Hepatitis C transmission and *treatment as prevention* – the role of the injecting network

Highlights

- Injecting networks powerfully influence HCV transmission; in particular, injecting relationships are strongly correlated with HCV transmission clusters.
- Real-world injecting networks restrict HCV transmission relative to the fully connected homogenous populations assumed in most models.
- Targeting treatment using a "bring your friends" approach is more effective than treating PWIDs randomly within the network. .

Key Words

Hepatitis C, injecting drug use, people who inject drugs, social network, injecting network

Abstract

Background

The hepatitis C virus (HCV) epidemic is a major health issue; in more developed countries it is driven by people who inject drugs (PWID). Injecting networks powerfully influence HCV

transmission. In this paper we provide an overview of 10 years of research into injecting networks and HCV, culminating in a network-based approach to provision of direct-acting antiviral therapy.

Methods

Between 2005 and 2010 we followed a cohort of 413 PWID, measuring HCV incidence, prevalence and injecting risk, including network-related factors. We developed an individual-based HCV transmission model, using it to simulate the spread of HCV through the empirical social network of PWID. In addition, we created an empirically grounded network model of injecting relationships using exponential random graph models (ERGMs), allowing simulation of realistic networks for investigating HCV treatment and intervention strategies. Our empirical work and modelling underpins the TAP study, which is examining the feasibility of community-based treatment of PWID with DAAs.

Results

We observed incidence rates of HCV primary infection and reinfection of 12.8 per 100 person-years (PY) (95%CI: 7.7–20.0) and 28.8 per 100 PY (95%CI: 15.0–55.4) respectively, and determined that HCV transmission clusters correlated with reported injecting relationships. Transmission modelling showed that the empirical network provided some protective effect, slowing HCV transmission compared to a fully connected, homogenous PWID population. Our ERGMs revealed that treating PWID and all their contacts was the most effective strategy and targeting treatment to infected PWID with the most contacts the least effective.

Conclusion

Networks-based approaches greatly increase understanding of HCV transmission and will inform the implementation of treatment as prevention using DAAs.

The hepatitis C virus (HCV) is a major health issue leading to significant morbidity and mortality, affecting an estimated 184 million people globally (Mohd Hanafiah, Groeger, Flaxman, & Wiersma, 2013). In more developed countries like Australia the epidemic is driven by people who inject drugs (PWID) (Mohd Hanafiah et al., 2013; Shepard, Finelli, & Alter, 2005). To reduce transmission of HCV it is important to understand the specific risk factors that drive it; some are individual behaviours like sharing needles and syringes, and others are related to the context in which injecting occurs (Morris et al., 2014). The injecting network – the pattern of relationships between people who inject drugs – is a contextual factor that powerfully influences HCV transmission.

For the past 10 years our group (comprising epidemiologists, immune-virologists, mathematical and network modellers and a team of field researchers experienced in working with PWID) has examined the role of the injecting network in influencing HCV transmission and explored network-related strategies to reduce disease transmission. This paper provides an overview of that research and briefly describes the Hepatitis C *Treatment and Prevention* (TAP) Study, which evaluates the effect of a network-based approach to provision of direct-acting antiviral (DAA) therapy on HCV prevalence and incidence.

Tracing HCV in networks of PWID

Between 2005 and 2010 we followed a cohort of PWID measuring HCV incidence, prevalence and injecting risk, including network-related factors (Aitken et al., 2008; Miller, Hellard, Bowden, Bharadwaj, & Aitken, 2009; Sacks-Davis et al., 2012). Four hundred and thirteen PWID were recruited to a longitudinal study of risk factors associated with the

transmission of hepatitis C, hepatitis B virus (HBV) and HIV. Participants completed detailed questionnaires on their drug use and risk behaviours, provided blood samples for serology testing, and were asked to nominate up to five injecting partners at each interview for the first three years of the study. Their nominated injecting partners were then recruited into the study (if possible) through direct introduction or data matching following independent encounters (Aitken et al., 2008; Sacks-Davis et al., 2012). The baseline prevalences of HCV, HBV and HIV were 70%, 34% and <1% respectively: the prevalences of HIV/HCV and HBV/HIV co-infection were <1% and 2% respectively (Miller et al., 2009). HCV primary infection and reinfection were examined in a subset of 188 participants; the incidence of primary infection was 12.8 per 100 person-years (PY) (95%CI: 7.7–20.0), reinfection was 28.8 per 100 PY (95%CI: 15.0–55.4) (Sacks-Davis et al., 2013).

We hypothesised that, within our cohort, HCV transmission occurred most often between people who reported injecting drugs together (at the same time, in the same space); this facilitates exposure to blood, and hence HCV, through needle-sharing and other behaviours. We studied HCV phylogeny within the cohort – that is, the genetic similarity (or relatedness) of the HCV sequences of our participants – and compared it with information about social-injecting relationships in the same group (Sacks-Davis et al., 2012). The phylogenetic component of the study used sequencing of the HCV core region. Genetic clusters were identified using bootstrapping (cut-off: 70%). An adjusted Jaccard similarity coefficient was used to measure the association between the reported injecting relationships and relationships defined by clustering in the phylogenetic analysis (We observed 244 HCV infections in 238 individuals (some were reinfections).. Overall, 16% of participants who were infected at

study entry and 40% of participants with newly acquired infections had molecular evidence of related infections with at least one injecting partner. A key finding was that likely transmission clusters identified in phylogenetic analysis correlated with reported injecting relationships (adjusted Jaccard coefficient: 0.300; $p<0.001$). Importantly, this was the first study to prove that HCV phylogeny was associated with the injecting network, highlighting its importance in HCV transmission (Sacks-Davis et al., 2012).

Modelling network influence on HCV transmission

In addition to establishing empirically that the social-injecting network was related to the HCV transmission network using phylogenetic analysis, we wanted to understand how the social network affected HCV transmission. We used mathematical modelling to explore this phenomenon in detail. First, we developed an individual-based HCV transmission model that could be applied to a social network of PWID (Rolls et al., 2012). We then used this model to simulate the transmission of HCV through the empirical social network of PWID observed in our study. A feature of our model is that sources of infection can be both network neighbours and non-neighbours via "importing" HCV; this was important to account for infection being introduced from outside the described network.

Key findings were that the empirical social network provided some protective effect on the time to primary HCV infection compared to an appropriately calibrated fully connected network which replicates thorough, instantaneous "mixing" of the population (mixing is an assumption built into dynamic compartmental models) (Andersson & Britton, 2000; Diekmann & Heesterbeek, 2000). The network structure "slowed" transmission through the

network, with a mean time to infection of 337 (95% CI: 334 – 349) days in the empirical social network compared to 272 (95% CI: 270 – 273) days in a fully connected network (Rolls et al, 2012). The incidence rates of infection across and between nodes (PWID) also differed within the model: we determined that individuals were at greater risk of infection if they had a higher frequency of injecting and more network partners (Figure 1) (Rolls et al., 2012). Another important observation in the model was that in the case of "gateway" nodes to a sub-network, the time to next infection in the sub-network was significantly greater when the gateway node cleared HCV spontaneously than if chronically infected. This suggests that if a gateway node can be "turned off" (i.e., made HCV RNA negative and therefore non-infectious) via spontaneous clearance or treatment, this substantially reduces the rate of HCV transmission through a part of the network.

Figure 1. Simulation results for incidence of HCV by number of network partners (nodes) and frequency of injecting. As expected, incidence increases with additional injecting partners and higher frequency of injecting. (Rolls et al., 2012)

Simulation of HCV treatment

A further objective was to learn how HCV is transmitted in social networks of injectors and identify strategies that could be used to reduce the frequency of HCV transmissions. To this end, after the development of the initial network-based transmission model, we developed an

empirically grounded network model of who might inject with whom (injecting occurs at the same time and space) using exponential random graph models (ERGMs). ERGMs are based on theories of social network formation, and can be used to simulate new networks with similar characteristics to empirically observed social networks. Because the network data resembled a snowball sample, model fitting required a recent technique developed for fitting ERGMs to snowball samples to avoid bias that may arise from ignoring the snowball nature of the data. In this case, the characteristics modelled included network features like transitivity (i.e., the friend of my friend is also my friend) and social circuit dependence (i.e., if the partners of individuals X and Y are connected then X and Y themselves are more likely to be connected). Four attributes (location, age, injecting frequency, gender) were also included in the model to capture aspects of homophily (i.e., "friends of a feather" flock together). The network parameter estimates were then used to create a novel model-dependent estimate of the size of the target population. The results made it possible to simulate realistic networks for investigating treatment and intervention strategies for reducing HCV prevalence (Rolls et al., 2013b).

Using these simulated networks, and focusing on large connected components of similar size as the most interesting for research into transmission, we examined HCV transmission and treatment, including the impact of spontaneously clearing nodes. Treatments were parameterised in anticipation of upcoming DAAs. With regard to transmission, as with our previous mathematical model, both the number of contacts (injecting partners) and injecting frequency were associated with reducing the time to primary infection and HCV incidence. The change from being a "less-" to "more frequent" injector was roughly similar to having

one additional network contact (Rolls et al., 2013a). In controlled comparisons, nodes that cleared their HCV infection (as would occur if a person was successfully treated) had a local effect on infection risk compared with nodes that did not. The total number of spontaneously clearing nodes, but not their specific location, had a network-wide effect on HCV primary and reinfection incidence. We then investigated the effect of various network-based HCV treatment strategies on incidence rates, with reinfection playing a large role in the effectiveness of treatment interventions. Strategies that treated PWID and all their contacts, analogous to ring vaccination, were the most effective in reducing the incidence rates of reinfection and combined infection. The strategy targeting infected PWID with the most contacts, analogous to targeted vaccination, was the least effective (Rolls et al., 2013a). This is in contrast to the widespread belief that targeted vaccination is generally the most effective vaccination strategy.

Next we examined how using a networks-based approach to treat PWID affects HCV prevalence. We created networks of 10 480 nodes by using an ERGM to simulate 20 subnetworks of 524 nodes at a time (Hellard et al., 2014). We then simulated transmission of HCV through these networks using a discrete time stochastic transmission model. Informed by dynamic transmission models developed by Martin and Vickerman (Martin et al., 2013), we modelled treatment of 15/1000, 25/1000 and 50/1000 PWID per year over 10 and 20 years using treatment efficacies of 60% and 80%. The effect of five treatment strategies on the prevalence of HCV was investigated: (1) treat highest-degree nodes first, (2) treat most uninfected neighbours first (3) treat least infected neighbours first (4) treat randomly selected nodes and (5) “bring your friends,” where an individual is chosen at random for treatment and

all their infected neighbours are treated (Figure 2). While the network-wide information that would enable strategies 1-3 (i.e., everyone's number of contacts, everyone's infection status) would generally not be available, they serve as important comparisons. The "bring your friends" strategy was considered plausible for use in a clinical setting.

Figure 2: Four treatment strategies using a network based approach (Hellard et al., 2014) .

As treatment coverage increased, HCV prevalence at 10 years reduced for both the 60% and 80% efficacy treatment. Within each set of parameters, the *bring your friends* strategy performed better than the random strategy, being most marked for higher-efficacy treatment. For example, over 10 years of treating 25 per 1,000 PWID at 80% treatment efficacy, HCV prevalence dropped from 50% to 40% using the random strategy and from 50% to 33% using the *treat your friends* strategy (6.5% difference; 95%CI: 5.1–8.1). (Figure 3). The *bring your friends* strategy was proposed because it seemed the most plausible real-world treatment strategy; most PWID will be unaware of the structure of their injecting network, but they know their immediate injecting partners. It seems reasonable to assume these injecting partners could be treated at the same time as the primary PWID, particularly with the advent of highly efficacious DAA treatment that has minimal reported side effects (Hellard et al., 2014).

Figure 3 Impact of hepatitis C treatment at 10 years with 80% treatment efficacy with coverage of 25 per 1,000 PWID per year. (Hellard et al., 2014)

Application of models to clinical trials

Informed by the results of our models, between 2014 and 2016 we are undertaking the Hepatitis C Treatment and Prevention (TAP) Study. The TAP study is designed to examine the feasibility of treating PWID in a community-based setting with a 12-week course of oral therapy that combines the DAAs sofosbuvir and ledipasvir (SOF + LDP) for participants infected with genotype 1 and SOF +LDP and ribavirin (Rib) for participants infected with all other genotypes. Another key aim of the study is to measure the effect of treating PWID using a "bring your friends" strategy to determine whether a network-based treatment approach impacts on rates of HCV primary infection and reinfection and reduces HCV prevalence among PWID. Participants are being sourced from the Burnet Institute's existing SuperMIX cohort, which comprises over 700 PWID, most with chronic HCV infection (Horyniak et al., 2013).

The TAP study comprises primary and secondary participants who are randomised to three treatment arms (Figure 4). Primary participants will be recruited from the SuperMIX cohort (n=120; 40 in each arm) and will be current PWID (injected last six months) and HCV RNA positive. Secondary participants (n=300; 100 in each arm) are current injecting partners of the primary participants identified using the "bring your friends" strategy, and will include a mix of HCV-positive and HCV-negative individuals Group A comprises primary and secondary participants who receive supportive care for 18 months. Examples of *supportive care* are BBV counselling, provision of sterile needles and syringes and the provision of free hepatitis

B vaccine if appropriate. In Group B, all primary participants will be treated with SOF + LDP (+/- RBV) for 12 weeks immediately and secondary participants receive supportive care only. In Group C, all primary participants, and those secondary participants with chronic HCV infection, will be treated with SOF + LDP (+/- RBV) for 12 weeks immediately; any Group C participants with primary infection or reinfection during the study will also receive immediate (re-)treatment.

Figure 4. Treatment strategy for the three arms of the TAP Study

Participants will be followed for 18 months after treatment, with the incidence of HCV primary infection and reinfection being measured every three months; at the end of the study HCV incidence will be compared across the three groups. Molecular sequencing will be undertaken to identify the probable sources of any reinfection events. At the completion of the study all participants who received supportive care will be offered treatment with SOF + LDP (+/- RBV).

The TAP Study will produce vital and novel data for future public health and treatment programs that aim to eliminate HCV infection.

Conclusion

Our work highlights the importance of using a networks-based approach to increase our understanding of HCV transmission and its role in informing the roll out of treatment as prevention. Nevertheless, we are yet to determine how differences in injecting networks, such as variation in the network structure, injecting risk behaviour and HCV prevalence, alter the influence of the injecting network. Further research is required to understand the broader impact of the injecting network on HCV incidence, prevalence and treatment as prevention.

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Figure 1. (Rolls et al., 2012)

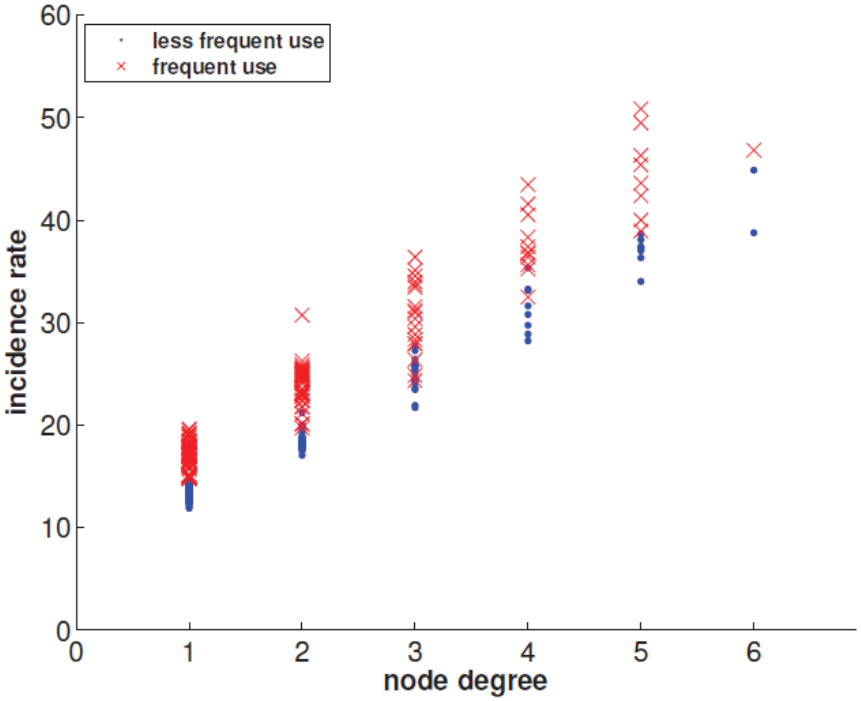

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Figure 2. (Hellard et al., 2014)

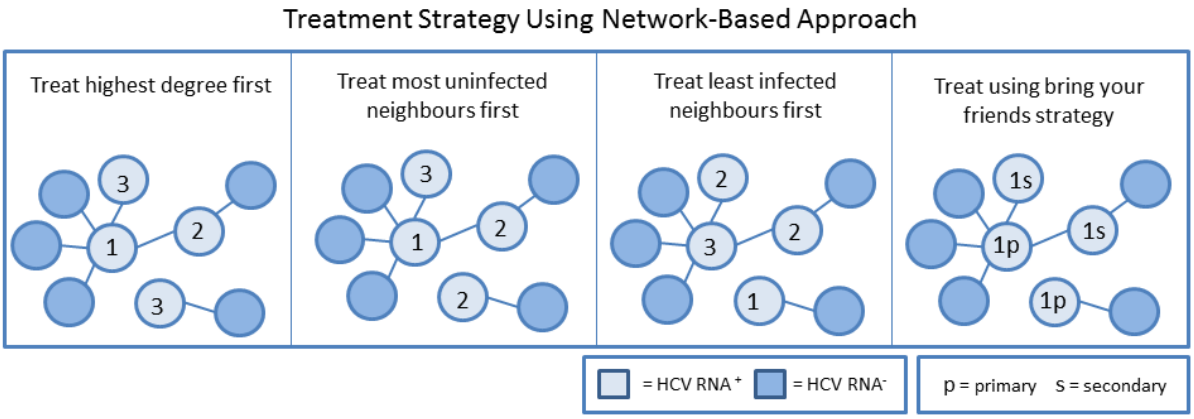


Figure 3. (Hellard et al., 2014)

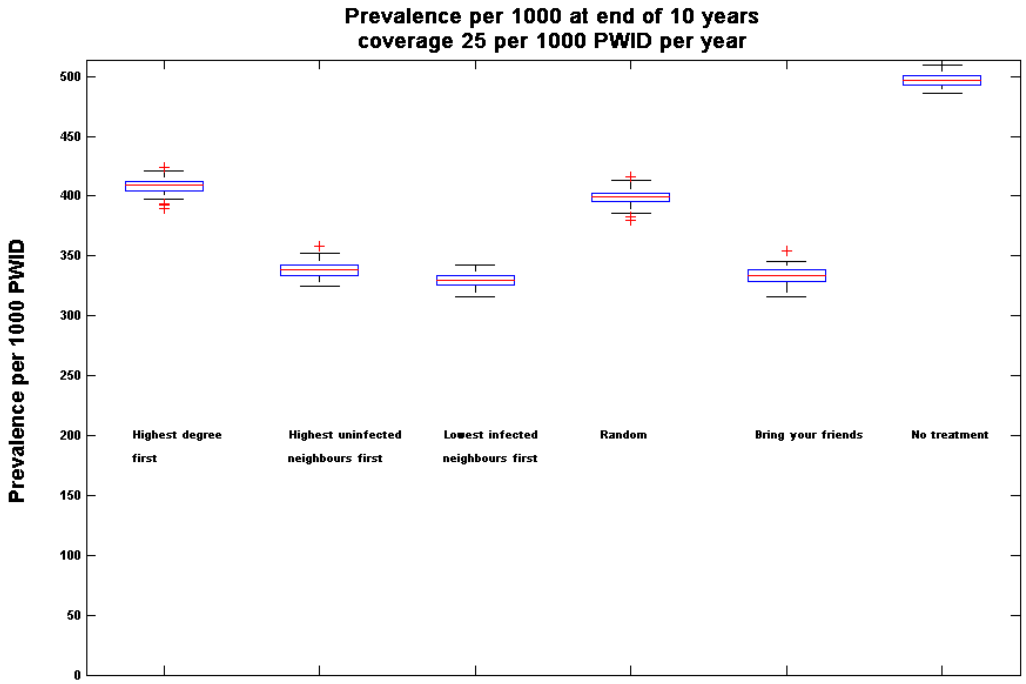
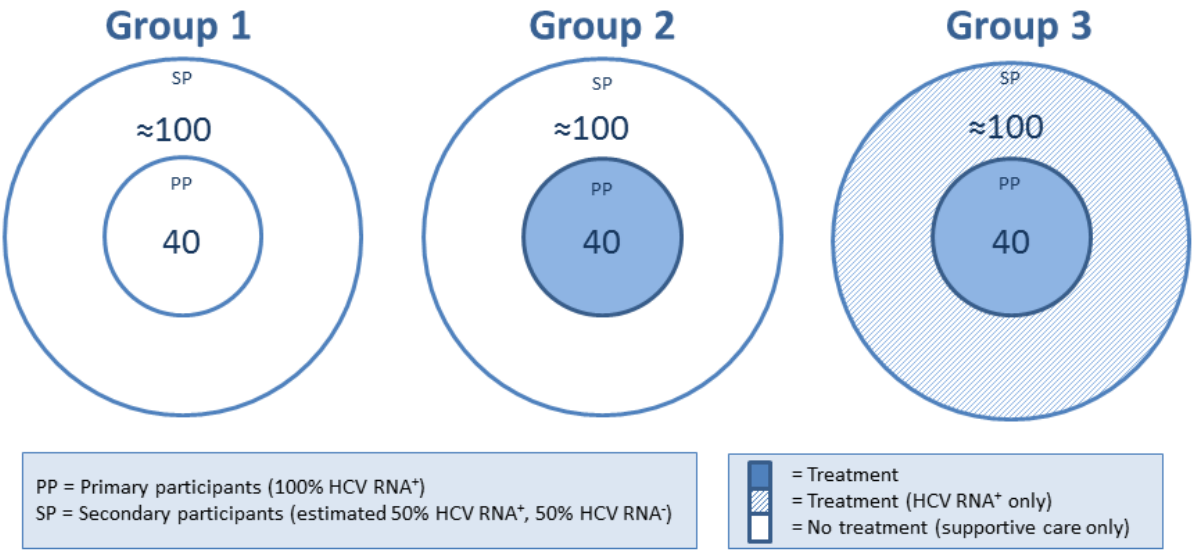


Figure 4.


Group 1
SP
≈100
PP
40
Group 2
SP
≈100
PP
40
Group 3
SP
≈100
PP
40
PP = Primary participants (100% HCV RNA+)
SP = Secondary participants (estimated 50% HCV RNA+, 50% HCV RNA-)
= Treatment
= Treatment (HCV RNA+ only)
= No treatment (supportive care only)