CAN A SEX BIAS BE A GOOD THING: MODELING SPONTANEOUS CLEARANCE AND SEXUAL SUSCEPTIBILITY IN HCV

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CAN A SEX BIAS BE A GOOD THING: MODELING SPONTANEOUS CLEARANCE AND SEXUAL SUSCEPTIBILITY IN HCV

by

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Hepatitis C virus (HCV) is a global epidemic that has been increasing for decades, afflicting millions of people who inject drugs (PWID) and is a major cause of liver disease. With novel direct-acting antivirals, treating the virus has become possible yet elimination remains out of reach. Prior research has shown significant differences in disease progression between men and women. These differences can lead to variation in incidence or what proportion of infections progress to chronic infections. We develop a mathematical model that accounts for potential differences between the sexes to evaluate the impacts on HCV transmission. We find that susceptibility is the strongest predictor of prevalence over time, but spontaneous clearance can lead to prevalence reductions, especially in women, when susceptibility is low. Finally, we test three hypothetical populations and discover that applying treatment against a natural bias in the population may prove more efficient than equal application.
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Introduction

Hepatitis C Virus (HCV) is a major cause of liver diseases and chronically affects as many as 71 million people globally (WHO, 2017). The ongoing HCV epidemic primarily concerns people who inject drugs (PWID) due to high prevalence in long-term users causing new users to quickly acquire HCV (Aceijas and Rhodes, 2007; Amato et al., 2005; Chen and Morgan, 2006; Degenhardt et al., 2017; Hagan et al., 2007; Larney et al., 2015; Page et al., 2013; Shepard et al., 2005; Suryaprasad et al., 2014). While transmission routes are mostly through susceptible individuals coming into direct contact with infectious blood, individuals in this population engage in several risky behaviors such as sharing injection syringes or “rinsing” their injections, which facilitates this contact (Evans et al., 2003; Gilchrist et al., 2017; Hahn et al., 2002; Lapane et al., 1998; Larney et al., 2015; Morris et al., 2015; 2017; 2018; Murray et al., 2003; Platt et al., 2016; 2018; Turner et al., 2011). As a largely asymptomatic infection, many infected individuals are unaware of their status and thus unknowingly transmit the infection to their injection partners (Chen and Morgan, 2006). Additionally, with no long-term immunity to the infection, even those who recover are susceptible to new infections and can rapidly acquire HCV again (Chen and Morgan, 2006; Grebely et al., 2012; Page et al., 2009). While the methods of treatment have improved over the past decade it has done little to curb the epidemic, indicating that optimization of interventions is a key area for future research.

In recent years, Direct-Acting Antiviral (DAA) treatments have reached high levels of efficacy (over 95%) and researchers have begun to consider widespread treatment as a form of prevention (Dahari et al., 2016; Hahn et al., 2002; Harris et al., 2015; Martin et al., 2011a; 2013a; Read et al., 2017; Zelenev et al., 2018). Under this plan, rather than focusing on
prevention with a vaccine, the principle is that large applications of treatment can reduce HCV prevalence to the point where there is little risk of transmission (Bajis et al., 2017; Martin et al., 2011b). While several models have shown that scaling up treatment application can lead to significant decreases in prevalence and thus transmission in certain populations; there has been little success in replicating these results on a global scale. (Grebely and Dore, 2014; Grebely et al., 2017; Larney et al., 2017; Martin et al., 2011a; Moreno et al., 2017; Palmateer et al., 2014; Platt et al., 2016; Scott et al., 2016; Ward et al., 2018).

In order to eliminate HCV as a public health threat across the globe, it is not enough to just consider upscaling treatment. A comprehensive intervention plan would not only include increasing diagnosis and treatment, but also scaling up current harm reduction programs such as syringe-service centers or opioid substitution therapy (WHO, 2017). Before we can consider these more expansive plans though, there are several factors which have yet to be explored. One such factor is the potential impact of sex on transmission or disease progression. Investigations into other human diseases indicate that sex plays a significant role in disease burden and treatment outcomes (Klein, 2000; Klein and Flanagan, 2016; Furman et al., 2014). These differences are not only a result of biological factors but can be a result of behavioral or social ones as well (Berg et al., 2004; Stockdale et al., 2007). Understanding the impact of sex on HCV, as well as other factors, would allow for more efficient interventions of the epidemic on a global scale.

It has been shown that several risk factors can lead to increased transmission and result in a higher susceptibility to HCV within certain populations (Alter, 1997; Awofeso, 2010; Degenhardt et al., 2017; Hagan et al., 2007; Hahn et al., 2002). Some of this risk is associated with societal barriers that may contribute to low levels of diagnosis or treatment,
such as reduced access to care or associated stigmas with the virus (Awofeso, 2010; Puzhko et al., 2017; Vickerman et al., 2012; Olsen et al., 2013). Other components of this increased risk seem to be biological, such as genetic differences between sexes or populations (Cai et al., 2014). Several of the factors associated with increased risk of acquiring infections have been shown to be associated with sex as well (Esmaeili et al., 2017; 2018; Evans et al., 2003; Iversen et al., 2010; 2015; Lidman et al., 2009; Page et al., 2013).

With HCV, another clear indicator of a biological difference between sexes is spontaneous clearance. Individuals are defined to be in an acute stage of the infection for the first 6 months after acquisition (Baden et al., 2014; Hajarizadeh et al., 2013). If the infection persists after 6 months, it is considered a chronic HCV infection (Baden et al., 2014; Hajarizadeh et al., 2013). Certain acutely infected individuals spontaneously recover from the virus without intervention (Fedorchenko et al., 2010; Grebely et al., 2012; Grebely et al., 2007; Micallef et al., 2006; Poustchi et al., 2011; Sarkar et al., 2013; Wang et al., 2007; Yeung et al., 2007). Such events are identified by detecting the presence of HCV antibodies in an individual without any detection of viral RNA. This process of spontaneous clearance occurs in women at a much higher rate than men (Bakr et al., 2006; Berg et al., 2004; Corsi et al., 2016; Fedorchenko et al., 2010; Grebely et al., 2007; Page et al., 2009; Wang et al., 2007; Yamakawa et al., 1996). Modeling work on HCV often includes a spontaneous clearance rate but leaves the rate flat across the entire population rather than different depending on sex, this is primarily because most models do not differentiate between the two sexes (Cousien et al., 2015; Fraser et al., 2018a; 2018b; Gountas et al., 2017; Li et al., 2015; Martin et al., 2011a; 2011b; 2013a; 2013b; Vickerman et al., 2012). A higher recovery rate without treatment could lead to lower overall prevalence within one part of the population.
Together, these factors could contribute to a differential susceptibility between sexes which might also impact treatment or transmission. In this paper, we develop a sex-structured model of HCV transmission to investigate the impact sex has on prevalence and treatment of the virus.
Methods

Model Structure

We developed a system of ordinary differential equations to model HCV transmission in the PWID population (Figure 1). The model is built upon the commonly used SIS model of infection, where individuals move from a susceptible population, acquire infections, and either die or recover and move back into the susceptible population. Our model includes one class for Susceptible Individuals (S) but stratifies the infectious population into sub-classes: Acute Infection (A), Chronic Infection (C), On Treatment (T), and Failed Treatment (F). Individuals exit each of these states at a per capita rate equal to the mortality rate ($\mu_1$) plus the injection cessation rate ($\mu_2$). As we are focused on the PWID population, individuals who stop injecting are no longer assumed to be contributing to transmission within the population. Individuals enter the susceptible population at a recruitment rate ($\theta$) which is set to keep the population constant at 100,000 individuals.

\[
\begin{align*}
\frac{dS_m}{dt} &= \theta + \epsilon_m \eta T_m + p_m \lambda A_m - \beta_m \frac{I}{N} S_m - (\mu_1 + \mu_2) S_m \\
\frac{dA_m}{dt} &= \beta_m \frac{I}{N} S_m - (\lambda + \mu_1 + \mu_2) A_m \\
\frac{dC_m}{dt} &= (1 - p_m) \lambda A_m - (\psi_m + \mu_1 + \mu_2) S_m \\
\frac{dT_m}{dt} &= \psi_m C_m - (\eta + \mu_1 + \mu_2) T_m \\
\frac{dF_m}{dt} &= (1 - \epsilon_m) \eta T_m - (\mu_1 + \mu_2) F_m \\
\frac{dS_f}{dt} &= \theta + \epsilon_f \eta T_f + p_f \lambda A_f - \beta_f \frac{I}{N} S_f - (\mu_1 + \mu_2) S_f \\
\frac{dA_f}{dt} &= \beta_f \frac{I}{N} S_f - (\lambda + \mu_1 + \mu_2) A_f \\
\frac{dC_f}{dt} &= (1 - p_f) \lambda A_f - (\psi_f + \mu_1 + \mu_2) S_f \\
\frac{dT_f}{dt} &= \psi_f C_f - (\eta + \mu_1 + \mu_2) T_f \\
\frac{dF_f}{dt} &= (1 - \epsilon_f) \eta T_f - (\mu_1 + \mu_2) F_f
\end{align*}
\]
Using this model structure, two different base-line models were constructed. In the null model, all individuals are grouped together in one of the five classes while the sex-structured model groups individuals into five classes for males and five for females, denoted by the subscripts $m$ and $f$ respectively. While in the susceptible population, individuals acquire new infections at a rate determined by the infection rate ($\beta$) and the proportion of infectious individuals in the population. In the sex-structured model, the population is assumed to be homogenously mixed, whereby the proportion of infectious individuals is the total of all males and females in the infectious classes over the entire population size. The classes which are assumed to contribute to the force of infection are acute, chronic, on treatment, and failed treatment. Acutely infected individuals leave at a per capita rate equivalent to assuming an average infection period of 6 months ($\frac{1}{\lambda}$). Individuals leaving the acute state either spontaneously recover (with probability $p$) or progress to chronic infection (with probability $1 - p$). Chronically infected individuals remain in their class until they are treated.

The null model is initialized with a susceptible population and a chronically infected population resulting in an initial prevalence of 16% based on cohort data from the U-Find-Out study. The sex-structured model has initial susceptible and chronically infected males and females but has the same initial prevalence over both sexes. Since data on acute
individuals is sparse, we assumed that there are no individuals in the acute class at the start of the model to prevent overestimation of disease burden. The model is then evaluated for several years and the final class populations are recorded.

_Treatment Mechanics_

We make a few assumptions about how treatment is distributed and utilized. In both models, a yearly maximum number of treatments is assigned (\( \omega \)) to represent a financial or logistical ceiling in the population. In the sex-structured model, these treatments are split with each sex being given a proportional amount of treatments depending on what percent of the total population they represent (i.e. if males make up 90% of the population, they receive 90% of the maximum treatments). At each time step, the number of chronically infected individuals is compared to this maximum number of treatments per year to generate a treatment proportion. If this treatment proportion is below our maximum treatment proportion (\( \text{mtp} \), the proportion of the population we realistically assume we can reach) we treat all chronic individuals. If this treatment proportion is above our \( \text{mtp} \) then we assume we can only treat up to the \( \text{mtp} \) (as in, we cannot treat individuals we cannot access). If the proportion of chronic individuals is less than our \( \text{mtp} \) for the entire year, we end up with excess treatments that were not used to treat anyone. At the end of each year in the model, these unused treatments are added up and included into the maximum number of treatments for the next year.

Individuals in the treated class are assumed to stay within the class for the average duration of treatment which is 12 weeks (\( \frac{1}{\eta} \)). Individuals who have been successfully treated (proportion \( \varepsilon \)) re-enter the susceptible population, while individuals who failed
treatment (proportion 1 - \(\varepsilon\)) enter the failed treatment population. Individuals who have failed treatment once are assumed to not be treated again.

**Sensitivity Analysis**

To investigate the impact of population ratio, viral susceptibility, and spontaneous clearance on the final prevalence of HCV we conducted a global sensitivity analysis. Using Latin hypercube sampling (LHS) we generated 10,000 parameter sets, assuming a uniform distribution for each of our 5 parameters. These parameters each had their own range, corresponding with what was assumed to match real scenarios. The 5 parameters we sampled were population ratio (0% male to 100% male populations), male viral susceptibility (0.2-0.8), female viral susceptibility (0.2-0.8), male spontaneous clearance (0.1-0.3), and female spontaneous clearance (0.2-0.4). Each parameter set was input into the sex-structured model and run for 30 years with no treatments applied and the final prevalence of HCV was calculated as a proportion of the population. We then ran the same 10,000 sets through the model again but over the 30 years applied a flat rate of treatment. We used local regression to estimate trends between each parameter with respect to the final prevalence of HCV at 30 years as well as calculated the average relative impact (ARI) on final prevalence. To calculate the ARI we used base values for each parameter drawn from the literature (Table 1). For the population ratio, we assumed a baseline population would match the global sex ratio of roughly 1:1 (WHO, 2020). Then for every sample of the LHS we compared the value of the parameter in that set to the base value as well as the final prevalence of that set compared to the base final prevalence (what the model predicted when
all parameters were at base values). By comparing the ratios between these two numbers we could estimate how much variation any one parameter contributed to the final prevalence. By averaging all these values for a given parameter we could get an estimate for how much influence that parameter had on the final prevalence over the entire sensitivity analysis. Parameters that have higher ARI values would indicate that small changes in that parameter’s value led to large changes in final prevalence.

\[
A.R.I(AverageRelativeImpact) = \frac{1}{n} \sum_{i=1}^{n} \frac{|FinalPrevalence_i - BaselinePrevalence|}{BaselinePrevalence} \times \frac{BaselinePrevalence}{|Parameter_i - BaselineParameter| / BaselineParameter}
\]

Predicting Treatment Efficacy

After identifying these prevalence-sensitive parameters, we compared the null model to the sex-structured one using several sample scenarios inspired by prior research. These three scenarios were: (1) a population made up of 70% males and 30% females (Unpublished U-Find-Out Cohort Data), (2) a population where women clear 40% of new infections while men clear only 15% (Micallef et al., 2006; Wang et al., 2007), and (3) a population where

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>units</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death Rate</td>
<td>$\mu_1$</td>
<td>per year</td>
<td>9/1000</td>
<td>Evans et al., 2012</td>
</tr>
<tr>
<td>Cessation Rate</td>
<td>$\mu_2$</td>
<td>per year</td>
<td>1/11</td>
<td>Sweeting et al., 2009</td>
</tr>
<tr>
<td>Recruitment Rate</td>
<td>$\theta$</td>
<td>per year</td>
<td>$\mu_1 + \mu_2$</td>
<td>-</td>
</tr>
<tr>
<td>Infection Rate</td>
<td>$\beta$</td>
<td>per year</td>
<td>0.4</td>
<td>*</td>
</tr>
<tr>
<td>Duration of Acute Infection</td>
<td>$\frac{1}{\lambda}$</td>
<td>months</td>
<td>6</td>
<td>Chen and Morgan, 2006</td>
</tr>
<tr>
<td>Spontaneous Clearance</td>
<td>$p$</td>
<td>-</td>
<td>0.25</td>
<td>Micallef et al., 2005</td>
</tr>
<tr>
<td>Treatment Duration</td>
<td>$\frac{1}{\eta}$</td>
<td>months</td>
<td>3</td>
<td>Lam et al., 2015</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>$\epsilon$</td>
<td>-</td>
<td>0.95</td>
<td>Lam et al., 2015</td>
</tr>
</tbody>
</table>

Table 1. Baseline parameter values
women are 25% more susceptible to new infections compared to men (Esmaeili et al., 2017). In the sex-structured model, the male population had one parameter value, while the female population had another parameter value. In the null model, which does not differentiate between sex, the parameters were averaged. The one exception was in the population ratio scenario, where the null model does not differentiate between sex and susceptible and chronic individuals were pooled. In any given scenario, only the parameters of interest were changed, while others were held at base values (Table 1). Both models were then run under each scenario with the maximum yearly treatments set to zero and scaled up incrementally to determine the minimum number of treatments required to reduce prevalence of HCV by 90% at the 30-year mark.
Results

For the global sensitivity analysis, population ratio, male and female susceptibility, and male and female spontaneous clearance all had significant linear relationships with final prevalence of HCV, though the effect size varied between them (Figure 2). Male and female susceptibility had the strongest positive effect, with higher susceptibility leading to a higher final prevalence regardless of other factors (Male – ARI: 0.55, p < 0.001; Female – ARI: 0.59, p < 0.001, Figure 2a, b).

Figure 2. Results of global sensitivity analysis without treatment. Trend lines are fit using local regression to capture relationship between parameters of interest (a) male susceptibility, (b) female susceptibility, (c) male spontaneous clearance, (d) female spontaneous clearance and final chronic prevalence of HCV. Final prevalence is reported as a proportion of the population after a time period of 30 years. Shaded regions correspond to 90% confidence intervals.
Population ratio had the strongest individual effect on final prevalence (ARI: 0.86) with small changes in highly male or female dominated populations leading to large changes in final prevalence, while only having small changes in balanced populations. (Figure 3a). While male and female clearance both had a significant

![Figure 3. Kernel density estimation of 10,000 samples of population ratio against final prevalence of HCV for the (a) untreated and (b) treated scenarios. Lower population ratio corresponds to a primarily female population, and higher ratio corresponds to a primarily male population. Final prevalence is reported as a proportion of the population after a time period of 30 years. Linear model estimation is denoted by the dashed line.](image)

negative correlation with final prevalence, the effect size was relatively small in comparison to susceptibility (Male – ARI: 0.06, p < 0.001, Female – ARI: 0.28, p < 0.001, Figure 2c, d). When susceptibility was restricted relative to one sex, a much stronger population ratio effect appeared, which depended on which sex had the lower susceptibility (Figure 4a). In the case of low female susceptibility, the population ratio had a positive effect on final prevalence (p < 0.001) while a negative effect was seen when males had low susceptibility (p < 0.001). The effect of clearance rates heavily depended on which sex had a lower relative susceptibility.
Figure 4. Results of global sensitivity analysis without treatment and with low female susceptibility. Linear model estimates are shown between (a) population ratio, (b) male clearance, (c) female clearance and final chronic prevalence of HCV. Final prevalence is reported as a proportion of the population after a time period of 30 years. Female susceptibility has been restricted to 0.2-0.3 and male susceptibility is at baseline value of 0.4. Shaded regions correspond to 90% confidence intervals.

When females had low susceptibility relative to males, female clearance had a significant negative relationship with final prevalence ($p < 0.001$, Figure 4c), whereas male clearance rate did not have a noticeable effect on final prevalence ($p = 0.23$, Figure 4b). In the case of low male susceptibility, this trend was reversed with male clearance having a slight negative effect on final prevalence ($p = 0.007$) while female clearance did not have a noticeable effect ($p = 0.19$).

In the treated populations, the sensitivity analysis showed that all five parameters maintained significant relationships with final prevalence (Figure 3b, Figure 5). In the case of susceptibility there was again a strong positive effect for both males and females on final prevalence (both $p$ values $< 0.001$, Figure 5a, b). The effect for the population ratio and clearance rates was less clear. Population ratio had a strong negative effect that resulted from a cluster of female dominated populations where final prevalence was much higher than in other parameter sets (ARI: 1222.39, Figure 3b). Such a high ARI indicates high variance in the parameter
Figure 5. Results of global sensitivity analysis with treatment. Trend lines are fit using local regression to capture the relationship between (a) male susceptibility, (b) female susceptibility, (c) male spontaneous clearance, (d) female spontaneous clearance and final chronic prevalence of HCV. Final prevalence is reported as a proportion of the population after a time period of 30 years. Treatment is applied at a constant rate over the time period. Shaded regions correspond with 90% confidence intervals.

which is matched in the male clearance rate for treated populations (ARI: 3649.11). Both ARI values were considerably higher than in the untreated simulations indicating that small changes in these parameter values resulted in large changes in final prevalence. The rest of the parameters were more comparable to the untreated analysis, although ARI’s were higher indicating an overall greater variance. When susceptibility was restricted once again, population ratio kept a strong relationship such that populations predominantly made up of the low susceptibility sex had lower final prevalence (p < 0.001). In the cases with low
female susceptibility, both male and female clearance had significant negative impacts on final prevalence unlike the untreated scenario ($p = 0.003$ and $0.001$ respectively). During scenarios of low male susceptibility though, male spontaneous clearance did not have a significant impact on final prevalence while female spontaneous clearance still did ($p = 0.791$ and $0.006$ respectively).

For the treatment efficacy comparison, when the null model was compared to the sex-structured model, as expected, there was no difference in treatments required when all parameters were at baseline (Table 1). In the high male population ratio scenario, both the sex-structured and null model required a minimum of 29.96 treatments/1000 person years to reduce prevalence by 90% at the 30-year mark. When treatment was applied opposite the bias, such as when females who only made up 30% of the population received 50% of the available treatments, the sex-structured model required a much lower minimum number of treatments to get the same reduction in prevalence (5.68 treatments/1000 person years, Figure 6a). Additionally, if given the minimum treatment rate of 29.96 from the null model, the sex-structured model showed quicker reductions in prevalence (S.I. Figure 2a). When treatment was allocated according to the bias present in the population both models required similar minimum treatment amounts but when treatment was distributed more equally the sex-structured model required less treatments to achieve the same goal. For the higher female clearance scenario, the sex-structured model required approximately 10 less treatments per 1000 person years (Null: 28.52 treatments/1000 person years Sex-structured: 15.78 treatments/1000 person years, Figure 6b). In addition, when the sex-structured model was run with the minimum treatments from the null model, it showed quicker reductions in prevalence (S.I. Figure 2b). Finally, in the higher female susceptibility scenario, the sex-
structured model required approximately 2 fewer treatments per 1000 person years (*Null:* 40.10 treatments/1000 person years *Sex-structured:* 38.16 treatments/1000 person years, **Figure 6c**). This scenario also showed quicker reductions in prevalence when the sex-structured model was run with the minimum treatments from the null model (S.I. **Figure 2c**).
Figure 6. Chronic Prevalence over 30 years given minimum treatment required to reduce prevalence by 90% for three specific scenarios: (a) 70% male to 30% female population ratio, (b) 15% male spontaneous clearance to 40% female spontaneous clearance, and (c) female susceptibility is 25% higher than males. Male and Female lines are from sex-structured model, while null line is from null model.
Discussion

Even with the development of effective treatment methods, we have still been unable to curb the rapid transmission of HCV across the globe. Our work builds on prior research through the use of sex-structured populations. This allows us to explore model dynamics by varying per-sex transmission, spontaneous clearance, and treatment rates. The results from these additional dynamics may lead to further refinement of intervention methods. Prior modeling work has either ignored or glossed over these differences for convenience (Cousien et al., 2015; Fraser et al., 2018a; 2018b; Gountas et al., 2017; Li et al., 2015; Martin et al., 2011a; 2011b; 2013a; 2013b; Vickerman et al., 2012). Not only does this allow us to investigate any sex-specific outcomes but given the case where there is no difference our model still displays the same dynamics as a null model.

Investigating the impact of sex differences on final prevalence highlights several key results. First, the strongest influence on final prevalence is how susceptible a population, or one sex, is to new infections (Figure 2a,b; Figure 5a,b). While the research on how much genetics influences HCV susceptibility is inconclusive (Cai et al., 2014; Esmaeili et al., 2017; 2018; Iversen et al., 2015; Tracy et al., 2014, Mekky and Abdelaziz, 2013), it is important when discussing interventions such as opioid substitution or needle exchange programs. These programs can be considered a type of susceptibility reduction because of suppressing high risk behaviors that contribute to HCV transmission (Amato et al., 2005; Edlin and Winkelstein, 2014; Lawrinson et al., 2008; Platt et al., 2018). We also found that population ratio demonstrated a high variance at the extremes which demonstrates that populations of mostly men or mostly women can have severely different disease burdens compared to each other (Figure 3a). If we relied solely on a linear model to determine if a given parameter had
a significant relationship with prevalence, some of this variation would be lost. As we were explicitly testing parameters that had an impact on one sex over another, these could lead to heavy transmission bias within the population. When a population consists of a high proportion of one sex, it naturally amplifies any resilience or susceptibility that sex has to infection. In a way, when one sex has high susceptibility and low clearance, a population dominated by that sex naturally trends to higher final prevalence, an “amplification” of their vulnerability. If one sex has low susceptibility and high clearance rates, the opposite will occur. Therefore, we calculated the ARI for each of our parameters as well as estimating the linear relationship between parameter and model outcome. A parameter with a high ARI indicates that either the parameter had a strong linear effect on the final prevalence or that there was a strong interaction with other parameters near the extremes.

While susceptibility has the clearest association with final prevalence in untreated populations, after its effect has been controlled for, there is a strong population ratio effect (Figure 4a). This is important considering that the population of PWID is often not reflective of the 50/50 sex ratio in the general population. Other literature finds that recruitment rates vary between male and female individuals which could lead to this population disparity (Ahamad et al., 2014; Doherty et al., 2000). We also see that when one sex had low susceptibility to new infections, spontaneous clearance becomes increasingly important to reducing final prevalence (Figure 4b,c). The only exception to this was when male susceptibility was low and yet male spontaneous clearance did not seem to significantly decrease final prevalence. This likely results from the narrower range of values for male spontaneous clearance compared to females (minimum 0.1 vs 0.2, maximum 0.3 vs 0.4). We
also observed an overall smaller effect size of male clearance than female clearance in all our tests which might result from the same bias.

When we perform the same analyses on a treated population the results are similar. While susceptibility is still the strongest relationship (Figure 5a,b), once it has been controlled for (depending on what level of susceptibility it was controlled at) there is also a strong population ratio effect. Additionally, while we still see a significant female clearance effect, we also see a significant male clearance effect (Figure 5c,d). This results from the fact that in our treated analysis the treatments applied each year were at a level to keep overall prevalence low. Thus, each spontaneous clearance event, whether male or female, was that much more impactful on reducing transmission and overall final prevalence.

Unique to the treatment sensitivity analysis, we saw a much higher level of variance for all five parameters indicated by the higher average ARIs. Like the untreated scenario, there was a strong polarizing effect of population ratio on final prevalence (Figure 3b). When populations were biased towards females we saw more “escape scenarios” where the final prevalence ended much higher than most other samples. When populations were biased towards males, we saw a similar number of “escape scenarios” yet these never reached the prevalence levels of the female biased populations. While these results are infrequent in comparison to the simulations with low final prevalence, they do pose an interesting question of how this difference occurs. When looking at the total samples for male and female susceptibility in treated scenarios we see a slight difference in their spread. Across the range of female susceptibility, prevalence seems to be low without a high level of female susceptibility while males can reach high prevalence at any level of susceptibility (S.I. Figure 1). This could be indicative of some type of threshold value in the female population,
below which transmission cannot proceed normally. As we only saw this threshold for female susceptibility under treatment regimes, focusing efforts on reducing female susceptibility might be the best option for populations with high levels of treatment already.

Each of our sample scenarios to compare treatment requirements were designed as hypothetical situations representing populations described in the literature. As some studies have reported differences in recruitment rates between males and females into the PWID population, it would be important to consider how a highly polarized sex ratio might impact interventions (Evans et al., 2003; 2012; Tracy et al., 2014). Additionally, there is a significant amount of evidence implying a higher level of clearance in women compared to the average value attributed to both sexes in previous modeling work (Bakr et al., 2006; Fedorchenko et al., 2010; Grebely et al., 2007; Micallef et al., 2006; Wang et al., 2007). Finally, while the question of susceptibility is still under investigation, there have been some studies that indicate a bias between the sexes (Esmaeili et al., 2017; 2018). The results of our three scenarios and how they might inform intervention methods for these unique populations is one of the major applications of a sex-structured model.

When we look at our sample scenarios, the sex-structured model shows higher treatment efficacy compared to the null model (Figure 6). A key finding of this is that the higher efficiency arises after applying treatment against the bias already present in the population. In the high male population scenario, the simulation modeled a population that was 70% male and 30% female and applied 70% of treatments to men and 30% to women. When this was the case, both models functioned very similarly. It was not until treatments were applied more equally (50% to men, 50% to women) that the reduction in minimum treatments was observed (Figure 6a). In other words, preferring to treat women even though
they make up a smaller part of the population led to a more efficient treatment regime. The same effect occurs for the other two scenarios; when females show increased susceptibility it might make sense to appropriate more treatments to them, but instead the more efficient method was to again apply treatments equally as was the case in the higher clearance scenario as well (Figure 6b). That is not to say that applying treatments opposite any bias present is the absolute best method. In all three scenarios, the lower level of initial treatments in the sex-structured model did lead to transient dynamics wherein the prevalence increased for a short period of time before transmission was controlled and reductions started to show, while the null model displayed immediate reductions in prevalence.

Given no monetary or logistic issues with larger numbers of treatments, the sex-structured model does predict a quicker time to reduce prevalence when compared to the null at any given number of treatments above the minimum (S.I. Figure 2). Thus, using the null model may overestimate the number of treatments required or underestimate the time to observe prevalence reductions in a population. Furthermore, while the sex-structured model does predict a lower minimum number of treatments, it does not automatically imply it is better. Depending on the circumstances within the population, it might be more important to be conservative, in which case the null model works well, or it might be more important to be strategic and efficient, in which case the sex-structured model allows for that. The key outcome of this research is the importance of considering the demographics and context in which the intervention is being applied.

There are several limitations to our study. Some assumptions about the transmission dynamics are made to simplify the model and thus might be unrealistic. Notably, assuming all infectious classes equally contribute to the force of infection (especially those on
treatment) most likely overestimates the force of infection. Also, we did not assume any type of age, social, or risk structure. It is well reported that individuals often inject with sexual partners or within social groups and that some are more likely to engage in risky behavior such as sharing needles, which would lead to some individuals in the population transmitting or receiving more infections proportionally (Morris et al., 2015; 2017; 2018; Tracy et al., 2014). Including this structure in future work will allow us to examine how sex might interact with these other factors to change HCV transmission. We also assumed that our initial populations had no individuals with an acute infection, as it is hard to find data on newly acquired HCV infections (Shepard et al., 2005). Since the duration of acute infection is relatively short compared to the time span of our simulations, this was assumed to have a negligible effect on final prevalence but would merit exploration as well. We also capped the proportion of our population accessible by treatment at 50%. This assumption was a conservative one as it is unlikely that any population will be able to access and treat their entire infected PWID population, but some may be able to reach higher proportions than what we set. In the sensitivity analysis, we sampled all parameters from a uniform distribution across their given range, but it is more likely that their values tend to fall in the center of the range rather than at the extremes. While we restricted our parameter ranges to avoid some of these extremes, we did not have any strong evidence to predict the actual distribution across the ranges we used. Future research that expands upon this would be useful for exploring the unusual differences between male or female biased populations in treated scenarios.

As a burgeoning global epidemic and a major public health issue HCV is a problem waiting to be solved. We have the tools at our disposal, now it is time to figure out how to
use them. The work presented here provides insight into how a few key sex-structured parameters can lead to large changes in treatment efficacy and overall transmission dynamics. Notably, it shows how understanding the population of interest and any bias that might be present is critical for determining the method of treatment application. Once that context is understood, it will not only lead to better intervention methods in the present, but also allow for more thorough evaluations of interventions going forward.
Supplemental Figures

Supplemental Figure 1. Kernel density estimation of 10,000 samples with (a) male and (b) female susceptibility versus final HCV prevalence with treatment. Final prevalence is reported as a proportion of the population after a time period of 30 years. Linear model estimation is denoted by the dashed line.
Supplemental Figure 2. Chronic Prevalence over 30 years for three specific scenarios: (a) 70% male to 30% female population ratio, (b) 15% male spontaneous clearance to 40% female spontaneous clearance, and (c) female susceptibility is 25% higher than males. Male and Female lines are from sex-structured model, while null line is from null model. Both models run with the same number of yearly treatments, as determined by minimum number required to reduce prevalence by 90% at the 30 year mark for the null model.
References


World Health Organization, Sex Ratio. SEARO n.d.