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ORIGINAL ARTICLE

Does Information about IDUs' Injecting Networks Predict Exposure to the Hepatitis C Virus?

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Background and Aims: **Many previous studies have used cross-sectional approaches to measure associations between injecting drug users' (IDUs') characteristics and hepatitis C virus (HCV) status, and identified independent predictors of antibody to HCV (anti-HCV) positivity including duration of injecting, needle-sharing history and prior imprisonment. Although HCV transmission between IDUs occurs primarily through blood transfer during close physical interactions, the contribution of social network data to prediction of HCV status has not been previously assessed.**

Methods: **215 injecting drug users and their injecting network members were recruited in Melbourne, Australia between July 2005 and August 2006. Logistic regression was used to analyze behavioral and social network data for predictors of HCV exposure.**

Results: **IDUs' HCV exposure status was independently associated with the age of first injection of their injecting network members (adjusted OR=2.82, P=0.019) and the HCV exposure status of those network members (adjusted OR = 6.17, P<0.001), in addition to several 'traditional' behavioral and lifetime variables.**

Conclusions: **Patterns of exposure to the hepatitis C virus are influenced by the characteristics of members of IDUs' social networks. HCV RNA and/or antibody testing are an important part of any HCV prevention strategy for IDUs; increased availability of testing and sharing HCV status information within social networks would enable more IDUs to avoid infection.**

Keywords: **Hepatitis C Virus, Social Networks, Injecting Drug Users, Cross-Sectional Analysis**

Introduction

Over the eighteen years since the hepatitis C virus (HCV) was formally identified, dozens of studies have used cross-sectional approaches to measure associations between injecting drug user's (IDUs') behavioral or other characteristics and hepatitis C virus status. Variables identified as independent predictors of antibody to HCV (anti-HCV) positive status include duration of injecting [1-5] frequency of injecting [2, 6-8], needle-sharing [7, 9-11], and prior imprisonment [1, 2, 9]. Lists of significant predictors of HCV status vary from study to study, even when IDU populations appear comparable, but with few exceptions include data drawn solely from individual research participant's descriptions of themselves and their past and present activities. Traditional participant-centered

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approaches to HCV epidemiology assume all actors are independent; they cannot account for the fact that blood-borne viruses (and many other infectious diseases) are transmitted through specific interactions in an interconnected social network [12]. It seems at least superficially plausible that incorporating knowledge of IDUs' social networks should add to our ability to explain patterns of hepatitis C virus infection.

For the purposes of this article, we hypothesized that the behavioral and other characteristics of IDUs' network members are significant predictors of hepatitis C status. If true, adding information about IDUs' injecting networks (including interviewees' descriptions of their risk relationships with specific network members and data network members supply about themselves) to a logistic regression model should substantially improve the explanatory power of the model.

Materials and Methods

Data collection

Between July 2005 and August 2006, five outreach research workers recruited, interviewed and took blood samples from 316 current IDUs as the first encounters in an ongoing longitudinal study. Recruitment took place in three locations dispersed widely across the city of Melbourne (the capital of Victoria, Australia; 2005 population 3,634,200) [13], each of which was home to an established illicit drug scene as a well as a dedicated, fixed-site needle and syringe program. Participants were interviewed using a study-specific, quantitative questionnaire developed from previous research [14]; they were asked to nominate and describe their network members (people with whom they had injected drugs, on the same occasion, in the same location, in the previous three months), and encouraged to introduce these individuals to us for potential recruitment. IDUs aged 25 years or younger were preferentially recruited. In all other important respects, interview procedures and the data collected were as previously described elsewhere [14]. Ethics approval for the study was obtained from the Victorian Department of Human Services Human Research Ethics Committee.

Serology and virology

Blood samples were screened for anti-HCV by a third-generation enzyme immunoassay (Abbott Laboratories, Chicago, Ill) and anti-HCV positive specimens were tested again by Murex anti-HCV version 4.0 (Murex Biotech, Kyalami, South Africa) for confirmation. Irrespective of anti-HCV status, all samples were tested for the presence of HCV RNA by the COBAS AMPLICOR HCV test version 2.0 (Roche, Branchberg, NJ).

Analysis

We set out to examine the importance of potential predictors of participants' HCV status using four sets of independent variables (Fig. 1):

Dataset 1: data supplied by participants about themselves (as collected in standard epidemiological studies)

Dataset 2: data supplied by participants about each network member and each relationship ('third party' data)

Dataset 3: data supplied by participants' network members about themselves (collected when network members were recruited and interviewed)

Dataset 4: Network members' anti-HCV and HCV RNA status.

Our datasets were culled to include only IDUs who described at least one network member who was also interviewed and bled (and thus was also a participant), resulting in a final count of 215

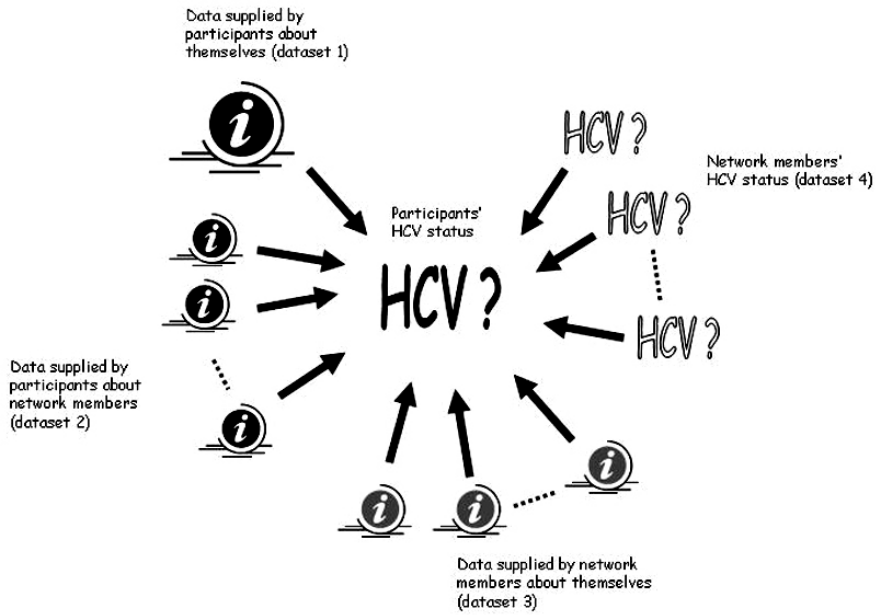

Figure 1. Schematic figure presenting potential predictors of participants' HCV status using four sets of independent variables.

participant records. This was necessary to ensure that the set of participant records remained constant throughout the analysis so that successive models were directly comparable. As a result, most (but not all) of the network members referred to our analysis are also participants. Being a participant means their HCV status is a datum in the dependent variable, their self-referential data are part of dataset 1, they supplied data about their own network members for inclusion in dataset 2, and at least one of their network members is a participant. Many (but not all) of the participants are in turn the network members of other participants.

If the direction of nomination is taken into account, as it is in our analyses, it is possible for a participant to *have* network members but not *be* the network member of any other IDUs and vice versa. Figure 2 shows a subcomponent of our entire network (slightly fictionalized, for demonstration purposes) with arrows representing directions of nomination from one IDU to another. IDU 3012 nominated and supplied information about seven injecting partners, but was not nominated by any other IDU, so is a participant but not a network member of any other participant. Conversely, IDUs 2012, 2029, 4011 and 7006 were nominated as network members but did not nominate any other interviewed IDUs, so are not participants and do not contribute to the dependent variable or datasets 1 or 2. Information about 2012, 2029, 4011 and 7006 may nevertheless be included in independent variables (datasets 3 and 4) serving to explain the HCV exposure status of the participants who nominated them (2009, 3012, 7003, 7005).

Because most participants listed more than one network member, in order to relate data about (dataset 2) or from (dataset 3) network members to the participants who nominated them, those variables had to be aggregated. Data supplied by participants about their network members (dataset 2) were aggregated by, in most cases, adding all the values for individual network members, or taking means in others; data supplied by network members about themselves (dataset 3) were always aggregated by taking means. The reasoning behind these differing aggregation procedures was as follows. Network member data were supplied by their nominating participants, and were complete - meaning we had data for every network member listed. Therefore, aggregating by adding data for multiple network members produced meaningful values for characteristics such as 'years of injecting' and 'number of injections in the past three months'; aggregating by means was appropriate for 'age' and 'gender' (proportion of females among network members). In contrast, network members' own data (dataset 3) exist only for those network members actually interviewed, and 31% of the network members listed by our interviewees had not been interviewed by the time of analysis - as stated earlier, to be included in this analysis every participant had to have at least one interviewed network member. Thus, mean values for all data from participants' network members were the appropriate method of aggregation, because they avoided bias that would have arisen from some participants having more interviewed network members. Likewise, network members' HCV test data were aggregated using means. After aggregation, continuous variables (*e.g.*, age of first injection) were dichotomized using median values or the closest whole numbers as midpoints.

Univariate associations with HCV status (any evidence of exposure to HCV, either antibody or polymerase chain reaction [PCR]) were assessed using chi-squared tests, and then binary logistic regression was used to find the model of best fit between HCV status and participants' personal data. Variables were chosen for inclusion in the logistic regression on the basis of a change in the likelihood ratio test at P=0.05. The resulting model was confirmed by backwards elimination of variables based on their significance in the full multivariate model; the Hosmer-Lemeshow test was applied to assess goodness-of-fit and residual plots were assessed for data points exerting undue influence. This process was repeated with successive inclusion of the extra information described in points two to four above.

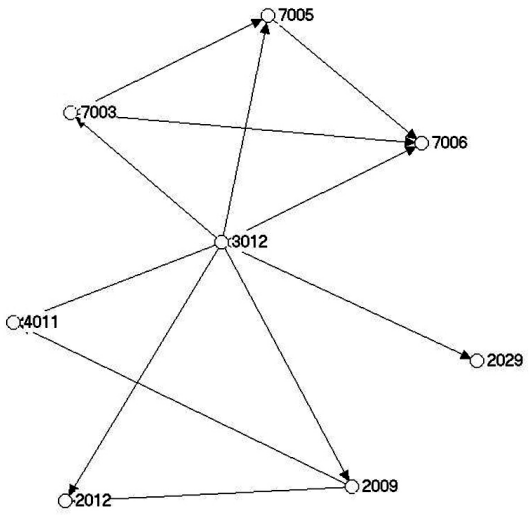

Figure 2. Schematic figure showing a subcomponent of our entire network (arrows representing directions of nomination from one IDU to another).

Results

Descriptive data

Table 1 shows our participants were a relatively young sample of IDUs by Australian standards, overwhelmingly unemployed and male, and mostly primary heroin users.

Table 1. Socio-demographic and drug-related information.

Variable	Mean	Median	Range	%
Age (years)	26.0	24.7	16.1-45.6	
Injecting career (years)	7.8	6.8	0.25-24.1	
Age of first injection (years)	18.2	17.0	12.0-43.0	
Female gender				34.9
Unemployed				70.2
Homeless/temp accommodation				27.3
Ever imprisoned				29.8
Primary heroin injector				72.1
Primary amphetamine injector				13.2
Primary buprenorphine injector				9.8
Ever shared a needle and syringe				67.0
Ever in drug treatment				80.9
In treatment at interview				52.6

Associations with HCV exposure; participants' data (dataset 1)

The first regression model was generated using only HCV status (the independent variable) and data supplied by participants about themselves. As table 2 shows, all the independent significant predictors of HCV status were 'lifetime' variables rather than recent behavioral variables.

The model described in table 2 provides a good fit to the data (Hosmer and Lemeshow test = 0.95, Nagelkerke R^2 = 0.38). Note the relative strength of odds ratios for past imprisonment and history of drug treatment.

Table 2. Regression model incorporating only participants' data (dataset 1).

Variable	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
In drug treatment, ever	5.46 (2.65-11.26)	.000	6.38 (2.59-15.72)	.000
Been in prison, ever	11.00 (3.29-36.74)	.000	13.60 (3.62-51.12)	.000
Injected with another IDUs' used N&S, ever	3.32 (1.76-6.26)	.000	2.48 (1.18-5.21)	.017
At least one body piercing	0.41 (0.22-0.77)	.006	0.35 (0.15-0.80)	.012
Female gender	0.77 (0.41-1.45)	.422	3.62 (1.48-8.86)	.005
Been vaccinated for HBV	0.68 (0.37-1.26)	.219	40 (.18-0.88)	.023

N&S: needles and syringes; HBV: hepatitis B virus.

Participants' data (dataset 1) plus third-party network member data (2)

None of the variables containing information supplied by participants about their network members (see figure 1) was able to improve the model detailed in table 2.

Participants' data (dataset 1) plus network members' data (3)

The model described in table 3 has a Hosmer and Lemeshow test value of 0.98 and a Nagelkerke R^2 of 0.41. Only one variable based on network members' personal data - signifying whether they had injected drugs (not necessarily sharing needles) with an average of five or more individuals in the three months prior to first interview - added significantly to the model's explanatory power.

Table 3. Regression model incorporating participants' data (dataset 1) and their network members' data (dataset 3).

Variable	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
In drug treatment, ever	5.46 (2.65-11.26)	.000	5.22 (2.09-13.03)	.000
Been in prison, ever	11.00 (3.29-36.74)	.000	14.45 (3.73-55.88)	.000
Injected with another IDUs' used N&S, ever	3.32 (1.76-6.26)	.000	.71 (1.26-5.80)	.010
At least one body piercing	0.41 (0.22-0.77)	.006	0.27 (0.11-0.64)	.003
Female gender	0.77 (0.41-1.45)	.422	3.43 (1.39-8.46)	.007
Been vaccinated for HBV	0.68 (0.37-1.26)	.219	0.46 (0.20-1.04)	.061
Injection ≥18 years	2.09 (1.10-3.96)	.025	2.71 (1.20- 6.14)	.017

N&S: needles and syringes; HBV: hepatitis B virus.

Participants' data (dataset 1), network members' data (3) and network members' HCV status (4)

The contributions of network members' anti-HCV and HCV RNA status were evaluated in turn, then simultaneously.

The model described in table 4 has a Hosmer and Lemeshow test value of 0.77 and a Nagelkerke R^2 of 0.45. In table 5, network members' HCV infection status (as measured by the presence of HCV RNA) is the final additional input.

HCV RNA status is highly correlated with anti-HCV status; with network members' HCV RNA status in the logistic regression, adding anti-HCV status made negligible difference. The model described in table 5 has a Hosmer and Lemeshow test value of 0.61 and a Nagelkerke R^2 of 0.50.

Table 4. Regression model incorporating participants' own data (dataset 1), their network members' own data (dataset 3), and network members' anti-HCV status (dataset 4).

Variable	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
In drug treatment, ever	5.46 (2.65-11.26)	.000	6.07 (2.32-15.88)	.000
Been in prison, ever	11.00 (3.29-36.74)	.000	11.490 (2.93-44.99)	.000
Injected with another IDUs' used N&S, ever	3.32 (1.76-6.26)	.000	2.77 (1.25-6.10)	.012
At least one body piercing	0.41 (0.22-0.77)	.006	0.28 (0.11-0.67)	.005
Female gender	0.77 (0.41-1.45)	.422	3.09 (1.21-7.91)	.019
Been vaccinated for HBV	0.68 (0.37-1.26)	.219	0.45 (0.20-1.05)	.066
NMs' mean age at 1st Injection ≥18 years	2.09 (1.10-3.96)	.025	2.96 (1.26-6.95)	.013
NMs all anti-HCV+	2.96 (1.58-5.53)	.001	3.17 (1.45-6.97)	.004

N&S: needles and syringes; NM: network member

Table 5. Regression model incorporating participants' own data (dataset 1), their network members' own data (dataset 3), and network members' HCV infection status (dataset 4).

Variable	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
In drug treatment, ever	5.46 (2.65-11.26)	.000	6.14 (2.25-16.75)	.000
Been in prison, ever	11.00 (3.29-36.74)	.000	10.63 (2.67-42.28)	.001
Injected with another IDUs' used N&S, ever	3.32 (1.76-6.26)	.000	2.78 (1.23-6.27)	.014
At least one body piercing	0.41 (0.22-0.77)	.006	0.28 (0.11-0.68)	.005
Female gender	0.77 (0.41-1.45)	.422	2.55 (0.98-6.63)	.056
Been vaccinated for HBV	0.68 (0.37-1.26)	.219	0.46 (0.19-1.09)	.077
NMs' mean age at 1st injection ≥18 years	2.09 (1.10-3.96)	.025	2.82 (1.19-6.68)	.019
NMs all HCV PCR+	5.44 (2.67-11.10)	.000	6.17 (2.54-15.02)	.000

N&S: needles and syringes; NM: network member

Discussion

There are fundamental problems inherent in attempts to identify predictors of HCV status in cross-sectional studies of IDUs, mostly associated with our inability to know duration of infection with any accuracy. There are several reasons for this, which can be summarized as follows:

- injecting illicit drugs is an illegal and therefore poorly documented phenomenon
- people may inject drugs for months, years or even decades
- HCV infection risk is highest at the start of an injecting career
- HCV infection in IDUs is almost invariably asymptomatic.

Because their behavior is highly stigmatized and criminally sanctioned, IDUs (the people at highest risk of HCV infection) do not congregate in identifiable groups that can be efficiently corralled for research purposes, unlike (for example) people living with hemophilia, cancer or diabetes [15]. When eventually recruited as subjects for a research project, IDUs may be a very long time into their drug-using careers; most studies (excepting those that explicitly seek to recruit new injectors) have reported mean injecting career lengths of 10 years or more. As infection risk is highest in the first year or two of injecting - plausibly due to new IDUs' poor injecting technique and lack of awareness about HCV and infection risks - the date of first infection is very likely to precede recruitment by a matter of years [16]. Finally, the vast majority of HCV infections are asymptomatic at the time of infection and for many years following, so passive identification of new cases is rare.

All the facts outlined above mean that cross-sectional research aimed at determining predictors of HCV infection is heavily handicapped, because most of the behavioral data that can be collected cannot be definitively tied to the occasion of infection. Certain characteristics - length of time injecting, ever shared needles - are 'lifetime' variables; in principle, they include information from the research participant's entire drug using career. But most, such as sharing frequency in the past six months, or number of people present at last injecting occasion, may refer only to a recent and small slice of that career. By investigating associations between measures of recent behavior and hepatitis C status, researchers make an implicit assumption that the drug-using participant's behavior has remained more or less unchanged over time (or, for participants with evidence of exposure to HCV, since he or she acquired the virus).

Despite these pitfalls, our results show that incorporating data from IDUs' social networks can significantly improve cross-sectional prediction of HCV status. The significance and predictive value of two 'network' variables implies that an IDU's location within the social network matters to his (or her) personal HCV status. If a participant's network members were on average 18 years or older when they began injecting, or all had evidence of exposure to HCV, then the participant was significantly more likely to have been exposed to HCV. In particular, our participants' HCV infection status was very strongly and independently associated with the

HCV status of their injecting network members (with an odds ratio of 6.17 (95% CI 2.54-15.02) it is second only to history of imprisonment). This is a finding that has been previously demonstrated for HIV infection in IDUs but not for HCV [17]. Indeed, our expectation on beginning this analysis was that the very high prevalence and early acquisition of HCV infection in IDUs relative to HIV would make the detection of significant network effects unlikely.

Six variables appeared in the final model (Table 5) and retained statistical significance. Prior imprisonment has been identified frequently in previous research as a predictor of HCV exposure, as has injecting with another IDUs' previously used needle. Drug withdrawal or maintenance programs (methadone, buprenorphine) are not commonly cited as associated with HCV exposure, but anti-HCV prevalence in treatment populations of greater than 75% have been described [18, 19]; thus a history of drug treatment is a plausible marker for other characteristics, such as length and intensity of injecting career. Having at least one body piercing was a negatively associated predictor; although body piercing is a parenteral procedure and a seemingly logical risk factor for HCV transmission, the practice has become 'mainstreamed' in Australia over the past decade or more, and the vast majority of piercings are (and were in our study) performed in licensed premises, so there is no reason to expect this variable to be positively associated with HCV exposure. The significance of body piercings as a negative predictor may be related to the greatly increased popularity of the practice among younger (and therefore, relatively likely to be HCV-unexposed) Australians in recent years [20]. The finding that network members' greater age at first injection was a positive predictor of participants' HCV exposure fits with the (nearly significant) univariate association between HCV exposure and age of first injection in participants (OR = 1.09, 95% CI = 1.0-1.18). It is plausible that, on average, people who begin to inject at a relatively greater age do so with people who are similarly aged but have longer injecting careers, so are more likely to have chronic hepatitis C virus infection.

Our finding that having at least one HCV RNA-negative IDU in your injecting network is associated with reduced odds of being exposed to HCV yourself is important. If HCV RNA-negative IDUs know their personal status and that of their injecting partners, they can exert more control over the makeup of their injecting network and hence lower their personal risk of HCV exposure; other authors have shown that knowledge of HCV status enables useful behavior change [21]. As few IDUs in Australia - and almost certainly elsewhere in the world - know their HCV RNA status, the obvious practical implication of our results is that these tests should be made more available. At present, IDUs who test positive for anti-HCV are assumed to be RNA-positive also, even though clearance rates of up to 40% two years or more after infection have been demonstrated [22, 23]. Polymerase chain reaction tests are also several-fold more expensive than anti-HCV antibody tests, a further disincentive for their use. Nevertheless, as networks members' anti-HCV status was shown to be a significant independent predictor of participants' HCV exposure status, albeit not as strong as RNA status, knowledge of one's injecting networks members' anti-HCV status is still helpful as a potential means of reducing one's risk of infection. These results are a sound argument for the utility of antibody testing as an HCV prevention strategy for IDUs, and thus increased availability of testing (including PCR testing if possible) at locations such as needle-syringe programs (NSPs) and primary health centers to enable more IDUs to avoid infection. The recent advent of reliable and inexpensive means of testing for HCV antibodies in saliva makes such a step more economically feasible [24].

Set against the increased explanatory power conferred by network data is the greater complexity, difficulty and cost of collecting and analyzing them. Attempting to recruit specific individuals nominated by previous participants (in order to generate the links that form social networks) is much more time-consuming than recruiting at NSPs and other services frequented by IDUs. In addition, in order to collect and manage our network data, we use electronic questionnaires loaded on personal digital assistants (PDAs, or handheld computers) which are regularly synchronized with a central database. While this system eliminates the data entry costs associated with traditional paper questionnaires, it has extra capital costs, is much more complicated and vulnerable to disruption, and requires considerable information technology support. Finally, to get the most out of network data necessitates some expertise in social network analysis, an esoteric and challenging field of mathematics. Despite these drawbacks, as we have attempted to show in this article, social network methods can generate rich datasets that lead to useful epidemiological insights.

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