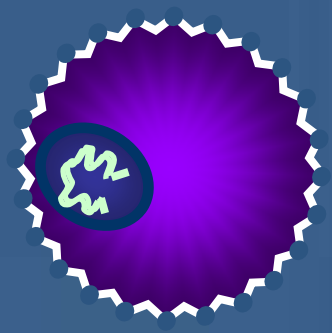
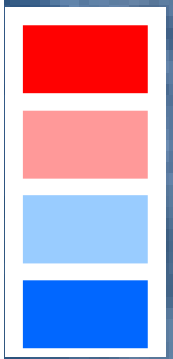
Immuno-epidemiology: bringing together within-host and between-host dynamics for measles

Jane Heffernan and Matt Keeling



Measles

- Significant cause of mortality and morbidity
  - A leading cause of death in young children
  - In 2007 197000 deaths, 74% decrease in deaths since 2000

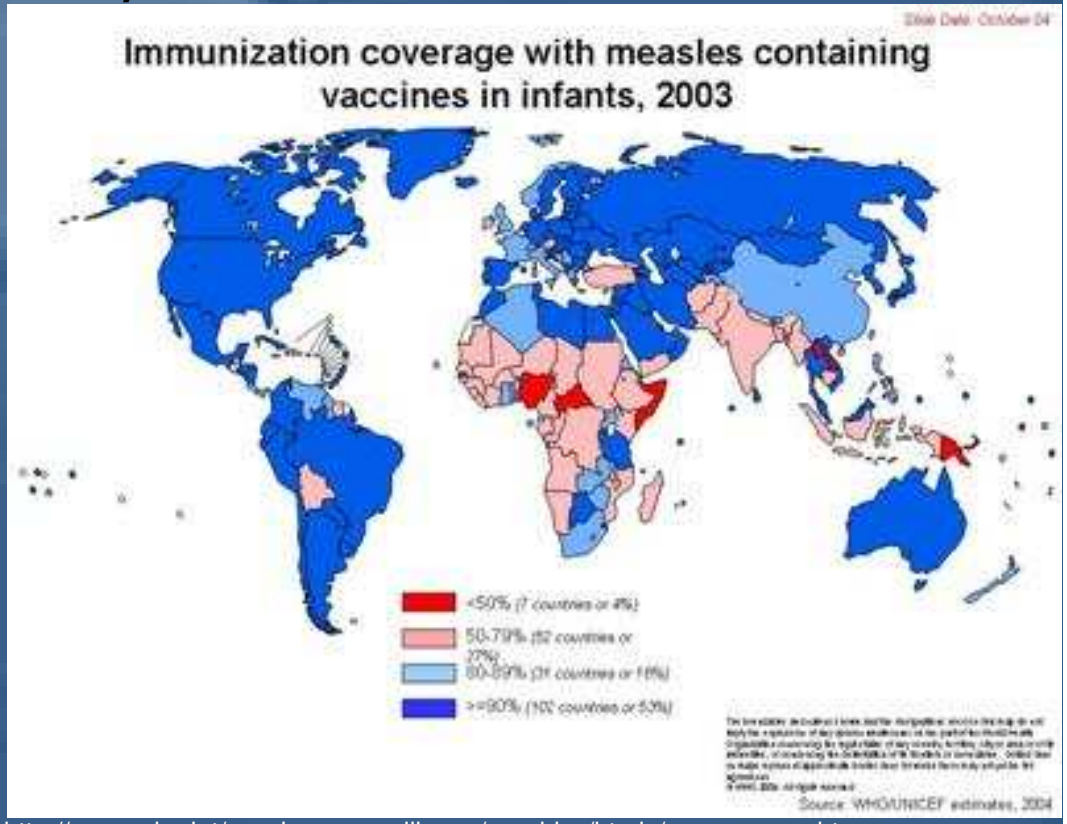


< 50% (7 countries or 4%)

50-79% (52 countries of 27%)

80-89% (31 countries or 18%)

>90% (102 countries or 53%)

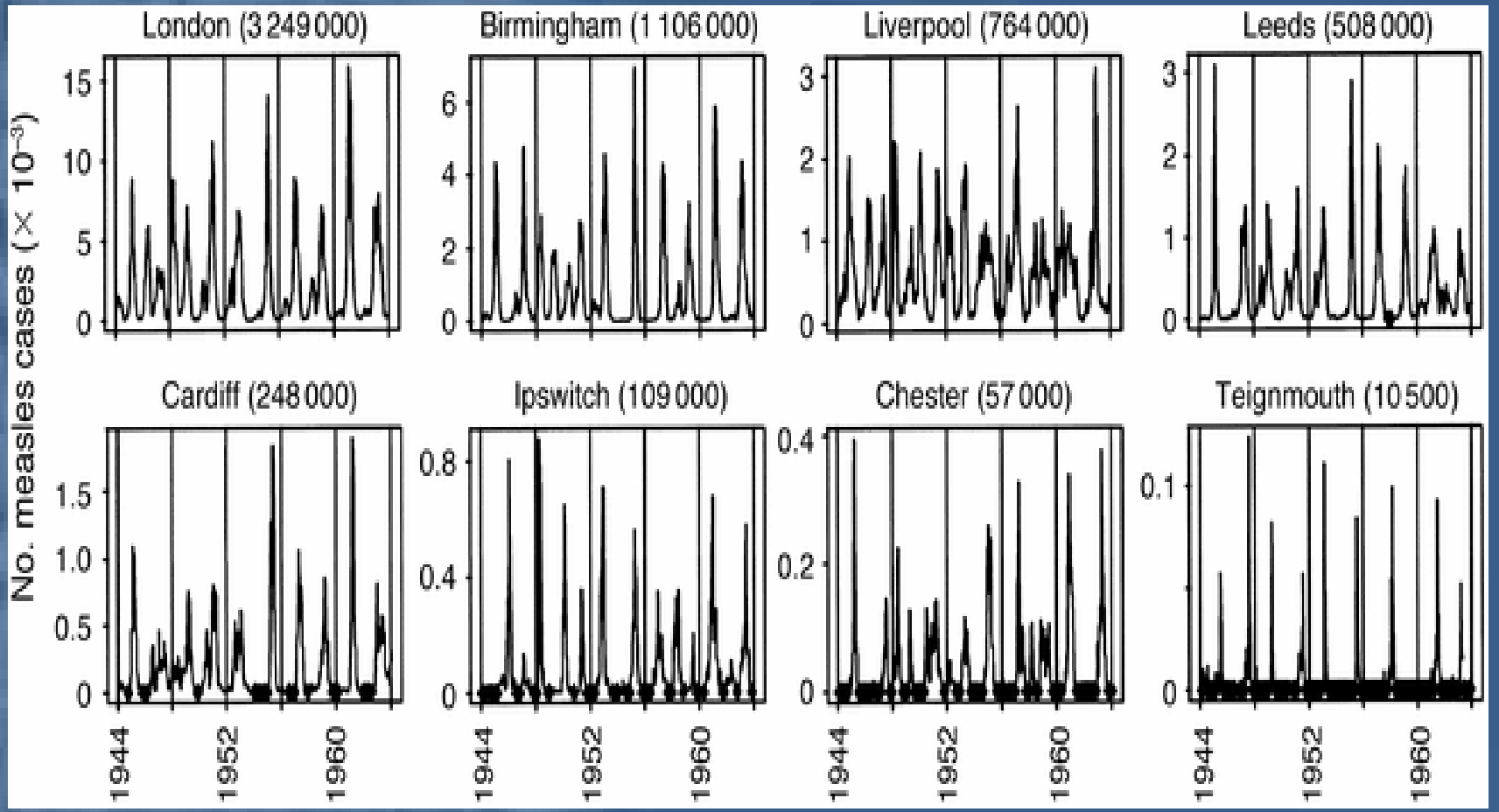


http://www.who.int/vaccines-surveillance/graphics/htmls/meacovmap.htm

- Vaccine
  - Live attenuated

Measles

- Interesting temporal dynamics:

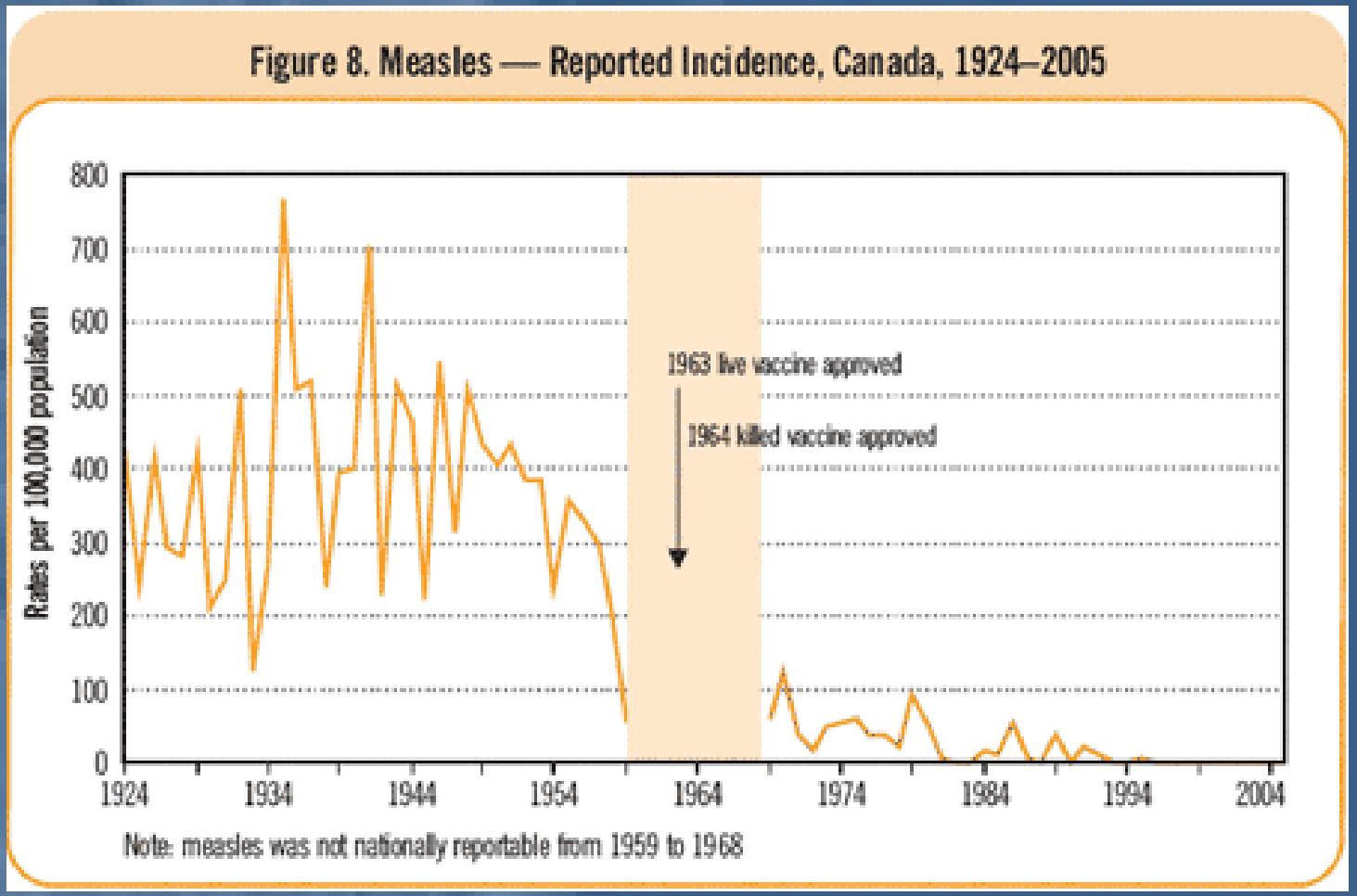


Bjornstad, Finkenstadt and Grenfell (2002), Ecological Moonographs, 72 p. 169-184

http://www.esajournals.org/perlserv/?request=get-document&issn=0012-9615&volume=072&issue=02&page=0169

Measles

- Interesting temporal dynamics:



Source: *Canadian Immunization Guide, 7th edition, 2006*

Measles

- **July 2008 - Measles Outbreak Declared Over**
  - The measles outbreak that began in Toronto in March 2008
  - no new cases reported in two consecutive incubation periods (42 days).
  - A total of 26 outbreak associated cases were reported to TPH
    - Vaccine - 2 confirmed doses – 1 person, 1 confirmed dose – 7 people, Zero doses – 10 people, Unknown – 8 people
  - Two individuals were infected with measles outside of Canada
  - Also, 30 outbreak associated cases were reported in Ontario outside Toronto.
- During this outbreak, TPH staff followed-up on over 4,300 contacts of cases and 128 individuals sick with measles-like symptoms who needed to be ruled out. In addition, TPH vaccinated 454 people, gave immune globulin to 28 individuals and excluded 429 individuals from work/public activities to prevent further spread

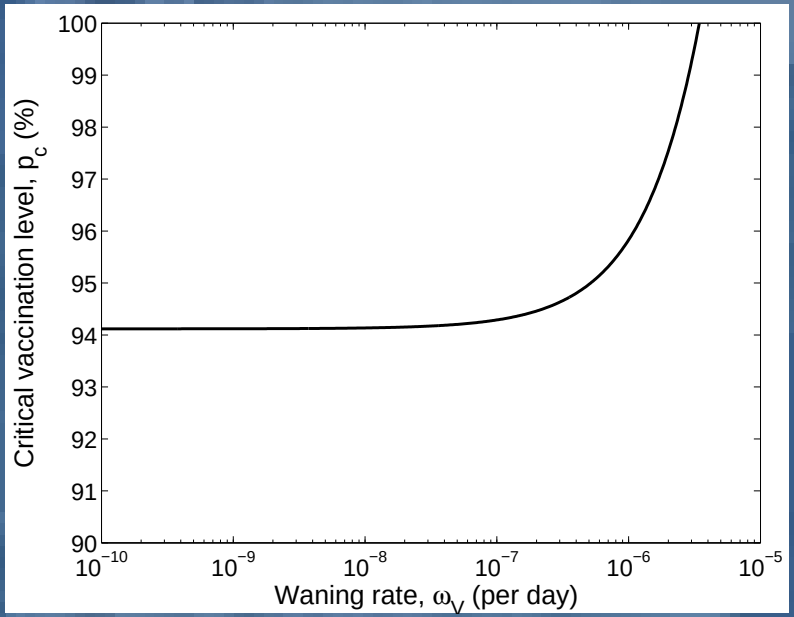
- Endemic in many countries, resurgence of measles is being observed throughout the world wherever vaccination coverage is inadequate.
- 2008 - the USA is experienced its largest measles outbreak in more than a decade, which spread to 15 states. Cases are primarily being seen in unimmunized children and groups.
- Measles has become endemic in the UK 14 years after transmission was halted.

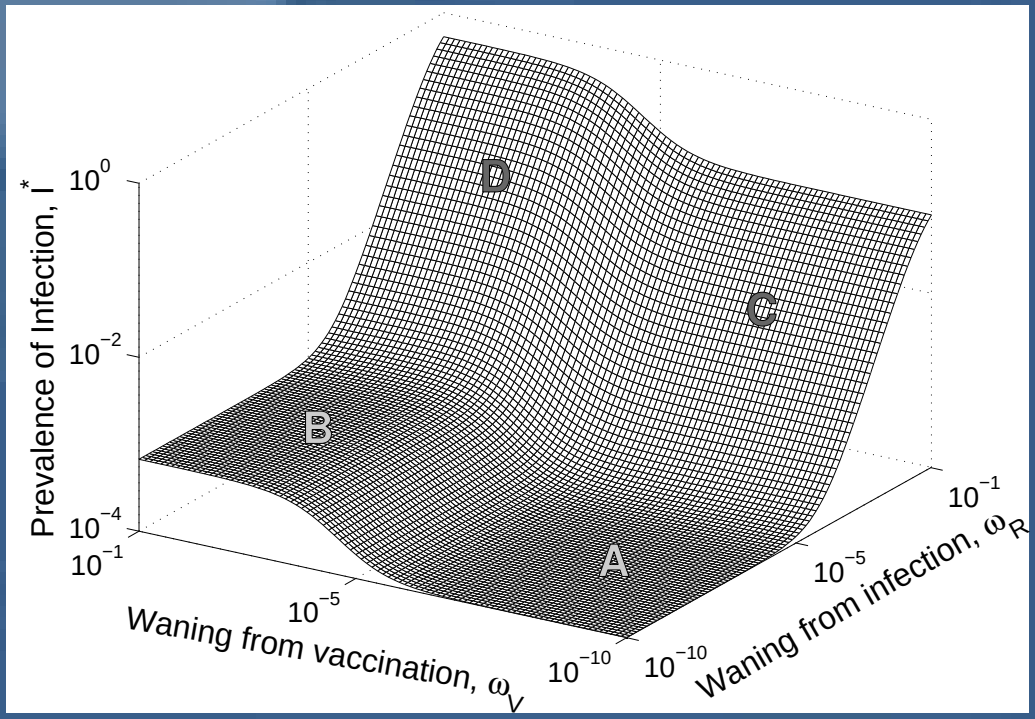
SIRV Model

- Simple model for waning immunity based on SIRV

$$p_c = \left(1 + \frac{w_v}{d}\right)\left(1 - \frac{1}{R_0}\right)$$

$$I^* = \frac{[(\beta - g - d)w_v + (\beta(1-p) - g - d)d](w_R + d)}{\beta(d + w_v)(g + d + w_R)}$$





Immune System

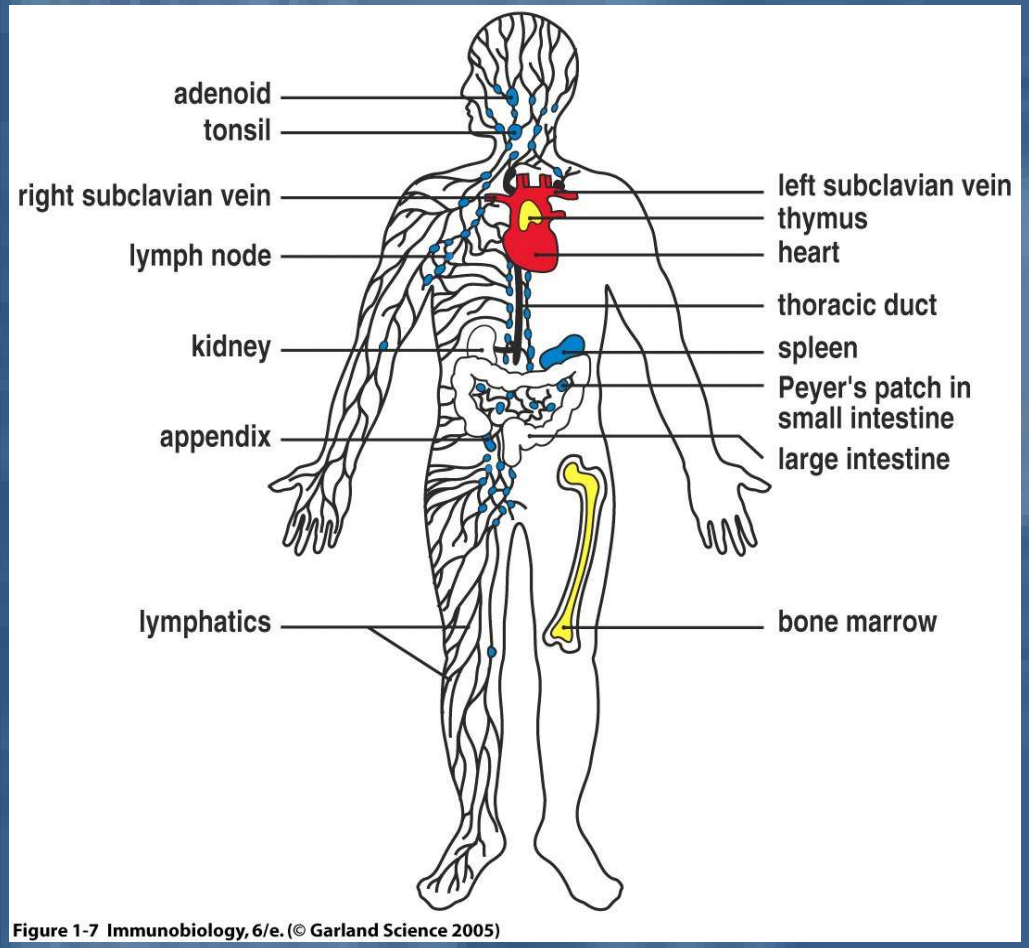


Figure 1-7 Immunobiology, 6/e. (© Garland Science 2005)

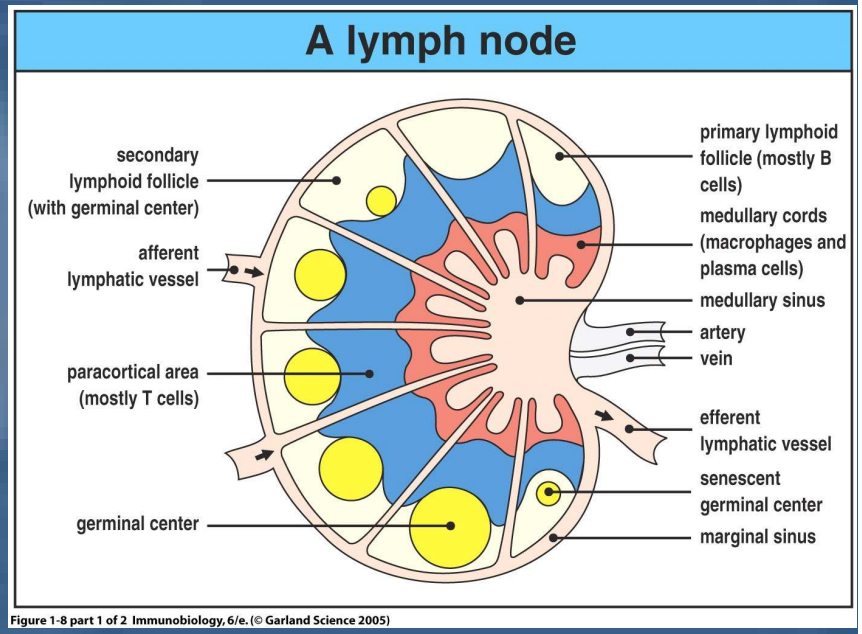


Figure 1-8 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Immune System

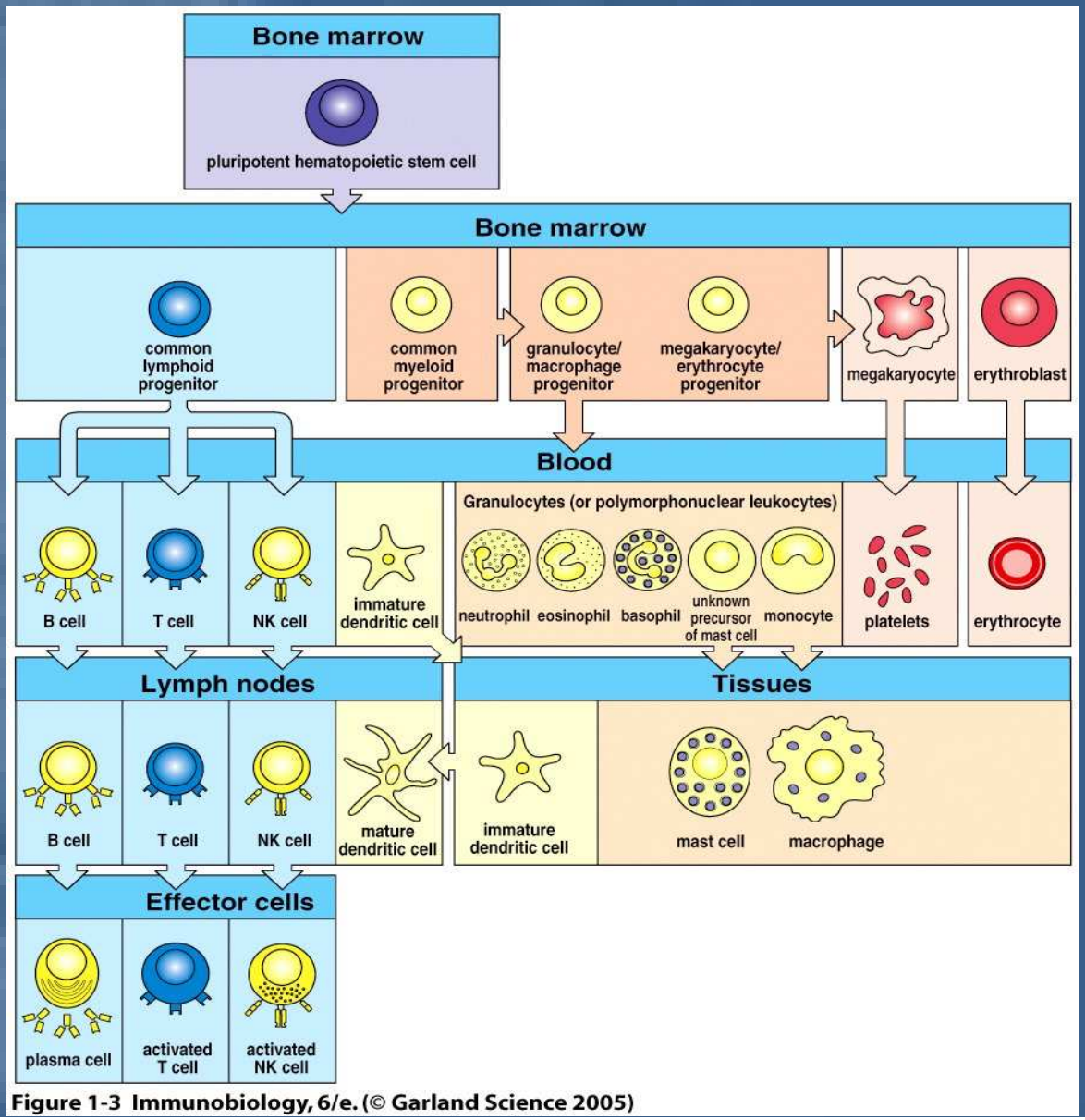
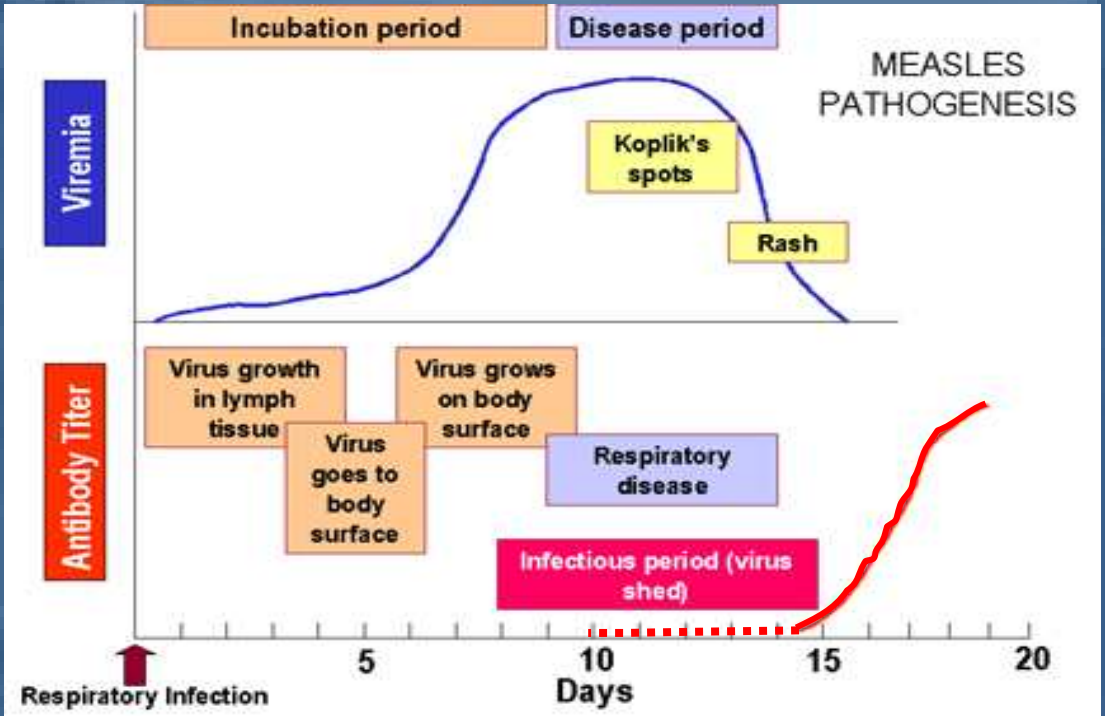


Figure 1-3 Immunobiology, 6/e. (© Garland Science 2005)

Measles

- Transmission
  - direct contact with nasal or throat secretions
  - by airborne transmission



- Acute infection
- Immune response:
  - Humoral immunity
  - Cellular immunity

Development of memory

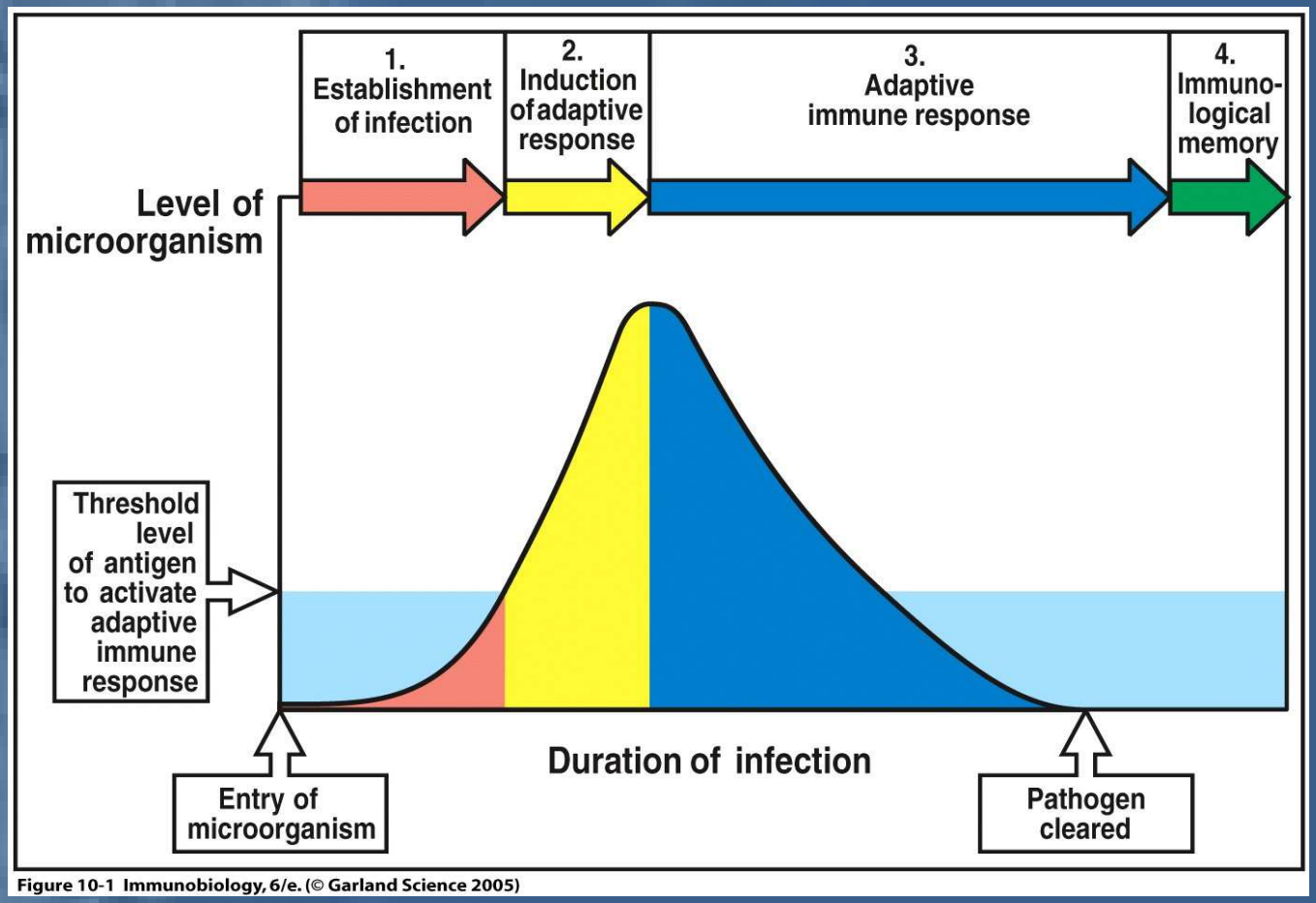
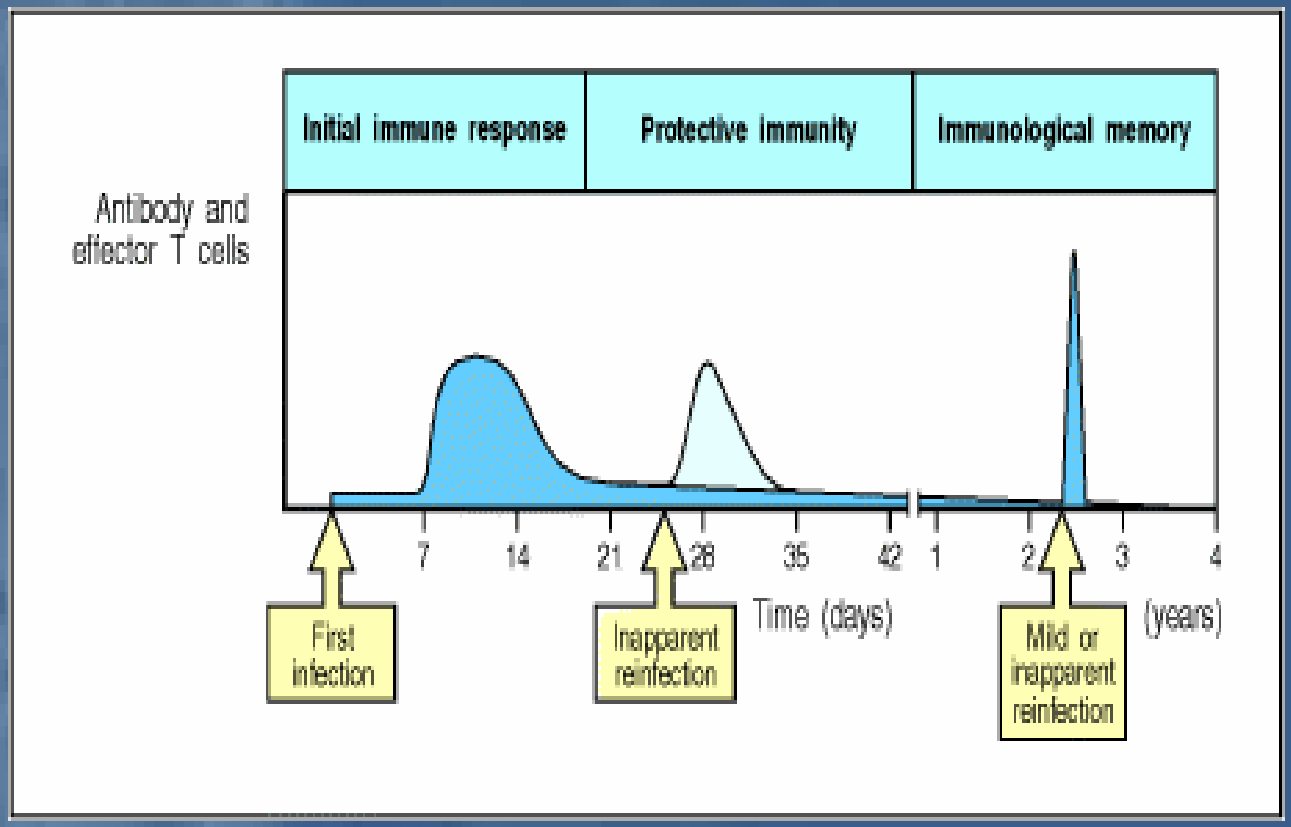


Figure 10-1 Immunobiology, 6/e. (© Garland Science 2005)

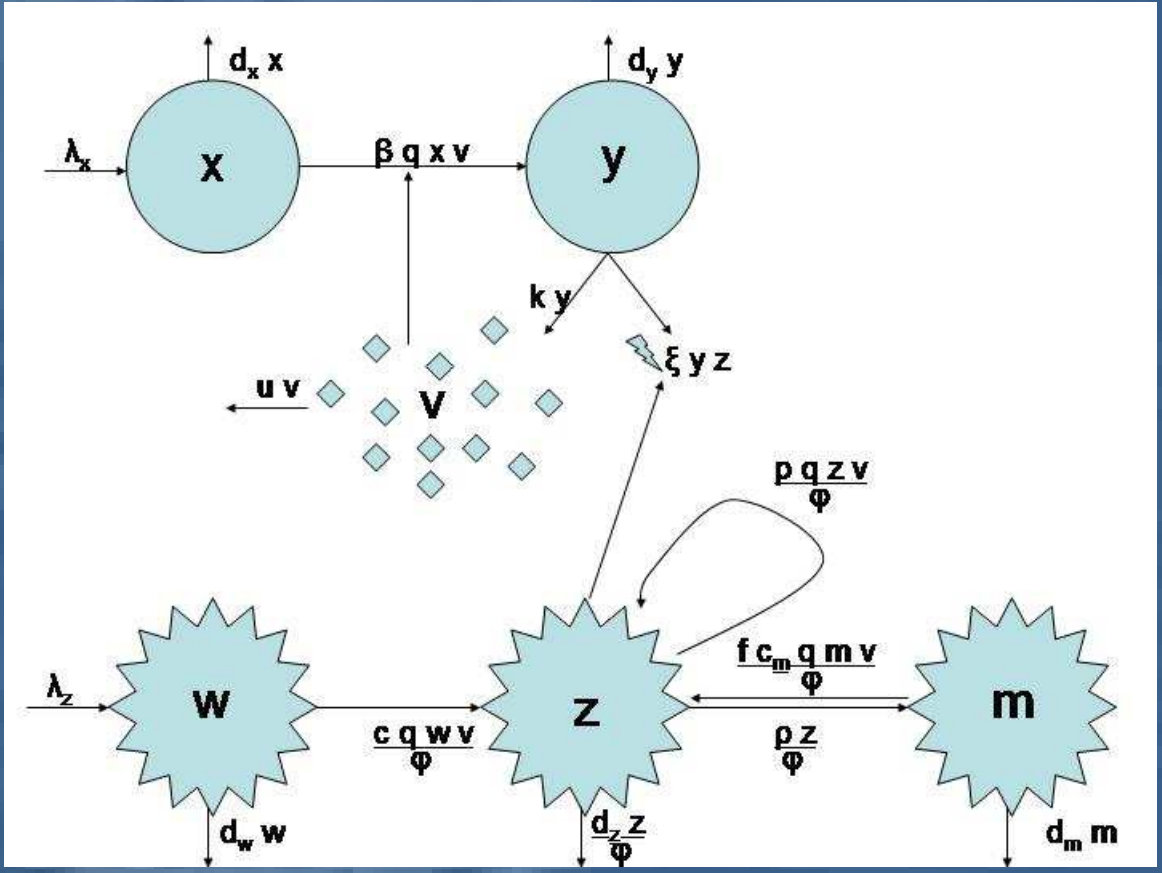
- The course of a typical acute infection
  - Naïve, activated, memory

Immunological Memory



- Protective immunity consists of preformed immune reactants and immunological memory.

In-host Model



- x, y – uninfected, infected cells
- v – virus
  - q - infectious
- w, z, m – naïve, activated and memory CD8 T-cells

- λ – incoming rate from thymus
- β – infection rate
- φ – density dependence
- ρ – convert to memory
- ξ – killing rate

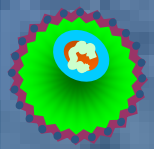
- $d_{x, y, w, z, m}$ – death rates
- u – clearance rate
- k – bud rate
- p – proliferation rate
- c, c_m – activation rates

In-Host Measles Model

$$\frac{dx}{dt} = \lambda_x - d_x x - \beta q x v$$

$$\frac{dy}{dt} = \beta q x v - d_y y - \xi y a$$

$$\frac{dv}{dt} = k y - u v - \beta q x v$$



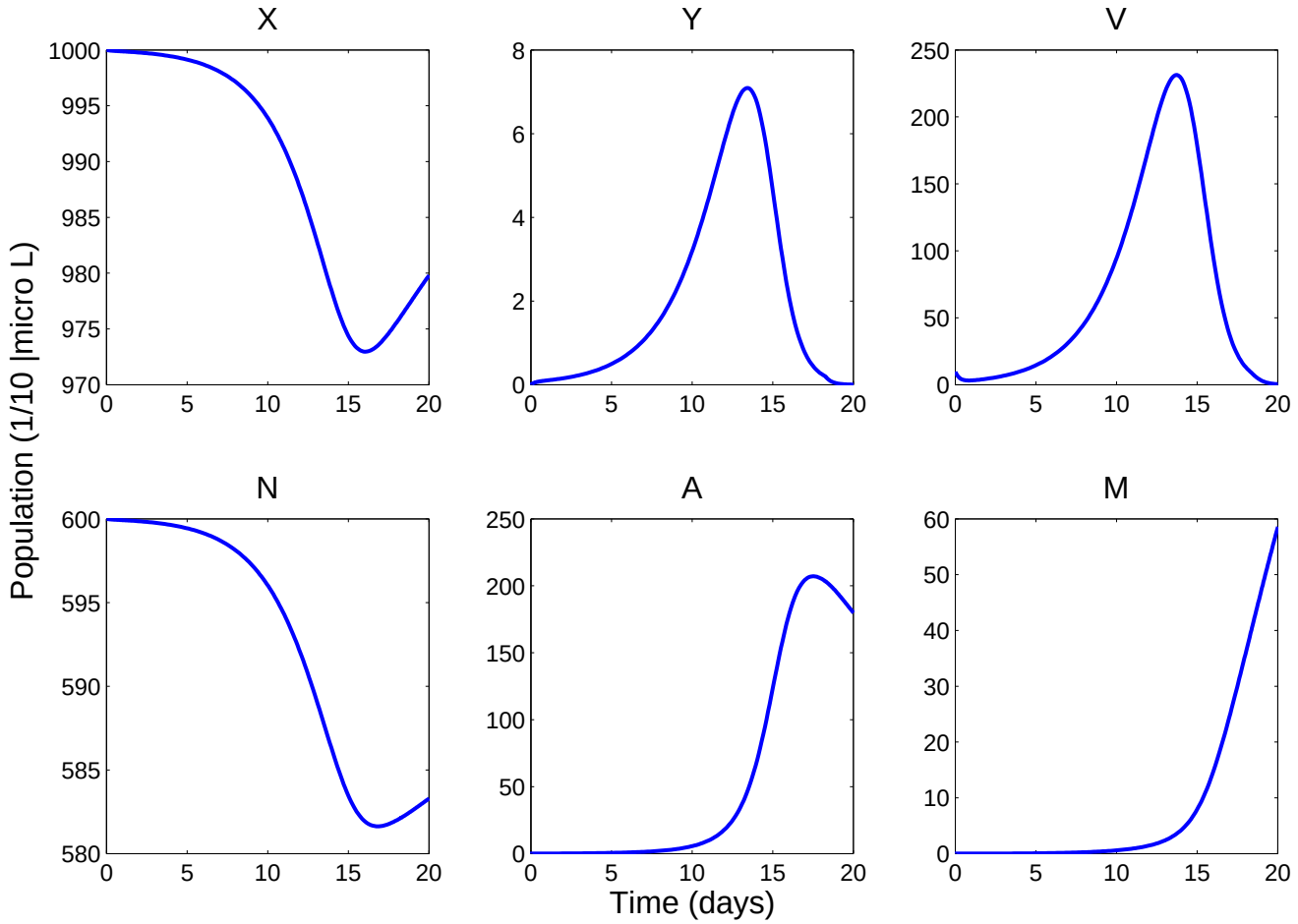
$$\frac{dn}{dt} = \lambda_z - \frac{cqnv}{Cqv + K} - d_n n$$

$$\frac{da}{dt} = \frac{cqnv}{Cqv + K} + \frac{pqva}{C_2 qv + K_2} - \frac{(\rho + d_a)a}{C_3 qv + K_3} + \frac{\sigma qmv}{C_4 qv + K_4}$$

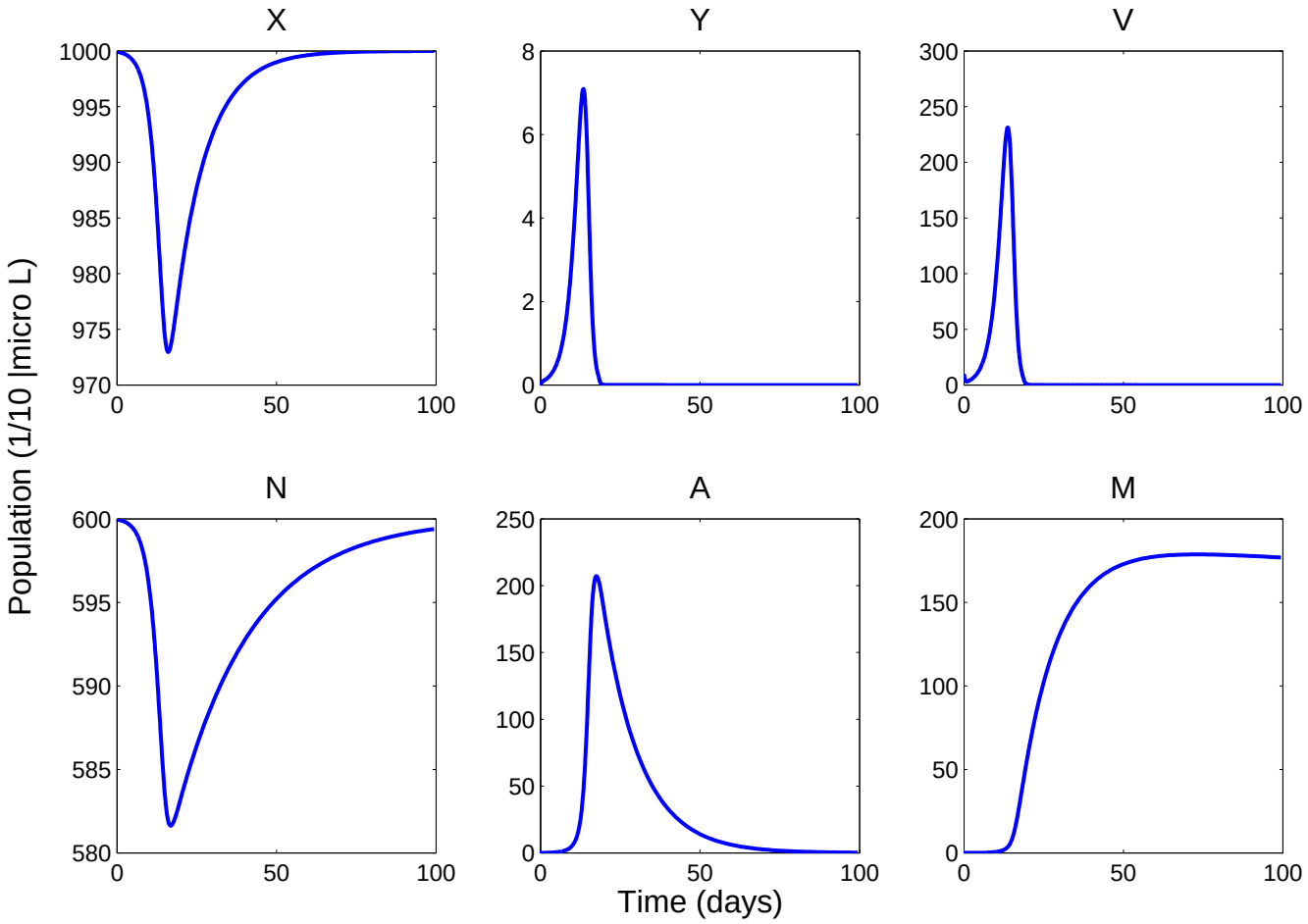
$$\frac{dm}{dt} = \frac{\rho a}{C_3 qv + K_3} - d_m m - \frac{\sigma qmv}{C_4 qv + K_4}$$

$$R_0 = \frac{k}{d_y} \frac{\beta q x_0}{\beta q x_0 + u}$$

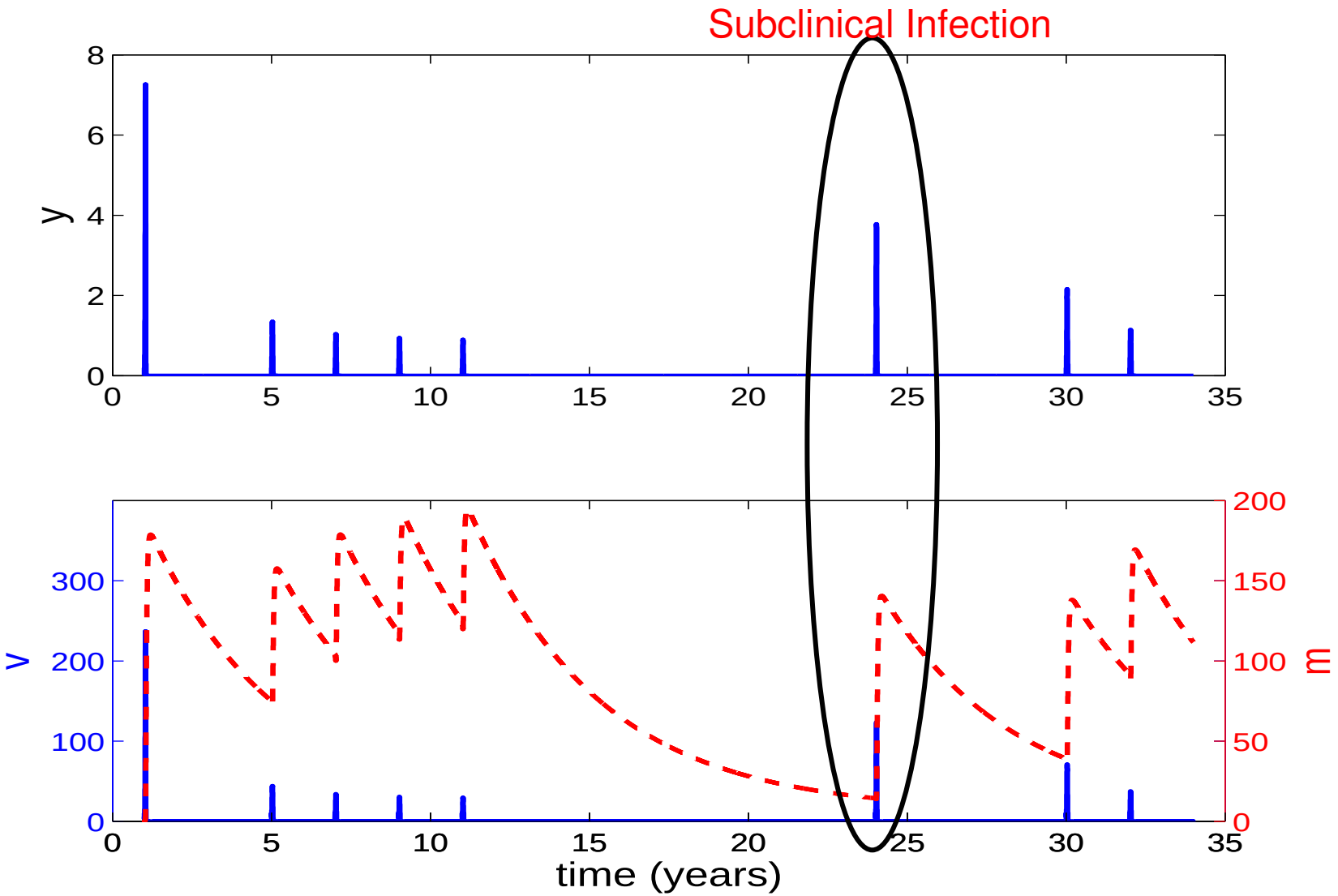
Measles Pathogenesis



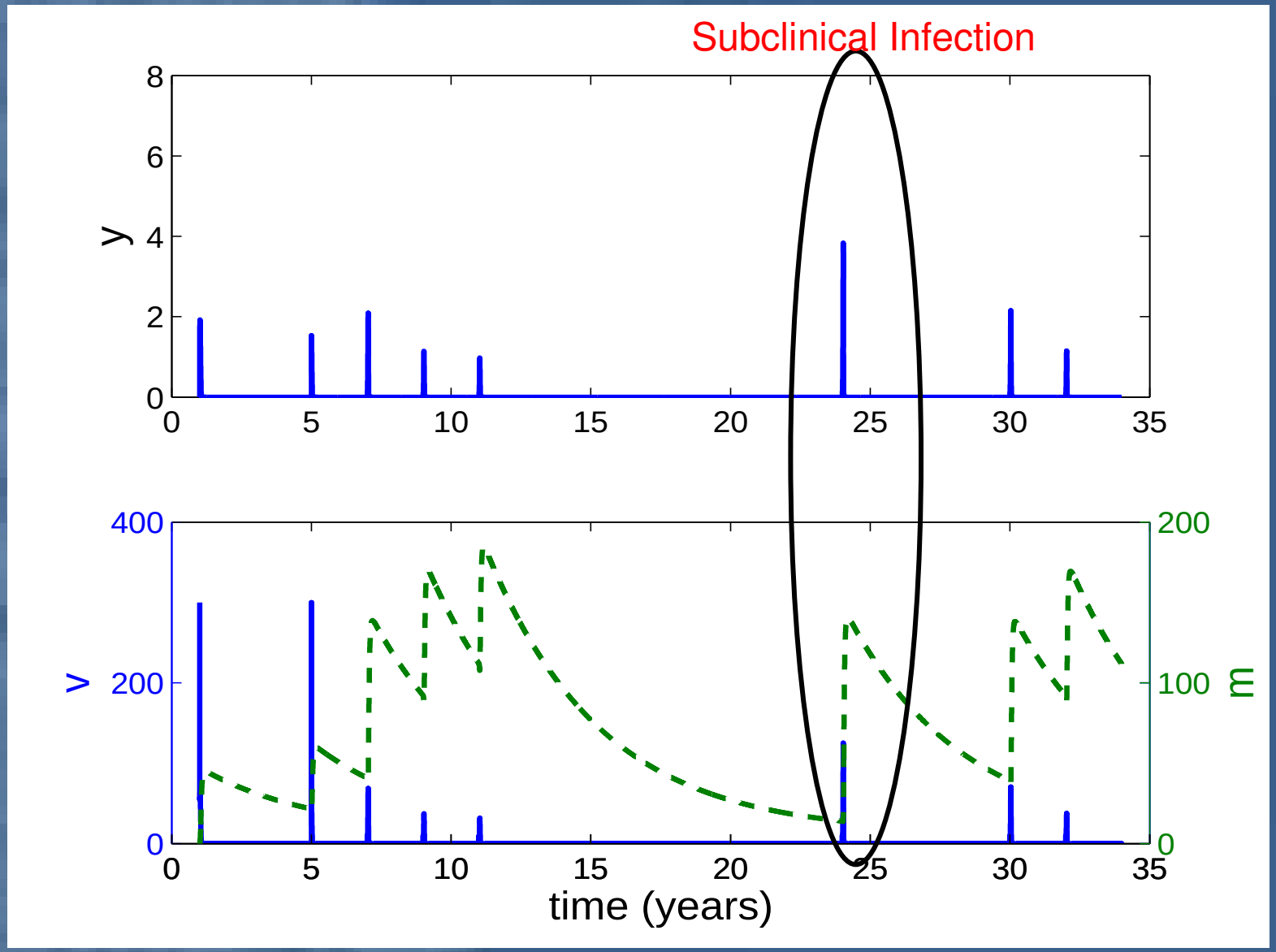
Measles Pathogenesis



Booster Infections



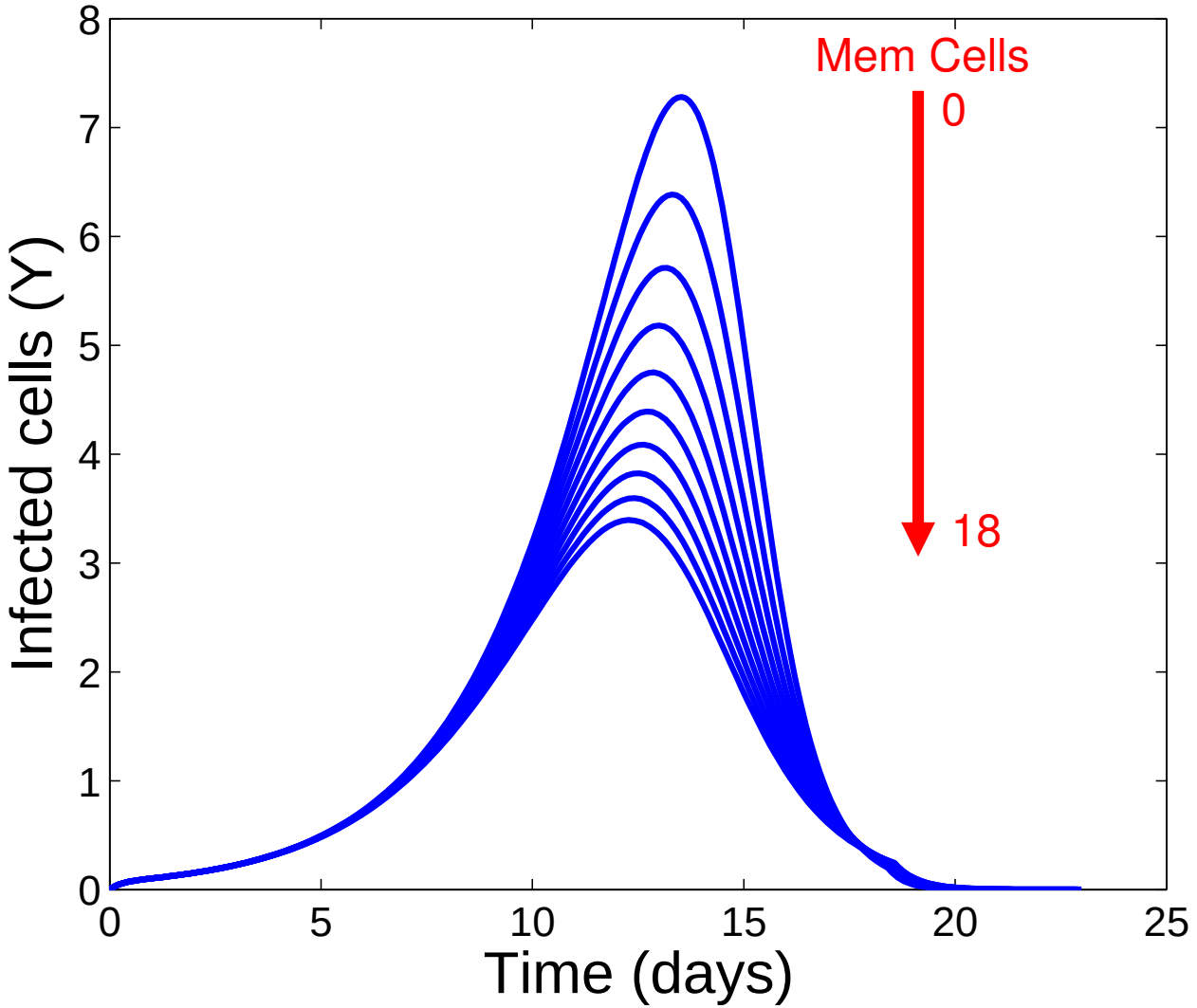
Booster Infections



Things we want to know

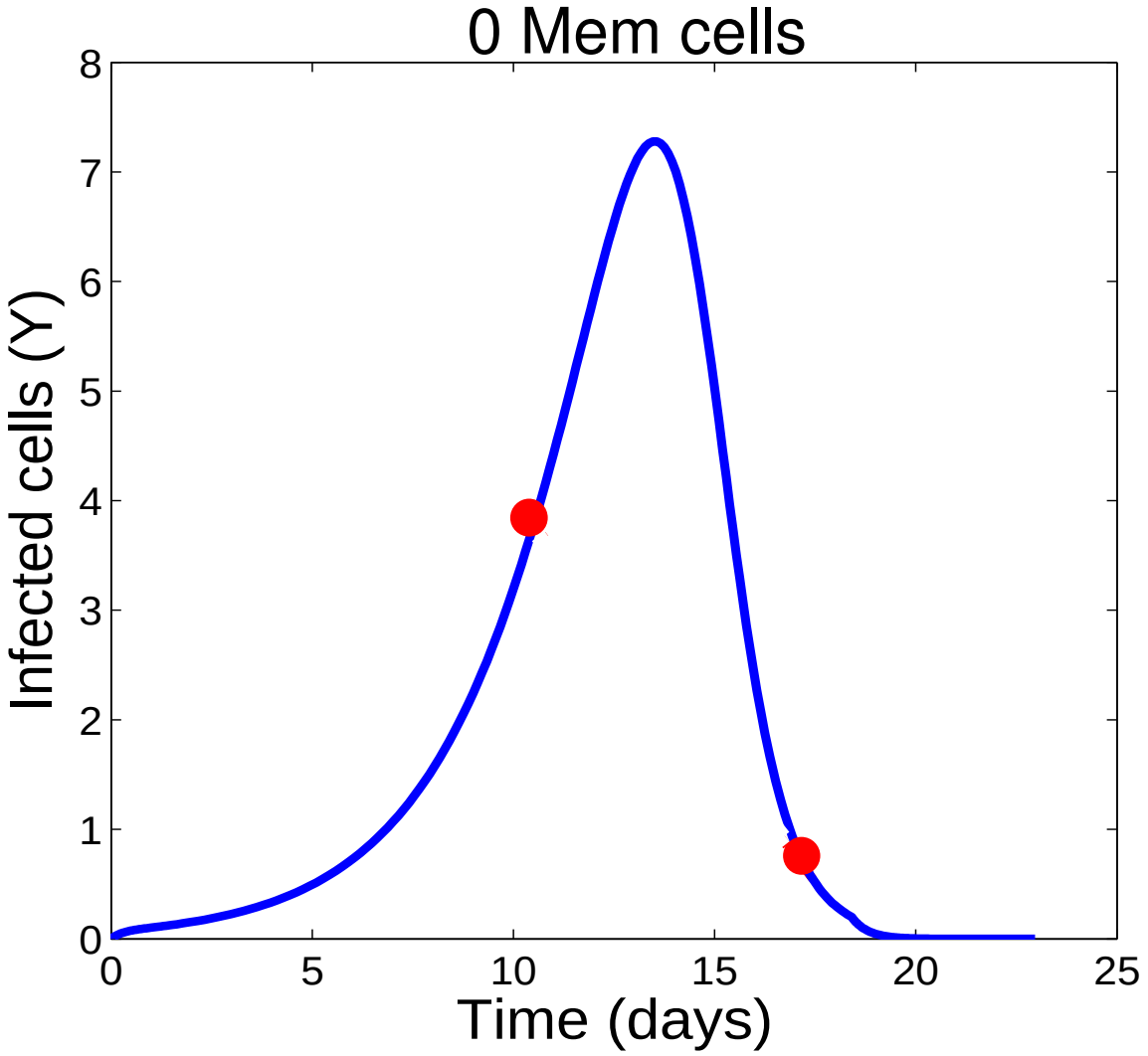
- Quanta expelled by infected person?
  - Relates to transmission between individual hosts
  - No lung infection data!
- Definition of asymptomatic infection
- Development of immunity with different initial levels of memory CD8
- Start time and length of infectious period for different initial levels of memory CD8
- Quantify level of infection for different initial levels of memory CD8

Infection Curves

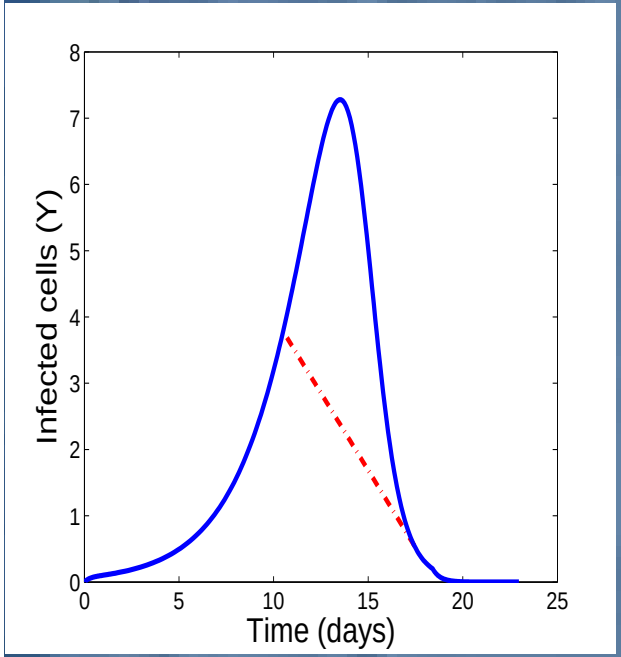


Infectious stage

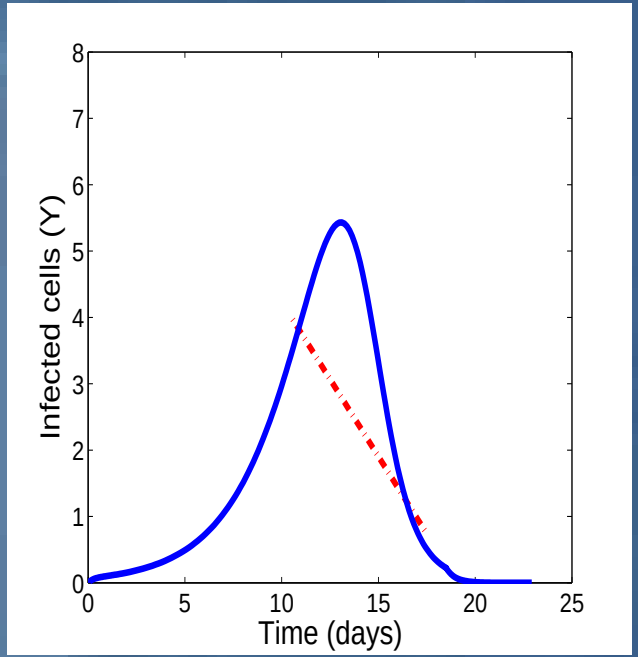
- R_0
  - Basic Reproductive Ratio
  - Number of secondary infections produced by a single infective in a totally susceptible population



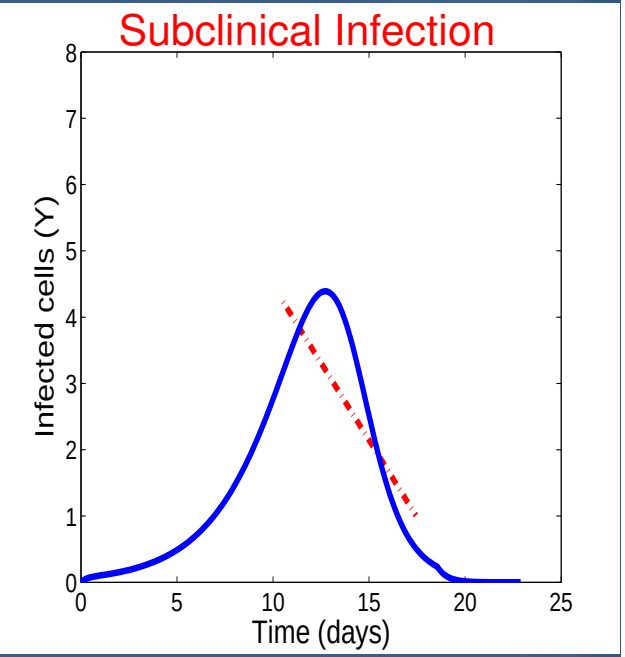
Basic Reproductive Ratio



0 mem cells



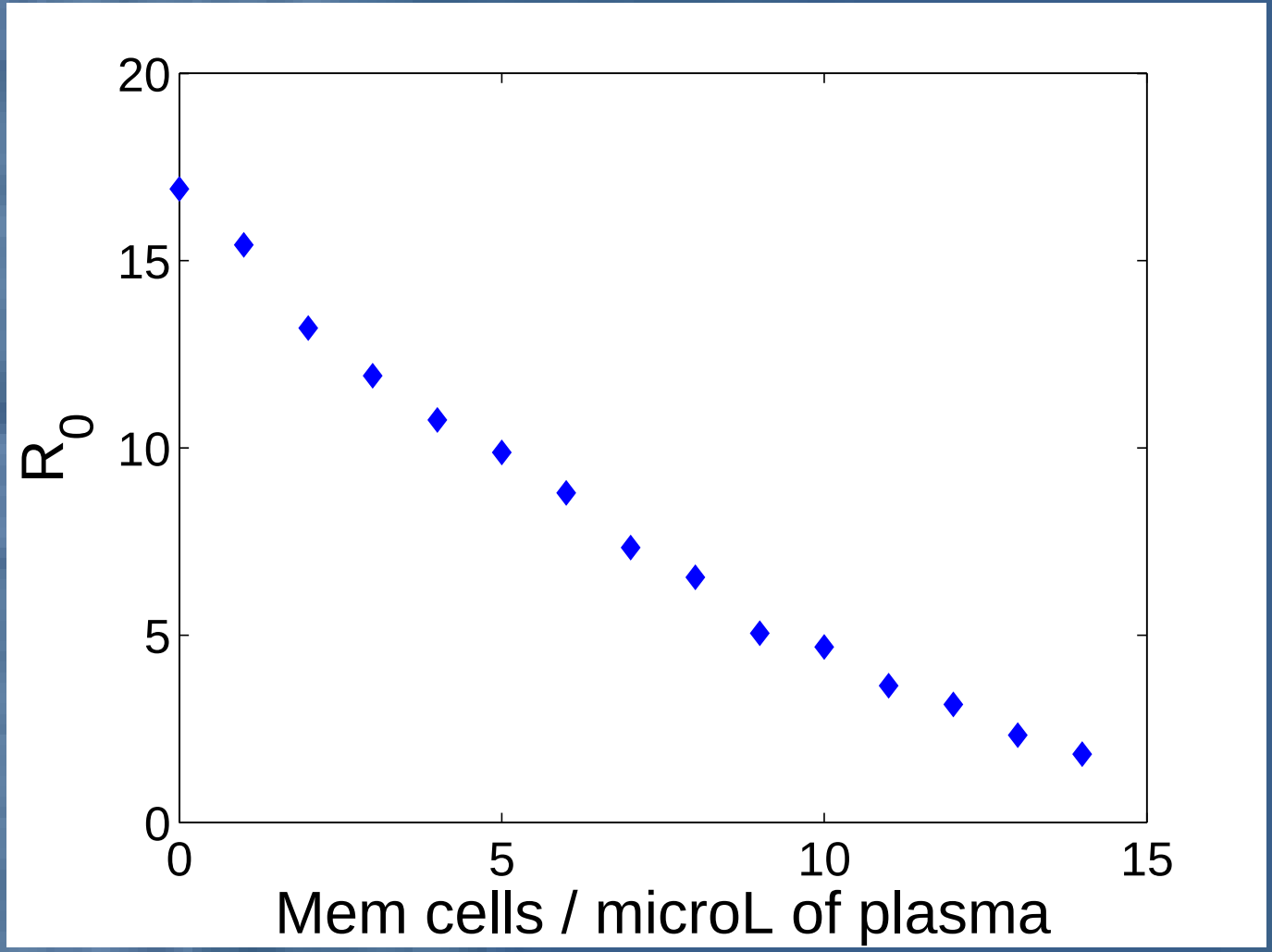
5 mem cells



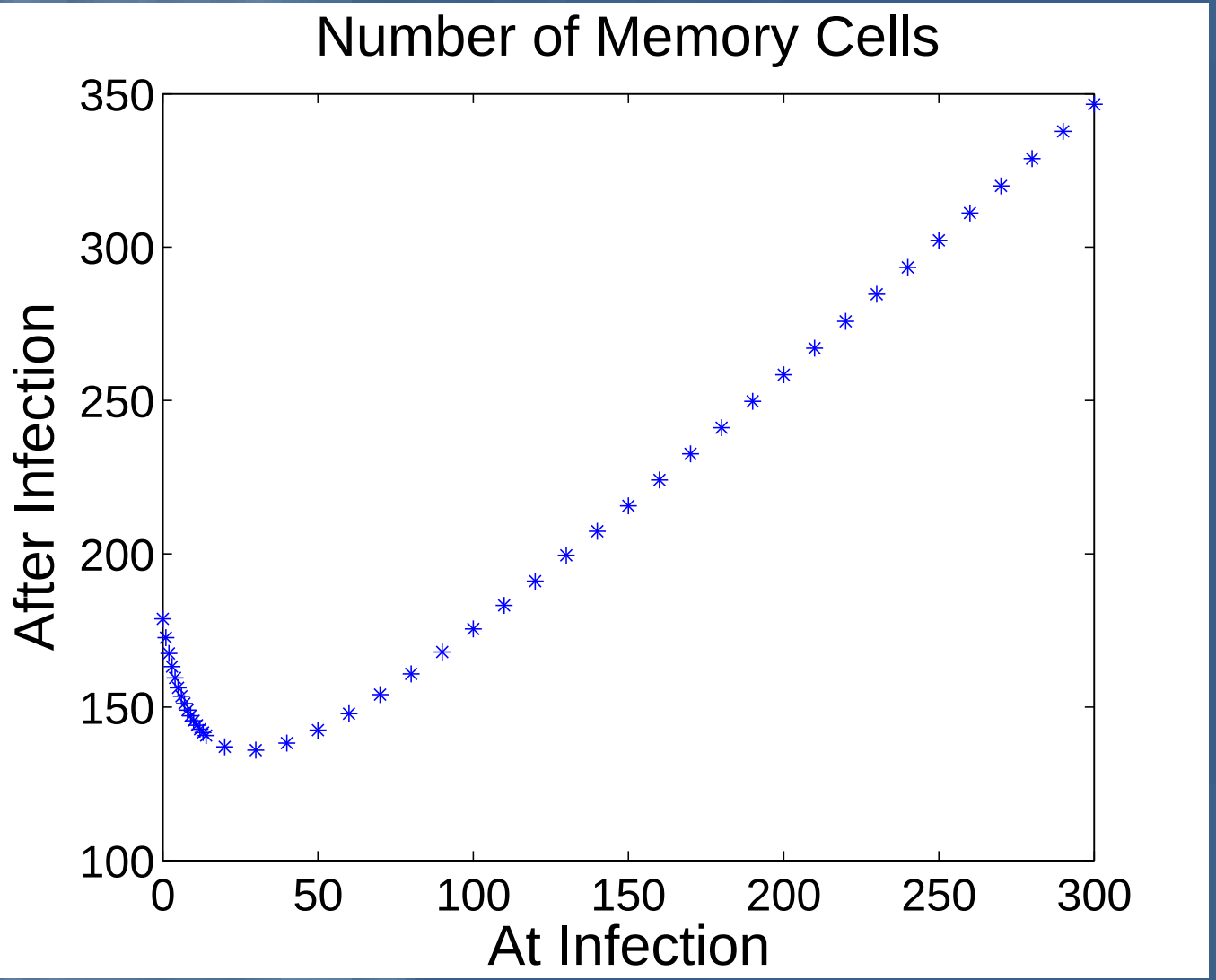
10 mem cells

- Accumulation of quanta in the lungs
- Find area bounded above by blue curve and below by red line

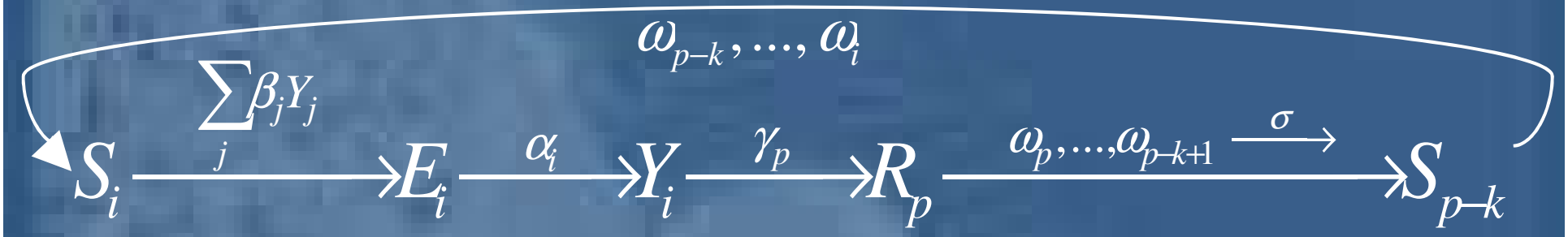
Basic Reproductive Ratio



Peak Memory Cells



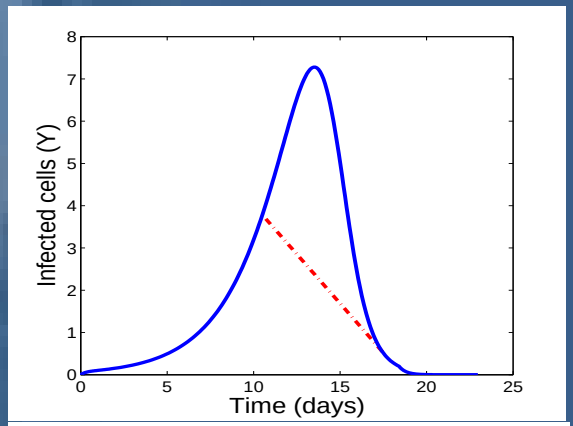
SEIRS Model

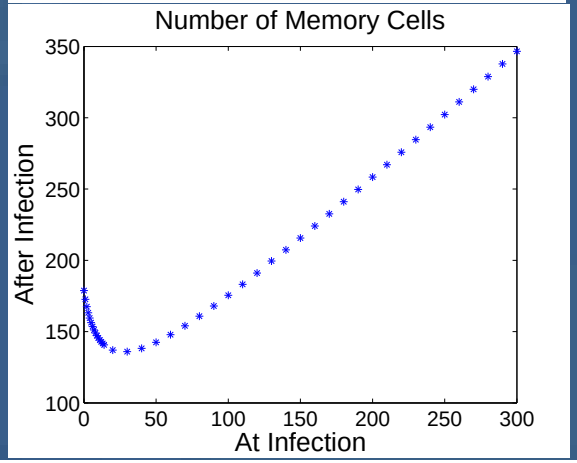


- Parameterize epidemiological model using in-host output

$$\beta_i, \alpha_i, \gamma_i, \omega_i, \sigma$$

- Other Parameters
  - Host natural death rate
  - Host immunity
    - vaccination distribution





SEIRS Model

$$\frac{dS_i}{dt} = \lambda_i - dS_i - S_i \sum_j \beta_j Y_j - \omega_i S_i + \omega_{i+1} S_{i+1} + \sigma R_i$$

$$\frac{dE_i}{dt} = S_i \sum_j \beta_j Y_j - \alpha_i E_i - dE_i$$

$$\frac{dY_i}{dt} = \alpha_i E_i - \gamma_i Y_i - dY_i$$

$$\frac{dR_p}{dt} = \sum_{f(j)=p} \gamma_j Y_j - \omega_p R_p + \omega_{p+1} R_{p+1} - \sigma R_p - dR_p$$

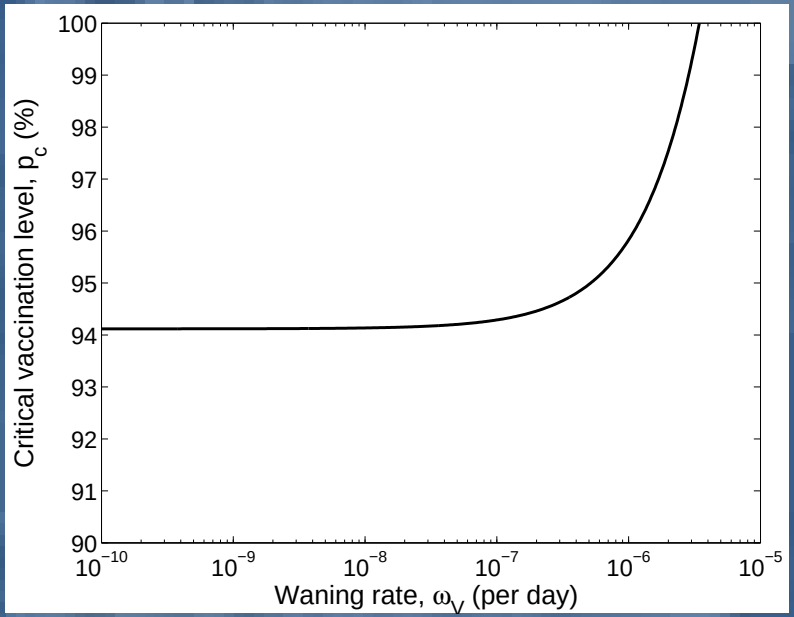
$$R_{0,i} = \frac{\beta_i \bar{S}}{\gamma_i + d} \frac{\alpha_i}{\alpha_i + d} \approx \frac{\beta_i \bar{S}}{\gamma_i}$$

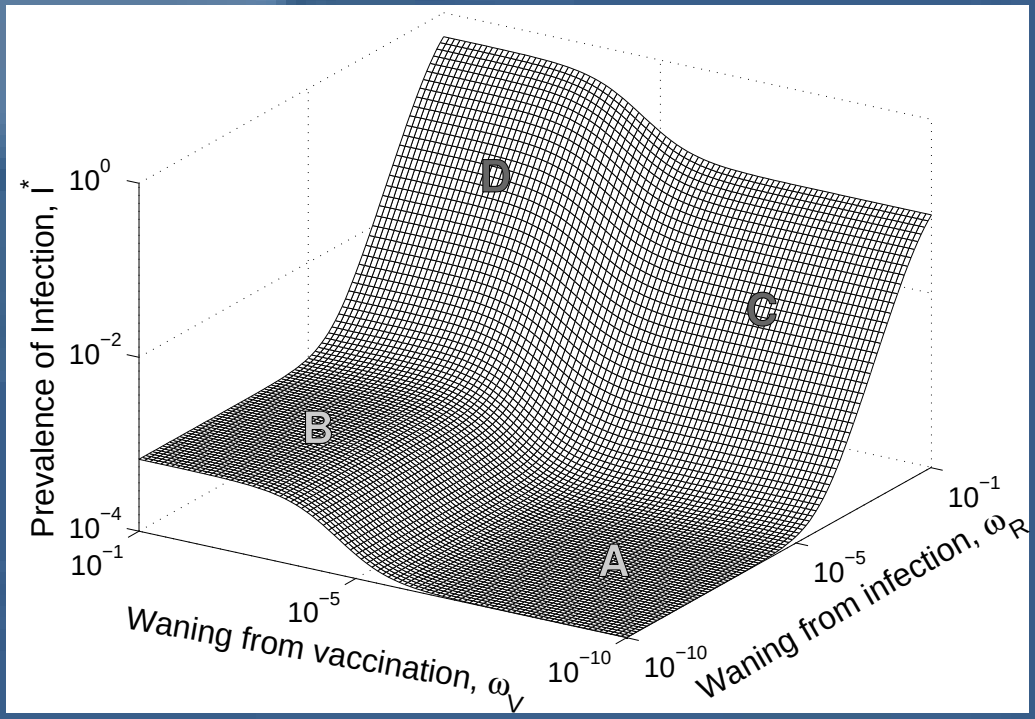
SIRV Model

- Simple model for waning immunity based on SIRV

$$p_c = \left(1 + \frac{w_v}{d}\right)\left(1 - \frac{1}{R_0}\right)$$

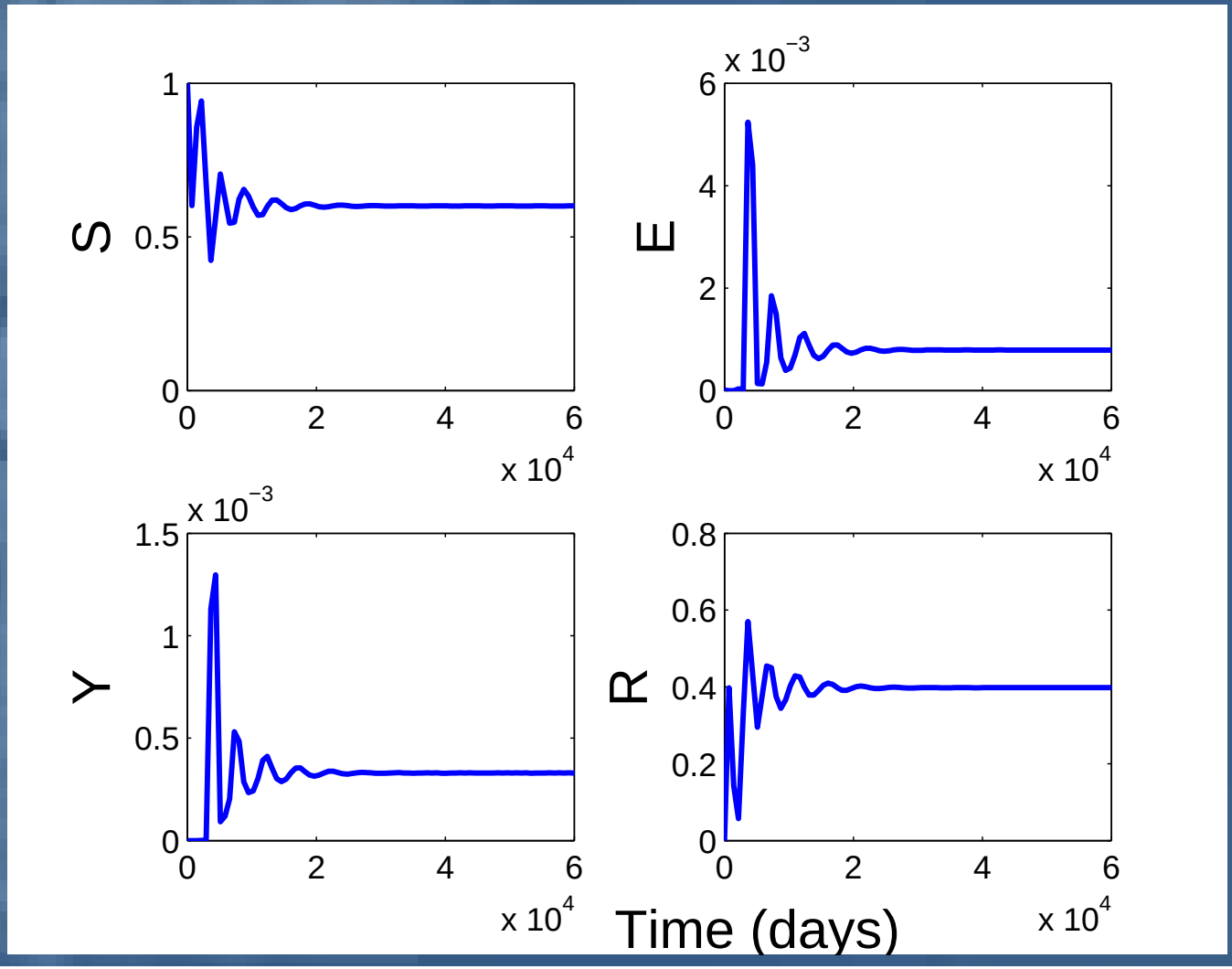
$$I^* = \frac{[(\beta - g - d)w_v + (\beta(1-p) - g - d)d](w_R + d)}{\beta(d + w_v)(g + d + w_R)}$$





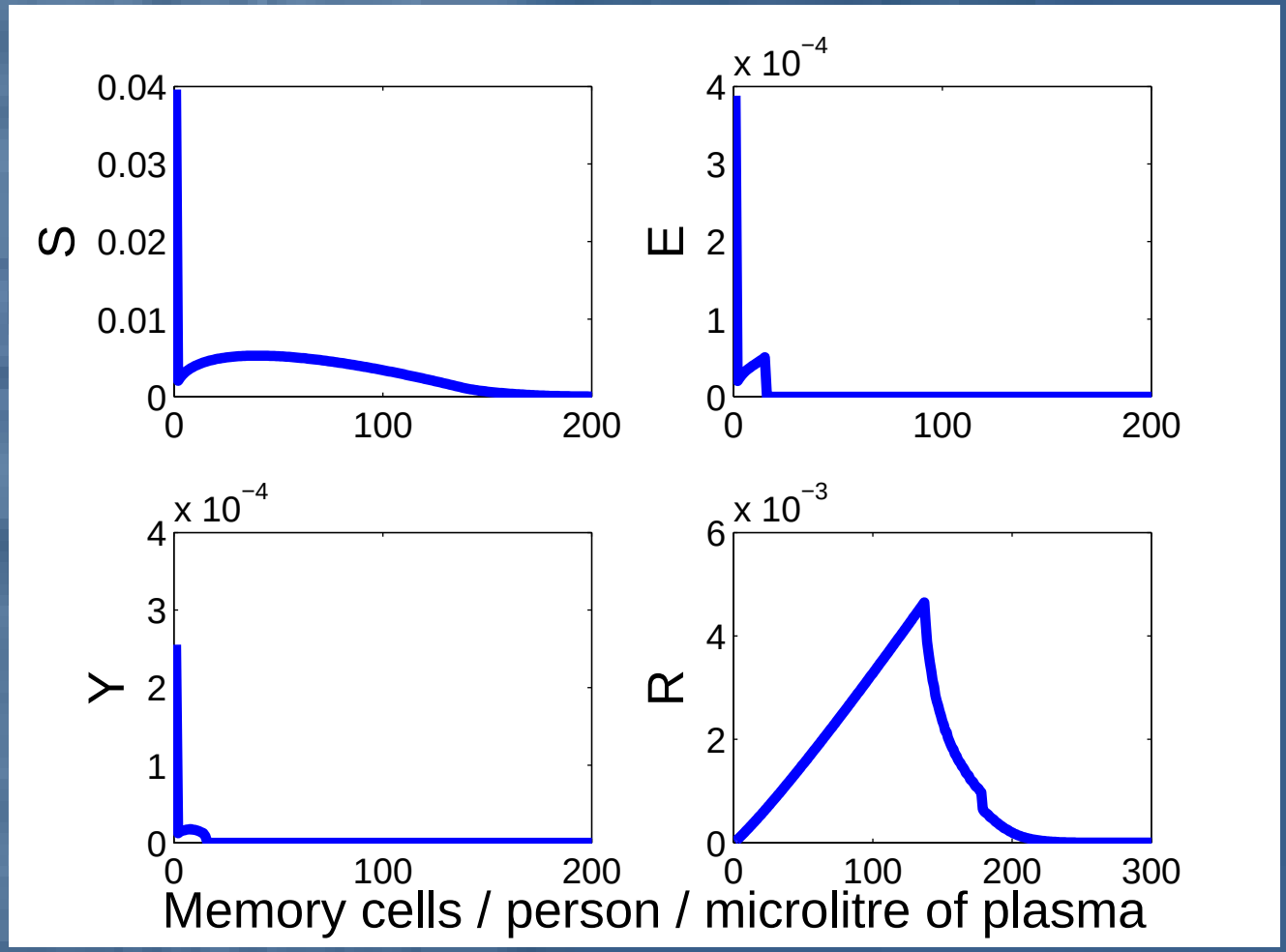
SEIRS Model

- Infected Equilibrium

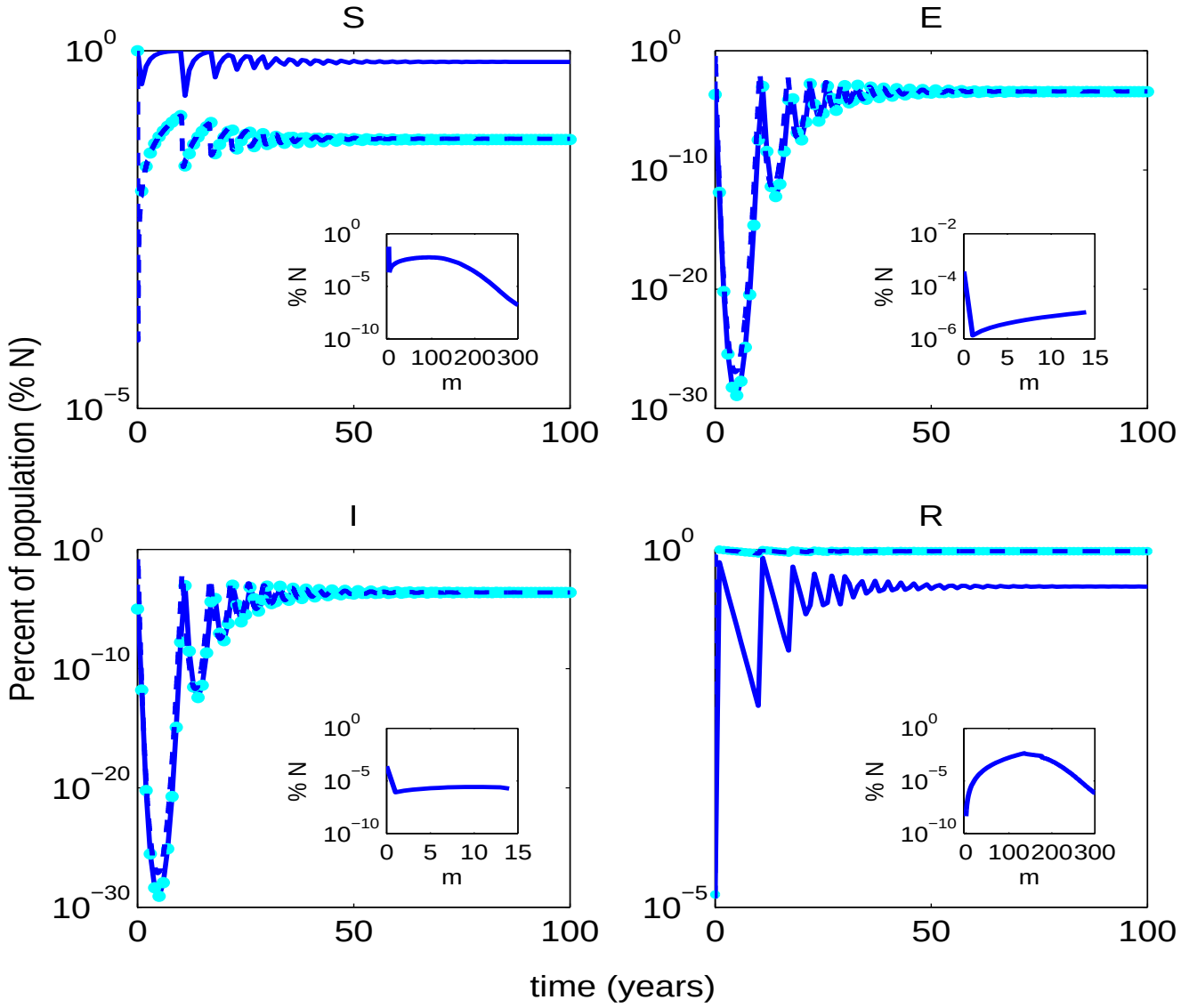


Distribution of Immunity

- Proportion of population in each class with i level of immunity at infected equilibrium



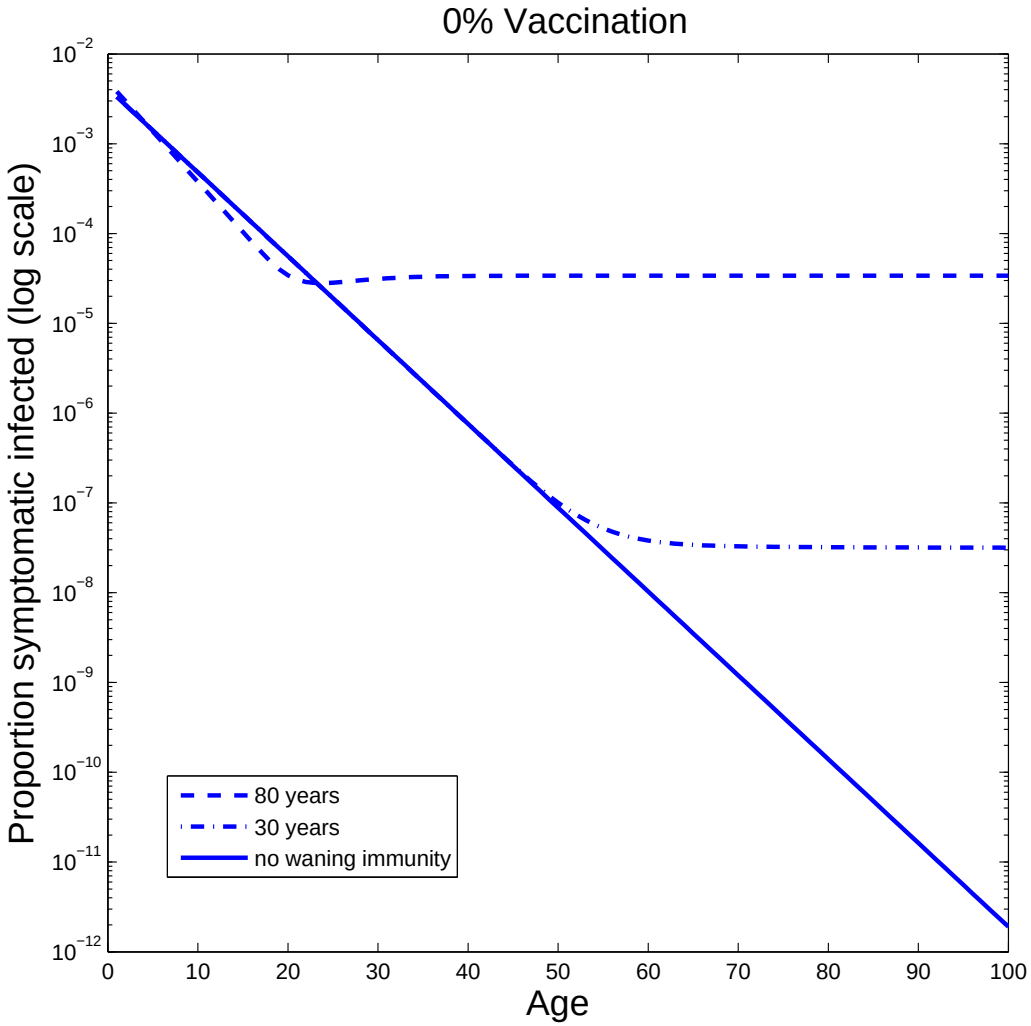
Comparison to SEIR model



Comparison to SEIR model

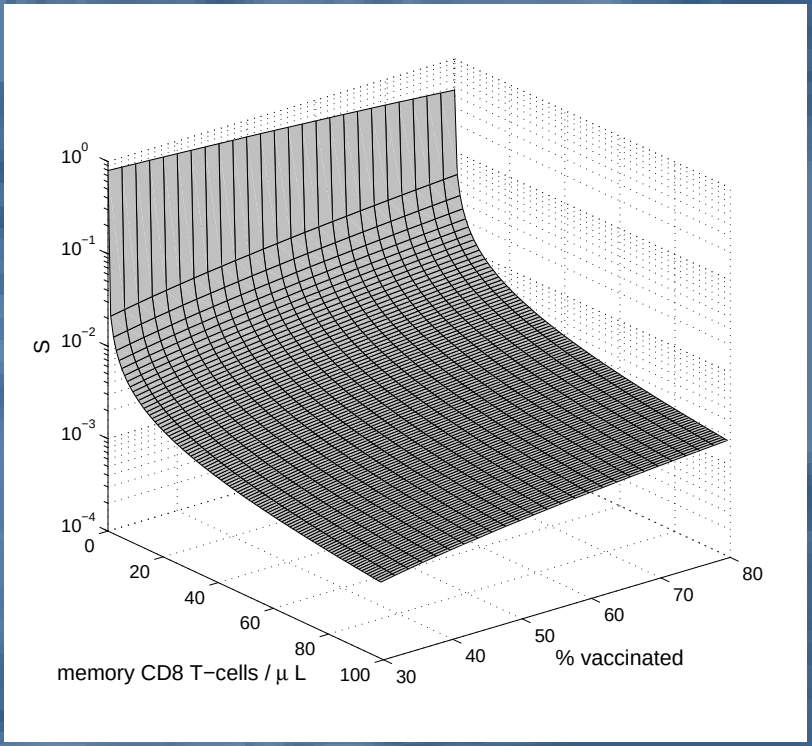
- Ignore birth to determine what happens to 1 individual under constant force of infection (i.e. infected equilbm)
- Start with one S0 (totally susceptible)
- Average age of 1st infection – 4 – 5 years (Anderson and May 1992)
- Immunity is then raised to high levels and decays over host's lifetime
- From system sum(Bi Ii) (rate of encountering infection) is independent of immune status
  - Individual is expected to be infected (and their immunity boosted) every 4-5 years
  - Tail of dist'n get infected and may transmit and may show symptoms
  - However most individuals will just experience boosts since time between exposure is relatively short – LIFELONG IMMUNITY

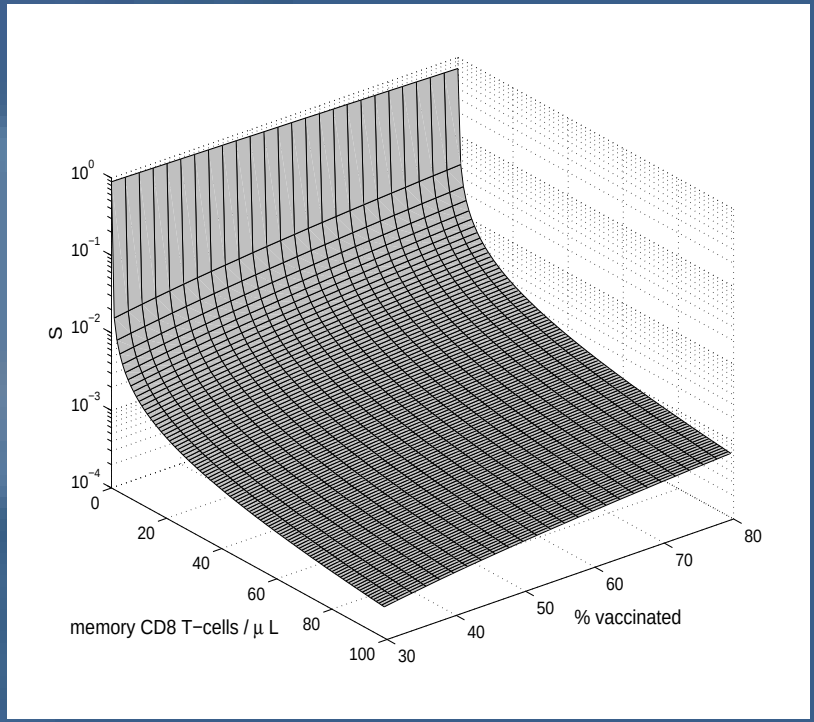
Comparison to SEIR model



- Proportion of population that is symptomatically infected as a function of age
- Variation from standard SEIR is slight and primarily occurs as a mild infection in older individuals

Vaccination

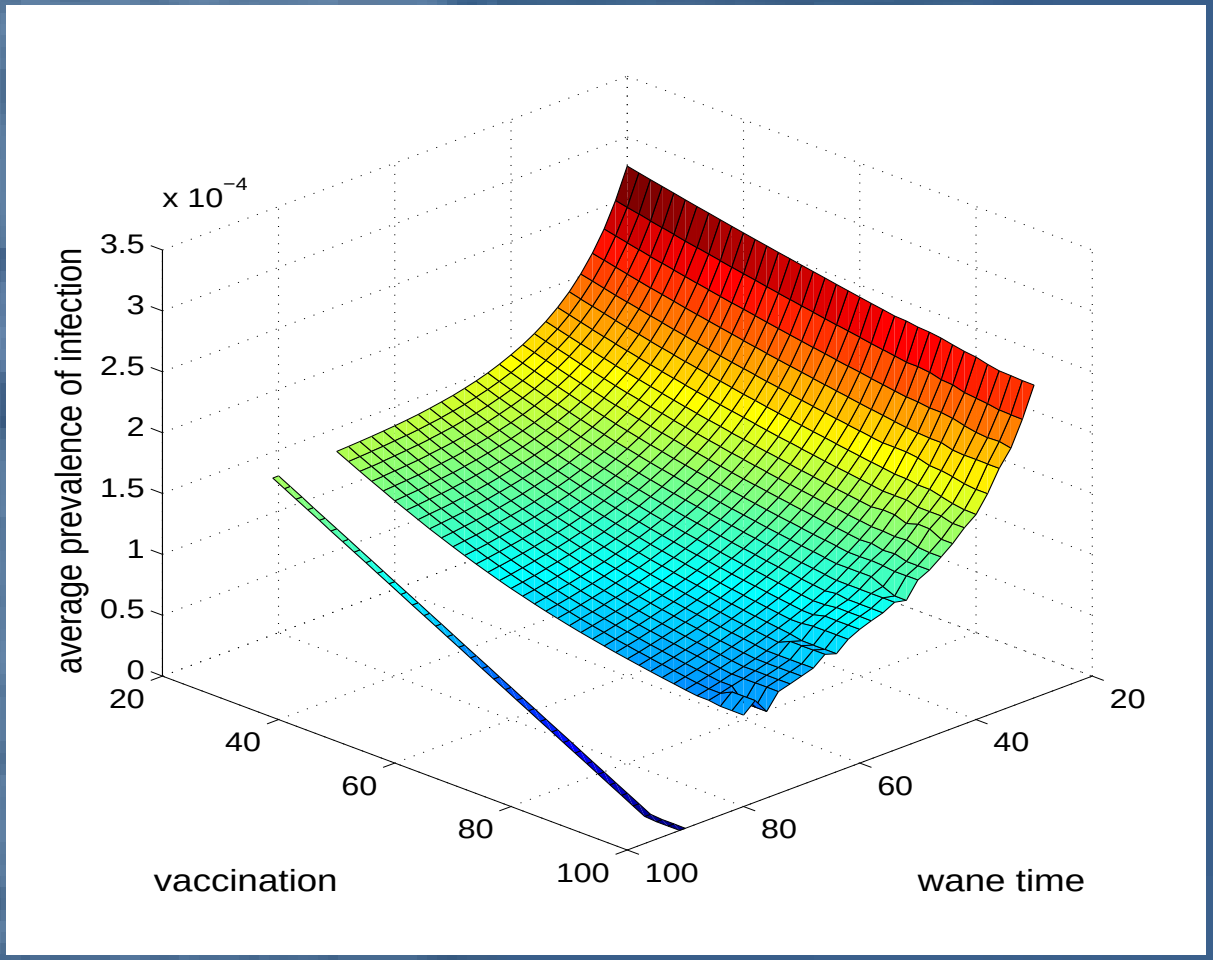




- Distribution of immunity – 30 and 80 years

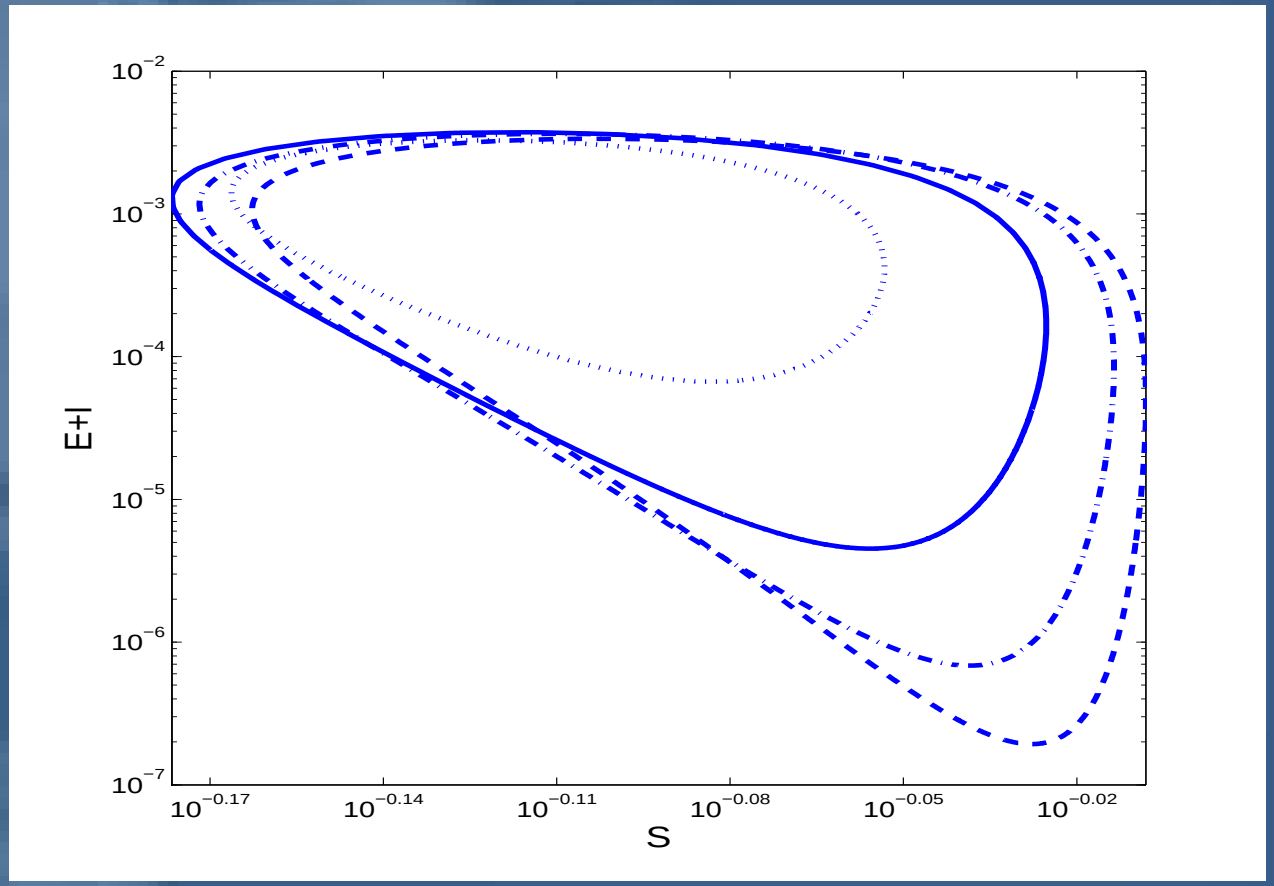
Vaccination

- Waning immunity can severely limit effects of vaccination
  - Prevalence of infection does not decrease linearly with vaccination coverage



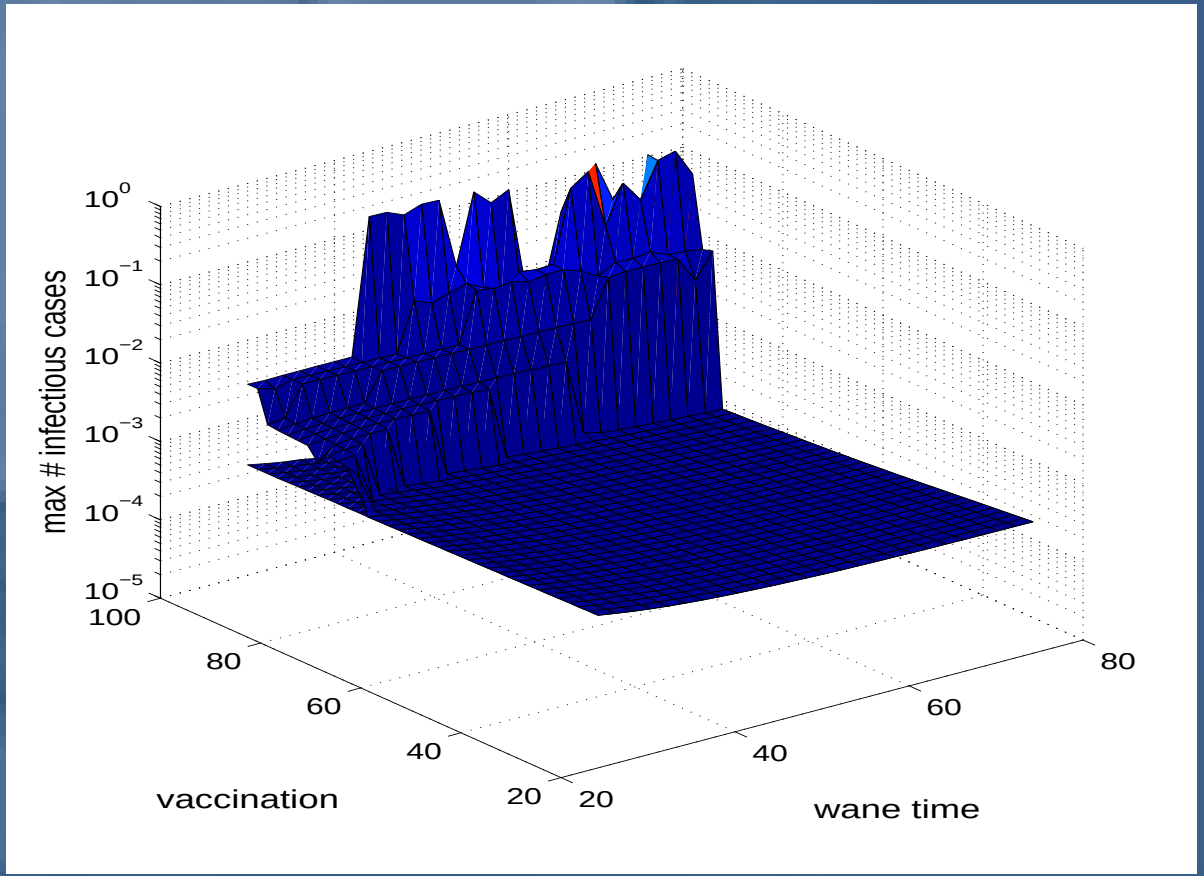
Vaccination

- High levels of vaccination (>70%) and moderate levels of waning immunity (>30 years) lead to large scale epidemic cycles
- 92 % vacc
- 30,40,50,60 years waning immunity

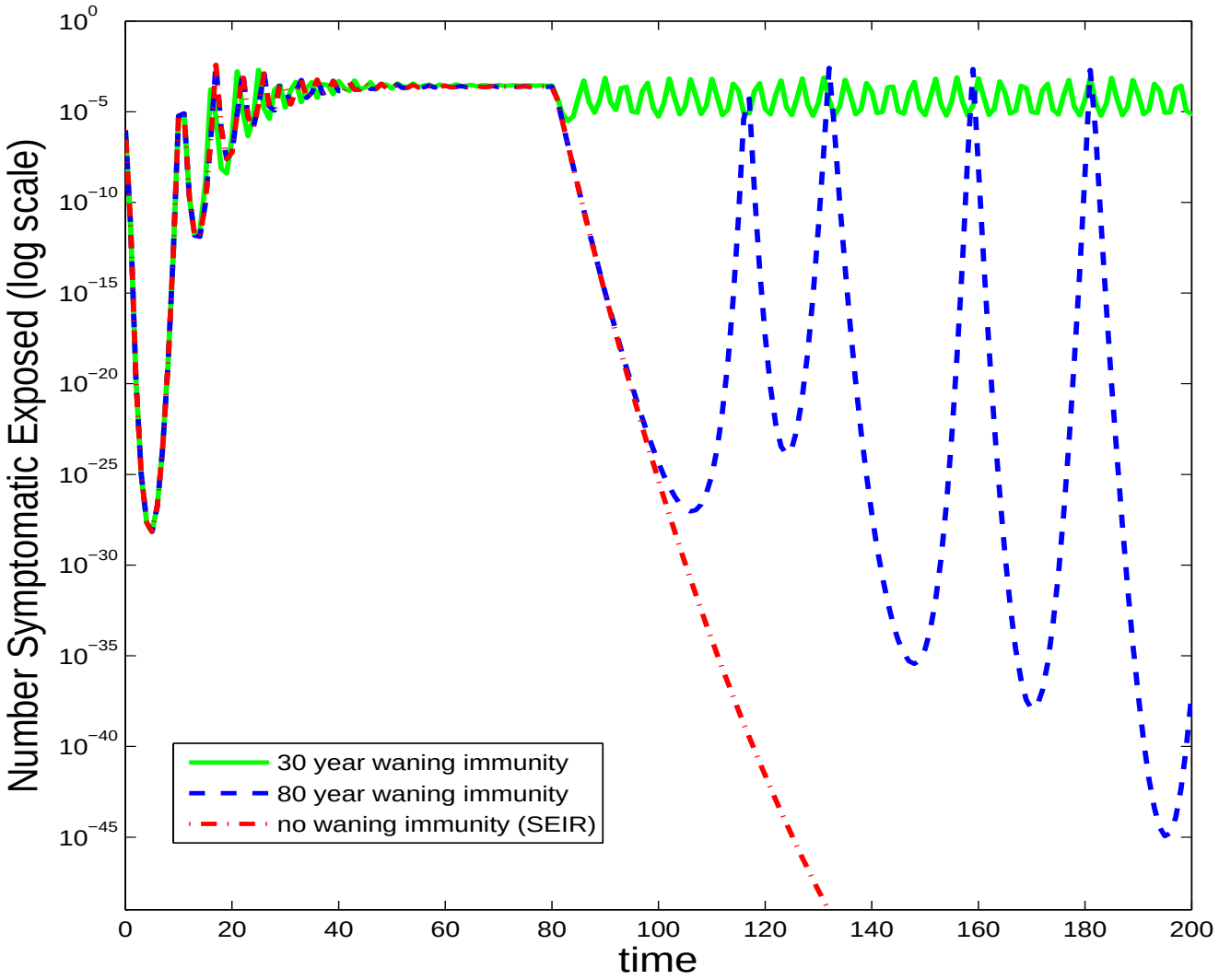


Vaccination

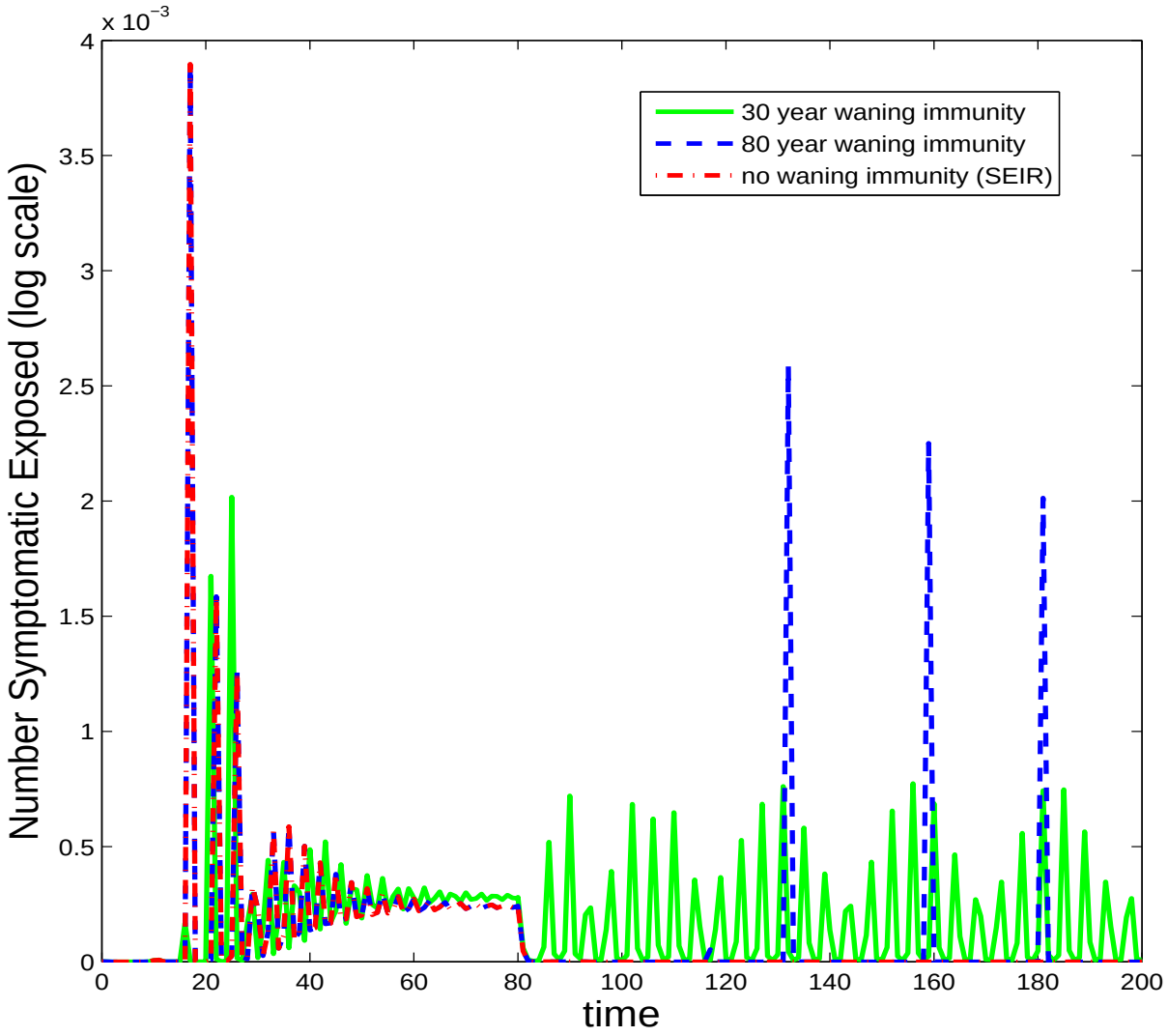
- Maximum proportion of infectious cases around the epidemic cycle compared with average
- Large relative amplitude of the infectious cycles



Vaccination



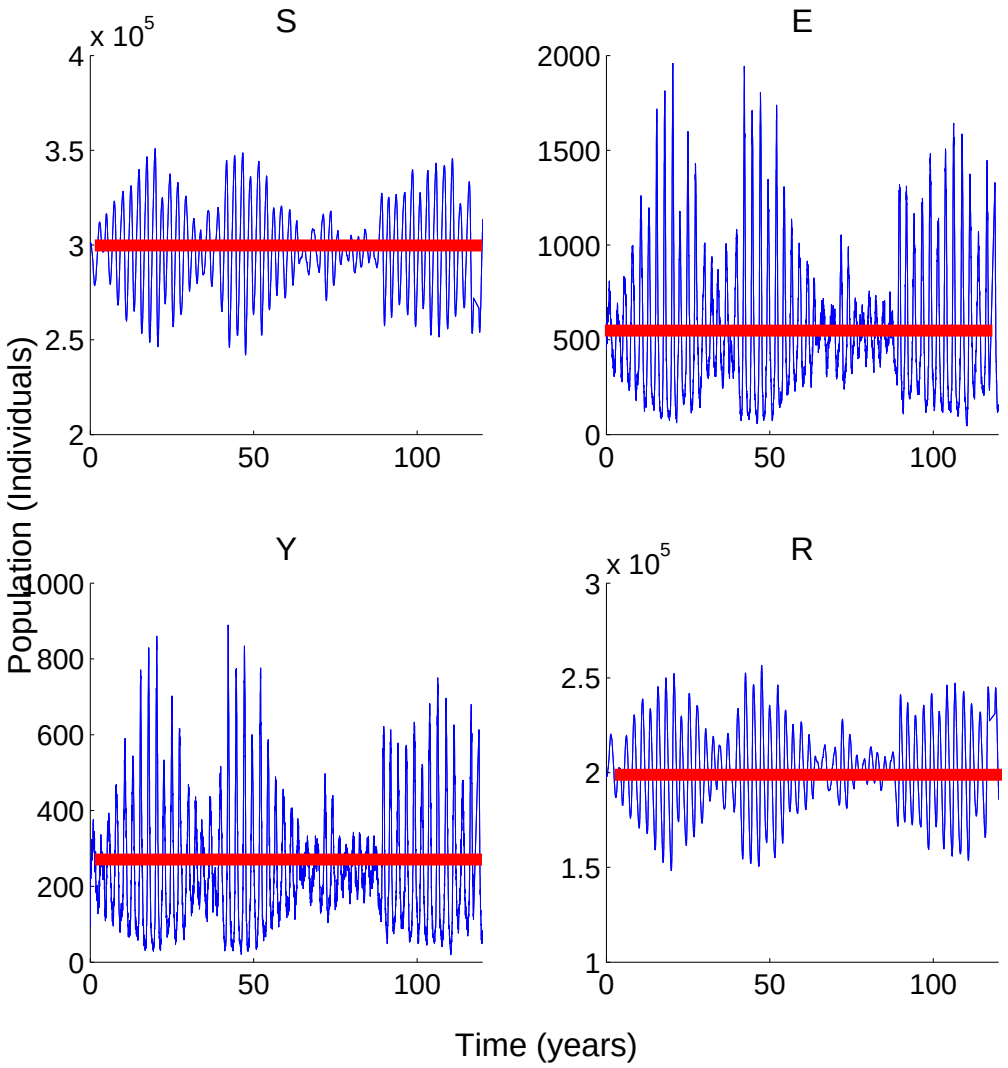
Vaccination



L=6 case

- Can do similar analysis
- Not very different
- Level of infectious cases is higher, but more are asymptomatic
- Magnitude and period is smaller for outbreaks
- Suboptimal boosting

SEIRS Stochastic Simulation



- Same infected equilibrium as the deterministic model
- Critical population size
  - No vaccine - 200,000 – 500,000
  - With vaccine – approx 10 million

Comments on model

- Including humoral immunity
- Seasonal forcing
  - Likely to amplify any short-duration epidemic cycles exhibited by the unforced model, particularly when the unforced period is annual or multi-annual
- Mixing by age
  - Mixing between different age groups is not well known
- Stochastic model
  - Computationally complex
    - Need to keep track of every individual's immune system

Future Work

- Small populations
- Vaccine uptake
  - Levels of vaccination, in-host parameters
- R0
  - age of infection, age of individual
- Networks
  - Contacts, social
- Other pathogens – flu - evolution

Thank You!

- Matt Keeling
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- References:

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