Research Article

Assessing the Impact of Drug Resistance on the Transmission Dynamics of Typhoid Fever

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1. Introduction

Typhoid fever is caused by Salmonella enterica serovar Typhi (S. Typhi), a gram-negative bacterium [1–3]. It continues to be a global public health problem with over 21.6 million cases and at least 250,000 deaths occurring annually [4–6]. Almost 80% of the cases and deaths are in Asia; the rest occur mainly in Africa and Latin America [3, 7]. In developing countries such as India, the disease occurs with an incidence ranging from 102 to 2,219 per 100,000 of the population [3, 8]. Several studies in areas of endemicity and outbreaks have shown that about one-quarter to one-third of pediatric typhoid fever cases are under five years of age, and that between 6% and 21% are under two years of age [9]. Varied presentations of typhoid fever are known in the pediatric age group, such as septicemia in neonates, as diarrhoea in infants, and as lower respiratory tract infections in older children [10–12]. Typical presentation in older children includes splenic abscess, liver abscess, cerebellar ataxia, meningitis, cholecystitis, chorea, palatal palsy, osteomyelitis, peritonitis, aphasia, and even psychosis [13–16]. Due to these varied and typical presentations, it is common for typhoid fever in children to be diagnosed late or even remain unrecognised. Also, no vaccine against typhoid fever is available commercially for children under two years of age [14]. To complicate matters further, in the last two decades, multidrug-resistant (MDR) S. Typhi strains have emerged and spread worldwide, resulting in high rates of morbidity and mortality [14, 15, 17].

Typhoid drug resistance emerged first in the UK within 2 years of the successful use of chloramphenicol on typhoid treatment [18, 19]. Subsequently, isolates carrying transferable chloramphenicol resistance were described from Greece [20] and Israel [21]. The emergence of drug resistance has great implications for therapy [22]. For example, children infected with such strains are more ill at presentation and have a longer duration of illness and a significantly higher mortality rate [23].

Motivated by the 2012 typhoid outbreak in Zimbabwe, this paper aims to assess the impact drug resistance on the transmission dynamics of typhoid fever, using a mathematical model. Mathematical models have become invaluable management tools for epidemiologists, both shedding light on the mechanisms underlying the observed dynamics as well as making quantitative predictions on the effectiveness of different control measures. The literature and development of mathematical epidemiology are well documented and can be found in [24–26]. Modeling the transmission dynamics of typhoid is an important and interesting topic for a lot
of researchers; see [27–32] to mention but a few. Lauria et al. [29] developed an optimization model for reducing typhoid cases in developing countries without increasing public spending. Their work suggested that the magnitude of herd protection effects greatly influences the total number of cases avoided and the value of public treatment cost savings. More recently, Kalajdzievska and Li [30] developed a mathematical model for assessing the effects of carriers on the transmission dynamics of infectious diseases such as typhoid. They concluded that carriers play a significant role in the transmission of infectious diseases.

The paper is structured as follows. Section 2 is the model formulation. Analytical results have been carried out in Section 3. Numerical results are presented in Section 4. A short discussion concludes the paper.

2. Model Formulation

In this section we formulate a mathematical model for typhoid which incorporates drug resistance. The host population is divided into the following epidemiological classes or subgroups: susceptible $S$, sensitive strain nonsymptomatic infectious individuals $I_s$, sensitive strain symptomatic infectious individuals $I$, drug-resistant infectious carriers $I_{cr}$, and drug-resistant symptomatic infectious individuals $I_{cr}$. Thus, the total population $N$ is given by $N = S + I_s + I + I_{cr} + I_{cr}$. We assume that individuals can be infected through direct contact with an infectious individual. Further, assuming homogeneous mixing of the population, individuals are recruited at constant rate $\Lambda$ (assumed susceptible). The model takes the form:

$$
\begin{align*}
S' &= \Lambda + \gamma I - (\lambda + \lambda_r)S - \mu S, \\
I_s' &= \rho \lambda S - \lambda I_s - (\mu + \alpha + d) I_s, \\
I' &= (1 - p) \lambda S + \alpha I_s - \lambda I - (\mu + \gamma + \delta) I, \\
I_{cr}' &= \rho \lambda_r (S + I) - (\mu + \phi + \omega) I_{cr}, \\
I_{cr}' &= (1 - p) \lambda_r (S + I) + \lambda I + \phi I_{cr} - (\mu + \gamma) I_{cr},
\end{align*}
$$

(1)

$\mu$ is the per capita natural mortality rate, $\gamma$ is the rate at which individuals infected with sensitive strain recover after successful treatment, $d$ and $\delta$ denote the per capita disease-induced death rate for typhoid patients in class $I_s$ and $I$, respectively, $\omega$ and $\nu$ denote the per capita disease-induced mortality rate for typhoid patients in class $I_{cr}$ and $I_s$, respectively, $\lambda = (\beta I_s + \theta I)$, where $\beta$ and $\theta$ denote the effective contact rate for typhoid transmission (sensitive strain) by nonsymptomatic infectious individuals and symptomatic infectious individuals, respectively. Reports on cases of reinfection with typhoid for successfully treated individuals have been on an increase since the year 2000 [33, 34]. In this study we assume that individuals infected with drug-sensitive strain can be reinfected with drug-resistant strain at rate $\lambda_r = (\beta_r I_{cr} + \theta_r I_s)$, where $\beta_r$ and $\theta_r$ denote the effective contact rate for typhoid transmission (sensitive strain) by nonsymptomatic infectious individuals and symptomatic infectious individuals, respectively. Upon infection a fraction $p$ of the infected individuals becomes chronic patients and the remainder $(1 - p)$ becomes symptomatic patients. Nonsymptomatic infectious individuals becomes infectious at rate $\alpha$ and $\phi$, for sensitive and resistant strain, respectively. The model flow diagram is depicted in Figure 1.

3. Analytical Results

3.1. Basic Properties of the Model. In this section, we study the basic results of solutions for model system (1), which are essential in the proofs of stability.

**Lemma 1.** The equations preserve positivity of solutions.

**Proof.** The vector field given by the right hand side of (1) points inward on the boundary of $\mathbb{R}_+^5 \setminus \{0\}$. For example, if $S = 0$, then $S' = \Lambda + \gamma I \geq 0$. All the other components are similar. \(\square\)

**Lemma 2.** Each positive solution is bounded in $L^1$ norm by \(\max\{N(0), \Lambda/\mu\}\).

**Proof.** The $L^1$ norm of each positive solution is $N$, and it satisfies the inequality $N' \leq \Lambda - \mu N$. Solutions to the arbitrary equation $M' = \Lambda - \mu M$ are monotone increasing and bounded by $\Lambda/\mu$ if $M(0) < \Lambda/\mu$. They are monotone decreasing and bounded above if $M(0) \geq \Lambda/\mu$. Since $N' \leq M'$, the claim follows. \(\square\)
3.3. Endemic Equilibrium and Its Stability. System (1) has three possible endemic equilibrium points, namely

(a) sensitive strain only,
(b) resistant strain only,
(c) coexistence of sensitive strain and resistant strain.

3.3.1. Sensitive Strain Endemic Equilibrium. In the absence of drug-resistant strain in the community, that is, \( I_{cr} = I_r = 0 \), system (1) becomes

\[
S' = \Lambda + yI - \lambda S - \mu S, \\
I_c' = \rho \lambda S - (\mu + \alpha + d) I_c, \\
I_r' = (1 - p) \lambda S + \alpha I_c - \lambda S - (\mu + y + \delta) I.
\]

For system (5), it can be shown that the region

\[
\Omega = \left\{ (S, I_c, I, I_{cr}, I_r) \in \mathbb{R}_+^5 : N \leq \frac{\Lambda}{\mu} \right\}
\]

is invariant and attracting. Thus, the dynamics of typhoid sensitive strain will be considered in \( \Omega \). System (5) has an endemic equilibrium given by

\[
E_s = \left\{ \frac{\Lambda}{\mu R_s}, \frac{p (R_s - 1)}{[d + \mu] (\mu + \delta + \phi + \gamma) + \alpha (\delta + \mu) R_s - 1}, \frac{(\mu + \alpha + d)}{[d + \mu] (\mu + \delta + \phi + \gamma) + (\delta + \mu) R_s - 1} \right\},
\]

which makes biological sense only whenever \( R_s > 1 \).

Theorem 7. If \( R_s > 1 \), then the endemic equilibrium point \( E_s \) exists.

We claim the following result (see Appendix B for proof).

Theorem 8. The endemic equilibrium \( E_s \) is globally asymptotically stable whenever conditions outlined on (B.5) are satisfied.

3.3.2. Drug-Resistant Strain Endemic Equilibrium. In the absence of drug-sensitive strain in the community, that is, \( I_c = I_r = 0 \), system (1) becomes

\[
S' = \Lambda + yI - \lambda S - \mu S, \\
I_c' = \rho \lambda S - (\mu + \alpha + d) I_c, \\
I_r' = (1 - p) \lambda S + \alpha I_c - \lambda S - (\mu + y + \delta) I.
\]

For system (8), it can be shown that the region

\[
\Delta = \left\{ (S, I_{cr}, I_r) \in \mathbb{R}_+^3 : N \leq \frac{\Lambda}{\mu} \right\}
\]

is invariant and attracting. Thus, the dynamics of typhoid sensitive strain will be considered in \( \Delta \). System (8) has an endemic equilibrium \( E_r \) given by

\[
E_r = \left\{ \frac{S^*}{\mu + \lambda_r^*}, \frac{I_{cr}^*}{\mu + \lambda_r^*} \right\},
\]

with \( \lambda_r^* = (\beta I_{cr}^* + \theta I_r^*) \), and \( k_3, k_4 \) are as defined earlier on (4).
Substituting $I^*_s$ and $I^*_r$ (from (10)) into $\lambda^*_r = \beta_s I^*_r + \theta I^*_r$, one gets

$$
\lambda^*_r \left( 1 - \frac{\Lambda (\theta_s (1 - p) k_1 + p (\alpha \theta_s + \beta_s k_4))}{(\lambda^*_r + \mu) k_3 k_4} \right) = 0. \tag{11}
$$

Equation (11) is a quadratic equation, with one of the solutions $\lambda^*_r = 0$ (which defines the existence of disease-free equilibrium). The second solution is given by

$$
\lambda^*_r = \mu \left( R_s - 1 \right), \tag{12}
$$

which defines the existence of the endemic equilibrium $E_r$, whenever $R_s > 1$. We have the following Theorem.

**Theorem 9.** If $R_s > 1$, then the endemic equilibrium point $E_r$ exists.

By Theorem 9 if $R_s > 1$, the infection persists. Regarding the fashion in which the infection persists, we establish in this section that when $R_s > 1$, the infection eventually stabilizes at an equilibrium level. More specifically, we have the following result. Theorem 10 has been established using the general method of Li and Muldowney [37] (see Appendix C for the proof).

**Theorem 10.** If $R_s > 1$, then $E_r$ exists and is globally asymptotically stable (GAS).

### 3.3.3. Interior Endemic Equilibrium

When both sensitive and resistant strains exist system (1) has an endemic equilibrium given by (not computed due to its complex nature)

$$
E_{rs} = (S^*, I^*_s, I^*_r, I^*_r). \tag{13}
$$

The following symmetric conditions will be used to determine the stability:

(a) $R_s < 1$ (typhoid-sensitive strain dies out) and $R_r > 1$ (typhoid-drug-resistant strain persists),

(b) $R_s > 1$ (typhoid-sensitive strain persists) and $R_r < 1$ (typhoid-resistant strain dies out),

(c) $R_h > 1$ (typhoid-sensitive strain persists) and $R_c > 1$ (typhoid-drug-resistant strain persists).

The symmetric conditions above may be summarized diagrammatically as shown in Figure 2.

Using the above symmetric conditions and results deduced on Theorems 6, 7, and 9, we deduce that, for $R_s > 1$, the endemic equilibrium will be globally asymptotically stable.

### 3.3.4. Impact of Drug-Resistant Strain Typhoid Dynamics

In many epidemiological models, the magnitude of the reproductive number is associated with the level of infection. The same is true for model (1). From the expressions of $R_s$ and $R_r$ we observe that $\Lambda$ and $\mu$ are the two parameters which are common; hence to investigate the impact of drug-resistant strain on typhoid dynamics, we will use implicit differentiation as follows:

$$
\frac{\partial R_s}{\partial \Lambda} = \frac{\partial R_s}{\partial \Lambda} + \frac{\partial R_s}{\partial \mu} \frac{\partial \mu}{\partial \Lambda} = 0.
$$

The symmetric conditions above may be summarized diagrammatically as shown in Figure 2.

Using the above symmetric conditions and results deduced on Theorems 6, 7, and 9, we deduce that, for $R_s > 1$, the endemic equilibrium will be globally asymptotically stable.

### 4. Numerical Results

In order to illustrate the results of the foregoing analysis, we have simulated model system (1) using the parameters in Table 1.

#### 4.1. Sensitivity Analysis

Sensitivity analysis assesses the amount and type of change inherent in the model as captured by the terms that define the reproductive number [38, 39]. If the reproductive number is very sensitive to a particular parameter, then a perturbation of the conditions that connect the dynamics to such a parameter may prove useful in identifying policies or intervention strategies that reduce epidemic prevalence. In this section we computed the partial
Table 1: Model parameters and their interpretations.

<table>
<thead>
<tr>
<th>Parameter definition</th>
<th>Symbol</th>
<th>Units</th>
<th>Point estimate</th>
<th>Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-induced mortality for $I_1$ class</td>
<td>$d$</td>
<td>/year</td>
<td>0.01</td>
<td>0.01–0.3</td>
<td>[31]</td>
</tr>
<tr>
<td>Disease-induced mortality for $I$ class</td>
<td>$\delta$</td>
<td>/year</td>
<td>0.012</td>
<td>0.01–0.3</td>
<td>[31]</td>
</tr>
<tr>
<td>Disease-induced mortality for $I_\alpha$ class</td>
<td>$\omega$</td>
<td>/year</td>
<td>0.015</td>
<td>0.01–0.3</td>
<td>[31]</td>
</tr>
<tr>
<td>Disease-induced mortality for $I_\epsilon$ class</td>
<td>$\gamma$</td>
<td>/year</td>
<td>0.02</td>
<td>0.01–0.3</td>
<td>[31]</td>
</tr>
<tr>
<td>Typhoid transmission for $I_1$ class</td>
<td>$\beta$</td>
<td>—</td>
<td>0.01</td>
<td>0.00001–0.025</td>
<td>Assumed</td>
</tr>
<tr>
<td>Typhoid transmission for $I_\alpha$ class</td>
<td>$\beta_\alpha$</td>
<td>—</td>
<td>0.015</td>
<td>0.00001–0.025</td>
<td>Assumed</td>
</tr>
<tr>
<td>Typhoid transmission for $I_\epsilon$ class</td>
<td>$\theta$</td>
<td>—</td>
<td>0.02</td>
<td>0.00001–0.025</td>
<td>Assumed</td>
</tr>
<tr>
<td>Typhoid transmission for $I_s$ class</td>
<td>$\theta_s$</td>
<td>—</td>
<td>0.025</td>
<td>0.00001–0.025</td>
<td>Assumed</td>
</tr>
<tr>
<td>Natural mortality rate</td>
<td>$\mu$</td>
<td>/year</td>
<td>0.0142</td>
<td>0.01–0.02</td>
<td>[38]</td>
</tr>
<tr>
<td>Rate of becoming symptomatic infectious for $I_\epsilon$ class</td>
<td>$\alpha$</td>
<td>/year</td>
<td>0.05</td>
<td>0.05–0.1</td>
<td>[31]</td>
</tr>
<tr>
<td>Rate of becoming symptomatic infectious for $I_\alpha$ class</td>
<td>$\phi$</td>
<td>/year</td>
<td>0.09</td>
<td>0.05–0.1</td>
<td>[31]</td>
</tr>
<tr>
<td>Proportion of individuals who join $I_\epsilon$</td>
<td>$p$</td>
<td>—</td>
<td>0.5</td>
<td>0.0–1.0</td>
<td>Assumed</td>
</tr>
<tr>
<td>Recruitment rate</td>
<td>$\Lambda$</td>
<td>People/year</td>
<td>1000000</td>
<td>—</td>
<td>[29, 31]</td>
</tr>
<tr>
<td>Recovery rate</td>
<td>$\gamma$</td>
<td>/year</td>
<td>0.150</td>
<td>0.0–0.2</td>
<td>Assumed</td>
</tr>
</tbody>
</table>

![Figure 3: Partial rank correlation coefficients showing the effects of parameter variation on $R$, using ranges in Table 1. Parameters with positive PRCCs will increase $R$ when they are increased, whereas parameters with negative PRCCs will decrease $R$ when they are increased.](image)

![Figure 4: Partial rank correlation coefficients showing the effects of parameter variation on $R$, using ranges in Table 1. Parameters with positive PRCCs will increase $R$ when they are increased, whereas parameters with negative PRCCs will decrease $R$ when they are increased.](image)

rank correlation coefficients (PRCCs) in order to estimate the correlation between the reproductive number and the model parameters which define the reproductive number. We begin by assessing the relationship between $R_s$ and the model parameters which define it.

Figure 3 illustrates the PRCCs using $R_s$ as an output variable. Results on Figure 3 suggest that an increase in human recruitment rate, typhoid transmission for both non-symptomatic and symptomatic individuals, and the proportion of carriers may increase the magnitude of $R_s$. We also noted that an increase on treatment level has the greatest influence on reducing the magnitude of $R_s$; hence typhoid treatment should be encouraged in order to control cumulative typhoid cases.

Results on Figure 4 suggest that an increase in human recruitment and typhoid transmission by non-symptomatic individuals has more influence on increasing the magnitude of $R_s$, compared to other model parameters. Since this paper considers no treatment for drug-resistant typhoid strain, results shown here suggest the need for typhoid intervention strategies in order to reduce cases of drug-resistant strain; these may include provision of clean water and typhoid vaccination.

The effects of increasing $p$ (the proportion of individuals who become infectious but non-symptomatic upon infection) in cumulative drug-sensitive typhoid cases and cumulative drug-resistant typhoid cases are shown on Figure 5. In Figure 5(a), we note that if $p$ increases, (despite its value) then cumulative drug-sensitive non-symptomatic cases increase from the first month and reaches the peak on the twentieth month; then the cases will start to decline to a low level. Figure 5(b) shows similar results to Figure 5(a); the only difference is that increasing $p$ does not give a more significant change as observed on Figure 5(a). We also note that an increase on $p$ may lead to an increase on drug-resistant cases. Further analysis of Figure 5 suggests that in a community where there is drug-sensitive typhoid and drug-resistant typhoid, drug-resistant strain cases may outnumber drug-sensitive cases with time.

In Figure 6, we observe the effects of different initial conditions on future trends of typhoid epidemic. Figure 6(a) suggests that when a typhoid outbreak occurs with more
drug-sensitive cases than drug-resistant cases, then it may take 10–15 months for symptomatic drug-resistant cases to outnumber all typhoid cases, and an average of 15–20 months for nonsymptomatic drug-resistant cases to outnumber both symptomatic and nonsymptomatic drug-sensitive cases. However, for an outbreak with slightly higher cases of drug-resistant than drug-sensitive cases, it may take less than 10 months for non-symptomatic and symptomatic drug resistant cases to outnumber all forms of drug sensitive cases (see Figure 6(b)). When a typhoid outbreak has almost the same cases of drug-sensitive and drug resistant then, it may take 10–14 months for symptomatic drug-resistant cases to outnumber all typhoid cases, and it takes an average of 15–20 months for nonsymptomatic drug-resistant cases to outnumber all drug-sensitive cases.

Simulation in Figure 7 suggests that treatment has a positive impact on reducing cumulative typhoid cases since an increase in treatment is associated with low cumulative drug-sensitive and drug-resistant cases even though the proposed model does not account for drug-resistant treatment.

5. Discussion
Typhoid fever continues to be an important cause of illness and death, particularly among children and adolescents in developing countries, where sanitary conditions remain poor. Drug resistance is becoming a major problem and treatment is becoming increasingly difficult, leading to patients taking longer to recover, suffering more complications and continuing to spread the disease to their family and to their community [3]. A mathematical model for investigating the impact of drug-resistant strain on the dynamics of typhoid is developed and analyzed. Comprehensive and robust mathematical techniques have been used to analyze the model steady states. It has been established that the model has a disease-free equilibrium which is globally asymptotically stable when the associated reproductive number is less than unity. Sensitivity analysis of the reproductive number has been carried out. Results from the sensitivity analysis of the reproductive number suggest that an increase in human recruitment rate, typhoid transmission by nonsymptomatic
and symptomatic individuals, and the proportion of individuals who become nonsymptomatic upon infection have the greatest influence on increasing the magnitude of the associated reproductive number. We also note that treatment has the greatest influence on reducing cumulative drug-sensitive typhoid cases. Analytical and numerical results have suggested that an increase of drug-resistant typhoid cases may outnumber typhoid drug-sensitive cases with time, and this will lead to high prevalence of typhoid in the community. With the aid of parameter values in Table 1, we deduce that the drug-resistant strain-induced reproductive number is greater than the drug-sensitive strain-induced reproductive number, and this is due to the fact that our study assumes that there is no treatment for drug-resistant typhoid patients.

The model developed in this paper has limitation(s), which should be acknowledged. We assumed that the disease is transmitted through human contact only although the disease can be acquired through consumption, mainly of water, but sometimes of food, that has been contaminated by sewage containing the excrement of people suffering from the disease. Furthermore, recruited individuals are assumed to be susceptible which might not be case in some communities.

**Appendices**

**A. Global Stability of the Disease-Free Equilibrium**

Following Kamgang and Sallet, (2008) [36], we write system (1) in the form:

\[ x_1' = A_1(x) \cdot (x_1 - x_1^*) + A_{12} \cdot (x_2), \]
\[ x_2' = A_2(x) \cdot x_2, \]

(A.1)

on the positively invariant set \( \Omega \subset \mathbb{R}_1^{n_1+n_2} \). Here \( x_1 = S \) and \( x_2 = (I_c, I, I_r) \). Here \( x_1 \in \mathbb{R}^1_1 \) denotes (its components) the number of uninfected individuals and \( x_2 \in \mathbb{R}^4_2 \) denotes
Figure 7: Simulations of model system (1) showing the effects of treatment rate \( \gamma \) on cumulative typhoid cases. The following initial conditions were used: (a) \( I_c = I = 500, I_{cr} = I_r = 150 \), (b) \( I_c = I = 50, I_{cr} = I_r = 150 \), and (c) \( I_c = I = 50, I_{cr} = I_r = 50 \), and the rest of parameters are fixed on their baseline values from Table I.

We have to prove that the following conditions:

\((H_1)\) the system is defined on a positively invariant set \( \Phi \) of the nonnegative orthant; the system is dissipative on \( \Phi \),

\((H_2)\) the subsystem \( x'_1 = A_1 \cdot (x_1, 0) \cdot (x_1 - x_1^*) \) is globally asymptotically stable at the equilibrium \( x_1^* \) on the canonical projection of \( \Phi \) on \( \mathbb{R}^{n_1}_+ \),

\((H_3)\) the matrix \( A_2(x) \) is Metzler (A Metzler matrix is a matrix with off-diagonal entries nonnegative [40]) and irreducible for any given \( x \in \Phi \),

\((H_4)\) there exists an upper-bound matrix \( \overline{A}_2 \) for \( \mathcal{M} = \{ A_2(x) | x \in \Phi \} \) with the property that either \( A_2 \notin \mathcal{M} \) or if \( A_2 \notin \mathcal{M} \) (i.e., \( A_2 = \max_{\Phi} \mathcal{M} \)), then, for any \( \overline{x} \in \Phi \) such that \( \overline{A}_2 = A_2(\overline{x}), \overline{x} \in \mathbb{R}^{n_1}_+ \times \{0\} \) (i.e., the points where the maximum is realized are contained in the disease-free submanifold),

\((H_5)\) \( \alpha(\overline{A}_2) \leq 0 \)

are satisfied. If conditions \((H_1-H_5)\) are satisfied, then \( \mathcal{S}^0 \) is globally asymptotically stable for \( \Phi \).

We express the subsystem \( x'_1 = A_1 \cdot (x_1, 0) \cdot (x_1 - x_1^*) \):

\[ S' = \Lambda - \mu S. \]  

System (A.2) is a linear system which is globally asymptotically stable at the origin. This equilibrium corresponds to \( \mathcal{S}^0 \), satisfying conditions \( H_1 \) and \( H_2 \). Hence, matrix \( A_2(x) \) is given by

\begin{equation}
A_2(x) = \begin{bmatrix}
-k_1 - p\beta S & p\beta S & 0 & 0 \\
(1 - p)\beta S + \alpha - (k_2 - (1 - p)\theta S) & 0 & 0 & 0 \\
0 & 0 - (k_3 - p\beta r S) & p\theta \phi S & 0 \\
0 & 0 & 0 & (1 - p)\beta_r S + \phi - (k_4 - (1 - p)\theta_r)S
\end{bmatrix}.
\end{equation}
Theorem 5 implies that \( k_1 > p \beta S \), \( (k_2 > (1 - p) \theta S) \), \( k_3 < p \beta S \), and \( k_4 > (1 - p) \theta S \); hence matrix \( A_2(x) \) is a Metzler matrix for any \( x \in \Phi \), and this satisfies condition \( H_3 \). With the notations of hypothesis \( (H_4) \), the diagonal block matrix \( \bar{A}_{11}^2 \) is bounded by the matrix

\[
\bar{A}_{11}^2 = \begin{bmatrix}
-\left( k_1 - p \beta \frac{\Lambda}{\mu} \right) & p \theta \frac{\Lambda}{\mu} \\
(1 - p) \beta \frac{\Lambda}{\mu} + \phi & -\left( k_2 - (1 - p) \theta \frac{\Lambda}{\mu} \right)
\end{bmatrix}, \tag{A.4}
\]

which is a maximum. This maximum is realized at point \( \Phi \) such that \( S = \frac{\Lambda}{\mu} \). This implies that these equations belong to the manifold with equations \( l_1 = I = I_c = I_e = 0 \). Now the diagonal block matrix \( \bar{A}_{22}^2 \) is bounded by the matrix:

\[
\bar{A}_{22}^2 = \begin{bmatrix}
-\left( k_3 - p \beta \frac{\Lambda}{\mu} \right) & p \theta \frac{\Lambda}{\mu} \\
(1 - p) \beta \frac{\Lambda}{\mu} + \phi & -\left( k_4 - (1 - p) \theta \frac{\Lambda}{\mu} \right)
\end{bmatrix}, \tag{A.5}
\]

which is a maximum. This maximum is realized at point \( \Phi \) such that \( S = \frac{\Lambda}{\mu} \). This implies that these equations belong to the manifold with equations \( l_1 = I = I_c = I_e = 0 \). Thereby the whole hypothesis \( (H_4) \) is fulfilled.

Then the condition \( (H_2) \) is equivalent to \( \mathcal{R}_0 \leq 1 \). The conditions \( \alpha(\bar{A}_{11}) \leq 0 \) and \( \alpha(\bar{A}_{22}) \leq 0 \) can be expressed by

\[
\Lambda \left[ \theta (1 - p) k_1 + (a \theta + \beta k_2) \right] \leq 1,
\]

\[
\Lambda \left[ \theta, (1 - p) k_2 + (a \theta + \beta k_4) \right] \leq 1,
\]

the maximum of the two quantities on the left hand side is \( \mathcal{R}_0 \). Thus, system (1) is globally asymptotically stable if \( \mathcal{R}_0 \leq 1 \) and unstable if \( \mathcal{R}_0 > 1 \); we summarize the result in Theorem 6.

**B. Global Stability of the Endemic Equilibrium \( \mathcal{E}^*_c \)**

In order to investigate the global stability of the endemic equilibrium \( \mathcal{E}^*_c \), we adopt the approach by Korobeinikov (2006) [41]. Let \( (\beta l_c + \theta I) S = g(S, I_c, I) \) be a positive and monotonic function, and define the following continuous function in \( \Phi \) (for more details, see Korobeinikov, 2006 [41]):

\[
V(S, I_c, I) = S \int_{I_c}^{S} \frac{g(S^*, I_c^*, I^*)}{g(S^*, I_c^*, I^*)} d\tau + I \int_{I_c}^{I} \frac{g(S, I_c^*, I^*)}{g(S, I_c^*, I^*)} d\tau + I \int_{I_c}^{I} \frac{g(S, I_c^*, I^*)}{g(S, I_c^*, I^*)} d\tau.
\]

If \( g(S, I_c, I) \) is monotonic with respect to its variables, then the endemic state \( \mathcal{E}^*_c \) is the only extremum and the global minimum of this function. Indeed if

\[
\frac{\partial V}{\partial S} = 1 - \frac{g(S^*, I_c^*, I^*)}{g(S, I_c^*, I^*)}, \quad \frac{\partial V}{\partial l} = 1 - \frac{g(S^*, I_c^*, I^*)}{g(S, I_c^*, I^*)}
\]

grow monotonically, then the function \( g(S, I_c, I) \) has only one stationary point. Further, since

\[
\frac{\partial^2 V}{\partial S^2} = \left[ \frac{g(S, I_c^*, I^*)}{g(S, I_c^*, I^*)} \right]^2 \frac{\partial g(S, I_c^*, I^*)}{\partial S}, \ldots
\]

\[
\frac{\partial^2 V}{\partial l^2} = \left[ \frac{g(S, I_c^*, I^*)}{g(S, I_c^*, I^*)} \right]^2 \frac{\partial g(S, I_c^*, I^*)}{\partial l}
\]

are nonnegative, then the point \( \mathcal{E}^*_c \) is a minimum; that is, \( V(S, I_c, I) \geq V(S^*, I_c^*, I^*) \), and hence \( V \) is a Lyapunov function, and its time derivative is given by

\[
\frac{dV}{dt} = S' - g(S^*, I_c^*, I^*) + I' \left( 1 - \frac{S}{S^*} \right) \left( 1 - \frac{g(S^*, I_c^*, I^*)}{g(S, I_c^*, I^*)} \right)
\]

\[
+ \frac{\gamma l^* (I - 1)}{I^*} \left( 1 - \frac{g(S^*, I_c^*, I^*)}{g(S_c^*, I_c^*, I^*)} \right)
\]

\[
+ \frac{g(S, I_c^*, I^*)}{g(S^*, I_c^*, I^*)} \left( 1 - \frac{g(S, I_c^*, I^*)}{g(S^*, I_c^*, I^*)} \right)
\]

\[
\times \left( 1 - \frac{g(S^*, I_c^*, I^*)}{g(S, I_c^*, I^*)} \right)
\]

\[
+ p g(S^*, I_c^*, I^*) \left( 1 - \frac{g(S, I_c^*, I^*)}{g(S^*, I_c^*, I^*)} \right)
\]

\[
+ \alpha l^* \left( I - 1 \right) \left( 1 - \frac{g(S^*, I_c^*, I^*)}{g(S^*, I_c^*, I^*)} \right)
\]

\[
+ \left( 1 - \frac{g(S, I_c^*, I^*)}{g(S^*, I_c^*, I^*)} \right) \left( 1 - \frac{g(S, I_c^*, I^*)}{g(S^*, I_c^*, I^*)} \right)
\]

(\text{B.4})

Since \( \mathcal{E}^*_c > 0 \), the function \( g(S, I_c, I) \) is concave with respect to \( P \), and \( \partial^2 g(S, I_c, I) / \partial l^2 \leq 0 \). Also
the monotonicity of $g(S, I_c, I)$ with respect to $S, I_c, I$ ensures that
\[
\left(1 - \frac{S}{S^*}\right) \left(1 - \frac{g(S', I_c', I')}{g(S, I_c, I)}\right) \leq 0,
\]
\[
\left(1 - \frac{I}{I^*} - 1\right) \left(1 - \frac{g(S', I_c', I')}{g(S, I_c, I)}\right) \leq 0,
\]
\[
\left(1 - \frac{g(S, I_c, I)}{g(S', I_c', I')} - \frac{1}{I_c}\right) \left(1 - \frac{g(S', I_c', I')}{g(S, I_c, I)}\right) \leq 0,
\]
\[
\left(\frac{1}{I^*} - \frac{g(S, I_c, I)}{g(S', I_c', I')}\right) \leq 0
\]
holds for all $S, I_c, I > 0$. We summarize the result in Theorem 8.

**C. Global Stability of the Endemic Equilibrium $E_r$**

Using the geometrical approach of Li and Muldowney in [37], we obtain simple sufficient conditions which show that $E^*_r$ is globally asymptotically stable. At first, we give a brief outline of this geometrical approach.

Let $x \mapsto f(x)$ be a $C^1$ for $x$ in an open set $D \subset \mathbb{R}^n$. Consider the differential equation:
\[
x' = f(x).
\]

Denote by $x(t, t_0)$ the solution to (C.1) such that $x(0, x_0) = x_0$. We make the following two assumptions:

$(H_1)$ there exists a compact absorbing set $K \subset D$.

$(H_2)$ equation (C.1) has a unique equilibrium $\bar{x}$ in $D$.

The equilibrium $\bar{x}$ is said to be globally stable in $D$ if it is locally stable, and all trajectories in $D$ converge to $\bar{x}$. For $n \geq 2$, by a Bendixson criterion we mean a condition satisfied by $f$ which precludes the existence of nonconstant periodic solution of (C.1). The classical Bendixson's condition $\nabla f(x) < 0$ for $n = 2$ is robust under $C^1$ local perturbations of $f$.

For higher-dimensional systems, the $C^1$ robust properties are discussed in [37, 42].

A point $x_0 \in D$ is wandering for (C.1) a neighborhood $U$ of $x_0$ and $T > 0$ such that $U \cap x(t, U)$ is empty for all $t > T$. Thus, for example, all equilibria and limit points are nonwandering. The following global-stability principle is established in Li and Muldowney [37] for autonomous systems in any finite dimension.

**Theorem 11.** Suppose that assumptions $(H_1)$ and $(H_2)$ hold. Assume that (C.1) satisfies a Bendixson criterion that is robust under $C^1$ local perturbations of $f$ at all nonequilibrium nonwandering points for (C.1). Then $\bar{x}$ is globally stable in $D$.

The following Bendixson criterion is given in [37] and shown to have the robustness required by Theorem II. Let $x \mapsto P(x)$ be an $(\frac{d}{2}) \times (\frac{d}{2})$ matrix-valued function, that is, $C^1$ for $x \in D$. Assume that $P^+(x)$ exists and is continuous for $x \in K$, the absorbing set. A quantity $\overline{q}_2$ is defined as

\[
\overline{q}_2 = \limsup_{t \to \infty} \sup_{x(t) \in K} \int_0^t m(Q(x(s, x_0))) \, ds,
\]

where
\[
Q = P_f P^{-1} + P_f^{[1]} P^{-1},
\]
and the matrix $P_f$ is obtained by replacing each entry $p_{ij}$ $P$ its directional derivative in the direction $f, \forall p_{ij} f$. The matrix $Df(x)^{[2]}$ is the second second additive compound matrix of the Jacobian matrix $Df(x)$. It is an $(\frac{d}{2}) \times (\frac{d}{2})$ matrix. The following global-stability result is due to Li and Muldowney (see [37], Theorem 8) Let $|\cdot|$ denote a vector norm in $\mathbb{R}^n$ and the corresponding matrix norm it induces. The Lozinski measure $m$ on matrices with respect to $|\cdot|$ is defined by (see [44])

\[
b(Q) = \lim_{h \to 0} \frac{|I + hA| - 1}{h}
\]

for an $n \times n$ matrix $A$. For properties and calculations of Lozinski i will refer the reader to [44]. It is shown in [37] that if $D$ is simply connected, the condition $\overline{q}_2 < 0$ rules out the presence of any orbit that gives rise to a simple closed rectifiable curve that is invariant for (C.1), such as periodic orbits, homoclinic orbits, and heteroclinic cycles. Moreover, it is robust under $C^1$ local perturbations of $f$ near any non-equilibrium point that is non-wandering. In particular, the following global stability result is proved in Li and Muldowney [37].

**Theorem 12.** Assume that $D$ is simply connected and that the assumptions $(H_1)$ and $(H_2)$ hold. Then the unique equilibrium $\bar{x}$ of (C.1) is globally stable in $D$ if $\overline{q}_2 < 0$.

Since $\overline{q}_2$ exists for $\overline{q}_2 > 1$. Then, the Jacobian matrix of (8) along a solution $(S, I_c, I)$ is

\[
J = \begin{bmatrix}
-\mu - (\beta I_c^* + \theta I_c) & \beta S & -\theta S \\
\rho (\beta I_c^* + \theta I_c) & \rho \beta S - (\mu + \phi + \omega) & \rho \theta S \\
(1 - p) (\beta I_c^* + \theta I_c) & (1 - p) \beta S + \phi & (1 - p) \theta S - \mu - \gamma
\end{bmatrix}.
\]
with $\omega = -2\mu - \nu - \phi - \omega + p\beta S + (1-p)\theta S$, set $P(x) = P(S, I_c, t) = \text{diag}(1, I_c/I_r, I_r/I_r, I_r/I_r)$.

Then, $P^{-1} = \text{diag}(0, I_c/I_c - I_c/I_r, I_c/I_r - I_c/I_r, I_c/I_r - I_c/I_r)$, and the matrix $Q = P^{-1} + P[2]P^{-1}$ can be written in block form:

$$Q = \begin{bmatrix} Q_{11} & Q_{12} \\ Q_{21} & Q_{22} \end{bmatrix},$$

(C.7)

where

$$Q_{11} = -2\mu - \phi - \omega - (\beta, I_c + \theta, I_r) + p\beta S,$$

$$Q_{12} = \begin{bmatrix} p\theta S & -2\mu - \nu (\beta, I_c + \theta, I_r) + (1-p)\theta S, \\
\phi + (1-p)\beta S, & -2\mu - \nu (\beta, I_c + \theta, I_r) + (1-p)\theta S, \end{bmatrix},$$

$$Q_{21} = \begin{bmatrix} -2\mu - \nu (1-p)\theta S - (\beta, I_c + \theta, I_r) + \frac{I_c}{I_r} \phi + \frac{I_c}{I_r} \nu (\beta, I_c + \theta, I_r), & \frac{I_c}{I_r}, \frac{I_r}{I_r}, \\
-2\mu - \nu (1-p)\theta S - (\beta, I_c + \theta, I_r) + \frac{I_c}{I_r} \phi + \frac{I_c}{I_r} \nu (\beta, I_c + \theta, I_r), & \frac{I_c}{I_r}, \frac{I_r}{I_r}, \end{bmatrix},$$

$$Q_{22} = \begin{bmatrix} -2\mu - \nu (1-p)\theta S - (\beta, I_c + \theta, I_r) + \frac{I_c}{I_r} \phi + \frac{I_c}{I_r} \nu (\beta, I_c + \theta, I_r), & \frac{I_c}{I_r}, \frac{I_r}{I_r}, \\
-2\mu - \nu (1-p)\theta S - (\beta, I_c + \theta, I_r) + \frac{I_c}{I_r} \phi + \frac{I_c}{I_r} \nu (\beta, I_c + \theta, I_r), & \frac{I_c}{I_r}, \frac{I_r}{I_r}, \end{bmatrix},$$

(C.8)

The second additive compound matrix of system (8) is

$$J[2] = \begin{bmatrix} -2\mu - \phi - \omega - (\beta, I_c + \theta, I_r) + p\beta S, \\
\phi + (1-p)\beta S, & -2\mu - \nu (\beta, I_c + \theta, I_r) + (1-p)\theta S, \beta S, \end{bmatrix}.$$  

(C.6)

Therefore

$$g_1 = -2\mu - \phi - \omega - (\beta, I_c + \theta, I_r) + p\left(\beta, I_c + \frac{I_c}{I_r}\right),$$

(C.13)

Recall that

$$\frac{I_c}{I_r} + (\mu + \phi + \omega) = p\left(\beta, I_c + \frac{I_c}{I_r}\right),$$

(C.14)

Thus, $g_1$ becomes

$$g_1 = -2\mu - \phi - \omega - (\beta, I_c + \theta, I_r) + \frac{I_c}{I_r} (\mu + \phi + \omega)$$

$$= \frac{I_c}{I_r} - \mu - (\beta, I_c + \theta, I_r)$$

$$\leq \frac{I_c}{I_r} - \mu.$$  

(C.15)

Further

$$g_2 = \frac{I_c}{I_r} - \frac{I_c}{I_r} - 2\mu - \nu (1-p)\theta S$$

$$+ p\beta S + (\mu + (1-p)\beta S) \frac{I_c}{I_r},$$

recall that $\frac{I_c}{I_r} = (\phi + (1-p)\beta S) (I_c/I_r) + (1-p) S - (\mu + \nu)$, so that

$$g_2 = \frac{I_c}{I_r} - \mu - (1-p) (\beta, I_c + \theta, I_r)$$

$$\leq \frac{I_c}{I_r} - \mu.$$  

(C.17)

Therefore,

$$m(Q) \leq \frac{I_c}{I_r} - \mu.$$  

(C.18)

Thus, there exists $T > 0$ such that when $t > T$, $(\ln I_c(t) - \ln I_c(0))/t < \mu/2$. As a result,

$$\frac{1}{t} \int_0^t m(Q) dt \leq \frac{1}{t} \int_0^t \left( \frac{I_c}{I_r} - \mu \right) dt$$

$$= \frac{\ln I_c(t) - \ln I_c(0)}{t} - \mu < -\frac{\mu}{2}$$

which implies $\alpha_2 < 0$, thus completing the proof.
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