# Extensions of the Kermack-McKendrick model

## MATH 8xyz – Lecture 05

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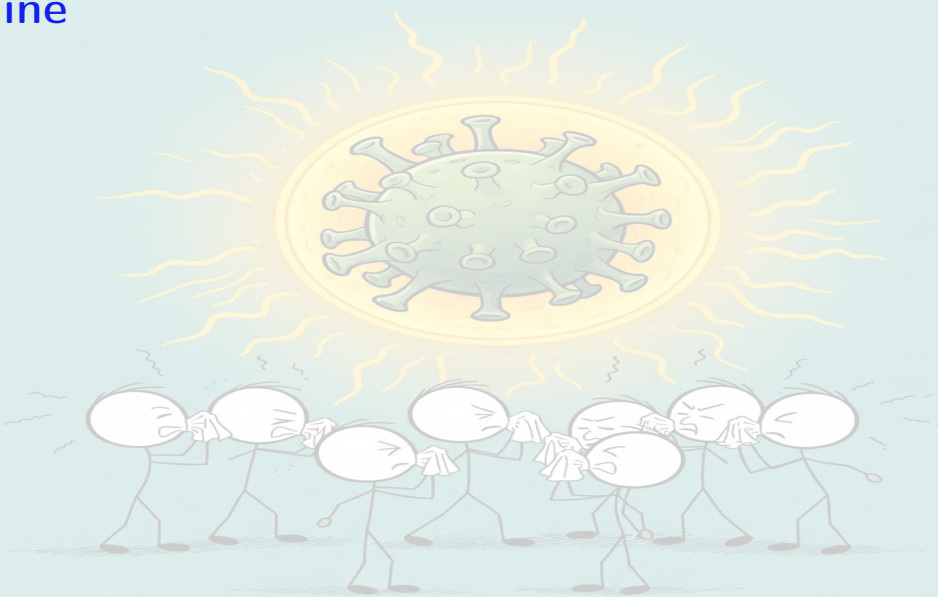
The University of Manitoba campuses are located on original lands of Anishinaabeg, Ininew, Anisininew, Dakota and Dene peoples, and on the National Homeland of the Red River Métis.
We respect the Treaties that were made on these territories, we acknowledge the harms and mistakes of the past, and we dedicate ourselves to move forward in partnership with Indigenous communities in a spirit of Reconciliation and collaboration.

# Outline

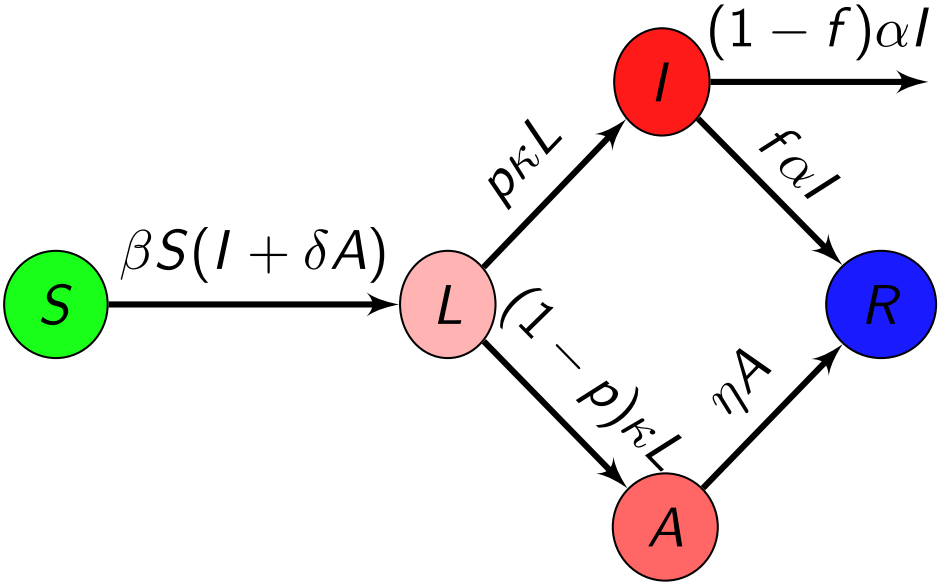



FIGS/Arino-etal-SLIAR.png

SIR is a little too simple for many diseases:

- No incubation period
- A lot of infectious diseases (in particular respiratory) have mild and less mild forms depending on the patient

$\Longrightarrow$ model with SIR but also L(atent) and (A)symptomatic individuals, in which I are now symptomatic individuals


$(1-f)\alpha I$
$I$
$p\kappa L$
$f\alpha I$
$\beta S(I+\delta A)$
$S$
$L$
$R$
$(1-p)\kappa L$
$\eta A$
$A$

# Basic reproduction number & Final size

We find the basic reproduction number

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

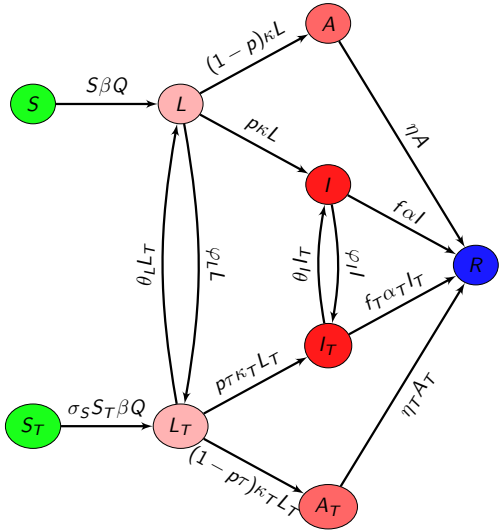
where

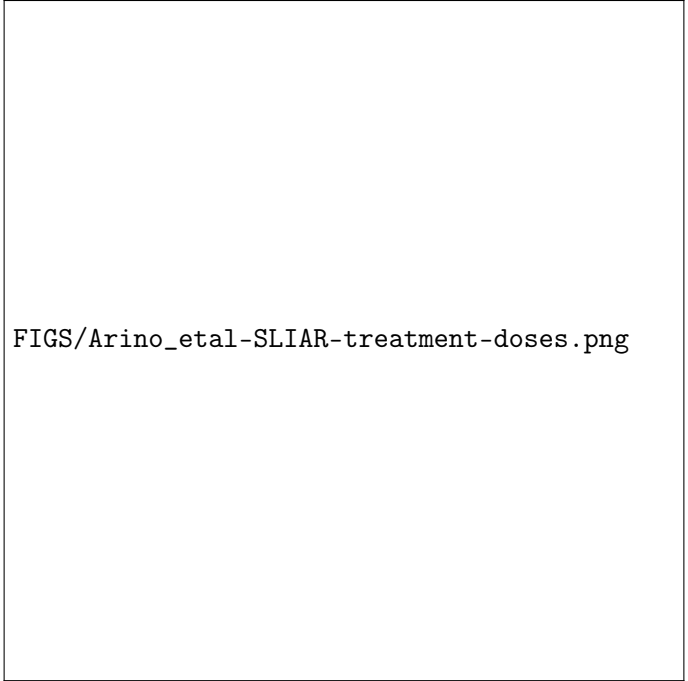
$$\rho = \alpha \left( \frac{p}{\alpha} + \frac{\delta(1-p)}{\eta} \right)$$

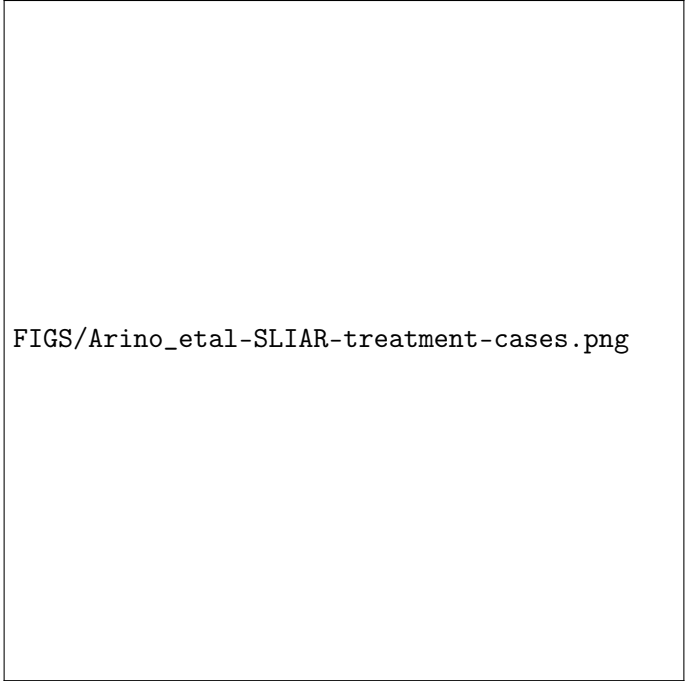
The final size relation takes the form

$$S_0(\ln S_0 - \ln S_\infty) = \mathcal{R}_0(S_0 - S_\infty) + \frac{\mathcal{R}_0 I_0}{\rho} \tag{2}$$

# Adding treatment




FIGS/Arino_etal-SLIAR-treatment-doses.png


FIGS/Arino_etal-SLIAR-treatment-cases.png


FIGS/Arino_etal-SLIAR-conclusions.png


FIGS/Arino-etal-final-size.png

# A method for computing $\mathcal{R}_0$ in epidemic models

- This method is not universal! It works in a relatively large class of models, but not everywhere

- If it doesn't work, the next generation matrix method does work, **but** should be considered only for obtaining the reproduction number, not to deduce LAS

- Here, I change the notation in the paper, for convenience

# Standard form of the system

Suppose system can be written in the form

$$\boldsymbol{S}' = \mathrm{b}(\boldsymbol{S}, \boldsymbol{I}, \boldsymbol{R}) - \boldsymbol{D}\boldsymbol{S}\beta(\boldsymbol{S}, \boldsymbol{I}, \boldsymbol{R})\boldsymbol{h}\boldsymbol{I} \tag{3a}$$

$$\boldsymbol{I}' = \boldsymbol{\Pi}\boldsymbol{D}\boldsymbol{S}\beta(\boldsymbol{S}, \boldsymbol{I}, \boldsymbol{R})\boldsymbol{h}\boldsymbol{I} - \mathrm{V}\boldsymbol{I} \tag{3b}$$

$$\boldsymbol{R}' = \mathrm{f}(\boldsymbol{S}, \boldsymbol{I}, \boldsymbol{R}) + \mathrm{W}\boldsymbol{I} \tag{3c}$$

where $\boldsymbol{S} \in \mathbb{R}^m$, $\boldsymbol{I} \in \mathbb{R}^n$ and $\boldsymbol{R} \in \mathbb{R}^k$ are susceptible, infected and removed compartments, respectively

IC are $\geq 0$ with at least one of the components of $\boldsymbol{I}(0)$ positive

$$\boldsymbol{S}' = \mathrm{b}(\boldsymbol{S}, \boldsymbol{I}, \boldsymbol{R}) - \boldsymbol{D}\boldsymbol{S}\beta(\boldsymbol{S}, \boldsymbol{I}, \boldsymbol{R})\boldsymbol{h}\boldsymbol{I} \tag{3a}$$

- $\mathrm{b} : \mathbb{R}_+^m \times \mathbb{R}_+^n \times \mathbb{R}_+^k \to \mathbb{R}^m$ continuous function encoding recruitment and death of uninfected individuals
- $\boldsymbol{D} \in \mathbb{R}^{m \times m}$ diagonal with diagonal entries $\sigma_i > 0$ the relative susceptibilities of susceptible compartments, with convention that $\sigma_1 = 1$
- Scalar valued function $\beta : \mathbb{R}_+^m \times \mathbb{R}_+^n \times \mathbb{R}_+^k \to \mathbb{R}_+$ represents infectivity, with, e.g., $\beta(\boldsymbol{S}, \boldsymbol{I}, \boldsymbol{R}) = \beta$ for mass action
- $\boldsymbol{h} \in \mathbb{R}^n$ row vector of relative horizontal transmissions

$$\boldsymbol{I}' = \boldsymbol{\Pi}\boldsymbol{D}\boldsymbol{S}\beta(\boldsymbol{S}, \boldsymbol{I}, \boldsymbol{R})\boldsymbol{h}\boldsymbol{I} - \mathsf{V}\boldsymbol{I} \tag{3b}$$

- $\boldsymbol{\Pi} \in \mathbb{R}^{n \times m}$ has $(i, j)$ entry the fraction of individuals in $j^{\text{th}}$ susceptible compartment that enter $i^{\text{th}}$ infected compartment upon infection
- $\boldsymbol{D} \in \mathbb{R}^{m \times m}$ diagonal with diagonal entries $\sigma_i > 0$ the relative susceptibilities of susceptible compartments, with convention that $\sigma_1 = 1$
- Scalar valued function $\beta : \mathbb{R}_+^m \times \mathbb{R}_+^n \times \mathbb{R}_+^k \to \mathbb{R}_+$ represents infectivity, with, e.g., $\beta(\boldsymbol{S}, \boldsymbol{I}, \boldsymbol{R}) = \beta$ for mass action
- $\boldsymbol{h} \in \mathbb{R}^n$ row vector of relative horizontal transmissions
- $\mathsf{V} \in \mathbb{R}^{n \times n}$ describes transitions between infected states and removals from these states due to recovery or death

$$\boldsymbol{R}' = \mathsf{f}(\boldsymbol{S}, \boldsymbol{I}, \boldsymbol{R}) + \mathsf{W}\boldsymbol{I} \tag{3c}$$

- $\mathsf{f} : \mathbb{R}_+^m \times \mathbb{R}_+^n \times \mathbb{R}_+^k \to \mathbb{R}^k$ continuous function encoding flows into and out of removed compartments because of immunisation or similar processes
- $\mathsf{W} \in \mathbb{R}^{k \times n}$ has $(i, j)$ entry the rate at which individuals in the $j^{\text{th}}$ infected compartment move into the $i^{\text{th}}$ removed compartment

Suppose $\boldsymbol{E}_0$ is a locally stable disease-free equilibrium (DFE) of the system without disease, i.e., an EP of

$$\boldsymbol{S}' = \mathrm{b}(\boldsymbol{S}, 0, \boldsymbol{R})$$
$$\boldsymbol{R}' = \mathrm{f}(\boldsymbol{S}, 0, \boldsymbol{R})$$

**Theorem 1**

*Let*

$$\mathcal{R}_0 = \beta(\boldsymbol{S}_0, 0, \boldsymbol{R}_0)\boldsymbol{h}\mathsf{V}^{-1}\boldsymbol{\Pi}\boldsymbol{D}\boldsymbol{S}_0 \tag{4}$$

- *If* $\mathcal{R}_0 < 1$, *the DFE* $\boldsymbol{E}_0$ *is a locally asymptotically stable EP of* (3)
- *If* $\mathcal{R}_0 > 1$, *the DFE* $\boldsymbol{E}_0$ *of* (3) *is unstable*

If no demography (epidemic model), then just $\mathcal{R}_0$, of course

# Final size relations

Assume no demography, then system should be writeable as

$$\boldsymbol{S}' = -\boldsymbol{D}\boldsymbol{S}\beta(\boldsymbol{S}, \boldsymbol{I}, \boldsymbol{R})\boldsymbol{h}\boldsymbol{I} \tag{5a}$$

$$\boldsymbol{I}' = \boldsymbol{\Pi}\boldsymbol{D}\boldsymbol{S}\beta(\boldsymbol{S}, \boldsymbol{I}, \boldsymbol{R})\boldsymbol{h}\boldsymbol{I} - \mathsf{V}\boldsymbol{I} \tag{5b}$$

$$\boldsymbol{R}' = \mathsf{W}\boldsymbol{I} \tag{5c}$$

For $w(t) \in \mathbb{R}^n_+$ continuous, define

$$w_\infty = \lim_{t\to\infty} w(t) \quad \text{and} \quad \hat{w} = \int_0^\infty w(t)\, dt$$

Define the row vector

$$\mathbb{R}^m \ni \mathbf{\Gamma} = (\Gamma_1, \ldots, \Gamma_m) = \beta(\boldsymbol{S}_0, 0, \boldsymbol{R}_0)\boldsymbol{h}\mathsf{V}^{-1}\mathbf{\Pi}\boldsymbol{D}$$

then

$$\mathcal{R}_0 = \mathbf{\Gamma}\boldsymbol{S}(0)$$

Suppose incidence is mass action, i.e., $\beta(\boldsymbol{S}, \boldsymbol{I}, \boldsymbol{R}) = \beta$ and $m > 1$

Then for $i = 1, \ldots, m$, express $\boldsymbol{S}_i(\infty)$ as a function of $\boldsymbol{S}_1(\infty)$ using

$$\boldsymbol{S}_i(\infty) = \boldsymbol{S}_i(0) \left( \frac{\boldsymbol{S}_1(\infty)}{\boldsymbol{S}_1(0)} \right)^{\sigma_i/\sigma_1}$$

then substitute into

$$\begin{aligned} \frac{1}{\sigma_i} \ln \left( \frac{\boldsymbol{S}_i(0)}{\boldsymbol{S}_i(\infty)} \right) &= \boldsymbol{\Gamma} \boldsymbol{D}^{-1} \left( \boldsymbol{S}(0) - \boldsymbol{S}(\infty) \right) + \beta \boldsymbol{h} \mathsf{V}^{-1} \boldsymbol{I}(0) \\ &= \frac{1}{\sigma_1} \ln \left( \frac{\boldsymbol{S}_1(0)}{\boldsymbol{S}_1(\infty)} \right) \end{aligned}$$

which is a final size relation for the general system when $\boldsymbol{S}_i(0) > 0$

If incidence is mass action and $m = 1$ (only one susceptible compartment), reduces to the KMK form

$$\ln\left(\frac{S_0}{S_\infty}\right) = \frac{\mathcal{R}_0}{S_0}(S_0 - S_\infty) + \beta \boldsymbol{h} \mathsf{V}^{-1} \boldsymbol{I}_0 \tag{6}$$

In the case of more general incidence functions, the final size relations are inequalities of the form, for $i = 1, \ldots, m$,

$$\ln\left(\frac{\boldsymbol{S}_i(0)}{\boldsymbol{S}_i(\infty)}\right) \geq \sigma_i \boldsymbol{\Gamma} \boldsymbol{D}^{-1} \left(\boldsymbol{S}(0) - \boldsymbol{S}(\infty)\right) + \sigma_i \beta(K) \boldsymbol{h} \mathsf{V}^{-1} \boldsymbol{I}(0)$$

where $K$ is the initial total population

# The SLIAR model

- Paper we have already seen: Arino, Brauer, PvdD, Watmough & Wu. Simple models for containment of a pandemic, *Journal of the Royal Society Interface* (2006)

- However, suppose additionally that $L$ are also infectious

Here, $\boldsymbol{S} = S$, $\boldsymbol{I} = (L, I, A)^T$ and $\boldsymbol{R} = R$, so $m = 1$, $n = 3$ and

$$\boldsymbol{h} = [\varepsilon\ 1\ \delta], \quad \boldsymbol{D} = 1, \quad \boldsymbol{\Pi} = \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad \mathsf{V} = \begin{pmatrix} \kappa & 0 & 0 \\ -p\kappa & \alpha & 0 \\ -(1-p)\kappa & 0 & \eta \end{pmatrix}$$

Incidence is mass action so $\beta(\boldsymbol{E}_0) = \beta$ and thus

$$\begin{aligned} \mathcal{R}_0 &= \beta \boldsymbol{h} \mathsf{V}^{-1} \boldsymbol{\Pi} \boldsymbol{D} \boldsymbol{S}_0 \\ &= \beta \, [\varepsilon\ 1\ \delta] \begin{pmatrix} 1/\kappa & 0 & 0 \\ p/\alpha & 1/\alpha & 0 \\ (1-p)/\eta & 0 & 1/\eta \end{pmatrix} \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix} S_0 \\ &= \beta S_0 \left( \frac{\varepsilon}{\kappa} + \frac{p}{\alpha} + \frac{\delta(1-p)}{\eta} \right) \end{aligned}$$

For final size, since $m = 1$, we can use (6):

$$\ln\left(\frac{S_0}{S_\infty}\right) = \frac{\mathcal{R}_0}{S_0}(S_0 - S_\infty) + \beta \boldsymbol{h} \mathsf{V}^{-1} \boldsymbol{I}_0$$

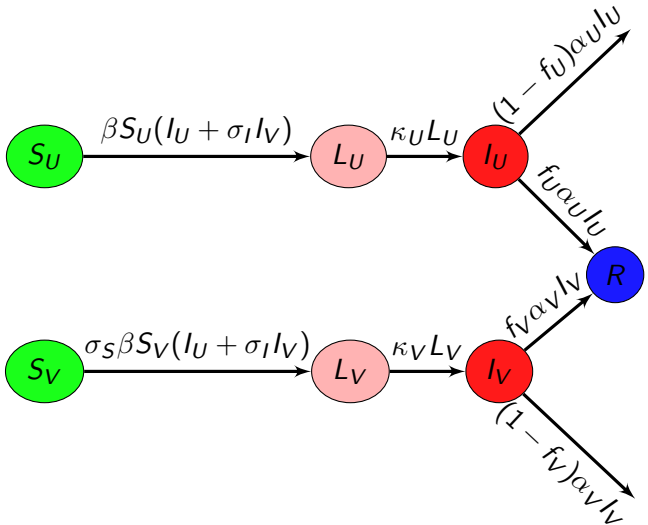
Suppose $\boldsymbol{I}_0 = (0, I_0, 0)$, then

$$\ln\left(\frac{S_0}{S_\infty}\right) = \mathcal{R}_0 \frac{S_0 - S_\infty}{S_0} + \frac{\beta}{\alpha} I_0$$

If $\boldsymbol{I}_0 = (L_0, I_0, A_0)$, then

$$\ln\left(\frac{S_0}{S_\infty}\right) = \mathcal{R}_0 \frac{S_0 - S_\infty}{S_0} + \beta\left(\frac{\varepsilon}{\kappa} + \frac{p}{\alpha} + \frac{\delta(1-p)}{\eta}\right) L_0 + \frac{\beta\delta}{\eta} A_0 + \frac{\beta}{\alpha} I_0$$

# A model with vaccination



# A model with vaccination

Fraction $\gamma$ of $S_0$ are vaccinated before the epidemic; vaccination reduces probability and duration of infection, infectiousness and reduces mortality

$$S_U{}' = -\beta S_U[I_U + \sigma_I I_V] \tag{7a}$$
$$S_V{}' = -\sigma_S \beta S_V[I_U + \sigma_I I_V] \tag{7b}$$
$$L_U{}' = \beta S_U[I_U + \sigma_I I_V] - \kappa_U L_U \tag{7c}$$
$$L_V{}' = \sigma_S \beta S_V[I_U + \sigma_I I_V] - \kappa_V L_V \tag{7d}$$
$$I_U{}' = \kappa_U L_U - \alpha_U I_U \tag{7e}$$
$$I_V{}' = \kappa_V L_V - \alpha_V I_V \tag{7f}$$
$$R' = f_U \alpha_U I_I + f_V \alpha_V I_V \tag{7g}$$

with $S_U(0) = (1-\gamma)S_0$ and $S_V(0) = \gamma S_0$

Here, $m = 2$, $n = 4$,

$$\boldsymbol{h} = [0\ 0\ 1\ \sigma_I], \quad \boldsymbol{D} = \begin{pmatrix} 1 & 0 \\ 0 & \sigma_S \end{pmatrix}, \quad \boldsymbol{\Pi} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \\ 0 & 0 \end{pmatrix}$$

and

$$\mathsf{V} = \begin{pmatrix} \kappa_U & 0 & 0 & 0 \\ 0 & \kappa_V & 0 & 0 \\ -\kappa_U & 0 & \alpha_U & 0 \\ 0 & -\kappa_V & 0 & \alpha_V \end{pmatrix}$$

So

$$\mathbf{\Gamma} = \begin{bmatrix} \frac{\beta}{\alpha_U} & \frac{\sigma_I \sigma_S \beta}{\alpha_V} \end{bmatrix}, \quad \mathcal{R}_c = S_0 \beta \left( \frac{1-\gamma}{\alpha_U} + \frac{\sigma_I \sigma_S \gamma}{\alpha_V} \right)$$

and the final size relation is

$$\ln\left(\frac{(1-\gamma)S_U(0)}{S_U(\infty)}\right) = \frac{\beta}{\alpha_U}[(1-\gamma)S_U(0) - S_U(\infty)] + \frac{\sigma_I \beta}{\alpha_V}[\gamma S_V(0) - S_V(\infty)] + \frac{\beta}{\alpha_U} I_0$$

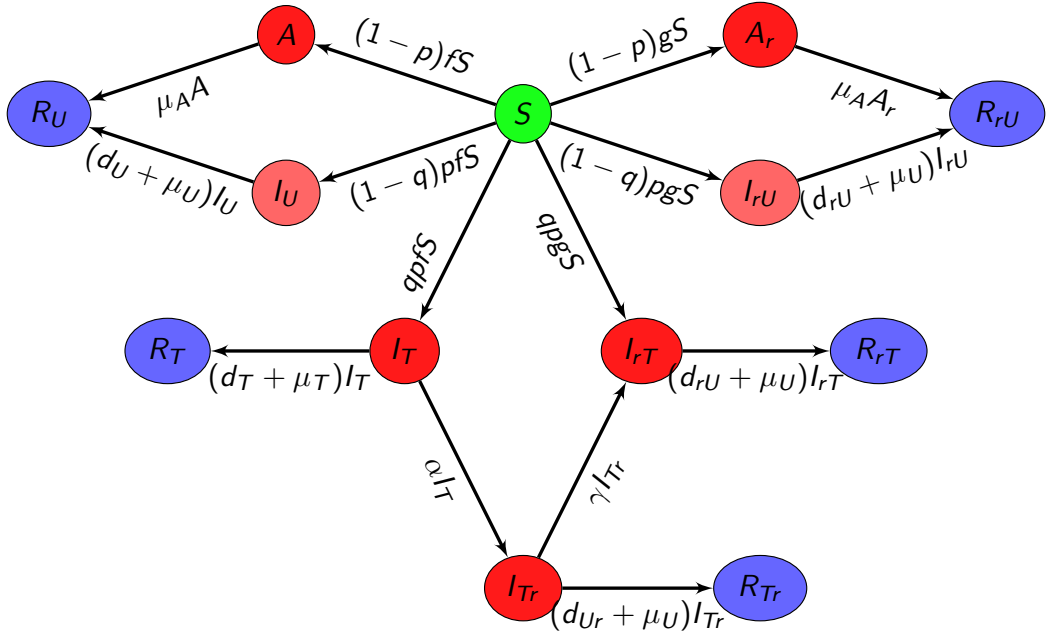
$$S_V(\infty) = \gamma S_U(0) \left( \frac{S_U(\infty)}{(1-\gamma)S_0} \right)^{\sigma_S}$$


FIGS/ArinoBowmanMoghadas.png

# Adapting treatment to counter emergence of resistance

This work was undertaken at the request of the Public Health Agency of Canada during the pandemic preparadness phase prior to the 2009 p-H1N1 pandemic

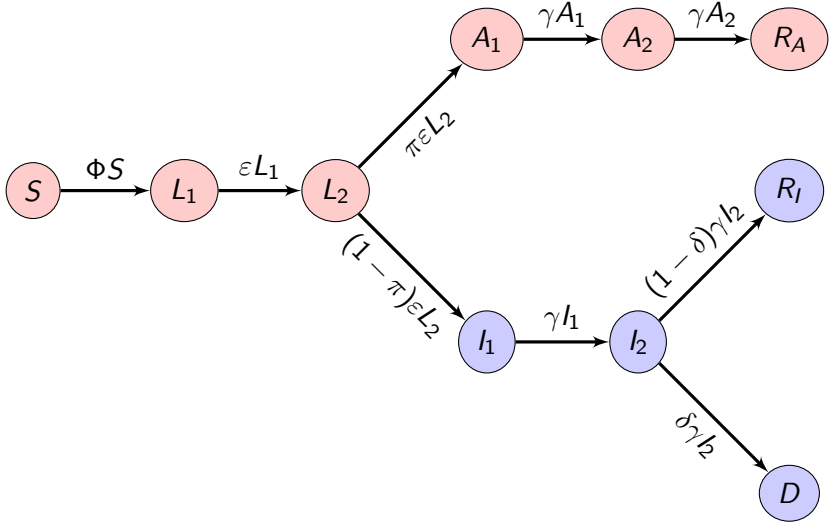
Problem: we have antivirals to use against influenza, either prophylactically or curatively. Using these antivirals may promote the emergence of antiviral-resistant strains. How do we minimise this risk?


A
$(1-p)fS$
$(1-p)gS$
$A_r$
$R_U$
$\mu_A A$
S
$\mu_A A_r$
$R_{rU}$
$(d_U+\mu_U)I_U$
$I_U$
$(1-q)pfS$
$(1-q)pgS$
$I_{rU}$
$(d_{rU}+\mu_U)I_{rU}$
$qpfS$
$qpgS$
$R_T$
$I_T$
$I_{rT}$
$R_{rT}$
$(d_T+\mu_T)I_T$
$(d_{rU}+\mu_U)I_{rT}$
$\alpha I_T$
$\gamma I_{Tr}$
$I_{Tr}$
$R_{Tr}$
$(d_{Ur}+\mu_U)I_{Tr}$


FIGS/ArinoPortet-2020.png

Extends the SLIAR model to take into account non-exponentially distributed stage durations (see course 02)

# The original model (well, almost the first one)



# Reinterpreting terms

Here $D$ stands for *detected*, $U$ is *undetected*

# Working out when the first COVID-19 case occurred

- Details of emergence and precise timeline before amplification started unknown
- Amplification in Wuhan
  - Cluster of pneumonia cases mostly related to the Huanan Seafood Market
  - 27 December 2019: first report to local government
  - 31 December 2019: publication
  - 8 January 2020: identification of SARS-CoV-2 as causative agent
  - $\sim$ 23 January 2020: lockdown Wuhan and Hubei province + face mask mandates
- By 2020-01-29, virus in all provinces of mainland CHN

# Evidence of earlier spread

- Report to Wuhan authorities on 27 December 2019

- First export detections in Thailand and Japan on 13 and 16 January 2020 (with actual importations on 8 and 6 January)

$\Longrightarrow$ amplification must have been occuring for a while longer

- France: sample taken from 42-year-old male (last foreign travel to Algeria in August 2019) who presented to ICU on 27 December 2019

- Retrospective studies in United Kingdom and Italy also showed undetected COVID-19 cases in prepandemic period

# Untangling the first case issue

▶ Robert, Rossman & Jaric. Dating first cases of COVID-19. *PLoS Pathogens* (2021)
Find likely timing of first case of COVID-19 in China as November 17 (95% CI October 4)

▶ Pekar, Worobey, Moshiri, Scheffler & Wertheim. Timing the SARS-CoV-2 index case in Hubei province. *Science* (2021)
Period between mid-October and mid-November 2019 is plausible interval when the first case of SARS-CoV-2 emerged in Hubei province

Important when trying to understand global spread, so let me illustrate with the model I used, taking into account model evolution since

# Back-calculating the start of spread (example of China)

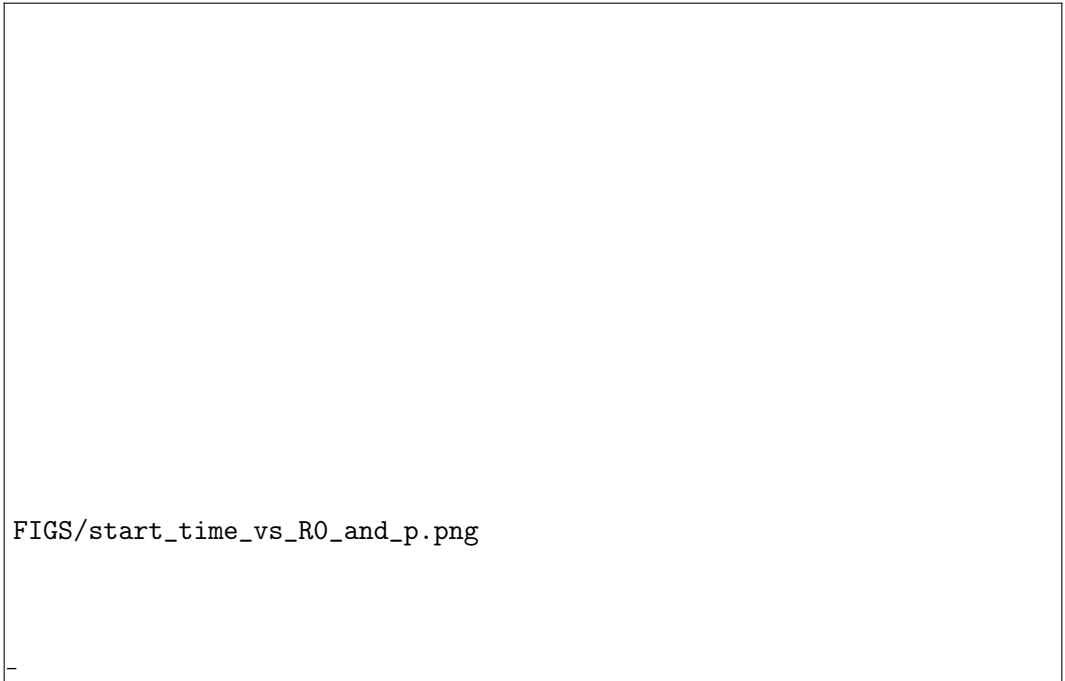
Cumulative confirmed case counts in China as reported to WHO was $c = 547$ cases on $t_c = 2020\text{-}01\text{-}22$

Let $u$ be a point in parameter space. Solve ODE numerically over $[0, t]$, with $S(0)$ the population of China, $L_1(0) = 1$ and other state variables 0. This gives a solution $x(t, t_0 = 0, u)$

Extracting $L_2(t, t_0 = 0, u)$ from this solution, obtain cumulative number of new detections as

$$C(t) = \int_{t_0=0}^{t} p\varepsilon_2 L_2(s, t_0, u)\, ds$$

Let $t^\star$ be s.t. $C(t^\star) = 547$; then $t_i = 2020\text{-}01\text{-}22 - t^\star$


FIGS/start_time_vs_R0_and_p.png

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## [1] "../CODE/L05-KMK-more.R"
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# Bibliography I