

Contact tracing for hepatitis C: The case for novel screening strategies as we strive for viral elimination

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ABSTRACT

Contact tracing has been a key element of the public health response to infectious diseases for decades. These practices have been powerful in slowing the spread of tuberculosis, HIV, and other sexually transmitted infections. Despite success in other contexts, contact tracing for hepatitis C virus (HCV) has historically been considered infeasible because of a long asymptomatic period, which often makes it difficult to pinpoint the time of acquisition. Additionally, individuals may be reluctant to identify injecting partners because of stigma or fear of criminal repercussions. However, multiple factors - including the improved curability of HCV with advances in direct acting antiviral agents (DAAs), the implementation of age-based screening, and the current opioid epidemic - have led to rapid changes in the landscape of HCV. HCV is increasingly concentrated among young people who inject drugs (PWID), many of whom are inadequately being reached by current screening practices. With the shift in the population most at risk for HCV and the fundamental changes in how we manage this disease, it's time to also rethink the public health response in identifying and informing those who may have been exposed. Contact tracing programs for HCV can augment existing screening strategies to provide curative treatment for patients and their partners, prevent reciprocal transmission of HCV between risk partners and within networks, and ultimately reach individuals who aren't yet engaged in healthcare and harm reduction. While there remain limitations to contact tracing for HCV, it has the potential to be a powerful tool in slowing the spread of the virus as we attempt to achieve viral elimination.

Introduction

With the advent of direct-acting antivirals (DAAs) for hepatitis C virus (HCV), the World Health Organization (WHO) has established the goal of HCV elimination by 2030 (*Combating Hepatitis B & C to Reach Elimination by 2030, 2016*; *Combating Hepatitis B & C to Reach Elimination by 2030, 2016*). To achieve these targets, dramatic changes in screening and treatment programs need to be instituted to halt the transmission of HCV between and within injection and sexual networks (*Combating Hepatitis B & C to Reach Elimination by 2030, 2016*; *Combating Hepatitis B & C to Reach Elimination by 2030, 2016*). Contact tracing, if implemented successfully, can be a tool to expand HCV screening and treatment, halt transmission between partners and within networks, and engage people who inject drugs (PWID) in harm reduction and risk counseling as we strive toward viral elimination.

Contact tracing has long been a mainstay of the public health response to outbreaks (Ferreira, Young, Mathews, Zunza, & Low, 2013).

Initially, contact tracing was utilized to identify and treat asymptomatic individuals that had been exposed to syphilis in the 1940s (Rutherford & Woo, 1988). These programs were part of a successful approach to interrupting the transmission of syphilis, and they have since been implemented for other sexually transmitted infections (STIs) including gonorrhea, chlamydia, and HIV (Ferreira et al., 2013; Rutherford & Woo, 1988). Contact tracing has also been utilized for mycobacterium tuberculosis (TB) (Kasaie, Andrews, Kelton, & Dowdy, 2014; Martinez et al., 2017), and tracing outbreaks in the community and health care setting of measles, multidrug resistant bacteria, and Ebola, among others (Marx et al., 2017; Sabin et al., 2018; Swanson et al., 2018). Contact tracing serves a dual goal. For the individual, it provides an opportunity for intervention to treat disease and/or reduce risk factors. For the population, it helps to break ongoing chains of transmission and reduce new incidence.

While contact tracing has been the cornerstone of the public health responses for decades, there has been minimal discourse about the

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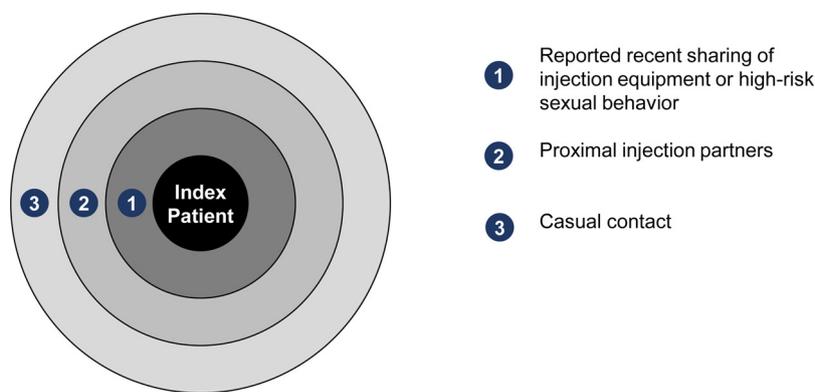


Fig. 1. Concentric circle approach to contract tracing.

application of these principles to HCV. Prior discussions recommend against routine HCV contact tracing on the grounds of the extended latency of infection, the often stigmatized and/or illegal mechanisms of transmission, and the expense of tracing and testing (Poll, 2013).

Given the recent rise in incident HCV among young PWID, and the availability of effective treatment, we argue that it is time to reconsider contact tracing programs for HCV. We will offer a model for contact tracing for HCV, discuss the potential benefits and limitations, and propose further research needed to build an evidence base evaluating this approach.

Effectiveness of contact tracing programs for infectious disease

Limited literature to date has explored the implementation of contact tracing for HCV. However, contact tracing programs for other infectious diseases provide a clear and compelling model. Contact tracing can take various forms: (1) patient referral, or healthcare providers encouraging an index patient to notify their partners (2) provider referral, or a third-party (including physicians, health educators, nurses, or public health officials) notifying potentially exposed individuals, and (3) contract referral, or encouragement of the index patient to notify those who may have been exposed with the understanding that a third party will notify these individuals if they do not present for care by a certain date (Ferreira et al., 2013).

Contact tracing programs for TB have been implemented and extensively studied for decades. Although TB diverges from HCV in mode of transmission, symptoms, and at-risk populations, these programs provide important insights for the creation of HCV contact tracing programs. The concentric circles approach (also known as the “stone in the pond” principle) (Tuberculosis: A Comprehensive International Approach, 2000), is a helpful model for prioritizing testing and treatment of those most at-risk. Close contacts are informed and screened first. If the rate of disease is higher in close contacts than the general population, the second ring of contacts will then be screened, and so on. However, if those screened are not found to have increased rate of infection, the contact tracing can be discontinued with that cohort. Though contact tracing for HCV will require a new framework for determining risk, this model provides an efficient and logical approach for determining how to identify and screen contacts.

Multiple studies have demonstrated that contact tracing is acceptable and effective as a public health response for HIV, and especially that network tracing of recently infected individuals will be more beneficial than tracing networks of longer-term HIV-positive patients (Nikolopoulos et al., 2016; Recommendations for Partner Services Programs for HIV Infection, Syphilis, Gonorrhea, & Chlamydial Infection, 2008). Anonymous provider notification has been demonstrated to be preferred by most index patients (Mathews et al., 2002). Additionally, provider referral has been shown to increase the rate of partners presenting for medical evaluation when compared to other

patient notification strategies (Ferreira et al., 2013; Mathews et al., 2002), though several studies have also demonstrated no clear benefit of one strategy (Hogben, McNally, McPheeters, & Hutchinson, 2007). Across a systematic review of HIV contact tracing, a mean of 67% of named partners were notified of a potential exposure, and of those individuals, 20% tested positive for HIV, justifying the U.S. Preventative Services Task Force (CPSTF) recommendation for routine partner notification for HIV (CPSTF, 2007; Hogben et al., 2007).

There is data suggesting that contact tracing is also useful in reducing future risky behaviors. For example, condom use is more prevalent in serodiscordant partners when one has been notified about previous potential HIV exposure (Hoxworth et al., 2003), suggesting that the notification helps drive safer sex behaviors in this population. Informing someone of past HIV exposure or diagnosing someone with HIV often substantially changes risk behaviors (Smoak, Scott-Sheldon, Johnson, & Carey, 2005). If patients are asymptotically infected with HIV, they may be unknowingly transmitting the virus to partners and networks, but if they test positive for HIV, they subsequently reduce high-risk activities by 50% or more (Lunny & Shearer, 2011).

Contact tracing has been successfully implemented and expanded for other sexually-transmitted infections (STIs) - including chlamydia, gonorrhea, and syphilis. Contact tracing for gonorrhea and chlamydia, paired with expedited partner treatment (EPT), is effective in decreasing recurrent and persistent chlamydia and gonorrhea infections and also increases the number of partners treated (Golden et al., 2005).

Contact tracing for HCV: a model

Who is considered a contact?

Adapting the “concentric circles” model, we can systematize our approach to contact tracing and prioritize individuals for screening [Fig. 1]. The first ring of the circle includes the highest risk contacts – those with whom the index patient reports recent sharing of injection equipment or high-risk sexual behaviors. Even if screening is negative, outreach to high-risk contacts is an opportunity for engagement in frequent re-screening, harm reduction programs, and risk counseling.

The next circle of the model includes moderate-risk contacts, such as proximal injection partners who may not report sharing of needles and syringes, but do report increased risk behaviors including buying or sharing drug, injecting drugs in the same location, minimal sharing of injecting equipment or injection surfaces, or injecting or receiving injection with/from a person (J.Eckhardt, Davis, Edlin, & Marks, 2018; Eckhardt, Scherer, Winkelstein, Marks, & Edlin, 2018). Those engaged in contact tracing should move to the second circle of the model if the first circle has a higher prevalence of HCV than expected for the sub-population. These proximal partners are still at risk for HCV infection and should be considered as contacts, although are a lower priority for outreach than those with whom index patients have directly shared

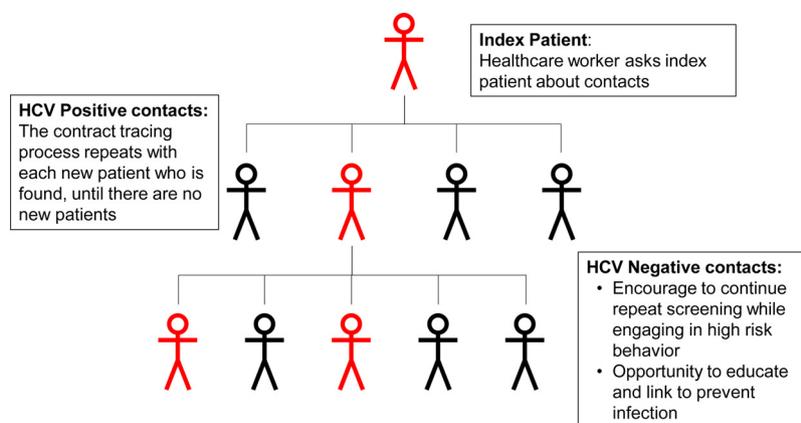


Fig. 2. Contract tracing overview.

injection equipment. The last priority for contact tracing is casual contacts of those diagnosed with acute HCV. These individuals likely would not require active screening beyond existing population screening recommendations. The appropriate recall period for eliciting contacts is not clear and would require further study. However, even remote contacts are likely to meet current indications for screening, so high-risk contacts may be prioritized even if a timeline cannot be established.

Who should be responsible for contact tracing?

Contact tracing programs should be individualized depending on the setting, but we argue that healthcare providers (specifically those who focus on care of current PWID) are one option to carry on contact tracing programs. Overall, research has demonstrated that patients prefer confidential, anonymous provider referral, and this method has been most effective in linking exposed individuals to care (Mathews et al., 2002; Nikolopoulos et al., 2016; Recommendations for Partner Services Programs for HIV Infection, Syphilis, Gonorrhea, & Chlamydial Infection, 2008). For PWID specifically, a third-party is preferred to locate and notify exposed partners (Brewer & Hagan, 2009). Healthcare providers can include doctors, nurses, health educators, social workers, and care coordinators – and future research should investigate which provider will most effectively lead these programs. Limitations to provider notification include the significant burden already placed on healthcare providers and limited provider education about contact tracing and notification methods. In contrast, a potential model for HCV contact tracing includes a top-down approach, led primarily by public health and administrative officials. This model would have the benefits of utilizing officials' training in epidemiology and expertise in tracing the spread of infectious disease. However, a public health driven approach is limited by patient reluctance to engage with government officials - especially when discussing stigmatized and illegal behaviors. Further research - including survey studies, qualitative analyses of preferences of PWID, and evaluations of existing models - must be conducted into the most appropriate model for HCV contact tracing programs.

Where should contact tracing occur?

Contact tracing will be most effective in an environment where recent infection is often diagnosed and treated, where there is access to harm reduction services, and where there is focus on a subpopulation. For these reasons, we argue that healthcare settings serving at-risk populations (e.g. harm reduction centers) are the best place to initiate contact tracing. These programs are on the front line of the opioid and HCV epidemics. Additionally, these centers likely mitigate stigma associated with risk-taking behaviors, involve regular provider visits

(along with social work, nursing, and health educators who may assist in management of disease), and can decrease risk of reinfection with the availability of sterile injecting equipment and health education (Eckhardt, Davis et al., 2018, 2018b). These factors would also allow providers to engage those with high-risk injection practices, even those who ultimately test negative for HCV, with resources and education to promote safer behaviors. Integration of an HCV treatment program in an inner-city clinic providing methadone maintenance and primary medical care has encouraged psychological and behavioral transformations - including increased self-care and decreased substance use - by addressing both individual and social level barriers (Batchelder, Peyser, Nahvi, Arnsten, & Litwin, 2015). Further, diagnosis and treatment of HCV in the harm reduction setting may reduce future risky behaviors by decreasing shame associated with HCV and substance use, reducing substance use, and encouraging disclosure of HCV status (Batchelder et al., 2015). And, peer support, specifically the collaboration between peer educators and medical providers in the harm reduction setting, has been demonstrated to increase HCV assessment and treatment uptake by overcoming feelings of mistrust toward the medical system (Crawford & Bath, 2013). Young PWID often engage in health-related prevention activities among their peers (Mateu-Gelabert et al., 2018), and could be active players in contact tracing programs to promote HCV screening, treatment, and risk reduction among their injection networks.

Scaling up screening to enable contact tracing programs

HCV screening plays an important role in contact tracing – frequent screening of patients at high-risk will improve our ability to identify recent HCV infections, and we can use contact tracing most effectively for patients who are recently infected. Reciprocally, contact tracing will augment current screening practices to engage individuals who are difficult to reach with existing strategies to propel screening efforts forward [Fig. 2]. Although guidelines currently recommend screening of those engaged in high-risk behaviors (Ngo-Metzger, Ward, & Valdiserri, 2013), we continue to significantly underdiagnose acute HCV infection ("Surveillance for Viral Hepatitis - United States, 2016,"). Many high-risk individuals, such as young PWID and MSM, may not be connected with the healthcare system. Those that are connected may not be asked about, or may not be willing to disclose, risk behaviors.

To increase screening of high-risk populations, education about screening guidelines and resources should be provided to all medical providers – not just those actively involved in HCV care. Additionally, community-based healthcare settings should integrate HCV screening in routine care. These settings have enormous potential for reaching and engaging PWID and can overcome many barriers of contact tracing including stigmatization and poor healthcare engagement (Eckhardt, Davis et al., 2018, 2018b). Advancements in point-of-care (POC) testing

for HCV, many of which are in the pipeline or have been recently launched but remain cost prohibitive, will be imperative to expand rapid diagnosis and linkage to care, as the constraints of utilizing both screening and diagnostic tests and delayed results can be burdensome for patients and are associated with increased loss to follow-up (Scott et al., 2018; Sheikh & Poustchi, 2018). By emphasizing the importance of frequent screening for those most at risk and by educating both patients and providers about guidelines and new treatments, we can better identify recent infections to implement contact tracing for these patients.

Benefits and limitations of contact tracing

Benefits of contact tracing for HCV

HCV mirrors other infectious diseases in that it has a lengthy asymptomatic period, socially stigmatized modes of transmission, and high-risk of transmission among social networks. However, we must also consider the unique features of HCV when discussing the implementation of contact tracing.

The epidemiology of HCV is changing dramatically, especially within developed countries. With the introduction of direct acting antiviral therapy, 12 countries are on track to meet World Health Organization goals, and eliminate HCV by 2030 (Razavi, 2018). Conversely, after years of stable HCV incidence (Onofrey et al., 2011), reported cases of acute HCV infection in the United States began increasing dramatically in 2004, including a 3.5-fold increase from 850 cases in 2010 to 2967 cases in 2016 ("Surveillance for Viral Hepatitis - United States, 2016," 2016; J. E. Zibbell et al., 2018). The increase in acute HCV is closely linked to the opioid epidemic (Miller et al., 2002; Onofrey et al., 2011; Quinn, Fong, Guarino, & Mateu-Gelabert, 2019; Tempalski et al., 2013; J. Zibbell et al., 2015; J. E. Zibbell et al., 2018). The sharing of injection equipment accounts for nearly four in five acute infections (Matthews et al., 2011), and states with the highest opioid prescribing rates have also had substantial increases in acute HCV diagnoses (Suryaprasad et al., 2014). Although it's admittedly a suboptimal use of resources to trace contacts of those who acquired the infection remotely, the shifting demographics of HCV increases the utility of contact tracing as more newly diagnosed cases are also recently acquired infections.

Due to the link with the opioid epidemic and the availability of effective HCV treatment, the demographics of patients with HCV are also shifting. In the United States, between 2005 and 2016, the largest increases in rates of HCV were in individuals ages 20–39, and this age group now has the highest number of reported acute HCV cases annually. Over this 11 year period, the number of acute infections for individuals 20–29 have increased almost 7-fold, from 0.4 cases per 100,000 population in 2005 to 2.2 cases per 100,000 population in 2016. (Surveillance for Viral Hepatitis - United States, 2016). Injection drug use continues to be the most commonly cited risk factor in this age group (Zibbell et al., 2015). Similarly in Australia, where viral elimination is on target, the highest rates of new infections remain in those aged 25–39 (Hepatitis B and C in Australia Annual Surveillance Report Supplement, 2016).

Not only have the demographics of HCV changed dramatically, but the testing and treatment practices have also evolved. Varying screening strategies have been implemented in different regions based on local epidemiology. For example, a one-time age-based screening for individuals in the United States born between 1945 and 1965 substantially increased testing rates when compared to risk-based testing (Barocas et al., 2017; Campos-Outcalt, 2012; Isenhour, Hariri, Hales, & Vellozzi, 2017; USPSTF, 2013). At the same time, direct-acting antiviral agents have revolutionized treatment with cure rates greater than 90% in the general populations, and similar efficacy for PWID (Hajarizadeh et al., 2018).

With curative treatment for HCV comes the possibility of viral

elimination, though this will require treating large populations of PWID to disrupt the cycle of transmission between partners and within networks. Simulations have suggested that social networks should be considered in HCV treatment strategies to accelerate reduction of HCV prevalence over the long-term and ensure DAAs can produce maximum community benefit (Hellard et al., 2014). Scaling up HCV treatment for PWID can significantly decrease the prevalence of disease by reducing onward transmission (Martin et al., 2013).

With the shifting demographics of HCV and the recent availability of curative treatment, it is time to adjust our public health response. Previously, the high proportion of older individuals living with chronic HCV made it logistically challenging and unreasonably expensive to contact decades of exposed individuals (Poll, 2013). However, these individuals are being increasingly recognized, treated, and cured of their infection due to age-based screening recommendation to promote routine testing in this population (Viner, Kuncio, Newbern, & Johnson, 2015). Concurrently, the highest rate of new infections is occurring in young people who inject drugs. Thus, HCV has progressively become a disease of those who inject drugs and/or are engaged in high-risk sexual behaviors, with a rapidly growing proportion of recently infected individuals (Danta et al., 2007; J. E. Zibbell et al., 2018).

Limitations of contact tracing for HCV

There are limitations to contact tracing for HCV. First, the long asymptomatic phase of HCV has been noted as a potential downside to contact tracing, though we argue this is actually a factor that supports the need for contact tracing. It has been argued that the asymptomatic nature of infection is problematic as people may not seek testing, and when diagnosed it can be challenging to ascertain when an individual was infected and who they may have exposed. Other reasons patients do not get tested for HCV are decreased awareness of HCV, limited understanding of risk for HCV, insufficient engagement with healthcare systems and/or lack of insurance (Viner et al., 2015). While the extended asymptomatic phase of HCV can be a barrier to patients accessing healthcare, this factor actually highlights the importance of contact tracing to reach those who likely do not know they are infected and are at increased risk of spreading the virus. Further, some have argued that the spontaneous clearance of HCV in many patients – estimated to be about 26% of patients at 2 years – makes contact tracing a poor use of resources (Micallef, Kaldor, & Dore, 2006). However, individuals who have been infected with HCV are likely engaging in high-risk behaviors and are at increased risk of re-infection. Engagement of these individuals with the health care system following possible HCV exposure will be beneficial in the long-term for them and for their community. Frequent screening of high-risk populations to diagnose recent HCV infections will be crucial for identifying recent infections, and subsequent contact tracing will augment screening strategies to engage hard-to-reach patients.

Additionally, contact tracing for HCV is complicated by the stigmatized and often illegal mechanisms by which the virus is transmitted, which may lead patients to be wary of communicating risk factors to healthcare providers. Further, patients may be cautious of "outing" individuals with whom they have injected drugs or engaged in risky sexual behaviors. For HIV contact tracing, it is been demonstrated that a general mistrust of public health officials may lead men who have sex with men (MSM) to be less willing to provide partner information. Also, some PWID may be wary of reporting those they inject with because they fear legal ramifications for themselves and their partners (Passin et al., 2006). Participants in a partner notification system for HIV voiced concerns about confidentiality with third-party involvement, aligning with prior findings that demonstrate a general mistrust of public health officials for marginalized groups (Mimiaga et al., 2009). Overcoming stigma is challenging, though dramatic measures - such as the decriminalization of drug use and expansion of social services - would significantly help. Importantly, co-locating contact tracing

within community-based healthcare settings - including syringe services programs (SSPs), Medication-Assisted Treatment (MAT) programs, supervised injection facilities (SIFs), mobile health care programs, and homeless health centers - will be an important way to overcome stigma of traditional medical and public health environments (Marlatt, 1996).

Similarly, many individuals may be unable to report contacts because sexual and injection relationships are frequently anonymous. There has been discussion in the literature about difficulties in contact tracing for HIV given the prevalence of infection among anonymous sexual partners and those exchanging sex for money and drugs (Götz et al., 2005). In a study about partner notification for STIs and HIV, 89% of 78 total participants reported not notifying some partners of exposure due to anonymous sexual encounters (Mimiaga et al., 2009). Further, meeting partners on the internet may increase high-risk sexual behaviors and prove difficult for finding partners to notify of exposure (Danta et al., 2007). Individuals who inject drugs also have been shown to forget a large proportion of those with whom they inject (D. B. Brewer & Garrett, 2001), and often do not have contact information or a way to reach those who may have been exposed (Hochberg, Berringer, & Schneider, 2015). One study of a combined social network and molecular phylogenetic approach to network tracing found the ability to track patterns of HCV infection was diminished by practical constraints of identifying and locating PWID in a busy and rapidly shifting street-drug scene (Aitken et al., 2004). Additionally, those who acquire HCV through injection drug use have been shown to be more socially disadvantaged and, thus, often without traditional means of contact, including cell phones or stable residences (Matthews et al., 2011). And, even if contact tracing programs are able to reach exposed individuals, many may not present for testing and treatment given decreased knowledge about HCV and barriers to medical care (Brewer & Hagan, 2009).

Additionally, PWID may not always endorse risk behaviors that expose others to HCV. It's been demonstrated that proximal partners are at risk for infection (J Eckhardt, Davis et al., 2018, 2018b), though these individuals are not always considered in risk assessments. This finding highlights the potential importance of injecting network treatment strategies to prevent reinfection. It also demonstrates that interventions must be more encompassing when discussing risk behaviors with PWID, so patients understand who is considered a "contact" and may have been exposed.

Lastly, a limitation of contact tracing programs is the concern about partner retribution either limiting efficacy of the program or becoming a safety concern. This is a topic that has been heavily studied in the contact tracing literature for HIV with mixed results. On one hand, physicians interviewed about partner notification report that 23% of patients were emotionally abused, 19% of patients were abandoned, and 8% were physically abused after individuals were notified of exposure by a partner (Rothenberg, Paskey, Reuland, Zimmerman, & North, 1995). In contrast, multiple quantitative studies demonstrated that patients self-reported few negative experiences, and several additionally noted that relationships did not dissolve as a result of partner notification. One quantitative study revealed that rates of physical and emotional abuse within relationships actually declined following notification (Hogben et al., 2007; Passin et al., 2006). However, disclosure of HCV status among PWID is alarmingly low - one study showing nearly one-third of PWID did not disclose their status to anyone and only 4% of PWID disclosed their status to current or former injection partners (Hofmeister et al., 2017). Reasons for the limited disclosure of HCV serostatus include fear of stigma, maintenance of privacy, and fatalism - for example, that HCV infection is inevitable and ubiquitous among PWID (Hofmeister et al., 2017). Patient education about the importance of notifying contacts and the availability of testing and curative treatment will be imperative for young PWID to become comfortable sharing their HCV status.

Contextual specificities and necessary infrastructure for HCV contact tracing

The most important factor in the success of contact tracing for HCV is that these programs must exist with unrestricted access to direct acting antiviral treatment, regardless of liver disease state and current substance use. And, as previously discussed, we must scale-up HCV screening to identify recent infections for contact tracing programs to be effective. One strategy includes enabling HCV testing in community-based centers such as MAT programs and SSPs. Providing health services on-site in opioid treatment programs is more effective than providing referrals to an outside site (Frimpong, DöAunno, & Jiang, 2014). However, SSPs are significantly more likely have on-site medical and social services for HIV than for HCV, despite reporting that clients test positive more frequently for HCV than HIV and that deaths from HCV exceed those from HIV (Behrends, Frimpong, & Schackman, 2018). Major barriers to HCV testing in community-based substance use treatment centers include clinic reimbursement for testing, staffing challenges, stigma of substance use, and difficulties with coordination of care (Behrends, V. Nugent et al., 2018).

To be effective, local epidemiology must be considered when creating HCV contact tracing programs. The value of contact tracing in a given environment will need to be balanced against the value of simply increasing resources dedicated to universal screening. For example, settings with a very high prevalence of infected individuals may find that spending resources on universal testing is more efficient. In these settings, commendations for universal screening of high-risk populations should not be abandoned. Contact tracing may be more appropriate for settings where viremic prevalence is low - either new outbreaks in communities where HCV has not yet been established (Götz et al., 2005; Peters et al., 2016), or communities where a large proportion of HCV-infected individuals have been treated but are susceptible to reinfection, including the several countries on target for HCV elimination by WHO guidelines. Once the effectiveness of contact tracing is better understood, epidemiologic and cost-effectiveness modeling can help communities choose the ideal approach based on local factors.

Notably, we must consider the different obstacles facing contact tracing programs in urban versus rural areas. Rural areas may have few, if any, harm reduction settings, so co-locating these programs in other community-based healthcare settings will be important. Urban areas may have patients with increased anonymity of contacts or increased difficulty reaching those who have been exposed. For anonymous sexual and injection partners who will likely be unreachable with current contact tracing programs, novel mechanisms for identifying and alerting anonymous contacts to exposure are in development and warrant future research. For example, innovative methods for informing individuals of exposure to HIV - including e-cards, text messages, and anonymous online or chatroom notifications (Hochberg et al., 2015; Klausner, Wolf, Fischer-Ponce, Zolt, & Katz, 2000) - have been created and could be a crucial tool in contact tracing for HCV within the setting of harm reduction.

Priorities for future research

Though we have created a model for HCV contact tracing given recent changes in epidemiology and treatment, there is a dearth of literature about the effectiveness and utility of these programs. Initial research efforts should use qualitative methodology to understand attitudes and concerns of patients and providers who are currently involved in HCV screening and management. Additionally, quantitative and survey studies can seek to understand efficacy and areas of improvement of existing programs. Research should also focus on the best strategies to scale up screening of HCV, as this will be crucial in identifying recent infections for contact tracing.

Future research should also focus on whether contact tracing should

occur in community healthcare centers or in public health departments, and who is best equipped to elicit and notify contacts - be it healthcare providers, social workers, or public health officials. Another key area of research includes how best to identify and notify patients who were exposed through an anonymous encounter or are without traditional means of contact like a stable address, phone, or email. We must also seek to understand the appropriate recall period for contacts of a patient diagnosed with HCV in an attempt to clarify the efficacy and potential of contact tracing programs.

Conclusion

We must reevaluate our public health response to HCV given the significant changes in demographics and treatment over the past decade. Contact tracing programs for HIV, syphilis, gonorrhea, and chlamydia have been utilized for decades with overall positive efficacy and favorability. Some have advocated against routine contact tracing for HCV in the past by citing insurmountable barriers including the association of HCV acquisition with illegal and stigmatized behaviors and the prevalence of chronic infections leading to difficulty recalling and informing contacts (Poll, 2013). Though limitations remain, these barriers are largely surmountable with increased research, education, and infrastructure.

Contact tracing will be an important tool to augment current screening practices. Located within the harm reduction setting, these programs will increase regular screening of at-risk individuals, identify and notify those who have been exposed to HCV, and engage all patients in HCV treatment and harm reduction. Contact tracing will be beneficial in identifying patients with HCV who are not yet reached by current screening initiatives, allowing for engagement in HCV treatment to reduce transmission. More importantly, contact tracing could reach individuals most at-risk who are not otherwise engaged in the healthcare system to reduce risk-taking behaviors and decrease reciprocal transmission within injection networks – a crucial step in the path toward viral elimination.

Author contributions

BE conceived of the manuscript and supervised the project. CK performed literature review and wrote the original manuscript. All authors discussed the analysis and contributed to the final manuscript.

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References

- Aitken, C. K., McCaw, R. F., Bowden, D. S., Tracy, S. L., Kelsall, J. G., Higgs, P. G., et al. (2004). Molecular epidemiology of hepatitis C virus in a social network of injection drug users. *The Journal of Infectious Diseases*, 190(9), 1586–1595. <https://doi.org/10.1086/424678>.
- Barocas, J. A., Wang, J., White, L. F., Tasillo, A., Salomon, J. A., Freedberg, K. A., et al. (2017). Hepatitis C testing increased among baby boomers following the 2012 change to CDC testing recommendations. *Health Affairs*, 36(12), 2142–2150. <https://doi.org/10.1377/hlthaff.2017.0684>.
- Batchelder, A. W., Peyser, D., Nahvi, S., Arnsten, J. H., & Litwin, A. H. (2015). "Hepatitis C treatment turned me around": Psychological and behavioral transformation related to hepatitis C treatment. *Drug and Alcohol Dependence*, 153, 66–71. <https://doi.org/10.1016/j.drugalcdep.2015.06.007>.

- Behrends, C., Frimpong, J., & Schackman, B. (2018). In W. C. M. College (Ed.). *Challenges and successes in providing on-site HIV and HCV testing in substance use disorder treatment programs*.
- Behrends, C., V. Nugent, A., Des Jarlais, D., A. Frimpong, J., Perlman, D., & Schackman, B. (2018). *Availability of HIV and HCV on-site testing and treatment at syringe service programs in the United States*, Vol. 79.
- Brewer, D. B., & Garrett, S. B. (2001). Evaluation of interviewing techniques to enhance recall of sexual and drug injection partners. *Sexually Transmitted Diseases*, 28(11), 666–677.
- Brewer, D. D., & Hagan, H. (2009). Evaluation of a patient referral contact tracing programme for hepatitis B and C virus infection in drug injectors. *Euro Surveillance : Bulletin Européen Sur Les Maladies Transmissibles = European Communicable Disease Bulletin*, 14(14), 5–9.
- Campos-Outcalt, D. (2012). Hepatitis C: New CDC screening recommendations. *The Journal of Family Practice*, 61(12), 744–746.
- Combating Hepatitis B and C to Reach Elimination by 2030 (2016). *Combating hepatitis B and C to reach elimination by 2030*. World Health Organization www.who.int.
- CPSTF (2007). Interventions to increase testing and identification of HIV-positive individuals through partner counseling and referral services. *American Journal of Preventive Medicine*, 33(2S).
- Crawford, S., & Bath, N. (2013). Peer Support Models for People With a History of Injecting Drug Use Undertaking Assessment and Treatment for Hepatitis C Virus Infection. *Clinical Infectious Diseases*, 57(suppl_2), S75–S79. <https://doi.org/10.1093/cid/cit297>.
- Danta, M., Brown, D., Bhagani, S., Pybus, O. G., Sabin, C. A., Nelson, M., et al. (2007). Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. *Aids*, 21(8), 983–991. <https://doi.org/10.1097/QAD.0b013e3281053a0c>.
- Eckhardt, B. J., Davis, L., Edlin, B., & Marks, K. (2018). *Can hepatitis C virus (HCV) re-infection be predicted and prevented among people who currently inject drugs? Paper Presented at the The International Symposium on Hepatitis Care in Substance Users, Portugal*.
- Eckhardt, B. J., Scherer, M., Winkelstein, E., Marks, K., & Edlin, B. R. (2018). Hepatitis C treatment outcomes for people who inject drugs treated in an accessible care program located at a syringe service program. *Open Forum Infectious Diseases*, 5(4), <https://doi.org/10.1093/ofid/ofy048> ofy048–ofy048.
- Ferreira, A., Young, T., Mathews, C., Zunza, M., & Low, N. (2013). Strategies for partner notification for sexually transmitted infections, including HIV. *The Cochrane Database of Systematic Reviews*(10), <https://doi.org/10.1002/14651858.CD002843.pub2> Cd002843.
- Frimpong, J. A., D'Aunno, T., & Jiang, L. (2014). Determinants of the availability of hepatitis C testing services in opioid treatment programs: Results from a national study. *American Journal of Public Health*, 104(6), e75–e82. <https://doi.org/10.2105/AJPH.2013.301827>.
- Golden, M. R., Whittington, W. L. H., Handsfield, H. H., Hughes, J. P., Stamm, W. E., Hogben, M., et al. (2005). Effect of expedited treatment of sex partners on recurrent or persistent gonorrhea or chlamydial infection. *The New England Journal of Medicine*, 352(7), 676–685. <https://doi.org/10.1056/NEJMoa041681>.
- Götz, H. M., van Doornum, G., Niesters, H. G., den Hollander, J. G., Thio, H. B., & de Zwart, O. (2005). A cluster of acute hepatitis C virus infection among men who have sex with men – Results from contact tracing and public health implications. *AIDS*, 19(9), 969–974. <https://doi.org/10.1097/01.aids.0000171412.61360.f8>.
- Hajarizadeh, B., Cunningham, E. B., Reid, H., Law, M., Dore, G. J., & Grebely, J. (2018). Direct-acting antiviral treatment for hepatitis C among people who use or inject drugs: A systematic review and meta-analysis. *The Lancet Gastroenterology & Hepatology*, 3(11), 754–767. [https://doi.org/10.1016/S2468-1253\(18\)30304-2](https://doi.org/10.1016/S2468-1253(18)30304-2).
- Hellard, M., Rolls, D. A., Sacks-Davis, R., Robins, G., Pattison, P., Higgs, P., et al. (2014). The impact of injecting networks on hepatitis C transmission and treatment in people who inject drugs. *Hepatology*, 60(6), 1861–1870. <https://doi.org/10.1002/hep.27403>.
- Hochberg, C. H., Berringer, K., & Schneider, J. A. (2015). Next-generation methods for HIV partner services: A systematic review. *Sexually Transmitted Diseases*, 42(9), 533–539. <https://doi.org/10.1097/olq.0000000000000335>.
- Hofmeister, M., Havens, J., Young, A., Hofmeister, M. G., Havens, J. R., & Young, A. M. (2017). Silence surrounding hepatitis C status in risk relationships among rural people who use drugs. *The Journal of Primary Prevention*, 38(5), 481–494. <https://doi.org/10.1007/s10935-017-0483-6>.
- Hogben, M., McNally, T., McPheeters, M., & Hutchinson, A. B. (2007). The effectiveness of HIV partner counseling and referral services in increasing identification of HIV-positive individuals: a systematic review. *American Journal of Preventive Medicine*, 33(2 Suppl), S89–100. <https://doi.org/10.1016/j.amepre.2007.04.015>.
- Hoxworth, T., Spencer, N., Peterman, T., Craig, T., Johnson, S., & Maher, J. (2003). Changes in partnerships and HIV risk behaviors after partner notification. *Sexually Transmitted Diseases*, 30, 75–82.
- Isenhout, C. J., Hariri, S. H., Hales, C. M., & Vellozzi, C. J. (2017). Hepatitis C antibody testing in a commercially insured population, 2005–2014. *American Journal of Preventive Medicine*, 52(5), 625–631. <https://doi.org/10.1016/j.amepre.2016.12.016>.
- Kasaie, P., Andrews, J. R., Kelton, W. D., & Dowdy, D. W. (2014). Timing of tuberculosis transmission and the impact of household contact tracing. An agent-based simulation model. *American Journal of Respiratory and Critical Care Medicine*, 189(7), 845–852. <https://doi.org/10.1164/rccm.201310-1846OC>.
- Klausner, J. D., Wolf, W., Fischer-Ponce, L., Zolt, I., & Katz, M. H. (2000). Tracing a syphilis outbreak through cyberspace. *JAMA*, 284(4), 447–449. <https://doi.org/10.1001/jama.284.4.447>.
- Lunny, C., & Shearer, B. D. (2011). A systematic review and comparison of HIV contact tracing laws in Canada. *Health Policy*, 103(2-3), 111–123. <https://doi.org/10.1016/j>

- healthpol.2011.07.011.
- Marlatt, G. A. (1996). Harm reduction: Come as you are. *Addictive Behaviors*, 21(6), 779–788. [https://doi.org/10.1016/0306-4603\(96\)00042-1](https://doi.org/10.1016/0306-4603(96)00042-1).
- Martin, N. K., Vickerman, P., Grebely, J., Hellard, M., Hutchinson, S. J., Lima, V. D., et al. (2013). Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology*, 58(5), 1598–1609. <https://doi.org/10.1002/hep.26431>.
- Martinez, L., Shen, Y., Mupere, E., Kizza, A., Hill, P. C., & Whalen, C. C. (2017). Transmission of Mycobacterium tuberculosis in households and the community: A systematic review and meta-analysis. *American Journal of Epidemiology*, 185(12), 1327–1339. <https://doi.org/10.1093/aje/kwx025>.
- Marx, G. E., Chase, J., Jasperse, J., Stinson, K., McDonald, C. E., Runfola, J. K., et al. (2017). Public Health Economic Burden Associated with Two Single Measles Case Investigations – Colorado, 2016–2017. *MMWR Morbidity and Mortality Weekly Report*, 66(46), 1272–1275.
- Mateu-Gelabert, P., Guarino, H., Quinn, K., Meylaks, P., Campos, S., Meylaks, A., et al. (2018). Young drug users: A vulnerable population and an underutilized resource in HIV/HCV prevention. *Current HIV/AIDS Reports*, 15(4), 324–335. <https://doi.org/10.1007/s11904-018-0406-z>.
- Mathews, C., Coetzee, N., Zwarenstein, M., Lombard, C., Guttmacher, S., Oxman, A., et al. (2002). A systematic review of strategies for partner notification for sexually transmitted diseases, including HIV/AIDS. *International Journal of STD & AIDS*, 13(5), 285–300. <https://doi.org/10.1258/0956462021925081>.
- Mathews, G. V., Pham, S. T., Hellard, M., Grebely, J., Zhang, L., Oon, A., et al. (2011). Patterns and characteristics of hepatitis C transmission clusters among HIV-Positive and HIV-Negative individuals in the Australian trial in acute hepatitis C. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 52(6), 803–811. <https://doi.org/10.1093/cid/ciq200>.
- Micallef, J. M., Kaldor, J. M., & Dore, G. J. (2006). Spontaneous viral clearance following acute hepatitis C infection: A systematic review of longitudinal studies. *Journal of Viral Hepatitis*, 13(1), 34–41. <https://doi.org/10.1111/j.1365-2893.2005.00651.x>.
- Miller, C. L., Johnston, C., Spittal, P. M., Li, K., LaLiberté, N., Montaner, J. S. G., et al. (2002). Opportunities for prevention: Hepatitis C prevalence and incidence in a cohort of young injection drug users. *Hepatology*, 36(3), 737–742. <https://doi.org/10.1053/jhep.2002.35065>.
- Mimiaga, M. J., Reisner, S. L., Tetu, A. M., Bonafide, K. E., Cranston, K., Bertrand, T., et al. (2009). Partner Notification After STD and HIV Exposures and Infections: Knowledge, Attitudes, and Experiences of Massachusetts Men Who Have Sex with Men. *Public Health Reports (1974-)*, 124(1), 111–119.
- Ngo-Metzger, Q., Ward, J. W., & Valdiserri, R. O. (2013). Expanded hepatitis C virus screening recommendations promote opportunities for care and cure. *Annals of Internal Medicine*, 159(5), 364–365.
- Nikolopoulos, G. K., Pavlitina, E., Muth, S. Q., Schneider, J., Psychogiou, M., Williams, L. D., et al. (2016). A network intervention that locates and intervenes with recently HIV-infected persons: The Transmission Reduction Intervention Project (TRIP). *Scientific Reports*, 6, 38100. <https://doi.org/10.1038/srep38100>.
- Onofrey, S., Church, D., Kludt, P., DeMaria, A., Cranston, K., Beckett, G. A., et al. (2011). Hepatitis C Virus Infection Among Adolescents and Young Adults - Massachusetts, 2002–2009. *Morbidity and Mortality Weekly Report Surveillance Summaries (Washington, DC : 2002)*, 60(17).
- Passin, W. F., Kim, A. S., Hutchinson, A. B., Crepaz, N., Herbst, J. H., & Lyles, C. M. (2006). A systematic review of HIV partner counseling and referral services: Client and provider attitudes, preferences, practices, and experiences. *Sexually Transmitted Diseases*, 33(5), 320–328. <https://doi.org/10.1097/01.olq.0000194597.16236.48>.
- Peters, P. J., Pontones, P., Hoover, K. W., Patel, M. R., Galang, R. R., Shields, J., et al. (2016). HIV Infection Linked to Injection Use of Oxycodone in Indiana, 2014–2015. *The New England Journal of Medicine*, 375(3), 229–239. <https://doi.org/10.1056/NEJMoa1515195>.
- Poll, R. (2013). Hepatitis C: The case against routine partner notification. *International Journal of STD & AIDS*, 24(3), 165–168. <https://doi.org/10.1177/0956462412472311>.
- Quinn, K., Fong, C., Guarino, H., & Mateu-Gelabert, P. (2019). Development, validation, and potential applications of the hepatitis C virus injection-risk knowledge scale (HCV-IRKS) among young opioid users in New York City. *Drug and Alcohol Dependence*, 194, 453–459. <https://doi.org/10.1016/j.drugalcdep.2018.11.010>.
- Razavi, H. (2018). In P. O. Collaborators (Ed.). *Global Cascade of care for HBV and HCV. Recommendations for Partner Services Programs for HIV Infection, Syphilis, Gonorrhea, and Chlamydial Infection* (2008). In CDC (Ed.). *Recommendations for partner services programs for HIV infection, syphilis, gonorrhoea, and chlamydial infection*cdc.gov.
- Rothenberg, K. H., Paskey, S. J., Reuland, M. M., Zimmerman, S. I., & North, R. L. (1995). Domestic violence and partner notification: Implications for treatment and counseling of women with HIV. *Journal of the American Medical Women's Association*, 50(3–4), 87–93 (1972).
- Rutherford, G. W., & Woo, J. M. (1988). Contact tracing and the control of human immunodeficiency virus infection. *JAMA*, 259(24), 3609–3610. <https://doi.org/10.1001/jama.1988.03720240071038>.
- Sabin, L., Hecht, E. M. S., Brooks, M. L., Singh, M. P., Yeboah-Antwi, K., Rizal, A., et al. (2018). Prevention and treatment of malaria in pregnancy: what do pregnant women and health care workers in East India know and do about it? *Malaria Journal*, 17(1), 207. <https://doi.org/10.1186/s12936-018-2339-9>.
- Scott, N., Sacks-Davis, R., Pedrana, A., Doyle, J., Thompson, A., & Hellard, M. (2018). Eliminating hepatitis C: The importance of frequent testing of people who inject drugs in high-prevalence settings. *Journal of Viral Hepatitis*, 25(12), 1472–1480. <https://doi.org/10.1111/jvh.12975>.
- Sheikh, M., & Poustchi, H. (2018). Point of care policy for eliminating hepatitis C, its applicability and acceptability. *Archives of Iranian Medicine*, 21(9), 425–427.
- Smoak, N., Scott-Sheldon, L., Johnson, B., & Carey, M. (2005). Sexual risk reduction interventions do not inadvertently increase the overall frequency of sexual behavior: a meta-analysis of 174 studies with 116,735 participants. *Journal of Acquired Immunoodeficiency Syndrome*, 39(4), 374–384.
- Surveillance for Viral Hepatitis - United States (2016). In CDC (Ed.). *Surveillance for viral hepatitis - United States, 2016*cdc.gov.
- Suryaprasad, A. G., White, J. Z., Xu, F., Eichler, B.-A., Hamilton, J., Patel, A., et al. (2014). Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006–2012. *Clinical Infectious Diseases*, 59(10), 1411–1419. <https://doi.org/10.1093/cid/ciu643>.
- Swanson, K. C., Altare, C., Wesseh, C. S., Nyenswah, T., Ahmed, T., Eyal, N., et al. (2018). Contact tracing performance during the Ebola epidemic in Liberia, 2014–2015. *PLoS Neglected Tropical Diseases*, 12(9), 1–14. <https://doi.org/10.1371/journal.pntd.0006762>.
- Tempalski, B., Pouget, E. R., Cleland, C. M., Brady, J. E., Cooper, H. L. F., Hall, H. I., et al. (2013). Trends in the population prevalence of people who inject drugs in US metropolitan areas 1992–2007. *PloS One*, 8(6), e64789. <https://doi.org/10.1371/journal.pone.0064789>.
- Tuberculosis: A Comprehensive International Approach (2000). *Tuberculosis: A comprehensive international approach*. New York, NY: Marcel Dekker Inc.
- USPSTF (2013). *Hepatitis C: Screening*.
- Viner, K., Kuncio, D., Newbern, E. C., & Johnson, C. C. (2015). The continuum of hepatitis C testing and care. *Hepatology*, 61(3), 783–789. <https://doi.org/10.1002/hep.27584>.
- Zibbell, J., Iqbal, K., Patel, R., Suryaprasad, A., Sanders, K., Moore-Moravian, L., et al. (2015). Increases in hepatitis C virus infection related to injection drug use among persons aged < 30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006–2012. *MMWR Weekly Report Retrieved from*.
- Zibbell, J. E., Asher, A. K., Patel, R. C., Kupronis, B., Iqbal, K., Ward, J. W., et al. (2018). Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, United States, 2004 to 2014. *American Journal of Public Health*, 108(2), 175–181. <https://doi.org/10.2105/AJPH.2017.304132>.