EPIDEMIC MODELS II

HETEROGENEOUS MIXING AND DRUG RESISTANCE

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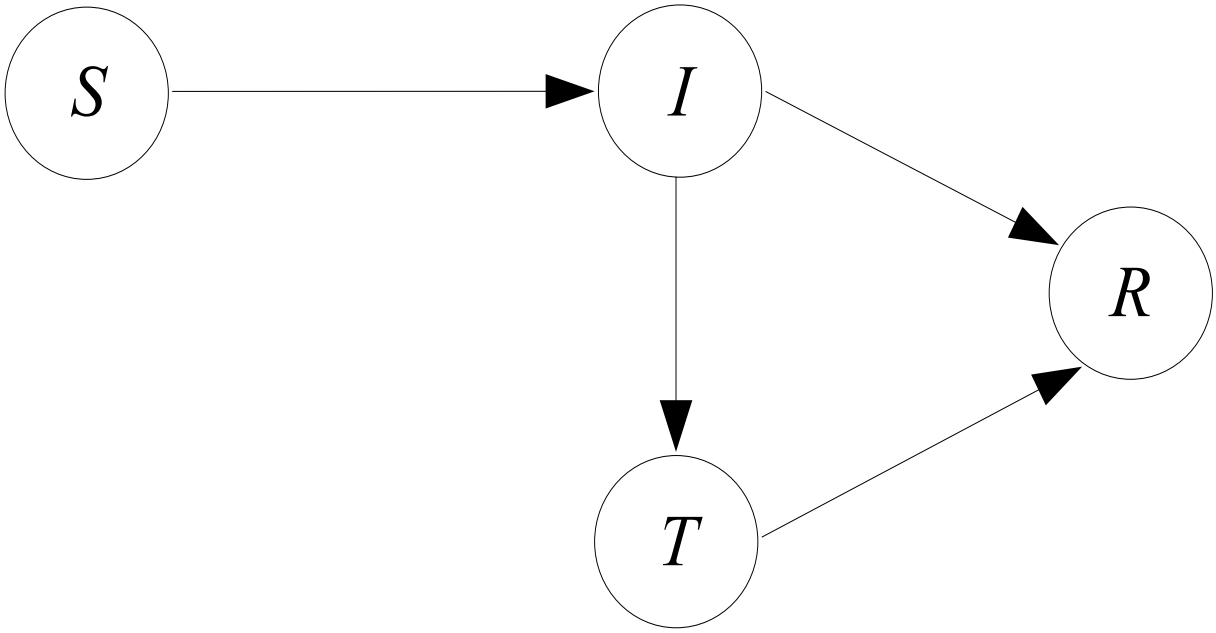
REVIEW: THE SIMPLE TREATMENT MODEL

Recall the basic treatment models under assumptions

- treatment moves infectives to a class T with infectivity decreased by a factor δ and with a recovery rate η
- treatment continues so long as an individual remains infective.
- Treatment is beneficial,

$$\eta > \delta\alpha.$$

Flow chart.



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Model is

$$\begin{aligned} S' &= -\beta S(I + \delta T), & S(0) &= S_0 \\ I' &= \beta S(I + \delta T) - (\alpha + \gamma)I, & I(0) &= I_0 \\ T' &= \gamma I - \eta T, & T(0) &= 0. \end{aligned}$$

Control reproduction number is

$$\mathcal{R}(\gamma) = \frac{\beta N}{\alpha + \gamma}\left[1 + \frac{\delta\gamma}{\eta}\right]$$

representing the mean number of secondary infections caused by a single infective introduced into a fully susceptible population and is a decreasing function of γ if $\eta > \delta\alpha$.

Final size relation is

$$\ln\frac{S_0}{S_\infty} = \mathcal{R}(\gamma)\left[1 - \frac{S_\infty}{N}\right].$$

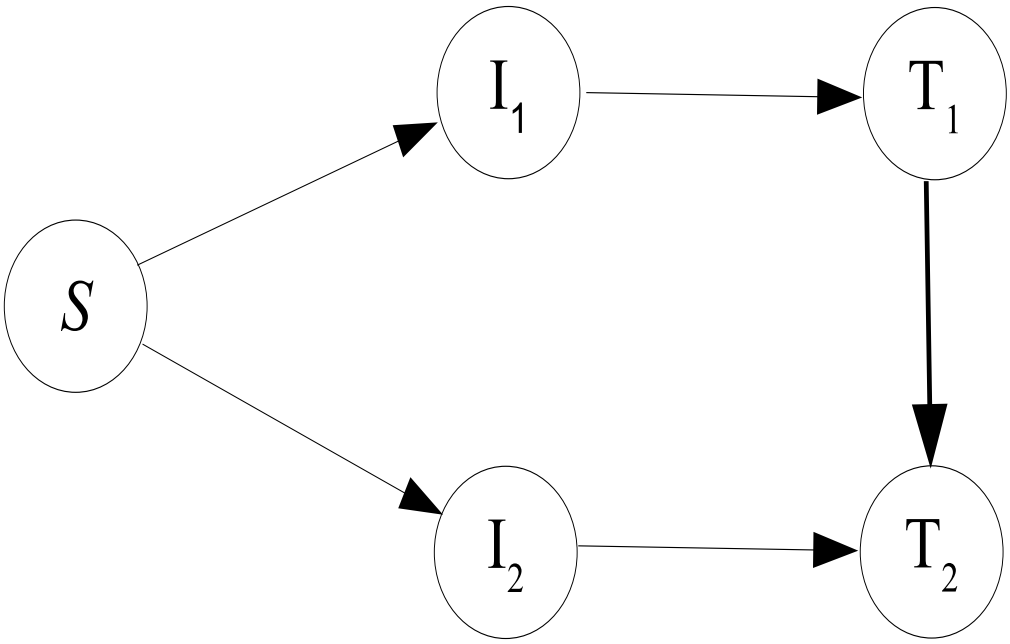
A TWO-STRAIN MODEL

Now introduce a two-strain epidemic model

- Two-strain epidemic model with treatment at a proportional rate γ in each infective class
- Population of constant total size N.
- I_1 is number of individuals with a drug-sensitive infection. and I_2 is number of individuals with a drug-resistant infection.
- Drug resistance develops in treated individuals infected with the drug-sensitive strain at a rate φ.
- Treatment of infectives with a drug-sensitive infection decreases infectivity by a factor δ
- Treatment has no effect on drug-resistant infections.
- Recovery rates are α_1 in I_1, η in T_1, and α_2 in I_2, T_2.
- Treatment is beneficial,

$$\alpha_1 \delta \leq \eta.$$

Flow chart.



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Model is

$$\begin{aligned} S' &= -S[\beta_1 Q_1 + \beta_2 Q_2] \\ I_1' &= S\beta_1 Q_1 - (\alpha_1 + \gamma) I_1 \\ T_1' &= \gamma I_1 - (\eta + \varphi) T_1 \\ I_2' &= S\beta_2 Q_2 - (\alpha_2 + \gamma) I_2 \\ T_2' &= \gamma I_2 - \alpha_2 T_2 + \varphi T_1, \end{aligned}$$

where

$$Q_1 = I_1 + \delta T_1, \quad Q_2 = I_2 + T_2.$$

Initial conditions are

$$S(0) = S_0, \quad I_1(0) = I_0, \quad T_1(0) = I_2(0) = T_2(0) = 0.$$

A single individual with a drug-sensitive infection introduced into a susceptible population generates

$$\mathcal{R}_1(\gamma) = \beta_1 N \left[\frac{1}{\alpha_1+\gamma} + \delta\frac{\gamma}{\alpha_1+\gamma}\frac{1}{\eta+\varphi}\right] + \frac{\beta_2 N}{\alpha_2}\frac{\gamma}{\alpha_1+\gamma}\frac{\varphi}{\eta+\varphi}$$

secondary infections, with the first term representing drug-sensitive infections and the second term representing drug-resistant infections.

A single individual with a drug-resistant infection introduced into a susceptible population generates

$$\mathcal{R}_2 = \frac{\beta_2 N}{\alpha_2}$$

secondary infections, all drug-resistant.

The control reproduction number is

$$\mathcal{R}(\gamma) = \max(\mathcal{R}_1(\gamma), \mathcal{R}_2).$$

The standard next generation matrix argument does not give the effect of secondary drug-resistant infections caused by a drug-sensitive individual, and thus does not determine $\mathcal{R}(\gamma)$ completely.

Integration of the equations gives

$$\begin{aligned} N - S_\infty &= (\alpha_1 + \gamma) \int_0^\infty I_1(s)ds \\ &\quad +(\alpha_2 + \gamma) \int_0^\infty I_2(s)ds \\ \ln \frac{S_0}{S_\infty} &= (\alpha_1 + \gamma)\frac{\mathcal{R}_1(\gamma)}{N} \int_0^\infty I_1(s)ds \\ &\quad +(\alpha_2 + \gamma)\frac{\mathcal{R}_2}{N} \int_0^\infty I_2(s)ds. \end{aligned}$$

If $\mathcal{R}_2 \leq \mathcal{R}_1(\gamma)$, then

$$\mathcal{R}_2 \left[1 - \frac{S_\infty(\gamma)}{N}\right] \leq \ln \frac{S_0}{S_\infty(\gamma)} \leq \mathcal{R}_1(\gamma) \left[1 - \frac{S_\infty(\gamma)}{N}\right].$$

Solution $S(R)$ of

$$\ln \frac{S_0}{S(R)} = R \left[1 - \frac{S(R)}{N}\right]$$

is a decreasing function of R, implying that $S_\infty(\gamma)$ is between $S(\mathcal{R}_1(\gamma))$ and $S(\mathcal{R}_2)$. However, we have only bounds for the epidemic final size rather than an equation.

Differentiation of expression for $\mathcal{R}_1(\gamma)$ shows that if $\mathcal{R}_1(0) > \mathcal{R}_2$, then $\mathcal{R}_1(\gamma)$ is a decreasing function of γ. If

$$(\eta + \varphi)\beta_2 < \delta\beta_1\alpha_2,$$

$\mathcal{R}_1(0) > \mathcal{R}_2$ for all γ. If

$$(\eta + \varphi)\beta_2 > \delta\beta_1\alpha_2,$$

there is a value

$$\gamma_c = \frac{(\eta + \varphi)(\beta_1\alpha_2 - \beta_2\alpha_1}{\eta\beta_2 - \delta\beta_1\alpha_2}$$

such that

$$\begin{aligned} \mathcal{R}_1(\gamma) &> \mathcal{R}_2, \quad 0 \leq \gamma < \gamma_c \\ \mathcal{R}_1(\gamma) &< \mathcal{R}_2, \quad \gamma < \gamma_c. \end{aligned}$$

In addition,

$$\lim_{\gamma \to \infty} \mathcal{R}_1'(\gamma) = 0.$$

To go further, we need to make an additional assumption, namely that the ratio of new infections in strain 2 to new infections in strain 1 is an increasing function of γ. Thus we assume

$$(\alpha_2 + \gamma) \int_0^\infty I_2(s)ds = \lambda(\gamma)(\alpha_1 + \gamma) \int_0^\infty I_1(s)ds,$$

with $\lambda'(\gamma) > 0$. Increasing γ decreases the mean period in I_1 and since treatment decrease infectivity and mean period, this decreases the number of infections starting in I_1. On the other hand, increasing γ does not change the number of new infections or the mean period in I_2 but does increase the number of new infections in T_2 caused by development of drug resistance in T_1. Thus the number of new infections in I_2 increases when γ increases.

Under this assumption,

$$N - S_\infty = (1 + \lambda(\gamma))(\alpha_1 + \gamma) \int_0^\infty I_1(s)ds$$

and

$$\begin{aligned} \ln \frac{S_0}{S_\infty} &= (\alpha_1 + \gamma)\hat{I}_1 \frac{\mathcal{R}_1(\gamma) + \lambda(\gamma)\mathcal{R}_2}{N} \\ &= \frac{\mathcal{R}_1(\gamma) + \lambda(\gamma)\mathcal{R}_2}{1 + \lambda(\gamma)} \left[1 - \frac{S_\infty(\gamma)}{N}\right] \\ &= R(\gamma) \left[1 - \frac{S_\infty(\gamma)}{N}\right] \end{aligned}$$

with

$$R(\gamma) = \frac{\mathcal{R}_1(\gamma) + \lambda(\gamma)\mathcal{R}_2}{1 + \lambda(\gamma)}.$$

Then $S_\infty(\gamma)$ is an increasing function of γ, so that increasing γ decreases the size of the epidemic if and only if $R(\gamma)$ is a decreasing function of γ. Now $R'(\gamma) < 0$ if and only if

$$\mathcal{R}_1'(\gamma)(1 + \lambda(\gamma)) + \lambda(\gamma)(\mathcal{R}_2 - \mathcal{R}_1(\gamma)) < 0.$$

There are two cases: If $\mathcal{R}_1(0) > \mathcal{R}_2$ and

$$(\eta + \varphi)\beta_2 > \delta\beta_1\alpha_2,$$

there is a value γ_c with $\mathcal{R}_1(\gamma_c) = \mathcal{R}_2$. For large γ, $\mathcal{R}'(\gamma) > 0$ and treatment eventually becomes counter-productive. For $\gamma \leq \gamma_c, \mathcal{R}'(\gamma) < 0$ and treatment decreases the size of the epidemic.

If $\mathcal{R}_1(0) > \mathcal{R}_2$ and

$$(\eta + \varphi)\beta_2 < \delta\beta_1\alpha_2,$$

$\mathcal{R}'(\gamma) < 0$ for all γ and treatment decreases the size of the epidemic for all γ.

The first case describes a situation that has been obtained by numerical simulations and gives a lower bound for the critical treatment rate. It has been suggested that in this case delaying the start of treatment may decrease the size of the epidemic.

QUESTION: Is the assumption on the ratio of new infections in the two strains reasonable, and if so, what is a suitable expression for this ratio?.

HETEROGENEOUS MIXING

Divide population into two groups with different contact rates. Extension to n groups is straightforward. Suppose mean infective period in group i is $1/\alpha_i$. Assume no disease deaths, so that the population sizes N_1, N_2 of groups are constant. Suppose group i members make a_i contacts in unit time and that the fraction of contacts made by a member of group i that is with a member of group j is
$p_{ij}, (i, j = 1, 2), p_{11} + p_{12} = p_{21} + p_{22} = 1.$

Two-group SIR epidemic model is

$$\begin{aligned}
S_1' &= -a_1 S_1 \left[p_{11} \frac{I_1}{N_1} + p_{12} \frac{I_2}{N_2} \right] \\
I_1' &= a_1 S_1 \left[p_{11} \frac{I_1}{N_1} + p_{12} \frac{I_2}{N_2} \right] - \alpha_1 I_1 \\
S_2' &= -a_2 S_2 \left[p_{21} \frac{I_1}{N_1} + p_{22} \frac{I_2}{N_2} \right] \\
I_2' &= a_2 S_2 \left[p_{21} a_2 \frac{S_2 I_1}{N_1} + p_{22} a_2 \frac{S_2 I_2}{N_2} \right] - \alpha_2 I_2
\end{aligned}$$

Prescribe initial values for $S_1(0), I_1(0), S_2(0), I_2(0)$ with

$$S_1(0) + I_1(0) = N_1, \quad S_2(0) + I_2(0) = N_2.$$

Then

$$S_1 \to S_1(\infty) > 0, \quad S_2 \to S_2(\infty) > 0,$$

as $t \to \infty$.

Calculate reproduction number by next generation matrix approach as largest eigenvalue of the matrix $K = FV^{-1}$, where

$$F = \begin{bmatrix} p_{11}a_1 & p_{12}a_1\frac{N_1}{N_2} \\ p_{21}a_2\frac{N_2}{N_1} & p_{22}a_2 \end{bmatrix} \quad V = \begin{bmatrix} \alpha_1 & 0 \\ 0 & \alpha_2 \end{bmatrix}.$$

Then

$$K = FV^{-1} = \begin{bmatrix} \dfrac{p_{11}a_1}{\alpha_1} & \dfrac{p_{12}a_1}{\alpha_2}\dfrac{N_1}{N_2} \\ \dfrac{p_{21}a_2}{\alpha_1}\dfrac{N_2}{N_1} & \dfrac{p_{22}a_2}{\alpha_2} \\ & . \end{bmatrix}$$

The basic reproduction number $\mathcal{R}_0$ is the larger of the two eigenvalues of K. It depends on the nature of the mixing between the two groups, determined by the two quantities p_{12}, p_{21} ($p_{11} = 1 - p_{12}$ and $p_2 = 1 - p_{21}$).

FINAL SIZE RELATION

The final size relation is the pair of equations

$$\ln \frac{S_1(0)}{S_1(\infty)} = a_1 \left[\frac{p_{11}}{\alpha_1} \left(1 - \frac{S_1(\infty)}{N_1} \right) + \frac{p_{12}}{\alpha_2} \left(1 - \frac{S_2(\infty)}{N_2} \right) \right]$$
$$\ln \frac{S_2(0)}{S_2(\infty)} = a_2 \left[\frac{p_{21}}{\alpha_1} \left(1 - \frac{S_1(\infty)}{N_1} \right) + \frac{p_{22}}{\alpha_2} \left(1 - \frac{S_2(\infty)}{N_2} \right) \right]$$

Final size relation can be expressed using the matrix

$$R = \begin{bmatrix} \dfrac{p_{11}a_1}{\alpha_1} & \dfrac{p_{12}a_1}{\alpha_2} \\ \dfrac{p_{21}a_2}{\alpha_1} & \dfrac{p_{22}a_2}{\alpha_2} \end{bmatrix}.$$

which is similar to the next generation matrix K since

$$T^{-1}KT = R,$$

with T the diagonal matrix

$$T = \begin{bmatrix} N_1 & 0 \\ 0 & N_2. \end{bmatrix}$$

The model and the final size relation generalize naturally to models with n groups,