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MODEL FOR HEPATITIS C VIRUS TRANSMISSIONS

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Dedicated to Carlos Castillo-Chavez on the Occasion of his 60th Birthday

Abstract. Hepatitis C virus (HCV) is a leading cause of chronic liver disease. This paper presents a deterministic model for HCV infection transmission and uses the model to assess the potential impact of antiviral therapy. The model is based on the susceptible-infective-removed-susceptible (SIRS) compartmental structure with chronic primary infection and possibility of reinfection. Important epidemiologic thresholds such as the basic and control reproduction numbers and a measure of treatment impact are derived. We find that if the control reproduction number is greater than unity, there is a locally unstable infection-free equilibrium and a unique, globally asymptotically stable endemic equilibrium. If the control reproduction number is less than unity, the infection-free equilibrium is globally asymptotically stable, and HCV will be eliminated. Numerical simulations suggest that, besides the parameters that determine the basic reproduction number, reinfection plays an important role in HCV transmissions and magnitude of the public health impact of antiviral therapy. Further, treatment regimens with better efficacy holds great promise for lowering the public health burden of HCV disease.

1. **Introduction.** Infection with hepatitis C virus (HCV) is a major global public health problem. According to the World Health Organization statistics, 3–4 million people are infected every year and the number of people currently infected with HCV worldwide is approximately 150 million [50]. HCV infection is the most common chronic blood-borne infection in the United States (US) with an estimated 3.2 million persons being chronically infected [5].

HCV is a single-stranded ribonucleic acid (RNA) virus that is transmitted primarily through direct percutaneous exposures to blood. In many countries, the two most common exposures associated with transmission of HCV are injecting-drug use and transfusion of blood from unscreened donors. Transmission can also result from occupational, perinatal, and sexual exposures.

Most of newly infected persons are asymptomatic (and are unaware of their infection) with a minority having symptoms such as jaundice, dark urine, fatigue, nausea, vomiting, and abdominal pain [27]. Approximately 10–20% spontaneously clear the virus and develop natural immunity. Following the acute period, a high

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proportion of HCV-infected persons develops chronic infection. Chronic infection with HCV can result in chronic liver disease or other HCV-related chronic diseases decades after infection [3, 16]. In the US, chronic HCV infection causes approximately 8,000–10,000 deaths each year and is the leading indication for liver transplantations [13].

Currently there is no vaccine for the prevention of HCV infection. Prior to the introduction of HCV protease-inhibitor-based triple therapy for chronic HCV genotype 1 infection in 2011[23], the standard of care for chronic HCV infection is a combination of a pegylated interferon alfa and ribavirin [24]. However, dual therapy is efficacious in less than half of the patients infected with the predominant genotype 1, and treatment may cause serious side effects.

Several mathematical models for HCV RNA kinetics were developed to assess the viral dynamics in vivo and the antiviral efficacy of therapy [40, 44]. However, very few studies of mathematical models of HCV transmission in a community have been conducted. Martcheva and Castillo-Chavez [35] introduced an epidemiologic model of hepatitis C with chronic infectious stage in a varying population. Their model does not include a recovered or immune class and falls within the susceptible-infected-susceptible (SIS) category of models. A susceptible-infected-removed (SIR) model is used by Kretzschmar and Wiessing [32] to study the transmission of HCV among injecting drug users (IDUs). Models that allow for waning immunity of the susceptible-infected-removed-susceptible (SIRS) type are used by Das et al. [17] and Zeiler et al. [51].

None of these models consider directly reinfection. Studies of the natural history of HCV infection suggest that recovery provides only partial, temporary immunity [46]. Secondary infections following recovery behave differently from primary infections. For example, higher spontaneous viral clearance rate and lower rate of chronic reinfection was observed in reinfected patients compared with primary infected patients. Also, viral load during episodes of reinfection is significantly lower compared with that of the primary infection in the same subjects, suggesting lower infectiousness of secondary infections [7, 25, 39].

This paper presents a deterministic model for HCV transmissions with the objective of assessing the potential public health impact of therapy. The model is rigorously analyzed to gain insight into its qualitative behavior. We then use realistic parameters values to numerically simulate the model and trace the transient dynamics following treatment. To take into account various sources of uncertainty in model inputs, we conduct uncertainty and sensitivity analyses.

The rest of the paper is organized as follows. Section 2 presents the model. Qualitative analysis of the model is presented in section 3. Section 4 describes parameters estimation and includes several numerical analyses. Final discussion is provided in section 5.

2. **Model.**

The transmission dynamics of HCV will be studied using an extended version of the simple Kermack-McKendrick-type model [30]. The model analyzes the transmission of an infectious agent in a homogeneously mixing population. The population is divided into several classes: susceptible to infection (S), acutely infected (I), persistently (chronically) infected (P), and removed (R). The model allows reinfection. Like primary infections, reinfection classes are divided into acute reinfection (V) and chronic reinfection (W) classes (Figure 1).

To focus on epidemiologic effects of treatment, we choose a simple demographic model with a constant rate of recruitment in the naïve class Λ and exit rate from all classes μ. Susceptible persons are infected at a per capita rate λ. This force of infection λ depends on the patterns of interaction between persons, the probability that an interaction between an infected and a susceptible person results in transmission of infection β, and the probability that a new contact is infected and the contact level of infectiousness.

Upon infection, the host moves into the I compartment and progresses to chronic stage at rate ε. A primary infected host can clear acute infection at rate σ and chronic infection at rate δ. A host acquires partial immunity upon clearing infection, and becomes less susceptible compared with a naïve host. The residual susceptibility of persons in class R is measured by ψ such that the force of infection is $\psi\lambda$. Because a host acquires partial immunity upon clearing infection, and becomes less or as susceptible compared with a naïve host, it is assumed that $\psi \leq 1$. Immunity of persons in compartment R wanes and eventually they return to the susceptible class S at rate γ. A reinfected host can clear acute infection at rate α and chronic infection at rate η faster than primary infection. The rate of progression to chronic stage of a reinfected host is κ slower than primary infection.

Chronically infected persons in classes P and W are treated at rate τ and ϕ and move to classes T and Q, respectively. After the treatment period of 24 to 48 weeks ends, a fraction of patients succeed in clearing HCV, also known as sustained virologic response (SVR), and move to class R at rate θ. The remainder fail treatment and move back to class P at rate ρ and class W at rate ζ. The degree of infectiousness of hosts in classes P, V, W, T and Q relative to that of hosts in class I is π, ν, $\omega\pi$, $\chi\pi$, and $\chi\pi$, respectively.

The ordinary differential equations that represent the model with treatment are

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

where

$$\begin{aligned}
\lambda &= \frac{\beta(I + \pi P + \nu V + \omega\pi W + \chi\pi T + \chi\pi Q)}{N},\\
N &= S + I + P + R + V + W + T + Q.
\end{aligned}$$

All variables and parameters are defined in Table 1. It should be noted that the model (1), in the absence of treatment, becomes an SIR when $\psi = \gamma = 0$ and an SIS model when $\psi = 1$.

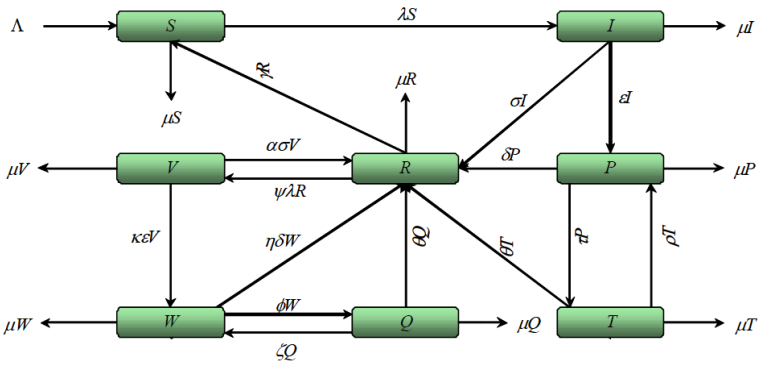

FIGURE 1. Transfer diagram of the HCV infection transmission model with treatment. The model divides the population into 8 major groups according to their susceptibilities and infectiousness. The force of infection is: $\lambda = \beta(I + \pi P + \nu V + \omega\pi W + \chi\pi T + \chi\pi Q)/N$.

3. **Qualitative analysis of the model.** We begin the analysis by considering a simpler version of the model in which reinfection behaves the same way as primary infection with regard to infectivity and rates of recovery, progression, and treatment. That is, $\kappa = \alpha = \eta = \omega = \nu = 1$, $\phi = \tau$, and $\zeta = \rho$. This allows us to include persons in class V with those in class I, persons in class W with those in class P, and combine class Q with class T. In order to avoid confusion we define $\bar{S} = S$, $\bar{I} = I + V$, $\bar{P} = P + W$, $\bar{R} = R$, $\bar{T} = T + Q$, and rewrite system (1) in terms of the variables $\bar{S}$, $\bar{I}$, $\bar{P}$, $\bar{R}$, and $\bar{T}$. The resulting system is

$$\begin{aligned}
\frac{d\bar{S}}{dt} &= \Lambda - \bar{\lambda}\bar{S} - \mu\bar{S} + \gamma\bar{R}, \\
\frac{d\bar{I}}{dt} &= \bar{\lambda}\bar{S} + \psi\bar{\lambda}\bar{R} - (\mu + \sigma + \varepsilon)\bar{I}, \\
\frac{d\bar{P}}{dt} &= \varepsilon\bar{I} + \rho\bar{T} - (\mu + \delta + \tau)\bar{P}, \\
\frac{d\bar{R}}{dt} &= \sigma\bar{I} + \delta\bar{P} + \theta\bar{T} - \psi\bar{\lambda}\bar{R} - (\mu + \gamma)\bar{R}, \\
\frac{d\bar{T}}{dt} &= \tau\bar{P} - (\mu + \rho + \theta)\bar{T},
\end{aligned} \tag{2}$$

with $\bar{\lambda} = \beta(\bar{I} + \pi\bar{P} + \chi\pi\bar{T})/\bar{N}$ and $\bar{N} = \bar{S} + \bar{I} + \bar{P} + \bar{R} + \bar{T}$.

Define the biologically feasible set for system (2) as

$$\mathfrak{D} = \left\{(\bar{S}, \bar{I}, \bar{P}, \bar{R}, \bar{T}) \in \mathbb{R}^5_+ : \bar{N} \leq \Lambda/\mu\right\}$$

The closed set $\mathfrak{D}$ is positively invariant with respect to the model (2). This can be verified as follows. The rate of change of the total population, obtained by adding

Symbol	Description	Value
Variables		
$S(t)$	Susceptible population	
$I(t)$	Acutely infected population	
$P(t)$	Chronically infected population	
$R(t)$	Recovered population with partial immunity	
$V(t)$	Acutely reinfected population	
$W(t)$	Chronically reinfected population	
$T(t)$	Chronically infected treated population	
$Q(t)$	Chronically reinfected treated population	
$\lambda(t)$	Force of infection	
Parameters		
Λ	New recruits into the population	39,600 year^{-1}
μ	Death or retirement rate from the population	0.09 year^{-1}
β	Contact rate	2.68 year^{-1}
σ	Recovery from acute infection	0.5 year^{-1}
δ	Recovery from chronic infection	0.002 year^{-1}
ε	Rate of progression to chronic infection	1.5 year^{-1}
ψ	Relative susceptibility of recovered population	0.5
α	Relative rate of recovery from acute reinfection	3.3
η	Relative rate of recovery from chronic reinfection	3.3
κ	Relative rate of progression to chronic reinfection	1/3.3
τ	Treatment rate of chronically infected population	0.04 year^{-1}
ϕ	Treatment rate of chronically reinfected population	0.04 year^{-1}
θ	Treatment cure rate	0.67 year^{-1}
ρ	Treatment failure rate of chronically infected population	0.82 year^{-1}
ζ	Treatment failure rate of chronically reinfected population	0.82 year^{-1}
γ	Rate of waning immunity	0.025 year^{-1}
π	Relative infectivity of chronically infected population	0.01
ν	Relative infectivity of acutely reinfected population	1/6.5
ω	Relative infectivity of chronically reinfected population	1/6.5
χ	Relative infectivity of treated population	0.5

TABLE 1. Description of variables and parameters. Sources for values of parameters are given in the text.

all the equations of the model (2), is given by

$$\frac{d\bar{N}}{dt} = \Lambda - \mu\bar{N} \tag{3}$$

The solution of equation (3) is

$$\bar{N}(t) = \frac{\Lambda}{\mu} + \left[\bar{N}(0) - \frac{\Lambda}{\mu}\right] e^{-\mu t}.$$

It follows that for all $\bar{N}(0) \leq \Lambda/\mu$, $\bar{N}(t) \leq \Lambda/\mu$ for all $t > 0$. Therefore, all solutions of the model with initial conditions in $\mathfrak{D}$ remain in $\mathfrak{D}$ for all $t > 0$. Thus, the set

$\mathfrak{D}$ is positively invariant with respect to the model (2). In the qualitative analyses, we will only consider the dynamics of the flow generated by (2) in this domain $\mathfrak{D}$.

3.1. **Infection-free equilibrium and reproduction numbers.** The model (2) has a disease-free equilibrium given by

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

A commonly used measures of the severity of an epidemic is the *basic reproduction number* R_0. It is defined as the expected number of new infections generated by a single infected person during his/her entire period of infectiousness when introduced in a completely susceptible population [4, 18, 26]. The basic reproduction number R_0 is typically defined in the absence of any control measures such as vaccination or treatment, and can be derived using the next generation operator technique [47]. Considering model (2) without treatment, the nonnegative matrix F and the non-singular M-matrix Q are given by

$$\begin{aligned} F &= \begin{pmatrix} \beta & \pi\beta \\ 0 & 0 \end{pmatrix}, \\ Q &= \begin{pmatrix} \mu+\sigma+\varepsilon & 0 \\ -\varepsilon & \mu+\delta \end{pmatrix}. \end{aligned}$$

The matrix F includes transmissions from the acutely and chronically infected persons (those in compartments I and P) to persons in other compartments (those in compartments S and R). The matrix Q corresponds to transitions between compartments and death such that the elements of Q^{-1} represent the expected time a person spend in a given epidemiologic class during his/her entire life [19]. R_0 is equal to the spectral radius of the matrix FQ^{-1}:

$$R_0 = \frac{\beta}{\varepsilon+\mu+\sigma}\left(1+\frac{\varepsilon\pi}{\delta+\mu}\right).$$

Because reinfection is ignored in the calculations of R_0, the term ψ does not appear in the formula for R_0. The result showing that the expression for R_0 is unchanged by the presence of reinfection is similar to the findings of Singer and Kirschner [45].

R_0 indicates the severity of an epidemic in the absence of any prevention or therapeutic program to control the spread of infection. A similar quantity, known as the *control reproduction number* R_c, is used to gauge the severity of an epidemic in the presence of a control measure such as treatment. It represents the average number of secondary infections acquired from a primary case introduced into a susceptible population where a control measure is applied on a fraction of the population [10]. We can follow the same approach as before and construct the matrices of transmission $\hat{F}$ and transition $\hat{Q}$ as:

$$\begin{aligned} \hat{F} &= \begin{pmatrix} \beta & \pi\beta & \pi\beta\chi \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \\ \hat{Q} &= \begin{pmatrix} \mu+\sigma+\varepsilon & 0 & 0 \\ -\varepsilon & \mu+\delta+\tau & -\rho \\ 0 & -\tau & \mu+\rho+\theta \end{pmatrix}. \end{aligned}$$

We can derive the reproduction number with treatment R_c as the spectral radius of the matrix $\hat{F}\hat{Q}^{-1}$:

$$R_c = \frac{\beta}{\varepsilon+\mu+\sigma}\left\{1+\frac{\pi\varepsilon(\theta+\mu+\rho+\tau\chi)}{(\delta+\mu)(\theta+\mu+\rho)+(\theta+\mu)\tau}\right\}.$$

It can be shown that $R_c = R_0$ when $\tau = 0$. As expected, the control reproduction number becomes the basic reproduction number in the absence of treatment.

It is instructive to investigate the sensitivity of R_c to changes in the treatment parameters τ, ρ, and θ. It can be shown that R_c is inversely related to τ provided $\theta+\mu > (\delta+\mu)\chi$. Thus, differentiating R_c with respect to τ yields

$$\frac{\partial R_c}{\partial \tau} = -\frac{\beta}{(\varepsilon+\mu+\sigma)}\frac{\pi\varepsilon(\theta+\mu+\rho)[(\theta+\mu)-(\delta+\mu)\chi]}{[(\delta+\mu)(\theta+\mu+\rho)+(\theta+\mu)\tau]^2}.$$

This condition is likely to be satisfied because the rate of recovery following treatment θ is greater than that following untreated chronic infection δ (i.e., $\theta > \delta$), and untreated chronic infections are as infectious as treated chronic infection ($1 \geq \chi$). Likewise, R_c is positively related to ρ provided $\theta+\mu > (\delta+\mu)\chi$. This can be shown by partially differentiating R_c with respect to ρ

$$\frac{\partial R_c}{\partial \rho} = \frac{\beta}{(\varepsilon+\mu+\sigma)}\frac{\pi\varepsilon\tau[(\theta+\mu)-(\delta+\mu)\chi]}{[(\delta+\mu)(\theta+\mu+\rho)+(\theta+\mu)\tau]^2}.$$

Regardless, R_c is positively related to χ and inversely related to θ:

$$\begin{aligned}\frac{\partial R_c}{\partial \chi} &= \frac{\beta}{(\varepsilon+\mu+\sigma)}\frac{\pi\varepsilon\tau}{[(\delta+\mu)(\theta+\mu+\rho)+(\theta+\mu)\tau]},\\ \frac{\partial R_c}{\partial \theta} &= -\frac{\beta}{(\varepsilon+\mu+\sigma)}\frac{\pi\varepsilon\tau[\rho+(\delta+\mu+\tau)\chi]}{[(\delta+\mu)(\theta+\mu+\rho)+(\theta+\mu)\tau]^2}.\end{aligned}$$

Therefore, higher treatment rates with drugs with higher and faster cure rates and lower failure rates will decrease the control reproduction number and the intensity of the epidemic.

Both R_0 and R_c are fundamental to understanding the epidemiology of infectious diseases because, in many cases, they completely characterize the dynamics of infection. Typically, a small influx of infected persons cannot generate outbreaks (infection dies out over time) when R_0 is less than unity, and the infection will persist if R_0 exceeds unity. Similarly, treatment with sufficient coverage can succeed in eliminating infection when R_c is below unity. Because R_c measures the intensity of the epidemic, treatment, by lowering R_c, can have significant public health impact even if it fails to eliminate infection in a specific population.

Following McLean and Blower [38], a measure of treatment impact based on the reproduction numbers can be defined as

$$\Phi(\tau) = 1-\frac{R_c}{R_0} = \frac{\varepsilon\pi\tau\,[\theta+\mu-(\delta+\mu)\chi]}{(\delta+\pi\varepsilon+\mu)\,[(\delta+\mu)(\theta+\mu+\rho)+(\theta+\mu)\tau]}.$$

Thus, population-level impact of treatment is always positive provided $\theta+\mu > (\delta+\mu)\chi$. As mentioned above, this condition is likely to be satisfied for treatment with currently licensed drugs. The implication of this is that widespread treatment is unlikely to cause perverse public health outcomes. Further, the population-level impact of treatment is large, the higher and faster are cure rates (τ and θ) and the lower are the failure rate (ρ) and relative infectivity rate (χ). As a function of τ,

the impact $\Phi(\tau)$ is concave, indicating that the impact increases at a diminishing rate as treatment level increases.

3.2. **Stability of infection-free equilibrium.** To simplify the stability analysis we let $\gamma = 0$ and assume, without any loss of generality, that the demographic process is at equilibrium and $\Lambda = \mu$, so that all the variables are expressed as fractions of the population. Given this, we have $\bar{S} + \bar{I} + \bar{P} + \bar{R} + \bar{T} = 1$. This equation can be used to eliminate $\bar{R}$ and rewrite model (2) as

$$\begin{aligned}
\frac{d\bar{S}}{dt} &= \mu - \bar{\lambda}\bar{S} - \mu\bar{S}, \\
\frac{d\bar{I}}{dt} &= (1-\psi)\bar{\lambda}\bar{S} + \psi\bar{\lambda}(1-\bar{I}-\bar{P}-\bar{T}) - (\mu+\sigma+\varepsilon)\bar{I}, \\
\frac{d\bar{P}}{dt} &= \varepsilon\bar{I} + \rho\bar{T} - (\mu+\delta+\tau)\bar{P}, \\
\frac{d\bar{T}}{dt} &= \tau\bar{P} - (\mu+\rho+\theta)\bar{T},
\end{aligned} \tag{4}$$

with $\bar{\lambda} = \beta(\bar{I} + \pi\bar{P} + \chi\pi\bar{T})$. We now prove the global stability of the infection-free equilibrium $\mathcal{E}_0 = (1, 0, 0, 0)$ when the reproduction number R_c is less than or equal to unity.

Theorem 3.1. *The infection-free equilibrium $\mathcal{E}_0$ of model (4) is globally asymptotically stable if $R_c \leq 1$ and unstable if $R_c > 1$.*

Proof. Consider the Lyapunov function (see, e.g., [22])

$$L_0 = (1-\psi)\left(\bar{S} - S^* - S^* \ln\frac{\bar{S}}{S^*}\right) + \bar{I} + A(\mu+\rho+\theta+\tau\chi)\pi\bar{P} + A\left[\chi(\mu+\delta+\tau)+\rho\right]\pi\bar{T},$$

where A is given by

$$A = \frac{\mu+\sigma+\varepsilon}{(\mu+\rho+\theta)(\mu+\delta+\pi\varepsilon) + \tau(\mu+\theta+\chi\pi\varepsilon)}.$$

L_0 is defined, continuous, and positive definite for all $\bar{S}, \bar{I}, \bar{P}, \bar{T} > 0$. Also, the global minimum $L_0 = 0$ occurs at the infection-free equilibrium $\mathcal{E}_0$. Further, function L_0, along the trajectories of system (4), satisfies

$$\begin{aligned}
\frac{dL_0}{dt} &= (1-\psi)(1-\frac{S^*}{\bar{S}})\frac{d\bar{S}}{dt} + \frac{d\bar{I}}{dt} + A(\mu+\rho+\theta+\tau\chi)\pi\frac{d\bar{P}}{dt} \\
&\quad + A\left[\chi(\mu+\delta+\tau)+\rho\right]\pi\frac{d\bar{T}}{dt} \\
&= (1-\psi)(1-\frac{S^*}{\bar{S}})(\mu S^* - \bar{\lambda}\bar{S} - \mu\bar{S}) \\
&\quad + (1-\psi)\bar{\lambda}\bar{S} + \psi\bar{\lambda}(1-\bar{I}-\bar{P}-\bar{T}) - (\mu+\sigma+\varepsilon)\bar{I} \\
&\quad + A\pi(\mu+\rho+\theta+\tau\chi)\left[\varepsilon\bar{I} + \rho\bar{T} - (\mu+\delta+\tau)\bar{P}\right] \\
&\quad + A\pi\left[\chi(\mu+\delta+\tau)+\rho\right]\left[\tau\bar{P} - (\mu+\rho+\theta)\bar{T}\right]\Big\}.
\end{aligned}$$

Simplifying and collecting terms for $\bar{I}$, $\bar{P}$, and $\bar{T}$ yield

$$\begin{aligned}\frac{dL_0}{dt} &= (1-\psi)\mu S^*(1-\frac{S^*}{\bar{S}})(1-\frac{\bar{S}}{S^*})+(1-\psi)\bar{\lambda}S^*+\psi\bar{\lambda}(1-\bar{I}-\bar{P}-\bar{T})\\ &\quad -A[(\mu+\rho+\theta)(\mu+\delta+\pi\varepsilon)+\tau(\mu+\theta+\chi\pi\varepsilon)-\varepsilon\pi(\mu+\rho+\theta+\tau\chi)]\bar{I}\\ &\quad -A\{(\mu+\rho+\theta+\tau\chi)(\mu+\delta+\tau)-[\chi(\mu+\delta+\tau)+\rho]\tau\}\pi\bar{P}\\ &\quad -A\left\{[\chi(\mu+\delta+\tau)+\rho](\mu+\rho+\theta)-(\mu+\rho+\theta+\tau\chi)\rho\right\}\pi\bar{T}\}\end{aligned}$$

Using the definition of A and further simplifying give

$$\begin{aligned}\frac{dL_0}{dt} &= (1-\psi)\mu S^*(1-\frac{S^*}{\bar{S}})(1-\frac{\bar{S}}{S^*})+(1-\psi)\bar{\lambda}S^*+\psi\bar{\lambda}(1-\bar{I}-\bar{P}-\bar{T})\\ &\quad -A\left[(\mu+\rho+\theta)(\mu+\delta)+\tau(\mu+\theta)\right](\bar{I}+\pi\bar{P}+\chi\pi\bar{T})\}\\ &= (1-\psi)\mu S^*(1-\frac{S^*}{\bar{S}})(1-\frac{\bar{S}}{S^*})+A\left[(\mu+\rho+\theta)(\mu+\delta)+\tau(\mu+\theta)\right]\\ &\quad \times(\bar{I}+\pi\bar{P}+\chi\pi\bar{T})\left\{\frac{\beta\left[(\mu+\rho+\theta)(\mu+\delta+\pi\varepsilon)+\tau(\mu+\theta+\chi\pi\varepsilon)\right]}{(\mu+\sigma+\varepsilon)\left[(\mu+\rho+\theta)(\mu+\delta)+\tau(\mu+\theta)\right]}\right.\\ &\quad \left.\left[(1-\psi)S^*+\psi(1-\bar{I}-\bar{P}-\bar{T})\right]-1\right\},\\ &= (1-\psi)\mu S^*(1-\frac{S^*}{\bar{S}})(1-\frac{\bar{S}}{S^*})+A\left[(\mu+\rho+\theta)(\mu+\delta)+\tau(\mu+\theta)\right]\\ &\quad \times(\bar{I}+\pi\bar{P}+\chi\pi\bar{T})\left\{R_c\left[(1-\psi)S^*+\psi(1-\bar{I}-\bar{P}-\bar{T})\right]-1\right\}.\end{aligned}$$

The term $(1-\psi)\mu S^*(1-S^*/\bar{S})(1-\bar{S}/S^*)=(1-\psi)\mu S^*(2-S^*/\bar{S}-\bar{S}/S^*)$ is less than or equal to zero by the arithmetic-geometric mean inequality (the geometric mean is always less than or equal to the arithmetic mean):

$$\left(\prod_{i=1}^{n}a_i\right)^{\frac{1}{n}}-\sum_{i=1}^{n}a_i/n\le 0,\quad a_i\ge 0,\quad i=1,2,...,n.$$

In this case, the geometric mean of $S^*/\bar{S}$ and $\bar{S}/S^*$ is $\sqrt{(S^*/\bar{S})(\bar{S}/S^*)}=1$ and the arithmetic mean is $(1/2)(S^*/\bar{S}+\bar{S}/S^*)$.

Recall that $S^*=1$, $\bar{I}+\bar{P}+\bar{T}\le 1$, and $0\le\psi\le 1$ so that $(1-\psi)S^*+\psi(1-\bar{I}-\bar{P}-\bar{T})\le 1$. Therefore, if $R_c\le 1$, $dL_0/dt\le 0$ for all $\bar{S}$, $\bar{I}$, $\bar{P}$, $\bar{T}>0$. The equality $dL_0/dt=0$ holds only (a) at the infection-free equilibrium $\mathcal{E}_0$ or (b) when $R_c\left[(1-\psi)S^*+\psi(1-\bar{I}-\bar{P}-\bar{T})\right]=1$ and $\bar{S}=S^*$. The latter case implies $\bar{I}=\bar{P}=\bar{T}=\bar{R}=0$ because

$$\begin{aligned}1 &\ge \bar{S}+\bar{I}+\bar{P}+\bar{R}+\bar{T}=S^*+\bar{I}+\bar{P}+\bar{R}+\bar{T}\\ &= 1+\bar{I}+\bar{P}+\bar{R}+\bar{T}.\end{aligned}$$

Therefore, the largest compact invariant subset of the set

$$M=\left\{(\bar{S},\bar{I},\bar{P},\bar{R},\bar{T})\in\mathfrak{D}:\frac{dL_0}{dt}=0\right\}$$

is the singleton $\{\mathcal{E}_0\}$. By the the LaSalle's Invariance Principle [28], the infection-free equilibrium $\mathcal{E}_0$ is globally asymptotically stable if $R_c\le 1$.

The relevant submatrix of the Jacobian matrix of the system (4) evaluated at the infection-free equilibrium $\mathcal{E}_0$ is

$$J=\begin{pmatrix}\beta-(\mu+\sigma+\varepsilon) & \pi\beta & \beta\chi\pi\\ \varepsilon & -(\mu+\delta+\tau) & \rho\\ 0 & \tau & -(\mu+\rho+\theta)\end{pmatrix}$$

The determinant of J (which is equal to the product of the three eigenvalues of J) is $(\varepsilon+\mu+\sigma)[(\delta+\mu)(\theta+\mu+\rho)+(\theta+\mu)\tau](R_c-1)$. If $R_c>1$, at least one of the eigenvalues of the Jacobian matrix evaluated at $\mathcal{E}_0$ has a positive real part. Therefore, the infection-free equilibrium $\mathcal{E}^\circ$ is unstable when $R_c>1$. □

3.3. **Existence of endemic equilibrium.** To explore the existence of endemic equilibrium, we set the right hand side of system (2) to zero, solve in terms of $\bar{\lambda}$, and substitute the result in the equation for $\bar{\lambda}$. Thus, the non-zero equilibria of the model satisfy the following quadratic equation (in terms of λ^{**})

$$a_2\lambda^{**2}+a_1\lambda^{**}+a_0=0,$$

where

$$\begin{aligned}
a_2 &= [(\delta+\varepsilon+\mu)(\theta+\mu+\rho)+(\varepsilon+\theta+\mu)\tau]\,\psi,\\
a_1 &= [(\delta+\varepsilon+\mu)(\theta+\mu+\rho)+(\varepsilon+\theta+\mu)\tau]\,(\gamma+\mu\psi)\\
&\quad +(\varepsilon+\mu+\sigma)\,[(\delta+\mu)(\theta+\mu+\rho)+(\theta+\mu)\tau]\,(1-\psi R_c)\,,\\
a_0 &= (\gamma+\mu)(\varepsilon+\mu+\sigma)\,[(\delta+\mu)(\theta+\mu+\rho)+(\theta+\mu)\tau]\,(1-R_c)\,.
\end{aligned}$$

Depending on the values of the parameters, this equation has one or two real solutions. The coefficient a_2 is always positive, and a_0 is positive (negative) if R_c is less than (greater than) unity. If $R_c>1$, the quadratic equation has only one positive solution regardless of the value of a_1. If $R_c\le 1$, a_1 is positive and a_0 is nonnegative. In this case (i.e., $R_c\le 1$), the quadratic equation has no positive solution. Hence, the following result is established.

Theorem 3.2. *If $R_c\le 1$, there is no positive endemic equilibrium and the infection-free equilibrium is the only equilibrium. If $R_c>1$, there exists a unique positive endemic equilibrium.*

3.4. **Stability of endemic equilibrium.** Because the bifurcation parameter R_c is independent of ψ, and hence ψ does not affect the qualitative behavior of the model (4), the stability of endemic equilibrium is studied under the simplifying assumption that partial immunity is fully protective (i.e., $\psi=0$). The implied model structure is SIR with a chronic infection state. Under this assumption the endemic equilibrium simplifies to

$$\begin{aligned}
\mathcal{E}_1 &= (S^{**},I^{**},P^{**},T^{**})\\
&= \left(\frac{1}{R_c},\frac{\mu\,(R_c-1)}{(\varepsilon+\mu+\sigma)R_c},\frac{\varepsilon\mu(\theta+\mu+\rho)\,(R_c-1)}{K(\varepsilon+\mu+\sigma)R_c},\frac{\varepsilon\mu\tau\,(R_c-1)}{K(\varepsilon+\mu+\sigma)R_c}\right),
\end{aligned}$$

where $K=(\delta+\mu)(\theta+\mu+\rho)+(\theta+\mu)\tau$.

Theorem 3.3. *The endemic equilibrium $\mathcal{E}_1$ of model (4) with $\psi=0$ is globally asymptotically stable whenever it exists.*

Proof. Consider the Lyapunov function

$$\begin{aligned}
L_1 &= \bar{S}-S^{**}-S^{**}\ln\frac{\bar{S}}{S^{**}}+\bar{I}-I^{**}-I^{**}\ln\frac{\bar{I}}{I^{**}}\\
&\quad +A\pi\left\{(\mu+\rho+\theta+\chi\tau)(\bar{P}-P^{**}-P^{**}\ln\frac{\bar{P}}{P^{**}})\right.\\
&\quad \left.+\,[\chi(\mu+\delta+\tau)+\rho](\bar{T}-T^{**}-T^{**}\ln\frac{\bar{T}}{T^{**}})\right\},
\end{aligned}$$

where A is as defined before. This function is defined, continuous, and positive for all $\bar{S}$, $\bar{I}$, $\bar{P}$, $\bar{T} > 0$. It can be verified that the function L_1 takes the value $L_1 = 0$ at the equilibrium point $\mathcal{E}_1$, and thus, the global minimum of L_1 occurs at the endemic equilibrium $\mathcal{E}_1$.

The time derivative of L_1 along the solutions of system (4), using the equilibrium relations, is

$$\begin{aligned}\frac{dL_1}{dt} &= (1-\frac{S^{**}}{\bar{S}})(\mu S^{**}+\beta I^{**}S^{**}+\beta\pi P^{**}S^{**}+\beta\pi\chi T^{**}S^{**}-\mu\bar{S}-\beta\bar{I}\bar{S}\\ &\quad -\beta\pi\bar{P}\bar{S}-\beta\pi\chi\bar{T}\bar{S})+(1-\frac{I^{**}}{\bar{I}})\left(\beta\bar{I}\bar{S}+\beta\pi\bar{P}\bar{S}+\beta\pi\chi\bar{T}\bar{S}-\beta S^{**}\bar{I}\right.\\ &\quad \left.-\beta\pi P^{**}S^{**}\frac{\bar{I}}{I^{**}}-\beta\pi\chi T^{**}S^{**}\frac{\bar{I}}{I^{**}}\right)\\ &\quad +\pi A(\mu+\rho+\theta+\chi\tau)(1-\frac{P^{**}}{\bar{P}})\left(\varepsilon\bar{I}+\rho\bar{T}-\varepsilon I^{**}\frac{\bar{P}}{P^{**}}-\rho T^{**}\frac{\bar{P}}{P^{**}}\right)\\ &\quad +\pi A[\chi(\mu+\delta+\tau)+\rho](1-\frac{T^{**}}{\bar{T}})\left(\tau\bar{P}-\tau P^{**}\frac{\bar{T}}{T^{**}}\right).\end{aligned}$$

Simplifying and collecting terms yield

$$\begin{aligned}\frac{dL_1}{dt} &= (\mu S^{**}+\beta I^{**}S^{**})\,(1-\frac{S^{**}}{\bar{S}})(1-\frac{\bar{S}}{S^{**}})\\ &\quad +\beta\pi P^{**}S^{**}\left(2+\frac{\bar{P}}{P^{**}}-\frac{S^{**}}{\bar{S}}-\frac{\bar{I}}{I^{**}}-\frac{I^{**}\bar{P}\bar{S}}{\bar{I}P^{**}S^{**}}\right)\\ &\quad +\beta\pi\chi T^{**}S^{**}\left(2+\frac{\bar{T}}{T^{**}}-\frac{S^{**}}{\bar{S}}-\frac{\bar{I}}{I^{**}}-\frac{I^{**}\bar{T}\bar{S}}{\bar{I}T^{**}S^{**}}\right)\\ &\quad +\pi A(\mu+\rho+\theta)\varepsilon I^{**}(1-\frac{P^{**}}{\bar{P}})(\frac{\bar{I}}{I^{**}}-\frac{\bar{P}}{P^{**}})\\ &\quad +\pi A\chi\tau\varepsilon I^{**}(1-\frac{P^{**}}{\bar{P}})(\frac{\bar{I}}{I^{**}}-\frac{\bar{P}}{P^{**}})\\ &\quad +\pi A\chi\tau\rho T^{**}(1-\frac{P^{**}}{\bar{P}})(\frac{\bar{T}}{T^{**}}-\frac{\bar{P}}{P^{**}})\\ &\quad +\pi A(\mu+\rho+\theta)\rho T^{**}(1-\frac{P^{**}}{\bar{P}})(\frac{\bar{T}}{T^{**}}-\frac{\bar{P}}{P^{**}})\\ &\quad +\pi A\tau\chi(\mu+\delta+\tau)P^{**}(1-\frac{T^{**}}{\bar{T}})(\frac{\bar{P}}{P^{**}}-\frac{\bar{T}}{T^{**}})\\ &\quad +\pi A\rho\tau P^{**}(1-\frac{T^{**}}{\bar{T}})(\frac{\bar{P}}{P^{**}}-\frac{\bar{T}}{T^{**}}).\end{aligned}$$

Because $\beta\pi P^{**}S^{**} = \pi A(\mu+\rho+\theta)\varepsilon I^{**}$ and $(\mu+\rho+\theta)T^{**} = \tau P^{**}$, we have

$$\begin{aligned}
\frac{dL_1}{dt} &= (\mu S^{**} + \beta I^{**}S^{**})\left(2 - \frac{S^{**}}{\bar{S}} - \frac{\bar{S}}{S^{**}}\right) \\
&\quad +\beta\pi P^{**}S^{**}\left(3 - \frac{S^{**}}{\bar{S}} - \frac{P^{**}\bar{I}}{\bar{P}I^{**}} - \frac{I^{**}\bar{P}\bar{S}}{\bar{I}P^{**}S^{**}}\right) \\
&\quad +\beta\pi\chi T^{**}S^{**}\left(2 + \frac{\bar{T}}{T^{**}} - \frac{S^{**}}{\bar{S}} - \frac{\bar{I}}{I^{**}} - \frac{I^{**}\bar{T}\bar{S}}{\bar{I}T^{**}S^{**}}\right) \\
&\quad +\pi A\chi\tau\varepsilon I^{**}\left(1 - \frac{\bar{P}}{P^{**}} + \frac{\bar{I}}{I^{**}} - \frac{P^{**}\bar{I}}{\bar{P}I^{**}}\right) \\
&\quad +\pi A\chi\tau\rho T^{**}\left(1 - \frac{\bar{P}}{P^{**}} + \frac{\bar{T}}{T^{**}} - \frac{P^{**}\bar{T}}{\bar{P}T^{**}}\right) \\
&\quad +\pi A\tau\chi(\mu+\delta+\tau)P^{**}\left(1 + \frac{\bar{P}}{P^{**}} - \frac{\bar{T}}{T^{**}} - \frac{T^{**}\bar{P}}{\bar{T}P^{**}}\right) \\
&\quad +\pi A\rho\tau P^{**}\left(2 - \frac{P^{**}\bar{T}}{\bar{P}T^{**}} - \frac{T^{**}\bar{P}}{\bar{T}P^{**}}\right).
\end{aligned}$$

Also, $(\mu+\delta+\tau)P^{**} = \varepsilon I^{**} + \rho P^{**}$. Thus,

$$\begin{aligned}
\frac{dL_1}{dt} &= (\mu S^{**} + \beta I^{**}S^{**})\left(2 - \frac{S^{**}}{\bar{S}} - \frac{\bar{S}}{S^{**}}\right) \\
&\quad +\beta\pi P^{**}S^{**}\left(3 - \frac{S^{**}}{\bar{S}} - \frac{P^{**}\bar{I}}{\bar{P}I^{**}} - \frac{I^{**}\bar{P}\bar{S}}{\bar{I}P^{**}S^{**}}\right) \\
&\quad +\beta\pi\chi T^{**}S^{**}\left(2 + \frac{\bar{T}}{T^{**}} - \frac{S^{**}}{\bar{S}} - \frac{\bar{I}}{I^{**}} - \frac{I^{**}\bar{T}\bar{S}}{\bar{I}T^{**}S^{**}}\right) \\
&\quad +\pi A\chi\tau\varepsilon I^{**}\left(2 - \frac{\bar{T}}{T^{**}} + \frac{\bar{I}}{I^{**}} - \frac{P^{**}\bar{I}}{\bar{P}I^{**}} - \frac{T^{**}\bar{P}}{TP^{**}}\right) \\
&\quad +\pi A\rho\tau(P^{**} + \chi T^{**})\left(2 - \frac{P^{**}\bar{T}}{\bar{P}T^{**}} - \frac{T^{**}\bar{P}}{\bar{T}P^{**}}\right).
\end{aligned}$$

Because $\beta\pi\chi T^{**}S^{**} = \pi A\chi\tau\varepsilon I^{**}$, we finally have

$$\begin{aligned}
\frac{dL_1}{dt} &= (\mu S^{**} + \beta I^{**}S^{**})\left(2 - \frac{S^{**}}{\bar{S}} - \frac{\bar{S}}{S^{**}}\right) \\
&\quad +\beta\pi P^{**}S^{**}\left(3 - \frac{S^{**}}{\bar{S}} - \frac{P^{**}\bar{I}}{\bar{P}I^{**}} - \frac{I^{**}\bar{P}\bar{S}}{\bar{I}P^{**}S^{**}}\right) \\
&\quad +\beta\pi\chi T^{**}S^{**}\left(4 - \frac{S^{**}}{\bar{S}} - \frac{P^{**}\bar{I}}{\bar{P}I^{**}} - \frac{T^{**}\bar{P}}{\bar{T}P^{**}} - \frac{I^{**}\bar{T}\bar{S}}{\bar{I}T^{**}S^{**}}\right) \\
&\quad +\pi A\rho\tau(P^{**} + \chi T^{**})\left(2 - \frac{P^{**}\bar{T}}{\bar{P}T^{**}} - \frac{T^{**}\bar{P}}{\bar{T}P^{**}}\right) \\
&\leq 0.
\end{aligned}$$

The terms between the larger brackets are less than or equal to zero by the inequality: the geometric mean less than or equal to the arithmetic mean. It should be noted that $dL_1/dt = 0$ holds if and only if $(\bar{S}, \bar{I}, \bar{P}, \bar{T})$ take the equilibrium values $(S^{**}, I^{**}, P^{**}, T^{**})$. Therefore, by the the LaSalle's Invariance Principle the endemic equilibrium $\mathcal{E}_1$ is globally asymptotically stable. □

4. **Quantitative analysis of the model.** In this section, we use realistic sets of parameters to assess the public health impact of treatment for chronic HCV infection using pegylated interferon plus ribavirin. The model considers HCV transmission in a high-risk population. In the United States, the most common mode of HCV transmission is injecting-drug use [12]. Although many currently infected HCV patients contracted the virus through blood transfusions in the 1970s and 1980s, post-transfusion HCV transmission has become a rare event after the implementation of effective screening programs of the blood supply for the presence of HCV in the 1990s. Because blood transfusion rarely accounts for recently acquired infections and other modes are relatively less important and/or not well-defined, the quantitative analysis focuses on HCV transmission among currently injecting drug users.

4.1. **Parameters values.** The baseline parameter estimates are summarized in Table 1. The baseline values were derived as follows. The removal rate μ consists of natural death and cessation of high-risk activity (e.g., injecting drug use). We set the natural death to 0.02 per year, implying that the average life expectancy of this population is 50 years. Estimates of the duration of injecting drug use vary, ranging from 8 to 41 years [29]. We assume that it is 14 years [15]. Thus, $\mu = 0.09$ $(= 0.02 + 0.07)$ per year.

According to data from the National Household Survey on Drug Abuse an estimated 440,000 persons reported IDU within the past year during the period 1979–2002 [6]. Assuming a steady state, this implies $\Lambda = 39,600$ per year.

The rate of recovery from acute infection σ is estimated at 0.5 per year and the rate of progression to chronic infection ε at 1.5 per year, which is equivalent to a mean duration of acute infection of 6 months and an overall rate of clearance of 25% [51]. The rate of recovery from chronic infection δ is estimated at 0.002 per year [8].

Reinfection occurs in approximately 50% of IDU who previously spontaneously controlled primary HCV infection, suggesting a ψ value of 0.5 [42]. Another study found that the odds of developing infection among persons previously cleared HCV infection compared with those infected for the first time is 0.23 (confidence interval, 0.10–0.51) [25]. Also, rates of viral clearance among reinfected patients are approximately 3.3 times faster than rates of clearance of primary infections [42]. Thus, we can assume $\alpha = \eta = 3.3$, and $\kappa = 1/3.3$.

Rate of antibody loss is low. One study estimated it at 0.6 per 100 person-years whereas another study found that antibodies were undetectable in 50% of patients 18–20 years after recovery [1, 46]. Thus, γ can range from 0.006 to 0.035. We choose the average of the two estimates and assume the average life span of antibodies is four decades ($\gamma = 0.025$).

Mainly because of lack of diagnosis and follow up, only a minority of chronically infected patients receive treatment. Estimates of annual treatment rates among IDUs in the US are as low as <1% [37]. Other estimates from other US populations vary from 2.6% of all prevalent cases to 11.8% among prevalent diagnosed cases [11, 48]. Because more than half of chronic infections are not diagnosed, an assumed value of τ and ϕ of 4% lies in the middle of the range of estimates of treatment rates.

The duration of treatment and its success depend on the regimen type. The combination of a pegylated interferon alfa and ribavirin is recommended for 48

weeks, with patients who have detectable HCV-RNA after 24 weeks stopping treatment [24]. To simplify we assume that all failures occur by week 24. Denoting the proportion failing treatment by f, average treatment duration is calculated as $24f + 48(1-f)$ weeks. The probability of achieving an SVR (i.e., considered permanently cured) using the combination of a pegylated interferon alfa and ribavirin in treatment-naïve patients $(1-f)$ is approximately 45%. Thus, the mean duration of treatment is 34.8 (=0.55*24+0.45*48) weeks. Noting that $\theta+\rho$ is the reciprocal of the mean duration of treatment in years (1 year = 52 weeks), we have

$$\theta + \rho = \frac{52}{24f + 48(1-f)}$$

or $\theta+\rho = 1.49$ per year. Because duration of treatment is assumed to be exponentially distributed, the probabilities of success and failure are related to the rates ρ and θ according

$$\begin{aligned} 1-f &= \frac{\theta}{\theta+\rho}\left(1-e^{-(\theta+\rho)48/52}\right), \\ f &= \frac{\rho}{\theta+\rho}\left(1-e^{-(\theta+\rho)48/52}\right). \end{aligned}$$

These two equations yield $\theta = (1-f)(\theta+\rho)$ and $\rho = f(\theta+\rho)$. We assume $\rho = \zeta$. Using the formula for $\theta+\rho$, and relating the 3 parameters to the probability of failing to achieve SVR f, we have

$$\begin{aligned} \theta &= \frac{52(1-f)}{48(1-f)+24f}, \\ \rho &= \zeta = \frac{52f}{48(1-f)+24f}. \end{aligned}$$

This gives $\theta = 0.67$ (=0.45*1.49) and $\rho = 0.82$ for the base case. In the uncertainty analysis, variability in θ, ρ, or ζ results from varying f only.

The infectivity of patients during the chronic phase of infection relative to acute infection is not known. One can use the relative magnitude of HCV RNA titers during the two phases to postulate how much infectivity falls during the chronic phase. This may be supported by some of the studies that have established a direct correlation between serum HCV viral titers and risk of HCV transmission [41]. One study found that the odds of HCV transmission increase by 1.05 fold for each 10^5 increase in HCV viral load [21]. Risk modeling can also be used to predict the probability of viral transmission from a single transfusion given viral load of the donor [49]. Here we make simple assumptions regarding the relative infectivity of persons in classes I, P, W, V, T, and Q. According to data from animal experiments, chronic phase plasma may be 75- to 100-fold less infectious than acute phase plasma [31]. Thus , we assume $\pi = 0.01$. Experimental data from reinfection of chimpanzees that have cleared HCV suggest that viremia levels are six to seven log fold lower compared with viremia levels during primary infection [33]. Thus, we assume $\nu = \omega = 1/6.5$. Because about half of patients on treatment with pegylated interferon alfa and ribavirin have undetectable HCV-RNA, we assume that they are 50% less infectious compared with untreated patients in the chronic phase. Thus, $\chi = 0.5$.

Estimates of the contact rate β can be inferred from data on incidence and seroprevalence of HCV among IDUs in the absence of widespread treatment. Estimates of HCV seroprevalence in the US vary widely, ranging from 18% to 90% [2]. Also,

HCV incidence among IDUs was high in the 1990s (10%–35% per year), but appears to have declined over the last decade. We use a recent estimate for seroprevalence of 34% [2]. The contact rate implied by the chosen baseline parameters and seroprevalence rate is $\beta = 2.68$. This yields a basic reproduction number R_0 of 1.49. The implied R_0 value is similar to other estimates in the literature [36, 43].

All parameters are included in the uncertainty and sensitivity analyses [9]. Because of lack of data to inform the choice of the distribution of parameters values, we assumed all parameters are uniformly distributed, with range of values given by ±10% of the baseline values. Uncertainties in the reinfection and treatment parameters ($\alpha\sigma$, $\eta\delta$, $\kappa\varepsilon$, $\omega\pi$, $\chi\pi$) are propagated through uncertainties in the relative parameters (α, η, κ, ω, χ) as well as the primary infection parameters (σ, δ, ε, π, π).

Most influential parameters are determined by calculating the partial rank correlation coefficient (PRCC) between each input parameter and the measure of public health impact [9, 34]. A higher absolute value of PRCC indicates a strong relationship between that parameter and the variable of interest. The nature of the qualitative relationship between each input and each variable is determined by the sign of the PRCC.

4.2. **Numerical simulations.** Using the baseline parameters values in Table 1, we numerically solve the model (1) assuming the system is initially in a steady state before treatment. Figures 2 and 3 show the reductions in incidence and prevalence relative to pretreatment values for three values of the reinfection parameter ψ: 0, 0.5, and 1. With low and baseline values of ψ, both HCV incidence and prevalence fall following treatment. The results also reveal that with high values (in this case $\psi = 1$), treatment can result in higher HCV incidence (Figure 2). This is because, by curing chronically infected patients, treatment increases the pool of susceptibles especially if ψ is high. However, despite the increase in incidence following treatment, HCV prevalence is lower (Figure 3). This is important because it is chronic infection that leads to disease, not acute infection. Thus, we may have situations where treatment increases incidence of HCV infections, but results in lower overall HCV prevalence and fewer cases of HCV-related disease.

The uncertainty in the results of the public health impact of treatment is summarized in plots of the cumulative number of infections prevented and % reduction in prevalence compared with no treatment as a function of time since initiation of treatment (Figures 4, 5). There is wide variation in the estimates of impact over time. For example, the cumulative number of infections prevented over 30 years ranges from –12,151 (indicating an increase in the number of cases) to 19,381. The mean number of cases prevented is 4,000. The cumulative number of infections prevented over 30 years is positive in 78.5% of the 10,000 simulations. Likewise, the mean % reduction in prevalence is 15.2% (range: 10.4–23%). All simulations show positive reduction in prevalence (Figure 5).

The sensitivity analysis identifies the most influential parameters in the impact of treatment by calculating PRCC between each input parameter and the two measures of public health impact (Table 2). Of all 18 parameters, 14 are highly influential in determining the cumulative number of infections prevented over 30 years. Also, the % reduction in prevalence is highly influenced by all parameters, with the exception of Λ, κ, ω, η, and ϕ. The cumulative number of infections prevented increases with higher values of ε, σ, π, τ, Λ, α, and κ; and decreases with higher values of β, ψ, μ, γ, f, ν, and χ. The ranking (from high to low) of relative importance (as measured

by the magnitude of the absolute value of PRCC) of each input in influencing the number of infections prevented is: β, ε, σ, π, ψ, μ, γ, τ, Λ, f, ν, χ, α, and κ. The ranking of each input in influencing the % reduction in prevalence is: f, β, τ, μ, ε, σ, π, γ, ψ, α, ν, δ, and χ. Of note is the lack of association between public health impact and treatment uptake among chronically reinfected persons ϕ. This is due to the assumption that chronic reinfection has higher spontaneous viral clearance rate and lower infectiousness compared with primary chronic infections. The highly significant influence of treatment failure on the % reduction in HCV prevalence indicates that treatment regimens with better efficacy holds great promise for lowering the public health burden of HCV disease.

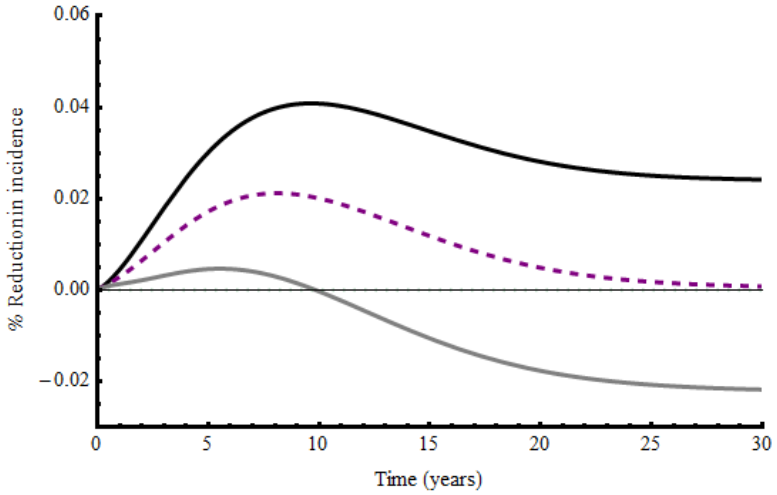

FIGURE 2. Simulated % reductions in incidence as a function of time with three values of the reinfection parameter ψ: top black curve (no reinfection, $\psi = 0$), middle dashed curve (baseline, $\psi = 0.5$), bottom gray curve (no immunity, $\psi = 1$).

5. **Discussion.** This paper presents a deterministic mathematical model of HCV infection transmission in a homogeneously mixing population. The model includes realistic features of HCV transmission such as partial immunity and reinfection. We derive explicit formula for the reproduction numbers that characterizes whether the epidemic will be contained following treatment or not. The importance of various properties of antiviral therapy in determining the impact of treatment was analyzed using a summary measure derived from the reproduction numbers.

By constructing suitable Lyapunov functions, we are able to resolve the global stability of system (4). We prove that the global dynamics of this model are determined by the reproduction number R_c. If R_c is less than unity, there is a unique infection-free equilibrium which is globally asymptotically stable. For R_c greater than unity, the infection-free equilibrium is unstable, and there is a unique endemic equilibrium which is globally asymptotically stable. However, the task of establishing the global stability of equilibria of the full model (1) is left for future research.

The paper addresses a number of key issues related to the epidemiologic consequences of treatment. Valuable insights are obtained from the numerical analysis

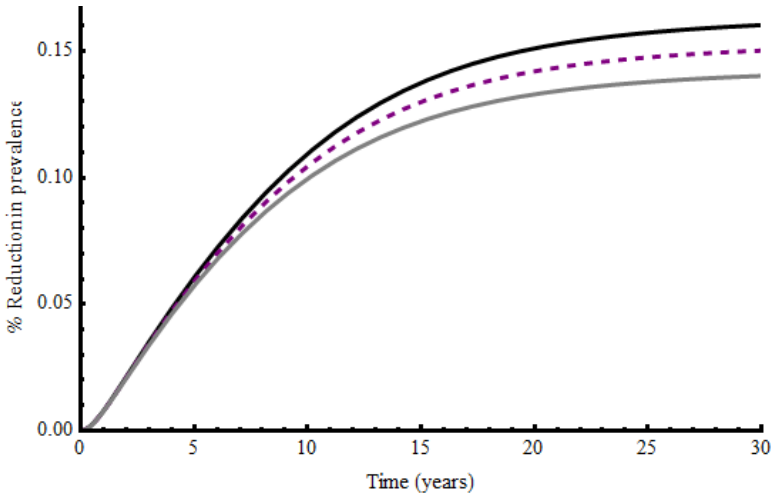

FIGURE 3. Simulated % reductions in prevalence as a function of time with three values of the reinfection parameter ψ: top black curve (no reinfection, $\psi = 0$), middle dashed curve (baseline, $\psi = 0.5$), bottom gray curve (no immunity, $\psi = 1$).

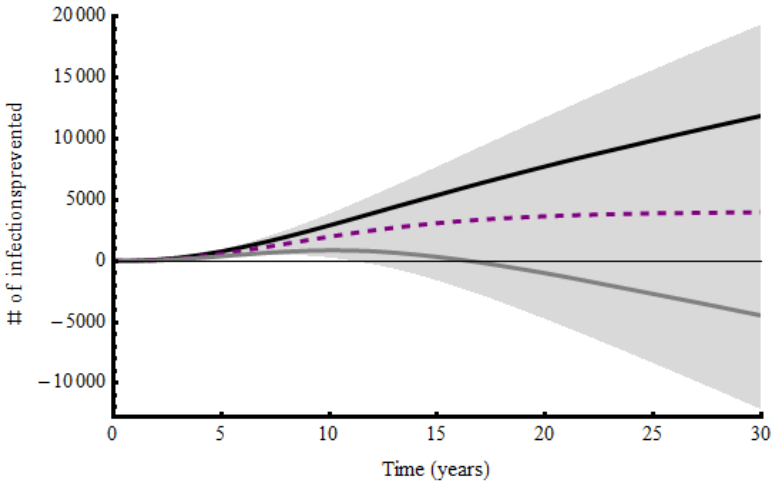

FIGURE 4. Range of cases of infection prevented as a function of time: top black curve (95% percentile), middle dashed curve (mean), bottom gray curve (5th percentile). The shaded area indicates the range of infections prevented from 10,000 Monte Carlo simulations.

of the model. It is shown that depending on the values of the reinfection parameter ψ, HCV incidence can rise or fall following treatment. However, regardless of the value of ψ HCV prevalence is lower compared with the case without treatment.

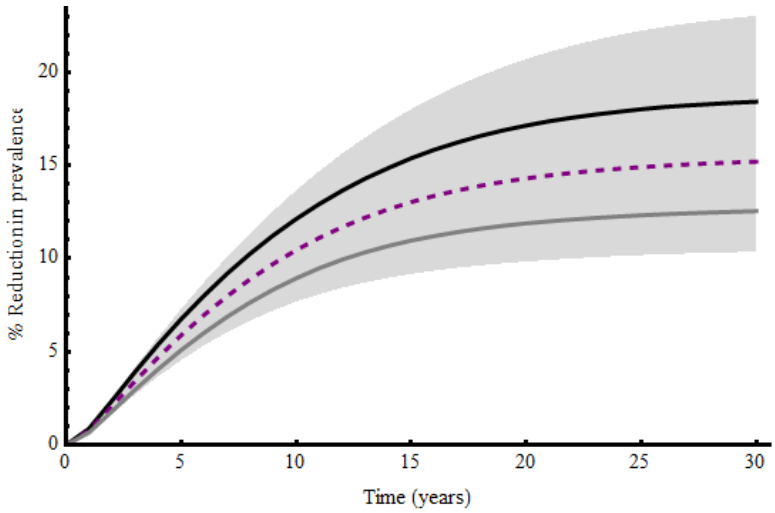

FIGURE 5. Range of % reductions in prevalence as a function of time: top black curve (95% percentile), middle dashed curve (mean), bottom gray curve (5th percentile). The shaded area indicates the range of % reductions in prevalence from 10,000 Monte Carlo simulations.

The model could be elaborated to take into account other factors that are important for the transmission of HCV infection. Such risk factors include age and heterogeneity of mixing between different types of IDUs. Other major modes of HCV transmissions such as unsafe therapeutic injections and transfusions, especially in developing countries, were also excluded from the model. Further, the model does not incorporate some important aspects of the natural history of HCV infection and HCV-related diseases. It is well known that chronic infection with HCV leads to many diseases, including cirrhosis and hepatocellular carcinoma. Most of these diseases progress through different stages with rates of progression and disease-induced mortality varying by stage. A natural extension of this work is to include heterogeneity in mixing between different social groups and allow for progression of infection along various disease states.

The standard of care for patients with chronic HCV infection is antiviral therapy with pegylated interferon alfa and ribavirin. Despite its demonstrated clinical benefits antiviral dual therapy has its limitations because of modest efficacy and the risk of severe adverse events. Two first-generation HCV protease inhibitors, to be used in combination with pegylated interferon and ribavirin, were approved for the treatment of chronic hepatitis C genotype 1 infection in 2011 [23]. Several antiviral therapy candidates with potentially better product profiles are currently in development [20]. In part because of advances in HCV care and treatment, the Centers for Disease Control and Prevention (CDC) has expanded its risk-based (e.g., history of injection-drug use) HCV testing recommendations, to include any person born during the years 1945–1965 [14].

This study provides useful tools for assessing the effectiveness and analyzing the potential population level impact of treatment. The study highlights important key parameters to be considered in assessing the public health impact of treatment.

Parameter	Infections prevented	% reduction in prevalence
Contact rate, β	– 0.97	– 0.91
Rate of progression to chronic infection, ε	0.95	0.88
Recovery from acute infection, σ	0.77	0.56
Relative infectivity of chronic infection, π	0.44	0.24
Relative susceptibility of recovered population, ψ	– 0.43	– 0.14
Death or retirement rate from the population, μ	– 0.36	– 0.88
Rate of waning immunity, γ	– 0.30	– 0.22
Treatment rate of chronically infected population, τ	0.27	0.89
New recruits into the population, Λ	0.24	0.01*
Treatment failure rate, f	– 0.24	– 0.92
Relative infectivity of acute reinfection, ν	– 0.17	– 0.07
Relative infectivity of treated population, χ	– 0.11	– 0.05
Recovery from acute reinfection, α	0.11	0.11
Relative rate of progression to chronic reinfection, κ	0.04	0.00*
Relative infectivity of chronically reinfected population, ω	– 0.01*	0.02*
Treatment rate of chronically reinfected population, ϕ	– 0.01*	– 0.02*
Relative rate of recovery from chronic reinfection, η	– 0.01*	0.00*
Recovery from chronic infection, δ	0.00*	– 0.05

TABLE 2. The partial rank correlation coefficients (PRCC) measuring the association between the input values of the parameters and cumulative cases prevented and percent reduction in prevalence over 30 years with 10,000 Monte Carlo simulations. The (*) indicates that the association is not statistically significant at the confidence level of 5 percent or lower.

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