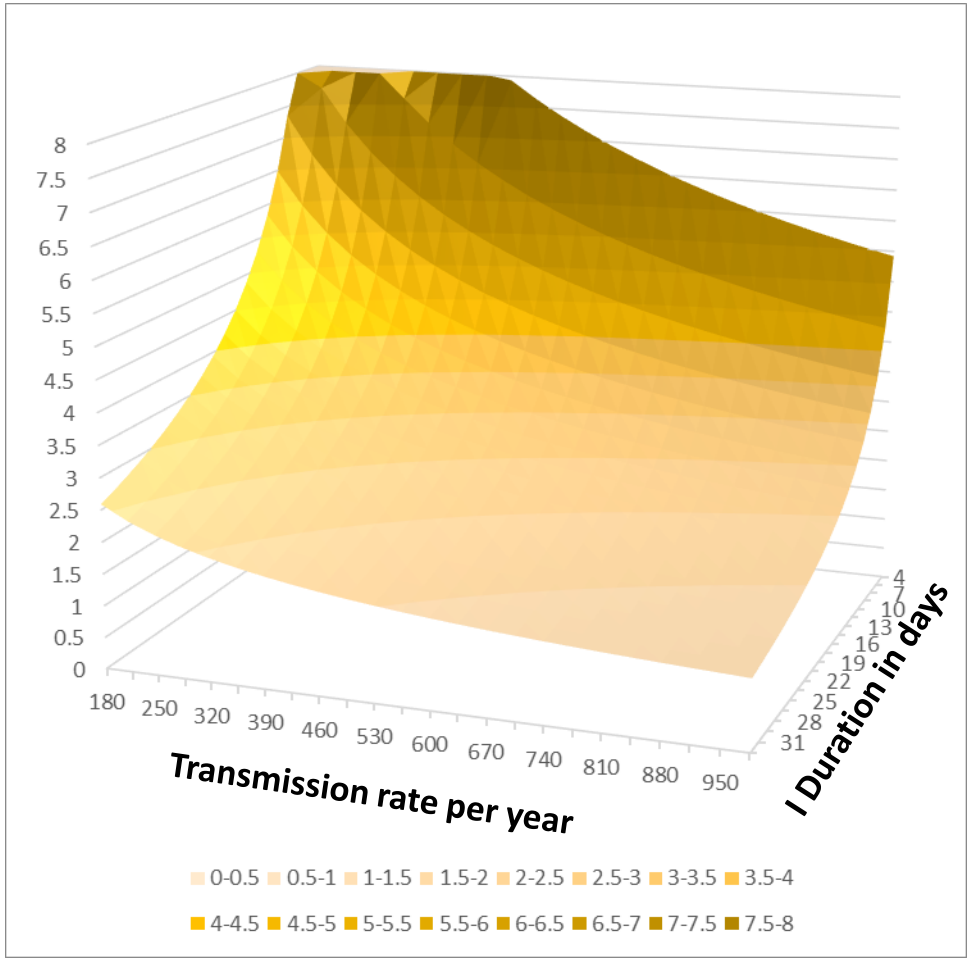
SIR model with demography: Damped Oscillatory Dynamics



SIR model with demography: Period of Oscillation



SIR model with demography: Period of Oscillation



$1/\mu$ = 70 years

Long oscillatory periods (T) with shorter duration of infectiousness and lower transmission rates

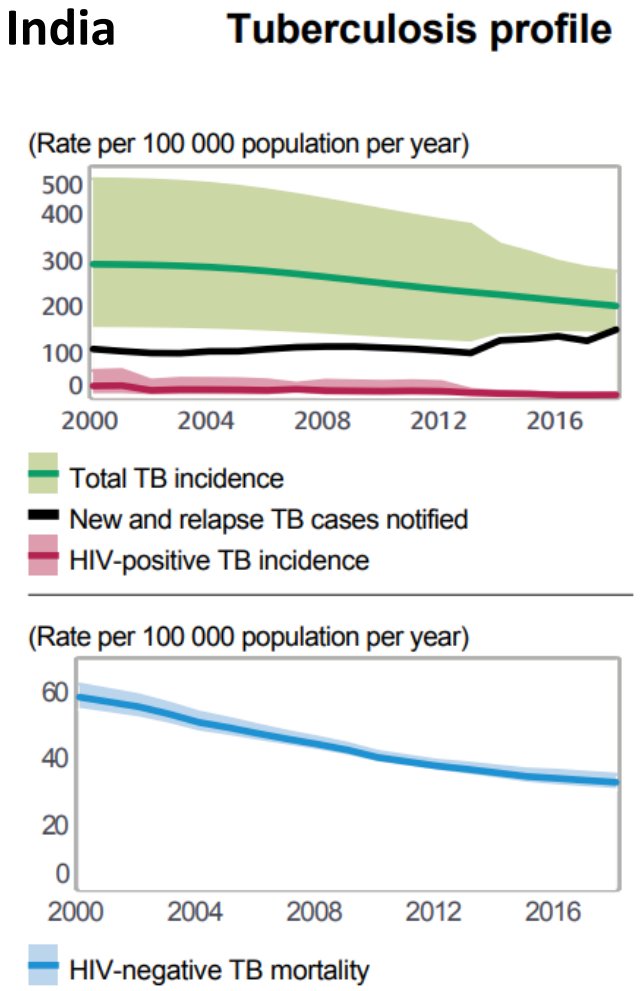
$$T \approx 2\pi\sqrt{AG}$$

A=Average Age of Infection

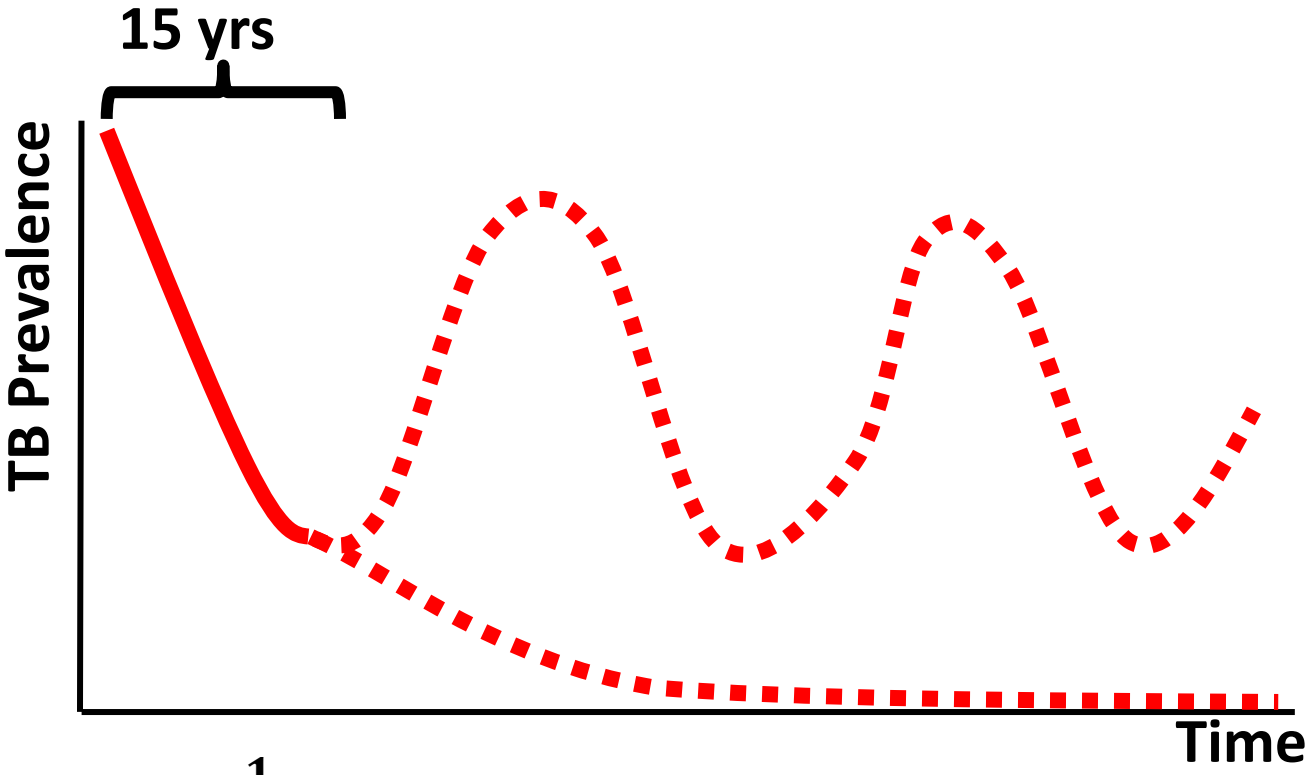
G=Duration of infectiousness

Tuberculosis

- TB is caused by *Mycobacterium tuberculosis*
- It affects the lungs (and other parts of the body less commonly).
- Active untreated TB infections lead to fever, cough, night sweats, and blood in sputum. They have a ~75% case fatality rate.
- TB infection is spread through the air via cough, breathing, and spitting.



Is Tuberculosis on its way to elimination in India?



$$\mu = \frac{1}{60yrs}; R_0 \approx 3.5; Duration\ of\ Infectiousness = 1yr$$

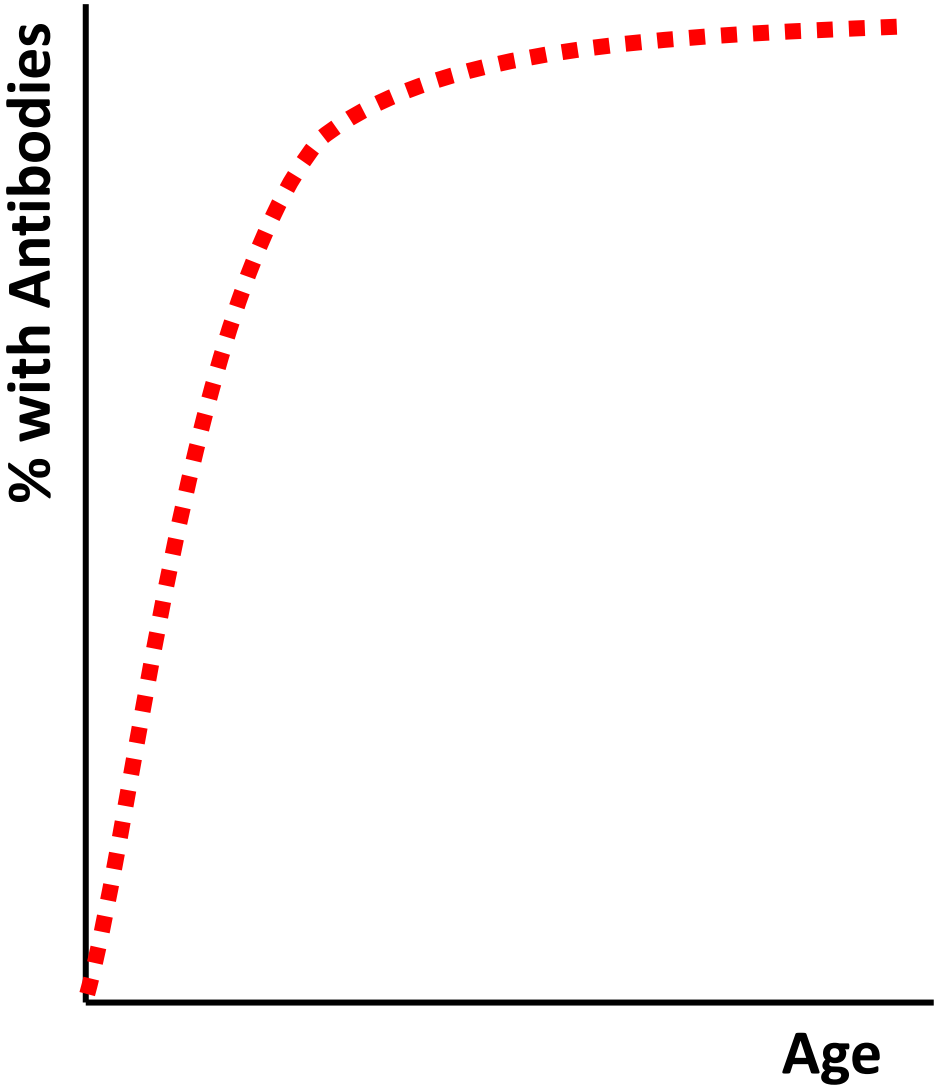
$$A \approx \frac{1}{\mu(R_0 - 1)} \Rightarrow \frac{60yrs}{(3.5 - 1)} = 24yrs$$

$$T \approx 2\pi\sqrt{24 * 1} \approx 30yrs$$

SIR model with demography:
Average Age of Infection

Seroprevalence survey:
Random sample of population to determine % of population in each age group that has antibodies to a particular pathogen (those that are Recovered and immune)

We can determine the average age of infection from the curve by summing the fraction without antibodies for each age.

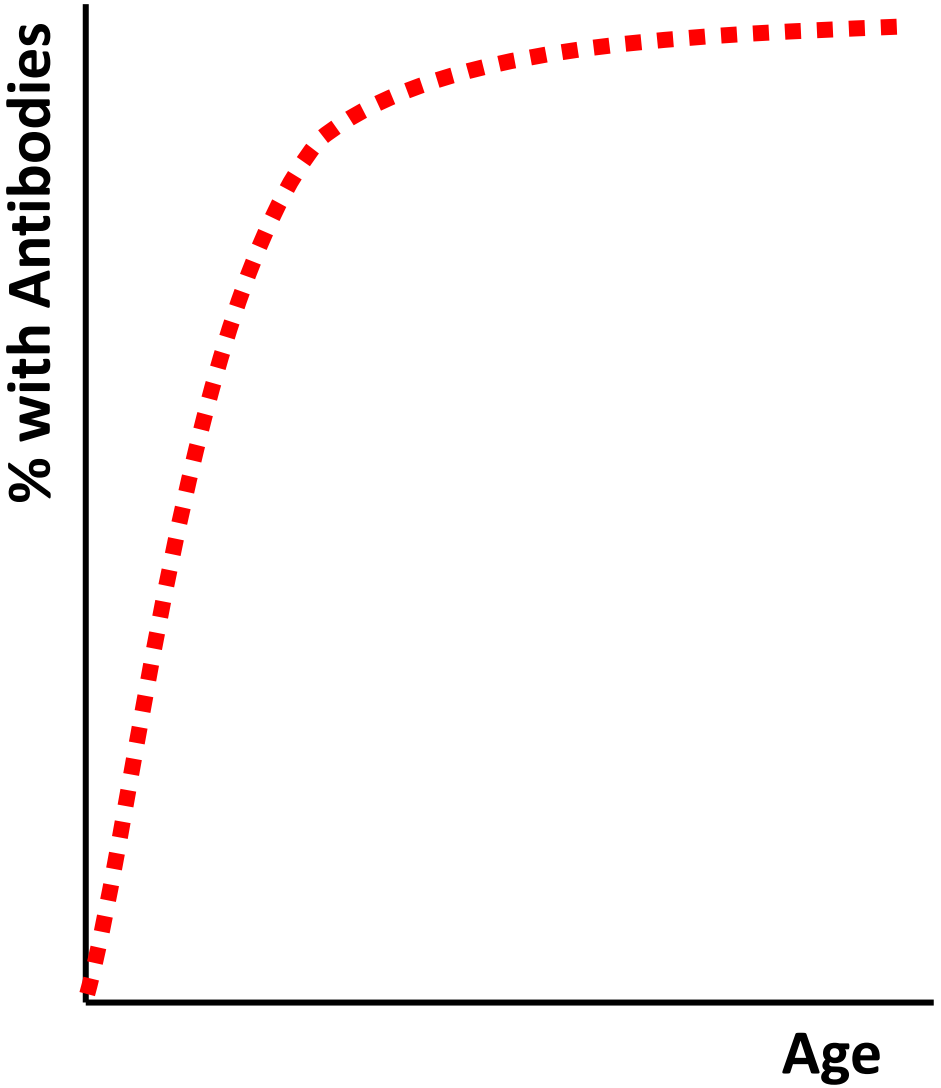


SIR model with demography: Average Age of Infection

We can use these data to help us parametrize our non-age structured SIR model with demography because

$$A \approx \frac{1}{\mu(R_0 - 1)}$$

This comes from the fact that at equilibrium the average period spent as a susceptible (hence average age at infection) is approximately $1/\beta I^*$ and I^* is $\mu/\beta\,(R_0 - 1)$



SIR model with demography:
Average Age of Infection

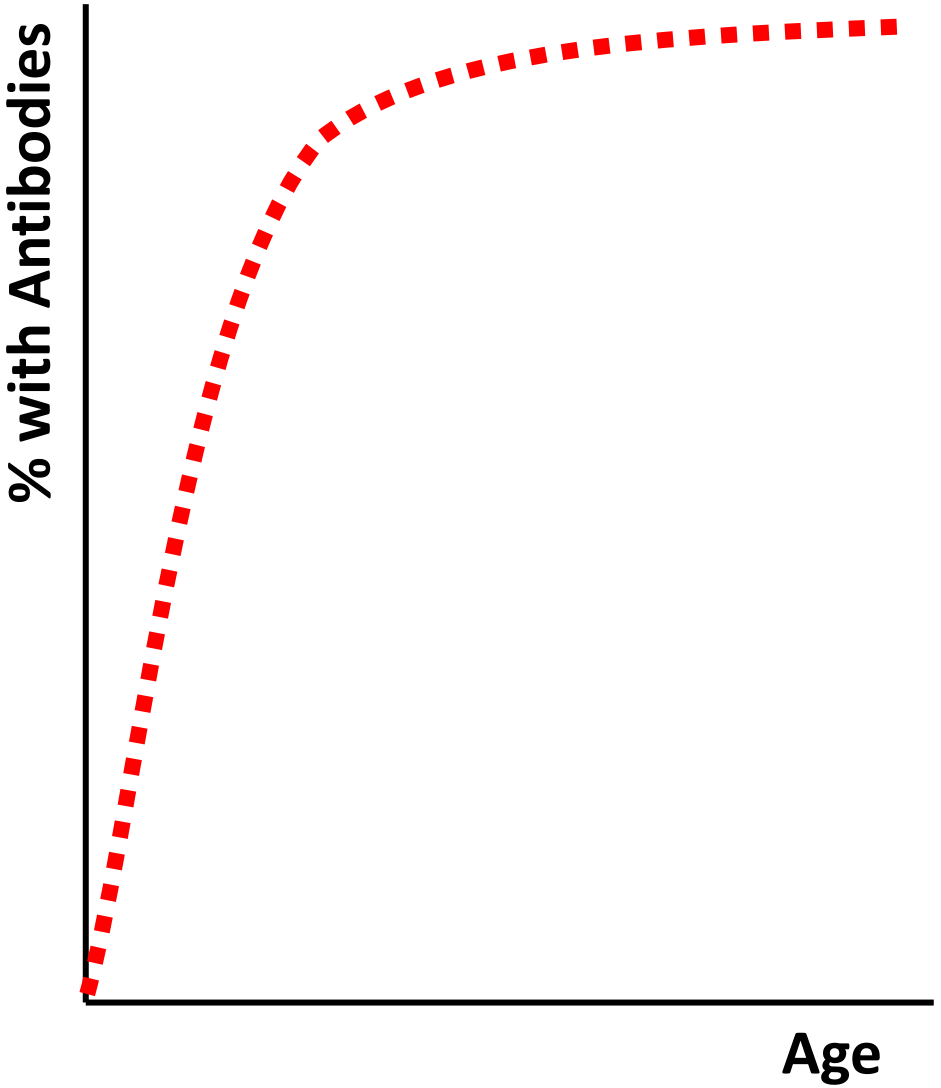
Since

$$A \approx \frac{1}{\mu(R_0 - 1)}$$

And since $\frac{1}{\mu}$ is equal to Life expectancy

The ratio of L/A = $(R_0 - 1)$

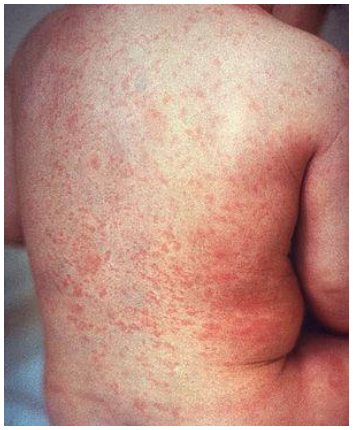
Pathogens/populations with higher R_0s have lower average ages of infection. Why?



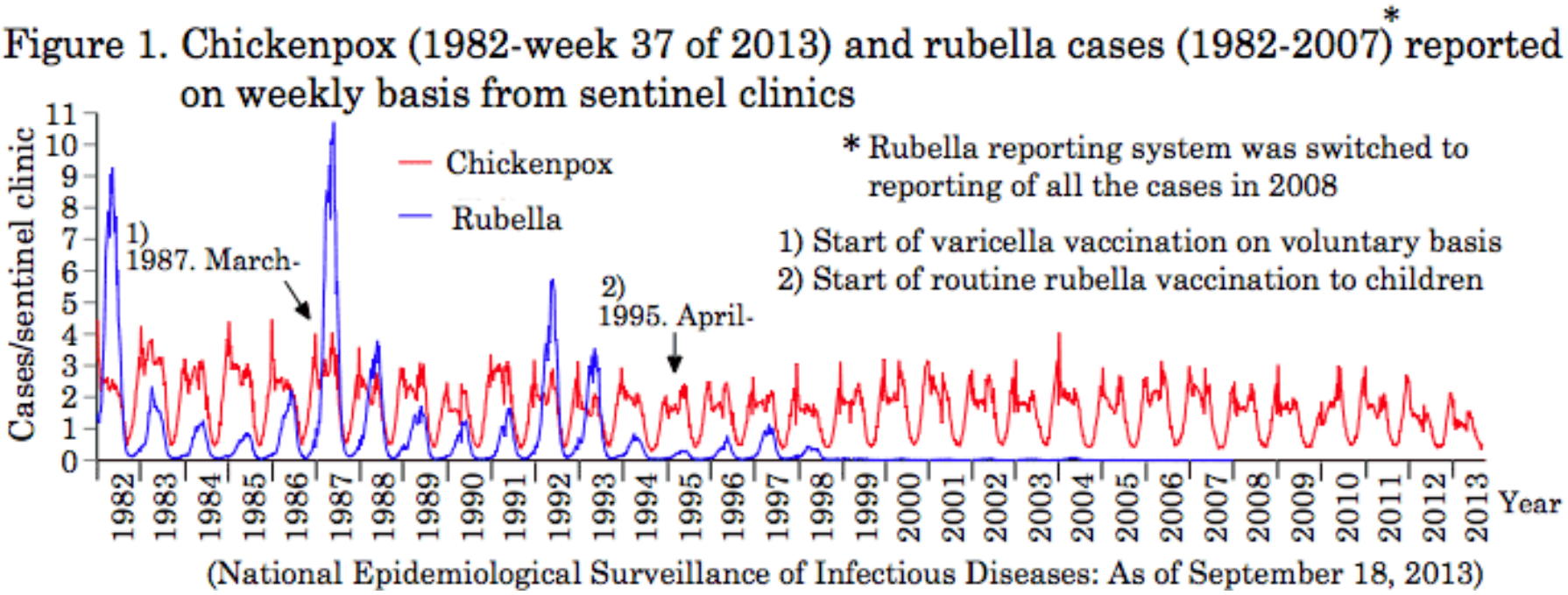
Practical Implication of Average Age of Infection: Example of Rubella

- Rubella is typically a syndrome in children
- However, pregnant women, if infected can have children with congenital rubella syndrome (cardiac defects, ocular defects, deafness, and other issues)
- Rubella R_0 estimated at 6-7; L=70
- A≈12.7 years

$$R_0 = \frac{\beta}{\gamma + \mu} \qquad A \approx \frac{1}{\mu(R_0 - 1)}$$



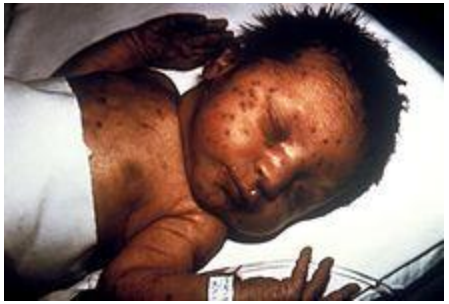
Practical Implication of Average Age of Infection: Example of Rubella



Practical Implication of Average Age of Infection: Example of Rubella

- Reduction in transmission through vaccination, if insufficient to reach the critical threshold (R_0<<1), could increase the average age
- Ex. If R_0=4, A≈ 23.3 years

$$R_0 = \frac{\beta}{\gamma + \mu} \qquad A \approx \frac{1}{\mu(R_0 - 1)}$$



SIR model with demography: Excess Mortality due to Infection

One approach: add a term *m*

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

$$\frac{dI}{dt} = \beta IS - \gamma I - \mu I - mI$$

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

Where *m* is a per capita disease-induced mortality rate for infected individuals

SIR model with demography: Excess Mortality due to Infection

Another PREFERRED approach: add a term *ρ*

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

$$\frac{dI}{dt} = \beta IS - (\gamma + \mu)I - \frac{\rho}{1-\rho}(\gamma + \mu)I$$

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

Where *ρ* is the probability of dying from the infection before either recovering or dying of natural causes

SIR model with demography: Excess Mortality due to Infection

If excess mortality due to infection generally occurs late in the infectious period, then we can write our equations like

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

$$\frac{dI}{dt} = \beta IS - (\gamma + \mu)I$$

$$\frac{dR}{dt} = (1 - \rho)\gamma I - \mu R$$

SIR model with demography: Excess Mortality due to Infection

Consequences of excess mortality due to infection

- **Population size no longer constant**
  - **Births (ν) no longer assumed to equal mortality (μ)**
  - **The equivalence of density and frequency-dependent transmission is broken (see 2.2.1.2 for details)**

$$\frac{dS}{dt} = \nu - \beta IS - \mu S$$

$$\frac{dI}{dt} = \beta IS - (\gamma + \mu)I - \frac{\rho}{1-\rho}(\gamma + \mu)I$$

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

$$\frac{dS}{dt} = \nu - \beta IS - \mu S$$

$$\frac{dI}{dt} = \beta IS - (\gamma + \mu)I$$

$$\frac{dR}{dt} = (1-\rho)\gamma I - \mu R$$

SIR model with demography: Excess Mortality due to Infection

Consequences of excess mortality due to infection

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$$\frac{dS}{dt} = \nu - \beta IS - \mu S$$

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

$$\frac{dS}{dt} = \nu - \beta IS - \mu S$$

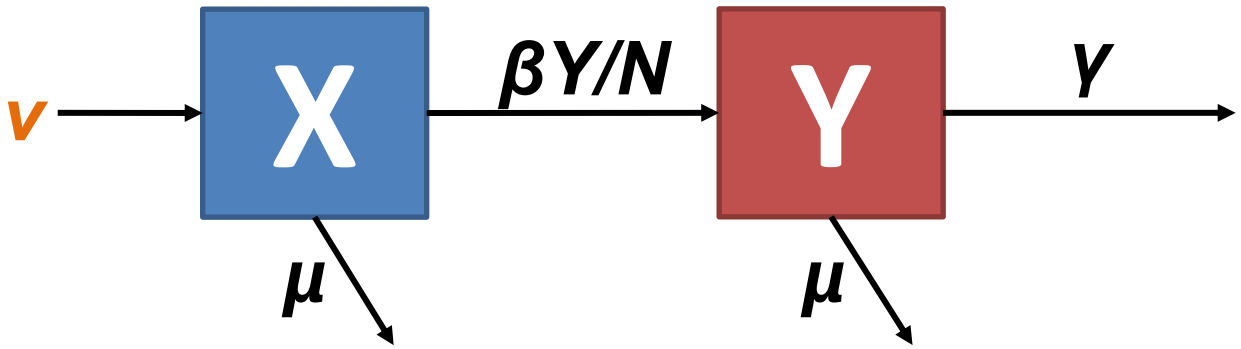
$$\beta IS - (\gamma + \mu)I$$

$$(1 - \rho)\gamma I - \mu R$$

The care we need to take about density vs. frequency-dependent transmission will continue for the rest of the examples in this lecture

EXTENSIONS TO SIR MODELS WITH DEMOGRAPHY

Models for Chronic Infections



$$\frac{dX}{dt} = \nu - \beta X\,{}^{Y}\!/_{N} - \mu X$$

$$\frac{dY}{dt} = \beta X\,{}^{Y}\!/_{N} - (\gamma + \mu)Y$$

What is the endemic equilibrium?

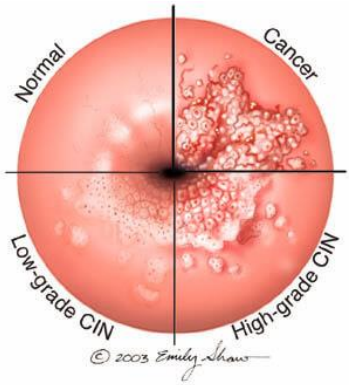
$$\left(\frac{\nu}{\beta - \gamma}, \frac{\nu(\beta - \gamma - \mu)}{(\beta - \gamma)(\gamma + \mu)}\right)$$

When $R_0 > \frac{\beta}{(\gamma+\mu)}$

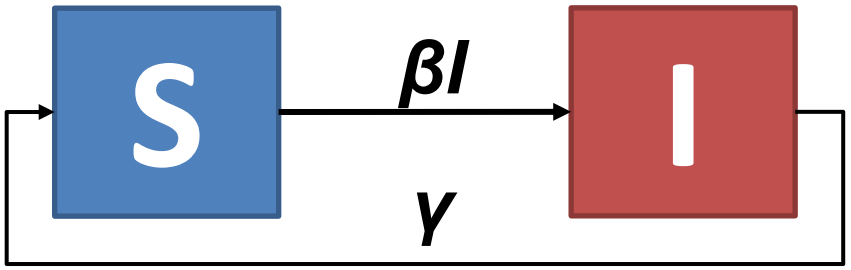
which comes from 2.2.2 when *ρ=1*

Relevance of Models for Chronic Infections

- Long-term chronic infections
  - HCV (hepatitis c virus)
  - HPV (human papillomavirus)
- Short-term highly fatal infections
  - Ebola
  - Bovine Spongiform Encephalopathy



Models for Infections without Immunity



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

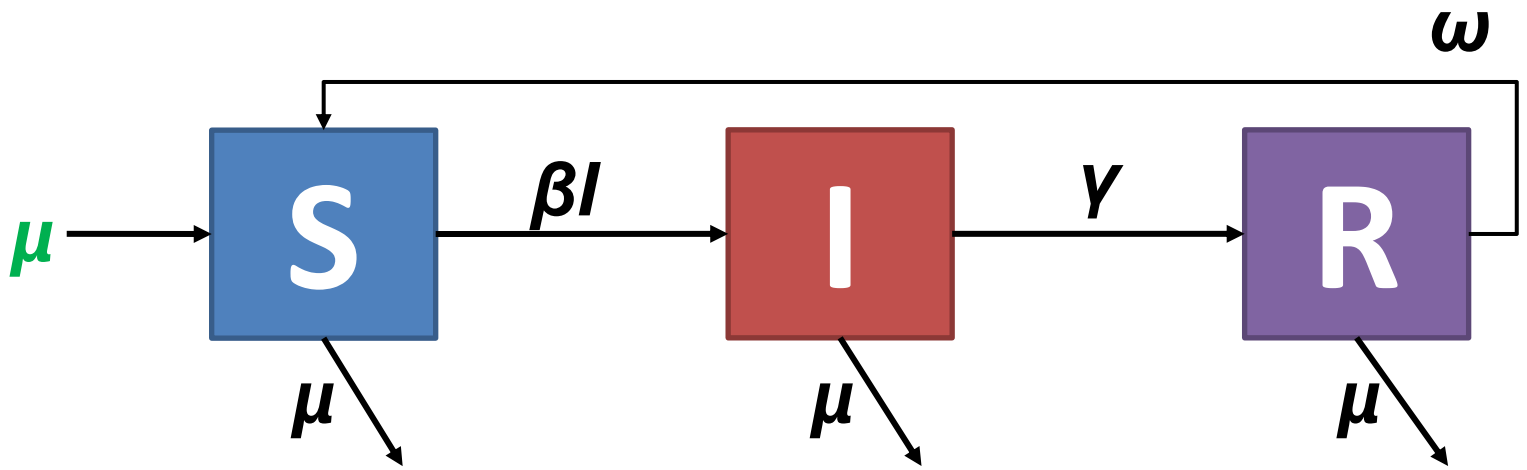
$$\frac{dI}{dt} = \beta SI - \gamma I$$

What is the endemic equilibrium?

$$\left(\frac{\gamma}{\beta}, 1 - \frac{\gamma}{\beta}\right)$$

When $R_0 > \frac{\beta}{\gamma}$ and endemic equilibrium reached w/o oscillations

SIR model with demography: Waning Immunity



$$\frac{dS}{dt} = \mu + \omega R - \beta IS - \mu S$$

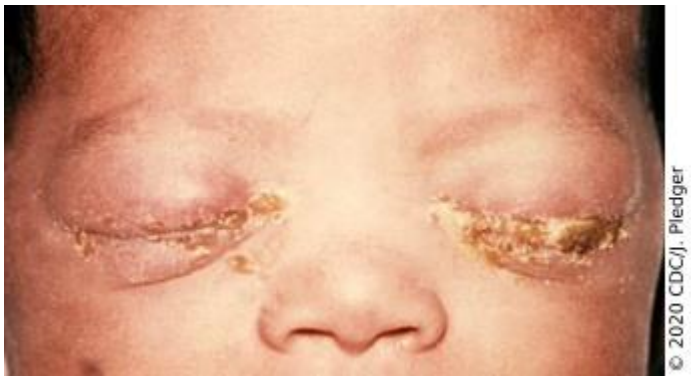
$$\frac{dI}{dt} = \beta IS - \gamma I - \mu I$$

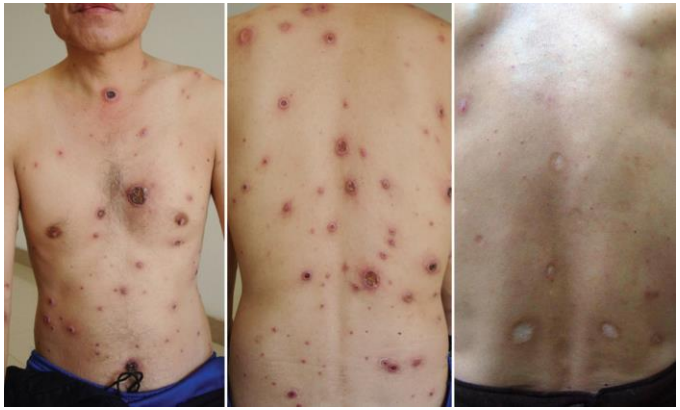
$$\frac{dR}{dt} = \gamma I - \omega R - \mu R$$

- When ω is 0: SIR with demography
- When ω is infinity: SIS with demography
- SIR with demography and waning immunity has oscillations whose period is more complicated to describe (see 2.4)

Relevance of Models without Immunity or with Rapidly Waning Immunity

- Gonorrhea
- Syphilis





Important Announcements