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A cholera model in a patchy environment with water and human movement

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ABSTRACT

A mathematical model for cholera is formulated that incorporates direct and indirect transmission, patch structure, and both water and human movement. The basic reproduction number $\mathcal{R}_0$ is defined and shown to give a sharp threshold that determines whether or not the disease dies out. Kirchhoff's Matrix Tree Theorem from graph theory is used to investigate the dependence of $\mathcal{R}_0$ on the connectivity and movement of water, and to prove the global stability of the endemic equilibrium when $\mathcal{R}_0 > 1$. The type/target reproduction numbers are derived to measure the control strategies that are required to eradicate cholera from all patches.

1. Introduction

Cholera is an infectious disease that causes diarrhea and dehydration, which can lead rapidly to death, especially in populations that are impoverished or have limited access to health care. The disease is caused by *Vibrio cholerae*, an aquatic bacterium that can persist for extended periods of time outside of human hosts. The movement of both humans [12] and water [25] have recently been suggested to influence the spatial spread of cholera in Haiti.

There are several cholera models that have been proposed in the literature to understand the spatial cholera outbreak in Haiti in 2010–2011 after a devastating earthquake. Bertuzzo et al. [7] proposed a patch model that incorporate both water movement (explicitly) and human movement (implicitly), incorporating only saturating indirect transmission. Human movement is combined together with the water movement, only affecting the rate of change of the pathogen levels in the water. In [26], Rinaldo et al. modified the model in [7] to separate the human and water movement by incorporating the effect of human movement into the incidence and shedding functions. Chao et al. [10] used a stochastic model and data from Haiti to investigate the effect of vaccination strategies on the spatial cholera outbreak. They incorporated both direct and indirect transmission, and both human and water movement in their model. Tuite et al. [33] proposed a multi-group model to explain the spatial spread of cholera in Haiti and identify optimal control interventions. Both direct (rapid) and indirect (environmental/delayed) mass action transmission are included in the model. Human movement is only incorporated in the model in terms of between-group direct transmission, ignoring the water movement and between-group indirect transmission. Analyses of the models cited above rely heavily on numerical simulations.

In this paper we propose a new cholera model for several patches that includes both direct and indirect transmission with nonlinear incidence functions, temporary immunity and explicitly incorporates both water and human movement between patches. Our model includes the cholera model in [7] (also see the model (2.5)–(2.7) in [6]) as a special case, and thus our analytical results can be applied to their models, providing new global model analysis. We derive the basic reproduction number and prove global stability results for our model. The type/target reproduction numbers are also defined and can be used to measure the control strategies that are required to eradicate cholera from all patches.

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2. Model

Consider the spatial spread of cholera in an environment of n patches, where cholera can spread from one patch to the other due to human and/or water movement. Let S_i, I_i, R_i denote the number of humans in patch i ($1 \leqslant i \leqslant n$) who are susceptible to, infectious with, and recovered from cholera, respectively. In addition to the standard susceptible, infectious, and recovered compartments, each patch also contains an environmental water source that can be contaminated with cholera bacteria, with W_i corresponding to the concentration (e.g. cells/ml) of cholera bacteria in the water source in patch i. A cholera model of type SIRSW in the patchy environment then takes the following form:

$$\begin{aligned}
S_i' &= A_i - f_i(S_i,I_i) - g_i(S_i,W_i) - d_iS_i + \sigma_iR_i + \sum_{j=1}^{n}(m_{ij}^S S_j - m_{ji}^S S_i),\\
I_i' &= f_i(S_i,I_i) + g_i(S_i,W_i) - (d_i+\alpha_i+\gamma_i)I_i + \sum_{j=1}^{n}(m_{ij}^I I_j - m_{ji}^I I_i),\\
R_i' &= \gamma_iI_i - (d_i+\sigma_i)R_i + \sum_{j=1}^{n}(m_{ij}^R R_j - m_{ji}^R R_i),\\
W_i' &= h_i(I_i) - \delta_iW_i + \sum_{j=1}^{n}(m_{ij}^W W_j - m_{ji}^W W_i), \quad i=1,2,\ldots,n.
\end{aligned} \tag{2.1}$$

The parameters in the model are summarized in the following list:

$A_i > 0$:	constant recruitment into patch i
$d_i > 0$:	natural death rate in patch i
$\alpha_i \geqslant 0$:	mortality rate due to the disease in patch i
$\gamma_i > 0$:	recovery rate of infectious individuals in patch i
$\sigma_i \geqslant 0$:	rate of losing immunity of recovered individuals in patch i
$\delta_i > 0$:	removal rate of pathogen in patch i
$m_{ij}^{\#} \geqslant 0$:	travel rate of susceptible/infectious/recovered individuals or pathogen from patch j to patch i; # represents S, I, R or W
$f_i(S_i,I_i) \geqslant 0$:	incidence function for direct transmission in patch i
$g_i(S_i,W_i) \geqslant 0$:	incidence function for indirect transmission in patch i
$h_i(I_i) \geqslant 0$:	pathogen shedding function in patch i

Basic assumptions on the incidence and shedding functions for all $1 \leqslant i \leqslant n$ are:

(H_1) $f_i(S_i,I_i) \geqslant 0$ and $f_i(S_i,0) = f_i(0,I_i) = 0$ for all $S_i, I_i \geqslant 0$;
(H_2) $g_i(S_i,W_i) \geqslant 0$ for all $S_i, W_i \geqslant 0$, and $g_i(S_i,W_i) = 0$ iff $S_i = 0$ or $W_i = 0$;
(H_3) $h_i(I_i) \geqslant 0$ for all $I_i \geqslant 0$, and $h_i(I_i) = 0$ iff $I_i = 0$.

Assumptions (H_1)–(H_3) ensure that solutions of (2.1) starting with nonnegative initial conditions stay nonnegative for all $t > 0$. Assumption (H_1) allows the possibility of $f_i \equiv 0$ for some patch i or all patches, but from (H_2) and (H_3) every patch has indirect transmission and shedding. Hence the multi-patch cholera model (2.1) includes as a special case and extends Eqs. (2.5)–(2.7) in [6] (also see Eq. (5) in [5] or Eq. (1) in [7]).

In the literature, incidence functions for direct transmission take different forms, such as separable incidence $f_i(S_i,I_i) = \phi_i(S_i)\psi_i(I_i)$ including mass action incidence $f_i(S_i,I_i) = \beta_iS_iI_i$ and saturating incidence $f_i(S_i,I_i) = \beta_iS_i\frac{I_i}{\kappa_i+I_i}$ with constant $\kappa_i > 0$, or frequency-dependent incidence $f_i(S_i,I_i) = \frac{\beta_iS_iI_i}{S_i+I_i}$ and $f_i(S_i,I_i) = \frac{\beta_iS_iI_i}{S_i+I_i+R_i}$. For indirect transmission, incidence functions can be mass action incidence [13,32] $g_i(S_i,W_i) = \lambda_iS_iW_i$, or saturating incidence [11,17] $g_i(S_i,W_i) = \lambda_iS_i\frac{W_i}{\nu_i+W_i}$ with constant $\nu_i > 0$. The pathogen shedding function h_i is usually assumed to be linear, that is, $h_i(I_i) = \xi_iI_i$. These forms all satisfy (H_1)–(H_3).

3. Equilibria

Let $M_S = [m_{ij}^S]$, $M_I = [m_{ij}^I]$, $M_R = [m_{ij}^R]$ and $M_W = [m_{ij}^W]$ denote the nonnegative movement matrices for susceptible, infectious, recovered individuals and pathogen, respectively, with $m_{ii}^{\#} = 0$, where # represents S, I, R or W. The matrices M_S, M_I, and M_R correspond to human travel between patches, while M_W corresponds to the movement of water containing cholera bacteria between patches. There are thus two different mechanisms for disease spread between patches, through the movement either of infectious individuals, or by movement of contaminated water.

Define $n \times n$ matrices

$$G_{\#} = \operatorname{diag}\left(\mu_i^{\#} + \sum_{j=1}^{n} m_{ji}^{\#}\right) - M_{\#},$$

where $\mu_i^S = d_i$, $\mu_i^I = d_i + \alpha_i + \gamma_i$, $\mu_i^R = d_i + \sigma_i$, and $\mu_i^W = \delta_i$, $i = 1,2,\ldots,n$. For example,

$$G_W = \begin{bmatrix}
\delta_1 + \sum_{j=1}^{n} m_{j1}^W & -m_{12}^W & \cdots & -m_{1n}^W \\
-m_{21}^W & \delta_2 + \sum_{j=1}^{n} m_{j2}^W & \cdots & -m_{2n}^W \\
\vdots & \vdots & \ddots & \vdots \\
-m_{n1}^W & -m_{n2}^W & \cdots & \delta_n + \sum_{j=1}^{n} m_{jn}^W
\end{bmatrix}. \tag{3.1}$$

Since all off-diagonal entries of the matrices above are nonpositive (i.e., the Z-sign pattern) and the sum of the entries in each column is positive, these matrices are non-singular M-matrices and $G_{\#}^{-1} \geqslant 0$ [[4, p. 137]], where # represents S, I, R or W.

To find the *disease-free equilibrium* (DFE) with all $I_i = 0$ of (2.1), consider the following linear systems

$$A_i - d_iS_i + \sigma_iR_i + \sum_{j=1}^{n}(m_{ij}^S S_j - m_{ji}^S S_i) = 0, \quad i = 1,2,\ldots,n, \tag{3.2}$$

$$-(d_i+\sigma_i)R_i + \sum_{j=1}^{n}(m_{ij}^R R_j - m_{ji}^R R_i) = 0, \quad i = 1,2\ldots,n, \tag{3.3}$$

$$-\delta_iW_i + \sum_{j=1}^{n}(m_{ij}^W W_j - m_{ji}^W W_i) = 0, \quad i = 1,2,\ldots,n, \tag{3.4}$$

or in the form of matrix systems $G_SS - \operatorname{diag}\{\sigma_1,\sigma_2,\ldots,\sigma_n\}R = A$, $G_RR = 0$, and $G_WW = 0$, where $S = (S_1,S_2,\ldots,S_n)^T$, $R = (R_1,R_2,\ldots,R_n)^T$, $W = (W_1,W_2,\ldots,W_n)^T$ and $A = (A_1,A_2,\ldots,A_n)^T$. Therefore, the linear system (3.2) has a unique positive solution $S^0 = (S_1^0,S_2^0,\ldots,S_n^0)^T = G_S^{-1}A$ with $S_i^0 > 0$ for all i; while linear systems (3.3) and (3.4) have only zero solutions. These statements give the following result.

Theorem 3.1. *There exists a unique disease-free equilibrium* $P_0 = (S_1^0,0,0,0,\ldots,S_n^0,0,0,0) \in \mathbb{R}_+^{4n}$ *for system* (2.1).

The stability of the DFE determines whether or not the disease dies out from the community. We study the local and global stability of the DFE in Sections 4 and 5, respectively.

Let $N = \sum_{i=1}^n N_i$, $N_i = S_i + I_i + R_i$, $i = 1,2,\dots,n$, $\overline{A} = \sum_{i=1}^n A_i$ and $d_* = \min\{d_i, i = 1,2,\dots,n\}$. Adding all equations for human individuals in (2.1) yields $N' \leqslant \overline{A} - d_* N$, which implies that $\limsup_{t\to\infty} N(t) \leqslant \frac{\overline{A}}{d_*}$. Let $\bar{h}_i = \max\{h_i(x),\ x \in [0, \frac{\overline{A}}{d_*}]\}$, $\bar{h} = \sum_{i=1}^n \bar{h}_i$ and $\delta_* = \min\{\delta_i, i = 1,2,\dots,n\}$. Adding all pathogen equations in (2.1) together leads to $(W_1 + \cdots + W_n)' \leqslant \bar{h} - \delta_*(W_1 + \cdots + W_n)$, giving $\limsup_{t\to\infty}(W_1(t) + \cdots + W_n(t)) \leqslant \frac{\bar{h}}{\delta_*}$. Therefore, the feasible region

$$\Gamma = \Big\{(S_1, I_1, R_1, W_1, \dots, S_n, I_n, R_n, W_n) \in \mathbb{R}_+^{4n} \,\Big|\, N = \sum_{i=1}^n (S_i + I_i + R_i) \leqslant \frac{\overline{A}}{d_*}, \sum_{i=1}^n W_i \leqslant \frac{\bar{h}}{\delta_*},\ i = 1,2,\dots,n\Big\}$$

is positively invariant with respect to system (2.1).

To consider patches that are strongly connected with respect to the disease, the movement matrix for infectious humans or for the pathogen is assumed to be irreducible. Under the assumptions stated in the following result, the disease-free equilibrium P_0 is the only equilibrium of (2.1) that lies on the boundary of Γ. When the movement matrix is reducible, the model system may be decoupled into several small systems and may have multiple boundary equilibria; see, for example, [9,35].

Theorem 3.2. *Suppose that assumptions (H_1)–(H_3) hold. If either M_I or M_W is irreducible, then there exists only one equilibrium whose coordinates include a zero, that is, the disease-free equilibrium P_0.*

Proof. First it is impossible to have $S_i = 0$ at any equilibrium, since at $S_i = 0$ the first equation of (2.1) becomes $A_i + \sigma_i R_i + \sum_{j=1}^n m_{ij}^S S_j > 0$. If $R_i = 0$ or $W_i = 0$ for some i, then it follows from the third or fourth equation of (2.1) and assumption (H_3) that $I_i = 0$. Therefore, it is enough to show that $I_i = 0$ for some i implies that $I_j = 0$ for all j. If $I_i = 0$, then it follows from the second equation of (2.1) that $g_i(S_i, W_i) = 0$ and $\sum_{j=1}^n m_{ij}^I I_j = 0$. Since $g_i(S_i, W_i) = 0$, by assumption (H_2) it follows that $W_i = 0$, and thus $\sum_{j=1}^n m_{ij}^W W_j = 0$ due to the last equation of (2.1). Therefore, for any $1 \leqslant i,\ j \leqslant n$,

$$W_i = 0 \quad \text{and} \quad m_{ij}^W > 0 \quad \Rightarrow \quad W_j = 0. \tag{3.5}$$

If M_W is irreducible, then there exists a sequence of ordered pairs $\{(i, r_1), (r_1, r_2), \dots, (r_m, j)\}$ such that $m_{ir_1}^W > 0, m_{r_1 r_2}^W > 0, \dots, m_{r_m j}^W > 0$, $1 \leqslant r_k \leqslant n$, $k = 1,2,\dots,m$ and $m \geqslant 0$ [[4, p. 30]]. Applying (3.5) to each pair in such a sequence and using $W_i = 0$, it follows that

$$W_{r_1} = 0, \quad W_{r_2} = 0, \quad \cdots, \quad W_{r_m} = 0, \quad W_j = 0.$$

Hence $W_j = I_j = 0$ for all j provided that M_W is irreducible. Similarly, if M_I is irreducible, it can be shown that $I_j = 0$ for all j. Therefore, by Theorem 3.1, the disease-free equilibrium P_0 is the only equilibrium whose coordinates include a zero. □

An endemic equilibrium $P^* = \{S_1^*, I_1^*, R_1^*, W_1^*, \dots, S_n^*, I_n^*, R_n^*, W_n^*\}$ of (2.1) with $S_i^*, I_i^*, R_i^*, W_i^* > 0$ for all i, if it exists, belongs to the interior of Γ, denoted by $\mathrm{int}(\Gamma)$. The existence and stability of P^* is studied in Section 6.

4. Basic reproduction number and water movement

4.1. Basic reproduction number $\mathcal{R}_0$

Assume $\lim_{x\to 0^+} \frac{f_i(S_i^0, x)}{x} = p_i$, $\lim_{x\to 0^+} \frac{g_i(S_i^0, x)}{x} = q_i$ and $\lim_{x\to 0^+} \frac{h_i(x)}{x} = r_i$ for all $i = 1,2,\dots,n$. In particular, $p_i = \frac{\partial f_i(S_i^0, 0)}{\partial I_i}$, $q_i = \frac{\partial g_i(S_i^0, 0)}{\partial W_i}$ and $r_i = h_i'(0)$ if f_i, g_i, h_i are differentiable.

Let $D_p = \mathrm{diag}\{p_1, p_2, \dots, p_n\}$, $D_q = \mathrm{diag}\{q_1, q_2, \dots, q_n\}$ and $D_r = \mathrm{diag}\{r_1, r_2, \dots, r_n\}$ be diagonal matrices. Define two $2n \times 2n$ matrices

$$F = \begin{bmatrix} D_p & D_q \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} G_I & 0 \\ -D_r & G_W \end{bmatrix}$$

so that the Jacobian matrix J of the infectious compartments of system (2.1) linearized at the DFE can be written as $J = F - V$, where F represents new infections and V represents transition terms. From assumption (H_1) and the definition of $G_\#$, it follows that $F \geqslant 0$ and V has the Z-sign pattern. Since $V^{-1} = \begin{bmatrix} G_I^{-1} & 0 \\ G_W^{-1} D_r G_I^{-1} & G_W^{-1} \end{bmatrix} \geqslant 0$, V is a nonsingular M-matrix. Following [34], the basic reproduction number $\mathcal{R}_0$ is defined as the spectral radius of the next generation matrix FV^{-1}, that is,

$$\mathcal{R}_0 = \rho(FV^{-1}) = \rho\Big(D_p G_I^{-1} + D_q G_W^{-1} D_r G_I^{-1}\Big). \tag{4.1}$$

We refer to R_0 as the *domain* basic reproduction number, to emphasize that the expression for R_0 is based upon the entire network (e.g. see [1]). It follows from Theorem 2 in [34] that the DFE of (2.1) is locally asymptotically stable if $\mathcal{R}_0 < 1$, whereas it is unstable if $\mathcal{R}_0 > 1$. With reasonable biological assumptions, these same results hold globally, with $\mathcal{R}_0 = 1$ acting as a sharp threshold between disease extinction and an endemic state. Precise assumptions, statements and proofs are given in Sections 5 and 6. Note that the domain $\mathcal{R}_0$ depends on the movement of infectious individuals and the water, and implicitly on the movement of susceptible individuals through S_i^0.

In the special case $n = 1$, the basic reproduction number has the explicit expression

$$\mathcal{R}_0 = \frac{p}{d + \alpha + \gamma} + \frac{qr}{\delta(d + \alpha + \gamma)},$$

in which the first term arises from direct transmission while the second term arises from indirect transmission.

In the special case of no water movement and no movement of infectious humans between patches (i.e., $M_W = M_I = 0$), the basic reproduction number $\mathcal{R}_0$ defined in (4.1) is given by the maximum value of basic reproduction numbers $\mathcal{R}_0^{(i)}$ in all patches. Namely,

$$\mathcal{R}_0 = \max_i \{\mathcal{R}_0^{(i)}\}$$

where

$$\mathcal{R}_0^{(i)} = \frac{p_i}{d_i + \alpha_i + \gamma_i} + \frac{q_i r_i}{\delta_i(d_i + \alpha_i + \gamma_i)}, \quad i = 1,2,\dots,n. \tag{4.2}$$

4.2. Bounds on $\mathcal{R}_0$

In the rest of this section, the movement of infectious humans is ignored, i.e., $M_I = 0$. We consider the dependence of $\mathcal{R}_0$ on the connectivity and movement of water. In order to do so, assume that $p_i = p$ and $d_i + \alpha_i + \gamma_i = d + \alpha + \gamma$ for all i. Hence, $\mathcal{R}_0 = \frac{p}{d+\alpha+\gamma} + \frac{1}{d+\alpha+\gamma}\rho(D_q G_W^{-1} D_r)$. We assume in addition that $\delta_i = \delta$ for all i; namely, the pathogen decays at the same rate in each patch. From spectral properties of nonnegative matrices, $\mathcal{R}_0$ can be bounded above and below.

Theorem 4.1. *Assume that $p_i = p, d_i + \alpha_i + \gamma_i = d + \alpha + \gamma$, $\delta_i = \delta$ for all i, and $M_I = 0$. Then*

$$\min_i \{R_0^{(i)}\} \leqslant \mathcal{R}_0 \leqslant \max_i \{\mathcal{R}_0^{(i)}\}.$$

Proof. The proof is motived by similar results in [19,28] and the fact that $D_q G_W^{-1} D_r$ is similar to $D_r D_q G_W^{-1}$. Let $G_W^{-1} = Y = [y_{ij}]$, $\mathbf{1} = (1,1,\dots,1)^T \in \mathbb{R}^n$, and $[\mathbf{1}^T D_r D_q G_W^{-1}]_i$ denote the sum of the entries in the ith column of $D_r D_q G_W^{-1}$. Since the column sum of G_W is δ, $\mathbf{1}^T G_W = \delta \mathbf{1}^T$, giving $\mathbf{1}^T Y = \frac{1}{\delta}\mathbf{1}^T$. That is, the column sum of Y is $1/\delta$. Then

$$[\mathbf{1}^T D_r D_q G_W^{-1}]_i = q_1 r_1 y_{1i} + q_2 r_2 y_{2i} + \cdots + q_n r_n y_{ni} \leqslant \max_i\{q_i r_i\}(y_{1i} + y_{2i} + \cdots + y_{ni}) = \max_i\{\frac{q_i r_i}{\delta}\}.$$

Similarly, $[\mathbf{1}^T D_r D_q G_W^{-1}]_i \geqslant \min_i\{\frac{q_i r_i}{\delta}\}$. The conclusion follows from the facts that $\rho(D_r D_q G_W^{-1})$ lies between its minimum and maximum column sums and that $\mathcal{R}_0 = \rho(D_q G_W^{-1} D_r) = \rho(D_r D_q G_W^{-1})$. □

4.3. Effect of water movement on $\mathcal{R}_0$

The general expression for $\mathcal{R}_0$ (4.1) is complicated. However, this simplifies considerably in certain limiting parameter regimes. Let d_W be a positive number measuring the speed of water movement; it can defined as the largest entry in the water movement matrix, $d_W = \max_{ij}\{m_{ij}^W\}$, or as a certain matrix norm $d_W = \|M_W\|$. Let $b_{ij} = m_{ij}^W/d_W \geqslant 0$ and consider the normalized water movement matrix $B = [b_{ij}] \geqslant 0$. A weighted digraph $\mathcal{G}$ with vertices labeled $1, 2, \ldots, n$, can be associated with B and is denoted as $(\mathcal{G}, B)$. In $(\mathcal{G}, B)$, an arc (i,j) with weight b_{ji} from vertex i to vertex j exists if and only if $b_{ji} > 0$. The Laplacian matrix of B is

$$L = \begin{bmatrix} \sum_{j=1}^n b_{j1} & -b_{12} & \cdots & -b_{1n} \\ -b_{21} & \sum_{j=1}^n b_{j2} & \cdots & -b_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ -b_{n1} & -b_{n2} & \cdots & \sum_{j=1}^n b_{jn} \end{bmatrix}.$$

Assume that the assumptions of Theorem 4.1 hold. It follows from (3.1) that $G_W = \delta\,\mathrm{Id} + d_W L$ where Id is the $n \times n$ identity matrix. Since the pathogen decay rate might be related to the water movement, it is better to combine these parameters by introducing $\epsilon = \delta/d_W$. The parameter ϵ is a ratio of the water movement and pathogen decay time scales, with small ϵ corresponding to rapid movement relative to decay, and large ϵ corresponding to rapid decay relative to water movement. In the following subsections we consider two limiting cases: fast pathogen decay and fast water movement. These give concrete examples of the form of $\mathcal{R}_0$ in the special case of the assumptions in Theorem 4.1.

4.3.1. Fast pathogen decay

In the limit $\epsilon \to \infty$ (i.e., $\delta \gg d_W$), $G_W^{-1} \to \frac{1}{\delta}\,\mathrm{Id}$. Thus $\mathcal{R}_0 \to \max_i\{\mathcal{R}_0^{(i)}\}$, where $\mathcal{R}_0^{(i)}$ is given by (4.2). Biologically, in this situation, the pathogen decay rate is much faster than the water movement, and the shedded pathogen dies out before arriving in other patches along with the water movement; essentially, each patch is isolated from the other, and the disease dynamics is independent from one patch to the other.

Proposition 4.2. *Assume that all assumptions in Theorem 4.1 hold. Then*

$$\mathcal{R}_0 \to \max_i\{\mathcal{R}_0^{(i)}\} \quad \text{as} \quad \epsilon \to \infty.$$

4.3.2. Fast water movement

In the limit $\epsilon \to 0$ (i.e., $\delta \ll d_W$), the following result (Lemma 4.3) describes the limit of G_W^{-1}, and can be used to derive an estimation for $\mathcal{R}_0$ (Theorem 4.4).

Let C_{ii} be the cofactor of the (i,i) entry of L. By Kirchhoff's Matrix Tree Theorem (see Appendix),

$$C_{ii} = \sum_{\mathcal{T} \in \mathbb{T}_i} \prod_{(j,k) \in E(\mathcal{T})} b_{kj} > 0, \tag{4.3}$$

where $\mathbb{T}_i$ is the set of all spanning trees $\mathcal{T}$ rooted at vertex i in the weighted digraph $(\mathcal{G}, B)$ and $E(\mathcal{T})$ denotes the set of arcs in $\mathcal{T}$. Define the *network risk* of patch i to be

$$u_i = \frac{C_{ii}}{\sum_{k=1}^n C_{kk}}, \quad 1 \leqslant i \leqslant n \tag{4.4}$$

and form the $n \times n$ matrix

$$U = [u_{ij}] \quad \text{with} \quad u_{ij} = u_i, \ 1 \leqslant i, j \leqslant n. \tag{4.5}$$

Lemma 4.3. *Using the above notation, $G_W^{-1} \to U/\delta$ as $\epsilon \to 0$.*

Proof. Recall that G_W is a non-singular M-matrix, thus G_W^{-1} exists and is nonnegative [[4, p. 137]]. Since $G_W = \delta\,\mathrm{Id} + d_W L$, it follows that $\det G_W$ is a polynomial in d_W with a possible order n, denoted by $P(d_W)$. Notice that $\det L = 0$, thus there is no term with power n in $P(d_W)$. The coefficient of d_W^{n-1} in $P(d_W)$ is calculated as $\delta\sum_{k=1}^n C_{kk}$. Therefore,

$$\det G_W = P(d_W) = d_W^{n-1}\delta\sum_{k=1}^n C_{kk} + O(d_W^{n-2}).$$

The cofactor of the (i,i) entry of G_W has highest power $n-1$ of d_W with coefficient C_{ii}. Hence, the (i,i) entry of G_W^{-1} has the form

$$G_W^{-1}(i,i) = \frac{C_{ii}d_W^{n-1} + O(d_W^{n-2})}{d_W^{n-1}\delta\sum_{k=1}^n C_{kk} + O(d_W^{n-2})} \to \frac{C_{ii}}{\delta\sum_{k=1}^n C_{kk}} = \frac{u_i}{\delta} \quad \text{as} \quad \epsilon \to 0.$$

Similarly, the (i,j) entry of G_W^{-1} has the form

$$G_W^{-1}(i,j) = \frac{C_{ij}d_W^{n-1} + O(d_W^{n-2})}{d_W^{n-1}\delta\sum_{k=1}^n C_{kk} + O(d_W^{n-2})}$$

and

$$G_W^{-1}(i,j) \to \frac{C_{ij}}{\delta\sum_{k=1}^n C_{kk}} = \frac{C_{jj}}{\delta\sum_{k=1}^n C_{kk}} = \frac{u_j}{\delta} \quad \text{as} \quad \epsilon \to 0,$$

since $C_{ij} = C_{jj}$ by Lemma 2.1 in [15]. □

The following theorem follows from Lemma 4.3, and shows that the basic reproduction number $\mathcal{R}_0$ (given in (4.1) with $G_I = (d + \alpha + \gamma)\,\mathrm{Id}$) has a limit as $\epsilon \to 0$ that depends on the network structure of the water movement.

Theorem 4.4. *Assume that all assumptions in Theorem 4.1 hold. Then*

$$\mathcal{R}_0 \to \sum_{i=1}^n u_i \mathcal{R}_0^{(i)} \quad \text{as} \quad \epsilon \to 0,$$

where u_i is defined in (4.4).

In the limit of fast water movement, under the assumption of Theorem 4.4, the domain $\mathcal{R}_0$ thus becomes a weighted average of the patch reproduction numbers, with weights given by the network risks.

5. Global dynamics when $\mathcal{R}_0 < 1$

If either one of the following condition holds,

(H_4) (permanent immunity) $\sigma_i = 0$ for all i, or
(H_5) (same travel rate for human individuals) $M_S = M_I = M_R$

then we can study system (2.1) in a subset of Γ

$$\Delta = \{(S_1, I_1, R_1, W_1, \ldots, S_n, I_n, R_n, W_n) \in \Gamma \,|\, S_i \leqslant S_i^0,\ i = 1, 2, \ldots, n\},$$

since it can be verified that Δ is positively invariant with respect to system (2.1) provided that assumption (H_4) or assumption (H_5)

holds. In fact, when permanent immunity is assumed (i.e., (H_4)), it follows from the first equation of (2.1) that when $S_i = S_i^0$ for some i and $S_j \leqslant S_j^0$ for all $j \neq i$,

$$S_i' \leqslant A_i - d_i S_i^0 + \sum_{j=1}^{n} (m_{ij}^S S_j - m_{ji}^S S_i^0) = \sum_{j=1}^{n} m_{ij}^S (S_j - S_j^0) \leqslant 0.$$

When the travel rates for susceptible, infectious and recovered individuals are assumed to be the same (i.e., (H_5)), adding the first three equations of (2.1) yields

$$N_i' \leqslant A_i - d_i N_i + \sum_{j=1}^{n} (m_{ij}^S N_j - m_{ji}^S N_i).$$

It follows that when $N_i = S_i^0$ for some i and $N_j \leqslant S_j^0$ for all $j \neq i$,

$$N_i' \leqslant A_i - d_i S_i^0 + \sum_{j=1}^{n} (m_{ij}^S N_j - m_{ji}^S S_i^0) = \sum_{j=1}^{n} m_{ij}^S (N_j - S_j^0) \leqslant 0.$$

Consider the following assumptions

- (A_1) $f_i(S_i, I_i) \leqslant p_i I_i$ for all $S_i, I_i \geqslant 0,\ i = 1, \ldots, n$;
- (A_2) $g_i(S_i, W_i) \leqslant q_i W_i$ for all $S_i, W_i \geq 0,\ i = 1, \ldots, n$;
- (A_3) $h_i(I_i) \leqslant r_i I_i$ for all $I_i \geqslant 0, i = 1, \ldots, n$;
- (A_4) $f_i(S_i, I_i) \leqslant p_i I_i$ for all $0 \leqslant S_i \leqslant S_i^0,\ I_i \geqslant 0,\ i = 1, \ldots, n$;
- (A_5) $g_i(S_i, W_i) \leqslant q_i W_i$ for all $0 \leqslant S_i \leqslant S_i^0,\ W_i \geq 0,\ i = 1, \ldots, n$.

Assumptions (A_1) and (A_2) hold for those frequency-dependent incidences discussed in Section 1, while assumptions (A_4) and (A_5) hold for both mass action and saturating incidence. Assumption (A_3) holds for a linear shedding function.

Theorem 5.1. *Suppose that assumptions (H_1)–(H_3) hold and either M_I or M_W is irreducible. Then the following conclusions hold for the system (2.1).*

1. *If $\mathcal{R}_0 < 1$ and either of the following holds*
   - (a) *assumptions (A_1)-(A_3) hold, or*
   - (b) *assumptions (A_3)-(A_5) hold, and either (H_4) or (H_5) holds, then the DFE is globally asymptotically stable in Γ.*
2. *If $\mathcal{R}_0 > 1$, then the DFE is unstable and system (2.1) is uniformly persistent.*

Proof. Suppose that (a) holds. Let $x = (I_1, I_2, \ldots, I_n, W_1, W_2, \ldots, W_n)^T$. Using assumptions (A_1)–(A_3), it follows that $x' \leqslant (F - V)x$. Let $b \geqslant 0$ be the left eigenvector of the nonnegative matrix $V^{-1}F$ with respect to the eigenvalue $\rho(V^{-1}F) = \mathcal{R}_0$, that is, $b^T V^{-1} F = \mathcal{R}_0 b^T$. Construct a Lyapunov function

$$L = b^T V^{-1} x.$$

Differentiating L along the system (2.1) yields

$$L' = b^T V^{-1} x' \leqslant b^T V^{-1}(F - V)x = b^T V^{-1} F x - b^T x = (\mathcal{R}_0 - 1) b^T x \leqslant 0 \quad \text{if} \quad \mathcal{R}_0 < 1.$$

If $\mathcal{R}_0 < 1$, then $L' = 0$ implies $b^T x = 0$, thus $I_i = 0$ or $W_i = 0$ for some i. It can be shown using the same argument in the proof of Theorem 3.2 that the only invariant set where $L' = 0$ is the singleton $\{P_0\}$ provided that M_I or M_W is irreducible. Therefore, by LaSalle's Invariance Principle [20], P_0 is globally asymptotically stable in Γ.

If (b) holds, then we can study the dynamical behavior of (2.1) in Δ. Hence, the same argument as above works in Δ, and can be used to prove the global asymptotic stability of P_0 in Δ. It can further be verified that the attraction region of P_0 is Γ.

If $\mathcal{R}_0 > 1$ and $x > 0$, it follows that

$$(\mathcal{R}_0 - 1) b^T x > 0. \tag{5.1}$$

The inequality (5.1) and continuity imply that $L' > 0$ in a small enough neighborhood of P_0 in $\text{int}(\Gamma)$. Therefore, solutions in $\text{int}(\Gamma)$ sufficiently close to P_0 move away from P_0 provided $\mathcal{R}_0 > 1$, and thus P_0 is unstable. Using a uniform persistence result from [14] and a similar argument as in the proof of Proposition 3.3 of [21], we can show that, when M_I or M_W is irreducible (and thus P_0 is the only equilibrium on the boundary of Γ), the instability of P_0 implies the uniform persistence of (2.1). □

6. Global dynamics when $\mathcal{R}_0 < 1$

Uniform persistence of (2.1) and the positive invariance of the compact set Γ imply the existence of an endemic equilibrium of (2.1) in $\text{int}(\Gamma)$ (see Theorem D.3 in [31] or Theorem 2.8.6 in [8]).

Theorem 6.1. *Suppose that assumptions (H_1)–(H_3) hold and either M_I or M_W is irreducible. If $\mathcal{R}_0 > 1$, then there exists at least one endemic equilibrium for system (2.1).*

In the rest of this section human movements are ignored (i.e., $M_S = M_I = M_R = 0$) and permanent immunity is assumed for each patch (i.e., $\sigma_i = 0$ for all i). Let $P^* = \{S_1^*, I_1^*, R_1^*, W_1^*, \ldots, S_n^*, I_n^*, R_n^*, W_n^*\}$ denote the endemic equilibrium, where $S_i^*, I_i^*, R_i^*, W_i^* > 0,\ 1 \leqslant i \leqslant n$, satisfy the equilibrium equations

$$\begin{aligned} &f_i(S_i^*, I_i^*) + g_i(S_i^*, W_i^*) + d_i S_i^* = A_i, \\ &f_i(S_i^*, I_i^*) + g_i(S_i^*, W_i^*) = (d_i + \alpha_i + \gamma_i) I_i^*, \\ &\gamma_i I_i^* = d_i R_i^*, \\ &h_i(I_i^*) + \sum_{j=1}^{n} m_{ij}^W W_j^* = \delta_i W_i^* + \sum_{j=1}^{n} m_{ji}^W W_i^*. \end{aligned} \tag{6.1}$$

Assume that

- (B_1) there exist a family of functions $\Phi_i : (0, \frac{A_i}{d_i}] \to \mathbb{R}_+, i = 1, 2, \ldots, n$, such that for all $1 \leqslant i \leqslant n, S_i, I_i, W_i > 0$,
$$(S_i - S_i^*)(\Phi_i(S_i) - \Phi_i(S_i^*)) > 0, \quad S_i \neq S_i^*;$$
$$\left(\frac{f_i(S_i, I_i)\Phi_i(S_i^*)}{f_i(S_i^*, I_i^*)\Phi_i(S_i)} - 1\right)\left(1 - \frac{f_i(S_i^*, I_i^*)\Phi(S_i) I_i}{f_i(S_i, I_i)\Phi(S_i^*) I_i^*}\right) \leqslant 0$$
and
$$\left(\frac{g_i(S_i, W_i)\Phi_i(S_i^*)}{g_i(S_i^*, W_i^*)\Phi_i(S_i)} - 1\right)\left(1 - \frac{g_i(S_i^*, W_i^*)\Phi_i(S_i) W_i}{g_i(S_i, W_i)\Phi_i(S_i^*) W_i^*}\right) \leqslant 0;$$
- (B_2) for all $I_i > 0,\ 1 \leqslant i \leqslant n$,
$$\left(\frac{h_i(I_i)}{h_i(I_i^*)} - 1\right)\left(1 - \frac{h_i(I_i^*) I_i}{h_i(I_i) I_i^*}\right) \leqslant 0.$$

Most functions f_i, g_k, and h_i that are commonly used in the literature satisfy the above assumptions (B_1) and (B_2). More details are provided at the end of this section.

Theorem 6.2. *Suppose that assumptions (H_1)–(H_3) and (B_1) and (B_2) hold. Assume that $M_S = M_I = M_R = 0, M_W$ is irreducible, and $\sigma_i = 0$ for all $i = 1, 2, \ldots, n$. If $\mathcal{R}_0 > 1$, then the endemic equilibrium of system (2.1) is unique and globally asymptotically stable in int(Γ).*

Proof. Motivated by the Lyapunov function for a 1-patch cholera model in [29], set

$$V_i = \int_{S_i^*}^{S_i} \frac{\Phi_i(\xi) - \Phi_i(S_i^*)}{\Phi_i(\xi)}\, d\xi + I_i - I_i^* - I_i^* \ln \frac{I_i}{I_i^*} + \frac{g_i(S_i^*, W_i^*)}{h_i(I_i^*)}\left(W_i - W_i^* - W_i^* \ln \frac{W_i}{W_i^*}\right).$$

Differentiating V_i along (2.1) and using the equilibrium Eqs. (6.1) give

$$\begin{aligned}V_i' &= \left(1-\frac{\Phi_i(S_i^*)}{\Phi_i(S_i)}\right)S_i' + \left(1-\frac{I_i^*}{I_i}\right)I_i' + \frac{g_i(S_i^*,W_i^*)}{h_i(I_i^*)}\left(1-\frac{W_i^*}{W_i}\right)W_i' \\ &= d_i(S_i^*-S_i)\left(1-\frac{\Phi_i(S_i^*)}{\Phi_i(S_i)}\right) + f_i(S_i^*,I_i^*)F_i + g_i(S_i^*,W_i^*)H_i \\ &\quad + \sum_{j=1}^{n} m_{ij}^W W_j^* \frac{g_i(S_i^*,W_i^*)}{h_i(I_i^*)}\left(\frac{W_j}{W_j^*} - \frac{W_j W_i^*}{W_j^* W_i} + 1 - \frac{W_i}{W_i^*}\right),\end{aligned}$$

where

$$F_i = 2 - \frac{\Phi_i(S_i^*)}{\Phi_i(S_i)} + \frac{f_i(S_i,I_i)\Phi_i(S_i^*)}{f_i(S_i^*,I_i^*)\Phi_i(S_i)} - \frac{I_i}{I_i^*} - \frac{f_i(S_i,I_i)I_i^*}{f_i(S_i^*,I_i^*)I_i}$$

and

$$\begin{aligned}H_i = 3 &- \frac{\Phi_i(S_i^*)}{\Phi_i(S_i)} + \frac{g_i(S_i,W_i)\Phi_i(S_i^*)}{g_i(S_i^*,W_i^*)\Phi_i(S_i)} - \frac{I_i}{I_i^*} - \frac{g_i(S_i,W_i)I_i^*}{g_i(S_i^*,W_i^*)I_i} + \frac{h_i(I_i)}{h_i(I_i^*)} \\ &- \frac{h_i(I_i)W_i^*}{h_i(I_i^*)W_i} - \frac{W_i}{W_i^*}.\end{aligned}$$

Let $\Theta(x) := 1 - x + \ln x$, for $x \in (0,\infty)$. It can be shown that $\Theta(x) \leqslant 0$ with $\Theta(x) = 0$ if and only if $x = 1$. Using the notation of Θ and assumptions (B_1) and (B_2), it follows that

$$\begin{aligned}F_i &= \Theta\left(\frac{\Phi_i(S_i^*)}{\Phi_i(S_i)}\right) + \Theta\left(\frac{f_i(S_i,I_i)I_i^*}{f_i(S_i^*,I_i^*)I_i}\right) + \Theta\left(\frac{f_i(S_i^*,I_i^*)\Phi_i(S_i)I_i}{f_i(S_i,I_i)\Phi_i(S_i^*)I_i}\right) \\ &\quad + \left(\frac{f_i(S_i,I_i)\Phi_i(S_i^*)}{f_i(S_i^*,I_i^*)\Phi_i(S_i)} - 1\right)\left(1 - \frac{f_i(S_i^*,I_i^*)\Phi(S_i)I_i}{f_i(S_i,I_i)\Phi(S_i^*)I_i^*}\right) \leqslant 0,\end{aligned}$$

$$\begin{aligned}H_i &= \Theta\left(\frac{\Phi_i(S_i^*)}{\Phi_i(S_i)}\right) + \Theta\left(\frac{h_i(I_i)W_i^*}{h_i(I_i^*)W_i}\right) + \Theta\left(\frac{g_i(S_i^*,W_i^*)\Phi_i(S_i)W_i}{g_i(S_i,W_i)\Phi_i(S_i^*)W_i^*}\right) \\ &\quad + \Theta\left(\frac{h_i(I_i^*)I_i}{h_i(I_i)I_i^*}\right) + \Theta\left(\frac{g_i(S_i,W_i)I_i^*}{g_i(S_i^*,W_i^*)I_i}\right) \\ &\quad + \left(\frac{g_i(S_i,W_i)\Phi_i(S_i^*)}{g_i(S_i^*,W_i^*)\Phi_i(S_i)} - 1\right)\left(1 - \frac{g_i(S_i^*,W_i^*)\Phi_i(S_i)W_i}{g_i(S_i,W_i)\Phi_i(S_i^*)W_i^*}\right) \\ &\quad + \left(\frac{h_i(I_i)}{h_i(I_i^*)} - 1\right)\left(1 - \frac{h_i(I_i^*)I_i}{h_i(I_i)I_i^*}\right) \leqslant 0\end{aligned}$$

and

$$\begin{aligned}\frac{W_j}{W_j^*} - \frac{W_j W_i^*}{W_j^* W_i} + 1 - \frac{W_i}{W_i^*} &= \Theta\left(\frac{W_j W_i^*}{W_j^* W_i}\right) + \frac{W_j}{W_j^*} - \ln\frac{W_j}{W_j^*} - \frac{W_i}{W_i^*} + \ln\frac{W_i}{W_i^*} \\ &\leqslant \frac{W_j}{W_j^*} - \ln\frac{W_j}{W_j^*} - \frac{W_i}{W_i^*} + \ln\frac{W_i}{W_i^*}.\end{aligned}$$

Combining all of these and using assumption (B_1) on the first term of V_i' yield

$$V_i' \leqslant \sum_{j=1}^{n} x_{ij}\left(\frac{W_j}{W_j^*} - \ln\frac{W_j}{W_j^*} - \frac{W_i}{W_i^*} + \ln\frac{W_i}{W_i^*}\right),$$

where $x_{ij} = m_{ij}^W W_j^* \frac{g_i(S_i^*,W_i^*)}{h_i(I_i^*)}$ is a nonnegative constant for each pair i, j. The $n \times n$ matrix $X = [x_{ij}]$ provides a different weighted version of the water network M_W. The rooted spanning trees of X provide a way to combine the V_i to form a Lyapunov function for system (2.1). Consider the transpose $Y = [y_{ij}] = X^T$, that is, $y_{ij} = x_{ji}$ for all i, j. Let $(\mathcal{G}, Y)$ be the weighted digraph with the weight matrix $Y = [y_{ij}]$. Choose c_i as given in Kirchhoff's Matrix Tree Theorem (see Appendix) with $(\mathcal{G}, Y)$, that is,

$$c_i = \sum_{\mathcal{T}\in\mathbb{T}_i}\prod_{(j,k)\in E(\mathcal{T})} y_{kj} = \sum_{\mathcal{T}\in\mathbb{T}_i}\prod_{(j,k)\in E(\mathcal{T})} x_{jk}, \tag{6.2}$$

where the notation is given below (4.3), but with weighted digraph $(\mathcal{G}, Y)$. Since M_W is irreducible, it follows that $c_i > 0$ for all i (see the Appendix). Therefore, $V = \sum_{i=1}^n c_i V_i$ is a Lyapunov function for (2.1), that is,

$$V' = \sum_{i=1}^{n} c_i V_i' \leqslant \sum_{i,j=1}^{n} c_i x_{ij}\left(\frac{W_j}{W_j^*} - \ln\frac{W_j}{W_j^*} - \frac{W_i}{W_i^*} + \ln\frac{W_i}{W_i^*}\right) = 0.$$

The last equality follows from the Tree Cycle Identity in [[22, Theorem 2.2]]. Notice that the orientation of spanning trees $\mathcal{T}$ defined here (in which every path is oriented towards the root; see Appendix) is opposite to the one in [22] (in which every path is oriented away from the root), which explains the introduction of the transpose matrix Y. Furthermore, using similar arguments as those in [15,16,22], we can prove that $V' = 0$, along with the property of irreducibility of M_W, implies that $S_i = S_i^*$, $I_i = \eta I_i^*$, and $W_i = \eta W_i^*$ for all i and some positive integer η. It follows from the first two equations of (2.1) that $A_i - d_i S_i^* - \eta(d_i + \alpha_i + \gamma_i)I_i^* = 0$. By the first two equations of (6.1), $\eta = 1$. That is, the only invariant set on which $V' = 0$ is the singleton $\{P^*\}$. Therefore, by LaSalle's Invariance Principle [20], P^* is globally asymptotically stable and thus unique in $\text{int}(\Gamma)$. □

If functions $f_i(S_i,I_i)$, $g_i(S_i,W_i)$, $h_i(I_i)$ are monotone increasing with respect to S_i, I_i, and $f_i(S_i,I_i)/I_i$, $g_i(S_i,W_i)/W_i$, $h_i(I_i)/I_i$ are monotone decreasing in I_i or W_i, then assumptions (B_1) and (B_2) are satisfied. For example, if $f_i(S_i,I_i) = \phi_i(S_i)\varphi_i(I_i)$ and $g_i(S_i,W_i) = \phi_i(S_i)\psi_i(W_i)$, where $\phi_i', \varphi_i', \psi_i' \geqslant 0$ and $\varphi_i'', \psi_i'' \leqslant 0$, then Φ_i in assumption (B_1) can be chosen as $\Phi_i(S_i) = \phi_i(S_i)$. Thus both mass action and saturating incidence satisfy assumption (B_1). If h_i is linear, then assumption (B_2) holds with equality. As a consequence, our global stability result (Theorem 6.2) holds for many cholera models in the literature that assume permanent immunity and no human movement, for example, the model in [7].

7. Cholera control strategies

To investigate different control strategies in model (2.1), it is convenient to split the Jacobian matrix of the infectious compartments of system (2.1) linearized at the DFE in a way different from that in Section 4. Now take $J = \tilde{F} - \tilde{V}$ with

$$\tilde{F} = \begin{bmatrix} D_p & D_q \\ D_r & 0 \end{bmatrix} \quad \text{and} \quad \tilde{V} = \begin{bmatrix} G_I & 0 \\ 0 & G_W \end{bmatrix},$$

giving

$$\tilde{F}\tilde{V}^{-1} = K = \begin{bmatrix} D_p G_I^{-1} & D_q G_W^{-1} \\ D_r G_I^{-1} & 0 \end{bmatrix}. \tag{7.1}$$

Since $\tilde{F}$ and $\tilde{V}$ have the same properties as F and V in Section 4, it follows that $\tilde{\mathcal{R}}_0 = \rho(K)$ and $\mathcal{R}_0$ in Section 4 agree at the threshold value, i.e., $\mathcal{R}_0 = 1 \iff \tilde{\mathcal{R}}_0 = 1$. Matrix K separates the direct and indirect transmission and pathogen shedding: $D_p G_I^{-1}$ counts the contribution due to direct human-to-human contacts, $D_q G_W^{-1}$ counts the contribution due to drinking contaminated water, and $D_r G_I^{-1}$ represents the pathogen shed from infectious hosts. In the following, using the matrix K, various type reproduction numbers [18,27] and target reproduction numbers [30] are calculated to measure the effort required to control cholera.

Vaccination: Assume that vaccination is employed in one patch [23], say patch i ($1 \leqslant i \leqslant n$), then the type reproduction number $\mathcal{T}_i = e_i^T P_i K(I - K + P_i K)^{-1} e_i$, with e_i the ith unit vector in $\mathbb{R}^{2n}$ and P_i the $2n \times 2n$ projection matrix (i.e., the (i,i) entry of P_i is 1 and all other entries are zero), can be used to guide the effective vaccine coverage provided $\rho(K - P_i K) < 1$. That is, if a proportion more than $1 - 1/\mathcal{T}_i$ of the host population in patch i acquires immunity from the vaccine, then cholera can be eradicated among all patches. If vaccination is employed in several patches, then a type reproduction number with a multiple-type form can be defined similarly; see [18,27].

Provision of clean water: Provision of clean water can reduce the chances that susceptible hosts drink contaminated water. For this case, the target reproduction number recently defined in [30] can be used to quantify the effort needed to control the disease. For example, if clean water is provided in all n patches, then the targeted entries are those entries in the $(1,2)$ block of K (i.e., $D_q G_W^{-1}$). The target set is $S = \{(i,j) | 1 \leqslant i \leqslant n,\ n+1 \leqslant j \leqslant 2n\}$. Following [30], define two index sets $S_1 = \{1,2,\ldots,n\}$ and $S_2 = \{n+1,\ldots,2n\}$, representing the first and second indices of the target set S. Then the target reproduction number is defined as $\mathcal{T}_S = \rho(P_{S_1} K P_{S_2} (I - K + P_{S_1} K P_{S_2})^{-1})$, where P_{S_1} and P_{S_2} are $2n \times 2n$ projection matrix on $S_1,\ S_2$, respectively (e.g., for projection matrix P_{S_1}, the (i,i) entry is 1 as long as $i \in S_1$ and all other entries are zero). Therefore, if a proportion more than $1 - 1/\mathcal{T}_S$ of the contribution due to drinking contaminated water (i.e., entries in $D_q G_W^{-1}$) can be reduced, then the disease can be eradicated provided $\rho(K - P_{S_1} K P_{S_2}) < 1$.

Isolation: Isolation can be used to reduce the direct human-to-human contact and thus reduce the entries in the $(1,1)$ block of K. Then the set of targeted entries in K is $S = \{(i,j) | 1 \leqslant i,j \leqslant n\}$. Thus the target reproduction number is defined as $\mathcal{T}_S = \rho(P_{S_1} K P_{S_2} (I - K + P_{S_1} K P_{S_2})^{-1})$ with $S_1 = S_2 = \{1,\ldots,n\}$.

Sanitation: One of the major control mechanisms recommended by the WHO is hygienic disposal of human faeces, targeting the entries in the $(2,1)$ block of K. The target set is $S = \{(i,j) | n+1 \leqslant i \leqslant 2n, 1 \leqslant j \leqslant n\}$ and the corresponding target reproduction number is $\mathcal{T}_S = \rho(P_{S_1} K P_{S_2} (I - K + P_{S_1} K P_{S_2})^{-1})$ with $S_1 = \{n+1,\ldots,2n\}$ and $S_2 = \{1,\ldots,n\}$.

8. Concluding remarks

Multi-patch epidemic models are commonly used in the literature to study the spatial spread of infectious diseases; see, for example, the survey articles [2,36]. In this paper, a general multi-patch model (2.1) is proposed for cholera transmission and spread in a patchy environment. This framework may be adapted for other waterborne diseases as well, including hepatitis A and E, giardiasis, cryptosporidiosis, and salmonellosis [3]. It is shown (Theorems 5.1 and 6.2) that, under biologically reasonable assumptions, cholera dynamics in the patchy environment are completely determined by the domain reproduction number $\mathcal{R}_0$ defined in (4.1). In particular, the global stability of the endemic equilibrium in the case of no human movement is proved by constructing a suitable Lyapunov function and applying a graph-theoretic approach [15,16,22] that is based on Kirchhoff's Matrix Tree Theorem (Proposition 8.1 in Appendix) from graph theory. These analytical results suggest that in order to eliminate cholera from the patchy environment, various control and intervention strategies can be applied. The type/target reproduction numbers derived in Section 7 can be used to quantify these strategies.

Kirchhoff's Matrix Tree Theorem is also used to investigate the dependence of $\mathcal{R}_0$ on the connectivity and movement of water. Specifically, in the fast water movement case, $\mathcal{R}_0$ becomes a weighted average of the patch reproduction numbers (Theorem 4.4), with weights given by the network risks (4.4) in terms of normalized weights of spanning trees in the network. The network structure and patch characteristics combine in nice ways to give the domain $\mathcal{R}_0$. The authors will further explore this topic in another manuscript under preparation.

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Appendix A. Kirchhoff's Matrix Tree Theorem

Let $(\mathcal{G}, A)$ be a weighted digraph with n vertices labeled $1,2,\ldots,n$, and $A = [a_{ij}] \geqslant 0$ be the $n \times n$ weight matrix. An arc (j,i) with weight a_{ij} from vertex j to vertex i exists if and only if $a_{ij} > 0$. A spanning tree $\mathcal{T}$ rooted at vertex i is a sub-digraph of G that is connected with no cycle, consists of n vertices and in which every path between a non-root vertex and the root is oriented towards the root. 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 [4]. The Laplacian matrix $L = [l_{ij}]$ of $(\mathcal{G}, A)$ is defined as $l_{ij} = -a_{ij}$ whenever $i \neq j$ and $l_{ii} = \sum_{k \neq i} a_{ki}$. Notice that the sum of each column in L equals zero. The following result is standard in graph theory, and customarily called Kirchhoff's Matrix Tree Theorem. We refer the reader to [24] for its proof.

Proposition 8.1. *Assume $n \geqslant 2$ and let c_i be the cofactor of l_{ii} in L. Then*

$$c_i = \sum_{\mathcal{T} \in \mathbb{T}_i} \prod_{(j,k) \in E(\mathcal{T})} a_{kj},$$

where $\mathbb{T}_i$ is the set of all spanning trees $\mathcal{T}$ rooted at vertex i in the weighted digraph $(\mathcal{G}, A)$ and $E(\mathcal{T})$ denotes the set of arcs in $\mathcal{T}$.

In particular, if $(\mathcal{G}, A)$ is strongly connected, then $c_i > 0$ for all i; see, for example, Lemma 2.1 in [15].

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