Case Study: Influenza Modeling

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Brief Facts About Influenza

The disease was first described in the 16th century in Italy
Thought to be due to the influence (*influenza* in Italian) of the moon and the stars

Influenza (flu) is a respiratory infection that occurs in humans, other mammals (e.g. pigs) and birds (e.g. chickens)
Symptoms include fever, aches, fatigue...

It is caused by an RNA virus with 3 main types in humans:
A (most important), B and C
Subtypes of A are distinguished by differences in two proteins abbreviated as HA and NA, e.g H1N1, H3N2
Subtypes are further divided into antigenically distinct strains

An annual influenza epidemic during winter in the N. Hemisphere during the rainy season June to August in India
caused by drift, i.e. the virus continually evolving and giving new strains

In addition there are infrequent influenza pandemic outbreaks (due to major antigenic shifts in virus)

In the 20th Century there were at least 3 major pandemics

- 1918-19: H1N1 influenza caused an estimated 50m deaths worldwide
- 1957-58: H2N2 influenza caused over 2m deaths worldwide
- 1968-69: H3N2 influenza caused over 1m deaths worldwide

Since 1997 avian influenza H5N1 has caused large outbreaks in chickens, and these can directly infect humans

Starting in April 2009 pandemic influenza H1N1 (swine flu) swept from Mexico to over 214 countries and caused over 18,366 laboratory-confirmed deaths [WHO data]

Starting in March 2013 influenza H7N9 started in China...

- Transmission of influenza virus can be airborne or by droplets
- Incubation period is 1-3 days, so model should include an exposed (latent) compartment (are infected but not yet infectious)
- Infectiousness can begin about 1 day before symptoms, so model should include an asymptomatic compartment (no symptoms but can infect others)
- Infectious period is 3-6 days
- Most individuals recover and are thought to have lifelong immunity to strains closely related to the infecting strain
- Influenza causes or contributes to death mostly among elderly people and young children

Since the 1960s vaccine has been available each year for seasonal flu and it contains strains of A: H1N1, H3N2, and B

Since about 1999 antiviral drugs have been available (NA inhibitors) and they can also be used prophylactically

Data limitations: Influenza has no reporting requirement and is easily confused with other respiratory diseases (e.g. common cold, respiratory syncytial virus (RSV))

So there are many modeling challenges!

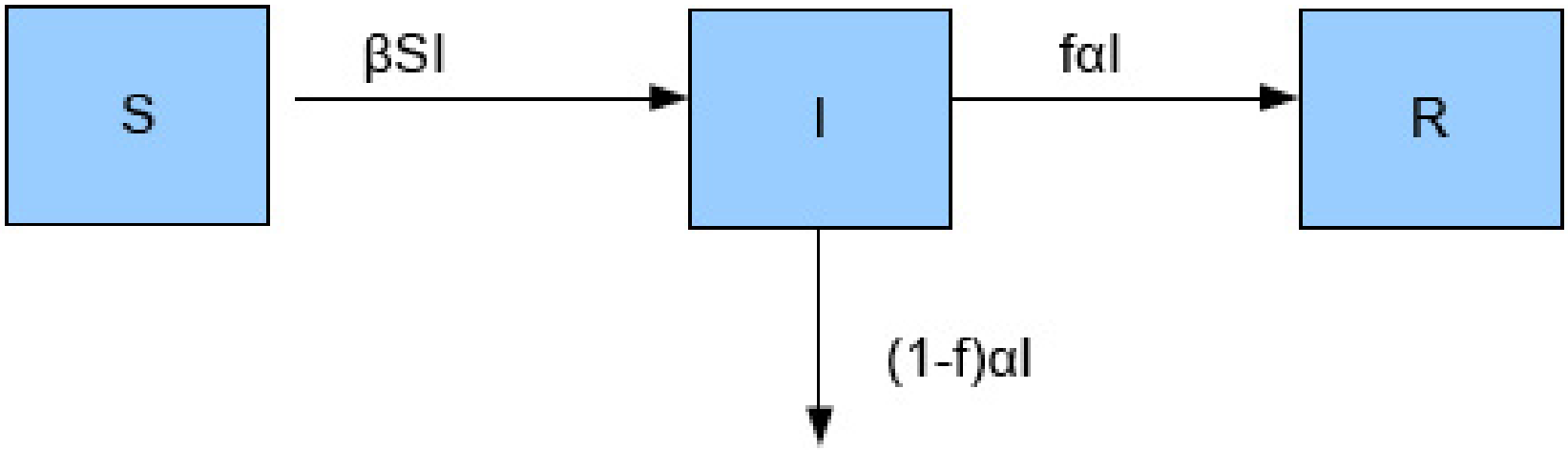
"All models are wrong, but some are useful" George E.P. Box

"A scientific theory should be as simple as possible, but no simpler" Albert Einstein

Some aims of influenza modeling are:

- Understanding the important parameters that influence influenza spread
- Quantifying strategies to control influenza, both seasonal and pandemic
  e.g. vaccination, antivirals, isolation

♦ SIR Compartmental Epidemic Model



S: susceptible *I*: infectious *R*: recovered compartments (classes)

β: transmission coefficient between *I* and *S*

Mass action incidence assumes homogeneous mixing

each individual has the same probability of meeting another individual

$\frac{1}{\alpha}$: mean infectious time *f*: fraction of *I* recovering

Write down the 3 ODEs describing the dynamics

System ODEs

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \alpha I \\ \frac{dR}{dt} &= f\alpha I \end{aligned}$$

Initial conditions: $S(0) = S_0 > 0, I(0) > 0, R(0) = 0$

Note that the system is well posed and solutions remain nonnegative

Disease free equilibrium (DFE): $S = S_0, \quad I = 0, \quad R = 0$

We can work with the infected equation

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

DFE is locally asymptotically stable (LAS) if $\mathcal{R}_0 = \dfrac{\beta S_0}{\alpha} < 1$
unstable if $\mathcal{R}_0 > 1$

$\mathcal{R}_0$ is the *basic reproduction number*
= (transmission coefficient)(mean infectious time) S_0

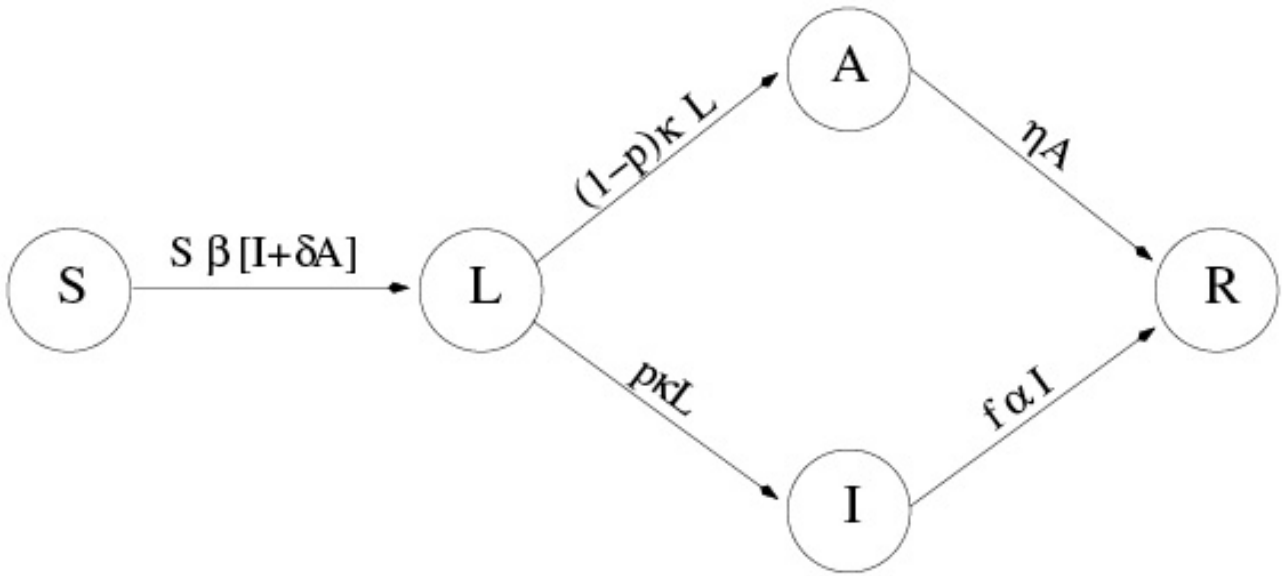
$\mathcal{R}_0$: average number of secondary infections caused by introducing one infectious individual into a susceptible population

$\mathcal{R}_0 < 1 \Rightarrow$ infectious number decreases monotonically to 0

$\mathcal{R}_0 > 1 \Rightarrow$ infectious number first increases (before $\to 0$)
i.e. an epidemic, so $\mathcal{R}_0$ is a disease threshold parameter

♦ Influenza Model: Latent and Asymptomatic People

[Arino, Brauer, vdD, Watmough, Wu 2006]



L: latent (infected not yet infectious)

A: asymptomatic but infectious

δ: reduction in infectiousness of A

$1/\kappa$: mean latent time

p: fraction of L developing symptoms

$1/\eta$: mean asymptomatic time

- Write down the 5D ordinary differential equations describing this model
- Find the DFE (if it exists)
- Identify the infected compartments
- Linearize the infected compartment equations about the DFE to find matrices F and V
- Compute $\mathcal{R}_0$ and interpret biologically
- Does influenza die out or is there an epidemic?

System ODEs

$$
\begin{aligned}
\frac{dS}{dt} &= -\beta S(I + \delta A) \\
\frac{dL}{dt} &= \beta S(I + \delta A) - \kappa L \\
\frac{dA}{dt} &= (1-p)\kappa L - \eta A \\
\frac{dI}{dt} &= p\kappa L - \alpha I \\
\frac{dR}{dt} &= f\alpha I + \eta A
\end{aligned}
$$

DFE: $S = S_0, \quad L = A = I = R = 0$

The infected compartments are L, A, I

Linearizing about the DFE:

$$\begin{bmatrix} -\kappa & \beta\delta S_0 & \beta S_0 \\ (1-p)\kappa & -\eta & 0 \\ p\kappa & 0 & -\alpha \end{bmatrix} = F - V$$

The DFE is locally stable if all eigenvalues have negative real parts

Need determinant $= -\kappa\eta\alpha + \beta\delta S_0(1-p)\kappa\alpha + \beta S_0\eta p\kappa < 0$

How is this related to $\mathcal{R}_0$?

Aside: Note that local stability does not in general imply global stability

For this influenza model: $\mathcal{R}_0 = \rho(FV^{-1})$

$$F = \begin{bmatrix} 0 & \beta\delta S_0 & \beta S_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \qquad V = \begin{bmatrix} \kappa & 0 & 0 \\ -(1-p)\kappa & \eta & 0 \\ -p\kappa & 0 & \alpha \end{bmatrix}$$

new infections transitions

F has rank 1, so need just $(1,1)$ entry of FV^{-1}

$$\mathcal{R}_0 = \beta S_0 \left[\frac{p}{\alpha} + \frac{\delta(1-p)}{\eta}\right] = \frac{\beta S_0}{\alpha} k$$

where k is correction factor accounting for asymptomatics

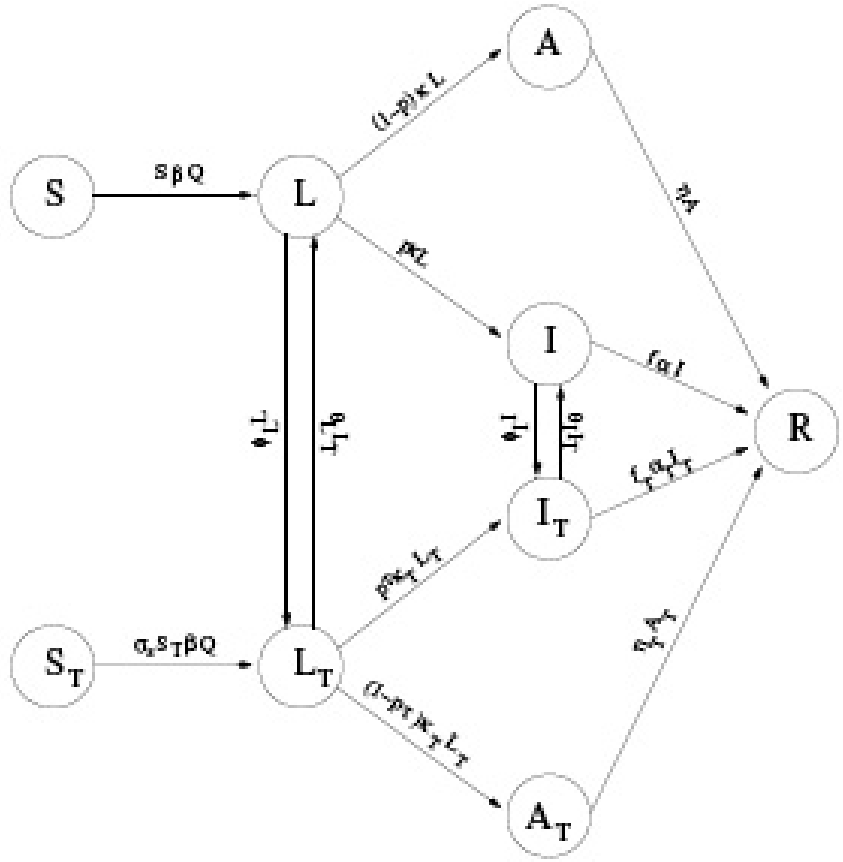
From influenza data [Longini et *al.* 2004] $k \approx 0.8$

Note: $\mathcal{R}_0 < 1 \iff$ previous inequality holds (i.e. matrix stable)

If $\mathcal{R}_0 < 1$ then influenza dies out, if $\mathcal{R}_0 > 1$ then there is an epidemic

♦ Influenza Model with Treatment

[Arino. Brauer, vdD, Watmough, Wu, 2008]



$$Q = \beta[I + \sigma_I I_T + \delta A + \delta\sigma_A A_T]$$

DFE: $S = (1-\gamma)S_0, \quad S_T = \gamma S_0$

where γ is fraction of susceptibles vaccinated before outbreak

$$F = \beta S_0 \begin{bmatrix} 0 & 0 & (1-\gamma) & (1-\gamma)\sigma_I & (1-\gamma)\delta & (1-\gamma)\sigma_A\delta \\ 0 & 0 & \gamma\sigma_S & \gamma\sigma_S\sigma_I & \gamma\sigma_S\delta & \gamma\sigma_S\sigma_A\delta \\ & & & 0 & & \end{bmatrix}$$

has rank 1. Let $D = diag(1, \sigma_S)$ with σ_S reduction in susceptibility

$$V = \begin{bmatrix} V_L & 0 & 0 \\ -V_{LI} & V_I & 0 \\ -V_{LA} & 0 & V_A \end{bmatrix}$$

V_L, V_I contain treatment rates ϕ_L, ϕ_I

Control reproduction number $\mathcal{R}_c = (1-\gamma)\mathcal{R}_u + \gamma\mathcal{R}_v$

$$[\mathcal{R}_u, \mathcal{R}_v] = \beta S_0 \left([1, \sigma_I] V_I^{-1} V_{LI} V_L^{-1} D + \delta [1, \sigma_A] V_A^{-1} V_{LA} V_L^{-1} D \right)$$

Special Cases: $\mathcal{R}_c = (1-\gamma)\mathcal{R}_u + \gamma\mathcal{R}_v$

(i) Pre-epidemic treatment only (annual flu vaccinations)

$\mathcal{R}_u = \beta S_0 \left[\frac{p}{\alpha} + \frac{\delta(1-p)}{\eta}\right]$ as before

$\mathcal{R}_v = \sigma_S \beta S_0 \left[\frac{\sigma_I p\tau}{\alpha_T} + \frac{\delta\sigma_A(1-p\tau)}{\eta_T}\right] < \mathcal{R}_u$

To control the epidemic, vaccinate a large enough fraction γ to make $\mathcal{R}_c < 1$, possible if $\mathcal{R}_v < 1$ in particular σ_S small (susceptibility to infection sufficiently reduced by vaccination)

(ii) Treatment with no pre-epidemic vaccination
as for a new strain of influenza with no vaccine
In this case $\gamma = 0$ so $\mathcal{R}_c = \mathcal{R}_u$
Various combinations of treatment rates ϕ_L and ϕ_I can bring $\mathcal{R}_c < 1$

Note that $\mathcal{R}_c$ is a linear function of β, which is a product of the average infectiousness of *I* and the number of contacts of *I* per day

Thus if *I* take precautions to prevent infecting or contacting (e.g. isolation) and *S* take precautions to prevent becoming infected (e.g. improved hygiene, vaccination, antivirals)
$\mathcal{R}_c$ can be lowered below one

To quote Chowell from a lecture on the 1918/19 influenza epidemic in Geneva:

> *"Get your shots, wash your hands,*
> *and steer clear of those who don't."*

Cautions

- Smallest $\mathcal{R}_c$ by letting treatment rate of infectious individuals $\phi_I \to \infty$, but probably $\phi_I < 2$ in practise (corresponds to $< 1/2$ day between developing symptoms and treatment)
  With parameters from 1957 data Longini et *al.* [2004] calculate that treatment of 80% of infectious individuals within 1.15 days would be required to bring $\mathcal{R}_c < 1$
- Number of doses needed to bring $\mathcal{R}_c < 1$ depends strongly on the number of infectious individuals introduced initially
- Model includes many assumptions, e.g.
  homogeneous mixing (mass action incidence), spatial homogeneity
  no drug resistance, no age structure, no social structure...
  To adddress some of these we should consider
  ♦ a metapopulation model
  and
  ♦ a network model