Backward Bifurcation in HCV Transmission Dynamics

by

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Abstract

The thesis is based on the use of mathematical theories and techniques to gain qualitative and quantitative insight into the transmission dynamics of hepatitis C virus (HCV) in an IDU (injecting drug user) population. A deterministic model, which stratifies the IDU population into eight mutually-exclusive compartments (based on epidemiological status), is considered. Rigorous qualitative analysis of the model (both in the absence or presence of anti-HCV treatment) establishes, for the first time, the presence of the phenomenon of backward bifurcation in HCV transmission dynamics. The presence of the backward bifurcation phenomenon, which is characterized by the co-existence of asymptotically-stable HCV-free and HCV-present equilibria when the associated reproduction number of the model is less than unity, makes effective control of the disease difficult (since, in a backward bifurcation situation, the classical epidemiological requirement of having the associated reproduction number of the model to be less than unity, while necessary, is no longer sufficient for such effective control (or elimination)). Three routes (or causes) to such a dynamic phenomenon have been established. Furthermore, five main parameters that play a dominant role on the transmission dynamics of the disease have been identified. Numerical simulations of the model show that the re-infection of recovered individuals has marginal effect on the HCV burden (as measured in terms of the cumulative incidence and prevalence of the disease) in the IDU community.

Acknowledgements

Foremost, I would like to express my sincere gratitude to my advisor Professor Abba B. Gumel whose expertise, understanding, and patience added considerably to my graduate experience. His guidance, enthusiasm and encouragement helped me throughout the period of my research work and writing of the thesis. I would like to thank the Department of Mathematics, together with the Faculty of Graduate Studies and the Faculty of Science, of the University of Manitoba, for the financial support during my M.Sc. program. I am thankful to the graduate students in the department for their friendship and support. I am deeply grateful to members of our research group (Aliya Alsaleh, Farinaz Forouzannia, Ali Javame and Lindsay Simpson) for their kindness and support. Finally, I acknowledge the support and love of my family, especially my parents who inspired me in all steps of my life.

Dedication

To my parents, who shine into my life like the sun.

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Glossary

Abbreviation	Meaning
DFE	Disease-free Equilibrium
EEP	Endemic Equilibrium Point
GAS	Globally-asymptotically Stable
HCV	Hepatitis C Virus
IDU	Injecting Drug User
LAS	Locally-asymptotically Stable
LHS	Latin Hypercube Sampling
ODE	Ordinary Differential Equation
$PRCC$	Partial Rank Correlation Coefficient

Chapter 1

Introduction

Hepatitis C, a blood-borne viral infectious disease caused by the single-strained RNA Hepatitis C virus (HCV) [2, 10], continues to pose major public health challenges globally. The World Health Organization (WHO) recently estimated the HCV prevalence to be between 2-3% (i.e., 130-170 million people currently live with HCV infection globally) [35, 43, 54, 56]. Countries in Africa and Asia have the highest reported prevalence rates, while industrialized countries in North America, Northern and Western Europe and Australia have lower prevalence (Germany (0.6%), Canada (0.8%), France (1.1%), and Australia (1.1%) have relatively low rates of HCV seroprevalence, with the USA (1.8%), Japan (1.5-2.3%), and Italy (2.2%) having slightly higher seroprevalence rates) [43, 54]. A global map of HCV, showing the geographic spread of the disease, is depicted in Figure 1.1.

The primary mode of HCV transmission is through blood contact [1, 56]. In particular, there are three main age-specific transmission patterns [1, 48]. The first is the 30-49 year age (middle age) group in developed countries (such as the United Kingdom and USA) [35, 48]. For this age group, injecting drug use (IDU) is the major cause of HCV infection (*via* needle and syringe-sharing; with over 80% of new cases attributed to injecting drugs use) [35, 48]. The second transmission pattern is for

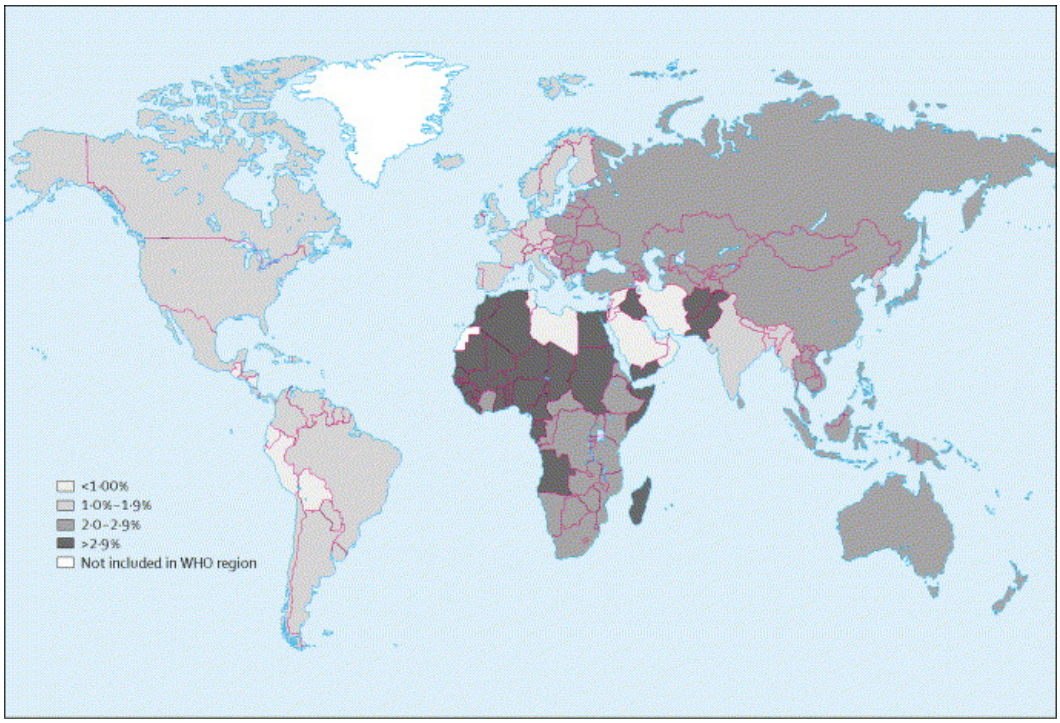

Figure 1.1: Estimated prevalence of HCV infection by WHO region [43].

the elderly (as is the case in Japan [30, 39, 48, 53]). The third transmission pattern entails all age groups. For these two later categories, the causes (or risk factors) of HCV infection include unsafe therapeutic injections (performed by both healthcare professionals and non-professionals) and blood transfusion from unscreened donors. In addition to the aforementioned HCV risk factors, other factors, such as exposure to blood by the healthcare workers (mostly through contact with contaminated needles), mother-to-child transmission, sex with an infected partner, sex with multiple partners and other healthcare-related procedures, further contribute to HCV transmission [43].

The common symptoms of HCV infection include jaundice, dark urine, fatigue, nausea, vomiting, and abdominal pain [14, 28]. While the majority of patients with acute HCV will progress to chronic infection [2, 10, 14], about 25% of cases clear the virus and build natural immunity against re-infection [21]. The mean incubation period for acute HCV infection is 7 weeks [27]. Unfortunately, up to 90%

of HCV-infected individuals (acute or chronic) may not be aware of their infection status (i.e., they are asymptomatically-infected). Consequently, if undetected and untreated, about $7-18\%$ of these (asymptomatically-infected) individuals will progress to develop liver disease, such as liver fibrosis, cirrhosis, hepatocellular carcinoma, within 20 years (and about 5%-7% of these patients may ultimately die) [2, 10, 14, 17, 28, 35, 54, 56].

1.1 Control Strategies

HCV-infected individuals can be treated using a combination therapy with *pegylated interferon* and *ribavirin* (having a response rate of 40% to 80%) [14, 19] (furthermore, several new anti-HCV drugs have recently been approved and/or are undergoing various stages of clinical trials [33]). Although there is currently no safe and effective vaccine for use against HCV infection in humans, efforts are underway to develop one [14, 17]. Another intervention strategy for controlling HCV transmission among IDUs is increasing the access to unused syringes and needles, aimed at reducing the frequency of sharing/unsafe injection needles (it should, however, be mentioned that although this approach may have positive effect on reducing HCV transmission, there is no evidence for substantial reductions in HCV prevalence) [36, 46, 49].

1.2 Literature Review

Several mathematical and statistical models have been developed and used to gain insight into the transmission dynamics of HCV in an IDU population [8, 9, 31, 35, 45, 51, 52]. Corson *et al.* [9] developed a deterministic compartmental mathematical model for the spread of HCV in an IDU population that has been separated into two groups (naive and experienced) based on the time since the onset of injection (and includes measures that allow for the prevention of HCV infection). Sutton *et al.* [45]

used statistical modelling to estimate the force of infection of HCV and hepatitis B virus in England and Wales (using saliva sample of IDUs) for 1998-2003.

Vickerman *et al.* [51] used a deterministic model to simulate the transmission of HCV in IDUs in London, England and assessed the impact of intervention measures that reduced string and needle sharing in some of the targeted IDU populations. Elbasha [14] introduced the effect of the re-infection of recovered chronically-infected individuals (and associated heterogeneity between re-infected individuals and primary infected individuals) on HCV transmission dynamics *via* the use of a deterministic model. Furthermore, Elbasha [14] provided a rigorous qualitative analysis of a special case of the model in [14] (where re-infected individuals behave in the same manner as primary infected individuals, with respect to disease infectivity, recovery, progression and treatment).

1.3 Objectives of the Thesis

The main purpose of this thesis is to gain qualitative insight into the effect of treatment on the transmission dynamics of HCV in an IDU population. To achieve this objective, the treatment model developed in [14] will be considered (and fully analysed, unlike the special case considered in [14]). Furthermore, the effect of uncertainties on the associated parameters of the model (on the overall simulation results obtained) will be assessed using Latin Hypercube Sampling (LHS) and Partial Ranked Correlation Coefficients (PRCC) [4, 34, 41]. Some of the specific questions to be addressed in the thesis include:

(1) What are the main qualitative features of a basic HCV transmission model (in the absence of treatment), which allows for the re-infection of recovered individuals? The aim here is to determine conditions for the existence and asymptotic stability of the associated equilibria of the basic model, as well as

to characterize the types of bifurcation the model may undergo.

(2) What is the qualitative impact of the use of anti-HCV drugs in HCV transmission dynamics? In particular, considering the fact that a few active IDUs are treated [36], does the use of anti-HCV treatment in the IDU population offer considerable effect on HCV prevalence in the population?

(3) What is the qualitative (and public health) impact of the heterogeneity between primary infection and re-infection (of recovered individuals) in HCV transmission dynamics? In particular, does the resulting model (which allows for such a heterogeneity) exhibit the phenomenon of backward bifurcation [24, 25, 38, 40, 42]? If yes, what are the main drivers (causes) of this dynamic behaviour?

(4) What is the qualitative, and quantitative, impact of the effectiveness levels of an anti-HCV treatment strategy implemented within the IDU population?

Since the models to be considered in this thesis monitor human populations, all their associated parameters are assumed to be non-negative.

1.4 Thesis Outline

The thesis is organized as follows. Chapter 1 covers the introductory epidemiological aspects of HCV transmission dynamics. The basic mathematical concepts relevant to the thesis are reviewed in Chapter 2. A basic treatment-free model for HCV transmission dynamics in an IDU population is considered, and rigorously analysed, in Chapter 3. The basic model is extended, in Chapter 4, to incorporate the effect of anti-viral drug treatment. The resulting treatment model is also rigorously analysed. Uncertainty and sensitivity analyses of both treatment-free and treatment models

are carried out in Chapters 3 and 4, respectively. Numerical simulation results are also presented.

Chapter 2

Mathematical Preliminaries

This chapter introduces some of the basic mathematical definitions, theories and methodologies relevant to the thesis.

2.1 Equilibria of Autonomous Systems of Ordinary Differential Equations (ODEs)

It should be mentioned that, in this thesis, only *autonomous* systems of ODEs, given by (where a dot represents differentiation with respect to time t)

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n, \tag{2.1}$$

are considered.

Definition 2.1. *A point $\bar{x} \in \mathbb{R}^n$ is called an equilibrium point of the autonomous system (2.1) if $f(\bar{x}) = 0$.*

Theorem 2.1. (Fundamental Existence- Uniqueness Theorem [40]). *Let E be an open subset of $\mathbb{R}^n$ containing x_0 and assume that $f \in C^1(E)$. Then, there exists an*

$a > 0$ such that the initial value problem:

$$\dot{x} = f(x), \quad x(0) = x_0,$$

has a unique solution $x(t)$ on the interval $[-a, a]$.

Definition 2.2. [40]. *The Jacobian matrix of f at the equilibrium $\bar{x}$, denoted by $Df(\bar{x})$, is the matrix,*

$$J(\bar{x}) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(\bar{x}) & \cdots & \frac{\partial f_1}{\partial x_n}(\bar{x}) \\ \vdots & \vdots & \vdots \\ \frac{\partial f_n}{\partial x_1}(\bar{x}) & \cdots & \frac{\partial f_n}{\partial x_n}(\bar{x}) \end{pmatrix},$$

of partial derivatives of f evaluated at $\bar{x}$.

Definition 2.3. [40]. *The linear system $\dot{x} = Ax$, with the matrix $A = Df(\bar{x})$, is called the linearization of the system (2.1) at the equilibrium $\bar{x}$.*

Definition 2.4. [40]. *An equilibrium point $\bar{x}$ is called a hyperbolic equilibrium point of the autonomous system (2.1) if none of the eigenvalues of $Df(\bar{x})$ has zero real part.*

Definition 2.5. [40]. *An equilibrium point that is not hyperbolic is called non-hyperbolic.*

2.2 Hartman-Grobman Theorem

Let,

$$\begin{aligned} \dot{x} &= f(x), \quad x \in \mathbb{R}^n, \\ \dot{y} &= g(y), \quad y \in \mathbb{R}^n, \end{aligned} \tag{2.2}$$

be two C^r $(r \geq 1)$ vector fields on $\mathbb{R}^n$.

Definition 2.6. [55]. *The dynamics generated by the vector fields f and g of (2.2) are said to be locally C^k conjugate ($k \leq r$) if there exists a C^k diffeomorphisim h which takes the orbits of the flow generated by f, $\phi(t,x)$, to the orbits of the flow generated by g, $\psi(t,y)$, preserving orientation and parameterization by time.*

Theorem 2.2. (Hartman-Grobman Theorem [55]). *Consider a $C^r(r \geq 1)$ vector field*

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n, \tag{2.3}$$

with domain of f to be a large open subset of $\mathbb{R}^n$. Suppose also that (2.3) has equilibrium solutions which are hyperbolic. Consider the associated linear vector field

$$\dot{\xi} = Df(\bar{x})\xi, \quad \xi \in \mathbb{R}^n. \tag{2.4}$$

Then the flow generated by (2.3) is C^0 conjugate to the flow generated by the linearized system (2.4) in a neighbourhood of the equilibrium point $x = \bar{x}$.

It should be noted that the Hartman-Grobman Theorem guarantees a homomorphism between the flow of the non-linear ODE system and that of its linearization. In general, near a hyperbolic equilibrium point $\bar{x}$, the non-linear system $\dot{x} = f(x)$ has the same qualitative structure as the linear system $\dot{x} = Ax$ with $A = Df(\bar{x})$.

2.3 Stability Theory

Definition 2.7. [55]. *The equilibrium $\bar{x}$ is said to be stable if given $\epsilon > 0$, there exists a $\delta = \delta(\epsilon) > 0$ such that, for any solution $y(t)$ of (2.1) satisfying $|\bar{x} - y(t_0)| < \delta$, $|\bar{x} - y(t)| < \epsilon$ for $t > t_0, t_0 \in \mathbb{R}$.*

Definition 2.8. [55]. *The equilibrium $\bar{x}$ is said to be asymptotically-stable if it is*

stable and there exists a constant $c > 0$ such that, for any solution $y(t)$ of (2.1) satisfying $|\bar{x} - y(t_0)| < c$, then $\lim_{t\to\infty} |\bar{x} - y(t)| = 0$.

Definition 2.9. [55]. *An equilibrium solution which is not stable is said to be unstable.*

Theorem 2.3. [55]. *Suppose all the eigenvalues of $Df(\bar{x})$ have negative real parts. Then the equilibrium solution $x = \bar{x}$ of the system (2.1) is locally asymptotically stable, and unstable if at least one of the eigenvalues has positive real part.*

2.4 Center Manifold Theory

Center Manifold theory is a mathematical technique for reducing the dimensionality of a given non-linear system near an equilibrium point. Consider the non-linear dynamical system (2.1). Let,

$$\dot{x} = Ax, \tag{2.5}$$

be the corresponding linearized system (with $A = Df(\bar{x})$) near a hyperbolic equilibrium point $\bar{x}$.

Definition 2.10. [55]. *The stable, unstable, and center subspaces of the linear system (2.5) are defined by (where $A \in M_{nn}(\mathbb{R})$)*

$$\begin{aligned} E^s &= span\left\{u_j, v_j; a_j < 0\right\}, \\ E^u &= span\left\{u_j, v_j; a_j > 0\right\}, \\ E^c &= span\left\{u_j, v_j; a_j = 0\right\}, \end{aligned}$$

where $w_j = u_j \pm iv_j$ are eigenvectors corresponding to the eigenvalues $\lambda_j = a_j \pm ib_j$.

Remark 2.1. [55]. *For a hyperbolic flow of a linear system, $\mathbb{R}^n = E^s \oplus E^c$. These subspaces become manifolds for nonlinear ODEs.*

Theorem 2.4. (Stable Manifold Theory [40]). *Let $f \in C^1(E)$ where E is an open subset of $\mathbb{R}^n$ containing the origin, and let ϕ_t be the flow of non-linear system (2.1). Suppose that $f(0) = 0$ and $Df(0)$ has k eigenvalues with negative real parts, and $q = n - k$ eigenvalues with positive real parts. Then, there exists a k-dimensional differentiable manifold S tangent to the stable subspace E^s of the linear system (2.5) at 0 such that for all $t \geq 0, \phi_t(S) \subset S$ and for all $x_0 \in S$*

$$\lim_{t\to\infty} \phi_t(x_0) = 0,$$

and there exists a q-dimensional differentiable manifold U tangent to the unstable subspace E^u of the linear system (2.5) at 0 such that for all $t \geq 0, \phi_t(U) \subset U$ and for all $x_0 \in U$

$$\lim_{t\to-\infty} \phi_t(x_0) = 0.$$

Definition 2.11. [40]. *Let ϕ_t be the flow of non-linear system (2.1). The global stable and unstable manifolds of (2.5) at 0, defined, respectively, by*

$$W^s(0) = \bigcup_{t\leq 0} \phi_t(S),$$

and,

$$W^u(0) = \bigcup_{t\geq 0} \phi_t(U),$$

are also, respectively, referred to as the global stable and unstable manifolds of the origin.

Theorem 2.5. [40]. *Let $f \in C^r(E)$ where E is an open subset of $\mathbb{R}^n$ containing the origin and $r \geq 1$. Suppose that $f(0) = 0$ and that $Df(0)$ has k eigenvalues with negative real parts, j eigenvalues with positive real parts, and $m = n - k - j$ eigenvalues with zero real parts. Then, there exists an $m-$ dimensional center manifold $W^c(0)$ of class C^r tangent to center subspace E^c of (2.5) which is invariant*

under the flow ϕ_t of (2.1).

Lemma 2.1. [40]. *The local center manifold of the system (2.1) at 0,*

$$W^c_{loc}(0) = \{(x, y) \in \mathbb{R}^m \times \mathbb{R}^k \mid y = h(x) \quad \text{for} \quad |x| < \delta\}, \tag{2.6}$$

for some $\delta > 0$, where $h \in C^r(N_\delta(0))$, $h(0) = 0$ and $Dh(0) = 0$ since $W^c(0)$ is tangent to the center subspace

$$E^c = \{(x, y) \in \mathbb{R}^m \times \mathbb{R}^k \mid y = 0\},$$

at the origin.

Theorem 2.6. (Center Manifold Theory [40]). *Let $f \in C^r(E)$ where E is an open subset of $\mathbb{R}^n$ containing the origin and $r \geq 1$. Suppose that $f(0) = 0$ and that $Df(0)$ has m eigenvalues with zero real parts and k eigenvalues with negative real parts, where $m + k = n$. The system (2.1) then can be written in diagonal form*

$$\begin{aligned} \dot{x} &= Cx + F(x, y), \\ \dot{y} &= Py + G(x, y), \end{aligned}$$

where $(x, y) \in \mathbb{R}^m \times \mathbb{R}^k$, C is a square matrix with m eigenvalues having zero real parts, P is a square matrix with k eigenvalues with negative real parts, and $F(0) = G(0) = 0$, $DF(0) = DG(0) = 0$; furthermore, there exists a $\delta > 0$ and a function $h \in C^r(N_\delta(0))$ that defines the local center manifold (2.6) and satisfies

$$Dh(x)[Cx + F(x, h(x))] - Ph(x) - G(x, h(x)) = 0$$

for $|x| < \delta$; and the flow on the center manifold $W^c(0)$ is defined by the system of

differential equations

$$\dot{x} = Cx + F(x, h(x))$$

for all $x \in \mathbb{R}^m$ *with* $|x| < \delta$.

Theorems 2.5 and 2.6 can be used to determine the flow near non-hyperbolic equilibrium points [5, 40].

2.5 Bifurcation Theory

Real-life systems arising in the natural and engineering sciences typically involve parameters which appear in their governing system of equations. As these parameters are varied, changes may occur in the qualitative structures of the solutions of the system of equations (modelling the real-life phenomenon) for certain parameter values. These changes are called *bifurcations* [26]. The parameter values where bifurcations occur are called *bifurcation* values (or *bifurcation points*). A formal definition of bifurcation at a point is given below.

Definition 2.12. [55]. *Let*

$$\dot{x} = f(x, \mu),\ x \in \mathbb{R}^n,\ \mu \in \mathbb{R}, \tag{2.7}$$

be a one-parameter family of one-dimensional ODEs. An equilibrium solution of (2.7) given by $(x, \mu) = (0, 0)$ *is said to undergo bifurcation at* $\mu = 0$ *if the flow for* μ *near zero and* x *near zero is not qualitatively the same as the flow near* $x = 0$ *at* $\mu = 0$.

There are numerous types of bifurcations, including saddle-node, forward (transcritical), pitchfork, Hopf, and backward bifurcation [24, 25, 38, 40, 42]. Two of these bifurcations (forward and backward) are relevant to the thesis, and are briefly discussed below.

2.5.1 Forward bifurcation

The dynamics of disease transmission models is often characterized by the reproduction number ($\mathcal{R}_0$), a threshold quantity which measures the average number of new cases generated by a typical infected individual when introduced into a completely-susceptible population [3, 12, 25]. Typically, when $\mathcal{R}_0$ is less than unity, a small stream of infected individuals will not generate large outbreaks (and the disease dies out in time). In such a case, the disease-free equilibrium (DFE) of the model is asymptotically-stable. On the other hand, the disease persists in the population if $\mathcal{R}_0$ exceeds unity (where, in this case, an asymptotically-stable endemic equilibrium point (EEP) exists [3, 25]). This phenomenon, where the DFE and an EEP of a model exchange their stability at $\mathcal{R}_0 = 1$, is known as *forward bifurcation* [22, 25, 42, 57]. Figure 2.1 depicts a forward bifurcation diagram.

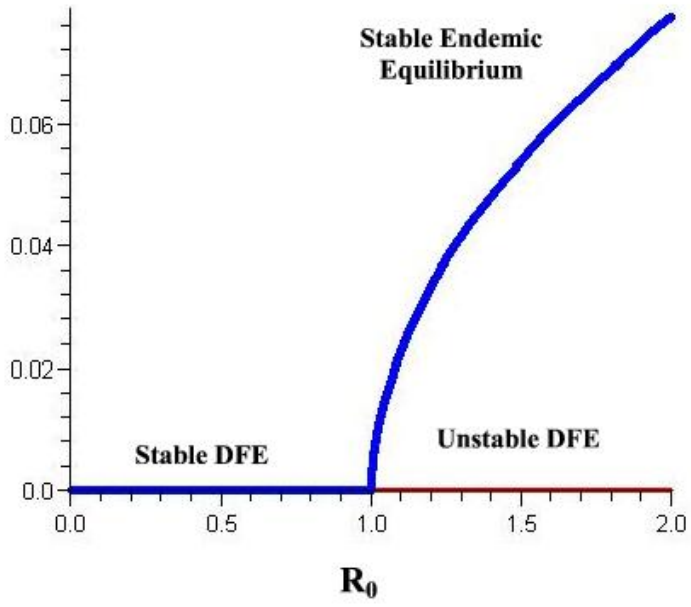

Figure 2.1: Forward bifurcation diagram, showing the infection rate (λ) as a function of the basic reproduction number ($\mathcal{R}_0$).

2.5.2 Backward bifurcation

In general, for models that exhibit forward bifurcation, the requirement $\mathcal{R}_0 < 1$ is necessary and sufficient for effective community-wide control (or elimination) of the disease being modelled. However, it has been observed in some other modelling studies, that although $\mathcal{R}_0 < 1$ is necessary for effective disease control (or elimination), the condition may not be sufficient. This is owing to a dynamic phenomenon known as *backward bifurcation* [24, 25, 38, 40, 42], where two stable attractors (typically the DFE and an asymptotically-stable EEP) of the model co-exist when $\mathcal{R}_0 < 1$. The public health implication of backward bifurcation is that disease control (or elimination), when $\mathcal{R}_0 < 1$, is dependent on the initial sizes of the sub-populations of the model. Thus, the presence of backward bifurcation in the transmission dynamics of a disease in a population makes its effective community-wide control difficult. Figure 2.2 depicts a backward bifurcation diagram.

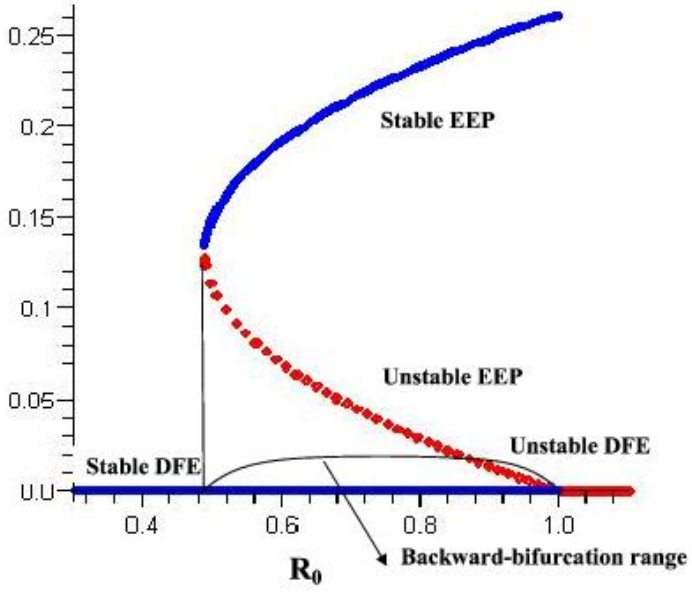

Figure 2.2: Backward bifurcation diagram, showing the co-existence of a stable DFE and two branches of endemic equilibria (a stable and an unstable branch).

The following theorem will be used to explore the possibility of the presence of

backward bifurcation in the models to be considered in Chapters 3 and 4 of this thesis.

Theorem 2.7. [6, 13, 50]. *Consider the following general system of ordinary differential equations with a parameter* ϕ

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \quad \textit{and} \quad f \in \mathbb{C}^2 \left(\mathbb{R}^n \times \mathbb{R}\right), \tag{2.8}$$

where 0 is an equilibrium point of the system (that is, $f(0, \phi) \equiv 0$ *for all* ϕ*) and assume*

A.1) $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ *is the linearization matrix of the system (2.8) around the equilibrium 0 with* ϕ *evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;*

A.2) Matrix A has a right eigenvector w *and a left eigenvector* v *(each corresponding to the zero eigenvalue).*

Let f_k *be the k-th component of* f *and*

$$\begin{aligned} a &= \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ b &= \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \end{aligned}$$

Then the local dynamics of the system around the equilibrium point 0 is totally determined by the signs of a and b. Particularly, if $a > 0$ *and* $b > 0$*, then a backward bifurcation occurs at* $\phi = 0$*.*

2.6 Lyapunov Function Theory

Definition 2.13. [40]. *A point $x_0 \in \mathbb{R}^n$ is called an $\omega-$limit point of $x \in \mathbb{R}^n$, denoted by $\omega(x)$, if there exists a sequence $\{t_i\}$ such that*

$$\phi(t_i, x) \to x_0 \quad \text{as} \quad t_i \to \infty.$$

Definition 2.14. [40]. *A point $x_0 \in \mathbb{R}^n$ is called an $\alpha-$limit point of $x \in \mathbb{R}^n$, denoted by $\alpha(x)$, if there exists a sequence $\{t_i\}$ such that*

$$\phi(t_i, x) \to x_0 \quad \text{as} \quad t_i \to -\infty.$$

Definition 2.15. [40]. *The set of all $\omega-$limit points of a flow is called the $\omega-$limit set. Similarly, The set of all $\alpha-$limit points of a flow is called the $\alpha-$limit set.*

Definition 2.16. [55]. *Let $S \subset \mathbb{R}^n$ be a set. Then, S is said to be invariant under the flow generated by $\dot{x} = f(x)$ if for any $x_0 \in S$ we have $\phi(t, x_0) \in S$ for all $t \in \mathbb{R}$.*

Lemma 2.2. [55]. *A set $S \subset \mathbb{R}^n$ is positively-invariant if for every $x_0 \in S$, $\phi(t, x_0) \in S$, $\forall t \geq 0$.*

Definition 2.17. [55]. *A function $V : \mathbb{R}^n \to \mathbb{R}$ is said to be positive-definite if:*

- *$V(x) > 0$ for all $x \neq 0$,*
- *$V(x) = 0$ if and only if $x = 0$.*

Definition 2.18. [55]. *Consider the system (2.1). Let, $\bar{x}$ be an equilibrium solution of (2.1) and let $V : U \to \mathbb{R}$ be a C^1 function defined on some neighbourhood U of $\bar{x}$ such that*

i) V is positive-definite,

ii) $\dot{V}(x) \leq 0$ in $U \setminus \{\bar{x}\}$.

Corollary 2.1. [55]. *Any function, V, that satisfies Conditions (i) and (ii) above is called a Lyapunov function.*

Theorem 2.8. (LaSalle's Invariance Principle [24]). *Consider the system (2.1). Let,*

$$S = \{x \in \bar{U} : \dot{V}(x) = 0\} \tag{2.9}$$

and M be the largest positive invariant set of (2.1) in S. If V is a Lyapunov function on U and $\gamma^+(x_0)$ is a bounded orbit of (2.1) which lies in S, then the $\omega-$limit set of $\gamma^+(x_0)$ belongs to M; that is, $x(t, x_0) \to M$ as $t \to \infty$.

Corollary 2.2. *If $V(x) \to \infty$ as $|x| \to \infty$ and $\dot{V} \leq 0$ on $\mathbb{R}^n$, then every solution of (2.1) is bounded and approaches the largest invariant set M of (2.1) in the set where $\dot{V} = 0$. In particular, if $M = \{0\}$, then the solution $x = 0$ is globally-asymptotically stable (GAS).*

2.7 Comparison Theorem

Consider the autonomous system

$$\dot{x} = f(x), x \in \mathbb{R}^n, \tag{2.10}$$

where f is continuously-differentiable on an open subset $\mathcal{D} \subset \mathbb{R}^n$. Let $\phi_t(x)$ denote the solution of the system (2.10) with initial value x.

Definition 2.19. [44]. *f is said to be Type $\mathcal{K}$ in $\mathcal{D}$ if for each i, $f_i(a) < f_i(b)$ for any two points in $\mathcal{D}$ satisfying $a \leq b$ and $a_i = b_i$.*

The Type $\mathcal{K}$ Condition can be identified from the sign structure of the associated Jacobian matrix of the system (2.10), as described above.

Definition 2.20. [44]. *$\mathcal{D}$ is P-convex if $tx + (1-t)y \in \mathcal{D}$ for all $t \in [0, 1]$ whenever $x, y \in \mathcal{D}$ and $x < y$.*

It is clear that if $\mathcal{D}$ is a convex set, then it is also p-convex. Furthermore, if $\mathcal{D}$ is a p-convex subset of $\mathbb{R}^n$ and

$$\frac{\partial f_i}{\partial x_j} \geq 0, \quad i \neq j, \quad x \in \mathcal{D},$$

then f is of Type $\mathcal{K}$ in $\mathcal{D}$.

Another approach for establishing the global asymptotic stability of equilibria of dynamical systems is by using the comparison theorem [44]. This entails comparing the solution of the non-linear system

$$\dot{x} = f(t, x), \tag{2.11}$$

with the solution of the differential inequality system,

$$\dot{z} \leq f(t, z), \tag{2.12}$$

or,

$$\dot{y} \geq f(t, y), \tag{2.13}$$

on an interval. This method requires that the solution of the system (2.11) is unique, and that f is of Type $\mathcal{K}$.

Theorem 2.9. (Comparison Theorem [44]). *Let f be continuous on $\mathbb{R} \times \mathcal{D}$ and of Type $\mathcal{K}$. Let $x(t)$ be a solution of* (2.11) *defined on $[a, b]$. If $z(t)$ is a continuous function on $[a, b]$ satisfying (2.12) on (a, b) with $z(a) \leq x(a)$, then $z(t) \leq x(t)$ for all t in $[a, b]$. If $y(t)$ is continuous on $[a, b]$ satisfying* (2.13) *on (a, b) with $y(a) \geq x(a)$, then $y(t) \geq x(t)$, for all t in $[a, b]$.*

2.8 Next Generation Operator Method

The next generation operator method [11, 50] is popularly used in the mathematical biology literature to compute the reproduction number ($\mathcal{R}_0$) of disease transmission models (and, subsequently, to establish the local asymptotic stability of the associated disease-free equilibrium of the model). The reproduction number ($\mathcal{R}_0$) measures the average number of new infection generated by a typical infected individual introduced into a completely susceptible population [11, 50]. The formulation given in [50] is briefly described below.

Suppose the given disease transmission model, with non-negative initial conditions, can be written in terms of the following autonomous system:

$$\dot{x}_i = f(x) = F_i(x) - V_i(x), \quad i = 1, ..., n, \tag{2.14}$$

where $V_i = V_i^- - V_i^+$ and the functions satisfy the following axioms below. First of all, let

$$\{X_s = x \geq 0 \mid x_i = 0; \quad i = 1, ..., m\},$$

be the set of disease-free states (non-infected state variables) of the model, where $x = (x_1, ..., x_n)^t$, $x_i \geq 0$ represents the number of individuals in each compartment of the model. Furthermore, consider the following axioms [50]:

(**A1**) If $x \geq 0$, then F_i, V_i^+, $V_i^- \geq 0$ for $i = 1, ..., m$.

(**A2**) If $x_i = 0$, then $V_i^- = 0$. In particular, if $x \in X_s$ then $V_i^- = 0$ for $i = 1, ..., m$.

(**A3**) $F_i = 0$ if $i > m$.

(**A4**) If $x \in X_s$, then $F_i(x) = 0$ and $V_i^+(x) = 0$ for $i = 1, ..., m$.

(**A5**) If $F(x)$ is set to zero, then all eigenvalues of $D(f(x_0))$ have negative real parts.

In the formulation above, $F_i(x)$ represents the rate of appearance of new infections in compartment i, $V_i^+(x)$ represents the rate of transfer of individuals into compartment i. It is assumed that these functions are at least twice continuously-differentiable in each variable [50].

Definition 2.21. [44] *(M-Matrix). An $n \times n$ matrix A is an M-matrix if and only if every of off-diagonal entriy of A is non-positive and the diagonal entries are all positive.*

Lemma 2.3. (van den Driessche and Watmough [50]). *If $\bar{x}$ is a DFE of (2.14) and $f_i(x)$ satisfy $(A1) - (A5)$, then the derivative $DF(\bar{x})$ and $DV(\bar{x})$ are partitioned as*

$$DF(\bar{x}) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, DV(\bar{x}) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

where F and V are the $m \times m$ matrices defined by,

$$F = \left[\frac{\partial F_i}{\partial x_j}(\bar{x})\right] \quad \text{and} \quad V = \left[\frac{\partial V_i}{\partial x_j}(\bar{x})\right] \quad \text{with} \quad 1 \leq i, j \leq m.$$

Furthermore, F is non-negative, V is non-singular M-matrix and J_3 and J_4 are matrices associated with the transition terms of the model, and all eigenvalues of J_4 have positive real parts.

Theorem 2.10. (van den Driessche and Watmough [50]). *Consider the disease transmission model given by (2.14) with f(x) satisfying axioms (A1)-(A5). If $\bar{x}$ is a DFE of the model, then $\bar{x}$ is LAS if $\mathcal{R}_0 = \rho(FV^{-1}) < 1$ (where ρ is the spectral radius), but unstable if $\mathcal{R}_0 > 1$.*

2.9 Latin Hypercube Sampling and Partial Rank Correlation Coefficients

Realistic disease transmission models often involve a large number of parameters (biological, demographic etc.). Consequently, uncertainties in the precise values of these parameters generally exist. The effect of such uncertainties on the numerical simulation results of the associated disease transmission model is often accounted for using an appropriate sampling technique, such as Latin Hyperbolic Sampling (LHS) [4, 41]. Furthermore, the sensitivity of each of these parameters (to a specified response/output function) can be accounted for using Partial Rank Correlation coefficients (PRCC). These methods are briefly described below.

Let $X_1, \ldots, X_d$ be input parameter values that are randomly chosen from a specified sample space (i.e., they are random variables). Furthermore, appropriate probability distribution functions (PDFs) [4, 37, 41] for each of the these parameters are chosen (based on the biology and/or epidemiology of the disease being modelled). Any specified PDF describes the range of possible values and the probability of occurrence of any specific value.

Definition 2.22. [37]. *Latin Hypercube Sampling (LHS) is a stratified sampling method for sampling the input parameter values. Using stratified sampling, the sample space S (possible range of each parameter) of X_i are partitioned into N disjoint strata of equal marginal probability $1/N$. LHS ensures us that all portions of sample space are sampled, and each of the input variables has all portions of its distribution represented by input parameter values.*

Definition 2.23. [4, 41]. *Uncertainty Analysis technique is used to investigate the uncertainty in the model output variable(s) that is generated from uncertainty in estimating the input parameter values.*

Definition 2.24. [4, 41]. *Sensitivity analysis follows uncertainty analysis to identify*

critical inputs (parameters and initial conditions) of a model and quantify how input uncertainty impacts model outcome(s).

Definition 2.25. [4]. *Partial Rank Correlation Coefficient (PRCC) can be used to evaluate the statistical relationships between each input parameter and each outcome variable, while keeping all of the other input parameters constant at their expected value.*

PRCC can only be used to assess the sensitivity of outcome variables that are monotonically related to the input parameters [4].

A PRCC between an input parameter X_j, and an output variable Y, can be calculated using the formula [4, 34]:

$$r_{X_jY} = \frac{Cov(X_j, Y)}{\sqrt{Var(X_j)Var(Y)}} = \frac{\sum_{i=1}^{N}(X_{ij} - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^{N}(X_{ij} - \bar{X})^2 \sum_{i=1}^{N}(Y_i - \bar{Y})^2}}, \tag{2.15}$$

where, $\mathrm{Cov}(X_j, Y)$ represents the covariance between X_j and Y, while $\mathrm{Var}(X_j)$ and $\mathrm{Var}(Y)$ are the variance of X_j and Y, respectively (the quantities $\bar{X}$ and $\bar{Y}$ are the respective sample means).

It is worth mentioning that PRCC always varies between -1 and $+1$. The sign of PRCC indicates the specific qualitative relationship between input and output variables. Furthermore, the magnitude of the PRCC indicates the importance of the uncertainty in estimating the value of the input variable due to the imprecision in predicting the value of the outcome variable [4, 41]. The relative importance of the input variables can be directly evaluated by comparing the PRCC values [4, 41].

Chapter 3

HCV Transmission Model with Differential Infectivity

3.1 Introduction

As stated in Chapter 1, a combination therapy with *pegylated interferon* and *ribavirin* are known to be quite effective against HCV infection [35]. Although the prevailing opinion among public health and medical practitioners in the US and UK, prior to 2002, was against treating active IDUs [35], IDUs are now not excluded from receiving anti-HCV treatment (owing to the increasing evidence showing that IDUs exhibit a similar response to anti-HCV treatment with non-IDUs [36]). Nevertheless, despite this fact, and the high number of IDUs infected, very few active IDUs have ever been treated [35]. Therefore, it is worthwhile to study the transmission dynamics of HCV among IDUs in both scenarios (with or without treatment of IDUs).

The aim of this chapter is to formulate a basic model for HCV spread in an IDU population in the absence of treatment (the case with treatment is studied in Chapter 4). The resulting treatment-free deterministic model, which allows for the re-infection of recovered individuals and loss of infection-acquired immunity (so that

re-infected individuals can revert to acute and chronic re-infection stages), will be rigorously analysed. Another notable feature of this model is that primary (newly)-infected individuals are assumed to behave different (*vis-a-vis* the infectiousness, recovery and progression of the disease) in comparison to re-infected individuals [14]. The public health impact of this (transmission) heterogeneity (between primary-infected and re-infected individuals) will be qualitatively analysed.

3.2 Model Formulation

The HCV transmission model to be considered in this study, which is a special case of the model given in [14], is based on splitting the total IDU population at time t, denoted by $N_{wt}(t)$, into the mutually-exclusive compartments of susceptible ($S(t)$), acutely-infected (I(t)), chronically-infected (P(t)), recovered with partial immunity (R(t)), acutely re-infected (V(t)) and chronically re-infected (W(t)) individuals, so that

$$N_{wt}(t) = S(t) + I(t) + P(t) + R(t) + V(t) + W(t).$$

The population of susceptible individuals (S) is increased by the recruitment of the new IDU individuals into the IDU population (at a rate Λ). It is further increased by the loss of infection-acquired immunity of recovered individuals (at a *per capita* rate, γ). It is decreased by infection, following effective contacts with infected individuals, at a rate λ_{wt}, given by

$$\lambda_{wt} = \frac{\beta(I + \pi P + \upsilon V + \omega\pi W)}{N_{wt}}. \tag{3.1}$$

In (3.1), β is the effective contact rate, π, υ and ω are modification parameters accounting for the relative infectiousness of chronically-infected, acutely-re-infected and

chronically-re-infected individuals, respectively (in comparison to acutely-infected individuals). This population is further decreased by natural death (at a rate μ; this rate is assumed, for mathematical convenience, to be the same for each of the epidemiological compartments). Thus,

$$\frac{dS}{dt} = \Lambda + \gamma R - \lambda_{wt} S - \mu S.$$

The population of acutely-infected individuals (I) is increased by the infection of susceptible individuals (at the rate λ_{wt}). It is decreased by recovery (at a rate σ), progression to chronic stage (at a rate ε) and natural death. Thus,

$$\frac{dI}{dt} = \lambda_{wt} S - (\sigma + \varepsilon + \mu) I.$$

The population of chronically-infected individuals (P) is generated at the rate ε. It is decreased by recovery (at a rate δ) and natural death. Hence,

$$\frac{dP}{dt} = \varepsilon I - (\delta + \mu) P.$$

The population of recovered individuals (R) is generated by recovery of acutely-infected individuals (at the rate σ), chronically-infected individuals (at the rate δ), acutely-re-infected individuals (at a rate $\alpha\sigma$, where $\alpha > 1$ is the modification parameter that accounts for the assumption that acutely-re-infected individuals recover at a faster rate in comparison to acutely-infected individuals), and chronically-re-infected individuals (at a rate $\eta\delta$ where $\eta > 1$ is the modification parameter that accounts for the assumption that chronically-re-infected individuals recover at a faster rate in comparison to chronically-infected individuals) [14]. This population is decreased by infection (at a reduced rate $\psi\lambda_{wt}$, where the modification parameter $0 < \psi < 1$ accounts for the assumption that recovered individuals acquire HCV infection at a rate lower than wholly-susceptible individuals). It is further decreased by the loss of

infection-acquired immunity (at the rate γ) and natural death. Thus,

$$\frac{dR}{dt} = \sigma I + \delta P + \alpha\sigma V + \eta\delta W - (\psi\lambda_{wt} + \gamma + \mu)R.$$

The population of the acutely re-infected individuals is increased by the re-infection of recovered individuals at the rate $\psi\lambda_{wt}$. It is decreased by progression to the chronic re-infection stage (at a rate $\kappa\varepsilon$, where $0 < \kappa < 1$ is the modification parameter accounting for the assumption that acutely-re-infected individuals progress to the chronically-re-infection stage (W) at a slower rate in comparison to acutely-infected individuals), recovery (at the rate $\alpha\sigma$) and natural death. Hence,

$$\frac{dV}{dt} = \psi\lambda_{wt}R - (\alpha\sigma + \kappa\varepsilon + \mu)V.$$

The population of the chronically-reinfected individuals is increased by the progression of acutely-reinfected individuals (at the rate $\kappa\varepsilon$). It diminishes by recovery (at the rate $\eta\delta$) and natural death. Thus,

$$\frac{dW}{dt} = \kappa\varepsilon V - (\eta\delta + \mu)W.$$

Based on the above assumptions and derivations, the treatment-free model for HCV transmission dynamics within an IDU population is given by the following deterministic system of non-linear differential equations [14]:

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda + \gamma R - \lambda_{wt} S - \mu S, \\
\frac{dI}{dt} &= \lambda_{wt} S - (\sigma + \varepsilon + \mu) I, \\
\frac{dP}{dt} &= \varepsilon I - (\delta + \mu) P, \\
\frac{dR}{dt} &= \sigma I + \delta P + \alpha\sigma V + \eta\delta W - \psi\lambda_{wt} R - (\gamma + \mu) R, \\
\frac{dV}{dt} &= \psi\lambda_{wt} R - (\alpha\sigma + \kappa\varepsilon + \mu) V, \\
\frac{dW}{dt} &= \kappa\varepsilon V - (\eta\delta + \mu) W,
\end{aligned}
\tag{3.2}
$$

where,

$$
\lambda_{wt} = \frac{\beta(I + \pi P + \upsilon V + \omega\pi W)}{N_{wt}}. \tag{3.3}
$$

It is worth noting that the treatment-free model (3.2) reduces to an SIR model in the absence of re-infection of recovered individuals ($\psi = 0$) and loss of infection-acquired immunity ($\gamma = 0$). Furthermore, it can be shown that the model (3.2) reduces to an SIS model if recovered individuals acquire HCV infection at the same rate as wholly-susceptible individuals ($\psi = 1$). A flow diagram of the model is depicted in Figure 3.1, and the associated variables and parameters are tabulated in Table 3.1. The treatment-free model (3.2) will now be analysed to gain insight into its qualitative features.

3.2.1 Basic properties

Theorem 3.1. *Let the initial data for the treatment-free model (3.2) be* $S(0) > 0, I(0) > 0, P(0) > 0, R(0) > 0, V(0) > 0$ *and* $W(0) > 0$. *Then, the solutions*

$$
(S(t), I(t), P(t), R(t), V(t), W(t))
$$

of the treatment-free model (3.2), with positive initial data, will remain positive for all time $t > 0$.

Proof. Let

$$t_1 = \sup\{t > 0 : S(t) > 0, I(t) > 0, P(t) > 0, R(t) > 0, V(t) > 0, W(t) > 0\} > 0.$$

It follows from the first equation of the model (3.2) that

$$\frac{dS}{dt} = \Lambda - \lambda_{wt}S - \mu S + \gamma R \geq \Lambda - \lambda_{wt}S - \mu S,$$

which can be written as,

$$\frac{d}{dt}\left\{S(t)\exp\left[\mu t + \int_0^t \lambda_{wt}(\tau)d\tau\right]\right\} \geq \Lambda\left\{\exp\left[\mu t + \int_0^t \lambda_{wt}(\tau)d\tau\right]\right\}.$$

Thus,

$$S(t_1)\exp\left[\mu t_1 + \int_0^{t_1} \lambda_{wt}(\tau)d\tau\right] - S(0) \geq \int_0^{t_1} \Lambda\left\{\exp\left[\mu y + \int_0^y \lambda_{wt}(\tau)d\tau\right]\right\}dy,$$

so that,

$$\begin{aligned} S(t_1) \geq\ & S(0)\exp\left[-\mu t_1 - \int_0^{t_1} \lambda_{wt}(\tau)d\tau\right] \\ & + \left\{\exp\left[-\mu t_1 - \int_0^{t_1} \lambda_{wt}(\tau)d\tau\right]\right\}\int_0^{t_1} \Lambda\left\{\exp\left[\mu y + \int_0^y \lambda_{wt}(\tau)d\tau\right]\right\}dy > 0. \end{aligned}$$

Similarly, it can be shown that $I(t) \geq 0,\ P(t) \geq 0,\ R(t) \geq 0,\ V(t) \geq 0$ and $W(t) \geq 0$ for all time $t > 0$. Hence, all solutions of the model (3.2) remain positive for all non-negative initial conditions, as required. □

Theorem 3.2. *The closed set*

$$\mathcal{D}_{wt} = \left\{ (S, I, P, R, V, W) \in \mathbb{R}^6_+ : N_{wt} \leq \frac{\Lambda}{\mu} \right\}$$

is positively-invariant and attracts all positive solutions of the model (3.2).

Proof. Adding the equations of the treatment-free model (3.2) gives

$$\frac{dN_{wt}}{dt} = \Lambda - \mu N_{wt}, \tag{3.4}$$

from which it is clear that $\frac{dN_{wt}}{dt}$ is negative if $N_{wt}(t) > \frac{\Lambda}{\mu}$. It follows from the solution of Equation (3.4), given by

$$N_{wt}(t) = \frac{\Lambda}{\mu} + \left[N_{wt}(0) - \frac{\Lambda}{\mu} \right] e^{-\mu t},$$

that if $N_{wt}(0) < \frac{\Lambda}{\mu}$, then $N_{wt}(t) \leq \frac{\Lambda}{\mu}$ for all $t > 0$. That is, all orbits of the treatment-free model (3.2) with initial conditions in $\mathcal{D}_{wt}$ remain in $\mathcal{D}_{wt}$ for all $t > 0$. Thus, the region $\mathcal{D}_{wt}$ is positively-invariant. Furthermore, if $N_{wt}(0) > \frac{\Lambda}{\mu}$, then either the solution enters $\mathcal{D}_{wt}$ in finite time or $N_{wt}(t)$ approaches $\frac{\Lambda}{\mu}$ as $t \to \infty$. Hence, the region $\mathcal{D}_{wt}$ attracts all solutions in $\mathbb{R}^6_+$. □

Since the region $\mathcal{D}_{wt}$ is positively-invariant, the unique solution of the treatment-free model (3.2) exists and depends continuously on the initial data of the model (hence, it is sufficient to study its asymptotic dynamics in the region $\mathcal{D}_{wt}$ [25]).

3.3 Existence and Stability of Equilibria

3.3.1 Local asymptotic stability of DFE

The DFE of the treatment-free model (3.2), obtained by setting the right-hand side of the equations in the model to zero, is given by

$$\mathcal{E}_0^{wt} = (S^*, I^*, P^*, R^*, V^*, W^*) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0\right). \tag{3.5}$$

Using the next generation operator method [50], the matrices $\mathcal{F}_{wt}$ (of the new infection terms) and $\mathcal{H}_{wt}$ (of the transition terms) associated with the model (3.2) are given, respectively, by

$$\mathcal{F}_{wt} = \begin{pmatrix} \beta & \pi\beta & \upsilon\beta & \pi\omega\beta \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \ \mathcal{H}_{wt} = \begin{pmatrix} G_1 & 0 & 0 & 0 \\ -\varepsilon & G_2 & 0 & 0 \\ 0 & 0 & G_3 & 0 \\ 0 & 0 & -\kappa\varepsilon & G_4 \end{pmatrix},$$

where, $G_1 = \mu + \sigma + \varepsilon,\ G_2 = \mu + \delta,\ G_3 = \mu + \alpha\sigma + \kappa\varepsilon,$ *and* $G_4 = \mu + \eta\delta$. It follows, from Theorem 2 in [50], that the *basic reproduction number* of the treatment-free model (3.2), defined by $\mathcal{R}_0 = \rho_{wt}(\mathcal{F}_{wt}\mathcal{H}_{wt}^{-1})$ (where ρ_{wt} is the spectral radius of the next generation matrix $\mathcal{F}_{wt}\mathcal{H}_{wt}^{-1}$), is given by

$$\mathcal{R}_0 = \frac{\beta}{\varepsilon + \mu + \sigma}\left(1 + \frac{\varepsilon\pi}{\delta + \mu}\right). \tag{3.6}$$

The result below follows from Theorem 2 of [50].

Theorem 3.3. *The DFE, $\mathcal{E}_0^{wt}$, of the treatment-free model (3.2), given by (3.5), is locally-asymptotically stable (LAS) if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

The epidemiological implication of Theorem 3.3 is that HCV can be effectively controlled in the community (when $\mathcal{R}_0 < 1$) if the initial sizes of the sub-populations of

the model (3.2) are in the basin of attraction of the DFE. As stated in Chapter 2, the threshold quantity, $\mathcal{R}_0$, represents the average number of secondary infections that one HCV-infected individual can generate if introduced into a completely-susceptible IDU population [50].

3.3.2 Existence of EEP

In this section, the possible existence of an endemic equilibrium (that is, an equilibrium of the treatment-free model (3.2) when the infected components are non-zero will be explored). Let,

$$\mathcal{E}_1^{wt} = (S^{**}, I^{**}, P^{**}, R^{**}, V^{**}, W^{**}), \tag{3.7}$$

be an arbitrary endemic equilibrium of the treatment-free model (3.2), where S^{**}, I^{**}, P^{**}, R^{**}, V^{**}, and W^{**} are obtained from setting the right-hand-sides of the equations in the model (3.2) to zero, given by

$$\begin{aligned} S^{**} &= \frac{\gamma R^{**} + \Lambda}{\lambda_{wt}^{**} + \mu}, \quad I^{**} = \frac{\lambda_{wt}^{**} S^{**}}{\sigma + \varepsilon + \mu}, \quad P^{**} = \frac{\varepsilon I^{**}}{\delta + \mu}, \\ R^{**} &= \frac{\sigma I^{**} + \delta P^{**} + \alpha\sigma V^{**} + \eta\delta W^{**}}{\mu + \gamma + \psi\lambda_{wt}^{**}}, \\ V^{**} &= \frac{\psi\lambda_{wt}^{**} R^{**}}{\alpha\sigma + \kappa\varepsilon + \mu}, \quad W^{**} = \frac{\kappa\varepsilon V^{**}}{\eta\delta + \mu}. \end{aligned} \tag{3.8}$$

Furthermore, let

$$\lambda_{wt}^{**} = \frac{\beta\mu(I^{**} + \pi P^{**} + \upsilon V^{**} + \pi\omega W^{**})}{\Lambda}, \tag{3.9}$$

(where the total population, $N_{wt}(t)$, is now replaced by its limiting value, $N_{wt}^{*} = \frac{\Lambda}{\mu}$) be the force of infection of the treatment-free model 3.2 at an endemic steady-state. Substituting the equations in (3.8) into (3.9), and simplifying, gives the following

quadratic equation (in terms of λ_{wt}^{**})

$$c_2(\lambda_{wt}^{**})^2 + c_1\lambda_{wt}^{**} + c_0 = 0, \tag{3.10}$$

where,

$$\begin{aligned} c_2 &= \psi(\mu+\delta)(\mu+\delta\eta+\varepsilon)(\mu+\sigma+\varepsilon), \\ c_1 &= \mu\psi(\delta+\mu)(\delta\eta+\varepsilon+\mu)(\varepsilon+\mu+\sigma)(1-\mathcal{R}_0) \\ &\quad +(\mu+\delta)(\mu+\sigma+\varepsilon)\left\{(\mu+\alpha\sigma+\kappa\varepsilon)(\mu+\eta\delta)-\beta\psi\left[\upsilon(\mu+\eta\delta)+\omega\pi\kappa\varepsilon\right]\right\}, \\ c_0 &= (\gamma+\mu)(\delta+\mu)(\delta\eta+\mu)(\varepsilon+\mu+\sigma)(\varepsilon+\mu+\alpha\sigma)\left(1-\mathcal{R}_0\right). \end{aligned} \tag{3.11}$$

The components of the endemic equilibrium are then obtained by solving for λ_{wt}^{**} from the quadratic equation (3.10), and substituting the positive values of λ_{wt}^{**} into the expressions in 3.8. Furthermore, it follows from (3.11) that the coefficient c_2, of the quadratic (3.10), is always positive, and c_0 is positive (negative) if $\mathcal{R}_0$ is less (greater) than unity. Hence, it follows from (3.11) that the quadratic (3.10) has a unique positive equilibrium (an endemic equilibrium) whenever $\mathcal{R}_0 > 1$. These results are summarized below.

Theorem 3.4. *The treatment-free model (3.2) has:*

(i) *a unique endemic equilibrium if* $c_0 < 0 \Leftrightarrow \mathcal{R}_0 > 1$*;*

(ii) *a unique endemic equilibrium if* $c_1 < 0$ *and* $c_0 = 0$ *or* $c_1^2 - 4c_0c_2 = 0$*;*

(iii) *two endemic equilibria if* $c_0 > 0, c_1 < 0$ *and* $c_1^2 - 4c_0c_2 > 0$*;*

(iv) *no endemic equilibrium otherwise.*

Item (iii) of Theorem 3.4 suggests the possibility of backward bifurcation (see, for instance, [7, 15, 18, 22, 25, 38, 42, 57], and some of the references therein) in the treatment-free model (3.2). As discussed in Chapter 2, the phenomenon of backward

bifurcation is characterized by the co-existence of a stable DFE and a stable EEP when the associated reproduction number of the model ($\mathcal{R}_0$) is less than unity. The epidemiological consequence of backward bifurcation is that disease control (when $\mathcal{R}_0 < 1$) is dependent on the initial sizes of the sub-populations of the model (see, for example, [42]). Hence, the presence of backward bifurcation in the transmission dynamics of a disease makes its effective control (or elimination) difficult. Consequently, it is instructive to explore the possibility of backward bifurcation in the treatment-free model (3.2). Before doing so, it is worth checking for the existence of an EEP of the model (3.2) when $\mathcal{R}_0 \leq 1$ (which is a signature for a backward bifurcation in disease transmission models [7, 15, 18, 22, 25, 38, 42, 57]). This is done below.

3.3.3 Existence of backward bifurcation

Theorem 3.5. *The treatment-free model (3.2) undergoes a backward bifurcation at $\mathcal{R}_0 = 1$ whenever the Inequality (A.5), given in Appendix A, holds.*

The proof of Theorem 3.5, based on using center manifold theory [5, 6, 13, 50], is given in Appendix A. A schematic description of the backward bifurcation phenomenon of the model (3.2) is depicted in Figure 3.4. It is worth stating that, to the author's knowledge, this is the first time the phenomenon of backward bifurcation has been established in the transmission dynamics of HCV in a population.

3.3.4 Non-existence of backward bifurcation

First of all, it should be mentioned that setting the re-infection parameter ψ, to zero reduces the treatment-free model (3.2) to an SIRS model, which is known not to undergo backward bifurcation [22]. That is, as in the case of other disease, such as TB [22], the re-infection of recovered individuals causes backward bifurcation in

HCV transmission dynamics.

Case (i) Effect of relative rate of progression of acute re-infected individuals (κ).

Consider the treatment-free model (3.2) for the case when acutely-re-infected individuals (V) progress to chronic re-infection stage (W) at the same rate as acutely-infected (I) individuals (i.e., $\kappa = 1$). For this case, the coefficients $c_0,\ c_1$ and c_2, of the quadratic (3.10), reduce to:

$$\begin{aligned} c_2 &= \psi(\mu+\delta)(\mu+\delta\eta+\varepsilon)(\mu+\sigma+\varepsilon), \\ c_1 &= \mu\psi(\delta+\mu)(\delta\eta+\varepsilon+\mu)(\varepsilon+\mu+\sigma)(1-\mathcal{R}_0) \\ &\quad +(\mu+\delta)(\mu+\sigma+\varepsilon)\left\{(\mu+\alpha\sigma+\varepsilon)(\mu+\eta\delta)-\beta\psi\left[\upsilon(\mu+\eta\delta)+\omega\pi\varepsilon\right]\right\}, \\ c_0 &= (\gamma+\mu)(\delta+\mu)(\delta\eta+\mu)(\varepsilon+\mu+\sigma)(\varepsilon+\mu+\alpha\sigma)\left(1-\mathcal{R}_0\right), \end{aligned} \tag{3.12}$$

from which the result below follows.

Theorem 3.6. *Consider the treatment-free model (3.2) with $\kappa = 1$. The model has a unique positive equilibrium if $\mathcal{R}_0 > 1$, and no positive endemic equilibrium otherwise.*

Proof. It is clear from (3.12) that $c_2 > 0$ and $c_0 \geq 0$ if $\mathcal{R}_0 \leq 1$. Furthermore, it can be shown that (since $\psi \leq 1$, $\upsilon \leq 1$ and $\omega \leq 1$)

$$\begin{aligned} c_1 &= \mu\psi(\delta+\mu)(\delta\eta+\varepsilon+\mu)(\varepsilon+\mu+\sigma)(1-\mathcal{R}_0) \\ &\quad +(\mu+\delta)(\mu+\sigma+\varepsilon)\left\{(\mu+\alpha\sigma+\kappa\varepsilon)(\mu+\eta\delta)-\beta\psi\left[\upsilon(\mu+\eta\delta)+\omega\pi\kappa\varepsilon\right]\right\}, \\ &> \mu\psi(\delta+\mu)(\delta\eta+\varepsilon+\mu)(\varepsilon+\mu+\sigma)(1-\mathcal{R}_0) \\ &\quad +(\mu+\delta)(\mu+\sigma+\varepsilon)\left\{(\mu+\alpha\sigma+\kappa\varepsilon)(\mu+\eta\delta)-\beta\left[(\mu+\eta\delta)+\pi\kappa\varepsilon\right]\right\}. \end{aligned} \tag{3.13}$$

Hence, it follows from the inequality $\mathcal{R}_0 < 1$ that $\beta < \frac{(\mu+\sigma+\varepsilon)(\mu+\delta)}{\pi\varepsilon+\mu+\delta}$. Thus, the coefficient c_1 can be re-written as

$$\begin{aligned} c_1 &> \mu\psi(\delta+\mu)(\delta\eta+\varepsilon+\mu)(\varepsilon+\mu+\sigma)(1-\mathcal{R}_0) + (\mu+\delta)(\mu+\sigma+\varepsilon) \\ &\left\{(\mu+\alpha\sigma+\kappa\varepsilon)(\mu+\eta\delta) - \frac{(\mu+\sigma+\varepsilon)(\mu+\delta)\left[(\mu+\eta\delta)+\pi\kappa\varepsilon\right]}{\pi\varepsilon+(\mu+\delta)}\right\}, \qquad (3.14) \\ &= \mu\psi(\delta+\mu)(\delta\eta+\varepsilon+\mu)(\varepsilon+\mu+\sigma)(1-\mathcal{R}_0) + (\mu+\delta)(\mu+\sigma+\varepsilon) \\ &\left\{\frac{(\mu+\alpha\sigma+\kappa\varepsilon)(\mu+\eta\delta)[\pi\varepsilon+(\mu+\delta)] - (\mu+\sigma+\varepsilon)(\mu+\delta)\left[(\mu+\eta\delta)+\pi\kappa\varepsilon\right]}{\pi\varepsilon+(\mu+\delta)}\right\}, \\ &= \mu\psi(\delta+\mu)(\delta\eta+\varepsilon+\mu)(\varepsilon+\mu+\sigma)(1-\mathcal{R}_0) + (\mu+\delta)(\mu+\sigma+\varepsilon)M, \end{aligned}$$

where,

$$M = \frac{M_1+M_2}{\pi\varepsilon+\mu+\delta},$$

with,

$$\begin{aligned} M_1 &= \pi\varepsilon[(\mu+\alpha\sigma+\kappa\varepsilon)(\mu+\eta\delta) - (\mu+\sigma+\varepsilon)(\mu+\delta)], \\ M_2 &= (\mu+\delta)(\mu+\eta\delta)(\alpha\sigma+\kappa\varepsilon-\sigma-\varepsilon). \end{aligned}$$

The sign of coefficient c_1 can be deduced from (3.14) as follows. Since $\eta > 1$ and $\alpha > 1$, it follows that $(\mu+\alpha\sigma+\varepsilon) > (\mu+\sigma+\varepsilon)$, $(\mu+\eta\delta) > (\mu+\delta)$ and $(\alpha\sigma+\varepsilon) > (\sigma+\varepsilon)$. Consequently, if $\mathcal{R}_0 < 1$ and $\kappa = 1$, then $c_1 > 0$ (and the quadratic (3.10) will have no endemic equilibrium for this special case). □

The above analysis (along with Theorem 3.6) reveals that the relative rate of progression of acute re-infected individuals to the chronic re-infection stage (κ) play a critical role in the existence of the phenomenon of backward bifurcation in the treatment-free model (3.2). In fact, setting $\kappa = 1$ in (3.11), and using the assump-

tions that $\eta \geq 1, \alpha \geq 1$ and $\upsilon \leq 1,\ \omega \leq 1$ and $\psi \leq 1$, it can be shown that the backward bifurcation coefficient (a), given by (A.3) in Appendix A, becomes negative (and, consequently, in line with Theorem 4.1 of [6], the treatment-free model (3.2) does not undergo backward bifurcation in this case). To do so, we just need to show that S_2, in the expression for the backward bifurcation coefficient a (given by (A.3) in Appendix A) is positive (in which case, $a < 0$). This is shown below.

$$\begin{aligned} S_2 &= G_3G_4 - \frac{G_1G_2\psi(\pi\varepsilon\kappa\omega + G_4\upsilon)}{(\pi\varepsilon + G_2)} = \frac{G_3G_4(\pi\varepsilon + G_2) - G_1G_2\psi(\pi\varepsilon\kappa\omega + G_4\upsilon)}{(G_2 + \pi\varepsilon)}, \\ &> \frac{G_3G_4(\pi\varepsilon + G_2) - G_1G_2(\pi\varepsilon\kappa + G_4)}{(\pi\varepsilon + G_2)}, \\ &= \frac{\pi\varepsilon(G_3G_4 - G_1G_2) + G_2G_4(G_3 - G_1)}{(\pi\varepsilon + G_2)} > 0, \end{aligned} \tag{3.15}$$

since, assuming $\kappa = 1$, $G_3 = \mu+\alpha\sigma+\varepsilon > G_1 = \mu+\sigma+\varepsilon$ and $G_4 = \mu+\eta\delta > G_2 = \mu+\delta$ (so that, $G_3G_4 - G_1G_2 > 0$ and $G_3 - G_1 > 0$). Thus, it follows, based on Theorem 3.6 and Item (iv) of Theorem 4.1 in [6], that the treatment-free model (3.2) does not undergo backward bifurcation in this case (with $\kappa = 1$). Hence, this thesis shows, for the first time, that the relative rate of progression from acute re-infection to chronic re-infection stage (κ) induces the phenomenon of backward bifurcation in HCV transmission dynamics.

Case (ii) Effect of infectiousness of acute and chronic re-infected individuals (υ, ω)

Consider, now, the special case of the treatment-free model (3.2) where acute and chronic re-infected individuals do not transmit HCV infection (i.e., $\upsilon = \omega = 0$). For this special case, it follows from (3.15) that $S_2 = G_3G_4 > 0$. Consequently, the backward bifurcation parameter, a (given by (A.3) in Appendix A), is negative (so that backward bifurcation does not occur in this case, in line with Theorem 2.7). It

is worth emphasizing that, for this scenario ($\upsilon = \omega = 0$), backward bifurcation does not occur in the treatment-free model even in the presence of re-infection ($\psi \neq 0$). Hence, this thesis shows, for the first time, that disease transmission by acute and chronic re-infection individuals also induces the phenomenon of backward bifurcation in HCV transmission dynamics.

3.4 Uncertainty and Sensitivity Analysis

The treatment-free model (3.2) contains 14 parameters, and the effect of the uncertainties in the estimates of the parameter values used in the numerical simulations of the model (3.2) [4, 41] will be assessed using Latin Hypercube Sampling (as discussed in Chapter 2). The LHS method involves defining baseline values and ranges for each of the parameters of the model (as in Table 3.2), where each parameter is assumed to obey a uniform distribution [14], and carrying out multiple runs ($N_R = 1000$) of the sampled data for the response output (the basic reproduction threshold, $\mathcal{R}_0$, in this case) [4, 41].

A boxplot of the basic reproduction number ($\mathcal{R}_0$) of the treatment-free model (3.2), as a function of the number of LHS runs carried out, is depicted in Figure 3.5, showing a range of $\mathcal{R}_0$ from 1.49 to 1.52 (which is consistent with the range reported in [14]). Furthermore, partial rank correlation coefficients (PRCC) [29] are used to measure the sensitivity of the parameters of the model (with $\mathcal{R}_0$ as a response variable). It follows from Table 3.3 that the parameters that most affect the value of $\mathcal{R}_0$ (hence, drive the HCV transmission dynamics within the IDU population) are the effective contact rate (β), the rate of progression to chronic infection (ε), the rate of recovery from acute infection (σ), the death or retirement rate from the population (μ) and the relative infectivity of chronically-infected individuals (π). Thus, this study identifies the main parameters that play a dominant role in the dynamics of

the disease within the IDU population.

The sensitivity of the aforementioned top-five PRCC-ranked parameters, on the cumulative incidence and prevalence of HCV, is further assessed by simulating the treatment-free model (3.2) for the case where the baseline values of these (top-five) parameters (given in Table 3.2) are increased or decreased by 10%. The results obtained, depicted in Figures 3.6 and 3.7, show that a 10% increase in the baseline values of these parameters leads to a corresponding increase in the cumulative incidence and prevalence of HCV in the population, respectively. However, a 10% decrease leads to a decrease in the cumulative incidence and prevalence of the disease during the first few years (about 10 years), and a marginal increase shortly thereafter. These simulations further confirm the sensitivities such uncertainties (of the input parameters) have on the simulation result (output/response) obtained, in line with the results tabulated in Table 3.3 and Figure 3.8.

3.5 Numerical Simulations

The treatment-free model (3.2) is further simulated, using the parameter values given in Table 3.2 (unless otherwise stated), to assess the impact of re-infection on the transmission dynamics of HCV among IDUs. The following initial data (relevant to an IDU population [14]) is used in the numerical simulations of the treatment-free model (3.2):

$$(S(0), I(0), P(0), R(0), V(0), W(0)) = (439000, 550, 350, 50, 30, 20).$$

Figure 3.9 shows the cumulative number of new HCV cases, as a function of time, for various values of the re-infection parameter (ψ), from which it is evident that re-infection has little or no effect on the cumulative incidence of HCV during the first few years (the effect is, however, noticeable after about 10 years). In other words,

this study shows that re-infection has marginal effect on HCV burden (as measured in terms of cumulative number of new cases) in the community in the short-term. Similar results are obtained for the prevalence of HCV (Figure 3.10). Although the progression rate from acute-re-infection to the chronic-re-infection stage (κ) plays an important role on the dynamics of HCV transmission, its effect on the cumulative incidence and prevalence of the disease is marginal (as shown in Figures 3.11 and 3.12, respectively).

3.6 Summary of the Chapter

This chapter focuses on the rigorous analysis of the treatment-free model of the HCV transmission model presented by Elbasha [14] (where only a special case of the model was analysed), with the aim of exploring the role of differential infectiousness of the infected and re-infected individuals in the dynamics of HCV which is not analysed in [14]. By using centre manifold theory, it was shown, unlike in [14], that the model undergoes the phenomenon of backward bifurcation when the associated basic reproduction number ($\mathcal{R}_0$) of the model is less than unity. This phenomenon is well-known to play a major role in the persistence or elimination of the disease [6]. In particular, in a backward bifurcation situation, disease control (when the associated basic reproduction number is less than unity) is dependent on the initial sizes of the sub-populations of the model. Hence, backward bifurcation makes effective disease control difficult. This thesis, arguably, represents the first time the phenomenon of backward bifurcation is established in the transmission dynamics of HCV.

The main result, derived from this chapter, is that two main cases where the backward bifurcation property of the HCV transmission dynamics can be removed are identified. The first is the absence of heterogeneity between primary infected and re-infected individuals with regard to infectivity. In other words, the model

will not undergo backward bifurcation if acutely-re-infected individuals progress to chronically-re-infection stage in the same rate of the progression of the acutely-infected individuals to the chronically-infection stage. Hence, this study shows that heterogeneity between primary infected individuals and re-infected individuals with regard to infectiousness can induce the phenomenon of backward bifurcation in the transmission dynamics of a disease (such as HCV). The second is that, in the presence of such heterogeneity, it is shown that the backward bifurcation phenomenon can be removed when acute and chronic re-infected individuals do not transmit infection (i.e., $\upsilon = \omega = 0$).

The treatment-free model (3.2) is shown to have a unique endemic equilibrium when the associated reproduction number ($\mathcal{R}_0$) exceeds unity (numerical simulations show that HCV will persist in the population when such an equilibrium exists). Results in this chapter provide answers to Questions 1 and 3 raised in Section 1.3.

Further simulations show that the re-infection of recovered individuals has marginal effect on the disease burden (as measured in terms of HCV cumulative incidence and prevalence in the community). It is also shown that, despite the fact that the parameter κ, (for the variability of progression to chronic stage between acutely re-infected and acutely infected individuals) plays a crucial role in the existence of backward bifurcation, it (κ) has only marginal effect on the cumulative incidence and prevalence of HCV in the IDU population.

Symbol	Description
Variables	
$S(t)$	Population of susceptible individuals
$I(t)$	Population of acutely-infected individuals
$P(t)$	Population of chronically-infected individuals
$R(t)$	Population of recovered individuals with partial immunity
$V(t)$	Population of acutely-reinfected individuals
$W(t)$	Population of chronically-reinfected individuals
Parameters	
Λ	Recruitment rate
μ	Natural death rate
β	Contact rate
σ	Recovery rate from acute infection
δ	Recovery rate from chronic infection
ε	Rate of progression from acute to chronic infection
ψ	Relative susceptibility of recovered individuals
α	Relative rate of recovery from acute re-infection
η	Relative rate of recovery from chronic re-infection
κ	Relative rate of progression from acute re-infection to chronic re-infection
γ	Rate of waning immunity
π	Relative infectivity of chronically-infected individuals
υ	Relative infectivity of acutely-re-infected individuals
ω	Relative infectivity of chronically-re-infected individuals

Table 3.1: Variables and parameters of the treatment-free model (3.2) [14].

Parameters	Baseline Values [14]	Ranges [14]
Λ	$39,600$ year^{-1}	[35640, 43560]
μ	0.09 year^{-1}	[0.081, 0.099]
β	2.68 year^{-1}	[2.444, 2.948]
σ	0.5 year^{-1}	[0.45, 0.55]
δ	0.002 year^{-1}	[0.0018, 0.0022]
ε	1.5 year^{-1}	[1.35, 1.65]
ψ	0.5	[0.45, 0.55]
α	3.3	[2.97, 3.36]
η	3.3	[2.97, 3.36]
κ	1/3.3	[0.2727, 0.3333]
γ	0.025 year^{-1}	[0.0225, 0.0275]
π	0.01	[0.009, 0.011]
υ	1/6.5	[0.1386, 0.1694]
ω	1/6.5	[0.1386, 0.1694]

Table 3.2: Baseline values and ranges of the parameters of the treatment-free model (3.2).

Parameters	PRCC($\mathcal{R}_0$)
β	0.988565581
ε	-0.968324197
σ	-0.847998641
μ	-0.763220923
π	0.691031894
δ	-0.030469363
Λ	0.018299972
η	0.015971663
γ	0.028006153
κ	-0.023995766
υ	-0.037000483
α	-0.007482013
ψ	-0.013614862
ω	-0.042066892

Table 3.3: PRCC values of the parameters of the treatment-free model (3.2), with $\mathcal{R}_0$ as the output. Parameter values and ranges used are as given in Table 3.2.

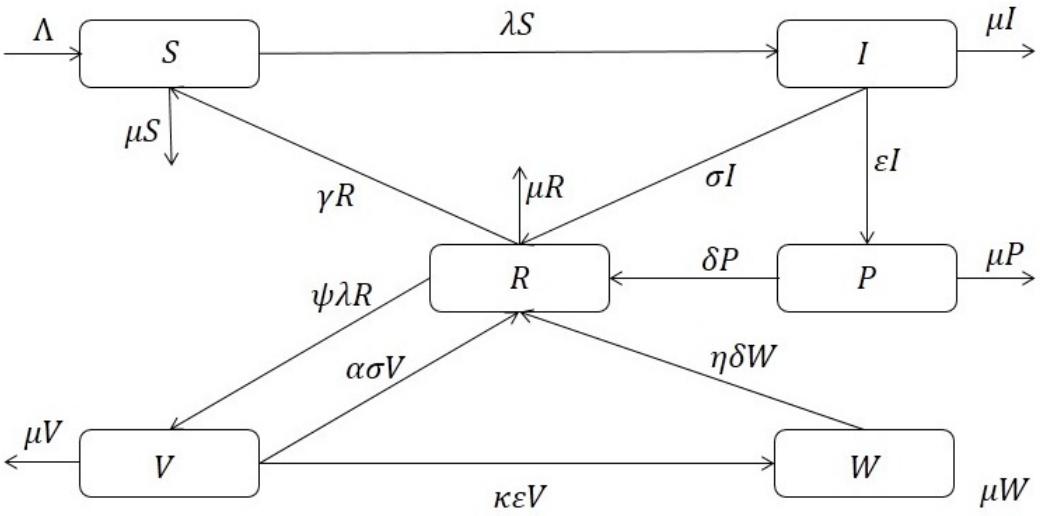

Figure 3.1: Schematic diagram of the treatment-free model (3.2) [14].

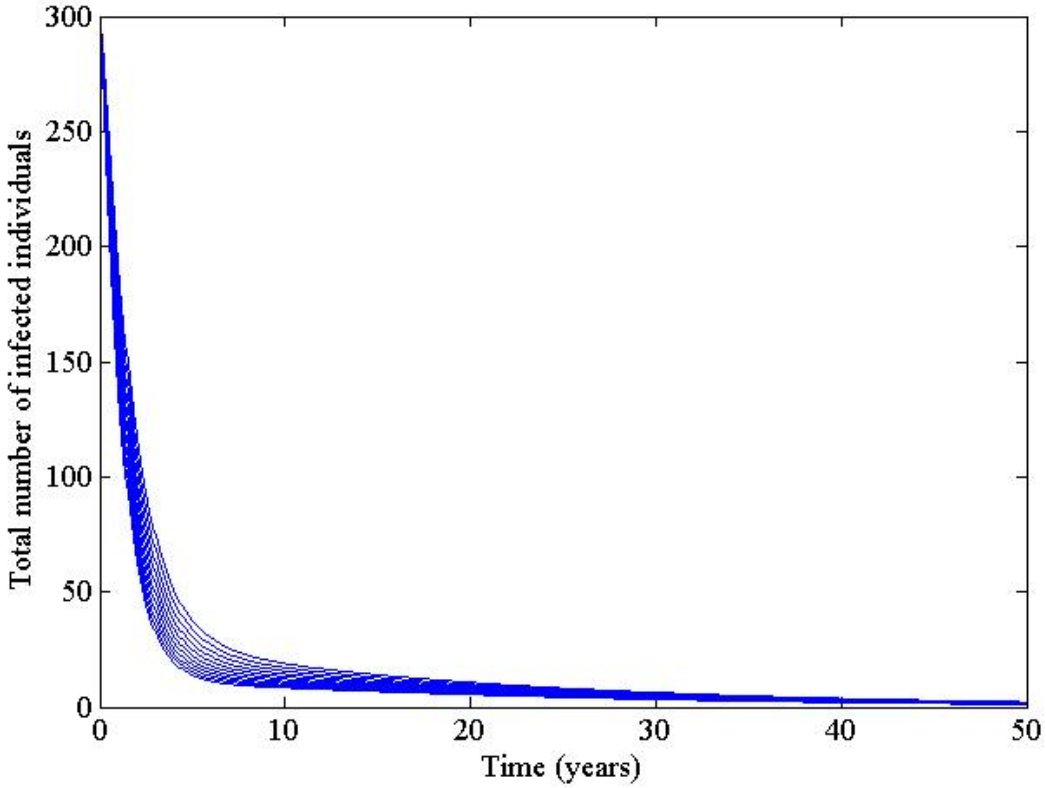

Figure 3.2: Simulations of the treatment-free model (3.2), showing the total number of infected individuals as a function of time, using various initial conditions. Parameter values used are as given in Table 3.2, with $\beta = 1.48$ (so that, $\mathcal{R}_0 = 0.8036$).

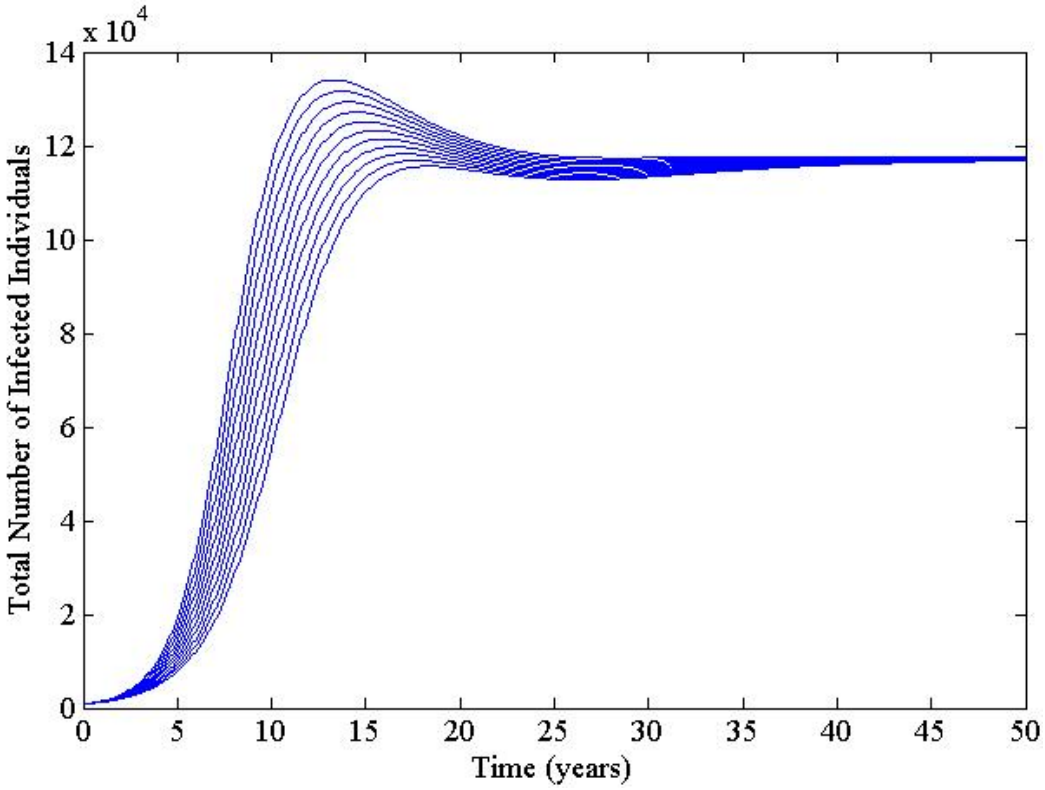

Figure 3.3: Simulations of the treatment-free model (3.2), showing the total number of infected individuals as a function of time, using various initial conditions. Parameter values used are as given in Table 3.2 (so that, $\mathcal{R}_0 = 1.4914$).

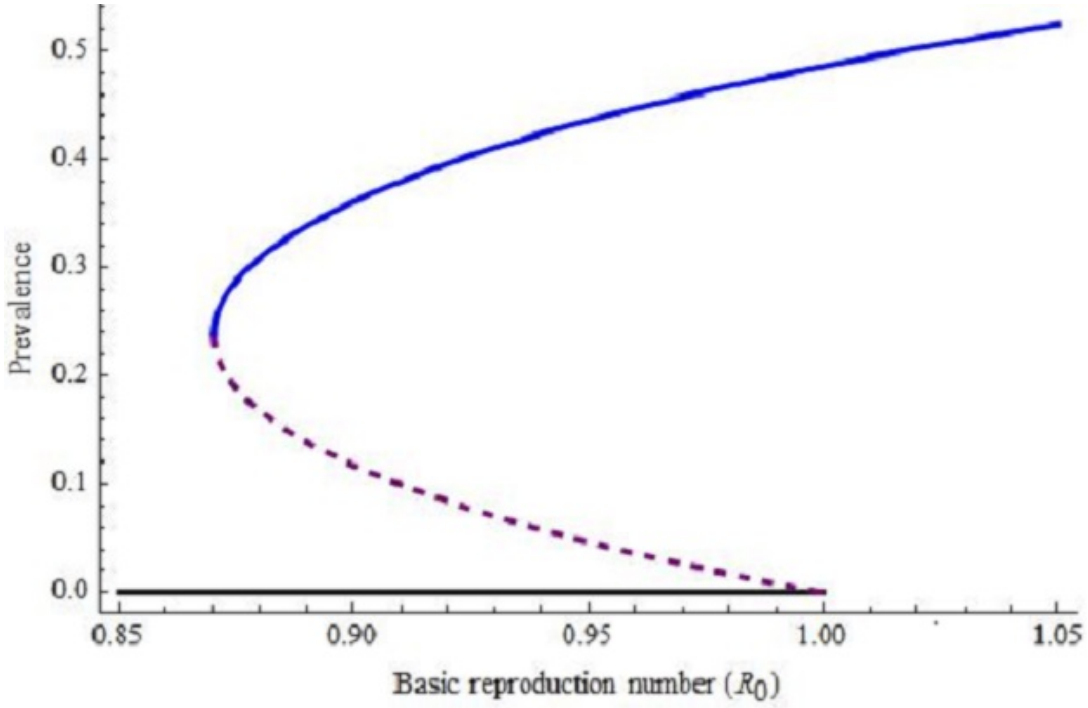

Figure 3.4: Backward bifurcation diagram for the treatment-free model (3.2), showing the prevalence as a function of the basic reproduction number ($\mathcal{R}_0$). Parameter values used are: $\Lambda = 40640$, $\beta^* = 3.324462329$, $\mu = 0.091$, $\sigma = 0.255$, $\delta = 0.0025$, $\varepsilon = 3.5$, $\psi = 0.70$, $\alpha = 3.3$, $\eta = 4.050$, $\kappa = 0.0827$, $\gamma = 0.0225$, $\pi = 0.019$, $\upsilon = 0.89999$ and $\omega = 0.89999$ (so that, $a = 0.0001180441877 > 0$; $\mathcal{R}_0 = 1$).

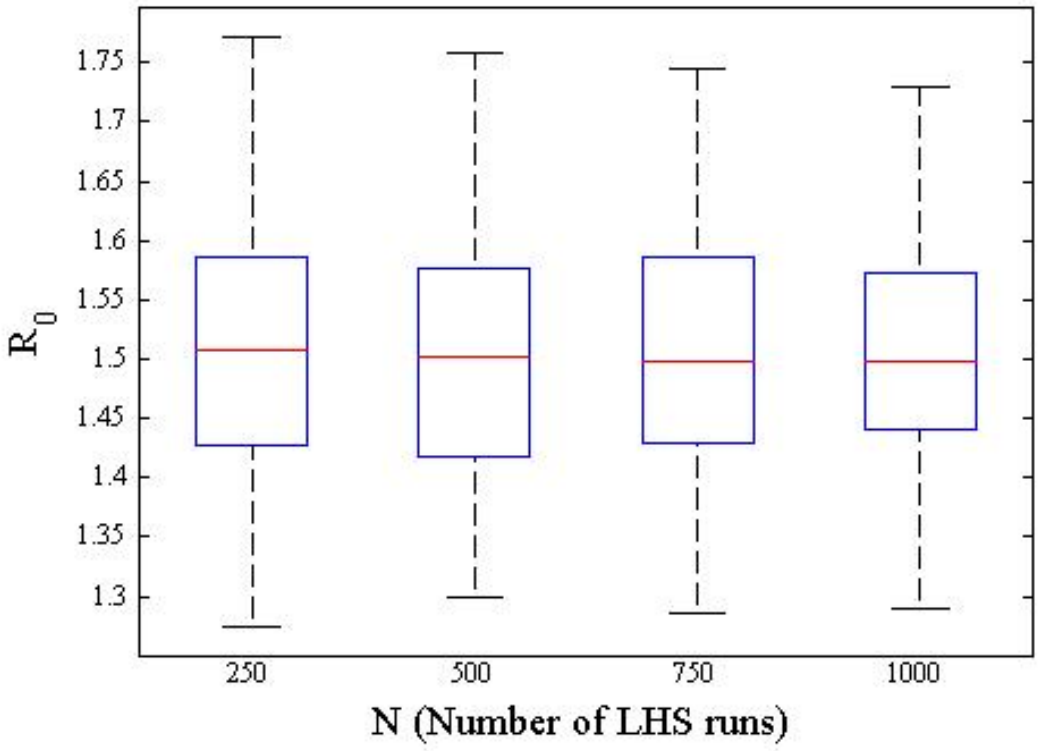

Figure 3.5: Boxplots of the basic reproduction number ($\mathcal{R}_0$), as a function of the number of LHS runs (N_R) carried out, for the treatment-free model (3.2).

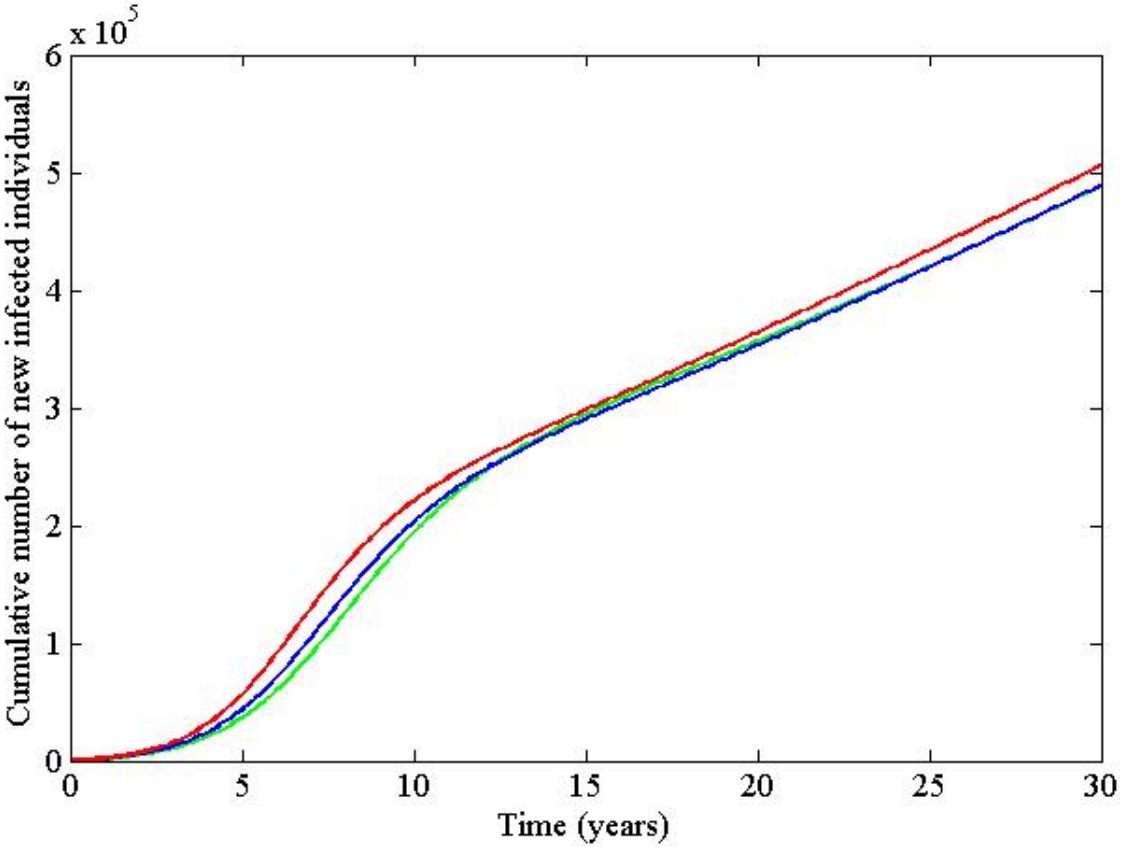

Figure 3.6: Simulations of the treatment-free model (3.2), showing the cumulative number of new infected individuals as a function of time, for various values of the top-five PRCC-ranked parameters in Table 3.3 (β, ε, σ, μ and π): green curve (10% decrease in the baseline values of the top-five PRCC-ranked parameters); blue curve (baseline values); red curve (10% increase in the baseline values of the top-five PRCC-ranked parameters). Parameter values used are as given in Table 3.2.

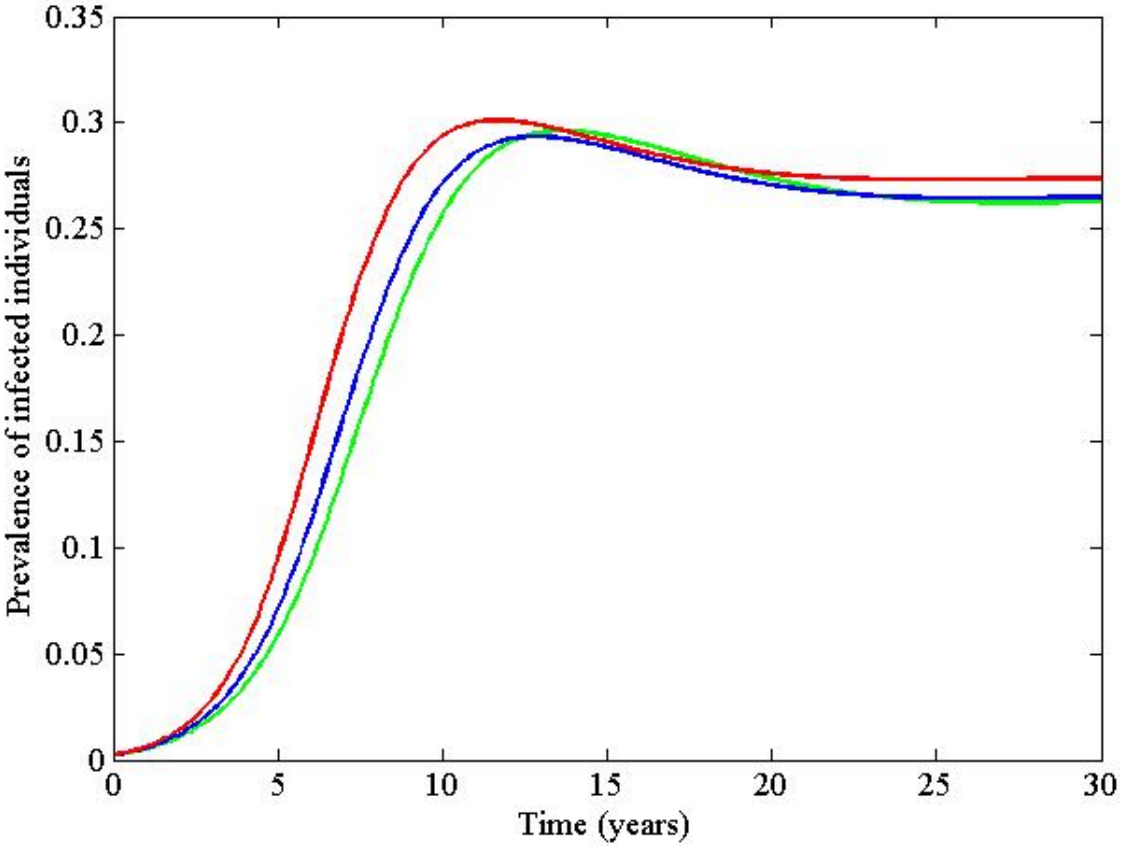

Figure 3.7: Simulations of the treatment-free model (3.2), showing the prevalence of HCV as a function of time, for various values of the top-five PRCC-ranked parameters in Table 3.3 (β, ε, σ, μ and π): green curve (10% decrease in the baseline values of the top-five PRCC-ranked parameters); blue curve (baseline values); red curve (10% increase in the baseline values of the top-five PRCC-ranked parameters). Parameter values used are as given in Table 3.2.

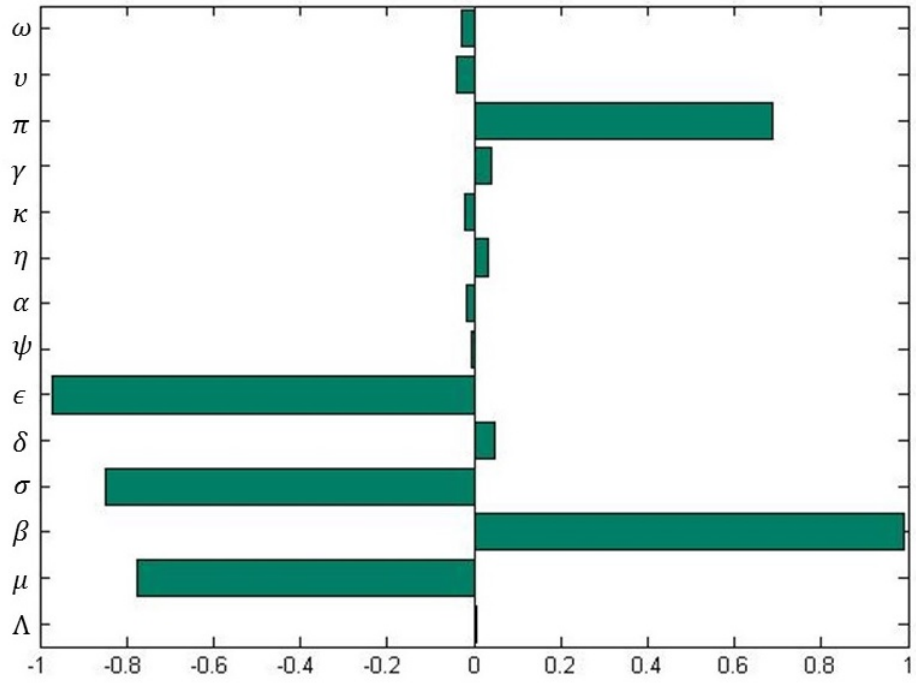

Figure 3.8: Distribution of PRCC values for the parameters of the treatment-free model (3.2). Parameter values and ranges used are as given in Table 3.2.

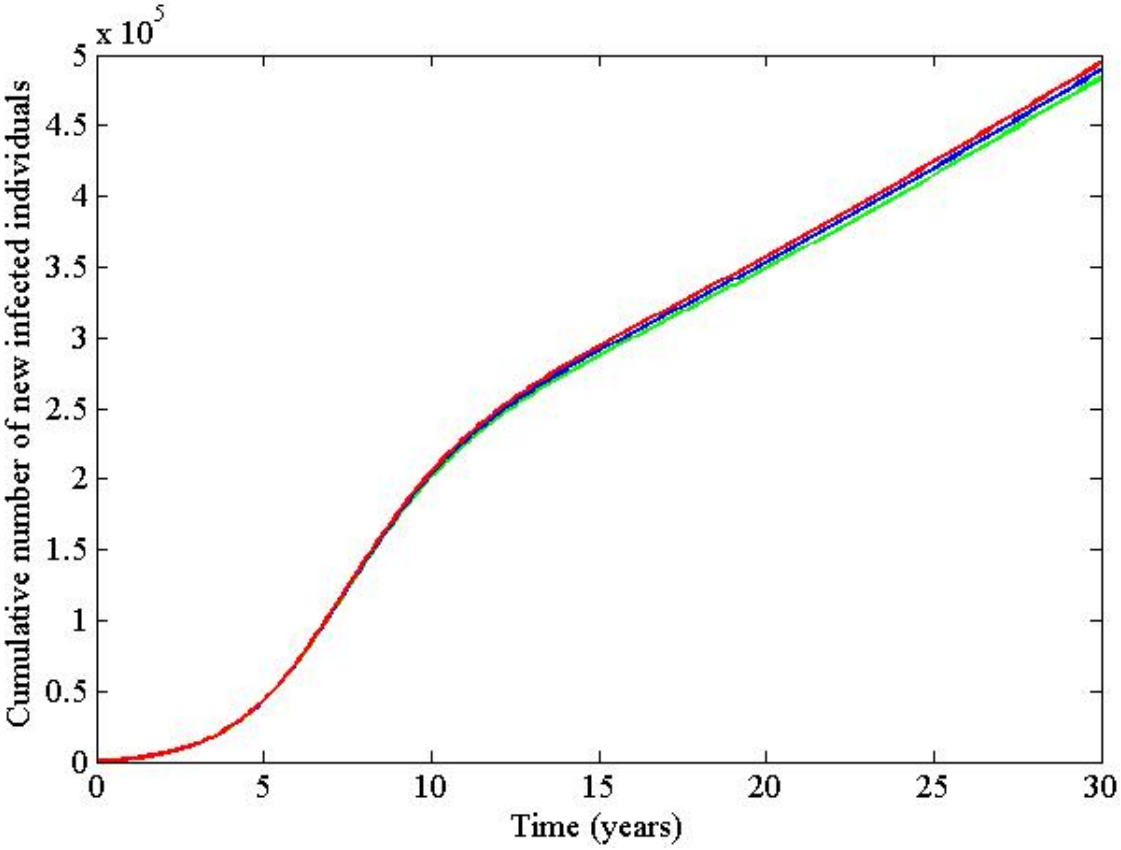

Figure 3.9: Simulations of the treatment-free model (3.2), showing the cumulative number of new infected individuals as a function of time, for various values of the re-infection parameter (ψ): green curve ($\psi = 0.0$), blue curve ($\psi = 0.5$) and red curve ($\psi = 1.0$). Parameter values used are as given in Table 3.2.

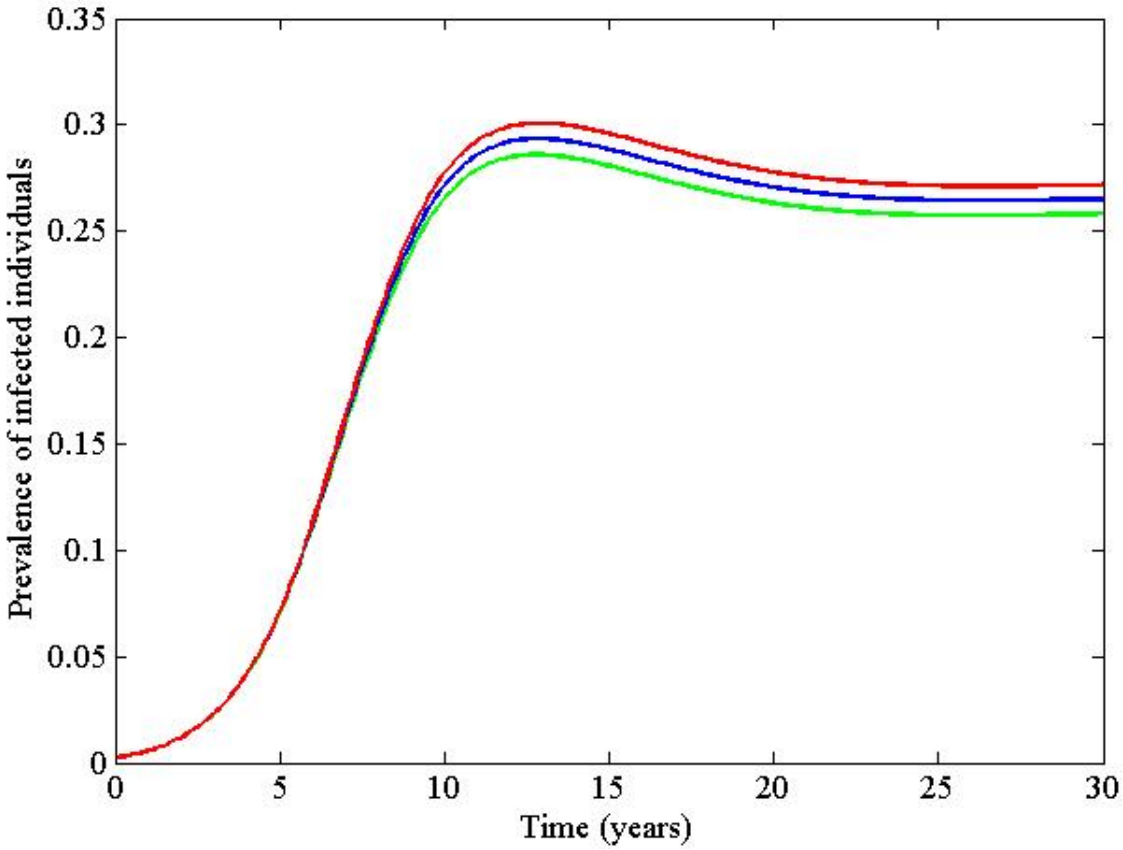

Figure 3.10: Simulations of the treatment-free model (3.2), showing the prevalence of HCV as a function of time, for various values of the re-infection parameter (ψ): green curve ($\psi = 0.0$), blue curve ($\psi = 0.5$) and red curve ($\psi = 1.0$). Parameter values used are as given in Table 3.2.

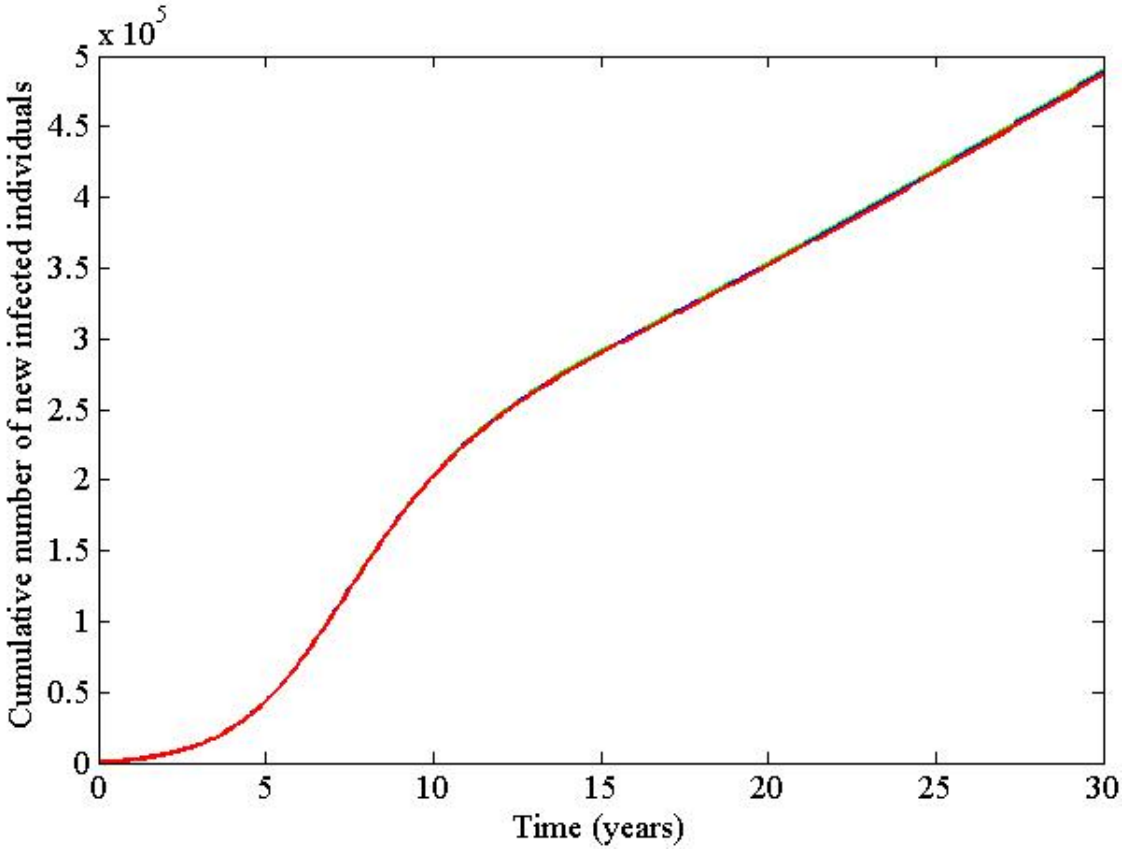

Figure 3.11: Simulations of the treatment-free model (3.2), showing the cumulative number of new infected individuals as a function of time, for various values of the relative rate of progression from acute to chronic infection stage (κ): green curve ($\kappa = 1/3.3$), blue curve ($\kappa = 0.65$) and red curve ($\kappa = 1.0$). Parameter values used are as given in Table 3.2.

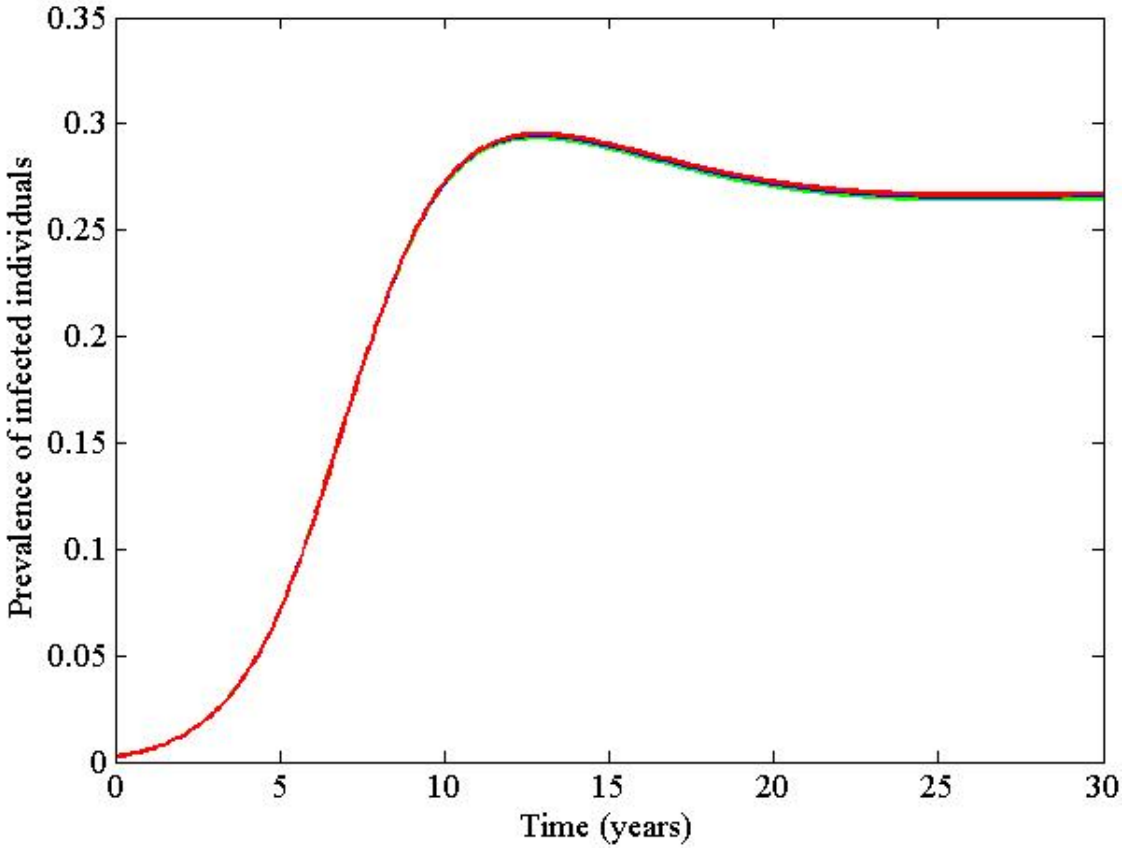

Figure 3.12: Simulations of the treatment-free model (3.2), showing the prevalence of HCV as a function of time, for various values of the relative rate of progression from acute to chronic infection stage (κ): green curve ($\kappa = 1/3.3$), blue curve ($\kappa = 0.65$) and red curve ($\kappa = 1$). Parameter values used are as given in Table 3.2.

Chapter 4

Analysis of HCV Model With Treatment

4.1 Introduction

In this chapter, the treatment model considered in Chapter 3 is extended to incorporate the effect of the use of anti-viral drug treatment (for chronically infected and re-infected IDUs) on the spread of HCV within an IDU population. As stated in Chapter 1, despite the fact that various effective drugs are currently being used to treat people infected by HCV, very few active IDUs are actually treated (less than 4% [36]). Furthermore, re-infection is one of the major challenges associated with the treatment of IDUs (since the currently available anti-HCV drugs only provide partial immunity against re-infection) [36]. However, recent results [36] (supported with the numerical simulations to be carried out in this chapter) suggest that despite the effect of re-infection, the low treatment rate of active (chronically infected and re-infected) IDUs can significantly reduce the burden of HCV in the IDU community.

Consequently, the aim of this chapter is to study the qualitative impact of treatment of chronically infected and re-infected individuals (especially for the scenario

where heterogeneity between primary infection and re-infection exists) on the transmission dynamics of HCV in an IDU population.

4.2 Model Formulation

The HCV transmission model to be considered in this chapter is based on extending the treatment-free model (3.2) to include anti-HCV treatment. The model, developed in [14], is formulated by splitting the total IDU population at time t, denoted by $N(t)$, into mutually-exclusive compartments of susceptible ($S(t)$), acutely-infected (I(t)), chronically-infected (P(t)), treated chronically infected (T(t)), recovered with partial immunity (R(t)), acutely re-infected (V(t)), untreated chronically re-infected (W(t)) and treated chronically re-infected (Q(t)) individuals, so that

$$N(t) = S(t) + I(t) + P(t) + R(t) + V(t) + W(t) + T(t) + Q(t).$$

The model is given by the following deterministic system of non-linear differential equations (denoted by treatment model) [14]

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda + \gamma R - \lambda S - \mu S, \\
\frac{dI}{dt} &= \lambda S - (\sigma + \varepsilon + \mu)\, I, \\
\frac{dP}{dt} &= \varepsilon I + \rho T - (\delta + \tau + \mu)\, P, \\
\frac{dR}{dt} &= \sigma I + \delta P + \alpha\sigma V + \eta\delta W + \theta T + \theta Q - \psi\lambda R - (\gamma + \mu)\, R, \\
\frac{dV}{dt} &= \psi\lambda R - (\alpha\sigma + \kappa\varepsilon + \mu)\, V, \\
\frac{dW}{dt} &= \kappa\varepsilon V + \zeta Q - (\eta\delta + \phi + \mu)\, W, \\
\frac{dT}{dt} &= \tau P - (\rho + \theta + \mu)\, T, \\
\frac{dQ}{dt} &= \phi W - (\zeta + \theta + \mu)\, Q,
\end{aligned}
\tag{4.1}
$$

where,

$$
\lambda = \frac{\beta\,(I + \pi P + \upsilon V + \pi\omega W + \pi\chi_T T + \pi\chi_Q Q)}{N}, \tag{4.2}
$$

is the infection rate. A flow diagram of the model is given in Figure 4.1, and the associated variables and parameters are tabulated in Table 4.1. The detailed derivation of the equations of the treatment model (4.1) are given in Appendix B (it closely follows the formulation in [14]).

The HCV transmission model (4.1) extends the treatment-free model (3.2) by, *inter alia*,

(a) adding the treatment of chronically-infected individuals (T(t));

(b) adding the treatment of chronically-re-infected individuals (Q(t));

(c) incorporating the effect of disease transmission by treated individuals.

It is worth stating that Elbasha [14] studied a special case of the HCV treatment model (4.1), where re-infection plays the same role as primary infection (i.e., the

model (4.1) with $\kappa = \alpha = \eta = \omega = \upsilon = 1$, $\chi_Q = \chi_T$, $\zeta = \rho$ and $\phi = \tau$), given by (the reduced model)

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \lambda S - \mu S + \gamma R, \\
\frac{dI}{dt} &= \lambda S - (\mu + \sigma + \varepsilon)\, I, \\
\frac{dP}{dt} &= \varepsilon I + \rho T - (\mu + \delta + \tau)\, P, \\
\frac{dR}{dt} &= \sigma I + \delta P + \sigma V + \delta W + \theta T + \theta Q - \psi\lambda R - (\mu + \gamma)\, R, \\
\frac{dV}{dt} &= \psi\lambda R - (\mu + \sigma + \varepsilon)\, V, \\
\frac{dW}{dt} &= \varepsilon V + \rho Q - (\mu + \delta + \tau)\, W, \\
\frac{dT}{dt} &= \tau P - (\mu + \rho + \theta)\, T, \\
\frac{dQ}{dt} &= \phi W - (\mu + \rho + \theta)\, Q,
\end{aligned} \tag{4.3}$$

where, now,

$$\lambda = \frac{\beta(I + \pi P + V + \pi W + \pi\chi_T T + \pi\chi_T Q)}{N}.$$

The above simplifications, made in [14], allow for the change of variables, $\bar{I} = I + V$, $\bar{P} = W + P$, $\bar{T} = T + Q$ (and, for consistency, $\bar{R} = R$ and $\bar{S} = S$), so that the reduced model (4.3) can be re-written as [14]:

$$
\begin{aligned}
\frac{d\bar{S}}{dt} &= \Lambda - \bar{\lambda}\bar{S} - \mu\bar{S} + \gamma\bar{R}, \\
\frac{d\bar{I}}{dt} &= \bar{\lambda}\bar{S} + \psi\bar{\lambda}\bar{R} - (\mu + \sigma + \varepsilon)\,\bar{I}, \\
\frac{d\bar{P}}{dt} &= \varepsilon\bar{I} + \rho\bar{T} - (\mu + \delta + \tau)\,\bar{P}, \\
\frac{d\bar{R}}{dt} &= \sigma\bar{I} + \delta\bar{P} + \theta\bar{T} - \psi\bar{\lambda}\bar{R} - (\mu + \gamma)\,\bar{R}, \\
\frac{d\bar{T}}{dt} &= \tau\bar{P} - (\mu + \rho + \theta)\,\bar{T},
\end{aligned}
\tag{4.4}
$$

with,

$$
\bar{\lambda} = \frac{\beta\left(\bar{I} + \pi\bar{P} + \pi\chi_T T\right)}{\bar{N}} \quad \text{and} \quad \bar{N} = \bar{S} + \bar{I} + \bar{P} + + \bar{R} + \bar{T}.
$$

It was shown in [14] that the DFE of the model (4.4) is globally-asymptotically stable whenever the associated reproduction number, given by,

$$
\bar{\mathcal{R}}_c = \frac{\beta}{\varepsilon + \mu + \sigma}\left[1 + \frac{\pi\varepsilon(\theta + \mu + \rho + \tau\chi_T)}{(\delta + \mu)(\theta + \mu + \rho) + (\theta + \mu)\tau}\right],
$$

is less than unity. It is further shown, for the special case of the treatment model (4.4) in the absence of re-infection ($\psi = 0$), that the unique endemic equilibrium of the reduced model (4.4) is globally asymptotically stable whenever it exists [14].

Unlike in [14], however, the full treatment model (4.1) will be rigorously analysed in this chapter (in particular, to determine whether or not it exhibits some dynamical features not seen in the reduced model (4.4), studied in [14]).

4.2.1 Basic properties

The following results can be proved using the approaches in Section 3.2.

Theorem 4.1. *Let the initial data for the treatment model (4.1) be* $S(0) > 0, I(0) >$

$0, P(0) > 0, R(0) > 0, V(0) > 0, W(0) > 0, T(0) > 0 and\ Q > 0$. *Then, the solutions*

$$(S(t), I(t), P(t), R(t), V(t), W(t), T(t), Q(t))$$

of the model (4.1), with positive initial data, will remain positive for all time $t > 0$.

Theorem 4.2. *The closed set*

$$\mathcal{D}_T = \left\{(S, I, P, R, V, W, T, Q) \in \mathbb{R}^8_+ : N \leq \frac{\Lambda}{\mu}\right\}$$

is positively-invariant and attracts all positive solutions of the treatment model (4.1).

4.3 Existence and Asymptotic Stability of Equilibria

4.3.1 Local asymptotic stability of DFE

The DFE of the treatment model (4.1) is given by

$$\mathcal{E}_0^T = (S^*, I^*, P^*, R^*, V^*, W^*, T^*, Q^*) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0, 0, 0\right). \tag{4.5}$$

Using the next generation operator method [50], as in Chapter 3, the matrices $\mathcal{F}_T$ and $\mathcal{H}_T$, associated with the treatment model (4.1), are given, respectively, by

$$\mathcal{F}_T = \begin{pmatrix} \beta & \pi\beta & \upsilon\beta & \pi\omega\beta & \pi\chi_T\beta & \pi\chi_Q\beta \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \; \mathcal{H}_T = \begin{pmatrix} K_1 & 0 & 0 & 0 & 0 & 0 \\ -\varepsilon & K_2 & 0 & 0 & -\rho & 0 \\ 0 & 0 & K_3 & 0 & 0 & 0 \\ 0 & 0 & -\kappa\varepsilon & K_4 & 0 & -\zeta \\ 0 & -\tau & 0 & 0 & K_5 & 0 \\ 0 & 0 & 0 & -\phi & 0 & K_6 \end{pmatrix},$$

where, $K_1 = \mu + \sigma + \varepsilon,\ K_2 = \mu + \delta + \tau,\ K_3 = \mu + \alpha\sigma + \kappa\varepsilon,\ K_4 = \mu + \eta\delta + \phi,\ K_5 = \mu + \rho + \theta$, and $K_6 = \mu + \zeta + \theta$. It follows, from Theorem 2 in [50], that the *control reproduction number* of the model (4.1), defined by $\mathcal{R}_T = \rho(\mathcal{F}_T\mathcal{H}_T^{-1})$, is given by (where $K_2K_5 - \rho\tau = (\mu + \delta + \tau)(\mu + \theta) + \mu\rho + \delta\rho > 0$, so that $\mathcal{R}_T > 0$)

$$\mathcal{R}_T = \rho\left(\mathcal{F}_T\mathcal{H}_T^{-1}\right) = \frac{\beta\left(K_2K_5 - \rho\tau + \pi\varepsilon K_5 + \chi_T\pi\varepsilon\tau\right)}{K_1(K_2K_5 - \rho\tau)}. \tag{4.6}$$

It should be mentioned that the expression for $\mathcal{R}_T$ is the same as that of $\bar{\mathcal{R}}_c$ in [14]. The result below follows from Theorem 2 of [50].

Theorem 4.3. *The DFE, $\mathcal{E}_0^T$, of the treatment model (4.1), given by (4.5), is LAS if $\mathcal{R}_T < 1$, and unstable if $\mathcal{R}_T > 1$.*

4.3.2 Existence of EEP

As in Chapter 3, let

$$\mathcal{E}_1^T = (S^{**}, I^{**}, P^{**}, R^{**}, V^{**}, W^{**}, T^{**}, Q^{**}), \tag{4.7}$$

be an arbitrary endemic equilibrium of the treatment model (4.1). Furthermore, let

$$\lambda^{**} = \frac{\beta\mu(I^{**} + \pi P^{**} + \upsilon V^{**} + \pi\omega W^{**} + \pi\chi_T T^{**} + \pi\chi_Q Q^{**})}{\Lambda}, \tag{4.8}$$

(where the total population, $N(t)$, is now replaced by its limiting value, $N^* = \frac{\Lambda}{\mu}$) be the force of infection at steady-state.

Solving the equations of the treatment model (4.1) at the endemic steady-state gives:

$$\begin{aligned}
S^{**} &= \frac{\gamma R^{**} + \Lambda}{\lambda^{**} + \mu}, \quad I^{**} = \frac{\lambda^{**} S^{**}}{K_1}, \quad P^{**} = \frac{\varepsilon I^{**} + \rho T^{**}}{K_2}, \\
R^{**} &= \frac{\sigma I^{**} + \delta P^{**} + \alpha\sigma V^{**} + \eta\delta W^{**} + \theta T^{**} + \theta Q^{**}}{(\mu + \gamma + \psi\lambda^{**})}, \\
V^{**} &= \frac{\psi\lambda^{**} R^{**}}{K_3}, \quad W^{**} = \frac{\kappa\varepsilon V^{**} + \zeta Q^{**}}{K_4}, \quad T^{**} = \frac{\tau P^{**}}{K_5}, \quad Q^{**} = \frac{\phi W^{**}}{K_6}.
\end{aligned} \tag{4.9}$$

Substituting the expressions in (4.9) into (4.8) gives:

$$(B_1 + B_2\lambda^{**})(B_3 + B_4\lambda^{**}) = B_5 B_6 \lambda^{**}, \tag{4.10}$$

where,

$$
\begin{aligned}
B_1 &= \gamma K_3(K_2K_5 - \rho\tau)(K_4K_6 - \zeta\phi)(\mu + \gamma)\\
B_2 &= \gamma(K_2K_5 - \rho\tau)[K_3\psi(K_4K_6 - \zeta\phi) - \psi(\alpha\sigma(K_4K_6 - \zeta\phi) + K_6\eta\delta\kappa\varepsilon + \theta\phi\kappa\varepsilon)],\\
B_3 &= \mu\gamma K_3(K_4K_6 - \zeta\phi)[K_1(K_2K_5 - \rho\tau) - \beta(K_2K_5 - \rho\tau + \pi\varepsilon K_5 + \chi\pi\varepsilon\tau),\\
B_4 &= \gamma K_1K_3(K_2K_5 - \rho\tau)(K_4K_6 - \zeta\phi),\\
B_5 &= \gamma K_3(K_2K_5 - \rho\tau)(K_4K_6 - \zeta\phi)\\
&\quad + \beta\mu\psi(K_2K_5 - \rho\tau)[\upsilon(K_4K_6 - \zeta\phi) + \kappa\varepsilon\omega\pi K_6 + \chi_Q\pi\phi\kappa\varepsilon],\\
B_6 &= \gamma K_3(K_4K_6 - \zeta\phi)[\sigma(K_2K_5 - \rho\tau) + \delta\varepsilon K_5 + \theta\varepsilon\tau].
\end{aligned}
\tag{4.11}
$$

It follows that the non-zero (endemic) equilibria of the treatment model (4.1) satisfy the following polynomial (in terms of λ^{**}),

$$
a_2(\lambda^{**})^2 + a_1\lambda^{**} + a_0 = 0, \tag{4.12}
$$

where,

$$
\begin{aligned}
a_2 &= \gamma^2K_1K_3A_1(K_4K_6 - \zeta\phi)(K_2K_5 - \rho\tau)^2,\\
a_1 &= \mu\gamma^2K_1K_3A_1(K_4K_6 - \zeta\phi)(K_2K_5 - \rho\tau)^2(1 - \mathcal{R}_T)\\
&\quad + \gamma^2K_3^2K_1(\mu + \gamma)(K_4K_6 - \zeta\phi)^2(K_2K_5 - \rho\tau)^2\\
&\quad - A_2[\gamma K_3(K_4K_6 - \zeta\phi)(\sigma(K_2K_5 - \rho\tau) + \delta\varepsilon K_5 + \theta\varepsilon\tau)],\\
a_0 &= \Lambda\gamma^2K_1K_3^2(\mu + \gamma)(1 - \mathcal{R}_T)(K_4K_6 - \zeta\phi)^2(K_2K_5 - \rho\tau)^2,
\end{aligned}
\tag{4.13}
$$

with,

$$A_1 = \psi(K_4K_6 - \zeta\phi)(\mu + \kappa\varepsilon) + K_6\psi\eta\delta\kappa\varepsilon + \psi\theta\phi\kappa\varepsilon, \tag{4.14}$$

$$A_2 = (K_2K_5 - \rho\tau)\{\gamma K_3(K_4K_6 - \zeta\phi) + \beta\mu[\upsilon\psi(K_4K_6 - \zeta\phi) + \kappa\varepsilon\psi\omega\pi K_6 + \chi\pi\phi\kappa\varepsilon\psi]\}.$$

The endemic equilibria of the treatment model (4.1) can then be obtained by solving for λ^{**} from (4.8), and substituting the positive values of λ^{**} into the steady-state expressions in (4.9). Furthermore, it follows from (4.13) that the coefficient a_2, of the quadratic (4.12), is always positive (it should be recalled, from Section 3.1, that $K_4K_6 - \zeta\phi = (\mu + \eta\delta + \phi)(\mu + \theta) + \zeta(\mu + \eta\delta) > 0$ and $K_2K_5 - \rho\tau > 0$) and a_0 is positive (negative) if $\mathcal{R}_T$ is less (greater) than unity. The quadratic has a unique endemic equilibrium whenever $\mathcal{R}_T > 1$. These results are summarized below.

Theorem 4.4. *The treatment model (4.1) has:*

(i) *a unique endemic equilibrium if* $a_0 < 0 \Leftrightarrow \mathcal{R}_T > 1$*;*

(ii) *a unique endemic equilibrium if* $a_1 < 0$ *and* $a_0 = 0$ *or* $a_1^2 - 4a_0a_2 = 0$*;*

(iii) *two endemic equilibria if* $a_0 > 0, a_1 < 0$ *and* $a_1^2 - 4a_0a_2 > 0$*;*

(iv) *no endemic equilibrium otherwise.*

Here, too, Item (iii) of Theorem 4.4 suggests the possibility of the backward bifurcation in the model (4.1). The backward bifurcation phenomenon in the treatment model (4.1) is explored below.

Theorem 4.5. *The treatment model (4.1) undergoes backward bifurcation at* $\mathcal{R}_T = 1$ *whenever the Inequality (C.5), given in Appendix C, holds.*

The proof of Theorem 4.5 is given in Appendix C (and a schematic description of the backward bifurcation phenomenon of the treatment model (4.1) is depicted in

Figure 4.4). It should be recalled that this (backward bifurcation) phenomenon does not occur in the reduced model (4.4), considered in [14]. In other words, the treatment model (4.1) has at least one dynamical feature (backward bifurcation) that is not present in the reduced model (4.4). Thus, like in the case of the treatment-free model (3.2), it is instructive to explore the possible causes of the backward bifurcation phenomenon in the treatment model (4.1). This is done below.

4.3.3 Non-existence of backward bifurcation

Two main cases will be considered, as follows.

Case 1: Absence of re-infection of recovered individuals ($\psi = 0$)

Consider the treatment model (4.1) in the absence of re-infection (i.e., $\psi = 0$). Setting the re-infection parameter (ψ) to zero in the expression of the backward bifurcation coefficient, a, given by (C.3) in Appendix C (it should be recalled that $K_4K_6 - \zeta\phi > 0$ and $K_2K_5 - \rho\tau > 0$) shows that

$$a = \frac{-2\mu v_2 w_2^2 K_1}{\Lambda K_3 (K_4K_6 - \zeta\phi)(K_2K_5 - \rho\tau)(\mu + \gamma)} [K_3(K_4K_6 - \zeta\phi)(\mu + \gamma)$$
$$(K_2K_5 - \rho\tau + \varepsilon K_5 + \tau\varepsilon) + K_3(K_4K_6 - \zeta\phi)F] < 0. \tag{4.15}$$

Thus, it follows from (4.15) and Appendix C (where the eigenvector $v_2 > 0$ and $F > 0$) that, in the absence of re-infection ($\psi = 0$), the bifurcation coefficient, a (given by (C.3)), is negative. Hence, based on the Item (iv) of Theorem 4.1 in [6], it can be concluded that the treatment model (4.1) dose not undergo backward bifurcation in the absence of re-infection. Hence, the re-infection of recovered individuals causes backward bifurcation in the treatment model (4.1). The reason that the treatment model (4.1) exhibits backward bifurcation, while the model (4.4) (considered in [14])

does not, is (clearly) the heterogeneity between primary infection and re-infection. In the model (4.4), re-infection and primary infection behave the same way (and, in such a case, re-infection does not cause backward bifurcation). To further confirm the absence of backward bifurcation for this special case, the following result is proved for the DFE of the model (4.1).

Theorem 4.6. *The DFE ($\mathcal{E}_0^T$) of the treatment model (4.1), with $\psi = 0$, is GAS in $\mathcal{D}_T$ whenever $\mathcal{R}_T < 1$.*

The proof, based on using Comparison Theorem [32], is given in Appendix D. Figure 4.2 depicts the solutions profile of the model (4.1) generated for the case when $\psi = 0$ and $\mathcal{R}_T < 1$, using various initial conditions, showing the convergence to the DFE (in line with Theorem 4.6).

Case 2: Presence of re-infection ($\psi \neq 0$).

Consider the treatment model (4.1) in the presence of re-infection of recovered individuals ($\psi \neq 0$). There are two cases to consider here, as follows:

(i) No heterogeneity between primary infection and re-infection.

For this case (with $\kappa = \alpha = \eta = \omega = \upsilon = 1$, $\chi_Q = \chi_T$, $\zeta = \rho$ and $\phi = \tau$), the treatment model (4.1) reduces to the model (4.4). Elbasha [14] proved the GAS property of the DFE of the model for this special case (ruling out the possibility of backward bifurcation in the model (4.4)). The result in [14] is further verified by applying the centre manifold theory on the model (4.4), as detailed in Appendix E (from which it is clear that the reduced model (4.4) does not undergo backward bifurcation). Thus, the analysis in Appendix E shows that the absence of the heterogeneity between re-infected and primary infected individuals removes the backward bifurcation property of the model (4.1), even in the presence of the re-infection of

recovered individuals.

(*ii*) Effect of infectivity of acute, chronic and treated re-infected individuals ($\upsilon \neq 0,\ \omega \neq 0,\ \chi_Q \neq 0$).

Consider the case of the treatment model (4.1) where acute, chronic and treated re-infected individuals do not transmit infection (i.e., $\upsilon = \omega = \chi_Q = 0$). For this case,

$$\hat{\lambda} = \lambda|_{\upsilon=\omega=\chi_Q=0} = \frac{\beta(I + \pi P + \chi_T \pi T)}{N},$$

where, $N = S + I + P + R + V + W + T + Q$. Setting $\upsilon = \omega = \chi_Q = 0$ in the expression of the backward bifurcation coefficient, a (given by (C.3) in Appendix C), and simplifying, shows that

$$\begin{aligned} a = \frac{-2\mu v_2 w_2^2 K_1}{\Lambda K_3 (K_4 K_6 \zeta\phi)(K_2 K_5 - \rho\tau)(\mu + \gamma)} \left[K_3 (K_4 K_6 - \zeta\phi)(\mu + \gamma)\right. \\ \left. (K_2 K_5 - \rho\tau + \varepsilon K_5 + \tau\varepsilon) + K_3 (K_4 K_6 - \zeta\phi) F\right] < 0. \end{aligned} \tag{4.16}$$

Thus, it follows, from (4.16) and Appendix C, that disease transmission by re-infected individuals causes backward bifurcation in HCV transmission dynamics. The above results are summarized below.

(*a*) The treatment model (4.1) does not undergo backward bifurcation in the absence of re-infection of recovered individuals ($\psi = 0$).

(*b*) In the presence of re-infection of recovered individuals ($\psi \neq 0$), the phenomenon of backward bifurcation can be removed *via* any of the following scenarios:

(*i*) the absence of heterogeneity between re-infected and primary infected individuals (i.e., $\kappa = \alpha = \eta = \omega = \upsilon = 1$, $\chi_Q = \chi_T$, $\zeta = \rho$, and $\phi = \tau$);

(*ii*) if re-infected individuals do not transmit HCV infection (i.e., $\upsilon = \omega = \chi_Q = 0$).

Furthermore it is shown, in Item (*ii*) of Case (b) above, that if individuals in the re-infected classes (V, W, Q) are not able to transmit the infection, then the treatment model (4.1) does not undergo backward bifurcation even in the presence of re-infection ($\psi \neq 0$). This fact is further illustrated by proving the global asymptotic stability of the DFE of the treatment model (4.1) for this special case, as below.

Theorem 4.7. *The DFE, $\mathcal{E}_0^T$, of the treatment model (4.1), with $\upsilon = \omega = \chi_Q = 0$, is GAS in $\mathcal{D}_T$ whenever $\mathcal{R}_T < 1$.*

The proof, based on using Comparison Theorem [32], is given in Appendix F. As in Chapter 3, the result given in Theorem 4.7 shows that HCV can be effectively-controlled (or eliminated) in the IDU population if the infectivity of re-infected individuals is negligible (or, for instance, cured IDUs change their behaviour, and cease being IDUs). Moreover, numerical simulations of the treatment model (4.1), for the case when $\mathcal{R}_T > 1$ (Figure 4.3), suggests that the associated unique endemic equilibrium ($\mathcal{E}_1^T$) is stable when it exists.

4.4 Assessment of Treatment Impact

Following Elbasha [14], the reproduction threshold ($\mathcal{R}_T$) is differentiated partially with respect to the treatment rate of chronically-infected individuals (τ), giving

$$\frac{\partial \mathcal{R}_T}{\partial \tau} = -\frac{\beta}{(\mu+\sigma+\varepsilon)} \frac{\pi\varepsilon(\mu+\rho+\theta)\triangle}{[(\mu+\delta)(\mu+\theta+\rho)+\tau(\mu+\theta)]^2}, \tag{4.17}$$

where,

$$\triangle = (\mu + \theta) - \chi_T(\mu + \delta).$$

Thus, $\mathcal{R}_T$ is a decreasing (increasing) function of τ whenever $\triangle > 0$ (< 0). Furthermore, $\frac{\partial \mathcal{R}_T}{\partial \tau} = 0$ if $\triangle = 0$. This leads to the following result (same result was also derived for the reduced model considered in [14]).

Theorem 4.8. *Consider the treatment model (4.1) in the absence of backward bifurcation. The treatment of chronically-infected individuals offers*

(i) *a positive population-level impact whenever* $\triangle > 0$ *;*

(ii) *no-population level impact if* $\triangle = 0$*;*

(iii) *a detrimental impact population-level (increase disease burden) if* $\triangle < 0$.

As noted by Elbasha [14], the threshold quantity, $\triangle$, is expected to always be positive since the cure rate (θ) is expected to exceed the natural recovery for chronically-infected individuals (δ), and that the relative infectiousness of treated individuals is small ($\chi_T < 1$). Similarly, differentiating the reproduction threshold ($\mathcal{R}_T$) partially with respect to the treatment failure rate for chronically-infected individuals (ρ) gives:

$$\frac{\partial \mathcal{R}_T}{\partial \rho} = \frac{\beta}{(\mu + \sigma + \varepsilon)} \frac{\pi \varepsilon \tau \triangle}{[(\mu + \delta)(\mu + \theta + \rho) + \tau(\mu + \theta)]^2}, \tag{4.18}$$

so that $\mathcal{R}_T$ is an increasing function of ρ whenever $\triangle > 0$, as expected.

4.5 Uncertainty and Sensitivity Analysis

As in Chapter 3, the impact of the uncertainties of the estimates of the parameters values (given in Table 4.2 and used in the numerical simulations of the treatment model (4.1)) are assessed. Furthermore, the sensitivity of the parameters of the

treatment model (4.1) is measured by finding PRCC between each parameter and control reproduction number ($\mathcal{R}_T$).

A boxplot of the control reproduction number ($\mathcal{R}_T$), as a function of the number of LHS runs carried out, is depicted in Figure 4.6, showing a range of $\mathcal{R}_T$ from 1.44 to 1.48 (which is consistent with the range in [14]). It is worth mentioning that the $\mathcal{R}_T$ range is marginally lower than the $\mathcal{R}_0$ range (given in Section 3.4) because a small treatment rate (4%) is used in the simulations for the boxplots in Figure 4.6. The boxplot corresponding to an increased treatment rate (70%) is depicted in Figure 4.7, showing a markedly decreased $\mathcal{R}_T$ range (of $\mathcal{R}_T \in [1.33, 1.37]$).

Furthermore, Table 4.3 and Figure 4.5 give the PRCC values of the parameters of the model, from which it follows that the parameters that most affect $\mathcal{R}_T$ (hence, drive the HCV transmission dynamics) are the effective contact rate (β), the rate of progression to chronic infection (ε), the rate of recovery from acute infection (σ), the death or retirement rate from the population (μ) and the relative infectivity of chronically-infected individuals (π). As in the case of the treatment-free model (3.2), further numerical simulations of the treatment model (4.1) (Figures 4.8 and 4.9) show that a 10% increase in the baseline values of these top-PRCC ranked parameters ($\beta,\ \varepsilon,\ \sigma,\ \mu$ and π) increases the cumulative incidence and prevalence of HCV in the community (and that a 10% decrease leads to a decrease in the cumulative incidence and prevalence of the disease during the first few years (about 10 years), and a marginal increase shortly thereafter).

4.6 Numerical Simulations

As in Chapter 3, the treatment model (4.1) is simulated using the parameters values given in Table 4.2 (unless otherwise stated). The following initial data (relevant to HCV dynamics in an IDU population [14]) is also used:

$$(S(0), I(0), P(0), R(0), V(0), W(0), T(0), Q(0)) = (439000, 550, 350, 50, 20, 10, 10, 10).$$

The cumulative number of new cases, as a function of time, for various values of the re-infection rate (ψ) is shown in Figure 4.10. It is evident from Figure 4.10 that re-infection has little or no effect on the cumulative incidence of HCV for the first few years. The effect is, however, noticeable after about 7 years. In other words, this study shows that re-infection has marginal effect on HCV burden (as measured in terms of cumulative number of new cases) in the community. Similar results are obtained for the prevalence of HCV (Figure 4.11).

The effect of treatment of chronically-infected individuals on the cumulative incidence and prevalence of the disease is depicted in Figures 4.12 and 4.13, respectively. It follows from these figures that, as expected, the treatment of chronically-infected individuals significantly reduces the cumulative incidence and prevalence of HCV in the community. Furthermore, Figure 4.14 shows that the treatment of active IDU's, even if only a tiny percentage is treated, has a positive population-level impact (i.e., minimizes HCV burden in the IDU population). This figure also shows that the treatment of a sizeable proportion of chronically-infected individuals (e.g., $\tau = 70\%$) significantly reduces the prevalence of HCV in the population.

These simulations provide the answer to Question 4 in Section 1.3.

4.7 Summary of the Chapter

This chapter focuses on the rigorous analysis of the HCV transmission model in the presence of treatment, presented by Elbasha [14]. The aim was to extend the qualitative analyses in [14] (where only a special case of the treatment model was analysed) and explore new dynamical features (of the model) not observed or estab-

lished in [14]. It was shown that the treatment model undergoes the phenomenon of backward bifurcation when the associated control reproduction number ($\mathcal{R}_T$) is less than unity. One of the notable contributions of this chapter is that three main scenarios where the backward bifurcation property of the treatment model can be removed are identified as follows.

The first is the absence of heterogeneity between primary infected and re-infected recovered individuals. In other words, the model will not undergo backward bifurcation if newly-infected and re-infected recovered individuals behave the same way (with respect to the rates of the infectivity recovery, disease progression and treatment). This result supports, and extends, the results reported in [14], where a special case (5-dimensional) of the 8-dimensional model (4.1) is analysed. Hence, this study shows that heterogeneity between primary infected individuals and reinfected individuals can induce the phenomenon of backward bifurcation in the transmission dynamics of a disease (such as HCV).

The second is in the presence of such heterogeneity, the backward bifurcation phenomenon can be removed *via* two cases, namely, (i) when re-infection of recovered individuals does not occur ($\psi = 0$); (ii) when acute, chronic and treated re-infected individuals do not transmit infection (i.e., $\upsilon = \omega = \chi_Q = 0$). For the case when re-infection does not occur, a comparison theorem is used to prove the global asymptotic stability of the disease-free equilibrium of the model when the associated reproduction number is less than unity.

The treatment model is shown to have a unique endemic equilibrium when the associated control reproduction number ($\mathcal{R}_T$) exceeds unity. In such a case, numerical simulations show that HCV will persist in the IDU population. These simulation results also provide answers to Questions 2 and 3 raised in Section 1.3.

Further simulations show that the re-infection of recovered individuals has marginal effect on the disease burden (as measured in terms of HCV cumulative incidence

and prevalence in the community). Moreover, it is shown (as expected) that the treatment of chronically-infected individuals significantly reduces the cumulative incidence and prevalence of HCV in the IDU community.

Symbol	Description
Variables	
$S(t)$	Population of susceptible individuals
$I(t)$	Population of acutely-infected individuals
$P(t)$	Population of chronically-infected individuals
$R(t)$	Population of recovered individuals with partial immunity
$V(t)$	Population of acutely-reinfected individuals
$W(t)$	Population of chronically-reinfected individuals
$T(t)$	Population of chronically-infected treated individuals
$Q(t)$	Population of chronically-reinfected treated individuals
Parameters	
Λ	Recruitment rate
μ	Natural death rate
β	Contact rate
σ	Recovery rate from acute infection
δ	Recovery rate from chronic infection
ε	Rate of progression from acute infection to chronic infection
ψ	Relative susceptibility of recovered individuals
α	Relative rate of recovery from acute re-infection
η	Relative rate of recovery from chronic re-infection
κ	Relative rate of progression from acute re-infection to chronic re-infection
τ	Treatment rate of chronically-infected individuals
ϕ	Treatment rate of chronically-re-infected individuals
θ	Treatment cure rate
ρ	Treatment failure rate of chronically-infected individuals
ζ	Treatment failure rate of chronically-re-infected individuals
γ	Rate of waning immunity
π	Relative infectivity of chronically-infected individuals
υ	Relative infectivity of acutely-re-infected individuals
ω	Relative infectivity of chronically-re-infected individuals
χ_T	Relative infectivity of treated infected individuals
χ_Q	Relative infectivity of treated re-infected individuals

Table 4.1: Description of variables and parameters of the treatment model (4.1) [14].

Parameters	Baseline Values [14]	Ranges [14]
Λ	$39,600$ year^{-1}	[35640, 43560]
μ	0.09 year^{-1}	[0.081, 0.099]
β	2.68 year^{-1}	[2.444, 2.948]
σ	0.5 year^{-1}	[0.45, 0.55]
δ	0.002 year^{-1}	[0.0018, 0.0022]
ε	1.5 year^{-1}	[1.35, 1.65]
ψ	0.5	[0.45, 0.55]
α	3.3	[2.97, 3.36]
η	3.3	[2.97, 3.36]
κ	1/3.3	[0.2727, 0.3333]
τ	0.04 year^{-1}	[0.036, 0.044]
ϕ	0.04 year^{-1}	[0.036, 0.044]
θ	0.67 year^{-1}	[0.603, 0.737]
ρ	0.82 year^{-1}	[0.738, 0.902]
ζ	0.82 year^{-1}	[0.738, 0.902]
γ	0.025 year^{-1}	[0.0225, 0.0275]
π	0.01	[0.009, 0.011]
υ	1/6.5	[0.1386, 0.1694]
ω	1/6.5	[0.1386, 0.1694]
$\chi_T = \chi_Q = \chi$	0.5	[0.45, 0.55]

Table 4.2: Baseline values and ranges of the parameters of the treatment model (4.1).

Parameters	PRCC($\mathcal{R}_T$)
β	0.989521805
ε	-0.972702393
σ	-0.852219599
μ	-0.703177587
π	0.637106865
θ	-0.11532655
τ	-0.097537395
δ	0.054609189
ρ	0.053632664
Λ	0.035866564
η	0.033461692
γ	-0.031457596
κ	-0.017800737
υ	-0.014450844
χ	0.011501931
ζ	-0.010004813
α	-0.006900158
ψ	0.004427847
ω	0.004084257
ϕ	0.002943497

Table 4.3: PRCC values of the parameters of the treatment model (4.1), with $\mathcal{R}_T$ as the output. Parameter values and ranges used are as given in Table 4.2.

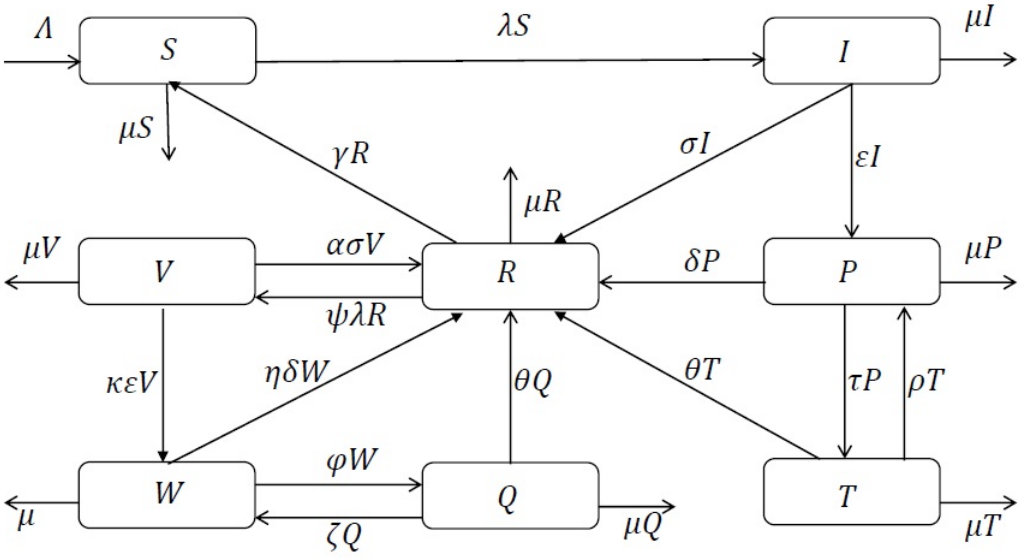

Figure 4.1: Schematic diagram of the treatment model (4.1) [14].

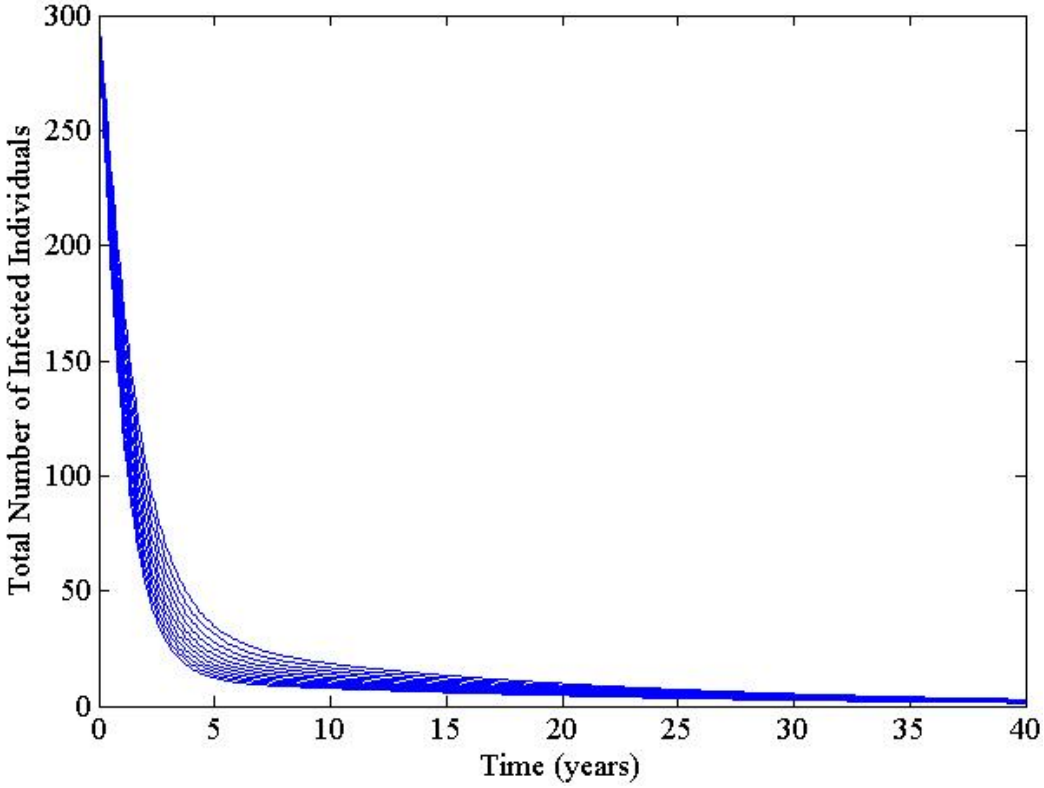

Figure 4.2: Simulations of the treatment model (4.1), showing the total number of infected individuals as a function of time, using various initial conditions. Parameter values used are as given in Table 4.2, with $\beta = 1.68$ (so that, $\mathcal{R}_T = 0.8323$).

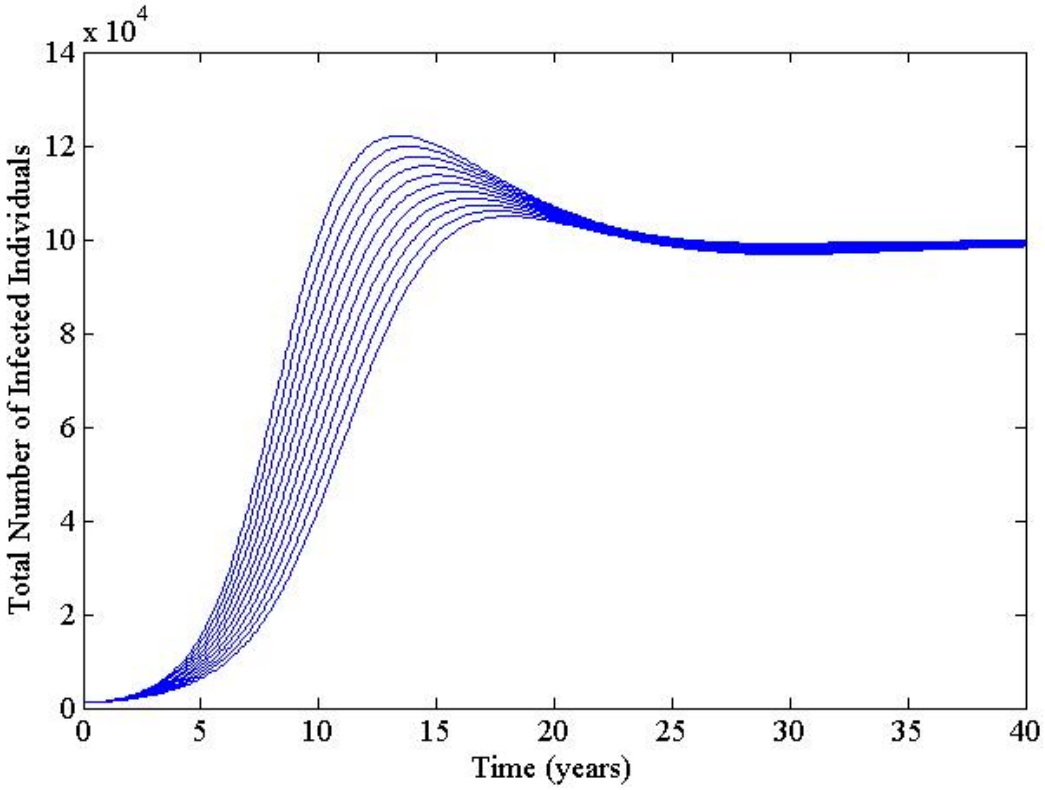

Figure 4.3: Simulations of the treatment model (4.1), showing the total number of infected individuals as a function of time, using various initial conditions. Parameter values used are as given in Table 4.2 (so that, $\mathcal{R}_T = 1.4574$).

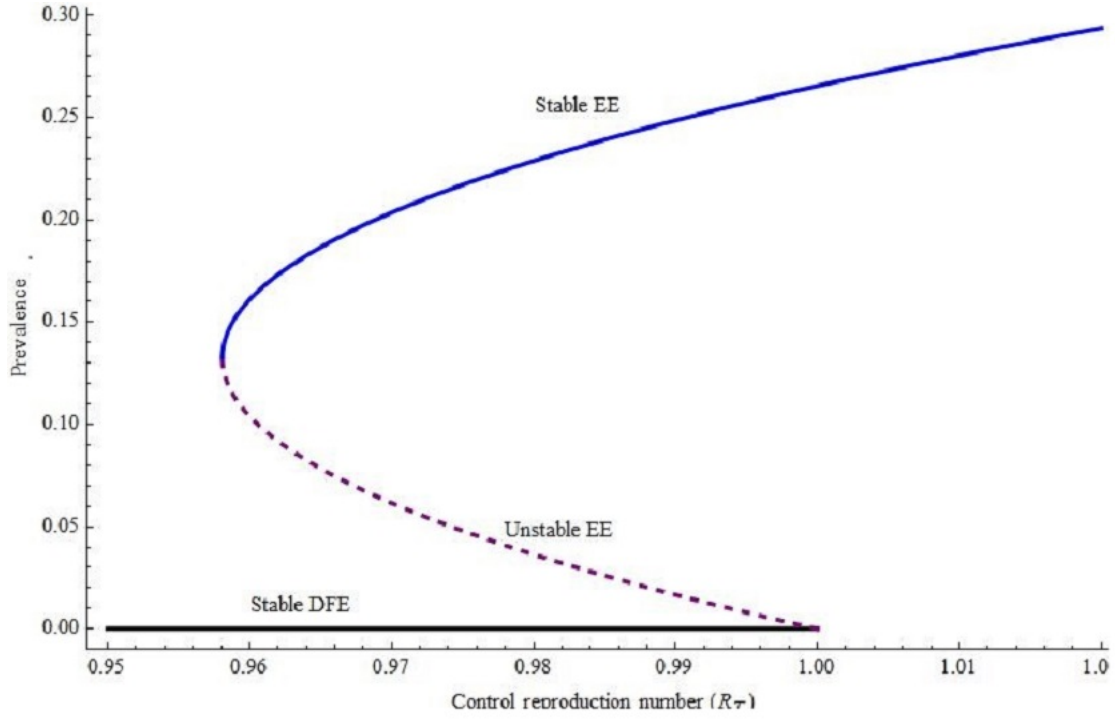

Figure 4.4: Backward bifurcation diagram for the treatment model (4.1), showing the prevalence as a function of the control reproduction number ($\mathcal{R}_T$). Parameter values used are: $\Lambda = 40640,\ \beta^* = 3.324462329,\ \mu = 0.091,\ \sigma = 0.255,\ \delta = 0.0025,\ \varepsilon = 3.5,\ \psi = 0.70,\ \alpha = 3.3,\ \eta = 4.050,\ \kappa = 0.0827,\ \tau = 0.70,\ \phi = 0.36,\ \theta = 0.7603,\ \zeta = 0.902,\ \rho = 0.638,\ \gamma = 0.0225,\ \pi = 0.019,\ \upsilon = 0.89999,\ \omega = 0.89999\ \chi_T = 0.35,$ and $\chi_Q = 0.745$ (so that, $a = 0.0001180441877 > 0$; $\mathcal{R}_T = 1$).

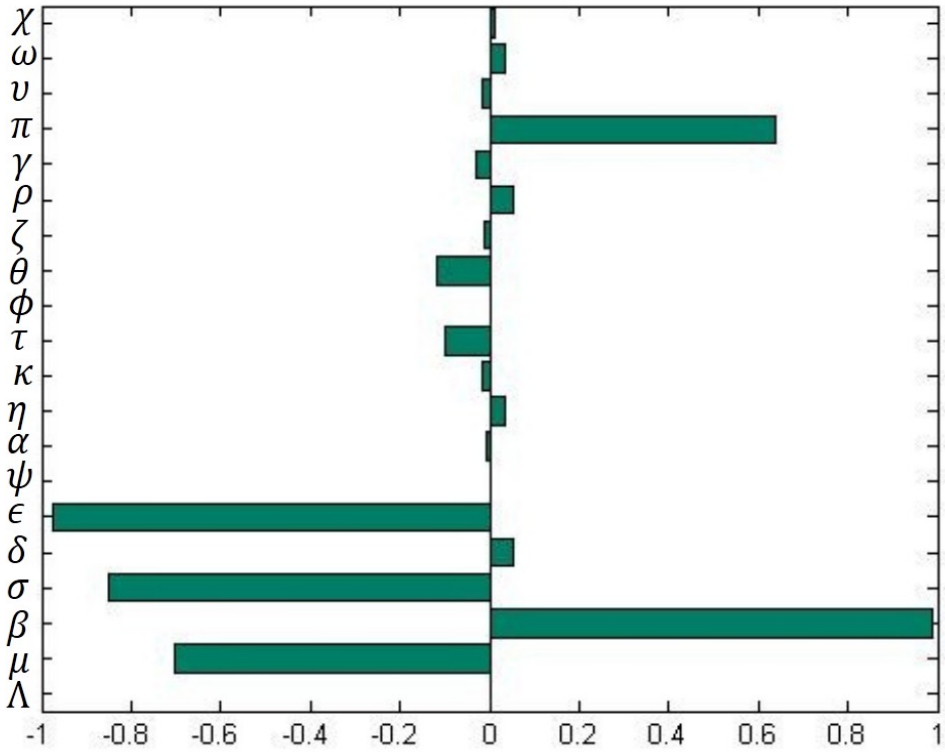

Figure 4.5: Distribution of PRCC values for the parameters of the treatment model (4.1). Parameter values and ranges used are as given in Table 4.2.

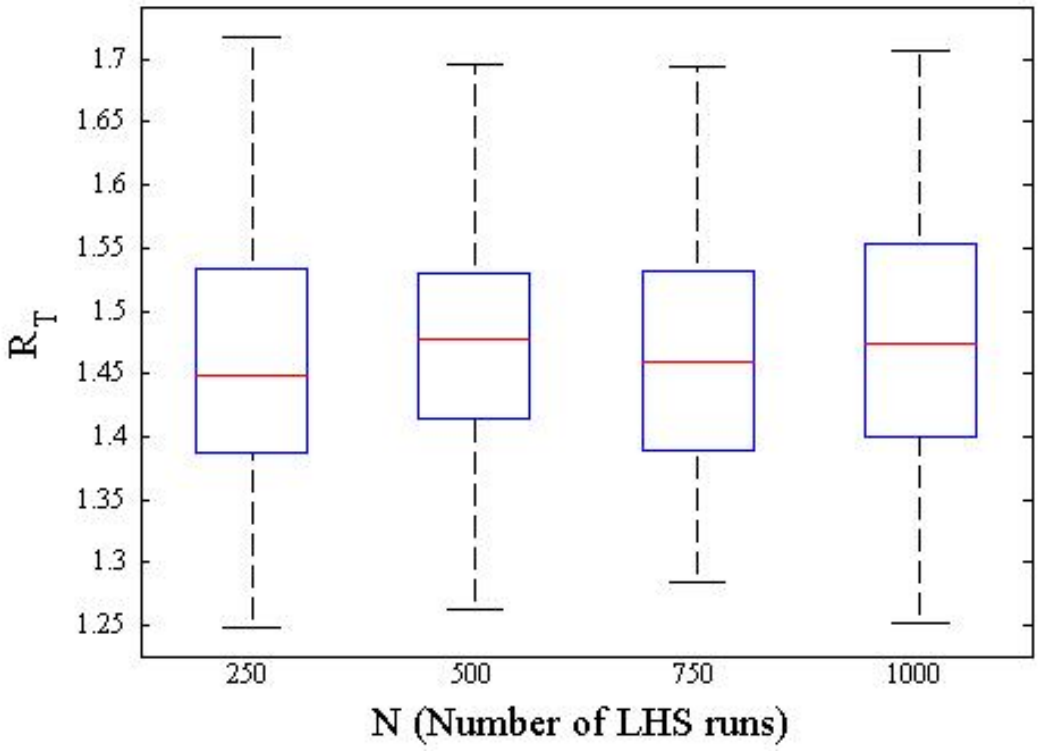

Figure 4.6: Boxplots of the control reproduction number ($\mathcal{R}_T$), as a function of the number of LHS runs (N_R) carried out, for the treatment model (4.1). Parameter values and ranges used are as given in Table 4.2.

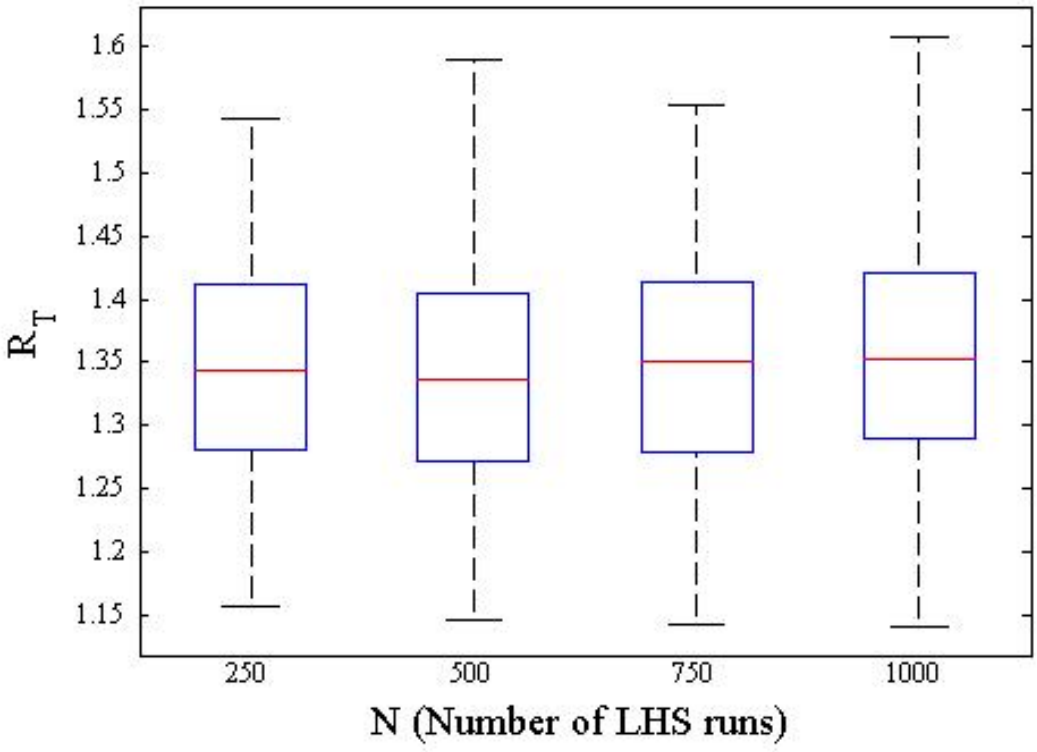

Figure 4.7: Boxplots of the control reproduction number ($\mathcal{R}_T$), as a function of the number of LHS runs (N_R) carried out, for the treatment model (4.1) with increased treatment rate ($\tau = 70\%$). Parameter values and ranges used are as given in Table 4.2.

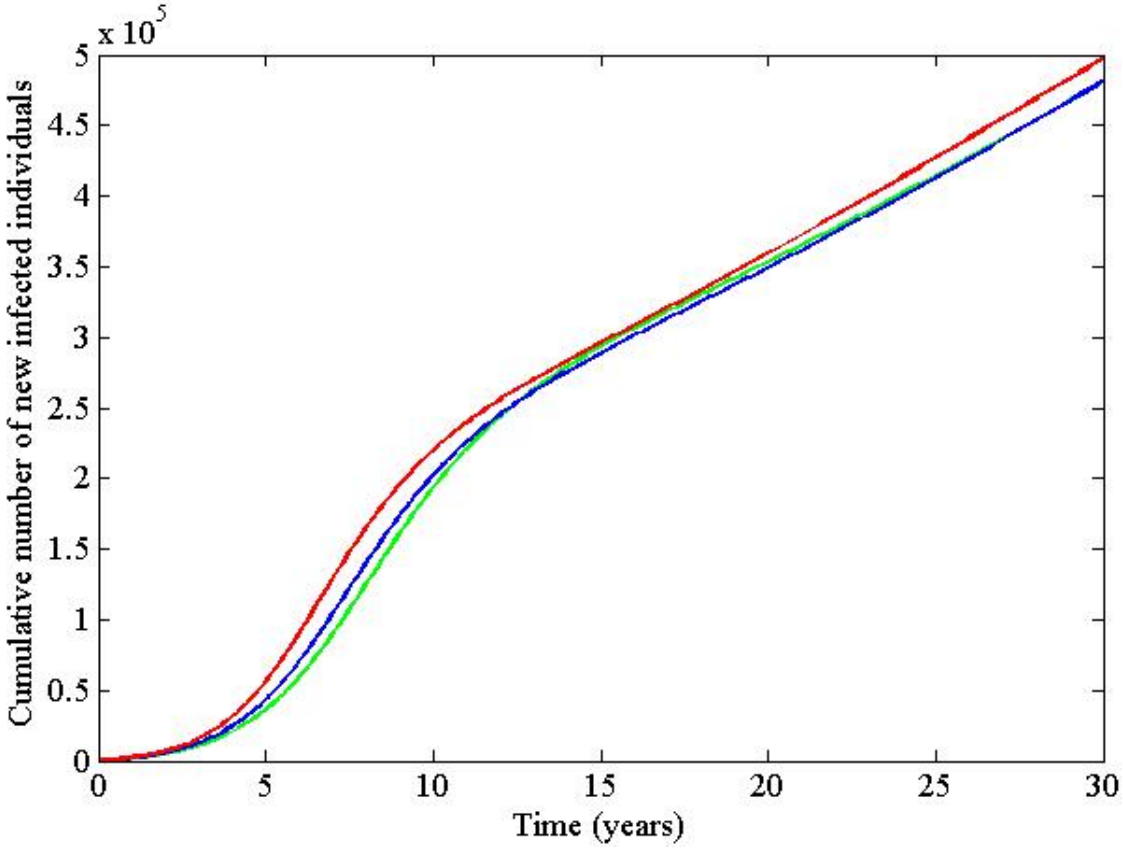

Figure 4.8: Simulations of the treatment model (4.1), showing the cumulative number of new infected individuals as a function of time, for various values of the top-five PRCC-ranked parameters in Table 4.3 (β, ε, σ, μ and π): green curve (10% decrease in the baseline values of the top-five PRCC-ranked parameters); blue curve (baseline values); red curve (10% increase in the baseline values of the top-five PRCC-ranked parameters). Parameter values used are as given in Table 4.2.

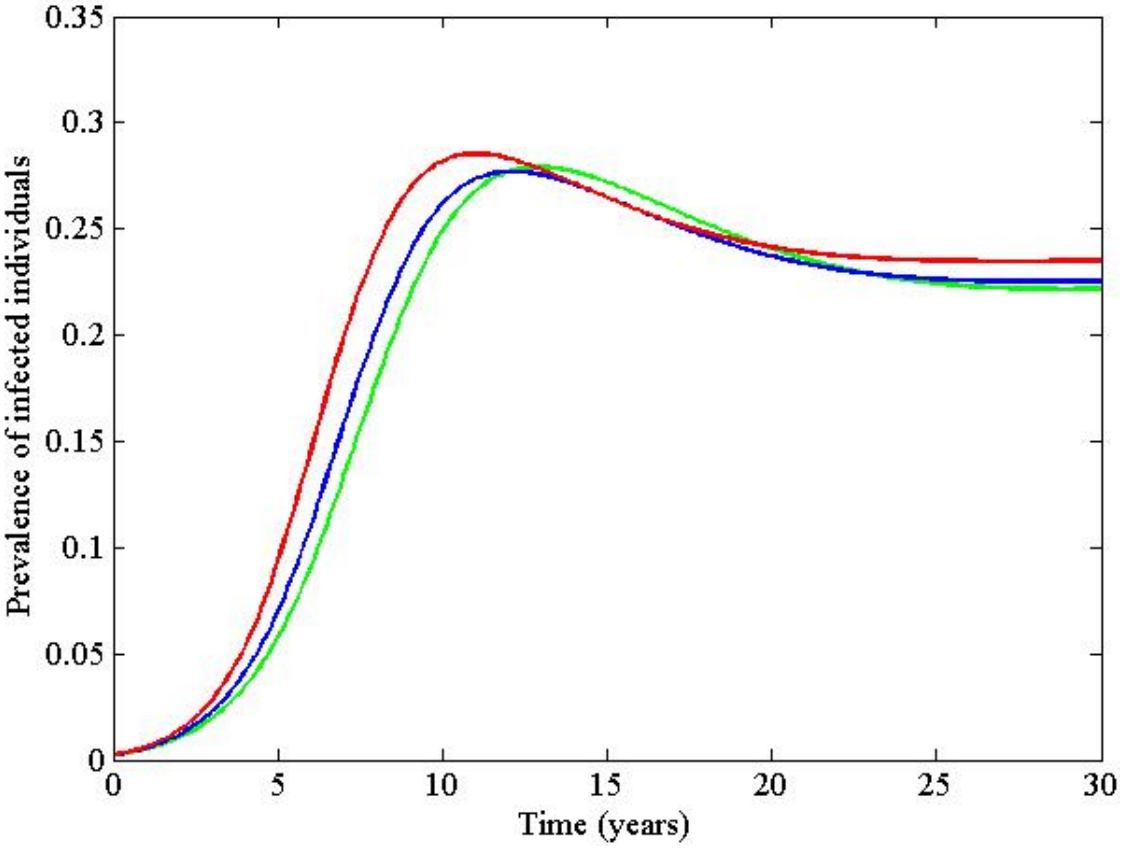

Figure 4.9: Simulations of the treatment model (4.1), showing the the prevalence of HCV as a function of time, for various values of the top-five PRCC-ranked parameters in Table 4.3 (β, ε, σ, μ and π): green curve (10% decrease in the baseline values of the top-five PRCC-ranked parameters); blue curve (baseline values); red curve (10% increase in the baseline values of the top-five PRCC-ranked parameters). Parameter values used are as given in Table 4.2.

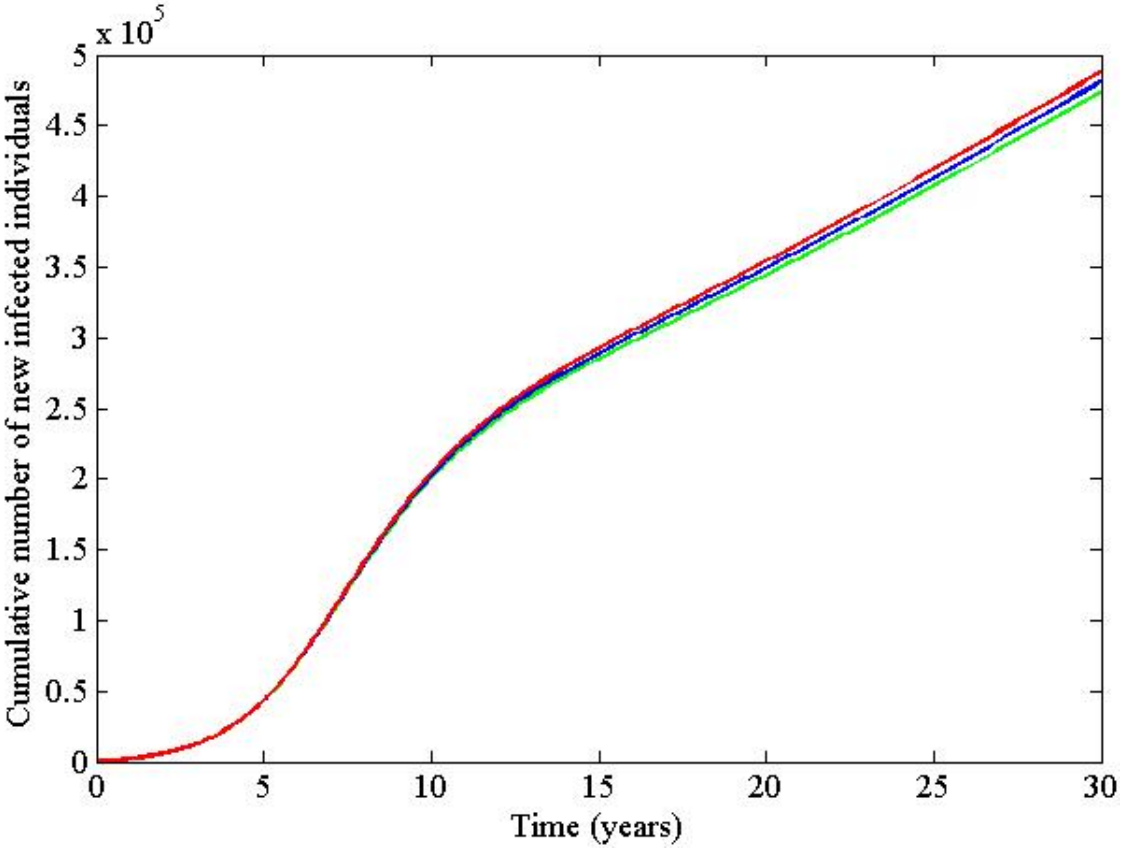

Figure 4.10: Simulations of the treatment model (4.1), showing the cumulative number of new infected individuals as a function of time, for various values of the re-infection parameter (ψ): green curve ($\psi = 0.0$), blue curve ($\psi = 0.5$) and red curve ($\psi = 1.0$). Parameter values used are as given in Table 4.2.

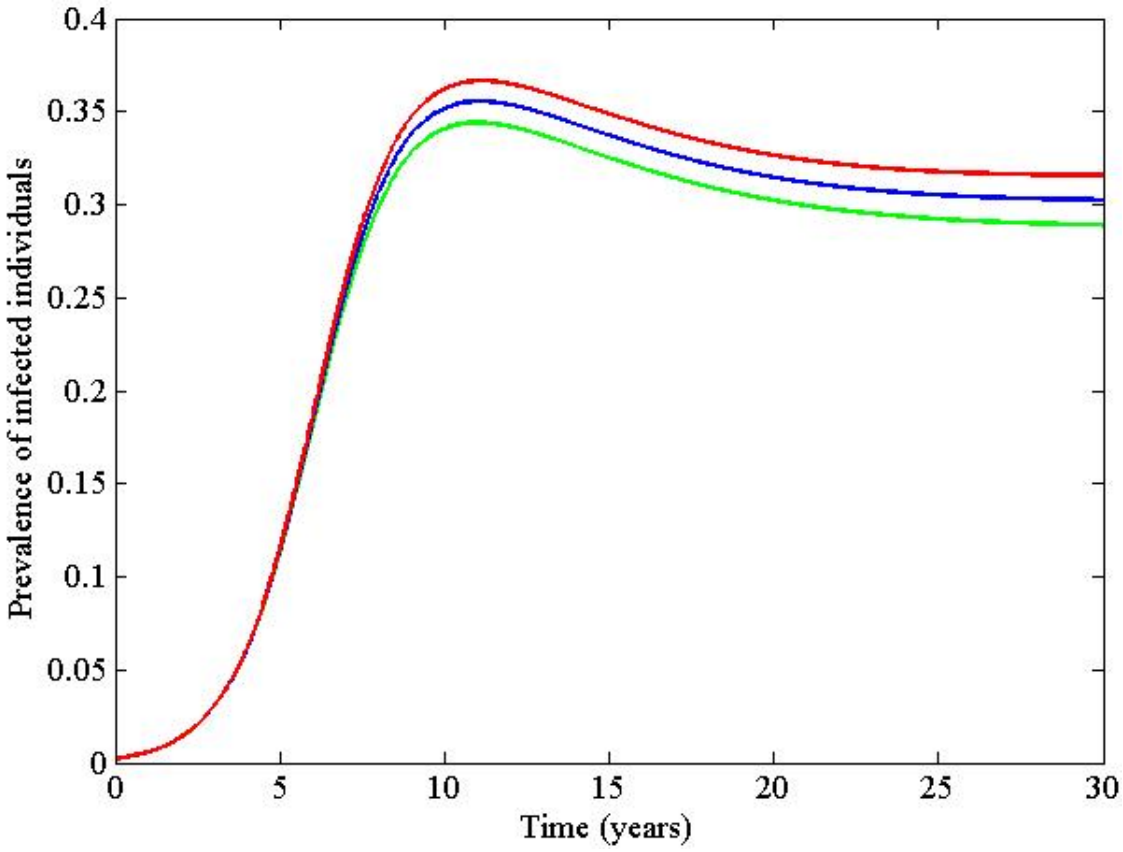

Figure 4.11: Simulations of the treatment model (4.1), showing the prevalence of total infected individuals as a function of time, for various values of the re-infection parameter (ψ): green curve ($\psi = 0.0$), blue curve ($\psi = 0.5$) and red curve ($\psi = 1.0$). Parameter values used are as given in Table 4.2.

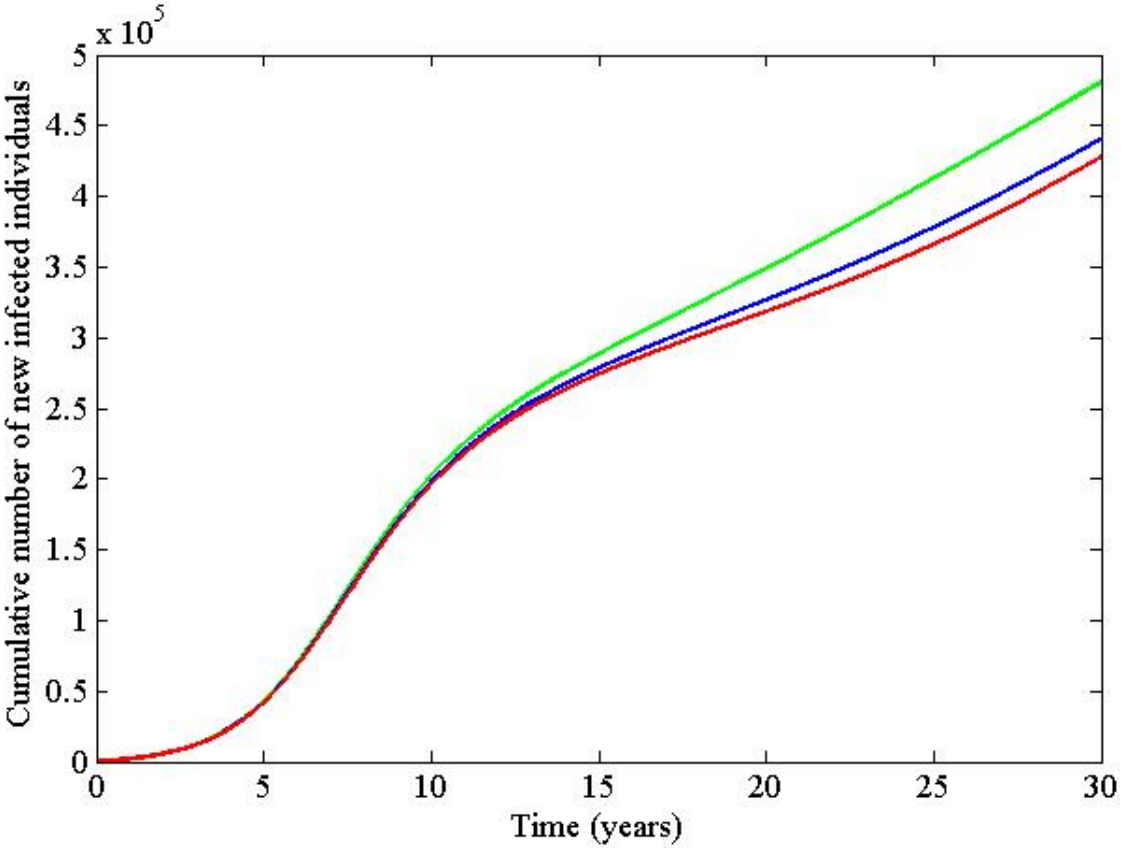

Figure 4.12: Simulations of the treatment model (4.1), showing the cumulative number of new infected individuals as a function of time, for various values of the treatment rate of chronically-infected individuals (τ): green curve ($\tau = 0.04$), blue curve ($\tau = 0.4$) and red curve ($\tau = 0.7$). Parameter values used are as given in Table 4.2.

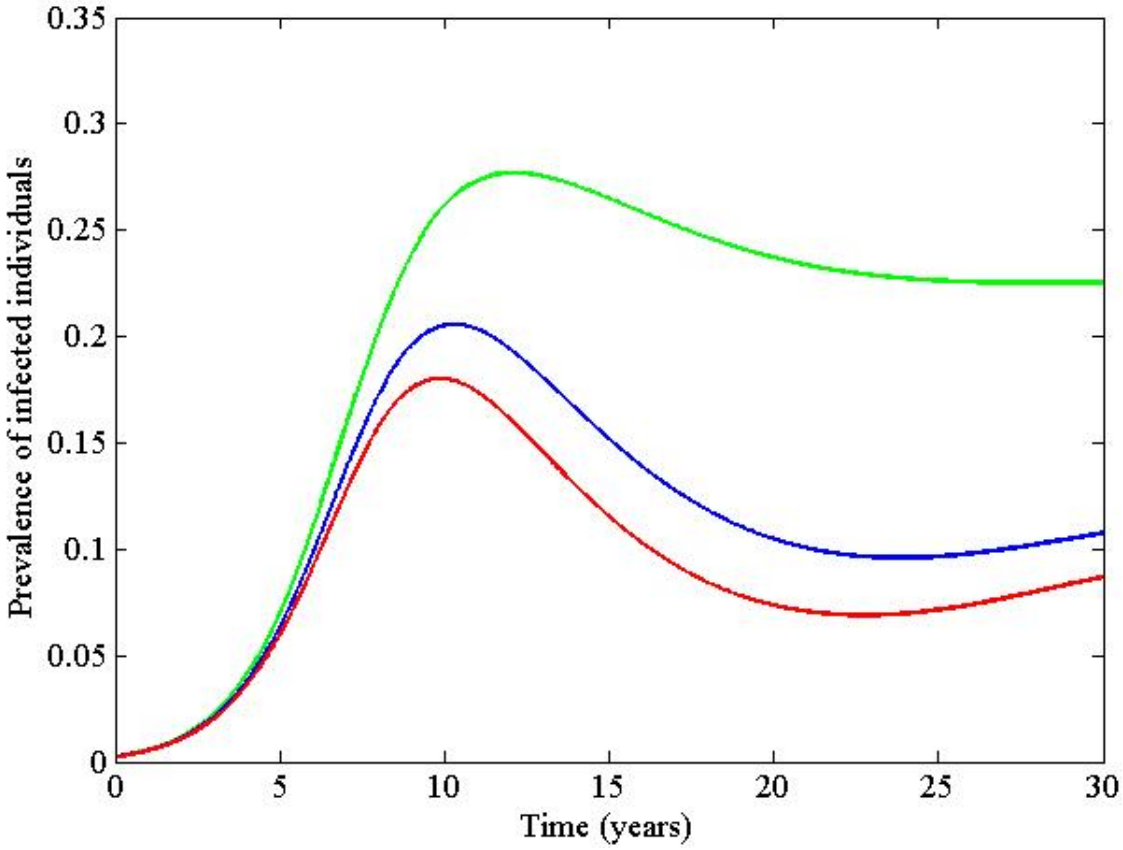

Figure 4.13: Simulations of the treatment model (4.1), showing the the prevalence of HCV as a function of time, for various values of the treatment rate of chronically-infected individuals (τ): green curve ($\tau = 0.04$), blue curve ($\tau = 0.4$) and red curve ($\tau = 0.7$). Parameter values used are as given in Table 4.2.

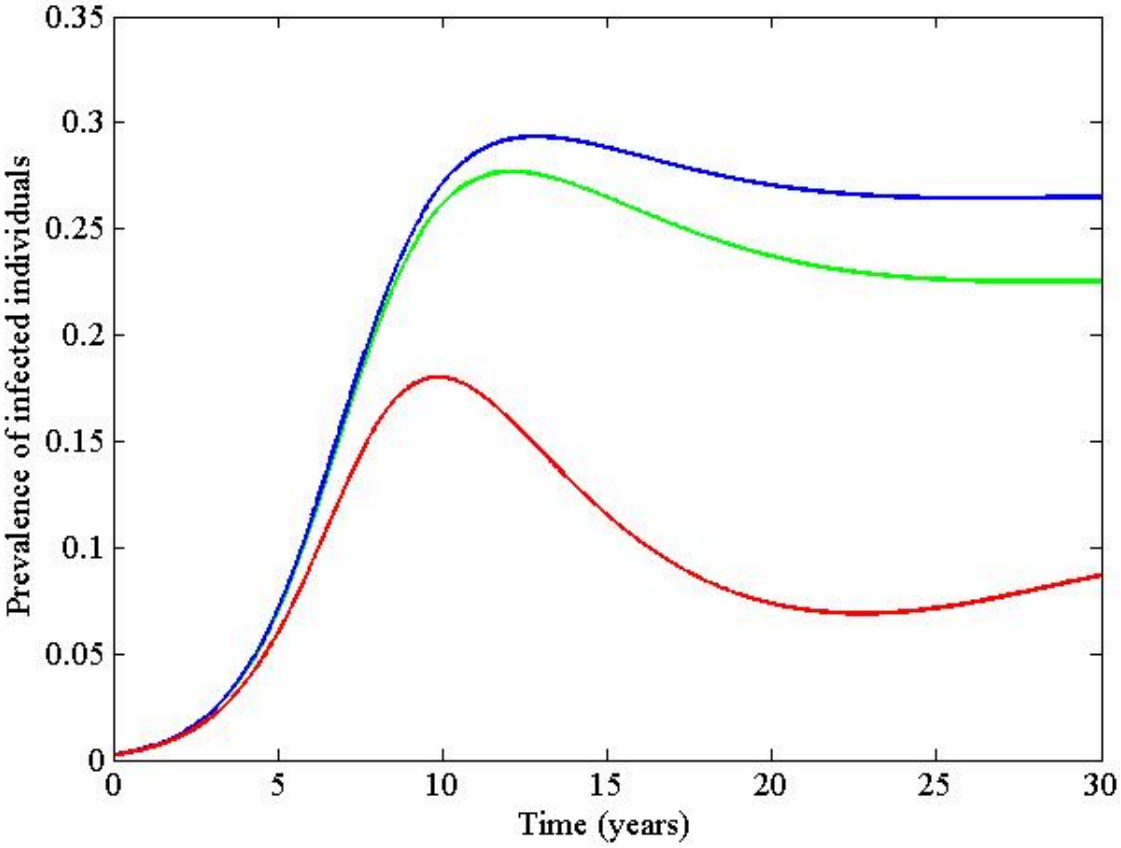

Figure 4.14: Simulations of the model (4.1), showing the prevalence of HCV as a function of time, in presence and absence of anti-HCV treatment: green curve shows the prevalence of HCV without treatment ($\tau = \phi = \zeta = \rho = \theta = \chi_T = \chi_Q = 0$), blue curve exhibit the prevalence where only 4% of chronically-infected IDUs are treated ($\tau = 0.04$) and red curve shows the prevalence of HCV for the case where 70% of chronically-infected IDUs are treated ($\tau = 0.7$). Other parameter values used are as given in Table 4.2.

Appendix A

Proof of Theorem 3.4

Proof. It is convenient to let

$$S = x_1,\ I = x_2,\ P = x_3,\ R = x_4,\ V = x_5,\ W = x_6,$$

so that the treatment-free model (3.2) can be re-written as:

$$\begin{aligned}
\frac{dx_1}{dt} =& f_1 = \ \Lambda - \lambda_{wt} x_1 - \mu x_1 + \gamma x_4, \\
\frac{dx_2}{dt} =& f_2 = \ \lambda_{wt} x_1 - (\mu + \sigma + \varepsilon)\, x_2, \\
\frac{dx_3}{dt} =& f_3 = \ \varepsilon x_2 - (\mu + \delta)\, x_3, \\
\frac{dx_4}{dt} =& f_4 = \ \sigma x_2 + \delta x_3 + \alpha\sigma x_5 + \eta\delta x_6 - \psi\lambda_{wt} x_4 - (\mu + \gamma)\, x_4, \\
\frac{dx_5}{dt} =& f_5 = \ \psi\lambda x_4 - (\mu + \alpha\sigma + \kappa\varepsilon)\, x_5, \\
\frac{dx_6}{dt} =& f_6 = \ \kappa\varepsilon x_5 - (\mu + \eta\delta)\, x_6,
\end{aligned} \tag{A.1}$$

where,

$$\lambda_{wt} = \frac{\beta(x_2 + \pi x_3 + \upsilon x_5 + \pi\omega x_6)}{\sum_{i=1}^{6} x_i},$$

and $\mathbf{f} = [f_1, \cdots, f_6]^T$ represents the vector field of the model (3.2). Evaluating the Jacobian of the system (A.1) at the DFE ($\mathcal{E}_0^{wt}$) gives:

$$J(\mathcal{E}_0^{wt}) = \begin{pmatrix} -\mu & -\beta & -\beta\pi & \gamma & -\beta\upsilon & -\beta\omega\pi \\ 0 & \beta - G_1 & \beta\pi & 0 & \beta\upsilon & \beta\omega\pi \\ 0 & \varepsilon & -G_2 & 0 & 0 & 0 \\ 0 & \sigma & \delta & -\mu - \gamma & \alpha\sigma & \eta\delta \\ 0 & 0 & 0 & 0 & -G_3 & 0 \\ 0 & 0 & 0 & 0 & \kappa\varepsilon & -G_4 \end{pmatrix}.$$

Consider the case of the model (A.1) with $\mathcal{R}_0 = 1$. Suppose, also, that β is chosen as the bifurcation parameter. Solving for β from $\mathcal{R}_0 = 1$ gives (where G_1 and G_2 are as defined in Subsection 3.3.1)

$$\beta^* = \frac{G_1 G_2}{\pi\varepsilon + G_2}. \tag{A.2}$$

The transformed system (A.1), with $\beta = \beta^*$, has a simple eigenvalue with zero real part (and all other eigenvalues have negative real parts). Hence, the centre manifold theory [6] can be used to analysed the dynamics of (A.1) near β^*. To apply the theory, the following computations are necessary.

Eigenvectors of $J(\mathcal{E}_0^{wt})|_{\beta=\beta^*}$:

Let $J(\mathcal{E}_0^{wt})|_{\beta=\beta^*} = J_{\beta^*}$. In order to apply the method described in [6], the following computations are necessary. The matrix J_{β^*} has a left eigenvector (associated with the zero eigenvalue) given by,

$$\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6],$$

where,

$$\begin{aligned} v_1 = 0,\ v_2 = v_2 > 0, \quad v_3 = \frac{\beta^* \pi}{G_2} v_2, \quad v_4 = 0, \\ v_5 = \frac{\beta^*(\pi\kappa\varepsilon\omega + \upsilon G_4}{G_3 G_4} v_2, \qquad v_6 = \frac{\beta^* \pi \omega}{G_4} v_2. \end{aligned}$$

Furthermore, the matrix J_{β^*} has a right eigenvector (associated with the zero eigenvalue) given by,

$$\mathbf{w} = [w_1, w_2, w_3, w_4, w_5, w_6]^T,$$

where,

$$\begin{aligned} w_1 = -\frac{\beta^*(\mu+\gamma)(\pi\varepsilon + G_2) - \gamma(\sigma G_2 + \delta\varepsilon)}{\mu G_2(\mu+\gamma)} w_2, \quad w_2 = w_2 > 0, \\ w_3 = \frac{\varepsilon}{G_2} w_2, \quad w_4 = \frac{\sigma G_2 + \delta\varepsilon}{G_2(\mu+\gamma)} w_2, \quad w_5 = 0, \quad w_6 = 0. \end{aligned}$$

Computation of bifurcation coefficients, a and b:

It follows from Theorem 4.1 of [6] that, for the system (A.1), the associated non-zero partial derivatives of (A.1) (at the DFE, $\mathcal{E}_0^{wt}$) are given by

$$\begin{aligned} \frac{\partial^2 f_1}{\partial x_2 \partial x_2} = \frac{2\beta^*\mu}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_3 \partial x_2} = \frac{\beta^*\mu}{\Lambda} + \frac{\beta^*\pi\mu}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_4 \partial x_2} = \frac{\beta^*\mu}{\Lambda}, \\ \frac{\partial^2 f_1}{\partial x_5 \partial x_2} = \frac{\beta^*\mu}{\Lambda} + \frac{\beta^*\upsilon\mu}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_6 \partial x_2} = \frac{\beta^*\mu}{\Lambda} + \frac{\beta^*\omega\pi\mu}{\Lambda}, \end{aligned}$$

$$\frac{\partial^2 f_1}{\partial x_2 \partial x_3} = \frac{\beta^* \pi \mu}{\Lambda} + \frac{\beta^* \mu}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_3 \partial x_3} = \frac{2\beta^* \pi \mu}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_4 \partial x_3} = \frac{\beta^* \pi \mu}{\Lambda},$$
$$\frac{\partial^2 f_1}{\partial x_5 \partial x_3} = \frac{\beta^* \pi \mu}{\Lambda} + \frac{\beta^* \mu \upsilon}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_6 \partial x_3} = \frac{\beta^* \pi \mu}{\Lambda} - \frac{\beta^* \pi \mu \omega}{\Lambda},$$
$$\frac{\partial^2 f_1}{\partial x_2 \partial x_4} = \frac{\beta^* \mu}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_3 \partial x_4} = \frac{\beta^* \pi \mu}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_5 \partial x_4} = \frac{\beta^* \mu \upsilon}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_6 \partial x_4} = \frac{\beta^* \pi \mu \omega}{\Lambda},$$
$$\frac{\partial^2 f_1}{\partial x_2 \partial x_5} = \frac{\beta^* \upsilon \mu}{\Lambda} + \frac{\beta^* \mu}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_3 \partial x_5} = \frac{\beta^* \upsilon \mu}{\Lambda} + \frac{\beta^* \pi \mu}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_5 \partial x_5} = \frac{\beta^* \upsilon \mu}{\Lambda},$$
$$\frac{\partial^2 f_1}{\partial x_5 \partial x_5} = \frac{2\beta^* \upsilon \mu}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_6 \partial x_5} = \frac{\beta^* \upsilon \mu}{\Lambda} + \frac{\beta^* \pi \mu \omega}{\Lambda},$$
$$\frac{\partial^2 f_1}{\partial x_2 \partial x_6} = \frac{\beta^* \omega \pi \mu}{\Lambda} + \frac{\beta^* \mu}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_3 \partial x_6} = \frac{\beta^* \omega \pi \mu}{\Lambda} + \frac{\beta^* \pi \mu}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_4 \partial x_6} = \frac{\beta^* \omega \pi \mu}{\Lambda},$$
$$\frac{\partial^2 f_1}{\partial x_5 \partial x_6} = \frac{\beta^* \omega \pi \mu}{\Lambda} + \frac{\beta^* \upsilon \mu}{\Lambda}, \quad \frac{\partial^2 f_1}{\partial x_6 \partial x_6} = \frac{2\beta^* \omega \pi \mu}{\Lambda},$$
$$\frac{\partial^2 f_2}{\partial x_2 \partial x_2} = -\frac{2\beta^* \mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_3 \partial x_2} = -\frac{\beta^* \mu}{\Lambda} - \frac{\beta^* \pi \mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_4 \partial x_2} = -\frac{\beta^* \mu}{\Lambda},$$
$$\frac{\partial^2 f_2}{\partial x_5 \partial x_2} = -\frac{\beta^* \mu}{\Lambda} - \frac{\beta^* \mu \upsilon}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_6 \partial x_2} = -\frac{\beta^* \mu}{\Lambda} - \frac{\beta^* \pi \mu \omega}{\Lambda},$$
$$\frac{\partial^2 f_2}{\partial x_2 \partial x_3} = -\frac{\beta^* \pi \mu}{\Lambda} - \frac{\beta^* \mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_3 \partial x_3} = -\frac{2\beta^* \pi \mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_4 \partial x_3} = -\frac{\beta^* \pi \mu}{\Lambda},$$
$$\frac{\partial^2 f_2}{\partial x_5 \partial x_3} = -\frac{\beta^* \pi \mu}{\Lambda} - \frac{\beta^* \mu \upsilon}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_6 \partial x_3} = -\frac{\beta^* \pi \mu}{\Lambda} - \frac{\beta^* \pi \mu \omega}{\Lambda},$$
$$\frac{\partial^2 f_2}{\partial x_2 \partial x_4} = -\frac{\beta^* \mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_3 \partial x_4} = -\frac{\beta^* \pi \mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_5 \partial x_4} = -\frac{\beta^* \mu \upsilon}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_6 \partial x_4} = -\frac{\beta^* \pi \mu \omega}{\Lambda},$$
$$\frac{\partial^2 f_2}{\partial x_2 \partial x_5} = -\frac{\beta^* \upsilon \mu}{\Lambda} - \frac{\beta^* \mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_3 \partial x_5} = -\frac{\beta^* \upsilon \mu}{\Lambda} - \frac{\beta^* \pi \mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_4 \partial x_5} = -\frac{\beta^* \upsilon \mu}{\Lambda},$$
$$\frac{\partial^2 f_2}{\partial x_5 \partial x_5} = -\frac{2\beta^* \upsilon \mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_6 \partial x_5} = -\frac{\beta^* \upsilon \mu}{\Lambda} - \frac{\beta^* \pi \mu \omega}{\Lambda},$$
$$\frac{\partial^2 f_2}{\partial x_2 \partial x_6} = -\frac{\beta^* \omega \pi \mu}{\Lambda} - \frac{\beta^* \mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_3 \partial x_6} = -\frac{\beta^* \omega \pi \mu}{\Lambda} - \frac{\beta^* \pi \mu}{\Lambda},$$
$$\frac{\partial^2 f_2}{\partial x_4 \partial x_6} = -\frac{\beta^* \omega \pi \mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_5 \partial x_6} = -\frac{\beta^* \omega \pi \mu}{\Lambda} - \frac{\beta^* \upsilon \mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_6 \partial x_6} = -\frac{2\beta^* \omega \pi \mu}{\Lambda},$$
$$\frac{\partial^2 f_4}{\partial x_4 \partial x_2} = -\frac{\beta^* \psi \mu}{\Lambda}, \quad \frac{\partial^2 f_4}{\partial x_4 \partial x_3} = -\frac{\beta^* \psi \pi \mu}{\Lambda}, \quad \frac{\partial^2 f_4}{\partial x_2 \partial x_4} = -\frac{\beta^* \psi \mu}{\Lambda},$$
$$\frac{\partial^2 f_4}{\partial x_3 \partial x_4} = -\frac{\beta^* \psi \pi \mu}{\Lambda}, \quad \frac{\partial^2 f_4}{\partial x_5 \partial x_4} = -\frac{\beta^* \psi \mu \upsilon}{\Lambda}, \quad \frac{\partial^2 f_4}{\partial x_6 \partial x_4} = -\frac{\beta^* \psi \pi \mu \omega}{\Lambda},$$
$$\frac{\partial^2 f_4}{\partial x_4 \partial x_5} = -\frac{\beta^* \psi \upsilon \mu}{\Lambda}, \quad \frac{\partial^2 f_4}{\partial x_4 \partial x_6} = -\frac{\beta^* \psi \omega \pi \mu}{\Lambda}, \quad \frac{\partial^2 f_5}{\partial x_4 \partial x_2} = \frac{\beta^* \psi \mu}{\Lambda}, \quad \frac{\partial^2 f_5}{\partial x_4 \partial x_3} = \frac{\beta^* \psi \pi \mu}{\Lambda},$$

$$\frac{\partial^2 f_5}{\partial x_2 \partial x_4} = \frac{\beta^* \psi \mu}{\Lambda}, \quad \frac{\partial^2 f_5}{\partial x_3 \partial x_4} = \frac{\beta^* \psi \pi \mu}{\Lambda}, \quad \frac{\partial^2 f_5}{\partial x_5 \partial x_4} = \frac{\beta^* \psi \mu \upsilon}{\Lambda}, \quad \frac{\partial^2 f_5}{\partial x_6 \partial x_4} = \frac{\beta^* \psi \pi \mu \omega}{\Lambda},$$
$$\frac{\partial^2 f_5}{\partial x_4 \partial x_5} = \frac{\beta^* \psi \upsilon \mu}{\Lambda}, \quad \frac{\partial^2 f_5}{\partial x_4 \partial x_6} = \frac{\beta^* \psi \omega \pi \mu}{\Lambda}.$$

It can be shown, by computing the non-zero partial derivatives of the right-hand side functions in (A.1), that the associated backward bifurcation coefficients, a and b, are given, respectively, by (see Theorem 4.1 in [6]):

$$a = \sum_{k,i,j=1}^{6} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(\mathcal{E}_0^{wt}, \beta^*) = \frac{-2\mu v_2 w_2^2 \beta^*}{\Lambda G_3 G_4 G_2^2 (\mu + \gamma)} \left[S_1 + (\varepsilon\delta + G_2\sigma) S_2 \right], \quad \text{(A.3)}$$

where,

$$S_1 = G_3 G_4 (\mu + \gamma)(G_2 + \varepsilon) > 0, \quad S_2 = G_3 G_4 - \frac{G_1 G_2 \psi (\pi \varepsilon \kappa \omega + G_4 \upsilon)}{G_2 + \pi\varepsilon}, \quad \text{(A.4)}$$

and,

$$b = \sum_{k,i=1}^{6} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta}(\mathcal{E}_0^{wt}, \beta^*) = \frac{(G_2 + \pi\varepsilon)}{G_2} v_2 w_2 > 0.$$

It follows from (A.3) that the bifurcation coefficient, a, is positive whenever

$$S_2 > 0, \quad \text{(A.5)}$$

Thus, it follows, from Theorem 4.1 of [6], that the treatment-free model (3.2) (or, equivalently, (A.1)) undergoes backward bifurcation at $\mathcal{R}_0 = 1$ whenever Inequality (A.5) holds. □

Appendix B

Model Formulation of the Treatment Model (4.1)

The population of susceptible individuals (S) is increased by the recruitment of new IDUs into the IDU population (at a rate Λ). It is further increased by the loss of infection-acquired immunity of recovered individuals (at a *per capita* rate γ). It is decreased by infection, following effective contacts with infected individuals, at a rate λ, given by

$$\lambda = \frac{\beta(I + \pi P + \upsilon V + \omega\pi W + \pi\chi_T T + \pi\chi_Q Q)}{N}, \tag{B.1}$$

In (B.1), β is the effective contact rate, π, υ, ω, χ_T and χ_Q are modification parameters accounting for the relative infectivity of chronically-infected, acutely-re-infected, chronically-re-infected, treated infected and treated re-infected individuals, in comparison to acutely infected individuals, respectively. This population is further decreased by natural death (at a rate μ; this rate is assumed, for mathematical convenience, to be the same for all of the epidemiological compartments). Thus,

$$\frac{dS}{dt} = \Lambda + \gamma R - \lambda S - \mu S.$$

The population of acutely-infected individuals (I) is increased by the infection of susceptible individuals (at the rate λ). It is decreased by recovery (at a rate σ), progression to chronic stage (at a rate ε) or natural death. Thus,

$$\frac{dI}{dt} = \lambda S - (\sigma + \varepsilon + \mu)I.$$

The population of chronically-infected individuals (P) is generated by progression of acutely-infected individuals to the chronically-infection (at the rate ε). It is also increased by treatment failure of chronically-infected individuals (at a rate ρ). This population is decreased by treatment (at a rate τ), recovery (at a rate δ) or natural death. Hence,

$$\frac{dP}{dt} = \varepsilon I + \rho T - (\delta + \tau + \mu)P.$$

The population of recovered individuals (R) is generated by the recovery of acutely-infected individuals (at the rate σ), chronically-infected individuals (at the rate δ), acutely-re-infected individuals (at a rate $\alpha\sigma$, where $\alpha > 1$ is the modification parameter accounting for the assumption that acutely-re-infected individuals recover at a faster rate in comparison to acutely-infected individuals), and chronically-re-infected individuals (at a rate $\eta\delta$ where, $\eta > 1$ is the modification parameter accounting for the assumption that chronically-re-infected individuals recover at a faster rate in comparison to chronically-infected individuals) [14]. It is also increased by the successfully treatment of chronically-infected and chronically-re-infected individuals (at a rate θ). This population is decreased by infection (at a reduced rate $\psi\lambda$, where $0 < \psi < 1$ accounting for the assumption that recovered individuals acquire HCV infection at a rate lower than susceptible individuals). It is further decreased by the loss of infection-acquired immunity (at the rate γ) and natural death. Thus,

$$\frac{dR}{dt} = \sigma I + \delta P + \alpha\sigma V + \eta\delta W + \theta T + \theta Q - \psi\lambda R - (\gamma + \mu)R.$$

The population of acutely re-infected individuals (V) is increased by the re-infection of recovered individuals (at the rate $\psi\lambda$). It is decreased by progression to the chronic re-infection stage (at a rate $\kappa\varepsilon$, where $0 < \kappa < 1$ is the modification parameter accounting for the assumption that acutely-re-infected individuals progress to the chronically-re-infection stage (W) at a slower rate in comparison to acutely-infected individuals), recovery (at the rate $\alpha\sigma$) or natural death. Hence,

$$\frac{dV}{dt} = \psi\lambda R - (\alpha\sigma + \kappa\varepsilon + \mu)V.$$

The population of chronically-reinfected individuals (W) is increased by the progression of acutely-reinfected individuals (at the rate $\kappa\varepsilon$) and by the failure of treatment in chronically-re-infected individuals (at a rate ζ). It diminishes by recovery (at the rate $\eta\delta$), treatment of chronically-re-infected individuals (at a rate ϕ) or natural death. Thus,

$$\frac{dW}{dt} = \kappa\varepsilon V + \zeta Q - (\eta\delta + \phi + \mu)W.$$

The population of chronically-infected treated individuals (T) is increased by the treatment of the chronically-infected individuals (at the rate τ). It is decreased by treatment failure or successful treatment of the chronically-infected individuals (at the rates ρ and θ, respectively) or by natural death. Thus,

$$\frac{dT}{dt} = \tau P - (\rho + \theta + \mu)T.$$

Similarly, the population of chronically-re-infected individuals (Q) is generated by the successful treatment of chronically-re-infected individuals (at the rate ϕ). It

diminishes by the treatment failure or successful treatment of the chronically-re-infected individuals (at the rates ζ or θ, respectively). It is further decreased by the natural death. Thus,

$$\frac{dQ}{dt} = \phi W - (\zeta + \theta + \mu)Q.$$

Appendix C

Proof of Theorem 4.5

Proof. It is convenient to let

$$S = x_1,\ I = x_2,\ P = x_3,\ R = x_4,\ V = x_5,\ W = x_6,\ T = x_7,\ Q = x_8,$$

so that the treatment model (4.1) can be re-written as:

$$\begin{aligned}
\frac{dx_1}{dt} =& f_1 = \ \Lambda - \lambda x_1 - \mu x_1 + \gamma x_4, \\
\frac{dx_2}{dt} =& f_2 = \ \lambda x_1 - (\mu + \sigma + \varepsilon)\, x_2, \\
\frac{dx_3}{dt} =& f_3 = \ \varepsilon x_2 + \rho x_7 - (\mu + \delta + \tau)\, x_3, \\
\frac{dx_4}{dt} =& f_4 = \ \sigma x_2 + \delta x_3 + \alpha\sigma x_5 + \eta\delta x_6 + \theta x_7 + \theta x_8 - \psi\lambda x_4 - (\mu + \gamma)\, x_4, \\
\frac{dx_5}{dt} =& f_5 = \ \psi\lambda x_4 - (\mu + \alpha\sigma + \kappa\varepsilon)\, x_5, \\
\frac{dx_6}{dt} =& f_6 = \ \kappa\varepsilon x_5 + \zeta x_8 - (\mu + \eta\delta + \phi)\, x_6, \\
\frac{dx_7}{dt} =& f_7 = \ \tau x_3 - (\mu + \rho + \theta)\, x_7, \\
\frac{dx_8}{dt} =& f_8 = \ \phi x_6 - (\mu + \zeta + \theta)\, x_8,
\end{aligned} \tag{C.1}$$

where,

$$\lambda = \frac{\beta(x_2 + \pi x_3 + \upsilon x_5 + \pi\omega x_6 + \pi\chi_T x_7 + \pi\chi_Q x_8)}{\sum_{i=1}^{8} x_i},$$

and $f = [f_1, \cdots, f_8]^T$ represents the vector field of the model (4.1). Evaluating the Jacobian of the system (C.1) at the DFE ($\mathcal{E}_0^T$) gives:

$$J(\mathcal{E}_0^T) = \begin{pmatrix} -\mu & -\beta & -\beta\pi & \gamma & -\beta\upsilon & -\beta\omega\pi & -\beta\chi_T\pi & -\beta\chi_Q\pi \\ 0 & \beta - K_1 & \beta\pi & 0 & \beta\upsilon & \beta\omega\pi & \beta\chi_T\pi & \beta\chi_Q\pi \\ 0 & \varepsilon & -K_2 & 0 & 0 & 0 & \rho & 0 \\ 0 & \sigma & \delta & -\mu - \gamma & \alpha\sigma & \eta\delta & \theta & \theta \\ 0 & 0 & 0 & 0 & -K_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \kappa\varepsilon & -K_4 & 0 & \zeta \\ 0 & 0 & \tau & 0 & 0 & 0 & -K_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & \phi & 0 & -K_6 \end{pmatrix}.$$

Consider the case of the model (C.1) with $\mathcal{R}_T = 1$. Suppose, also, that β is chosen as the bifurcation parameter. Solving for β from $\mathcal{R}_T = 1$ gives

$$\beta^* = \frac{K_1(K_2K_5 - \rho\tau)}{K_2K_5 - \rho\tau + \pi\varepsilon K_5 + \pi\chi_T\tau\varepsilon}. \tag{C.2}$$

The transformed system (C.1), with $\beta = \beta^*$, has a simple eigenvalue with zero real part (and all other eigenvalues have negative real parts). Hence, the centre manifold theory [6] can be used to analysed the dynamics of (C.1) near β^*.

As in Appendix A, let $J(\mathcal{E}_0^T)|_{\beta=\beta^*} = J_{\beta^*}$. Define the left and right eigenvectors

of J_{β^*}, respectively, by

$$\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8], \text{ and } \mathbf{w} = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8]^T,$$

where,

$$\begin{aligned}
&v_1 = 0,\ v_2 = v_2 > 0,\ v_3 = \frac{\beta^*(\pi K_5 + \pi\chi_T\tau)}{(K_2K_5 - \rho\tau)}v_2,\ v_4 = 0,\\
&v_5 = \frac{\beta^*(K_6\pi\kappa\varepsilon\omega + \upsilon(K_4K_6 - \zeta\phi) + \pi\phi\kappa\varepsilon\chi_Q)}{K_3(K_4K_6 - \zeta\phi)}v_2,\\
&v_6 = \frac{\beta^*(\pi\omega K_6 + \pi\chi_Q\phi)}{(K_4K_6 - \zeta\phi)}v_2,\ v_7 = \frac{\beta^*(\pi\chi_T K_2 + \pi\rho)}{(K_2K_5 - \rho\tau)}v_2,\ v_8 = \frac{\beta^*(\pi\chi_Q K_4 + \pi\zeta\omega)}{K_4K_6 - \zeta\phi}v_2.
\end{aligned}$$

and,

$$\begin{aligned}
&w_1 = -\frac{\beta^*(\mu+\gamma)(K_2K_5 - \rho\tau + \pi\varepsilon K_5 + \pi\chi_T\tau\varepsilon) - \gamma(\sigma(K_2K_5 - \rho\tau) + \delta\varepsilon K_5 + \tau\varepsilon\theta)}{\mu(\mu+\gamma)(K_2K_5 - \rho\tau)}w_2,\\
&w_2 = w_2 > 0, \quad w_3 = \frac{\varepsilon K_5}{(K_2K_5 - \rho\tau)}w_2, \quad w_4 = \frac{\sigma(K_2K_5 - \rho\tau) + \delta\varepsilon K_5 + \tau\varepsilon\theta}{(K_2K_5 - \rho\tau)(\mu+\gamma)}w_2,\\
&w_5 = 0, \quad w_6 = 0, \quad w_7 = \frac{\tau\varepsilon}{(K_2K_5 - \rho\tau)}w_2, \quad w_8 = 0.
\end{aligned}$$

It can be shown (by computing the associated non-zero partial derivatives of (C.1) at the DFE ($\mathcal{E}_0^T$)) that the associated backward bifurcation coefficients, a and b, are given, respectively, by:

$$
\begin{aligned}
a &= \sum_{k,i,j=1}^{8} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(\mathcal{E}_0^T, \beta^*), \\
&= \frac{-2\mu v_2 w_2^2 K_1}{\Lambda K_3 (K_4 K_6 - \zeta\phi)(K_2 K_5 - \rho\tau)(\mu + \gamma)} \left(C_1 + C_2 F - \beta^{**} \psi F C_3\right), \qquad \text{(C.3)}
\end{aligned}
$$

where,

$$
\begin{aligned}
C_1 &= K_3(K_4 K_6 - \zeta\phi)(\mu + \gamma)(K_2 K_5 - \rho\tau + \varepsilon K_5 + \tau\varepsilon), \\
C_2 &= K_3(K_4 K_6 - \zeta\phi), \qquad \text{(C.4)} \\
C_3 &= (K_4 K_6 - \zeta\phi)\upsilon + K_6 \varepsilon\kappa\pi\omega + \phi\varepsilon\kappa\pi\chi_Q, \\
F &= \sigma(K_2 K_5 - \rho\tau) + \delta K_5 \varepsilon + \tau\varepsilon\theta,
\end{aligned}
$$

and (noting that $K_2 K_5 - \rho\tau > 0$ and $K_4 K_6 - \zeta\phi > 0$),

$$
b = \sum_{k,i=1}^{8} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta}(\mathcal{E}_0^T, \beta^*) = \frac{(K_2 K_5 - \rho\tau + \pi\varepsilon K_5 + \pi\chi_T \tau\varepsilon)}{(K_2 K_5 - \rho\tau)} v_2 w_2 > 0.
$$

It follows from (C.3), with (C.4), that the bifurcation coefficient, a, is positive whenever

$$
J_2 > J_1, \qquad \text{(C.5)}
$$

where,

$$J_1 = K_3(K_4K_6 - \zeta\phi)F + K_3(\mu + \gamma)(K_4K_6 - \zeta\phi)(K_2K_5 - \rho\tau + \varepsilon K_5 + \tau\varepsilon),$$

$$J_2 = \beta^*\psi[(K_4K_6 - \zeta\phi)\upsilon + K_6\varepsilon\kappa\pi\omega + \phi\varepsilon\kappa\pi\chi_Q]F.$$

Thus, it follows, from Theorem 4.1 of [6], that the treatment model (4.1) (or, equivalently, (C.1)) undergoes backward bifurcation at $\mathcal{R}_T = 1$ whenever Inequality (C.5) holds. □

Appendix D

Proof of Theorem 4.6

Proof. It should, first of all, be mentioned that the system (D.1) satisfies the Type K condition [44] (hence, Comparison Theorem can be used [32]). Furthermore, consider the following reduced model (D.1) of the treatment model (4.1) for the special case with $\psi = 0$, given by:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \lambda S - \mu S + \gamma R, \\
\frac{dI}{dt} &= \lambda S - (\mu + \sigma + \varepsilon)\, I, \\
\frac{dP}{dt} &= \varepsilon I + \rho T - (\mu + \delta + \tau)\, P, \\
\frac{dR}{dt} &= \sigma I + \delta P + \alpha\sigma V + \eta\delta W + \theta T + \theta Q - (\mu + \gamma)\, R, \\
\frac{dV}{dt} &= -(\mu + \alpha\sigma + \kappa\varepsilon)\, V, \\
\frac{dW}{dt} &= \kappa\varepsilon V + \zeta Q - (\mu + \eta\delta + \phi)\, W, \\
\frac{dT}{dt} &= \tau P - (\mu + \rho + \theta)\, T, \\
\frac{dQ}{dt} &= \phi W - (\mu + \zeta + \theta)\, Q.
\end{aligned} \tag{D.1}$$

It follows from (D.1) that $V(t) \to 0$ as $t \to \infty$. Hence, the equation for $\frac{dV}{dt}$ can be temporal removed from (D.1). The infected components of the model (D.1) (with the equation for $\frac{dV}{dt}$ removed) can be re-written as:

$$\frac{d}{dt}\,\mathbf{x} = (\mathcal{F}_1 - \mathcal{H}_1)\mathbf{x} - J\mathbf{x}, \tag{D.2}$$

where,

$$\mathbf{x} = [I(t), P(t), W(t), T(t), Q(t)]^T,$$

$$\mathcal{F}_1 = \begin{pmatrix} \beta & \pi\beta & \omega\pi\beta & \chi_T\pi\beta & \chi_Q\pi\beta \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad \mathcal{H}_1 = \begin{pmatrix} K_1 & 0 & 0 & 0 & 0 \\ -\varepsilon & K_2 & 0 & -\rho & 0 \\ 0 & 0 & K_4 & 0 & -\zeta \\ 0 & -\tau & 0 & K_5 & 0 \\ 0 & 0 & -\phi & 0 & K_6 \end{pmatrix},$$

(with $K_1,\ K_2,\ K_4,\ K_5$ and K_6 as defined in Section 4.1) and,

$$J = \left[1 - \frac{\mu S(t)}{\Lambda}\right] \begin{pmatrix} \beta & \pi\beta & \omega\pi\beta & \chi_T\pi\beta & \chi_Q\pi\beta \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

Thus, J is a non-negative matrix since

$$S(t) \leq N(t) \leq \frac{\Lambda}{\mu} \text{ in } \mathcal{D}_T.$$

Hence, it follows from (D.2) that

$$\frac{d}{dt}\,\mathbf{x} \leq (\mathcal{F}_1 - \mathcal{H}_1)\mathbf{x}. \tag{D.3}$$

Since $\mathcal{R}_T|_{\psi=0} = \rho(\mathcal{F}_1\mathcal{H}_1^{-1}) = \mathcal{R}_T \leq 1$ (or, equivalently, the eigenvalues of the matrix $\mathcal{F}_1 - \mathcal{H}_1$ all have negative real parts), it follows that the linearized differential inequality system (D.3) is stable whenever $\mathcal{R}_T < 1$. Thus, it follows, by Comparison Theorem [32], that

$$\lim_{t\to\infty}(I(t), P(t), W(t), T(t), Q(t)) \to (0, 0, 0, 0, 0).$$

Substituting $I(t) = P(t) = W(t) = T(t) = Q(t) = 0$ into the (D.1) and using the fact that $V(t) \to 0$ as $t \to \infty$ show that $S(t) \to S^*$ as $t \to \infty$ (for $\mathcal{R}_T < 1$). Therefore,

$$\lim_{t\to\infty}(S(t), I(t), P(t), V(t), W(t), T(t), Q(t)) \to (S^*, 0, 0, 0, 0, 0, 0) = \mathcal{E}_0^T|_{\psi=0}.$$

Hence, the DFE ($\mathcal{E}_0^T$) of the reduced model (D.1) is GAS in $\mathcal{D}_T$ whenever $\mathcal{R}_T < 1$. □

Appendix E

Proof of Non-existence of Backward Bifurcation in the Reduced Model (4.4)

Proof. Consider the reduced model (4.4). For this model [14], the disease-free equilibrium is

$$\bar{\mathcal{E}}_0 = (\bar{S}^*, \bar{I}^*, \bar{P}^*, \bar{R}^*, \bar{T}^*) = (\frac{\Lambda}{\mu}, 0, 0, 0, 0),$$

and,

$$\bar{\mathcal{R}}_c = \frac{\beta(\bar{K}_2\bar{K}_3 - \rho\tau + \pi\varepsilon\bar{K}_3 + \pi\chi_T\tau\varepsilon)}{\bar{K}_1(\bar{K}_2\bar{K}_3 - \rho\tau)},$$

where $\bar{K}_1 = \mu + \sigma + \varepsilon,\ \bar{K}_2 = \mu + \delta + \tau,\ \bar{K}_3 = \mu + \rho + \theta$. It can be shown, as in Appendix C, that the associated backward bifurcation coefficients, a and b, are given, respectively, by (see Theorem 4.1 in [6]):

$$\bar{a} = \frac{-2\mu\bar{v}_2\bar{w}_2^2}{\Lambda(\bar{K}_2\bar{K}_3 - \rho\tau)^2(\mu+\gamma)}\left[\bar{K}_1(\bar{K}_2\bar{K}_3 - \rho\tau)(\mu+\gamma)(\bar{K}_2\bar{K}_3 - \rho\tau + \varepsilon\bar{K}_3 + \tau\varepsilon)\right.$$
$$\left. + \bar{K}_1(\bar{K}_2\bar{K}_3 - \rho\tau)\bar{F} - \bar{\beta}^*\psi(\bar{K}_2\bar{K}_3 - \rho\tau + \pi\varepsilon\bar{K}_3 + \pi\chi_T\tau\varepsilon)\bar{F}\right], \tag{E.1}$$

where,

$$\bar{\beta}^* = \frac{\bar{K}_1(\bar{K}_2\bar{K}_3 - \rho\tau)}{\bar{K}_2\bar{K}_3 - \rho\tau + \pi\varepsilon\bar{K}_3 + \pi\chi_T\tau\varepsilon}, \qquad \bar{F} = \sigma(\bar{K}_2\bar{K}_3 - \rho\tau) + \delta\bar{K}_3\varepsilon + \tau\varepsilon\theta, \tag{E.2}$$

$$\bar{b} = \frac{\left(\bar{K}_2\bar{K}_3 - \rho\tau + \pi\varepsilon\bar{K}_3 + \pi\chi_T\tau\varepsilon\right)}{(\bar{K}_2\bar{K}_3 - \rho\tau)}\bar{v}_2\bar{w}_2 > 0, \tag{E.3}$$

where $\bar{\mathbf{v}}$ and $\bar{\mathbf{w}}$ are, respectively, the left and right eigenvectors corresponding to zero eigenvalue of the Jacobian of the system (4.4), evaluated at the associated disease-free equilibrium ($\bar{\mathcal{E}}_0$), given by:

$$\bar{J}|_{\bar{\beta}^*}(\bar{\mathcal{E}}_0) = \begin{pmatrix} -\mu & -\bar{\beta}^* & -\bar{\beta}^*\pi & \gamma & -\bar{\beta}^*\chi_T\pi \\ 0 & \bar{\beta}^* - \bar{K}_1 & \bar{\beta}^*\pi & 0 & \bar{\beta}^*\chi_T\pi \\ 0 & \varepsilon & -\bar{K}_2 & 0 & \rho \\ 0 & \sigma & \delta & -\mu-\gamma & \theta \\ 0 & 0 & \tau & 0 & -\bar{K}_3 \end{pmatrix},$$

with $\bar{\mathbf{v}} = [\bar{v}_1, \bar{v}_2, \bar{v}_3, \bar{v}_4, \bar{v}_5]$, where,

$$\bar{v}_1 = 0,\ \bar{v}_2 = \bar{v}_2 > 0,\ \bar{v}_3 = \frac{\beta^*(\pi\bar{K}_3 + \pi\chi_T\tau)}{(\bar{K}_2\bar{K}_3 - \rho\tau)}\bar{v}_2,\ \bar{v}_4 = 0,\ \bar{v}_5 = \frac{\bar{\beta}^*(\pi\chi_T\bar{K}_2 + \pi\rho)}{(\bar{K}_2\bar{K}_5 - \rho\tau)}\bar{v}_2,$$

and $\bar{\mathbf{w}} = [\bar{w}_1, \bar{w}_2, \bar{w}_3, \bar{w}_4, \bar{w}_5]^T$, with,

$$\bar{w}_1 = -\frac{\bar{\beta}^*(\mu+\gamma)(\bar{K}_2\bar{K}_3 - \rho\tau + \pi\varepsilon\bar{K}_3 + \pi\chi_T\tau\varepsilon) - \gamma[\sigma(\bar{K}_2\bar{K}_3 - \rho\tau) + \delta\varepsilon\bar{K}_3 + \tau\varepsilon\theta]}{\mu(\mu+\gamma)(\bar{K}_2\bar{K}_3 - \rho\tau)}\bar{w}_2,$$

$$\bar{w}_2 = \bar{w}_2 > 0, \quad \bar{w}_3 = \frac{\varepsilon\bar{K}_3}{(\bar{K}_2\bar{K}_3 - \rho\tau)}\bar{w}_2, \quad \bar{w}_4 = \frac{\sigma(\bar{K}_2\bar{K}_3 - \rho\tau) + \delta\varepsilon\bar{K}_3 + \tau\varepsilon\theta}{(\bar{K}_2\bar{K}_3 - \rho\tau)(\mu+\gamma)}\bar{w}_2,$$

$$\bar{w}_5 = \frac{\tau\varepsilon}{(\bar{K}_2\bar{K}_3 - \rho\tau)}\bar{w}_2.$$

Substituting (E.2) into (E.1) gives:

$$\begin{aligned}\bar{a} = \frac{-2\mu\bar{v}_2\bar{w}_2^2}{\Lambda(\bar{K}_2\bar{K}_3 - \rho\tau)^2(\mu+\gamma)} \big[&\bar{K}_1(\bar{K}_2\bar{K}_3 - \rho\tau)(\mu+\gamma)(\bar{K}_2\bar{K}_3 - \rho\tau + \varepsilon\bar{K}_3 + \tau\varepsilon) \\ &+ \bar{K}_1(\bar{K}_2\bar{K}_3 - \rho\tau)\bar{F} - \psi\bar{K}_1(\bar{K}_2\bar{K}_3 - \rho\tau)\bar{F}\big],\end{aligned}$$

$$\begin{aligned}= \frac{-2\mu\bar{v}_2\bar{w}_2^2}{\Lambda(\bar{K}_2\bar{K}_3 - \rho\tau)^2(\mu+\gamma)} \big[&\bar{K}_1(\bar{K}_2\bar{K}_3 - \rho\tau)(\mu+\gamma)(\bar{K}_2\bar{K}_3 - \rho\tau + \varepsilon\bar{K}_3 + \tau\varepsilon) \\ &+\bar{K}_1(\bar{K}_2\bar{K}_3 - \rho\tau)(1-\psi)\bar{F}\big].\end{aligned}$$

Since $\psi < 1$, the bifurcation coefficient $\bar{a}$ is always negative. Furthermore, the bifurcation coefficient $\bar{b}$ is always positive. Thus, it follows from Item (iv) of Theorem 4.1 in [6], that the reduced model (4.4) does not undergo backward bifurcation in this case. □

Appendix F

Proof of Theorem 4.7

Proof. Consider the treatment model (4.1) for the special case $\upsilon = \omega = \chi_Q = 0$. It follows, from the next generation operator method [50] that $\hat{\mathcal{R}}_T$ (the associated *control reproduction number* of the treatment model (4.1) with $\lambda = \hat{\lambda}$) is given by:

$$\hat{\mathcal{R}}_T = \rho\left[\hat{\mathcal{F}}\hat{\mathcal{H}}^{-1}\right] = \frac{\beta\left[(K_2K_5 - \rho\tau) + \pi\varepsilon K_5 + \chi_T\pi\varepsilon\tau\right]}{K_1(K_2K_5 - \rho\tau)} = \mathcal{R}_T, \tag{F.1}$$

where, the matrices $\hat{\mathcal{F}}$ (of new infection terms), and $\hat{\mathcal{H}}$ (of the transition terms) evaluated at the DFE ($\mathcal{E}_0^T$) are given, respectively, by:

$$\hat{\mathcal{F}} = \begin{pmatrix} \beta & \pi\beta & \chi_T\pi\beta \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \text{ and } \hat{\mathcal{H}} = \begin{pmatrix} K_1 & 0 & 0 \\ -\varepsilon & K_2 & 0 \\ 0 & -\tau & K_5 \end{pmatrix},$$

with, K_1, K_2 and K_5, as defined in Section 4.1.

The proof is based on the Comparison Theorem [32]. First of all, as in Appendix D, it should be mentioned that the equations of the infected components of the treatment model (4.1), with $\lambda = \hat{\lambda}$, satisfies the Type K condition [44] (hence, Comparison Theorem can be used [32]). Furthermore, the infected components of

the treatment model (4.1), with $\lambda = \hat{\lambda}$, can be re-written as:

$$\frac{d}{dt}\mathbf{x} = (\hat{\mathcal{F}} - \hat{\mathcal{H}})\mathbf{x} - \hat{J}\mathbf{x}, \tag{F.2}$$

where,

$$\mathbf{x} = [I(t), P(t), T(t)]^T,$$

and,

$$\hat{J} = \left[1 - \frac{\mu S(t)}{\Lambda}\right] \begin{pmatrix} \beta & \pi\beta & \chi_T \pi\beta \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Thus, $\hat{J}$ is a non-negative matrix since

$$S(t) \leq N(t) \leq \frac{\Lambda}{\mu} \text{ in } \mathcal{D}_T.$$

Hence, it follows from (F.2) that

$$\frac{d}{dt}\mathbf{x} \leq (\hat{\mathcal{F}} - \hat{\mathcal{H}})\mathbf{x}. \tag{F.3}$$

Since $\hat{\mathcal{R}}_T = \rho(\hat{\mathcal{F}}\hat{\mathcal{H}}^{-1}) = \mathcal{R}_T \leq 1$ (or, equivalently, the eigenvalues of the matrix $(\hat{\mathcal{F}} - \hat{\mathcal{H}})$ all have negative real-parts), it follows that the linearized differential inequality system (F.3) is stable whenever $\mathcal{R}_T < 1$. Thus, it follows, by Comparison Theorem [44], that

$$\lim_{t\to\infty}(I(t), P(t), T(t)) \to (0, 0, 0).$$

It should be noted that setting $I(t) = P(t) = T(t) = 0$ implies $\hat{\lambda} = 0$. Hence, substituting $\hat{\lambda} = 0$ into the equation for $\frac{dv}{dt}$ in (4.1) gives $V(t) \to 0$, as $t \to \infty$.

Substituting $(I(t), P(t), V(t), T(t)) = (0, 0, 0, 0)$ into the model (4.1) gives the following system of linear equations

$$\begin{aligned} \frac{dW}{dt} &= \zeta Q - (\mu + \eta\delta + \phi)\, W, \\ \frac{dQ}{dt} &= \phi W - (\mu + \zeta + \theta)\, Q, \end{aligned} \tag{F.4}$$

from which it is clear that the system (F.4) has only one equilibrium, $(W^*, Q^*) = (0, 0)$, which is stable (hence, globally-asymptotically stable, since the system is linear and eigenvalues of the associated Jacobin evaluated at $(0, 0)$ have negative real part). Thus, $(W(t), Q(t)) \to (0, 0)$, as $t \to \infty$. Finally, substituting

$$(I(t), P(t), V(t), W(t), T(t), Q(t)) = (0, 0, 0, 0, 0, 0),$$

into the equations for $\frac{dR}{dt}$ and $\frac{dS}{dt}$ in the treatment model (4.1) shows that $R(t) \to 0$ and $S \to S^* = \frac{\Lambda}{\mu}$, as $t \to \infty$ when $\mathcal{R}_T < 1$. Therefore,

$$\begin{aligned} &\lim_{t\to\infty}(S(t), I(t), P(t), R(t), V(t), W(t), T(t), Q(t)) \to (S^*, 0, 0, 0, 0, 0, 0, 0) \\ &= \mathcal{E}_0^T|_{\upsilon=\omega=\chi_Q=0}. \end{aligned}$$

Hence, the DFE $(\mathcal{E}_0^T)$, of the treatment model (4.1), with $\lambda = \hat{\lambda}$, is GAS in $\mathcal{D}_T$ whenever $\mathcal{R}_T < 1$.

□

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