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A review of network simulation models of hepatitis C virus and HIV among people who inject drugs

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Abstract

Network modelling is a valuable tool for simulating hepatitis C virus (HCV) and HIV transmission among people who inject drugs (PWID) and assessing the potential impact of treatment and harm-reduction interventions. In this paper, we review literature on network simulation models, highlighting key structural considerations and questions that network models are well suited to address. We describe five approaches (Erdös-Rényi, Stochastic Block, Watts-Strogatz, Barabási-Albert, and Exponential Random Graph Model) used to model partnership formation with emphasis on the strengths of each approach in simulating different features of real-world PWID networks. We also review two important structural considerations when designing or interpreting results from a network simulation study: 1) dynamic vs. static network and 2) injection only vs. both injection and sexual networks. Dynamic network simulations allow partnerships to evolve and disintegrate over time, capturing corresponding shifts in individual and population-level risk behaviour; however, their high level of complexity and reliance on difficult-to-observe data has driven others to develop static network models. Incorporating both sexual and injection partnerships increases model complexity and data demands, but more accurately represents HIV transmission between PWID and their sexual partners who may not also use drugs. Network models add the greatest value when used to investigate how leveraging network structure can maximize the effectiveness of health interventions and optimize investments. For example, network models have shown that features of a given network and epidemic influence whether the greatest community benefit would be achieved by allocating hepatitis C or HIV treatment randomly, versus to those with the most partners. They have also demonstrated the potential for syringe services and “buddy sharing” programs to reduce disease transmission.

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Conflicts of Interest

The authors declare no conflicts of interest.

Keywords

Network modelling; Hepatitis C; HIV; People who inject drugs; Review

Background

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) pose major public health threats, with an estimated 71 million and 37 million prevalent infections worldwide in 2015 (WHO, 2017). Within the United States, in 2016, 2.4 million people had hepatitis C and 1.1 million were living with HIV, including 300,000 co-infected with hepatitis C (CDC, 2016, 2017a; Hofmeister et al., 2019). Hepatitis C is a leading cause of cirrhosis, liver cancer, and liver failure; and without substantial changes in current epidemiological trends, the annual cost of hepatitis C in the U.S. is expected to reach $9.1 billion by 2024 (CDC, 2017b; Razavi et al., 2013). The cost of HIV is also predicted to rise, surpassing the $25 billion in federal funding allocated to domestic HIV care and prevention in 2019 (KFF, 2019). As in other high-income settings, people who inject drugs (PWID) are disproportionally affected by HCV and HIV in the U.S., accounting for at least 69% of new HCV infections and 10% of new HIV diagnoses (CDC, 2016; Yehia et al., 2014).

Mathematical modelling has proven a useful tool to simulate the spread of HCV and HIV among PWID, as well as to assess the benefits of treatment as prevention (TasP) and harm-reduction strategies, including peer education, medications for opioid use disorder, and syringe services programs (Pitcher et al., 2018; Scott et al., 2016). The majority of published models of HCV and HIV transmission among PWID are compartmental (Johnson & White, 2011; Pitcher et al., 2018). Using sets of differential equations, PWID move through compartments that they are assigned to based on their infection state and other attributes, such as demographic characteristics and incarceration status. The compartments influence how quickly individuals progress through disease states and how likely they are to transmit an infection to partners. Simple compartmental models assume a homogenous and completely mixed population, meaning that each member has contact with every other member (Anderson & May, 1991). Many approaches have been devised to capture heterogeneous mixing of PWID in compartmental models, but doing so requires multiplication of the number of compartments, adding complexity to the model (Pollack, 2001a; Vickerman et al., 2007). Therefore, addressing real-world heterogeneity is a challenge when using a compartmental approach.

Over the past decade, attention has shifted toward network simulations to address questions regarding disease transmission among PWID. Network simulation models depict individuals as a set of vertices of a graph, called “nodes”, with “ties” connecting two nodes. Ties represent specific types of partnerships between the nodes, such as needle sharing or sexual relationships. The simplest network models are based only on information regarding “mean degree,” or the average number of ties connected to a node in the network. More complex models reproduce characteristics of real-world networks, such as the tendency for two people who share a common relationship with a third person to be connected themselves (“transitivity”), the tendency for people who share traits like gender, race, and injection

frequency to be connected (“homophily”), and the presence of nodes with an unusually high number of partners (“hubs”). See Box 1 for a glossary of common modelling terms.

Generally, network models are well suited to simulate individual-level heterogeneity. This makes them particularly apt for the study of PWID networks, where variations in injection frequency (Marmor et al., 1987; Mather & Crofts, 1999), duration of injection career (Chitwood et al., 1995; Zeldis et al., 1992), and number of needle/syringe sharing partners (van Ameijden et al., 1994) have long been linked to differential HIV acquisition risk (De et al., 2007), and more recently to differential HCV transmission risk (Wylie et al., 2006). Researchers have shown that models that allow for greater individual heterogeneity are better able to reproduce observed HIV prevalence and incidence trends among PWID (Bernard & Brandeau, 2017; Metzig et al., 2017; Monteiro et al., 2016).

Nevertheless, network modelling is associated with a unique set of challenges. It is rarely possible to describe an entire social network, due to the difficulty of gathering empirical data on each partnership, so assumptions must be made regarding structure and behaviour. This is particularly relevant for PWID populations. Due to high rates of homelessness and incarceration among their members, PWID networks are often in flux, with partnerships forming and dissolving as individuals enter and exit the population. This makes it challenging to identify each member. Furthermore, individuals may not remember all of their injection equipment sharing and sexual partners or may not want to disclose them due to stigmatization (Bell et al., 2000; Brewer et al., 1999).

We performed a comprehensive review of the literature to identify network simulation models of HCV and HIV infections among PWID. Hepatitis B virus (HBV), another infection transmitted through PWID needle sharing and sex networks, was also included in our search, but was not featured in any of the network modelling studies we identified in the literature. In this paper, we first characterize model constructions, describing five network modelling frameworks. Next, we explore the trade-offs of two important structural choices required when developing a network simulation: 1) the decision to build a static model, where population and partnerships are held constant over time, or a dynamic model; and 2) the decision to incorporate or exclude sexual transmission routes that overlap with injection drug use. Finally, we discuss HCV and HIV infection interventions that have been explored using network models, including the relative effectiveness of directing treatment and harm-reduction efforts, and the impact of syringe services and “buddy sharing” programs. Network modelling remains in a nascent stage yet is being used to tackle complex issues in PWID populations and beyond. The aim of this review is to summarize the existing literature, highlighting the strengths and limitations of current methodology and the potential of network models to aid in HIV and HCV program planning.

Methods

In February and March of 2019, we identified eligible studies through PubMed, Academic Search Premier, and Web of Science searches. The following search terms were used: [Title/Abstract] (“HCV” OR “Hepatitis C” OR “HBV” OR “Hepatitis B” OR “HIV” OR “human immunodeficiency virus”) AND (“drug use” OR “drug abuse” OR “substance abuse” OR

"substance use" OR "injection" OR "people who inject drugs" OR "person who injects drugs" OR "PWID" OR "opioid" OR "IDU" OR "methamphetamine") AND ("network" OR "mathematical model" OR "ERGM" OR "stochastic block model" OR "agent-based model"). Additional studies were identified by collaborators engaged in network modelling and from the reference lists of eligible studies.

We included studies written in English that described an HCV, HBV, or HIV network model focused on PWID in the review. One researcher (MB) screened each study for eligibility, first eliminating papers based on a title and abstract review, then performing a full text review of those remaining. Each eligible network simulation study was read to develop a list of key modelling approaches, interventions examined, and findings. From this list, we identified a few major decisions that distinguish models and impact simulation results to highlight in the paper. We also selected a set of interventions to discuss that have been explored in multiple network models included in the review.

Search Results

Our search yielded 45 relevant network modelling papers (Figure 1). Five were reviews of existing modelling literature, 10 modelled HCV alone, 25 modelled HIV alone, and five modelled both HCV and HIV. No papers fitting the inclusion criteria modelled hepatitis B. The full list of included studies is provided in Table 1.

Types of Network Simulation Models

Typically, it is not feasible to identify and characterize every partnership within a population of PWID. The role of simulations is to make inferences regarding network structure based on a sample of that network. To do so, researchers employ a variety of network simulation techniques, "models," to approximate sexual and needle/syringe sharing networks. Network simulation models typically fall under the umbrella of agent-based models, in which individuals are assigned traits and rules governing their behaviours and interactions with one another. For example, each individual could be given a unique race, injection frequency, duration of drug use, rate of unprotected sex, and disease status, ideally based on observed population data. A number of frameworks have been developed to model the formation of ties within a network, including Erdös-Réyni random graph model (Erdos & Reyni, 1959), stochastic block model (Frank & Harary, 1982; Snijders & Nowicki, 1997), Watts-Strogatz small-world model (Watts & Strogatz, 1998), Barabási-Albert preferential attachment model (Barabâsi et al., 2002), and exponential random graph model (Frank & Strauss, 1986). We describe key features of each and discuss examples of their application to HCV and HIV transmission among PWID. A summary of each framework's approach to tie formation and network fitting is provided in Table 2.

Erdös-Réyni Random Graph Model

Random graph models assume that there are a fixed number of nodes in a network and randomly assign ties to each node. Therefore, they differ from true networks in an important way: in real networks, new nodes tend to form ties with more connected nodes in a phenomenon known as "preferential attachment." In addition, the Erdös-Réyni

model is not suited to represent hubs, because in a random population, individuals are statistically expected to have a comparable number of contacts. In a large network, the Erdös-Réyni model can have long average path lengths, meaning that there are many degrees of separation between individuals. For these reasons, the Erdös-Réyni model has been criticized for mischaracterizing human social networks (Robins et al., 2001; Watts & Strogatz, 1998). Others argue that this approach is a useful starting point for understanding hidden populations with unknown social structure. Accordingly, it has been widely used to map HIV and HCV transmission among PWID (Cousien et al., 2017; Cousien et al., 2016; Crawford et al., 2018; Marshall et al., 2014; Marshall et al., 2012; Young et al., 2013; Zhong et al., 2018). In addition, Cousein et al. (2017; 2016) and Marshall et al. (2014) used the Erdös-Réyni model to simulate increased testing and reduced loss to follow-up.

Stochastic Block Model (SBM)

The stochastic block model is a type of random graph model that captures the tendency of human social networks to be organized into groups or communities. Nodes are partitioned into subsets, called blocks, and the probability of a tie existing between two nodes depends on the blocks to which the nodes belong. In early SBMs, each node was affiliated with a single block, and therefore played a limited, latent role in the network. The framework was later extended by Airoldi et al. (2008) to allow for mixed membership, through which nodes can assume membership in multiple blocks depending on who they interact with. Zelenev et al. (2018) selected a stochastic block model for their study of HCV and HIV infection interventions, as it had the best goodness-of-fit to the degree distribution, clustering coefficient, and average path length observed in a sample of their Hartford PWID network during the calibration process.

Watts-Strogatz Small World Model

Small world models are based on the notion that no matter how large the network, each individual is connected to every other individual by only a small number of ties. This principle is implemented in small world models through short average path lengths. The Watts-Strogatz model extends this framework by incorporating clustering in addition to the small-world property of short path lengths. This structure has proven useful for simulating HCV transmission among PWID, because clustering allows for the inclusion of hubs, and short average path lengths result in disease passing quickly from infected to uninfected nodes. A Watts-Strogatz model was developed by Cui et al. (2009) to recreate the interior, highly clustered PWID network within a larger social network, (simulated using a random graph model) in Yunnan province, China. Zelenev et al. (2018) also built a small world model for their above-mentioned study of HCV and HIV, but found that it was less able to match network parameters, such as degree distribution, compared to other model types, and therefore was not used to simulate interventions.

Barabási-Albert (BA) Preferential Attachment Model

In the Barabási-Albert model, networks are formed based on preferential attachment, such that new nodes are more likely to form ties to existing nodes with a high degree. This results in the presence of hubs. In addition, BA networks are assumed to be scale-free, meaning that their degree distribution follows a power law. The “rich-get-richer” nature of BA models has

been criticized by network researchers who argue that forming ties primarily on the basis of degree cannot approximate real-world networks where factors such as homophily strongly influence partnership formation (Broido & Clauset, 2018). Dombrowski et al. (2013b) found that while this criticism held for the sexual network of PWID in Brooklyn, New York, the injection network was approximately scale-free due to the presence of a core of highly connected drug users. A BA model was also employed by Rutherford et al. (2016) to analyse harm-reduction strategies to reduce HIV prevalence among PWID and female sex workers. The researchers note that while the BA algorithm did not capture some aspects of the network's topology, it provided a good approximation of the degree distribution.

Exponential Random Graph Model (ERGM)

ERGMs use logistic regression to estimate the probability that a tie exists between any two nodes. Using observed data, the ERGM approach first develops a regression equation that estimates the probability of a tie existing as a function of various covariates selected by the investigators. For example, the probability of a tie existing could be a function of the age, sex, and race of the first person in the partnership (the index node), as well as the difference in ages between the two partners, the degree of the index partner, and the number of ties in the network. After estimating the odds that a tie exists, the model converts those odds into a probability used to determine whether to implement the tie in the simulation. By querying each potential tie in the network, the ERGM is able to generate simulated networks that match target statistics in the observed network.

ERGMs were originally developed to analyse complete network datasets, which are difficult to obtain; however, they can be used with incomplete data when simplifying assumptions are applied (Handcock & Gile, 2010; Krivitsky & Morris, 2017). ERGMs were used by Hellard et al. (2014) and Rolls et al. (2013a) to investigate network-based interventions to reduce hepatitis C prevalence, and by Khan et al. (2013) to explore HIV transmission within a PWID network in New York during the peak of the epidemic in the 1990's. This approach was selected because it allows for the inclusion of partnership formation patterns, such as homophily and transitivity, which have been shown to play an important role in PWID networks (Dombrowski et al., 2013b; Fujimoto et al., 2015).

Data Demands and Calibration

Calibrating a network model to ensure that the structure matches the observed network is a challenge, as data on a full PWID network are rarely available, and the sample of the network used may be biased to favor specific partnerships while leaving out others. In addition, the model types described each require different "levels" of statistics describing the network structure for calibration. For example, mean degree falls on a nodal level, homophily on a dyad level, and transitivity on a network level. Erdös-Réyni and scale-free models, such as the BA model, require few parameter inputs, and are often considered to be calibrated to the real-world network if they can match the network's mean degree. Meanwhile, ERGM and SBM typically require higher levels of network statistics. When data are scarce, it may not be feasible to calibrate an ERGM or SBM model to higher levels without relying on broad assumptions regarding network statistics. Another aspect of calibration focuses on disease transmission. Data on disease transmission parameters

are almost always unavailable from the PWID network being investigated, so network models make inferences based on datasets from other geographical locations or drug-using populations. This may introduce bias, as disease transmission dynamics vary between networks.

The studies included in this review vary widely in their rigor and the extent to which they are supported directly by empirical data. While some of the models serve as weaker representations of the underlying PWID population structures, others are better-validated against empirical networks. Zelenev et al. (2018) provides an example of a more comprehensive calibration approach. Their calibration procedure involved reconstructing non-sampled edges of the network by estimating key network statistics from an observed Hartford PWID data set, including degree distribution, assortativity, clustering, and average path length, then examining multiple network model types to select the one that best fit the empirical data, in particular ensuring that the mean degree fell within 95%CI of the observed. They also calibrated the model against four different baseline HCV prevalence scenarios that reflected the heterogeneity of HCV among PWID across U.S. cities. Although many existing network models calibrate only to egocentric values like mean degree, the field is evolving, and modelers are starting to calibrate to other sociometric measures, such as average path length, homophily, and transitivity.

To test the robustness of modelling assumptions, studies may also include sensitivity analyses. For example, Zelenev et al. (2018) and Cousien et al. (2017) each performed a suite of sensitivity analyses to determine how model predictions would change according to parameter distributions. In Zelenev et al. (2018), these included fitting the lower and upper bound of U.S. HIV prevalence, considering shorter duration of injection and duration of injection partnerships, and changing propensity to share equipment. Ultimately, these analyses indicated that the findings from the main model were not sensitive to variability in parameters or assumptions. Cousien et al. (2017) similarly varied a host of parameters including infection rate, time before linkage to care, average duration of injecting career, number of injecting partners, and rate of spontaneous recovery. In this case, results were sensitive to multiple parameters. For example, prevalence after 10 years was most sensitive to treatment initiation rate and mean time to cessation of injection. As modelling assumptions can matter for predicting epidemiological outcomes, additional research on network modelling methodology is needed to ensure that modelled networks are faithful representations of the underlying population dynamics.

Key Structural Decisions for Network Modelling

Static or Dynamic Network

Choosing whether to develop a static or dynamic network model is one of the major decisions required at the start of a network simulation effort. Early models of HCV infections among PWID assumed static networks in which partnerships were held constant over time or analysed at a single moment in time (Cousien et al., 2017; Cousien et al., 2016; Hellard et al., 2014; Rolls et al., 2012; Rolls et al., 2013a; Rolls et al., 2013b; Rutherford et al., 2016). While these static models continue to serve as the foundation of HCV infection modelling, some have argued that dynamic models are critical for investigating long-term

infections like HCV, where partner turnover could be high (Hellard et al., 2014; Metzig et al., 2017; Rolls et al., 2013a). Due to factors such as homelessness and incarceration, PWID networks may be highly fluid, with ties forming and dissolving frequently (Aitken et al., 2009; Aitken et al., 2004; Costenbader et al., 2006). Dynamic models are able to capture this fluidity by allowing for partnership changes and movement into and out of the network. As a result, there has been an upsurge in the number of dynamic PWID network models published in the last five years (Campbell et al., 2017; Cousien et al., 2018; Dombrowski et al., 2013b; Dombrowski et al., 2017; Dombrowski et al., 2013c; Fu et al., 2016; Fu et al., 2018; Gutfraind et al., 2015; Hutchinson et al., 2006; Khan et al., 2013; Khan et al., 2018; Marshall et al., 2014; Marshall et al., 2012; Metzig et al., 2017; Mills et al., 2013; Monteiro et al., 2016; Nucit & Randon-Furling, 2017; Zelenev et al., 2018).

A key reason to favour a dynamic approach is that shifts in network composition and injection partnerships have been shown to increase the probability of disease transmission (Costenbader et al., 2006; Curtis et al., 1995; Hoffmann et al., 1997). For example, in a longitudinal study of HIV risk behaviours among PWID, Costenbader et al. (2006) found that individuals who reported an entirely new set of drug-using contacts at follow-up were three times more likely to be in the increased risk behaviour group. Dombrowski et al. (2017) and Khan et al. (2013) underscored the importance of network turnover by demonstrating a “firewall effect” to the spread of HIV in Brooklyn in the early 1990’s: when partnerships remained stable over time, HIV prevalence rates stabilized at levels well below population saturation. First described by Friedman et al. (2000), this effect is possible because the viral loads of newly infected individuals spike in the first six weeks of HIV infection, then moderate to lower levels. The positioning of long-infected individuals with lower viral loads at key breakpoints in the network could slow the spread of disease from newly infected nodes with high viral loads to non-infected segments of the network. This finding led the authors to hypothesize that programs that force PWID to re-order their networks by causing a large inflow or outflow of PWID, such as mass arrests or urban renewal projects, lead to increases in HIV incidence. Indeed, Mehta et al. (2017) used molecular data from seroconverters in Tijuana, Mexico alongside qualitative and geospatial data to show that public policies that dispersed and relocated homeless populations resulted in more risk taking behaviour and reduced access to prevention services. In recognition of the importance of network changes, Rolls et al. (2012) adjusted their static model to include “imported” infections from sources that are not network neighbours. This modification, or a dynamic approach that allows susceptible nodes to enter the network, is also needed to prevent rapid saturation in situations where incidence of infection is high.

Dynamic models are also valuable for capturing the movement of PWID into and out of networks due to incarceration. In 1994, a 12-city study found that over 60% of PWID reported a history of incarceration, and today PWID remain vastly overrepresented among prison populations (Ball et al., 2017; Dolan et al., 2015). As a consequence, there is a high burden of HCV and HIV among prisoners, with an estimated one-quarter of inmates (equating to 1.65 million) with a chronic HCV infection (Dolan et al., 2015; Larney et al., 2013). While none of the network models included in this review explicitly model prison populations, the field of HCV and HIV research would benefit from models that capture those leaving prisons to return to old networks or form new ones.

In addition to allowing for changes in partnerships over time, some dynamic models allow the parameters governing tie formation and dissolution to vary over time. This is valuable, because studies have shown that individual risk behaviours, such as injection and needle sharing frequency, shift over the length of an injection career, often following predictable patterns that influence disease acquisition. For example, new injection drug users have been shown to display higher risk behaviour than long-time injectors, and represent an important pool of susceptible individuals (Fennema et al., 1997). Marshall et al. (2014) noted that a major limitation of many network models, including their own, is that they do not account for changes in individual attributes and risk behaviours over time.

Alongside these benefits, there are a number of drawbacks to using dynamic models. As noted by Rolls et al. (2012), dynamic network models are complicated to develop due to the subtleties of tie formation and dissolution. In situations where little data exist to inform network models, investigators have argued that a static model requires fewer assumptions and is, therefore, a better choice (Cousien et al., 2017; Hellard et al., 2014). Moreover, for networks with relatively stable injection or sexual partnerships, a static model may accurately approximate network dynamics. In a Melbourne PWID network, the median length of a partnership was fairly long at three years, so a static model was deemed appropriate (Hellard et al., 2014). However, there are large between-study variations in partnership duration. For example, a survey of 345 PWID in San Francisco showed a mean injection partnership duration of 4.5 months, while in the Hartford network and a network of PWID in rural Appalachia, average tie duration was greater than 10 years (Havens et al., 2013; Morris et al., 2014; Zelenev et al., 2018). Thus, it is useful to consider the stability of network ties when selecting a static or dynamic modelling approach.

In addition, when interventions are simulated over a short period of time, network fluctuations are less significant and may not need to be incorporated. For example, to mitigate the limitations of their static model, Rolls et al. (2012) reported values based on one simulated year after the burn-in period. Meanwhile, for their 15 and 40 year-long simulations, Dombrowski et al. (2017) and Hutchinson et al. (2006) used dynamic models. While shorter time horizons may allow static models to produce more reliable outputs, previous modelling studies have indicated that the full impact of combined HCV/HIV infection prevention strategies only accrues after 10 to 15 years (Alistar et al., 2011; Alsallaq et al., 2013). This trade-off may have influenced Hellard et al. (2014)’s and Cousien et al. (2016)’s decisions to simulate interventions over 10 and 40 years, respectively, despite using static models. In short, the scarcity of data regarding the long-term behaviour of injection drug use networks limits researchers’ abilities to comprehensively evaluate the performance of dynamic network models.

Incorporating a Sexual Transmission Network

Another structural decision that has differed across PWID network models is whether sexual exposure is included as a transmission pathway. While few hepatitis C cases have historically been attributed to sexual transmission (Price et al., 2018), justifying its exclusion from many HCV models, sexual contact between PWID and their non-injecting sexual partners is an important route of HIV transmission (Blower et al., 1991; Terrault

et al., 2013). Indeed, Campbell et al. (2017) determined that sex was the most frequent transmission route during the 2016 HIV epidemic among PWID in St. Petersburg, Russia, and multiple models have shown that reducing the injection frequency of current PWID reduces HIV prevalence among their non-drug-using sexual partners (Mills et al., 2013; Rutherford et al., 2016). However, developing a network of both sexual and injection relationships adds model complexity and requires detailed partnership data or strong assumptions. For these reasons, a number of models exclude sexual partnerships and only simulate HIV transmission through injection equipment sharing among PWID (Cousien et al., 2017; Cousien et al., 2016; Kretzschmar & Wiessing, 1998; Richardson & Grund, 2012; Rolls et al., 2012).

Among the many PWID network models that have considered sexual transmission, a variety of approaches have been taken to incorporating sexual network data. Mills et al. (2013) opted to build a network including only sexual ties, as well as a separate stochastic, compartmental model to capture transmission via needle/syringe sharing, then considered the results of both models together. Others have created bi-layer networks to simulate HIV transmission via sexual contacts and needle sharing (Fu et al., 2016; Fu et al., 2018; Zhong et al., 2018). For example, Zhong et al. (2018) developed a bi-layer network including one layer representing unprotected sex relationships between PWID and female sex workers, and a second representing needle sharing among PWID, with bridges connecting individuals in both layers. Using this framework, they found that individuals who bridge the two networks are key contributors to the scale and speed of HIV transmission, and therefore should be the target of network-based interventions.

Rather than constructing two overlapping networks to incorporate both transmission routes, many models include a single “risk network.” In some risk networks, each tie represents a specific partnership category: 1) sex only, 2) injection only, or 3) sex and injection (Campbell et al., 2017; Escudero et al., 2017; Escudero et al., 2016; Marshall et al., 2014; Marshall et al., 2012; Monteiro et al., 2016), while in others, ties represent a general risk relationship, where sex and needle sharing cannot be de-coupled (Fujimoto et al., 2015; Rutherford et al., 2016; Young et al., 2013). For example, in the Rutherford et al. (2016) BA model of PWID and female sex workers in Vancouver, Canada, sexual and needle/syringe sharing ties are collapsed into a single tie type, because sexual and injection relationships are frequently coincident among the modelled population. Likewise, the Young et al. (2013) model does not differentiate between sex and injection ties, but rather assigns each individual a risk behaviour value based on the sum of their weighted responses to questions regarding frequencies of condom use, needle and cooker sharing, and unprotected sex. Network ties were further simplified in Fujimoto et al. (2015), such that each tie represented any reported sexual or drug using (rather than solely injection drug using) relationship.

Where do Network Models Add the Greatest Value?

In general, network simulation models add the greatest value when used to investigate a question about how to leverage the structure of a network to maximize the effectiveness of a public health intervention. For example, in 2016, the World Health Organization set

the ambitious target of eliminating HCV transmission among PWID by the year 2030, but the best strategy, or mix of strategies, to achieve that goal is not certain (WHO, 2017). An important question toward this aim is how to focus increased hepatitis C testing and treatment among PWID. On one hand, there is intuitive appeal to the idea of randomly distributing testing and treatment among PWID, as doing so would not require collecting data on partnerships or risk behaviours. On the other hand, such an approach might cure many PWID who have few ties to the network, therefore conferring limited prevention benefit for other susceptible PWID, while missing high-degree individuals who could transmit disease to more partners and re-seed the network with HCV.

Targeting by Degree

Understanding how we can leverage "degree" to improve the effectiveness of elimination strategies is a question to which network simulations are well suited. Fu et al. (2016), for example, designed a model to determine whether to target a Chicago-based hepatitis C peer education program to PWID with the highest degree, and found that targeting in such a manner led to a three-fold increase in the number of HCV infections averted over a 10-year period compared to allocating the intervention randomly. Zhong et al. (2018) similarly observed greater reductions in HIV prevalence when they prevented the highest degree nodes in their model from transmitting HIV than when they prevented transmission from randomly selected nodes. However, the modellers did not specify a particular intervention to curtail transmission and note that the level of network detail required to identify which nodes have the highest degrees may be challenging to obtain in real-world settings. In the U.S., this information is often routinely collected through public health surveillance programs focused on contact tracing and partner notification, but it is difficult to ensure that each individual in the network is surveyed.

In contrast, Zelenev et al. (2018) found that randomly allocated hepatitis C treatment resulted in greater reductions in prevalence than all strategies where PWID were treated based on degree. In addition, in networks with high transitivity, such as the Brooklyn PWID network modelled by Dombrowski et al. (2013b), treating only those with the highest degrees without treating their partners could result in a high risk of re-infection.

To address re-infection risk, a third strategy for allocating HCV and HIV infection prevention efforts has been explored, in which the injection contacts of randomly selected PWID are targeted. Injection contacts may be defined strictly as needle/syringe sharing partners or more loosely as those who use drugs in the same space at the same time. Under the umbrella of targeting contacts, models have also considered *which* contacts are most effective to target. Rolls et al. (2013a) found that treating HCV positive contacts of uninfected PWID was the most effective contact targeting strategy. Treating all infected primary and secondary contacts was slightly more effective in reducing prevalence than treating only primary contacts, as doing so reduces the rate of re-infection; however, in a real-world intervention, the small difference in prevalence between these two strategies may be outweighed by the additional cost of locating and treating secondary contacts. Among models that have simulated all three strategies (i.e. targeting by degree, random targeting, and targeting contacts), targeting contacts has held the top or middle ranking in all. Rolls

et al. (2013a) and Hellard et al. (2014) found that treating contacts of PWID in Melbourne, Australia resulted in the greatest declines in HCV infection incidence compared to random allocation and allocation based on node degree, while Zelenev et al. (2018) and Fu et al. (2016) observed that the benefit from treating contacts fell between that of the other two approaches.

There are a number of factors that may have contributed to these discrepancies in network strategy effectiveness, including network characteristics, epidemic duration, and the type of intervention being simulated. Rolls et al. (2013a) hypothesized that targeting based on degree was likely to be more effective in a network with hubs and a high average number of injecting partners. This idea is supported by the finding that targeting peer education to PWID hubs was the most effective approach to averting new HCV infections in Chicago (Fu et al., 2016). However, when treatment, rather than harm reduction, is simulated, the presence of hubs and higher average numbers of injection partners may paradoxically allow for high re-infection risk, rendering the strategy ineffective. This result was seen in the Zelenev et al. (2018) network where the average number of partners was high (4.2). Meanwhile in networks without hubs, where PWID have few partners on average, such as the Melbourne network described in Rolls et al. (2013a), treating contacts rather than high-degree nodes was the strongest approach.

Epidemic stage may also influence which network-based strategies will produce the greatest reductions in incidence. Campo and Khudyakov (2018) compared the efficacy of network-based hepatitis C interventions within a PWID population in Indiana during a long-established epidemic and a hypothetical outbreak situation. They found that in an established epidemic, removing high degree nodes led to the largest reductions in incidence, while in an outbreak setting, random removal was most effective. This finding is in concert with that of other modelling studies focused on outbreak settings (Bartlett et al., 2017; Zelenev et al., 2018).

One important message that emerges from the network simulation approach is that there is likely no single answer to the question of how to allocate an intervention. The optimal strategy for focusing effort depends on the characteristics of the network itself, the epidemic, and the intervention being considered.

Needle and Syringe Services

Network models have also proven useful for predicting the impact of interventions to reduce injection equipment sharing, such as syringe services and “buddy sharing” programs. Syringe services, sometimes referred to as needle and syringe exchange programs (NSPs), are community-based programs that provide access to sterile injection equipment free of cost and facilitate safe disposal of used needles and syringes. Many offer additional prevention materials, such as alcohol swabs, sterile water, and condoms, education on safer injection practices, testing for HIV and HCV infections, and counselling. Nearly two decades ago, Pollack et al. (2001a, 2001b) used a compartmental model to show that NSPs could produce minor reductions in HCV transmission. However, the authors note that because their model did not account for heterogeneity in number of injection partnerships or injection frequency, it may have overestimated the impact of NSPs in their PWID population. NSPs have been

simulated using a number of other compartmental models (Corson et al., 2013; Vickerman et al., 2007; Vickerman et al., 2012) and network models (Kretzschmar & Wiessing, 1998; Marshall et al., 2014; Rutherford et al., 2016).

Among network modelling studies, Kretzschmar and Wiessing (1998) found that reducing needle sharing frequency could lower HIV incidence if targeted toward new PWID, who had higher baseline needle sharing frequencies and infectivity in the model. In addition, Marshall et al. (2014) predicted that increased NSP coverage, resulting in 10% of PWID sharing syringes per year (compared to 20% in the status quo scenario), would lead to a 34% reduction in HIV incidence by 2040. When applied in the real world, syringe services programs can trigger a series of inter-dependent benefits beyond reducing injection equipment sharing, such as improving access to substance use disorder treatment, which in turn increases the rate at which HIV-positive PWID initiate treatment (Hagan et al., 2000). Indeed, when the NSP scenario was combined with increased HIV testing, greater access to substance use disorder treatment, and scaled-up TasP, the model showed reductions in incidence as high as 62% (Marshall et al., 2014). Likewise, Rutherford et al. (2016) found that reducing syringe sharing was likely to have a significant impact on HIV prevalence.

Network models are particularly well suited to explore the impact of “buddy sharing” programs, as they depend on information regarding network structure. Through these programs, PWID are encouraged **by health workers and through promotional materials** to only share needles and syringes with a single “buddy,” or long-term injection partner. To simulate this intervention, network models can incorporate observed data on the reciprocity of injection ties (i.e. if both partners reported an injection relationship), duration of injection partnerships, and frequency of needle sharing. In their network model of PWID in the Netherlands, Kretzschmar and Wiessing (1998) distinguished between stable buddy relationships, in which injecting equipment is shared on a regular basis between two long-term injecting partners, and incidental sharing with strangers. They found that when the fraction of sharing events that occurred with buddies rose above 0.5, HIV prevalence declined. Buddy sharing is just one example of the utility of network models for understanding interventions targeting specific partnership types or groups of PWID.

What’s Next?

As public health leaders design interventions to tackle HIV and HCV transmission among PWID, network modelling may serve as a valuable tool. Using network models, researchers can compare which targeting strategies or programs may achieve the greatest reductions in disease incidence or prevalence. However, for models to accurately predict the results of an intervention, they should be consistent with empirical data from the relevant networks, and opportunities or direct empirical validation are presently limited by a lack of network data. As the field of network modelling develops, both data availability and calibration approaches will likely improve, allowing for more confidence in model outputs. In addition, as network-based interventions are implemented among real populations of PWID, observed outcomes can be compared to initial modelling results to both test the strength of a given model and gain a greater insight into the ways in which modelling assumptions can influence simulated outcomes.

Conclusions

Network modelling can be used to address critical knowledge gaps among public health decision makers and program planners. When developing a network simulation, it is important to recognize that different model frameworks are better suited to capture specific sets of network characteristics and have different data demands. However, each model within one of the broader model types described has a unique structure that influences its ability to fit real world networks and address specific questions. Therefore, in this review, we have avoided comparing the strengths and weaknesses of each model type. Rather, we outline some of the benefits and trade-offs of adding complexity to models through dynamic partnership formation and dissolution, population turnover, and sexual transmission routes, and discuss how each may affect the results of simulated interventions. The network modelling studies reviewed in this paper demonstrate that PWID network characteristics, such as injection partnership stability, degree distribution, and epidemic duration, may have a significant impact on the effectiveness of treatment and harm reduction interventions. They also highlight the potential of network simulations to serve as powerful guides for local governmental agencies' HIV and HCV infection prevention and control efforts.

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Box 1.

Glossary of common modelling terms

Term*	Meaning	Synonyms
Network Structure		
Network	A collection of entities and the set of relationships among them.	Graph
Node	The entity of interest in a network. In infectious disease modelling, a node represents an individual.	Vertex, Actor
Tie	A connection between two nodes. In infectious disease modelling, ties exist between nodes with a non-zero probability of disease transmission. For example, a needle sharing or sexual partnership through which HIV or HCV transmission could occur.	Edge, Link, Connection, Line
Hub	A node with a large number of ties in comparison to other nodes in the network.	Cluster
Bridge	A tie that connects two otherwise disconnected components of the network.	
Degree	The number of ties a given node has to other nodes.	
Average degree	The average number of ties per node.	
Degree distribution	The set of probabilities P(k) where k=1,2,… that a randomly selected node has degree k.	
Network density	A measure of the proportion of possible ties that are actualized among members of a network. Calculated by dividing the number of actual ties in the network by the number of possible ties. While needle sharing ties could hypothetically exist between all nodes in a network of only people who inject drugs, the number of possible sexual ties is restricted by sex partner preferences (e.g. MSM, heterosexual).	
Clustering coefficient	Measure of the degree to which nodes in the network are clustered together. A measure of the density of ties around a given node.	
Path length	The number of ties along the shortest path connecting two nodes. In other words, the degrees of separation between two individuals.	Distance
Average path length	The average distance between all pairs of nodes in a network.	
Network diameter	The maximum path length between any pair of nodes in the network.	
Network Features		
Heterogeneity *(vs. homogeneity)*	Demographic, biological, or behavioural attributes are assigned to individuals separately. For example, each individual can be given a specific race, rate of unprotected sex, and injection frequency, which influence their partnership formation and probability of disease transmission. A key characteristic of network models is their ability to incorporate individual heterogeneity.	
Homogeneity *(vs. heterogeneity)*	Individuals in each disease state are assumed to have the same characteristics. Demographic, biological, or behavioural differences are introduced by dividing the population into additional sub-compartments, rather than by attributing these differences to each individual separately. Each individual in a sub-compartment has the same rate and probability of contact with other individuals.	
Homophily	The preference for nodes to form ties with nodes that are similar to themselves in some way. In human networks, the	Assortativity, Assortative mixing

Term*	Meaning	Synonyms
	tendency for people who share traits like gender and race to be connected.	
Transitivity	The tendency for two people who share a common relationship with a third person to be connected themselves. Often described with the saying "a friend of my friend is also my friend."	Clustering
Preferential attachment	The tendency of new nodes to form ties with more connected nodes. Sometimes referred to as the "rich-get-richer" hypothesis.	
Scale-Free	A scale free network has a degree distribution that follows a power law. That is, the fraction $P(k)$ of nodes in the network with degree k follows the formula: $P(k) \sim k^{-\gamma}$ where γ is a parameter whose value falls in the range $2 < \gamma < 3$. Notable characteristics of scale-free networks include the presence of hubs and a clustering coefficient that decreases as the average node degree increases. The result is that low-degree nodes belong to dense network of sub-components and those sub-components are connected to each other through hubs. For example, a social network where individuals are grouped into highly connected communities, but have a few acquaintance relationships outside of their communities.	
Modelling Types		
Network model	A model type in which the full contact structure of individuals over a period of time are represented.	
Compartmental model	This model type stratifies the population into different compartments, such as health states. Compartments are assumed to represent homogenous subpopulations where all members share the same characteristic, such as age, sex, and risk of infection.	
Static model *(vs. dynamic model)*	In a static model, all variables are constant and independent of time. In a static network model, population, risk behaviours, and partnerships remain fixed over time and in equilibrium.	
Dynamic model *(vs. static model)*	A dynamic model contains at least one time dependent variable. Using a dynamic network model, populations and partnerships can be made to shift over time as a result of factors such as births, deaths, migration, and changes in disease prevalence.	
Deterministic model *(vs. stochastic model)*	This model type describes the average behaviour of a system without taking into account chance events in single entities (e.g. individuals). Therefore, these models are often applied to situations with large numbers of individuals where stochastic variation becomes less important and heterogeneity can be accounted for using subpopulations. The outputs of this model type are fully determined by the initial inputs and conditions.	
Stochastic model *(vs. deterministic model)*	A type of model where parameters and variables are described by probability distributions and account for random variation in risk, transmission, and other factors over time, the result being that the same initial conditions can produce different outputs with each model run.	
Modelling Process		
Parameter	A quantity used to describe the relationships between model variables. For instance, a parameter can describe the likelihood of disease transmission between two individuals or how long an individual remains in a given disease state. Parameters can be selected based on empirical data, model calibration, or assumptions.	
Calibration ("calibrate")	The process of adjusting model parameters so that outputs agree with the data used for model development.	
Goodness-of-fit	The extent to which observed data match the values predicted by the model.	

Term*	Meaning	Synonyms
Burn-in	The practice of discarding some iterations at the beginning of a model simulation run, because early samples may not accurately represent the desired distribution.	
Time horizon	The chosen time at which the effects of an intervention will be evaluated.	
Sensitivity analysis	An assessment of the impact that input parameters have on model predictions. They are used to determine the robustness of the results to changes in initial conditions and the external validity of model outcomes outside of the simulation setting.	

* Terms may have alternative definitions. The definitions selected apply to modelling HCV and HIV transmission among networks of people who inject drugs.

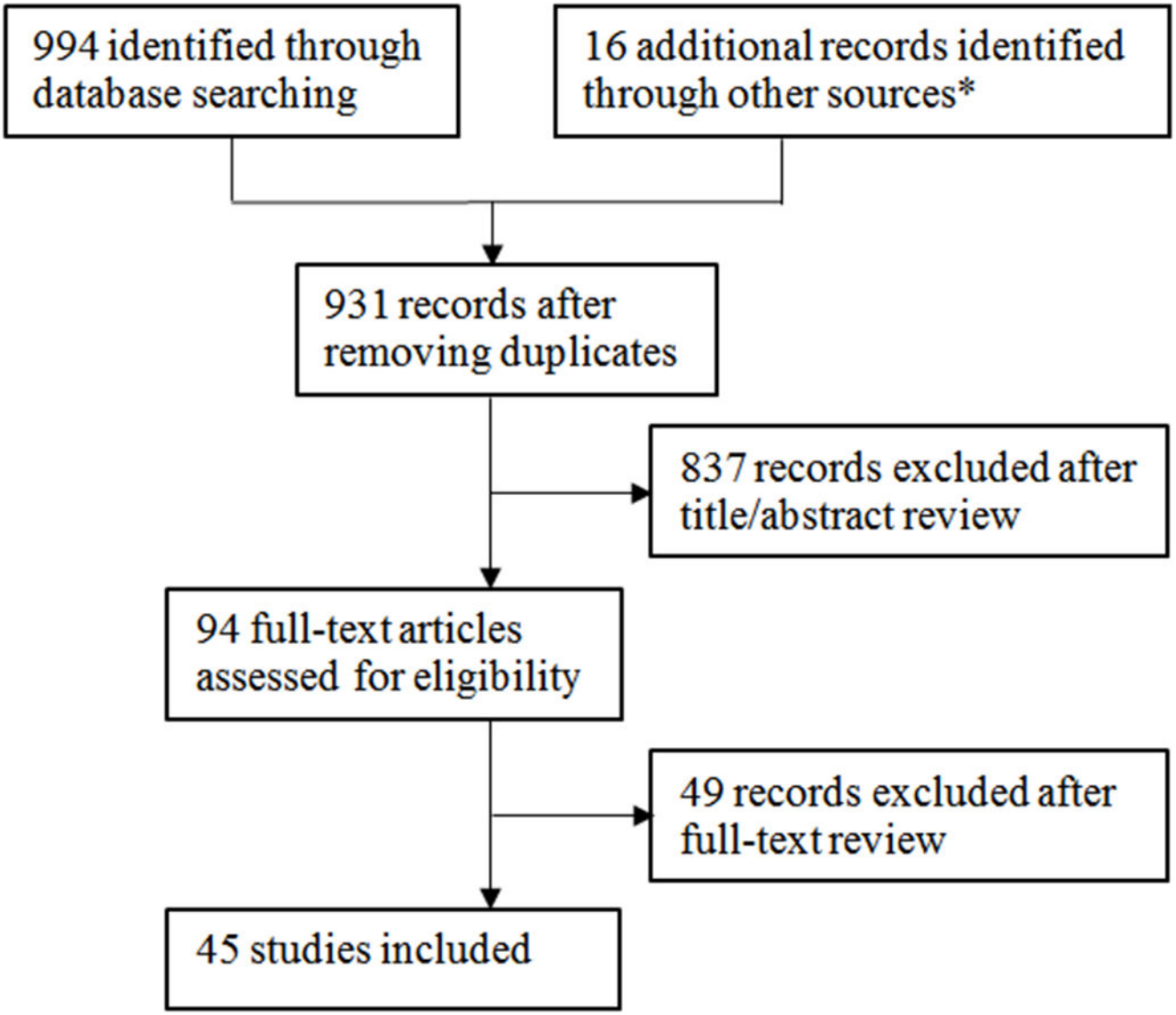

Figure 1.
Flow diagram of studies assessed for review
*Other sources include reference lists of eligible studies and personal databases of collaborators involved in network modelling

Table 1.

Network models identified through literature review

Author	Year	Disease(s)	Setting	Model framework	Primary focus or interventions examined
Campbell et al.	2017	HIV	Indiana, USA	Original network (no tie simulation), dynamic	Map transmission pathways during 2016 HIV outbreak using social and genetic distance data
Campo & Khudyakov	2018	HCV/HIV	Indiana, USA	ABM, dynamic	Random or targeted removal of nodes in a sustained or new HCV epidemic
Cousien et al.	2017	HCV	Montreal, Canada	Erdös-Rényi, static	Improved treatment, linkage to care
Cousien et al.	2016	HCV	5 cities, France	Erdös-Rényi, static	Improved treatment, linkage to care
Cousien et al.	2015	HCV	(review)		
Cousien et al.	2018	HCV	Melbourne, Australia	ABM, dynamic	Cost effectiveness of improved treatment, linkage to care, and harm reduction
Crawford et al.	2018	HIV	St. Petersburg, Russia	Erdös-Rényi, static	Estimate PWID population size
Cui et al.	2009	HIV	Yunnan Province, China	ABM, Small world, dynamic	Build ABM network
Delva et al.	2016	HIV	(review)		
Dombrowski et al.	2013a	HIV	New York City, USA	BA, dynamic	Compare topology of an injection and sexual network
Dombrowski et al.	2017	HIV	New York City, USA	ERGM, dynamic	Explore firewall effect to spread of HIV
Dombrowski et al.	2013b	HIV	New York City & Colorado Springs, USA	ERGM, dynamic	Determine importance of attribute and degree homophily in PWID networks
Escudero et al.	2017	HIV	New York City, USA	ABM, dynamic	Determine proportion of HIV transmission attributable to acute HIV infection among PWID
Escudero et al.	2016	HIV	New York City, USA	ABM, dynamic	Estimate HIV incidence and number of transmission acts at each care continuum stage
Friedman et al.	2000	HIV	New York City, USA	Original network (no tie simulation), static	Explore firewall effect to spread of HIV
Fu et al.	2016	HCV/HIV	Chicago, Illinois, USA	ABM, dynamic	Random or targeted peer education
Fu et al.	2018	HIV	Chicago, Illinois, USA	ABM, dynamic	Random or targeted enrollment in PrEP
Fujimoto et al.	2015	HIV	Houston, Texas, USA	ERGM, dynamic	Explore venue based ties and role of homophily
Gile & Handcock	2011	HIV	Mykolaiv, Ukraine	ERGM, static	Develop ERGM; estimate of HIV prevalence
Gutfraind et al.	2015	HCV	Chicago, Illinois, USA	ABM, dynamic	Map incidence and prevalence trends
Hellard et al.	2015	HCV/HIV	(review)		
Hellard et al.	2014	HCV/HIV	Melbourne, Australia	ERGM, static	Random or targeted treatment
Khan et al.	2013	HIV	New York City, USA	ERGM, dynamic	Explore firewall effect to spread of HIV
Khan et al.	2018	HCV/HIV	New York City, USA	ABM, dynamic	Increased DAA treatment, improved syringe access and MAT
Kretzschmar & Wiessing	1998	HIV	Rotterdam, Netherlands	Random, static	Reduce needle sharing in new or long-term PWID, share with a single “buddy”

Author	Year	Disease(s)	Setting	Model framework	Primary focus or interventions examined
Marshall et al.	2014	HIV	New York City, USA	ABM, Erdös-Rényi, dynamic	Improved treatment, NSPs, combinations of treatment, and harm reduction interventions
Marshall et al.	2012	HIV	New York City, USA	ABM, Erdös-Rényi, dynamic	Build ABM network
McCloskey et al.	2016	HIV	10 locations across globe	BA, static	Estimate structural parameters of PWID network
Metzig et al.	2017	HCV	London, UK	Exponential clustered network, dynamic	Compare exponential clustered, Erdös-Rényi, and compartmental SIS models; improved treatment and behavior change
Mills et al.	2012	HCV	Bristol, UK	Configuration model, static	Determine impact of assortivity on prevalence and incidence
Mills et al.	2013	HIV	St. Petersburg, Russia	ABM, dynamic	Estimate HIV prevalence
Monteiro et al.	2016	HIV	New York City, USA	ABM, dynamic	Determine impact of incorporating greater heterogeneity in model
Nucit & Randon-Furling	2017	HCV/HIV	3 cities, France	Scale-free, dynamic	Map hypothetical spread of HCV between major cities
Pitcher et al.	2018	HCV	(review)		
Richardson & Grund	2012	HIV	New York City, USA	ABM, static	Determine how diffusion patterns change depending on level of structural complexity in the model; explore role of shooting galleries
Rolls et al.	2012	HCV	Melbourne, Australia	ABM, static	Build ABM network
Rolls et al.	2013a	HCV	Melbourne, Australia	ERGM, static	Random or targeted treatment
Rolls et al.	2013b	HCV	Melbourne, Australia	ERGM, static	Build ERGM; estimate PWID population size
Rolls et al.	2015	HCV	Melbourne, Australia	ERGM, static	Compare ERGM, Erdös-Rényi, and configuration models
Rutherford et al.	2016	HIV	Vancouver, Canada	BA, static	Improved treatment, reductions in syringe sharing, time to diagnosis, and time to treatment
Scott et al.	2016	HCV	(review)		
Shahesmaeili et al.	2015	HIV	Kerman City, Iran	MMMM, static	Determine how location of individuals in a network relates to HIV transmission risk
Young et al.	2013	HIV	Appalachia, Kentucky, USA	Erdös-Rényi & original network (no tie simulation), static	Compare features of randomly generated networks to observed network and discuss implications for HIV risk
Zelanev et al.	2018	HCV/HIV	Hartford, Connecticut, USA	Stochastic block, dynamic	Compare fit of stochastic block, ERGM, small world models; random or targeted treatment
Zhong et al.	2018	HIV	(unspecified)	BA & Erdös-Rényi, static	Determine role of nodes that bridge a sexual and injection network

Abbreviations: ABM (agent-based model), BA (Barabási and Albert), DAA (direct acting antiviral), ERGM (Exponential Random Graph Model), HCV (Hepatitis C), HIV (Human Immunodeficiency Virus), MAT (medically assisted treatment), MMMM (Multiple membership multilevel model), NSPs (needle and syringe exchange programs), PWID (people who inject drugs), SIS (susceptible-infected-susceptible)

Table 2.

Approaches to modelling tie formation in network models.

Approach	Allowance for heterogeneity in tie probabilities	Typical target statistic(s) for fitting networks	Key assumptions	Examples
Erdös-Rényi Random Graph Model	None	Mean degree	There are a fixed number of nodes in a network Ties are independent Each tie is equally likely to occur, so clustering is rare	(Cousien et al., 2017; Cousien et al., 2016; Crawford et al., 2018; Marshall et al., 2014; Marshall et al., 2012; Young et al., 2013; Zhong et al., 2018)
Stochastic Block Model	Tie probability is dependent on the blocks that each node belongs to	Mean degree Average path length Clustering coefficient	Nodes within a block are connected to nodes in other blocks according to their block membership alone	(Zelenev et al., 2018)
Watts Strogatz Small World Model	None	Mean degree Average path length Clustering coefficient	Each node is connected to every other node in the network by a small number of ties Networks are clustered	(Cui et al., 2009)
Barabási-Albert Preferential Attachment Model	Tie probability is based on preferential attachment	Mean degree	New nodes form ties based on degree alone Older nodes have more ties on average than newer nodes	(Dombrowski et al., 2013b; Rutherford et al., 2016; Zhong et al., 2018)
Exponential Random Graph Model	Tie probability is a function of covariates selected by investigators (e.g. sex, race, and degree of index node, age difference between nodes)	Many targets selected by investigators, (e.g. homophily in sex and race, mean degree, average path length, clustering coefficient)	The shape of the network (i.e. the possible set of configurations of the nodes) is constrained by the statistics of the observed network provided by investigators	(Dombrowski et al., 2013a; Dombrowski et al., 2017; Fujimoto et al., 2015; Hellard et al., 2014; Khan et al., 2013; Rolls et al., 2013a; Rolls et al., 2013b)