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Research Article

Mathematical Modeling of Antibiotic Resistance in Hospital with Dysbiosis

Luzz Claire P. Llenos, Ivy Lorelei G. Miranda, Andrei A. Domogo and Juancho A. Collera*

Department of Mathematics and Computer Science, University of the Philippines Baguio, Baguio City 2600 Philippines

*Author for correspondence; e-mail: jacollera@up.edu.ph

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ABSTRACT

In this paper, we propose and study a transmission model among individuals in a hospital of antibiotic-resistant bacteria considering dysbiosis. The transmission of such bacteria in a hospital setting has been the focus of several previous researches. However, the aspect and contribution of antibiotic-induced dysbiosis was not considered in the existing literature. Antibiotics impact the human intestinal microbiome for it unintentionally affects the needed gut microbiota diversity which are fundamental drivers of health and disease in humans. This unintentional destabilization of the healthy human microbiome results in microbial imbalance called *dysbiosis*. The goal of this paper is to analyze the dynamics of the proposed model in order to come up with insights and possible strategies to control antibiotic-resistant bacterial transmission among individuals in a hospital considering dysbiosis. Possible equilibria of the model system include the resistance-free equilibrium and the endemic equilibrium. The stability of the former means that the antibiotic resistance dies out, while the stability of the latter implies that the antibiotic resistance persists. We determined using sensitivity analysis that the most influential parameter is the drug 1 treatment rate. Moreover, we found a threshold value for this parameter, using numerical continuation, where the antibiotic resistance persists. These results provide insights on how to strategize to control the transmission of antibiotic-resistant bacteria in this setting.

Keywords: antibiotic resistance, dysbiosis, sensitivity analysis, numerical continuation

1. INTRODUCTION

The development of antibiotics saved people from infections which were previously incurable. One of the most common effects of antibiotic treatment is enhanced bacterial expression of antibiotic resistance genes [1]. Antibiotic resistance is presently one of the growing global health threats, specifically to effective prevention and treatment of infections due to antibiotic-resistant bacteria [1]. Antibiotic resistance takes place more frequently in hospitals. This is because of the growing need of the health care sector for antibiotics prescribed for the increasing number of patients and other procedures done in a hospital.

In [2], a study of the transmission of antibiotic-resistant bacteria among individuals within a hospital was carried out. The model that they studied concerns two strains of a single bacterial species with two antimicrobial agents. To differentiate the antimicrobial agents, we will refer to them as drug 1 and drug 2. Bacteria are categorized to be either sensitive or resistant to drug 1 treatment. Moreover, both strains are sensitive to

treatment using drug 2. Individuals are partitioned into those that are free from the bacterial strains (X), and those that carry the bacterial strains. The latter group is further subdivided depending if the bacterial strain they carry is resistant (R) or sensitive (S) to treatment using drug 1. Here, it is assumed that $X + S + R = 1$.

Figure 1 shows the flow of transmission between groups of individuals in a hospital as studied in [2]. The parameters τ_1 and τ_2 are, respectively, the drug 1 and the drug 2 per-capita treatment rates. Patients are being admitted and discharged in the hospital at a rate μ. Note that β is the per-capita colonization or primary transmission rate, while m is the proportion of admitted individuals already carrying bacteria that are sensitive to drug 1. The per-capita immune-response induced bacteria clearance rate is the parameter γ, and σ is the secondary colonization rate relative to that of the primary colonization. It is also assumed that a bacterial strain resistant to treatment using drug 1 has fitness cost represented by the parameter c. Table 1 provides a summary of these parameters, their description, and range of values from [2].

In terms of equations, the transmission dynamics depicted in Figure 1 yields the following system

$$\begin{aligned}
&dS/dt \\
&= m\mu + \beta SX - (\tau_1 + \tau_2 + \gamma + \mu)S + \sigma\beta SR \\
&\quad - \sigma\beta(1 - c)SR, \\
&dR/dt \\
&= \beta(1 - c)RX - (\mu + \tau_2 + \gamma)R - \sigma\beta SR \\
&\quad + \sigma\beta(1 - c)SR, \\
&dX/dt \\
&= (1 - m)\mu + (\tau_1 + \tau_2 + \gamma)S + (\tau_2 + \gamma)R \\
&\quad - \beta SX - \beta(1 - c)RX - \mu X. \qquad (1)
\end{aligned}$$

Since $X + S + R = 1$, the dynamics of this system can be studied using just the first two equations with X replaced by $1 - S - R$.

Antibiotics impact the human intestinal microbiome of the host for it unintentionally affects the needed gut microbiota diversity [3]. The gut microbiota is considered an "essential organ" that contains bacterial species which are

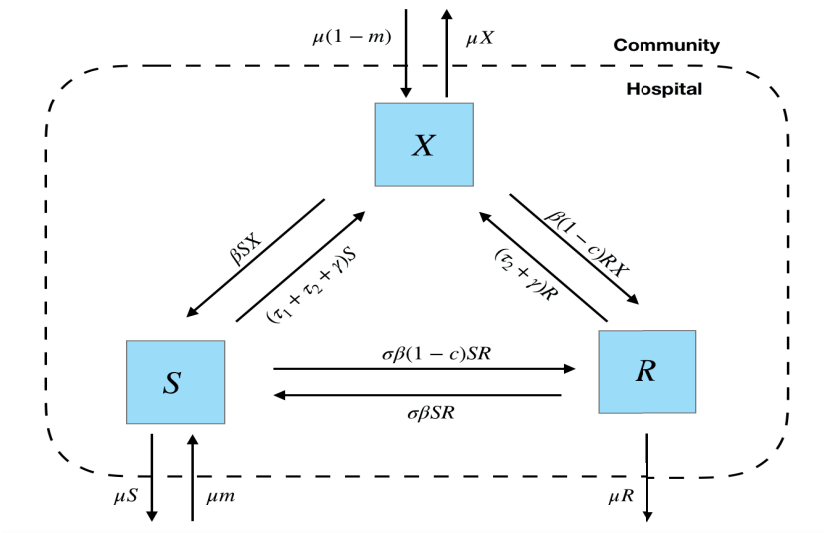

Figure 1. The compartmental model studied in [2] of bacterial transmission dynamics in a hospital among individuals S (carrying sensitive strain), R (carrying resistant stain) and X (uncolonized individuals).

Table 1. Description and range of values of the parameters in the system (1).

Parameter	Description	Range
μ	Per-capita patient turnover rate	> 0
β	Per-capita primary transmission rate (colonization)	> 0
τ_1	Per-capita treatment rate of drug 1	≥ 0
τ_2	Per-capita treatment rate of drug 2	≥ 0
γ	Per-capita clearance rate of bacteria due to immune response	> 0
σ	Relative rate of secondary colonization to that of the primary colonization	[0, 1]
m	Proportion of admitted individual already colonized with sensitive bacteria	[0, 1]
c	Fitness cost of a bacterial strain resistant to drug 1	[0, 1)

fundamental drivers of health and disease in humans, facilitating digestion, metabolism, and protection against pathogenic microbes, as well as immune system and inflammatory problems [4]. Since antibiotic treatment affects a person's microbiome compositions, there is a need to understand the mechanisms underlying the gut microbiota's wide range of roles in human health since it is crucial in resisting pathogen colonization and in the host immune system's maturation [5].

When prescribed appropriately, antibiotics target pathogenic bacteria during infectious periods. However, most administered antibiotics expose a wide range of gut microbes which are not pathogenic [6]. This unintentional destabilization of a healthy human microbiome results in microbial imbalance called *dysbiosis*. Antibiotic-induced dysbiosis decreases the diversity of bacteria in the microbiota which indicates "weaker microbiome" and is a common feature of a disease state [7]. Reduced abundance and diversity of healthy microbial communities impair immune responses of the host and result in reduction in resisting colonization. Consequently, the host becomes more susceptible to colonization of antibiotic-resistant bacteria [8].

Our proposed model generalizes the model given in the system (1) by incorporating the role of dysbiosis. The model is adapted where there is an ecological competition between gut microbiota within the host and bacterial pathogens disrupted by the antibiotic-induced dysbiosis, causing colonization between host to pathogen similar to the approach taken in [9]. Competition for limited resources within the host, e.g. on space nutrients, happens due to co-colonizing bacteria. This causes the reduction of potential competitors due to antibiotics that may favor the pathogen persistence. We consider the reduced rate of pathogen clearance γ due to immune response among individuals. That is, we have $\gamma_\eta = \gamma(1-\eta)$ as the new immune response of hosts undergoing dysbiosis, where η is the resource competition. We assume that interactions between microbiome and pathogen are species specifics. In that case, η and the relative rate of antibiotics induce dysbiosis, denoted by ϕ, are equally distributed [9]. Here, we still assume that the uncolonized individuals and the individuals carrying sensitive strains of bacteria can be treated with both drugs, while individuals carrying bacteria that are of resistant strains can only be treated with drug 2 since it is already resistant to drug 1.

Shown in Figure 2 is the proposed compartmental model that reflects the transmission flow of a single bacterial species within the hospital setting among the individuals considering dysbiosis. Similar to the previous model given in the system (1), this proposed model considers a single bacterial species with two different strains and with two

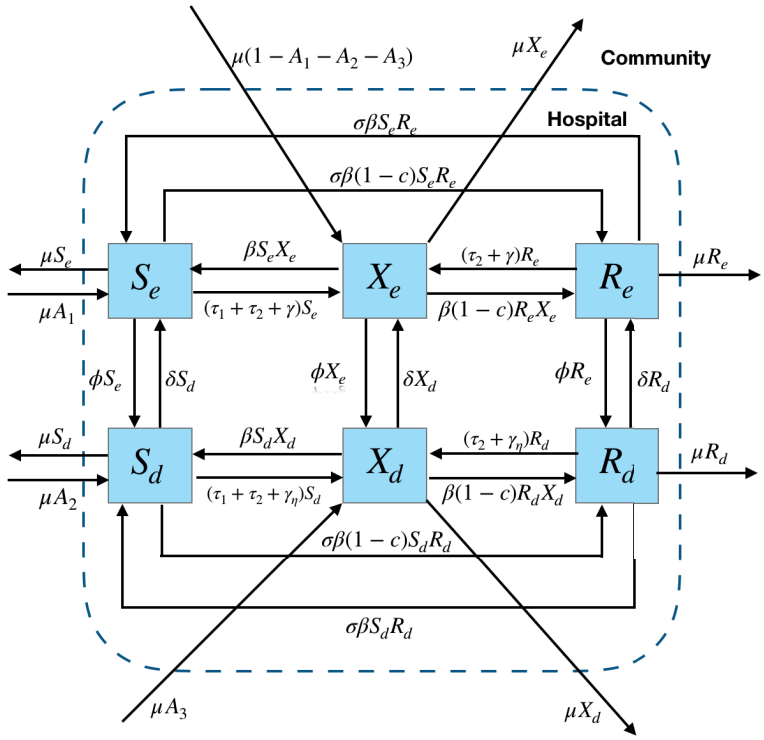

Figure 2. The proposed compartmental model that reflects the transmission flow of a single bacterial species within the hospital setting among individuals S_e (carrying sensitive strain with balanced microbiome), S_d (carrying sensitive strain undergoing dysbiosis), X_e (uncolonized with balanced microbiome), X_d (uncolonized undergoing dysbiosis), R_e (carrying resistant strain with balanced microbiome), and R_d (carrying resistant strain undergoing dysbiosis).

antimicrobial agents. Likewise, individuals are partitioned depending on the strain of bacteria they carry. That is, individuals possibly carry bacterial strains that are either resistant (R) or sensitive (S) to treatment using drug 1, or individuals do not carry these bacteria (X). However, in our proposed model, we consider two host types for a single pathogen. Those with subscript e are the proportion of individuals with balanced microbiome while those with subscript d are the proportion of individuals undergoing dysbiosis. That is, individuals within the hospital are partitioned into individuals who are carrying sensitive strain with balanced microbiome S_e, individuals who are carrying sensitive strain undergoing dysbiosis S_d, individuals who are uncolonized with balanced microbiome X_e, individuals who are uncolonized undergoing dysbiosis X_d, individuals who are carrying resistant strain with balanced microbiome R_e, and individuals who are carrying resistant strain undergoing dysbiosis R_d. The relationship between these two host types is called antibiotic-induced dysbiosis and the rate $\phi = a\theta$, where a is the prevalence of antibiotic exposure and θ is the rate at which antibiotic exposure will induce dysbiosis. Meanwhile, we also assume that the microbiome recovers at a rate δ. The proportions of admitted individuals that are already colonized with sensitive bacteria and with a microbiome undergoing dysbiosis and those with a balanced

microbiome are given, respectively, by A_2 and A_1, while the proportion of admitted uncolonized with a microbiome undergoing dysbiosis is given by A_3. Table 2 provides a summary of the additional parameters introduced in the proposed model. The range of values for these parameters are taken from [9].

The system of equations describing the bacterial transmission in a hospital among individuals as illustrated in Figure 2 is given below

$$\begin{aligned}
dS_e/dt &= \mu A_1 + \beta S_e X_e - \kappa S_e + \sigma\beta S_e R_e \\
&\quad - \sigma\beta(1-c)S_e R_e + \delta S_d - \phi S_e - \mu S_e ,\\
dS_d/dt &= \mu A_2 + \beta S_d X_d - \nu S_d + \sigma\beta S_d R_d \\
&\quad - \sigma\beta(1-c)S_d R_d - \delta S_d + \phi S_e - \mu S_d ,\\
dR_e/dt &= \beta(1-c)R_e X_e - (\tau_2+\gamma)R_e \\
&\quad + \sigma\beta(1-c)S_e R_e - \sigma\beta S_e R_e \\
&\quad + \delta R_d - \phi R_e - \mu R_e ,\\
dR_d/dt &= \beta(1-c)R_d X_d - (\tau_2+\gamma_\eta)R_d \\
&\quad + \sigma\beta(1-c)S_d R_d - \sigma\beta S_d R_d \\
&\quad - \delta R_d + \phi R_e - \mu R_d ,\\
dX_d/dt &= \mu A_3 + \nu S_d - \beta S_d X_d - \beta(1-c)R_d X_d \\
&\quad + (\tau_2+\gamma_\eta)R_d - \delta X_d + \phi X_e - \mu X_d ,\\
dX_e/dt &= \mu(1 - A_1 - A_2 - A_3) \\
&\quad - \beta(1-c)R_e X_e + (\tau_2+\gamma)R_e \\
&\quad - \beta S_e X_e + \kappa S_e + \delta X_d - \phi X_e - \mu X_e ,
\end{aligned} \tag{2}$$

where $\kappa = \tau_1 + \tau_2 + \gamma$ and $\nu = \tau_1 + \tau_2 + \gamma_\eta$. Similar to the system (1), the dynamics of the system (2) can be studied using the reduced system composed of the first 5 equations of the system (2) with X_e replaced by $1 - S_e - S_d - R_e - R_d - X_d$. This reduced system is given as follows

$$\begin{aligned}
dS_e/dt &= \mu A_1 \\
&\quad + \beta S_e(1 - S_e - S_d - R_e - R_d - X_d) \\
&\quad - pS_e + c\sigma\beta S_e R_e + \delta S_d ,\\
dS_d/dt &= \mu A_2 + \beta S_d X_d \\
&\quad - (\tau_1 + \tau_2 + \gamma_\eta + \delta + \mu)S_d \\
&\quad + c\sigma\beta S_d R_d + \phi S_e ,
\end{aligned}$$

Table 2. Description and range of parameter values of the model in the system (2) in addition to the parameters listed in Table 1.

Parameter	Description	Range
A_1	Proportion of admitted already colonized with sensitive bacteria with a balanced microbiome	[0, 1]
A_2	Proportion of admitted already colonized with sensitive bacteria with a microbiome undergoing dysbiosis	[0, 1]
A_3	Proportion of admitted uncolonized with a balanced microbiome	[0, 1]
γ_η	Per-capita clearance rate of bacteria due to immune response undergoing dysbiosis, where $\gamma_\eta = \gamma(1-\eta)$	> 0
η	Resource competition	[0.2, 0.8]
ϕ	Relative rate of antibiotics induce dysbiosis which depends on a and θ, i.e., $\phi = a\theta$	[0, 1]
a	Antibiotic exposure prevalence	[0, 1]
θ	Rate at which antibiotic exposure causes dysbiosis	[0, 1]
δ	Recovery rate of microbiome	> 0

$$
\begin{aligned}
dR_e/dt &= \beta(1-c)R_e(1-S_e-S_d-R_e-R_d-X_d) \\
&\quad -(\tau_2+\gamma+\phi+\mu)R_e - c\sigma\beta S_e R_e + \delta R_d\,, \\
dR_d/dt &= \beta(1-c)R_d X_d - (\tau_2+\gamma_\eta+\delta+\mu)R_d \\
&\quad - c\sigma\beta S_d R_d + \phi R_e\,, \\
dX_d/dt &= \mu A_3 + qS_d - \beta S_d X_d - \beta(1-c)R_d X_d \\
&\quad + (\tau_2+\gamma_\eta)R_d - sX_d \\
&\quad + \phi(1-S_e-R_e-R_d)\,, \qquad (3)
\end{aligned}
$$

where, for sake of brevity, we introduce the following notations $p = \tau_1 + \tau_2 + \gamma + \phi + \mu$, $q = \tau_1 + \tau_2 + \gamma_\eta - \phi$ and $s = \delta + \mu + \phi$. Our proposed model given in the system (2) is a generalization of the model studied in [2] which is given in the system (1). The original model only has the variables X, S, and R but in the proposed model, each of these groups of individuals is further subdivided based on whether their microbiome is balanced (X_e, S_e, and R_e) or imbalanced due to dysbiosis (X_d, S_d, and R_d). Moreover, the proposed model is new and is different from the original model studied in [2], nor from the model in [9] where the idea of partitioning the individuals based on the status of their microbiome was derived.

The solutions of the system (3) become biologically meaningful when the state variables are all non-negative and are bounded. That is, we consider solutions in the region Ω where $\Omega = \{(S_e, S_d, R_e, R_d, X_d) \in \mathbb{R}^5 \mid S_e, S_d, R_e, R_d, X_d \geq 0$ and $S_e + S_d + R_e + R_d + X_d \leq 1\}$, and initial values $(S_e^0, S_d^0, R_e^0, R_d^0, X_d^0) \in \Omega$. In the next section, we show that Ω is a positively invariant region under the flow the system (3).

The goal of this paper is to analyze the dynamics of the proposed model given in the system (3) in order to come up with insights and possible strategies to control antibiotic-resistant bacterial transmission among individuals in a hospital considering dysbiosis. We do this by computing the basic reproduction number, and determining how the equilibrium solutions of the model behave based on this number. We also determine the most influential model parameter and then use it in the numerical bifurcation analysis. These procedures then provide us with a threshold value for the most influential parameter and a scheme to manage antibiotic resistance.

The paper is organized as follows. In the next section, we first show the positivity and boundedness of solutions of the system (3). Next, we provide an expression for the basic reproduction number, and discuss the possible equilibria of the proposed model. We then examine the local stability of the equilibria and relate it to the basic reproduction number. The simulations that follow include sensitivity analysis and numerical continuation. We end with a summary and thoughts of the paper in the conclusion section.

2. Equilibrium solutions and the basic reproduction number

We first show that solutions of the system (3) that start in the positive region Ω remains in Ω for all time $t \geq 0$. Suppose that $S_e(\hat{t}) = 0$, for some positive time $\hat{t}$. Then, from the first equation of the system (3), we have $dS_e(\hat{t})/dt = \mu A_1 + \delta S_d(\hat{t}) > 0$ for $S_d(\hat{t}) \geq 0$. That is, solutions that start in positive region Ω cannot escape Ω through the plane $S_e = 0$. Similarly, one can show that solutions that start in Ω cannot exit through the remaining planes, and thus must remain non-negative for all time $t \geq 0$. Next, we show that solutions of the system (3) can not escape through the boundary where $S_e + S_d + R_e + R_d + X_d = 1$. To see this, observe that at this boundary, we have

$$
\begin{aligned}
d(S_e+S_d+R_e+R_d+X_d)/dt &= -(1-A_1-A_2-A_3)\mu - (\tau_1+\tau_2+\gamma)S_e \\
&\quad -(\tau_2+\gamma)R_e - \delta X_d \;<\; 0.
\end{aligned}
$$

That is, solutions that touch this boundary have to move inward Ω. Similarly, solutions starting in Ω can not escape Ω through the remaining boundaries, and thus must remain bounded. Therefore, combining the positivity and boundedness properties, the solutions of the system (3) that start in Ω remains in Ω for all time $t \geq 0$.

An equilibrium solution of system (3) satisfies the equations $dS_e/dt = 0$, $dS_d/dt = 0$, $dRe/dt = 0$, $dR_d/dt = 0$ and $dX_d/dt = 0$, and therefore can be computed by solving the system of equations where the time derivatives are replaced with the right-hand side functions in system (3). In particular interest to us are the so-called *resistance-free equilibrium* $E_0 = (S_e^*, S_d^*, 0, 0, X_d^*)$ and the *endemic equilibrium* $E_1 = (S_e^+, S_d^+, R_e^+, R_d^+, X_d^+)$ where the non-zero components of each equilibrium are positive. The resistance-free equilibrium E_0 can be obtained by solving for a positive solution (S_e^*, S_d^*, X_d^*) to the following system of equations

$$\begin{aligned}
&\mu A_1 + \beta S_e(1 - S_e - S_d - X_d) - lS_e + \delta S_d = 0,\\
&\mu A_2 + \beta S_d X_d - mS_d + \phi S_e = 0,\\
&\mu A_3 + nS_d - \beta S_d X_d - fX_d + \phi(1 - S_e) = 0,
\end{aligned} \tag{4}$$

while the endemic equilibrium E_1 can be computed by solving for a positive solution $(S_e^+, S_d^+, R_e^+, R_d^+, X_d^+)$ to the following system of equations

$$\begin{aligned}
f_1 &= \mu A_1 + \beta S_e(1 - S_e - S_d - R_e - R_d - X_d)\\
&\quad - pS_e + c\sigma\beta S_e R_e + \delta S_d = 0,\\
f_2 &= \mu A_2 + \beta S_d X_d - (\tau_1 + \tau_2 + \gamma_\eta + \delta + \mu)S_d\\
&\quad + c\sigma\beta S_d R_d + \phi S_e = 0,\\
f_3 &= \beta(1 - c)R_e(1 - S_e - S_d - R_e - R_d - X_d)\\
&\quad - (\tau_2 + \gamma + \phi + \mu)R_e - c\sigma\beta S_e R_e + \delta R_d = 0,\\
f_4 &= \beta(1 - c)R_d X_d - (\tau_2 + \gamma_\eta + \delta + \mu)R_d\\
&\quad - c\sigma\beta S_d R_d + \phi R_e = 0,\\
f_5 &= \mu A_3 + qS_d - \beta S_d X_d - \beta(1 - c)R_d X_d\\
&\quad + (\tau_2 + \gamma_\eta)R_d - sX_d + \phi(1 - S_e - R_e - R_d)\\
&\quad = 0.
\end{aligned} \tag{5}$$

A stable resistance-free equilibrium means that the antibiotic resistance dies out, while a stable endemic equilibrium means that the antibiotic resistance persists. Succeeding examples will show these equilibria for different parameter sets. But before these examples, we first introduce the notion of the reproduction number to put the examples in context.

In epidemiology, there is this threshold value used for predicting disease outbreaks. The so-called *reproduction number*, which we will denote by R_0, is the expected number of cases generated by an individual in a population where everyone is susceptible [10]. Hence, if $R_0 < 1$, the infections eventually die out, while if $R_0 > 1$, the infections persist. This means that the expression for R_0 in terms of the model parameters is important in coming up with control strategies [11, 12]. To compute R_0, we use the next-generation method first introduced in [13]. That is, we calculate the dominant eigenvalue of the next-generation matrix $\mathbf{FV}^{-1}$ where the 2-by-2 matrices are given by $\mathbf{F} = [f_{ij}]$ and $\mathbf{V} = [v_{ij}]$ with entries $f_{11} = g_1, f_{12} = 0, f_{21} = 0, f_{22} = g_2$ for $\mathbf{F}$, and $v_{11} = g_3$, $v_{12} = -\delta$, $v_{21} = -\phi$, $v_{22} = g_4$ for $\mathbf{V}$, where $g_1 = \beta(1 - c)(1 - S_e^* - S_d^* - X_d^*) + \sigma\beta(1 - c)S_e^*$, $g_2 = \beta(1 - c)X_d^* + \sigma\beta(1 - c)S_d^*$, $g_3 = \tau_2 + \gamma + \phi + \mu + \sigma\beta S_e^*$, and $g_4 = \tau_2 + \gamma_\eta + \delta + \mu + \sigma\beta S_d^*$. We obtain the following expression for the reproduction number corresponding to our proposed model in the system (3)

$$R_0 = \{(a_1 + a_4) + [(a_1 + a_4)^2 - 4(a_1 a_4 - a_2 a_3)]^{1/2}\} / 2$$

where $a_1 = g_1 g_4/(g_3 g_4 - \phi\delta)$, $a_2 = g_1\delta/(g_3 g_4 - \phi\delta)$, $a_3 = g_2\phi/(g_3 g_4 - \phi\delta)$, and $a_4 = g_2 g_3/(g_3 g_4 - \phi\delta)$.

In the following examples, we consider two cases where each case uses a different set of parameter values. In the first example, the reproduction number $R_0 < 1$, while in the second example, $R_0 > 1$. We compute all the feasible equilibria of system (3) in both examples. The parameter values used here are taken from [2, 9, 14, 15], and are within the range of acceptable values.

Example 1. For system (3) with parameter values $A_1 = 0.5$, $\beta = 1$, $\sigma = 0.25$, $c = 0.05$, $\mu = 0.1$, $a = 0.2$, $\theta = 1$, $\phi = 0.2$, $\delta = 1/7$, $A_2 = 0.2$, $\tau_1 = 0.20$, $\tau_2 = 0.19$, $\gamma = 1/30$, $\eta = 0.5$, $\gamma_\eta = 1/60$ and $A_3 = 0.0001$, the only feasible equilibrium is the resistance-free equilibrium $E_0 \approx (0.184908,$

0.174261, 0, 0, 0.322535), which is obtained by solving the system (4).

Example 2. For system (3) with parameter values $A_1 = 0.5, \beta = 2, \sigma = 0.25, c = 0.05, \mu = 0.1, a = 0.2, \theta = 1, \phi = 0.2, \delta = 1/7, A_2 = 0.2, \tau_1 = 0.37, \tau_2 = 0.10, \gamma = 1/30, \eta = 0.5, \gamma_\eta = 1/60$ and $A_3 = 0.0001$, we have two feasible equilibria, the resistance-free equilibrium $E_0 \approx$ (0.267025, 0.268652, 0, 0, 0.228145) and the endemic equilibrium $E_1 \approx$ (0.118810, 0.085551, 0.247677, 0.306076, 0.105170), obtained by solving the system (5).

Notice that the endemic equilibrium only exists in the second case where $R_0 > 1$, while the resistance-free equilibrium exists in both cases. Moreover, observe that the third and fourth components of E_0 in the above examples are both zero. Since these components correspond to the individuals who are carrying resistant strain with balanced microbiome (R_e) and individuals who are carrying resistant strain undergoing dysbiosis (R_d), respectively, the equilibrium E_0 reflects the state where we have the absence of antibiotic resistance. An asymptotically stable E_0 then means that antibiotic resistance eventually dies out. In contrast, the components R_e and R_d are both nonzero in E_1. That is, E_1 reflects a state where antibiotic resistance is present, and an asymptotically stable E_1 then means that antibiotic resistance persists in the system. The following section discusses the local asymptotic stability of E_0 and E_1.

3. LOCAL STABILITY ANALYSIS OF THE EQUILIBRIUM SOLUTIONS

The local stability of an equilibrium of the proposed model given in the system (3) can be determined by performing a local stability analysis which studies the linearized system about the equilibrium. For a non-hyperbolic equilibrium E_* of the system (3), its local stability follows the stability of the zero solution of the corresponding linearized system

$$\dot{\mathbf{X}} = \mathbf{AX}$$

where $\mathbf{X} = [x_1, x_2, x_3, x_4, x_5]^\top$ and the Jacobian matrix $\mathbf{A} = [\, a_{ij} \,]$ where the entries $a_{ij} = \partial f_i / \partial x_j$ evaluated at E_* and the functions f_i (x_1, x_2, x_3, x_4, x_5) are given in the system (5) with (S_e, S_d, R_e, R_d, X_d) = (x_1, x_2, x_3, x_4, x_5).

The characteristic equation corresponding to the linearized system about the resistance-free equilibrium E_0 has the following form where the left-hand side factors into quadratic and cubic polynomials

$$(\lambda^2 + B_1\lambda + B_2)\,(\lambda^3 + B_3\lambda^2 + B_4\lambda + B_5) = 0. \qquad (6)$$

From here, one can use the well-known Routh-Hurwitz criteria to provide conditions so that E_0 is locally asymptotically stable. For the scenario given in Example 1, the coefficients in the characteristic equation (6) are $B_1 \approx 0.368557$, $B_2 \approx 0.003867$, $B_3 \approx 1.149144$, $B_4 \approx 0.394552$ and $B_5 \approx 0.037388$. Since all these coefficients are positive and $B_3B_4 > B_5$, the local asymptotic stability of the resistance-free equilibrium E_0 follows. Figure 3 shows the time-series plot of the state variables, using the parameter values from Example 1, showing that E_0 is locally asymptotically stable.

We now move on with the local stability analysis of the endemic equilibrium E_1. The characteristic equation corresponding to the linearized system about E_1 takes the following form

$$\lambda^5 + C_1\lambda^4 + C_2\lambda^3 + C_3\lambda^2 + C_4\lambda + C_5 = 0. \qquad (7)$$

The Routh-Hurwitz criterion guarantees that the roots of the above degree-5 polynomial equation all have negative real part if and only if all coefficients are positive and the following conditions are satisfied

$$C_1C_2C_3 > C_3^2 + C_1^2C_4 \quad \text{and} \quad (C_1C_4 - C_5)(C_1C_2C_3 - C_3^2 - C_1^2C_4) > C_5(C_1C_2 - C_3)^2 + C_1C_5^2. \qquad (8)$$

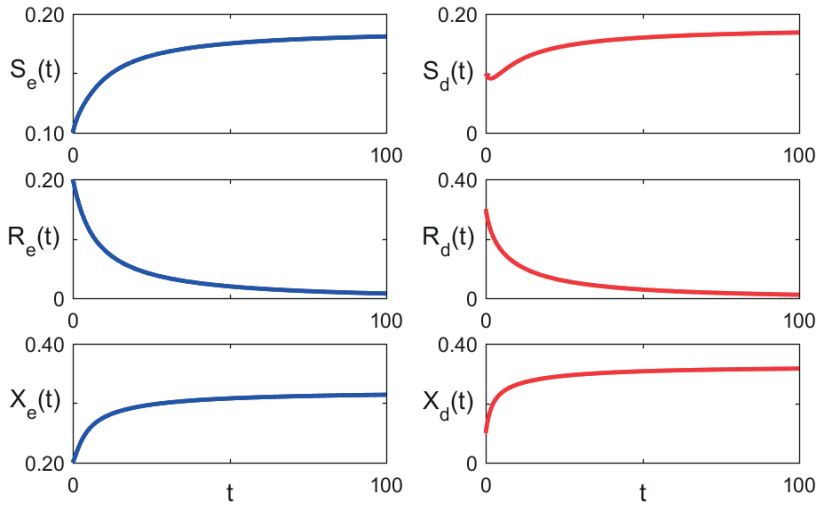

Figure 3. Plot of time evolution of state variables using parameter values from Example 1 showing that the resistance-free equilibrium E_0 is locally asymptotically stable. The initial values used here are $(S_e^0, S_d^0, R_e^0, R_d^0, X_e^0, X_d^0) = (0.1, 0.1, 0.2, 0.3, 0.2, 0.1)$.

For the scenario given in Example 2, where E_1 exists, we obtain the following the coefficients of the degree-5 polynomial in equation (7) $C_1 \approx 2.369124$, $C_2 \approx 1.958186$, $C_3 \approx 0.685405$, $C_4 \approx 0.092361$ and $C_5 \approx 0.001990$. It can be easily verified that these values satisfy the conditions derived from the Routh-Hurwitz criteria given in the inequalities (8). This implies the local asymptotic stability of the endemic equilibrium E_1 in this case. Figure 4 shows the time-series plot of the state variables, using the parameter values from Example 2, showing that E_1 is locally asymptotically stable. Meanwhile, using the parameter values given in Example 2, we have $B_1 \approx -0.075965$, $B_2 \approx -0.027984$, $B_3 \approx 1.384372$, $B_4 \approx 0.516922$ and $B_5 \approx 0.042861$. Since $B_2 < 0$, clearly the quadratic factor in the left-hand side of equation (6) yields a positive root of the characteristic equation and consequently, E_0 is unstable for this case. We remark that for the case given in Example 2 where $R_0 > 1$, E_1 is locally asymptotically stable while E_0 is unstable. In other words, Example 2 provides a scenario where antibiotic resistance persists.

4. NUMERICAL SIMULATION

As shown previously, the decline or persistence of the antibiotic resistance depends on the value of the reproduction number R_0. In this section, we use numerical simulation to examine the relationship of R_0 to the model parameters firstly by performing a sensitivity analysis. We then use the most influential parameter, derived from the sensitivity analysis, as the bifurcation parameter in the numerical continuation and bifurcation analysis that follows.

To analyze the sensitivity of the reproduction number R_0 on variations of the parameter values, we perform a local sensitivity analysis using the so-called *sensitivity index*. For a given parameter k, the corresponding sensitivity index S_k of R_0 is given by

$$S_k = (k/R_0) \times (\partial R_0/\partial k) \tag{9}$$

where k/R_0 is a normalizing factor, and the partial derivative in equation (9) is approximated as follows

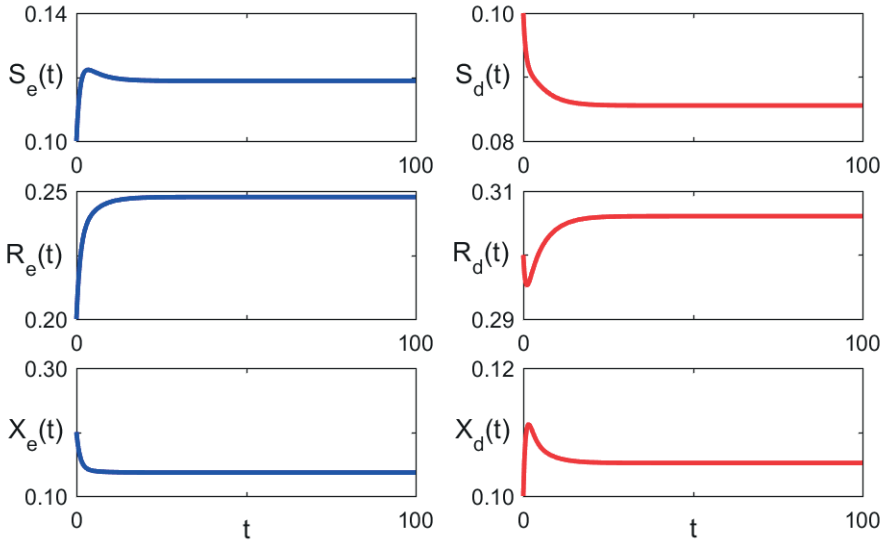

Figure 4. Plot of time evolution of state variables using parameter values from Example 2 showing that the endemic equilibrium E_1 is locally asymptotically stable. The initial values used here are (S_e^0, S_d^0, R_e^0, R_d^0, X_e^0, X_d^0) = (0.1, 0.1, 0.2, 0.3, 0.2, 0.1).

$$\partial R_0 / \partial k \approx [R_0(t, k + r) - R_0(t, k)] / r \qquad (10)$$

where k is the value of a parameter, r is the parameter variation and t is time [16].

Figure 5 shows the sensitivity index ranking using the parameter set in Example 2 for different values of r. Recall that r is the parameter variation used in the approximation for the partial derivative in expression (10). The most influential parameter is τ_1, which is the treatment rate of drug 1. This is followed by β, the primary transmission rate (colonization) which brings positive change in R_0 and μ, the patient turnover rate, which has a negative effect on R_0. The parameters η, the resource competition, γ_η, the immune-response clearance rate of bacteria undergoing dysbiosis, and A_3, the proportion of admitted uncolonized with microbiome undergoing dysbiosis, have the least effect on R_0.

We now examine the dynamical behavior of the proposed model varying the most influential parameter τ_1. We carry out a one-parameter numerical continuation and bifurcation analysis using *MatCont* [17, 18]. The development and maintenance of this interactive graphical software package are led by W. Govaerts, Y.A. Kuznetsov and H.G.E. Meijer, and is used together with the Matlab platform in studying, particularly, continuous parameterized dynamical systems (ODEs). MatCont can compute branches of equilibria and limit-cycle solutions, and detect various steady-state and limit-cycle bifurcations.

Figure 6 shows branches of equilibrium solutions of the proposed model when the main parameter τ_1 is varied. Here, the graph of the portion of individuals carrying the antibiotic-resistant bacteria R_e in terms of the treatment rate of drug 1 parameter τ_1 is presented. The resistance-free-equilibrium branch (horizontal line) has parts that are stable and parts that are unstable parts. These are shown in solid and dashed lines, respectively. The stability switch along this branch occurs at $\tau_1 = \tau_1^* \approx 0.11606$ where the endemic-equilibrium branch (curve) bifurcates. Note that for $\tau_1 < \tau_1^*$,

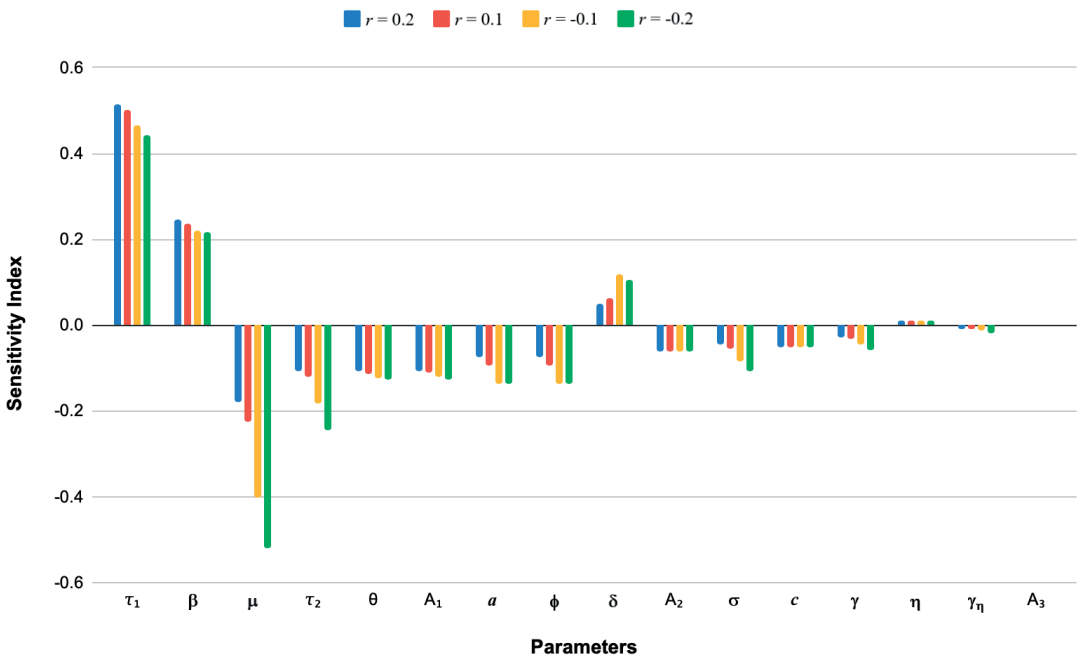

Figure 5. Sensitivity index ranking using different values of r showing that τ_1, the drug 1 treatment rate, is the most influential parameter.

the resistance-free equilibrium solely exists and is locally asymptotically stable. In contrast, when $\tau_1 > \tau_1^*$, the resistance-free equilibrium switches to instability, and its stability is passed on to the endemic equilibrium that bifurcated when $\tau_1 = \tau_1^*$.

It is also worth noting that the case when $\tau_1 = \tau_1^*$ is equivalent to the case when the reproduction number $R_0 = 1$. Moreover, the case when $\tau_1 < \tau_1^*$ corresponds to the case when $R_0 < 1$ where the antibiotic resistance dies out. Similarly, the case when $\tau_1 > \tau_1^*$ corresponds to the case when $R_0 > 1$ where the antibiotic resistance persists. Knowing the threshold value τ_1^* is significant since it allows us to strategize when treating using drug 1 in order to control the antibiotic-resistant bacterial transmission in our setting.

5. SUMMARY AND CONCLUSION

The antibiotic-resistant bacterial transmission in hospital environments has been the focus of several previous researches. However, the aspect and contribution of antibiotic-induced dysbiosis was not considered in the existing literature. Antibiotics impact the human intestinal microbiome for it unintentionally affects the needed gut microbiota diversity which are fundamental drivers of health and disease in humans. This unintentional destabilization of a healthy human microbiome results in microbial imbalance called dysbiosis.

In this current work, we proposed and analyzed a model of antibiotic-resistant bacterial transmission among individuals in a locale, e.g. hospitals, considering dysbiosis with the goal of coming up with insights and control strategies. The possible equilibria of the model system include the resistance-free equilibrium and the endemic equilibrium. We examined the behavior of these equilibria using local stability analysis and its relation to a threshold value which is the basic reproduction number. The stability of

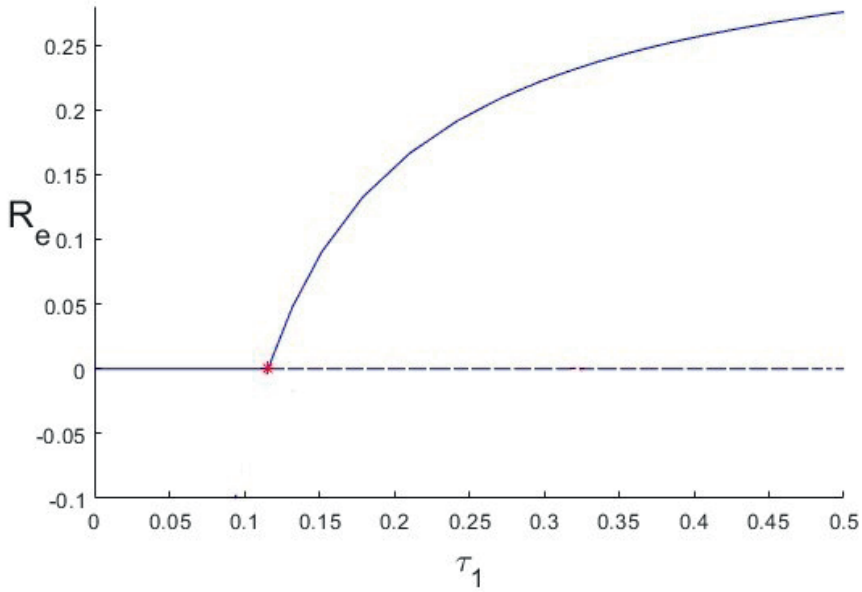

Figure 6. Branches of equilibrium solutions of system (3) obtained using numerical continuation varying the parameter τ_1 which is the treatment rate of drug 1. The branching point occurs at $\tau_1 = \tau_1^* \approx 0.11606$ which is equivalent to the case when the reproduction number $R_0 = 1$.

the resistance-free equilibrium means that the antibiotic resistance dies out, while the stability of the endemic equilibrium implies the persistence of antibiotic-resistant bacteria. We also performed a local sensitivity analysis, which determined the drug 1 treatment rate as the most influential parameter. This parameter is then used in the numerical continuation where a threshold value of this parameter was obtained where the antibiotic resistance persists. These results provide insights on how to strategize, using the most influential parameter or possibly consider other influential parameters, to control antibiotic-resistant bacterial transmission in this setting.

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Conflict of interest statement

The authors declare no conflicts of interest.

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