



Hepatitis C transmission in young people who inject drugs: Insights using a dynamic model informed by state public health surveillance

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ABSTRACT

Increasing injection of heroin and prescription opioids have led to increases in the incidence of hepatitis C virus (HCV) infections in US young adults since the early 2000s. How best to interrupt transmission and decrease HCV prevalence in young people who inject drugs (PWID) is uncertain.

We developed an age-stratified ordinary differential equation HCV transmission model of PWID aged 15–64, which we fit to Michigan HCV surveillance data among young PWID aged 15–29. We used Latin hypercube sampling to fit to data under 10,000 plausible model parameterizations. We used the best-fitting 10% of simulations to predict the potential impact of primary (reducing injection initiation), secondary (increasing cessation, reducing injection partners, or reducing injection drug use relapse), and tertiary (HCV treatment) interventions (over the period 2017–2030) on acute and chronic HCV cases by the year 2030.

Treating 3 per 100 current and former PWID per year could reduce chronic HCV by 27.3% (range: 18.7–30.3%) and acute HCV by 23.6% (range: 6.7–29.5%) by 2030 among PWID aged 15–29 if 90% are cured (i.e. achieved sustained virologic response [SVR] to treatment). Reducing the number of syringe sharing partners per year by 10% was predicted to reduce chronic HCV by 15.7% (range: 9.4–23.8%) and acute cases by 21.4% (range: 14.2–32.3%) among PWID aged 15–29 by 2030. In simulations of combinations of interventions, reducing injection initiation, syringe sharing, and relapse rates each by 10% while increasing cessation rates by 10% predicted a 27.7% (range: 18.0–39.7%) reduction in chronic HCV and a 38.4% (range: 28.3–53.3%) reduction in acute HCV.

Our results highlight the need for HCV treatment among both current and former PWID and the scale up of both primary and secondary interventions to concurrently reduce HCV prevalence and incidence in Michigan.

1. Introduction

The epidemiology of hepatitis C virus (HCV) infections in the United States (US) has changed dramatically over the last decade, with notable increases in HCV incidence among young people aged approximately 15–29 years (Tempalski et al., 2013; Koh and Valdiserri, 2013; Zibbell et al., 2015; Jordan et al., 2017; CDC, 2018). These changes in incidence have been associated with increases in opioid and injection drug use (IDU) (Tempalski et al., 2013; Koh and Valdiserri, 2013; Zibbell et al., 2015; Jordan et al., 2017; CDC, 2018). In the US, up to 2.6% of adults have injected drugs in their lifetime and more than half of US people who inject drugs (PWID) have HCV infection (Lansky

et al., 2014; Armstrong et al., 2006; Denniston et al., 2014; Edlin et al., 2015; Degenhardt et al., 2017; Rosenberg et al., 2017). IDU is the primary risk factor for new HCV infections in the US (CDC, 2018). After decades of asymptomatic chronic infection, HCV leads to liver-associated morbidity and mortality (e.g. cirrhosis and hepatocellular carcinoma) (Smith et al., 2012; AASLD and IDSA, 2016).

In the US, transmission modeling studies have shaped HCV screening, treatment, and prevention policies by increasing our understanding of HCV transmission dynamics, forecasting prevalence of HCV-related liver diseases, and simulating the impact, costs, and benefits of highly effective direct-acting antivirals (DAAs) among PWID and other groups disparately burdened by HCV (Smith et al., 2012; Moyer

Abbreviations: HCV, hepatitis C virus; IDU, injection drug use; NA, not applicable; NS, not sampled; NSDUH, National Survey on Drug Use and Health; ODE, ordinary differential equation; MDHHS, Michigan Department of Health and Human Services; PWID, people who inject drugs; SVR, sustained virologic response; US, United States

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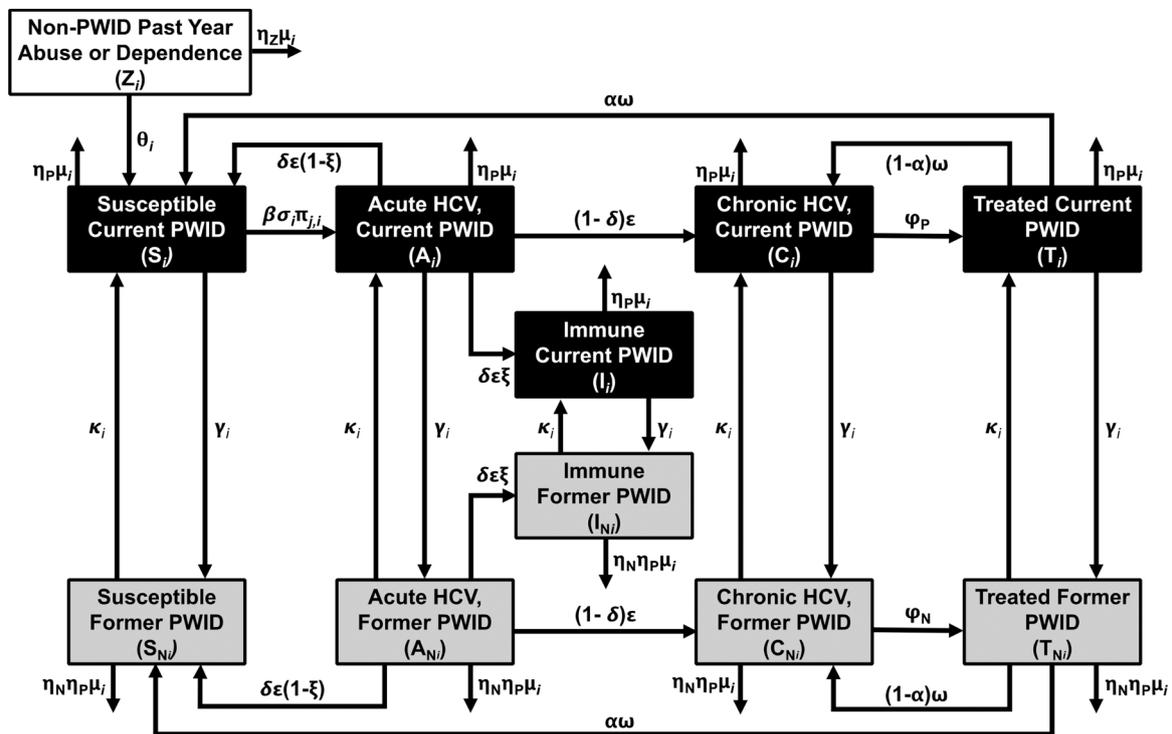


Fig. 1. Hepatitis C transmission model among people who inject drugs: model states and parameters. This model diagram outlines states and parameters controlling flows between states of an HCV transmission model among PWID in Michigan. Non-PWID with substance abuse or dependence (Z_j) begin injecting drugs (S_i) at a rate θ_i and acquire acute infection (A_i) through effective contact with an HCV-infected PWID (A_j or C_j or T_j) of the same or discordant age (informed by a contact matrix $\Pi_{j,i}$) at a transmission rate (β). Chronic infection (C_i) develops at a rate ϵ among a proportion of acute cases, $(1 - \delta)$, and resolves in the remaining δ acute cases, of whom ξ develop sterilizing immunity and the remaining $(1 - \xi)$ become susceptible to reinfection. Chronic infection can be treated (T_i) at a rate ϕ_p , for a duration of ω^{-1} years, after which point susceptibility to reinfection ensues. PWID stop injecting drugs at a rate γ_i and transition to former PWID states (denoted by $State_{N_i}$). Former PWID can begin injecting drugs after a period of abstinence at a rate κ_i . Death occurs at a rate μ_i , which is elevated among current PWID by a factor η_p and among non-PWID by a factor η_z . Former PWID mortality rates are closer to mortality rates from the general Michigan population (μ_i) by multiplying the current PWID mortality increase factor by a protective factor η_N . Subscript i denotes parameter or state age class (1: 15–19 years, 2: 20–25 years, 3: 26–29, 4: 30–64 years) and subscript j denotes the age group of contacts from whom susceptible current PWID (S_i) can acquire infection. Individuals move through age groups based on the duration predicted by the age range captured in each group (ν_i , not depicted for simplicity) and new 15 year-olds are added to the non-PWID compartment each year at a rate ($\nu_0 \rho_0 P_0$, not depicted for simplicity).

and USPSTF, 2013; Echevarria et al., 2015; Hickman et al., 2015; Leidner et al., 2015; Durham et al., 2016; Linthicum et al., 2016). Multiple studies support the cost-effectiveness of treating PWID with DAAs to interrupt HCV transmission, a strategy known as ‘treatment as prevention.’ (Echevarria et al., 2015; Hickman et al., 2015; Durham et al., 2016; Martin et al., 2011a, 2011b, 2011c, 2012, 2013a, 2013b, 2015, 2016; Durier et al., 2012; Hellard et al., 2012; de Vos and Kretzschmar, 2014; Bennett et al., 2015, 2016; Innes et al., 2015; Lima et al., 2015; Scott et al., 2015, 2016; Ayoub and Abu-Raddad, 2016; Cousien et al., 2016, 2017; Rozada et al., 2016; van Santen et al., 2016; Gountas et al., 2017; Stone et al., 2017)

HCV treatment may be particularly impactful in reducing HCV prevalence among young PWID. Echevarria et al. suggested that treating just 5 per 1000 young PWID (< 30 years) in Chicago could halve HCV prevalence in this age group over 10 years (from 10% to 5%) (Echevarria et al., 2015). This large predicted reduction from a modest intervention stemmed in part from the low baseline HCV prevalence among young PWID in Chicago compared with their older counterparts (Echevarria et al., 2015; Boodram et al., 2010; Garfein et al., 2007). HCV seroprevalence studies in several US cities (Baltimore, Chicago, Los Angeles, New York City, San Diego, and Seattle) suggest that HCV prevalence among young US PWID varies widely across the US, with estimates ranging 10–53%; however, estimates are unavailable for a majority of states and cities (Echevarria et al., 2015; Boodram et al., 2010; Garfein et al., 2007; Amon et al., 2008; Garfein et al., 1998, 2013; Jordan et al., 2015). This absence of local HCV seroprevalence estimates limits our ability to evaluate prevalence trends and the potential

impact of interventions in modeling studies. We demonstrate here that HCV public health surveillance data collected as part of nationally notifiable and state-reportable condition surveillance might be used to evaluate the potential impact of interventions among young PWID in locations without a systematic characterization of HCV prevalence (MDCH, 2013).

HCV incidence increases in young adults were first identified using HCV public health surveillance data (Koh and Valdiserri, 2013; Church et al., 2011; Onofrey et al., 2011). As part of HCV surveillance, laboratories and physicians report positive HCV lab results to state health departments, who apply standard case definitions to stage HCV as acute or chronic (Hepatitis C, 2012a, 2012b, 2016a, 2016b). Underreporting of HCV cases limits use of surveillance data for purposes other than description and outbreak monitoring (Koh and Valdiserri, 2013). Klevens et al. estimated the magnitude of acute HCV under-reporting at approximately 12.3–16.8 cases per case reported in a nationwide study (Klevens et al., 2014). In addition to under-reporting, there is high variability in capacity to collect risk factor or demographic information, trace contacts, and connect people with HCV infection to further testing and treatment (Koh and Valdiserri, 2013; CDC, 2018). These limitations have discouraged use of public health surveillance data for HCV transmission modeling.

We developed an HCV transmission model fit to HCV surveillance data among 15–29 year olds in Michigan during 2000–2016 that adjusts for case under-reporting. We reviewed the literature to identify ranges for model parameters and simulated the model across 10,000 plausible scenarios using Latin hypercube sampling, a form of stratified random

sampling (MDCH, 2013; Marino et al., 2008). We then evaluated the potential impact of several interventions implemented during 2017–2030, including primary prevention (reduced injection initiation), secondary prevention (behavioral initiatives), and tertiary initiatives (HCV treatment) in a counterfactual framework by summarizing the predicted reduction in HCV prevalence (chronic cases) and incidence (acute cases) in the year 2030. This modeling framework could be applied to HCV surveillance data from other states and/or adapted for use in other nationally or state-notifiable conditions.

2. Methods

A detailed discussion of the model parameters, initial conditions, surveillance data, and parameter estimation process is available in the supplemental material. Matlab (The MathWorks Inc, Natick, MA) code for model simulation and R (R Foundation for Statistical Computing, Vienna, Austria) code for figures is freely available at <https://github.com/epimath/Hepatitis-C-in-Young-PWID>.

2.1. Model structure

An HCV ordinary differential equation (ODE) transmission model of PWID with preferential age mixing was developed and implemented in Matlab R2017b. The model consists of 11 states per age group that reflect the natural history and transmission of HCV (Fig. 1). The model is simulated among four age groups: 15–19 years, 20–25 years, 26–29 years, and 30–64 years. The 11 model compartments per age class include uninfected, non-PWID with substance abuse or dependence (Z_i), uninfected current or former PWID (S_i or S_{N_i} , respectively), acutely infected current or former PWID (A_i or A_{N_i} , respectively), chronically infected current or former PWID (C_i or C_{N_i} , respectively), immune current or former PWID (I_i or I_{N_i} , respectively), and treated current or former PWID (T_i or T_{N_i} , respectively). Current PWID are those who currently inject drugs whereas former PWID are those who injected drugs in the past but do not currently inject. We multiplied US national prevalence estimates by the Michigan population size for each age group (P_i) as initial conditions for the number of people with substance use disorders, current PWID, and former PWID (Supplemental Methods) (Tempalski et al., 2013; Lansky et al., 2014; ICPSR, 2018).

Movement through the 11 compartments is governed by a set of 44 differential equations shown in Eq. (1), where subscript i denotes the age class (1: 15–19 years, 2: 20–25 years, 3: 26–29 years, 4: 30–64 years) of individuals moving through compartments and subscript j denotes the age class of effective contacts. In the youngest age class, non-PWID without HCV infection are added each year to the Z_1 compartment. The number of non-PWID introduced per year is based on the prevalence of substance abuse or dependence among 15–19 year olds from the National Survey on Drug Use and Health (NSDUH, ψ_0) and the average population size of 15-year-olds during 2000–2016 in Michigan ($\nu_0 P_0$, see Supplemental Table 1 for a complete description of parameters) (ICPSR, 2018; Friede et al., 1993; CDC Wonder, 2019a). Individuals exit each compartment through aging (individuals age to the subsequent age class at a rate ν_i) or death. To account for the elevated mortality among people who use substances relative to the general population, we multiplied age-specific mortality rates in Michigan (μ_i) by standardized mortality ratios for people who use substances, current PWID, and former PWID (η_Z , η_P , and η_N , respectively) (Friede et al., 1993; CDC Wonder, 2019b; Mathers and Degenhardt, 2014; Degenhardt et al., 2011; Evans et al., 2012; Vlahov et al., 2008; Veldhuizen and Callaghan, 2014).

Non-PWID (Z_i) begin injecting drugs (transition to S_i) at an estimated injection initiation rate (θ_i) calibrated to fit acute case data (described further below and in the Supplemental Methods). Susceptible PWID (S_i) acquire new infections through effective contact with an acutely (A_j) or chronically (C_j) infected individual in any age class. A proportion (τ) of treated current PWID (T_j) also transmit HCV

during intervention simulations (described further below). We model the number of new infections per year as the product of the probability of infection per contact (β), the number of susceptible current PWID (S_i), the total number of syringe sharing partners per susceptible per year (σ_i), and the proportion of contacts that are infected. We incorporate age-assortative syringe sharing by adjusting the proportion of infected individuals per age class by a scaling factor that reflects age-assortative syringe sharing ($\pi_{j,i}$) using a study of PWID in Baltimore (Supplemental Methods) (Smith et al., 2018). Other HCV transmission modes (e.g. perinatal acquisition, unregulated tattoos, sexual transmission) are not considered as IDU is the primary risk factor for new HCV infections in the US (CDC, 2018).

$$\begin{aligned}
 \frac{dZ_i}{dt} &= \theta_i Z_i + \nu_{i-1} Z_{i-1} - \nu_i Z_i - \mu_i \eta_Z Z_i, \\
 &\text{where } Z_0 = \psi_0 P_0 \\
 \frac{dS_i}{dt} &= \theta_i Z_i - \beta \sigma_i S_i \sum_{j=1}^4 \pi_{j,i} \frac{A_j + C_j + \tau T_j}{S_j + A_j + C_j + I_j + \tau T_j} + \omega \alpha T_i + \delta \varepsilon (1 - \xi) A_i \\
 &\quad + \kappa_i S_{N_i} - \gamma_i S_i + \nu_{i-1} S_{i-1} - \nu_i S_i - \mu_i \eta_P S_i \\
 \frac{dA_i}{dt} &= \beta \sigma_i S_i \sum_{j=1}^4 \pi_{j,i} \frac{A_j + C_j + \tau T_j}{S_j + A_j + C_j + I_j + \tau T_j} - \varepsilon A_i + \kappa_i A_{N_i} - \gamma_i A_i \\
 &\quad + \nu_{i-1} A_{i-1} - \nu_i A_i - \mu_i \eta_P A_i \\
 \frac{dC_i}{dt} &= (1 - \delta) \varepsilon A_i + (1 - \alpha) \omega T_i - \phi_P C_i + \kappa_i C_{N_i} - \gamma_i C_i \\
 &\quad + \nu_{i-1} C_{i-1} - \nu_i C_i - \mu_i \eta_P C_i \\
 \frac{dI_i}{dt} &= \delta \varepsilon \xi A_i + \kappa_i I_{N_i} - \gamma_i I_i + \nu_{i-1} I_{i-1} - \nu_i I_i - \mu_i \eta_P I_i \\
 \frac{dT_i}{dt} &= \phi_P C_i - \omega T_i + \kappa_i T_i - \gamma_i T_i + \nu_{i-1} T_{i-1} - \nu_i T_i - \mu_i \eta_P T_i \\
 \frac{dS_{N_i}}{dt} &= \delta \varepsilon (1 - \xi) A_{N_i} + \alpha \omega T_{N_i} + \gamma_i S_i - \kappa_i S_{N_i} + \nu_{i-1} S_{N_{i-1}} - \nu_i S_{N_i} - \mu_i \eta_N \eta_P S_{N_i} \\
 \frac{dA_{N_i}}{dt} &= -\varepsilon A_{N_i} + \gamma_i A_i - \kappa_i A_{N_i} + \nu_{i-1} A_{N_{i-1}} - \nu_i A_{N_i} - \mu_i \eta_N \eta_P A_{N_i} \\
 \frac{dC_{N_i}}{dt} &= (1 - \delta) \varepsilon A_{N_i} + (1 - \alpha) \omega T_{N_i} - \phi_N C_{N_i} + \gamma_i C_i - \kappa_i C_{N_i} \\
 &\quad + \nu_{i-1} C_{N_{i-1}} - \nu_i C_{N_i} - \mu_i \eta_N \eta_P C_{N_i} \\
 \frac{dI_{N_i}}{dt} &= \delta \varepsilon \xi A_{N_i} + \gamma_i I_i - \kappa_i I_{N_i} + \nu_{i-1} I_{N_{i-1}} - \nu_i I_{N_i} - \mu_i \eta_N \eta_P I_{N_i} \\
 \frac{dT_{N_i}}{dt} &= \phi_N C_{N_i} - \omega T_{N_i} + \gamma_i T_i + \kappa_i T_{N_i} + \nu_{i-1} T_{N_{i-1}} - \nu_i T_{N_i} - \mu_i \eta_N \eta_P T_{N_i}
 \end{aligned} \tag{1}$$

Newly infected PWID (A_i) have acute HCV infection for a duration of 6 months (ε^{-1}), at which point 50–85% ($1 - \delta$) develop chronic infection (C_i) (Chung, 2005; Heller and Rehmann, 2005; Thomas and Seeff, 2005; Westbrook and Dusheiko, 2014). We assume that the acute phase lasts exactly 6 months to be consistent with national case definitions for acute HCV used to fit our model, though some heterogeneity in HCV clearance time exists (Thomas and Seeff, 2005; Westbrook and Dusheiko, 2014; Hajarizadeh et al., 2012). A fraction (ξ , 0–45%) of acutely infected individuals who spontaneously clear their HCV infection have sterilizing immunity and move to the immune class (I_i) while the remaining individuals ($1 - \xi$) move back to the susceptible class (S_i) where they can be re-infected at the same rate as infection-naïve individuals (Mehta et al., 2002). During treatment intervention simulations described below, chronically infected individuals can be treated (T_i and T_{N_i}) at rates ϕ_P and ϕ_N for a duration of ω^{-1} . Treated current PWID become susceptible to HCV re-infection after treatment (i.e. return to the susceptible class, S_i). We assumed that there was no HCV treatment during the period 2000–2016.

Individuals from any of the current PWID classes stop injecting drugs and move to their adjacent former PWID class at a cessation rate γ_i . Former PWID can begin injecting again after a period of injection abstinence and enter the current PWID class at a relapse rate κ_i . To maintain a realistic ratio of current to former PWID during model fitting to data, we calculated age-specific relapse rates for each simulation using the sampled cessation rates and prevalence of current and former

PWID in the US based on national survey data (Supplemental Methods) (Tempalski et al., 2013; Lansky et al., 2014; ICPSR, 2018).

2.2. Surveillance data, parameter estimation, and parameter sampling

The Michigan Department of Health and Human Services (MDHHS) receives reports of HCV diagnoses from healthcare providers and laboratories and stages cases as acute or chronic using standardized national case definitions (Hepatitis C, 2012a, 2012b, 2016a, 2016b). We obtained the number of newly identified acute and chronic HCV cases per year during 2000–2016 and made two adjustments to the acute case series to facilitate model fitting to data (Supplemental Table 2). First, we adjusted the number of 2016 cases to the number that would have been detected by the 2012 case definition (Hepatitis C, 2012a, 2016a). We assumed that only 74% of 2016 cases would have met the 2012 definition in accordance with an unpublished case series review conducted by MDHHS. Second, we adjusted for under-detection of acute cases by MDHHS surveillance using a correction factor developed by Klevens et al. (i.e. 1 case detected per 12.3–16.8 acute infections) (Klevens et al., 2014; Onofrey et al., 2015).

To incorporate parameter uncertainty, we drew a stratified random sample of 10,000 parameter sets across plausible ranges using Latin hypercube sampling (Supplemental Table 1). All parameters were sampled from uniform distributions created from the minimum and maximum bounds we identified through literature review. We used an initial (year 2000) lifetime HCV prevalence of 10–28% among 15–19 year olds, 17–36% among 20–25 year olds, 28–53% among 26–29 year olds, and 41–68% among 30–64 year olds in alignment with prevalence estimates from several US locations; no data were available for Michigan (Degenhardt et al., 2017; Echevarria et al., 2015; Boodram et al., 2010; Garfein et al., 2007; Amon et al., 2008; Garfein et al., 1998, 2013; Jordan et al., 2015). To optimize model fit to data, we estimated four unknown parameters (the transmission rate $[\beta]$ and three age-specific injection initiation rates $[\theta_i]$) in each simulation using un-weighted least squares assuming normally distributed measurement error with equal variances for each data point (Supplemental Methods). The rate of injection initiation for 30–64 year olds was sampled (rather than estimated) as we had no data to fit to for this age group and because the focus of our analysis was on young PWID. Demographic parameters (i.e. population sizes and mortality rates, and age group sizes) were not sampled. The duration of acute HCV infection was also not sampled to be consistent with the HCV data we used in model fitting (Hepatitis C, 2012a, 2012b).

Residual sum of squares (RSS) values provided a summary of model fit to acute HCV data after parameter estimation. To determine if a certain range appeared more consistent with data, we plotted histograms by quartile of RSS (Supplemental Fig. 1). Parameter estimation and simulations were run using `fminsearchbnd` and the `ODE15S` solver in Matlab (due to stiffness in some simulation runs) (MathWorks, 2012). Details for the selection of initial conditions and bounds for estimated parameters used in `fminsearchbnd` and a discussion of our reasons for expanding injection initiation rate bounds from values found in the literature are discussed in Supplemental Methods (Parriott and Auerswald, 2009; Roy et al., 2003, 2007; Ompad et al., 2005; Stein et al., 2009; Young and Havens, 2012; Chami et al., 2013; Arreola et al., 2014; Lake et al., 2016; Bluthenthal et al., 2017; Reddon et al., 2018).

2.3. Intervention simulations

We selected the best-fitting 10% of parameter sets (i.e. the 1000 simulations with the lowest RSS values) to simulate the potential impact of interventions on acute and chronic HCV in Michigan during the period 2017–2030. We simulated interventions by scaling one or more parameters in each parameter set during the period 2017–2030. We summarized the expected percent reduction in acute or chronic HCV

cases in the presence of interventions compared to predicted cases with no intervention at the end of the simulation period (year 2030).

Supplemental Table 3 outlines the three types of interventions we conducted, which include single interventions wherein just one parameter was altered, combinations of interventions that altered multiple parameters, and sensitivity analyses that further examined HCV treatment interventions. We simulated several interventions, including reduced injection initiation (θ_i), decreased syringe sharing (σ_i), decreased IDU relapse (κ_i), increased IDU cessation (γ_i), and treating former (φ_N) or current PWID (φ_P) for HCV infection. Injection initiation, syringe sharing, and IDU relapse reduction interventions involved reducing each parameter by 10%, 20%, and 40% of their 2000–2016 value whereas IDU cessation interventions involved increasing 2000–2016 cessation rates by 10%, 20%, or 40%. To facilitate comparison with prior work, we simulated treatment rates of 3, 6, and 24 per 100 PWID per year (Zelenev et al., 2018). To facilitate comparison, we also classify interventions by their most immediate roles as primary (reduced injection initiation), secondary (syringe sharing, IDU cessation, and relapse), and tertiary prevention interventions (HCV treatment) (National Institute on Drug Abuse, 2019).

We conducted four intervention sensitivity analyses further characterize HCV treatment interventions and the duration of IDU. First, we examined the impact of sustained virologic response (SVR), a measure of the percentage cured by HCV treatment (Ferreira et al., 2017). We assumed that approximately 90% of individuals achieved SVR in main intervention simulations (parametrized by α) in alignment with a recent meta-analysis of DAAs, and examined 60–100% cure in sensitivity analyses to summarize the potential impact of treatment incompleteness among PWID (Ferreira et al., 2017; Hellard et al., 2009; Aspinall et al., 2013; Butner et al., 2017; Saeed et al., 2017; Eckhardt et al., 2018; Trabut et al., 2018). Second, we examined expected case counts when a proportion of current PWID receiving HCV treatment also transmitted HCV (parametrized by τ). We assumed that 50% of treated current PWID transmitted HCV in the main results, and compared values of 0–100% in sensitivity analyses. Third, we simulated a treatment duration of 12 weeks for the main analysis, and examined 8 and 16 week durations in sensitivity analyses. All are typical treatment durations for currently approved DAAs (AASLD and IDSA, 2016). Finally, we compared the predicted reductions in HCV cases for parameter sets with a long versus short duration of injecting drugs during the pre-intervention period (i.e. 2000–2016). Long injecting durations were defined as parameter sets with $>$ median cessation rate and \leq median relapse rate whereas short durations had \leq median cessation and $>$ median relapse rates. Long injecting durations included scenarios with permanent cessation wherein relapse rates were so low that there was no possibility of relapse given the duration of our simulation period.

3. Results

3.1. Model fit to acute HCV surveillance data

The model fit acute HCV surveillance data well, especially for the 1000 best-fitting parameter sets used to simulate interventions (Fig. 2). Acute cases were expected to increase through 2030 for the best-fitting scenarios. Similar to prior work, chronic HCV prevalence generally declined early in the simulation period due to increases in PWID prevalence and high mortality among current PWID, and later increased under some conditions (Supplemental Fig. 2) (Fraser et al., 2018). There was a wide range in predicted prevalence due to the variability of conditions assessed. A variety of scenarios across sampled parameter ranges fit the data well (Supplemental Fig. 1). Better-fitting parameter sets had a slight tendency toward lower total contacts among 15–19 year olds and more total contacts among 20–25 and 30–64 year olds (Supplemental Fig. 1).

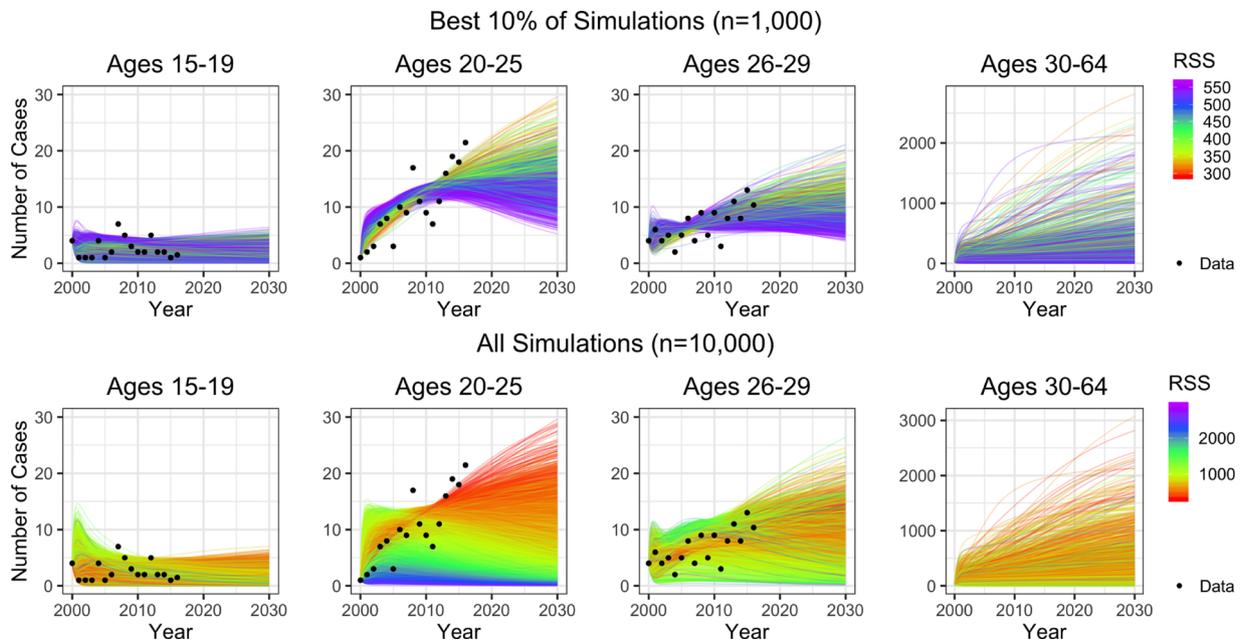


Fig. 2. Model fit to acute HCV cases detected by HCV surveillance in Michigan among PWID during 2000–2016 and predicted cases through 2030. An ordinary differential equation HCV transmission model among PWID was fit to HCV surveillance-detected acute HCV cases aged 15–29 years reported to the Michigan Department of Health and Human Services during the years 2000–2016 and simulated until 2030. Parameters were sampled across plausible ranges using 10,000 Latin hypercube samples. Model fit (colored lines) to data (black points) is shown by the residual sum of squares values. Results are shown for the best fitting 10% of simulations (top) and for all 10,000 simulations (bottom) for each age group. We did not fit to data for PWID aged 30–64 and instead show predicted acute HCV cases.

3.2. Intervention simulations

We simulated the potential impact of primary (reducing injection initiation), secondary (increasing cessation, reducing injection partners, or reducing injection drug use relapse), and tertiary (HCV treatment) interventions on acute and chronic HCV cases among young (aged 15–29 years) PWID during 2017–2030. On average, decreasing the

number of syringe sharing partners was associated with the highest predicted reduction to acute and chronic HCV among the primary and secondary interventions we simulated. Reducing the number of syringe sharing partners per year by 10% predicted a 15.7% (range: 9.4–23.8%) reduction in chronic cases and a 21.4% (range: 14.2–32.3%) reduction in acute cases among PWID aged 15–29 relative to their expected values in 2030 without intervention (Fig. 3).

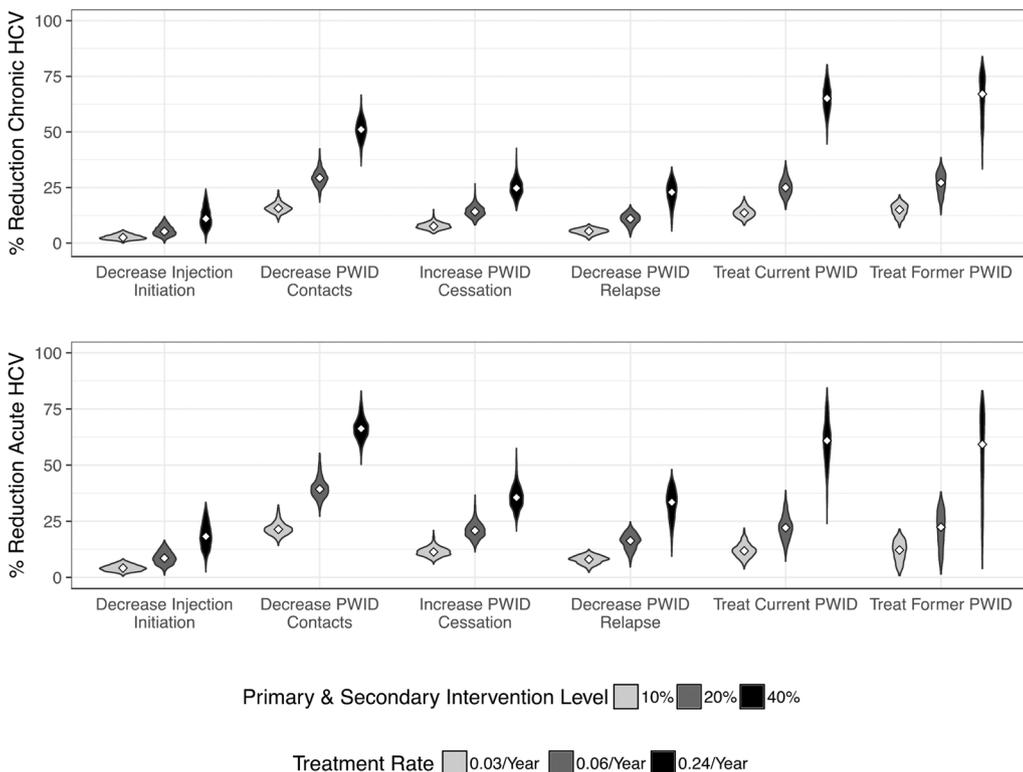


Fig. 3. Predicted reductions in chronic and acute HCV cases during 2030 among young PWID aged 15–29 from simulated primary, secondary, and tertiary interventions. The distribution of predicted percent reduction in chronic HCV (top) and acute HCV (bottom) among young PWID aged 15–29 years for 6 interventions for the best-fitting 10% of parameter sets to data are depicted as violin plots. Diamonds denote the median percent reduction and percent reductions are relative to the predicted case count in 2030 from no intervention. On average, decreasing PWID contacts reduced cases more than other primary and secondary interventions. Treatment of current and former PWID predicted the largest reductions to chronic HCV case counts on average, though there was high variability in predicted results across tested scenarios.

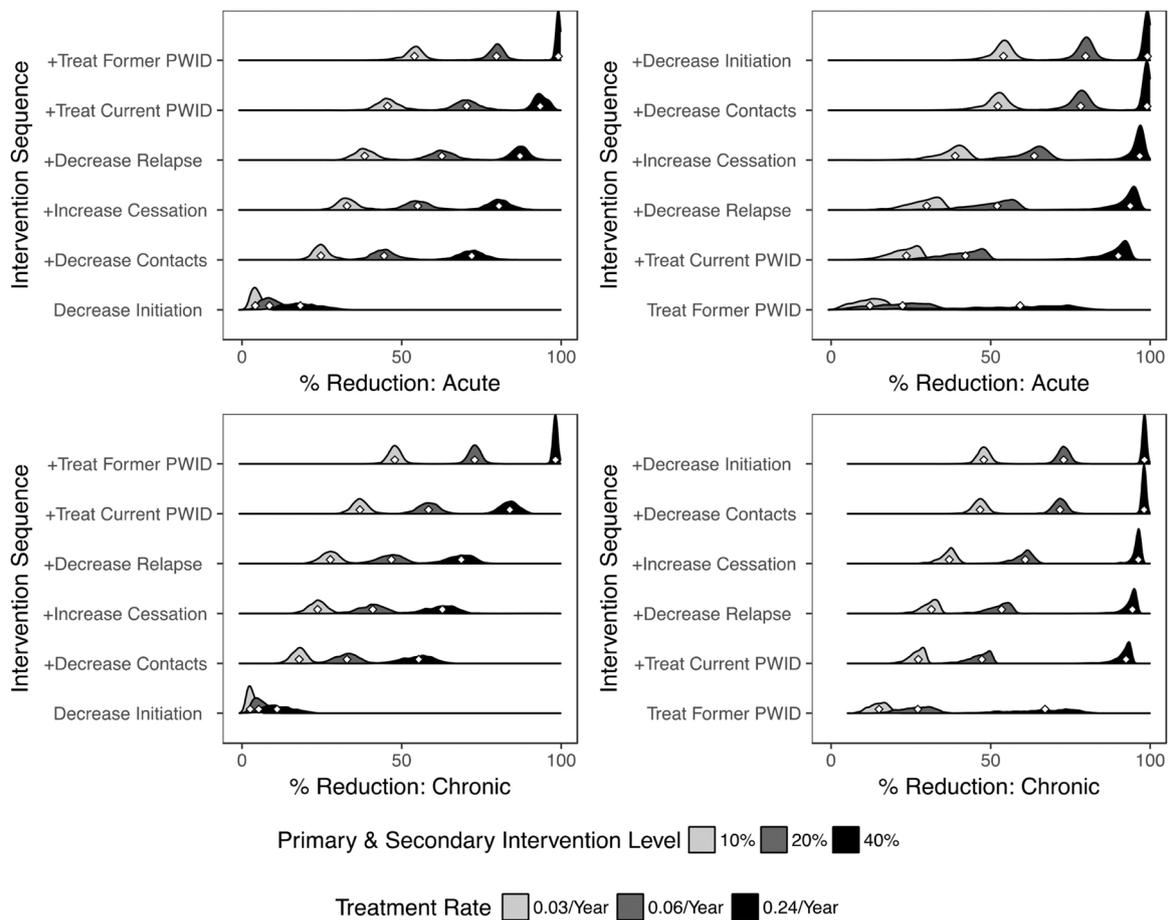


Fig. 4. Predicted reductions in chronic and acute HCV infections from combined interventions in 2030 among young PWID aged 15–29 years. Histograms of the predicted percent reduction in acute (top) and prevalence (bottom) among 15–29 year olds during the year 2030 are plotted using the best fitting 1000 parameter sets. All percent reductions are relative to the predicted case count in 2030 from no intervention and interventions are sequentially added from a base of primary (left) versus tertiary (right) interventions. Diamonds denote the median percent reduction. Treating both former and current PWID treatment predicted both prevalence and incidence reductions and the precision of predicted reductions grew with higher intensity interventions or when secondary interventions were combined with treatment.

In general, the predicted case reductions from treatment were highly dependent on parameter values, and therefore the predicted case reductions associated with treatment spanned a large range, especially among former PWID and for the expected reduction in acute cases. Treating current and former PWID resulted in similar median predicted reductions in chronic HCV cases among 15–29 year olds by 2030, with more variability among former than current PWID treatment (Fig. 3). These predicted reductions were more variable among PWID aged 30–64 (Supplemental Fig. 3).

When simulated in combination, adding secondary interventions enhanced the predicted reductions from primary prevention initiatives (reduced injection initiation) and HCV treatment (Fig. 4). Treating former and current PWID together reduced some of the uncertainty in treatment effect compared to treatment of former or current PWID alone. Treating 3 per 100 current PWID per year and 3 per 100 former PWID per year predicted a reduction in chronic HCV cases by 27.3% (range: 18.7–30.3%) and acute cases by 23.6% (range: 6.7–29.5%) among PWID aged 15–29 when we assumed that 90% were cured (i.e. achieved SVR). Reducing injection initiation, syringe sharing, and relapse rates each by 10% while increasing cessation rates by 10% predicted a 27.7% (range: 18.0–39.7%) reduction in chronic HCV and a 38.4% (range: 28.3–53.3%) reduction in acute HCV by 2030.

3.3. Sensitivity analyses

We assessed the impact of three aspects of treatment on reduction to

acute and chronic HCV among 15–29 year olds. Reducing the proportion of treated current PWID who achieved cure (i.e. sustained virologic response) modestly attenuated the percent reduction in HCV prevalence and incidence (Supplemental Fig. 4). The magnitude of these effects was similar for former PWID (data not shown). Treatment duration and the proportion of treated current PWID who shared syringes (and contributed to transmission during treatment) did not impact predicted treatment results (Supplemental Fig. 4).

We also examined how the duration of injecting may have impacted the predicted reductions in PWID aged 30–64 (Supplemental Figs. 5 and 6). As expected, treating former PWID for HCV led to greater predicted reductions in chronic HCV than treating current PWID when injection duration was short (i.e. high cessation rates and low injection relapse). Conversely, the predicted reductions from treating current PWID approached (and sometimes exceeded) the predicted reductions from treating former PWID when the duration of injecting was long.

4. Conclusions

We developed and implemented an HCV transmission model among PWID informed by Michigan HCV surveillance data, and leveraged our model to evaluate the potential benefits of primary, secondary, and tertiary interventions for reducing HCV prevalence and incidence. The incorporation of state-level surveillance data allowed us to evaluate interventions in a framework consistent with the HCV incidence trends in Michigan. Simulation results suggested that HCV treatment could be

a highly effective strategy to reduce HCV prevalence among young PWID, especially when both former and current PWID receive treatment. Especially in combination with primary and secondary prevention measures, such as decreasing injection initiation, decreasing relapse, increasing cessation, and decreasing syringe sharing, treatment could substantially reduce chronic HCV infections by 2030. In line with the concept of ‘treatment as prevention,’ treatment also yielded reductions to acute HCV, though the impact was highly uncertain. We found no differences in the predicted impact of treatment when PWID continued to share syringes and contribute to transmission during treatment, supporting current recommendations that all PWID be provided treatment, regardless of their IDU behaviors (AASLD and IDSA, 2016).

Our findings suggest that treatment rates $> 0.24/\text{year}$ may be required to eliminate HCV among young PWID in Michigan by 2030. These treatment rates were higher than prior research by Zelenev *et al.*, who found that HCV could be eliminated in Hartford, CT by treating > 12 per 100 PWID per year for 10 years when initial HCV prevalence was $< 60\%$, and with Fraser *et al.*, who found that treating 15.9 per 100 PWID would be required to eliminate rural Indiana by 2030 in the absence of other interventions (Zelenev *et al.*, 2018; Fraser *et al.*, 2018). There are several notable caveats to our findings about HCV treatment. First, the predicted impact of treatment was highly uncertain across scenarios tested, all of which represent reasonable approximations to the current HCV epidemic and PWID prevalence, given their parametrization using findings from empirical studies. In addition, compartmental HCV models that do not account for the dynamic network structure of syringe sharing are known to overestimate treatment effects, including their treatment as prevention potential (Metzig *et al.*, 2017). Incorporating network structure was beyond the scope of this model; however, we did incorporate some heterogeneity in IDU contact patterns based on age to examine HCV treatment’s potential effectiveness under several potential scenarios. Nonetheless, the predicted impacts of treatment should be taken as an upper bound of the potential treatment effect and the integration of a network model within our current framework is an area for future model development. Finally, treatment results were somewhat sensitive to cure rates. Taken together, these results emphasize the importance of engaging PWID in treatment until cure, and highlight the need to incorporate behavioral interventions that complement treatment, given the uncertainty about its population-level effects.

Secondary prevention interventions that reduce syringe sharing, promote injection cessation, and prevent relapse, and primary prevention interventions that reduce injection initiation consistently predicted reductions in acute and chronic HCV. These results were robust across tested scenarios (i.e. parameter sets) and were associated with less uncertainty than treatment or relapse prevention interventions. Thus, these interventions should be implemented alongside HCV treatment and relapse prevention programs (e.g. addiction treatment).

Though we cannot implement them directly, our simulated primary and secondary interventions are meant to represent real-world initiatives known to decrease HCV transmission. For example, expanded access to addiction treatment services and medication-assisted treatments promote cessation of drug use and prevent relapse (Kampman and Jarvis, 2015; SAMHSA, 2018). Several real-world harm reduction interventions, including the “Staying Safe,” “Break the Cycle,” or “Change the Cycle” interventions, help prevent people who use drugs from initiating IDU while concurrently promoting safe drug injection (Werb *et al.*, 2013; Mateu-Gelabert *et al.*, 2014). Simulated reductions in the number of syringe sharing partners emulate syringe services programs that provide PWID with sterile injecting equipment to reduce transmission of HCV and other bloodborne viruses (Des Jarlais *et al.*, 2015). With respect to treatment, several studies have found that providing HCV treatment within existing addiction treatment or syringe services programs led to similar cure rates to those seen in randomized controlled trials of DAAs among non-PWID, even when patients

continue to use drugs (Ferreira *et al.*, 2017; Butner *et al.*, 2017; Eckhardt *et al.*, 2018; Trabut *et al.*, 2018). A necessary step before HCV treatment, regardless of the location, is the identification of HCV infection through screening. All PWID are recommended to be screened for HCV infection (Smith *et al.*, 2012). Similar to HCV treatment, addiction treatment and syringe services programs are settings increasingly recognized as integral to improving HCV diagnosis rates (Des Jarlais *et al.*, 2015; Frimpong, 2013).

In addition to reducing the public health impacts of HCV directly, interventions that include behavioral risk reduction focused on IDU could concurrently reduce the economic costs of HCV, which increase with earlier age of infection, and the economic and societal costs of heroin and other opioid use disorders (Razavi *et al.*, 2013; Jiang *et al.*, 2017). Our results therefore reinforce the need for an integrated care model. For example, harm reduction programs could provide co-located services that include provision of sterile injecting equipment, bystander overdose response training, bloodborne virus testing and referral to (or coordination of) treatment for HCV and Human Immunodeficiency Virus, and other services, such as mental health counseling, substance use disorder treatment, or opioid maintenance therapy (HHS, 2016).

4.1. Limitations

Like all modeling exercises, we made several simplifying assumptions, and we were limited by existing data. Our model only considers HCV acquisition through IDU and we focus results on PWID aged 15–29 given available data. Our results may not be generalizable to other risk groups and simulated intervention outcomes among 30–64 year olds should be interpreted cautiously. Cases with missing risk factor data were assumed to be PWID, consistent with PWID being the most common risk factor for HCV (Zibbell *et al.*, 2015; CDC, 2018; Suryaprasad *et al.*, 2014). Because surveillance data suffers from under-reporting and missing data, we applied a reporting rate to adjust for under-detection of cases by surveillance during the time period under study, although the true number of undetected cases is unknown (Klevens *et al.*, 2014). We were unable to stratify our analysis by HCV genotype given the available data, though, like the rest of the US, we expected that nearly three-quarters of infections are with genotype 1a (Petruzzello *et al.*, 2016). Similarly, we were unable to incorporate geographic heterogeneity in HCV prevalence, transmission, or syringe sharing in Michigan. To address uncertainty in model parameter values, we sampled nearly all parameters and used values most consistent with surveillance data to simulate interventions.

We also made several simplifying assumptions about the natural history of HCV infection. We used Latin hypercube sampling to include several possibilities for spontaneous HCV clearance and sterilizing immunity; however, we did not incorporate partial or waning immunity. Susceptibility to reinfection was the same as susceptibility to primary infection and we assumed that HCV was similarly infectious across the acute, chronic, and treatment stages, and for first or reinfections. These parameters can impact transmission dynamics in the context of HCV elimination and should be examined in future work (Nazari *et al.*, 2015).

Our model assumed homogeneous mixing beyond age and used a syringe sharing contact matrix from Smith *et al.* among PWID in Baltimore, which may not reflect the age-related patterns in syringe sharing in Michigan (Smith *et al.*, 2018). We therefore expanded the assortative age-based syringe sharing patterns from Smith *et al.* to capture many plausible syringe sharing scenarios, including proportional mixing by age. However, treatment effects may still be overestimated and should be interpreted as the maximum possible impact of treatment (Metzig *et al.*, 2017). Treatment interventions also assumed a treatment-naïve population during 2000–2016, which is likely realistic given the historically low treatment rates among PWID during that period (Mehta *et al.*, 2008; Grebely *et al.*, 2008; Bajis *et al.*, 2017; GHR, 2017). Further, our model examined the potential impact of

interventions on chronic and acute HCV. Other outcomes, such as hepatocellular carcinoma and liver-related mortality, could be examined in future work. While simulated interventions are an approximation to real-world initiatives and provide an estimate of the potential efficacy of interventions, they do not include the full scope of intervention implementation and adherence challenges that impact intervention effectiveness in the real-world. Finally, in some simulations, our model's estimated injection initiation rates exceeded values found in the literature (Parriott and Auerswald, 2009; Roy et al., 2003, 2007; Ompad et al., 2005; Stein et al., 2009; Young and Havens, 2012; Chami et al., 2013; Arreola et al., 2014; Lake et al., 2016; Bluthenthal et al., 2017; Reddon et al., 2018). This discrepancy in injection initiation rates could be for several reasons, including that injection initiation rates were not available for Michigan, that available studies were conducted among specific populations (e.g. Canadian street youth), or because high estimated values of injection initiation rates were artifacts of poorly fitting simulations or ill-suited initial conditions to data. Intervention simulations were conducted using the best fitting 10% of simulations, and these include injection initiation rates consistent with empirical studies and higher values.

4.1.1. Conclusions

HCV surveillance data is a valuable source of information for understanding HCV transmission and identifying local intervention opportunities among young PWID. In Michigan, HCV treatment could reduce prevalence and incidence by 2030. The impact of treatment is more certain when both former and current PWID are treated and when treatment is combined with behavioral interventions that reduce injection drug use initiation or syringe sharing, increase injection cessation, and reduce relapse. PWID at all stages of use or recovery should be connected to HCV treatment alongside primary and secondary prevention interventions.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.epidem.2019.02.003>.

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