8-28-2018 12:00 AM

# The Epidemiology of Infective Endocarditis Among People Who Inject Drugs in London, Ontario.

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics

# Abstract

Infective endocarditis is an infectious disease that affects the valves of the heart. Injection drug use is currently a leading risk factor among patients with endocarditis. We conducted a prospective study using data from hospital chart records among patients with endocarditis in London, Ontario, which has a relatively high prevalence of people who inject drugs to assess the severity of the issue and the major risk factors of mortality pertaining to this population. This study had a sample size of 353 and included a review of the incidence of admissions of endocarditis, as well as a survival analysis, using both univariate and multivariate methods. We found the incidence to be rising among both people who inject drugs and those who do not. In the total group, the use of injection drugs (HR: 2.50, 95% C.I. 1.41 to 4.34), age (HR: 1.03 per year, 95% C.I. 1.01 to 1.05), methicillin resistant staphylococcus aureus infection (HR: 3.23, 95% C.I. 1.79 to 5.84) and methicillin sensitive staphylococcus aureus (HR:1.74, 95% C.I. 1.05 to 2.87) infection were shown to be significantly associated with all-cause mortality. With the ongoing proliferation of injection drug use, additional harm reduction strategies to further reduce the incidence and impact of endocarditis among people who inject drugs is important.



## Keywords

Infective endocarditis, people who inject drugs, injection drug use, IDU-associated infective endocarditis, incidence analysis, survival analysis.

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# Acknowledgments

I would like to acknowledge my co-supervisors, Dr. Saverio Stranges for his assistance in the structuring and development of this thesis, as well as Dr. Michael Silverman for his clinical expertise and assistance in writing the thesis. I would also like to acknowledge my supervisory committee, with Dr. Yun-Hee Choi providing helpful guidance to ensure all statistical procedures were coded and performed appropriately, as well as Dr. Greta Bauer's methodological and structural expertise which assisted in the proper and timely completion of this work. Thanks to Dr. Adeel Sherazi and Dr. Esfandiar Shojaei for collecting and organizing all the chart review data that was used in this analysis. Lastly, thank you to Laura Ball for permission to use the photographs of crushed hydromorph contin under a microscope.

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# Chapter 1

# 1 Introduction

The use of injection drugs and the adverse health outcomes associated with them has become a growing concern in developed countries over the past few decades. Mainstream media has been effective in highlighting the repercussions associated with what is referred to as the "opioid crisis" in North America and around the world. More specifically, addictions and overdoses from highly potent opioids such as fentanyl have become alarming realities that are regularly discussed in mainstream sources. The death toll due to opioid overdose has continued to rise, taking 2,458 Canadian lives in 2016 (GoC, 01/2018). In the United States, the number of overdose deaths attributable to prescription opioid misuse from 1999 to 2015 is over 183,000 according to the Centers for Disease Control and Prevention (CDC, 08/2017).

In the US, publications have suggested that the rates of injection drug use have been decreasing in the past couple decades (Roy et al, 2016), which at face value seems like good news. While the total number of people who inject drugs appear to be decreasing, the most at-risk population has changed as the number of people who inject drugs (PWID) aged 15-29 are increasing (Roy et al, 2016). This is aligned with the findings of Wurcel et al (2016) who used the Health Care and Utilization Project National Inpatient Sample (HCUP-NIS) dataset to find proportion of IE hospitalizations from injection drug use (IDU) associated IE increased from 7% in 2000 to 12.1% in 2013 (Wurcel et al, 2016). They found significant increases of IDU-IE hospitalizations among 15- to 34-year-olds (27.1%–42.0%; $P < .001$) and among whites (40.2%–68.9%; $P < .001$). The tendency for young individuals to be at an

elevated risk may represent a significant Public Health issue, although there is unfortunately no available data to predict national trends in Canada (Roy et al, 2016). In 2001, Health Canada estimated there to be 100,000 PWID in Canada. A decade later, the Public Health Agency of Canada (PHAC) estimated the population grew to approximated 113,000, although no trends can be reliably predicted from these estimates (Roy et al, 2016). Most research targeting populations of PWID is cross-sectional by nature as there are commonly attrition issues that prevent long-term prospective cohort studies.

People who inject drugs (PWID) may have one or several comorbidities including, but not limited to, HCV, HIV, diabetes, psychiatric disorders, and the focus of this thesis, Infective Endocarditis (IE). I-track, a surveillance system that tracks HIV/HCV prevalence among PWID, has been successful in uncovering the high lifetime prevalence of chronic diseases such as HIV and Hepatitis C, with proportions reaching 5.5% and 79.1%, respectively in London, Ontario (MLSU, 2013). This is compared to I-tracks Canadian national averages of 11% and 68% (MLHU, 2013), which shows London to have a lower incidence of HIV (5.5% less) and higher incidence of Hepatitis C (11.1% greater) relative to national averages. Incidence of HCV infection may be used as a surrogate for unsafe injection practices (Brooks, 2016), as HCV is much more infectious than HIV and is most often associated with injection drug use (Brooks, 2016). In the United State, more than 70% of new HCV infections since 2006 have unsafe injection practices as the most significant risk factor (Zibbell, 2015). The high prevalence of HCV indicates that London, Ontario may be a fertile ground for infectious diseases, and the low proportion of HIV indicates a high susceptibility to future HIV epidemics. In a vulnerability assessment conducted by Van Handel et al (2016), their models suggested that prescription opioid sales, per capita income, unemployment, and Caucasian ethnicity to be four of the six indicators for at-risk

populations, or populations with the greatest potential for an infectious disease outbreak (Van Handel et al, 2016). Although the Ontario Southwest LHIN (Local Health Integration Network) has lower total opioid prescriptions per 10,000 persons in comparison to the provincial average (1,403 vs. 1,431), the prescription rates of Hydromorphone Contin, an opioid that is commonly used by PWID in London, are higher per 10,000 than the provincial average (214 vs. 168). With regards to unemployment, although the unemployment rate is not particularly low London has an *employment* rate of 57% indicating 43% of the population is either unemployed (6.2%) or not in the labour force (38.8%) (StatCan, 2018). The unemployment rate is generally used to explain the percentage of people that are not working. This suggests that although the unemployment figure specifically is not high, the number of people without employment is. Both the mean and median income of individuals in London, Ontario aged 15 years or greater ($39,229 and $29,478, respectively) are lower than both the provincial ($42,264 and $30,526) and national ($40,650 and $29,878) statistics. Lastly, London is disproportionately Caucasian compared to provincial averages as only 16% of the population is a visible minority (MacTaggart et al, 2013). Despite the many contributions made by publications such as the I-track study mentioned earlier, there remains no publicly available data on relatively acute, potentially fatal diseases such as Infective Endocarditis, nor on the total number of at risk PWID. The data does suggest, however, that London, Ontario represents a fertile ground for infectious disease outbreaks in the PWID population.

IE is widely recognized as a major issue among PWID and presents a major problem as the recurrence rates following treatment remain high (Saydain et al, 2010). Infective Endocarditis (IE) is an infection of the heart valve and requires a syndrome diagnosis, meaning a collection of signs and symptoms to classify a patient as “possible” or “definite”

IE, most commonly via the modified Duke Criteria (Li et al, 2000). Many studies that explore first-episode infective endocarditis find PWID to have more favorable outcomes than non-injection-drug-users (non-PWIDs) (Ruotsalainen et al, 2006), as they tend to have right-sided IE which has a more promising prognosis (Cahill et al, 2016). PWID patients tend to be much younger, have higher rates of readmission, develop recurrent IE and therefore have poor *long-term* prognoses despite their favourable short-term prognosis following their first-episode of IE (Rosenthal et al, 2016). The young age is attributable to the lifestyle induced infective endocarditis. Since the causal lifestyle often remains upon leaving the hospital, readmissions for recurrent IE are common.

The mechanism behind PWID-associated IE is twofold in that it requires a blemished heart valve as well as the presence of bacteria in the blood. There are nuances to both conditions, although the most common explanation found in the literature is that PWID inject sharp particulate matter directly into the bloodstream, scratching and blemishing the tricuspid valve as the blood returns to the heart (Frontera et al, 2000). PWID-associated IE is generally associated with right-sided endocarditis for this reason.

In non-PWIDs, left-sided infective endocarditis is found to be more common. Patients also tend to be much older, display pre-existing heart complications such as congenital heart disease or have prosthetic valves. As such, their pathophysiology is different, and their prognosis is worse upon first admission, although they have lower rates of readmission than PWID.

# Chapter 2

## 2 Literature Review and Objectives

This review begins with definitions and inclusion criteria for the diagnosis of infective endocarditis. Next, there is a review of injection drug use, infectious disease in general, and the relationships between them, which come together to form the population focused on in this thesis: patients with infective endocarditis (an infectious disease) that use injection drugs. Then follows the incidence and survival of patients diagnosed with infective endocarditis. The mechanisms and pathogenesis of infective endocarditis are also reviewed, as well as injection drug use in London, Ontario. Lastly, this section includes study objectives and rationales.

## 2.1 Definition and Diagnostic Criteria for IE

Infective Endocarditis (IE) is an infectious disease affecting the heart valve. *Infective* is alluding to the transmissible nature of the disease, *endo* refers to the endothelium, or the single layer of cells lining the blood vessels within the body (Félétou, 2011), *card*ium refers to the heart, and *itis* indicating inflammation. Infective Endocarditis is thereby an infectious disease characterized by bacterial vegetations that accumulate on the heart valve in response to valvular endothelial damage.

Infective Endocarditis is clinically diagnosed via the modified Duke Criteria. This is a syndrome diagnosis (Li et al, 2000), meaning a collection of signs and symptoms that in

conjunction with one another are indicative of "possible" or "definite" endocarditis. The original Duke Criteria (Durack et al, 1994) demonstrated a high sensitivity and specificity (Cecchi et al, 1997) (Li et al, 2000), although the clinical diagnosis of "possible IE" was frequently criticized. A "possible IE" diagnosis required the patient not meet "rejected IE" requirements and have one minor criterion present was suggested to be too inclusive (Li et al, 2000). To "raise the diagnostic floor" on possible IE cases (Li et al, 2000) and decrease the type I error rate, Li et al (2000) proposed a modification to "possible IE" diagnostic criteria. The Modified Duke Criteria defines "definite" endocarditis as presenting two major criteria, whereas "possible" IE occurs when either one major and one minor criteria, or three minor criteria are present (Li et al, 2000). Major Criteria include bacteremia known to cause IE, echocardiographic evidence such as vegetations, and new valvular regurgitation or leaky heart valves. Minor Criteria include predisposing conditions such as intravenous drug use and diabetes, vascular phenomena, immune phenomena, fever, and blood cultures that are not belonging to the Duke Major Criteria (Li et al, 2000). The criteria have been arranged in a table by Li et al (2000) and is included in the appendix (table 1).

## 2.2 Infectious Diseases and Injection Drug Use

People who use injection drugs are at an elevated risk of death from acute and chronic infectious diseases as well as drug overdose in comparison to those who do not inject drugs (Mathers et al, 2012). In a systematic review conducted by the World Health Organization (WHO), standardized mortality ratios (SMRs) were used to assess the excess mortality that has resulted among PWID. SMR is a summary index ratio that calculates the relationship

between the observed and expected values based on crude counts (Fleiss et al, 2004) or age- and sex-specific rates in a standard population (NM-IBIS, 2017). An SMR may be calculated for all-cause mortality or for mortality attributable to a particular cause in a given population, and the expected number of deaths. In this case, excess mortality was calculated with death rate among PWID in terms of person-years as the numerator, and death rate in the general population as the denominator. Researchers at the WHO calculated an SMR of 11.19 (95% C.I. 3.58 to 18.80) (Mathers et al, 2012) indicating that all else being equal, PWID in North America are at an 11.19 times greater risk of mortality than non-PWIDs. Among PWID, crude global estimates found that all-cause mortality was three times greater (3.15, 95% C.I. 2.76 to 3.50) and risk of drug overdose death was two times greater (1.99, 95% C.I. 1.31 to 3.04) for those diagnosed with HIV compared to those without (Mathers et al, 2012).

Overdoses are responsible for the most fatalities among PWID in Europe and North America (Copeland et al, 2004) although this may not be the case universally. An analysis of a Vancouver inner-city cohort by Deans et al (2013) suggests that infection may have surpassed overdose with regards to mortality (Deans et al, 2013). Of the 374 deaths that occurred among the 2913 participants, 97 (25.9%) were infections, and 37 (9.9%) were from external causes which included accidents, assault and intentional self-harm (Deans et al, 2013). Excess mortality was highest among participants infected with HCV, HIV, or both (Deans et al, 2013), suggesting that infectious diseases associated with injection drug use may be more significant relative to overdose in Canada than larger American studies suggest.

There are many overlapping risk factors among various infectious diseases which why HCV, which is approximately 10 times more infectious than HIV (Budd and Robertson, 2005), is used as a surrogate indicator for the fertility of a given population for infectious

disease epidemics (Zibbell et al, 2015). In reviewing the health consequences associated with injection drug use, blood borne viral infections tend to be the most discussed, particularly HCV and HIV, although many PWID are more familiar with bacterial infections such as cellulitis and, less commonly, Infective Endocarditis. While blood borne viruses require sharing needles or reusing paraphernalia to make transmission of the virus possible, bacterial infections do not. The bacteria most commonly found among PWID with infective endocarditis are common, even among healthy individuals (Ryan, 2003).

In North America, *S. aureus* is present in over half of the infective endocarditis cases (Slipczuk et al, 2013). Furthermore, *S. aureus* and *streptococcus* species together account for 80% of first-episode infective endocarditis cases (Hoen, 2013). The mouth, specifically the buccal and tongue mucosa, are home to many streptococci species which can be transferred by the hands to drug paraphernalia or the drugs themselves. *S. aureus* is present in 25-30% of healthy people at any given time and can be spread from hand-to-nose contact (Ryan, 2003). Even with antiseptic washing is difficult to eliminate all potentially pathogenic microbes from the skin (Ryan, 2003).

## 2.3 Incidence and Survival of Patients with IE

Studies vary in their incidence estimation for infective endocarditis, with large reviews reporting incidence rates of 2.4 to 11.6 per 100,000 person-years (Klein et al, 2016), and proportions 3-10 per 100,000 people (Cahill et al, 2016). Of these, hospital-acquired infective endocarditis has accounted for 25-30% of the cases within recent cohorts, with the average patient age being greater than 70 years (Cahill et al, 2016). Degenerative valve

disease, particularly that of the mitral valve, is shown to be present in approximately 30% of cases (Klein et al, 2016). These statistics are for the population at large, although the epidemiological findings for PWID with PWID-associated Infective Endocarditis suggest a greater incidence, a younger patient age (Shrestha et al, 2015)(Tung et al, 2015), a more benign first-episode of IE (palepu et al, 2002), and less hospital-acquired infection (Wilson et al, 2002) as endocarditis is acquired via the injection drug use itself. In a prospective study of IE among PWID in New York City between February, 1988 and March, 1989, Wilson et al (2002) found an incidence of 7.1 cases per 1000 person-years (95% C.I 5.88 to 8.51). That is approximately 700 cases per 100,000 person-years, compared to the previously mentioned incidence of 2.4 to 11.6 cases per 100,000 in the general population. The 95% confidence intervals suggest a 60- to nearly 300-fold increased incidence of IE for PWID relative to the total population, which includes the PWID themselves.

The population of PWID is not a homogeneous group, as is revealed by stratifying based on comorbidities. Immunosuppression, or more specifically a CD4 count less than 400, among HIV-seropositive PWID further increases the risks of infection and death in general (Wilson et al, 2002). This is consistent with more recent data in Vancouver, British Columbia (Deans et al, 2013). The incidence of HIV-related deaths in this cohort was 46 (95% C.I. 37 to 58) per 10,000 person-years, higher than drug-related and liver-related deaths, combined (Deans et al, 2013).

The concerns regarding incidence are a function of the morbidity and mortality associated with the disease. With regards to survival metrics, American studies have shown Infective Endocarditis carries a 16% *in-hospital* mortality rate for the population at large. Wallace et al (2002) continued to follow their cohort of patients for another 6 months

following discharge to determine a 6-month mortality rate of 27% (Wallace et al, 2002). In a Belgian prospective study, the six-month mortality was 22% (Hill et al, 2007).

When comparing the survival between PWID and non-PWID with IE, a multinational prospective cohort (Murdoch et al, 2009) found that the in-hospital mortality for PWID without intracardiac devices was 9.7%, whereas non-injection drug users were 17.1%, and the entire cohort was 17.7% (as it included patients with intracardiac devices). In a regional study from British Columbia, PWID-associated IE and non-PWID-associated IE were compared, revealing that the mean age for PWID was 38.3 +/- 8.2 years, compared to 70.7 +/- 13.9 years with non-PWIDs (Tung et al, 2014). The authors also mentioned that "there was a trend toward lower inpatient mortality" among PWID which they attributed to increased operations (Tung et al, 2014). These studies highlight the "favourable" prognoses for PWID with IE are likely attributable to the differences in age and, as shown in other research (Shrestha et al, 2015), the short follow-up period. Shrestha et al (2015) followed up for a longer period and found that the 90-day survival free of operation (no mortality, no operation) corresponded to a hazard ratio of 0.38 (95% C.I. 0.05 to 3.07) for PWID, indicating a non-significant survival trend that favoured PWID. The cumulative incidence of mortality specifically, as opposed to the combined mortality and reoperation, was much lower for PWID at 90 days. At the 1000-day mark however, the cumulative incidence of mortality was very similar for both PWID and non-PWIDs at just over 20%. "The ultimate survival was no different (for non-PWIDs) than that of patients who did not inject drugs" (Shrestha et al, 2015). This is statistically demonstrated via a log-rank test for overall survival which produced a probability value of 0.57, indicating there was no difference in overall survival between PWID and non-PWIDs (Shrestha et al, 2015). In conclusion, the in-hospital survival of patients with Infective Endocarditis is consistently between 16-19%, with

PWID demonstrating much lower short-term mortality rates due to their young age relative to non-PWIDs, although the 5-year mortality rate is similar for both groups.

These studies on survival outcomes amongst patients with IE have also shed light on which patient characteristics are most commonly associated with both favorable and unfavourable patient outcomes. Using multivariable regressions and bootstrap modelling, Murdoch et al (2009) isolated variables that can demonstrate associations with in-hospital mortality. These variables are mentioned below, with a rationale provided by other research into the pathophysiology of endocarditis and further statistics wherever possible:

a. Age in 10-year intervals [OR: 1.30 (95% C.I. 1.17 to 1.46)] (Murdoch et al, 2009)

A decrease in immune function is recognized as a property of aging, as elderly individuals do not respond as effectively to unfamiliar antigens compared to younger populations (Montecino-Rodriquez et al, 2013).

b. prosthetic valve endocarditis [OR: 1.47 (1.13 to 1.90)] (Murdoch et al, 2009)

Bacteria associated with infective endocarditis contain surface adhesins that bind to mechanical structures, producing a biofilm (Nataloni et al, 2010) that contributes directly to infective endocarditis (Holland et al, 2017). This biofilm prevents host defenses from destroying the potential pathogen (Nataloni et al, 2010) and protects against antimicrobial treatment, permitting "device-associated vegetation propagation" (Holland et al, 2017).

c. Staphylococcus aureus infection [OR: 1.54 (1.14 to 2.08)] (Murdoch et al, 2009)

These finding are consistent with results from Chu et al (2004) [OR: 2.06 (1.01 to 4.20)]. The associations may be attributable to *S. aureus* containing proteins that allow for greater adherence to valve tissues relative to other bacteria (Frontera et al, 2000). The adhesins in *S. aureus* have also been shown to rapidly coat intracardiac devices (Frontera et al, 2000), exacerbating the effects of the biofilm mentioned previously.

d. Mitral valve vegetation [OR: 1.34 (1.06 to 1.68)] (Murdoch et al, 2009)

The mitral valve is in the left side of the heart, separating the left atrium and ventricle and is the most common site of IE amongst the general population, with three leading mechanisms to explain this phenomenon. The left side of the heart contains higher pressures and more turbulent blood flow, left sided blood is more richly oxygenated, and congenital/acquired lesions are more common on the left side of the heart (Frontera et al, 2000).

e. Diabetes mellitus [OR: 1.28 (0.88 to 1.86)] (Murdoch et al, 2009)

Diabetes being significantly associated with in-hospital mortality was also shown in a study by Chu et al (2004) [OR: 2.48 (1.24 to 4.96)] and the bootstrap model by Murdoch et al (2009) [OR: 1.45 (1.08 to 1.85)]. It has been suggested that the adverse effects of hyperglycemia on a patient's immune function may be responsible for the unfavourable outcomes associated with diabetes (Chu et al, 2004).

Other risk factors associated with increased short-term mortality include paravascular complications, embolic events, pulmonary edemas, and APACHE II score, while surgery and viridans streptococcal infection were associated with reduced odds of mortality (Murdoch et al, 2009).

## 2.4 Risks associated with Injection Drug Use

With regards to PWID-associated Infective Endocarditis, there are indirect effects that extend beyond the direct effects caused by particulate matter blemishing the valves of the heart. Indirect effects include vasoconstriction and increased blood pressure, damage to the endothelial cells lining the blood vessels (referred to as intimal damage), formation of blood clots, and generally decreased immune function of PWID (Tahamtan et al, 2016)

(Frontera, 2000). Indirect effects differ depending on whether the PWID uses opioids such as hydromorphone or stimulants such as methamphetamine and cocaine. Different drugs will be explained below their respective sequence.

In a qualitative analysis by Roy et al (2011), public health concerns surrounding the injection of prescription opioids were uncovered within the cohort of participants in the study. With regards to Hydromorph Contin, there are reasons why it is preferable over heroin. "Hydros", as they are referred to, and Dilaudid are not distributed by criminal organization as is the case with cocaine and heroin. They are easy to find, inexpensive, and of uniform quality (Roy et al, 2011). Prices in Montreal begin at less than $10 for a 1mg Dilaudid, resulting in a relatively low barrier to entry. There are however new patterns of risk taking that are being uncovered because of the growing popularity of prescription opioids. Firstly, there are many more daily injections with prescription opioids (Roy et al, 2011). Due to the high accessibility, users will often use lower doses more frequently, rather than save for a larger dose that will last a longer period. If a larger capsule such as a 30mg Hydromorphone Contin ("red rocket") is purchased, the user must use more water to draw out the medicine and as such, there may be multiple injections in one sitting. In this circumstance, it is common to use the same needle to aspirate each time. The leftover residue, referred to as a "wash", may then be given away or sold, in which case a potentially contaminated cooker/filter is being reused, despite the efforts to never share equipment by the users (Roy et al, 2011). Hydromorph Contin may be consumed orally, as is intended, and injected.

There are immunomodulatory effects that vary depending on the particular opioid being consumed. Morphine and oxycodone are considered immunosuppressive, as opposed to hydromorphone and codeine which are *not* considered immunosuppressive (Plein et al,

2017). In another review by Tahamtan et al (2016), they discussed both in vivo and in vitro studies that suggest opioids have the potential to impair host immune response and increase risks of exposure, although they did not differentiate between opioids. Opioids have also been shown to suppress intestinal immune function by increasing gut barrier permeability (Plein et al, 2017) (Tahamtan et al, 2016), potentially leading to bacteremia despite sterile injection practices. Lastly, studies have shown withdrawal-induced immunosuppression effects can be strong (Roy et al, 2011), which may be a daily occurrence for many PWID. The magnitude of effect of these indirect risks associated with opioids is still largely unknown.

In a review by Salamanca et al (2015), it was suggested that a major risk associated with methamphetamine consumption are the devastating effects on host immunity (Salamanca et al, 2015), which may predispose PWID to infectious diseases by impairing the user's immune system from fighting it off. Methamphetamine use is also associated with enhanced sexual pleasure and unsafe sexual practices, thereby increasing the risks of contracting sexually transmitted infectious diseases such as HIV (Salamanca et al, 2015). This risk may be exacerbated by the sharing of drug paraphernalia and unsafe injection practices such as the "shake-and-bake" method to dissolve the drug into water for injection. Like any disinhibiting psychoactive drug, the decisions made under the influence of the substance may be more consequential than the substance itself.

Among stimulant users (cocaine, methamphetamine, Ritalin, etc.), pulmonary hypertension, or increased blood pressure in the vasculature around the lungs, places stress on the heart and exposes individuals to acute increases in pressure gradients specifically affecting the pulmonary and mitral valves (left side of the heart) (Frontera, 2000). Pulmonary Hypertension is typically a chronic disease (Shah, 2012) which increases

the risk of left-sided infective endocarditis regardless of PWID history. This places PWID within an at-risk population for left-sided, as well as the previously discussed right-sided, infective endocarditis.

## 2.5 Mechanism and Pathogenesis of IE among general population and PWID

Historically, rheumatic heart disease (RHD), an acute or chronic cardiac inflammatory disease caused by group A streptococci that damages the valves of the heart (Marijon et al, 2012), has caused most infective endocarditis cases. This is still the case in low-income countries, although in higher-income countries the improved living standards and accessibility to antibiotics has decreased the prevalence of RHD (Thanavaro, 2014). Today, some of the major risk factors include congenital heart disease, degenerative heart disease, diabetes, cancer, and intracardiac devices (Thanavaro, 2014) (Cahill, 2016). These risk factors are associated with predominantly left-sided, specifically the mitral or aortic valve, infective endocarditis (Frontera et al, 2000). In a review by Frontera et al (2000), left-sided IE is attributable to 3 factors. First, higher pressure exerted by the left side of the heart produces a relatively turbulent flow in comparison to the right side, potentially leading to damage of the mitral and aortic valves. Second, the left atrium only contains oxygenated blood coming from the lungs which is more favorable for bacterial proliferation. Lastly, congenital and acquired lesions are more common on the left side of the heart (Frontera, 2000). None of these three factors are a function of lifestyle and preventative interventions are not feasible. The focus of the thesis, intravenous drug use, is a risk factor (Shrestha et al, 2015) that is overwhelmingly associated with right-sided IE.

Epidemiological data collected by Cahill and Prendergast (2016) found that the average patient age has nearly doubled since the 1980's (Cahill et al, 2016). This is largely attributable to an increased frequency of cardiac implantable devices, which are a risk factor for IE based on the Duke Criteria (Thanavaro, 2014). The rising age was also noted in a review of hospital-based studies by Slipczuk et al (2013), with a mean age in the 1980s of 45.3 years (95% C.I. 40.2 to 50.5) and a mean age in the 2000's of 57.2 years (95% C.I. 54.7 to 59.7) (Slipczuk et al, 2013). Slipczuk et al (2013) also found non-significant increases in the frequency of prosthetic valve IE, which may explain a discrepancy in their findings compared with Thanavaro et al (2014). While infective endocarditis continues to occur later and later in life among patients with congenital heart defects, populations of PWID are facing a more disturbing reality.

With regards to people who inject drugs, risk factors are largely attributable to the injection of drugs themselves, as opposed to congenital heart conditions. Native-valve infective endocarditis occurs on damaged valvular endothelium, or the single layer of cells lining the heart valves, which permits bacterial colonization with "specific adherence properties" (Hoen, 2013). These properties are found among streptococci and staphylococci bacteria, and these microorganisms are most commonly isolated from patients with first-episode, native-valve infective endocarditis. These microorganisms have been shown to account for 80% of cases of IE (Hoen, 2013).

IE vegetations may occur via bacterial proliferation on the heart valve and/or by the endogenous clotting process that is meant to repair the blemished valve, both of which require a blemished valve. Once an endothelial lesion occurs, the clotting process for damaged tissues requires fibrin, a fibrous mesh to impede blood flow (Shah, 2012), and platelets which form the origin of the vegetation that commonly characterizes infective

endocarditis (Klein et al, 2016). This damage may be a result of intravenous injection of solid particles, which has a direct effect on cardiac valves, particularly the right-sided tricuspid valve, via "repetitive bombardment with particulate matter that is present in injected material" (Frontera et al, 2000). In a lab experiment conducted by Laura Ball, a medical student at Western university, it was found that Hydromorph Contin that has been prepared for injection contains particulate matter greater than 5 microns, even when using a filter to aspirate. When drawing only sterile water through a pressed cotton filter with a needle, the cotton filters themselves have been found within injectate which could theoretically scrape and physically damage the endothelium. These images and explanatory captions can be found within the appendix (figures 1 and 2).

The pathophysiology of IE begins with endothelial damage, but also requires bacteremia, or the presence of bacteria in the blood, to cause an infection. Non-hospital acquired bacterial exposures may include non-sterile injection practices and/or contaminated drugs themselves. Non-sterile injection practices include, but are not limited to, failing to cleanse the skin with alcohol swabs before injection, using non-sterile tap water as a solvent, reusing/sharing contaminated paraphernalia, licking needle wounds, licking needles themselves, and handling drugs with contaminated hands (Haverkos, 1990). Unsanitary environments may also be an issue, as 2017 study by Scheim et al (2017) found that more than 70% of participants that participated fully in the study (n = 196) reported using injection drugs publicly in the past 6 months due to convenience (69.5%) and homelessness (39.7%) (Scheim et al, 2017). Non-prescription drugs such as cocaine and methamphetamine may be exposed to bacteria in the production process and/or during packaging by street level distributors. With regards to hydromorphone specifically, re-soaking used pill residue,

henceforth referred to as “washes”, may create an opportunity for repeated exposures from one contaminated pill/cooker/filter. PWID reusing filters has occurred since before the William S. Burroughs novel *Junky*, which was originally published in 1953 (Burroughs, 1977), although the additional exposure of the wash residue may be driving infective endocarditis in regions where it is popular such as South-Western Ontario (London-Middlesex region) (Richmond, 2017), South-Eastern Ontario (Kingston and surrounding areas), Champlain (Ottawa and Cornwall), and many parts of Northern Ontario (Ontario narcotics atlas, 2016). Furthermore, many injection drugs, including crystal methamphetamine and Hydromorph contin, do not require heating to extract the medicine into water which may have otherwise been helpful to reduce harm associated with PWID (Haverkos, 1990).

## 2.6 Injection Drug Use in London

Different drugs represent unique risk profiles and pathophysiology. Most often, drug classes are broken down into two broad groups: Opioids and stimulants. In a systematic review by the WHO, the SMR of all-cause mortality between opioids and stimulants showed no significant differences across studies (1.25, 95% C.I. 0.60 to 2.61) (Mathers, 2012).

Epidemiological trends in Canada have demonstrated a reduction in daily cocaine and daily heroin injection, whereas numbers for prescription opioids and crystal methamphetamine have “increased substantially” (Roy et al, 2016). Based on I-TRACK survey data, this appears to be consistent with the current situation locally in London. These

changes in drug use trends may present a new set of challenging circumstances for healthcare providers caring for PWID.

In London, Ontario, there is over 20% more PWID who inject non-prescribed morphine, dilaudid, and OxyContin than the national averages. With regards to crystal methamphetamine, there were no national comparators, but 68% of participants injected methamphetamine in the past 6 months (I-TRACK LONDON). In a preliminary analysis drawn from a separate case-control dataset attempting to identify risk factors for IE, it was found that PWID in London may be using more crystal methamphetamine than previously recorded. The trend previously indicated in the research by Roy et al (2016) towards prescription opioids and crystal methamphetamine appear to exist in London as well. Below is a list of statistics drawn from an unpublished case-control study (Silverman et al, 2017). Of the 120 London participants from the study;

- 47.5% (n=57) said that opioids were their preferred drug, where 27.5% (n=33) specifically stated that they preferred Hydromorph Contin as opposed to opioids in general.
- 83.3% (n=100) disclosed having used Hydromorph Contin intravenously within the past 3 months. There was a selection bias in the recruitment as many of the participants were interviewed at the needle and syringe program in London.
- 82.5% (n=99) disclosed having used Crystal Methamphetamine within the past 3 months.
- 12.4% (n=15) disclosed having used heroin within the past 3 months.

The remainder of the paper will be focusing on the chart review dataset which is explained in the next section.

## 2.7 Objectives, Hypothesis, and FINER Criteria

The following include the objective and hypothesis for all sections of the analysis, with the structure adapted from Farrugia et al (2010):

**Section:** Baseline Characteristics.

**Research Question**: Which variables are significantly different between the PWID and non-IDU subsets?

**Research Hypothesis**: Consistent with the literature, a significant majority of right-sided, specifically affecting the tricuspid valve, infective endocarditis occurs among PWID, with Streptococci species being most prevalent throughout both groups. Also, due to the stigma associated with the use of injection drugs, number of patients receiving surgery will be significantly higher among non-IDU patients.

**Objective**: Investigate how characteristics differ among patients with infective endocarditis depending on their use of injection drugs.

**Section:** Incidence Estimation Analysis.

**Research Question:** How has the incidence of infective endocarditis changed over time relative to the growth of the population?

**Research Hypothesis:** Infective endocarditis has been growing at a greater pace among PWID than non-PWID.

**Objective:** Determine the incidence of Infective Endocarditis in London, Ontario by injection drug use status.

**Section:** Survival Analysis.

**Research Question:** How does the use of injection drugs influence survival outcomes without accounting for other covariates (Kaplan-Meier)?

**Research Hypothesis:** PWID are at a lower risk of death initially, although over the timespan of the dataset their cumulative hazard surpasses non-PWID in a statistically significant way.

**Objective:** Assess the influence that the use of injection drugs has on the probability of survival over time.

**Section:** Survival Analysis.

**Research Question:** Which variables are associated with an increased hazard of death among PWID patients with infective endocarditis (Cox PH model)?

**Research Hypothesis:** HIV, age in years, MRSA infection, and HCV are most significantly associated with death in the model.

**Objective:** Determine which variables have the greatest influence on survival in PWID after adjusting for other clinically relevant variables.

The FINER criteria for a good research question (Farrugia et al, 2010) will be used to further build the rationale underlying this thesis topic.

**F**easibility - There were 377 total patients included in the analysis, 204 of which were PWID. The number of PWID patients exceeded that of all single-city studies that have been reviewed in the introduction and literature review.

**I**nteresting - The number of endocarditis patients in London, Ontario that use injection drugs is an anomaly in terms of magnitude and proportion, which increases interest among researchers of PWID. The influence of this high rate of IE leads to interesting questions regarding the incidence of IE relative to common estimates found in the literature. This rich dataset also allows for a thorough examination of PWID with IE and the unique risk factors that influence this subset of the population.

**N**ovel - Considering there is no dataset found in the literature that contains the proportion of PWID with IE that are found in London, the results of this study are certain to be novel.

**E**thical - All data was collected with the approval of an ethics committee.

**R**elevant - With the rise of prescription opioid injection drug use in North America, understanding the associated risks is relevant. These findings have the potential to influence funding for addiction treatment and harm reduction services, as well as future research into other health outcomes associated with the use of injection drugs.

# Chapter 3

# 3 Data and Methods

This analysis used data from a medical chart review of all patients in London, Ontario that have been admitted with definite infective endocarditis. Missingness was found throughout the dataset. When possible, values were inputted using a clinical rationale. The analysis was conducted using R and it's many useful statistical packages. The methods include an assessment of baseline characteristics, an incidence analysis, a univariate survival analysis (Kaplan-Meier), and a Cox Proportional Hazards multivariable analysis.

## 3.1 Data

This dataset included all first-episode patients from February 28, 2007 to March 15, 2016 with a discharge diagnosis of Infective Endocarditis. Patients with ages greater than 65 years old upon admission were included at a later date and as such, their censoring dates were as recent as July of 2017. All cases were reviewed by resident physicians Dr. Adeel Sherazi and Dr. Esfandiar Shojaei to assure that they fulfilled the modified Duke criteria for *definite* IE. The resultant dataset included 371 first episode patients over the 9-year timespan, all of which have confirmed definite IE. The start time in this dataset occurs upon the clinical diagnosis of infective endocarditis and as such this is a historical cohort (Szklo, pg. 23). There was little opportunity for informative censoring because in Ontario, deaths must be confirmed by a medical professional and would therefore be available on a chart review for a patient (handbook on medical certification of death, 2010). The type of censoring that occured with this dataset would be considered "administrative censoring" as some patients had not yet died by the end of the data collection period (Moore, pg. 3).

The possibility of informative censoring may exist among PWID that did not seek medical treatment for IE. Any death that occurred because of inadequate treatment would possibly fail to be attributed to infective endocarditis. Overdose or sepsis may have been concluded despite the true cause of death being directly related to infective endocarditis.

Some data from the introduction was taken from a separate case-control separate study. This data was collected by myself (Brian Hallam), Laura Ball (UWO medical student), Ryan Wong (Medical Sciences Undergraduate student), and Dr. Michael Silverman (Infectious Disease Physician). This dataset had some unavoidable limitations such as the recall bias with time-dependent covariates (i.e. changes in injection drug use frequency). The selection of participants was highly susceptible to selection bias as the interviews were conducted at a needle exchange, a hospital, or an HIV clinic. As such, the analytics found in this paper focused exclusively on the chart review dataset.

## 3.2 Missingness

The problem of missingness is a serious one as it requires imputation or omission, both of which may create bias and lead to difficulties in the analysis. Dealing with missingness is particularly problematic when the observations are not missing at random, as is likely the case with our dataset. For example, the HIV-positive variable contained 190 unclear responses. In this case, missingness is very unlikely to occur at random. "UNC", or unclear, was written for all patients who were not questioned regarding their HIV status. As such, their information is unavailable and would be coded as such for analysis. This is a major issue as people who inject drugs are much more likely to be questioned for infectious

diseases, whereas it may not be deemed necessary to ask patients who do not use injection drugs.

In this situation it is intuitive to code the "unclear" observations as not having HIV, as it can be assumed that the physician decided it was not relevant. Of course, if the patient had HIV, a concurrent infectious disease would be pertinent, and therefore written down. The same assumptions were made with unclear HCV statuses, for which there are 138 unclear observations. This was a limitation of the study.

## 3.3 Methods Overview

The full analysis was conducted with a desire to ensure reproducibility. All analyses, including clean-up, were conducted using R software (R Core Team, 2013). Beginning with a .xlsx file format, I created a sheet titled "Thesis" that included all the variables required for the analysis, imported that dataset into R, then cleaned and performed the analysis transparently and in a reproducible manner while providing a rationale for any modifications. Effort was made to create an output that was tidy based on the Hadley Wickham definition (each column is a variable and each row is an observation) (Wickham, 2014).

The dataset included hospital chart review data of all definite cases of first-episode infective endocarditis in London from 2007-2016. (1) baseline characteristics such as demographic information, the frequency and proportions of right-sided versus left-sided endocarditis, and types of bacteria will be explored, differentiating by both PWID versus non-PWID as well as by the outcome variable of interest, Death. Next, an (2) incidence calculation using annual first-episode IE relative to the population of London, Ontario. The

population data was publicly available from Statistics Canada (Statistics Canada, 2017) and is available for viewing in the appendix (Table 3). To assess the influence of infective endocarditis on survival, we then performed a (3.1) survival analysis using Kaplan-Meier survival curves to differentiate those who inject drugs with non-PWIDs, with a corresponding log-rank test to formally assess whether differences in survival exist between these two groups. Lastly, to determine which factors have the greatest influence on mortality, a (3.2) Cox proportional hazards model models was calculated, with brief rationales for each independent variable included. All models were based on first-episode patients only, and injection drug use was modelled as an independent variable to assess the influence on death, one of the major objectives of this analysis.

## 3.4 Baseline Characteristics

Baseline characteristics include values for the entire sample, PWID-only, and non-IDU-only subgroups using frequencies and proportions with binary indicators and median and standard deviation for age, the only continuous variable. The design of the baseline characteristics table found below is largely influenced by the baseline table found in an endocarditis study by Shrestha et al (2015). The probability values were calculated using tests of two independent proportions (chi-square tests of independence) where appropriate (BU, 2016). In situations where counts were less than five, Fisher's exact test were used (D'Agostino, pg. 375). Independent and dependent baseline characteristic variables of interest as well as a brief rationale regarding significance are provided in table 4 from the appendix.

## 3.5 IE Incidence in London, Ontario

Incidence analyses are used for categorical dichotomous outcomes (Szklo, pg. 47), and in our case that outcome was a confirmed diagnosis ("definite case") of infective endocarditis. Incidence takes the form:

$$Incidence = \frac{Annual\ number\ of\ new\ diagnoses}{100\ 000\ person\ years}$$

The annual number of new diagnoses were gathered using the chart review (first-episode only) and creating subsets for each year. The denominator, population size of London, is publicly available from Statistics Canada. Table 3 from the appendix shows column headings that include variables for Year, Annual Incidence, Population Size, and Incidence Rate. This data will then be illustrated in a bar plot (appendix: Figure 3), in a dodged position (side-by-side) to differentiate PWID with non-PWIDs and overlaid with a line containing a slope that was determined in a linear model of year on population.

Predicted incidence and plotting was conducted manually using ggplot2 (Wickham, 2009) as well as the Incidence package in R (Jombart et al, 2017). This package is used to compute, visualize, and model incidence of dated events (Jombart et al, 2017) which makes it useful for analyzing the endocarditis dataset. First, we manually plot the annual incidence, differentiating PWID and non-PWIDs, like the plot mentioned above. Next, we modelled the incidence using a log-linear regression which takes the form:

$$\log(y) = rt + b$$

Where *r* is the growth rate, *t* is time, and *b* is the intercept. Recall that an increasing logarithmic function indicates that the outcome variable, y, is increasing at an increasing rate. This can be demonstrated algebraically:

$$y = e^{(rt+b)}$$

The outcome variable, incidence of infective endocarditis, would increase exponentially for all positive values of r, assuming $b \geq 0$, which makes sense given that you cannot have less than zero cases. The outcome of the fitted model, both the parameter estimates and the confidence interval, would shed light on the existence of an increasing, decreasing, or linear trend. The accompanying visualization plots the fitted values from the log-linear regression on a linear scale.

## 3.6 Time-to-Event Modelling: Survival Analysis

Simply put, "Survival analysis is the study of survival times and the factors that influence them" (Moore, pg. 1). Time-to-event modelling is effective in its ability to deal with observations that are terminated before the event (death) occurs. This is referred to as censored data, which is not a major issue when the majority of observations experience an "event" within the data collection period. In our case, censoring occurs among 249 of 371 observations, as these patients survive beyond January 1, 2016. Their death may have been two days after, or 50 years after, and as such we must use statistical methods that adequately account for this problem.

With binary outcomes and confounding covariates, logistic regression models are most commonly used to make inferences about the data. The coefficients for dichotomous

covariates are interpreted as the change in odds of death given the presence of a particular covariate, holding all other independent variables constant. The problem with logistic modelling in this circumstance is that they do not account for different lengths of follow-up (D'Agostino et al, pg. 586). Alternatively stated, logistic regressions are ineffective at dealing with censored data and ignore survival times (Kleinbaum et al, pg.98). A survival analysis on the other hand can make use of all available time-to-event data to compare groups with respect to time to an event (D'Agostino et al, pg. 586).

Groups with incomplete follow-up, loss to follow-up, or censoring in cohorts are traditionally comprised of individuals who drop out for reasons unrelated to the study, such as becoming disinterested and withdrawing their consent to participate, moving to another district, not answering calls to collect information, etc. With the chart review dataset, we assumed that the patients remained in the London-Middlesex region and were included for the entirety of the data collection period. This is because all participants would have their information collected by physicians in the region and would therefore be accessible by the researchers that gathered the data. It is possible that participants left London-Middlesex and subsequently died within the study period, and this was a limitation of the study.

Censoring with survival data must be non-informative. This would mean that any individual that is censored at the end of the follow-up period should be representative of all other subjects with the same values for explanatory variables that are also censored (Cox et al, 1984). In the regression modelling, this assumption is met through the inclusion of pertinent independent variables that would likely affect the rate of censoring, such as age, vegetation location, intravenous drug use, primary bacteremia, etc.

### 3.6.1 The Kaplan-Meier Method

The survival analysis was conducted using the Survival package in R (Therneau, 2015) (Therneau and Grambsch, 2000). The analysis begins with the Kaplan-Meier method which takes the form:

$$\hat{S}(t_{(f-1)}) = \prod_{i=1}^{f-1} \widehat{Pr}(T > t_{(i)} | T \geq t_{(i)})$$

This provides estimates for the survival function, *S*, which is a product of the probabilities, *Pr*, of individuals within a chosen group surviving past the previous failure time, $t_{(f-1)}$, given that they were alive at time *t* (Kleinbaum et al, pg. 66). *T* represents time in days since the admission until an "event", or in our case, death. A simpler description is provided by Goel et al (2010), as they described the product limit estimate as a product of survival over time intervals, where each is calculated by taking the number of subjects living at the start less the number of subjects that died during that period, all over the number living at the start (Goel et al, 2010). The shorter these time intervals are, the more accuracy is contained in the calculation. With the chart review dataset, we were fortunate to have time of death right down to the second, although the variables were reformatted from date *and* time (POSIXct) to date-only for the analysis.

The survival outcome was then transformed into an illustration, the Kaplan-Meier curve, which is a monotonic (never increasing in this case) step function (Kleinbaum et al, pg.53). The Kaplan-Meier method creates a new interval each time there is an event, utilizing conditional probabilities to plot survival over time. The Kaplan-Meier method, however, is unable to account for covariates without running separate subgroup

analyses. This is a limitation of the method, although the upside to using the Kaplan-Meier method is that it provides easily interpretable outcomes. A more thorough analysis was completed using Cox proportional hazard regression models later in this section.

In our plot, each survival function used grouped data based on one variable of interest to generate each respective survival curve. The first effect parameters in the Kaplan-Meier analysis are PWID vs. non-PWID. We will use our data to answer how the probability of survival using all-cause mortality varies over time, differentiating by injection drug use status. This is followed by a log-rank test that tests the hypothesis that there is no difference between groups. The corresponding p-values determine the probability of differences being at least as large as is calculated using the method, given the null hypothesis is true, or that the two groups are truly the same. Alpha values below 0.05 will be considered statistically significant. Kaplan-Meier analyses was also performed using first-episode PWID *only*, investigating the survival curves associated with:

1. HCV positive vs. negative
2. HIV positive vs. negative
3. Homeless vs. Housed

In these circumstances, the PWID-only dataset must be used as there are insufficient events for non-IDUs.

The log-rank test was chosen instead of the Wilcoxon statistic or other options due to its sensitivity to test differences in groups at later points in time (Allison, pg.42). The Wilcoxon statistic is the *weighted* sum of deviations between observed and expected effects, whereas the log-rank test is the sum of deviations between observed and expected. As such, more weight is given to the events that occur earlier in the study period with the Wilcoxon

statistic. In the literature review it was shown that in-hospital, or short-term, mortality rates do not have statistically significant differences between PWID and non-PWIDs (Wallace et al, 2002) (Chu et al, 2004). The significant separations occur more than 6 months after diagnosis (Wallace et al, 2002). Being sensitive to the differences when they are most likely to occur is therefore necessary for this type of analysis.

### 3.6.2 Cox Proportional Hazard Model

A more rigorous analysis is conducted using a Cox Proportional Hazard model which determines the instantaneous risk of the outcome, death, compared with a baseline as a multiple of the underlying hazard (Szklo, pg. 266). The coefficients from a Cox PH model are the log hazard ratios, which is a multiplicative measure of association (Szklo, pg. 267). For example, the interpretation of a coefficient would be, "a one-unit increase in $x_1$ corresponds to a $e^{\beta_1}$ *times* increase in the outcome variable, adjusted for other variables in the model."

As mentioned previously, logistic regressions are not suitable for this type of analysis because they do not account for censoring or survival times. Although the Cox model is more accommodating for time-to-event data, it is a semiparametric model with no interpretable intercept, only a baseline hazard. If the covariates are centered (replace X with X-E[X]), only the baseline hazard changes and the coefficients remain the same (Klein, pg. 9). This means that our inferences are only relative to the reference for any particular covariate holding all others equal. This is the type of modelling is used in health and medical sciences because of its flexibility (Moore, pg. 25). The Cox proportional hazards model uses

*partial* likelihood to loosen the assumptions via an unspecified baseline survival distribution (Moore, pg. 56). For example, the coefficient corresponding to PWID, call it β, represents an $e^{\beta}$ hazard ratio, or an $e^{\beta}$ increased hazard of the outcome relative to non-PWIDs, holding all other independent variables equal. As with the Kaplan-Meier method, the Cox model can describe the hazard of the outcome for a subject with specific covariate values given that they are still alive at time $t$ (Vach, pg. 88). The ability to extend this model with many different covariates is what makes the Cox model particularly useful.

Whereas linear models assume a linear relationship between outcome variable and predictors, logistic regressions do the same on a logit scale (Stoltzfus, 2011), the Cox proportional hazards model assumes a constant proportional relationship. This would mean that holding all else equal, any given predictor corresponds to a constant $e^{\beta}$ times increase in the hazard of death over the life course. Alternatively stated, the variables in the model are time-independent (Kleinbaum et al, pg.95). With the chart review data, the time-independence assumption is suboptimal although not a major flaw as the data collection period is less than a decade.

In the presence of ties, for which there are 21 durations repeated twice and one duration repeated three times, the Efron method was used. This method was chosen as it has been shown in estimation studies to be preferable over the Breslow method (Hertz-Picciatto and Rockhill, 1997).

#### 3.6.2.1 Predictor Selection Procedure for Full Model

The goal of the model is to determine the minimally confounded estimate of injection drug use on survival (Vittinghoff, pg. 222). To minimize the risks of over-fitting, variable

specification was based on all clinically relevant data that had been motivated in the introduction and literature review (Vittinghoff, pg. 401). Attention was also paid to temporality to prevent the inclusion of mediating variables in the model. A simple example of this would be found in a model that includes both bone/joint infection (Y/N) and Septic Shock as independent variables. In this example, the bone/joint infection would mediate the sepsis and therefore provide biased estimates for both as they pertain to death, downward in the case of bone/joint infection and upward in the case of sepsis.

*Bone infection* → *Sepsis* → *Death*

A mediation analysis is not conducted as it was not considered in the original hypothesis, although a clinical rationale will be applied to prevent mediating variables from being included in the model.

In concordance with events per variable minimum of ten events per variable (EPV) (Peduzzi et al, 1995), all pertinent variables that were discussed in the introduction/literature review and do not mediate the effect of more proximal variables were included in the model. The results of this analysis suggest the influence of injection drug use on survival outcomes, which is one of the main objectives of this paper.

There are cases when variables were omitted despite the presence of more than ten events. This was done to avoid confounding variables. A strong example of a variable that was omitted to prevent confounding was with the variable *Negative,* indicating tests for bacteria in the blood returned negative. To be a Duke "definite" case of endocarditis, which all the patients included in the dataset were confirmed to be, required either two major criteria, one major and three minor, or five minor criteria (refer to table 2 from the

appendix). Given that a positive blood culture cannot be one of the criteria (hence, *negative*) and the number of people that had vegetations present was 367 (97.1%) and there is not a reliable way to determine the severity of the vegetations, the negative would have indicated between three and five minor criteria present. One of these minor criteria would be the *use of injection drugs*, which presents a clear multicollinearity problem. The takeaway is that the use of *negative* in the model would be guaranteed to carry multicollinearity problems due to conditions of the inclusion criteria for the dataset.

The variables in the model included:

1. Age - continuous variable representing age in terms of years
2. Female - representing the female sex relative to males
3. Fever - patients presenting fever upon admission
4. PWID - people who inject drugs
5. Microorganism - MSSA, MRSA, Enterococci
6. Valve Affected - Aortic, Mitral, Tricuspid, Multi-valve

Limited Right-sided infective endocarditis was not included in the model despite meeting the minimum event threshold. This is because of the interaction that would exist between the variables *limited right-side* and *tricuspid*, as most of the patients affected with tricuspid valve IE would also be limited to the right side. The variables *Skin and Soft Tissue Infection, Bone/Joint Infection, Respiratory Infection, Septic Shock, Renal Failure,* and *Surgery* were not included in the model due to the temporality bias that would introduce. As mentioned previously, these variables are often not presented upon admission. Many of the variables

mediate death, and as the most proximal variable to the outcome, they would dominate the variables that we are interested in determining the significance of.

#### 3.6.2.2 Predictor Selection for Secondary (PWID-only and non-IDU-only) Models

Like the Kaplan-Meier analysis, a separate Cox proportional hazards analysis was performed using a PWID-only subset of data. This included clinically relevant variables that were omitted in the previous model due to an unsatisfactory number of events per variable among non-IDUs. These variables have all been written in italics and underlined. The variables in the PWID-only model include:

1. Age - continuous variable representing age in terms of years
2. Female - representing the biological sex relative to males
3. Fever - patients presenting fever upon admission
4. *Homeless* – no registered address or identified as homeless
5. Microorganism - MSSA, MRSA, Enterococci, *Polymicrobial*
6. Valve Affected - Aortic, Mitral, Tricuspid, Multi-valve
7. *HCV +* - Positive for Hepatitis C Virus
8. *HIV+* - Positive for HIV

The variable indicating *Both Right- and Left-sided Vegetations* is not included in the model as its effects are captured within the variable *Multi-valve*.

The same process and rationale will be used in the third and final model, using the non-IDU patients only. Again, modifications from the *total* model will be italicized and underlined.

1. Age - continuous variable representing age in terms of years
2. Female - representing the female sex relative to males
3. Fever - patients presenting fever upon admission
4. Microorganism - MSSA, MRSA, Enterococci, *Alpha-Hemolytic Streptococci*, *Coagulase Negative Staphylococci*
5. Valve Affected - Aortic, Mitral, Tricuspid, Multi-valve, *Prosthetic Valve*
6. *Intracardiac Device and/or Pacemaker*

# Chapter 4

## 4 Results

The results are broken down into baseline characteristics, incidence analysis, and survival analyses. This section is devoted to stating the results and interpretation of the analysis. Impact and significance will be explored further in the discussion section.

## 4.1 Description of the Sample

| | Total Sample N=377 | Non-IDU N=173 | PWID N=204 | p-value |
|---|---|---|---|---|
| Age upon Admission | 46.7 (17.5) | 59.9 (15.0) | 35.5 (10.1) | <0.001 |
| Sex: | | | | 0.006 |
| Male | 221 (58.6%) | 115 (66.5%) | 106 (52.0%) | |
| Female | 156 (41.4%) | 58 (33.5%) | 98 (48.0%) | |
| Homeless | 35 (9.38%) | 0 (0.00%) | 35 (17.3%) | <0.001 |
| Death | 122 (32.6%) | 54 (31.8%) | 68 (33.3%) | 0.833 |
| Fever upon Admission | 296 (78.7%) | 134 (77.9%) | 162 (79.4%) | 0.819 |
| Blood Culture: | | | | 0.686 |
| Negative | 25 (6.63%) | 10 (5.78%) | 15 (7.35%) | |
| Positive | 352 (93.4%) | 163 (94.2%) | 189 (92.6%) | |
| Microorganism: | | | | <0.001 |
| MSSA | 154 (41.8%) | 39 (23.1%) | 115 (57.8%) | |
| MRSA | 61 (16.6%) | 16 (9.47%) | 45 (22.6%) | |
| Alpha-Hemolytic Streptococci | 63 (17.1%) | 55 (32.5%) | 8 (4.02%) | |
| Enterococci | 31 (8.42%) | 20 (11.8%) | 11 (5.53%) | |
| Coagulase Negative Staphylococci | 18 (4.89%) | 18 (10.7%) | 0 (0.00%) | |
| Fungus | 2 (0.54%) | 1 (0.59%) | 1 (0.50%) | |
| Beta-Hemolytic Streptococci | 8 (2.17%) | 5 (2.96%) | 3 (1.51%) | |
| Gram Negative Aerobic Bacilli | 9 (2.45%) | 6 (3.55%) | 3 (1.51%) | |
| Polymicrobial organisms | 17 (4.62%) | 4 (2.37%) | 13 (6.53%) | |
| Other | 5 (1.36%) | 5 (2.96%) | 0 (0.00%) | |
| Valve Affected: | | | | <0.001 |
| Aortic | 99 (27.0%) | 71 (41.5%) | 28 (14.4%) | |
| Mitral | 83 (22.7%) | 60 (35.1%) | 23 (11.8%) | |
| Tricuspid | 133 (36.3%) | 12 (7.02%) | 121 (62.1%) | |
| Pulmonic | 5 (1.37%) | 3 (1.75%) | 2 (1.03%) | |
| Aortic + Mitral | 20 (5.46%) | 14 (8.19%) | 6 (3.08%) | |
| Mitral + Tricuspid | 11 (3.01%) | 1 (0.58%) | 10 (5.13%) | |
| Aortic + Tricuspid | 6 (1.64%) | 4 (2.34%) | 2 (1.03%) | |
| Tricuspid + Pulmonic | 2 (0.55%) | 1 (0.58%) | 1 (0.51%) | |
| Other | 7 (1.91%) | 5 (2.92%) | 2 (1.03%) | |
| Limited right-sided IE | 143 (37.9%) | 17 (9.83%) | 126 (61.8%) | <0.001 |
| Both Right- and Left-sided Vegetations | 18 (4.77%) | 5 (2.89%) | 13 (6.37%) | 0.181 |
| Intracardiac Device and/or Pacemaker | 13 (3.47%) | 12 (6.94%) | 1 (0.50%) | 0.002 |
| Prosthetic Valve | 36 (10.9%) | 34 (27.0%) | 2 (0.98%) | <0.001 |
| HIV Positive | 20 (5.33%) | 4 (2.33%) | 16 (7.88%) | 0.031 |
| Hepatitis-C Positive | 145 (38.8%) | 2 (1.17%) | 143 (70.4%) | <0.001 |
| Skin and Soft Tissue Infection | 34 (9.02%) | 11 (6.36%) | 23 (11.3%) | 0.139 |
| Bone or Joint Infection | 56 (14.9%) | 26 (15.0%) | 30 (14.7%) | 1.000 |
| Respiratory Infection | 162 (43.0%) | 20 (11.6%) | 142 (69.6%) | <0.001 |
| Septic Shock | 113 (30.0%) | 36 (20.8%) | 77 (37.7%) | 0.001 |
| Renal Failure | 94 (24.9%) | 53 (30.6%) | 41 (20.1%) | 0.025 |
| Liver Failure | 9 (2.39%) | 4 (2.31%) | 5 (2.45%) | 1.000 |
| Patient Received IE Surgery | 138 (36.6%) | 99 (57.2%) | 39 (19.1%) | <0.001 |

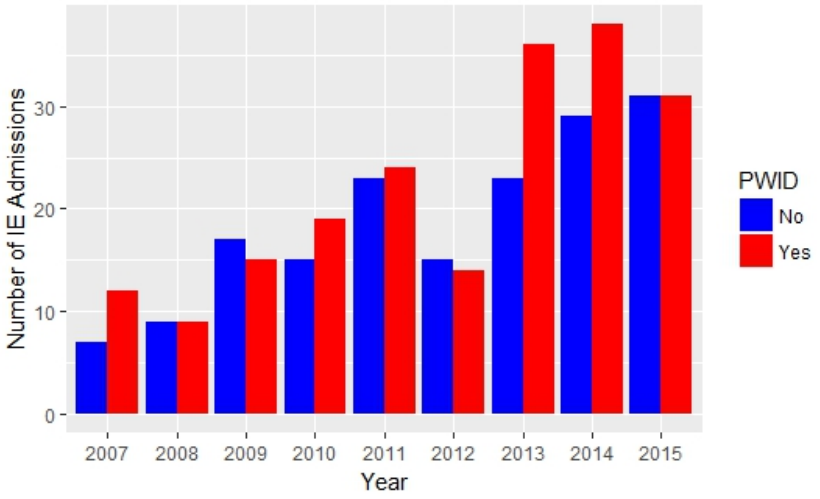
**Table 6: Results for baseline characteristics, differentiated by total group, PWID and non-IDU.**

This sample contained 377 patients with first-episode of Infective Endocarditis, 204 (54%) of which used injection drugs based on the chart review. The baseline characteristics by injection drug use (found in table 5) illustrated many significant differences between

PWID and those who do not use injection drugs. The age upon admission for PWID with first-episode endocarditis showed PWID to be younger by 24.4 years (95% C.I. 21.7 to 27.0, $p < 0.001$). This difference was also clinically significant and suggests that any inferences derived from the Kaplan-Meier curve should not be considered too deeply, as these two populations are very different in terms of a variable that has a very strong relationship with the probability of death: Age. The majority of PWID with IE are male, although the ratio of male:female is much lower for PWID than non-IDU with IE. This suggests that all else being equal, men appear to be more likely to be diagnosed with infective endocarditis in general, although among PWID the difference in proportional diagnosis between men and women is not significant in this sample. Homelessness, on the other hand, is a variable that is found solely among PWID. Of the 35 patients in this sample that had no known address, all were PWID. The proportion of the sample that died was not significantly different between the two groups, nor was the proportion that had positive blood cultures. Since there were 11 levels for the categorical variable microorganism, only a chi-square test of association was performed to prevent the risk of spurious relationships. Notable differences occurred with MSSA (57.8% of PWID and 23.1% non-IDU), MRSA (22.6% of PWID and 9.47% non-IDU), and Alpha-Hemolytic Streptococci groups (4.02% of PWID and 32.5% non-IDU). The categorical variable indicating which valve the vegetation occurred on was similarly only tested using a measure of association, which showed very significant (p-value $< 0.001$) differences between PWID and non-IDUs. The non-IDUs had both relative and absolute greater levels of Aortic (41.5% vs. 14.4%) and Mitral (35.1 vs. 11.8%) vegetations, both of which occur on the left side of the heart, whereas PWID had the majority of Tricuspid vegetations (7.02% vs. 62.1%). PWID also had significantly higher frequencies of HIV, HCV, skin and soft tissue infections, respiratory infections and septic shock. Non-IDU

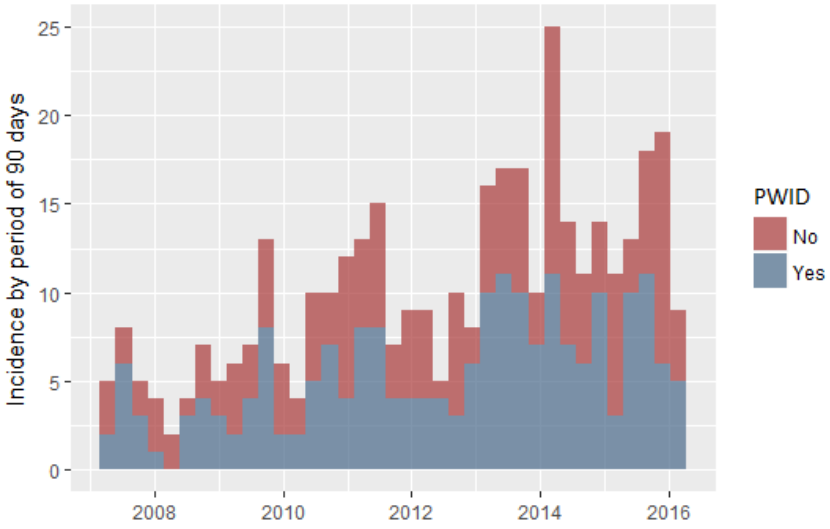
had higher frequencies of intracardiac devices, prosthetic valves, renal failure, and surgery for IE.

## 4.2 IE Incidence in London, Ontario




The data suggests there is an increasing annual incidence of infective endocarditis within all groups (total, PWID, and non-IDU). The total model was able to estimate the incidence rate as a function of the population of London, Ontario. Since we did not have estimates regarding the size of the underlying PWID population, we were only able to provide estimates based off the annual count. The cases of IE are rising faster among PWID, with a linear regression (predicting number of PWID cases over time) showing a coefficient value of 3.33 (95% CI 1.47 to 5.20) for PWID compared to 2.87 (95% CI 1.79 to 3.94) for non-IDUs, which indicates that with each year, there is an increase in IE of 3.33 and 2.87 cases, respectively. These confidence intervals intersect, indicating that there is not a statistically significant difference in annual incidence between PWID and non-IDUs. The year 2016 was omitted from the plot as the year was not complete at the end of the data

collection period and created a downward bias in the regression lines. There was a relatively low incidence in 2012 for both PWID and non-IDUs, although the counts returned to trend the following year for both groups.

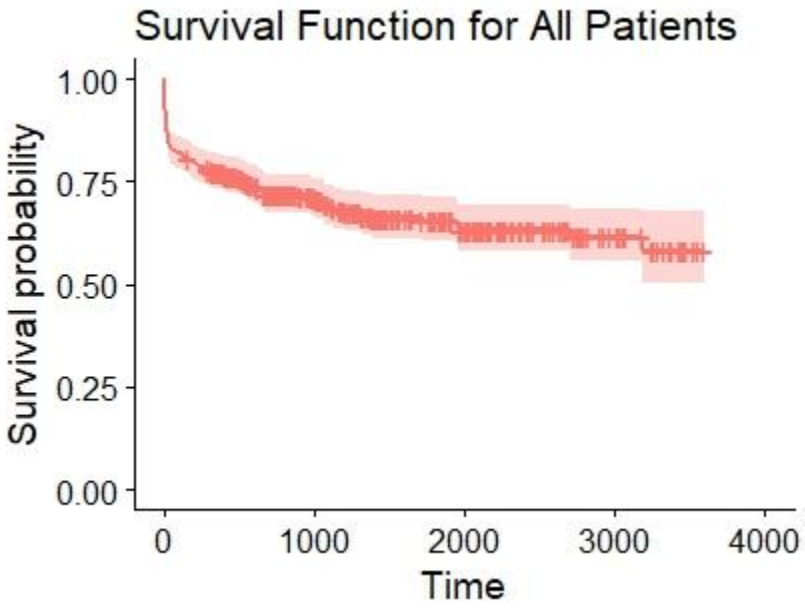



When broken down into 3-month intervals as shown in the adjacent figure, the log-incidence model exploring the growth rate that influences the incidence of Endocarditis yielded a parameter estimate of 1.16 (95% C.I. 1.10 to 1.21). This positive, statistically significant estimate indicates that the rate of infective endocarditis is increasing, and at an increasing rate. When differentiating log-incidence by IDU status, we find that the growth rate is only significant for non-IDU patients (1.14, 95% C.I. 1.07 to 1.21), although the absolute value of the coefficient is higher for PWID (1.15, 95% C.I. -1.02 to 1.34). The magnitude of increase is larger (albeit statistically insignificantly) for PWID in comparison to persons who do not use injection drugs. Although the data may be suggestive of a larger magnitude of growth among PWID, the results do not have sufficient significance to draw conclusions. We are unable to conclude that there is a significantly widening gap in the rate of infective endocarditis based on the results of this analysis.

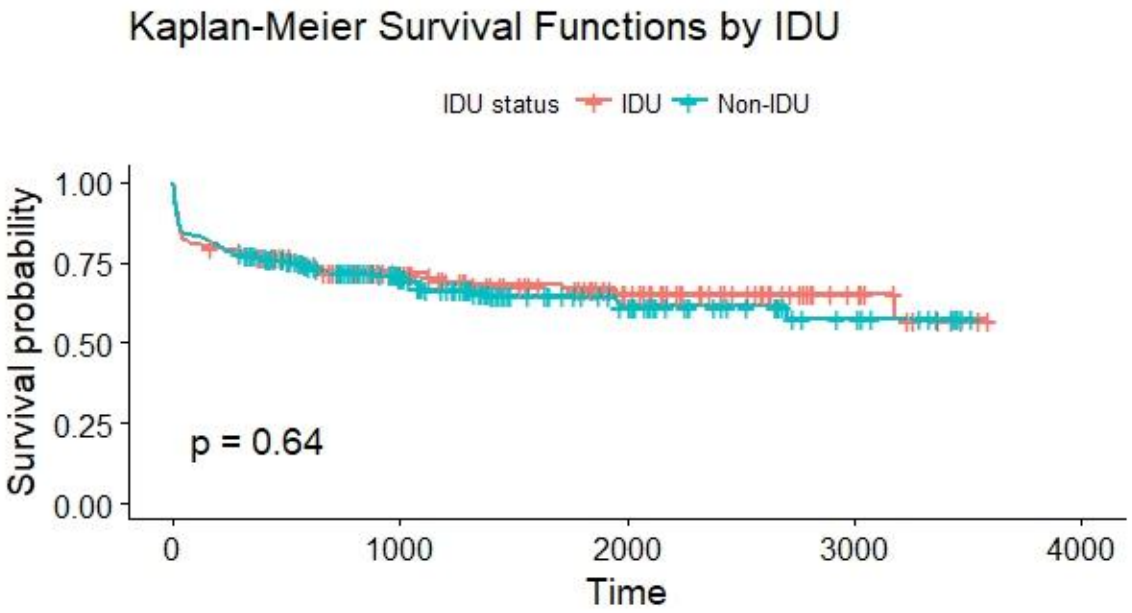
## 4.3 Survival Analysis

This analysis includes a univariate Kaplan-Meier analysis of IDU status on death, as well as HCV status, HIV status, and homelessness. Next, a Cox proportional hazards model explores the variables associated with death, controlling for other variables in the model.

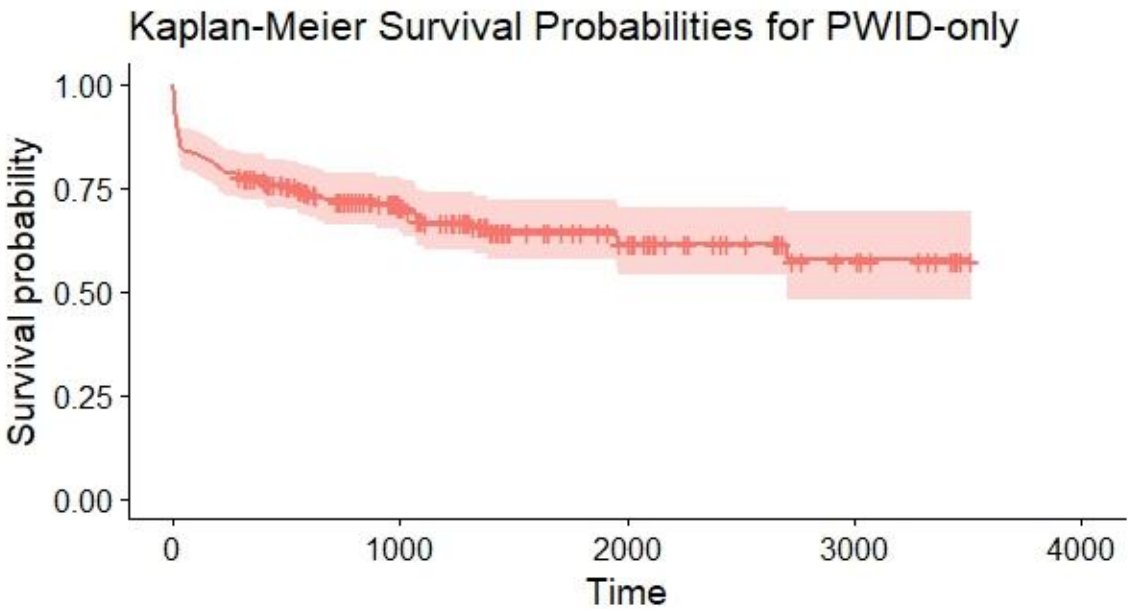
### 4.3.1 Kaplan-Meier Method and Log-Rank Test



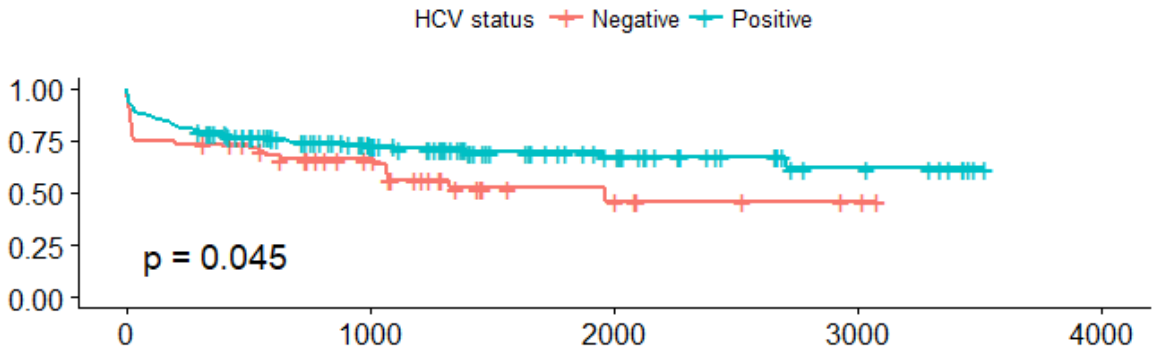

The Kaplan-Meier method demonstrated that participants in the sample experienced a sharp decrease in survival probability upon admission, which gradually tapered off. Within 30 days, the survival probability for both groups combined was 85.3% (95% C.I. 81.8% to 89%) which is consistent with the literature's 16-19% in-hospital mortality rate.

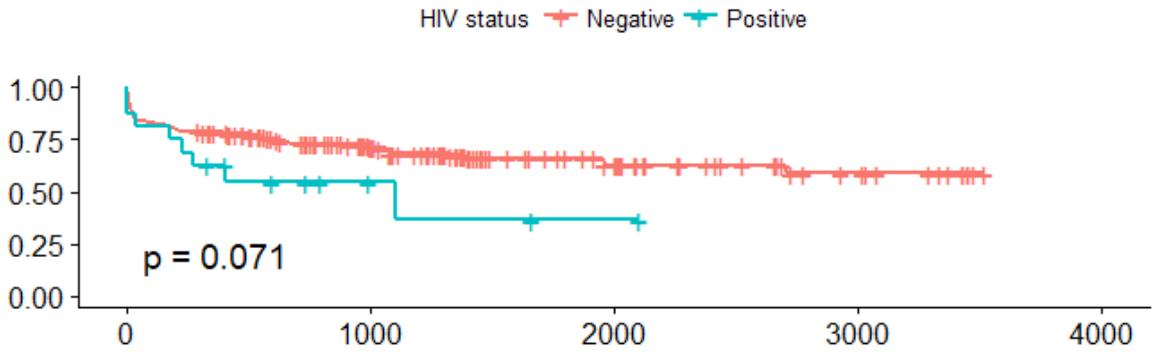


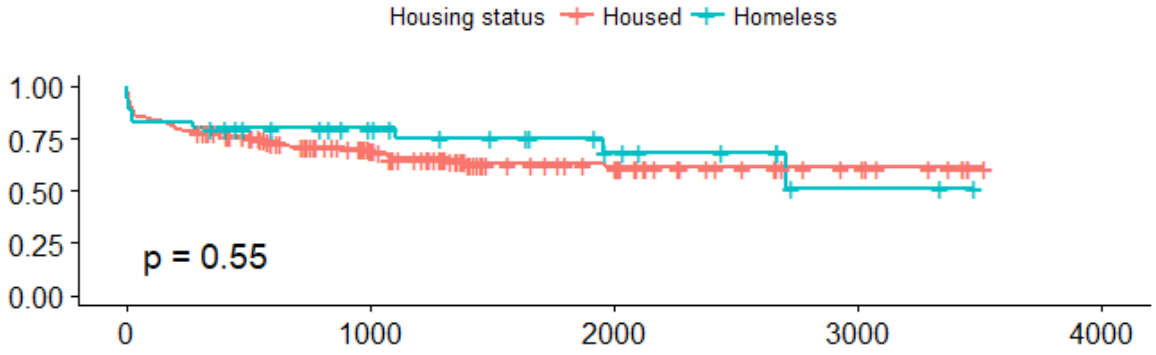

Regarding 30-day survival, the results were similar to the total for both non-IDU (0.853, 95% C.I. 0.801 to 0.908) and PWID (0.848, 95% C.I. 0.800 to 0.899). During the entire course of follow-up, the survival probability reached lows of 0.572 for non-IDU in 8.7 years (95% C.I 0.429 to 0.764) and 0.576 for PWID in 7.4 years (95% C.I. 0.480 to 0.692). The Log-Rank test for differences in survival distributions yielded a probability value of 0.641, indicating that there were not statistical differences between groups (non-IDU vs. PWID). This p-value states that distribution differences as large or larger can be found within the same sample nearly 65% of the time, which is much greater than the traditional cutoff of 5%. The summary statistics showing survival functions for each time interval can be found in the appendix (Output 1).




This represents the same illustration as shown above it, less the survival curve for non-IDUs. Below, the figures indicate that there are many more variables that influence survival beyond the use of intravenous drugs. Summary statistics can be found in the appendix (Output 2).




A majority of the PWID subset had Hepatitis-C Virus, although based off this univariate analysis it appeared to be protective, and significantly so as the log-rank test statistic contained a probability value of 0.045. Likely due to the inadequate power that results from relatively few number of patients with HIV, the difference in survival outcomes between HIV-positive and HIV-negative patients was not statistically significant. Lastly, using a univariate analysis, being housed did not appear to have independently predictive value regarding survival.

### 4.3.2 Cox Proportional Hazard Models

#### 4.3.2.1.1 Full Model

The full model contained all patients without omitted data, which resulted in an analysis of 353 patients with infective endocarditis. MRSA was found to be the most significant variable in the model, suggesting that the presence of MRSA is most strongly associated with an increased hazard of death after controlling for other variables. Patients with Methicillin-Resistant Staphylococcus Aureus infections were found to have a 3.23 (95% C.I. 1.79 to 5.84) times greater hazard of death after controlling for other variables than patients without an MRSA infection. In order of statistical significance, the next variable was age. A one-year increase in age corresponded to a 1.03 (95% C.I. 1.01 to 1.05) increase in hazard of death after controlling for other variables in the model. Intravenous drug use, one of the major objectives of the hypothesis, was found to be associated with a 2.50 (95% C.I. 1.41 to 4.34) times increase in hazard of death after controlling for the other variables in the model. Lastly, MSSA was also shown to be associated with death (1.74, 95% C.I. 1.05 to 2.87). Summary statistics may be found in the appendix (Output 3).

#### 4.3.2.1.2 PWID and non-IDU-only Models

The following models were generated using PWID-only data and non-IDU-only data, respectively, and therefore produced results that are not necessarily aligned with those found in the full dataset. All interpretations may be preceded by, “After controlling for intravenous drug use”. This model permitted the inclusion of infectious diseases (HIV and HCV), which were both found to be statistically significantly associated with the hazard of death. A patient with an HIV-positive status had a 3.62 (95% C.I. 1.45 to 9.04) times greater hazard of

death relative to patients that were HIV-negative after controlling for other variables. An HCV-positive patient, as demonstrated in the Kaplan-Meier curves, are at a lower hazard of death in our models (0.52, 95% C.I. 0.30 to 0.93). Summary statistics for PWID-only and non-IDU-only models may be found in the appendix (Output 4 and Output 5, respectively).

# Chapter 5

# 5 Discussion

This chapter discusses the research findings in the context of the literature provided in the earlier chapters. Key findings pertaining to each objective will be interpreted and their potential implications discussed. Strengths and limitations of this research will then be explored, with an emphasis on the omitted variables bias that exists within this work. Lastly, a discussion on the generalizability of the findings and directions for future research.

## 5.1 Baseline Characteristics

The baseline characteristics of this sample were unique in both their frequency and proportion of injection drug users. The number of patients with infective endocarditis who used injection drugs totaled 204, or 54% of the sample. Comparably, Wurcel et al (2016) commented on the rising IDU-associated IE in the United States as they have reached a high of 12.1% in 2013, substantially less than that which is found in London, Ontario. The more recent analysis by Tung et al (2015) in British Columbia found the proportion of IDU-associated IE in their samples to rise from 5% in their first cohort (2002-2006) to 15% in their second (2009-2013), which is less than a third of what was found in London. The high proportion of IDU-associated IE has significant implications regarding risks of mortality and costs associated with high recurrence rates. These peculiarities can result in misleading admission data, as the number of people being treated will increasingly often have had endocarditis at a previous time. Beyond placing an excessive financial strain on the hospital,

each admission following the first-episode would place the patient at a higher risk of death. This is the rationale for using only first-episode data in the analysis.

Beginning with the main outcome of all the models, all-cause mortality, the tests of proportions and log-rank test indicate that there was no significant difference between patient groups. Recall, research conducted by the World Health Organization suggested that the standardized mortality ratio for PWID in North America was 11.19 (95% C.I. 3.58 to 18.80). Our dataset includes *only* patients with infective endocarditis, and therefore only accounts for those that die from/with IE and not a true representation of all-cause mortality. With that being said, for this SMR calculation to be accurate in London, Ontario, it would require approximately 4.98% of the population to use injection drugs (calculations can be found within the appendix: Equation 1). This number is unlikely to be accurate due the WHO SMR being derived from the population, not those with a disease that is particularly prevalent among PWID. This percentage is therefore unreasonable and likely to be quite inflated. It is, however, reasonable to suggest that the risk of death associated with infective endocarditis for PWID relative to non-IDUs is much higher than the SMR of 11.19 that was calculated by the WHO.

With regards to differences in proportions between PWID and those who do not use injection drugs, staphylococci and streptococci species *were* most common in all subgroups within the sample, with MSSA representing 41.8% of the patients and MRSA 16.6%. This is consistent with the findings in the North American literature. Staphylococci species have adherence properties that increase their likelihood of forming a bacterial vegetation on the heart valve. Regarding PWID, 80.4% of patients in the sample had MSSA (n = 115, 57.8%) or MRSA (n = 45, 22.6%), which meets the estimations found within the literature for streptococci and staphylococci *combined*. When you add alpha- (n = 8, 4.02%) and beta-

hemolytic streptococci (n = 3, 1.51%), that proportion rises to 85.93%. For non-IDU patients, staphylococci and streptococci species also make up a strong majority of the primary organisms (n = 133, 78.73%), although the distribution is quite different. Among staphylococci species, MSSA (n = 39, 23.1%) and MRSA (n = 16, 9.47%) were joined by Coagulase Negative Staphylococci (n = 18, 10.7%), which had zero cases amongst PWID. The most common bacteremia for non-IDU patients were alpha-hemolytic streptococci species, representing 55 (32.5%) of the cases amongst non-IDU patients. The tendency towards MSSA and MRSA among PWID may be attributed to the unique adherence properties of staphylococci species (Frontera et al, 2000). The adherence properties are usually discussed in the context of prosthetic valves, although among PWID the adherence may occur to the particulate matter which is then injected intravenously. Repeated washes provide a useful explanation for how this may occur. As suggested by Roy et al (2011), users often require multiple injections in one sitting and leftover residue is often saved for later or sold. This provides an exposure whereby bacteria such as staphylococcus aureus can latch on and receive a free ride to the tricuspid valve.

The tricuspid valve *was* most common among PWID, appearing in 62.1% of cases compared to 7.02% among non-IDU (p-value; < 0.001). The cox models also demonstrated that among both the total and PWID-only subset, right-sided (tricuspid) IE was associated with a more favourable prognosis, as was suggested in the introduction by Cahill et al (2016). This may be a rationale for why PWID are much less likely to receive surgery for their endocarditis. Regarding surgery for IE, 99 (57.2%) of non-IDU patients received surgery, compared to 39 (19.1%) of PWID resulting in highly significant differences between the two groups (p-value; < 0.001). While this information alone is inadequate to reliably infer the explanation for this phenomenon, an implication would be that those who use

injection drugs as they are less likely to be viable candidates for surgery. Guidelines by the American College of Cardiology state that indications for surgery for native valve endocarditis are a function of the severity of the condition, such as the presence of valve stenosis regurgitation, elevated left ventricular end-diastolic or left atrial pressure, and those caused by highly resistant organisms (O'Gara, 2007). Highly resistant organisms, such as MRSA, appear to be much more common among PWID, although it is possible that they present with less severe vascular damage, on average. Alternatively, it is possible that some surgeons are averse to operating on patients that are likely to continue the adverse lifestyles that are associated with premature infectious diseases, injection drug use in this instance. Analogous to the alcoholic that is ineligible for a liver transplant, PWID may not be priorities due to their risk of recurrence and the finite supply of cardiac surgeons.

There were many significant differences found between characteristics of PWID vs. non-IDU that have not yet been discussed, similar to that which is most commonly found in the literature. Furthermore, some pertinent characteristics such as HIV-positive status, HCV-positive status, prosthetic valves, homelessness and many of the microorganisms could not be accurately compared between the two subgroups due to a lack of events in one of the groups. Among the PWID-only subgroup, the proportion of those with HIV were 7.88%, compared to 5.5% found within the I-track London sample and 11% found in the national sample. Regarding HCV-positive patients, the PWID-only subset contained 70.4% compared to 79.1% with I-track London and 68% across the country. The proportions of PWID with these infectious diseases seem to be consistent, with our data lying between the local and national I-track numbers.

## 5.2 Incidence Estimation

The results of our incidence analysis failed to reject the null hypothesis, which was that the incidence of infective endocarditis was increasing at a faster rate among PWID in comparison to non-IDUs. This should be interpreted cautiously as the size of the base population for PWID is unknown and may have changed over this timespan. The results were statistically insignificant, although as a group the log-incidence was positive and significant. The implication of this finding is that the number of cases of first-episode infective endocarditis can be expected to not only increase, but increase at an increasing rate over time. The public health implications in terms of person-years will become increasingly substantial over time, and the costs associated with the treatment of this condition will become increasingly burdensome. With constraints on healthcare funding and medical expertise, London will continue to face great difficulties in overcoming the physical and financial toll of infective endocarditis among both PWID and non-IDUs.

Much larger studies have shown that the incidence of Infective Endocarditis to be between 2.4 to 11.6 cases per 100,000 person-years. Using London data, the incidence was on the lower end at the beginning of the collection period (3.97, 3.74 for 2007 and 2008, respectively), then gradually increased to reach 11.85 cases per 100,000 person-years in 2013, and a high of 12.25 in 2015. There was a substantial drop in 2012 (9.60 in 2011 to 5.87 in 2012) which promptly returned to trend in 2013 (11.84 per 100,000 person-years). This is largely driven by PWID, as they represent most of the patients in the data set. As discussed previously, estimates of the source population would be required to provide incidence data as it pertains to the PWID subgroup, and this is unavailable. In any case, the incidence in London, Ontario is above that which has been found in reviews by Klein et al

(2016) and Cahill et al (2016) suggesting a serious public health crisis. It is also worth reinforcing the fact that this is *only* using first-episode IE patients. This does not account for the readmissions that are common among PWID, and PWID are disproportionately represented with an unprecedented majority in this patient sample. Quantifying the health implications and costs associated with infective endocarditis in London, Ontario is a direction for future research, particularly considering the constraints on hospitals and healthcare services.

## 5.3 Survival Analysis

### 5.3.1 Kaplan-Meier Method

In the combined sample, 30-day mortality (14.7%) was similar to that found throughout the literature (16-19%). The first date that has a recorded death after 90 days was at the 107-day mark, which corresponds to a survival probability of 81.9% (95% C.I. 0.781 to 0.859), or a mortality probability of 18.1% (95% C.I. 0.14 to 0.22). This is compared to 6-month estimates of 27% (Wallace et al, 2002) and 22% (Hill et al, 2007). This indicates a more favourable prognosis in our sample, particularly so if the patient survives past the first 30-days.

The use of injection drugs alone was *not* associated with a decreased probability of survival in a univariate, Kaplan-Meier survival analysis. This lack of statistical significance has large implications as the population characteristics differ so substantially with regards to age, microorganisms, and valves affected. The PWID subsample mean age was nearly 25 years younger than their non-IDU comparators (35.5 vs. 59.9). Also, the literature suggests

that PWID typically have a *more benign* first episode of IE (Palepu et al, 2002), which is not the case here. Given the universally recognized significance of aging and the increasing prevalence of IE among younger adults, this lack of significance is alarming.

The additional analyses provided some unexpected findings. We found significant differences in survival outcomes for those with HCV, although they have *favorable* outcomes. This is counterintuitive as it is generally safe to assume that a viral infection does not increase your odds of survival, although this has been found in the literature previously. In examining the differences in outcomes between patients with and within chronic hepatic diseases, Seminari et al (2016) found intravenous drug use to be a protective factor that reduced risk of death (Seminari et al, 2016). This is after controlling for age, diabetes, chronic hepatic disease, cancer, staphylococcus aureus infection, and prosthetic valve IE. Patients whom did *not* use injection drugs were found to be at an increased risk from bacteremia for reasons that were not specified or speculated upon.

HIV-positive status was found nearly exclusively amongst the PWID subgroup. Within the PWID sample, there was a strong trend towards HIV-positive status being associated with a lower probability of survival, although statistical significance was not reached. This may be due to the study duration, an inadequate sample size, or due to the high rate of mortality among the total sample, regardless of infective disease and drug use status.

Homelessness was not associated with a difference in survival compared to individuals that were housed. This metric was flawed in that the definition of homeless is not specific and varies depending on the lifestyle of the patient. For example, a patient may have an old address on their identification, or a relative's address, despite the fact they have not been there in years. If asked, couch-surfing may not be considered homeless by many people, although the most precise definition would indicate couch-surfing is indicative of a

*lack* of home ownership or stability, thereby making one homeless. The reality of the situation is that the patient would have been asked, “are you homeless?” or they would have been considered homeless if there was no known address. But even given this information, those meeting the definition of homeless would be within a particularly high-risk subset of those that do not own/rent property, which makes the lack of significance surprising.

The original hypothesis, PWID are at a lower risk of death initially (30-day), then surpass non-IDUs over time (>90-day), was shown to not be true. A univariate analysis on the use of injection drugs as a predictor of mortality showed that survival outcomes are not statistically different between PWID and non-IDUs. This is not to say that injection drugs do not play a role in survival outcomes, as was explored in the next section.

### 5.3.2 Cox Proportional Hazards Model

#### 5.3.2.1 Full Model

The initial model, *Total Group*, was used to assess if the use of intravenous drugs had any predictive value regarding survival outcomes. As expected, the use of IV drugs within this sample showed a 2.50 (95% C.I. 1.44 to 4.34, p-value = 0.001) times greater hazard of death than not using IV drugs, adjusted for all variables in the model. Given the risks associated with the use of injection drugs that have been explained previously, this is outcome is unsurprising. The analysis was necessary to warrant the *IDU* model.

1. Age - This is an unsurprising finding as the aging process corresponds to an increased hazard of death throughout the literature at large, with endocarditis patients being no exception. The results may seem trivial (1.03, 95% C.I. 1.01 to 1.05) although the magnitude of effect for differences in age is the hazard estimate exponentiated by the number of years. To avoid this misleading result, it is common to present age in terms of decades as was shown with studies in the introduction (Murdoch et al, 2009). To utilize all available information, one-year intervals were maintained in the analysis. Recall, the sample contained an age difference of 24.4 years (95% C.I. 21.7 to 27.0, $p < 0.001$) between PWID and non-IDUs. This would result in a hazard of: $1.029824.4=2.05$, which indicates that non-IDUs are, on average, at a 2.05 times greater risk of death due to their age, adjusted for all other variables in the model. Despite this, the Kaplan-Meier estimator suggests that there are non-significant differences in survival between PWID and non-IDUs.
2. MRSA and MSSA - as mentioned in the baseline characteristics discussion, staphylococcus aureus contains unique adherence properties that adhere to prosthetic valves, particulate matter, and blemished cardiac valves. The significant mortality associated with *s. aureus* infection is likely attributable to the organism's aggressiveness (Guerrero et al, 2009). Due to the epidemiological nature of *s. aureus*' association with mortality, the specific reason why this is the case is unknown, although most likely multifactorial (Miro et al, 2005). Among PWID, the presence of *s. aureus* may be a surrogate indicator of non-sterile injection practices. The individual that never reuses equipment, brings a flame to the cooker, and uses alcohol swabs *before* injection would theoretically be less likely to be exposed to *s. aureus.* Methicillin resistance, the MR in MRSA, indicates that the

bacteria is resistant to some antibiotics that are often found to be helpful with other strains, such as MSSA. This explains the discrepancy in the association with mortality, with MRSA being more clinically significant due to its greater magnitude. Adjusted for other variables in the model, MRSA was associated with a 3.23 (95% C.I. 1.79 to 5.84) times greater probability of death relative to *not* having MRSA present. Alternatively, once adjusted for other variables in the model, MSSA was associated with a 1.74 (95% C.I. 1.05 to 2.87) times greater probability of death relative to *not* having MSSA present.

#### 5.3.2.2 PWID-only and non-IDU-only Models

Recall, the research question for the Cox model was: Which variables are associated with an increased hazard of death among PWID patients with infective endocarditis? The answer: HCV-positive status and HIV-positive status. Surprisingly, neither age, biological sex, housing status, affected valve, or bacteremia were able to reach significance as a risk factor for death in this model. The only variables to pass the alpha threshold of 0.05 were HCV-positive and HIV-positive.

1. Hepatitis C Virus - all else being equal, patients with HCV had a 0.52 (95% C.I 0.30 to 0.93, p-value = 0.026) times hazard of death as those without HCV. This indicates that Hepatitis-C is *protective*. Despite the counterintuitive findings, as viral infections are generally associated with a less favourable prognosis, this phenomenon has been found in the literature. For example, research on infective endocarditis in

patients with chronic hepatic diseases by Seminari et al (2016) found that PWID was a significant protective factor in their multivariate analysis. This is not the same, although the counterintuitive relationship between injection drug use and chronic liver disease is similar. Another study by Perez de Isla et al (2003) found that chronic liver disease had a significant impact on prognosis, although intravenous drug use was *not* a significant variable in their cox model. What these studies have in common is congestive heart failure (CHF) being associated with mortality. The frequency of heart failure is low in patients with liver disease (Perez de Isla, 2003) and heart failure is associated with mortality. The lack of heart failure in this group may have resulted the protective signal, despite the possibility that any individual is worse off having a chronic liver disease. There may also be a relationship between tricuspid valve endocarditis, which corresponds to a low incidence of complications, and injection drug use. The implications of this finding are that there are likely other relationships that exist between the use of injection drugs, hepatitis C, and infective endocarditis.

2. HIV - Adjusted for other variables in the model, the hazard of death is 3.62 times higher (95% C.I. 1.45 to 9.04) for HIV-positive patients relative to HIV-negative. This finding was consistent with the pre-existing literature. Based on findings in work by Cicalini et al (2001), there may be may relationships that exist between HIV-positive patients. They disproportionately tend to use injection drugs, have staphylococci as the primary organism, and have the tricuspid valve as the most common site of infection. Of the 20 patients in the sample that are HIV-positive, 80% (n = 16) used injection drugs, 60% (n = 12) had MSSA and 20% (n = 4) had MRSA as primary bacteria, and 60% (n = 12) had a vegetation present on their tricuspid valves. It is difficult to parse out specifically which of these variables is

influencing the outcome with the size of our sample. What we can gather is that there are relationships present and they are commonly found among PWID that are diagnosed with infective endocarditis.

It is also possible that a diagnosis of HCV-positive changes the wellness and lifestyle considerations of the patient. An individual that might be inclined to share washes or reuse equipment may face their teachable moment upon diagnosis. The issue that presents itself is that if this phenomenon is to be true, would it not also apply to HIV-positive patients? The sample size for HIV is low, although being positive is significantly associated with an increased odds of mortality.

The final model, the non-IDU-only analysis, was similar in that there were few significant variables found to be associated with mortality. These variables included: Age, biological sex, MSSA, and MRSA. The rationale for each has been discussed previously in the *total group* analysis.

Pacemakers and prosthetic valves did not reach significance. In evaluating the predictors of mortality among patients with prosthetic valve infective endocarditis, Elbey et al (2013) found that age, C-reactive protein, creatinine, New York Heart Association (NYHS) functional classification, and large vegetations were associated with mortality. The only variable that was included in our model was age, which *did* reach significance. Similar to the explanation suggested for HCV-positive patients, having surgery that implants a prosthetic valve may provide the incentive to change a patient's lifestyle, cause them to optimize their health and wellness, and prevent reoccurrence of infective endocarditis.

## 5.4 Limitations

The limitations of this research may be broken into two categories: bias from omitted variables and inadequately precise data collection.

### 5.4.1 Omitted Variables Bias

Omitted variables bias, a term traditionally used in economics and other social sciences, occurs when a relevant independent variable is not included within an estimation model (McCall, 2014). This is a problem in all statistical models, as a perfect model does not exist. This phenomenon is usually explained through a variable such as *ability*. In estimating wages or earning potential, many demographic and educational variables are predictive, although the innate *ability* of the individual is always unknown and therefore unaccounted for. One may use proxy variables, such as *IQ score* or *Parent's income* to determine the potential for an individual, but there are flaws with both proxies and the underlying omitted variables bias remains. In our context, there are a handful of pertinent variables that were unable to be included in the model. These include rather abstract personal factors such as *mental wellness, childhood traumas, sense of purpose, sense of community, quality of support networks,* as well as *faith and belief systems.* More reliably quantifiable examples of potentially significant omitted variables might include *annual income, net earnings, employment status, number of dependents, credit score, education, size of residence, number of roommates*, et cetera. Even these variables serve as a proxy for the underlying influences. For example, with a variable like *education*, the degree to which an individual pursues higher education may be influenced by the environment in which that individual was raised. A child of a parent with post-graduate education is more likely to also

pursue post-graduate education. Research by Ford and Thompson (Ford et al, 2016) went a step further and found that children up parents are three-fold as likely to attend the *same* university as their parents. This is like a child of a medical doctor being more likely to become a medical doctor, or the child of a professional basketball player being more likely to become a professional basketball player.

Omitted variables bias is an issue with all statistical models, although there were some medically relevant variables that would have been desirable in a perfect world. The list begins with the Duke Criteria, as it would be helpful to know if certain diagnostic criteria carry relatively more or less risks and if those risks are different based on whether the patient uses injection drugs:

1. Major Criteria: Organism typical to Infective Endocarditis for two separate blood cultures.

We were able to include this variable. We did not differentiate based on major/minor microorganism, but instead for groups of microorganisms based on virality and family.

2. Major Criteria: Evidence of vegetation.

This variable was not included in the multivariate regression analyses, although very few patients in the sample did *not* have evidence of vegetation. It may not be reasonable to suspect that a binary variable indicating vegetation present versus no vegetation present is adequate in this analysis. Determining the size is pertinent in parsing out the effects of microorganisms with the effects of vegetation size (Leitman et al, 2012). It has been shown that among older patients, staphylococcal endocarditis *and* large vegetations is associated with 50% risks of mortality according to research by Leitman et al (2012). Additional research focusing on lead associated endocarditis found that *s. aureus* was most often responsible for large (>1cm) vegetations (Greenspon et al, 2014). This suggests that omitting

vegetation size may be associated with an upward bias with the magnitude of effect for *s. aureus* IE, assuming that larger vegetations are more strongly associated with mortality, which has been consistently shown throughout the literature.

3. Major Criteria: New valvular regurgitation

Valvular regurgitation, or leaky valves, were not included in the analysis due to the amount of missing data. Also, the onset of a new valvular regurgitation would be difficult to estimate and therefore introduce bias into the survival analysis. It is unreasonable to perform echocardiograms daily due to cost and invasiveness (transthoracic echocardiography), so reliable, precise data collection is not available.

4. Minor Criteria: Predisposing heart condition

Rheumatic heart disease is a historical leading cause of infective endocarditis and remains a leading cause in developing countries today. It is no longer a major cause of IE in developed countries due to advances in technology and medicine.

5. Minor Criteria: Intravenous Drug Use

This was included in the dataset.

6. Minor Criteria: Fever >= 38 degrees Celsius

This was included in the dataset.

7. Minor Criteria: Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions

The number of missing events, the inclusiveness, and the unknown timing of these events were suboptimal. There were many different types of vascular phenomena, with different risks associated with them making it heterogenous group of morbidities. The occurrence of the events would have presumably been during the hospital stay, at least for a portion of

them, and we do not have time stamps for their discoveries. The focus of this analysis was with admission data.

8. Minor Criteria: Immunologic phenomena (glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor)

Most patients in this dataset did not have this data available and they were therefore omitted from this analysis.

9. Minor Criteria: positive culture not typically found with IE

All bacteremia that had a sufficient number of events within the dataset was included in the analysis.

Beyond the diagnostic criteria for IE, other potentially influential omitted variables that are particularly relevant to the population of interest, PWID, include:

1. Drug Type/preferences and Polydrug Use

This is an interesting topic that may influence the risks of infective endocarditis among PWID. Some intuition regarding drug preferences may be inferred by a meta-analysis exploring the price elasticity of illicit drugs (Gallet, 2014). In this study, it was consistently found that both cocaine and heroin are much more elastic (sensitive to price adjustments) than marijuana. This means that an individual is much more likely to change their drug consumption with changes in price. In discussing the possible explanations for this phenomenon, the authors suggested "because heroin and cocaine users are more often polydrug users, they may perceive greater substitutability among hard drugs, thus leading them to be more responsive to price" (Gallet, 2014). This indicates that any external factors that increase the cost associated with drug acquisition, such as refusing a prescription or

delisting opioids from the ODB drug formulary, may result in a transition to a more affordable, and possibly more dangerous, alternatives. This phenomenon is demonstrated by the infamous OxyContin fueled opioid epidemic in the United States. OxyContin, a prescription opioid produced by Purdue Pharmaceuticals, has been widely criticized in popular media for introducing addictive opioids to the market on an unprecedented scale, and upon their removal many patients turn to Heroin (Berman, 2014). This situation does not seem to be the case in London, Ontario, as preliminary data suggests there to be relatively low consumption, possibly due to cost, quality and access of heroin, although various prescription opioids such as Hydromorphone Contin, Dilaudid, and Morphine Sulphate are common. There is also the issue of polydrug use in terms of alternating between Opioids and Stimulants, more specifically Hydromorphone and Crystal Methamphetamine. Substitutability may seem counterintuitive given the different addictive properties between drugs, although this is not a new phenomenon.

In the 1880's, David Musto described the use of cocaine in the United States "as a cure for the opium, morphine, and alcohol habits" (Freud, xxviii). Sigmund Freud was also a strong proponent of cocaine as a cure for opiate addiction. Sir William Halsted, one of the founders of John Hopkins medical school in 1893, replaced his dependence of cocaine with a dependence on morphine in his later years (Imber, 2011) (Freud, xxxi). Later in life, Freud changed his beliefs on cocaine and began to understand the substitution of an opiate for cocaine resulted more in a "double addiction" than a therapy (Freud, xxxiii), although there have been studies that suggest he was not entirely wrong earlier in life. In a study of naloxone-precipitated opioid withdrawal in both rats and humans, cocaine use was shown to reduce the severity of the withdrawal (Kosten, 1990). The point worth highlighting is that there is a historically documented short-term interchangeability between opioids and

stimulants, despite their different effects and mechanisms. This lends an explanation for polydrug use among PWID, particularly so after considering the costs associated with different drugs. Peer reviewed research has not been able to provide literature on the average costs of drugs throughout regions in Canada, although community and online sources have suggested that in order from most to least expensive, there is: cocaine, opioids, and then crystal methamphetamine (Reddit, 2015). There are many more drugs that are commonly used, although these are the common cost considerations made by PWID in London, Ontario. The takeaway here being that as drugs become restricted and harder to access, different, possibly more harmful drugs are substituted. Knowing when an individual used which drug as well as the date of onset for IE would have been helpful in this analysis.

2. Frequency of Drug Use

How often one uses injection drugs influences the exposure to particulate matter which may increase the risks of IE. This data is unavailable, and in survey data it is unreliable. It is unreasonable to expect an individual to have the ability to recall the frequency of daily injection for a long period of time. When a behaviour becomes an integral part of your life, the frequency any given day begins to blur, particularly when many users do not have the luxury of consistent dependable supply that they can build a "lifestyle" around.

3. Recent Dental Procedures

This is applicable to both PWID and non-IDUs. Dental procedures may result in cuts within an individual's mouth that allow bacteria to access the bloodstream. Patients with periodontal (gum) disease are at risk of bacteremia from brushing their teeth (Ito, 2006).

4. Length of Drug Use

Length of IVDU would influence total exposure. An individual that has used injection drugs a handful of times would be at a lower risk of exposure than an individual

that has used injection drugs thousands of times, all else being equal. Knowing this information would be helpful in distinguishing new and long-term drug users and what influence length has on outcomes and the effects of covariates in the model.

5. Drug Use Practices

As mentioned in sections 2.4 and 2.5, different drugs are associated with different risk profiles and pathophysiologies. Compounds that are often homemade such as crystal methamphetamine carry risks that differ based on the ingredients and sanitation standards of the manufacturer and may influence the outcomes of a patient with IE.

### 5.4.2 Accuracy and Data Collection

There were variables that were collected with a great deal of precision. These include age, sex, bacteria (MSSA, MRSA, Enterococci, Alpha-Hemolytic Streptococci, Coagulase Negative Staphylococcus), valve affected (Aortic, Mitral, and Tricuspid), intracardiac device, prosthetic valve, and fever. Age and biological sex are collected from the patients' Ontario Health Insurance Plan (OHIP) card. The bacteremia is recorded after having blood work completed in the hospital. It is possible, however, that there were bacteria present that was not included in the dataset, as the blood tests were not occurring with enough frequency to ensure that any nosocomial bacteria did not present itself after the initial tests. Body temperature as indicated by a binary fever variable is taken upon admission to the hospital and regularly throughout a patient's stay. This is hospital protocol and is thereby a reliable statistic. The valve affected was determined via a transthoracic echocardiogram or, if inconclusive, a transesophageal echocardiogram. It is possible that a vegetation was missed upon examination by a physician after an echocardiogram, although there is no reason to

believe there was a systemic bias present. Regarding prosthetic valves and intracardiac devices, there would be medical records of the procedure, so it would be on the medical charts.

Other variables may be less accurate and lead to bias in the results. These variables include homelessness, intravenous drug use, HCV-positive, and HIV-positive.

1. Homelessness - The issue with this variable is the poor definition. Individuals that do not have housing accommodations may be couch surfing among friends and relatives, but are they homeless? Defining homelessness as an individual with no known address may not include the patients that have their parents addresses on file, although they do not have a home themselves per say. Also, as homelessness is not a common question to ask, it is possible that it is disproportionately asked to admitted users of intravenous drugs, and not asked among non-IDUs. This could present a downward bias on non-IDUs.
2. Intravenous drug use - Many users of intravenous drugs are uncomfortable disclosing the frequency of their use, or the fact that they use at all. I have personally experienced situations where patients have tested positive for drugs that were not prescribed, then denied ever having used them. The stigma surrounding intravenous drugs, or illicit drugs in general, creates a dishonest environment where patients may be inclined to tell the physician what they believe the physician would like to hear, instead of the truth. Also, patients that are well presented or older may not be asked about illicit drug use. Alternatively, the patients with clear indications of drug addiction would be asked and that would be included in their charts. The clear indications may include scarring, abscesses, malnutrition, poor hygiene, or any

stereotypical characterization of those with drug addictions. This may also create a bias as those with clear indications of drug use may be the only ones being asked whether they are currently using injection drugs.

3. HIV- and HCV-positive: The cases of HIV/HCV in the dataset were confirmed by blood testing, although as mentioned in the Data and Methods section, 190 of the 378 patients were "unclear" for HIV. Among these patients, we have no way to confirm whether these variables were determined based on the inquiry by a physician or if each patient had their blood draws tested for HIV/HCV.

## 5.5 Generalizability

This dataset is unique in its proportion of PWID. While there are other communities around North America, such as in Vancouver and pockets of larger American urban centers, where there are large numbers of PWID, the incidence of infective endocarditis may not be dominated by PWID in those cities. There would, however, be large populations of PWID in these places that would be comparable to the PWID sample in London, Ontario. The information on the variables that do and do not significantly influence survival among PWID is generalizable to other PWID with similar drug cultures, particularly referring to the use of crystal methamphetamine.

While drugs like cocaine and heroin use plants that are grown outside of North America, crystal methamphetamine can be produced locally (Shukla, 2012). This, in addition to the abundant supply from abroad and the relative cost-effectiveness in terms of the effects produced by consuming the drug, it would be unsurprising to see the findings of this research become increasingly generalizable to communities in the coming decades.

## 5.6 Strengths

The major strengths of this dataset and analysis included reliability/accuracy of the data, comprehensiveness and richness of variables to choose, and size. Working with PWID is inherently difficult, as many biases present themselves. For example, as mentioned in the previous section, recall bias makes pertinent variables like drug use frequency unfeasible. This rich dataset overcomes this issue by relying solely on the observations and testing results that were recorded by medical doctors. Although there are issues with missing data, the quality and accuracy of the data is excellent relative to recall. This was the main reason for using this dataset to answer these questions.

This dataset is reliable *and* comprehensive, and although the list of strengths is not quite as long as the limitations, the magnitude of each strength is substantial. Observational data is never perfect, but large dataset and statistical theory allow researchers to circumvent this issue to some extent, given that the actual data you are working with is *accurate*. Although there may have been situations where the physician asked the patient a question, such as, "do you use injection drugs", and then recorded the answer based on what the patient says. This is more of an issue with Hepatitis-C and HIV response bias, although having tested positive previously in a hospital setting would have made it into the charts and therefore into the dataset. The physicians are interested in providing the best treatment for patients, and if there was any question regarding the honesty of a patient, the physician would be inclined to perform tests to determine for themselves rather than take the patients word for it. This was shown in a study by Shah et al (2015) whereby immigrant stroke patients with a language barrier showed more favourable health outcomes because the

language barrier prevented physicians from asking patients, which introduces response bias, and instead relied solely on medical testing. "Differences in quality of care may have arisen because of language barriers: the healthcare team may have sought more intensive evaluation of patients with whom their communication was impeded" (Shah et al, 2015). While not perfectly analogous, the takeaway is that if physicians are unable to reliably ask the patient, or the patient is unable to communicate well to the physician, the physician would be more inclined to perform tests and find out for themselves.

The dataset that was utilized for this research is large in terms of both participants and variables and the number of PWID. This increased the power to detect effects even when using a PWID-only subgroup, which is rarely found within the endocarditis literature.

These three reasons: reliability/accuracy, comprehensiveness, and size make this dataset optimal as a starting point for infective endocarditis in this local environment. Despite these strengths, there is still much more room for improvement.

## 5.7 Future Directions

As a study based on historical hospital chart records, there are inherent limitations which would be optimal to overcome for future research. Further studies should incorporate time-dependent covariates such as date and time data for the occurrence of each independent event with examples including sepsis and leaving against medical advice. This would answer additional questions pertaining to what causes these dangerous outcomes to occur. This was not the case and as such, our analysis will assume that the events occurred upon admission which is not necessarily true (some of the patients acquired endocarditis *in* the hospital, not before admission). Time-dependent covariates would also influence the survival analysis

results and may provide more clarity as to which variables increase the hazards of death among patients with IE.

Regarding the outcomes that were measured in this study, a very important and interesting future direction for research would be to incorporate drug-related data. Determining which drugs were consumed, how often they were consumed, the method by which they were consumed, the environment they were consumed in, and the duration of lifetime consumption. These drug variables would provide very informative insights and may provide opportunities to target advice to the specific subpopulations that are most greatly affected.

Since this research was conducted, a safe injection site has been introduced to London, Ontario. Using the data collected for this research and contrasting it with data collected since the inception of the safe injection site may provide some insights regarding the effectiveness of such measures and whether the injection site is benefiting the community at large. This may also influence the willingness for other cities throughout Canada to participate in harm reduction, as infectious diseases among PWID are extremely costly to manage and it is difficult to do so due to recurrence rates, at least with infective endocarditis.

London, Ontario tends to draw older populations and retirees from central Ontario. The aging population that is commonly mentioned in academic literature refers to a young population that ages, not an aging population that relocates to a new region, thereby causing it to age. A future direction for research should include age-matched samples to ensure that comparability between the younger PWID populations can exist and it is not a matter of sick, older individuals moving to London and skewing the analysis.

Lastly, there should be a national database that collects and stores information pertaining to PWID, or the population in general, that permits comparative analysis between

cities and provinces. The generalizability is difficult to assess because of the lack of national data available in Canada. Coordinating initiatives that gather health data at the federal level may assist smaller regions in recognizing other areas that have similar issues, facilitating a collaboration to improve outcomes among those afflicted with infectious diseases across the country.

## 5.8 Conclusions

The most significant contribution made by this research is highlighting the magnitude of the public health issues that face London, Ontario regarding PWID. With regards to IE, we found the incidence to be rising among both PWID and non-IDUs. Univariate models demonstrated a non-significant mortality risk difference between PWID and non-IDU, despite the substantial (24.4 years, 95% C.I. 21.7 to 27.0) difference in ages between the two populations. Multivariable analyses demonstrated that in the total group, injection drugs (HR: 2.50, 95% C.I. 1.41 to 4.34), age (HR: 1.03 per year, 95% C.I. 1.01 to 1.05), MRSA infection (HR: 3.23, 95% C.I. 1.79 to 5.84) and MSSA (HR:1.74, 95% C.I. 1.05 to 2.87) infection were shown to be significantly associated with all-cause mortality. PWID-only subgroups showed a significant hazard only with coinfections, specifically patients that were HIV-positive (3.62, 95% C.I. 1.45 to 9.04) and/or HCV-positive (0.52, 95% C.I 0.30 to 0.93). With the ongoing epidemic of drug non-prescribed drug misuse that is found throughout the developed world, more efforts are required to reduce the incidence and impact of IE among PWID.

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# Appendices

Tables, figures, and outputs can be found below. For tables and figures, the captions are all found below their respective items.

Definition of terms used in the proposed modified Duke criteria for the diagnosis of infective endocarditis (IE), with modifications shown in boldface.

| |
|---|
| Major criteria |
| Blood culture positive for IE |
| Typical microorganisms consistent with IE from 2 separate blood cultures: |
| Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus;* or |
| Community-acquired enterococci, in the absence of a primary focus; or |
| Microorganisms consistent with IE from persistently positive blood cultures, defined as follows: |
| At least 2 positive cultures of blood samples drawn >12 h apart; or |
| All of 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart) |
| **Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1 : 800** |
| Evidence of endocardial involvement |
| Echocardiogram positive for IE **(TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients)**, defined as follows : |
| Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or |
| Abscess; or |
| New partial dehiscence of prosthetic valve |
| New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient) |
| Minor criteria |
| Predisposition, predisposing heart condition or injection drug use |
| Fever, temperature >38°C |
| Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions |
| Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor |
| Microbiological evidence: positive blood culture but does not meet a major criterion as noted above[a] or serological evidence of active infection with organism consistent with IE |
| **Echocardiographic minor criteria eliminated** |

NOTE. TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a] Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

**Table 1: Definition of Major and Minor Criteria. Extracted with permission from Li et al (2000).**

Definition of infective endocarditis according to the proposed modified Duke criteria, with modifications shown in boldface.

| |
|---|
| Definite infective endocarditis |
| Pathologic criteria |
| (1) Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or |
| (2) Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis |
| Clinical criteria |
| (1) 2 major criteria; or |
| (2) 1 major criterion and 3 minor criteria; or |
| (3) 5 minor criteria |
| Possible infective endocarditis |
| (1) **1 major criterion and 1 minor criterion**; or |
| (2) **3 minor criteria** |
| Rejected |
| (1) Firm alternate diagnosis explaining evidence of infective endocarditis; or |
| (2) Resolution of infective endocarditis syndrome with antibiotic therapy for ≤4 days; or |
| (3) No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤4 days; or |
| (4) Does not meet criteria for possible infective endocarditis, as above |

**Table 2: Clinical criteria for infective endocarditis. Extracted with permission by Li et al (2000).**

| | year | IDU | nonIDU | population | Total_Cases | PersonYears | Rate |
|---|---|---|---|---|---|---|---|
| 1 | 2007 | 12 | 6 | 478492 | 18 | 4.78492 | 3.761818 |
| 2 | 2008 | 9 | 9 | 481249 | 18 | 4.81249 | 3.740268 |
| 3 | 2009 | 15 | 17 | 483045 | 32 | 4.83045 | 6.624642 |
| 4 | 2010 | 19 | 15 | 486129 | 34 | 4.86129 | 6.994028 |
| 5 | 2011 | 24 | 23 | 489461 | 47 | 4.89461 | 9.602399 |
| 6 | 2012 | 14 | 15 | 494108 | 29 | 4.94108 | 5.869162 |
| 7 | 2013 | 36 | 23 | 498097 | 59 | 4.98097 | 11.845082 |
| 8 | 2014 | 38 | 29 | 501866 | 67 | 5.01866 | 13.350177 |
| 9 | 2015 | 31 | 31 | 506009 | 62 | 5.06009 | 12.252746 |
| 10 | 2016 | 6 | 5 | 512431 | 11 | 5.12431 | 2.146630 |

**Table 3: Population and incidence data for London, ON.**

Using data from Statistics Canada (**population**: population totals for London, Ontario) and medical chart data (**IDU**, **nonIDU**, and **Total_Cases**), the number of per 100 000 person-years (**PersonYears**: population / 100 000) was calculated, then used to find incidence rate per 100 000 person-years (**Rate**: total cases / 100 000 person-years).

| Variable | Description | Significance |
|---|---|---|
| Age | Age of patient at onset of first-episode IE | Average patient age has been increasing (currently > 70) and PWID tend to have a much younger patient age which may influence patient outcomes |
| Sex | The patient's sex (M/F) | Men are disproportionately affected by infective endocarditis |
| Homeless | Unstable housing indicator (Y/N) | Unstable and unsanitary living conditions may influence immune function |

| | | |
|---|---|---|
| Death | All-cause mortality | This is the outcome of interest in the survival analysis |
| Native Valve IE | IE present on an innate heart valve | This represents most infective endocarditis cases |
| Intracardiac Device | Includes prosthetic valves and any medical devices found in the heart | May be particularly susceptible to adherence by bacteria |
| Vegetation Location | Aortic, Mitral, Pulmonic, Tricuspid, and any combination of the two | Mitral valve IE is most common in the population at large and the majority of Tricuspid valve IE is found among persons who inject drugs. |
| Bilateral | Vegetations present on both the left (Aortic and/or Mitral) *and* right (Tricuspid and/or pulmonic) sides of the heart | Indicating a rally severe form of infective endocarditis |
| Micro-biology | MRSA, MSSA, Coagulase Negative Staphylococcus, Alpha-Hemolytic Streptococcus, Enterococcus, Beta-Hemolytic Streptococcus, Gram-Negative Aerobic Bacilli, Fungus, Negative, Other | Bacteria groups formed in consultation with Dr. Silverman, Chair of Infectious Diseases at SJHC, based on their treatment, where they originate within the body, and virulence (infectiousness) |
| HIV | Positive for HIV | HIV+ patients with low CD4 cell count are also at a higher risk of mortality from IE |
| HCV | Positive for Hepatitis C Virus | Liver disease caused by HCV may be exacerbated by IE and lead to increased mortality (Zignego et al, 2012) |
| Infections | Skin and Soft Tissue Infection, Bone or Joint Infection, and Respiratory Infection | Suggest a compromised immune function and may place an individual at a greater risk of further infection |
| Septic Shock | Patient experiencing Sepsis in response to an infection | Closely related to mortality among patients with IE (Olmos et al, 2012) |
| Fever | Patient presenting a fever upon admission into the hospital | A body temperature greater than 38°C, seen in ~90% of cases (Cahill, 2015) |

| | | |
|---|---|---|
| Leaving AMA | Abandoning treatment at the hospital against the opinion of physicians | discontinuation of treatment may be associated with poor health outcomes |
| Surgery | Patient received surgical intervention to treat their IE | May improve prognosis following a diagnosis of IE, although not everyone is able to receive surgery |

**Table 4: Variables used to differentiate baseline characteristics between the total group, PWID, and non-IDU patients in the dataset.**

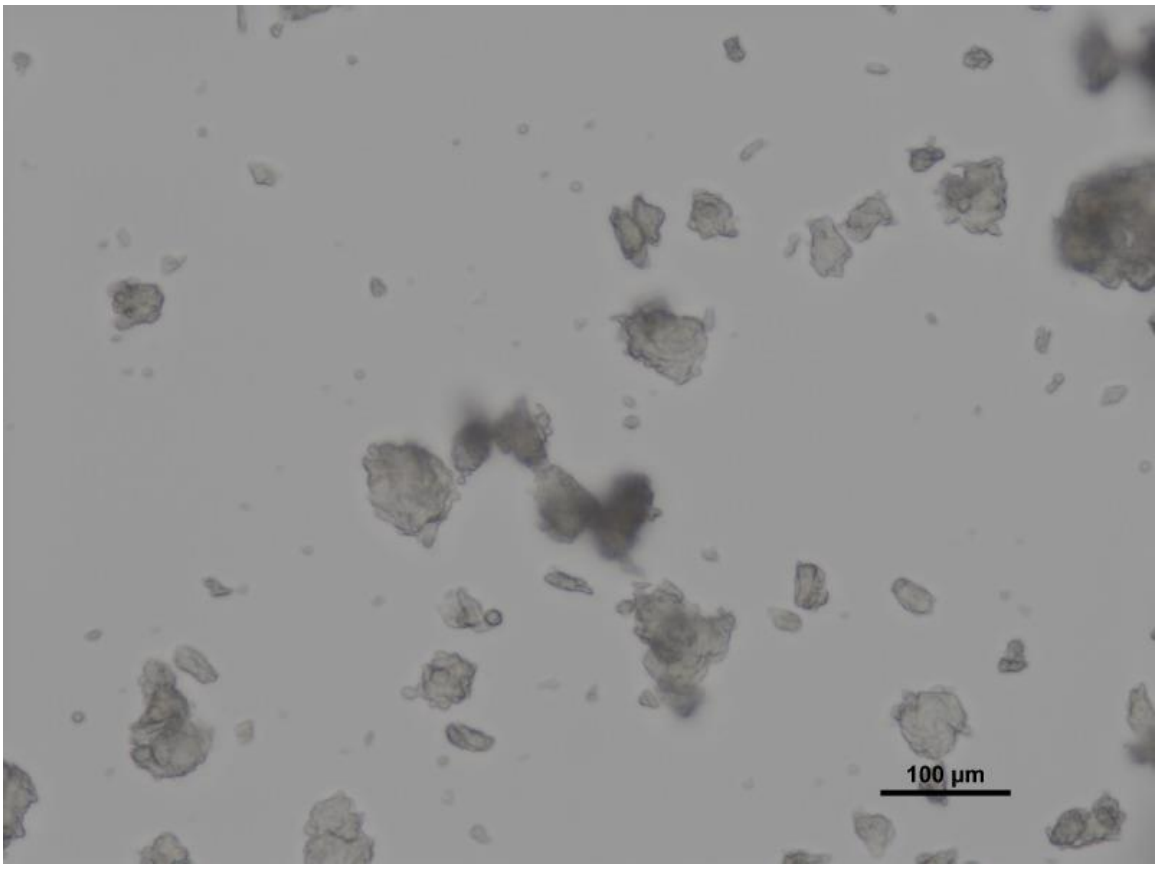


**Figure 4: Long acting Hydromorph Contin after being drawn through a 25-gauge syringe (unfiltered). Used with permission by Laura Ball.**

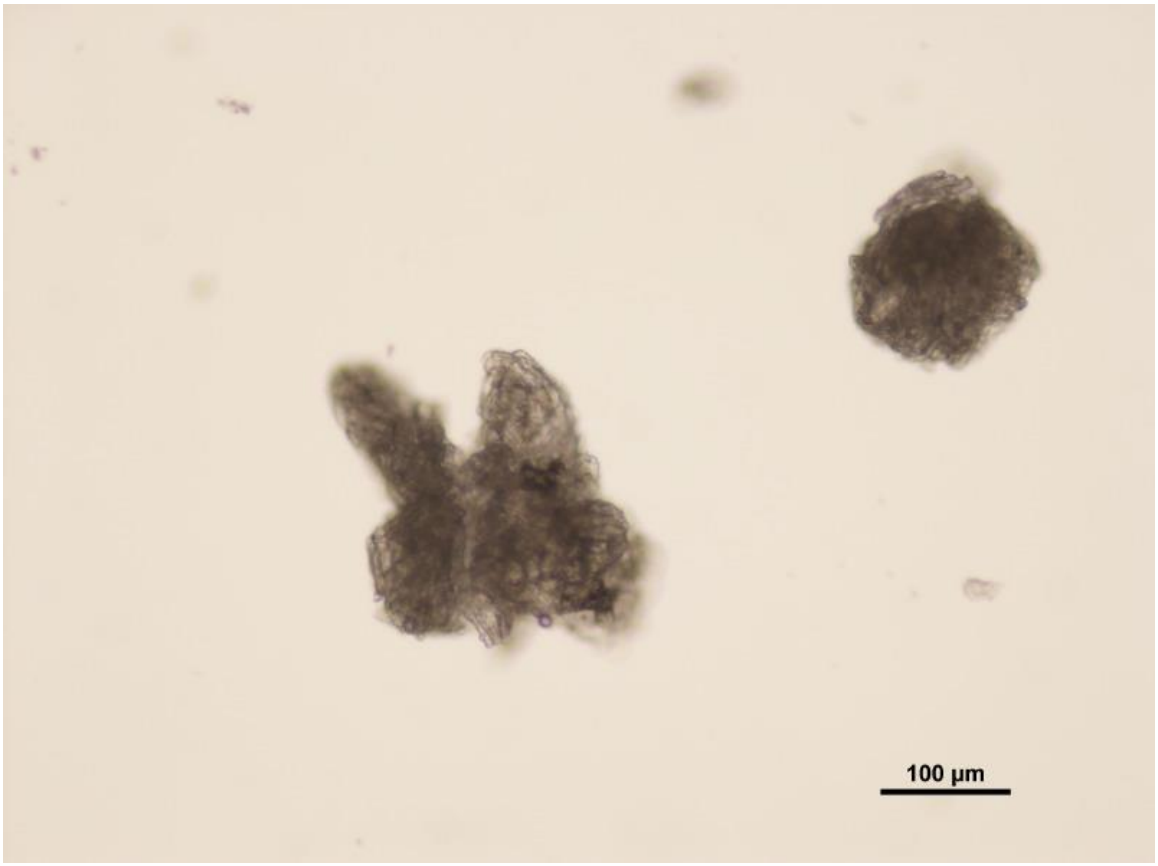


**Figure 5: Long acting Hydromorph contin being drawn through a 25-gauge syringe (filtered). Used with permission by Laura Ball.**

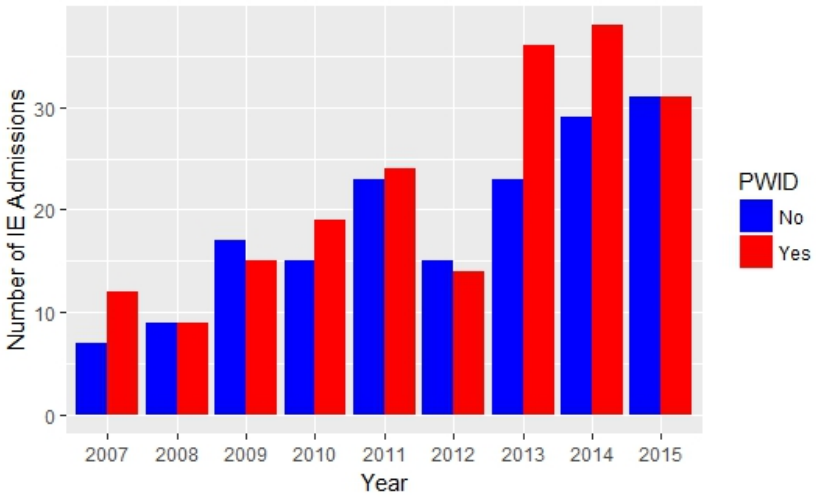


**Figure 6: a dodged bar plot showing incidence of infective endocarditis for PWID and non-IDU patients.**

The next section includes outputs from Kaplan-Meier and Cox Proportional Hazards survival analyses and calculations to estimate prevalence. Each caption may be found above the respective output.

**Output 1: Results for Kaplan-Meier survival analysis demonstrating the probability of survival over each time period in days for non-IDU.**

4 observations deleted due to missingness

IVDU=No

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 0 | 170 | 1 | 0.994 | 0.00587 | 0.983 | 1.000 |
| 4 | 169 | 3 | 0.976 | 0.01163 | 0.954 | 1.000 |
| 5 | 166 | 3 | 0.959 | 0.01524 | 0.929 | 0.989 |
| 7 | 163 | 1 | 0.953 | 0.01624 | 0.922 | 0.985 |
| 9 | 162 | 1 | 0.947 | 0.01717 | 0.914 | 0.981 |
| 10 | 161 | 1 | 0.941 | 0.01805 | 0.906 | 0.977 |
| 11 | 160 | 2 | 0.929 | 0.01964 | 0.892 | 0.969 |
| 13 | 158 | 1 | 0.924 | 0.02038 | 0.884 | 0.964 |
| 14 | 157 | 2 | 0.912 | 0.02175 | 0.870 | 0.955 |
| 15 | 155 | 1 | 0.906 | 0.02239 | 0.863 | 0.951 |
| 22 | 154 | 1 | 0.900 | 0.02301 | 0.856 | 0.946 |
| 23 | 153 | 3 | 0.882 | 0.02471 | 0.835 | 0.932 |
| 24 | 150 | 2 | 0.871 | 0.02574 | 0.822 | 0.923 |
| 25 | 148 | 1 | 0.865 | 0.02623 | 0.815 | 0.918 |
| 26 | 147 | 1 | 0.859 | 0.02671 | 0.808 | 0.913 |
| 31 | 146 | 1 | 0.853 | 0.02716 | 0.801 | 0.908 |
| 32 | 145 | 1 | 0.847 | 0.02761 | 0.795 | 0.903 |
| 33 | 144 | 1 | 0.841 | 0.02803 | 0.788 | 0.898 |
| 36 | 143 | 1 | 0.835 | 0.02845 | 0.781 | 0.893 |
| 39 | 142 | 1 | 0.829 | 0.02885 | 0.775 | 0.888 |
| 41 | 141 | 1 | 0.824 | 0.02924 | 0.768 | 0.883 |
| 42 | 140 | 1 | 0.818 | 0.02962 | 0.762 | 0.878 |
| 62 | 139 | 1 | 0.812 | 0.02998 | 0.755 | 0.873 |
| 71 | 138 | 1 | 0.806 | 0.03033 | 0.749 | 0.868 |
| 124 | 137 | 1 | 0.800 | 0.03068 | 0.742 | 0.862 |
| 177 | 135 | 1 | 0.794 | 0.03102 | 0.736 | 0.857 |
| 228 | 134 | 1 | 0.788 | 0.03135 | 0.729 | 0.852 |
| 293 | 132 | 1 | 0.782 | 0.03167 | 0.722 | 0.847 |
| 321 | 131 | 1 | 0.776 | 0.03199 | 0.716 | 0.842 |
| 366 | 128 | 1 | 0.770 | 0.03231 | 0.709 | 0.836 |
| 520 | 115 | 1 | 0.763 | 0.03272 | 0.702 | 0.830 |
| 538 | 114 | 1 | 0.757 | 0.03311 | 0.695 | 0.824 |
| 550 | 112 | 1 | 0.750 | 0.03349 | 0.687 | 0.819 |
| 618 | 110 | 1 | 0.743 | 0.03388 | 0.680 | 0.813 |
| 640 | 108 | 1 | 0.736 | 0.03425 | 0.672 | 0.807 |
| 660 | 107 | 1 | 0.729 | 0.03462 | 0.665 | 0.801 |
| 667 | 106 | 1 | 0.723 | 0.03497 | 0.657 | 0.794 |
| 969 | 93 | 1 | 0.715 | 0.03545 | 0.649 | 0.788 |
| 1127 | 83 | 1 | 0.706 | 0.03605 | 0.639 | 0.780 |
| 1134 | 81 | 1 | 0.697 | 0.03664 | 0.629 | 0.773 |
| 1201 | 78 | 1 | 0.688 | 0.03725 | 0.619 | 0.766 |
| 1320 | 72 | 1 | 0.679 | 0.03794 | 0.608 | 0.758 |
| 1715 | 61 | 1 | 0.668 | 0.03891 | 0.596 | 0.749 |
| 1954 | 49 | 1 | 0.654 | 0.04044 | 0.580 | 0.738 |
| 3183 | 8 | 1 | 0.572 | 0.08428 | 0.429 | 0.764 |

**Output 2: Results for Kaplan-Meier survival analysis demonstrating the probability of survival over each time period in days for PWID.**

IVDU=Yes

| time | n.risk | n.event | survival | std.err | lower 95% CI | upper 95% CI |
|---|---|---|---|---|---|---|
| 1 | 204 | 1 | 0.995 | 0.00489 | 0.986 | 1.000 |
| 2 | 203 | 2 | 0.985 | 0.00843 | 0.969 | 1.000 |
| 3 | 201 | 3 | 0.971 | 0.01183 | 0.948 | 0.994 |
| 4 | 198 | 1 | 0.966 | 0.01274 | 0.941 | 0.991 |
| 5 | 197 | 1 | 0.961 | 0.01359 | 0.935 | 0.988 |
| 6 | 196 | 1 | 0.956 | 0.01438 | 0.928 | 0.984 |
| 7 | 195 | 2 | 0.946 | 0.01581 | 0.916 | 0.978 |
| 9 | 193 | 1 | 0.941 | 0.01647 | 0.909 | 0.974 |
| 10 | 192 | 3 | 0.926 | 0.01827 | 0.891 | 0.963 |
| 11 | 189 | 1 | 0.922 | 0.01882 | 0.885 | 0.959 |
| 13 | 188 | 2 | 0.912 | 0.01986 | 0.874 | 0.952 |
| 16 | 186 | 1 | 0.907 | 0.02035 | 0.868 | 0.948 |
| 17 | 185 | 2 | 0.897 | 0.02128 | 0.856 | 0.940 |
| 18 | 183 | 1 | 0.892 | 0.02172 | 0.851 | 0.936 |
| 20 | 182 | 2 | 0.882 | 0.02256 | 0.839 | 0.928 |
| 21 | 180 | 2 | 0.873 | 0.02335 | 0.828 | 0.920 |
| 25 | 178 | 1 | 0.868 | 0.02373 | 0.822 | 0.915 |
| 29 | 177 | 3 | 0.853 | 0.02480 | 0.806 | 0.903 |
| 30 | 174 | 1 | 0.848 | 0.02513 | 0.800 | 0.899 |
| 38 | 173 | 1 | 0.843 | 0.02546 | 0.795 | 0.895 |
| 45 | 172 | 1 | 0.838 | 0.02578 | 0.789 | 0.890 |
| 83 | 171 | 1 | 0.833 | 0.02609 | 0.784 | 0.886 |
| 107 | 170 | 1 | 0.828 | 0.02640 | 0.778 | 0.882 |
| 121 | 169 | 1 | 0.824 | 0.02669 | 0.773 | 0.878 |
| 146 | 168 | 1 | 0.819 | 0.02698 | 0.767 | 0.873 |
| 161 | 167 | 1 | 0.814 | 0.02726 | 0.762 | 0.869 |
| 175 | 166 | 1 | 0.809 | 0.02753 | 0.757 | 0.865 |
| 186 | 165 | 1 | 0.804 | 0.02780 | 0.751 | 0.860 |
| 197 | 164 | 1 | 0.799 | 0.02806 | 0.746 | 0.856 |
| 198 | 163 | 1 | 0.794 | 0.02831 | 0.741 | 0.852 |
| 217 | 162 | 1 | 0.789 | 0.02856 | 0.735 | 0.847 |
| 230 | 161 | 1 | 0.784 | 0.02880 | 0.730 | 0.843 |
| 274 | 160 | 1 | 0.779 | 0.02903 | 0.725 | 0.838 |
| 301 | 158 | 1 | 0.774 | 0.02926 | 0.719 | 0.834 |
| 400 | 152 | 1 | 0.769 | 0.02951 | 0.714 | 0.829 |
| 406 | 150 | 1 | 0.764 | 0.02976 | 0.708 | 0.825 |
| 416 | 148 | 1 | 0.759 | 0.03000 | 0.703 | 0.820 |
| 497 | 141 | 1 | 0.754 | 0.03027 | 0.697 | 0.815 |
| 546 | 136 | 1 | 0.748 | 0.03055 | 0.691 | 0.810 |
| 568 | 133 | 1 | 0.743 | 0.03083 | 0.685 | 0.805 |
| 595 | 129 | 1 | 0.737 | 0.03112 | 0.678 | 0.800 |
| 632 | 126 | 1 | 0.731 | 0.03142 | 0.672 | 0.795 |
| 656 | 124 | 1 | 0.725 | 0.03172 | 0.665 | 0.790 |
| 667 | 123 | 1 | 0.719 | 0.03200 | 0.659 | 0.785 |
| 897 | 107 | 1 | 0.712 | 0.03240 | 0.652 | 0.779 |
| 994 | 98 | 1 | 0.705 | 0.03288 | 0.644 | 0.773 |
| 1017 | 92 | 1 | 0.697 | 0.03340 | 0.635 | 0.766 |
| 1064 | 90 | 1 | 0.690 | 0.03392 | 0.626 | 0.760 |
| 1069 | 89 | 1 | 0.682 | 0.03441 | 0.618 | 0.753 |
| 1071 | 88 | 1 | 0.674 | 0.03488 | 0.609 | 0.746 |
| 1104 | 83 | 1 | 0.666 | 0.03539 | 0.600 | 0.739 |
| 1326 | 68 | 1 | 0.656 | 0.03620 | 0.589 | 0.731 |
| 1390 | 61 | 1 | 0.646 | 0.03717 | 0.577 | 0.723 |
| 1952 | 42 | 1 | 0.630 | 0.03934 | 0.558 | 0.712 |
| 1965 | 41 | 1 | 0.615 | 0.04127 | 0.539 | 0.701 |
| 2705 | 16 | 1 | 0.576 | 0.05368 | 0.480 | 0.692 |

**Output 3: Results for Cox Proportional Hazards Model survival analysis for the Full model.**

```
coxph(formula = coxsurv ~ AdmitAge + Female + IVDU + Fever +
    Aortic + Mitral + Tricuspid + MultiV + MSSA + MRSA + Enterococci,
    data = ds)

  n= 353, number of events= 118
   (25 observations deleted due to missingness)

                coef exp(coef)  se(coef)      z Pr(>|z|)
AdmitAge     0.029346  1.029781  0.008036  3.652 0.000260 ***
Female       0.318458  1.375005  0.194464  1.638 0.101502
IVDUYes      0.916277  2.499966  0.281501  3.255 0.001134 **
FeverYes    -0.033943  0.966626  0.226615 -0.150 0.880935
Aortic       0.731005  2.077166  0.734536  0.995 0.319643
Mitral       0.708008  2.029943  0.735210  0.963 0.335547
Tricuspid   -0.244449  0.783136  0.736895 -0.332 0.740095
MultiV      -0.038994  0.961756  0.026658 -1.463 0.143537
MSSA         0.554371  1.740846  0.255581  2.169 0.030078 *
MRSA         1.173189  3.232285  0.302107  3.883 0.000103 ***
Enterococci  0.100950  1.106221  0.355982  0.284 0.776731
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

            exp(coef) exp(-coef) lower .95 upper .95
AdmitAge       1.0298     0.9711    1.0137     1.046
Female         1.3750     0.7273    0.9392     2.013
IVDUYes        2.5000     0.4000    1.4399     4.341
FeverYes       0.9666     1.0345    0.6200     1.507
Aortic         2.0772     0.4814    0.4923     8.764
Mitral         2.0299     0.4926    0.4805     8.576
Tricuspid      0.7831     1.2769    0.1848     3.320
MultiV         0.9618     1.0398    0.9128     1.013
MSSA           1.7408     0.5744    1.0549     2.873
MRSA           3.2323     0.3094    1.7880     5.843
Enterococci    1.1062     0.9040    0.5506     2.223

Concordance= 0.664  (se = 0.028 )
Rsquare= 0.118   (max possible= 0.975 )
Likelihood ratio test= 44.2  on 11 df,   p=6.715e-06
Wald test            = 44.03  on 11 df,   p=7.188e-06
Score (logrank) test = 45.32  on 11 df,   p=4.266e-06
```

**Output 4: Results for cox proportional hazard survival analysis using PWID-only data.**

```
coxph(formula = pwid.coxsurv ~ AdmitAge + Female + Homeless +
    Fever + Aortic + Mitral + Tricuspid + MultiV + MSSA + MRSA +
    Enterococci + Polymicrobial + HCV_pos + HIV_pos, data = pwid_data)

  n= 186, number of events= 63
   (18 observations deleted due to missingness)

                    coef  exp(coef)   se(coef)      z Pr(>|z|)
AdmitAge       6.001e-03  1.006e+00  1.541e-02  0.389  0.69706
Female        -4.868e-02  9.525e-01  3.074e-01 -0.158  0.87418
Homeless      -4.693e-01  6.254e-01  4.091e-01 -1.147  0.25128
FeverYes      -2.176e-01  8.044e-01  3.250e-01 -0.670  0.50312
Aortic         1.678e+01  1.947e+07  3.246e+03  0.005  0.99587
Mitral         1.673e+01  1.846e+07  3.246e+03  0.005  0.99589
Tricuspid      1.549e+01  5.342e+06  3.246e+03  0.005  0.99619
MultiV        -6.135e-01  5.414e-01  1.159e+02 -0.005  0.99578
MSSA           1.916e-02  1.019e+00  4.569e-01  0.042  0.96655
MRSA           6.195e-01  1.858e+00  5.136e-01  1.206  0.22772
Enterococci   -1.267e+00  2.816e-01  7.263e-01 -1.745  0.08099 .
Polymicrobial -3.304e-02  9.675e-01  6.083e-01 -0.054  0.95669
HCV_pos       -6.458e-01  5.243e-01  2.905e-01 -2.223  0.02622 *
HIV_pos        1.285e+00  3.616e+00  4.676e-01  2.749  0.00597 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

              exp(coef) exp(-coef) lower .95 upper .95
AdmitAge      1.006e+00  9.940e-01 9.761e-01 1.037e+00
Female        9.525e-01  1.050e+00 5.214e-01 1.740e+00
Homeless      6.254e-01  1.599e+00 2.805e-01 1.394e+00
FeverYes      8.044e-01  1.243e+00 4.254e-01 1.521e+00
Aortic        1.947e+07  5.137e-08 0.000e+00       Inf
Mitral        1.846e+07  5.418e-08 0.000e+00       Inf
Tricuspid     5.342e+06  1.872e-07 0.000e+00       Inf
MultiV        5.414e-01  1.847e+00 1.153e-99 2.542e+98
MSSA          1.019e+00  9.810e-01 4.163e-01 2.496e+00
MRSA          1.858e+00  5.382e-01 6.790e-01 5.084e+00
Enterococci   2.816e-01  3.551e+00 6.782e-02 1.169e+00
Polymicrobial 9.675e-01  1.034e+00 2.937e-01 3.187e+00
HCV_pos       5.243e-01  1.907e+00 2.967e-01 9.265e-01
HIV_pos       3.616e+00  2.765e-01 1.446e+00 9.043e+00

Concordance= 0.718  (se = 0.038 )
Rsquare= 0.194   (max possible= 0.963 )
Likelihood ratio test= 40.23  on 14 df,   p=0.0002351
Wald test            = 38.75  on 14 df,   p=0.0003984
Score (logrank) test = 45.2  on 14 df,   p=3.792e-05
```

**Output 5: Output for cox proportional hazard model using non-IDU-only data.**

```
coxph(formula = nonIDU.coxsurv ~ AdmitAge + Female + Aortic +
    Mitral + Tricuspid + MultiV + MSSA + MRSA + Enterococci +
    AHS + CoNS + ICD_pacemaker + Prosthetic_Valve, data = nonIDU_data)

  n= 164, number of events= 53
   (9 observations deleted due to missingness)

                       coef exp(coef) se(coef)      z Pr(>|z|)
AdmitAge            0.03044   1.03090  0.01155  2.635  0.00843 **
Female              0.89330   2.44317  0.29170  3.062  0.00220 **
Aortic             -0.42609   0.65306  0.85363 -0.499  0.61767
Mitral             -0.57382   0.56337  0.84188 -0.682  0.49549
Tricuspid          -0.40314   0.66822  0.89681 -0.450  0.65305
MultiV              0.01024   1.01029  0.03211  0.319  0.74985
MSSA                1.33461   3.79852  0.66122  2.018  0.04355 *
MRSA                1.73984   5.69645  0.69739  2.495  0.01260 *
Enterococci         0.80633   2.23968  0.70116  1.150  0.25014
AHS                -0.18187   0.83371  0.69869 -0.260  0.79463
CoNS                1.21699   3.37701  0.68655  1.773  0.07629 .
ICD_pacemakerYes   -1.26542   0.28212  1.12544 -1.124  0.26086
Prosthetic_ValveYes 0.18203   1.19965  0.38215  0.476  0.63384
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

                   exp(coef) exp(-coef) lower .95 upper .95
AdmitAge              1.0309     0.9700   1.00782     1.055
Female                2.4432     0.4093   1.37929     4.328
Aortic                0.6531     1.5313   0.12256     3.480
Mitral                0.5634     1.7750   0.10819     2.934
Tricuspid             0.6682     1.4965   0.11523     3.875
MultiV                1.0103     0.9898   0.94866     1.076
MSSA                  3.7985     0.2633   1.03939    13.882
MRSA                  5.6965     0.1755   1.45206    22.347
Enterococci           2.2397     0.4465   0.56671     8.851
AHS                   0.8337     1.1995   0.21198     3.279
CoNS                  3.3770     0.2961   0.87931    12.969
ICD_pacemakerYes      0.2821     3.5446   0.03108     2.561
Prosthetic_ValveYes   1.1997     0.8336   0.56724     2.537

Concordance= 0.762  (se = 0.041 )
Rsquare= 0.262   (max possible= 0.955 )
Likelihood ratio test= 49.77  on 13 df,   p=3.27e-06
Wald test            = 42.39  on 13 df,   p=5.65e-05
Score (logrank) test = 50.86  on 13 df,   p=2.121e-06
```

**Equation 1: Calculations for SMR estimation.**

$$\frac{death_{PWID}/Population_{PWID}}{death_{total}/population_{total}} = 11.19$$

We can then insert the numbers from Statistics Canada:

$$\frac{68/population_{PWID}}{122/380{,}000} = 11.19$$

Then perform some algebra:

$$population_{PWID} = 18{,}928$$

Which would result in the PWID population representing 4.98% of the total population, or 18,928 people.

# Curriculum Vitae

| | |
|---|---|
| **Name:** | Brian Hallam |
| **Post-secondary Education and Degrees:** | University of Guelph-Humber<br>Etobicoke, Ontario, Canada<br>2009-2013 B.A.Sc. |
| | York University<br>North York, Ontario, Canada<br>2014-2016 B.A. |
| **Honours and Awards:** | Province of Ontario Graduate Scholarship<br>2017-2018 |
| | Vanier Vingt-Deaux Honour Roll<br>2016 |
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