

DYNAMICS OF AN AGE-OF-INFECTION CHOLERA MODEL

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In honour of the 60th birthday of our friend and colleague Carlos Castillo-Chavez

ABSTRACT. A new model for the dynamics of cholera is formulated that incorporates both the infection age of infectious individuals and biological age of pathogen in the environment. The basic reproduction number is defined and proved to be a sharp threshold determining whether or not cholera dies out. Final size relations for cholera outbreaks are derived for simplified models when input and death are neglected.

1. **Introduction.** Cholera is a diarrheal disease caused by the bacterium *Vibrio cholerae*, which leads to infection in the small intestine of humans. Although infection is mostly mild, in some cases it may develop into severe diarrhea and vomiting that if untreated may lead to death within a few hours due to dehydration and electrolyte imbalance. The World Health Organization estimates 3-5 million cholera cases per year with 100,000 deaths spread over 40-50 countries [26]; for example, the recent outbreaks in Haiti [6, 8, 22], Zimbabwe [13, 17, 25], and Angola [24] have led to a large number of infections and received worldwide attention. Like other waterborne diseases, cholera has multiple transmission pathways: it can be transmitted directly to humans by person-to-person contact or indirectly to humans via contaminated water. Tien and Earn [21] propose a system of ordinary differential equations (ODEs) to model the spread of waterborne diseases incorporating both direct and indirect transmission. They also propose a staged progression model to incorporate multiple stages of infectious individuals due to differential infectivity in direct transmission. Differential infectivity is also important for indirect transmission; for example, laboratory studies suggest hyperinfectivity of freshly shed pathogen [9]. Hence it is important in modelling cholera to track both the infection age of infectious individuals and age of pathogen. These features can be incorporated in a multi-stage ODE model [18] by taking compartments for multiple stages of infectious individuals and multiple infectious states of pathogen.

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Age structure is also an important characteristic in the modeling of other infectious diseases. In general, there are two different age structures in disease models: biological age and infection age. Correspondingly, two types of age-related models exist in the literature; that is, age-structured models (see, e.g., [7, 23]) and age-of-infection models (see, e.g., [5, Section 2.4], [19, Chapter 9] and [20]). These age-related models are normally in the form of partial differential equations (PDEs) or integro-differential equations (IDEs), and their dynamical analyses are particularly challenging. Due to this challenge in mathematical analysis, staged progression/multi-stage ODE models that consist of multiple-stage compartments are commonly used in the literature to approximate these PDE/IDE models, such as the multi-stage cholera models mentioned above and models for HIV infection (e.g., see [12]).

In this paper, a PDE cholera model is formulated that incorporates simultaneously the age-of-infection structure of individuals and the age structure of pathogen with infectivities given by kernel functions. To the best of our knowledge, this is the first cholera model including the infection age of individuals. Our model is different from the one proposed in [1], which incorporates the biological age of individuals in modeling cholera. For our cholera model, the basic reproduction number \mathcal{R}_0 is defined and proved to be a sharp threshold determining whether or not the disease dies out (see Theorem 3.1). Specifically, if $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium is globally asymptotically stable, and cholera dies out; whereas if $\mathcal{R}_0 > 1$, then there exists a unique endemic equilibrium that is globally asymptotically stable, and the disease persists at the endemic level. The global stability for these equilibria is proved by constructing suitable Lyapunov functionals as in [11, 15].

This paper is organized as follows. In Section 2 we formulate the PDE cholera model. In Section 3 we study equilibria, calculate the basic reproduction number \mathcal{R}_0 , and state our main result (Theorem 3.1). The proof of Theorem 3.1 is given in Sections 4 and 5. In Section 6 final size relations are derived for simplified models when input and death are neglected. We conclude in Section 7 with a discussion.

2. Formulation of the model. Let $S(t)$ denote the number of susceptible individuals at time $t \geq 0$, $i(t, a)$ denote the number of infected individuals of infection age $a \geq 0$ at time t , and $p(t, b)$ denote the quantity of pathogen of age $b \geq 0$ at time t in the contaminated water. Consider a PDE cholera model for $t > 0$

$$\begin{aligned} \frac{dS(t)}{dt} &= A - \mu S(t) - \beta_d S(t) \int_0^\infty k(a) i(t, a) da - \beta_i S(t) \int_0^\infty q(b) p(t, b) db, \\ \left(\frac{\partial}{\partial a} + \frac{\partial}{\partial t} \right) i(t, a) &= -\theta(a) i(t, a), \quad a > 0, \\ \left(\frac{\partial}{\partial b} + \frac{\partial}{\partial t} \right) p(t, b) &= -\delta(b) p(t, b), \quad b > 0, \end{aligned} \tag{2.1}$$

with boundary conditions

$$\begin{aligned} i(t, 0) &= \beta_d S(t) \int_0^\infty k(u) i(t, u) du + \beta_i S(t) \int_0^\infty q(v) p(t, v) dv, \quad t > 0, \\ p(t, 0) &= \int_0^\infty \xi(u) i(t, u) du, \quad t > 0, \end{aligned}$$

and initial conditions

$$S(0) = S_0 > 0, \quad i(0, a) = i_0(a) \in L_+^1(0, \infty), \quad p(0, b) = p_0(b) \in L_+^1(0, \infty).$$

$S^*, i^*(a), p^*(b)$ are positive and satisfy the following equilibrium equations

$$\begin{aligned}
 A - \mu S^* - \beta_d S^* \int_0^\infty k(a) i^*(a) da - \beta_i S^* \int_0^\infty q(b) p^*(b) db &= 0, \\
 \frac{d}{da} i^*(a) &= -\theta(a) i^*(a), \\
 \frac{d}{db} p^*(b) &= -\delta(b) p^*(b), \\
 i^*(0) &= \beta_d S^* \int_0^\infty k(u) i^*(u) du + \beta_i S^* \int_0^\infty q(v) p^*(v) dv, \\
 p^*(0) &= \int_0^\infty \xi(u) i^*(u) du.
 \end{aligned}
 \tag{3.1}$$

Solving the second and third equations of (3.1) yields

$$i^*(a) = i^*(0) e^{-\int_0^a \theta(w) dw} \tag{3.2}$$

and

$$p^*(b) = p^*(0) e^{-\int_0^b \delta(w) dw} = e^{-\int_0^b \delta(w) dw} \int_0^\infty \xi(u) i^*(u) du. \tag{3.3}$$

Plugging (3.2)-(3.3) into the $i^*(0)$ equation in (3.1) gives

$$\begin{aligned}
 i^*(0) &= \beta_d S^* \int_0^\infty k(u) i^*(0) e^{-\int_0^u \theta(w) dw} du \\
 &\quad + \beta_i S^* \int_0^\infty q(v) \left(\int_0^\infty \xi(u) i^*(0) e^{-\int_0^u \theta(w) dw} du \right) e^{-\int_0^v \delta(w) dw} dv.
 \end{aligned}$$

Solving S^* from the above equality gives

$$S^* = \frac{1}{\beta_d K + \beta_i X Q},$$

where

$$K = \int_0^\infty k(u) e^{-\int_0^u \theta(w) dw} du, \quad X = \int_0^\infty \xi(u) e^{-\int_0^u \theta(w) dw} du,$$

and

$$Q = \int_0^\infty q(v) e^{-\int_0^v \delta(w) dw} dv.$$

System (2.1) has a unique endemic equilibrium $P^* = (S^*, i^*(a), p^*(b))$ iff $\mathcal{R}_0 > 1$, where

$$\mathcal{R}_0 = \beta_d S^0 K + \beta_i S^0 X Q, \tag{3.4}$$

$S^* = \frac{S^0}{\mathcal{R}_0}, i^*(a) = A \left(1 - \frac{1}{\mathcal{R}_0}\right) e^{-\int_0^a \theta(w) dw} > 0$, and $p^*(b) = e^{-\int_0^b \delta(w) dw} \int_0^\infty \xi(u) i^*(u) du$. In the expression for \mathcal{R}_0 , the first term represents new infections transmitted directly by a single infectious individual inserted into a totally susceptible population, while the second term represents secondary infections caused by this individual indirectly through shedding of pathogen. Thus \mathcal{R}_0 is the basic reproduction number for model (2.1).

The following result shows that the basic reproduction number \mathcal{R}_0 serves as a sharp threshold parameter, completely determining the global dynamics of (2.1). Biologically, if $\mathcal{R}_0 \leq 1$, then the disease dies out eventually; whereas if $\mathcal{R}_0 > 1$, then the disease persists at the unique endemic equilibrium level.

Theorem 3.1. Consider model (2.1) with \mathcal{R}_0 defined in (3.4).

- (a) The disease-free equilibrium P^0 is globally asymptotically stable if $\mathcal{R}_0 \leq 1$ while unstable if $\mathcal{R}_0 > 1$.
- (b) If $\mathcal{R}_0 > 1$, the endemic equilibrium P^* is global asymptotically stable with respect to solutions with initial conditions $S_0 > 0$ and $i_0(a), p_0(b) > 0$ bounded away from zero.

The proof of Theorem 3.1 is given in Sections 4 and 5 by constructing suitable Lyapunov functionals.

4. Global stability of the disease-free equilibrium. In this section, we study the global stability of the disease-free equilibrium P^0 , providing a proof for Theorem 3.1-(a).

Following [11], construct a Lyapunov functional $L = L_1 + L_2 + L_3$, where $L_1 = S - S^0 - S^0 \ln \frac{S}{S^0}$, $L_2 = \int_0^\infty \Phi(a)i(t, a) da$, $L_3 = \int_0^\infty \Psi(b)p(t, b) db$. Here nonnegative kernel functions $\Phi(a)$ and $\Psi(b)$ will be determined later. Using (3.1), differentiation of L_1 along the solutions of (2.1) yields

$$\begin{aligned} L_1' &= \frac{S - S^0}{S} \left(\mu S^0 - \mu S - \beta_d S \int_0^\infty k(a)i(t, a) da - \beta_i S \int_0^\infty q(b)p(t, b) db \right) \\ &= -\frac{\mu}{S} (S - S^0)^2 - \beta_d S \int_0^\infty k(a)i(t, a) da - \beta_i S \int_0^\infty q(b)p(t, b) db \\ &\quad + \beta_d S^0 \int_0^\infty k(a)i(t, a) da + \beta_i S^0 \int_0^\infty q(b)p(t, b) db \\ &= -\frac{\mu}{S} (S - S^0)^2 - i(t, 0) + \beta_d S^0 \int_0^\infty k(a)i(t, a) da + \beta_i S^0 \int_0^\infty q(b)p(t, b) db. \end{aligned}$$

Using (2.2), L_2 becomes

$$\begin{aligned} L_2 &= \int_0^t \Phi(a)i(t - a, 0)e^{-\int_0^a \theta(w) dw} da + \int_t^\infty \Phi(a)i_0(a - t)e^{-\int_{a-t}^a \theta(w) dw} da \\ &= \int_0^t \Phi(t - r)i(r, 0)e^{-\int_0^{t-r} \theta(w) dw} dr + \int_0^\infty \Phi(t + r)i_0(r)e^{-\int_r^{t+r} \theta(w) dw} dr. \end{aligned}$$

Differentiation yields

$$\begin{aligned} L_2' &= \Phi(0)i(t, 0) + \int_0^t \Phi'(t - r)i(r, 0)e^{-\int_0^{t-r} \theta(w) dw} dr \\ &\quad - \int_0^t \Phi(t - r)i(r, 0)\theta(t - r)e^{-\int_0^{t-r} \theta(w) dw} dr \\ &\quad + \int_0^\infty \Phi'(t + r)i_0(r)e^{-\int_r^{t+r} \theta(w) dw} dr \\ &\quad - \int_0^\infty \Phi(t + r)i_0(r)\theta(t + r)e^{-\int_r^{t+r} \theta(w) dw} dr \\ &= \Phi(0)i(t, 0) + \int_0^\infty \left(\Phi'(a) - \theta(a)\Phi(a) \right) i(t, a) da. \end{aligned}$$

The last equality follows from (2.2). Similarly, using (2.3),

$$L_3' = \Psi(0) \int_0^\infty \xi(u)i(t, u) du + \int_0^\infty \left(\Psi'(b) - \delta(b)\Psi(b) \right) p(t, b) db.$$

Adding L'_1 , L'_2 and L'_3 together gives

$$\begin{aligned} L' &= -\frac{\mu}{S}(S - S^0)^2 - i(t, 0) + \Phi(0)i(t, 0) \\ &\quad + \int_0^\infty \left(\beta_d S^0 k(a) + \Phi'(a) - \theta(a)\Phi(a) + \Psi(0)\xi(a) \right) i(t, a) da \\ &\quad + \int_0^\infty \left(\beta_i S^0 q(b) + \Psi'(b) - \delta(b)\Psi(b) \right) p(t, b) db. \end{aligned}$$

Now let

$$\Psi(b) = \int_b^\infty \beta_i S^0 q(v) e^{-\int_b^v \delta(w) dw} dv,$$

and

$$\Phi(a) = \int_a^\infty \left(\beta_d S^0 k(u) + \Psi(0)\xi(u) \right) e^{-\int_a^u \theta(w) dw} du.$$

By differentiating the above equations, it can be verified that

$$\beta_i S^0 q(b) + \Psi'(b) - \delta(b)\Psi(b) = 0,$$

$$\beta_d S^0 k(a) + \Phi'(a) - \theta(a)\Phi(a) + \Psi(0)\xi(a) = 0.$$

Also notice that $\Psi(0) = \beta_i S^0 Q$ and

$$\Phi(0) = \int_0^\infty \beta_d S^0 k(u) e^{-\int_0^u \theta(w) dw} du + \Psi(0) \int_0^\infty \xi(u) e^{-\int_0^u \theta(w) dw} du = \mathcal{R}_0.$$

Hence, it follows that

$$L' = -\frac{\mu}{S}(S - S^0)^2 - (1 - \mathcal{R}_0)i(t, 0) \leq 0 \quad \text{if } \mathcal{R}_0 \leq 1. \tag{4.1}$$

Notice that $L' = 0$ implies that $S = S^0$. It can be verified that the largest invariant set where $L' = 0$ is the singleton $\{P^0\}$. Therefore, by the Lyapunov-LaSalle asymptotic stability theorem, the disease-free equilibrium P^0 is globally asymptotically stable if $\mathcal{R}_0 \leq 1$.

If $\mathcal{R}_0 > 1$, then by continuity and (4.1), $L' > 0$ in a neighborhood of P^0 . Positive solutions of (2.1) close to P^0 move away from P^0 , implying that P^0 is unstable.

5. Global stability of the endemic equilibrium. In this section we provide a proof for Theorem 3.1-(b). Assume $\mathcal{R}_0 > 1$, then there exists a unique endemic equilibrium $P^* = (S^*, i^*(a), p^*(b))$, where $S^*, i^*(a), p^*(b)$ satisfy the equilibrium equations (3.1). Define $G(x, y) := x - y - y \ln \frac{x}{y}$ for $x, y > 0$. Construct a Lyapunov functional $V = V_1 + V_2 + V_3$ with $V_1 = G(S, S^*)$, $V_2 = \int_0^\infty \Phi(a)G(i(t, a), i^*(a)) da$, and $V_3 = \int_0^\infty \Psi(b)G(p(t, b), p^*(b)) db$. Here nonnegative functions $\Psi(b)$ and $\Phi(a)$ satisfy

$$\Psi(b) = \int_b^\infty \beta_i S^* q(v) e^{-\int_b^v \delta(w) dw} dv, \tag{5.1}$$

and

$$\Phi(a) = \int_a^\infty \left(\beta_d S^* k(u) + \Psi(0)\xi(u) \right) e^{-\int_a^u \theta(w) dw} du, \tag{5.2}$$

respectively. The Lyapunov functional V defined above is of the same type as those in [11, 15].

The following lemmas evaluate the derivatives of V_1 , V_2 and V_3 along the solutions of (2.1), respectively.

Lemma 5.1. *Let $V_1 = G(S, S^*)$ be defined as above. Then*

$$V_1' = -\frac{\mu}{S}(S - S^*)^2 + i^*(0) - i(t, 0) - i^*(0)\frac{S^*}{S} + i(t, 0)\frac{S^*}{S}. \tag{5.3}$$

Proof. Using the equilibrium equations (3.1), differentiating V_1 along the solutions of (2.1) gives

$$\begin{aligned} V_1' &= \frac{S - S^*}{S}(A - \mu S - i(t, 0)) = \frac{S - S^*}{S}(\mu S^* + i^*(0) - \mu S - i(t, 0)) \\ &= -\frac{\mu}{S}(S - S^*)^2 + i^*(0) - i(t, 0) - i^*(0)\frac{S^*}{S} + i(t, 0)\frac{S^*}{S}. \end{aligned}$$

□

Lemma 5.2. *Let $V_2 = \int_0^\infty \Phi(a)G(i(t, a), i^*(a)) da$. Then*

$$V_2' = \Phi(0)G(i(t, 0), i^*(0)) + \int_0^\infty (\Phi'(a) - \theta(a)\Phi(a))G(i(t, a), i^*(a)) da.$$

Proof. Using (2.2), rewrite

$$\begin{aligned} V_2 &= \int_0^t \Phi(a) G\left(i(t - a, 0)e^{-\int_0^a \theta(w) dw}, i^*(a)\right) da \\ &\quad + \int_t^\infty \Phi(a) G\left(i_0(a - t)e^{-\int_{a-t}^a \theta(w) dw}, i^*(a)\right) da \\ &= \int_0^t \Phi(t - r) G\left(i(r, 0)e^{-\int_0^{t-r} \theta(w) dw}, i^*(t - r)\right) dr \\ &\quad + \int_0^\infty \Phi(t + r) G\left(i_0(r)e^{-\int_r^{t+r} \theta(w) dw}, i^*(t + r)\right) dr. \end{aligned}$$

Differentiation and using (3.2) yield

$$\begin{aligned} V_2' &= \Phi(0)G(i(t, 0), i^*(0)) + \int_0^t \Phi'(t - r) G\left(i(r, 0)e^{-\int_0^{t-r} \theta(w) dw}, i^*(t - r)\right) dr \\ &\quad - \int_0^t \Phi(t - r)\theta(t - r) \left[i(r, 0)e^{-\int_0^{t-r} \theta(w) dw} G_x\left(i(r, 0)e^{-\int_0^{t-r} \theta(w) dw}, i^*(t - r)\right) \right. \\ &\quad \left. + i^*(t - r)G_y\left(i(r, 0)e^{-\int_0^{t-r} \theta(w) dw}, i^*(t - r)\right) \right] dr \\ &\quad + \int_0^\infty \Phi'(t + r) G\left(i_0(r)e^{-\int_r^{t+r} \theta(w) dw}, i^*(t + r)\right) dr \\ &\quad - \int_0^\infty \Phi(t + r)\theta(t - r) \left[i_0(r)e^{-\int_r^{t+r} \theta(w) dw} G_x\left(i_0(r)e^{-\int_r^{t+r} \theta(w) dw}, i^*(t + r)\right) \right. \\ &\quad \left. + i^*(t + r)G_y\left(i_0(r)e^{-\int_r^{t+r} \theta(w) dw}, i^*(t + r)\right) \right] dr \\ &= \Phi(0)G(i(t, 0), i^*(0)) + \int_0^\infty (\Phi'(a) - \theta(a)\Phi(a))G(i(t, a), i^*(a)) da. \end{aligned}$$

The last equality follows from (2.2) and the fact that $xG_x(x, y) + yG_y(x, y) = G(x, y)$. □

Lemma 5.3. *Let $V_3 = \int_0^\infty \Psi(a)G(p(t, a), p^*(a)) da$. Then*

$$V_3' = \Psi(0)G(p(t, 0), p^*(0)) + \int_0^\infty (\Psi'(a) - \delta(a)\Psi(a))G(p(t, a), p^*(a)) da.$$

The proof for Lemma 5.3 is similar to the one for Lemma 5.2 and thus is omitted.

It follows from (5.1) and (5.2) that

$$\Psi(b)\delta(b) - \Psi'(b) = \beta_i S^* q(b), \tag{5.4}$$

and

$$\Phi(a)\theta(a) - \Phi'(a) = \beta_d S^* k(a) + \Psi(0)\xi(a). \tag{5.5}$$

Also notice that $\Psi(0) = \beta_i S^* Q$ and $\Phi(0) = \beta_d S^* K + \beta_i S^* QX = S^* \frac{R_0}{S_0} = 1$. Hence by Lemmas 5.2, 5.3 and equalities (5.4)-(5.5)

$$\begin{aligned} V'_2 &= \int_0^\infty \left(\beta_d S^* k(a) + \Psi(0)\xi(a) \right) \left(i^*(a) - i(t, a) + i^*(a) \ln \frac{i(t, a)}{i^*(a)} \right) da \\ &\quad + i(t, 0) - i^*(0) - i^*(0) \ln \frac{i(t, 0)}{i^*(0)}, \end{aligned} \tag{5.6}$$

and

$$\begin{aligned} V'_3 &= \int_0^\infty \beta_i S^* q(b) \left(p^*(b) - p(t, b) + p^*(b) \ln \frac{p(t, b)}{p^*(b)} \right) db \\ &\quad + \beta_i S^* Q \left(p(t, 0) - p^*(0) - p^*(0) \ln \frac{p(t, 0)}{p^*(0)} \right). \end{aligned} \tag{5.7}$$

Hence, adding (5.3), (5.6)-(5.7) together yields

$$\begin{aligned} V' &= -\frac{\mu}{S}(S - S^*)^2 - i^*(0)\frac{S^*}{S} + i(t, 0)\frac{S^*}{S} + \int_0^\infty \beta_d S^* k(a) \left(i^*(a) - i(t, a) \right. \\ &\quad \left. + i^*(a) \ln \frac{i(t, a)}{i^*(a)} \right) da + \beta_i S^* Q \int_0^\infty \xi(a) i^*(a) \ln \frac{i(t, a)}{i^*(a)} da - i^*(0) \ln \frac{i(t, 0)}{i^*(0)} \\ &\quad + \int_0^\infty \beta_i S^* q(b) \left(p^*(b) - p(t, b) + p^*(b) \ln \frac{p(t, b)}{p^*(b)} \right) db - \beta_i S^* Q p^*(0) \ln \frac{p(t, 0)}{p^*(0)} \\ &= -\frac{\mu}{S}(S - S^*)^2 - i^*(0)\frac{S^*}{S} + i^*(0) + \int_0^\infty \beta_d S^* k(a) i^*(a) \ln \frac{i(t, a)}{i^*(a)} da \\ &\quad + \beta_i S^* Q \int_0^\infty \xi(a) i^*(a) \ln \frac{i(t, a)}{i^*(a)} da - i^*(0) \ln \frac{i(t, 0)}{i^*(0)} \\ &\quad + \int_0^\infty \beta_i S^* q(b) p^*(b) \ln \frac{p(t, b)}{p^*(b)} db - \beta_i S^* Q p^*(0) \ln \frac{p(t, 0)}{p^*(0)} \\ &= -\frac{\mu}{S}(S - S^*)^2 + \beta_d S^* \int_0^\infty k(a) i^*(a) \left(1 - \frac{S^*}{S} + \ln \frac{i(t, a)}{i^*(a)} - \ln \frac{i(t, 0)}{i^*(0)} \right) da \\ &\quad + \beta_i S^* \int_0^\infty q(b) p^*(b) \left(1 - \frac{S^*}{S} + \ln \frac{p(t, b)}{p^*(b)} - \ln \frac{i(t, 0)}{i^*(0)} \right) db \\ &\quad + \beta_i S^* Q \int_0^\infty \xi(a) i^*(a) \left(\ln \frac{i(t, a)}{i^*(a)} - \ln \frac{p(t, 0)}{p^*(0)} \right) da. \end{aligned} \tag{5.8}$$

Notice that

$$\begin{aligned} &\beta_i S^* Q \int_0^\infty \xi(a) i^*(a) \left(1 - \frac{i(t, a) p^*(0)}{i^*(a) p(t, 0)} \right) da \\ &= \beta_i S^* Q \left(\int_0^\infty \xi(a) i^*(a) da - \frac{p^*(0)}{p(t, 0)} \int_0^\infty \xi(a) i(t, a) da \right) \\ &= \beta_i S^* Q \left(p^*(0) - \frac{p^*(0)}{p(t, 0)} p(t, 0) \right) \\ &= 0, \end{aligned} \tag{5.9}$$

and

$$\begin{aligned}
 & \beta_d S^* \int_0^\infty k(a) i^*(a) \left(1 - \frac{S i^*(0) i(t, a)}{S^* i(t, 0) i^*(a)}\right) da \\
 & \quad + \beta_i S^* \int_0^\infty q(b) p^*(b) \left(1 - \frac{S i^*(0) p(t, b)}{S^* i(t, 0) p^*(b)}\right) db \\
 & = \beta_d S^* \int_0^\infty k(a) i^*(a) da + \beta_i S^* \int_0^\infty q(b) p^*(b) db - \frac{i^*(0)}{i(t, 0)} \beta_d S \int_0^\infty k(a) i(t, a) da \\
 & \quad - \frac{i^*(0)}{i(t, 0)} \beta_i S \int_0^\infty q(b) p(t, b) db \\
 & = i^*(0) - \frac{i^*(0)}{i(t, 0)} i(t, 0) \\
 & = 0.
 \end{aligned} \tag{5.10}$$

Adding (5.8), (5.9) and (5.10) together yields

$$\begin{aligned}
 V' & = -\frac{\mu}{S} (S - S^*)^2 \\
 & + \beta_d S^* \int_0^\infty k(a) i^*(a) \left(1 - \frac{S^*}{S} + \ln \frac{S^*}{S} + 1 - \frac{S i^*(0) i(t, a)}{S^* i(t, 0) i^*(a)} + \ln \frac{S i^*(0) i(t, a)}{S^* i(t, 0) i^*(a)}\right) da \\
 & + \beta_i S^* \int_0^\infty q(b) p^*(b) \left(1 - \frac{S^*}{S} + \ln \frac{S^*}{S} + 1 - \frac{S i^*(0) p(t, b)}{S^* i(t, 0) p^*(b)} + \ln \frac{S i^*(0) p(t, b)}{S^* i(t, 0) p^*(b)}\right) db \\
 & + \beta_i S^* Q \int_0^\infty \xi(a) i^*(a) \left(1 - \frac{i(t, a) p^*(0)}{i^*(a) p(t, 0)} + \ln \frac{i(t, a) p^*(0)}{i^*(a) p(t, 0)}\right) da \\
 & \leq 0,
 \end{aligned}$$

since $1 - x + \ln x \leq 0$ for all $x > 0$ with equality holding iff $x = 1$. Hence, $V' = 0$ implies that $S = S^*$ and

$$\frac{i(t, a)}{i^*(a)} = \frac{p(t, b)}{p^*(b)} = \frac{i(t, 0)}{i^*(0)}, \quad \text{for all } a, b \geq 0.$$

It can be verified that the largest invariant set where $V' = 0$ is the singleton $\{P^*\}$. Therefore, if $\mathcal{R}_0 > 1$, then it follows that P^* is globally asymptotically stable with respect to solutions with initial conditions $S_0 > 0$ and $i_0(a), p_0(b) > 0$ bounded away from zero.

Note that for the proof of the global asymptotic stability of the endemic equilibrium (Theorem 3.1 (b)), we assumed that $i_0(a)$ and $p_0(b)$ are bounded away from zero. For biological realism it is important to weaken this assumption to positivity of $i_0(a)$ and $p_0(b)$. We believe that the same result would still hold, but verification remains open.

6. Final size relations. In this section we first study the final size problem for a simplified version of (2.1), then extend the result to a staged progression model. Similar final size relations for a waterborne disease outbreak are derived by Tien and Earn [21] using different methods. We refer readers to [2, 3, 14] for final size relations of age-of-infection models for directly transmitted diseases.

6.1. A simple epidemic model. Let $\varphi(t) = \int_0^\infty k(u) i(t, u) du$ and $\psi(t) = \int_0^\infty q(v) p(t, v) dv$ represent the total infectivity of individuals with age of infection t and the total infectivity of the pathogen that was first present t time units ago (i.e., with

pathogen age t), respectively. In the absence of recruitment and death (that is, $A = \mu = 0$ and $\alpha(a) = 0$ for all a) and using (2.2)-(2.3), (2.1) becomes

$$\begin{aligned} \frac{dS(t)}{dt} &= S'(t) = -S(t)[\beta_d\varphi(t) + \beta_i\psi(t)], \\ \varphi(t) &= \varphi_0(t) + \int_0^t [-S'(t-u)]P(u) du, \\ \psi(t) &= \psi_0(t) + \int_0^t r(t-u)\varphi(t-u)Q(u) du. \end{aligned} \tag{6.1}$$

Here $\varphi_0(t) = \int_t^\infty k(u)i_0(u-t)e^{-\int_{u-t}^u \gamma(w) dw} du$ represents the total infectivity of individuals at time t who were already infected at $t = 0$, $\psi_0(t) = \int_t^\infty q(v)p_0(v-t)e^{-\int_{v-t}^v \delta(w) dw} dv$ represents the total infectivity of pathogen at time t that was already present at time $t = 0$,

$$P(u) = k(u)e^{-\int_0^u \gamma(w) dw}, \quad Q(u) = q(u)e^{-\int_0^u \delta(w) dw}, \tag{6.2}$$

and $r(t)\varphi(t) = \int_0^\infty \xi(u)i(t,u) du$. Assume that $\xi(u) = rk(u)$ with $r > 0$; biologically, this assumes that for infectious individuals, the strength/ability of shedding pathogen is proportional to the infectivity. It follows that $r(t) \equiv r$, thus model (6.1) becomes

$$\begin{aligned} S'(t) &= -S(t)[\beta_d\varphi(t) + \beta_i\psi(t)] \\ \varphi(t) &= \varphi_0(t) + \int_0^t [-S'(t-u)]P(u) du \\ \psi(t) &= \psi_0(t) + \int_0^t r\varphi(t-u)Q(u) du. \end{aligned} \tag{6.3}$$

This model describes a single outbreak (epidemic) of cholera, rather than the long term dynamics. We comment that the final size relations derived in this section hold for model (6.3) with more general kernel functions $P(u)$ and $Q(u)$. For example, $P(u), Q(u)$ could be arbitrary functions such that $\int_0^\infty Q(u) du < \infty$ and $\int_0^\infty P(u) du < \infty$, rather than the chosen functions given in (6.2).

Without loss of generality, assume that the population size is constant N as recruitment and death are neglected. Thus for the model (6.3), the basic reproduction number defined in (3.4) becomes

$$\mathcal{R}_0 = \beta_d N \int_0^\infty P(u) du + r\beta_i N \int_0^\infty P(u) du \int_0^\infty Q(v) dv.$$

Integration of the equation for S in (6.3) gives

$$\ln \frac{S_0}{S_\infty} = \beta_d \int_0^\infty \varphi(t) dt + \beta_i \int_0^\infty \psi(t) dt. \tag{6.4}$$

Routine calculations involving interchange of the order of integration give

$$\begin{aligned} \int_0^\infty \varphi(t) dt &= \int_0^\infty \varphi_0(t) dt + [S_0 - S_\infty] \int_0^\infty P(u) du \\ \int_0^\infty \psi(t) dt &= \int_0^\infty \psi_0(t) dt + r \int_0^\infty \varphi(u) du \int_0^\infty Q(v) dv \\ &= \int_0^\infty \psi_0(t) dt + r \int_0^\infty Q(v) dv \int_0^\infty \varphi_0(u) du \\ &\quad + r [S_0 - S_\infty] \int_0^\infty P(u) du \int_0^\infty Q(v) dv. \end{aligned}$$

Then substitution into (6.4) gives

$$\begin{aligned} \ln \frac{S_0}{S_\infty} &= \mathcal{R}_0 \left[\frac{S_0 - S_\infty}{N} \right] + \beta_d \int_0^\infty \varphi_0(t) dt \\ &\quad + r \beta_i \int_0^\infty Q(t) dt \int_0^\infty \varphi_0(t) dt + \beta_i \int_0^\infty \psi_0(t) dt. \end{aligned} \tag{6.5}$$

If all infections at time zero have infection age zero, then

$$\varphi_0(t) = [N - S_0]P(t), \quad \int_0^\infty \varphi_0(t) dt = [N - S_0] \int_0^\infty P(u) du,$$

and if the entire pathogen concentration at time zero has age zero, then

$$\psi_0(t) = \psi_0 Q(t), \quad \int_0^\infty \psi_0(t) dt = \psi_0 \int_0^\infty Q(v) dv$$

with some constant ψ_0 . In this case, the final size relation (6.5) takes the form

$$\ln \frac{S_0}{S_\infty} = \mathcal{R}_0 \left[1 - \frac{S_\infty}{N} \right] + \beta_i \psi_0 \int_0^\infty Q(v) dv. \tag{6.6}$$

This final size relation has a term arising from an initial pathogen concentration that tends to decrease S_∞ . If there are no infectious individuals initially, so that the epidemic is started by the pathogen, then $\varphi_0(t) = 0$, but because $S_0 = N$, (6.6) remains valid.

In general, if the assumptions at time zero do not hold, but if both kernel functions P and Q are monotone non-increasing, then it follows that

$$\begin{aligned} \int_0^\infty \psi_0(t) dt &\leq \psi_0 \int_0^\infty Q(v) dv, \\ \int_0^\infty \varphi_0(t) dt &\leq [N - S_0] \int_0^\infty P(u) du. \end{aligned}$$

In this case (6.6) becomes the inequality

$$\ln \frac{S_0}{S_\infty} \leq \mathcal{R}_0 \left[1 - \frac{S_\infty}{N} \right] + \beta_i \psi_0 \int_0^\infty Q(v) dv. \tag{6.7}$$

However, if P is not monotone, which may occur, for example, if there is an exposed stage followed by an infectious stage with higher infectivity, this is not necessarily true. If there are disease deaths, then β_i should be assumed to be a non-increasing function of N , and the final size inequality (6.7) would be reversed [5].

The results in this section have been established under the assumption that the shedding rate is proportional to the infectivity (i.e., $\xi(u) = rk(u)$). In the

next section we analyze a special case of an age-of-infection model for which this assumption on the shedding rate can be relaxed.

6.2. A staged progression epidemic model. Now consider an epidemic with progression from S through k infected stages I_1, \dots, I_k with $I_1(t) = \int_{u \in J_1} i(t, u) du$, $I_2(t) = \int_{u \in J_2} i(t, u) du, \dots, I_k(t) = \int_{u \in J_k} i(t, u) du$, where J_j is the infection age interval of individuals in stage I_j . Assume that the relative infectivity in stage j is ε_j , that is, $k(u) \equiv \varepsilon_j$ if $u \in J_j$. Notice that $\varphi(t) = \sum_{j=1}^k \varepsilon_j I_j(t)$. Also assume that the distribution of stay in the stage I_j is given by P_j with $P_j(0) = 1, \int_0^\infty P_j(u) du < \infty$, and P_j is monotone non-increasing, so that the infectivity of an individual in stage j is $\varepsilon_j P_j(u)$. The shedding rate $\xi(u)$ is assumed to depend on the stage of the infectious individual, say $\xi(u) \equiv \varepsilon_j r_j$ for $u \in J_j$, where r_j is the shedding rate in stage I_j . This assumption on the shedding rate is more general than that in Section 6.1. With the above assumptions, the total infectivity of the pathogen satisfies

$$\begin{aligned} \psi(t) &= \psi_0(t) + \int_0^t Q(u) \int_0^\infty \xi(v) i(t-u, v) dv du \\ &= \psi_0(t) + \int_0^t Q(u) \left(\sum_{j=1}^k \varepsilon_j r_j I_j(t-u) \right) du. \end{aligned}$$

Let $\psi_j(t)$ represent the infectivity of pathogen shed by infectious individuals in stage I_j , then $\psi(t) = \sum_{j=1}^k \psi_j(t)$ where

$$\psi_j(t) = \psi_{j,0}(t) + \int_0^t r_j I_j(t-u) Q_j(u) du, \tag{6.8}$$

with $Q_j(u) = \varepsilon_j Q(u)$ representing the distribution of stay of pathogen shed by infectious individuals in stage I_j . Assume that $Q_j(0) = 1, \int_0^\infty Q_j(u) du < \infty$, and $Q_j(u)$ is monotone non-increasing. There are no disease deaths and the total population size N is constant. Initial conditions are

$$S(0) = S_0, \quad I_1(0) = I_0 = N - S_0, \quad I_2(0) = I_3(0) = \dots = I_k(0) = 0, \quad R(0) = 0.$$

Note that another way to formulate the age-of-infection model with staged progression for a directly transmitted disease is given in [4].

A single infectious individual introduced into a wholly susceptible population while in infection stage j approximately causes $\beta_d N$ secondary infections per unit time directly for a period of $\int_0^\infty P_j(u) du$. In addition, this individual sheds a quantity r_j of pathogen per unit time for a time period $\int_0^\infty P(u) du$, and this pathogen causes $\beta_i N$ infections per unit time for a time period $\int_0^\infty Q(v) dv$. This shows that the basic reproduction number is

$$\mathcal{R}_0 = N \left[\beta_d \sum_{j=1}^k \varepsilon_j \int_0^\infty P_j(u) du + \beta_i \sum_{j=1}^k r_j \int_0^\infty P_j(u) du \int_0^\infty Q_j(v) dv \right].$$

We assume that all initial infectious individuals are in the first stage with infection age zero at $t = 0$. Then the equation for I_1 in the model is

$$I_1(t) = I_1^0(t) + \int_0^t [-S'(t-u)] P_1(u) du,$$

with $I_1^0(t) = I_0P_1(t)$. Then by integrating the last equation

$$\begin{aligned} \int_0^\infty I_1(t) dt &= I_0 \int_0^\infty P_1(t) dt + \int_0^\infty \int_0^t [-S'(t-u)]P_1(u) du dt \\ &= I_0 \int_0^\infty P_1(t) dt + \int_0^\infty \left[\int_u^\infty [-S'(t-u)] dt \right] P_1(u) du \\ &= I_0 \int_0^\infty P_1(t) dt + [S_0 - S_\infty] \int_0^\infty P_1(t) dt \\ &= [N - S_\infty] \int_0^\infty P_1(t) dt. \end{aligned}$$

The same calculation as made in [4] now gives

$$\int_0^\infty I_j(t) dt = [N - S_\infty] \int_0^\infty P_j(u) du, \quad j = 1, 2, \dots, k. \tag{6.9}$$

Using (6.9), integration of (6.8) gives

$$\begin{aligned} \int_0^\infty \psi_j(t) dt &= \int_0^\infty \psi_j^0(t) dt + r_j \int_0^\infty I_j(u) du \int_0^\infty Q_j(v) dv \\ &= \int_0^\infty \psi_j^0(t) dt + r_j [N - S_\infty] \int_0^\infty P_j(u) du \int_0^\infty Q_j(v) dv. \end{aligned} \tag{6.10}$$

Just as for the model (6.3) of the previous section,

$$S'(t) = -S(t)[\beta_d S(t)\varphi(t) + \beta_i \psi(t)] = -S(t) \left[\beta_d \sum_{j=1}^k \varepsilon_j I_j(t) + \beta_i \sum_{j=1}^k \psi_j(t) \right],$$

and integration gives

$$\ln \frac{S_0}{S_\infty} = \beta_d \sum_{j=1}^k \varepsilon_j \int_0^\infty I_j(u) du + \beta_i \sum_{j=1}^k \int_0^\infty \psi_j(u) du. \tag{6.11}$$

For simplicity, we assume that all individuals infected at time zero have infection age zero for $t = 0$, and also that there is a new quantity of pathogen ψ_0 introduced at time zero, so that $\psi_0(t) = \psi_0 Q(t)$. Then, with the aid of (6.9) and (6.10), the relation (6.11) reduces to the final size relation

$$\begin{aligned} \ln \frac{S_0}{S_\infty} &= [N - S_\infty] \left(\beta_d \sum_{j=1}^k \varepsilon_j \int_0^\infty P_j(u) du + \beta_i \sum_{j=1}^k r_j \int_0^\infty P_j(u) du \int_0^\infty Q_j(v) dv \right) \\ &\quad + \beta_i \psi_0 \int_0^\infty Q(v) dv \\ &= \mathcal{R}_0 \left[1 - \frac{S_\infty}{N} \right] + \beta_i \psi_0 \int_0^\infty Q(v) dv, \end{aligned} \tag{6.12}$$

which is the same expression as (6.6). As for the model (6.3), if there are initially no infectious individuals and the epidemic is started by indirect transmission from the pathogen, the final size relation (6.12) remains valid. If some individuals infected at time 0 have a positive infection age and kernel functions P_i, Q_i are monotone non-increasing, then (6.12) provides an upper bound on the final size. In [21] a final size relation equivalent to (6.12) for a staged progression waterborne disease model [21, (A.11)] is derived by cleverly selecting a function that is constant along solution trajectories.

7. Discussion. A PDE cholera model (2.1) is proposed here to incorporate the infection age of infectious individuals and the biological age of pathogen. Under our assumptions, the global dynamics of (2.1) is shown to be determined completely by the basic reproduction number \mathcal{R}_0 , which depends on both direct and indirect transmission. The disease dies out if \mathcal{R}_0 is below or at the threshold value 1 and otherwise the disease persists. For a given set of parameters for a cholera outbreak, a sensitivity analysis of \mathcal{R}_0 could be used to guide disease control strategies. Following the construction of Lyapunov functionals used in [11, 15], two Lyapunov functionals are constructed to show the global stability of the disease-free and endemic equilibria. We remark that these two Lyapunov functionals have the same form at the bifurcation point $\mathcal{R}_0 = 1$. Indirect transmission affects the basic reproduction number and also gives an additional contribution (if there is an initial pathogen concentration) to the final size relation.

When choosing kernel functions for differential infectivity in direct and indirect transmission, model (2.1) contains several multi-stage ODE models, such as the staged progression model in [21] and the mass-action model in [18]. In [10, 16], delay models are regarded as special cases of age-of-infection models with only direct transmission. By taking appropriate kernel functions, our model (2.1) also contains delay cholera models, and our global stability result (Theorem 3.1) provides the global dynamics for these delay models.

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