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MODELING THE WITHIN-HOST DYNAMICS OF CHOLERA: BACTERIAL-VIRAL-IMMUNE INTERACTION

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Abstract We present a mathematical model to investigate the within-host dynamics of cholera. We formulate a system of nonlinear differential equations to describe the evolution and interplay of the pathogenic bacteria at different stages, the viruses, and the immune response inside the human body. Our analysis shows that the basic reproduction number of this model is determined collectively by the bacterial, viral and immune reproduction numbers, and that the bacterial-viral-immune interaction shapes the complex dynamics of cholera infection within a human host.

Keywords Cholera modeling, within-host dynamics, equilibrium analysis.

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1. Introduction

Mathematical modeling is an effective theoretical tool to study infectious diseases, and has long provided useful insight into the transmission and spread of diseases and the design of control strategies [15]. Traditional mathematical epidemic models are focused on population-level dynamics, typically using theory of differential equations and dynamical systems to investigate the persistence and extinction of an infection. In recent years, there has been increasing interest in understanding pathogen evolution and interaction within a human body and their connection to the population-level disease transmission and spread (see [3, 7, 10, 18] and references therein). In particular, the authors in [6, 8, 9] coupled the between-host and within-host dynamics of an environmentally-driven infectious disease and conducted mathematical analysis based on the separation of scales. Meanwhile, a nested modeling approach has been applied to link the between-host/within-host dynamics of several diseases [11, 12, 16, 17, 22].

The present paper is concerned with the within-host modeling of cholera, which is a severe waterborne infection caused by the bacterium *Vibrio cholerae*. An ancient

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disease, cholera has re-emerged as a major health threat to a number of developing countries and caused several major outbreaks in recent years, including those in Zimbabwe from 2008 to 2009 [19], in Haiti from 2010 to 2012 [27] and in Yemen from 2016 to 2017 [14], with wide-spread infections and high morbidity and mortality levels. Cholera can be transmitted through both the indirect, environment-to-human route and the direct, human-to-human route. Populations lacking sufficient sanitation, hygiene and medical resources especially suffer from cholera [1, 20].

Numerous mathematical models have been published for the investigation of cholera dynamics [4, 13, 14, 19, 21, 23, 25, 26, 30–32], most of which are focused on the population level between-host transmission. On the other hand, cholera infection involves complicated within-host dynamics that are distinct from many other infectious diseases. In particular, the authors in [29] found that a virus played an essential role in the pathogenesis of the vibrios within the human body. This virus, referred to as the cholera toxin phage (CTXϕ), induces a horizontal gene transfer of the bacteria that leads to an infectivity several hundreds of times higher than that of the vibrios ingested from the environment.

Following the notion in [33, 34], we use the term 'environmental vibrios' for those pathogenic bacteria originated from the environment which usually have a low infectivity, and 'human vibrios' for those bacteria generated within the human body (for example, through the bacterial-viral interaction) which have a much higher infectivity. Human cholera, with the major symptom of severe diarrhea, is a direct consequence of the highly infective human vibrios. At the same time, the host immune system is inevitably involved in the interaction with the bacteria and viruses as an important means to protect the human body.

The within-host dynamics of cholera may constitute an important step in the development of a cholera epidemic and could impact the transmission and spread of the disease at the population level. Particularly, when the highly infective vibrios are shed out of the human body, they remain active for a period of several hours during which time these vibrios can be transmitted directly through the human-to-human pathway [13, 19, 26]. For example, in places where basic hygiene and sanitation are not available (or otherwise not paid attention to), a person who is infected with cholera may use dirty hands to prepare food for family members, or shake hands with other people, so that the infection risk of those people who are in direct contact with this person would be significantly increased.

There have been a few efforts to mathematically quantify the within-host dynamics of cholera. A model that links the between-host and within-host dynamics of cholera was proposed in [33], which was then analyzed by the separation of two time scales: the fast scale for the pathogen dynamics inside the human body, and the slow scale for the disease transmission among human hosts and the environmental evolution of the vibrios. The model in [33] was extended to incorporate some heterogeneities of the individual hosts [35]. The within-host dynamics in both studies, however, take a very simple form, represented by a single differential equations describing the increased toxicity of the pathogen inside the human body. In another recent study [34], the within-host dynamics of cholera was investigated in more detail, where the vibrios ingested from the environment (with lower infectivity) and those transformed inside the human body (with higher infectivity) are distinguished, and their interaction with the virus (CTXϕ) is taken into account. The model, however, does not involve the host immune response.

We aim to conduct a deeper investigation of the cholera within-host dynamics

in the present work, by describing and analyzing the nontrivial interaction among different stages of the pathogen, the virus, and the immune response inside the human body. Specifically, in our model, environmental vibrios are infected by viruses (CTXϕ) and are transformed into highly toxic human vibrios; new viruses are generated consequently. Meanwhile, the host immune system responds to the invasion by trying to eliminate the pathogenic vibrios and viruses so as to protect the human body. As such, by modeling the interaction among environmental vibrios, human vibrios, viruses, and host immunity, we hope to gain improved understanding of the complex within-host dynamics of cholera.

We organize the remainder of the paper as follows. In Section 2, we describe the within-host cholera model based on a system of nonlinear differential equations and introduce necessary assumptions. In Section 3, we conduct a careful equilibrium analysis for both the trivial and non-trivial equilibria of the system. In Section 4, we present some numerical simulation results to verify our main analytical findings. Finally, we conclude the paper in Section 5 with some discussion.

2. Model formulation

We use the following system of differential equations to describe the within-host dynamics of cholera:

$$\begin{aligned}
\frac{dB}{dt} &= \Lambda - \alpha\frac{B}{\kappa+B}V - \delta_1 B - \gamma_1\frac{B}{\kappa_B+B}T,\\
\frac{dZ}{dt} &= g(Z) + \theta_1\alpha\frac{B}{\kappa+B}V - \delta_2 Z - \gamma_2\frac{Z}{\kappa_Z+Z}T,\\
\frac{dV}{dt} &= \theta_2\alpha\frac{B}{\kappa+B}V - \delta_3 V - \gamma_3 VT,\\
\frac{dT}{dt} &= q(T) + \theta_3\gamma_1\frac{B}{\kappa_B+B}T + \theta_4\gamma_2\frac{Z}{\kappa_Z+Z}T + \theta_5\gamma_3 VT - \delta_4 T,
\end{aligned} \tag{2.1}$$

where B and Z represent the concentrations of the environmental vibrios and human vibrios, respectively, V denotes the concentration of the virus (CTXϕ), and T is the concentration of the immune cells (e.g., natural killer cells and T cells), inside the human body. The bacteria (i.e., the environmental and human vibrios) are subject to saturation effects [13,19,34] in their interactions with the viruses and immune cells, with associated half-saturation rates κ, κ_B and κ_Z; the viral-immune interaction, instead, is modeled by a bilinear form [2, 24]. The parameter Λ denotes the ingestion rate of the environmental vibrios, α is the contact rate between environmental vibrios and viruses, γ_i $(i = 1, 2, 3)$ represents the contact rate of immune cells with environmental vibrios, human vibrios, and viruses, respectively, and δ_i $(i = 1, 2, 3, 4)$ denotes the natural death rate in each compartment. New human vibrios are generated through the interaction between the environmental vibrios and viruses, which at the same time produces new viruses. We let θ_1 and θ_2 be the rescaled coefficients that capture the generation rates of Z and V, respectively, through the bacterial-viral interaction. We also let θ_3, θ_4 and θ_5 be the rescaled coefficients to depict the production rates of the immune cells through their interactions with the environmental vibrios, human vibrios and viruses, respectively.

Meanwhile, we introduce two general functions $g(Z)$ and $q(T)$ to account for the intrinsic growth of human vibrios Z and immune cells T, respectively. We make the following assumptions

(**H1**) $g(0) = 0,\ g'(Z_g) < \delta_2$ for some $Z_g \geq 0$, and $g''(Z) \leq 0$ on $[0, \infty)$.

(**H2**) $q(0) = 0,\ q'(T_q) < \delta_4$ for some $T_q \geq 0$, and $q''(T) \leq 0$ on $[0, \infty)$.

Biologically, the assumption (H1) states that in the absence of the bacterial-viral interaction, the human vibrios cannot grow with zero initial concentration, that their intrinsic growth will be outcompeted by the natural death at some point, and that their intrinsic growth is subject to a saturation effect. Similar interpretation holds for the assumption (H2) with respect to the intrinsic growth of the immune cells. It can be easily verified that several common growth forms, such as the linear growth and logistic growth, satisfy these assumptions. We additionally remark that since viruses do not multiply by themselves and their replication relies on interactions with other microorganisms (e.g., bacteria), we do not consider the intrinsic growth of viruses in our model.

It is clear that $\mathbb{R}^4_+$ is positively invariant for system (2.1). Denote

$$G(Z) = g(Z) - \delta_2 Z \tag{2.2}$$

and

$$Q(T) = q(T) - \delta_4 T. \tag{2.3}$$

Assumptions (H1) and (H2) imply that $G(0) = 0,\ G'(Z) < 0$, for $Z \geq Z_g$ and $Q(0) = 0, Q'(T) < 0$, for $T \geq T_q$. Since $\frac{dB}{dt} \leq \Lambda - \delta_1 B$ and $\frac{d(\theta_2 B + V)}{dt} \leq \theta_2 \Lambda - \min\{\delta_1, \delta_3\}(\theta_2 B + V)$, then $\limsup_{t \to +\infty} B(t) \leq \dfrac{\Lambda}{\delta_1}$ and $\limsup_{t \to +\infty}(\theta_2 B(t) + V(t)) \leq \dfrac{\theta_2 \Lambda}{\min\{\delta_1, \delta_3\}}$. Hence, V has an upper bound $V_{\max} > 0$. In fact, one can verify the following inequality

$$\begin{aligned}\frac{d(\theta_3 B + \theta_4 Z + \theta_5 V + T)}{dt} \leq & A - \min\{\delta_1, \delta_3, -G'(Z_g), -Q'(T_q)\} \\ & (\theta_3 B + \theta_4 Z + \theta_3 V + T)\end{aligned}$$

for $Z > Z_g$ and $T > T_q$, where

$$\begin{aligned}A =& \theta_3 \Lambda + \alpha V_{\max} |\theta_4 \theta_1 + \theta_5 \theta_2 - \theta_3| + \theta_4 (G(Z_g) - Z_g G'(Z_g)) + Q(T_q) - T_q Q'(T_q) \\ >& 0.\end{aligned}$$

Thus, Z and T have upper bounds $Z_{\max} > 0$ and $T_{\max} > 0$, respectively. Therefore, we have the following biologically feasible domain for system (2.1):

$$\Gamma = \left\{ (B, Z, V, T) \in \mathbb{R}^4_+ : B \leq \frac{\Lambda}{\delta_1},\ Z \leq Z_{\max},\ V \leq V_{\max},\ T \leq T_{\max} \right\}.$$

3. Equilibrium analysis

3.1. Trivial equilibrium

It is clear to observe that system (2.1) has a unique trivial equilibrium at

$$x_0 = (B_0,\ 0,\ 0,\ 0) = (\frac{\Lambda}{\delta_1},\ 0,\ 0,\ 0). \tag{3.1}$$

Using the notations in [28], the new infection matrix $\mathcal{F}$ and the transition matrix $\mathcal{V}$ are given by

$$\mathcal{F} = \begin{bmatrix} g'(0) & \frac{\theta_1 \alpha B_0}{\kappa + B_0} & 0 \\ 0 & \frac{\theta_2 \alpha B_0}{\kappa + B_0} & 0 \\ 0 & 0 & q'(0) + \frac{\theta_3 \gamma_1 B_0}{\kappa_B + B_0} \end{bmatrix} \quad \text{and} \quad \mathcal{V} = \begin{bmatrix} \delta_2 & 0 & 0 \\ 0 & \delta_3 & 0 \\ 0 & 0 & \delta_4 \end{bmatrix}. \tag{3.2}$$

It follows that the next-generation matrix is given by

$$\mathcal{F}\mathcal{V}^{-1} = \begin{bmatrix} \frac{g'(0)}{\delta_2} & \frac{\theta_1 \alpha B_0}{\delta_3(\kappa + B_0)} & 0 \\ 0 & \frac{\theta_2 \alpha B_0}{\delta_3(\kappa + B_0)} & 0 \\ 0 & 0 & \frac{1}{\delta_4}\left(q'(0) + \frac{\theta_3 \gamma_1 B_0}{\kappa_B + B_0}\right) \end{bmatrix}. \tag{3.3}$$

The basic reproduction number of model (2.1) is then defined as the spectral radius of the matrix $\mathcal{F}\mathcal{V}^{-1}$; i.e.,

$$\mathcal{R}_0 = \rho(\mathcal{F}\mathcal{V}^{-1}) = \max\{R_1, R_2, R_3\}, \tag{3.4}$$

where

$$R_1 = \frac{g'(0)}{\delta_2}, \quad R_2 = \frac{\theta_2 \alpha B_0}{\delta_3(\kappa + B_0)}, \quad R_3 = \frac{1}{\delta_4}\left(q'(0) + \frac{\theta_3 \gamma_1 B_0}{\kappa_B + B_0}\right).$$

Here R_1 is referred to as the *bacterial reproduction number*, which measures the ratio of the initial intrinsic growth rate of the human vibrios and their natural death rate; R_2 is referred to as the *viral reproduction number*, which characterizes the relative strength between the generation rate and the natural death rate of the viruses; R_3 is referred to as the *immune reproduction number*, which characterizes the generation rate of the immune cells (from both the intrinsic growth and stimulated growth) in comparison with their natural death rate. Thus, the risk of cholera infection inside the human body is determined collectively by the bacterial, viral and immune reproduction numbers, representing the interplay among these three critical components in the within-host dynamics of cholera.

Based on this definition of the basic reproduction number $\mathcal{R}_0$, we have the following property for the trivial equilibrium x_0.

Theorem 3.1. *If $\mathcal{R}_0 \leq 1$, then system (2.1) has a unique equilibrium; i.e., the trivial equilibrium x_0, and it is globally asymptotically stable in Γ. If $\mathcal{R}_0 > 1$, x_0 attracts all the points on the B-axis but becomes unstable in Γ.*

In order to prove Theorem 3.1, we first consider the following subsystem of (2.1) which represents a virus-free state:

$$\begin{aligned} \dot{B} &= \Lambda - \delta_1 B - \gamma_1 \frac{B}{\kappa_B + B} T, \\ \dot{Z} &= g(Z) - \delta_2 Z - \gamma_2 \frac{Z}{\kappa_Z + Z} T, \\ \dot{T} &= q(T) + \left(\theta_3 \gamma_1 \frac{B}{\kappa_B + B} + \theta_4 \gamma_2 \frac{Z}{\kappa_Z + Z} - \delta_4\right) T, \end{aligned} \tag{3.5}$$

where, and in what follows, we use the dot notation $\dot{x}$ interchangeably with $\frac{dx}{dt}$. It is clear that

$$\Omega = \{(B, Z, T) \in \mathbb{R}^3_+ : B \leq B_0,\ Z \leq Z_{\max},\ T \leq T_{\max}\}$$

is a biologically meaningful and positively invariant domain for the subsystem (3.5).

Lemma 3.1. *If $R_1 \leq 1$ and $R_3 \leq 1$, the virus-free subsystem (3.5) has a unique equilibrium $s_0 = (B_0, 0, 0)$, and it is globally asymptotically stable in Ω.*

Proof. It is clear that $\mathcal{L} = Z$ is a Lyapunov function on Ω for subsystem (3.5) since $R_1 \leq 1$ and $\dot{Z} = 0$ implies $Z = 0$. Since $q''(T) \leq 0$ and $q(0) = 0$, we have

$$\left(\frac{q(T)}{T}\right)' = \frac{1}{T}\left(q'(T) - \frac{q(T)}{T}\right) \leq 0. \tag{3.6}$$

When $Z = 0$, one can choose $\phi(B, T) = \frac{1}{T}$ such that

$$\operatorname{div}\left(\phi\dot{B}, \phi\dot{T}\right) = \frac{\partial(\phi\dot{B})}{\partial B} + \frac{\partial(\phi\dot{T})}{\partial T} = -\frac{\delta_1}{T} - \frac{\gamma_1\kappa_B}{(\kappa_B + B)^2} + \left(\frac{q(T)}{T}\right)' < 0$$

in $\mathbb{R}^2_+$. Hence, the planar subsystem $\{\dot{B}, \dot{T}\}|_{Z=0}$ of system (3.5) has no non-constant periodic solution in $\mathbb{R}^2_+$ by the Bendixson-Dulac theorem. Since $R_3 \leq 1$, there is a unique equilibrium $(B_0, 0)$ for the planar subsystem $\{\dot{B}, \dot{T}\}|_{Z=0}$ and it is globally asymptotically stable in $\mathbb{R}^2_+$. Hence, by LaSalle's invariance principle, s_0 is globally asymptotically stable in Ω. □

Based on Lemma 3.1, we proceed to prove Theorem 3.1.

Proof of Theorem 3.1. Assume (B, Z, V, T) is an equilibrium of system (2.1), then the first equation of system (2.1) implies $B \leq B_0$. Accordingly, we obtain $V = 0, Z = 0$ and $T = 0$ one after another by the third, the second, and the fourth equations of system (2.1) since $R_2 \leq 1, R_1 \leq 1$ and $R_3 \leq 1$, respectively. Thus, the trivial equilibrium x_0 is the unique equilibrium of system (2.1) if $\mathcal{R}_0 \leq 1$.

Consider a Lyapunov function $\mathcal{L} = V$ and differentiate $\mathcal{L}$ along the solutions of system (2.1), we have

$$\dot{\mathcal{L}} = \dot{V} = \theta_2\alpha\frac{B}{\kappa + B}V - \delta_3 V - \gamma_3 TV \leq \delta_3(R_2 - 1)V - \gamma_3 TV \leq 0.$$

Hence, $\dot{\mathcal{L}} = 0$ implies $V = 0$, or $R_2 = 1, B = B_0, T = 0$. Note that the largest invariant sets on $\{x \in \Gamma : V = 0\}$ and $\{x \in \Gamma : B = B_0, T = 0\}$ are $\{x \in \Gamma : V = 0\}$ and $\{x_0\}$, respectively. Hence, the largest invariant set on $\{x \in \Gamma : \dot{\mathcal{L}} = 0\}$ is $\{x \in \Gamma : V = 0\}$. By LaSalle's invariance principle and Lemma 3.1, the trivial equilibrium x_0 is globally asymptotically stable in Γ.

In contrast, if $\mathcal{R}_0 > 1$, x_0 attracts all the points on the B-axis since B_0 is globally asymptotically stable on the one-dimensional subsystem $\dot{B} = \Lambda - \delta_1 B$. Consider the Jacobian matrix of system (2.1) at x_0, which is given by

$$J_0 = \begin{bmatrix} -\delta_1 & 0 & -\frac{\alpha B_0}{\kappa + B_0} & -\frac{\gamma_1 B_0}{\kappa_B + B_0} \\ 0 & \delta_2(R_1 - 1) & \frac{\theta_1\alpha B_0}{\kappa + B_0} & 0 \\ 0 & 0 & \delta_3(R_2 - 1) & 0 \\ 0 & 0 & 0 & \delta_4(R_3 - 1) \end{bmatrix}.$$

Obviously, J_0 has at least one positive eigenvalue, hence the trivial equilibrium x_0 is unstable. □

3.2. Non-trivial equilibria

We already know that there is only one equilibrium x_0 for system (2.1) when $\mathcal{R}_0 \leq 1$. Next, we investigate the equilibria of system (2.1) when $\mathcal{R}_0 > 1$, which is equivalent to that at least one of the following three inequalities holds: (i) $R_1 > 1$; (ii) $R_2 > 1$; (iii) $R_3 > 1$. We discuss these three cases separately.

Case (i): $R_1 > 1$. Then there exists a unique $Z^* \in (0, Z_g)$ satisfying $G'(Z^*) = 0$, where the function G is defined in equation (2.2). Hence, we have a nonzero solution $Z_0 > Z^*$ such that $G(Z_0) = 0$ and $G(Z) > 0$ for $Z \in (0, Z_0)$, $G(Z) < 0$ for $Z > Z_0$. Moreover, $V = 0$ is always a solution of the equation

$$\theta_2 \alpha \frac{B}{\kappa + B} V - \delta_3 V - \gamma_3 V T = 0, \tag{3.7}$$

and the solution for $V > 0$ is dependent on $R_2 > 1$, which we will discuss later in case (ii). Here we examine the equilibrium just for $V = 0$. Apparently,

$$x_{01} = (B_0, Z_0, 0, 0)$$

is an equilibrium of system (2.1) representing a virus-free, immunity-free state. For $T > 0$, solve the virus-free subsystem (3.5) at an equilibrium; i.e., the following equations

$$\begin{aligned} &\Lambda - \delta_1 B - \gamma_1 \frac{B}{\kappa_B + B} T = 0, \\ &G(Z) - \gamma_2 \frac{Z}{\kappa_Z + Z} T = 0, \\ &\frac{q(T)}{T} + \theta_3 \gamma_1 \frac{B}{\kappa_B + B} + \theta_4 \gamma_2 \frac{Z}{\kappa_Z + Z} - \delta_4 = 0, \end{aligned} \tag{3.8}$$

and one obtains $T(B) = \frac{\delta_1 (B_0 - B)(\kappa_B + B)}{\gamma_1 B} \in (0, +\infty), B \in (0, B_0)$ from the first equation of (3.8). Since $T'(B) < 0$, $B \in (0, B_0)$, $T(B)$ is invertible on $(0, B_0)$. Hence, it follows from the second equation of (3.8) that

$$B(Z) = T^{-1} \left(\frac{(\kappa_Z + Z) G(Z)}{\gamma_2 Z} \right) \in (0, B_0), \quad Z \in (0, Z_0).$$

Note that $T = \frac{(\kappa_Z + Z) G(Z)}{\gamma_2 Z} := \widetilde{T}(Z)$ from the second equation of (3.8). We introduce

$$F(Z) = \frac{q(\widetilde{T}(Z))}{\widetilde{T}(Z)} + \frac{\theta_3 \gamma_1 B(Z)}{\kappa_B + B(Z)} + \frac{\theta_4 \gamma_2 Z}{\kappa_Z + Z} - \delta_4, \ Z \in (0, Z_0). \tag{3.9}$$

If $F(0+)F(Z_0-) < 0$, then there exists at least a $Z_1 \in (0, Z_0)$ such that $F(Z_1) = 0$. Since

$$F(0+) = \frac{q(\widetilde{T}(0+))}{\widetilde{T}(0+)} + \frac{\theta_3 \gamma_1 B(0+)}{\kappa_B + B(0+)} - \delta_4 < q'(0) + \frac{\theta_3 \gamma_1 B_0}{\kappa_B + B_0} + \frac{\theta_4 \gamma_2 Z_0}{\kappa_Z + Z_0} - \delta_4 = F(Z_0-),$$

where $\widetilde{T}(0+) = \frac{\kappa_Z G'(0)}{\gamma_2}$ and $B(0+) = T^{-1}(\widetilde{T}(0+))$, we obtain that $F(0+)F(Z_0-) < 0$ is equivalent to the following condition

(C1) $\frac{1}{\delta_4}\left(\frac{q(\widetilde{T}(0+))}{\widetilde{T}(0+)}+\frac{\theta_3\gamma_1 B(0+)}{\kappa_B+B(0+)}\right)<1<R_3+\frac{\theta_4\gamma_2 Z_0}{\delta_4(\kappa_Z+Z_0)}$.

Thus, we have at least one virus-free equilibrium

$$x_1=(B_1,Z_1,0,T_1)=\left(T^{-1}\left(\frac{(\kappa_Z+Z_1)G(Z_1)}{\gamma_2 Z_1}\right),Z_1,0,\frac{(\kappa_Z+Z_1)G(Z_1)}{\gamma_2 Z_1}\right)$$

for system (2.1) if condition (C1) holds. Moreover, the Jacobian matrices of system (2.1) at x_{01} and x_1 are given by

$$J_{01}=\begin{bmatrix}-\delta_1 & 0 & -\frac{\alpha B_0}{\kappa+B_0} & -\frac{\gamma_1 B_0}{\kappa_B+B_0}\\ 0 & G'(Z_0) & \frac{\theta_1\alpha B_0}{\kappa+B_0} & -\frac{\gamma_2 Z_0}{\kappa_Z+Z_0}\\ 0 & 0 & \delta_3(R_2-1) & 0\\ 0 & 0 & 0 & F(Z_0-)\end{bmatrix}$$

and

$$J_1=\begin{bmatrix}-\delta_1-\frac{\gamma_1\kappa_B T_1}{(\kappa_B+B_1)^2} & 0 & -\frac{\alpha B_1}{\kappa+B_1} & -\frac{\gamma_1 B_1}{\kappa_B+B_1}\\ 0 & G'(Z_1)-\frac{\kappa_Z G(Z_1)}{Z_1(\kappa_Z+Z_1)} & \frac{\theta_1\alpha B_1}{\kappa+B_1} & -\frac{\gamma_2 Z_1}{\kappa_Z+Z_1}\\ 0 & 0 & \frac{\theta_2\alpha B_1}{\kappa+B_1}-\delta_3-\gamma_3 T_1 & 0\\ \frac{\theta_3\gamma_1\kappa_B T_1}{(\kappa_B+B_1)^2} & \frac{\theta_4\gamma_2\kappa_Z T_1}{(\kappa_Z+Z_1)^2} & \theta_5\gamma_3 T_1 & q'(T_1)-\frac{q(T_1)}{T_1}\end{bmatrix},$$

respectively. The characteristic polynomial of J_1 is given by

$$\det(\lambda I-J_1)=\left(\lambda-\frac{\theta_2\alpha B_1}{\kappa+B_1}+\delta_3+\gamma_3 T_1\right)(\lambda^3+a_1\lambda^2+b_1\lambda+c_1),$$

where one can verify that if $G'(Z_1)\le\frac{\kappa_Z G(Z_1)}{Z_1(\kappa_Z+Z_1)}$, then $a_1>0, b_1>0, c_1>0$, and $a_1b_1>c_1$. Hence, if $G'(Z_1)\le\frac{\kappa_Z G(Z_1)}{Z_1(\kappa_Z+Z_1)}$ and $\frac{\theta_2\alpha B_1}{\kappa+B_1}-\delta_3-\gamma_3 T_1<0$, by Routh-Hurwitz criterion, all eigenvalues of J_1 have negative real parts. Thus, x_1 is locally asymptotically stable. Obviously, x_{01} is locally asymptotically stable if $R_2<1$ and $F(Z_0-)<0$ based on the matrix J_{01}. In fact, when $R_2\le 1$ and $R_1>1$, one can verify that

$$\Gamma_1=\{(B,Z,V,T)\in\mathbb{R}^4_+ : B\le B_0, Z\le Z_0, V\le V_{\max}, T\le T_{\max}\}$$

is a biologically feasible domain for system (2.1). We will show in Theorem 3.2 that x_{01} is globally asymptotically stable in $\mathring{\Gamma}_1$ provided that $R_2\le 1$ and $F(Z_0-)\le 0$.

Case (ii): $R_2>1$. This implies $B_0>\frac{\delta_3\kappa}{\theta_2\alpha-\delta_3}>0$. When $Z\ge Z_0$, $G(Z)$ is invertible and $G(Z)\le 0$, hence we can easily obtain an immunity-free equilibrium of system (2.1):

$$x_2=(B_2,Z_2,V_2,0)=\left(\frac{\delta_3\kappa}{\theta_2\alpha-\delta_3},\ G^{-1}\left(-\frac{\theta_1\alpha B_2 V_2}{\kappa+B_2}\right),\ \frac{\delta_1(\kappa+B_2)(B_0-B_2)}{\alpha B_2},\ 0\right).$$

Now we consider a possible interior equilibrium of system (2.1) by solving the following equations

$$\Lambda-\alpha\frac{B}{\kappa+B}V-\delta_1 B-\gamma_1\frac{B}{\kappa_B+B}T=0, \tag{3.10}$$

$$g(Z) + \theta_1\alpha\frac{B}{\kappa+B}V - \delta_2 Z - \gamma_2\frac{Z}{\kappa_Z+Z}T \;=\; 0, \tag{3.11}$$

$$\theta_2\alpha\frac{B}{\kappa+B} - \delta_3 - \gamma_3 T \;=\; 0, \tag{3.12}$$

$$\frac{q(T)}{T} + \theta_3\gamma_1\frac{B}{\kappa_B+B} + \theta_4\gamma_2\frac{Z}{\kappa_Z+Z} + \theta_5\gamma_3 V - \delta_4 \;=\; 0. \tag{3.13}$$

The equation (3.12) yields

$$T(B) = \frac{\theta_2\alpha B}{\gamma_3(\kappa+B)} - \frac{\delta_3}{\gamma_3} = \frac{\delta_3\kappa(B-B_2)}{\gamma_3 B_2(\kappa+B)} \tag{3.14}$$

and thereby $T'(B) > 0$. Substituting equation (3.14) into equation (3.10), we obtain

$$V(B) = \frac{\delta_1(\kappa+B)(B_0-B)}{\alpha B} - \frac{\gamma_1\delta_3\kappa(B-B_2)}{\alpha\gamma_3 B_2(\kappa_B+B)}. \tag{3.15}$$

One can verify that $V'(B) < 0$ and $V(B_2) > 0 > V(B_0)$. Then there exists a $\widetilde{B} \in (B_2, B_0)$ such that $V(\widetilde{B}) = 0$ and hence we only need to focus on the interval $(B_2,\, \widetilde{B})$. By computing $\theta_4 \times (3.11) + T \times (3.13)$, one can obtain

$$G(Z) = -\frac{\theta_1\alpha BV(B)}{\kappa+B} - \left(\frac{q(T(B))}{T(B)} + \frac{\theta_3\gamma_1 B}{\kappa_B+B} + \theta_5\gamma_3 V(B) - \delta_4\right)\frac{T(B)}{\theta_4}. \tag{3.16}$$

Denote

$$h(B) = \frac{q(T(B))}{T(B)} + \frac{\theta_3\gamma_1 B}{\kappa_B+B} + \theta_5\gamma_3 V(B) - \delta_4, \quad \phi(B) = -\frac{\theta_1\alpha BV(B)}{\kappa+B} - \frac{h(B)T(B)}{\theta_4}.$$

Assume the following condition holds:

(**C2**) $\alpha\theta_3\kappa_B B_2 \le \theta_5\delta_3\kappa(\kappa_B + B_2)$.

Then

$$h'(B) = \left(\frac{q(T(B))}{T(B)}\right)' - \frac{\theta_5\gamma_3\delta_1}{\alpha}\left(1 + \frac{\kappa B_0}{B^2}\right) + \gamma_1 \cdot \frac{\alpha\theta_3\kappa_B B_2 - \theta_5\delta_3\kappa(\kappa_B+B_2)}{\alpha B_2(\kappa_B+B)^2} < 0.$$

If we further assume $h(B_2+) \le 0$, then $h(B) < 0$ on $(B_2, \widetilde{B})$. It follows from (3.10) that

$$\left(\frac{\alpha BV(B)}{\kappa+B}\right)' = -\delta_1 - \gamma_1\left(\frac{\kappa_B T(B) + (\kappa_B+B)BT'(B)}{(\kappa_B+B)^2}\right) < 0.$$

Hence,

$$\phi'(B) = -\left(\frac{\theta_1\alpha BV(B)}{\kappa+B}\right)' - \frac{h'(B)T(B) + h(B)T'(B)}{\theta_4} > 0.$$

Since $\phi(B_2+) = -\frac{\theta_1\alpha B_2 V_2}{\kappa+B_2} < 0 < -\frac{h(\widetilde{B})T(\widetilde{B})}{\theta_4} = \phi(\widetilde{B}-)$, there exists a $B^* \in (B_2, \widetilde{B})$ such that $\phi(B^*) = 0$ and $\phi(B) < 0, B \in (B_2, B^*)$. Hence, we could define

$$\psi_1(B) := G^{-1}(\phi(B)), \quad B \in (B_2,\ B^*), \tag{3.17}$$

which is a decreasing function since

$$\psi_1'(B) = (G^{-1})'(\phi(B))\phi'(B) < 0, \quad B \in (B_2,\ B^*).$$

Notice that $G(Z) < 0$ for all $Z > 0$ if and only if $R_1 \leq 1$. Hence, (B_2, B^*) is the maximum interval of existence for the interior solution if $R_1 \leq 1$. Meanwhile, solving equation (3.13), we obtain

$$Z = \frac{-\kappa_Z h(B)}{\theta_4\gamma_2 + h(B)} := \psi_2(B), \quad B \in (B_2,\ B^*) \tag{3.18}$$

and

$$\psi_2'(B) = \frac{-\kappa_Z\theta_4\gamma_2 h'(B)}{(\theta_4\gamma_2 + h(B))^2} > 0, \quad B \in (B_2,\ B^*).$$

Obviously, the intersection of the two curves $Z = \psi_1(B)$ and $Z = \psi_2(B)$, $B \in (B_2,\ B^*)$, in $\mathbb{R}^2_+$ determines the interior equilibrium of system (2.1). Since $\psi_1(B)$ is a strictly decreasing function with $\psi_1(B_2) = Z_2 > 0 = \psi_1(B^*)$ and $\psi_2(B)$ is a strictly increasing function with $\psi_2(B) \neq 0$ on $(B_2,\ B^*)$. Thus, the two curves has an intersection if and only if $0 \leq \psi_2(B_2+) < \psi_1(B_2) = Z_2$, which is equivalent to the following condition

(**C3**) $\frac{-\theta_4\gamma_2 Z_2}{\kappa_Z + Z_2} < h(B_2+) \leq 0$.

Therefore, system (2.1) has a positive interior equilibrium, denoted by

$$x_* = (B_*, Z_*, V_*, T_*),$$

if conditions (C2) and (C3) hold, and x_* is unique if additionally $R_1 \leq 1$. The Jacobian matrices of system (2.1) at x_2 and x_* are given by

$$J_2 = \begin{bmatrix} -\frac{\alpha\kappa V_2}{(\kappa+B_2)^2} - \delta_1 & 0 & -\frac{\alpha B_2}{\kappa+B_2} & -\frac{\gamma_1 B_2}{\kappa_B+B_2} \\ \frac{\theta_1\alpha\kappa V_2}{(\kappa+B_2)^2} & G'(Z_2) & \frac{\theta_1\alpha B_2}{\kappa+B_2} & -\frac{\gamma_2 Z_2}{\kappa_Z+Z_2} \\ \frac{\theta_2\alpha\kappa V_2}{(\kappa+B_2)^2} & 0 & \frac{\theta_2\alpha B_2}{\kappa+B_2} - \delta_3 & -\gamma_3 V_2 \\ 0 & 0 & 0 & h(B_2+) + \frac{\theta_4\gamma_2 Z_2}{\kappa_Z+Z_2} \end{bmatrix}$$

and

$$J_* = \begin{bmatrix} -\frac{\alpha\kappa V_*}{(\kappa+B_*)^2} - \delta_1 - \frac{\gamma_1\kappa_B T_*}{(\kappa_B+B_*)^2} & 0 & -\frac{\alpha B_*}{\kappa+B_*} & -\frac{\gamma_1 B_*}{\kappa_B+B_*} \\ \frac{\theta_1\alpha\kappa V_*}{(\kappa+B_*)^2} & G'(Z_*) - \frac{\gamma_2\kappa_Z T_*}{(\kappa_Z+Z_*)^2} & \frac{\theta_1\alpha B_*}{\kappa+B_*} & -\frac{\gamma_2 Z_*}{\kappa_Z+Z_*} \\ \frac{\theta_2\alpha\kappa V_*}{(\kappa+B_*)^2} & 0 & 0 & -\gamma_3 V_* \\ \frac{\theta_3\gamma_1\kappa_B T_*}{(\kappa_B+B_*)^2} & \frac{\theta_4\gamma_2\kappa_Z T_*}{(\kappa_Z+Z_*)^2} & \theta_5\gamma_3 T_* & q'(T_*) - \frac{q(T_*)}{T_*} \end{bmatrix},$$

respectively. It is easy to find that the characteristic polynomial of J_2 is

$$\det(\lambda I - J_2) = (\lambda - G'(Z_2))(\lambda - a_2)(\lambda^2 + b_2\lambda + c_2),$$

where $a_2 = h(B_2+) + \frac{\theta_4\gamma_2 Z_2}{\kappa_Z+Z_2}$, $b_2 = \frac{\alpha\kappa V_2}{(\kappa+B_2)^2} + \delta_1 > 0$, $c_2 = \frac{\theta_1\alpha^2\kappa B_2 V_2}{(\kappa+B_2)^3} > 0$. Note that $G'(Z_2) < 0$ since $G(Z_2) < 0$. Therefore, x_2 is locally asymptotically stable if $a_2 < 0$, and unstable if $a_2 > 0$. On the other hand, the stability analysis of x_* involves tedious algebraic manipulations and is not presented here. We, instead, conduct a bifurcation analysis of x_* which clarifies the stability property of x_* near the bifurcation point $\mathcal{R}_0 = 1$. The details are provided in the Appendix.

Case (iii): $R_3 > 1$. Based on our previous discussion, now we only need to focus on this case with $R_1 \leq 1$, $R_2 \leq 1$ and $T > 0$. Consider the following equations

$$\Lambda - \delta_1 B - \gamma_1 \frac{B}{\kappa_B + B} T = 0, \tag{3.19}$$

$$\frac{q(T)}{T} + \theta_3 \gamma_1 \frac{B}{\kappa_B + B} - \delta_4 = 0. \tag{3.20}$$

Since $T'(B) < 0$ and $T(B) > 0$ for $B \in (0, B_0)$ from equation (3.19), then $H'(B) > 0$, where

$$H(B) = \frac{q(T(B))}{T(B)} + \theta_3 \gamma_1 \frac{B}{\kappa_B + B} - \delta_4, \quad B \in (0, B_0). \tag{3.21}$$

Note that

$$\lim_{B \to 0+} \frac{q(T(B))}{T(B)} = \lim_{T \to +\infty} \frac{q(T)}{T} = \lim_{T \to +\infty} \frac{q(T) - q(T_q)}{T - T_q} < q'(T_q).$$

Hence, $H(0+) < 0$ and $H(B_0-) = \delta_4(R_3 - 1) > 0$. Thus, there exists a unique $B_3 \in (0, B_0)$ such that $H(B_3) = 0$. Therefore, we obtain another equilibrium

$$x_3 = (B_3, 0, 0, T_3)$$

for system (2.1) that represents a human vibrio-free, virus-free state, where $T_3 = \frac{\delta_1(B_0 - B_3)(\kappa_B + B_3)}{\gamma_1 B_3}$. The Jacobian matrix of system (2.1) at x_3 is

$$J_3 = \begin{bmatrix} -\delta_1 - \frac{\gamma_1 \kappa_B T_3}{(\kappa_B + B_3)^2} & 0 & -\frac{\alpha B_3}{\kappa + B_3} & -\frac{\gamma_1 B_3}{\kappa_B + B_3} \\ 0 & G'(0) - \frac{\gamma_2 T_3}{\kappa_Z} & \frac{\theta_1 \alpha B_3}{\kappa + B_3} & 0 \\ 0 & 0 & \frac{\theta_2 \alpha B_3}{\kappa + B_3} - \delta_3 - \gamma_3 T_3 & 0 \\ \frac{\theta_3 \gamma_1 \kappa_B T_3}{(\kappa_B + B_3)^2} & \frac{\theta_4 \gamma_2 T_3}{\kappa_Z} & \theta_5 \gamma_3 T_3 & q'(T_3) - \frac{q(T_3)}{T_3} \end{bmatrix},$$

for which the characteristic polynomial is

$$\det(\lambda I - J_3) = \left(\lambda - \frac{\theta_2 \alpha B_3}{\kappa + B_3} + \delta_3 + \gamma_3 T_3\right) \left(\lambda - G'(0) + \frac{\gamma_2 T_3}{\kappa_Z}\right) (\lambda^2 + b_3 \lambda + c_3),$$

where

$$b_3 = \delta_1 + \frac{\gamma_1 \kappa_B T_3}{(\kappa_B + B_3)^2} + \frac{q(T_3)}{T_3} - q'(T_3) > 0,$$

$$c_3 = \frac{\theta_3 \gamma_1^2 \kappa_B B_3 T_3}{(\kappa_B + B_3)^3} + \left(\delta_1 + \frac{\gamma_1 \kappa_B T_3}{(\kappa_B + B_3)^2}\right) \left(\frac{q(T_3)}{T_3} - q'(T_3)\right) > 0.$$

Hence, x_3 is locally asymptotically stable if $G'(0) < \frac{\gamma_2 T_3}{\kappa_Z}$ and $\frac{\theta_2 \alpha B_3}{\kappa + B_3} - \delta_3 - \gamma_3 T_3 < 0$, or equivalently, $R_1 < 1 + \frac{\gamma_2 T_3}{\delta_2 \kappa_Z}$ and $R_2 < \left(1 + \frac{\kappa(B_0 - B_3)}{B_3(\kappa + B_0)}\right) \left(1 + \frac{\gamma_3 T_3}{\delta_3}\right)$. In fact, we will show in Theorem 3.2 that x_3 is globally asymptotically stable in $\mathring{\Gamma}$ if $R_1 \leq 1$ and $R_2 \leq 1$.

Remark 3.1. Clearly, if $R_1 \leq 1$ (resp. $R_2 \leq 1$, $R_3 \leq 1$), then x_{01} and x_1 (resp. x_2 and x_*, x_3) will vanish.

Before summarizing the results above, we revisit the virus-free subsystem (3.5) and prove the lemma below.

Lemma 3.2. *Let* $r = 1 - \frac{\theta_4\gamma_2 Z_0}{\delta_4(\kappa_Z + Z_0)}$ *when* $R_1 > 1$. *We have the following statements for the virus-free subsystem* (3.5).

(a) If $R_1 \leq 1$ *and* $R_3 > 1$, *the* ω*-limit set* $w(s) \in \{s_0, s_3\}$ *for all* $s \in \Omega$, *where* $s_0 = (B_0, 0, 0)$ *and* $s_3 = (B_3, 0, T_3)$. *Particularly, the trajectories on the* B*-axis approach* s_0 *along this axis, and* s_3 *is globally asymptotically stable in* $\Omega\backslash\{B\text{-axis}\}$.

(b) If $R_1 > 1$ *and* $R_3 \leq r$, *we have* $w(s) \in \{s_0, s_{01}\}$ *for all* $s \in \Omega$, *where* $s_{01} = (B_0, Z_0, 0)$. *Specifically,* s_0 *attracts all points on the* B*-axis and* s_{01} *is globally asymptotically stable in* $\Omega\backslash\{B\text{-axis}\}$.

Proof. (a) Similar to the proof of Lemma 3.1, since $R_1 \leq 1$, by choosing a Lyapunov function $\mathcal{L} = Z$, it is clear that $w(s) \in \{(B, Z, T) \in \Omega : Z = 0\}$ for all $s \in \Omega$ and the two-dimensional subsystem $\{\dot{B}, \dot{T}\}|_{Z=0}$ has two equilibria $\{(B_0, 0), (B_3, T_3)\}$ and no closed orbit. Hence, $w(s) \in \{s_0, s_3\}$ for all $s \in \Omega$. It is obvious that the trajectories on the B-axis approach s_0 since B_0 is globally asymptotically stable on the B-axis for the one-dimensional system $\dot{B} = \Lambda - \delta_1 B$. Assume that there is a point $(B(0), Z(0), T(0)) \in \Omega\backslash\{B\text{-axis}\}$ such that

$$\lim_{t\to+\infty} ||(B(t), Z(t), T(t)) - s_0|| = 0. \tag{3.22}$$

Then $\lim_{t\to+\infty} T(t) = 0$ and for any $\varepsilon \in (0, \delta_4(R_3 - 1))$, there is a t_1 such that $\frac{q(T)}{T} > q'(0) - \frac{\varepsilon}{2}$ and $\frac{\theta_3\gamma_1 B}{\kappa_B + B} > \frac{\theta_3\gamma_1 B_0}{\kappa_B + B_0} - \frac{\varepsilon}{2}$ for all $t > t_1$. Thus,

$$\dot{T} \geq T(\delta_4(R_3 - 1) - \varepsilon) > 0, \tag{3.23}$$

for all $t > t_1$. This leads to a contradiction with $\lim_{t\to+\infty} T(t) = 0$, which indicates that all points on $\Omega\backslash\{B\text{-axis}\}$ approach s_3 as $t \to +\infty$; i.e., s_3 is globally asymptotically stable in $\Omega\backslash\{B\text{-axis}\}$.

(b) Since $R_3 \leq r$, one can verify that $\mathcal{L} = T$ is a Lyapunov function of subsystem (3.5) on Ω and $w(s) \in \{(B, Z, T) \in \Omega : \dot{T} = 0\} = \{(B, Z, T) \in \Omega : T = 0\}$ for all $s \in \Omega$. It is obvious that $w(s) \in \{s_0, s_{01}\}$ for all $s \in \Omega$ since the two-dimensional subsystem $\{\dot{B}, \dot{Z}\}|_{T=0}$ can be decoupled as two one-dimensional subsystems $\dot{B}|_{T=0}$ and $\dot{Z}|_{T=0}$. Assume there is a point $(B(0), Z(0), T(0)) \in \mathring{\Omega}$ such that equation (3.22) holds. Then, $\lim_{t\to+\infty} Z(t) = 0$ and for any $\varepsilon \in (0, \delta_2(R_1 - 1))$, there exsits a t_2 such that $\frac{G(Z)}{Z} > G'(0) - \frac{\varepsilon}{2} = \delta_2(R_1 - 1) - \frac{\varepsilon}{2}$ and $\frac{\gamma_2 T}{\kappa_Z} < \frac{\varepsilon}{2}$ for all $t > t_2$. Note that $Z(0) > 0$ implies $Z(t) > 0$ for all $t \geq 0$. We have

$$\dot{Z} \geq Z\left(\frac{G(Z)}{Z} - \frac{\gamma_2 T}{\kappa_Z}\right) > Z(\delta_2(R_1 - 1) - \varepsilon) > 0 \tag{3.24}$$

for all $t > t_2$, which contradicts with $\lim_{t\to+\infty} Z(t) = 0$ and thereby s_{01} is globally asymptotically stable in $\Omega\backslash\{B\text{-axis}\}$. □

We now state our main result regarding the system dynamics when $\mathcal{R}_0 > 1$.

Theorem 3.2. *If* $\mathcal{R}_0 > 1$, *in addition to the trivial equilibirum* x_0, *the system* (2.1) *has multiple non-trivial equilibria described by the following:*

(i) If $R_1 > 1$, system (2.1) has a boundary equilibrium $x_{01} = (B_0, Z_0, 0, 0)$, which is unique and globally asymptotically stable in $\Gamma_1\backslash\{B\text{-axis}\}$ if $R_2 \le 1$ and $R_3 \le r$. System (2.1) has another boundary equilibrium $x_1 = (B_1, Z_1, 0, T_1)$ provided that condition (C1) holds, and it is locally asymptotically stable if $G'(Z_1) \le \frac{\kappa_Z G(Z_1)}{Z_1(\kappa_Z+Z_1)}$ and $\frac{\theta_2\alpha B_1}{\kappa+B_1} - \delta_3 - \gamma_3 T_1 < 0$.

(ii) If $R_2 > 1$, system (2.1) has a boundary equilibrium $x_2 = (B_2, Z_2, V_2, 0)$, which is locally asymptotically stable if $h(B_2) + \frac{\theta_4\gamma_2 Z_2}{\kappa_Z+Z_2} < 0$ and unstable if $h(B_2)+\frac{\theta_4\gamma_2 Z_2}{\kappa_Z+Z_2} > 0$. Moreover, system (2.1) has a positive interior equilibrium $x_* = (B_*, Z_*, V_*, T_*)$ provided that conditions (C2) and (C3) hold, and x_* is unique and locally asymptotically stable if additionally $R_1 \le 1$ and $R_3 \le 1$.

(iii) If $R_3 > 1$, system (2.1) has a boundary equilibrium $x_3 = (B_3, 0, 0, T_3)$, which is locally asymptotically stable if $R_1 < 1+\frac{\gamma_2 T_3}{\delta_2\kappa_Z}$ and $R_2 < \left(1 + \frac{\kappa(B_0-B_3)}{B_3(\kappa+B_0)}\right)\left(1+\frac{\gamma_3 T_3}{\delta_3}\right)$. In addition, x_3 is unique and globally asymptotically stable in $\Gamma\backslash\{B\text{-axis}\}$ if $R_1 \le 1$ and $R_2 \le 1$.

Proof. According to the discussion above, it is only necessary to prove the uniquenesses and global stabilities of x_{01} in (i) and x_3 in (iii). Since they have a condition $R_2 \le 1$ in common, we consider $\mathcal{L} = V$ as a Lyapunov function on $\widetilde{\Omega}$, where $\widetilde{\Omega} = \Gamma$ or Γ_1. Then the largest invariant set on $\{x \in \widetilde{\Omega} : \dot{V} = 0\}$ is $\{x \in \Omega_1 : V = 0\}$.

(i) The uniqueness of x_{01} follows from equation (3.9), where we have the fact

$$F(Z) < q'(0) + \frac{\theta_3\gamma_1 B_0}{\kappa_B + B_0} + \frac{\theta_4\gamma_2 Z_0}{\kappa_Z + Z_0} - \delta_4.$$

So, $\delta_4(R_3 - 1) + \frac{\theta_4\gamma_2 Z_0}{\kappa_Z+Z_0} \le 0$ implies $R_3 \le 1$ and $F(Z) < 0$. Consequently, there is no solution for $F(Z) = 0$ and thereby x_{01} is the only equilibrium for system (2.1).

By Lemma 3.2(b), we have $w(s) \in \{s_0, s_{01}\}$ for all $s \in \Omega$. Thus, $w(x) \in \{x_0, x_{01}\}$ for all $x \in \Gamma_1$. If there exists a point $(B(0), Z(0), V(0), T(0)) \in \Gamma_1\backslash\{B\text{-axis}\}$ such that

$$\lim_{t\to+\infty} ||(B(t), Z(t), V(t), T(t)) - x_0|| = 0, \tag{3.25}$$

then $\lim_{t\to+\infty} Z(t) = 0$. Similar to the proof of Lemma 3.2(b), we still have (3.24) holds for sufficiently large t. Thus, $\lim_{t\to+\infty} Z(t) \ne 0$ and this proves the global asymptotic stability of x_{01} in $\Gamma_1\backslash\{B\text{-axis}\}$.

(iii) The uniqueness of x_3 is obvious since $R_1 \le 1$ and $R_2 \le 1$. Similarly, it follows from Lemma 3.2(a) that $w(x) \in \{x_0, x_3\}$ for all $x \in \Gamma$. In addition, by the same proof of Lemma 3.2(a), one can easily obtain that any trajectory in $\Gamma\backslash\{B\text{-axis}\}$ cannot approach to x_0 and thereby x_3 is globally asymptotically stable in $\Gamma\backslash\{B\text{-axis}\}$. □

4. Numerical results

In this section, we conduct numerical simulation to verify the main analytical results, summarized in Theorems 3.1 and 3.2, associated with our within-host cholera model (2.1). For illustration, we assume that the intrinsic growth functions for the human vibrios and immune cells both take the logistic form: $g(Z) = g_0 Z\left(1 - \frac{Z}{K_Z}\right)$ and $q(T) = q_0 T\left(1 - \frac{T}{K_T}\right)$, with positive constants g_0, K_Z and q_0, K_T.

Theorem 3.1 states that when $\mathcal{R}_0 \leq 1$, there exists a unique trivial equilibrium x_0 that is globally asymptotically stable. A numerical evidence is provided in Figure 1, where $R_1 = 0.64$, $R_2 = 0.9$, $R_3 = 0.81$, $\mathcal{R}_0 = \max\{R_1, R_2, R_3\} = 0.9$, and the orbit of the solution approaches the trivial equilibrium x_0 over time.

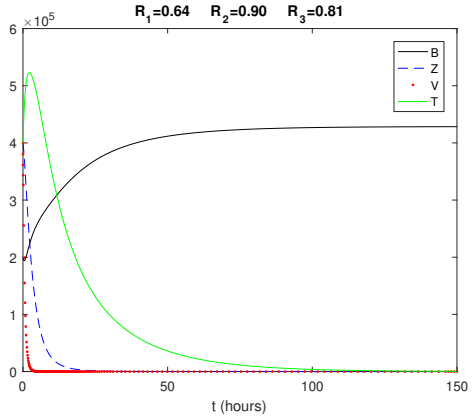
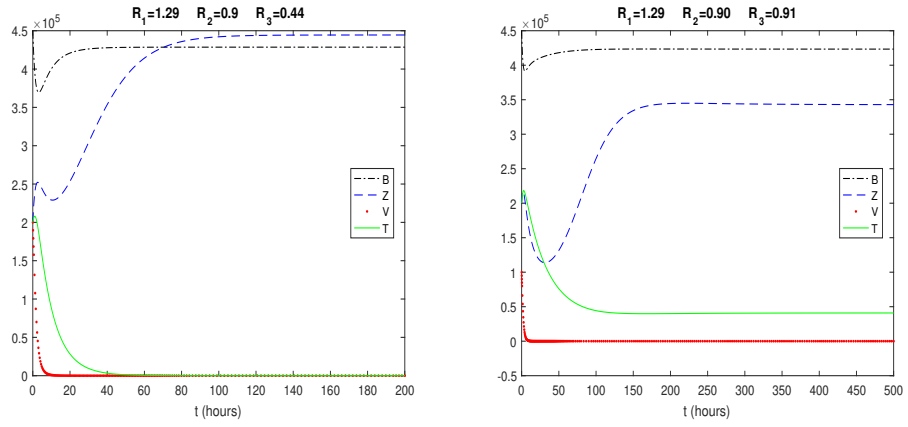


Figure 1. A typical scenario showing that solutions of system (2.1) converge to the trivial equilibrium x_0 when $\mathcal{R}_0 < 1$. In this particular case $\mathcal{R}_0 = 0.9$ and $x_0 = (428571, 0, 0, 0)$.

When $\mathcal{R}_0 > 1$, there could be multiple non-trivial equilibria depending on the values of R_1, R_2 and R_3, as predicted by Theorem 3.2. Figure 2 shows two typical scenarios when $\mathcal{R}_0 = R_1 > 1$, where the model parameters are chosen such that $r = 1 - \frac{\theta_4 \gamma_2 Z_0}{\delta_4(\kappa_Z + Z_0)} = 0.9$. In Figure 2(a), $R_3 = 0.44 < r$, and the solution converges to the virus-free, immunity-free equilibrium x_{01}. In Figure 2(b), $R_3 = 0.91 > r$, and the solution converges to the virus-free equilibrium x_1. These observations are consistent with the analytical prediction in Theorem 3.2(i).



(a) (b)

Figure 2. Two typical scenarios for the solutions of system (2.1) when $\mathcal{R}_0 = R_1 > 1$: (a) Solutions converge to the virus-free, immunity-free equilibrium x_{01}, where $x_{01} = (428571, 444444, 0, 0)$ in this particular case; (b) Solutions converge to the virus-free equilibrium x_1, where $x_1 = (423353, 342820, 0, 40939)$ in this particular case.

Figure 3 illustrates the typical solution behaviors when $\mathcal{R}_0 = R_2 > 1$, as described in Theorem 3.2(ii). In Figure 3(a), the parameter values are selected to satisfy the condition $h(B_2+) + \frac{\theta_4\gamma_2 Z_2}{\kappa_Z + Z_2} = -0.28 < 0$, and the solution orbit approaches the immunity-free equilibrium x_2. In Figure 3(b), the parameter values are such that $h(B_2+) = -0.017 < 0 < h(B_2+) + \frac{\theta_4\gamma_2 Z_2}{\kappa_Z + Z_2} = 0.016$, and the solution converges to the positive interior equilibrium x_*.

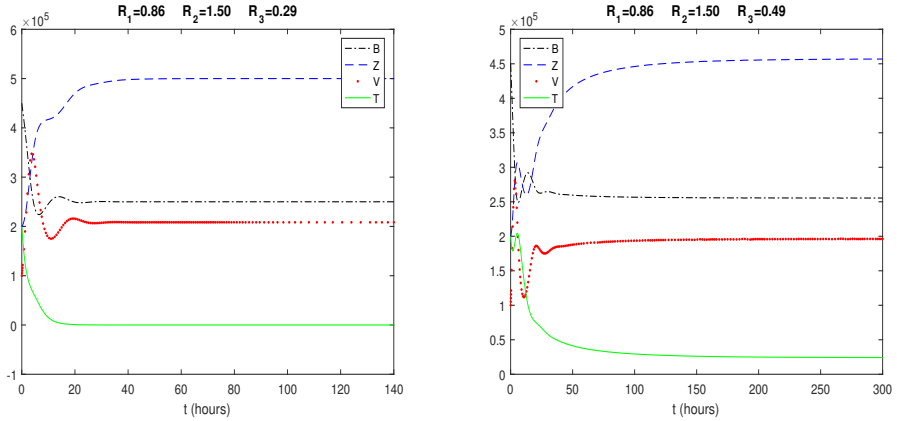


Figure 3. Two typical scenarios for the solutions of system (2.1) when $\mathcal{R}_0 = R_2 > 1$: (a) Solutions converge to the immunity-free equilibrium x_2, where $x_2 = (250000, 500000, 208333, 0)$ in this particular case; (b) Solutions converge to the positive interior equilibrium x_*, where $x_* = (255392, 457221, 196223, 24052)$ in this particular case.

Finally, Figure 4 displays a typical case for $\mathcal{R}_0 = R_3 > 1$, where the solution converges to the equilibrium x_3 which is free of human vibrios and viruses. This pattern is consistent with the statement in Theorem 3.2(iii).

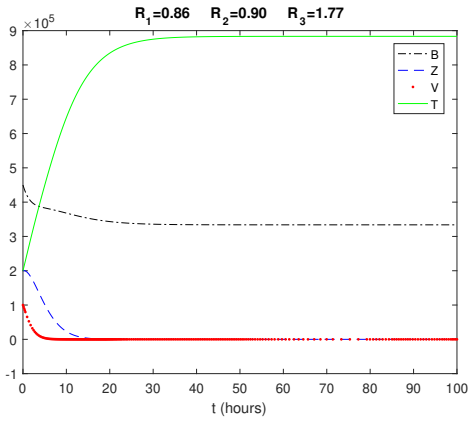


Figure 4. A typical scenario showing that solutions of system (2.1) converge to the equilibrium x_3 free of human vibrios and viruses, when $\mathcal{R}_0 = R_3 > 1$. In this particular case $x_3 = (333819, 0, 0, 883388)$.

5. Discussion

We have proposed a new deterministic model for the within-host dynamics of cholera. Our focus is the interaction among the environmental vibrios (with low infectivity), the human vibrios (with high infectivity), the viruses (which transduce environmental vibrios into human vibrios), and the immune response (which attempts to eliminate the pathogenic vibrios and viruses) within a human host. Such an interaction is critical in shaping the evolution of the pathogen within the human body and could directly contribute to the epidemiology of cholera at the population level.

The basic reproduction number $\mathcal{R}_0$ of this model is determined collectively by the intrinsic growth dynamics of the human vibrios (measured by the bacterial reproduction number R_1), the generation of new viruses through the bacterial-viral interaction (measured by the viral reproduction number R_2), and the intrinsic and stimulated dynamics of the host immune response (measured by the immune reproduction number R_3). A unique trivial equilibrium occurs when $\mathcal{R}_0 \leq 1$; equivalently, when $R_j \leq 1$ for $1 \leq j \leq 3$. In contrast, when $\mathcal{R}_0 > 1$, multiple and non-trivial equilibria occur depending on the values of R_j $(1 \leq j \leq 3)$. We have established the existence, uniqueness and stability for the trivial equilibrium and for each non-trivial boundary equilibrium, including the virus-free and immunity-free equilibria in particular. For the positive interior equilibrium, we are able to clarify the existence, uniqueness and its bifurcation behavior at the threshold point $\mathcal{R}_0 = 1$.

Our main finding is that the within-host dynamics of cholera are shaped by the interplay of the bacteria, viruses, and host immune response. Specifically, when the bacterial reproduction number is high; i.e., $R_1 > 1$, there exists a virus-free equilibrium x_1 and a virus-free, immunity-free equilibrium x_{01} which are stable under additional assumptions. These two equilibria represent the scenario where the viral effects are not present and where the intrinsic growth of the human vibrios sustains the state of the infection inside the human body. From the disease control point of view, in order to eliminate these two infectious states we will need to better understand such intrinsic bacterial growth mechanism so that we will be able to find effective means to suppress or weaken the bacterial growth and reduce R_1 below unity.

When the viral reproduction number is high; i.e., $R_2 > 1$, there exists an immunity-free equilibrium x_2 which represents the scenario that in the absence of the host immunity, the infectious state is determined by the bacterial-viral interaction. Under additional conditions, a unique positive interior equilibrium x_* occurs which indicates an 'endemic' state of the within-host cholera dynamics, representing a balance of the contributions from the bacteria, the viruses and the host immune response. These two equilibria highlight the important role played by the virus CTXϕ and indicate that control measures targeting the reduction of the viral generation rate so that $R_2 < 1$, could effectively eliminate these two infectious states.

When the immune reproduction number is high; i.e., $R_3 > 1$, there exists an equilibrium x_3 which represents a state free of human vibrios and viruses. This is perhaps the 'best' scenario among all the nontrivial equilibria since the human vibrios are not present (and will not be refueled by the viruses) in this case. An implication is that if we can boost the host immune response to cholera, which

would lead to $R_3 > 1$, then that would significantly reduce the severity of the infection. Furthermore, if we can combine the immunity boosting strategy with the suppression of human vibrio growth and viral generation such that $R_3 > 1$ and $R_1,\ R_2 \leq 1$, then the equilibrium x_3 is globally asymptotically stable (see Theorem 3.2(iii)), indicating that the individual host would not generate the highly infectious human vibrios and thus would not transmit human vibrios to other hosts, which consequently reduces the overall transmission risk of cholera at the population level.

The present study is focused solely on the within-host dynamics of cholera. Though our findings could provide some useful insight toward cholera transmission, in order to gain more detailed information on the population-level transmission and spread of cholera it will be necessary to connect the within-host model with a between-host cholera model. In all the numerical results presented in this paper, we observe that the convergence to an equilibrium is typically fast, ranging from several hours to a few days. Hence, compared to the typical time frame of the between-host cholera transmission and spread (where a cholera epidemic usually lasts several months), the within-host dynamics of cholera is a fast-scale process [20, 33]. Consequently, coupling the within- and between-host cholera dynamics will involve both fast and slow time scales, and multi-scale modeling, analysis and computation techniques will be particularly useful. The work in [33] makes an initial effort for such coupled dynamics of cholera, though the within-host model takes a very simple form with a single equation describing the increased toxicity of the vibrios inside the human body. Based on the improved within-host model proposed in this paper, we will further explore the multi-scale modeling and analysis of cholera in our future work.

Another limitation in our current model is that we have actually only considered the effects of the innate host immunity, which makes instantaneous responses to invading pathogens. On the other hand, the adaptive immunity, which kicks in with delayed responses but often leads to more sustained protection of the human body, also plays an important role in the human immunity system. The adaptive immune response can be mathematically represented by adding a time delay into the differential equations, and this can be an interesting topic to explore in our future efforts.

Appendix: Bifurcation of the interior equilibrium

Let us consider the system $\dot{y} = f(y, \mathcal{R}_0)$, where $y = \begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \end{bmatrix} = \begin{bmatrix} B \\ Z \\ V \\ T \end{bmatrix}, f = \begin{bmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{bmatrix}$ with $f_1 = \dot{B}$, $f_2 = \dot{Z}$, $f_3 = \dot{V}$, $f_4 = \dot{T}$, and f is at least twice continuously differentiable on both y and $\mathcal{R}_0$. Note that at the equilibrium x_0,

$$\mathcal{F} - \mathcal{V} = \begin{bmatrix} \delta_2(R_1 - 1) & \frac{\theta_1 \alpha B_0}{\kappa + B_0} & 0 \\ 0 & \delta_3(R_2 - 1) & 0 \\ 0 & 0 & \delta_4(R_3 - 1) \end{bmatrix}.$$

Without loss of generality, we assume that R_1, R_2 and R_3 are distinct so that they do not take on the value of unity at the same time. This implies that the zero eigenvalue of $\mathcal{F}-\mathcal{V}$ is simple when $\mathcal{R}_0=1$, and then the existence and stability of the positive interior equilibrium near the threshold point could be established by the center manifold theory [5,28]. We may calculate

$$a=\frac{v}{2}D_{yy}f(x_0,1)w^2=\frac{1}{2}\sum_{i,j,k=1}^{4}v_iw_jw_k\frac{\partial^2 f_i}{\partial y_j\partial y_k}(x_0,1),$$
$$b=vD_{y\mathcal{R}_0}f(x_0,1)w=\sum_{i,j=1}^{4}v_iw_j\frac{\partial^2 f_i}{\partial y_j\partial \mathcal{R}_0}(x_0,1),$$

where v and w are the left and right nullvectors of $D_yf(x_0,1)$, which is the linearization matrix of system (2.1) at $(x_0,1)$, given by

$$D_yf(x_0,1)=\begin{bmatrix}-\delta_1 & 0 & -\frac{\alpha B_0}{\kappa+B_0} & -\frac{\gamma_1 B_0}{\kappa_B+B_0}\\ 0 & \delta_2(R_1-1) & \frac{\theta_1\alpha B_0}{\kappa+B_0} & 0\\ 0 & 0 & \delta_3(R_2-1) & 0\\ 0 & 0 & 0 & \delta_4(R_3-1)\end{bmatrix}.$$

An application of the center manifold theory shows that the sign of a and b can determine the nature of the positive interior equilibrium near the bifurcation point $(x_0,1)$ [5].

If $\mathcal{R}_0=R_1>\max\{R_2,R_3\}$, then there exists $v_3=\frac{\theta_1\alpha B_0}{\delta_3(1-R_2)(\kappa+B_0)}$ such that $v=(0,1,v_3,0)$, $w=\begin{bmatrix}0\\1\\0\\0\end{bmatrix}$. Suppose that $g''(0)\neq 0$, we have

$$a=\frac{1}{2}\frac{\partial^2 f_2}{\partial y_2^2}(x_0,1)=\frac{g''(0)}{2}<0,\quad b=\frac{\partial^2 f_2}{\partial y_2\partial\mathcal{R}_0}(x_0,1)=\delta_2>0.$$

If $\mathcal{R}_0=R_2>\max\{R_1,R_3\}$, then there exists $w_1=-\frac{\alpha B_0}{\delta_1(\kappa+B_0)}<0, w_2=\frac{\theta_1\alpha B_0}{\delta_2(1-R_1)(\kappa+B_0)}$ such that $v=(0,0,1,0)$, $w=\begin{bmatrix}w_1\\w_2\\1\\0\end{bmatrix}$. Hence,

$$a=w_1\frac{\partial^2 f_3}{\partial y_1\partial y_3}(x_0,1)=\frac{w_1\theta_2\alpha\kappa}{(\kappa+B_0)^2}<0,\quad b=\frac{\partial^2 f_3}{\partial y_3\partial\mathcal{R}_0}(x_0,1)=\delta_3>0.$$

If $\mathcal{R}_0=R_3>\max\{R_1,R_2\}$, then there exists $w_1=\frac{-\gamma_1 B_0}{\delta_1(\kappa_B+B_0)}<0$ such that

$v = (0, 0, 0, 1),\ w = \begin{bmatrix} w_1 \\ 0 \\ 0 \\ 1 \end{bmatrix}$. Hence,

$$a = \frac{q''(0)}{2} + \frac{w_1\theta_3\gamma_1\kappa_B}{(\kappa_B + B_0)^2} < 0, \quad b = \delta_4 > 0.$$

Thus, we have $a < 0$, and $b > 0$ in each of these cases, and thereby when $\mathcal{R}_0 - 1$ changes from negative to positive, $x = x_0$ changes its stability from stable to unstable. Correspondingly, a negative unstable equilibrium becomes a positive and locally asymptotically stable equilibrium x_*.

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