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ORIGINAL ARTICLE

Injecting network structure determines the most efficient strategy to achieve Hepatitis C elimination in people who inject drugs

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Abstract

Transmission of Hepatitis C (HCV) continues via sharing of injection equipment between people who inject drugs (PWID). Network-based modelling studies have produced conflicting results about whether random treatment is preferable to targeting treatment at PWID with multiple partners. We hypothesise that differences in the modelled injecting network structure produce this heterogeneity. The study aimed to test how changing network structure affects HCV transmission and treatment effects. We created three dynamic injecting network structures connecting 689 PWID (UK-net, AUS-net and USA-net) based on published empirical data. We modelled HCV in the networks and at 5 years compared prevalence of HCV 1) with no treatment, 2) with randomly targeted treatment and 3) with treatment targeted at PWID with the most injecting partnerships (degree-based treatment). HCV prevalence at 5 years without treatment differed significantly between the three networks (UK-net (42.8%) vs. AUS-net (38.2%), $p < 0.0001$ and vs. USA-net (54.0%), $p < 0.0001$). In the treatment scenarios UK-net and AUS-net showed a benefit of degree-based treatment with a 5-year prevalence of 1.0% vs. 9.6% $p < 0.0001$ and 0.15% vs. 0.44%, $p < 0.0001$. USA-net showed no significant difference (29.3% vs. 29.2%, $p = 0.0681$). Degree-based treatment was optimised with low prevalence, moderate treatment coverage conditions whereas random treatment was optimised in low treatment coverage, high prevalence conditions. In conclusion, injecting network structure determines the transmission rate of HCV and the most efficient treatment strategy. In real-world injecting network structures, the benefit of targeting HCV treatment at individuals with multiple injecting partnerships may have been underestimated.

KEYWORDS
elimination, Hepatitis C, injecting, model, network, prevention, treatment

1 | INTRODUCTION

The World Health Organisation (WHO) aims to eliminate Hepatitis C (HCV) as a global public health threat by 2030.[1] Currently, injecting drug use is the most frequent source of incident infections in highly developed countries.[2] Numerous studies have shown that the scale up of treatment for people who inject drugs (PWID) will lead to a dramatic reduction in HCV prevalence. This effect is augmented by treatment preventing onward transmission to injecting partners – a phenomenon known as treatment as prevention (TasP).[3] However, the clinical reality is that in most areas treatment coverage for PWID is limited and these dramatic effects are unlikely to be seen with current levels of treatment provision.[4] It is therefore important to have an efficient strategy where the benefit of each treatment has maximal impact on prevalence. Unfortunately, there is uncertainty about how this strategy should look. This is perpetuated by conflicting results in modelling studies that have specifically addressed this question.

These studies use models that utilize empirical 'injecting networks' to measure the impact of targeting treatment at individual PWID with different characteristics. For example, in one scenario the impact of randomly treating PWID on incidence of infection may be tested. In another, PWID with the most injecting partners may be treated. The two largest models use baseline networks from the United States of America (USA)[5] and Australia.[6] These studies have shown that random treatment is as good as or better than targeting treatment at PWID with multiple partners (so-called degree-based treatment). This has important implications with clinical practice. It means that treating more stable HCV positive PWID who are already engaging with harm reduction services is just as (or more) effective than treating more chaotic actively injecting individuals with multiple sharing partnerships. In simple terms, this means that where treatment coverage is limited the additional time and resources needed to engage the latter group are unwarranted.

However, a third modelling study from the United Kingdom (UK) has shown the opposite.[7] In this study degree-based treatment partners reduced transmission and the overall prevalence of HCV at one year.

Careful examinations of the three studies highlight multiple differences that could account for the contrasting results. The studies from Australia and the USA model a larger population, a longer time horizon and have a higher baseline prevalence of HCV than the UK study. However, also notable is a marked contrast in the mathematical structures of the injecting networks between the studies. Investigating this uncertainty further is important as it could mean the difference between achieving and missing the global elimination target. Contact network structure is known to have a profound impact on infectious disease transmission,[8] and this is likely to be the case in HCV.[9]

We therefore hypothesise that it is differences in injecting network structure that has led to these studies concluding that different approaches are most effective. To test this hypothesis, we create three dynamic injecting networks based on the characteristics of these real-world networks. In each network we then compare two treatment approaches: random treatment and targeted treatment at PWID with lots of injecting partners.

Significance statement

Hepatitis C causes thousands of deaths each year. The World Health Organisation aims to eliminate the virus in the next 10 years. However, it is still transmitted by injecting drug use. Treatment can disrupt transmission of Hepatitis C but the best strategy to achieve this is unclear. In this study we highlight one reason why previous modelling studies have different results. We show that it is because the pattern of injecting relationships used in each model form different shapes. We conclude that because of this we may have previously underestimated the benefit of treating people who inject drugs with lots of partners.

2 | MATERIALS AND METHODS

2.1 | Modelling approach

We used a network-based model to explore the influence of network structure on relative effectiveness of random and degree-based treatment strategies for HCV, in relation to the goal of reduction in prevalence and eventual elimination from the PWID population. The model comprised two steps: first, the generation of injection networks with specific structural properties seen in previous modelling studies of treatment for HCV based on real-world network data; second, the simulation of HCV transmission on these networks with different treatment strategies and observation of the effect on prevalence at 5 years.

2.2 | Network properties

A PWID population is represented in the model by a network composed of nodes, representing individuals, connected by edges, representing an injecting relationship; that is, the connected individuals routinely inject drugs in the same place at the same time and may share injecting equipment. In the model the network size is fixed but the structure is altered according to two parameters: degree sequence and clustering coefficient.

We select these two properties as they are known to have significant impact on the spread of infection in a contact network.[10] A degree sequence is a list containing one value for each node in the network, where that value is the number of edges of which that node is an endpoint. In the case of the injecting network, therefore, this is a list containing the number of injection partners of each individual

in the network. The clustering coefficient (also known as transitivity) is a measure of the number of triangles in the network, i.e., in how many cases two nodes with a common neighbour are themselves neighbours.[11]

We altered the degree sequence and clustering coefficient to produce three different network structures. The values we used were based on network data from Melbourne (Australia), Hartford (Connecticut, USA), and the Isle of Wight (UK).[5-7,12] We henceforth refer to the three network structures as AUS-net, UK-net, and USA-net, to denote the network structure derived from the corresponding prior study.

The degree distribution used as input to the model for each of the three networks is shown in Figure 1. In the case of AUS-net and UK-net, specific degree distributions were available and were sampled directly to generate input degree sequences. For USA-net, only the mean degree and centiles were available, so these were fitted to a power-law with cut-off distribution, which was then sampled; details are given in the Supporting Information and Figure S1. The clustering coefficients used were 0.38, 0.13, and 0.01 for AUS-net, UK-net, and USA-net, respectively.

In order to preserve the network structure under investigation, the network was not explicitly dynamic, but instead allowed nodes to leave the network and be replaced by a newly joining node with a fixed probability of existing chronic infection (Table 1). One hundred networks per structure were generated using an adaptation of the algorithm presented by Bansal et al., implemented in Python 3 using NetworkX version 2.5 (see Supporting Information for more detail regarding the algorithm).[13,14]

2.3 | Model parameters

Wherever possible model parameters correspond to real-world characteristics of the HCV epidemic, the PWID and HCV treatment service in Southampton, UK (Table 1). Southampton is a medium-sized city[15] with an estimated population of 689 PWID.[16] Projected treatment coverage by the clinical service over 2021 is six PWID per month with capacity limited by nursing availability and testing coverage rather than drug cost or availability. The time horizon for the model is five years as this is in keeping with the local HCV elimination target.

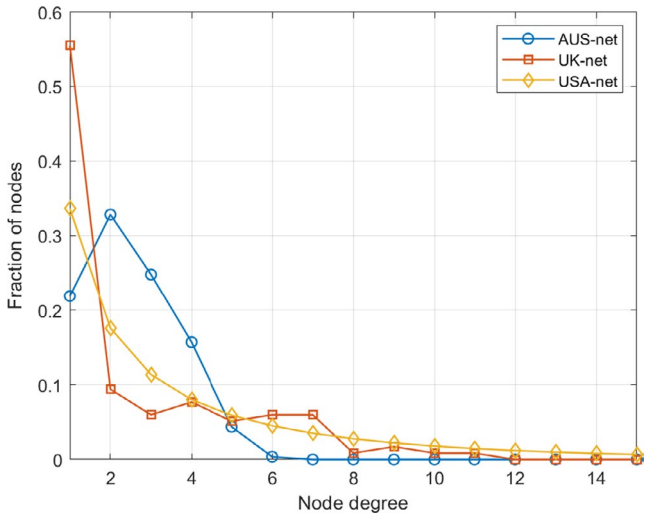

FIGURE 1 Degree distributions used as input to the network models

Data on the frequency of injecting and the probability of sharing equipment were taken from a recent study describing PWID behaviours in a population geographically close to Southampton (Table 1).[7] Parameters relating to the natural history of HCV infection and response to treatment were taken from the available published literature (Table 1). We assumed that the rate of sustained virological response (SVR) was the same for all treated nodes; this is consistent with recent studies that have shown PWID have comparable rates treatment completion[17] and SVR[18] to non-PWID.

2.4 | Simulation of transmission and treatment

HCV transmission on the network was simulated using a susceptible-infected-susceptible (SIS) model, as shown in Figure 2. The model was implemented in Python 3 using the *epydemic* framework (version 1.0.0).[19]

For all scenarios, 100 simulations were run over each of the generated networks, resulting in 100,000 total runs for each scenario. Baseline prevalence was achieved by randomly seeding 30% of nodes as having chronic HCV and running the simulation without treatment for a 'burn-in' period until prevalence reached the relevant baseline. Hundred post-burn-in states, each from a different random seed, were saved for each individual generated network in order to enable valid comparison of treatment strategies by starting from the same state.

We verified the model by setting the time horizon, baseline prevalence, and range of treatment coverage to those used in the prior study with the corresponding network structures and confirming that our model produced consistent results to the prior studies concerning the relative effectiveness of TasP strategies (supplementary material and Figure S2). In order to isolate the effects of network structure on transmission and treatment, we then set all parameters to fixed values selected or calculated from the literature, as shown in Table 1.

We ran the simulation over each network to 5 years, for three scenarios: no treatment, random treatment (infected node(s) chosen at random with uniform probability to be treated each month), and degree-based treatment (infected node(s) with the highest number of injection partners chosen for treatment each month). In each treatment scenario, six PWID were treated per month, in line with current treatment capacity in Southampton. The primary outcome was prevalence of chronic HCV at 5 years. Prevalence at 5 years was compared using a paired sample t-test in MATLAB R2016b for WINDOWS.

TABLE 1 Summary of model parameters

Parameter	Value	Reference
Network size	689	16
Proportion of nodes with chronic HCV at baseline	0.417	16
New nodes rate/year (as proportion of network size)	0.176	38
Proportion of new nodes with HCV	0.0484	Model calibration
Node turnover/year as the proportion of network size	0.176	38
Frequency of injection with each neighbour – proportion of nodes	6x/week - 0.12 3x/week - 0.22 1x/week - 0.43 0.5x/week - 0.23	7
Probability of equipment sharing	0.4 (AES) 0.33 (RNS)	7
Transmission probability when sharing	0.0023 (AES) 0.0073 (RNS)	39
Spontaneous clearance rate of acute infection	0.25	39
Treatment duration (weeks)	8	40,41
Treated persons coverage per month at baseline	6	†
Rate of sustained virological response (SVR)	0.95	40,41

Abbreviations: AES, axillary equipment sharing; HCV, Hepatitis C virus; RNS, receptive needle sharing.

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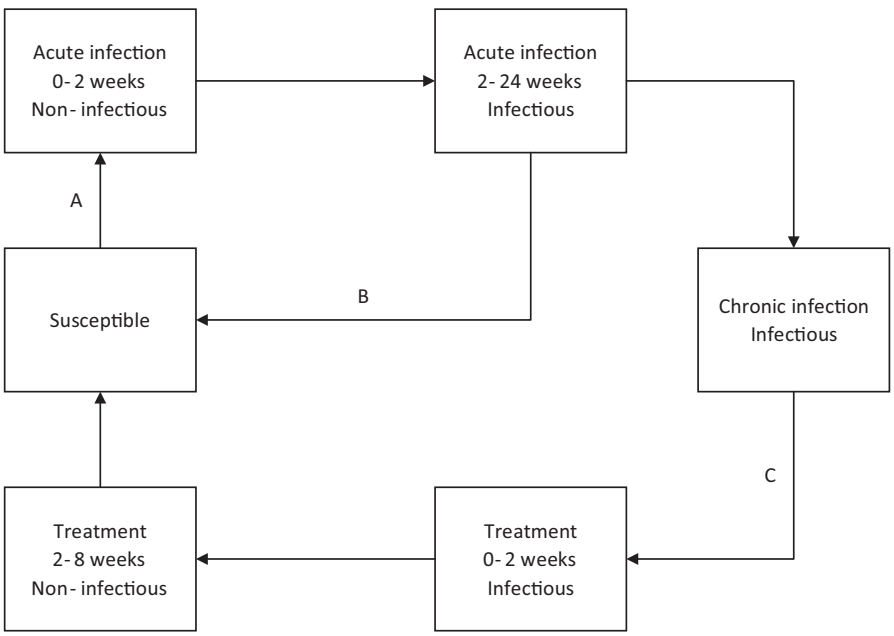

FIGURE 2 Diagrammatic representation of the transmission model. Boxes represent states, and arrows represent possible transitions between states. Non-default events are denoted by arrow labels as follows: A, transmission via sharing event with infected neighbour; B, spontaneous clearance of virus; C, start of ultimately successful course of treatment (success is determined at transition to treatment because if treatment fails, the individual is assumed to remain in the chronic infection state throughout)

2.5 | Sensitivity analysis

We independently altered baseline prevalence, treatment coverage rate and the prevalence of receptive needle sharing (RNS) to test the effect on the primary outcome. Treatment coverage and baseline prevalence are known to have an important impact on TasP effects,[9] and change in RNS rate was found to be the greatest determinant of the relative effectiveness of different treatment strategies in a prior study.[7]

3 | RESULTS

3.1 | Network generation

Using the empirically pre-defined parameters for clustering coefficient and degree distribution, we created three distinct injecting networks (UK-net, AUS-net and USA-net). A representation of each structure is displayed in Figure 3. As well as matching empirical networks by quantitative measures for clustering coefficient

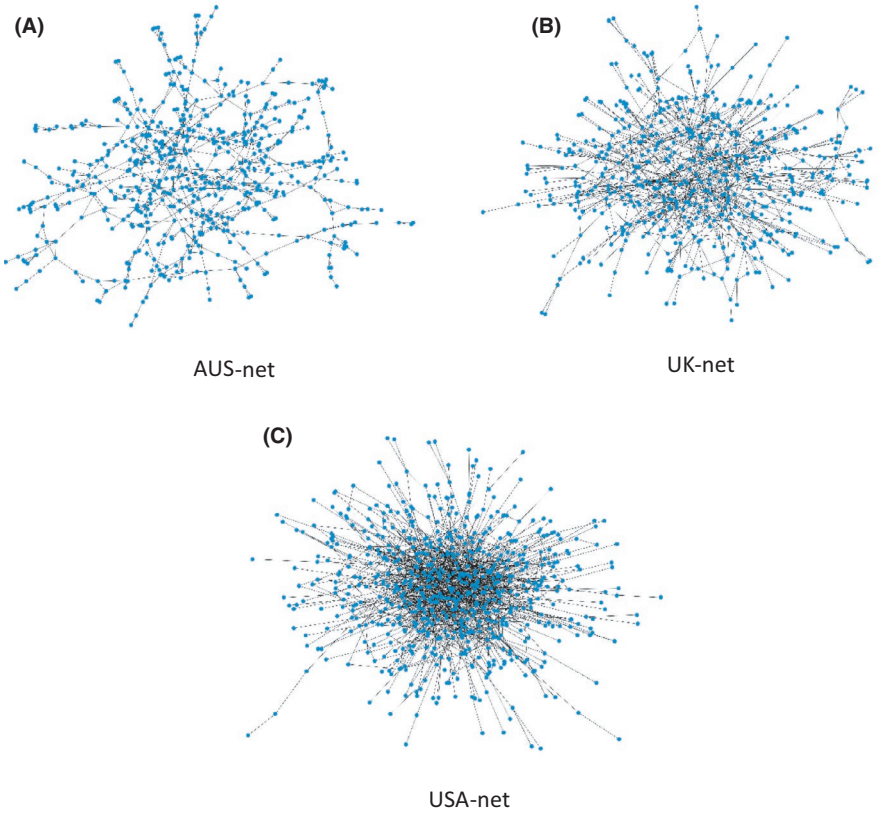

FIGURE 3 Visual representation of the three networks structures tested in the model

and degree distribution, they are qualitatively visually similar to the networks depicted by the authors of the respective prior studies. For example, AUS-net features long loops of nodes, whilst USA-net appears 'spiky' with single strands emanating from the central network.

3.2 | Impact of network structure on HCV transmission

The proportion of new nodes entering the network with HCV was calibrated to ensure the prevalence without treatment remained stable in UK-net. Using this as a baseline, we assessed the relative impact of the AUS-net and USA-net structures on the transmission of HCV over a 5-year period without treatment. The median prevalence from 100 simulations at 5 years in UK-net was 42.8%; under the same conditions it naturally decreased in the AUS-net (median 38.2%, $p < 0.0001$) and increased in the USA-net networks (median 54.0%, $p < 0.0001$) (Figure 4).

3.3 | Comparing HCV treatment strategies

To assess the relative effectiveness of treating PWID at random or targeting HCV treatment at well-connected PWID with the most injecting partnerships ('high-degree nodes'), we ran two treatment strategies for each of the three network structures. Firstly, we randomly selected PWID for treatment in each network; secondly, we preferentially selected PWID with the most injecting partnerships. In the baseline analysis six PWID were selected for treatment per month over a 5-year time horizon. The results are summarised in Figure 4B. In UK-net there was a clear benefit in targeting treatment at PWID with the most injecting partnerships (median 5-year prevalence 1.0% with degree-based treatment compared to 9.6% treating at random, $p < 0.0001$) while AUS-net shows a smaller benefit (0.15% compared to 0.44%, $p < 0.0001$), and in USA-net there is no significant difference (29.3% degree-based, 29.2% random, $p = 0.0681$).

To investigate why degree-based treatment was favoured in AUS-net and UK net, we looked at the comparative number of primary infections and reinfections (Figure 5). In the base-case analysis where six PWID were treated per month, it was a significant reduction in the number of primary infections in UK-net (141 vs. 242 $p<0.0001$) and AUS-net (113 vs. 149 $p<0.0001$) that contributed to the overall significant reduction in prevalence at 5 years. In USA-net a reduction in primary infections (381 vs. 457 $p<0.0001$) was countered by a significant increase in the number of reinfections (293 vs. 216 $p<0.0001$).

3.4 | Sensitivity analyses

We performed further simulations to assess the effect of baseline prevalence, rates of RNS and treatment coverage in relation to

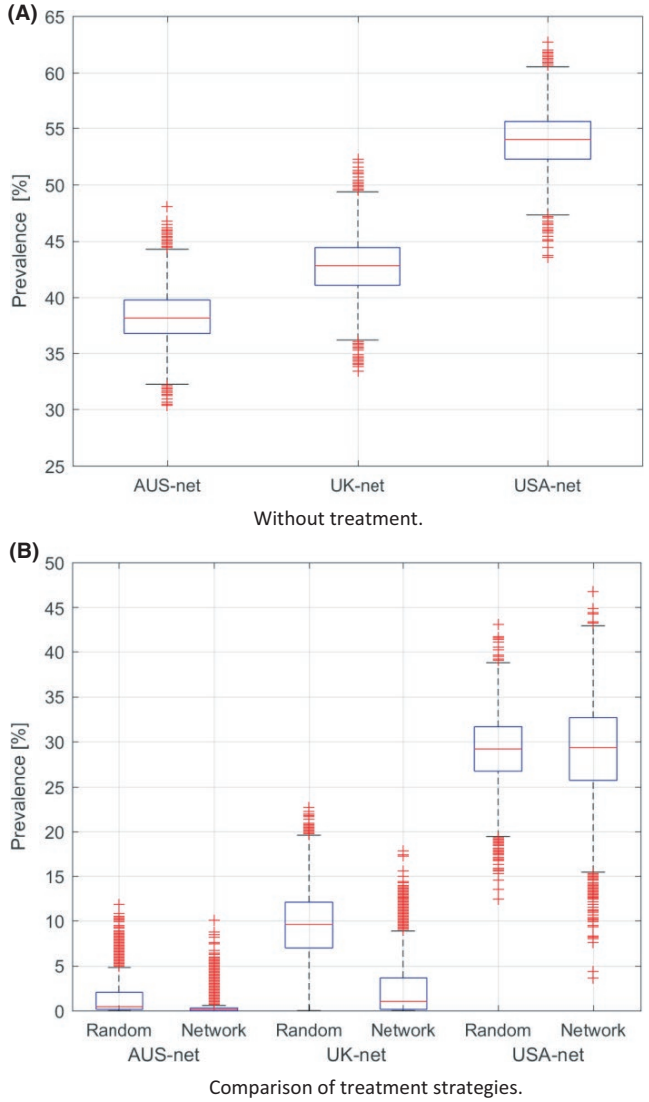

FIGURE 4 Box plots showing prevalence of Hepatitis C at 5 years, for each network structure from a baseline prevalence of 41.7%: A, without treatment; B, treating 6 people who inject drugs per month by either a random or degree-based strategy. The ends of the boxes are the upper and lower quartiles, a horizontal line inside each box marks the median value, the whiskers extend to extreme values at most 1.5x the inter-quartile range, and outliers beyond this range are indicated by crosses. AUS-net, UK-net and USA-net refer to the three different underlying injecting network structures within the model

these results. Varying treatment coverage showed that the strategy achieving the greatest reduction in HCV prevalence depends on both the network structure and treatment coverage level (Figure S3). Specifically, for each of the three structures, random treatment results in a lower 5-year prevalence than degree-based treatment at lower treatment coverage, but there is a structure-dependent level of coverage at which degree-based treatment becomes more effective. The reason for this is highlighted in Figure 5. As treatment coverage increases, reinfection rates increased in all three networks across both treatment scenarios. However, the rate of primary infection decreases as coverage increases, and this decline is most marked in the degree-based treatment strategy.

Varying baseline prevalence revealed that increased baseline prevalence increases the coverage level at which degree-based treatment becomes better than random treatment (Figure S3). Likewise, an increased RNS rate reduced the relative effectiveness of the degree-based treatment (Figure S3).

4 | DISCUSSION

We report two key findings. Firstly, in otherwise identical conditions, injecting network structure affects the transmission of HCV and explains variation in TasP effects. Secondly, network structure alters the most efficient treatment strategy to achieve HCV elimination in PWID, and this is attributed to changing reinfection dynamics of treated individuals.

Our first finding is consistent with other published studies. Contact network structure is known to affect transmission of infectious diseases,[8,20] and a recent study using theoretical rather than empirical networks highlighted how network structure impacts the effectiveness of TasP for HCV with random treatment.[9]

Our second finding is novel. To assess the impact of this on the global HCV elimination objective, it is important to consider three questions. Why do the different structures respond differently to HCV treatment strategies? Why are the empirical networks so structurally different, and, finally, does one structure most accurately depict real-world injecting network structure?

Changes to the mathematical injecting network structure alters the reinfection dynamics of HCV.[9] Reinfection dynamics are central in determining the best treatment strategy. This is highlighted in our analysis and is supported by other authors.[9,21] In the sensitivity analysis, degree-based treatment was optimised with moderate treatment levels and with lower baseline prevalence because reinfection rates in the high-degree nodes were low in this setting. Conversely, random treatment was optimised with higher baseline prevalence and lower treatment coverage because reinfection rates in the randomly treated nodes (with a lower average degree) were relatively low in this setting.

In our model we assess network structures based on empirical data collected in Australia, the USA and the UK. It is possible that each network structure is a close representation of the 'true' pattern of injecting relationships in each setting. This is a reasonable assumption considering the structures are taken from fieldwork with PWID on three different continents and in a mixture of urban and rural settings. However, this hypothesis is inconsistent with the literature that describes naturally occurring human network structures are remarkably conserved across geographically dispersed cultures.[22-24]

An alternative view is that the variation is accounted for by the different methods that were used to collect the network data in the three studies. Firstly, we will consider the degree distribution, which was similar in the USA-net and UK-net but very different

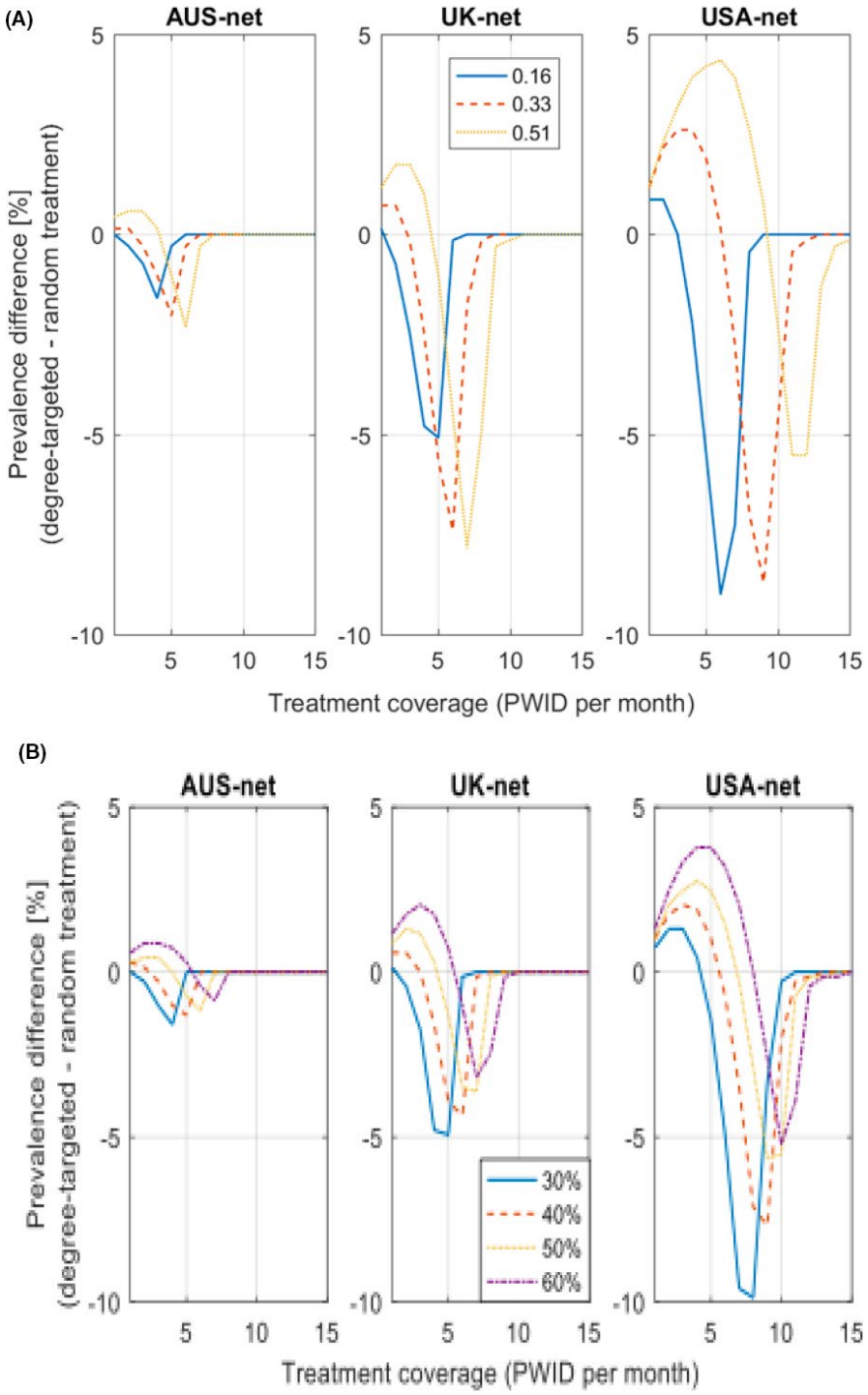

FIGURE 5 The number of primary infections and re-infections over 5 years in the three injecting network structures: AUS-net, UK-net and USA-net. Incident infections are shown for two treatment strategies – degree-based treatment, where therapy is targeted at people who inject drugs with multiple injecting partners, and random treatment. The strategies are compared across different levels of treatment coverage

in AUS-net. Buchanan et al. (UK-net) and Zelenev et al. (USA-net) used respondent-driven sampling (a type of chain referral sampling (first described in 1997 by Douglas Heckathorn[25]) but included injecting partners named by participants in the survey even if they did not come forward to participate themselves. Rolls et al. (AUS-net) also used a form of 'peer-referral' recruitment (described by Miller et al.[26]) for the survey but only included survey participants in the network. This meant the number of injecting partners in each participant's network was capped by the number that also took part in the survey. This limited the degree size of nodes within AUS-net and explains the 'stringy' appearances of the network.

Secondly, we consider the clustering coefficient; this was similar in AUS-net and the UK-net but very different in the USA-net. Again, the variation could be accounted for by the sampling approach. As Rolls et al. only used survey participants, it is likely a relatively high proportion of friends of friends would know each other. By including all named injecting partners in the network, Zelenev et al. are likely to have missed friends of friend ties in the network – decreasing the clustering coefficient. However, Buchanan et al. and Zelenev

et al. have contrasting clustering coefficients but very similar sampling techniques.[5,7] This variation may be accounted for by the study setting.

The UK study was set on a small island, and the sampling fraction of the total PWID population was estimated to be well over 50%,[7] whereas the US study was set in a city experiencing an epidemic of injecting drug use so the sampling fraction was probably much smaller.[27] This means ties between friends of friends were more likely to have been missed in USA-net.

Due to the difficulties in mapping injecting networks in PWID, it is impossible to be certain which structure most accurately reflects reality. Other authors have reported sexual and injecting networks[28] or social support networks connecting PWID[29] but to our knowledge none report injecting networks that could be meaningfully compared with the structures we have assessed. However, a large number of other naturally occurring networks that are more easily visualised have been mapped.

In these networks several features are consistently expressed that are relevant here. The networks exhibit relatively large values of clustering (usually between 0.1 and 0.5), indicating the phenomenon that friends of friends tend to know one another, as well as a power-law degree distribution (with exponential cut-off), such that there are many nodes with few connections and a small but not insignificant number of nodes with a large number of connections.[30-32]

Of the network structures we assessed, the degree distribution in USA-net and UK-net is closest to a power law, and UK-net and AUS-net (0.13 and 0.38 respectively) have clustering coefficients closest to those consistently occurring elsewhere. Taken together UK-net appears to exhibit the closest balance of clustering and degree distribution.

This is potentially important. Of the original publications, the study that described the UK-net structure was an outlier in showing a striking benefit of degree-based therapy over random treatment.[7] If this structure is the closest to 'real-world' networks then the TasP effects of targeting HCV treatment at individuals with the largest numbers of injecting partnerships may have been underestimated. Such an approach is practically possible by engaging PWID with HCV treatment via peer-led referral,[33] and the increasing availability of point of care RNA testing will support monitoring for reinfection in high risk PWID.[34,35]

The parameters we used in our model are based on available published empirical data. The representativeness of this data is limited by the known challenges sampling PWID, and in some cases the parameters are based on a single publication describing a single survey. The model is a simplification of a real-world injecting network of PWID and how it changes over five years. The model is dynamic in that it includes a probability that PWID join and leave the network, but other features are artificially fixed. For example, in contrast to dynamic deterministic models (e.g. Martin et al.[36]), it does not include a differential rate of needle sharing across the network, and we assumed SVR rates were comparable for all PWID in the model – whether they had few or many injecting partners. Importantly the model does not assume any change in the behaviour in treated PWID. There is reasonable evidence to suggest that HCV treatment can be a catalyst for positive behaviour change and may be associated with fewer risk taking behaviours or the cessation of drug use altogether.[37] The extent of behaviour change following treatment requires further research. However, if it occurs uniformly across the network then this model has probably underestimated the positive impact of degree-based treatment.

Despite these limitations we believe our model is sufficient to test our research hypothesis. It has shown that network structure does affect the best strategy to treat HCV in PWID and, when the likely real-world structure of injecting networks is considered, the potential benefits of targeting treatment at PWID with multiple injecting partners may have been underestimated. The targeting of PWID with multiple injecting partners is practically possible, and therefore our findings have implications for the global HCV elimination strategy.

AUTHOR CONTRIBUTIONS

Dr Ryan Buchanan acts as guarantor for the integrity of this research. MW, CC, JP, SIK and RB identified the research question and designed the study. RB, CC, RS-D and MS built the model in Python, RB, MS, CB conducted the data analysis, and MS designed the figures. MW, CC, JP, CB, RB and R S-D prepared the manuscript for submission. All authors approved the final version of this manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest with this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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