Social Structural and Behavioral Underpinnings of Hyperendemic Hepatitis C Virus Transmission in Drug Injectors


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Background. Hepatitis C virus (HCV) is hyperendemic in drug injectors, yet social structural and behavioral factors underlying transmission are not well established.

Methods. We conducted a case-control study of HCV seroconversion in drug injectors, focusing on transmission within networks. Incident case subjects (n = 17) and seronegative control subjects (n = 42) reported injection and sex partners and referred as many as 5 for interviewing and blood testing. We performed nucleotide sequencing of HCV isolates from infected individuals.

Results. Seventy-eight percent of recent injection partnerships involved behavior that could transmit HCV. Case subjects and control subjects were similar demographically and behaviorally. Case subjects, however, had more HCV-infected partners and consequently engaged in injection risk behavior with more infected partners. The injection network was mostly connected, dense, and cyclic, but the sexual network was highly fragmented. Although participants generally injected with partners of similar age, most HCV-uninfected participants recently had injected with infected partners. In at least 1 of 4 pairs of genetically linked infections, transmission appeared to be due to sharing of injection equipment other than syringes. Except for transmission pairs, network distance between incident case subjects and genetic distance between their HCV variants were uncorrelated.

Conclusions. Without dramatic reductions in injection risk behaviors, shattering of cohesive injection networks, and/or broad coverage of an effective vaccine, HCV will likely remain hyperendemic in drug injectors.

Hepatitis C virus (HCV) infection is hyperendemic among drug injectors worldwide [1–3]. The annual incidence of HCV infection in seronegative injectors has ranged from ~10% to ~40% [2, 4–6]. Sharing of syringes and other injection paraphernalia is associated with HCV seroconversion [4, 5, 7, 8]. Several research teams have also studied social structural influences on disease transmission in injection drug users (IDUs), investigating aspects of injection networks and the relationship between prevalent HIV infection and network position [9–13]. For other infectious diseases, properties of contact networks covary with the speed and scope of transmission; for instance, the connectivity, cyclicity, density, and concurrency of sexual networks are associated with the incidence of sexually transmitted disease [14–18].

Building on this foundation, we examined the social structural and behavioral factors underlying hyperendemic HCV transmission in IDUs. We measured associations between network and behavioral variables and incident infection. We also assessed injection and sexual network structures for their transmission potential and described patterns of mixing by serostatus and age. Finally, we documented the risk behaviors in
partnerships with genetically linked infections—reflecting transmission—and investigated the correspondence between genetic and network distance among incident case subjects.

METHODS

Study Design
We conducted a case-control study of HCV seroconversion in IDUs, focusing on transmission within networks. Case subjects were IDUs with incident HCV infection, defined as either previously HCV antibody (anti-HCV)–negative individuals who were anti-HCV positive at their most recent test or new injectors (<8 months since their first drug injection) who were anti-HCV positive at study enrollment. Control subjects were anti-HCV–negative IDUs. Both case subjects and control subjects referred their injection and sex partners for interviewing and blood testing. Informed consent was obtained from all participants, and study procedures were approved by the Institutional Review Boards of the University of Washington and the Washington State Department of Health.

Index Individuals
For this study, we recruited index individuals from a large prospective cohort of drug injectors in Seattle [7, 19]. Individuals were eligible to participate if they had injected drugs at least once during the preceding 12 months, were ≥14 years of age, and were English speaking. Cohort study participants were scheduled for HCV antibody testing and interviews about their risk behaviors every 6 months. Those meeting case criteria were invited to participate in the present study. For each case subject participating as an index individual, we recruited up to 4 anti-HCV–negative study participants similar in age.

Seventeen case subjects and 42 control subjects were enrolled between December 2000 and January 2002. Two index individuals had missing or indeterminate anti-HCV status and were included in network analyses only. These 61 index individuals successfully referred 146 contacts (133 injection partners and 13 injection/sex partners). Twenty-one contacts had already been enrolled as a case subject or control subject, and 14 persons were successfully referred as a contact by multiple index individuals.

Procedure

Interviews of index individuals and referral of partners. Interviewers elicited each index individual’s injection and sex partners for the period during which the index individual could have possibly acquired HCV (typically 12 months, given the testing interval in the cohort study and window period of the anti-HCV test; range, 5–12 months). Most (68%) of the interviews of the index individuals were conducted on the ending date of the recall period. However, 17% (10) of the index individuals (including 5 case subjects and 4 control subjects) were interviewed >90 days (maximum, 489 days) after the end of the recall period, partly because we sought to include as many incident case subjects as possible. Index individuals’ recall periods were 67% concurrent. That is, the sum of the pairwise temporal overlap between index individuals’ date-specific recall periods was 67% of the sum of the maximum possible overlap of their recall periods if the precise dates could be shifted with the durations kept constant. Therefore, most reported partnerships occurred within the same, relatively short period (mid-2000–mid-2001). Interviewers elicited index individuals’ injection and sex partners separately. Injection partners were defined as persons with whom an index individual had injected drugs, regardless of whether they shared needles [20]. Sex partners were defined as anal, oral, and vaginal sex partners, regardless of the context in which sexual contact occurred [20]. To enhance recall of partners, interviewers administered supplementary elicitation techniques after index individuals freely recalled partners, and these techniques boosted reporting substantially (D.D.B., H.H., and E.H., unpublished data).

Next, index individuals identified partners whom they could refer to the study. Interviewers then asked the index individual to refer all such partners (if <6); if an index individual had >5 partners whom he or she could refer, the interviewer designated a systematic random sample of 5 for referral. Interviewers gathered first names/nicknames and physical and demographic descriptions of the selected partners; for partners not selected, only first names/nicknames were collected. Index individuals received $15 for participating in the interview and $10 for each partner successfully referred. Index individuals received vouchers to give to partners whom they were to refer.

Interviewing and testing of partners. When partners came to the study site, interviewers determined whether the partner matched (by name, physical description, and voucher number) the individual reported by the index individual (see the Appendix, which is available at the Journal’s Web site [http://www.journals.uchicago.edu/JID/journal/home.html]). Partners referred to the study within 21 days of the index individual’s interview received $5 for redeeming a voucher and an additional $20 for participating in an interview and testing. Seventy-three percent of referrals were successful (146 partners referred successfully of 200 partners sought). Each enrolled partner completed an interviewer-administered questionnaire about the partner’s injection and sexual risk behavior with the index individual and provided a blood specimen. The recall period for most risk-behavior questions in the interviews of partners matched that for the referring index individual. Interviewers did not elicit partners’ other partners.

The key measures derived from interviews of partners include whether the partner reported injecting with the referring index
individual and the index individuals’ receptive syringe sharing and receptive injection risk. Receptive syringe sharing indicates whether the partner reported the index individual had used a needle/syringe the partner had previously used during the specific recall period. Receptive injection risk indicates whether the partner reported the index individual had engaged, during the specific recall period, in any of the following behaviors that may involve risk of acquisition: (1) used a needle/syringe after the partner had used it (regardless of bleaching); (2) used a “cooker” (i.e., a container for heating drugs into solution) after the partner had used it; (3) used a “cotton” (i.e., a filter to block undissolved contaminants when drawing drug solution into the syringe) after the partner had used it; (4) used the same rinse water (for cleaning the syringe after injection) or same rinse water container as the partner; or (5) divided drugs with the partner using an unsterile, previously used needle (“backloading” or “frontloading”). “Don’t know” and missing partner responses were classified as “no” in analysis. The receptive injection risk measure may be slightly liberal, because the questions regarding shared use of rinse water and syringe-mediated sharing of drugs did not specify the order in which participants had used the rinse water or syringe. Our use of partners’ reports for these measures may lessen any bias arising from social desirability.

**Laboratory procedures.** Within 3 h after collection, blood specimens from all participants (index individuals and partners) were sent to the laboratory to be centrifuged and then aliquoted for storage at −70°C. Anti-HCV testing was performed with EIA (version 2.0, Abbott Laboratories); reactive specimens were retested in duplicate by EIA and were interpreted as being anti-HCV positive if either or both specimens were reactive. We evaluated samples with a low signal:cutoff ratio [21] by using the Recombinant Immunoblot Assay (Chiron). All participants received pre- and posttest HCV counseling.

The stored specimens from participants who tested anti-HCV positive were submitted for DNA sequencing of both the HCV envelope 1 (E1) gene and the hypervariable region 1 (HVR1) of the envelope 2 (E2) gene. Viral RNA was extracted from 160 µl of serum with the QIAamp viral RNA isolation kit (Qiagen). cDNA was synthesized using oligonucleotide primers and Moloney murine leukemia virus reverse transcriptase [22]. Nested polymerase chain reaction (PCR) was performed with Advantage High Fidelity 2 DNA polymerase (BD Biosciences) [23]. Purified PCR products were directly sequenced with an Applied Biosystems automated sequencer (model 377) (see the Appendix, which is available at the Journal’s Web site [http://www.journals.uchicago.edu/JID/journal/home.html]).

Nucleotide sequences were optimally aligned with the CLUSTAL W program [24]. Phylogenetic analysis was performed with programs from the PHYLIP package (version 3.5c) [26]. We estimated nucleotide distances between all pairs of sequences with the DNADIST program (Kimura 2-parameter option) and generated a neighbor-joining tree [26]. Genotype was determined by comparing isolate sequences to HCV sequences of known genotype from Genbank (http://www.ncbi.nlm.nih.gov/Genbank/). Sequencing was possible for only 31 of 58 anti-HCV–positive participants (including 10 of 17

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### Table 1. Demographic and behavioral characteristics of participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case subjects (n = 17)</th>
<th>Control subjects (n = 42)</th>
<th>All participants (n = 164)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>26 (8)</td>
<td>26 (6)</td>
<td>29 (10)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>41</td>
<td>57</td>
<td>70</td>
</tr>
<tr>
<td>White race, %</td>
<td>94</td>
<td>90</td>
<td>89</td>
</tr>
<tr>
<td>High school diploma/GED, %</td>
<td>71</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>Living on streets/in shelter, %</td>
<td>44</td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>Primary drug injected—top 2 (%)b</td>
<td>Heroin (63), amphetamines (31)</td>
<td>Heroin (60), amphetamines (40)</td>
<td>Heroin (57), amphetamines (32)</td>
</tr>
<tr>
<td>Sexually active, % overallc</td>
<td>74</td>
<td>77</td>
<td>84</td>
</tr>
<tr>
<td>Men who have sex with men, %</td>
<td>8</td>
<td>5</td>
<td>11</td>
</tr>
</tbody>
</table>

**NOTE.** For demographic variables, values for index individuals are based on responses at their last prospective cohort study interviews before the present study. None of the differences between case subjects and control subjects are statistically significant (P<.05), as determined by the appropriate inferential test (t test or χ² test).

a Includes all unduplicated index individuals and interviewed injection partners; across variables, sample sizes ranged between 13 and 17 for case subjects, between 39 and 42 for control subjects, and between 152 and 164 for all participants.

b During specific recall period.

c Based on sex of sex partners during specific recall period; codings for index individuals are based on inferences from partners’ first names/nicknames. Index individuals were excluded from these summaries if none of their sex partners could be unambiguously classified by sex (4 case subjects and 4 control subjects were excluded). Only 1 female index individual (a control subject) reported any same-sex sexual contact.
Table 2. Injection risk behaviors with injection partners: comparisons between case subjects and control subjects.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD)</th>
<th>Case patients</th>
<th>Control subjects</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners elicited, no.</td>
<td>22 (21)</td>
<td>16 (15)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Partners interviewed, no.</td>
<td>3.0 (1.7)</td>
<td>2.7 (1.5)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Elicited partners interviewed, %</td>
<td>34 (35)</td>
<td>32 (28)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Receptive syringe sharing, % of interviewed partners</td>
<td>23 (36)</td>
<td>15 (30)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Receptive injection risk, % of interviewed partners</td>
<td>72 (31)</td>
<td>62 (41)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>HCV+ partners interviewed, no.</td>
<td>1.5 (0.9)</td>
<td>1.0 (1.1)</td>
<td>0.21 (0.18)</td>
<td></td>
</tr>
<tr>
<td>HCV+ partners interviewed, %</td>
<td>60 (33)</td>
<td>35 (38)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Receptive syringe sharing with HCV+ partners interviewed, no. of partners</td>
<td>0.4 (0.5)</td>
<td>0.1 (0.3)</td>
<td>0.38 (0.38)</td>
<td></td>
</tr>
<tr>
<td>Receptive syringe sharing with HCV+ partners interviewed, % of interviewed partners</td>
<td>22 (38)</td>
<td>3 (17)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Receptive injection risk with HCV+ partners interviewed, no. of partners</td>
<td>1.0 (0.9)</td>
<td>0.7 (0.8)</td>
<td>0.23 (0.20)</td>
<td></td>
</tr>
<tr>
<td>Receptive injection risk with HCV+ partners interviewed, % of interviewed partners</td>
<td>44 (39)</td>
<td>22 (31)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Partner age, years</td>
<td>29 (7.0)</td>
<td>28 (8.2)</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. For number of partners elicited, 17 case subjects and 42 control subjects were included in analysis; otherwise, 13 case subjects were included in all analyses (except for measures involving partner HCV status, with 12 case subjects), and 34 control subjects were included in all analyses (except for partner age, with 33 control subjects). From our coding “don’t know”/missing partner reports of specific behaviors as “no” responses, receptive injection risk and syringe sharing could have been misclassified for up to 2% and 8% of partnerships, respectively (proportionally distributed in cases and controls). Pearson (point biserial) correlation coefficient.

a The median number of partners elicited was 16 and 11, for case subjects and control subjects, respectively.
b Index individuals with few elicited partners successfully referred somewhat more partners than did index individuals with many elicited partners.
c Partial correlation, controlled for number of partners interviewed.
d .P < .1
e .P < .05

incident case subjects), due to either insufficient blood specimens, low viral loads, or cleared infections.

Statistical Analysis

Before performing network analyses, we identified participants and reported partners as uniquely as possible by using participants’ anonymous study codes, multiply mentioned uncommon street nicknames of partners, and multiply mentioned uncommon first names of partners (see the Appendix, which is available at the Journal’s Web site [http://www.journals.uchicago.edu/JID/journal/home.html]). We treated each mention of a relatively common nickname or first name not unduplicated by anonymous code as a different individual.

We calculated univariate descriptive statistics to summarize participants’ demographic characteristics, risk behaviors, and partner distributions. We computed the distribution of components (disjoint sets of participants connected directly or indirectly via partnerships) [27] separately for the injection network and the sexual network.

To assess the tendency of injection partners to be anti-HCV concordant, we computed measures of network autocorrelation (Geary’s C and Moran’s I [28–30]) and associated randomization test probability values based on 10,000 permutations. Geary’s C ranges from 0 to 2 and is 1 when no autocorrelation is present; values <1 represent positive autocorrelation (i.e., clustering of participants with similar characteristics). Moran’s I ranges from −1 to 1 and is −1/(n−1) when no autocorrelation is present; values >0 represent positive autocorrelation. We also used these measures to examine the tendency of participants to inject with partners of similar age (as reflected by absolute age difference in years). Furthermore, we computed matrix correlations and associated randomization tests (10,000 permutations each) [31] between pairs of incident case subjects’ injection network (geodesic) [27] distances and genetic distances of their HCV variants.

To compare case subjects and control subjects in terms of risk behaviors with their injection partners and positions in the injection network (membership in the main component), we computed Pearson (point-biserial and ϕ) correlation coefficients (r), odds ratios (ORs), and corresponding probability values. Data management and analysis were performed with Microsoft Access 97, SPSS (version 7.5), UCINET 6 for Win-
Figure 1. Main component of injection network after reduction (see the “Injection and sexual network structure” subsection of Results), as rendered by a spring-embedder algorithm [33] with slight manual adjustments for clarity. Nodes denote index individuals (triangles) and partners (some successfully referred, others not) who were not index individuals (circles); shading denotes whether the participant’s anti–hepatitis C virus status was unknown (white), negative (light gray), or positive (dark gray).

dows [32], NetDraw [33], and custom programs written in FreeBasic (http://www.freebasic.net).

RESULTS

Characteristics of participants. Case subjects and control subjects were very similar demographically and behaviorally (table 1). Participants were mostly young, white, and heterosexual injectors who primarily injected heroin or amphetamines. Almost half of participants were homeless.

Case-control comparisons of injection risk behaviors. Table 2 shows the comparisons between case subjects and control subjects on several injection risk behaviors with their interviewed injection partners. Case subjects and control subjects engaged in receptive syringe sharing and receptive injection risk with similar proportions of their partners. However, case subjects had nonsignificantly more HCV-infected partners, on average, and consequently tended to have had more HCV-infected partners with whom they engaged in receptive syringe sharing and receptive injection risk.

Injection and sexual network structure. Index individuals recalled a mean of 18 injection partners (median, 12 [SD, 18]; interquartile range [IQR], 5–26; range, 1–74). Of the partners interviewed, 88% confirmed that they had injected with the index individual during the specific recall period, 19% reported syringe sharing with the index individual during that period, and 78% reported engaging in any injection risk with the index individual during that period. The overall reported injection network comprised 15 components, and the largest component included 78% (128/165) of all participants. The 5 next largest components each included 2%–4% of participants. Figure 1 depicts the largest component of the injection network after removal of uninterviewed partners who were mentioned only once or not uniquely identified. This component is dense and pervaded by cycles. Of the reported partnerships, 78% (146/188) were identified by anonymous code (when the partner was successfully referred), and the rest were identified by uncommon names (when the partner was not referred).

Forty-seven sexually active index individuals recalled a mean of 3.7 sex partners (median, 3 [SD, 3.8]; IQR, 1–4; range, 1–17). The corresponding sexual network comprised 45 components; the largest included only 1% of participants.

Distribution of HCV infection and age across the injection network. HCV infection was evenly distributed across the injection network of participants (Geary’s C = 0.80 [P > .05]; Moran’s I = .05 [P > .05]). Figure 1 shows this fairly uniform scattering of anti-HCV–positive IDUs in the main component, with the nodes (individuals) shaded by serostatus. Similar proportions of incident case subjects (81% [13/16]) and control subjects (74% [32/43]) were in the main component of the injection network (Pearson [r] r, .07; OR, 1.5 [P > .05]). The thorough mixing of HCV-infected injectors in this network is further evidenced by control subjects’ network proximity to HCV-infected participants. At least 65% (28/43) of control subjects had injected with anti-HCV–positive participants; 79% (34/43) were within 2 steps (partners of partners) of HCV-infected participants, and 86% (37/43) were within 3 steps of them. Participants tended to inject with individuals of similar age (Geary’s C = 0.48 [P < .0001]; Moran’s I = .36 [P < .0001]).
Foundations of HCV Transmission in IDUs

**DISCUSSION**

In our case-control study of HCV seroconversion and social networks in young drug injectors, nearly one-quarter of reported injection partnerships involved syringe sharing during a 12-month period, and almost four-fifths involved injection behavior that could transmit HCV. Incident case subjects and seronegative control subjects were demographically and behaviorally similar, including the proportion of injection partners with whom they engaged in syringe sharing and any injection risk behavior. Case subjects, however, had somewhat more HCV-infected partners than did control subjects and consequently engaged in injection risk behavior with a greater number and proportion of infected partners. The injection network was fairly connected, dense, and cyclic, but the sexual network was highly fragmented and was unable to serve as a scaffold for sustained transmission by itself. HCV-infected participants were relatively evenly distributed across the injection network, although injectors displayed moderate assortative mixing by age with their partners. As anticipated previously [2], most HCV-uninfected injectors were quite close, in network terms, to infected injectors, typically having injected with at least 1 HCV-infected partner during the preceding year. Four pairs of injectors had genetically closely related infections, indicating transmission either from 1 member of the pair to the other or from a third individual to both individuals. In 3 pairs,
Figure 4. Risk behaviors in transmission pairs, as reported by 1 or both partners in the pair. Each pair consisted of a male and a female. Unless otherwise noted, reports refer to behaviors in which the pair engaged with each other during the specific recall period.

Pair A:
- syringe sharing with syringe “rarely” bleached
- cooker, cotton, and rinse water sharing
- syringe-mediated drug sharing, usually with a new sterile needle
- sex, always without a condom

Pair B:
- syringe sharing with no bleaching
- no other injection risk except for syringe-mediated drug sharing, but always with a new sterile needle
- sex, “rarely” with a condom

Pair C:
- no syringe sharing (ever)
- “rare” cooker and cotton sharing (but not reported for specific recall period), tourniquet sharing (in specific recall period)
- syringe-mediated drug sharing, but always with a new sterile needle
- no sex (ever)

The linked infections were confirmed by reported injection contact between the 2 members of a pair. Transmission in at least 1 of the 4 pairs appeared to be due to sharing of injection equipment other than syringes. Apart from transmission pairs, though, network distance between incident case subjects and genetic distance between their HCV variants were uncorrelated.

Our observation that sharing of injection equipment other than syringes was the probable mode of transmission in at least 1 transmission pair extends previous work that indicates that such “indirect sharing” is independently associated with HCV seroconversion in drug injectors [4, 5, 7, 8]. Indeed, in a late 1990s Seattle cohort of IDUs we found that the population attributable fraction of HCV infections due to shared cookers and/or cottons was 13% [7].

The injection network that we observed was mostly connected, dense, and cyclic, which comports with prior observations of needle sharing [9, 34], injection [12, 13], and combined injection and sexual networks [11, 35]. The economics, illegality, logistics, and social aspects of illicit drug injection probably contribute to such network structures. Although age is a moderate correlate of prevalent HCV infection in IDUs in the present (data not shown) and other studies [19], the assortative mixing by age in the injection network was not strong enough to prevent an almost even distribution of HCV-infected participants across the injection network. Because case subjects and control subjects were similar in their injection risk behavior with their partners overall, seroconversion was mostly an accident of network position—that is, injecting with more individuals who happened to be HCV infected. With turnover in injection partners, we expect most HCV-uninfected IDUs will eventually be in similar positions in the injection network and subsequently acquire HCV. Therefore, our data suggest that, without massive reductions in all injection risk behaviors, shattering of cohesive injection networks, and/or broad coverage with an effective vaccine, HCV will remain hyperendemic in similar populations of drug injectors.

We found a larger fraction of closely related pairs of infections that were confirmed by reported injection contact between the persons involved (3/4) than Aitken et al. did (12/66) [12]. This difference may be partly due to our longer recall period for eliciting partners and sequencing envelope regions of the HCV genome that experience higher rates of mutation [36, 37] than the core and nonstructural protein 5a regions they sequenced [12]. We also found no correspondence between ge-
netic and network distance in incident case subjects after excluding distances between the transmission pair of incident case subjects. This result resembles Aitken et al.'s [12] observation of no consistent relationship in prevalent cases, although they did not exclude closely related infections from analysis. Our focus on incident cases made the 2 measures more temporally comparable and presumably increased the chances of finding a meaningful correspondence. The lack of correspondence in both studies is likely the consequence of the multiplicity of circulating genotypes and variants throughout the injection network, incomplete network ascertainment [20, 38], spontaneous clearance of infection [39–41] after transmission to others, reinfection/superinfection/mixed infection [42–45], and/or possible changes over time in or rapid evolution of the dominant variant within infected individuals [46, 47]. Hence, genetic distance—except when very small—is probably a poor proxy for network distance.

Our study has several limitations. The network data are incomplete, primarily because we did not elicit partners’ partners and lacked sufficient identifying information to “unduplicate” all reported partners and secondarily because of incomplete reporting, despite our use of supplementary elicitation techniques [20]. Therefore, the “true” injection network structure may be more connected, dense, and cyclic—and thus more likely to propagate infection—than that which we observed. The design-based incomplete ascertainment also prevented meaningful analysis of several positional and structural properties. Nevertheless, underascertainment of the network was independent of participants’ ages, behaviors, serostatuses, and HCV variants. We did not assess risk behaviors for all elicited partnerships, but only for those involving successful partner referral. For these partnerships, partners reported the frequency of risk behaviors in relative (i.e., “never,” “rarely,” “sometimes,” “usually,” “always”) rather than absolute terms, preventing more detailed dose-response analyses. Our analyses treated the injection and sexual networks as static entities rather than as the dynamic structures that they are [48], because we did not elicit specific partnership dates. Most partnerships, however, occurred within the same, relatively short time period. Moreover, the sample was fairly small, and we gathered no data on HIV status, anal sex, administering injections to/receiving injections from others, injection with previously discarded syringes, and homosexual exposures other than illicit drug injection.

With adjustments to address such limitations, the kind of research design we implemented—tracing risk networks of incident case subjects and control subjects, gathering detailed data on exposures within partnerships, and sequencing infected persons’ isolates—may serve as one model for investigating modes of infectious disease transmission and the corresponding social structural substrates. This approach combines advantages of other designs (prospective cohort, network description of population affected, contact tracing, and molecular analysis), bringing the investigation to levels that are crucial for understanding transmission—the dyad and network. Furthermore, this approach has the potential to narrow the investigative scope to particular events within dyads, if testing methods for detecting very recently acquired infections are used. Such integrated designs could be effectively employed to establish the key modes of transmission of a pathogen in settings where they have been studied only at the individual and ecological levels [49].

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References


