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FACULTY OF MEDICINE

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The social and genetic epidemiology of Hepatitis C in an isolated network of people who inject drugs

By

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Dedication:

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ABSTRACT

FACULTY OF MEDICINE

Thesis for the degree of Doctor of Philosophy

THE SOCIAL AND GENETIC EPIDEMIOLOGY OF HEPATITIS C IN AN ISOLATED NETWORK OF PEOPLE WHO INJECT DRUGS

Ryan Malcolm Buchanan

Background and Aims

Hepatitis C (HCV) causes liver cirrhosis, liver cancer and is a leading cause of death worldwide. In the UK the commonest risk factor for HCV is current or previous injecting drug use but many cases are undiagnosed and many known cases are disengaged from treatment services. The Isle of Wight (IOW) is a deprived, rural and geographically isolated population but suffers from the same obstacles to HCV care as larger nearby mainland populations.

The overall aim of this thesis is to understand the burden of HCV in people who inject drugs (PWID) on the IOW and how their social network could be utilised in an HCV elimination strategy.

Method

A sequential mixed method research design was used. Qualitative methods informed the design of a quantitative survey, which recruited PWID via respondent driven sampling (RDS) for a social network questionnaire and HCV bio-behavioural survey. This was used to estimate the population prevalence of HCV and the total population size of PWID on the IOW. Data from the social network survey were combined with a phylogenetic analysis of HCV RNA positive cases and qualitative narratives to give a representation of the HCV transmission network in PWID. This network was then used in an individual-based model (IBM) testing different treatment strategies.

Results

Sixty-nine PWID participated in the HCV bio-behavioural and social network surveys. The estimated prevalence of HCV was 29% (95% CI 13.3-44%) and the estimated total population size was 262 individuals.

The social network survey described 179 PWID, connected together into a cohesive network component via injecting partnerships. Phylogenetic analysis indicated that a number of these partnerships had led to the transmission of HCV and that genotype 3a virus had been transmitted between PWID living on the IOW.

In the IBM the preferential treatment of well-connected PWID, via injecting and social relationships, led to significantly fewer new infections of HCV than treating at random (9.56 vs. 6.58 $P<0.01$ and 9.56 vs. 7.84 $p=0.011$ respectively).

Conclusion

The burden of HCV in PWID on the IOW is lower than expected and existing case-finding initiatives are effective. The qualitative and quantitative results indicate that PWID are linked together in a dense network and the treatment of well-connected nodes within this network may be an effective treatment as prevention strategy for the elimination of HCV on the IOW.

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Published articles:

Buchanan R, Coad J, Grellier L, Khakoo SI, Parkes J. Hepatitis C bio-behavioural surveys in people who inject drugs—a systematic review of sensitivity to the theoretical assumptions of respondent driven sampling. Harm Reduction Journal. 2017; 14(44).

Buchanan R, Hassan-Hicks P, Noble K, Grellier L, Parkes J, Khakoo SI. Integrating community pharmacy testing for hepatitis C with specialist care. *Clin Pharm*. 2016;8(8): 47-56.

Buchanan R, Coad J, Parkes J, Khakoo S, Grellier L. PROSPERO International prospective register of systematic reviews Respondent driven sampling methodology for estimating Hepatitis C epidemiology in people who inject drugs : a systematic review. 2015. Available online: http://www.crd.york.ac.uk/PROSPERO/DisplayPDF.php?ID=CRD42015019245.

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Buchanan R, Shalabi A, Grellier L, Khakoo SI. PTU-112 Hepatology outreach services to overcome inequalities in hepatitis c care in an isolated uk population. *Gut*. 2015; 64 (Suppl 1) A111.1.

Buchanan R, Coad J, Grellier L, Khakoo SI, Parkes J. Estimating the prevalence of Hepatitis C in people who inject drugs using respondent driven sampling – a systematic review. ePoster 149. EASL New Perspectives in Hepatitis C virus infection – Roadmap to cure conference. Available online: https://events.easl.eu/Abstract/Statistics/FlatAbstractList.aspx?EventCode=SP2016.

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DECLARATION OF AUTHORSHIP

I, Ryan Buchanan declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

The social and genetic epidemiology of Hepatitis C in an isolated network of people who inject drugs

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;

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3. Where I have consulted the published work of others, this is always clearly attributed;

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5. I have acknowledged all main sources of help;

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Signed: .....

Date: .....

Abbreviations*

AES – Ancillary equipment sharing

AGD – Average geodesic distance

BBV – blood borne virus

C-RC – capture-recapture

DAA – Directly acting anti-viral drugs

DBS – Dry blood spot

Deff – design effect

DSC – Drug support centre (there is only one drug support centre on the Isle of Wight)

EU – Exposed uninfected

HCV – Hepatitis C virus

IBM – Individual based model

IFN- α – Interferon alpha

IOW – Isle of Wight

OST - Opiate substitution therapy

PHE – Public Health England

PWID – People who inject drugs

RCT – randomised control trial

RDS – Respondent driven sampling

RNS – Receptive needle sharing

SBS – Snow-ball sampling

SNA – Social network analysis

* All abbreviations are redefined at the start of each chapter

SOP – Standard operating procedure

SVR – sustained virological response

TLS – Time location sampling

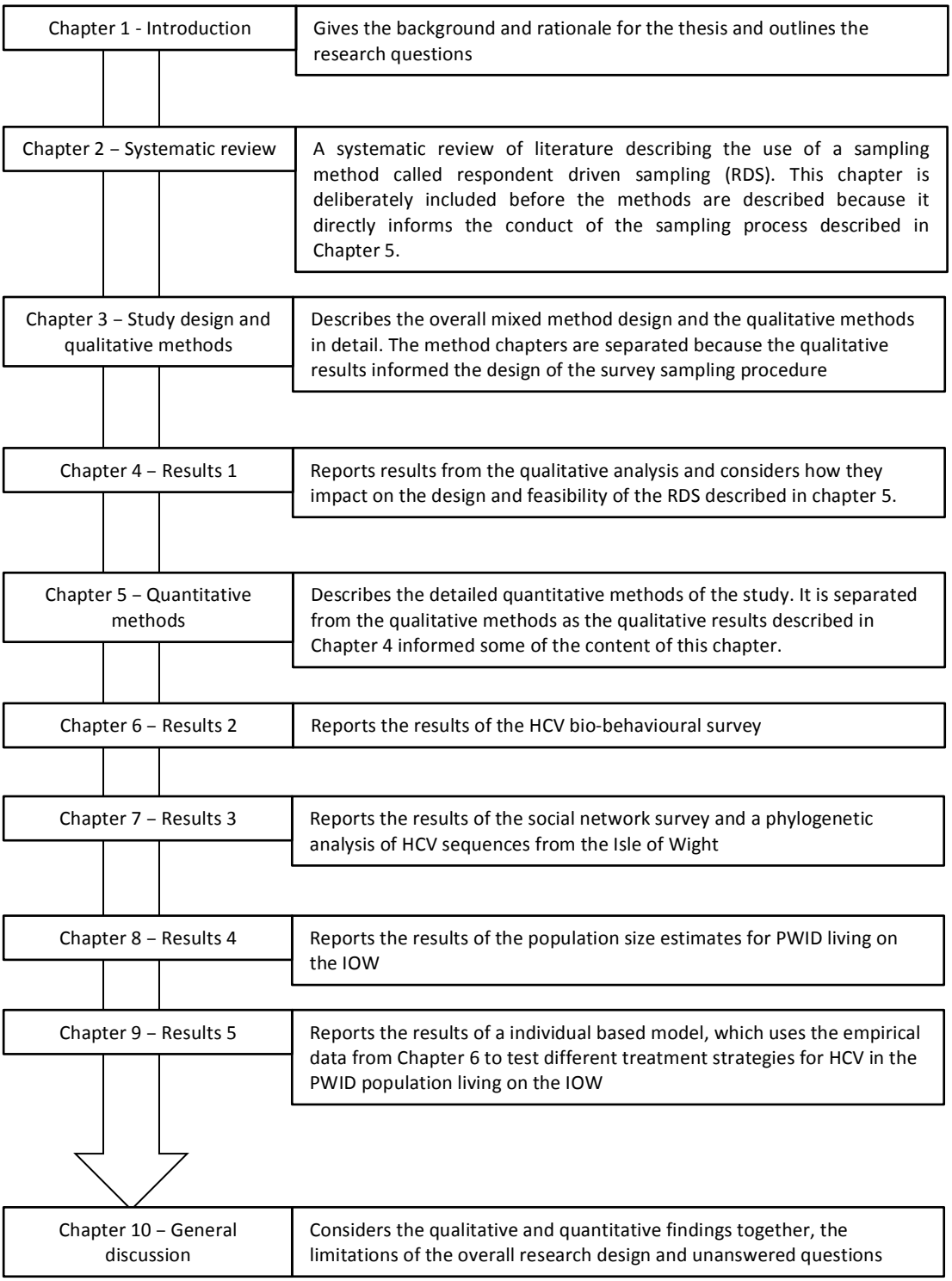
TAP – treatment as prevention

UAM – Unlinked anonymous monitoring

V-H estimator – Volz Heckathorn estimator

WHO – World Health Organisation

Overview of this thesis



1. Introduction

In Chapter 1, I outline the rationale for the content of this thesis and document the overall research objectives. The chapter also describes the epidemiology of Hepatitis C (HCV) and introduces a novel survey technique for quantifying the prevalence of the virus in people who inject drugs (PWID). Finally the chapter outlines some of the current challenges in HCV care and specifically how these apply to the study location – the Isle of Wight (IOW).

1.1 Hepatitis C

HCV is a blood-borne positive stranded RNA virus within the genus *Hepacivirus* and family *Flaviviridae*[1].

Most people who contract HCV (70-80%) do not develop symptoms. However, in a minority of cases individuals may experience nausea, dark urine, anorexia, abdominal pain and jaundice[2]. Only a minority of cases (15-40%) spontaneously clear the acute infection[2] with women[3], younger persons[4] and those with favourable genetic polymorphisms[5] being less likely to develop chronic disease.

Chronic HCV can be asymptomatic but may be characterised by a range of non-specific symptoms including, sweats, rashes and mood disturbances, which, whilst often considered mild and non-specific, are associated with a reduced quality of life[6].

Over 20 years approximately 20% of persons with chronic HCV will develop severe scarring of the liver, known as cirrhosis, but this process can be accelerated in persons who consume excessive quantities of alcohol[7] or who are co-infected with HIV (human immunodeficiency virus)[8]. Cirrhosis itself may be asymptomatic but it can lead to decompensated liver disease, which is characterised by jaundice, bleeding and fluid within the abdomen (ascites) and primary cancer of the liver known as hepatocellular carcinoma. Chronic HCV

infection can reduce life expectancy by 8-12 years[9]. People with compensated cirrhosis (where there is liver scarring but essentially normal function) have a prognosis of approximately 12 years, but if they develop decompensated disease median survival falls to just 2 years[10]. The morbidity and mortality of HCV worldwide has recently been the subject of an international study, which was published in 2016 in the Lancet. The study showed that the consequences of chronic HCV infection, including liver, cirrhosis and hepatocellular carcinoma, combined with those of Hepatitis B, were the seventh leading cause of global mortality and one of the few to have increased in the early 21st century[11].

HCV was not identified until 1989 but its existence had been suspected in blood transfusion recipients in the United States who developed a post-transfusion hepatitis despite testing negative for Hepatitis A and B[12,13]. Since its discovery the introduction of viral screening practices for donated blood products has greatly reduced transfusion related transmission and presently the primary risk factor for HCV infection is current or previous injecting drug use. It is this practice that led to the epidemic in the second half of the 20th Century that continues today.

The scale of the epidemic within PWID has been described through clinical observation and phylogenetic analysis and there are now thought to be over 10 million infections in PWID[14,15]. However, the true burden of disease in PWID and importantly former PWID is poorly understood. Even in the UK where estimates are relatively robust, data are largely based on people currently injecting drugs who are engaged with service providers in large urban centres[16–18]. Little is known about viral epidemiology in more rural areas, those who have a distant history of injecting drugs or those who are disconnected from support services.

1.2 Genetic epidemiology of Hepatitis C

The HCV RNA genome consists of a singe open reading frame of 9500 nucleotides encoding a single polypeptide of 3000 amino acids, which is bounded by 5' and 3' untranslated regions of 341 and 230 nucleotides respectively[1]. HCV is highly mutagenic and within a single host the viral population contains distinct quasispecies. Globally HCV is divided into seven genotypes and a further series of subtypes, which are in some cases, associated with distinct geographical areas and in others, particular modes of transmission[19].

The presence and frequency of HCV genotypes within a population can give an indication about possible routes and sources of HCV transmission into a population. For example, in Montenegro and Cyprus the diversity of HCV genotypes indicates that multiple introductions of HCV have occurred and specifically in Cyprus, the presence of different genotypes among the local infected PWID population suggests limited transmission during injecting drug use and the effectiveness of harm reduction interventions[20,21].

Within genotypes and subtypes there is considerable genetic variation and therefore they can only give a 'rough' representation of probable transmission dynamics. For granularity, some authors have sequenced part of the viral genome. In most cases the non-structural (NS) 5B region has been sequenced - a relatively well conserved region that codes for the viral RNA polymerase[1]. By sequencing the NS5B region, Forbi *et al.* demonstrated evidence of intra-familial transmission in a remote Nigerian community and Lampe *et al.* demonstrated evidence of transmission between PWID and non-PWID populations in Brazil[20,22]. Therefore both studies highlighted routes of transmission that were not necessarily expected and could lead to public health interventions. Other authors have sequenced the core E2 protein, a large glycoprotein within the structure of the viral envelope and gained similar insights. Sack-Davis *et al.* in Melbourne, Australia reported evidence of numerous recent transmission events of HCV genotype 1a virus between PWID, and Jacka *et al*. in Canada identified clusters of infection associated with syringe sharing[23,24].

In addition to understanding the current transmission dynamics of HCV and informing real-time public health interventions, the genome has given insights into the historical evolution and spread of HCV. This understanding has relied on basic concepts of molecular evolution, which contextualise genetic variation through time (Figure 1-1).

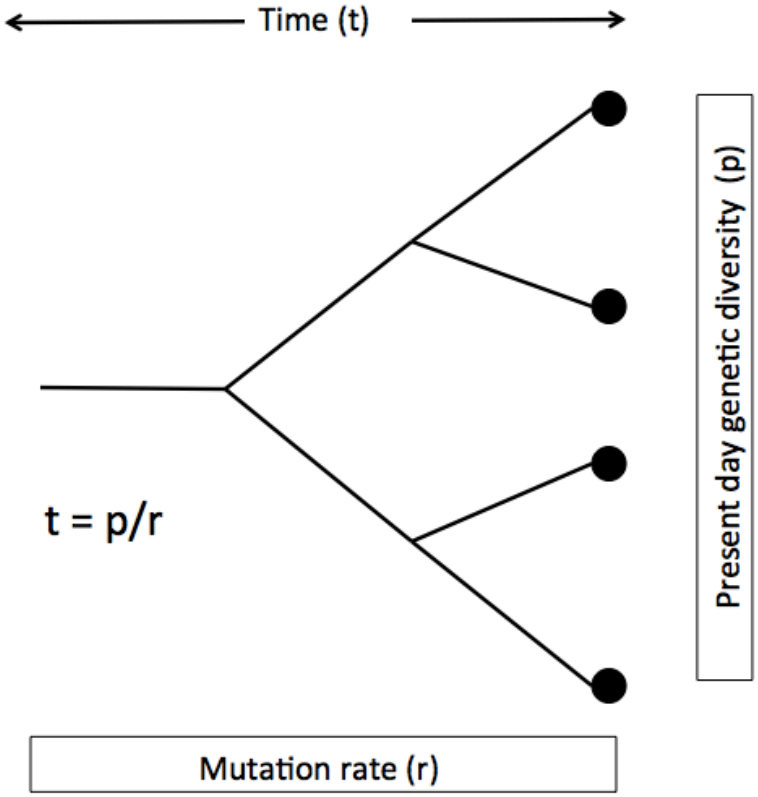


Figure 1-1 A simple representation of a phylogenetic tree of the emergence of new HCV variants. Genetic diversity and a known mutation rate can be used to date a most recent common ancestor of the present day species.

A considerable body of work on the 'genetic history' of HCV has been conducted by Oliver Pybus at the University of Oxford, UK. Using a Bayesian inference framework he has described the transmission events from the likely origin of HCV in West and Central Africa to the Americas – possibly via the slave trade[25,26], and explained the exceptionally high prevalence of HCV in Egypt[27]. A key aspect of these analyses is the calculation of a 'fixed mean mutation' rate. When this is combined with the present genetic variation within a given population, it is possible count backwards to the most recent common ancestor of that viral population and estimate when it existed (Figure 1-1). The

calculation of a fixed average mutation rate for HCV involves numerous assumptions but is based on empirical data, including an interesting study of Irish women who were infected from the same batch of anti-D[28]. By looking at the genetic variation of the NS5 sequences in these women and considering the time between when their samples were taken and when they received the anti-D it has been possible to calculate a mean mutation rate for HCV[29].

1.3 Sampling in hidden populations

Understanding HCV epidemiology within PWID is inherently difficult. Due to the illegality of their practice and the associated social stigma, PWID represent a hidden and hard to reach population[30].

Hidden or hard to reach populations are poorly defined in the literature and the terms are frequently used interchangeably. However, PWID, migrants, female sex workers, men who have sex with men and victims of abuse all constitute good examples and share the lack of a clear sampling frame for survey based research. This means that in each population participants have an unknown probability of selection and therefore survey findings cannot be generalised more widely[31].

To reduce the impact of these limitations, survey design in hard to reach populations should be carefully considered and incorporate a robust sampling strategy. However, with rare and dispersed target populations this can be extremely difficult and mechanisms to achieve it convey an inherent risk of introducing bias[31]. Disproportionate stratification may be used to focus screening on part of the general population where the prevalence of eligible participants is higher. This has the effect of increasing screening efficiency but at the cost of introducing unequal selection probabilities. For example, location sampling, where eligible participants are identified at services or resources where they are likely to be encountered, has been widely used but there is an inherent and unquantifiable risk of bias from over sampling individuals closely connected with the survey location[30,31].

Network based sampling is another approach to increasing sampling efficiency. In simple terms, individuals from the target population identify their peers, who they think also meet the eligibility criteria for the survey, to the researcher or alternatively provide research data on their behalf. Pitfalls with this method are plentiful, the initial participants need to be willing to divulge information about others and the researchers need to have satisfied ethical regulators that it is appropriate for them to do so. The accuracy of information, particularly where recall is involved, may be compromised and

perhaps most importantly the final sample would be markedly skewed towards those with many eligible contacts within their social network[31].

Nevertheless since the 1960s a network-based method called snowball sampling (SBS) has been widely applied in a range of research fields[32,33]. At its conception SBS was intended for use in populations with a known sampling frame where simple random sampling was also possible i.e. not hidden populations. In this context its foundation was to study the connections between people within social networks rather than draw broad conclusions about population characteristics such as disease prevalence[32,33]. However, over the years, SBS has been used as a sampling tool to access hidden populations, but in this field it has significant limitations. In 1979 Erikson (quoted in Heckathorn 2011[34]) described how a snowball sample begins with a bias of unknown magnitude and this bias is compounded as the sample expands wave by wave[35]. This shortcoming has been exacerbated by a lack of clarity from some authors using the method about the representativeness of their final sample[34,35]. In many respects SBS in hidden populations is such a deviation in application from its original intention the term has become a misnomer and forced Leo Goodman to write a commentary 50 years after his first publication on the subject emphasizing the differences between SBS in hidden and non-hidden populations[36].

However, in the wake of the HIV epidemic, global interest in gaining representative samples of hidden populations has grown. In 1997 Douglas Heckathorn introduced a new method that attempted to systematically eliminate the bias associated with SBS[37]. Called respondent driven sampling (RDS) this new method has since been used in hundreds of surveys in hard to reach populations world-wide[38]. RDS, and specifically how it has been used for HCV research, is explored further in Chapter 2.

1.4 Social networks and people who inject drugs

The act of contracting HCV from injecting drug use is directly related to drug preparation and injection such as sharing needles or filters. However, the 'risk environment' within which the HCV epidemic is sustained is a far more complex mesh of social, political and economic factors[39].

Injecting drug use has been described as a social ritual and is often conducted in communal locations, sometimes with many participants. This contrasts with legal drugs such as tobacco and is driven by the illegality of injecting drug use and its associated risks, such as arrest, overdose and infection. These factors create a unique environment which fosters strong social bonds between 'users' that can act as barriers to harm reduction and health care services[40].

All communities are intertwined with a mesh of social connections that have far reaching implications for health and social care. However, there is a big gap between our intuitive understanding of these connections and the more precise understanding that allows the implementation of interventions to improve social conditions and ultimately improve health[41]. Social network analysis (SNA), incorporating theoretical concepts, specific survey design, computer software and statistical analysis, is an attempt to bridge this gap. The field now incorporates a vast body of literature covering diverse topics such as business, health and education[41].

SNA has its origins in the two disparate research fields of graph theory and social science. It therefore uses outwardly complex and overlapping terminology[42]. Before considering SNA in PWID, it is necessary to introduce some of the key concepts and terminology used consistently throughout this thesis. The choice of the specific terminology used henceforth is a reflection of similar published literature (Table 1-1)[43].

Table 1-1 Specific terminology used in this thesis to describe social networks[43, 44]

Term	Definition in a whole network	Definition in an *ego*-network
Node	A member of a whole network	
Ego		The individual at the centre of an *ego*-network
Alter		An individual connected to ego in an *ego*-network
Tie	A relationship between two nodes	A relationship between *ego* and an *alter* or between two *alters*
Dyad	Two connected nodes	An *ego-alter* or *alter-alter* partnership
Degree	The number of relationships concerning an individual node	The number of relationships concerning *ego*

There are two main types of social network; *ego* networks and whole networks (Figure 1-2). *Ego* networks are based around a central individual known as the '*ego'* that is connected to contacts or acquaintances (known as *alters*) through connections called ties. This network information is usually gathered in the context of a research study where a name generator question such as 'list people you work with' is posed to *ego*. E*go* may also describe *alter* attributes, such as age; sex; pay grade and which *alters'* also work together (known as *alter-alter* ties). On a simple level this reveals the *degree* size (number of *alters* connected to *ego*) and density (number ties between *alters* divided by the number of possible ties) of the *ego* network. This may be of interest for addressing a hypothesis such as, 'those in higher paid positions have greater network density'[44].

Whole networks are more complex. Rather than involving a central *ego,* they include a number of connected nodes. A good example might be friendships in a school classroom where the children are the nodes and the ties are friendships between classmates. In general, whole network data is more challenging to collect as all the nodes need to participate in the study and they need to identify the other nodes to which they are connected[41].

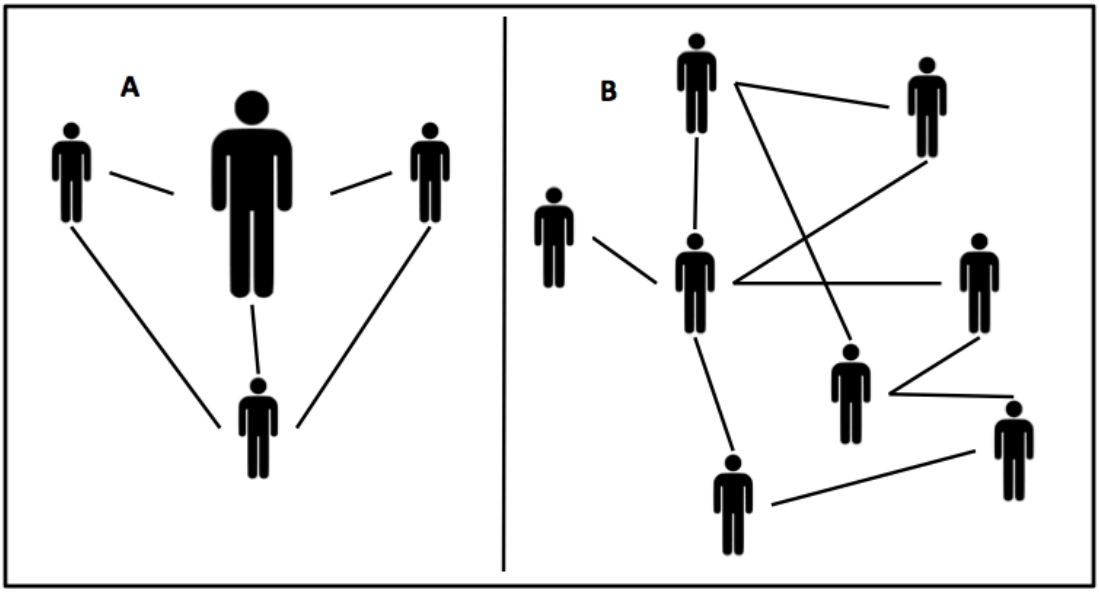


Figure 1-2 *Ego* and whole network structure[44]

An *ego*-network (A), with *ego* at the centre and lines representing relationships (*ties*) with and between acquaintances (*alters*), contrasted with a whole network (B) with network members (node*s*) and ties to other nodes in the network.

Social network research in PWID is challenging for a number of reasons. Firstly, there is no clear sampling frame (such as the classroom register in the example above) and secondly, PWID may be unwilling to take part, or unwilling to describe and identify their associates. Nevertheless, a small number of studies have described at least a representation of a whole network structure connecting PWID and investigated how the network affects the transmission of infectious diseases[45–49].

A study by Young *et al.* in rural Appalachia, USA is part of the very limited available literature specifically examining the association between PWID networks and HCV infection. The study showed an association between *ego*-network measures and HCV infection but no association with the overall network structure or a PWID's overall position within the network[43].

There is more extensive literature describing how social networks can be utilised in harm reduction strategies in PWID. Heckathorn described the impact of the HIV epidemic on PWID networks in the USA in the 1990s, and the

'network mobilization' that occurred where PWID helped their peers by distributing bleach, condoms and advice in a 'culture of survival'[50]. Interventional studies and a randomized controlled trial (RCT) support these observations and have demonstrated the effectiveness of network based programs compared to individually focused education in reducing injecting risk behaviour[51-53].

However, evidence that these measures actually have an impact on the incidence of HCV infection is lacking[51]. The reasons for this are unclear but a possible explanation is that the prevalence of HCV within some PWID networks can be exceptionally high, and as the virus is more easily transmitted than HIV, the window of opportunity to prevent HCV infection following the initiation of injecting drug use is small[54]. However, this does not mean that there is no potential benefit from studying and understanding the network context of HCV in PWID. Whilst attempting to use it in primary prevention may be limited, its potential value may extend to addressing other pertinent challenges in HCV care such as case identification and engagement in treatment.

1.5 Mathematical modelling of Hepatitis C transmission and treatment in people who inject drugs

In 2015, Cousien *et al.* conducted a review which identified 32 articles that described the mathematical modelling of HCV transmission within PWID[55]. The majority were compartmental models. A compartmental model categorises a population according to their infection status such as susceptible, infected or immune, and transition probabilities dictate the likelihood of moving from one state to another (Figure 1-3). Such models have limitations in that they treat the individuals in each state as homogenous and assume complete and entirely random mixing, i.e. anyone can give the infection to anyone. Clearly PWID are very heterogenous and HCV cannot be transmitted from a single individual to anyone in the population as even the most well connected PWID only have a limited number of risk relationships.

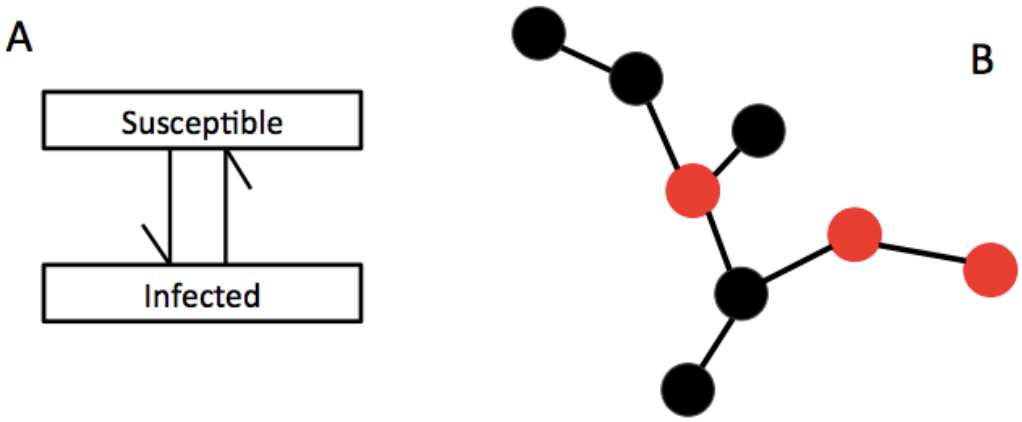


Figure 1-3 A simple representation of a compartmental model for HCV (A) and a IBM (B), which in this case incorporates injecting relationships (black lines) and individual characteristics such as HCV positivity (red nodes). An IBM can keep track of changing individual characteristics as the model passes through time.

Cousien *et al.* also identified a smaller number of studies that used individual based models (IBMs) to examine HCV transmission in PWID. Unlike compartmental models, IBMs do not assume complete random mixing between individuals. Instead IBMs use real or likely relationships based on real-world survey data such as geographical proximity between PWID[56], social network information[57] and injecting degree size[58]. Additionally IBMs can treat PWID as a

heterogenous group and therefore take into account important personal factors related to the likelihood of transmission including the frequency of injecting and the frequency of risk taking behaviours such as sharing injecting paraphernalia. However, IBMs also have limitations. They are more mathematically complex and the collection of the survey data required for an IBM is costly, time consuming and requires access to the population for the necessary fieldwork.

Perhaps for these reasons, just a single study has incorporated a representation of the real-world injecting network of PWID into an IBM. Roll's *et al.* modelled the transmission of HCV through a real-world injecting network of PWID in Melbourne, Australia and demonstrated that transmission took longer than when complete mixing was assumed – with implications for the feasibility of public health interventions. However, even this model has limitations[59]. Due to the challenges in collecting social network data (discussed in Section 1.4) the population in the model did not include the majority of PWID in the Melbourne area and missed potential transmission relationships. Furthermore the model only passed to a time-horizon of 12 months because the network dynamics between PWID (i.e. how frequently relationships end and form) are unknown[57].

1.6 Hepatitis C treatment, people who inject drugs and the elimination agenda

The treatment of HCV has changed dramatically in recent decades. In the late 1980s interferon alpha (IFNα) was used to treat patients with 'non-A non-B' hepatitis but many patients did not respond or later relapsed. A second drug, ribavirin, was then added to a longer acting IFNα preparation (pegylated-interferon) and the number of patients with a sustained virological response (SVR) increased significantly[60]. This became the mainstay of treatment until 2010, but many patients, particularly with genotype 1 HCV, still did not achieve a SVR and treatment was associated with numerous side effects[61]. Consequently, patients (10-20%) withdrew from therapy and others (20-30%) needed dose modification during treatment[61]. Furthermore, treatment had numerous contraindications including decompensated liver disease (meaning those who were most severely affected by HCV could not receive treatment) and pre-existing severe psychiatric illnesses.

From 2011, a new class of directly acting anti-viral drugs (DAAs) called protease inhibitors were developed and given in combination with PEG-interferon and ribavirin to patients with genotype 1 disease (so-called 'triple therapy'). This improved the proportion of patients achieving SVR but continued to be associated with side effects, contraindications to therapy, and drug-drug interactions[62,63]. This has led to the development of other classes of DAAs including NS3/4A inhibitors, NS5A inhibitors and NS5B inhibitors. Given in combination these drugs are over 90% effective at achieving SVR and because they can be given without PEG-interferon or ribavirin, they have few side effects and few contraindications[64,65].

Disease eradication is defined as the 'permanent reduction to zero of the world-wide incidence of infection caused by a specific agent' [Dowdle, 1998, p23][66]. The dramatic progress in drug development for HCV and specifically the development of DAA drugs has led to this term being used to describe the future for HCV. However, without an effective vaccine, eradication is unfeasible and instead the World Health Organisation (WHO) has set a target for HCV *elimination* by 2030. Elimination is subtly different from eradication in being defined as the 'reduction to zero of the incidence of infection by a

specific agent in a defined geographical area…' and importantly it occurs through 'deliberate and continued measures to prevent re-establishment of transmission' [Dowdle, 1998, p23][66]. Accordingly the WHO have highlighted that a key part of achieving this goal is reducing the number of undiagnosed HCV infections as well as increasing the number of persons engaged with treatment[67].

As indicated in Section 1.1, most chronic HCV infections in the UK are in PWID. Up to 50% of these individuals are not aware they are infected and many of those that are, have not been engaged with treatment services[68]. This is important because studies using compartmental models have highlighted that treating PWID can actually prevent further infections[69] and lead to a faster reduction in the overall population prevalence of HCV[70]. It therefore follows that to achieve the WHO target the identification of HCV in PWID and the treatment of these cases is a priority.

Unfortunately there remain numerous barriers to testing and treatment in PWID that need to be overcome[71–74]. Attempts have been made to address these, in the UK a series of national action plans and guidance have urged action to increase HCV testing[75,76] and this has prompted initiatives such as GP record screening for people at risk of HCV, screening in emergency departments, screening in prisons and widespread testing in drug support centres[77–80].

There is also growing evidence of the potential effectiveness of HCV testing and treatment in community pharmacies. In Dundee (Scotland, UK) a feasibility cluster randomised trial has indicated that PWID are significantly more likely to engage with treatment if they were managed through their community pharmacy[81]. Furthermore a randomised control trial in Melbourne, Australia is recruiting to a peer led treatment referral program which by engaging well connected PWID (at the greatest risk of transmitting the virus) has the potential to maximise the potential for treatment to prevent new infections[82].

1.7 Hepatitis C on the Isle of Wight

The IOW is a 150sqkm island three miles off the south coast of England. It is home to 138,000 residents living in rural villages and small towns and has the lowest population density in the South East region of England, the least inward migration[83] and some of the most deprived communities in the UK[84].

In 2011 a report by the Health Protection Agency (HPA) estimated there to be 348 cases of HCV in the IOW community[85]. This report was based on a health needs assessment by local public health services*, which made the calculation by incorporating local data into a Public Health England (PHE) model[86].

In 2014 a review of real-world positive HCV tests on the IOW identified 101 individuals who had been diagnosed with chronic HCV over the previous 10 years on the IOW. This review almost certainly missed positive cases and it is possible the health needs assessment over-estimated the local HCV prevalence by incorporating estimates extrapolated from urban rather than rural populations[18]. However, it seemed likely that there were a significant number of unidentified cases of chronic HCV living on the IOW.

This discrepancy, an ineffective care pathway, and the lack of locally available HCV treatment, prompted a service review by local clinicians in 2014. This showed that patients with HCV on the IOW were older, had a significantly higher prevalence of liver cirrhosis and a higher liver related mortality[87] than patients living in Southampton on the UK mainland. The causes for this were not clear and may have simply reflected the contrasting ages of the underlying population. However, these results and the suggestion that the IOW had a significant burden of undiagnosed HCV prompted service development. This mobilized a range of health professionals working with individuals thought to be at risk of HCV and led to a public health awareness campaign 'Are you 1 of the MISSING 200', which raised the profile of HCV within the local community and signposted at-risk individuals to a pharmacy based testing initiative (Figure 1-3)[88].

* Unpublished health needs assessment 'Hepatitis C on the Isle of Wight' by Dominique Le Touze in 2009

Figure 1-4 A bus side advertisement from the IOW HCV awareness campaign in 2015 (used with permission).

The community pharmacy based testing initiative for HCV on the IOW began in September 2014. By September 2016, 186 dry-blood spot tests had been conducted in twenty community pharmacies. The most commonly disclosed risk factor in persons presenting for a test was injecting drug use (32% of tests) of which nine were positive. By September 2016, only one had successfully received treatment despite all positive cases attending a 'point of diagnosis' appointment in the pharmacy with a Hepatitis specialist (Figure 1-5).

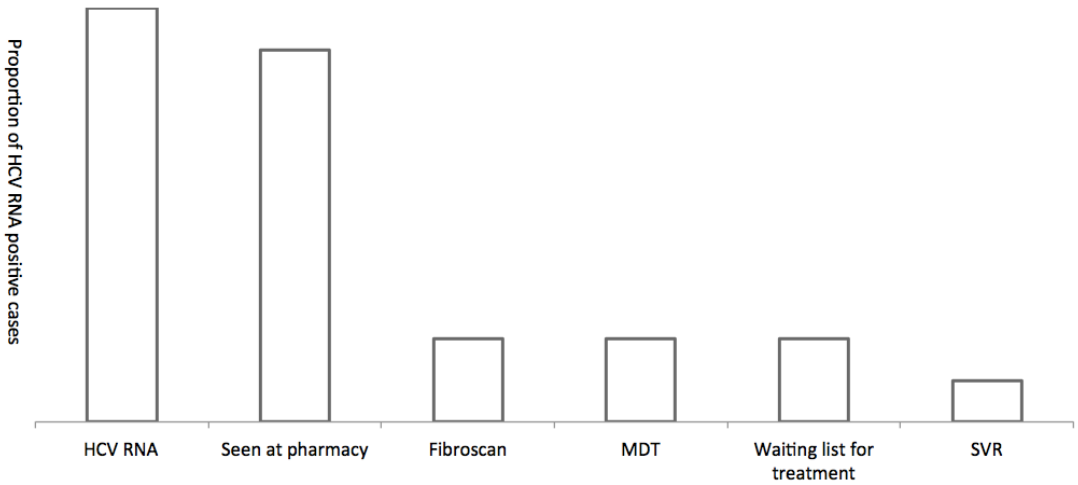


Figure 1-5 The care continuum for HCV positive persons diagnosed at a community pharmacy (unpublished, real-time data as of September 2016).

This raised specific questions about the epidemiology and clinical management of HCV on the IOW. Although it represented a small sample of PWID, the prevalence of HCV in those reporting injecting drug use was considerably lower than the estimate used in the PHE calculator, indicating that the number of missing cases may be lower than first thought. In addition, it was clear that there remained a disconnection between diagnosis and

treatment in PWID. The initiative therefore highlighted that for HCV elimination on the IOW to become a reality, a more accurate estimate of the number of cases of HCV and measures to engage PWID with treatment were needed.

These challenges informed the research questions, objectives and content of this thesis.

1.8 Rationale

HCV is prevalent in PWID around the world but data on HCV epidemiology in rural UK populations are lacking. PWID are known to have extensive social connections between each other but little is known about how these connections may be utilised in HCV elimination strategies. PWID living on the IOW are geographically isolated from the UK mainland but suffer from the same obstacles to HCV care as larger mainland populations. As a contained community within a stable population the IOW provides a unique and exciting opportunity to understand the epidemiology of HCV within a network of PWID, explore the effectiveness of existing care initiatives for HCV and consider how these can be optimised to provide a 'blue-print' method to achieve disease elimination. Accordingly this thesis aims to address the following research questions and objectives:

1.9 Research questions

1) How many individuals with chronic HCV live on the IOW?

2) How can the social network connecting PWID on the IOW be utilised in a local HCV elimination strategy?

1.10 Research objectives

- To explore the feasibility of undertaking RDS in PWID from an isolated, rural community
- To estimate the population prevalence for HCV antibody among PWID living on the IOW
- To determine the total number of HCV cases among PWID living on the IOW
- To understand how HCV transmission is related to the social network of PWID
- To demonstrate how the social network of PWID can be utilised in a local elimination strategy for HCV

1.11 Conclusion

HCV is a leading cause of death worldwide and in the UK the virus is most prevalent in PWID. With new, more effective treatments a target of viral elimination has been set by the WHO, however, without widespread treatment in PWID and the accurate epidemiological data required to guide service delivery this prospect is unlikely to become a reality.

In this thesis I investigate the genetic and social epidemiology of HCV in a small isolated UK community living on the IOW and use this understanding to test a 'treatment as prevention' elimination strategy in PWID.

2. Hepatitis C bio-behavioural surveys in people who inject drugs – a systematic review of sensitivity to the theoretical assumptions of respondent driven sampling

2.1 Chapter overview

Chapter 2 is a systematic review of literature that describes the use of a survey method, called respondent driven sampling (RDS), to estimate the prevalence of Hepatitis C (HCV) in people who inject drugs (PWID). I have included this chapter before the main method chapters (Chapters 3 and 5) because it directly informed the conduct of my own survey, which used RDS to identify participants.

2.2 Introduction

PWID are hidden by social stigma and the illegality of their practice and therefore it is difficult to obtain representative samples that are necessary to make population prevalence estimates[89]. Interest and experience in studying hidden populations developed substantially during the HIV epidemic in the 1990's. At this time the difficultly of obtaining representative samples with existing survey techniques prompted the development of a method called RDS[37].

RDS begins with a sample of *seeds* (the first participants) from the target population who are keen to participate in the survey and usually socially well connected. The *seeds* are then asked to refer a pre-defined number, or 'quota', of contacts to the survey who form *wave* 1 of recruitment, these responders are then asked to refer *wave* 2 and so on. In this way a sample with maximal

recruitment (i.e. a full quota of new recruits in each *wave*) expands geometrically. Recruitment throughout the *waves* is driven by a primary incentive for taking part and usually a secondary incentive for recruiting others[37].

Harnessing social influence through the use of incentives gives RDS the potential to reach participants who would not normally come forward to a researcher and the limited recruitment quota (usually three) minimises selection bias for those with large social networks[37]. This allows the characteristics of a sample to reach a steady state or 'equilibrium' quickly – often after just four *waves* of recruitment[37] (Figure 2-1). In addition specific software has been developed which incorporates estimators to calculate prevalence estimates for the entire target population from data collected during the sampling process[90,91].

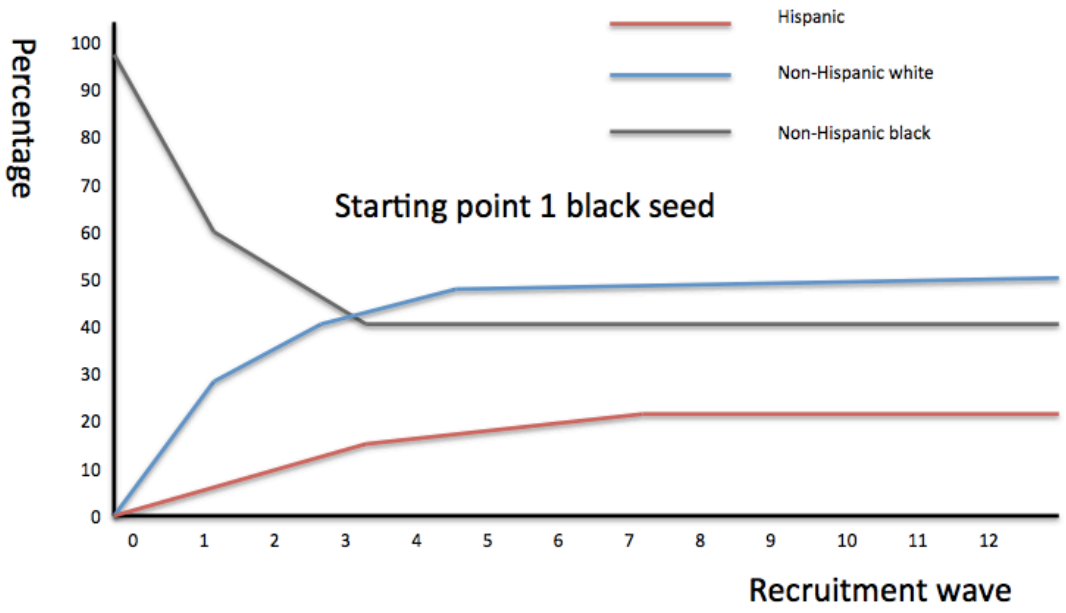


Figure 2-1 Equilibrium in RDS

The changing sample proportion according to ethnicity as RDS passes through sequential recruitment waves. In this example from *wave* five the proportion of each ethnicity stops changing. At this point the sample has reached equilibrium. (Graph adapted from Heckathorn *et al.*[37])

However, these estimators rely on methodological assumptions. These relate to the underlying size and network structure of the target population, as well as participant behaviour[92,93].

Previous reviews of RDS in HIV bio-behavioural surveys [38,94] have highlighted concerns about the quality of reporting and led to the publication of the STROBE-RDS reporting check-list in 2015[95]. This document aims to improve the quality of reporting and includes 22 items that outline how studies should report survey data collected using RDS. Importantly it incorporates criteria that indicate sensitivity to the assumptions underlying the population estimates.

Whilst the use of RDS in HIV epidemiology has been the subject of several systematic reviews, its use in the investigation of HCV epidemiology and specifically the sensitivity of prevalence estimates to the assumptions of RDS is not described[38,94]. The aim of this systematic review is to identify published studies documenting the use of RDS in HCV bio-behavioural surveys of PWID and describe the sensitivity of population estimates to the theoretical assumptions of RDS. To do so, the reported operational and analytical conduct of each study is compared against selected criteria from the STROBE-RDS checklist[95]. In so doing, the findings from this chapter directly inform the conduct and analytical method of sampling to the bio-behavioural and social network survey described in Chapter 5.

2.3 Method

The systematic review protocol was published on the Prospero website under registration number CRD 42015019245 prior to commencing the literature search and the review was conducted according to the PRISMA statement[96,97].

2.3.1 Information sources and literature search

I conducted two scoping searches using MedLine in March 2015 with no date or language limitations. The first used the terms “PWID* or IDU* or Injecting drug user* AND Hepatitis C or HCV AND respondent driven sampl*”. From title and abstract review 14 potentially eligible studies were identified, this was then compared to a second scoping search for the term “respondent driven sampl*”, which identified three additional studies.

This suggested my initial search was too specific and therefore in the final search I used MedLine, SCOPUS and WEB of SCIENCE online databases with no language or date limitations to search for the term "*respondent driven sampl*".* This was undertaken between the 10th April 2015 and 31th December 2016 and was followed by a forward and backward citation search in the SCOPUS database and a manual citation search through selected papers.

I conducted further searches through 'grey literature' sources including institution and key author websites, which included Respondentdrivensampling.org (Cornell University) and lisagjohnston.com. Specific search phrases in these domains varied but reflected the inclusion and exclusion criteria. An expert with experience undertaking surveys and teaching in this field was also contacted and asked to comment on the included studies and suggest others that may meet the inclusion criteria[*].

2.3.2 Inclusion criteria and study selection

Peer-reviewed studies written in English were included if they:

- Reported a survey in a population of PWID

AND

- Reported the use of RDS as the sampling method

AND

- Reported a sample prevalence or an estimated population prevalence for HCV

As HCV can remain asymptomatic and therefore undiagnosed for many decades after infection, I interpreted 'PWID' as anyone who had ever injected drugs[98]. Studies using mixed sampling methods (for example, combined convenience sampling and RDS) and not reporting results separately were excluded, as were non-English language papers because translation services were beyond the resources of this review. However, this was deliberately not a

[*] Lisa G Johnston, University of Tulane, New Orleans, USA

specific search criterion so I could assess the quantity of otherwise eligible non-English literature.

Duplicated studies from selected titles and abstracts were removed. Myself and Dr Jonathan Coad[*] independently assessed the selected titles and abstracts for inclusion using a selection tool and resolved discrepancies by discussion with a third researcher, Dr Julie Parkes[†]. The full papers of selected abstracts were obtained and subject to further independent review for inclusion. Where two studies reported data from the same survey and both published HCV prevalence, I included the study that was published first.

2.3.3 Data extraction

Data was extracted under three headings: 1) survey overview, 2) survey outcomes and 3) reporting against selected STROBE-RDS criteria.

Data was extracted independently and where referenced, additional papers describing the survey method in more detail were accessed and further details recorded.

[*] Jonathan Coad, Hepatology NIHR Academic Clinical Fellow, University of Southampton
[†] Julie Parkes, Associate Professor of Public Health, University of Southampton

2.4 Results

2.4.1 Search results

The initial search of the online databases identified 4,060 titles, of these 1,815 were duplicates leaving 2,245 separate studies. Abstract and title review identified 50 studies potentially meeting the inclusion criteria. Citation, 'grey literature' searches and expert recommendation identified a further 10 studies for full paper review (Figure 2-2). Sixty studies were obtained and reviewed in full. A further 29 were excluded at this stage with 31 remaining that met the inclusion criteria. Figure 1 outlines the specific reasons for exclusion.

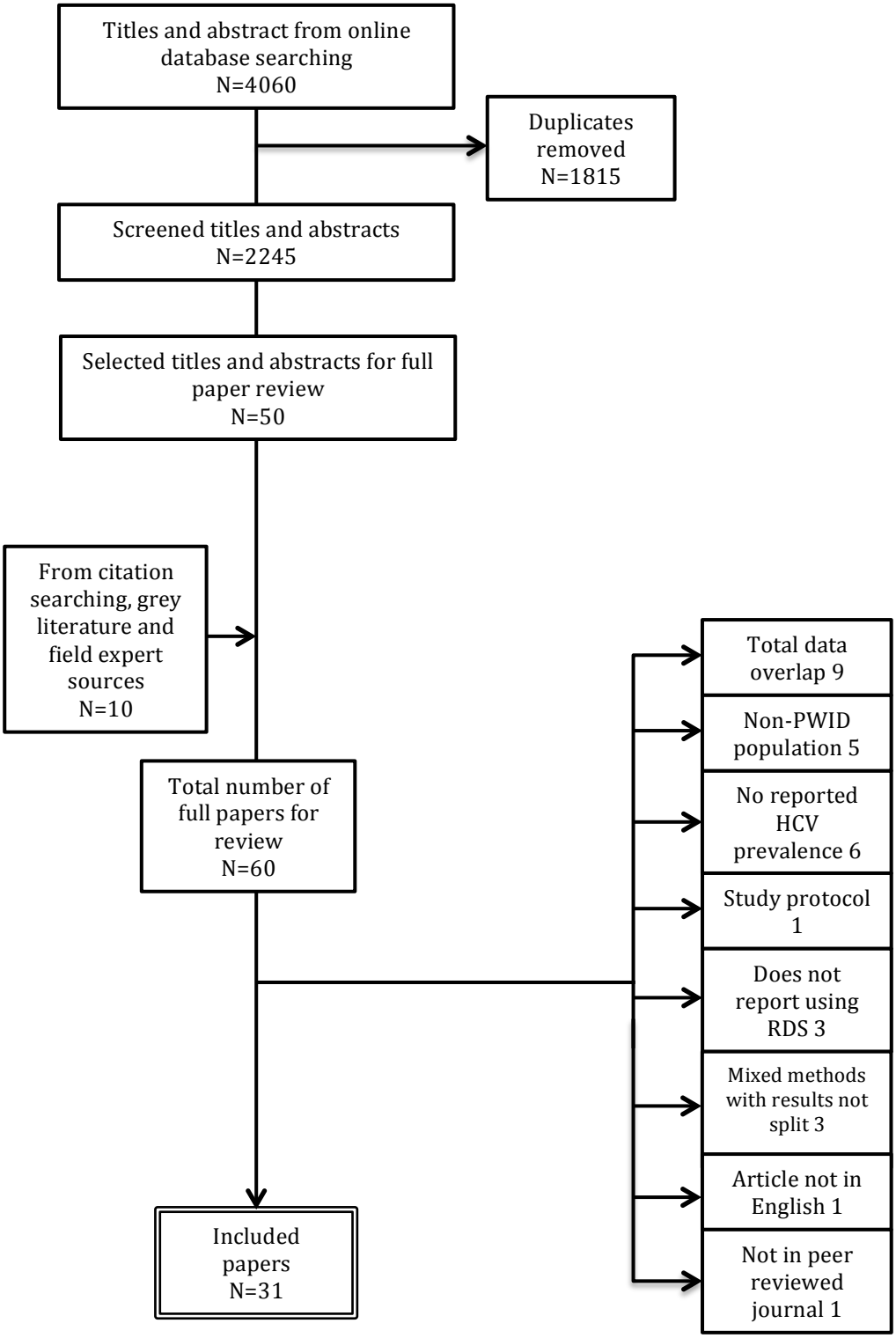


Figure 2-2 Flow diagram of studies screened and assessed for inclusion. Specific reasons for exclusion are indicated.

2.4.2 Overview of included surveys

Included studies were published between 2006 and 2016 and reported either a sample or population prevalence of HCV in PWID. They included surveys from Europe, North America, Asia, the Middle East, Africa and Australasia.

Eighteen studies (58%) conducted RDS in a single target population although this varied with the largest taking place in 15 cities across India[99]. Of the studies reporting from multiple locations, two used overlapping data from the same survey[100,101] and one study included survey sites that did not use RDS[102].

All studies clearly defined their eligibility criteria for participation and reported how the sample prevalence of HCV was obtained (Table 2-1). Fifteen surveys (48%) reported how participants were followed up by the research team, in most of these participants were advised to collect their testing results and were traced back to these via a 'linked anonymous record' i.e. the participant retained a unique identifier that connected them to their blood sample. However, two studies actually reported incentivising participants to return to collect their results[100,101], three described a direct referral pathway from the research team to specialist services[100,103,104] and one of these also took the opportunity to give out harm reduction advice and, where necessary, vaccination against Hepatitis A and Hepatitis B[100].

Twenty studies (65%) reported the time taken to reach the final sample size and seventeen studies (55%) documented a target sample size although of these only seven reported the value of the design effect (*deff)* used in making the calculation (Table 2-1). The final sample size at each survey site was reported in most studies (97%) (mean 382, range 81-1000) and in accordance with the inclusion criteria all the selected papers published either the sample HCV prevalence or a population prevalence estimate.

Two studies (6%) went on to use sampling data in combination with 'service multipliers' to calculate a total population size of PWID and therefore gave an indication of the total number of cases of HCV in the target population for the survey[105,106].

Table 2-1 An overview of studies meeting the inclusion criteria.

First author	Year of publication	Country	Survey duration (Months)	Target populations	Target sample size per population *(deff)*	Eligibility criteria	HCV test
Abadie *et al.*[104]	2016	Puerto Rico	3	4		>18years injected in last 30 days	POC antibody
Bacak *et al.*[107]	2013	Montenegro	4	1		18-51 years, injected in last 30 days	POC antibody
Baumbach *et al.*[1002]	2008	USA/Mexico	5	2		≥ 18 years, injected in last 30 days	Venepuncture antibody
Bouscaillou *et al.*[103]	2014	Georgia		1	193	≥18 years, injected in last 30 days	POC antibody & RNA
Burt et al.[108]	2009	USA	5	1		>18 years, injected in last 12 months	Self report
Cepeda *et al.*[109]	2013	Russia	23	2		≥18 years, injected last 30 days, drinks alcohol	Venepuncture antibody
Eritsyan *et al.*[110]	2013	Russia	2	8	300(0)	≥18 years, injected in last 30 days	Venepuncture antibody
Frost *et al.*[101]	2006	USA/Mexico	3	2	200	≥18 years, injected in last 30 days	Venepuncture antibody
Gelpi-Acosta *et al.*[111]	2011	USA	30	1	500	18-40 years, injected in last 12 months	Venepuncture antibody
Handanagic *et al.*[112]	2016	Croatia	4	3	350-400	>18 years, injected in last 30 days	Venepuncture antibody
Heimer *et al.*[113]	2014	USA		1		≥18 years, injected in last 30 days	Venepuncture antibody
Hope *et al.*[114]	2011	UK	3	1		≥18 years, injected in last 30 days	DBS antibody & RNA
Jarlais *et al.*[115]	2016	Vietnam	<1	1	600	>18years, currently injecting	Venepuncture antibody
Johnston *et al.*[105]	2011	Mauritius	3	1[2]	500(2)	≥15 years, injected in last 30 days	Venepuncture antibody
Judd *et al.*[116]	2009	Serbia and Montenegro	2	2		≥18 years, injected in last 30 days	DBS Antibody
Lausevic *et al.*[117]	2015	Montenegro		1	376	≥18 years, injected in last 30 days	Venepuncture antibody

First author	Year of publication	Country	Survey duration (Months)	Target populations	Target sample size per population *(deff)*	Eligibility criteria	HCV test
Li *et al.*[106]	2014	China		1	362	≥18 years, injected in last 6 months	Venepuncture antibody
Mahanta *et al.*[118]	2008	India	11	5	400	Males ≥18 years, injected in last 6 months	DBS antibody
Mahfoud *et al.*[119]	2010	Lebanon	2	1		≥15 years, injected in last 12 months	DBS antibody and RNA
Malekinejad *et al.*[120]	2011	USA	8	1		18-70 years, IDU in last 12 months	Self report
Mirzoyan *et al.*[121]	2013	Libya	5	1		≥15 years old 30 days	Venepuncture antibody
Nadol *et al.*[102]	2015	Vietnam	13	4	291-310 (1.2)	≥18 years, injected in last 30 days	Venepuncture antibody
Paintsil *et al.*[122]	2009	Russia	2-7	1		≥18 years, injected in last 6 months	Venepuncture antibody
Paquette *et al.*[123]	2011	Australia	5	1	258(1.5)	>18 years, IDU in last 30 days	Self report
Sarna *et al.*[124]	2012	India	5	2	760(1.5)	Male, >16 years, IDU in last 6 months	Self report
Solomon *et al.*[99]	2015	India	1.5	15	1000	≥18 years, injected in last 2 years	Venepuncture antibody
Stulhofer *et al.*[125]	2012	Israel	3	1		18 to 56 years, injected in last 30 days	Venepuncture antibody
Tun *et al.*[126]	2013	Nigeria	1.5	1	400(1.4)	≥18 years, injected in last 12 months	Venepuncture antibody
Vorobjov *et al.*[127]	2009	Estonia		1		≥18 years, injected in last 2 months	Venepuncture antibody
Wenz *et al.*[128]	2016	Germany	2	8	200-400	>16 years, injected in last 12 months	DBS antibody and RNA
Zamani *et al.*[129]	2010	Iran	3	1	130(1.5)	≥18 years, injected in last 30 days	Venepuncture antibody

[1]Where no information available cells left blank; [2]additional survey site excluded as reported earlier by Frost *et al.*[101]; [3]two separate survey locations were used in Mauritius but as there was cross recruitment between sites the results were treated as a single population.

Deff – design effect; IDU – injecting drug use; POC – Point of care test; DBS – dry blood spot test

2.4.3 Sensitivity to RDS assumptions

A population prevalence estimate is where the proportion of HCV positive cases in the sample is extrapolated to represent the proportion in the entire target population. As explained in Section 2.2, using RDS it is possible to report a population prevalence estimate with a caveat that the estimate is dependent on assumptions underlying the RDS process.

Twenty-seven of the included studies either calculated or reported the intention to calculate a population prevalence estimate for HCV. The remaining four studies deliberately treated their survey data as a convenience sample and did not report any intention to calculate population estimates.

Table 2-2 outlines of how studies that included a population prevalence estimate for HCV compared against selected STROBE-RDS criteria. These criteria are selected because they give an indication about the sensitivity and adherence of each study to the assumptions underlying the RDS process. In the following section I describe how these 27 studies reported against the criteria and where there was specific evidence that the assumptions were not met.

Table 2-2 STROBE-RDS criteria indicating adherence or sensitivity to RDS assumptions in included studies reporting or intending to report a population prevalence estimate for HCV.

Study	Research venue	Incentive Pri/Secondary	Number of *seeds* per site	Max recruitment *waves*	*Seed* data in analysis	Software used
Abadie *et al.*[104]	NSP	£/£	2			RDSAT/RDS-A
Bacak *et al.*[107]	HIV counselling office	£/£				RDSAT
Baumbach *et al.*[100]	NGO clinic	£/£	5			RDSAT
Bouscaillou *et al.*[103]	Drug support drop in centre	£/		9		RDSAT
Frost *et al.*[101]	Mobile bus & NGO clinic	£/£	12	8	Excluded	RDSAT
Gelpi-Acosta *et al.*[111]	Field office or mobile van	£/£			Excluded	RDSAT
Handanagic *et al.* [112]		Food coupon/food coupon	13.7			RDS-A
Heimer *et al.* [113]			82			RDSAT
Hope *et al.*[114]		£/£		17		RDSAT
Jarlais *et al.*[115]		£/£	12			RDSAT
Johnston *et al.*[105]	NGO centre, rented space	£/£	6	13	Included	RDSAT
Judd *et al.*[116]	Shopping mall and NGO centre	£/£	3			RDSAT
Lausevic *et al.*[117]		£/	5	10	Excluded	RDS-A
Li *et al.*[106]	Drop in centre	£/£	5	11		RDSAT
Mahanta *et al.*[118]			3			RDSAT
Mahfoud *et al.*[119]	NGO centres	£/£				RDSAT

Study	Research venue	Incentive Pri/Secondary	Number of *seeds* per site	Max recruitment *waves*	*Seed* data in analysis	Software used
Malekinejad *et al.*[120]		£/£	16	27		RDSAT
Mirzoyan *et al.*[121]		£/£	7	10		RDSAT
Nadol *et al.*[102]		£/£		8		RDS-A
Paintsil *et al.*[122]		Gifts/Gifts	23		Excluded	STATA
Paquette *et al.*[123]	NSP	£/£	5	16		RDSAT
Sarna *et al.*[124]	NGO centre	£/£	4.5		Excluded	RDSAT
Solomon *et al.*[99]	Drop in centre	/£	2.1	50		RDSAT
Stulhofer *et al.*[125]		£/£	7	12	Excluded	RDSAT
Tun *et al.*[126]	NGO centre	£/£	7			RDSAT
Wenz *et al.*[128]	Drop in centre	£/£	7-19	20	Included	RDSAT
Zamani *et al.*[129]	Drop in centre	Gift/None	10	8		RDSAT

Where no information available cells left blank.

RDS – respondent driven sampling; NGO – Non-governmental organisation; NSP – needle syringe programme; BBV – blood borne virus; STI – sexually transmitted infection; £ - financial incentive given; RDSAT see reference[90]; RDS-A - see reference[91]

Assumption 1: Participant social networks are linked into a single component

There were indications given in three studies (11%) that the underlying network structure adversely affected recruitment[100,113,119] and of these, Wenz *et al.* specifically reported that clustering within the network affected the validity of population prevalence estimates[128]. These studies did not describe formative research to explore the structure of the social network in advance of the survey but this was described in nine other studies. Among these there was variation in the scale and methods used; some studies reported the use of informal interviews with local stakeholders, whilst others described focus groups, qualitative interviews, and ethnography or cited a published preliminary study. Only Zamani *et al.* specifically described how this formative work was used to optimise recruitment from all parts of the network[129].

Assumption 2: Recruiters do not pass coupons to strangers and ties are reciprocal

Two studies (7%) reported a number of participants being recruited to the survey by strangers but neither described how these participants were handled in the analysis[125,129]. Overall sixteen studies (59%) reported the recording of the relationship between the recruiter and recruit, however only Paquette *et al.* precisely defined the question that was used to assess this[123].

Assumption 3: Estimates are independent of seed characteristics

Eight studies (30%) reported the purposive selection of *seeds* through ethnography or via consultation with key stakeholders in the field. Nineteen studies (70%) described the number of *seeds* used to initiate recruitment (range 2 to 82) although only two met the STROBE-RDS checklist by describing clearly how many *seeds* were added to boost recruitment after the survey had started[112,120]. The data from the survey by Heimer *et al.* could not be used to calculate a population prevalence for HCV because too many *seeds* had been needed to reach the target sample size[113].

The recruitment quota, or number of coupons given to each *seed,* was reported in all studies and ranged from 2 to 4 but the number of recruitment *waves* per *seed* was poorly described with only three studies including diagrammatic recruitment 'trees' within the main text[101,120,128]. However, 15 studies (56%) reported the number of *waves* achieved in the longest recruitment chain (range 5-50) and another reported a median chain length across 15 survey sites[99]. Seven studies (26%) reported measuring 'sampling equilibrium' after a certain number of recruitment *waves* for key criteria to indicate independence of the sample from *seed* characteristics and one used this as the point to stop sampling[106].

Whether *seed* data was included in the analysis was not explicitly reported in most studies although six (22%) did describe deliberately excluding *seed* data from population prevalence estimates whereas two (7%) specifically documented its inclusion[105,128].

Assumption 4: Recruiters pass coupons randomly to eligible network members and these individuals are equally likely to participate

One study clearly described how participants were trained to recruit social network members to the survey[120] but there were concerns expressed in a number of studies about non-random recruitment. Eight studies (30%) reported difficulty recruiting female participants despite, in one, the deliberate use of female *seeds*[103]. Sarna *et al.* considered whether this was a true representation of the underlying population structure[124], but three other studies expressed concern about 'response bias' attributed to cultural barriers within the target population[103,117,121] and non-recruitment of participants from particular ethnic backgrounds[123], socio-economic groups[113] or geographical areas[120,123]. To test recruitment bias, three studies (11%) reported measuring homophily for selected characteristics between recruits and recruiters[104,112,128]. Abadie *et al.*, observed homophily between persons with a known HCV positive status[104].

Sixteen studies (59%) described the venue used for the survey and Handanagic *et al.* raised concerns that the venue may have influenced participation[112]. The incentives used for recruiting others to the survey were described in twenty-one studies (78%) and 19 of these described a financial primary and secondary

incentive, the value for which ranged from $50 and $20 respectively in the USA[111] and $1 and $0.8 in India[99,124]. Where reported, the remaining surveys used gifts or food coupons[112,129,130]. Zamani *et al.* recorded a concern that the financial incentive may have led to bias towards poorer PWID and did not use a secondary incentive for this reason[129] and Bouscaillou *et al.* considered whether the offer (as part of participation) of being linked directly to HCV care may have encouraged a disproportionate number of PWID with HCV to attend[103].

Assumption 5: Participants only take part once and are eligible members of the target population

Judd *et al.* described participants attempting to attend more than once and non-eligible individuals trying to take part[116]. The method used to screen survey participants for eligibility (i.e. proof they had injected drugs) was recorded in 15 studies (56%) but only four described how repeat attenders were identified. Of these, Paintsil *et al.* recorded identifiers such as tattoos or anthropometric measurements[122] and Solomon *et al.* used finger print records[99].

Assumption 6: Participants accurately report their degree size

Fifteen studies (56%) reported recording the *degree* size for each recruit and of these, three precisely described the question or questions used to define this[100,120,128]. No studies reported testing the sensitivity of prevalence estimates against variations in *degree* size.

Assumption 7: Sampling occurs with replacement

The majority (85%) of included studies used a version of RDSAT software[90] to calculate prevalence estimates. RDSAT incorporates an estimator that is constrained by this assumption[93,131,132]. However, only Abadie *et al.* measured how this may have affected the HCV prevalence estimate by comparing it against an estimate calculated with a successive sampling estimator[104].

Assumption 8: An estimate of total target population size is known in advance of the survey

Four studies (15%) used a successive sampling estimator integrated within RDSanalyst software[91] to calculate population estimates and therefore needed a target population size estimate to make the calculation. Two specifically reported the use of such an estimate and referenced its source[102,112].

2.5 Discussion

The studies included in this review used RDS to recruit over 25,000 PWID to bio-behavioural surveys across five continents. The studies were consistent in documenting the use of standard RDS methods including: recruitment coupons, recruitment quotas, and incentives to facilitate the coupon exchange, but varied considerably in scale, duration and operational conduct.

The quality of reporting against the STROBE-RDS criteria, in some instances, made an assessment about the sensitivity of survey results to the underlying assumptions of RDS difficult. The incomplete reporting of the sampling method in surveys using RDS has been described before[38,94] and is not surprising here given that the STROBE-RDS checklist was published after most of the included studies[95]. Nevertheless, from what was reported, there were indications that the assumptions were not met in some studies and in two cases this led to study authors being unable to use survey data to calculate a population prevalence estimate. This is consistent with reports elsewhere which describe recruitment via non-reciprocal relationships[133], inaccurate *degree* size reporting[134], biased recruitment according to ethnicity[135] and limited recruitment due to disparate social networks within the target population[136] .

The collective understanding of the implications of not meeting the assumptions of RDS has advanced in recent years through literature 'testing the assumptions'[134,137–140]. Simulation studies have reported the scale of biases associated with *seeds*, recruitment *waves*, high recruitment homophily and sampling *without* replacement[139], whilst work based on real-world surveys has demonstrated the bias associated with inaccurate reporting of *degree* size[134]. This has led to the evolution of the original RDS estimator[93,131,141], new estimators based on successive sampling and *ego* network data[142,143] and development of RDS technical procedure - an iterative temporal transformation that may account for some of the variation seen in the included studies.

Specifically this has led to development in how to accurately ascertain *degree* size, how to handle *seed* data in the analysis[139] (a contrast with earlier literature[93]), how to measure sample independence from *seed* characteristics using convergence rather than equilibrium[92] and the use of *ego*-network data

to assess recruitment bias[143].

This systematic review is the first to describe the use of RDS in HCV epidemiology and explore sensitivity to the methodological assumptions underlying RDS in these studies. In so doing it draws attention to reporting criteria for surveys using RDS and highlights recent technical developments. However, it also has areas of potential bias, for example, the search strategy, by including only peer-reviewed publications, excluded survey data within 'grey literature' such as public health reports. This may have led to bias towards the more successful, robustly designed surveys that have a higher chance of publication. In so doing this review may have over estimated the quality of reporting relating to the assumptions of RDS and underestimated sensitivity to these assumptions.

2.6 Conclusion

RDS can improve our understanding of HCV epidemiology in PWID and therefore has the potential to make an important contribution to the global elimination strategy for HCV. This robust systematic review included 31 studies and showed that operational procedures varied between studies and were frequently incompletely reported. There were also widespread indications of sensitivity to the methodological assumptions of RDS that, in some studies, prevented the estimation of HCV population prevalence.

The findings of this systematic review have informed the procedural and analytical method of the RDS reported in this thesis (Chapter 5). More broadly it has highlighted the need that future surveys using RDS to explore the epidemiology of HCV within PWID should convey sensitivity to the assumptions by reporting in accordance with the STROBE-RDS checklist and should also consider using recent advances in the procedural and analytical methods of RDS in order to maximise the validity of prevalence estimates.

3. Research design and qualitative methods used in this thesis

Chapter 3 outlines the mixed method research design I used in this thesis and describes in detail the qualitative methods that I used to give the results described in Chapter 4. The qualitative results informed the design of the quantitative methods and therefore these are described separately in Chapter 5.

3.1 Research design & methodology

Pragmatism accepts that research is neither exclusively data or theory driven and that in reality it constantly moves between areas of induction and deduction[144]. This fits well with health care practice, where objective and subjective measures are routinely combined in order to understand the social and biological process of disease[145] and specifically with the present inquiry where I seek to understand the diverse biological and social phenomena involved in Hepatitis C (HCV) epidemiology.

Mixed method research can be seen as a pragmatic approach to identify insights and phenomena that would be missed if qualitative and quantitative methods were used in isolation and as a way of enhancing the validity of results by offsetting the bias associated with each method[146,147].

Mixed method study design can be very varied, Greene *et al.* conducted an empirical review of 57 articles that clearly described the use of mixed methods and identified five purposes for conducting a study as well as a variety of research designs associated with each (Table 3-1)[147].

Table 3-1 The five purposes of undertaking mixed method research as identified by Green *et al.*[147]

Purposes of mixed method research (adapted from Greene *et al.* 1989)	
Triangulation	Convergence & corroboration of results from different methods.
Complementarity	Elaboration, enhancement, illustration and clarification of results through using different methods.
Developmental	Using the results of one method to develop a further method.
Expansion	Increasing the scope of enquiry by using different methods to investigate different inquiry components.
Initiation	Seeking conflict in results through different methods to generate new research ideas and areas of inquiry.

Building on this work and applying it specifically to social network research, Hollstein defined mixed method network studies as being based on quantitative and qualitative data collection and analysis, with the integration of results from both strands of enquiry to reach final conclusions. Holstein then went further and described research designs, which address different social network related research questions. These included sequential, parallel, fully integrated and embedded designs, which are characterised by how the qualitative and quantitative strands are approximated to one another i.e. whether one method follows the other or whether they are conducted in parallel[148].

The overall design of this thesis follows a *sequential exploratory and explanatory design*, used, according to Hollstein, when "the primary purpose of the qualitative pre-test is to support the development of instruments for the main (quantitative) study" (Hollstein 2014, p12) and when "the qualitative inquiry is meant to deepen and further elucidate the results obtained by the quantitative analysis" (Hollstein 2014, p12)[148]

In this thesis I use qualitative methods firstly to support the design of a quantitative survey (refer to Chapter 4) and secondly to elaborate and enhance the findings of this survey (refer to the General Discussion - Chapter 10) (Figure 3-1). The qualitative methods used in this thesis are described in detail in this chapter (Section 3.3 onwards) and the quantitative methods are

described in detail in Chapter 5. The methods are described separately because results from the qualitative methods, reported in Chapter 4, informed the development of the quantitative methods.

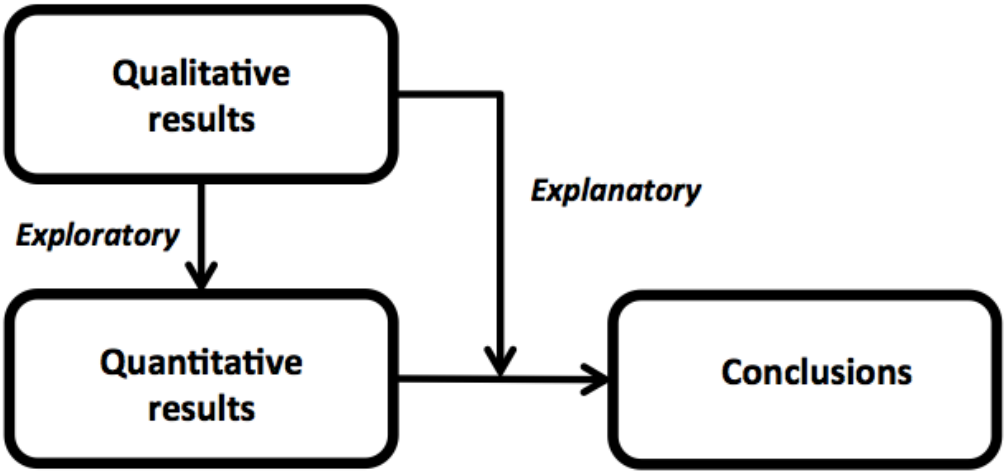


Figure 3-1 Overall research design

The combined exploratory and explanatory sequential design of this thesis including how the qualitative and quantitative strands relate to one another and how the methods used lead to the research outcomes. Semi-structured interviews with people who inject drugs (PWID) and a single focus group with drug support centre (DSC) staff inform the design of a bio-behavioural and social network survey the results of which are elaborated and enhanced by qualitative data.

3.2 Ethical considerations

Ethical approval was obtained from the University of Southampton, the local research and development team based at St Mary's Hospital on the IOW and the UK national research ethics committee (East London REC office, REC reference number 15/LO/1076) (Appendix 1). This approval covered the methods described in this Chapter and, unless specifically stated, those described in Chapter 5.

3.3 Qualitative methods

To gain a comprehensive understanding of the following research objectives, I used multiple qualitative methods including a focus group and semi-structured interviews.

Objectives addressed through qualitative methods:

- *Establish the feasibility of undertaking respondent driven sampling (RDS) in people who inject drugs (PWID) living in an isolated and rural community.*
- *Understand how HCV transmission is related to the social network of PWID.*

Objective 1 was addressed using qualitative methods in isolation, whereas to meet Objective 4 the results from qualitative and quantitative methods are combined in the General Discussion (Chapter 10) before drawing final conclusions.

3.3.1 Focus group with drug support centre staff

I undertook a single focus group with drug support professionals from the local drug support centre (DSC). Focus groups are a quick and inexpensive way of acquiring research data when compared to other qualitative methods such as ethnography, and allow freedom for participants to highlight key topics that are either unknown or have been deemed unimportant by researchers[149]. There are however potential draw backs including, the potential for participants to take one another 'off topic', hierarchies between participants affecting disclosure and the unnatural environment a group setting can create[149]. In planning this focus group careful attention was therefore given to the survey location, recruitment and topic guide.

3.3.1.1 Eligibility criteria

Any staff member working directly with clients who had a history of drug abuse on the IOW was eligible to participate. I deliberately did not invite the General Practitioner based at the DSC as I was concerned about introducing a 'knowledge hierarchy' that might negatively affect disclosure.

3.3.1.2 Participant selection and recruitment

I considered staff at the DSC, which has managed over 800 individual interactions with PWID over the last 10 years*, to have an appropriate level of knowledge about PWID on the IOW to give meaningful results. I informed the DSC manager and blood-borne virus testing nurse at an early stage about the study and the latter acted as a 'gatekeeper'[150] for recruitment by sending an email to all eligible staff advertising the focus group and the free lunch that was available on the day.

3.3.1.3 Focus group venue

I was aware that study locations near professional responsibilities can lead to distractions but equally that familiar surrounding can be of benefit to focus group disclosure[151,152]. I therefore chose a quiet room at the back of the DSC as the venue as this was convenient for staff to attend in their lunch break but also well away from the distraction of professional areas.

3.3.1.4 Consent

Once participants were seated they read an information sheet and signed a written consent form (Appendix 2).

3.3.1.5 Data collection

The discussion was recorded on a digital recorder and as moderator, I used a topic guide (Appendix 3) to give some underlying structure to the session. An observer† recorded the start of each sentence to aid transcription.

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* From personal correspondence with DSC manager
† Thanks to medical student Ryan Youde, University of Southampton

3.3.2 Semi-structured interviews in those with a history of injecting drug use

I undertook semi-structured interviews with current and former PWID. Semi-structured interviews are effective for revealing the personal context of the participant[153] but unlike unstructured interviews, balance the depth of the responses against a predetermined agenda, ensuring the research question is addressed[154]. Focus groups can be similarly effective but I had concerns, based on conversations with DSC staff, about the potential for conflict to arise between participants. This would have affected disclosure and could potentially have led to harm so it was not an option that I considered further.

3.3.2.1 Eligibility criteria

To be eligible for inclusion, potential participants had to have previously injected or be currently injecting drugs on the IOW, be over 18 years of age, and able to undertake an interview in English.

3.3.2.2 Participant selection and recruitment

I used a purposive sampling strategy to ensure PWID with a range of experiences were interviewed[150]. To facilitate this, participants were recruited from the DSC and the local hospital. DSC professionals were informed about the details of the study via email and they booked interested clients into slots to meet with me for an interview. At the hospital clinical staff from the HCV and sexual health service identified potential participants who, if interested, I approached directly or via letter (Appendix 4).

I communicated with the hospital and DSC staff to ensure a varied sample of PWID were invited to interview. A £10 shopping voucher was given on completion of the interview as a thank you to each participant.

3.3.2.3 Interview venue

At the DSC, I conducted the interviews in a quiet room that was set up for counselling sessions provided at the centre. I recognised that the hospital was not an ideal environment to conduct an interview as it is important participants feel comfortable[155] and therefore individuals recruited at the hospital were given the opportunity to undergo the interview in their own home.

3.3.2.4 Consent

All participants were given an information sheet and completed a written consent form (Appendix 5).

3.3.2.5 Data collection

A topic guide (Appendix 6) was used to give structure to each interview, this was adapted from key questions outlined by Johnston *et al*. (see Table 4-1) with a broad structure based on Yeo *et al.*[155,156]. The topic guide was reviewed after every three interviews and iteratively revised. As part of each interview I asked participants to complete a concentric circle diagram (Appendix 7)[157] and a card sorting exercise[158,159], where participants were asked to write down possible survey venues and incentives for participation and visually rank them according to what they thought would be most effective. The objective of the concentric circle diagram was to create a representation of their social environment and allow them construct a narrative around it[160]. I recorded each interview using a digital device.

3.3.3 Qualitative data analysis

The focus group and interviews were subject to a deductive thematic analysis which is a widely applied method for qualitative data analysis and is a particularly useful tool for researchers with limited experience in qualitative methods[161]. During this process the focus group was examined as a whole without delineation between the individual contributors[162].

There are five stages to thematic analysis: Phase 1 involves data immersion and familiarisation, phase 2 involves the documentation of a range of potential codes of related content that are present in the material, in phase 3 emerging themes are identified from the coding ideas, and in phase 4 these candidate themes are reviewed to ensure the coding fits a coherent pattern and reflect the content of the research material[161]. Finally in stage 5 the data within each theme is considered with the 'message' from each theme defined in relation to the research question (Figure 3-2).

Transcription is an important part of the first phase of data analysis as it involves prolonged immersion in the recorded data[163]. However, it is also time-consuming[164]. Accordingly, to facilitate a self-reflection on interview technique and amendments to the interview topic guide I transcribed the first three interviews and the focus group, but sent the remaining interviews for professional transcription.

Potential codes relating to the social network structure and feasibility of conducting a RDS survey are well defined in the published literature[156] and therefore coding was a deductive or theoretical process that I applied to the focus group and interview transcripts (Table 4-1). I used NVivo software[165] to facilitate the organisation of codes from both methods into themes throughout the analysis.

3.3.4 Maintaining rigour in qualitative research

3.3.4.1 Transparency, validity and reliability

It is essential that during the planning, conduct, analysis and reporting of qualitative research good practice is maintained to reassure the reader of its reliability and validity[164]. In addition to being transparent by documenting in detail how the analysis took place, I attempted to maximise the validity of emerging themes by looking specifically for dissonance between sources and by getting a rough 'quantitative' idea about how many sources contributed to each[164]. The reliability of the results i.e. what was the likelihood the same results would be generated were the work to be repeated, was increased by undertaking 'dual coding'[164] where I asked an additional researcher with experience in qualitative methodology to code three interviews*. Codes were then compared and candidate themes discussed.

3.3.4.2 Reflexivity to account for bias

I wrote field notes immediately after each encounter in an attempt to account for how I (as the interview and focus group moderator) might have influenced

* Thanks to Dr. Sophie Chambers, research fellow in Addiction at the University of Southampton for acting as a second coder for three transcripts.

the narrative. As a qualitative researcher it is important to try and maintain neutrality throughout the enquiry and therefore strive to minimize bias wherever possible[166]. It is also necessary to accept that whatever is seen or heard during the conduct of qualitative research must pass through the researcher and that it is important to be transparent about how what is presented may have been influenced by the researcher[167,168]. I felt my influence could take two forms: 1. Verbal factors such as, what questions I ask, how I asked them and my responses to the participant and 2. Non-verbal factors, such as my job, dress and gender. I attempted to document how these factors may have affected the interview dialogue in my field notes and used these to help minimise bias in subsequent interviews and aid interpretation of the results before drawing conclusions (Figure 3-2).

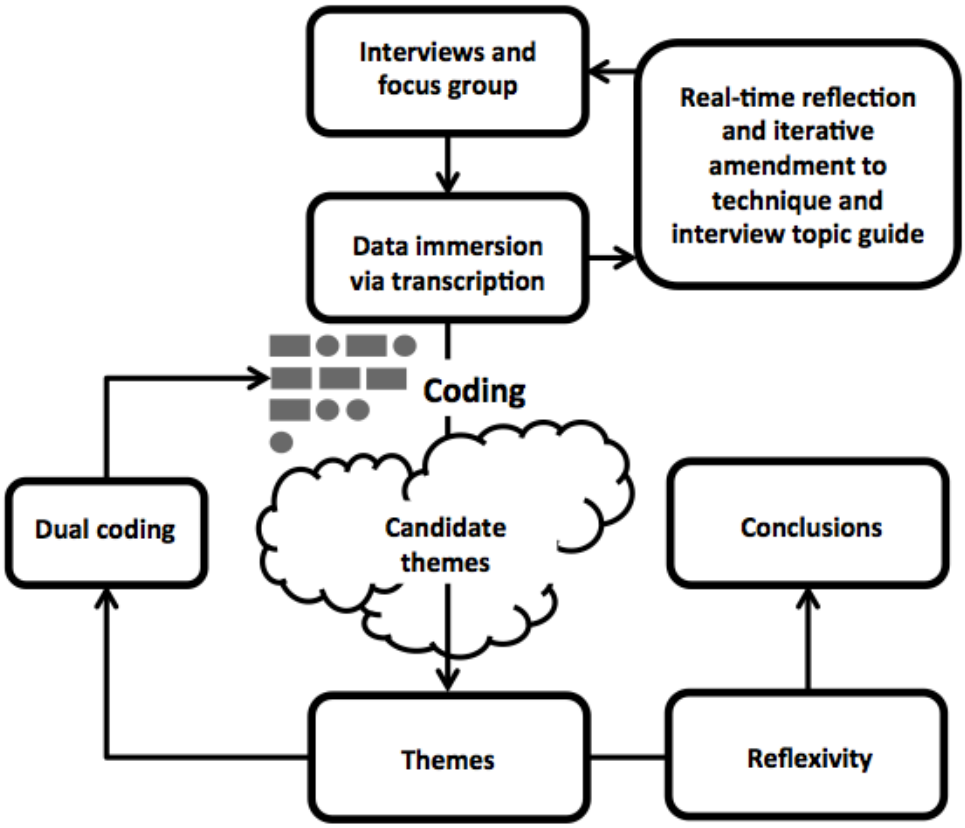

Figure 3-2 Summary of the thematic analytical process.

4. The social network of people who inject drugs on the Isle of Wight and the feasibility of undertaking respondent driven sampling

4.1 Chapter overview

Chapter 4 reports the results of the deductive thematic analysis of the semi-structured interviews with people who inject drugs (PWID) and focus group with drug support centre (DSC) professionals. Themes describe the social network of PWID and specific findings relevant to the feasibility of respondent driven sampling (RDS). The chapter addresses the following research objectives:

- *Explore the feasibility of undertaking RDS in PWID from an isolated, rural community.*
- *Understand how HCV transmission is related to the social network of PWID.*

4.2 Introduction

The importance of the social network of PWID in Hepatitis C (HCV) disease transmission has been introduced in Chapter 1, Section 1.7. A key requirement for successful RDS is a sufficiently connected target population, where the denser the network the better sampling performs[169]. However, many other factors also play an important role in sampling success and it is essential these are explored in advance of undertaking a survey[170].

The National HIV behavioural surveillance system (NHBS) is a large-scale HIV surveillance program that uses RDS to survey PWID and other groups at risk of blood-borne viruses on a rotational basis across the United States[171]. A formative phase of research at each survey site is well described for this

program. It is used to determine the appropriateness of RDS as a survey method and to establish local practicalities, such as the survey venue, the specific content of questionnaires, coupon design, *seed* selection and support from key stakeholders[171]. This preparatory or formative phase of the survey is primarily defined by the use of qualitative research methods. These can include ethnography, interviews and focus groups which, although time consuming and costly, are necessary in order to gain in-depth understanding of the community in question[171].

Formative work prior to an RDS survey is not exclusive to large-scale national surveillance programs. Simic *et al*. describe the formative phase of four smaller surveys[172] which highlighted potential problems concerning the value of incentives, trust between potential participants and official agencies, and the structure of underlying social network. This data acted to either revise survey protocols (such as increase the incentive) or explain inadequate recruitment and suggest ways it could be optimised[172].

Hundreds of surveys have now been undertaken using RDS and the majority undertake some formative data collection to inform the survey protocol[38]. Many surveys have used single qualitative methods whilst others have combined methods in a similar manner to the US NHBS. The questions that need to be addressed by the formative enquiry are now well defined[156] (Table 4-1).

Table 4-1 Areas to be addressed in advance of a RDS survey.

Area to be addressed	Specific questions
Network properties	Is the network density sufficient to facilitate recruitment?
	Do local PWID comprise one single network or isolated cliques and sub networks?
Acceptability of RDS	Will local PWID be happy to participate in the survey?
	What are the attitudes of related professionals towards the survey and particularly the use of incentives?
Seed selection	Can individuals be identified who would be willing to begin recruitment?
	Are these individuals sufficiently connected across the network?
Survey logistics	What is an appropriate incentive to encourage recruitment to the survey?
	When and where would it be acceptable for PWID to take part in the survey?

The work presented here is the result of a deductive thematic analysis[161] of interviews with PWID and a focus group with professionals working at the DSC and quotes reflect the views and experiences of PWID and professionals.

4.3 Methods

The qualitative methods used in this Chapter are described in Chapter 3.

4.4 Results

4.4.1 Sample characteristics

The focus group with DSC staff took place prior to the participant interviews in May 2015. On the day, six centre staff members attended, all worked directly with PWID on the IOW, and the majority had been doing so for many years (in two cases over 20 years). Only one member of staff who was invited to the focus group was unable to attend due to ill health. Two participants had recently moved to the centre from another drug support site, which had closed down, and had therefore only been working at the centre for a few months. The focus group took place during lunch break, which limited the duration to 62 minutes.

I interviewed 16 PWID with diverse characteristics including a range of ages (34-62 years; mean 44 years), injected substances and geographical experience of injecting drug use with some having injected drugs in mainland cities (Table 4-2). Interviews ranged in duration from 24-52 minutes and took place between October 2015 and April 2016. Fourteen of the participants (86%) were recruited by DSC staff, 13 were known to drug addiction support services whilst one was known through needle exchange only. Of the two participants recruited at the hospital, one was known to the hepatology service with HCV and the other was identified by the sexual health service.

Table 4-2 Interview participant characteristics.

Pseudonym	Gender	Age	HCV status	Currently injecting drugs*	Time since last injected	Primary drug use on IOW	Injected drug of choice	Interview location
Jill	F	35-39	-	No	18 months	Yes	H	DSC
Brian	M	50-54	RNA+	Yes		Yes	H	DSC
John	M	30-34	-	Yes		No	LH	DSC
Ric	M	45-49	-	Yes		Yes	H	DSC
Sally	F	40-44	-	No	10 years	Yes	H	DSC
Matt	M	35-39	-	Yes		Yes	H, LH	DSC
Jerry	M	60-64	RNA+	No	3 years	No	H	Hospital
Alan	M	40-44	-	Yes		Yes	H	DSC
Sam	M	30-34	-	No	6 years	No	H	DSC
Leigh	F	40-44	-	Yes		Yes	H	DSC
Tony	M	40-44	-	No	6 years	Yes	A, H	DSC
Ben	M	55-59	Antibody+	Yes		Yes	A, H	DSC
Mark	M	40-44	-	No	5 years	Yes	H	DSC
Lucy	F	35-39	-	No	6 months	Yes	H	Hospital
Rob	M	35-39	RNA+	No	2 months	Yes	H	DSC
Malcolm	M	60-64	-	Yes		Yes	S	Pharmacy

Key: H – Heroin; LH – 'Legal' highs; A – Amphetamines; S – Anabolic steroids; RNA+ - Chronic infection with HCV; Antibody+ – previous exposure to HCV; DSC – Drug support centre

*Defined here as having injected a substance in the last 30 days

4.4.2 Themes

Three themes emerged from the deductive thematic analysis of the interview and focus group transcripts. These themes along with their respective sub-themes are summarised in Table 4-3.

Table 4-3 Summary of themes

Theme	Description	Subthemes (*In vivo* codes indicated by italics)
Theme 1 - Cohesion	How PWID on the IOW are connected in network and why this is the case?	*'like the London Underground'*
		'dry spells'
Theme 2 - Cliques & isolation	Groups who are considered isolated from other PWID	*'keep the wolves away'*
		'drug fraternities' and 'old heads'
Theme 3 - Acceptability	The thoughts of PWID and drug support service professionals about a RDS survey taking place on the IOW	*'the domino effect'*
		'two lives'
		Incentives and research venues

4.4.2.1 Theme 1: Cohesion

Theme 1 describes how PWID on the IOW are densely connected to one another and how this contrasts with experiences of injecting drug use elsewhere. Furthermore, this theme outlines how the difficulty obtaining drugs (particularly heroin) on the IOW brings PWID together.

Sub theme: *"Like the London Underground"*

> *"I mean it's a network like the London underground...I mean if you look at the London underground map there are people on the extremes, the other ends, that won't be so well known, essentially, they... there is a link somewhere... generally speaking there is, I mean...I know that they if they don't actually know them they would know who they are. And they'd know whether they're injecting, its like the London underground map."* **Focus group participant G**

This focus group participant describes her impression of the overall connectivity between PWID on the IOW and uses the London Underground as a metaphor to do so. This metaphor was consistent with two of her personal observations, firstly that injecting drug users are all connected to one another and secondly that there are those on the 'extremes' with fewer and weaker 'links'. She did not clarify whether the metaphor was consistent with a further feature of the London Underground map – that those people on the 'extremes' are connected to the centre or core of the network rather than each other. This story of a 'network', which users could be *'inside'*, where everyone knows others with a history of injecting drug use, was repeated consistently throughout interviewees, including Lucy (see extract below). Discussion often facilitated by completion of the concentric circle diagram (Figure 4-1).

> *"Everyone knows everyone. The island's small. You can't piss or shit without everyone inside knowing about it. You get what I mean. The island's so small. Word gets about very quickly."* **Lucy**

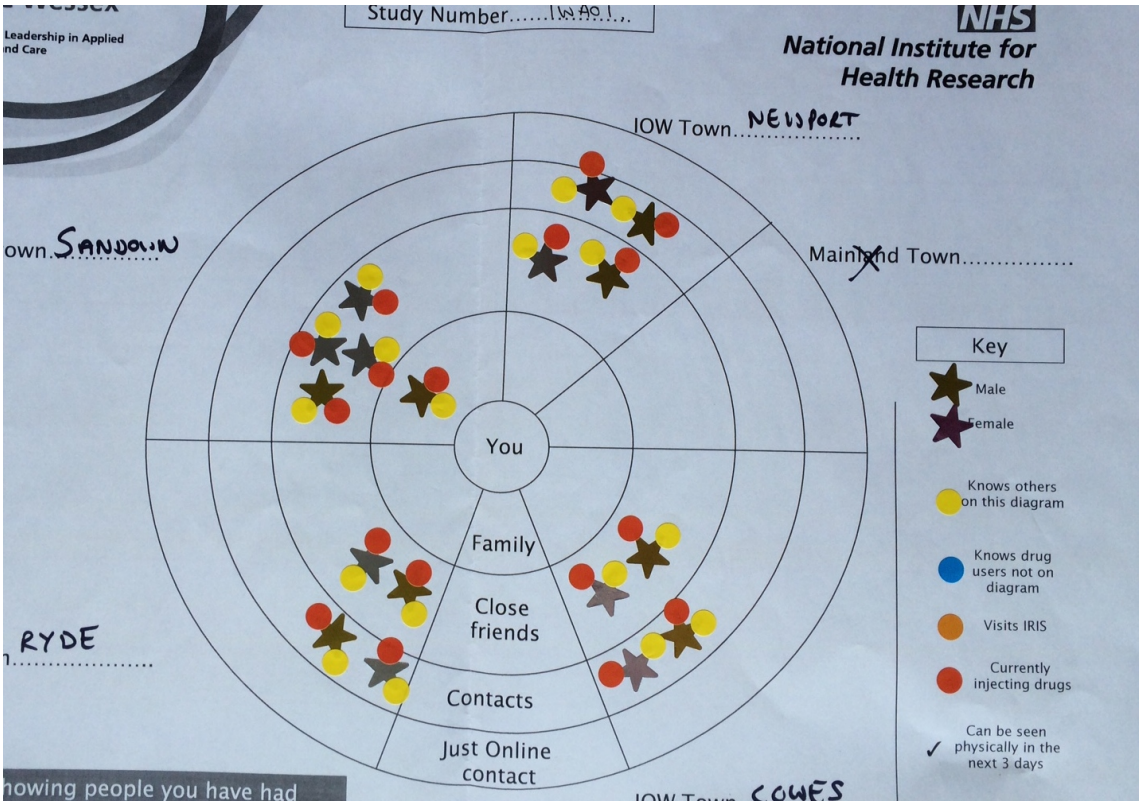

Figure 4-1 A completed concentric circle diagram where each participant was asked to indicate the geographical location of other PWID who they know living on IOW, and give an indication about the strength of their relationship. This was a typical example with a range of male and female contacts across the IOW known to each other as well as the interview participant.

The closeness of the 'network' on the IOW was in contrast to many participants experiences of injecting drug use on the mainland. In their minds 'mainland PWID' were characterised by not having such close relationships and in particular not necessarily knowing the person selling them drugs. This is described in the extract below by a female participant who had injected drugs on the IOW and in a community on the mainland:

> *"You don't even know who these people are that you are buying it off [...] But down here, it's totally different. It's not what you know, it's who you know. You've got to get to people to get drugs. People don't drive around dropping off drugs, like they do in London [...] People out in the sticks, most of them don't do drugs. They live in towns, like Ryde, Newport, close to this network."* **Sally**

This extract hints at two explanations for the relative strength of the 'links' between PWID on the IOW compared to the mainland. Firstly the participant indicates you need to know others to buy drugs as dealers will not sell to people they do not know and secondly it suggests that dealers will not travel to deliver drugs which means most PWID tend to live in close proximity to their drug supply and therefore, presumably, each other. This was a consistent finding in the interviews and some expanded on it further, for example:

> *"[…] Here it's totally different. Like [on the mainland] literally you make a phone call and within five minutes it's delivered to your door. You don't have to go out and wait on corners and look for it […] It's a big issue because the dealer […] they wait until there are a few people and then they'll come out to you…"* **Brian**

Brian had lived and used drugs on the mainland for many years before moving to the IOW. He went on to describe how the action of buying drugs on the IOW, by driving his car to the dealers houses and waiting with others to be served, had actually led to him meeting many other PWID in a way that would not happen where drugs were more freely available. Through constant repetition of this process, described as a 'ticking clock' in the extract below, some participants felt they knew almost every other PWID living on the island:

> *"Just word of mouth, out and about. Meet one person, who knows him, gives you the number. You know him. It just goes like that, like a clock. Tick, tick, tick, tick. Before you know it because it's an island, you know everyone. That's what happens."* **Ric**

Sub theme: *"dry spells"*

> *"…while I was there […] the reason being was yesterday nobody was on […] which means you get a lot of sick people on that day […] so I went round this morning […], I was only there about 25 minutes, but while I was there… there must have been eight to ten people and that's before 9:15 this morning."* **Brian**

In this extract the challenges of finding a dealer who 'was on' (i.e. selling) bought a large number of PWID together. The reason why there were so many people at that particular location early in the morning was because there had been no drugs available the day before and people had started to withdraw

from heroin. The occasional lack of heroin on the Island was a consistent finding and was described in more than one interview as a 'dry spell':

> *"Say, for instance, someone in Cowes has not got [...] they are connected and scratch each other's backs [...] If there's ever any dry spells or anything like that.*
>
> ***Interview moderator:*** *Dry spells being...?*
>
> *There's not much gear about or the gear that's about is really shit. People find out who's got decent gear and the person who's got the best gear would be flooded with people coming to him and stuff..."* **Rob**

The impact of 'dry spells' was profound in bringing PWID together. They were more likely to meet attempting to find drugs and some described sharing cars to reach a dealer who 'was on'. At times, as described by the female participant in the extract below, 'dry spells' led to trips across to the mainland to 'bring back for other people' whilst these 'others' would wait in her home and take turns in looking after her children:

> *"There's been some very dry spells in the years that I've been doing it. A long time ago, I'd go over the Southampton to score a couple of bags. [...] Sometimes, I wouldn't just go for me, I'd collect some money in from different people and go with a large amount of money and bring back for other people."* **Lucy**

There were indications given in some interview explaining why PWID would group together in this way to 'score' on the mainland rather than travelling separately to alleviate the '*dry spell'*. One reason was financial, associated with the costs of travel but the second was that many PWID were only connected to others on the Island and lacked the *'contacts'* on the mainland necessary to purchase drugs, this was described in the extract below:

> *"[...] like most users haven't got contacts over on the mainland. They have to go through the dealers because if they did have contacts with mainland, they would go to mainland because it's so much cheaper. Even though you have got to pay for your fares to go over, it would still work out a hell of a lot cheaper, but they haven't got that contact, hence that's why they've got to do it this way."* **Brian**

In this extract Brian also refers to the relative high cost of drugs (in this case specifically heroin) on the IOW. This was supported in other interviews and the focus group and was described as another factor that bought users together, as described in the extract below:

> *"I know people that go together because it is cheaper to buy it as a team than it is to buy a bag...you get more of it, so they'll do a collection and then share it out between them, so they get more for their money doing it that way because they are buying in bulk."* **Focus group participant**

4.4.2.2 Theme 2: Cliques and isolation

Theme 2 describes how, whilst many PWID on the IOW are closely connected, there are those that are relatively isolated from others. These include those who are deliberately isolating themselves from others as part of rehabilitation and those who inject former 'legal highs' and anabolic steroids instead of heroin.

Subtheme: *"Keep the wolves away"*

At the time of interview, a number of participants had stopped injecting drugs and were involved in a recovery programme. However, stopping on the IOW was made more difficult by dealers deliberately trying to re-engage ex-PWID with drug use via the delivery of free heroin, as described in the focus group:

> *"...and I know that they actually give drugs out to people that have got themselves clean to try and bring them back in."* **Focus group participant**

To avoid returning to injecting drug use and facilitate a successful recovery interviewees consistently reported that an important part of remaining 'clean' was to limit or entirely cease meeting other PWID and therefore prevent reintegration into the social network:

> *"It has to because you can't continue to hang about with people that their only interest in life is getting drugs, you know. If your only interest in life is staying away from it, you can't mix with someone who is just about getting it. Even though you might have been best friends, you can't, you've just got to separate your ways."* **Brian**

PWID in the early stages of recovery would go to great lengths to isolate themselves from other PWID, including deleting all contact information from their phones, changing the locks on doors, ignoring friends grieving after the loss of a partner and, as described in this extract, repeatedly moving house to keep other PWID ('wolves') away:

> *"I've done it again now, with the house I'm in now, […] I'm more up on the roundabout. […] It keeps the wolves away from the door, so I like it."* **Sally**

Total isolation as part of rehabilitation was not however universally reported in the interviews and after a time in recovery some PWID felt able to reintegrate with old injecting 'friends' and acquaintances – sometimes in a supportive capacity.

Subtheme: *'drug fraternities' and 'old heads'*

The idea of the 'London Underground' being a representation of the social connections between PWID on the IOW was disputed by focus group participant A who interjected during the discussion to stress that there was division between users according to their favoured injected substance, or as described below, between 'drug fraternities':

> *"But...there are different types of drug fraternities, if you like, you get the heroin lot or the opiate users...[…] If they are using just one then they tend to be a bit more separate."* **Focus group participant A**

In support of this interview participants consistently referred to an increase in the injection of so-called former 'legal highs' on the IOW particularly, from what they had witnessed, among teenagers. Most interview participants seemed disconnected from this younger group and some spoke passionately about the health risks of injecting such drugs. However, there were individuals, known to some as 'old heads' who used both 'legal highs' and heroin and therefore acted as a 'link' between the two groups:

> *"There's the old lot, what we call the heads, the old heads, that are still using. So they've been using a long time […] Obviously if they're to keep their heroin habit going then they made it into the legal high, start selling the legal high to the younger generation..."* **Tony**

However, several participants described how 'legal highs' could also be obtained from a shop (which had recently been closed down), order them over the Internet and get them delivered in the post. One interview participant (John), who exclusively used 'M-Cat' (Mephedrone, a former so-called 'legal-high') described how, since moving to the IOW, he had repeatedly tried but failed to integrate with the local network of PWID. This lack of integration forced him to source his M-Catt on the mainland through liaisons he arranged on social media:

> *"[…] I was literally on the Red Jet going across [to the mainland], and the plan was to meet up with this guy literally when I got off the boat, buy some M-Cat, inject each other, have sex, and then go. That was the plan. In the end I didn't meet him, I met one of his friends, got the drugs, had sex, quickly used, and then went back."* **John**

Those injecting anabolic steroids in the context of bodybuilding were also described as being 'close-knit' but also entirely separate from other substance users as illustrated by Malcolm in the extract below:

> *"Steroid users will always stick with steroids to separate that from that. That is the rule, you take one or the other. You either want to be a fitness fanatic and take your steroids you go there, and if you want to have a drink and party and take cocaine or whatever you want to take you go there."* **Malcolm**

This division was apparently driven by a lack of a shared outlook. Steroid users saw themselves as working people, with a social life centred at the gym and fastidious about their health. Indeed, Malcolm's narrative actually seemed to stigmatise users of other drugs for their lack of employment, lack of self-control, violence and the money they wasted on their addiction.

Like the wider PWID network, the links between of steroid users were described as being driven by the illegal nature of the practice as it was necessary to ask other users how, where and what to buy. However, Malcolm placed more emphasis on bonding in a peer support capacity, for example, educating other bodybuilders about how to administer steroids safely and how to get maximal effect from their use.

4.4.2.3 Theme 3: Acceptability

Theme 3 illustrates how a network-based survey might work in principle, where such a survey could be conducted and what incentives might lead to successful recruitment. Participants also illustrated how some PWID, whilst being well connected to others, may be less willing to participate in the survey.

Subtheme: *'the domino effect'*

The idea of undertaking a network-based survey was generally well received. One participant described (unprompted) a close representation of a RDS survey as a good way to reach his peers:

> *"…if you say to them, 'Have you got any friends that you know use drugs', and all that, […] If you could bring them in for a test, give them like a voucher or whatever for every three or four they bring in. If you said to them, 'Here is a £10 voucher for every four people you brought in', then that would be an incentive for them…"* **Brian**

Another interview participant explained how a survey that relies on peer led recruitment might work in reality and be effective at recruiting those who wouldn't normally come forward, those he described as 'incognito':

> *"Yes, they will be because they're incognito, aren't they? […] Eventually, if it carries on, it will get brought up in conversation and again, you go back to that sort of domino effect, 'Oh, yes, I went and picked up that today and I had a test."* **Mark**

The professionals in the focus group were collectively very positive about the idea of a network-based survey and particularly the idea of peer led testing for HCV. They felt trusting PWID to participate and recruit their peers for testing would have beneficial effects that extend beyond their physical health:

> *"I think actually really it's validating, they feel useful and that's all we want is to feel useful and have hope in life. Most of them have got incredibly low self-esteem […], so to give them a healthy way of supporting each other might actually be very empowering… then you are trusting them to do something as well which is good. The trust."* **Focus group participant's G and W.**

Sub theme: *'Two lives'*

However, the notion that a RDS survey could feasibly reach a cross section of PWID was disputed by a number of interview participants because some PWID have more to lose than others if their drug taking behaviour were to become widely known. This included those with families, for example:

> *"…I didn't think there was such a thing, you can have two total different lives. Some of the people who would come into that room, they would have to have a different life out of that room. They'd come there just to use and then you would see them and they would be walking down the road with their family…"* **Mark**

The interviews and focus group were consistent in describing PWID who have roles and responsibilities beyond just purchasing and injecting drugs. Some PWID had families who were unaware or only partially aware of their drug related behaviours and others had jobs and careers. One individual reported repeatedly travelling to the mainland to purchase drugs and one was engaged at a mainland drug support centre so he wouldn't have to access clean needles at the local pharmacy, which was also used by his wife who remained in the dark about his drug use.

In the following extract a focus group participant refers to the difficulty engaging those supplying drugs with drug support services because the support offered by opiate substitution is not required when they have a 'never ending supply' of drugs that they can keep for their own use:

> *"That's the issue with suppliers is that they have a never ending supply of heroin themselves, […] so they're the hardest to reach…"* **Focus group participant G**

This paradox where suppliers, well connected in business terms across the island, are in some respects isolated was expanded on in some of the participant interviews:

> *"…a few of them are dealers so they're just trying to be quite private, […] They try and be private in the fact that, services and stuff like that, so yes, if someone said, 'Go and do a survey,' then chances are they'd be*

paranoid about it, and like I said, the fear would be enough to make them stay away." **Rob**

Sub theme: Incentives and research venues

Many participants thought that through the use of incentives, RDS on the IOW would recruit PWID in large numbers. However, some debated how effective incentives would be for people who had already entered a recovery program, and others expressed ethical concerns about using cash or shopping vouchers (which could be sold for cash). However, it was consistently reported that these would be the most effective incentive.

Two venues were consistently thought to be the best potential survey sites in the participant interviews. The DSC was put forward by many of the participants, as it was known to many PWID, somewhere they feel safe and somewhere many already attend for opiate prescriptions and catch up with friends from all over the island. However, some pointed out that PWID not engaged with the centre, because of concerns about being identified as a substance user, would be less likely to participate. From the extract below it seems that attending the centre identifies people as being a substance user:

"I came here, my second time coming here, I came out, I walked half way down the road, this guy came up to me, never seen him before in my life, he went, 'Do you use [the drug support centre]?' I was like, 'Yes'. Literally, he got in his pocket, he waved a tenner in front of my face, 'Can you get me some gear'. […]'You go to [the drug support centre], don't you?' I was like, 'Fuck, do I look that bad?'" **John**

Interview participants repeatedly suggested community pharmacies as an alternative venue. Like the DSC, interviewees explained that PWID already attend pharmacies to pick up methadone scripts and to access needle exchange, and they benefit from being more local to many PWID living outside the town where the DSC is based. In addition some described a close and trusting relationship with their local pharmacists:

"Chemist, because they're always going to pick their script up every day. […] They're not going out of their way; they're not having to get a bus to here from Ventnor or wherever, you know. A lot of pharmacies, because

you're so close, nip down here – we're quite close with names. We all know each other." **Sally**

A few participants however, were less positive about the use of pharmacies; they expressed concerns that whilst having a survey venue so close might be convenient, it raised issues with privacy and anonymity in the local community:

"You might go in the chemist and the lady behind the counter might be a mum from school or someone, so you have to walk straight back out of it." **Leigh**

4.5 Discussion

4.5.1 Implications for the conduct of RDS

The results presented in this Chapter broadly indicate the feasibility of undertaking RDS in PWID living on the IOW. However, it has highlighted areas that need to be carefully considered when planning the survey (Table 4-4).

PWID on the IOW appear to be closely and densely linked with one another and probably are to a greater degree than on the UK mainland. However, there were also indications that certain groups of PWID on the IOW have weaker links to the rest of the network and may therefore be harder to identify during RDS.

The density of connections of PWID is important because it is possible this may overcome the challenges posed by the relative geographical dispersion of PWID on the IOW, which is known to adversely affect recruitment during RDS[135,173]. The potential weakness of ties to certain groups e.g. those injecting 'legal highs' could have implications for the representativeness of the survey sample but this could be managed during RDS through the purposive selection of *seeds* with at least the potential to access these groups[174].

There were indications given in the interviews that during RDS network members (if given a recruitment coupon) would not be equally likely to participate. This violates an underlying assumption of RDS[133] and could introduce selection bias into a survey that would be difficult to quantify. However, by carefully choosing research venues that different PWID are equally likely to feel able to attend and choosing an incentive that is broadly attractive, this could be minimised.

Both the DSC and community pharmacies were frequently put forward as potential research venues. Pharmacies have not been used in previous RDS surveys but appear to be geographically convenient and somewhere PWID visit routinely. The DSC was clearly very familiar to many PWID including those in recovery programs and is accessed from all over the island. Both have potential drawbacks; in pharmacies PWID may meet friends and relatives from their local community who are unaware of their injecting drug use and there is a risk of stigma associated with attending the DSC. Additionally, in both venues there is

a risk of bias from recruiters, for convenience, handing coupons straight over to PWID who happen to be attending such services at the time.

Table 4-4 A summary of the findings from the interviews and focus group and the implications for RDS design.

Area to be addressed	Findings	Implications for RDS
Network properties	PWID are densely connected to other PWID including those from different parts of the IOW. However this network probably doesn't include people who only inject anabolic steroids.	People who inject only anabolic steroids are not part of the target population but the structure of the remaining PWID network should facilitate RDS.
Acceptability of RDS	Potential participants and key stakeholders (DSC staff) see the potential benefit of incentivised network-based sampling.	PWID are likely to engage with the survey and the use of cash incentives or food vouchers at a higher value (*e.g.* £10 cash, or a £20 voucher as the primary incentive), is acceptable.
Seed selection	Certain groups including those new to the IOW, exclusively using 'legal highs' or other less common drugs of choice, drug suppliers and those in drug rehabilitation may be harder to reach through network-based sampling	Select a combination of *seeds* who: • Inject both 'legal highs' and heroin • Are drug suppliers • Are engaged in drug rehabilitation
Survey logistics	The DSC or community pharmacies are potential research venues but there may be barriers that prevent certain PWID from attending both.	Use a combination of venues but collect data on why potential participants refuse to accept the recruitment coupon.

4.5.2 Understanding the social network of PWID on the IOW

The apparent density of the social network between PWID on the IOW was consistently attributed to the availability (or lack) of drug supply. However, there was also an indication that this network was difficult to penetrate by those who had moved to the IOW from elsewhere or who injected substances other than heroin. This could have important public health implications.

Existing qualitative literature describing injecting networks of PWID focuses on personal relationships within *ego* networks. Through an ethnographic enquiry Bourgois *et al*. highlighted increased equipment sharing than that reported in quantitative public health literature and Treloar *et al.* showed how preconceived ideas about HIV status may influence decisions to share equipment[175,176].

Rather than using qualitative methods to describe personal relationships and personal risk behaviours, I have attempted to describe a 'bird's eye' view of the injecting network structure. This has not been done before and has inherent weaknesses. Participants such as the individual who claimed 'everyone knows everyone' is highly unlikely to know whether this is actually the case and the DSC professional who described the network as being 'like the London underground' was probably describing her perception of connections among the clients attending services.

However, the themes described above are based on consistent reporting from a sample of professionals and PWID and when they are combined with the quantitative representation of the injecting network from Chapter 7 they will add depth to the overall understanding. The qualitative and quantitative findings are considered together in the General Discussion (Chapter 10).

4.6 Reflexivity on the focus group and interviews

PWID and drug support professionals were successfully recruited for semi-structured interview and a focus group in order to inform the feasibility of RDS in PWID living on the IOW and explore the social network connecting PWID. The semi-structured interview format, dictated by the topic guide and interactive exercises, was able to address the research objectives but also gave participants enough freedom to highlight unexpected phenomena, such as the injection of 'legal highs', with important implications for the design of a RDS survey.

Purposive sampling was used to select participants to ensure interviews were conducted with PWID who have a range of experiences. However, due to challenges in accessing this population the majority of participants were recruited by DSC staff from their client lists and therefore this sample, whilst deliberately varied, probably included an over representation of heroin users engaged in opiate substitution therapy. This may have led to an exaggeration of how densely connected PWID are on the IOW, as those with heroin addiction are reliant on supplier-buyer relationships, which appear to be a major driver for network cohesion. 'Legal high' injectors, by contrast, are able to get their drugs from other sources, and are therefore not necessarily connected in this way. As a group they were probably under-represented; we did not hear the perspective of any of the teenage 'legal high' users described in some of the interviews and therefore important issues concerning acceptability and feasibility of RDS among this group may have been missed.

Data saturation, where the same phenomena emerge consistently across interviews, is usually considered to be the point where the required sample size in qualitative research has been reached[177]. Certain phenomena, particularly those relating to heroin addiction, were repeated consistently across several interviews. However, where participants had more unique experiences, such as Malcolm, who injected himself exclusively with anabolic steroids, data saturation was not achieved and it would have been beneficial to have interviewed other steroid users, particularly younger and less experienced individuals, to see if Malcolm's experiences were common.

As the interviewer and focus group moderator I played a pivotal role in data collection and interpretation. My professional relationship with DSC staff and some PWID as a clinical Hepatologist was a strength in that it facilitated recruitment and enhanced disclosure due to the trust built in the pre-existing relationship. The following extract describes how my professional relationship with a participant facilitated disclosure during a research interview:

> *"I was aware of many aspects about his past before we started (e.g. injecting drug use, viral status) and we already had good rapport so the beginning of the interview was very smooth and we accessed interesting phenomena of which I was not aware very quickly"* **Field notes following interview with Jerry**

Despite this advantage, my dual role as a clinician and researcher bought significant limitation. Richards *et al.* describe how a medically trained interviewer can influence the content of interviews and I observed this first-hand in the opening interview where I was introduced as the 'Hepatitis doctor'[178]. This led to dialogue from the participant that was out of context from the open question she had been asked:

> *"When we started talking generally about the injecting drug use on the IOW, she immediately started explaining how she had never taken unnecessary risks with injecting behaviours and described the irresponsibility of others at some length. This was not really the question I had asked her…"* **Field notes following interview with Jill**

In light of this, I requested that DSC staff introduce me to all future participants as 'a researcher'.

As a male interviewer I suspect the way I influenced the dialogue with male and female participants varied. In general, male participants seemed more open and were unconcerned by the possible sanctions, such as incarceration, that could result from the disclosure of their illegal behaviours. By contrast, as illustrated in the following extract, several of the female participants seemed haunted by the sanction of 'losing' children to social services because of active drug addiction and I suspected they found me, as a male interviewer, difficult to relate to on this issue. I think this led to females being more guarded about what they disclosed.

> *"Like the previous female participant I got a sense throughout the interview that she was holding back information and was less willing than most of the male participants to openly disclose illegal behaviour"* **Field notes following interview with Sally**

Not only were interview participants influenced by my gender and profession but also by things that I did and said during the interactions. I had preconceived ideas about HCV and injecting drug use based on my clinical experience that influenced the questions I asked, the nature of my responses and therefore what the participant disclosed. Through reflection and by reading some of the early interview transcripts I tried hard to minimise these by ensuring I ask open questions as much as possible and being aware of non-verbal cues.

As a clinician my experience as an interviewer and focus group moderator is limited. Through the course of the interviews I improved my ability to maximise disclosure and minimise my personal influence over the participant. However, the focus group took place only once and therefore I did not have an opportunity for iterative self-development. Additionally moderating a focus group is a different skill, considered by some to be more challenging than conducting a simple semi-structured interview, and experience is needed to facilitate interaction between participants to avoid the narrative taking on a structure like a 'group interview'[179].

A strength of this study is the transparency with which I have tried to describe my method, the analytical process of the interview and focus group transcripts, and a detailed description in the study's conduct. Alongside this I also tried to increase reliability of my findings by 'dual coding' the transcripts and increase their validity by not 'cherry picking' sensationalist quotes but looking instead for 'typical' themes and conflicts of ideas between participants[164]. However, seeking 'respondent validation', where conclusions are fed back to the participants for comment, could have increased their trustworthiness further. This is not appropriate in all qualitative research as conclusions not supported by participants are not necessarily wrong. However in this context, where one objective was to assess the feasibility of undertaking a survey within a social network of which the participants were a part, this validity check may have been useful and reassuring[164].

4.7 Conclusion

The results of the interviews and focus group suggested that RDS would be feasible within this population but highlighted key areas that should be addressed in advance of sampling to maximise its representativeness (Table 4-4). The findings in this chapter also highlighted the social cohesion between those injecting drugs on the IOW and contrasted this with the mainland. This will be considered further alongside the results of the quantitative survey and wider published literature in the General Discussion (Chapter 10).

5. Quantitative methods

5.1 Chapter overview

The quantitative methods described in this Chapter address the following research objectives:

- *Estimate the population prevalence for HCV antibody among PWID living on the IOW*
- *To determine the total number of HCV cases among PWID living on the IOW*
- *Understand how HCV transmission is related to the social network of PWID*
- *Demonstrate how the social network of PWID can be utilised in a local elimination strategy for HCV*

The results of the qualitative methods presented in Chapter 4 and systematic review in Chapter 2 directly informed the conduct of the sampling to a Hepatitis C (HCV) bio-behavioural and social network survey in people who inject drugs (PWID). The results of these were then used alongside harm reduction service data and HCV phylogenetic data to estimate the population prevalence of HCV on the Isle of Wight (IOW), the injecting network structure of PWID on the IOW, the total population size of PWID on the IOW and the transmission and treatment dynamics of HCV in PWID on the IOW.

Accordingly the methods described in this chapter are interconnected. The results of some provide the baseline data for another level of analysis or validate other results. The complexity of these connections and where a description for each method can be found in this Chapter is displayed in Figure 5-1.

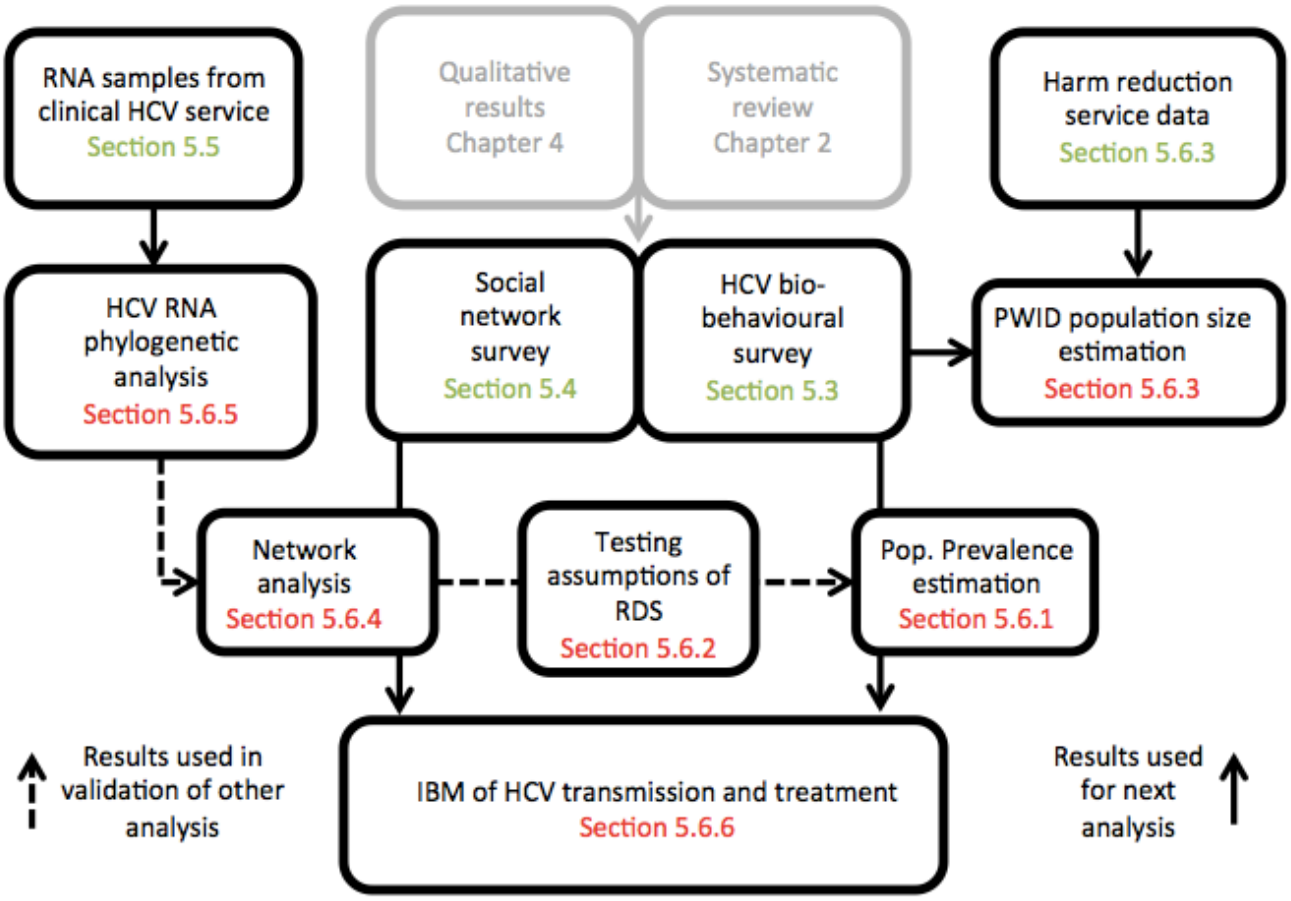

Figure 5-1 A guide to Chapter 5, including an overview of how the methods are connected. The chapter sections are described as follows, green sections describe the collection of raw data and red sections describe data analysis. Chapter 2 and Chapter 4 (greyed out) both informed the sampling, data collection and analysis. Dashed arrows indicate where the results of one analytical method have been used to validate results from another method. Solid arrows indicate where the results from one method have been used as the raw data in another.

IBM – Individual based model, HCV – Hepatitis C virus, PWID – People who inject drugs

5.2 Participant sampling for the bio-behavioural and social network survey

I chose respondent driven sampling (RDS) as the sampling method for the bio-behavioural survey and social network survey because it is widely used, has a track record of recruiting PWID to test for blood-borne viruses[38,94] and has an extensive body of literature documenting its use, theoretical basis and limitations (for example see Gile *et al.*[139]). Additionally, there is specially designed software for weighting the results[90] and it has been adopted by the World Health Organisation (WHO). This has led to the development of specific training materials[170] and training courses to inform its proper use.

There are alternative methods for sampling hidden populations[30]. For example, time-location sampling (TLS), like RDS, can provide a population estimate for disease prevalence[180]. However, TLS requires significant resources in terms an ethnographic preliminary study, which raised considerable safety and logistical challenges. It lacks a substantial body of literature describing its use, and because it is necessary to identify all the venues frequented by the hidden population in question, I considered it less feasible for a survey of PWID[180].

Chapter 2 provided a detailed overview of the practical method of RDS. This chapter describes the sampling procedures used in this survey (Section 5.2.1 to section 5.2.8).

5.2.1 Seed selection, coupons and incentives

I selected *seeds* (the participants that began recruitment) purposively on the basis of their enthusiasm to participate in the survey and their likely ability to recruit a cross-section of PWID. Starting with the *seeds,* I gave each participant three coupons (Figure 5-2) to invite eligible members of their social network to participate after being given standardised verbal guidance on how to undertake recruitment (Appendix 6). Based on feedback from participants who had taken part in the interviews, I made the coupons deliberately non-stigmatising, (i.e. they did not refer to HCV or injecting drug use) and brightly coloured to help prevent them becoming lost (Figure 5-2) although the exact design changed during the survey (see section 5.2.8).

I gave ten pounds cash for participation in the survey and a £5 secondary incentive if a participant successfully recruited another participant. Participants could recruit a maximum of three additional participants and therefore the maximum any single individual could receive was £25 (this value changed during the survey – see Section 5.2.8).

I recorded data on who was recruited by whom via the unique serial number on the large and small tabs on the recruitment coupon. I carefully recorded the number on each participant's coupon and the numbers on the coupons that were given to recruit others in a coupon management system, which had been designed by a team in Croatia and was used with their permission[181].

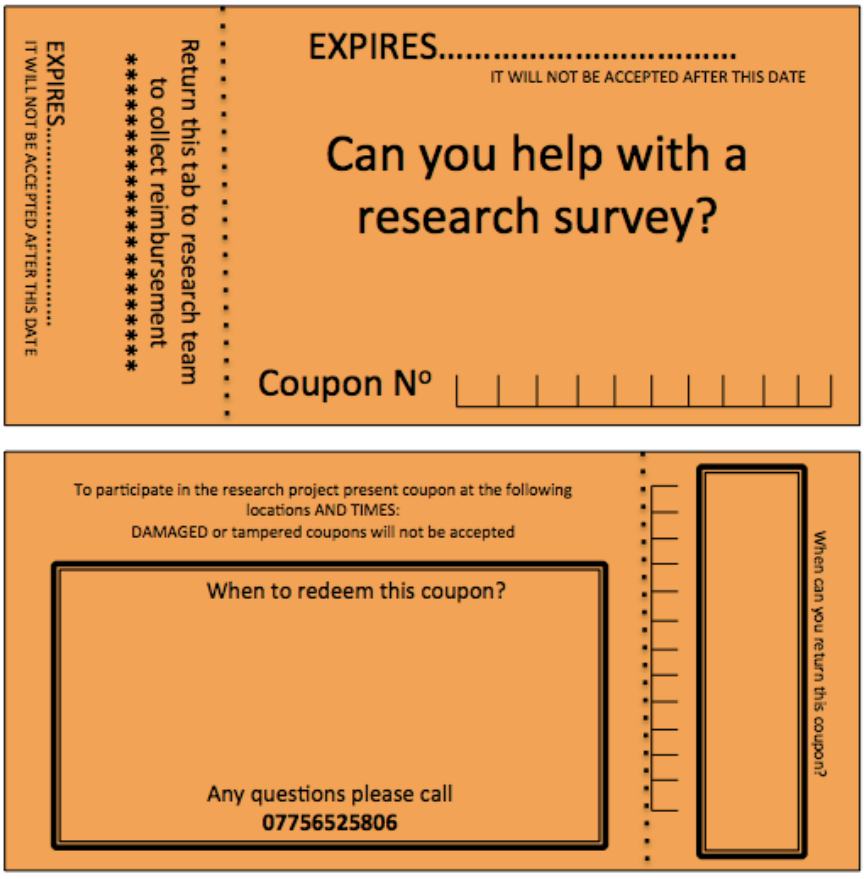

Figure 5-2 The recruitment coupon given to participants for distribution to eligible members of their social network. The larger portion was given to potential new participants and the recruiter kept the smaller tab. If the recruiter was successful at encouraging someone else to participate, they could use the tab to collect a secondary incentive.

5.2.2 Survey venues

I conducted RDS at four geographically dispersed community locations across the IOW. These were the drug support centre (DSC) (there is only one such centre on the IOW) and three community pharmacies. I selected the pharmacies on the basis of the frequency of needle exchange and opiate substitution delivery*, as well as the availability of a private treatment room. Two of the three pharmacies offered needle exchange, opiate substitution services and blood-borne virus (BBV) testing services, whilst the third offered needle exchange only (Table 5-2).

Table 5-1 Summary of the survey venues for RDS and the services offered routinely to PWID at each site.

Site code	Venue type	Services offered	Geographical location*
1	DSC	Addiction rehabilitation services OST NEP BBV testing	Outskirts of town (pop. 20,000)
2	Pharmacy	Routine pharmacy services NEP BBV testing OST	Main high street of town (pop. 20,000)
3	Pharmacy	Routine pharmacy services	Main high street in small town (pop. 7,000)
4	Pharmacy	Routine pharmacy services OST NEP	Shopping plaza in small town (pop. 4,000)

**Population estimates based on UK census 2011 and exact location not disclosed to protect participant anonymity*

DSC – Drug support centre; OST – Opiate substitution therapy; NEP – Needle exchange programme; BBV – blood borne virus

* Based on PharmOutcomes™ community pharmacy service provision data

5.2.3 Eligibility criteria

Participants had to be over 18 years, resident on the IOW, have a history of injecting drugs on the IOW and be able to understand written and spoken English. On arrival at the survey setting I asked each potential participant eligibility questions (Appendix 9). I developed the questions with the participants of the interviews described in Chapter 4 and they were intended to identify people masquerading as PWID in order to claim the primary incentive for participation.

5.2.4 Consent

If eligible, I gave the potential participant an information sheet and if they happy to participate I then asked them to read and sign a consent form (Appendix 10).

5.2.5 Data collection for RDS weighting

All surveys using RDS must collect specific data to test how closely the recruitment process adheres to some of the underlying assumptions of the RDS method (discussed further in Chapter 2, Section 2.4). Accordingly, I recorded the relationship between each recruiter and the respondent in a short questionnaire, which was completed when the recruiter returned to pick up their secondary incentive (Appendix 11). The eligible network size of each participant was then carefully quantified using a cascade of three questions incorporated into the behavioural survey (Appendix 12).

5.2.6 Sample size calculation

I used the following equation (5.1) to calculate a target sample size of 80 based on a predicted HCV prevalence of 30%, total target population size of 350 and a design effect (*deff)* of 2. This was in accordance with WHO guidance

on RDS surveys[170] but as shown in equation 5.1 below, I incorporated a *finite population coefficient*[182] to account for the small target population.

$$\sigma_{ps} = \sqrt{D\frac{Z_{1-\propto}{}^2 P(1-P)}{n}} \times \sqrt{\frac{N-n}{N-1}} \tag{5.1}$$

$$\sigma_{ps} = revised\ standard\ error, \quad n = target\ sample\ size, \quad D = design\ effect$$

$$P = predicted\ disease\ prevalence, \quad N = estimated\ total\ population\ size$$

$$Z_{1-\propto} = 1.96\ for\ 95\%\ confidence\ intervals$$

This gave a target sample size of 80. The relationship between confidence intervals, sample size and the estimated prevalence of HCV within the population is displayed in Table 5-2. As indicated by the green cell, if the prevalence of HCV was 10%, the sample size to estimate this to within ±5% (as recommended by the WHO[170]) would be 140. However, based on HCV testing data from community pharmacies[88] it is likely the prevalence of HCV among PWID on the IOW is closer to 30% and so it is unrealistic to achieve an estimate with a precision of 5% because in this case the sample size required would exceed 200 individuals. Therefore I considered a precision of 10% to be acceptable and the target sample size was therefore 80 participants.

Table 5-2 Population prevalence estimate precision according to sample size and HCV prevalence.

SAMPLE SIZE	HCV PREVALENCE							
	0.05	**0.10**	**0.15**	**0.20**	**0.25**	**0.30**	**0.35**	**0.40**
60	0.059	0.093	0.110	0.123	0.134	0.141	0.147	0.151
70	0.045	0.077	0.091	0.102	0.111	0.117	0.122	0.125
80	0.036	0.067	0.080	0.089	0.097	0.102	0.106	0.109
90	0.028	0.059	0.071	0.079	0.086	0.091	0.094	0.097
100	0.028	0.059	0.070	0.079	0.085	0.090	0.094	0.096
110	0.028	0.059	0.070	0.079	0.085	0.090	0.094	0.096
120	0.027	0.058	0.069	0.078	0.084	0.089	0.093	0.095
130	0.027	0.058	0.069	0.077	0.084	0.088	0.092	0.095
140	0.017	0.050	0.060	0.067	0.073	0.077	0.080	0.082
150	0.016	0.050	0.059	0.066	0.072	0.076	0.079	0.081
160	0.015	0.049	0.059	0.066	0.071	0.075	0.078	0.081
170	0.015	0.049	0.058	0.065	0.071	0.075	0.078	0.080
180	0.014	0.048	0.058	0.064	0.070	0.074	0.077	0.079
190	0.013	0.048	0.057	0.064	0.070	0.074	0.077	0.079
200	0.013	0.048	0.057	0.064	0.070	0.074	0.077	0.079

5.2.7 Pilot of sampling process and data collection materials

In advance of undertaking the survey I piloted each element of the researcher-participant interaction included in a draft RDS standard operating procedure (SOP). This took place in three stages, firstly with patient and public involvement (PPI) representatives, then with PWID living on the IOW who had undertaken the semi-structured interviews described in Chapter 4, and finally I practised the process of recruitment and data collection with staff at the DSC. More detail about each stage of the pilot process is available as Appendix 15.

5.2.8 Amendments to RDS standard operating procedure

During the course of the survey I made iterative amendments to the SOP. The number of coupons given to participants was reduced from three to two in

order to maximise the number of waves of recruitment and the value of the secondary incentive was increased from £5 per person (maximum three) to £15 for the first person to be successfully recruited and £10 for the second (maximum 2). The design of the recruitment coupon also changed to allow more free text for me to describe when the coupon could be redeemed.

5.3 Hepatitis C bio-behavioural data collection

To ascertain the prevalence of HCV, associated risk behaviours and engagement with harm reduction services, participants completed a self-administered questionnaire and interview-based survey (Appendix 12 & 13). The questionnaire was adapted from a template provided by the WHO for data collection in behavioural surveys of PWID and a previous HCV bio-behavioural survey conducted in Croatia[170,183]. The interview based survey was developed specifically for PWID on the IOW primarily to assess utilisation of services related to HCV. The material was developed with patient and public involvement (PPI) representatives and with PWID who participated in the interviews described in Chapter 4. A full description of the development process is available in Appendix 15.

After pre-test counselling participants gave an oral fluid specimen for a validated[184] point of care test (OraQuick ADVANCE™) for HCV antibody. In the event of a positive result I sign-posted participants to confirmatory (RNA) testing with a dry-blood spot test at a local pharmacy or the DSC.

5.4 Social and injecting network data collection

To understand how HCV transmission is related to the social network of PWID each participant completed a social network triangulation matrix (Appendix 14)[185]. This collected *ego* network data by getting participants to describe seven persons* to whom they considered themselves 'closest', had seen in the

* The pilot survey indicated that the number of *alters* in the adjacency matrix should be limited due to the time constraints of each interaction (see Appendix 15)

last 30 days and who had also injected drugs on the IOW. If the participant asked what was meant by "closest" I gave a standardised response:

"Start with family and close friends and then describe acquaintances or just people you know"

I then asked the participant information about each contact (henceforth known as *alter*). Including the nature of their relationship, whether they had injected drugs in the same venue at the same time, had sexual contact and whether they were Facebook 'friends'. In addition I asked each participant to describe *alter-alter* ties within their *ego*-network.

Participants were asked to identify each *alter* by giving their first name and second initial. The results of a pilot survey suggested that some participants would be unwilling to give this information and therefore I considered just giving initials was acceptable (see Appendix 15).

5.5 Hepatitis C RNA data collection

To further explore how the social network of PWID on the IOW is related to transmission of HCV I consented HCV positive persons presenting to the clinical Hepatitis service on the IOW for a blood test and phylogenetic analysis of HCV RNA (Appendices 17 and 18). Due to time pressures during the RDS, venous blood was not collected from HCV positive persons presenting as part of the bio-behavioural survey. However, a proportion of patients attending the clinical Hepatitis service were also recruited to the bio-behavioural survey. The extent of this overlap is described in Chapter 7, Section 7.6.

After collection the samples were coded and link-anonymised, transported for storage to the University of Southampton and later sent them to University of Glasgow for HCV RNA whole genome next generation sequencing. I collected the blood samples and conducted the analysis with separate ethical approval from the bio-behavioural and social network survey – REC 06/Q1704/142.

5.6 Data analysis

Section 5.6 describes how I analysed the data from the HCV bio-behavioural survey, social network survey, and whole genome HCV RNA viral sequences to address the research objectives.

5.6.1 Population prevalence estimation

I recorded the bio-behavioural survey results and recruitment data, including participant coupon numbers, in Microsoft Excel (Microsoft Excel for Mac 2011, NY, USA)*. I then uploaded this to RDSanalyst software, which I used to calculate population prevalence estimates with the Gile's SS estimator[91,142].

5.6.2 Testing the assumptions of RDS

The assessment of sampling against the assumptions underlying RDS is a fundamental part of RDS procedure and it is now part of routine guidance on the survey conduct and reporting [95,170].

In accordance with the STROBE-RDS checklist and recent analytical developments (discussed in Chapter 2), I took steps to test the sensitivity of the HCV prevalence estimate against the theoretical assumptions underlying the sampling process. The measures I took to test some of the key assumptions are outlined in Table 5-3.

* This document incorporated a 'coupon' checker which automatically assigned coupon numbers to each participant – it had been used in a previous survey in Croatia[181]

Table 5-3 Key assumptions of respondent driven sampling and the actions taken to test the sensitivity of the population prevalence estimates to each assumption.

	Assumption	**Action taken to assess sensitivity to the assumption**
1	Participant social networks are linked into a single whole network component	Qualitative exploration of network structure (see Chapter 4)
2	Recruiters choose randomly from their eligible social network	Compare homophily between *ego*-recruit and *ego*-non-recruits in each *ego* network Measure association between relationship type and recruitment to the survey
3	Estimates are independent of *seed* characteristics	Test sample convergence for key variables
4	Participants accurately report their *degree* size	Report 'rounding' of *degree* size Report sensitivity analyses using different definitions of *degree* size
5	Sampling occurs *with* replacement	Report the sensitivity of population prevalence estimates to sampling *with* and *without* replacement by using different estimators

A fundamental assumption of RDS is that the target population is connected into a single network component where each node is connected indirectly or directly to all the other nodes in the network. To assess this I conducted the qualitative feasibility study described in Chapter 4.

A further assumption of RDS is that participants are selected randomly from within the *ego*-network of their recruiter. The collection of network data during the survey allowed me to compare the characteristics of participants against non-participants and whether particular types of relationship were preferentially associated with recruitment. For example, did recruiters preferentially recruit people to whom they shared a 'sexual' relationship?

To assess for non-random recruitment by *alter* characteristics within each *ego*-network (e.g. did *ego* preferentially recruit *alters* with a similar age?), I compared homophily (measured as Yule's Q, see Section 5.6.4.2) between *ego*-recruits dyads and *ego*-non-recruit dyads.

An accurate self reported d*egree* size is essential to accurately calculate population prevalence estimates from RDS. I assessed for 'rounding' and 'rough guesses' of *degree* size by looking for clustering at multiples of 5 and 10 and then tested the sensitivity of the estimates to variations of degree size including the 'empirical *degree*' which was actually observed in the 'whole island' social network (see Section 5.6.4.2).

Convergence is the point during sampling when the prevalence in the sample meets the final sample prevalence and then remains constant. The earlier this occurs, the less influence the *seeds* have on the overall characteristics of the sample and the less 'clustering' for a given characteristic is present in the network[92]. I used convergence to assess the independence of the sample from the characteristics of the *seeds* that began the recruitment chains. I measured convergence for six key variables, which were selected because they were either a variable of interest e.g. anti-HCV, or, from the qualitative work, may be associated with clustering within the network – e.g. "legal high" injection.

From the outset of the survey I was aware that the small target population size would probably lead to a violation of the assumption "sampling occurs *with* replacement. Therefore I used the Gile's SS estimator, which is not dependent on this assumption, but to test the extent to which this decision affected the

prevalence estimate, I compared it against results from an estimator that *is* dependent on sampling *without* replacement.

5.6.3 Estimating the population size of people who inject drugs on the Isle of Wight

Data capture-recapture (C-RC) has been widely used to estimate the size of populations. It has been used in zoological surveys and in a range of human populations including immigrants[186], the homeless[187] and PWID[188].

C-RC methods use two or more data sources to estimate the population size. This is achieved by using the number of individuals common to both sources to estimate the number missing from both sources using a 2x2 contingency table, such as Table 5-4[189].

Table 5-4 A 2x2 contingency table showing the distribution of capture and re-capture populations.

	Recaptured		Total captured
Captured	Included	Not included	
Included	x_{11}	x_{12}	x_{1+}
Not included	x_{21}	x_{22}	
Total recaptured	x_{+1}		

The numbers from the contingency table can then be incorporated into Equation 5.4 where the number of persons missing (x_{22}) from both data sets is calculated from the proportion recaptured (x_{+1}), divided by the number captured in both $(\frac{x_{11}}{x_{1+}})$. This can then be used to make an estimate for the total population size $(\widehat{N})$.

$$\widehat{N} = \frac{x_{+1}}{(\frac{x_{11}}{x_{1+}})} \qquad (5.4)$$

However, C-RC relies on two related assumptions that in reality are often not met. Firstly, the data sources should be independent of each other, i.e. the probability of being captured in one data set should not influence the probability of being recaptured in another, and secondly, all members of the target population should have an equal chance of being in each data set[189].

I made three separate estimates using C-RC and then added a fourth based on the recruitment pattern in the bio-behavioural survey described in Chapter 6[190]. The first estimate was a network based C-RC[191]; it used the survey participants as the capture population and *alters* described in triangulation matrices as the recapture population (see Section 5.5 for how this data was collected). For example, if a participant was identified in another participant's *ego*-network, that individual had been 'captured' in the survey and 'recaptured' in the social network survey, whereas if an individual was identified in the social network survey but had not been a bio-behavioural survey participant they had been recaptured but not captured.

The second and third C-RC estimates used service multipliers[192]. Again the capture population were the participants in the bio-behavioural survey but this time the recapture population were PWID undergoing a HCV test at a local community pharmacy or PWID collecting opiate substitution therapy (OST) from community pharmacies. To assess which of the survey participants had also been recaptured in these datasets they were asked the following questions about service engagement in the bio-behavioural survey:

"Have you been tested at a pharmacy on the IOW in the last 12 months?"

"Have you collected methadone or subutex from an Island pharmacy in the last 12 months?"

Bio-behavioural survey participants who responded positively to one or both of these questions were 'recaptured' whereas those who did not had been 'captured' and not 'recaptured'.

The fourth population size estimate is described by Handcock *et al*. [190] and was calculated using a Bayes framework around the recruitment pattern in the RDS survey. The four estimates for $\widehat{N}$ were combined to give an overall population size estimate.

5.6.3.1 Calculating confidence intervals for capture-recapture estimates

I used parametric bootstrapping to calculate 95% confidence intervals around the estimates using RScript software[193]. In simple terms this means the population was resampled, with replacement, $\widehat{N}$ times to give new values for x_{11}, x_{12}, x_{21} and x_{22}. The number of unselected persons i.e. neither captured nor recaptured (x_{22}) was discarded and $\widehat{N}$ recalculated according to equation 5.4. This value was stored and the procedure then repeated 1000 times for each capture-recapture estimate. I took the 95% confidence intervals from the distribution of these values.

5.6.4 Social network data analysis

5.6.4.1 Building the adjacency matrix and attribute file

I gave each survey participant a code (henceforth known as NAGH code) formed from their initials (N), age (A), gender (G) and the closest town to their home address (H). These codes were entered into a 1 by 1 adjacency matrix in Microsoft Excel (Microsoft Excel for Mac 2011, NY, USA) and recruitment ties, i.e. who recruited who to the survey, were entered into the matrix by placing a number in the cells between the two participants.

The *alters* described in each triangulation matrix formed the *ego*-network of each participant. Based on the reported information in the triangulation matrices it was possible to construct a NAGH code for each *alter*.

By cross checking these NAGH codes with other participants, I could identify non-recruitment relationships where one participant described another as a friend or acquaintance even though they had not recruited each other to the survey. I could then add these relationships to the matrix to form a social network between the participants.

As described elsewhere[194], I considered recruitment relationships and physical relationships such as sex and injecting partnerships to be reciprocal, i.e. if only one person identified another as being an injecting partner it was assumed they were both injecting partners. Conversely, I considered a simple friendship to be a directed relationship i.e. if one person described another as a friend it was not assumed this was reciprocated.

Different types of relationship were defined in the matrix by attributing a different number to each. For example, in Figure 5-2 the number 2 indicates a simple friendship between John and Bill, whereas, the number 3 indicates an injecting partnership between Susan and John. Notice in this example that the friendship between Bill and John is not reciprocal whereas the injecting partnership is reciprocal and would have been even if the partnership were only described by one of the partners.

	John	Bill	Susan
John		2	3
Bill	0		0
Susan	3	0	

Figure 5-3 An example adjacency matrix where relationships correspond to a number placed in a box between two individuals. These relationships could be directed, by only filling one box e.g. John and Bill have a one-way relationship, and defined by using different numbers to indicate different types of relationship.

After relationships between participants had been entered into the matrix, NAGH codes remained which did not correspond to survey participants. I assumed that these represented un-sampled PWID, and in keeping with a previous study[195], I added these non-participants and their relationships to the matrix to create a representation of the 'whole island' network of PWID. I excluded partial NAGH codes, where participants had been reluctant or unable to give the minimum data required, from the matrix. However, I recorded their attributes to test whether there was bias in how participants provided identifiers for members of their social network.

The attributes of survey participants in the network corresponded to their responses in the bio-behavioural survey. However, non-participant attributes were limited to what had been described via peer report and therefore only included, age, gender, HCV status, current attendance at the DSC and whether they were believed to be currently injecting drugs. I had concerns about the accuracy of peer reported HCV status so assessed this by examining reporting between survey participants against the oral mouth swab test results (described in Section 5.3), which acted as a gold standard against which peer reporting could be compared.

I uploaded the 'participant' and 'whole island' matrices and their respective attribute files to UCInet software[196] for social network analysis. In UCInet I extracted the injecting partners sub-networks from the overall social network, treated these as the transmission networks for HCV and subjected them to the network analysis described below.

5.6.4.2 Selection of network measures

Network level measures

Network measures give an overview of the network structure and facilitate comparison between networks[197]. Network cohesion is important when considering the overall structure of a network and to describe this within the injecting partners network between PWID on the IOW I used the following measures: number of components, mean *degree*, the network density, the network diameter, average geodesic distance (AGD) and the clustering coefficient. To explain what these measures mean Figure 5-4 demonstrates cohesion within a simple network of five nodes.

The network in Figure 5-4 consists of a single component as all five nodes are connected either directly or indirectly to all the other nodes. The average *degree* is the sum of the *degree* of each node (where: A=1, B=4, C=2, etc.) divided by the total number of nodes, and the density is the number of ties (6) divided by the number of possible ties (10). The diameter is the longest distance (number of ties) between a pair of nodes, which in this example is just 2, and the AGD is the sum of the distance between each pair of nodes divided by the number of pairs. Finally, the clustering coefficient, in simple terms is a measure of how often 'the friends of your friends are your friends'[198,199], which, using more complex terminology, is the number of triads within the network divided by the total number of possible triads. In Figure 5-4 there are two complete triads (BCD and BDE) and two incomplete triads (ABE and ABC) so the clustering coefficient in this example is 0.5.

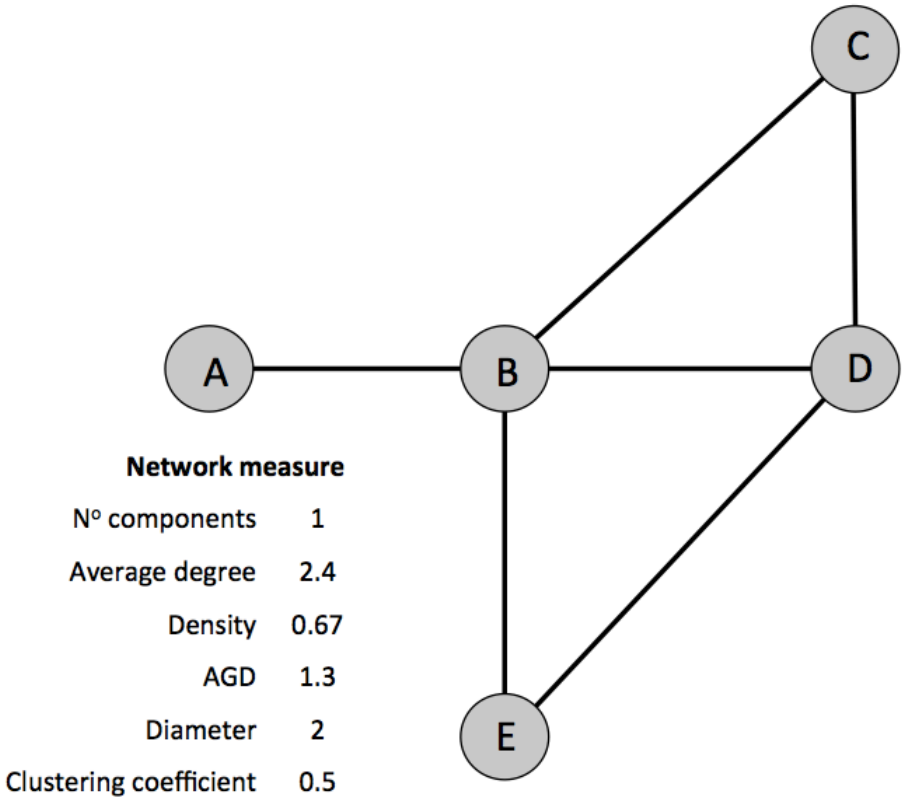

Figure 5-4 A simple network between five nodes demonstrating measures of cohesion.

Due to a lack of comparable studies, I compared the network level measures of the PWID network on the IOW against 1000 random networks generated using the Erdos-Renyi[200] method, a functionality of UCInet software. This has been done elsewhere[194] and allowed me to compare my network structure against networks containing the same number of nodes with the same overall density.

Measuring node network position - centrality

Centrality – as defined by Valente is 'the extent to which a person inhabits a prestigious or critical position within a network' (Valente 2010, p 16)[201]. There are numerous measures of centrality as there are many different ways in which a node can be important to the structure of a network[202,203]. I based my selection of centrality measures on two considerations, firstly, which are most relevant to the spread of an infectious disease and secondly, which are most reliable when the network structure is incomplete.

Degree centrality is the most intuitive measure of centrality in being simply the sum of a node's ties divided by the total number of potential ties within the network. I used *in-degree* centrality for two reasons: because non-participants had not completed an adjacency matrix they had no recorded *out-degree* and it is the most robust measure when network data is missing[201]. However, *degree* centrality does not consider the position of the node relative to the rest of the network and therefore I also calculated 2-step reach centrality (measured as the sum of the number of nodes within 2 links of a given node), which is considered a valid measure for vulnerability to infection[202,203].

Ego-network measures

I analysed *ego*-network data to test the influence of local network effects on HCV status and bias in the RDS process. To assess for clustering within *ego*-networks I calculated the proportion of *alters* with specific characteristic, which could then be compared between groups, to address questions such as 'if *ego* has HCV are they more likely to describe relationships with *alters* who also have HCV?'

This is one of several ways to measure homophily within *ego*-networks. However, when summarising overall homophily within the network it is important (if possible) to contextualise *ego-network* homophily within the pool from which the ties have been drawn[204]. For example: if an HCV positive *ego* has a network size of four, and two of these are HCV positive, *ego* has homophily for HCV of 0.5. However, this value has more meaning if the prevalence of HCV among other nodes in the population pool is taken into consideration.

This can be achieved by using a Yules Q (Q) homophily score for dichotomous categorical variables according to Equation 5.3[204].

$$Q = \frac{IY - EX}{IY + EX} \quad (5.3)$$

Where:

	Same category as *ego*	Different category from *ego*
Ego has a tie	*Number of alters (I)*	*Number of alters (E)*
Ego does not have a tie	*Number of nodes (X)*	*Number of nodes (Y)*

I specifically used a Q score to assess for non-random recruitment during the RDS (see Section 5.7.2).

5.6.4.3 Network visualisation

I displayed the participant and whole network matrices as graphs using Netdraw software[205]. Netdraw calculated the distribution of nodes within these graphs automatically, according to the *geodesic* distance between nodes and two caveats: 1. Nodes should not be so close as to obscure one another and 2. Ties between nodes should be roughly equal in length[206].

5.6.4.4 Statistical measures

To investigate for significant associations between categorical attributes I used a *Chi*-squared test and to test the association between continuous variables I used an independent *t* test. Variables with a *p* of <0.2 and those deemed to be important by other authors were added into a logistic regression model[43,181]. All analyses were conducted with SPSS[207].

5.6.4.5 Missing network attribute data

Due to the reliance on peer reporting in the 'whole network', attribute data was incomplete. To account for this I used multiple imputations - where

missing data are replaced with plausible values in imputed datasets and then the statistical tests rerun with each[208]. To ascertain the values I constructed a multiple imputation model using the variables from the logistic regression model and an auxiliary variable, social network *in-degree,* which was inversely correlated with the likelihood of 'missingness'[209].

In keeping with the proportion of missing data for HCV status, I created 30 imputation datasets[210]. The pooled results were then compared to the original data where I had simply excluded individuals with missing data.

5.6.5 Phylogenetic data analysis

HCV RNA sequences underwent whole genome next generation sequencing at the University of Glasgow. This is an effective technique when sequencing samples with a low viral load and where there are mixed genotypes[211]. Firstly, the sample was washed with DNase to remove human DNA from the whole blood specimens and then the viral RNA was converted to cDNA with reverse transcriptase. Magnetic DNA oligonucleotide probes then extracted the viral cDNA. This was then sequenced using an Illumina® Nextseq 500 system*. I aligned sequences with greater than 70% coverage across the genome in MEGA version 7.0[212] and constructed a maximum likelihood phylogenetic tree. I then constructed a further tree with the IOW sequences and 400 sequences from the HCV UK database[213†].

5.6.6 Individual-based-model for Hepatitis C transmission and treatment in people who inject drugs on the Isle of Wight

The methods described in section 5.6.4 led to a representation of an injecting network connecting PWID on the IOW which is displayed Chapter 7, Figure 7-4. This presented an opportunity to measure the spread of HCV through a real-world network of PWID and assess the potential impact of treatment. Sections

* The laboratory work was performed by Dr. Chris Davies a post-doctoral researcher at the University of Glasgow
† Used with permission from Dr. Emma Thomson, Associate professor of Virology, University of Glasgow

5.6.6.1 to 5.6.6.8 describe how a collaborator, Dr. Rudabeh Meskarian* and I constructed an individual based model (IBM) that used this empirical data to test five treatment scenarios for HCV. Dr. Meskarian took responsibility for programming the software we used for the model and preparing the model guide.

5.6.6.1 Baseline population and network connections

The nodes in the 'injecting network and their attributes formed the baseline population for the model (see Chapter 7; Figure 7-4). Injecting partnerships, defined as injecting at the same time in the same place within this network, represented the potential transmission pathways for HCV within the model via 'injecting events'.

5.6.6.2 'Injecting events'

An 'injecting event' in the model occurred when an HCV positive person injected at the same time and the same place as another individual in the model.

Survey participants were asked how frequently they injected drugs and this was used to randomly assign an injecting frequency with a fixed distribution to the injecting network. It was not assumed however, that all injecting partners were present at each injection, so the 'injecting event' frequency of HCV positive nodes within the model also accounted for the number injecting partners that were typically present at the time of injection.

5.6.6.3 Risk taking behaviours

We did not assume that all 'injecting events' incorporated a transmission risk due to engagement with harm reduction services. However, based on the survey responses a risk of equipment sharing – either ancillary equipment or receptive needle sharing, occurred with a fixed probability in the model and each of these behaviours was attributed a transmission risk in accordance with recent literature (Table 5-6)[58].

* Post-doctoral research fellow in Mathematics at the University of Southampton

5.6.6.4 HCV transmission

In the model if HCV was transmitted at an 'injecting event' the susceptible individual developed acute infection, which progressed to chronic infection at 24 weeks with a fixed probability (Table 5-6). Like other authors we did not adjust the susceptibility of infection in exposed uninfected individuals, as the data concerning this are limited and conflicting[57]. Transmission could only occur between actively injecting HCV positive individuals and their susceptible partners (Figure 5-5).

5.6.6.5 HCV treatment

In all treatment scenarios one individual was treated per month, which is in keeping with real-world capacity of local Hepatology services on the IOW. We assumed all individuals were treatment naïve, non-cirrhotic, completed the full course of treatment and received directly acting antiviral therapy with a sustained virological response (SVR) rate in both genotypes 1 and 3 of 95% (Table 5-6).

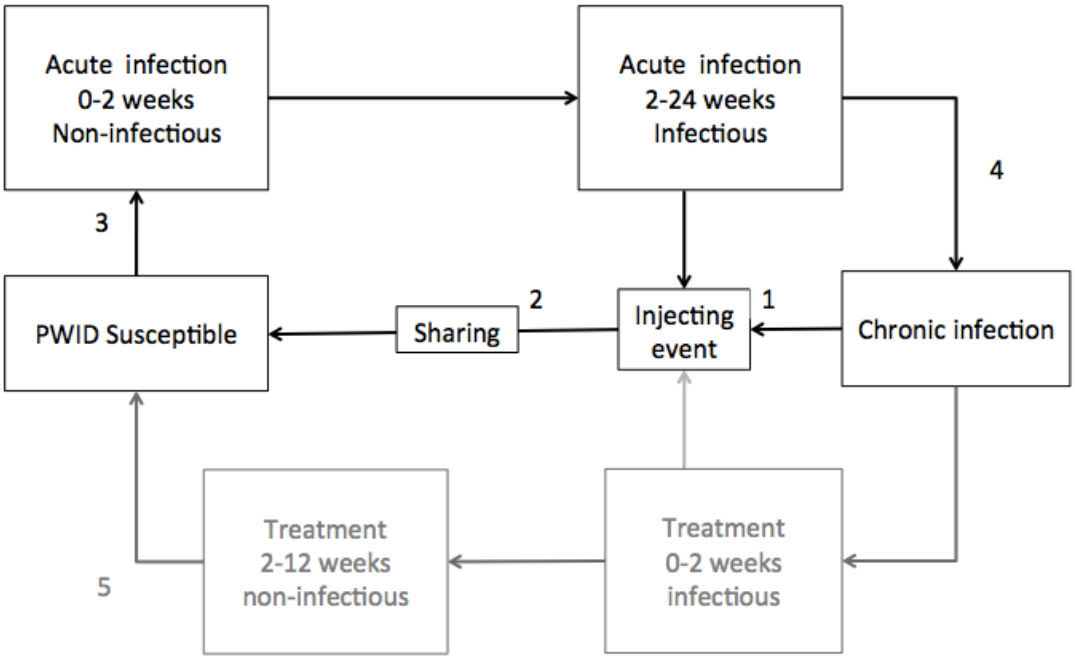

Figure 5-5 Stochastic model of HCV transmission and treatment in PWID on the IOW. Treatment pathway (greyed out) is applicable in scenarios 1-4. Numbers correspond to specific transition probabilities between states in the model (see Table 5-5).

Table 5-5 Transition probabilities used in a individual based model of HCV transmission and treatment in PWID on the IOW.

	Parameter	Transition (95% CIs)	Sensitivity analysis	Ref.
1	Injecting event frequency	Varies according to bio-behavioural survey data	+/- 20%	*
2	Likelihood of sharing per injecting event	AES 0.40 RNS 0.33 (16.2-51.1)	95% CIs	*
3	Likelihood of developing acute infection per sharing event	AES 0.0033 RNS 0.0073	0-0.0006 0.0073-0.02	58
4	Likelihood of spontaneous resolution of acute infection	0.25 (0.22-0.29)	95% CIs	58,214
5	Treatment success	0.95 (92-98)	95% CIs	64,215

*Values from bio-behavioural survey results reported in Chapter 6. AES – ancillary equipment sharing, RNS – receptive needle sharing

The primary outcome was the number of new chronic HCV infections at 12 months and the secondary outcome was number of chronic re-infections at 12 months in the following five scenarios:

0. If no treatment was available
1. If a single individual with chronic HCV was randomly selected for treatment per month
2. A single individual who is actively injecting drugs and injecting with others was randomly selected each month
3. If the individual with the greatest risk *degree* (the most injecting partners) was treated each month
4. If the individual with the greatest social network *in-degree* (the most socially connected individual within the network) was treated each month

Scenario 4 modelled a real-world 'treat your friends' approach to treatment provision as the person with the greatest social network *in-degree* is the most socially connected individual and therefore the most likely to be engaged with treatment via a peer. This could then be compared with the more hypothetical scenario 3 where the person with the most injecting partners was to be engaged with treatment services.

In keeping with 'injecting event' frequency, the duration of treatment and progression of infection from acute to chronic disease the model cycled at weekly intervals for 12 months. This short time frame is inkeeping with a similar model[57] and is important here because we assumed that: 1) relationships did not form, change or cease during the time frame; 2) injecting behaviour remained constant and 3) individuals did not leave or join the network.

5.6.6.6 Missing network model data

A number of nodes within the network had an undefined HCV status. To account for this we took the number of positive cases among these nodes estimated from 30 repetitions of a multiple imputation model (see Section 5.6.4.2) and randomly assigned positive HCV status to a fixed number of these nodes within the model.

5.6.6.7 Sensitivity analysis

To account for intrinsic variability within the model from the random assignment of injecting event frequency, treatment and HCV status (for those nodes with an undefined status at baseline), we ran 50 replications through the model until HCV prevalence estimates stabilised for each scenario. We also altered four key transition probabilities in Table 5-6 to the extent of their 95% confidence intervals, a value used in a previous model or, where neither was available, to 20% above and below the baseline value.

5.6.6.8 Analytical software

We built the model in Anylogic software (https://www.anylogic.com/)*. The risk-relationships were uploaded directly as a 1 by 1 adjacency matrix in Microsoft Excel (Microsoft Excel for Mac 2011, NY, USA) and attribute data for each individual was uploaded as a separate file. Risk *degree* and social network *in-degree* were calculated separately with UCInet software[196].

* Software coding was conducted by Dr. Rudabeh Meskarian, a mathematics post-doctoral researcher at the University of Southampton

6. The sero-prevalence of Hepatitis C in people who inject drugs on the Isle of Wight

6.1 Chapter overview

Chapter 6 presents the results of the bio-behavioural survey of people who inject drugs (PWID) living on the Isle of Wight (IOW) to address the following research objective::

Estimate the population prevalence for HCV antibody among PWID living on the IOW

I also report an assessment of the validity of these results via testing the assumptions underlying the respondent driven sampling (RDS) method that was used to identify members of the target population for the survey. Part of this assessment used data that were collected in the social network survey that was also completed by the participants of the bio-behavioural survey. It may therefore be necessary to refer to Chapter 5; Section 5.4), which explains how the social network data were collected.

6.2 Method

The detailed methods used in this Chapter are described in Chapter 5.

6.3 Hepatitis C bio-behavioural survey

I recruited five *seeds* to begin the recruitment chains. Fieldwork lasted from 3rd April 2016 to 14th June 2016 and included 24 full days. Four of the five seeds recruited another participant to the survey with two chains accounting for the majority of the final sample size (Table 6-1) (Figure 6-1). In total I distributed 143 coupons to PWID and 65 were redeemed. Therefore including the five seeds the total sample size was 70, although this was revised to 69 as a single participant was found to have completed the survey on a second occasion by masquerading as someone else.

Table 6-1 The purposive sample of *seeds* and their characteristics used to start each recruitment chain.

Seed	Sex	Age	HCV RNA	Currently injecting drugs	Injecting drug of choice	Reason for selection
1	F	48	+	No	H	Connected to former PWID in recovery
2	M	35	+	Yes	H, LH	Connected to 'legal high' users
3	M	42	-	Yes	H	Well connected 'supplier'*
4	M	31	-	Yes	LH, A, H	Well connected 'supplier'*
5	M	49	-	Yes	H	Well connected 'supplier'*

LH – 'Legal highs', H – Heroin, A – Amphetamines, *Based on observations of DSC staff or community pharmacist

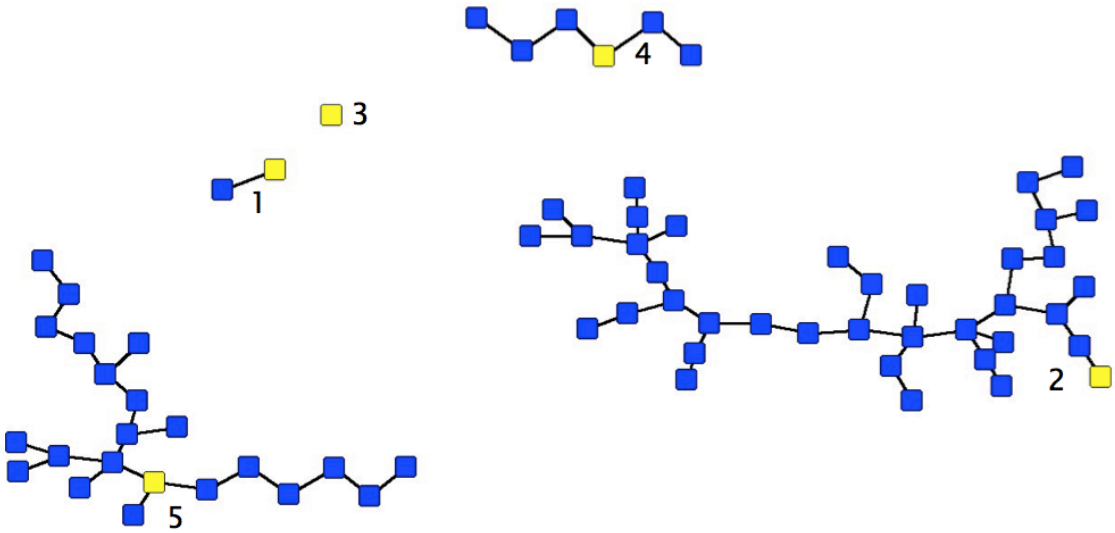

Figure 6-1 Recruitment chains from RDS with the five *seeds* coloured in yellow and non-*seed* survey participants blue (displayed with Netdraw software[205]).

The majority of survey participants were male (74%), had a history of incarceration (67%) and had been injecting drugs for many years (mean 17 years; SD 9.2). Almost all participants had injected heroin (93%), but many had injected other substances including so-called 'legal-highs' (39%), 'crack' (55%) and amphetamine (39%). There was widespread engagement with harm reduction including needle exchange (93%), HBV vaccination (65%) and opiate substitution therapy (54%). The majority of participants had undergone a previous test for HCV (93%).

Table 6-2 Sample characteristics and population prevalence estimates.

		Mean years (range, SD)	n (%) N=69		Pop. Estimate[1] (95%CI)		Est. *deff*
Age (years)		38.8 (18-58, 9.16)			37.3	(33.1-41.4)	4
Gender (male)			51	(73.9)	68.2	(50.2-86.2)	3
Prison history			46	(66.7)	63.1	(46.3-80.1)	3
Injecting behaviour	Injecting career – mean years	16.9 (1-36, 9.72)			13.7	(10.7-16.7)	2
	Active IDU last 30 days		38	(55.1)	39.2	(23.6-54.9)	2
	Active IDU last 6 months		49	(71.0)	69.7	(55.8-83.8)	2
	NS risk behaviour		17	(24.6)	33.5	(16.2-51.1)	3
History of Injected substances	Legal highs		27	(39.1)	31.5	(18.1-45.0)	2
	Amphetamine		27	(39.1)	32.1	(17.1-46.8)	2
	Heroin		64	(92.8)	87.3	(73.0-100)	4
	'Crack'		38	(55.1)	44.0	(27.9-60.0)	2
Harm reduction	Current use of OST		37	(53.6)	42.6	(27.0-57.8)	2
	Current use of NES		62	(92.5)	93.2	(86.0-100)	2
	Previous HBV vaccination		45	(65.2)	55.5	(37.4-72.9)	3
HCV test *a priori*			64	(92.8)	89.5	(78.6-100)	3
HCV antibody positive			18	(26.8)	29.4	(13.3-44.4)	3

[1]Calculated with RDSanalyst software[91] using the Gile's SS estimator, the selected 'prior' population size was 325 (with a 250 lower bound, and a 400 upper bound).

SD – standard deviation; OST – Opiate substitution therapy; NES – needle exchange services; IDU – injecting drug use; NS – Needle or syringe; HBV – Hepatitis B virus; HCV – Hepatitis C virus; *deff* – design effect

Eighteen participants (27%) were anti-HCV positive giving a population prevalence estimate of 29% (95% CI 13-44%) (Table 6-2). Just a single individual had spontaneously resolved their infection and all had been previously diagnosed. Although most RNA positive participants had seen a specialist about their HCV (65%), only two had completed treatment and achieved sustained virological response (SVR) (12%). Figure 6-2 shows the care continuum for anti-HCV positive survey participants.

Testing positive for anti-HCV in the survey was significantly associated with taking a risk with a needle or syringe during the participant's last injection (p=0.03). Although being older tended to be associated with being positive (p=0.08), other important variables were not, including incarceration (p>0.1), the length of injecting 'career' (p>0.1) and sharing ancillary injecting equipment (although this question was only posed to those who had injected in the last 30 days) (p>0.1).

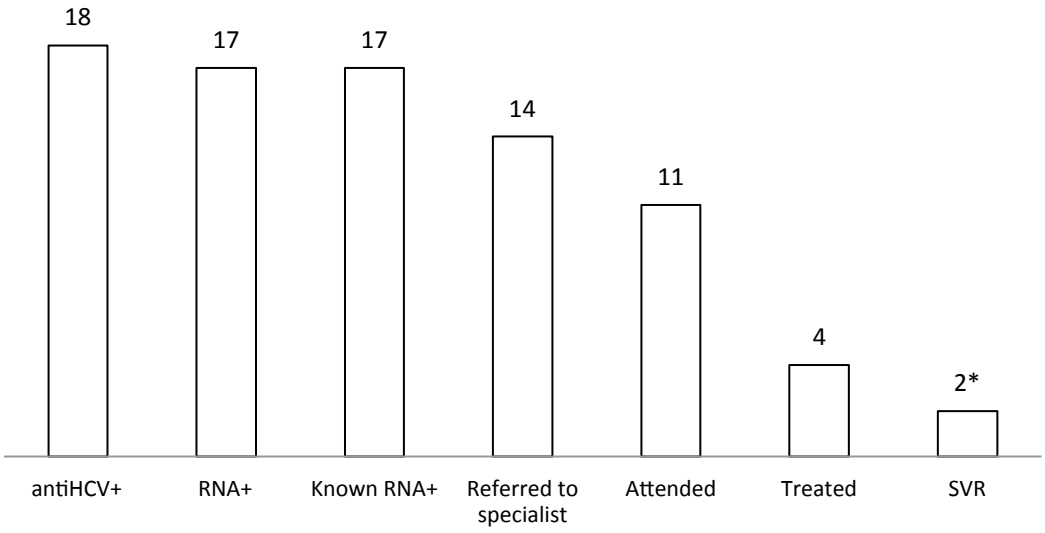

Figure 6-2 Care continuum for anti-HCV positive survey participants. All RNA positive cases had been previously diagnosed with HCV, the majority had seen a specialist on one or more occasions but only two had been treated and achieved SVR.

*At the time of the survey one participant was on treatment so the outcome was unknown

Table 6-3 Association of demographic and behavioural characteristics with anti-HCV.

	HCV antibody positive n(%) N=18	HCV antibody negative n(%) N=51	*p*
Gender (male)	15 (83.3)	36 (70.6)	*0.49*
Mean age (mean years)	42	38	*0.08*
Previous incarceration	13 (72.2)	33 (64.7)	*0.24*
IDU last 6 months	12 (66.7)	38 (74.5)	*0.29*
IDU 30 days	9 (50)	29 (56.9)	*0.43*
Length of injecting career (mean years)	20	16	*0.13*
AE sharing*	4 (50.0)	14 (46.7)	*0.87*
NS risk behaviour	8 (44.4)	9 (17.6)	*0.03*
Use of OST	11(61.1)	36 (70.6)	*0.66*
NES	17 (94.4)	46 (90.2)	*0.56*

p values are calculated with SPSS[207] using *chi-squared* test for categorical variables and *t-test* for continuous variables. NS – Needle or syringe, AE – ancillary equipment, IDU – injecting drug use, OST – opiate substitution therapy, NES – needle exchange services.

*Sharing of ancillary equipment assessed in those reporting injecting drug use in last 30 days only, therefore N varied

6.4 Testing the assumptions of respondent driven sampling

The validity of the population prevalence estimate for HCV presented in this chapter is dependent on the representativeness of the RDS. As I described in Chapter 2, this sampling process is itself dependent on numerous theoretical assumptions, which have not been met in other surveys. In this section the sampling process is assessed against these assumptions* in accordance with the STROBE-RDS reporting checklist[95] and recent literature[139,143].

Participants of the bio-behavioural survey also completed a social network survey. The results of this are presented in Chapter 7 however, in order to test some of the assumptions it is necessary to refer to the network data. Where this is required in this chapter the reader is referred onward to Chapter 7.

6.4.1 Recruiters do not pass coupons to strangers and ties are reciprocal

There was no evidence that participants recruited complete strangers to the survey. All 32 recruiters who returned to collect a secondary incentive indicated that the person they handed the coupon to "would have done the same for them" and all participants described a relationship with their recruiter.

6.4.2 Estimates are independent of *seed* characteristics

Convergence and box plots were calculated for anti-HCV (D in Figures 6-3 and 6-4) and variables identified in the qualitative analysis as potentially being associated with clustering, including the injection of legal highs and active drug use (defined as within the last 30 days).

Most sampling proportions converged and remained stable from approximately the 40th participant onwards. The sample proportion testing positive for anti-HCV was the most stable characteristic as it changed little

* See also Chapter 4 for a qualitative assessment of the assumption that the social network of PWID on the IOW was appropriate for RDS

from roughly the 20th participant onwards. This is important because although it appears the early participants had a slightly higher prevalence than the 'average', this had a limited impact on the prevalence seen in the final sample. This indicates that the prevalence of HCV was very stable as sampling progressed, which is inkeeping with an absence of clusters of HCV cases.

To further assess clustering, convergence graphs per *seed* were calculated for the same variables to assess disparity between recruitment chains. Reassuringly the two longest recruitment chains generated by *seeds* two and five were broadly similar across all six variables even though, in the case of anti-HCV, *seed* 2 was positive and *seed* 5 was negative (Figure 6-4).

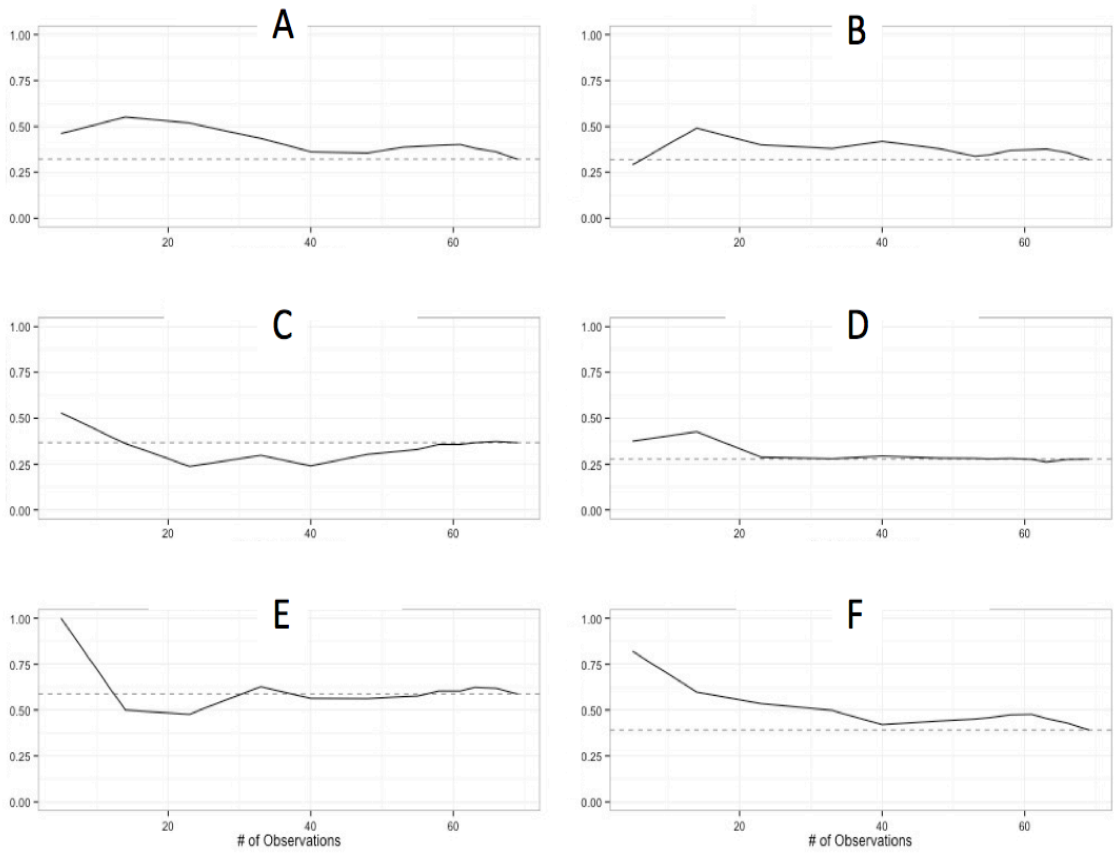

Figure 6-3 How the sample proportion (y axis) changes for 6 key variables (A-F) as sampling progresses (x axis). D (positive anti-HCV) shows the earliest convergence, whereas the proportions actively injecting drugs (F) and injecting amphetamines or 'legal highs' converge later.

A="Legal high' use; B=Amphetamine use; C=Pharmacy based test for HCV; D=Anti-HCV positive; E=Currently attending DSC; F=Injecting drug use in last 30days.

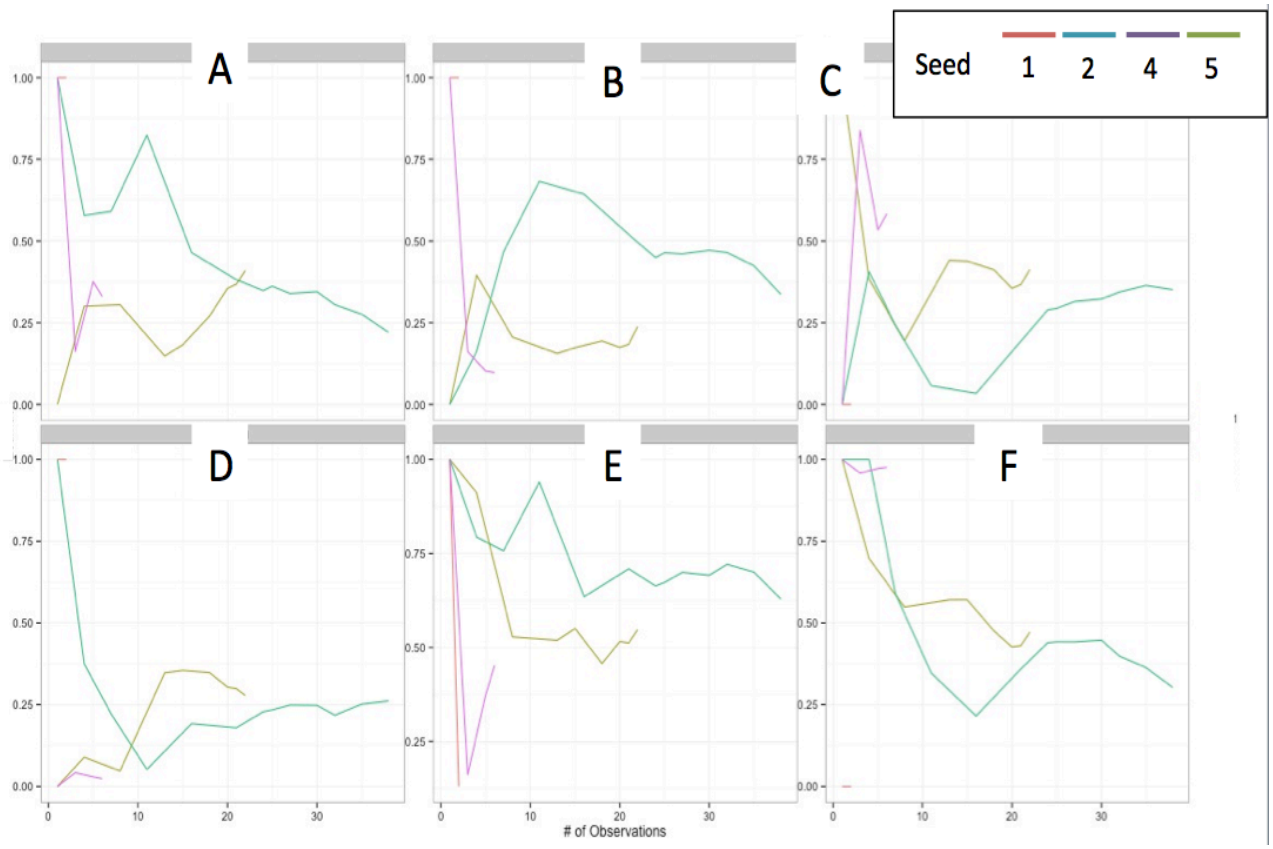

Figure 6-4 How the sample proportion (y axis) changes for 6 key variables (A-F) as sampling progresses (x axis) in different recruitment chains. *Seed*s 2 and 5 (blue and green respectively) led to the longest chains and at the conclusion of sampling, generally included participants with similar characteristics.

A=”Legal high’ use; B=Amphetamine use; C=Pharmacy based test for HCV; D=Anti-HCV positive; E=Currently attending DSC; F=Injecting drug use in last 30days.

6.4.3 Recruiters choose randomly from their eligible social network and network members are equally likely to participate

In the secondary incentive survey (Appendix 11) eight recruiters reported the refusal of coupons. Reasons for refusal included "couldn't be bothered" (2, 25%), being "too suspicious" (2, 25%), "already participated" (2, 25%), "having to go to work" (1, 13%) and "having to pick up children" (1, 13%).

Comparison of demographic and behavioural variables between participant and non-participant nodes in the 'whole island' social network (presented in Chapter 7) is shown in Table 6-4. Reported current injecting drug use was significantly associated with being a non-participant ($p<0.01$) but there was no significant difference with other variables.

Table 6-4 A demographic comparison of survey participants and non-participants in the social network of PWID.

	Participant N=69 (%)	Non-participant n/N (%)	*p*
Gender (male)	51 (74)	74/110 (67)	0.35
Mean Age (years)	39	37	0.37
Attends DSC	45 (65)	69/105 (66)	0.95
Active IDU (last 30 days)	38 (55)	91/106 (86)	<0.001

p values are calculated with SPSS[207] using *chi-squared* test for categorical variables and *t-test* for continuous variables. DSC - Drug support centre; IDU – Injecting drug use

The collection of network data facilitated an assessment of whether non-random recruitment took place, and specifically I used it to address two questions: Firstly, were participants more likely to recruit members of their social network with characteristics like themselves and secondly, were participants more likely to recruit persons with whom they had a particular relationship? Figure 6-4 shows homophily (measured as Yule's Q) between *ego* and *alters* recruited and not recruited to the survey. There was homophily within *ego*-networks (i.e. *egos* and *alters* tended to be similar rather than different) and this was the case regardless of whether the *alter* was recruited or not. However, *alters* recruited to the survey were more likely to be living in the same town as *ego* and were less likely to be within the same age category.

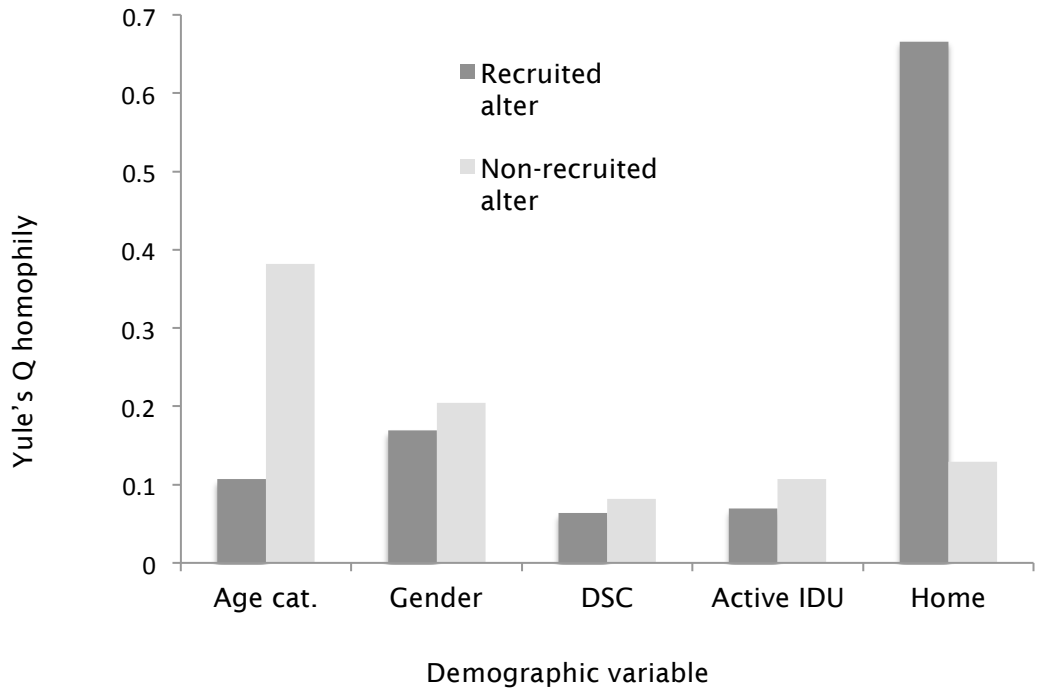

Figure 6-4 Assessing recruitment bias according to *alter* attribute by comparing similarity (as measured by Yules Q homophily) between *ego* and recruits and non-recruits. A Yules Q score of 1 would indicate complete homophily e.g. if *ego* is female all *alters* are also female. Whereas a score of -1 would indicate complete heterophily.

Age cat. = <35 ≥35

To assess whether persons were recruited because they shared a particular relationship with a participant, I compared recruitment *ties* with non-recruitment *ties* within each *ego* network (see Chapter 7 for the presentation of this network data). These were generally similar with the exception of sexual relationships, which were significantly associated with recruitment to the survey (p<0.01) (Table 6-5).

Table 6-5 A comparison of relationship types that did or did not lead to recruitment to the survey.

	Recruitment tie[1] N=64, (%)	Non recruitment tie[1] N=275, (%)	*p*
'Friendship'	41 (64.1)	168 (61.1)	*0.52*
'Acquaintance'	19 (29.7)	93 (33.8)	*0.43*
'Relative'	4 (6.3)	7 (2.5)	*0.34*
'Sexual partner'	10 (15.6)	10 (3.6)	<0.001
'Injecting partner'	42 (65.6)	196 (71.3)	*0.67*
'Facebook friend'	19 (29.7)	73 (26.5)	*0.71*

p values are calculated with SPSS[207] using *chi-squared* test for categorical variables and *t-test* for continuous variables.

[1]Cumulative percentages are greater than 100 because some relationships were multiple e.g. they incorporated, friendship and injecting partnerships

6.4.4 Participants only take part once and are members of the target population

One individual used a false name and participated in the survey on two occasions. They did not recruit any additional participants on the second occasion and therefore they could easily be excluded from further analysis. On three occasions I was unsure about eligibility after responses to the three screening questions. On each occasion the individual was able to demonstrate needle track marks to confirm eligibility.

6.4.5 Sampling occurs with replacement

I used a successive sampling estimator[142] as I anticipated that sampling would occur without replacement because of the small target population size on the IOW. I noted evidence suggesting that this was the case in the field where I observed participants attempting to recruit persons who had already participated. Further indications were from the reasons given for coupon refusal, where some recruiters described trying to hand coupons to friends who had already taken part and the failure to reach the intended sample size.

To test to what extent the population prevalence estimate for HCV was actually sensitive to this assumption I compared the original estimate with an estimate made using the Volz-Heckathorn (V-H) estimator[90], which is dependent on sampling with replacement. I found that there was only a minimal change (a slight reduction) in the estimated HCV prevalence (Figure 6-5).

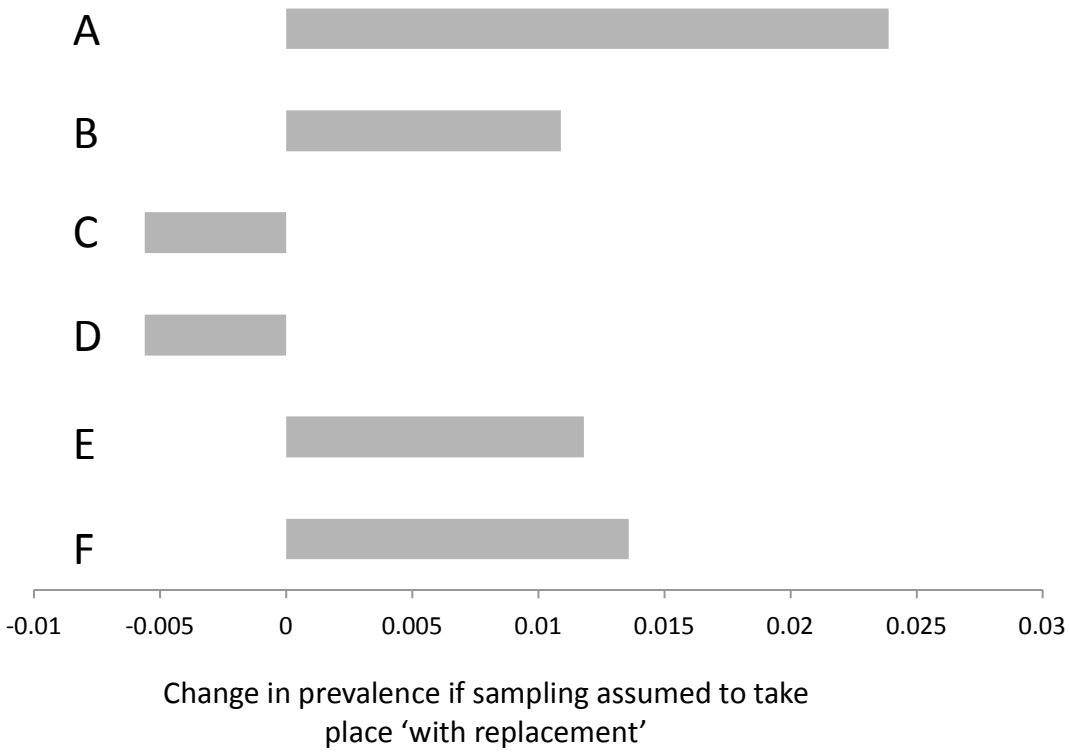

Figure 6-5 Testing the effect of sampling 'with replacement' on the prevalence estimates by comparing estimates calculated with the V-H estimator against the Gile's SS estimator. The estimate for variable A (the injection of 'legal highs') was most affected, whereas D (anti-HCV positive) was least affected.

A="Legal high' use; B=Amphetamine use; C=Pharmacy based test for HCV; D=Anti-HCV positive; E=Currently attending DSC; F=Injecting drug use in last 30days

6.4.6 Participants accurately report *degree* size

The reported mean *degree* decreased as expected through the cascade of questions Q1 to Q3 in the interview based survey (Appendix 13) (Table 6-6) (for a definition of *degree* see Table 1-1). Using the social network data, presented later in Chapter 7 (Figure 7-3), it was also possible to compare Q3 (which was used as the '*degree* size' to calculate prevalence estimates) to an empirical *degree* size (*E*) that was actually measured for each of the nodes within the social network. When compared, there was a positive correlation ($r=0.38$; $p<0.01$) and as expected both decreased through the recruitment *waves* (Figure 6-6).

This finding was reassuring as it indicated that the probability of recruitment to the survey was proportional to *degree size*, which is important for the validity of the prevalence estimates. There were outlier values for Q3 in *waves* seven and nine (Figure 6-6) but as these were not reflected in *E* they are more consistent with inaccurate self-reporting of *degree* size than sampling anomalies.

Table 6-6 Reported *degree* sizes to the cascade of network size assessment questions posed to survey participants (Q1-Q3), where Q3 represents the *degree* size used in population prevalence calculations. The empirical *degree* measured in the 'whole island' network (E) is the sum of ties connecting each node within the network that is reported in Chapter 7 (Figure 7-3).

	Network question cascade	Mean	Range
Q1	How many people have you ever known that inject drugs?	80	3-1000
Q2	How many of these individuals currently live on the IOW?	49	2-300
Q3	How many of these individuals have you seen in the last 4 weeks?	16	1-100
E	Empirical *degree* in PWID social network	7	1-18

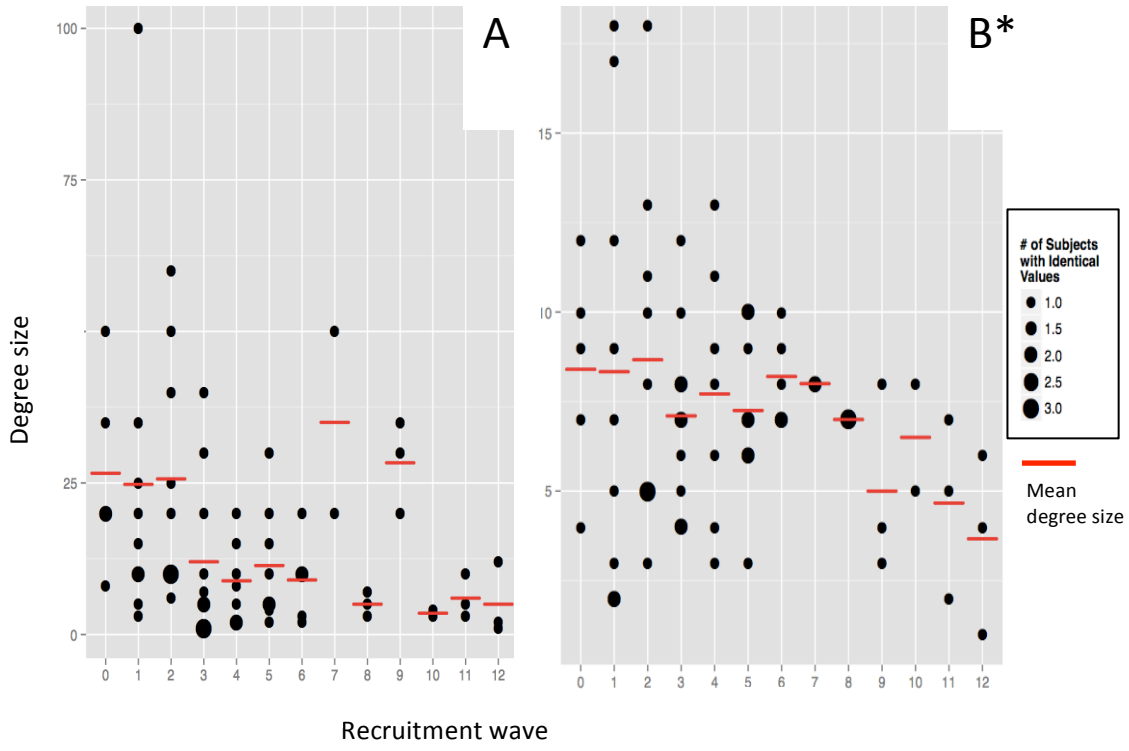

Figure 6-6 Change in mean for Q3 (A) and *E* (B) through successive *waves* of RDS (note different scales on y-axis). As expected there is a decrease as sampling progresses, indicating that *degree* size is reported with relative accuracy and that the probability of inclusion in the sample *was* proportional to *degree*.

*2 patients in *waves* 8 and 11 refused to give *ego*-network data in both cases their empirical *degree* was assumed to equal their social network *in-degree*.

There was clustering in reported *degree* size around multiples of 5 and 10 (Figure 6-7), which is a concern as it indicates that participants rounded and estimated their *degree* size. There was also sensitivity of prevalence estimates to variations in *degree* size. To assess this I compared the original prevalence estimates made using Q3 as the *degree* size to prevalence estimates for the same variables made by substituting Q3 for Q1, Q2 and *E* (with values defined in Table 6-6). I was also aware that inaccurate reporting by persons with a small *degree* size could have a particularly profound impact on prevalence estimates[134] so I also created a 'composite' *degree* size (Q3+*E)*, where those participants reporting a small Q3 (<9) had the value substituted for *E*.

The results are displayed in Figure 6-8. Unsurprisingly the greatest variation was observed when Q3 was substituted for Q1, where one variable differed by 13%. But there was also variation when Q3 was substituted for *E* and Q3+*E*. For example, the prevalence of HCV was 3% lower when Q3 was substituted for *E*+Q3 (Figure 6-8 - D).

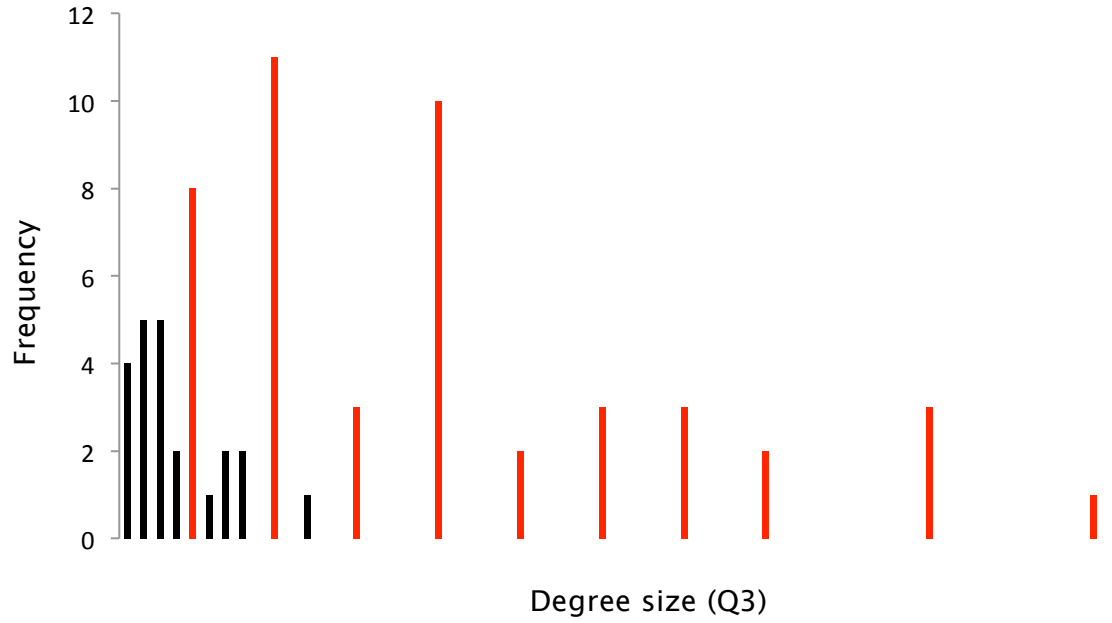

Figure 6-7 Clustering of reported *degree* size (Q3) from 69 survey participants at multiples of 5. Red columns indicate a *degree* size that is a multiple of 5 and grey columns are other numbers. A single reported *degree* size of 100 is not shown.

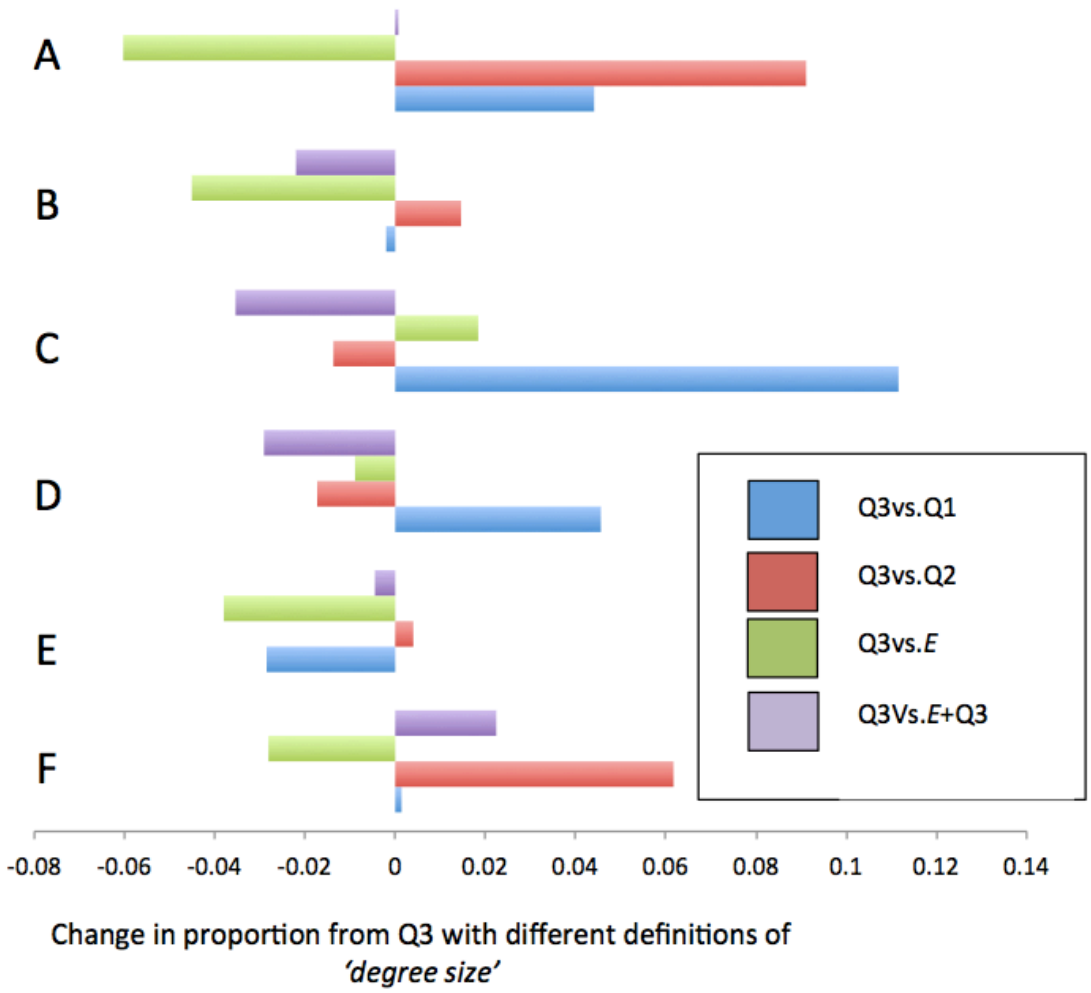

Figure 6-8 Change in population proportion estimates for six selected variables according to the value used as '*degree* size' in the estimator. *E*+Q3 is a composite *degree* size where *E* was used if Q3 was <9.

A="Legal high' use; B=Amphetamine use; C=Pharmacy based test for HCV; D=Anti-HCV positive; E=Currently attending DSC; F=Injecting drug use in last 30days.

6.5 Discussion

In Chapter 6 I present a population prevalence estimate for HCV in PWID on the IOW and test the validity of this estimate. I have also shown that 'case-finding' for HCV in PWID on the IOW appears to be effective but that engagement with treatment services is limited.

The population prevalence estimate I present is lower than that observed in other UK areas[18], including in another study that used RDS[114] and importantly it is below the estimate used to quantify the number of HCV cases on the IOW*[86]. However, this is the first published attempt at a 'cross-sectional' survey in non-urban PWID in the UK and therefore it is likely this variation is attributable to heterogeneity between the surveyed populations. This will be discussed further in Chapter 10.

The prevalence estimate for HCV is based on a survey that used RDS to identify participants. RDS, as discussed in Chapter 2, is a well-described, method for obtaining population estimates from hidden populations. However, its validity is dependent on the success of the sampling process and the theoretical assumptions underlying the method.

In total, I used five *seeds* to recruit a total of 69 eligible participants in recruitment chains that passed through 12 *waves*. Three out of five *seeds* were 'generative' (defined as recruiting more than one additional participant) which compares favourably with other surveys conducted in non-urban populations[194,216]. However, the chains grew much slower than theoretically possible and many coupons were not redeemed for the financial incentive. This limited the sample size and the target was not achieved – leading to broad confidence intervals around the HCV population prevalence estimate.

Careful *seed* selection is central to a successful RDS survey but identifying *seeds* that are likely to be 'generative' is difficult[217]. The addition of *seeds* as a means to increase recruitment in RDS, especially where social networks are small and dispersed has been proposed[136]. However, *seeds,* in being recruited by the research team, are inherently biased and therefore their number should

* From an unpublished health needs assessment by Dominique Le Touze, 2011.

be kept to a minimum to avoid invalidating population estimates. In the early stages of recruitment in this survey, it was clear that participants were not attending from the largest town on the IOW and therefore two additional *seeds* from this area were needed to 'boost' recruitment (taking the total to five). This highlighted how geographical dispersion affected recruitment even in a well-connected target population and stressed the importance of using multiple survey venues in different geographical areas.

Barriers to RDS recruitment have been described and include, inadequate incentives and disconnected, small social networks[136,156]. However, there was evidence in this survey that it was the small target population that limited recruitment. I observed one participant attempting to recruit two individuals who had already taken part in the survey and in another example a participant returned the coupons and explained that he had been unable to recruit anyone as his acquaintances had already participated.

I took measures during the operational conduct of the sampling to maximise the number of recruitment *waves* despite the small target population. Only two rather than three coupons were distributed to the majority of participants and a greater incentive was given for recruiting the first additional participant than the second. However, these measures, whilst maximising chain length, may have limited the final sample size by effectively 'thinning' the recruitment trees. In addition the use of 'asymmetric' secondary incentives has not been previously reported, and the statistical impact of this leading to participants not fulfilling their recruitment quotas is a concern.

Increasing incentives further may have encouraged participants to recruit from further afield although evidence supporting an increase in primary incentive is limited[136,218] and ethically it was felt the secondary incentive could not be increased any further. Another measure that may have facilitated recruitment would have been simultaneously operational research venues rather than the cyclical 'one after another' approach used in this survey. Practically this could have facilitated the transfer of recruitment coupons between different geographical areas, but would have come at considerable cost in terms of time and resources.

RDS has previously been conducted in a range of venues including, mobile vans and needle exchange centres[38]. However, the use of the community

pharmacy has not been described. These venues worked well, it was clear that they were geographically central to the local sub-network of PWID and they out performed other sites in terms of the number and speed of respondents recruited. The use of the pharmacies as a venue was acceptable to the pharmacists themselves, although being small premises and frequented by non-PWID, careful management may be required in larger populations to stop them getting overrun in the manner described elsewhere[219].

Ethical issues surrounding RDS are complex and warrant specific discussion in the context of the survey reported here. The underlying premise that gives RDS an advantage over other sampling methods is the harnessing of social influence via the use of secondary incentives[37]. Whilst this is a key feature of RDS methodology, there is a fine line between benign social influence and coercion leading to poor judgement. However, Semaan *et al*. argue that undue influence is only that which leads to individuals being exposed to risks beyond what they experience in daily life and that RDS, in recruiting participants to undertake simple surveys, does not do this[220]. However, researchers using RDS have been sufficiently concerned about this and other ethical issues that safeguards have been built into and added to the sampling procedure. These include the limited recruitment quota to prevent participants becoming 'professional' recruiters, the collection of informed written consent from all participants in a private environment and the use of only modest financial incentives[220]. In addition, some larger surveys have used ethnography to observe the conduct of the survey in the field and have reported some serious (although widely contested) ethical dilemmas associated specifically with RDS[221,222].

In the present survey, I made efforts to understand and minimise the ethical implications of the sampling procedure. During the qualitative feasibility enquiry, (see Chapter 4) the acceptability of financial incentives was explored with potential survey participants and DSC professionals, and the value of this incentive was kept to a minimum (the primary incentive was roughly equal to the bus fare between two survey locations).

In addition to the logistical and ethical challenges encountered during the conduct of the sampling procedure, I was aware that the validity of the HCV prevalence estimates are dependent on the theoretical assumptions underlying

the method. However, by understanding the assumptions and planning the survey and analysis accordingly I have tried to account for the assumptions in accordance with new guidance and recent literature[95,139].

In this survey I identified several potential violations of the assumptions: Participants preferentially recruited network members from the local area with whom they shared a sexual relationship and there was evidence *degree* size was inaccurately reported.

The impact of these violations on the HCV prevalence estimate probably varied. I demonstrated that the sample proportion of HCV positive individuals converged and remained stable from an early stage of the sampling process. This indicated that sampling didn't encounter clusters of disease in a way that has affected the validity of estimates elsewhere[128]. Therefore non-random recruitment probably had a limited impact on the estimate. However, I demonstrated that inaccurate *degree* size reporting could have had a significant effect on the value of the estimates. In particular, I showed that inaccurate reporting by those with a small *degree* size had a profound effect which supports other published findings[134].

The routine collection of data to facilitate an assessment of the sensitivity to the theoretical assumptions is now incorporated into international guidance on the conduct of RDS[95,170]. However, an additional strength of this survey was the collection of *ego*-network data from participants as it facilitated a more in-assessment of participant behaviour. The collection of *ego*-network data for this purpose has been proposed in the literature, but to my knowledge I am the first to incorporate it into real-world practice[143].

6.6 Conclusion

In this chapter I have presented a revised prevalence estimate for HCV in PWID on the IOW and describe high engagement with harm reduction initiatives including HCV testing. Overall, RDS was effective at identifying a considerable proportion of the PWID living on the IOW to undertake a HCV bio-behavioural survey. The sampling was novel in terms of the use of pharmacy venue, asymmetric incentives and non-urban target population. However, it highlighted some challenges of conducting RDS in a rural environment.

7. Hepatitis C within the social and injecting network of people who inject drugs on the Isle of Wight

7.1 Chapter overview

Chapter 7 presents the results of the social network survey that was completed by the participants of the bio-behavioural survey, described in Chapter 6, and a phylogenetic analysis of persons with Hepatitis C virus (HCV) living on the Isle of Wight (IOW).

In Chapter 7 I aim to address the following objective:

Understand how HCV transmission is related to the social network of PWID

Initially I describe how the participants were connected to each other and then, by adding people who they described who were not participants, I present a representation of the 'whole island' network of people who inject drugs (PWID). This network is referred to throughout within inverted commas because it is my 'best effort' to map the network and it inevitably is affected by missing data.

In this chapter I also present the results of a whole genome sequencing study of people with HCV presenting to the HCV service on the IOW. This included some individuals who were also in the 'whole island' network, which therefore facilitated an assessment of whether the relationships I observed in the network had actually led to the transmission of HCV. More generally it allowed me to gain an overview of HCV on the IOW at a molecular genetic level.

In this chapter there is a reliance on specific social network terminology, I therefore refer the reader to Chapter 1, Section 1.6 where this is introduced.

7.2 Method

The detailed methods for the work presented in this chapter are described in Chapter 5.

7.3 Participant network

Sixty-seven of the participants of the bio-behavioural survey reported in Chapter 6 also completed a triangulation matrix which described their *ego* network with other PWID living on the IOW. Some of the *alters* in each *ego* network were other participants and these ties, alongside the recruitment ties, formed a social network between the participants (Figure 7-1). Ties within this network included social relationships as well as so-called 'risk relationships', which included sexual and injecting partnerships. When only injecting partnerships were considered, (defined as injecting at the same time and the same place) the network fragmented (Figure 7-2) and five nodes, became isolated. However, most participants remained connected in a single network component of 59 nodes.

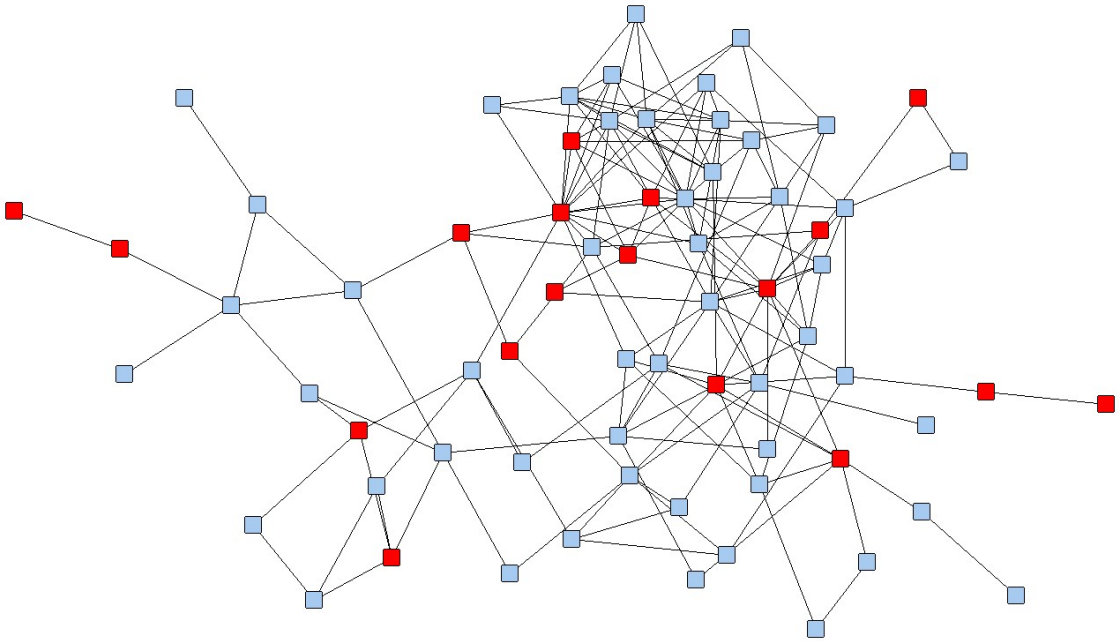

Figure 7-1 The social network connecting survey participants. Red nodes are HCV antibody positive and blue nodes are HCV antibody negative. Lines indicate any social relationship.

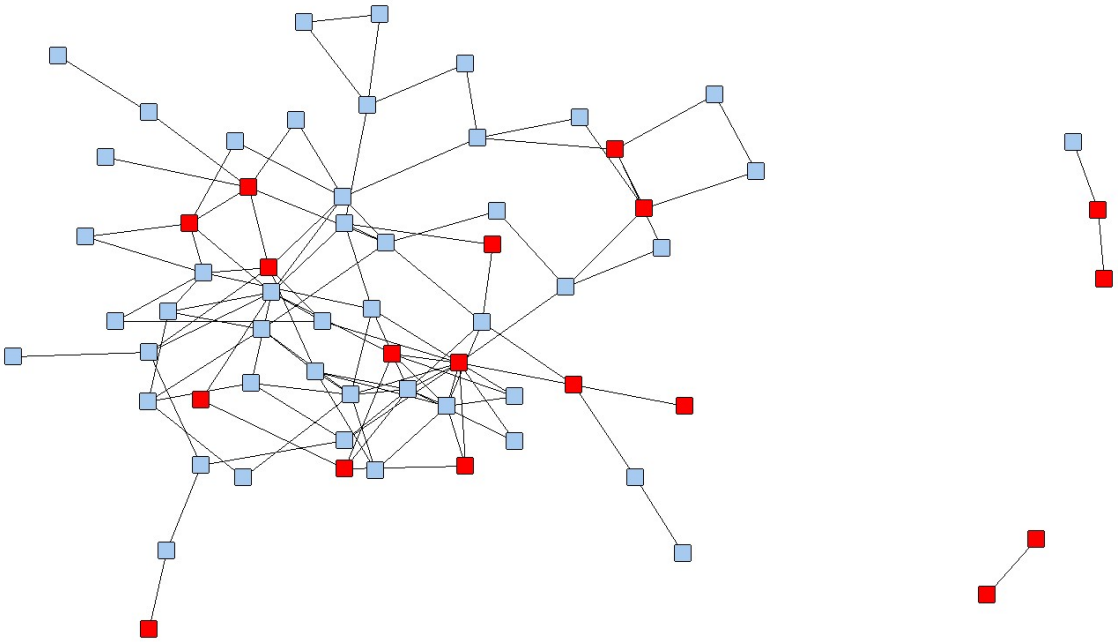

Figure 7-2 The participant injecting partners network connecting survey participants. The social network fragments when only ties that involve injecting in the same place at the same time are included. Five isolated nodes without such ties are not displayed – they were all HCV antibody negative.

The position of nodes within the network (measured as 2-step reach centrality) was not associated with being anti-HCV positive (p=0.788). However, there was a significant association with certain *ego*-network measures including the anti-HCV status of injecting partners (p<0.01) and needle and syringe risk behaviours of injecting partners (p<0.01) (Table 7-1).

Table 7-1 The association between *ego* and socio-centric network measures in the social and risk networks connecting survey participants and anti-HCV status.

Network measure	Anti-HCV+ (N=18)	Anti-HCV- (N=51)	*p*
***Ego* network measures**			
Injecting partners anti-HCV positive	48%	27%	0.01
Injecting partners NS risk	48%	22%	<0.001
Injecting partners age (Mean years)	41	39	0.09
Socio-centric network measures			
Social network *in-degree* (n)	3.26	2.84	0.56
Injecting network *degree* (n)	3.53	3.22	0.65
Injecting network *K*2 step (n)	11.89	12.56	0.79

p values are calculated with SPSS[207] using the independent *t-test* .

NS – needle and syringe; HCV – Hepatitis C virus.

7.4 'Whole island' network of PWID

In the adjacency matrices participants described *alters* who matched participant codes but also many that did not. Where complete, these codes were attributed to network members who had not participated in the survey and they were added to a second larger adjacency matrix to form a representation of a 'whole island' PWID social network consisting of 179 nodes (Figure 7-3).

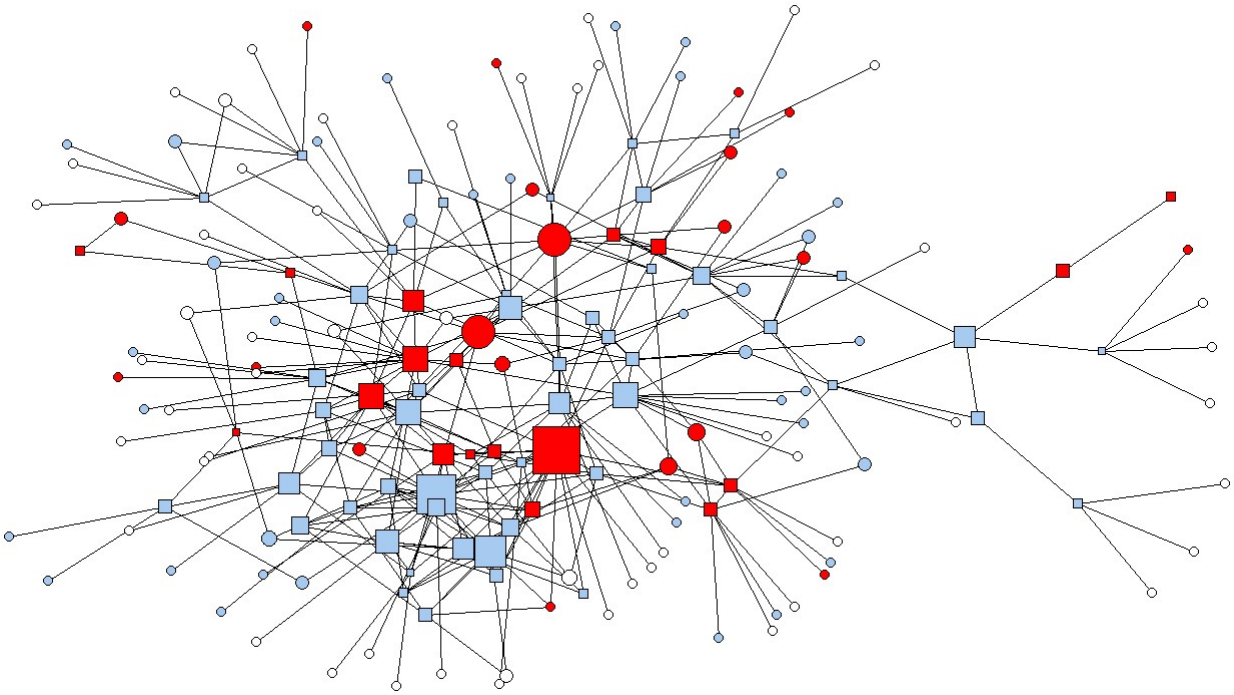

Figure 7-3 Social network connecting PWID living on the IOW in a single component. This network includes the 69 survey participants (square nodes) and an additional 110 non-participants (round nodes), sized according to *in-degree* centrality. HCV status* (where red indicates a node who is HCV positive) was determined by *ego-alter* report for non-participants. White nodes in this matrix are where HCV status was reported as 'unknown'. Lines indicate ties between nodes and represent any social relationship.

*In Chapter 7 from section 7.4 onwards 'positive HCV status' is used rather than 'anti-HCV positive' because there was no distinction given from peer-reporting, between being positive for RNA and antibody, or just antibody.

However, not enough information was given on all *alters* in the adjacency *matrices* to reliably identify them as a known or new node. Therefore 38 partial codes had to be excluded from the 'whole island' network. Where possible the characteristics of these could be compared against included nodes to assess for bias and this showed that partial codes were significantly more likely to be attributed to male individuals (Table 7-2).

As described, the 110 non-participant nodes in the network were ascribed attributes based on peer-reporting. Importantly, 52 nodes did not have a peer-reported HCV status (the person or persons that described them stated they didn't know whether these were positive or negative). Accordingly, I estimated the number of these individuals that would be HCV positive using a multiple imputation model. When this was taken into account the prevalence dropped in the 'whole island network' from 29.9% to 27.9%.

Table 7-2 Demographic and bio-behavioural measures for the 179 whole network node*s* compared with 38 excluded *partial codes.*

Demographic variable[1]		Included nodes N=179 (%)	Excluded partial codes N=38 (%)	*p*
Mean Age (years)		38 (range 18-65, SD 9.811)	37 (range 23-57, SD 8.652)	*0.57*
Gender (male)		125 (70)	34 (90)	*0.01*
Attends DSC		114 (64)	-	-
Current IDU		129 (72)	-	-
Home town[2]	1	10 (5.6)	3 (13)	*0.41*
	2	11 (6.1)	2 (8)	
	3	57 (31.8)	11 (46)	
	4	43 (24)	5 (21)	
	5	32 (18)	1 (4)	
	6	6 (3.4)	0 (0)	
	7	13 (7.3)	1 (4)	
	8	3 (1.7)	1 (4)	
HCV positive		38/127 (29.9)	5 (13.2)	*0.40*[3]
HCV positive (pooled multiple imputation)		50/179 (27.9)		

p values are calculated with SPSS[207] using *chi-squared* test for categorical variables and *t-test* for continuous variables.

[1]In the whole network variables were determined by the results of the bio-behavioural survey for the 69 survey participants and peer-reporting by these participants in the social network survey.

[2]For 14 excluded partial codes this information was not available. Name of town or village not described to protect anonymity and therefore assigned a number 1-8.

[3]Compared against included nodes where unknown HCV status was assumed to be negative.

DSC – Drug support centre; IDU – Injecting drug user; HCV – Hepatitis C virus.

Like the participant network, the 'whole island' social network of PWID fragmented only when injecting partnerships were considered. However, there remained a large component containing 151 nodes with a mean *degree* (number of injecting partners) of 2.6.

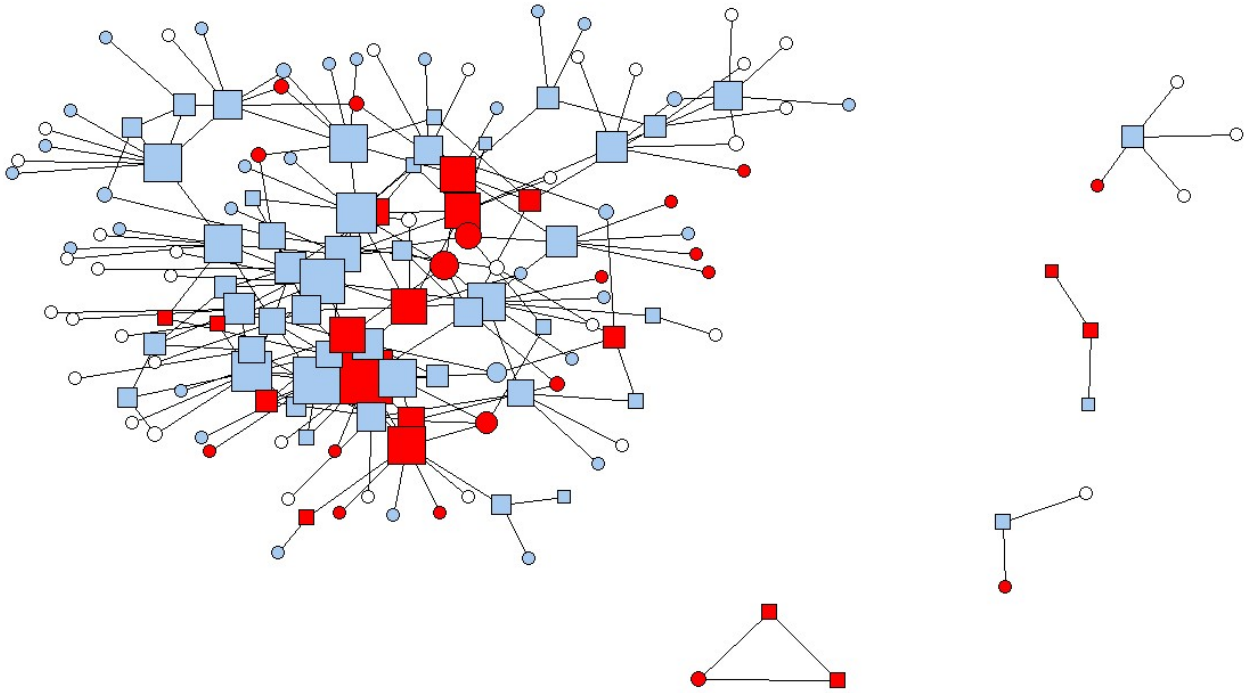

Figure 7-4 The injecting network, with isolated nodes excluded, sized according to *in-degree* centrality. Red nodes are HCV positive*, blue nodes are HCV negative and white nodes have an undetermined HCV status. Lines indicate an injecting partnership between two nodes.

*In Chapter 7 'positive HCV status' is used rather than 'anti-HCV positive' because there was no distinction given from peer-reporting about whether peers were positive for just antibody or RNA and antibody.

I measured cohesiveness of the injecting network by measuring the cohesion coefficient, density, average geodesic distance (AGD) and the network diameter. However, as there is no directly comparable literature, these figures in isolation have limited meaning. I therefore compared the results against 1000 randomly generated networks with the same number of nodes and number of ties (Figure 7-5). The IOW network had more isolates (i.e. nodes without an injecting partner) and therefore contained more components than the random networks. However, in terms of network AGD, diameter and clustering coefficient it was more cohesive.

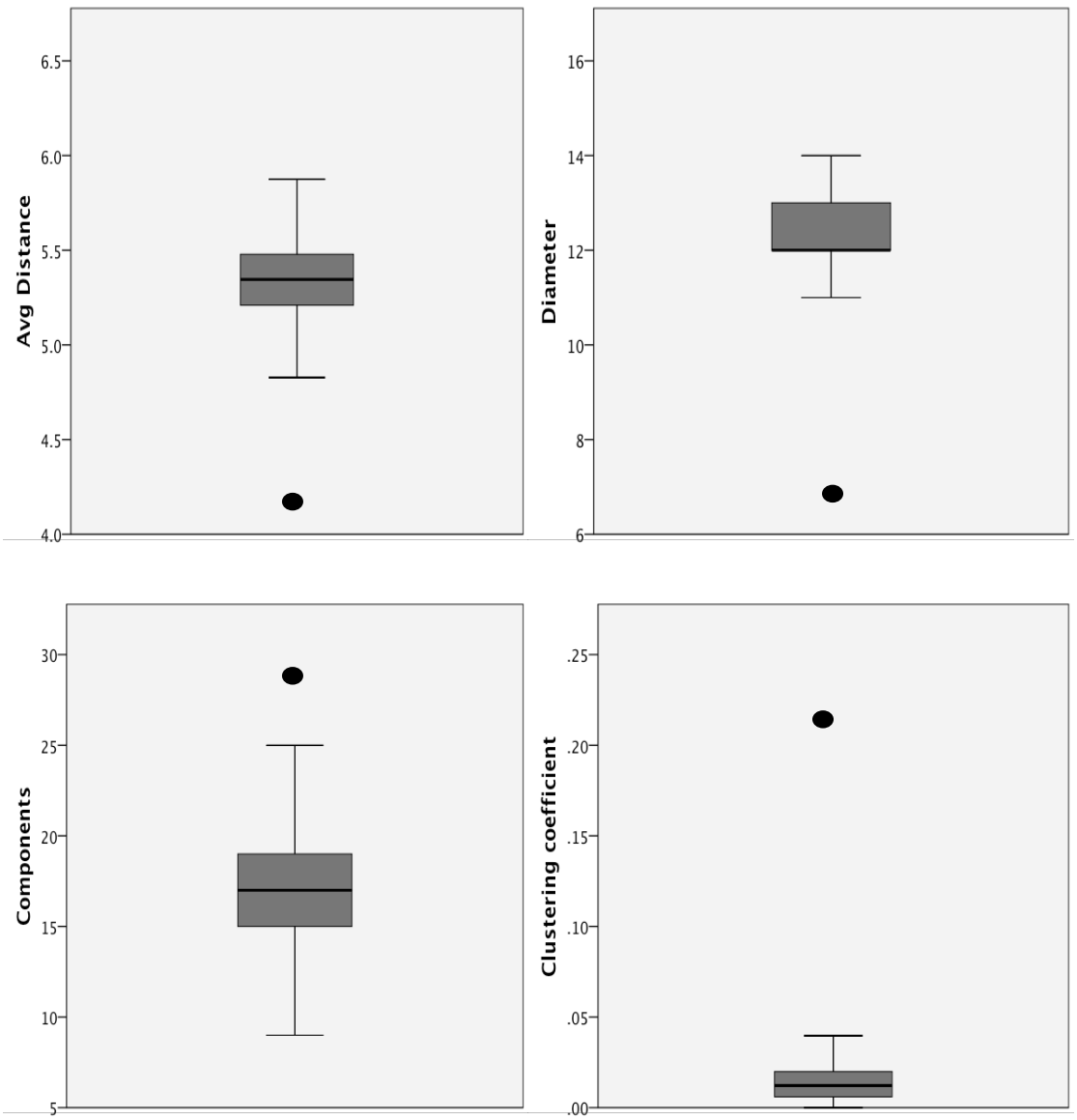

Figure 7-5 Box and whisker plots showing the cohesion of the 'whole island' injecting partners network (black nodes) against 1000 randomly generated networks, where the ends of the boxes are the upper and lower quartiles, the median value is marked by a horizontal line inside the box, and the whiskers extend to the highest and lowest observations.

In the injecting network increasing age and the proportion of HCV positive injecting partners was significantly associated with HCV in both univariable and multivariable analysis (both p<0.01) (Tables 7-3 and 7-4). However, as I reported in the participants injecting network, HCV status was independent of the nodes overall position in the network, as measured by *in-degree* centrality and 2-step reach centrality.

Table 7-3 Association of demographic, behavioural and social network measures with HCV status in the 'whole island' network.

	HCV n/N(%)	No HCV n/N(%)	*p**
Gender (male)	27/38 (71.1)	63/89 (70.8)	0.90
Mean Age – (years)	43.2	37.9	0.003
Attends DSC	26/35 (74.3)	62.0/89 (69.7)	0.61
Current IDU	27/37 (73.0)	60/88 (68.2)	0.63
Injecting partners HCV+	0.4	0.2	0.006
Social network in-*degree*	3.0	2.2	0.08
Injecting *degree*	3.3	3.3	0.95
Injecting partners K 2 step	15.2	14.6	0.78

*The significant variables (<0.01) did not change with analysis of pooled multiple imputation data. *p values* are calculated with SPSS[207] using *chi-squared* test for categorical variables and *t-test* for continuous variables.

HCV– Hepatitis C; DSC – Drug support centre; IDU – injecting drug user.

Table 7-4 Logistic regression of network, behavioural and demographic associations with positive HCV antibody status in the 'whole island' injecting network.

		OR (95 % CI)	95% C.I.		p^*
			Lower	Upper	
Age		1.06	1.01	1.11	0.01
Gender (male)		0.87	0.37	2.32	0.77
Social network in-*degree*		1.12	0.95	1.32	0.21
Injecting partners HCV positive	Increase by 1 tertile	2.07	0.79	5.47	0.14
	Increase by 2 tertiles	3.75	1.2	11.4	0.02

Logistic regression calculated in SPSS[207]. *Significance did not change with analysis of pooled multiple imputation data set.

7.5 Accuracy of peer reported Hepatitis C status in the 'whole island' network

The HCV status of non-survey participants within the 'whole island' network was determined by peer report. I tested the accuracy of this by examining the reporting between survey participants who also underwent a mouth swab test for anti-HCV.

Within the participant network, (Figure 7-1) there were 137 *ego-alter* reports of HCV status. On 69 occasions *ego* indicated whether the *alter* was HCV positive or negative, whilst on 68 occasions they 'didn't know'. The accuracy of these reports is displayed in Table 7-5. However, based on the assumption that PWID only disclose a positive HCV test result to some friends and acquaintances, the HCV status of non-participants in the network was determined via *network-nodal* reporting. If a single node identified another in the network as positive that node was assigned a 'positive status'. Whereas if no one had indicated they were positive then they were assumed to be negative.

Four true positive nodes were not reported as positive by another node in the network (one had been diagnosed just a month before the survey) and five were falsely identified by at least one node as being positive. It follows therefore that network nodal reporting may have slightly overestimated the number of cases of HCV in the network. The accuracy of *network-nodal* reporting is displayed in Table 7-5.

Table 7-5 The accuracy of peer reported HCV status in the 'whole island' social network.

	Specificity	Sensitivity	PPV	NPV
Ego-alter HCV status report accuracy (n=69)	0.81	0.82	0.84	0.79
Network-nodal report accuracy (n=69)	0.90	0.78	0.74	0.92

NPV – Negative predicative value, PPV – positive predictive value

7.6 Phylogenetics of Hepatitis C within the PWID network

In parallel to the HCV bio-behavioural and social network survey, I consented patients presenting to the clinical HCV service on the IOW to be tested for HCV RNA phylogenetic analysis. The objective of this parallel study was to give a further indication about the nature of transmission of HCV on the IOW.

Fifty-four individuals participated, the mean age was 54 years (range 27-77) and the majority were male (76%). The majority of participants also reported current or historical injecting drug use as their main risk factor for HCV (83%) and most had potentially been exposed to HCV on the IOW, either through injecting drug use or a sexual relationship with a person known to have injected drugs on the IOW (63%).

The majority of samples were genotype 3a (50%) or 1a (37%). There were just two genotype 1b samples which both came from participants who were exposed to HCV in southern Europe. There was no association between the genotype distribution and the age of the participants (p>0.1) (Figure 7-6).

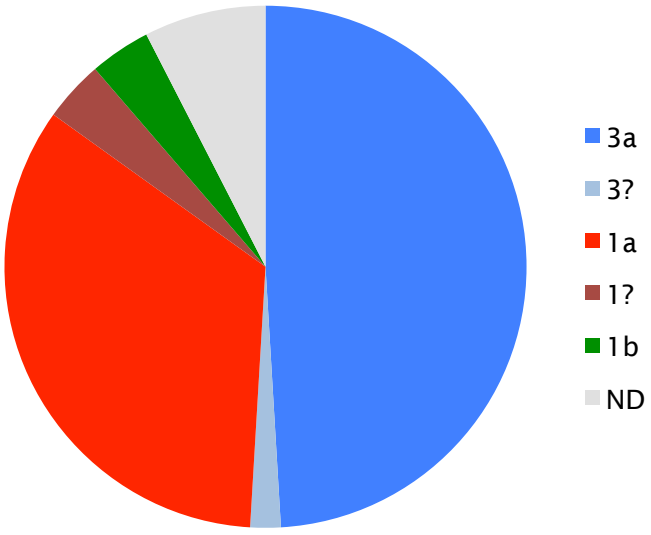

Figure 7-6 Genotype frequency in persons with HCV living on the IOW and presenting to the Hepatitis clinical service.

ND=Not reported

All 54 samples underwent whole genome next generation sequencing at the Centre for Virus Research, University of Glasgow*. Fifty-two sequences were successfully generated and these were compared against 400 reference sequences from the HCV UK database[213] (Figure 7-7). The genotype 1a sequences were generally phylogenetically dispersed within other UK sequences, but there was clustering within the genotype 3a sequences. However, those participants with genotype 3a virus were no more likely to have been exposed to HCV exclusively on the IOW and were actually more likely (although not significantly) to have put themselves at risk either on the UK mainland or abroad (p=0.13).

*Next generation sequencing was conducted by Dr. Christopher Davis, a post-doctoral research fellow at the Centre for Virus research, University of Glasgow.

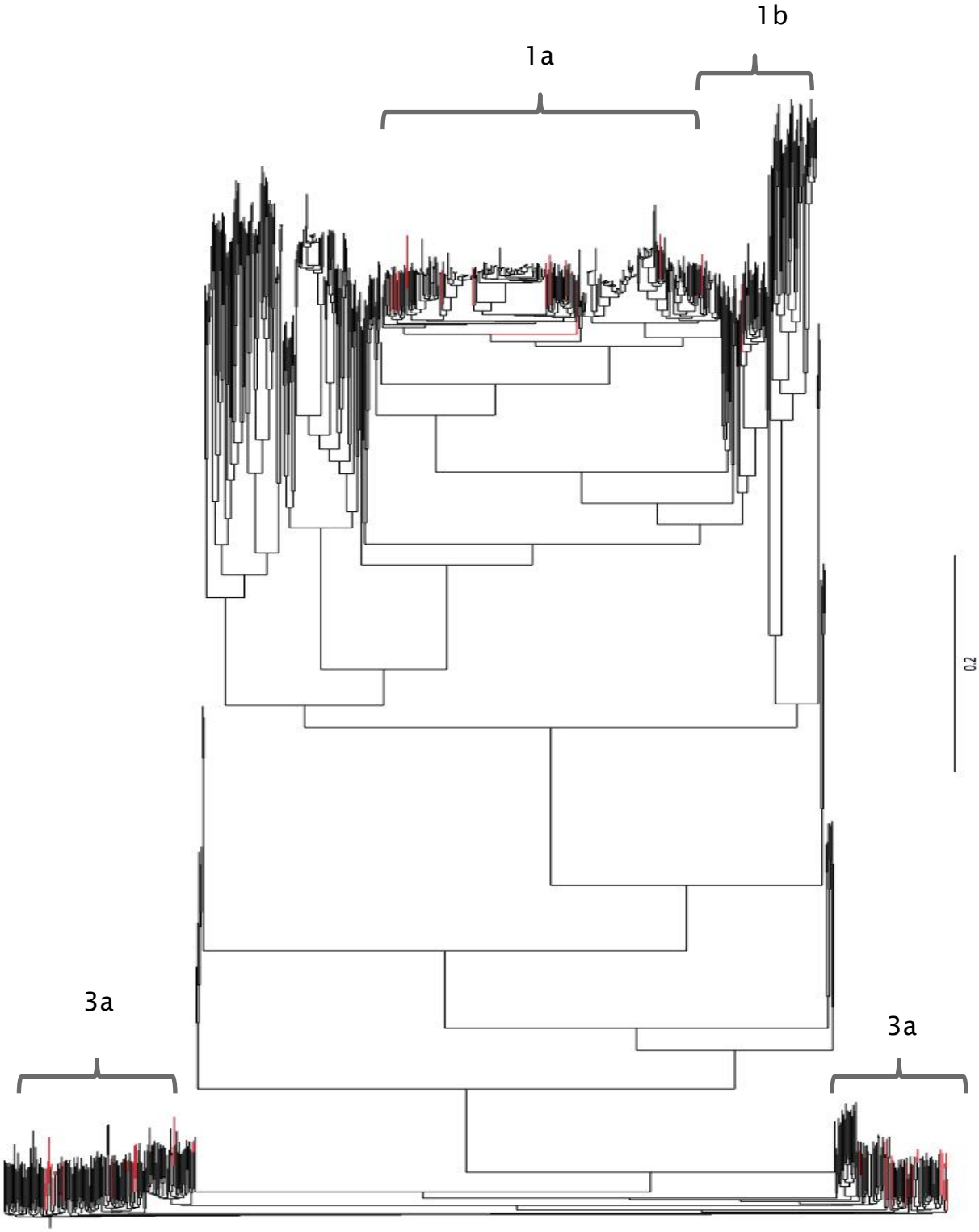

Figure 7-7 The phylogenetic distribution of HCV RNA sequences from the IOW patients (in red) in the context of 400 other UK sequences

Of those sequences taken from participants who had actually injected drugs on the IOW, 15 (44%) were also part of the injecting network described in section 7-3 (see Figure 7-4). Of these, four pairs of genotype 3a sequences were phylogenetically approximate and two of these pairs described a corresponding injecting relationship within the injecting network.

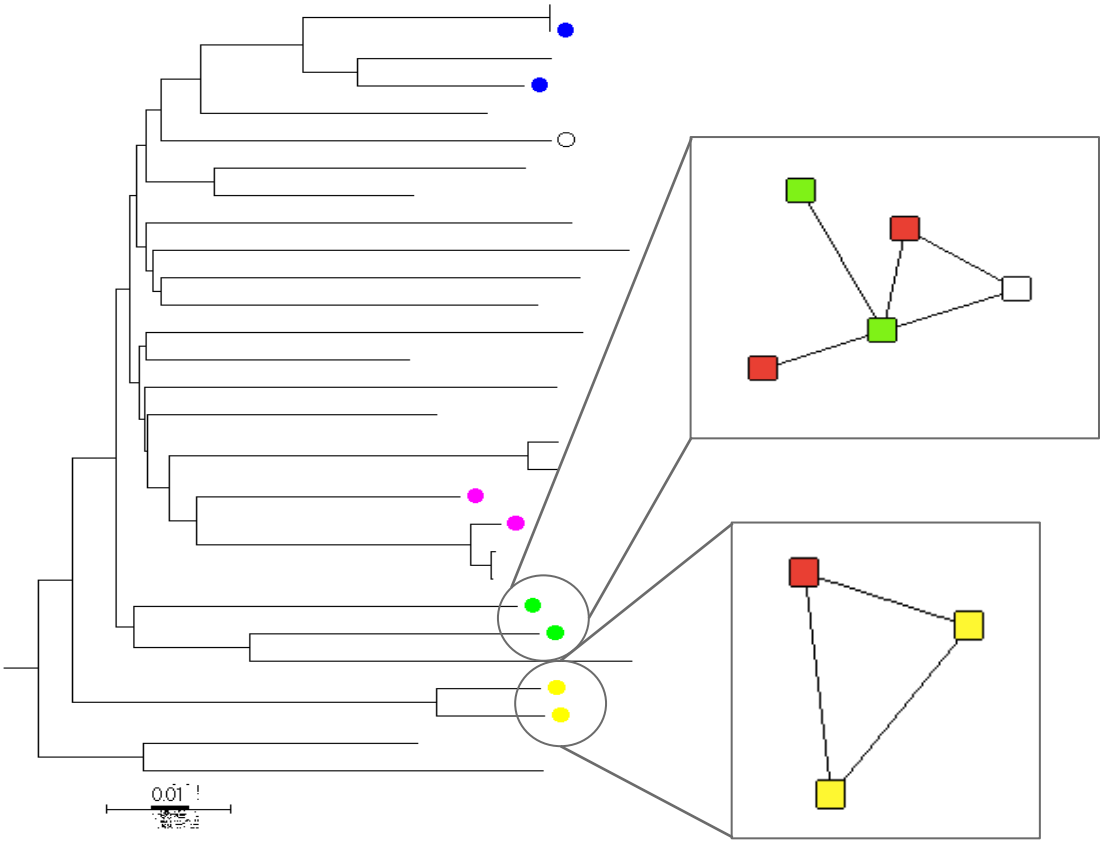

Figure 7-8 A maximum likelihood phylogenetic tree of genotype 3a sequences from the IOW and injecting *ego*-networks around two injecting dyads (green and yellow nodes) with phylogenetically similar sequences. All coloured nodes in the phylogenetic tree were also captured in the injecting network (Figure 7-4). Red nodes in the *ego*-networks were also HCV positive and the white node was HCV negative.

One of these pairs (the yellow nodes in Figure 7-8) had a multiplex relationship that involved sexual intercourse as well as an injecting partnership. They were in an isolated injecting component comprised of a single triad. The other node in the triad was also anti-HCV positive but had spontaneously resolved the infection. The other pair (green nodes) had a long-standing injecting partnership, and one described an injecting relationship with two other positive nodes (both coloured red in Figure 7-8), both were also genotype 3a.

Other phylogenetically similar sequences were not represented by an injecting dyad (see pink and blue nodes in Figure 7-8).

7.7 Discussion

The findings in this chapter indicate that PWID on the IOW are connected together via injecting partnerships into a large cohesive network component and that HCV within the network is associated with being older and having more positive injecting partners.

This is inkeeping with findings elsewhere. Young *et al.* described a cohesive network structure in a rural population of drug users in the USA and showed social 'clustering' of HCV positive individuals. Without phylogenetic data, they speculated that this might be explained by sero-sorting (i.e. the deliberate selection of an injecting partner on the basis of shared HCV status), as well as direct transmission[43]. Given the accurate peer awareness of HCV status in this network, sero-sorting is certainly a possible explanation for the clustering I observed.

However, through whole genome phylogenetic analysis I was also able to make some assessment of whether injecting network clustering *was* a result of direct transmission. Fourteen whole genome sequences were from individuals in the injecting network and among these there was evidence supporting the assertion that the observed injecting partnerships led to the transmission of HCV genotype 3a. However, there were other injecting partnerships where the HCV sequences were more distantly related and conversely, phylogenetically related HCV sequences without an observed injecting relationship. These findings are consistent with heterogeneity within the wider literature and fits with the understanding that the network I have described is: incomplete, a snapshot in time and HCV is often contracted soon after the initiation of injecting drug use[23,122,223].

When I compared all 54 IOW HCV sequences against 400 whole genome sequences from the HCV-UK database[213], there was evidence of clustering among HCV genotype 3a sequences. This indicates that although there have been multiple introductions of HCV to the IOW, in the case of genotype 3a, there has been transmission between PWID. Indeed, the phylogenetic

clustering on the IOW exceeds that reported in another island-based study of HCV phylogeny[21,224] in PWID, which is consistent with the cohesiveness of the injecting network I observed and its geographical isolation.

However, compared to other studies of HCV phylogenetics in PWID the genotype 1a sequences presented in this chapter were less closely related. Sack-Davis *et al.* in Melbourne, Australia, and Jacka *et al.* in Vancouver, Canada have both demonstrated dense clusters of phylogenetically similar genotype 1a sequences (defined in the latter as having a p distance of <0.05)[23,24]. This is surprising as both studies were conducted in large metropolitan areas rather than the isolated, cohesive population I have described.

However, the difference can probably be attributed to heterogeneity in the study populations. The participants of the phylogenetic study presented here were not the same as the bio-behavioural survey (although there was some overlap). They were older, some had stopped or had never injected drugs and they had engaged with clinical hepatitis services. The participants in the Melbourne study by contrast were young, actively injecting and recruited through fieldwork. A limitation of this study is the genetic validation of the injecting network and investigation of HCV transmission on the IOW was not centred on the actively injecting network. Therefore I probably missed genetic sequences that mapped to contemporary transmission events.

The collection of social network data in PWID is challenging. In conventional social network research, to study a whole network, all the nodes need to participate and ideally all the connections between them should be established[225]. Clearly when studying PWID this is not possible. On the IOW I had no network 'boundary', I didn't know who all the nodes in the network were, and many of those who were identified in peer-reporting were not actually recruited. Furthermore, of those PWID who did take part, it is highly likely that their network data was fragmented and incomplete. This may have occurred through deliberate or accidental recall bias, or the design of the triangulation matrix - which only allowed participants to describe up to eight injecting partners. Indeed, I observed a significant association between male gender and incomplete disclosure of identifiers, which led to an excess of males being excluded from the 'whole island' network. I can only speculate about why this may have been the case: Were the identities of male PWID being

deliberately hidden because they were dealers? Or were they being under-reported simply because males were more likely to go by a nickname, so fewer survey participants actually knew their initials?

Despite these challenges in the 'whole island' network, I was able to include 110 nodes that did not actually participate in the survey. However, I was entirely dependent on the accuracy of peer-reporting to create their NAGH code, (for a NAGH code definition see Chapter 5) which defined their existence and their attributes. This had the benefit of maximising the completeness of the network structure. For example, if two unconnected participants described the same non-participant *alter* in their triangulation matrices, they became indirectly connected when the network was assimilated. However, it came with a cost in terms of the amount of available attribute data for each node and its accuracy.

It is therefore the case that in this network there are several potential sources of missing or inaccurate data. In addition to the excessive exclusion of male PWID from the network, closely related HCV RNA sequences were not always mapped to a recorded injecting relationship, potentially indicating a missing tie. Such inaccuracies are important because statistical network measures are sensitive to missing data[201,226]. However, I attempted to limit the impact of this by using a test for centrality (*in-degree* centrality), which is robust in the presence of missing nodes[201]. In addition, I assumed all injecting relationships were reciprocal, which is a recognised way of dealing with missing relationship data[203]. Furthermore, I used RDS to recruit participants to the social network survey. By design, this preferentially recruited central nodes which mitigates the impact of missing nodes that has been reported elsewhere[227].

7.8 Conclusion

Despite the limitations imposed by missing data, PWID on the IOW are densely connected to one another via social and injecting relationships. HCV status is widely shared within this network and HCV infection is related to local network factors, rather than an individuals' actual position within the network. There is evidence that HCV has been transmitted through the existing relationships within the injecting network and that genotype 3a has been transmitted intrinsically on the IOW.

These findings will be considered further alongside the other quantitative results and the qualitative exploration of the PWID network in the General Discussion (Chapter 10).

8. Estimating the total population size of people who inject drugs on the Isle of Wight

8.1 Chapter overview

This chapter reports an estimate for the total population size of people who inject drugs (PWID) living on the Isle of Wight (IOW). This is important because when combined with the estimated population prevalence for Hepatitis C (HCV) in PWID, it is possible to calculate the total number of cases and therefore address the following objective of this thesis:

To determine the total number of HCV cases among PWID living on the IOW

The final estimate is a mean value from four estimates. Three rely on data capture-recapture (C-RC) and the fourth is based on the recruitment pattern in the respondent driven sampling (RDS) described in Chapter 6.

8.2 Method

The methods used to calculate the population size estimates are described in Chapter 5.

8.3 Data capture recapture estimates

The distribution of individuals among the C-RC populations used for the C-RC estimates is displayed in contingency Tables 8-1. In each table the capture population are the participants from the HCV bio-behavioural survey but the recapture population varied. In A, the recapture population were individuals described in the social network survey; in B, they are PWID picking up opiate substitution therapy (OST) from community pharmacies at the time of the survey; and in C, they are PWID undertaking a dry-blood spot test (DBS) test for HCV at a community pharmacy in the 12 months prior to the survey.

The capture population was adjusted in the OST estimate to include only participants with a history of using opiates, and the size of the DBS recapture population was adjusted to account for under-reporting of injecting drug use at the time of undertaking the test. The distribution of 1000 parametric bootstrapped estimates for each recapture population are displayed in Figure 8-1.

Table 8-1 Distribution of PWID in capture and recapture population where recapture was defined as the *ego*-network of survey participants (A), currently picking up OST from a community pharmacy (B) and having a DBS test for HCV at a community pharmacy in the 12 months prior to the survey (C).

A	***Ego* network *alter* (Recapture)**		Total captured
Captured	Included	Not included	
Included	42	27	69
Not included	110	nk	
Total recaptured	152		

B	**Current OST (Recapture)**		Total captured
Captured	Included	Not included	
Included	41	23	64[1]
Not included	157	nk	
Total recaptured	198		

C	**DBS last 12 months (Recapture)**		Total captured
Captured	Included	Not included	
Included	17	52	69
Not included	58	nk	
Total recaptured	75[2]		

[1]Number adjusted to include only those with a history of opiate use. [2]Number adjusted for under reporting of injecting drug use at time of under taking DBS test. nk – not known; DBS – dry-blood spot test, OST – opiate substitution therapy.

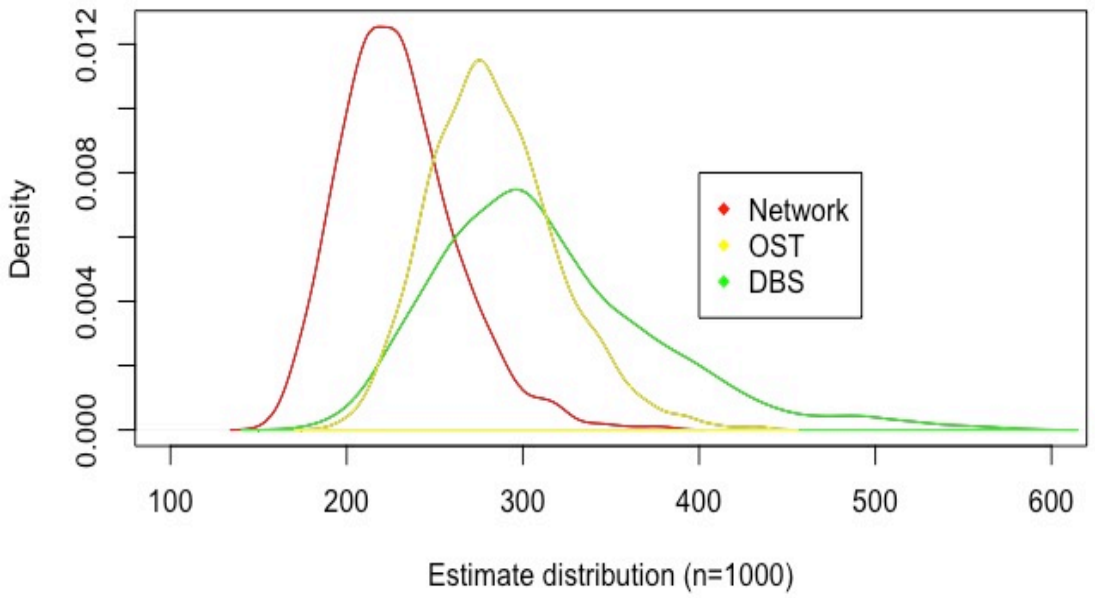

Figure 8-1 Kernel plots showing 1000 bootstrap estimates for the size of the PWID population on the IOW in network based capture-recapture (Network) and two service multiplier methods (OST and DBS). For each estimate the capture population were the bio-behavioural survey participants.

8.4 Overall population size estimate

The estimated population size from the Handcock estimator was 184 (95% CI 69-455). To make this calculation a 'prior' estimate was needed. The value for this was based on the estimated PWID population size that predated this thesis[228].

The mean value of the four estimates was 262 (Table 8-2).

Table 8-2 A summary of population size estimates for PWID on the IOW.

		Estimate	95% CI
Network based C-RC		250	175-308
Service multiplier C-RC	OST	309	223-366
	DBS	306	219-475
Handcock estimate[1]		184	69-455
Mean population size (SD)		262 (59)	

[1]Selected prior from published previous estimate[228]

PWID – people who inject drugs; IOW – Isle of Wight; C-RC – capture – recapture; OST – opiate substitution therapy; DBS – dry-blood spot test; SD – standard deviation.

8.5 Discussion

In this chapter I have presented an estimate for the total population size of PWID on the IOW. At 262 this figure is well below existing estimates[228] and importantly, is well below that used in the Public health England (PHE) model to calculate the total number of cases of HCV on the IOW[86].

There are possible explanations for this discrepancy. The estimate in the PHE model is based on a C-RC analysis by King *et al.*, which used service data from 2005-2006, and included data sets from the probation and prison services[229]. It is possible that since the collection of this data that the PWID population size, in keeping with the national trend[230], has reduced. It is also possible that due to the large IOW based prison population, a significant number of non-residents in the prison services were included.

My estimate is potentially more accurate as it specifically excludes PWID within the prison service; it was conducted in 2016, and is based on a cross-sectional survey of the target population. However, it is also subject to potential bias and limitations.

In each C-RC estimate I incorporated just two data sets, which gives less accurate estimates than three sample C-RC[231,232] and I did not increase the validity of the estimate by comparing it against an external source of evidence, such as the number of drug related deaths on the IOW[233]. Furthermore I simply averaged the estimates to give a mean, which attributes equal weight to each despite varying risks of bias[232].

I could have also used more estimates to give greater triangulation to my results. For example, Sulberidze *et al.* combined the results of six methods to estimate the size of the men who have sex with men population in Tbilisi, Georgia[234]. Of these six methods, the 'unique object multiplier" could have been applied in this study. This is where, in advance of a survey, unique objects are circulated within the target population and the population size calculated from the number of unique objects circulated and the proportion of survey participants receiving an object.

More specifically, the network based C-RC and Handcock methods I used both estimate the size of the PWID social network and therefore are likely to underestimate the total population size by excluding isolated PWID. Additionally, in network-based C-RC an individuals' likelihood of being recaptured is not independent of their likelihood of being captured. Independence between the capture and recapture populations is a fundamental assumption of C-RC and any violation is likely to reduce the size of the estimate[189,191].

However, it is likely that the effect of this underestimation is countered by the service multiplier estimates. The OST estimate is likely to have included persons no longer injecting drugs but who are still accessing substitution therapy and the DBS estimate may have included persons injecting anabolic steroids.

8.6 Conclusion

The PWID population size estimate presented in this chapter indicates that the number of PWID living on the IOW may be considerably lower than indicated by previous estimates.

9. Individual based model of Hepatitis C transmission and treatment within the 'injecting network'

9.1 Chapter overview

Chapter 9 reports the results of an individual based model (IBM) of Hepatitis C (HCV) transmission and treatment through the injecting network of people who inject drugs (PWID) on the Isle of Wight (IOW) which was described in Chapter 7.

In this chapter I address the following research objective:

Demonstrate how the social network of PWID can be utilised in a local elimination strategy for HCV

As described in Chapter 5, the model was built with expert input from Dr. Rudabeh Maskarian, a post-doctoral research fellow at the University of Southampton. Where the following text refers to 'we', it is because we conducted that part of the analysis together.

9.2 Method summary

Chapter 5 gives a detailed description of the method used to generate the results presented in this chapter.

9.3 Results

The model ran through five treatment scenarios to establish an optimal treatment strategy within the network. In each, there were two primary outcomes: 1) The total number of new chronic infections at 12 months, and 2) The total number of re-infected nodes at 12 months.

The five scenarios are summarised in Chapter 5, Section 5.6.6.5. In Scenario 0, no one within the network received treatment and therefore it simply modelled the transmission of HCV through the network over 12 months. Scenario 1 modelled the random treatment of HCV positive nodes within the network. In Scenarios 2, 3 and 4 treatment was focused on persons currently injecting drugs with at least one injecting partnership. In scenario 2, treatment was randomly assigned to these individuals. In scenario 3, they were selected in accordance with their injecting *degree,* (those with the highest injecting *degree* being treated first) and in scenario 4, they were selected in accordance with their social network *in-degree,* (again, those with the highest social network *in-degree* being treated first).

Due to the random allocation of the injecting frequency among those PWID currently injecting drugs, the random selection of who receives treatment (in scenarios 1 and 2), and the random allocation of HCV to 12 of the 52 nodes with an undetermined HCV status, there was inherent variability within the model. Accordingly, each scenario was run 50 times until the outcome value stabilised.

Figure 9-1 shows the number of new cases of chronic HCV at 12 months in each scenario. Prioritising treatment to those with the greatest injecting *degree* was significantly more effective at preventing new chronic infections of HCV than treating at random (median new cases after 12 months 9.56 vs. 6.58, $p<0.01$), as was treating those PWID with the greatest social *in-degree* (median new cases after 12 months 9.56 vs. 7.84, $p=0.011$). In all scenarios, less than one person was re-infected and developed chronic infection after receiving treatment. Therefore there was no significant difference between the scenarios for this outcome.

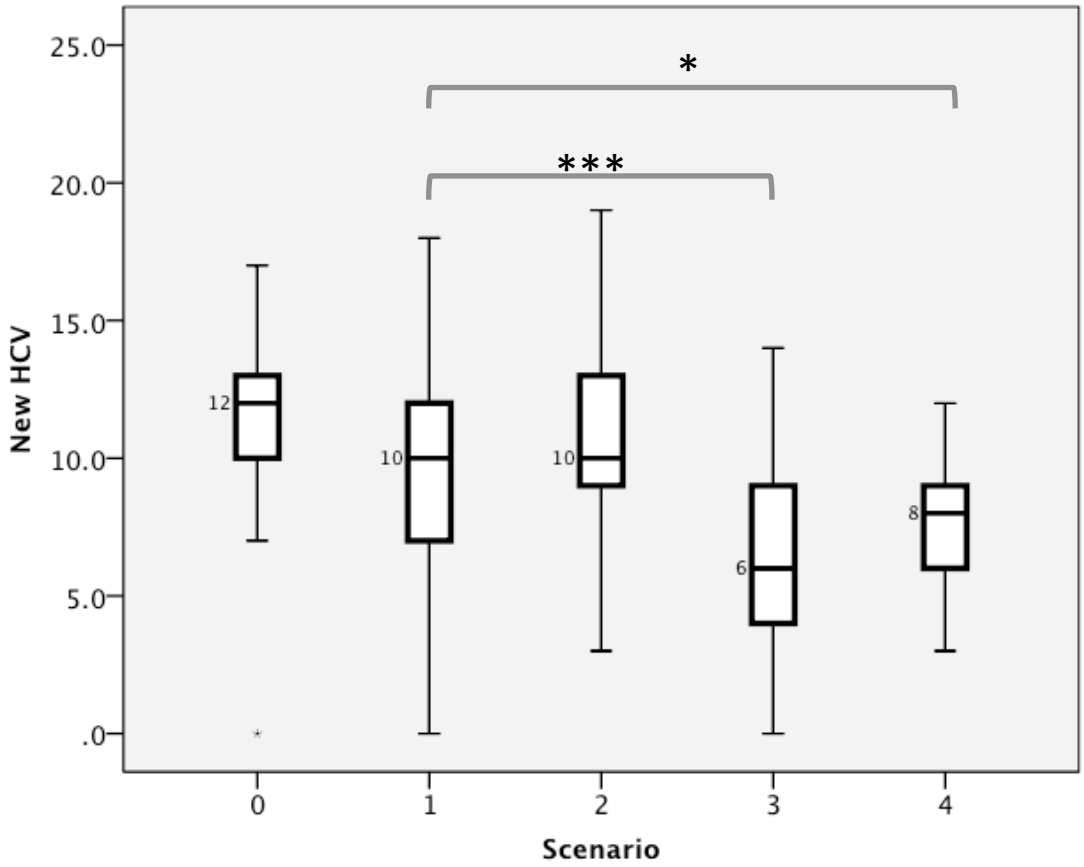

Figure 9-1 Box and whisker plot showing the distribution of new chronic infections of HCV after 12 months through 50 repetitions of each scenario. The ends of the boxes are the upper and lower quartiles, a horizontal line inside the box marks the median value, and the whiskers extend to the highest and lowest observations (***p<0.001, *p<0.05).

9.3.1 Sensitivity analysis

We tested the sensitivity of the outcomes to variations in four key transition probabilities used in the model, including: the frequency of equipment sharing, the treatment efficacy, injecting frequency, and the likelihood of spontaneous resolution (see Chapter 5, Table 5-6). These were adjusted separately in accordance with the 95% confidence intervals or a pre-defined value where these were unavailable (see Table 5-6, Chapter 5). The model was most sensitive to variation in the injecting frequency, and when this was reduced by 20%, the significant difference between scenario 1 and 4 was lost (2.6 vs. 2.4, p=0.441). However, for all other variations from baseline, scenarios 3 and 4 continued to be significantly associated with reduced

transmission of HCV. Figures 9-3 and 9-4 show how transmission changed with variation in the transmission probability associated with equipment sharing.

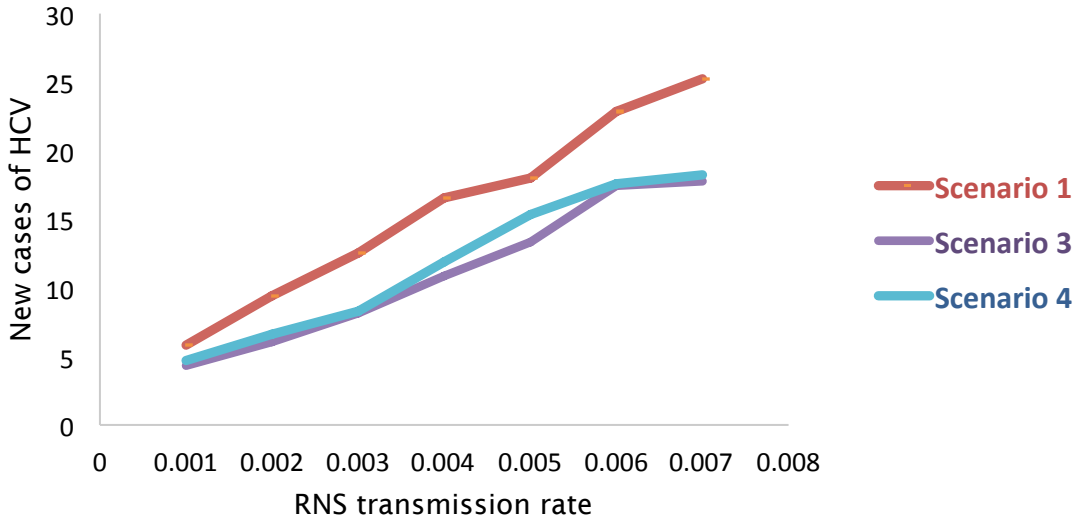

Figure 9-2 The number of new chronic HCV infections after 12 months, with variation in the transmission probability associated with receptive needle sharing. HCV – Hepatitis C; RNS – receptive needle sharing.

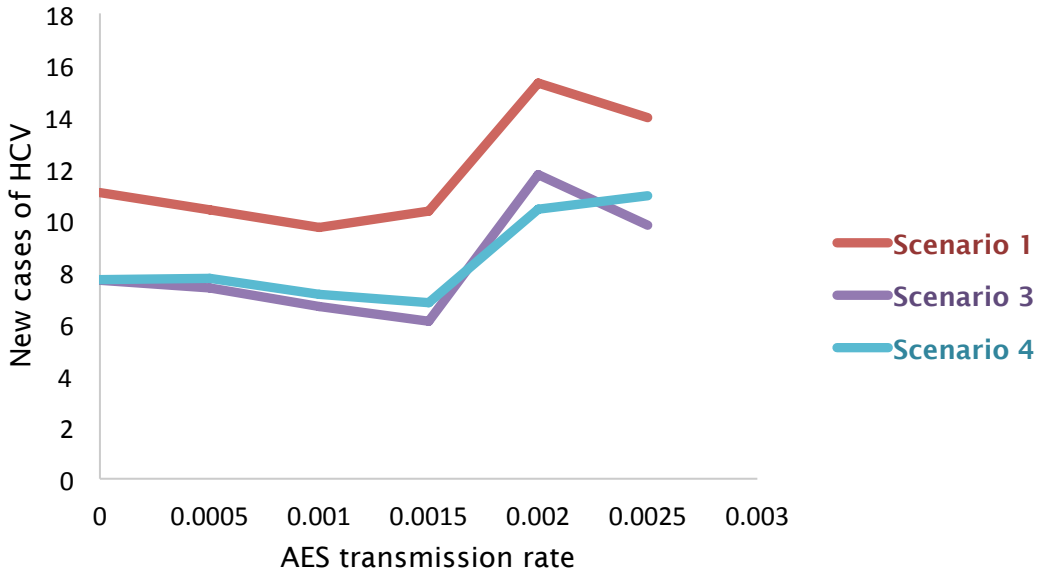

Figure 9-3 The number of new chronic HCV infections after 12 months, with variation in the transmission probability associated with auxiliary equipment sharing. HCV – Hepatitis C; AES – ancillary equipment sharing.

9.4 Discussion

'Treatment as prevention' (TAP) for HCV in PWID has been described[235], and its potential effectiveness has been the subject of modelling studies. To explore the effectiveness of such an approach on the IOW, I constructed a stochastic IBM that incorporated the real-world injecting partnerships seen in the injecting partners network, alongside attribute data from the bio-behavioural and social network surveys.

The model showed that after 12 months, treating the most well connected PWID (those with the highest 'injecting *degree*') was superior at preventing new chronic HCV infection, when compared to treating PWID at random. I also showed that treating PWID with the highest social *in-degree* significantly reduced viral transmission.

There is limited real-world evidence indicating that TAP in PWID works. The existing literature primarily comprises compartmental models that predict its potential effectiveness[42,69]. However, these are not based on empirical networks of PWID and therefore include assumptions around potential transmission relationships within the population. An exception is the study of Rolls *et al.* (Melbourne, Australia), which to my knowledge is the only other study to have modelled HCV transmission and treatment in an empirically grounded network model. They demonstrated that reinfection was the main source of new infections and therefore, treating positive individuals around the treated person, in a so-called 'ring' strategy, was the most effective approach to TAP. In contrast to my findings, they showed that prioritising treatment to the most well-connected PWID was no more effective than treating at random[236].

This difference is striking and potentially very important. If my findings are correct, then it is possible the relative importance of reinfection in a network of PWID have been over-estimated. The reason for the contrast with our findings can probably be attributed to differences in empirical network structure within each model, with my network being very cohesive and the

Melbourne network more dispersed. This is considered further in the General discussion (Chapter 10).

Some of the limitations and implications of missing data in the empirical network used in this model have been discussed in Chapter 7. It is possible missing network data affected the results presented here.

In the model, the only way a node in the network could become infected was if they were connected via an injecting partnership to an infected node. In reality, my network would have had 'permeable' boundaries where HCV could be imported into the network via other types of relationships such as sexual contact or via injecting partnerships with PWID in other communities.

Roll's *et al.* accounted for 'missing' routes of transmission by including an 'importation rate', which is the likelihood a node will become infected from outside the empirical network[226]. I did not include an 'importation rate' for three reasons: 1) the likelihood I missed an important node was low because I had a comparatively high sampling fraction, 2) I reported a comparatively low background prevalence of HCV, and 3) by using RDS, I was less likely to have missed important central nodes.

Further limitations apply specifically to the model specifications. I limited the time-horizon of the IBM to just 12 months because of the unknown network dynamics, such as the turnover of injecting partnerships through time, and the numbers of PWID joining and leaving the network. This is consistent with Roll's *et al.* who modelled transmission over 12 months, but other studies have looked at a longer time-horizon by estimating an 'initiation rate' and 'cessation rate' of injecting drug use[58,237].

9.5 Conclusion

I show that engaging well connected PWID with treatment on the IOW would be an effective measure to prevent future disease transmission. I also highlight the need for further research on PWID injecting network structure, as this may have an impact on the success of similar interventions elsewhere.

10. General discussion

10.1 Overview

The work in this thesis has taken place against a backdrop of profound change in the provision of Hepatitis C (HCV) care. At a global level this has involved the development, marketing and widespread use of almost 100% effective, direct-acting anti-viral therapies for HCV[64,215]. The availability of these drugs has prompted the development of a global HCV elimination strategy. Specifically in people who inject drugs (PWID), it has prompted a frame-shift in the way HCV treatment can be delivered[67].

At a local level on the Isle of Wight (IOW), these changes prompted a service redesign. This included the local provision of HCV treatment from October 2015, and the intensive case finding initiative to identify the estimated 'Missing 200' cases of HCV described in Chapter 1[88]. However, during the early stages of this initiative there were indications that the number of missing cases on the IOW may in fact be lower than was first thought. This suspicion, the emerging HCV elimination agenda, and the perceived feasibility with which elimination could be achieved in the isolated population living on the IOW, led to the research questions of this thesis:

1) How many individuals with HCV live on the IOW?
2) How can the social network connecting PWID on the IOW be utilised in a local HCV elimination strategy?

To address these questions I have presented a pragmatic mixed method study. This has re-defined the number of PWID with HCV on the IOW, made a qualitative and quantitative assessment of the social and injecting network between PWID, and demonstrated the potential impact of a network based 'treatment as prevention' (TAP) strategy for HCV. In so doing, I hope to have presented the social, genetic and epidemiological data necessary to

understand the risk environment for HCV on the IOW, and guide a feasible elimination strategy.

According to Tim Rhodes, writing in 2009, a risk environment is:

'A space whether - social or physical - in which a variety of factors interact to increase the risk of harm occurring'[238].

By reporting the epidemiology of HCV and contextualising this within the injecting network connecting PWID I have described and understand the risk environment for HCV transmission on the IOW. The work in this thesis has therefore become part of a wider 'paradigm shift' in public health towards understanding reciprocal relationships that propagate harm, and is away from the more traditional focus on individual risks. Described by Rhodes as 'an obsession with risk factorology'[238].

Understanding the risk environment, and specifically social networks, has led to benefits in HIV prevention. For example, consider the network mobilisation, including the distribution of bleach, condoms and clean injecting equipment, that occurred to prevent the transmission of HIV in the USA[50]. However, this has not been the case in HCV[239]. The reasons for this aren't clear, but its perceived ubiquity and relative low importance to PWID (compared to HIV), are likely to be contributory factors[239].

With the recent changes in HCV treatment it is possible that utilising the social network, rather than facilitating conventional harm reduction initiatives, could be key to facilitate engagement with treatment. As I have shown such an approach could not only reduce personal harm but also reduce risk in the wider environment.

The focus of the General Discussion is to draw on qualitative and quantitative findings of this thesis and use these alongside the existing literature to draw final conclusions.

10.2 A revised estimate for the disease burden of Hepatitis C

Both the HCV prevalence estimate in PWID and the total population size for PWID were lower than previous estimates. Accordingly, the number of estimated cases of HCV on the IOW reduced when the new estimates were incorporated into the Public Health England (PHE) template[86] (Table 10-1).

Risk Group	Group size	Revised estimate	HCV Prevalence in group (%)	Revised prevalence (%)	Cases	Revised cases
PWID	474	262	39	29	181	76
Ex-PWID	311		24		75	
General pop.	130,000		0.006		65	
Non-white ethnic.	400		0.01		2	
			Total		323	**218**

Table 10-1 The change in estimated disease burden of HCV on the IOW, with the incorporation of a new HCV population prevalence and PWID population size estimate.

The previous estimate for HCV prevalence was based on the cyclical unlinked anonymous survey of PWID, known as the 'UAM' survey[68]. This survey samples 'clients' from a broadly representative sample of drug treatment and harm reduction settings across England. Data from these locations is then extrapolated to areas that do not participate in the survey by considering the number of people in drug treatment, crime levels, and the ages of those attending harm reduction settings. The estimate for the IOW was an extrapolation and had some of the broadest 80% credible intervals[240]. My estimate is at the lower limit of these intervals. If this was the case in other rural areas then it is likely that the estimated overall burden of HCV in the UK would be an overestimate. This would have important implications for National Health Service logistical and financial planning.

The limitations of my PWID population size and HCV prevalence estimates are discussed in Chapters 8 and 6 respectively. However, as indicated by Table 10-1, it is important to consider that I have made no amendment to the estimated number of ex-PWID with HCV - also a key determinant of overall disease prevalence.

An ex-PWID is defined as someone who has not injected for 12 months[241]. In reality this is a very diverse group, which would include individuals continuing to access harm reduction services and individuals who have not injected drugs for decades. The conduct of a representative survey of ex-PWID would therefore be a very difficult task and this is reflected in the existing estimates for ex-PWID population size which are based on unrepresentative data[241].

My qualitative findings and specifically the subtheme '*Keep the wolves away'* indicated that part of the transition to becoming an ex-PWID is the act of distancing or entirely cutting oneself away from the social network. This is important because it means ex-PWID are unlikely to be identified in respondent driven sampling (RDS). A survey of ex-PWID on the IOW would therefore need an alternative sampling strategy, which was beyond the scope of this thesis.

The epidemiologic investigation and clinical management of ex-PWID in an HCV elimination strategy should be the subject of a further study. However, I believe the academic and clinical focus of this thesis is well placed, as the investigation and treatment of current PWID is most important to achieve viral elimination.

10.2.1 Why is the number of cases of Hepatitis C on the Isle of Wight lower than expected?

The reduced estimated number of HCV cases on the IOW reported here could be a reflection of the temporal changes in injecting drug use; characterised by greater engagement with harm reduction[68], falling total numbers of PWID[230], and gradually increasing engagement with HCV treatment. It is worth noting that in the latest PHE report on HCV in the UK, the stated estimate for the disease burden in England was based on primary data collected in 2005[242].

There are also other possible explanations. The low prevalence could be an indication of heterogeneity in the behaviour of PWID between urban and comparatively under-researched rural populations. It is also possible that in being an isolated population the IOW has unique environmental factors that have contributed. By considering the qualitative and quantitative findings together it is possible to recognise some potentially protective factors.

Engagement with harm reduction has been increasing across the UK[68]. However, I report widespread coverage of opiate substitution therapy (OST) in opiate users, which was higher than a mainland study[114], and widespread utilisation of needle exchange services. The qualitative findings gave indications about why engagement with OST might be so widespread. It is possible the so-called 'dry spells' forced heroin users to engage with OST in order to bridge them through periods of interrupted heroin supply.

A further possible explanation for the low prevalence of HCV in PWID on the IOW, is the unique island based injecting environment and specifically the injecting network structure. Narratives in Chapter 4 consistently corroborated the structure of the cohesive network described in Chapter 7 and indicated that it may be more cohesive than mainland networks.

A study tracking a syphilis outbreak in a network of sexual partners demonstrated that transmission was proportional to network cohesion[243]. However, although one might assume with would also be the case with blood-borne viruses there is actually a lack of literature exploring how network structure affects transmission HIV or HCV. Indeed, in this network, and elsewhere, HCV was not associated with a node's overall position in the network, e.g. those in the centre were not significantly more likely to have HCV[43]. Instead, HCV was significantly associated with features of the node's immediate injecting environment, including the attributes of injecting partners[43].

It is possible that the network structure on the IOW actually protected PWID from HCV. A potential protective effect of the network cohesion was highlighted in Chapter 4 by the contrasting experiences of *Jane* and *John. Jane* travelled to the mainland on behalf of a group of PWID to purchase drugs, and therefore prevented the transient exposure of her associates to another network. Whereas *John*, by not being integrated into the network, was

effectively ‘forced’ into a high-risk transient liaison with a complete stranger at a ferry terminal.

Personal network stability has been shown to be protective against HIV transmission[244]. There were indications in Chapter 4 that relationships within the injecting network were more stable than in mainland cities. It is possible that knowing each other better facilitated the accurate peer HCV status awareness I observed. This awareness could in itself lead to altruistic protective behaviours between PWID, with positive persons protecting their injecting partners and the injecting partners taking more care.

10.3 Can the social network between PWID be utilised in an effective elimination strategy?

In addition to the network cohesion being potentially protective from HCV, I have also demonstrated that it may facilitate its elimination via TAP. In contrast to a study by Rolls *et al.*[236], I showed that treating well connected PWID could reduce the number of new HCV infections. Furthermore, the high peer HCV status awareness that I observed would make it practically possible to engage well-connected PWID with treatment services via a 'treat you friends' approach.

However, when planning the implementation of such a strategy it is important to consider more isolated PWID who are less likely to be engaged through a network connection. Based on the qualitative results in Chapter 4, these may include PWID in recovery, those with '*two lives'* (and therefore potentially more to lose from being identified as injecting drugs), and those injecting substances such as anabolic steroids.

The World Health Organisation (WHO) has set a target for the global elimination of HCV by 2030[67]. It is therefore important to consider to what extent the findings reported here can be applied to other populations.

In many respects the IOW is not a typical UK population. It is geographically isolated, older, and ethnically less diverse than the UK average[83]. Additionally, the UK is not necessarily representative of HCV affected communities worldwide, in terms of viral transmission, viral genotype and health care infrastructure. However, what is important when considering the application of these findings elsewhere is the typicality of the PWID network, PWID characteristics and the behaviours of the individuals within that network.

I have already highlighted how PWID on the IOW may differ from mainland UK populations in terms of HCV prevalence and engagement with harm reduction. Additionally, the experiences of PWID on the IOW consistently highlighted contrasts between the cohesion of the IOW network and those on the mainland, indicating that the IOW might be unusual.

The importance of this potential contrast in network structure is apparent when the empirical network used in my individual based model (IBM), is compared with the network used by Roll's *et al.*[236]

The Melbourne network is less cohesive and more linear, and therefore the main source of new infection was re-infection from an infected partner rather than primary infection. However, Roll's *et al.* did not use RDS to recruit PWID to their network study and therefore did not, by design, recruit from the central part of the network[*]. In addition, the Roll's network was a proportionally smaller sample of the likely total population size of PWID and therefore the potential for missing nodes and ties was probably higher[236].

It is therefore possible that the Melbourne network was just a fraction of a much larger, more cohesive structure similar to that presented here. However, this is speculation that needs confirmation. Firstly, I should conduct a sensitivity analysis within my model to test the impact of altering the network structure on HCV incidence in each treatment scenario. Secondly, empirical data should be sought that gives a representation of network structure in urban areas (see Section 10.5). Without completing these steps it is difficult to conclude that my findings have broader implications for HCV elimination.

[*] In RDS the probability of being identified to researchers is proportional to social network *degree*. Therefore, if this sampling strategy is used to recruit for a social network survey the more central denser part of the network is sampled.

10.4 Overall strengths and limitations of this thesis

I have discussed strengths and limitations relating to each specific method used in this thesis at the end of each corresponding results chapter. However, the strengths and limitations of the overall study design and conduct warrant further discussion here.

The use of mixed methods is a key strength of this thesis that delivered two benefits. Firstly, the qualitative enquiry into the feasibility of RDS maximised the representativeness and success of recruitment to the bio-behavioural and social network surveys. Secondly, the qualitative exploration of the social network connecting PWID on the IOW gave me an understanding of what the quantitative network, described in Chapter 7, is like from the inside, through the perspective of the PWID it connects. This conveys a degree of confidence that the quantitative representation is broadly accurate, as well as giving interesting insights about why it has the structure it does, how it compares to other networks and how it has changed over time.

However, the methods could have been combined differently. The overall research design was a sequential, mixed methods social network analysis and therefore the qualitative methods preceded the quantitative. Alternative study designs include, implementing the methods in parallel or, conducting further qualitative interviews with injecting network members after the survey was complete (Figure 10-1)[148]. This would have allowed me to review the injecting network representation with PWID and ask: How do you see yourself in this network? Why are you on the fringes/in the centre of this network? Or, how do you think this represents what you know about the relationships between PWID on the IOW?

The conduct of semi-structured interviews after the RDS, would have been a further opportunity to understand the sampling process. The secondary incentive survey (Appendix 11) collected data about recruitment, e.g. reasons given for coupon refusal, but did not make an in depth qualitative assessment by addressing questions like: why did you recruit the people you did?

Furthermore, these interviews could have provided an opportunity to assess the ethical impact of the RDS process.

Large-scale HIV surveillance surveys in the United States have, in some instances, incorporated ethnographic fieldwork to observe the RDS process[221]. Ethnography is defined as the study of people and communities in naturally occurring environments[166]. It has been described as the 'synergising method' that forms a 'thick description of social phenomena'[245]. As a qualitative method it has been used to gain insights about the conduct of harm reduction for PWID[246], and social network surveys have used it to confirm the existence of relationships between participants. Ethnography, as described by Maher, where the researcher is present for the purchase, preparation and administration of illegal drugs, was beyond the scope, resources and safety requirements of this thesis[246]. However, as the results presented here rely almost entirely on accurate reporting by the participants, ethnography could have further validated the RDS process and added additional depth to the understanding of the structure of the injecting network of PWID. If the study was to be repeated in a larger urban area an external assessment by a researcher of the social network connections and sampling process would be especially valuable (Figure 10-1).

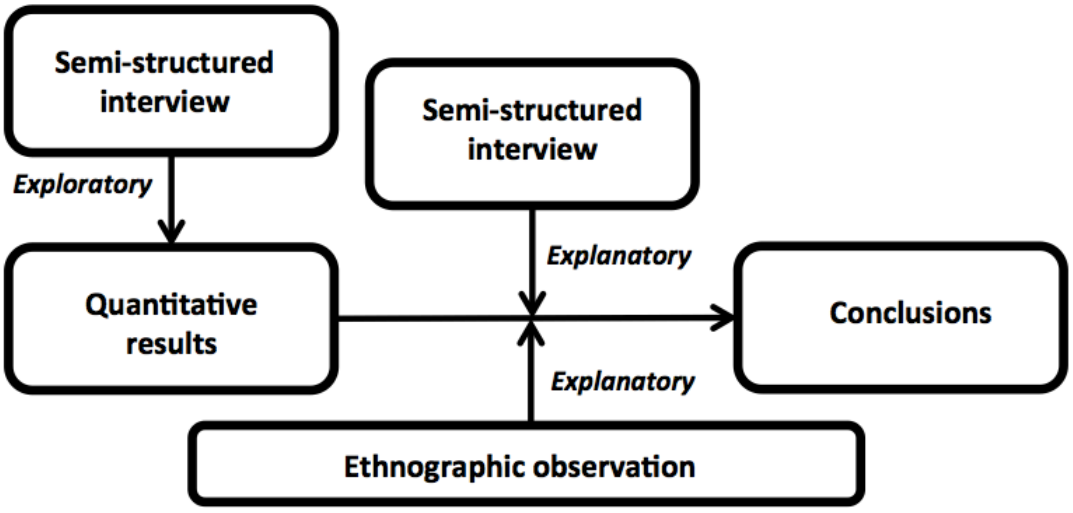

Figure 10-1 An alternative mixed methods research design. Repeating qualitative interviews and conducting ethnographic observation could have led to interesting insights about network structure and the RDS process.

10.5 Further work and research questions

Research question 1: What is the phylogenetic history of Hepatitis C on the IOW?

The injecting network described in Chapter 7 was partly validated as the actual HCV transmission network by the clustering of some phylogenetic sequences that matched observed injecting relationships. More broadly, the phylogenetic analysis gave an indication that genotype 3a disease had been transmitted between PWID on the IOW. However, the phylogenetic sequences could also be used to describe the epidemic history of HCV on the IOW. This has been done elsewhere and has informed our understanding of how HCV spread from West Africa, and more recently how it spread through injecting drug use[15,25]. The epidemic history of HCV can be calculated from the genetic distance of sequences and a known rate of genetic mutation[28]. When modelling the transmission of HCV this would be useful as it could give an indication of the 'importation rate' of the virus into a population. This could therefore facilitate more accurate predictions (Figure 10-2).

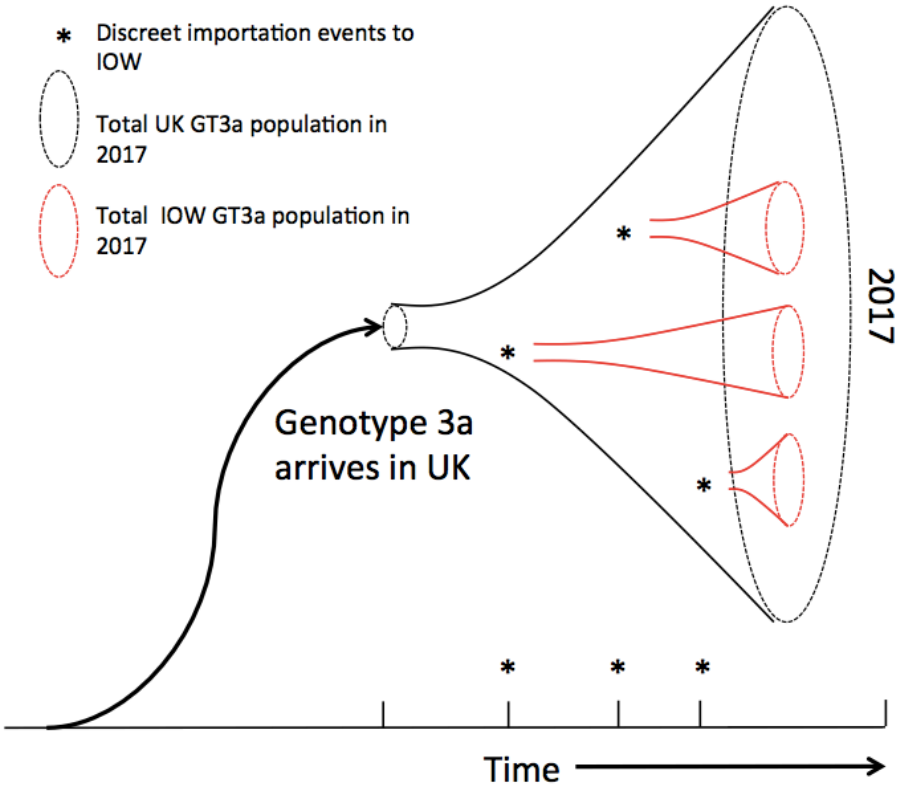

Figure 10-2 A simplified representation of the possible phylogenetic history of genotype 3a HCV on the IOW in the context of the UK population. The cylinders and cones represent populations of HCV-infected individuals through time (where cones represent the growing population in PWID). Cross-sections (dashed circles) represent the current size of the UK and IOW population. The curved arrow indicates the seeding event into the UK and stars* represent discreet introductions to the IOW. Through phylogenetic analysis it may be possible to work out when these occurred and therefore calculate an importation rate into the IOW. Figure adapted from Pybus *et al.*[15]

Research question 2: Why do some individuals in the network have anti-HCV whilst other do not?

The network I presented in Chapter 7 contained anti-HCV positive nodes, antibody and RNA positive nodes, and PWID without antibody. Whilst it is probable that a small number of antibody negative individuals had acute HCV infection (and therefore have a viraemia without antibody), the majority appear to have never developed antibody against HCV despite, in many cases, having an injecting relationship with positive nodes (Figure 10-3). These individuals have been described elsewhere as exposed-uninfected (EU) PWID. Other authors have highlighted genetic differences between EU and anti-HCV positive persons[247]. However, the wider literature defines EU as a high-risk person without antibody or RNA, but do not necessarily describe more certain exposure via an injecting partnership[247]. In describing an injecting network it is therefore possible to more accurately define a cohort of EU PWID and study reasons for the heterogeneous response to HCV. This could have broad implications for understanding of the human response to viral pathogens.

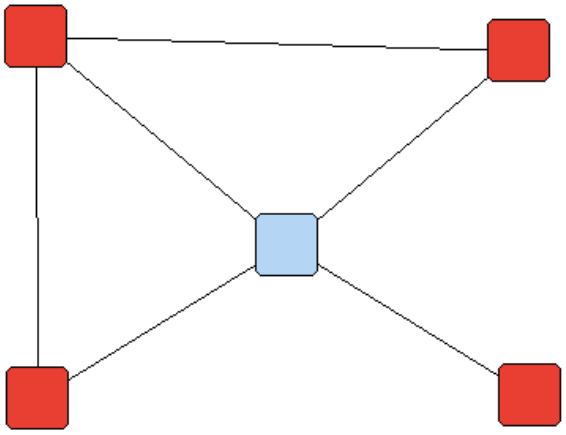

Figure 10-3 The injecting *ego*-network for node 19 from the 'whole Island' injecting network (see Chapter 7). Node 19 (blue) had been injecting for 16 years on the IOW and typically did so with 'many others'. However, despite being surrounded by three anti-HCV positive injecting partners (red nodes) he had never developed antibody against HCV. Is this effective harm reduction, good fortune or are other factors implicated?

Unanswered question 3

What is the structure of urban injecting networks?

The qualitative results indicate that the network cohesion I describe exceeds that seen in nearby mainland networks. However, this remains speculative because I conducted no comparator network survey in an urban area. The contrasting results of the IBM and those of another in an urban population[236], indicate that the network structure of PWID could have important implications for future disease elimination strategies (Figure 10-4). There is a lack of literature describing the structure of urban PWID injecting networks. Additionally, where urban networks have been studied, the sampling strategy and large size of the target population means that any results are affected by missing data[57].

Therefore, there is a strong argument for further research into the structure of urban PWID networks to facilitate more accurate modelling of HCV transmission and treatment. Where possible, future studies should use similar sampling strategies and statistical network measures to enable meaningful comparisons. RDS is a good strategy to be used in future work because by design it preferentially recruits PWID from the centre of injecting networks. It is also well defined and increasingly well validated.

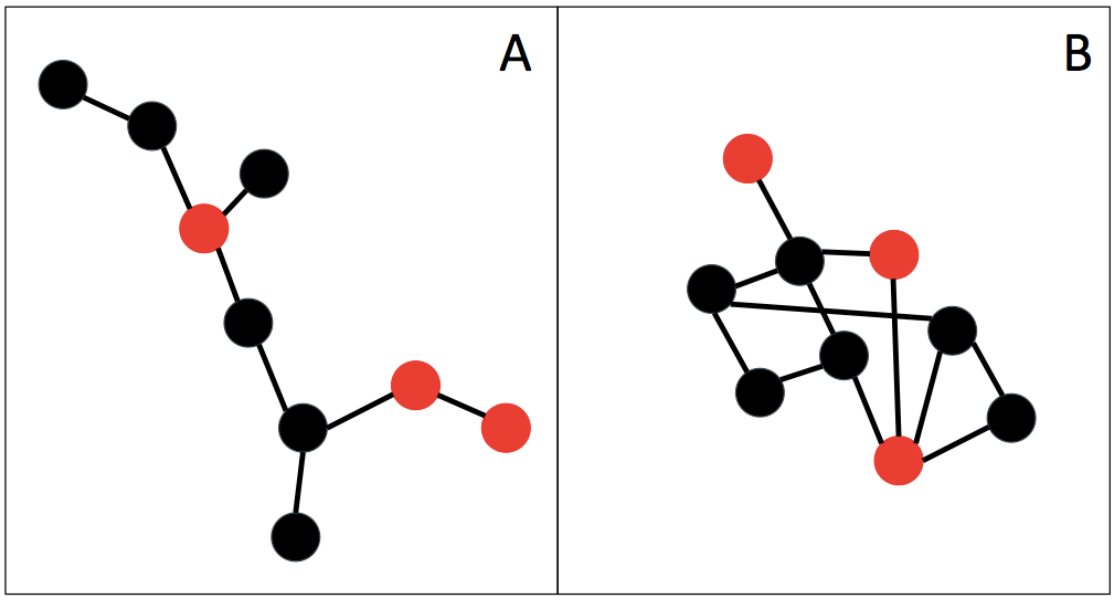

Figure 10-4 Showing a representation of a dispersed (A) and cohesive (B) PWID injecting network structure. Nodes are represented by circles and injecting partnerships by black lines. My results indicate that the transmission of HCV (red nodes) may be dictated by the network structure and that the best treatment strategy may therefore vary. However, there is a lack of research in this area, particularly in urban populations.

10.6 Conclusion

In this thesis I present the first bio-behavioural survey of HCV in a rural population of PWID in the UK. The revised estimate for the total number of HCV cases suggests that it may have been overestimated and it is reasonable to suspect this may also be the case in other rural areas. This has implications for the potential future morbidity from HCV in the UK and the logistical provision of HCV services at a regional and national level.

I also highlight that existing case-finding initiatives in PWID on the IOW are effective but that further efforts need to focus on engaging HCV positive PWID with treatment services. By understanding the injecting network structure connecting PWID and the genetic relatedness of HCV RNA within this population, I demonstrate the potential feasibility and effectiveness of a TAP elimination strategy.

By using mixed methods, I present the most complete representation of an injecting network of PWID in the scientific literature. Importantly, there are potential discrepancies about the best approach to treat HCV in PWID. Therefore more research is needed into injecting network structure and the implications this has on achieving viral elimination.

APPENDICES

A. 1 Research Ethics Committee (REC) approval letter

NHS
Health Research Authority

NRES Committee London - City & East
Bristol Research Ethics Committee Centre
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Level 3, Block B
Lewins Mead
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20 July 2015

Prof Salim Khakoo
Professor of Hepatology
University of Southampton
Department of Hepatology, Level E, South Academic block, University Hospital Southampton
University Hospital Southampton, Tremona Road
Southampton
SO16 6YD

Dear Prof Khakoo

Study title:	**Hepatitis C within a network of people with a history of intravenous drug use living in an isolated UK community**
REC reference:	**15/LO/1076**
Protocol number:	**N/A**
IRAS project ID:	**177753**

The Research Ethics Committee reviewed the above application at the meeting held on 02 July 2015. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Mr Rajat Khullar, nrescommittee.london-cityandeast@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Conditions of the favourable opinion

1. As discussed, advice with regards to HIV/HCV tests should be clarified in the PIS.

2. As discussed at the meeting, instead of access to medical records it should be mentioned that the GP will contacted to confirm the information provided.

3. It should be made clear what will happen to the recorded interviews, where would that be stored and when would that be destroyed.

4. There are a number of grammatical mistakes in the PIS. There are some technical terms and complicated language that may not be understood by lay readers. Information Sheet could be revised to make it simpler and lay reader friendly.

5. It should be made clear in the PIS that when and how the payments will be made.

The favourable opinion is subject to the following conditions being met prior to the start of the study.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Summary of discussion at the meeting

Social or scientific value; scientific design and conduct of the study

The Committee queried about the timing and duration of the study as it can be quite relevant to the location of the study. Mr Buchanan explained that the plan is to do the sample A interviews around autumn this year and sampling survey during summer next year. He added that the end of data collection would be towards end of 2016 and the end of the PhD is around September of 2017. However it is difficult to give exact duration.

The Committee commended Mr Buchanan on very good study design.

Recruitment arrangements and access to health information, and fair participant selection

The Committee noted that the study excludes non- English speakers. Mr Buchanan clarified that 96% of people on the Isle of Wight speak English so majority of population will be included.

Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)

The Committee queried if the person who recommends or gives out the vouchers would know who has participated in the study so the confidentiality could be broken. Mr Buchanan explained that they would know who have been given coupons and if all three decide to take part then they would know exactly who have entered the study. The Committee queried if there is an alternative to this method so the confidentiality of the participants is maintained. Mr Buchanan explained that they have used this method and there were no issues noted.

The Committee queried if all the interviews will be done at homes of the participants and if that would be safe. Mr Buchanan explained that they are interested in the users who inject drugs but have now stopped injecting drugs and the best way to find out about them is through Hepatitis services. The reason to offer interviews at their homes is because there is no other more suitable place available to approach this group. Mr Buchanan confirmed that they will follow the lone worker policy from the University.

The Committee queried if the participants will be asked to do dry blood spot tests for HCV or HIV. Mr Buchanan explained that the NICE guidelines specify that if they approach someone

who bene taking drugs they should be advised to take a HCV and HIV test and therefore he will advise them to take the tests. This is not a part of the study, no data will be collected and results will not be fed back into the study. The Committee acknowledged that it is routine advice however this should be clarified in the PIS.

The Committee noted that the Consent Form ask for permission to access medical records to the participants. It is however not clear why medical records would need to be accessed. Mr Buchanan explained that he would need access to medical records to corroborate if they have or do not have HIV/HCV. The Committee queried if this information cannot be checked through the GP because “access to medical records” is quite a vague term. Mr Buchanan agreed that he could change that to say that he will contact their GP.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

The Committee expressed concerns that by agreeing to take part in the study and providing information through questionnaires, the participants will be admitting that they are drug users which raises issues related to confidentiality of information in a research study. Mr Buchanan replied that he is aware of this issue and the success of the study is mainly based on trust between the participants and the research team. He added that they have done similar study previously and participants have been able to provide confidential information as they were able to trust and there were no issues.

Informed consent process and the adequacy and completeness of participant information

The Committee noted that group A will have interviews recorded but group B will not. This has not been explained very well in the application and the PIS. It should also be made clear what will happen to the recorded interview, where would that be stored and when would that be destroyed. Mr Buchanan agreed to provide the same.

The Committee noted a number of grammatical mistakes in the PIS. There are some technical terms and complicated language that may not be understood by lay readers. Information Sheet could be revised to make it simpler and lay reader friendly.

It should be made clear in the PIS that when and how the payments will be made.

Other general comments

The Committee queried how would the people who recommending receive their money. Mr Buchanan clarified that there will be details on the tear off part of the coupon of the centres where they can approach and receive their money.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		23 July 2014
Interview schedules or topic guides for participants [Appendix 6]	1.0	05 May 2015
Letters of invitation to participant [Appendix 1]	1.0	05 May 2015
Non-validated questionnaire [Appendix 11]		05 May 2015
Other [Recruitment coupon]	1.0	05 May 2015
Other [Concentric circle diagram]	1.0	05 May 2015

Other [Concentric circle diagram (2)]	1.0	05 May 2015
Other [Card sorting exercise]	1.0	05 May 2015
Participant consent form [Appendix 9]	1.0	05 May 2015
Participant information sheet (PIS) [Appendix 2]	1.0	05 May 2015
Participant information sheet (PIS) [Appendix 12]	1.0	05 May 2015
Participant information sheet (PIS) [Appendix 3]	1.0	05 May 2015
REC Application Form [REC_Form_19062015]		19 June 2015
Research protocol or project proposal [Protocol]	1.0	05 May 2015
Summary CV for Chief Investigator (CI) [CV]	2.0	01 January 2007
Summary CV for student [CV Student]		
Validated questionnaire [Appendix 10a]	1.0	05 May 2015
Validated questionnaire [Appendix 10b]	1.0	05 May 2015

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

There were no declarations of interest

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

15/LO/1076	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp Dr John Keen
Chair

E-mail: nrescommittee.london-cityandeast@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

"After ethical review – guidance for researchers"

Copy to: *Ms Diana Galpin*
Mrs Alexandra Punter, IOW NHS Trust

A.2 Focus group information sheet & consent form

What is the feasibility and acceptability of respondent driven sampling in PWIDs on the IOW?

STUDY INFORMATION SHEET Version 2.0

We'd like you to take part in this research study. The decision to take part is entirely up to you, but before you decide it is important you understand what might be involved. One of the research team will go through this information sheet with you. Please ask questions about the study if anything seems unclear.

What is the aim of the study?

This study aims to understand more about how people who currently or have previously injected drugs are connected to one another and what would encourage them to participate in research interviews and blood testing. This study will assist further research that aims to build on our understanding of the hepatitis C virus within the local community.

Am I the right person to take part?

To be eligible to take part you must work directly with people who inject drugs (PWIDs) on the IOW at the IRIS centre.

What will it involve?

Participation will involve a focus group with 5 of your colleagues and two researchers. The lead researcher will guide a 60-90minute discussion about PWIDs on the Isle of Wight focusing on how they are socially connected and what factors are likely to engage them in research. A focus group is a facilitated discussion between participants that allows researchers to gain an understanding of the thoughts and feelings of the group towards a particular topic.

The interview will be recorded but your details and any identifiable data on the recording will only be seen or heard by the research team and any data that is later published will be completely anonymous.

You are free to leave the focus group at any time.

Are there any disadvantages to taking part?

The researchers will require 60-90minutes of your time (probably your lunch time). Whilst unlikely focus groups can reveal conflicts between participants, if this occurs the researchers and the centre management will resolve this during and after the group.

Are there any advantages to taking part?

Participation will contribute to our understanding of the research area. However, it is important you are aware that it will not benefit you directly.

During the focus group lunch will be provided for the participants

Who is running this study and how do I contact them if I have further questions?

The study is run by a research team from the University of Southampton. Funding for the study has been provided by CLAHRC (Collaboration in Leadership in Applied Health Research and Care) and GILEAD LTD.

You can contact Ryan Buchanan the lead researcher 9-5pm Monday to Friday on:

07756525806 (research phone)

Thank you for your consideration

Research Consent Form:

Study: An exploration of Hepatitis C within a network of injecting drug users in an isolated UK population

Researchers: Prof Salim Khakoo, Dr Julie Parkes, Dr Leonie Grellier, Dr Ryan Buchanan

IRIS Focus group 21st May

The attendees should each complete the whole of this form themselves

Please ring as appropriate and initial:

Have you read the information sheet? Yes/No

Have you had the opportunity to ask questions and discuss this study? Yes/No

Have you received a satisfactory answer to your questions? Yes/No

Have you received enough information about the study? Yes/No

Who have you spoken to?.....

Do you understand you are free to withdraw from this study:

At any time? Yes/No
Without giving a reason? Yes/No

Do you agree to take part in this study? Yes/No

Signed (Participant)…… Date……..

Name (Block capitals)……..

Signed (Researcher)…… Date……..

Name (Block capitals)……..

A.3 Focus group topic guide

Topic guide

Focus group to assess the acceptability and feasibility of undertaking respondent driven sampling in injecting drug users on the Isle of Wight

Introduce researchers:

We are a research team from University of Southampton

Why are we doing this study?

We do not know what proportion of people who inject drugs (PWIDs) on the Isle of Wight (IOW) are tested for blood borne viruses such as HIV and Hepatitis C. In order to understand this we need to obtain a sample of the PWIDs network which is representative of the rest of the network. To do this we plan to undertake an incentivised sampling strategy.

We are interested in eliciting your thoughts on whether you think this is feasible and acceptable.

Ground rules

Before we start I hope you have read the information sheet and signed the consent form.

- Please respect each other's confidentiality, what is discussed in the room stays in this room
- Please do not talk over each other
- You are free to leave at any point
- Mobiles on silent please
- You are welcome to enjoy lunch whilst we are talking
- We will be tape recording the meeting

Check Consent forms

Tape on

Introductions around the group – reintroduce moderator for purposes of the tape

.....

To start please consider this short fictional case study:

"Martin is 36, he has lived in Newport all his life and works as a part-time chef. He has injected drugs since he was 19 and has had intermittent contact with IRIS over the last 15 years, however, unfortunately he continues to inject drugs."

1. **Does this person sound familiar to those you encounter in everyday practice?** If not, how would you describe a typical IRIS client?

2. **How many friends or associates do you think Martin has who are also PWIDs?**

Probe

How often do you think he mixes with these contacts?

Do you think his contacts know each other?

Do you think he has connections to PWIDs in other parts of the Island?

3. **Can you think of any PWID on the Island who you would describe as socially isolated?**

Probe:

What might define someone from the PWID community who is more likely to be isolated?

Can you think of a good way to access them?

4. **Are you aware of any cliques within the PWIDs on the IOW?**

Probe:

Are you aware of any groups in parts of the Island who have little or no social connectedness with others?

If yes, how would you define these groups?

5. **How much do you think Martin might use social media?**

Probe:

Is he likely to have access to technology like smart phones?

Do you think he is likely to be connected with other injecting drug users via social media?

6. **What do you think is likely to motivate Martin to attend for BBV testing and an interview with a researcher?**

Probe:

How far is he likely to travel for testing?

What time or day of the week do you think would be best?

What incentives might encourage him to attend?

7. **What do you think would be a suitable reward for Martin if he successfully bought a contact who also injects drugs back for an interview and testing?**

8. **What do you think about researchers running incentivised interviews and testing for BBV in PWIDs on IRIS premises?**

Probe:

Do you have any ideas about how this could happen?

Summary and Conclusions

- Brief summary and feedback from moderator
- Any last comments?

A.4 Recruitment letter for qualitative interview

Dear [Mr. / Ms. LAST NAME],

I am writing to tell you about the a research study being conducted by the University of Southampton looking into Hepatitis C on the Isle of Wight. I received permission from your care provider [INSERT NAME] to contact you.

The purpose of this research study is to understand more about the Hepatitis C virus within the Isle of Wight community.

You may be eligible for this study if you have ever injected drugs on the Isle of Wight either recently or many years ago.

It is important to know that this letter is not to tell you to join this study. It is your decision. Your participation is voluntary. Whether or not you participate in this study will have no effect on your relationship with [NAME INSTITUTION] as a client/patient [DELETE AS APPROPRIATE].

If you are interested in learning more, please review the enclosed information, complete the enclosed form, and mail it back to us in the pre-paid envelope. You can also call us on **07756 525806**.

You do not have to respond if you are not interested in this study. If you do not respond, no one will contact you.

Thank you for your time and consideration. We look forward to hearing from you.

Yours sincerely,

Dr. Ryan Buchanan — **Lead Investigator**

Professor Salim Khakoo — **Chief Investigator**

Attachments:

Study information sheet

A.5 Interview information sheet & consent form

Participant INFORMATION SHEET (Sample A)

Study: An exploration of Hepatitis C within a network of injecting drug users in an isolated UK population

Researcher: Prof Salim Khakoo, Dr Julie Parkes, Dr Leonie Grellier, Dr Ryan Buchanan

REC submission No: 17753

University of Southampton study number: 14529

We'd like you to take part in this research study. The decision to take part is entirely up to you, but before you decide it is important you understand what might be involved. One of the research team will go through this information sheet with you. Please ask questions about the study if anything seems unclear.

What is the aim of the study?

This study aims to understand more about Hepatitis C on the Isle of Wight, including how it is passed from person to person and how to offer testing for the virus to those at risk of infection.

Am I the right person to take part?

To be eligible to take part you must have: previously injected drugs; be over 18 years of age; have adequate English language skills to undertake an interview and live on the Isle of Wight.

What will it involve?

Participation will involve an approximately 60 minute audio-recorded face-to-face interview with a researcher. During the interview you will be asked to describe your relationship with friends, family or acquaintances who have also injected drugs, you will not, however, be asked to identify them.

You are free to stop the interview at any time.

Are there any disadvantages to taking part?

Sometimes research interviews may bring up difficult or sensitive issues, whilst this is unlikely, if it does occur the research team will endeavour to help or refer you to those who can after the interview is complete. The only circumstances where something may be disclosed to someone outside the interview room without your explicit consent is if something comes to light which suggests there is a risk of harm to yourself or others.

Are there any advantages to taking part?

Your participation will contribute to our understanding of the research area, however, it will not benefit you directly.

To reimburse for the time you have taken to complete the interview you will be given a £10 supermarket voucher.

Is participation anonymous?

All the study paperwork will be coded with a unique identifier rather than your name. However, the research team will keep a record of your details separately on a paper record that will be kept locked in the University of Southampton.

The interview will be audio recorded but your details and any identifiers on the recording will only be seen or heard by the research team. Any data that is later published will be completely anonymous.

The recording device will be wiped immediately after downloading the interview to a University research computer. The recording will be completely destroyed no later than September 2017.

Who is running this study and how do I contact them if I have further questions?

A research team runs the study from the University of Southampton. Funding for the study has been provided by CLAHRC (Collaboration in Leadership in Applied Health Research and Care) and GILEAD LTD.

The Chief investigator is Salim Khakoo based at the University of Southampton, details are at the top of the page. You can contact Ryan Buchanan who is the lead researcher 9-5pm Monday to Friday on: **07756525806**

In case of complaint please contact: Research integrity and governance team, research governance manager. rgoinfor@soton.ac.uk. 02380595058

Thank you for your consideration

CONSENT FORM (*2.0*)

Title of project: An exploration of Hepatitis C within a network of injecting drug users in an isolated UK population

Researcher: Prof Salim Khakoo, Dr Julie Parkes, Dr Leonie Grellier, Dr Ryan Buchanan

University of Southampton study reference: 14529

REC submission No:

Participant ID:.....

Please initial the box(es) if you agree to the above statements

I confirm that I have read the information sheet dated 21st July 2015 (version 2.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

I give permission for my details to be stored on a paper record in a locked facility at the University of Southampton ☐

I give permission for interview and questionnaire data to be stored at the University of Southampton. ☐

The 'validity' of my consent is conditional upon the University complying with the Data Protection Act and I understand that I can request my details be removed from this database at any time. ☐

I understand that the research team based of the University of Southampton may contact my GP to review tests results for Hepatitis C. ☐

I agree to take part in the above study and agree for my data to be used in the above study. ☐

Signed (Participant)……
Date……..

Name (Block capitals)……

Signed (Researcher)……
Date……..

Name (Block capitals)……

A.6 Interview topic guide

SEMI-STRUCTURED INTERVIEW TOPIC GUIDE

Introduction of the researcher, check the participant has read the information sheet and signed the consent form?

Does the participant have any further questions before the interview starts?

[Tape on]

Introductory questions

What is your experience with injecting drug use on the Isle of Wight?

Probe:

How and why did you start injecting?

Can you describe the kind of places you inject(ed)?

If you have stopped, can you describe how and why?

How would you describe the injecting drug 'scene' on the Island?

Probe:

How does it compare to other communities?

How do you think it has changed over time?

Section 1: Social network discussion

[Work through concentric circle network exercise with the participant]

How are you connected to others with a history of injecting drug use in this community?

Prompt:

How do you know them?

Probe:

Would you describe them as family, friends or contacts?

What areas of IOW are your friends or contacts from?

How many could you contact or find today if needed?

How are these contacts connected to each other?

Prompt

Do they know each other?

Probe

If there are any you would describe as socially isolated what defines them?

How do you know these individuals have also injected drugs?

What, if any, influence did the contacts on the diagram have on you starting to inject drugs?

Section 2(a) – Testing for HCV

What do you know about Hepatitis C?

What is your understanding of how HCV and injecting drugs is linked?

Probe:

What and where are the potential risks?

What is you experience of testing for HCV on the IOW?

Probe

Describe the kind of places you have been tested

If you have been tested what was it that made you get tested?

If you haven't why not?

Describe any advertising for Hepatitis testing you may have seen on the Isle of Wight

Probe

What effect did it have on you?

What, if any, impact has your contacts had on your willingness to get tested for HCV?

Describe how Hepatitis C affects your social (injecting) network?

If one or more of your contacts have HCV how has it affected your relationship?

[For those positive for HCV] Section 2(b) HCV diagnosis

If you have a positive diagnosis of HCV how has it affected your relationship with others who have a history of drug use?

When you were told you had a positive diagnosis of HCV how did you feel about telling the contacts on the diagram?

Were you encouraged to?

Did you think you needed to?

What, if any, impact did your contacts have on your feelings towards undergoing treatment for HCV?

Section 3: Recruitment and incentives for research

If you were to encourage your contacts to attend for further research interviews…

What kind of incentive would encourage them to attend? (Use card-sorting exercise 1)

Probe: Why have you made the choices indicated in the exercise?

Prompt: Can you think of anything else?

What kind of location would be most convenient for them to attend? (Use card-sorting exercise 2)

Probe: Why have you made the choices indicated in the exercise?

Prompt: Can you think of anything else?

How do you think either the choice of research location or incentive affect your responses to questions about injecting drug behaviours within your social network?

How would the person interviewing you impact on your responses?

Probe:

For example what if they were a doctor, pharmacist or nurse?

How do you feel about inviting the contacts you indicted on the first diagram to take part in research interviews?

Prompt: Do you think this would be feasible?

Prompt: Do you think their feelings about it would be any different from your own?

Prompt: What would encourage you to recruit your contacts to attend?

If you were to use a coupon to invite them and to enable you to claim a reward for recruiting them what design features would you find attractive?

Prompt: What do you like about this particular design?

Prompt: Does it contain the necessary information?

Section 4: Social Media in a network of PWIDs

What do you understand by 'social media'?

What is your experience with using social media?

Prompt: Describe your access to necessary hardware

Prompt: Why do you use it?

Prompt: How do you use it to interact with friends?

[If used…return to the concentric circle diagram]

Could you indicate on the diagram who you are linked to via social media

Probe: do your contacts have a similar experience with social media to you?

Probe: if not how do you differ?

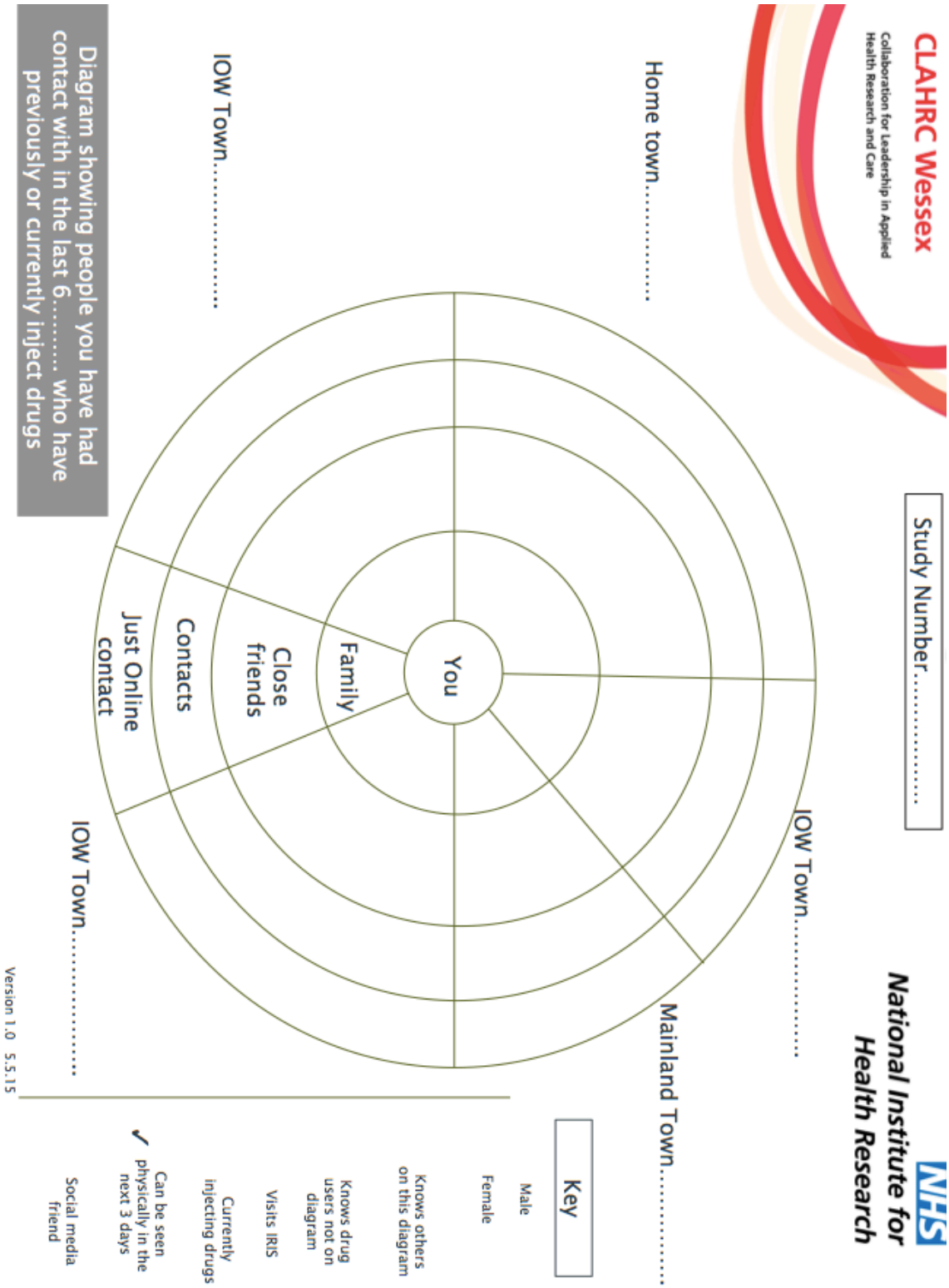
What do your feelings about sharing health advice through social media?

Probe: Is this something you have ever done?

Closing remarks

Thank you for completing this interview. You have added to our understanding of the topics we have discussed. I don't have any further questions but is there anything else you would like to ask

A.7 Concentric circle diagram



A.8 Standardised recruiter guidance

Version 1.0 5th May 2015

Guidance for peer recruiters in the Isle of Wight Respondent driven sampling survey

Study: An exploration of Hepatitis C within a network of injecting drug users in an isolated UK population

Researcher: Prof Salim Khakoo

REC submission No: 177753

University of Southampton study number: 14529

Thank you for taking part in the research survey. As has been explained to you we would like you to invite friends and contacts from within the Isle of Wight community to also attend for an interview.

To be eligible to take part your friends or contacts MUST:

- Have NOT previously taken part in this survey
- Live on the Isle of Wight
- Have previously injected drugs on the Isle of Wight (including performance enhancing drugs like steroids)
- Be 18 or over
- Speak English

For each person you invite who attends and completes the interview you will be eligible for £5 as compensation for the time you have taken to find someone who is eligible and willing to take part. However, if your friend or contact does not complete the interview or is ineligible to take part you will not receive this compensation.

It is important that when you invite them you inform them about what they are being asked to do. Please make sure they are aware of the following:

- They are being asked to take part in a survey and questionnaire
- It will last about 40 minutes
- They need to attend at the time and place on the coupon or book an appointment via the phone number
- All their answers will be completely confidential
- They will receive £10 compensation for their time
-

Thank you again for your help with this research project. If you have any questions please contact the research team on the number below.

Contact information: Dr. Ryan Buchanan, research phone number 07756 525806

A.9 Eligibility questionnaire for bio-behavioural and social network survey

Eligibility screening Questionnaire

Coupon number: |__|__|__|__|__|__|__|__|__|__|

History of injecting drug use? Yes No

History of injecting drug use on the Isle of Wight? Yes No

Aged 18 years and over? Yes No

Understands written and spoken English? Yes No

Valid coupon Yes No

Ring as appropriate

If the answer to any of these questions is 'No' then they are ineligible for the survey

If you have doubts about the participants eligibility with respect to previous injecting drug use ask one or more of the following questions:

Screening Questions

1. What is a works?
   [Correct answer – a needle and syringe]
2. What dose of Naloxone would you give to reverse an overdose?
   [Correct answer - 100-400mcg]
3. What would you call an injecting needle?
   [Correct answer - a spike]
4. Describe how you would use a filter in liquid drug preparation
   [Correct answer – draw up drug through it e.g. rest needle tip on cotton wool and draw]

A.10 Information sheet and consent form for bio-behavioural and social network survey

Version 3.2 14th March 2016

Participant INFORMATION SHEET (Sample B)

Study: An exploration of Hepatitis C within a network of injecting drug users in an isolated UK population

Researcher: Prof Salim Khakoo, Dr Julie Parkes, Dr Leonie Grellier, Dr Ryan Buchanan

REC submission No: 17753

University of Southampton study number: 14529

We would like you to take part in this research study. The decision to take part is entirely up to you, but before you decide, it is important you understand what will be involved. One of the researchers will go through this information sheet with you. Please ask questions about the study if anything seems unclear.

What is the aim of the study?

This study aims to add to our understanding of Hepatitis C is on the Isle of Wight.

Am I the right person to take part?

To be eligible to take part you must: have previously injected drugs on the Isle of Wight; be over 18 years of age; have adequate English language skills to undertake an interview and questionnaire; and live on the Isle of Wight.

What will it involve?

Participation will involve a short questionnaire and a 15-minute face-to-face interview with a researcher. As part of this you will be asked to annotate a diagram and during the interview you will be asked to describe your relationship with friends, family and acquaintances who have also injected drugs.

You will be free to stop at any time.

The study also involves a mouth swab test for Hepatitis C, this takes a moment to do and the result comes back in 20-30minutes. If it is positive it confirms that you have been exposed to the infection in the past but further tests (which are not part of this study) will be needed to confirm whether you still have it.

If these are needed the researchers will tell you how to get them done and explain how to access the appropriate medical care thereafter. The research team will not pass the result on to anyone else and the sample will be disposed of immediately after the interview.

At the conclusion of the interview you will be asked to take 3 coupons and use them to invite 3 friends who also have a history of injecting drugs on the Isle of Wight to participate in the same research. Further instructions on how to go about this will be given at the conclusion of the interview.

After the interview the research team may contact your GP to clarify the details of your previous test results for Hepatitis C.

Are there any disadvantages to taking part?

Sometimes research interviews may bring up difficult or sensitive issues. Whilst this is unlikely, if it does occur the research team will endeavour to help or refer you to someone else who can help after the interview is complete.

The only circumstances where something may be disclosed to someone outside the interview room without your explicit consent is if something comes to light which suggests there is a risk of harm to yourself or others.

Are there any advantages to taking part?

Participation will contribute to our understanding of the research area. However, it will not benefit you directly.

If you complete the interview you will be given £10 cash for your time. For every other person (maximum 3) you invite to attend for an interview and who takes part you will receive an addition cash payment for the time you have spent doing this. This will be paid on return of the coupon stub to the research team at the designated place and time (written on the stub).

Is participation anonymous?

All the study paperwork and you mouth swab result will be coded with a unique number rather than your name or other personal details. The research team will keep a record of your details separately on a paper record that will be kept locked in the University of Southampton. Only the research team will have access to these locked records and any data that is later published will be completely anonymous. The mouth swab sample will not be stored; it will be disposed of immediately after the interview.

Who is running this study and how do I contact them if I have further questions?

A research team runs the study from the University of Southampton. Funding for the study has been provided by CLAHRC (Collaboration in Leadership in Applied Health Research and Care) and GILEAD LTD.

The chief investigator is Professor Salim Khakoo at the University of Southampton (details at the top of the page). You can contact Ryan Buchanan the lead researcher 9-5pm Monday to Friday on: **07756525806. If you have any complaints please contact: Research integrity and governance team, research governance manager. rgoinfor@soton.ac.uk. 02380595058**

Thank you for your consideration

SAMPLE B CONSENT FORM (*3.0*)

Title of project: An exploration of Hepatitis C within a network of injecting drug users in an isolated UK population

Researcher: Prof Salim Khakoo, Dr Julie Parkes, Dr Leonie Grellier, Dr Ryan Buchanan

University of Southampton study reference: 14529

REC submission No:

Participant ID:.....

Please initial the box(es) if you agree to the above statements

I confirm that I have read the information sheet dated 29th Dec 2015 (version 3.1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

I give permission for my details to be stored on a paper record in a locked facility at the University of Southampton ☐

I give permission for interview and questionnaire data to be stored at the University of Southampton. ☐

I understand I will undertake a mouth swab test for Hepatitis C and will be given the result after the interview ☐

The 'validity' of my consent is conditional upon the University complying with ☐

the Data Protection Act and I understand that I can request my details be removed from this database at any time.

I understand that the research team based of the University of Southampton may contact my GP to review tests results for Hepatitis C. ☐

I agree to take part in the above study and agree for my data to be used in the above study. ☐

Signed (Participant)……
Date……..

Name (Block capitals)……

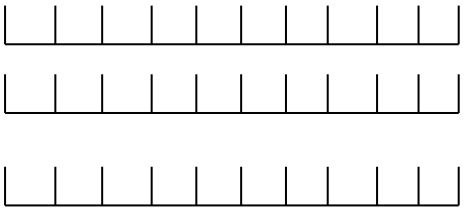
Signed (Researcher)……
Date……..

Name (Block capitals)……

A.11 Secondary incentive claim form

This form is to be completed by the screener when those who participated come to pick up a secondary incentive

Coupon stub number(s):



Is this the first time you have been to claim reimbursement?

Yes No

[If yes continue to ask questions about activity since they last claimed]

How many coupons have you distributed?.....

After the interview how long did you wait before you distributed your coupons (days)?

Coupon 1.....

Coupon 2.....

Coupon 3.....

Do you think the person to whom you gave the coupon would also have given one to you in the same situation?

Coupon 1 Yes No

Coupon 2 Yes No

Coupon 3 Yes No

How many people refused to accept a coupon?.....

What was the principle reasons for refusal? (Tick appropriate boxes)		
1	Very busy/no time	
2	Afraid of being associated with drugs	
3	Incentive too low	
4	Survey site too far away	
5	Not interested	
6	Afraid to get tested for HCV	
7	Had never injected drugs	
8	Does not live on the Isle of Wight	
9	Already had a coupon	
10	Already taken part in this survey	
11	Other	
Other……		

A.12 Bio-behavioural questionnaire

Date…… Supervised by……

Questionnaire

Study number: |_|_|_|_|

PART 1: Background information

RING THE CORRECT ANSWER

1.0 What is the nearest town to where you live?

1. E Cowes
2. W Cowes
3. Ryde
4. Newport
5. Shanklin
6. Sandown
7. Ventnor

Other……..

1.1 What sex are you?

1. Male
2. Female
3. Transgender

4. Other……..

1.2 How old are you? ☐

1.3 What sort of accommodation do you live in now?

1. Own house/flat
2. Hostel/Bedsit
3. Homeless

4. Home of relative
5. Home of friend/partner
6. Other…….

1.4 What is your level of education?

1. GCSE/O-levels
2. A-Levels
3. University
4. Apprentice
5. Left school before 16
6. Other……

1.5 What is your status?

1. Single
2. Married
3. Co-habiting
4. Civil partnership
5. Divorced

1.6 Do you currently work?

1. Full time
2. Part time
3. Temporary/variable work
4. Unemployed/sickness/disability benefits
5. Retired

1.7 How would your describe your ethnicity or race?

1. White British
2. White other
3. Asian
4. Mixed race
5. Other……..

1.8 Have you spent time in prison?

1. Yes
2. No

1.9 If yes, was this on the Isle of Wight?

1. Yes
2. No

3. Not applicable

PART 2: DRUG USE

2.0 When did you last inject drugs?

1. Last 30 days
2. Less than 6months ago
3. Less than 3years ago
4. Less than10years ago
5. More than 10 years ago

2.1 What age were you when you first injected drugs? ☐

2.2 How many years have you been/were you injecting drugs on the IOW?

1. <1year
2. 1-3 years
3. 3-10 years
4. Longer

2.3 Have you ever injected drugs elsewhere?

1. No
2. UK mainland
3. In a foreign country

Which City(Cities) on UK mainland?.....

2.4 Which of these do/did you inject?

1. Body enhancing drug (like steroids)
2. Heroin
3. Amphetamine
4. Crack/cocaine
5. So called 'Legal highs' (like M-Catt)

6. Other……

2.5 In which venue(s) do/did you inject? *(Ring all that apply)*

1. Hostel

2. Friends house

3. Squat/bedsit/shooting gallery

4. Public areas (e.g. toilets, loos, park)

5. Own home

6. Other……

2.6 How many people do/did you typically inject with?

1. Just you
2. 1 other
3. 2-3 others
4. Many others
5. Varies

Part 3: Injecting risk behaviours over the last month

[If you have injected in the last 30 days complete section 3, if you haven't go to section 4]

3.0 Over the last 30 days how often have you injected drugs with a needle and syringe?

1. Several times a day

2. Daily

3. Weekly

4. Just once or twice

Over the last 30 days have you:

3.1 Injected drugs by using a syringe in which someone else has put a drug from his/her syringe?

1. Yes
2. No

3.2 Used a filter or cotton wool, which someone else has previously used?

1. Yes
2. No

3.3 Taken a drug solution into the syringe from a spoon or dish for mixing drugs, which someone else had previously used?

1. Yes
2. No

3.4 Used water, which somebody else had previously used for washing or rinsing the syringes?

1. Yes
2. No

Part 4: What happened the last time you injected drugs?

4.0 Did somebody else use the needle/syringe after you?

1. Yes
2. No

4.1 Did somebody else use the needle/syringe before you?

1. Yes
2. No

4.2 Did you use a sterile needle and syringe?

1. Yes
2. No

4.3 Did you try to clean or disinfect the needle/syringe you used?

1. Yes
2. No
3. Not applicable

A.13 Service engagement interview based survey

Date…… Completed by……

Participant number: ⌊ ⌋⌊ ⌋⌊ ⌋

Interview based survey

Part 1: Network information

1.1 Roughly how many contacts do you have who have ever injected drugs?
(Definition of a 'contact' is someone you recognise and know by first name or nickname)

☐

1.2 How many that you could name and recognise live on the Isle of Wight?

☐ **NETWORK SIZE**

[If number >8 persons in network ask 1.3]

1.3 How many of these have you seen physically in the last 6 weeks?

☐

COMPLETE SOCIAL NETWORK DIAGRAM for up to 8 contacts

Part 2: Blood borne virus testing history

2.1 Have you ever been tested for HCV?

1. YES
2. NO

[If No proceed to SECTION A]

[If 'Yes' - proceed to SECTION B]

SECTION A [For those never tested for HCV]

2.2 Why have you never been tested?

2.3 What would encourage you to get tested?

[Proceed to PART 3]

SECTION B [Referring to all those tested for HCV (positive or negative)]

2.4 How many times have you been tested for HCV in total (including positive and negative tests)?

1. Once
2. 2-5x
3. 6-10x
4. >10x

2.5 How many of these tests have been on the IOW?

1. None
2. Some
3. Most
4. All

2.6 When were you last tested?

1. Last month
2. 1-3 months
3. 3-12 months
4. >12 months ago

2.7 Where have you been tested?

1. Hospital
2. GP
3. Pharmacy
4. IRIS centre

5. Other……

2.8 Have you been tested at a pharmacy on the IOW in the last 12 months?

1. Yes
2. No

2.9 On the last occasion why were you tested?

2.10 Have you seen recent advertising regarding Hepatitis C testing on the IOW?

1. Yes
2. No

2.11 If so where have you seen/heard it?

1 Buses

2 Radio
3 Newspaper
4 Pharmacy
5 IRIS centre
6 Internet
7 Other……..

2.12 Has it encouraged you to get tested?

1. Yes
2. No
3. Not sure

N/A

2.13 Have you ever tested positive?

1. YES
2. NO
3. Don't know

[If YES proceed to section C, If NO proceed to part 3]

SECTION C [For those with a positive test for HCV]

2.14 When did you last test positive for HCV?

1. Last month
2. 1-6 months
3. 6-24 months
4. >24 months ago

2.15 How many times have you tested positive before this test?

1. Never
2. Once
3. 1-3x
4. 4-10x
5. >10x

2.16 How long ago was your first positive test?

1. 1-6 months
2. >6 months - 2 years
3. 2-5years

4. >5 years ago

2.17 Where was your (first) positive test?

1 Hospital
2 GP
3 Pharmacy
4 IRIS centre
5 Prison

6 Other……

2.18 Were you referred to a specialist on this occasion?

1. Yes
2. No
3. Don't know

2.19i If yes…did you attend the appointment?

1. Yes
2. No

2.19ii If No…why not?

2.20i Have you received treatment?

1. Yes
2. No

2.20ii If you have not received treatment, why not?

2.20iii If you have received treatment, why did you get treated?

2.21 Was the treatment successful?

1. Yes
2. No
3. Don't know

2.22i Are you now under active follow up (regular clinic appointments) with a specialist?

1. Yes
2. No

2.22ii If NO – why not?

2.22ii Have you ever seen a specialist liver doctor in a pharmacy, the sexual health service or the IRIS centre?

1. Yes

2. No

Part 3: Engagement with health care services

3.1 Which of the following health services have you ever used on the IOW?

(Tick those that apply)

- O Have you completed an HBV vaccination schedule?
- O Do you use pharmacies on the IOW? (Complete part 3A)
- O Have you visited IRIS drug support centre (Complete **part 3B**)?
- O Have you used GP or Hospital services (Complete **part 3C**)?
- O Sexual health services (Complete **part 3D**)?
- O None (Proceed to finish)

Part 3A [For those using pharmacies]

3.2 Do you use pharmacy based needle exchange?

1 Yes
2 No
[If No go to next applicable section]

3.3 Have you collected clean needles from a pharmacy in the last 12 months?

1. Yes
2. No

3.4 Who did you collect equipment for?

1 Friends
2 Family
3 Partner
4 Contacts
5 Strangers
6 Just yourself

3.5 When you access needle exchange… how often are you offered testing for HCV?

1. Every time
2. Sometimes
3. Rarely
4. Never

3.6 Do you use the pharmacies for opiate substitution?

1. Yes
2. No

3.7 Have you collected methadone or subutex from an Island pharmacy in the last 12 months?

1. Yes
2. No
3. N/A

Part 3B [For those using IRIS support centre]

3.8 What services are/were you accessing?

1. Alcohol support
2. Opiate substitution (methadone or buprenorphine scripts)
3. Other…….

3.9 Are you currently on an opiate substitution script at the IRIS support centre?

1. Yes
2. No

3.10 How often do/did you visit the IRIS centre or use its services?

1. Daily
2. Weekly
3. Monthly
4. Rarely

Part 3C [For those using IOW NHS services]

3.11 Have you visited A&E as a patient on the IOW?

1. Yes
2. No

[If No… go to 3.17]

3.12 If yes how many times in the last 12 months?

1. None
2. Once
3. 2-3 times
4. 4-8 times
5. >8 times

3.13 When you last visited why were you there?

1. Overdose
2. Head injury
3. Alcohol intoxication
4. Other trauma

5. Other……

3.14 Did you disclose your history of injecting drug use to staff?

1. Yes
2. No
3. You assumed they knew already
4. Don't know

3.15 Were you offered a test for Hepatitis C?

1. Yes
2. No
3. Don't know

3.16 Are you registered with a GP on the IOW?

1. Yes
2. No
3. Don't know

3.17 Have you ever visited a GP on the IOW?

1. Yes
2. No

[If No…go to next applicable section]

3.18 If yes how often do you visit your/a GP?

1. Weekly
2. Monthly
3. Yearly
4. Rarely

3.19 Is your GP aware of you history of drug use?

1. Yes
2. No
3. Don't know

N/A

3.20 How often are you offered a test for HCV?

1. Every visit
2. Some visits
3. Rarely
4. Never

N/A

3.21 Are your GP visits related to injecting drug use? (E.g. methadone prescriptions)

1. Every visit
2. Some visits
3. Rarely
4. Never

N/A

Part 3D [For those using sexual health services]

3.22 How many times have you visited the sexual health service?

1. Just once
1. 2-3 times
2. 4-6 times
3. more than 6

3.23 What prompted your attendance?

1. A sexual encounter
2. Injecting drugs
3. Symptoms
4. Contact referral

5. Other……

3.24 Were you offered a test for HCV?

1. Yes
2. No

Thank you for taking the time to compete this interview, your answers will add to our understanding of Hepatitis C in this community.

Do you have any questions?

We would now like to talk to you about you inviting friends and contacts to undergo an interview.

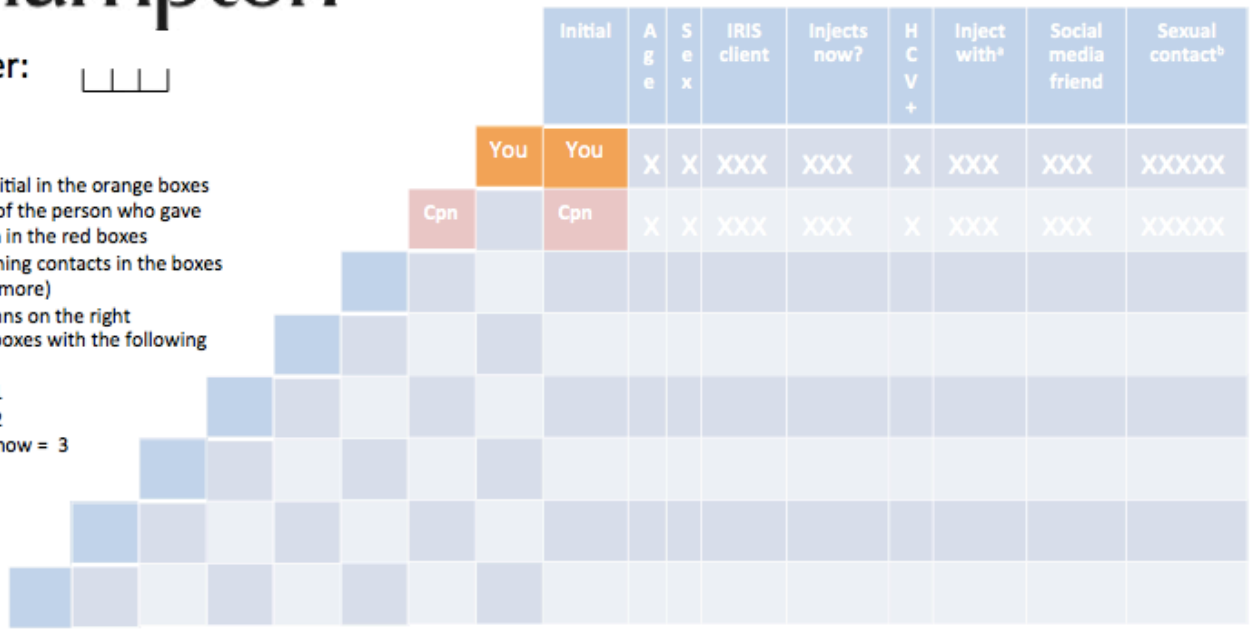
ORAL MOUTH SWAB	

UNIVERSITY OF Southampton

Study Number: ⌊⌊⌊⌋

1. Put your first initial in the orange boxes
2. Put the initials of the person who gave you the coupon in the red boxes
3. Put your remaining contacts in the boxes below (max 10 more)
4. Fill in the columns on the right
5. Now fill in the boxes with the following numbers:
   Family = 1
   Friend = 2

Just someone you know = 3



Version 2.0 9.11.15

[a]Ever injected in the same location/venue
[b]Penetrative or oral sex

A.15 Pilot survey method and results

In advance of undertaking the respondent driven sampling (RDS) survey each element of the researcher-participant interaction was piloted. As part of the survey design the concept and the content of specific materials including the consent form, information sheet, questionnaire and interview based survey (IBS) were discussed with the study Patient and Public Involvement (PPI).

The interview and questionnaire was then given to staff at Southampton University who pretended to be people who inject drugs (PWID). At this point I realised the content was far too long and well beyond the resource capacity for this survey. The content was therefore substantially revised and focused much more on to our specific research questions.

The interview based survey (IBS) and questionnaire was then given to five of the Sample A participants at the end of their recorded qualitative interviews. At this point I also tested the utility of a concentric circle diagram as a means to collect quantitative social network data. This proved cumbersome and I therefore switched to using a triangulation matrix, which proved better at drawing the data from the participant.

The entire interaction, including the use of network-based sampling was then piloted in drug support centre (DSC) staff. This is described in more detail below. Figure 1 summarises the piloting process for the survey and the final stage of the pilot, a run through the RDS process, is described in more detail in the text that follows.

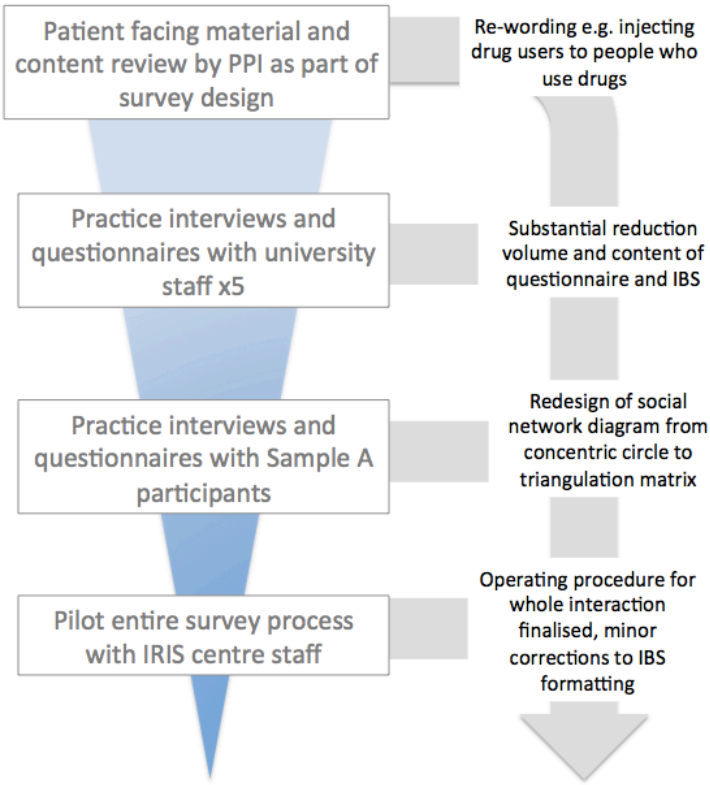


Figure 1

An overview of the piloting stages of the bio-behavioural and social network survey

(IBS – interview based survey, PPI – patient & public involvement)

Notes from pilot at the DSC centre on 7/12/15

Objectives

- To get an idea of how long each interaction will take
- To gain familiarity with the coupon management system
- To establish when and how to undertake the OraQuick™ mouth swabs
- To practice explaining the coupon recruitment process to participants
- Practice data entry format and upload to RDS analyst, Netdraw and UCInet programs

Method

All the study staff attended this pilot including, myself as the lead investigator, a research nurse (Joy Wilkins) and a medical student Ryan Youde. Six participants took part, all were DSC staff, for the purposes of the pilot they were asked to pretend to be one of their clients who meets the study eligibility criteria. I started with an initial *seed* (the local BBV nurse), she completed the survey and was then given two coupons to recruit other staff members. Recruitment was facilitated by a cake as the primary incentive and a piece of fruit as the secondary incentive. Unfortunately no one claimed his or her secondary incentive.

Outcomes

The mini-pilot was good exposure to the whole interaction and the recruitment process for the research team. Specifically the coupon management system worked well and was easy to use but it was time-consuming to fill this and the paper tracking form in at the same time therefore the paper form will only be completed at the end of the day each day.

Mouth swabs were quick and easy to use but should be done before the questionnaire to allow sufficient time to get the result. Concerns that eating or drinking before the interaction would invalidate the anti-HCV swab results were probably irrelevant because by the time eligibility screening and consent has taken place at least 10 minutes has already passed.

Paperwork should be labelled with the study number and not the coupon number for speed and to reduce the likelihood of mistakes. The questionnaire was without fault for each participant and the triangulation matrix worked well although the Joy wanted more practice with this. Part of the IBS needs rearranging but was otherwise reasonable.

The interaction appears to keep to the desired time-scale. More complex participants (e.g. one of our fake participants was diagnosed with Hepatitis C antibody on the mouth swab and needed counselling and another had 12 contacts to describe on the triangulation matrix) took about 35 minutes. More straightforward participants took about 20minutes. We were therefore, able to complete 6 interactions in a morning, which met my objective to complete 8 per day.

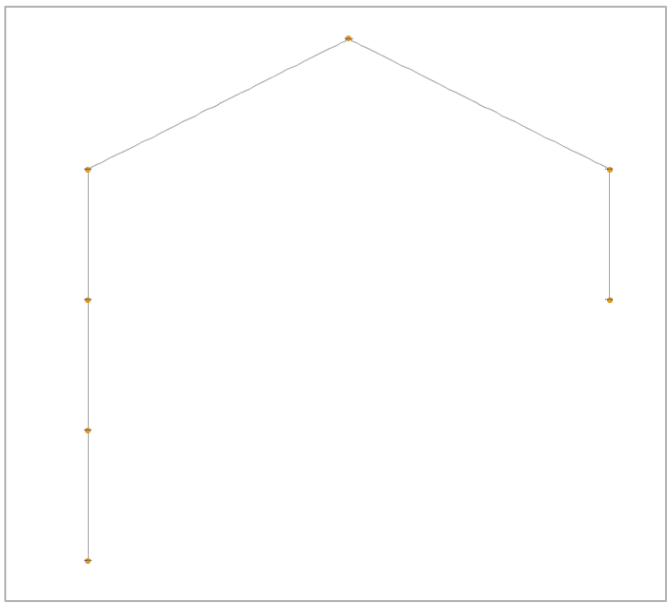


Figure 2

Recruitment tree of the pilot survey displayed using RDS analyst, during the real survey this will be viewed weekly to ensure coupons have been recorded correctly

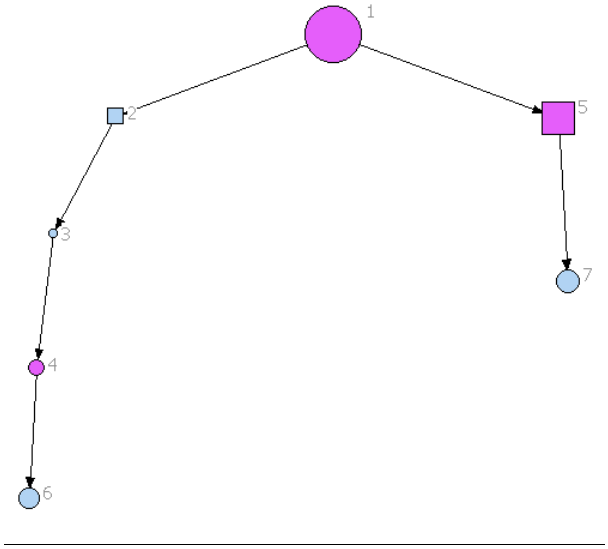


Figure 3

Recruitment tree for the pilot survey displayed using Netdraw software. Larger nodes have a larger documented network size, round nodes are female, and blue nodes have previously been incarcerated.

Potential shortcomings of the pilot process

I made an active decision to just pilot individual parts of the interaction with PWID during the qualitative interviews and not the entire survey process because I did not want to jeopardise the integrity of what is a fairly small target population on the Isle of Wight (IOW). I considered accessing a mainland PWID community but in the available time-scale I was restricted from doing so by ethical constraints.

I therefore chose a close and accessible surrogate in the staff at the DSC centre. Whilst not actively using drugs them-selves they are well acquainted with the local PWID community and some even have a history of drug abuse on the Island. However, due to their professional insights I cannot be certain that the real survey participants will behave in the same way.

A.16 Standard operating procedure

Before starting			
Ensure the following • You have adequate equipment for 8 participants: Mouth swabs, participant folders, envelopes (each with £5 cash inside), study folder, clip boards			
Operation	**Materials**		**Time**
Participant arrives at pharmacy /IRIS desk and presents coupon	N/A	Local staff	N/A
Staff member brings potential participant to research area or asks them to wait	N/A	Local staff	N/A
Convey waiting time to potential participant and offer chance to book an appointment for another time	N/A	Person 2	1min
Open project folder and study lap top			

Meet participant Check coupon, complete eligibility screening questionnaire on blue clip board If eligible place questionnaire in participant folder, if ineligible place back in study folder	Eligibility screening form	Person 1	
Record coupon number against participation code in coupon tracker (keep coupon to place in participant folder) Record personal details in written record and computer record	Coupon tracker Participation record	Person 2	2mins
Open participant folder			
Go through information sheet	Participant info sheet	Person 1/2	4 min
If participant refuses to take part enquire why and record on refusal form	Refusal form	Person 1/2	N/A
Sign consent form and return it to participant folder	Consent form	Person 1/2	2 min

Open mouth swab			
Give participant swab mouth* Ask them to pass it once between teeth and gums top and bottom then hold out bottle for them to place it in	Swab	Person 1/2	1 min
Leave swab on side	Swab stand	Person 1/2	
Return to participant folder			
Hand over questionnaire and ask participant to complete (Whilst they complete questionnaire check coupon code is recorded correctly and all paperwork is properly labelled)	Questionnaire	Participant	5min
Go through questionnaire to check for missing answers/address participant questions	Questionnaire	Person 1 or 2	2 min
Ask network questions	IBS	Person 1	2min

* Wait at least 15 minutes after consuming food or drink or chewing gum

Complete network based diagram with participant*	Network diagram	Person 1	7min
Complete interview based survey	IBS	Person 1	5 min
Record dispensed coupons in tracker spread sheet, label coupons clearly with coupon number, and date/place they can be redeemed	Coupon tracker	Person 2	
Go through recruiter information sheet but do not give this to take away	Recruiter info sheet (keep in folder)	Person 1	3 min
Hand over coupons with primary incentive in envelope (£10)		Person 1/2	
Record dispensation of primary incentive	Coupon tracker	Person 2	
Convey result of HCV mouth swab and record on last sheet of interview based survey	Yellow bin	Person 1	5 min

* If participant refuses to give initials, use single initial only, if they even refuse to do this get unlabeled network data e.g. P1, P2 etc

Dispose of swab in clinical waste			
Sign post to appropriate further testing services – if appropriate (it should be stressed that complete testing for blood borne viruses is available at pharmacies and the IRIS centre)		Person 1	1 min
File all forms		Person 2	
Close interview – 40minutes max			

Standard operating procedure – reclaiming secondary incentive

Operation	Materials	Person	Time
Recruiter presents coupon stubs to reception area	Coupon stubs	Receptionist	N/A
Greet recruiter Enter stub numbers in to coupon tracker to check whether coupons have been reclaimed		Person 2	3min
Enter coupon numbers onto reclaim questionnaire in project folder	Reclaim questionnaire	Person 1	
Go through questionnaire	Reclaim questionnaire		2min
If coupons have been reclaimed give appropriate secondary incentives and record transaction in tracker	Coupon tracker		1 min

At the end of each day			
Remove consent forms from folder and place in site folder in IOW R&D office	Site folder in R&D		
Place completed folders in R&D store drawers next to Joy's desk			
Leave Project folder in R&D store, not in car			
Unused equipment can remain in car boot			

A. 17 Hepatitis C RNA collection – Participant information sheet

Isle of Wight NHS Trust

PATIENT INFORMATION SHEET version 3.1

You should retain a copy of this sheet together with the signed consent form for your records

1. **Study title**

THE GENETICS OF THE IMMUNE RESPONSE TO HEPATITIS C VIRUS

2. **Invitation paragraph**

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

3. **What is the purpose of the study?**

The aim of the study is to understand how the genes of the immune system are involved in clearing hepatitis C virus.

The background to this study is as follows. We have recently found a combination of genes of the immune system that are important for individuals who clear hepatitis C virus. These genes are very slightly different in different individuals. Thus some individuals may have more favourable genes, or combinations of genes that control the immune response than others. We therefore now want to follow this work up to study other genes in the immune system that may also play an important role in this. The study is due to last about five years in total.

4 . **Why have I been chosen?**

You have been chosen because you have been exposed to hepatitis C. We are offering all such individuals the opportunity to participate.

5. **Do I have to take part?**

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

6. Signing the consent form

The consent form is in two separate parts. The first part (Part A) is to request a general consent for your overall participation in the study. The second part (Part B) specifically concerns the storage of your DNA sample and whether you would be willing for the sample to be used for future studies. Prior to both testing and storage we will give the sample a code number. This number will be used, instead of your name, to identify it. We will keep a paper record which will allow us to identify subsequently which individual the sample came from so that we can correlate the results of the tests with your medical records. This method of storing information is called "linked anonymised".

7. **What will happen to me if I take part?**

If you agree to take part then we would like to take a 20 ml (four teaspoonfuls) blood sample from you. We will endeavour to do this at a time when you attend your routine outpatient appointment with the specialist nurse so that no additional venepunctures (needles) are involved. However if you are not due to have a routine blood test then we request that we can take this extra blood sample or a sample of saliva. We may take up to four further blood samples.

8. **What do I have to do?**

There are no specific measures that you have to take for this study. It involves only an extra blood test when you come for your routine clinic visit.

9. **What will happen to my sample?**

We will take DNA from your saliva or blood sample and test it for the genes of the immune system. We will also test how those genes affect how your immune cells react. In addition we will analyse the sequence of the virus that is circulating in your blood. This will allow us to find out how your genes affect the virus in your blood. If you have given blood and you give your approval we would like to make a cell line from your blood. This cannot be done from a saliva sample. The cell line is made by infecting your cells in the laboratory with a virus (Epstein-Barr virus). This virus makes some the cells in the blood "immortal" such that they can be grown in the laboratory and acts as a renewable source of your DNA for us to test. This means that we will be able to test for many genes from this single blood sample. It may also allow us to test for genes which are not part of this specific study. Any further testing will only be performed if you give us your consent to do this and if the study is approved by the local Research Ethics Committee. We may request a further sample of blood for this study in the future, if we use up all the DNA from the original sample. This would be less likely to happen if we make a cell line from your original blood sample.

The DNA and cells will be stored by the research team of Professor Salim Khakoo at Southampton General Hospital. If we make a cell line then that will also be stored in the same building. You will not be immediately identifiable from the sample. However we will keep a code which will allow us to link back the sample to you, so that we can correlate any genetic findings from the sample with your medical records.

10. **What is the drug or procedure that is being tested?**

No drugs or procedures are being tested.

11. **What are the side effects of any treatment received when taking part?**

The side effects of the study are bruising related to taking a blood sample from you. However as these may be taken for your routine care we will try to minimize the additional risks. We do not anticipate that the findings from the

study will have any immediate implications for the management of your health. However if we do find out anything that has implications for your health then if you wish, we will inform you and then request your permission to inform your doctor. If you have any concerns or wish to discuss the potential implications of the results of the tests that we perform then you can call: Professor Salim Khakoo at Southampton General Hospital 02381 204004

12. **What are the possible disadvantages and risks of taking part?**

The only disadvantage to this study is that of taking a saliva or an extra blood sample, which may involve additional time spent with the nurse of one to two minutes.

13. **What are the possible benefits of taking part?**

There is no clear benefit to you if you take part. However if this study is successful it will give us important ideas about how the immune system interacts with hepatitis C virus.

14. **What happens when the research study stops?**

When the study finishes we request that we can retain your DNA sample for further analysis of new genes that may be important for the immune response to hepatitis C. However if you wish for your sample to be destroyed then we will do this.

15. **What if something goes wrong?**

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

16. **Will my taking part in this study be kept confidential?**

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

17. **What will happen to the results of the research study?**

The results from the study will be published in a medical journal and may be presented at scientific meetings. You will not be identified in any publication.

18. **Who is organising and funding the research?**

The Wellcome Trust, which is a charitable organisation is funding this project.

The individuals conducting the research are not being paid additionally for performing this study.

19. **Who has reviewed the study?**

The study has been reviewed by Senior Consultant Physicians at Southampton General Hospital and the Southampton and South West Hampshire Research Ethics Committee.

20. **Contact for Further Information**

Please contact details for research team: Professor Salim Khakoo, Professor of Hepatology, Mailpoint 811, Level E South Block, Southampton General Hospital, Tremona Road Southampton, SO16 6YD. Tel: 023 8120 4004, McDonal Mupudzi Study nurse Southampton: 07584206918 or Dr Ryan Buchanan on 07756 525806 or Joy Wilkins (Isle of Wight Research Nurse) 01983 822099 ex: 5748.

Thank you for considering taking part in this study!

A. 18 Hepatitis C RNA collection – Participant consent form

Isle of Wight NHS Trust

CONSENT FORM V2.5 20/10/2014

STAGED CONSENT FOR RESEARCH USING Human Biological Samples

Thank you for reading the information about our research project. If you would like to take part, please read and sign this form.

Study Number: RHM MED0707 Subject Identification Number for this trial:……

Title of project: The genetics of the Immune response to hepatitis C

Name of researcher: Professor Salim Khakoo

Contact details for research team: Professor Salim Khakoo, Professor of Hepatology, Mailpoint 811, Level E South Block, Southampton General Hospital, Tremona Road Southampton, SO16 6YD. Tel: 023 8120 4004, McDonal Mupudzi Study nurse Southampton: 07584206918 or Dr Ryan Buchanan on 07756 525806 or Joy Wilkins (Isle of Wight Research Nurse) 01983 822099 ex: 5748.

PART A: Consent for the current study

(samples to be destroyed on study completion unless part B completed)

PLEASE INITIAL THE BOXES IF YOU AGREE WITH EACH SECTION:

1. I have read the patient information sheet dated 20th October 2014 (version 3.1) for the above
   study and have been given a copy to keep. I have been able to ask questions about the study and I understand why the research is being done and any risks involved.

2. I agree to give a sample of blood for research in this project.
   I understand how the sample will be collected, that giving a sample for this research is voluntary and that I am free to withdraw my approval for use of the sample at any time without my medical treatment or legal rights being affected.

3. I give permission for a cell line to be made from my blood sample. I understand that I am free to request that this cell line be destroyed at any time without my medical treatment or legal rights being affected

4. I give permission for someone from the research team to look at my medical records to get information on my medical history and my potential exposure to the hepatitis C virus. I understand that the information will be kept confidential.

5. I understand that I may be informed if any of the results of tests done as part of the research are important for my health. However, I also understand that the research may not directly benefit my health.

6. I understand that I will not benefit financially if this research leads to the development of a new treatment or test.

7. I know how to contact the research team if I need to.

_____	_____	_____
Name of Patient	Date	Signature

_____	_____	_____
Name of Person taking consent	Date	Signature

Samples for storage and use in possible future studies

PART B *Linked or linked anonymised samples:*

8. I give permission for my sample and the information gathered about me to be stored by Professor Salim Khakoo at Southampton General Hospital for possible use in future projects, as described in the information sheet. I understand that some of these projects may be carried out by other researchers, including researchers working for commercial companies. I understand that future studies will be reviewed and approved by a Research Ethics Committee prior to my sample being used, and that I can alter these decisions at any stage by letting the research team know.

   a) I give permission for the sample to be used for research about Hepatitis C infection ☐

   b) I give permission for the sample to be used for other unrelated research studies the precise nature of which will depend upon future scientific advances. ☐

9. I want / do not want (*delete as applicable)* to be told the results of any future test which may have health implications for me. ☐

10. I give permission for sections of my medical notes to be looked at by responsible individuals where it is relevant to such future study. I expect that my medical notes will be treated confidentially at all times. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

1 for patient, 2 for researcher, 1 to be kept with hospital notes

Glossary

Alter – A person to whom *ego in an ego*-network has a relationship

Centrality – A measure of someone's (or a node's) position within a network

Convergence – How the proportion of individuals with a given characteristic changes as sampling to a respondent driven sampling progresses and when this value meets the final value

Compartmental model – A model which abstracts a population into compartments based on health status with respect to a specific pathogen

Degree – A measure of the number of links to or from a person in a social network, it is a basic measure of centrality

Dyad – two connected individuals within a network

Ego – the individual at the centre of a personal network

Equilibrium – As respondent driven sampling passes through recruitment waves it is the point at which the proportion of individuals, with a given characteristic within each wave, changes by less than 2%

Ex people who inject drugs (ex PWID) – A person who has injected drugs but has not done so in the last 12 months

Hidden population – this refers to a population which is difficult to identify and therefore difficult to sample with conventional survey methodology. Often used interchangeably with 'hard-to-reach' population

Homophily – A measure of the similarity between two individuals or a group of individuals

Individual based model (IBM) – A computational model that simulates the interactions of autonomous individuals to establish the effect on the population as a whole

Multiplex *tie* – A link between two individuals involving more than one type of relationship e.g. sex and drug use

Glossary

Node – a member of a 'whole network'

Respondent driven sampling (RDS) – A network based sampling method where participants identify other participants. Used to calculate population prevalence estimates in hidden populations such as people who inject drugs

Seed – The participant selected and recruited by the research team to initiate a recruitment chain in a respondent driven sampling survey

Snowball sampling (SBS) – A network based sampling method where participants identify other participants

Sustained Virological Response (SVR) – the absence of Hepatitis C RNA on PCR three months after completing anti-viral treatment

Tie – A link between two individuals

Treatment as prevention – The concept where the treatment of HCV in an individual prevents transmission to others

Wave – The recruitment pattern observed in respondent driven sampling when participants recruit their peers to undertake the research survey, each *wave* represents a new 'generation' of participants

Yules Q homophily (Q) – a measure of the similarity between two individuals which takes into account the characteristics of other individuals within the network

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