Can Treatment Increase the Epidemic Size?

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Outline

Emergence of Drug Resistance

Influenza in UK, 2009

How Does Antiviral Resistance Happen?

▶ Large/Improper antiviral treatment

▶ Antiviral exposure

▶ Mutation of virus / adaptive of bacteria (parasites)

Benefits of Antiviral Treatment

- Reduce infectiousness

- shorten the duration of illness

- Alleveiate the unfomfortableness

Treatment vs Emergence of Drug-resistance

Experimental studies suggest that the rate of developing resistance increases with time, as resistant mutants in viruses isolated from treated patients were mostly detected several days after the start of treatment [M. KISO et al. 2004 and P. WARD et al. 2005].

BALANCE?

Probability of NOT Developing Drug-resistance

$\alpha(a)$: The probability of being in the treated class (I_T) at time a following the initiation of treatment without developing drug-resistance.

(H) $\alpha(a) : [0, \infty) \longrightarrow [0, 1]$ is a non-increasing, piecewise continuous function with possibly finite number of jumps, $\lim_{a \to \infty} \alpha(a) = 0$, and $\int_0^\infty \alpha(a) \, \mathrm{d}a$ is bounded.
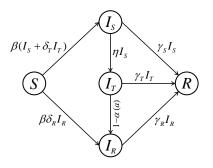
Flow Chart

Figure: Model diagram for transitions between subpopulations.

Assumptions

- No demographic birth and death $\Leftrightarrow$ Total population N is a constant.

- Treatment reduces the infectiousness, and therefore transmissibility, of the drug-sensitive infection $\Leftrightarrow \delta_T < 1$ [M.E. HALLORAN et al. 2006]

- Treatment may also shorten the infectious period $\Leftrightarrow$ $1/\gamma_T \leq 1/\gamma_S$ [S. Moghadas et al. 2008]

- Resistance generally emerges with compromised transmission fitness $\Leftrightarrow \delta_R < 1$ [E. DOMINGO et al. 1997]

Mathematical Model

$$
\begin{aligned}
S'(t) &= -\beta(I_S + \delta_T I_T + \delta_R I_R)S, \\
I'_S(t) &= \beta(I_S + \delta_T I_T)S - (\gamma_S + \eta)I_S, \\
I_T(t) &= \int_0^t \eta I_S(\xi) e^{-\gamma_T(t-\xi)} \alpha(t-\xi)\,\mathrm{d}\xi, \\
I'_R &= N - S(t) - I_S(t) - I_T(t) - I_R(t), \\
R'(t) &= \gamma_S I_S + \gamma_T I_T + \gamma_R I_R,
\end{aligned}
$$

Simplified Model

$$
\begin{aligned}
S' &= -\beta(I_S + \delta_T I_T + \delta_R I_R)S, \\
I_S' &= \beta(I_S + \delta_T I_T)S - (\gamma_s + \eta)I_S, \\
I_T' &= \eta I_S + \int_0^t \eta I_S(\xi)e^{-\gamma_T(t-\xi)}\alpha'(t-\xi)\,\mathrm{d}\xi - \gamma_T I_T, \\
I_R' &= \delta_R \beta I_R S - \int_0^t \eta I_S(\xi)e^{-\gamma_T(t-\xi)}\alpha'(t-\xi)\,\mathrm{d}\xi - \gamma_R I_R.
\end{aligned}
$$

Remark: The model can be derived by age-structure PDE system as well.

Basic Reproduction Number

In the absence of treatment, it can be easily seen that the basic reproduction number for the drug-sensitive infection is

$$\mathcal{R}_0 = \beta N / \gamma_s.$$

Let

$$\alpha^* := \lim_{t \to \infty} \int_0^t e^{-\gamma_T \xi} \alpha(\xi) \, d\xi.$$

Then,

$$0 < \alpha^* \le \lim_{t \to \infty} \int_0^t e^{-\gamma_T \xi} \, d\xi = \frac{1}{\gamma_T},$$

and therefore $\gamma_T \alpha^*$ represents the probability that an infected individual will recover during the course of treatment.

Control Reproduction Number

When treatment is implemented, introduction of one infection with drug-sensitive strain brings

$$\mathcal{R}_c^s = \left(\frac{\gamma_s}{\gamma_s + \eta} + \frac{\delta_T \eta \gamma_T \alpha^*}{\gamma_s + \eta} + \frac{\delta_R \eta (1 - \gamma_T \alpha^*)}{\gamma_s + \eta} \right) \mathcal{R}_0.$$

Introduction of an individual infected with the resistant strain into the population will result in

$$\mathcal{R}_R = \frac{\delta_R \gamma_s}{\gamma_R} \mathcal{R}_0.$$

Therefore,

$$\mathcal{R}_c = \max \{ \mathcal{R}_c^s, \mathcal{R}_R \}.$$

Epidemic Final Size

Final size relations:

$$\beta \Delta \hat{I}_S = \delta_R \beta (N - S_\infty) - \gamma_R \log \frac{S_0}{S_\infty},$$

$$\beta \Delta \hat{I}_R = (\gamma_S + \gamma_T \eta \alpha^*) \log \frac{S_0}{S_\infty} - \beta (1 + \delta_T \eta \alpha^*)(N - S_\infty),$$

where $\Delta = \delta_R (\gamma_S + \gamma_T \eta \alpha^*) - \gamma_R (1 + \delta_T \eta \alpha^*)$, and $\hat{f}$ denotes $\int_0^\infty f(t) \, dt$, $f = I(t) \, \text{or} \, R(t)$.

Epidemic Final Size

Denote

$$\mathcal{R}^*(\eta) := \frac{1 + \delta_T \eta \alpha^*}{\gamma_s + \gamma_T \eta \alpha^*} \beta N = \frac{\gamma_s (1 + \delta_T \eta \alpha^*)}{\gamma_s + \gamma_T \eta \alpha^*} \mathcal{R}_0.$$

We have

- $\mathcal{R}^*(0) = \mathcal{R}_0$;
- $\lim_{\eta \to \infty} \mathcal{R}^*(\eta) = \delta_T \gamma_s \mathcal{R}_0 / \gamma_T$; and
- $\exists \eta^* = (\gamma_s \delta_R - \gamma_R) / [\alpha^* (\gamma_R \delta_T - \gamma_T \delta_R)] > 0$ such that $\mathcal{R}^*(\eta^*) = \mathcal{R}_R$.

Epidemic Final Size

The final size inequalities

$$\mathcal{R}_R < \frac{\gamma_R \log \dfrac{S_0}{S_\infty(\eta)}}{\gamma_s \left[1 - \dfrac{S_\infty(\eta)}{N}\right]} < \mathcal{R}^*(\eta), \quad \eta < \eta^*,$$

and

$$\mathcal{R}_R > \frac{\gamma_R \log \dfrac{S_0}{S_\infty(\eta)}}{\gamma_s \left[1 - \dfrac{S_\infty(\eta)}{N}\right]} > \mathcal{R}^*(\eta), \quad \eta > \eta^*.$$

If $\eta = \eta^*$ exists, we have the final size relation:

$$\log \frac{S_0}{S_\infty(\eta^*)} = \frac{\gamma_s}{\gamma_R} \mathcal{R}_R \left[1 - \frac{S_\infty(\eta^*)}{N}\right].$$

Epidemic Final Size

We define the ratio of these two numbers as a function of η by

$$\lambda(\eta) = \frac{\gamma_R \hat{I}_R}{(\gamma_S + \gamma_T \eta \alpha^*)\hat{I}_S}.$$

By computation, we can get

$$\left(\frac{E(\eta)}{N} - \frac{1}{S_\infty(\eta)}\right) S_\infty'(\eta) = E'(\eta)\left(1 - \frac{S_\infty(\eta)}{N}\right),$$

where

$$E(\eta) = \frac{\gamma_S\left[\mathcal{R}^*(\eta) + \mathcal{R}_R \lambda(\eta)\right]}{\gamma_R\left[1 + \lambda(\eta)\right]}.$$

Epidemic Final Size

Theorem

Suppose $\lambda'(\eta) \geq 0$.

1. *If $\delta_R/\gamma_R \leq \delta_T/\gamma_T$, then increasing treatment rate reduces the epidemic final size.*

2. *If $\delta_R/\gamma_R > \delta_T/\gamma_T$, then either the epidemic final size decreases as the treatment rate increases for $\eta \geq 0$; or there exists an $\eta_0 > 0$ such that the epidemic final size decreases in the interval of $0 \leq \eta < \eta_0$, and has a local minimum at η_0.*
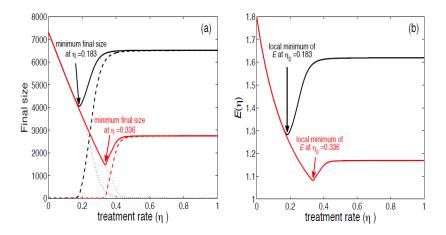
$$\alpha(a) = e^{-\kappa a}$$

Figure: (a) Solid, dotted, and dashed curves correspond to the total number of infections (final size), total number of untreated and treated sensitive infections, and total number of resistant infections, respectively, for $\delta_R = 0.65$ (red curves) and $\delta_R = 0.9$ (black curves). (b) Local minimum of $E(\eta)$ for $\delta_R = 0.65$ (red curve) and $\delta_R = 0.9$ (black curve). Other parameter values are $\mathcal{R}_0 = 1.8$, $\gamma_S = 1/4$ day^{-1}, $\gamma_T = 1/3$ day^{-1}, $\gamma_R = 1/4$ day^{-1}, $\kappa = 10^{-5}$ day^{-1}, and $\delta_T = 0.4$. Initial values of sub-populations are $S_0 = 10^4 - 1$, $I_S(0) = 1$, and $I_T(0) = I_R(0) = 0$.
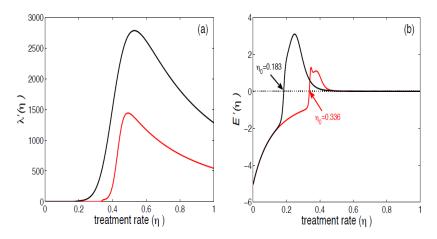
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Figure: (a) $\delta_R = 0.65$ (red curve) and $\delta_R = 0.9$ (black curve). (b) $\delta_R = 0.65$ (red curve) and $\delta_R = 0.9$ (black curve). Other parameter values are $\mathcal{R}_0 = 1.8$, $\gamma_S = 1/4$ day^{-1}, $\gamma_T = 1/3$ day^{-1}, $\gamma_R = 1/4$ day^{-1}, $\kappa = 10^{-5}$ day^{-1}, and $\delta_T = 0.4$. Initial values of sub-populations are $S_0 = 10^4 - 1$, $I_S(0) = 1$, and $I_T(0) = I_R(0) = 0$.

$$\alpha(a) = \begin{cases} 1, & a \leq \tau, \\ 0, & a > \tau. \end{cases}$$
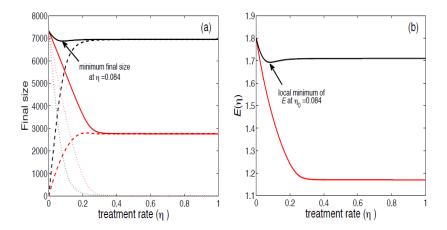

Figure: (a) $\delta_R = 0.65$ (red curves) and $\delta_R = 0.9$ (black curves). (b) Behaviour of $E(\eta)$ for $\delta_R = 0.65$ (red curve) and $\delta_R = 0.9$ (black curve). Other parameter values are $\mathcal{R}_0 = 1.8$, $\gamma_S = \gamma_T = \gamma_R = 1/4$ day^{-1}, $\tau = 3$ days, and $\delta_T = 0.4$. Initial values of sub-populations are $S_0 = 10^4 - 1$, $I_S(0) = 1$, and $I_T(0) = I_R(0) = 0$.

Summary

- Treatment is not always efficient for the control of epidemic final size;

- An opitmal treatment rate will minimize the epidemic size;

- Optimal treatment rates associate with the transmissibility/duration of illness of drug-resistant strain (or, the difference between two strains) .

Thank you!