HEPATITIS C ANTIBODY AND RNA TESTS FOR ADULTS IN PROVINCIAL AND FEDERAL CORRECTIONAL FACILITIES IN ONTARIO, CANADA: A POPULATION-BASED STUDY

by

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Abstract

BACKGROUND: Prevalence of Hepatitis C virus (HCV) has been shown to be high in correctional facilities. Testing for HCV begins with a blood test for antibodies followed by an HCV ribonucleic acid (RNA) test to establish active infection. Receiving the RNA test is a required step in the cascade of care for HCV management.

PURPOSE: This thesis had two main objectives. The first was to determine an association between the facility of first testing positive for HCV antibodies and the time to receiving the RNA test. The facilities of interest were community medical facilities, provincial correctional institutions, and federal correctional institutions. The second objective sought to describe the number of duplicate antibody tests performed at Public Health Ontario Laboratories (PHOL). Once an individual tests positive for HCV antibodies, subsequent antibody tests are considered redundant.

METHODS: Both objectives used a subset of PHOL data that included all HCV tests performed at PHOL from 1999-2014. A Cox's proportional hazards model was used to determine an association between the facility of first antibody test and time to receiving the RNA test while controlling for other variables. The second objective counted the number of antibody tests performed at PHOL after an individual had demonstrated HCV positivity.

RESULTS: Individuals who first tested HCV-positive in a provincial facility took longer to receive an RNA test when compared to those first tested in the community or federal prison; females were longer to receive the test when compared to males (hazard ratio [HR]=0.43; 95% confidence interval [CI]=0.37, 0.49 provincial vs. community for females in 2009-2014; HR=0.56; 95%CI=0.51, 0.62 provincial vs. community for males in 2009-2014).

A total of 94,076 duplicate antibody tests were performed on adults who were antibody positive during the study period. This represented 51.9% of all antibody tests performed on these individuals.

CONCLUSION: The identification of an at-risk group of individuals for delayed HCV RNA testing allows for targeted interventions. The acknowledgment of duplicate antibody testing is an essential step in developing strategies to eliminate the problem of repeat testing. Both objectives provide unique pieces of the complicated puzzle of eradicating HCV.

Co-Authorship

This thesis is the written work of Chad McClintock under the supervision of both Dr. Wendy Wobeser and Dr. Paul Peng. Obtaining the dataset from Public Health Ontario Laboratories was facilitated by Dr. Wobeser and prior work on the dataset was performed by Kinsey Beck. Additional clinical consultation was provided where required by Dr. Anna Majury and Dr. Tony Mazzulli.

The statistical analyses were performed by Chad McClintock using SAS software version 9.4 (SAS Institute, Cary NC). Both Dr. Peng and Dr. Wobeser provided feedback regarding the analysis and writing process.

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List of Abbreviations

BC-HTC - British Columbia Hepatitis Testers Cohort

CSC – Correctional Service of Canada

DAA – Direct-acting antiviral

HBV – Hepatitis B Virus

HCV - Hepatitis C Virus

HIV- Human Immunodeficiency Virus

ICES - Institute for Clinical Evaluative Sciences

MCSCS - Ministry of Community Safety and Correctional Services

MOHLTC – Ministry of Health and Long-Term Care

OHIP – Ontario Health Insurance Plan

OR/aOR – Odds ratio/adjusted odds ratio

PHAC – Public Health Agency of Canada

PHOL – Public Health Ontario Laboratories

PWID – People who inject drugs

RNA – Ribonucleic acid

RR – Relative risk

SES – Socioeconomic status

WHO – World Health Organization

95%CI – 95% confidence interval

Chapter 1

Introduction

1.1 General background

Hepatitis C is classified as an infectious disease caused by HCV infecting the liver. Approximately 0.64% to 0.71% of the Canadian population are infected with HCV[1,2] and the prevalence in Ontario is an estimated 0.87%.[3] In 2017, 4,967 new cases were reported in Ontario at a rate of 33.0 per 100,000 people.[4] Around 42-45% of those infected are unaware of their infection status.[5] Among reported cases in Canada between 1991 and 2010, more than 50% were in those born between 1946 and 1965.[6] HCV prevalence has been shown to be consistently higher in penitentiary and remand facilities; one study found the prevalence of HCV infection to be 15.9% and 30.2% in men and women in remand facilities in Ontario, respectively.[7] Estimates for histories of infection as high as 24% and 28% for federal and provincial institutions, respectively, have been published.[1]

HCV is spread through blood-to-blood contact and several risk factors for HCV have been identified, with injection drug use being the most prominent. Among individuals with a history of injection drug use, estimates of chronic HCV prevalence ranges from 53-61%[3,6]. Estimates of injection drug use as high as 80% have been suggested among acute HCV cases.[3,8,9] A study by Calzavara et. al.[7] found that the prevalence of HCV among inmates in Ontario remand facilities was 54.7% if they reported injection drug use. Approximately one quarter of individuals infected with HCV will spontaneously clear the infection; a large majority of those that do not clear the virus will go on to have chronic HCV infection and the disease sequelae that may follow.[6] Approximately 50% of individuals with chronic HCV will develop liver cirrhosis.[10]

Although blood transfusions represent a risk of infection, donated blood in Canada is tested for HCV and succeeds in maintaining low levels of risk. According to Statistics Canada, the risk of HCV transmission through transfusion as a result of contaminated blood is 1 in 12.6 million donations.[5] This encouraging statistic, however, is in contrast to a well-known public health crisis in the late 1970's and 1980's where contaminated blood led to the infection of HCV in an estimated 30,000 individuals in Canada.[11] New diagnoses may still be a result of this catastrophe that has since been rectified.

The prevalence of HCV in Egypt is an astonishing 15-20% with unsafe medical practices, including poor sterilization techniques, representing a significant risk.[12] Unsafe medical procedures and contaminated transfusions are thought to be the main culprit for transmission in the developing world. In Canada, the estimated risk of transmission related to syringe reuse is 0.5-6.3 cases per one million procedures.[13] There is growing evidence to suggest that HCV rates are also higher among HIV positive-men who have sex with men with no history of injection drug use when compared to the general population.[14] Other lower-risk modes of transmission in Canada include the sharing of personal hygiene products, tattooing, and mother-to-child transmission.[15]

Recently introduced curative treatments, called direct-acting antivirals (DAAs), for HCV have proven to be highly effective; approximately 90% of those treated are cured of HCV.[16] This medical breakthrough has changed the landscape of HCV management dramatically. The first DAAs were approved in Canada in 2011.[17,18] Initiatives to identify those infected and provide therapy is imperative in the effort to eradicate HCV.

There does not appear to be any difference in terms of reinfection following treatment between those who spontaneously clear the infection and those that receive curative treatment.[19]

Studies investigating rates of reinfection are contradictory. One pooled-analysis estimate suggested low risk of reinfection among people who inject drugs (PWID): 2.4 cases per 100 person-years.[20] This is in contrast to another study that found 17% of prisoners were re-infected in a retrospective study spanning 12 years.[21]

1.1.1 HCV as a health care burden

HCV is often asymptomatic and may remain undetected for decades; however, chronic infection can lead to significant liver complications and is the predominant cause of liver cirrhosis, liver cancer, and liver transplants.[6,16] When considering health-adjusted life years (HALYs) as an outcome measure, one study found HCV to be the most burdensome infectious disease in the Ontario.[22] The results of this study showed that 90% of the 9,807 annual HALYs lost were due to years of life lost as a result of premature mortality. In addition, HCV is estimated to be responsible for 7.5% of deaths caused by infectious disease. Another study demonstrated that the 10-year survival for those infected with HCV was significantly lower than the age- and sex-matched general population; however, those who achieved sustained virologic response (absence of the virus 24 weeks after treatment) had survival outlooks similar to the general population.[23] This highlights the importance of receiving timely treatment for the infection.

HCV not only leads to unfavourable health outcomes, but it also represents a substantial financial burden to our health care system. A study by Myers et al.[24] estimated that the average lifetime health care cost for an individual with HCV infection in 2013 was $64,694 in Canada; the largest proportion of this estimate was related to costs associated with care and complications of cirrhosis. This estimate is highly variable and largely dependent on the stage of the disease. For example, an individual receiving a liver transplant may cost upwards of $325,000 over their

lifetime. Furthermore, a study by El Saandany et al.[25] used an incidence-based estimate approach to predict the impact of HCV prevention over a 40-year period of time starting in 2001. They predicted that each incident case that could be prevented results in a cost savings of $6,300. Prevention of incident cases alone over the same time period yielded a savings of approximately $14.6 million.

1.1.2 Testing for HCV

There typically exists an incubation period of approximately 6-9 weeks where HCV infection cannot be detected through testing.[26] Testing for HCV begins with a blood test to look for HCV antibodies and then, contingent on the results, further testing to determine the presence of HCV ribonucleic acid (RNA). A positive antibody result indicates that an individual has been exposed to HCV at some point; however, they may not have active infection. Depending on the RNA test conducted, viral load is used to describe the quantity of virus in the blood. If the RNA test is positive, the individual is considered to have an active infection. If the RNA test is negative, it suggests that the individual cleared the infection naturally, the individual received prior curative treatment, or the antibody test was a false positive. Once an individual tests positive for HCV antibodies, they typically test positive for life.[16] As such, when an individual is tested repeatedly for HCV antibodies once they demonstrate positivity, the subsequent tests are considered duplicates and represent redundant tests that should not have been performed. The step between testing positive for antibodies and receiving confirmatory RNA testing is essential to provide the individual with a full understanding of their personal health and allows them to make informed decisions about their well-being. Absence of this information is neglectful and disrespectful to the patient and is required to start the process of providing treatment for the individual if they indeed have an active infection.

The current recommendations for screening for HCV in Canada are risk-based and target individuals born between 1945-1970. The Public Health Agency of Canada (PHAC) recommends screening based on the following risk factors:[2,27]

- For PWID or have a history of injecting drugs
- Individuals who have received health care under circumstances where there is a lack of infection control practices
- Individuals who have received blood transfusions or organ transplants prior to 1992 in Canada
- Individuals born or who lived in countries with high HCV prevalence
- Individuals who share person care items with another individual who has HCV

Chemiluminescent microparticle immunoassay (CMIA) is the primary test used in Ontario for the antibody blood test.[28] The specificity and sensitivity of this test are consistently reported as being excellent[29], with one study demonstrating 99.6% and 99.7%, respectively.[30] Results of the test are reported to the practitioner identified on the test requisition. HCV is a notifiable infection in Ontario and a positive antibody test must be reported to the Medical Officer of Health.[28] Currently in Ontario, RNA testing is typically determined through an RNA polymerase chain reaction (PCR) test typically using the Roche Taqman HCV RNA RT-PCR Assay;[31] however, several other methods are available. These results are also reported back to the ordering physician. Although reporting results from this test are not considered mandatory, the diagnosis of HCV is notifiable. The Ontario Ministry of Health and Long-Term Care (MOHLTC) statement on reporting requirements is as follows: “Laboratory confirmed cases shall be reported to the medical officer of health by persons required to do so under the Health

Protection and Promotion Act, R.S.O. 1990."[26] Confirmation of active HCV infections requires a positive RNA test. Further details of the types of RNA tests can be seen in Appendix A.

A summary of HCV testing and infection sequelae is demonstrated in Figure 1.

1.2 Correctional facilities

A brief familiarity with the correctional system in Canada is required to understand the main objective of this thesis. Provincial institutions are for offenders who are sentenced to less than two years and federal institutions are for those sentenced for two or more years.[32] Remand is spent in provincial facilities and is reserved for those awaiting trial or sentencing and their detention is typically quite short, often less 10 than days in Ontario.[33,34] The median number of days spent in Ontario provincial institutions in 2010/2011 was 20 days.[35] In federal institutions, approximately one quarter of inmates are serving life sentences. HCV screening and testing practices vary between these types of facilities and those in the community. Since there is no provincial HCV screening program, between facility variability is inevitable. In addition, differences in the mobility and rates of returning to the community between prison populations is different. Individuals who are screened positive for HCV antibodies in a correctional facility and released back to the community with no plan for medical follow-up may present a challenge with respect to receiving necessary HCV RNA testing.

According to Statistics Canada, in 2016-2017 the average daily count for those in custody in Ontario correctional facilities was 7,799 inmates.[36] The daily count in federal institutions across Canada was 14,425 and the approximate capacity of federal inmates in Ontario is 4,707 inmates. Of those in Ontario provincial institutions, 5,254 were in remand and outnumbered those in sentenced custody. Another 43,074 individuals in Ontario were under community

supervision. This includes those on probation, conditional sentencing, parole, and long-term supervision.

Prisons are settings that contain populations with substantial health demands. Higher rates of communicable diseases, mental health conditions, and substance abuse have been reported.[34] The prison population tends to be younger, male, and more likely to identify as Aboriginal when compared to the general population.[34,37] The unmet health needs of this population is amplified by the fact that inmates are less likely to have a primary care provider in the community.[38]

A list of federal and provincial institutions in Ontario is provided in Appendix B. A map is also provided demonstrating the geographical distribution of the respective intuitions included in this study and contains information that will be referred back to in Chapter 3.

1.3 Objectives

The empirical objectives of this study are as follows:

1) To determine an association between facility of first positive antibody test and time to receiving an HCV RNA test while controlling for additional risk factors and considering appropriate interactions. Facility of first test is at either a community medical facility, provincial institution, or federal institution and is considered the primary exposure of interest.
2) To describe the number of duplicate antibody tests performed at Public Health Ontario Laboratories (PHOL) between 1999 and 2014.

1.4 Public health significance

The Canadian Treatment Action Council (CTAC), a non-governmental organization dedicated to the fight against HCV, has committed to the World Health Organization (WHO) goal of eliminating HCV by 2030.[39] This objective has been made more achievable in the past number of years with the discovery of highly effective curative treatments for HCV using DAAs.[16,39] Prohibitively high costs of treatment (between $45,000 and $100,000 CAD per patient)[40] have historically presented a barrier for many individuals to receive treatment; however, recent efforts from the pan-Canadian Pharmaceutical Alliance to reduce the cost of the medications along with avenues for coverage in Ontario, through the Ontario Drug Benefit (ODB) Program and the Trillium Drug Program, have made receiving treatment more accessible for many Ontario residents.[39,41,42] Several new drugs were added to the ODB Program as recently as February 2017.[43] These initiatives make it imperative that those infected with HCV are identified and made aware of their status; only after confirmation of active infection can treatment begin.

Access to curative treatment has the direct benefit of preventing the affliction from the devastating sequelae that may follow chronic HCV infection. While infection diagnosis and access to treatment is of considerable interest, a main objective of this study is to describe the timeliness of diagnosis; that is, where there is a delay between the positive antibody test and receiving the RNA test to confirm active inflammation. The time component has important public health implications with respect to infection transmission. Recent guidelines from the WHO recommend the "detection of HCV RNA directly following a positive HCV serological test."[44] The shorter the time to diagnosis and treatment, the less time an infected individual has to transmit infection. This is particularly relevant among those who are not equipped with

appropriate harm reduction strategies. The higher rates of needle sharing and frequency of injection drug use in correctional and remand facilities puts this group of individuals at high priority for receiving timely testing.[34,45,46]

In addition to transmission times, the longer an individual goes undiagnosed, the more likely it becomes that they are lost to follow-up and never receive a diagnosis and treatment. Transient and under-housed individuals who test positive, like those with short sentences in provincial correctional facilities, require low barrier access to health care and active follow-up intervention plans when they return to the community following their release. Some of these individuals will also have spontaneously cleared the infection and face unnecessary stigma and discrimination associated with infection.[44] It is imperative to identify individuals who are most likely to experience delays in RNA testing in an effort to target where more effective practices may be required.

With respect to objective (2), preliminary research and clinical expertise suggests that many individuals in Ontario receive multiple HCV antibody tests in their lifetime, even after they have tested positive. Given that an individual remains positive for life, any duplicate antibody testing is not just unnecessary, but a burden to the individual and represents financial and personnel costs to the health care system. Repeated and wasteful testing can be indicative of several social and health care system related issues. Although not explicitly described in the literature, the stigma surrounding those with a history of incarceration, injection drug use, and immigrants from countries with a high prevalence of HCV may be at risk of duplicate testing. The recurrent testing itself could have the negative consequence of serving to reinforce the stigmatization and isolation the individual feels themselves. From a patient care perspective, ordering physicians may lack access to complete patient histories and be unaware of HCV

antibody positivity. This speaks to inefficiencies in centralized, electronic documentation technologies and practices. Describing the frequency of duplicate testing practices is the first step in generating an understanding of the magnitude of the problem and, ultimately, towards eliminating redundancies all together.

1.5 Thesis Organization

This manuscript style thesis is in accordance with formatting as outlined by Queen's University.[47] Chapter 2 is a complete literature review related to objectives (1) and (2). The use of a conceptual model is presented to guide the review and to assist the reader in understanding the practical implications of the research. Chapter 3, manuscript 1, analyzes the time to HCV RNA testing following a positive antibody test based on the facility of first antibody test. Chapter 4, manuscript 2, describes the number of duplicate HCV antibody tests performed at PHOL during the study period. Chapter 5 is a general discussion of the implications of the study results, including study strengths, limitations, and avenues for future research. Appendices are included at the end of the thesis to provide additional information and explanation where necessary.

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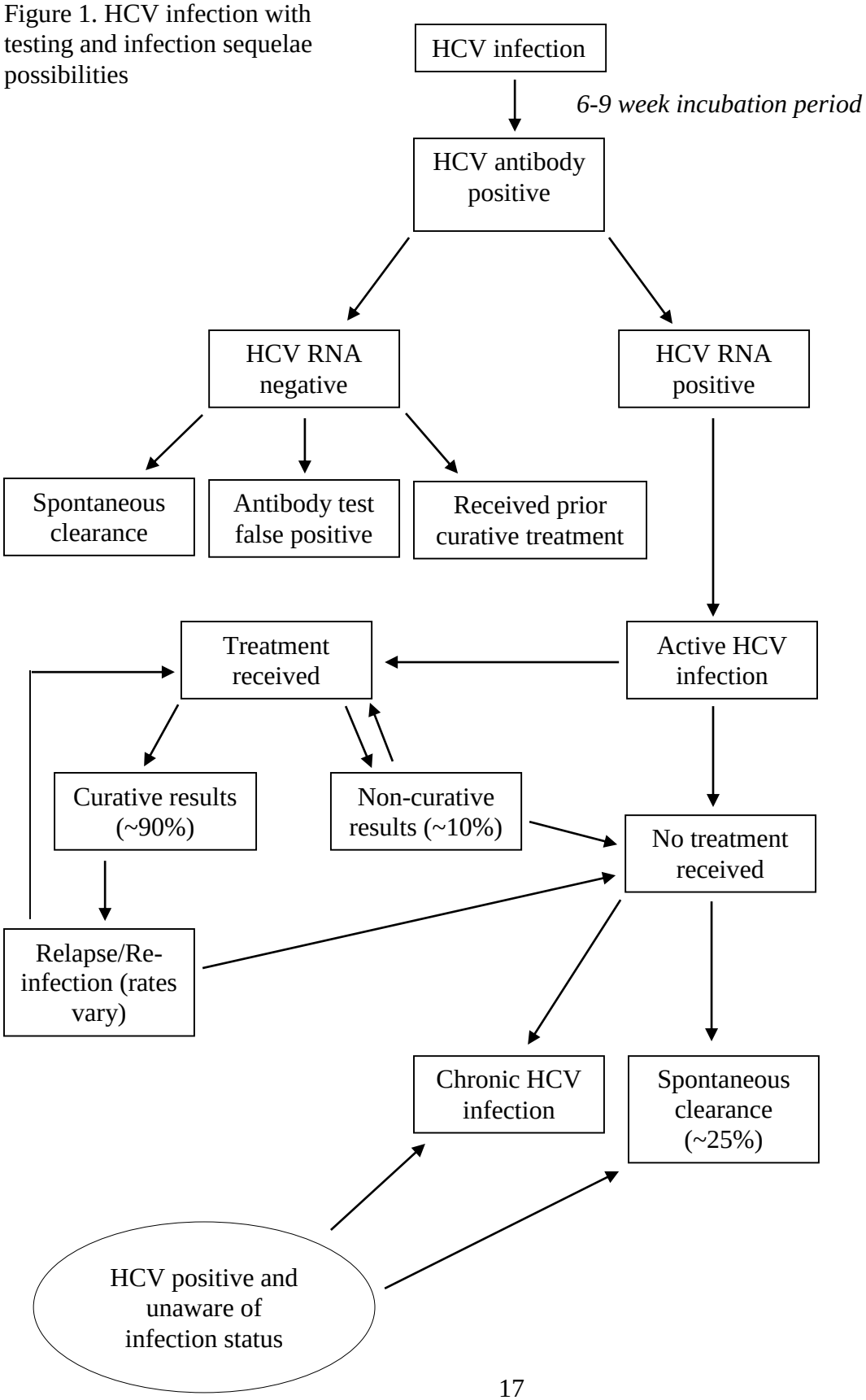
Figure 1. HCV infection with testing and infection sequelae possibilities



Chapter 2

Literature Review

2.1 Introduction

The purpose of the literature review is to provide a concrete understanding of the existing scientific evidence regarding the association between HCV testing practices and facility of first testing; more specifically, where the facility of testing involves correctional institutions. This process will aid in revealing potential confounders, effect modifiers, and mediators in the relationships under investigation. The first part of the literature review focuses on the Canadian health care system and differences that exist provincially and throughout the corrections system. The subsequent section describes factors associated with the exposure and outcome related to the first objective: time to HCV RNA testing. Lastly, research around duplicate HCV antibody testing is described and associative dynamics are discussed.

2.2 Key terms and concepts

In order to be fully tested for HCV, an individual who receives a positive antibody test must have the HCV RNA test to confirm or refute active infection. The term *complete testing* in this thesis implies that an individual has had both tests within the study period. *Incomplete testing* suggests that there is evidence of a positive antibody test, but no corresponding RNA test. Note that an RNA test is not required for patients who have tested antibody-negative.

The concept of *duplicate* HCV antibody testing also requires explanation. As mentioned briefly in Chapter 1, once an individual tests positive for HCV antibodies, there is no need for them to ever receive another antibody test. A positive test reflects exposure to HCV at some point in the past and if an individual tests positive once, they typically test positive for life. The

term *duplicate* throughout this thesis refers to any antibody test that occurs after an individual has received their first positive antibody test.

The *HCV cascade of care* is often referred to in the literature. When referring to the cascade, this thesis will be consistent with the definition provided within the British Columbia Hepatitis Testers Cohort (BC-HTC).[1] Monitoring HCV at a population level involves six stages: (1) estimating prevalence; (2) HCV antibody seropositive result; (3) HCV RNA testing received; (4) HCV genotype determined; (5) treatment initiated; and (6) viral clearance. Although this thesis focuses on steps (2) and (3), progression through the cascade is essential to reach the ultimate goal of clearing the infection.

2.3 Health care differences by facility

Before discussing the main literature as it relates to the current research questions, a review of information regarding health care provision differences between provincial institutions, federal institutions and community settings is useful for perspective. This section discusses some of these differences and provides evidence as to how the settings differ from one another.

Canada's publicly funded health care is provided by revenue raised through federal, provincial, and territorial taxation. Provincial and territorial governments provide and administer the majority of health care services to their respective province or territory. The federal government provides assistance through federal money transfers.[2] Federal legislation, under the *Canada Health Act*[3], describes conditions that the provinces and territories must meet to receive cash and tax transfers. The federal government is responsible, however, for health care provision for certain groups, including federal penitentiary inmates, First Nations peoples living on

reserves, Inuit, Canadian Forces members and veterans, and refugees who have not yet received landing status.

The *Canada Health Act* stipulates that those in provincial correctional facilities receive the same care as those living in the community; however, differences in care received seem to exist between the two types of settings.[4] Health care for individuals living in the community is under the responsibility of the Ministry of Health and Long-Term Care (MOHLTC). Health care for those in provincial institutions falls on the Ministry of Community Safety and Correctional Services (MCSCS). In Ontario, provincial regulation (under the *Ministry of Correctional Services Act*[5]) requires the Superintendent of provincial facilities to manage the health needs of their respective institution and it is unclear as to whom they are accountable to. In most circumstances, physicians are contracted to provide on-site health care under the Ontario Health Insurance Plan (OHIP).[6] This not only makes the delivery of care different in correctional facilities compared to a community setting, but between-institution variation is inevitable as well. The John Howard Society of Ontario has highlighted some of the difficulties with this structure.[4] Inmates of provincial facilities often spend very short periods of time incarcerated and are at risk of being disconnected from care upon their return to the community. This unique challenge is augmented by the fact that the MCSCS lacks the resources available to the MOHLTC to manage the demands of a population that tends to have a higher incidence of acute and chronic health conditions. One of the cited reasons for reduced resources is the facilities' struggle with hiring and retaining health care professionals.[7] An absence of electronic health records in provincial facilities inhibits health care providers from accessing necessary information from the community and linking care with external medical centers. Prisoners

released from correctional facilities also face the challenge of accessing necessary care upon re-entry to the community.[4]

Health care for federal institutions fall under the charge of the federal government as outlined under the *Corrections and Conditional Release Act*[8] and federal inmates are excluded from insurance defined in the *Canada Health Act*.[9] Accreditation is rigorous and proof of compliance with ministry standards is required every four years. Correctional Service of Canada (CSC) has the responsibility of providing "essential health care, and reasonable access to non-essential mental health care that will contribute to the inmate's rehabilitation and successful reintegration into the community."[10] CSC provides care for the inmates; if CSC is unable to deliver care, prisoners may be referred for care outside of the institution.[11] Screening for infectious diseases is offered to all prisoners on admission and on request. Upwards of 70-80% of federal inmates are screened at some point during their incarceration for HCV.[12,13] This structure creates a health care system that is different from that experienced in the community and the standard of care could vary between federal institutions.[14] While there is no formal mechanism for ensuring proper follow-up care, the reintegration of prisoners upon their release back to the community is suggested as a top priority. For example, mental health practitioners support inmates by preparing appropriate discharge plans to encourage continuity of care in the community and provide resources to link with community organizations.[15] Despite these efforts, however, there are complex sociodemographic reasons recently released individuals may experience attenuated health care in the community following their sentence when CSC is no longer responsible for their care. Many ex-convicts experience discrimination based on their criminal record and it may be difficult for them to find a physician who will accept them into their practice.[16]

In terms of accessing care while in prison, the Canadian Journal of Public Health conducted a review to provide a health needs assessment of federal inmates.[17] One of the factors described in the article is the utilization of health services by offenders compared to the Canadian population. The authors discovered that federal prisoners had a higher frequency of visits to family physicians, medical specialists, and nurses while incarcerated compared to the general population. The results need to be interpreted with caution, however. The visit numbers were based on mean number of visits and may have been inflated by a few inmates with high frequencies of medical visits.[17,18] In terms of the current thesis research question, federal inmates may have greater opportunity for HCV testing during their sentence; this circumstance is inevitably different from the experience of those in the community and provincial institutions.

A recent retrospective cohort study sought to describe primary care utilization among those who spent time in a provincial prison. Kouyoumdjian et al.[6] compared the number of visits to a general practitioner or family physician during sentencing and in the months following release from prison to visits seen in the general population. They included all persons released from a provincial institution in Ontario in 2010 and then age- and sex-matched cases with controls from the general population. Data was accessed through the Institute for Clinical Evaluative Sciences (ICES). This allowed for the linkage of data with an encoded OHIP number to obtain more information about the subjects. Individuals transferred to a federal institution or who left for reasons related to immigration were excluded from the analysis. Variables available for analysis included income quantile, rurality indicators, comorbidities (including HIV infection), age, race, and sex. Right censoring occurring with death, loss of OHIP eligibility, re-admission to prison, or 2 years after release. Primary care utilization was observed during the prison sentence and in the 2 years following release. Controlling for rurality and income, the rate

of primary care utilization was significantly higher in those who spent time in prison during their stay and in the months following release when compared to the general population. This effect remained after adjusting for comorbidities. For example, the rate ratio of primary care visits was 6.1 (95%CI=5.9, 6.2) while in prison and 2.5 (95%CI=2.4, 2.6) in the 90-179 days following release when comparing the prison-release group to the general population. The authors suggested these results could reflect an increase in comorbidity burden, acute illnesses, and a low threshold of seeking primary care while in prison. Despite these findings, only a small proportion of the prison-release individuals actually accessed primary care in the first few months following release. The authors highlighted that this may be a problem given the elevated morbidity identified in this group of individuals. Limitations of the study include the fact that the reasons for visits were not available. Visits while in prison may represent administrative assessments that were required by the ministry. These results are contradictory to the notion that individuals who spend time in a provincial institution are disconnected from care upon release.

Kouyoumdjian et al.[19] performed a similar study using the same dataset comparing medical visits based on ambulatory care visits, emergency department visits, psychiatric hospitalizations, and medical-surgical hospitalizations during sentencing and in the months following release. Again, this was compared to an age- and sex-matched general population. Health service utilization was observed during the sentence and in the 3 months following release. Controlling for rurality and income, the rate of health care utilization was significantly higher in those who spent time in prison during their stay and in the 3 months following release when compared to the general population. As an example, the rate ratio of emergency department visits for those in prison compared to the general population was 3.5 (95% CI=3.3, 3.7). Interestingly, among individuals who spent some time in prison, visits to the emergency

department and hospitalizations increased after their release compared to during their time spent in prison. The authors suggest this result could reflect a worsening of health status due to changes in behaviours, lack of housing, or poor access to primary care on release. Limitations of the study include the fact that the reasons for visits were often not available, court-ordered treatments could not be identified, comorbid diagnoses may have been inaccurate, and First Nations individuals were not identified.

2.4 HCV testing

This section discusses the various topics and relevant literature as it relates to HCV antibody and RNA testing and factors associated with each. A conceptual model summarizing the association between facility of first antibody test and time to HCV RNA testing can be seen in Figure 1 at the end of this chapter.

2.4.1 Incomplete testing

Several studies have attempted to identify factors that are associated with an increased risk of incomplete testing for HCV. This subject knowledge is relevant for this thesis since factors associated with incomplete testing present potential covariates in the time to RNA testing analysis. The majority of the evidence does not include a time component; however, factors associated with incomplete testing may also be related to longer follow-up times in the current thesis.

The BC-HTC includes 1.5 million individuals who were tested for various infectious diseases in BC from 1990 to 2013.[20] Janjua et al.[1] analyzed this data in an attempt to explain the HCV cascade of care in the province. The data used was from a centralized public health laboratory dataset and included all individuals in BC tested for HCV between 1990 and 2013.

They discovered that 74.1% of diagnosed HCV cases demonstrated at least one HCV RNA test in the dataset. Males compared to females were at greater odds of experiencing incomplete testing (aOR=1.23; 95% CI=1.18, 1.28). Older individuals were increasingly likely to be missing the RNA test, with those born <1945 being the most likely to not have had the test compared to those born ≥1975 (aOR 1.88; 95% CI=1.70, 2.07). With respect to comorbidities, those with HIV coinfection or those diagnosed with a mental illness were more likely to receive HCV RNA testing (aOR=0.63; 95% CI=0.57, 0.69 and aOR=0.70; 95% CI=0.67, 0.73, respectively). This is in contrast to those with HBV coinfection or a history of illicit drug use who were more likely to have no evidence of RNA testing (aOR=1.67; 95% CI=1.52, 1.83 and aOR=1.08; 95% CI=1.03, 1.13, respectively). While this study lacks data regarding individuals with a history of incarceration or location of screening, it does indicate several factors that seem to be associated with incomplete HCV testing. Interestingly, different comorbidities may have differing effects on whether or not an individual receives the HCV RNA test.

A study by McGibbon et al.[21] looked at whether or not health care practitioners in New York, USA were ordering HCV RNA tests for their patients that were antibody-positive. The researchers sampled individuals in a New York City HCV surveillance system who had their first positive antibody result in the system. The process involved randomly sampling subjects from a database (using a random procedure in SAS) every 2-3 months starting July 1, 2009. They found that of the 245 antibody-positive subjects sampled, 33% of them did not receive the necessary RNA test to confirm active inflammation. Of the 81 subjects not sent for follow-up testing, 14.8% were initially tested in prison and 29.6% had their positive antibody test conducted in a drug or alcohol rehabilitation facility. Clinicians were asked through a questionnaire reasons why those patients did not receive appropriate follow-up tests: 34.6% of the patients did not return for

follow-up, 22.2% were seen in facilities that did not do HCV RNA testing and may have been referred elsewhere, and the fact that some of the patients were tested in prison. A strength of this study includes the random sampling method used in an attempt to obtain a representative sample of the state of New York. The researchers also had access to the patient charts and contact with the referring physician for follow-up questions. A limitation of the study is attributed to the fact that negative RNA tests are not notifiable in New York and negative tests may not have been captured in the dataset. This highlights one of the advantages of using laboratory data for analysis. The authors indicate this is likely rare since they had contact with all clinicians involved in the patient's circle of care to search for missing test results. Another limitation, not noted by the authors, is the absence of statistical significance or confidence intervals in their results to discuss the magnitude of effect. Lastly, the short follow-up time of 2 years may have led to an overestimation of those who never had RNA testing; some of these patients may have been tested given enough follow-up time.

A study by Rongey and colleagues[22] looked at patients from a network of Veterans Affairs treatment facilities in the United States and found that 24% of those who tested antibody-positive did not receive RNA testing. They found that patients who had decompensated liver functioning (RR=1.14; 95% CI=1.1, 1.2), other viral hepatitis infections (RR=1.04; 95% CI=1.0, 1.07), or elevated liver enzyme activities (RR=1.08; 95% CI=1.05, 1.1) were statistically significantly more likely to receive follow-up testing. This finding supports the notion that certain comorbidities may increase the opportunity for RNA follow-up due to the fact that these populations are already being followed for other medical reasons. Patients who were over the age of 65 (RR=0.89; 95% CI=0.8, 0.99) or used illicit drugs (RR=0.98; 95% CI=0.96, 0.99) were less likely to have RNA testing. In addition, they found that patients being tested in facilities that

incorporated routine HCV RNA testing procedures were 1.5 (95% CI=1.48, 1.52) times more likely to be tested for RNA after a positive antibody test. The 5-year study period, however, may have missed a number of RNA tests for analysis, especially where individuals were tested for antibodies towards the end of the study. A sensitivity analysis that excluded those individuals first demonstrating antibody positivity toward the end of the study period would have been useful.

A cohort study by Moorman et al.[23] analyzed the electronic health records of over 1.6 million individuals sampled across various health centers in the United States between 2006 and 2008. Although the primary purpose of the study was to describe baseline characteristics of those infected with HCV, they found that 37.7% of those who tested antibody-positive had no evidence of RNA testing follow-up in the database up until 2010. The two-year gap between end of the sampling period and the end of the study period allowed for a buffer such that those included at the end of the sampling period had ample time to be tested for HCV RNA and show up in the database. A limitation of this study as it relates to the current thesis was that institutionalized individuals were underrepresented.

A highly relevant study by Spradling et al.[24] looked at the trends in HCV RNA testing across 4 different organizations in the United States. Of interest was to determine the number of adults (age≥18 years) who received an HCV RNA test within 6 months of having a positive antibody test; the positive antibody test date was considered the index date. The study period was from 2003-2011 and subjects who were first tested in 2011 were excluded to allow sufficient follow-up time. They found that 60.9% of those who tested positive for HCV antibodies had an RNA test performed during the study period. Additionally, 80% of those who actually received the procedure had their test performed within 6 months of the positive antibody result. A

significant trend (P<0.001, trend) showed that the percentage of those receiving an RNA test within 6 months of a positive antibody test was improving over the study period. The covariate for calendar year was considered as the year in which the antibody test was conducted. They identified several covariates that were significantly associated with having the RNA test performed within 6 months of the antibody result: age, sex, and income (using a census track geocode). Compared with subjects born after 1965, those born between 1945-1954 and 1955-1965 were less likely to receive HCV RNA testing within 6 months of positive screening (OR=0.69; 95% CI=0.51, 0.94 and OR=0.76; 95% CI=0.58, 0.99, respectively). Females were more likely than males to have the RNA test within 6 months (OR=1.33; 95% CI=1.06, 1.66). Compared to individuals with a lower annual income (<$30,000), those with higher incomes were more likely to receive the test within 6 months. The largest effect was found in those earning $75,000 or more (OR=2.68; 95% CI=1.44, 4.97). It should be pointed out that the authors were unable to determine if the income effect was related to insurance coverage, which is an important consideration with respect to access to health care in the United States. A limitation to the study noted by the authors is that they only had data from 4 centers; if the subjects had testing done elsewhere, they would not have been identified in the dataset and misclassified as not having had the RNA test. In addition, it was impossible to determine instances where the tests were ordered but not performed. This could have been due to non-adherence to physician recommendation or a lack of awareness of screening implications.[25] An advantage of this study as it relates to the current thesis is the incorporation of an element of time to follow-up; that is, within 6 months of screening.

In a study funded by the Centers for Disease Control and Prevention (CDC), 104 HCV testing sites were recruited with the primary purpose of determining birth-cohort patterns of

undiagnosed HCV, testing practices, and linkage to care.[26] Previously undiagnosed individuals born between 1945 and 1965 were tested for HCV antibodies; the researchers followed these individuals forward to describe their care. The study period ran between October 2012 and June 2014 and included a 90-day additional monitoring period after June 2014 to allow time for supplementary follow-up information. 2,900 (11.6%) of these subjects tested positive, demonstrating a substantial number of individuals who were unaware of their exposure to HCV. Of those who tested positive, 72.7% received an HCV RNA test within the study period; 51.6% of these individuals received their RNA test on the same day as their positive antibody result. Interestingly, the proportion of complete testing was 89.9% and 90.3% in those with a history of injection drug use and those who injected drugs within the preceding 12 months, respectively. As with previously mentioned studies, there may have been subjects who received RNA tests outside of the designated testing facilities.

An HCV surveillance study in Philadelphia, Pennsylvania looked to assess the cascade of HCV care in the city using electronic laboratory test results.[27] The researchers were able to link the data to state death certificates to exclude those who died during the study period of January 2010 to December 2013. Of those who were antibody positive, only 47% showed evidence of RNA testing in the database; however, negative RNA tests results were not reported in this dataset and a follow-up period outside of the inclusion dates was not included. This represents a fracturing of care and record keeping as all relevant health information ought to be available. Underreporting of positive results was considered unlikely. Young, Caucasian males were particularly unlikely to receive confirmatory testing. The mean time between antibody testing and RNA confirmation was 51 days. The authors compared mean time to RNA testing in dates before and after national testing recommendations for those born between 1945-1965 were put in

place. The mean time from screening to RNA testing prior to the recommendation was 81 days and after the guidelines were announced it dropped to 15 days ($p<0.00001$). While this is a promising finding, it is not certain that the recommendations had a causal effect. Although the mean time diminished, the proportion of individuals with confirmatory RNA tests pre- and post-recommendations was not statistically significant.

In an initiative to improve HCV continuum-of-care practices, the Cherokee Nation Health Services implemented a strategy where a reminder to clinicians for clinical decision making and HCV education was placed in the electronic health records of individuals from the Cherokee Nation.[28] This practice led to an increase in HCV antibody testing from previous years; however, 31.7% of antibody-positive individuals remained untested for HCV RNA. Although these findings are not generalizable to all populations, the results highlight the struggle in improving on the proportion of individuals who experience complete HCV testing practices and the need to develop effective care integration strategies.

An unusually high proportion of complete testing practices was found in a national database for the Veterans Health Administration (VHA) in the US between 1999 and 2013.[29] The authors discovered that 95.8% of those who were antibody-positive had follow-up RNA tests. According to the study, the VHA outperforms the rest of the country in the initial steps of the HCV cascade of care. Reasons for this discrepancy may be related to follow-up and treatment differences in the patient population or more efficient, centralized electronic documentation technologies. Although the results in the study are not generalizable, it offers optimism in achieving extremely high levels of complete testing procedures.

Rates of incomplete testing in studies outside of North America reveal similar results. An Australian study, based on surveillance data from the state of Victoria, suggested that 58.2%

(95% CI=42.2%, 72.4%) of antibody-positive individuals did not receive an HCV RNA test between 2001 and 2012 and young males were particularly unlikely to have complete testing.[30] Another Australian-based study by Iversen and colleagues[31] assessed the HCV cascade of care using cross-sectional data obtained from a survey conducted at 47 Needle and Syringe Programs across the country. Among PWID and were antibody-positive, 46% reported having an HCV RNA test completed at some point in their lives. They found that those who had some type of HCV testing within the preceding 12 months were more likely to have had an RNA confirmatory test (aOR 2.00; 95% CI=1.31, 3.06). The subject's reports were not confirmed through medical records and are subject to recall error and bias.

Several of the studies mentioned in this section took place in the United States and RNA testing practices are likely to be quite different in Ontario, Canada. This is especially probable given our much different health care systems; however, there are still issues with access to care in a public health care system and similar trends seem logical. There are no studies to date that have used survival analysis to investigate time to RNA testing following a positive antibody test in Ontario based on differences between federal, provincial, and community facilities.

2.4.2 Factors associated with testing facility

In order to build upon the subject knowledge required to describe potential confounders, mediators, and effect modifiers in this association, specific factors related to the exposure are explored in this section. Individuals in the PHOL dataset who were tested in a correctional facility were indeed incarcerated at some point; there is no need to suspect misclassification in this instance. Given this fact, it is relevant to explore elements that are associated with being incarcerated as a way to determine factors related to being tested in a correctional facility.

A recent report from Statistic Canada highlighted the disproportionate number of males, young adults, and Aboriginal adults in Canadian correctional facilities in 2015-2016.[32] Females represented 16% of adults admitted to provincial and territorial corrections; 14% of remand admissions and 11% of sentenced custody at the provincial or territorial level were women. Federally, 8% of admissions to sentenced custody, respectively, were females. In Ontario, 15% of the total individuals under correctional supervision were females. Custodial admissions to provincial and territorial services were largely under 35 years old, at 58% of the total. In the federal system, 52% were under the age of 35. Aboriginals were overrepresented in prison and, in other reports, approximately one third of women sentenced identified as an Aboriginal person.[33,34] In Ontario, 12% of those under correctional supervision were Aboriginal despite the fact that approximately 2.8% of the population in Ontario identify as either First Nations, Métis, or Inuit.[35,36] In terms of entry into the corrections system, 53% of initial entries in Ontario were through remand.[32] Initial entry represents an individual's first contact with the corrections system during a period of correctional supervision. This is a relevant statistic when considering the type of correctional facility and its association with first antibody testing; this may be the first opportunity for many inmates to be tested for HCV outside of the community. In addition, on any given day, approximately 47% of the total population under correctional supervision were in a remand facility.[32]

Kouyoumdjian et at.[13] described the health status and social determinants of health for those in correctional facilities in Canada in a recent narrative review. In corroboration with the statistics mentioned previously, those younger than 35 years represented more than half of those sentenced compared to less than 33% of the Canadian population. They also highlighted the disproportionate number of males and Aboriginal individuals who were in custody. A significant

number of individuals reported a history of family violence; parental absenteeism; poverty; alcohol abuse; and at least 50% reported childhood emotional, physical, and sexual abuse. 10% of individuals reported a history of injection drug use prior to admission. The socioeconomic status (SES) of the incarcerated population was low and rates of homelessness was much higher than the general population. High rates of unemployment prior to admission have been reported.[17,37] More than half of those admitted to federal custody in 2011 did not have a high school diploma. Those in prison were much more likely to have been diagnosed with a mental health disorder. For example, 4 out of 5 youth in corrections in BC and Ontario met clinical criteria for at least one disorder compared to 30.6% of Ontarians from a community sample.

Simply being in a federal corrections facility may increase an individual's likelihood of being tested for HCV antibodies. Studies have suggested that more than 70% of individuals are screened at some point for HCV during their sentence[13] and all inmates are offered screening upon entry.[38,39] One survey from CSC found that 67% of women and 52% of men were screened for HCV at admission. Testing at admission was seen to be higher for non-Aboriginal self-identification.[12] The same survey found that 83% of women reported being tested at some point during their sentence compared to 74% of men. The report explains that those who had recent negative test results in the community and lacked high risk behaviours may avoid HCV screening. Systematic screening is not being conducted in Ontario provincial prisons[40] and is thought to occur less frequently in these facilities.[13]

Injection drug use is demonstrably higher in correctional facilities when compared to the general population. Many inmates report using injection drugs both prior to and during admission.[12,13,36,41] One CSC survey found that 70% of federal inmates indicated some sort of substance abuse history, with 34% admitting to injection drug use prior to incarceration.[37] In

addition, the use of injection drugs is highly associated with transmitting HCV and may be one of the factors that explains why the prevalence of HCV is higher in corrections facilities.[42,43] The current recommendation in Canada is to screen those who are at elevated risk for HCV.[44] The Canadian Task Force of Preventative Health Care has identified both a history of injection drug use and time spent in a correctional facility as separate criterion that would warrant ordering an antibody test. The very fact that an inmate has a history of injection drug use (or is assumed to have used injection drugs at some point) may make it more likely that they are to experience antibody testing in the prison; in many cases, this may be the facility of their first antibody test.

As mentioned previously, a number of health conditions and comorbidities are elevated in the prison population. Of particular interest is those who are co-infected with HIV, another blood-borne disease that shares many of the same risk factors as HCV. An estimated 20-30% of Canadians infected with HIV are also infected with HCV[45] and both viruses are more prevalent in correctional institutions. One study found that 1.8% and 2.1% of women and men, respectively, in Ontario remand facilities were infected with HIV; this is in contrast to 0.2% of the Canadian population.[46] Risk guidelines for HCV screening have included a diagnosis of HIV.[44] Those who are HIV positive are more likely to be screened for HCV and the overrepresentation of HIV in prisons may increase the likelihood that an individual is first tested in a correctional facility.

To complicate matters with respect to HIV co-infection, some individuals who are immunocompromised may not produce HCV antibodies and a false negative may result;[45] however, this is quite rare. Some researchers and clinicians recommend considering direct HCV RNA testing under these circumstances.[47] Although this factor is unlikely to have a major impact on the total number of positive antibody tests, it could make those who are HIV positive and

immunocompromised slightly less likely to receive an antibody test in the first place, regardless of testing facility.

Green and colleagues[48] conducted a survey of inmates in a single provincial facility in Ontario regarding access to primary health care and health status. The survey revealed that 32.2% (95% CI=23.0%, 40.8%) of respondents did not have access to primary care or a family doctor in the 12 months preceding admission to custody. This is in sharp contrast to the most recent numbers from Statistics Canada that suggest that 9.7% of Ontarians are without a primary care provider, with males being less likely than females to have access to regular care.[49] The authors described how reduced access to care leads this marginalized group to visit the emergency department more often and have elevated amounts of unmet health needs compared to the general population.[48] In some instances, being incarcerated may present the opportunity for some individuals to receive health care. Notable limitations of this study were that the results were not necessarily generalizable to all provincial facilities and the survey involved written responses; those with high literacy may have been overrepresented and literacy is likely to be associated with improved access to care. This limitation implies that the proportion of those in the prison without a primary care provider may have been even greater than the numbers estimated in the study.

Stigma plays a complicated role in terms of exposure. At the level of the individual, there may be a disincentive to receive screening. For example, reports have suggested that inmates feel rejected by fellow prisoners following a positive test for HIV.[50] The stigmatization following HCV diagnosis has been suggested to contribute to social isolation, deterioration of relationships, and perceived blame.[51] A frequent concern in discussions related to systematic screening is the notion of stigma.[44] Stigma is present in community and correctional settings; both situations will

have individuals preferring to avoid a diagnosis.[52] Stigma and stereotyping are likely to affect health care providers as well. In a correctional setting, the stereotypes attached to the prison population with high rates of injection drug use and HCV infection may augment the number of screening tests where the health care provider persuades the inmate to receive the test. Again, this may lead to an increased number of individuals being first tested in a provincial or federal institution.

The Public Health Agency of Canada (PHAC) released a report in 2017 describing trends in positive HCV antibody tests between 2005 and 2014.[53] Using the Canadian Notifiable Disease Surveillance System (CNDSS), the report provides a descriptive analysis of positive tests by age, province/territory, sex, and year of diagnosis. In corroboration with previously described findings, males tended to have higher rates of positivity than females and the most at-risk age group were individuals between 20 and 59 years old. The researchers described the trends of reported cases and found an overall decrease in cases over the last decade;[53,54] an absolute decrease in cases was also seen for both males and females separately. The decrease was found to be larger in males and, since prevalence is higher in males, sex differences have started to narrow. Several age groups, however, experienced an increase in rates of positivity, including males aged 20-24 and over 60 years and females aged 15-19. The authors attribute the overall decrease in rates to advances in blood donation screening, infection control practices in health centers, and public health initiatives. While the results of this study have limitations with respect to estimating HCV positivity, the information is pertinent to this thesis as it discusses positive antibody reports. Estimations of antibody positivity need to consider the fact that Canada does not perform population-based screening.

In terms of trends over time, there are inevitably differences in screening practices over the years between community facilities, federal institutions, and provincial institutions. This is especially true given the fact that the responsibility for the provision of health care falls to different branches of government depending on the service facility type.[4,55] In addition, evidence from CSC reports indicate that testing for HCV has increased over time in federal institutions.[56] Provincial facilities are not expected mirror the changes over calendar years experienced in federal facilities.

2.4.3 Factors associated with access to HCV RNA testing

This section focuses on variables that may be associated with receiving testing for HCV RNA. Much of the focus is on access to health care services.

There is reason to suspect that there could be significant differences in the time to first RNA test on the basis of the primary exposure, the facility of first positive antibody testing. As illustrated previously, the organizational differences that exist between the three testing facility classifications of interest are likely to introduce variability in health care received and could influence follow-up. Of particular interest is the fact that federal inmates may access health care services more compared to the general population.[17] This is pertinent when considering the probability of not only receiving the RNA test, but also receiving it in a timely fashion. With higher frequencies of exposure to health care professionals who are cognizant of the inmate's health needs, an argument could be made that they are likely to receive the confirmatory test faster than those first tested in the community or a provincial institution.

The opposite situation may be apparent in the those tested in provincial facilities in terms of the cascade of care. Where these individuals are tested initially in prison, their short length of stay could have a tremendous impact on determining whether or not they receive an RNA test

within an appropriate timeframe. Based on data from 2015 and 2016, a report from Statistics Canada described the length of time spent in custody for remand and provincial institutions in Canada. Just over half of adults released from remand spent one week or less and 76% stayed for one month or less in custody. In provincial and territorial institutions, approximately 30% were held for one week or less and 59% spent one month or less in prison.[32] Ontario lengths of stay show similar patterns to these national numbers. From 2010 to 2011, the median number of days spent in Ontario remand and provincial facilities was approximately 7 days and 20 days, respectively.[4,57] As previously demonstrated, these individuals are less likely to have a family doctor before even entering the corrections system.[48] If these individuals test positive for HCV antibodies and do not receive the follow-up RNA test while in custody or have well established avenues for accessing care upon their release, they may be more likely to demonstrate a delay in the time to their first confirmatory RNA test and be lost to follow-up.

For individuals first tested in the community, there are a number of factors that might have an effect on time to RNA test. If an individual is first tested in the community during a physician visit or at a clinic for HCV, we might deduce that they have some degree of access to care to begin with; otherwise, they would not have received the antibody test in the first place. Some community dwellers, however, may first be tested upon hospitalization for something unrelated and may lack a family practitioner. A report from Statistics Canada in 2016 revealed that younger males (aged 18 to 34) are the most unlikely and those over the age of 65 are the most likely to have a family doctor.[49] The data showed that 19.9% and 11.9% of males and females, respectively, in Canada did not have a regular care provider. Ontario has a lower proportion of individuals without access to primary care at 9.7%. A functional follow-up

program is required to establish linkage to care for RNA testing in those individuals who do not have a primary care provider in the community.

Those living remotely are often underserviced in terms of accessing appropriate health care.[58] There exists the possibility that those who live rurally will experience greater barriers to receiving complete HCV testing. This may be especially true for inmates who have been released after serving their sentence and return to a remote community with limited health resources; short-stay offenders, like those in provincial and remand facilities, may be at the highest risk. Living in a rural or urban area may not, however, have an impact on federal inmates. With sentences being 2 years or longer, their greatest opportunity for testing may be within the prison; their address outside of the facility would be irrelevant when determining any association between residential address and time to RNA testing if they remained in the institution for the duration of the study period.

Even with a family doctor, adherence to medical advice is essential to proceed through the cascade of care, regardless of first testing facility. Non-adherence can take several forms and is influenced by a variety of factors. Recommendations provided by a practitioner with respect to necessary follow-up or treatment for a particular condition can be misunderstood by the patient, forgotten, ignored, or the patient may take the wrong steps to completing the advised measures.[59] If a patient has an illness but is asymptomatic, they may be less likely to follow medical advice as they feel they may not have the disease or there is no incentive to receive care or, in the case of HCV, further testing.[60]

Education and literacy, especially health literacy, are thought to play an integral part in patient adherence. Patients must be able to understand the recommendations given to them and appreciate the repercussions in failing to comply. Non-adherence has been shown to be high

among individuals who cannot read basic written instructions.[59] This effect is compounded when patients are given a large amount of information they not only misunderstand, but feel overwhelmed by; these situations make it more likely they will forget or neglect much of the information they receive.[61] One cross-sectional study in the US found that among some 2500 patients in two public hospital facilities, 60% of individuals were unable to understand a typical consent form and 25% misinterpreted when their next appointment was planned.[62] In the Canadian context, an estimated 47% of Ontarians are defined as having "inadequate literacy" as defined by the Programme for the International Assessment of Adult Competencies.[63,64] When looking at individual groups in Ontario, approximately 61% of established immigrants and 52% of Aboriginals are inadequately literate. A particularly at-risk group are those in the corrections system. Offenders are three times more likely to have literacy challenges when compared to the general Canadian population.[65] Poor literacy presents a unique challenge for health care providers to ensure that their patients are following through the cascade of care for HCV testing. Those with literacy limitations may be more likely to experience a delay in RNA testing; they may have in fact been referred by their care providers but failed to follow through with the instructions.

Related to education, knowledge and awareness of HCV is thought to promote engagement in health care and encouragement of treatment seeking. Using results originating from several cohort studies in Vancouver, BC, Mah et al.[66] sought to determine an association between HCV knowledge and willingness to participate in treatment among those who had a history of injection drug use. They found several factors to be statistically significantly associated with increased HCV knowledge: Caucasian ancestry, being employed, and a history of being diagnosed with a mental health condition. Residence in a specific downtown area with

high densities of poverty and drug use was associated with significantly lower knowledge of HCV. Living in this particularly disadvantaged neighborhood was also associated with a decreased willingness to start HCV treatment. The authors discussed the notion that the combination of these factors indicate complex SES barriers to disease knowledge and, in turn, treatment. These variables could also be related to delayed time to RNA testing.

Social factors related to therapeutic relationships affect adherence. Patients who develop a positive rapport with their primary care provider are more likely to adhere to their advice.[59,67] Good communication and the encouragement of active involvement on behalf of the patient are elements that seem to improve adherence and patients who place trust in their provider tend to adhere more often.[68] One study found that men who were HIV positive were more likely to adhere to secondary prevention strategies if they had a quality relationship with their care provider (OR=2.5; 95% CI=1.58, 4.04).[69] With respect to HCV RNA testing, therapeutic relationships would of course only affect those with a regular care provider; those with a constructive patient-provider relationship may be more likely to adhere to a referral for the RNA test and demonstrate shorter follow-up times.

A complex area related to adherence that cannot be understated is individual attitudes and personalities. There is an abundance of intrinsic personal characteristics that could influence whether a patient even intends on following through with health recommendations; some of these traits can be quite intangible while others can be described. A systematic review attempted to summarize attitudes that seemed to be associated with better adherence. Two of these included whether a patient believes the disease could cause significant health complications and if they were convinced that therapy would be effective.[70] Personality traits, like *conscientiousness*, have also been found to be associated with adherence.[71] In the opposite direction, misconceptions,

flawed beliefs, and low motivation could augment poor adherence behaviours. For example, if a patient believes that HCV treatment is ineffective or that they will not be able to access treatment regardless of their diagnosis, they may choose to opt out of the RNA test step.

Inconsistent results regarding the relationship between ethnicity, gender, and age with medical adherence make it difficult to ascertain the direction of these associations. According to a review by Jin et al.[70], studies looking at the effect of ethnicity have been criticized as being confounded by SES and language barriers. Some studies found that females were more likely to be adherent while other studies found no gender effect. While most studies found an increase in adherence with increasing age, especially among the elderly, other studies came to contradictory conclusions. At the moment, there is no effective way of determining who will adhere to medical advice in terms of individual characteristics.

Comorbidities may also play an integral role in patient adherence. One of the strongest identified associations is between depression and non-adherence. A meta-analysis conducted by DiMatteo et al.[72] sought to describe the effect of depression on adherence. Articles were included if they measured adherence to medical prescriptions and treatments, exercise, diet, screening, vaccination, and appointments. They calculated a standardized odds ratio of 3.03 (95%CI=1.96, 4.89) of depressed compared to non-depressed individuals and non-adherence. The authors suggest that depression could reduce adherence through feelings of hopelessness, social isolation, and memory impairments. Caution in determining causality, however, is required. Feedback loops where non-adherence intensifies depression is possible and the association may be confounded by other variables including overall poor health, alcohol abuse, or other mental health conditions.

Treatment and testing complexity is thought to affect adherence such that more complicated protocols might be less adhered to.[70] If the HCV RNA test were more invasive and complicated to receive, this may have an impact on the number of individuals who receive the test. This is not the case. Both the antibody and RNA tests are blood tests, involve similar procedures to obtain, and there are no appreciable side effects.[73,74] There is no reason to suspect that RNA testing complexity or invasiveness is a factor. The very fact, however, that the RNA test requires a second medical visit could provide an opportunity for loss to follow-up.

While the cost for the HCV RNA test is covered in Ontario, the therapies have historically been quite expensive.[75] This may have been a disincentive, especially for individuals with lower incomes, to receive the test and adhere to recommendations. Although avenues exist for coverage, the patients may not have been aware of these opportunities. The implications and details of treatment can influence adherence; if a patient believes they cannot afford the drugs, they may neglect to have a confirmatory test for HCV. In this way, those with extended health insurance, higher incomes, and possibly those of higher SES, may be more motivated to receive the test and get started on therapy as soon as possible. To complicate matters, some federal inmates may have had treatment covered and could have also been more likely to undergo RNA testing in a timelier fashion.[76] Federal budgets have been variable over time, however, and reductions in treatment have been noted between 2007 and 2013.[77] Correctional institutions have had periods where they were provided with limited funding and health providers had to prioritize who ought to receive treatment before budget renewals the following fiscal year. The allowable expenditure for HCV treatment tripled from 2013-2014 to 2015-2016 in federal corrections;[10] years with higher budgets for treatment could incentivize ordering RNA testing to confirm diagnosis. Recent dramatic increases in federal institution budgets for HCV in 2017-2018 have

made it possible for all federal inmates to be eligible for treatment;[78] however, these changes are relatively recent and fall outside the study period for this thesis.

Expanding on the concept of calendar year, there are changes during the study period that may have influenced referral practices for HCV RNA testing. Interferon-based therapies have been available since around 2000; however, these treatments have been shown to have low levels of effectiveness and high rates of toxicity.[79] The recent introduction of highly effective direct-acting antiviral (DAA) therapies have objectively improved the prognosis of patients who are infected with HCV.[54,75,80] Canada recently approved several of these drugs as the standard of care for HCV.[10,79] This change in HCV treatment landscape could have the effect of expediting the diagnosis process in an effort to begin curative treatment. In addition, new treatment options have inspired knowledge translation and awareness initiatives, like the series of seminars called the Canadian Symposium on Hepatitis C Virus that began in 2012.[81] In April 2014, the World Health Organization (WHO) released global guidelines for the diagnosis and treatment for persons infected with HCV.[82] Part of these guidelines include the recommendation for the "detection of HCV RNA directly following a positive HCV serological test."[83] As national and international efforts evolve and the medical community targets this infection more aggressively, the impetus to get patients tested and treated will expand.

Even if optimistic treatment results are expected, stigma can have an effect on the outcome as well. At the level of the health care provider, fears of reinfection, especially among PWID, is a cited reason as to why practitioners will not provide treatment.[81,84] One survey in Canada revealed that only 20% of specialist practitioners were willing to provide treatment for HCV for PWID.[85] If the intention to treat is not in place, the impetus to order RNA testing may be lacking. A review by Gail Butt[52] found that the most frequently cited HCV-related

stigmatizing experiences occurred at the level of interpersonal relationships with health care providers. At the level of the individual, the existence of stigma, especially with its association to injection drug use, can delay access to care when individuals avoid diagnosis and, in turn, treatment.[52] Treatment avoidance and reduced access to care may be compounded by some of the consequences of stigma like feelings of blame, deservedness of punishment, social isolation, loss of income, and declines in health.[52]

2.5 Duplicate HCV antibody testing

This segment reviews the literature related to duplicate antibody testing. While the second objective in this thesis is descriptive, an understanding of factors associated with repeat testing could prove useful in generating hypotheses for future work.

2.5.1 Factors related to duplicate antibody tests

A study by Tsai et al.[86] used surveillance records collected in New York City between 2006 and 2010 to identify factors related to duplicate HCV antibody testing. They rationalized that any repeat antibody test represented a poor use of resources and may indicate a lack of coordination of medical care. In their analysis, any evidence of antibody testing after a first positive result was considered duplicate. 50% of the 58,886 eligible subjects had evidence of duplicate testing. The researchers categorized the number of duplicate tests and used polytomous logistic regression to determine associations with the multiple outcomes. Males appeared to be at greater risk of duplicate testing and the researchers defined sex as an effect modifier between substance abuse treatment recipients and duplicate antibody tests; therefore, they stratified the regression models by sex. Those who were ever tested in a substance abuse facility or in a corrections facility were more likely to undergo duplicate testing. More specifically, in the

stratified model for males and with 0 duplicate tests as the reference group, those tested in a correctional facility were more likely to receive 2-3 and 4-37 duplicate tests (aOR=1.75; 95% CI=1.62, 1.89 and aOR=4.62; 95% CI=4.24, 5.03, respectively). In the stratified model for females, those tested in a corrections facility were also more likely to receive 2-3 and 4-37 duplicate tests (aOR=1.83; 95% CI=1.56, 2.14 and aOR=5.30; 95% CI=4.49, 6.25, respectively). Even larger effects were observed for those treated in substance abuse facilities. For example, individuals treated in a substance abuse facility were more likely to have 4-37 duplicate tests (males: aOR=9.95; 95% CI=9.18, 10.79; females: aOR=7.29; 95% CI=6.44, 8.24). Age ≥66 years was associated with decreased odds of receiving more than 4 duplicate tests (males: aOR=0.79; 95% CI=0.64, 0.97; females: aOR=0.67; 95% CI=0.53, 0.85). The authors indicated that the findings suggest patients may be unaware of their HCV positivity. Even if patients are aware of their status, they may not be informed as to the repercussions of the results. In addition, a lack of medical chart portability, especially where electronic documentation is not utilized, could increase an individual's likelihood of receiving multiple duplicate antibody tests. This risk could be compounded where patients are treated at multiple facilities. These factors were not explicitly explored and represent limitations to their findings.

In another US-based study, Yehia et al.[87] analyzed HCV testing practices among individuals living with HIV. One of the aspects of screening they were interested in was the number of duplicate HCV antibody tests among those who were already at risk of repeat testing. Data was obtained from 12 different HIV treatment sites between 2006 and 2011. Duplicate testing was defined as any evidence of HCV antibody test in those with prior positivity. 40% of HCV positive individuals had evidence of duplicate antibody testing. Using logistic regression, the dependent variable in this part of the analysis was 1 or more compared to 0 duplicate tests.

Heterosexual men and PWID were at higher risk of duplicate testing. The researchers also found that inpatient and outpatient medical visits were associated with increased odds of receiving multiple antibody tests (aOR=1.09; 95% CI=1.01, 1.19 and aOR=1.03; 95% CI=1.01, 1.04, respectively). The causality of this association ought to be questioned, however, since the reasons for these visits were not described. The researchers suggest that an inadequacy in patient information sharing, lack of HCV status awareness, and failure to check prior test results could have played a role in producing these findings. These results are not generalizable across the country and they may only be relevant among those infected with HIV. Also, many individuals included in the analysis may have been tested outside of the HIV treatment facilities and the number of duplicate tests may be higher than described in the results.

The absence of effective medical electronic documentation may be related to inflated numbers of duplicate tests.[88] If an ordering physician is unaware of prior testing or has difficulty accessing the results, they may simply order a new test where it is not required. In describing the causality of this concept, a study by Niès and colleagues[90] looked at the impact of repeat serological HBV tests in a cardiovascular surgery department. A new electronic notification system was implemented at a university teaching hospital in France that would inform physicians of recent HBV antigen tests with the results; these alerts would be triggered when the physician logged in to order a new lab test. The researchers performed a time series analysis and discovered a small, but statistically significant decrease in monthly proportions of duplicate tests (-0.4%; 95% CI=-0.7%, -0.1%) in the period of time after the system was implemented. When the prior test was positive, compliance with the alert appeared to be much higher compared to negative tests results. The relatively small effect observed in this study is consistent with other studies investigating on-screen medical reminders.[89,90] Regardless, ordering physicians with

access to medical records, especially systems with alerts, may be less likely to order duplicate HCV antibody tests once an individual has already been shown to test positive. The authors of this study also highlighted the notion that a change in a patient's status and symptoms could have led them to override the alert. In the context of HCV, individuals with symptomatic HCV may be more at risk of receiving multiple antibody tests.

Changes in electronic health records and laboratory information system procedures have changed in Ontario during the study period. According to email contact with PHOL, they claim to have a system in place whereby HCV antibody tests are cancelled if there is evidence of past positivity. Due to changes in PHOL information systems, this was apparently not an option as of May 2010 until the problem was rectified in November 2012. During this time, the work fell to the ordering provider to search for past positive results. Even if HCV knowledge and awareness is improving within the medical community, this would have a profound effect on the number of tests appearing in the dataset. The dataset from PHOL would only be capturing tests performed at the facility and would not indicate individuals who had a test sent to PHOL but was cancelled due to past positivity.

As with discussions in the preceding sections, stigmatization could influence the number of antibody tests an individual receives. On the one hand, the stigma and stereotyping associated with prisoners and PWID could lead health practitioners to assume HCV infection and order antibody tests without properly looking into the patient's medical history. On the other hand, fear of discrimination and the repercussions of HCV-related stigma might prevent individuals from seeking a diagnosis and avoid medical contact.[91,92] In this way, stigma could not only serve to increase the number of duplicate antibody tests ordered on the part of the health care provider, but it may reduce testing by way of medical contact avoidance.

Education, patient knowledge of HCV, and SES could have an impact on the outcome by affecting the patient's willingness to participate in their own care.[66] If an individual understands the testing process and is able to recognize the redundancy of multiple antibody tests, they are in a better position to advocate for themselves and avoid duplicate testing. Being aware of past positivity and the insight in proceeding to the next step, the RNA test, could attenuate the probability of receiving redundant tests.

2.6 Implications of the current study

The first manuscript of this thesis utilizes a novel approach to investigating HCV testing practices in Ontario. No other studies were identified that utilized a survival analysis to look at the time from antibody testing to the completion of the diagnosis process through RNA testing. Survival time in this context refers to the time to receiving the RNA test following a positive antibody result. In other words, the time spent until complete HCV testing. Failure to adjust for time is a major limitation of the current literature. Many of the studies reviewed failed to have an appropriate additional follow-up time after the study period to allow time to receive an RNA test among those who first tested antibody positive towards the end of the study.

The element of time itself is pertinent in the efforts to eradicate HCV by identifying those who are at most risk of delays in testing where they are unaware of their HCV status and are, therefore, not receiving treatment. Apart from the obvious health benefits from receiving curative treatment, the longer an individual remains infected with HCV, the greater the likelihood they will transmit the infection to others. A significant number of potential confounders were identified in the literature review; however, a limited number of variables are available for analysis purposes.

The second objective aims to describe the magnitude of duplicate HCV antibody tests performed at PHOL during the study period. Duplicate tests are not only a waste of operational and financial resources, but they are a burden to the individual being repeatedly tested. Descriptive statistics could be very informative in terms of inefficiencies in the Ontario health care system.

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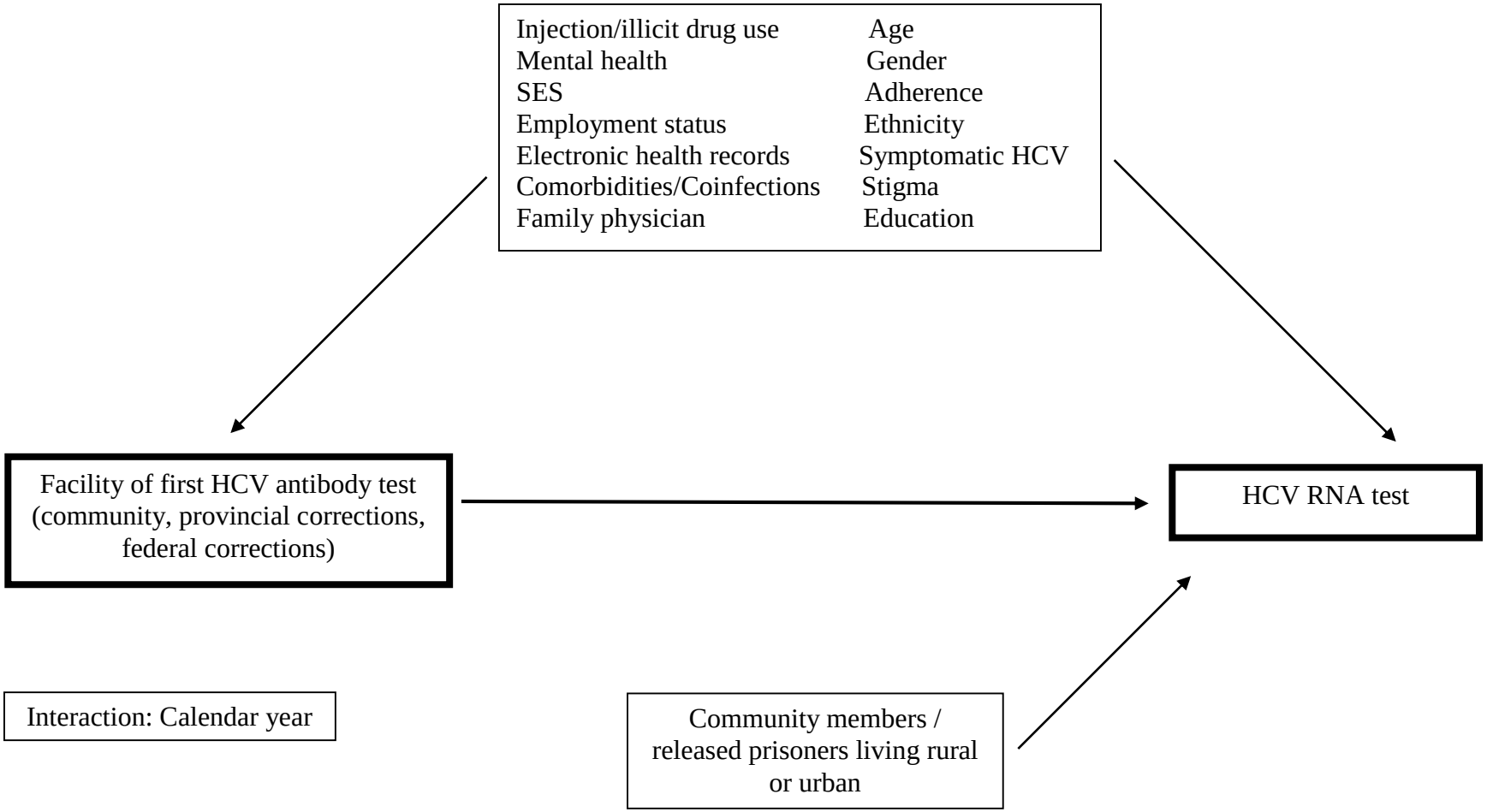

Figure 1. Conceptual model of the association between the facility of first positive HCV antibody test and the time to the first HCV RNA test

Chapter 3

Time to hepatitis C RNA testing following first positive antibody test in those first tested in a correctional facility or the community in Ontario, Canada

3.1 Abstract

PURPOSE: Identifying delays from an individual's first positive hepatitis C virus (HCV) antibody test to their first HCV ribonucleic acid (RNA) test is of considerable public health interest in the effort to eradicate the virus. This study sought to describe an association between the facility of a first positive antibody test and the time to RNA testing. The facilities of interest were community facilities, provincial correctional institutions, and federal correctional facilities.

METHODS: Lab results performed at Public Health Ontario between 1999-2014 were obtained. Adults during the study period who demonstrated a positive HCV antibody test were considered eligible. The date and facility of their first positive antibody test was defined as the index date and facility. The facility of testing was further described as a community facility, provincial correctional institution, or a federal correctional institution. Any evidence of HCV RNA testing was considered the event date for the multivariable Cox's proportional hazards model.

RESULTS: Controlling for age at first testing and birth year, males and females who were first tested in a provincial facility took longer to receiving their HCV RNA test across all calendar years in the study when compared to those first tested in the community. In the latter years of the study, both males and females were faster to receiving an RNA test if they were first tested in a federal institution compared to the community. Females took longer than males to receive the test when first tested in a provincial penitentiary.

CONCLUSION: When compared to those first tested in the community, individuals first testing positive for HCV antibodies in a provincial correctional institution may be longer to receiving the required HCV RNA follow-up test. The identification of higher risk groups for receiving appropriate HCV care provides opportunities for public health interventions to aid those most vulnerable to experiencing barriers to accessing health care in Ontario, Canada.

3.2 Introduction

Current estimates are that approximately 0.64% to 0.71% of the Canadian population are hepatitis C virus (HCV) antibody positive[1] and the prevalence in Ontario is 0.87%.[2] Infection is often asymptomatic and a large majority of those infected are unaware of their infection status.[3,4] HCV is estimated to be the infectious disease with the highest burden in Ontario.[5] The costs of chronic HCV include management for end-stage liver disease, liver cancer, and liver transplants.[4,6,7] HCV has consistently been shown to disproportionately affect individuals in correctional facilities[1,8–10] where histories of injection drug use are higher than the general population.[11–14] The landscape of HCV management has changed dramatically with the recent introduction of highly effective direct-acting antiviral (DAA) therapies that are curative in most cases, making it even more pertinent to diagnose and promptly treat individuals with HCV.[4,15]

Prisons are settings that contain populations with substantial health demands and demonstrate higher rates of communicable diseases, mental health conditions, and substance abuse.[13] The unmet health needs of this population is amplified by the fact that inmates are less likely to have a primary care provider in the community.[16] In Ontario, provincial prisons are for individuals sentenced to two years less a day and federal institutions are for inmates serving sentences that are two years or longer.[13]

Testing for HCV begins with a blood test to look for HCV antibodies and then, contingent on the results, further testing to determine the presence of HCV ribonucleic acid (RNA). If the RNA test is positive, the individual is considered to have an active infection. If the RNA test is negative, it suggests that the individual cleared the infection naturally, the individual previously received curative treatment, or the antibody test was a false positive. Once an individual tests positive for HCV antibodies, they typically test positive for life.[4] The step

between testing positive for antibodies and receiving RNA testing is an essential component of the cascade of care for HCV and is a requirement for complete HCV testing. Several studies have shown that many individuals who test antibody-positive do not receive the RNA test.[17–20] While several risk factors for incomplete testing have been described, limited information exists regarding those first tested in prison, especially in the context of Ontario, Canada.

While describing where incomplete testing practices are present is of considerable interest, a time component to testing has important public health implications with respect to disease transmission. The shorter the time to diagnosis and treatment, the less time an individual with HCV has to potentially transmit the infection. The relative absence of harm reduction strategies in correctional facilities puts this group of individuals at high priority for receiving timely testing and, potentially, treatment as prevention.[21,22] In addition to transmission times, the longer an individual goes undiagnosed, the more likely it becomes that they are lost to follow-up and never receive a diagnosis[23] and, if necessary, treatment. Transient groups who test antibody-positive, like those with short sentences in provincial correctional facilities, may lack well detailed and clear follow-up opportunities when they return to the community following their release.[18]

There is no study to date that has utilized a survival analysis to describe HCV RNA testing after a positive antibody test between the testing facilities described in this study. Survival time in this context refers to the time to receiving the RNA test following a positive antibody result. In other words, the time spent until complete HCV testing. The purpose of this study is to determine an association between the facility of an individual's first positive antibody test and the time to their first HCV RNA test. More specifically, the facilities of interest are community medical facilities, federal correctional institutions, and provincial correctional

institutions in Ontario, Canada. Identifying groups that have delayed times to confirmatory testing could provide valuable information regarding whom to target with appropriate public health interventions.

3.3 Methods

Dataset, study population and study design

A subset of data from Public Health Ontario Laboratories (PHOL) was used in this retrospective cohort study. This subset contained information regarding all HCV antibody and RNA tests conducted at PHOL, including inconclusive tests, with their respective dates performed. There were 331,069 available test results between January 1999 and December 2014 where individuals showed HCV positivity at some point during the study period. Subjects were considered eligible for this study if they had a positive antibody result at any point during the study period and they were at minimum 18 years old the year of their first test. Individuals who had evidence of an RNA test with no prior antibody test or their first antibody test was on the same day as their first RNA test were excluded from the analysis.

In order to maintain subject confidentiality, unique patient identifier numbers were used that could not be linked and followed back to any specific individual. This identifier followed the subject across all available tests in the dataset. Information regarding the subject's year of birth and sex were available as well as the facilities from which the bloodwork was submitted to PHOL. A detailed list of the submitting correctional institutions, the geographic location of the submitters, and descriptions of the tests submitted by facility can be seen in Appendix B. This study was approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HRREB) and can be viewed in Appendix C.

Cleaning of PHOL dataset and covariates

The dataset was imported into SAS software version 9.4 (SAS Institute, Cary NC) where the cleaning and statistical analyses were completed. Based on the submitting institution information, a variable characterizing the testing facility was created and classified into one of three categories: (1) community medical facility, (2) federal corrections facility, or (3) provincial corrections facility. The testing facility of each subject's first positive antibody test was identified as the primary covariate of interest in this study.

The test date was utilized for several purposes. First, it was used to determine, along with birth year, the subject's age at the time of testing. Second, it was used to define the calendar year during which the individual first tested antibody-positive. This variable was further categorized to represent 5-6 year intervals during the study period. Third, the date of the first positive antibody test represented each subject's index date from which time in the analysis could be measured. Fourth, the test date of the first HCV RNA result represented the event for the analysis. For subjects with no evidence of RNA testing, the end of the study period represented their censoring date. Time was represented in weeks since first positive antibody test.

Subjects who were under the age of 18 in the year of their first positive antibody result were removed. Any subject with an RNA test but no evidence of antibody testing prior to this date were also deleted. The resulting dataset was used in the statistical analysis.

Statistical analysis

Descriptive statistics were employed to describe the study population and make appropriate comparisons between different exposure groups. The proportion of subjects in each of the following categorical variables was described: facility of first positive antibody test (community facility, federal institution, provincial institution), sex (male, female, unknown),

calendar year at first positive antibody test (1999-2003, 2004-2008, 2009-2014), and birth year (<1946, 1946-1965, >1965). Age at first testing was initially considered as a continuous variable; however, issues concerning the functional form of the variable made it more practical to describe in terms of categories (18-29, 30-39, 40-49, 50-59, and 60+ years). At first glance, age intuitively seems the same as birth year. The long study period creates a situation where these two variables are not exactly collinear. For example, a "baby boomer" (born between 1946-1965) first tested in 2000 could have been as young as 35 years old. In contrast, an individual born between 1946 and 1965 at the end of the study period could have been 60+ years old.

Individuals were censored if there was no evidence of RNA testing in the dataset and they represented individuals potentially experiencing incomplete testing practices. Further descriptions of the categorical variables by the primary exposure of interest were provided and χ^2 tests were used to determine statistically significant associations.

Kaplan-Meier curves were used to visualize the crude probability of incomplete testing and stratified curves for all categorical variables were produced. The log-rank test was used to compare curves stratified by the facility of first positive antibody test. Curve patterns were inspected and any obvious line crossings were noted in a preliminary attempt to identify potentially problematic variables for a proportional hazards (PH) model.

Univariate analyses for each independent variable association with follow-up time was performed at a significance level of 0.05 along with respective hazard ratios (HR). Next, a multivariable Cox's proportional hazards model was fit with all covariates. The Breslow approximation for dealing with ties was deemed appropriate, especially considering a significant number of ties was not expected.[24] A backward selection method with a statistically significant cutoff level of 0.05 was decided a priori. Testing for interactions was primarily based on subject

matter knowledge and a consideration of clinically meaningful outcomes was considered. Once the model was fit, the PH assumption was assessed. First, log(-log(incomplete testing estimate)) vs. log(time) curves, stratified separately for each appropriate covariate, were visually inspected for crossings which could violate the PH assumption. Next, Schoenfeld residuals were produced for each covariate and plotted against time; LOESS curves were fit to visualize any apparent trends over time.[25] The score residuals process to assess the PH assumption was not possible in SAS due to the large sample size. Deviance residuals were produced and plotted against each covariate to look for suspicious patterns and poorly fitted observations.

After the model was validated, HRs were calculated for the effects of interest. These HR estimates were accompanied by 95% confidence intervals (CI), where intervals that crossed 1 were not considered statistically significant. In order to demonstrate the time to an RNA test, probabilities of incomplete testing at various times based on the Cox's PH model were assessed and example probabilities (along with 95% CIs) were provided.

A sensitivity analysis addressing issues of exposure misclassification and inaccurate follow-up times was required. Subjects who had a positive antibody test prior to 2004 were removed. This produced a dataset where all individuals had at least 5 years of lead-up time where there was no evidence of antibody testing. This improved on the reliability of the subject's actual first antibody test date and, consequently, facility of first test. In addition, many individuals in the dataset demonstrated more than one antibody test over the study period. This allowed for an alternate censoring date for these individuals at the last available HCV antibody test. Censored individuals where no follow-up antibody tests were available were also removed in this part of the analysis. Kaplan-Meier curves and model diagnostic procedures described

above were also completed for the sensitivity analysis. A schematic illustrating differences between the main and sensitivity analysis is shown in Figure 1.

3.4 Results

A total of 94,594 unique subjects had evidence of a positive antibody test in the dataset. 1,042 (1.1%) had age missing and 1,577 (1.7%) were under the age of 18 the year of their first test and were removed from the dataset. An additional 10,643 (11.3%) subjects were excluded as they had their first RNA test on the same day as their first positive antibody test result; 95.3%, 4.0% and 0.7% of these individuals were first tested in the community, federal institution, and provincial institution, respectively. 5,409 (5.7%) individuals had an RNA test with no prior evidence of antibody positivity; they were also excluded. 31 subjects (0.03%) had their first antibody test from a submitting institution outside of Ontario. They were also removed. The total study sample size for analysis was 75,892 subjects. A flow chart illustrating the study sample is illustrated in Figure 2.

A summary of the baseline population characteristics is shown in Table 1. A description of the categorical variables, along with χ^2 tests for association, by facility of first testing is provided in Table 2. All associations were statistically significant at an alpha level of 0.05. Males were much more likely to have first been tested in a provincial (76.4%) or federal institution (90.8%). Very few numbers of individuals born prior to 1946 were first tested in either type of correctional facility (0.5% and 1.0% provincially and federally tested, respectively). Differences in testing facilities were seen across calendar years. Only 8.6% of those first tested in a provincial facility were tested between 1999 and 2003; 18.4% of individuals first tested in a federal institution were tested between 2009 and 2014.

Kaplan-Meier curves stratified by first testing facility can be seen in Figure 3. A total of 26,582 (35.0%) individuals were censored. 24,662 (34.6%), 586 (28.8%), and 1,334 (52.8%) of subjects in the community, federal, and provincial groups were censored, respectively. The distributions were statistically significantly different (log-rank test: p-value<0.0001), with the provincial facility group appearing to have longer times to first RNA testing. The distributions between the community and federal facility groups were not statistically significantly different from one another (separate log-rank test: p=0.14) The median times to complete testing based on these curves for those first tested in the community, a federal institution, or provincial institution were 122.1 (95% CI=117.8, 126.3), 117.9 (95% CI=93.4, 145.0), and 341.9 (95% CI=312.4, 385.1) weeks, respectively. While there is a small amount of overlap between the community and federal correction groups, there is no evidence that the provincial institution group overlaps or crosses the other two groups in the curves or the log(-log(incomplete testing estimates)) vs. log(time) curves (Figure 3 and Figure 4). There is no visual evidence of significant crossing when these curves are stratified by calendar year of testing, sex, or birth year; however, there is some concern with curves crossing when stratified by age group (Appendix D).

Univariate associations of each independent variable with the outcome in Cox's PH models can be seen in Table 3. While the type 3 test of effect for facility of first test was statistically significant (p<0.0001), individuals first tested in a federal institution were not significantly different from those first tested in the community (HR=1.04; 95% CI=0.99, 1.09). In contrast, those first tested in a provincial facility demonstrated a statistically significant difference compared to those first tested in the community (HR=0.66; 95% CI=0.62, 0.70). All other variables demonstrated statistical significance (Table 3).

In the multivariable Cox's PH regression analysis, the main effects of the variables and the interactions between facility of first test and calendar year of first test and facility of first test and sex were included. Schoenfeld residuals plotted against time revealed a potential violation of the PH assumption with the variable for age at first testing; this was in corroboration with the crossing of Kaplan-Meier curves. In order to allow age to vary with time, a stratification method was used to allow each age group to have a different function of time.[25] Birth year demonstrated a similar pattern concerning the schoenfeld residuals where there may have been a trend with time; however, given the lack of crossing of the Kaplan-Meier curves, an interaction with time or stratification in the model was not deemed essential. In addition, the inclusion of a time interaction with birth year had a negligible impact on the parameter estimates for facility of first test (HR changes were less than 2% at all levels). No significant outliers were identified looking at likelihood displacement scores. The deviance residuals plotted against each covariate are presented in Appendix E along with all other model diagnostics. The final model with the respective parameter estimates and statistical significance is demonstrated in Appendix F.

HRs for all covariates are summarized in Table 4. The HRs comparing the provincial institution with the community group was significantly less than one across all calendar years for both males and females. In contrast, the effect in the federal group appeared to be improving over the calendar years relative to the community group. Comparing females first tested in a federal institution with females first tested in the community, the HR changed from 0.68 (95% CI=0.55, 0.84) to 1.42 (95% CI=1.14, 1.77) between 1999-2003 and 2009-2014, respectively. The effect for males was 1.01 (95% CI=0.93, 1.09) in 1999-2003 and 2.11 (95%CI=1.88, 2.37) for those first tested between 2009-2014. A similar trend was observed where sex was unknown (Appendix G).

A direct comparison between males and females at each testing facility is presented in Table 4. Females were slightly sooner to receive the RNA test when first tested in the community (HR=1.06; 95%CI=1.04, 1.08) and later than males when first tested in either a provincial (HR=0.81; 95%CI=0.70, 0.93) or federal institution (HR=0.72; 95%CI=0.59, 0.88). Where sex was unknown, the risk of receiving the RNA test was less than males at all testing facilities (Appendix G).

The delay in RNA testing was further emphasized when looking at probabilities of incomplete testing at different follow-up times. Predicted probabilities and median number of weeks to complete testing for several 40-49 year old individuals at 20 and 52 weeks post first positive antibody test are presented in Table 5. It is shown that the probabilities of incomplete testing for the individuals described who are first tested in a provincial facility are higher than the other two groups; that is, they are more likely at the specified times to not have had the RNA test completed. For example, for a male born between 1946-1965 first tested in a provincial facility between 2009-2014, the probability of making it to 20 weeks without an RNA test is 74.2%. This is in contrast to a male of the same profile but first tested in a federal prison 20 weeks prior who is only 32.7% likely to not have had the test completed. The median number of weeks to complete testing for the two individuals described above is 188.4 [95% CI=146.3, 233.7) and 10.4 [95% CI=9.0, 12.1) weeks, respectively.

Those born <1945 and 1946-1965 demonstrate statistically significantly longer times to receive RNA tests compared to those born >1965. Due to the stratification method, the effect of age cannot be determined in this model.

Sensitivity analysis

A total of 25,294 individuals with a positive antibody test prior to 2004 were removed. An additional 11,910 subjects were removed where only one antibody test was available and were originally censored at the end of the study period. A total of 38,688 subjects remained for the sensitivity analysis; 5,326 (13.8%) did not demonstrate an HCV RNA test but had an additional antibody follow-up date that served as the censoring date for these subjects. A summary of the baseline characteristics and associations with the primary exposure for the sensitivity analysis are displayed in Appendix H. The resulting proportion of individuals in each category is quite similar between the sensitivity and main analysis. 77.1% and 22.8% of those first tested in a provincial institution were males and females, respectively. 90.4% and 8.8% of individuals first tested in a federal institution were males and females, respectively. Table 1 and Table 3 in Appendix H show the characteristics of those removed for the sensitivity analysis. As a percentage of those included in the main analysis, 40.1% of males and 39.6% of females first tested in a provincial institution were removed; 59.9% of males and 55.0% of females who were first tested in a federal institution were excluded. Only 14.9% of subjects first tested in a federal institution in 2009-2014 were removed. Those born prior to 1946 had high proportions of removal for the sensitivity analysis in all three testing facilities (64.6% community, 69.2% provincial, and 85.0% federal).

Kaplan-Meier curves stratified by facility of first test for the sensitivity analysis are included in Appendix H. The curves remain statistically significantly different (log-rank test: p-value<0.0001). In the sensitivity analysis, the community and federal groups were also significantly different from one another (separate log-rank test: p-value<0.0001). The median times to complete testing based on these sensitivity analyses curves for those first tested in the

community, a federal institution, or provincial institution were 19.7 (95% CI=19.1, 20.1), 9.0 (95% CI=8.0, 10.3), and 93.6 (95% CI=83.0, 111.1) weeks, respectively. These median estimates are much smaller than those from the main analysis; this is not surprising given the removal of subjects who contributed large censoring times.

A Cox PH model was fit with an interaction between facility of first test and calendar year and facility of first test and sex. As with the main analysis, the model was stratified by age group. All covariates, including the respective interaction terms, remained statistically significant. No concerning influential points, as assessed by likelihood displacement scores, were identified or removed. Table 6 presents the HRs for the facility of first test and sex effect produced from the sensitivity model. The effect of facility of first test is in the same direction as the main analysis. Of note is the effect in 2009-2014 of those first tested in a federal prison (Males: HR=2.06; 95%CI=1.83, 2.32; Females: HR=1.98; 95%CI=1.54, 2.54) and provincial institution (Males: HR=0.68; 95%CI=0.62, 0.74; Females: HR=0.55; 95%CI=0.48, 0.64). While males and females were no longer statistically different from one another when first tested in the community or a federal institution, females remained longer to receive an RNA test when first tested in a provincial facility (HR=0.81; 95%CI=0.70, 0.94).

3.5 Discussion

This study sought out to determine an association between the facility of the first positive HCV antibody test and the time to receiving the necessary HCV RNA test. The use of a Cox's PH model allowed for the assessment of effect of testing facility on receiving HCV RNA testing in terms of HR, or an approximation of relative risk[26], and time to receiving the test. The results suggest that there is a difference in terms of time to and risk of receiving the RNA test between those first tested in the community, a federal corrections institution, or a provincial corrections

institution. The event in this analysis, the RNA test, represents a desirable outcome and, consequently, an elevated risk is favourable; that is, more quickly to receive the RNA test.

After controlling for birth year and age of first positive HCV antibody test, both males and females first tested in a provincial institution took significantly longer to receive an RNA test compared to those first tested in the community regardless of the calendar year of receiving the first positive antibody result. This result makes intuitive sense after considering the social situation of many offenders in provincial corrections. Those sentenced to provincial institutions often serve short sentences, typically less than 20 days.[27,28] These individuals are thought to be at risk of being disconnected from health care services upon their re-entry to the community.[18,29] In addition, there is an overrepresentation of individuals in this population with significant health needs.[13] Even if they access health care during their sentence or upon release, they may have competing comorbidities that are perceived as a higher priority; chronic infections like HCV may be neglected. A lack of electronic health records has been cited as a deficiency in these facilities[29] and inmates have been shown to be less likely to have a family doctor in the community.[16] The situation may be further complicated by a lack of standardized screening programs across provincial facilities.

The experience of those first tested in a federal institution may be quite different where their sentence length is a minimum of 2 years.[27] Those spending time in federal institutions are less likely than the general public to have access to a physician in the community prior to sentencing and may be similar in terms of demographics, comorbidities, and unmet health needs when compared to those spending time in provincial institutions; however, their stay at the federal facility may very well represent their greatest opportunity for accessing care and they may be followed more closely than they would in the community or a provincial institution. In

this way, access to care may act as a mediator to receiving the RNA test for those in a federal prison. To substantiate this notion, a health needs assessment in Canada revealed that federal prisoners had a higher frequency of visits to medical personnel during their incarceration compared to the general public.[30] The results in the current study corroborate these data; however, the effect is dependent on the calendar year of first testing for both males and females. Both the main and the sensitivity analysis suggest that males and females first tested in a federal institution between 2009 and 2014 were faster to receive an RNA test compared to males and females first tested in the community. The main analysis suggested that males were faster than females to receive the test when first tested federally; however, this result was not supported by the sensitivity analysis.

Concerted efforts are required to ensure that all individuals are receiving an HCV RNA test following a positive antibody result. Outreach programs connecting patients to follow-up care, especially after release from prison, are especially relevant for those with short sentences. Prisons are unique settings where HCV prevalence is high and risk reduction strategies may be limited. Reaching out to these groups, who may have otherwise gone without care, is essential to provide treatment for those most vulnerable.[22] In addition, several sources have advocated for the integration of reflex testing for HCV.[6,19,23,31,32] A reflex test implies that a positive antibody result automatically triggers an additional test for HCV RNA. The results from this study support the argument that reflex testing may be a necessary method to reach those not receiving appropriate follow-up.

Where sex is unknown, significant effects were observed. These individuals were much less likely to receive a follow-up test in the main analysis across testing facilities when compared to both males and females. A large proportion of these individuals were censored when

compared to individuals where sex was indicated (77.2%) and their true follow-up time may not have been accurate. These subjects represented a small proportion of the total sample size (0.6%) and when the model was re-run with their exclusion, the parameter estimates where essentially unchanged for all other covariates. For this reason, this variable remained in the model. Further research into this particular cohort may be required to determine an explanation for this potential effect.

This study has several limitations. Establishing a reliable censoring time was not possible given the dataset. In the primary analysis, the end of the study period represented the censoring date for those not appearing to have been tested during the study period. Individuals who were tested in another province would not show up in the results and could have contributed a long and incorrect follow-up time. Only one center, the Children's Hospital of Eastern Ontario, is known to perform in-house RNA testing; RNA tests conducted here may not be sent to PHOL and could result in a censoring of subjects. Similarly, since we did not have any other information regarding the subject's status, deceased individuals may have been represented as censored individuals who were not censored at the correct time. This is especially problematic when a subject remained in the analysis for many years after their death. Long and incorrect censoring times may have led to a Cox's PH model with poor fit. This concern, however, was greatly mitigated by the sensitivity analysis; in particular, the analysis revealed remarkably similar results after removing many individuals with the longest censoring times. More subjects were removed from the provincial institution group for reasons related to censoring. This explains why the Kaplan-Meier curve observed in the sensitivity analysis (Appendix H) converged with the other two curves when compared to the curves seen in the main analysis. Many of these individuals removed would have in fact represented individuals who were tested

in prison and then lost to proper follow-up on their release back to the community. Those who were tested in a correctional facility likely represent a less mobile cohort and were not as likely to have moved out of province. Even after removing these individuals who contributed a great deal of follow-up time, a similar effect was observed.

The date of first positive antibody test may not have been the individual's true index date. Those tested out-of-province, prior to the study period, or at a facility that performed in-house antibody testing may not have been captured in the study. If these subjects had an additional test antibody test at PHOL, their date of first testing would therefore be incorrect. This information error could lead to bias, especially with labs that perform their own testing. These settings would be hospital or private labs in the community. If those first tested in the community had an index date that was further back in time, it would bias the results by increasing the magnitude of effect between the community and provincial group and attenuate the difference between the community and federal group.

If a substantial number of subjects were tested in facilities that performed their own HCV antibody tests, they may not have been included in the study and present the possibility of selection bias. All federal prisons have the capability of in-house testing and samples are sent to PHOL; therefore, this type of bias would mainly affect the community group or provincial inmates who were outsourced to a private lab for testing. There is no reason to suspect individuals tested in a facility that does not submit to PHOL to be different from those who do. The concern for selection bias is therefore quite low.

If an individual had a prior positive antibody test date not captured in the dataset, not only is the index date incorrect, but there remains the possibility of misclassification of facility of first test. Some individuals had multiple antibody tests and include tests that were at different

locations from the facility of first antibody test. The sensitivity analysis also attempted to deal with this concern. By including only those subjects who were first tested in 2004, a lead-up time of 5 years without being tested increased the confidence that the index date was indeed the subject's first test. This strengthens the validity of the index date and eliminates many inevitable cases of misclassification. More detail regarding this type of misclassification is provided in Chapter 5 and Appendix I.

Differential misclassification could also have occurred in situations where an individual who was in prison was sent for testing in the community. This would have led to those being tested in a correctional setting being misclassified as tested in the community; community-tested individuals would not be misclassified as being first tested in corrections under these circumstances as community dwellers would never be sent to a prison to be tested for HCV. This is very unlikely in federal institutions as they tend not to outsource bloodwork and HCV tests would be sent to PHOL. There is currently no available data as to how often outsourcing occurs in provincial institutions; however, it is likely quite common. In addition, many individuals on remand who are in and out of prison may seek testing in the community. Substantial differential misclassification such as this would most likely result in an attenuation of the HR for the provincial group when comparing to those first tested in the community.

There remains the possibility of uncontrolled confounding. Several variables that may be associated with the exposure and outcome were not available in this particular dataset. For example, information was missing regarding each subject's history of injection drug use, race, access to primary care, mental health, and socioeconomic status. People who inject drugs (PWID) are likely to experience significant stigma and may not be sent for RNA testing if the individual is suspected to continue using drugs.[21,33] The impetus for confirmatory testing may be

minimized if the ordering practitioner fears the individual will become re-infected even if they receive curative treatment.[34] The intention of the patient to receive treatment could also play a major role in avoiding confirmatory testing. If they plan to continue to inject drugs or do not have the perceived means to obtain treatment, they may neglect to attend an appointment for RNA testing.

Another important missing variable is whether the subjects lived remotely or not. This would only be applicable to individuals in the community and those who had been released from prison, however, and would not apply to persons spending time in a federal institution since the prison is likely their place of residence. Future research on the topic must consider collecting more information to include all possible confounders.

A major strength of this study is the corroboration of findings in the sensitivity analysis which served to increase the confidence in the results of the main analysis. This particular sensitivity analysis represented a worst-case scenario where subjects who likely had the longest follow-up times were removed. In addition, the delayed index date helped to mitigate the potential impact of exposure misclassification.

Another strength includes the fact that the results are based on laboratory collected data. Where results rely on medical records, the possibility of missing results is much greater. The majority of RNA tests for adults in Ontario are sent to PHOL and therefore captured in this dataset; all RNA tests for the federal and provincial facilities would be sent to PHOL. This allowed for a reliable event date if the subject was tested in the province.

This is the only study to date that has compared the three different testing facilities in terms of time to receiving the HCV RNA test in Ontario. The use of survival analysis accounted for follow-up time among those who had not received the RNA test during the study period.

Similar studies describing the risk and odds of receiving the test have failed to consider this follow-up time and biased results are possible.

3.6 Conclusion

Despite the limitations, the results of this study revealed a potentially vulnerable group with respect to receiving and accessing appropriate testing for HCV. Those who first tested positive for HCV antibodies in a provincial correctional institution appeared to take longer to receive an HCV RNA test to establish active infection when compared to those first tested in the community or a federal institution. In particular, females in this group seemed to be at higher risk than males of not receiving the test. While the reintegration upon re-entry to the community of inmates has been deemed a top priority by Correctional Services Canada[35], provincial inmates, especially those with short sentences, may need to be monitored more closely as a particularly high-risk group. Prison settings present an opportunity to access individuals with unmet health needs who would otherwise have gone untested and untreated. Providing care to this vulnerable population with higher rates of HCV is a necessary step in the efforts to eradicate HCV.

Regardless of the methods employed to ensure appropriate follow-up for HCV testing, a multidisciplinary approach involving all key stakeholders is required. The availability of curative treatments for HCV has only served to amplify the need to identify and reach those with active infection.

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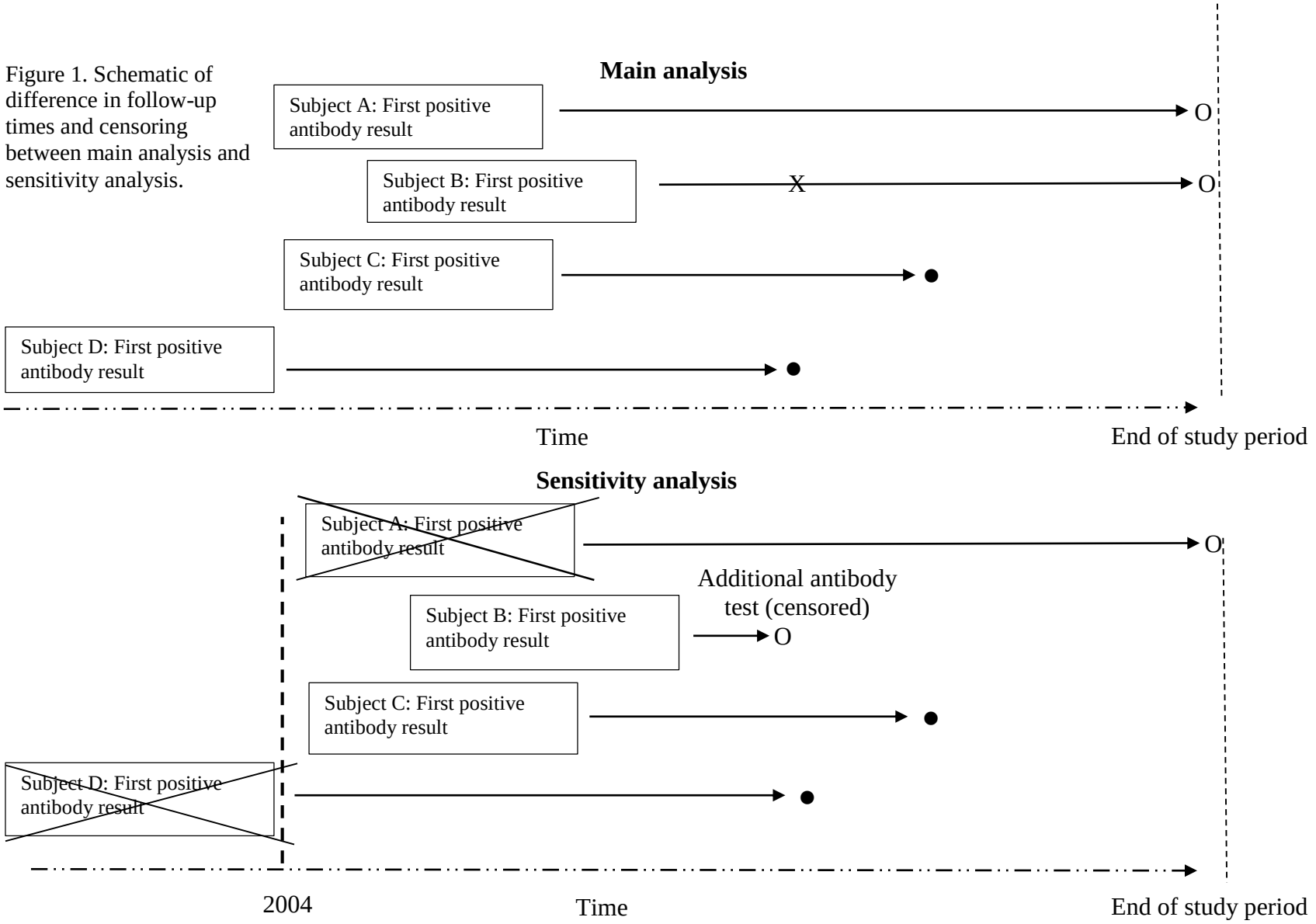
Figure 1. Schematic of difference in follow-up times and censoring between main analysis and sensitivity analysis.



Legend: Arrows indicate time to RNA test; O *represents censoring event;* X *represents additional antibody test;* ● *represents RNA tests; crossed out boxes in sensitivity analysis indicates where a subject was removed*

Figure 2. Flow chart of sample size from PHOL dataset

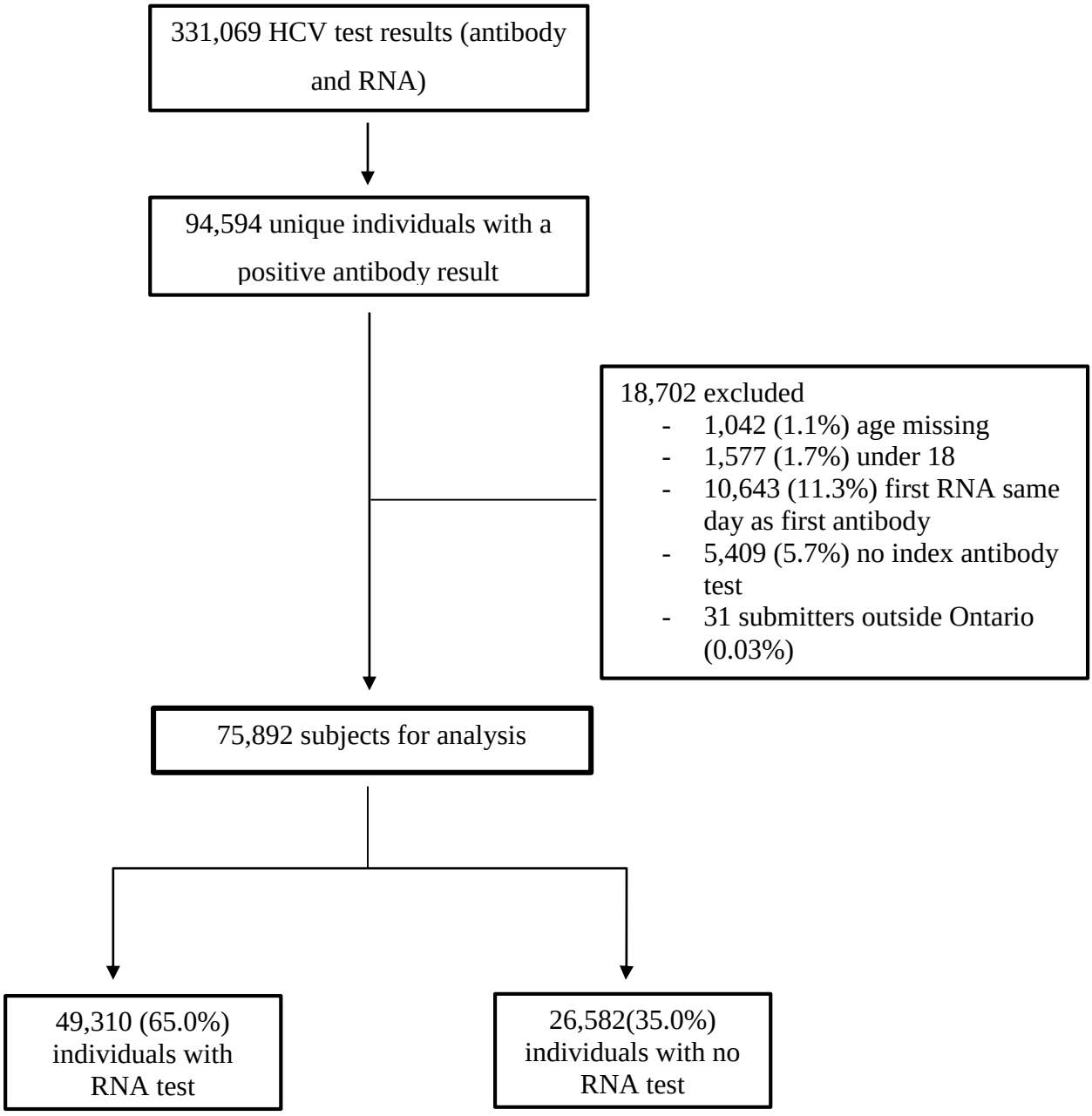


Table 1. Population characteristics

Characteristic	*N*	*%*
Facility of first test		
Community*	71,327	94.0
Federal	2,037	2.7
Provincial	2,528	3.3
Sex		
Male	47,999	63.2
Female	27,442	36.2
Unknown	451	0.6
Calendar year of first test		
1999-2003	25,294	33.3
2004-2008	24,392	32.1
2009-2014	26,206	34.5
Birth year		
<1946	7,771	10.2
1946-1965	41,934	55.3
>1965	26,187	34.5
Age at first testing (years)		
18-29	9,492	12.5
30-39	16,697	22.0
40-49	23,429	30.9
50-59	16,824	22.2
60+	9,450	12.4

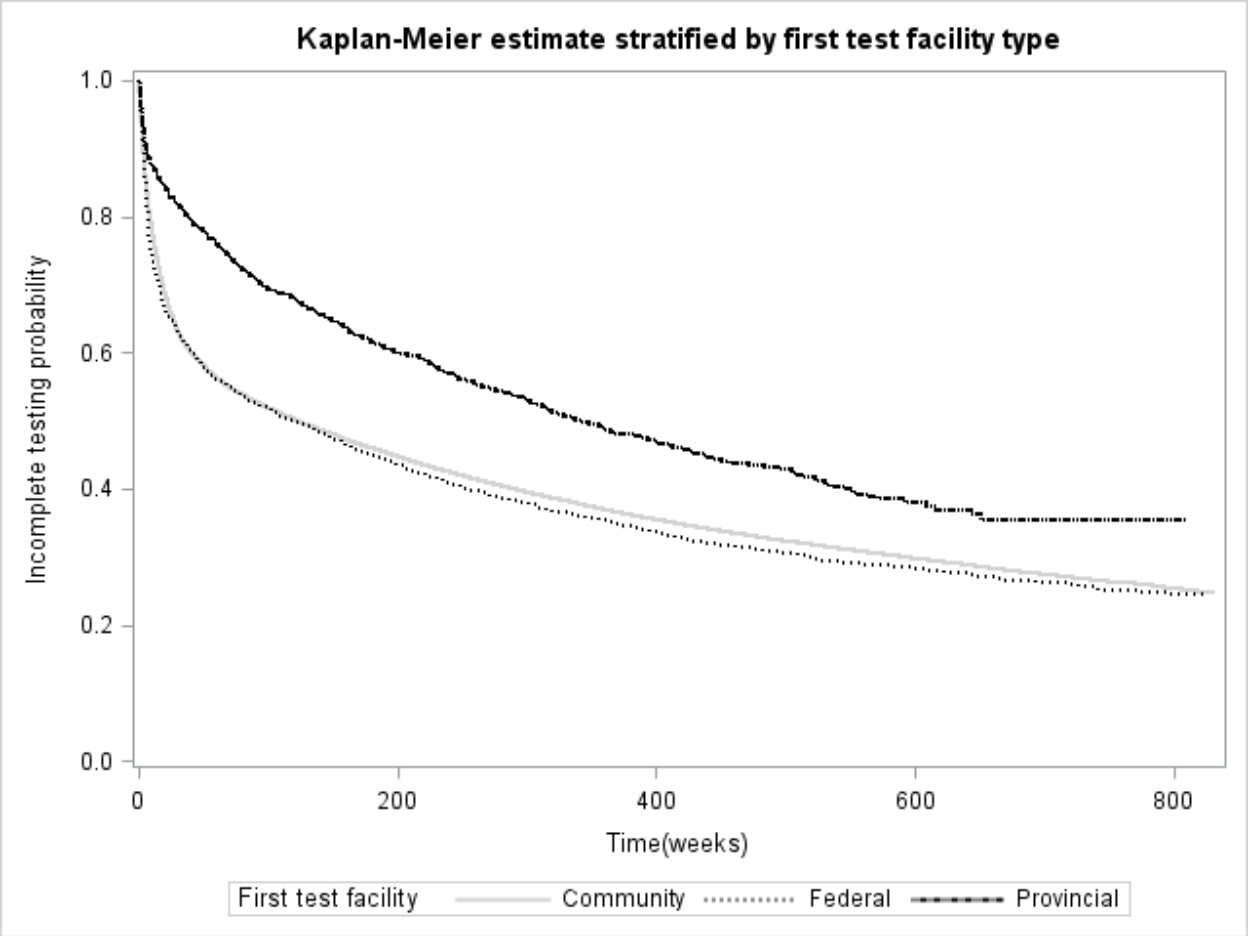
** 9,407 individual submitters were available from the community.*
Details regarding federal and provincial submitters are provided in Appendix B

Table 2. Population characteristics by first testing facility

	Facility of first HCV antibody test			
Characteristic	*Community (n=71,327) N(percent)*	*Provincial institution (n=2,528) N(percent)*	*Federal institution (n=2,037) N(percent)*	*P-value*[*]
Sex				
Male	44,217 (62.0)	1,932 (76.4)	1,850 (90.8)	
Female	26,714 (37.5)	568 (22.5)	160 (7.9)	
Unknown	396 (0.5)	28 (1.1)	27 (1.3)	<0.0001
Calendar year				
1999-2003	24,040 (33.7)	218 (8.6)	1,036 (50.9)	
2004-2008	22,690 (31.8)	1,076 (42.6)	626 (30.7)	
2009-2014	24,597 (34.5)	1,234 (48.8)	375 (18.4)	<0.0001
Birth year				
<1946	7,738 (10.8)	13 (0.5)	20 (1.0)	
1946-1965	40,407 (56.6)	578 (22.9)	949 (46.6)	
>1965	23,182 (32.5)	1,937 (76.6)	1,068 (52.4)	<0.0001
Age at first test (years)				
18-29	8,187 (11.5)	921 (36.4)	384 (18.8)	
30-39	14,995 (21.0)	876 (34.7)	826 (40.6)	
40-49	22,235 (31.2)	573 (22.7)	621 (30.5)	
50-59	16,510 (23.1)	132 (5.2)	182 (8.9)	
60+	9,400 (13.2)	26 (1.0)	24 (1.2)	<0.0001

[*] *p-value represents results from χ^2 test of association between characteristic and facility of first testing*

Figure 3. Kaplan-Meier curves: time to complete testing



Note: Incomplete testing probability is the probability of not having an RNA test by time t as a function of t. Censoring not shown.

Figure 4. Log of negative log of incomplete testing estimates stratified by first test facility type

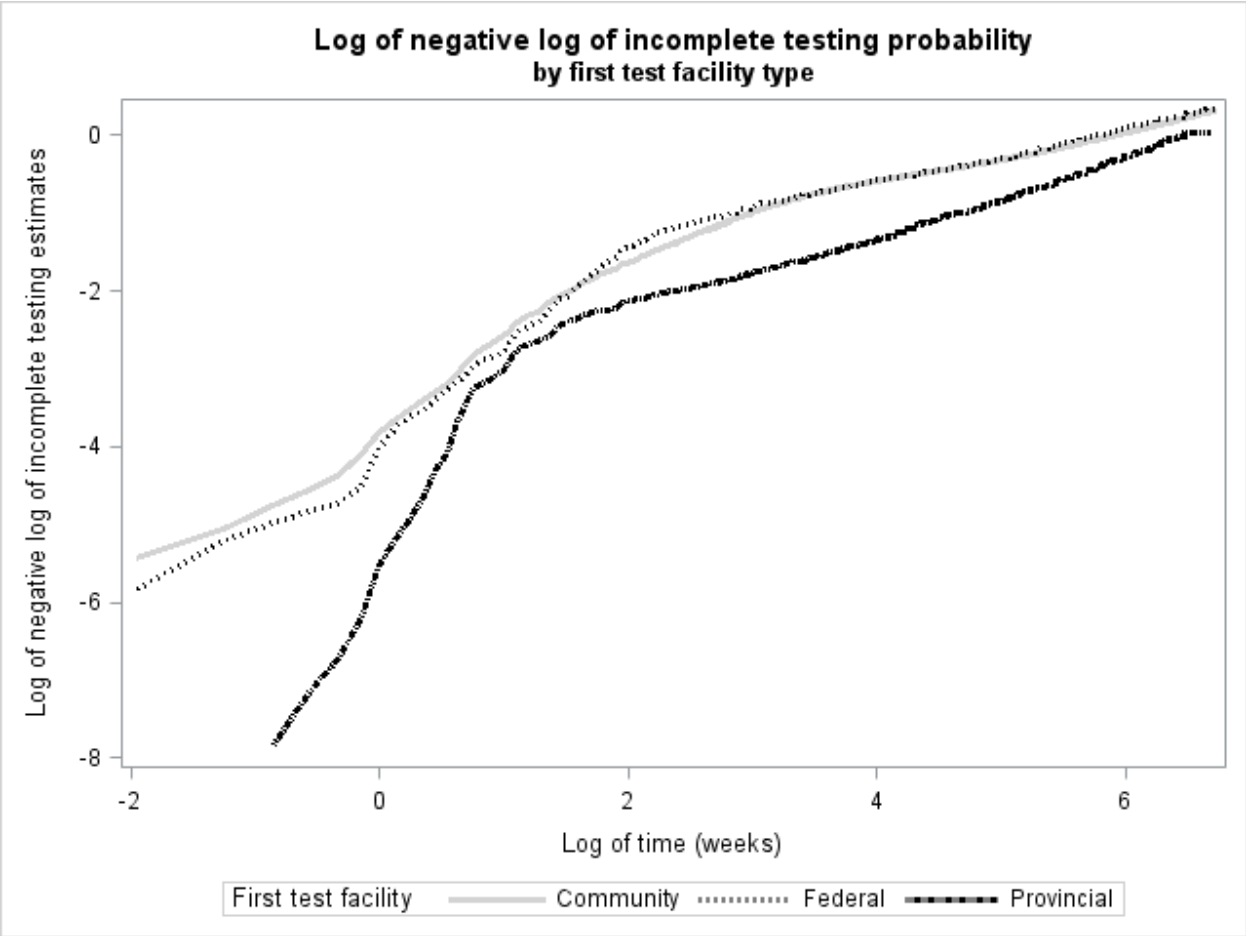


Table 3. Univariate analysis

Independent variable	*Hazard ratio (95% CI)*	*p-value*
Facility of first test (reference=Community)		
Community	_____	_____
Federal	1.04 (0.99, 1.09)	0.15
Provincial	0.66 (0.62, 0.70) †	<0.0001
Sex (reference=Male)		
Male	_____	_____
Female	1.04 (1.03, 1.06) †	<0.0001
Unknown	0.28 (0.23, 0.35) †	<0.0001
Calendar year of first test (reference=1999-2003)		
1999-2003	_____	_____
2004-2008	1.51 (1.47, 1.54) †	<0.0001
2009-2014	2.45 (2.40, 2.51) †	<0.0001
Birth year (reference= >1965)		
<1946	0.60 (0.58, 0.62) †	<0.0001
1946-1965	0.92 (0.90, 0.94) †	<0.0001
>1965	_____	_____

† *indicates statistical significance (p<0.05)*
Note: Age at first testing not provided due to concerns with PH assumption

Table 4. Hazard ratios in multivariable Cox's PH regression

Measures of effect	
Covariate	Hazard ratio (95% CI)
Facility of first test by calendar year for females (reference=Community)	
Federal at 1999-2003	0.68 (0.55, 0.84) †
Federal at 2004-2008	0.94 (0.76, 1.16)
Federal at 2009-2014	1.42 (1.14, 1.77) †
Provincial at 1999-2003	0.55 (0.44, 0.69) †
Provincial at 2004-2008	0.45 (0.39, 0.52) †
Provincial at 2009-2014	0.43 (0.37, 0.49) †
Facility of first test by calendar year for males (reference=Community)	
Federal at 1999-2003	1.01 (0.93, 1.09)
Federal at 2004-2008	1.39 (1.27, 1.53) †
Federal at 2009-2014	2.11 (1.88, 2.37) †
Provincial at 1999-2003	0.73 (0.61, 0.88) †
Provincial at 2004-2008	0.59 (0.54, 0.65) †
Provincial at 2009-2014	0.56 (0.51, 0.62) †
Sex by testing facility (reference=Males)	
Females at community	1.06 (1.04, 1.08) †
Females at federal	0.72 (0.59, 0.88) †
Females at provincial	0.81 (0.70, 0.93) †
Birth year (reference= >1965)	
1946-1965	0.93 (0.90, 0.97) †
<1945	0.70 (0.66, 0.75) †

† *indicates statistical significance (p<0.05)*

Table 5. Incomplete testing probabilities and median time to complete testing based on Cox's multivariable model: 40-49 years of age first tested 2009-2014

Description of individual	Weeks since first test	Incomplete testing probability (95%CI)	Median weeks to complete testing [95%CI)
Community Male 1946-1965	20	0.59 (0.58, 0.60)	33.0 [31.0, 35.3)
Community Male >1965	20	0.57 (0.56, 0.58)	28.7 [27.0, 30.9)
Federal Male 1946-1965	20	0.33 (0.29, 0.37)	10.4 [9.0, 12.1)
Federal Male >1965	20	0.30 (0.26, 0.35)	9.6 [8.3, 11.1)
Provincial Male 1946-1965	20	0.74 (0.72, 0.76)	188.4 [146.3, 233.7)
Provincial Male >1965	20	0.73 (0.70, 0.75)	155.6 [118.6, 201.0)
Community Male 1946-1965	52	0.44 (0.43, 0.45)	33.0 [31.0, 35.3)
Community Male >1965	52	0.42 (0.41, 0.43)	28.7 [27.0, 30.9)
Federal Male 1946-1965	52	0.18 (0.15, 0.22)	10.4 [9.0, 12.1)
Federal Male >1965	52	0.16 (0.13, 0.20)	9.6 [8.3, 11.1)
Provincial Male 1946-1965	52	0.63 (0.61, 0.66)	188.4 [146.3, 233.7)
Provincial Male >1965	52	0.61 (0.58, 0.64)	155.6 [118.6, 201.0)

Note: description of individual order is facility of first test, sex, birth year (strata=40-49 years). The probability displayed is the probability of not having an RNA test at the number of weeks specified for the particular combination of covariates. The median CIs are based on linear limit transformations

Table 6. Measures of effect: sensitivity analysis

Measures of effect	
Covariate	Hazard ratio (95% CI)
Facility of first test by calendar year for females (reference=Community)	
Federal at 2004-2008	1.42 (1.11, 1.82) †
Federal at 2009-2014	1.98 (1.54, 2.54) †
Provincial at 2004-2008	0.54 (0.47, 0.62) †
Provincial at 2009-2014	0.55 (0.48, 0.64) †
Facility of first test by calendar year for males (reference=Community)	
Federal at 2004-2008	1.48 (1.35, 1.63) †
Federal at 2009-2014	2.06 (1.83, 2.32) †
Provincial at 2004-2008	0.66 (0.60, 0.72) †
Provincial at 2009-2014	0.68 (0.62, 0.74) †
Sex by testing facility (reference=Males)	
Females at community	0.99 (0.97, 1.02)
Females at federal	0.96 (0.74, 1.23)
Females at provincial	0.81 (0.70, 0.94) †

† *indicates statistical significance ($p<0.05$)*

Chapter 4

Duplicate HCV antibody tests in adults in Ontario, Canada

4.1 Abstract

PURPOSE: Antibodies generated by a hepatitis C virus (HCV) infection persist through life for the vast majority of cases.[1,2] Subsequent antibody tests are considered strictly unnecessary and could represent a burden to the individual and the health care system. This observational study sought to describe duplicate HCV antibody testing in adults who have tested positive for HCV in Ontario between 1999-2014. Of particular interest in this field of research is the number of duplicate of tests coming from provincial and federal correctional institutions.

METHODS: A subset of data was obtained from Public Health Ontario Laboratories (PHOL). This dataset contains all HCV tests performed at PHOL between 1999 and 2014. A subject's index date was determined as the first date of testing positive for HCV; antibody tests completed after this date were summed for each subject. The total number of antibody tests in the dataset over this study period were determined, including the number of tests performed each calendar year and the number of tests coming from the community facilities, provincial institutions, and federal institutions. Instances where an HCV ribonucleic acid (RNA) test was recorded at the same time as an antibody test were also described.

RESULTS: 96,044 unique individuals with proof of HCV positivity were included in the study. 181,287 antibody tests were indicated in the dataset during the study period and 94,076 (51.9%) were considered duplicate. Approximately half of all individuals demonstrated at least one duplicate antibody test during the study period. The distribution of antibody tests over the study calendar years revealed potential issues related to data quality and test recording practices. In particular, PHOL may be cancelling some tests where previous exposure to HCV was evident. A significant proportion (22.2%) of duplicate tests were performed at the same time as an HCV RNA test.

CONCLUSION: Duplicate antibody testing in Ontario is common. Describing where redundancies exist and eliminating unwarranted testing may improve efficiencies overall and help alleviate a significant burden from the individuals tested and the health care system. The promotion of reflex testing practices in Ontario is corroborated by these findings.

4.2 Introduction

Hepatitis C virus (HCV) is prevalent in approximately 0.87% of the Ontario population and 0.64% to 0.71% of the Canadian population.[3,4] Testing for HCV in Canada is based on risk-based screening recommendations.[5] Some of these risk factors include a history of injection drug use, those who have received health care where infection control and sterilization techniques lack, recipients of blood transfusions or organ transplants prior to 1992, and individuals born in countries where HCV prevalence is high.[2,5] In addition, HCV exposure rates remain particularly high in incarcerated populations, with prevalence estimates ranging from 16-30% in federal and provincial institutions.[6,7]

Testing for HCV begins with a blood test screening for HCV antibodies. If this test is positive, an HCV ribonucleic acid (RNA) test is required to establish the diagnosis of an active infection. A negative RNA test suggests the individual has cleared the infection naturally, been successfully treated for the virus, or, less likely, the antibody test was a false-positive result. The RNA test is an essential step in the cascade of care for HCV to begin treatment. The recent introduction of highly effective, curative direct-acting antiviral (DAA) therapies has made it even more imperative that individuals infected with HCV are identified and receive treatment.[2,8]

In order to promote ubiquitous RNA testing following a positive HCV antibody result, the use of reflex testing methods has been suggested.[8] A reflex test implies that a positive antibody result automatically triggers an additional test for HCV RNA. This helps to ensure the

individual is indeed tested for HCV RNA and the required bloodwork can be performed on a single medical visit.[9,10]

Once an individual tests positive for HCV antibodies, they typically test positive for life.[2] Given this fact, any HCV antibody test ordered after an individual demonstrates positivity signifies a duplicate test. Several studies have described possible risk factors associated with exposure to duplicate testing.[1,11] A study by Tsai et al.[1] found that 50% of study subjects in New York City had evidence of repeat testing. Males and individuals ever tested in a substance abuse or corrections facility were more likely to experience duplicate antibody tests. At the level of the health care system, these tests represent financial and personnel costs. Repeat testing may indicate poor uses of resources and a lack of coordination of care. Absence of modern medical electronic documentation systems might explain a communication disconnect that seems to exists between various medical facilities.[12,13]

At the individual level, duplicate HCV antibody tests can be a significant physical and mental burden. Although not explicitly described in the literature, duplicate testing may be the product of the stigma and stereotyping related to those who have spent time in prison or inject drugs. For those being repeatedly tested, the effect may augment the discrimination they feel from the health care system and contribute to social isolation and perceived blame.

The objective of this study was to perform a descriptive analysis of the number of duplicate antibody tests conducted through Public Health Ontario Laboratories (PHOL) in Ontario, Canada between 1999 and 2014. The original intended objective was to determine risk factors associated with duplicate testing using a count data multivariable regression analysis; however, the descriptive analysis revealed potential data quality concerns and possible inconsistencies related to how repeat tests were dealt with at PHOL over the study years. The

results are thus intended to gain further understanding of the PHOL dataset, appreciate the magnitude of duplicate tests, provide PHOL with details of where duplicate antibody tests were being performed, generate hypotheses for future work, and make relevant recommendations. Of particular interest is the number of duplicate tests coming from federal and provincial institutions. Time spent in a prison represents a possible exposure for future research that may have an association with duplicate antibody testing. Only once accurate antibody testing counts are determined can a risk assessment be conducted. This report is a necessary preliminary step in understanding these patterns. Eliminating duplicate testing can not only reduce superfluous costs to the taxpayer, but also alleviate part of the burden experienced by those who are exposed to redundant tests for HCV and, ultimately, support HCV elimination.

4.3 Methods

Dataset, study population, and study design

A subset of data was obtained from PHOL. This dataset allowed for the retrospective analysis of HCV antibody testing frequencies. The PHOL dataset contained information pertaining to all HCV antibody and RNA tests performed at PHOL between January 1999 and December 2014. This included positive, negative, and inconclusive results with the dates they were conducted. Subjects were considered eligible if they demonstrated HCV positivity through either a positive antibody or HCV RNA test at some point during the study period. A positive HCV RNA result was also an acceptable index date as it confirmed active HCV infection and antibody testing after this was considered redundant. Only those who were at least 18 years of age at some point during the year of their first positive result were included in the analysis.

Identification numbers unique to each subject, but could not be linked to any particular individual, were utilized and followed the subject across the study period. Each subject's year of

birth, sex, and location of test submitting institution was available. A detailed list of the correctional submitting institutions available in the study can be viewed in Appendix B.

Cleaning of PHOL dataset

The PHOL dataset was imported into SAS software version 9.4 (SAS Institute, Cary NC). All cleaning and statistical analyses described were completed in SAS. Based on the submitting institution, each facility was classified as either a community medical facility, federal institution, or provincial institution.

Evidence of HCV positivity was defined as any positive HCV antibody or RNA test result; the first positive test was considered the index test. The number of HCV antibody tests appearing in the dataset following the index test were summed to provide a total number of antibody tests performed following evidence of positivity. The number of duplicate antibody tests was defined as the total number of antibody tests minus 1. For example, an individual who demonstrated 2 positive HCV antibody tests in the dataset had one duplicate test. Negative and inconclusive results that occurred prior to proof of positivity were not included in the summation of antibody tests. Figure 1 provides a visual explanation of the counting process.

Analysis

The number of duplicate antibody tests for each individual was described and a graphical distribution was produced. The total number of duplicate antibody tests in the PHOL dataset during the study period was provided. This was further assessed in terms of the relative number of individuals with duplicate testing each year. Every time an individual tested positive for HCV, they added to the population that was eligible for duplicate testing. As the study period moved forward, the total eligible sample size increased. As a result, the number of subjects with at least one duplicate test divided by the cumulative eligible study population was determined. The

absolute and relative numbers of duplicate antibody tests coming from community medical facilities, provincial institutions, and federal institutions were provided.

4.4 Results

331,069 HCV test results on individuals who showed HCV positivity were available in the PHOL dataset. A total of 98,878 unique subjects demonstrated HCV positivity through either a positive antibody test or HCV RNA test between 1999 and 2014. 1,218 (1.2%) and 1,616 (1.6%) subjects were removed where age was missing and where age was under 18 years during their first year of positivity, respectively. The total eligible study population for analysis was 96,044 individuals. A flow chart of the study sample size is demonstrated in Figure 2. Population characteristics are described in Table 1.

Among adults who demonstrated HCV positivity, 181,287 antibody tests were recorded during the study period; 2.9% and 2.4% of these tests were in federal and provincial institutions, respectively. 94,076 (51.9%) of the antibody tests represented duplicate tests during the study period. Of the total number of duplicate tests, 2,821 (3.0%) and 1,769 (1.9%) came from federal and provincial institutions, respectively (Table 2). When considered further by calendar year, the proportion of duplicate tests coming from each respective facility classification was increasing towards the end of the study period; this is demonstrated in Figure 3. A substantial proportion of antibody tests performed at the end of the study period represented duplicate tests. For example, 76% of antibody tests from the community in 2014 performed on individuals who were HCV positive were duplicate tests. The highest percentage was in federal institutions in 2013 where 82.4% of all antibody tests on HCV-positive individuals were duplicates. A distribution of the number of duplicate tests per individual is displayed in Figure 4. 51.5% of subjects demonstrated at least one duplicate antibody assessment and 24.7% of the total population had 2 or more

duplicate tests. The absolute number of antibody tests coming from each respective testing facility type by calendar year is illustrated in Figure 5 and Figure 6. The number of individuals, by each testing facility, with at least one duplicate test expressed as a percentage of the total eligible population in each calendar year is shown in Figure **7** and Figure 8.

31,086 positive antibody tests (17% of the total) were ordered at the same time as an HCV RNA test. 10,230 (32.9%) of such tests were performed on the index date while the remaining were conducted after proof of positivity. This number indicates that 10.9% of all index antibody tests had an associated RNA test. This amounts to 11.9%, 16.2%, and 2.5% of the total index antibody tests that came from community, federal, and provincial facilities, respectively. Among antibody tests that were performed at the same time as an RNA test but after proof of past positivity, 19,712 (94.5%), 1,021 (4.9%), and 123 (0.6%) were from the community, federal institutions, and provincial institutions, respectively. This represents 22.0%, 36.2%, and 7.0% of the duplicate test from each of those respective facilities. Overall, these tests make up 22.2% of all duplicate antibody tests. These results are summarized in Table 3.

4.5 Discussion

The results of this study indicate that a substantial number of antibody tests appearing in the PHOL dataset between 1999 and 2014 were duplicate. It is important to reiterate that the sample population included subjects who tested antibody positive at some point during the study period. Individuals who only ever tested antibody-negative were not included in this study and therefore total antibody numbers refer to total antibody tests on individuals known to be positive for HCV antibodies.

Approximately half of the tests performed on adults who demonstrated prior exposure to HCV in this study represented tests that did not need to be performed. When considered by

calendar year, a substantial proportion of HCV antibody tests were duplicates in all testing facilities (Figure 3). By the end of the study period, upwards of 60-80% of anitbody tests on HCV positive individuals represented duplicates. To put this in clinically meaningful terms, 60-80% of antibody tests performed in the latter years of the study were on individuals who already had evidence of past positivity. The proportion of duplicate tests in the early years of the study may be an underrepresentation since many of these individuals may have had a positive antibody result prior to the study period.

Half of individuals who were HCV positive demonstrated at least one duplicate antibody test during the study period. This is a clinically relevant finding that indicates poor linkage of health records across medical facilities. The proportion of individuals who had duplicate tests is also likely an underrepresentation of the actual number of patients who experience repeat testing. Individuals who demonstrated positivity towards the end of the study period had short follow-up times and may have been tested again beyond the end of the study period at December 31, 2014.

While this study contained antibody results submitted to PHOL, some private clinics and hospital labs performed in-house testing not submitted to PHOL. For example, Mt. Sinai Hospital in Toronto is known to perform some in-house antibody testing. Any results that pass a specific threshold are not sent to PHOL. Antibody tests missing from these facilities will inevitably contain duplicate antibody tests not described in this study. As such, the duplicate tests described in this report are strictly related to those tests performed at PHOL.

In instances where RNA tests were ordered at the same time as a positive antibody result, several explanations exist. These results could in theory indicate a reflex test; however, it is more likely that evidence of past antibody-positivity is missing from the dataset. In situations where evidence of exposure to HCV does exists, it is unclear as to the intention of these tests. The

submitted test may have been intended for HCV RNA and an additional, and duplicate, antibody test was performed. It should be emphasized that data input errors were possible and offer another explanation for the appearance of antibody tests alongside RNA results. Even if it was the case that antibody tests were incorrectly recorded in combination with RNA tests, there were still over 73,000 duplicate antibody tests in isolation of RNA tests. Regardless, promoting the ubiquitous use of reflex testing practices would ensure that all individuals are tested for HCV RNA.[10] By combining reflex testing with effective follow-up plans and intervention strategies, the patient can remain connected with the health care system and may have the effect of reducing the number of duplicate antibody tests they are exposed to.

The duplicate antibody tests identified in this study represent a sizeable economic cost to our health care system. Absolute numbers of duplicate tests do not appear to be decreasing over the calendar years in any of the testing facility classifications (Figure 5 and Figure 6). This pattern is still evident after adjusting for the number of eligible subjects over calendar years (Figure 7 and Figure 8).

Duplicate antibody testing patterns over calendar years (Figure 5-8) also indicate possible discrepancies over time in how PHOL collected and recorded the results. Obvious differences were seen during 2005-2006 and 2010 and beyond across all testing facility types. An increase in duplicate tests over the study period would not be surprising given that the eligible study population is increasing as time moves forward and more individuals have an index date; however, after adjusting for the cumulative eligible population, a similar trend was observed over calendar years (Figure 7 and Figure 8). The drop in number of duplicate tests between 2007 and 2009 may be suggestive of programmatic differences in how duplicate tests were dealt with. According to email contact with PHOL, a number of software changes have occurred over the

past number of years. In the past, PHOL reports to have had the ability to cancel incoming antibody tests where proof of past positivity was evident. With changes to their software systems, this was apparently not an option between May 2010 and November 2012. While this may help explain the increased number of tests in those calendar years, it does not clarify why other years show inflated duplicate tests or why there are repeat tests in the dataset at all. It remains possible that many HCV antibody tests were submitted to PHOL, cancelled, and not included in the dataset. The frequency of this ought to be determined before the data is used to investigate risk factors for duplicate antibody testing in the general population.

While tests that are cancelled represent a cost savings for the lab, it fails to capture the burden placed on the patients who had bloodwork for a test that was not required. Future work in this field may seek to gather data on the number of tests that were cancelled as a result of past positivity. In these situations, it is up to the ordering practitioner to obtain past results for the patient they are planning to test. Advances in electronic documentation and linkages of patient records present opportunities for physicians to be able to access past results and prevent some of these duplicate tests.

The crude number of duplicate tests coming from provincial institutions was lower than the other two facility categories; however, duplicate tests appeared to be increasing towards the end of the study period. Interestingly, the spike in absolute and relative duplicates seen in 2005 and 2006 in the community and federal institutions was not as obvious in the provincial institutions. Antibody tests that were associated with HCV RNA tests appeared to be much lower when coming from provincial institutions. This may reflect the notion that individuals tested in provincial prisons were less likely to receive an RNA test at all. It is clear from these data that duplicate tests were not an isolated problem from any one particular type of testing facility. The

magnitude of the issue was greatest in the community and the problem of duplicate tests did not seem to be improving in the latter years of the study period.

4.6 Conclusion

This study highlighted the pervasiveness of duplicate antibody tests in Ontario. The descriptive results present opportunities to acknowledge the magnitude of the problem and hopefully aid in eliminating the practice at the level of the laboratory. Strategies used to identify where past HCV positivity is evident and incoming tests are cancelled ought to be revisited and may be the first step in trying to rectify this problem.

Where antibody and RNA tests are recorded on the same day, the intention and validity of these results need to be considered. Reflex testing would ensure that the individual tested has a result describing whether or not they have active HCV infection. Where the individual shows evidence of a previous positive antibody test, subsequent RNA tests need not be conducted alongside a duplicate antibody test.

The data shown in this study may be an underestimation of the problem for the individuals tested and at the level of the ordering physician. A multidisciplinary approach to link practitioners with test results is essential. This requires the collaboration of health care providers and information technology specialists. Eliminating redundant testing alleviates an unwanted burden to the individuals being tested as well as the health care system in Canada.

4.7 References

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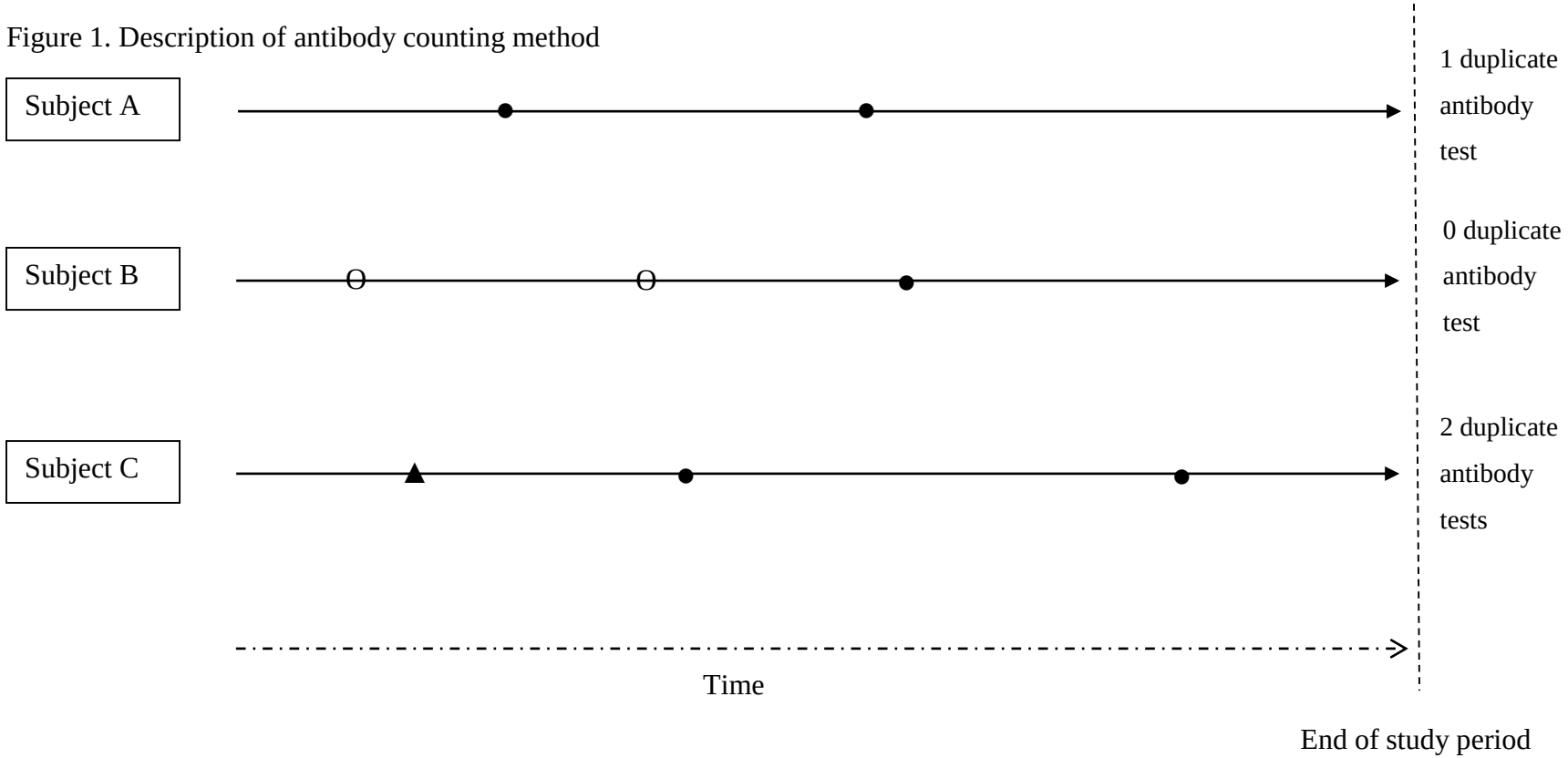
Figure 1. Description of antibody counting method



Note: this schematic represents the difference between three separate theoretical subjects and the differences in the way their antibody test results were summed for the analysis.

Legend: Arrows indicate study follow-up time; ● is a positive antibody result; O is a negative antibody result; ▲is a positive RNA result

Table 1. Population characteristics

Characteristic	*N*	*%*
Sex		
Male	60,680	63.2
Female	34,610	36.0
Unknown	754	0.8
Birth year		
<1946	10,198	10.6
1946-1955	23,005	24.0
1956-1965	32,465	33.8
>1965	30,376	31.6
Age at first testing (years)		
18-29	10,802	11.3
30-39	20,389	21.2
40-49	31,140	32.4
50-59	21,914	22.8
60+	11,799	12.3

Figure 2. Flow chart of study subjects

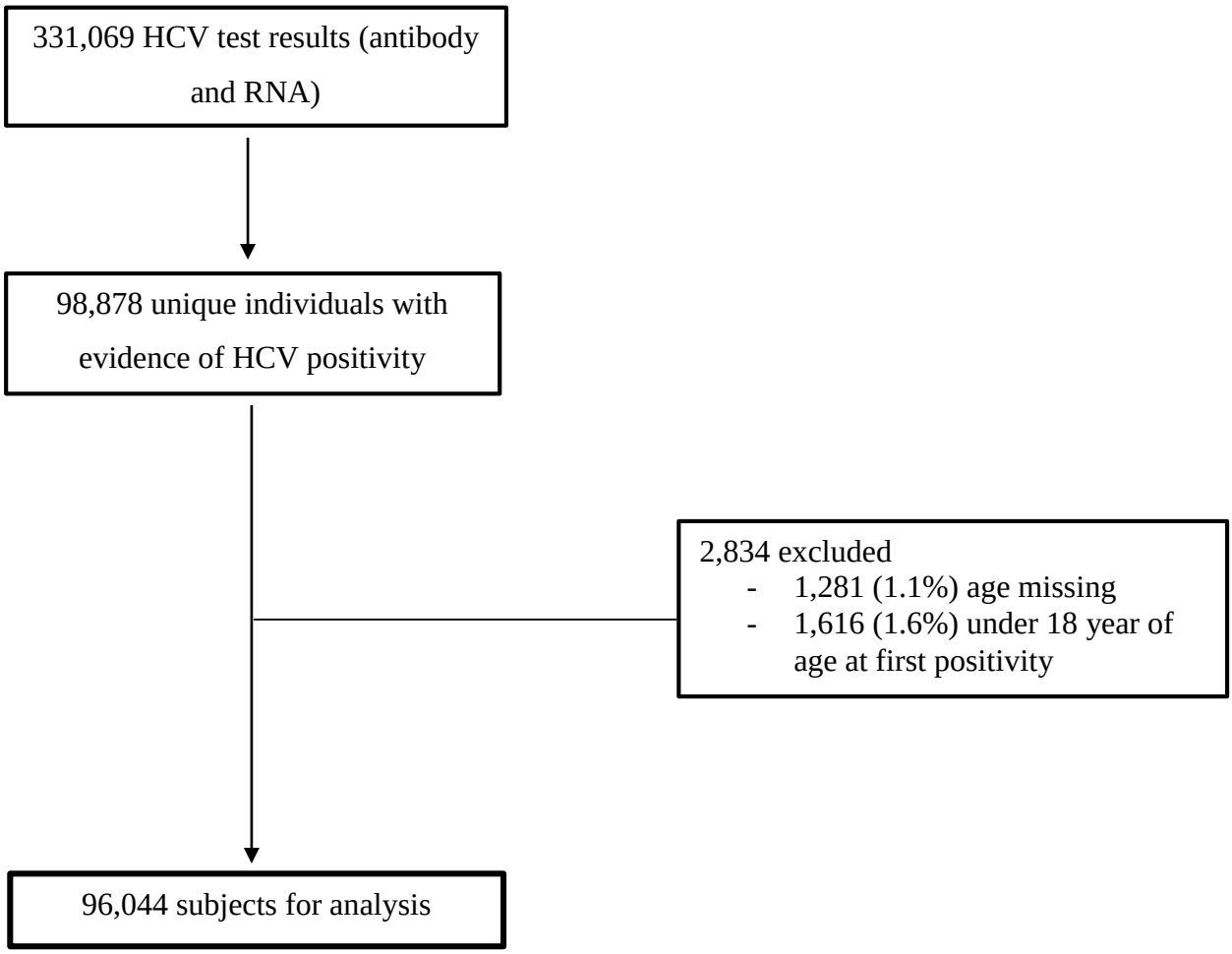
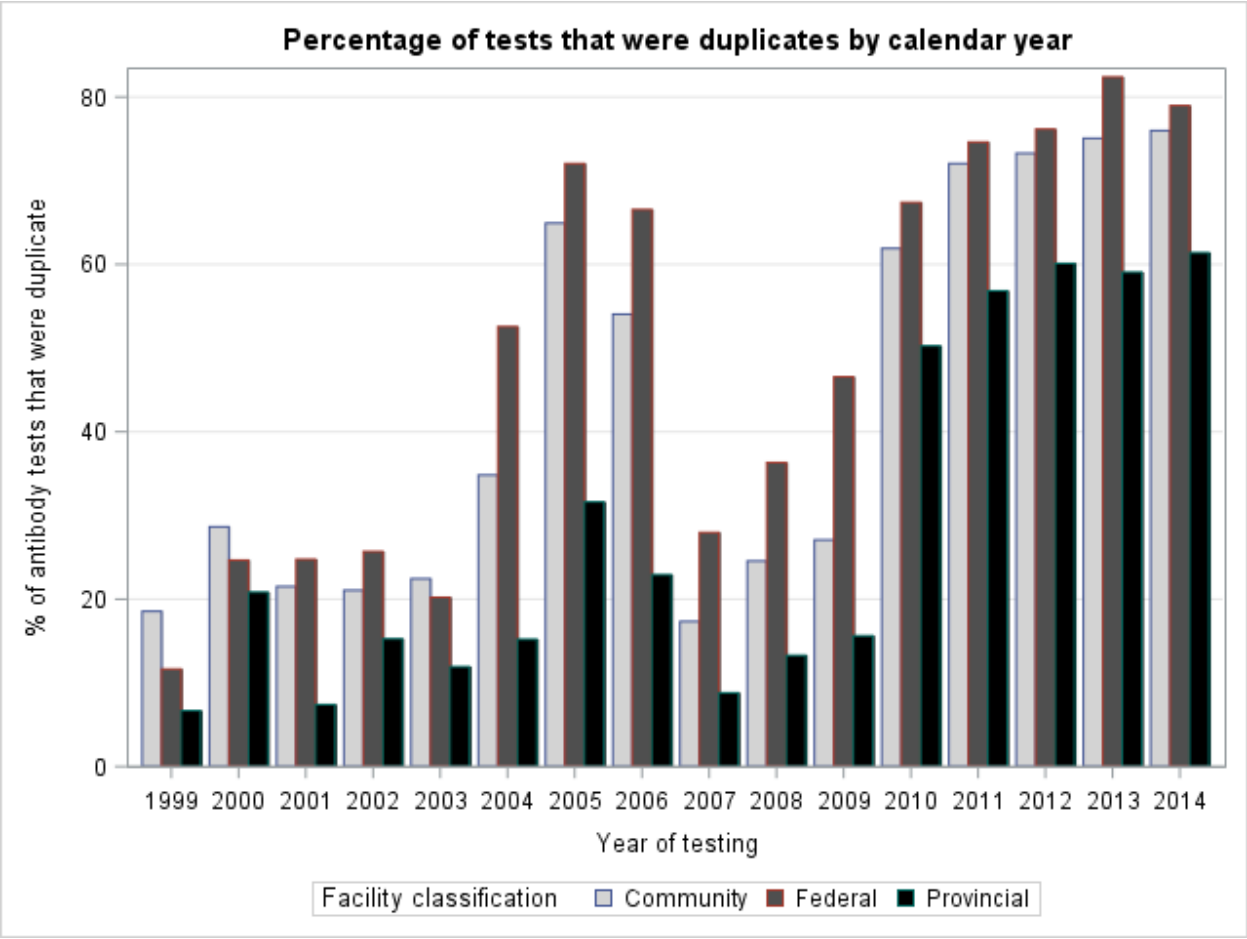


Table 2. Total antibody tests and duplicate antibody tests by testing facility type

Antibody testing totals			
Submitting facility	Total antibody tests N (percent)	Duplicate antibody tests N (percent)	Overall percent that are duplicate
Community	171,609 (94.7),	89,486 (95.1)	52.1%
Federal	5,304 (2.9)	2,821 (3.0)	53.2%
Provincial	4,374 (2.4)	1,769 (1.9)	40.4%
Total	181,287	94,076	51.9%

Figure 3. Duplicate tests by calendar year expressed as a percentage of total antibody tests performed that year



Note: the denominator includes only individuals known to be antibody-positive at some point during the study period

Figure 4. Distribution of duplicate antibody tests

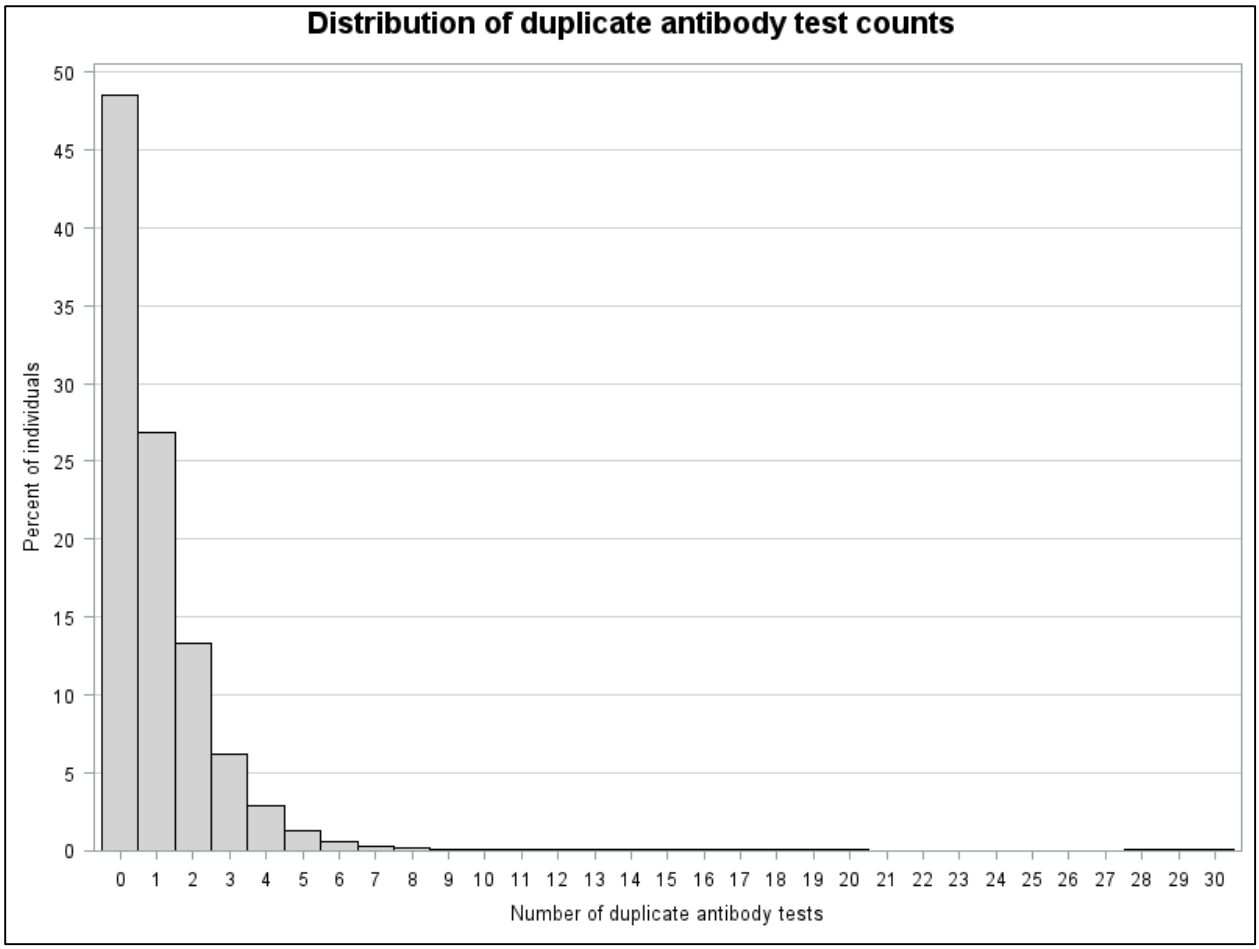


Figure 5. Absolute number of duplicate tests coming from community facilities by calendar year

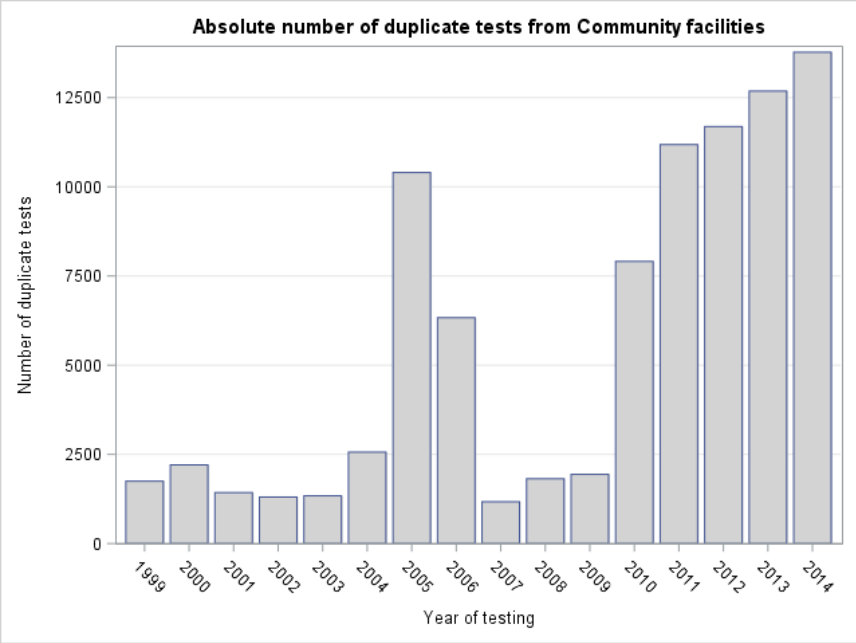


Figure 6. Absolute number of duplicate tests coming from federal and provincial institutions by calendar year

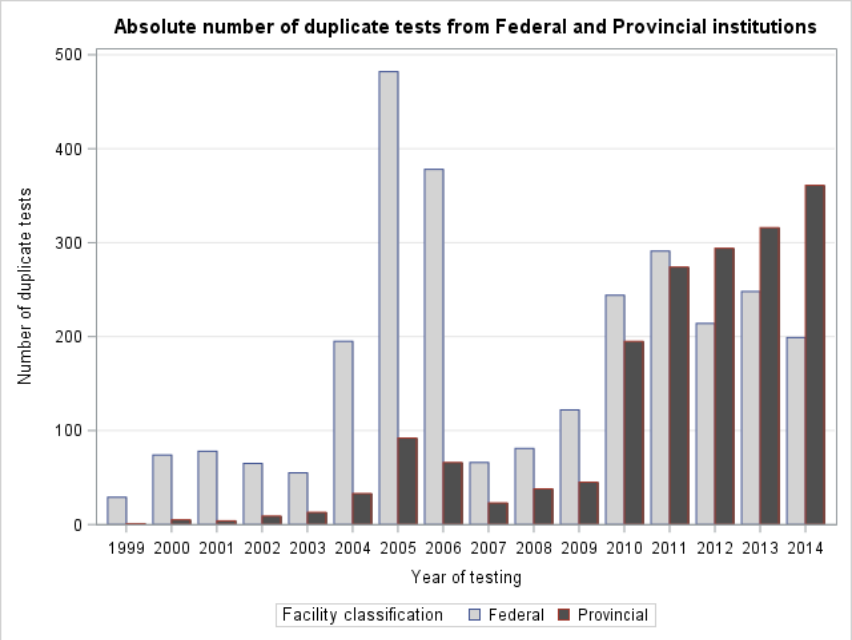


Figure 7. Percentage of individuals with at least one duplicate test in the community

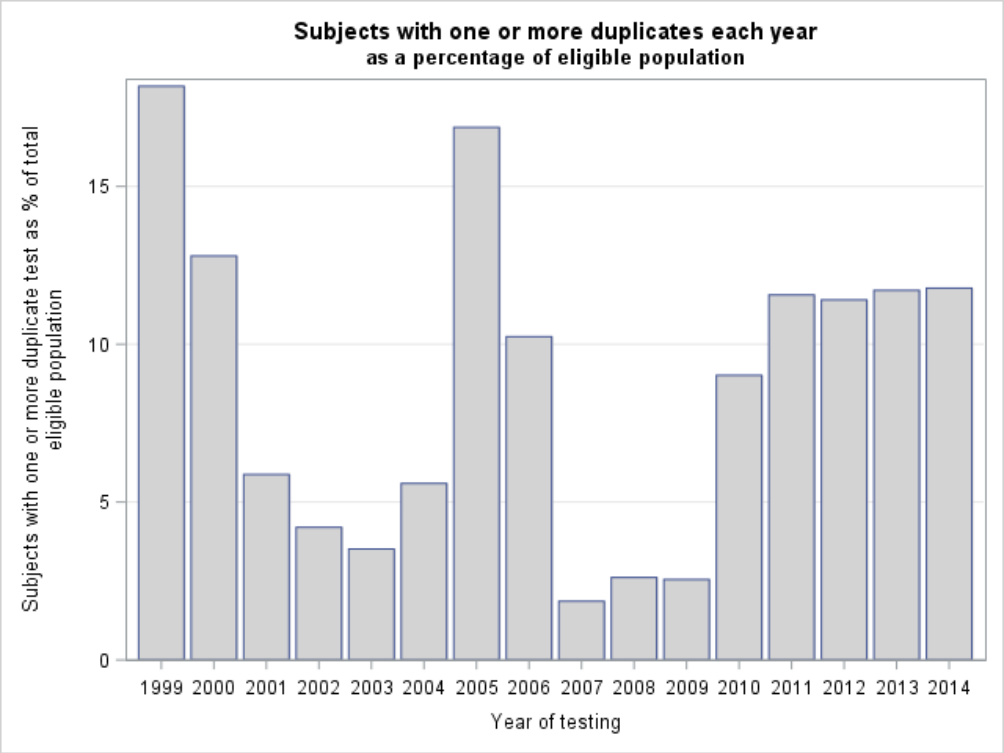


Figure 8. Percentage of individuals with at least one duplicate test in federal and provincial prisons

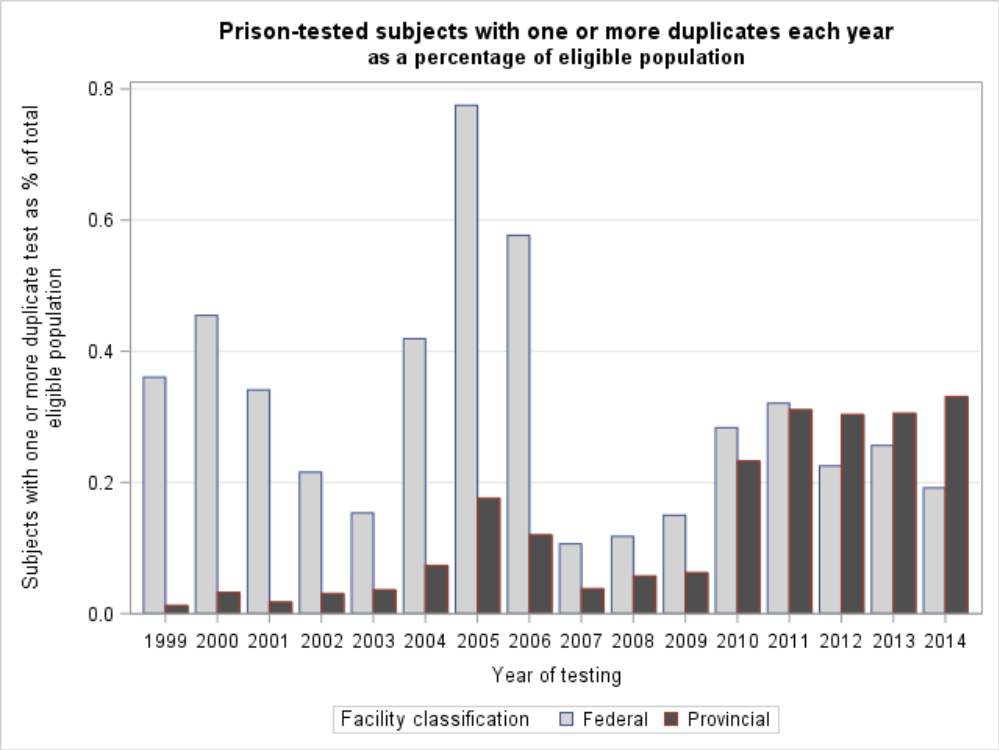


Table 3. Description of positive antibody tests and RNA tests performed on the same day (Number of tests, row percent)

Positive antibody and RNA tests ordered on same day				
	Submitting facility			
	Community	Federal	Provincial	Total
RNA and antibody performed on index date (% of all index tests)	9,761 95.4 (11.9)	403 3.9 (16.2)	66 0.6 (2.5)	10,230 (10.9)
RNA and antibody performed after proof of positivity (% of all duplicate tests)	19,712 94.5 (22.0)	1,021 4.9 (36.2)	123 0.6 (7.0)	20,856 (22.2)
Total	29,473	1,424	189	31,086

Note: the row percent (the second number down in each row) represents the percentage of RNA tests performed at the same time as an antibody test in each of the submitting testing facility types. The number in brackets in the first row is the percent of all index antibody tests that were RNA plus antibody test that were conducted together on the date of the first positive result (or the index date). In the second row, the number in brackets indicates the percentage of all duplicate antibody tests that had an RNA test performed with it.

Chapter 5

General discussion

5.1 Thesis summary

My thesis set out to explore two primary aspects of the cascade of care for hepatitis C virus (HCV) testing in Ontario, Canada. The first objective explored the time between first testing positive for HCV antibodies and receiving the essential follow-up HCV ribonucleic acid (RNA) test to confirm active infection. The primary exposure of interest was initial antibody testing facility; in the community, in a federal corrections facility, or in a provincial corrections facility. The second objective sought to describe duplicate HCV antibody tests performed at Public Health Ontario Laboratories (PHOL) on adults who have tested HCV positive. Both objectives were explored using a subset of PHOL data which contained information regarding all HCV tests conducted at PHOL, including antibody and HCV RNA results, between January 1999 and December 2014.

5.1.1 Time to HCV RNA testing following first positive antibody test in those first tested in a correctional facility or the community in Ontario, Canada

Section 5.1 discusses the findings, strengths, limitations, epidemiological issues, and public health significance as they relate to the content in Chapter 3.

5.1.2 Summary of major findings

Individuals who first tested antibody positive in a provincial correctional institution appeared to take longer to have HCV RNA testing compared to individuals first tested in a community-based facility or in a federal penitentiary. This finding was in contrast to individuals first tested in a federal institution who were faster to receive the RNA test compared to those first

tested in the community in the latter years of the study. This effect seemed to depend on the calendar year of first testing and sex; however, the direction of effect was the same across calendar years for those first tested in a provincial facility. The magnitude of effect was greater for females and females took longer than males to receive RNA testing when first tested in a provincial facility, regardless of calendar year first tested. The results from the main analysis were corroborated by a sensitivity analysis that removed individuals with long, and potentially incorrect, follow-up times. The direction of effect for the main exposure was the same in the sensitivity analysis and the results remained statistically significant.

5.1.3 Additional findings

A finding not presented in Chapter 3 concerns the effect of calendar year controlling for all other variables. An improvement over calendar years can be seen in all testing facility classifications (Appendix K). For example, the hazard ratio (HR) comparing those first tested in a federal institution in 2009-2014 to those first tested in a federal institution in 1999-2003 was 4.93 (95% confidence interval [CI]=4.30, 5.66). The HR comparing those first tested in a provincial institution in 2009-2014 to those first tested in a provincial institution in 1999-2003 was 1.83 (95%CI=1.49, 2.23). A similar effect was seen in the community group across the same calendar years. These results suggest that an improvement in testing practices is apparent in the latter years of the study. This finding is consistent with the notion that knowledge translation and HCV management initiatives are becoming more widespread.[1] World Health Organization (WHO) guidelines have placed a greater demand on health care providers to ensure proper HCV diagnoses are made through accepted testing practices.[2,3] This finding may also reflect advancements in medical documentation procedures; in particular, electronic documenting where accessing patient medical histories is available.

5.1.4 Strengths

This study has several strengths. The first is the availability of a large sample size. This helped to attenuate concerns regarding random sampling error that is often associated with small sample sizes.[4] This led to a highly-powered study where small differences were detectable (see Appendix L for power calculation). In addition, the sensitivity analysis required the removal of a significant number of subjects; the large baseline sample size left plenty of room for their removal and an adequate number of subjects remained for this part of the analysis.

The sensitivity analysis itself is a major strength of this study. After the removal of potentially problematic subjects, the results from the main analysis were corroborated by several forms of sensitivity analyses (Appendix J). The sensitivity analysis removed many individuals who had potentially long follow-up times and were censored in the main analysis. Many of those removed likely represented individuals who did not receive RNA testing during the testing period. The sensitivity analysis also helped to reduce concerns related to bias that will be explained in the next section.

Given that the majority of RNA tests for adults are sent to PHOL, if an RNA test had been conducted in Ontario during the study period, it is likely to have shown up in the dataset. Furthermore, all RNA tests conducted in correctional facilities are sent to PHOL. This resulted in a reliable event date where it was available. This is one of the advantages of using laboratory datasets over medical records. If the study had relied on clinical notes, there is a stronger possibility of missing results.

5.1.5 Internal validity

This section discusses the internal validity of this study. Internal validity is the degree to

which the results reflect what is truly occurring in the population of interest. Of particular interest is an assessment of the threats produced from bias, chance, and confounding.[4] As mentioned above, the large sample size in this study makes it unlikely that the results are due to chance alone.

Selection bias

Selection bias occurs when those that are included in the study differ from those who are not included or differ in a systematic way to groups being compared for analysis.[4] This study attempted to represent all individuals in Ontario who tested antibody positive. The risk of selection bias into the study was minimized given that all individuals who were tested at PHOL were considered for inclusion. Where there is potential for selection bias is situations where individuals were tested for antibodies in settings that did not submit to PHOL and would therefore not be included in the dataset. This would include private labs and hospital settings that performed their own tests. For example, Mt. Sinai Hospital in Toronto performs some in-house antibody testing and may not have submitted their results to PHOL. There is no reason, however, to suspect these individuals to be different from the other individuals first tested in the community. This is especially true given that antibody testing is covered by OHIP and financial costs would not present a barrier to receiving screening. This form of selection bias would not be strong in the federal group as most tests would be submitted to PHOL. The number of other facilities that perform their own antibody tests is unknown; however, there is still no reason to believe subjects tested in these locations to differ from the population selected for this study.

Information bias

A common type of information bias in epidemiological studies is misclassification.[4]

Misclassification can result in the erroneous classification of an exposure or outcome. Differential misclassification occurs when the error is disproportionally greater in one group compared to another. Differential misclassification of the facility of first testing was discussed in Chapter 3, but some situations are worth elaborating on. If an individual had a prior positive antibody test date not captured in the dataset, not only is the index date incorrect, but there remains the possibility of misclassification of facility of first test. Best practice would suggest that individuals will not have further antibody testing after their first positive finding since once an individual tests positive, they test positive for life. With these individuals, there is no cause for concern regarding misclassification. This is not always the case, however, and some individuals are unnecessarily retested for antibodies. Nearly half of those tested in this dataset had evidence of antibody testing even after a positive result and some of these individuals were tested at different testing facility types. Given the small relative number of those first tested in prison compared to the community, misclassifications where community-classified subjects who were in fact first tested in prison at an earlier date would have less of an impact on the results. More significant misclassifications are expected where those classified as being first tested in prison were in reality first tested in the community and could indeed result in bias. For example, if a subject was classified as first tested in a provincial facility but were truly first tested in the community, based on the direction of the results found in this study, they may be more likely to receive the RNA test. This would diminish the difference in effect observed between the community and provincial groups. The severity of potential misclassification is presented in Appendix I and it is likely that a significant number of subjects were misclassified across all testing facilities. The sensitivity analysis included only those subjects who were first tested in

2004 and the lead-up time of 5 years without being tested increased the confidence that the index facility was the subject's first test. This eliminated many inevitable cases of misclassification.

Misclassification of the outcome was possible in the context of this study where an individual had an RNA test out of province and was incorrectly censored. This would not affect those who were classified as having an event; the event date is accurate and we know they indeed had an RNA test. Errors in classification of the outcome would bias the results such that those who were misclassified would contribute erroneously long follow-up times. In Ontario in 2015/2016, approximately 0.45% of the population moved out of the province.[5] Individuals who were in prison, especially federal prisons, would be much less likely to receive testing out of province; therefore this differential misclassification of the outcome would have a greater effect on the community group. This would bias the results in the direction of the null comparing the community group to the provincial group and increase the difference observed between the community and federal group. This would only bias the results, however, if the individuals that moved out of province actually received the test somewhere else. This type of bias could also be viewed as a type of selection bias where there is differential loss to follow-up. The sensitivity analysis removed those individuals with potentially lengthened follow-up times.

Information error occurs if the index date was incorrect where an individual was tested out of province, outside of the study period, or at a facility where in-house antibody tests were performed. In some instances, this could lead to bias. Uncaptured tests prior to the index date would lengthen the amount of time an individual should have contributed to the analysis. To explore the impact of potential bias, consider the situation of Mt. Sinai. If this were a concern with respect to Mt. Sinai, it would have had an effect on those first tested in the community given that it is a community facility. If a significant number of tests were missing from this

center, the results would be biased such that the community group is receiving tests faster than what is their true follow-up time. This would imply, however, that the individuals tested here ended up getting another test at another location during the study period that was captured by PHOL; otherwise, they would simply not have been captured in this study to begin with. Bias in this direction would attenuate the difference between those first tested in a federal facility and those first tested in the community and exaggerate the difference between those first tested in a provincial institution and those first tested in the community.

Uncontrolled confounding

A confounder is a variable that is related to both the exposure and the outcome and may represent an alternate explanation for an observed association.[4] In multivariate models, like the Cox's proportional hazards (PH) model, confounders are controlled for as covariates in the model. Uncontrolled confounding occurs when information regarding potentially important confounders is unavailable. Several variables that would be worth exploring as confounders were missing from the limited information available in the PHOL dataset.

As mentioned in Chapter 3, information was missing regarding each subject's history of injection drug use, access to primary care, mental health, and socioeconomic status. Perhaps the most relevant absent variable was a history of or current use of injection drugs. This was a common variable noted in the literature and would very likely be associated with both the facility of first testing and receiving the RNA test. The stigma surrounding the use of injection drugs is of particular interest and stereotyping has many negative repercussions on the individuals themselves.[6] Stigma can also influence health care providers and lead to judgements and decisions that alter the cascade of care for HCV. If an ordering practitioner fears that a patient will become re-infected after they have received curative treatment, they may be less likely to

order the RNA test.[1,7] In one Canadian survey, only 20% of specialist physicians were willing to provide treatment for individuals who currently inject drugs.[8] If the there is no intention to treat on the part of the physician following a positive antibody result, the RNA test may not be ordered in the first place.

Given that injection drug use is such a strong risk factor for HCV infection, this behaviour may be the most impactful; however, stigma surrounding other characteristics could have a similar effect. For example, individuals with multiple comorbidities or coinfections (especially HIV) and individuals in lower socioeconomic brackets may be at risk of marginalization and, therefore, experience delayed time to RNA testing. Disproportionate numbers of Aboriginals in correctional institutions and the higher rates of HCV infection in this group represents another important confounder that ought to be explored in future research.[9–11]

A lack of information regarding differences in practices between health care facilities could also have led to a spurious association observed in this study. Of significant interest is the use of electronic medical documentation technologies. This type of documentation has the advantage of including the medical history of patients should they see multiple care providers. In addition, the incorporation of reminders to order a particular test, in this case HCV RNA testing, could be an effective way to increase testing coverage.[12] The availability of electronic documentation in the provincial corrections system is lacking and this may very well be the highest risk group.[13] Although outside of the study period, in 2016 all federal institutions transitioned to an electronic medical documentation platform.

Future research should consider obtaining information regarding the mobility of those individuals tested in the study. Information regarding movements in and out of province could be helpful. More complex information regarding transfers between prisons should also be

considered. For example, many individuals who end up in a federal prison often spend the first part of their sentence in a provincial institution.[14] Those classified as first tested in a provincial facility and then subsequently moved to a federal institution likely have a different testing experience than those individuals who return to the community directly from the provincial prison. If those spending time in a federal institution truly have a better opportunity for obtaining HCV RNA testing, then those individuals classified as provincially tested but move to a federal facility will be more likely to receive testing. Following this logic, the effect of the provincial group could be even greater such that those tested in a provincial prison and return directly to the community could have even longer follow-up times. Several prisons closed during the study period. One federal institution, Kingston Penitentiary (along with the Kingston Regional Treatment Centre), closed in September 2013. Transfer location information for the inmates was not available.

More detailed descriptions of the community facilities could prove to be very informative. For example, differences may exist between outpatient rehabilitation clinics, walk-in clinics, and family health teams. Many of the submitter names for those tested in the community were the names of the ordering physicians and not the facility itself. Inevitably, there will be centers in the community where individuals are followed more closely and have shorter times to receiving the RNA test. Identifying where this is occurring would be helpful both from an analytical and clinical perspective.

Uncontrolled confounding is perhaps the most noteworthy threat to the internal validity of this study. The results need to be interpreted with caution and an understanding that another explanatory factor could be responsible for the association observed between testing facility type

and HCV RNA testing. Further investigation is required where more information is collected prior to the analysis.

5.1.6 External validity

In order for a study to have adequate external validity, it needs to be internally valid and generalizable to the population of interest.[4] Given the concern of uncontrolled confounding, it would be inappropriate to suggest a causal effect of facility of first testing on the risk of HCV RNA testing. The effect of facility of first testing, however, very likely has an association with time to RNA testing. While other explanatory factors may be required to validate the results, the individuals included in this study are representative of individuals who test positive for HCV antibodies in Ontario. The HCV testing experience reflects the respective situations in each of the three testing facility classifications. The increased risk of incomplete testing practices experienced by those first tested in a provincial facility may indeed be generalizable to that population in the province.

Note that this study only included those individuals who had evidence of HCV antibody testing at some point during the study period. Other investigations would be required to identify individuals infected with HCV who have never been tested for HCV antibodies and, consequently, are unaware of their infection status. As a result, any external generalizability of the results would only apply to those individuals whom have been tested for HCV antibodies.

5.1.7 Causation

While an association may be observed in an epidemiological study, the findings do not necessarily imply causation. As mentioned previously, the inference of causality may not be applicable in this study. Regardless, a more thorough narrative of the assessment of causality is

useful as a discussion and the relevant components are provided in this section. The components are based on the aspects of association discussed by Bradford Hill.[4,15]

Temporality

Temporality implies that the exposure occurred prior to the event.[4] In the context of this study, the antibody test must have occurred before the RNA test. This factor is inherent in the study design; only those who had evidence of antibody-positivity *before* RNA testing confirmation were included in the analysis. Individuals with RNA testing and no prior index date were excluded.

Strength of association

While a strong association between an exposure and outcome is not an absolute for determining causality, Hill argued that the greater the magnitude of effect, the more likely a variable is causal.[15] Conversely, a weak association does not rule out causal relationships.[4] Complex research questions, like this current thesis, are often multi-factorial and involve several important risk factors. Nonetheless, the relationship observed in this study was moderate for the facility of first testing. With the community-tested group as the reference, the risk of not being tested was moderate for the provincial group and the HR of being tested was moderate for the federal group (this is particularly true in the latter calendar years of the study for both males and females). Webb and Bain[4] define a moderate association as 2.0.

Consistency

When an effect is consistent across similar studies, it makes it more likely the results are not artefact.[4] This concept was explored thoroughly in Chapter 2. Many of the studies explored neither represented incarcerated or previously incarcerated individuals[16,17] nor incorporated

appropriate statistical significance with magnitudes of effect in the results.[18,19] While much of the literature review supports the plausibility of the association, no study was found that had a similar exposure definition and use of survival analysis. A lack of comparable studies is certainly no reason to rule out an observed association; rather, more research is required in this area.

Plausibility and coherence

As previously discussed in this Chapter and in the discussion of Chapter 3, the effect of facility of first testing holds against the test of logic. The observed effects are highly plausible when considering the differing situations experienced by those first tested in the three defined testing facility types. A coherent explanation can be made of the association even after accounting for other confounding variables.

5.1.8 Public health significance and future considerations

This study identified a group of individuals potentially at high risk of incomplete and delayed testing practices for HCV in Ontario. Individuals, especially females, who are identified as HCV antibody positive in a provincial correctional institution may require more effective means of obtaining HCV RNA testing and, in turn, access to curative treatment. Active interventions with clear follow-up plans and low-barrier access to health care is essential. This is especially relevant to offenders who have short sentences, are under-housed, and have no primary care provider in the community. HCV prevalence is much higher in correctional facilities and represent unique opportunities in the efforts to eliminate HCV. Prisons should be places where we can provide treatment to those who may otherwise lack access to care and educate on risk reduction strategies to decrease rates of infection transmission.

The delays in RNA testing observed at the provincial level is in contrast to the effect seen in federal prisons. Longer sentencing may explain part of the reason why federal inmates appeared to be more likely to receive RNA testing. A less transient group that can be followed more closely presents an opportunity to provide care; these individuals may have had access to care while they were in prison. In this way, access to care may act as a mediator to receiving the RNA test. In addition, federal institutions have provided mandatory education regarding infectious diseases, all inmates are offered screening upon admission, and streamlined approaches to infectious disease management offer other explanations as to the relative success at these prisons. Individuals being released from federal prisons, however, still require the same type of follow-up strategies that individuals leaving a provincial institution ought to receive.

Women in prison represent a particularly marginalized group. Although there are more men in prison than women, women who are incarcerated suffer disproportionately from chronic conditions and may have even greater barriers to accessing testing and treatment for infectious diseases while in prison.[20] Many women in corrections report problems with substance abuse and are more likely than men to have a history of injection drug use.[21] More women in corrections identify as Aboriginal compared to men.[21,22] In the efforts to eradicate HCV, it is imperative that women receive the same testing and follow-up opportunities as men in all settings.

While higher risk groups were observed, the analysis revealed a significant number of individuals who lacked evidence of HCV RNA testing and had long follow-up times in all groups. This is still unacceptable medical practice and even low-risk individuals require appropriate care. The results in this study support the notion that Ontario should consider reflex testing for HCV.[23] In the context of HCV, reflex testing implies that an RNA test is automatically implemented where a positive antibody result is discovered. The RNA test can be

carried out on the same specimen as the original antibody result[24] or multiple specimens can be obtained in one visit for further testing where required.[25] Both situations ensure that a complete description of the infection status of the patient is available and there is no need for a follow-up appointment for additional bloodwork.

A model of care that incorporated a reflex test and up-to-date electronic medical documenting was trialed by the Kaiser Permanente Mid-Atlantic States, an integrated health delivery program.[25] Among those identified as HCV antibody-positive, 100% received RNA testing and the results were communicated with the patient. Follow-up options were provided and supported by the medical team. Figure 1 demonstrates the cascade of care for HCV where this type of reflex test and follow-up is incorporated. It is important to point out that an RNA test is still useful in cases where treatment is deemed inappropriate. Those who are actively infected with HCV need to be aware of their infection status even if they will not be receiving treatment. These individuals will still need education on reducing the risk of transmission to others, especially if they continue to be involved in behaviours associated with a risk of infection and transmission. Efforts to educate and provide risk reduction strategies following successful treatment or clearance of infection must also be included in the treatment plan. This includes, but is not limited to, drug addiction and counselling programs, access to needle and syringe initiatives, and access to additional testing should a concern for reinfection reemerge.

Correctional Service of Canada (CSC) significantly increased their budget for HCV treatment for federal inmates in 2017/2018. The increase amounted to four-times that which was available in 2010.[26,27] At the time of writing, no such commitment had been made to serve those chronically infected with HCV in provincial or territorial institutions. Nadine Kronfli, the author of a report in the Canadian Medical Association Journal, notes several challenges in managing

those infected with HCV in provincial facilities, including short sentences leading to poor follow-up and continuity of care, frequent prison transfers, and the high cost of curative treatments.[27] Curative treatment results have been demonstrated to be higher in those who complete therapy while in prison compared to those who are transferred or released during therapy[28]; however, Kronfli argues that the feasibility of effective continuity of care initiatives are an effective way to reach those who are released from prison during the course of a treatment.[27] A few possible options, which have been successful in the care retention for individuals with HIV, include detailed pre-release discharge planning with appointment bookings and transportation options following release.[29] A multidisciplinary approach to care along with patient-centered education and linkage to primary care needs to be provided prior to their return to the community in an effort to optimize testing and treatment adherence.

Recognizing the risk presented to those in provincial facilities, in 2018 a grant was provided by Gilead Canada to The Ottawa Hospital Viral Hepatitis Program to conduct a pilot project for HCV screening and access to care for those serving sentences in provincial institutions.[30] This contribution provides a sense of optimism that targeted interventions are in the process of being implemented.

Direct-acting antiviral therapies were only approved in Canada towards the end of the study period.[31] Further research and an update on testing practices in Ontario may reveal different results as treatment becomes more accessible and ubiquitous.

There is no single solution to solve this complicated public health issue. A combination of evidence-based practices need to be incorporated in a multidisciplinary approach to reach those underserved. While program and systematic methods are essential components to improve on testing and treatment coverage, societal shifts in attitudes towards those infected with HCV is

also required. This applies to both the health care community and the general population. More universal information surrounding HCV testing practices and treatment options should be promoted. Together, these initiatives can all work collectively with the common goal of eradicating HCV.

5.2 Duplicate Hepatitis C antibody tests in adults who have tested positive for HCV in Ontario, Canada

This section discusses the findings and public health significance as they relate to the content in Chapter 4.

5.2.1 Summary of major findings

Among adults who had evidence of HCV-positivity in Ontario between 1999-2014 in the PHOL dataset, 94,076 (51.9%) of the 181,287 antibody tests identified were deemed redundant. Among individuals who were HCV antibody positive, approximately half received at least one duplicate antibody test during the study period. Notably, the number of duplicate tests performed towards the end of the study period were high across all testing facility classifications. In the latter years of the study period, upwards of 80% of positive antibody results were on individuals who already had proof of past positivity.

This descriptive analysis was performed to gain an understanding of the dataset and present the findings to PHOL in an effort to work towards eliminating duplicate testing practices. Further research needs to be done in order for a risk assessment of duplicate testing to be performed. In particular, the methods used by PHOL to cancel incoming antibody tests where previous positivity is evident ought to be described. In addition, a significant number of antibody tests were performed at the same time as an HCV RNA test; 22% of the duplicate tests identified

had an associated RNA test. The intention and validity of these tests needs to be determined and the use of reflex testing practices is encouraged. The amount of duplicate tests identified may be an underestimation of the actual number experienced by patients in Ontario and this topic is worth further exploration to benefit both the individuals exposed to repeat testing and the healthcare system as a whole.

5.2.2 Original intention

The intended objective of this chapter at the onset of the thesis writing was to describe risk factors associated with duplicate HCV antibody testing. In the context of this thesis, whether an individual was ever tested during the study period in a correctional facility was meant to represent the primary exposure. This exposure would have been assessed while controlling for other variables available in the dataset. The plan was to utilize methods that could handle count data to fit a multivariable regression model describing risk of duplicate testing. Depending on the descriptive results, a Poisson or negative binomial model were to be considered. The problems with the dataset described here and in Chapter 4 caused us to abandon the analysis in favour of providing a general description of the dataset. In order for this type of analysis to work, we would need to be able to identify instances where patient samples were sent in to PHOL but were cancelled at the level of the laboratory; this information was not available. A reliable dataset is a necessary requirement for this type of analysis so as to avoid producing spurious results.

5.2.3 Limitations

Several factors may have led to an underrepresentation of the duplicate tests described during the study period. First, a number of antibody tests may have been conducted in private clinics in the community and would not have been captured in the dataset. As such, the number of tests described only relate to those tests explicitly conducted at PHOL and does not capture

information regarding individuals who were repeatedly tested in other laboratories. Second, the number of cancelled tests could not be determined based on this particular dataset. Tests that were sent to PHOL but not performed due to evidence of past HCV positivity still represent a burden to the individual and need to be considered. Third, many of the subjects may have experienced duplicate tests beyond the study period. Those first tested towards the end of the study had shorter follow-up times and, consequently, less opportunity to have additional testing. Similarly, some individuals may have tested positive prior to the study period and the first available test in this dataset would have in fact represented a duplicate test.

5.2.4 Strengths

This descriptive analysis has several pragmatic strengths. The duplicate tests described may have in fact been an underestimation of the frequency of such tests being ordered at the level of the submitting practitioner. Unless there were substantial data collection errors, these findings still represent real lab tests that were performed at PHOL and pose a significant concern in terms of squandered time and resources. In the event that any data input errors occurred in the production of the dataset, it is still useful to be aware of these errors for future research and surveillance purposes.

As mentioned in earlier, the data relied on laboratory results and not medical charts. The results presented included all HCV antibody tests that were performed at PHOL and represented accurately the outcome of interest.

5.2.5 Public health significance and future considerations

At the level of the laboratory, an awareness of the magnitude of duplicate tests being performed could provide the impetus to modify strategies used to identify and cancel redundant tests. For the taxpayer and the health care system, this represents opportunities for savings in

terms of the actual dollars required to perform the tests and better use of available resources from the required personnel and laboratory equipment. Collaboration with all appropriate stakeholders at PHOL may be required to investigate the issue further and come up with a solution of how to properly identify and eliminate the practice of duplicate tests.

Even if duplicate testing at the level of the laboratory is completely eliminated, the results still demonstrate that practitioners are sending in redundant tests to PHOL. This is still a problem for the individuals being repeatedly tested, even if the sample is not tested at the lab. Patients would still be required to attend a medical appointment and have blood drawn for specimen submission. This does not represent best-practice medical care and individuals with HCV do not deserve repeated exposure to redundant testing. Duplicate tests are an unnecessary burden to the individual and may serve to reinforce stigmatization surrounding HCV infection. The results of this study suggest the need for a risk assessment to describe individuals who are most likely to be subject to duplicate testing practices. An awareness of who is at elevated risk may be helpful in the dissemination of information surrounding duplicate testing practices. A risk assessment could fill a gap in the literature that seeks to determine an association between stigmatization and duplicate HCV antibody testing.

At the level of the ordering practitioner, strategies are required to link medical records so they are aware of a patient's past exposure to HCV and to provide education on the required cascade of care for HCV management. Electronic documentation that provides detailed histories and reminders to order an RNA test following a positive antibody result could help to mitigate this problem.[32,33] It needs to be appreciated that this objective is incredibly complex and will require the cooperation of multiple stakeholders and experts from various fields. Medical

practitioners will be required to work with computer technology experts to establish consistent strategies to deliver and provide simple access to HCV testing histories.

From a data quality and surveillance perspective, it would be helpful to have a mechanism in place whereby all testing laboratories in Ontario are required to submit their results to a central database at PHO. This would allow public health experts to more accurately monitor duplicate HCV testing patterns across the province. It would also have the added benefit of creating a comprehensive list of all private testing labs that perform HCV testing in the province.

This problem of duplicate testing affects several areas of the health care system. While Canada and the WHO are aiming to eradicate HCV, it is well worth considering strategies to mitigate the burden on the individual and health care system caused by duplicate testing. A collaborative effort is required among all stakeholders in the fight against HCV.

5.3 Conclusion

This thesis has investigated two separate issues related to HCV management in Ontario. The description of a high risk cohort of individuals, those first tested in a provincial correctional facility, for delayed HCV RNA testing provides opportunities for interventions related to accessing proper HCV care and follow-up. The description of duplicate antibody testing practices represents an area that could be targeted to alleviate burden at the level of the individual and a cost savings at the level of the health care system. The fight against HCV is incredibly complex and multifaceted; this thesis adds another useful piece of the puzzle in the ongoing effort to eradicate HCV.

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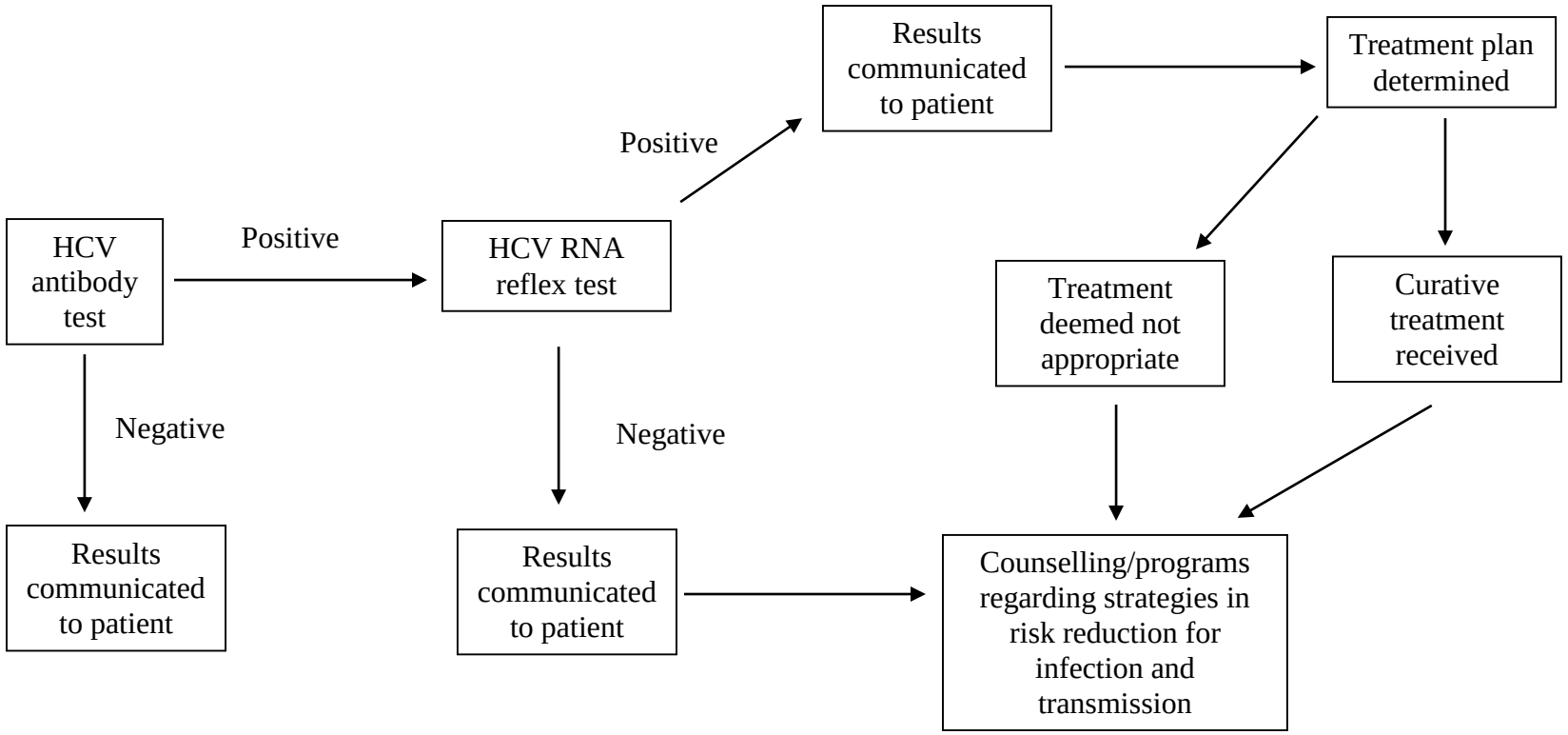
32. Nies J, Colombet I, Zapletal E, Gillaizeau F, Chevalier P, Durieux P. Effects of automated alerts on unnecessarily repeated serology tests in a cardiovascular surgery department : a time series analysis. *BMC Health Serv Res*. 2010;10(70). doi:10.1186/1472-6963-10-70.

33. Shojania KG, Jennings A, Mayhew A, Ramsay CR, Eccles MP, Grimshaw J. The effects of on-screen, point of care computer reminders on processes and outcomes of care. *Cochrane Database Syst Rev*. 2011. doi:10.1002/14651858.CD001096.pub2.

Figure 1. Cascade of care incorporating a reflex test



Appendix A

HCV RNA testing methods

Qualitative HCV Test: The goal of the qualitative test is to detect the presence of HCV RNA and is useful to confirm the presence of active infection, identify resolved cases of HCV and screen donors. Qualitative testing has the advantage of detecting much lower levels of HCV than a quantitative test; however, it does not quantify how much of the virus is present. The test result is reported as HCV RNA "detected" or "not detected".[1]

Quantitative HCV Test: These tests are used to determine what is referred to as viral load. The viral load is the actual quantity of HCV RNA copies in the individual's blood. Results from this test can be useful in monitoring response to treatment, especially in the earlier parts of therapy. A positive qualitative test coupled with a quantitative test that demonstrates no detectable RNA would suggest that the individual has very low levels of infection.[1]

It is important to note that the level of viral load has no bearing on neither the severity of the infection on the liver nor the prognosis of the HCV progression.[1]

[1] Barbeau JM, Goforth J, Caliendo AM, Nolte FS. Performance Characteristics of a Quantitative TaqMan Hepatitis C Virus RNA Analyte-Specific Reagent Performance Characteristics of a Quantitative TaqMan Hepatitis C Virus RNA Analyte-Specific Reagent. *Society*. 2004;42(8):3739-3746. doi:10.1128/JCM.42.8.3739.

Appendix B

Submitting institution descriptions

Table 1. Federal correctional institutions in Ontario

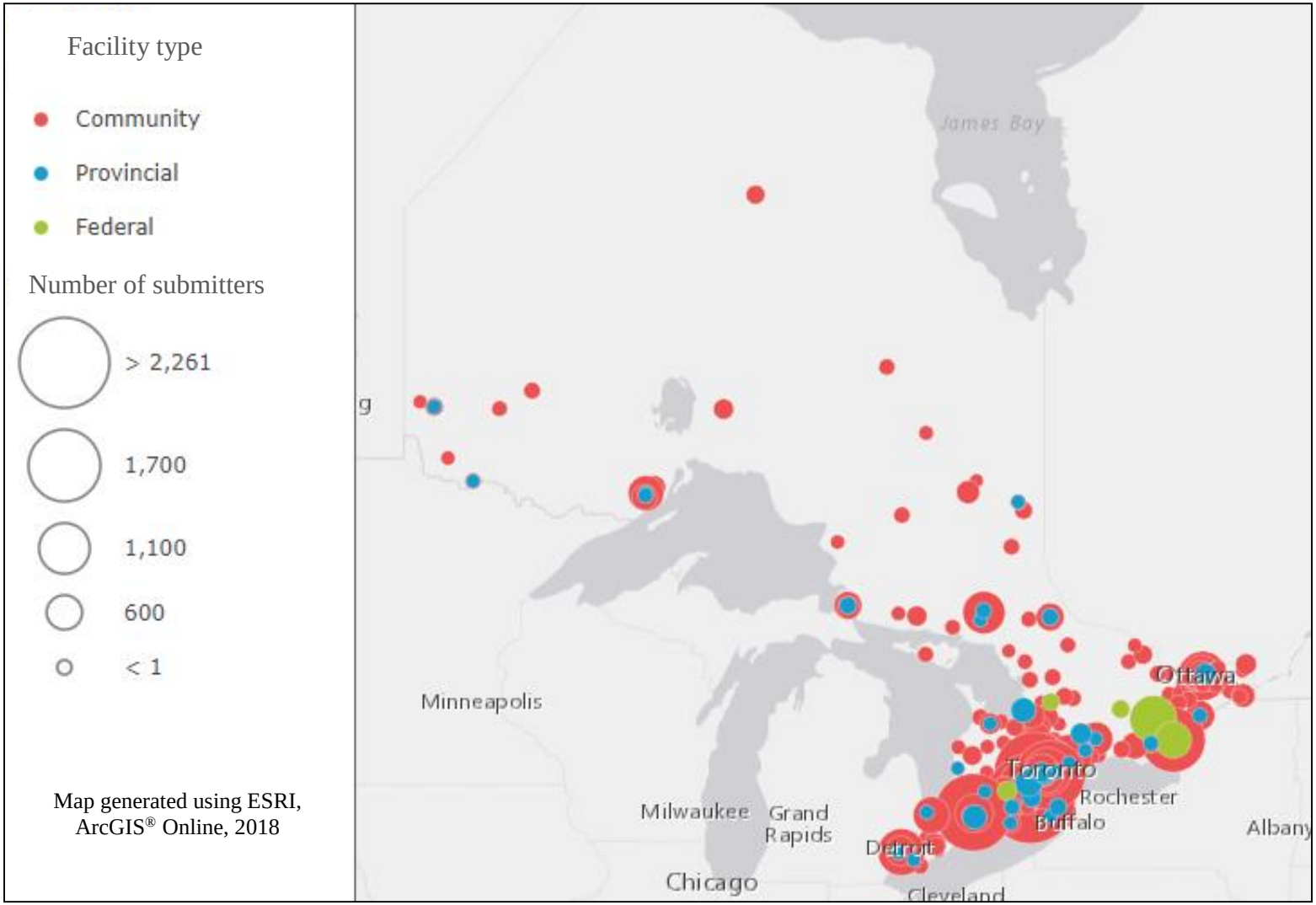
Federal Institutions				
Facility Name	**Open/Closed (as of 2015)**	**Dataset status**	**Number of first antibody tests (%)**	**Rated capacity**
Kingston Penitentiary	Closed 2013	Available	196 (9.6)	564
Kingston Regional Treatment Centre	Closed 2013	Available	Submitted as Kingston Penitentiary	
Millhaven Institution	Open	Available	925 (45.4)	496
Colins Bay Institution	Open	Available	99 (4.9)	760
Joyceville Institution	Open	Available	228 (11.2)	752
Warkworth Institution	Open	Available	115 (5.6)	537
Bath Institution	Open	Available	62 (3.0))	516
Fenbrook Institution	Amalgamated with Beaver Creek Institution on April 2014	Available	103 (5.1)	Included in Beaver Creek capacity
Frontenac Institution	Open	Available	37 (1.82)	150
Beaver Creek Institution	Open	Available	11 (0.5)	717
Pittsburg Institution	Amalgamated with Joyceville April 2014	Available	57 (2.8)	Included in Joyceville capacity
Grand Valley Institution for Women	Open	Available	154 (7.6)	215
Prison for Women Institution	Closed May 2000	Available	2 (0.1)	Unavailable

Note: all federal institutions opened prior to 1999. Capacity information available at www.csc-scc.gc.ca/institutions. Total capacity is 4,707 inmates.

Table 2. Provincial correctional institutions in Ontario

Provincial Institutions							
Facility Name	**Open/Closed (as of 2015)**	**Dataset status**	**No. first ab tests(%)**	**Facility Name**	**Open/Closed (as of 2015)**	**Dataset status**	**No. first ab tests(%)**
Algoma Treatment and Remand Centre	Open	Available	99 (3.9)	Peterborough Jail	Open	Available	1 (0.04)
Barrie Jail	Closed 2001	Missing	0	Peninisula Youth Centre	Open	Available	1 (0.04)
Bluewater Youth Centre	Closed 2012	Available	1 (0.04)	Project (or Camp) Turnaround	Closed 2004	Missing	0
Brantford Jail	Open	Available	60 (2.4)	Quinte Detention Centre	Open	Available	47 (1.9)
Brockville Jail	Open	Available	37 (1.5)	Renfrew County Goal	Closed 2004	Missing	0
Burtch Correctional Centre	Closed 2003	Missing	0	Rideau Correctional and Treatment	Closed 2004	Available	2 (0.1)
Central East Correctional Centre	Opened 2002	Available	208 (8.2)	Roy McMurtry Youth Centre	Opened 2009	Missing	0
Central North Correctional Centre	Opened 2001	Available	317 (12.5)	Sarnia Jail	Open	Available	14 (0.6)
Chatham Jail	Closed 2014	Missing	0	Sault Ste. Marie District Jail	Closed 2003	Missing	0
				Southwest Detention Centre	Open	Available	2 (0.8)
Cornwall Jail	Closed 2002	Missing	0	Sprucedale Youth Centre	Open	Available	1 (0.04)
Elgin-Middlesex Detention	Open	Available	307 (12.1)	St. Lawrence Valley Correctional & Treatment Centre	Open	Available	1 (0.04)
Fort Francis Jail	Open	Available	3 (0.1)	Stratford Jail	Open	Available	2 (0.1)
Guelph Correctional Centre	Closed 2003	Available	0	Sudbury Jail	Open	Available	63 (2.5)
Hamilton-Wentworth Detention Centre	Open	Available	151 (6.0)	Thunder Bay Correctional Centre	Open	Available	37 (1.5)
Kenora Jail	Open	Available	19 (0.7)	Thunder Bay Jail	Open	Available	28 (1.1)
Lindsay Jail	Closed 2003	Missing	0	Toronto (Don) Jail	Closed 2014	Available	0
Maplehurst Correctional Complex	Open	Available	176 (7.0)	Toronto East Detention Centre	Open	Available	48 (1.9)
Millbrook Correctional Centre	Closed 2003	Available	13 (0.5)	Toronto South Detention Centre	Opened 2014	Available	7 (0.3)
Mimico Correctional Centre	Closed 2011	Available	13 (0.5)	Toronto Youth Assessment Centre	Open	Available	0
Monteith Correctional Complex	Open	Available	13 (0.5)	Toronto West Detention Centre	Closed 2014	Available	177 (7.0)
Niagra Detention Centre	Open	Available	107 (4.2)	Vanier Centre for Women	Opened 2003	Available	216 (8.5)
North Bay Jail	Open	Available	94 (3.7)	Walkerton Jail	Closed 2011	Available	0
Ontario Correctional Institution	Open	Available	16 (0.6)	Waterloo Detention Centre	Closed 2001	Missing	0
Ottawa-Carleton Detention	Open	Available	204 (8.1)	Wellington Detention Centre	Closed 2001	Missing	0
Owen Sound Jail	Closed 2011	Available	12 (0.5)	Whitby Jail	Closed 2003	Available	1 (0.04)
Parry Sound Jail	Closed 2001	Missing	0	Windsor Jail	Closed 2014	Available	30 (1.2)
Pembroke Jail	Closed 2004	Missing	0	York Detention Centre	Open	Available	0

Figure 1. Geographic location of submitting institutions for manuscript 1



Location of submitter determined using forward sortation area (FSA) codes from the physician or medical facility submitting the bloodwork to PHOL.

Appendix C

Ethics clearance

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD (HSREB)

HSREB Initial Ethics Clearance

January 15, 2018

Mr. Chad McClintock
Department of Public Health Sciences
Queen's University

ROMEO/TRAQ: #6022705
Department Code: EPID-606-17
Study Title: Time to RNA testing for Hepatitis C Virus in ever incarcerated populations in Ontario, Canada
Co-Investigators: Dr. W. Wobeser, Dr. Y.P. Peng
Review Type: Delegated
Date Ethics Clearance Issued: January 15, 2018
Ethics Clearance Expiry Date: January 15, 2019

Dear Mr. McClintock,

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the application and granted ethics clearance for the documents listed below. Ethics clearance is granted until the expiration date noted above.

- Approval Emails – Supervisors
- CORE Certificate – C. McClintock

Amendments: No deviations from, or changes to the protocol should be initiated without prior written clearance of an appropriate amendment from the HSREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

Renewals: Prior to the expiration of your ethics clearance you will be reminded to submit your renewal report through ROMEO. Any lapses in ethical clearance will be documented on the renewal form.

Completion/Termination: The HSREB must be notified of the completion or termination of this study through the completion of a renewal report in ROMEO.

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information.

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint.

Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete.

Yours sincerely,

Albert J. Clark.

Chair, Health Sciences Research Ethics Board

The HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations, Canadian General Standards Board, and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP). Federalwide Assurance Number: FWA#:00004184, IRB#:00001173

HSREB members involved in the research project do not participate in the review, discussion or decision.

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD (HSREB)

HSREB Renewal of Ethics Clearance

January 09, 2019

Mr. C. McClintock
Department of Public Health Sciences
Queen's University

ROMEO/TRAQ #:6022705
Department Code: EPID-606-17
Study Title: Time to RNA testing for Hepatitis C Virus in ever incarcerated populations in Ontario, Canada
Review Type: Delegated
Date Ethics Clearance Effective: January 09, 2019
Ethics Clearance Expiry Date: January 09, 2020

Dear Mr. McClintock,

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the application. This study, including all currently approved documentation has been granted ethical clearance until the expiry date noted above.

Prior to the expiration of your ethics clearance, you will be reminded to submit your renewal report through ROMEO. Any lapses in ethical clearance will be documented below.

Lapses in Ethics Clearance: N/A

Yours sincerely,

Albert F. Clark, PhD
Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board

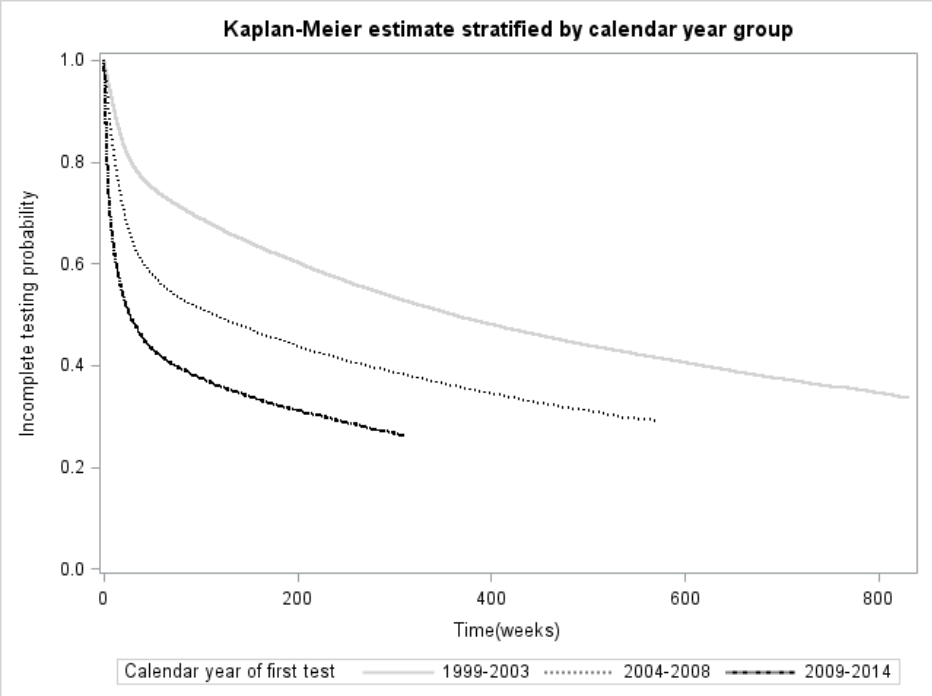
The HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri--Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations, and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP). Federalwide Assurance Number: FWA#:00004184, IRB#:00001173

HSREB members involved in the research project do not participate in the review, discussion or decision

Appendix D

Incomplete testing curves: main analysis

Figure 1. Kaplan-Meier curves and log(-log) curves stratified by calendar year



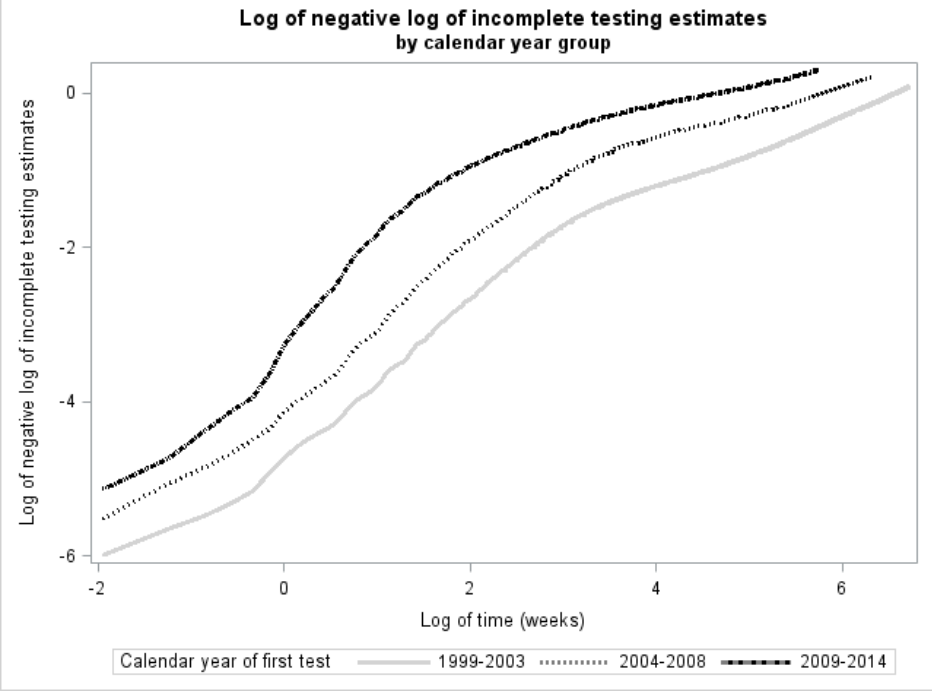
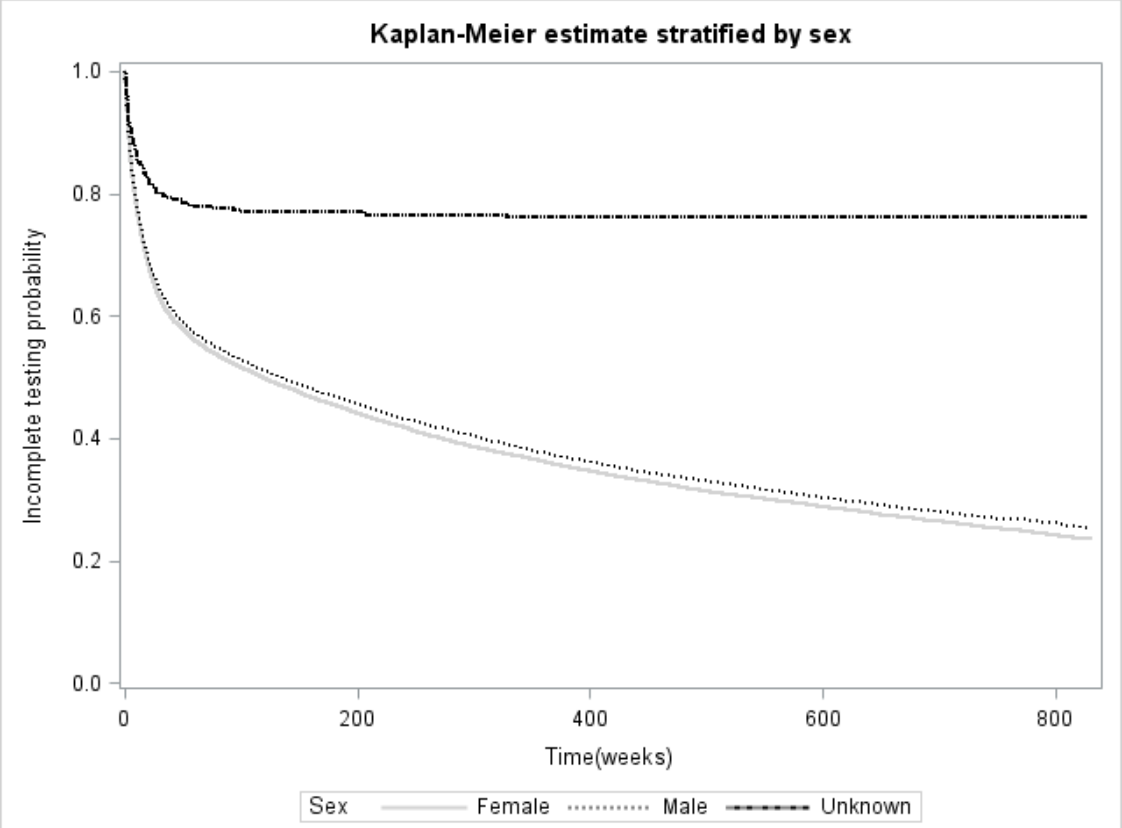


Figure 2. Kaplan Meier curves and log(-log) curves stratified by sex



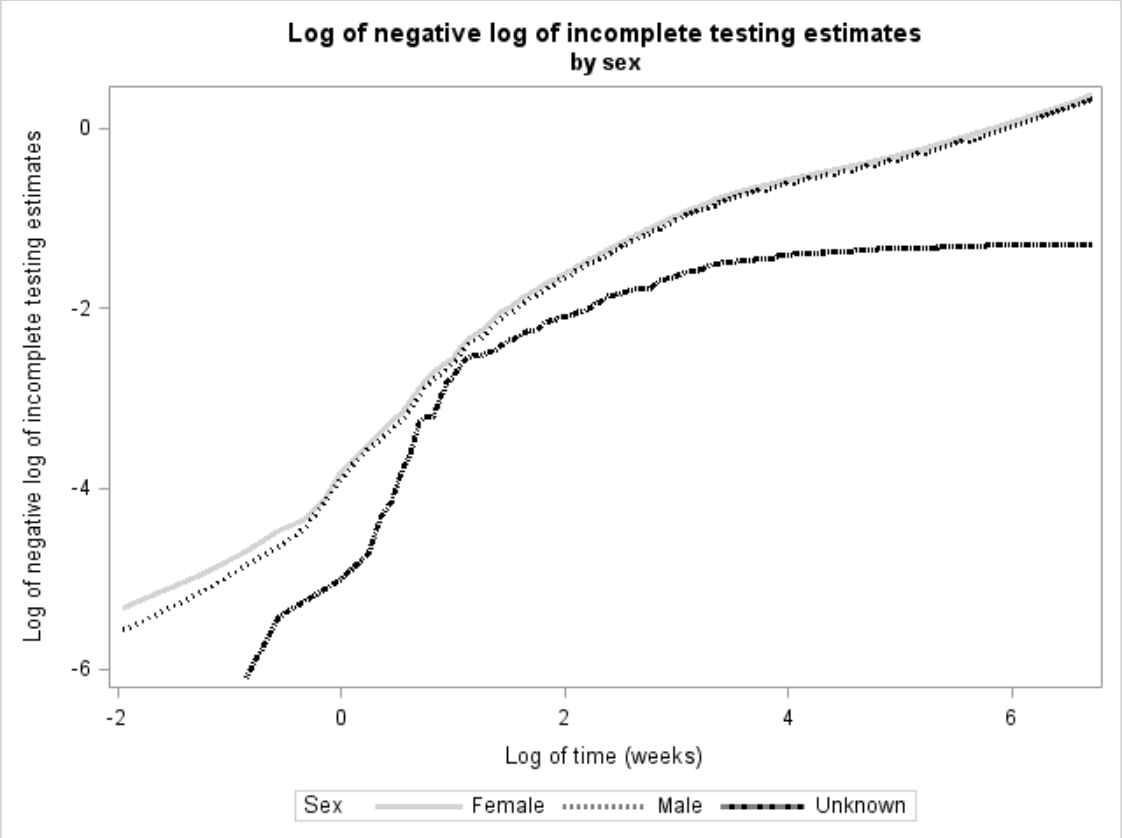
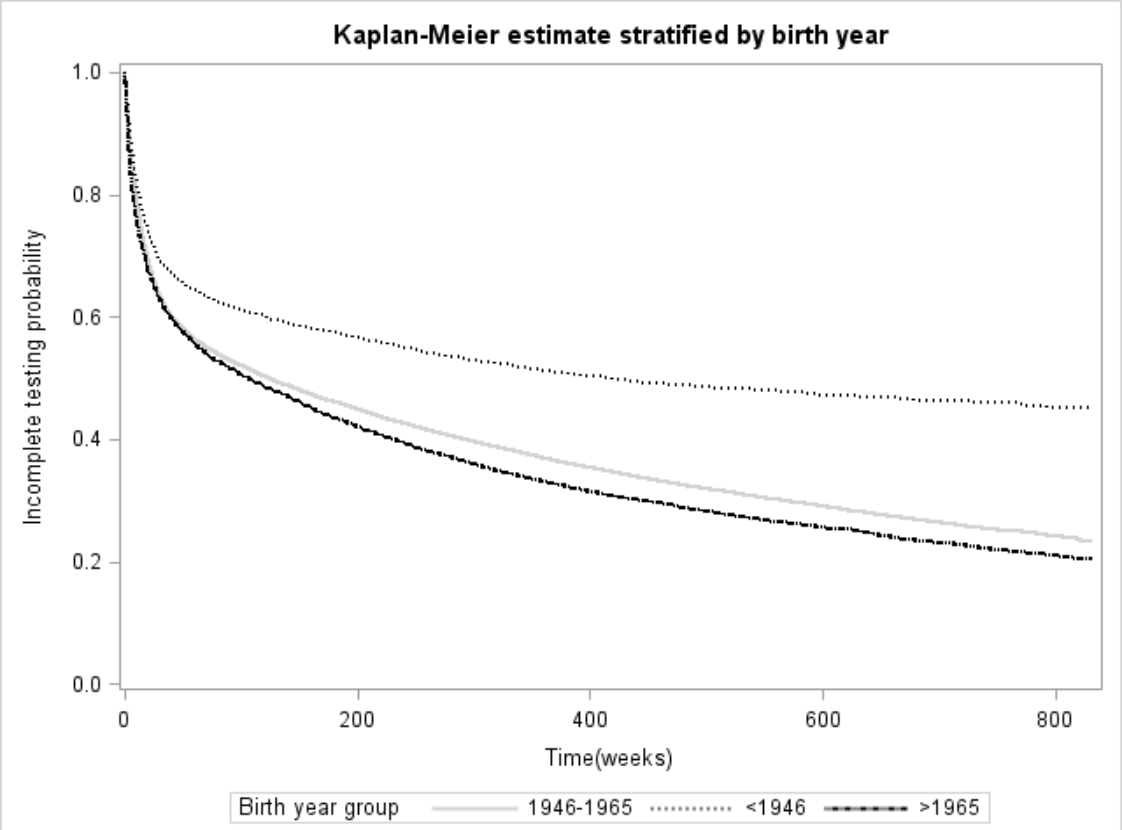


Figure 3. Kaplan Meier curves and log(-log) curves stratified by birth year



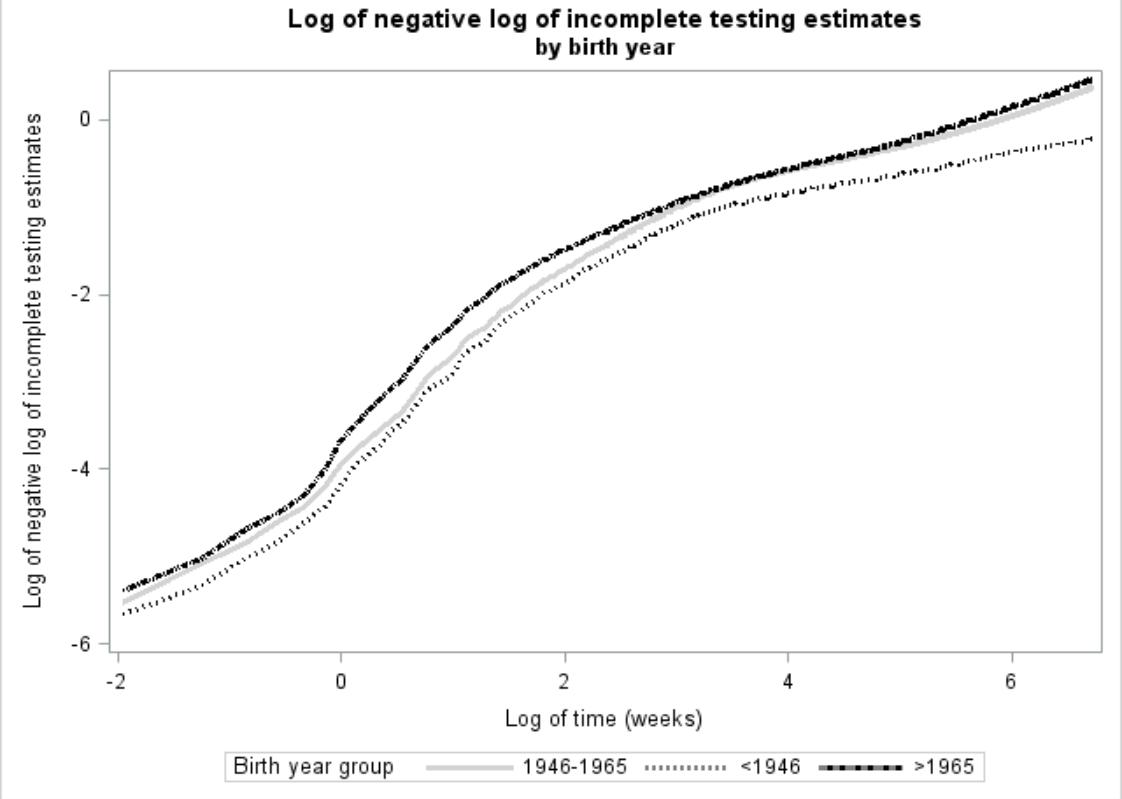
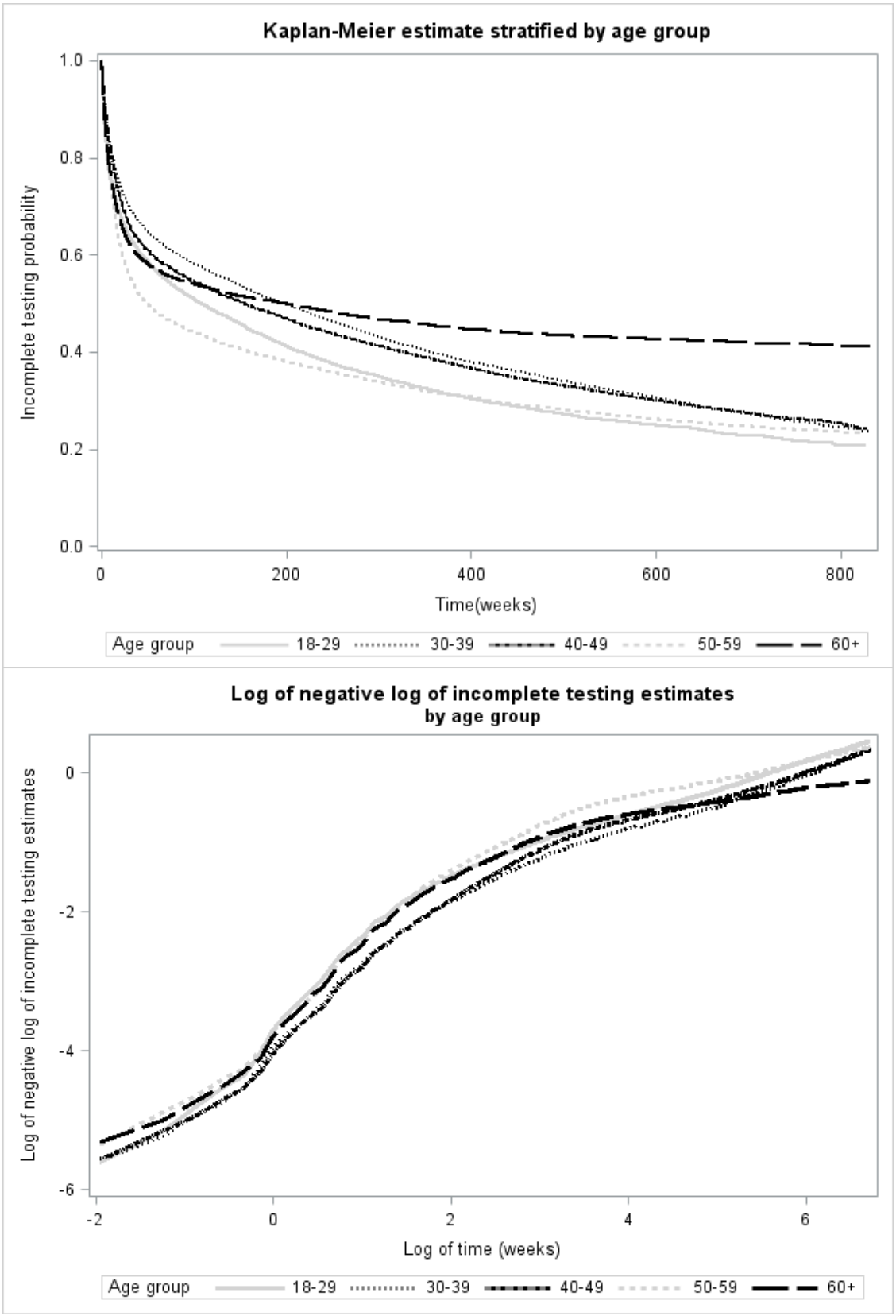


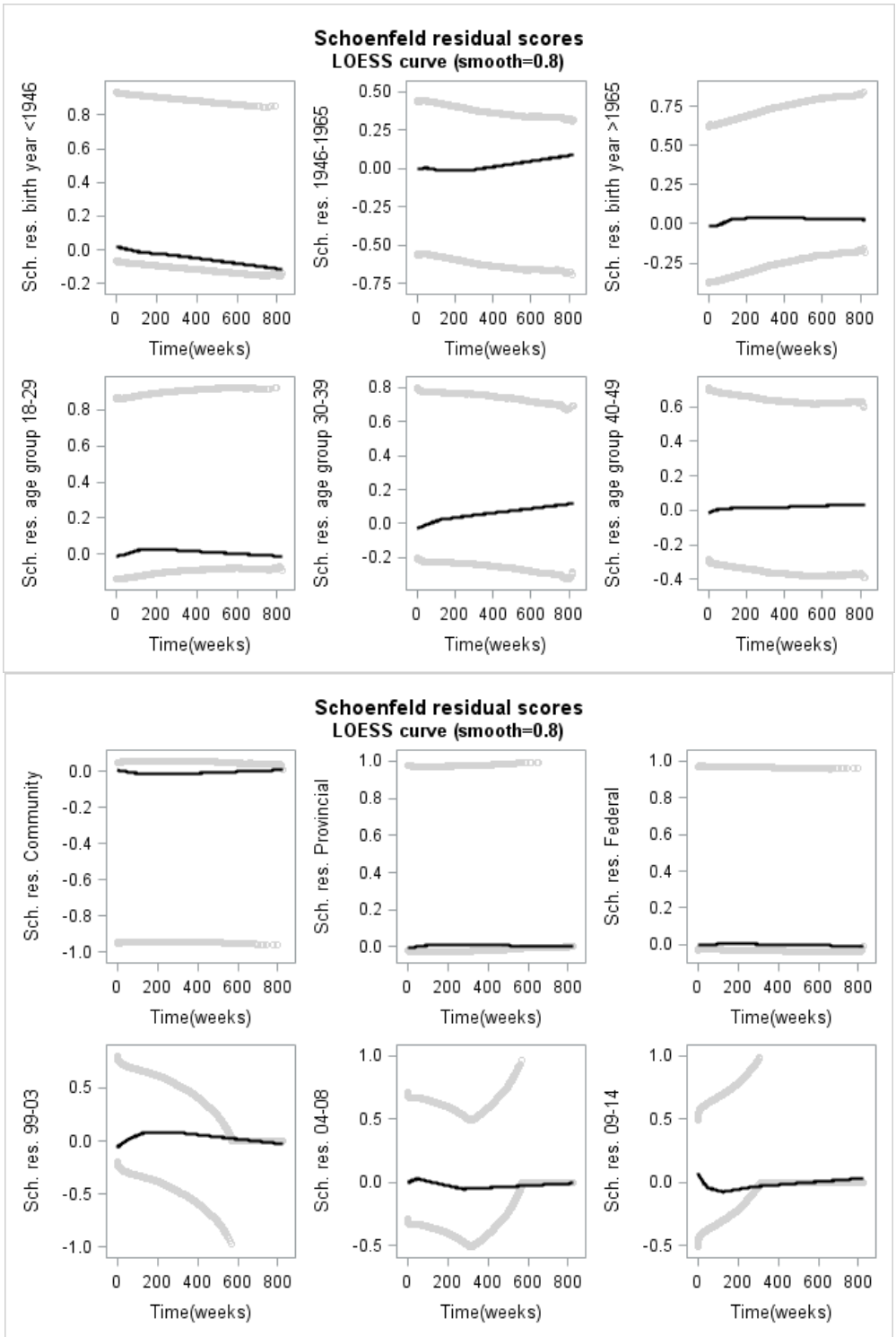
Figure 4. Kaplan Meier curves and log(-log) curves stratified by age group



Appendix E

Model diagnostics: main analysis

Figure 1. Schoenfeld residuals plotted against time for all covariates



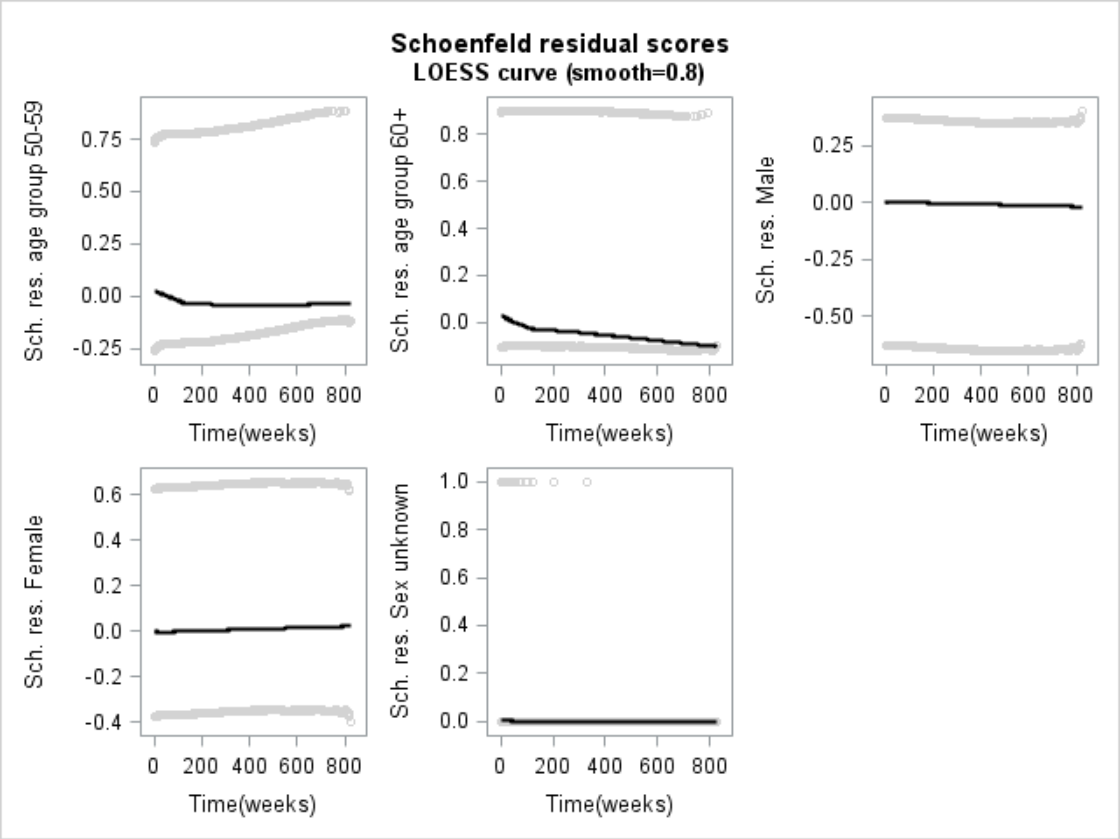
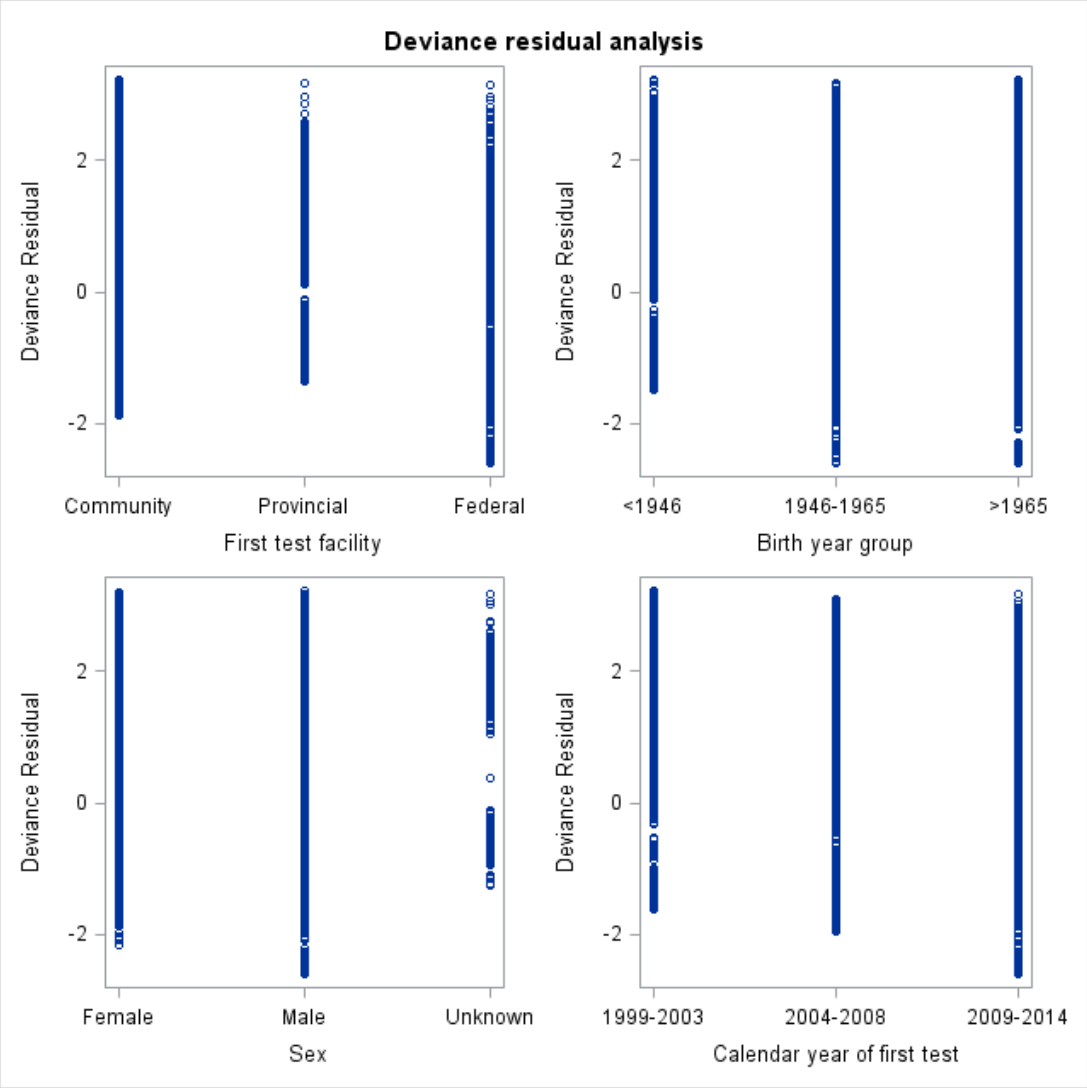

Schoenfeld residual scores
LOESS curve (smooth=0.8)
Sch. res. age group 50-59
Sch. res. age group 60+
Sch. res. Male
Sch. res. Female
Sch. res. Sex unknown
Time(weeks)
0
200
400
600
800

Figure 2. Deviance residuals plotted against covariates



Appendix F

Parameter estimates: main analysis

Table 1. Parameter estimates for multivariable Cox's PH model

Analysis of Maximum Likelihood Estimates					
Parameter		Parameter Estimate	Standard error	Chi-Square	p-value
First test facility	Federal	0.02842	0.04012	0.5016	0.4788
(ref=Community)	Provincial	-0.29161	0.09455	9.5128	0.0020
Sex	Female	0.06149	0.00966	40.5489	<.0001
(ref=Male)	Unknown	-1.26860	0.10447	147.4679	<.0001
Calendar year group	2004-2008	0.39212	0.01236	1006.3655	<.0001
(ref=1999-2003)	2009-2014	0.86848	0.01373	3999.3862	<.0001
Birth year group	1946-1965	-0.01802	0.01713	1.1065	0.2928
(ref=>1965)	<1946	-0.45989	0.03365	186.7384	<.0001
First test facility*Calendar year interaction	Federal*2004-2008	-0.04461	0.01640	7.4008	0.0065
	Federal*2009-2014	0.00639	0.02023	0.0998	0.7520
	Provincial*2004-2008	0.10155	0.02343	18.7855	<.0001
	Provincial*2009-2014	0.06429	0.03268	3.8704	0.0491
First test facility*sex interaction	Federal*Female	0.29641	0.06119	23.4675	<.0001
	Federal*Unknown	0.68828	0.07040	95.5905	<.0001
	Provincial*Female	-0.21029	0.10333	4.1414	0.0418
	Provincial*Unknown	-0.31412	0.10347	9.2159	0.0024

Appendix G

Sex unknown effects

Table 1. Measures of effect where sex is unknown

Measures of effect	
Covariate	Hazard ratio (95% CI)
First test facility by calendar year for sex unknown (reference=Community)	
Federal at 1999-2003	0.85 (0.44, 1.65)
Federal at 2004-2008	1.17 (0.60, 2.28)
Federal at 2009-2014	1.78 (0.93, 3.42)
Provincial at 1999-2003	0.17 (0.02, 1.22)
Provincial at 2004-2008	0.14 (0.02, 0.99)
Provincial at 2009-2014	0.13 (0.02, 0.94)
Sex by test facility (reference=Males)	
Unknown at community	0.28 (0.23, 0.34)
Unknown at federal	0.24 (0.13, 0.44)
Unknown at provincial	0.06 (0.01, 0.46)

Appendix H

Sensitivity analysis supplementary material

Table 1. Baseline characteristics and those removed: sensitivity analysis

Characteristic	*N included in sensitivity analysis*	*%*	*N removed*	*%*	*% of main analysis removed*
First test facility					
Community	36,365	94.0	34,962	94.0	49.0
Federal	821	2.1	1,216	3.3	60.0
Provincial	1502	3.9	1,026	2.7	40.6
Sex					
Male	24,043	62.1	23,956	64.4	49.9
Female	14,554	37.6	12,888	34.6	47.0
Unknown	91	0.2	360	1.0	79.8
Calendar year of first test					
1999-2003	0	0	25,303	68.0	100.0
2004-2008	18,816	48.6	5,576	15.0	22.9
2009-2014	19,872	51.4	6,334	17.0	24.2
Birth year					
<1946	2,746	7.1	5,025	13.5	65.7
1946-1965	19,766	51.1	22,168	59.6	52.9
>1965	16,176	41.8	10,011	26.9	38.2
Age at first testing (years)					
18-29	5,901	15.3	3,591	9.7	37.8
30-39	7,388	19.1	9,309	25.0	55.7
40-49	10,629	27.4	12,800	34.4	54.6
50-59	10,203	26.4	6,621	17.8	39.4
60+	4,567	11.8	4,883	13.1	51.7

Table 2. Characteristics by first test facility. Sensitivity analysis.

	Facility of first HCV antibody test			
	Community	*Provincial institution*	*Federal institution*	
Characteristic	*N(percent)*	*N(percent)*	*N(percent)*	*P-value*[†]
Sex				
Male	22,143 (60.9)	1,158 (77.1)	742 (90.4)	
Female	14,139 (38.9)	343 (22.8)	72 (8.8)	
Unknown	83 (0.2)	1 (0.1)	7 (0.8)	<0.0001
Calendar year				
2004-2008	17,597 (48.4)	717 (47.7)	502 (61.1)	
2009-2014	18,768 (51.6)	785 (52.3)	319 (38.9)	<0.0001
Birth year				
<1946	2,739 (7.5)	4 (0.3)	3 (0.4)	
1946-1965	19,209 (52.8)	259 (17.2)	298 (36.3)	
>1965	14,417 (39.7)	1,239 (82.5)	520 (63.3)	<0.0001
Age at first test (years)				
18-29	5,091 (14.0)	619 (41.2)	191 (23.3)	
30-39	6,590 (18.1)	525 (35.0)	273 (33.3)	
40-49	10,097 (27.8)	279 (18.6)	253 (30.8)	
50-59	10,042 (27.6)	71 (4.7)	90 (11.0)	
60+	4,545 (12.5)	8 (0.5)	14 (1.7)	<0.0001

Table 3. Characteristics by first test facility of those removed for the sensitivity analysis

Characteristic	*Facility of first HCV antibody test*		
	Community N(percent of main analysis)	*Provincial institution N(percent of main analysis)*	*Federal institution N(percent of main analysis)*
Sex			
Male	22,074 (49.9)	774 (40.1)	1,108 (59.9)
Female	12,575 (47.1)	225 (39.6)	88 (55.0)
Unknown	313 (79.0	27 (96.4)	20 (74.1)
Calendar year			
1999-2003	24,040 (100.0)	218 (100.0)	1,036 (100.0)
2004-2008	5,093 (22.4)	359 (33.4)	124 (19.8)
2009-2014	5,829 (23.7)	449 (36.4)	56 (14.9)
Birth year			
<1946	4,999 (64.6)	9 (69.2)	17 (85.0)
1946-1965	21,198 (52.5)	319 (55.2)	651 (68.6)
>1965	8,765 (37.8)	698 (36.0)	548 (51.3)
Age at first test (years)			
18-29	3,096 (37.8)	302 (32.8)	193 (50.3)
30-39	8,405 (56.0)	351 (40.1)	553 (66.9)
40-49	12,138 (54.6)	294 (51.3)	368 (59.3)
50-59	6,468 (39.2)	61 (46.2)	92 (50.6)
60+	4,855 (51.6)	18 (69.2)	10 (41.7)

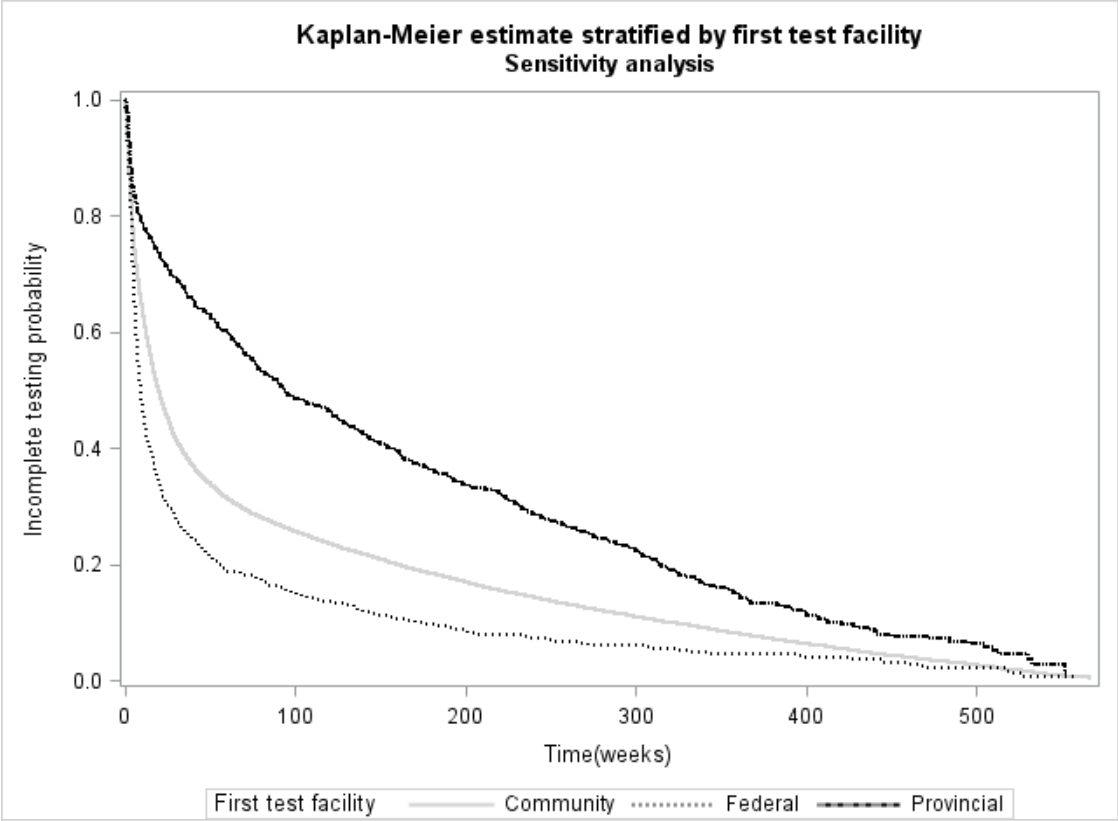
Note: the percentage (%) indicated in this table represents the percentage of the main analysis that were removed for the sensitivity analysis.

Table 4. Univariate analysis in the sensitivity analysis

Independent variable	*Hazard ratio (95% CI)*
First test facility (reference=Community)	
Community	_____
Federal	1.38 (1.29, 1.48)
Provincial	0.60 (0.56, 0.64)
Sex (reference=Male)	
Male	_____
Female	0.98 (0.96, 1.01)
Unknown	2.23 (1.89, 2.90)
Calendar year of first test (reference=1999-2003)	
2004-2008	_____
2009-2014	1.96 (1.92, 2.01)
Birth year (reference= >1965)	
<1946	1.10 (1.06, 1.15)
1946-1965	1.06 (1.04, 1.09)
>1965	_____

Note: Age at first testing not provided due to concerns with PH assumption

Figure 1. Kaplan Meier curves and log(-log) curves stratified by first test facility



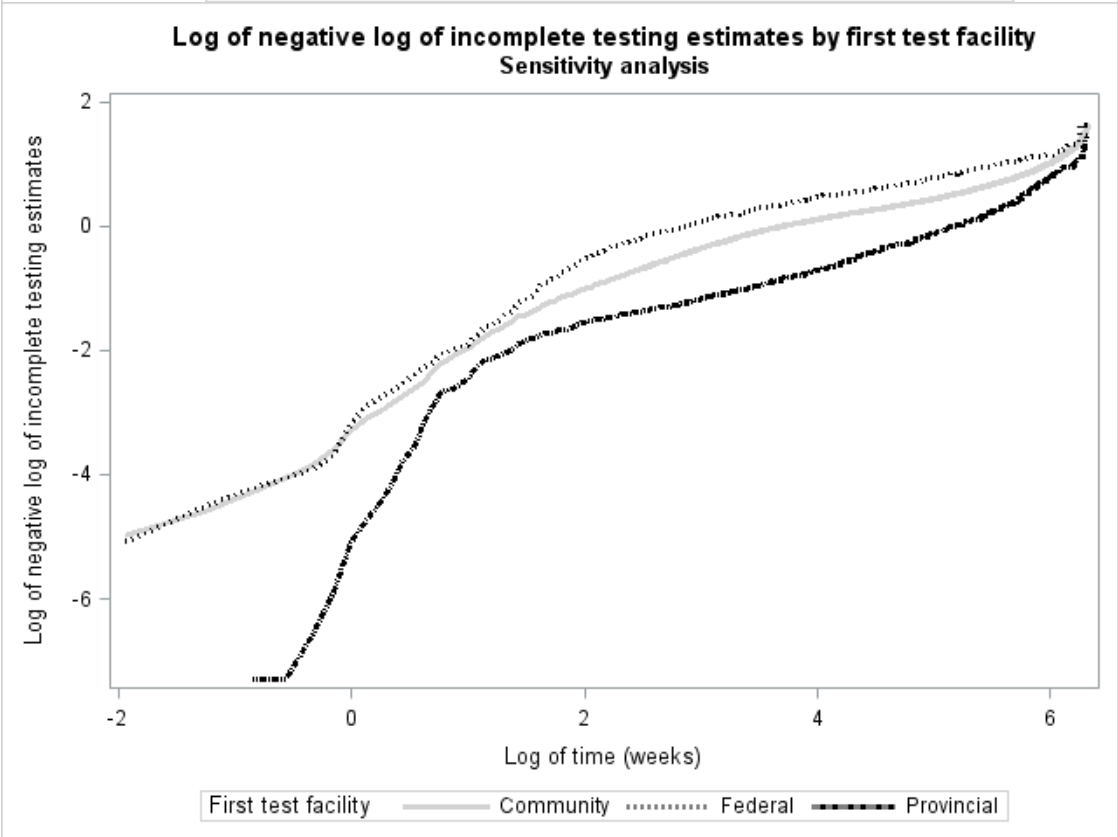
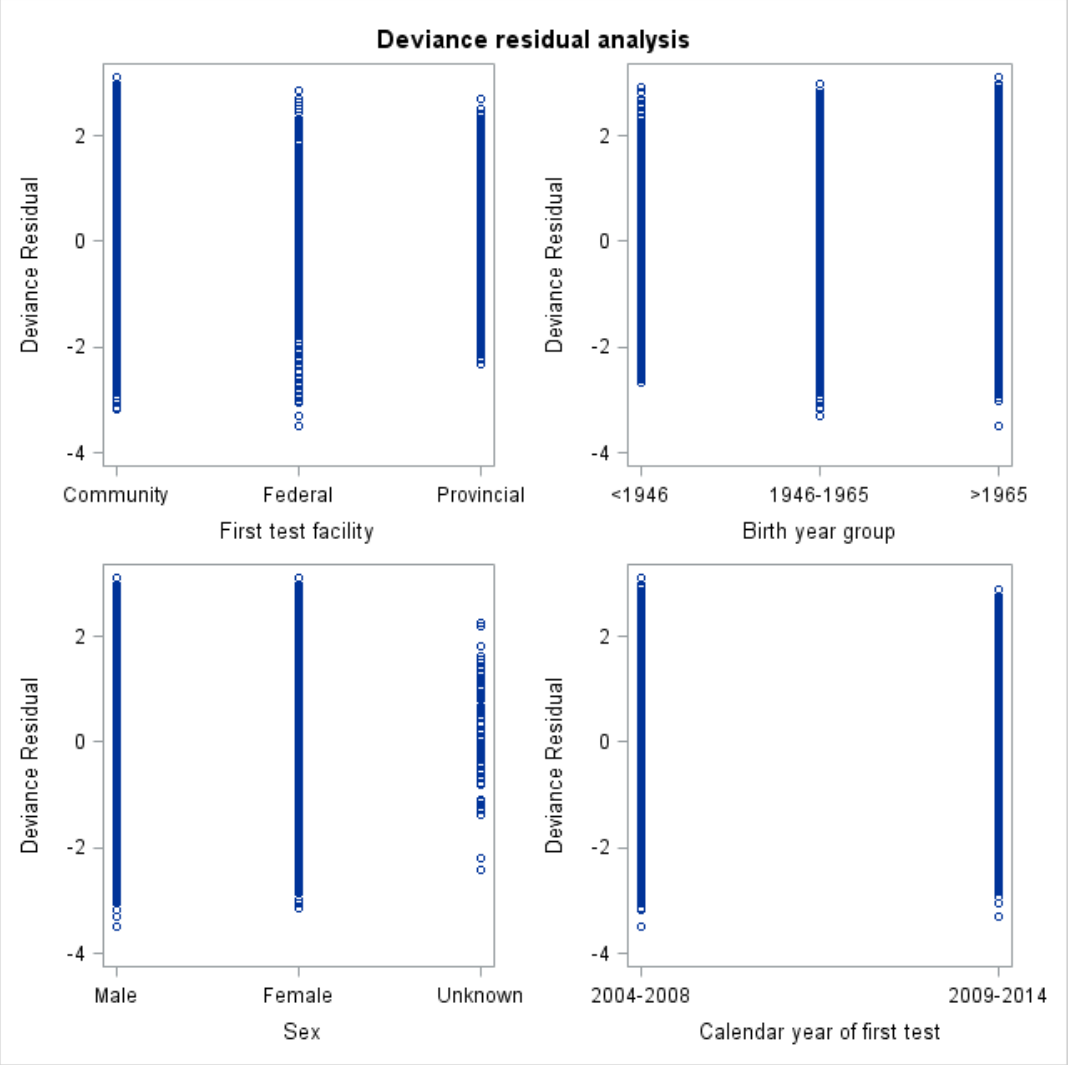


Figure 2. Deviance residuals plotted against covariates in the sensitivity analysis



Appendix I

Misclassification of exposure

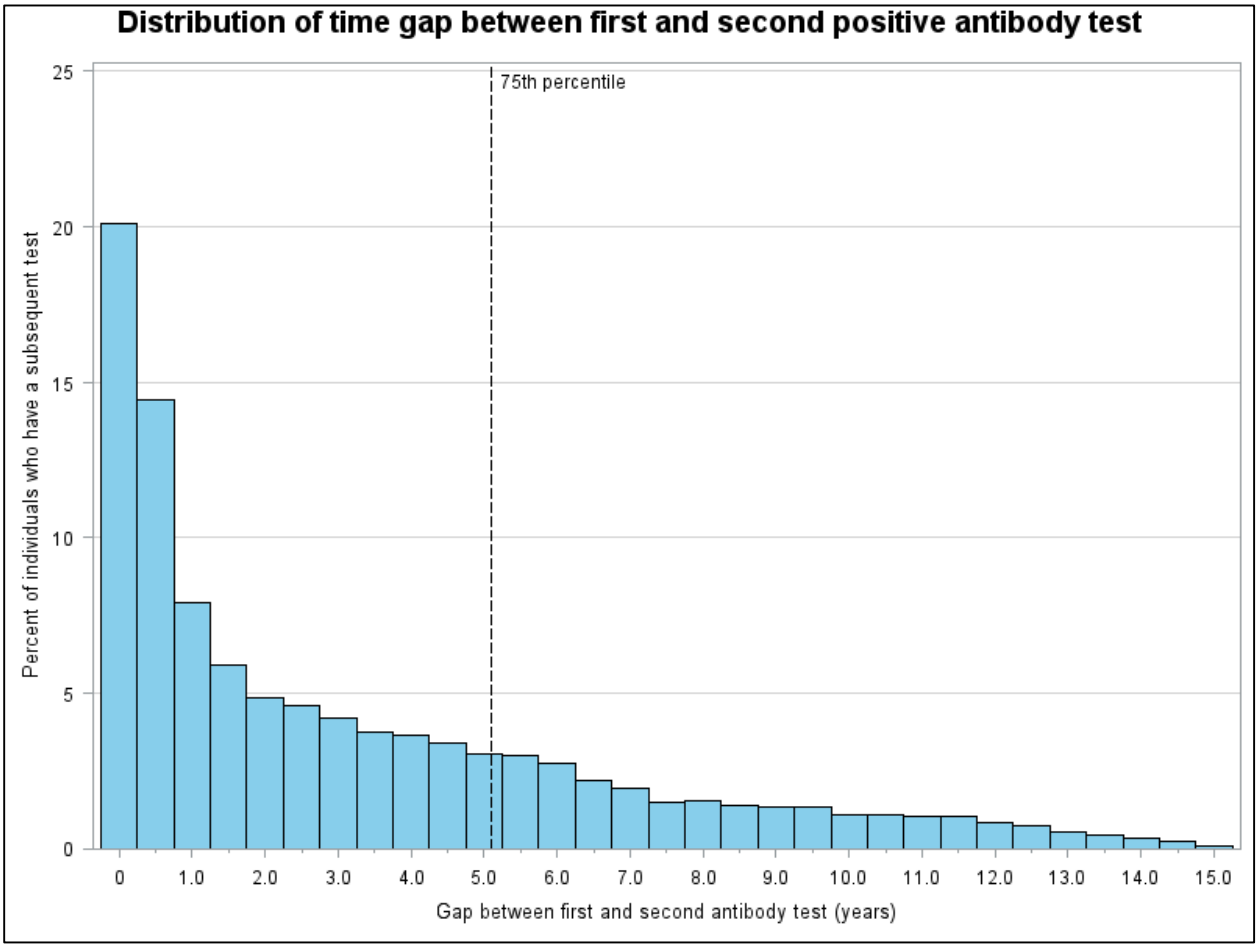
Table 1 represents a hypothetical scenario for misclassification. Those who have evidence of second testing could have been misclassified if the second test was the first test available in the PHOL dataset; therefore, the second test represents a possible classification of testing status. The shaded boxes represent correct hypothetical classifications. The most impactful misclassification would be those misclassified as being first tested in a provincial or federal facility when they were in fact first tested in the community. In this scenario, 389 of the 1,960 (19.8%) subjects classified as provincially tested would fit this description. 445 of the 2,145 (20.7%) subjects classified as tested first in a federal institution would in fact have been first tested in the community. In contrast, only 1.8% of those classified as first tested in the community would have in fact been first tested in prison (0.6% provincial, 1.2% federal).

This scenario is likely an overestimation of the misclassification given the long follow-up period of the study. The misclassification would be stronger in the early part of the study as there were likely to be more subjects with a recent history of testing not captured in the dataset. To further explore this concept, the distribution of time between first and second antibody tests is presented in Figure 1. The third quartile suggests that among those who have a subsequent test, 75% will have the test within 5.1 years of receiving the first positive results. This finding supports the notion of presenting a sensitivity analysis where the index date includes a 5-year lead-up time where no antibody results are evident. Even if a test was missing from 5 years prior, the new index date may represent a first test experience that is clinically similar to an actual first test given that the individual went 5 years without being tested for HCV antibodies.

Table 1.Potential misclassification. Total number, row percent, and column percent displayed

Facility of first antibody test	Facility of second antibody test				
	Community	Federal	Provincial	No evidence of second test	Total
Community	35391	445	389	35133	71358
	49.60	0.62	0.55	49.23	
	96.47	35.49	46.92	94.56	
Federal	411	675	60	891	2037
	20.18	33.14	2.95	43.74	
	1.12	53.83	7.24	2.40	
Provincial	883	134	380	1131	2528
	34.93	5.30	15.03	44.74	
	2.41	10.69	45.84	3.04	
Total	36685	1254	829	37155	75923

Figure 1. Distribution of time gap between first and second antibody test where more than one test is available



Appendix J
Model building details

This appendix describes in detail the model building process and the assumptions of the statistical models in Chapter 3. In addition, the exploration of different sensitivity analysis options is presented.

Representations of the categorical variables required knowledge of the current literature in the field of HCV testing practices. A significant number of studies in the literature were interested in those born between 1946 and 1965, or the "baby boomer" generation.[1] Part of this has to do with current screening recommendations in Canada and the United States.[2] In an effort to be consistent with existing literature, this birth year group was selected and included as a category for this variable.

Calendar year was determined based on changes to the HCV management landscape. This is especially relevant with the introduction of effect direct-acting antivirals (DAAs) as curative therapies over the past number of years.[3,4] In 2011, the first DAAs were approved for use in Canada[5,6] and second-generation DAAs became available in November 2013[7]; initiatives to promote proper testing and screening began prior to this. The effect across smaller calendar year intervals was considered. The HRs did not vary considerably across the latter years of the study period and a 2009-2014 category yielded easily interpretable results and represented a period of increasing HCV awareness and knowledge translation.[8] Additionally, there was no expectation that testing practices would drastically change from one day to another and the evolution of HCV management is a gradual process. For these reasons, it was decided to not have a discrete date representing the introduction of a new DAA as a cutoff for a calendar year group.

The process of building the multivariable Cox's PH regression model involved the consideration of clinically relevant effects. The large sample size presented the difficulty of being overpowered. Many different combinations of interactions, for example, were statistically significant. Subject matter knowledge was used to test the interactions that calendar year and sex had with facility of first test. The change in main effect with the incorporation of other interactions was observed and results that were not considered clinically meaningful for interpretation were excluded in an attempt to present a parsimonious model. For example, a significant interaction between facility of first test and birth year existed; however, the effect was in the same direction for both males and females first tested in a provincial facility across all birth year categories. The conclusion would therefore remain the same: those first tested in a provincial facility experience longer follow-up times compared to those first tested in the community. Females still demonstrated longer time to RNA testing when compared to males first tested in either type of correctional facility.

Assessment of the PH assumption was based mainly on the visual observation of the Kaplan-Meier survival curves, the log(-log(survival)) vs. log(time) curves, and the patterns over time of the schoenfeld residuals. Where concerns were present, an interaction with time was tested and stratification methods were considered. The stratification of age at first testing was deemed necessary and supported by all assessment methods mentioned above. While the independent effect of age could not be determined, this method was preferred over the inclusion of a time interaction for two main reasons. First, the interaction with time made interpretation difficult and the crossing of HRs yielded results that were not clinically meaningful. The interpretation of the main effect of first testing facility remained the same with either the stratification method or including an interaction between time and age at first testing. Second, the

ability to perform model diagnostics in SAS is no longer an option in the presence of a time interaction. This was deemed an important part of the model building process.

Clustering was considered for this model. Although the facility classification of first testing was considered a fixed effect, the actual submitting institutions could represent units where survival times were clustered. The problem, however, with the submitter variable is that in the instance of community tests, the submitter was represented as either a facility or an individual ordering physician who may or may not belong to an unidentified medical program. In addition, the specific ordering physician may be more relevant when considering who ordered the RNA test; this variable would not be applicable to those who were censored. Despite this, a clustered model was run for exploratory purposes. The method of using a robust sandwich covariance matrix to consider correlation within clusters was consistent with the method described by SAS support.[9] Inflation of the standard errors of the parameter estimates resulted in an interpretation of the HRs for the primary exposure levels to be identical to the model without clustering. It was decided to omit the clustering effect from the final model.

A very small number of subjects in the analysis had an HCV genotype test performed with no available RNA test result. Genotyping is required when considering treatment plans and would be involved in determining infection status. For these individuals, this test date was considered as their event date. This applied to only 17 subjects in the dataset (0.018%).

Model assumptions: Kaplan-Meier survival estimators

1) *The survival probabilities are the same for subjects who are included at the onset and the latter part of the study period.*[10]

The differing survival curves between calendar years suggests that this could indeed present a violation. This result is expected, however, based on subject matter knowledge. It is for

this reason that a variable for calendar year was incorporated in the Cox's PH regression analysis.

2) The event occurs at the time specified in the dataset.[10]

There is no reason to believe that this assumption was violated. This is especially true given that the dataset was obtained from laboratory results and not patient medical charts.

3) Independence of censoring and the event.

This was not a significant concern. There is no reason to suspect that the reasons for being censored were correlated with the probability of having an event (or RNA test).

Model assumptions: Multivariable Cox's PH regression

1) Independence of censoring.

Similar to the description regarding the independence of censoring and the event with the Kaplan-Meyer estimators. The reasons for being censored are not likely to be related to having an event; rather a non-event would give us informative censoring and satisfy the assumption.

2) The hazards remain proportional over time.[11]

As previously mentioned, the proportional hazards assumption was assessed by looking at Kaplan-Meier survival and log(-log(survival)) vs. log(time) curves to look for the crossing of lines that would indicate a violation of this assumption. In addition, schoenfeld residuals were considered to observe patterns over time.

3) A linear relationship between the log hazard and each covariate exists.

All variables included in the final models were categorical and violations of this assumption are not of concern. A continuous representation of age at first testing was considered; however, concern existed regarding the functional form of this variable and its representation as a categorical variable was more convenient for interpretive purposes.

Sensitivity analysis

Several versions of a sensitivity analysis were explored. Two that were not described in the main chapters are as follows:

1) The index date included those first tested at any point during the study period. The last available antibody test (for individuals with more than one antibody result) was used as the censoring date and those who were censored at the end of the study period were removed. While this analysis dealt with possible censoring time errors, it did not address the issue of exposure misclassification.
2) The end of the study period served as a censoring date, but the analysis included only those tested after 2004. This analysis addressed the complication of exposure misclassification and inaccuracy of index date. It did not, however, take into account those with potentially erroneous follow-up times as a result of censoring at the conclusion of the study period.

The sensitivity analysis chosen for the manuscript involved a combination of the described methods. The two sensitivity analysis methods described above yielded the same conclusions regarding the effect of facility of first testing as the main analysis and the complete sensitivity analysis described in Chapter 3.

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Appendix K

Calendar year effect

Table 1. Calendar year effect

Measures of effect: calendar year trend	
Covariate interaction	Hazard Ratio (95% CI)
2004-2008 vs 1999-2003 at Community	1.48 (1.44, 1.52)
2009-2014 vs 1999-2003 at Community	2.36 (2.30, 2.42)
2004-2008 vs 1999-2003 at Federal	2.04 (1.81, 2.30)
2009-2014 vs 1999-2003 at Federal	4.93 (4.30, 5.66)
2004-2008 vs 1999-2003 at Provincial	1.21 (0.99, 1.48)
2009-2014 vs 1999-2003 at Provincial	1.83 (1.49, 2.23)

Appendix L

Power calculation

The power equation used is from the textbook Fundamentals of Biostatistics: Seventh Edition by Bernard Rosner.[1]

$$\text{Power} = \Phi\left\{\frac{\left(\sqrt{km}*|HR-1|\right)}{kHR+1} - z_{1-\alpha/2}\right\}$$

Where k is the ratio of group 1 (first tested in a community facility) compared to group 2 (first tested in a provincial institution) who have had a positive antibody test. Since the provincial group was thought the be at highest risk and of most interest, the comparison is between these two groups and not the federally tested group.

Based on the analysis, $n_1 = 71{,}327$ and $n_2 = 2{,}528$.

$\therefore k = n_1/n_2 = 71327/2528 = 28.2$

HR is the hazard ratio we wish to detect over the study period. Based on the literature review and providing a conservative estimate, a HR = 0.9 would be acceptable. This would suggest a lower hazard for those first tested in a provincial facility for receiving the HCV RNA test.

m is the expected total number of HCV RNA tests over the study period over both groups. The community group had 46,665 RNA tests and the provincial group had 1,194 RNA tests.

$\therefore m=46665 + 1194 = 47859$

$$\text{Power} = \Phi\left\{\frac{\left(\sqrt{28.23*47861}*|0.9-1|\right)}{(28.23*0.9)+1} - 1.96\right\}$$

$$= \Phi(2.44)$$

$\therefore$ Power >0.99

[1] 1. Rosner B. *Fundamentals of Biostatistics: Seventh Edition*. 7th ed. Boston MA: Brooks/Cole; 2011.