Infectious Disease Management

Insights from simple models

The Anatomy of an Epidemic

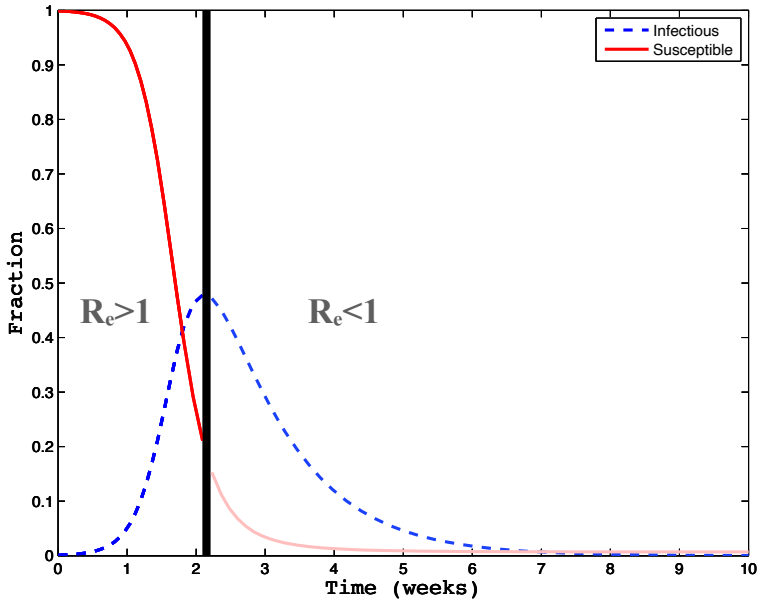
Initially, exponential growth (proportional to R_0, specifically $\gamma(R_0 - 1)$)

But, depletes susceptibles, so R_0 no longer useful

Instead, define effective value of R_0 (call it R_e)

R_e scales with proportion of susceptibles in population (S=X/N), ie $R_e = R_0 S$

when $R_e<1$, each infectious individual infects fewer than one new person, breaking transmission chain



Vaccination

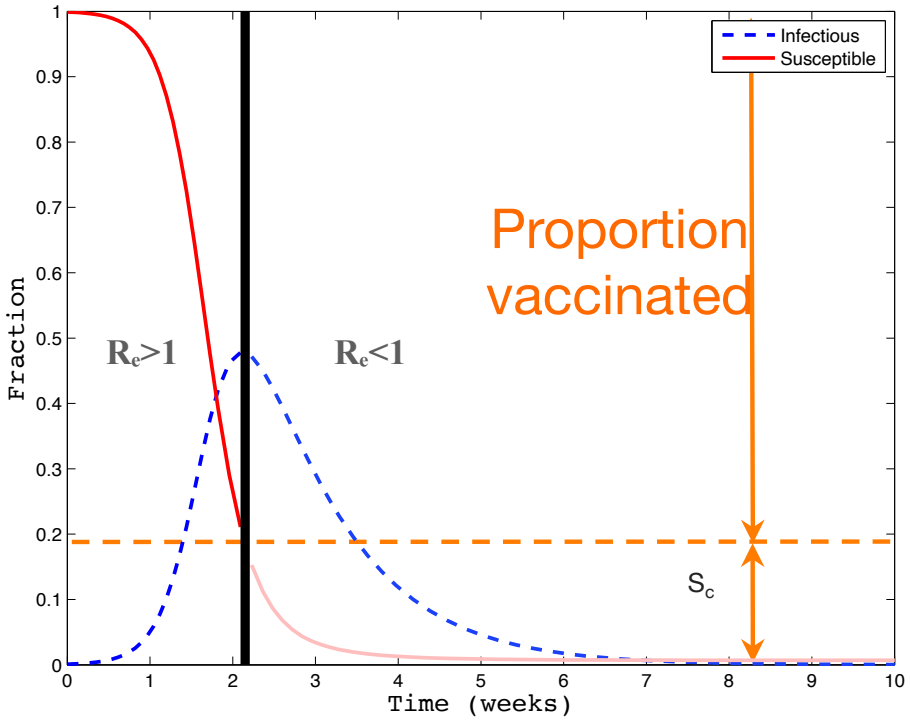
If, by vaccination, we can reduce proportion of susceptibles below a critical level, S_c, then $R_e<1$ and infection cannot invade

Recall: $R_e = R_0X/N$

So, $S_c=1/\mathbf{R_0}$ represents $R_e=1$ and will achieve our goal

So, critical vaccination proportion to eradicate is

$p_c = 1-S_c = 1-1/\mathbf{R_0}$



Mathematically ...

- Consider rate of change of invectives:

$$\frac{dY}{dt} = \beta X \frac{Y}{N} - \gamma Y$$

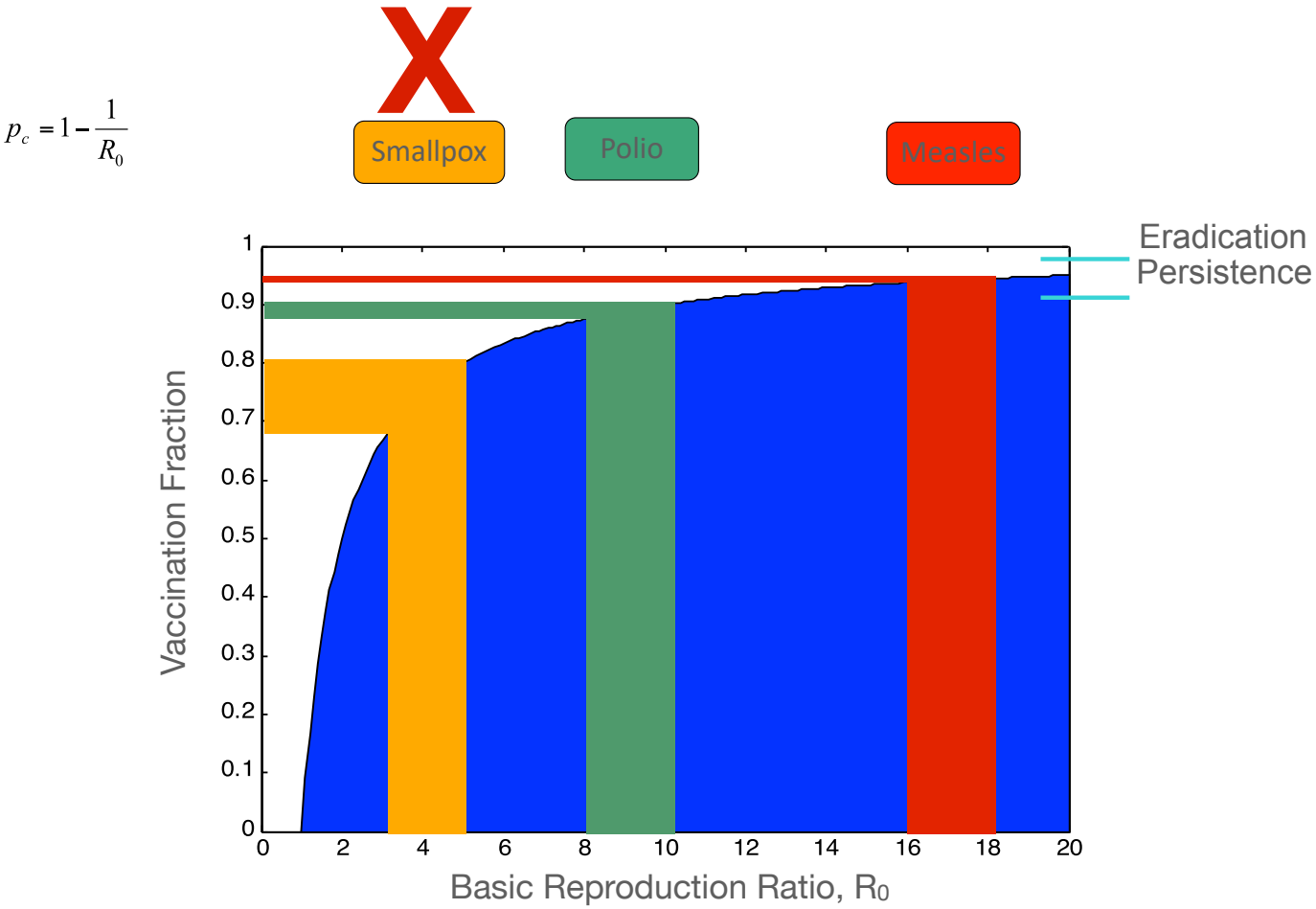
- Hence, preventing initial spread (dY/dt <0) requires

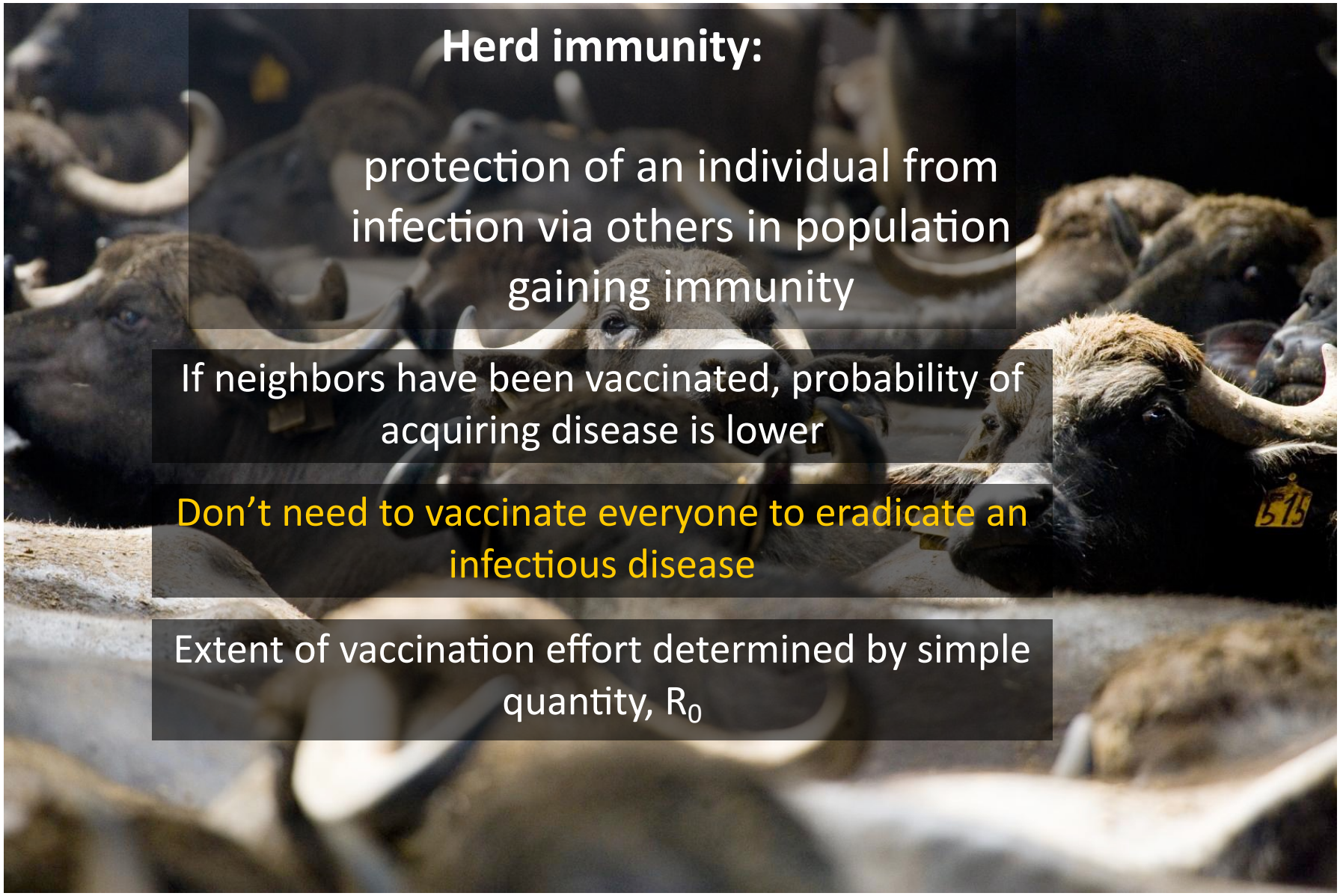
$$\beta \frac{X}{N} < \gamma$$

$$\implies \frac{X}{N} < \frac{\gamma}{\beta} = \frac{1}{R_0}$$

Eradication Criterion

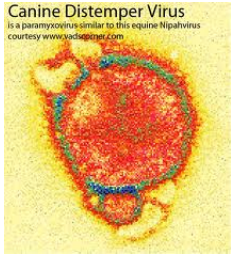
$$p_c = 1 - \frac{1}{R_0}$$




Herd immunity:
protection of an individual from infection via others in population gaining immunity
If neighbors have been vaccinated, probability of acquiring disease is lower
Don’t need to vaccinate everyone to eradicate an infectious disease
Extent of vaccination effort determined by simple quantity, R_0

1. Random Immunization

- Consider wildlife diseases
- Or a pandemic!
- Pragmatically, will need continuous vaccination instead



“Random immunization”

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

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

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

- After some algebra:

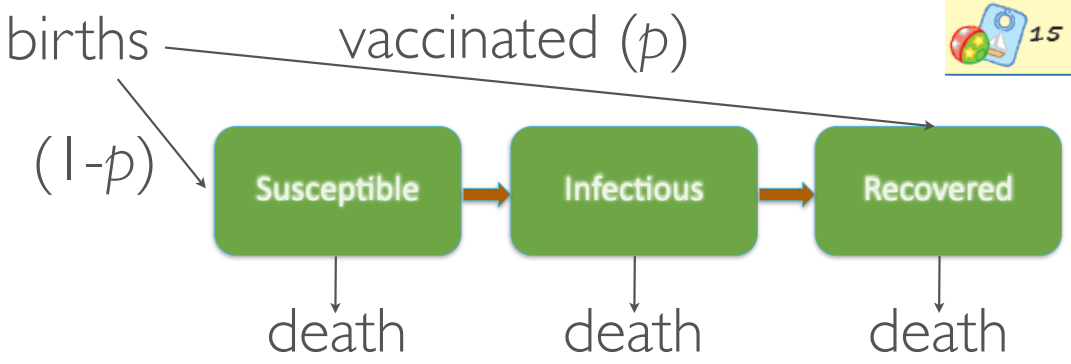
$$I^* = \frac{\mu}{\beta}\left(R_0 - 1 - \frac{\rho}{\mu}\right)$$

- Eradication → I*=0
- Requires $\rho \geq \mu\left(R_0 - 1\right)$
- This is **rate** of susceptibles to be immunized for (eventual) control
- What does criterion tell us, biologically?

2. “Paediatric immunization”

- Familiar with infant immunization
- Generally treated as fraction, p, of newborns vaccinated

at birth	HepB
2 months	HepB (1-2 mos) + DTaP + PCV13 + Hib + Polio + RV
4 months	DTaP + PCV13 + Hib + Polio + RV
6 months	HepB (6-18 mos) + DTaP + PCV13 + Hib + Polio (6-18 mos) + RV
12 Months	MMR (12-15 mos) + PCV13 (12-15 mos) + Hib (12-15 mos) + Varicella (12-15 mos) + HepA (12-23 mos)
15 months	DTaP (15-18 mos)



2. “Paediatric immunization”

- Model this (as one time event)

$$\frac{dS}{dt} = \mu(1-p) - \beta SI - \mu S$$
$$\frac{dI}{dt} = \beta SI - (\mu + \gamma)I$$
$$\frac{dR}{dt} = \mu p + \gamma I - \mu R$$

  - Now what?
  - Let’s derive expression for I*

“Paediatric immunization”

$$\frac{dS}{dt} = \mu(1-p) - \beta SI - \mu S$$

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

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

- After some algebra:

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

- Eradication implies I*=0
- Requires $p = 1 - 1/R_0$

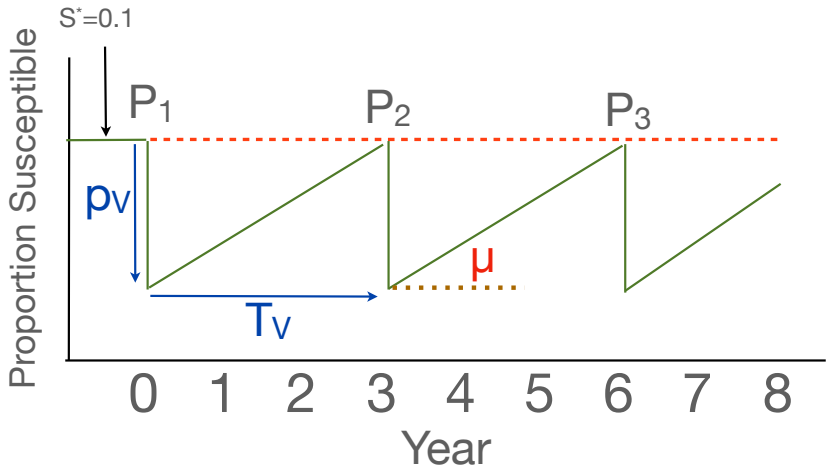
  - This is **fraction** of newborns to be immunized for (eventual) control

3. “Pulsed” Vaccination

- Routine infant & Continuous vaccination schemes require sound infrastructure for vaccine delivery
  - may be challenging in many settings

- Alternative, perhaps more economic and logistically efficient strategy may be pulsed vaccination: immunize specific age cohorts at specified intervals

Pulsed Vaccination



- Assume R_0 = 10
- p_V = 60% and *per capita* annual birth rate = 2%
- For dI/dt<0, need to ensure S < 1/10
- After any pulse, S = 1/10 * 0.4 = 0.04
- Since μ=0.02, it'll take 3 years for S to reach 0.1
- So, pulse period = 3 yrs

More formally …

- For an SIR model:

$$\frac{dS}{dt} = \mu - \beta SI - \mu S - p_V \sum_{n=0}^{\infty} S(nT^-)\delta(t - nT)$$

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

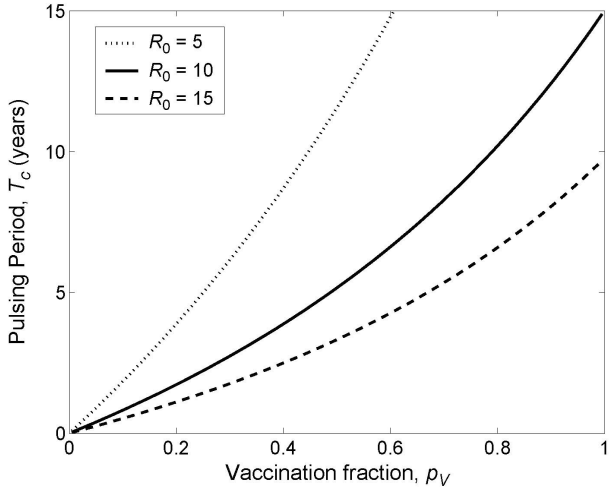
Vaccination fraction

Susceptibles prior to PV

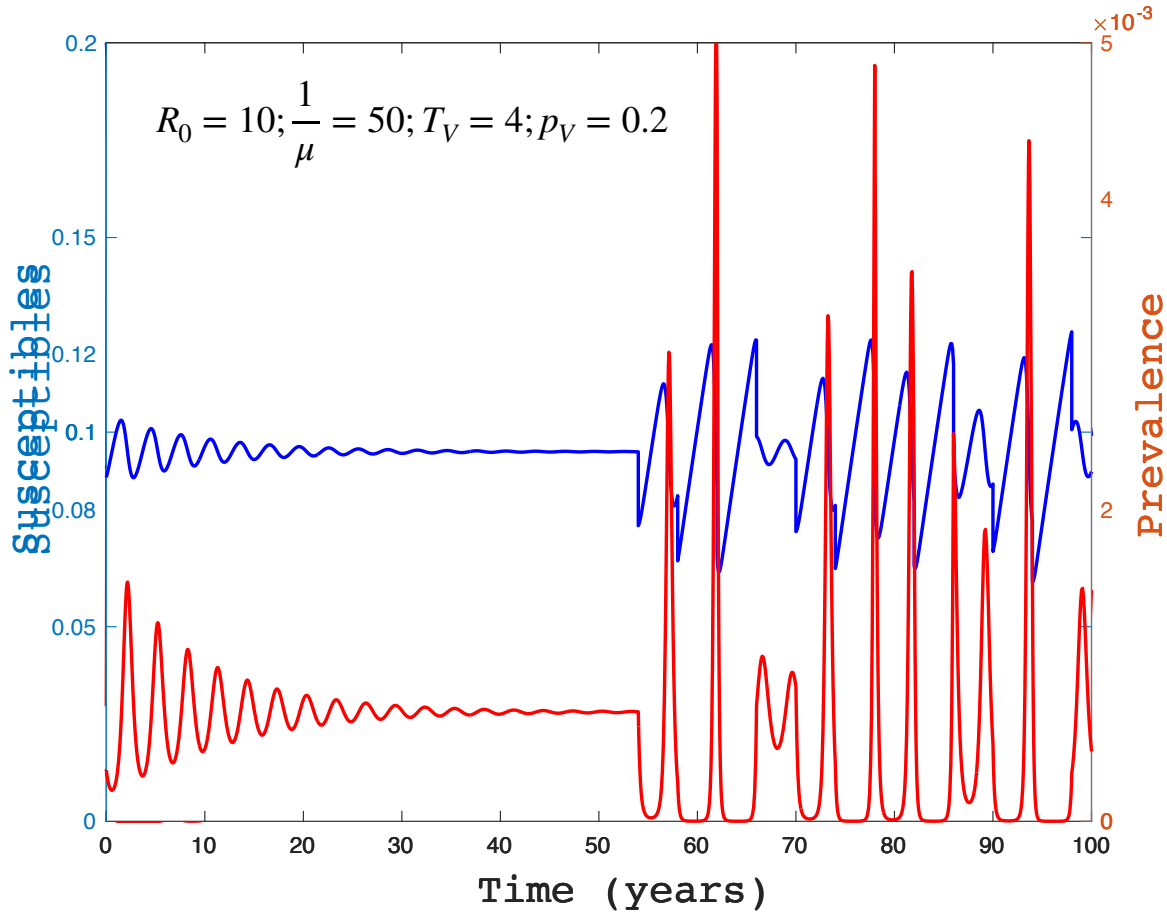
Dirac delta function

- Shulgin *et al.* (1998; Bull Math Biol): Linear stability analysis reveals eradication criterion

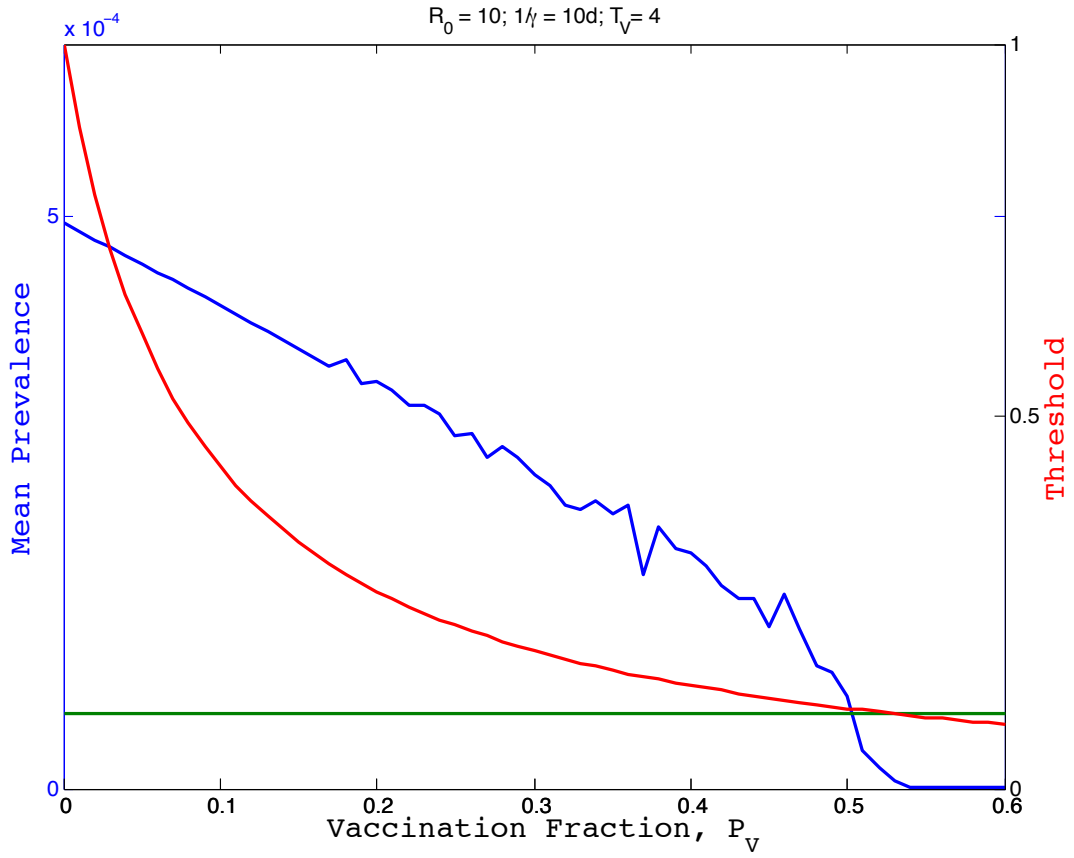
$$\frac{(\mu T - p_V)(e^{\mu T} - 1) + \mu p_V T}{\mu T(p_V - 1 + e^{\mu T})} < \frac{1}{R_0}$$



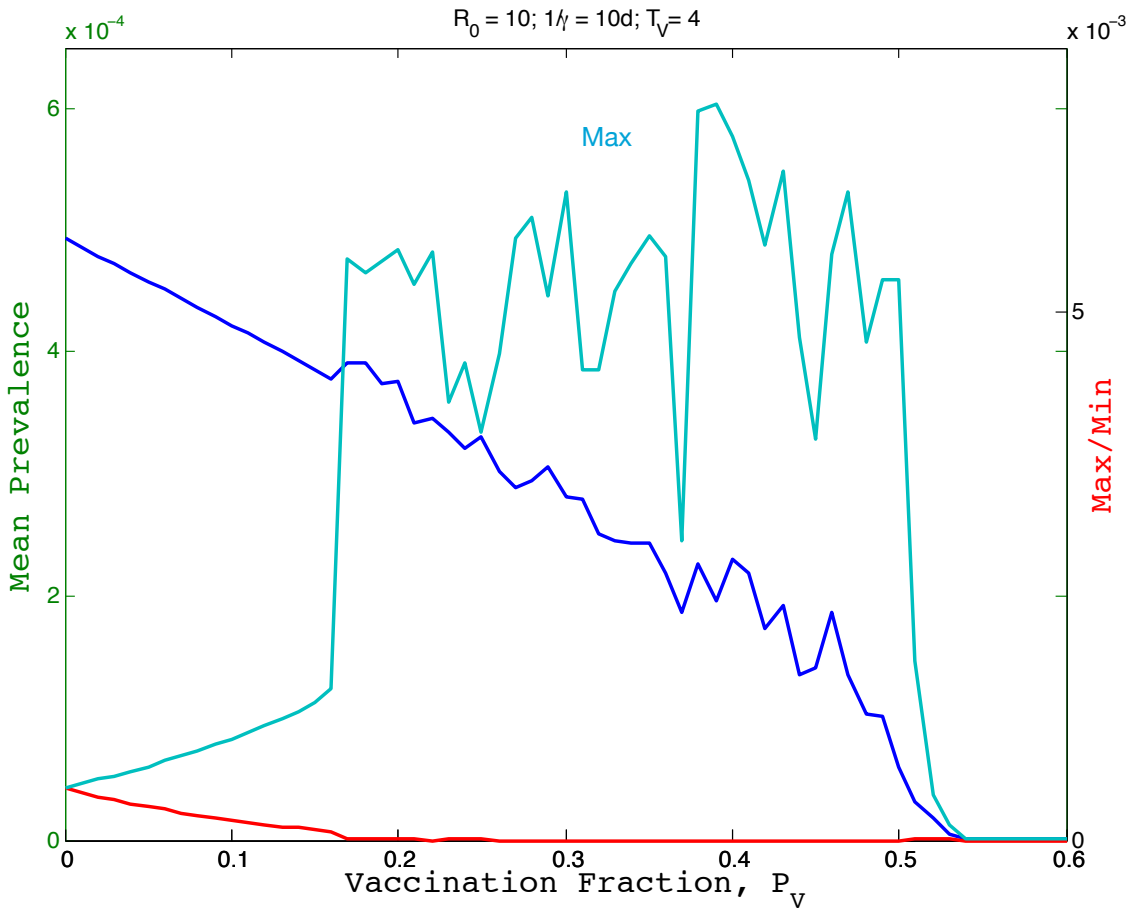
Pulsed Vaccination in Action!



Programming:

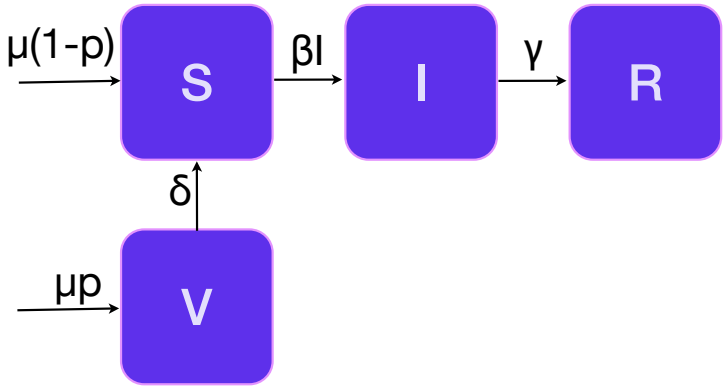


Programming Challenge:



Aside: Imperfect Vaccines

- What if –as is at times the case– immunity derived from a vaccine wanes over time?



$$\frac{dS}{dt} = \mu(1-p) - \beta SI - \mu S + \delta V$$

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

$$\frac{dV}{dt} = \mu p - (\mu + \delta)V$$

Aside: Imperfect Vaccines

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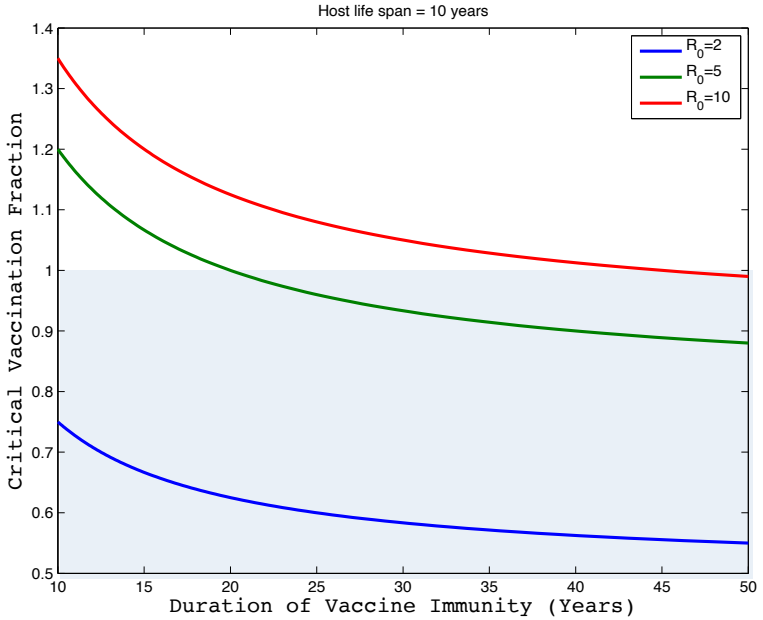
$$\frac{dV}{dt} = \mu p - (\mu + \delta)V$$

Eradication requires (Check this)

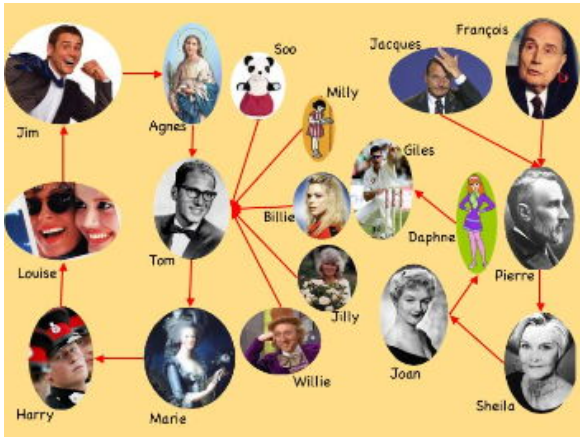
$$p = \left(1 - \frac{1}{R_0}\right)\left(1 + \frac{\delta}{\mu}\right)$$

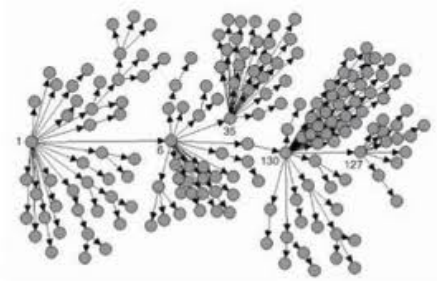


Eradication will require boosters

4. Non-Pharmaceutical Interventions

- "Social distancing"
- Isolation and quarantining
- We should also find (or trace) their contacts





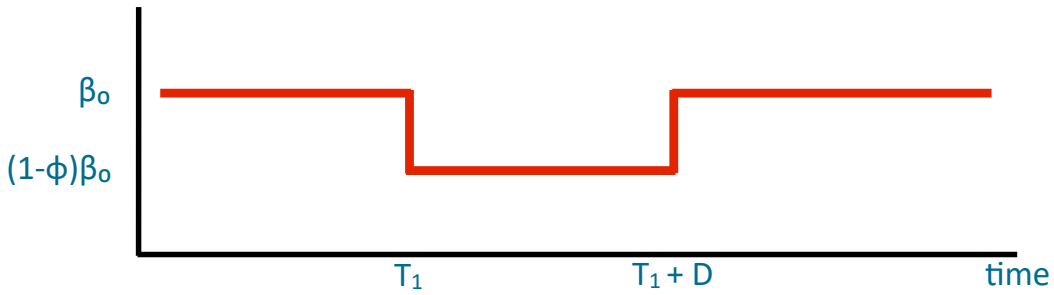
Background

- Pandemic planning
  - Consider emerging pathogen
  - Everyone susceptible
  - No pharmaceutical defense (drugs/vaccines)
  - Only Non-Pharmaceutical Interventions would work

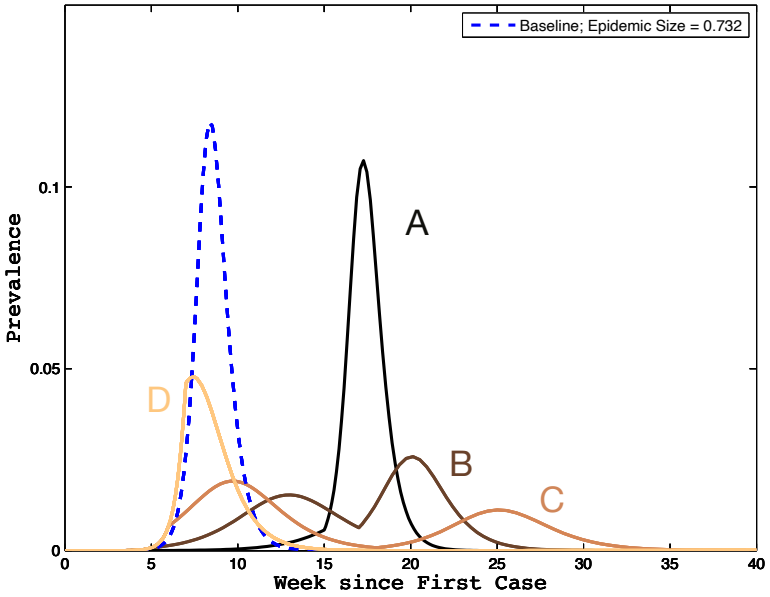
Social distancing
  - How long?
  - What extent?

Protocol

- Basic reproduction ratio $R_0 = 1.8$
- Recovery rate $\gamma = 1/2.6$ day^{-1}
  - Generation time 2.6 days
- Baseline transmission rate $\beta_0 = R_0 \gamma$
- Population size $n = 58.1$ million (UK)

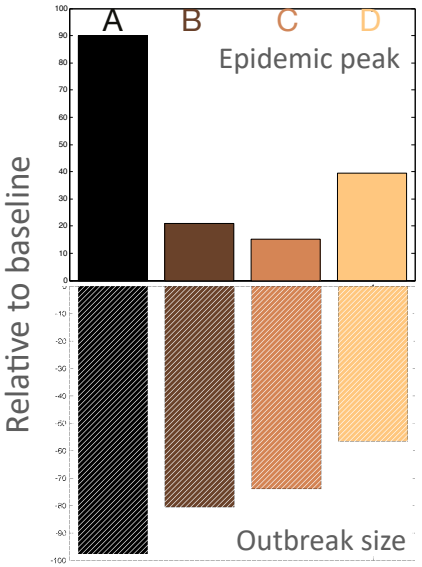


Intervention D=12 weeks



Intervention $\phi = 0.333$
Start (week)

- A: $T_1 = 3$
- B: $T_1 = 5$
- C: $T_1 = 6$
- D: $T_1 = 7$



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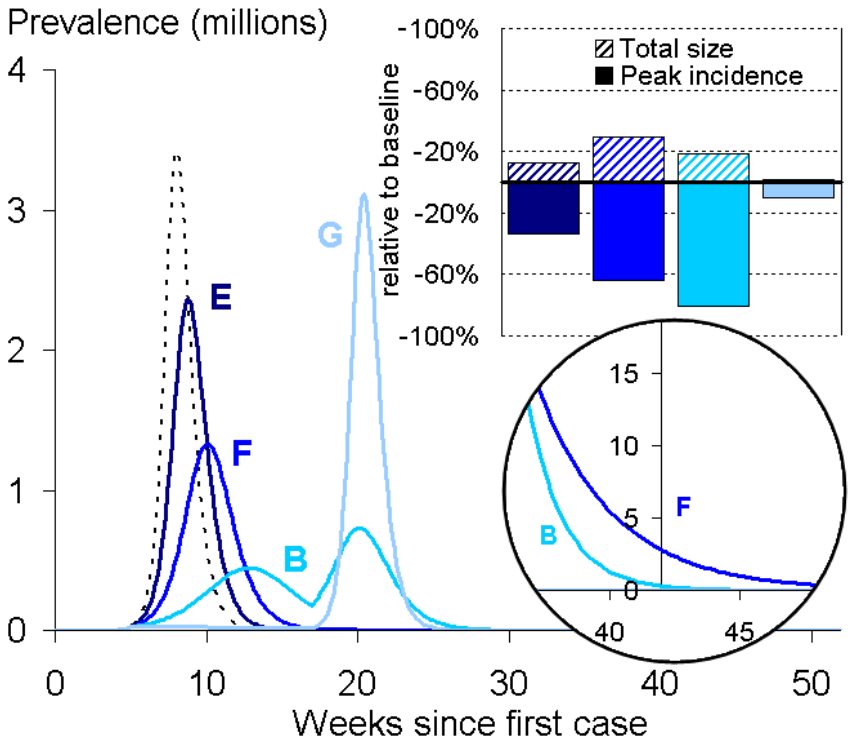


- Start (week) $T_1 = 5$
- Intervention

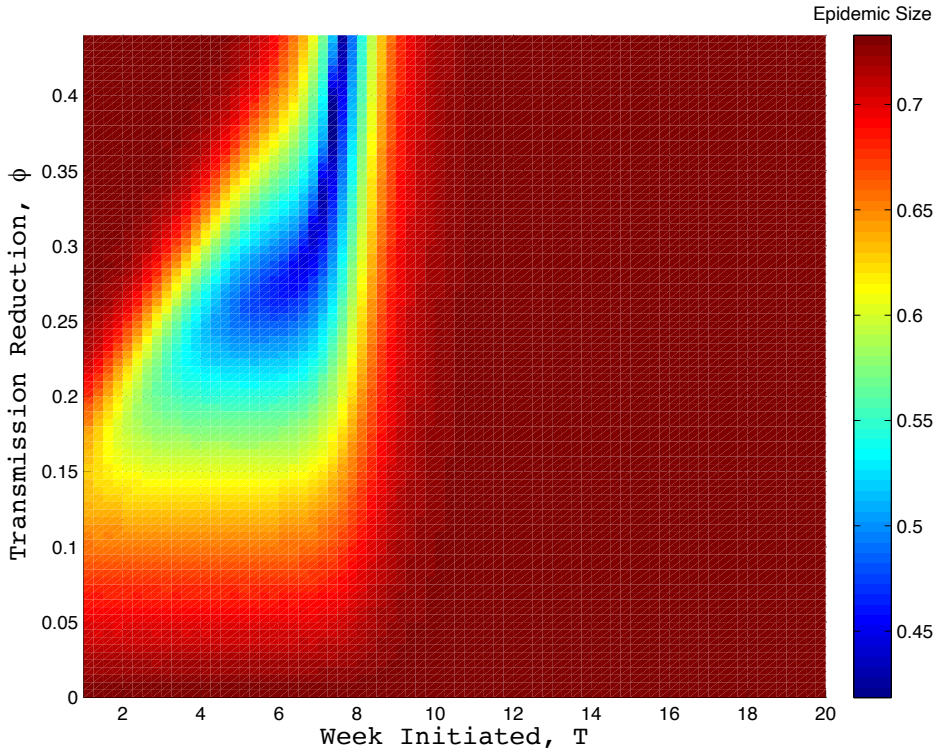
E: $\phi = 0.111$

F: $\phi = 0.222$

B: $\phi = 0.333$

G: $\phi = 0.444$

Intervention D=12 weeks



Depending on aims of control, efforts that are too early or too severe may be counter-productive

Modeling NPI

Assume average contact rate, κ

Transmission probability, ν

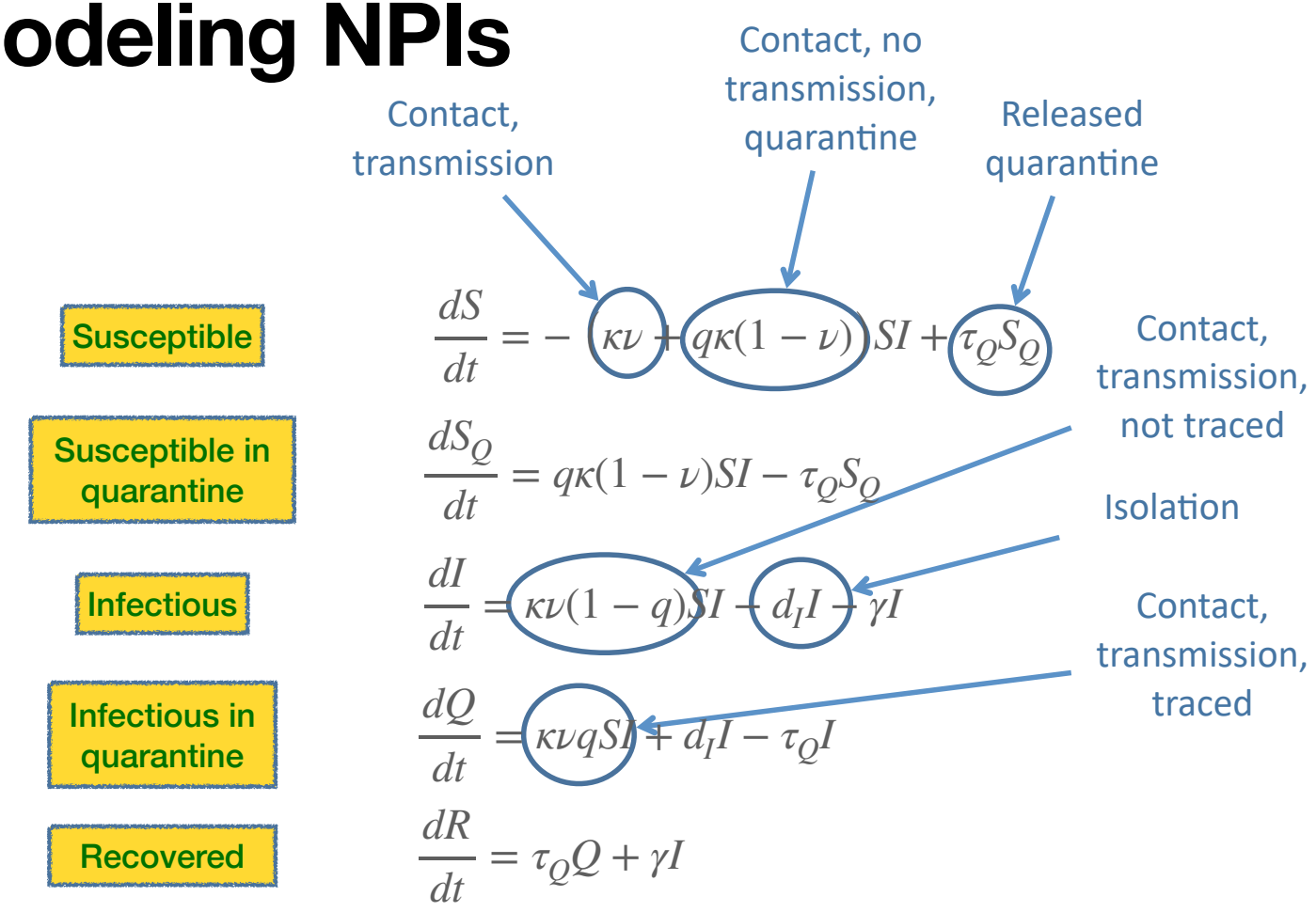
Infectious individuals immediately symptomatic

Infectious isolated at *rate* d_I

Fraction *q* of contacts with infectious quarantined

Kept in quarantine for average τ_Q

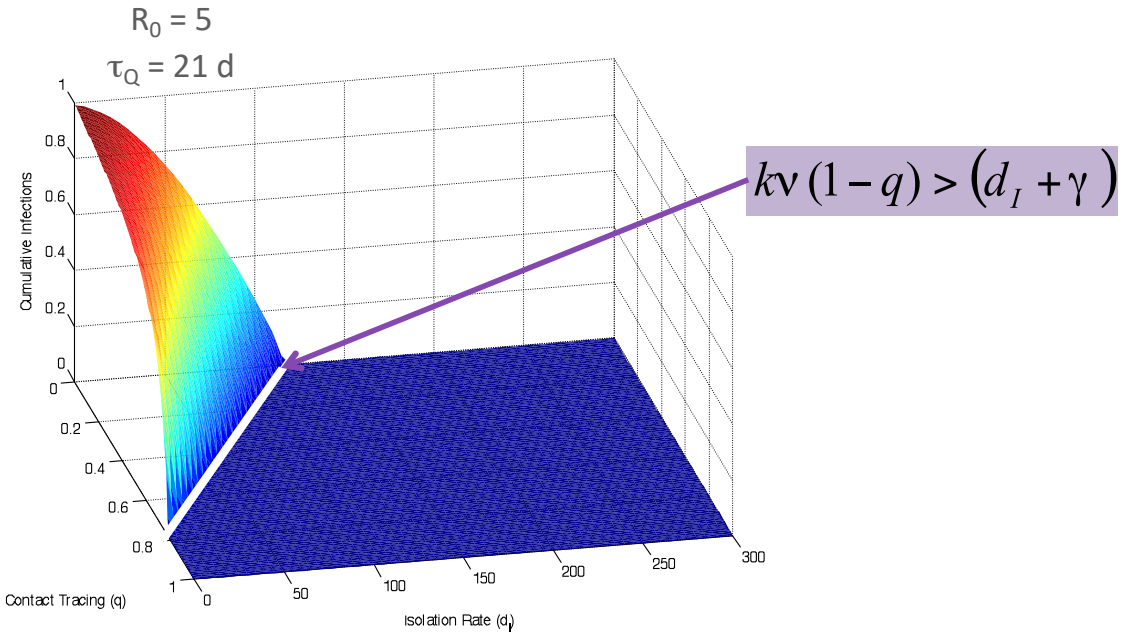
Modeling NPIs



What does it tell us?

Can show control requires

$$S < \frac{(d_I + \gamma)}{k\nu(1-q)}$$



Yes, but …

Key realities we've ignored:

1. Assumed infectious individuals immediately symptomatic (often, clinical presentation a few days after infectiousness, eg SARS)
2. Uncertainties & delays in identifying and isolating potential contacts

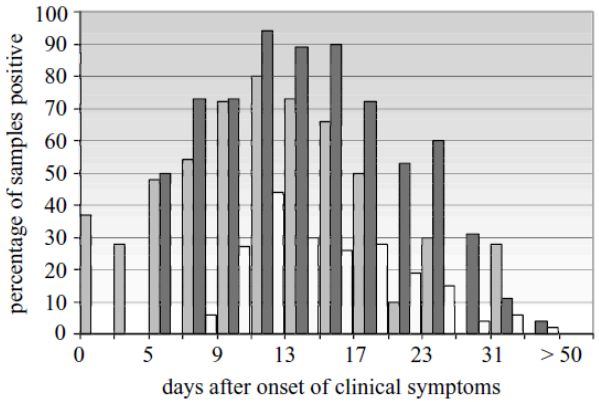
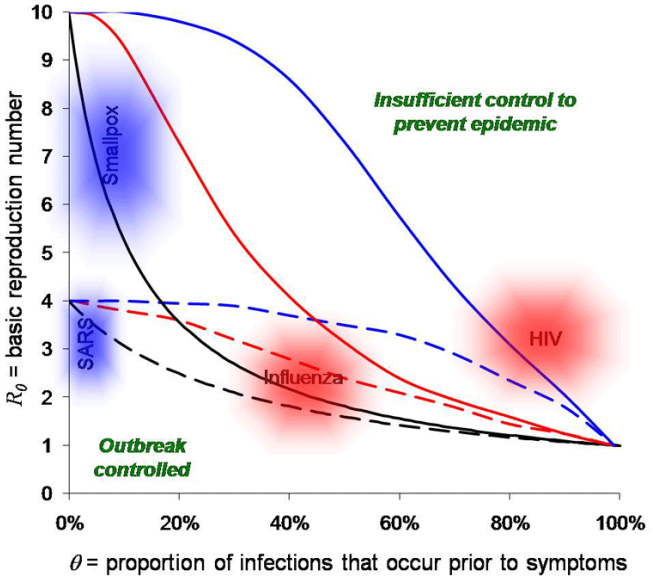


Figure 4. Studies of viral shedding in SARS patients on various days following the onset of clinical symptoms, in stool (dark-grey bars), urine (white bars) and naso-pharangeal aspirate (light-grey bars) (Peiris *et al.* 2003*a*).

Yes, but …

Fraser *et al.* (2004; *PNAS*) examined 'controllability' of an infectious disease, based on its epidemiology and pathogenesis

Infectious disease with much 'silent' transmission are harder to control this way



Yes, another but …

Back to our NPI example:

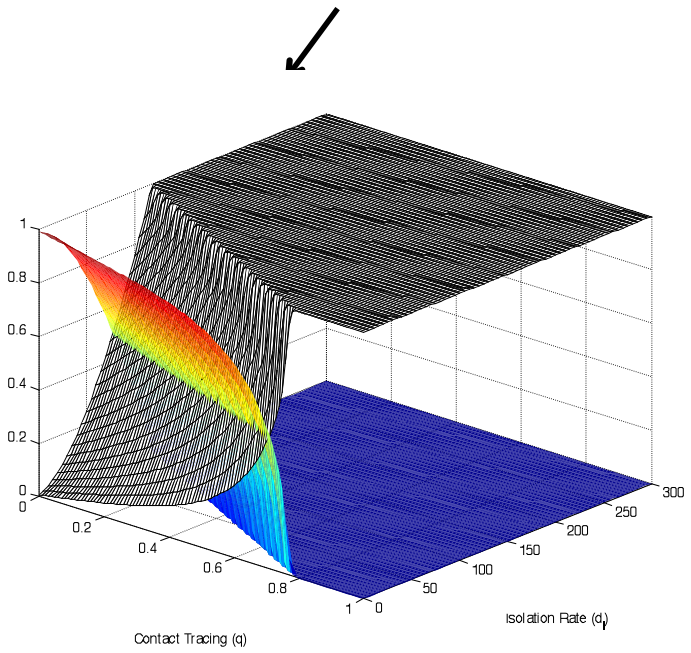
If contact tracing and quarantining efficient enough, invasion can be controlled

But …

Let's consider remaining susceptible population, post-control

NPI measures leave population vulnerable to re-exposure

Fraction susceptible after outbreak



Lecture Summary …

- Models can generate predictions about immunization levels required for eradication
- Similarly, extent of non-pharmaceutical interventions can be gauged
- NPIs leave many susceptibles behind
  - Important for re-introductions
- Infections with much silent transmission very difficult to control with NPIs