Hepatitis C virus modeled as an indirectly-transmitted infection highlights the centrality of injection drug equipment in disease dynamics

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***Abstract*— The Hepatitis C virus (HCV) epidemic often occurs through the persistence of injection drug use. Mathematical models have been useful in understanding various aspects of the HCV epidemic, and especially, the importance of new treatment measures. Until now, however, few models have attempted to understand HCV in terms an interaction between the various actors in an HCV outbreak—hosts, viruses and the needle injection equipment. In this study, we apply perspectives from the ecology of infectious diseases to model the transmission of HCV among a population of injection drug users. The products of our model suggest that modeling HCV as an indirectly-transmitted infection—where the injection equipment serves as an environmental reservoir for infection—facilitates a more nuanced understanding of disease dynamics, by animating the underappreciated actors and interactions that frame disease. This lens may allow us to understand how certain public health interventions (e.g. needle exchange programs) influence HCV epidemics. Lastly, we argue that this model is of particular importance in light of the modern opioid epidemic, which has already been associated with outbreaks of viral diseases.**

I. INTRODUCTION

While the ecology of infectious disease is a rich field with decades worth of empirical evidence and theory, there are aspects that remain relatively under-explored. One example is the importance of the free-living survival stage of certain pathogens, where diseases are transmitted indirectly between hosts through an environmental reservoir intermediate. These include infections transmitted indirectly between hosts via a surface or reservoir intermediate—often abiotic—where the pathogen lives freely and independently of a host [1]–[18], sometimes described as "sit and wait" infections [19]. Other studies have focused on systems where pathogens are growing in the environment [9], or have explored indirectly-transmitted infections in theoretical terms [12], [15]. While frameworks already exist for studying indirect environmental transmission, most are engineered with constraints that render their application necessarily narrow [6], limiting their relevance for a wider number of indirectly-transmitted infections.

One class of diseases where the indirect transmission paradigm has been scarcely applied are those spread through injection drug use in urban settings, such as the Human Immunodeficiency Virus (HIV) and Hepatitis C virus (HCV). HIV has been the object of many important mathematical models [20], [21], some of which have implemented injection drug use effectively, even focusing on the specific dynamics of injection equipment [22]–[25]. HCV has also been studied using modeling methods, many focusing on treatment [26]–[28], and others on the particulars of transmission in injection drug user communities [29]–[35]. Importantly, none of these existing dynamical models consider the peculiar ecology of HCV transmission, where transmission events occur through an environmental reservoir (injection equipment) that resembles a disease vector [36]. Unlike an insect vector, however, injection equipment is not an organism and is more realistically considered an abiotic reservoir for infection, similar to the role that the water supply serves in an outbreak of cholera or other waterborne diseases" [37]. As HCV continues to be a public health burden in many settings, there is a need to understand how the dynamics of injection equipment influence HCV transmission. This is especially important for informing the utility of harm reduction programs, such as needle exchange, which have been effective in decreasing transmission of HIV and HCV [38], [39]. Lastly, but perhaps most importantly, the urgency for understanding these dynamics has increased dramatically in recent years with the growth of the modern opioid epidemic, much of it involving injection drug use [40], [41]. The lack of models of HCV that specifically consider injection equipment, and increased social urgency related to the modern opioid epidemic implore more adaptable mathematical models of injection-drug use that could facilitate a better understanding of and predictions for the trajectory of modern HCV infections.

In this study, we model Hepatitis C virus as an indirectly (or environmentally) transmitted infection, where the drug paraphernalia serves as the environmental reservoir. As

HCV epidemics are partly defined by injection drug users and injection drug equipment, we argue that this indirectly transmitted lens captures aspects that prior models haven't. As an introduction, we first introduce a theoretical iteration of an indirectly-transmitted infection using a standard epidemiological model imbued with an environmental reservoir compartment. We describe analytical equations of such a system, and derive the reproductive number (R_0) using analytical methods. We then introduce the HCV mathematical model, demonstrating how it allows one to examine several otherwise-overlooked features of disease dynamics. We pontificate on these results in light of the ecology of infectious diseases, and in terms of public health policies, especially as they relate to the modern opioid epidemic.

II. AN ELEMENTARY ADAPTED S-I-R INDIRECTLY-TRANSMITTED ITERATION

A. Description

While the emphasis of our examination will reside in how we analyze a Hepatitis C virus epidemic, for explanatory purposes we will begin by describing how it modifies very basic concepts in a classic, purposefully prosaic susceptible-infected-recovered (S-I-R or SIR) mathematical model. We will explain the basic structure of a model of indirect-transmission, after which the HCV-specific iteration will be discussed.

While there are several existing frameworks that can be used to describe infections spreading through an environmental reservoir, we have conveniently labeled ours the waterborne, abiotic and indirectly transmitted (W.A.I.T.) infection model. Many diseases can be modeled using this kind of approach, but this study applies it to HCV in a community of injection drug users, which has not been previously modeled in this manner.

We utilize a standard S-I-R framework, where dynamics are defined by changes in a population of susceptible ("S"), infected ("I") and recovered ("R") hosts. Classically, flow of infection through the system is defined by contact between susceptible and infected individuals, often driven by a β factor, or transmission coefficient. Figure 1 is a compartmental model that depicts this interaction, and adds two additional compartments, labeled with a W (for W.A.I.T.), which influence the flow of hosts from the susceptible to infected compartments—indicated by the dashed lines in the figure.

B. The adapted SIR compartmental diagram

The S, I and R compartments represent the usual *susceptible*, *infected* and *recovered* populations of hosts. W_u and W_i represent uninfected and infected populations of *environmental* agents, respectively.

In traditional SIR models, the rate of new infection (arrow from the S compartment to the I) is generally proportional to the product of the susceptible and the infected populations, i.e. proportional to SI. In the W.A.I.T. framework, the environmental compartment plays a role analogous to the infected *host* compartment in driving the rate of infection. In this specific example, the W_i compartment contributes to the rate of infection as a fraction, $W_i/(W_i + W_u)$, which appears as a factor in the rate terms.

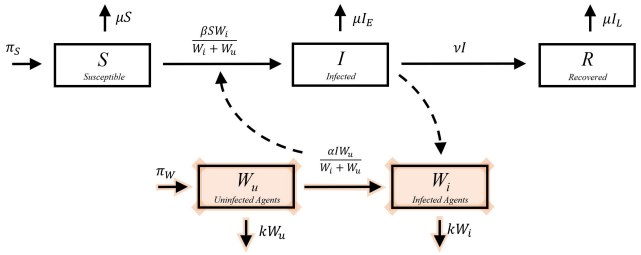

Fig. 1: ***Adapted SIR* compartmental diagram.** This depicts a standard SIR style compartmental model with the added compartments (shaded) corresponding to the W.A.I.T. environment. Note the dynamical properties of the W_i and W_u compartments. It is these dynamics that set the W.A.I.T. perspective apart from others: environments are often dynamical systems, with an ecology of their own.

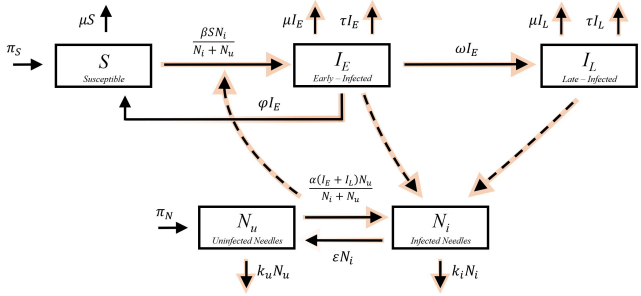

Fig. 2: ***HCV compartmental diagram***. Red arrows highlight flow of disease through the system, and where there is a color/transparency gradient there is a flow of infection away from an infected compartment towards an uninfected one.

The epidemic is then driven by a series of interactions: between uninfected (susceptible) hosts S and the infected (transmitting) environmental compartment W_i, and interactions between infected individuals I and the uninfected environmental compartment W_u. The epidemic is sustained through infected hosts I depositing pathogen into the environmental reservoir, creating new infections, which can then infect more susceptible hosts S (in a process resembling a feedback loop). These dynamics can be captured by the set of dynamical equations and visualized with the diagram in Figure 1.

$$\frac{dS}{dt} = \pi_S - \beta S \frac{W_i}{W_u + W_i} - \mu S \quad (1)$$

$$\frac{dI}{dt} = \beta S \frac{W_i}{W_u + W_i} - \nu I - \mu I \quad (2)$$

$$\frac{dR}{dt} = \nu I - \mu R \quad (3)$$

$$\frac{dW_u}{dt} = \pi_W - \alpha I \frac{W_u}{W_u + W_i} - k W_u \quad (4)$$

$$\frac{dW_i}{dt} = \alpha I \frac{W_u}{W_u + W_i} - k W_i \quad (5)$$

Equations 1–5 define an extension of the prosaic SIR model. π_S is the birthrate of new susceptible hosts and μ is the fractional death rate of hosts. In this context, β represents the *strength* of the interaction between the susceptible hosts S and the environmental reservoir. This will generally be proportional to the rate of contact between the two. Similarly, α characterizes the strength of interaction between infected hosts I and the environmental reservoir, and is also generally proportional to the contact rate between the two. α and β will generally have incorporated in them a factor that characterizes the transmissibility of the infection, either from host to reservoir or from reservoir to host. ν represents the fractional recovery rate, π_W is the birthrate of new uninfected environmental agents and k is the fractional death rate of environmental agents.

C. W.A.I.T. framework influences the basic reproductive number in a standard SIR model

Next, we briefly consider how the value of the basic reproductive ratio R_0 in this model compares to its SIR counterpart. While R_0 can have different theoretical formulations, we rely on definitions as provided by Jones (2007) [42] and Diekmann and colleagues (2009) [43]. In a density-dependent SIR model with constant birth of susceptible hosts π_S and death rate proportional to the host population $-\mu S$, the R_0 value is given by:

$$R_0^{SIR} = \frac{\beta \pi_S}{\nu \mu} \quad (6)$$

or sometimes, more simply, $R_0^{SIR} = \beta/\nu$, depending on the form of the SIR equations used, e.g. frequency-dependent, constant population, etc. β in this equation is the traditional transmission coefficient. It represents the coupling strength between infected and uninfected hosts, two non-environmental agents. Whereas, in the W.A.I.T. model, what is analogous to β is a pair of parameters α *and* β, which govern the interaction strengths between hosts and the environment. π_S, μ and ν have the same interpretation as in the W.A.I.T. model.

In the case of the W.A.I.T. iteration, the value of R_0 takes the form:

$$R_0^{WAIT} = \sqrt{\frac{\alpha \beta \pi_S}{\mu(\mu + \nu)\pi_W}}. \quad (7)$$

There are some notable differences in the R_0 formulae of the SIR and W.A.I.T. models: the square root in the W.A.I.T. version arises as a consequence of implementing two infected agents (I and W_i) into the model, as opposed to just one in the SIR case. Next, one notices that the β factor in the SIR formula is augmented by the additional factor α in the W.A.I.T. formula, representing a kind of shared dependence between the couplings controlling the I-interaction (α) and the S-interaction (β), with the environment. Analogously, what was the responsibility of π_S in the SIR formula, now presents itself as a shared dependence, π_S/π_W, the ratio of the birthrate of susceptible hosts to that of uninfected environmental agents. In this case, the two appear as a ratio under the square root, as opposed to a product in the $\alpha\beta$ case, indicating that whereas α and β contribute to R_0 in the same way, π_S and π_W contribute in opposite ways: when π_S is increased, R_0 increases, but when π_W is increased, R_0 decreases.

It is possible to view R_0^{WAIT} as a geometric mean of two R_0 values. Namely, there is the reproductive ratio associated with the number of secondary host infections caused by a single infected environmental agent, and there is the reproductive ratio associated with the number of secondary environmental agent infections caused by a single infected host. We denote the former by R_0^H and the latter by R_0^W (H for hosts and W for the W.A.I.T. compartment). From equations 1–5, one can see that the rate of new host infection due to infected environmental agents W_i is given by $\beta S W_i/(W_i + W_u)$. Near the disease-free equilibrium (DFE), $S \approx \pi_S/\mu$ and $W_i/(W_i + W_u) \approx k W_i/\pi_W$ (near the DFE, $W_i << W_u$), which implies that near the DFE, the rate of new host infection per *infected* environmental agent is $\approx \beta \pi_S k/(\mu \pi_W)$. The average amount of time an infected environmental agent remains infected is $1/k$, i.e. the reciprocal of the exit rate of the infected state. Thus, the number of new host infections caused by an infected environmental agent in the time that the agent is infected, and while the system is near the DFE, is given by $\beta \pi_S k/(\mu \pi_W) \times 1/k = \beta \pi_S/(\mu \pi_W)$. That is,

$$R_0^H = \frac{\beta \pi_S}{\mu \pi_W} \quad (8)$$

Similarly, the rate of new infection of environmental agents, caused by infected hosts, is given by $\alpha I W_u/(W_i + W_u)$. Near the DFE, this rate, per infected host, is $\approx \alpha$ (since $W_u/(W_i + W_u) \approx 1$), and the average time that an infected host remains infected is given by $1/(\mu+\nu)$, the reciprocal of the exit rate of the infected state. Thus, the number of new environmental agent infections caused by an infected host in the time that the host is infected (near the DFE) is given by,

$$R_0^W = \frac{\alpha}{\mu + \nu} \quad (9)$$

One can see that the the value of R_0 given in equation (7) is the geometric mean of the two R_0 values calculated above,

$$R_0^{WAIT} = \sqrt{\frac{\beta\pi_S}{\mu\pi_W}} \times \sqrt{\frac{\alpha}{\mu+\nu}} = \sqrt{R_0^H R_0^W} \tag{10}$$

From this perspective, one can observe how a characteristic feature of the epidemic is modified by *indirect* transmission. By stressing the role of environmental reservoirs, this modelling perspective has the capacity to dissect properties of dynamics that other models may omit.

III. THE HEPATITIS C VIRUS MODEL

A. Description

Our HCV model represents an adaptation of the adapted SIR W.A.I.T. model outlined in section II, but engineered around the particulars of HCV. Our model simulates a population of approximately 170,000 individuals—based on estimates of the size of the injection-drug user (IDU) community in New York City [44]—where infected injection drug users may migrate into the population. In this model, injection paraphernalia serve as the environmental reservoir for HCV and the sharing of this equipment will constitute the means of transmitting new infections. While the entirety of injection paraphernalia might contain other components, many parameters in this model are based on the use of needle and syringe as the instrument of injection and sharing. Consequently, we use the term "needle" in this manuscript as a synecdoche for the entire injection apparatus. It is also important to note that HCV can be transmitted sexually [45], but in this study we restrict our attention to transmission through infected needles. This main text focuses on the main structure and dynamical properties of the model. Further model details and discussion can be found in the Supplemental Appendix.

B. HCV W.A.I.T. model: Compartmental diagram

We model the dynamics of needle populations and injection drug users through a series of five ordinary differential equations. The compartments, labeled S, I_E, I_L, N_u and N_i represent the populations of susceptible individuals, early-stage infected individuals (acute HCV infection), late-stage infected individuals (chronic HCV infection), uninfected needles and infected needles, respectively. Here, we refer to all needles in circulation within the entire IDU community. This model is defined by several features:

- The susceptible compartment refers to individuals who are injecting drugs and who are sharing needles with other members in the IDU community.
- The needle population is divided into two compartments: infected and uninfected, and we model the dynamics of each compartment separately. This is analogous to the W_i and W_u terms discussed in the preliminary model.
- New infections (of both hosts and needles) will depend on the *fraction* of infected or uninfected needles in circulation.
- Newly infected individuals enter the early-stage compartment I_E first before either spontaneously clearing the infection or moving into the late-stage compartment I_L, from which we assume no spontaneous clearance occurs—individuals may leave I_L either by treatment or death only, since cases of spontaneously clearing *chronic* HCV are rare.
- There are various estimates for the ability of HCV to survive in needles [46] [47]. We incorporate HCV free-living survival via the parameter ϵ, which quantifies the rate at which the virus decays on infected needles.

C. HCV W.A.I.T. model: Analytic equations and parameters

The dynamics of the HCV transmission process are governed by equations 11–15. The population of individuals that are being treated and those who have recovered are not explicitly modeled in this iteration, as the dynamics of treatment and recovery are not central to the questions explored in this study. There are, however, several modeling studies of HCV that focus on treatment [26]–[28], [48], and their effects are not ignored in the HCV W.A.I.T. model. Entering treatment (and re-entering the susceptible population, as in case of drug relapse in the IDU population) are incorporated via removal terms $-\tau I_L$ and $-\tau I_E$ and the susceptible "birth" term π_S.

$$\frac{dS}{dt} = \pi_S + \phi(I_E + I_L) - \beta S \frac{N_i}{N_i + N_u} - \mu S \tag{11}$$

$$\frac{dI_E}{dt} = \beta S \frac{N_i}{N_i + N_u} - (\omega + \tau + \mu + \phi) I_E \tag{12}$$

$$\frac{dI_L}{dt} = \omega I_E - (\mu + \tau) I_L \tag{13}$$

$$\frac{dN_u}{dt} = \pi_N - \alpha(I_E + I_L)\frac{N_u}{N_i + N_u} - k_u N_u + \epsilon N_i \tag{14}$$

$$\frac{dN_i}{dt} = \alpha(I_E + I_L)\frac{N_u}{N_i + N_u} - k_i N_i - \epsilon N_i \tag{15}$$

π_S is the birthrate of new members into the community of IDUs either via migration, first-time use, or recovery *from* treatment—not from spontaneous *self-clearance*. ϕ represents the daily fractional rate that individuals infected with HCV spontaneously clear the infection. α represents the per capita injection rate, scaled by the fraction of injection events by infected users that render a needle infectious. β represents the per capita injection rate, scaled by the fraction of injection events with an infected needle that leave a susceptible host infectious. μ is the combined fractional death and IDU-cessation rate (individuals who leave the IDU community). ω is the daily fractional rate that early-stage infected individuals progress to the late-stage of infection. τ is the daily fractional rate that infected individuals go into treatment. π_N is the rate of introduction of uninfected needles into the IDU population. k_u is the daily fractional discard rate of uninfected needles. k_i is the daily fractional discard rate of infected needles. Lastly, ϵ is the daily fractional rate that infected needles clear the infection due to

de-activation (or "death") of virus populations on the needle. Parameter values and sources can be seen in Table I.

D. HCV W.A.I.T. model parameters influence the R_0

Having constructed and elaborated on the details of the HCV W.A.I.T. model, we now explore how parameters related to the environmental reservoir (in this case, those framing the population of infected needles) influence the R_0. We directly measured the influence of parameters on the R_0 by considering the *Partial Rank Correlation Coefficient* (PRCC), discussed below. The value of R_0 was calculated using established methods [42], [43] and is outlined in the Supplemental Appendix.

$$R_0 = \sqrt{\frac{\alpha\beta k_u \pi_S(\mu+\tau+\omega)}{\pi_N \mu(\epsilon+k_i)(\mu+\tau)(\mu+\tau+\phi+\omega)}} \tag{16}$$

We emphasize that in a manner analogous to our example discussed in earlier (Section II), we can regard our R_0 value as a geometric mean of two other R_0 values:

$$R_0 = \sqrt{\frac{\alpha(\mu+\tau+\omega)}{(\mu+\tau)(\mu+\tau+\phi+\omega)}} \times \sqrt{\frac{\beta k_u \pi_S}{\mu(\epsilon+k_i)\pi_N}} \tag{17}$$

The left-most factor (under the square root) can be interpreted as the number of secondary infections of *needles* in the average time that a *host* is infected (near the DFE), and the right-most factor can be regarded as the number of secondary infections of *hosts* in the average time that a *needle* remains infected. Further discussion of this result can be found in the Supplemental Appendix. As with traditional values of R_0, we find that our value is consistent with the statement that $sign(R_0-1) = sign(\lambda)$, where λ is the maximal eigenvalue of the Jacobian of the infected subsystem—composed of the infected compartments of the ODE system: I_E, I_L, and N_i—calculated at the DFE (all eigenvalues of the Jacobian were real-valued). This shows that the DFE is unstable when $R_0 > 1$.

We determine the sensitivities of our parameters on the value of R_0 by calculating the partial rank correlation coefficient (PRCC) with respect to equation 16—we base our calculation of PRCC on methods used in prior studies [49]. We find that parameters related to an interaction with the environmental reservoir (the population of needles) such as α and β, the couplings between hosts and needles, are at least as central to HCV dynamics as parameters traditionally associated with an epidemic, such as π_S, the birthrate of susceptibles, μ, the combined death and cessation rate of IDUs and τ, the rate of progressing to treatment (Figure 3). This fortifies the notion that W.A.I.T.-specific properties dictate the spread of HCV, providing opportunities to explore more precise targeting by public health interventions.

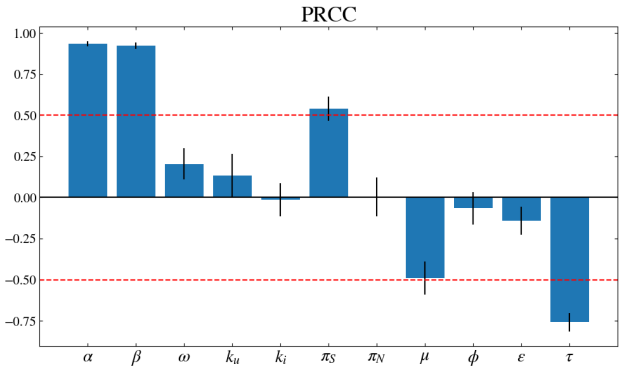

Fig. 3: **R_0 sensitivity in HCV: the Partial Rank Correlation Coefficient (PRCC)**. A PRCC calculation was performed for R_0 using Latin Hypercube Sampling. Parameters were sampled from uniform distributions with widths specified by the ranges given in Table I. The PRCC calculation was repeated for 50 independent iterations. The averages of these iterations are shown here, with the standard deviations for each parameter shown as the error bars.

E. HCV W.A.I.T. model and simulated interventions: needle-exchange programs

Having demonstrated the relevance of injection drug equipment in terms of how it influences the basic reproductive number, we can consider the utility of the model with respect to other properties, including how it offers insight into potential interventions.

One such intervention may be the implementation of needle-exchange programs. Needle-exchange programs are an example of "harm reduction" public health strategies that aim to reduce harm stemming from behaviors that put the affected individuals or communities at risk [50]. These policies can be contentious, but have been demonstrated to be effective interventions for HIV and HCV in certain settings [39]. With respect to the HCV W.A.I.T. model, some of these programs (especially ones targeting injection equipment, like safe injection sites) can increase the discard rate of infected needles by providing a safe location to use and discard needles, while also providing uninfected needles to IDUs. In our model, parameters like the needle discard rate, k_i and k_u, the transfer rate of needles from the infected state to the uninfected one ϵ and the dispersal rate of clean needles π_N are affected by needle exchange programs. Figure 4 demonstrates how R_0 is affected by these parameters. In the left figure, one can see that R_0 can be reduced by increasing k_i—the infected needle discard rate—along a fixed value of π_N—the birthrate of uninfected needles—and that increasing π_N along a fixed value of k_i has the same effect. It is also evident that R_0 can be reduced more rapidly by increasing k_i and π_N simultaneously, as expected. In this way, the proportion of infected needles is reduced because of an increase in clean needles and a reduction of infected ones, lowering R_0.

In the right panel in Figure 4, we demonstrate how changing k_u and k_i modifies the value of R_0. Notice that R_0

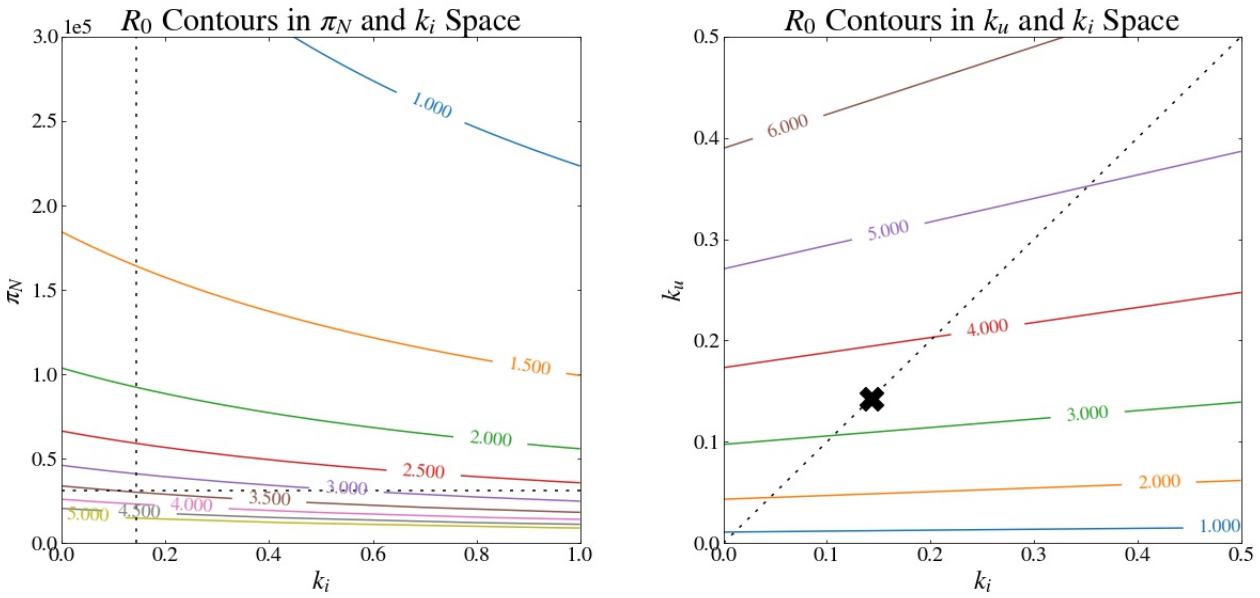

Fig. 4: **HCV R_0 as a function of various model features**. **Left**: The relationship between the rate of acquisition of clean needles π_N and the discard rate of infected needles k_i with respect to various values of R_0. The curves are contours of R_0 and are labelled as such. The vertical and horizontal dashed lines indicate the chosen values for their respective parameters. **Right**: The relationship between the infected and uninfected needle discard rate, with respect to R_0. The diagonal line represents where $k_u = k_i$. The "x" indicates the value chosen for k_u and k_i in the model (we set $k_u = k_i$ in the model). Notice that moving upwards along this diagonal increases R_0.

is reduced by increasing k_i across fixed values of k_u, and the opposite effect—increasing the R_0—is observed when increasing k_u along fixed values of k_i. That is, removing infected needles at an increased rate may decrease infection risk in a population of IDUs, while removing uninfected needles can increase the risk. One can also see that increasing k_u and k_i simultaneously, along the dashed line—where $k_u = k_i$—will increase R_0. Evidently, for the parameters chosen in this model, removing needles from a population, without taking care to distinguish between infected and uninfected types, can potentially exacerbate an epidemic.

Next, we considered how certain interventions can modify the transfer rate of needles from infected to uninfected states, through modifying the ϵ parameter in our study (Figure 5). A high ϵ value would indicate a scenario where needles move quickly from an infected state to an uninfected state. This would apply to settings where viral decay on a needle is high, or when infected needles are directly exchanged for uninfected ones (as in certain needle exchange programs). The model is run with all uninfected populations initialized at their disease free equilibrium values ($S = 170,000$ and $N_u = 220,000$), and we initialize $I_E = N_u = 1$, and $I_L = 0$. In the high ϵ scenario, we observe generally slower dynamics and higher overall susceptible population sizes, along with lower infected populations (on long time scales).

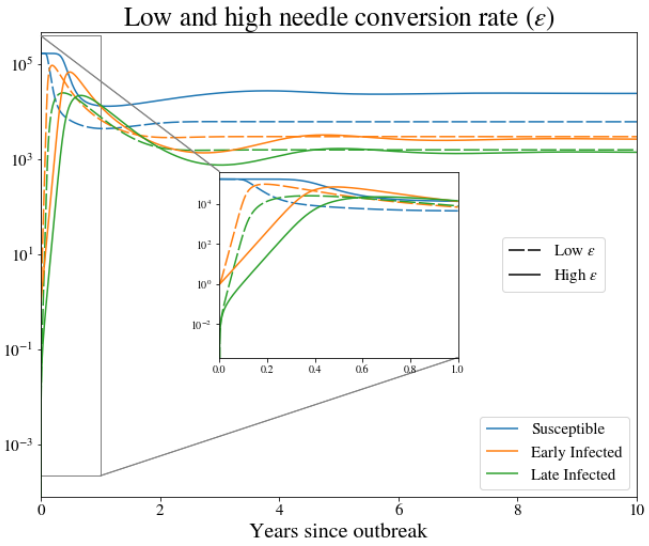

Fig. 5: The dynamics of susceptible (blue), early-infected (orange), and late-infected (green) populations in two parameter regimes: high and low ϵ, the conversion rate of needles from infected to uninfected. The solid lines represent the dynamics for $\epsilon = 2$ day^{-1} (high ϵ), and dashed lines are the dynamics for $\epsilon = 0.33$ day^{-1} (low ϵ). In the high-ϵ regime, we find that the susceptible population at equilibrium is ≈ 4 times that of the low-ϵ regime, and the infected populations are each $\approx 89\%$ of the their low-ϵ counterparts at equilibrium (note the log scale on the y-axis).

Label	Value	Units	Description	Sources
π_S	47 ± 10	*person / day*	Birthrate of susceptibles (chosen to keep $\pi_N/\mu \approx 170,000$)	Estimate
ϕ	$(4.7 \pm 0.5) \cdot 10^{-3}$	*% / day*	Daily fractional self-clearance rate	[26] [51]
α	4 ± 3	$injections/(person \cdot day)$	Injection rate times infection of needle probability	[52]
β	0.072 ± 0.05	$injections/(person \cdot day)$	Injection rate times infection of host rate	[53]
μ	$(2.7 \pm 0.5) \cdot 10^{-4}$	*% / day*	Fractional rate of removal from IDU community due to cessation & death	[54]
ω	0.006 ± 0.005	*% / day*	Fractional transfer rate into late-stage infection	[55] [56]
τ	0.011 ± 0.005	*% / day*	Fractional rate of entering treatment	[57] [58]
π_N	$(3.14 \pm 0.01) \cdot 10^4$	*needles / day*	Birthrate of uninfected needles (chosen to keep $\pi_N/k_u \approx 220,000$)	[59] [60]
k_u	0.143 ± 0.005	*% / day*	Fractional discard rate of uninfected needles	Estimate
k_i	0.143 ± 0.005	*% / day*	Fractional discard rate of infected needles	Estimate
ϵ	1.17 ± 0.05	*% / day*	Fractional decay rate of HCV infection in needles	[47]

TABLE I: HCV model parameters

IV. DISCUSSION

While diseases transmitted through injection drug use have been the object of prior modeling efforts, none have specifically investigated how injection equipment plays a role in the dynamics of HCV. Prior models of injection equipment have focused on HIV [24], [25], and/or been so complicated that their structure is not easily translated to any other settings [23]. In this study, we model HCV as an indirectly transmitted infection, where the injection equipment is modeled as the environmental reservoir, just as a water source might be modeled in a waterborne infection [8], [19]. We label our approach as the "Waterborne, abiotic and other indirectly transmitted" (W.A.I.T.) model, one that incorporates features of other approaches to studying environmentally transmitted pathogens [6], [11], but grounding them in a fungible model that can be neatly applied to HCV. Our approach offers several specific insights. For example, we demonstrate that the composite R_0 that defines the entire dynamical system is the product of the geometric mean of the R_0 used to describe each of two sub-components: disease flow through the hosts and flow through the injection equipment (equation 10). This observation offers a practical suggestion for studying diseases like HCV: epidemiologists and modelers must understand, through empirical studies, properties of all major actors in the system (hosts and environmental injection drug equipment in the case of HCV).

The mathematical model of HCV presented in this manuscript (described as a W.A.I.T. model; see sections II and III) also offers nuanced findings about the dynamics of disease. Firstly, our model highlights the differing roles of uninfected and infected injection on disease dynamics. Specifically, the model speaks to the potential utility of harm reduction policies: indiscriminately removing injection equipment from a system—without an overall shift in needle populations from infected to uninfected—might increase the rate of infection. In order to attenuate an epidemic, intervention strategies should focus on steering the population of needles towards being more uninfected. Therefore, ideal intervention efforts should aim to decrease sharing events on an infected needle. This helps to explain why programs like safe injection might be effective [61]: they don't change the number of infected needles in the system directly, but can alter the sharing rate, and consequently, the probability of sharing an infected needle.

Finally, understanding the dynamical properties of disease transmitted through injection drug use is now especially relevant as a result of the modern opioid epidemic. This epidemic is typified by use of prescription and illicit opioids recreationally, with injection drug use being a major route through which drugs are consumed [41]. The relevance of viral diseases among opioid users gained national attention during a 2015 outbreak of HIV in rural Indiana that was driven by an injected opioid called oxymorphone [62], [63]. This outbreak raised alarms in the public health community, and officials are increasingly aware of the potential for future outbreaks. However, it wasn't until relatively recently that the role of the opioid crisis in Hepatitis C virus transmission has been examined [64], [65]. We propose, in closing, that modeling approaches (in general, and not necessarily similar to the proposed methods proposed) are crucial for understanding, attenuating or preventing explosive outbreaks of HCV in an age when a new opioid epidemic has emerged.

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CODE AVAILABILITY

Code for the mathematical models presented in this manuscript are available on GitHub (https://github.com/ogplexus/WAIT).

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