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Modelling and control of cholera on networks with a common water source

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A mathematical model is formulated for the transmission and spread of cholera in a heterogeneous host population that consists of several patches of homogeneous host populations sharing a common water source. The basic reproduction number $\mathcal{R}_0$ is derived and shown to determine whether or not cholera dies out. Explicit formulas are derived for target/type reproduction numbers that measure the control strategies required to eradicate cholera from all patches.

Keywords: cholera; common water source; global stability; disease control strategy; target reproduction number

1. Introduction

Cholera is a bacterial disease caused by *Vibro cholerae*, an aquatic bacterium that occurs in brackish water, estuaries and contaminated water. Cholera can be transmitted directly via person-to-person contact (direct transmission), or indirectly through ingestion of contaminated water (indirect transmission). *V. cholerae* can produce toxic proteins in the intestine of an infected host leading to watery diarrhoea, which sheds pathogen into the environment and contaminates the water. Symptoms of infected individuals are mostly mild, but can be extremely severe in some cases, several outbreaks in Haiti [14,22,30] and Zimbabwe [20] leading to rapid death due to dehydration if left untreated. Recent severe outbreaks in [5,20,22,30] highlight the global burden of cholera in public health. For example, the contamination of the Artibonite River, the common water source for villagers along this river, triggered the Haiti cholera outbreak in October 2010 [21]; as of 8 February 2014, the number of reported cholera cases in Haiti is 699,197, with 8549 deaths [18].

Several mathematical models have been proposed to understand the transmission of cholera [6,13,26,28,29], while more complicated heterogeneous models have been used to investigate the spatial cholera spread due to human and water movement [4,8,20,22,30]. The interplay

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between human and water movement often makes the model analysis very challenging due to the complexity and large scale of these heterogeneous cholera models. Thus it is difficult to apply these model studies to address spatial differences in the force of infection and effective disease control/intervention strategies. A multi-patch model has recently been proposed in [24] to address specifically the effect of a common water source on the transmission of cholera in a heterogeneous host population. Rigorous analysis has been carried out in [24] to show how heterogeneity affects the cholera invasibility in terms of the basic reproduction number $\mathcal{R}_0$ and the efficacy of intervention measures.

In this paper we propose a new multi-patch cholera model that incorporates general nonlinear incidence functions for both direct and indirect cholera transmission in a heterogenous host population that shares a common water source. Our model includes and extends the model in [24] where mass action incidence is assumed for both transmission pathways. The proposed model can be regarded as a coupled system on a star network where the hub vertex corresponds to the common water source and the leaf vertices correspond to the patches where host live. For example, baris in Bangladesh, a country where cholera remains endemic [17], refer to multiple household structures in which groups of related families live and often share the same water source [1,10]. In this situation, each bari represents a patch and thus a leaf vertex in the network, while the common water source represents the hub vertex in the network. It is of significance to investigate whether or not cholera can invade such a star network and how public health authority could implement effective cholera control strategies. To address the first question, the basic reproduction number $\mathcal{R}_0$ is derived and shown to completely determine the global disease dynamics. Specifically, if $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium is globally asymptotically stable and cholera dies out from all patches; while if $\mathcal{R}_0 > 1$, then there exists a unique endemic equilibrium that is globally asymptotically stable and cholera persists at an endemic level in all patches. The proofs of these global stability results utilize a new matrix-theoretic approach [27, Section 2] to the construction of Lyapunov functions (for the disease-free equilibrium) and a graph-theoretic approach (for the endemic equilibrium) recently developed in a series of papers [11,12,16,27]. For the second question, the star network structure allows the derivation of explicit formulas for target/type reproduction numbers [14,23,25] that can be used to measure the disease control and intervention strategies needed to eradicate cholera from all patches.

The paper is organized as follows. The new cholera model is formulated in Section 2. Equilibria analysis and the basic reproduction number are given in Section 3. In Section 4 the global dynamics of the proposed model are established. Various cholera control strategies and target/type reproduction numbers are investigated in Section 5. The paper concludes with a discussion in Section 6.

2. Model

In this section we formulate a new mathematical model for cholera transmission and spread in a heterogeneous host population that shares a common water source. The heterogeneous host population is divided into *n* patches, depending on either their geographic location or their social network structure [10]. The classic susceptible-infectious-recovered compartmental model is used to model the disease dynamics within patches; infectious individuals can shed the pathogen into the common water source and susceptible individuals can be infected via either direct contact with infectious individuals or ingestion of contaminated water in the common source. Let $S_j(t), I_j(t), R_j(t)$ denote the number of humans in patch j $(1 \leq j \leq n)$ who are susceptible to, infectious with, and recovered from cholera at time t, respectively, and $W(t)$ denote the concentration of *V. cholerae* at time t in the common water source. The proposed multi-patch cholera model

takes the following form:

$$
\begin{aligned}
S_j' &= \Lambda_j - f_j(S_j, I_j) - g_j(S_j, W) - d_j S_j, \quad j = 1, \dots, n, \\
I_j' &= f_j(S_j, I_j) + g_j(S_j, W) - (d_j + \alpha_j + \gamma_j) I_j, \quad j = 1, \dots, n, \\
W' &= -\delta W + \sum_{k=1}^{n} h_k(I_k)
\end{aligned}
\tag{1}
$$

and

$$
R_j' = \gamma_j I_j - d_j R_j, \quad j = 1, \dots, n.
\tag{2}
$$

The disease transmission diagram for model (1)–(2) is depicted in Figure 1, and the parameters are summarized in the following list:

$\Lambda_j > 0$:   constant recruitment into patch j
$d_j > 0$:   natural death rate in patch j
$\alpha_j \geq 0$:   mortality rate due to the disease in patch j
$\gamma_j > 0$:   recovery rate of infectious individuals in patch j
$\delta > 0$:   removal rate of pathogen in the common water source
$f_j(S_j, I_j) \geq 0$:   incidence function for direct transmission in patch j
$g_j(S_j, W) \geq 0$:   incidence function for indirect transmission in patch j
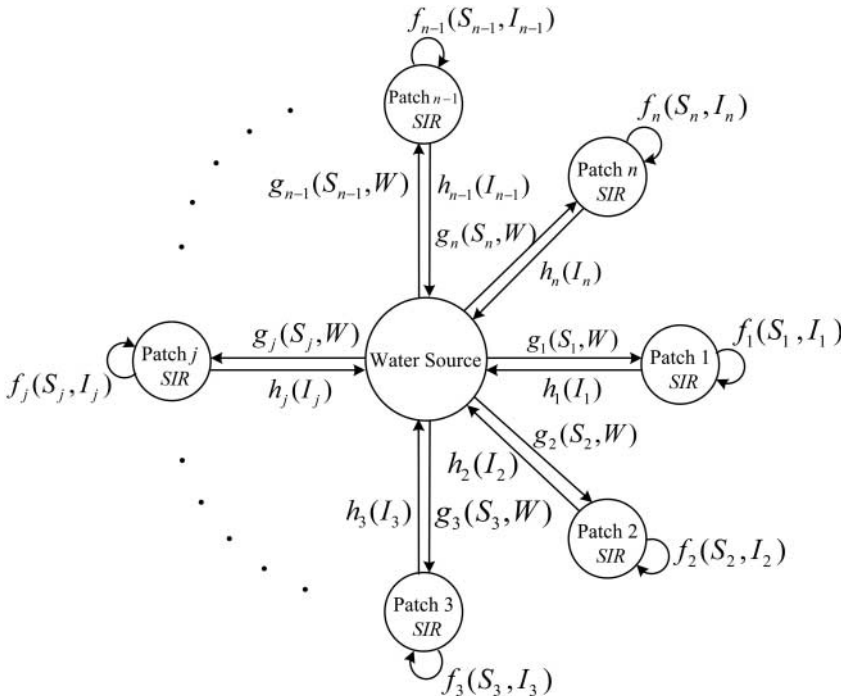$h_j(I_j) \geq 0$:   pathogen shedding function in patch j

Figure 1. Disease transmission diagram for multi-patch cholera model (1)–(2).

Functions $f_j, g_j, h_j, 1 \leq j \leq n$, are assumed to be continuous and sufficiently smooth so that solutions to Equations (1) and (2) with nonnegative initial conditions exist and are unique. The following assumptions are also assumed throughout the paper:

(H_1) $f_j(S_j, I_j) \geq 0$ and $f_j(S_j, 0) = f_j(0, I_j) = 0$ for all $S_j, I_j \geq 0$;
(H_2) $g_j(S_j, W) \geq 0$ for all $S_j, W \geq 0$, and $g_j(S_j, W) = 0$ iff $S_j = 0$ or $W = 0$;
(H_3) $h_j(I_j) \geq 0$ for all $I_j \geq 0$, and $h_j(I_j) = 0$ iff $I_j = 0$.

Assumptions (H_1)–(H_3) ensure that solutions of Equations (1) and (2) starting with nonnegative initial conditions stay nonnegative for all $t > 0$.

The multi-patch cholera model (1)–(2) includes as a special case the model (31) in [24] in which the incidence functions f_j, g_j take the form of mass action, and shedding functions h_j are linear, namely,

$$f_j(S_j, I_j) = \beta_j S_j I_j, \quad g_j(S_j, W) = \lambda_j S_j W, \quad h_j(I_j) = \xi_j I_j, \tag{3}$$

with constants $\beta_j, \lambda_j, \xi_j > 0$. In the literature, other choices for the incidence functions are used, such as the saturating incidence $g_j(S_j, W) = \lambda_j S_j(W/(\kappa + W))$ with constants $\lambda_j, \kappa > 0$ [6,13].

Since the variables R_j do not appear in the equations of (1), it suffices to first study the dynamics of Equation (1), and the dynamics of R_j then follow directly from Equation (2). Let $N_j = S_j + I_j + R_j$ denote the size of the human population in patch $j, j = 1, \ldots, n$. Adding the first two equations of (1) and the one in Equation (2) together yields

$$N_j' = \Lambda_j - d_j N_j - \alpha_j I_j \leq \Lambda_j - d N_j,$$

and thus $\limsup_{t \to \infty} N_j(t) \leq \Lambda_j/d_j$ for all j. In particular, $\limsup_{t \to \infty} S_j(t) + I_j(t) \leq \Lambda_j/d_j$ and $\limsup_{t \to \infty} I_j(t) \leq \Lambda_j/d_j$. Set $\Pi_k = \max_{0 \leq I_k \leq \Lambda_k/d_k}\{h_k(I_k)\}$ and $\Pi = \sum_{k=1}^{n} \Pi_k$. It follows that

$$W' \leq -\delta W + \sum_{k=1}^{n} \Pi_k = -\delta W + \Pi.$$

This implies that $\limsup_{t \to \infty} W(t) \leq \Pi/\delta$. Therefore, the feasible region

$$\Gamma = \left\{ (S_1, I_1, \ldots, S_n, I_n, W) \in \mathbb{R}_+^{2n+1} \,\middle|\, S_j + I_j \leq \frac{\Lambda_j}{d_j}, \, 1 \leq j \leq n, \, W \leq \frac{\Pi}{\delta} \right\}$$

is positively invariant with respect to Equation (1).

3. Equilibria and basic reproduction number

System (1) admits a unique *disease-free equilibrium*, which lies in $\partial\Gamma$, the boundary of Γ, $P_0 = (S_1^0, 0, \ldots, S_n^0, 0, 0)$ with $S_j^0 = \Lambda_j/d_j, 1 \leq j \leq n$. There are no other equilibria on $\partial\Gamma$. A possible *endemic equilibrium* $P^* = (S_1^*, I_1^*, \ldots, S_n^*, I_n^*, W^*) \in \text{int}(\Gamma)$ might exist; the existence and uniqueness of P^* are discussed in Section 4.

Assume for all $j = 1, \ldots, n$,

(H_4)

$$\lim_{x \to 0^+} \frac{f_j(S_j^0, x)}{x} = p_j \geq 0, \quad \lim_{x \to 0^+} \frac{g_j(S_j^0, x)}{x} = q_j > 0, \quad \text{and} \quad \lim_{x \to 0^+} \frac{h_j(x)}{x} = r_j > 0.$$

It can been verified that $p_j = \partial f_j(S_j^0, 0)/\partial I_j$, $q_j = \partial g_j(S_j^0, 0)/\partial W$, and $r_j = h_j'(0)$ when f_j, g_j, h_j are differentiable. For example, when incidence functions take the form of mass action and shedding functions are linear, i.e., f_j, g_j, h_j satisfy Equation (3), it follows that

$$p_j = \beta_j S_j^0, \quad q_j = \lambda_j S_j^0, \quad \text{and} \quad r_j = \xi_j. \tag{4}$$

Following the next-generation matrix method [31], let

$$x = (I_1, \ldots, I_n, W)^{\mathrm{T}} \tag{5}$$

denote the disease compartments, and the two $(n + 1) \times (n + 1)$ matrices

$$F = \begin{bmatrix} p_1 & 0 & \cdots & 0 & q_1 \\ 0 & p_2 & \cdots & 0 & q_2 \\ \vdots & & \ddots & & \vdots \\ 0 & 0 & \cdots & p_n & q_n \\ 0 & 0 & \cdots & 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} v_1 & 0 & \cdots & 0 & 0 \\ 0 & v_2 & \cdots & 0 & 0 \\ \vdots & & \ddots & & \vdots \\ 0 & 0 & \cdots & v_n & 0 \\ -r_1 & -r_2 & \cdots & -r_n & \delta \end{bmatrix}, \tag{6}$$

with $v_j := d_j + \alpha_j + \gamma_j$ for all j, denote the new infection and disease transition matrices, respectively. Note that the pathogen shedding is regarded as a disease transition in the next-generation matrix method. Hence, by Diekmann *et al.* [7], van den Driessche and Watmough [31], the *basic reproduction number* $\mathcal{R}_0$ of Equation (1) is defined as the spectral radius, denoted by ρ, of the nonnegative *next-generation matrix* FV^{-1}. Since the last row of F consists of only zero entries, the spectral radius of FV^{-1} is determined by the $n \times n$ block. Therefore,

$$\mathcal{R}_0 = \rho \left(\begin{bmatrix} \dfrac{p_1}{v_1} + \dfrac{q_1 r_1}{\delta v_1} & \dfrac{q_1 r_2}{\delta v_2} & \cdots & \dfrac{q_1 r_n}{\delta v_n} \\ \dfrac{q_2 r_1}{\delta v_1} & \dfrac{p_2}{v_2} + \dfrac{q_2 r_2}{\delta v_2} & \cdots & \dfrac{q_2 r_n}{\delta v_n} \\ \vdots & \vdots & \ddots & \vdots \\ \dfrac{q_n r_1}{\delta v_1} & \dfrac{q_n r_2}{\delta v_2} & \cdots & \dfrac{p_n}{v_n} + \dfrac{q_n r_n}{\delta v_n} \end{bmatrix} \right). \tag{7}$$

It follows from Theorem 2 in [31] that the disease-free equilibrium P_0 of Equation (1) is locally asymptotically stable if $\mathcal{R}_0 < 1$, whereas it is unstable if $\mathcal{R}_0 > 1$. The global stability of P_0 is established in Section 4.

Note that the matrix in Equation (7) can be written as

$$\mathrm{diag}\left\{ \frac{p_1}{v_1}, \ldots, \frac{p_n}{v_n} \right\} + \left[\frac{q_1}{\delta}, \ldots, \frac{q_n}{\delta} \right]^{\mathrm{T}} \cdot \left[\frac{r_1}{v_1}, \ldots, \frac{r_n}{v_n} \right]$$

and the second term above is a matrix of rank 1. Hence, when each patch is similar (in terms of its population size, etc.) so that $p_j = p$ and $v_j = v$ for all j (i.e. each patch has the same direct transmission rate and the same removal rate of infectious individuals), the basic reproduction number has an explicit expression

$$\mathcal{R}_0 = \frac{p}{v} + \frac{1}{\delta v} \sum_{j=1}^{n} q_j r_j.$$

The first term corresponds to the direct transmission while the second term sums up the indirect transmission through the water in all patches.

4. Global dynamics

In this section the global dynamics of system (1) are established under biologically reasonable assumptions by constructing suitable Lyapunov functions. Specifically, the matrix-theoretic approach using Perron eigenvectors in [27, Section 2] is applied to prove the global stability of the disease-free equilibrium (Theorem 4.1) while the graph-theoretic approach in [11,12,16,27] is used to establish the global stability of the endemic equilibrium (Theorem 4.2).

The following assumptions on incidence and shedding functions f_j, g_j, h_j are needed to establish the global stability of the disease-free equilibrium, indicating that nonlinear system (1) is dominated by its linearization.

(A_1) $f_j(S_j, I_j) \leq p_j I_j$ for all $0 \leq S_j \leq S_j^0, I_j \geq 0, j = 1, \ldots, n$;
(A_2) $g_j(S_j, W) \leq q_j W$ for all $0 \leq S_j \leq S_j^0, W \geq 0, j = 1, \ldots, n$; and
(A_3) $h_j(I_j) \leq r_j I_j$ for all $I_j \geq 0, j = 1, \ldots, n$.

It can be easily verified that assumptions (A_1) and (A_2) hold for both mass action and saturating incidence functions, and assumption (A_3) holds for the linear shedding function.

THEOREM 4.1 *Suppose the assumptions* (H_1)–(H_4) *hold. Then the following statements hold for system* (1).

(i) *If $\mathcal{R}_0 \leq 1$ and* (A_1)–(A_3) *hold, then the disease-free equilibrium P_0 is globally asymptotically stable in Γ.*
(ii) *If $\mathcal{R}_0 > 1$, then P_0 is unstable, system* (1) *is uniformly persistent and admits at least one endemic equilibrium P^* in int(Γ).*

Proof Let x, F, V be defined as in Equations (5) and (6). By assumption (H_4), the $(n + 1) \times (n + 1)$ matrix $V^{-1}F$ is nonnegative and irreducible. Let w denote a positive left Perron eigenvector of $V^{-1}F$, that is, $w^T V^{-1}F = \rho(V^{-1}F)w^T = \mathcal{R}_0 w^T$. Since $S_j \leq S_j^0$ in Γ and assumptions (A_1)–(A_3) hold, $x' \leq (F - V)x$. By Theorem 2.1 in [27], $L = w^T V^{-1} x$ is a global Lyapunov function for (1). Furthermore, L can be used to prove the global stability of P_0, as shown in Theorem 2.2 and the remark following this in [27]. Specifically,

$$L' = w^T V^{-1} x' \leq w^T V^{-1}(F - V)x = (\mathcal{R}_0 - 1)w^T x \leq 0, \quad \text{if } \mathcal{R}_0 \leq 1. \tag{8}$$

It can be verified that the largest invariant subset of Γ where $L' = 0$ is the singleton $\{P_0\}$. Therefore, by LaSalle's invariance principle [15], P_0 is globally asymptotically stable in Γ.

When $\mathcal{R}_0 > 1$ and $x > 0$, $(\mathcal{R}_0 - 1)w^T x > 0$. The continuity, assumption (H_4), and a similar evaluation as Equation (8) imply that $L' > 0$ in a small neighbourhood of P_0 in int(Γ). Thus the instability of P_0 and the uniform persistence of Equation (1) follow similarly as in the proof of Theorem 2.2 in [27]. The existence of P^* follows from the uniform persistence and the positive invariance of the compact set Γ; see, for example, the proof of Theorem 2.2 in [27]. ∎

Now consider $\mathcal{R}_0 > 1$, and let $P^* = (S_1^*, I_1^*, \ldots, S_n^*, I_n^*, W^*)$ denote an endemic equilibrium of Equation (1), where S_j^*, I_j^*, W^* are positive and satisfy the following equilibrium equations:

$$\Lambda_j = f_j(S_j^*, I_j^*) + g_j(S_j^*, W^*) + d_j S_j^*, \quad j = 1, \ldots, n, \tag{9}$$

$$v_j I_j^* = f_j(S_j^*, I_j^*) + g_j(S_j^*, W^*), \quad j = 1, \dots, n, \tag{10}$$

$$\delta W^* = \sum_{k=1}^{n} h_k(I_k^*). \tag{11}$$

Assume that as in [8, Theorem 6.1]

(B_1) there exist a family of functions $\Phi_j : (0, \Lambda_j/d_j] \to \mathbb{R}_+, j = 1, 2, \dots, n$, such that for all $1 \le j \le n, S_j, I_j, W > 0$,

$$(S_j - S_j^*)(\Phi_j(S_j) - \Phi_j(S_j^*)) > 0, \quad S_j \neq S_j^*;$$

$$\left(\frac{f_j(S_j, I_j)\Phi_j(S_j^*)}{f_j(S_j^*, I_j^*)\Phi_j(S_j)} - 1 \right) \left(1 - \frac{f_j(S_j^*, I_j^*)\Phi_j(S_j)I_j}{f_j(S_j, I_j)\Phi_j(S_j^*)I_j^*} \right) \le 0;$$

and

$$\left(\frac{g_j(S_j, W)\Phi_j(S_j^*)}{g_j(S_j^*, W^*)\Phi_j(S_j)} - 1 \right) \left(1 - \frac{g_j(S_j^*, W^*)\Phi_j(S_j)W}{g_j(S_j, W)\Phi_j(S_j^*)W^*} \right) \le 0;$$

(B_2) for all $I_j > 0, 1 \le j \le n$,

$$\left(\frac{h_j(I_j)}{h_j(I_j^*)} - 1 \right) \left(1 - \frac{h_j(I_j^*)I_j}{h_j(I_j)I_j^*} \right) \le 0.$$

If functions $f_j(S_j, I_j), g_j(S_j, W), h_j(I_j)$ are monotone increasing with respect to S_j, I_j, W, and $f_j(S_j, I_j)/I_j, g_j(S_j, W)/W, h_j(I_j)/I_j$ are monotone decreasing in I_j and W, then assumptions (B_1)–(B_2) are satisfied. Both mass action and saturating incidence functions satisfy (B_1) with identity functions Φ_j, while the linear shedding function satisfies (B_2).

THEOREM 4.2 *Suppose the assumptions* (H_1)–(H_4) *and* (B_1)–(B_2) *hold. If* $\mathcal{R}_0 > 1$, *then the endemic equilibrium* P^* *of Equation* (1) *is unique and globally asymptotically stable in* int(Γ).

Proof We prove the global stability of P^* by constructing a suitable Lyapunov function, and thus the uniqueness of P^* holds. Define

$$D_j = \int_{S_j}^{S_j^*} \frac{\Phi_j(\zeta) - \Phi_j(S_j^*)}{\Phi_j(\zeta)} \, d\zeta + I_j - I_j^* - I_j^* \ln \frac{I_j}{I_j^*}, \quad j = 1, \dots, n$$

and

$$D_{n+1} = W - W^* - W^* \ln \frac{W}{W^*}.$$

Differentiating D_j along Equation (1) and using the equilibrium equations (9) and (10) yield

$$
\begin{aligned}
D_j' &= \left(1 - \frac{\Phi_j(S_j^*)}{\Phi_j(S_j)}\right)(f_j(S_j^*, I_j^*) + g_j(S_j^*, W^*) + d_j S_j^* - f_j(S_j, I_j) - g_j(S_j, W) - d_j S_j) \\
&\quad + \left(1 - \frac{I_j^*}{I_j}\right)\left(f_j(S_j, I_j) + g_j(S_j, W) - f_j(S_j^*, I_j^*)\frac{I_j}{I_j^*} - g_j(S_j^*, W^*)\frac{I_j}{I_j^*}\right) \\
&= -\frac{d_j}{\Phi_j(S_j)}(S_j - S_j^*)(\Phi_j(S_j) - \Phi_j(S_j^*)) \\
&\quad + f_j(S_j^*, I_j^*)\left(\frac{f_j(S_j, I_j)\Phi_j(S_j^*)}{f_j(S_j^*, I_j^*)\Phi_j(S_j)} - 1\right)\left(1 - \frac{f_j(S_j^*, I_j^*)\Phi_j(S_j)I_j}{f_j(S_j, I_j)\Phi_j(S_j^*)I_j^*}\right) \\
&\quad + f_j(S_j^*, I_j^*)\left(3 - \frac{\Phi_j(S_j^*)}{\Phi_j(S_j)} - \frac{f_j(S_j, I_j)I_j^*}{f_j(S_j^*, I_j^*)I_j} - \frac{f_j(S_j^*, I_j^*)\Phi_j(S_j)I_j}{f_j(S_j, I_j)\Phi_j(S_j^*)I_j^*}\right) \\
&\quad + g_j(S_j^*, W^*)\left(\frac{g_j(S_j, W)\Phi_j(S_j^*)}{g_j(S_j^*, W^*)\Phi_j(S_j)} - 1\right)\left(1 - \frac{g_j(S_j^*, W^*)\Phi_j(S_j)W}{g_j(S_j, W)\Phi_j(S_j^*)W^*}\right) \\
&\quad + g_j(S_j^*, W^*)\left(3 - \frac{\Phi_j(S_j^*)}{\Phi_j(S_j)} - \frac{g_j(S_j, W)I_j^*}{g_j(S_j^*, W^*)I_j} - \frac{g_j(S_j^*, W^*)\Phi_j(S_j)W}{g_j(S_j, W)\Phi_j(S_j^*)W^*} - \frac{I_j}{I_j^*} + \frac{W}{W^*}\right) \\
&\leq f_j(S_j^*, I_j^*)\left(3 - \frac{\Phi_j(S_j^*)}{\Phi_j(S_j)} - \frac{f_j(S_j, I_j)I_j^*}{f_j(S_j^*, I_j^*)I_j} - \frac{f_j(S_j^*, I_j^*)\Phi_j(S_j)I_j}{f_j(S_j, I_j)\Phi_j(S_j^*)I_j^*}\right) \\
&\quad + g_j(S_j^*, W^*)\left(3 - \frac{\Phi_j(S_j^*)}{\Phi_j(S_j)} - \frac{g_j(S_j, W)I_j^*}{g_j(S_j^*, W^*)I_j} - \frac{g_j(S_j^*, W^*)\Phi_j(S_j)W}{g_j(S_j, W)\Phi_j(S_j^*)W^*} - \frac{I_j}{I_j^*} + \frac{W}{W^*}\right).
\end{aligned}
$$

The last inequality follows from the three inequalities in assumption (B_1). Similarly, differentiating D_{n+1} along (1) yields

$$
\begin{aligned}
D_{n+1}' &= \left(1 - \frac{W^*}{W}\right)\left(-\delta W + \sum_{k=1}^{n} h_k(I_k)\right) = \left(1 - \frac{W^*}{W}\right)\sum_{k=1}^{n}\left(-h_k(I_k^*)\frac{W}{W^*} + h_k(I_k)\right) \\
&= \sum_{k=1}^{n} h_k(I_k^*)\left(\frac{h_k(I_k)}{h_k(I_k^*)} - 1\right)\left(1 - \frac{h_k(I_k^*)I_k}{h_k(I_k)I_k^*}\right) \\
&\quad + \sum_{k=1}^{n} h_k(I_k^*)\left(2 - \frac{h_k(I_k)W^*}{h_k(I_k^*)W} - \frac{h_k(I_k^*)I_k}{h_k(I_k)I_k^*} + \frac{I_k}{I_k^*} - \frac{W}{W^*}\right) \\
&\leq \sum_{k=1}^{n} h_k(I_k^*)\left(2 - \frac{h_k(I_k)W^*}{h_k(I_k^*)W} - \frac{h_k(I_k^*)I_k}{h_k(I_k)I_k^*} + \frac{I_k}{I_k^*} - \frac{W}{W^*}\right),
\end{aligned}
$$

where the second equality follows from the equilibrium equation (11) and the last inequality follows from the assumption (B_2). The coefficients in the inequalities for derivatives of D_j and D_{n+1} define a nonnegative $(n + 1) \times (n + 1)$ matrix $A = [a_{ij}]$, which represents the disease transmission cycles in the network. A network here can be mathematically regarded as a weighed digraph $(\mathcal{G}, A)$, which consists of $n + 1$ vertices labelled $1, 2, \ldots, n + 1$ with $1, \ldots, n$ corresponding to patches and $n + 1$ to the common water source. In $(\mathcal{G}, A)$, an arc (i, j) from vertex j to vertex i exists if and only if $a_{ij} > 0$, and its weight is a_{ij} whenever it exists; see appendix for more information

on weighed digraphs. Specifically, the entries of A satisfy $a_{jj} = f_j(S_j^*, I_j^*)$, $a_{j,n+1} = g_j(S_j^*, W^*)$, $a_{n+1,j} = h_j(I_j^*)$, for $1 \le j \le n$, and zero otherwise. The weighed digraph $(\mathcal{G}, A)$ is depicted in Figure 2(a), and can be regarded as the disease transmission diagram (Figure 1) evaluated at the endemic equilibrium P^*. Following the graph-theoretic approach in [27] (also see [11,12,16]), a Lyapunov function $\tilde{D}$ for Equation (1) can be constructed using a linear combination of D_j and D_{n+1}; that is, $\tilde{D} = \sum_{j=1}^{n} c_j D_j + c_{n+1} D_{n+1}$. The coefficients c_j in the linear combination are given by the sum of weights of all spanning trees in $(\mathcal{G}, A)$ rooted at vertex j. Direct calculations show that

$$c_j = \frac{h_j(I_j^*)}{g_j(S_j^*, W^*)} \prod_{k=1}^{n} g_k(S_k^*, W^*), \quad 1 \le j \le n,$$
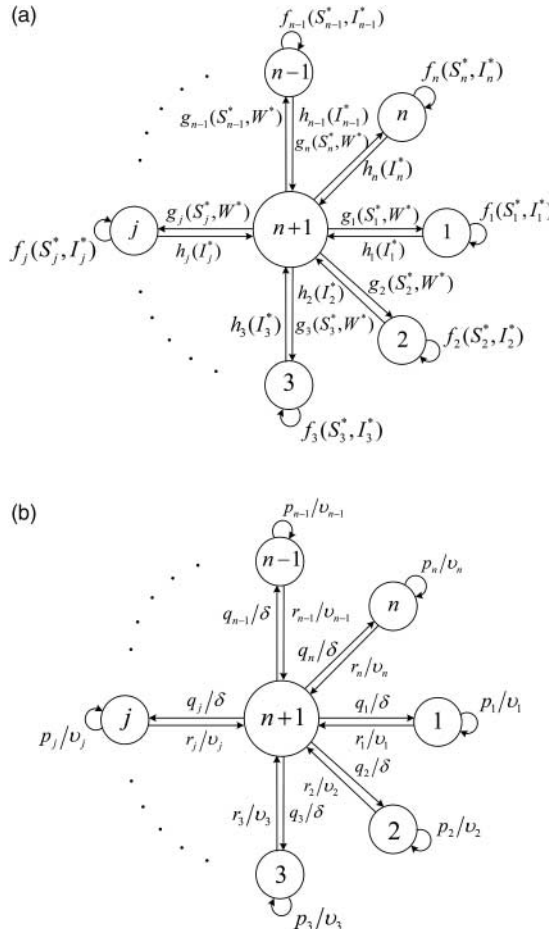
and

$$c_{n+1} = \prod_{k=1}^{n} g_k(S_k^*, W^*).$$

Figure 2. Weighted digraphs (a) $(\mathcal{G}, A)$, (b) $(\mathcal{G}, K)$ have the same vertex and arc sets, but different weights for each arc.

Note that all coefficients $c_j, 1 \le j \le n + 1$, in $\tilde{D}$ have the common factor $\prod_{k=1}^{n} g_k(S_k^*, W^*)$, thus we could construct another Lyapunov function D from $\tilde{D}$ by dividing by the common factor; that is

$$D = \sum_{j=1}^{n} \frac{h_j(I_j^*)}{g_j(S_j^* W^*)} D_j + D_{n+1}.$$

is a Lyapunov function for Equation (1). In fact,

$$
\begin{aligned}
D' &\le \sum_{j=1}^{n} \frac{h_j(I_j^*)}{g_j(S_j^*, W^*)} \Bigg[f_j(S_j^*, I_j^*) \left(3 - \frac{\Phi_j(S_j^*)}{\Phi_j(S_j)} - \frac{f_j(S_j, I_j)I_j^*}{f_j(S_j^*, I_j^*)I_j} - \frac{f_j(S_j^*, I_j^*)\Phi(S_j)I_j}{f_j(S_j, I_j)\Phi(S_j^*)I_j^*} \right) \\
&\quad + g_j(S_j^*, W^*) \left(3 - \frac{\Phi_j(S_j^*)}{\Phi_j(S_j)} - \frac{g_j(S_j, W)I_j^*}{g_j(S_j^*, W^*)I_j} - \frac{g_j(S_j^*, W^*)\Phi_j(S_j)W}{g_j(S_j, W)\Phi_j(S_j^*)W^*} - \frac{I_j}{I_j^*} + \frac{W}{W^*} \right) \Bigg] \\
&\quad + \sum_{k=1}^{n} h_k(I_k^*) \left(2 - \frac{h_k(I_k)W^*}{h_k(I_k^*)W} - \frac{h_k(I_k^*)I_k}{h_k(I_k)I_k^*} + \frac{I_k}{I_k^*} - \frac{W}{W^*} \right) \\
&= \sum_{j=1}^{n} \frac{f_j(S_j^*, I_j^*)h_j(I_j^*)}{g_j(S_j^*, W^*)} \left(3 - \frac{\Phi_j(S_j^*)}{\Phi_j(S_j)} - \frac{f_j(S_j, I_j)I_j^*}{f_j(S_j^*, I_j^*)I_j} - \frac{f_j(S_j^*, I_j^*)\Phi_j(S_j)I_j}{f_j(S_j, I_j)\Phi_j(S_j^*)I_j^*} \right) \\
&\quad + \sum_{j=1}^{n} h_j(I_j^*) \left(5 - \frac{\Phi_j(S_j^*)}{\Phi_j(S_j)} - \frac{g_j(S_j, W)I_j^*}{g_j(S_j^*, W^*)I_j} - \frac{g_j(S_j^*, W^*)\Phi_j(S_j)W}{g_j(S_j, W)\Phi_j(S_j^*)W^*} - \frac{h_j(I_j)W^*}{h_j(I_j^*)W} - \frac{h_j(I_j^*)I_j}{h_j(I_j)I_j^*} \right) \\
&\le 0,
\end{aligned}
$$

where the last inequality follows from the arithmetic geometric mean inequalities

$$
\begin{aligned}
&\frac{\Phi_j(S_j^*)}{\Phi_j(S_j)} + \frac{f_j(S_j, I_j)I_j^*}{f_j(S_j^*, I_j^*)I_j} + \frac{f_j(S_j^*, I_j^*)\Phi_j(S_j)I_j}{f_j(S_j, I_j)\Phi_j(S_j^*)I_j^*} \\
&\ge 3 \sqrt[3]{\frac{\Phi_j(S_j^*)}{\Phi_j(S_j)} \cdot \frac{f_j(S_j, I_j)I_j^*}{f_j(S_j^*, I_j^*)I_j} \cdot \frac{f_j(S_j^*, I_j^*)\Phi_j(S_j)I_j}{f_j(S_j, I_j)\Phi_j(S_j^*)I_j^*}} = 3
\end{aligned}
$$

and

$$
\begin{aligned}
&\frac{\Phi_j(S_j^*)}{\Phi_j(S_j)} + \frac{g_j(S_j, W)I_j^*}{g_j(S_j^*, W^*)I_j} + \frac{g_j(S_j^*, W^*)\Phi_j(S_j)W}{g_j(S_j, W)\Phi_j(S_j^*)W^*} + \frac{h_j(I_j)W^*}{h_j(I_j^*)W} + \frac{h_j(I_j^*)I_j}{h_j(I_j)I_j^*} \\
&\ge 5 \sqrt[5]{\frac{\Phi_j(S_j^*)}{\Phi_j(S_j)} \cdot \frac{g_j(S_j, W)I_j^*}{g_j(S_j^*, W^*)I_j} \cdot \frac{g_j(S_j^*, W^*)\Phi_j(S_j)W}{g_j(S_j, W)\Phi_j(S_j^*)W^*} \cdot \frac{h_j(I_j)W^*}{h_j(I_j^*)W} \cdot \frac{h_j(I_j^*)I_j}{h_j(I_j)I_j^*}} = 5.
\end{aligned}
$$

It can be verified that the largest invariant set where $D' = 0$ is the singleton $\{P^*\}$. Therefore, by LaSalle's invariance principle [15], P^* is globally asymptotically stable and thus unique in int(Γ). ∎

When mass action incidence functions f_j, g_j and linear shedding functions h_j are chosen as given in Equation (3), system (1) includes the model (31) in [24] as a special case, and thus Theorems 4.1 and 4.2 establish, for the first time, the complete global disease dynamics of the model in [24]. Namely, if the basic reproduction number $\mathcal{R}_0$ in Equation (7) with p_j, q_j, r_j as given in Equation (4) is not above one, then the disease-free equilibrium is globally asymptotically stable and cholera dies out from all patches, whereas if $\mathcal{R}_0$ is above one, then there is a unique endemic equilibrium that is globally asymptotically stable and cholera persists at an endemic level in all patches.

5.   Cholera control strategies: calculating target reproduction numbers

The basic reproduction number $\mathcal{R}_0$ has been shown to determine whether cholera can invade a star network in which individuals share a common water source. In order to eradicate cholera from the network, various control and intervention strategies, such as oral cholera vaccine [2], and water, sanitation, and hygiene interventions [9], might be used to reduce the disease transmission and pathogen shedding in the network and thus decrease the *control reproduction number* below one. The implicit formula (7) for the basic reproduction number makes it difficult for public health authorities to quantify these disease control strategies. It turns out that the type reproduction numbers defined in [14,23] can be used to measure the effort required to eradicate an infectious disease from a heterogeneous host population when control is targeted at a particular or several host types. The target reproduction numbers [25] extend such numbers to disease control targeting contacts between types. These target/type reproduction numbers often have explicit formulas and can also serve as a sharp threshold determining whether or not the disease dies out. In this section we calculate these reproduction numbers for various cholera control strategies on the star network.

In order to keep and apply the star network structure of system (1), let

$$
\tilde{F} = \begin{bmatrix}
p_1 & 0 & \cdots & 0 & q_1 \\
0 & p_2 & \cdots & 0 & q_2 \\
\vdots & & \ddots & & \vdots \\
0 & 0 & \cdots & p_n & q_n \\
r_1 & r_2 & \cdots & r_n & 0
\end{bmatrix}
\quad \text{and} \quad
\tilde{V} = \begin{bmatrix}
\nu_1 & 0 & \cdots & 0 & 0 \\
0 & \nu_2 & \cdots & 0 & 0 \\
\vdots & & \ddots & & \vdots \\
0 & 0 & \cdots & \nu_n & 0 \\
0 & 0 & \cdots & 0 & \delta
\end{bmatrix}.
$$

Since $F - V = \tilde{F} - \tilde{V}$, it can be verified that $\mathcal{R}_0 = \rho(FV^{-1})$ as given in Equation (7) and $\tilde{\mathcal{R}}_0 = \rho(\tilde{F}\tilde{V}^{-1})$ agree at the threshold value 1. Let

$$
K = \tilde{F}\tilde{V}^{-1} = \begin{bmatrix}
\dfrac{p_1}{\nu_1} & 0 & \cdots & 0 & \dfrac{q_1}{\delta} \\
0 & \dfrac{p_2}{\nu_2} & \cdots & 0 & \dfrac{q_2}{\delta} \\
\vdots & & \ddots & & \vdots \\
0 & 0 & \cdots & \dfrac{p_n}{\nu_n} & \dfrac{q_n}{\delta} \\
\dfrac{r_1}{\nu_1} & \dfrac{r_2}{\nu_2} & \cdots & \dfrac{r_n}{\nu_n} & 0
\end{bmatrix}.
$$

Note that the weighted digraph associated with K is a star graph of $n + 1$ vertices (e.g. see Figure 1 in [24]). The hub vertex is labelled as $n + 1$, corresponding to the common water source, while each leaf vertex is labelled as j, with $1 \leq j \leq n$, corresponding to patch j. Let $(\mathcal{G}, K)$ be the weighed digraph associated with K; see Figure 2(b). Note that the two weighted digraphs $(\mathcal{G}, K)$ and $(\mathcal{G}, A)$ defined in the proof of Theorem 4.2 have the same vertex and arc sets, but different weights for each arc.

Vaccination: Assume that vaccine is employed in patch j, then the type reproduction number $\mathcal{T}_j = e_j^{\mathrm{T}} P_j K (I - K + P_j K)^{-1} e_j$, with e_j being the jth unit vector in $\mathbb{R}^{n+1}$ and P_j the $(n + 1) \times (n + 1)$ projection matrix (i.e. the (j, j) entry of P_j is 1 and all other entries are zero), can be used to estimate vaccine coverage provided $\rho(K - P_j K) < 1$. That is, if a proportion more than $1 - 1/\mathcal{T}_j$ of the host population in patch j acquires immunity from the vaccine, then cholera can be eradicated from all patches. If $\rho(K - P_j K) > 1$, then $\mathcal{T}_j$ is not defined as the disease cannot be eradicated by targeting only hosts in patch j. A new combinatorial formula for $\mathcal{T}_j$ in

[19, Theorem 5.3] involves cycles of $(\mathcal{G}, K)$, and can be applied to the star network structure of $(\mathcal{G}, K)$, giving

$$\mathcal{T}_j = \frac{p_j}{v_j} + \frac{q_j r_j}{\delta v_j} \cdot \frac{1}{1 - l_j},$$

where

$$l_j = \sum_{\substack{k=1 \\ k \neq j}}^{n} \frac{q_k r_k}{\delta v_k} \cdot \frac{1}{1 - p_k/v_k}. \tag{12}$$

Here p_j/v_j is the weight of the loop (i.e. the arc (j,j)) at leaf vertex j, $q_j r_j/\delta v_j$ is the weight of the cycle consisting of the hub vertex and leaf vertex j, and l_j corresponds to the cycles that do not contain the leaf vertex j.

Water treatment: Assume that water treatment is applied to the common water source, then the type reproduction number $\mathcal{T}_{n+1} = e_{n+1}^{\mathrm{T}} P_{n+1} K (I - K + P_{n+1} K)^{-1} e_{n+1}$ has the following explicit expression (applying the new formula in [19, Theorem 5.3])

$$\mathcal{T}_{n+1} = \sum_{k=1}^{n} \frac{q_k r_k}{\delta v_k} \cdot \frac{1}{1 - p_k/v_k}.$$

Isolation: Assume that isolation has been used to reduce the direct person-to-person contact in patch j and thus reduce the entry (j,j) of K. Then the target reproduction number $\mathcal{T}_{jj} = \rho(P_j K P_j (I - K + P_j K P_j)^{-1})$ can be calculated explicitly as (using a new combinatorial formula in [19, Theorem 4.1])

$$\mathcal{T}_{jj} = \frac{p_j}{v_j} \cdot \frac{1}{1 - (q_j r_j/\delta v_j) \cdot (1/(1 - l_j))}$$

with l_j given in Equation (12).

Sanitation: Assume that hygienic disposal of human faeces is applied in patch j, targeting the $(n+1, j)$ entry of K. Then the corresponding target reproduction number $\mathcal{T}_{n+1,j} = \rho(P_{n+1} K P_j (I - K + P_{n+1} K P_j)^{-1})$ has the explicit expression

$$\mathcal{T}_{n+1,j} = \frac{q_j r_j}{\delta v_j} \cdot \frac{1}{1 - p_j/v_j} \cdot \frac{1}{1 - l_j},$$

with l_j given in Equation (12).

Provision of clean water: Provision of clean water in patch j can reduce the indirect transmission, targeting the $(j, n+1)$ entry of K. It turns out, by Theorem 4.1 in [25], that

$$\mathcal{T}_{j,n+1} = \mathcal{T}_{n+1,j} = \frac{q_j r_j}{\delta v_j} \cdot \frac{1}{1 - p_j/v_j} \cdot \frac{1}{1 - l_j},$$

since the star network $(\mathcal{G}, K)$ contains cycles of length 1 (loops) and length 2 only, and thus is weight-balanced.

Since target reproduction numbers $\mathcal{T}$ calculated above stay the same side of one as the basic reproduction number $\mathcal{R}_0$ (see, for example, [25, Theorem 2.1]), each of them also serves as a sharp threshold determining whether or not the disease dies out. Hence, Corollary 5.1 follows immediately from Theorems 4.1 and 4.2.

COROLLARY 5.1 *Suppose the assumptions* (H_1)–(H_4) *hold. Let* $\mathcal{T}$ *be any target reproduction number calculated above.*

(i) *If* $\mathcal{T} \leq 1$ *and* (A_1)–(A_3) *hold, then the disease-free equilibrium* P_0 *is globally asymptotically stable in* Γ.

(ii) *If* $\mathcal{T} > 1$ *and* (B_1)–(B_2) *hold, then the endemic equilibrium* P^* *is globally asymptotically stable in* $\text{int}(\Gamma)$.

6. Discussion

In this paper a new multi-patch model is formulated to model the transmission and spread of cholera in a heterogeneous host population that shares a common water source. The heterogeneous host population is categorized as patches of homogeneous host populations. The proposed model incorporates nonlinear incidence for both direct and indirect transmission, and thus can be adapted to model other waterborne diseases such as typhoid fever. The basic reproduction number $\mathcal{R}_0$ is derived and shown to determine whether or not cholera can invade such a network. Various target/type reproduction numbers are explicitly calculated to measure cholera control and intervention strategies. Integrated with suitable surveillance data for cholera and other waterborne diseases, these studies might assist public health authorities to make better evaluations of cholera prevention and control policies.

Studies in this paper highlight the importance of understanding infectious disease transmission networks, e.g. the star network for cholera transmission diagram in Figure 1 and the companion networks of the same type in Figure 2. These network structures often can be used to analyse disease dynamics (e.g. the construction of Lyapunov functions using Figure 2(a) in Section 4), but also evaluate disease control strategies (e.g. derivations of target reproduction numbers using Figure 2(b) in Section 5). Further investigation is required to determine in general how a disease transmission diagram relates to its companion networks used in disease dynamic analysis and control strategy evaluation.

Acknowledgements

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Appendix. Notation and terminology from graph theory

Let $\mathcal{G} = (\mathcal{G}, A)$ be a *weighted digraph* with n vertices labelled $1, 2, \ldots, n$ with $A = [a_{ij}] \geq 0$ the $n \times n$ *weight matrix* is constructed in the following way: an arc (j, i) with weight a_{ij} from initial vertex j to terminal vertex i exists if and only if $a_{ij} > 0$. A digraph is *strongly connected* if, for any ordered pair of distinct vertices i, j, there exists a directed path from i to j (and also from j to i). A weighted digraph $(\mathcal{G}, A)$ is strongly connected if and only if the weight matrix A is irreducible [3]. A subdigraph $\mathcal{H}$ of $\mathcal{G}$ is *spanning* if $\mathcal{H}$ and $\mathcal{G}$ have the same vertex set. The *weight* of a subdigraph $\mathcal{H}$ is the product of the weights on all its arcs. A connected subdigraph $\mathcal{T}$ of $\mathcal{G}$ is a *tree* if it contains no cycles, directed or undirected. A tree $\mathcal{T}$ is *rooted* at vertex j, called the root, if j is not a terminal vertex of any arc, and each of the remaining vertices is a terminal vertex of exactly one arc. We refer the reader to [32] for additional notation in graph theory.