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Clostridium difficile infection incidence and mortality in Alberta

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Clostridium difficile infection incidence and mortality in Alberta

by

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Abstract

Clostridium difficile infection (CDI) is the leading cause of hospital-acquired diarrhea. It causes significant morbidity and mortality, manifesting in life threatening conditions such as pseudomembranous colitis. This study determined the incidence of CDI in Alberta, investigated risk factors associated with mortality amongst Alberta CDI patients, and investigated the inter-rater reliability between the Death Attribution Rules for Patients Infected by *C. difficile* (DARPIC) algorithm and IPC physicians. Incidence of CDI in Alberta hospitals, continuing care facilities, and the community provided a comprehensive understanding of CDI in Alberta. Although CDI is predominantly a nosocomial infection, 47% of the CDI cases identified in this study occurred in the community. Risk factors for mortality amongst hospitalized CDI patients were increasing age and comorbidity count, liver disease, and metastatic solid tumour. Attributing death to CDI is difficult and opinions vary by clinicians, to accurately and consistently report attributable CDI mortality a standardized approach is necessary.

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Glossary

Continuing Care (CC) resident: Those who reside in an Alberta continuing care facility.

Incidence: Is an epidemiology measure of the development of new cases of disease.

Comorbidity: Pertaining to a disease of other pathological process that occurs simultaneously with another.

Personal Health Number (PHN): Number who uniquely identifies an Alberta resident who receives the Alberta Health Care Insurance Plan.

Unique Lifetime Identifier (ULI): A unique identifier for Alberta for individuals who are not registered with the Alberta Health Care Insurance Plan. May include individuals who reside outside of Alberta or Albertans with federal medical coverage.

Postal code translation file: Is a digital file that links the six character postal code and Statistics Canada standard geographical areas.

Admissions: Number of individuals formally admitted to an acute care facility during a specified time.

Resident-days: Collective number of days residents have resided in continuing care facilities during a specified time.

Data linking/matching: A deterministic match using an individual's unique identifier (i.e. PHN/ULI) from one data source or dataset and match to that individual's information from another data source or dataset.

Data extract: A set of electronic information.

Data coding: A process of categorizing data for analysis.

Zone: Alberta standard geographical areas.

Anatomical Therapeutic Chemical (ATC) Code: A classification code developed by World Health Organization that is used to classify active ingredients of drugs according to the organ or system they act upon. It consists of five levels which differ in their level of specificity (i.e. first level: anatomical group, fifth level: exact chemical substance).

Chapter One: Introduction

Clostridium difficile is an anaerobic, spore-forming, Gram-positive bacterium[1]. It was first isolated in 1935 from a healthy infant. In 1978, it was discovered *C. difficile* caused the majority of antibiotic-associated diarrhea. Since it forms spores it is highly resistant to desiccation or disinfectants and can remain in the environment for an extended period of time creating environmental reservoirs that increase the likelihood of transmission. It is also highly resistant to extreme temperatures, UV light, antibiotics, and can survive the harsh environment of the gastrointestinal tract[2].

C. difficile infection (CDI) is the leading cause of hospital-acquired diarrhea causing significant morbidity and mortality[1,3]. Increases in incidence of CDI have been linked to increased antibiotic use, aging populations with comorbidities, antibiotic resistance, and the emergence of a hypervirulent strain, BI/NAP1/027[3]. In 2009 *C. difficile* became a notifiable disease in Canada[4].

Historically, CDI was recognized as a nosocomial infection only, presenting in patients with traditional risk factors such as advanced age and antibiotic use[3,5]. However, individuals without traditional risk factors and/or without healthcare exposure started to develop CDI, likely due to the emergence of hypervirulent *C. difficile* strains[5]. It has been estimated that 20 to 40% of CDI is community-associated[3,6]; however, these estimates are not recent. In 2011, a nested case-control study reported an incidence of 11.2 community-associated CDI cases per 100,000 person-years, which was comparable to their hospital-acquired rates[7]. Incidence is used to demonstrate changing patterns of disease[8]. Overall incidence portrays the actual current state of CDI in a population. Accurate CDI

incidence provides a platform for developing interventions, monitoring the effect those interventions, and reflects the burden it has on public health and hospitals[9].

CDI is associated with increased morbidity and mortality[1]. Case-fatality rates have been reported between 6 and 30%[10]. Comorbidities, increasing age, antibiotic exposure, and treatment have all been implicated in increasing CDI mortality[11,12]. The presence of comorbidities associated with CDI mortality identifies those with CDI who are at higher risk of dying, and has implications on an individual's clinical management[13], with intervention to help reduce mortality attributed to CDI[11].

There has been a four-fold increase in CDI attributable mortality in Canadian hospitals from 1997 to 2005[1]. Life-threatening conditions manifested from CDI are pseudomembranous colitis, bowel perforation, toxic megacolon, and sepsis[1,10]. Methods for accurately identifying CDI-related deaths are needed to accurately report mortality. Currently, Infection Prevention & Control (IPC) physicians in Alberta are reviewing deaths that have occurred within 30 days of CDI diagnosis. The IPC physicians may use the Death Attribution Rules for Patients Infected by *C. difficile* (DARPIC) algorithm, which helps determine CDI's role in the death. Deaths can be classified as direct, contributed, unrelated, or indeterminate (i.e. unable to determine). The DARPIC algorithm has not been validated; however, it is in use nationally by the Canadian Nosocomial Infection Surveillance Program (CNISP) CDI surveillance protocol[14]. Accurate mortality data are imperative for measuring the impact CDI has on a population and in turn support the development of measures to prevent CDI[15] and its complications.

In summary, this study determined the overall incidence of CDI in Alberta, investigated risk factors and comorbidities associated with mortality amongst patients

with CDI, and investigated the inter-rater reliability between the DARPIC algorithm and IPC physicians.

Chapter Two: Research Objectives

In this study the three research objectives were:

1. Determine the overall incidence of CDI in Alberta in the adult population.
2. Investigate comorbidities and/or variables associated with mortality amongst hospitalized CDI patients.
3. Inter-rater reliability between the DARPIC algorithm and expert reviewers for CDI death attribution.

Chapter Three: Background

3.1 Pathogenesis

C. difficile mode of transmission is the fecal-oral route. In its spore form it is able to resist the stomach acid activity and once in the small intestine it germinates into its vegetative form[16]. *C. difficile* adheres to the intestinal epithelium of the large intestine[2]. The large intestine has a microbiome, which consists of indigenous microorganisms that protect against pathogenic microorganism via competition for nutrients and room for attachment. Disruption of the microbiome through antibiotic consumption, or other mechanisms such as chemotherapy and surgery, allows *C. difficile* to colonize the large intestine as the healthy microorganisms are killed and *C. difficile* spores remain as they are highly resistant to antibiotics[17].

Infection may only occur if a toxigenic strain of *C. difficile* has colonized the large intestine[17]. Two large exotoxins, toxin A and B encoded on genes tcdA and tcdB, are responsible for the signs and symptoms of infection. These toxins cause actin depolymerisation and cell death, stimulating an inflammatory cascade that results in inflammation, tissue damage, diarrhea, and pseudomembranous colitis[16,17]. A third toxin named binary toxin, encoded on genes ctdA and ctdB, is produced by some strains of *C. difficile*[16]. The binary toxin is associated with increased virulence; however, its exact mechanism(s) are not known[16,18]. Although one well-defined mechanism is through increased bacterial adherence as this toxin results in long microtubule protrusions[18–20].

3.2 Molecular Epidemiology

In the early 2000's BI/NAP1/027 strain of *C. difficile* emerged, causing epidemics in Canada and the United States[17]. This strain is commonly found in Canada, the United States, and Europe and in certain areas is the predominant *C. difficile* strain[2,16,17]. The strain is named based on restriction endonuclease analysis type BI, North American pulsed-field gel electrophoresis type 1 (NAP1), and polymerase chain reaction (PCR) ribotype 027[16]. This strain has been associated with increased incidence, more severe disease, higher mortality, relapses and recurrent infections, and causing infection in individuals considered low-risk (i.e. community, young, and healthy)[2,16,17,21]. Characteristics of hypervirulence include increased toxin production, presence of the binary toxin, high fluoroquinolone resistance, and potentially improved toxin binding[17]. Compared to historical *C. difficile* strains, BI/NAP1/027 strain increases toxin A and B production by 10- and 23-fold, respectively[2]. However, not all studies found BI/NAP1/027 strain to be associated with increased morbidity and mortality. Nonetheless, a Canadian study found increased mortality in patients between 60 and 90 years of age[2]. Other strains of *C. difficile* have also been associated with more severe disease and poor outcomes[21].

3.3 Diagnosis of *Clostridium difficile* Infection

3.3.1 Laboratory and Pathology Methods

C. difficile and its toxins are identified from stool samples. Stool for laboratory testing should be collected shortly after diarrhea onset. Only unformed, loose, or watery stool should be sent for testing[1]. Stool laboratory tests for *C. difficile* include culture, glutamate dehydrogenase assay (GDH), toxigenic culture, toxin enzyme immunoassay

(EIA), and PCR[17,22]. Glutamate dehydrogenase assay (GDH) detects *C. difficile* antigen but does not distinguish between toxigenic and nontoxigenic strains[17]. EIA detects *C. difficile* toxins antigens. The most commonly used laboratory test is EIA, as it inexpensive, rapid, and has high specificity[16,17,22]. Sensitivity and specificity depend upon the reference sample[23]. Sensitivity is a measure of a screening tests ability to detect those with the disorder (i.e. percentage of those with the disorder who test positive). Specificity is a measure of a screening tests ability to detect those without the disorder (i.e. percentage of those without the disorder who test negative)[24].

For *C. difficile* laboratory testing, the gold standard (i.e. reference sample) is the toxigenic culture[17]. The toxigenic culture involves two steps: culture of *C. difficile* and confirmation of toxin production. Culturing *C. difficile* can take up to 5 days. Toxin production is either confirmed by cell culture cytotoxin neutralization (CCNA) or PCR[25]. Cell culture cytotoxin neutralization (CCNA) involves stool filtrate being injected into a human cell and if the toxin is present the cell structurally deforms[26]. With PCR, if the toxins genes are present they will be amplified until they are at a detectable level. The sensitivity and specificity for toxigenic culture range from 90-100% and 98-100%, respectively[27]. As results from toxigenic culture are slow, it is not a feasible testing method in clinical settings; however, as this method has high sensitivity and specificity it is considered the gold standard[17]. Compared to toxigenic culture, the sensitivity and specificity for EIA range from 60 to 81% and 91 to 99%, respectively[25]. A meta-analysis of PCR accuracy for *C. difficile* reported a sensitivity and specificity mean (95% confidence interval) of 90% (88-92%) and 96 (95-96%), respectively[27].

The identification of *C. difficile* in the pediatric population is complicated by increased false positives. False positives may be a result of low prevalence of *C. difficile*

in the pediatric population; thereby, resulting in a laboratory tests with low positive predictive value[28]. Additionally, a high rate of colonization is found among infants and young children as well as hospitalized children and children with cancer or inflammatory bowel disease[29]. Even though colonized, the child may have detectable levels of *C. difficile* in their stool[28]. It has been estimated 70% of infants' under one year of age with *C. difficile* are colonized. The proportion of colonization decreases with age[30]. Potential reasons for colonization, without symptomatic disease, in infants are the premature immune system and maternal antibodies[31].

In certain circumstances, endoscopic exams (e.g. colonoscopy, sigmoidoscopy) or abdominal radiographs are used to diagnosis CDI. If CDI is strongly suspected but the laboratory tests are negative, these exams may be performed. Evidence of pseudomembranous colitis is indicative of CDI and is found through endoscopic exams[2,17,22]. On radiographs, bowel wall thickening, pericolonic stranding, and fold thickening can be evidence of CDI. However, with both of these exams the results are more indicative of severe CDI as CDI does not always cause these physiological changes[22].

In 2013 Alberta laboratories began to standardize their screening of *C. difficile* in the province. Firstly, a GDH/toxin EIA combined test is performed and if this test is positive a positive *C. difficile* result is reported. However, if the results are indeterminate the sample is sent for confirmatory PCR testing. Contrary, Calgary Laboratory Services, which serves the Calgary Zone, since 2010 has used PCR testing. Prior to 2013 the other Alberta laboratories were not standardized, some laboratories performed the first method noted while others did not do the confirmatory PCR testing in cases of indeterminate results; rather, would re-run the toxin EIA test. If the result was still indeterminate, they

would report an indeterminate result and suggest repeat testing if the individual was still symptomatic.

3.3.2 Clinical Criteria

For diagnosis of CDI a positive *C. difficile* laboratory result is usually not enough evidence; rather, the individual must also have clinical signs of infection such as abdominal pain and/or diarrhea[22]. For surveillance purposes, Canadian Nosocomial Infection Surveillance Program (CNISP), Public Health Agency of Canada derived a protocol to standardize case definition for CDI in inpatient settings[32].

Table 1. Canadian Nosocomial Infection Surveillance Program *C. difficile* infection definition.

According to CNISP, CDI is defined as:
• Diarrhea* or fever, abdominal pain and/or ileus AND laboratory confirmation of a positive toxin for *C. difficile* OR • Physician diagnosis of pseudomembranes on endoscopy or histological/pathological diagnosis of CDI OR • Diagnosed with toxic megacolon
*Diarrhea is defined as:
• 6 or more watery stools in a 36 hour period OR • 3 or more unformed stools in a 24 hour period AND is new or unusual for the patient

3.4 *Clostridium difficile* Infection Incidence

3.4.1 Identification of Clostridium difficile Infection

The method in which CDI is identified and reported can depend on the resources available and the purpose (i.e. surveillance vs. research). For surveillance in hospitals, an

active surveillance is recommended if there are resources available (i.e. dedicated staff). With active surveillance of healthcare-associated infections, there are infection control professionals (ICP) who perform surveillance in an active, patient-centered, and prospective manner. A positive laboratory *C. difficile* result prompts the ICP to investigate the case to determine if the patient has symptoms of CDI. This is the gold-standard for CDI surveillance[33]. As mentioned prior, CNISP has a standardized definition for CDI, which is used at Canadian hospitals participating in CNISP as well as in all Alberta acute care hospitals.

Most CDI research studies use hospital discharge and/or laboratory data to identify CDI[34]. CDI can be approximated by identifying positive laboratory results of *C. difficile,* but by only using these it is not possible to determine which patients are symptomatic and actually have CDI. This may result in an overestimate of the amount of CDI as some individuals may be colonized[34]. However, it is explicitly stated only individuals with diarrhea should have their stool sent for *C. difficile* laboratory testing. A recent study conducted by IPC Surveillance in Alberta found the use of laboratory data to capture cases had similar results to using a clinical definition[35]. Furthermore, Scheurer et al. reported 14% of *C. difficile* toxin positive (according to cytotoxic assay) patients were asymptomatic[36].

Upon discharge from hospitals, medical coder read the patient's hospital medical chart and translate their diagnoses and procedures to codes. Diagnosis codes are standardized from the International Classification of Diseases (ICD). In Canada, the 10th revision is used, while the United States has only recently transitioned from the 9th to the 10th revision. A04.7 is the ICD-10 code for "enterocolitis due to *C. difficile*" and 008.45 is the ICD-9 code for "infection due to *C. difficile*"[7,37]. Studies may use ICD-9 or ICD-10

codes to identify cases of CDI in hospitals. Using discharge diagnoses is an inexpensive and quick method of identifying CDI[33]. But hospital discharge data requires an individual to be admitted to the hospital and cases that present in the community only are missed[34]. However, insurance claims also use ICD codes; therefore, this is a possible method of determining CDI in the community.

Studies have investigated the accuracy of ICD coding compared to laboratory *C. difficile* positives (e.g. toxin assay, or toxigenic culture). Overall, these studies found ICD-9 and ICD-10 had a sensitivity and specificity range of 35-78% and 99-100%, respectively[33,36–39]. Three of these fives studies reported CDI incidence is underestimated with the use of ICD codes solely[36-38]. All studies assumed a laboratory positive was evidence of CDI as only unformed stool was tested (i.e. symptomatic patient)[33,36–39].

3.4.2 Incident and Case Classification Definitions

As individuals can have multiple CDIs, a set time between cases of CDI is used to determine new cases. Generally, a new incident case is defined as the individual not having a positive laboratory *C. difficile* result in the prior 8 weeks[6,33,40–42]. However, other timeframes have been used such as 6 month[43].

For incident CDI cases identified in the hospital, the time of symptom presentation or laboratory collection date may be used to classify the CDI as being acquired in the hospital or community. Common words used in conjunction with hospital and community are onset, associated, and acquired. Hospital-onset, hospital-acquired, and healthcare-associated are commonly used interchangeably. While community-onset, community-associated, and community-acquired are also used interchangeably. Overall, these are termed case classifications. Hospital-acquired CDI is generally defined as CDI occurring

48 or 72 hours or 3 calendar days after hospital admission[34,40,42,44–46]. While community-associated CDI is generally defined as CDI occurring within 48 or 72 hours or 3 calendar days of hospital admission and the patient must also not have had a hospitalization in the prior 4 or 12 weeks depending on the study[6,34,46,47].

Case classification can also be done when CDI is identified using discharge diagnoses. Primary and secondary diagnosis is assigned to ICD-9 diagnosis codes. Primary diagnosis is the reason for admission. Therefore, primary diagnosis of an ICD-9 CDI code can be interpreted as community-associated while secondary diagnosis of an ICD-9 CDI code can be interpreted as hospital-associated[7,33]. However, Dubberke et al. study found using primary and secondary diagnosis of the ICD-9 CDI code was not comparable to using time of culture date for determining case classification, resulting in an overestimation of hospital-associated cases. As stated prior, these codes are assigned at discharge and there is no information regarding date[33]. In Canada, pre- and post-admit are assigned with the diagnosis codes. This became mandatory for U.S. Medicare patients in October 2007[33]. It is important to note. Although, ICD codes are assigned primary diagnosis or pre-admit, further misclassification of attribution could arise because the CDI may have presented on admission, but it could have been related to a previous healthcare admission[48].

3.5 Epidemiology of *Clostridium difficile* Infection

3.5.1 In Hospitals

C. difficile infection (CDI) causes the majority of hospital-acquired diarrhea, and in some areas of the United States is now the most common hospital-acquired infection[21,44]. Additionally, it is estimated CDI causes 15 to 25% of all antibiotic-associated diarrhea[21].

From the 1970's to the 2000's, incidence and severity of CDI remained low and constant. Until the 2000's when incidence and severity began to rise, CDI was not considered a public health threat but a manageable consequence of antimicrobial use[21,44]. In the early 2000s, increase in CDI incidence, severity, and mortality was reported in the United States, Canada, and Europe[21].

In the United States, hospital discharges with diagnosis of CDI increased from 3.8 to 8.8 cases per 1,000 discharges from 2000 to 2008, respectively. This increase was mainly seen in those 65 years and older[16]. Another study reported the national incidence of CDI amongst hospitalized adults increased from 4.5 to 8.2 cases per 1,000 adult discharges from 2001 to 2010[49]. However, both reports used ICD-9 discharge diagnosis of CDI to calculate incidence, which mentioned prior could underestimate or overestimate the true incidence as the literature is contradictory[33,36–39]. Khanna et al. reported in a Minnesota county from 1991-93 to 2003-05 there was a 19.3-fold increase in hospital-acquired CDI[34]. The US Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (HCUP) found hospitalizations for CDI from 1993 to 2009 increased four-fold. Additionally, in 2009 CDI was associated with 1% of all hospital stays. Although all these studies have reported an increase of CDI in hospitals from the 1990's to early 2000's, the HCUP report noted the CDI rates in United States started levelling off in 2009[50].

The rate of *C. difficile* colonization in hospitalized adults has been estimated at 20 to 40% compared to 2 to 3% in healthy adults[2]. Patients, healthcare workers, and the hospital environment can be reservoirs for *C. difficile*, facilitating transmission to vulnerable patients. Generally, hospitalized patients are older and sicker with weakened host defenses and have increased antibiotic usage[44]. Weakened host defenses and

antibiotic use allows *C. difficile* to proliferate and cause infection. The hospital environment and its patients create an ideal setting for *C. difficile* to spread and cause infection; thus, explains the continued high rates of CDI in hospitals.

As mentioned prior, many studies focus on identifying CDI using hospital laboratory or discharge data. These cases then can be classified as hospital-associated or community-associated. Rates are more readily available from hospital studies but CDI is also frequently found in continuing care and the community. A comprehensive view of CDI in a population requires investigation into not only incidence in hospitals but as well as in continuing care and the community.

3.5.2 In Continuing Care

As with hospitalized patients, residents of continuing care (CC) facilities are at increased risk for CDI due to their advanced age, increased antibiotic use, communal environment, and numerous comorbid conditions. Reinfections and asymptomatic carriage are frequent issues for CDI in CC[51]. It has been estimated that 50% of CC residents are asymptomatic carriers of *C. difficile*. Asymptomatic carriage can contribute to environmental contamination and spread of disease[52,53].

Residents of CC facilities are frequently hospitalized and it has been hypothesized the residents acquire *C. difficile* in the hospital but develop the infection shortly after admission to the CC facility[41,51]. It has been reported patients with developing CDI tend to be discharged to CC facilities[51]. From 2000 to 2003 in the United States, the amount of patients with a diagnosis of CDI discharged to CC had doubled[41]. The CDC has created case classifications of CC-CDI to differentiate CDI occurring with and without previous

hospitalizations. The CDC found 67% of residents with CDI occurring greater than 48 hours into CC admission had a hospital discharge in the previous 4 weeks[51].

Continuing care residents are at greater risk for CDI as they frequently have risk factors for CDI. The two primary risk factors for CDI are antibiotic use and advanced age, both of which are common for CC residents[51]. Additionally, they are frequently hospitalized and for a longer length of time, increasing their exposure to both *C. difficile* spores in the hospital environment as well as antibiotics[41,51]. Other risk factors include decreased gastric acid production, comorbidities, and weakened host defenses. The type of CC facility has also been reported to have differing levels of risk for CDI. A study reported incidence of CDI was higher in rehabilitation and sub-acute CC wards compared to traditional wards in the same facility[51].

Although the hospital and CC populations are similar in risk factors, the incidence of CDI remains lower in CC. Campbell et al. reported, based on 2006 Ohio data, a CC-CDI rate of 1.7 to 2.9 cases per 10,000 resident-days compared to a hospital-CDI rate of 6.4 to 7.9 cases per 10,000 patient-days. However, the reported the absolute number of CDI in CC was almost double the number in the hospitals. The amount of resident-days is much larger than patient-days; therefore, the resulting CC-CDI rate was lower[43]. In a similar study conducted in 2010 in Monroe County, New York, the incidence of CDI in CC was 2.3 cases per 10,000 resident-days compared to 9.2 cases per 10,000 patient-days in the hospitals[41]. From 2009 to 2011, four nursing homes in Buffalo, New York reported incidence ranging from 1.3 to 2.9 cases per 10,000 resident-days[54]. But identification of CDI and incident case definition varied between these three studies. Campbell et al. used active surveillance, without symptom component, to identify cases and a new incident case every 6 months[43]. Pawar et al. used laboratory *C. difficile* positives to identify cases

and a new incident case if no positives in the prior 8 weeks[41]. Mylotte et al. used active surveillance to identify cases and a new incident case if no positives in the prior 8 weeks[54]. These differences, as well as geographic difference in CDI burden, could explain the differences in incidence of CDI in CC facilities. Even with difference in study design and study time, the CC-CDI rates were similar and considerably lower than the incidence in hospitals.

3.5.3 In the Community

CDI was previously believed to be an infection associated with hospitalizations. However, in the last 15 years CDI began to affect those without traditional risk factors[22]. Community-associated CDI largely affects those previously deemed low risk, e.g. young, fewer comorbidities, and no recent hospitalization or antibiotic use[34,42,44,47]. Antibiotic and hospital exposure are two common risk factors for CDI; however, Wilcox et al. found approximately one-third of community CDI cases had neither risk factors[47]. The mechanism of transmission in the community is poorly understood[9]. Four proposed sources of transmission are: person-person contact, animal-person contact, food contamination, and environment-person contact. As demonstrated in the hospital, an infected or colonized individual can spread *C. difficile* to other individuals. Animals, such as dogs, cats, livestock, can have and shed *C. difficile* as well[44]. Contaminated food products, such as meat, vegetables, and water, have been suggested as potential sources. Environmental contamination of surfaces is also possible as well as soil itself can contain *C. difficile* spores[2,44].

Various methods have been used to report community-associated CDI. In studies of community CDI, active surveillance, insurance claim coding, diagnosis codes, and

positive *C. difficile* laboratory results have all been used to identify incident CDI cases[6,7,34,46,47]. Another distinct difference is the setting in which the incident CDI cases are identified. Studies have either drawn estimates from inpatient or outpatient data or used a combination of both inpatient and outpatient data. Therefore, the methodology in which the CDI cases are identified is important when reviewing these studies as it impacts the estimates of CDI. Additionally, the term community-associated can be used interchangeably. Community CDI identified in the hospital reflects the severity of the CDI, as individuals experiencing more severe symptoms are more likely admitted to the hospital.

Discharges with a CDI diagnosis levelled off in 2009; however, overall CDI rates continued to rise. This suggests diagnosis of CDI in the community is likely increasing. Community-associated CDI is estimated at 40% of all CDI cases[44]. Few studies have estimated the incidence of CDI in the community. Wilcox et al. used laboratory positives (only in diarrheal patients) from medical clinics to calculate an annual incidence of 29.5 and 20.2 cases per 100,000 individuals in urban and semi-rural settings, respectively[47]. Kuntz et al. used insurance claims for CDI from inpatient and outpatients to determine a rate of 11.2 cases per 100,000 person-years[7]. Khanna et al. used CDI diagnosis codes for inpatients and outpatients to calculate a rate for both 1991-93 and 2003-05. From 1991-93 the rate was 2.8 cases per 100,000 person-years and from 2003-05 it was 14.9 cases per 100,000 person-years, a five-fold increase[34]. In Quebec, the rate of CDI from 1991 to 2003 increased from 65.6 to 156.3 cases per 100,000 population. The proportion of patients that developed toxic megacolon, perforation, shock, or required a colectomy, or died increased from 7.1 to 18.2% from 1991 to 2003[55]. It has been suggested increases in

incidence of CDI in the community could be due to increased *C. difficile* testing, as clinicians are more aware of CDI[22].

3.5.4 In Alberta

Alberta Health Services (AHS) and its contracted partner Covenant Health (COV) provide healthcare at 101 acute care facilities across five geographic Zones in Alberta. AHS/COV IPC monitor healthcare-associated infections, including CDI. At AHS/COV acute care facilities ICPs identify inpatient positive *C. difficile* results, investigate if the patient meets CDI definition according to a CDI protocol derived from CNISP, case classifies the record, and enters it into a web-based platform IPC Surveillance uses to analyze and report data on healthcare-associated infections in Alberta.

In 2013-14, IPC Surveillance reported a provincial total CDI incidence of 5.4 cases per 1,000 admissions; hospital-acquired (HA) incidence of 4.3 cases per 10,000 patient-days and a community-acquired incidence of 1.8 cases per 1,000 admissions. Of the HA-CDI, there was an even split in gender and a mean and median age of 68.5 and 72.0 years. In the same fiscal year, the 30-day attributable mortality (i.e. CDI directly caused death or contributed to death) was reported at 3.6 cases per 100 CDI cases[56]. IPC Surveillance conducts active surveillance for CDI only in the hospitals and does not include continuing care facilities or the community.

In 2016, IPC Surveillance generated its first report for CDI in continuing care facilities for historical data. In 2013-14, the provincial incidence of CDI in continuing care was 3.6 cases per 100,000 resident-days[57]. These records were classified into four case classifications derived from the CDC NHSN definitions[58]. The majority of CC-CDI were either CC-onset or CC-onset with a hospital discharge in the previous 4 weeks.

Additionally, majority were female, and both the mean and median ages were above 80 years[57]. Contrary to CDI surveillance in hospitals, the continuing care CDI surveillance used positive *C. difficile* laboratory results only to identify CDI. Additionally, various administrative data sources were used to determine case classification.

3.6 Risk Factors for *Clostridium difficile* Infection

Risk factors traditionally associated with CDI include increasing age, antibiotic use, comorbid conditions, prolonged hospitalization, prior hospitalizations, and residence at a long-term care (LTC) facility[7,59–63]. Comorbidity or underlying conditions associated with risk of CDI are inflammatory bowel disease, chronic kidney disease, malignant lesions, solid organ transplants, heart failure, chronic obstructive pulmonary disease, diabetes, liver disease, and conditions causing immunodeficiency or requiring the use of immunosuppressants, chemotherapy, or proton-pump inhibitors (PPI)[22,44,64,65]. The method in which these comorbidities increase risk of CDI is multifactorial, including frequent hospitalizations with prolonged length of stay, exposure to antibiotics, and exposure to specific medications (e.g. PPI and immunosuppressants)[21].

Individuals over the age of 65 years are considered more at risk of developing CDI as many of the risk factors are strongly associated with increasing age[61,62]. Using CDI discharge diagnoses, it was reported the rate of CDI was seven-fold higher for patients ≥65 years of age compared to the 45-64 year age group. Patients ≥85 years of age were reported to have a CDI incidence of 10.9 cases per 10,000 population[44]. With increasing age, an individual has a weakened immune response, is more likely to require hospitalization for a longer length of time, be a resident of a LTC facility, have multimorbidity, have more severe comorbidities, and require antibiotic treatment[21,62].

The development of CDI is highly associated with antibiotic exposure[12]. Antibiotic use decreases the normal gut flora; consequently, can allow *C. difficile* to proliferate[13]. Antibiotic use can increase the risk of CDI by 6 times[12]. The risk is the highest in the following three months[21]. The risk of CDI is also increased when multiple antibiotics are used and the longer the antibiotics are taken[62,63]. Conversely, a single-dose, such as surgical prophylaxis, increases the risk of CDI[21]. Antibiotics typically noted as risk factors for CDI are broad-spectrum antibiotics, including clindamycin, cephalosporins, fluoroquinolones, and ampicillin/amoxicillin[66]. However, the risk associated with the antibiotic can depend on the strain of CDI. The J strain of CDI is more resistant to clindamycin, while ribotype 027 strain is more resistant to fluoroquinolones[21]. Even the antibiotics used for CDI treatment, metronidazole and vancomycin, have been associated with risk of CDI[21,66].

The previously listed risk factors explain CDI in hospitalized patients and residents of continuing care; however, these risk factors are not always present in the community population that develops CDI. As mentioned prior, community-associated CDI is largely found in young healthy individuals with no recent hospitalization, antibiotic use, or comorbid conditions[44]. Nonetheless, healthcare exposure, antibiotic use, and comorbidities can still be associated with increased risk of community-associated CDI[21,45]. A meta-analysis on risk factors for community-associated CDI found inflammatory bowel disease, renal failure, leukemia, and lymphoma were strong risk factors for community-associated CDI, while PPI were not risk factors which was the opposite for hospital-associated CDI[45]. Females may be more at risk for community-associated CDI; however, females have been found to be at higher risk for hospital-

associated CDI as well[40]. There appears to be no clear evidence as others report males at higher risk of CDI in general[66].

3.7 *Clostridium difficile* Infection Mortality

3.7.1 Mortality and Risk Factors

Patients hospitalized for CDI tend to be more severely ill than the general hospitalized patients; thus, at higher risk for mortality[21]. In Quebec, CDI 30-day mortality increased from 4.7 to 13.8% from 1991 to 2003[55]. In the United States the number of deaths listed as enterocolitis due to *C. difficile* as the primary death certificate cause of death increased from 793 in 1999 to 7,483 in 2008. Additionally, in 2008 93% of *C. difficile* deaths occurred in individuals 65 years and older and was the 18th leading cause of death in that age group[16]. Increasing age is a risk for 30-day mortality amongst those with CDI. Mortality for those under 40 years has been approximated at 3.4% while it was 41% for those >90 years of age[67]. Furthermore, a 3.5-fold increase in attributable mortality has been reported when comparing those ≥65years of age to those 18-64 years of age[21]. Gender has not been identified as a risk factor for mortality[11,67].

Antibiotic exposure has been implicated as a risk factor for mortality. Exposure to fluoroquinolones within 60 days of CDI diagnosis has been found as a risk factor for CDI death. Furthermore, the duration of use has been associated with CDI mortality[12]. Another study reported piperacillin/tazobactam and meropenem were associated with 90-day mortality[68].

A systematic review in 2012 focusing on risk factors and comorbidities for mortality amongst patients with CDI identified 26 studies[11]. The authors noted interest in risk factors and comorbidities for CDI mortality was recent as two-thirds of the reviewed

studies were published since 2009. This comorbidities associated with mortality included renal and pulmonary insufficiency, ischemic heart disease, and conditions that require steroid use, or acid suppressors[13,69]. Another study found cancer, cognitive impairment, cardiovascular, respiratory and renal conditions were associated with 30-day mortality. The author also believed liver disease would have likely been a significant risk factor, if not for low statistical power[70]. Charlson comorbidity index is used to determine a score indicating the risk of death according to the presence of certain comorbidities. The higher the Charlson comorbidity score, the higher risk of mortality for patients with CDI[12,68,71,72]. Comorbidities risk for death has been reported to be modified by age[70]. Other suggested predictors of mortality include hypo-albuminemia, leukocytosis, high serum creatinine, albumin, or urea, ribotype 027 strain, long prior hospitalizations, being admitted from another hospital, and glucocorticoid use[12,59,71,73].

Majority of studies investigating risk factors for CDI mortality focus on comparing those with CDI who die and do not die[11,67,70,73,74]. However, there are few studies who compare mortality amongst those with and without CDI[75–78]. Hensgens et al. reported patients with CDI had a 2.5-fold increase in 30-day mortality compared to patients without CDI even when adjusted for age, sex, and underlying disease[77]. Stewart et al. found slight increase in death for females and those with congestive heart failure, coagulopathy, and liver disease. Surprisingly, they also reported lower risk of death for those with chronic renal disease and diabetes[75].

Although many studies have looked at comorbidities and risk factors associated with mortality amongst those with CDI, regional variations have been shown[75] and Alberta's population has yet been investigated. The authors suggested regional

differences in CDI mortality could be due to regional variations in distribution of *C. difficile* strains, antibiotic stewardship, or patient care[75].

3.7.2 Clostridium difficile Infection Death Attribution

Reviewing the literature on attributing death due to CDI resulted in many papers concerned about the ability to do so[67,79–81]. Individuals who die and have CDI usually are the elderly with multiple comorbidities[67,79,80]. These comorbidities may have contributed to death; thus, make it difficult to determine CDI's role in that death[21]. It has been proposed 30-day all-cause mortality is a suitable measure for CDI attributable death[10]. Furthermore, experts have suggested that until there are improved protocols that prevent reviewer subjectivity, crude mortality should be reported[81]. These experts believe uniform standards must be applied if results are to be compared. Additionally, experts have suggested the use of comorbidity scores when considering CDI's contribution to death[80].

Dr. Mark Miller and CNISP developed the DARPIC algorithm to help guide physicians and ICPs in determining CDI's involvement in patients' deaths[32]. This algorithm is to be used to ascertain relatedness of death to CDI, when death occurs within 30 days of CDI diagnosis. The DARPIC algorithm has been widely used even though it ability to ascertain CDI's relation to death has not been investigated. There are no published papers in regards to the DARPIC algorithm accuracy. The DARPIC algorithm appears to be the only guideline that tries to standardize the method in attributing CDI to death.

3.8 Summary

In summary, CDI causes significant morbidity and mortality[1,3]. Hospitalized patients commonly have risk factors for CDI; therefore, not surprisingly historically CDI was mainly a nosocomial infection[3,5]. However, over the last 15 years incidence of CDI in continuing care and in the community has increased[5]. Studies of community CDI are not recent and in Alberta incidence of CDI is only investigated in acute care hospitals and in continuing care facilities. This study investigated CDI in three populations (hospital, continuing care, and community) using a population view of identifying incident CDI. A comprehensive understanding of CDI in a population requires investigation into all these populations.

Positive *C. difficile* laboratory results have been used as a proxy for CDI even though the symptom component of CDI is not evaluated. A prior study in Alberta found positive laboratory results to be a reasonable proxy for CDI[35]. Even though colonization of CDI can occur and has been reported between 20 and 50% in hospitalized patients and continuing care residents[2,52], Scheurer et al. reported 14% of *C. difficile* toxin positive results positive (according to cytotoxic assay) occurred in asymptomatic patients[36]. For this study, positive *C. difficile* laboratory results were used to identify CDI as it was a feasible method and determining symptoms would have been expensive and labour intensive as it would have required chart reviews[33]. High incidence of colonization is found in pediatric populations in which asymptomatic children could have a positive *C. difficile* laboratory result[29]. Those under 18 years of age were excluded from this study.

Risk factors for mortality amongst CDI patients have been investigated[11]. Risk factors include increasing age, antibiotic use, and comorbidities such as cancer, renal and liver disease[12,68,70,80]. Although this has been investigated it has been proposed regional

variations could exist and this has not been investigated in the Alberta hospital population. Commonly 30-day mortality is used when investigating risk factors for mortality[10,12,77]. Additionally, majority of studies investigating risk factors for CDI mortality focus on mortality amongst those with CDI. A potential reason is this study design identifies those with CDI who are at risk of dying, and can have implications on an individual's clinical management[13]. Attributing CDI to a patient's death is difficult as these patients are usually very ill. The DARPIC algorithm tries to aid and standardize CDI's attribution to death; however, it appears this algorithm has not been externally compared to IPC physicians with expertise in CDI.

Chapter Four: Methodology

4.1 Introduction

The methodology chapter includes study population, study design, data sources, operational definitions, study procedure, data analysis, and ethical considerations.

Chapter's Commonly Used Acronyms

- ACCIS: Alberta Continuing Care Information System
- AHS: Alberta Health Services
- ATC: Anatomical Therapeutic Chemical
- CCI-CDI: continuing care identified primary CDI case
- CDI: *Clostridium difficile* infection
- CI-CDI: community identified primary CDI case
- DAD: Discharge Abstract Database
- DARPIC: Death Attribution Rules for Patient Infected by *C. difficile*
- EIA: Enzyme Immunoassay
- HI-CDI: hospital identified primary CDI case
- HI/RM: Health Information/Records Management
- ICD-10-CA: International Classification of Diseases, 10th revision, Canada
- IPC: Infection Prevention & Control
- LPED: Laboratory Process Excellence Department
- MRN: Medical Requisition Number
- PCR: Polymerase Chain Reaction
- PHN: Personal Health Number
- PIN: Pharmaceutical Information Network
- SCM: Sunrise Clinical Manager
- ULI: Unique Lifetime Identifier

4.2 Study Population

The study population included individuals 18 years of age and older who had a positive *C. difficile* laboratory result test in Alberta between April 1, 2011 and March 31, 2014. Individuals under 18 years of age were excluded as the pediatric population is known to have high *C. difficile* colonization rates. This is particularly important as in this study a positive *C. difficile* laboratory result was used to determine CDI[29,31,82].

4.3 Study Design

Multiple quantitative research designs were required to address the research objectives.

Research objective 1: Determine the overall incidence of CDI in Alberta in the adult population.

To address research objective 1, a retrospective cohort study was used. Laboratory data alone were used to determine overall CDI incidence. Individuals 18 years of age and older who had a positive *C. difficile* laboratory result between April 1, 2011 and March 31, 2014 were included in the study as having CDI. An individual could have had more than one incident (primary) CDI case.

Research objective 2: Investigate comorbidities and/or variables associated with mortality amongst hospitalized CDI patients.

To address research objective 2, a retrospective cohort study was used. The study population was hospital identified primary CDI cases in Alberta from April 1, 2011 to

March 31, 2014. At 30 day post *C. difficile* collect date, CDI non-deaths and CDI deaths were analyzed.

Research objective 3: Inter-rater reliability between the DARPIC algorithm and expert reviewers for CDI death attribution.

A cross-sectional research design was used to assess inter-rater reliability. The study population consisted of those identified by IPC Surveillance between April 1, 2011 to March 31, 2014 who had CDI in a Calgary hospital and died within 30 days of diagnosis while in hospital. Student and experts review results were compared.

4.4 Data Sources

4.4.1 Administrative Data Sources

Four entities governed the eight data sources used for this study. The four entities were AHS IPC Surveillance, AHS Analytics, Alberta Health, and Health Information Management. Appendix A contains data variables for each data source.

AHS IPC Surveillance:

ProvSurv was used to identify the Calgary CDI deaths used for research objective 3. ProvSurv is a web-based surveillance system used by AHS IPC Surveillance. IPC Surveillance has mandatory surveillance of inpatient *C. difficile* cases meeting CDI case definition. These records are either classified as Primary or For Information. Primary records were defined as new CDI episodes occurring more than 8 weeks from a previous primary with symptom resolution in between. These primary records required mandatory 30-day adverse outcome follow-up, which included death.

Laboratory data were used to identify all positive *C. difficile* laboratory results tested in Alberta. These data were originally obtained from AHS Laboratory Process Excellence Department (LPED), but access for this study was requested through IPC Surveillance as they were the custodians of the dataset. Although consent was only required from IPC Surveillance, LPED was advised this study would use their original data. Four information systems contained the microbiology laboratory results: Cohort, Meditech, Millennium, and Sunquest.

AHS Analytics:

Discharge Abstract Database (DAD) was used to identify positive *C. difficile* laboratory results occurring in Alberta acute care hospitals. DAD captures patient information including demographics, administrative, and clinical information upon hospital discharge. Clinical information includes but not limited to diagnosis (ICD-10-CA) and procedure (Canadian Classification of Health Interventions, CCI) codes. Upon discharge from hospital, medical coders translate information from patients' medical records into the numerous data elements of DAD.

Alberta Health:

Pharmaceutical Information Network (PIN) was used to determine antibiotics dispensed in the community in the 90-days prior to positive *C. difficile* laboratory result. PIN is an application through Alberta NetCare Electronic Health Record that provides information on patient prescriptions dispensed in the Alberta community.

Vital statistics was used to identify individuals in the study population who died. Vital statistics are records that contain birth, marriage, and death certificates. In Alberta it is the responsibility of the spouse, next of kin, or person who has information regarding the deceased's death to complete a Registration of Death form. This form is used by the physician or medical examiner to produce the death certificate[14].

Alberta Continuing Care Information System (ACCIS) was used to identify positive *C. difficile* laboratory results occurring in Alberta continuing care facilities. This database provides information on continuing care interaction in Alberta including admit dates, discharge dates, and continuing care facilities.

Provincial Client Registry was used to determine Zone of community positive *C. difficile* laboratory results via postal code. The registry contains healthcare encounters such as hospitalizations, medical clinic visits, etc. At each healthcare encounter various demographic information are collected including postal code.

Health Information/Records Management (HI/RM):

Sunrise Clinical Manager (SCM) and **hospital medical charts** were reviewed for patients identified from ProvSurv as Calgary CDI deaths. SCM is an electronic patient medical record that is used in the Calgary Zone for patient management. It includes medical and nursing orders, medication administration records, clinical documentation, diagnostic imaging, and laboratory results. Hospital medical charts are paper-based and include similar information recorded on SCM, but also contain multidisciplinary progress reports (i.e. notes written by the patient care team) as well as consultation reports. Since

the implementation of SCM, Calgary Zone has a hybrid state of health information (i.e. electronic and paper format).

4.4.2 Denominator Data Sources

Three data sources provided the appropriate denominator for calculating incidence.

AHS Analytics

Alberta resident-days for 2011-12, 2012-13, and 2013-14 fiscal years were required for calculating continuing care CDI incidence. These were calculated from length of stay (LOS) of residents identified in the ACCIS database. Resident-days for only those 18 years and older (i.e. at each fiscal quarter) were included and were stratified by gender.

Number of Alberta hospital admissions for 2011-12, 2012-13, and 2013-14 fiscal years were required for calculating hospital identified CDI incidence. These were obtained from the Admission, Discharge, Transfer (ADT) database and contained all admissions.

Alberta Health:

Population-based denominator data were extracted from the Alberta Health, Surveillance & Assessment Branch-Adjusted Population Estimates[83]. Mid-year (June 30th) estimates are derived from the Alberta Health Care Insurance Plan (AHCIP) Population Registry. This registry excludes Armed Forces, RCMP, inmates in federal penitentiaries, or those who have opted out of coverage. However, as of April 1, 2013 RCMP began to be covered under AHCIP. Population estimates for only those 18 years and older were included and were stratified by gender.

4.5 Operational Definitions

- **Positive *C. difficile* laboratory result**: Positive EIA toxin assay and/or *C. difficile* PCR.
- ***C. difficile* infection (CDI)**: Positive *C. difficile* laboratory result.
    - Although CDI diagnosis requires both a positive laboratory result and the presence of symptoms of the disease, for this study a laboratory result alone was used to indicate CDI.
- **Time of CDI**: Positive *C. difficile* laboratory specimen collect date.
- **Primary CDI case**: New CDI or repeat CDI that was at least 8 weeks from a previous primary CDI case.
- **Hospital identified (HI) primary CDI case (HI-CDI)**: Primary CDI case that was collected during an acute care hospital admission.
- **CC-identified (CCI) primary CDI case (CCI-CDI)**: Primary CDI case that was collected during a continuing care admission.
- **Community identified (CI) primary CDI case (CI-CDI)**: Primary CDI case that was not collected during an acute care hospitalization or while in continuing care.
- **CDI incidence**: Number of primary (incident) CDI cases during a specified time divided by the population value at risk (denominator).
- **CDI death**: All deaths of individuals with HI-CDI that occurred within 30 days from time of CDI regardless of cause of death.
- **CDI non-death**: Individuals with HI-CDI that did not die within 30 days from time of CDI.
- **CDI-related death**: CDI either was directly related or contributed to death.

    - **Directly related**: CDI was the only condition that would have caused death.
    - **Contributed**: CDI contributed to death but was not the primary cause.
- **CDI-unrelated death**: CDI did not directly cause or contribute to death.
- **Unable to determine** (regarding CDI mortality): CDI cannot be attributed as related or unrelated to death due to lack of information and/or CDI contribution to death could not be determined because death was imminent.
- **Age**: Individual's exact age, in years, calculated as the difference between the time of CDI and date of birth. For research objective 2 regression analysis, age was centred at median age (73.0 years).
- **Gender**: Dichotomized into either male or female (synonymous with sex).
- **Zone**: Classified according to the five geographic Zones of Alberta (Appendix B). For HI-CDI and CCI-CDI the acute care and continuing facility name determined the Zone. For CI-CDI, the individual's postal code provided at the healthcare encounter closest to the time of CDI provided the Zone.
- **Recurrence**: More than one primary CDI cases. Reported as yes or no.
- **Antibiotic exposure**: Antibiotic dispensed in the community in the 90 days prior to time of CDI. Reported as yes or no.
- **Continuing care**: For research objective 2, defined as being a continuing care resident at the time of HI-CDI.
- **Total comorbidity count**: The total Charlson comorbidity count, identified for individuals from the individuals' last HI-CDI hospitalization. Although a count this variable was treated as continuous.

4.6 Study Procedure

4.6.1 Research Objective 1 & 2

4.6.1.1 Data Acquisition and Cleaning

As this study coincided with several IPC Surveillance quality improvement projects that were similar, the data required from LPED, ACCIS, vital statistics, PIN, and DAD were requested by IPC Surveillance. IPC Surveillance requested, from the LPED, all positive *C. difficile* laboratory results tested in Alberta laboratories between April 1, 2011 and March 31, 2015. Once this data extraction was complete, IPC Surveillance became the custodians of the dataset. The laboratory data were the basis of the study population and the data were "cleaned" prior to additional data requests. This included removing tests that were indeterminate with EIA and negative with PCR or that were inconclusive. Also included updating missing identifiers (i.e. PHN/ULI), removing duplicates records, and records with collect dates prior to April 1, 2011. The laboratory data were considered unique at PHN/ULI, collect date, and accession number. The "cleaned" laboratory data were securely provided to Alberta Health and AHS Analytics for the additional data requests. Using PHN/ULI and date of birth from the laboratory data, the data were matched to PIN, ACCIS, vital statistics, and DAD data.

From PIN, antibiotics dispensed in the community 90 days prior to *C. difficile* collect date were identified and extracted. For ACCIS, individuals with continuing care admissions were identified as well as all their admits and discharges. From vital statistics, for those who died death dates were extracted. For DAD, acute care admissions that the *C. difficile* collect date occurred during or one-day after were extracted. Admissions that occurred one-day after *C. difficile* collect dates were included as these *C. difficile* tests were likely collected in the emergency department prior to hospital admission; thus, were

considered hospital identified. After the data requests from Alberta Health and AHS Analytics were completed, permission to use these data for this study was requested. Permission was either through consent or a research agreement. Once permitted to use the data, the data were prepared for this study. Positives occurring after the study period (i.e. after March 31, 2014) were removed as well as positives occurring in individuals under the age of 18 years.

An additional data request for research objective 1 involved matching cases occurring in the community to Alberta Health's Provincial Client Registry for postal code data. Postal codes from the healthcare encounter closest to the *C. difficile* collect date were used. These postal codes were linked to the Alberta Health postal code translation file to determine Zone. Postal code translation file is a digital file that links the six character postal code and Statistics Canada standard geographical areas. Therefore, the individuals' residence postal code was used to indicate the Zone of CI-CDI.

All data were provided in formats supported by Microsoft Excel (2010).

4.6.1.2 Data Linkages and Coding

Data linkages and/or coding were performed in Microsoft Excel (2010), Statistical Package for the Social Sciences version 19 (IBM SPSS Statistics, Armonk, NY), and Stata version 10 (StataCorp, College Station, TX). Figure 1 is a flowchart that illustrates the extracts and matching for research objective 1 and 2. From the "clean" laboratory data, primary CDI cases were identified. These included the first CDI case for an individual followed by any CDI cases occurring 56 days (i.e. 8 weeks) from the previous primary CDI case. Recurrent primary CDI cases were coded. These primary CDI cases were linked using PHN/ULI, collect date, and accession number to the DAD data extract

to identify HI-primary CDI cases. For those HI-primary CDI cases that occurred upon transfer, the previous acute care facility was assigned the case. Those not identified as occurring in the hospital were then linked to the ACCIS data extract using PHN/ULI. For those individuals identified as continuing care residents, the time of CDI was used to determine if the CDI occurred between a continuing care admit and discharge date. Additionally, the continuing care facility where the CDI occurred was recorded. If the CCI-CDI case occurred on facility transfer, the previous continuing care facility was assigned the case. For those not discharged at the time the ACCIS data were extracted, the date of extract was used as a proxy for discharge date.

The order of linkage (i.e. DAD followed by ACCIS) was important as a primary CDI case could have been identified as occurring during a continuing care admission but may have actually been a hospital identified case. Continuing care facilities hold residents beds while the individuals are hospitalized; therefore, hospital admission at time of CDI needs to be ruled out first. Primary CDI cases not identified in either the hospital or continuing care were by default classified as community identified cases. This process identified the three populations for research objective 1.

All primary CDI cases were linked to PIN and vital statistics datasets using PHN/ULI. PIN duplicates (i.e. same PHN/ULI, ATC code, and antibiotic dispense date) were removed. At this point all data linkages were complete; hence, the personal identifiers were removed and replaced with unique identifiers. By taking the difference between the time of CDI and antibiotic dispense date, the antibiotics were checked to ensure only those antibiotics dispensed in the 90 days prior to the time of CDI were included. Using ATC Code translation[84], the antibiotics were described at ATC 4th level and similar antibiotics were grouped (Appendix C).

For research objective 2, the last HI-CDI case was selected as an individual could have had more than one HI-CDI case. Comorbidities were coded based on ICD-10-CA codes in DxCodes1 to 25 fields. Charlson comorbidity index, using the method described by Quan et al.[85], was used to classify the comorbidities. A hierarchical approach for Charlson comorbidities was used, meaning if an individual had ICD-10-CA codes for both diabetes uncomplicated and complicated only diabetes complicated was recorded. Total Charlson comorbidity count was calculated for each case. For those who died, the time to death was calculated by taking the difference between death date and time of CDI. Deaths that occurred within 30 days of time of CDI were coded as CDI deaths. Those who died not die within 30 days were coded as CDI non-deaths. Those who resided in continuing care at the time of their HI-CDI were coded as a continuing care resident.

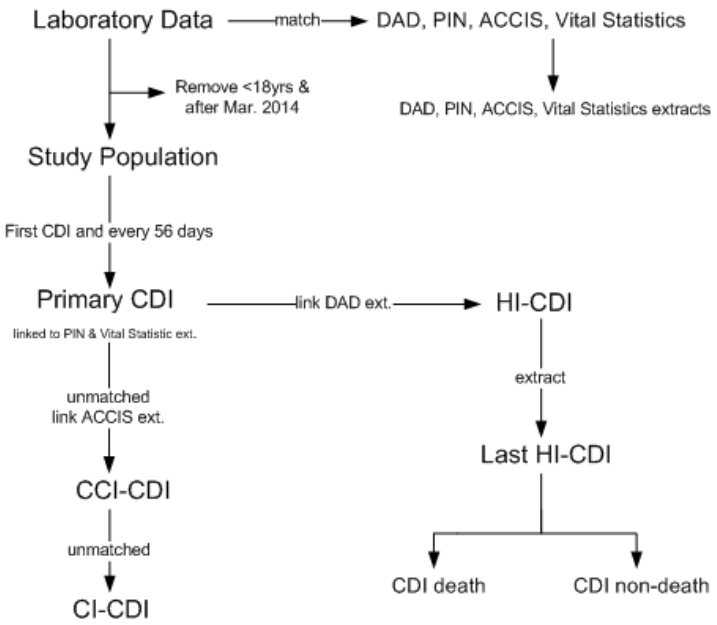

Figure 1. Flowchart of data linkages and coding.

Note: A visual representation of the information written in section 4.6.1.1 and 4.6.1.2. ext; extract. Figure generated using Microsoft Visio (2010).

4.6.2 Research Objective 3

4.6.2.1 Data Acquisition and Cleaning

Primary CDI cases occurring between April 1, 2011 and March 31, 2014 in the four adult Calgary hospitals (Foothills Medical Centre, Rockyview General Hospital, Peter Lougheed Centre, and South Health Campus) were requested from IPC Surveillance. Only patients who died within 30 days from time of CDI were of interest. Before the data were provided for this study, these deaths were reviewed to ensure the death occurred in hospital and at the hospital indicated in the data. Those that did not meet the criteria were removed. Each patient was assigned a unique identifier. PHN/ULI were used to access the patients' electronic medical record on SCM. From SCM, medical requisition number (MRN) was recorded as HI/RM requests medical charts using MRN and not PHN/ULI. Only the admission in which death occurred was requested and reviewed.

4.6.2.2 Data Collection and Review

All chart reviews were completed using the standardized collection form (Appendix D). The data collection form was derived from "Tool for Sharing Information with IPC Physicians" created by an Alberta IPC physician. Additional data fields were added to the data collection form for this study under the direction of the expert reviewers (i.e. IPC physicians) apart of the death attribution review.

First, at a secure AHS computer desk SCM was reviewed. After completing the required training, viewing access of SCM was granted. Any information indicated on the data collection form and available in SCM was collected. Second, using MRN, date of birth, and admit date, the patient's medical chart for the admit in which death occurred was requested from the HI/RM department of the facility where death occurred. The paper-based medical charts were reviewed in the facilities secure HI/RM department. Lists of unique identifiers with personal identifiers were used to match the data collection forms already underway with the correct medical chart.

A single student reviewer completed chart reviews between May and August 2016. A copy of the data collection forms were provided to each expert reviewer for their own reviews.

4.6.2.3 Death Attribution

The information collected on the data collection form were used to determine CDI's contribution to death. The deaths were classified as CDI-related (directly related or contributed), CDI-unrelated, or unable to determine. The student reviewer strictly used the DARPIC algorithm to assign CDI's contribution to death (Appendix E)[32]. The expert reviewers used their clinical expertise to assign CDI's contribution to death. The expert

reviewers' definition of unable to determine included both deaths with a lack of information as well as deaths that were imminent; therefore, death attribution could not be determined. While for the DARPIC algorithm, unable to determine is only assigned when death was imminent and there is no category for lack of information.

4.6.2.4 Expert Reviewers

Between the two expert reviewers there was a single death decision for each case. For analysis the student reviewer's death decisions were compared to the reconciled expert reviewers' death decisions. Firstly, the two expert reviewers reviewed all data collection forms independently. After the first review, the student reviewer complied the two expert reviewers' results and identified discordant death decisions. The expert reviewers were provided with each other's death decisions and they re-reviewed their decisions again independently. Any remaining discordant death decisions were reviewed as a group. The group included the two original expert reviewers, the student reviewer, and a third expert reviewer who was a fellow IPC physician. The student reviewer did not provide any information regarding their own death decisions. At this meeting any remaining discordant death decisions were reconciled.

4.7 Data Analysis

4.7.1 Descriptive and Comparative Statistics

Categorical variables were expressed as counts and proportions and continuous variables were expressed as means and medians. Comparisons of groups were conducted using a two sample test of proportion for categorical variables (performed in Stata version 10) and Student t test or Mann-Whitney U-test for continuous variables (performed in

SPSS version 19). A two-sided p-value of less than 0.05 was considered statistically significant.

4.7.2 Incidence

Denominator

The denominator acquired for the number of hospital admissions included those under 18 years of age. Age was not available in the ADT dataset; therefore, the proportion of patients discharged who were 18 years and older was used to estimate the number of hospital admissions in those 18 years and older, in order to calculate the HI-CDI incidence. Based on 2013-14 discharges (sourced from DAD), 79% of discharges were those 18 years and older. Additionally, 60% of these discharges were female, which was used to estimate the stratified gender denominator.

Example Calculation:

Original Denominator:

South 2013-14 hospital admissions = 31,066

Estimated Denominator:

18+ South 2013-14 hospital admissions = 31,066 x 0.79

= 24,594

----END OF EXAMPLE----

Incidence

Annual incidence for total, HI-, CCI-, and CI-CDI was calculated for each fiscal year (2011-12, 2012-13, and 2013-14) using Microsoft Excel (2010). Incidence for HI-, CCI-, and CI-CDI was based per 1,000 admissions, 10,000 resident-days, and 10,000 population, respectively. Gender and Zone specific incidence were also reported.

4.7.3 Univariate Analysis

For research objective 2, univariate analyses were used to measure the association between death and demographic and clinical characteristics (i.e covariates). Odds ratios, 95% confidence intervals, and p-values were reported. All odds ratios were estimates; however, for readability the word estimated was omitted. A two-sided p-value of less than 0.05 was considered statistically significant. These analyses were performed in Stata version 10.

4.7.4 Regression Analysis

For research objective 2, multivariate logistic regression analyses were performed using Stata version 10. The predictor variables of main interest were the 17 Charlson comorbidities. The characteristics (i.e. covariates) were assessed as possible confounders or effect modifiers. Odds ratios, 95% confidence intervals, and p-values were reported. All odds ratios were estimates; however, for readability the word estimated was omitted. A two-sided p-value of less than 0.05 was considered statistically significant.

4.7.4.1 Variables for Logistic Regression

Dependent Variable

- CDI death – (Death30)

Independent Variables (or predictor variables)

Main variable of interest (or exposure):

- 17 Charlson comorbidities
    - AIDS/HIV – (HIV)
    - Cerebrovascular Disease – (CER)
    - Chronic Pulmonary Disease – (CPD)
    - Congestive Heart Failure – (CHF)
    - Dementia – (DEM)
    - Diabetes Complicated – (DCC)
    - Diabetes Uncomplicated – (DUN)
    - Malignancy – (CAN)
    - Metastatic Solid Tumour – (MTC)
    - Mild Liver Disease – (MLD)
    - Moderate/severe Liver Disease – (SLD)
    - Myocardial Infarction – (MI)
    - Paraplegia or Hemiplegia – (PH)
    - Peptic Ulcer Disease – (PEP)
    - Peripheral Vascular Disease – (PVD)
    - Renal Disease – (RND)
    - Rheumatic Disease – (RHE)

Covariates:

- Age (centred at median age) – (AgeCen)
- Gender – (G)
- Antibiotic exposure – (Anti)
- Continuing care – (CC)
- Recurrence – (Recur)
- Total comorbidity count – (TCC)

4.7.4.2 Logistic Regression Assumptions

Five key assumptions of logistic regression are:

1. The dependent variable (i.e. outcome) is dichotomous and mutually exclusive and exhaustive.
2. There are one or more independent variables (i.e. predictors) that are either continuous or categorical.
3. The observations are independent and there is no relationship between observations.
4. There is no collinearity amongst the predictor variables.
5. There is a linear relationship between continuous predictor variables and the log odds of the outcome.

4.7.4.3 Checking Logistic Regression Assumptions

Study design or statistical tests determined if the assumptions of logistic regression were violated. The first assumption was met as the outcome variable was mortality and was dichotomous and mutually exclusive and exhaustive, meaning an observation could

only be in one of the outcome categories (i.e. death or no death) and an observation had to be in one of the outcome categories. The second assumption was met as the logistic regression model included one or more predictor variable(s) that were either continuous or categorical. The third assumption was met as the observations were independent of each other and were not matched nor pre and post test.

The two remaining assumptions were checked using statistical tests. Collinearity of predictor variables was assessed by creating a correlation matrix with the calculation of Pearson's correlation coefficients for pairs of variables. Correlation measures the strength and direction of a linear relationship between two variables. Multicollinearity of predictor variables was also assessed by calculating variance inflation factor. Multicollinearity is similar to collinearity but considers multiple variables and not only two. Linearity was assessed by plotting the continuous predictor variables versus log odds of the outcome using a lowess smoothing curve. These curves were also plotted for subgroups (i.e. each comorbidity).

Collinearity, multicollinearity, and linearity assumptions were tested using analyses performed using Stata version 10. Collinearity and multicollinearity were assessed pre-estimate (i.e. prior to logistic regression). Linearity was assessed post-estimate for age and total comorbidity count as these two were the only continuous predictor variables. The assessment of collinearity, multicollinearity, and linearity is reported in Appendix F.

4.7.4.4 Model Construction

Each of the 17 Charlson comorbidities were considered the "exposure" and individual logistic regression models for each of the comorbidities were created. The final logistic regression model for each comorbidity was created by backwards elimination.

With backwards elimination the first model is the full model, meaning all covariates and interaction terms are included and the model is reduced by removing non-significant interaction terms and covariates that are not confounders. Interaction terms consisted of each covariate interacting (i.e. multiplied) with the comorbidity being assessed as the exposure.

To evaluate if interaction terms could be removed, a likelihood ratio test was performed. Likelihood ratio tests are used to compare two nested models, one complex model and a simpler nested model. The likelihood ratio test results in a p-value from a chi-square distribution. The null hypothesis for this statistical test is the goodness of fit does not differ between the two models. A significant p-value indicates the null hypothesis is to be rejected and the nested model does not reflect the findings of the more complex model. For this study, a significant p-value from the likelihood ratio test would have indicated at least one of the interaction terms were significant; thus, an effect modifier.

There is no statistical test for confounding. To evaluate for confounding, the change in the beta coefficient(s) in the logistic regression model was used. If no covariates were modifiers (i.e. no significant interaction terms), the beta coefficient for the comorbidity was compared when each covariate was included and excluded. Marked changes, deemed of important value, of the beta coefficient when the covariate was included or excluded suggested confounding by the covariate. If there was modification by a covariate, the change in the beta coefficient for the interaction term was also considered when checking for confounding.

Example: Backwards Elimination for Malignancy (CAN):

Full Model (m1):

log(odds of death) $=\beta_0+\beta_1$CAN$+\beta_2$AgeCen$+\beta_3$TCC$+\beta_4$G$+\beta_5$Anti$+\beta_6$CC $+\beta_7$Recur

$+\beta_8$AgeCen*CAN$+\beta_9$TCC*CAN$+\beta_{10}$G*CAN$+\beta_{11}$Anti*CAN$+\beta_{12}$Recur*CAN

$+\beta_{13}$CC*CAN

Death30	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
CAN	.2898091	.3476288	0.83	0.404	-.3915308	.971149
AgeCen	.0362885	.0031997	11.34	0.000	.0300172	.0425599
TCC	.377428	.0363146	10.39	0.000	.3062527	.4486032
G	.3961327	.0852724	4.65	0.000	.2290019	.5632634
Anti	.2927621	.0865096	3.38	0.001	.1232064	.4623177
CC	.6626151	.1627255	4.07	0.000	.343679	.9815512
Recur	-.1597014	.1341732	-1.19	0.234	-.4226761	.1032733
AgeCen*CAN	.002053	.010037	0.20	0.838	-.0176191	.0217251
TCC*CAN	-.2149084	.1241065	-1.73	0.083	-.4581527	.0283359
G*CAN	-.262963	.2659952	-0.99	0.323	-.784304	.2583779
Anti*CAN	.0860704	.2663774	0.32	0.747	-.4360197	.6081604
Recur*CAN	-.253411	.4872262	-0.52	0.603	-1.208357	.7015348
CC*CAN	.9869592	.704075	1.40	0.161	-.3930025	2.366921
_cons	-2.60948	.0927673	-28.13	0.000	-2.791301	-2.42766

Figure 2. Stata output for full logistic regression model (m1).

Note: Coef.: β coefficient; Std. Err.: standard error; z: z-score; P>|z|: p-value; 95% Conf. Interval: 95% confidence interval.

Nested Model (m2):

log(odds of death) $=\beta_0+\beta_1$CAN$+\beta_2$AgeCen$+\beta_3$TCC$+\beta_4$G$+\beta_5$Anti$+\beta_6$CC$+\beta_7$Recur

Death30	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
CAN	-.2564997	.1324612	-1.94	0.053	-.5161189	.0031196
AgeCen	.036099	.0030161	11.97	0.000	.0301876	.0420104
TCC	.3606416	.0345544	10.44	0.000	.2929162	.4283671
G	.3746263	.0807295	4.64	0.000	.2163995	.5328532
Anti	.3016635	.081666	3.69	0.000	.1416012	.4617259
CC	.7109802	.1570907	4.53	0.000	.403088	1.018872
Recur	-.1807784	.1286997	-1.40	0.160	-.4330251	.0714683
_cons	-2.576052	.08862	-29.07	0.000	-2.749744	-2.40236

Figure 3. Stata output for nested logistic regression model (m2).

Note: Coef.: β coefficient; Std. Err.: standard error; z: z-score; P>|z|: p-value; 95% Conf. Interval: 95% confidence interval.

Likelihood ratio test results

```
Likelihood-ratio test                                 LR chi2(6)  =      5.95

(Assumption: m2 nested in m1)                         Prob > chi2 =    0.4292
```

Figure 4. Stata output for Likelihood-ratio test.

CONCLUSION: Failed to reject the null hypothesis. The simpler model was nested in the full model. Therefore, no interaction between the covariates and malignancy.

Assessing for confounding

	Model	β_1
Model 2	log(odds of death) $=\beta_0+\beta_1$CAN$+\beta_2$AgeCen$+\beta_3$TCC$+\beta_4$G$+\beta_5$Anti$+\beta_6$CC$+\beta_7$Recur	-0.256
Model 3	log(odds of death) $=\beta_0+\beta_1$CAN$+\beta_2$AgeCen$+\beta_3$TCC$+\beta_4$G$+\beta_5$Anti$+\beta_6$CC	-0.252
Model 4	log(odds of death) $=\beta_0+\beta_1$CAN$+\beta_2$AgeCen$+\beta_3$TCC$+\beta_4$G$+\beta_5$Anti	-0.275
Model 5	log(odds of death) $=\beta_0+\beta_1$CAN$+\beta_2$AgeCen$+\beta_3$TCC$+\beta_4$G	-0.260
Model 6	log(odds of death) $=\beta_0+\beta_1$CAN$+\beta_2$AgeCen$+\beta_3$TCC	-0.222
Model 7	log(odds of death) $=\beta_0+\beta_1$CAN$+\beta_2$AgeCen	0.006
Model 8	log(odds of death) $=\beta_0+\beta_1$CAN$+\beta_3$TCC	-0.356

Figure 5. Comparing β_1 coefficients across 7 logistic regression models to assess for confounding.

CONCLUSION: With the removal of age or total comorbidity count the beta coefficient (β_1) associated with the exposure of interest (i.e. malignancy) changed considerably; therefore, age and total comorbidity count confounded the relationship between malignancy and death.

----END OF EXAMPLE----

Although 17 unique individual logistic regression models were created using backwards elimination, only one final model was used for each of the comorbidities. Meaning if majority of comorbidities were confounded by a particular covariate then all comorbidities were adjusted by that covariate. The purpose of adjusting all comorbidities the same was so the results of all comorbidities could be presented and discussed the same. The individual models created by backwards elimination for each comorbidity is reported in Appendix G.

Each comorbidities final model was adjusted for age (centred at median age) and total comorbidity count. Both of these covariates were identified as confounders for majority of the comorbidities, 13 of 17 confounded by age and 15 of 17 confounded by total comorbidity count.

4.7.4.5 Model Discrimination

A model's ability to discriminate can be assessed by the Receiver Operating Characteristic (ROC) curve which produces an area under the curve (AUC) that is a measure of fit for the model. AUC is a probability measure that indicates how well the model assigns a higher predicted probability to an observation with the outcome if a

randomly selected pair, one with and one without the outcome, is chosen[86]. AUC value of 0.5 indicates no discrimination ability and a value of 1.0 indicates perfect discrimination ability[87]. AUC is synonymous with C- statistic. A logistic regression model with an AUC of 0.7 has reasonable discrimination and a model with an AUC of 0.8 has strong discrimination[88].

4.7.4.6 Causality

To determine if the association between the predictor variables and outcome variable is causal, firstly random error, bias, and confounding should be ruled out as potential sources for the resulting statistical association. Secondly, Hills six postulates can be used to determine the likeliness of causality[24].

1. *Temporality*: The predictor variables (i.e. exposure) occur prior to outcome.
2. *Strong Association*: For example, higher odds ratios may indicate causality is more probable.
3. *Consistent Association*: Other studies corroborate the results.
4. *Dose-response relationship*: Increase in exposure results in a higher frequency of the outcome.
5. *Biological Plausibility*: Biologically the association is probable.
6. *Experimental Evidence*: Well-designed studies, such as clinical trials, have similar results.

4.7.5 Inter-rater Reliability

For research objective 3, the student reviewer's death decisions and reconciled expert reviewers death decisions were analyzed using a kappa statistic to assess for inter-

rater reliability. A kappa statistic compares the variation observed between raters (i.e. student reviewer versus expert reviewers) to variation that would be expected due to chance. Kappa statistics are measured on a scale from -1 to 1, where 1 is perfect agreement, 0 is poor agreement (expected value on chance alone), and negative values represent less than chance and indicate systematic disagreement[89]. Positive values above 0 indicate the raters observations agree more than chance alone. Table 2 provides interpretation of the kappa statistic values[90]. Firstly, a non-weighted kappa statistic was calculated using Stata version 10. Secondly, kappa statistics per death category were calculated also using Stata version 10. Individually each of the three categories were compared to the remaining categories combined.

Table 2. Interpretation of kappa statistic according to Landis and Koch (1977).

Kappa Statistic	Agreement
< 0.00	Poor
0.00 - 0.20	Slight
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Substantial
0.81 – 1.00	Almost Perfect

4.8 Ethical Considerations

Conjoint Health Research Ethics Board (CHREB) at the University of Calgary reviewed and provided ethics approval. From each data custodian, signatures approving this study were obtained.

Consent

As this study did not involve patient contact or intervention and used existing data (i.e. secondary data), there was minimal risk to the participants. A waiver of consent was approved based on the retrospective nature of the study, the great number of data records in the study (i.e. >10,000), and a portion of the individuals were deceased. Therefore, obtaining consent was impractical and not feasible.

The IPC Surveillance department directed and supervised the study as this study coincided with similar quality improvement projects and the department provided the data. SCM was requested for research purposes and training was completed prior to access.

Privacy Protection

Management, use, and protection of the data followed the Health Information Act and ethical guidelines. All identifiable electronic data were securely sent either via password-protected email or by accessing a restricted network drive. Identified electronic data were stored behind the AHS firewall as an encrypted file on a restricted network drive. Once all administrative data linkages were complete, as identifiers were required for data linkages, the identifiers were removed from the data and replaced with unique identifiers. A unique identifier provided anonymity.

As research objective 3 required chart review, identifiers had to be used to search for patients on SCM or when requesting and reviewing the paper-based medical chart. Unique identifiers were assigned to each patient and only that number was documented on the data collection form; thereby, separating the personal information from a personal identifier. The lists of unique identifiers with personal identifiers used to match data

collection forms and medical charts were shredded after completing the review of the listed charts.

All published data are presented in aggregate form. At this level, identification of an individual is not possible.

Chapter Five: Results

5.1 Introduction

This chapter will describe the result of data cleaning, descriptive statistics (proportion, means, medians), and when appropriate comparative statistics, univariate analysis, and regression analysis. Each research objective results will be reported in sections with similar flow.

5.2 Data Cleaning Results

The original laboratory data provided to IPC Surveillance had 24,680 records. Prior to data requests conducted by IPC Surveillance, 1,859 (7.5%) records were removed as the results were either inconclusive/negative, collected prior to April 1, 2011, missing a personal identifier, or were duplicates. Of 22,821 records, 5,969 (26.2%) records occurred after the study period and 1,215 (5.3%) occurred in individuals under 18 years of age; therefore, were removed for this study.

5.3 Research Objective 1

5.3.1 Descriptive Statistics

From April 1, 2011 to March 31, 2014, 12,226 primary *C. difficile* infection (CDI) cases were identified in Alberta. In Table 3, 2011-14 total CDI cases and the three populations are displayed; hospital identified (HI), continuing care identified (CCI), and community identified (CI). Between April 1, 2011 and March 31, 2014, there were 6,056 (49.5%) HI-CDI cases, 5,729 (46.9%) CI-CDI cases, and 441 (3.6%) CCI-CDI cases. Majority of the primary CDI cases occurred in females, which was particularly evident

with 62.7% (n=3,590) of CI-CDI cases identified in females. Of the three populations, CCI-CDI cases occurred in the very elderly (i.e. >80 years), while CI-CDI cases were markedly younger (i.e. low fifties). For each of the populations, no less than 30% of the cases had antibiotic exposure in the 90 days prior to developing CDI. For CI-CDI cases nearly 60% (n=3,301) had antibiotic exposure. Recurrent CDI cases were more likely to be identified in the CCI-CDI population with 32.9% (n=145) of the CCI-CDI cases being subsequent primaries. Thirty-day all-cause mortality for HI-, CCI-, and CI-CDI cases were 13.4%, 17.0%, and 1.3%, respectively.

Table 3. Characteristics of total, HI-, CCI-, and CI-CDI cases for the whole study period.

Characteristics	2011-14 CDI			
	Total n=12,226	**HI n=6,056**	**CCI n=441**	**CI n=5,729**
Gender				
Female n(%)	7,156 (58.5)	3,293 (54.4)	273 (61.9)	3,590 (62.7)
Age				
Mean (SD)	62.0 (20.4)	69.3 (17.6)	82.1 (12.0)	52.7 (19.5)
Median (IQR)	64.0 (31.0)	73.0 (24.0)	85.0 (14.0)	53.0 (31.0)
Antibiotic Exposure				
Yes n(%)	5,554 (45.4)	2,115 (34.9)	138 (31.3)	3,301 (57.6)
Recurrence				
Yes n(%)	1,518 (12.4)	708 (11.7)	145 (32.9)	665 (11.6)

Note. Column percentages. CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified; SD: standard deviation; IQR: interquartile range.

Of the 12,226 CDI cases, 1,518 cases were recurrent, meaning another CDI case was reported prior to that CDI case. Every 56 days an individual was eligible for another primary CDI case. Figure 6 is a frequency histogram of the days between recurrent cases. The mean and median days between recurrent cases were 148.9 and 90.0 days, respectively. Table 4 reports the counts and proportions for recurrences. Nearly 72%

(n=1,091) of the recurrent CDI cases occurred in the same fiscal year as another CDI case.

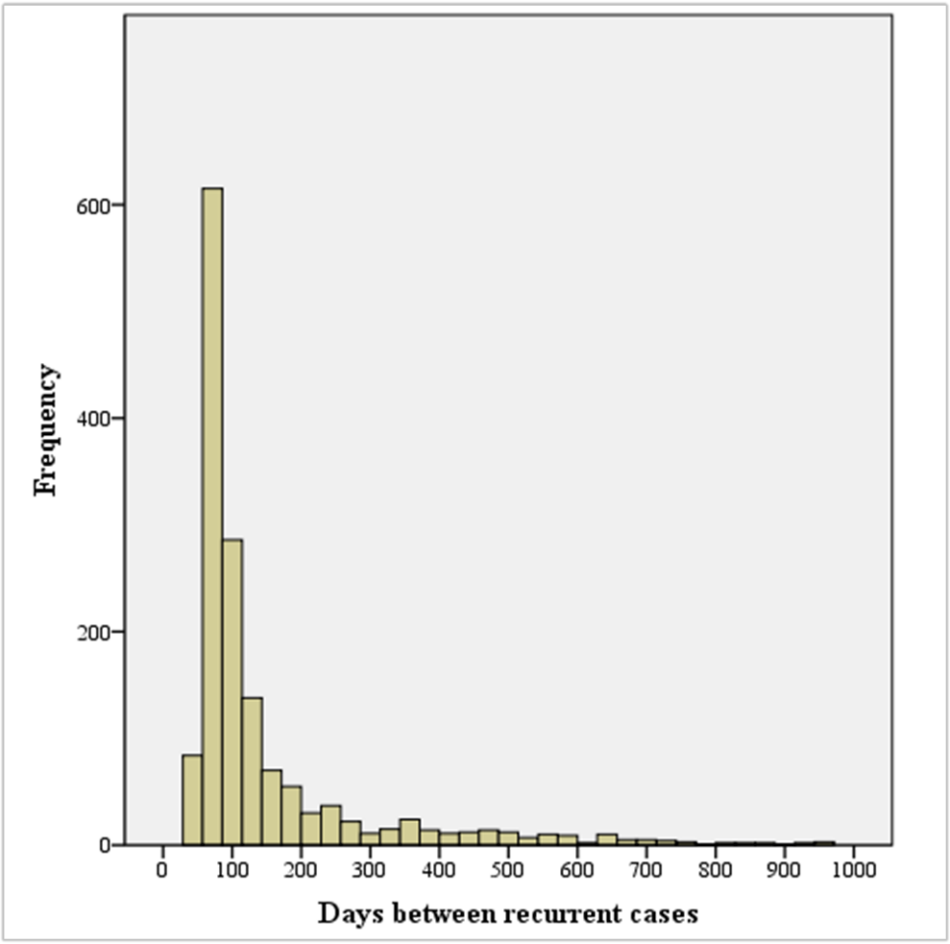

Figure 6. Frequency histogram of the days between recurrent cases for the whole study period.

Note: Figure generated using IBM SPSS Statistics version 19.

Table 4. Counts and proportions for the number of CDI recurrences for all recurrent cases and for the whole study period.

Number of recurrences	Count n(%)
1	1,200 (79.1)
2	231 (15.2)
3	55 (3.6)
4	19 (1.3)
5	7 (0.5)
6	4 (0.3)
7	1 (0.1)
8	1 (0.1)
Total	**1,518**

In Table 5, the total number of CDI cases identified between April 1, 2011 and March 31, 2014 by gender are displayed. Slight differences in age (mean and median) between males and females with CDI were observed. Compared to males, females with CCI-CDI cases were notably older and females with CI-CDI cases were slightly younger. Gender differences in antibiotic exposure in the 90 days prior to developing CDI was found, for all populations females had a larger proportion of antibiotic exposure. The percentage of antibiotic exposure for females was approximately eight percent higher than males for each population. Between genders, there were slight to no difference in recurrence.

Table 5. Characteristics of total, HI-, CCI-, and CI-CDI cases for the whole study period separated by gender.

Characteristics	Males 2011-14 CDI			
	Total n=5,070	**HI n=2,763**	**CCI n=168**	**CI n=2,139**
Age				
Mean (SD)	62.3 (19.2)	68.0 (17.0)	77.9 (12.6)	53.8 (18.9)
Median (IQR)	64.0 (28.0)	71.0 (23.0)	81.0 (15.0)	55.0 (30.0)
Antibiotic Exposure				
Yes n(%)	2,059 (40.6)	872 (31.6)	45 (26.8)	1142 (53.4)
Recurrence				
Yes n(%)	643 (12.7)	330 (11.9)	58 (34.5)	255 (11.9)
	Females 2011-14 CDI			
	Total n=7,156	**HI n=3,293**	**CCI n=273**	**CI n=3,590**
Age				
Mean (SD)	61.7 (21.3)	70.4 (18.0)	84.6 (10.8)	52.0 (19.8)
Median (IQR)	64.0 (34.0)	74.0 (24.0)	87.0 (12.0)	52.0 (32.0)
Antibiotic Exposure				
Yes n(%)	3495 (48.8)	1243 (37.7)	93 (34.1)	2159 (60.1)
Recurrence				
Yes n(%)	875 (12.2)	378 (11.5)	87 (31.9)	410 (11.4)

Note. Column percentages. CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified; SD: standard deviation; IQR: interquartile range.

The majority of CDI cases were identified in the Calgary (n=4,710) and Edmonton (n=4,551) Zone (Table 6). In the Edmonton Zone, 59.7% (n=2,717) of the CDI cases were identified in the hospital. Conversely, in the Calgary Zone, more CDI cases were identified in the community; 50.9% (n=2,399) cases were CI-CDI compared to 46.2% (n=2,175) of cases were HI-CDI. The North Zone had the lowest percentage of HI-CDI cases (30.5%; n=280) and the largest percentage of CI-CDI cases (66.2%; n=608). Overall, CDI cases were least likely to be identified in continuing care facilities for all zones with the lowest number of cases observed in the South Zone (2.7%; n=22) and the highest found in the Edmonton Zone (4.6%; n=208). Of the 5,729 CI-CDI cases identified, 66 (1.2%) were in individuals who resided outside of Alberta (OAB) or their

residence could not be determined as the PHN/ULI was incorrect (here on called unknown/OAB).

Table 6. Zone stratification of total, HI-, CCI-, and CI-CDI cases for the whole study period.

Zone	2011-14 CDI			
	Total n=12,226	**HI n=6,056**	**CCI n=441**	**CI n=5,663**
South	820	401 (48.9)	22 (2.7)	397 (48.4)
Calgary	4,710	2,175 (46.2)	136 (2.9)	2,399 (50.9)
Central	1,161	483 (41.6)	45 (3.9)	633 (54.5)
Edmonton	4,551	2,717 (59.7)	208 (4.6)	1,626 (35.7)
North	918	280 (30.5)	30 (3.3)	608 (66.2)

Note. Row percentages n(%).CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified. Sixty-six records of CI-CDI not reported as Zone could not be determined.

Table 7 reports Zone identified CDI cases for each population by gender. For all Zones, more females than males were identified with CDI, ranging from 57.1% (n=524) to 60.1% (n=2,832). Compared to females, for each Zone the proportion of HI-CDI cases identified in males were higher except in the Central Zone. With the exception of the Central Zone where the proportion of HI-CDI cases was higher in females than males, the remaining four Zones proportions of HI-CDI cases per gender were notably higher for males. Slight differences in gender was exhibited per Zone amongst cases of CCI-CDI. In the Edmonton and North Zone, the proportion of females identified with cases of CCI-CDI was higher, while the opposite was observed in the Central Zone. With the exception of the Central Zone, the proportion of CI-CDI cases identified in females was larger than males. In the North Zone, 70% (n=367) of CDI cases identified in females were CI-CDI.

Table 7. Zone stratification of total, HI-, CCI-, and CI-CDI cases for the whole study period separated by gender.

Zone	Males 2011-14 CDI			
	Total n=5,046	**HI n=2,763**	**CCI n=168**	**CI n=2,115**
South	341 (41.6)	182 (53.4)	9 (2.6)	150 (44.0)
Calgary	1,878 (39.9)	991 (52.8)	48 (2.6)	839 (44.7)
Central	479(41.3)	190 (39.7)	24 (5.0)	265 (55.3)
Edmonton	1,954 (42.9)	1258 (64.4)	76 (3.9)	620 (31.7)
North	394 (42.9)	142 (36.0)	11 (2.8)	241 (61.2)
	Females 2011-14 CDI			
	Total n=7,114	**HI n=3,293**	**CCI n=273**	**CI n=3,548**
South	479 (58.4)	219 (45.7)	13 (2.7)	247 (51.6)
Calgary	2,832 (60.1)	1184 (41.8)	88 (3.1)	1560 (55.1)
Central	682 (58.7)	293 (43.0)	21 (3.1)	368 (54.0)
Edmonton	2,597 (57.7)	1459 (56.2)	132 (5.1)	1006 (38.7)
North	524 (57.1)	138 (26.3)	19 (3.6)	367 (70.0)

Note. HI, CCI, and CI presented as row percentages n(%). Total CDI presented as proportion of Zone total (i.e. gender proportion per Zone). CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified. Sixty-six records of CI-CDI not reported as Zone could not be determined.

Table 8 displays the three populations separated by fiscal year. Thirty-eight percent (n=4,651) of the total CDI cases were identified in the 2013-14 fiscal year. The characteristics' proportions for the three populations remained similar over the three fiscal years. Overall, the characteristics of the three populations reported with the three years combined (Table 4) were similar to the three years reported separately (Table 8), indicating very little change in the populations characteristics over the three fiscal years. However, the proportion of recurrence did increase over the three fiscal years.

Table 8. Characteristics of total, HI-, CCI-, and CI-CDI cases for the whole study period stratified by fiscal year.

Characteristics	2011-12 CDI n=3,898			2012-13 CDI n=3,677			2013-14 CDI n=4,651		
	HI n=1,910	CCI n=139	CI n=1,849	HI n=1,875	CCI n=136	CI n=1,666	HI n=2,271	CCI n=166	CI n=2,214
Gender									
Female n(%)	1,071 (56.1)	88 (63.3)	1,139 (61.6)	1,006 (53.7)	82 (60.3)	1,062 (63.7)	1,216 (53.5)	103 (62.0)	1,389 (62.7)
Age									
Mean (SD)	70.2 (17.5)	81.9 (10.3)	51.6 (19.5)	69.2 (17.5)	82.4 (11.4)	53.0 (19.1)	68.6 (17.7)	81.9 (13.7)	53.2 (19.7)
Median (IQR)	74.0 (23.0)	84.0 (12.0)	52.0 (31.0)	73.0 (25.0)	85.0 (15.0)	53.0 (29.0)	71.0 (28.0)	85.0 (14.0)	54.0 (32.0)
Antibiotic Exposure									
Yes n(%)	685 (35.9)	37 (26.6)	1,071 (57.9)	661 (35.3)	49 (36.0)	993 (59.6)	769 (33.9)	52 (31.3)	1237 (55.9)
Recurrence									
Yes n(%)	171 (9.0)	38 (27.3)	144 (7.8)	216 (11.5)	43 (31.6)	202 (12.1)	321 (14.1)	64 (38.6)	319 (14.1)

Note. Column percentages. CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified; SD: standard deviation; IQR: interquartile range.

The three populations stratified by Zone and separated by fiscal year are presented in Table 9. Amongst the South Zone, the highest proportion of CDI cases varied between HI and CI. For Calgary, Central, and the North Zone, CI-CDI cases were identified the most for all three fiscal years. The highest proportions of HI-CDI cases were reported in the Edmonton Zone, ranging from 56.8% (n=1,079) in 2013-14 to 62.4% (n=806) in 2012-13. Additionally, the Edmonton Zone had the highest percentage of CCI-CDI cases compared to the other Zones. The Edmonton Zone had the highest percentage of HI- and CCI-CDI cases for all three fiscal years. The North Zone had the highest percentage of CI-CDI cases for all the years ranging from 65.0% (n=251) in 2013-14 to 68.3% (n=198) in 2011-12. Of CI-CDI cases, unknown/OAB cases were 1.7% (n=31) in 2011-12, 1.0% (n=16) in 2012-13, and 0.9% (n=19) in 2013-14.

Table 9. Zone stratification of total, HI-, CCI-, and CI-CDI cases for each fiscal year.

Zone	2011-12 CDI			2012-13 CDI			2013-14 CDI		
	HI n=1,910	**CCI n=139**	**CI n=1,818**	**HI n=1,875**	**CCI n=136**	**CI n=1,650**	**HI n=2,271**	**CCI n=166**	**CI n=2,195**
South	113 (46.7)	4 (1.7)	125 (51.7)	134 (52.1)	11 (4.3)	112 (43.6)	154 (48.0)	7 (2.2)	160 (49.8)
Calgary	742 (45.4)	49 (3.0)	843 (51.6)	717 (46.7)	41 (2.7)	777 (50.6)	716 (46.5)	46 (3.0)	779 (50.6)
Central	136 (39.8)	13 (3.8)	193 (56.4)	144 (42.9)	14 (4.2)	178 (53.0)	203 (42.0)	18 (3.7)	262 (54.2)
Edmonton	832 (61.1)	68 (5.0)	459 (33.8)	806 (62.4)	61 (4.7)	424 (32.8)	1,079 (56.8)	79 (4.2)	743 (39.1)
North	87 (30.0)	5 (1.7)	198 (68.3)	74 (30.6)	9 (3.7)	159 (65.7)	119 (30.8)	16 (4.1)	251 (65.0)

Note. Fiscal year row percentages n(%).CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified. Sixty-six records of CI-CDI not reported as Zone could not be determined.

The number of antibiotics dispensed in the community in the 90 days prior to CDI were reported and categorized into 14 groups based on similarities at ATC level 4 (Table 10). Table 10 displays the sum of antibiotics separated by population. A primary CDI case could have had more than one similar antibiotic dispensed in the community in the 90 days prior to the time of CDI; therefore, sum of antibiotics dispensed were reported. For HI-CDI cases there were 3,822 antibiotics dispensed to 2,115 cases (i.e. the number of HI-CDI cases that had antibiotic exposure). For CCI-CDI cases there were 286 antibiotics dispensed to 138 cases. For CI-CDI cases there were 5,581 antibiotics dispensed to 3,301 cases. For each of the populations, on average more than one antibiotic was dispensed to those with antibiotic exposure. Majority of the antibiotics used were clindamycin, cephalosporins, fluoroquinolones, and penicillins. However, clindamycin use was more prominent for cases of CI-CDI compared to the other populations. Of the antibiotics dispensed, 0.7% (n=72) and 1.4% (n=132) were metronidazole and vancomycin, respectively. For metronidazole, 8.3% (n=6) were used in the 90 days prior to a recurrent CDI case. For vancomycin, 41.7% (n=55) were used in the 90 days prior to a recurrent CDI case

Table 10. The number of antibiotics dispensed in the community in the 90 days prior to total, HI-, CCI-, and CI-CDI cases during the whole study period.

Antibiotic Groups	2011-14 CDI			
	Total	**HI**	**CCI**	**CI**
Carbapenems	33 (0.3)	17 (0.4)	1 (0.3)	15 (0.3)
Cephalosporins	2,191 (22.6)	830 (21.7)	71 (24.8)	1,290 (23.1)
Clindamycin	1,372 (14.2)	289 (7.6)	16 (5.6)	1,067 (19.1)
Fluoroquinolones	2,389 (24.7)	1,140 (29.8)	69 (24.1)	1,180 (21.1)
Macrolides	447 (4.6)	202 (5.3)	7 (2.4)	238 (4.3)
Metronidazole	72 (0.7)	15 (0.4)	7 (2.4)	50 (0.9)
Nitrofurantonin	358 (3.7)	193 (5.0)	14 (4.9)	151 (2.8)
Other aminoglycosides	21 (0.2)	10 (0.3)	0 (0.0)	11 (0.2)
Other antimicrobials	14 (0.1)	8 (0.2)	0 (0.0)	6 (0.1)
Penicillins	1,869 (19.3)	631 (16.5)	48 (16.8)	1,190 (21.3)
Sulfonamides/trimethoprim	661 (6.8)	386 (10.1)	33 (11.5)	242 (4.3)
Tetracyclines	122 (1.3)	59 (1.5)	4 (1.4)	59 (1.1)
Trimethoprim	8 (0.1)	4 (0.1)	0 (0.0)	4 (0.1)
Vancomycin	132 (1.4)	38 (1.0)	16 (5.6)	78 (1.4)
Total[1]	**9,689**	**3,822**	**286**	**5,581**

Note: Column percentages of column total n(%). [1] Total is the sum of antibiotics dispensed. CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified.

5.3.2 Incidence

Incidence was calculated for each fiscal year and stratified for total, HI-, CCI-, and CI-CDI cases (Table 11). Total CDI incidence is reported per 10,000 population. HI-CDI incidence is reported per 1,000 admissions. CCI-CDI incidence is reported per 10,000 resident-days. CI-CDI incidence is reported per 10,000 population. The incidence of total, HI-, and CI-CDI were the highest in 2013-14. The incidence of CCI-CDI remained constant over the three fiscal years. With the exception of CCI-CDI population, the incidence of total, HI-, and CI-CDI decreased from 2011-12 to 2012-13 and increased from 2012-13 to 2013-14.

Table 11. Incidence of total, HI-, CCI-, and CI-CDI stratified by fiscal year.

	CDI Cases	Denominator	Incidence
Total			
2011-12	3,898	3,032,408	12.9
2012-13	3,677	3,132,858	11.7
2013-14	4,651	3,227,052	14.4
HI-CDI			
2011-12	1,910	286,571	6.7
2012-13	1,875	299,142	6.3
2013-14	2,271	306,842	7.4
CCI-CDI			
2011-12	139	5,063,304	0.3
2012-13	136	5,084,576	0.3
2013-14	166	5,067,727	0.3
CI-CDI			
2011-12	1,849	3,032,408	6.1
2012-13	1,666	3,132,858	5.3
2013-14	2,214	3,227,052	6.9

Note: CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified. Incidence for HI: per 1,000 admissions; CCI: per 10,000 resident-days; CI and total: per 10,000 population.

Table 12 reports the incidence over the three fiscal years stratified for population and for gender. In total, females had higher incidence compared to males. However, the incidence for HI-CDI were markedly higher for males. Amongst incidence of CCI-CDI, the incidence of CDI were slightly higher for males. As expected, the number of resident-days (i.e. denominator) were much larger for females. For incidence of CI-CDI, the incidence was markedly higher in females than in males. In general, the incidence of CDI decreased from 2011-12 to 2012-13 and increased from 2012-13 to 2013-14 regardless of gender.

Table 12. Incidence of total, HI-, CCI-, and CI-CDI stratified by fiscal year and gender.

	Male			Female		
	CDI Cases	Denominator	Incidence	CDI Cases	Denominator	Incidence
Total						
2011-12	1,600	1,532,688	10.4	2,298	1,499,720	15.3
2012-13	1,527	1,587,018	9.6	2,150	1,545,840	13.9
2013-14	1,943	1,637,039	11.9	2,708	1,590,013	17.0
HI-CDI						
2011-12	839	115,957	7.2	1,071	170,614	6.3
2012-13	869	121,044	7.2	1,006	178,098	5.7
2013-14	1,055	124,160	8.5	1,216	182,682	6.7
CCI-CDI						
2011-12	51	1,684,000	0.3	88	3,379,304	0.3
2012-13	54	1,714,441	0.3	82	3,370,126	0.2
2013-14	63	1,743,112	0.4	103	3,324,615	0.3
CI-CDI						
2011-12	710	1,532,688	4.6	1,139	1,499,720	7.6
2012-13	604	1,587,018	3.8	1,062	1,545,840	6.9
2013-14	825	1,637,039	5.0	1,389	1,590,013	8.7

Note: CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified. Incidence for HI: per 1,000 admissions; CCI: per 10,000 resident-days; CI and total: per 10,000 population.

Zone incidence of CDI stratified by total, population (i.e. HI, CCI, and CI), and fiscal year is displayed in Table 13. For total CDI incidence, the prior trend noted of a decrease in 2012-13 and increase in 2013-14 was also found when stratified by Zone with the exception of the South Zone. The South Zone total CDI incidence increased over the three fiscal years. Among HI-CDI incidence, all Zones but Calgary exhibited their highest incidence in the 2013-14 fiscal year. Over the three fiscal years, Calgary Zone HI-CDI incidence decreased while in the Central Zone HI-CDI incidence increased. In 2013-14, the highest HI-CDI incidence was in the Edmonton Zone at 10.4 cases per 1,000 admissions, while the North Zone had the lowest at 3.4 cases per 1,000 admissions. Amongst the Zones, Edmonton Zone had the higher incidence of CCI-CDI; however, the

North Zone had the most marked increase with 0.1 cases per 10,000 resident-days in 2011-12 to 0.4 cases per 10,000 resident-days in 2013-14.

Overall the Zone incidence of CI-CDI decreased in 2012-13 and increased in 2013-14, except in the Calgary Zone which had a constant decrease over the three fiscal years. Calgary Zone had the highest CI-CDI incidence from 2011-2013 but in 2013-14 Edmonton Zone had the highest CI-CDI incidence and Calgary Zone had the lowest amongst the five Zones. Edmonton Zone CI-CDI incidence increased from 4.8 cases per 10,000 population in 2011-12 to 7.2 cases per 10,000 population in 2013-14. The cases and denominator used to calculate the incidence in Table 13 is reported in Appendix H.

Table 13. Zone incidence of CDI stratified by total, population (HI, CCI, and CI) and fiscal year.

Zone	CDI Incidence		
	2011-12	2012-13	2013-14
Total			
South	10.8	11.5	14.4
Calgary	14.3	13.4	13.5
Central	9.7	9.5	13.6
Edmonton	14.1	13.4	19.7
North	8.4	7.0	11.2
HI-CDI			
South	4.5	5.5	6.3
Calgary	8.0	7.0	6.7
Central	3.7	4.0	5.7
Edmonton	8.6	8.0	10.4
North	2.5	2.1	3.4
CCI-CDI			
South	0.1	0.4	0.3
Calgary	0.3	0.2	0.3
Central	0.2	0.2	0.2
Edmonton	0.4	0.4	0.5
North	0.1	0.2	0.4
CI-CDI			
South	5.6	4.9	7.0
Calgary	7.4	6.6	6.4
Central	5.5	4.9	7.1
Edmonton	4.8	4.2	7.2
North	5.7	4.5	6.9

Note: CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified. Incidence for HI: per 1,000 admissions; CCI: per 10,000 resident-days; CI and total: per 10,000 population. Sixty-six records of CI-CDI not reported as Zone could not be determined.

The Zone incidence by gender are reported in Table 14. For all Zones, with the exception of the Central Zone, males had a higher HI-CDI incidence. In 2011-12 and 2012-13 females in the Central Zone had a slightly higher incidence of HI-CDI. For all Zones, females had higher CI-CDI incidence. The Calgary Zone incidence of HI- and CI-CDI for both females and males decreased over the three fiscal years. These decreases

were more apparent for females. The cases and denominator used to calculate the incidence in Table 14 is reported in Appendix H.

Table 14. Zone incidence of CDI by total, population (HI, CCI, and CI), fiscal year, and gender.

Zone	Male CDI Incidence			Female CDI Incidence		
	2011-12	2012-13	2013-14	2011-12	2012-13	2013-14
Total						
South	4.7	4.5	6.0	6.1	7.0	8.3
Calgary	5.6	5.4	5.5	8.7	8.1	8.0
Central	4.1	4.0	5.4	5.6	5.5	8.2
Edmonton	5.9	5.9	8.4	8.2	7.5	11.2
North	3.8	2.8	4.8	4.6	4.2	6.4
HI-CDI						
South	5.6	5.7	7.1	4.0	5.4	5.7
Calgary	8.8	7.8	7.7	7.4	6.4	5.9
Central	3.5	4.1	5.3	3.8	3.8	5.9
Edmonton	9.0	9.6	12.2	8.2	7.0	9.2
North	3.2	2.6	4.3	2.0	1.8	2.8
CCI-CDI						
South	0.3	0.5	0.1	0.1	0.3	0.3
Calgary	0.3	0.3	0.2	0.3	0.2	0.3
Central	0.3	0.2	0.3	0.1	0.2	0.2
Edmonton	0.4	0.3	0.6	0.4	0.4	0.4
North	0.1	0.2	0.3	0.1	0.2	0.4
CI-CDI						
South	4.3	3.4	5.5	6.9	6.5	8.5
Calgary	5.0	4.5	4.5	9.7	8.7	8.2
Central	4.6	4.2	5.7	6.3	5.7	8.6
Edmonton	4.0	3.1	5.1	5.5	5.4	9.2
North	4.6	3.1	5.1	6.9	6.0	8.8

Note: CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified. Incidence for HI: per 1,000 admissions; CCI: per 10,000 resident-days; CI and total: per 10,000 population. Sixty-six records of CI-CDI not reported as Zone could not be determined.

5.4 Research Objective 2

5.4.1 Descriptive and Comparative Statistics

The last HI-CDI case an individual had was selected as the last CDI event was used for analysis for this research objective. This resulted in a reduction from 6,056 HI-CDI cases during the study period to 5,461 (90.2%) individuals who had HI-CDI case. Of these, 810 (14.8%) died within 30 days from the identified HI-CDI event. Gender-specific 30-day all-cause mortality were 13.2% (n=394) and 16.8% (n=416) for females and males, respectively. Hospitalization mean and median length of stay, censored at 30 days post time of CDI, for the HI-CDI admit were 31.5 and 21.0 days for CDI non-death and 27.7 and 21.0 days for CDI death. CDI death group had a slightly shorter length of hospitalization.

Characteristics and group comparisons are presented in Table 15. Compared to CDI non-death, CDI deaths were older, had more antibiotic exposure, were more likely a resident of continuing care, and had slightly more comorbidities. Of those who died 40.9% (n=331) had antibiotic exposure, while those who lived 36.5% (n=1,696) had antibiotic exposure. Only 4.0% (n=218) of HI-CDI individuals were residents of continuing care at the time of the HI-CDI event; however, there were marked differences in the proportion between the two groups, those who died had a larger proportion of continuing care residency. Although the mean and median total comorbidity count for both groups were approximately one or two, total comorbidity count ranged from zero to seven. A comorbidity count of zero was more prevalent for those who lived while those who died had a higher proportion of two or more comorbidities (Figure 7). There were statistically significant differences between these two groups for gender, age, antibiotic exposure, total comorbidity count, and continuing care.

Table 15. Characteristics and comparisons of CDI death and CDI non-death amongst HI-CDI individuals.

Characteristics	2011-14 HI-CDI			
	Total n=5,461	**CDI death n=810**	**CDI non-death n=4,651**	**p-value**
Gender				
Female n(%)	2,980 (54.6)	394 (48.6)	2,586 (55.6)	<0.05
Age				
Mean (SD)	69.1 (17.9)	77.6 (14.0)	67.6 (18.1)	<0.05
Median (IQR)	73.0 (25.0)	81.0 (18.0)	71.0 (25.0)	<0.05
Antibiotic Exposure				
Yes n(%)	2,027 (41.6)	331 (40.9)	1,696 (36.5)	<0.05
Recurrence				
Yes n(%)	616 (11.3)	86 (10.6)	530 (11.4)	0.52
Continuing Care				
Yes n(%)	218 (4.0)	72 (8.9)	146 (3.1)	<0.05
Total Comorbidity Count				
Mean (SD)	1.3 (1.1)	1.8 (1.1)	1.2 (1.1)	<0.05
Median (IQR)	1.0 (2.0)	2.0 (1.0)	1.0 (2.0)	<0.05

Note: Column percentages. P-values from two sample test of proportion for categorical variables. Student t-test for mean and Mann-Whitney U-test for median. P-value less than 0.05 was statistically significant. CDI: *C. difficile* Infection; HI: hospital identified; SD: standard deviation; IQR: interquartile range.

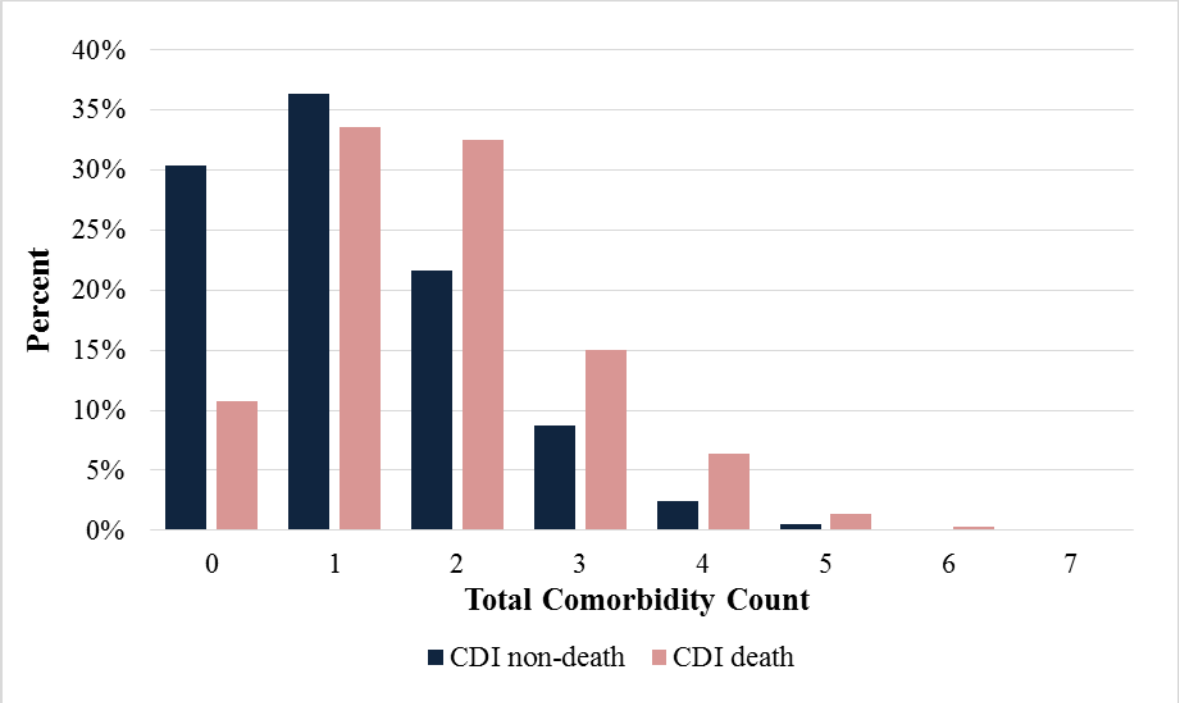

Figure 7. Percent contribution of each total comorbidity count stratified by CDI non-death and CDI death amongst HI-CDI individuals.

Note: Each total comorbidity count percent is reported per group, meaning each group's percentages add up to 100%. Figure generated using Microsoft Excel (2010).

Table 16 compares, between the CDI death and CDI non-death groups, community antibiotic exposure in the 90 days prior to being identified with an HI-CDI event. Each antibiotic was counted only once as exposure and not the amount of exposure was of interest. Cephalosporins (11.3%; n=617) and fluoroquinolones (15.9%; n=868) were the most frequent antibiotic exposures. Individuals who died had more exposure to these antibiotics compared to those who lived. However, only fluoroquinolone exposure was statistically significant different between the two groups.

Table 16. Comparison of CDI death and CDI non-death groups community antibiotic exposure amongst HI-CDI individuals.

Antibiotics	2011-14 HI-CDI			
	Total n=5,461	CDI death n=810	CDI non-death n=4,651	p-value
Carbapenems	6 (0.1)	1 (0.1)	5 (0.1)	0.90
Cephalosporins	617 (11.3)	107 (13.2)	510 (11.0)	0.06
Clindamycin	249 (4.6)	33 (4.1)	216 (4.6)	0.47
Fluoroquinolones	868 (15.9)	158 (19.5)	710 (15.3)	<0.05
Macrolides	151 (2.8)	25 (3.1)	126 (2.7)	0.55
Metronidazole	12 (0.2)	1 (0.1)	11 (0.2)	0.53
Nitrofurantonin	155 (2.8)	20 (2.5)	135 (2.9)	0.49
Other aminoglycosides	6 (0.1)	2 (0.2)	4 (0.1)	0.20
Other antimicrobials	4 (0.7)	0 (0.0)	4 (0.9)	0.40
Penicillins	489 (9.0)	80 (9.9)	409 (8.8)	0.31
Sulfonamides/trimethoprim	248 (4.5)	38 (4.7)	210 (4.5)	0.82
Tetracyclines	41 (0.8)	4 (0.5)	37 (0.8)	0.36
Trimethoprim	4 (0.1)	1 (0.1)	3 (0.1)	0.57
Vancomycin	25 (0.5)	2 (0.2)	23 (0.5)	0.34

Note: Column percentages of "n". Each antibiotic only counted once to indicate exposure in the 90 days prior. P-values from two sample test of proportion. P-value less than 0.05 was statistically significant. CDI: *C. difficile* Infection; HI: hospital identified.

Comorbidities defined by the Charlson comorbidity index are presented in Table 17. For the HI-CDI individuals, the three most common comorbidities were diabetes complicated (18.4%; n=1,004), chronic pulmonary disease (17.8%; n=971), and congestive heart failure (15.2%; n=831). For individuals who were a CDI death, the more frequent comorbidities were chronic pulmonary disease (26.5%; n=215), congestive heart failure (26.2%; n=212), diabetes complicated (23.5%; n=190), and dementia (20.1%; n=163). For individuals who were a CDI non-death, the more frequent comorbidities were diabetes complicated (17.5%; n=814), chronic pulmonary disease (16.3%; n=756), congestive heart failure (13.3%; n=619), and malignancy (11.2%; n=522). Although the most frequent comorbidities were similar between the two groups, the CDI death individuals had a larger proportion of these comorbidities. A p-value less than 0.05

identified statistically significant differences in comorbidities between the two groups and these were chronic pulmonary disease, congestive heart failure, dementia, diabetes complicated and uncomplicated, metastatic solid tumor, mild and moderate/severe liver disease, myocardial infarction, and renal disease.

Table 17. Comparison of CDI death and CDI non-death Charlson comorbidities amongst HI-CDI individuals.

Charlson Comorbidity	2011-14 HI-CDI			
	Total n=5,461	CDI death n=810	CDI non-death n=4,651	p-value
AIDS/HIV	12 (0.2)	1 (0.1)	11 (0.2)	0.53
Cerebrovascular Disease	322 (5.9)	55 (6.8)	267 (5.7)	0.24
Chronic Pulmonary Disease	971 (17.8)	215 (26.5)	756 (16.3)	<0.05
Congestive Heart Failure	831 (15.2)	212 (26.2)	619 (13.3)	<0.05
Dementia	666 (12.2)	163 (20.1)	503 (10.8)	<0.05
Diabetes Complicated	1,004 (18.4)	190 (23.5)	814 (17.5)	<0.05
Diabetes Uncomplicated	370 (6.8)	36 (4.4)	334 (7.2)	<0.05
Malignancy	605 (11.1)	83 (10.2)	522 (11.2)	0.41
Metastatic Solid Tumour	328 (6.0)	105 (13.0)	223 (4.8)	<0.05
Mild Liver Disease	176 (3.2)	36 (4.4)	140 (3.0)	<0.05
Moderate/severe Liver Disease	124 (2.3)	28 (3.5)	96 (2.1)	<0.05
Myocardial Infarction	349 (6.4)	97 (12.0)	252 (5.4)	<0.05
Paraplegia or Hemiplegia	159 (2.9)	17 (2.1)	142 (3.1)	0.14
Peptic Ulcer Disease	148 (2.7)	21 (2.6)	127 (2.7)	0.82
Peripheral Vascular Disease	230 (4.2)	38 (4.7)	192 (4.1)	0.46
Renal Disease	543 (9.9)	134 (16.5)	409 (8.8)	<0.05
Rheumatic Disease	112 (2.1)	15 (1.9)	97 (2.1)	0.66

Note: Column percentages. P-values from two sample test of proportion. P-value less than 0.05 was statistically significant. CDI: *C. difficile* Infection; HI: hospital identified.

5.4.2 Univariate Analysis

Univariate odds ratios were calculated comparing characteristics (i.e. covariates) between those who died and did not die (Table 18). With the exception of recurrence, all characteristics were statistically significant and were identified as risk factors for

mortality. Age (centred at median age) and total comorbidity count were continuous variables. For each additional year of age, the odds ratio increased by 1.1. For each additional comorbidity count, the odds ratio increased by 1.6. Being male or exposed to antibiotics were slight risk factors for death as the crude odds ratios were just above one. The odds of death were 3.0 times greater among those who were a continuing care resident than those who were not (95% CI: 2.2, 4.1). Although male gender, age, and antibiotic exposure were statistically significant, their 95% confidence interval lower limits were just above one meaning these characteristics were likely only slight risk factors if a risk factor at all. However, increasing from the median age also increases the odds ratio for age. For example, at 93 years the crude odds ratio would be 2.2 (Appendix I).

Table 18. Univariate analysis of characteristics amongst HI-CDI individuals, reporting mortality crude odds ratios, 95% confidence intervals, and p-values.

Characteristics	Crude Odds Ratio	95% Confidence Interval	p-value
Male	1.3	(1.1 – 1.6)	<0.05
Age (c=73yrs)	1.1	(1.0 – 1.1)	<0.05
Antibiotic Exposure	1.2	(1.0 – 1.5)	<0.05
Recurrence	0.9	(0.7 – 1.2)	0.52
Continuing Care	3.0	(2.2 – 4.1)	<0.05
Total Comorbidity Count	1.6	(1.4 – 1.7)	<0.05

Note: Age and total comorbidity count were continuous variables. Age was centred at median age (c=73yrs). P-value less than 0.05 was statistically significant.

Charlson comorbidities crude odds ratios are reported in Table 19. The odds ratios ranged from 0.5 to 3.0. Comorbidities identified as statistically significant risk factors for death were chronic pulmonary disease, congestive heart failure, dementia, diabetes complicated, metastatic solid tumour, mild and moderate/severe liver disease, myocardial

infarction, and renal disease. The only other significant comorbidity was diabetes uncomplicated reporting a protective effect with an odds ratio of 0.6. Some of the comorbidities identified as significant risk factors for death had a 95% confidence interval lower limit of one or just above (e.g. mild and moderate/severe liver disease and diabetes complicated). Comorbidities with higher crude odds ratios were metastatic solid tumour (3.0), myocardial infarction (2.4), and congestive heart failure (2.3). The odds of death were 3.0 times greater among those with metastatic solid tumor than those without metastatic solid tumour (95% CI: 2.2, 3.8).

Table 19. Univariate analysis of Charlson comorbidities amongst HI-CDI individuals, reporting mortality crude odds ratios, 95% confidence intervals, and p-values.

Charlson Comorbidity	Crude Odds Ratio	95% Confidence Interval	p-value
AIDS/HIV	0.5	(0.0 – 3.6)	0.53
Cerebrovascular Disease	1.2	(0.9 – 1.7)	0.24
Chronic Pulmonary Disease	1.9	(1.5 – 2.3)	<0.05
Congestive Heart Failure	2.3	(1.9 – 2.8)	<0.05
Dementia	2.1	(1.6 – 2.6)	<0.05
Diabetes Complicated	1.4	(1.2 – 1.8)	<0.05
Diabetes Uncomplicated	0.6	(0.4 – 0.9)	<0.05
Malignancy	0.9	(0.6 – 1.2)	0.41
Metastatic Solid Tumour	3.0	(2.2 – 3.8)	<0.05
Mild Liver Disease	1.5	(1.0 – 2.2)	<0.05
Moderate/severe Liver Disease	1.7	(1.0 – 2.7)	<0.05
Myocardial Infarction	2.4	(1.8 – 3.1)	<0.05
Paraplegia or Hemiplegia	0.7	(0.3 – 1.2)	0.14
Peptic Ulcer Disease	0.9	(0.5 – 1.6)	0.82
Peripheral Vascular Disease	1.1	(0.7 – 1.7)	0.47
Renal Disease	2.1	(1.6 – 2.6)	<0.05
Rheumatic Disease	0.9	(0.4 – 1.6)	0.66

Note: P-value less than 0.05 was statistically significant.

5.4.3 Regression Analysis

As the main variables of interest were each comorbidity, the covariates were only considered as potential confounders or effect modifiers. Each comorbidities logistic regression model after backwards elimination is reported in Appendix G. Majority of the comorbidities were confounded by age (centred at median age) and total comorbidity count; therefore, each comorbidity was adjusted for these covariates. Table 20 reports each comorbidities odds ratio adjusted for age (centred at median age) and total comorbidity count.

Statistically significant comorbidities after adjusting for age and total comorbidity count were cerebrovascular disease, diabetes uncomplicated, metastatic solid tumour, mild and moderate/severe liver disease, paraplegia or hemiplegia, peptic ulcer disease, and peripheral vascular disease. Comorbidities identified as protective against death were cerebrovascular disease, diabetes uncomplicated, paraplegia or hemiplegia, peptic ulcer disease, and peripheral vascular disease. With the exception of diabetes uncomplicated, these comorbidities were only significantly identified as protective after adjusting for age and total comorbidity count. The odds of death were 0.6 times less among those with cerebrovascular disease than those without cerebrovascular disease after adjusting for age and total comorbidity count (95% CI: 0.4, 0.9). Meaning for those of the same age and same total comorbidity count the presence of cerebrovascular disease was protective against death. However, it should be noted the upper 95% confidence limit was just below one.

Comorbidities identified as risk factor for death were mild and moderate/severe liver disease, and metastatic solid tumour. Prior to adjustment these comorbidities were already identified as significant risk factors; however, after adjustment the odds ratios

slightly increased. The odds of death were 2.0 times greater among those with moderate/severe liver disease than those without moderate/severe liver disease after adjusting for age and total comorbidity count (95% CI: 1.2, 3.2). Meaning for those of the same age and same total comorbidity count the presence of moderate/severe liver disease was a risk factor for death. Therefore, even after adjusting for variables that are likely associated with death (i.e. increasing age and total comorbidity count) moderate/severe liver disease still increased the odds of death.

With the addition of adjusting for age and total comorbidity count, six comorbidities originally identified as risk factors for death with a univariate analysis were no longer statistically significant. These were chronic pulmonary disease, congestive heart failure, dementia, diabetes complicated, myocardial infarction, and renal disease.

Table 20: Univariate analysis compared to regression analysis for Charlson comorbidities amongst HI-CDI individuals, reporting mortality crude and adjusted odds ratios, crude and adjusted p-values, and adjusted 95% confidence interval.

Charlson Comorbidity	Crude Odds Ratio	p-value	Adjusted Odds Ratio	95% CI	p-value
AIDS/HIV	0.5	0.53	0.9	(0.1 – 7.4)	0.94
Cerebrovascular Disease	1.2	0.24	0.6	(0.4 – 0.9)	<0.05
Chronic Pulmonary Disease	1.9	<0.05	1.1	(0.8 – 1.3)	0.62
Congestive Heart Failure	2.3	<0.05	1.1	(0.8 – 1.3)	0.62
Dementia	2.1	<0.05	1.0	(0.7 – 1.3)	0.78
Diabetes Complicated	1.4	<0.05	0.9	(0.7 – 1.1)	0.25
Diabetes Uncomplicated	0.6	<0.05	0.6	(0.3 – 0.9)	<0.05
Malignancy	0.9	0.41	0.8	(0.6 – 1.1)	0.09
Metastatic Solid Tumour	3.0	<0.05	3.2	(2.4 – 4.2)	<0.05
Mild Liver Disease	1.5	<0.05	1.7	(1.1 – 2.6)	<0.05
Moderate/severe Liver Disease	1.7	<0.05	2.0	(1.2 – 3.2)	<0.05
Myocardial Infarction	2.4	<0.05	1.2	(0.9 – 1.7)	0.12
Paraplegia or Hemiplegia	0.7	0.14	0.4	(0.2 – 0.8)	<0.05
Peptic Ulcer Disease	0.9	0.82	0.6	(0.3 – 1.0)	<0.05
Peripheral Vascular Disease	1.1	0.47	0.7	(0.4 – 1.0)	<0.05
Renal Disease	2.1	<0.05	1.2	(0.9 – 1.5)	0.16
Rheumatic Disease	0.9	0.66	0.6	(0.3 – 1.1)	0.09

Note: Univariate analysis results correspond to the second and third column. The remaining columns are the logistic regression results for the comorbidities adjusted by age (centred at median age) and total comorbidity count. P-value less than 0.05 was statistically significant. CI; confidence interval.

The odds ratios for age (centred at median age) and total comorbidity count were similar amongst all 17 Charlson comorbidity logistic regression models. The odds ratio for age and total comorbidity count were approximately 1.1 and 1.5, respectively. For instance the odds ratio for age using congestive heart failure as an example means the odds of death for individuals with the same congestive heart failure status (i.e. either both with or without congestive heart failure) and same total comorbidity count increased 1.1 times for each additional year. Similarly, the odds of death for individuals with the same congestive heart failure status and same age increased 1.5 times for each additional comorbidity count.

Area under the curve (AUC) was calculated for each of the 17 Charlson comorbidity logistic regression models using a ROC curve (Table 21). With the exception of metastatic solid tumour which had a larger AUC, the AUC for all comorbidities were approximately 0.71. These values indicate the discrimination ability for all models was reasonable.

Table 21. Charlson comorbidities logistic regression models area under the curve (AUC).

Charlson Comorbidity	AUC
AIDS/HIV	0.706
Cerebrovascular Disease	0.707
Chronic Pulmonary Disease	0.706
Congestive Heart Failure	0.705
Dementia	0.706
Diabetes Complicated	0.706
Diabetes Uncomplicated	0.708
Malignancy	0.705
Metastatic Solid Tumour	0.723
Mild Liver Disease	0.707
Moderate/severe Liver Disease	0.708
Myocardial Infarction	0.706
Paraplegia or Hemiplegia	0.709
Peptic Ulcer Disease	0.707
Peripheral Vascular Disease	0.707
Renal Disease	0.706
Rheumatic Disease	0.706

Note: AUC: area under the curve.

5.5 Research Objective 3

5.5.1 Descriptive Statistics

Between April 1, 2011 and March 31, 2014, IPC Surveillance identified 140 primary CDI cases where death occurred within 30 days of CDI diagnosis and at one of the four adult Calgary hospitals. Of these only 135 (96.4%) deaths could be reviewed for this study as access to five of the paper-based medical charts was not possible due to legal issues or the chart being recently requested by another party.

After the first independent review by the expert reviewers, they had 52 (38.5%) discordant death decisions. After reviewing the information for a second time, 24 (17.8%) death decisions remained discordant. The remaining discordant death decisions were reconciled after a group discussion.

Table 22 reports the two groups' results for each of the three death categories. With the use of the DARPIC algorithm, the student reviewer compared to the expert reviewers identified slightly fewer cases of CDI being directly related or contributing to death, 30.4% (n=41) compared to 39.3% (n=53), respectively. Additionally, with the use of the DARPIC algorithm the student reviewer categorized far more cases of CDI being unrelated to death compared to the expert reviewers (60.7%; n=82 compared to 41.5%; n=56). However, the expert reviewers classified considerably more deaths as unable to determine. Amongst both reviewer groups, CDI-related deaths were no more than 40% of the population reviewed.

Table 22. Student reviewer and expert reviewers' death decisions.

Death Decision	Student Reviewer n(%)	Expert Reviewers n(%)
CDI-related	41 (30.4)	53 (39.3)
CDI-unrelated	82 (60.7)	56 (41.5)
Unable to determine	12 (8.9)	26 (19.3)

Note: Column percentages.

Table 23 3 x 3 table stratifies the student reviewer and expert reviewers' concordance and discordance by death category. Concordance is defined as the student reviewer and expert reviewers having the same death decision. Discordance is defined as the student reviewer and expert reviewers having different death decisions. Of the CDI-related deaths, there were 32 concordant death decisions. Of those deemed CDI-related by the student reviewer, there were fewer discordant pairs compared to those deemed CDI-related by the expert reviewers. For example, eight (19.5%) of the 41 CDI-related deaths determined by the student reviewer were classified as CDI-unrelated by the expert reviewers, the remaining discordant death decision was deemed unable to determine by the expert reviewers. While 21 (39.6%) of the 53 CDI-related deaths determined by the expert reviewers were classified as CDI-unrelated by the student reviewer. For CDI-unrelated deaths there was more discordance amongst the student reviewer and expert reviewers; however, 43 death decisions were concordant. Of unable to determine, seven were concordant. Eighteen (69.2%) of the 26 deaths reviewed by expert reviewers and categorized as unable to determine were classified as CDI-unrelated by the student reviewer.

Table 23. A 3 x 3 table of the student reviewer and expert reviewers' death decisions.

Student Reviewer	Expert Reviewers		
	CDI-related	CDI-unrelated	Unable to determine
CDI-related	32	8	1
CDI-unrelated	21	43	18
Unable to determine	0	5	7

Note: Student reviewer results reported per row. Expert reviewers' results reported per column.

5.5.2 Inter-rater reliability

The kappa statistic calculated, between student review and expert reviewers, was 0.36, indicating a fair agreement. The overall agreement and expected agreement was also calculated. The overall agreement reports the observed agreement as a percentage. The overall agreement was 60.7%. The expected agreement reports the percentage that would be expected to agree if the two groups randomly assigned death decisions. The expected agreement was 38.8%. The overall agreement was markedly larger than the expected agreement.

Kappa statistics for the three death categories (CDI-related, CDI-unrelated, and unable to determine) were also calculated. The kappa statistic for CDI-related was 0.51, for CDI-unrelated was 0.23, and for unable to determine was 0.27. The highest agreement was found with deaths classified as CDI-related, while the lowest was for deaths classified as CDI-unrelated. The kappa statistic for CDI-related was higher than the overall kappa statistic first reported.

Chapter Six: Discussion

6.1 Introduction

In this chapter the study findings are discussed and compared to findings in the literature. Strengths, limitations, and biases are also discussed.

6.2 Research Objective 1

6.2.1 Discussion of Study Findings

The first research objective was to determine the overall incidence of CDI in Alberta in the adult population and amongst three populations; hospital, continuing care, and community. Of the three populations, more CDI cases were identified in the hospital, which was not surprising as CDI is largely associated with hospitalization. However, it was surprising the number of community CDI cases were near that observed in the hospital. There were very few cases of CDI in continuing care. The mean and median ages of continuing care identified CDI (CCI-CDI) cases were above 80 years. Residents of continuing care facilities are those who require assistance and constant care and this is more necessary in individuals of advanced age; thus, it was not surprising cases of CCI-CDI were identified in the very elderly. AHS/COV IPC Surveillance reports cases of CDI in continuing care for all of Alberta and reported a mean and median age similar to what was observed in this study[57]. Compared to hospital identified CDI (HI-CDI) cases, cases of community identified CDI (CI-CDI) were younger. The mean and median ages for HI-CDI cases were early seventies compared to early fifties for CI-CDI cases. Although those under 65 years of age contribute more to the number of hospitalizations, individuals under the age of 65 years are less at risk of developing CDI[61,62], which was supported by

this study findings of HI-CDI cases having a mean and median age greater than 65 years. Additionally, those of advanced age are at higher risk of developing severe CDI and having poorer outcomes[21,62], which may have contributed to these individuals being hospitalized; thus, being identified as having CDI in the hospital. Younger individuals are healthier; therefore, they are more likely to have mild CDI and have successful treatment in the community, meaning they would not require hospitalization and be identified with CDI in the community.

IPC Surveillance conducts CDI surveillance for inpatient *C. difficile* laboratory positives meeting CDI clinical criteria. These cases are then classified as hospital-acquired (HA), healthcare-associated (HCA), and community-acquired (CA). The definition of healthcare-associated includes, but not limited to, hospitalized patients who present with CDI symptoms on admission and are residents of long-term care. Although the populations described in this study are based on where the CDI was identified, the mean and median age trend exhibited between the three populations in this study and the three case classifications of IPC CDI surveillance were similar[91]. The mean and median age of HCA-CDI cases (i.e. similar to CCI-CDI cases in this study) reported in 2013-14 by IPC Surveillance was the oldest compared to the other two case classifications. Additionally, CA-CDI cases (i.e. similar to CI-CDI cases) was the youngest case classification. However, the reported mean and median age of CA-CDI cases was in the low sixties compared to the low fifties observed in this study. This is likely due to CA-CDI cases being defined in a hospital population (i.e. CDI symptoms on admission) and not including cases of CDI presenting in the community. As mentioned prior, older individuals are more likely to be admitted to the hospital; therefore, could explain CA-CDI cases being identified in older individuals than the CI-CDI cases.

The proportion of recurrence for each of the populations increased over the three fiscal years. As the time into the study period increased, the likelihood of identifying subsequent recurrent incident cases increased. Therefore, the proportion of recurrence found in the 2011-12 fiscal year was likely an underestimate as cases occurring prior to the start of the study period were not captured. Recurrent CDI cases were identified significantly more in the CCI-CDI population (32.9%; [n=145] compared to 11.7%; [n=708] for HI-CDI population). Risk factors for recurrent CDI include older age, previous severe CDI, higher Charlson comorbidity score, and fluoroquinolone use[12,68]. The continuing care population is older, more likely to have severe CDI, and have more comorbid conditions; hence, could explain the higher proportion of CCI-CDI cases being recurrent.

Depending on the follow-up period, the proportion of recurrent CDI cases has been reported between 5 to 66%, with an average of 20%[92]. A recent study reported a recurrence rate of 22.9% in the following year after the initial case[93]. Although recurrence in this study was measured for the whole study period and not for set defined follow-up period, the proportion of CDI cases with recurrence were low, with the exception of CCI-CDI cases. Of HI-CDI cases 11.7% (n=708) were recurrent cases and of CI-CDI cases 11.6% (n=665) were recurrent cases. The proportion of recurrence found for HI- and CI-CDI cases were lower than that reported in the literature. However, this study only counted new cases every 8 weeks; therefore, studies which counted recurrence after successful treatment of CDI could have had a shorter timeframe between cases. Furthermore, majority (71.9%) of the recurrent cases occurred in the same fiscal year as a previous CDI case, suggesting individuals are more prone to have a recurrent CDI case in the same year as they were originally diagnosed.

All-cause mortality in the 30 days after developing CDI was highest in cases of CCI-CDI. As mentioned prior, CCI-CDI cases were identified in the very elderly. This population is at the end stage of their life and higher mortality rates would be expected. Pawar et al. study found residents with CDI in continuing care had a 30-day all-cause inpatient mortality of 23%[41]. This percentage is larger than the 17.0% reported in this study. A potential reason the other study found a slightly higher percentage was it focused on residents admitted to the hospital post CDI case. These residents admitted to hospital were likely more ill and had a higher chance of dying. All-cause mortality at 180 days for continuing care residents with CDI has been approximated at 35%[41].

A 13.4% 30-day all-cause mortality for cases of HI-CDI was observed in this study. A systematic review found patients with CDI had a 30-day all-cause mortality range of 12.1% to 38.0%[11]. Gravel et al. study investigating hospital-acquired CDI reported a similar mean age as observed in this study (i.e. mean of 70 years) and found a 30-day all-cause mortality of 16.3%[94]. This study found a similar mortality percentage but was near the lower end of the range reported in the literature. Thirty-day all-cause mortality for cases of CI-CDI was markedly lower at 1.3 per 100 cases, which would be expected with those of middle age. Chitnis et al. reported a 1.6% 30-day all-cause mortality for community-associated CDI[6], which supports the mortality percentage reported in this study for CI-CDI cases.

Of the CDI cases reported, more were identified in females. This was particularly evident in CCI- and CI-CDI cases with over 60% of these cases being females. Females are more at risk of community-associated CDI; thus, may explain the larger number of female CI-CDI cases[40]. In 2013-14 IPC Surveillance reported more cases of total CDI (i.e. all inpatient CDI) occurred in females, approximately 54%[56]. The methodology for

HI-CDI cases in this study is similar to total CDI cases reported by IPC Surveillance and this study found similar results of 54.4% (n=3,293) HI-CDI cases occurring in females. Female cases of CCI-CDI were markedly older than males, mean age of 84.6 years compared to 77.9 years for males. Females live longer than males; therefore, it is probable females in continuing care are older. Compared to males, females had a larger proportion of antibiotics dispensed in the community 90 days prior to CDI (48.8%; [n=3,495] compared to 40.6%; [n=2,059]). A recent review including 11 studies from nine countries found women were 27% more likely than males to be prescribed antibiotics in the community[95].

Of the three fiscal years, more cases of CDI were identified in the 2013-14 fiscal year. Compared to 2012-13, there were nearly 1,000 more cases in 2013-14. In early 2013 *C. difficile* laboratory testing began to be standardized in the province and the laboratory test being implemented was more sensitive. With a higher sensitivity more laboratory tests would be positive. This will be discussed further in section 6.5.1. Overall, the characteristics of the three CDI populations remained similar over the three fiscal years as reported in Tables 4 and 8.

The majority of antibiotics dispensed in the community in the 90 days prior to CDI were broad-spectrum antibiotics that are known to be associated with increased risk of CDI. These included clindamycin, fluoroquinolones, and cephalosporins[5,96,97]. When comparing the three populations, more cases of CI-CDI had antibiotic exposure (57.6%; n=3,301) and more antibiotics (n=5,581) were dispensed to these cases. However, the data used to identify antibiotic exposure was based solely on antibiotics dispensed in the community. This will be discussed further in section 6.5.1. Overall, of those with antibiotic exposure on average more than one antibiotic was dispensed in the 90 days

prior to developing CDI. It is not surprising that clindamycin, fluoroquinolones, and cephalosporins were amongst the most antibiotics dispensed. These antibiotics are commonly used in the community as they have good bioavailability when given orally[96,98]. Although all populations' antibiotics were assessed only using community dispensing, there were evident differences in the predominance of clindamycin and fluoroquinolone use across the three populations. Of antibiotics dispensed per population, clindamycin was more likely to be dispensed in the CI-CDI population, over 19% compared to approximately 5% reported for the remaining two populations. Clindamycin is routinely used to treat skin and soft tissue infections, as well as prophylaxis after dental procedures[98,99]. It could be hypothesized as the CI-CDI population is younger and likely healthier, they had more dental procedures; thus, being prescribed and exposed to clindamycin more than the other populations. Fluoroquinolones are commonly used to treat respiratory and urinary tract infections[100]. HI- and CCI-CDI cases had slightly higher proportions of fluoroquinolone dispensing compared to CI-CDI cases. It could be hypothesized as the HI- and CCI-CDI populations were older, they were more likely to have respiratory and urinary tract infections; therefore, more likely to be prescribed fluoroquinolones. The exact reasoning for the difference in clindamycin and fluoroquinolone dispensing amongst the populations is unknown.

Metrodinazole and vancomycin are antibiotics used in the treatment of CDI. Of antibiotics dispensed in the community, only very small proportions (i.e. less than 1.5%) of each were used. Use of these antibiotics could infer the individuals were being treated for CDI prior to being identified with CDI in the study. This is important with recurrent cases as the individual's prior CDI case may have not been successfully treated and the individual may have been having a continuation of the previous primary CDI case and the

subsequent case could have been incorrectly classified as a new primary CDI case. However, such a small percentage of these antibiotics were dispensed and only a small proportion of that proportion were identified in recurrent primary CDI cases. This overall suggests incident CDI classification every 8 weeks was appropriate. However, the impact of not having hospital antibiotic data is unknown.

Calgary and Edmonton Zone had majority of the CDI cases. These two Zones account for approximately 70% of the whole AHCIP registry. As these two Zones service more individuals, it is not surprising more cases of CDI were identified in these Zones. The Edmonton Zone had a larger proportion of CDI identified in the hospital compared to the community, suggesting those in Edmonton with CDI are more likely to be admitted to the hospital or those in Edmonton hospitals are at higher risk of developing CDI. The Edmonton Zone largely has the NAP1 strain, which can result in more severe CDI and with more severe CDI the individual would be more likely to be hospitalized. Conversely, there could be more acquisition of CDI in Edmonton Zone hospitals compared to hospitals in other Zones. Changes in patient flow protocols in Edmonton starting in 2011 resulted in unit over-capacity, which may have contributed to increased transmission. From 2012-13 to 2013-14 Edmonton Zone had an additional 300 community CDI cases, indicating an increase in CDI in the community as well. In the North Zone significantly more CDI cases were identified in the community compared to the hospital. This suggests individuals with CDI in the North Zone are less likely to be admitted to the hospital. The North Zone is geographically very large and it may be that individuals are more likely to be treated in the community rather than hospitalized, either because of poor access to hospitals or the population is healthier. Of the five Zones, North Zone has a slightly

younger population. Additionally, in the North Zone 70.0% (n=367) of cases of community CDI were identified in females compared to 61.2% (n=241) for males.

The proportion of HI-CDI cases reported per gender was higher in males than females, with the exception of the Central Zone where the proportion of HI-CDI cases was higher for females. Central Zone's variance from the trend of a higher proportion of CDI cases in males being identified in the hospital is unexplained as Central Zone's population does not appear to differ significantly in age or gender compared to Edmonton or Calgary Zone[101].

Although over the three fiscal years females had 600 to 700 more cases than males, females only had the higher incidence of total and CI-CDI; thus, signifying the importance of calculating incidence. The Alberta female population was slightly smaller than males; therefore, the female denominator for total and CI-CDI incidence was slightly smaller. Males had a higher incidence of HI-CDI, as well as a slightly higher incidence of CCI-CDI. Although males had less cases of HI-CDI, the number of hospital admissions (i.e. denominator) was markedly lower for males than females. More females are admitted to hospital than males, which is particularly evident in childbearing ages. The gender denominator for HI-CDI incidence was determined by the proportion of male and female discharges (i.e. 60% of 2013-14 discharges were females). The denominators for CCI-CDI incidence (i.e. resident-days) were also lower for males. Resident-days for males were less than half of that for females. As mentioned prior females live longer than males; therefore, are more likely to be residents of continuing care, as well as for a longer length of time.

Amongst the Zones, in 2013-14 Edmonton Zone had a significantly larger incidence of HI-CDI than the other four Zones. Calgary and Edmonton Zone had similar number of

admissions; however, Calgary Zone had a decrease in the number of HI-CDI cases over the three fiscal years, while Edmonton Zone had an increase. The incidence of CCI-CDI were similar amongst most Zones, slightly higher in the Edmonton Zone. Even though Calgary Zone had a similar number of resident-days as the Edmonton Zone, Calgary Zone CCI-CDI incidence were smaller. In 2011-12 Calgary Zone had a markedly higher incidence of CI-CDI than the other Zones, the same was identified in 2012-13; however, in 2013-14 Calgary Zone had the lowest CI-CDI incidence. In 2013-14 all Zones had similar CI-CDI incidence. Overall for all populations and for all Zones with the exception of Calgary Zone, the incidence increased. As mentioned earlier and to be explained more in depth in section 6.5.1, laboratory testing changed in early 2013. However, Calgary Zone changed laboratory testing earlier and has had the same laboratory testing since 2010; thus, could explain the lack of increase in CDI cases in 2013-14 as observed in the other Zones.

Another potential reason for the increase of total CDI in the Edmonton Zone and slight decrease in Calgary Zone is the temporal difference in *C. difficile* strains. It has been hypothesized the NAP1 (and similar hypervirulent strains of *C. difficile*) appeared in the Calgary Zone prior to the Edmonton Zone. If the Calgary Zone had the NAP1 strain earlier, they had more time to establish Infection Prevention & Control measures to reduce transmission and incidence. With the Edmonton Zone potentially seeing the NAP1 strain years after Calgary Zone, at the time of this study the strain may have still been taking over the existing strains and establishing itself as the endemic strain. In the Calgary Zone and Edmonton Zone there are facilities that participate in CNISP CDI surveillance, including strain typing. From 2011 to 2014 at participating Calgary facilities CDI cases with strain typing reported a decrease in NAP1, 46% to 21%. While the

Edmonton Zone facility reported an increase from 2011 to 2013, with 60% of CDI being NAP1 in 2013.

6.2.2 CDI Incidence of the Literature and Surveillances

Using discharge diagnoses, studies of hospital CDI reported incidence of 8.8 cases per 1,000 discharges in 2008 and 8.2 cases per 1,000 discharges in 2010[16,49]. Other studies have reported hospital CDI incidence per 10,000 patient-days, with a range from 6.4 to 9.2 cases per 10,000 patient-days[41,43]. Incidence reported per 10,000 patient-days cannot be compared to the HI-CDI incidence reported in this study as the denominator was number of hospital admissions. However, those reported based on discharges can. For HI-CDI incidence, all fiscal years had incidence below the incidence reported in the literature[16,49]. However, males in 2013-14 had an incidence above 8.0 cases per 1,000 admissions. Additionally, Edmonton Zone HI-CDI incidence for all three fiscal years were at or above the comparable incidence reported in the literature. As mentioned in section 3.4.1, diagnosis codes (i.e. ICD-9 and ICD-10) may or may not under-report the true amount of CDI[33,36–39]. Therefore, these incidence reported in the literature could be underestimates or overestimates. For the remaining Zones, HI-CDI incidence were markedly below (e.g. North and Central Zone) or similar (e.g. Calgary Zone) to the numbers reported in the literature. In 2013-14 the total CDI incidence reported by AHS/COV IPC Surveillance was 5.4 cases per 1,000 admissions. AHS/COV IPC CDI surveillance is an active surveillance using clinical criteria. With the exception of the clinical criteria, the methodology for HI-CDI cases used in this study is similar to total CDI cases reported by IPC Surveillance. The HI-CDI incidence reported in this study were greater than the incidence reported by IPC Surveillance. This is likely due to the

strict clinical criteria used by IPC Surveillance which results in the reporting of true CDI only. Therefore, the HI-CDI cases identified in this study were potentially overestimates because they were laboratory identified only.

IPC Surveillance Zone total CDI cases per 1,000 admissions, in 2013-14, were 4.8, 5.2, 4.4, 8.9, and 2.0 for South, Calgary, Central, Edmonton, and North, respectively[91]. This study 2013-14 incidence of HI-CDI cases per 1,000 admissions in the same order were 6.3, 6.7, 5.7, 10.4, and 3.4. The sequential order of lowest to highest incidence for both IPC Surveillance and HI-CDI in 2013-14 were the same, with both reporting hospital CDI incidence lowest in the North Zone and highest in the Edmonton Zone. However, for all Zones the HI-CDI incidence reported in this study were higher than the incidence reported by IPC Surveillance. Further supporting the methodology used by this study overestimates HI-CDI and likely for the other two populations as well.

Incidence of CDI in continuing care has been investigated. Ohio 2006 continuing care CDI was reported between 1.7 and 2.9 cases per 10,000 resident-days[43]. Similar incidence were reported in Buffalo (2009 to 2011) and Monroe County, NY (2010) with a range between 1.3 and 2.9 cases per 10,000 resident-days[41,54]. The current study CCI-CDI incidence were approximately 10-fold less than that reported in the literature. These studies were conducted in the United States and this comparison suggests CDI in continuing care may be more of an issue in the United States than Alberta. AHS/COV IPC Surveillance conducts laboratory-event surveillance for CDI in continuing care. The reported 2013-14 incidence of CDI in continuing care was 3.6 cases per 100,000 resident-days for the province of Alberta. If reported per 10,000 resident-days this would be very similar to the incidence reported in this study. The methodology used in this study is very similar to IPC Surveillance of CDI in continuing care, with both using laboratory *C.*

difficile positives to determine CDI. But IPC Surveillance incident cases are identified solely on a continuing care population view and not an Alberta population view as this study did, meaning incident cases were identified only from those in continuing care versus this study identified incident cases from all settings then determined where the CDI occurred.

Of all CDI it has been estimated 40% are community-associated[44]. This study found approximately 47% of CDI from 2011-14 was community identified. Few studies have reported incidence of CDI in the community and of those who have there is marked variation. In the UK in 1999, the incidence in urban and semi-rural communities were reported at 29.5 and 20.2 cases per 100,000 individuals, respectively[47]. From 2004-2007 residents of Iowa and South Dakota, with a specific insurance carrier, had a community-associated incidence of 11.2 cases per 100,000 person-years[7]. Khanna et al. study from 2003-05 of Olmsted County, MN reported a community-associated incidence of 14.9 cases per 100,000 person-years[34]. A Canadian study in Quebec reported a community incidence of 156.3 cases per 100,000 in 2003[55]. The community CDI incidence observed in this study for Alberta were distinctively higher than the United States studies if compared at the same population value (i.e. both per 100,000 population). But the CI-CDI incidence of this study were less than that of the Quebec study; however, areas of Quebec were experiencing an NAP1 epidemic of CDI at the time[71]. The high incidence of community CDI found in this study could be attributed to the use of positive laboratory results alone. Studies have indicated incidence of community-associated CDI may be increasing due to increased testing as clinicians become more aware of CDI[22].

Although comparable community CDI studies generally report incidence per person-years, reporting per person-years in this study was not possible. Studies in the

literature reporting per person-years had their whole denominator at an individual level, meaning they were able to calculate the amount of time each person in the denominator was at risk for CDI. In this study, the denominator was aggregated and it was not possible to calculate the amount of time each individual was at risk for CDI and it was assumed each person in the denominator was at risk for CDI the whole year. At an individual level it would have been possible to calculate the time at risk for when a person turns 18 years of age, dies, or moves in or out of the population (i.e. Alberta).

6.2.3 Summary

In summary, the findings of research objective 1 were similar to previously reported literature and local surveillance. Overall, cases of CDI in Alberta were identified in the elderly, and more in females. Average age varied amongst the three populations, with the youngest being cases of CI-CDI and the oldest being cases of CCI-CDI. More cases of CDI were identified in 2013-14, and in the Calgary and Edmonton Zone. Compared to local CDI surveillance conducted by IPC Surveillance, the HI-CDI incidence reported in this study were higher. In this study only laboratory *C. difficile* positives were used to diagnosis CDI; therefore, the HI-CDI incidence reported were likely overestimates, which also is likely the scenario for CCI- and CI-CDI incidence as well. Although the HI-CDI incidence were likely overestimates, the incidence was lower than those reported in the literature, with a few exceptions. CCI-CDI incidence was considerably lower than comparable literature incidence, while CI-CDI incidence was markedly higher than the literature and comparable to incidence during a CDI epidemic.

6.3 Research Objective 2

6.3.1 Discussion of Study Findings

The second research objective was to investigate comorbidities and/or variables associated with mortality amongst hospitalized CDI patients. For this research objective the last HI-CDI case for an individual was selected. An individual could be identified with a HI-CDI case more than once. By definition there had to be at least 8 weeks between new primary CDI cases. Death was measured at 30 days post developing CDI. Therefore, to accurately represent mortality at an individual level the last HI-CDI case was included for this objective. Five-hundred and ninety five (9.8%) prior HI-CDI case duplicates were excluded.

Of the remaining 5,461 population, 14.8% (n=810) died within 30 days. Thirty-day all-cause mortality was higher for males (16.8%; n=416) compared to females (13.2%; n=394). Furthermore, there was a statistically significant difference in the proportion of females who were a CDI death, with less females in the CDI death group. Males were more likely to have a CDI death, which is not surprising as males die younger.

The mean and median age for CDI death group was approximately 10 years higher than the CDI non-death group. This is not surprising as older age is a predictor of death. Furthermore, being a resident of continuing care was also significantly different between the two groups, with a higher proportion of continuing care residency identified in the CDI death group. Again was likely related to age as those of advanced age are more likely to be residents of continuing care. Archbald-Pannone et al. reported the proportion of hospitalized CDI patients admitted from long-term care was significantly different amongst those who lived or died[72].

The mean and median total comorbidity count was significantly higher for those who were a CDI death; although, it was only slightly higher. Total comorbidity count is an ordinal variable; however, for this study it was considered continuous, commonly done in research studies[11,12,72]. On average, those individuals who died had a total comorbidity count of two while those who lived had a total comorbidity count of one. For this study total comorbidity count, equivalent to Charlson comorbidity index, was used instead of Charlson comorbidity score. The main reason was Charlson comorbidity score uses weighted estimates created in 1987 and medical care and treatment has vastly changed and improved since[102]; therefore, these scores likely do not represent the current risk of mortality. Although in the relevant literature calculating a score is a more common use of Charlson comorbidity index[68,71], count of comorbidities has been used as well[69]. Furthermore, Charlson comorbidity index rather than score has been used in similar studies[77]. Index is not the weighted estimate (i.e. score); however, Charlson comorbidity index and score are often used interchangeably in the literature. Therefore, it is hard to know if the index reported in Hensgens et al. is count or score. Nonetheless, for this study it was decided total comorbidity count was the better option as the weighted estimates are outdated.

Antibiotic exposure prior to developing CDI was significantly higher amongst the CDI death group. Antibiotic exposure is a known risk factor for mortality amongst patients with CDI[12,68]. But as with the previous research objective this antibiotic exposure was only measured according to antibiotics dispensed in the community in the 90 days prior to developing CDI. Therefore, the association found between antibiotic exposure and death could be true as it is supported by the literature or conversely could be due to an error in research design. Those who died had a shorter length of hospital stay

compared to those who lived; therefore, in the 90 days prior to developing CDI those who died may have had more opportunity to have antibiotics dispensed and included in the study while those who lived may have been in the hospital in the 90 days prior. Exposure to fluoroquinolone significantly differed between the two groups, those who died had significantly more exposure. Fluoroquinolone exposure in the 60 days prior to CDI diagnosis has been identified as a risk factor for mortality[12].

Of the comorbidities, cerebrovascular disease, chronic pulmonary disease, congestive heart failure, dementia, diabetes complicated, metastatic solid tumour, mild and moderate/severe liver disease, myocardial infarction, peripheral vascular disease, and renal disease had a higher proportion in those who died than lived. Conversely, HIV/AIDS, diabetes uncomplicated, malignancy, paraplegia or hemiplegia, peptic ulcer disease, and rheumatic disease had a higher proportion in those who lived. Suggesting these comorbidities were not predictors of death for this population. However, of those comorbidities only diabetes uncomplicated significantly differed between the two groups, with 4.4% (n=36) in CDI death and 7.2% (n=334) in CDI non-death.

Findings of significance did not differ between the comparative statistics used and univariate analyses as the statistical tests were similar. With the univariate analysis odds ratios and confidences intervals were calculated. A 95% confidence interval can be used to determine significance but also magnitude and precision of the estimate. Although male gender and antibiotic exposure were significant risk factors, their 95% confidence interval lower limit was just above one. An odds ratio of one indicates no difference between the two groups. Male gender and antibiotic exposure were identified as significant risk factors even though their lower limits were only slightly above an odds ratio of one, suggesting the large sample size likely caused these characteristics to be

identified as significant. Even though the p-values were significant, it is possible these characteristics are truly not risk factors for death amongst patients with CDI.

Age was centred age of zero was not meaningful; since, the youngest included individuals were 18 years of age. Furthermore, age was centred at the median as majority of the HI-CDI data were distributed around this value. For each additional year of age, the odds ratio increased by 1.1. Total comorbidity count was not centred. For each additional comorbidity count, the odds ratio increased by 1.6. For example, with a comorbidity count of three the crude mortality odds ratio would be 3.9. Increases in age or total comorbidity count resulted in increasing odds of death. This is unsurprising as increasing age is a predictor of death as well, as having more comorbid conditions.

Recurrence was not identified as a risk factor for mortality amongst patients with CDI. Cadena et al. found recurrent CDI cases were significantly associated with 90-day mortality based on a univariate analysis[68]. For this research objective a smaller timeframe of 30 days was used; therefore, could explain the difference found in this study compared to Cadena et al. However, in that study recurrent CDI cases were not a significant risk factor in the multivariable regression model. Labbe et al. reported prior episodes of CDI was not a risk factor for 30-day all-cause mortality[71]; therefore, the findings of this study may be accurate.

Comorbidities that were significant based on univariate analyses were chronic pulmonary disease, congestive heart failure, dementia, diabetes complicated and uncomplicated, metastatic solid tumour, mild and moderate/severe liver disease, myocardial infarction, and renal disease. With the exception of diabetes uncomplicated, all significant comorbidities were identified as risk factors for death. Although diabetes uncomplicated was identified as protective against death, the 95% confidence upper limit

was just below one, suggesting this comorbidity was not really protective. Furthermore, the proportion of diabetes uncomplicated was higher for those who lived possibly surmising prognosis is fair for those with this comorbidity. In conclusion, univariate analyses identified nine of the 17 Charlson comorbidities as risk factors for death amongst patients with CDI. However, age and total comorbidity count confounded the comorbidity-death relationship for majority of the comorbidities; therefore, all comorbidities were adjusted by age and total comorbidity count. Since not all comorbidities were confounded by age and total comorbidity count; rather, had differing confounders and modifiers, adjustment by these two covariates could have impacted the results of this study.

The interpretation of some comorbidities changed with the adjustment by age and total comorbidity count. Chronic pulmonary disease, congestive heart failure, dementia, diabetes complicated, myocardial infarction, and renal disease were no longer identified as significant risk factors for death. Meaning for those of the same age and total comorbidity count, the presence of these comorbidities did not increase the odds of death, suggesting age and total comorbidity count were the predictors for death and not these comorbidities. Comorbidities that were identified as protective after adjustment were cerebrovascular disease, paraplegia or hemiplegia, peptic ulcer disease, and peripheral vascular disease. Diabetes uncomplicated remained protective against death. For these comorbidities the 95% confidence upper limits were just below one, suggesting these comorbidities may not really be protective. Mild and moderate/severe liver disease and metastatic solid tumour remained risk factors after adjustment, suggesting the presence of these comorbidities were risk factors for death regardless of age or total comorbidity count.

Although the 95% confidence interval lower limits were just under one, the findings of cerebrovascular disease, paraplegia or hemiplegia, peptic ulcer disease, and peripheral vascular disease being protective against death was peculiar. Either the large sample size resulted in spurious significant associations where truly there were none or the explanations were due to the logistic model construction or biological plausibility.

The proportions of HI-CDI individuals with paraplegia or hemiplegia and peptic ulcer disease were slightly higher for those who lived than those who died, suggesting these comorbidities were not important predictors of death. Again the proportions of HI-CDI individuals with HIV/AIDS, malignancy, and rheumatic disease were slightly higher for those who lived than those who died; however, after adjusting for age and total comorbidity count these comorbidities were not identified as significant protective factors as was the case for paraplegia or hemiplegia and peptic ulcer disease. The number of individuals with malignancy was considerably larger than those with either paraplegia or hemiplegia, or peptic ulcer disease; thus, large sample size appears to not explain the apparent significant protective association. Inspection of the lowess smooth curve plot for both age and total comorbidity count for paraplegia or hemiplegia and peptic ulcer disease provided a plausible explanation for the apparent protective effect. For both these comorbidities and for both age and total comorbidity count, the log odds of death were higher for those without these comorbidities. This suggests at any age and total comorbidity count those without these comorbidities were at higher risk of death, suggesting either those without these comorbidities had other conditions contributing to death or these comorbidities were biologically protective. The latter seems unlikely as there is no apparent biological explanation for protectiveness. Therefore, after adjusting for age and total comorbidity count those without paraplegia or hemiplegia, or peptic

ulcer disease likely had other conditions contributing to mortality, more severe CDI, or the associations found here were spurious.

Of the Charlson comorbidities, two are vascular diseases and strangely both were deemed protective after controlling for age and total comorbidity count. A large sample size could have resulted in a spurious association between these comorbidities and death; however, model construction or biological plausibility were other factors to be considered. The proportion of HI-CDI individuals with either cerebrovascular disease or peripheral vascular disease were slightly higher for those who died; therefore, the prognosis for those with these comorbidities seemed to be slightly poorer. Inspection of the lowess smooth curve plot for total comorbidity count for cerebrovascular disease and peripheral vascular disease provided a plausible explanation for the apparent protective effect. For both these comorbidities the log odds of death were higher for those without these comorbidities at any total comorbidity count, suggesting either those without these comorbidities had other conditions contributing to death or these comorbidities were biologically protective. These findings were not found with age as at any age those with these comorbidities were at a higher risk of death. There is no apparent biological explanation for these vascular comorbidities to provide protectiveness against death amongst CDI patients. Therefore, after adjusting for age and total comorbidity count for those without cerebrovascular disease or peripheral vascular disease they must have had others conditions contributing to mortality, more severe CDI, or the association found here were spurious.

Patients with liver disease are at high risk for developing CDI[65]. Yet only approximately 6% of the study population for research objective 2 had liver disease. However, after controlling for age and total comorbidity count both mild and

moderate/severe liver disease increased the odds of death. Liver disease is associated with increased mortality; furthermore, patients with both liver disease and CDI are at higher risk of mortality compared to those without CDI or with other infections[103,104].

CDI patients who are immunocompromised are a higher risk of dying[11]. Patients with cancer are immunocompromised, either due to the cancer itself or due to chemotherapy. Although cancer has been identified as risk factor for mortality amongst patients with CDI[12,70], only metastatic solid tumour comorbidity was identified as a risk factor and not malignancy as well. Individuals with cancer that metastasized have poorer prognosis; therefore, could explain why only metastatic solid tumour was a risk factor for death.

Each comorbidity logistic regression model adjusted for age and total comorbidity count had an AUC of approximately 0.71, indicating the final models had fair discrimination ability. Thus, it appears the final models chosen were appropriate and the results of analyses were reliable.

6.3.2 Study Risk Factors Compared to the Literature

Increasing age is a risk factor for death 30 days after CDI diagnosis[67]. As mentioned prior, it has been estimated 93% of CDI deaths occur in those 65 years of age and older[16]. Studies investigating age as a risk factor for mortality amongst patients with CDI traditionally dichotomize age or create age groups. Death increases with increasing age groups and the resulting mortality odds ratios were larger[11]. However, there have been CDI mortality studies which used continuous age and they reported odds ratios similar to the findings of this study[11]. Similar findings in the literature support age was correctly identified as a risk factor for mortality amongst CDI patients. In addition to this

criteria for causality (i.e. consistent association), three other Hill's postulates were met: temporality, dose-response relationship, and biological plausibility. Consistent association since age is consistently supported as a risk factor in the literature. Temporality as age came before death. Dose-response relationship as with increasing age an individual is at higher risk of death. Biological plausibility as biologically it makes sense increasing age is associated with higher risk of death.

Findings in the literature did not support the findings here of male gender being a significant risk factor for mortality[11,69]. Although no significant findings have been reported for male gender, the reporting odds ratios suggest males die more often than females. Bloomfield et al. reported 11 studies that had investigated gender as a risk factor for death and found the odds ratios were slightly elevated in favour to males[11]. As mentioned prior the 95% confidence interval lower limit for male gender was just above one, suggesting the significance found in this study was a result from large sample size and may truly not be a risk factor. Or conversely previous studies did not have such a large sample as this study and were unable to identify gender as a risk factor for death.

In this study population, increasing total comorbidity count resulted in higher odds of death. These findings are supported by the literature; however, these studies investigated Charlson comorbidity scores and not counts[12,68,71,72]. Nonetheless, the findings of those studies were similar to this study. Two studies found per increment increase in Charlson comorbidity score the odds ratio increased by 1.2[12,68]. This study's univariate analysis odds ratio was 1.6 per unit increase in total comorbidity count, while multivariate analyses the odds ratios were approximately 1.5 per unit increase. Total comorbidity count is likely a risk factor for mortality amongst patients with CDI and appears to meet five of the six Hill's postulates (temporality, strong association,

consistent association, dose-response relationship, and biological plausibility). Strong association as the resulting estimate of association (i.e. odds ratio) is high.

Antibiotic exposure and continuing care were discussed and compared to the literature in section 6.3.1; therefore, will not be reiterated here.

Prior to controlling for age and total comorbidity count, comorbidities identified as risk factors for mortality amongst CDI patients were chronic pulmonary disease, congestive heart failure, dementia, diabetes complicated, metastatic solid tumour, mild and moderate/severe liver disease, myocardial infarction, and renal disease. Previous studies have investigated these comorbidities as potential risk factors for death amongst individuals with CDI. However, the definition of these comorbidities varied amongst the studies (i.e. inclusion criteria) and studies either used univariate or multivariate analyses. Furthermore, within the literature there appears to be inconsistencies in the findings of these comorbidities as risk factors. For chronic pulmonary disease, the findings are contradictive with studies reporting pulmonary disease as a risk factor, while others failed to prove so[13,45,69,70]. In the literature it appears myocardial infarction and congestive heart failure are categorized together under cardiovascular disease. Overall, the literature appears to agree with these as risk factors for death with the exception of one study reporting no significance, but likely due to low power[12,13,45,70]. A multivariate logistic regression model in one study reported cognitive impairment as a risk factor for mortality amongst CDI patients. Other reported significant variables in the multivariate logistic regression model were older age, cancer, cardiovascular disease, respiratory disease, and renal disease[70]. Majority of published findings found diabetes to not be a significant risk factor for mortality[11,13,69], while one reported it as an important predictor of mortality[105]. However, these studies did not differentiate by severity of diabetes; therefore, could

explain why this study found diabetes complicated as a risk factor as complications could have led to poorer outcomes. The literature findings on cancer as a risk factor are inconsistent, with a few studies indicating it as a risk factor[45,70,105,106], while others not finding this association[11,13,69]. However, as with diabetes these studies did not differentiate between stages of cancer; therefore, could explain why this study found metastatic solid tumour as a risk factor; since, cancer that has spread has poorer prognosis. Liver disease appears to be a significant risk factor for mortality for individuals with CDI[103–105,107]. Welfare et al. did not find liver disease as a significant risk factor; however, believed it was due to low power[70]. The findings of renal disease as a risk factor are inconsistent[11,69,70,105].

After adjustment of all comorbidities, chronic pulmonary disease, congestive heart failure, dementia, diabetes complicated, myocardial infarction, and renal disease were no longer identified as significant risk factors for death. With the exception of cardiovascular disease, the literature findings are inconsistent on these comorbidities; therefore, it is impossible to say the literature supports the findings of this study. Additionally, none of these studies controlled for both age and total comorbidity count; therefore, comparing to these studies may be inappropriate. For these comorbidities, age and total comorbidity count were likely the strong predictors of death and not the comorbidities themselves.

Comorbidities that were identified as protective after adjustment were cerebrovascular disease, paraplegia or hemiplegia, peptic ulcer disease, and peripheral vascular disease. Diabetes uncomplicated remained protective against death. No findings in the literature support this studies finding of these comorbidities as protective against death. Mild and moderate/severe liver disease and metastatic solid tumour remained risk factors after adjustment and the odds ratios slightly increased. As mentioned prior, the

literature findings on cancer as a risk factor are inconsistent, but again these studies defined cancer with a wider scope. In this study malignancy was not found as a risk factor, but metastatic solid tumor was; therefore, this distinction was likely the important factor. Overall the literature appears to support the findings of liver disease as a significant risk factor for mortality for patients with CDI. For metastatic solid tumour, it appears three of Hill's postulates for causality were met: temporality, strong association, and biological plausibility. For liver disease, it appears three of Hill's postulates for causality were also met: temporality, consistent association, and biological plausibility.

Although the associations between death, age, total comorbidity count, mild and moderate/severe liver disease, or metastatic solid tumour did not appear to be spurious and each met various Hill's postulates for causality, this study investigated all-cause mortality; therefore, variables identified here as risk factors cannot be concluded as the definite causal factor for the death; however, the associations found were likely accurate.

6.3.3 Summary

Covariates identified as statistically significant risk factors for death amongst hospitalized CDI patients were male gender, older age, antibiotic exposure, and more comorbid conditions. With the exception of male gender, these findings were supported by the literature. Significant associations found between comorbidities and death differed between univariate and multivariate (i.e. adjusted for age, and total comorbidity count) analyses. With the exception of liver and cardiovascular disease, comorbidities identified as risk factors for death amongst CDI patients is inconsistent in the literature. There was no literature supporting cerebrovascular disease, paraplegia or hemiplegia, peptic ulcer disease, and peripheral vascular disease as protective against death. In general given the

large numbers, statistical significance must be viewed with caution and only those characteristics and comorbidities viewed as clinical significant by clinicians should be considered significant contributors to death.

6.4 Research Objective 3

6.4.1 Discussion of Study Findings

The third research objective was to investigate inter-rater reliability between the DARPIC algorithm and expert reviewers for CDI death attribution. Of the study population reviewed, the two groups (student reviewer and expert reviewers) found 30% and 39% of the deaths that occurred within 30 days of CDI diagnosis were attributable to CDI (i.e. CDI either directly related or contributed to death). The attributable percentages reported in this study are similar to those reported in the literature. Previous studies reported attributable CDI mortality of 35% and 40%[67,94].

The student reviewer and expert reviewers reported 41 and 53 deaths as CDI-related, respectively. However, the two groups were only concordant on 32 of these deaths. The expert reviewers deemed more deaths as CDI related than the student reviewer. The strict nature of the DARPIC algorithm likely contributed to the potential underreporting of CDI-related deaths by the student. With the strict use of the DARPIC algorithm, the student reviewer was more likely to classify a death as unrelated to CDI compared to the expert reviewers whose discordant results were either classified as related to CDI (n=21) or unable to determine (n=18). The expert reviewers classified markedly more deaths as unable to determine, this is likely due to the fact the expert reviewers also used this category when there was a lack of information available to make a decision regarding death. The DARPIC algorithm does not have a category for such

instances; thereby, likely contributes to the student reviewer reporting more CDI-unrelated deaths.

The kappa statistic assessing for inter-rater reliability between the student reviewer and expert reviewers indicated a fair agreement (kappa=0.36). However, if reported on a scale the resulting kappa would be closer to poor agreement than to perfect agreement. The corresponding p-value was not reported as it does not measure the strength of agreement but that the kappa is not due to chance. The p-value was significant meaning the resulting kappa was not due to chance. The kappa statistics for CDI-related, CDI-unrelated, and unable to determine were 0.51, 0.23, and 0.27. The kappa statistic for CDI-related was higher than the overall kappa statistic and its value indicates moderate agreement. The other two categories kappa statistics indicated fair agreement. Overall, agreement between the student reviewer and expert reviewers was better for deaths classified as CDI-related.

The kappa statistic only crudely reports the agreement between two groups and does not assess for validity. This is appropriate in this study as a gold standard was not assigned; although, it could be argued as the expert reviewers are IPC physicians their death decisions could be considered the gold standard. However, as noted prior many experts are concerned about the ability to determine attributable CDI mortality[67,79–81]; therefore, assigning a gold standard may not be appropriate. It is also important to note three reviews were necessary to reconcile the expert reviewers' death decisions. In the first review 39% were discordant and decreased to 18% after the second review.

6.4.2 Death Attribution Issues

There were two marked issues for death attribution. Thirty-days from CDI diagnosis is crudely used to include or exclude deaths for review; however, individuals CDI symptoms or lack of symptoms is not considered in this timeframe. Individuals' symptoms may have resolved prior to death, yet how to consider this into CDI death attribution is unclear. Additionally, individuals may have died greater than 30 days from CDI diagnosis but may have been experiencing continual CDI symptoms, suggesting no resolution.

Another issue with death attribution in this population was noted in section 3.7.2. Individuals who die and have CDI usually are the elderly with multiple comorbidities[67,79,80]. Therefore, assigning CDI attribution to death in circumstances where the individual is very ill and potentially near death is extremely difficult. Using their clinical judgment, the expert reviewers mitigated this by trying to determine if CDI exacerbated demise (i.e. contributed) or if the individual would have died even without CDI (i.e. unrelated).

6.4.3 DARPIC Algorithm Issues

Although the DARPIC algorithm is relatively easy to use and fairly clear, issues arose during the student review. Many of the issues found in this study were that the elements used in the algorithm were rarely relevant or reported in the medical charts. For the patients in this study, death certificates were rarely completed; therefore, relying on this information for death attribution was not feasible. "Death from another rare but obviously direct result of CDI" element of the algorithm is very broad and fairly unclear

as death could be obviously due to CDI but maybe not due to a rare complication as the example provided in the algorithm.

For unable to determine the algorithm only assigns this category when "death of patient expected within 7-14 days from underlying or coincident disease(s)". The student reviewer noted potential issues with this element regarding how specific it is and what it does not include. The attending physicians rarely assigned a time value to the patient's survival expectancy. If noted at all it usually was noted as "poor condition", "condition is grave", and only in a few instances less than a few days or week(s) were charted. As it can be unclear if the patient's death is imminent, these instances would be classified as CDI-unrelated according to the algorithm. Additionally, this category does not include individuals where death attribution is unclear and strictly using this algorithm, as the student reviewer did, results in these instances categorized as CDI-unrelated. The expert reviewers include deaths where there was a lack of information regarding death attribution in the unable to determine category, which does seem appropriate. The algorithm does not include this in the unable to determine category and neither in the whole algorithm.

Other elements of the algorithm that arose as issues due to the information not reliably charted were the number of diarrheal episode near time of death and if there was abdominal pain. This will further be discussed in the next section regarding data collection issues.

The last issue regarding the DARPIC algorithm was with the definition of CDI contributing to death only being "death due to sudden deterioration of a 'stable' pre-existing medical condition". Two major issues were the ability to determine if the condition was stable and that being noted in the medical chart. Furthermore, it was

questionable if this definition was even inclusive for all potential circumstances of CDI contributing to death. Using the DARPIC algorithm, the student reviewer had to assign deaths as CDI-unrelated when CDI likely contributed to death because the information available could not support death due to a sudden deterioration in a stable pre-existing condition.

6.4.4 Data Collection Issues

A common theme noted in the DARPIC algorithm issues section was poor charting in patients' medical records. Many of the elements necessary for the DARPIC algorithm were not reliably charted. Besides the specific nature of the DARPIC algorithm, the expert reviewers found a lot of valuable information incomplete on the data collection form. During the chart review, the student reviewer collecting the information found stool charting and abdominal pain charting to be very incomplete and inconsistent. Additionally, the probable cause of death was rarely noted. A common situation found was a patient transferring to inpatient hospice prior to death and once in hospice bloodwork was not conducted and usually charting in the multidisciplinary progress notes stopped. Therefore, many elements of the DARPIC algorithm and information vital for the expert reviewers were not available near time of death. This likely contributed to the high number of unable to determine by the expert reviewers. Unfortunately, as mentioned prior the DARPIC algorithm does not account for lack of information which in certain instances these cases were classified as CDI-unrelated. However, there were instances where unable to determine could be assigned as death within 7-14 days from underlying disease was clear.

Valuable information missing from the data collection may not solely be due to poor charting, but could have been missed by the student reviewer. Although the student reviewer has considerable knowledge regarding CDI and CDI mortality, the student reviewer was not a physician. Therefore, information a physician may clearly know to be important could have been missed by the student reviewer. The elements included in the data collection form were thoroughly reviewed by the expert reviewers to help mitigate this issue; however, for this study it is impossible to know if important information was missed during the chart review.

The retrospective nature of this review also was evident as a limitation to data collection. From the time of the chart review and the last patient who died in the study was greater than 2 years. Any information not documented in the medical charts was lost. Currently, in a clinical setting the expert reviewers who conduct CDI death attribution may discuss patients' deaths with attending physicians and nurses if more information was necessary. Many of the issues that arose for the expert reviewers and student reviewer were due to the retrospective nature of the study. Some issues noted with the DARPIC algorithm would have likely not been issues if a prospective study was conducted (i.e. stool charting, patient's coinciding conditions, etc.). Fortunately, death 30 days post CDI diagnosis is infrequent, but that would be a limitation to conducting a study like this prospectively. A prospective study would have taken too long to complete and would have not been feasible.

6.4.5 Summary

In summary, inter-rater reliability between the student reviewer and expert reviewers' death attributions were fair to moderate depending on the death decision, with

CDI-related deaths having the highest kappa statistic and CDI-unrelated deaths having the lowest. The expert reviewers decided more deaths were CDI-related than the student reviewer. Additionally, the expert reviewers decided more deaths were unable to determine than the student reviewer. The findings of this objective revealed for further use of the DARPIC algorithm in the clinical setting, modifications must be made. The DARPIC algorithm originally was created for a different purpose. Therefore, for routine and practical use of this algorithm by Infection Control staff, it should be modified and issues identified in this review should be considered as revision points.

6.5 Strengths, Limitations, and Biases

6.5.1 Research Objective 1

A unique aspect of this study was the identification of CDI cases at a population level. Although CDI cases were reported for three (sub)populations, the incident CDI cases were not identified at these subpopulation levels; rather, all positive *C. difficile* results for an individual were considered when determining incident cases, regardless of where the specimen was collected. For example, new incident cases were defined as new CDI or repeat CDI that was at least 8 weeks from a previous primary CDI case; thus, CDI was measured at an Alberta population view. Traditional surveillance mainly reports CDI identified in the hospital; thereby, identifying incident CDI cases at a hospital population level. With traditional surveillance, CDI cases that do not occur in hospital are not investigated, measured, or reported. A narrow view of identifying CDI cases only in subpopulations allows for over count of cases of CDI, as what is occurring at an individual level is not considered. For example, an individual could have been reported with a CDI case in hospital, discharged then re-tested in the community within 8 weeks

and if there was no consideration about CDI occurring in the hospital the individual could again be reported with CDI but now in the community. However, in this study the community CDI case would have not been considered a new primary CDI case as it would be within 8 weeks of the previous primary. Very few studies have investigated and reported CDI cases in the community. Additionally, this had never been reported for all of Alberta.

The sheer number of CDI cases identified in this study ensured the characteristics reported in this study were representative of the populations (e.g. age, gender). Furthermore, thorough investigation into age, gender, and Zone was done and comparisons of means and proportions across the three populations could be made. For example, this study uniquely allowed for the comparison of gender-specific incidence over three fiscal years per population and down to the Zone level. With three fiscal years reported, differences over the years could be observed. Unfortunately, as the denominators were different between the three populations (e.g. hospital admissions, resident-days, and population) incidence could not be compared. Only incidence with similar denominators could be compared. Nonetheless, trending and comparisons within populations at gender and Zone level were possible in this study.

Traditional surveillance CDI diagnosis requires both a positive laboratory result and the presence of disease symptoms (i.e. abdominal pain and diarrhea)[108]. Or in rare circumstances diagnosis of pseudomembranous colitis or toxic megacolon is used to diagnosis CDI. However, for research objectives 1 and 2 a positive *C. difficile* laboratory result alone was used to identify a case of CDI. These research objectives involved over 12,000 and 5,000 cases of CDI, respectively. Identifying symptoms for over 12,000 cases would be impractical and not feasible. Consequently, as this study did not consider the

clinical criteria necessary to diagnosis CDI, CDI cases may have been overestimated; thus, resulted in overestimates of the incidence as well. This study relied on laboratory-event surveillance which compared to traditional surveillance could overcall CDI incidence[109]. However, laboratory-event surveillance may be a better option compared to other non-traditional surveillance measures such a discharge diagnosis, which could markedly underestimate CDI[36,37,38].

As described in section 3.5, individuals with *C. difficile* can be asymptomatic carriers. Asymptomatic carriage differs amongst various populations, and is not always associated with antibiotic or healthcare exposure[110]. Relevant to this study is asymptomatic carriage in the hospitals, continuing care, and community. Vastly different asymptomatic carriage rates have been reported for the general hospital population, with reports of 4 to 29% and other suggesting between 20 and 30%[2,108]. For residents of continuing care, approximately 0 to 51% may be asymptomatic carriers[108]. While the healthy population, which could be assumed to be equivalent to the community population, has asymptomatic carriage rate between 0 and 15%[2,108]. Therefore, depending on the population a certain proportion of the CDI cases identified in this study could have been in individuals who truly did not have CDI, but rather a positive *C. difficile* laboratory result only. However, individuals with asymptomatic carriage do not always have a positive *C. difficile* result as positive results are usually indicative of active disease. The laboratory methods' identify *C. difficile* toxin production and as the symptoms arise from toxin production those without symptoms (i.e. asymptomatic carriers) are less likely to have detectable levels of toxin; thus, have a negative result. However, this is not always the case and is why the clinical criteria is important in the diagnosis of CDI[108]. As reported by Scheurer et al., 14% of *C. difficile* toxin positive

results (according to cytotoxic assay) occurred in asymptomatic patients[36]. The laboratory method used and population at risk influences the amount of individuals who test positive for *C. difficile* and are asymptomatic. Scheurer et al. is one of the few studies, none of which are recent, that has approximated a value of positive results occurring in asymptomatic individuals[36]. Fourteen percent would indicate a slight overcall of CDI when using laboratory-event surveillance, but according to an Alberta study positive *C. difficile* laboratory results alone were a good proxy for CDI[35]. Furthermore, laboratory confirmation should only be performed for symptomatic patients (i.e. active diarrhea).

The methodology used to identify CDI likely resulted in misclassification bias, a type of systematic error. Misclassification bias results from measurement errors of the exposures, covariates, or outcomes. There are two types of misclassification biases; differential and non-differential. Differential misclassification occurs when the probability of the variable being misclassified is disproportional over groups within the study. Non-differential misclassification occurs when the probability of a variable being misclassified is uniform over groups within the study[24]. Given that the population at risk and the laboratory method used could influence the proportion of positive *C. difficile* laboratory results that were truly not CDI, the misclassification bias was likely differential.

The two step *C. difficile* laboratory method introduced in Alberta in early 2013 has both a high sensitivity and specificity (i.e. range from 80-100%), meaning the method is superior at identifying true cases of *C. difficile*, while also being superior at indicating non-cases of *C. difficile*. Prior to 2013, PCR was not widely used in the confirmation of indeterminate results, with the exception of Calgary Zone. Prior to 2013, EIA toxin was used. EIA toxin has a high specificity, but a low to moderate sensitivity, meaning the

likelihood of false-positives is low, but the chance of false-negatives is high. Overall, would result in an underestimation of *C. difficile*. With the implementation and wide use of PCR as well as EIA in early 2013, the sensitivity of the laboratory identification method increased; thus, increasing the detection of *C. difficile*. Tartof et al. noted a 34% increase in incidence rate with the implementation of PCR testing[111]. As mentioned in the discussion for research objective 1, in all Zones except the Calgary Zone the number and incidence of CDI increased in 2013-14. The increase observed in four of the Zones could be due to the switch to a more sensitive *C. difficile* laboratory method. This is further supported by the fact cases of CDI did not increase in the Calgary Zone in 2013-14 as a more sensitive method was already in use. Although all laboratories in Alberta were to standardize their *C. difficile* laboratory methods, it is not possible to know if it occurred in a timely manner or if all laboratories are truly performing the same methodology. Therefore, Zone comparisons of CDI cases should be viewed cautiously.

The positive *C. difficile* laboratory results were categorized into three populations depending upon where the specimen was collected; hospital, continuing care, or community. Where the specimen was collected may have not been where the CDI was acquired or could be attributed to. For example, an individual could have tested positive for *C. difficile* in the community a couple days after a hospital discharge and in this study these cases would be classified as a CI-CDI case when truly it may have been hospital-acquired. Or the individual may have be positive for *C. difficile* upon hospital admission and the CDI case was acquired in the community. To determine attribution much more personal information would have been required such as hospital discharges in the four weeks prior to any *C. difficile* positive and exposure to dialysis. The definitions used to attribute CDI are not straight forward and trying to use such definitions with

administrative data would have been difficult. It would have been more time-consuming and the value that it would have added to this study is unknown. IPC CDI surveillance already reports the attribution of hospital CDI cases. Of hospital total CDI cases, in 2013-14, reported by IPC Surveillance, 64% were hospital-acquired, 31% were community-acquired, and the remaining 5% were healthcare-associated. These proportions could be used to estimate CDI attribution for this studies HI-CDI cases. However, the number of CI-CDI cases that were truly hospital-acquired could not be estimated. Knowing when symptoms of CDI started is crucial in determining CDI attribution; therefore, solely relying on timeframes of when a positive *C. difficile* result occurred in relation to hospitalization(s) or continuing care admission may not be appropriate for attributing CDI acquisition. For the purpose of this study to describe and compare the populations, identification of where CDI cases occurred was suitable.

Antibiotic exposure was defined according to antibiotics dispensed in the community 90 days prior to the CDI case. Pharmaceutical Information Network (PIN) only includes information on pharmaceuticals dispensed in the community and data for the whole province is collectively stored. There is no such database for antibiotics dispensed in the hospitals nor continuing care facilities that have their own pharmacies. Individuals hospitalized at the time of CDI or in the 90 days prior to developing CDI would have their inpatient antibiotic data stored in hospital or local inpatient pharmacy databases. These databases are not set up to extract information for specific individuals; rather, all individuals with antibiotics dispensed would be included in the data extraction. To accurately report inpatient antibiotics for this study, all patients with inpatient antibiotics dispensed, likely at all hospitals in Alberta, for the three fiscal years would have been necessary. Millions of records would have likely resulted and acquiring that

much personal information for this research study would have likely not been ethical. It was also estimated this data extraction could have taken more than a year. For this study, acquiring antibiotics dispensed in the hospital would have been impractical if not impossible currently.

As only antibiotics in the community could be identified for this study, this is likely why CDI cases in the community had more antibiotic exposure and to more antibiotics. Individuals identified with HI- or CCI-CDI case may have been hospitalized or in continuing care in the 90 days prior to the CDI case; therefore, would have no available information in the PIN database. This would not only be a problem for HI- and CCI-CDI cases but cases of CI-CDI where the individuals were hospitalized in the 90 days prior to developing CDI. By only using antibiotics dispensed in the community, misclassification bias of antibiotic exposure resulted. The misclassification bias was likely differential as cases of HI-CDI were more likely to be missing antibiotic information due to the lack of inpatient antibiotic data. With the exception of community cases with no recent hospitalizations, true antibiotic history was not determined in this study. Therefore, comparisons of antibiotics dispensed amongst the three groups should be made cautiously and with consideration of this study limitation.

Recurrent CDI cases were defined as repeat primaries at least 8 weeks from a previous primary. As the time into the study period increased, the likelihood of identifying subsequent primary cases increased. The proportion of recurrent cases found in the 2011-12 fiscal year was likely an underestimate as cases occurring prior to the start of the study period were not captured. Additionally, recurrence occurring after the study period was not evaluated either. Future work could include defining a recurrent follow-up time such as one year and including a period of time prior to the start of the study period.

With both of these in mind the inclusion time surrounding the study period would be longer. The proportion of recurrence observed amongst the three populations should have not been impacted by the study design; thus, could be compared. The only difference that could be explained by study design was the increase in recurrence proportion over the three fiscal years. The misclassification of recurrence was likely differential as the probability of being identified with a recurrent case changed over the study period. It could be argued recurrence should only be defined if the individual had been successfully treated for CDI and had symptom resolution in between cases. Therefore, determining recurrence with administrative data alone may not be appropriate.

HI-CDI hospital admission denominators used for this study were calculated using an estimate of discharges from 2013-14 Alberta hospitals (i.e. 79% of discharges were those 18 years and older, with 60% of those being females). Unfortunately, the current ADT dataset used to calculate hospital admissions does not include age and gender. The estimated HI-CDI denominator for males was smaller than females, which overall resulted in a higher HI-CDI incidence for males even though fewer cases of HI-CDI were identified in males. Potentially, the estimate used to calculate HI-CDI gender denominators may have been oversimplified. HI-CDI cases were identified in older individuals and this older age group may have had a different proportion of males to females. For example, the age group over childbearing age but before advanced age could have had more male than female discharges meaning the 60% (for females) used to separate the hospital admission by gender may have been incorrect. However, females live longer than males; thus, more discharges of the very elderly would likely be females. The impact of the estimate used to calculate HI-CDI gender denominators on the gender HI-CDI incidence is unknown. Nonetheless, it could be argued the likely fluctuations in

the proportion of female and male discharges over age are not an issue if not stratified by age as the overall gender distribution of hospital admissions is revealed.

Resident-days from the ACCIS database were used to calculate CCI-CDI incidence for this study. This database includes age and gender; therefore, there should have been no issues with the CCI-CDI denominators. The denominators used to calculate incidence of CDI in the community were derived from the Alberta Health Care Insurance Plan (AHCIP) Population Registry. As mentioned in section 4.4.2, this registry excludes Armed Forces, RCMP, inmates in federal penitentiaries, or those who have opted out of coverage. However, as of April 1, 2013 RCMP began to be covered under AHCIP. Using this registry could have resulted in a slight underestimation of the Alberta population. However, there was also the chance of overestimation as individuals may be registered with AHCIP but could live out of province. At the time, AHCIP was free so individuals who previously lived or worked in Alberta may have taken advantage of this situation and kept their AHCIP after moving out of province. Situations with either under- or overestimation are likely rare and would have had a small impact on the large CI-CDI denominators. The ACHIP registry included age and gender and was the only population data source known to stratify by Zone; therefore, was the most appropriate denominator for calculating incidence of CDI in the community.

Another systematic error besides misclassification bias is selection bias. Selection bias is when those included or retained in the study are systematically different from the source population; therefore, no longer representative of the population being studied[24]. For research objective 1, there would have been no issues with selection bias as all those in the study population were eligible to be included. Systematic errors such as selection and misclassification bias effect the internal validity of a study. Threats to external

validity include generalizability[24]. The findings of research objective 1 are likely not generalizable to those under 18 years of age as they were excluded from this study. The generalizability of these results to other populations outside of Alberta may depend on the population demographics (i.e. age), *C. difficile* strain, and endemicity of CDI. However, there is no evident reason these results could not be generalizable to other provinces. Random error is a type of non-systematic error where variability is due to chance alone[24]. Increasing the study size decreases random error. Research objective 1 study population was over ten thousand; therefore, random error was likely not an issue.

In summary, the large, population view investigation of CDI in Alberta done by this study was novel. Many studies investigate subpopulations, such as cases occurring only in the hospital. Furthermore, this was the first study to report cases of community CDI in all of Alberta. However, this study used *C. difficile* laboratory positives to diagnosis CDI and did not use clinical criteria as well; thus, the number of CDI cases reported in this study were likely overestimates. The change to a more sensitive *C. difficile* laboratory method in early 2013 likely contributed to the increase in CDI cases in 2013-14. Although all laboratories in Alberta were to standardize their *C. difficile* laboratory methods, it is not possible to know if that occurred. Misclassification bias likely occurred for antibiotic exposure and recurrent CDI cases. There were no issues with selection bias and the results are likely generalizable to other provinces with similar demographics and endemicity of CDI.

6.5.2 Research Objective 2

The strengths, limitations, and biases of using of positive *C. difficile* laboratory results to indicate CDI cases has already been discussed in section 6.5.1; therefore, will

not be repeated in this section. Similarly, the limitations of CDI identification, antibiotic exposure, and recurrence have already been discussed and will not be discussed in this section.

Administrative data are widely used in epidemiological studies and is an important resource for these studies[112]. Administrative data are an efficient, timely, and inexpensive resource in the conduction of population-based studies[113–115]. These data are readily available for large populations geographically dispersed[114–116].

Administrative data are commonly used to identify comorbidities. Comorbidities are important determinants of patient outcomes and can confound the exposure-outcome relationship[114,115,117]. The advantage of using a comorbidity index is it allows for multiple comorbidities to be incorporated into a single value, in which overall comorbidity burden can be controlled for rather than individual comorbidities[112,114,118,119]. The most common comorbidity index is the Charlson comorbidity index, published in 1987, that was originally developed to predict one-year mortality. Originally, there were 19 comorbidities, later reduced to 17 comorbidities. Charlson comorbidity scores can be calculated using weighted estimates[112,117,119]. Charlson comorbidity index has been validated in different patient populations (i.e. >30,000 patients) with varying diagnoses, surgical procedures, and for non-death clinical outcomes[114,115]. Additionally, methodology using ICD-10 codes to determine Charlson comorbidities has been developed[85]. Measuring comorbidities accurately is vital when assessing the impact comorbidities have on outcomes or to control for comorbidity confounding[112].

Administrative data are not created for research purposes; rather, when used as such it is a secondary use. The accuracy of the data needs to be considered[120]. The accuracy of the ICD-10 codes to identify and classify comorbidities is relevant for this study. It has

been stated “diagnoses are occasionally erroneous, often coded incorrectly, and frequently omitted from administrative data”[118]. Overall, the literature agrees administrative data underreports comorbid conditions[115,118,119,121] and the degree of variation can be due to differences in populations, methods, or the comorbid condition[118,121].

Charlson comorbidities defined by administrative data are commonly compared to chart reviews to assess for validity and reliability. Chart reviews are commonly used as the gold standard[119]. Schneeweiss et al. reported comorbidity scores of 0, 1, 2, and 3+ were 38%, 32%, 18%, and 12% for chart review and 65%, 27%, 7%, and 1% for administrative data, supporting comorbidities are underreported in administrative data[118]. A systematic review on the validity of administrative data for comorbidities reported 11 studies that compared either ICD-9(-CM) or ICD-10 to chart review. For individual comorbidities, the review reported wide ranges of sensitivity from 13 to 82% and specificities greater than 97%. Of the 11 studies, seven calculated Charlson comorbidities scores. Kappa agreements were reported from 0.30 to 0.56[119]. A Northern Demark study compared Charlson comorbidities defined by ICD-10 codes to chart review for all hospitalizations between 1998 and 2007 and found a positive predictive value range of 82 to 100% for individual comorbidities and combined value of 98.0% (95% CI: 96.9-98.8)[112].

A previous study has compared the Charlson comorbidity coding methodology used in this study to chart reviews. Sensitivities, positive predictive values, specificities, negative predictive values, and kappa statistics were reported for each comorbidity. Sensitivity ranged from 40.6% (liver disease) to 96.5% (rheumatic disease). Positive predictive value ranged from 58.9% (hemiplegia or paraplegia) to 100.0% (HIV/AIDS).

Every comorbidity had specificities greater than 98%. Negative predictive value ranged from 94.6% (myocardial infarction) to 99.7% (HIV/AIDS). Kappa statistic ranged from 0.50 (peripheral vascular disease) to 0.83 (metastatic solid tumor)[121]. Overall, these findings support administrative data will underreport Charlson comorbidities and by how much depends on each comorbidity, with the exception of renal disease. For example, it could be assumed liver disease would be underreported more than rheumatic disease. All comorbidities had high specificities; therefore, false positives (i.e. comorbidity being identified when truly not) are very unlikely.

Given the literature, misclassification bias of the comorbidities could have resulted due to inadequate data that was either unavailable or unreliable. There are a few reasons this misclassification was likely differential. It has been reported the accuracy of identifying comorbidities from administrative data depend upon the comorbid condition. Furthermore, there was the possibility the coding accuracy varied amongst those who lived and died. For example, those who lived had a longer length of hospital stay and it could be argued a longer length of stay provided more opportunity for documentation in the medical chart. Conversely, it could be argued those who died were more severely ill; therefore, a more thorough work-up could have been documented in the medical chart. Regardless, it appears the misclassification bias is differential and the misclassification resulted in an underestimation. Misclassification of the outcome would have been unlikely and could have occurred if there was incorrect information on death status or death date.

Other issues with administrative data are variability in coding, resulting in coding error or differences in coding within and between facilities[119]. Health coders are professionally trained to assign ICD-10 codes from patients' medical charts according to

national standards[121]. Therefore, variation in coding within and between facilities are likely minimal and reliability is not effected. However, these health coders rely on medical charts to perform their duties, issues with completeness, biases in documentation of comorbid conditions, and illegibility of handwriting impact the validity of the coding[119].

In this study comorbidities were identified only from the one admit the HI-CDI case was identified. To accurately measure comorbidities from administrative data, multiple admits should be considered if possible. Not all comorbidities for patients are coded at each of their hospitalizations as only those comorbidities pertinent to the patient's admission, treatment, and course during the hospitalization are mandatory coding. A patient could be hospitalized for an acute infection; therefore, their chronic comorbid condition(s) may or may not have been coded[112]. The longer the time in which a comorbidity can be identified increases the sensitivity[120]. Using only one admit to identify comorbidities was a study limitation. It has also been suggested relying on administrative data from hospitalizations only does not accurately represent an individual's clinical history. Primary care records from individual's family physician should also be used to accurately identify comorbidities[122].

As the outcome for this research objective was 30-day all-cause mortality, deaths could not be attributed to CDI. Thirty-days was chosen to mitigate this issue as with less time the higher the possibility CDI was associated with death. Comorbidities that were identified as risk factors for mortality amongst hospitalized CDI patients may not be equivalent to comorbidities that are risk factors for attributable CDI mortality.

Administrative data are less subject to selection bias. Individual consent is not necessary; therefore, patients refusing study enrolment does not occur nor does patients

dropping out of the study[115]. Selection bias has to be both related to the exposure and outcome[24]. Although this research objective was retrospective, the outcome status was not known when the exposure status was identified. All those with a HI-CDI case were included; regardless, of their comorbidities or outcome. Therefore, selection bias was not an issue.

An advantage of using administrative data is improved generalizability[115]. This study investigated risk factors for mortality amongst patients identified with CDI in the hospital. Thus, the generalizability of these results to other population such as continuing care and community is questionable. But to identify comorbidities consistently, only patients with recent hospitalizations should be included; thus, was the reason only HI-CDI individuals were investigated.

As mentioned in section 6.5.2, increasing the study size decreases random error. Research objective 2 study population was over five thousand; therefore, random error was likely not an issue. Furthermore, the width of the confidence intervals is also used to evaluate random error. As the confidence intervals reported for this research objective were narrow, random error was not an issue.

Important risk factors not included or accurately accounted for in this study were *C. difficile* strain, CDI severity, previous healthcare exposure (and comorbidities), complete antibiotic exposure in the 90 days prior, and treatment used for CDI. All of these can be risk factors for mortality amongst CDI patients and could have been key factors missing from this analysis.

In summary, using administrative data to identify Charlson comorbidities is an efficient, timely, and inexpensive approach. Charlson comorbidity index is widely used and its application using administrative data have been studied. Compared to chart

review, sensitivity and specificity of the ICD-10 codes vary amongst the comorbidities. Therefore, misclassification of the comorbidities likely occurred and would vary by the comorbidity. As all the HI-CDI population was reviewed, selection bias was likely not an issue. These results are likely generalizable to other hospital CDI populations. The major strength of this study was the large sample size over various geographic locations that included investigating multiple variables as potential risk factors for mortality.

6.5.3 Research Objective 3

This study appears to be the first to compare the DARPIC algorithm to expert reviewers. The expert reviewers had no knowledge of the death decisions made by the student reviewer who used the DARPIC algorithm. As mentioned prior the expert reviewers consisted of IPC physicians who currently conduct investigations into CDI's attribution to death. These physicians are familiar with the DARPIC algorithm; thus, their familiarity with the DARPIC algorithm could have impacted their death decisions and cause them to attribute death similar to the DARPIC algorithm. However, the expert reviewers were instructed to use their clinical judgement and conduct the reviews similar to how they currently do in their profession.

A potential limitation was that all information used to attribute death was collected only by the student reviewer. As mentioned previously the student reviewer is not a physician and it is possible not having this clinical experience could have resulted in important information missed during chart review. However, this would have impacted the validity of the results and not the reliability. Reliability was the focus of this research objective. The student reviewer and expert reviewers reviewed the same information; therefore, reliability assessment was not impacted.

In summary, the expert reviewers previous knowledge of the DARPIC algorithm could have influenced them to attribute deaths similar to the algorithm; thus, inflating the inter-rater reliability results. However, that did not appear to be the case as the inter-rater reliability found was fair to moderate. As reliability and not validity was the outcome of measure the fact the student reviewer collected all the information did not impact the findings.

Chapter Seven: Implications

7.1 Introduction

This chapter highlights the importance and conclusion of the study findings and future work that should be considered.

7.2 Research Objective 1

This study highlighted females were more at risk of CDI. The Alberta female population is smaller than the male population, yet more cases of CDI were identified in females. Although more females were identified with CDI for all three populations, the incidence of hospital identified CDI (HI-CDI) was higher for males. This study supported previous findings of age differences amongst the three populations. Cases of HI-CDI were identified in individuals with an age around the high sixties and low seventies. Continuing care identified CDI (CCI-CDI) cases were identified in those of advanced age and community CDI cases effected those younger aged.

Although the community identified CDI (CI-CDI) incidence could not be compared to the other two populations, compared to literature the community incidence found in this study were markedly higher, suggesting incidence of CDI in the Alberta community is higher than other areas and is a public health issue. Alberta total CDI reported in this study was near that of the epidemic incidence reported in Quebec in the early 2000's[55]. The key finding here is further investigation of CDI in the community is required. This would include investigating how much of the community CDI reported in this study was true CDI (i.e. with clinical criteria) and if recent discharge from a hospital was a risk factor for community CDI.

In general, Edmonton Zone had the highest incidence of CDI for all populations over the three fiscal years. Although it was suggested the increase in CDI in the Edmonton Zone could have been due to the change in laboratory method, the Edmonton Zone total CDI incidence reported by IPC Surveillance increased from 2012-13 to 2013-14[56,123]. Further investigation into this population would be imperative to understand if the characteristics of the population put them at higher risk of CDI, if *C. difficile* strain contributes, if Infection Control practices need to be improved, or if other interventions could reduce CDI incidence, such as probiotics.

The North Zone's proportion of community CDI cases was markedly higher than the other four Zones. Potential explanations are the population is younger and healthier, or CDI is less severe in this Zone. Both of these result in less individuals with CDI requiring hospitalization; therefore, more cases are identified in the community. A more troubling explanation could be the North Zone population is vulnerable to hospital treatment barriers. This is a real concern as the North Zone is geographically very large and mainly rural. Further investigation into North Zone CDI cases could reveal specific barriers and target solutions to improve healthcare access.

The proportion of recurrent CDI cases was highest amongst the CCI-CDI population. As mentioned this is unsurprising as those who are older and sicker are more likely to have recurrence. Even if it is unsurprising it reveals an important difference in risk of CDI recurrence that should be considered when determining the best course of treatment for elderly continuing care residents. Currently, first line treatment for CDI is metronidazole and the more powerful antibiotic vancomycin is only first line treatment for severe CDI. CDI treatment failure and recurrence is slightly less for those treated with vancomycin[124]. Therefore, in this elderly population vulnerable to recurrence and other

complications, vancomycin or other novel CDI treatment may be the better first line treatment.

A thorough investigation into antibiotics that includes prescribing in the hospital would be an important follow-up to this study, only then antibiotic exposure could accurately be investigated. This study did find nearly half of those with CDI had antibiotics dispensed in the community in the 90 days prior to developing CDI; however, to understand if this proportion indicated high antibiotic exposure that would require comparing to a comparable population without CDI. Studies have reported prior antibiotic exposure is higher for patients with CDI than patients without CDI[125,126]. Of the antibiotics dispensed, clindamycin use was higher for CI-CDI population when compared to the other populations. Although antibiotic exposure in this study was not complete and did not include antibiotics dispensed in the hospital, clindamycin use is restricted in the hospital[96]; therefore, it would be very unlikely the proportions of clindamycin reported in this study would differ if antibiotics dispensed in the hospitals were included as well. Based on that it appears the differences in clindamycin use amongst the three populations is valid and individuals with community CDI have more clindamycin use. Clindamycin is a well-known risk factor for CDI[96]; therefore, could be an important factor in the development of CDI in the Alberta community. Further investigation is warranted.

7.3 Research Objective 2

This study highlighted specific demographic and clinical characteristics that are risk factors for mortality amongst hospitalized Alberta CDI patients. Significant non-comorbidity risk factors found were male gender, age, antibiotic exposure, continuing

care residency, and total comorbidity count. Continuing care residency was likely a risk factor as it is associated with increasing age.

Controlling for age and total comorbidity count was important for the interpretation of comorbidities as risk factors for mortality. Significant comorbidity risk factors, after adjustment for age and total comorbidity count, were mild and moderate/severe liver disease and metastatic solid tumour. Liver disease has previously been found to be a risk factor for mortality for patients with CDI[103-105,107]. The findings for cancer as a risk factor is not as clear[11,13,69,70,105,106,108]. However, this study highlighted the importance of liver disease and metastatic solid tumour in the prediction of death amongst CDI patients. As these comorbidities indicate higher risk of death, vigilant clinical management of CDI patients with these comorbidities should be done, which could include more aggressive treatment or surgical options[13]. Although recurrence and treatment failure differs between the use of metronidazole and vancomycin with vancomycin being the slightly superior treatment option[124], no significant differences in mortality have been reported[127]. However, Rokas et al. reported in the treatment of critically ill CDI patients a combination of oral vancomycin and IV metronidazole resulted in a lower mortality rate compared to oral vancomycin alone[128].

Significant comorbidity protective factors, after adjustment for age and total comorbidity count, were cerebrovascular disease, diabetes uncomplicated, paraplegia or hemiplegia, peptic ulcer disease, and peripheral vascular disease. There were no apparent biological explanations for why these comorbidities for CDI patients is protective against death. Therefore, the association found was likely spurious. However, it was interesting that both vascular comorbidities were identified as protective after adjusting for age and

total comorbidity count. Further investigation into the impact vascular disease has on mortality amongst CDI patients is likely warranted.

Additional future work could include the creation of individual models for each comorbidity rather than using the majority conclusion to determine which covariates the comorbidities were adjusted by. With the exception of cerebrovascular disease, comorbidities identified as protective were adjusted correctly according to their individual models (Appendix G). However, for mild and moderate/severe disease and metastatic solid tumour effect modifiers were identified. Therefore, future work for these comorbidities could include creating individual models. Prior to creating these individual models, other important risk factors should be included or accurately account for such as *C. difficile* strain, CDI severity, previous healthcare exposure (and comorbidities), complete antibiotic exposure in the 90 days prior, and treatment used for CDI.

7.4 Research Objective 3

In conclusion, death attribution for patients with CDI is difficult and death decisions vary by approach. These patients are usually the elderly with multiple comorbidities making CDI attribution problematic. This study found the agreement between the DARPIC algorithm and expert reviewers was low. Furthermore, the agreement amongst the expert reviewers was initially low prior to reconciliation. However, the study found deaths classified as CDI-related had better inter-rater reliability. As noted in the literature, death attribution can be subjective and clinicians can vary in their interpretations[94]; therefore, the implementation of a standardized approach is necessary if attributable CDI deaths are reported and especially if comparisons of attributable death is of interest. Otherwise, it could be argued all-cause mortality is the

better option for reporting CDI mortality if subjectiveness of CDI death attribution is not minimized.

A new algorithm inspired by the DARPIC algorithm that incorporates findings and limitations found in this study should be developed to improve consistency of CDI death attribution, especially if attributable death is reported and compared. This new algorithm should be created in collaboration with IPC physicians and Infection Control staff. Key study findings were a category for lack of information should be included, clearly define how symptom resolution should impact death attribution, and a more inclusive and clear definition for CDI contributing to death.

Another important finding discovered during this study was the importance of documenting and investigating factors that may contributed to death attribution. These included investigating delays in diagnosis, delays in treatment, the type of treatment, and the response to treatment. It was noted further investigation into these areas could reveal potential intervention points where death due to CDI could be prevented. For example, with delays in diagnosis and treatment the patient may have poorer outcomes and even death. Furthermore, the treatment used and response to treatment is known to be important in preventing CDI attributable deaths.

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APPENDIX A: Data variables by data source

Table 24. Laboratory data variables.

Field	Data type	Description
PHN/ULI	Number	Personal identifier
Date of birth	Date	Personal identifier
Sex	String	M-male, F-female
Collect date	Date	Date of specimen collection
Received date	Date	Date of specimen received at laboratory
Accession	String	Unique specimen identifier
Result code	String	Y-positive, N-negative
Result description	String	Description of result

Note: PHN/ULI: personal health number/unique lifetime identifier.

Table 25. ProvSurv data variables.

Field	Data type	Description
PHN/ULI	Number	Personal identifier
Date of birth	Date	Personal identifier
Sex	String	M-male, F-female
Encounter site	String	Facility the case was identified
Encounter date	Date	Date of admission to facility
Diagnosis date	Date	Date of specimen collection or CDI diagnosis
Death date	Date	Date of death

Table 26. Discharge Abstract Database data variables.

Field	Data type	Description
PHN/ULI	Number	Personal identifier
Date of birth	Date	Personal identifier
Sex	String	M-male, F-female
Admit date	Date	Date of acute care admission
Discharge date	Date	Date of acute care discharge
Institution name	String	Facility name
DxCode 1-25	String	ICD-10-CA codes

Table 27. Pharmaceutical Information Network data variables.

Field	Data type	Description
PHN/ULI	Number	Personal identifier
Date of birth	Date	Personal identifier
ATC code	String	Unique ATC descriptor
Dispense date	Date	Date antibiotic dispensed

Note: ATC: anatomical therapeutic chemical.

Table 28. Vital Statistics data variables.

Field	Data type	Description
PHN/ULI	Number	Personal identifier
Date of birth	Date	Personal identifier
Death date	Date	Date of death

Table 29. Alberta Continuing Care Information System data variables.

Field	Data type	Description
PHN/ULI	Number	Personal identifier
Date of birth	Date	Personal identifier
Admit date	Date	Date of admission to continuing care
Discharge date	Date	Date of discharge from continuing care
Facility	String	Continuing care facility

Table 30. Provincial Client Registry data variables.

Field	Data type	Description
PHN/ULI	Number	Personal identifier
Date of birth	Date	Personal identifier
Postal code	String	1st 3-digits
Zone	String	Alberta Zone

APPENDIX B: Alberta Health Services Zone Map

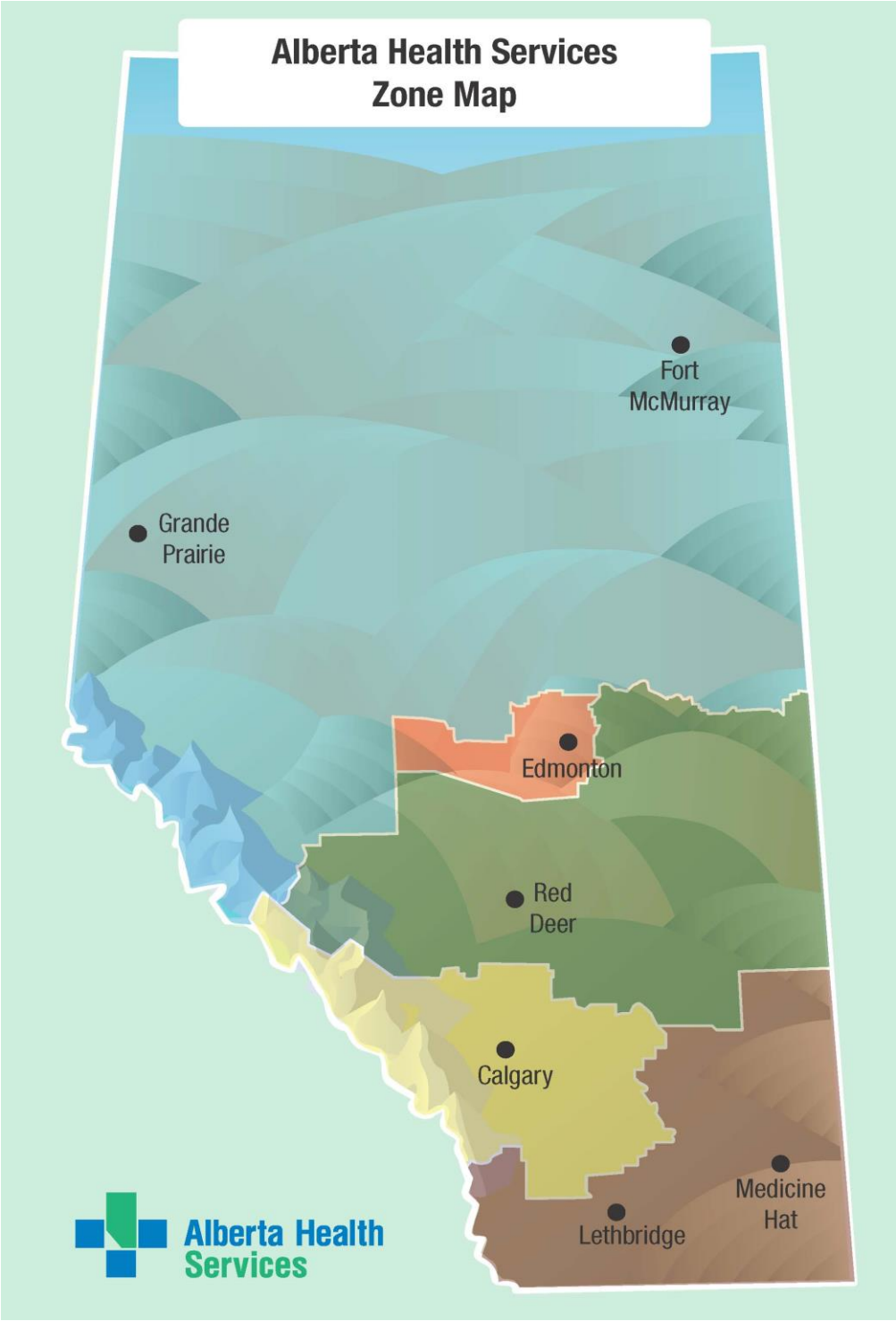


Figure 8. Alberta Health Services Geographic Zones.
Source: Alberta Health Services Insite.
<https://myahs.ca/insite/assets/comm/vis/images/comm-vis-map-zones-major-cities.jpg>
Note: Zones top to bottom are North (Grande Prairie), Edmonton, Central (Red Deer), Calgary, and South (Lethbridge).

APPENDIX C: Antibiotic group from Anatomical Therapeutic Chemical (ATC) Classification System

Table 31. Antibiotic group from Anatomical Therapeutic Chemical (ATC) Classification System.

ATC 4th Level Code	ATC 4th Level Classification	Antibiotic Group
J01AA	Tetracyclines	Tetracyclines
J01CA	Penicillins with extended spectrum	Penicillins
J01CE	Beta-lactamase Sensitive Penicillins	Penicillins
J01CF	Beta-lactamase Resistant Penicillins	Penicillins
J01CR	Combination of Penicillins and Beta-lactamase Inhibitors	Penicillins
J01DB	First Generation Cephalosporins	Cephalosporins
J01DC	Second Generation Cephalosporins	Cephalosporins
J01DD	Third Generation Cephalosporins	Cephalosporins
J01DH	Carbapenems	Carbapenems
J01EA	Trimethoprim and derivatives	Trimethoprim
J01EE	Combination Sulphonamides Trimethoprim	Sulfonamides/Trimethoprim
J01FA	Macrolides	Macrolides
J01FF	Lincosamides	Clindamycin[1]
J01GB	Other Aminoglycosides	Other Aminoglycosides
J01MA	Fluoroquinolones	Fluoroquinolones
J01XA	Glycopeptide Antibacterials	Vancomycin[1]
J01XD	Imidazole derivatives	Metronidazole[1]
J01XE	Nitrofuran derivatives	Nitrofurantonin
J01XX	Other Antibacterials	Other Antibacterials

Note: [1]The only antibiotic at ATC 7th level.

APPENDIX D: Data collection form for hospital medical chart

Identifier:		Admission date:	
Hospital:		CDI lab positive:	
		Death date:	

Patient's age and gender:

_____

Presenting complaint on admission:

_____

Any known history of antibiotic use prior to admission (within 3 months):

Pre-existing medical conditions (e.g. cardiomyopathy, cirrhosis), underlying or coincident diseases (e.g. severe CVA, terminal palliative cancer): _____

If so, was death expected within 7-14 days from any above conditions: _____

At time of CDI diagnosis:

Date of symptom onset:

_____

Duration of diarrhea in days:

_____

Number of bowel movements per day:

_____

WBC count:

_____

Albumin:

_____

Creatinine:

_____

Lactate level:

_____

Presence of abdominal pain:

_____

Date CDI testing order written:

_____

Date CDI lab specimen submitted:

_____

Initial treatment regimen and response, specifically antibiotics: _____

_____

_____

If CDI treatment changed to vancomycin, when and what dosing:

_____

If CT abdomen or flat plate showing ileus, bowel thickening, distension, or toxic megacolon, date and description:

_____

_____

_____

If colectomy performed, describe any resulting complications: _____

_____

_____

_____

Any ICU admission due to CDI, comment: _____

_____

_____

Any antibiotics given for concomitant infections while in hospital or any other relevant medications during hospitalization (e.g. antimetabolites, chemotherapy, salicylate prep):

_____

_____

_____

Metabolic abnormalities:

☐ Hypokalemia serum potassium level <3.5 mmol/L	Date:	_____	Comment:	_____
☐ Hypovolemic shock loss of >20% of body blood/fluid	Date:	_____	Comment:	_____
☐ Acute renal failure	Date:	_____	Comment:	_____

_____

_____

_____

Was there:

☐Intra-abdominal sepsis	Date:	Comment:
☐Bowel perforation	Date:	Comment:
☐Septic shock	Date:	Comment:
☐Lower GI bleed	Date:	Comment:
☐Death in ICU	Date:	Comment:

At time of death:

☐Diarrhea >3 times/day Comment:

☐Abdominal pain Comment:

☐WBC count >15,000 Comment:

☐X-ray Abnormality Comment:
Abdominal X-ray showing ileus, distension, or toxic megacolon

☐Deteriorations in pre-existing conditions Comment:

At time of death:

Creatinine:

Sodium level:

Potassium level:

Primary cause of death on death certificate: _____

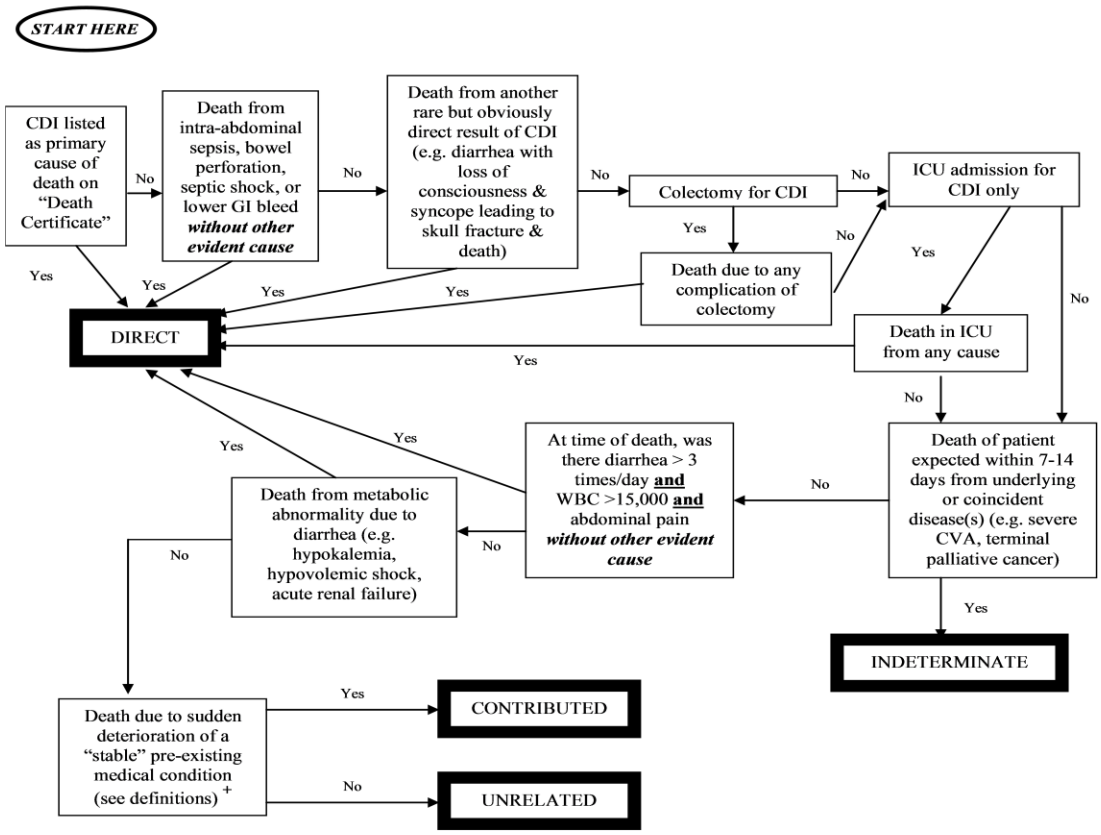
Any secondary, related, or contributing causes noted of death certificate: _____

Additional notes on discharge summary or death certificate: _____

Clinical course in ICU or on ward (e.g. worsening or improving): _____

APPENDIX E: Death attribution algorithm for *C. difficile* infection

***DARPIC algorithm*: "Death Attribution Rules for Patients Infected by C. difficile"**
Used for ascertaining relatedness of death to CDI when death occurs within 30 days of CDI diagnosis
Mark Miller, MD (McGill University)



Definitions

DIRECT: CDI caused death directly
CONTRIBUTED: CDI contributed to death
UNRELATED: Death unrelated to CDI
INDETERMINATE: CDI/death causality cannot be determined with confidence

+ Deterioration due to pre-existing medical conditions

Condition	Deterioration
CAD, cardiomyopathy, valve disease	MI or sudden Death
Cirrhosis or hepatic insufficiency	Coagulopathy or encephalopathy or variceal bleeding
Chronic renal failure	Acute renal failure

Figure 9. Death Attribution Rules of Patients Infected by *C. difficile* (DARPIC) algorithm.

APPENDIX F: Checking assumptions of logistic regression

Table 32. Variable abbreviations.

Variable	Abbreviation
AIDS/HIV	HIV
Cerebrovascular Disease	CER
Chronic Pulmonary Disease	CPD
Congestive Heart Failure	CHF
Dementia	DEM
Diabetes Complicated	DCC
Diabetes Uncomplicated	DUN
Malignancy	CAN
Metastatic Solid Tumour	MTC
Mild Liver Disease	MLD
Moderate/severe Liver Disease	SLD
Myocardial Infarction	MI
Paraplegia or Hemiplegia	PH
Peptic Ulcer Disease	PEP
Peripheral Vascular Disease	PVD
Renal Disease	RND
Rheumatic Disease	RHE
Age (centred at median age)	AgeCen
Gender	G
Antibiotic exposure	Anti
Continuing Care	CC
Recurrence	Recur
Total comorbidity count	TCC

Collinearity:

Positive or negative values close to 1.000 indicate strong positive or negative linear relationship; therefore, suggest collinearity between the two variables. There is no set correlation coefficient value that is used to determine collinearity; however, no variable pairs appear to indicate high correlation (Table 33).

Table 33. Correlation matrix for predictor variables.

	AgeCen	G	Anti	Recur	CC	TCC
AgeCen	1.000					
G	-0.066	1.000				
Anti	-0.037	-0.066	1.000			
Recur	0.032	-0.033	-0.062	1.000		
CC	0.125	-0.017	-0.002	0.060	1.000	
TCC	0.272	0.079	-0.057	0.049	0.080	1.000
HIV	-0.053	-0.011	0.021	0.033	-0.010	0.034
CER	0.070	0.018	-0.072	-0.013	0.028	0.283
CPD	0.153	0.011	0.005	0.031	0.052	0.429
CHF	0.222	0.008	-0.025	0.018	-0.001	0.483
DEM	0.306	-0.078	-0.049	0.012	0.164	0.271
DCC	0.077	0.064	-0.012	0.050	0.046	0.427
DUN	-0.024	-0.003	-0.002	0.010	0.016	0.110
CAN	-0.042	0.080	0.038	-0.017	-0.042	0.165
MTC	-0.015	0.005	0.028	-0.010	-0.048	0.089
MLD	-0.093	0.027	-0.033	-0.030	-0.011	0.133
SLD	-0.075	0.041	-0.015	0.008	-0.031	0.105
MI	0.93	0.073	-0.043	0.002	0.019	0.348
PH	-0.015	0.048	-0.070	0.004	0.070	0.183
PEP	0.019	0.033	-0.026	-0.006	-0.005	0.174
PVD	0.048	0.034	0.005	0.020	-0.020	0.235
RND	0.109	0.037	-0.003	0.023	0.010	0.327
RHE	0.024	-0.062	-0.015	0.014	0.023	0.114

Note: Values reported are correlation coefficients. Comorbidities were not paired with each other as two or more comorbidities did not act as predictor variables in one model.

Multicollinearity:

The square root of the variance inflation factors (VIF) indicates how many times the standard error of the predictor variable is over inflated. No VIF indicated multicollinearity (Table 34).

Table 34. Variance inflation factors (VIF) for each comorbidity and covariates.

	HIV	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.01	1.11	1.01	1.02	1.02	1.01	1.10
	CER	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.09	1.10	1.02	1.02	1.02	1.01	1.19
	CPD	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.23	1.10	1.01	1.02	1.02	1.01	1.32
	CHF	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.32	1.12	1.01	1.02	1.02	1.01	1.38
	DEM	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.18	1.16	1.01	1.04	1.03	1.01	1.15
	DCC	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.23	1.10	1.01	1.02	1.02	1.01	1.33
	DUN	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.02	1.11	1.01	1.02	1.02	1.01	1.11
	CAN	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.05	1.11	1.01	1.02	1.02	1.01	1.13
	MTC	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.01	1.10	1.01	1.02	1.02	1.01	1.11
	MLD	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.04	1.12	1.01	1.02	1.02	1.01	1.13
	SLD	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.02	1.11	1.01	1.02	1.02	1.01	1.12
	MI	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.14	1.10	1.01	1.02	1.02	1.01	1.23
	PH	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.05	1.11	1.02	1.03	1.02	1.01	1.14
	PEP	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.03	1.10	1.01	1.02	1.02	1.01	1.13
	PVD	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.06	1.10	1.01	1.02	1.02	1.01	1.16
	RND	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.12	1.10	1.01	1.02	1.02	1.01	1.21
	RHE	AgeCen	Anti	CC	G	Recur	TCC
VIF	1.02	1.10	1.01	1.02	1.02	1.01	1.11

Note: Comorbidities were not paired with each other as two or more comorbidities did not act as predictor variables in one model.

Linearity:

All lowess smooth curve plots were generated using Stata version 10. Figure 10 plots age (centred at median) versus the log odd of death. This continuous predictor variable does not appear to violate the assumption of linearity. Not only was linearity assessed overall for age, but the linearity of subgroups (i.e. comorbidities) were assessed as well. Figure 11 is one example; however, all subgroups were assessed and age did not appear to violate the assumption of linearity.

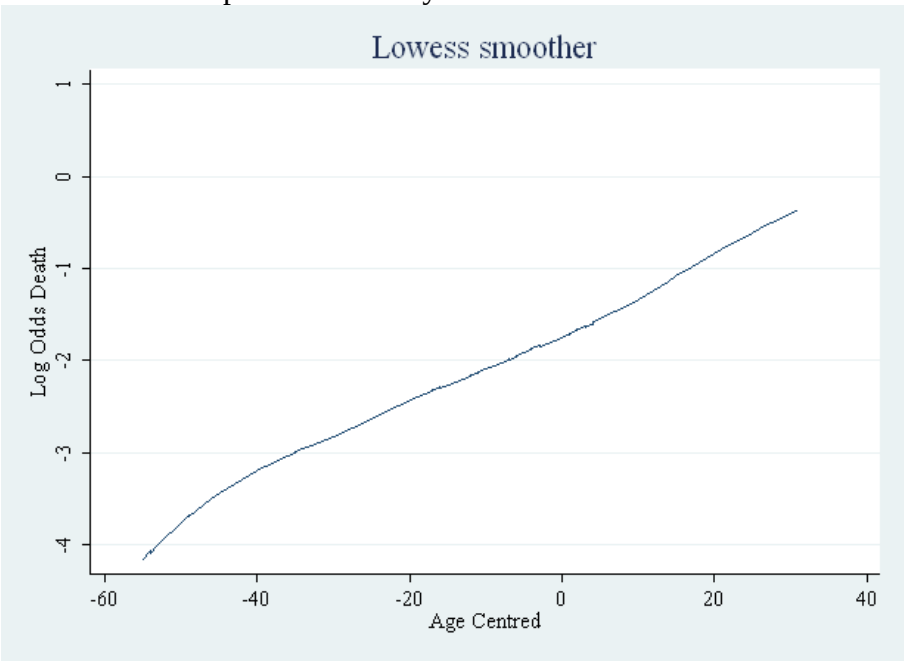


Figure 10. Lowess smooth curve for age centred versus log odds of death.

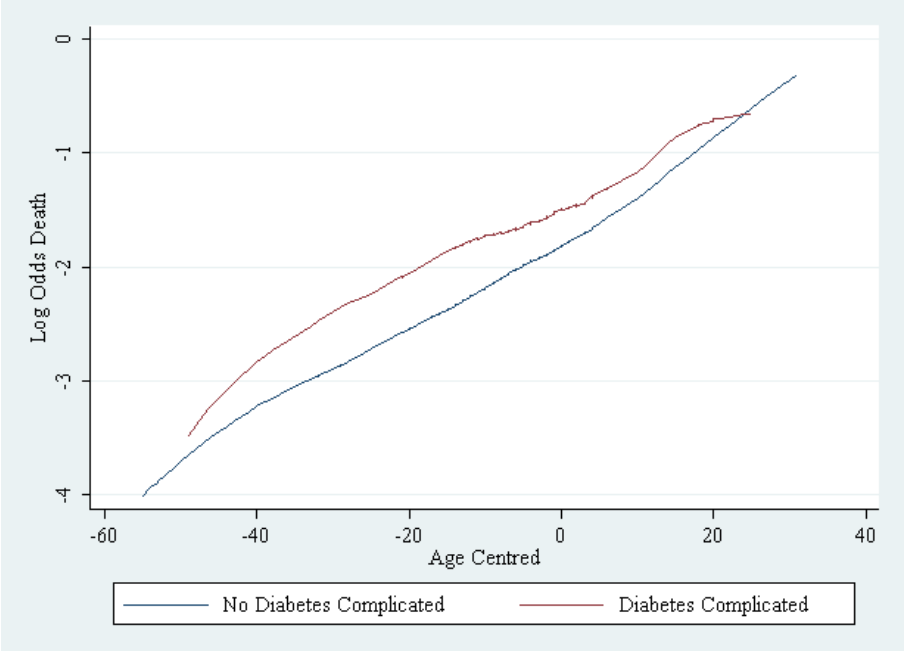


Figure 11. Lowess smooth curve for age centred versus log odds of death for those with and without diabetes complicated. Note: Diabetes complicated is the top line.

Figure 12 plots total comorbidity count versus the log odd of death. This continuous predictor variable does not appear to violate the assumption of linearity. Not only was linearity assessed overall for total comorbidity count, but the linearity of subgroups (i.e. comorbidities) were assessed as well. Figure 13 is one example; however, all subgroups were assessed and total comorbidity count did not appear to violate the assumption of linearity.

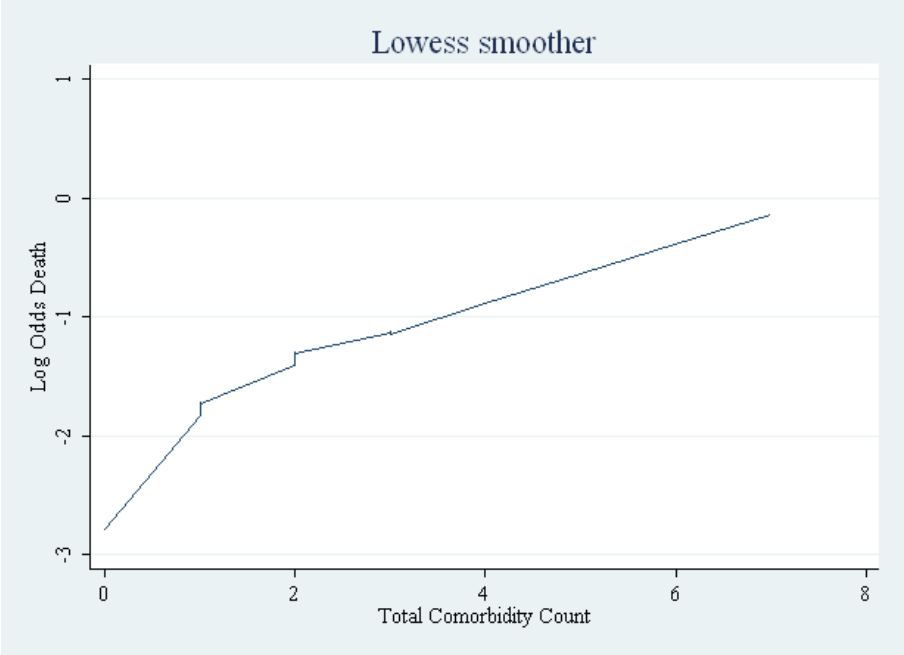


Figure 12. Lowess smooth curve for total comorbidity count versus log odds of death.

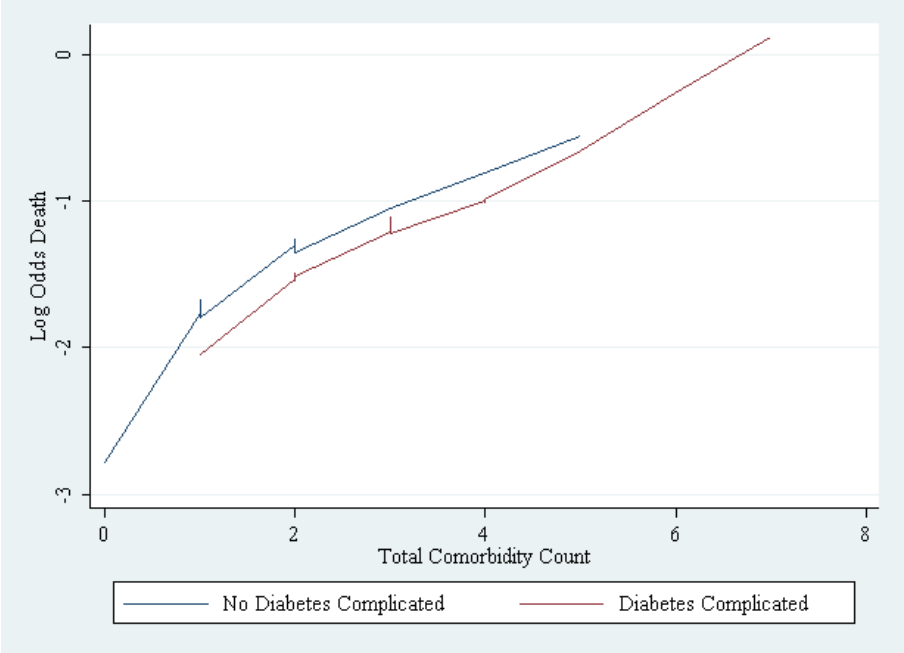


Figure 13. Lowess smooth curve for total comorbidity count versus log odds of death for those with and without diabetes complicated. Note: Diabetes complicated is the top line.

APPENDIX G: Individual logistic regression models after backwards elimination

Refer to Table 32 in Appendix F for variable abbreviations.

AIDS/HIV – (HIV)

$\log(\text{odds of death}) = \beta_0 + \beta_1 HIV + \beta_2 AgeCen + \beta_3 TCC$

Cerebrovascular disease – (CER)

$\log(\text{odds of death}) = \beta_0 + \beta_1 CER + \beta_2 TCC$

Chronic Pulmonary Disease – (CPD)

$\log(\text{odds of death}) = \beta_0 + \beta_1 CPD + \beta_2 TCC$

Congestive Heart Failure – (CHF)

$\log(\text{odds of death}) = \beta_0 + \beta_1 CHF + \beta_2 AgeCen + \beta_3 TCC + \beta_4 TCC*CHF$

Dementia – (DEM)

$\log(\text{odds of death}) = \beta_0 + \beta_1 DEM + \beta_2 AgeCen + \beta_3 TCC + \beta_4 TCC*DEM$

Diabetes Complicated – (DCC)

$\log(\text{odds of death}) = \beta_0 + \beta_1 DCC + \beta_2 AgeCen + \beta_3 TCC$

Diabetes Uncomplicated – (DUN)

$\log(\text{odds of death}) = \beta_0 + \beta_1 DUN + \beta_2 AgeCen + \beta_3 TCC$

Malignancy – (CAN)

$\log(\text{odds of death}) = \beta_0 + \beta_1 CAN + \beta_2 AgeCen + \beta_3 TCC$

Metastatic Solid Tumour – (MTC)

$\log(\text{odds of death}) = \beta_0 + \beta_1 MTC + \beta_2 AgeCen + \beta_3 TCC + \beta_4 AgeCen*MTC$

Mild Liver Disease – (MLD)

$\log(\text{odds of death})$

$= \beta_0 + \beta_1 MLD + \beta_2 AgeCen + \beta_3 TCC + \beta_4 Anti + \beta_5 AgeCen*MLD + \beta_5 Anti*MLD$

Moderate/severe Liver Disease – (SLD)

$\log(\text{odds of death}) = \beta_0 + \beta_1 SLD + \beta_2 AgeCen + \beta_3 TCC + \beta_4 Recur + \beta_5 Recur*SLD$

Myocardial Infarction – (MI)

$\log(\text{odds of death}) = \beta_0 + \beta_1 MI + \beta_2 AgeCen + \beta_3 TCC$

Paraplegia or Hemiplegia – (PH)

$\log(\text{odds of death}) = \beta_0 + \beta_1 PH + \beta_2 AgeCen + \beta_3 TCC$

Peptic Ulcer Disease – (PEP)

$\log(\text{odds of death}) = \beta_0 + \beta_1 PEP + \beta_2 AgeCen + \beta_3 TCC$

Peripheral Vascular Disease – (PVD)

$\log(\text{odds of death}) = \beta_0 + \beta_1 PVD + \beta_2 AgeCen + \beta_3 TCC$

Renal Disease – (RND)

$\log(\text{odds of death}) = \beta_0 + \beta_1 RND + \beta_2 AgeCen + \beta_3 TCC$

Rheumatic Disease – (RHE)

$\log(\text{odds of death}) = \beta_0 + \beta_1 RHE + \beta_2 AgeCen + \beta_3 TCC + \beta_4 G + \beta_5 G*RHE$

APPENDIX H: Zone incidence calculations

Table 35. Zone incidence calculations by fiscal year.

Zone CDI	2011-12		2012-13		2013-14	
	Cases	Denominator	Cases	Denominator	Cases	Denominator
Total						
South	242	223,549	257	223,549	321	223,549
Calgary	1,634	1,142,475	1,535	1,142,475	1,541	1,142,475
Central	342	353,984	336	353,984	483	353,984
Edmonton	1,359	966,737	1,291	966,737	1,901	966,737
North	290	345,663	242	345,663	386	345,663
HI-CDI						
South	113	24,461	134	24,412	154	24,594
Calgary	742	93,371	717	103,166	716	107,571
Central	136	36,910	144	36,500	203	35,776
Edmonton	832	97,280	806	100,293	1,079	103,562
North	87	34,548	74	34,771	119	35,339
CCI-CDI						
South	4	295,519	11	285,968	7	285,936
Calgary	49	1,806,914	41	1,831,862	46	1,820,214
Central	13	776,254	14	784,742	18	772,864
Edmonton	68	1,734,761	61	1,747,639	79	1,752,943
North	5	449,856	9	434,356	16	435,770
CI-CDI						
South	125	223,549	112	226,680	160	229,929
Calgary	843	1,142,475	777	1,185,168	779	1,226,179
Central	193	353,984	178	361,340	262	367,443
Edmonton	459	966,737	424	1,001,984	743	1,036,820
North	198	345,663	159	357,686	251	366,681

Note: CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified. Sixty-six records of CI-CDI not reported as Zone could not be determined.

Table 36. Zone incidence calculations by fiscal year for males.

Zone CDI	Males					
	2011-12		2012-13		2013-14	
	Cases	Denominator	Cases	Denominator	Cases	Denominator
Total						
South	106	223,549	100	223,549	135	223,549
Calgary	637	1,142,475	613	1,142,475	628	1,142,475
Central	144	353,984	143	353,984	192	353,984
Edmonton	570	966,737	568	966,737	816	966,737
North	131	345,663	98	345,663	165	345,663
HI-CDI						
South	55	9,898	56	9,878	71	9,952
Calgary	331	37,781	325	41,745	335	43,527
Central	52	14,935	61	14,769	77	14,476
Edmonton	356	39,363	391	40,582	511	41,905
North	45	13,979	36	14,070	61	14,299
CCI-CDI						
South	3	101,422	5	101,587	1	98,377
Calgary	16	582,976	20	605,834	12	616,336
Central	9	275,265	6	277,345	9	278,383
Edmonton	21	546,774	19	558,444	36	577,223
North	2	177,563	4	171,231	5	172,793
CI-CDI						
South	48	112,060	39	113,634	63	115,239
Calgary	290	574,754	268	597,208	281	618,634
Central	83	178,555	76	182,671	106	185,810
Edmonton	193	486,084	158	505,504	269	524,382
North	84	181,235	58	188,001	99	192,974

Note: CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified. Twenty-four records of CI-CDI not reported as Zone could not be determined.

Table 37. Zone incidence calculations by fiscal year for females.

Zone CDI	Females					
	2011-12		2012-13		2013-14	
	Cases	Denominator	Cases	Denominator	Cases	Denominator
Total						
South	136	223,549	157	223,549	186	223,549
Calgary	997	1,142,475	922	1,142,475	913	1,142,475
Central	198	353,984	193	353,984	291	353,984
Edmonton	789	966,737	723	966,737	1,085	966,737
North	159	345,663	144	345,663	221	345,663
HI-CDI						
South	58	14,563	78	14,534	83	14,642
Calgary	411	55,590	392	61,421	381	64,044
Central	84	21,975	83	21,731	126	21,300
Edmonton	476	57,917	415	59,711	568	61,657
North	42	20,569	38	20,702	58	21,040
CCI-CDI						
South	1	194,097	6	184,381	6	187,559
Calgary	33	1,223,938	21	1,226,028	34	1,203,878
Central	4	500,989	8	507,397	9	494,481
Edmonton	47	1,187,987	42	1,189,195	43	1,175,720
North	3	272,293	5	263,125	11	262,977
CI-CDI						
South	77	111,489	73	113,046	97	114,690
Calgary	553	567,721	509	587,960	498	607,545
Central	110	175,429	102	178,669	156	181,633
Edmonton	266	480,653	266	496,480	474	512,438
North	114	164,428	101	169,685	152	173,707

Note: CDI: *C. difficile* Infection; HI: hospital identified; CCI: continuing care identified; CI: community identified. Forty-two records of CI-CDI not reported as Zone could not be determined.

APPENDIX I: Sample odds ratio calculation

Refer to Table 32 in Appendix F for variable abbreviations.

Model: log(odds of death) $=\beta_0+\beta_1$AgeCen

Death30	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
AgeMCen	.0401835	.0028201	14.25	0.000	.0346563	.0457107
_cons	-1.751481	.0401705	-43.60	0.000	-1.830213	-1.672748

Figure 14. Stata output for logistic regression model assessing age impact on death.

log(odds of death) $=\beta_0+\beta_1$(Age-73)

- At age 73: β_0
- At age 93: $\beta_0+\beta_1(93-73)$

Log odds ratio: $\beta_1(93-73) = 0.0401835(20)$

Odds ratio = $e^{0.0401835(20)} = 2.2$