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Optimal Treatment Strategy for Infectious Diseases with Two Treatment Stages

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Abstract

In this paper, a disease transmission model with two treatment stages is proposed and analyzed. The results indicate that the basic reproduction number is a critical threshold for the prevalence of the disease. If the basic reproduction number is less than one, the disease free equilibrium is globally asymptotically stable. Otherwise, the endemic equilibrium is globally asymptotically stable. Therefore, besides the basic reproduction number, a new marker for characterizing the seriousness of the disease, named as dynamical final infective size, is proposed, which differs from traditional final size because the proposed model includes the natural birth and death. Finally, optimization strategies for limited medical resources are obtained from the perspectives of basic reproduction number and dynamical final infective size, and the real-world disease management scenarios are given based on these finding.

Keywords

Infectious Diseases, Basic Reproduction Number, Global Dynamics, Dynamical Final Infective Size, Optimal Treatment Strategy

1. Introduction

Contagious disease epidemics, mostly caused by viruses, such as influenza, hepatitis, acquired immune deficiency syndrome (AIDS), coronavirus disease 2019, and so on, has always been a major threat to global public health. To understand the transmission dynamics of the infectious diseases, several mathematical models have been proposed and analyzed [1] [2] [3] [4] [5]. A central idea in mathematical epidemiology is that the threshold for many epidemiology models is the basic reproduction number $\Re_0$, *i.e.*, the threshold $\Re_0 = 1$ is the dividing line between the infection dying out and the onset of an epidemic. Here the basic

reproduction number is defined as the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible [6].

After virus infection, the host usually displays several different stages according to the course of disease [7] [8] [9], such as the asymptomatic and symptomatic stage, or the acute and chronic infection stage. At each stage, drug therapy is effective, although the effectiveness of treatment may vary at different stages, and recovered infectives usually are immune against reinfection. According to the above mentioned characteristics, we can divide the population into four compartments, named as susceptible (S), the asymptomatic/acute infected (A), the symptomatic/chronic infected (I), and recovered (R) individuals. **Figure 1** illustrates the flowchart of the four compartments, which describes how individuals can move among the states.

Based on the flowchart in **Figure 1**, the dynamic model can be described by the following autonomous differential equations:

$$\begin{cases} S' = \lambda - d_1 S - (\beta_1 A + \beta_2 I) S, \\ A' = (\beta_1 A + \beta_2 I) S - (d_1 + \mu_1 + \varepsilon_1 \delta_1) A, \\ I' = \mu_1 A - (d_1 + d_2 + \mu_2 + \varepsilon_2 \delta_2) I, \\ R' = \varepsilon_1 \delta_1 A + (\mu_2 + \varepsilon_2 \delta_2) I - d_1 R, \end{cases} \tag{1}$$

in which λ means the recruitment rate of individuals, d_1 denotes natural death rate, d_2 is death rate due to infection. Corresponding to classes A and I respectively, β_1 and β_2 are the infection coefficient, $1/\mu_1$ and $1/\mu_2$ are the infectious period, δ_1 and δ_2 are the treated fractions, and ε_1 and ε_2 are the corresponding effectiveness. Obviously, δ_1 and δ_2 are connected with the medical resource. Hence, from the perspective of treatment strategy, we can also interpret δ_1 and δ_2 as medical resource for classes A and I, respectively. Note that natural birth and death rates are incorporated in our model (1) because many viral diseases, such as influenza, hepatitis and AIDS, cannot be eliminated and have persisted decades or more than one hundred years.

Due to the independence of variable R in system (1), the R' equation can be eliminated from the system. Thus, in the following text, we only consider the reduced system:

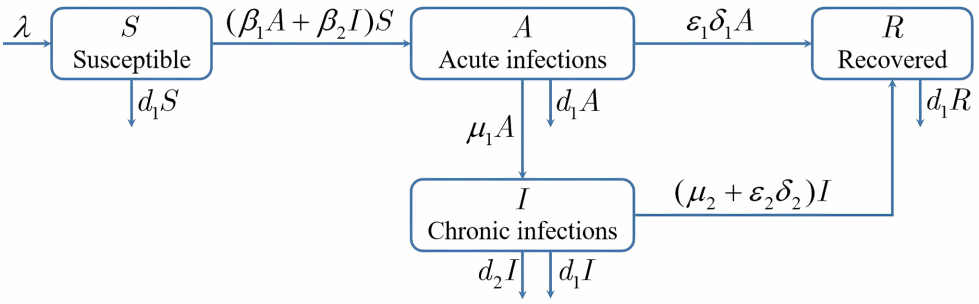

Figure 1. Flow diagram for the *SAIR* model (1).

$$\begin{cases} S' = \lambda - d_1 S - (\beta_1 A + \beta_2 I) S, \\ A' = (\beta_1 A + \beta_2 I) S - (d_1 + \mu_1 + \varepsilon_1 \delta_1) A, \\ I' = \mu_1 A - (d_1 + d_2 + \mu_2 + \varepsilon_2 \delta_2) I. \end{cases} \tag{2}$$

In this study, we will focus on how the treatment strategy δ_1 and δ_2 should be arranged to optimize the effect of limited medical resource. The rest of this paper is organized as follows. In Section 2, we present dynamic analysis, including the basic reproduction number $\Re_0$ of system (2), the existence and globally stability of equilibria. Analytical and numerical results for optimal treatment strategy are given in Section 3. Finally, a short discussion completes the paper.

2. Global Dynamics Analysis

Since we are interested in the dynamics of infectious diseases, and not the initial processes of infection, we assume that the initial condition of (2) has the form $S(0) > 0$, $A(0) > 0$ and $I(0) > 0$. Based on the initial conditions, it is easy to show that the solutions of system (2) are non-negative and ultimately bounded. The equilibria of (2) are the solutions of the following algebraic equations:

$$\begin{cases} \lambda - d_1 S - (\beta_1 A + \beta_2 I) S = 0, \\ (\beta_1 A + \beta_2 I) S - \omega_1 A = 0, \\ \mu_1 A - \omega_2 I = 0. \end{cases} \tag{3}$$

Here, for the sake of simplicity of notation, we always let $\omega_1 = d_1 + \mu_1 + \varepsilon_1 \delta_1$ and $\omega_2 = d_1 + d_2 + \mu_2 + \varepsilon_2 \delta_2$ in the following text.

Clearly, the disease free equilibrium $E_0 = (\lambda / d_1, 0, 0)$ of (2) always exists. Using the next generation matrix terminology in [6], we can easily obtain the basic reproduction number of system (2) as

$$\Re_0 = \frac{\beta_1 \lambda}{d_1 \omega_1} + \frac{\beta_2 \lambda \mu_1}{d_1 \omega_1 \omega_2}. \tag{4}$$

To obtain endemic equilibrium of model (2), solving the algebraic Equations (3), we can obtain that model (2) exists unique endemic equilibrium $E_1 = (S^*, A^*, I^*)$ if and only if $\Re_0 > 1$, in which

$$S^* = \frac{\lambda \omega_2}{d_1 \omega_2 + (\beta_1 \omega_2 + \beta_2 \mu_1) A^*}, \quad A^* = \frac{d_1 \omega_2 (\Re_0 - 1)}{\beta_1 \omega_2 + \beta_2 \mu_1}, \quad I^* = \frac{\mu_1}{\omega_2} A^*. \tag{5}$$

In order to obtain the stability of above mentioned equilibria, we first give the Jacobian matrix J of system (2) at (S, A, I),

$$J = \begin{pmatrix} -(d_1 + \beta_1 A + \beta_2 I) & -\beta_1 S & -\beta_2 S \\ \beta_1 A + \beta_2 I & \beta_1 S - \omega_1 & \beta_2 S \\ 0 & \mu_1 & -\omega_2 \end{pmatrix}. \tag{6}$$

So we have the following result on the global stability of the disease free equilibrium E_0.

Theorem 1. *The disease free equilibrium E_0 is globally asymptotically stable if $\Re_0 < 1$, and it is unstable when $\Re_0 > 1$.*

Proof. According to (6) and the expression of E_0, we know that $-d_1$ is the eigenvalue of $J(E_0)$, and the other two eigenvalues of $J(E_0)$ are determined by the following sub-matrix

$$J_1 = \begin{pmatrix} \frac{\beta_1\lambda}{d_1} - \omega_1 & \frac{\beta_2\lambda}{d_1} \\ \mu_1 & -\omega_2 \end{pmatrix}.$$

Simple calculations imply

$$\operatorname{tr}(J_1) = \frac{\beta_1\lambda}{d_1} - \omega_1 - \omega_2 < 0$$

and

$$\det(J_1) = \omega_1\omega_2(1-\Re_0) > 0$$

if $\Re_0 < 1$. Thus, the real parts of the eigenvalues of J_1 are negative, *i.e.*, E_0 is locally asymptotically stable if $\Re_0 < 1$. When $\Re_0 > 1$, we have $\det(J_1) < 0$, so E_0 is unstable in this case.

Let

$$V = \frac{1}{2}\left(S - \frac{\lambda}{d_1}\right)^2 + k_1 A + k_2 I.$$

Here k_1 and k_2 are non-negative constants which will be determined. By the first two equations of system (2), it follows

$$\begin{aligned} S' &= -d_1\left(S - \frac{\lambda}{d_1}\right) - (\beta_1 A + \beta_2 I)\left(S - \frac{\lambda}{d_1}\right) - \frac{\lambda(\beta_1 A + \beta_2 I)}{d_1}, \\ A' &= (\beta_1 A + \beta_2 I)\left(S - \frac{\lambda}{d_1}\right) - \omega_1 A + \frac{\lambda(\beta_1 A + \beta_2 I)}{d_1}. \end{aligned}$$

Taking the time derivative of V along the solution of system (2), and using the above-mentioned equations, we have

$$\begin{aligned} V'|_{(2)} &= \left(S - \frac{\lambda}{d_1}\right)\left[-d_1\left(S - \frac{\lambda}{d_1}\right) - (\beta_1 A + \beta_2 I)\left(S - \frac{\lambda}{d_1}\right) - \frac{\lambda(\beta_1 A + \beta_2 I)}{d_1}\right] \\ &\quad + k_1\left[(\beta_1 A + \beta_2 I)\left(S - \frac{\lambda}{d_1}\right) - \omega_1 A + \frac{\lambda(\beta_1 A + \beta_2 I)}{d_1}\right] + k_2(\mu_1 A - \omega_2 I) \\ &= -(d_1 + \beta_1 A + \beta_2 I)\left(S - \frac{\lambda}{d_1}\right)^2 + \left(k_1 - \frac{\lambda}{d_1}\right)(\beta_1 A + \beta_2 I)\left(S - \frac{\lambda}{d_1}\right) \\ &\quad + \left(\frac{k_1\beta_1\lambda}{d_1} + k_2\mu_1 - k_1\omega_1\right)A + \left(\frac{k_1\beta_2\lambda}{d_1} - k_2\omega_2\right)I. \end{aligned}$$

When $\Re_0 < 1$, we know $d_1\omega_1 - \beta_1\lambda > 0$. Setting

$$k_1 = \frac{\lambda}{d_1} > 0, \quad k_2 = \frac{\lambda(d_1\omega_1 - \beta_1\lambda)}{\mu_1 d_1^2},$$

after some algebraic calculations, we have

$$\frac{k_1\beta_1\lambda}{d_1}+k_2\mu_1-k_1\omega_1=0,\ \frac{k_1\beta_2\lambda}{d_1}-k_2\omega_2=\frac{\lambda\omega_1\omega_2}{d_1\mu_1}(\Re_0-1).$$

Thus,

$$V'|_{(2)}=-(d_1+\beta_1A+\beta_2I)\left(S-\frac{\lambda}{d_1}\right)^2+\frac{\lambda\omega_1\omega_2}{d_1\mu_1}(\Re_0-1)I\le 0$$

if $\Re_0<1$, and $V'=0$ only if $S=\lambda/d_1$ and $I=0$. In this case, it is easy to obtain that the maximal invariant subset in $\{(S,A,I):V'=0\}$ is the singleton $\{E_0\}$. As a result, E_0 is globally asymptotically stable based on the LaSalle's invariance principle [10].

Note that system (1) has same structure as system (1) in Tien and Earn [11]. Tien and Earn [11] have proved that endemic equilibrium is globally asymptotically stable if it exists. Thus, we have the following result on the global stability of the endemic equilibrium E_1.

Theorem 2. *When $\Re_0>1$, the endemic equilibrium E_1 is globally asymptotically stable.*

3. Optimal Treatment Strategy

According to Theorem 1 and Theorem 2, we know that $\Re_0$ can predict the disease. When $\Re_0>1$, the disease is an endemic disease, and the endemic equilibrium E_1 is globally asymptotically stable. In this case, E_1 gives the dynamical final size for different subpopulations. Therefore, the dynamical final infective size $Z=A^*+I^*$ can indicate the seriousness of the disease. So then, we will show how treatment strategies δ_1 and δ_2 should be arranged to press $\Re_0$ and Z small if limited medical resources are given in this section. Here, the term "dynamical final infective size" is different from "final size" in [12] [13], where the model did not include the natural birth and death. The term "dynamic" means that the rates of entering into and leaving from infective subpopulation are equal.

Firstly, we give the optimal treatment strategy to control the basic reproduction number $\Re_0$. In this case $\Re_0$ will be considered as a function of δ_1 and δ_2. Simple calculations imply

$$\frac{\partial\Re_0}{\partial\delta_1}=-\frac{\lambda\varepsilon_1(\beta_1\omega_2+\beta_2\mu_1)}{d_1\omega_1^2\omega_2}<0,$$
$$\frac{\partial\Re_0}{\partial\delta_2}=-\frac{\beta_2\lambda\mu_1\varepsilon_2}{d_1\omega_1\omega_2^2}<0,$$

which means that when medical resource is abundant enough, whether increasing δ_1 or δ_2 can reduce $\Re_0$. However, when medical resources are limited, what is the optimal treatment strategy?

Let $|\partial\Re_0/\partial\delta_1|=|\partial\Re_0/\partial\delta_2|$. After some algebraic operations, we have

$$\left|\frac{\partial\Re_0}{\partial\delta_1}\right|=\left|\frac{\partial\Re_0}{\partial\delta_2}\right|\Leftrightarrow\delta_1=a_2\delta_2^2+a_1\delta_2+a_0\triangleq\varphi_1(\delta_2),\tag{7}$$

in which

$$a_2 = \frac{\beta_1\varepsilon_2}{\beta_2\mu_1},\ a_1 = \frac{2\beta_1(d_1+d_2+\mu_2)+\beta_2\mu_1}{\beta_2\mu_1},$$
$$a_0 = \frac{\varepsilon_1(d_1+d_2+\mu_2)\left(\beta_1(d_1+d_2+\mu_2)+\beta_2\mu_1\right)-\beta_2\mu_1\varepsilon_2(d_1+\mu_1)}{\beta_2\mu_1\varepsilon_1\varepsilon_2}.$$

Obviously, curve (7) divides the first quadrant of the δ_2-δ_1 plane into following two regions:

$$\begin{aligned}\Omega_1 &\triangleq \left\{(\delta_2,\delta_1):\left|\frac{\partial\Re_0}{\partial\delta_1}\right|<\left|\frac{\partial\Re_0}{\partial\delta_2}\right|,\delta_1>0,\delta_2>0\right\},\\ \Omega_2 &\triangleq \left\{(\delta_2,\delta_1):\left|\frac{\partial\Re_0}{\partial\delta_1}\right|>\left|\frac{\partial\Re_0}{\partial\delta_2}\right|,\delta_1>0,\delta_2>0\right\}.\end{aligned} \tag{8}$$

Therefore, based on the size of $\left|\partial\Re_0/\partial\delta_1\right|$ and $\left|\partial\Re_0/\partial\delta_2\right|$ in the region, corresponding optimization strategies of reducing the basic reproduction number $\Re_0$ as quickly as possible can be obtained. For more intuitive interpretation, a graphical representation of the regions is shown in Figure 2 under the following fixed artificial parameters:

$$\begin{aligned}&\lambda=0.5,\ \beta_1=0.081081,\ \beta_2=0.2835,\\ &d_1=0.00005,\ d_2=0.002,\ \mu_1=0.66,\ \varepsilon_1=0.9.\end{aligned} \tag{9}$$

Next, we give the optimal treatment strategy to control the dynamical final infective size Z. In this case, $\Re_0>1$ is always valid and Z will be considered as a function of δ_1 and δ_2. Simple calculations imply

$$\begin{aligned}Z &= A^*+I^* = \frac{d_1(\omega_2+\mu_1)(\Re_0-1)}{\beta_1\omega_2+\beta_2\mu_1},\\ \frac{\partial Z}{\partial\delta_1} &= -\frac{\lambda\varepsilon_1(\omega_2+\mu_1)}{\omega_1^2\omega_2}<0,\\ \frac{\partial Z}{\partial\delta_2} &= \frac{d_1\mu_1\varepsilon_2(\beta_2-\beta_1)(\Re_0-1)}{(\beta_1\omega_2+\beta_2\mu_1)^2}-\frac{\beta_2\lambda\mu_1\varepsilon_2(\omega_2+\mu_1)}{\omega_1\omega_2^2(\beta_1\omega_2+\beta_2\mu_1)}.\end{aligned} \tag{10}$$

Clearly, $\partial Z/\partial\delta_2<0$ if $\beta_2\le\beta_1$. Otherwise, when $\beta_2>\beta_1$, we have

$$\begin{aligned}\frac{\partial Z}{\partial\delta_2}<0 &\Leftrightarrow \frac{d_1\mu_1\varepsilon_2(\beta_2-\beta_1)(\Re_0-1)}{(\beta_1\omega_2+\beta_2\mu_1)^2}<\frac{\beta_2\lambda\mu_1\varepsilon_2(\omega_2+\mu_1)}{\omega_1\omega_2^2(\beta_1\omega_2+\beta_2\mu_1)}\\ &\Leftrightarrow \Re_0-1<\frac{\beta_2\lambda(\omega_2+\mu_1)(\beta_1\omega_2+\beta_2\mu_1)}{d_1\omega_1\omega_2^2(\beta_2-\beta_1)}.\end{aligned}$$

Furthermore, using the expression (4) of the basic reproduction number, after some algebraic operations, we have

$$\frac{\beta_2\lambda(\omega_2+\mu_1)(\beta_1\omega_2+\beta_2\mu_1)}{d_1\omega_1\omega_2^2(\beta_2-\beta_1)}=\frac{\beta_2}{\beta_2-\beta_1}\left(1+\frac{\mu_1}{\omega_2}\right)\Re_0.$$

Thus,

$$\frac{\partial Z}{\partial\delta_2}<0\Leftrightarrow 1<\frac{\beta_2}{\beta_2-\beta_1}\left(1+\frac{\mu_1}{\omega_2}\right)\frac{\Re_0}{\Re_0-1}.$$

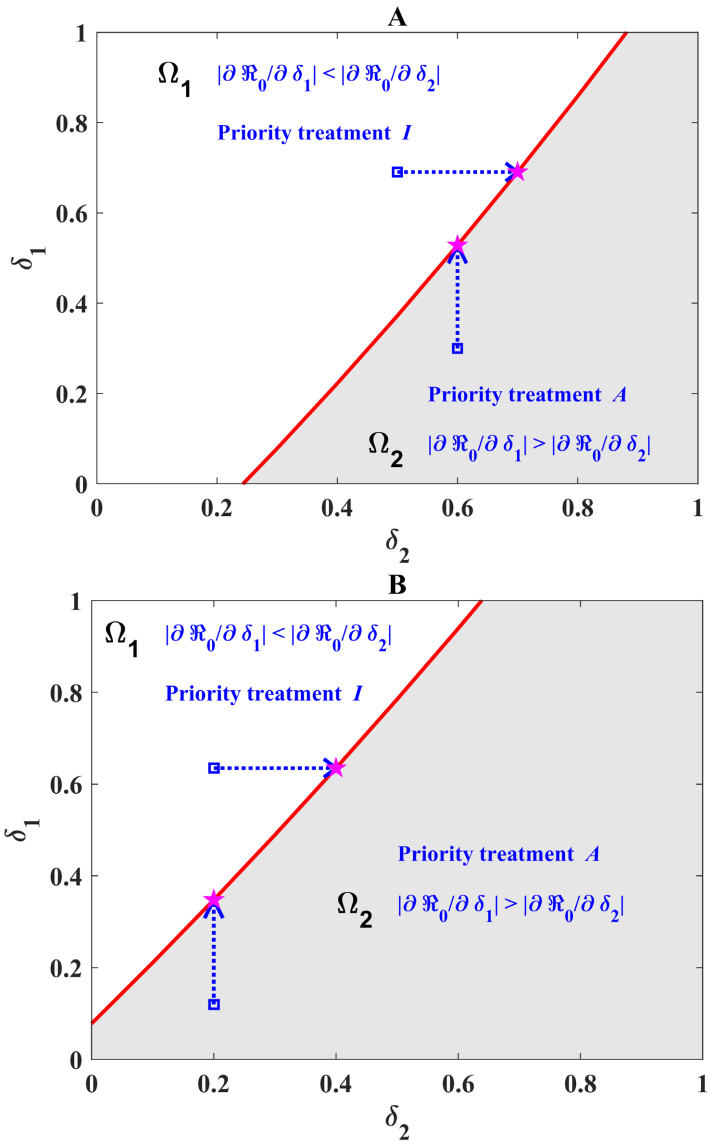

Figure 2. Illustration of optimal treatment strategy to control $\Re_0$ as the function of treatment coefficients δ_1 and δ_2. Here $\mu_2 = 0.2597, \varepsilon_2 = 0.7$ and $a_0 = -0.317$ in (A), $\mu_2 = 0.35, \varepsilon_2 = 0.5$ and $a_0 = 0.0781$ in (B), and the other parameters are taken in (9). The red line is the curve $\delta_1 = \varphi_1(\delta_2)$ in (7), Ω_1 and Ω_2 are defined in (8).

Because $\beta_2 > \beta_1$ and $\Re_0 > 1$, both $\beta_2/(\beta_2 - \beta_1) > 1$ and $\Re_0/(\Re_0 - 1) > 1$ are valid. As a result, we know $\partial Z/\partial \delta_2 < 0$ is always valid.

According to (10), we know $\partial Z/\partial \delta_1 < 0$ is always valid. Thus, whether increasing δ_1 or δ_2 will always be beneficial for controlling the total scale of the disease if there are abundant medical resource.

After some algebraic operations, we know $|\partial Z/\partial \delta_1| = |\partial Z/\partial \delta_2|$ is equivalent to the following equation:

$$\lambda\left(\omega_1\omega_2^2 + \mu_1\varepsilon_1\omega_2 - \mu_1\varepsilon_2\omega_1\right)\left(\beta_1\omega_2 + \beta_2\mu_1\right)^2 - d_1\mu_1\varepsilon_2\left(\beta_2 - \beta_1\right)\omega_1^2\omega_2^2 = 0 \quad (11)$$

Using the implicit function theorem, we know that (11) contains the function

$\delta_2 = \varphi_2(\delta_1)$, although the analytical expression of $\delta_2 = \varphi_2(\delta_1)$ cannot be obtained because (11) is too complex with respect to δ_1 and δ_2.

For more intuitive interpretation, we give some numerical simulations under the fixed artificial parameters (9). Similar to (7), we find that the curve $\delta_2 = \varphi_2(\delta_1)$ may still divide the first quadrant of the δ_1-δ_2 plane into two regions, with $|\partial Z/\partial\delta_1| < |\partial Z/\partial\delta_2|$ in Ω_1 and the opposite in Ω_2. As a result, the corresponding optimal treatment strategy of reducing the dynamical final infective size Z as quickly as possible can be obtained in different regions, which is shown in Figure 3.

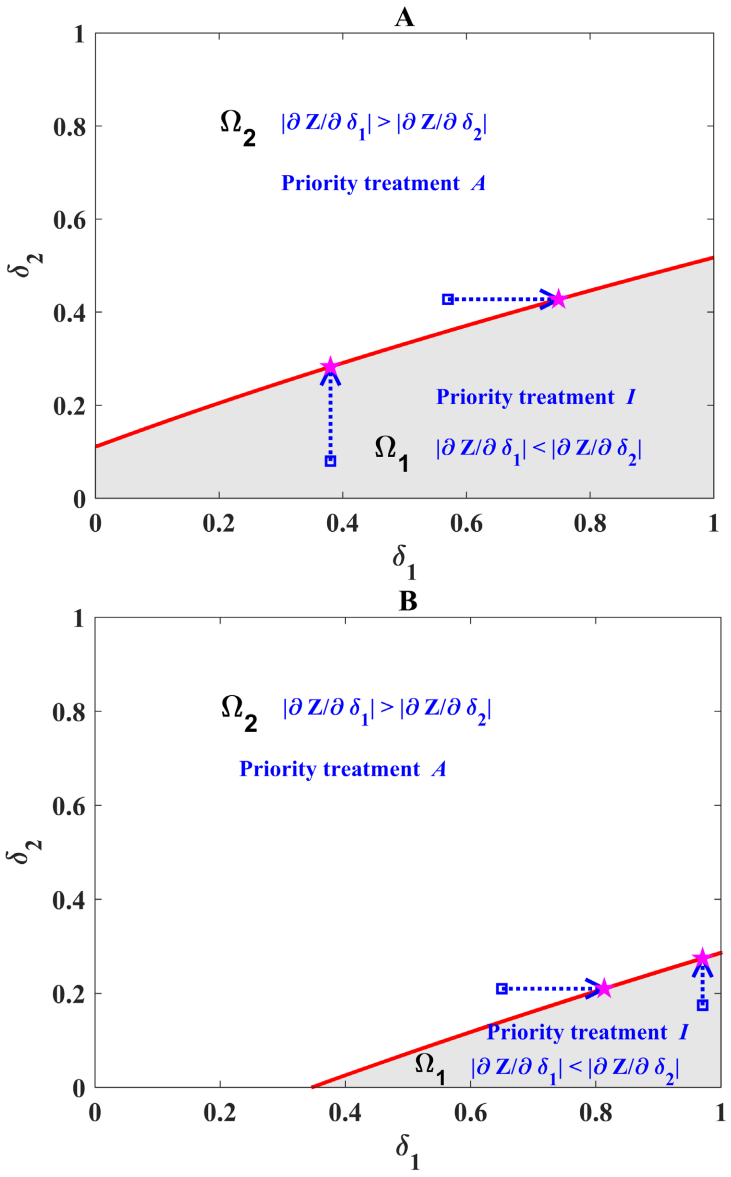

Figure 3. Illustration of optimal treatment strategy to control Z as the function of treatment coefficients δ_1 and δ_2. Here $\mu_2 = 0.2597, \varepsilon_2 = 0.7$ in (A), $\mu_2 = 0.35, \varepsilon_2 = 0.5$ in (B), and the other parameters are taken in (9). The red line is the curve $\delta_2 = \varphi_2(\delta_1)$ implied by (11), Ω_1 and Ω_2 are defined based on the size of $|\partial Z/\partial\delta_1|$ and $|\partial Z/\partial\delta_2|$.

4. Discussion

In this paper, a disease transmission model with two treatment stages is proposed and analyzed. When medical resources are limited, the following optimization strategies from the perspectives of basic reproduction number and dynamical final infective size can be drawn:

- When the parameters lie in region Ω_1, because increasing δ_2 can decrease $\Re_0$ (or Z) more greatly than increasing δ_1, the optimal treatment strategy is priority treatment I class until $\left|\partial\Re_0/\partial\delta_1\right| = \left|\partial\Re_0/\partial\delta_2\right|$ (or $\left|\partial Z/\partial\delta_1\right| = \left|\partial Z/\partial\delta_2\right|$).
- On the contrary, when the parameters lie in region Ω_2, the optimal treatment strategy is priority treatment A until $\left|\partial\Re_0/\partial\delta_1\right| = \left|\partial\Re_0/\partial\delta_2\right|$ (or $\left|\partial Z/\partial\delta_1\right| = \left|\partial Z/\partial\delta_2\right|$).
- The curve $\left|\partial\Re_0/\partial\delta_1\right| = \left|\partial\Re_0/\partial\delta_2\right|$ (or $\left|\partial Z/\partial\delta_1\right| = \left|\partial Z/\partial\delta_2\right|$) is the optimal treatment strategy under limited medical resources.

In practical application, if the goal is to eliminate diseases, it is better to optimize the control of the basic reproduction number and ultimately make it less than 1. When the disease has become an endemic disease and it is difficult to achieve the target of the basic reproduction number less than 1, then optimal control of the dynamic final effective size should be carried out to minimize the scale of the endemic disease as much as possible. Furthermore, in order to better prevent and control the epidemic, further studies are warranted to optimizing the control of the basic reproduction number and dynamic final effective size simultaneously.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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