UNIVERSITY OF CALIFORNIA SAN DIEGO

Modelling Hepatitis C Virus (HCV) Treatment Intervention Scale Up for Achieving HCV Elimination In San Diego County by 2030

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of

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by

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ABSTRACT OF THE THESIS

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by

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Master of Public Health

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Objectives: We use dynamic epidemic modeling to determine what level of treatment scale-up and targeting strategy is required to achieve the Eliminate Hepatitis C San Diego County Initiative goals: 1)80% reduction in hepatitis C virus (HCV) incidence and 2)65% reduction in HCV-related mortality by 2030.

Methods: A dynamic, deterministic, compartmental HCV transmission model was developed and stratified by population group risk (people who inject drugs (PWID), men who have sex with men (MSM), and the general population, each further stratified by gender and HIV infection status [positive/negative] for a total of 10 population groups), HCV infection/disease progression status, and age. Transmission rates among MSM and PWID were calibrated to 2018 seroprevalence estimates in these groups, and the model was initialized in 2018 with an estimated

55,354 people with a history of HCV infection in San Diego County. Baseline treatment was 5%/year from 2018, and scenarios were selected to examine the level of scale-up required after 2021 to achieve the incidence and mortality targets among different subpopulations.

Results: The HCV-related mortality reduction target of a 65% reduction was met at baseline and all intervention scenarios. The incidence elimination target was met among MSM using a lower treatment rate of 21.6%/year, and among PWID using a slightly higher treatment rate of 34.5%/year.

Conclusion: San Diego County is on track to achieve its HCV-related mortality elimination target, but in order to achieve the HCV incidence elimination goal, treatment scale-up is required among those especially at risk of transmission, such as MSM and PWID.

INTRODUCTION

Hepatitis C is a liver infection that is caused by the hepatitis C virus (HCV) and it is usually transmitted via contact with blood from an infected individual.[1] The most common way HCV transmission occurs in the United States is through injection drug use. Transmission can also occur via birth to an infected mother, and less frequently via sexual intercourse, especially among HIV+ men who have sex with other men (MSM).[1] HCV causes acute infection, but for more than half the people that become infected, it can become a long-term chronic infection. Those with chronic infection often do not show any symptoms until they develop some form of advanced liver disease such as cirrhosis.[1] Individuals with cirrhosis can progress to developing hepatocellular carcinoma and decompensated cirrhosis, both of which have an increased risk of death.[1] There is currently no effective vaccine for HCV, however, effective treatments do exist.[1]

According to the CDC, there were 3,621 acute cases of hepatitis C reported in 2018 in the United States with rates being high among 20-39 year olds.[31,32] After considering underreporting, it is estimated that there were approximately 50,300 acute infections of HCV in 2018.[2] When taking into consideration data from previous years, there is an increasing trend of HCV infection across the United States.[2] In 2015, the World Health Organization set up strategic guidelines and goals to reduce the global burden of viral hepatitis. These include better service coverage and greater impact leading to elimination.[3] In terms of elimination, the two pivotal targets include an 80% reduction in incidence of chronic HCV infections and 65% reduction in HCV related mortality by 2030.[3]

Similar programs also exist on a national, statewide and county-wide level. The Eliminate Hepatitis C San Diego County Initiative is one such private-public joint endeavor between the San Diego County Health Department and the American Liver Foundation that seeks to draft

recommendations and establish a pathway to reduce new HCV infections by 80% and HCV-related mortality by 65% by 2030.[4] This will be done via better screening strategies and linkage to treatment and care, addressing and removing barriers to cure, preventing re-infection, and supporting policies that facilitate HCV elimination.[4]

Prior work, such as a recent study for HCV burden in San Diego County, estimated that there are 55,354 individuals that are currently HCV sero-positive in San Diego County.[5] Estimates also show that certain vulnerable populations, such as people who inject drugs (PWID) and MSM, have higher a higher burden of disease. HCV sero-prevalence was estimated at 65% for PWID, 4.6% for MSM, and 1.3% among the general population, with those between the ages of 55 and 74 having a HCV seroprevalence of 3.5%.[5]

However, it is unknown what level of HCV treatment scale-up is required to achieve the elimination targets. This thesis addresses that knowledge gap, by using dynamic epidemic modeling of HCV transmission and disease progression, to determine what level of treatment scale-up and targeting is required to achieve an 80% reduction in HCV incidence and 65% reduction in HCV-related mortality in San Diego County by 2030.

Introduction is coauthored with Martin, Natasha K. and Cheema, Jaskaran S. The thesis author was the primary author of this chapter.

METHODS

Model Description

We developed a dynamic compartmental model of HCV transmission and disease progression in San Diego County. In our compartmental model, we assume that individuals enter the model as susceptible and can become infected with some being able to spontaneously clear their infection. Those that get infected remain infectious and progress through the disease stages unless treated. Successfully treated individuals exhibit a sustained virologic response (SVR) – which makes relapse highly unlikely, however, they are still susceptible to re-infection.

Model Stratification

The model was stratified in three ways: Hepatitis C infection & disease progression status (figure 2), age, and population sub-type (figure 1). The population sub-type stratification includes further stratification by gender, HIV status, PWID, and MSM. The 11 hepatitis C infection and disease stages, represented by *n* are: (i) Susceptible, (ii) Spontaneous Clearance or SVR from no/mild liver disease, (iii) Susceptible Moderate Liver Disease, (iv) Susceptible Compensated Cirrhosis, (v) Susceptible Decompensated Cirrhosis, (vi) Susceptible Hepatocellular Carcinoma, (vii) No/Mild Liver Disease, (viii) Moderate Liver Disease, (ix) Compensated Cirrhosis, (x) Decompensated Cirrhosis, (xi) Hepatocellular Carcinoma. The 4 age stages represented by *i* are: (i) 18-39, (ii) 40-54, (iii) 55-74, and (iv) 75+ years. The 10 population sub-types represented by *j* are: (i) MSM, (ii) MSM HIV+, (iii) PWID/ex-PWID Male, (iv) Non-PWID Male, (v) PWID HIV+/ex-PWID HIV+ Male, (vi) Non-PWID HIV+ Male, (vii) PWID/ex-PWID Female, (viii) Non-PWID Female, (ix) PWID HIV+/ex-PWID HIV+ Female,

(x) Non-PWID HIV+ Female. Therefore, our model has 11x4x10 for a total of 440 compartments.

Hepatitis C Infection & Disease Progression

In terms of hepatitis C infection and disease progression, individuals enter the model in the susceptible compartment (X_1), and once acutely infected can either transition to the no/mild liver disease compartment (X_7) or they may spontaneously clear infection and move to the spontaneous clearance or SVR from no/mild liver disease compartment (X_2). The force of infection, or the rate at which susceptible individuals become infected per unit time is denoted by the term foi_i^j. The proportion of individuals that may spontaneously clear infection is denoted by the terms, p for all non-HIV+ individuals, and p_{HIV} for all HIV+ individuals who have a lower probability of spontaneous clearance. In order to move from a non-infectious compartment to an infectious compartment, a susceptible individual must become infected and be unable to spontaneously clear their infection. From the no/mild liver disease compartment (X_7), individuals continue to progress through the disease stages as infected, unless they are successfully treated. The rate of disease progression between the compartments is denoted by rop_x, where x = 1, 2, 3, 4, 5, 6, 7, 8. Successful treatment stops progression of any HCV related disease unless an individual has already reached the compensated cirrhosis stage (X_9). After reaching this stage, treatment does allow the individual to move to a non-infectious state, but disease progression still occurs, albeit at a much slower rate once treated. In the model, those individuals that have been successfully treated move into a susceptible compartment. The proportion of infected individuals that are treated is denoted by the term trt_x, where x = 1, 2, 3, 4, 5. In order to get the number of individuals that successfully complete treatment, trt_x is multiplied by the cure rate, c and c_{HIV} for individuals with HIV. Individuals that have already progressed to one of the two

decompensated cirrhosis compartments (I_4 & S_4) or hepatocellular carcinoma compartments (I_5 & S_5), can exit the population via HCV-related mortality ν_x, where x = 1, 2, 3, 4.

HCV Transmission

In terms of HCV transmission, our model assumes that individuals enter the population at 18 years old and into one of the 10 possible population sub-type compartments, which are further stratified by gender, HIV status, PWID status and by MSM (see figure 1). The model assumes assortative mixing in the population, with the force of infection of an individual being dependent on which population sub-type compartment they are in. The MSM and PWID compartments have transmission rates defined as the per capita number of effective transmission contacts per unit time (b_{MSM}, b_{PWID_m} & b_{PWID_f} respectively). In our model, we assume no transmission among the general population currently, as the vast majority of transmission occurs among PWID and MSM. In the model, it is assumed that PWID inject between the ages of 18-39 and then transition to a compartment of former injection drug use, defined as "ex-PWID" for readability. Therefore, the model assumes individuals over the age of 39 are either ex-PWID or non-PWID. Another assumption of the model is that all HIV+ individuals enter the first age compartment of the model as an 18 year old HIV+ and there is no further change in HIV+ status by age in the model across any compartments.

Model Parameterization and Calibration

Setting

The model was parametrized and calibrated to the current hepatitis C epidemic in San Diego County. Our model was calibrated to data obtained from *Estimated hepatitis C prevalence and key population sizes in San Diego* by Wynn et al, which estimated the burden of hepatitis C

among adults in San Diego County by using multiple published and unpublished sources, including national and state-level data.[5] The estimations they obtained are for the year 2018 and do not include individuals below the age of 18 years old.[5] Their study also includes estimates for incarcerated persons who are residents of San Diego County, but could be incarcerated in prisons throughout California[5], so this population was excluded from our model.

Baseline Parameters

Hepatitis C disease progression (rop_x) & mortality parameters (ν_x) were obtained from published literature.[6,7,8,9] Other baseline parameters such as proportion of spontaneous clearance (p & p_{HIV}), cure rates (c & c_{HIV}), and HIV+ transmission (RR_{HIV_tr}) and susceptibility terms (RR_{HIV_s}) were also obtained from published literature (tables 1 & 2). Background mortality parameters (μ_i) were obtained from CDC life tables.[10] For the first three age compartments, the annual background mortality rate was obtained by identifying the mid-point of each respective age range and selecting the probability of dying for that age. For the fourth age compartment, the background mortality rate was obtained by dividing 1 with the expectation of life at age 75-76. Further details are provided in the tables section.

Calibration

The transmission rates for PWID and MSM (b_{MSM}, b_{PWID_m} & b_{PWID_f}) were calibrated to the 2018 data obtained from Wynn et al on the number of hepatitis C seropositive individuals in those population groups. In order to generate the calibrated parameters, we started the model in the year 1800 and ran the model to steady state. The calibrated point estimates and number of hepatitis C seropositives for MSM & PWID are provided in Table 8.

Simulation Scenarios

Once we obtained the calibrated transmission rate parameters, the model was initialized in 2018. This allowed for the inclusion of infections which occurred in the 1970s and 80s due to injecting drug use patterns which were markedly different than today and which we were unable to recreate without data on previous PWID population size estimates (as both PWID populations size and risk were likely higher, but no estimates are available). Therefore, we used the exact point estimates and HCV sero-prevalence estimates from Wynn et al for each of the non-PWID age groups. To account for previous treatment among the general population, 75% of the chronically infected non-PWID were allocated to infected compartments and 25% were allocated to the corresponding SVR stage, consistent with estimates of past treatment with SVR in the U.S. and San Francisco in 2018.[29,30] Further details are provided in Table 6. The initial conditions for the model at 2018 are listed in Table 8.

The model was simulated using the following treatment scenarios. For all scenarios, we assumed a treatment rate of 2%/year from 1996 to the end of 2017, and 5%/year from 2018. Scenarios 2, 3 and 4 were selected to identify treatment rates which could achieve elimination among the different groups in the population (MSM, PWID, and the total population).

Scenario 1: Baseline (status quo). Treatment with 5%/year from 2021 onwards

Scenario 2: Treatment of 21.6%/year from 2021 onwards

Scenario 3: Treatment of 31.7%/year from 2021 onwards

Scenario 4: Treatment of 34.5%/year from 2021 onwards

Scenario 5: Treatment of 50%/year from 2021 onwards

We ran the model from 2018 to 2030 with the baseline treatment and all intervention scenarios. We plotted the incidence of HCV among MSM, PWID, and the overall population

from 2018 to 2030. We also plotted HCV-related mortality in San Diego County over the 12-year time period. In our baseline assessment, we assume that all individuals are equally likely to be treated, irrespective of what disease stage they are in and what population sub-type they belong to. This was based on current guidelines, which recommend providing treatment to all chronically infected HCV patients except those with a short life expectancy.[33,34] The outputs for these scenarios are listed in Tables 9 & 10 and Figures 3 & 4.

Sensitivity Analysis

In our baseline scenarios, we assumed all individuals that are eligible for treatment would be equally likely to be treated. However, the degree to which PWID, MSM or individuals with advanced liver disease, such as cirrhosis, should receive treatment is uncertain. Therefore, we did a sensitivity analysis to assess how the treatment proportion would change if: (i) people with advanced liver disease (X_4, X_5, X_6, X_9, X_{10}, X_{11},) are targeted at 80% while others are treated at baseline levels; (ii) PWID are not treated while others receive treatment scale-up at 30%; (iii) PWID are targeted for treatment at 30% while others receive treatment at baseline levels. All sensitivity analysis scenarios were started in 2021. All analyses were done using MATLAB version R2019b.

Methods is coauthored with Martin, Natasha K. and Cheema, Jaskaran S. The thesis author was the primary author of this chapter

RESULTS

The calibrated model accurately matched 2018 estimates for MSM and PWID (Table 5). In our full model simulation from 2018 to 2030, we obtained the incidence over time for MSM, PWID and the total population, along with projections for HCV-related mortality. The model estimates a total of 674 incident HCV infections in 2018, comprised of 188 new infections among MSM and 486 among PWID. HCV-related mortality was estimated at 1,089 deaths for 2018. In order to reduce hepatitis C incidence by 80% and HCV-related mortality by 65% by 2030, the estimates for incidence among MSM, PWID and the total population would need to be below 38, 97 and 135, while the estimate for HCV-related mortality would need to be below 381 deaths for 2030. All pertinent outputs from the model in terms of hepatitis C incidence and HCV-related mortality are provided in Tables 9, 10, 11 & 12, respectively. Additionally, 2018-2030 projection plots are provided in Figures 3, 4 & 5.

Baseline Status Quo Scenario (*trt* = 5%)

In the baseline scenario, treatment proportion remains constant at 5% for all population subtypes and disease stages. The model projected a slight decrease in hepatitis C incidence for MSM, PWID and the total population to 151, 451 and 602 respectively at 2030. This translated into a 17%, 7% and 11% relative reduction among MSM, PWID, and the total population, respectively. Therefore, in the baseline scenario the incidence elimination target is not met by 2030.

HCV-related mortality was projected to show a sharp decrease with baseline projections estimating 372 deaths in 2030, with an estimated reduction of 66%. Therefore, the baseline

scenario meets the goal of a 65% reduction in HCV-related mortality by 2030. As long as treatment proportion remains above 4.2% among all population groups and disease stages, a 65% reduction in mortality can be met.

Treatment Scale-up @ 21.6%

When the proportion of infected individuals treated (or treatment proportion) was scaled up to 21.6%/year uniformly across all population subtypes and disease stages, there was a substantial decrease in incidence across MSM, PWID and the total population. Incidence among MSM shows an 80% decrease from the 2018 value, and a 75% decrease from the projected 2030 value compared to the status quo scenario. Incidence among PWID and among the total population also shows a substantial decrease with 2030 estimates at 232 and 269, respectively. Although the decrease in incidence from the 2018 value is 52% for PWID and 60% for the total population, the goal of an 80% reduction in hepatitis C incidence is not met at this scale up level.

HCV-related mortality shows an even greater decline at a treatment scale-up of 21.6%. Projections estimate the number of HCV-related deaths to be 250 in 2030, a decrease of 76% from 2018 numbers and a decrease of 28% compared to the status quo scenario at 2030.

Treatment Scale-up @ 31.7% & @ 34.5%

Scaling up treatment proportion to 31.7% and 34.5% uniformly across all population sub-types and disease stages, shows an even greater decrease in incidence across MSM, PWID and the total population when compared to a 21.6% treatment scale-up. The incidence of hepatitis C in MSM, PWID and the total population is projected to be 16, 119 & 134 respectively for a 31.7% treatment scale-up and 13, 97 & 110 respectively for a 34.5% treatment scale-up. The

80% reduction in incidence goal is met for the total population at a 31.7% treatment proportion scale-up and for PWID at a 34.5% treatment proportion scale-up.

HCV-related mortality shows a similar trend as treatment scale-up of 21.6%, with there being a sharp decrease in the number of deaths until 2023 and the value slowly tapering off by 2030. Number of deaths at 2030 were projected to be at 237 for a 31.7% treatment scale-up and at 231 for a 34.5% treatment scale-up. The projected HCV-related mortality decreases by about 78% for a 31.7% treatment scale-up and 79% for a 34.5% treatment scale-up when compared to 2018. The decrease in the number of HCV-related deaths at 2030 when compared to baseline projections with a treatment proportion of 5% is 36% for the 31.7% treatment scale-up scenario and 38% for the 34.5% treatment scale-up scenario.

Treatment Scale-up @ 50%

Our final scenario scaled-up the treatment proportion to 50% uniformly across all population sub-types and disease stages. In this treatment scale-up scenario, incidence of hepatitis C for all three groups (MSM, PWID, total population) drops sharply until 2023 and then decreases slowly till 2030. The projected incidence at 2030 was found to be 3, 29 and 33 for MSM, PWID and the total population, respectively.

In terms of HCV-related mortality, the number of deaths sharply decrease until 2025 and then slowly decrease by 2030. Number of HCV-related deaths at 2030 are projected to be 212, which is an 81% decrease from 2018. The decrease in the number of HCV-related deaths at 2030 is around 43% when compared to the status quo scenario with a treatment proportion of 5%.

Sensitivity Analysis

In our sensitivity analysis, we ran three scenarios. The output values are provided in Tables 11 & 12, and projection plots are provided in Figure 5.

In scenario (i), treatment proportion was scaled up to 80% for individuals in advanced liver disease stages and kept at baseline (5%) for all others. The incidence is projected to decrease moderately for MSM, and decrease slightly for PWID and the total population in this scenario. HCV-related mortality, on the other hand, is projected to drop substantially. While the mortality target is projected to be met, incidence reduction targets are not.

In scenario (ii), PWID were not treated at all, while treatment was scaled-up to 30% for other groups. The incidence is projected to decrease substantially for MSM, slightly for PWID and substantially for the total population. HCV-related mortality is also projected to drop substantially, however, the drop is not as steep as in scenario (i). The HCV-related mortality target is projected to be met and incidence reduction targets are projected to be met for MSM only.

In scenario (iii), the treatment proportion was scaled-up to 30% for PWID and remained at baseline (5%) for all others. The incidence among MSM is projected to follow the same projection as the baseline scenario, among PWID and the total population, however, the decrease is substantial. HCV-related mortality, on the other hand, follows a similar trend as the baseline projections.

Results is coauthored with Martin, Natasha K. and Cheema, Jaskaran S. The thesis author was the primary author of this chapter

DISCUSSION

The Eliminate Hepatitis C San Diego County Initiative is a private-public joint endeavor that seeks to draft recommendations and establish a pathway to reduce new HCV infections by 80% and HCV-related mortality by 65% by 2030.[4] In order to accomplish these goals, five committees were established which went on to draft nine recommendations, including implementing prevention strategies, HCV screening, ensuring linkage to care and treatment, as well as ensuring access to direct-acting antivirals (DAA's).[4] While a few of these recommendations focus on prevention strategies, a majority of the recommendations pertain to accomplishing better treatment strategies through direct and indirect methods. However, the recommendations do not include projections for different treatment scale-up levels. This model hopes to bridge that gap and allow stakeholders to allocate resources effectively in order to meet the incidence and mortality reduction goals by 2030.

Promisingly, our model indicates that the HCV-related mortality target is likely to be met with current treatment rates. HCV-related mortality was estimated to be 1,089 deaths for 2018 and declining to 372 in 2030 with status quo treatment rates. The reason for a high and declining mortality is predominantly due to aging of the 1945-1965 birth cohort. Members of this cohort engaged in injection drug use in their 20s and most of them with chronic HCV infection may be progressing to advanced liver disease stages by 2018.

However, our model indicates that in order to meet the goal of an 80% reduction in hepatitis C incidence, scale-up of treatment is required – to an estimated one-third of infections treated per year. Obtaining the target among MSM specifically required slightly lower rates due to a lower burden of HCV infections.[5]

A reduction in the prevalence of infection among MSM and PWID through better screening strategies and linkage to care and treatment will reduce overall transmission. While our treatment scale-up projections do provide some targets, providing strategies on how to achieve those levels of treatment scale-up is beyond the scope of this model. The nine recommendations provided by the advisory committees to the Eliminate Hepatitis C San Diego County Initiative are a good starting point for future models.[4] Models can be constructed to determine how resources can be allocated within those nine recommendations in order to reach the pertinent treatment scale-up level from our model.

The sensitivity analysis provided some valuable insights into how resources could be allocated to reduce hepatitis C incidence and HCV-related mortality among the population. Scaling-up treatment for those with advanced liver disease had the greatest impact in terms of decreasing HCV-related mortality compared to the status quo scenario, but did not affect hepatitis C incidence at all. Scaling-up treatment for all groups while not treating PWID also had a substantial effect on decreasing HCV-related mortality compared to the status quo scenario. It also had a substantial effect on decreasing hepatitis C incidence among the total population, particularly among MSM. Scaling-up treatment for PWID, while keeping it at baseline for others, saw the largest decrease in hepatitis C incidence among PWID and the total population, while hepatitis C incidence among MSM was completely unaffected and followed the status quo scenario. HCV-related mortality decreased slightly compared to the status quo scenario. Therefore, a scale-up of treatment efforts among PWID will have the largest effect on a reduction in incidence, while a higher scale-up of treatment among people with advanced liver disease will have the greatest effect on a reduction in HCV-related mortality compared to the status quo scenario. A scale-up of treatment among MSM and the general population achieves

both, a reduction in hepatitis C incidence among the total population and a reduction in HCV-related mortality compared to the status quo scenario. Thus, the best possible course of action would be to scale-up treatment among MSM and PWID, along with a relatively greater scale-up among persons with advanced liver disease, particularly those with compensated cirrhosis.

Limitations

Historical data pertaining to injection drug use, particularly among PWID, and HCV sero-prevalence is limited for San Diego County. Therefore, calibrating our model to historical data was a challenge. In order to overcome this issue to some extent, we tried to calibrate our model to 2018 estimates and aimed to obtain a relatively stable population, both in terms of number of PWID, and HCV sero-prevalence. We were able to obtain very accurate outputs for MSM and PWID (Table 5), however, the initial model outputs for the number of HCV sero-positive non-PWID were not in congruence with the population estimates for 2018 by Wynn et al.[5] The 1945-1965 birth cohort, most of whom are members of the 55-74 age group in 2018, have the highest number of HCV sero-positive individuals out of any other group.[5] This may be due to an acute increase in the PWID population around the 1970s and 1980s, where many members from the 1945-1965 birth cohort may have been partaking in injection drug use during their 20s. This acutely heightened engagement in injection drug use may be responsible for the increased number of HCV sero-positive individuals in the 55-74 age group in 2018. In order to capture this and calibrate the model outputs with 2018 estimates, we tried to incorporate multiple changes within the model. However, the number of PWID and risk behavior during that time period was not the same as the behavior of current PWID. Therefore, our initial model was unable to capture this increased number of HCV sero-positive non-PWID in the age group of 55-

74. In order to rectify this limitation in our calibration, we calibrated MSM and PWID transmission rates to 2018 data, and initialized the model in 2018 using these transmission rates prospectively.

Another limitation with the model is in relation to the data we calibrated to. The 2018 estimates by Wynn et al themselves use multiple data streams, some of which provide newer estimates and others, older.[5] For instance, in order to estimate the population size of PWID in San Diego County, they used an older study which itself estimated annual population sizes of PWID between 2002 and 2007. This was done as newer estimates of the PWID population size were not available.[5] Therefore, the burden of HCV among PWID is uncertain due to this uncertainty in the size estimates of the PWID population itself. Investing in better surveillance systems grounded on a stronger harm reduction infrastructure in San Diego County would allow addressing these issues.

One of the main limitations of the model from translating the results into recommendations is that while we were able to generate projections for multiple treatment scale-up values, the model does not incorporate ways to identify screening strategies for HCV-infected individuals.

Further, our analysis does not incorporate the potential benefit of scale-up of harm reduction programs, which can serve to additionally prevent HCV infection and reinfection. The scale-up of these programs would reduce the number of individuals who require treatment to achieve the HCV incidence goals.

Finally, our work does not consider the cost implications of these elimination scenarios. Further work should examine the most cost-effective HCV elimination strategies, and budgetary impact of achieving HCV elimination.

Conclusion

HCV elimination is achievable in San Diego County. Reaching the HCV mortality target is likely achievable with current treatment rates due to projected natural declines in mortality due to demographic change. However, further treatment scale-up is required to reach the HCV incidence elimination goal, especially in MSM and PWID.

Discussion is coauthored with Martin, Natasha K. and Cheema, Jaskaran S. The thesis author was the primary author of this chapter

TABLES

Values calculated using two different sources have the superscript “c”

Table 1: Baseline HCV model Parameters

Notation	Parameter description	Unit (annual)	Value Used	Source
c	proportion of individuals that are cured of HCV	proportion	0.50 (<2013) 0.95 (≥2013)	16-23
c_{HIV}	proportion of HIV+ individuals that are cured of HCV	proportion	0.25 (<2013) 0.95 (≥2013)	16-23
p	proportion of individuals that spontaneously clear HCV infection	proportion	0.26	24
p_{HIV}	proportion of HIV+ individuals that spontaneously clear HCV infection	proportion	0.15	25, 26
RR_{HIV_tr}	Relative risk of HCV transmission for HIV+ persons compared to HIV-	multiplier (RR)	2.6	27
RR_{HIV_s}	Relative HCV susceptibility for HIV+ persons compared to HIV-	multiplier (RR)	2.0	28-30

Table 2: HCV disease progression & mortality parameters

Notation	Parameter description	Unit (annual)	Value Used	Source
rop_1	rate of disease progression from mild (I1) to moderate liver disease (I2)	transition probability	0.0255	7
rop_2	rate of disease progression from moderate liver disease (I2) to compensated cirrhosis (I3)	transition probability	0.0385	7
rop_3	rate of disease progression from compensated cirrhosis (I3) to decompensated cirrhosis (I4)	transition probability	0.0341	7
rop_4	rate of disease progression from compensated cirrhosis (I3) to HCC (I5)	transition probability	0.0203	7
rop_5	rate of disease progression from decompensated cirrhosis (I4) to HCC (I5)	transition probability	0.0203	7
HR_{dc}	hazard ratio of progression to decompensated cirrhosis after SVR	ratio	0.115	8
HR_{hcc}	Hazard ratio of progression to HCC after SVR	ratio	0.255	9
rop_6	rate of disease progression from susceptible compensated cirrhosis (S3) to susceptible decompensated cirrhosis (S4)	transition probability	0.0039	7
rop_7	rate of disease progression from susceptible compensated cirrhosis (S3) to susceptible HCC (S5)	transition probability	0.0052	7
rop_8	rate of disease progression from susceptible decompensated cirrhosis (S4) to susceptible HCC (S5)	transition probability	0.0052	7
ν_1	progression from decompensated cirrhosis (I4) to death	transition probability	0.13	7
ν_2	progression from HCC (I5) to death	transition probability	0.43	7
ν_3	progression from susceptible decompensated cirrhosis (S4) to death	transition probability	0.13	7
ν_4	progression from susceptible HCC (S5) to death	transition probability	0.43	7

The values for rop_6, rop_7 & rop_8 are obtained by multiplying the value used of "hazard ratio(s) of progression to DC & HCC" by the relevant rop_3, rop_4 & rop_5 terms. SVR = Sustained virologic response. The values for HCV-related death progression of S4 & S5 were not explicitly stated so the corresponding reference values for I4 & I5 were used

Table 3: Population background mortality parameters

Notation	Parameter description	Unit (annual)	Value Used	Calculation	Source
$\mu_{i=1}$	background mortality rate for age stage 18-39	rate	0.001209	probability of dying between ages 28-29	10
$\mu_{i=2}$	background mortality rate for age stage 40-54	rate	0.003091	probability of dying between ages 47-48	10
$\mu_{i=3}$	background mortality rate for age stage 55-74	rate	0.011915	probability of dying between ages 64-65	10
$\mu_{i=4}$	background mortality rate for age stage 75+	rate	0.081301	1/expectation of life at age 75-76	10

Table 4: Population Characteristics in San Diego County

Statistic	**Year**	**Point Estimate**	**HCV sero-prevalence**	**# HCV sero+**	**Point Estimate Source** (calculations)	**Source**
Total Population	2018	2,614,213	0.0204	53,336	-	5
Total HIV+	2018	20,942[c]			(#HIV+ male)[5,12]/(89.8% of all HIV+ are males)[6]	5, 12
HIV+ male	2018	18,806[c]			(#MSM HIV+)[5]/(90.6% of all HIV+ males are MSM)[6]	5, 12
HIV+ female	2018	2,136[c]			(Total HIV+)[5,12]/(10.2% of all HIV+ are female)[12]	5, 12
Total MSM	2018	88,770	0.0460	4,086	-	5
MSM HIV+	2018	17,038	0.1654	2,818	-	5
MSM HIV-	2018	71,732	0.0177	1,268	-	5
Total PWID	2018	25,935	0.6560	17,005	-	5
Total PWID HIV+ (includes MSM PWID)	2014 2018	2,464[c]	0.50[13]	1,232[c]	(9.5% of all PWID are HIV+)[13]*(total PWID)[5]	5, 13
Total PWID male	2014 2018	18,933[c]			(73% of all PWID are male)[13]*(total PWID)[2]	5, 13
PWID HIV+ male	2018	752[c]			(4% of HIV+ non-MSM males are PWID)[12] *(#HIV+ male)[5,12]	5, 12
PWID HIV- male		18,180[c]			-	5, 12
Total PWID female	2014 2018	6,717[c]			(25.9% of all PWID are female)[13]*(total PWID)[5]	5, 13
PWID HIV+ female	2018	423[c]			(19.8% of HIV+ females are PWID)[12]*(#HIV+ female)[5,12]	5, 12
PWID HIV- female		6,294[c]			-	5, 12
Total non-PWID	2018	2,499,508		32,245	-	5
Total non-PWID male	2018	1,200,515	0.0173	20,807	-	5
non-PWID HIV+ male	2018	940[c]			(5% of HIV+ males)[12] *(#HIV+ male)[5,12]	5, 12
non-PWID HIV- male		1,199,575[c]				5, 12
Total non-PWID female	2018	1,298,993	0.0088	11,438	-	5
non-PWID HIV+ female	2018	1,713[c]			(80.2% of HIV+ females)[12]*(#HIV+ female)[5,12]	5, 12
non-PWID HIV- female		1,297,280[c]			-	5, 12
Total non-PWID (55-74)	2018	635,436	0.0347	22,066	-	5
non-PWID male (55-74)	2018	290,355	0.0470	13,769	-	5
non-PWID female (55-74)	2018	345,081	0.0240	8,297	-	5

(1) Total population does not include people incarcerated in SD County or under 18 years old
(2) In cases where the source is not [5], the point estimates have been calculated by multiplying the proportion obtained from a different source with the point estimates obtained from [5]
(3) In cases where multiple sources are used, each source will be listed as a superscript as well as in the source column
(4) non-PWID HIV+ males were 5% of total HIV+ males (MSM excluded)
(5) non-PWID HIV+ females were 80% of total HIV+ females
(6) HIV+ Calculation: via sources [5] from which number of MSM HIV+ were extracted & [12] from which the population breakdown % was extracted

Table 5: 2018 HCV Calibration Data

Statistic	Point Estimate	#HCV sero-positive	Model Output (Point Estimate)	Model Output (#HCV sero+)
MSM HIV+	17,038		16,820	
MSM HIV-	71,732		71,020	
Total MSM		4,086		4,086
Total PWID male	18,933		17,950	
Total PWID female	6,717		6,397	
Total PWID		17,005		17,010

Calibration data obtained from "Estimated hepatitis C prevalence and key population sizes in San Diego" by Wynn et al.

Table 6: HCV treatment terms (baseline)

Notation	Parameter description	Unit (annual)	Value Used
trt_1	proportion of individuals treated from no/mild liver disease (I1)	proportion	0.05 (≥ 2018) 0.02 (≥1996) 0.00 (<1996)
trt_2	proportion of individuals treated from moderate liver disease (I2)	proportion	0.05 (≥ 2018) 0.02 (≥1996) 0.00 (<1996)
trt_3	proportion of individuals treated from compensated cirrhosis (I3)	proportion	0.05 (≥ 2018) 0.02 (≥1996) 0.00 (<1996)
trt_4	proportion of individuals treated from decompensated cirrhosis (I4)	proportion	0.05 (≥ 2018) 0.02 (≥1996) 0.00 (<1996)
trt_5	proportion of individuals treated from HCC (I5)	proportion	0.05 (≥ 2018) 0.02 (≥1996) 0.00 (<1996)

Sources used for treatment proportion values are [29] & [30]. Unable to find data on treatment proportion by population sub-type so uniform treatment proportion values used.

Table 7: Calibrated Beta terms for HCV model

Notation	Parameter description	Unit (annual)	Value Used
$beta_{MSM}$	Per capita number of effective contacts per unit time for MSM	annual rate	0.03845
$beta_{PWID\_m}$	Per capita number of effective contacts per unit time for PWID (males)	annual rate	0.07226
$beta_{PWID\_f}$	Per capita number of effective contacts per unit time for PWID (females)	annual rate	0.07226

Table 8: HCV Model Initial Conditions (at 2018)

Population Sub-type	Point Estimate	#HCV sero+	Data Source
MSM HIV+	16,820		calibrated
MSM HIV-	71,020		calibrated
Total MSM		4,086	calibrated
Total PWID male	17,950		calibrated
Total PWID female	6,397		calibrated
Total PWID		17,010	calibrated
Total non-PWID male	1,200,515	20,807	Wynn et al
Total non-PWID female	1,298,993	11,438	Wynn et al
			Wynn et al
non-PWID male (18-39)	550,514	0	Wynn et al
non-PWID female (18-39)	530,782	0	Wynn et al
			Wynn et al
non-PWID male (40-54)	283,080	6,053	Wynn et al
non-PWID female (40-54)	307,829	3,141	Wynn et al
			Wynn et al
non-PWID male (55-74)	290,355	13,769	Wynn et al
non-PWID female (55-74)	345,081	8,297	Wynn et al
			Wynn et al
non-PWID male (75+)	76,566	985	Wynn et al
non-PWID female (75+)	115,301	0	Wynn et al

Non-PWID HIV+ was set to 0 at 2018 due to lack of age stratified data for non-PWID HIV+

Table 9: Modeled HCV incidence with different treatment scenarios

Population sub-type	2018	Goal (2030)	Projections for 2030 by annual treatment proportion (*trt*)				
			0.05	**0.216**	**0.317**	**0.345**	**0.50**
MSM	188	38	151	37*	16	13	3
PWID	486	97	451	232	119	97*	29
Total	674	135	602	269	134*	110	33

* Achievement of HCV elimination goals for incidence

Table 10: Modeled HCV-related deaths with different treatment scenarios

	2018	Goal (2030)	Projections for 2030 by annual treatment proportion (*trt*)					
			0.042	**0.05**	**0.216**	**0.317**	**0.345**	**0.5**
Deaths	1,089	381	380	372	266	237	231	212

Table 11: Sensitivity analysis on HCV incidence outcomes

Population sub-type	2018	2030 (Goal)	Projections for 2030 by sensitivity analysis scenarios		
			Scenario (i)	**Scenario (ii)**	**Scenario (iii)**
MSM	188	38	135	18	151
PWID	486	97	441	422	134
Total	674	135	576	440	285

Table 12: Sensitivity analysis on HCV-related mortality outcomes

	2018	2030 (Goal)	Projections for 2030 by sensitivity analysis scenarios		
			Scenario (i)	**Scenario (ii)**	**Scenario (iii)**
Deaths	1,089	381	213	268	350

FIGURES

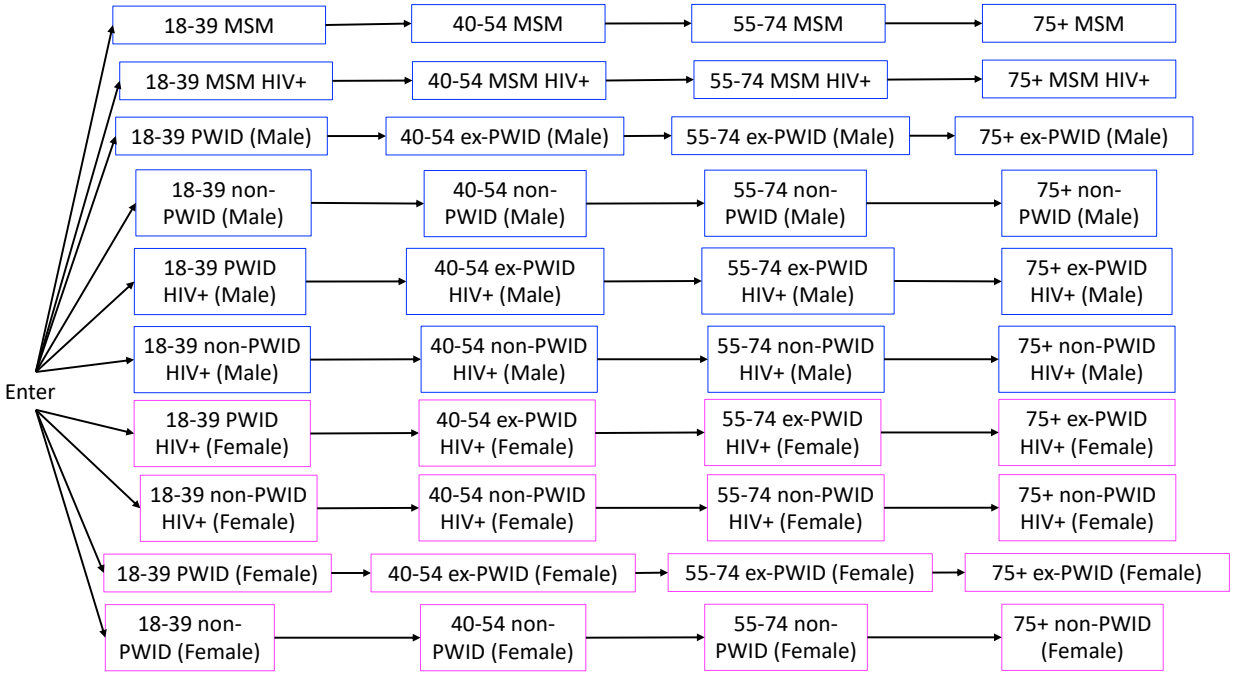

Figure 1: Model Schematic (by Age & Population sub-type)

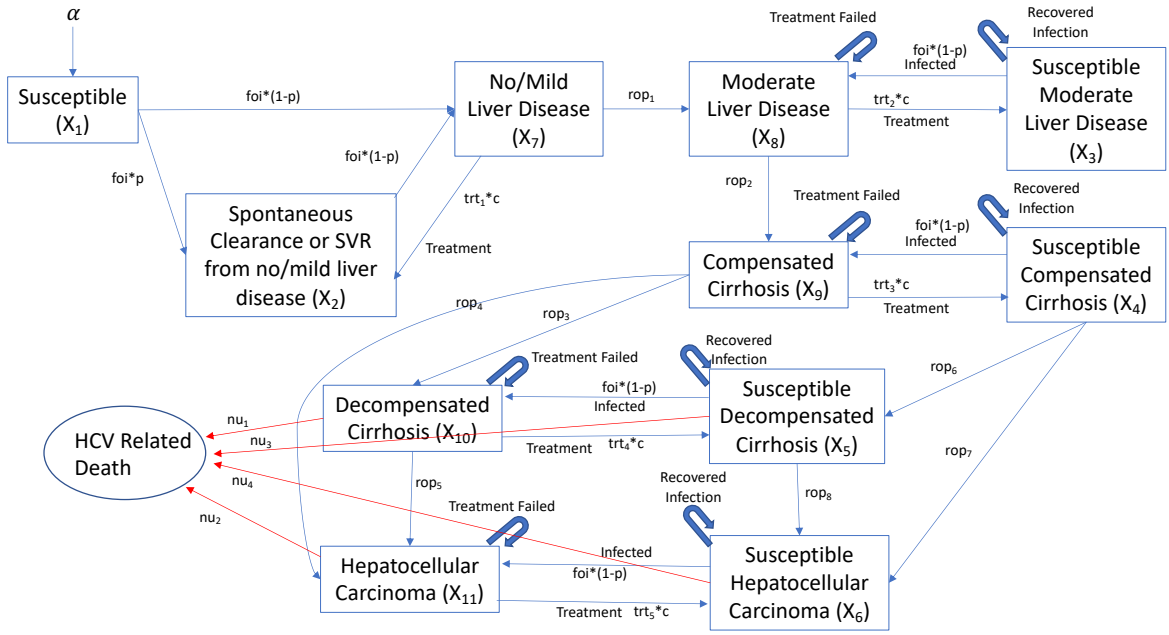

Figure 2: Model Schematic (by Infection & Disease Stages)

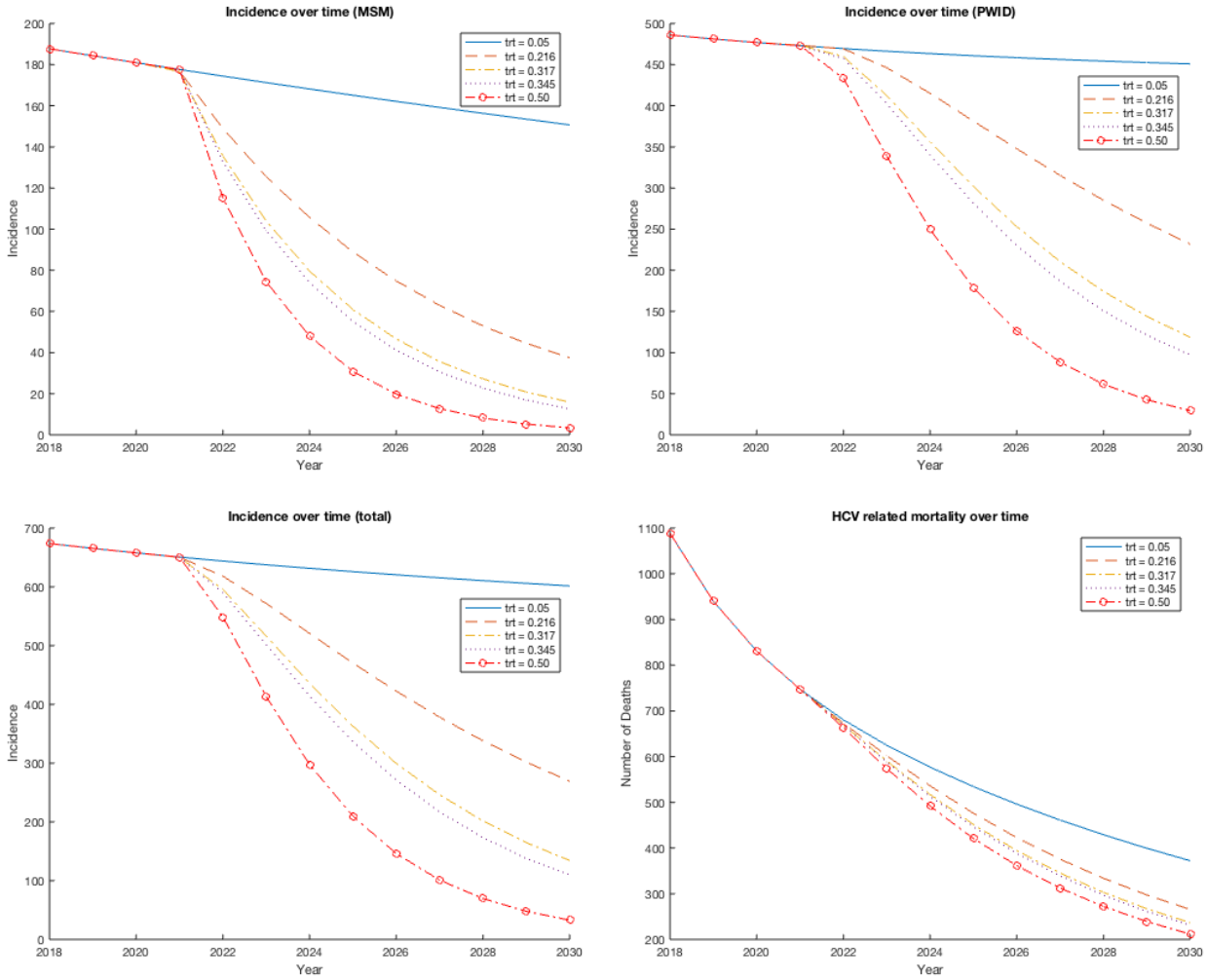

Figure 3: Uniform Treatment Scale-Up Projection Plots

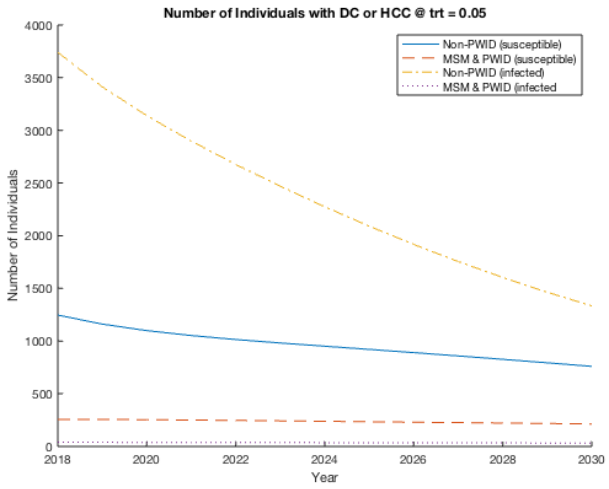

Figure 4: Number of Individuals with DC/HCC at *trt* = 0.05

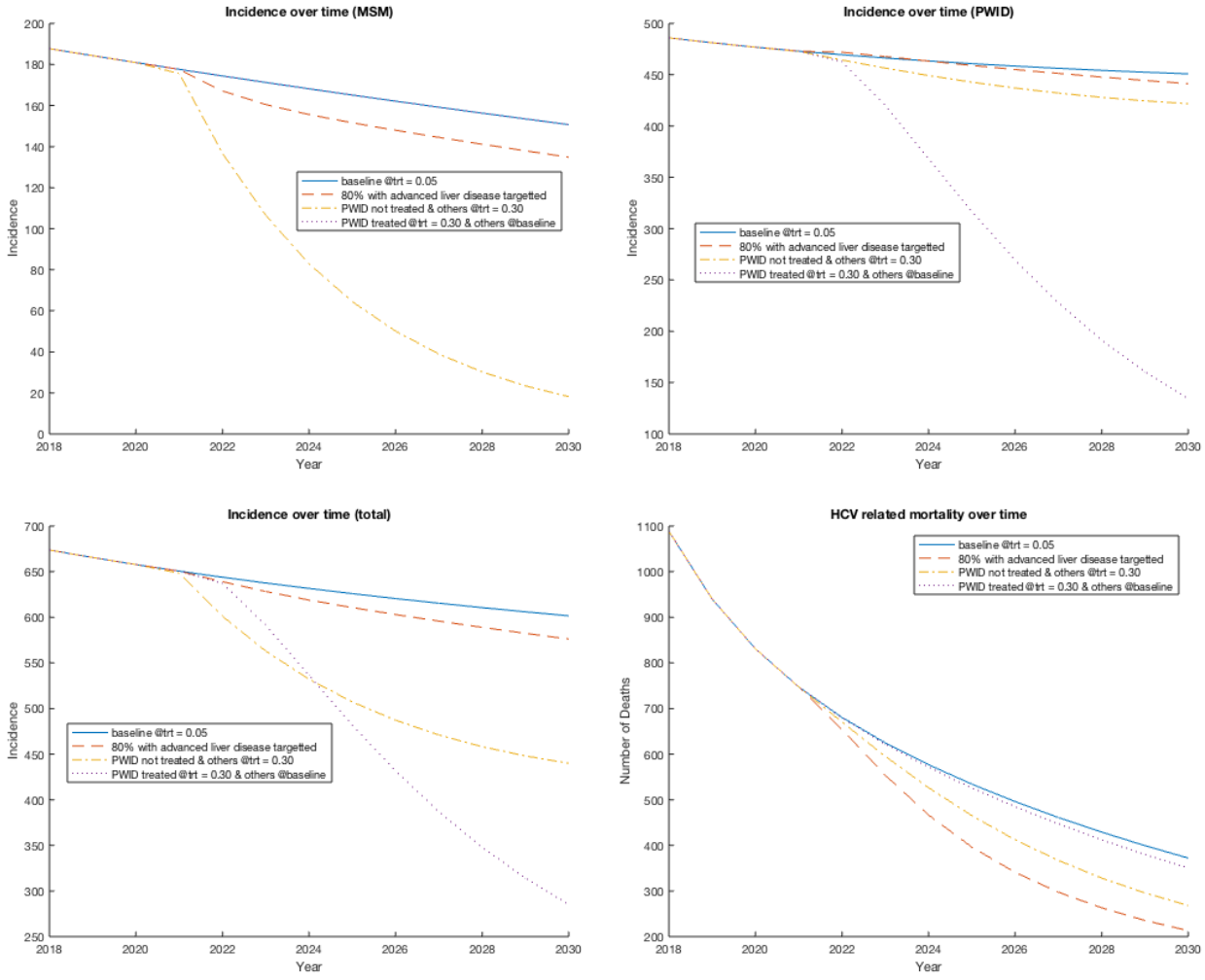

Figure 5: Sensitivity Analysis Plots
scenario(1): 80% with advanced liver disease targeted; scenario(2): PWID not treated & others at trt = 0.30; scenario(3): PWID treated at trt = 0.30 & others at baseline

Tables & Figures is coauthored with Martin, Natasha K. and Cheema, Jaskaran S. The thesis author was the primary author of this chapter

MODEL EQUATIONS

A description of all values is provided in the tables above (Tables 1, 2, 3, 6 & 7) and the model schematics illustrate the model flows (Figures 1 & 2).

For the below equations:

i = age stage (1-4), where,
i = 1: 18-39-year olds
i = 2: 40-54-year olds
i = 3: 55-74-year olds
i = 4: 75+ year olds

j = population sub-type (1-10), where,
j = 1: MSM
j = 2: MSM HIV+
j = 3: PWID/ex-PWID Male
j = 4: Non-PWID Male
j = 5: PWID HIV+/ex-PWID HIV+ Male
j = 6: Non-PWID HIV+ Male
j = 7: PWID/ex-PWID Female
j = 8: Non-PWID Female
j = 9: PWID HIV+/ex-PWID HIV+ Female
j = 10: Non-PWID HIV+ Female

X_n denotes the infection/disease stages, where,
n = infection/disease stages, and
n = 1: Susceptible (X_1)
n = 2: Spontaneous Clearance or SVR from no/mild liver disease (X_2)
n = 3: Susceptible Moderate Liver Disease (X_3)
n = 4: Susceptible Compensated Cirrhosis (X_4)
n = 5: Susceptible Decompensated Cirrhosis (X_5)
n = 6: Susceptible Hepatocellular Carcinoma (X_6)
n = 7: No/Mild Liver Disease (X_7)
n = 8: Moderate Liver Disease (X_8)
n = 9: Compensated Cirrhosis (X_9)
n = 10: Decompensated Cirrhosis (X_{10})
n = 11: Hepatocellular Carcinoma (X_{11})

φ_i = population ageing rate, where,
φ_1 = ageing rate from i = 1 to i = 2
φ_2 = ageing rate from i = 2 to i = 3
φ_3 = ageing rate from i = 3 to i = 4

$\varphi_0 = \varphi_4 = 0$

μ_i = background mortality rate, where the rate is dependent on age

ν_x = HCV-related death rate, where,
$\nu_{x=1}$ = progression from decompensated cirrhosis ($X^j_{i,n=10}$) to death
$\nu_{x=2}$ = progression from HCC ($X^j_{i,n=11}$) to death
$\nu_{x=3}$ = progression from susceptible decompensated cirrhosis ($X^j_{i,n=5}$) to death
$\nu_{x=4}$ = progression from susceptible HCC ($X^j_{i,n=6}$) to death

$trt^j_{i,x}(t)$ = treatment proportion, where,
$trt^j_{i,x=1}(t)$ = proportion of individuals treated from no/mild liver disease ($X^j_{i,n=7}$)
$trt^j_{i,x=2}(t)$ = proportion of individuals treated from moderate liver disease ($X^j_{i,n=8}$)
$trt^j_{i,x=3}(t)$ = proportion of individuals treated from compensated cirrhosis ($X^j_{i,n=9}$)
$trt^j_{i,x=4}(t)$ = proportion of individuals treated from decompensated cirrhosis ($X^j_{i,n=10}$)
$trt^j_{i,x=5}(t)$ = proportion of individuals treated from HCC ($X^j_{i,n=11}$)

rop_x = rate of disease progression, where,
$rop_{x=1}$ = rate of disease progression from ($X^j_{i,n=7}$) to ($X^j_{i,n=8}$)
$rop_{x=2}$ = rate of disease progression from ($X^j_{i,n=8}$) to ($X^j_{i,n=9}$)
$rop_{x=3}$ = rate of disease progression from ($X^j_{i,n=9}$) to ($X^j_{i,n=10}$)
$rop_{x=4}$ = rate of disease progression from ($X^j_{i,n=9}$) to ($X^j_{i,n=11}$)
$rop_{x=5}$ = rate of disease progression from ($X^j_{i,n=10}$) to ($X^j_{i,n=11}$)
$rop_{x=6}$ = rate of disease progression from ($X^j_{i,n=4}$) to ($X^j_{i,n=5}$)
$rop_{x=7}$ = rate of disease progression from ($X^j_{i,n=4}$) to ($X^j_{i,n=6}$)
$rop_{x=8}$ = rate of disease progression from ($X^j_{i,n=5}$) to ($X^j_{i,n=6}$)

p^j = proportion of individuals that spontaneously clear HCV infection
p_{HIV} = proportion of HIV+ individuals that spontaneously clear HCV infection

$c^j(t)$ = proportion of individuals that are cured of HCV
$c_{HIV}(t)$ = proportion of HIV+ individuals that are cured of HCV

Alpha & Mu Terms

The entry rate at any time point *t* is denoted by the term, α. In order to calculate the entry rate by population sub-type, the background mortality at any time point *t* was summed up by each age stage and population sub-type to obtain a total background mortality term μ_{total} at any time point *t*. This term was then divided by the proportion of individuals in each population sub-type at time point ($t = 0$). The population values at $t = 0$ are provided in Table 5. The entry rate for PWID compartments was artificially increased by 20% in order to obtain a stable PWID population. In order to have the entry rate equal to the total background mortality, the entry rate for the non-PWID compartments was reduced. The sum of all α terms was "1.0175". This sum was subtracted from 1 and the remainder, "0.0175" was then subtracted from the two non-PWID HIV- compartments. Non-PWID males Calculation is provided below where α is denoted by $\alpha_{i=1}^{j}$:

$$\alpha_{i=1}^{j=1} = \frac{71732}{2614213}(\mu_{total}) = 0.0274(\mu_{total})$$

$$\alpha_{i=1}^{j=2} = \frac{17038}{2614213}(\mu_{total}) = 0.0065(\mu_{total})$$

$\alpha_{i=1}^{j=3} = \frac{18180}{1122944}(\mu_{total}) = 0.0162(\mu_{total}) => 0.0194(\mu_{total})$; after 20% increase

$\alpha_{i=1}^{j=4} = (\frac{1199575}{2614213} - 0.0084)(\mu_{total}) = (0.4895 - 0.0084)(\mu_{total}) = 0.4505(\mu_{total})$; 0.0084 subtracted, i.e. (48% of 0.0175)

$\alpha_{i=1}^{j=5} = \frac{752}{1122944}(\mu_{total}) = 0.0007(\mu_{total}) => 0.0008(\mu_{total})$; after 20% increase

$$\alpha_{i=1}^{j=6} = \frac{940}{2614213}(\mu_{total}) = 0.0004(\mu_{total})$$

$\alpha_{i=1}^{j=7} = \frac{423}{1122944}(\mu_{total}) = 0.0004(\mu_{total}) => 0.0005(\mu_{total})$; after 20% increase

$$\alpha_{i=1}^{j=8} = \frac{1713}{2614213}(\mu_{total}) = 0.0007(\mu_{total})$$

$\alpha_{i=1}^{j=9} = \frac{6294}{1122944}(\mu_{total}) = 0.0056(\mu_{total}) => 0.0067(\mu_{total})$; after 20% increase

$\alpha_{i=1}^{j=10} = \left(\frac{1297280}{2614213} - 0.0091\right)(\mu_{total}) = (0.4962 - 0.0091)(\mu_{total}) = 0.4871(\mu_{total})$; 0.0091 subtracted, i.e. (52% of 0.0175)

and,

$$\mu_{total} = \mu_i\ X_{i,n=1}^{j} + \mu_i\ X_{i,n=2}^{j} + \mu_i\ X_{i,n=3}^{j} + \mu_i\ X_{i,n=4}^{j} + \mu_i\ X_{i,n=5}^{j} + \mu_i\ X_{i,n=6}^{j} + \mu_i\ X_{i,n=7}^{j} + \mu_i\ X_{i,n=8}^{j} + \mu_i\ X_{i,n=9}^{j} + \mu_i\ X_{i,n=10}^{j} + \mu_i\ X_{i,n=11}^{j}$$

Force of Infection Terms

People in HIV+ compartments having an additional relative risk term of transmissibility (RR_{HIV_tr}), and susceptibility (RR_{HIV_s}).

For MSM (j = 1, 2 and i = 1, 2, 3, 4)

$$\frac{I\_MSM(t)}{N\_MSM(t)} = \frac{\sum_{i=1}^{4} \sum_{n=7}^{11} (X_{i,n}^{j=1} + RR_{HIV\_tr} X_{i,n}^{j=2})}{\sum_{i=1}^{4} \sum_{n=7}^{11} (X_{i,n}^{j=1} + RR_{HIV\_tr} X_{i,n}^{j=2}) + \sum_{i=1}^{4} \sum_{n=1}^{6} (X_{i,n}^{j=1} + RR_{HIV\_tr} X_{i,n}^{j=2})}$$

Force of infection for MSM HIV-: $foi_i^{j=1} = b_{MSM} \left[\frac{I\_MSM(t)}{N\_MSM(t)}\right]$

Force of infection for MSM HIV+: $foi_i^{j=2} = b_{MSM} RR_{HIV\_s} \left[\frac{I\_MSM(t)}{N\_MSM(t)}\right]$

For PWID (j =3, 5, 7, 9 and i = 1)

$$\frac{I\_PWID(t)}{N\_PWID(t)} = \frac{\sum_{n=7}^{11} (X_{i=1,n}^{j=3} + X_{i=1,n}^{j=5} + RR_{HIV\_tr}(X_{i=1,n}^{j=7} + X_{i=1,n}^{j=9}))}{\sum_{n=7}^{11} (X_{i=1,n}^{j=3} + X_{i=1,n}^{j=5} + RR_{HIV\_tr}(X_{i=1,n}^{j=7} + X_{i=1,n}^{j=9})) + \sum_{n=1}^{6} (X_{i=1,n}^{j=3} + X_{i=1,n}^{j=5} + RR_{HIV\_tr}(X_{i=1,n}^{j=7} + X_{i=1,n}^{j=9})}$$

Force of infection for PWID Male HIV-: $foi_{i=1}^{j=3} = b_{PWID\_m} \left[\frac{I\_PWID(t)}{N\_PWID(t)}\right]$

Force of infection for PWID Male HIV+: $foi_{i=1}^{j=5} = b_{PWID\_m} RR_{HIV\_s} \left[\frac{I\_PWID(t)}{N\_PWID(t)}\right]$

Force of infection for PWID Female HIV-: $foi_{i=1}^{j=9} = b_{PWID\_f} \left[\frac{I\_PWID(t)}{N\_PWID(t)}\right]$

Force of infection for PWID Female HIV+: $foi_{i=1}^{j=7} = b_{PWID\_f} RR_{HIV\_s} \left[\frac{I\_PWID(t)}{N\_PWID(t)}\right]$

For ex-PWID (j = 3, 5, 7, 9 and i = 2, 3, 4)

Force of infection for ex-PWID: $foi_{i=2,3,4}^{j=3,5,7,9} = 0$

For non-PWID (j = 4, 6, 8, 10 and i = 1, 2, 3, 4)

Force of infection for non-PWID: $foi_{i=1,2,3,4}^{j=4,6,8,10} = 0$

Model Equations

The model equations are as follows

$$\frac{dX_{n=1}}{dt} = \alpha_{i=1}^{j} - foi_i^j X_{i,n=1}^j (1-p^j) - foi_i^j X_{i,n=1}^j p^j \ - \mu_i \ X_{i,n=1}^j - \varphi_i X_{i,n=1}^j + \varphi_{i-1} X_{i-1,n=1}^j$$

$$\frac{dX_{n=2}}{dt} = foi_i^j X_{i,n=1}^j p^j \ - foi_i^j X_{i,n=2}^j (1-p^j) + trt_{i,x=1}^j(t) X_{i,n=7}^j c - \mu_i \ X_{i,n=2}^j - \varphi_i X_{i,n=2}^j + \varphi_{i-1} X_{i-1,n=2}^j$$

$$\frac{dX_{n=3}}{dt} = trt_{i,x=2}^j(t) X_{i,n=8}^j c^j \ (t) \ - foi_i^j X_{i,n=3}^j (1-p^j) - \mu_i \ X_{i,n=3}^j - \varphi_i X_{i,n=3}^j + \varphi_{i-1} X_{i-1,n=3}^j$$

$$\frac{dX_{n=4}}{dt} = trt_{i,x=3}^j(t) X_{i,n=9}^j c^j \ (t) \ - foi_i^j X_{i,n=4}^j (1-p^j) - rop_{x=6} X_{i,n=4}^j - rop_{x=7} X_{i,n=4}^j - \mu_i \ X_{i,n=4}^j - \varphi_i X_{i,n=4}^j + \varphi_{i-1} X_{i-1,n=4}^j$$

$$\frac{dX_{n=5}}{dt} = trt_{i,x=4}^j(t) X_{i,n=10}^j c^j \ (t) \ + rop_{x=6} X_{i,n=4}^j - foi_i^j X_{i,n=5}^j (1-p^j) - rop_{x=8} X_{i,n=5}^j - \ \nu_{x=3} X_{i,n=5}^j - \mu_i \ X_{i,n=5}^j - \varphi_i X_{i,n=5}^j + \varphi_{i-1} X_{i-1,n=5}^j$$

$$\frac{dX_{n=6}}{dt} = trt_{i,x=5}^j(t) X_{i,n=11}^j c^j \ (t) \ + rop_{x=7} X_{i,n=4}^j + rop_{x=8} X_{i,n=5}^j - foi_i^j X_{i,n=6}^j (1-p^j) - \ \nu_{x=4} X_{i,n=6}^j - \mu_i \ X_{i,n=6}^j - \varphi_i X_{i,n=6}^j + \varphi_{i-1} X_{i-1,n=6}^j$$

$$\frac{dX_{n=7}}{dt} = foi_i^j X_{i,n=1}^j (1-p) + foi_i^j X_{i,n=2}^j (1-p^j) - rop_{x=1} X_{i,n=7}^j - trt_{i,x=1}^j(t) X_{i,n=7}^j c^j \ (t) - \mu_i \ X_{i,n=7}^j - \varphi_i X_{i,n=7}^j + \varphi_{i-1} X_{i-1,n=7}^j$$

$$\frac{dX_{n=8}}{dt} = rop_{x=1} X_{i,n=7}^j + foi_i^j X_{i,n=3}^j (1-p^j) - rop_{x=2} X_{i,n=8}^j - trt_{i,x=2}^j(t) X_{i,n=8}^j c^j \ (t) \ - \mu_i \ X_{i,n=8}^j - \varphi_i X_{i,n=8}^j + \varphi_{i-1} X_{i-1,n=8}^j$$

$$\frac{dX_{n=9}}{dt} = rop_{x=2} X_{i,n=8}^j + foi_i^j X_{i,n=4}^j (1-p^j) - rop_{x=3} X_{i,n=9}^j - rop_{x=4} X_{i,n=9}^j - trt_{i,x=3}^j(t) X_{i,n=9}^j c^j \ (t) - \mu_i \ X_{i,n=9}^j - \varphi_i X_{i,n=9}^j + \varphi_{i-1} X_{i-1,n=9}^j$$

$$\frac{dX_{n=10}}{dt} = rop_{x=3} X_{i,n=9}^j + foi_i^j X_{i,n=5}^j (1-p^j) - rop_{x=5} X_{i,n=10}^j - trt_{i,x=4}^j(t) X_{i,n=10}^j c^j \ (t) - \nu_{x=1} X_{i,n=10}^j - \mu_i \ X_{i,n=10}^j - \varphi_i X_{i,n=10}^j + \varphi_{i-1} X_{i-1,n=10}^j$$

$$\frac{dX_{n=11}}{dt} = rop_{x=4} X_{i,n=9}^j + rop_{x=5} X_{i,n=10}^j + foi_i^j X_{i,n=6}^j (1-p^j) - trt_{i,x=5}^j(t) X_{i,n=11}^j c^j \ (t) - \ \nu_{x=2} X_{i,n=11}^j - \mu_i \ X_{i,n=11}^j - \varphi_i X_{i,n=11}^j + \varphi_{i-1} X_{i-1,n=11}^j$$

In the above model equations:

1) ∀ HIV+ compartments (i.e. $j \in (2, 5, 6, 7, 8)$), $p^j = p_{HIV}$ & $c^j(t) = c_{HIV}(t)$

Model Equations is coauthored with Martin, Natasha K. and Cheema, Jaskaran S. The thesis author was the primary author of this chapter

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