Mathematical analysis of hepatitis C model for intravenous drug misusers: Impact of antiviral therapy, abstinence and relapse

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Abstract
Despite advances in hepatitis C therapy and better knowledge of viral/host factors related to disease progression, hepatitis C virus (HCV) remains the leading cause of chronic liver disease, causing progression to end-stage liver disease (ESLD) as well as the development of hepatocellular carcinoma. In this paper a mathematical model for assessing the impact of antiviral therapy, abstinence and relapse on the transmission dynamics of HCV is formulated and analyzed. A threshold quantity known as the reproductive number has been computed, and the stability of the steady states has been investigated. The dynamical analysis reveals that the model has globally asymptotically stable steady states. The impacts of antiviral therapy, abstinence and relapse on the transmission dynamics of HCV are discussed through the basic reproductive number and numerical simulations.

Keywords
Hepatitis C virus (HCV), intravenous drug misusers, treatment, abstinence, relapse, reproductive number, sensitivity analysis.

I. Introduction
Hepatitis C virus (HCV) is a major contributing factor of liver disease and one of the most important health issues worldwide. Hepatitis C has a Global Disease Burden of approximately 175 million which represents almost 3% of the whole population in the world, and each year three to four million new patients with HCV are diagnosed. The disease remains endemic in many countries in the world. Statistics based on a general healthy population revealed that HCV has 5.3% seroprevalence in Pakistan, 2.2% in Turkey and 7.7% in Zimbabwe.

Despite advancements in the management of chronic hepatitis C and suggestions that treatment of recently acquired hepatitis C can lead to sustained virological response (SVR) rates of up to 98%, there continues to be a low rate of treatment uptake among current intravenous drug users (IDUs). Studies conducted among intravenous drug use (IDU) populations in developed countries suggest that very few IDUs infected with hepatitis C have received antiviral therapy. The Australian annual survey at needle and syringe programs (2001–2007) reported that 90% of persons who know that they are infected with HCV have never received treatment, and only 0.9%–2.4% were receiving treatment at the time of the survey. In a cohort of 597 American IDUs, only 26 participants received treatment, and the rate of treatment in this cohort remained relatively stable at < 1% per year. Before 2001, treatment guidelines and recommendations for the management of hepatitis C in many developed countries proscribed treatment of IDUs. Although revised guidelines have tended to advocate treating IDUs who fulfill other inclusion criteria, the low rate of treatment uptake suggests that clinicians remain reluctant to treat patients who inject drugs.

A brief survey on previous works provides the context of this paper. Various theoretical studies have been carried out on mathematical modeling of HCV transmission dynamics, focusing on a number of different issues; see Bhunu and Mushayabasa, Mushayabasa and Bhunu, Martin et al., Mushayabasa et al. and Zhang and...
Zhou, Zhang and Zhou proposed a deterministic mathematical model for HCV, evaluating the role of antiviral therapy and HCV carriers on the transmission dynamics of HCV among intravenous drug misusers. Using HCV epidemic data for China, they predicted the future trends for HCV infection. Although a number of mathematical models for HCV have been proposed, none of these studies has considered the effect of antiviral therapy, abstinence and relapse (of HCV-infected individuals who would have abstained from drug injection misuse activity) on the transmission dynamics of HCV. It is therefore against this background that this study finds its relevance and motivation, by formulating a mathematical model to investigate the impact of antiviral therapy, abstinence and relapse on the transmission dynamics of HCV epidemics among intravenous drug misusers. 

In recent years understanding of infectious disease epidemiology and control has greatly increased through mathematical modeling. Insights from this exciting and increasingly important field are now informing policymaking at the highest levels and playing a growing role in research. When data are not there or not yet there, mathematical modeling provides a realistic guide to support decision making in public health problems; for example, some models have been developed for estimating non-observable putative risks of importance in terms of public health, such as the risk of cancer after exposure to diagnostic radiations, the residual infectious risks in blood transfusion, or the future size of an emerging epidemic.

In addition, mathematical modeling provides insights into the role of possible determinants of diseases that are overlooked in non-mathematical models.

The paper is structured as follows. The HCV transmission model is formulated in the next section. Methods and important results of the paper are in section 3. A brief discussion rounds up the paper.

2. Model framework

Based on the individuals’ epidemiological status the total population denoted by \( N \) is constituted by the following classes of intravenous drug misusers: susceptible \( S \), infectious individuals who are not on treatment \( I \), infectious individuals on treatment and have abstained from drug misuse activity \( A \), and infectious individuals who are on treatment and are still active on intravenous drug misuse, but have reduced the number of needle-sharing partners, \( B \). Thus, \( N = S + I + A + B \). Although intravenous drug misusers on HCV treatment are encouraged to abstain from drug misuse activities, some fail to adhere to this encouragement due to a number of reasons which may include addiction and peer influence. However, some will try to respond to the advice through reducing the partner acquisition rate. Susceptible intravenous drug misusers acquire HCV infection through sharing contaminated needles or syringes at rate

\[
\lambda = (1 - \delta) \frac{\beta (cl + \theta (1 - \omega)B)}{N}
\]

where \( \beta \) is the probability of HCV transmission per needle-sharing, \( \epsilon \) is the average number of needle-sharing partners for individuals in class \( I \) per year, \( \theta (\theta < c) \) is the partner acquisition rate for individuals in class \( B \) per year, \( \omega \) is a modification parameter accounting for the assumed reduced likelihood of HCV infection by individuals in class \( B \) compared to those in class \( I \), and the acute infection spontaneously clears with proportion \( \delta \). Individuals in subgroup \( I \) seek treatment at rate \( \gamma \). Upon commencing treatment a proportion \( p \) of infectious individuals is assumed to abstain from drug misuse activities and the complementary proportion \( (1 - p) \) fails to totally abstain from intravenous drug misuse activities, but is assumed to positively change its behavior (that is, individuals reduce their frequency of unsafe injecting practices and the number of needle-sharing partners), and thus join class \( B \). After successful treatment, a proportion \( (1 - \kappa) \) from class \( B \) recovers at rate \( \phi \) and join the susceptible class. A proportion \( (1 - q) \) of individuals who successfully recover from treatment in class \( A \) exit the model at rate \( \psi \). The natural mortality rate \( \mu \) is assumed to be constant in all classes. Due to drug addiction HCV-infected individuals in class \( A \) are assumed to relapse to drug misuse activities at rate \( \alpha \). Since class \( A \) is composed of HCV-infected individuals who would have fully abstained from drug misuse activities, we assume that a proportion \( f \) of those individuals who relapse join class \( I \) and the complementary proportion \( (1 - f) \) move to class \( B \). Assuming homogeneous mixing of the population and a constant recruitment of new intravenous drug misusers into the susceptible class at rate \( \Lambda \), the model takes the form

\[
\begin{align*}
\frac{dS}{dt} &= \Lambda - (1 - \delta) \frac{\beta (cl + \theta (1 - \omega)B)}{N} - \mu S + (1 - \kappa) \phi B \\
\frac{dI}{dt} &= (1 - \delta) \frac{\beta (cl + \theta (1 - \omega)B)}{N} + \alpha (fA + B) - (\gamma + \mu) I \\
\frac{dB}{dt} &= (1 - p) \gamma I + (1 - f) \alpha A - (\alpha + (1 - \kappa) \phi + \mu) B \\
\frac{dA}{dt} &= p \gamma I - (\alpha + (1 - q) \phi + \mu) A
\end{align*}
\]

(1)

The model flow diagram is depicted in Figure 1.
3. Methods and results

3.1. Basic properties of the model

Based on the computations in Appendix A, we study the solutions of system (1) in the closed set

$$\Omega = \left\{ (S, I, A, B) \in \mathbb{R}^4_+ : N \leq \frac{\Lambda}{\mu} \right\}$$ \hspace{1cm} (2)

3.2. Model steady states and the reproductive number

In the absence of HCV infection among intravenous drug misusers system (1) gives an equilibrium state known as the disease-free equilibrium (denoted by $E_0$), given by

$$E_0 = (S_0, I_0, A_0, B_0) = \left( \frac{\Lambda}{\mu}, 0, 0, 0 \right)$$

The linear stability of $E_0$ is governed by the basic reproductive number often called $R_0$, which is defined as the spectral radius of an irreducible or primitive non-negative matrix.\(^{18}\) Biologically, the basic reproductive number can be interpreted as the expected number of secondary infections produced by a single infectious individual during his/her infectious period when introduced in a completely susceptible population. Using the notation in Van den Driessche and Watmough,\(^{19}\) the non-negative matrix $F$ and the non-singular matrix $V$ for the new infection terms and the remaining transfer terms are respectively given (at the disease-free equilibrium) by

$$F = \begin{bmatrix} \beta \gamma (1-\delta) & \beta \theta (1-\delta)(1-\omega) \\ 0 & 0 \end{bmatrix}$$ \hspace{1cm} (3)

and

$$V = \begin{bmatrix} \mu + \gamma & -\alpha \\ -(1-p)\gamma & \alpha + \mu + (1-\kappa)\phi \end{bmatrix}$$ \hspace{1cm} (4)

We now analyze all the possible cases of the reproductive number.

3.2.1. Case (a) Total abstinence and no relapse for HCV-infected individuals on treatment. We set $\alpha = 0$, $p = 1$. Then the spectral radius is given by

$$R_a = \frac{\beta \gamma (1-\delta)}{(\gamma + \mu)}$$ \hspace{1cm} (5)

Biologically, $R_a$ represents the average number of secondary hepatitis C cases produced by a single HCV-infected individual during his or her infectious period in the presence of HCV treatment with total abstinence from drug misuse activities for individuals on treatment.

3.2.2. Case (b) No abstinence during treatment. We set $p = 0$. Then the spectral radius is given by

$$R_{na} = \frac{\beta (1-\delta)[c(\alpha + (1-\kappa)\phi + \mu) + (1-\omega)\theta \gamma]}{\alpha \mu + (\gamma + \mu)(\mu + \phi(1-\kappa))}$$

$$= \left( 1 + \frac{\gamma (c\alpha + \theta(\gamma + \mu)(1-\omega))}{c(\alpha \mu + (\gamma + \mu)(\mu + (1-\kappa)\phi))} \right) \frac{\beta \gamma (1-\delta)}{(\gamma + \mu)}$$

$$= \Theta_1 R_a$$ \hspace{1cm} (6)

where

$$\Theta_1 = 1 + \frac{\gamma (c\alpha + \theta(\gamma + \mu)(1-\omega))}{c(\alpha \mu + (\gamma + \mu)(\mu + (1-\kappa)\phi))} > 1$$

Biologically $R_{na}$ measures the average number of new HCV cases generated by a single HCV-infected individuals during his/her infectious period, in the presence of HCV treatment associated with non-abstinence from drug misuse activities of HCV-infected individuals on treatment. A comparison between equation (5) and equation (6) reveals that $R_a < R_{na}$, (since $\Theta_1 > 1$). Thus, HCV treatment without drug misuse abstinence for individuals on treatment may have less impact on controlling HCV within the community compared to a scenario where HCV treatment is associated with total abstinence from drug misuse abstinence for individuals on treatment.

3.2.3. Case (c) No relapse of individuals who would have abstained. We set $\alpha = 0$. Thus the spectral radius is given by

$$R_p = \frac{\beta (1-\delta)[c(\mu + (1-\kappa)\phi) + (1-\omega)\theta \gamma]}{(\gamma + \mu)(\mu + (1-\kappa)\phi)}$$

$$= \left( 1 + \frac{(1-\omega)\theta \gamma}{c(\mu + (1-\kappa)\phi)} \right) \frac{\beta \gamma (1-\delta)}{(\gamma + \mu)}$$

$$= \Theta_2 R_a$$ \hspace{1cm} (7)
where
\[ \Theta_2 = 1 + \frac{(1-p)(1-\omega)\theta y}{c(\mu + (1-\kappa)\phi)} > 1 \]

Biologically, \( R_p \) measures the average number of new secondary HCV infections generated by a single HCV-infected individual during his or her infectious period. \( R_p \) is introduced in a population of wholly susceptible IDUs in the presence of HCV treatment associated with abstinence, behavior change and no relapse of HCV-infected individuals on treatment into drug misuse activities. Since \( \Theta_2 > 1 \), it follows that \( R_a < R_p \), suggesting that total abstinence of HCV individuals on treatment may have more impact on reducing HCV cases among intravenous drug misusers compared to partial abstinence of individuals on treatment and no relapse.

3.2.4 Case (d) The general case. In the presence of partial abstinence, positive behavior adjustment and relapse, the spectral radius is given by
\[ R_c = \frac{\beta(1-\delta)[c(\alpha + \mu + (1-\kappa)\phi) + (1-p)(1-\omega)\theta y]}{[\gamma(\phi + \mu) + (\gamma + \mu)(\mu + (1-\kappa)\phi)] \beta c(1-\delta)} \]
\[ = \frac{(\gamma + \mu)[c(\alpha + \mu + (1-\kappa)\phi) + (1-p)(1-\omega)\theta y]}{c[\alpha(\phi + \mu) + (\gamma + \mu)(\mu + (1-\kappa)\phi)]} \]
\[ = \Theta_3 R_a \]
(8)

Biologically \( R_c \), can be interpreted as the average number of new HCV infections produced by a single infectious HCV-infected IDU during his or her infectious period when introduced in a population of wholly susceptible IDUs in the presence of HCV treatment associated with abstinence, behavior change and relapse.

We now examine the effects of varying the average number of needle-sharing partners on the reproductive number.

Figure 2 illustrates the effect of varying the average number of needle-sharing partners \( c \) on the reproductive number. Results in Figure 2 clearly suggest that increasing the number of needle-sharing partners has a positive influence on increasing the magnitude of the associated reproductive number. From the results in Figure 2 we also noted that total abstinence has the greatest influence on reducing HCV prevalence.

3.3. Sensitivity analysis

In this section we perform a sensitivity analysis of the reproductive number for the general case \( (R_a) \). Sensitivity analysis assesses the amount and type of change inherent in the model as captured by the terms that define the reproductive number. If \( R_c \) 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. This allows us to identify parameters which play the most significant role in HCV transmission dynamics. For the sensitivity analysis, we have calculated a partial rank correlation coefficient (PRCC). PRCCs are widely used in sensitivity analyses in system biology and disease transmission models to determine the importance of a parameter on a given output while fixing the other parameters at their expected value.

Figure 3 illustrates the PRCCs using \( R_c \) as an output variable. Results here suggests that infection rate and the average number of needle-sharing partners for HCV-infected individuals who are not on treatment have the greatest influence on increasing the magnitude of \( R_c \) thereby increasing new secondary HCV cases. The impact of parameters capable of decreasing the magnitude of \( R_c \) when increased is not highly significant, though treatment
rate is the one with the greatest influence on decreasing $R_c$ when increased. Since infection rate and average number of needle-sharing partners have the greatest influence on changing the magnitude of $R_c$ we now use Monte Carlo simulations to investigate the impact of each of these parameters on $R_c$.

Figure 4 illustrates the effect that varying two sample parameters will have on $R_c$. Results here support earlier
Figure 5. Time series plots showing the effect of increasing relapse rate ($\alpha$) on (a) susceptible population $S$, (b) HCV-infected population not on HCV therapy $I$, (c) HCV-infected individuals on treatment who have changed their intravenous drug misuse behavior and (d) HCV-infected individuals on treatment who have completely abstained from drug misuse activities, over a period. The rest of the parameters are fixed on their baseline values in Table 1, and the following assumed initial conditions were used: $S = 1000$, $I = 300$, $B = 200$, $A = 100$.

**Table 1.** Model parameters and their baseline values.

<table>
<thead>
<tr>
<th>Parameter description</th>
<th>Symbol</th>
<th>Units</th>
<th>Point estimate</th>
<th>Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse rate</td>
<td>$\alpha$</td>
<td>/year</td>
<td>0.1</td>
<td>0.01–0.3</td>
<td>Assumed</td>
</tr>
<tr>
<td>Infection rate</td>
<td>$\beta$</td>
<td>/year</td>
<td>0.1</td>
<td>0.0084–0.1</td>
<td>12</td>
</tr>
<tr>
<td>Treatment rate</td>
<td>$\gamma$</td>
<td>/year</td>
<td>0.02</td>
<td>0.01–0.02</td>
<td>13</td>
</tr>
<tr>
<td>Abstinence ratio</td>
<td>$\rho$</td>
<td>—</td>
<td>0.5</td>
<td>0.01–0.6</td>
<td>Assumed</td>
</tr>
<tr>
<td>1/treatment duration</td>
<td>$\phi$</td>
<td>/year</td>
<td>1.5</td>
<td>0.9–1.992</td>
<td>14</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>15</td>
</tr>
<tr>
<td>Modification parameter</td>
<td>$\omega$</td>
<td>—</td>
<td>0.5</td>
<td>0.0–1.0</td>
<td>Assumed</td>
</tr>
<tr>
<td>New injector entrance rate</td>
<td>$\Lambda$</td>
<td>per 1000 IDUs annually</td>
<td>85</td>
<td>—</td>
<td>14</td>
</tr>
<tr>
<td>Average number of needle-sharing partners for individuals in class $I$</td>
<td>$c$</td>
<td>people/year</td>
<td>5.0</td>
<td>1–10</td>
<td>12</td>
</tr>
<tr>
<td>Partner acquisition for individuals in class $B$</td>
<td>$\theta$</td>
<td>people/year</td>
<td>3.0</td>
<td>1–10</td>
<td>12</td>
</tr>
<tr>
<td>Proportion of infections spontaneously clear</td>
<td>$\delta$</td>
<td>—</td>
<td>0.26</td>
<td>0.01–0.26</td>
<td>14, 12</td>
</tr>
<tr>
<td>Proportion of infections cured by treatment for class $A$</td>
<td>$q$</td>
<td>—</td>
<td>0.6</td>
<td>0.5–0.625</td>
<td>14</td>
</tr>
<tr>
<td>Proportion of infections cured by treatment for class $B$</td>
<td>$\kappa$</td>
<td>—</td>
<td>0.5</td>
<td>0.5–0.625</td>
<td>14</td>
</tr>
<tr>
<td>Proportion of relapse into class $I$</td>
<td>$f$</td>
<td>—</td>
<td>0.3</td>
<td>0–0.3</td>
<td>22</td>
</tr>
</tbody>
</table>
findings in Figure 3, that an increase in infection rate \((\beta)\) and average number of needle-sharing partners \((c)\) leads to an increase in the reproductive number thereby increasing hepatitis C among IDUs.

The following results follow from computations in Appendix B.

**Theorem 3.1.** \(E_0\) is globally asymptotically stable if \(R_0 \leq 1\), and unstable otherwise.

**Theorem 3.2.** The endemic equilibrium \(E_*\) is globally asymptotically stable if \(R_0 > 1\).

### 3.4. Simulation results of population level effects

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

Our first set of simulations (Figure 5) depicts the effect of increasing relapse rate on HCV transmission dynamics over a period of time (in years). It suggests that when relapse cases increase then the size of HCV-infected population \((I)\) increases significantly, which leads to a decrease in the susceptible population \((S)\) due to the marked increase in the risk of exposure to HCV. We also note that an increase in relapse rate also leads to a decrease in the population of individuals on treatment \((A\) and \(B)\), with a more pronounced change in \(A\). An intervention which ensures a higher reduction rate of relapse might be crucial in order to control HCV among IDUs.

The next set of simulations (Figure 6) illustrates the effect of increasing the proportion of HCV-infected individuals who fully abstain from intravenous misuse activities over a period of 50 years. It suggests that when abstinence ratio increases then new secondary HCV cases...
decrease: this is shown through the decrease of variables $I$ and $B$ which are responsible for generation of new infections. We note however that the impact of different abstinence levels may become significant in all the infectious populations $(I, B, A)$ after a period of 10 years.

The final set of simulations (Figure 7) presents the long-term dynamics of the cumulative new infections for different initial levels of $A$ and $B$. In Figure 7(a) we note that after a period of 10 years from the start the population of HCV-infected individuals from class $B$ will outnumber the population of HCV-infected individuals in class $A$, though initially $A(0) > B(0)$, suggesting that if the population of HCV-infected individuals who fully abstain from intravenous drug misuse activities is twice that of HCV-infected individuals who partially abstain from drug misuse activities, then reducing relapse may be crucial if
implemented in the early stages. In Figure 7(b) we note that if the initial population of class $B$ is higher than that of $A$, then this scenario may never change in the long run. Figure 7(c) suggests that if initial population of class $B$ is equal to that of $A$, then in the long run it may become distinct that the population of HCV-infected individuals in class $B$ will outnumber that of HCV-infected individuals in class $A$ after a period of five years, and the situation may remain like that for ever.

4. Discussion

HCV is a blood-borne infection that can lead to progressive liver failure, cirrhosis, hepatocellular carcinoma and death. Despite the availability of effective antiviral treatment, which is usually associated with counseling (encouraging drug misusers to abstain from drug misuse activities), very few active intravenous drug misusers are treated, and with those who are, few of them are able to completely abstain from drug injection misuse during and after successful treatment. In this paper we propose a mathematical model of HCV transmission amongst active intravenous drug misusers, and examine the potential effects of antiviral treatment coupled with abstinence and relapse. The reproductive number of the model has been computed and used to investigate the stability of the equilibrium points of the model, namely the disease-free equilibrium and the endemic equilibrium. It has been established that the two steady-steady states (disease-free and endemic) of the model are globally asymptotically stable (whenever the reproductive number is less than unity, and greater than unity, respectively). Sensitivity analysis and numerical simulations of the model were performed using the MATLAB ODE solver, ode45. The PRCCs were calculated to estimate the correlation between values of the reproductive number and the epidemiological model parameters. It has been observed that an increase in treatments has the greatest influence on reducing the magnitude of the reproductive number than any other epidemiological parameter, while HCV infection rate and the average number of needle-sharing partners for HCV-infectious individuals not on treatment have more influence on increasing the magnitude of the reproductive number than any other epidemiological parameter, respectively, thereby increasing cumulative HCV cases among intravenous drug misusers. Further, we noted that if an initial population of infectious individuals who have positively changed their behavior is the same as that of HCV-infected individuals on treatment who have totally abstained from intravenous drug misuse activities, then in the long run it may become distinct that the population of infectious individuals who have positively changed their behavior will outnumber that of individuals who would have completely abstained from intravenous drug misuse activities, after a period of five years, and the situation may remain like that for ever. These results suggest that increasing total abstinence coupled with a reduction in relapse may have a significant impact on reducing HCV transmission among intravenous drug misusers.

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References

Appendix A: Basic properties of the model

In this section, we study the basic properties of the solutions of model system (1), which are essential to 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 \( \mathbb{R}^4_+ \setminus \{0\} \). For example, if \( S = 0 \), then \( S' \leq \Lambda - \mu N \). In an analogous manner, the same result can be shown for the other model components (variables).

\[ N' = S' + I' + A' + B' \]
\[ N' = \Lambda - \mu N - (1 - q)\phi A \]
\[ N' \leq \Lambda - \mu N \]

Therefore all feasible solutions of system (1) enter the region

\[ \Omega = \left\{ (S, I, A, B) \in \mathbb{R}^4_+ : N \leq \frac{\Lambda}{\mu} \right\} \]

(9)

Thus, \( \Omega \) is positively invariant and it is sufficient to consider solutions of system (1) in \( \Omega \). Existence, uniqueness and continuation results for system (1) hold in this region, and all solutions of system (1) starting in \( \Omega \) remain in \( \Omega \) for all \( t \geq 0 \). All parameters and state variables for model system (1) are assumed to be non-negative (for biological relevance) \( \forall t \geq 0 \) since it monitors human population.

Appendix B: Stability analysis of model steady states

B.1 Global stability of the disease-free equilibrium

Following Castillo-Chavez et al. (2002), we write system (1) in the form

\[ X'(t) = F(X, Y) \]
\[ Y'(t) = G(X, Y), \quad G(X, 0) = 0 \]

(10)

where \( X = S \) and \( Y = (I, A, B) \). Here \( X \in \mathbb{R}^4_+ \) denotes (its components) the number of uninfected individuals and \( Y \in \mathbb{R}^3_+ \) denotes (its components) the number of infected individuals. The disease-free equilibrium is now denoted by \( E_0 = (X_0, 0) \) where \( X_0 = \Lambda/\mu \). We have to prove that the two conditions

\( (H1) \) For \( X'(t) = F(X, 0), X \) is globally asymptotically stable

\( (H2) \) \( \hat{G}(X, Y) = UY - G(X, Y), \hat{G}(X, Y) \geq 0 \) for \( (X, Y) \in \Omega \)

(11)

are satisfied where \( \Omega \) is a positively invariant attracting domain. Consider
F(X, 0) = |Λ - μS|

\[ U = \begin{bmatrix} \beta c(1 - \delta) - (\gamma + \mu) & \beta\theta(1 - \delta)(1 - \omega) + \alpha \\ (1 - p)\gamma & -(\alpha + (1 - \kappa)\phi + \mu) \\ p\gamma & 0 \end{bmatrix} \begin{bmatrix} f\alpha \\ (1 - f)\alpha \end{bmatrix} \]

Thus,

\[ \tilde{G}(X, Y) = \begin{bmatrix} \tilde{G}_1(X, Y) \\ \tilde{G}_2(X, Y) \\ \tilde{G}_3(X, Y) \end{bmatrix} = \begin{bmatrix} \beta(cI + \theta(1 - \omega)B)(1 - \frac{S}{N}) \\ 0 \\ 0 \end{bmatrix} \]

Since \( S \leq N \) at \( E_0 \), it follows that \( \tilde{G}(X, Z) \geq 0 \). We summarize the result in Theorem 3.1.

**B.2 Endemic equilibrium and its stability analysis**

Endemic equilibrium points are steady-state solutions where the disease persists in the population (all state variables are positive). The endemic equilibrium of system (1) is given by

\[ E_* = (S_*, I_*, A_*, B_*) \]

Since the disease-free equilibrium is globally asymptotically stable it follows that there is no coexistence of the disease-free equilibrium and the endemic equilibrium point, and thus model system (1) has a unique endemic equilibrium point.

We now employ the center manifold theory\(^{24}\) to analyze the stability of this equilibrium point as described in Theorem 4.1,\(^ {25}\) to establish the local asymptotic stability of the endemic equilibrium. To apply the center manifold theory, the following simplifications and changes of variables are made first. Let \( S = x_1, I = x_2, A = x_3, B = x_4 \) and

\[ \Lambda = (1 - \delta)\beta c(x_2 + \theta(1 - \omega)x_3) \]

Further, by using vector notation \( x = (x_1, x_2, x_3, x_4)^T \), model system (1) can be written in the form \( dx/dt = F(x) \), with \( F = (f_1, f_2, f_3, f_4)^T \), such that

\[ x' = f_1 = \Lambda - \lambda x_1 - \mu x_1 + (1 - \kappa)\phi x_4 \]

\[ x_2 = f_2 = (1 - p)\gamma x_2 + (1 - f)\alpha x_4 - k_2 x_3 \]

\[ x_3 = f_3 = (1 - p)\gamma x_2 + (1 - f)\alpha x_4 - k_2 x_3 \]

\[ x_4 = f_4 = p\gamma x_2 - k_3 x_4 \]

with \( k_1 = (\gamma + \mu), k_2 = (\alpha + (1 - \kappa)\phi + \mu) \) and \( k_3 = (\alpha + (1 - \gamma)\phi + \mu) \). Linearizing system (13) about \( E^0 \) one gets

\[ J(E^0) = \begin{bmatrix} -\mu & -\beta c(1 - \delta) - (\gamma + \mu) & (1 - \kappa)\phi - \beta\theta(1 - \omega)(1 - \omega) & 0 \\ 0 & \beta c(1 - \delta) - k_1 & \beta\theta(1 - \omega)(1 - \omega) + \alpha & f\alpha \\ 0 & (1 - p)\gamma & k_2 & (1 - f)\alpha \\ 0 & p\gamma & 0 & k_3 \end{bmatrix} \]

from which it can be shown that the reproductive number is

\[ R_c = \frac{\beta(1 - \delta)(c(\alpha + \mu + (1 - \kappa)\phi) + (1 - p)(1 - \omega)\theta) \gamma}{(\alpha(p\gamma + \mu) + (\gamma + \mu)(\mu + (1 - \kappa)\phi))} \]

If \( \beta \) is taken as a bifurcation parameter and if we consider the case \( R_c = 1 \) and solve for \( \beta \), we obtain

\[ \beta = \beta^* = \frac{(\alpha(p\gamma + \mu) + (\gamma + \mu)(\mu + (1 - \kappa)\phi))}{\beta(1 - \delta)(c(\alpha + \mu + (1 - \kappa)\phi) + (1 - p)(1 - \omega)\theta)} \]

Note that the linearized system of the transformed (13) with the bifurcation point \( \beta^* \) has a simple zero eigenvalue. Hence, the center manifold theory\(^{24}\) can be used to analyze the dynamics of (13) near \( \beta = \beta^* \). It can be shown that the Jacobian of (13) at \( \beta = \beta^* \) has a right eigenvector associated with the zero eigenvalue given by \( w = (w_1, w_2, w_3, w_4)^T \), where

\[ w_1 = -\frac{\left[ \beta(c(1 - \delta) - (\gamma + \mu) + \beta\theta(1 - \omega)(1 - \omega))k_2 + 1 - (1 - \theta)k_2 \right]}{\gamma k_2}, w_2 > 0 \]

\[ w_3 = \frac{\gamma[(1 - f)p\gamma + (1 - \omega)\theta]}{k_2 k_3}, w_2, w_4 = \frac{w_3}{k_2} \]

\[ (17) \]
The left eigenvector of $J(\mathcal{E}_0)$ associated with the zero eigenvalue at $\beta = \beta^*$ is given by $v = [v_1, v_2, v_3, v_4]^T$, where

$$v_1 = 0, v_2 > 0, v_3 = \frac{(\beta^* + \delta(1 - \delta)(1 - \omega) + \alpha)}{k_2} v_2,$$

$$v_4 = \left( f \alpha + \frac{\alpha(1 - f)(\beta^* + \delta(1 - \delta)(1 - \omega) + \alpha)}{k_2} \right) \frac{v_2}{k_3} \quad (18)$$

Further, we use Theorem 6 from Castillo-Chavez and Song,\textsuperscript{24} stated below for elucidation.

**Theorem B.1** Consider the following general system of ordinary differential equations with parameter $\phi$:

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \quad (19)$$

Without loss of generality, it is assumed that $0$ is an equilibrium for system (19) for all values of the parameter $\phi$, that is, $f(0, \phi) = 0$ for all $\phi$ and assume:

A1: \[
A = D_2 f(0, 0) = \left( \frac{\partial f}{\partial x_j} (0, 0) \right)
\]

is the linearization of system (19) around the equilibrium $0$ with $\phi$ evaluated at 0. Zero is a simple eigenvalue of $A$ and other eigenvalues of $A$ have negative real parts.

A2: Matrix $A$ has a right eigenvector $w$ and a left eigenvector $v$ corresponding to the zero eigenvalue.

Let $f_k$ be the $k$th component of $f$ and

$$a = \sum_{k,j=1}^{n} v_k w_j \frac{\partial^2 f_k}{\partial x_j \partial x_i} (0, 0),$$

$$b = \sum_{k,j=1}^{n} v_k w_j \frac{\partial^2 f_k}{\partial x_j \partial \phi} (0, 0) \quad (20)$$

The local dynamics of (19) around $0$ are totally governed by $a$ and $b$:

i. $a > 0$, $b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, $0$ is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, $0$ is unstable and there exists a negative and locally asymptotically stable equilibrium.

ii. $a < 0$, $b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, $0$ is unstable; when $0 < \phi \ll 1$, asymptotically stable, and there exists a positive unstable equilibrium.

iii. $a > 0$, $b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, $0$ is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, $0$ is stable, and a positive unstable equilibrium appears.

iv. $a < 0$, $b > 0$. When $\phi$ changes from negative to positive, $0$ changes its stability from stable to unstable. Correspondingly, a negative equilibrium becomes positive and locally asymptotically stable.

**B.3 Computations of $a$ and $b$**

For system (13), the associated non-zero partial derivatives of $F$ at the disease-free equilibrium associated with $a$ are given by

$$\frac{\partial^2 f_2}{\partial x^2} = - \frac{2\beta(1 - \delta)\mu}{\Lambda} \frac{\partial^2 f_2}{\partial x \partial x_3} = - \frac{2\beta(1 - \delta)\mu[c + \theta(1 - \omega)]}{\Lambda} \quad (21)$$

From (21) it follows that

$$a = - \frac{2\beta(1 - \delta)}{\Lambda} \left( 1 + \frac{\gamma((1 - f)p\alpha + (1 - p)k_1)}{k_2 k_3} \left( c + \frac{\gamma(1 - \omega)((1 - f)p\alpha + (1 - p)k_1)}{k_2 k_3} \right) \mu w_2 v_2 < 0 \right) \quad (22)$$

For the sign of $b$, it is associated with the following non-vanishing partial derivatives of $F$:

$$\frac{\partial^2 f_2}{\partial x_2 \partial \beta^*} = c, \quad \frac{\partial^2 f_2}{\partial x_3 \partial \beta^*} = \theta(1 - \omega) \quad (23)$$

It follows from expressions in (23) that

$$b = \left( 1 + \frac{\gamma[1 - \omega((1 - f)p\alpha + (1 - p)k_1)]}{k_2 k_3} \right) w_2 v_2 > 0 \quad (24)$$

Thus, $a < 0$ and $b > 0$ and using Theorem B.1, we have established the following result.

**Theorem B.2** The unique endemic equilibrium $\mathcal{E}$, guaranteed by Theorem B.1 is locally asymptotically stable for $R_0 > 1$ but close to 1.

**B.4: Global stability of the endemic equilibrium point $\mathcal{E}^*$**

To investigate the global stability of the endemic equilibrium point $\mathcal{E}$, we utilize the geometric approach of Li and Muldowney.\textsuperscript{26} Let $\mu N = \Lambda$, $s = S/N, i = I/N, b = B/N$ and $a = A/N$. Using $a = 1 - s - i - b$ we can reduce system (1) to the following three-dimensional system:
\[ s' = \mu - \beta(1 - \delta)[ci + \theta(i - \omega)b]s - \mu s + (1 - \kappa)\phi b \]
\[ i' = \beta(1 - \delta)[ci + \theta(i - \omega)b]s + (1 - f)\alpha b \\
+ f\alpha(1 - s - i) - (\gamma + \mu)i \]
\[ b' = (1 - p)\gamma i + (1 - f)\alpha(1 - s - i - b) \\
- (\alpha + (1 - \kappa)\phi + \mu)b \]

(25)

\[ J = \begin{pmatrix}
-\mu - \beta(1 - \delta)[ci + \theta(i - \omega)b] \\
\beta(1 - \delta)[ci + \theta(i - \omega)b] - f\alpha \\
\alpha - (1 - f)\alpha
\end{pmatrix}
\]

Consider the system of differential equations \( \dot{x} = f(x) \) subject to initial conditions \((s_0, i_0, b_0)^T = x_0\). Let \( x(t, x_0) \) be a solution of the system. System (25) has a unique endemic equilibrium point \( E^* \) in \( D \) and there exists a compact absorbing set \( K \subset D \). It is further assumed that system (25) satisfies the Bendixson criterion, which is robust under \( C^1 \) local perturbations of \( f \) at all non-equilibrium non-wandering points of the system. Let \( x \rightarrow M(x) \) be a \( 3 \times 3 \) matrix–valued function that is \( C^1 \) for \( x \in D \). It is also assumed that \( M^{-1}(x) \) exists and is continuous for \( x \in K \). Then the unique endemic equilibrium point \( E^* \) is globally stable in \( D \) if

\[ \tilde{q}_2 = \limsup_{t \rightarrow \infty} \sup_{x_0 \in K} \frac{1}{t} \int_0^t m(Q(x(s, x_0)))ds \]

where \( Q = P_f P^{-1} + P_f \tilde{J}^2 P^{-1} \). The value \( P_f \) is obtained by replacing each entry \( p_{ij} \) in \( P \) by its directional derivative in the direction of \( f, \nabla p_{ij}^* f \) and \( m(Q) \) in the Lozinskii measure of \( Q \) with respect to a vector norm \( |\cdot| \) in \( \mathbb{R}_3^+ \), defined by (see Coppel\(^{26}\))

\[ m(Q) = \lim_{h \rightarrow 0^+} \frac{|y + h\tilde{J} - y|}{h} \]

The Jacobian matrix of system (25) along \((s, i, b)\) is

\[ \begin{pmatrix}
-\beta(1 - \delta)cs - \beta(1 - \delta)(1 - \omega)s + (1 - \kappa)\phi \\
(1 - \delta)cs - \gamma - \mu - f\alpha \\
(1 - \delta)cs - \gamma - (1 - f)\alpha
\end{pmatrix} \]

The corresponding associated second compound matrix \( J^{(2)} \) (for a detailed discussion of compound matrices, their properties and their relations to differential equations, the readers are referred to Muldowney\(^{26}\)) is given by

\[ J^{(2)} = \begin{pmatrix}
A_1 & \beta(1 - \delta)(1 - \omega)s + (1 - f)\alpha & \beta(1 - \delta)(1 - \omega)s + (1 - \kappa)\phi \\
(1 - f)\alpha & \beta(1 - \delta)(1 - \omega)s + (1 - f)\alpha & (1 - \delta)cs \\
(1 - f)\alpha & (1 - f)\alpha & \beta(1 - \delta)cs
\end{pmatrix} \]

with

\[ A_1 = -2\mu - \gamma - f\alpha - \beta(1 - \delta)[ci + \theta(i - \omega)b] + \beta cs \]
\[ A_2 = -2\mu - (1 - \kappa)\phi - (2 - f) - \beta(1 - \delta)[ci + \theta(i - \omega)b] \]
\[ A_3 = -2\mu - 2\alpha - \gamma - (1 - \kappa)\phi + \beta(1 - \delta)cs \]

Set \( P(x) = P(s, i, b) \) as

\[ P(s, i, b) = \begin{pmatrix}
1 & 0 & 0 \\
0 & i & 0 \\
0 & 0 & i
\end{pmatrix} \]

Then

\[ P_f P^{-1} = \begin{pmatrix}
0 & \frac{i'}{i} & 0 \\
0 & 1 & \frac{b'}{b} \\
0 & 0 & \frac{b'}{i}
\end{pmatrix} \]

and the matrix \( Q = P_f P^{-1} + P_f \tilde{J}^2 P^{-1} \) in (3.3) can be written in block form:

\[ Q = \begin{bmatrix}
Q_{11} & Q_{12} \\
Q_{21} & Q_{22}
\end{bmatrix} \]

where
\[ Q_{11} = -2\mu - \gamma - f\alpha - \beta(1 - \delta)[ci + \theta(1 - \omega)b] + \beta(1 - \delta)cs \]
\[ Q_{12} = \left( (\beta\theta(1 - \delta)(1 - \omega)s + (1 - f)\alpha) \frac{b}{i} \right) \beta(1 - \delta)(1 - \omega)b \]
\[ Q_{21} = \left( \frac{(1 - p)\gamma - (1 - f)\alpha}{b} \right) \right) \]
\[ Q_{22} = \left( -2\mu - \phi - (2 - f) - \beta(1 - \delta)[ci + \theta(1 - \omega)b] \right) \beta(1 - \delta)[ci + \theta(1 - \omega)b] - f\alpha \]

Let \((x, y, z)\) be a vector in \(\mathbb{R}^3\). We choose a vector norm in \(\mathbb{R}^3\) as
\[ |(x, y, z)| = \max \{|x|, |y|, |z|\} \]
for any vector \((x, y, z)\) \(\in \mathbb{R}^3\). Let \(m\) denote the Lozinskii measure with respect to this norm. We can then obtain
\[ m(Q) \leq \sup \{g_1, g_2\} \]
with
\[ g_1 = m_1(Q_{11}) + |Q_{12}| \]
\[ g_2 = |Q_{21}| + m_1(Q_{22}) \]

Here \(|Q_{12}|\) and \(|Q_{21}|\) are matrix norms with respect to the \(L_1\) vector norm, and \(m_1\) denotes the Lozinskii measure with respect to the \(L_1\) norm. More specifically,
\[ m_1(Q_{11}) = -2\mu - \gamma - f\alpha - \beta(1 - \delta)[ci + \theta(1 - \omega)b] + \beta(1 - \delta)cs \]
\[ m_1(Q_{22}) = -2\mu - 2\alpha - (1 - \kappa)\phi + \sup \{-\gamma, 0\} \]

Therefore
\[ g_1 = -2\mu - \gamma - f\alpha - \beta(1 - \delta)[ci + \theta(1 - \omega)b] + \beta(1 - \delta)cs + [\beta\theta(1 - \delta)(1 - \omega)s + (1 - f)\alpha] \frac{b}{i} \]
\[ g_2 = -2\mu - 2\alpha - (1 - \kappa)\phi + (1 - p)\gamma \frac{i}{b} + \frac{i'}{i} \frac{b'}{b} \]

Since \(0 \leq i(t) \leq 1\), there exists \(T > 0\) such that when \(t > T\),
\[ \frac{\ln i(t) - \ln i(0)}{t} < \frac{(\mu + f\alpha)}{2} \]

As a result,
\[ \frac{1}{t} \int_0^T m(Q) dt \leq \frac{1}{t} \int_0^T \left( \frac{i'}{i} - \mu \right) dt \]

which implies \(\tilde{q}_2 < 0\), thus completing the proof. We summarize the result in Theorem 3.2.