Dynamical analysis and control strategies in modeling cholera

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Abstract

We conduct rigorous stability analysis for the well-known cholera model proposed by Codeço [7]. Using theory of monotone dynamical systems, we prove that the endemic equilibrium, when it exists, of the model is globally asymptotically stable, implying the persistence of the disease in the absence of interventions. We then modify Codeço's model by incorporating various control strategies, and study the subsequent dynamics. We find that with strong control measures, the basic reproduction number will be reduced below 1 so that the disease-free equilibrium is globally asymptotically stable. With weak controls, instead, a unique and globally stable endemic equilibrium would still occur, though at a lower infection level. The analytical predictions are confirmed by numerical simulation results.

Keywords: dynamical systems, local and global stability, cholera model

1 Introduction

Cholera is a severe water-borne infectious disease caused by the bacterium *Vibrio cholerae*. Recent years have seen a strong trend of cholera outbreaks in developing countries, including, among others, those in Kenya (2010), Vietnam (2009), Zimbabwe (2008-2009), Iraq (2008), Congo (2008) and India (2007). According to the World Health Organization (WHO), "there are an estimated 3 - 5 million cholera cases and 100,000 - 120,000 deaths due to cholera every year", among which only a small portion were officially reported because of poor surveillance and incomplete records [42]. Due to its huge impacts on public health and social and economic development, cholera has been a subject of extensive studies in clinical, experimental and theoretical fields [2, 14, 16, 29, 32, 34, 39].

Mathematical modeling provides a unique approach to gain basic knowledge in cholera dynamics, based on which effective prevention and intervention strategies can be possibly designed. Mathematical cholera studies dated back to Capasso and Paveri-Fontana [5] when they proposed a simple deterministic model to study a cholera epidemic occurred in the Mediterranean in 1973. Other representative works include those by Pourabbas *et al.* [35], Codeço [7], Ghosh *et al.* [11], Hartley *et al.* [12], King *et al.* [16], and Mukandavire *et al.* [30].

A notable example among these is the deterministic model proposed by Codeço [7] in 2001 which, in the first time, explicitly incorporated the environmental component, i.e., the *V. cholerae* concentration in the water supply (denoted by B), into a regular SIR system to form a combined human-environment (SIR-B) epidemiological model. This model enables a careful study on the complex interaction between human hosts and environmental pathogen towards better understanding the cholera transmission mechanism, and, as such, it has motivated the development of several other cholera models (e.g., [12, 30, 40]).

Specifically, the model of Codeço consists of the following differential equations:

$$\frac{dS}{dt} = nH - nS - a\lambda(B)S\,, \tag{1.1}$$

$$\frac{dI}{dt} = a\lambda(B)S - rI\,, \tag{1.2}$$

$$\frac{dB}{dt} = eI - mB\,, \tag{1.3}$$

where H stands for the total human population, n denotes the natural human birth/death rate, $r = n + \gamma$ with γ denoting the recovery rate, and $m = mb - nb$ representing the net death rate of vibrios (mb : loss rate; nb : growth rate). The incidence, which determines the rate of new infection, is represented by

$$a\lambda(B) = a\frac{B}{K+B} \tag{1.4}$$

with a being the contact rate with contaminated water and K the half saturation rate (i.e., ID_{50} , the infectious dose in water sufficient to produce disease in 50% of those exposed). In addition, the equation for R , which is not needed in the model analysis (since $R = H - S - I$), takes the form

$$\frac{dR}{dt} = \gamma I - nR\,. \tag{1.5}$$

The local stability of this model was originally analyzed by Codeço, and the following theorem was implicitly stated in [7]:

Theorem 1.1 *The basic reproduction number of the model (1.1)-(1.3) is*

$$R_0 = \frac{ae}{Kmr}\,H\,. \tag{1.6}$$

When $R_0 < 1$, there is a unique disease-free equilibrium (DFE) $X_0 = (H, 0, 0)$ which is locally asymptotically stable; when $R_0 > 1$, the DFE becomes unstable, and there is a unique positive endemic equilibrium X^* which is locally asymptotically stable.

The global asymptotic stability of the DFE and endemic equilibrium, however, was not discussed in [7]. Particularly, the global stability of the endemic equilibrium has long been a challenging problem in epidemiological models. The difficulty stems from the fact that most epidemiological models constitute high-dimensional (≥ 3) nonlinear autonomous systems for which the classical Poincaré-Bendixson theory [13] is no longer valid. On the other hand, the global dynamics is essential in understanding the basic mechanism in disease

initiation, spread and persistence, especially for the long term behavior of the disease and its relationship with the initial infection size. Such information will provide important guidelines for the public health administrations to design prevention and intervention strategies and to properly scale their efforts.

The present paper aims to make contribution to this topic by analyzing the global stability of the system (1.1)-(1.3) based on the theory of monotone dynamical systems (see [36] for a complete review). The framework of monotone dynamical systems is one of the most successful approaches in extending the Poincaré-Bendixson theory from two dimension to higher dimensions. For a class of three-dimensional dynamical systems which possess monotonicity (e.g., competitive systems [22]), the Poincaré-Bendixson property is preserved and the existence of non-constant periodic solutions can be ruled out by the orbital asymptotic stability, thus establishing the global stability of the positive endemic equilibria. This method has been applied to quite a few epidemiological models in the form of regular SEIR, SIRS and SEIRS formulations (see, e.g., [21–24, 26, 28, 37, 38, 41]). In contrast, the system considered in this paper, (1.1)-(1.3), is a combined human-environment (SIR-B) epidemiological model, the dynamics of which is complicated by the incorporation of the environmental component, B. The incidence function $\lambda(B)$ which is a rational function instead of a polynomial makes the analysis more difficult. It is thus a goal of this paper to conduct a thorough and rigorous study on this model.

Based on the analysis and results of the original model (1.1)-(1.3), we can then add various control strategies, including vaccination, therapeutic treatment and water sanitation, into the system and carefully study the resulting dynamics. We find that the incorporation of the control terms does not change the essential mathematical feature of the system and, consequently, the method of monotone dynamical systems can be similarly applied to analyze the control model.

We organize this paper in the following order. In Section 2, we conduct global stability analysis for the no-control model (1.1)-(1.3) using the method of monotone dynamical systems. In Section 3, we add control measures into the original system and analyze the dynamics of the control model. In Section 4, we present numerical simulation results to confirm the analytical predictions. Finally, we close the paper by conclusion and discussion.

2 Global stability analysis

We consider the model (1.1)-(1.3). Note that

$$B' = eI - mB \le eH - mB\,.$$

It is easy to verify that the feasible region

$$\Delta = \Big\{ (S, I, B) \,\Big|\, S \ge 0,\ I \ge 0,\ 0 \le S + I \le H,\ 0 \le B \le \frac{eH}{m} \Big\} \tag{2.1}$$

is positively invariant for the system (1.1)-(1.3). We will denote the interior of Δ by Δ°, and the boundary of Δ by $\partial\Delta$.

The variational matrix (Jacobian) of the system (1.1)-(1.3) is given by

$$J = \begin{bmatrix} -n - a\lambda(B) & 0 & -a\lambda'(B)S \\ a\lambda(B) & -r & a\lambda'(B)S \\ 0 & e & -m \end{bmatrix}. \tag{2.2}$$

By evaluating J at the DFE and computing the characteristic polynomial of $J(X_0)$, it is straightforward to obtain that when $R_0 < 1$, all the three eigenvalues are negative which establishes the local stability of X_0 (as stated in Theorem 1.1). Furthermore, we have the following result on the global stability of X_0.

Theorem 2.1 *When $R_0 < 1$, the DFE of the system (1.1)-(1.3) is globally asymptotically stable in Δ.*

Proof We define a Lyapunov function

$$L = eI + rB.$$

Clearly $L \geq 0$. Consider its orbital derivative:

$$\begin{aligned} L' = eI' + rB' &= ea\frac{B}{K+B}S - rmB = B\frac{aeH}{K}\big(\frac{K}{K+B}\frac{S}{H} - \frac{1}{R_0}\big) \\ &\leq B\frac{aeH}{K}\big(\frac{K}{K+B} - \frac{1}{R_0}\big) \leq 0, \end{aligned}$$

since $\frac{K}{K+B} < 1$ and $R_0 < 1$. We see that $L' = 0$ if and only if $B = 0$. The largest compact invariant subset in $\big\{(S, I, B) \in \Delta \,\big|\, L' = 0\big\}$ is the singleton $\{X_0\}$. From La Salle's invariance principle [10], X_0 is a global attractor. ■

Next we study the global stability of the endemic equilibrium X^* using a method based on monotone dynamical systems, as developed in [24]. Below we briefly review this method and several related concepts.

Given a C^1 function $x \mapsto F(x) \in \mathbb{R}^n$ for x in a bounded convex open set $D \subset \mathbb{R}^n$. Define the system of differential equations

$$\frac{dx}{dt} = F(x). \tag{2.3}$$

Denote by $x(t, x_0)$ the solution of (2.3) such that $x(0, x_0) = x_0$.

Definition 2.2 *A subset K is said to be absorbing in D if $x(t, K_1) \subset K$ for any compact subset $K_1 \subset D$ and sufficiently large t.*

We state the following two conditions which are important in studying the global stability of an equilibrium solution for the system (2.3).

(H1) There exists a compact absorbing set $K \subset D$.

(H2) The system (2.3) has a unique equilibrium point $\overline{x}$ in D.

Definition 2.3 *The system (2.3) is said to be uniformly persistent if there exists a constant $c > 0$ such that each component of any solution $x(t)$ with $x(0) = x_0 \in D$ satisfies*

$$\liminf_{t\to\infty} x_1(t) > c\,, \quad \liminf_{t\to\infty} x_2(t) > c\,, \quad \cdots\,, \quad \liminf_{t\to\infty} x_n(t) > c\,. \tag{2.4}$$

Lemma 2.4 [4] *If the system (2.3) is uniformly persistent in a bounded convex open domain D, then condition* (**H1**) *holds.*

Definition 2.5 *The system (2.3) is called competitive if there exists a diagonal matrix H with entries ± 1 such that each off-diagonal entry of $H\frac{\partial F}{\partial x}H$ is nonpositive in D, where $\frac{\partial F}{\partial x}$ is the Jacobian matrix of (2.3).*

An important feature of a three-dimensional competitive system is that it possesses the Poincaré-Bendixson property:

Theorem 2.6 [36] *For a competitive system defined in a three-dimensional convex open domain, if a nonempty compact $\omega-$limit set contains no equilibria, then it is a closed orbit.*

We list below some basic definitions related to orbital stability of a periodic orbit [8].

Definition 2.7 *Suppose (2.3) has a periodic solution $x = p(t)$ with the least period $\omega > 0$ and orbit $\gamma = \{p(t)\,|0 \le t \le \omega\}$. This orbit is orbitally stable if for each $\varepsilon > 0$, there exists a $\delta > 0$ such that any solution $x(t)$, for which the distance of $x(0)$ from γ is less than δ, remains at a distance less than ε from γ for all $t \ge 0$. It is asymptotically orbitally stable if the distance of $x(t)$ from γ also tends to zero as $t \to \infty$. The orbit γ is asymptotically orbitally stable with asymptotic phase if it is asymptotically orbitally stable and there is an $\eta > 0$ such that, any solution $x(t)$, for which the distance of $x(0)$ from γ is less than η, satisfies $|x(t) - p(t-\tau)| \to 0$ as $t \to \infty$ for some τ which may depend on $x(0)$.*

We now state a criterion given in [31] for the asymptotic orbital stability of a periodic orbit of (2.3).

Theorem 2.8 *A sufficient condition for a periodic orbit $\gamma = \{p(t)\,|0 \le t \le \omega\}$ of (2.3) to be asymptotically orbitally stable with asymptotic phase is that the linear system*

$$\frac{dz}{dt} = \Big(\frac{\partial F^{[2]}}{\partial x}\big(p(t)\big)\Big)\, z(t) \tag{2.5}$$

is asymptotically stable, where $\frac{\partial F^{[2]}}{\partial x}$ is the second compound matrix of the Jacobian $\frac{\partial F}{\partial x}$, as defined below.

Definition 2.9 *Let $A = (a_{ij})$ be a matrix of dimension $n \times n$. the second additive compound matrix of A, denoted by $A^{[2]}$, is a $\binom{n}{2} \times \binom{n}{2}$ matrix defined by*

$$A^{[2]} = D_+(I + hA)^{(2)}|_{h=0}\,, \tag{2.6}$$

where $(I + hA)^{(2)}$ is the second exterior power of $(I + hA)$, and D_+ is the corresponding right-hand derivative [31]. *For example, when $n = 2$, $A^{[2]} = \mathrm{Tr}A$. When $n = 3$,*

$$A^{[2]} = \begin{bmatrix} a_{11}+a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11}+a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22}+a_{33} \end{bmatrix}.$$

Next we state a theorem implicitly given in [24].

Theorem 2.10 *Assume that*

(1) conditions (**H1**) *and* (**H2**) *hold;*

(2) $\overline{x}$ *is locally asymptotically stable;*

(3) the system (2.3) satisfies the Poincaré-Bendixson Property;

(4) each periodic orbit of (2.3) in D *is orbitally asymptotically stable.*

Then the unique equilibrium $\overline{x}$ *is globally asymptotically stable in* D*.*

We now examine the system (1.1)-(1.3). We have two propositions which imply that the system is persistent.

Proposition 2.11 *The disease-free equilibrium point* X_0 *is the only* ω*-limit point of the system (1.1)-(1.3) on the boundary,* $\partial\Delta$ *, of* Δ*.*

Proof It is easy to check that the vector field of the system (1.1)-(1.3) is transversal to the boundary of Δ on all its faces except the $S-$axis. For example, the face corresponding to $S + I = H$ has direction (1, 1, 0) and the inner product with the vector field is $1\big(n(H - S) - a\lambda(B)S\big) + \big(a\lambda(B)S - rI\big) = n(H - S) - rI = (n - r)I < 0$. Thus, the vector field on this face points toward the region Δ . The $S-$axis, instead, is invariant. On the $S-$axis, the system is reduced to $S' = n(H - S)$, so $S(t) \to H$ as $t \to \infty$. Thus X_0 is the only ω-limit point on $\partial\Delta$. ■

Proposition 2.12 *When* $R_0 > 1$ *,* X_0 *cannot be the* ω*-limit point of any orbit starting in the interior,* Δ° *, of* Δ*.*

Proof Consider the function $L = eI + rB \geq 0$. The orbital derivative of L is $L' = B\frac{aeH}{K}(\frac{K}{K+B}\frac{S}{H} - \frac{1}{R_0})$. When $R_0 > 1$, for any point (S, I, B) in Δ° that is sufficiently close to $X_0 = (H, 0, 0)$, we have $L' > 0$. So it cannot approach X_0. Hence, X_0 cannot be the ω-limit point of any orbit starting in Δ° . ■

Based on Propositions 2.11 and 2.12, we obtain

Theorem 2.13 *The system (1.1)-(1.3) is uniformly persistent.*

Now consider the Jacobian J given in equation (2.2). If we set $H = \text{diag}\,(1, -1, 1)$, then we can easily observe that the off-diagonal entries of HJH are all nonpositive. Hence, it is a three-dimensional competitive system which possesses the Poincaré-Bendixson property [36]. We have the following theorem.

Theorem 2.14 *Any compact* $\omega-$*limit set of the system (1.1)-(1.3) in the interior of* Δ *is either a closed orbit or the endemic equilibrium* X^**.*

Proof Suppose γ is an $\omega-$limit set of the system (1.1)-(1.3) in Δ°. If γ does not contain X^*, then it contains no equilibria since X^* is the only interior equilibrium point. Theorem 2.6 implies that γ is a closed orbit. If, instead, γ contains X^*, then any orbit that gets arbitrarily close to X^* will converge to X^* since X^* is locally asymptotically stable. Thus $\gamma = X^*$. ■

For the system (1.1)-(1.3), Theorems 1.1, 2.13 and Lemma 2.4 ensure that conditions (1) and (2) in Theorem 2.10 hold, whereas Theorem 2.14 guarantees condition (3) in Theorem 2.10. The following theorem states that condition (4) in Theorem 2.10 also holds for this system.

Theorem 2.15 *The trajectory of any nonconstant periodic solution of the system (1.1)-(1.3), if it exists, is asymptotically orbitally stable with asymptotic phase.*

Proof The second compound matrix of the system (1.1)-(1.3) is given by

$$J^{[2]} = \begin{bmatrix} -n-r-a\lambda(B) & a\lambda'(B)S & a\lambda'(B)S \\ e & -n-m-a\lambda(B) & 0 \\ 0 & a\lambda(B) & -r-m \end{bmatrix}. \tag{2.7}$$

Then the second compound system defined along the periodic solution $(S(t), I(t), B(t))$ of the system (1.1)-(1.3) is given by

$$\begin{aligned} X'(t) &= -\big(n+r+a\lambda(B)\big)X + a\lambda'(B)SY + a\lambda'(B)SZ\,, && (2.8)\\ Y'(t) &= eX - \big(n+m+a\lambda(B)\big)Y\,, && (2.9)\\ Z'(t) &= a\lambda(B)Y - (r+m)Z\,. && (2.10) \end{aligned}$$

Based on Theorem 2.8, if we can prove the system (2.8)-(2.10) is asymptotically stable, then the periodic solution is asymptotically orbitally stable with asymptotic phase.

We define a Lyapunov function

$$V(X,Y,Z,S,I,B) = \sup\left\{|X|, \frac{I}{B}(|Y|+|Z|)\right\}.$$

Since the system (1.1)-(1.3) is persistent, any periodic solution $(S(t), I(t), B(t))$ is at a positive distance from the boundary $\partial\Delta$. So $\frac{I}{B}$ is well-defined, and there is a constant $c > 0$ such that $\frac{I}{B} > c$. Hence, for some positive constant c_0, we have

$$V(X,Y,Z,S,I,B) \geq c_0 \sup\{|X|, |Y|, |Z|\},$$

for any $(X,Y,Z) \in \mathbb{R}^3$ and any periodic solution $(S(t), I(t), B(t))$ of the system (1.1)-(1.3).

Let us estimate the right-derivative of V along a solution $(X(t), Y(t), Z(t))$ of the system (2.8)-(2.10) and $(S(t), I(t), B(t))$ of the system (1.1)-(1.3).

$$\begin{aligned} &D_+|X(t)| \leq -\big(n+r+a\lambda(B)\big)|X| + \frac{a\lambda'(B)SB}{I}\frac{I}{B}\big(|Y|+|Z|\big)\,,\\ &D_+|Y(t)| \leq e|X| - \big(n+m+a\lambda(B)\big)|Y|\,,\\ &D_+|Z(t)| \leq a\lambda(B)|Y| - (r+m)|Z|\,, \end{aligned}$$

and

$$
\begin{aligned}
&D_+\frac{I}{B}(|Y|+|Z|)\\
&=(\frac{I'}{I}-\frac{B'}{B})\frac{I}{B}(|Y|+|Z|)+\frac{I}{B}D_+(|Y|+|Z|)\\
&\le(\frac{I'}{I}-\frac{B'}{B})\frac{I}{B}(|Y|+|Z|)+\frac{I}{B}(e|X|-(n+m)|Y|-(r+m)|Z|)\\
&\le(\frac{I'}{I}-\frac{B'}{B})\frac{I}{B}(|Y|+|Z|)+e\frac{I}{B}|X|-(n+m)\frac{I}{B}(|Y|+|Z|)\\
&=e\frac{I}{B}|X|+\big(\frac{I'}{I}-\frac{B'}{B}-(n+m)\big)\frac{I}{B}\big(|Y|+|Z|\big)\,.
\end{aligned}
$$

Therefore,

$$D_+V(t)\le\max\{g_1(t),\,g_2(t)\}\,V(t)\,,$$

where

$$
\begin{aligned}
g_1(t) &= -n-r-\frac{aB}{K+B}+\frac{aK}{(K+B)^2}\frac{SB}{I}\,,\\
g_2(t) &= e\frac{I}{B}+\frac{I'}{I}-\frac{B'}{B}-(n+m)\,.
\end{aligned}
$$

From the system (1.1)-(1.3), we have $\frac{B'}{B}=e\frac{I}{B}-m$. Then

$$g_2(t)=\frac{I'}{I}-n\,.$$

Similarly, $\frac{I'}{I}=\frac{a}{K+B}\frac{BS}{I}-r$. Then

$$g_1(t)=-n-r-\frac{aB}{K+B}+\frac{K}{K+B}\big(\frac{I'}{I}+r\big)=\frac{K}{K+B}\frac{I'}{I}-n-\frac{(a+r)B}{K+B}\,.$$

Hence,

$$\max\{g_1(t),\,g_2(t)\}\le\frac{I'}{I}-n\,.$$

Denote the period of the periodic solution $(S(t),I(t),B(t))$ by τ. We have

$$\int_0^\tau\max\{g_1(t),\,g_2(t)\}\,dt\le\int_0^\tau\big(\frac{I'}{I}-n\big)\,dt=\ln I(t)\big|_0^\tau-n\tau=-n\tau\,<\,0\,.$$

Thus, the system (2.8)-(2.10) is asymptotically stable. Then, the periodic solution $(S(t),I(t),B(t))$ is asymptotically orbitally stable with asymptotic phase. ■

We are now ready to state the main result in this section:

Theorem 2.16 *When $R_0>1$, the endemic equilibrium X^* of the system (1.1)-(1.3) is globally asymptotically stable in Δ°.*

The proof follows Theorem 2.10 by combining Theorems 1.1 and 2.13 - 2.15.

3 Cholera dynamics with controls

Building on the analysis and results presented in Section 2, we can now study cholera dynamics with control strategies incorporated. We modify the original model (1.1)-(1.3) by adding three types of controls: vaccination, therapeutic treatment (including hydration therapy, antibiotics, etc.), and water sanitation. We make the following assumptions.

- Vaccination is introduced to the susceptible population at a rate of v, so that vS individuals per time are removed from the susceptible class and added to the recovered class.
- Therapeutic treatment is applied to infected people at a rate of u, so that uI individuals per time are removed from the infected class and added to the recovered class.
- Water sanitation leads to the death of vibrios at a rate of w.
- Another type of vaccination is applied to (some) newborns so that only a proportion P $(0 < P \leq 1)$ of individuals entering the total population are susceptible.

As a result, we obtain the following modified system:

$$\frac{dS}{dt} = PnH - (n+v)S - \frac{aBS}{K+B}, \tag{3.1}$$

$$\frac{dI}{dt} = \frac{aBS}{K+B} - (r+u)I, \tag{3.2}$$

$$\frac{dB}{dt} = eI - (m+w)B, \tag{3.3}$$

together with the equation for R:

$$\frac{dR}{dt} = (1-P)nH + (r-n+u)I - nR + vS. \tag{3.4}$$

It is clear that $\frac{d}{dt}(S+I+R) = 0$ so that $H = S+I+R$ remains a constant. The feasible region is

$$\Delta = \left\{ (S,I,B) \,\middle|\, S \geq 0,\ I \geq 0,\ 0 \leq S+I \leq H,\ 0 \leq B \leq \frac{eH}{m+w} \right\}, \tag{3.5}$$

and it can be easily verified that Δ is positively invariant for the system (3.1)-(3.3).

To proceed, it is convenient to set

$$\bar{r} = r+u, \qquad \text{and} \qquad \bar{m} = m+w.$$

It is obvious that the system (3.1)-(3.3) has a unique DFE

$$X_0 = \left(\frac{nPH}{n+v},\ 0,\ 0 \right). \tag{3.6}$$

The Jacobian of the system is given by

$$J = \begin{bmatrix} -\frac{aB}{K+B} - n - v & 0 & -\frac{aSK}{(K+B)^2} \\ \frac{aB}{K+B} & -\bar{r} & \frac{aSK}{(K+B)^2} \\ 0 & e & -\bar{m} \end{bmatrix}. \tag{3.7}$$

Substituting the DFE in equation (3.6) into the Jacobian (3.7) and calculating the characteristic polynomial, we obtain

$$\text{Det}\left(\lambda I - J(X_0)\right) \;=\; (\lambda + n + v)(\lambda + n)\Big[(\lambda + \bar{r})(\lambda + \bar{m}) - \frac{anePH}{K(n+v)}\Big].$$

It is then straightforward to see that X_0 is locally asymptotically stable if and only if

$$\bar{r}\bar{m} - \frac{anePH}{(n+v)K} \;>\; 0\,,$$

which yields

$$H \;<\; \frac{(r+u)(m+w)(n+v)K}{aneP}\,. \tag{3.8}$$

The inequality in (3.8) implies that

$$R_0^c \;=\; \frac{ane}{K(r+u)(m+w)(n+v)}\,PH\,. \tag{3.9}$$

Equation (3.9) is the expression of the basic reproduction number for the model with controls. Here we have used the notation R_0^c to distinguish from R_0 defined in equation (1.6) for the original no-control model. Clearly $R_0^c < R_0 = \frac{ae}{Kmr}H$. The result in equation (3.9) shows that, mathematically, each of the three types of individual controls can reduce the value of R_0^c lower than 1 so that the disease will be eradicated. For example, if $v = w = 0$ and $P = 1$, we would just need $u > \frac{ae}{mK}H - r$ to ensure $R_0^c < 1$. Practically, however, the strength of each control strategy would be limited by social and economic factors and available resources, and the combination of different intervention approaches would possibly achieve the best result.

Indeed, like the original model, the DFE (3.6) is also globally asymptotically stable when $R_0^c < 1$. This can be established based on the following theorem:

Theorem 3.1 [6] *Consider a model system written in the form*

$$\frac{dX_1}{dt} = F(X_1,\, X_2)\,; \qquad \frac{dX_2}{dt} = G(X_1,\, X_2) \quad \text{with} \quad G(X_1,\, 0) = 0\,,$$

where $X_1 \in \mathbb{R}^m$ denotes (its components) the number of uninfected individuals and $X_2 \in \mathbb{R}^n$ denotes (its components) the number of infectious individuals; $X_0 = (X_1^E\,,\, 0)$ denotes the disease-free equilibrium of the system.

Also assume the conditions (A1) *and* (A2) *below:*

(A1) *For* $\dfrac{dX_1}{dt} = F(X_1,\, 0)\,,\ X_1^E$ *is globally asymptotically stable;*

(A2) $G(X_1,\, X_2) = A\,X_2 - \hat{G}(X_1,\, X_2)\,,\ \hat{G}(X_1,\, X_2) \geq 0$ *for* $(X_1,\, X_2) \in \Omega$, *where the Jacobian* $A = \dfrac{\partial G}{\partial X_2}\,(X_1^E\,,\, 0)$ *is an* M*-matrix (the off-diagonal elements of* A *are nonnegative) and* Ω *is the region where the model makes biological sense.*

Then the DFE $X_0 = (X_1^E\,,\, 0)$ *is globally asymptotically stable provided that* $R_0 < 1\,.$

Applying Theorem 3.1 to the control model (3.1)-(3.3), with equation (3.1) being the uninfected subsystem and equations (3.2) and (3.3) being the infectious subsystem, we can easily verify that conditions (A1) and (A2) hold. Therefore, we obtain

Theorem 3.2 *If* $R_0^c < 1\,,$ *where* R_0^c *is defined in equation (3.9), the DFE of the system (3.1)-(3.3) is globally asymptotically stable.*

Suppose, now, that the effects of these controls are not strong enough to reduce R_0^c below $1\,.$ Then the DFE becomes unstable and the disease will persist. Let us study the endemic dynamics in details.

At the endemic equilibrium $X^* = (S^*,\, I^*,\, B^*)\,,$ we have

$$I^* \;=\; \frac{anePH - \bar{r}\bar{m}(n+v)K}{\bar{r}e(a+n+v)}\,, \tag{3.10}$$

$$B^* \;=\; \frac{e}{\bar{m}}I^*\,, \tag{3.11}$$

$$S^* \;=\; \frac{\bar{r}(K+B^*)}{aB^*}I^*\,. \tag{3.12}$$

From equation (3.10), it is straightforward to see that a positive endemic equilibrium exists if and only if

$$H \;>\; \frac{\bar{r}\bar{m}(n+v)K}{aneP}\,, \qquad \text{i.e.,} \quad R_0^c \;>\; 1\,. \tag{3.13}$$

We have the following result on the local stability of the endemic equilibrium.

Theorem 3.3 *When* $R_0^c > 1\,,$ *the unique positive endemic equilibrium of the system (3.1-3.3) is locally asymptotically stable.*

Proof Evaluating the Jacobian (3.7) at the endemic equilibrium, we obtain

$$J(X^*) = \begin{bmatrix} -T-n-v & 0 & -Q \\ T & -\bar{r} & Q \\ 0 & e & -\bar{m} \end{bmatrix}\,,$$

with $T = \frac{aB^*}{K+B^*} > 0$ and $Q = \frac{aS^*K}{(K+B^*)^2} > 0\,.$ The characteristic polynomial is given by

$$\text{Det}\left(\lambda I - J(X^*)\right) \;=\; a_0\lambda^3 + a_1\lambda^2 + a_2\lambda^1 + a_3\,,$$

where

$$\begin{aligned} a_0 &= 1\,, \\ a_1 &= \bar{r}+\bar{m}+n+v+T\,, \\ a_2 &= n\bar{r}+n\bar{m}+v\bar{r}+v\bar{m}+T\bar{r}+T\bar{m}+(\bar{r}\bar{m}-Qe)\,, \\ a_3 &= (n+v)(\bar{r}\bar{m}-Qe)+T\bar{r}\bar{m}\,. \end{aligned}$$

Based on the Routh-Hurwitz criterion [17, 33], the sufficient and necessary conditions for local stability are:

$$a_1>0\,, \qquad a_2>0\,, \qquad a_3>0\,, \qquad a_1a_2-a_0a_3>0\,.$$

Note that $a_1>0$ is obvious. Meanwhile, from equations (3.10)-(3.12), we obtain

$$\bar{r}\bar{m}-Qe=\frac{ae^2\bar{m}S^*I^*}{(\bar{m}K+eI^*)^2}\;>\;0.$$

It is then clear to see $a_2>0$ and $a_3>0$. In addition, we observe that

$$\begin{aligned} a_1a_2-a_0a_3 &= \bar{r}^2(n+v+T)+(n+v)\bar{r}\bar{m}+(\bar{r}+\bar{m})(n+v+T)(\bar{r}+2\bar{m}+T) \\ &\quad +(\bar{r}+\bar{m}+T)(\bar{r}\bar{m}-Qe)\;>\;0\,, \end{aligned}$$

which completes the proof. ■

Now we consider the global stability of the endemic equilibrium for the control model. We note that Propositions 2.11 and 2.12 also apply to the system (3.1)-(3.3). For example, to show Proposition 2.12, set the function $L=eI+\bar{r}B$ and observe that

$$L'=B\frac{aeS_0}{K}\Big(\frac{K}{K+B}\frac{S}{S_0}-\frac{1}{R_0}\Big)\;>\;0$$

when $R_0>1$, for any point (S,I,B) sufficiently close to $X_0=(S_0,\,0,\,0)$ where $S_0=\frac{nPH}{n+v}$. Hence, X_0 cannot be the ω-limit point of any orbit starting in Δ°.

Meanwhile, it can be easily verified that the system (3.1)-(3.3) is competitive; with $H=\mathrm{diag}(1,\,-1,\,1)$, all the off-diagonal entries of HJH are non-positive, where the Jacobian J is defined in equation (3.7).

In addition, the second compound matrix of the system (3.1)-(3.3) can be written as

$$J^{[2]}=\begin{bmatrix} -\bar{n}-\bar{r}-a\lambda(B) & a\lambda'(B)S & a\lambda'(B)S \\ e & -\bar{n}-\bar{m}-a\lambda(B) & 0 \\ 0 & a\lambda(B) & -\bar{r}-\bar{m} \end{bmatrix}, \tag{3.14}$$

where $\bar{n}=n+v$. We observe that this matrix takes the same symbolic form as the second compound matrix of the no-control model given in equation (2.7), if we replace r, m and n by $\bar{r}$, $\bar{m}$ and $\bar{n}$, respectively. Thus, Theorem 2.15 can be similarly established for the system (3.1)-(3.3).

Based on these observations and Theorem 3.3, we can clearly see the following result holds:

Theorem 3.4 *When $R_0^c > 1$, the endemic equilibrium X^* of the system (3.1)-(3.3) is globally asymptotically stable in Δ°.*

It is, however, interesting to compare the size of the infection at the endemic equilibria in these two cases, i.e., with and without controls. Let us denote the infectious endemic equilibrium of the original model by I_o^*, and that of the control model by I_c^*. Equation (3.10) gives the expression for I_c^*, whereas

$$I_o^* = \frac{aneH - rmnK}{re(a+n)}, \tag{3.15}$$

which can be simply obtained from equation (3.10) by setting $u = v = w = 0$ and $P = 1$, i.e., removing all controls. After some simple algebra, we can readily see

$$I_o^* - I_c^* > 0. \tag{3.16}$$

This result can be naturally expected. It shows that, even though the control measures are not strong enough to eliminate the epidemicity, they have the effects of reducing the size of the infection, particularly for the long-term disease dynamics. When I_c^* is close to 0, an endemic state would be unlikely to occur or persist in reality, since practical endemism requires a reasonably higher value for I^* [1, 7].

4 Numerical results

In this section, we present some numerical simulation results to confirm our analytical predictions on the global dynamics of the cholera models.

We first consider the original no-control model (1.1)-(1.3). We set the total population as $H = 10,000$, and take the values of the parameters a, e, n, m, r and K from Codeço's paper [7]. Using equation (1.6), we find $R_0 \approx 1.51$, indicating that there is a unique positive endemic equilibrium, where $I^* \approx 16.98$ based on equation (3.15). We pick five different initial conditions with $I(0) = 1,\ 100,\ 200,\ 600,\ 1000$, respectively, and plot these five solution curves by the phase plane portrait of I vs. S in Figure 1. We clearly see that all these five orbits converge to the endemic equilibrium, showing the global asymptotic stability of the endemic equilibrium.

With the same configurations, we now add control measures and simulate the control model (3.1)-(3.3). Let us consider two hypothetical scenarios here: one with "strong" controls, by setting $u = 0.5r$, $v = 0.5n$, and $w = 0.5m$; the other with "weak" controls, by setting $u = 0.1r$, $v = 0.1n$, and $w = 0.1m$. We fix $P = 0.9$ in both cases, meaning that 90% of newborns are susceptible. Using equation (3.9), we obtain $R_0^c \approx 0.40$ in the first case, indicating that the DFE is globally asymptotically stable and the disease would die out over time. The phase plane portrait in Figure 2-(a) confirms this prediction. In contrast, for the second case we have $R_0^c \approx 1.03$, indicating the existence of a globally stable endemic equilibrium, where $I^* \approx 0.66$ based on equation (3.10). This is confirmed by the phase plane portrait in Figure 2-(b).

The comparison between the control and no-control models can be further demonstrated by looking at the time evolution of the infection curves. For illustration, we set the initial

condition with $I(0) = 100$, and plot I vs. t for the three cases: no controls, strong controls, and weak controls, in Figure 3-a. We set a relatively short time interval (50 weeks) to show the details of epidemic dynamics. The total population $H = 10,000$ is unchanged. We observe that for the model without controls ($R_0 \approx 1.51$), an epidemic outbreak occurs with a peak value about 450, showing a relatively high infection level. For the model with weak controls ($R_0^c \approx 1.03$), epidemicity also occurs but with a much lower infection level; the peak value is about 170. For the model with strong controls ($R_0^c \approx 0.40$), the DFE becomes globally asymptotically stable and no epidemicity occurs; the infection curve quickly declines to zero and the disease dies out. In order to examine the long term dynamics of the disease, we plot the infection curves again for the no-control model and the weak-control model in Figure 3-b, with a much longer period (2,000 weeks). We clearly see that after the initial epidemic outbreak, the no-control infection curve exhibits several epidemic oscillations with decaying magnitudes, which are separated by small time intervals of length $100 - 200$ weeks (or $2 - 4$ years), before it finally ($t \geq 1,500$ weeks) rests at the endemic equilibrium $I^* \approx 16.98$. In contrast, for the weak-control infection curve, there is almost no oscillation visible after the initial epidemic outbreak. It quickly converges to its endemic equilibrium at a very low infection level ($I^* \approx 0.66$), a consequence of the control strategies.

5 Conclusion and Discussion

We have conducted a global stability analysis for the cholera model proposed in [7], using the theory and method based on monotone dynamical systems. Our results have completely determined the global dynamics of this model, thus establishing R_0 as a sharp threshold for local and global stability exchange between the DFE and endemic equilibrium. This study builds the ground for modeling and analyzing prevention and intervention strategies on cholera. Consequently, we have incorporated three types of controls, including the vaccination, therapeutic treatment, and water sanitation, and analyzed the local and global dynamics of the cholera model with controls. Since the control model also possesses the nice feature of monotonicity, the analytical techniques developed for the original no-control model can be similarly applied, thus making the analysis of the control model much easier.

We have found that the dynamical pattern of the control model is similar to that of the original model in that $R_0^c = 1$ is a forward transcritical bifurcation point for stability exchange. Thus the strength of the controls is crucial in determining the dynamics of the control model. With strong controls, the value of R_0^c can be reduced to a level below the threshold 1, thus eradicating the disease. With weak controls, the value of R_0^c could be still above 1; consequently, an endemic state exists, though at a (much) lower infection level than that without controls. Our analytical predictions have been confirmed by numerical simulation results. The work in this paper can provide useful guidelines for public health administrations to effectively design prevention and intervention strategies against cholera outbreak, and to properly scale their efforts.

The method based on monotone dynamical systems has its limitation. Specifically, it requires the dynamical systems to possess monotonicity, a condition not satisfied by many epidemiological models. Alternatively, there are several different approaches for global stability analysis of high-dimensional dynamical systems. The classical method of Lyapunov

functions [15, 18] has been known for many decades and widely applied in various scientific disciplines. The disadvantage, however, is that there is no systematic way to construct Lyapunov functions so that its success largely depends on the types of problems. As such, trial and error is the standard process for its implementation. Another method, the geometric approach, originally proposed by Li and Muldowney [9, 25, 27], has gained some popularity in recent years (see, e.g., [3, 20]) as it is applicable to more general dynamical systems. The key part of this approach is to check a high-dimensional Bendixson criterion which is robust under C^1 local perturbations, based on which the local asymptotic stability leads to global stability. The procedure to check this criterion, however, is highly nontrivial. Hence, like the method of monotone dynamical systems, all these methods have their strength and weakness, and the "best" approach for general high-dimensional dynamical systems does not exist yet.

The study presented in this paper can be extended in several ways. First, the theory and method based on monotone dynamical systems can be applied to the model (1.1)-(1.3) with more general incidence function $\lambda(B)$, as can be verified such types of systems are competitive. Meanwhile, we may incorporate the control measures into more sophisticated cholera models, such as those proposed in [12, 30, 40], and conduct similar analysis. In addition, this work builds the ground for an "optimal study" of the control strategies which is especially important in practical application. For example, suppose we want to minimize the number of cholera infections while also minimizing the effort of the controls, then we may seek to minimize the following functional in a given time interval:

$$J(u,\, v) = \int_0^T \big[I(t) + C_1(u) + C_2(v) + C_3(w)\big]\, dt\,,$$

where C_1, C_2 and C_3 are appropriate functions representing the costs related to vaccination, therapeutic treatment and water sanitation, respectively. Our dynamical analysis and simulation can be combined with an optimal control technique [19] to seek an answer for this type of problem. We plan to explore this topic in our future work.

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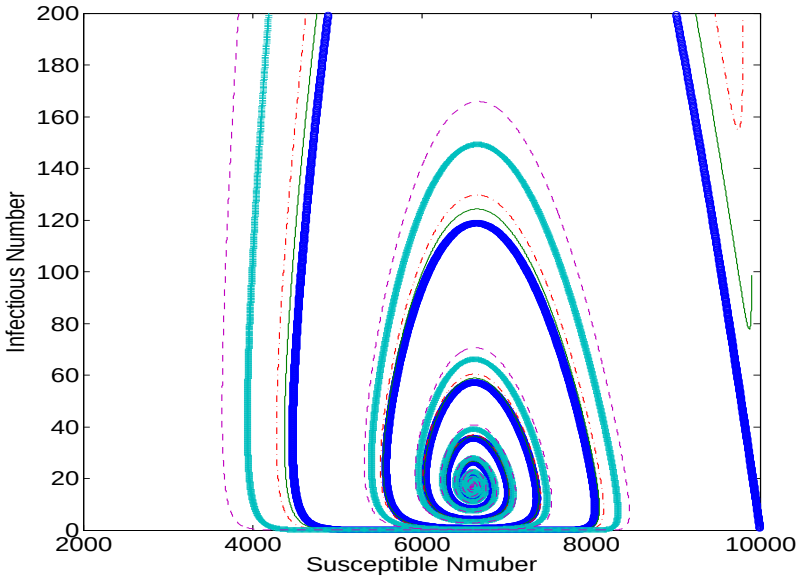
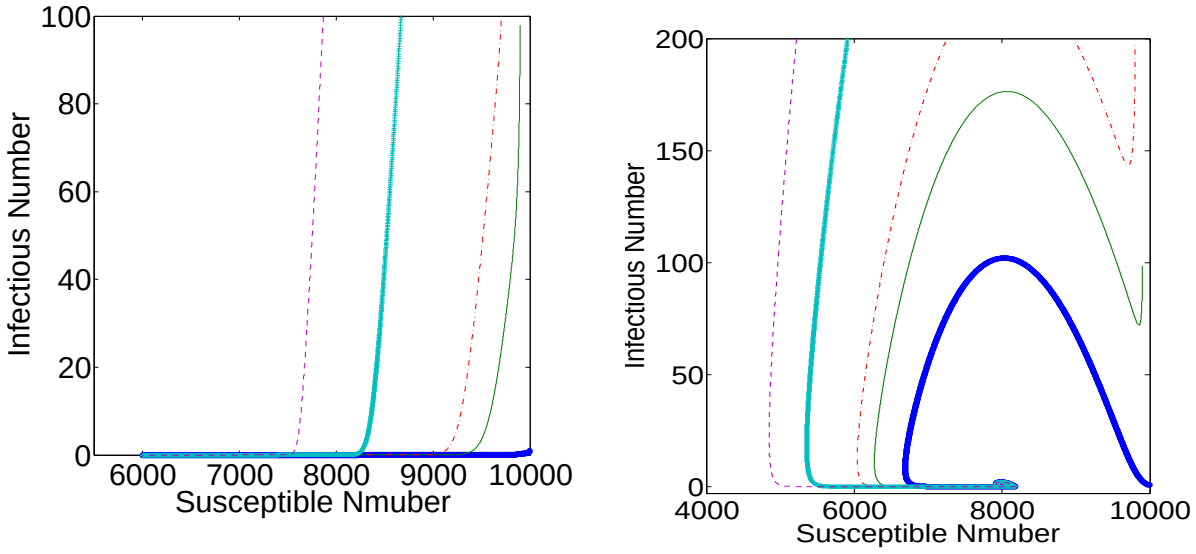
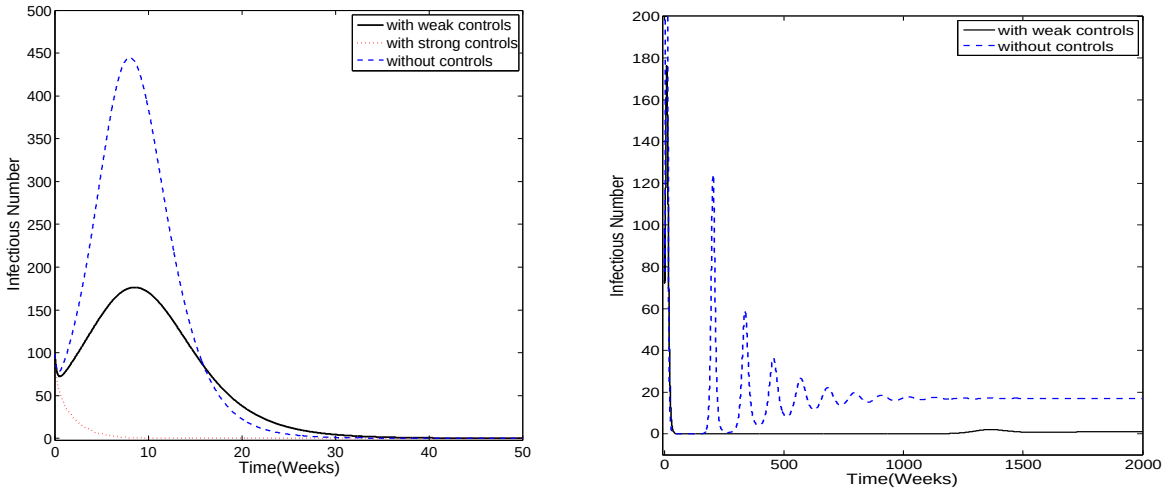


Figure 1: The phase plane portrait of I vs. S for the the original model (1.1)-(1.3). The five curves correspond to five initial conditions with $I(0) = 1,\ 100,\ 200,\ 600,\ 1000$, respectively. All these orbits converge to the endemic equilibrium: $I^* \approx 16.98$, $S^* \approx 6603$.



(a) (b)

Figure 2: The phase plane portraits of I vs. S for the control model (3.1)-(3.3). In each case the five curves correspond to five initial conditions with $I(0) = 1,\ 100,\ 200,\ 600,\ 1000$, respectively. (a) Strong controls, with $R_0^c \approx 0.40$. All the orbits converge to the DFE: $I_0 = 0$, $S_0 = 6000$. (b) Weak controls, with $R_0^c \approx 1.03$. All the orbits converge to the endemic equilibrium: $I^* \approx 0.66$, $S^* \approx 7986$.



(a) (b)

Figure 3: The infection curves I vs. t, with $I(0) = 100$. (a) Infection curves of no controls (dashed line), strong controls (dotted line) and weak controls (solid line) within a short time interval. (b) Infection curves of no control (dashed line) and weak controls (solid line) for a long period.