Modeling hepatitis C virus transmission among people who inject drugs: Assumptions, limitations and future challenges

Nick Scott¹,², Margaret Hellard¹,²,³, and Emma Sue McBryde¹,⁴,⁵,*

¹Centre for Population Health; Burnet Institute; Melbourne, VIC Australia; ²Department of Epidemiology and Preventive Medicine; Monash University; Clayton, VIC Australia; ³Infectious Disease Unit; The Alfred Hospital; Melbourne, VIC Australia; ⁴Department of Medicine; The University of Melbourne, Parkville; VIC Australia; ⁵Australian Institute of Tropical Health and Medicine; James Cook University; Townsville, QLD Australia

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The discovery of highly effective hepatitis C virus (HCV) treatments has led to discussion of elimination and intensified interest in models of HCV transmission. In developed settings, HCV disproportionately affects people who inject drugs (PWID), and models are typically used to provide an evidence base for the effectiveness of interventions such as needle and syringe programs, opioid substitution therapy and more recently treating PWID with new generation therapies to achieve specific reductions in prevalence and / or incidence. This manuscript reviews deterministic compartmental S-I, deterministic compartmental S-I-S and network-based transmission models of HCV among PWID. We detail typical assumptions made when modeling injecting risk behavior, virus transmission, treatment and re-infection and how they correspond with available evidence and empirical data.

Introduction

Hepatitis C virus (HCV) is a major global health problem affecting approximately 170 million people worldwide causing significant morbidity and mortality.¹ Treatment for chronic HCV has been available for some time, however with low cure rates (30–80%, depending on genotype) and significant side effects,²,³ treatment uptake has been low.⁴–⁷ Recently, ‘direct-acting antiviral’ (DAA) treatments have become available that are highly tolerable and have greater than 90% efficacy,⁸–¹⁰ offering hope to reduce the future burden of disease. At the same time, a number of HCV vaccines are also currently in development,¹¹ creating discussion on what their role might be in eliminating HCV transmission as a public health problem.¹²

HCV is transmitted via exposure to infected blood, most commonly through intravenous drug use, blood transfusions, organ transplants, from mother-to-child or through sexual contact,¹³ although the sexual transmission of HCV is very inefficient outside the setting of HIV.¹⁴,¹⁵ In developed settings blood screening and healthcare practices have virtually eliminated iatrogenic spread, meaning that HCV transmission occurs almost exclusively among people who inject drugs (PWID).¹,¹⁶–¹⁸ Compared to the estimated world-wide HCV prevalence of 2–3%,¹⁹ the prevalence of HCV among PWID ranges from 10% to 97% globally,¹⁸,²⁰ and is estimated to be greater than 50% in many countries.²⁰ As a result, modeling studies that investigate ways to slow the HCV epidemic or reduce the number of incident cases focus on PWID, because this is where interventions are likely to have the most significant impact on the overall future burden of disease.²¹

Once infected with HCV, an estimated 26% of people spontaneously clear the virus,²² typically within a 6 month asymptomatic ‘acute’ phase.²³ Individuals who fail to clear their HCV infections may remain asymptomatic for many years, yet face substantial risk of liver disease.²⁴ Chronic HCV infection has been attributable to approximately 27% of cirrhosis cases and 25% of hepatocellular carcinoma cases worldwide,²⁵ and given the slow rates of liver disease progression and peaks in transmission that occurred in the 1990s, many countries are yet to experience the full burden of HCV-related liver disease.²⁶

Since its was first isolated in 1989,²⁷ HCV has been the topic of many modeling studies. This review looks at transmission models of HCV among PWID, focusing on assumptions that are made about the population at risk and transmission of the virus and how they correspond with empirical data. These models are particularly relevant for developed settings, and are typically used to provide an evidence base for the effectiveness of public health interventions such as needle and syringe programs (NSPs), opioid substitution therapy (OST) and more recently treating PWID with DAA.

S-I Models

Deterministic compartmental S-I models of HCV transmission among people who inject drugs

One of the most basic models of HCV transmission involves classifying PWID into 2 compartments: susceptible (S), or chronically infected (I). PWID enter this model (start their
injecting career) in the S compartment, possibly move from the S to the I compartment (if they become infected), and eventually leave (end their injecting career) from either compartment. These movements—in particular becoming infected—can be described by either an ordinary differential equation (ODE) or by a probabilistic ('stochastic') mechanism. Models described by ODEs are referred to as deterministic, since for given initial conditions the outcomes are always the same. Stochastic models are appropriate for modeling the initial spread of a disease through a population or for modeling small numbers of people—for example an infectious disease outbreak within a single hospital, where probabilistic transmission plays an important role—while deterministic models are appropriate for well-established epidemics and larger scales. Because HCV is approximately endemic among PWID in most countries, deterministic approaches are suitable and hence typically used.

**Population characteristics**

Deterministic compartmental models of HCV transmission among PWID necessarily include, sometimes implicitly, a minimum of 3 features describing the population: 1) the duration of PWID; at risk of infection or transmission (the ‘length of injecting career’); 2) the injecting risk behavior of PWID during this period (assumptions about the frequency of injecting, frequency of sharing and the characteristics of injecting networks); and 3) the transmissibility of HCV among PWID (the transmission risk per ‘sharing’ event between discordant individuals). The third feature is typically used, in conjunction with the first 2, to calibrate chronic prevalence in the model and is discussed in the next section. The illict nature and stigmatisation of injecting drug use make these parameters challenging to determine through epidemiological studies: it is difficult to recruit representative samples of PWID; sharing of injecting paraphernalia may be underreported; and drug markets frequently change, leading to different consumption patterns. Moreover, where estimates are available they are unlikely to extend to different settings due to cultural or socio-demographic differences.

There is considerable variation in the length of injecting careers around the world, ranging from a short time period up to 30 years prior to cessation. Individuals may also go through periods of cessation and relapse within their injecting careers. This variation in injecting length and cycling in and out of injecting is an issue, as many deterministic models assume a constant rate of flow out of the model that is based on a single estimate for the length of injecting career—usually assumed to be an average of between 7 and 14 years, depending on setting—producing outcomes that are sensitive to this parameter. Injecting risk behavior is also difficult to measure. Firstly, individuals cycles through periods of high and low injecting frequency. Secondly, injecting paraphernalia is mostly shared through social networks, in particular with current sex partners. Both of these factors make the risk of transmission per injection highly heterogeneous and dynamic across the population. To address this, deterministic models often approximate risk heterogeneity dichotomously (or categorically) by including ‘high risk’ and ‘low risk’ PWID. This involves estimating a relative risk factor and allowing individuals to continuously cycle between risk groups. Some degree of assortative mixing is also often used to approximate social groups, but ultimately deterministic models are based on restrictive assumptions about risk behaviours and mixing of PWID. This may be reasonable for estimating injecting frequency in the absence of treatment programs such as OST, which have been shown to reduce injecting frequency and sharing risk; the average injecting frequency may be fairly constant. However, deterministic models are limited in their ability to approximate injecting risk (i.e. the number and turnover of sharing partners), as they are unable to capture the properties of injecting networks that have been shown to be important for blood borne virus transmission.

**Transmission**

Transmission is generally modeled to occur only through ‘sharing’, the quantitation of which can be imprecise given the number of ways in which injecting equipment can be shared or (imperfectly) cleaned before re-use. Clinically the risk of acquiring HCV per needle stick injury is at least roughly known (0.31% per event), however this is also likely to depend on the strain of the virus, but the ambiguity of a sharing event and difficulties estimating the frequency and characteristics of ‘sharing’ partners limit how these estimates can be used. However unlike transmission risk, it is much simpler to estimate chronic HCV prevalence—a model outcome. Data sources such as NSPs and cohort studies can objectively determine HCV prevalence among PWID where blood samples are taken, and estimates are available for many countries. Although sometimes the infectivity per sharing event is assumed and the resulting prevalence predicted, the more common approach is the reverse: the model is solved for a transmission parameter that—given the assumptions about the length of injecting career and injecting risk behavior—produces an equilibrium HCV prevalence matching what has been observed in epidemiological studies.

As an illustrative example, consider the following open deterministic S-I model. Let S be the proportion of the population who are susceptible, I be the proportion of the population who are infectious (so that $S + I = 1$), and assume an average length of injecting career $1/\mu$. This model is described by the equations

$$\begin{align*}
\frac{dS}{dt} &= \mu(S + I) - \beta SI - \mu S \\
\frac{dI}{dt} &= \beta SI - \mu I
\end{align*}
$$

(Equation 1)

that can be solved for an infection parameter $\beta$ that gives correct equilibrium prevalence ($I_\infty$): namely $\beta = \mu/(1 - I_\infty)$. A consequence of calibrating transmission this way is that the HCV epidemic is assumed to be in equilibrium prior to the implementation of any interventions. Modeling suggests that in developed settings HCV incidence has greatly reduced from a peak in the 1990s due to a combination of blood supply screening and harm reduction interventions such as NSPs, so that even if prevalence currently approximates an equilibrium, liver fibrosis and disease stage among the aging chronically infected
population does not. For models that compare strategies for reducing prevalence by means of reducing incidence—such as NSP or OST implementation or scale up—this may be appropriate. However many cost-effectiveness analyses require further disaggregation of chronic infection, given the slow disease progression and the differences in care and quality of life for later stages of fibrosis. Where these models estimate the total costs of future healthcare they should consider how the burden of disease is changing.

S-I-S Models

Deterministic compartmental S-I-S models: including treatment

Deterministic compartmental S-I-S models extend the S-I model by allowing the possibility of infected individuals returning to the susceptible compartment, for example through treatment. Although the S-I-S model assumes treated individuals are identical to infection naive individuals, there are many variations that do not. In general, complete or partial immunity after treatment can be modeled by including a recovered (R) compartment (the S-I-R or S-I-R-S models), but for HCV even though some immunity has been observed following clearance of infection, it is uncertain how long is currently unclear, making the S-I-S model an appropriate way to include treatment.

Modeling treatment numbers

With the advent of DAAs, models must realistically include a treatment feature—firstly to reduce the morbidity and mortality associated with HCV, and secondly because of the potential impact of ‘treatment as prevention’ (TasP). The usual approach is to implement treatment rates that are proportional to the total PWID population size (which may include a period of scale up) rather than the total infected population. For example, treatment rates of 40/1000 PWID per year might be assumed, which represents the maximum number of PWID (less if there are not enough people infected) who are moved from the I compartment to the S compartment each year. This is a more plausible assumption than the alternative: if treatment rates were assumed to be proportional to the size of the infected population, for example 2% of infected PWID per year, this would imply the bulk of infrastructure requirements would be in initial rather than later years, but the generally low engagement of PWID in care makes this scenario unrealistic for HCV treatment.

A consequence of assuming treatment rates that are proportional to the total population is that the epidemic can collapse quickly once treatment numbers pass a critical threshold, compared to if treatments were given to a proportion of the infected population which has slower and more asymptotic effects.

Modeling re-infection

Models that include treatment must make assumptions about re-infection. High rates of re-infection have been documented among PWID, however it is difficult to estimate as it requires frequent testing of large cohorts of PWID. Further, it is not always clear what is meant by re-infection. Biologically re-infection is defined as an initial infection being completely resolved prior to a subsequent infection, and requires discrimination from an individual’s infection relapsing. Viral sequencing can be necessary to distinguish examples such as an individual having only one strain of a co-infection (simultaneous acquisition of 2 or more HCV strains) cured. Deterministic compartmental S-I-S models rarely include this level of complexity, and as a result re-infection is usually assumed to occur at the same rate as initial infection. These rates should be interpreted with caution, since as discussed above, models often use the infection parameter to calibrate the model prevalence.

Network models

Network models portray individuals as a set of vertices (‘nodes’) of a graph, with edges connecting 2 nodes if the corresponding individuals have some non-zero probability of disease transmission. For example, for HCV transmission among PWID, edges may exist between partners, members of the same social network or current inmates of the same prison. The network structure removes many of the restrictive assumptions of deterministic models: network models no longer rely on perfect mixing and can incorporate large amounts of heterogeneity among individuals. This has been a successful approach to modeling the HIV epidemic, establishing the importance of social ties and networks among PWID for prevention strategies.

Estimating network structure

Estimating the network structure underlying these types of models remains difficult. Surveys of PWID struggle to gain information beyond the nodal degree of the respondent (the number of people they have shared equipment with) and the basic characteristics of nearest neighbors, and can experience reporting bias due to the stigmatisation of injecting risk behaviors. Further, the ‘hidden’ nature and high incarceration rate of PWID means that disruptions and changes to social networks are substantial. This dynamic nature of injecting networks is thought to play an important role in transmission, in addition to its structure.

It is often assumed that the injecting networks of PWID can be modeled using Exponential Random Graph Models with social circuit dependence. With this assumption, survey data collected through cohort studies and samples of PWID can be used to estimate features of the larger injecting networks from which the respondents come, and this technique has been successfully used to model the spread of infectious disease among PWID. However, given the underreporting of sharing and imperfect abilities of surveys to capture network structure, modeling closed networks of PWID is unrealistic, and efforts to calibrate transmission to achieve initial prevalence have previously relied on some ‘infection import’ probabilities. The importation of infections is required because the closed network
cannot explain the incidence data and the imported cases represent unobserved processes not captured by the network data. Currently these type of models also assume a static network structure, and further work is required to test how the temporal nature of social networks influences transmission and interventions. Nevertheless, network models of HCV transmission have shown that the injecting network itself plays an important role in transmission, and that significant reductions can be made if needle sharing is confined to one person.

**Implementing interventions**

Assumptions about how interventions are implemented are also important for network models. For example, interventions such as TasP have been shown to be more effective when network dependent approaches are taken, such as when PWID and their immediate injecting network are treated together—a ‘treat-your-friends’ strategy—rather than treating PWID individually. Using network-based strategies for public health interventions in this way is not new, and underpins the contact tracing strategy used to treat and control sexually transmitted infections (STIs). The difference is that instead of aiming to protect the health of an individual’s past network, treat-your-friends aims to protect an individual from re-infection through their current network. Interventions involving current injecting networks of PWID are likely to be more effective for HCV than for STIs because firstly, the prevalence of HCV among PWID is much higher than the prevalence of many STIs in the community—meaning that reinfection plays a much more significant role in the HCV epidemic that it does for STIs—and secondly, the hidden nature and stigmatisation of injecting drug use make contact tracing a difficult exercise in practice. Network models are an extremely useful tool for testing these ideas.

**Sensitivities**

Outcomes of models and their sensitivities to underlying assumptions

Models of HCV transmission are typically used to estimate the benefits of interventions, for example the effects of reducing syringe sharing, or combinations of OST and NSP. The high cost of new treatments has led to much recent focus on the benefits that can be gained by treating PWID, in particular given the possibility of re-infection and need for re-treatment. This has been looked at from a healthcare cost-effectiveness perspective, and alternatively by estimating the number of onwards transmissions that a cured individual will no longer cause. The latter is a part of the TasP concept that has featured prominently in global HIV policy. Typically, TasP models for HCV have been used to estimate the treatment rates required to achieve meaningful reductions in overall prevalence.

Although some vaccines are currently in development, their properties are unclear, as are their costs. Understanding how a vaccine’s properties and cost influence which HCV elimination strategies are the most cost-effective will be vital for future decision making, and models have been used to estimate how effective a vaccine would need to be to be useful, what a vaccine might mean for the future burden of disease, what settings it would be most useful in, and whether or not this would be cost-effective compared to treatment.

**Sensitivity to length of injecting career**

Most of these outputs are sensitive to assumptions about the length of injecting career, since the method described for calibrating transmission means that the rate of infection is a function of the length of injecting career. For example, in Equation 1, \( \beta \propto \mu \). Hence doubling (or halving) the length of injecting career leads to a halving (or doubling) of the infection parameter, and hence of the incidence, while achieving the same equilibrium prevalence. The assumption of a long injecting career causes the epidemic in the model to be driven by longer chronic infections rather than by new cases, and has important implications for interventions: anything designed to reduce prevalence by reducing incidence, such as NSP and OST, will be more effective when the length of injecting career is shorter; while interventions for chronic infections such as treatment will be more effective where injecting careers are longer. Similarly, models that allow new population members to enter the model at a stage in which they are already infected require a lower force of infection to achieve equilibrium prevalence, and so will predict greater benefits for interventions such as treatment and reduced benefits for OST and NSP. This may be particularly evident in models that include injecting cessation and subsequent relapse, where a person can enter the model already HCV infected from their previous period of injecting, as opposed to new or naive PWID assumed to be HCV negative.

**Sensitivity to heterogeneity**

Model outputs are often sensitive to risk heterogeneity, both in terms of relative risk difference and the length of cycles between high and low risk behavior. For example, consider the following open deterministic S-I transmission model with injecting risk heterogeneity:

\[
\frac{dS_{\text{high}}}{dt} = \mu (S_{\text{high}} + I_{\text{high}}) - \beta \Psi S_{\text{high}} - \mu S_{\text{high}} \\
\frac{dS_{\text{low}}}{dt} = \mu (S_{\text{low}} + I_{\text{low}}) - \beta \Psi S_{\text{low}} - \mu S_{\text{low}} \\
\frac{dI_{\text{high}}}{dt} = \beta \Psi S_{\text{high}} - \mu I_{\text{high}} \\
\frac{dI_{\text{low}}}{dt} = \beta \Psi S_{\text{low}} - \mu I_{\text{low}}
\]

Here, PWID are categorised dichotomously as high or low injecting risk; with relative difference in transmission risk \( \Gamma \); are assumed to mix proportionally and not cycle between risk categories; and

\[
\Psi = \begin{cases} 
\Gamma (I_{\text{low}} + \Gamma I_{\text{high}}), & \text{high risk PWID} \\
(I_{\text{low}} + \Gamma I_{\text{high}}), & \text{low risk PWID}
\end{cases}
\]
is the force of infection with transmission parameter $\beta$ (to be calibrated). In this example $I_{\text{low}} + I_{\text{high}}$ represents the number of individuals who are infected in the effective population, $I_{\text{low}} + S_{\text{low}} + \Gamma(I_{\text{high}} + S_{\text{high}})$. This can also been interpreted as the number of contaminated syringes among all shared syringes. Calibrating $\beta$ to achieve the desired equilibrium prevalence gives $\beta$ as a decreasing function of both the length of injecting career and $\Gamma$ (Fig. 1).

Thus for a fixed population prevalence, as the injecting risk heterogeneity in the model increases, the transmission parameter decreases, which shifts the epidemic toward more chronic infections and again predicts greater benefits for treatment but reduced benefits for OST and NSPs. Conversely, if the above model were modified to allow PWID to cycle between risks categories, as the time spent in each category decreases, so does the heterogeneity of the model (as the risk is more evenly spread throughout the population and the virus can more easily reach the whole population). This has been found to predict reduced benefits of treatment and increased benefits of injecting risk targeted interventions.

There is some benefit in models being sensitive to these parameters. Since the length of injecting career and any heterogeneity is often implemented as an approximation to highly heterogeneous human behavior, they are almost always included in sensitivity analyses, and therefore have their impacts tested against the conclusions of the study.

**Challenges For The Future**

**Strains**

Since HCV was first isolated, 7 different genotypes and more than 50 subtypes have been identified circulating worldwide. Different strains of HCV have different subtype-specific transmission patterns, yet very little attention has been paid to multi-strain models. In particular, co-infection and superinfection (individuals with chronic HCV infection, who, after re-exposure to HCV, present with a new and different HCV viral strain) can have implications for the effectiveness of treatment interventions, which will become increasingly important with the emergence of drug-resistance.

**HCV and HIV co-infection**

HCV infected individuals are at high risk of acquiring HIV since both infections share transmission routes. Although the prevalence of HCV/HIV co-infection among HCV infected PWID varies considerably globally, it is estimated to be as high as 95% in many Asian countries. This is important because HCV/HIV co-infection can significantly change the dynamics of the HCV epidemic: infection with HIV reduces the likelihood of spontaneously clearing a newly acquired HCV infection, accelerates the progression of HCV-related liver cirrhosis, and leads to more rapid death from end stage liver disease. Given the current lack of empirical data on the dynamics of co-infection, the best approach to simultaneously model HCV and HIV is not so clear; however, with increasingly sophisticated surveillance systems being implemented in many countries this is likely to be an important area for future work. In particular, co-infection models have already provided insight into the extent of the sexual transmission of HIV and have helped to better understand the impacts of NSPs on prevalence and the effectiveness of HCV treatments.

**Compartmental versus network based models**

Compartmental models are typically used because network level data is expensive to collect and often unavailable for the desired setting. This makes it important to understand when they make similar predictions and whether it is possible to make reasonable adjustments so that the models are more comparable. This is an active field of research and the relationships between different types of models are highly dependent on the characteristics of the disease and population being modeled.

For example, compartmental models have been developed that approximate the effects of a sexual partner network on STI transmission, but the approximation breaks down as population heterogeneity increases. For this reason there would be benefit to investigating, in the specific context of HCV, the size and direction of errors when compartmental models are used to approximate what is predominately a network problem. Although this would require extensive data to parametrise both types of models, it may enable future studies to know when compartmental models could be used to approximate the results of network models without having to collect empiric network data. This could

![Image](57x545 to 393x721)
significantly increase the accuracy and reduce the costs of future projects.

**Conclusion**

With HCV recently considered ‘curable’ due to advancements in DAA therapy, modeling public health responses to HCV among PWID is, and will continue to be, an active area of research. Better understanding of injecting careers, injecting equipment sharing and injecting networks is required in order to improve the accuracy of these models. Empirical studies suggest that these parameters are enormously heterogeneous, yet they are often implemented as point values. Little is known of what this means for the predictions of the simple deterministic models that are commonly used. It is important to investigate what the potential inclusion of more accurate empirical data and more sophisticated mathematical models could mean for previous models’ predictions of HCV transmission.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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