Research Article

A Schistosomiasis Model with Praziquantel Resistance

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A compartmental model is established for schistosomiasis with praziquantel resistance. The model considers the impact of genetic resistance and drug treatment on the transmission of schistosomiasis. We calculate the basic reproductive number and discuss the existence and stability of disease-free equilibrium, boundary equilibrium, and coexistence equilibrium. Our analysis shows that regardless of whether drug treatment leads to the emergence of resistance, once the impact of genetic resistance is larger, the resistant strain will be dominant, which is detrimental to the control of schistosomiasis. In addition, once the proportion of human with drug-resistant strain produced by drug treatment is larger, the number of human and snails with resistant strain is larger. This is not a good result for drug treatment with praziquantel.

1. Introduction

Currently, treatment of human beings infected by schistosomiasis primarily focuses on chemotherapy with praziquantel (PZQ). PZQ appeared as a new schistosomicidal compound during the 1970s [1]. In recent years, PZQ has become the drug of choice in most endemic areas because of its efficacy, its ease of administration, its tolerable side-effects, and its cost [1]. Although the effectiveness of PZQ against schistosomiasis is well documented, the precise mode of action of the drug has not clearly defined [2]. It is reported that the chemotherapy of many helminth infections is complicated by the occurrence of drug resistance and drug tolerance (a natural resistance) to certain anthelmintics [2]. Not surprisingly, recent epidemiological evidence suggests the emergence of PZQ-resistant\tolerant schistosomes [1, 3, 4]. Resistance is defined as a genetically transmitted loss of sensitivity in a parasite population that was previously sensitive to a given drug [2]. Tolerance is an innate insusceptibility of a parasite to a drug, with the caveat that the parasite must not have been previously exposed to the drug [2]. The first report of possible PZQ resistance came from an intensive focus in northern Senegal, where the drug had produced very low cure rates (18–39%) [5, 6]. And snails collected in the area carried schistosoma strains. When tested in the laboratory, those snails had a decreased susceptibility to PZQ [7, 8].

Additional PZQ-resistant evidence was collected in Egypt [4, 9]. Preliminary studies have begun on these isolates to identify genetic, physiological, and morphological characteristics associated with PZQ resistance, and some of these may find use as markers for monitoring whether or not resistance is developing in endemic areas, where the drug is used [10].

Many papers have reported that drug treatment results in the emergence of schistosome resistance to PZQ [11–13]. Drug treatment can remove drug-susceptible parasites in infected human beings, while resistant parasites survive. However, many investigations find that traits of PZQ resistance of *Schistosoma mansoni* are dominant inheritance [14–16]. The resistant worms can reproduce and pass the resistant genes to the next generation. Furthermore, the resistance of *Schistosoma mansoni* to PZQ can be expressed in eggs, miracidia, cercariae, adults, and all stages of development [14–16]. In other words, some definitive hosts carrying resistant schistosomes can infect snails and make those snails carry resistant schistosomes. On the contrary, some snails carrying resistant schistosomes can infect definitive hosts and also make those definitive hosts carry resistant schistosomes. It goes on, the control of schistosomiasis will face enormous difficulties. Therefore, it is necessary to study the impact of this schistosome genetic resistance on the transmission of schistosomiasis.

In previous schistosomiasis models, resistant problems have been studied by considering that the resistance of schistosomiasis is due to drug treatment [11–13]. In [11, 13], the authors proposed a multistrain schistosome model including sensitive and resistant parasite strains. Their goal was to infer the impact of drug treatment on the maintenance of schistosome genetic diversity. In their assumptions, the drug-sensitive parasite strain had an additional per capita death rate, σ, due to treatment. For a parasite strain that had developed drug resistance with a resistance level θ ($\theta > 1$), this treatment-related death rate was assumed to be reduced by the factor θ to σ/θ. Their results implied that higher treatment rate could allow for coexistence between sensitive and resistant parasite strains. In [12], the authors formulated a deterministic model with multiple strains of schistosomes in order to explore the role of drug treatment in the maintenance of a polymorphism of parasite strains that differed in their resistance levels. And snails infected by parasite strains were divided into multistrain subclasses according to the different level θ_i of parasite strains. Analysis of the model showed that the likelihood that resistant strains would increase in frequency depended on the interplay between their relative fitness, the cost of resistance, and the degree of selection pressure exerted by drug treatments.

Motivated by [11–13], we establish a new model considering hosts with sensitive and resistant strains in this paper. Our purpose is mainly to study the impact of drug treatment and genetic resistance on the transmission of schistosomiasis.

Our paper is organized as follows. In Section 2, we establish a mathematical model with praziquantel resistance and obtain basic reproductive number and existence of equilibria. And then the stability of disease-free equilibrium is obtained in Section 3. Section 4 devotes to stability analysis of boundary equilibria. In Section 5, stability analysis of endemic equilibrium is performed.

2. Mathematical Model

According to different level of parasite strains, we divide infected hosts into sensitive and resistant strains. Considering resistance and inheritance of resistance, new resistant strains are composed of two parts. We classify definitive and intermediate hosts as susceptible, sensitive and resistant in the following:

   (i) $X_s(t)$, the population of susceptible human;
   (ii) $X_i(t)$, the population of human infected with sensitive parasite strain;
   (iii) $X_r(t)$, the population of human infected with resistant parasite strain;
   (iv) $Y_s(t)$, the population of susceptible snail host;
   (v) $Y_i(t)$, the population of snail host carrying sensitive parasites;
   (vi) $Y_r(t)$, the population of snail host carrying resistant parasites.

We follow some of the available models for schistosomiasis [17–19] and assume that the reproduction rate of hosts is

constant, and we ignore the recovery class of host since the life span of infected is short in comparison to that of human [18, 20]. All parameters in the model are assumed to be non-negative constants:

   (i) Λ_1, recruitment rate of human;

   (ii) μ_1, per capita natural death rate of human;

   (iii) α_1, per capita disease-induced death rate of human;

   (iv) β_1, per capita contact transmission rate from infected snails to susceptible human;

   (v) Λ_2, recruitment rate of snails;

   (vi) μ_2, per capita natural death rate of snails;

   (vii) α_2, per capita disease-induced death rate of snails;

   (viii) β_2, per capita contact transmission rate from infected human to susceptible snails;

   (ix) θ, the rate of treatment for infected human;

   (x) ρ, the proportion of human with drug-resistant strain produced by treatment;

   (xi) k, represents the impact of inheritance and the cost of resistance on transmission rate, we assume that $k \leq 1$ since the transmission rate is reduced due to resistance [12];

   (xii) k_1, represents the impact of resistance on disease-induced death rate of human;

   (xiii) k_2, represents the impact of resistance on disease-induced death rate of snails.

Then, we have a model with the form:

$$\frac{dX_s}{dt} = \Lambda_1 - \beta_1 X_s Y_i - k\beta_1 X_s Y_r - \mu_1 X_s + (1-\rho)\sigma X_i,$$

$$\frac{dX_i}{dt} = \beta_1 X_s Y_i - \mu_1 X_i - \alpha_1 X_i - \sigma X_i,$$

$$\frac{dX_r}{dt} = k\beta_1 X_s Y_r + \rho\sigma X_i - \mu_1 X_r - k_1\alpha_1 X_r,$$

$$\frac{dY_s}{dt} = \Lambda_2 - \beta_2 Y_s X_i - k\beta_2 Y_s X_r - \mu_2 Y_s,$$

$$\frac{dY_i}{dt} = \beta_2 Y_s X_i - \mu_2 Y_i - \alpha_2 Y_i,$$

$$\frac{dY_r}{dt} = k\beta_2 Y_s X_r - \mu_2 Y_r - k_2\alpha_2 Y_r.$$

(1)

Using standard methods, it is easy to see that disease free equilibrium $E_0 = (\Lambda_1/\mu_1, 0, 0, \Lambda_2/\mu_2, 0, 0)$ always exists. Let $X_{s0} = \Lambda_1/\mu_1$, $Y_{s0} = \Lambda_2/\mu_2$, $m_1 = \mu_1 + \alpha_1 + \sigma$, $m_2 = \mu_1 + k_1\alpha_1$, $m_3 = \mu_2 + \alpha_2$, and $m_4 = \mu_2 + k_2\alpha_2$. According to the concept of next generation matrix [21] and the formula of the basic

reproductive number for ODE compartmental models [22], if we let

$$F = \begin{pmatrix} 0 & 0 & \beta_1 X_{s0} & 0 \\ 0 & 0 & 0 & k\beta_1 X_{s0} \\ \beta_2 Y_{s0} & 0 & 0 & 0 \\ 0 & k\beta_2 Y_{s0} & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} m_1 & 0 & 0 & 0 \\ 0 & m_2 & 0 & 0 \\ 0 & 0 & m_3 & 0 \\ 0 & 0 & 0 & m_4 \end{pmatrix},$$

(2)

one can calculate that the eigenvalues of the next generation matrix FV^{-1} are given by

$$R_{0i} = \sqrt{\frac{\beta_1 \beta_2 X_{s0} Y_{s0}}{m_1 m_3}}, \qquad R_{0r} = \sqrt{\frac{k^2 \beta_1 \beta_2 X_{s0} Y_{s0}}{m_2 m_4}}. \qquad (3)$$

Then, it follows that the basic reproductive number for the system (1) is given by

$$R_0 = \max \{R_{0i}, R_{0r}\}. \qquad (4)$$

To obtain other equilibria, we let the right-hand side of (1) equal to zero and obtain

$$\Lambda_1 - \beta_1 X_s Y_i - k\beta_1 X_s Y_r - \mu_1 X_s + (1 - \rho)\sigma X_i = 0, \qquad (5)$$

$$\beta_1 X_s Y_i - \mu_1 X_i - \alpha_1 X_i - \sigma X_i = 0, \qquad (6)$$

$$k\beta_1 X_s Y_r + \rho\sigma X_i - \mu_1 X_r - k_1\alpha_1 X_r = 0, \qquad (7)$$

$$\Lambda_2 - \beta_2 Y_s X_i - k\beta_2 Y_s X_r - \mu_2 Y_s = 0, \qquad (8)$$

$$\beta_2 Y_s X_i - \mu_2 Y_i - \alpha_2 Y_i = 0, \qquad (9)$$

$$k\beta_2 Y_s X_r - \mu_2 Y_r - k_2\alpha_2 Y_r = 0. \qquad (10)$$

If $X_i = 0$, we have $Y_i = 0$ and a formula of X_r as follows:

$$\left(k^2 \beta_1 \beta_2 \Lambda_2 m_2 + \mu_1 m_2 m_4 k\beta_2\right) X_r = k^2 \beta_1 \beta_2 \Lambda_1 \Lambda_2 - \mu_1 \mu_2 m_2 m_4. \qquad (11)$$

Note that $R_{0r} > 1$ equals to $k^2 \beta_1 \beta_2 \Lambda_1 \Lambda_2 > \mu_1 \mu_2 m_2 m_4$. Hence, if $R_{0r} > 1$, there exists a boundary equilibrium with only resistant type, given as $E_{0r} = (X_{sr}, 0, X_{rr}, Y_{sr}, 0, Y_{rr})$, where

$$X_{sr} = \frac{\Lambda_1 \left(\mu_1 m_4 R_{0r}^2 + k\beta_1 \Lambda_2\right)}{\left(\mu_1^2 m_4 + k\beta_1 \mu_1 \Lambda_2\right) R_{0r}^2},$$

$$X_{rr} = \frac{\mu_1 \mu_2 m_4 \left(R_{0r}^2 - 1\right)}{\left(\mu_1 m_4 + k\beta_1 \Lambda_2\right) k\beta_2},$$

$$Y_{sr} = \frac{\Lambda_2 \left(\mu_1 m_4 + k\beta_1 \Lambda_2\right)}{\mu_1 \mu_2 m_4 R_{0r}^2 + k\beta_1 \Lambda_2 \mu_2},$$

(12)

$$Y_{rr} = \frac{\Lambda_2 \mu_1 \left(R_{0r}^2 - 1\right)}{\mu_1 m_4 R_{0r}^2 + k\beta_1 \Lambda_2}.$$

If drug treatment does not lead to drug resistance, that is, $\rho = 0$, then when $R_{0i} > 1$, we can obtain the other boundary equilibrium with only sensitive type, given as $E_{0i} = (X_{si}, X_{ii}, 0, Y_{si}, Y_{ii}, 0)$, where

$$X_{si} = \frac{\Lambda_1 m_1 m_3 + (\mu_1 + \alpha_1)\mu_2 m_1 m_3}{\beta_1 \beta_2 \Lambda_2 (\mu_1 + \alpha_1) + \mu_1 m_1 m_3},$$

$$X_{ii} = \frac{\mu_1 \mu_2 m_1 m_3 \left(R_{0i}^2 - 1\right)}{\beta_1 \beta_2 \Lambda_2 (\mu_1 + \alpha_1) + \mu_1 m_1 m_3},$$

$$Y_{si}$$

$$= \frac{\beta_1 \beta_2 \Lambda_2^2 (\mu_1 + \alpha_1) + \Lambda_2 \mu_1 m_1 m_3}{\beta_2 \mu_1 \mu_2 m_1 m_3 \left(R_{0i}^2 - 1\right) + \beta_1 \beta_2 \Lambda_2 \mu_2 (\mu_1 + \alpha_1) + \mu_1 \mu_2 m_1 m_3},$$

$$Y_{ii}$$

$$= \frac{\Lambda_2 \beta_2 \mu_1 \mu_2 m_1 \left(R_{0i}^2 - 1\right)}{\beta_2 \mu_1 \mu_2 m_1 m_3 \left(R_{0i}^2 - 1\right) + \beta_1 \beta_2 \Lambda_2 \mu_2 (\mu_1 + \alpha_1) + \mu_1 \mu_2 m_1 m_3}. \qquad (13)$$

Now, we study existence of coexistence equilibrium for the system (1). From (5)–(10), we obtain

$$\left[\beta_1 \beta_2 \Lambda_2 (\mu_1 + \alpha_1) + \mu_1 m_1 m_3 \beta_2\right] X_i + \left(\mu_1 m_1 m_3 k\beta_2 + \beta_1 \beta_2 \Lambda_2 m_2\right) X_r \qquad (14)$$

$$= \beta_1 \beta_2 \Lambda_1 \Lambda_2 - \mu_1 \mu_2 m_1 m_3.$$

Following (6), (7), (9), and (10), we have

$$\frac{Y_i}{Y_r} = \frac{km_1 X_i}{m_2 X_r - \rho\sigma X_i} = \frac{m_4 X_i}{km_3 X_r}. \qquad (15)$$

In the case that $\rho = 0$, (15) leads to

$$\frac{km_1 X_i}{m_2 X_r} = \frac{m_4 X_i}{km_3 X_r}. \qquad (16)$$

Note that $R_{0i} = R_{0r}$ equals to $km_1/m_2 = m_4/km_3$. It is easy to see that if $R_{0i} \neq R_{0r}$, (16) cannot hold, which implies that there is not coexistence equilibrium. If $R_{0i} = R_{0r}$, (16) always holds. Hence, if $R_{0r} = R_{0i} > 1$, that is, $\beta_1 \beta_2 \Lambda_1 \Lambda_2 > \mu_1 \mu_2 m_1 m_3$, (14) represents the existence of coexistence equilibrium in the form of a line.

In the case that $\rho \neq 0$, (15) leads to

$$m_4 \rho\sigma X_i = \left(m_2 m_4 - k^2 m_1 m_3\right) X_r. \qquad (17)$$

Note that $R_{0i} > R_{0r}$ equals to $m_2 m_4 - k^2 m_1 m_3 > 0$. Following (14) and (17), we can obtain that if $R_{0i} > R_{0r}$ and $R_{0i} > 1$,

then the unique coexistence equilibrium is given by $E_c = (X_{sc}, X_{ic}, X_{rc}, Y_{sc}, Y_{ic}, Y_{rc})$, where

$$
\begin{aligned}
X_{rc} &= m_4 \rho \sigma \left(\beta_1 \beta_2 \Lambda_1 \Lambda_2 - \mu_1 \mu_2 m_1 m_3 \right) \\
&\quad \times \left(\left[\beta_1 \beta_2 \Lambda_2 \left(\mu_1 + \alpha_1 \right) + \mu_1 m_1 m_3 \beta_2 \right] \right. \\
&\quad \times \left(m_2 m_4 - k^2 m_1 m_3 \right) \\
&\quad \left. + m_4 \rho \sigma \left(\mu_1 m_1 m_3 k \beta_2 + \beta_1 \beta_2 \Lambda_2 m_2 \right) \right)^{-1}, \\
X_{ic} &= \frac{m_2 m_4 - k^2 m_1 m_3}{m_4 \rho \sigma} X_{rc}, \\
Y_{sc} &= \frac{\Lambda_2}{\beta_2 X_{ic} + k \beta_2 X_{rc} + \mu_2}, \\
Y_{rc} &= \frac{k \Lambda_2 \beta_2 X_{rc}}{m_4 \left(\beta_2 X_{ic} + k \beta_2 X_{rc} + \mu_2 \right)}, \\
Y_{ic} &= \frac{\beta_2 Y_{sc} X_{ic}}{\mu_2 + \alpha_2}, \\
X_{sc} &= \frac{\Lambda_1 + (1 - \rho) \sigma X_{ic}}{\beta_1 Y_{ic} + k \beta_1 Y_{rc} + \mu_1}.
\end{aligned}
\tag{18}
$$

Summarizing above analyses, we have the following result.

Lemma 1. *The existence of equilibria for the system* (1) *is as follows:*

(1) *the disease free equilibrium E_0 always exists;*

(2) *if $R_{0r} > 1$, there exists a boundary equilibrium with only resistant type E_{0r};*

(3) *if $\rho = 0$ and $R_{0i} > 1$, there exists a boundary equilibrium with only sensitive type E_{0i};*

(4) *if $\rho = 0$ and $R_{0i} = R_{0r} > 1$, there exists coexistence equilibrium in the form of a line* (14);

(5) *if $\rho \neq 0$ and $R_{0i} > R_{0r}$, and $R_{0i} > 1$, there exists a unique coexistence equilibrium E_c.*

The following section shows that the basic reproductive number R_0 provides a threshold condition for schistosoma extinction in (1).

3. Stability Analysis of the Disease Free Equilibrium

In this section, we will analyze stability of the disease free equilibrium of the model (1). The stability of the disease free equilibrium determines whether schistosomiasis will be permanent in an uninfected population. The following result shows that schistosome will go extinct if $R_0 < 1$.

Theorem 2. *The disease free equilibrium E_0 of the system* (1) *is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof. The Jacobian matrix for the system (1) is given by

$$
J = \begin{pmatrix}
-\beta_1 Y_i - k\beta_1 Y_r - \mu_1 & (1-\rho)\sigma & 0 & 0 & -\beta_1 X_s & -k\beta_1 X_s \\
\beta_1 Y_i & -m_1 & 0 & 0 & \beta_1 X_s & 0 \\
k\beta_1 Y_r & \rho\sigma & -m_2 & 0 & 0 & k\beta_1 X_s \\
0 & -\beta_2 Y_s & -k\beta_2 Y_s & -\beta_2 X_i - k\beta_2 X_r - \mu_2 & 0 & 0 \\
0 & \beta_2 Y_s & 0 & \beta_2 X_i & -m_3 & 0 \\
0 & 0 & k\beta_2 Y_s & k\beta_2 X_r & 0 & -m_4
\end{pmatrix}.
\tag{19}
$$

Then, the eigenvalues of E_0 are $-\mu_1$, $-\mu_2$ and roots of the following equations:

$$
\begin{aligned}
\lambda^2 + (m_1 + m_3) \lambda + m_1 m_3 - \beta_1 \beta_2 X_{s0} Y_{s0} &= 0, \\
\lambda^2 + (m_2 + m_4) \lambda + m_2 m_4 - k^2 \beta_1 \beta_2 X_{s0} Y_{s0} &= 0.
\end{aligned}
\tag{20}
$$

Note that $R_0 < 1$ equals to $R_{0i} < 1$ and $R_{0r} < 1$, which leads to $m_1 m_3 - \beta_1 \beta_2 X_{s0} Y_{s0} > 0$ and $m_2 m_4 - k^2 \beta_1 \beta_2 X_{s0} Y_{s0} > 0$. Hence, if $R_0 < 1$, then all the roots of (20) have negative real parts. Hence, using the Routh-Hurwitz criterion, we can obtain that the disease free equilibrium E_0 of the system (1) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. □

Now, we turn to the study of the global stability of the disease free equilibrium of the model (1) by using Metzler matrix theory and the technique of Kamgang and Sallet [23].

Consider systems of the following form:

$$
\begin{aligned}
\frac{dx_1}{dt} &= f(x_1, x_2), \\
\frac{dx_2}{dt} &= g(x_1, x_2),
\end{aligned}
\tag{21}
$$

where $x_1 \in R_+^{n_1}$, $x_2 \in R_+^{n_2}$, and f and g are C^1. We denote by $x = (x_1, x_2)$ the state of the system and $(x_1^*, 0)$ is a disease free equilibrium on a positively invariant set $\Omega \subset R_+^{n_1 + n_2}$. Now rewrite (21) as

$$
\begin{aligned}
\frac{dx_1}{dt} &= A_1(x) \cdot (x_1 - x_1^*) + A_{12}(x) \cdot x_2, \\
\frac{dx_2}{dt} &= A_2(x) x_2.
\end{aligned}
\tag{22}
$$

For the system (22), we make the following assumptions.

(h_1) The system is defined on the positively invariant set Ω of the nonnegative orthant. The system is dissipative on Ω.

(h_2) The subsystem $dx_1/dt = A_1(x) \cdot (x_1 - x_1^*)$ is globally asymptotically stable at the equilibrium x_1^* on the canonical projection of Ω on $R_+^{n_1}$.

(h_3) The matrix $A_2(x)$ is Metzler and irreducible for any given $x \in \Omega$.

(h_4) There exists an maximum matrix $\overline{A}_2$, then for any $\overline{x} \in \Omega$ such that $\overline{A}_2 = A_2(\overline{x})$, $\overline{x} \in R_+^{n_1} \times \{0\}$.

(h_5) $\alpha(\overline{A}_2) \leq 0$, that is, the greatest real part of eigenvalues of $\overline{A}_2$ is nonnegative.

For convenience, we state two lemmas due to Kamgang and Sallet [23].

Lemma 3. *If the above hypotheses, h_1–h_5, are satisfied, then the disease free equilibrium is globally asymptotically stable in Ω.*

Lemma 4. *If the same notations and hypotheses in Lemma 3 hold and if, furthermore, we have $\overline{A}_2 = A_2(x_1^*, 0)$, the disease free equilibrium is globally asymptotically stable if and only if $\alpha(\overline{A}_2) \leq 0$.*

Next, we discuss the global stability of the disease free equilibrium E_0 of the system (1) using the above two Lemmas.

From the system (1), we know

$$
\begin{aligned}
&\frac{d\left(X_s + X_i + X_r\right)}{dt} \\
&\quad = \Lambda_1 - \mu_1\left(X_s + X_i + X_r\right) - \alpha_1 X_i - k_2\alpha_1 X_r \\
&\quad \leq \Lambda_1 - \mu_1\left(X_s + X_i + X_r\right), \\
&\frac{d\left(Y_s + Y_i + Y_r\right)}{dt} \\
&\quad = \Lambda_2 - \mu_2\left(Y_s + Y_i + Y_r\right) - \alpha_2 Y_i - k_4\alpha_2 Y_r \\
&\quad \leq \Lambda_2 - \mu_2\left(Y_s + Y_i + Y_r\right).
\end{aligned}
\tag{23}
$$

This proves that the set

$$
\begin{aligned}
\Omega = \Big\{ &(X_s, X_i, X_r, Y_s, Y_i, Y_r) \in \mathbb{R}_+^5 \mid X_s + X_i + X_r \\
&\leq \frac{\Lambda_1}{\mu_1}, Y_s + Y_i + Y_r \leq \frac{\Lambda_2}{\mu_2} \Big\}
\end{aligned}
\tag{24}
$$

is a compact positively invariant absorbing set contained in the nonnegative orthant. Thus, the system (1) is dissipative on Ω because the trajectories of (1) are forward bounded. Now, we will study the system (1) on Ω.

We set for system (1) $x_1 = (X_s, Y_s)$, $x_2 = (X_i, X_r, Y_i, Y_r)$, and $x_1^* = (\Lambda_1/\mu_1, \Lambda_2/\mu_2)$. As in [23], we express the subsystem as $dx_1/dt = A_1(x_1, 0)(x_1 - x_1^*)$ and

$$
\begin{aligned}
\frac{dX_s}{dt} &= \Lambda_1 - \mu_1 X_s, \\
\frac{dY_s}{dt} &= \Lambda_2 - \mu_2 Y_s.
\end{aligned}
\tag{25}
$$

This is a linear system, and its unique equilibrium $(A_1/\mu_1, A_2/\mu_2)$ (corresponding to the disease free equilibrium of (1)) is globally asymptotically stable, hence the assumptions (h_1) and (h_2) are satisfied.

The matrix $A_2(x)$ is given by

$$
A_2(x) = \begin{pmatrix}
-m_1 & 0 & \beta_1 X_s & 0 \\
\rho\sigma & -m_2 & 0 & k\beta_1 X_s \\
\beta_2 Y_s & 0 & -m_3 & 0 \\
0 & k\beta_2 Y_s & 0 & -m_4
\end{pmatrix}.
\tag{26}
$$

As required by hypothesis h_3, for any $x \in \Omega$, the matrix $A_2(x)$ is irreducible.

Now, let us check (h_4). There is a maximum which is uniquely realized in Ω if $X_s = \Lambda_1/\mu_1$ and $Y_s = \Lambda_2/\mu_2$, which corresponds to the disease free equilibrium. This maximum matrix is then J_2, the subblock of the Jacobian matrix at the disease free equilibrium, corresponding to the matrix $A_2(x)$. The matrix J_2 is given by

$$
J_2 = \begin{pmatrix}
-m_1 & 0 & \beta_1 X_{s0} & 0 \\
\rho\sigma & -m_2 & 0 & k\beta_1 X_{s0} \\
\beta_2 Y_{s0} & 0 & -m_3 & 0 \\
0 & k\beta_2 Y_{s0} & 0 & -m_4
\end{pmatrix}.
\tag{27}
$$

Therefore, we are in the situation of Lemma 4, where the maximum is attained at the disease free equilibrium.

The hypothesis (h_5) requires that $\alpha(J_2) \leq 0$. Writing J_2 as a block matrix $J_2 = \begin{pmatrix} A_{2\times2} & B_{2\times2} \\ C_{2\times2} & D_{2\times2} \end{pmatrix}$. Since A is already a Metzler stable matrix, the condition $\alpha(J_2) \leq 0$ is equivalent to the condition $\alpha(D - CA^{-1}B) \leq 0$ [23], where

$$
D - CA^{-1}B = \begin{pmatrix}
\dfrac{\beta_1\beta_2 X_{s0} Y_{s0}}{m_1} - m_3 & 0 \\
\dfrac{\rho\sigma k\beta_1\beta_2 X_{s0} Y_{s0}}{m_1 m_2} & \dfrac{k^2\beta_1\beta_2 X_{s0} Y_{s0}}{m_2} - m_4
\end{pmatrix}.
\tag{28}
$$

Then,

$$
\begin{aligned}
&\alpha\left(D - CA^{-1}B\right) \\
&\quad = \max\left\{\frac{\beta_1\beta_2 X_{s0} Y_{s0} - m_1 m_3}{m_1}, \frac{k^2\beta_1\beta_2 X_{s0} Y_{s0} - m_2 m_4}{m_2}\right\}.
\end{aligned}
\tag{29}
$$

Hence, the condition $\alpha(D - CA^{-1}B) \leq 0$ is equivalent to $R_0 \leq 1$. We have seen that the hypotheses (h_1), (h_2), (h_3), (h_4), and (h_5) are satisfied. Then, by Lemma 4, we have the following result.

Theorem 5. *The disease free equilibrium E_0 of the system (1) is globally asymptotically stable if $R_0 \leq 1$.*

4. Stability Analysis of the Boundary Equilibria

In this section, we turn to study stability of the two boundary equilibria. From Lemma 1, we know that if $R_{0r} > 1$, there exists a boundary equilibrium with only resistant type E_{0r}. Through calculations, we can obtain the characteristic equation as following:

$$
\begin{aligned}
&\{(\lambda + m_1)(\lambda + m_3) - \beta_1\beta_2 X_{sr}Y_{sr}\} \\
&\quad \times \{(\lambda + m_2)(\lambda + m_4)(\lambda + \mu_1 + k\beta_1 Y_{rr}) \\
&\quad \times (\lambda + \mu_2 + k\beta_2 X_{rr}) \\
&\quad - k^2\beta_1\beta_2 X_{sr}Y_{sr}(\lambda + \mu_1)(\lambda + \mu_2)\} = 0.
\end{aligned} \tag{30}
$$

Hence, the eigenvalue of E_{0r} are roots of the following equations:

$$
\lambda^2 + (m_1 + m_3)\lambda + m_1 m_3 - \beta_1\beta_2 X_{sr}Y_{sr} = 0, \tag{31}
$$

$$
\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0. \tag{32}
$$

Here,

$$
\begin{aligned}
a_1 &= m_2 + m_4 + \frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}} > 0, \\
a_2 &= m_2 m_4 + (m_2 + m_4)\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right) \\
&\quad + \frac{\Lambda_1}{X_{sr}}\frac{\Lambda_2}{Y_{sr}} - k^2\beta_1\beta_2 X_{sr}Y_{sr}, \\
a_3 &= m_2 m_4\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right) + (m_2 + m_4)\frac{\Lambda_1}{X_{sr}}\frac{\Lambda_2}{Y_{sr}} \\
&\quad - k^2\beta_1\beta_2 X_{sr}Y_{sr}(\mu_1 + \mu_2), \\
a_4 &= m_2 m_4\frac{\Lambda_1}{X_{sr}}\frac{\Lambda_2}{Y_{sr}} - k^2\beta_1\beta_2 X_{sr}Y_{sr}\mu_1\mu_2.
\end{aligned} \tag{33}
$$

From (12), we can obtain $X_{sr}Y_{sr} = X_{s0}Y_{s0}/R_{0r}^2 = m_2 m_4/k^2\beta_1\beta_2$. Then,

$$
m_1 m_3 - \beta_1\beta_2 X_{sr}Y_{sr} = m_1 m_3 - \frac{m_2 m_4}{k^2}. \tag{34}
$$

It is easy to see that $R_{0i}^2/R_{0r}^2 = (m_2 m_4/k^2)/m_1 m_3$. Then, $R_{0i} < R_{0r}$ equals to $m_1 m_3 > \beta_1\beta_2 X_{sr}Y_{sr}$, which implies that the roots of (31) have negative real parts if $R_{0i} < R_{0r}$.

Based on $(\Lambda_1/X_{sr})(\Lambda_2/Y_{sr}) = \mu_1\mu_2 R_{0r}^2$ and $k^2\beta_1\beta_2 X_{sr}Y_{sr} = m_2 m_4$, we can obtain

$$
\begin{aligned}
a_2 &= (m_2 + m_4)\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right) + \frac{\Lambda_1}{X_{sr}}\frac{\Lambda_2}{Y_{sr}} > 0, \\
a_3 &= m_2 m_4\left[\frac{k\beta_1\mu_1\Lambda_2\left(R_{0r}^2 - 1\right)}{\mu_1 m_4 R_{0r}^2 + k\beta_1\Lambda_2} + \frac{\mu_1\mu_2 m_4\left(R_{0r}^2 - 1\right)}{\mu_1 m_4 + k\beta_1\Lambda_2}\right] \\
&\quad + (m_2 + m_4)\mu_1\mu_2 R_{0r}^2, \\
a_4 &= m_2 m_4\mu_1\mu_2\left(R_{0r}^2 - 1\right).
\end{aligned} \tag{35}
$$

Here, $a_3 > 0$ and $a_4 > 0$ if $R_{0r} > 1$.

If $R_{0r} > 1$, let $k\beta_1\mu_1\Lambda_2(R_{0r}^2 - 1)/(\mu_1 m_4 R_{0r}^2 + k\beta_1\Lambda_2) = p_1 > 0$ and $\mu_1\mu_2 m_4(R_{0r}^2 - 1)/(\mu_1 m_4 + k\beta_1\Lambda_2) = p_2 > 0$, then $\Lambda_1/X_{sr} = p_1 + \mu_1 > \mu_1$ and $\Lambda_2/Y_{sr} = p_2 + \mu_2 > \mu_2$. Note that $m_2 = \mu_1 + k_1\alpha_1 > \mu_1$ and $m_4 = \mu_2 + k_2\alpha_2 > \mu_2$, then $m_2 + m_4 > \mu_1 + \mu_2$ and $m_2 m_4 > \mu_1\mu_2$. Hence, we can obtain

$$
H_1 = a_1 > 0,
$$

$$
\begin{aligned}
H_2 &= \begin{vmatrix} a_1 & a_3 \\ 1 & a_2 \end{vmatrix} = a_1 a_2 - a_3 \\
&= \left(m_2^2 + m_4^2 + m_2 m_4 + \mu_1\mu_2 R_{0r}^2\right)\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right) \\
&\quad + (m_2 + m_4)\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right)^2 + m_2 m_4(\mu_1 + \mu_2) > 0,
\end{aligned}
$$

$$
\begin{aligned}
H_3 &= \begin{vmatrix} a_1 & a_3 & 0 \\ 1 & a_2 & 0 \\ 0 & a_1 & a_3 \end{vmatrix} = a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 \\
&= (m_2 + m_4)^2 m_2 m_4\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right)^2 \\
&\quad + (m_2 + m_4)^3\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right)\mu_1\mu_2 R_{0r}^2 \\
&\quad + \mu_1\mu_2 R_{0r}^2(m_2 + m_4)m_2 m_4\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right) \\
&\quad + (m_2 + m_4)m_2 m_4\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right)^3 \\
&\quad + (m_2 + m_4)^2\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right)^2\mu_1\mu_2 R_{0r}^2 \\
&\quad + (m_2 + m_4)\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right)\mu_1^2\mu_2^2 R_{0r}^4 \\
&\quad + 2(\mu_1 + \mu_2)m_2^2 m_4^2\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right) \\
&\quad + (m_2 + m_4)\mu_1\mu_2 R_{0r}^2 m_2 m_4(\mu_1 + \mu_2) \\
&\quad + (m_2 + m_4)^2\mu_1\mu_2 m_2 m_4
\end{aligned}
$$

$$+ 2\left(m_2 + m_4\right)\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right)\mu_1\mu_2 m_2 m_4$$

$$+ \left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right)^2 \mu_1\mu_2 m_2 m_4$$

$$- \left(m_2 + m_4\right)^2 m_2 m_4 \left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right)\left(\mu_1 + \mu_2\right)$$

$$- \left(m_2 + m_4\right) m_2 m_4 \left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right)^2 \left(\mu_1 + \mu_2\right)$$

$$- \mu_1\mu_2 R_{0r}^2 \left(\mu_1 + \mu_2\right) m_2 m_4 \left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right)$$

$$- \left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right)^2 m_2^2 m_4^2 - m_2^2 m_4^2 \left(\mu_1 + \mu_2\right)^2$$

$$- 2 m_2 m_4 \left(m_2 + m_4\right)\left(\frac{\Lambda_1}{X_{sr}} + \frac{\Lambda_2}{Y_{sr}}\right)\mu_1\mu_2 R_{0r}^2$$

$$- m_2 m_4 \left(m_2 + m_4\right)^2 \mu_1\mu_2 R_{0r}^2$$

$$> \left(m_2^2 + m_4^2\right)^2 m_2 m_4 \left(p_1^2 + p_2^2 + p_1 p_2 + p_1\mu_1 + p_2\mu_2\right)$$

$$+ m_2^2 m_4^2 \left(p_1^2 + p_2^2 + 2p_1\mu_1 + 2p_2\mu_2\right) > 0,$$

$$H_4 = \begin{vmatrix} a_1 & a_3 & 0 & 0 \\ 1 & a_2 & a_4 & 0 \\ 0 & a_1 & a_3 & 0 \\ 0 & 1 & a_2 & a_4 \end{vmatrix} = a_4 H_3 > 0.$$

$$(36)$$

It follows from Routh-Hurwitz criterion that all roots of (32) have negative real parts if $R_{0r} > 1$. Summering above analyses, we have the following result.

Theorem 6. *The boundary equilibrium E_{0r} of the system (1) is locally asymptotically stable if $R_{0r} > 1$ and $R_{0i} < R_{0r}$.*

Now, we study the global stability of the boundary equilibrium E_{0r}. Consider the Lyapunov function

$$V_1 = d_1 X_i + d_2 Y_i, \tag{37}$$

where $d_1 = (m_3 + \beta_2(\Lambda_2/\mu_2))/m_1 m_3 (R_{0i} + 1)$ and $d_2 = (m_1 + \beta_1(\Lambda_1/\mu_1))/m_1 m_3 (R_{0i} + 1)$. The Lyapunov derivative is

$$\begin{aligned} \frac{dV_1}{dt} &= d_1 \left(\beta_1 X_s Y_i - m_1 X_i\right) + d_2 \left(\beta_2 Y_s X_i - m_3 Y_i\right) \\ &\leq \left(d_1 \beta_1 \frac{\Lambda_1}{\mu_1} - d_2 m_3\right) Y_i + \left(d_2 \beta_2 \frac{\Lambda_2}{\mu_2} - d_1 m_1\right) X_i \\ &\leq \left(R_{0i} - 1\right)\left(Y_i + X_i\right) \\ &\leq 0 \quad \text{for } R_{0i} \leq 1. \end{aligned}$$

$$(38)$$

This implies that the sensitive type dies out if $R_{0i} \leq 1$. Then the largest compact invariant set of the system (1) in the set

$\{dV_1/dt = 0\}$ is $\Omega_1 = (X_s, X_i, X_r, Y_s, Y_i, Y_r) \in \Omega \mid X_i = Y_i = 0$. Using the LaSalle-Lyapunov theorem, we know that all trajectories in Ω eventually tend to Ω_1 as $t \to \infty$. Then, we only need to study the dynamical behavior of (1) in Ω_1. At this time, (1) reduces to the following system

$$\begin{aligned} \frac{dX_s}{dt} &= \Lambda_1 - k\beta_1 X_s Y_r - \mu_1 X_s, \\ \frac{dX_r}{dt} &= k\beta_1 X_s Y_r - m_2 X_r, \\ \frac{dY_s}{dt} &= \Lambda_2 - k\beta_2 Y_s X_r - \mu_2 Y_s, \\ \frac{dY_r}{dt} &= k\beta_2 Y_s X_r - m_4 Y_r. \end{aligned}$$

$$(39)$$

To show that all trajectories of (39) in the interior of Ω_1 approach the point $(X_{sr}, X_{rr}, Y_{sr}, Y_{rr})$ corresponding to the boundary equilibrium E_{0r}, consider the Lyapunov function

$$\begin{aligned} V_2 &= \bar{d}_1 \left\{ \left[X_s - X_{sr} - X_{sr} \ln\left(\frac{X_s}{X_{sr}}\right) \right] \right. \\ &\quad \left. + \left[X_r - X_{rr} - X_{rr} \ln\left(\frac{X_r}{X_{rr}}\right) \right] \right\} \\ &\quad + \bar{d}_2 \left\{ \left[Y_s - Y_{sr} - Y_{sr} \ln\left(\frac{Y_s}{Y_{sr}}\right) \right] \right. \\ &\quad \left. + \left[Y_r - Y_{rr} - Y_{rr} \ln\left(\frac{Y_r}{Y_{rr}}\right) \right] \right\}, \end{aligned}$$

$$(40)$$

where positive constants $\bar{d}_1$ and $\bar{d}_2$ are defined in the following. It is easy to see that $V_2 \geq 0$ for $(X_s, X_r, Y_s, Y_r) \in \Omega_1$, and $V_2 = 0 \Leftrightarrow (X_s, X_r, Y_s, Y_r) = (X_{sr}, X_{rr}, Y_{sr}, Y_{rr})$. Hence, the function V_2 is positive definite with respect to the point $(X_{sr}, X_{rr}, Y_{sr}, Y_{rr})$.

Computing the derivative of V_2 along solutions of system (39), we have

$$\begin{aligned} \frac{dV_2}{dt} &= \bar{d}_1 \left\{ \left[\frac{dX_s}{dt} - \frac{dX_s}{dt}\left(\frac{X_{sr}}{X_s}\right) \right] + \left[\frac{dX_r}{dt} - \frac{dX_r}{dt}\left(\frac{X_{rr}}{X_r}\right) \right] \right\} \\ &\quad + \bar{d}_2 \left\{ \left[\frac{dY_s}{dt} - \frac{dY_s}{dt}\left(\frac{Y_{sr}}{Y_s}\right) \right] + \left[\frac{dY_r}{dt} - \frac{dY_r}{dt}\left(\frac{Y_{rr}}{Y_r}\right) \right] \right\} \\ &= \bar{d}_1 \left[\Lambda_1 - \mu_1 X_s - \frac{X_{sr}}{X_s}\Lambda_1 + k\beta_1 X_{sr} Y_r + \mu_1 X_{sr} \right. \\ &\quad \left. - m_2 X_r - k\beta_1 X_s Y_r \frac{X_{rr}}{X_r} + m_2 X_{rr} \right] \\ &\quad + \bar{d}_2 \left[\Lambda_2 - \mu_2 Y_s - \frac{Y_{sr}}{Y_s}\Lambda_2 + k\beta_2 Y_{sr} X_r + \mu_2 Y_{sr} \right. \\ &\quad \left. - m_4 Y_r - k\beta_2 Y_s X_r \frac{Y_{rr}}{Y_r} + m_4 Y_{rr} \right]. \end{aligned}$$

$$(41)$$

Substituting $\Lambda_1 = k\beta_1 X_{sr}Y_{rr} + \mu_1 X_{sr}$, $\Lambda_2 = k\beta_2 Y_{sr}X_{rr} + \mu_2 Y_{sr}$, $m_2 X_{rr} = k\beta_1 X_{sr}Y_{rr}$ and $m_4 Y_{rr} = k\beta_2 Y_{sr}X_{rr}$ into dV_2/dt, we obtain

$$
\begin{aligned}
\frac{dV_2}{dt} \\
= \bar{d}_1 \Bigg\{ &\mu_1 X_{sr}\left(2 - \frac{X_s}{X_{sr}} - \frac{X_{sr}}{X_s}\right) + (k\beta_1 X_{sr}Y_r - m_2 X_r) \\
&+ \left[2k\beta_1 X_{sr}Y_{rr} - k\beta_1 Y_{rr}\frac{(X_{sr})^2}{X_s} - k\beta_1 X_s Y_r \frac{X_{rr}}{X_r}\right] \Bigg\} \\
+ \bar{d}_2 \Bigg\{ &\mu_2 Y_{sr}\left(2 - \frac{Y_s}{Y_{sr}} - \frac{Y_{sr}}{Y_s}\right) + (k\beta_2 Y_{sr}X_r - m_4 Y_r) \\
&+ \left[2k\beta_2 Y_{sr}X_{rr} - k\beta_2 X_{rr}\frac{(Y_{sr})^2}{Y_s} - k\beta_2 Y_s X_r \frac{Y_{rr}}{Y_r}\right] \Bigg\}.
\end{aligned}
\tag{42}
$$

Let $\bar{d}_1 = k\beta_2 Y_{sr}X_{rr}$ and $\bar{d}_2 = k\beta_1 X_{sr}Y_{rr}$. Following from $m_2 X_{rr} = k\beta_1 X_{sr}Y_{rr}$ and $m_4 Y_{rr} = k\beta_2 Y_{sr}X_{rr}$, we have

$$
\bar{d}_1(k\beta_1 X_{sr}Y_r - m_2 X_r) + \bar{d}_2(k\beta_2 Y_{sr}X_r - m_4 Y_r) = 0. \tag{43}
$$

Hence, for all $(X_s, X_r, Y_s, Y_r) \in \Omega_1$,

$$
\begin{aligned}
\frac{dV_2}{dt} = \bar{d}_1 \Bigg\{ &\mu_1 X_{sr}\left(2 - \frac{X_s}{X_{sr}} - \frac{X_{sr}}{X_s}\right) \\
&+ k\beta_1 X_{sr}Y_{rr}\left[2 - \frac{X_{sr}}{X_s} - \frac{X_s Y_r X_{rr}}{X_{sr}Y_{rr}X_r}\right] \Bigg\} \\
+ \bar{d}_2 \Bigg\{ &\mu_2 Y_{sr}\left(2 - \frac{Y_s}{Y_{sr}} - \frac{Y_{sr}}{Y_s}\right) \\
&+ k\beta_2 Y_{sr}X_{rr}\left[2 - \frac{Y_{sr}}{Y_s} - \frac{Y_s X_r Y_{rr}}{Y_{sr}X_{rr}Y_r}\right] \Bigg\} \\
= \bar{d}_1\mu_1 X_{sr}&\left(2 - \frac{X_s}{X_{sr}} - \frac{X_{sr}}{X_s}\right) + \bar{d}_2\mu_2 Y_{sr}\left(2 - \frac{Y_s}{Y_{sr}} - \frac{Y_{sr}}{Y_s}\right) \\
+ \bar{d}_1\bar{d}_2&\left(4 - \frac{X_{sr}}{X_s} - \frac{X_s Y_r X_{rr}}{X_{sr}Y_{rr}X_r} - \frac{Y_{sr}}{Y_s} - \frac{Y_s X_r Y_{rr}}{Y_{sr}X_{rr}Y_r}\right) \le 0.
\end{aligned}
\tag{44}
$$

It is easy to see that

$$
\frac{dV_2}{dt} = 0 \Longleftrightarrow X_s = X_{sr}, \qquad X_r = aX_{rr}, \\
Y_s = Y_{sr}, \qquad Y_r = aY_{rr},
\tag{45}
$$

where a is an arbitrary positive number. Substituting $X_s = X_{sr}, X_r = aX_{rr}, Y_s = Y_{sr}$, and $Y_r = aY_{rr}$ into the first equation of system (39), we obtain

$$
0 = \Lambda_1 - ak\beta_1 X_{sr}Y_{rr} - \mu_1 X_{sr}, \tag{46}
$$

and then the above formula holds if and only if $a = 1$. Therefore, the only compact invariant subset of the set where

$dV_2/dt = 0$ is the point $(X_{sr}, X_{rr}, Y_{sr}, Y_{rr})$, corresponding to the boundary equilibrium E_{0r}. By LaSalle's Invariance Principle, E_{0r} is globally asymptotically stable if $R_{0r} > 1$ and $R_{0i} \le 1$. Summering above analyses, we have the following result.

Theorem 7. *The boundary equilibrium E_{0r} of the system* (1) *is globally asymptotically stable if $R_{0r} > 1 \ge R_{0i}$.*

Now, we turn to the other boundary equilibrium. From Lemma 1, we know that if $\rho = 0$ and $R_{0i} > 1$, the boundary equilibrium with only sensitive type E_{0i} exists. Through calculations, we can obtain the characteristic equation as following:

$$
\begin{aligned}
\big\{ &(\lambda + m_2)(\lambda + m_4) - k^2\beta_1\beta_2 X_{si}Y_{si}\big\} \\
\times \big\{ &(\lambda + m_1)(\lambda + m_3)(\lambda + \mu_1)(\lambda + \mu_2 + \beta_2 X_{ii}) \\
&+ \beta_1 Y_{ii}(\lambda + m_3)(\lambda + \mu_2 + \beta_2 X_{ii})(\lambda + m_1 - \sigma) \\
&- \beta_1\beta_2 X_{si}Y_{si}(\lambda + \mu_1)(\lambda + \mu_2)\big\} = 0.
\end{aligned}
\tag{47}
$$

Hence, the eigenvalue of E_{0i} are roots of the following equations:

$$
\lambda^2 + (m_2 + m_4)\lambda + m_2 m_4 - k^2\beta_1\beta_2 X_{si}Y_{si} = 0, \tag{48}
$$

$$
\lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4 = 0. \tag{49}
$$

Here,

$$
\begin{aligned}
b_1 =& \; m_1 + m_3 + \mu_1 + \mu_2 + \beta_2 X_{ii} + \beta_1 Y_{ii} > 0, \\
b_2 =& \; \mu_1(m_1 + m_3 + \mu_2 + \beta_2 X_{ii}) + m_1(m_3 + \mu_2 + \beta_2 X_{ii}) \\
&+ m_3(\mu_2 + \beta_2 X_{ii}) + \beta_1 Y_{ii}(m_1 - \sigma + m_3 + \mu_2 + \beta_2 X_{ii}) \\
&- m_1 m_3 \\
=& \; \mu_1(m_1 + m_3 + \mu_2 + \beta_2 X_{ii}) + m_1(\mu_2 + \beta_2 X_{ii}) \\
&+ m_3(\mu_2 + \beta_2 X_{ii}) + \beta_1 Y_{ii}(\mu_1 + \alpha + m_3 + \mu_2 + \beta_2 X_{ii}) \\
>& \; 0, \\
b_3 =& \; \mu_1 m_1(m_3 + \mu_2 + \beta_2 X_{ii}) + m_1 m_3(\mu_2 + \beta_2 X_{ii}) \\
&+ \beta_1 Y_{ii}[m_3(\mu_2 + \beta_2 X_{ii}) + (m_1 - \sigma)(m_3 + \mu_2 + \beta_2 X_{ii})] \\
&- m_1 m_3(\mu_1 + \mu_2) \\
=& \; \mu_1 m_1(\mu_2 + \beta_2 X_{ii}) + m_1 m_3\beta_2 X_{ii} \\
&+ \beta_1 Y_{ii}[m_3(\mu_2 + \beta_2 X_{ii}) + (\mu_1 + \alpha)(m_3 + \mu_2 + \beta_2 X_{ii})] \\
>& \; 0, \\
b_4 =& \; \mu_1 m_1 m_3(\mu_2 + \beta_2 X_{ii}) + \beta_1 Y_{ii}m_3(\mu_2 + \beta_2 X_{ii})(m_1 - \sigma) \\
&- m_1 m_3\mu_1\mu_2 \\
=& \; \mu_1 m_1 m_3\beta_2 X_{ii} + \beta_1 Y_{ii}m_3(\mu_2 + \beta_2 X_{ii})(\mu_1 + \alpha) > 0.
\end{aligned}
\tag{50}
$$

From (13), we can obtain that $\beta_1\beta_2 X_{si}Y_{si} = m_2m_4$. Then, it is easy to see that the roots of (48) have negative real parts if $R_{0i} > R_{0r}$. Similarly to the case of E_{0r}, using Routh-Hurtwiz criterion, we can obtain that all roots of (49) have negative real parts if $R_{0i} > 1$. Summering above analysis, we have the following result.

Theorem 8. *When* $\rho = 0$*, the boundary equilibrium* E_{0i} *of the system* (1) *is locally asymptotically stable if* $R_{0i} > 1$ *and* $R_{0i} > R_{0r}$.

Now, we study the global stability of the boundary equilibrium E_{0i}. Consider the Lyapunov function

$$L_1 = l_1 X_r + l_2 Y_r, \tag{51}$$

where $l_1 = (m_4 + k\beta_2(\Lambda_2/\mu_2))/m_2m_4(R_{0r} + 1)$ and $l_2 = (m_2 + k\beta_1(\Lambda_1/\mu_1))/m_2m_4(R_{0r} + 1)$. The Lyapunov derivative is

$$\begin{aligned}
\frac{dL_1}{dt} &= l_1\left(k\beta_1 X_s Y_r - m_2 X_r\right) + l_2\left(k\beta_2 Y_s X_r - m_3 Y_r\right) \\
&\leq \left(l_1 k\beta_1\frac{\Lambda_1}{\mu_1} - l_2 m_4\right)Y_r + \left(l_2 k\beta_2\frac{\Lambda_2}{\mu_2} - l_1 m_2\right)X_r \\
&\leq (R_{0r} - 1)(Y_r + X_r) \\
&\leq 0 \quad \text{for } R_{0r} \leq 1.
\end{aligned} \tag{52}$$

This implies that the resistant type dies out if $R_{0r} \leq 1$. Then, the largest compact invariant set of the system (1) in the set $\{dL_1/dt = 0\}$ is $\Omega_2 = \{(X_s, X_i, X_r, Y_s, Y_i, Y_r) \in \Omega \mid X_r = Y_r = 0\}$. Using the LaSalle-Lyapunov theorem, we know that all trajectories in Ω eventually tend to Ω_2 as $t \to \infty$. Then, we only need to study the dynamical behavior of (1) in Ω_2. At this time, (1) reduces to the following system:

$$\begin{aligned}
\frac{dX_s}{dt} &= \Lambda_1 - \beta_1 X_s Y_i - \mu_1 X_s + \sigma X_i, \\
\frac{dX_i}{dt} &= \beta_1 X_s Y_i - m_1 X_i, \\
\frac{dY_s}{dt} &= \Lambda_2 - \beta_2 Y_s X_i - \mu_2 Y_s, \\
\frac{dY_i}{dt} &= \beta_2 Y_s X_i - m_3 Y_i.
\end{aligned} \tag{53}$$

To show that all trajectories of (53) in the interior of Ω_2 approach the point $(X_{si}, X_{ii}, Y_{si}, Y_{ii})$ corresponding to the boundary equilibrium E_{0i}, consider the Lyapunov function

$$\begin{aligned}
L_2 = \bar{l}_1 &\left\{\left[X_s - X_{si} - X_{si}\ln\left(\frac{X_s}{X_{si}}\right)\right] \right. \\
&\left. + \left[X_i - X_{ii} - X_{ii}\ln\left(\frac{X_i}{X_{ii}}\right)\right]\right\} \\
+ \bar{l}_2 &\left\{\left[Y_s - Y_{si} - Y_{si}\ln\left(\frac{Y_s}{Y_{si}}\right)\right]\right. \\
&\left. + \left[Y_i - Y_{ii} - Y_{ii}\ln\left(\frac{Y_i}{Y_{ii}}\right)\right]\right\},
\end{aligned} \tag{54}$$

where positive constants $\bar{l}_1$ and $\bar{l}_2$ are defined in the following. It is easy to see that $L_2 \geq 0$ for $(X_s, X_i, Y_s, Y_i) \in \Omega_1$ and $L_2 = 0 \Leftrightarrow (X_s, X_i, Y_s, Y_i) = (X_{si}, X_{ii}, Y_{si}, Y_{ii})$. Hence, the function L_2 is positive definite with respect to the point $(X_{si}, X_{ii}, Y_{si}, Y_{ii})$.

Computing the derivative of L_2 along solutions of system (39), we have

$$\begin{aligned}
\frac{dL_2}{dt} &= \bar{l}_1\left\{\left[\frac{dX_s}{dt} - \frac{dX_s}{dt}\left(\frac{X_{si}}{X_s}\right)\right] + \left[\frac{dX_i}{dt} - \frac{dX_i}{dt}\left(\frac{X_{ii}}{X_i}\right)\right]\right\} \\
&\quad + \bar{l}_2\left\{\left[\frac{dY_s}{dt} - \frac{dY_s}{dt}\left(\frac{Y_{si}}{Y_s}\right)\right] + \left[\frac{dY_i}{dt} - \frac{dY_i}{dt}\left(\frac{Y_{ii}}{Y_i}\right)\right]\right\} \\
&= \bar{l}_1\left[\Lambda_1 - \mu_1 X_s - \frac{X_{si}}{X_s}\Lambda_1 + \beta_1 X_{si}Y_i + \mu_1 X_{si} - m_1 X_i \right. \\
&\qquad \left. - \beta_1 X_s Y_i\frac{X_{ii}}{X_r} + m_1 X_{ii} + \sigma X_i\left(1 - \frac{X_{si}}{X_s}\right)\right] \\
&\quad + \bar{l}_2\left[\Lambda_2 - \mu_2 Y_s - \frac{Y_{si}}{Y_s}\Lambda_2 + \beta_2 Y_{si}X_i + \mu_2 Y_{si} - m_3 Y_i \right. \\
&\qquad \left. - \beta_2 Y_s X_i\frac{Y_{ii}}{Y_i} + m_3 Y_{ii}\right].
\end{aligned} \tag{55}$$

Substituting $\Lambda_1 = \beta_1 X_{si}Y_{ii} + \mu_1 X_{si} - \sigma X_{ii}$, $\Lambda_2 = \beta_2 Y_{si}X_{ii} + \mu_2 Y_{si}$, $m_1 X_{ii} = \beta_1 X_{si}Y_{ii}$, and $m_3 Y_{ii} = \beta_2 Y_{si}X_{ii}$ into dL_2/dt, we obtain

$$\begin{aligned}
\frac{dL_2}{dt} &= \bar{l}_1\left\{\mu_1 X_{si}\left(2 - \frac{X_s}{X_{si}} - \frac{X_{si}}{X_s}\right) + (\beta_1 X_{si}Y_i - m_1 X_i) \right. \\
&\qquad + \sigma(X_i - X_{ii})\left(1 - \frac{X_{si}}{X_s}\right) \\
&\qquad \left. + \left[2\beta_1 X_{si}Y_{ii} - \beta_1 Y_{ii}\frac{(X_{si})^2}{X_s} - \beta_1 X_s Y_i\frac{X_{ii}}{X_i}\right]\right\} \\
&\quad + \bar{l}_2\left\{\mu_2 Y_{si}\left(2 - \frac{Y_s}{Y_{si}} - \frac{Y_{si}}{Y_s}\right) + (\beta_2 Y_{si}X_i - m_3 Y_i) \right. \\
&\qquad \left. + \left[2\beta_2 Y_{si}X_{ii} - \beta_2 X_{ii}\frac{(Y_{si})^2}{Y_s} - \beta_2 Y_s X_i\frac{Y_{ii}}{Y_i}\right]\right\}.
\end{aligned} \tag{56}$$

Note that for the limiting system $X_s + X_i = X_{si} + X_{ii} = \Lambda_1/\mu_1$, then $(X_i - X_{ii})(X_s - X_{si}) \leq 0$. Let $\bar{l}_1 = \beta_2 Y_{si}X_{ii}$ and $\bar{l}_2 = \beta_1 X_{si}Y_{ii}$. Following from $m_1 X_{ii} = \beta_1 X_{si}Y_{ii}$ and $m_3 Y_{ii} = \beta_2 Y_{si}X_{ii}$, we have

$$\bar{l}_1(\beta_1 X_{si}Y_i - m_1 X_i) + \bar{l}_2(\beta_2 Y_{si}X_i - m_3 Y_i) = 0. \tag{57}$$

Hence, for all $(X_s, X_i, Y_s, Y_i) \in \Omega_2$,

$$\frac{dL_2}{dt} \leq \bar{l}_1 \left\{ \mu_1 X_{si} \left(2 - \frac{X_s}{X_{si}} - \frac{X_{si}}{X_s} \right) \right.$$

$$\left. + \beta_1 X_{si} Y_{ii} \left[2 - \frac{X_{si}}{X_s} - \frac{X_s Y_i X_{ii}}{X_{si} Y_{ii} X_i} \right] \right\}$$

$$+ \bar{l}_2 \left\{ \mu_2 Y_{si} \left(2 - \frac{Y_s}{Y_{si}} - \frac{Y_{si}}{Y_s} \right) \right.$$

$$\left. + \beta_2 Y_{si} X_{ii} \left[2 - \frac{Y_{si}}{Y_s} - \frac{Y_s X_i Y_{ii}}{Y_{si} X_{ii} Y_i} \right] \right\}$$

$$\leq \bar{l}_1 \mu_1 X_{si} \left(2 - \frac{X_s}{X_{si}} - \frac{X_{si}}{X_s} \right) + \bar{l}_2 \mu_2 Y_{si} \left(2 - \frac{Y_s}{Y_{si}} - \frac{Y_{si}}{Y_s} \right)$$

$$+ \bar{l}_1 \bar{l}_2 \left(4 - \frac{X_{si}}{X_s} - \frac{X_s Y_i X_{ii}}{X_{si} Y_{ii} X_i} - \frac{Y_{si}}{Y_s} - \frac{Y_s X_i Y_{ii}}{Y_{si} X_{ii} Y_i} \right) \leq 0. \tag{58}$$

It is easy to see that

$$\frac{dL_2}{dt} = 0 \Longleftrightarrow X_s = X_{si}, \qquad X_i = X_{ii},$$
$$Y_s = Y_{si}, \qquad Y_i = Y_{ii}. \tag{59}$$

Therefore, the only compact invariant subset of the set where $dL_2/dt = 0$ is the point $(X_{si}, X_{ii}, Y_{si}, Y_{ii})$, corresponding to the boundary equilibrium E_{0i}. By LaSalle's Invariance Principle, E_{0i} is globally asymptotically stable if $R_{0i} > 1$ and $R_{0r} \leq 1$. Summering above analysis, we have the following result.

Theorem 9. *When $\rho = 0$, the boundary equilibrium E_{0i} of the system (1) is globally asymptotically stable if $R_{0i} > 1 \geq R_{0r}$.*

5. Stability Analysis of the Coexistence Equilibrium

In this section, we turn to study the local stability of the coexistence equilibrium E_c in the limiting system of (1) by using Krasnoselskii sublinearity trick [24], as in [25, 26]. In detail, if $x' = f(x)$ is a system of differential equations and x^* is an equilibrium point, then to prove the local asymptotical stability of x^* is to prove that the linearized equation $Z' = f'(x^*)Z$ has no solutions of the form

$$Z(t) = Z_0 e^{\omega t}, \tag{60}$$

with $Z_0 \in C^n$, $\omega \in C$ and, $\text{Re}\,\omega \geq 0$. This implies that the eigenvalues of the characteristic polynomial associated with the linearized equations have negative real part, that is, $\text{Re}\,\omega < 0$. Then, the coexistence equilibrium E_c is locally asymptotically stable.

Considering the limiting system

$$\frac{dX_i}{dt} = \beta_1 (N_1 - X_i - X_r) Y_i - m_1 X_i,$$

$$\frac{dX_r}{dt} = k\beta_1 (N_1 - X_i - X_r) Y_r + \rho\sigma X_i - m_2 X_r,$$

$$\frac{dY_i}{dt} = \beta_2 (N_2 - Y_i - Y_r) X_i - m_3 Y_i,$$

$$\frac{dY_r}{dt} = k\beta_2 (N_2 - Y_i - Y_r) X_r - m_4 Y_r, \tag{61}$$

where $N_1 = \Lambda_1/\mu_1$ and $N_2 = \Lambda_2/\mu_2$. In this way, let $Z_0 = (Z_1, Z_2, Z_3, Z_4)$, $Z_i \in C$. Substituting a solution of the form (60) into the linearized system (61) of the coexistence equilibrium E_c, we obtain the following linear equations:

$$\omega Z_1 = -(\beta_1 Y_{ic} + m_1) Z_1 - \beta_1 Y_{ic} Z_2$$
$$+ \beta_1 (N_1 - X_{ic} - X_{rc}) Z_3,$$

$$\omega Z_2 = (\rho\sigma - k\beta_1 Y_{rc}) Z_1 - (k\beta_1 Y_{rc} + m_2) Z_2$$
$$+ k\beta_1 (N_1 - X_{ic} - X_{rc}) Z_4,$$

$$\omega Z_3 = \beta_2 (N_2 - Y_{ic} - Y_{rc}) Z_1 - (\beta_2 X_{ic} + m_3) - \beta_2 X_{ic} Z_4,$$

$$\omega Z_4 = k\beta_2 (N_2 - Y_{ic} - Y_{rc}) Z_2 - k\beta_2 X_{rc} Z_3$$
$$- (k\beta_2 X_{rc} + m_4) Z_4, \tag{62}$$

which is equivalent to the system

$$\left[1 + \frac{1}{m_1} (\omega + \beta_1 Y_{ic}) \right] Z_1 = -\frac{\beta_1 Y_{ic}}{m_1} Z_2$$
$$+ \frac{\beta_1 (N_1 - X_{ic} - X_{rc})}{m_1} Z_3,$$

$$\left[1 + \frac{1}{m_2} (\omega + k\beta_1 Y_{rc}) \right] Z_2 = \frac{(\rho\sigma - k\beta_1 Y_{rc})}{m_2} Z_1$$
$$+ \frac{k\beta_1 (N_1 - X_{ic} - X_{rc})}{m_2} Z_4,$$

$$\left[1 + \frac{1}{m_3} (\omega + \beta_2 X_{ic}) \right] Z_3 = \frac{\beta_2 (N_2 - Y_{ic} - Y_{rc})}{m_3} Z_1$$
$$- \frac{\beta_2 X_{ic}}{m_3} Z_4,$$

$$\left[1 + \frac{1}{m_4} (\omega + k\beta_2 X_{rc}) \right] Z_4 = \frac{k\beta_2 (N_2 - Y_{ic} - Y_{rc})}{m_4} Z_2$$
$$- \frac{k\beta_2 X_{rc}}{m_4} Z_3. \tag{63}$$

Moving all the negative terms to the left-hand side, after some manipulations we obtain the system

$$[1 + F_1(\omega)] Z_1 + [1 + F_2(\omega)] Z_2 = (HZ)_1 + (HZ)_2,$$
$$[1 + F_3(\omega)] Z_3 + [1 + F_4(\omega)] Z_4 = (HZ)_3 + (HZ)_4,$$
(64)

where

$$F_1(\omega) = \frac{\omega + \beta_1 Y_{ic}}{m_1} + \frac{k\beta_1 Y_{rc}}{m_2},$$

$$F_2(\omega) = \frac{\omega + k\beta_1 Y_{rc}}{m_2} + \frac{\beta_1 Y_{ic}}{m_1},$$

$$F_3(\omega) = \frac{\omega + \beta_2 X_{ic}}{m_3} + \frac{k\beta_2 X_{rc}}{m_4},$$

$$F_4(\omega) = \frac{\omega + k\beta_2 X_{rc}}{m_4} + \frac{\beta_2 X_{ic}}{m_3},$$

$$H = \begin{pmatrix} 0 & 0 & \frac{\beta_1(N_1 - X_{ic} - X_{rc})}{m_1} & 0 \\ \frac{\rho\sigma}{m_2} & 0 & 0 & k\beta_1(N_1 - X_{ic} - X_{rc}) \\ \frac{\beta_2(N_2 - Y_{ic} - Y_{rc})}{m_3} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{k\beta_2(N_2 - Y_{ic} - Y_{rc})}{m_4} \end{pmatrix}.$$
(65)

Note that the matrix H has nonnegative entries, and $E_c = (X_{ic}, X_{rc}, Y_{ic}, Y_{rc})$ satisfies

$$E_c = HE_c.$$
(66)

To show that $\operatorname{Re}\omega < 0$, we distinguish two cases: $\omega = 0$ and $\omega \neq 0$. In the first case, (62) is a homogeneous linear system. Through calculations, we have the determinant of (62) is

$$\Delta = \begin{vmatrix} -(\beta_1 Y_{ic} + m_1) & -\beta_1 Y_{ic} & \beta_1 X_{sc} & 0 \\ \rho\sigma - k\beta_1 Y_{rc} & -(k\beta_1 Y_{rc} + m_2) & 0 & k\beta_1 X_{sc} \\ \beta_2 Y_{sc} & 0 & -(\beta_2 X_{ic} + m_3) & -\beta_2 X_{ic} \\ 0 & k\beta_2 Y_{sc} & -k\beta_2 X_{rc} & -(k\beta_2 X_{rc} + m_4) \end{vmatrix}$$
$$= -(\beta_1 Y_{ic} + m_1) A_1 + \beta_1 Y_{ic} A_2 + \beta_1 X_{sc} A_3,$$
(67)

where

$$A_1 = m_1 m_3 k^2 \beta_2 X_{ic} + m_1 m_3^2 k^2 - m_4 k\beta_1\beta_2 X_{ic} Y_{rc}$$
$$- m_3 k^2 \beta_1\beta_2 X_{rc} Y_{rc} - m_3 m_4 k\beta_1 Y_{rc} - m_2 m_4\beta_2 X_{ic}$$
$$- m_2 m_3 k\beta_2 X_{rc} - m_2 m_3 m_4,$$

$$A_2 = \rho\sigma(m_3 k\beta_2 X_{rc} + m_4\beta_2 X_{ic} + m_3 m_4) - m_4 k\beta_1\beta_2 X_{ic} Y_{rc}$$
$$- m_3 k^2 \beta_1\beta_2 X_{rc} Y_{rc} - m_3 m_4 k\beta_1 Y_{rc} - m_1 m_3 k^2\beta_2 X_{rc},$$

$$A_3 = k^2 \beta_1\beta_2^2 X_{sc} Y_{sc}^2 + \rho\sigma k\beta_2^2 X_{ic} Y_{sc} - k^2\beta_1\beta_2^2 X_{ic} Y_{rc} Y_{sc}$$
$$- \beta_2 Y_{sc}(k^2\beta_1\beta_2 X_{rc} Y_{rc} + m_4 k\beta_1 Y_{rc}$$
$$+ m_2 k\beta_2 X_{rc} + m_2 m_4).$$
(68)

Then, we can obtain

$$\Delta = \rho\sigma(m_3 k\beta_1\beta_2 X_{rc} Y_{ic} + m_4\beta_1\beta_2 X_{ic} Y_{ic}$$
$$+ m_3 m_4\beta_1 Y_{ic} + m_1 m_3 k\beta_2 X_{ic})$$
$$+ (\beta_1\beta_2 X_{ic} Y_{ic} + m_1\beta_2 X_{ic} + m_3\beta_2 Y_{ic})$$
$$\times (m_2 m_4 - m_1 m_3 k^2) + \beta_1\beta_2 X_{rc} Y_{ic} m_3 k(m_2 - m_1 k)$$
$$+ \beta_1\beta_2 X_{ic} Y_{rc} m_1 k(m_4 - m_3 k).$$
(69)

Note that the coexistence equilibrium E_c exists under the condition $R_{0i} > R_{0r}$, that is, $m_2 m_4 > m_1 m_3 k^2$. Then $\Delta > 0$ if $m_2 - m_1 k \geq 0$ and $m_4 - m_3 k \geq 0$. Hence, for the case that $\omega = 0$, (62) has only the trivial solution if $m_2 - m_1 k \geq 0$ and $m_4 - m_3 k \geq 0$. This implies that $\omega \neq 0$.

Now assume that $\omega \neq 0$ and $\operatorname{Re}\omega \geq 0$. Let $F(\omega) = \min\{|1 + F_i(\omega)|, i = 1, 2, 3, 4\}$. It is easy to prove that $|1 + F_i(\omega)| > 1$ for all i, and therefore $F(\omega) > 1$. In the other hand, since the coordinates of E_c are positive, if $\overline{Z}$ is any solution of (64), then there exists a minimal positive real number s such that

$$|\overline{Z}| \leq sE_c,$$
(70)

where $|\overline{Z}| = (|Z_1|, |Z_2|, |Z_3|, |Z_4|)$, and $|\cdot|$ is the norm in C. Note that s is also the minimal positive real number such that

$$|Z_1| + |Z_2| \leq s(X_{ic} + X_{rc}), \qquad |Z_3| + |Z_4| \leq s(Y_{ic} + Y_{rc}).$$
(71)

Taking norms on both side of (64) and using (66), (71), and the fact that H is nonnegative, we obtain

$$F(\omega)(|Z_1| + |Z_2|) \leq H(|Z|)_1 + H(|Z|)_2 \leq s(X_{ic} + X_{rc}),$$
(72)

that is,

$$|Z_1| + |Z_2| \leq \frac{s}{F(\omega)}(X_{ic} + X_{rc}) < s(X_{ic} + X_{rc}),$$
(73)

which contradicts the minimality of s. Hence, $\operatorname{Re}\omega < 0$.

Summering above analysis, we have the following result.

Theorem 10. *When $\rho \neq 0$, the coexistence equilibrium E_c of the system* (1) *is locally asymptotically stable if $k \leq \min\{m_2/m_1, m_4/m_3\}$ and $R_{0i} > 1$.*

The existence and stability of equilibria can be summered in Table 1.

6. Discussion

In this paper we established a new schistosomiasis model. In contrast to previous schistosomiasis models with drug resistance, the model established in this study consider many aspects. First, snail is considered as a variable in the model since the resistance of schistosoma to PZQ can be expressed in snails [14–16]. Second, previous models considered that

Table 1: Existence and stability of equilibria. The sign "∃ !" means the existence and uniqueness. LAS means locally asymptotically stable, and GAS means globally asymptotically stable.

	$\rho = 0$		$\rho \neq 0$	
	Existence	Stability	Existence	Stability
E_0	∃ !	If $R_0 < 1$, LAS; If $R_0 \leq 1$, GAS	∃ !	If $R_0 < 1$, LAS; If $R_0 \leq 1$, GAS
E_{0i}	If $R_{0i} > 1$, ∃ !	If $R_{0i} > 1$ and $R_{0i} > R_{0r}$, LAS; If $R_{0i} > 1 \geq R_{0r}$, GAS	Not exist	/
E_{0r}	If $R_{0r} > 1$, ∃ !	If $R_{0r} > 1$ and $R_{0r} > R_{0i}$, LAS; If $R_{0r} > 1 \geq R_{0i}$, GAS	If $R_{0r} > 1$, ∃ !	If $R_{0r} > 1$ and $R_{0r} > R_{0i}$, LAS; If $R_{0r} > 1 \geq R_{0i}$, GAS
E_c	If $R_{0i} = R_{0r} > 1$, a line	/	If $R_{0i} > 1$ and $R_{0i} > R_{0r}$, ∃ !	If $R_{0i} > 1$ and $k \leq \min\{m_2/m_1, m_4/m_3\}$, LAS

resistance was caused by drug treatment, while a large number of the literature show that some cases are due to inheritance [1, 3, 4]. Therefore, in this study, we consider the reasons for resistance are drug treatment and genetic. Last, in previous models a resistance level (θ) was used to discount the treatment rate. But the resistance level could not be measured, and its value was assumed. This model consider what percentage of infected human after treatment will recover and what percentage will emerge drug resistance. In medicine, from the occurrence of cases the value of this ratio can be identified. For example, this ratio was given in [27, 28] ($1 - \rho = 0.28 \sim 0.609$). Therefore, it is easy to operate. In addition, we separate the discussion of the case that treatment will cause resistance ($\rho \neq 0$) and treatment will not cause resistance ($\rho = 0$).

The reproductive number R_{0i} and R_{0r} of the sensitive and resistant strains are given, respectively. It is easy to see that R_{0i} is a decreasing function of σ, and R_{0r} is an increasing function of k. If the basic reproductive number $R_0 = \max\{R_{0i}, R_{0r}\}$ of the model (1) is less than 1, one can prove the stability of the disease free equilibrium. This means that the spread of schistosomiasis can be effectively controlled. When the basic reproductive number R_0 is greater than 1, we first consider the case that $\rho = 0$. If $R_{0i} = R_{0r} > 1$, the two strains can coexist. There is a line of coexistence equilibria in this case. The infected human will evolve to one of them with higher reproductive number (see Table 1).

When drug treatment can not cause resistance ($\rho = 0$), that is, the new resistant strain is due to the inheritance of resistance, the sensitive strain will dominate if the treatment rate is smaller and the impact of the inheritance of resistance is smaller such that $R_{0i} > 1 \geq R_{0r}$. This result accords to the results of previous models. On the other hand, if the treatment rate and the impact of the inheritance of resistance are both larger such that $R_{0r} > 1 \geq R_{0i}$, the resistant strain will dominate. This shows that although the assumption is that drug treatment does not result in the emergence of drug resistance, once the treatment rate is greater than a value, and the impact of genetic resistance is larger, there will still be the emergence of resistant strain, and the resistant strain is dominant. This further shows that genetic resistance has a great impact on the system.

When drug treatment can cause resistance ($\rho \neq 0$), we can show that the sensitive strain either does not appear or coexist with the resistant strain under certain condition. If $R_{0r} > 1$, there is only resistant strain. It can be seen that, regardless of whether drug treatment leads to the emergence of resistance, once the impact of genetic resistance is larger, resistant strain will be dominant, which is detrimental to the control of schistosomiasis.

Finally, from the formula of the coexistence equilibrium E_c, it is easy to see that the value of the resistant strain is increased with the value of ρ. This means once the proportion of human with drug-resistant strain produced by drug treatment is larger, the number of human and snails with resistant strain is larger. This is not a good result for drug treatment with praziquantel.

Hence, for poor treatment, there are two possible reasons: drug therapy and genetic. An important priority in developing new control strategies is to search new drug targets, in combination with selection of genetic methods such as that viable vaccine candidates. And there is already a need for alternative drugs to treat PZQ-resistant schistosomiasis, such as already exists in northern Senegal [10].
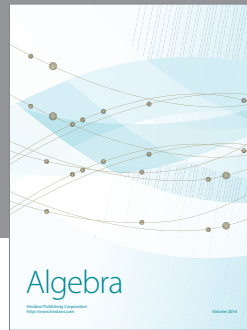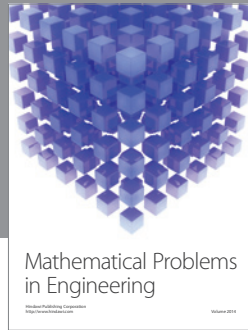
Acknowledgments

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