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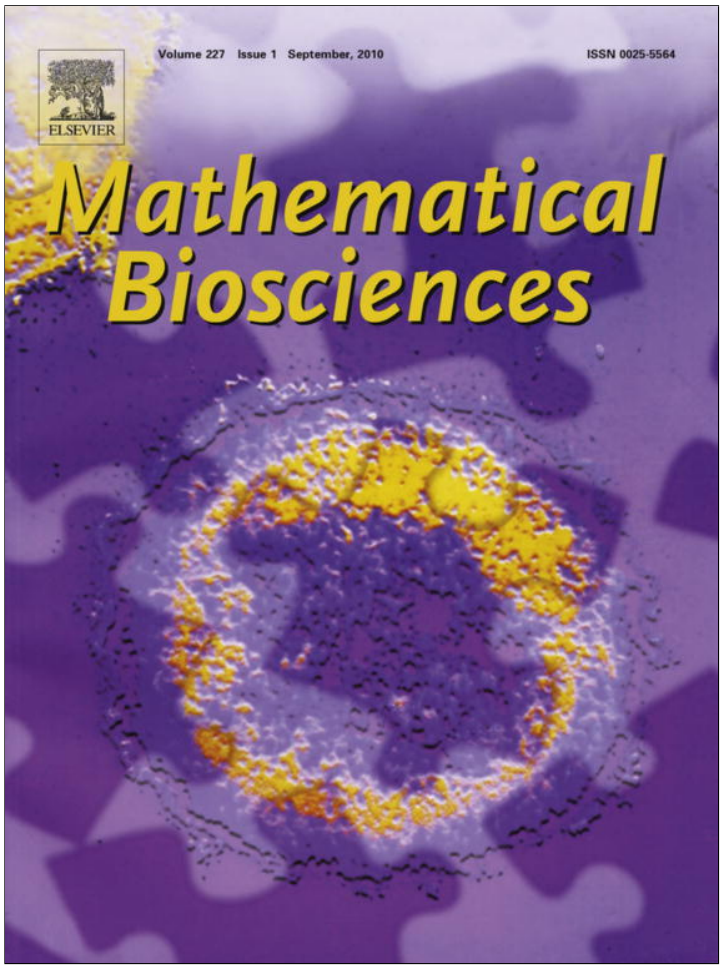

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Mathematical Biosciences 227 (2010) 56–67

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Qualitative analysis of models with different treatment protocols to prevent antibiotic resistance

Hong-Rui Sun [a,1], Xinxin Lu [b,2], Shigui Ruan [c,*,3]

[a] School of Mathematics and Statistics, Lanzhou University, Lanzhou, Gansu 730000, China
[b] Department of Clinical Laboratory, Beijing Tongren Hospital, Capital Medical University, Beijing 100041, China
[c] Department of Mathematics, University of Miami, P.O. Box 249085, Coral Gables, FL 33124-4250, USA

ARTICLE INFO

Article history:
Received 20 July 2009
Received in revised form 11 June 2010
Accepted 16 June 2010
Available online 25 June 2010

Keywords:
Antibiotic resistance
Mathematical model
Basic reproduction number
Equilibrium
Stability

ABSTRACT

This paper is concerned with the qualitative analysis of two models [S. Bonhoeffer, M. Lipsitch, B.R. Levin, Evaluating treatment protocols to prevent antibiotic resistance, Proc. Natl. Acad. Sci. USA 94 (1997) 12106] for different treatment protocols to prevent antibiotic resistance. Detailed qualitative analysis about the local or global stability of the equilibria of both models is carried out in term of the basic reproduction number R_0. For the model with a single antibiotic therapy, we show that if $R_0 < 1$, then the disease-free equilibrium is globally asymptotically stable; if $R_0 > 1$, then the disease-endemic equilibrium is globally asymptotically stable. For the model with multiple antibiotic therapies, stabilities of various equilibria are analyzed and combining treatment is shown better than cycling treatment. Numerical simulations are performed to show that the dynamical properties depend intimately upon the parameters.
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1. Introduction

Infections caused by antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant *enterococci* (VRE), are increasing rapidly throughout the world and pose a serious threat to public health [19,15,21]. The transmission dynamics of antibiotic-resistant bacteria in hospitals are complex which involve the patients, health-care workers, and their interactions. Antibiotic exposure is crucial to the emergence and spread of these resistant bacteria [12]. Compared to infections caused by antimicrobial-susceptible bacteria, infections with antimicrobial-resistant bacteria cause higher mortality rates, longer hospital stays and greater hospital costs [14]. It was estimated that in 2005 the deaths in patients with invasive methicillin-resistant *S. aureus* in the United Sates exceeded the total number of deaths due to HIV/AIDS in the same year [17].

Recently, mathematical models have been extensively used to simulate the spread of the antibiotic-resistant bacteria, to identify various factors responsible for the prevalence of the antibiotic-resistant bacteria, to examine different antibiotic treatments, and to help design effective control programs [2–7,12,24]. We refer to the survey papers of Grundmann and Hellriegel [16] and Temime et al. [23] for more details and references on this topic.

To generate predictions concerning the effects of various patterns of antibiotic treatment at the population level, Bonhoeffer et al. [6] proposed two mathematical models. In the first model, patients with bacterial infections may be treated with a single antibiotic. The model consists of three ordinary differential equations:

$$\begin{cases} \frac{dx}{dt} = \Lambda - dx - bx(y_w + y_r) + r_w y_w + r_r y_r + fh(1-s)y_w, \\ \frac{dy_w}{dt} = (bx - c - r_w - fh)y_w, \\ \frac{dy_r}{dt} = (bx - c - r_r)y_r + fhsy_w, \end{cases} \tag{1.1}$$

where $x(t)$, $y_w(t)$, and $y_r(t)$ denote the density of uninfected patients, infected by sensitive (wild type) bacteria to the treating antibiotic, and infected by resistant bacteria to the treating antibiotic at time t, respectively. We refer to Fig. 1A in [6] for a chart diagram for the three compartment model. Λ is the recruitment rate of the population, d is the per capita removal rate from the population, b is the transmission rate parameter, c is the death rate of the infected host, which includes natural and disease-associated mortality. r_w and r_r are the rates of patients infected with wild type and resistant bacteria recover from the infection in the absence of treatment. Patients infected with wild type bacteria are removed from the wild type infected compartment at a rate fh, where f is a scaling parameter (between 0 and 1) reflecting the fraction of patients treated and h is the maximum rate when all patients are treated. A fraction s of treated wt-infected develops resistance during treatment.

* Corresponding author.
E-mail address: ruan@math.miami.edu (S. Ruan).
[1] Research was supported by NSFC (10801065) and NSF of Gansu Province of China (0803RJZA096).
[2] Research was partially supported by NSFC (30970126).
[3] Research was partially supported by NIH (R01GM083607).

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doi:10.1016/j.mbs.2010.06.002

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Bonhoeffer et al. [6] considered treatment with a single antibiotic and resistance to that antibiotic and analyzed the model to predict the consequences of different usage patterns.

In the second model, two antibiotics A and B are used. The model takes the following form:

$$\begin{cases} \frac{dx}{dt} = \Lambda - dx - bx(y_w + y_a + y_b + y_{ab}) + r_w y_w + r_a y_a + r_b y_b + r_{ab} y_{ab} \\ \quad +h(1-q)f_{ab}y_w + h(1-s)((f_a+f_b)y_w + f_a y_b + f_b y_a + f_{ab}(y_a+y_b)), \\ \frac{dy_w}{dt} = (bx - c - r_w - h(f_a+f_b+f_{ab}))y_w, \\ \frac{dy_a}{dt} = (bx - c - r_a - h(f_b+f_{ab}))y_a + hsf_a y_w, \\ \frac{dy_b}{dt} = (bx - c - r_b - h(f_a+f_{ab}))y_b + hsf_b y_w, \\ \frac{dy_{ab}}{dt} = (bx - c - r_{ab})y_{ab} + hs(f_{ab}(y_a+y_b) + f_a y_b + f_b y_a) + qhf_{ab}y_w, \end{cases} \tag{1.2}$$

where the variables are $x(t)$ for the susceptible, $y_w(t)$, $y_a(t)$, $y_b(t)$ and $y_{ab}(t)$ for patients infected with wild type (wt), A-resistant (A-res), B-resistant (B-res), and AB-resistant (AB-res) bacteria, respectively (see Fig. 1B in [6] for a chart diagram for the model). Λ is the recruitment rate of the population, d is the per capita removal rate from the population, b is the transmission rate parameter, c is the death rate of the infected host, which includes natural and disease-associated mortality. r_w, r_a, r_b and r_{ab} are the recovery rates of wt, A-res, B-res and AB-res infected, respectively; f_a, f_b and f_{ab} reflect the fraction of patients treated with antibiotic A, B, or AB, they fulfill the relation $0 \leqslant f_a, f_b, f_{ab} \leqslant 1$, and $f_a + f_b + f_{ab} \leqslant 1$. h is the maximum rate when all patients are treated. A fraction s or q of treated wt-infected develop resistance with single antibiotic treatment or two antibiotics treatment. Bonhoeffer et al. [6] analyzed the population-level consequences of different usage patterns of the two antibiotics and made various conclusions based on numerical analysis of their models. In this paper we provide detailed qualitative analysis of the two mathematical models (1.1) and (1.2), including the existence and stability of all possible equilibria, and numerical simulations to support these conclusions.

We would like to make some remarks about the comparisons of models (1.1) and (1.2) with the competition models of resources (see, for example, [1,22]) and the multi-strain models in epidemiology (see [9,25]). Firstly models (1.1) and (1.2) are not competition models since the two strains of bacteria, sensitive and resistant, are not competitors. Secondly, patients infected with the sensitive strain can be infected with the resistant strain due to the treatment of antibiotics or the interaction from the contaminated health-care workers, and patients infected with the resistant strain can be cleaned due to treatment. So models (1.1) and (1.2) are different from the multi-strain models in epidemiology (see [9]) and the two-resistant strains model studied by Webb et al. [25]. Moreover, our results are not about which strain will win, it is about how the resistant strains establish in the patients and how to control that.

The paper is organized as follows. In Section 2, we consider the compartment model (1.1) with a single antibiotic therapy and evaluate a threshold, the basic reproduction number R_0 [8], for two cases: (i) in the absence of treatment $fh = 0$ and (ii) with treatment $fh > 0$. The disease-free equilibrium always exists and is globally stable if $R_0 < 1$ and the disease-endemic equilibrium exists and is globally stable if $R_0 > 1$. Section 3 is devoted to discussing the existence and stability of equilibria of the model (1.2) with multiple antibiotic therapies. In order to understand how antibiotic usage patterns may be optimized to preserve or restore antibiotic effectiveness, we consider four different modes of antibiotic therapy, namely, (i) in the absence of treatment $f_a = f_b = f_{ab} = 0$; (ii) cycling treatment $f_a = 1, f_b = f_{ab} = 0$ or $f_b = 1, f_a = f_{ab} = 0$; (iii) 50–50 treatment $f_a = f_b = \frac{1}{2}$, $f_{ab} = 0$; and (iv) combination treatment $f_a = f_b = 0, f_{ab} = 1$. We present stability results for all different cases. In Section 4, we present some numerical simulations to illustrate the obtained results and present a brief discussion.

2. The model with a single antibiotic therapy

In this section, we discuss the existence and stability of equilibria of the compartment model (1.1). In this model, we assume that the fitness cost associated with resistance is manifest by a higher rate of clearance of the infection (recovery) of hosts infected with resistant bacteria relative to those infected with sensitive ($r_r > r_w$) and the death rate of infected patients is higher than that of susceptible one, that is $c > d$ [6].

Because of the biological meaning of the components ($x(t), y_w(t), y_r(t)$), we focus on the model in the first octant of R^3. We first consider the existence of equilibria of system (1.1). By some calculation, we find that system (1.1) has at most three equilibria:

$$E_0 = (\Lambda/d, 0, 0), \quad E_r = \left(\frac{c+r_r}{b}, 0, \frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_r}{bc}\right),$$

and

$$\widetilde{E} = \left(\frac{c+r_w+fh}{b}, \frac{(r_r - r_w - fh)(\Lambda - d(c+r_w+fh)/b)}{c(r_r - r_w - fh(1-s))}, \frac{fhs(\Lambda - d(c+r_w+fh)/b)}{c(r_r - r_w - fh(1-s))}\right),$$

under certain conditions (to be specified later).

We define the basic reproduction number as follows:

$$R_0 = \max\left\{\frac{b\Lambda}{d(c+r_w+fh)}, \frac{b\Lambda}{d(c+r_r)}\right\}.$$

First we determine the stability of the disease-free equilibrium E_0. The Jacobian matrix of system (1.1) at E_0 is given by

$$J_{E_0} = \begin{bmatrix} -d & -\frac{b\Lambda}{d} + r_w + fh(1-s) & -\frac{b\Lambda}{d} + r_r \\ 0 & \frac{b\Lambda}{d} - c - r_w - fh & 0 \\ 0 & fhs & \frac{b\Lambda}{d} - d - r_r \end{bmatrix}.$$

We can see that E_0 is locally stable if $R_0 < 1$.

In the following, we shall study the existence and stability property of other equilibria of model (1.1). We consider two cases.

2.1. In the absence of treatment: $fh = 0$

We first consider the case of absence of therapy, that is $fh = 0$. To deduce the threshold for the antibiotic resistance in the patient, we analyze the existence of equilibria and their stability for model (1.1). Now the basic reproduction number is $R_0 = \frac{br}{d(c+r_w)}$. By examining the linearized form of system (1.1) at the equilibrium, we obtain the following result.

Theorem 2.1. *Assume $fh = 0$, then $R_0 = \frac{b\Lambda}{d(c+r_w)}$.*

(i) *If $R_0 < 1$, then system (1.1) has a disease-free equilibrium $E_0 = (\Lambda/d, 0, 0)$, which is locally asymptotically stable.*

(ii) *If $R_0 > 1$, then system (1.1) has two or three equilibria, the disease-free equilibrium $E_0 = (\Lambda/d, 0, 0)$, which is a saddle point and unstable, the non-trivial equilibrium*

$$E_w = \left(\frac{c+r_w}{b}, \frac{d(c+r_w)(R_0-1)}{bc}, 0\right),$$

which is locally asymptotically stable, and another non-trivial equilibrium

$$E_r = \left(\frac{c+r_r}{b}, 0, \frac{d(c+r_w)(R_0-1)}{bc} - \frac{d(r_r - r_w)}{bc}\right),$$

which is unstable if it exists.

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2.2. With treatment: $fh > 0$

We first consider the case $r_r < r_w + fh$. In this case

$$R_0 = \max\left\{\frac{b\Lambda}{d(c+r_w+fh)}, \frac{b\Lambda}{d(c+r_r)}\right\} = \frac{b\Lambda}{d(c+r_r)}$$

and system (1.1) has at most two equilibria, the disease-free equilibrium E_0 and the semitrivial equilibrium $E_r = \left(\frac{c+r_r}{b}, 0, \frac{d(c+r_r)(R_0-1)}{bc}\right)$ if $R_0 > 1$.

The Jacobian matrix of system (1.1) at E_r is

$$J_{E_r} = \begin{bmatrix} -R_0 d - \frac{dr_r}{c}(R_0-1) & -c - r_r + r_w + fh(1-s) & -c \\ 0 & r_r - r_w - fh & 0 \\ d(1+r_r/c)(R_0-1) & fhs & 0 \end{bmatrix}.$$

It follows that E_r is locally asymptotically stable under the assumption of $R_0 > 1$.

From the above discussion, we have the following result.

Theorem 2.2. *Suppose $r_r < r_w + fh$, then $R_0 = \frac{b\Lambda}{d(c+r_r)}$. If $R_0 < 1$, then system (1.1) has a disease-free equilibrium $E_0 = (\Lambda/d, 0, 0)$, which is locally asymptotically stable. If $R_0 > 1$, then E_0 is unstable, and the semitrivial equilibrium $E_r = \left(\frac{c+r_r}{b}, 0, \frac{d(c+r_r)(R_0-1)}{bc}\right)$ exists and is locally asymptotically stable.*

Next we discuss the case $r_r > r_w + fh$. In this case

$$R_0 = \frac{b\Lambda}{d(c+r_w+fh)}$$

and system (1.1) may have three equilibria, the disease-free equilibrium E_0,the semitrivial equilibrium with the resistant strain E_r and a positive equilibrium $\widetilde{E} = (\tilde{x}, \tilde{y}_w, \tilde{y}_r)$. For convenience, we denote

$$\tilde{y}_w = \frac{(r_r - r_w - fh)(\Lambda - d(c+r_w+fh)/b)}{c(r_r - r_w - fh(1-s))},$$
$$\tilde{y}_r = \frac{fhs(\Lambda - d(c+r_w+fh)/d)}{c(r_r - r_w + fh(1-s))}.$$

From the expressions of $\tilde{y}_w$ and $\tilde{y}_r$, we know that $\widetilde{E}$ exists if and only if $R_0 > 1$. The Jacobian matrix of system (1.1) at $\widetilde{E}$ is

$$J_{\widetilde{E}} = \begin{bmatrix} -d - b(\tilde{y}_w + \tilde{y}_r) & -c - fhs & r_r - r_w - fh - c \\ b\tilde{y}_w & 0 & 0 \\ b\tilde{y}_r & fhs & fh + r_w - r_r \end{bmatrix}.$$

Therefore, the corresponding characteristic equation is

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{2.1}$$

where

$$a_1 = b(\tilde{y}_w + \tilde{y}_r) + r_r - r_w - fh + d,$$
$$a_2 = bc(\tilde{y}_w + \tilde{y}_r) + b\tilde{y}_w(r_r - r_w - fh(1-s)) + d + r_r - r_w + fh,$$
$$a_3 = bc\tilde{y}_w(r_r - r_w - fh(1-s)).$$

Furthermore, by the relation

$$(r_w + fh - r_r)\tilde{y}_r + fhs\tilde{y}_w = 0,$$

we have

$$a_2 = bc\tilde{y}_w\left(1 + \frac{fhs}{r_r - r_w - fh}\right) + b\tilde{y}_w(r_r - r_w - fh(1-s)) + d(r_r - r_w + fh).$$

Thus, in view of the new expression of a_2, it is easy to see that $a_1, a_2, a_3 > 0$ and $a_1a_2 - a_3 > 0$. By Routh–Hurwitz criteria (see [18, Section 1.6-6(b)]), all roots of Eq. (2.1) have negative real parts. Therefore, when $R_0 > 1$, the positive equilibrium $\widetilde{E}$ is locally stable. Thus, we have the following conclusion.

Theorem 2.3. *Assume $r_r > r_w + fh$, then $R_0 = \frac{b\Lambda}{d(c+r_w+fh)}$. If $R_0 < 1$, then system (1.1) has a disease-free equilibrium $E_0 = (\Lambda/d, 0, 0)$, which is locally asymptotically stable. If $R_0 > 1$, then E_0 is unstable and the disease-endemic equilibrium*

$$\widetilde{E} = \left(\frac{c+r_w+fh}{b}, \frac{d(c+r_w+fh)(r_r - r_w - fh)(R_0-1)}{bc(r_r - r_w - fh(1-s))}, \frac{dfhs(c+r_w+fh)(R_0-1)}{bc(r_r - r_w - fh(1-s))}\right)$$

is locally asymptotically stable. Furthermore, if $R_0 > 1 + \frac{r_r - r_w - fh}{c + r_w + fh}$, then the semitrivial equilibrium with the resistant strain

$$E_r = \left(\frac{c+r_r}{b}, 0, \frac{d}{bc}((c+r_w+fh)(R_0-1) - (r_r - r_w - fh))\right)$$

exists and is unstable.

To explore the global stability of the positive equilibrium, we define the new variables

$$X = \frac{d}{\Lambda}x, \quad Y_w = \frac{d}{\Lambda}y_w, \quad Y_r = \frac{d}{\Lambda}y_r,$$

and parameters

$$\tilde{t} = dt, \quad \tilde{b} = \frac{b}{d}, \quad \tilde{r}_w = \frac{r_w}{d}, \quad \tilde{r}_r = \frac{r_r}{d}, \quad \tilde{h} = \frac{h}{d}, \quad \tilde{c} = \frac{c}{d}.$$

Using these changes of variables and parameters, system (1.1) becomes

$$\begin{cases} \frac{dX}{d\tilde{t}} = 1 - X - \frac{\tilde{b}\Lambda}{d}X(Y_w + Y_r) + \tilde{r}_w Y_w + \tilde{r}_r Y_r + f\tilde{h}(1-s)Y_w, \\ \frac{dY_w}{d\tilde{t}} = \left(\frac{\tilde{b}\Lambda}{d}X - \tilde{c} - \tilde{r}_w - f\tilde{h}\right)Y_w, \\ \frac{dY_r}{d\tilde{t}} = \left(\frac{\tilde{b}\Lambda}{d}X - \tilde{c} - \tilde{r}_r\right)Y_r + f\tilde{h}sY_w \end{cases} \tag{2.2}$$

with $\widetilde{N}(t) = X(t) + Y_w(t) + Y_r(t)$. The equation for the total population $\widetilde{N}$ is

$$\frac{d\widetilde{N}}{d\tilde{t}} = 1 - X - \tilde{c}Y_w - \tilde{c}Y_r. \tag{2.3}$$

Clearly, $\widetilde{N} \in (0, 1]$ since at the disease-free equilibrium $\widetilde{N} = X = 1$ and the natural expectation is that the spread of the disease in the population will reduce $\widetilde{N}$ (that is $\widetilde{N} < 1$). Therefore, we study the stability of the model (2.2) in the region

$$D = \left\{(X, Y_w, Y_r) \in R^3_+ : 0 \leqslant X + Y_w + Y_r \leqslant 1\right\}.$$

Consider the subset D^* of D given by

$$D^* = \{(X, Y_w, Y_r) \in D : X + \tilde{c}Y_w + \tilde{c}Y_r = 1\}.$$

From (2.3), it is obvious that $\frac{d\widetilde{N}}{d\tilde{t}} = 0$ in D^*. If $X + \tilde{c}Y_w + \tilde{c}Y_r > 1$, then $\frac{d\widetilde{N}}{d\tilde{t}} < 0$ and if $X + \tilde{c}Y_w + \tilde{c}Y_r < 1$, then $\frac{d\widetilde{N}}{d\tilde{t}} > 0$. It follows that D^* is a positively invariant set in D. Thus the ω-limit set of each solution of model (2.2) is contained in D^*. Moreover, it is easy to see that $\widetilde{E}_0$ attracts the region $D_0 = \{(X, Y_w, Y_r) \in D : Y_w = Y_r = 0\}$.

In the next result, we will show that there cannot be any closed orbit around the equilibrium.

Lemma 2.4. *The model (2.2) has no periodic orbits, homoclinic orbits or polygons in D^*.*

Proof. Let f_1, f_2, f_3 denote the three functions on the right hand sides in system (2.2), respectively. Denote $f = (f_1, f_2, f_3)^T$ (T denotes transpose), $g(X, Y_w, Y_r) = \frac{1}{XY_wY_r} \cdot r \times f$, (where $r = (X, Y_w, Y_r)^T$), then

$$g \cdot f = 0.$$

By straightforward calculation, we have in the interior of domain D that

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$$(curlg)_1 = \frac{\partial g_3}{\partial Y_w} - \frac{\partial g_2}{\partial Y_r} = \frac{\tilde{b}\Lambda}{dY_r} - \frac{\tilde{Y}_w + f\tilde{h}(1-s)}{XY_r} - \frac{f\tilde{h}s}{Y_r^2} + \frac{\tilde{b}\Lambda}{dY_w} - \frac{\tilde{r}_r}{XY_w},$$

$$(curlg)_2 = -\frac{\partial g_3}{\partial X} + \frac{\partial g_1}{\partial Y_r} = -\frac{\tilde{b}\Lambda}{dY_r} - \frac{\tilde{r}_r}{X^2} - \frac{1 + (f\tilde{h} + \tilde{r}_w)Y_w}{X^2 Y_r},$$

$$(curlg)_3 = \frac{\partial g_2}{\partial X} - \frac{\partial g_3}{\partial Y_w} = -\frac{\tilde{b}\Lambda}{dY_w} - \frac{1 + \tilde{r}_r Y_r}{X^2 Y_w} - \frac{\tilde{r}_w + f\tilde{h}(1-s)}{X^2} - \frac{f\tilde{h}s}{XY_r}.$$

Using the normal vector $\mathbf{n} = (1, \tilde{c}, \tilde{c})$ on D^*, it can be shown that

$$curlg \cdot (1, \tilde{c}, \tilde{c}) = -(\tilde{c}-1)\frac{\tilde{b}\Lambda}{d}\left(\frac{1}{r_r} + \frac{1}{r_w}\right) - \frac{\tilde{Y}_w + f\tilde{h}}{XY_r} - \frac{f\tilde{h}s}{Y_r^2} - \frac{\tilde{r}_r}{XY_w} - \frac{\tilde{r}_r}{X^2} - \frac{1 + (f\tilde{h} + \tilde{r}_w)Y_w}{X^2 Y_r} - \frac{1 + \tilde{r}_r Y_r}{X^2 Y_w} - \frac{\tilde{r}_w + f\tilde{h}(1-s)}{X^2} - \frac{f\tilde{h}s}{XY_r}.$$

In view of the assumption of $\tilde{c} > 1$, we have that $curlg \cdot (1, \tilde{c}, \tilde{c})$ is negative on $D \backslash \partial D$. From Corollary 4.2 in [10], there are no solutions of the stated type in $D \backslash \partial D$. The desired result is obtained. □

From Theorems 2.1, 2.2, 2.3 and Lemma 2.4, the following theorem can be obtained.

Theorem 2.5. *For system (1.1), the following results hold.*

(i) *Assume $fh < r_r - r_w$, then system (1.1) has at most three equilibria $E_0, E_r, \widetilde{E}$ with $R_0 = \frac{b\Lambda}{d(c+r_w+fh)}$. If $R_0 < 1$, then the DFE E_0 is globally asymptotically stable, if $R_0 > 1$, E_0 is unstable, the positive equilibrium $\widetilde{E}$ is globally asymptotically stable, the semitrivial equilibrium E_r is unstable if it exists.*

(ii) *Assume $fh > r_r - r_w$, then system (1.1) has at most two equilibria E_0, E_r with $R_0 = \frac{b\Lambda}{d(c+r_r)}$. If $R_0 < 1$, then the DFE E_0 is globally stable, if $R_0 > 1$, E_0 is unstable, the semitrivial equilibrium E_r is globally asymptotically stable.*

The above results can be summarized in Table 1 (BRN = basic reproduction number).

3. The model with multiple antibiotic therapies

In this section we consider model (1.2), where we assume that the fitness cost associated with resistance is manifest by a higher rate of clearance of the infection (recovery) of hosts infected with resistant bacteria relative to those infected with sensitive bacteria ($r_r > r_w$) and the death rate of infected patients is higher than that of susceptible one, that is $c > d$ [6].

Because of the components of $(x(t), y_w(t), y_a(t), y_b(t), y_{ab}(t))$ have to be non-negative, we focus on the model in the first octant of R^5. We first consider the existence of equilibria of system (1.2). For any values of parameters, model (1.2) always has a disease-free equilibrium $E_0 = (\Lambda/d, 0, 0, 0, 0)$.

We first determine the stability of the disease-free equilibrium E_0. The Jacobian matrix of system (1.2) at E_0 is

$$J_0 = \begin{bmatrix} -d & j_{12} & j_{13} & j_{14} & j_{15} \\ 0 & j_{22} & 0 & 0 & 0 \\ 0 & hsf_a & j_{33} & 0 & 0 \\ 0 & hsf_a & 0 & j_{44} & 0 \\ 0 & hqf_{ab} & hs(f_{ab}+f_b) & hs(f_a+f_{ab}) & j_{55} \end{bmatrix},$$

where

$$\begin{aligned} j_{12} &= -b\Lambda/d + r_w + h(1-q)f_{ab} + h(1-s)(f_a + f_b), \\ j_{13} &= -b\Lambda/d + r_a + h(1-s)(f_b + f_{ab}), \\ j_{14} &= -b\Lambda/d + r_b + h(1-s)(f_a + f_{ab}), \\ j_{15} &= -b\Lambda/d + r_{ab}, \\ j_{22} &= b\Lambda/d - c - r_w - h(f_a + f_b + f_{ab}), \\ j_{33} &= b\Lambda/d - c - r_a - h(f_b + f_{ab}), \\ j_{44} &= b\Lambda/d - c - r_b - h(f_a + f_{ab}), \\ j_{55} &= b\Lambda/d - c - r_{ab}. \end{aligned}$$

The eigenvalues of J_0 are $-d, j_{22}, j_{33}, j_{44}, j_{55}$. So from the expressions of $j_{ii} (i = 2,3,4,5)$, we can see that the steady state E_0 is locally asymptotically stable if

$$b\Lambda/d - c < \min\{r_w + h(f_a + f_b + f_{ab}), r_a + h(f_b + f_{ab}), r_b + h(f_a + f_{ab}), r_{ab} + h(f_a + f_{ab}), r_{ab}\},$$

and unstable if

$$b\Lambda/d - c > \min\{r_w + h(f_a + f_b + f_{ab}), r_a + h(f_b + f_{ab}), r_b + h(f_a + f_{ab}), r_{ab} + h(f_a + f_{ab}), r_{ab}\}.$$

By using the next generation operator approach as described by Diekmann et al. [13], we obtain the basic reproduction number as follows:

$$R_0 = \frac{b\Lambda}{d} \frac{1}{c + \min\{r_w + h(f_a + f_b + f_{ab}), r_a + h(f_b + f_{ab}), r_b + h(f_a + f_{ab}), r_{ab}\}}.$$

Observe that

$$\begin{aligned} &b\Lambda/d - c - \min\{r_w + h(f_a + f_b + f_{ab}), r_a + h(f_b + f_{ab}), \\ &\quad r_b + h(f_a + f_{ab}), r_{ab}\} = (R_0 - 1)\min\{r_w + h(f_a + f_b + f_{ab}), \\ &\quad r_a + h(f_b + f_{ab}), r_b + h(f_a + f_{ab}), r_{ab}\}. \end{aligned}$$

We have the following result.

Theorem 3.1. *For model (1.2), the disease-free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

In order to analyze the stability of other equilibria of model (1.2), we consider four cases.

3.1. In the absence of treatment: $f_a = f_b = f_{ab} = 0$

Theorem 3.2. *When $f_a = f_b = f_{ab} = 0$, for system (1.2), there are at most five possible steady state*

$$\begin{aligned} E_0 &= (\Lambda/d, 0, 0, 0, 0), \\ E_w &= \left(\frac{c + r_w}{b}, \frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_w}{bc}, 0, 0, 0\right), \\ E_a &= \left(\frac{c + r_a}{b}, 0, \frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_a}{bc}, 0, 0\right), \\ E_b &= \left(\frac{c + r_b}{b}, 0, 0, \frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_b}{bc}, 0\right), \\ E_{ab} &= \left(\frac{c + r_{ab}}{b}, 0, 0, 0, \frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_{ab}}{bc}\right). \end{aligned}$$

The existence and stability of equilibria are described in Table 2.

Table 1
Stability chart for system (1.1).

Condition	BRN	Cases	E_0	E_r	$\widetilde{E}$
$fh < r_r - r_w$	$R_0 = \frac{b\Lambda}{d(c+r_w+fh)}$	$R_0 < 1$	Globally stable	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	If exist, unstable	Globally stable
$fh > r_r - r_w$	$R_0 = \frac{b\Lambda}{d(c+r_r)}$	$R_0 < 1$	Globally stable	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	Globally stable	$\nexists$

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Table 2
Existence and stability chart for system (1.2) with no treatment.

Condition	BRN	Cases	E_0	E_w	E_a	E_b	E_{ab}
$r_w < \min\{r_a, r_b, r_{ab}\}$	$R_0 = \frac{b\Lambda}{d(c+r_w)}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	Stable	$*$	$*$	$*$
$r_a < \min\{r_w, r_b, r_{ab}\}$	$R_0 = \frac{b\Lambda}{d(c+r_a)}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	$*$	Stable	$*$	$*$
$r_b < \min\{r_w, r_a, r_{ab}\}$	$R_0 = \frac{b\Lambda}{d(c+r_b)}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	$*$	$*$	Stable	$*$
$r_{ab} < \min\{r_w, r_a, r_b\}$	$R_0 = \frac{b\Lambda}{d(c+r_{ab})}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	$*$	$*$	$*$	Stable

Here $*$ represents that if the equilibrium exists, it is unstable.

Proof. When $f_a = f_b = f_{ab} = 0$, the Jacobian matrix of system (1.2) at the non-trivial equilibrium E_w is

$$J_{E_w} = \begin{bmatrix} -d - b\left(\frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_w}{bc}\right) & -c & -c - r_w + r_a & -c - r_w + r_b & -c - r_w + r_{ab} \\ -b\left(\frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_w}{bc}\right) y_w & 0 & 0 & 0 & 0 \\ 0 & 0 & r_w - r_a & 0 & 0 \\ 0 & 0 & 0 & r_w - r_b & 0 \\ 0 & 0 & 0 & 0 & r_w - r_{ab} \end{bmatrix}.$$

We can see that the eigenvalues of J_{E_w} are $r_w - r_a$, $r_w - r_b$, $r_w - r_{ab}$, and the roots of the polynomial equation

$$\lambda^2 + \left(d + b\left(\frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_w}{bc}\right)\right)\lambda + bc\left(\frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_w}{bc}\right) = 0.$$

Thus, under the condition $r_w < \min\{r_a, r_b, r_{ab}\}$, if $R_0 < 1$, namely $\frac{\Lambda}{c} < \frac{d}{b} + \frac{dr_w}{bc}$, the equilibria E_w, E_a, E_b, E_{ab} do not exist and the trivial equilibrium E_0 is locally stable. If $R_0 > 1$, all eigenvalues of J_{E_w} have negative real parts, so E_w is locally stable. Equilibria E_a, E_b, E_{ab} are unstable, since their corresponding Jacobian matrices have positive eigenvalues $r_a - r_w$, $r_b - r_w$, $r_{ab} - r_w$, respectively.

For the other cases, the discussion is similar, we omit it here. □

$$E_{ab} = \left(\frac{c + r_{ab}}{b}, 0, 0, 0, \frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_{ab}}{bc}\right),$$

$$E_{w,a} = \left(\frac{c + r_w + h}{b}, \frac{(r_a - r_w - h)(\Lambda - d(c + r_w + h)/b)}{c(r_a - r_w - h(1 - s))}, \frac{hs(\Lambda - d(c + r_w + h)/b)}{c(r_a - r_w - h(1 - s))}, 0, 0\right),$$

$$E_{b,ab} = \left(\frac{c + r_b + h}{b}, 0, 0, \frac{(r_{ab} - r_b - h)(\Lambda - d(c + r_b + h)/b)}{c(r_{ab} - r_b - h(1 - s))}, \frac{hs(\Lambda - d(c + r_b + h)/b)}{c(r_{ab} - r_b - h(1 - s))}\right).$$

The basic reproduction number is defined by

$$R_0 = \frac{b\Lambda}{d} \frac{1}{c + \min\{r_w + h, r_a, r_b + h, r_{ab}\}}.$$

Theorem 3.3. *When $f_a = 1$, $f_b = f_{ab} = 0$, the existence and stability of equilibria are described in Table 3.*

Proof.

(i) When $f_a = 1$, $f_b = f_{ab} = 0$, the Jacobian matrix of system (1.2) at the semitrivial equilibrium E_a is

$$J_{E_a} = \begin{bmatrix} -d - b\left(\frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_a}{bc}\right) & r_w + h(1 - s) - c - r_a & -c & r_b + h(1 - s) - c - r_a & -c - r_a + r_{ab} \\ 0 & r_a - r_w - h & 0 & 0 & 0 \\ b\left(\frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_a}{bc}\right) & hs & 0 & 0 & 0 \\ 0 & 0 & 0 & r_a - r_b - h & 0 \\ 0 & 0 & 0 & hs & r_a - r_{ab} \end{bmatrix}.$$

3.2. Cycling treatment: $f_a = 1$, $f_b = f_{ab} = 0$ or $f_b = 1$, $f_a = f_{ab} = 0$

When $f_a = 1$, $f_b = f_{ab} = 0$, system (1.2) becomes

$$\begin{cases} \frac{dx}{dt} = \Lambda - dx - bx(y_w + y_a + y_b + y_{ab}) + r_w y_w + r_a y_a \\ \qquad + r_b y_b + r_{ab} y_{ab} + h(1 - s)(y_w + y_b), \\ \frac{dy_w}{dt} = (bx - c - r_w - h) y_w, \\ \frac{dy_a}{dt} = (bx - c - r_a) y_a + hs y_w, \\ \frac{dy_b}{dt} = (bx - c - r_b - h) y_b, \\ \frac{dy_{ab}}{dt} = (bx - c - r_{ab}) y_{ab} + hs y_b. \end{cases} \tag{3.1}$$

It has at most five possible steady state

$$E_0 = (\Lambda/d, 0, 0, 0, 0),$$

$$E_a = \left(\frac{c + r_a}{b}, 0, \frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_a}{bc}, 0, 0\right),$$

It follows that $r_a - r_w - h$, $r_a - r_b - h$, $r_a - r_{ab}$ are the eigenvalues of J_{E_a}, the other two eigenvalues of J_{E_a} are the roots of the quadratic polynomial equation

$$\lambda^2 + \left(d + b\left(\frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_a}{bc}\right)\right)\lambda + bc\left(\frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_a}{bc}\right) = 0.$$

In view of the assumption and above discussion, the existence and stability the equilibrium E_a can be obtained. For the other equilibria, the discussion is similar, we omit it here.

(ii) The existence and stability of E_{ab} is similar to that of E_a, we omit it.

(iii) By the expression of $E_{w,a}$, we find that when $r_w + h < r_a$ and $\Lambda < d(c + r_w + b)/b$, the semitrivial equilibrium $E_{w,a}$ exists. For the convenience of discussion, we denote

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Table 3
Existence and stability chart for system (1.2) with cycling treatment.

Condition	BRN	Cases	E_0	E_a	E_{ab}	$E_{w,a}$	$E_{b,ab}$
$r_a < \min\{r_w + h, r_b + h, r_{ab}\}$	$R_0 = \frac{b\Lambda}{d(c+r_a)}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	Stable	$*$	$*$	$*$
$r_{ab} < \min\{r_w + h, r_a, r_b + h\}$	$R_0 = \frac{b\Lambda}{d(c+r_{ab})}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	$*$	Stable	$*$	$*$
$r_w + h < \min\{r_a, r_b + h, r_{ab}\}$	$R_0 = \frac{b\Lambda}{d(c+r_w+h)}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	$*$	$*$	Stable	$*$
$r_b + h < \min\{r_w + h, r_a, r_{ab}\}$	$R_0 = \frac{b\Lambda}{d(c+r_b+h)}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	$*$	$*$	$*$	Stable

Here $*$ represents that if the equilibrium exists, it is unstable.

$$\hat{y}_w = \frac{(r_a - r_w - h)(\Lambda - d(c + r_w + h)/b)}{c(r_a - r_w - h(1-s))},$$
$$\hat{y}_a = \frac{hs(\Lambda - d(c + r_w + h)/b)}{c(r_a - r_w - h(1-s))}.$$

Then the Jacobian matrix of system (3.2) at the equilibrium $E_{w,a} = ((c + r_w + fh)/b, \hat{y}_w, \hat{y}_a, 0, 0)$ has the form

$$J_{E_{w,a}} = \begin{bmatrix} -d - b(\hat{y}_w + \hat{y}_a) & -c - hs & r_a - c - r_w - h & r_b - c - r_w - hs & r_{ab} - c - r_w - h \\ b\hat{y}_w & 0 & 0 & 0 & 0 \\ b\hat{y}_a & hs & r_w + h - r_a & 0 & 0 \\ 0 & 0 & 0 & r_w - r_b & 0 \\ 0 & 0 & 0 & hs & r_w + h - r_{ab} \end{bmatrix}.$$

It is easy to see that $r_w - r_b$ and $r_w + h - r_{ab}$ are the eigenvalues of $J_{E_{w,a}}$. After some algebra, we can find that the other three eigenvalues of $J_{E_{w,a}}$ are the roots of

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$$

with

$$\begin{aligned} a_1 &= b(\hat{y}_w + \hat{y}_a) + d + r_a - r_w - h, \\ a_2 &= bc(\hat{y}_w + \hat{y}_a) + b\hat{y}_w(r_a - r_w - h(1-s)) + d(r_a - r_w - h) \\ &= bc\hat{y}_w\left(\frac{hs}{r_a - r_w - h} + 1\right) + b\hat{y}_w(r_a - r_w - h(1-s)) + d(r_a - r_w - h), \\ a_3 &= bc\hat{y}_w(r_a - r_w - h(1-s)). \end{aligned}$$

From the expressions of a_1, a_2, a_3, it is easy to see that under the assumption $r_w + h < \min\{r_a, r_b + h, r_{ab}\}$, we have $a_1, a_2, a_3 > 0$ and $a_1a_2 - a_3 > 0$. Therefore, by Routh–Hurwitz criteria [18], the local stability of $E_{w,a}$ is obtained. Equilibria E_a, E_{ab} and $E_{b,ab}$ are unstable since their corresponding Jacobian matrices have positive eigenvalues $r_a - r_w - h$, $r_{ab} - r_w - h, r_b - r_w$ respectively.

(iv) The existence and stability discussion of $E_{b,ab}$ is similar to that of $E_{w,a}$, we omit it here. □

The case that $f_b = 1$, $f_a = f_{ab} = 0$ can be analyzed similarly and analogue results can be obtained.

3.3. 50–50 treatment: $f_a = f_b = \frac{1}{2}$, $f_{ab} = 0$

When $f_a = f_b = \frac{1}{2}$, $f_{ab} = 0$, system (1.2) becomes

$$\begin{cases} \frac{dx}{dt} = \Lambda - dx - bx(y_w + y_a + y_b + y_{ab}) + r_w y_w + r_a y_a \\ \qquad + r_b y_b + r_{ab} y_{ab} + h(1-s)(y_w + \frac{1}{2}y_a + \frac{1}{2}y_b), \\ \frac{dy_w}{dt} = (bx - c - r_w - h)y_w, \\ \frac{dy_a}{dt} = (bx - c - r_a - \frac{h}{2})y_a + \frac{h}{2}sy_w, \\ \frac{dy_b}{dt} = (bx - c - r_b - \frac{h}{2})y_b + \frac{h}{2}sy_w, \\ \frac{dy_{ab}}{dt} = (bx - c - r_{ab})y_{ab} + \frac{h}{2}s(y_a + y_b). \end{cases} \tag{3.2}$$

It has at most five possible steady state

$$E_0 = (\Lambda/d, 0, 0, 0, 0), \quad E_{ab} = \left(\frac{c + r_{ab}}{b}, 0, 0, 0, \frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_{ab}}{bc}\right),$$
$$E_{a,ab} = \left(\frac{c + r_a + h/2}{b}, 0, \frac{(r_{ab} - r_a - h/2)(\Lambda - d(c + r_a + h/2)/b)}{c(r_{ab} - r_a - h(1-s)/2)}, 0, \frac{hs(\Lambda - d(c + r_a + h/2)/b)}{2c(r_{ab} - r_a - h(1-s)/2)}\right),$$
$$E_{b,ab} = \left(\frac{c + r_b + h/2}{b}, 0, 0, \frac{(r_{ab} - r_b - h/2)(\Lambda - d(c + r_b + h/2)/b)}{c(r_{ab} - r_b - h(1-s)/2)}, \frac{hs(\Lambda - d(c + r_b + h/2)/b)}{2c(r_{ab} - r_b - h(1-s)/2)}\right),$$
$$\widetilde{E} = (\tilde{x}, \tilde{y}_w, \tilde{y}_a, \tilde{y}_b, \tilde{y}_{ab}),$$

where

$$\tilde{x} = \frac{c + r_w + h}{b},$$
$$\tilde{y}_w = \left(1 + \left(1 + \frac{hs/2}{r_{ab} - r_w - h}\right)\left(\frac{hs/2}{r_a - r_w - h/2} + \frac{hs/2}{r_b - r_w - h/2}\right)\right)^{-1} \times \frac{b\Lambda - d(c + r_w + h)}{bc},$$
$$\tilde{y}_a = \frac{hs/2}{r_a - r_w - h/2}\bar{y}_w,$$
$$\tilde{y}_b = \frac{hs/2}{r_b - r_w - h/2}\bar{y}_w,$$
$$\tilde{y}_{ab} = \frac{hs/2}{r_{ab} - r_w - h}\left(\frac{hs/2}{r_a - r_w - h/2} + \frac{hs/2}{r_b - r_w - h/2}\right)y_w.$$

The basic reproduction number is defined by

$$R_0 = \frac{b\Lambda}{d}\frac{1}{c + \min\{r_w + h, r_a + h/2, r_b + h/2, r_{ab}\}}.$$

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Table 4
Existence and stability chart for system (1.2) with 50–50 treatment.

Condition	BRN	Cases	E_0	E_{ab}	$E_{a,ab}$	$E_{b,ab}$	$\tilde{E}$
$r_{ab} < \min\{r_w + h, r_a + \frac{h}{2}, r_b + \frac{h}{2}\}$	$R_0 = \frac{bA}{d(c+r_{ab})}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	Stable	$*$	$*$	$*$
$r_a + \frac{h}{2} < \min\{r_w + h, r_b + \frac{h}{2}, r_{ab}\}$	$R_0 = \frac{bA}{d(c+r_a+h/2)}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	$*$	Stable	$*$	$*$
$r_b + \frac{h}{2} < \min\{r_w + h, r_a + \frac{h}{2}, r_{ab}\}$	$R_0 = \frac{bA}{d(c+r_b+h/2)}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	$*$	$*$	Stable	$*$
$r_w + h < \min\{r_a + \frac{h}{2}, r_b + \frac{h}{2}, r_{ab}\}$	$R_0 = \frac{bA}{d(c+r_w+h)}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	$*$	$*$	$*$	Stable

Here $*$ represents that if the equilibrium exists, it is unstable.

Table 5
Existence and stability chart for system (1.2) with combining treatment.

Condition	BRN	Cases	E_0	E_{ab}	$E_{a,ab}$	$E_{b,ab}$	$E_{w,ab}$
$r_{ab} < \min\{r_w + h, r_a + h, r_b + h\}$	$R_0 = \frac{bA}{d(c+r_{ab})}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	Stable	$*$	$*$	$*$
$r_a + h < \min\{r_w + h, r_b + h, r_{ab}\}$	$R_0 = \frac{bA}{d(c+r_a+h)}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	$*$	Stable	$*$	$*$
$r_b + h < \min\{r_w + h, r_a + h, r_{ab}\}$	$R_0 = \frac{bA}{d(c+r_b+h)}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	$*$	$*$	Stable	$*$
$r_w + h < \min\{r_a + h, r_b + h, r_{ab}\}$	$R_0 = \frac{bA}{d(c+r_w+h)}$	$R_0 < 1$	Stable	$\nexists$	$\nexists$	$\nexists$	$\nexists$
		$R_0 > 1$	Unstable	$*$	$*$	$*$	Stable

Here $*$ represents that if the equilibrium exists, it is unstable.

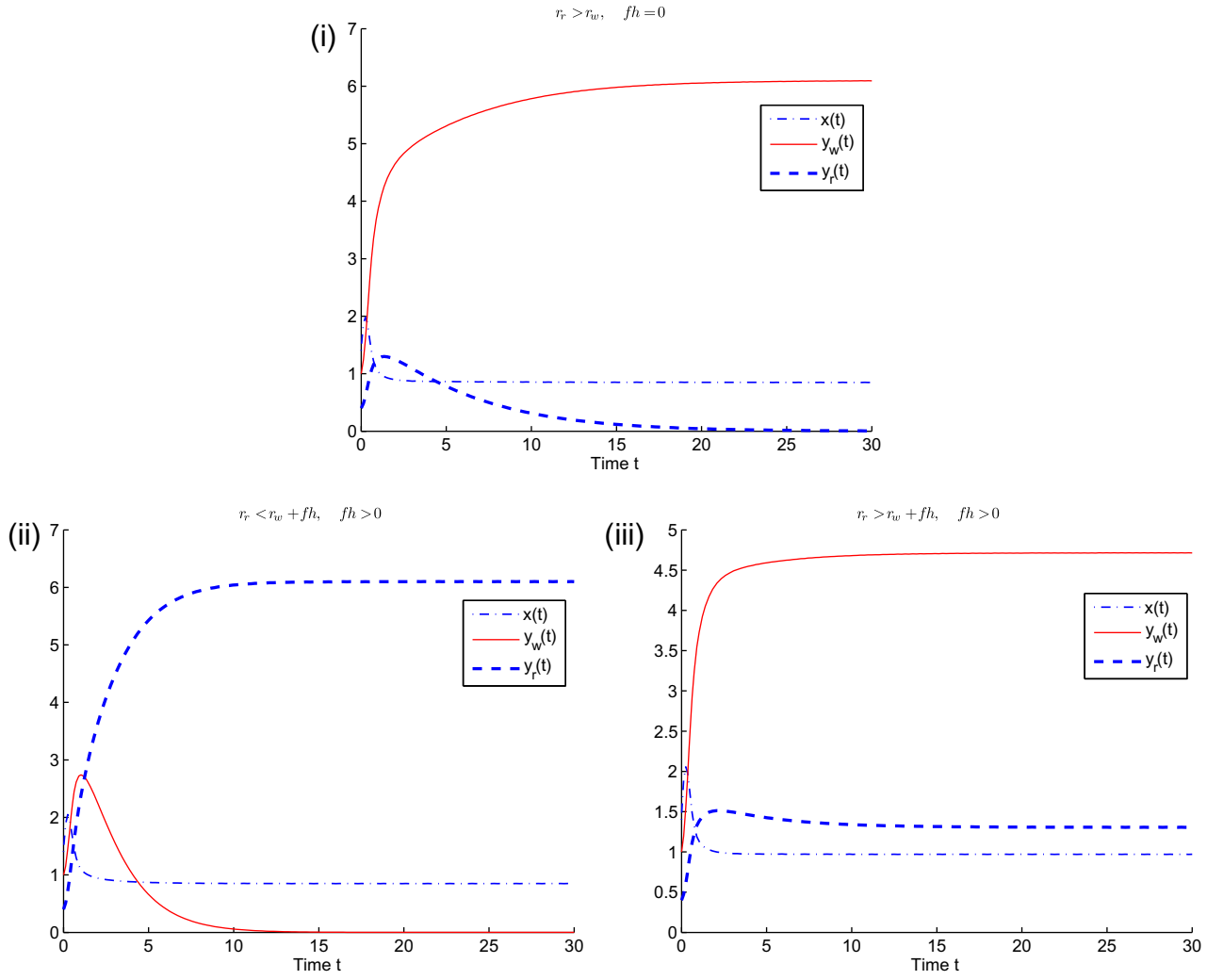

Fig. 4.1. Solution trajectories of the model with a single antibiotic therapy, the parameters $\Lambda = 10$, $d = 1$, $b = 2$, $s = 0.3$, $c = 1.5$ and initial values $x(0) = 1.4$, $y_w(0) = 1$, $y_r(0) = 0.4$ are fixed and the parameters r_w, r_r, f, h vary such that $R_0 > 1$. (i) When $r_r > r_w$ and $fh = 0$, the semitrivial equilibrium E_w is stable; (ii) when $r_r < r_w + fh$ and $fh > 0$, the semitrivial equilibrium E_r is stable; (iii) when $r_r > r_w + fh$ and $fh > 0$, the endemic equilibrium $\tilde{E}$ is stable.

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Theorem 3.4. *When $f_a = f_b = 1/2$, $f_{ab} = 0$, the existence and stability of equilibria can be summarized in Table 4.*

Proof. We find the steady states of system (3.2) by equating the derivatives on the left-hand sides to zero and solving the resulting algebraic equations. The discussion (acquirement) of the trivial or semitrivial equilibria easy, we omit it here. Now we consider the existence of the positive equilibrium.

From the corresponding second equilibrium equation of (3.2), we obtain the solution $\tilde{x} = \frac{c+r_w+h}{b}$. Substituting $\tilde{x} = \frac{c+r_w+h}{b}$ into the corresponding third, fourth, fifth equilibrium equations of (3.2), we obtain

$$\left(r_w + \frac{h}{2} - r_a\right)\tilde{y}_a + \frac{hs}{2}\tilde{y}_w = 0, \tag{3.3}$$

$$\left(r_w + \frac{h}{2} - r_b\right)\tilde{y}_b + \frac{hs}{2}\tilde{y}_w = 0, \tag{3.4}$$

$$(r_w + h - r_{ab})\tilde{y}_{ab} + \frac{hs}{2}(\tilde{y}_a + \tilde{y}_b) = 0. \tag{3.5}$$

Combining Eqs. (3.3)–(3.5) with the first one of (3.2), after some calculation we obtain that

$$\tilde{y}_w + \tilde{y}_a + \tilde{y}_b + \tilde{y}_{ab} = \frac{1}{c}(\Lambda - d\tilde{x}) = \frac{1}{c}\left(\Lambda - \frac{d}{b}(c + r_w + h)\right).$$

Thus, when $r_w + h < \min\{r_a + h/2, r_b + h/2, r_{ab}\}$ and $\Lambda > \frac{d}{b}(c + r_w + h)$, system (3.2) has a unique componentwise positive equilibrium $\tilde{E}$.

Linearizing system (3.2) about the positive equilibrium $(\tilde{x}, \tilde{y}_w, \tilde{y}_a, \tilde{y}_b, \tilde{y}_{ab})$ yields the Jacobian matrix $J_{\tilde{E}}$.

$$J_{\tilde{E}} = \begin{bmatrix} -d - b(\tilde{y}_w + \tilde{y}_a + \tilde{y}_b + \tilde{y}_{ab}) & r_w + h(1-s) - b\tilde{x} & r_a + \frac{h(1-s)}{2} - b\tilde{x} & r_b + \frac{h(1-s)}{2} - b\tilde{x} & r_{ab} - b\tilde{x} \\ b\tilde{y}_w & b\tilde{x} - c - r_w - h & 0 & 0 & 0 \\ b\tilde{y}_a & \frac{hs}{2} & b\tilde{x} - c - r_a - \frac{h}{2} & 0 & 0 \\ b\tilde{y}_b & \frac{hs}{2} & 0 & b\tilde{x} - c - r_b - \frac{h}{2} & 0 \\ b\tilde{y}_{ab} & 0 & \frac{hs}{2} & \frac{hs}{2} & b\tilde{x} - c - r_{ab} \end{bmatrix}.$$

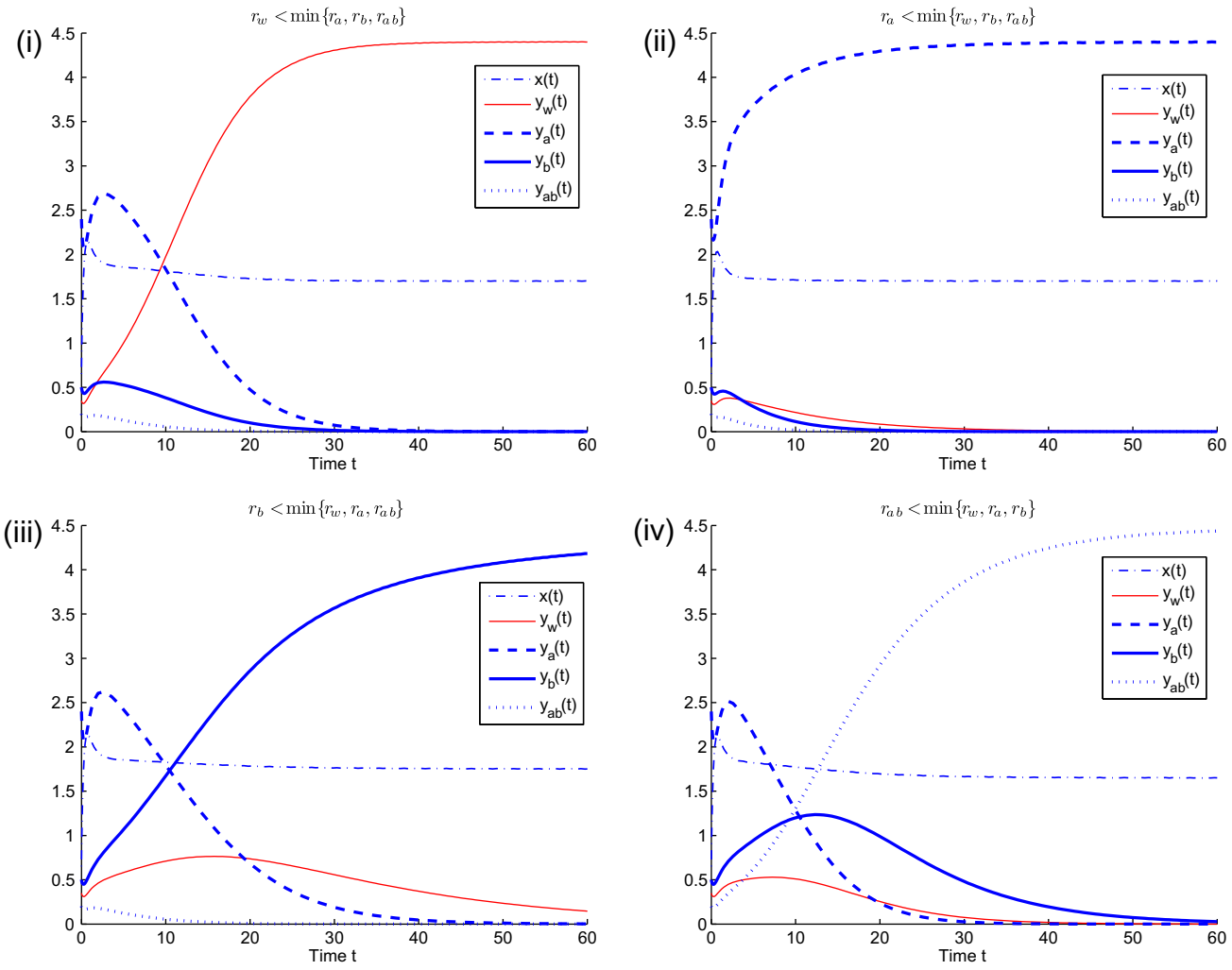

Fig. 4.2. System (1.2) with no treatment, i.e. $f_a = f_b = f_{ab} = 0$, we choose parameters $\Lambda = 10$, $d = 2$, $b = 1$, $q = 0.1$, $s = 0.3$, $c = 1.5$, $h = 0.2$, initial values $x(0) = 0.65$, $y_w(0) = 0.35$, $y_a(0) = 2.4$, $y_b(0) = 0.5$, $y_{ab}(0) = 0.2$, and let r_w, r_a, r_b, r_{ab} and h vary such that $R_0 > 1$. (i) When $r_w < \min\{r_a, r_b, r_{ab}\}$, the semitrivial equilibrium E_w is stable; (ii) when $r_a < \min\{r_w, r_b, r_{ab}\}$, the semitrivial equilibrium E_a is stable; (iii) when $r_b < \min\{r_w, r_a, r_{ab}\}$, the semitrivial equilibrium E_b is stable; (iv) when $r_{ab} < \min\{r_w, r_a, r_b\}$, the semitrivial equilibrium E_{ab} is stable.

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Substituting $\tilde{x} = (c + r_w + h)/b$ into $J_{\tilde{E}}$ and expanding the determinant of the obtained matrix $\lambda I - J_{\tilde{E}}$ by the second row, after some calculation, it can be seen that the eigenvalues are $r_w + \frac{h}{2} - r_a, r_w + \frac{h}{2} - r_b$, and the roots of

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0,$$

where

$$a_1 = b(\tilde{y}_w + \tilde{y}_a + \tilde{y}_b + \tilde{y}_{ab}) + d + r_{ab} - r_w - h,$$
$$a_2 = bc(\tilde{y}_w + \tilde{y}_a + \tilde{y}_b + \tilde{r}y_{ab}) + (b(\tilde{y}_w + \tilde{y}_a + \tilde{y}_b) + d)(r_{ab} - r_w - h) + \frac{bhs}{2}(\tilde{y}_a + \tilde{y}_b),$$
$$a_3 = bc(\tilde{y}_w + \tilde{y}_a + \tilde{y}_b + \tilde{y}_{ab})(r_{ab} - r_w - h).$$

It is noted that in the expression of a_3, we have used the relation

$$\frac{hs}{2}(\tilde{y}_a + \tilde{y}_b) = (r_{ab} - r_w - h)\tilde{y}_{ab}.$$

From the expressions of a_1, a_2, a_3, it is clear that under the assumption $r_w + h < \min\{r_a + h/2, r_b + h/2, r_{ab}\}$, we have $a_1, a_2, a_3 > 0$ and $a_1a_2 - a_3 > 0$. Therefore, by Routh–Hurwitz criteria [18], the stability of the positive equilibrium $\tilde{E}$ is established. □

3.4. Combination treatment: $f_a = f_b = 0$, $f_{ab} = 1$

When $f_a = f_b = 0$, $f_{ab} = 1$, system (1.2) becomes

$$\begin{cases} \frac{dx}{dt} = \Lambda - dx - bx(y_w + y_a + y_b + y_{ab}) + r_w y_w + r_a y_a + r_b y_b + r_{ab} y_{ab} \\ \qquad +h(1-q)y_w + h(1-s)(y_a + y_b), \\ \frac{dy_w}{dt} = (bx - c - r_w - h)y_w, \\ \frac{dy_a}{dt} = (bx - c - r_a - h)y_a, \\ \frac{dy_b}{dt} = (bx - c - r_b - h)y_b, \\ \frac{dy_{ab}}{dt} = (bx - c - r_{ab})y_{ab} + hs(y_a + y_b) + hqy_w. \end{cases} \tag{3.6}$$

The basic reproduction number is defined as

$$R_0 = \frac{b\Lambda}{d}\frac{1}{c + \min\{r_w + h, r_a + h, r_b + h, r_{ab}\}}.$$

It has at most five possible steady state

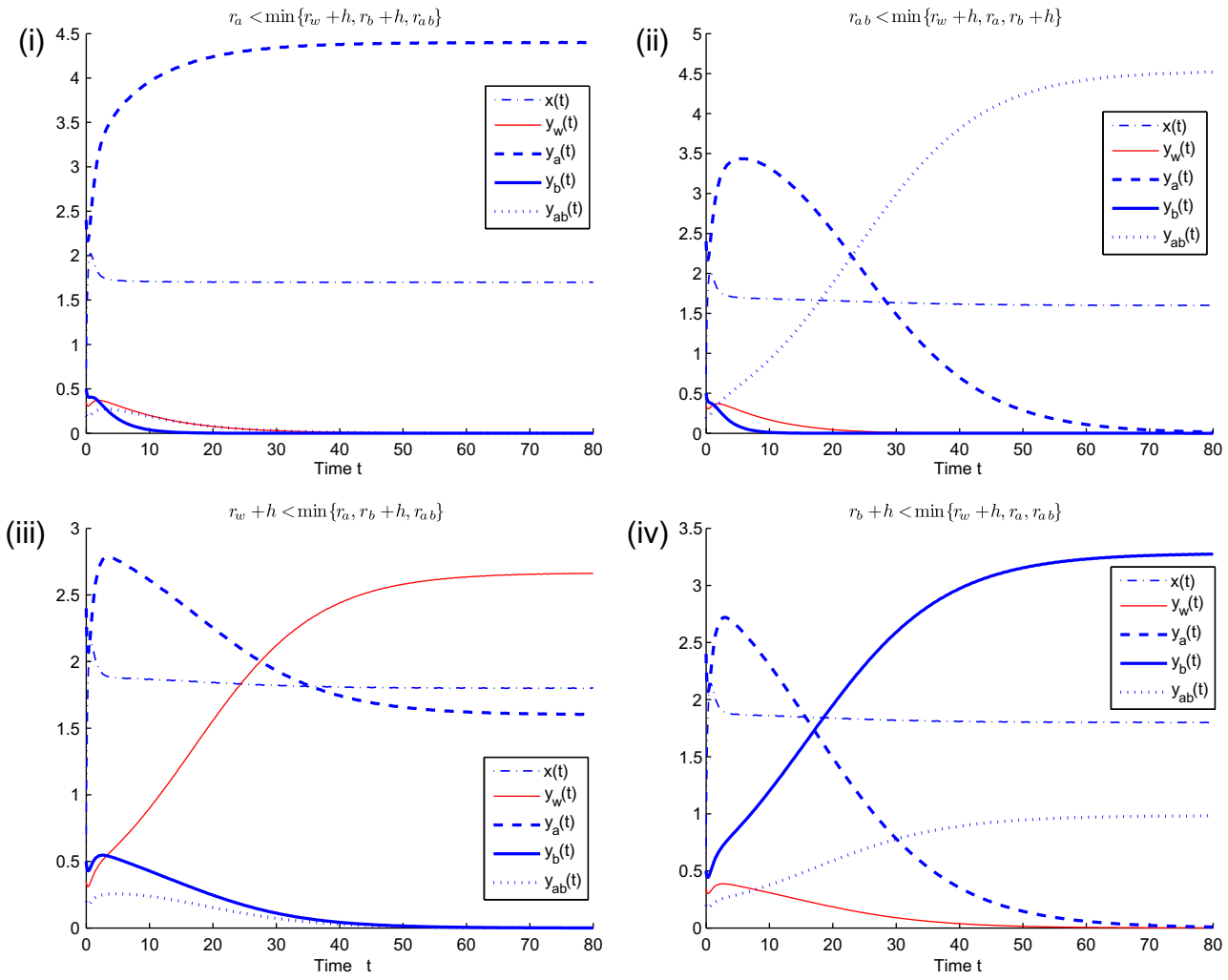

Fig. 4.3. System (1.2) with cycling treatment, i.e., when $f_a = 1$, $f_b = f_{ab} = 0$, we choose parameters $\Lambda = 10$, $d = 2$, $b = 1$, $q = 0.1$, $s = 0.3$, $c = 1.5$, $h = 0.2$, initial values $x(0) = 0.65$, $y_w(0) = 0.35$, $y_a(0) = 2.4$, $y_b(0) = 0.5$, $y_{ab}(0) = 0.2$, and let r_w, r_a, r_b, r_{ab} and h vary such that $R_0 > 1$. (i) When $r_a < \min\{r_w + h, r_b + h, r_{ab}\}$, the semitrivial equilibrium E_a is stable; (ii) when $r_{ab} < \min\{r_w + h, r_a, r_b + h\}$, the semitrivial equilibrium E_{ab} is stable; (iii) when $r_w + h < \min\{r_a, r_b + h, r_{ab}\}$, the semitrivial equilibrium $E_{w,a}$ is stable; (iv) when $r_b + h < \min\{r_w + h, r_a, r_{ab}\}$, the semitrivial equilibrium $E_{b,ab}$ is stable.

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$$E_0 = (\Lambda/d, 0, 0, 0, 0), \quad E_{ab} = \left(\frac{c + r_{ab}}{b}, 0, 0, 0, \frac{\Lambda}{c} - \frac{d}{b} - \frac{dr_{ab}}{bc}\right),$$

$$E_{a,ab} = \left(\frac{c + r_a + h}{b}, 0, \frac{(r_{ab} - r_a - h)(\Lambda - d(c + r_a + h)/b)}{c(r_{ab} - r_a - h(1 - s))}, 0, \frac{hs(\Lambda - d(c + r_a + h)/b)}{c(r_{ab} - r_a - h(1 - s))}\right),$$

$$E_{b,ab} = \left(\frac{c + r_b + h}{b}, 0, 0, \frac{(r_{ab} - r_b - h)(\Lambda - d(c + r_b + h)/b)}{c(r_{ab} - r_b - h(1 - s))}, \frac{hs(\Lambda - d(c + r_b + h)/b)}{c(r_{ab} - r_b - h(1 - s))}\right),$$

$$E_{w,ab} = \left(\frac{c + r_w + h}{b}, \frac{(r_{ab} - r_w - h)(\Lambda - d(c + r_w + h)/b)}{c(r_{ab} - r_w - h(1 - q))}, 0, 0, \frac{hq(\Lambda - d(c + r_w + h)/b)}{c(r_{ab} - r_w - h(1 - q))}\right).$$

Similar to the discussion of the case $f_a = 1$, $f_b = f_{ab} = 0$, we have the following conclusion.

Theorem 3.5. *When $f_a = f_b = 0$, $f_{ab} = 1$, the existence and stability of equilibria of system (3.6) are described in Table 5.*

4. Numerical simulations

In this section, we perform some numerical simulations on the two models to illustrate the results obtained in Sections 2 and 3. For the purpose of simulations, we fix most of the parameters in the models and let the other parameters vary.

For the model with single antibiotic therapy, we fix the values of Λ, d, b, s, c as $\Lambda = 10$, $d = 1$, $b = 2$, $s = 0.3$, $c = 1.5$ and initial values $x(0) = 1.4$, $y_w(0) = 1.0$, $y_a(0) = 0.4$, let the parameters r_w, r_r, f, h vary such that $R_0 > 1$. When $r_r > r_w$ and $fh = 0$, the semitrivial equilibrium with the wild type strain E_w is stable (Fig. 4.1(i)). When $r_r < r_w + fh$ and $fh > 0$, the semitrivial equilibrium with the resistant strain E_r is stable (Fig. 4.1(ii)). When $r_r > r_w + fh$ and $fh > 0$, the endemic equilibrium with both the wild type strain and resistant strain $\tilde{E}$ is stable (Fig. 4.1(iii)).

For the model with multiple antibiotic therapies, we first consider the case in the absence of treatment, that is, $f_a = f_b = f_{ab} = 0$. We choose parameters $\Lambda = 10$, $d = 2$, $b = 1$, $q = 0.1$, $s = 0.3$, $c = 1.5$, $h = 0.2$ and initial values $x(0) = 0.65$, $y_w(0) = 0.35$, $y_a(0) = 2.4$, $y_b(0) = 1.5$, $y_{ab}(0) = 0.2$, and let r_w, r_a, r_b, r_{ab} and h vary such that $R_0 > 1$. When $r_w < \min\{r_a, r_b, r_{ab}\}$, the semitrivial equilibrium with the wild type strain E_w is stable (Fig. 4.2(i)). When $r_a < \min\{r_w, r_b, r_{ab}\}$, the semitrivial equilibrium with the resistant strain A E_a is stable

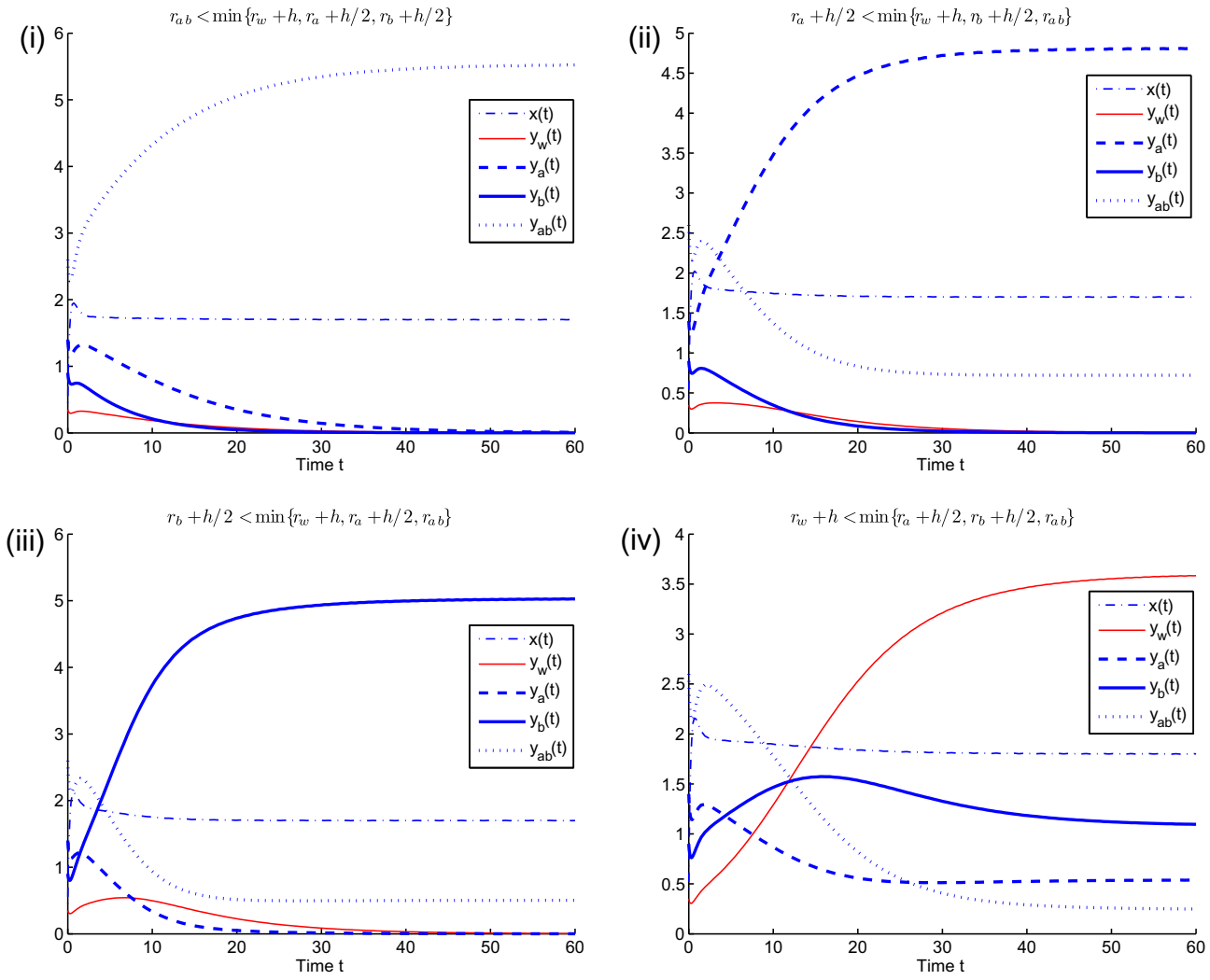

Fig. 4.4. System (1.2) with 50–50 treatment, i.e., when $f_a = f_b = \frac{1}{2}$, $f_{ab} = 0$, we choose the same parameters $\Lambda = 10$, $d = 1$, $b = 1$, $q = 0.1$, $s = 0.3$, $c = 1.5$, $h = 0.2$, the same initial values $x(0) = 0.45$, $y_w(0) = 0.35$, $y_a(0) = 1.4$, $y_b(0) = 0.9$, $y_{ab}(0) = 2.6$, and let r_w, r_a, r_b, r_{ab} and h vary such that $R_0 > 1$. (i) When $r_{ab} < \min\{r_w + h, r_a + h/2, r_b + h/2\}$, the semitrivial equilibrium E_{ab} is stable; (ii) when $r_a + h/2 < \min\{r_w + h, r_b + h/2, r_{ab}\}$, the semitrivial equilibrium $E_{a,ab}$ is stable; (iii) when $r_b + h/2 < \min\{r_w + h, r_a + h/2, r_{ab}\}$, the semitrivial equilibrium $E_{b,ab}$ is stable; (iv) when $r_w + h < \min\{r_a + h/2, r_b + h/2, r_{ab}\}$, the positive equilibrium $\tilde{E}$ is stable.

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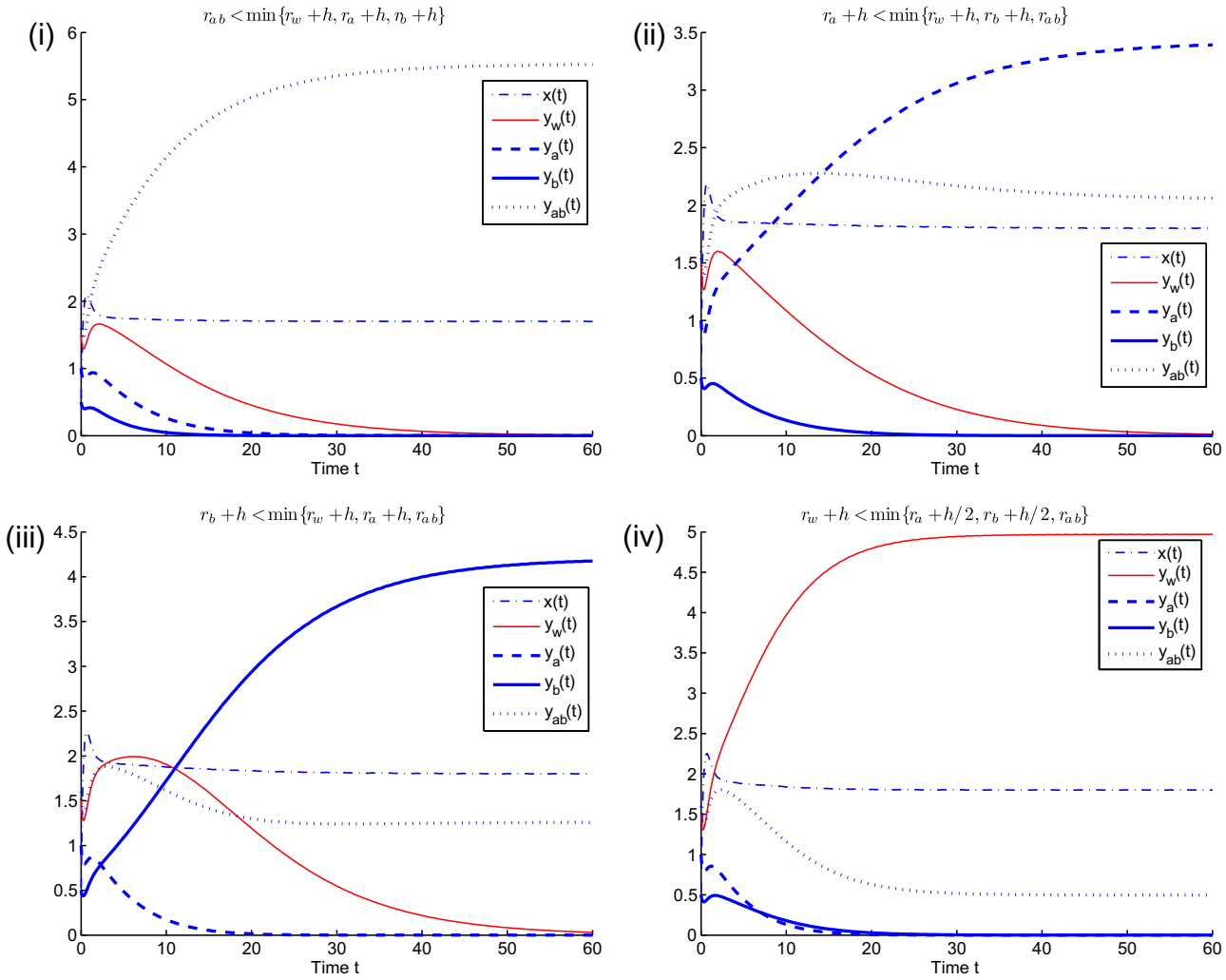

Fig. 4.5. System (1.2) with combining treatment, i.e., when $f_a = f_b = 0, f_{ab} = 1$, we choose the same parameters $\Lambda = 10$, $d = 1$, $b = 1$, $q = 0.1$, $s = 0.3$, $c = 1.5$, $h = 0.2$, the same initial values $x(0) = 0.45$, $y_w(0) = 1.5$, $y_a(0) = 1.0$, $y_b(0) = 0.5$, $y_{ab}(0) = 1.6$, and let r_w, r_a, r_b, r_{ab} and h vary such that $R_0 > 1$. (i) When $r_{ab} < \min\{r_w + h, r_a + h, r_b + h\}$, the semitrivial equilibrium E_{ab} is stable; (ii) when $r_a + h < \min\{r_w + h, r_b + h, r_{ab}\}$, the semitrivial equilibrium $E_{a,ab}$ is stable; (iii) when $r_b + h < \min\{r_w + h, r_a + h, r_{ab}\}$, the semitrivial equilibrium $E_{b,ab}$ is stable; (iv) when $r_w + h < \min\{r_a + h, r_b + h, r_{ab}\}$, the semitrivial equilibrium $E_{w,ab}$ is stable.

(Fig. 4.2(ii)). When $r_b < \min\{r_w, r_a, r_{ab}\}$, the semitrivial equilibrium with the resistant strain B E_b is stable (Fig. 4.2(iii)). When $r_{ab} < \min\{r_w, r_a, r_b\}$, the semitrivial equilibrium with the resistant strains A and B E_{ab} is stable (Fig. 4.2(iv)).

Next we consider the case with cycling treatment, that is, $f_a = 1$, $f_b = f_{ab} = 0$. Choose parameters $\Lambda = 10$, $d = 2$, $b = 1$, $q = 0.1$, $s = 0.3$, $c = 1.5$, $h = 0.2$ initial values $x(0) = 0.65$, $y_w(0) = 0.35$, $y_a(0) = 2.4$, $y_b(0) = 0.5$, $y_{ab}(0) = 0.2$, and let r_w, r_a, r_b, r_{ab} and h vary such that $R_0 > 1$. When $r_a < \min\{r_w + h, r_b + h, r_{ab}\}$, the semitrivial equilibrium with resistant strain A E_a is stable (Fig. 4.3(i)). When $r_{ab} < \min\{r_w + h, r_a, r_b + h\}$, the semitrivial equilibrium with the resistant strains A and B E_{ab} is stable (Fig. 4.3(ii)). when $r_w + h < \min\{r_a, r_b + h, r_{ab}\}$, the semitrivial equilibrium with wild type strain and resistant strain A $E_{w,a}$ is stable (Fig. 4.3(iii)). (iv) when $r_b + h < \min\{r_w + h, r_a, r_{ab}\}$, the semitrivial equilibrium with resistant strain B and both strains $E_{b,ab}$ is stable (Fig. 4.3(iv)).

Now we consider the case with 50–50 treatment, that is, $f_a = f_b = \frac{1}{2}$, $f_{ab} = 0$, Choose the parameters $\Lambda = 10$, $d = 1$, $b = 1$, $q = 0.1$, $s = 0.3$, $c = 1.5$, $h = 0.2$, initial values $x(0) = 0.45$, $y_w(0) = 0.35$, $y_a(0) = 1.4$, $y_b(0) = 0.9$, $y_{ab}(0) = 2.6$, and let r_w, r_a, r_b, r_{ab} and h vary such that $R_0 > 1$. When $r_{ab} < \min\{r_w + h, r_a + h/2, r_b + h/2\}$, the semitrivial equilibrium with both resistant strains A and B E_{ab} is stable (Fig. 4.4(i)). When $r_a + h/2 < \min\{r_w + h, r_b + h/2, r_{ab}\}$, the semitrivial equilibrium with resistant strain A and both resistant strains A and B $E_{a,ab}$ is stable (Fig. 4.4(ii)). When $r_b + h/2 < \min\{r_w + h, r_a + h/2, r_{ab}\}$, the semitrivial equilibrium with resistant strain B and both resistant strains A and B $E_{b,ab}$ is stable (Fig. 4.4(iii)). When $r_w + h < \min\{r_a + h/2, r_b + h/2, r_{ab}\}$, the positive equilibrium with all strains $\tilde{E}$ is stable (Fig. 4.4(iv)).

Finally we consider the case with combining treatment, that is, $f_a = f_b = 0$, $f_{ab} = 1$. Choose parameters $\Lambda = 10$, $d = 1$, $b = 1$, $q = 0.1$, $s = 0.3$, $c = 1.5$, $h = 0.2$, initial values $x(0) = 0.45$, $y_w(0) = 1.5$, $y_a(0) = 1.0$, $y_b(0) = 0.5$, $y_{ab}(0) = 1.6$, and let r_w, r_a, r_b, r_{ab} and h vary such that $R_0 > 1$. When $r_{ab} < \min\{r_w + h, r_a + h, r_b + h\}$, the semitrivial equilibrium with both resistant strains A and B E_{ab} is stable (Fig. 4.5(i)). When $r_a + h < \min\{r_w + h, r_b + h, r_{ab}\}$, the semitrivial equilibrium with resistant strain A and both resistant strains A and B $E_{a,ab}$ is stable (Fig. 4.5(ii)). When $r_b + h < \min\{r_w + h, r_a + h, r_{ab}\}$, the semitrivial equilibrium with resistant strain B and both resistant strains A and B $E_{b,ab}$ is stable (Fig. 4.5(iii)). When $r_w + h < \min\{r_a + h, r_b + h, r_{ab}\}$, the semitrivial equilibrium with the wild type strain and both resistant strains A and B $E_{w,ab}$ is stable (Fig. 4.5(iv)).

5. Discussion

We provided qualitative analysis of models for different treatment protocols to prevent antibiotic resistance. For the model with a single antibiotic therapy, we carried out a global qualitative

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analysis and studied the existence and stability of the disease-free and endemic equilibria. In terms of the basic reproduction number $R_0 = \frac{b\Lambda}{d(c+\min\{r_w+fh,r_r\})}$, our results indicate that when $R_0 < 1$, then the disease-free equilibrium is globally asymptotically stable. If $R_0 > 1$, when the rate of patients infected with wild type bacteria recover from the wild type infected compartment (fh) is less than the difference of the rates of patients infected with resistant bacteria (r_r) and wild type (r_w) recover from the infection in the absence of treatment, the endemic equilibrium with both strains is globally stable; when $fh > r_r - r_w$, the semitrivial equilibrium with the resistant strain is globally stable. Which shows that preventing the initiation or enhancing the discontinuation of unnecessary antibiotic therapy will have a great impact to preserve antibiotic effectiveness [6].

For the model with multiple antibiotic therapies, stability of various equilibria are analyzed. The model allows quantification of the consequences of different therapy regimens and hospital controls in terms of the complex dynamics of competing bacterial strains [6]. The results show that, in the absence of treatment, when $R_0 < 1$, the disease-free equilibrium is stable, when $R_0 > 1$, the semitrivial equilibrium with the strain which has the lowest recovery rate is stable. The results for the cases with 50–50 treatment, cycling treatment and combining treatment demonstrate the essential difficulties in controlling the advance of resistant bacterial infections in hospitals. When more than one antibiotic is employed, as shown by Bonhoeffer et al. [6], Bergstrom et al. [4], Reluga [20], D'Agata et al. [11], cycling use of different antibiotics is not as good as that with a combination of antibiotics.

An ultimate goal is to validate these models by applying it to a particular hospital to compare the predicted endemic states with the prevalence data. We leave this for future study.

Acknowledgments

The authors thank the referee and the handling Editor for their helpful comments and suggestions.

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