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MODELING CHOLERA DISEASE WITH EDUCATION AND CHLORINATION

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Cholera, characterized by severe diarrhea and rapid dehydration, is a water-borne infectious disease caused by the bacterium *Vibrio cholerae*. Haiti offers the most recent example of the tragedy that can befall a country and its people when cholera strikes. While cholera has been a recognized disease for two centuries, there is no strategy for its effective control. We formulate and analyze a mathematical model that includes two essential and affordable control measures: water chlorination and education. We calculate the basic reproduction number and determine the global stability of the disease-free equilibrium for the model without chlorination. We use Latin Hypercube Sampling to demonstrate that the model is most sensitive to education. We also derive the minimal effective chlorination period required to control the disease for both fixed and variable chlorination. Numerical simulations suggest that education is more effective than chlorination in decreasing bacteria and the number of cholera cases.

Keywords: Cholera; Mathematical Model; Half-Saturation; Latin Hypercube Sampling.

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1. Introduction

Cholera is a severe water-borne infectious disease caused by the bacterium *Vibrio cholerae* (*V. cholerae*). Recent years have seen a strong trend of cholera outbreaks in developing countries, including Haiti (2010–2011), Cameroon (2010–2011), Kenya (2010), Vietnam (2009), Zimbabwe (2008–2009), Iraq (2008), the Democratic Republic of Congo (2008) and India (2007).[1] Due to its huge impact on public health, and social and economic development, cholera has been the subject of extensive studies in clinical, experimental and theoretical fields. It remains an important global cause of morbidity and mortality, capable of causing periodic epidemic disease.[2] Cholera is an example of a bacterial disease whose primary mode of infection is indirect, which is caused when individuals ingest fecal-contaminated water containing the bacteria *V. cholera*.[1] Transmission between humans and reservoirs of pathogens implies that disease transmission includes an indirect route other than human-to-human contacts.

Education is a key tool in disease management that is often overlooked.[3] It requires investment in people, rather than investment in biomedical interventions, but it has the potential to lead to enormous benefits for relatively low cost. Indeed, behavioral interventions have been solely responsible for the near-eradication of Guinea Worm Disease.[4,5] Conversely, a lack of information can have a severe impact on worsening the disease. For example, 60% of gay men attending an STD clinic in urban South Africa were unaware that anal sex was a risk factor for HIV.[6]

Cholera-specific education includes advising people with symptoms to seek medical care promptly, and improving sanitation and hygienic practices.[7] Failures of health education can be traced to barriers at one of six sites: to be effective, messages have to (1) reach the intended audience, (2) gain attention, (3) be correctly understood, (4) be accepted, (5) result in changed behavior and (6) result in improvement in health.[8] Health education during the 1994 cholera epidemic of Guinea-Bissau demonstrated that local preventive rituals, radio and word-of-mouth communication were effective educational tools.[7] In this study, messages reached subject participants, all of whom rapidly sought medical treatment, but none could identify how cholera was transmitted. The KwaZulu-Natal Department of Health in South Africa has recommended that health-education messages on cholera should emphasise home management (increasing fluid intake, specifically sugar-salt solutions and oral rehydration salts) and early-care-seeking at rehydration centers, clinics or hospitals.[9]

The first scientists to suggest disinfecting water with chlorine were Louis-Bernard Guyton de Morveau (in France) and William Cumberland Cruikshank (in England), both around the year 1800, as it was found that water that has been treated with chlorine is effective in preventing the spread of water-borne diseases.[10] However, disinfection by chlorination can be problematic in some circumstances. Chlorine can react with naturally occurring organic compounds found in the water supply to produce disinfection byproducts (DBPs) such as trihalomethanes and

haloacetic acids. Due to the potential carcinogenicity of these compounds, drinking-water regulations across the developed world require regular monitoring of the concentration of these compounds in the distribution systems of municipal water systems. The World Health Organization has stated that risks to health from DBPs are extremely small in comparison with inadequate disinfection.[11]

Understanding the fundamental mechanism in the disease transmission is crucial for effective prevention and intervention strategies against a cholera outbreak. To this effect, mathematical modeling provides a unique approach to gain basic insights into the dynamics of infectious diseases. Therefore, by exploring the potential effects of disease-control strategies such as water chlorination, mathematical modeling can predict the dynamics of explosive epidemics often associated with cholera outbreaks.

Previous models of cholera have consisted of simple SIR models,[12] incorporated hyperinfectivity and low-infected bacteria states,[13,14] examined vaccination and education[15] and also education, sanitation and chlorination.[16] However, none of these models gives a clear idea about the effect of chlorination and education, and the best time of applying them, nor do they distinguish between the force of infection inside and outside water. Moreover, due to limited resources and infrastructure, continuous chlorination of water-distribution sources is neither feasible nor desirable.[5]

Here, we develop a compartmental transmission model that characterizes the population as susceptible to infection, infected and infectious to others, or recovered or otherwise removed from risk for further infection. Our objective is to formulate and analyze a model for cholera that includes relevant biological detail and accounts for a basic intervention strategy not considered before in cholera models; namely, water chlorination at discrete, not necessarily fixed, times.

This paper is organized as follows. In Sec. 2, we introduce the continuous model (without chlorination). In Sec. 3, we study the existence of the endemic equilibrium under some conditions and analyze the stability of the disease-free equilibrium. In Sec. 4, we analyze the impulsive chlorination model. In Sec. 5, we perform numerical simulations to support our analytical results. Finally, we conclude with a discussion.

2. The Model

Our model accommodates the diverse dynamics of a cholera outbreak determined by population-specific parameters such as the rate of water chlorination and the rate of bacteria ingestion. Figure 1 depicts our initial model compartment and flows, which is interpreted as a system of four ordinary differential equations. A complex system of interactions occurs between the human host, pathogen and environment.

The model classifies the human population $N(t)$ into three classes: susceptible individuals $S(t)$, infected individuals $I(t)$ and recovered individuals $R(t)$, so that

$$N(t) = S(t) + I(t) + R(t). \tag{2.1}$$

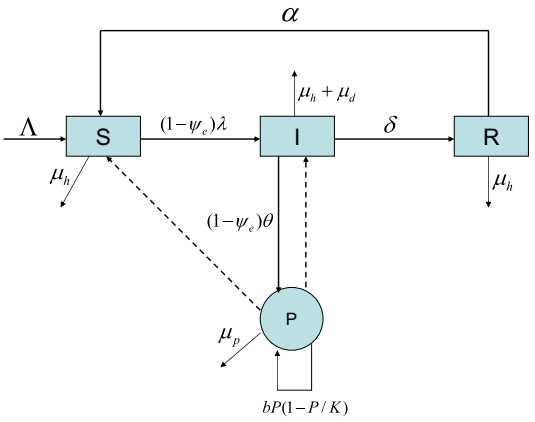


Fig. 1. The model. Individuals can be susceptible, infected or recovered. We assume logistic growth for bacteria with per capita growth rate b and carrying capacity K. Susceptible individuals enter the model with recruitment rate Λ and are exposed to a force of infection λ. Infected individuals recover with a rate δ and may become susceptible again at rate α. The natural human mortality and disease death rates are μ_h and μ_d, respectively, while the bacteria death rate is μ_p. Direct education (ψ_e) reduces both the force of infection and the bacteria shed rate θ.

The pathogen population is $P(t)$, which represents the concentration of bacteria in the aquatic environment. It is assumed that, at any moment in time, there is constant inflow Λ into the susceptible class (human recruitment rate). Susceptible individuals acquire infection at a time-dependent rate in two ways: the first is $\frac{\beta_p P(t)}{H_p+P(t)}$ (Holling type-II functional response) where $\beta_p > 0$ is the contact rate for humans and contaminated water, $\frac{P(t)}{H_p+P(t)}$ is the probability that an individual in contact with untreated water is infected with cholera and H_p is the half-saturation constant[17]; i.e., the concentration of *V. cholerae* in water that yields a 50% chance of getting cholera. We choose a Holling type-II functional response based on the fact that, even though the spread of cholera is rapid, there is always a saturation point. A Holling type-II functional response captures this saturation/inhibitory effect as the number of infectives becomes large.

The second method of acquiring infection is the force of infection associated with cholera, given by $\frac{\beta_i I(t)}{H_i+I(t)}$, where $\beta_i > 0$ is the effective contact rate (contact sufficient to result in cholera infection) and H_i is the half-saturation constant outside water. Infected individuals may recover at rate δ; this depends on nutrition, medication, immunity and age. Recovered individuals become susceptible at a rate α, while μ is the natural human mortality rate and μ_d is the cholera-induced mortality rate.

We assume that bacteria enter the pathogen reservoir of *V. cholerae* at a rate $b(1 - \frac{P(t)}{K})$, proportional to bacteria density in this class, where $b > 0$ is the per capita growth rate for *V. cholerae*, $K > 0$ is the environmental carrying capacity for *V. cholerae* in the water supply, μ_p is the death rate for bacteria and $\theta > 0$ is the average contribution of each infected individual to the pathogen population

of *V. cholerae*. Finally, $0 \leq \psi_e \leq 1$ is a constant representing direct cholera-related education. This is a composite parameter encapsulating behavior changes that result from avoiding contact with infected people and avoiding contaminating water sources. We assume this would be achieved as a result of a formalized information and communication strategy.

Putting the above formulations and assumptions together gives the following system of differential equations:

$$\begin{aligned} S'(t) &= \Lambda + \alpha R(t) - ((1-\psi_e)\lambda + \mu_h)S(t), \\ I'(t) &= (1-\psi_e)\lambda S(t) - (\mu_h + \delta + \mu_d)I(t), \\ R'(t) &= \delta I(t) - (\alpha + \mu_h)R(t), \\ P'(t) &= b\left(1 - \frac{P(t)}{K}\right)P(t) + (1-\psi_e)\theta I(t) - \mu_p P(t), \end{aligned} \tag{2.2}$$

where

$$\lambda = \frac{\beta_p P(t)}{H_p + P(t)} + \frac{\beta_i I(t)}{H_i + I(t)} \tag{2.3}$$

is the force of infection.

The state variables and the associated parameters are described in Table 1. There are two equilibria for this system:

(i) The disease-free equilibrium (DFE) given by $E_0 = (\frac{\Lambda}{\mu_h}, 0, 0, 0)$.
(ii) The endemic equilibrium (EE) given by $E_e = (S_e, I_e, R_e, P_e)$ with S_e, I_e, R_e, $P_e > 0$. We will prove the stability conditionally upon existence.

3. Saturation Constants and the Endemic Equilibrium

The saturation constant H_p represents the bacteria concentration in water at which the force of infection is half the transmission rate. Thus, it will be subject to general education about sanitation and cleanliness, which can have a large effect on disease control.[5] Similarly, H_i represents contact between susceptible and infected individuals and is also subject to general education about disease prevention methods, such as the use of gloves and hand-washing (in clean water) when in contact with infected individuals. We refer to these methods of disease control as indirect education, as they pertain to general health, rather than the direct avoidance of contamination that ϕ_e represents. As a result, we examine the limiting cases of the two saturation constants, as a proxy for broader education initiatives.

The limiting cases for the saturation constants are illustrated in Fig. 2. The cases are:

(1) $H_k \to \infty$ for $k = p, i$ (force of infection is zero), which implies the DFE and a degenerate EE, $(S_e, 0, 0, P_e)$ with $P_e > 0$, both exist.
(2) $H_p \to \infty$ and $H_i \to h_i \notin \{0, \infty\}$ (force of infection is independent of bacteria density in water, disease is one that is solely transmitted outside water), which

Table 1. Variables, sample values and sensitivity ranges for parameters. K, ψ_r and α have no range because R_0 is independent of them.

Variables and parameters	Description	Range	Sample value	Unit	Reference
$S(t)$	Number of susceptible individuals				
$I(t)$	Number of infected individuals				
$R(t)$	Number of recovered individuals				
$P(t)$	Concentration of pathogen population (in a pool of *V. cholerae*)				
Λ	Constant human recruitment rate	0.0528–0.0572	0.0548	people $\cdot$ day^{-1}	Assumed
μ_h	Natural human mortality rate	$5.24e-5$–$5.72e-5$	$5.48e-5$	day^{-1}	18
β_p	Per capita contact rate for humans and contaminated water	0.2073–0.2213	0.2143	day^{-1}	13
β_i	Effective contact rate between individuals (contact sufficient to result in cholera infection)	0.057–0.157	0.107	day^{-1}	Assumed
δ	Recovery rate of infected humans	0.015–0.05	0.03	day^{-1}	16
μ_d	Cholera-induced mortality rate of infected individuals	0.0125–0.0175	0.015	day^{-1}	18
H_p	*V. cholerae* biomass level at which half of all contacts with contaminated water produce infection	$0.5e+6$–$1.5e+6$	$e+6$	cell L^{-1}	19
H_i	*V. cholerae* biomass level at which half of all contacts with contaminated water produce infection	$0.5e+6$–$1.5e+6$	$e+6$	cell L^{-1}	Assumed
K	Carrying capacity for *V. cholerae*	—	$e+7$	cell L^{-1}	Assumed
θ	Bacteria shed rate into the water supply by infected humans	50–150	100	cell L^{-1} day^{-1} person^{-1}	19
b	(Maximum) per capita growth rate for *V. cholerae* bacteria	0–1	0.73	day^{-1}	15
μ_p	Mortality rate for bacteria, including phage degradation	0.33–1.58	1.06	day^{-1}	15
$(1-\psi_e)$	Education parameter	0–1	0.6	—	15
ψ_r	Chlorination parameter	—	0.75	—	Assumed
α	Per capita rate at which recovered humans are susceptible	—	0.01	day^{-1}	Assumed
$S(0)$	Initial number of susceptible individuals	—	1000	people	Assumed
$I(0)$	Initial number of infected individuals	—	5	people	Assumed
$R(0)$	Initial number of recovered individuals	—	0	people	Assumed
$P(0)$	Initial pathogen concentration	—	10^5	cell L^{-1}	Assumed

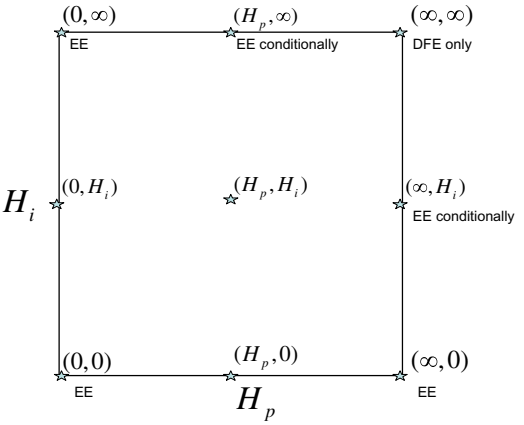


Fig. 2. Limiting cases for the saturation constants, illustrating the nine extreme cases listed in Sec. 3. The square represents a Cartesian product of two intervals; i.e., $[0,\infty] \times [0,\infty]$. Any pair (H_p, H_i) can be described depending on the values of H_p and H_i (values are 0, ∞ or a positive, finite number).

implies an EE (S_e, R_e, I_e, P_e) exists conditionally, given by

$$S_e = \frac{(\mu_h + \delta + \mu_d)}{(1-\psi_e)\lambda_e} I_e, \tag{3.1}$$

$$R_e = \frac{\delta}{\alpha + \mu_h} I_e, \tag{3.2}$$

$$I_e = \frac{\Lambda(1-\psi_e)\beta_i - \mu_h H_i(\mu_h + \delta + \mu_d)}{(1-\psi_e)\beta_i\big(\big(1 + \frac{\mu_h}{(1-\psi_e)\beta_i}\big)(\mu_h + \delta + \mu_d) - \frac{\alpha\delta}{\alpha+\mu_h}\big)}. \tag{3.3}$$

Here we used

$$\lambda_e = \frac{\beta_i I_e}{H_i + I_e}, \tag{3.4}$$

to evaluate I_e (in Eq. (3.3)). The value of P_e is not evaluated because the bacteria in water makes no contribution to cholera in this case. We need the condition $\Lambda(1-\psi_e)\beta_i - \mu_h H_i(\mu_h + \delta + \mu_d) > 0$ to have a positive EE.

(3) $H_p \to h_p \notin \{0, \infty\}$ and $H_i \to \infty$ (force of infection is independent of human infected cases, disease is solely transmitted via water), which implies an EE (S_e, R_e, I_e, P_e) exists unconditionally, given by

$$S_e = \frac{(\mu_h + \delta + \mu_d)}{(1-\psi_e)\lambda_e} I_e, \tag{3.5}$$

$$R_e = \frac{\delta}{\alpha + \mu_h} I_e, \tag{3.6}$$

$$I_e = \frac{\Lambda}{(1 + \frac{\mu_h}{(1-\psi_e)\lambda_e})(\mu_h + \delta + \mu_d) - \frac{\alpha\delta}{\alpha+\mu_h}}, \tag{3.7}$$

with

$$\lambda_e = \frac{\beta_p P_e}{H_p + P_e}. \tag{3.8}$$

(4) $H_p \to \infty$ and $H_i \to 0$ (force of infection is independent of the density of bacteria in water and independent of the bacteria dose outside water). In this case, the EE exists unconditionally and is given by

$$S_e = \frac{(\mu_h + \delta + \mu_d)}{(1-\psi_e)\lambda_e} I_e, \tag{3.9}$$

$$R_e = \frac{\delta}{\alpha + \mu_h} I_e, \tag{3.10}$$

$$I_e = \frac{\Lambda}{\left(\left(1 + \frac{\mu_h}{(1-\psi_e)\beta_i}\right)(\mu_h + \delta + \mu_d) - \frac{\alpha\delta}{\alpha+\mu_h}\right)}. \tag{3.11}$$

Here P_e is out of our interest. Note that $I_e > 0$.

(5) $H_p \to 0$ and $H_i \to \infty$ (force of infection is independent of bacteria dose in water and independent of infected cases). A similar result to that in Case 4 is applied here, with β_i replaced by β_p, so the EE exists unconditionally.

(6) $H_k \to 0$ for $k = p, i$, which implies $\lambda = \beta_p + \beta_i$ (force of infection is constant; that is, independent of human infected cases and bacteria density). A similar result to Case 4 is applied here, with β_i replaced by $\beta_i + \beta_p$, so the EE exists unconditionally.

(7) $H_p \to 0$ and $H_i \to h_i \notin \{0, \infty\}$.

(8) $H_p \to h_p \notin \{0, \infty\}$ and $H_i \to 0$.

(9) $H_k \to h_k \notin \{0, \infty\}$ for $k = p, i$.

It is hard to give an explicit formula for the EE in the last three cases, so the analysis of the EE will be given in general in Sec. 3.2.

Remark. Note that the importance of education is clear in the EE in Eq. (3.3), in which if $\psi_e \to 1$, then the EE does not exist.

3.1. *Stability of the DFE*

To study the stability of the DFE, we have the Jacobian matrix

$$J(E_0) = \begin{pmatrix} -\mu_h & -\frac{\Lambda}{\mu_h}(1-\psi_e)\frac{\beta_i}{H_i} & \alpha & -\frac{\Lambda}{\mu_h}(1-\psi_e)\frac{\beta_p}{H_p} \\ 0 & \frac{\Lambda}{\mu_h}(1-\psi_e)\frac{\beta_i}{H_i} - (\mu_h + \delta + \mu_d) & 0 & \frac{\Lambda}{\mu_h}(1-\psi_e)\frac{\beta_p}{H_p} \\ 0 & \delta & -(\alpha + \mu_h) & 0 \\ 0 & (1-\psi_e)\theta & 0 & b - \mu_p \end{pmatrix}, \tag{3.12}$$

which has the eigenvalues $\lambda = -\mu_h, -(\mu_h + \alpha)$ and the eigenvalues of the matrix

$$A = \begin{pmatrix} \frac{\Lambda}{\mu_h}(1-\psi_e)\frac{\beta_i}{H_i} - (\mu_h + \delta + \mu_d) & \frac{\Lambda}{\mu_h}(1-\psi_e)\frac{\beta_p}{H_p} \\ (1-\psi_e)\theta & b - \mu_p \end{pmatrix}. \tag{3.13}$$

Note that A has eigenvalues with negative real part if $\mathrm{tr}(A) < 0$ and $\det(A) > 0$. This occurs when

$$\mu_p - b > 0. \tag{3.14}$$

In this case,

$$R_0 \equiv \frac{\Lambda(1-\psi_e)}{\mu_h(\mu_h + \delta + \mu_d)} \left(\frac{\beta_i}{H_i} + \frac{(1-\psi_e)\beta_p\theta}{(\mu_p - b)H_p} \right). \tag{3.15}$$

Here, R_0 is the basic reproduction number.[20] R_0 is a useful threshold for disease eradication if there is a forward bifurcation at $R_0 = 1$.[21] This disease-threshold quantity, R_0, measures the average number of secondary cases generated by a single individual in a population of susceptibles at a demographic steady state. In models with only two steady states and a forward bifurcation, $R_0 > 1$ implies that the endemic state is stable (infection persists), and $R_0 < 1$ implies that the uninfected state is stable (infection is eliminated).

Remark. The limiting cases for the saturation constants can be related to R_0 as follows.

(a) $H_k \to \infty$ for $k = p, i$. In this case, $R_0 = 0$ and the DFE is locally asymptotically stable. This implies that, when infection is independent of the concentration of bacteria, the disease is under control.
(b) $H_p \to \infty$ and $H_i \to h_i \notin \{0, \infty\}$. In this case, $R_0 \equiv \frac{\Lambda(1-\psi_e)}{\mu_h(\mu_h+\delta+\mu_d)}\frac{\beta_i}{H_i}$. Moreover, the EE exists only for $R_0 > 1$. The proof of the second statement follows from Eq. (3.3), which implies that $I_e < 0$ for $R_0 < 1$, and $I_e > 0$ for $R_0 > 1$.

Theorem 3.1. *If* (3.14) *holds, then, for* $R_0 < 1$, *the DFE* E_0 *is locally asymptotically stable, and, for* $R_0 > 1$, E_0 *is unstable.*

Remark. If (3.14) does not hold, then $P(t) \not\to 0$ as $t \to \infty$, which means the disease persists in the absence of any other controls.

Note that $R_0 = 1$ is equivalent to $\beta_i(\mu_p - b)H_p + \beta_p\theta(1-\psi_e)H_i = \beta_c$, where $\beta_c \equiv \frac{\mu_h(\mu_h+\delta+\mu_d)}{\Lambda(1-\psi_e)}$.

Corollary 3.1. (1) *For* $\beta_i(\mu_p - b)H_p + \beta_p\theta(1-\psi_e)H_i < \beta_c$, *the DFE* E_0 *is locally asymptotically stable.*
(2) *For* $\beta_i(\mu_p - b)H_p + \beta_p\theta(1-\psi_e)H_i > \beta_c$, *the DFE* E_0 *is unstable.*

Theorem 3.2. *If* (3.14) *holds, then, for* $R_0 < 1$, *the DFE is globally asymptotically stable and unstable for* $R_0 > 1$.

Proof. We use the comparison theorem.[22] We have

$$\begin{bmatrix} I'(t) \\ P'(t) \end{bmatrix} = (F - V) \begin{bmatrix} I(t) \\ P(t) \end{bmatrix} + \begin{bmatrix} -\frac{\Lambda}{\mu_h}(1-\psi_e)\frac{\beta_i}{H_i} I(t) + \frac{\beta_i I(t)}{H_i + I(t)}(1-\psi_e)S(t) \\ -b\frac{P^2(t)}{K} \end{bmatrix}$$

$$\leq (F - V) \begin{bmatrix} I(t) \\ P(t) \end{bmatrix} \tag{3.16}$$

because $\frac{S(t)}{H_i + I(t)} \leq \frac{\Lambda}{\mu_h H_i}$ for t sufficiently large. Here

$$F - V = \begin{bmatrix} \frac{\Lambda}{\mu_h}(1-\psi_e)\frac{\beta_i}{H_i} - (\mu_h + \delta + \mu_d) & \frac{\Lambda}{\mu_h}(1-\psi_e)\frac{\beta_p}{H_p} \\ (1-\psi_e)\theta & b - \mu_p \end{bmatrix},$$

which has negative eigenvalues when $R_0 < 1$, which means $(I(t), P(t)) \to (0, 0)$ as $t \to \infty$. This implies that $(S(t), R(t)) \to (\frac{\Lambda}{\mu_h}, 0)$. The result follows. □

Thus R_0 has useful threshold properties.[21]

3.2. *Stability of the endemic equilibrium*

Theorem 3.3. *For $R_0 > 1$, if (3.14) holds, then any endemic equilibrium is locally stable.*

Proof. We utilize Theorem 4 in Ref. 23. First, note that the Jacobian matrix for the DFE has eigenvalues $\lambda = -\mu_h, -\mu_h - \alpha$, $b - \mu_p + \frac{\Lambda}{\mu_h}(1-\psi_e)\frac{\beta_i}{H_i} - (\mu_h + \delta + \mu_d)$ and 0, when $\beta_i(-b + \mu_p)H_p + \beta_p\theta(1-\psi_e)H_i = \beta_c$. Also, the zero eigenvalue has right eigenvector (u_1, u_2, u_3, u_4) and left eigenvector (v_1, v_2, v_3, v_4), where

$$u_1 = -\frac{(\mu_p - b)}{\theta(1-\psi_e)} u_4 \left(1 + \frac{\mu_d}{\mu_h} - \frac{\delta}{\theta(\alpha + \mu_h)}\right),$$

$$u_2 = \frac{(\mu_p - b)}{\theta(1-\psi_e)} u_4 \quad u_3 = \frac{\delta(\mu_p - b)}{\theta(\alpha + \mu_h)(1-\psi_e)} u_4,$$

and $u_4 > 0$ is free. Also, $v_1 = v_3 = 0$,

$$v_2 = \frac{\mu_h H_p(-b + \mu_p)}{\Lambda\beta_p(1-\psi_e)} v_4,$$

and $v_4 > 0$ is free. We have

$$\begin{aligned} a &= \sum_{i,j,k}^{n} v_k u_i u_j \frac{\partial^2 f_k}{\partial_{x_i}\partial_{x_j}}(E_0, \beta_c) \\ &= 2(1-\psi_e)\frac{\beta_i}{H_i} v_2 u_1 u_2 + 2(1-\psi_e)\frac{\beta_p}{H_p} v_2 u_1 u_4 - 2(1-\psi_e)\frac{\Lambda\beta_i}{\mu_h H_i^2} v_2 u_2^2 \\ &\quad - 2(1-\psi_e)\frac{\Lambda\beta_p}{\mu_h H_p^2} v_2 u_4^2 - 2\frac{b}{K} v_4 u_4^2 \\ &< 0, \end{aligned}$$

where E_0 is the DFE. This implies that (i) or (iv) in Theorem 4 of Ref. 23 are applicable. However, for $\beta < \beta_C$, E_0 is locally asymptotically stable. As a result, (iv) is the only applicable case. This means that when β changes from $\beta < \beta_C$ to $\beta > \beta_C$, E_0 changes from stable to unstable and any EE changes from negative to positive and becomes locally asymptotically stable. □

To summarize, we have analyzed the continuous chlorination model. We calculated the basic reproduction number and used it to prove global stability of the DFE and local stability of the EE.

4. Discrete Chlorination

Assume that chlorination reduces the pathogen population by a proportion ψ_r, satisfying $0 \leq \psi_r < 1$, and that it occurs at distinct times t_k $(k = 0, 1, 2, \ldots)$. We thus have a system of impulsive ODEs. That is, between impulses t_k, the continuous system (for $t \neq t_k$) is

$$\begin{aligned}
S'(t) &= \Lambda + \alpha R(t) - ((1-\psi_e)\lambda + \mu_h)S(t),\\
I'(t) &= (1-\psi_e)\lambda S(t) - (\mu_h + \delta + \mu_d)I(t),\\
R'(t) &= \delta I(t) - (\alpha + \mu_h)R(t),\\
P'(t) &= b\left(1 - \frac{P(t)}{K}\right)P(t) - \mu_p P(t) + (1-\psi_e)\theta I(t),
\end{aligned}$$

for $t \neq t_k$. For $t = t_k$ (the impulsive condition), we have

$$P^+ = (1-\psi_r)P^- \quad t = t_k. \tag{4.1}$$

Here $(\,)^+$ and $(\,)^-$ are the left and right limits at t_k.

Note that

$$I'(t) \leq I^* - (\mu_h + \delta + \mu_d)I(t), \tag{4.2}$$

with $I^* = \frac{\Lambda(1-\psi_e)(\beta_p+\beta_i)}{\mu_h}$, which implies

$$I(t) \leq I^{**} + (I(0) - I^{**})\exp(-(\mu_h + \delta + \mu_d)t), \tag{4.3}$$

with $I^{**} = \frac{I^*}{\mu_h+\delta+\mu_d}$. Note that, for large t, (4.3) implies that

$$I \leq I^{**} + \epsilon \equiv \hat{I}, \tag{4.4}$$

for some $0 < \epsilon \ll 1$. Then

$$P'(t) \leq (1-\psi_e)\theta\hat{I} - rP, \tag{4.5}$$

with $r = \mu_b - b$.

Now define

$$\hat{\Lambda} \equiv (1-\psi_e)\theta\hat{I}. \tag{4.6}$$

Therefore, the pathogen population at time t (for t and k large) is given by

$$P(t) \leq \frac{\hat{\Lambda}}{r}(1 - e^{-r(t-t_k)}) + P(t_k^+)e^{-r(t-t_k)}. \tag{4.7}$$

As a result, the pathogen population immediately before the $(k+1)$st chlorination time (for large k) satisfies

$$P(t_{k+1}) \leq \frac{\hat{\Lambda}}{r}(1 - e^{-r(t_{k+1}-t_k)}) + (1 - \psi_r)P(t_k^-)e^{-r(t_{k+1}-t_k)}. \tag{4.8}$$

Theorem 4.1. *Suppose that* (3.14) *holds. If chlorination occurs at fixed times* $\tau = t_{k+1} - t_k$ *(for* k *sufficiently large), then the fixed point of the recurrence relation* (4.8) *satisfies*

$$\tilde{P} \leq \frac{\hat{\Lambda}}{r}\left(1 - \frac{\psi_r e^{-r\tau}}{1 - (1 - \psi_r)e^{-r\tau}}\right). \tag{4.9}$$

Proof. Similar to Theorem 4.1 in Refs. 24 and 25, we can solve Eq. (4.8) sequentially. We have

$$P(t_n) \leq \frac{\hat{\Lambda}}{r}\left(1 - \sum_{i=1}^{n-1} \psi_r(1 - \psi_r)^{n-i-1}e^{-r(t_n-t_0)} - (1 - \psi_r)^{n-1}e^{-r(t_n-t_0)}\right)$$
$$+ (1 - \psi_r)^n P(0)e^{-r(t_n-t_0)}, \tag{4.10}$$

which is equivalent to

$$P(t_n) \leq \frac{\hat{\Lambda}}{r}\left(1 - \frac{\psi_r e^{-r\tau} - (1 - \psi_r)^{n-1}\psi_r e^{-r\tau}}{1 - (1 - \psi_r)e^{-r\tau}} - (1 - \psi_r)^{n-1}e^{-r\tau}\right)$$
$$+ (1 - \psi_r)^n P(0)e^{-rn\tau}. \tag{4.11}$$

This implies (4.9) as $n \to \infty$ because $0 \leq \psi_r < 1$. □

Remarks. (1) Suppose that (3.14) holds. Note that $\lim_{n\to\infty,\tau\to 0} P(t_n) = 0$, which means that the pathogen population tends to zero in the long run, as the period between chlorination events tends to zero.

(2) Note that if $\psi_e \to 1$ and (3.14) holds, then $\hat{\Lambda} \to 0$ (Eq. (4.6)) and $\lim_{n\to\infty} P(t_n) = 0$, which means that the pathogen population tends to zero in the long run, regardless of the time between chlorination events. This shows the important of education in controlling cholera.

Corollary 4.1. *Suppose that* (3.14) *holds. Then, to reduce the total pathogen population below a desired threshold* $\tilde{P}$*, the minimum chlorination effectiveness satisfies*

$$\tilde{\psi}_r = 1 - \left(1 - \frac{\hat{\Lambda}}{r\tilde{P}}(1 - e^{-r\tau})\right)e^{r\tau}. \tag{4.12}$$

Equivalently, the minimum chlorination period satisfies

$$\tilde{\tau} = -\frac{1}{r}\ln\left[\frac{\hat{\Lambda} - r\tilde{P}}{\hat{\Lambda} + r\tilde{P}(\psi_r - 1))}\right]. \tag{4.13}$$

Proof. See Corollary 4.3 of Ref. 24. In fact, as $n \to \infty$, the right-hand side of (4.11) tends to $\frac{\hat{\Lambda}}{r}(1 - \frac{\psi_r e^{-r\tau}}{1-(1-\psi_r)e^{-r\tau}})$. The result follows by solving

$$\frac{\hat{\Lambda}}{r}\left(1 - \frac{\psi_r e^{-r\tau}}{1-(1-\psi_r)e^{-r\tau}}\right) \leq \tilde{P}. \tag{4.14}$$

for $\tilde{\psi}_r$ and $\tilde{\tau}$ respectively. □

As a result, the minimal chlorination effectiveness and the minimal chlorination period can be found in terms of birth and death rates for both human and pathogen population, the carrying capacity for the pathogen population, chlorination and education effectiveness.

The next theorem follows via the same technique used to prove Theorem 4.4 of Smith? and Hove-Musekwa.[24]

Theorem 4.2. *Suppose that* (3.14) *holds and* k *is sufficiently large. Assume that chlorination occurs at non-fixed times and the two previous chlorination events are known. Then the population of the pathogen can be reduced below the threshold* $\tilde{P}$ *if the next chlorination event is applied at*

$$t_{k+1} \leq t_k - \frac{1}{r}\ln\left[\frac{2 - \psi_r - \frac{\tilde{P}r}{\hat{\Lambda}}}{1 + \psi_r(1-\psi_r)\exp(-r(t_k - t_{k-1}))}\right]. \tag{4.15}$$

Proof. From (4.10), we have

$$P(t_n^-) \leq \frac{\hat{\Lambda}}{r}\left(1 - e^{-r(t_n - t_0)}\right). \tag{4.16}$$

By substituting this in the left-hand side of (4.8), then solving it for t_{n+1} at the threshold value $\bar{P}$, the result follows. □

As in Theorem 4.5 of Smith? and Hove-Musekwa,[24] we can derive the "next best" chlorination events for non-fixed chlorination by assuming that the time between the current chlorination and three chlorination events previously is sufficiently large. The next theorem follows immediately from Ref. 24.

Theorem 4.3. *If non-fixed chlorination occurs indefinitely, then there exists a minimum chlorination effectiveness* r_0*, satisfying* $0 < r_0 < 1$*, such that variable chlorination is only effective for* $r_0 = r = 1$*. Furthermore, on this interval, the minimum chlorination interval for indefinite non-fixed chlorination is always less than the minimum chlorination interval for regular chlorination.*

As a result, the minimal chlorination effectiveness and the minimal chlorination period can be found in terms of human and bacteria birth and death rates for both

human and pathogen populations, the carrying capacity for the pathogen population, and chlorination and education effectiveness. Also, the "next best" chlorination event for non-fixed chlorination is derived, by assuming that the time between the current chlorination and three chlorination events previously is sufficiently large.

5. Numerical Results

In this section, we will study the sensitivity of R_0 to different parameters. For the purpose of simulations, we chose the initial conditions

$$(S(0), I(0), R(0), P(0)) = (990, 10, 0, 10^5)$$

to study the effect of education and discrete chlorination in the long run.

5.1. *Sensitivity analysis*

Due to the degree of uncertainty in the parameter values, we considered a range of parameters to examine the dependence of R_0 on parameter variation for the continuous chlorination model. We used Latin Hypercube sampling and partial rank correlation coefficients (PRCCs) to identify which parameters R_0 is most sensitive to.[26] Latin Hypercube Sampling is a statistical sampling method that evaluates sensitivity of an outcome variable to all input variables. PRCCs measure the relative degree of sensitivity to each parameter, regardless of whether the parameter has a positive or negative influence on the outcome variable.

Figure 3 plots PRCCs for each input parameter. This demonstrates that R_0 is most sensitive to variations in ψ_e, b and μ_p, respectively. Figure 4 shows that the disease is reliably controlled only for high education rates.

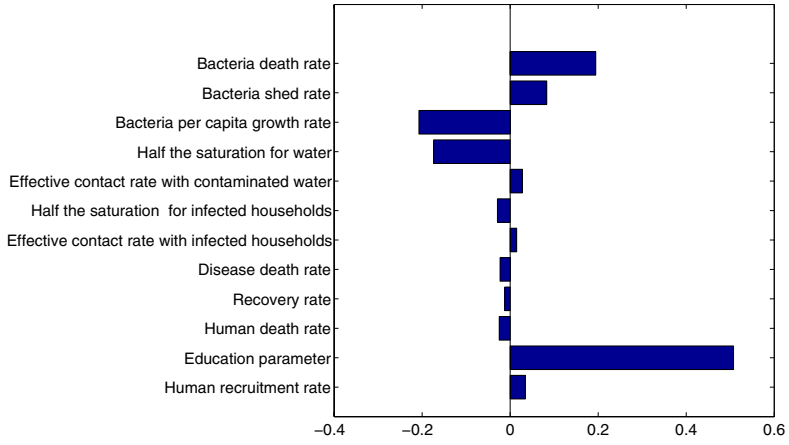


Fig. 3. Partial rank correlation coefficients indicate that education has the greatest effect on R_0 followed by the bacteria growth and death rates. Parameters with PRCCs > 0 will increase R_0 when they are increased, while parameters with PRCCs < 0 will decrease R_0 when they are increased.

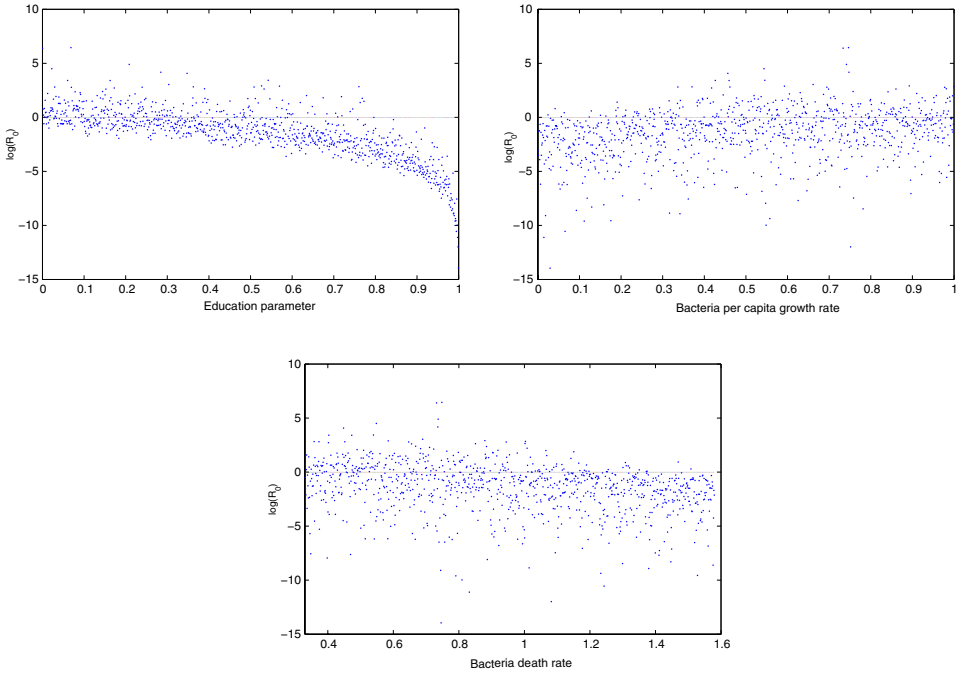
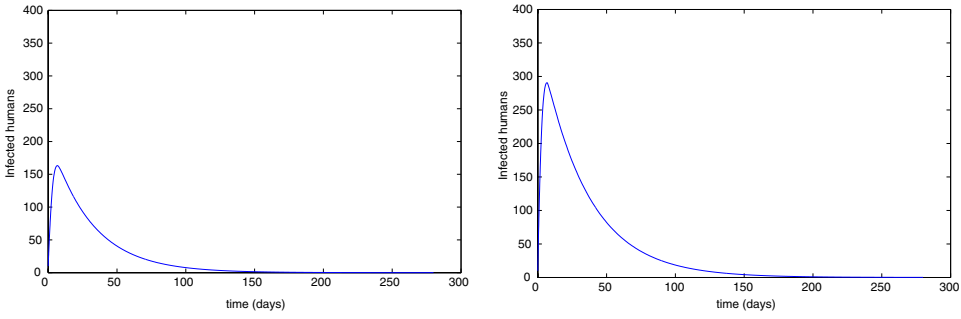
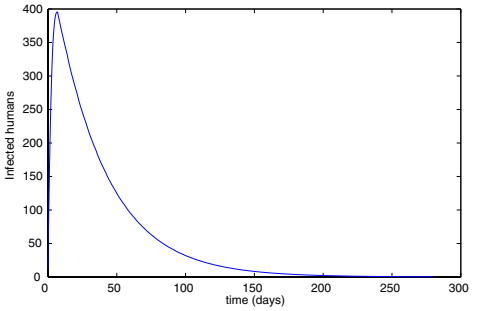


Fig. 4. Monte Carlo simulations for 1000 runs drawn from parameter ranges using Latin Hypercube Sampling for the three parameters with the greatest effect on R_0 as indicated in Fig. 3. If ψ_e is sufficiently close to one and the bacteria death rate is sufficiently large, then the disease can be controlled.



(a) (b)

Fig. 5. Number of infected individuals as a function of time when chlorination is applied weekly with $(\psi_e, \psi_r) = (0.75, 0.25), (0.5, 0.5)$ and $(0.25, 0.75)$ from (a) to (c) respectively. Education is more effictive than chlorination. Here we consider a growing population with $b = 0.75$ and $\mu_p = 0.6$.



(c)

Fig. 5. (*Continued*)

5.2. *Chlorination and education effect*

In Fig. 5, we investigate whether education or chlorination is more effective. Consequently, we investigate three scenarios: moderate education and low chlorination rates $(\psi_e, \psi_r) = (0.75, 0.25)$; medium education and chlorination $(\psi_e, \psi_r) = (0.5, 0.5)$; and low education and moderate chlorination $(\psi_e, \psi_r) = (0.25, 0.75)$. It is clear that education is more effective than chlorination in controlling the disease.

In Fig. 6, we plot the minimal effective chlorination period $\tilde{\tau}$ as a function of the chlorination parameter ψ_r. We found that the minimal effective chlorination period increases as the efficiency of chlorination increases.

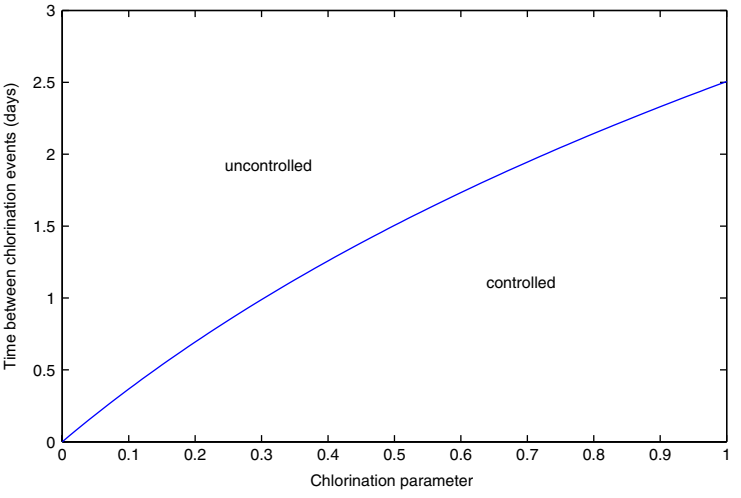


Fig. 6. Minimal effective chlorination period $\tilde{\tau}$ as a function of chlorination parameter ψ_r when we need to keep the concentration of bacteria less than or equal $0.25H_i$ per liter (equivalent to requiring that only 1/8 of the contacts produce disease). It is clear that the higher the chlorination rate, the bigger the minimum period of chlorination. Here $\psi_e = 0.6$.

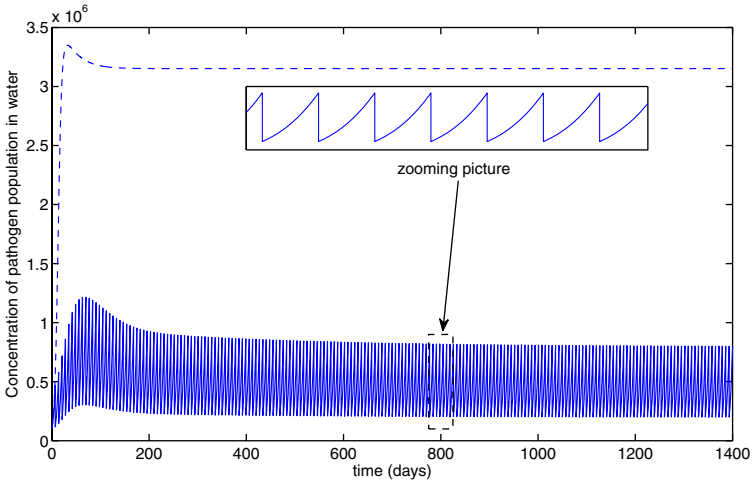


Fig. 7. Bacteria concentration P per liter as a function of time when there is no chlorination and no education (dashed curve) and bacteria concentration P per liter when 75% effective chlorination is applied weekly with $\psi_e = 0.6$ (solid curve). The concentration of bacteria is tracked for 1400 days (around four years).

In Fig. 7, we track the concentration of bacteria in water with time to show the effect of daily chlorination. It is clear that the concentration decreases over time.

6. Discussion

In our model, people are either susceptible, infected or recovered. Recovered individuals retain only temporary immunity before becoming susceptible again. *V. cholerae* grow logistically with a given carrying capacity. Susceptible individuals may become infected by drinking dirty water or by exposure to infected individuals. Education and chlorination are used to control the disease: the former by reducing the transmission rate, the latter by reducing the pathogen directly.

We proposed and investigated an impulsive mathematical model in an attempt to understand the effects of education and chlorination in controlling cholera. For the continuous model (no chlorination), the disease-free equilibrium is shown to be globally stable when the reproduction number is less than one. The comparison theorem is used to prove the global stability for the DFE. Center Manifold Theory is employed to show that if the endemic equilibrium exists then it is locally asymptotically stable when the reproduction number is greater than one and does not exist when the basic reproduction number is less than one. Moreover, some explicit values are given for the EE depending on some limiting values for saturation constants.

For the full impulsive model, we used classical methods to solve the impulsive ODEs. Values for the minimum effective chlorination times and the effective chlorination constants are given explicitly for fixed and variable chlorination. The minimum chlorination period is derived in terms of the model parameters. For

given values of the parameters, we showed that the effective chlorination time was 2.5 days. It should be noted that we considered the season in which bacteria are growing for our simulations (the most extreme case).

A sensitivity analysis of the basic reproduction number shows that it is most sensitive to education, the per capita birth rate and the death rate. The per capita birth rate is out of our control, but the death rate can be increased by chlorination. Reducing the concentration of bacteria (by education, sanitization and chlorination) below the thresholds H_p (inside water) and H_i (outside water) plays a major role in reducing the disease (Fig. 8).

It should be noted that chlorination and education are not the only methods of cholera control that have been successful. For example, cloth filters, employed in 65 rural Bangladeshi villages yielded a 48% reduction in cholera compared to the control.[27] Boiling water before drinking is also effective, as it kills waterborne pathogenic microoganisms[28]; however, this is not always possible in rural locations.[27]

Our model has some limitations, which should be noted. One limitation is the estimation of the parameters, a number of which were assumed. Our model also ignored some important factors like nutrition and environmental factors, which may play a role in the promotion of disease among poor communities.[29] For example, the disease is more fatal for poor children and for those with inadequate nursing. We also conflated the effect of household sensitizing and cleaning into the saturation constants. Direct education was considered uniform and applied equally to human and pathogen contact. The population mixing pattern, which plays a major role on

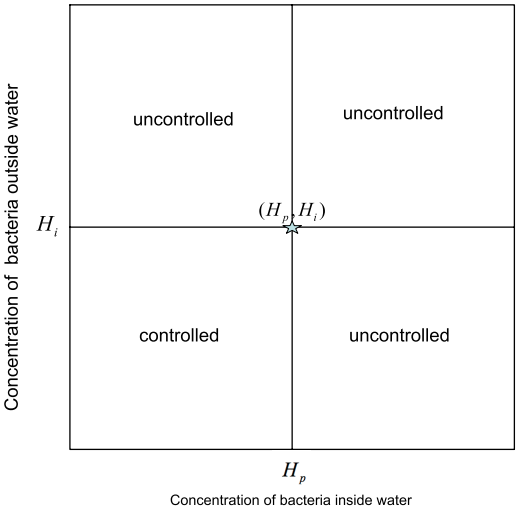


Fig. 8. Cartesian plane with the x-axis representing bacteria concentration in water and the y-axis representing bacteria concentration outside water. H_p and H_i are the half-saturation constants. The first quadrant is divided into four regions depending on the ability to control the disease.

disease spread and control, is assumed homogeneous; however, this limitation could be improved by considering heterogeneous mixing.

In summary, any program to control cholera should consider both chlorination and education. Education, both direct and indirect, is a critical factor in cholera control that has a greater and longer-lasting effect on disease management than technological interventions such as chlorination. Education should therefore target both human-to-human contact and also the intake of pathogen material. We thus recommend that any cholera-control program be developed in collaboration with culturally specific population-level education of susceptible and infected individuals.

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