The impact of injecting networks on hepatitis C transmission and treatment in people who inject drugs.

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Abstract –

Introduction: With the development of new highly efficacious direct acting antiviral treatments (DAAs) for hepatitis C (HCV), the concept of treatment as prevention is gaining credence. To date the majority of mathematical models assume perfect mixing with injectors having equal contact with all other injectors. This paper explores how using a networks based approach to treat people who inject drugs (PWID) with DAAs affects HCV prevalence.

Method: Using observational data we parameterized an Exponential Random Graph Model containing 524 nodes. We simulated transmission of HCV through this network using a discrete time, stochastic transmission model. The effect of five treatment strategies on the prevalence of HCV was investigated; two of these strategies were 1) treat randomly selected nodes and 2) "treat your friends" where an individual is chosen at random for treatment and all their infected neighbours are treated.

Results: As treatment coverage increases, HCV prevalence at 10 years reduces for both the high efficacy and low efficacy treatment. Within each set of parameters, the "treat 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 1000 PWID, the prevalence drops from 50% to 40% for the random strategy, and to 33% for the "treat your friends" strategy (6.5% difference, 95% CI 5.1 - 8.1%).

Discussion: "Treat your friends" is a feasible means of utilising network strategies to improve treatment efficiency. In an era of highly efficacious and highly tolerable treatment such an approach will benefit not just the individual but the community more broadly by reducing the prevalence of HCV amongst PWID.

Introduction

Hepatitis C (HCV) is a major global health problem affecting approximately 3% of the world's population. [1] Its transmission is mediated by interrelated behavioural and biological factors as well as social and structural issues;[2] these include injecting behaviours such as sharing needles and syringes,[3-6] the shared use of drug preparation equipment,[3, 4, 6-8] and the duration and frequency of injecting.[8-11] Immunovirological factors include the HCV genotype and viral load[12, 13], and independent variables such as gender[14, 15] and genetic polymorphisms.[16, 17] Whilst these risk factors are important in HCV transmission, it is increasingly recognised that contact networks also affect the transmission dynamics of HCV and other viruses.[18] While considerable research exists on the role of social networks (primarily sexual contact networks) in HIV transmission,[19] few such studies have addressed HCV.[20-23]

With the advent of new HCV treatments, the concept of treatment as prevention is gaining credence.[24] Modelling based on the standard treatment of pegylated interferon and ribavirin (Peg/Riba) predicted that treating 25 per 1000 PWID could reduce HCV prevalence by 50% within 30 years.[25-27] With the introduction of new highly efficacious HCV therapies,[28] HCV prevalence can be reduced by as much as 70% at 30 years if 25/1000 PWID are treated annually.[25, 29]

Mathematical modelling enables projections of the HCV epidemic [29-31] and assessment of the benefits of therapeutic and behavioural interventions.[26, 27, 29, 32, 33]. To date the vast majority of mathematical models assume perfect mixing: injectors have equal contact with all other injectors in the population.[7, 31, 33-36] These models are typically deterministic, using differential equations to model quantities such as the total numbers of susceptible and infected individuals in "compartments".[33-35] Even those models that use stochastic simulations [7, 30, 36] lack empirically-grounded, disease-relevant contact patterns (networks), so fail to capture individual heterogeneity. An exception to this modelling is work by Hutchinson et al, who used a basic non-mixing approach to randomly assign and remove needle-sharing partners to create a simple random network which varies from year to year.[30] In general, mathematical modelling of the HCV epidemic could be enhanced by incorporating social network concepts.

In order to examine the role of social networks in HCV transmission, we recruited a cohort of PWID (the Networks Cohort) in Melbourne, Australia between 2005 and 2007. We collected

injecting risk behaviour information and blood samples for HCV testing, as well as detailed information about the participants' social networks.[37, 38] The Networks Cohort was followed for five years, allowing us to estimate HCV incidence (both primary and reinfection) and HCV clearance.[37] This paper briefly describes an individual-based stochastic model of HCV transmission based on an empirical social network of PWID from the Networks 2 Cohort.[39] The observed network has now been parameterised using an exponential random graph model (ERGM), allowing the formulation of a more general set of models.[40] Using this model we have recently demonstrated that the number of contacts and the frequency of injecting impact on the time to primary infection. [41] As well, treating PWIDs and all their contacts in the network was most effective in reducing the incidence rates of re-infection and combined infection [41]. Building on that work, this paper explores how treating increased numbers of PWID with new highly efficacious HCV treatment affects HCV prevalence and how that effect is modulated by the injecting network.

METHODS

Observed network

Between 2005 and 2007, PWID who injected at least once in the previous six months were recruited from three major street drug markets located across metropolitan Melbourne using modified snowball sampling; our field team asked participants to introduce up to five people with whom they injected but not necessarily shared injecting equipment.[38, 42] Importantly, although the data collection used network-based methods, the entire network was not sampled. Rather, the network can be conceptualised as a snowball sample, consisting of seed nodes (wave 0) and nodes in waves 1 and 2. This observed network included 258 people.

Simulated networks

After taking into consideration the snowball sampling method, the observed network –which has 258 nodes is likely to represent a group of approximately 524 individuals.[40] We previously developed an ERGM for the this network, which included network characteristics and personal attributes.[40] Network parameters estimated include edges, singletons, and the newer alternating *k*-star, alternating *k*-triangle and alternating *k*-2-path parameters of Snijders *et al*.[43] that are often used to achieve parsimonious model specifications.

In ERGM networks the parameters represent the propensity of the corresponding configuration to appear in the network. Negative numbers represent a propensity for the

configuration to not appear in the network. For example, as the observed graph was stripped of isolates (who are not of interest from the perspective of modelling transmission on a network) the parameter for isolates is strongly negative.

Additional estimates from Rolls *et al.*[40] used in the current study were the size of each drug using network that this snowball sample represents (which was argued to be 524 individuals) and the observed fraction of the population by location (three sites were used in the study), age groups (below and above 25 years) and gender.

New networks with the same characteristics as the original network were simulated using Pnet, which generates ERGM networks using a Metropolis-Hastings MCMC method.[44] A fixed number of nodes (n=524) was used, and nodes were randomly assigned attributes according to the probabilities given in Table 1. Networks were generated by accepting or removing randomly proposed edges based on the ERGM specifications provided in Table 2.

The ERGM parameters are a valid representation of a group of PWID when simulated with 524 nodes at time but they cannot validly be used to simulate different sized groups at one time. The number of PWID in Melbourne and other large Australian cities is much larger than 524, estimated to be in the order of 10,000. We wished to examine stochastic effects and impact of treatment on a population at this scale and estimate treatment effects including stochastic variability on a scale comparable to the number of PWID in Melbourne. We therefore evaluated networks comprised of 20 sub-networks, each of size 524, in order to both maintain the validity of the ERGM parameters and to estimate the effects of our intervention strategies on a city-wide scale,

We generated 100 sub-networks, each of size 524, using a fixed node number and Pnet's standard Metropolis-Hastings MCMC.[44] To do this, we discarded the first 60 million sub-networks as burn-in, and for the next 100 million thinned by selecting one in every one million sub-networks produced. Once these sub-networks were constructed, networks were analysed based on results of a random selection of 20 such sub-networks, creating networks of size 10,480. One hundred networks each of 20 sub-networks make up the final structure for analysis.

Transmission model

Our disease transmission model, depicting various stages of hepatitis C infectiousness, is a simplified two-compartment model adapted from those described previously.[25-27] People

are classified as susceptible or infectious. Susceptible people include those who have never been infected, have cleared infection, or had successful treatment. The infectious compartment includes the untreated infected people, those currently receiving treatment (throughout the course, regardless of treatment type or duration) and those who have failed treatment. In this study we assume no immunity is provided by prior infection and all those treated or who clear infection are infected at the same rate as those who have never been infected. Similarly we assume all those who fail treatment are as infectious as those who have never received treatment. The numbers of people susceptible and infected at time *t* are *S(t)* and *I(t)*, respectively.

A discrete time, stochastic, individual-based network model was used to simulate transmission of hepatitis C across the network. Parameters governing the transitions between susceptible and infectious compartments are given, with their meanings and values, in Table 3. A departure from previous work is that infection is assumed to arise from within the network, without external importation.

For each simulation month, susceptible nodes were examined; if they were connected to infected nodes, a hazard of transmission was calculated and a transmission event is determined stochastically, using the following probability: For individual *k*

$$\Pr[S_k(t) \to I_k(t+\Delta t)] = (1-\pi)e^{-(\beta \sum I_n)\Delta t} + \varphi(\Delta t)$$

where β is the annual transmission rate for a connected discordant pair, $\sum I_n$ is the total number of infectious neighbours of *k*, π is the proportion of people who clear infection, and $o(\Delta t)$ represents small order probabilities, which we approximated as zero. As the time-step of one month is the lower limit of the incubation period, it was assumed that those PWID infected became infectious the following month.

The annual transmission rate for a connected discordant pair, β, was fitted to ensure that the long term prevalence would be 50%, in keeping with previous observations. Using a series of 100 simulated networks over 20 years, the equilibrium value of 50% was achieved when β took the value 0.20.

The probability of a particular infected node completing treatment in a given year was dependent on the treatment coverage and the strategy used. Where α was the cure rate, μ the background death rate and σ the duration of injecting, the probability of moving from

Infected to *Susceptible* compartments given that treatment was completed in a particular time interval, Δt, was given by:

$$\Pr\big(\mathrm{I}_k(\mathrm{t}) \rightarrow \mathrm{S}_k(\mathrm{t}+\Delta t)\big) = \alpha + (1-\alpha) * (\sigma + \mu)\Delta t.$$

For those not offered treatment that came to completion during the time interval, the probability was given by:

$$\Pr\left(\mathrm{I}_k(\mathrm{t}) -> \mathrm{S}_k(\mathrm{t}+\Delta t)\right) = (\sigma + \mu)\Delta t.$$

The fraction who failed treatment $(1-\alpha)$, did not die and did not move from the injecting network were assumed to remain infectious and never get retreated.

Model simulations on parameterised networks: intervention strategies

The effect of five community treatment strategies on the prevalence of HCV was investigated and two different treatment efficacies were used (60% and 80%) to reflect old and new regimen success rates. Population coverage rates investigated were 5, 15 and 25 per 1000 PWIDs per year. For each treatment efficacy/coverage combination, 100 simulations were performed, each with 20 randomly selected networks of size 524, producing 10,048 nodes. The simulated 10,048-node network was seeded with an infected node randomly chosen from each sub-network of size 524. A period of contiguous transmission was allowed to occur until further transmission did not take place for a given time step at which point an additional node was chosen at random until the starting prevalence of 50% was reached when new infection balanced rates of cessation of injecting and death.

For each simulation, after the starting 50% prevalence was reached, the five different treatment strategies and a "no treatment" control strategy were applied.

The five treatment strategies were as follows.

1. Treat the infected node with the highest degree first. This theoretical approach assumes knowledge of the whole network and the most highly connected nodes are treated by preference.
2. Treat the infected node with the greatest number of uninfected node-neighbours. Similar to strategy 1, this assumes knowledge of the network.
3. Treat the infected node with the lowest number of infected node-neighbours. Again, similar to strategy 1, this assumes knowledge of the network.

4. Treat randomly selected nodes: selects a node at random at each treatment epoch from the infected nodes that have never failed treatment.
5. "Treat your friends": choose a node at random as in 4, treat this node (the primary node) and treat all of its infected neighbours (secondary nodes). Continue choosing random nodes until coverage is reached for that time period. (Figure 1)

Results of simulations on networks

Effect of coverage on transmission and prevalence

As treatment coverage increases, HCV prevalence at 10 years reduces for both the high efficacy and low efficacy treatment (Figure 2). For a given efficacy and treatment strategy, prevalence declines as coverage increases. The drop in prevalence with increasing coverage is most marked with higher efficacy moving from coverage of 5 to 15 PWID per 1000 per year.

Effect of treatment efficacy on prevalence

As expected, treatment efficacy of 80% leads to lower prevalence than treatment efficacy of 60% (Figure 2). The difference becomes more marked as coverage increases.

Simulations on networks: effect of intervention strategies

Figure 2 shows the outcome of these five strategies expressed as prevalence per 1000 people with different treatment coverage, with both high and low efficacy treatments and over ten years. Within each set of parameters, all treatments perform better than no treatment, and all other strategies perform at least as well as random selection (strategy 4). The benefit of the "treat your friends" strategy (strategy 5) over the random strategy is most marked for higher efficacy treatment. For example at 10 years, treating 25 per 1000 PWID, the prevalence drops from 50 to 40% for the random strategy, and to 33% for the "treat your friends" strategy (6.5% difference, 95% CI 5.1 to 8.1%). At lower coverage, the effect is less marked.

Figure 2 shows that the "highest degree first" strategy also performs poorly. Again, this becomes more marked as coverage increases, and is more marked with more efficacious treatment.

Discussion

We developed several simulated networks with network characteristics informed by the observed injecting partner network among PWID in Melbourne, Australia. We conducted simulations of hepatitis C transmission across the simulated networks by seeding the networks and following probabilistic rules about transmission through the network until the baseline infection prevalence of 50% was reached. We then used these simulated networks and further simulated transmission and interventions. Intervention effectiveness was examined based on treatment coverage, treatment efficacy and treatment strategy. Our results suggest that taking the injecting network into account when treating PWID significantly impacts on HCV prevalence in the population over 5 and 10 years.

The majority of HCV models assume homogenous mixing of PWID, which is equivalent to assuming that the injecting network is fully connected. In reality this is not the case – not every PWID has an equal probability of injecting or sharing needles with some other PWID. It makes sense to consider the effect of the PWID network on HCV transmission, particularly if the average path length of the network is relatively long as is observed in our PWID network. A member of the network can be "protected" from HCV through the number of transmission required to reach that particular individual. It also follows that PWIDs whose network members are HCV-infected are at increased risk of HCV infection and are likely to acquire HCV faster than PWIDs in a network containing no or few infected network members at a given time.

As with our previous work on HCV incidence [41], our simulations suggest that PWIDs' social networks should be considered in treatment strategies. The current work differs from previous work in that it uses a parsimonious model in which people are either susceptible or infectious. Spontaneous clearance of virus occurs randomly across all infections in this model, rather than being a characteristic of a particular individual (as in Rolls *et al*. [41]). Additionally, unlike in Rolls *et al*., the current study assumes the source of infection is from within the network. While it is unrealistic to assume that we can observe all of a the network of PWID, we suggest that hepatitis C infection is highly likely to arise from an injector's network, even if not from the observed network. Since in this study we explicitly simulate inferred and unobserved nodes in the model, we think it reasonable to assume that hepatitis C has arisen within the network.

Hence this study poses the question "even if we knew all network details, does a network-based strategy perform better than a simpler strategy of treating an individual's immediate injecting partners?" We examine strategies that attempt to treat those with the lowest risk of

reinfection, treating those with the fewest infected neighbours first and we examine network strategies that attempt to treat those most likely to spread infection, treating the people with the most susceptible neighbours first. The results of the simulations are that under all coverage, duration and treatment efficacy scenarios that we examined, the full network-based strategies did not out-perform the "treat your friends strategy", and the "treat your friends" strategy was superior to the random treatment strategy.

Despite differences in methodology, this study has findings in common with those of Rolls *et al.* in that treating immediate injecting partners is a favourable strategy and treating those with the largest number of injecting partners is a poor strategy.[41]

Under fully connected or homogenous mixing assumptions, random selection of nodes for treatment would perform as well as any other strategy. In our empirically grounded simulated networks this is not the case. Network structure modulates a treated individual's risk of reinfection by affecting the risk to the treated individual posed by infected neighbours. The strategy of treating the highest-degree PWID first seems useful as it should lead to the greatest reduction in outward risk (risk from the infected person to others); however, this is only the case for high treatment coverage and efficacy, because PWID have a high risk of HCV reinfection. Also, using strategies based on ranking within the network (strategies 1–3) is not practical as they require full knowledge of the injecting network – highly unlikely in the real world. However, treatment strategy 5 (treat your friends) only requires an individual seeking treatment to be able to identify current network neighbours (people with whom they inject drugs). Strategy 5 performs as well as the more complex strategies in the simulations of this model, which covered realistic parameters for treatment coverage and efficacy.

Most models assume random mixing of PWID, which is not realistic. In contrast, our model assumes the network is reasonably stable over time or does not differ in such a way that any observed network structure is lost over months or a few years. The median time for a partnership of injecting drug use (an edge of the network) in our observed network was approximately three years [45], making the static network assumptions used in the model relevant at least out to this time. If network mixing is highly dynamic then our model is likely to overestimate the benefit of a network strategy; on the other hand, random mixing models may overestimate the efficacy of random treatment. The truth is likely to fall somewhere between the two, and future research should take into consideration the dynamic nature of injecting networks.

Our findings are particularly pertinent as new direct-acting antiviral agents for HCV treatment become available over the next five years. Treatment must remain the choice of the individual PWID and their treating physician, but in the context of limited resources and the likelihood of treatment costing at least $20,000 per course it makes sense that treatment should be targeted whenever possible and appropriate. As our data show, targeting treatment of current PWID using network structure accelerates reduction of the prevalence of HCV over the long term [25, 26]. Targeting could include asking PWID undergoing treatment to encourage their injecting network partners to seek treatment advice. The new therapies will have fewer side effects than the Peg/Riba regime [28] thus simplifying treatment of partners or people in the same social group around the same time. Also, the long path length of PWIDs' network structure (as observed in this study) allows interventions to disconnect regions of low prevalence from regions of high prevalence.

This study has limitations. Simulated networks based on a snowball sample were used, not a full empirical contact network. The simulated networks are designed to have features in common with the observed networks, but are potentially different if the un-sampled regions of the network are quite different. Additionally, dynamic changes in the network structure were not considered, nor were unobserved acquisitions of HCV outside the network. A dynamic structure is more realistic and may lead to different estimates of network based treatment effects. Both of these limitations could be addressed in future extensions of this model. The model also assumes equal probability of HCV transmission between each discordant pair of PWID who inject together, without stratifying risk based on duration of injecting, reported needle-sharing behaviour, behavioural risk mitigation strategies and frequency of use. These features could be added to the model in future work. Additionally, the networks of size 524 include singletons and isolated pairs of PWID, although they were not specifically modelled by the ERGM. The presence of large numbers of PWID in isolation will impact any network-based strategy.

In summary, the structure of PWIDs' injecting network influences HCV transmission and impacts significantly on the effectiveness of treatment strategies. As well as benefiting individual PWID by reducing their risk of HCV reinfection, taking PWIDs' networks into account will ensure that new HCV treatments produce maximum community benefit by reducing the prevalence of HCV amongst PWID.

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Table 1. Proportion of the PWID population with each set of attributes (taken from Rolls *et al*.[40])

Location	Gender	Age	Population estimate (%)
1	M	> 25	21.9
1	F	> 25	11.8
2	M	> 25	16.4
2	F	> 25	8.9
3	M	> 25	9.5
3	F	> 25	5.1
1	M	< 25	7.3
1	F	< 25	3.9
2	M	< 25	6.4
2	F	< 25	3.4
3	M	< 25	3.5
3	F	< 25	1.9

Table 2. Parameter estimates associated with individual attributes and subgraph structures, derived by Rolls et al.[40]

Parameter	Estimate	Standard Error
Edge	-8.384	1.006
Isolates	-9.308	0.000
Alt. k-star	0.611	0.424
Alt. k-triangle	1.707	0.157
Alt. k-2-path	-0.563	0.157
Same location	2.111	0.253
Same gender	0.28	0.174
Same age<25	0.787	0.174
Same user frequency (daily versus less frequent)	0.429	0.156

Table 3. Parameters used in this model, their values and reason for choice of parameter.

Parameter	Meaning	Value	Reference
α	efficacy of treatment	0.6 representing 0.45 SVR for genotype 1 and 0.8 SVR for genotype 2 or 3 ->0.8 PI based therapies	IFN-based therapies NCHECR (2006, pp. 29) [46] Ferenci *et al.* [47]
π	risk of transmission per discordant pair	0.20	Fitted to model to achieve 50% prevalence
δ	probability of clearing infection	0.26	Micallef *et al.* [48] NCHECR (2006, p.27&74)[46]
μ	death rate	0.01	Stoove *et al.* 2008 [49]
ϕ	number of people treated per 1000 PWID	15 25 50	This parameter was varied to assess achievable coverage
ρ	prevalence at baseline	50%	Aitken *et al.* 2008 [37] Miller *et al.* 2009 [38]
σ	1/duration of injecting	14	Dore *et al.* 2010 [50]

Figure 1. Five treatment strategies using a network based approach

Figure 2 – Impact of hepatitis C treatment at 10 years with 60% and 80% treatment efficacy.

2a. Low efficacy treatment (60%) with coverage of 5 per 1000 PWID per year

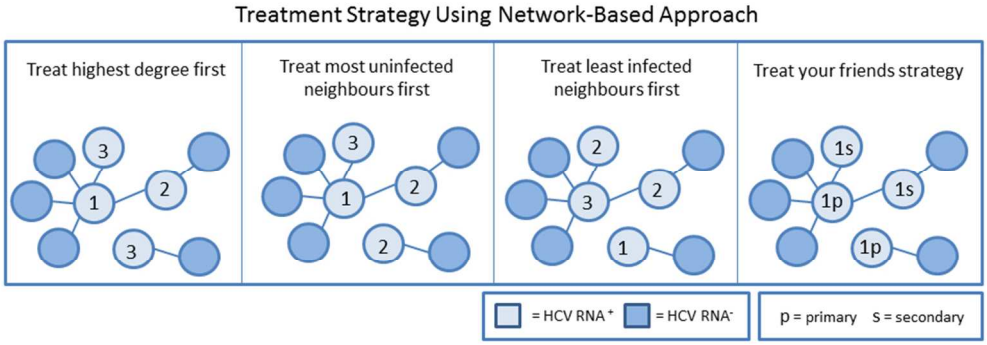
2b. Low efficacy treatment (60%) with coverage of 15 per 1000 PWID per year

2c. Low efficacy treatment (60%) with coverage of 25 per 1000 PWID per year

2d. High efficacy treatment (80%) with coverage of 5 per 1000 PWID per year

2e. High efficacy treatment (80%) with coverage of 15 per 1000 PWID per year

2f. High efficacy treatment (80%) with coverage of 25 per 1000 PWID per year



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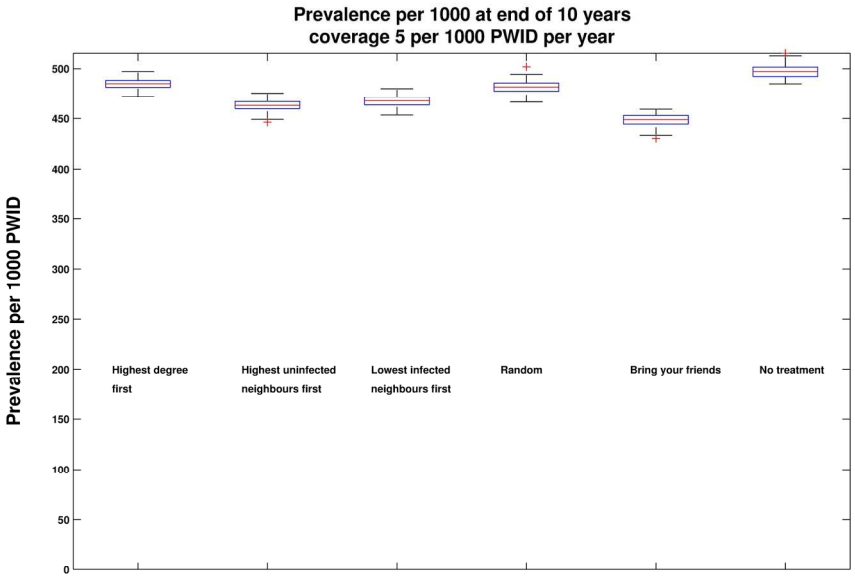

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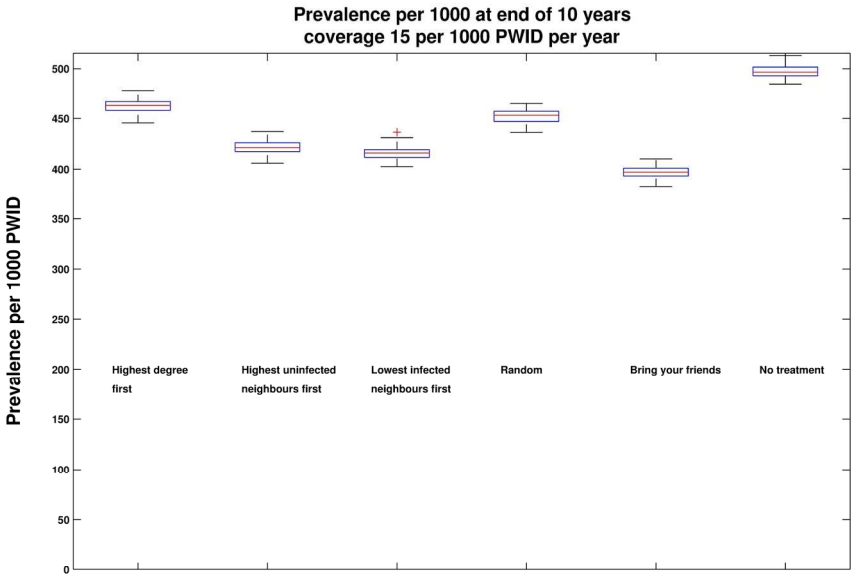

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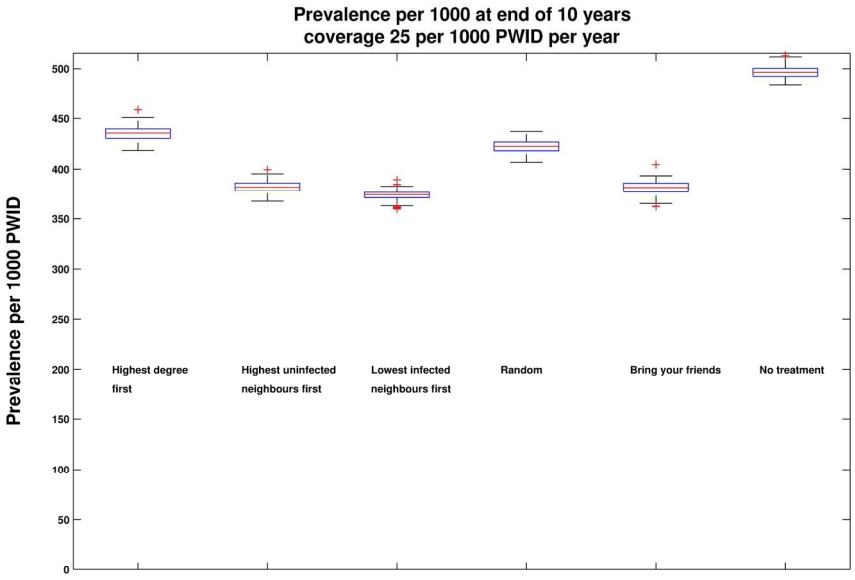

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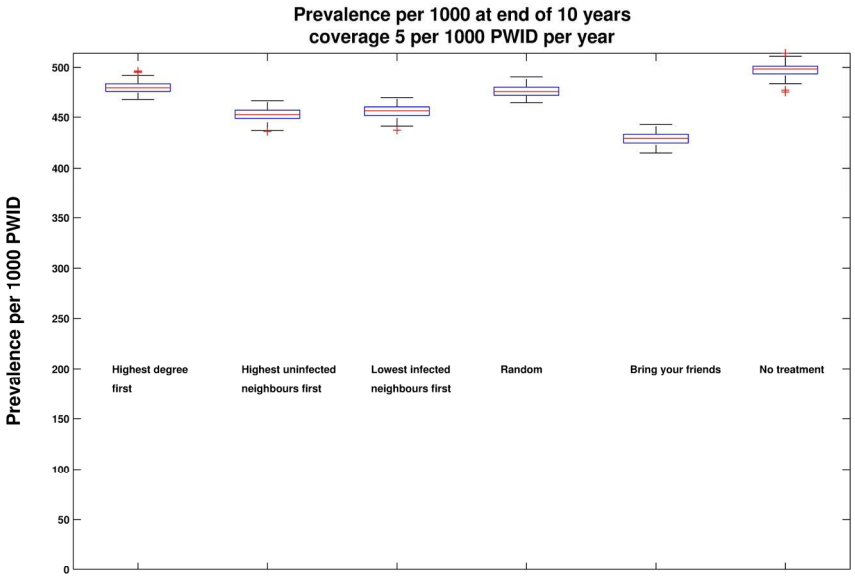

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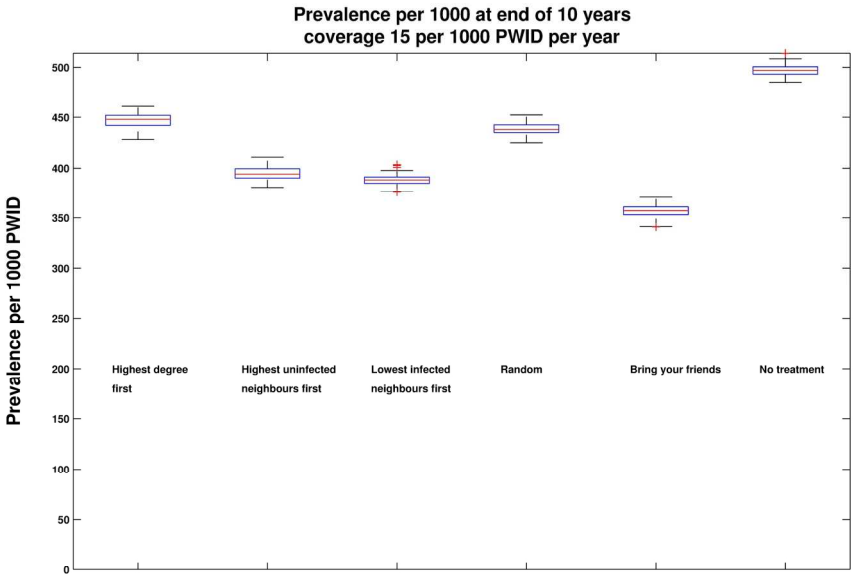

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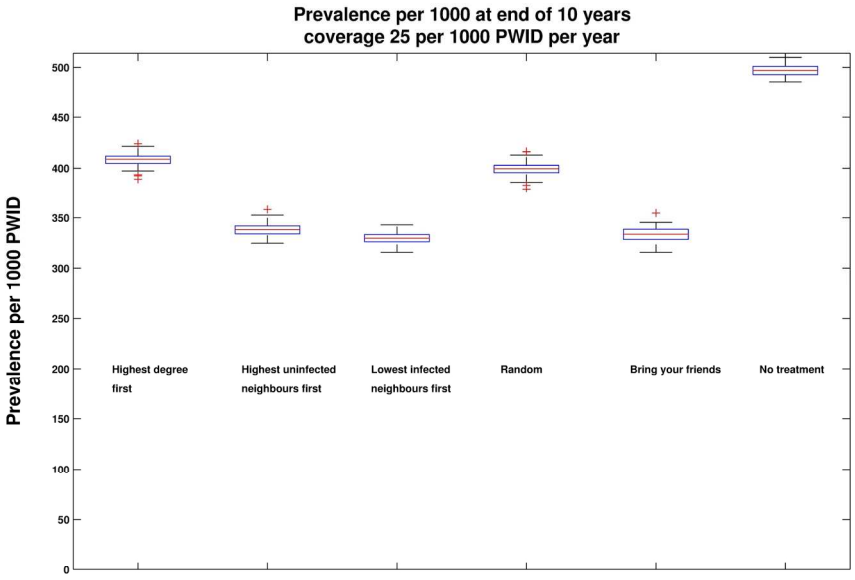

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