HHS Public Access

Author manuscript

Math Biosci. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Math Biosci. 2015 May ; 263: 121–132. doi:10.1016/j.mbs.2015.02.007.

Antibiotic resistance as collateral damage: the tragedy of the commons in a two-disease setting

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Abstract

We propose a simple two-disease epidemic model where one disease exhibits only a drug-sensitive strain, while the other exhibits both drug-sensitive and drug-resistant strains. Treatment for the first disease may select for resistance in the other. We model antibiotic use as a mathematical game through the study of individual incentives and community welfare. The basic reproduction number is derived and the existence and local stability of the model equilibria are analyzed. When the force of infection of each disease is unaffected by the presence of the other, we find that there is a conflict of interest between individual and community, known as a tragedy of the commons, under targeted treatment towards persons infected by the single strain disease, but there is no conflict under mass treatment. However, we numerically show that individual and social incentive to use antibiotics may show disaccord under mass treatment if the restriction on the transmission ability of the dually infected people is removed, or drug resistant infection is worse than drug sensitive infection, or the uninfected state has a comparative disutility over the infected states.

Keywords

drug-resistance; game theory; two diseases; tragedy of the commons; mass treatment; targeted treatment

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1 Introduction

In recent years, the problem of bacterial antibiotic resistance has led to suggestions that antibiotics are overprescribed [8, 27], and that decreasing the use of antibiotics could benefit society as a whole by minimizing the emergence of drug-resistance [36, 12]. It has been argued that antibiotic efficacy should be considered as a common good [7], and that collective action may be needed to preserve this common good against overuse. Some authors believe that individual incentives may drive overuse of antibiotics, leading to a "tragedy of the commons" [1]. The concept of the tragedy of the commons originated from an example on population control proposed by Lloyd [29] in 1833 and later developed by Hardin [18] in the 1960s. One example of this is seen in simple mathematical models of drug resistance, where increasing treatment of mild or early disease may benefit the individual, despite the fact that such an outcome may lead to an increase in drug-resistant bacteria and thus a decrease in the overall efficacy of antibiotic treatment [38].

An important example of how drug-resistance occurs is the use of broad spectrum antibiotics [20]. In this case, treatment of one infection or disease may select for resistance in other organisms which are present [50]. This phenomenon has been observed during the use of mass azithromycin to eliminate trachoma due to *Chlamydia trachomatis*, a leading cause of infectious blindness in the world [52]. The World Health Organization promotes antibiotic treatment for trachoma control, using mass administration of single-dose oral azithromycin [44, 52]. While *Chlamydia trachomatis* has never exhibited epidemiologically important drug resistance [49, 21], the emergence of macrolide-resistant pneumococcus due to mass administration of azythromycin has been observed [28, 47], though such resistance has declined after cessation of treatment [47, 19]. Fears of increased mortality have proven unfounded, e.g. [39, 17, 24, 25].

In this paper, based on the pattern seen for pneumococcus and *Chlamydia trachomatis*, we propose and analyze a simple model of coinfection and cotransmission of two infectious agents in order to determine whether antibiotic resistance is a tragedy of the commons in a two diseases setting. For one infectious agent, we assume that both sensitive and resistant strains are possible, while for the other, only drug sensitive strains are present. Both are modeled as simple SIS (susceptible-infectious-susceptible) processes [23]. Coinfection by multiple pathogens or diseases is a global challenge for public health. It has attracted increasing attention in the field of mathematical epidemiology since the pioneering works by Dietz [14], Bremermann and Thieme [5], and others. For example, a number of mathematical models for HIV/TB coninfection [32, 45, 2, 43], HIV/malaria coinfection [34], HIV/gonorrhea coinfection [35], malaria and meningitis coinfection [26], and CA-MRSA/HA-MRSA co-colonization [11, 40] have been developed in recent years.

Our model assumes that treatment is targeted to the agent that only has sensitive strains, but can select for resistance in the other infectious agent (as a type of "collateral damage"). We will assume that the population as a whole has a particular treatment rate, which gives rise to an equilibrium prevalence of both infections. A single individual in the population who changes her or his treatment rate will then experience either more or less infection. When increasing infection rate for an individual causes that individual to spend less time infected,

that individual has an incentive to increase treatment. However, if increasing the population rate of treatment causes a higher population cost, a tragedy of the commons results. Previously we used this method to analyze the tragedy of the commons resulting from incentives to treat early or mild disease ([38]; see [42] for a general exposition), and in this paper we will apply the same method to a simple model of cotransmission.

2 The model

We recently analyzed a simple SIS model (susceptible-infective-susceptible) of drug resistance [38] for one disease, denoted by *P*. The state of a single individual may be completely susceptible, infected with drug-susceptible organisms only, or infected with drug-resistant organisms only. We consider a single individual in a large population, subject to constant forces of infection. Let $X^{(i)}$, $X^{(i)}$, $Y_S^{(i)}$, and $Y_R^{(i)}$ denote the probability the individual is susceptible, infected with the sensitive strain, or infected with the resistant strain, respectively. Treatment, occurring at rate $\theta_P^{(i)}$, may lead to a new clinical appearance of drug resistance with probability $\delta \in (0, 1)$. Let ρ_P denote the recovery rate. Denoting the force of infection (only dependent on the number of individuals infected, and independent of individual choice of treatment) due to sensitive strains by λ_S and due to resistant strains by λ_R, a single individual follows the Markov chain

$$\frac{dX^{(i)}}{dt} = -(\lambda_S+\lambda_R)X^{(i)}+(\rho_P Y_S^{(i)}+\rho_P Y_R^{(i)})+\theta_P^{(i)}(1-\delta)Y_S^{(i)},$$

$$\frac{dY_S^{(i)}}{dt} = \lambda_S X^{(i)} - \rho_P Y_S^{(i)} - \theta_P^{(i)} Y_S^{(i)},$$

$$\frac{dY_R^{(i)}}{dt} = \lambda_R X^{(i)} - \rho_P Y_R^{(i)} + \theta_P^{(i)} \delta Y_S^{(i)},$$

which is Model 1 in the previous paper ([38]).

We now extend this model to include a second disease, denoted by *C*. Motivated by the example of *Chlamydia*, we again assume a simple SIS process for the second disease, and assume no drug resistance is possible for this second disease. Nevertheless, treating individuals with this disease may select for drug resistance in the first disease (since this first disease might be present). We now denote the recovery rate for the second disease by ρ_C, and the force of infection by λ_C. Let $X^{(i)}$ denote the probability that a single individual in a large population is infected with no infectious agent, $Y_S^{(i)}$ the probability the individual is infected by the drug-sensitive strain of the first agent (and not infected with the second agent), $Y_R^{(i)}$ the probability the individual is infected by the drug-resistant strain of the first agent (and not infected with the second agent), $Y_C^{(i)}$ the probability the individual is infected

by the second agent (and not infected with either strain of the first agent), $Y_{SC}^{(i)}$ the probability the individual is infected by the drug-sensitive strain of the first agent and also by the second agent, and finally $Y_{RC}^{(i)}$ the probability the individual is infected by the drug-resistant strain of the first agent and also by the second agent. The treatment rate for individuals infected by the second infectious agent only is $\theta_C^{(i)}$; the treatment rate for individuals infected simultaneously by both agents is denoted $\theta_{PC}^{(i)}$. Here, a susceptible individual who contacts a dually infected person could become infected only with the first, the second or both agents as a result of the single contact; we thus have infection rates of $\lambda_{SC\to S}$, $\lambda_{SC\to C}$ and $\lambda_{SC\to SC}$ (or $\lambda_{RC\to R}$, $\lambda_{RC\to C}$ and $\lambda_{RC\to RC}$), correspondingly. Then, we have

$$\begin{aligned}\frac{dX^{(i)}}{dt} =& -(\lambda_S+\lambda_R+\lambda_C+\lambda_{SC\to S}+\lambda_{SC\to SC}+\lambda_{SC\to C}\\ &+\lambda_{RC\to R}+\lambda_{RC\to RC}+\lambda_{RC\to C})X^{(i)}+(\rho_P Y_S^{(i)}+\rho_P Y_R^{(i)}+\rho_C Y_C^{(i)})\\ &+(\theta_C^{(i)}Y_C^{(i)}+\theta_{PC}^{(i)}(1-\delta)Y_{SC}^{(i)}+\theta_P^{(i)}(1-\delta)Y_S^{(i)}),\end{aligned}$$

$$\frac{dY_S^{(i)}}{dt}=(\lambda_S+\lambda_{SC\to S})X^{(i)}-(\lambda_C+\lambda_{SC\to C}+\lambda_{SC\to SC}+\lambda_{RC\to C}+\lambda_{RC\to RC})Y_S^{(i)}+(\rho_C Y_{SC}^{(i)}-\rho_P Y_S^{(i)})-\theta_P^{(i)}Y_S^{(i)},$$

$$\begin{aligned}\frac{dY_R^{(i)}}{dt}=&(\lambda_R+\lambda_{RC\to R})X^{(i)}-(\lambda_C+\lambda_{SC\to C}+\lambda_{SC\to SC}+\lambda_{RC\to C}+\lambda_{RC\to RC})Y_R^{(i)}\\ &+(\rho_C Y_{RC}^{(i)}-\rho_P Y_R^{(i)})+(\theta_{PC}^{(i)}Y_{RC}^{(i)}+\theta_{PC}^{(i)}\delta Y_{SC}^{(i)}+\theta_P^{(i)}\delta Y_S^{(i)}),\end{aligned} \tag{2.1}$$

$$\begin{aligned}\frac{dY_C^{(i)}}{dt}=&(\lambda_C+\lambda_{SC\to C}+\lambda_{RC\to C})X^{(i)}-(\lambda_S+\lambda_R+\lambda_{SC\to S}+\lambda_{SC\to SC}+\lambda_{RC\to R}\\ &+\lambda_{RC\to RC})Y_C^{(i)}+(\rho_P Y_{SC}^{(i)}+\rho_P Y_{RC}^{(i)}-\rho_C Y_C^{(i)})-\theta_C^{(i)}Y_C^{(i)},\end{aligned}$$

$$\begin{aligned}\frac{dY_{SC}^{(i)}}{dt}=&\lambda_{SC\to SC}X^{(i)}+(\lambda_C+\lambda_{SC\to C}+\lambda_{SC\to SC}+\lambda_{RC\to C}+\lambda_{RC\to RC})Y_S^{(i)}\\ &+(\lambda_S+\lambda_{SC\to S}+\lambda_{SC\to SC})Y_C^{(i)}-(\rho_P+\rho_C)Y_{SC}^{(i)}-\theta_{PC}^{(i)}Y_{SC}^{(i)},\end{aligned}$$

$$\begin{aligned}\frac{dY_{RC}^{(i)}}{dt}=&\lambda_{RC\to RC}X^{(i)}+(\lambda_C+\lambda_{SC\to C}+\lambda_{SC\to SC}+\lambda_{RC\to C}+\lambda_{RC\to RC})Y_R^{(i)}\\ &+(\lambda_R+\lambda_{RC\to R}+\lambda_{RC\to RC})Y_C^{(i)}-(\rho_P+\rho_C)Y_{RC}^{(i)}-\theta_{PC}^{(i)}Y_{RC}^{(i)}.\end{aligned}$$

We omit human migration, birth, natural and disease-induced death; the total probability satisfies $X^{(i)}+Y_S^{(i)}+Y_R^{(i)}+Y_C^{(i)}+Y_{SC}^{(i)}+Y_{RC}^{(i)}=1$. For any given set of forces of infection, these linear equations can be solved for the equilibrium values of the probabilities of being in each state. We denote the equilibrium by $\bar{E}^{(i)}=(\overline{X}^{(i)}, \bar{Y}_S^{(i)}, \bar{Y}_R^{(i)}, \bar{Y}_C^{(i)}, \bar{Y}_{SC}^{(i)}, \bar{Y}_{RC}^{(i)})$.

As indicated above, we wish to consider a particular individual who chooses treatment rates $\theta_P^{(i)}, \theta_C^{(i)}$ or $\theta_{PC}^{(i)}$, faced by a unanimous choice θ_P, θ_C or θ_{PC} made by all other individuals. The following system of equations describing the corresponding community-level transmission dynamics:

$$\begin{aligned}\frac{dX}{dt}=&-(\lambda_S+\lambda_R+\lambda_C+\lambda_{SC\to S}+\lambda_{SC\to SC}+\lambda_{SC\to C}\\&+\lambda_{RC\to R}+\lambda_{RC\to RC}+\lambda_{RC\to C})X+(\rho_P Y_S+\rho_P Y_R+\rho_C Y_C)\\&+(\theta_C Y_C+\theta_{PC}(1-\delta)Y_{SC}+\theta_P(1-\delta)Y_S),\end{aligned}$$

$$\frac{dY_S}{dt}=(\lambda_S+\lambda_{SC\to S})X-(\lambda_C+\lambda_{SC\to C}+\lambda_{SC\to SC}+\lambda_{RC\to C}+\lambda_{RC\to RC})Y_S+(\rho_C Y_{SC}-\rho_P Y_S)-\theta_P Y_S,$$

$$\frac{dY_R}{dt}=(\lambda_R+\lambda_{RC\to R})X-(\lambda_C+\lambda_{SC\to C}+\lambda_{SC\to SC}+\lambda_{RC\to C}+\lambda_{RC\to RC})Y_R+(\rho_C Y_{RC}-\rho_P Y_R)+(\theta_{PC}Y_{RC}+\theta_{PC}\delta Y_{SC}+\theta_P\delta Y_S), \quad (2.2)$$

$$\frac{dY_C}{dt}=(\lambda_C+\lambda_{SC\to C}+\lambda_{RC\to C})X-(\lambda_S+\lambda_R+\lambda_{SC\to S}+\lambda_{SC\to SC}+\lambda_{RC\to R}+\lambda_{RC\to RC})Y_C+(\rho_P Y_{SC}-\rho_P Y_{RC}-\rho_C Y_C)-\theta_C Y_C,$$

$$\frac{dY_{SC}}{dt}=\lambda_{SC\to SC}X+(\lambda_C+\lambda_{SC\to C}+\lambda_{SC\to SC}+\lambda_{RC\to C}+\lambda_{RC\to RC})Y_S+(\lambda_S+\lambda_{SC\to S}+\lambda_{SC\to SC})Y_C-(\rho_P+\rho_C)Y_{SC}-\theta_{PC}Y_{SC},$$

$$\begin{aligned}\frac{dY_{RC}}{dt}=&\lambda_{RC\to RC}X+(\lambda_C+\lambda_{SC\to C}+\lambda_{SC\to SC}+\lambda_{RC\to C}+\lambda_{RC\to RC})Y_R\\&+(\lambda_R+\lambda_{RC\to R}+\lambda_{RC\to RC})Y_C-(\rho_P+\rho_C)Y_{RC}-\theta_{PC}Y_{RC},\end{aligned}$$

where X, Y_S, Y_R, Y_C, Y_{SC}, and Y_{RC} are the proportion of each disease state in the whole population; $X + Y_S + Y_R + Y_C + Y_{SC} + Y_{RC} = 1$. A state transition diagram for the disease transmission is shown in Figure 1. We assume that the forces of infection are proportional to the prevalence fractions and the force of infection of one agent is not affected by the presence of the other:

(A1) $\lambda_S = \beta_S Y_S$, $\lambda_R = \beta_R Y_R$ where $\beta_R < \beta_S$; $\lambda_C = \beta_C Y_C$;

(A2) $\lambda_{SC\to SC} = \beta_{11} Y_{SC}$, $\lambda_{SC\to S} = \beta_{10} Y_{SC}$, $\lambda_{SC\to C} = \beta_{01} Y_{SC}$,

$$\lambda_{RC\to RC}=\beta'_{11}Y_{RC},\ \lambda_{RC\to R}=\beta'_{10}Y_{RC},\ \lambda_{RC\to C}=\beta'_{01}Y_{RC};$$

(A3) $\beta_{11}+\beta_{10}=\beta_S$ and $\beta_{11}+\beta_{01}=\beta_C$, $\beta'_{11}+\beta'_{10}=\beta_R$ and $\beta'_{11}+\beta'_{01}=\beta_C$.

Here β_S, β_R, and β_C are transmission coefficients of the drug-sensitive strain of the first agent, drug-resistant strain of the first agent, and the second agent, respectively. Note that an individual in a large population is subject to constant exogenous forces of infection (unaffected by the decision of that single individual), while the forces of infection at the population level are determined by the overall disease prevalence in the community. In many cases the emergence of drug resistance is indeed associated with a fitness cost [31], i.e., $\beta_R < \beta_S$, but a fitness cost of resistance may not be universally exhibited (e.g. [13]). Also, we do not assume that both infections in dually infected people are simply transmitted independently. Cotransmission from dually infected people is assumed possible, as a single infectious contact could contain a sufficient dose of both infectious agents. It is assumed that all model parameters are positive, with the exception of treatment rates $\theta_P^{(i)}, \theta_C^{(i)}, \theta_{PC}^{(i)}$, θ_P, θ_C, θ_{PC} and parts of transmission coefficients β_{11}, β_{10}, β_{01}, $\beta'_{11}, \beta'_{10}, \beta'_{01}$ which can be zero.

In general, we let D_P and D_C be an average health state disutility of infection or colonization by the first or second agent, respectively; we assume no difference in disutility between drug susceptible and drug resistant strains. Rather, individuals who are infected with a drug resistant strain are at a disadvantage because we assume treatment will be less effective (leading to longer mean durations of infection). We also assume no interaction between the agents, so that the disutility of being infected by both agents is the sum of the separate disutilities. Thus, for a single individual we wish to minimize

$$J^{(i)}=D_P J_P^{(i)}+D_C J_C^{(i)},$$

where $J_P^{(i)}=\bar{Y}_S^{(i)}+\bar{Y}_R^{(i)}+\bar{Y}_{SC}^{(i)}+\bar{Y}_{RC}^{(i)}$ and $J_C^{(i)}=\bar{Y}_C^{(i)}+\bar{Y}_{SC}^{(i)}+\bar{Y}_{RC}^{(i)}$ represent the probabilities being infected by the first or second agent, respectively, and $\bar{E}^{(i)}=(\overline{X}^{(i)}, \bar{Y}_S^{(i)}, \bar{Y}_R^{(i)}, \bar{Y}_C^{(i)}, \bar{Y}_{SC}^{(i)}, \bar{Y}_{RC}^{(i)})$ is the stable equilibrium of the individual equations. Analogously, for a community we can define its average disutility as

$$J=D_P J_P+D_C J_C,$$

where $J_P = \bar{Y}_S + \bar{Y}_R + \bar{Y}_{SC} + \bar{Y}_{RC}$ and $J_C = \bar{Y}_C + \bar{Y}_{SC} + \bar{Y}_{RC}$ represent the fractions being infected by the first or second agent, respectively, and $\bar{E} = (X, \bar{Y}_S, \bar{Y}_R, \bar{Y}_C, \bar{Y}_{SC}, \bar{Y}_{RC})$ is the stable steady state of the community equations.

We will examine these equations under two treatment strategies: (a) mass treatment, and (b) treatment targeted towards persons infected by disease *C*. In the first case, we assume $\theta_P = \theta_C = \theta_{PC} = \theta$, so that all individuals are equally likely to be treated, regardless of their infection status, as would be the case during mass administration of azithromycin to eliminate trachoma. In the second case, we assume $\theta_P = 0$ and $\theta_C = \theta_{PC} = \theta$. Here, targeting infectives with the second agent may select for drug resistance in the first agent. Similarly,

we assume $\theta_P^{(i)}=\theta_C^{(i)}=\theta_{PC}^{(i)}=\theta^{(i)}$, and $\theta_P^{(i)}=0$ and $\theta_C^{(i)}=\theta_{PC}^{(i)}=\theta^{(i)}$, respectively, for an individual under the two treatment strategies.

The disutility to each individual is determined not only by that individual's choice of treatment, but also by all other individuals' average choice. We followed standard methods ([42, 38]) to calculate the disutility of an individual, and determined whether individual incentives always parallel to community outcomes. To analyze individual incentives for treatment, we first determined the equilibrium dynamics of infection. We then examined a single individual whose forces of infection (for each agent that is circulating) are determined by the overall treatment rate in the entire population, and determined the expected amount of time that would be spent infected in each disease if this individual chose a different treatment rate rather than the population as a whole.

3 Main results

In this section, we derive the basic reproduction number for the population-level model, and then study the existence and local stability of feasible equilibria. The possibility of the occurrence of a tragedy of the commons under mass treatment or targeted treatment is analytically investigated.

3.1 The basic reproduction number

We consider the community equations (2.2) in which the forces of infection are not exogenous, but determined by the disease prevalence. It is clear that E_0 = (1, 0, 0, 0, 0, 0) is the unique disease free equilibrium of system (2.2). Following the method and notations of van den Driessche and Watmough [51], we find

$$F=\begin{pmatrix} \beta_S & 0 & 0 & \beta_S-\beta_{11} & 0 \\ 0 & \beta_R & 0 & 0 & \beta_R-\beta_{11}' \\ 0 & 0 & \beta_C & \beta_C-\beta_{11} & \beta_C-\beta_{11}' \\ 0 & 0 & 0 & \beta_{11} & 0 \\ 0 & 0 & 0 & 0 & \beta_{11}' \end{pmatrix}$$

and

$$V=\begin{pmatrix} \rho_P+\theta_P & 0 & 0 & -\rho_C & 0 \\ -\theta_P\delta & \rho_P & 0 & -\theta_{PC}\delta & -\rho_C-\theta_{PC} \\ 0 & 0 & \rho_C+\theta_C & -\rho_P & -\rho_P \\ 0 & 0 & 0 & \rho_P+\rho_C+\theta_{PC} & 0 \\ 0 & 0 & 0 & 0 & \rho_P+\rho_C+\theta_{PC} \end{pmatrix}.$$

The basic reproduction number $\mathscr{R}_0$ of model (2.2) is defined as the spectral radius of the next generation matrix $F\cdot V^{-1}$, i.e., $\mathscr{R}_0=\max_{1\le i\le 5}\mathscr{R}_{i0}$ where

$$\mathscr{R}_{10}=\frac{\beta_S}{\rho_P+\theta_P},\mathscr{R}_{20}=\frac{\beta_R}{\rho_P},\mathscr{R}_{30}=\frac{\beta_C}{\rho_C+\theta_C},\mathscr{R}_{40}=\frac{\beta_{11}}{\rho_P+\rho_C+\theta_{PC}}\text{and}\mathscr{R}_{50}=\frac{\beta_{11}'}{\rho_P+\rho_C+\theta_{PC}}.$$

For $i = 1, \ldots, 5$, $\mathscr{R}_{i0}$ is the reproduction number corresponding to epidemiological classes Y_S, Y_R, Y_C, Y_{SC}, and Y_{RC}, respectively. In case of mass treatment or targeted treatment, we know $\mathscr{R}_{40} < \min\{\mathscr{R}_{10}, \mathscr{R}_{30}\}$, $\mathscr{R}_{50} < \min\{\mathscr{R}_{20}, \mathscr{R}_{30}\}$, and hence $\mathscr{R}_0 = \max_{1 \le i \le 3} \mathscr{R}_{i0}$. Moreover, E_0 is locally asymptotically stable if $\mathscr{R}_0 < 1$ and unstable if otherwise.

3.2 The equilibria

For an individual subject to constant exogenous forces of infection (unaffected by the treatment strategy that person chooses), the coefficient matrix of its individual equations (2.1), denoted by $A = (a_{ij})_{6\times 6}$, is (or can be reduced to) a constant irreducible matrix (or submatrix) with nonnegative off-diagonal entries and zero column sums. It follows from Corollary 4.3.2 in Smith [48] or Lemma 1 in Cosner et al. [10] that (2.1) has a unique nonnegative equilibrium $\bar{E}^{(i)} = (\overline{X}^{(i)}, \bar{Y}_S^{(i)}, \bar{Y}_R^{(i)}, \bar{Y}_C^{(i)}, \bar{Y}_{SC}^{(i)}, \bar{Y}_{RC}^{(i)})$ which is globally stable in the hyperplane

$$\{(X^{(i)}, Y_S^{(i)}, Y_R^{(i)}, Y_C^{(i)}, Y_{SC}^{(i)}, Y_{RC}^{(i)}) \in \mathbb{R}_+^6 : X^{(i)} + Y_S^{(i)} + Y_R^{(i)} + Y_C^{(i)} + Y_{SC}^{(i)} + Y_{RC}^{(i)} = 1\}.$$

Direct computations find that the community model equations (2.2) can have up to four types of steady states as follows. The detailed derivation and stability analysis appear in Appendix A.

Theorem 3.1—*Let* $\Re(z)$ *be the real part of a complex number z. For system* (2.2) *under mass treatment or targeted treatment, we have*

- **i.** *The no-disease or disease free equilibrium* $E_0 = (1, 0, 0, 0, 0, 0)$ *always exists and it is stable if* $\mathscr{R}_0 < 1$ *and unstable otherwise.*
- **ii.** *One-strain equilibrium:*
  - **a.** $E_1 = \left(\frac{1}{\mathscr{R}_{10}}, 1 - \frac{1}{\mathscr{R}_{10}}, 0, 0, 0, 0\right)$ *exists if and only if* $\mathscr{R}_{10} > 1$ *and* $\theta_P = 0$ *(targeted treatment).* E_1 *is stable if and only if* $\mathscr{R}_{10} > \max\{1, \mathscr{R}_{20}, \mathscr{R}_{50}\}$ *and* $\mathscr{R}_{30} < 1$.
  - **b.** $E_2 = \left(\frac{1}{\mathscr{R}_{20}}, 0, 1 - \frac{1}{\mathscr{R}_{20}}, 0, 0, 0\right)$ *exists if and only if* $\mathscr{R}_{20} > 1$. E_2 *is stable if and only if* $\mathscr{R}_{20} > \max\{1, \mathscr{R}_{10}, \mathscr{R}_{40}\}$ *and* $\mathscr{R}_{30} < 1$.
  - **c.** $E_3 = \left(\frac{1}{\mathscr{R}_{30}}, 0, 0, 1 - \frac{1}{\mathscr{R}_{30}}, 0, 0\right)$ *exists if and only if* $\mathscr{R}_{30} > 1$. *Targeted treatment:* E_3 *is stable if and only if* $\mathscr{R}_{30} > 1$, $\mathscr{R}_{20} < 1$, $\Re\lambda_3^+ < 0$ *and* $\Re\lambda_3^- < 0$. *Mass treatment:* E_3 *is stable if and only if* $\mathscr{R}_{10} < 1$, $\mathscr{R}_{20} < 1$, *and* $\mathscr{R}_{30} > 1$. *Here* $\lambda_3^{\pm}$ *denote the roots of* $\lambda^2 + M_1\lambda + M_0 = 0$ *with*

$$M_1 = (1 - \mathscr{R}_{10})\rho_P + \left(1 - \frac{\mathscr{R}_{40}}{\mathscr{R}_{30}}\right)(\rho_P + \rho_C + \theta) + \beta_C\left(1 - \frac{1}{\mathscr{R}_{30}}\right),$$

$$M_0=(1-\mathscr{R}_{10})\rho_P+\left(\left(1-\frac{\mathscr{R}_{40}}{\mathscr{R}_{30}}\right)(\rho_P+\rho_C+\theta)+\beta_C\left(1-\frac{1}{\mathscr{R}_{30}}\right)\right)+\theta(\beta_C+\beta_S)\left(1-\frac{1}{\mathscr{R}_{30}}\right).$$

iii. *Two-strain equilibrium:*

a. $E_{12}=\left(\frac{1}{\mathscr{R}_{10}}, Y_{12}, 1-\frac{1}{\mathscr{R}_{10}}-Y_{12}, 0, 0, 0\right)$ *exists if and only if* $\mathscr{R}_{10} > \mathscr{R}_{20}$, $\mathscr{R}_{10} > 1$, *and* $\theta_P > 0$. E_{12} *is stable if and only if* $\mathscr{R}_{30} < 1$. *Here*

$$Y_{12}=\frac{(1/\mathscr{R}_{20}-1/\mathscr{R}_{10})(1-1/\mathscr{R}_{10})}{1/\mathscr{R}_{20}-1/\mathscr{R}_{10}+\delta\theta_P/\beta_R}\in\left(0,\frac{1}{\mathscr{R}_{10}}\right).$$

b. $E_{13}=\left(X_{13}, \frac{1}{\mathscr{R}_{30}}-X_{13}, 0, \frac{1}{\mathscr{R}_{10}}-X_{13}, \frac{(\beta_S+\beta_C)(\frac{1}{\mathscr{R}_{10}}-X_{13})(\frac{1}{\mathscr{R}_{30}}-X_{13})}{(\beta_S+\beta_C-\beta_{11})X_{13}}, 0\right)$ *exists if and only* $\mathscr{R}_{10} > 1$, $\mathscr{R}_{30} > 1$ *and* $\theta_P = \theta_C = \theta_{PC} = 0$ *(no treatment).* E_{13} *is stable if and only if* $\beta_S > \beta_R$. *Here* $X_{13} \in [1/(\mathscr{R}_{10}\mathscr{R}_{30}), \min\{1/\mathscr{R}_{10}, 1/\mathscr{R}_{30}\})$ *is the smaller root to*

$$\beta_{11}X^2-\left(\left(\frac{1}{\mathscr{R}_{10}}+\frac{1}{\mathscr{R}_{30}}-1\right)\beta_{11}+(\beta_S+\beta_C)\right)X+(\beta_S+\beta_C)\frac{1}{\mathscr{R}_{10}\mathscr{R}_{30}}=0$$

if $\beta_{11} > 0$ *and equals* $1/(\mathscr{R}_{10}\mathscr{R}_{30})$ *if* $\beta_{11} = 0$.

c. $E_{23}=\left(X_{23}, 0, \frac{1}{\mathscr{R}_{30}}-X_{23}, \frac{1}{\mathscr{R}_{20}}-X_{23}, 0, \frac{(\beta_R+\beta_C)(\frac{1}{\mathscr{R}_{20}}-X_{23})(\frac{1}{\mathscr{R}_{30}}-X_{23})}{(\beta_R+\beta_C-\beta'_{11})X_{23}}\right)$ *exists if and only if* $\mathscr{R}_{20} > 1$ *and* $\mathscr{R}_{30} > 1$. *Mass treatment:* E_{23} *is stable if and only if* $\mathscr{R}_{10} < \mathscr{R}_{20}$. *Targeted treatment:* E_{23} *is stable if and only if* $\Re\lambda^+_{23}<0$ *and* $\Re\lambda^-_{23}<0$. *Here* $X_{23} \in [1/(\mathscr{R}_{20}\mathscr{R}_{30}), \min\{1/\mathscr{R}_{20}, 1/\mathscr{R}_{30}\})$ *is the smaller root to*

$$\beta'_{11}X^2-\left(\left(\frac{1}{\mathscr{R}_{20}}+\frac{1}{\mathscr{R}_{30}}-1\right)\beta'_{11}+(\beta_R+\beta_C)\right)X+(\beta_R+\beta_C)\frac{1}{\mathscr{R}_{20}\mathscr{R}_{30}}=0$$

if $\beta'_{11}>0$ *and equals* $1/(\mathscr{R}_{20}\mathscr{R}_{30})$ *if* $\beta'_{11}=0$. *Here* $\lambda^{\pm}_{23}$ *are solutions to* $\lambda^2 + H_1\lambda + H_0 = 0$ *with*

$$H_1=\left(1-\frac{\mathscr{R}_{10}}{\mathscr{R}_{20}}\right)\rho_P+(\beta_C+\rho_P-\beta_{11}X_{23}),$$

$$H_0=\left(1-\frac{\mathscr{R}_{10}}{\mathscr{R}_{20}}\right)\rho_P(\beta_C+\rho_P-\beta_{11}X_{23})+\theta\left((\beta_C-\rho_C-\theta)+\beta_S\left(\frac{1}{\mathscr{R}_{20}}-X_{23}\right)\right).$$

iv. *Coexistence equilibrium of the form* $\tilde{E}=(X, \tilde{Y}_S, \tilde{Y}_R, \tilde{Y}_C, \tilde{Y}_{SC}, \tilde{Y}_{RC})$ *in which all the components are positive.* $\tilde{E}$ *exists only if* $\mathscr{R}_{10}>1$, $\mathscr{R}_{30}>1$, $\mathscr{R}_{10}>\mathscr{R}_{20}$ *and* $\theta_C>0$.

Remark 3.2—Note that if $\mathscr{R}_{10}<1$ and $\mathscr{R}_{30}>1$ then $M_1>0$ and $M_0>0$. Thus E_3 is stable if $\mathscr{R}_{30}>1$, $\mathscr{R}_{20}<1$ and $\mathscr{R}_{10}<1$. In particular, when $\theta=0$, E_3 is stable if and only if $\mathscr{R}_{30}>1$, $\mathscr{R}_{20}<1$ and $\mathscr{R}_{10}<1$. However, for a non-zero targeted treatment rate θ, E_3 can remain stable even if $\mathscr{R}_{10}>1$. For example, given $\beta_S=1.1$, $\beta_R=0.5$, $\beta_C=3$, $\rho_P=1$, $\rho_C=0.5$, $\theta=1$, $\beta_{11}=0.5$, we have $\mathscr{R}_{30}=2>1$, $\mathscr{R}_{20}=0.5<1$, $\mathscr{R}_{10}=1.1>1$, but $M_1=3.65$ and $M_0=1.675$. In addition, if $\beta_{11}=0$ then $M_0>0$ implies $M_1>0$.

Remark 3.3—Under targeted treatment, E_{23} is stable if $\mathscr{R}_{10}<\mathscr{R}_{20}$. However, it is possible that E_{23} remains stable even if $\mathscr{R}_{10}>\mathscr{R}_{20}$. For example, given $\beta_S=2$, $\beta_R=1.5$, $\beta_C=3$, $\rho_P=1$, $\rho_C=1$, $\theta=1$, $\beta_{11}=0$, $\beta'_{11}=0$, we have $\mathscr{R}_{10}=2>\mathscr{R}_{20}=1.5>1$ and $\mathscr{R}_{30}=1.5>1$, but $H_1=11/3$ and $H_0=1/9$. In addition, if $\beta_{11}=\beta'_{11}=0$ then $H_0>0$ implies $H_1>0$.

Remark 3.4—By comparing the existence and stability condition of equilibria, we find that there exists at most one stable equilibrium under mass treatment, or under targeted treatment if $\mathscr{R}_{10}<1$ or $\mathscr{R}_{10}<\mathscr{R}_{20}$. In particular, when the coexistence equilibrium exists under mass treatment, it is the only possibly stable equilibrium.

Moreover, numerical calculations suggest that there exists exactly one stable equilibrium for any parameter setting and the coexistence equilibrium is stable whenever it exists.

3.3 The tragedy of the commons

Given a set of parameter values, we first solve for the stationary solutions of (2.2) and substitute the stable solution into the exogenous forces of infection of the individual model (2.1), and then find the proportion in each infected state. From these proportions, we can then compute the disutility of an individual. An individual has an incentive to increase antibiotic treatment if the individual disutility $J^{(i)}$ is decreasing in terms of $\theta^{(i)}$, i.e., more treatment produces less disutility. A community benefits from treatment if the community disutility J is decreasing in θ. Locally, a tragedy of the commons occurs when the goal of the individual conflicts with that of the community. Mathematically, this means that for a fixed parameter set, we have

$$\left(\frac{\partial J^{(i)}}{\partial \theta^{(i)}}\cdot\frac{\partial J}{\partial \theta}\right)\Big|_{\theta^{(i)}=\theta=\theta_0}<0 \quad \text{for some} \quad \theta_0>0.$$

Let $\lambda_S^*=\lambda_S+\lambda_{SC\to S}+\lambda_{SC\to SC}=\beta_S(\bar{Y}_S+\bar{Y}_{SC})$, $\lambda_R^*=\lambda_R+\lambda_{RC\to R}+\lambda_{RC\to RC}=\beta_R(\bar{Y}_R+\bar{Y}_{RC})$ and $\lambda_C^*=\lambda_{RC\to RC}+\lambda_{RC\to C}+\lambda_{SC\to SC}+\lambda_{SC\to C}+\lambda_C=\beta_C(\bar{Y}_C+\bar{Y}_{SC}+\bar{Y}_{RC})$. Recall that under mass treatment, we assume all infected people are treated at the same rate ($\theta_P=\theta_{PC}=\theta_C=\theta$ and $\theta_P^{(i)}=\theta_{PC}^{(i)}=\theta_C^{(i)}=\theta^{(i)}$), while under targeted treatment, that individuals with C are treated, whether or not they exhibit the other infection ($\theta_P=0$, $\theta_{PC}=\theta_C=\theta$ and $\theta_P^{(i)}=0, \theta_{PC}^{(i)}=\theta_C^{(i)}=\theta^{(i)}$). The proof of the following is postponed to Appendix B.

Theorem 3.5—*Modeling a single individual according to* (2.1) *implies*

$$J_P^{(i)}=\frac{\lambda_R^*(\rho_P+\theta^{(i)})+\lambda_S^*(\rho_P+\delta\theta^{(i)})}{\lambda_R^*(\rho_P+\theta^{(i)})+\lambda_S^*(\rho_P+\delta\theta^{(i)})+\rho_P(\rho_P+\theta^{(i)})}$$

under mass treatment, and

$$J_C^{(i)}=\frac{\lambda_C^*}{\lambda_C^*+\rho_C+\theta^{(i)}}$$

under mass treatment or targeted treatment, respectively.

The community model (2.2) *implies that*

$$J_P=\max\left\{1-\frac{\rho_P+\theta}{\beta_S},0\right\}=\max\left\{1-\frac{1}{\mathscr{R}_{10}},0\right\}$$

under mass treatment, and

$$J_C=\max\left\{1-\frac{\rho_C+\theta}{\beta_C},0\right\}=\max\left\{1-\frac{1}{\mathscr{R}_{30}},0\right\}$$

under mass treatment or targeted treatment, respectively.

In addition, under targeted treatment, there exist some parameter sets such that $J_P^{(i)}$ *(or* J_P*) is increasing in* $\theta^{(i)}$ *(or* θ*).*

Thus, under mass treatment, both $J^{(i)}=D_P J_P^{(i)}+D_C J_C^{(i)}$ and $J = D_P J_P + D_C J_C$ are decreasing in $\theta^{(i)}$ and θ, respectively, for any $D_P > 0$ and $D_C > 0$. This indicates that increasing mass treatment increases the utility of both the individual and community, and there is no tragedy of the commons in two diseases setting under mass treatment.

However, $J = D_P J_P + D_C J_C$ can increase in θ for some $D_P > 0$ and $D_C > 0$ (e.g. $D_P \gg D_C$) under targeted treatment. For this reason, the incentives for the individual and community do not always coincide, and a tragedy of the commons may occur provided that only infectives with the second agent receive treatment.

Theorem 3.6—*For system* (2.2) *under targeted treatment, assume that there always exists a globally stable equilibrium. If* $\mathscr{R}_{10} > 1$, $\mathscr{R}_{10} > \mathscr{R}_{20}$ *and* $\mathscr{R}_{30} > 1$ *at* $\theta = 0$, *then* $J_P < 1 - 1/\mathscr{R}_{10}$ *for* $\theta \in (0, \beta_C - \rho_C)$, *and* $J_P = 1 - 1/\mathscr{R}_{10}$ *for* $\theta \in \{0\} \cup [\beta_C - \rho_C, \infty)$.

Proof: No treatment ($\theta = 0$): E_{13} is the unique stable equilibrium and $J_P = 1 - 1/\mathscr{R}_{10}$.

Small treatment ($0 < \theta < \beta_C - \rho_C$): one of E_3, E_{23} and $\tilde{E}$ is stable. If E_3 is stable, then $J_P = 0$; else if E_{23} is stable, then $J_P = 1 - (X_{23} + 1/\mathscr{R}_{20} - X_{23}) = 1 - 1/\mathscr{R}_{20} < 1 - 1/\mathscr{R}_{10}$; else if $\tilde{E}$ is stable then, $J_P < 1 - 1/\mathscr{R}_{10}$ due to $(\rho_P - \beta_S(X + \tilde{Y}_C))(\tilde{Y}_S + \tilde{Y}_{SC}) = -\theta \tilde{Y}_{SC} < 0$.

High values for the treatment rate ($\theta \geq \beta_C - \rho_C$): disease C disappears. E_1 is stable and $J_P = 1 - 1/\mathscr{R}_{10}$.

Remark 3.7—Under targeted treatment, we define $Q(\theta) = \theta \bar{Y}_{SC}/(\bar{Y}_S + \bar{Y}_{SC})$ as the treatment rate for the sensitive strain of disease P at a stable equilibrium $\bar{E}(\theta)$. Assume that there always exists a globally stable equilibrium, it follows from the proof of Theorem 3.6 that

$$\frac{dQ}{d\theta} = -\beta_S \frac{dJ_P}{d\theta}$$

which implies that $\max_{\theta \geq 0} Q(\theta) = \min_{\theta \geq 0} J_P$, namely, the fraction of population being infected with the first agent is minimized (or maximized) whenever the treatment rate for the first infectious agent reaches its maximum (or minimum).

However, if there is no cotransmission from Y_{RC}, i.e., $\beta'_{11} = 0$, then $J_P^{(i)}$ is decreasing in $\theta^{(i)}$, which implies that $J^{(i)}$ is decreasing in $\theta^{(i)}$ for any $D_P > 0$ and $D_C > 0$ (see Appendix B). In addition, if disease C has higher disutility than disease P, i.e., $D_C \geq D_P$, then $J^{(i)}$ is constantly decreasing in $\theta^{(i)}$. We omit the straightforward but tedious proof.

4 Numerical simulations

The above analysis shows that a tragedy of the commons does not exist under mass treatment. However, as defined above, a tragedy of the commons can appear for the case of targeted treatment. In this case, individuals who choose treatment rates which are larger than those adopted by the community achieve lower disutility, even though the entire community will experience more disease if everyone increases their treatment rates in the same way. But in this case—targeted treatment—the treatment rates apply only to dual infection; as the treatment rate increases, eventually the second disease is completely eliminated, and with it, all opportunity to treat the first infection. In a sense, this is not a classical tragedy of the commons, because it is removable after a change of treatment strategy from targeted treatment to mass treatment. However, the same two-disease model can exhibit a conflict of interest between individual and society under mass treatment if (i) assumption (A3) is not required, namely, the force of infection of dually infected hosts is different from singly infected hosts, or (ii) drug sensitive and drug resistant strains of the first disease have different disutility, or (iii) the uninfected has significant disutility.

In general, the relationship between antimicrobial resistance and virulence is not straightforward (e.g. [6]). While in some cases, a clear fitness cost of resistance is believed to apply, it cannot be assumed that drug resistant strains are less virulent (e.g. [13], but see [15]). In some cases, drug resistance genes are present on a plasmid which also includes virulence factors (e.g. [33]), but in other cases evolution of drug resistance may simply alter

expression of virulence factors [22]. To explore this possibility in our model, we assume the resistant infection could have higher disutility than the sensitive infection. One disadvantage of the use of broad-spectrum antibiotics in general, including azithromycin, is the disruptive effect such treatments have on the normal microbiome, which may permit the overgrowth of other harmful organisms [3]. This is particularly true in the case of *Clostridium difficile* in the gastrointestinal tract for example (e.g. [37]). Could colonization (though of course not infection) by pneumococcus have *benefits* in preventing the growth of other organisms? While some literature supports the notion that pneumococcal colonization is not beneficial [46], we explore the consequences of assuming that individuals in the susceptible state for pneumococcus have a comparative disutility over the colonized (infectious) states. In these two cases, we can define the individual and community disutility as

$$J^{(i)}=D_U X^{(i)}+D_S(\bar{Y}_S^{(i)}+\bar{Y}_{SC}^{(i)})+D_R(\bar{Y}_R^{(i)}+\bar{Y}_{RC}^{(i)})+D_C(\bar{Y}_C^{(i)}+\bar{Y}_{SC}^{(i)}+\bar{Y}_{RC}^{(i)})$$

and

$$J=D_U X+D_S(\bar{Y}_S+\bar{Y}_{SC})+D_R(\bar{Y}_R+\bar{Y}_{RC})+D_C(\bar{Y}_C+\bar{Y}_{SC}+\bar{Y}_{RC}),$$

respectively, where D_U, D_S, D_R and D_C are, respectively, the average disutility of the uninfected, the sensitive and resistant infections of the first disease, and the infections of the second disease. In what follows, we will give numerical examples to consolidate our analytical arguments.

Example 4.1

The tragedy of the commons under targeted treatment. Consider community model (2.2) with $\beta_S = 3$, $\beta_R = 1.2$, $\beta_C = 1.8$, $\beta_{11} = 1$, $\beta'_{11}=1$, $\delta = 0.3$, $\rho_P = 1$, $\rho_C = 1$, and $\theta \in [0, 1]$. β_{10}, β_{01}, β'_{10}, β'_{01} can be determined accordingly by (A3). Figures 2a shows the probability of an individual being infected by agent *P* and Figure 2b represents the individual disutility under targeted treatment with $D_P = 1$ and $D_C = 0.05$. Here an individual gets better if s/he departs from the community strategy and treats more, but things are worse if everyone does that. For the same parameter values, the tragedy of the commons under targeted treatment remains even if there is no cotransmission, i.e., $\beta_{11}=\beta'_{11}=0$. However, the tragedy of the commons disappears when the ratio D_P: D_C decreases below a certain threshold value.

Example 4.2

The tragedy of the commons under mass treatment without (A3). The values of parameters are $\beta_S = 2.1$, $\beta_R = 2$, $\beta_C = 1.2$, $\beta_{11} = 0.6$, $\beta_{10} = 1.4$, $\beta_{01} = 0.6$, $\beta'_{11}=0.1, \beta'_{10}=0.1, \beta'_{01}=1.1$, $\delta = 0.5$, $\rho_P = 1$, $\rho_C = 0.4$, and $\theta \in [0, 1]$. Figures 3a shows the probability of an individual being infected by agent *P* and Figure 3b represents the individual disutility under mass treatment with $D_P = 1$ and $D_C = 0.25$. Here disease *C* is assumed to differentially suppresse the resistant strain of disease *P*, namely, the transmission of the resistant strain of disease *P* from Y_{RC} is much lower than the transmission of the sensitive strain of disease *P* from

$Y_{SC}(\beta_R/\beta_S > (\beta'_{11}+\beta'_{10})/(\beta_{11}+\beta_{10}))$. Note that the formulae for $J_C^{(i)}$ and $J_P^{(i)}$ are the same as the case of mass treatment with assumption (A3) (see Theorem 3.5). As $\theta > 0.43$, the sensitive strain of disease P goes extinct in the community which leads to $\lambda_S^* = 0$. Thus $J_P^{(i)} = \lambda_R^*/(\lambda_R^* + \rho_P)$ and it is independent of personal choice of treatment when $\theta > 0.43$. In this scenario, a higher treatment rate for the sensitive strain of the first infectious agent, $Q(\theta) = \theta$, could cause a larger proportion of people being infected with the first agent, J_P.

Example 4.3

The tragedy of the commons under mass treatment with $D_S \neq D_R$ or $D_U > 0$. Choose the same parameter as in Example 4.1 except that $\beta_R = 1.5$, $\delta = 0.1$, and the average disutility of infection/noninfection are different. Figures 4a and 4b represent the individual disutility under mass treatment with $D_U = 0$, $D_S = 1 < D_R = 2$ and $D_C = 0.05$, and $D_U = 0.7$, $D_S = D_R = 1$ and $D_C = 0.05$, respectively. In both cases there is a conflict of interest between individual and society: good for individual but bad for community.

It is worth noting that under certain circumstance individual incentives may favor under-treatment while increasing treatment will benefit community. Again choose the same parameter as in Example 4.1 except the average disutility of infection/noninfection. Figures 5a and 5b represent the individual disutility under mass treatment with $D_U = 0$, $D_S = 1 < D_R = 2.5$ and $D_C = 0.05$, and $D_U = 1.2$, $D_S = D_R = 1$ and $D_C = 0.5$, respectively. In both cases an increasing in treatment rate could be bad for individual but good for community.

5 Discussion

Rational antibiotic policy must consider the possibility that individual incentives to use antibiotics may drive overtreatment. Such overtreatment may lead to increasing drug resistance in other organisms, yielding a tragedy of the commons [1]. In a previous paper [38], we studied two single disease models of drug resistance: a simple SIS model and a two-stage (mild and severe) model, and found that a conflict of interest between individual and society does not occur for the former but is possible for the later under certain circumstances—individual incentives can favor overtreatment of mild infection leading to a worse outcome for society. However, mass administration of azithromycin during trachoma control provides a possible example of second mechanism for a conflict of interest between individual and society: treatment of one disease can lead to drug resistance in another organism.

In this paper, we extend previous game theory models of antibiotic policy to a setting of two infectious diseases which are cocirculating. In this model, treatment of one disease selects for resistance in the other, mimicking the behavior of induced resistance in pneumococcus caused by treatment of chlamydia. Mass antibiotic distributions for trachoma elimination are known to select for macrolide resistance in pneumococcus [47], although the prevalence of such resistance has been seen to rapidly decline after cessation of mass distribution [19]. Our model was designed to reflect specific features of chlamydia and pneumoccus in this setting, but we did not restrict the analysis to parameters reflecting the biology of pneumococcus and chlamydia. In this specific setting, for a base case scenario, we assumed that the two

infections do not interact competitively (the presence of one organism does not reduce transmission of the other). In our model, treatment induces drug resistance in one organism (pneumococcus) but not in the other. We examined two scenarios: *mass treatment*, in which *individual treatment* is not based on knowledge of chlamydial infection status, and targeted treatment, in which individuals without chlamydia are not treated. The occurrence of a tragedy of the commons resulting from individual incentives to be treated is strongly influenced by the choice of mass versus targeted treatment, as well as by the health state utility of the various epidemiological states of individuals.

More specifically, we find that the model can imply conflicting individual and social incentives to use antibiotics. Such discord arises for a given population rate of treatment when individuals who diverge from it do better (or worse), while if all individuals make the same choice, all do worse (or better). Moreover, for a given parameter set, such discord may arise for some treatment values but not others. Also, individual incentives can favor underuse as well as overuse. We identified four different examples of discord between the individual and the community in our model.

First, suppose that infection or colonization by drug resistant pneumococcus is worse than infection or colonization by drug sensitive pneumococcus (the health state utility is lower for drug resistant infection or colonization). For specific parameter values, it is possible that individuals who choose rates higher than the population lower their health state utility because of the acquisition of drug resistance during treatment. Yet if the entire population chooses this new, higher treatment rate, the overall prevalence of infection is lower and the population benefits.

However, this example is far from the only way that individual incentives can lead to socially undesirable outcomes. Suppose now that the uninfected state has a *lower* utility than the infected states, because pneumococcal colonization is protecting the individual against infection by a third organism (whose presence is not explicitly modeled). Numerical scenarios reveal that for low treatment rates, the individual and community incentives can favor increased treatment, due to the benefits of curing chlamydia. But for higher treatment rates, individuals who choose higher rates than the community begin to experience worse outcomes, because the assumed disadvantage of curing pneumococcal colonization outweighs the benefits of clearing chlamydial infection. It is possible for individual incentives to favor lower treatment rates despite the fact that the population as a whole could continue to benefit from higher treatment, leading to another example of individual incentives leading to underuse of antibiotics.

These examples aside, in our model, a true tragedy of the commons can arise in which individual incentives can drive overuse of antibiotics. In our base case scenario, we assumed that for pneumococcus, drug susceptible and drug resistant infection (or colonization) have the same health state utility, and that it is better to be uninfected or uncolonized. While pneumococcus and chlamydia themselves are unlikely to interact competitively—each is unlikely to reduce the transmission of the other—infectious agents of course can be in competition, and we considered the following example in which the drug resistant strain of pneumococcus is less fit in the presence of chlamydia than the drug sensitive strain of

pneumococcus. In other words, a fitness cost of drug resistance in pneumococcus is manifested by reduced ability to spread in the presence of chlamydia. Under these assumptions, under mass treatment, a tragedy of the commons may arise. Population level treatment rates can be found for which individuals do better if they exceed the population treatment rate. If the entire population, however, chooses a higher rate of treatment, the resulting reduction in chlamydia leads to an overcompensating degree of drug resistant pneumococcus, because (in this hypothetical scenario) chlamydia is no longer inhibiting drug resistant pneumococcus to the same degree. We found that for mass treatment, such a tragedy of the commons is impossible if the two organisms do not interact competitively.

If we depart from the assumption of mass treatment and allow targeted treatment, individual incentives can again drive socially disadvantageous treatment rates, but for a different reason. Under this assumption, individuals are only treated if they show signs of chlamydia (unlike in a mass administration campaign). Pneumococcus is only treated for individuals who are coinfected with chlamydia, so that the effective rate of pneumococcal treatment becomes smaller as the prevalence of chlamydia drops. Even when we assume identical health utility of drug sensitive and drug resistant pneumococcal colonization and infection, that either is worse than being uncolonized or uninfected, and that chlamydia and pneumococcus do not interact competitively, a kind of tragedy of the commons arises. Here, individual incentives favor increased treatment, but if the population as a whole chooses a larger rate of treatment, the declining prevalence of chlamydia reduces opportunities to treat pneumococcus. Individual incentives drive overuse, but this mathematical tragedy of the commons is unrelated to drug resistance and can be avoided by a different choice of antibiotic policy.

Our model does not reflect all features of trachoma mass drug administration in practice. Specifically, we did not include cocirculation of multiple pneumococcal strains, the role of strain-specific immunity in pneumococcus [9], the presence of pneumococcal vaccination, or the timing of mass drug administration. We only included a single organism for which resistance can be induced, and we have ignored age structure, demography, latency, multiple chlamydial strains, chlamydial cross immunity, and network effects. We also observe that the mathematical analysis of the current model has not revealed explicit criteria for the existence, uniqueness, and stability of the coexistence equilibrium. Numerical simulations suggest that under the base scenario there always exists exactly one (globally) stable equilibrium and the coexistence equilibrium is (globally) stable whenever it exists. Finally, the relationship between antibiotic use and drug resistance may be more complex than simple selection models would imply [30]. We cannot conclude that a tragedy of the commons is impossible in a more general setting.

Recent recommendations to improve antibiotic stewardship include efforts to avoid overuse of broad spectrum antibiotics (e.g. [4]), in part because of a belief that broad spectrum antibiotic use promotes drug resistance [41]. Simple game theory models as we present here can be our first step in understanding the forces which shape the epidemiology of drug resistance. If antibiotic use exceeds the socially optimal level, it is important to understand whether such excessive antibiotic use really benefits the individuals who use them. Overuse of antibiotics based on a mistaken belief that they are helpful does not reflect a true conflict

of interest between the individual and society, but a true conflict of interest does arise if individuals have genuine health incentives to use antibiotics at a level exceeding the socially optimal value. This work suggests that a tragedy of the commons does not arise in simple models of trachoma control through the use of mass treatment. More realistic models of the population biology of drug resistant strains may provide examples of the tragedy of the commons due to treatment of unrelated organisms.

Acknowledgement

The work was partially supported the Models of Infectious Disease Agent Study (MIDAS) (NIGMS U01GM087728) and the TANA study (NEI U10EY016214). We thank our colleagues for helpful comments and discussions.

References

1. Baquero F, Campos J. The tragedy of the commons in antimicrobial chemotherapy. Rev Esp Quimioter. 2003; 16(1):11–13. [PubMed: 12750754]
2. Bhunu C, Garira W, Mukandavire Z. Modeling HIV/AIDS and tuberculosis coinfection. Bulletin of Mathematical Biology. 2009; 71(7):1745–1780. [PubMed: 19475456]
3. Blaser MJ, Falkow S. What are the consequences of the disappearing human microbiota? Nature Reviews Microbiology. 2009; 7(12):887–894.
4. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, Kaplan SL, Mace SE, McCracken GH, Moore MR, St Peter SD, Stockwell JA, Swanson JT. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clinical Infectious Diseases. 2011; 53(7):e25–e76. [PubMed: 21880587]
5. Bremermann HJ, Thieme HR. A competitive exclusion principle for pathogen virulence. Journal of Mathematical Biology. 1989; 27(2):179–190. [PubMed: 2723551]
6. Cameron DR, Howden BP, Peleg AY. The interface between antibiotic resistance and virulence in *Staphylococcus aureus* and its impact upon clinical outcomes. Clinical Infectious Diseases. 2011; 53(6):576–582. [PubMed: 21865195]
7. Cars O, Högberg LD, Murray M, Nordberg O, Sivaraman S, Lundborg CS, So AD, Tomson G. Meeting the challenge of antibiotic resistance. BMJ. 2008; 337:a1438. [PubMed: 18801866]
8. CDC. Mission critical: Preventing antibiotic resistance. 2012
9. Cobey S, Lipsitch M. Niche and neutral effects of acquired immunity permit coexistence of pneumococcal serotypes. Science. 2012; 335(6074):1376–1380. [PubMed: 22383809]
10. Cosner C, Beier JC, Cantrell RS, Impoinvil D, Kapitanski L, Potts MD, Troyo A, Ruan S. The effects of human movement on the persistence of vector-borne diseases. Journal of Theoretical Biology. 2009; 258(4):550–560. [PubMed: 19265711]
11. D'Agata EMC, Webb GF, Pressley J. Rapid emergence of co-colonization with community-acquired and hospital-acquired methicillin-resistant *Staphylococcus aureus* strains in the hospital setting. Mathematical Modelling of Natural Phenomena. 2010; 5(03):76–93. [PubMed: 20740067]
12. Davies SC. Annual Report of the Chief Medical Officer, Volume Two, 2011, infections and the rise of antimicrobial resistance. 2013
13. Dharan NJ, Gubareva LV, Meyer JJ, Okomo-Adhiambo M, McClinton RC, Marshall SA, George KS, Epperson S, Brammer L, Klimov AI, Bresee JS, Fry AM. for the Oseltamivir-Resistance Working Group. Infections with oseltamivir-resistant influenza (a(h1n1)united states.
14. Dietz K. Epidemiologic interference of virus populations. Journal of Mathematical Biology. 1979; 8(3):291–300. [PubMed: 501225]
15. Duan S, Boltz DA, Seiler P, Li J, Bragstad K, Nielsen LP, Webby RJ, Webster RG, Govorkova EA. Oseltamivir–resistant pandemic H1N1/2009 influenza virus possesses lower transmissibility and fitness in ferrets. PLoS Pathogens. 2010; 6(7):e1001022. [PubMed: 20686654]

16. Gao D, Porco TC, Ruan S. Coinfection dynamics of two diseases in a single host population. submitted.
17. Gebre T, Ayele B, Zerihun M, House JI, Stoller NE, Zhou Z, Ray KJ, Gaynor BD, Porco TC, Emerson PM, Lietman TM, Keenan JD. Latrine promotion for trachoma: assessment of mortality from a cluster-randomized trial in Ethiopia. The American Journal of Tropical Medicine and Hygiene. 2011; 85(3):518. [PubMed: 21896815]
18. Hardin G. The tragedy of the commons. Science. 1968; 162(5364):1243–1248. [PubMed: 5699198]
19. Haug S, Lakew T, Habtemariam G, Alemayehu W, Cevallos V, Zhou Z, House J, Ray K, Porco T, Rutar T, Keenan J, Lietman T, Gaynor B. The decline of pneumococcal resistance after cessation of mass antibiotic distributions for trachoma. Clinical Infectious Diseases. 2010; 51(5):571–574. [PubMed: 20649409]
20. Hersh AL, Shapiro DJ, Pavia AT, Shah SS. Antibiotic prescribing in ambulatory pediatrics in the United States. Pediatrics. 2011; 128(6):1053–1061. [PubMed: 22065263]
21. Hong KC, Schachter J, Moncada J, Zhou Z, House J, Lietman TM. Lack of macrolide resistance in *chlamydia trachomatis* after mass azithromycin distributions for trachoma. Emerging Infectious Diseases. 2009; 15(7):1088–1090. [PubMed: 19624926]
22. Howden BP, Peleg AY, Stinear TP. The evolution of vancomycin intermediate *Staphylococcus aureus* (VISA) and heterogenous-VISA. Infection, Genetics and Evolution. 2014; 21(0):575–582.
23. Keeling, MJ.; Rohani, P. Modeling Infectious Diseases in Humans and Animals. Princeton: Princeton University; 2008.
24. Keenan JD, Ayele B, Gebre T, Zerihun M, Zhou Z, House JI, Gaynor BD, Porco TC, Emerson PM, Lietman TM. Childhood mortality in a cohort treated with mass azithromycin for trachoma. Clinical Infectious Diseases. 2011; 52(7):883–888. [PubMed: 21427395]
25. Keenan JD, Emerson PM, Gaynor BD, Porco TC, Lietman TM. Adult mortality in a randomized trial of mass azithromycin for trachoma. JAMA Internal Medicine. 2013; 173(9):821–823. [PubMed: 23545893]
26. Lawi G, Mugisha J, Omolo-Ongati N. Mathematical model for malaria and meningitis co-infection among children. Applied Mathematical Sciences. 2011; 5(47):2337–2359.
27. Laxminarayan R, Duse A, Wattal C, Wattal AK, Wertheim HF, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, et al. Antibiotic resistancethe need for global solutions. The Lancet Infectious Diseases. 2013; 13(12):1057–1098. [PubMed: 24252483]
28. Leach AJ, Shelby-James TM, Mayo M, Gratten M, Laming AC, Currie BJ, Mathews JD. A prospective study of the impact of community-based azithromycin treatment of trachoma on carriage and resistance of *streptococcus pneumoniae*. Clinical Infectious Diseases. 1997; 24(3): 356–362. [PubMed: 9114185]
29. Lloyd, WF. Two Lectures on the Checks to Population. Oxford, England: Oxford University Press; 1833.
30. MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. Clinical Microbiology Reviews. 2005; 18(4):638–656. [PubMed: 16223951]
31. Maher MC, Alemayehu W, Lakew T, Gaynor BD, Haug S, Cevallos V, Keenan JD, Lietman TM, Porco TC. The fitness cost of antibiotic resistance in *Streptococcus pneumoniae*: insights from the field. PLoS One. 2012; 7(1):e29407. [PubMed: 22272234]
32. Massad E, Burattini MN, Coutinho FAB, Yang HM, Raimundo SM. Modeling the interaction between AIDS and tuberculosis. Mathematical and Computer Modelling. 1993; 17(9):7–21.
33. McCarthy AJ, Lindsay JA. The distribution of plasmids that carry virulence and resistance genes in staphylococcus aureus is lineage associated. BMC Microbiology. 2012; 12(1):104. [PubMed: 22691167]
34. Mukandavire Z, Gumel A, Garira W, Tchuenche J. Mathematical analysis of a model for HIV-malaria co-infection. Math. Biosci. Eng. 2009; 6(2):333–359. [PubMed: 19364156]
35. Mushayabasa S, Tchuenche J, Bhunu C, Ngarakana-Gwasira E. Modeling gonorrhea and HIV co-interaction. BioSystems. 2011; 103(1):27–37. [PubMed: 20869424]
36. Neu HC. The crisis in antibiotic resistance. Science. 1992; 257(5073):1064–1073. [PubMed: 1509257]

37. O'Connor KA, Kingston M, O'Donovan M, Cryan B, Twomey C, O'Mahony D. Antibiotic prescribing policy and *Clostridium difficile* diarrhoea. QJM. 2004; 97(7):423–429. [PubMed: 15208430]
38. Porco TC, Gao D, Scott JC, Shim E, Enanoria WT, Galvani AP, Lietman TM. When does overuse of antibiotics become a tragedy of the commons? PloS ONE. 2012; 7(12):e46505. [PubMed: 23236344]
39. Porco TC, Gebre T, Ayele B, House J, Keenan J, Zhou Z, Hong KC, Stoller N, Ray KJ, Emerson P, Gaynor BD, Lietman TM. Effect of mass distribution of azithromycin for trachoma control on overall mortality in Ethiopian children: a randomized trial. JAMA. 2009; 302(9):962–968. [PubMed: 19724043]
40. Pressley J, D'Agata EMC, Webb GF. The effect of co-colonization with community-acquired and hospital-acquired methicillin-resistant *Staphylococcus aureus* strains on competitive exclusion. Journal of Theoretical Biology. 2010; 264(3):645–656. [PubMed: 20347850]
41. Pulcini C, Gyssens IC. How to educate prescribers in antimicrobial stewardship practices. Virulence. 2013; 4(2):192–202. [PubMed: 23361336]
42. Reluga TC, Galvani AP. A general approach for population games with application to vaccination. Mathematical Biosciences. 2011; 230(2):67–78. [PubMed: 21277314]
43. Roeger L, Feng Z, Castillo-Chavez C. Modeling TB and HIV co-infections. Math. Biosci. Eng. 2009; 6(4):815–837. [PubMed: 19835430]
44. Schachter J, West SK, Mabey D, Dawson CR, Bobo L, Bailey R, Vitale S, Quinn TC, Sheta A, Sallam S, Mkocha H, Mabey D, Faal H. Azithromycin in control of trachoma. Lancet. 1999; 354(9179):630–635. [PubMed: 10466664]
45. Sharomi O, Podder C, Gumel A, Song B. Mathematical analysis of the transmission dynamics of HIV/TB coinfection in the presence of treatment. Math. Biosci. Eng. 2008; 5(1):145. [PubMed: 18193936]
46. Simell B, Auranen K, Käyhty H, Goldblatt D, Dagan R, O'Brien KL. The fundamental link between pneumococcal carriage and disease. Expert Review of Vaccines. 2012; 11(7):841–855. [PubMed: 22913260]
47. Skalet A, Cevallos V, Ayele B, Gebre T, Zhou Z, Jorgensen J, Zerihun M, Habte D, Assefa Y, Emerson P, Gaynor B, Porco T, Lietman T, Keenan J. Antibiotic selection pressure and macrolide resistance in nasopharyngeal *Streptococcus pneumoniae*: a cluster-randomized clinical trial. PLoS Med. 2010; 7(12):e1000377. [PubMed: 21179434]
48. Smith, HL. Monotone Dynamical Systems: An Introduction to the Theory of Competitive and Cooperative Systems. Vol. 41. Providence, RI: American Mathematical Society; 1995.
49. Solomon AW, Mohammed Z, Massae PA, Shao JF, Foster A, Mabey DCW, Peeling RW. Impact of mass distribution of azithromycin on the antibiotic susceptibilities of ocular *chlamydia trachomatis*. Antimicrobial Agents and Chemotherapy. 2005; 49(11):4804–4806. [PubMed: 16251338]
50. Spellberg B, Blaser M, Guidos RJ, Boucher HW, Bradley JS, Eisenstein BI, Gerding D, Lynfield R, Reller LB, Rex J, Schwartz D, Septimus E, Tenover FC, Gilbert DN. Combating antimicrobial resistance: Policy recommendations to save lives. Clinical Infectious Diseases. 2011; 52(supp. 5):S397–S428. [PubMed: 21474585]
51. van den Driessche P, Watmough J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Mathematical Biosciences. 2002; 180(2):29–48. [PubMed: 12387915]
52. WHO. Progress report on elimination of trachoma, 2010. Weekly Epidemiological Record. 2012; 87:161–168. [PubMed: 22574352]

Appendix

A. Proof of Theorem 3.1

The calculation of boundary equilibria for the community equations (2.2) is straightforward and simple except that of E_{13} and E_{23} which can be found in Gao et al. [16]. So we will only

focus on the stability analysis. By substituting $X = 1 - (Y_S + Y_R + Y_C + Y_{SC} + Y_{RC})$ into the last five equations of (2.2), we obtain a qualitatively equivalent 5-dimensional ODEs system, denoted by (2.2)′, with respect to Y_S, Y_R, Y_C, Y_{SC}, and Y_{RC}. We represent the equilibria corresponding to the reduced system by $E_0^{'}, E_1^{'}, E_2^{'}, E_3^{'}, E_{12}^{'}, E_{13}^{'}, E_{23}^{'}$, and $\tilde{E}^{'}$, where the first component of E_0, E_1, E_2, E_3, E_{12}, E_{13}, E_{23}, and $\tilde{E}$ is removed, respectively. The Jacobian matrix of (2.2)′ at an equilibrium $E' \in \{E_0^{'}, E_1^{'}, E_2^{'}, E_3^{'}, E_{12}^{'}, E_{13}^{'}, E_{23}^{'}, \tilde{E}'\}$ and that of (2.2) at the corresponding equilibrium $E \in \{E_0, E_1, E_2, E_3, E_{12}, E_{13}, E_{23}, \tilde{E}\}$ have the same set of nonzero eigenvalues.

Local stability of E_0

The Jacobian matrix of (2.2)′ at $E_0^{'}$ is $J(E_0^{'})=F-V$ and the set of its eigenvalues is

$$\{\beta_S-\rho_P-\theta_P, \beta_R-\rho_P, \beta_C-\rho_C-\theta_C, \beta_{11}-\rho_P-\rho_C-\theta_{PC}, \beta_{11}^{'}-\rho_P-\rho_C-\theta_{PC}\}.$$

The no-disease equilibrium E_0 is stable if $\mathscr{R}_0 < 1$ and unstable otherwise.

Local stability of E_1

The Jacobian matrix of system (2.2)′ at $E_1^{'}$ is $J(E_1^{'})$ and the set of its eigenvalues is

$$\left\{(1-\mathscr{R}_{10})\rho_P, \left(\frac{\mathscr{R}_{20}}{\mathscr{R}_{10}}-1\right)\rho_P, (\mathscr{R}_{30}-1)(\rho_C+\theta), \left(\frac{\mathscr{R}_{40}}{\mathscr{R}_{10}}-1\right)(\rho_P+\rho_C+\theta)+\beta_S\left(\frac{1}{\mathscr{R}_{10}}-1\right), \left(\frac{\mathscr{R}_{50}}{\mathscr{R}_{10}}-1\right)(\rho_P+\rho_C+\theta)\right\}.$$

under targeted treatment. Recall that $E_1^{'}$ (or E_1) exists if and only if $\mathscr{R}_{10} > 1$ and $\theta_P = 0$ which means that $E_1^{'}$ (or E_1) does not exist under mass treatment.

Targeted treatment: since $\mathscr{R}_{10} > 1$ and $\mathscr{R}_{10} > \mathscr{R}_{40}$, the first and fourth eigenvalues of $J(E_1^{'})$ are negative. E_1 is stable if and only if $\mathscr{R}_{10} > \max\{1, \mathscr{R}_{20}, \mathscr{R}_{50}\}$ and $\mathscr{R}_{30} < 1$.

Local stability of E_2

The Jacobian matrix of system (2.2)′ at $E_2^{'}$ is $J(E_2^{'})$ and the set of its eigenvalues is

$$\left\{\left(\frac{1}{\mathscr{R}_{20}}-\frac{1}{\mathscr{R}_{10}}\right)\beta_S, (1-\mathscr{R}_{20})\rho_P, (\mathscr{R}_{30}-1)(\rho_C+\theta), \left(\frac{\mathscr{R}_{40}}{\mathscr{R}_{20}}-1\right)(\rho_P+\rho_C+\theta), \left(\frac{\mathscr{R}_{50}}{\mathscr{R}_{20}}-1\right)(\rho_P+\rho_C+\theta)+(1-\mathscr{R}_{20})\rho_P\right\}.$$

under either targeted treatment or mass treatment.

Since $\mathscr{R}_{20} > 1$ and $\mathscr{R}_{20} > \mathscr{R}_{50}$, the second and last eigenvalues of $J(E_2^{'})$ are negative. E_2 is stable if and only if $\mathscr{R}_{20} > \max\{1, \mathscr{R}_{10}, \mathscr{R}_{40}\}$ and $\mathscr{R}_{30} < 1$.

Local stability of E_3

The Jacobian matrix of system (2.2)′ at E_3' is $J(E_3)$ and the set of its eigenvalues is

$$\left\{\lambda_3^+, (\mathscr{R}_{20}-1)\rho_P, (1-\mathscr{R}_{30})(\rho_C+\theta), \lambda_3^-, \left(\frac{\mathscr{R}_{50}}{\mathscr{R}_{30}}-1\right)(\rho_P+\rho_C+\theta)+\beta_C\left(\frac{1}{\mathscr{R}_{30}}-1\right)\right\}$$

under targeted treatment, where λ_3^+ and λ_3^- denote the roots of $\lambda^2 + M_1\lambda + M_0 = 0$, or

$$\{(\mathscr{R}_{10}-1)(\rho_P+\theta), (\mathscr{R}_{20}-1)\rho_P, (1-\mathscr{R}_{30})(\rho_C+\theta), \left(\frac{\mathscr{R}_{40}}{\mathscr{R}_{30}}-1\right)(\rho_P+\rho_C+\theta)+\beta_C\left(\frac{1}{\mathscr{R}_{30}}-1\right), \left(\frac{\mathscr{R}_{50}}{\mathscr{R}_{30}}-1\right)(\rho_P+\rho_C+\theta)+\beta_C\left(\frac{1}{\mathscr{R}_{30}}-1\right)\}$$

under mass treatment.

Targeted treatment: E_3 is stable if and only if $\mathscr{R}_{30} > 1$, $\mathscr{R}_{20} < 1$, $\Re\lambda_3^+ < 0$ and $\Re\lambda_3^- < 0$.

Mass treatment: E_3 is stable if and only if $\mathscr{R}_{10} < 1$, $\mathscr{R}_{20} < 1$, and $\mathscr{R}_{30} > 1$.

Local stability of E_{12}

Recall that E_{12} exists if and only if $\mathscr{R}_{10} > \mathscr{R}_{20}$, $\mathscr{R}_{10} > 1$, and $\theta_P > 0$ (mass treatment). The Jacobian matrix of system (2.2)′ at E_{12}' is $J(E_{12}')$ and the set of its eigenvalues is

$$\{(\mathscr{R}_{30}-1)(\rho_C+\theta), \lambda_{12}^+, \lambda_{12}^-, \tilde{\lambda}_{12}^+, \tilde{\lambda}_{12}^-\},$$

where $\lambda_{12}^{\pm}$ and $\tilde{\lambda}_{12}^{\pm}$ are solutions to

$$\lambda^2+K_1\lambda+K_0=0 \text{and} \lambda^2+L_1\lambda+L_0=0,$$

respectively. Here

$$K_1=\frac{\beta_R(\rho_P+\theta)(\mathscr{R}_{10}-1)+\rho_P(\rho_P+\theta)(\mathscr{R}_{10}-\mathscr{R}_{20})}{\beta_S}+(\beta_S-\beta_R)Y_{12}>0,$$

$$K_0=(\rho_P(\rho_P+\theta)(\mathscr{R}_{10}-\mathscr{R}_{20})+\beta_S\delta\theta)Y_{12}>0,$$

$$L_1=(\rho_P+\rho_C+\theta)((\mathscr{R}_{10}-\mathscr{R}_{40})+(\mathscr{R}_{10}-\mathscr{R}_{50}))/\mathscr{R}_{10}+\beta_R(\mathscr{R}_{10}-1)/\mathscr{R}_{10}+(\beta_S-\beta_R)Y_{12}>0,$$

$$L_0=\beta_R(\rho_P+\rho_C+\theta)(\mathscr{R}_{10}-\mathscr{R}_{40})(1-1/\mathscr{R}_{10}-Y_{12})/\mathscr{R}_{10} +(\rho_P+\rho_C+\theta)(\mathscr{R}_{10}-\mathscr{R}_{50})((\rho_P+\rho_C+\theta)(\mathscr{R}_{10}-\mathscr{R}_{40})/\mathscr{R}_{10}^2+(\rho_P+\theta)Y_{12})>0,$$

which imply that E_{12} is stable if and only if $\mathscr{R}_{30} < 1$.

Local stability of E_{13}

Recall that E_{13} exists if and only if $\mathscr{R}_{10} > 1$, $\mathscr{R}_{30} > 1$ and $\theta = 0$ (no treatment). The Jacobian matrix of system (2.2)′ at E'_{13} is $J(E'_{13})$ and the set of its eigenvalues is

$$\{-\beta_S+\rho_P, (\beta_R-\beta_S)\rho_P/\beta_S, -\beta_C+\rho_C, -(\beta_C-\beta'_{11}X_{13})-\rho_P,) -(\beta_S+\beta_C-\beta_{11})-\beta_{11}(\rho_P/\beta_S+\rho_C/\beta_C-2X_{13}).\}$$

It follows from $X_{13} < \min\{\rho_P/\beta_S, \rho_C/\beta_C\}$ and $\beta_S > \beta_R$ that E_{13} is stable when it exists.

Local stability of E_{23}

Recall that E_{23} exists if and only if $\mathscr{R}_{20} > 1$ and $\mathscr{R}_{30} > 1$. The Jacobian matrix of system (2.2)′ at E'_{23} is $J(E'_{23})$ and the set of its eigenvalues is

$$\{(\mathscr{R}_{10}/\mathscr{R}_{20}-1)(\rho_P+\theta), -\beta_R+\rho_P, -\beta_C+\rho_C+\theta, -(\beta_C-\beta_{11}X_{23})-\rho_P,$$
$$-(\beta_R+\beta_C-\beta'_{11})-\beta'_{11}(\rho_P/\beta_R+(\rho_C+\theta)/\beta_C-2X_{23})\}$$

under mass treatment or

$$\{\lambda^+_{23}, -\beta_R+\rho_P, -\beta_C+\rho_C+\theta, \lambda^-_{23}, -(\beta_R+\beta_C-\beta'_{11})-\beta'_{11}(\rho_P/\beta_R+(\rho_C+\theta)/\beta_C-2X_{23})\}$$

under targeted treatment where $\lambda^{\pm}_{23}$ are solutions to $\lambda^2 + H_1\lambda + H_0 = 0$.

Mass treatment: E_{23} is stable if and only if $\mathscr{R}_{10} < \mathscr{R}_{20}$.

Targeted treatment: E_{23} is stable if and only if $\Re\lambda^{\pm}_{23}<0$.

Existence of $\tilde{E}$

It follows from (2.2) that the equilibrium $\tilde{E}$ satisfies

$$(\rho_C+\theta-\beta_C(\tilde{X}+\tilde{Y}_S+\tilde{Y}_R))(\tilde{Y}_C+\tilde{Y}_{SC}+\tilde{Y}_{RC})=0,$$

$$(\rho_P+\theta-\beta_S(\tilde{X}+\tilde{Y}_C))(\tilde{Y}_S+\tilde{Y}_{SC})=0,$$

$$(\rho_P-\beta_R(\tilde{X}+\tilde{Y}_C))(\tilde{Y}_R+\tilde{Y}_{RC})=\delta\theta(\tilde{Y}_S+\tilde{Y}_{SC})>0$$

under mass treatment or

$$(\rho_C+\theta-\beta_C(\tilde{X}+\tilde{Y}_S+\tilde{Y}_R))(\tilde{Y}_C+\tilde{Y}_{SC}+\tilde{Y}_{RC})=0,$$

$$(\rho_P - \beta_S(\tilde{X}+\tilde{Y}_C))(\tilde{Y}_S+\tilde{Y}_{SC}) = -\theta\tilde{Y}_{SC} < 0,$$

$$(\rho_P - \beta_R(\tilde{X}+\tilde{Y}_C))(\tilde{Y}_R+\tilde{Y}_{RC}) = \delta\theta\tilde{Y}_{SC} > 0.$$

under targeted treatment. Hence, in both cases, a necessary condition for the existence of $\tilde{E}$ is that: $\mathscr{R}_{10} > 1$, $\mathscr{R}_{30} > 1$, $\mathscr{R}_{10} > \mathscr{R}_{20}$ and $\theta > 0$. For a simple case: $\beta_{11} = \beta'_{11} = 0$ under mass treatment, we can solve the equilibrium equations by substitution and rigorously prove that there exists at most one positive equilibrium. In addition, $\rho_C + \theta - \beta_C$ is an eigenvalue of the Jacobian $J(\tilde{E}')$ (or $J(\tilde{E})$).

B. Proof of Theorem 3.5

Denote the k-th equilibrium equation of the individual equations (2.1) and community equations (2.2) as eq_k and EQ_k, respectively. Let $\lambda^*_S = \lambda_S + \lambda_{SC\to S} + \lambda_{SC\to SC} = \beta_S(\bar{Y}_S + \bar{Y}_{SC})$, $\lambda^*_R = \lambda_R + \lambda_{RC\to R} + \lambda_{RC\to RC} = \beta_R(\bar{Y}_R + \bar{Y}_{RC})$ and $\lambda^*_C = \lambda_{RC\to RC} + \lambda_{RC\to C} + \lambda_{SC\to SC} + \lambda_{SC\to C} + \lambda_C = \beta_C(\bar{Y}_C + \bar{Y}_{SC} + \bar{Y}_{RC})$.

Community model under mass treatment ($\theta_P = \theta_{PC} = \theta_C = \theta$)

The sum of EQ_4, EQ_5 and EQ_6 gives

$$-(\rho_C + \theta - \beta_C(\overline{X} + \bar{Y}_S + \bar{Y}_R))(\bar{Y}_C + \bar{Y}_{SC} + \bar{Y}_{RC}) = 0$$

Since $\bar{X} + \bar{Y}_S + \bar{Y}_R + \bar{Y}_C + \bar{Y}_{SC} + \bar{Y}_{RC} = 1$, we have

$$J_C = \bar{Y}_C + \bar{Y}_{SC} + \bar{Y}_{RC} = 1 - (\rho_C + \theta)/\beta_C = 1 - 1/\mathscr{R}_{30} \text{ if } \mathscr{R}_{30} > 1 \text{ or } 0 \text{ if } \mathscr{R}_{30} \le 1.$$

The sums of EQ_2 and EQ_5, and, EQ_3 and EQ_6 give

$$-(\bar{Y}_S + \bar{Y}_{SC})(\rho_P + \theta - \beta_S(\overline{X} + \bar{Y}_C)) = 0,$$

$$-\rho_P(\bar{Y}_R + \bar{Y}_{RC}) + \delta\theta(\bar{Y}_S + \bar{Y}_{SC}) + \beta_R(\overline{X} + \bar{Y}_C)(\bar{Y}_R + \bar{Y}_{RC}) = 0.$$

Direct calculations yield

$$\overline{X} + \bar{Y}_C = \frac{\rho_P + \theta}{\beta_S} = \frac{1}{\mathscr{R}_{10}},$$

$$\bar{Y}_S+\bar{Y}_{SC}=\frac{(\beta_S-\rho_P-\theta)(\beta_S\rho_P-\beta_R(\rho_P+\theta))}{\beta_S(\beta_S(\rho_P+\delta\theta)-\beta_R(\rho_P+\theta))}=\frac{(1-1/\mathscr{R}_{10})(1-\mathscr{R}_{20}/\mathscr{R}_{10})\rho_P}{\delta\theta+\rho_P(1-\mathscr{R}_{20}/\mathscr{R}_{10})}, \quad (5.1)$$

$$\bar{Y}_R+\bar{Y}_{RC}=\frac{\delta\theta(\beta_S-\rho_P-\theta)}{\beta_S(\rho_P+\delta\theta)-\beta_R(\rho_P+\theta)}=\frac{\delta\theta(1-1/\mathscr{R}_{10})}{\delta\theta+\rho_P(1-\mathscr{R}_{20}/\mathscr{R}_{10})},$$

and hence

$$J_P=1-(\rho_P+\theta)/\beta_S=1-1/\mathscr{R}_{10}\text{if}\mathscr{R}_{10}>1\text{or}0\text{if}\mathscr{R}_{10}\leq 1.$$

Community model under targeted treatment ($\theta_P = 0$, $\theta_{PC} = \theta_C = \theta$)

The derivation of J_C for community model under targeted treatment is exactly the same as that for community model under mass treatment. J_P is not always a decreasing function of community treatment rate θ. For example, given a parameter set under targeted treatment: $\beta_S = 3$, $\beta_R = 1.2$, $\beta_C = 1.8$, $\beta_{11} = 1$, $\beta'_{11}=1$, $\delta = 0.3$, $\rho_P = 1$, $\rho_C = 1$, we have $\partial J_P/\partial\theta \approx 0.121952 > 0$ at $\theta = 0.7$. For the same parameter values except that $\beta_{11}=\beta'_{11}=0$, we still have $\partial J_P/\partial\theta \approx 0.113367 > 0$ at $\theta = 0.7$.

Individual model under mass treatment ($\theta_P^{(i)}=\theta_{PC}^{(i)}=\theta_C^{(i)}=\theta^{(i)}$)

The sum of eq_4, eq_5 and eq_6 gives

$$\lambda_C^*(\overline{X}^{(i)}+\bar{Y}_S^{(i)}+\bar{Y}_R^{(i)})-(\rho_C+\theta^{(i)})(\bar{Y}_C^{(i)}+\bar{Y}_{SC}^{(i)}+\bar{Y}_{RC}^{(i)})=0.$$

Since $\overline{X}^{(i)}+\bar{Y}_S^{(i)}+\bar{Y}_R^{(i)}+\bar{Y}_C^{(i)}+\bar{Y}_{SC}^{(i)}+\bar{Y}_{RC}^{(i)}=1$, we have

$$J_C^{(i)}=\bar{Y}_C^{(i)}+\bar{Y}_{SC}^{(i)}+\bar{Y}_{RC}^{(i)}=\lambda_C^*/(\lambda_C^*+\rho_C+\theta^{(i)}).$$

The sums of eq_2 and eq_5, and, eq_3 and eq_6 give

$$-(\rho_P+\theta^{(i)})(\bar{Y}_S^{(i)}+\bar{Y}_{SC}^{(i)})+\lambda_S^*(\overline{X}^{(i)}+\bar{Y}_C^{(i)})=0,$$

$$-\rho_P(\bar{Y}_R^{(i)}+\bar{Y}_{RC}^{(i)})+\delta\theta^{(i)}(\bar{Y}_S^{(i)}+\bar{Y}_{SC}^{(i)})+\lambda_R^*(\overline{X}^{(i)}+\bar{Y}_C^{(i)})=0.$$

Again since $\overline{X}^{(i)}+\bar{Y}_S^{(i)}+\bar{Y}_R^{(i)}+\bar{Y}_C^{(i)}+\bar{Y}_{SC}^{(i)}+\bar{Y}_{RC}^{(i)}=1$, we get three linear equations with respect to $\overline{X}^{(i)}+\bar{Y}_C^{(i)}$, $\bar{Y}_S^{(i)}+\bar{Y}_{SC}$ and $\bar{Y}_R^{(i)}+\bar{Y}_{RC}^{(i)}$. Direct calculations yield

$$\overline{X}^{(i)}+\bar{Y}_{C}^{(i)}=\frac{\rho_P(\rho_P+\theta^{(i)})}{\lambda_R^*(\rho_P+\theta^{(i)})+\lambda_S^*(\rho_P+\delta\theta^{(i)})+\rho_P(\rho_P+\theta^{(i)})},$$

$$\bar{Y}_{S}^{(i)}+\bar{Y}_{SC}=\frac{\rho_P\lambda_S^*}{\lambda_R^*(\rho_P+\theta^{(i)})+\lambda_S^*(\rho_P+\delta\theta^{(i)})+\rho_P(\rho_P+\theta^{(i)})},$$

$$\bar{Y}_{R}^{(i)}+\bar{Y}_{RC}^{(i)}=\frac{(\rho_P+\theta^{(i)})\lambda_R^*+\delta\theta^{(i)}\lambda_S^*}{\lambda_R^*(\rho_P+\theta^{(i)})+\lambda_S^*(\rho_P+\delta\theta^{(i)})+\rho_P(\rho_P+\theta^{(i)})},$$

and hence

$$J_{P}^{(i)}=\frac{\lambda_R^*(\rho_P+\theta^{(i)})+\lambda_S^*(\rho_P+\delta\theta^{(i)})}{\lambda_R^*(\rho_P+\theta^{(i)})+\lambda_S^*(\rho_P+\delta\theta^{(i)})+\rho_P(\rho_P+\theta^{(i)})}.$$

Moreover, it follows (5.1) that $J_C^{(i)}$ and $J_P^{(i)}$ can be explicitly written in terms of model parameters and we can study an individual's disutility in community treatment rate.

Individual model under targeted treatment $(\theta_P^{(i)}=0, \theta_{PC}^{(i)}=\theta_C^{(i)}=\theta^{(i)})$

The derivation of $J_C^{(i)}$ for individual model under targeted treatment is exactly the same as that for individual model under mass treatment.

Now we give an outline of the proof to the statement: $J_P^{(i)}$ is not necessarily decreasing in $\theta^{(i)}$. First, we solve the individual equations and simplify the derivative of $J_P^{(i)}$ with respect to $\theta^{(i)}$. We find that the sign of $\partial J_P^{(i)}/\partial\theta^{(i)}$ is the same as a polynomial in $\theta^{(i)}$ of the form

$$h(\theta^{(i)})=-(c_4*(\theta^{(i)})^4+c_3*(\theta^{(i)})^3+c_2*(\theta^{(i)})^2+c_1*(\theta^{(i)})+c_0),$$

where

$$c_4=c_4(\lambda_{SC\to SC},\lambda_{SC\to C},\lambda_{SC\to S},\lambda_{RC\to RC},\lambda_{RC\to C},\lambda_S,\lambda_C,\rho_P,\rho_C),$$

$$\begin{aligned}c_3=&c_{30}(\lambda_{SC\to SC},\lambda_{SC\to C},\lambda_{SC\to S},\lambda_{RC\to RC},\lambda_{RC\to C},\lambda_{RC\to R},\lambda_S,\lambda_R,\lambda_C,\rho_P,\rho_C)\\&-c_{31}(\lambda_{SC\to SC},\lambda_{SC\to C},\lambda_{SC\to S},\lambda_{RC\to RC},\lambda_{RC\to C},\lambda_S,\lambda_C,\rho_P)\delta,\end{aligned}$$

$$c_2=c_{20}(\lambda_{SC\to SC},\lambda_{SC\to C},\lambda_{SC\to S},\lambda_{RC\to RC},\lambda_{RC\to C},\lambda_{RC\to R},\lambda_S,\lambda_R,\lambda_C,\rho_P,\rho_C)$$
$$-c'_{20}(\lambda_{SC\to S},\lambda_{RC\to RC},\lambda_{RC\to R},\lambda_S,\lambda_R,\rho_P)$$
$$-c_{21}(\lambda_{SC\to SC},\lambda_{SC\to C},\lambda_{SC\to S},\lambda_{RC\to RC},\lambda_{RC\to C},\lambda_{RC\to R},\lambda_S,\lambda_R,\lambda_C,\rho_P,\rho_C)\delta,$$

$$c_1=c_1(\lambda_{SC\to SC},\lambda_{SC\to C},\lambda_{SC\to S},\lambda_{RC\to RC},\lambda_{RC\to C},\lambda_{RC\to R},\lambda_S,\lambda_R,\lambda_C,\rho_P,\rho_C),$$

$$c_0=c_0(\lambda_{SC\to SC},\lambda_{SC\to C},\lambda_{SC\to S},\lambda_{RC\to RC},\lambda_{RC\to C},\lambda_{RC\to R},\lambda_S,\lambda_R,\lambda_C,\rho_P,\rho_C),$$

and $c'_{20}=\lambda_{RC\to RC}(\lambda_{SC\to S}+\lambda_S)\rho_P^2(\lambda_{SC\to S}+\lambda_{RC\to R}+\lambda_S+\lambda_R+\rho_P)$. Here c_0, c_1, c_{20}, c_{21}, c_{30}, c_{31} and c_4 are the addition of some positive terms. Furthermore, we find that $c_{20} > c_{21}$ and $c_{30} > c_{31}$ which imply that $c_2 > -c'_{20}$ and $c_3 > 0$. In particular, if cotransmission of R and C is rare, i.e., $\beta'_{11}=0$, then $c'_{20}=0$ and $h(\theta^{(i)}) < 0$ for any $\theta^{(i)}$.

Nevertheless, it is possible that $h(\theta^{(i)}) > 0$ for some $\theta^{(i)}$ when $\beta'_{11}>0$. To construct such a counterexample, we observe that $\lambda_{SC\to SC}$, $\lambda_{SC\to C}$, $\lambda_{RC\to C}$, λ_C, ρ_C do not appear in c'_{20} but in other coefficients. Let $\lambda_{SC\to SC} = \lambda_{SC\to C} = \lambda_{RC\to C} = \lambda_C = \rho_C = 0$ and then $h(\theta^{(i)})$ takes the form

$$\hat{h}(\theta^{(i)})=-\lambda_{SC\to SC}^2(\hat{c}_4*(\theta^{(i)})^4+\hat{c}_3*(\theta^{(i)})^3+\hat{c}_2*(\theta^{(i)})^2+\hat{c}_1*(\theta^{(i)})+\hat{c}_0),$$

where

$$\hat{c}_2=\hat{c}_{20}-c'_{20}/\lambda_{RC\to RC}\text{ and}\hat{c}_4=\lambda_{SC\to S}+\lambda_S+\rho_P(\lambda_{SC\to S}+\lambda_S)/\lambda_{RC\to RC}.$$

Here $\hat{c}_0$, $\hat{c}_1$, $\hat{c}_{20}$, $\hat{c}_3$ are polynomials. Thus, c'_{20} can dominate the sign of $\hat{h}(\theta^{(i)})$ as $\lambda_{RC\to RC} \to 0$. For example, given a parameter set under targeted treatment: $\lambda_{SC\to SC} = 0.0001$, $\lambda_{SC\to C} = 0.0001$, $\lambda_{SC\to S} = 1$, $\lambda_{RC\to RC} = 0.001$, $\lambda_{RC\to C} = 0.0001$, $\lambda_{RC\to R} = 1$, $\lambda_S = 1$, $\lambda_R = 1$, $\lambda_C = 0.0001$, $\rho_P = 1$, $\rho_C = 0.0001$, $\delta = 0.5$, we have $\partial J_P^{(i)}/\partial\theta^{(i)}=6.55516\times10^{-7}>0$ at $\theta^{(i)} = 1$.

However, if $D_C \geq D_P$, then we find that $\partial J^{(i)}/\partial\theta^{(i)}$ is constantly negative and hence an individual always benefits from increasing his/her treatment.

Highlights

- A two-disease epidemic model with drug-resistance is proposed.
- Treatment for one disease may select for resistance in the other.
- Antibiotic use is modeled as a mathematical game between individual and society.
- The tragedy of the commons for mass treatment and targeted treatment are discussed.
- A conflict of interest between individual and society can occur in several cases.

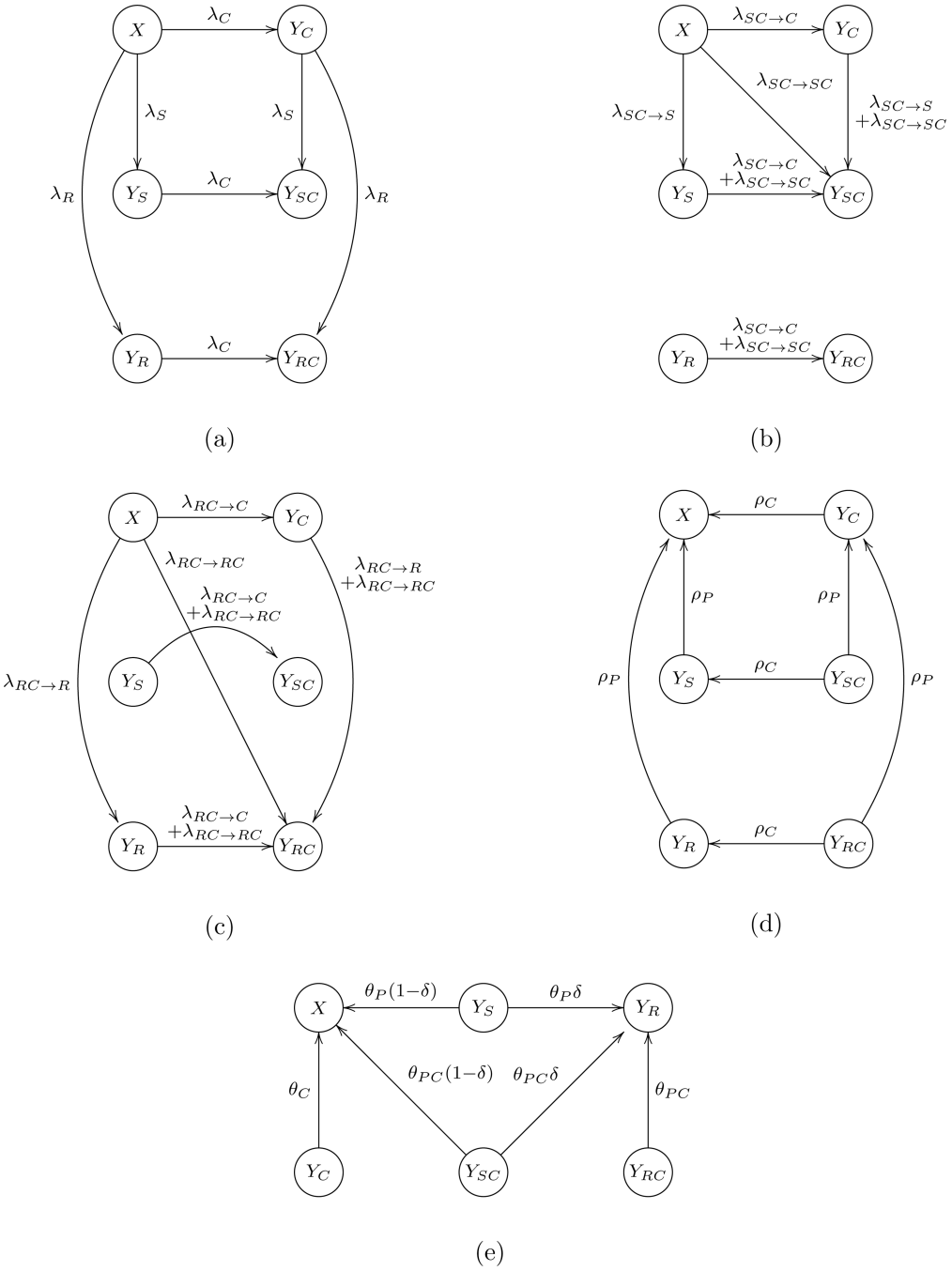

Figure 1.

Flow diagram of the model. Infection process: (a) encounter Y_S, Y_R and Y_C, respectively, and get infected; (b) encounter Y_{SC} and get infected; (c) encounter Y_{RC} and get infected. (d) Recovery process. (e) Treatment process.

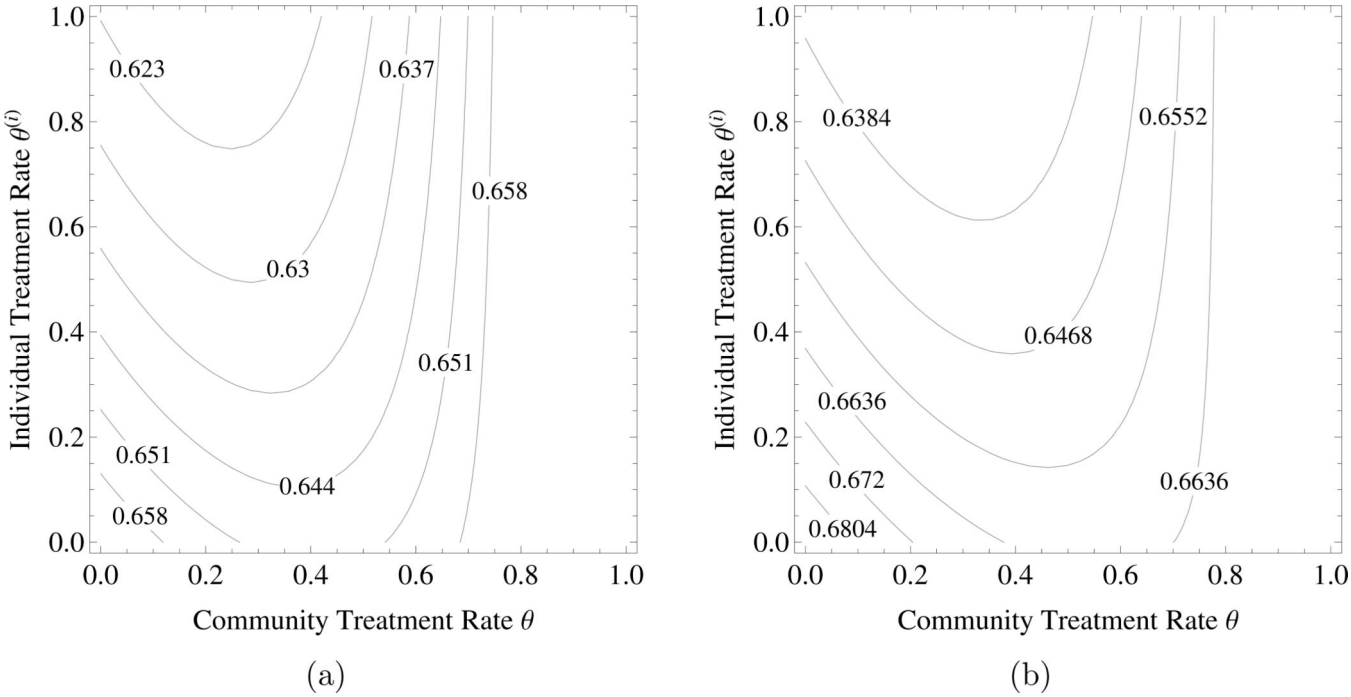

Figure 2.

The tragedy of the commons under targeted treatment. a) The probability of an individual being infected by agent $P - J_P^{(i)}$, b) the individual disutility due to both diseases – $J^{(i)} = D_P J_P^{(i)} + D_C J_C^{(i)}$. The parameter values are as in the text. The horizontal axis is the community level of targeted treatment rate and the vertical axis is the level of targeted treatment rate chosen by an individual within the community.

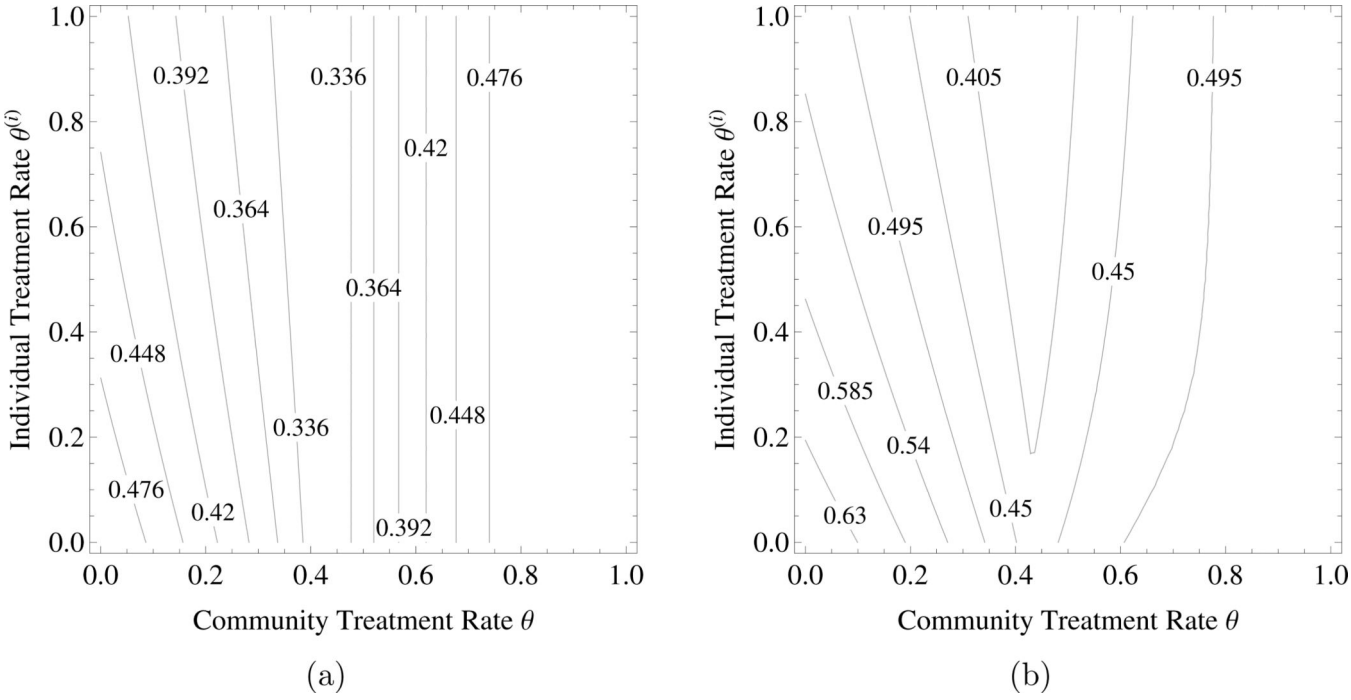

Figure 3.

The tragedy of the commons under mass treatment without assumption (A3). a) The probability of an individual being infected by agent $P - J_P^{(i)}$, b) the individual disutility due to both diseases – $J^{(i)} = D_P J_P^{(i)} + D_C J_C^{(i)}$. Parameters are as in the text. The horizontal axis is community level of mass treatment rate and the vertical axis is the level of mass treatment rate chosen by an individual within the community.

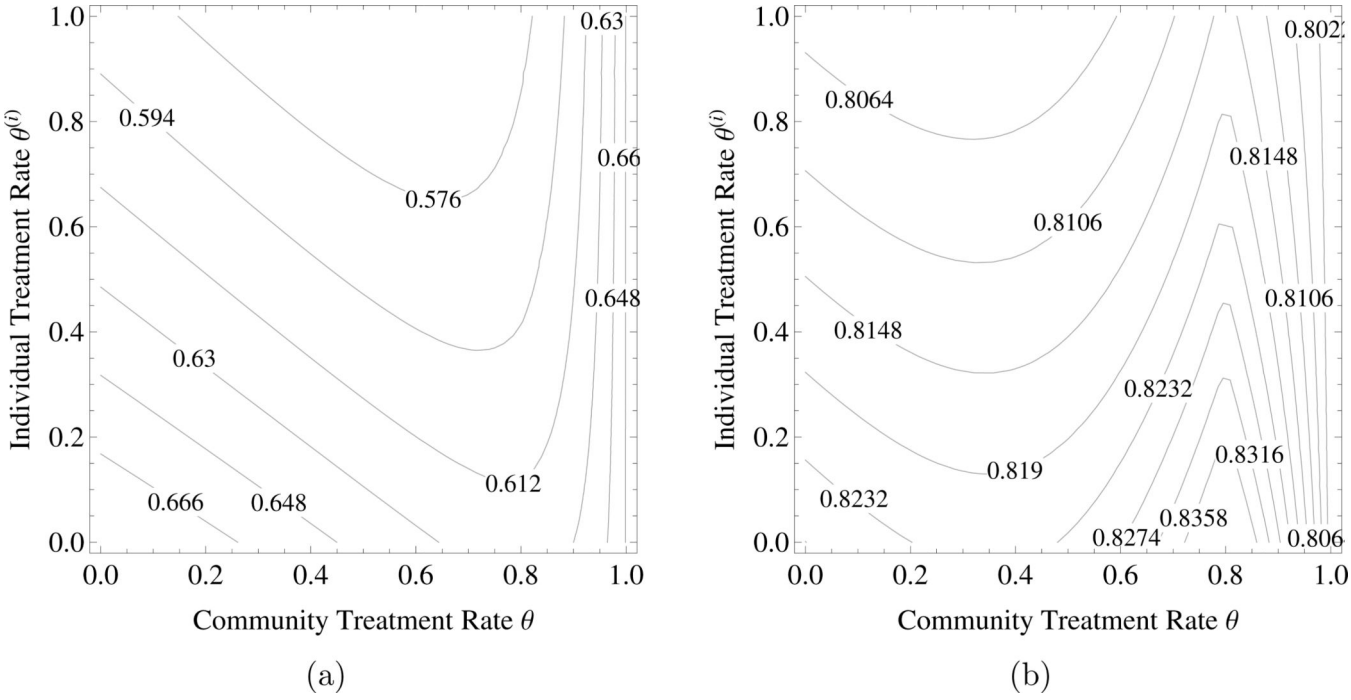

Figure 4.

The tragedy of the commons under mass treatment with $D_S \neq D_R$ or $D_U > 0$. a) the individual disutility $J^{(i)}$ when resistant infection has higher disutility than sensitive infection, b) the individual disutility $J^{(i)}$ when the uninfected has significant disutility. Parameters are as in the text. The horizontal axis is community level of mass treatment rate and the vertical axis is the level of mass treatment rate chosen by an individual within the community.

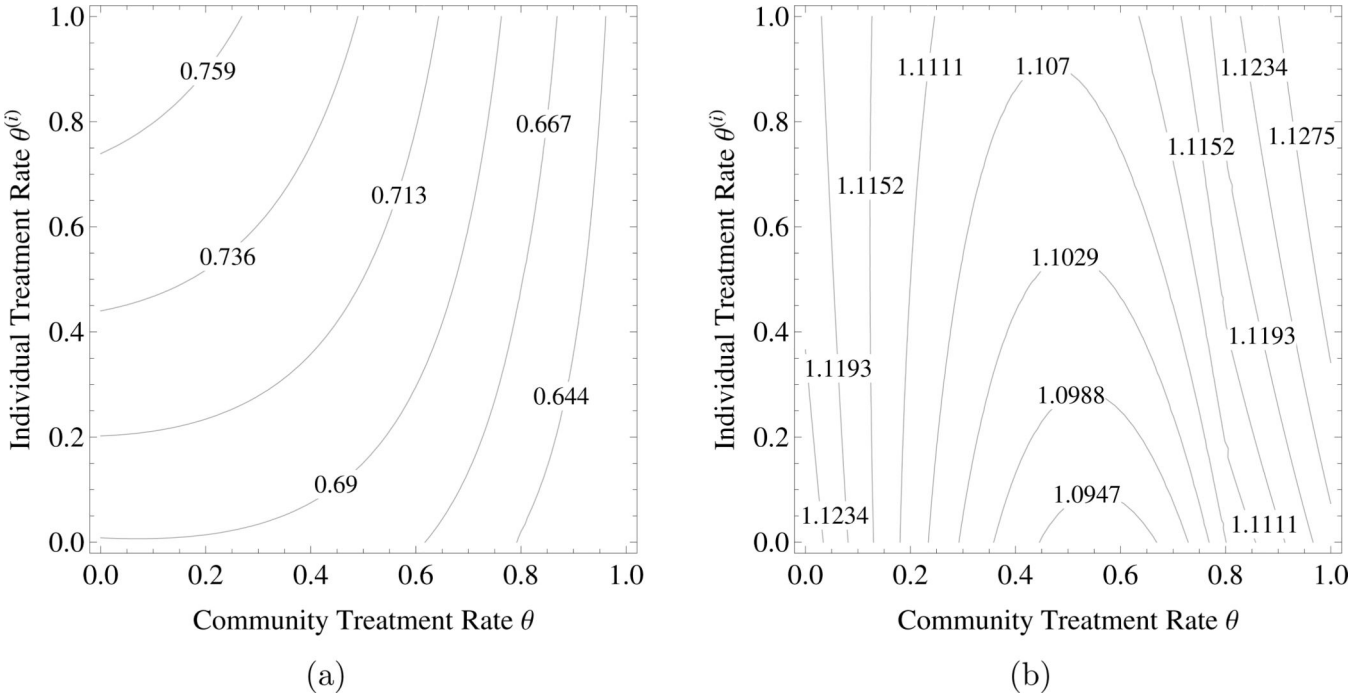

Figure 5.

Individual incentives which may favor undertreatment in case of mass treatment with $D_S \neq D_R$ or $D_U > 0$. a) the individual disutility $J^{(i)}$ when resistant infection has higher disutility than sensitive infection, b) the individual disutility $J^{(i)}$ when the uninfected state has a lower utility than the infected states. Parameters are as in the text. The horizontal axis is community level of mass treatment rate and the vertical axis is the level of mass treatment rate chosen by an individual within the community.