Potential impact of prison-based interventions on hepatitis C transmission among people who inject drugs in Montréal, Canada

Insights from mathematical modelling

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Résumé

Contexte

La transmission du virus de l'hépatite C (VHC) est principalement concentrée chez les utilisateurs de drogues injectables (UDI), une population souvent en contact avec le système de détention provincial où les sentences sont plus courtes que deux ans. Les UDI et les personnes en prison ont été identifiés comme des populations prioritaires pour l'élimination du VHC en tant que menace pour la santé publique. Néanmoins, la chaîne de soin en prison et la liaison avec les soins de santé dans la collectivité demeurent des défis de taille pour les services correctionnels en raison du taux de roulement, des transferts fréquents et de l'absence de cheminement clinique standardisé. Avec l'arrivée des antiviraux à action directe (AAD) efficaces, dont la durée de traitement est courte, les personnes en prison pourraient être priorisées pour un traitement durant ou après leur incarcération. Cependant, le dépistage systématique du VHC n'est pas implanté dans les prisons provinciales, ce qui freine l'identification de nouveaux cas. De plus, les comportements à risque après la libération impliquent un potentiel de réinfection chez les individus traités en prison. Dans ce contexte, il est urgent d'évaluer de façon robuste les interventions ciblant le VHC en milieu carcéral.

Objectif

Évaluer l'impact potentiel de stratégies d'intervention en milieu carcéral sur la transmission du VHC à l'échelle de la population des UDI de Montréal.

Méthodes

Un modèle mathématique dynamique de la transmission du VHC chez les UDI de Montréal a été développé. Celui-ci est stratifié par sexe (homme, femme), statut d'incarcération (jamais, présentement, récemment libéré, déjà incarcéré) et statut d'injecteur (UDI actif, passé, sous traitement par agoniste opioïde). Le modèle a été calibré à des données locales provenant de sondages bio-comportementaux menés dans la population carcérale (2003, 2014) et annuellement chez les UDI (2003-2014). Trois types d'intervention en prison ont été explorés : **1)** le dépistage et le traitement en prison (90% testés et 75% traités en prison), **2)** la prise en charge à la libération (90% testés en prison, 75% traités à la libération) et **3)** la réduction du risque à la libération (réduction de 50%). L'impact de ces scénarios a été évalué sur dix ans à partir de 2018 par rapport à un scénario contrefactuel gardant les taux de dépistage et

de traitement constants et alors qu'aucune intervention n'est initiée en prison. L'évaluation d'impact a été réalisée en termes de réduction relative de la prévalence (P) et de l'incidence (I), ainsi qu'en termes de fraction de nouvelles infections prévenues (IP).

Résultats

Le modèle reproduit l'épidémie de VHC chez les UDI de Montréal, en prison comme dans la collectivité. Après dix ans, l'intervention de dépistage et de traitement en prison (P : $27\%(95\%CrI = 20-34\%)$; I : $19\%(95\%CrI = 9-28\%)$; IP : $7\%(95\%CrI = 4-10\%)$) et de prise en charge à la libération (P : $30\%(95\%CrI = 22-38\%)$; I : $23\%(95\%CrI = 11-33\%)$; PF : $9\%(95\%CrI = 5-14\%)$) réduisent toutes deux la prévalence en plus de ralentir la transmission du VHC chez les UDI de Montréal. En présence de réduction du risque à la libération, le dépistage et le traitement en prison (P : $32\%(95\%CrI = 25-41\%)$; I : $30\%(95\%CrI = 17-41\%)$; PF : $10\%(95\%CrI = 6-17\%)$) ainsi que la prise en charge à la libération (P : $36\%(95\%CrI = 28-45\%)$; I : $33\%(95\%CrI = 20-45\%)$; PF : $13\%(95\%CrI = 7-20\%)$) ont un impact soutenu sur la prévalence et la transmission du virus.

Conclusion

Ces résultats suggèrent qu'offrir le dépistage systématique du VHC en prison et le traitement des cas chroniques pendant ou après l'incarcération, pourraient potentiellement changer la trajectoire de l'épidémie chez les UDI de Montréal. Parmi les différents scénarios, les modèles de soins intégrant la réduction du risque peuvent avoir l'impact le plus important pour diminuer la transmission du VHC.

Abstract

Background

The Canadian burden of chronic hepatitis C (HCV) is highly concentrated among people who inject drugs (PWID), a population with high incarceration rates in the provincial prison system, where the duration of sentences is less than 2 years. PWID and people in prison have been identified as key populations for HCV transmission and to eliminate HCV as a public health threat by 2030. However, the treatment and care continuum for HCV in provincial prisons, as well as the link with community services still represent challenges because of high turnover rates, frequent prison transfers, and the lack of standardized care pathways. Because of short-course direct-acting antivirals (DAA) with high safety and tolerability, people in provincial prisons could be prioritized for treatment during or after their stay in prison. However, universal HCV screening has yet to be implemented in these settings, which precludes case identification. Further, the heightened risk of HCV acquisition and transmission post-release creates a potential for reinfection among individuals treated in prison. There is an urgent need to build the evidence base regarding prison-based interventions to reduce HCV transmission.

Aims

This study aims to assess the potential population-level impact of prison-based intervention strategies on HCV transmission among PWID in Montréal.

Methods

A dynamic compartmental model of HCV transmission among PWID in Montréal was developed. The model is stratified by sex (male, female), incarceration status (never, currently, recently or previously released), and injecting status (active, past, and on opioid agonist therapy). It was calibrated in a Bayesian framework to local epidemiological data from bio-behavioural surveys conducted annually among PWID (2003-2014) and twice among the general prison population (2003, 2014). Among other scenarios, three broad types of intervention strategies were explored: **1)** prison-based test-and-treat (90% tested, and 75% treated in prison), **2)** linkage to care post-release (90% tested in prison, and 75% treated post-release), and **3)** risk reduction interventions, which halve the elevated post-release risk. The impact of these interventions was estimated over ten years from 2018 on prevalence (P),

incidence (I), and prevented fraction of new infections (PF), as compared to a status quo counter-factual where no specific intervention is implemented in prison for HCV.

Results

The model reproduces the HCV epidemic among PWID in Montréal, both inside and outside of prison settings. After ten years, prison-based test-and-treat (P: $27\%(95\%CrI = 20-34\%)$; I: $19\%(95\%CrI = 9-28\%)$; PF: $7\%(95\%CrI = 4-10\%)$) and linkage to care post-release (P: $30\%(95\%CrI = 22-38\%)$; I: $23\%(95\%CrI = 11-33\%)$; PF: $9\%(95\%CrI = 5-14\%)$) would both reduce prevalence and slow down HCV transmission among active PWID in Montréal. Combined with risk reduction, test-and-treat interventions (P: $32\%(95\%CrI = 25-41\%)$; I: $30\%(95\%CrI = 17-41\%)$; PF: $10\%(95\%CrI = 6-17\%)$), and linkage to care (P: $36\%(95\%CrI = 28-45\%)$; I: $33\%(95\%CrI = 20-45\%)$; PF: $13\%(95\%CrI = 7-20\%)$) would lead to a sustained impact.

Conclusion

These results suggest that offering universal HCV testing in prison and increasing treatment for PWID in or upon release from provincial prisons could change the course of the HCV epidemic in Montéal. Among all scenarios, models of care that integrate risk reduction measures post-release have the greatest potential to reduce HCV transmission among PWID.

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À mes parents

Finally, from so little sleeping
and so much reading, his brain
dried up and he went
completely out of his mind.

Don Quixote - Cervantes

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Author contribution

AG, JC, MMG, and NK conceptualized the project. AG conceived and designed the model. MA granted access to prison survey microdata. AG obtained, performed, and interpreted secondary analyses of prison survey microdata. AG, JC, MA, MMG, and NK contributed to model development and/or revision. AG performed the analyses and all authors contributed to results interpretation. AG drafted the manuscript and all authors critically reviewed it for important intellectual content.

Introduction

The Hepatitis C virus (HCV) is a blood-borne infection that represents a pressing public health problem worldwide. It has a substantial impact on the global burden of liver-disease, and is responsible for more years of life lost than any other infectious disease [1]. Due to HCV, end-stage liver disease and liver cancer are expected to increase in the coming years [2]. The World Health Organization (WHO) recently set targets for HCV elimination as a public health threat by 2030. These objectives include a reduction of 80% in new chronic HCV infections, as well as a reduction of 65% in liver mortality for prevalent cases [3].

The general population of Canada had an estimated chronic prevalence of 0.96% in 2011 [4]. HCV is a mandatory notifiable disease, and only a few cases are diagnosed every year in Canada and in Québec. In 2016, the overall incidence among the general population of Québec was of 12.6 cases per 100,000 person-years (PY), higher for men (16.5 per 100,000 PY) than for women (8.5 per 100,000 PY) [5]. Importantly, most new diagnoses of HCV infection occur in the 40 to 55 years old age group [5].

Even though rare in the general population, HCV is highly prevalent and has a high incidence in vulnerable population subgroups. Such subgroups include people who inject drugs (PWID), people in prison, indigenous people, and men who have sex with men living with HIV [5]. These groups are important to overall transmission dynamics of the virus. Over the last two decades, the overall incidence and prevalence among PWID in Québec was around 23 cases per 100 PY and 63.4% respectively, which is much higher than any other group [6].

PWID also have high incarceration rates, often related to minor drug charges, and this cycle of (re)incarceration has been identified as an epidemic driver [7]. This results from the elevated risk of HCV acquisition and transmission upon release from prison, which is in part due to withdrawal symptoms experienced during incarceration but also to an unstable environment post-release [8]. In the Québec prison system, the prevalence of HCV was estimated at 12% among men and 16% among women in 2014 [9]. Given the high prevalence in this group, interventions should be put in place to address this disease burden. However, contrary to the federal prison system, there currently exist no HCV-specific intervention

strategies in provincial prisons in Canada, except in British Colombia [10].

Reaching HCV elimination as a public health threat will require numerous specific measures targeted at population subgroups with very different characteristics. On the one hand, a large fraction of the burden of disease resides among an older population with no ongoing risk factors and latent advanced infections [2]. On the other hand, the core driver of the epidemic is located among a younger population of PWID who acquired their infections more recently and are contributing to ongoing transmission [11]. Further, marginalized subgroups such as people in prison and indigenous people, are disproportionately contributing to the disease burden [12; 13].

Canada is currently not on track to achieve the elimination targets set forth by WHO, and a recent national initiative, has made recommendations to establish HCV-specific public health interventions at the provincial level [14]. Given the potential importance of the key population of incarcerated PWID to HCV elimination efforts, evaluating the potential population-level impact of specific prison-based continuum of care interventions remains a priority in Canada.

Overall aim

In light of the current gaps in the continuum of HCV care for PWID and people in prison, the overall aim of the current study is to:

- Assess the impact of different prison-based continuum of care interventions to reduce HCV prevalence and incidence in the broader community of PWID in Montréal (Qc, Canada) over a ten year horizon, starting in 2018.

This thesis is organized in five chapters. An overview of HCV epidemiology, examining the natural history of the disease, the cascade of care, and potential interventions to achieve elimination as a public health threat by 2030 is first presented (Chapter 1). Chapter 2 presents the specific aims of this work. Then, a mathematical model of HCV transmission among the PWID population is described (Chapter 3). This model was calibrated to local epidemiological data and used to project population level impact of potential prison-based interventions, these results are provided in Chapter 4. The final chapter (Chapter 5) discusses main findings, strengths and limitations, as well as comparison of this work to the current literature.

Chapter 1

Literature review

This narrative review will first give an overview of HCV's natural history, the cascade of treatment and care, and present the main modes of transmission as well as the populations most at risk. It will then discuss the concept of micro-elimination and different intervention strategies that could be implemented in prison settings. Last, an overview of the tools that exist to build evidence for prison-based interventions will be presented.

1.1 Hepatitis C Epidemiology

1.1.1 Natural history

HCV is transmitted by blood-to-blood contacts and the virus targets the liver of infected individuals. The disease has a highly heterogeneous genome, with 7 genotypes, all with multiple subtypes. Upon being infected by HCV, an individual will experience a mild or asymptomatic acute stage, which makes early case identification difficult [15; 16]. In about 25% of cases, the innate and adaptive immune responses allow a spontaneous clearance of the infection. In such instances, the individual does not experience viral persistence, but develops HCV antibodies that remain in the blood for life [17]. Several predictors of spontaneous clearance have already been suggested, and include sex, symptomatic infection, and genetic factors [18; 19]. When HCV-RNA persists in the blood after six months, individuals are considered chronically infected [15].

Chronic HCV infection is one of the driving factors for end-stage liver disease in Canada [2]. It is characterized by liver fibrosis, which is assessed on the Metavir scale: from no fibrosis (F0), to mild fibrosis (F1-F3), and eventually to cirrhosis (F4) [20; 21]. HCV progresses in a slow and non-linear fashion, and it takes years, if not decades, before substantial damage to the liver can be noticed. Multiple factors are also associated with fibrosis progression, such as being born male, alcohol intake, and HIV co-infection [20]. A recent meta-analysis

estimated the average time from HCV-infection to cirrhosis at 37.5 years, which was shown to vary according to fibrosis progression predictors [21]. The slow progression of the disease is crucial to understand the importance of active HCV diagnosis, because patients are often asymptomatic until late fibrosis stages [21]. Further, HCV symptoms such as jaundice and fatigue are rare and non-specific [15; 16]. Hence, case identification remains a major problem in chronically infected individuals, especially the identification of early chronic cases.

Patients are frequently diagnosed following complications of end-stage liver disease or hepatocellular carcinoma (HCC), a type of liver cancer [15]. In the United States (USA), mortality due to cirrhosis increased since 2009 and is expected to triple by 2030 [22; 23]. Canada is witnessing a similar situation, with HCV-related liver complications among chronic cases projected to increase from 8.7% in 2013 to 23% by 2035 [2]; with concomitant rises in decompensated cirrhosis, HCC cases, and liver-related mortality [24; 2]. The risk of HCC in people living with HCV increases as fibrosis progresses, and people most at risk of HCC are those who already developed cirrhosis [25]. As such, in North America HCV was the most indicated primary diagnosis among liver transplantation recipients at their first graft overall [25; 26][1]. A further concern is that infection of the graft is expected to occur in all patients who are infected at time of transplant, with a faster disease progression due to immunosuppression [15]. Hence, untreated chronic infections could greatly contribute to the end-stage liver disease burden as well as mortality [2]. The advent of direct acting antiviral (DAA) therapy will most likely reduce this problem, as it was shown effective to slow disease progression in graft patients [27].

1.1.2 HCV cascade of care

The high heterogeneity of the viral HCV genome, made the search for a cure a tedious enterprise. It was only in the 1990s that a first viral clone was discovered, which allowed the development of a sensitive diagnostic antibody test in 1992 [28]. This test was implemented in routine blood product screening, and significantly reduced transmission from contaminated blood products in medical settings (e.g. transfusion) [29]. The current testing algorithm combines two types of tests. First, an enzyme immunoassay (ELISA) identifies HCV-antibodies in the blood or saliva of infected or previously exposed individuals. Because of the persistence of the antibody response following spontaneous clearance or cure, these antibody tests have good sensitivity, but relatively poor specificity to detect chronic (or active) HCV infections [17; 30]. Second, polymerase chain reaction (PCR), assesses the presence of HCV-RNA in the blood [31; 30]. This test has a better specificity compared to the ELISA, because patients who cleared the infection or were cured do not have HCV-RNA

[1] Canadian data exclude Québec because of under-reporting over the 2006-2015 period

persistence in their blood and non-chronic infections are ruled-out by the test. Hence, confirmed chronic HCV infections are diagnosed by first using the cheaper antibody test, and second the more expensive PCR test [32].

Testing may constitute a rate-limiting step among PWID, a hard-to-reach population with a high loss to follow-up rate. Notably, many of the PWID who are tested for HCV-RNA never receive confirmation of their infection status [33; 34]. Multiple reasons account for this problem. The lack of point-of-care tests entails that several visits are currently required to obtain a diagnosis. This is important for populations with low engagement in healthcare, as any delay can lead to loss to follow-up [35]. Other reasons include poor knowledge of HCV among general practitioners and patients. A limited experience in addiction medicine or gastroenterology can constitute a barrier for general practitioners to provide proper HCV diagnosis and care. Also, individuals who have lower engagement in healthcare can be misinformed about HCV prevention, diagnosis, care, and treatment [36; 37; 38]. Hence, strategies are being developed and implemented to enhance testing in hard-to-reach populations, such as dried bloodspot or point-of-care testing. By improving the turnaround time for diagnosis, these strategies could greatly enhance diagnosis, infection status confirmation, and subsequent linkage to care [35; 39]. According to current guidelines, any positive patient should be referred to treatment if there is no contraindication [32]. To be considered cured of HCV, there should be no HCV-RNA persistence in the blood at 12 to 24 weeks following treatment completion. This is called a sustained virologic response (SVR) [15].

The history of antiviral treatment for HCV can be divided in two distinct eras. The first type of drugs developed was based on interferon (IFN). An experimental wave of treatment was initiated in the 1990s with an IFN monotherapy, which resulted in SVR in about 5% of cases after 24 weeks of treatment [40]. Treatment was then developed by adding ribavirin (RBV), which substantially increased SVR to 30% for a 24-week course. The optimized pegylated-interferon/ribavirin (PEG-IFN/RBV) combination of the early 2000s also provided a notable increase in SVR (60% for a 48-week course) [41; 40]. This last combination was composed of a weekly injection of PEG-IFN and two RBV pills taken daily [41; 42]. Because of the intensive medication intake necessary for completion, treatment adherence was low, especially in hard-to-reach populations such as PWID [43]. Further, the different treatment components had important side effects. Ribavirin could cause haemolytic anaemia, which often lead to dose reduction or discontinuation, and negatively impacted SVR [41]. Interferon had multiple side effects, such as flu-like symptoms (e.g. headaches, fever, etc.), psychiatric effects (e.g. irritability, fatigue, severe depression, etc.), and the development of autoimmune thyroiditis [41; 42]. These side effects were frequent and had a negative impact on adherence, because they were aggressive and often necessitated supplementary medication to be taken alongside standard treatment [43]. Also, even with an increased efficacy of treatment, and guidelines

including PWID, many healthcare providers remained reluctant to treat PWID because of the potential for non-adherence and the high risk of reinfection, resulting in low treatment rates in this specific population [44].

Direct acting antivirals (DAA) were developed to overcome the problems of PEG-IFN and target HCV-specific viral functions [45]. The first generation of DAA were protease inhibitors administered with PEG-IFN/RBV. Even with an increased SVR for all genotypes, important side effects remained, and barriers to drug resistance were very low, which meant that drug-resistant mutant viruses were likely to emerge [45; 40]. The second generations of DAA addressed most of these problems, with a reduction in side effects and improved barriers to drug resistance. In recent years, IFN-free DAA therapies have been approved and administration of ribavirin depends on the stage of liver disease [45]. Current SVR rates with the latest DAA generation are superior to a 95% efficacy for most genotypes [46]. Hence, these new therapies represent a complete paradigm shift in treatment, which now has a shorter duration, superior efficacy, and improved tolerability and safety profiles. On average, a treatment course for HCV now lasts between eight and twelve weeks with one to three pills daily [40; 47; 48]. Reported side effects are minors compared to the IFN era, and drug-drug interaction issues are less prominent than in the early DAA era. Further, as multiple regimens are available and drug-resistance not of concern, treatment of reinfected individuals is now indicated [49; 45]. In addition, multiple regimens are pangenotypic, which makes the need for genotyping less important than in the PEG-IFN era. The cost of DAA therapy still represents a major barrier, which is being addressed by numerous government agencies that negotiate with pharmaceutical companies [50; 51]. Nonetheless, this important shift in the treatment landscape spurred WHO to establish a strategy for HCV elimination as a public health threat [3].

1.2 Burden of disease and key populations

1.2.1 People born between 1944-1975

At the onset of the HCV epidemic, contaminated medical blood supplies was the main mode of transmission in Canada. Several thousands of people are estimated to have been exposed to HCV-infected blood products during medical procedures [2; 29]. Fortunately, with the development of diagnostic testing and systematic screening of blood products in the 1990s, iatrogenic infections sharply decreased, and multiple cases were identified by targeted lookback procedures [52; 53]. It was estimated that about 70% of the Canadian population living with HCV was born between 1944 and 1978 [2]. Hence, an important proportion of the disease burden is borne by the birth cohort of baby boomers. However, most prevalent

cases in this group remain unaware of their infection because of its asymptomatic nature [15; 42]. Further, these cases have no ongoing risk factor, which rules them out of traditional risk-based screening. Recommendations have thus been made to implement a one-time birth cohort screening strategy for people born between 1944 and 1975 [2; 32]. Unless case identification is substantially scaled-up, this key population will remain at high risk of developing end-stage liver disease complications and/or HCC [32].

1.2.2 Migrants

Individuals born outside of Canada account for nearly 30% of all cases countrywide, with prevalence being twice that of the population born in Canada [54]. HCV among foreign-born Canadians is typically acquired in the country of origin, with a majority infected from unknown sources [54]. Evidence from Québec administrative data (1998-2008) indicates that few foreign-born cases acquire HCV through drug use (<3%) [55]. Hence, there have been multiple calls to implement systematic screening of immigrants upon arrival in Canada coming from endemic countries (countries with a prevalence of more than 2%) [55]. Evidence suggests that health system barriers exacerbate health inequalities for members of this group. HCV-infected individuals born outside Canada are typically diagnosed 10 years after their arrival, often at late stages of liver disease caused by HCV [54]. Further, immigrants to Canada are more likely to develop liver cirrhosis and HCC as a result of an HCV infection than non-immigrants living with HCV, and are more likely to die of liver-related complications during hospitalization than their non-immigrant counterparts [56].

1.2.3 People who inject drugs

Currently, in high-income countries, the primary mode of transmission is injection drug use (IDU). Infections mostly occur when people engage in injecting risk behaviors. The most frequent risk behavior for HCV acquisition is injecting with contaminated needles and syringes [11]. HCV can survive for prolonged periods of time in syringes, which depends on the conservation temperature and the syringe type [57]. Re-use of other drug paraphernalia, such as filters, rinse water, and mixing containers has also been identified as a potential risk factor [58; 59; 60]. Drug preparation behaviors could also have an impact on the risk of HCV acquisition among PWID. For instance, "backloading", the procedure by which drugs are shared through the container of one syringe to another syringe, can result in HCV transmission [61; 62]. Disentangling the individual effects of drug preparation and equipment re-use on HCV transmission risk is difficult because all these behaviors often occur concurrently [59]. Pouget et al. [11] found that filters, rinse water, as well as "backloading" were all associated with HCV sero-conversion.

An important predictor of the risk of HCV transmission is drug type. It remains difficult to measure the contribution of specific drug type on transmission risk because poly-injecting drug use is widespread. Nevertheless, injection of cocaine has long been identified as the main risk factor for HCV acquisition in Montréal, Canada [63; 64; 65]. Multiple injections in a day, as well as high risk behaviors associated with cocaine injections, are believed to be a cause [64; 65]. However, the drug market is cyclical, and drug use patterns are influenced by the availability of drugs [66]. This has been observed in Montréal, with the rise of prescription opioids (PO) from the end of the 2000s until today [64; 6]. PO are a major concern and their use has been discussed as an important risk factor for HCV acquisition. This is because the volume of water necessary to dissolve an opioid tablet is typically too large to fit in single syringe, which often leads to multiple injections in a short amount of time, and could increase the risk of re-using injecting materials [63; 67; 68]. Further, these cheap and easy-to-access PO are potential pathways leading to injection of traditional drugs such as heroin [69; 70].

The risk of HCV infection in PWID varies according to multiple interrelated factors, such as injection with previously used needles and syringes, the drug most frequently injected, and specific injecting behaviors. In SurvUDI, a bio-behavioural surveillance system of PWID in the province of Québec, HCV antibody prevalence remained stable at 63% on average from 2003 to 2016. However, this measure is for antibody prevalence which rules-in people who recently cleared or were cured of their infection, and overestimates chronic HCV prevalence [6]. Incidence also remained stable over that same time interval at around 21.9 per 100 PY on average. In Montréal, where most of Québec's PWID population is located, prevalence was 68% on average over 2003-2016, and incidence was approximately 23.5 per 100 PY ($95\%CI : 20.9 - 26.2$ per 100 PY) [6]. PWID remain a key population for ongoing disease transmission and effective interventions are needed to achieve HCV elimination as a public health threat by 2030 [3].

1.2.4 People in prison

Data from provincial prisons in Canada suggest that antibody prevalence is over 40-fold higher than that of the general population [9; 4]. This can be in part explained by the over-representation of PWID in the incarcerated population [9; 71]. A recent survey conducted in provincial prisons in Québec found that 21% of incarcerated people reported IDU in the past 6 months [9]. Most often, incarcerated people will stay for very short time periods in provincial prisons, where sentences are under two years [9]. In 2014, HCV antibody prevalence was estimated to be 12% and 19% among all incarcerated men and women, respectively, in Québec [9]. This prevalence was much higher among incarcerated people reporting IDU, with $53\% - 56\%$ having been exposed to HCV [9; 72]. Similar data has been

observed in other Canadian settings [73].

In prison settings, the risk of HCV infection is heightened because access to sterile materials for IDU is difficult or impossible [9; 74]. Even though data is scarce on IDU behaviors and HCV in prison settings, there is a large body of qualitative evidence that suggests that high risk behaviors, such as needle and syringe re-use, are common in prison [75; 76; 74]. PWID often share injecting materials sequentially, following a precise order, which depends on who owns the syringe and/or the drug used [74]. Even though IDU in prison is generally unsafe, it is less frequent than in the community, because drugs and injecting materials are more difficult to obtain, hereby inhibiting many PWID from injecting during their incarceration [9]. Another mode of transmission in prison is tattooing, a very frequent yet strictly prohibited practice in provincial prisons. In 2014, 37% of men in Québec prisons reported tattooing during at least one incarceration period of which 13% reported using unsterile materials, down from 27% in 2003. Overall, women reported much less tattooing while incarcerated compared to men [9; 72].

Incarcerated PWID in the provincial system often spend short periods of time in prison. In the Québec prison system, time spent in prison per incarceration increased from 33 days in 1999, to 67 days in 2007, and to 74 days in 2012 [77]. Further, PWID often experience more incarceration episodes compared to the non-PWID population and the number of incarcerations is associated with HCV status in prison [9; 72]. HCV acquisition and transmission also occurs upon release from prison, as PWID often face unstable housing conditions and economic deprivation with frequent and rapid relapse to drug use as a coping mechanism [78; 79]. Resuming IDU in this context is associated with greater risk of infectious diseases transmission (HIV, HCV), such as re-use of needles and syringes [78; 79]. Recent incarceration has been associated with an increased risk of HCV transmission and acquisition up to 6 months following release [8]. Further, recent release is associated with higher risk of death among PWID, especially drug-related mortality [80]. When PWID are incarcerated, their substance tolerance usually fades with time. Yet, upon release people may start injecting with the same dosage they used prior to incarceration, which increases the risk of both non-lethal and lethal overdose [80; 81].

1.2.5 Indigenous people

In Canada, HCV antibody prevalence is 5-fold higher among indigenous people than the non-indigenous population. Indigenous scholars have attributed this to the lasting effects of colonialism and the associated historical trauma created important risk for IDU. In turn, this lead to an over-representation of indigenous communities in high risk groups for HCV acquisition, such as street youth or PWID [13]. Such risks are further compounded by

unstable housing conditions and family statuses, as well as frequent contact with the criminal justice system, with indigenous people spending more time in prison than non-indigenous Canadians. Finally, they have greater unmet health needs, and are largely under-represented in the HCV cascade of care. Hence, indigenous people are at high risk of HCV acquisition and historical trauma led to their over-representation in high risk groups [13]. It has been suggested that, in order to address the pressing ongoing needs of these communities, trauma-informed holistic care approaches are required [13].

1.3 Micro-elimination

The problem of HCV elimination as a public health threat requires drastic reductions in both mortality and incidence. To reduce mortality and the end stage liver disease burden, there is an urgent necessity to identify cases among people born between 1944 and 1975 and initiate treatment before liver-disease complications occur [2; 29]. However, this approach will not reduce incidence, since these people have no ongoing risk factors, and contribute little to disease transmission [29]. To impact incidence, PWID need to be targeted, as the majority of incident HCV cases occur among this group. This population is younger than the baby boomer birth cohort, so their HCV infection might not be advanced in terms of liver damage, but they have ongoing risk factors of HCV transmission [2]. In addition, PWID are marginalized and face important barriers in accessing HCV diagnosis and care [82]. There is a pressing need to find individuals living with HCV, treat their infection, and prevent further infections. Hence, the road to HCV elimination requires targeting two very distinct populations in terms of risk factors.

Canada has pledged to meet the WHO goals for HCV elimination as a public health threat but is currently not on track to achieve them [14]. A recent national initiative has made several recommendations to inform policymakers at the provincial level [14]. The structure of the Canadian HCV epidemic requires stakeholders to develop innovative intervention frameworks that could allow reaching elimination targets. In its elimination strategy for viral hepatitis, WHO puts a strong emphasis on the concept of micro-elimination [3]. In that framework, HCV elimination can only be reached by breaking the response in smaller pieces that are targeted and adapted to specific key populations [3]. In high income countries, interventions must specifically be tailored to the needs of hard-to-reach risk groups among which transmission is concentrated. PWID, and people in prison were identified as two key populations to be specifically targeted in this micro-elimination framework [12; 3].

1.4 Injecting drug use, prison, and the potential to intervene

In Canada, the prison system is organized in provincial and federal levels. Penitentiaries of the federal system are for people with sentence lengths greater than two years. Individuals with sentences shorter than two years are incarcerated in the provincial prison system. In federal penitentiaries, universal treatment of chronic HCV cases with DAA was implemented in 2017 [83]. With the short duration of current regimens, at 12 weeks, treatment can be completed during incarceration [83].

Provincial prisons are currently being neglected in the HCV response despite an important burden among inmates [9]. The only intervention currently in place in Canada is a universal opt-in screening strategy upon admission to provincial prisons in British Colombia [84]. Nevertheless, prison-based interventions could play a key role in response to the HCV epidemic, given the short incarceration time at this level and the elevated risk of HCV transmission among PWID upon release. Treating people in provincial prisons or increasing linkage to care post-release could reduce onward HCV transmission by decreasing chronic HCV prevalence among people with elevated post-release risk of onward transmission [85].

Multiple barriers hinder the development of prison-based public health interventions for HCV. In provincial institutions, incarceration time is often shorter than current treatment duration, which makes completion impossible within that time frame [9; 86]. This is especially important for people incarcerated on remand (awaiting trial, decision, or sentencing). This population constitutes the largest number of new admissions in correctional services, and largely outnumbers the population of sentenced individuals [86]. Additionally, poor follow-up after prison transfer can be challenging for ongoing HCV care, and treatment completion [84; 9]. The cost of DAA therapy is further deterrent to HCV treatment in provincial prison, especially given the potential high risk of reinfection upon release [84; 8]. Lastly, interventions aimed at improving linkage to care post-release are lacking in most provinces. However, these interventions have been shown to be effective in other contexts, such as nurse-led models in Australia, and could be key to maximize treatment completion for people with short sentences initiating treatment while incarcerated [87; 88; 84]. The main potential interventions are summarized in the following sub-sections of this chapter.

1.4.1 Treatment as prevention

The latest generation of DAAs led to an important shift in strategies targeted at reducing HCV in PWID because of increased SVR rate, and fewer side effects. DAA can be considered in the perspective of treatment as prevention (TasP) [89]. This concept originates from the

HIV literature and considers treatment also has potential preventive benefits by reducing prevalence in at-risk networks [89]. For instance, an individual will directly reap benefits of having an SVR following treatment, and people in the injecting network of that individual will indirectly benefit from that SVR, because their probability of effective contact with an infected person will be lowered [89; 51]. These treatment benefits could be greater for HCV compared to HIV, because treatment duration is shorter and leads to a cure, whereas HIV therapy is a lifelong process [90]. However, these potential benefits may also be compounded by the potential for reinfection upon HCV cure, which is high among PWID [90]. If treatment is scaled-up in key populations, important indirect benefits from the prevention of further infections could be attained.

A substantial body of evidence from the modelling literature supports this idea. For instance, it was found that scaling-up DAA therapy could substantially reduce chronic prevalence in the United Kingdom (UK) and other high income settings, and that the intervention would be cost-effective if not delayed [91; 92; 93]. However, Martin et al. [93] put a strong emphasis on integrated models of care, and harm reduction measures to enhance the prevention benefits of such interventions. The authors also mention costs of treatment as the greatest barrier to scale-up. Other authors found that, in settings with high prevalence ($\geq$ 85%), TasP would not lead to important reduction in HCV transmission [51]. However, in settings with moderate to low prevalence ($<$ 60%) treatment scale-up would lead to a reduction in HCV transmission [51]. With regard to implementing a TasP approach in prison, the literature to that end is still scarce. One modelling of the Scotland epidemic has shown that DAA scale-up in prison could reduce HCV incidence and prevalence in the general community of PWID [7]. However, this study also emphasizes the need for harm reduction strategies to reduce HCV transmission in the whole community of PWID. In the United States, a study found that a universal opt-out testing and treatment approach among the general prison population could potentially prevent 5500-12700 new infections [94]. These studies highlight an important need for empirical evidence on the effectiveness and cost-effectiveness of prison-based TasP for HCV [90].

1.4.2 Opioid agonist therapy

Medication-assisted treatment or opioid agonist therapy (OAT), is one of the main harm reduction measure. It consists of prescribing an opioid agonist, or partial agonist, to a person with opioid use disorder in order to reduce illicit or prescribed opioid use [95]. According to current guidelines, buprenorphine (Suboxone), a partial agonist, is the preferred first-line regimen, as it has proven safer than other options and easier for take-home dosing [96]. Methadone is the second-line regimen, when buprenorphine is not indicated or has failed. It works as a complete agonist and is the oldest opioid use disorder treatment. Buprenorphine is

more flexible than methadone, which requires daily pharmacy visits, and can enhance access to OAT [96]. Both of these treatment options are proven to improve quality of life and reduce the risk of adverse health outcomes related to IDU, such as HIV or HCV acquisition, and overdose death [97; 96]. Even though OAT can help reduce high risk behaviors, it might not totally stop people from injecting. Polydrug use is frequent among PWID and, even on OAT, a person could inject stimulants [98; 99]. Further, the impact of this harm reduction measure could be limited in settings where the prevalence of opioid use disorder is considered low, such as Montréal [100]. Nonetheless, OAT alone could help reduce the risk of HCV acquisition by half according to a recent meta-analysis [100]. This is important in the context of an increasing prevalence of prescription opioids injection over the past decade in Canada [95; 6]. Data from SurvUDI suggest about a 34% of participants reported having been on OAT in the previous 6 months, and 28% reported being on OAT in the past month [6]. Current guidelines do not allow OAT to be initiated in provincial prisons, as no official program exists in these settings. However, a person who has been prescribed OAT prior to incarceration cannot be denied this intervention, although treatment interruptions have been reported [101].

Modelling studies have looked at the contribution of OAT to reduce HCV transmission in different populations. It was often stressed that OAT would not be sufficient to eliminate HCV transmission, mostly because of poly-injecting drug use. However, modelling results tend to indicate that OAT is an important building-block to reduce HCV transmission among active PWID. In the UK, Martin et al. [102] showed OAT may help reduce HCV transmission by 50% over ten years if used as part of a strategy that also comprises treatment scale-up in the PEG-IFN era. Fraser et al. [103] found that OAT could be necessary and complementary to treatment scale-up in order to reduce HCV transmission in rural American settings where the epidemic is on an upward trend. In prison, the evidence on the effectiveness of OAT measures is still scarce. Stone et al. [7] found that OAT in Scottish prison would improve the outcomes of TasP interventions. The authors found that a DAA scale-up combined with prison-based OAT could further reduce HCV incidence and prevalence, as compared to a treatment scale-up alone. Hence, even if OAT is not sufficient to reduce HCV transmission in PWID, it represents an important part of the intervention strategy, and can improve the outcome of treatment scale-up by reducing the risk of reinfection [91; 103]. Further, OAT has other health benefits, such as reducing the risk of HIV, all-cause, and overdose-related mortality [104; 105]. However, in provincial prisons there are still difficulties in managing ongoing treatment, such as inappropriate dosage and poor links with community-based services [101; 10].

1.4.3 Needle and syringe programs

Needle and syringe programs (NSP) represent the other important building-block of harm reduction measures. The objective of such programs is to make sterile injecting materials available to all PWID to reduce sharing and/or re-use of needle, syringes, and the whole injecting paraphernalia [100]. By increasing the volume of sterile materials in injecting networks, the time to disposal of infected materials will decrease, which should eventually impact HIV and HCV transmission [106]. In Québec, NSP were established in a network called the *Centre d'accès au matériel d'injection* (CAMI), comprised of community organization, pharmacies, and fixed-site centers. [107]. Over the last decade, there has been an increase in the number of syringes and other material distributed by the *Direction de la santé publique* to CAMI, rising from 1.8 million syringes in 2005-2006 to 2.6 million syringes in 2015-2016 [107]. Over the same period, there was a substantial decrease in self-reported needle and syringe re-use in the SurvUDI network [6]. The proportion of injections performed with re-used or unsterile materials decreased from 43% in 1995 to 14% in 2015 [6]. Probing empirical data is still needed to completely assess the effectiveness of NSP in Canada, yet there seems to be a decrease in risk behaviors associated with HCV acquisition [6]. Modelling studies also looked at the potential impact of NSP programs outside of prison settings. Martin et al. [102] emphasize the importance of high coverage needle and syringe programs to reduce the risk of further infection in PWID. Fraser et al. [103] found NSP to be a key component to reduce HCV incidence in rural settings, a treatment scale-up would not be sufficient to curb an epidemic if it is in exponential growth phase. There is currently no modelling evidence on the impact of prison-based NSP programs on the reduction of HCV incidence. A concern is retention in the program upon release, which depends on many structural factors such as housing instability and employment [7].

In 2018, the Canadian Correctional Services announced the implementation of a prison-needle exchange program in two penitentiaries. There is still no data on this program, but a national roll-out is expected if the pilot project is conclusive [108]. No such program currently exists at the provincial level and correctional services are reluctant to implement them because of safety concerns, fear of increased IDU, as well as a higher workload for correctional agents [109]. Prison-based NSP programs have been implemented in Germany, Spain, and Switzerland where very few adverse events or injection initiations were reported and no new HCV infections occurred in the prisons where they were implemented [110].

1.4.4 Integrated and community-based models of care

Traditional harm reduction measures and treatment scale-up alone may not be sufficient to significantly reduce HCV transmission among PWID [7]. Multidimensional factors can

impact the engagement of PWID in these programs. For instance, even if OAT is available, not all PWID inject opioids, and many won't benefit from this intervention [64]. This is especially important for Montréal, where the epidemic among PWID is cocaine-driven [6]. The effectiveness of other continuum of care interventions, from diagnosis to treatment, could also be compromised by the marginalized status of PWID. The lived experience of PWID in the healthcare system tends to be negative and stigmatizing, which is to be considered in developing interventions tailored to that population [82; 38].

In the context of potential provincial prison-based treatment scale-up, the duration of DAA therapy often exceeds time spent in prison by PWID, such that important gaps in the transition between prison and community services could jeopardize treatment effectiveness [84]. Enhancing the engagement of PWID in healthcare as well as in harm reduction programs is crucial, and comprehensive care packages that are tailored to the needs of community and incarcerated PWID are required. Different types of interventions could potentially be implemented to enhance testing, linkage to care, and treatment completion among incarcerated PWID, including: pre-discharge planning and transportation [111; 112], nurse-led based models [113; 88; 87], and/or peer navigator programs [114; 115; 116; 117]. Such comprehensive models of care are important to ensure successful HCV treatment but their reach goes further, as they positively impact multiple social determinants of health [116]. In a meta-analysis of interventions that seek to optimize the care continuum for HCV, nurse-led interventions and health counseling improved treatment completion, as well as uptake and adherence [118]. All of these interventions could supplement a treatment scale-up, or harm reduction measures by alleviating structural factors that negatively impact trust, compliance, and adherence.

1.5 Building the evidence for prison-based interventions

People in prison are an important group that need to be targeted by micro-elimination efforts. However, the evidence base for effective, scalable, and sustainable prison-based interventions is scarce – despite their potentially critical role in HCV elimination efforts.

Interventions for infectious diseases have both direct and indirect (or herd) effects. In the context of prison-based interventions, indirect effects encompass the public health benefits reaped by both incarcerated and non-incarcerated PWID, which originate from the reduced prevalence in their injecting networks. The population-level impact of prison-based intervention, which includes both direct and indirect benefits, is the measure of importance for public health planning. The gold standard to estimate the population-level effect of infectious diseases interventions is the cluster-randomized controlled trial [119]. In this design,

people are randomized as groups and not as individuals. Hence, the impact of the intervention encompasses both types of effects. This study design has been extensively used in vaccine research to study the benefits of vaccines in terms of direct protective effects and herd immunity [119; 120]. Despite this important advantage, cluster randomized trials are costly, time-consuming, and require a large sample size to be efficient [119; 120]. Further, randomized trials can pose important ethical issues regarding the incarcerated population. The ability to provide informed consent when randomized as a group is a concern for vulnerable populations such as PWID and people in prison [120; 121]. Further, as DAA are highly efficacious, withholding this intervention from the control arm of the trial would be considered unethical.

An alternative for assessing the potential impact of different intervention strategies is mathematical modelling. It has gained importance in recent years as a tool to design trials or observational studies for infectious diseases interventions, and inform policy-making [122]. It consists of developing a conceptual framework of disease transmission that traces links between risk factors, interventions, and infection, effectively reproducing the transmission dynamics. Modelling also allows conceptualization of social behaviors associated with transmission dynamics, such as mixing patterns among injecting peers [122]. Mathematical models allow researchers to examine the impact of a wide range of "what if" scenarios on HCV transmission. This method is much less expensive than a cluster-randomized trial both in terms of resources and time. As such, mathematical modelling can play an important role to inform health policy in support of HCV elimination as public health threat.

1.6 Concluding remarks

The HCV treatment and care landscape has substantially changed in the past decade, and HCV elimination is now on the global agenda [14]. However, as was outlined in this review, the HCV epidemic is complex and involves several populations. In order to achieve the overall elimination of HCV as a public health threat, micro-elimination strategies targeted at specific key populations will be necessary. Because PWID contribute to most of the disease transmission, have high incarceration rates and potentially elevated risk of HCV post-release, prisons have been identified as key settings in a micro-elimination framework. Multiple interventions such as TasP, harm reduction, or integrated models of care could be implemented, but little evidence on their effectiveness exist in the Canadian setting. In order to fill this knowledge gap, modelling the HCV epidemic among PWID and assessing the potential impact of different prison-based intervention scenarios will help inform micro-elimination efforts.

Chapter 2

Aims

The main objective of this study is to estimate the population-level impact of three broad types of prison-based interventions on transmission dynamics from 2018 to 2028 in Montréal.

1. Test-and-treat, where people admitted to prison are tested during their incarceration and people found chronically infected are treated in prison.
2. Post-release linkage to care interventions where people are tested in prison settings and initiate treatment upon release from prison.
3. Risk reduction interventions where the risk of transmission and acquisition post-release is halved.

More specifically, the impact of the scenarios was estimated with or without a community universal screening and DAA scale-up, and with combinations of a) or b) with c) on three main outcomes:

1. Relative reduction in chronic HCV prevalence
2. Relative reduction in chronic HCV incidence
3. Cumulative prevented fraction of new chronic HCV infections

Chapter 3

Methods

The potential effectiveness of HCV intervention scenarios needs to capture both direct and indirect effects of the interventions. To do so, a model of HCV transmission among PWID in Montréal was developed. The model is detailed in the following section.

3.1 Model structure

A dynamic compartmental mathematical model of HCV transmission among PWID was developed in Montréal (Canada), the nexus of the epidemic in the province of Québec. The model is stratified by sex and considers three distinct but overlapping dynamics: 1) HCV transmission, 2) incarceration, and 3) injection behaviors. The model has an open population and is deterministic in nature. Stochasticity was not included because HCV prevalence is high among the PWID population and elimination is defined in terms of public health targets, which means that incidence cannot be null [6; 9; 72].

The model population is open, and people are susceptible to HCV when entering the population at a rate θ chosen to fit PWID population size estimates in 2003 and 2010 [123]. Individuals who enter the model are active PWID (i.e. current injection) and have never been incarcerated. PWID either leave the model by all-cause (μ) or liver-related (μ_1) mortality at advanced disease stages ($C_{F3-4}(t)$, $T_{F3-4}(t)$). Individuals who are active PWID, and those recently released from prison have an increased risk of death (Π). People who are on treatment can only die of other causes of deaths, excluding HCV-related deaths, during that short period.

3.2 HCV transmission dynamics

The model, based on previous work by Stone et al. [7], considers HCV's natural history as well as the HCV treatment and care cascade. The structure of the model is presented in Figure 3.1. Individuals start in the susceptible compartment ($S(t)$). They can then acquire HCV and transition to the acute stage ($A(t)$) depending on a time-varying force of infection $\lambda(t)$. The force of infection represents the annual per capita rate of HCV acquisition and is a function of chronic prevalence among injecting contacts, incarceration status, and coverage of interventions. For instance, currently incarcerated people can only be infected by other incarcerated individuals, because their only effective contacts are with that group. Further details and assumptions on mixing are provided in section 3.3.2.

Once individuals are acutely infected with HCV, they either clear the infection at a probability of α_{ab} after 6 months, or progress to early chronic infection ($C_{F0-2}(t)$). Those who clear the infection become susceptible to reinfection but are antibody positive to HCV ($S_{ab+}(t)$). They can then be reinfected ($A_{ab+}(t)$) at the same force of infection $\lambda(t)$. This is a conservative assumption that can be justified by the limited evidence regarding immunity conferred by past exposures to the virus. Upon reinfection, individuals can still spontaneously clear the infection, at the same probability (α_{ab}) after six months. Evidence concerning an enhanced clearance rate at six months in people who previously cleared the infection is still scarce, yet it was recently suggested that it could be higher, but with important uncertainty concerning the magnitude of the effect size [124].

Once chronically infected, individuals progress through two fibrosis stages at a rate of ξ, which represents the number of fibrosis units gained on the Metavir scale per year [21]. As a simplifying assumption, fibrosis was dichotomized between early ($C_{F0-2}(t)$) and late ($C_{F3-4}(t)$) stages. Only people living with chronic infection are allowed to be diagnosed and treated, which is in line with current guidelines [32]. Individuals are first tested for HCV at a time-dependent rate $\tau_p(t)$, which also varies by incarceration status. Only diagnosed individuals ($Dx_{F0-2}(t)$, $Dx_{F3-4}(t)$) can be treated at a time varying rate $\sigma_p(t)$, which also varies by incarceration status. Because of the reluctance to treat PWID in the PEG-IFN era, a treatment rate of zero was assumed before the widespread arrival of DAA in 2015. Between 2015-2018, only people with late chronic infection ($Dx_{F3-4}(t)$) are eligible for DAA therapy. In line with the most recent Canadian guidelines on HCV management, it was conservatively assumed that people with early chronic infection ($Dx_{F0-2}(t)$) are eligible for treatment from 2018, but treated at a rate which is half that of late stage infection. As done in previous studies and reflecting the paucity of the data on treatment initiation rate among

active PWID, the treatment rates in the community ($\sigma_c(t)$) were fixed as follows [7]:

$$\sigma_c^{F0-2}(t) = \begin{cases} 0 & t < 2018 \\ 0.5\sigma_c^{F3-F4}(t) & t \geq 2018 \end{cases} \quad \text{and} \quad \sigma_c^{F3-4}(t) = \begin{cases} 0 & t < 2015 \\ 0.01 & t \geq 2015 \end{cases}$$

Treatment ($T(t)$) has two distinct outcomes: SVR or failure [7]. People on treatment achieve SVR at a probability α_{svr}, after an average treatment duration of 12 weeks. Following SVR, successfully treated people remain antibody positive for the rest of their life ($S_{ab+}(t)$) [125]. As there is currently no convincing evidence of DAA-treatment conferred immunity, treated individuals are susceptible to reinfection at the standard force of infection $\lambda(t)$. People who are reinfected transition to the acutely infected but antibody positive compartment ($A_{ab+}(t)$). Those who do not achieve SVR return to the diagnosed stages, either $Dx_{F0-2}(t)$ or $Dx_{F3-4}(t)$, proportionally to the number of individuals treated from each stage. As such, people with reinfections are eligible for retreatment at the same rate as people with primary infections. This last assumption is justified by the availability of pan-genotypic drugs, which allow treatment of reinfected individuals with little concern for drug resistance [45]. The full system of ordinary differential equations is presented below for individual with sex g with the incarceration status p and injection status i.

$$\begin{aligned}
\frac{dS_{gpi}(t)}{dt} &= \theta(t) - (\lambda_{gpi}(t) + \mu)S_{gpi}(t) \\
\frac{dS_{gpi}^{ab+}(t)}{dt} &= \frac{\alpha}{D_A}\left(A_{gpi}(t) + A_{gpi}^{ab+}(t)\right) + \frac{\alpha_{svr}}{D_T}T_{gpi}(t) - (\lambda_{gpi}(t) + \mu)S_{gpi}^{ab+}(t) \\
\frac{dA_{gpi}(t)}{dt} &= \lambda_{gpi}(t)S_{gpi}(t) - \left(\frac{1}{D_A} + \mu\right)A_{gpi}(t) \\
\frac{dA_{gpi}^{ab+}(t)}{dt} &= \lambda_{gpi}(t)S_{gpi}^{ab+}(t) - \left(\frac{1}{D_A} + \mu\right)A_{gpi}^{ab+}(t) \\
\frac{dC_{gpi}^{F0-2}(t)}{dt} &= \frac{(1-\alpha)}{D_A}\left[A_{gpi}(t) + A_{gpi}^{ab+}(t)\right] - \left(\frac{\xi}{D_C} + \tau_p(t) + \mu\right)C_{gpi}^{F0-2}(t) \\
\frac{dC_{gpi}^{F3-4}(t)}{dt} &= \frac{\xi}{D_C}C_{gpi}^{F0-2}(t) - \left(\tau_p(t) + \mu + \mu_1\right)C_{gpi}^{F3-4}(t) \\
\frac{dDx_{gpi}^{F0-2}(t)}{dt} &= \tau_p(t)C_{gpi}^{F0-2}(t) + \left(\frac{p_{F0-2}(1-\alpha_{svr})}{D_T}\right)T_{gpi}(t) \\
&\quad - \left(\frac{\xi}{D_C} + \sigma_p^{F0-2}(t) + \mu\right)Dx_{gpi}^{F0-2}(t) \\
\frac{dDx_{gpi}^{F3-4}(t)}{dt} &= \tau_p(t)C_{gpi}^{F3-4}(t) + \left(\frac{p_{F3-4}(1-\alpha_{svr})}{D_T}\right)T_{gpi}(t) + \frac{\xi}{D_C}Dx_{gpi}^{F0-2}(t) \\
&\quad - \left(\sigma_p^{F3-4}(t) + \mu + \mu_1\right)Dx_{gpi}^{F3-4}(t) \\
\frac{dT_{gpi}(t)}{dt} &= \sigma_p^{F0-2}(t)Dx_{gpi}^{F0-2}(t) + \sigma_p^{F3-4}(t)Dx_{gpi}^{F3-4}(t) - \frac{1}{D_T}T_{gpi}(t)
\end{aligned} \tag{3.1}$$

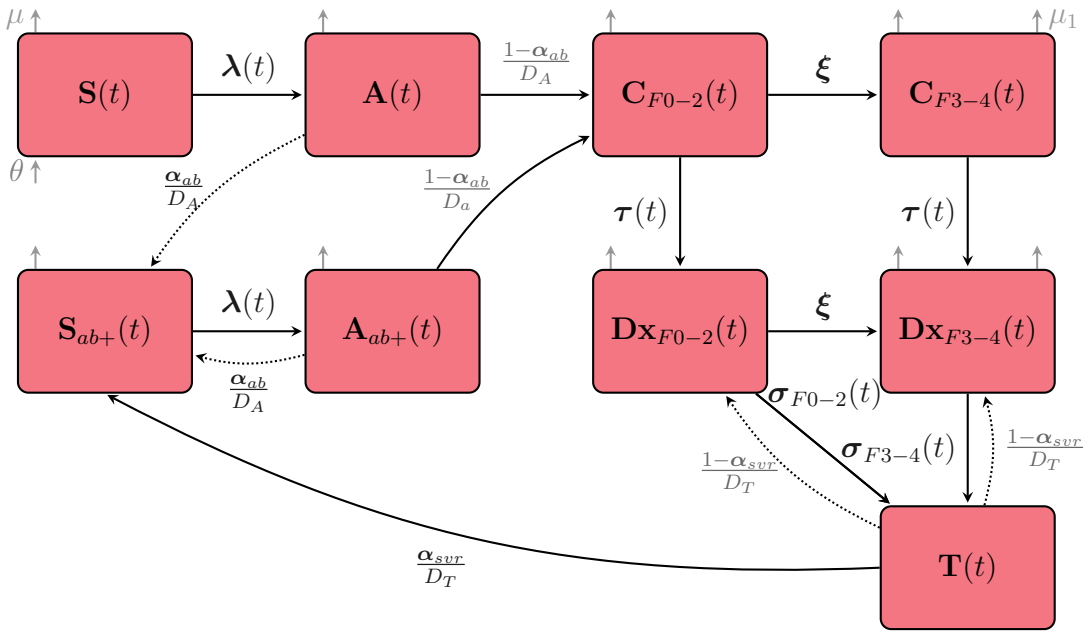


Figure 3.1 – Hepatitis C (HCV) natural history and cascade of care. The model is open, and people initiate injection as susceptible ($\mathbf{S}(t)$) at a rate θ. Upon an effective contact, they become acutely infected ($\mathbf{A}(t)$) at a time-dependent force of infection $\boldsymbol{\lambda}(t)$. People spontaneously clear the infection after six months at a probability α_{ab} and become susceptible but antibody postitive ($\mathbf{S}_{ab+}(t)$). Otherwise, they become chronically infected ($\mathbf{C}_{F0-2}(t)$) and progess in fibrosis stages until late HCV infection ($\mathbf{C}_{F3-4}(t)$), where they can die of liver-related mortality μ_1. Chronically infected people can be diagnosed ($\mathbf{Dx}_{F0-2}(t)$, $\mathbf{Dx}_{F3-4}(t)$) without regards to disease stage at a rate $\boldsymbol{\tau}$ and then linked to treatment ($\mathbf{Tx}(t)$) at a time varying rate that depends on fibrosis stage ($\boldsymbol{\sigma}_{F0-2}(t)$, $\boldsymbol{\sigma}_{F3-4}(t)$). Treatment either leads to failure or sustained viral response and people become susceptibles but antibody positive. People who spontaneously cleared or were cured of the disease are susceptible to reinfection with HCV ($\mathbf{A}_{ab+}$) at the same force of infection $\boldsymbol{\lambda}(t)$.

3.3 Force of infection and mixing patterns

3.3.1 Force of infection

The force of infection is the per capita rate at which individuals acquire HCV and depends on multiple factors. First, it is a function of HCV prevalence (chronic and acute cases) among injecting contacts. This, in turns, depends on the characteristics of the injecting contacts and is parameterized using mixing matrices. Second, the force of infection is influenced by the availability of sterile injecting materials, which varies with respect to time. Third, the force of infection varies by setting. For instance, it is lower during the incarceration period, but elevated upon the short period following release from prison. Specifically, the force of infection is the product between the mixing matrix and the element-wise multiplication of the rate ratio and prevalence vectors. For an individual of sex g, with the incarceration and injection statuses p and i, respectively, the force of infection is the following.

$$\boldsymbol{\lambda}_{gpi}(t) = \beta \cdot (1 - (cov_p(t) \cdot (1 - eff))) \cdot (m_{gpi} \times rr_{gpi} \cdot p_{gpi}(t)) \tag{3.2}$$

Where β is the probability of transmission per effective contact; $cov_p(t)$ is the coverage of NSP, calculated from SurvUDI data as the complement of the proportion of injections performed with previously used needles and syringes (coverage is assumed to be null in prison); eff is the effectiveness of NSP programs as estimated from a recent meta-analysis [100]; m_{gpi} is a vector of mixing per individual category (further details on the mixing matrix are provided below); rr_{gpi} is a vector of rate ratios for HCV transmission; and $p_{gpi}(t)$ is the prevalence vector for groups that varies with time and is weighted by the rate ratio vector to allow for increased of decreased risk of acquisition.

3.3.2 Mixing patterns

The mixing matrix considers how contact patterns are structured according to incarceration $\mathbf{M}_p$, injection status $\mathbf{M}_i$, and sex $\mathbf{M}_g$. The full mixing matrix $\mathbf{M}$ is developed from the Kronecker product of smaller mixing matrices. This method consists of multiplying the elements of a matrix with another matrix. The complete contact matrix can be defined as the following, where the mixing probabilities p_{jk}, i_{jk} and g_{jk}, are defined in sections below

$$
\begin{aligned}
\mathbf{M} &= \mathbf{M}_p \otimes \mathbf{M}_g \otimes \mathbf{M}_i \\
&= \begin{bmatrix} p_{11} & p_{12} & p_{13} & p_{14} \\ p_{21} & p_{22} & p_{23} & p_{24} \\ p_{31} & p_{32} & p_{33} & p_{34} \\ p_{41} & p_{42} & p_{43} & p_{44} \end{bmatrix} \otimes \begin{bmatrix} g_{11} & g_{12} \\ g_{21} & g_{22} \end{bmatrix} \otimes \begin{bmatrix} i_{11} & i_{12} & i_{13} \\ i_{21} & i_{22} & i_{23} \\ i_{31} & i_{32} & i_{33} \end{bmatrix} \\
&= \begin{bmatrix} p_{11}g_{11}i_{11} & p_{11}g_{11}i_{12} & \cdots & p_{14}g_{12}i_{13} \\ p_{11}g_{11}i_{21} & p_{11}g_{11}i_{22} & \cdots & p_{14}g_{12}i_{23} \\ \vdots & \vdots & \ddots & \vdots \\ p_{41}g_{21}i_{31} & p_{41}g_{21}i_{32} & \cdots & p_{44}g_{22}i_{33} \end{bmatrix}
\end{aligned}
$$

Incarceration

The contact matrix for incarceration has dimensions 4×4, the first of which corresponds to the individual's incarceration status and the second to the incarceration status of the contact. On each dimension, elements are 1) never incarcerated, 2) currently incarcerated, 3) recently released, and 4) previously released. Such that, p_{13} would represent the mixing pattern between a never incarcerated person and a person recently released. There is important uncertainty regarding mixing of individuals according to their incarceration status. Specifically, uncertainty was taken into account with a parameter that varied mixing between proportional and assortative. In the first case, mixing occurs randomly according to the proportion of each category in the population. In the second case, mixing occurs strictly between people of the same category (i.e. like-with-like). The degree of assortative mixing

is defined by the parameter $mix_p \in [0,1]$) and the final mixing matrix is

$$\mathbf{M}_p = (1 - mix_p)\mathbf{M}_{prop} + mix_p\mathbf{M}_{assor}$$

Where, $\mathbf{M}_{prop}$ is a matrix of contact according to the relative presence of individuals in the community. It was assumed that no effective contact could occur between people in the community and incarcerated people. This is conceptualized as the null values on line and row 2, except for contacts between inmates. The matrix $\mathbf{M}_{assor}$ is a perfectly assortative setting, such that it is the identity matrix.

$$\mathbf{M}_{prop} = \begin{bmatrix} p_{11} & 0 & p_{13} & a_{14} \\ 0 & 1 & 0 & 0 \\ p_{31} & 0 & p_{33} & p_{34} \\ p_{41} & 0 & p_{43} & p_{44} \end{bmatrix}$$

$$\mathbf{M}_{assor} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

Injection

The matrix for injection dynamics ($\mathbf{M}_i$) is of format 3×3, and its structure is similar to mixing by incarceration status. On each dimension, the elements are 1) active PWID, 2) on OAT, 3) ex-PWID. In the case of injection dynamics a mixing matrix that took into account the underlying uncertainty of contact patterns was also conceptualized, allowing the matrix to vary between proportional and assortative mixing. The degree of assortative mixing was defined as mix_i, and, as before, the complete mixing matrix $\mathbf{M}_i$.

$$\mathbf{M}_i = (1 - mix_i)\mathbf{M}'_{prop} + mix_i\mathbf{M}'_{assor}$$

Where $\mathbf{M}'_{prop}$ is the proportional mixing matrix, and $\mathbf{M}'_{assor}$ the assortative setting. It is assumed that PWID can only have contacts with other PWID or people on OAT. Hence, ex-PWID do not have injecting behaviors putting them at risk of acquiring or transmitting

HCV such that the mixing matrices are

$$\mathbf{M}'_{prop} = \begin{bmatrix} i_{11} & i_{12} & 0 \\ i_{21} & i_{22} & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$\mathbf{M}'_{assor} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

Sex

Finally, the specification of the overall mixing matrix is completed by taking sex into account. Sex-based contact pattern data is scarce for IDU, as it is difficult to empirically measure such behaviors. A study of contacts between PWID according to gender, age and race in Baltimore found mixing to be slightly assortative with respect to gender for females and assortative for male. The mixing matrix for sex was built by using contact data of PWID according to gender from Smith et al. [126] as it represents the best available evidence for sex-based mixing patterns.

$$\mathbf{M}_g = \begin{bmatrix} g_{11} & g_{12} \\ g_{21} & g_{22} \end{bmatrix} = \begin{bmatrix} 0.512 & 0.488 \\ 0.382 & 0.618 \end{bmatrix} \tag{3.3}$$

3.3.3 Incarceration dynamics

Incarceration dynamics are modelled as transitions between the community and the prison system. A graphical representation of those transitions can be found in figure 3.2(a). People initiate IDU and are assumed to have never been incarcerated ($P_0(t)$) [6; 9]. They can then be incarcerated for the first time at a time-dependent rate $\eta_0(t)$. This rate was derived from survey data as well as data from correctional services. The overall rate of incarceration was estimated from the size of the incarcerated population ($P_1(t)$) relative to the number of new admissions in the prison system and the size of the population of PWID in the community during the prior year ($N_{pwid}(t-1)$). This population have either experienced or not the prison system (p_{ever}) and people with experience have a higher rate of (re)incarceration (Γ). The overall rate of incarceration can thus be calculated as follows.

$$\begin{aligned} P_1(t) &= \eta_0(t)\left((1-p_{ever}) + \Gamma p_{ever}\right) N_{pwid}(t-1) \\ \Leftrightarrow \eta_0(t) &= \frac{P_1(t)}{\left((1-p_{ever}) + \Gamma p_{ever}\right) N_{pwid}(t-1)} \end{aligned}$$

Incarcerated individuals are released at a time-dependent rate $\eta_1(t) = 1/D_{P_1}(t)$, where $D_{P_1}(t)$ is the average duration of time spent in prison per incarceration, collected from correctional data. This definition was used because sentence lengths could overestimate time spent in prison per year, and thus underestimate the release rate. In most provincial prisons, people spend less time per incarceration than their sentence prescribes because of good behaviors, overcrowding, etc. [77; 9].

The literature on mortality and risk of HCV acquisition shows an increased risk for individuals recently released from prison [127][8]. The model therefore differentiates between recently released and previously released individuals [128]. Upon release, and for the following 6 months, individuals are considered at a higher risk of HCV acquisition, transmission, and drug-related mortality (P_2). After 6 months ($\eta_2 = 1/2$), they transition to the previously released compartment (P_3) where they are subject to the same mortality and HCV acquisition risk as the never incarcerated individuals. The reincarceration rate is the same for all individuals with experience of the prison system (recently or previously), and is equal to the rate of incarceration multiplied by a rate ratio computed from prison surveys [9; 72]. The system of ordinary differential equations describing incarceration dynamics is defined below.

$$\begin{aligned}
\frac{dP_0(t)}{dt} &= \theta(t) - \eta_0(t)P_0(t) \\
\frac{dP_1(t)}{dt} &= \eta_0(t)P_0(t) + \eta_3(t)\left(P_2(t) + P_3(t)\right) - \eta_1 P_1(t) \\
\frac{dP_2(t)}{dt} &= \eta_1 P_1(t) - \left(\eta_2 - \eta_3(t)\right)P_2(t) \\
\frac{dP_3(t)}{dt} &= \eta_2 P_2(t) - \eta_3(t)P_3(t)
\end{aligned} \tag{3.4}$$

3.3.4 Injection dynamics

Injection dynamics describe how PWID cease to inject or initiate (and stop) OAT as represented in figure 3.2(b). Briefly, active PWID ($I_0(t)$) cease to inject at a rate δ_0. This rate is computed as the inverse length of an individual's injecting career, which was shown to vary between 5 and 23 years [129]. We chose a wide range, because there is a lot of uncertainty regarding the duration of injecting drug use. Once in the ex-PWID compartment ($I_1(t)$), these individuals do not contribute to HCV transmission, as they have no injecting risk behaviors and cannot re-initiate injection. Otherwise, PWID can initiate OAT ($O(t)$) at a rate $\boldsymbol{\delta}_1$, which was estimated from the average yearly OAT coverage in SurvUDI. Once on OAT, people are allowed to continue injection, albeit at a reduced rate. This assumption is justified when modelling the Montréal epidemic, which is driven by cocaine and where poly-injecting drug use is frequent. Thus, OAT is often not sufficient to reduce injecting risk behaviors if people inject other substances. After one year, a proportion ϵ transitions back

to active injection, while the rest stays on OAT. This is the retention rate of OAT, and was estimated from a meta-analysis [130]. People can remain on OAT until they stop injecting completely, which is simply the same injecting career length parameter as before. Being on OAT reduces the risk of HCV transmission and acquisition by half, as was stated in a recent meta-analysis [100]

$$\begin{aligned}
\frac{dI_0(t)}{dt} &= \theta(t) + \epsilon(t) - (\delta_0 + \delta_1)\, I_1(t) \\
\frac{dI_1(t)}{dt} &= \delta_0\, (I_1(t) + O(t)) \\
\frac{dO(t)}{dt} &= \delta_1 I_1(t) - (\epsilon + \delta_0) O(t)
\end{aligned} \tag{3.5}$$

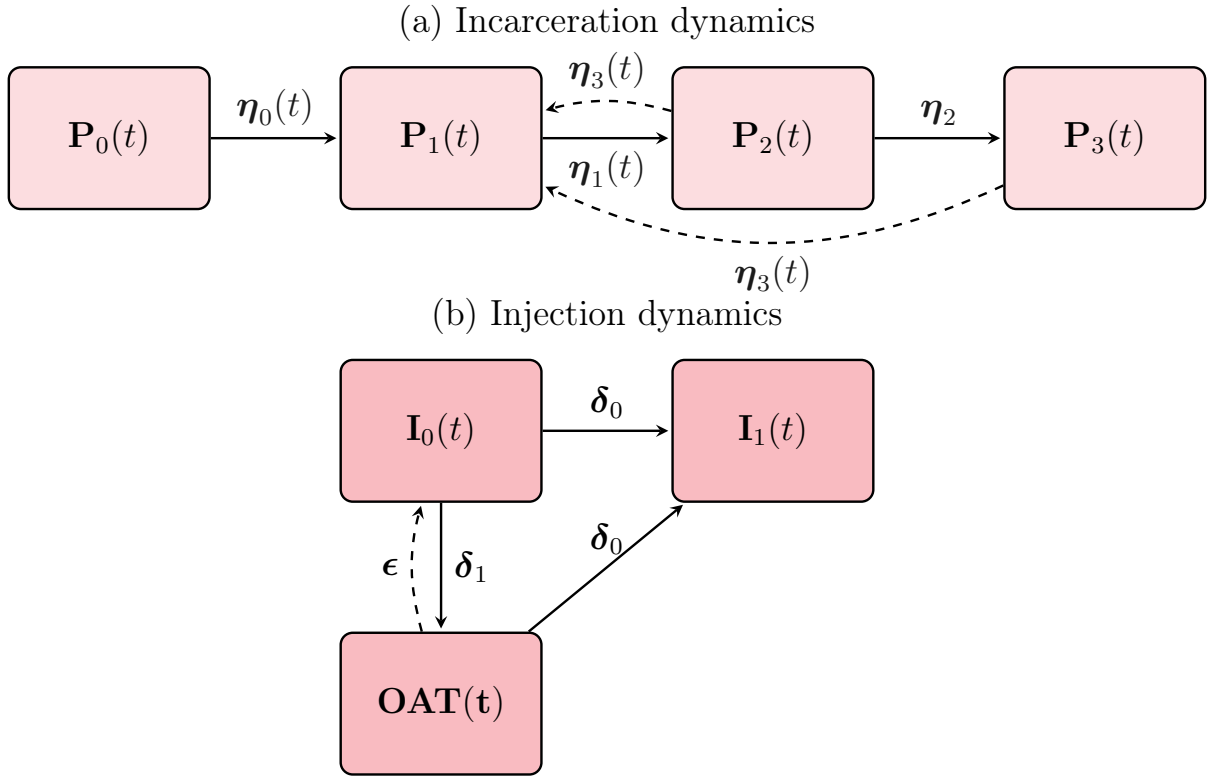


Figure 3.2 – (a) People who initiate injection have never been incarcerated ($\mathbf{P}_0(t)$) and can be incarcerated at a time-dependent rate $\boldsymbol{\eta}_0(t)$. They are then released back to the community at a time-dependent rate $\boldsymbol{\eta}_1(t)$ and are considered recently released for 6 months ($\mathbf{P}_2(t)$) after which they become previously released ($\mathbf{P}_3(t)$). People with experience in the prison system can be reincarcerated at a rate $\boldsymbol{\eta}_3(t)$. (b) People who inject drugs (PWID, $\mathbf{I}_0(t)$) completely stop injecting at a rate which is defined as the inverse of the average injecting duration ($\boldsymbol{\delta}_0$). They can also initiate OAT at a constant rate $\boldsymbol{\delta}_1$. On OAT, people can continue injecting and only stop after the average duration of injection $\boldsymbol{\delta}_0$. Once people have stopped they cannot go back to injecting.

3.4 Model parametrization

3.4.1 Data

Two major sources of data were used to inform parameters for this study: repeated cross-sectional surveys of PWID in Montréal (SurvUDI, 2003-2015) and two large prison surveys conducted in 7 of the 17 provincial prisons in Québec (in 2003 and 2014) [6; 72; 9]. These two data sources are further detailed below. Parameters that could not be estimated from these local surveys were obtained from the relevant peer-reviewed literature. Where data was not available from meta-analyses, the most robust studies to inform model parameters were used. All parameters and their data source can be found in table 3.1.

3.4.2 SurvUDI

SurvUDI is a surveillance network of PWID in the province of Québec as well as in the city of Ottawa, and was first established in 1995 [6]. It was then associated with the pan-Canadian I-track survey. It is designed as repeated cross-sectional bio-behavioural surveys and recruitment is multisettings, occurring both in NSP, fixed-sites, and community outreach activities. As such SurvUDI uses a convenience sampling design, and all sites working in collaboration with the SurvUDI network have their own sampling procedure. For instance, at *Cactus Montréal*, one of the main recruiting site in Montréal, recruitment happens continuously on a fixed schedule [6]. Over the whole history of the network, 1,509 women and 4,835 men participated in the study in Montréal and a total of 13,286 survey questionnaires were completed. Repeaters were used to assess longitudinal outcomes such as incidence. Prevalence was defined as the prevalence of HCV at the first lifetime visit in the network, such that individuals could contribute to more than one year but not twice in the same year [6]. This survey provides information on a wide range of parameters and outcomes as detailed in table 3.1. All data from these surveys were abstracted from official reports produced by the *Institut national de la santé publique du Québec* (INSPQ). Because of the convenience sampling approach, a design effect was used to account for a potentially greater uncertainty around point estimates. A design effect of 2 was applied to all uncertainty estimates in SurvUDI, which is standard in studies targeting hidden populations, as no value was provided for SurvUDI [131; 132].

3.4.3 Prison Survey

Two cross-sectional bio-behavioural surveys were conducted in prison settings in 2003 and 2014 [72; 9]. The first survey was performed in 7 of the 17 provincial prisons in Québec, representing about half of the prison population and collected information on 1607 inmates.

One male prison (Bordeaux or *Établissement de détention de Montréal*) and one female prison (Maison Tanguay) were located in Montréal. The second survey, conducted in 2014, was performed in the same 7 prisons that participated in 2003 and used a comparable survey methodology and instruments to collect information on 1581 incarcerated individuals. People could not participate more than once in the surveys. The research team were granted access to the microdata from the survey and performed secondary analyses to inform a wealth of parameters, which can be found in table 3.1.

Table 3.1 – Parameters, their estimates, prior distribution, and the source of data from which parameters were gathered

Parameter	Symbol	Value or range	Units	Distribution	Source
HCV[¶] transmission model					
Transmission rate	$\boldsymbol{\beta}$	$0.3 - 0.6$	-	Uniform	Model fitting
Assortative degree					
Incarceration	mix_p	$0 - 1$	-	Uniform	Model fitting
Injection status	mix_i	$0 - 1$	-	Uniform	Model fitting
Recruitment rate	$\boldsymbol{\theta}$	$100 - 300$	people per year	Uniform	Model fitting
Background mortality rate	$\boldsymbol{\mu}$	2.64	per 100 PY[¶]	-	[127]
Liver-related mortality rate	$\boldsymbol{\mu}_1$	0.7	per 100 PY	-	[133]
Spontaneous clearance rate	$\boldsymbol{\alpha}_{ab-}$	25	%	-	[134]
Acute stage duration	$\mathbf{D}_A$	0.5	year	-	[15]
Fibrosis progression rate	$\boldsymbol{\xi}$	$0.024 - 0.029$	metavir units/year	Uniform	[21]
Testing rate	$\boldsymbol{\tau}(t)$	$5 - 30$	per 100 PY	Uniform	Model fitting
Treatment efficacy	$\boldsymbol{\alpha}_{svr}$	90	%	-	[47]
Treatment rate (F3-4)					
<2015	$\boldsymbol{\sigma}_p^{F3-4}(t)$	0	per 100 PY	-	Assumption
>2015		0.01			
Treatment duration	$\mathbf{D}_T$	1/3	year	-	[45]
Reduced HCV risk on OAT	$\mathbf{rr}_{oat}$	$mean = 0.51, sd = 0.07$	-	Lognormal	[100]
Increased HCV risk release	$\mathbf{rr}_{rel}$	$mean = 1.62, sd = 0.12$	-	Lognormal	[8]
Increased death risk release	Π	$mean = 7.42, sd = 0.14$	-	Lognormal	[80]
Incarceration dynamics model					
Incarceration rate [†]	$\boldsymbol{\eta}_0(t)$	$min(t) - max(t)$	per 100 PY	Uniform	[72; 9; 135]
Release rate [‡]					
2003	$\boldsymbol{\eta}_1(t)$	7.1	per 100 PY	-	[72; 9; 135]
2014		4.5			
Duration in recently released	$\frac{1}{\boldsymbol{\eta}_2}$	0.5	year	-	[128]
Rate ratio reincarceration [§]	Γ	6.5	-	-	[72; 9]
Injection dynamics model					
Duration of injecting career	$\frac{1}{\delta_0}$	$1/23 - 1/5$	per year	Uniform	[129]
OAT coverage	δ_1	33.7	$per 100p - y$	-	[6]
Rate of retention OAT	ϵ	0.504	per 100 PY	-	[130]

[¶] HCV: hepatitis C virus, PY: Person-year, OAT: opioid agonist therapy

[†] For $t \in [2003, 2014]$ and where min(t) and max(t) were linearly interpolated between 2003 and 2014 from the lower and upper bound of the empirically estimated 95% confidence interval of the incarceration rate. For instance, the prior range in 2003 was of $[10.69, 12.41]$ per 100 PY.

[‡] Where the release rate was interpolated between 2003 and 2014

[§] There was no significant difference in the rate ratios between 2003 and 2014 in the prison survey so it was kept constant over time.

3.5 Model calibration

The objective of model calibration is to reproduce temporal trends in relevant epidemiological outcomes using statistical techniques that select the best combination of parameters. The epidemiological outcomes used in model calibration are informed by both SurvUDI and the two prison surveys. In SurvUDI, reported annual estimates of antibody prevalence (2003-2014) are computed among participants at their first lifetime visit in the network [6]. Because SurvUDI is repeated annually at the same recruitment sites, it is possible to uniquely identify participants and estimate HCV incidence in the network from 2003 to 2014. As this incidence only measures new antibody positive cases, it cannot account for reinfections [6]. The model was also calibrated to antibody prevalence among incarcerated individuals self-reporting IDU in the past six months in 2014. For the 2003 survey, prevalence among people with IDU in the past six months is extrapolated by applying the observed prevalence ratio in people with a history of IDU to recent IDU of the 2014 survey [9; 72].

Given its flexibility, a Bayesian framework was adopted for model calibration and appropriate prior distributions were elicited as described in table 3.1. More specifically, a sampling importance resampling algorithm was used to approximate the posterior distributions of model outcomes. Using this algorithm 25,000 parameter sets were first sampled from their prior distributions using Latin hypercube sampling, a technique which allows a good exploration of the whole parameter space. For each parameter sets, the model was first run for 75 years using baseline parameter values from 2003 so that endemic equilibrium could be reached before the start of the epidemic simulations. Then, the model was run from 2003 to 2015 and yearly prevalence and incidence were calculated for the relevant population stratification (prison or community). The likelihood of each parameter set was then calculated for the prevalence and incidence outcomes. The overall model likelihood was obtained by summing the log-likelihood of the model outcomes.

$$\log(\mathcal{L}) = \log(\mathcal{L}^{c}_{prev}) + \log(\mathcal{L}^{p}_{prev}) + \log(\mathcal{L}_{inci})$$

Where $\mathcal{L}^{c}_{prev}$ is the binomial likelihood for prevalence in the community over the time interval from $t = 2003$ to $t = 2014$ for the yearly survey of sample size n_t, with x_t prevalent cases, and the estimated model prevalence during that year p_t.

$$\begin{aligned}
\log(\mathcal{L}^{c}_{prev}) &= \sum_{t=2003}^{2014} \log\left(\binom{n_t}{x_t} p_t^{x_t}(1-p_t)^{n_t-x_t}\right) \\
&= \sum_{t=2003}^{2014} \left(\log\binom{n_t}{x_t} + x_t \log(p_t) + (n_t - x_t)\log(1-p_t)\right)
\end{aligned}$$

In prison the likelihood ($\mathcal{L}^{p}_{prev}$) has an identical structure except for the fact that there are only two surveys (2003, 2014).

$$\log(\mathcal{L}^{p}_{prev}) = \sum_{t\in\{2003,2014\}} \left(\log \binom{n_t}{x_t} + x_t \log\left(p_t\right) + (n_t - x_t)\log(1-p_t) \right)$$

Incidence in the community follows a Poisson likelihood $\mathcal{L}_{inci}$ over the same interval. With the sample size of the survey at a given year n_t, with x_t new cases observed in that survey, the estimated model incidence $\lambda'(t)$, and a constant c.

$$\log(\mathcal{L}_{inci}) = \sum_{t=2003}^{2014} (-n_t\lambda'_t + \log(\lambda'_t)x_t - c)$$

Finally, the posterior distributions of the quantities of interest were obtained by sampling with replacement 20,000 parameter sets proportionally to their likelihood weight. The weights are defined as below for parameter i

$$w_i = \frac{e^{\log(\mathcal{L}_i)-\log(\mathcal{L}_{max})}}{\sum_{i=1}^{n} e^{\log(\mathcal{L}_i)-\log(\mathcal{L}_{max})}}$$

This procedure allows the selection of parameter sets that have the greatest concordance to the empirical data and to propagate parameter uncertainty to the model's prediction. To ensure that the model was reliable, cross-validation of model predictions for HCV status awareness, and both background, and HCV-related mortality was performed. The ordinary differential equations system was implemented in Python 3.6 and solved with a validated Runge-Kutta algorithm of the 4^{th} order from the SciPy module.

3.6 Model scenarios

Once calibrated to empirical data, multiple scenarios were implemented and results projected over the 2018 to 2028 period. Specifically, the population-level impact of these interventions was assessed on chronic HCV prevalence, incidence, and the cumulative fraction of new infections prevented. These projections were compared to a counterfactual scenario, which kept the rates of testing, treatment and intervention coverage at their 2018 levels. Last, the impact of the scenarios on knowledge of HCV status, distribution of fibrosis (early or late disease stages), and HCV-related mortality was assessed. A total of 11 scenarios were implemented and are summarized in table 3.2. They can be categorized in 3 main groups: testing and treatment interventions, linkage to care post-release, and post-release risk reduction measures. All interventions were modelled in the absence or in the presence of a community scale-up of DAA and the impact of combining different strategies was also explored.

3.6.1 Status quo (counterfactual) and community scale-up scenarios

The status quo scenario (**SQ**), assumed that rates of testing, treatment, and intervention coverage would remain at their 2018 levels. Hence, no supplemental testing, treatment, or any other harm reduction intervention would happen in prison. To investigate how further community scale-up of testing and treatment would affect the course of the HCV epidemic, the **Scale-up** scenario was implemented. It involved increasing HCV testing and treatment rates in community settings while no additional interventions were implemented in prison. This scenario assumed an immediate increase in testing such that non-incarcerated PWID were tested on average once per year with systematic treatment of chronic cases starting in 2018.

3.6.2 Prison-based test-and-treat

To assess how prison-based interventions could strengthen the HCV treatment and care cascade, three scenarios were developed. The first scenario assumed testing 95% of people during their stay in prison (**PB Test**) while treatment rates remained the same. The second scenario added prison-based treatment of chronic cases such that 95% people admitted to prison were tested for chronic HCV and those found positive systematically initiated and completed treatment in prison (**PB T-Tx(A)**). This approach didn't account for the fact that not all people would undergo screening and even fewer people would receive and complete treatment. These assumptions were relaxed and a third scenario was developed imposing constraints on testing and treatment in prison. Specifically, 90% of people entering prison were tested for HCV during their stay, and 75% of those found chronically infected received treatment (**PB T-Tx(B)**).

3.6.3 Prison-based testing and linkage to care upon release

Offering treatment to people with sentences shorter than the treatment duration could be a challenge from a programmatic point of view. An alternative approach would be to test 95% of all incarcerated people during incarceration, and treat those chronically infected upon release in the community (**PB T-L(A)**). This approach seeked to mimic a pre-discharge planning intervention or a nurse-led model, that would enhance linkage to care post-release. This scenario was optimistic and assumed that nearly all incarcerated people were tested for HCV and all those with chronic infections systematically treated upon release. Because of the poor engagement of this population in healthcare services, an additional scenario was conceived. Specifically, it was assumed that 90% of people entering prison were tested for HCV during their stay, and that 60% of those found chronically infected received treatment

upon release from prison (**PB T-L(B)**). Because of the delay between testing and treatment initiation, a lower rate of treatment was assumed compared prison-based testing and in-prison treatment scenario described above (**PB T-Tx(B)**).

3.6.4 Prison-related risk reduction interventions

The two preceding scenarios did not include potential interventions for risk reduction upon release from prison. Given the high risk of HCV acquisition and transmission post-release, interventions targeted at PWID during this critical period could contribute to curb HCV transmission [115; 116; 117]. Potential interventions, such as promotion of safer injecting practices, peer-navigators, and/or housing support, that could reduce by 50% the elevated post-release risk of HCV transmission and death were modelled (**PB Risk**). This scenario is in line with the development of integrated models of care targeted at key populations in a micro-elimination framework [84].

3.6.5 Combined interventions

Previous intervention scenarios were not mutually exclusive and the impact of implementing a prison-based treatment scale-up along with an integrated healthcare model for released individuals was also ascertained (**PB T-Tx(A)** or **(B) + Risk**). Post-release linkage to care strategy along with the same integrated model of care were modelled (**PB T-L(A)** or **(B) + Risk**). These interventions, parts of a comprehensive care approach that considers special needs of PWID, could further contribute to HCV micro-elimination. These interventions are holistic in nature, because they consider some important social determinants of the health of PWID. Table 3.1 provides a summary of the different interventions and their impact on key model parameters.

3.7 Ethics

Investigators were granted access to microdata from the surveys conducted in prison settings in 2003 and 2014 [72; 9]. The secondary analyses of these anonymized and de-identified datasets required ethics approval which was obtained from the Research Ethics Board of McGill University (IRB Study Number: A06-E43-18A). As the data from SurvUDI network was extracted from publicly available reports, no ethics approval was necessary [6].

Table 3.2 – Implemented scenarios and their impact on key model parameters for transmission dynamics of HCV among people who inject drugs

Scenario	**Testing**	**Treatment**		**Risk post-release**	
		Prison	Post-release	HCV	Mortality
	% [a]	%[b]	%[c]	-	-
PB Test	95	-	-	-	-
PB T-Tx(A)	95	100	-	-	-
PB T-Tx(B)	90	75	-	-	-
PB T-L(A)	95	-	100	-	-
PB T-L(B)	90	-	60	-	-
PB Risk	-	-	-	Halved	Halved
PB T-Tx(A) + Risk	95	100	-	Halved	Halved
PB T-Tx(B) + Risk	90	75	-	Halved	Halved
PB T-L(A) + Risk	95	-	100	Halved	Halved
PB T-L(B) + Risk	90	-	60	Halved	Halved

[a] Percentage of people tested during their stay in prison
[b] Percentage of people treated during their stay in prison
[c] Percentage of people linked to care and treated upon release

Chapter 4

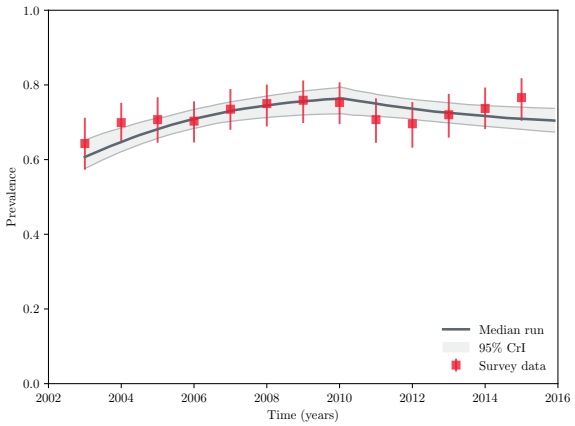
Results

4.1 Model calibration

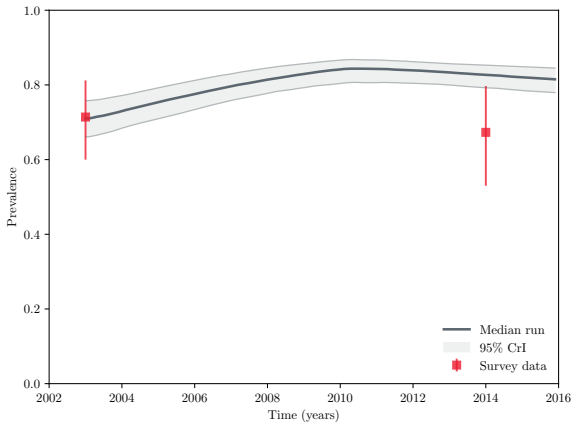
The calibration procedure resulted in 287 unique parameter sets, which reproduced the antibody prevalence and incidence estimates from the SurvUDI network. Indeed, model predictions match trends in incidence and prevalence between 2003 and 2014, and most predictions are within the confidence interval of the empirical data (Figure 4.1; 4.1c). The model was also calibrated to antibody prevalence among people declaring IDU in the past six months in the two prison surveys. The empirical data point from the 2014 prison survey was slightly overestimated, but this could have been caused by under-reporting of IDU in the past 6 months (Figure 4.1b). Posterior distributions of model parameters can be found in appendix A. The model was also cross-validated to knowledge of HCV status and mortality, the first of which is estimated in SurvUDI. In terms of awareness, the model reproduces the data from SurvUDI with the greatest fraction of PWID being aware of their infection in 2005 (71%) and 2016 (81%) (Appendix D). In terms of mortality, the model shows an increased mortality in PWID and only a few HCV-related death over the whole time period, which was expected (Appendix E).

4.2 Impact of intervention scenarios

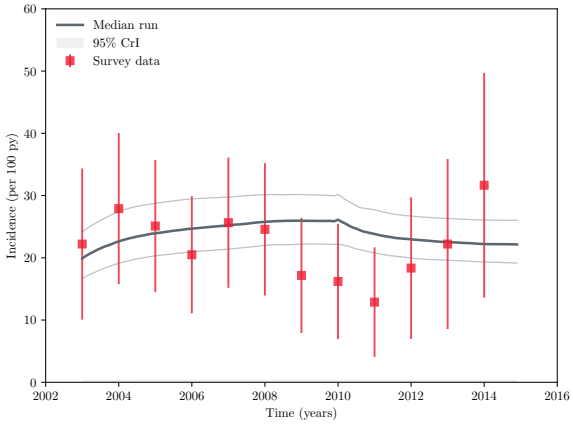
For all scenarios, knowledge of HCV status and fibrosis stages are presented in appendix C. The 5- and 10-year impacts of all interventions in the presence and in the absence of a community DAA scale-up are summarized in table 4.1.



(a) Antibody prevalence in the community



(b) Antibody prevalence in prison



(c) Incidence in the community

Figure 4.1 – Model calibration to (a) antibody prevalence in the community, (b) in prison, and (c) to incidence in the community for 287 unique parameter sets from 2003 to 2014. The empirical data points in (a) are estimates of antibody prevalence from the SurvUDI network among people at their first visit in the network. The empirical data points in (b) are estimates of antibody prevalence from the prison surveys among people who reported injecting drug use in the past six months. The empirical data points in (c) are estimates of incidence from the SurvUDI network.

4.2.1 Epidemic trajectory under status quo and community scale-up scenarios

Status quo

Under the status quo, rates of testing, treatment, and coverage of harm reduction were kept at the same level as 2018. This scenario did not cause noticeable changes in prevalence and incidence compared to 2018 (Figure 4.3a; 4.2a). Knowledge of HCV status slightly increased over time and the proportion of early infection decreased over the same period (Figure D.1).

Scale-up

With the implementation of an immediate community testing and DAA scale-up, a broad reduction in prevalence was observed after 10 years (Figure 4.3b). Incidence was also lowered by this community-based intervention (Figure 4.2b). Knowledge of HCV status decreased with the immediate community DAA scale-up while the proportion of earlier infections increased (Figure 4.4b).

4.2.2 Prison-based universal testing

Without community testing and DAA scale-up

As compared to the status quo scenario described above, testing 95% of people during incarceration (**PB Test**), without a community DAA scale-up, did not result in reductions of chronic HCV prevalence and incidence, and did not prevent new infections (Figures 4.2a; 4.3a; 4.4a). Prison-based universal testing did, however, increase knowledge of HCV status by 10% over a ten-year horizon (Figure D.2).

With community testing and DAA scale-up

When testing and treatment were scaled-up in the community, such that all PWID were tested once per year and all chronic cases treated, additional prison-based testing had small impact on community chronic prevalence, but a larger impact in terms of prevalence in prison. Overall, reductions in incidence and prevented fractions were small as compared to the scale-up of DAA alone (Figures 4.2b; 4.4b).

4.2.3 Prison-based test-and-treat

Without community testing and DAA scale-up

Prison-based test-and-treat interventions had a substantial impact on all outcomes compared to the status quo scenario. Testing 95% of people and treating all chronically infected during their stay in prison (**PB T-Tx(A)**) reduced community prevalence by $37\%(95\%CrI = 29 - 45\%)$ after ten years, with the bulk of the impact occurring in the first five years (Figure 4.3a). In prison, the impact was even higher with a 95% reduction in prevalence the first year ($95\%CrI = 93 - 96\%$). The reduction in incidence in the overall community was similar, with $29\%(95\%CrI = 17 - 40\%)$ after ten years (Figure 4.2a). This prison-based test-and-treat intervention also prevented 12% of new infections as compared to the status quo (Figure 4.4a).

Using slightly less optimistic testing and treatment assumptions, where 90% of people were tested and only 75% of those found chronically infected treated during their stay in prison (**PB T-Tx(B)**), resulted in a lower impact on transmission. For instance, prevalence was reduced by 24% and 72% in the community and in prison after ten years, respectively. Similarly modest decreases in incidence and lower prevented fractions were also observed (Figure 4.3a; 4.2a; 4.4a).

With community testing and DAA scale-up

The epidemiological impact of a community scale-up of DAA was magnified by prison-based test-and-treat: prevalence was reduced by an additional 10% in the community and 28% in prison settings when 100% of people in prison with chronic HCV are treated. When 75% of people were treated in prison, the reduction was slightly lower but still had important impacts in the community and especially in prison settings (Figure 4.3b). The impact on community incidence was similar for both **PB T-Tx(A)** and **(B)**, which brought supplemental reductions in incidence to that observed under the DAA community scale-up. The scenarios with 100% and 75% of diagnosed chronic infection treated in prison prevented $23\%(95\%CrI = 14-29\%)$ and $14\%(95\%CrI = 8-20\%)\%$ of new infections after ten years, respectively, compared to the status quo (Figure 4.4b).

4.2.4 Prison-based universal testing and linkage to care post-release

Without community testing and DAA scale-up

It could prove challenging to treat all individuals with diagnosed chronic infection in prison. In an intervention testing 95% of people in prison, and treating all people with chronic infection upon release (**PB T-L(A)**), prevalence was reduced by $40\%(95\%CrI = 31-49\%)$ and incidence by $34\%(95\%CrI = 21-45\%)$ after ten years. The impact was similar to what was observed under the prison-based test-and-treat intervention in terms of prevalence but was higher for incidence (Figure 4.3a; 4.2a). Post-release linkage to care also allowed preventing $16\%(95\%CrI = 10-22\%)$ of new infections compared to the status quo (Figure 4.4a).

When only 60% of people diagnosed with chronic HCV were treated post-release (**PB T-L(B)**), reductions in prevalence, and in incidence were at 30% and 23% respectively after 10 years, while fewer infections were prevented (Table 4.1). However, the impact for all outcomes was still more important than that of the test-and-treat intervention where 75% of people were treated (**PB T-Tx(B)**). In terms of HCV status awareness, the post-release linkage to care strategy increased overall HCV status awareness over time and the proportion of early infection (F0-2) was reduced (Figure D.4).

With community testing and DAA scale-up

A post-release linkage to care intervention also complemented well the impact of a community DAA scale-up. When all chronic cases were treated upon release, prevalence was reduced by $96\%(95\%CrI = 94-97\%)$ compared to the status quo scenario after ten years, which is 15% more than community scale-up alone (Figure 4.3b). The intervention also had a similar relative decrease in incidence compared to the status quo (Figure 4.2b). Relative to the scale-up scenario, post-release linkage to care had a growing impact with time in terms of prevalence and incidence (Figure 4.3b; 4.2b). This scenario also prevented the largest fractions of new infections after ten years compared to the scale-up with 29% when all were treated and 19% when only 60% were treated upon release (Figure 4.4b).

4.2.5 Post-release risk reduction

Without community testing and DAA scale-up

The post-release risk reduction intervention (**PB Risk**) had little impact on chronic prevalence as compared to the status quo scenario, both in community and prison settings (Figure 4.3a; B.1a). It had a notable impact on incidence, however, with $14\%(95\%CrI = 7-22\%)$ at five years, which slightly increased until the tenth year of the intervention (Figure 4.2a). This trend was also observed for the cumulative prevented fraction of new infections (Figure 4.4b).

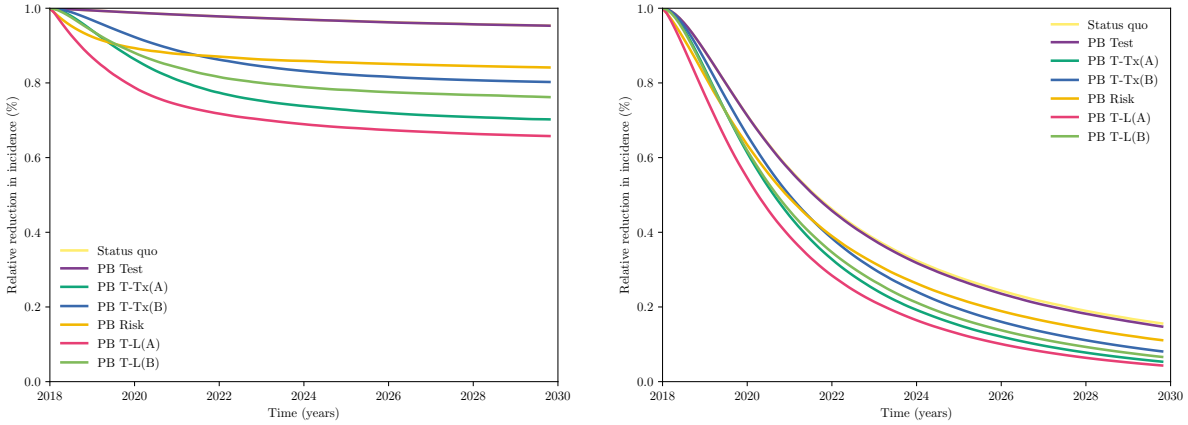
With community testing and DAA scale-up

Implementing a risk reduction intervention for people released from prison, along with a DAA scale-up, only had a minimal reduction of 1% in prevalence compared to the scale-up alone after ten years (Figure 4.3b). However, it helped reduce incidence by nearly 10% after ten years (Figure 4.2b). Compared to the status quo, a risk-reduction intervention post-release prevented up to $8\%(95\%CrI = 2-15\%)$ of new infections after ten years (Figure 4.2b; 4.4b).

4.2.6 Prison-based test-and-treat and post-release risk reduction

Without community testing and DAA scale-up

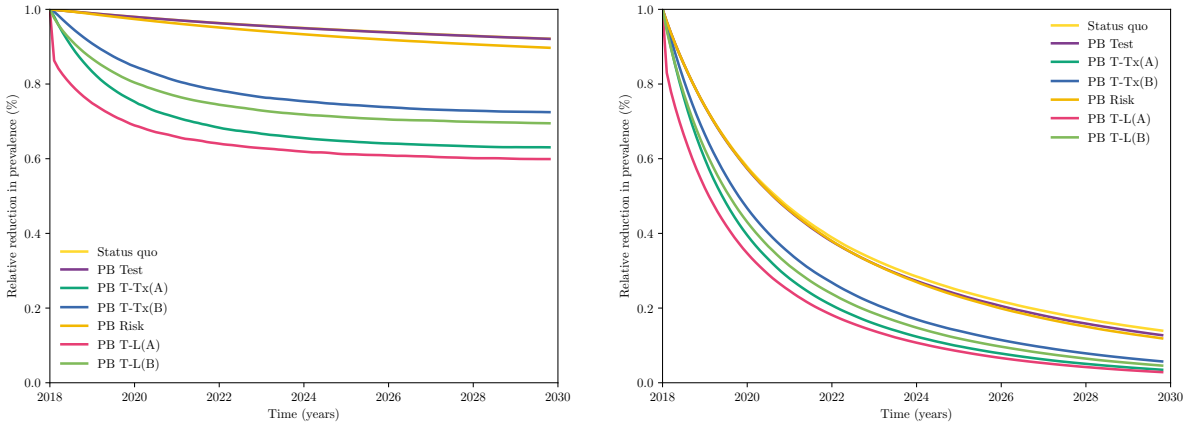
Combining interventions had a greater impact on prevalence, incidence and prevention of new infections compared to the implementation of single interventions. The scenario treating all chronic cases during their stay in prison and reducing the post-release risk (**PB T-L(A) + Risk**) allowed a sustained 10-year decrease in prevalence of $41\%(95\%CrI = 33-50\%)$ with a similar decrease in incidence and the bulk of the impact occurring in the first five years of the intervention (Figure 4.6a; 4.5a). Treating all people with chronic HCV in prison



(a) Status quo

(b) Community scale-up of DAA

Figure 4.2 – Relative reduction in incidence for single interventions among active PWID in the community from 2018 to 2030 compared to (a) a counterfactual with no community scale-up of testing and DAA (b) a counterfactual with community scale-up of testing and DAA. Where **PB Test** is a testing intervention in which 95% of people are tested in prison without treatment; **PB T-Tx(A)(B)** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated while in prison; **PB T-L(A)(B)** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release; and **PB Risk** is an intervention where the elevated post-release risk is halved.

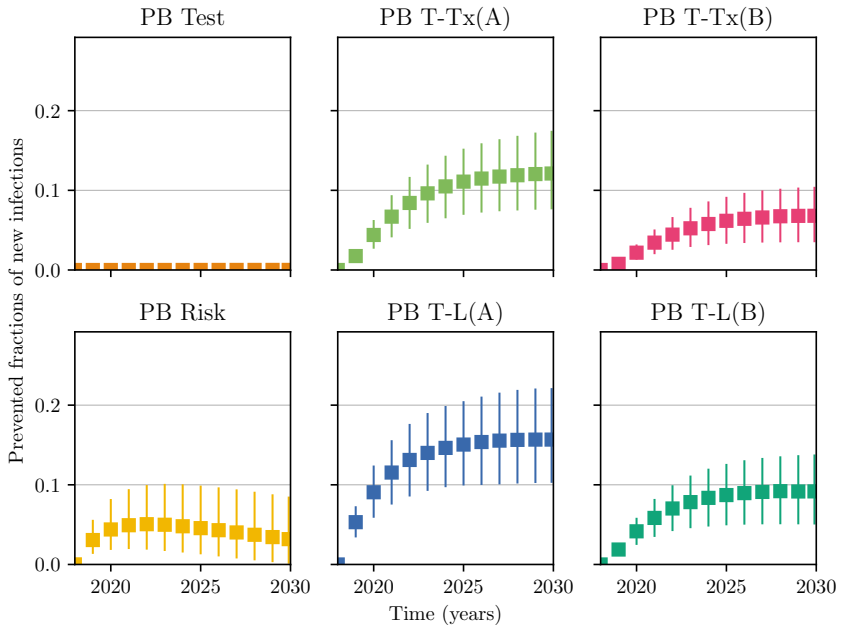


(a) Status quo

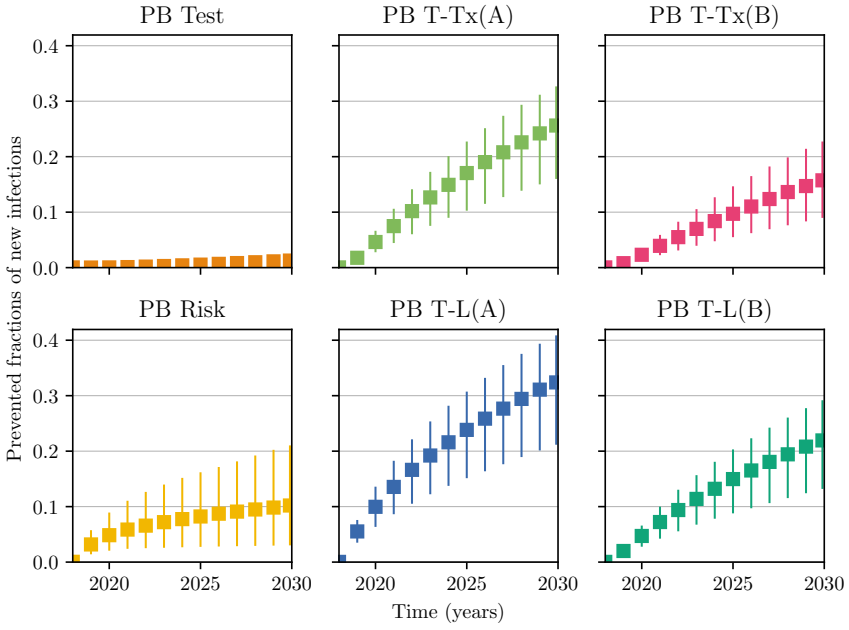
(b) Community scale-up of DAA

Figure 4.3 – Relative reduction in chronic prevalence for single interventions in active PWID in the community from 2018 to 2028 compared to (a) a counterfactual with no community scale-up of testing and DAA (b) a counterfactual with community scale-up of testing and DAA. Where **PB Test** is a testing intervention in which 95% of people are tested in prison without treatment;**PB T-Tx(A)(B)** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated while in prison;**PB T-L(A)(B)** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release; and **PB Risk** is an intervention where the elevated post-release risk is halved.

settings prevented 15% of new infections after ten years ($95\%CrI = 6 - 18\%$) as compared to the status quo scenario(Figure C.1). As before, treating 75% of people in prison resulted



(a) Status quo



(b) Community scale-up of DAA

Figure 4.4 – Prevented fractions of new infections for single interventions among active PWID from 2018 to 2028 compared to a counterfactual (a) with and (b) without a community scale-up of testing and DAA. Where **PB Test** is a testing strategy in which 95% of people are tested in prison without treatment;**PB T-Tx(A)(B)** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated while in prison; **PB T-L(A)(B)** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release; and **PB Risk** is an intervention where the elevated post-release risk is halved.

in smaller impacts on prevalence and incidence, and prevented fewer new infections with only $10\%(95\%CrI = 6-17\%)$ at ten years (Figure C.1).

With community testing and DAA scale-up

Prison-based interventions improved the impact of scaling-up DAA therapy in the community. After ten years, prevalence in the community was brought down by $96\%(95\%CrI = 92-97\%)$ compared to the status quo, which is 20% higher than under the scale-up scenario alone. The impact was more important in prison settings, where HCV prevalence was rapidly reduced (Figure B.2b). The reduction in incidence was also greater when test-and-treat and risk reduction post-release were implemented alongside a community DAA scale-up (Figure 4.5b). When treating all people found chronically infected in prison, the intervention prevented about $28\%(95\%CrI = 17-38\%)$ of new infections after ten years compared to the scale-up alone (Figure C.2).

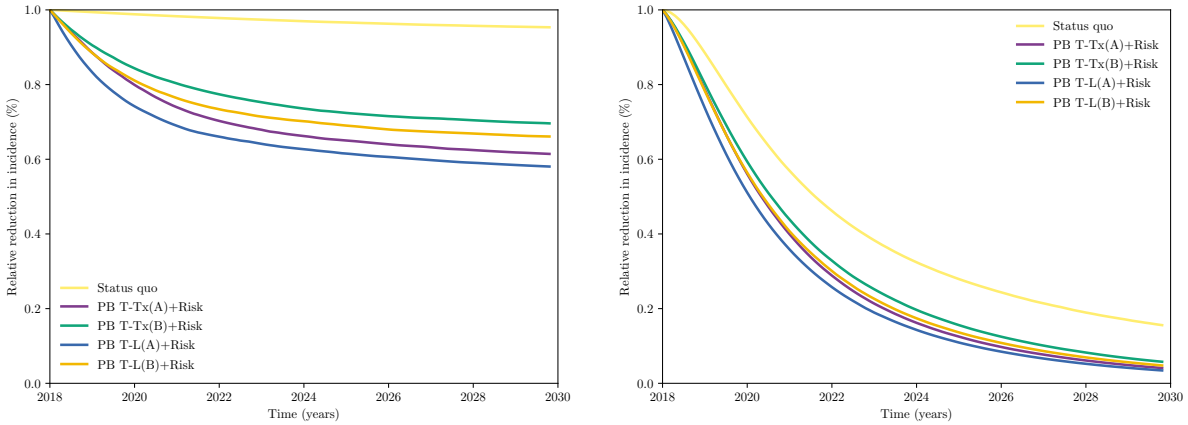
4.2.7 Prison-based post-release linkage to care and risk reduction

Without community testing and DAA scale-up

The implementation of post-release linkage to care and risk reduction measures (**PB T-L(A)** or **(B)** + **Risk**) had an even more important impact than prison-based test-and-treat interventions in reducing prevalence, and incidence. Treating all chronic HCV cases upon release reduced prevalence by $44\%(95\%CrI = 35-53\%)$ and incidence by $41\%(95\%CrI = 27-53\%)$ after ten years in the community as compared to the status quo (Figure 4.6a; 4.5a). This intervention prevented $18\%(95\%CrI = 11-28\%)$ of new infections compared to the status quo at ten years (Figure C.1). As before, imposing more realistic treatment assumptions resulted in lower impacts for all outcomes.

With community testing and DAA scale-up

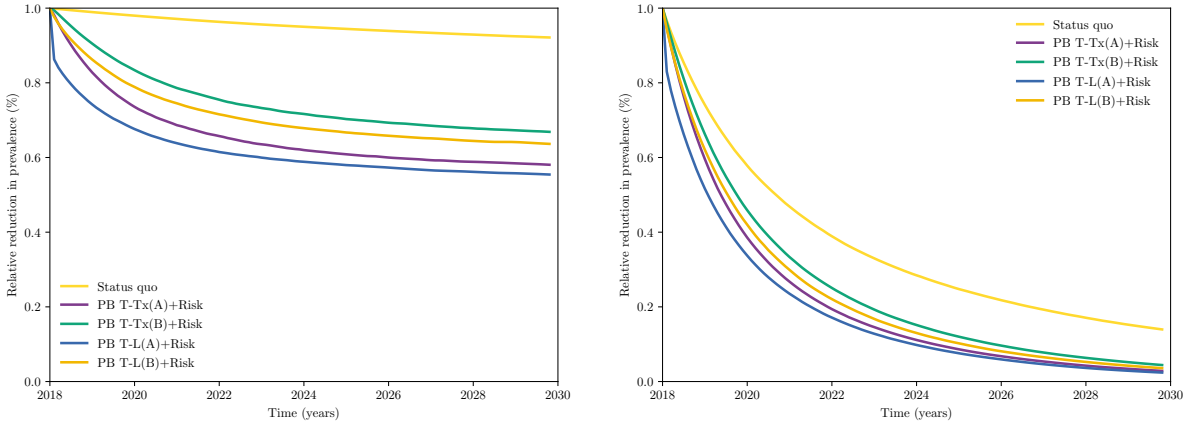
Post-release integrated models of care also improved the overall impact of a community scale-up of testing and DAA therapy. After ten years, prevalence in the community was reduced by $96\%(95\%CrI = 94-98\%)$ compared to the status quo, which is 21% higher than under the scale-up alone. Incidence also had a faster reduction when linkage to care and risk reduction post-release were implemented with a community DAA scale-up (Figure 4.5b). Notably, treating only 60% of people upon release prevented about 26% of new infections compared to the scale-up (Figure C.2).



(a) Status quo

(b) Community scale-up of DAA

Figure 4.5 – Relative reduction in incidence for combined interventions in active PWID in the community from 2018 to 2028 compared to (a) a counterfactual with no community scale-up of testing and DAA (b) a counterfactual with community scale-up of testing and DAA. Where **PB T-Tx(A)(B)+Risk** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated in prison, and elevated risk post-release is halved; **PB T-L(A)(B)+Risk** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release, and the elevated post-release risk is halved.



(a) Status quo

(b) Community scale-up of DAA

Figure 4.6 – Relative reduction in chronic prevalence for combined interventions in active PWID in the community from 2018 to 2028 compared to (a) a counterfactual with no community scale-up of testing and DAA (b) a counterfactual with community scale-up of testing and DAA. Where **PB T-Tx(A)(B)+Risk** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated in prison, and the elevated risk post-release is halved; **PB T-L(A)(B)+Risk** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release, and the elevated post-release risk is halved.

Table 4.1 – Community impact of single and combined intervention scenarios on prevalence and incidence reduction as compared to the status quo as well as prevented fractions of new infection (PF) as compared to the appropriate community intervention after 5 and 10 years with 95% credible intervals

Scenario	**Prevalence**$(95\%CrI)^{\ddagger}$		**Incidence**$(95\%CrI)$		**PF**$^{\dagger}(95\%CrI)$	
	5 years	10 years	5 years	10 years	5 years	10 years
Status quo						
PB Test	0.04 (0.03-0.06)	0.07 (0.04-0.10)	0.03 (0.01-0.04)	0.04 (0.01-0.07)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
PB T-Tx(A)	0.33 (0.27-0.40)	0.37 (0.29-0.45)	0.25 (0.15-0.33)	0.29 (0.17-0.40)	0.10 (0.06-0.13)	0.12 (0.07-0.17)
PB T-Tx(B)	0.24 (0.19-0.30)	0.27 (0.20-0.34)	0.16 (0.08-0.22)	0.19 (0.09-0.28)	0.05 (0.03-0.08)	0.07 (0.04-0.10)
PB T-L(A)	0.37 (0.30-0.44)	0.40 (0.31-0.49)	0.30 (0.20-0.39)	0.34 (0.21-0.45)	0.14 (0.09-0.19)	0.16 (0.10-0.22)
PB T-L(B)	0.27 (0.21-0.34)	0.30 (0.22-0.38)	0.20 (0.11-0.27)	0.23 (0.11-0.33)	0.08 (0.05-0.11)	0.09 (0.05-0.14)
PB Risk	0.06 (0.03-0.09)	0.09 (0.05-0.14)	0.14 (0.07-0.22)	0.16 (0.07-0.25)	0.05 (0.02-0.10)	0.04 (0.01-0.09)
PB T-Tx(A) + Risk	0.37 (0.30-0.43)	0.41 (0.33-0.50)	0.32 (0.20-0.43)	0.38 (0.24-0.49)	0.13 (0.08-0.20)	0.15 (0.09-0.23)
PB T-Tx(B) + Risk	0.27 (0.21-0.33)	0.32 (0.25-0.41)	0.25 (0.15-0.35)	0.30 (0.17-0.41)	0.10 (0.05-0.15)	0.10 (0.06-0.17)
PB T-L(A) + Risk	0.40 (0.33-0.47)	0.44 (0.35-0.53)	0.36 (0.24-0.47)	0.41 (0.27-0.53)	0.17 (0.11-0.24)	0.18 (0.11-0.26)
PB T-L(B) + Risk	0.31 (0.25-0.37)	0.36 (0.28-0.45)	0.29 (0.18-0.39)	0.33 (0.20-0.45)	0.12 (0.07-0.18)	0.13 (0.07-0.20)
Community scale up of DAA						
PB Test	0.68 (0.65-0.72)	0.84 (0.80-0.88)	0.62 (0.58-0.66)	0.82 (0.77-0.85)	0.00 (0.00-0.01)	0.01 (0.00-0.02)
PB T-Tx(A)	0.84 (0.81-0.87)	0.95 (0.92-0.96)	0.75 (0.71-0.79)	0.92 (0.89-0.94)	0.13 (0.08-0.17)	0.23 (0.14-0.29)
PB T-Tx(B)	0.79 (0.75-0.82)	0.92 (0.89-0.94)	0.70 (0.66-0.73)	0.89 (0.85-0.91)	0.07 (0.04-0.11)	0.14 (0.08-0.20)
PB T-L(A)	0.86 (0.83-0.89)	0.96 (0.94-0.97)	0.79 (0.73-0.82)	0.94 (0.90-0.96)	0.19 (0.12-0.25)	0.29 (0.19-0.38)
PB T-L(B)	0.81 (0.78-0.84)	0.94 (0.90-0.95)	0.73 (0.69-0.77)	0.91 (0.87-0.93)	0.11 (0.07-0.16)	0.19 (0.12-0.26)
PB Risk	0.68 (0.64-0.71)	0.85 (0.82-0.88)	0.68 (0.65-0.72)	0.86 (0.83-0.89)	0.07 (0.03-0.14)	0.10 (0.03-0.19)
PB T-Tx(A) + Risk	0.85 (0.83-0.88)	0.96 (0.94-0.97)	0.79 (0.74-0.82)	0.94 (0.91-0.96)	0.17 (0.10-0.25)	0.28 (0.17-0.38)
PB T-Tx(B) + Risk	0.81 (0.78-0.84)	0.94 (0.91-0.95)	0.75 (0.71-0.79)	0.92 (0.89-0.94)	0.13 (0.07-0.21)	0.21 (0.12-0.32)
PB T-L(A) + Risk	0.87 (0.84-0.90)	0.96 (0.94-0.98)	0.81 (0.76-0.85)	0.95 (0.92-0.97)	0.22 (0.14-0.30)	0.33 (0.21-0.43)
PB T-L(B) + Risk	0.83 (0.80-0.86)	0.95 (0.93-0.96)	0.77 (0.73-0.81)	0.93 (0.90-0.95)	0.17 (0.10-0.24)	0.26 (0.16-0.36)

† As compared to the community intervention

‡ Numbers in parenthesis represent 95% credible interval

Chapter 5

Discussion

5.1 Main findings

With the advent of highly efficacious DAA therapies, HCV elimination as a public health threat has received renewed political impetus. Achieving important and sustainable reductions in HCV prevalence and transmission is a public health priority to prevent projected increase of the liver-disease burden and mortality [2]. Despite a long-standing commitment to reduce the HCV burden among different key populations, Canada is currently not on track to meet the elimination targets set by WHO [14; 3]. The diversity of both key populations and provincially-managed health systems within Canada hinders the development of a national action plan for HCV elimination, and some priority populations are still not properly reached by current interventions. A recent national initiative has highlighted the importance of incarceration in the transmission dynamics of HCV among PWID, and noted that HCV care in provincial prison settings, as well as the link between correctional and community services are inadequate [14]. PWID have high incarceration rates and are frequently in contact with the prison system, yet have limited engagement in the healthcare system. In prison settings, there is a potential to reach this population and enhance their engagement in proper HCV prevention, care, and treatment. Hence, prison-based interventions targeted at incarcerated PWID have the potential to contribute to HCV elimination as a public health threat [14].

Using a dynamic mathematical model of HCV transmission among PWID in Montréal, it was shown that a prison-based test-and-treat approach treating 75% of people in prison would reduce incidence by 19%($95\%CrI = 9 - 28\%$) over the next 10 years, compared to a counterfactual status quo scenario. Nonetheless, implementation of strategies that aim to treat all those diagnosed with chronic HCV infection in provincial prisons raise several feasibility issues, as the average duration of stay is often far shorter than a DAA treatment

course [9]. Further, concerns of DAA treatment while incarcerated include that treatment could be compromised and/or discontinued after release, and that PWID could rapidly be reinfected during the period of heightened injecting risk following incarceration [84]. The present model suggests that interventions improving post-release linkage to care and treating 75% upon release would provide important decreases in prevalence (30%) and incidence (23%) after ten-year compared to the status quo. These results indicate that post-release linkage to care interventions are to be considered by public health officials. For instance, pre-discharge planning, where people plan all their community appointments prior to release from prison, and where transportation to these appointments is provided, have shown a positive impact in enhancing treatment uptake among recently released PWID [111].

The current HCV care landscape misses out on some priority populations because interventions are not tailored to their particular needs. PWID and people in prison suffer from stigma and are marginalized in the healthcare system [82]. Further, there is considerable overlap between the two groups, as PWID have high incarceration rates and people in prison frequently report history of IDU. Among PWID, the elevated risk of HCV acquisition post-release is not only caused by withdrawal symptoms, but also by an unstable environment, which promotes drug use as a coping mechanism [114; 112]. This vicious circle is difficult to break, and interventions that only seek to treat HCV infection are insufficient to lead to sustainable reductions in disease transmission if they are not accompanied by complementary measures to reduce the elevated risk of transmission in the post-release period. This type of integrated models of care, which include both a linkage to care intervention where 75% of people are treated upon release, and risk-reduction measures (reducing risk of transmission and acquisition by 50%), have the greatest and most sustainable impact at ten years, reducing prevalence by $36\%(95\%CrI = 28 - 45\%)$ incidence by $33\%(95\%CrI = 20 - 45\%)$, compared to the status quo. This suggests the potential effectiveness of comprehensive intervention packages targeted at chronically infected people recently released from prison. Although a hypothetical intervention reducing the elevated risk by 50% was modelled in the present work, several real-world interventions could play this role.

In nurse-led interventions, PWID can be engaged in the continuum of care and followed closely by a nurse practitioner under specialist supervision [113]. The nurse practitioner can help PWID in the treatment process and can also provide insight on fibrosis, liver disease, harm reduction programs, and safer injecting behaviors. Nurse-lead interventions can notably help increase treatment compliance, reduce risk behaviors, and help manage the disease burden [113; 88; 87]. A similar role could be played by peer navigators/workers programs in which PWID are followed by persons with similar lived experience who guide them through the HCV treatment and care cascade, and/or steer them toward appropriate harm reduction programs. This type of intervention seeks to reduce the risk of IDU post-release

and enhances engagement in the healthcare system by increasing mutual trust and reducing perceived stigma [114]. Peer-based interventions in the community can increase engagement in healthcare and improve social determinants of health, such as housing and employment [115; 116]. In Ireland, healthcare workers and PWID alike perceived peer navigators as highly positive to enhance HCV screening and treatment among incarcerated people, and as potential facilitators in the transition back to the community upon release [117]. As such, comprehensive interventions have a significant importance in the treatment of HCV, and their reach goes well beyond HCV care.

Population-specific interventions conceived within a micro-elimination framework address one piece of the overall elimination puzzle. By leveraging contexts, settings, and characteristics, these interventions allow reaching these specific populations efficiently. However, broader elimination strategies are still needed to achieve elimination. This is especially true in high prevalence settings, such as the PWID community of Montréal [51]. The results of this modelling exercise suggest that DAA must be concomitantly scaled-up in the community for prison-based interventions to substantially reduce incidence and prevalence. Interestingly, prison-based strategies were shown to have a synergistic impact with community DAA scale-up to reduce incidence and prevent new infections (Figure C.2). The current national initiative to create provincial action plans mentions the importance of both broad and targeted micro-elimination interventions [14]. The results support this statement and suggest that a micro-elimination strategy targeted at incarcerated PWID would substantially benefit from strategies aimed at non-incarcerated PWID.

5.2 Comparison with previous studies

This study is the first attempt to model the population of community and incarcerated PWID in Canada. In Europe, Stone et al. [7] modelled the impact of incarceration on HCV transmission among PWID in Scotland. The authors found that continuing with the current rate of treatment would have no impact on the HCV epidemic. They also found that testing and treating people in prison would have a significant impact on the HCV epidemic and that this impact would be strengthened by risk-reduction interventions post-release. Results presented above point in the same direction, even though it was found that linkage to care interventions have the greatest impact to reduce HCV among the broader PWID community. This could be explained by the different conceptualization of time spent in prison by Stone et al. [7]. In their model, a large fraction of the prison population is eligible for treatment, whereas PWID in Montréal have a shorter average duration of stay in prison with few people who can complete treatment during their incarceration. Model findings also suggests that post-release risk-reduction interventions are important for prison-based test-

and-treat interventions to achieve a sustained epidemiological impact in Montréal. Hence, linkage to care post-release seems to be a better alternative in this setting. In the USA, He et al. [94] investigated the impact of testing and treatment on HCV prevalence in the general prison population. They found that testing and treatment could prevent between 5500 and 12700 new HCV cases over 30 years for the general population and that this approach would be highly cost effective to reduce HCV prevalence in prison. In relative terms, this is a prevented fraction of new infections of 7.5% compared to no screening and treatment, which is similar to findings presented above in terms of testing and subsequent treatment in prison. The present analyses differ because the model is restricted to the PWID population whereas their study included the general prison population. Also in the USA, models of treatment-as-prevention were not shown to substantially reduce HCV prevalence where it is already high, but could have a significant impact otherwise [51]. The present work also finds that without a broader community scale-up of DAA the impact of prison-based micro-elimination efforts will remain limited.

Overall, model results are in line with the relevant modelling literature on prison-based interventions to reduce HCV prevalence and incidence in prison. Notably, it was found that linkage to care interventions and risk-reduction measures post-release have the highest potential to reduce HCV prevalence and transmission among PWID in Montréal. A broader community response would also be necessary to achieve elimination in that population. This study thus fills a knowledge gap on the potential impact of interventions seeking to improve linkage to care and reduce the risk of HCV transmission in the crucial period following release from prison.

5.3 Limitations

Results of this study should be interpreted considering several limitations. First, an important caveat, which is not unique to this study, is the self-reported nature of behavioral data analyzed from SurvUDI and prison surveys. For instance, stigmatized injecting behaviors could have been under-reported in these surveys, which could have led to an underestimation of the force of infection. This problem often arises in studies targeted at hard-to-reach populations, which often use convenience sampling approaches. Nonetheless, these are the best data available with large sample sizes, good temporal coverage, and biomarkers measured accurately. Second, the model is stratified by sex, but not by risk groups or ethnicity, which could have obscured smaller subgroups with potentially different intervention needs. However, even in the absence of such stratifications, the model reproduces the epidemic trends for prevalence and incidence. Third, even though uncertainty exists regarding available data on the PWID population size of Montréal, estimate suggest an important decline between

1996 and 2010 going from 11700 to 3908 [123]. Without additional evidence on demographic trends, the population was modelled as stable from 2010 onward. Fourth, drug trends are cyclical and can impact transmission dynamics. The Montréal drug market has highly diversified in the past years, and even though cocaine remains the main drug of choice, crack and PO have increased substantially [64; 6]. This could have led to observed increases in HCV incidence, as drug type impacts injecting risk behaviors. Fifth, HIV/HCV co-infections are not explicitly considered [7]. Co-infected individuals are known to have a faster liver disease progression and therefore HCV mortality could have been slightly underestimated [20]. Given that only 12% of HCV antibody positive participants in SurvUDI are living with HIV, this underestimation is probably small. Finally, the results could only be generalizable to settings with similar polydrug use patterns, incarceration dynamics, and demographic characteristics as the ones prevailing in Montréal.

5.4 Strengths

This study also has multiple strengths. First, the model is able to reproduce the Montréal epidemic in the community and in to some extent in prison, two settings that are often difficult to study simultaneously. The research team also had access to exhaustive data which allowed robust quantification of model parameters. Indeed, SurvUDI provides important yearly information on prevalence and incidence of HCV across several sites in Québec. From these cross-sectional surveys, the model was calibrated to more than ten years of prevalence and incidence data [6]. Access to the microdata from two large prison surveys was also granted, which allowed to perform secondary analyses and calibration to HCV antibody prevalence among people reporting IDU in the past six months [9; 72]. Hence, even under simplifying assumptions, the model is validated by local data. Another strength is that the structure of the model is quite flexible and could potentially be expanded to include other stratifications. Further, the model conservatively assumed a 12-week duration and an SVR rate of 90% for DAA therapy, with perfect compliance. However, new drugs with 8 weeks duration and potentially higher SVR rates are currently evaluated in multiple settings and could further enhance the ease of treating people with chronic HCV in prison or upon release [48]. This model would be relevant to answer other research questions for micro-elimination of HCV among key populations.

Conclusion and summary

Sustainably curbing HCV transmission among PWID in Montréal will require the rapid scale-up of interventions in both prison and community settings. Interventions that increase linkage between community and prison healthcare services would have the greatest impact on disease burden in this priority population. Furthermore, public health authorities should consider implementing risk reduction initiatives targeted at the short period right after release from prison. Overall, the results presented above suggest that reaching the goal of HCV elimination among PWID in Montréal would be made easier by improving integration and coordination of both correctional and public health services. In Canada, only three provinces (Nova Scotia, Alberta, and British Colombia) have integrated prison health care in the public health system. Elsewhere, the ministry responsible for corrections is in charge of prisoners' health care [136]. Transitioning toward a more integrated system could prove challenging, however, and studies should be conducted to assess acceptability, feasibility, and sustainability of such initiatives. These results can guide current stakeholders closing the gaps between these two distinct settings. This work also highlights the importance of a community-based scale-up of testing and treatment to have a sustained impact on disease transmission among PWID. With concomitant interventions in the community and in prison, HCV prevalence and incidence could be significantly reduced among all PWID. This is crucial to HCV elimination efforts, but could also improve the health of an otherwise marginalized group of Québecois and Canadian PWID with limited access and engagement in healthcare services.

Appendix A

Posteriors

Table A.1 – Posterior distribution for parameters produced by 287 unique curves obtained through model calibration procedure

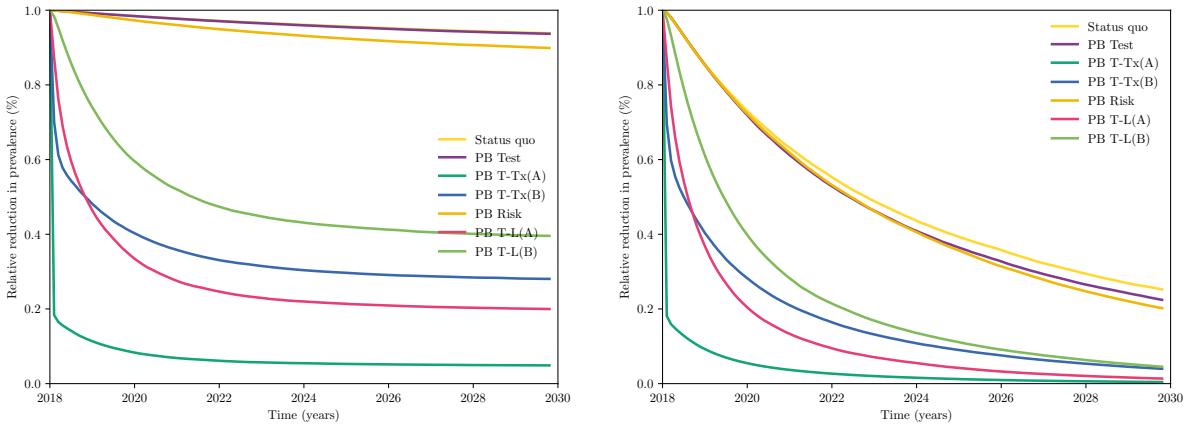
Parameter	**Symbol**	**Median**	**95%CrI**	**Units**
HCV transmission model				
Transmission rate	$\boldsymbol{\beta}$	0.436	$0.365 - 0.525$	-
Assortative degree				
Incarceration	mix_p	0.404	$0.020 - 0.963$	-
Injection status	mix_i	0.549	$0.048 - 0.966$	-
Recruitment rate	$\boldsymbol{\theta}$	298	$192 - 346$	people per year
Fibrosis progression rate	$\boldsymbol{\xi}$	0.027	$0.025 - 0.029$	metavir units/year
Testing rate	$\boldsymbol{\tau}(t)$	25.1	$10.9 - 39.3$	per 100 PY
Reduced HCV risk on OAT	$\mathbf{rr}_{oat}$	0.497	$0.431 - 0.580$	-
Increased HCV risk release	Γ	1.593	$1.269 - 2.019$	-
Increased death risk release	Π	7.424	$5.702 - 9.941$	-
Incarceration dynamics model				
Incarceration rate †				
2003	$\boldsymbol{\eta}_0(2003)$	11.5	$10.7 - 12.4$	per 100 PY
Release rate †				
2003	$\boldsymbol{\eta}_1(2003)$	779	$703 - 847$	per 100 PY
Injection dynamics model				
Duration of injecting career	$\frac{1}{\delta_0}$	0.055	$0.044 - 0.075$	per year

HCV: hepatitis C virus, OAT: opioid agonist therapy

† To lighten the table, only the posterior for 2003 was shown for these two quantities. Similar distributions were observed over the years.

Appendix B

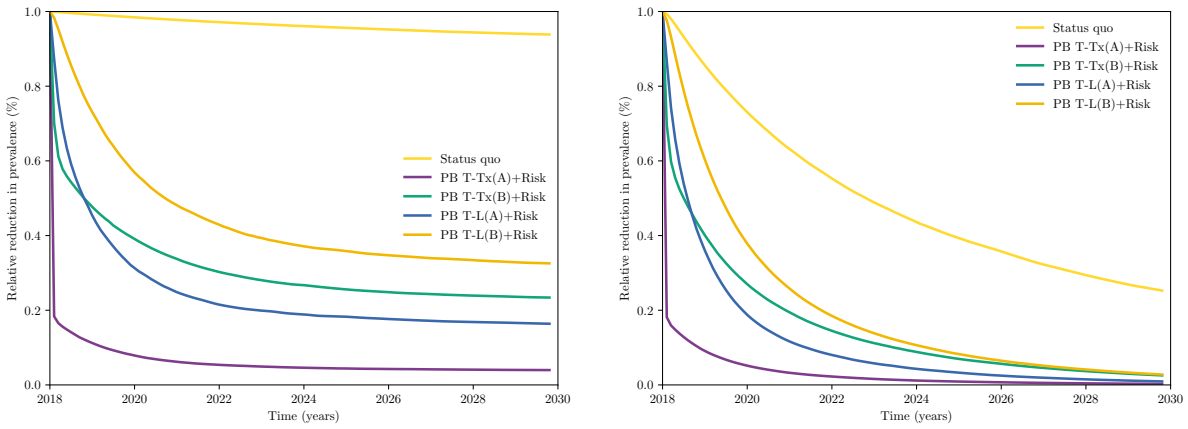
Impact on prevalence in prison settings



(a) Status quo

(b) Community scale-up of DAA

Figure B.1 – Relative reduction in prevalence for single interventions in active PWID in prison from 2018 to 2028 compared to (a) a counterfactual with no community scale-up of testing and DAA (b) a counterfactual with community scale-up of testing and DAA. Where **PB Test** is 95% testing strategy in prison without treatment; **PB T-Tx(A)(B)** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated while in prison; **PB T-L(A)(B)** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release; and **PB Risk** is an intervention where the elevated post-release risk is halved.



(a) Status quo

(b) Community scale-up of DAA

Figure B.2 – Relative reduction in prevalence for combined interventions in active PWID in prison from 2018 to 2028 compared to (a) a counterfactual with no community scale-up of testing and DAA (b) a counterfactual with community scale-up of testing and DAA. Where **PB T-Tx(A)(B)+Risk** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated in prison, and elevated risk post-release is halved; **PB T-L(A)(B)+Risk** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release, and the elevated post-release risk is halved.

Appendix C

Prevented fractions

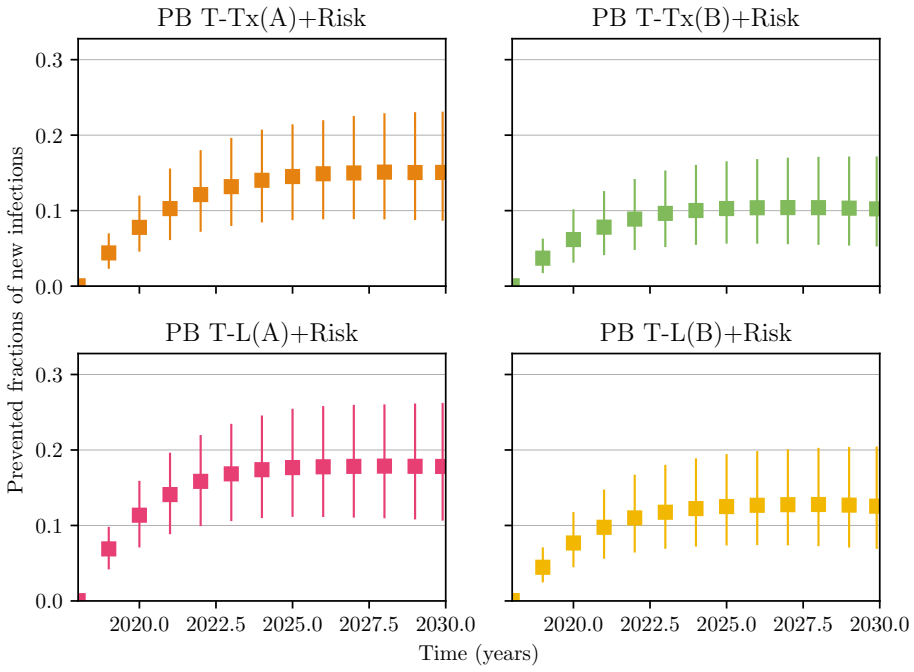


Figure C.1 – Prevented fractions of new infections for combined interventions among active PWID from 2018 to 2030 compared to a counterfactual without a community scale-up of testing and DAA. Where **PB T-Tx(A)(B)+Risk** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated while in prison, and elevated risk post-release is halved; and **PB T-L(A)(B)+Risk** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release, and the elevated post-release risk is halved.

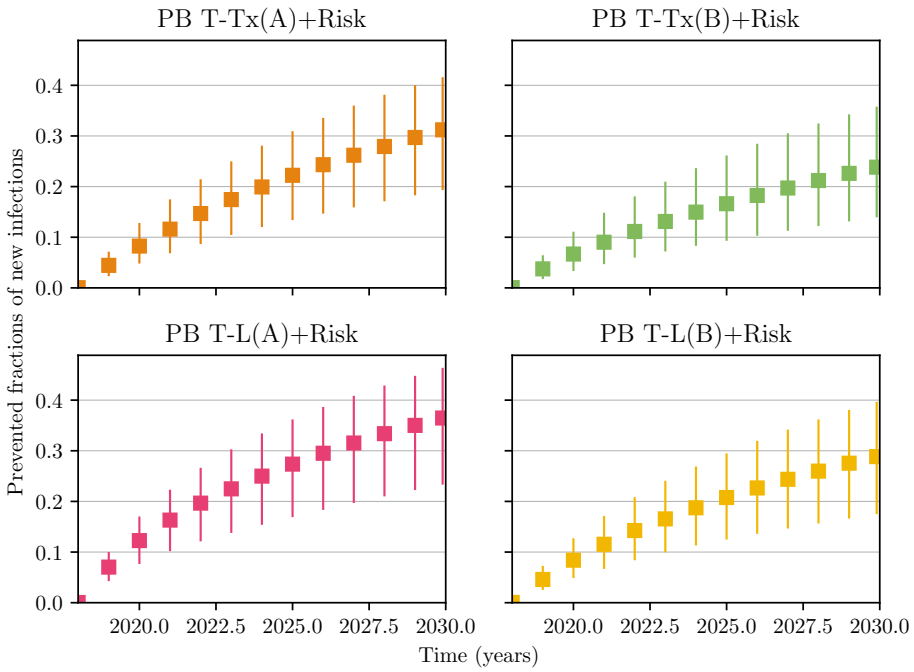
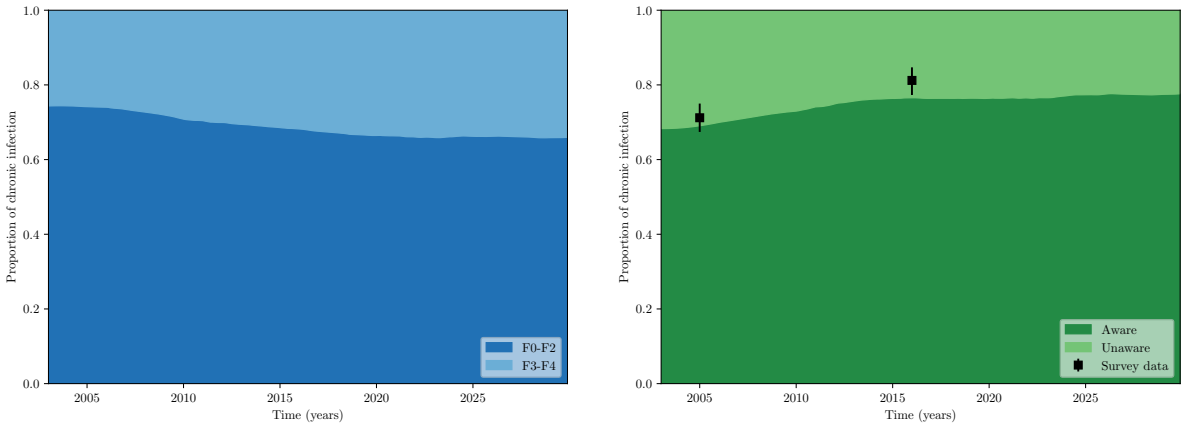


Figure C.2 – Prevented fractions of new infections for combined interventions among active PWID from 2018 to 2030 compared to a counterfactual with a community scale-up of testing and DAA. Where **PB T-Tx(A)(B)+Risk** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated while in prison, and elevated risk post-release is halved; and **PB T-L(A)(B)+Risk** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release, and the elevated post-release risk is halved.

Appendix D

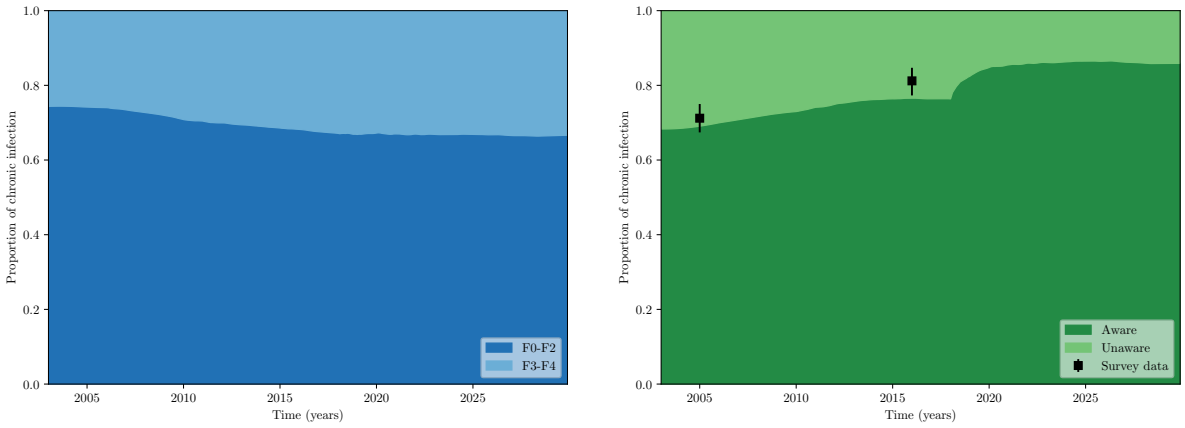
Knowledge of HCV status and fibrosis



(a) Fibrosis

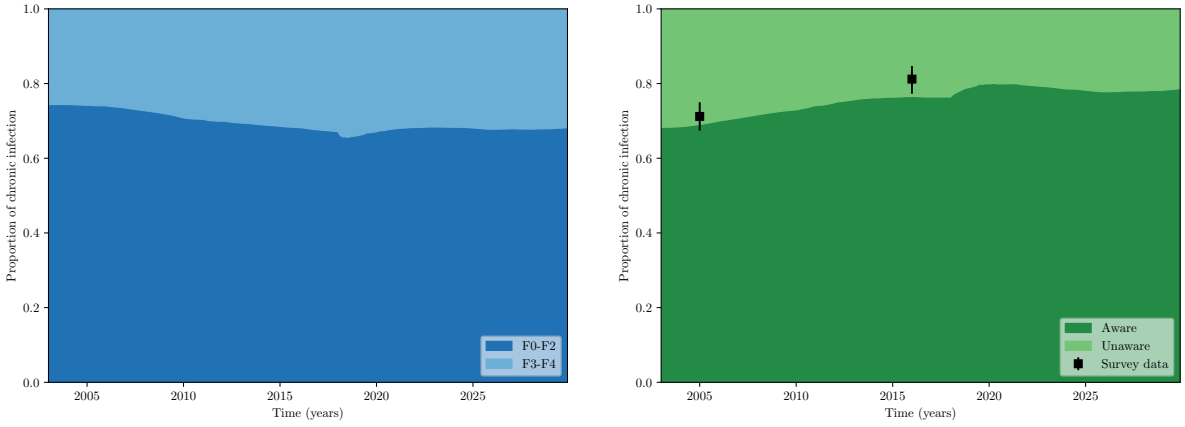
(b) Knowledge of HCV status

Figure D.1 – (a) Fibrosis level and (b) knowledge of HCV status among all PWID from 2003 to 2030 under the **Status quo** scenario without a community scale-up of testing and DAA



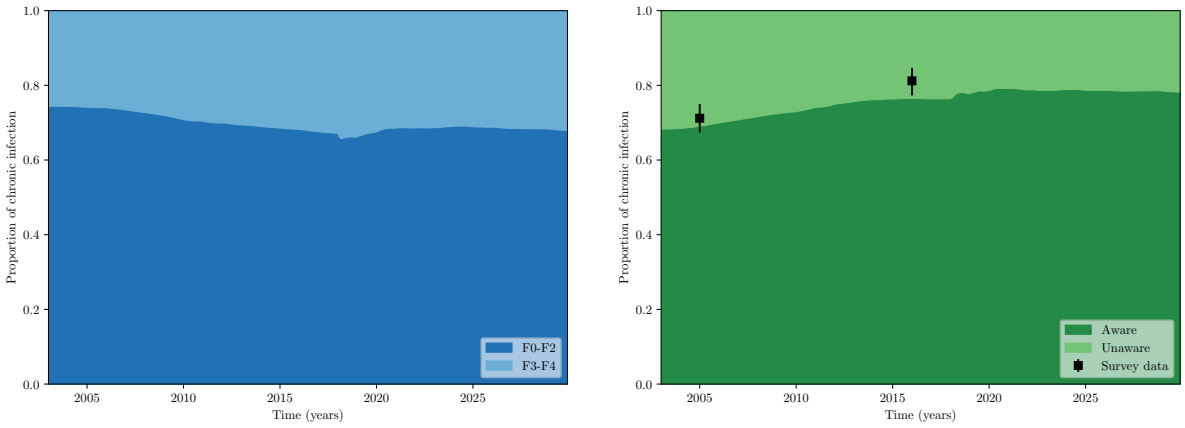
(a) Fibrosis (b) Knowledge of HCV status

Figure D.2 – (a) Fibrosis level and (b) knowledge of HCV status under a testing intervention in prison where 95% of people are tested during their incarceration (**PB Test**) among all PWID from 2003 to 2030 without a community scale-up of testing and DAA



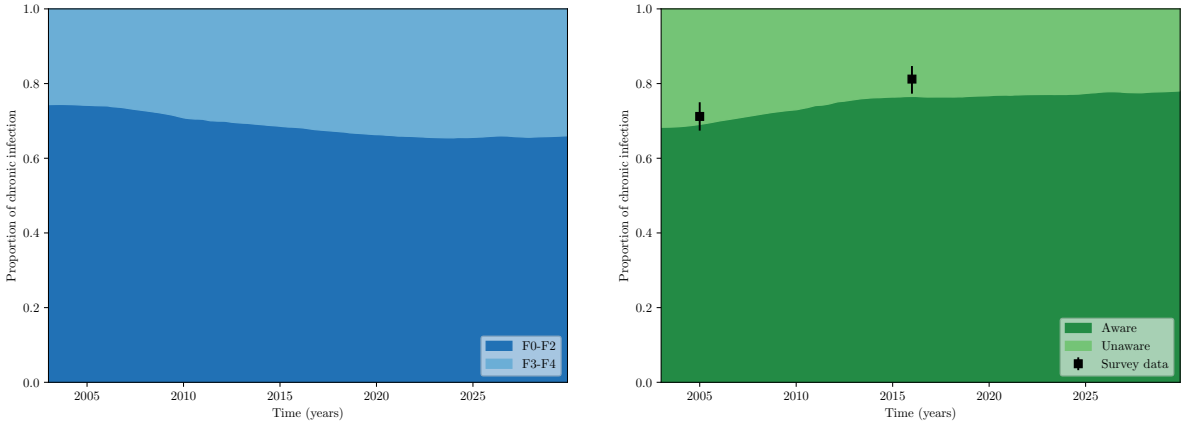
(a) Fibrosis (b) Knowledge of HCV status

Figure D.3 – (a) Fibrosis level and (b) knowledge of HCV status under a test-and-treat intervention (**PB T-Tx(B)**) where 90% of people are tested and 75% are treated in prison for all PWID from 2003 to 2030 without a community scale-up of testing and DAA



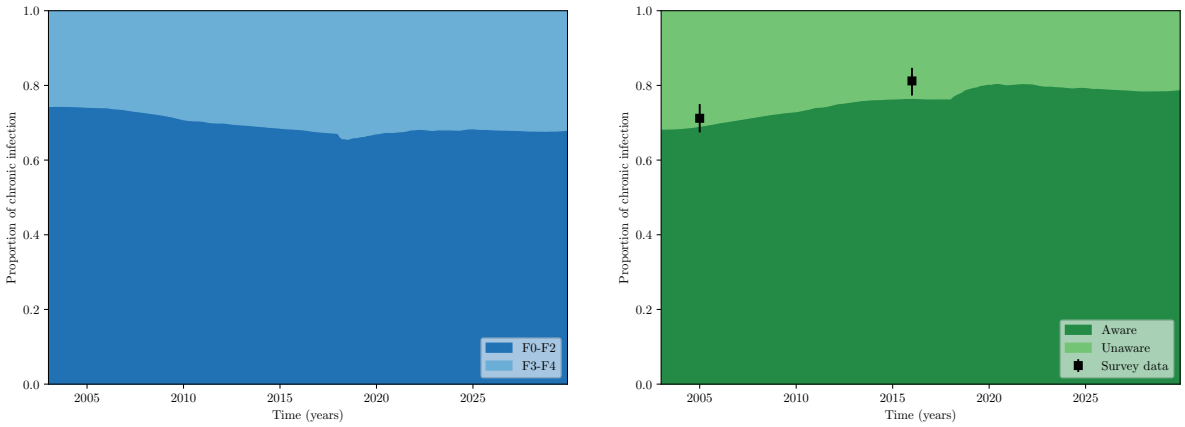
(a) Fibrosis (b) Knowledge of HCV status

Figure D.4 – (a) Fibrosis level and (b) Knowledge of HCV status under a post-release linkage to care intervention (**PB T-L(B)**) where 90% of people are tested in prison and 60% are treated upon release for all PWID from 2003 to 2030 without a community scale-up of testing and DAA



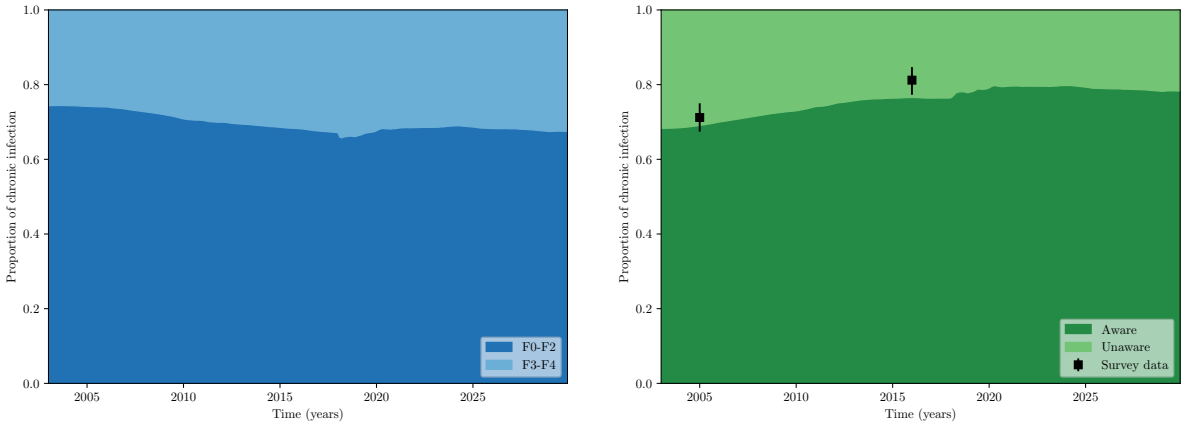
(a) Fibrosis (b) Knowledge of HCV status

Figure D.5 – (a) Fibrosis level and (b) knowledge of HCV status under a risk reduction intervention (**PB Risk**) where the elevated post-release risk for all PWID from 2003 to 2030 without a community scale-up of testing and DAA



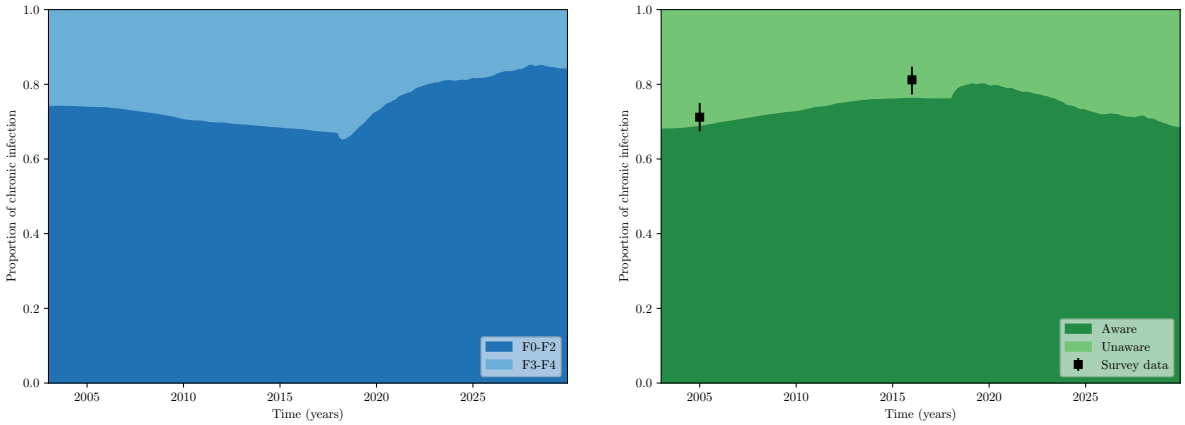
(a) Fibrosis (b) Knowledge of HCV status

Figure D.6 – (a) Fibrosis level and (b) knowledge of HCV status under a combined test-and-treat intervention (**PB T-Tx(B)+Risk**) where 90% of people are tested and 75% are treated in prison and the elevated risk post-release is halved for all PWID from 2003 to 2030 without a community scale-up of testing and DAA



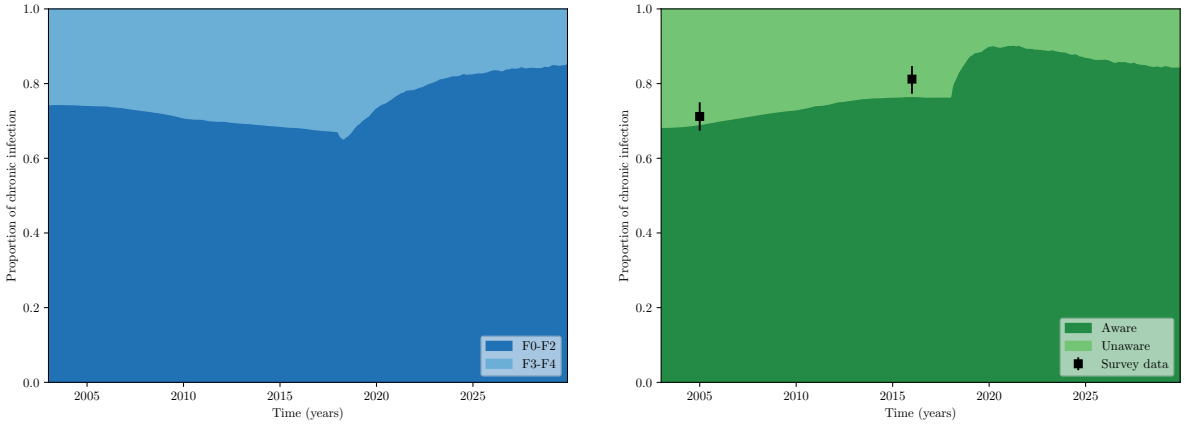
(a) Fibrosis (b) Knowledge of HCV status

Figure D.7 – (a) Fibrosis level and (b) knowledge of HCV status under a combined post-release linkage to care intervention (**PB T-L(B)+Risk**) where 90% of people are tested in prison and 60% are treated upon release and the elevated post-release risk is halved for all PWID from 2003 to 2030 without a community scale-up of testing and DAA



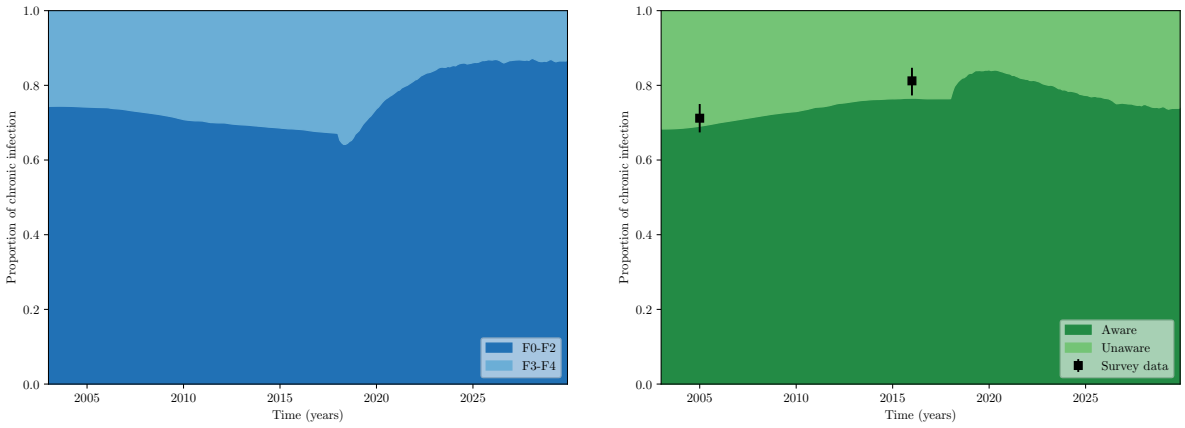
(a) Fibrosis (b) Knowledge of HCV status

Figure D.8 – (a) Fibrosis level and (b) knowledge of HCV status among all PWID from 2003 to 2030 under a community scale-up of testing and DAA scenario (**Scale up**)



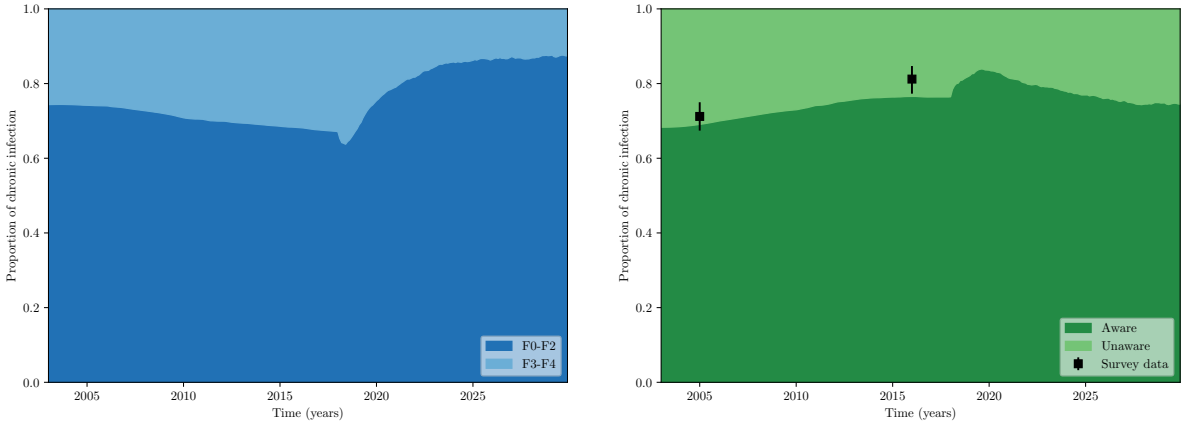
(a) Fibrosis (b) Knowledge of HCV status

Figure D.9 – (a) Fibrosis level and (b) kowledge of HCV status for intervention in prison where 95% of people are tested in prison (**PB Test**) among all PWID from 2003 to 2030 with a community scale-up of testing and DAA



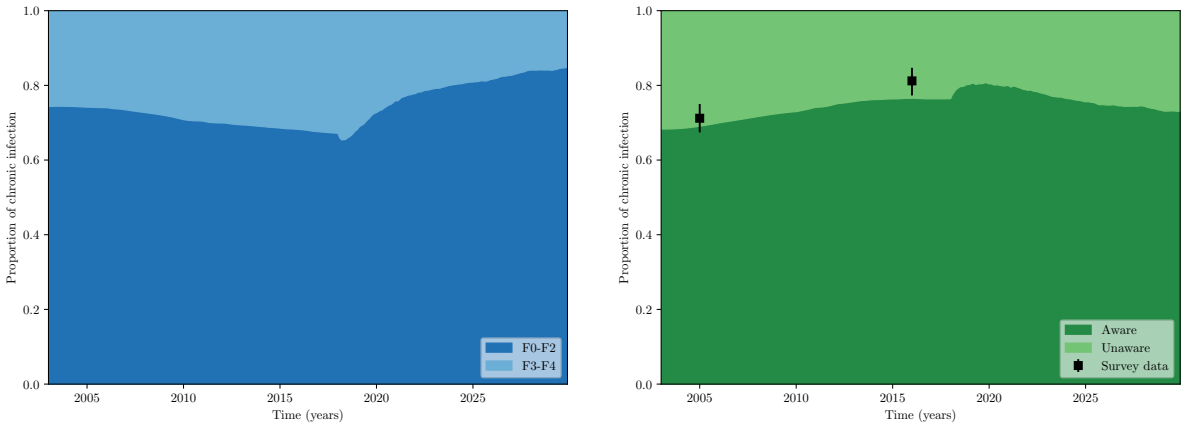
(a) Fibrosis (b) Knowledge of HCV status

Figure D.10 – (a) Fibrosis level and (b) knowledge of HCV status under a test-and-treat intervention (**PB T-Tx(B)**) where 90% of people are tested and 75% are treated in prison for all PWID from 2003 to 2030 with a community scale-up of testing and DAA



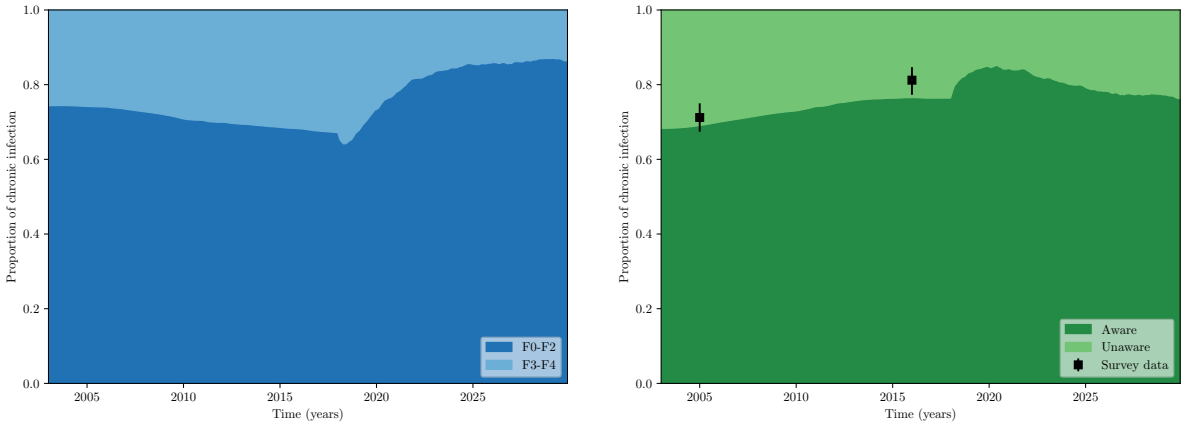
(a) Fibrosis (b) Knowledge of HCV status

Figure D.11 – (a) Fibrosis level and (b) knowledge of HCV status under a post-release linkage to care intervention (**PB T-L(B)**) where 90% of people are tested in prison and 60% are treated upon release for all PWID from 2003 to 2030 with a community scale-up of testing and DAA



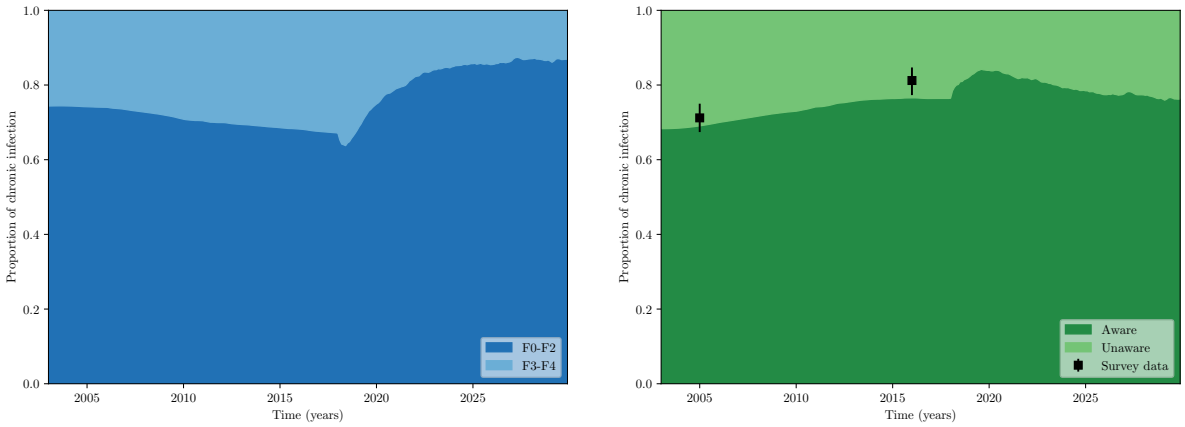
(a) Fibrosis (b) Knowledge of HCV status

Figure D.12 – (a) Fibrosis level and (b) knowledge of HCV status under a risk reduction intervention (**PB Risk**) where the elevated post-release risk for all PWID from 2003 to 2030 with a community scale-up of testing and DAA



(a) Fibrosis (b) Knowledge of HCV status

Figure D.13 – (a) Fibrosis level and (b) knowledge of HCV status under a combined test-and-treat intervention (**PB T-Tx(B)+Risk**) where 90% of people are tested and 75% are treated in prison and the elevated risk post-release is halved for all PWID from 2003 to 2030 with a community scale-up of testing and DAA



(a) Fibrosis

(b) Knowledge of HCV status

Figure D.14 – (a) Fibrosis level and (b) knowledge of HCV status under a combined post-release linkage to care intervention (**PB T-L(B)+Risk**) where 90% of people are tested in prison and 60% are treated upon release and the elevated post-release risk is halved for all PWID from 2003 to 2030 with a community scale-up of testing and DAA

Appendix E

Mortality

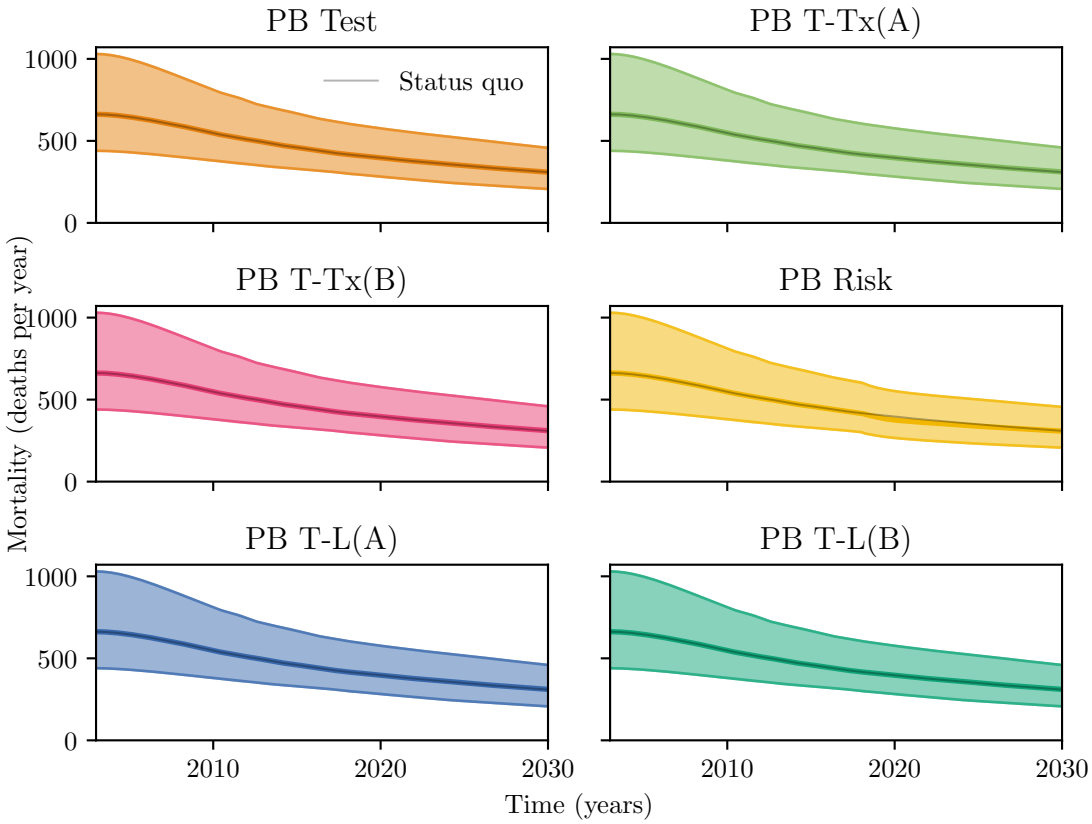


Figure E.1 – Natural mortality for all single interventions among all active PWID from 2003 to 2030 under a baseline with no community universal testing and scale-up of DAA. Where **PB Test** is a testing strategy in which 95% of people are tested in prison without treatment;**PB T-Tx(A)(B)** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated while in prison; **PB T-L(A)(B)** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release; and **PB Risk** is an intervention where the elevated post-release risk is halved.

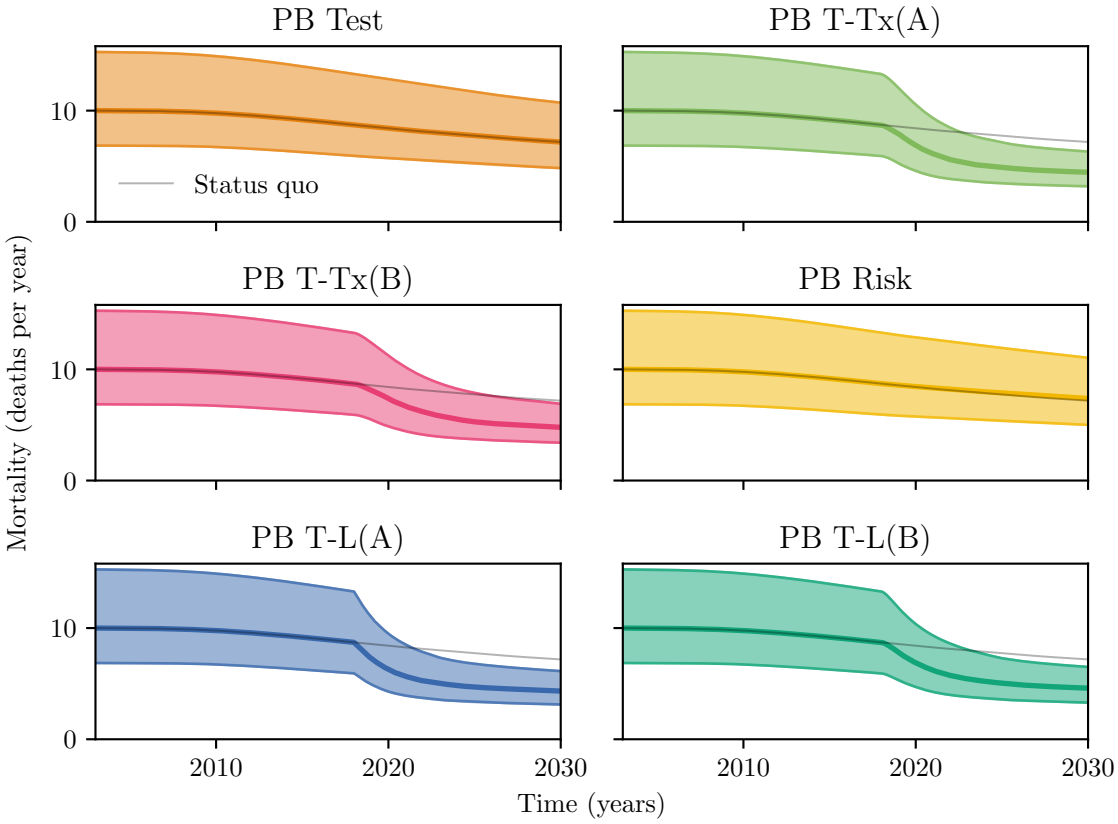


Figure E.2 – HCV mortality for all single interventions among all active PWID from 2003 to 2030 under a baseline with no community universal testing and scale-up of DAA. Where **PB Test** is a testing strategy in which 95% of people are tested in prison without treatment;**PB T-Tx(A)(B)** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated while in prison; **PB T-L(A)(B)** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release; and **PB Risk** is an intervention where the elevated post-release risk is halved.

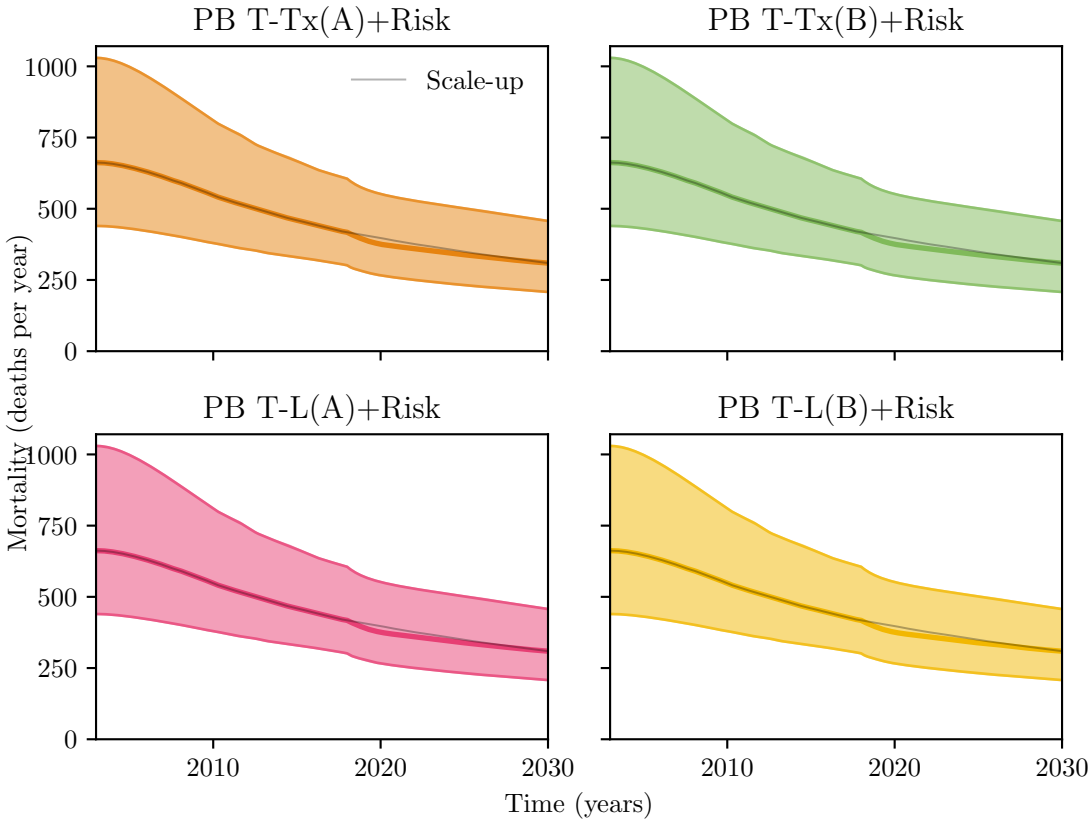


Figure E.3 – Natural mortality for combined interventions among all active PWID from 2003 to 2030 under a baseline with no community universal testing and scale-up of DAA. Where **PB T-Tx(A)(B)+Risk** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated in prison, and elevated risk post-release is halved; **PB T-L(A)(B)+Risk** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release, and the elevated post-release risk is halved.

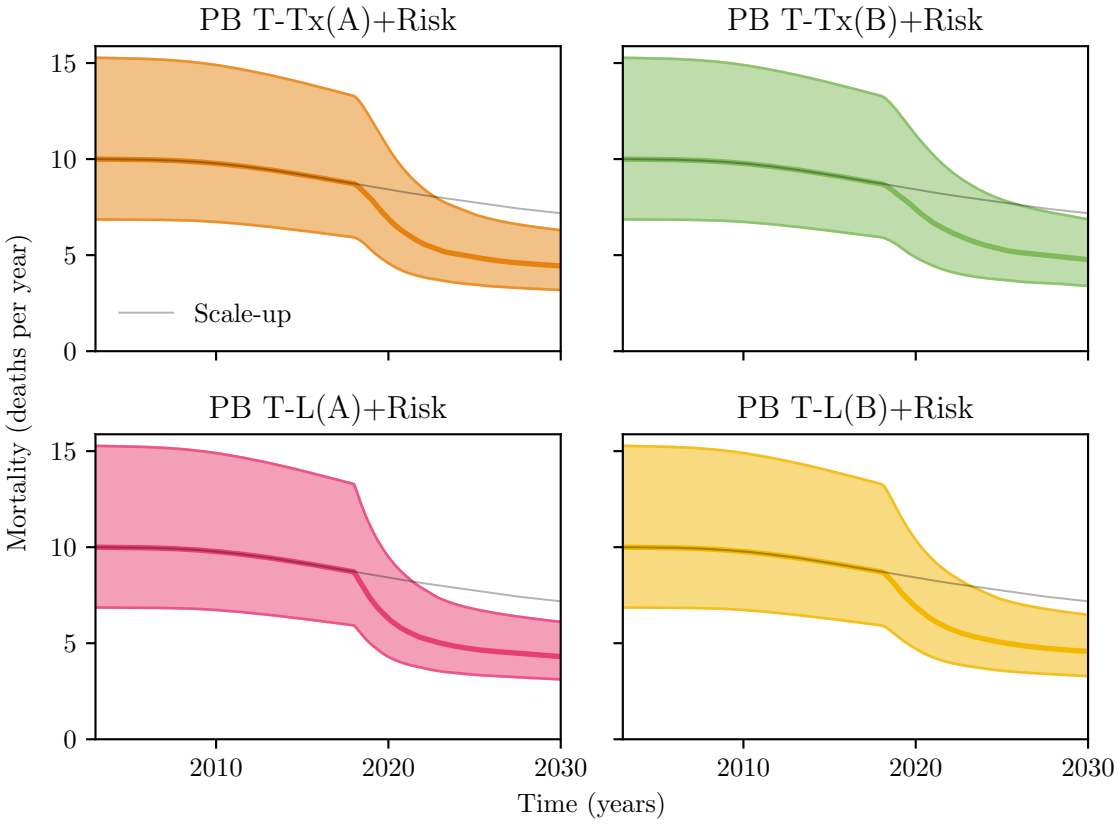


Figure E.4 – HCV mortality for combined interventions among all active PWID from 2003 to 2030 under a baseline with no community universal testing and scale-up of DAA. Where **PB T-Tx(A)(B)+Risk** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated in prison, and elevated risk post-release is halved; **PB T-L(A)(B)+Risk** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release, and the elevated post-release risk is halved.

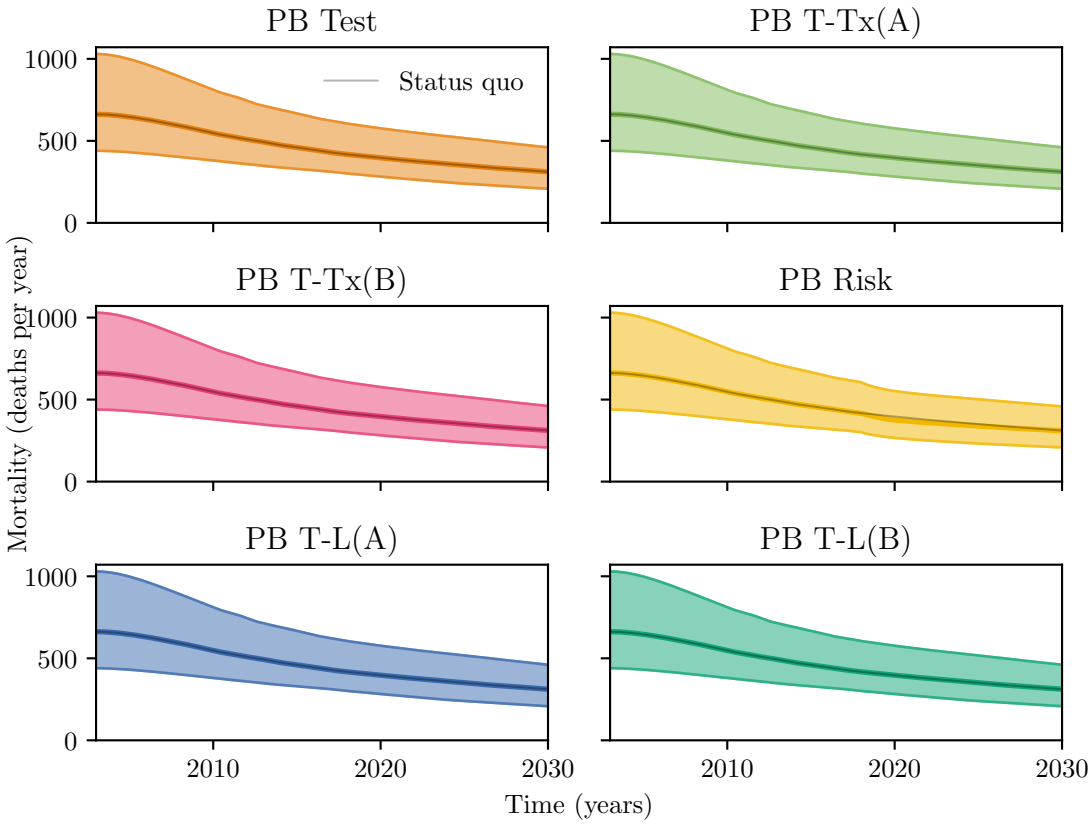


Figure E.5 – Natural mortality for all single interventions among all active PWID from 2003 to 2030 under a baseline with no community universal testing and scale-up of DAA. Where **PB Test** is a testing strategy in which 95% of people are tested in prison without treatment;**PB T-Tx(A)(B)** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated while in prison; **PB T-L(A)(B)** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release; and **PB Risk** is an intervention where the elevated post-release risk is halved.

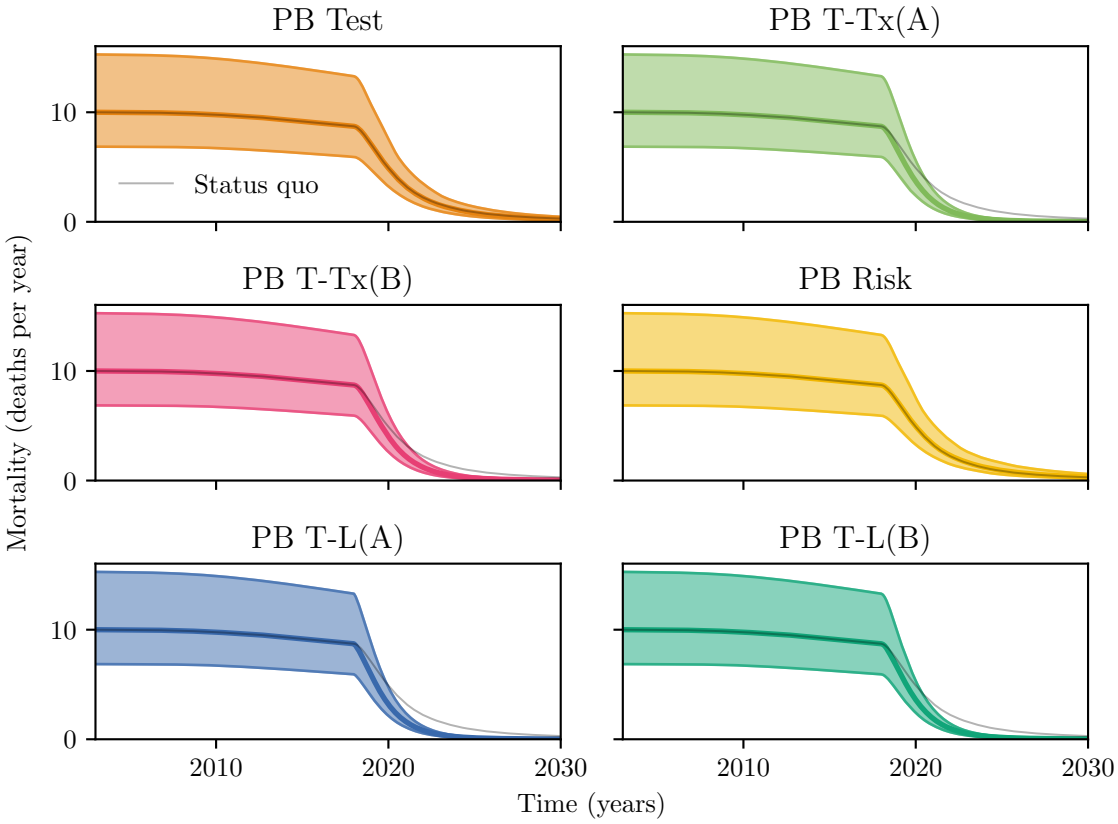


Figure E.6 – HCV mortality for all single interventions among all active PWID from 2003 to 2030 under a baseline with no community universal testing and scale-up of DAA. Where **PB Test** is a testing strategy in which 95% of people are tested in prison without treatment;**PB T-Tx(A)(B)** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated while in prison; **PB T-L(A)(B)** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release; and **PB Risk** is an intervention where the elevated post-release risk is halved.

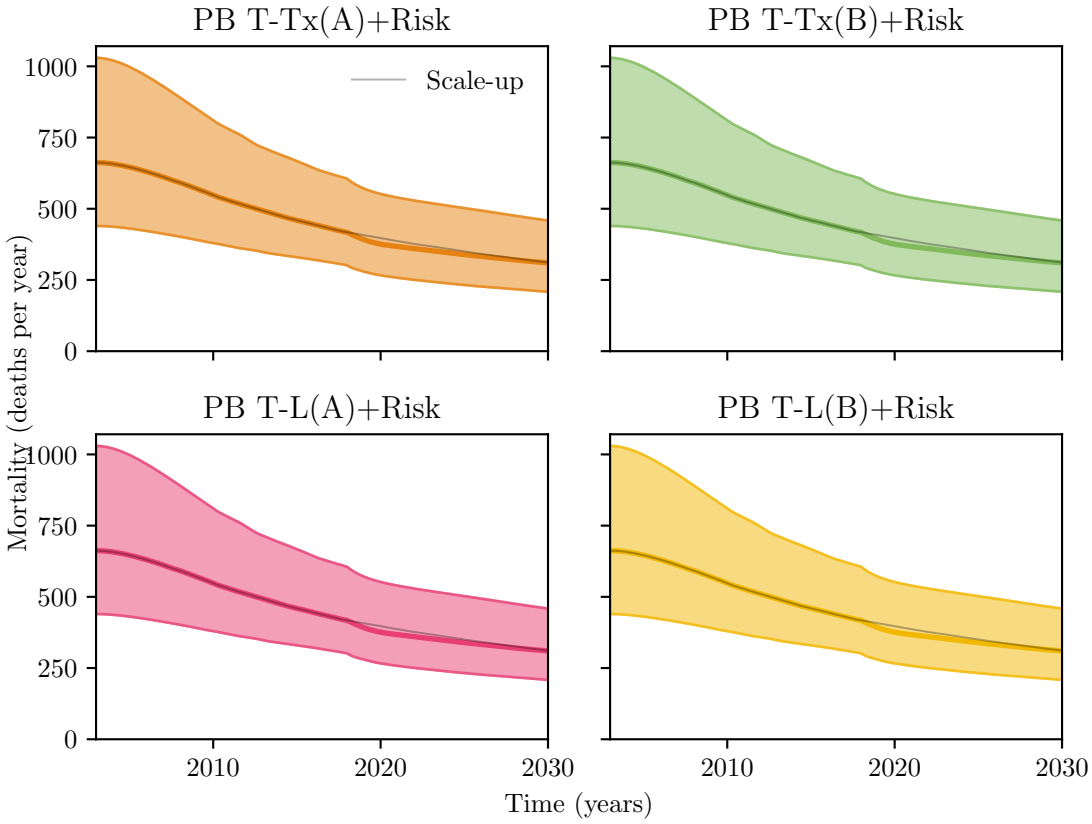


Figure E.7 – Natural mortality for combined interventions among all active PWID from 2003 to 2030 under a baseline with no community universal testing and scale-up of DAA. Where **PB T-Tx(A)(B)+Risk** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated in prison, and elevated risk post-release is halved; **PB T-L(A)(B)+Risk** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release, and the elevated post-release risk is halved.

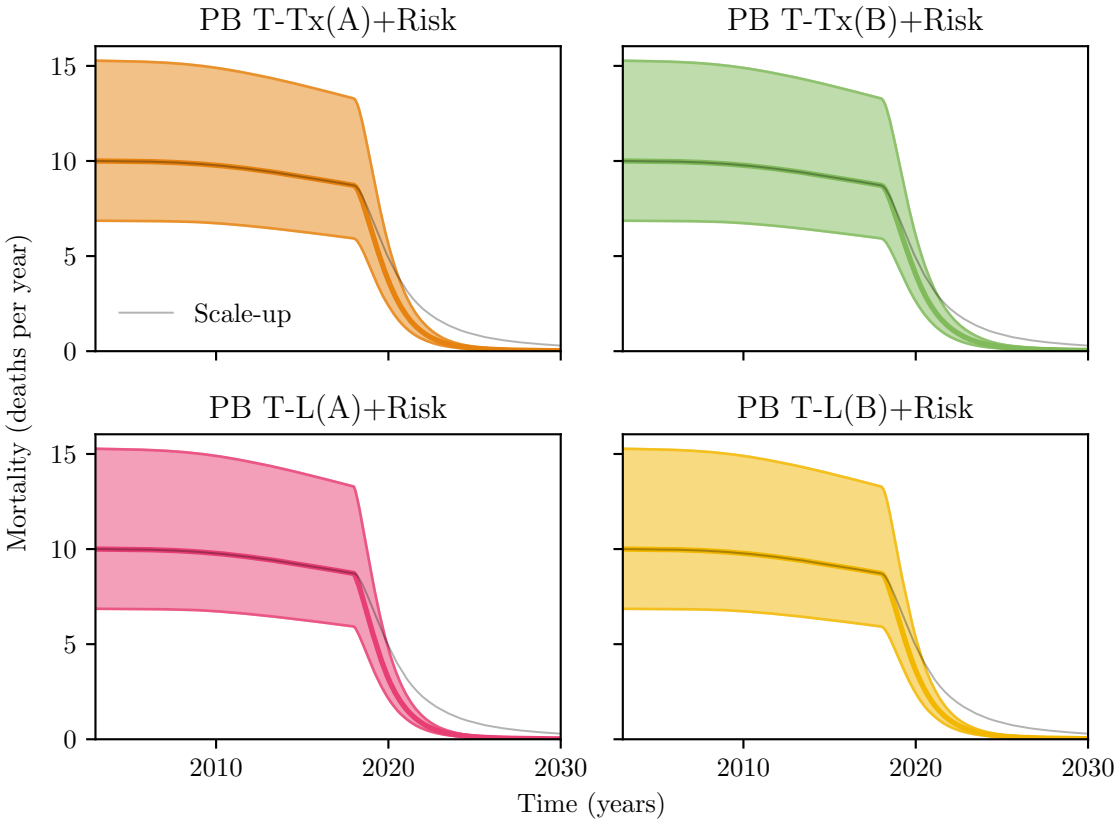


Figure E.8 – HCV mortality for combined interventions among all active PWID from 2003 to 2030 under a baseline with no community universal testing and scale-up of DAA. Where **PB T-Tx(A)(B)+Risk** are test-and-treat interventions in which 95%(90%) are tested and 100%(75%) of chronic cases are treated in prison, and elevated risk post-release is halved; **PB T-L(A)(B)+Risk** are post-release linkage to care interventions where 95%(90%) of people are tested in prison and 100%(60%) are treated upon release, and the elevated post-release risk is halved.

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