THE EPIDEMIOLOGY OF COMMUNITY-ACQUIRED
***CLOSTRIDIUM DIFFICILE* IN**
THE NIAGARA REGION, ONTARIO, CANADA,
BETWEEN SEPTEMBER 2011 AND DECEMBER 2013

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Abstract

Clostridium difficile infections (CDIs) have historically been associated with exposure to healthcare settings. In recent years, however, the incidence of community-acquired *Clostridium difficile* infections (CA-CDI), along with the number of patients requiring hospitalization for it, has been increasing. This research uses a framework grounded in Complex Adaptive Systems (CAS) to reveal new and different epidemiological findings on CA-CDI to indicate novel health equity leverage points. It explores the epidemiology and established risk factors associated with CA-CDI in the Niagara Region, Ontario, and compares them with those of healthcare-associated CDI (HA-CDI) in the same area.

The first manuscript evaluates the literature on existing evidence of risk factors for CA-CDI by applying *The Joanna Briggs Institute (JBI) Reviewers' Manual 2015, Methodology for JBI Scoping Reviews.* The review identifies that CA-CDI is seen more often than HA-CDI in younger and female populations. Exposure to antimicrobials is common but not as common as in HA-CDI cases. The scoping review establishes the need for further epidemiological studies on CA-CDI. The second manuscript provides a nonparametric descriptive analysis, comparing CA-CDI and HA-CDI cases in Niagara Health System (NHS) hospitals, based on a retrospective case series design. Hospitalized CA-CDI patients have a lower median age and less exposure to antimicrobials and other medications. Gender proportions are similarly distributed between the two groups. The emerging recommendation is that CA-CDI must be considered as a potential diagnosis in patients admitted to hospital with diarrhea, even in the absence of conventional CDI risk factors. The third and final manuscript evaluates the spatial and genotype features of CA-CDI and HA-CDI. It finds that geographical clustering, temporal patterns, and genotypic features are unique in each category. These studies point to the need for a better understanding of

transmission routes between communities and healthcare settings; further research is required to establish community CA-CDI risk factors.

Together, these evaluations establish that we must develop a systems approach to explore health problems and respond effectively at a population level. The research and policy environment must be strengthened by modifying current practices, setting priorities, and providing funding for empirical studies and equitable health policies.

Dedication

To my family, together we overcame many…

To my mother Soraya, who encouraged me with her infinite love and sacrificed many years of her life for my aspirations.

In loving memory of my father, Reza Salaripour, who always reminded me that the path to women's independence is through education.

To my brother Amir, whose unconditional and affectionate support was always there when I needed it.

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Maryam

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List of Abbreviations

APIC	Association for Professionals in Infection Control and Epidemiology
CA-CDI	Community-acquired *Clostridium difficile* infection
CAS	Complex Adaptive System
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CHA	*Canada Health Act*
CIHR	Canadian Institutes of Health Research
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CNISP	Canadian Nosocomial Infection Surveillance Program
CPHA	Canadian Public Health Association
CQI	Continuous Quality Improvement
FSA	Forward sortation area
HA-CDI	Hospital-acquired *Clostridium difficile* infection
IPAC	Infection prevention and control
IPAC-Canada	Infection Prevention and Control–Canada
MERS	Middle East Respiratory Syndrome
MMLVA	Modified, multiple-locus, variable-number, tandem-repeat analysis
NAAT	Nucleic Acid Amplification Test
NHS	Niagara Health System
PCPHN	Pan-Canadian Public Health Network
PCR	Polymerase-Chain Reaction
PFGE	pulsed-field gel electrophoresis
PHAC	Public Health Agency of Canada
PIDAC	Provincial Infectious Diseases Advisory Committee
PPI	Proton Pump Inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QOL	Quality of life
SARS	Severe Acute Respiratory Syndrome
SPC	Statistical process control
TB	Tuberculosis
WHO	World Health Organization

Chapter One – Introduction

Specific Aims of the Study

Recent studies in North America point to the rising occurrence of community-acquired *Clostridium difficile* infections (CA-CDI) (Khanna et al., 2012). Indeed, up to one third of hospitalized *Clostridium difficile* infection (CDI) cases now originate in the community (CDC, 2008; Dumyati et al., 2012; Khanna et al., 2012; Levy et al., 2015; McLeod, 2017). Concern is growing that what used to be an exclusively healthcare-associated infection is now increasingly a cause of infectious diarrhea in the community (Khanna & Pardi, 2010; Khanna et al., 2012).

HA-CDI cases are a major source of concern for hospitals and healthcare systems. Although many years of clinical and epidemiological studies have established the risk factors, clinical presentation, and treatment options, the growing incidence of this infection in communities (from 1/100,000 to 22 /100,000 population between 1994 and 2004 in the United States), presenting in individuals without the traditional risk factors, calls for more complete studies on the epidemiology of CA-CDI and the identification of transmission patterns that can inform focused preventive strategies in hospital and in communities. Knowledge about the epidemiological patterns of CA-CDI may also help postulate future research questions about novel and unknown reservoirs of this infection in communities.

The aim of this dissertation was to gain insight into the epidemiology and the risk factors associated with CA-CDI in the Niagara Region from 2011 through 2013 and compare them with those of HA-CDI in the same area. The three specific research objectives and their corresponding research questions explored during the process of this dissertation are:

1. To document and collect the research on epidemiology of CA-CDI by conducting a scoping study.

   Research question 1: What is our current knowledge about the epidemiology of CA-CDI?

2. To document the epidemiology of hospitalized CA-CDI in Niagara Health System's (NHS) hospitals and for the Niagara Region. This involves the descriptive univariate analysis of the characteristics and epidemiology of CA-CDI and its comparison with HA-CDI.

   Research question 2: Is the epidemiology (demographic, patient characteristics) of CA-CDI in the Niagara region different from that of HA-CDI in NHS hospitals?

   Question 2 originates from the assumption that systems-level study of hospitalized CA-CDI cases in the Niagara Region has a new narrative that may be different from that found by other studies and that certainly varies from the HA-CDI experience in the same region.

3. To document the incidence, identify seasonal and temporal patterns, study the spatial distribution of CA-CDI cases, and examine the differences in strain variations of CA-CDI and HA-CDI in the Niagara Region.

   Research question 3: Are the temporal, spatial, and strain assortment patterns of CA-CDI different from those of HA-CDI?

The postulations guiding this research and its three main questions are rooted in a population-level exploration of the risk factors, patient characteristics, strains of pathogens, and the temporal and spatial epidemiology of CA-CDI. Figure 1.1 depicts the main objectives and identifies the gaps in current practice and knowledge.

Background and Significance

Clostridium difficile as a pathogen.

Clostridium difficile (*C. difficile*), a gram-positive, spore-forming anaerobic bacillus, is one of the most common enteropathogens isolated from stool cultures (Dumyati et al., 2012). Different strains of *C. difficile* are able to produce various toxins (A, B, and/or binary (CDT)). In recent years, the spread of a new and more virulent strain of CDI (027/BI/NAP1), presenting more serious complications and a higher mortality rate, has caught the attention of hospital epidemiologists throughout North America and around the world (He, 2013). *C. difficile* was first isolated from the stool cultures of asymptomatic (colonized) neonates (Barbut & Petit, 2001). In susceptible individuals, *C. difficile* can cause infection, with symptoms ranging from self-limiting, mild diarrhea to severe diarrhea, with or without pseudomembrane formation, toxic megacolon, perforation, and peritonitis in susceptible hosts, especially the elderly (Poxton, Mcoubrey, & Blair, 2001). However, up to 15% of healthy adults can be asymptomatic carriers of the spores (Viscidi, Willey, & Bartlett, 1981).

CDI cases have predominantly been attributed to antimicrobial exposure and the resulting imbalance in the normal flora in the colon due to the selection of organisms resistant to the antimicrobial agent. This may result in an increase of the colonization of *C. difficile* (asymptomatic cases that carry the pathogen in their gut flora), but one third of susceptible individuals will end up presenting the signs of infection listed above (Poxton et al., 2001; Wilcox, 2009). In addition to an imbalance of flora, direct or indirect acquisition of *C. difficile* has been attributed to ingestion or to environmental exposure to surfaces or devices contaminated with spores of the organism (Patterson, Johnson, & Schmulen, 1984). This can happen in healthcare settings due to insufficient hygiene practices throughout the processes of

care (Barbut & Petit, 2001). If spores of a toxigenic strain of *C. difficile* are ingested, they can survive exposure to gastric acid and cause colonization or infection—two outcomes that are based on host susceptibility (immune status or degree of comorbidities) or on the virulence of the *C. difficile* strain.

C. difficile is a ubiquitous organism and has been isolated from soil and flood water, farm animals, and commercial poultry and meat (Keessen, Harmanus, Dohmen, Kuijper, & Lipman, 2013; Lin, Wade, & Hilborn, 2015; Rodriguez et al., 2017; Rodriguez-Palacios, Staempfli, Duffield, & Weese, 2007; Weese, Reid-Smith, Avery, & Rousseau, 2010). Therefore, exposure to *C. difficile* can be a threat for individuals who have contact with it in occupations other than those of health care, such as farming, agriculture or meat production. This characteristic of *C. difficile,* along with the increased incidence of CDI in communities, indicates the need for further exploration of factors contributing to the appearance of CA-CDI in the community.

> **The burden of *Clostridium difficile* infections, diagnosis, and treatment.**

CDIs are the main source of healthcare-associated infectious diarrhea in developed countries (Collins, Hawkey, & Riley, 2013). In 2013, the Center for Disease Prevention and Control in the United States declared CDI an "immediate public health threat," with over 450,000 infections and an estimated 29,000 deaths annually attributed to all cases of this infection (CDC, 2013; Lessa et al., 2015). In Canada, the overall burden of CDI cases was estimated to have been more than 37,000 cases in 2012 (Levy et al., 2015).

In addition to the overall increase of incidence, the mortality rate due to CDI has been increasing gradually, from 1.5% in 1997 to 5.4% in 2010 (PHAC, 2013). To place this in a financial context, the economic burden of all CDIs in the United States has been estimated at ≥$496 USD million in hospital costs, ≥$547 USD million in third-party payer costs, and ≥$796

million in societal costs (McGlone et al., 2012). However, considering that many of these studies and statistics rely heavily on HA-CDI cases as a source of information (Table 1.1), the true burden of CA-CDIs is unclear and is likely to be much higher.

Although the definitions for CA-CDI and HA-CDI point to an important differentiation in their etiology, most focused costing studies have been conducted on HA-CDI (Greco et al.). A patient with CA-CDI is somewhat arbitrarily defined as a person who has not had exposure to any healthcare facility in the previous four weeks or has not had HA-CDI in the past eight weeks. A CA-CDI case is usually either admitted to hospital with signs and symptoms of CDI (diarrhea, with laboratory confirmation of the sample taken upon admission or within 72 hours of admission, or visualization of pseudomembranes on sigmoidoscopy, or colonoscopy, or histological/ pathological diagnosis of pseudomembranous colitis) or experiences the onset of the symptoms within the first 72 hours of hospitalization. An HA-CDI patient is a case who did not have symptoms or a positive laboratory test in the eight weeks prior to hospitalization, does not present with CDI upon admission, and shows symptoms more than 72 hours after admission. Another definition is that an HA-CDI case is hospitalized for CDI symptoms related to a hospitalization in the same healthcare facility within the previous four weeks (PIDAC, 2011).

Diagnostic tests to confirm CA-CDI or HA-CDI use a range of laboratory methods, including enzyme immunoassay (EIA) and PCR, checking for *C. difficile* toxins or anaerobic microbiological culture, and glutamate dehydrogenase assays, checking for the bacterium in the stool samples (Cohen et al., 2010). An unformed stool sample from a symptomatic patient is collected and used for diagnostic testing, that is, predominantly toxin testing methods for cost-effectiveness purposes. Guidelines for treatment of confirmed cases of CDI recommend use of metronidazole and vancomycin as first-line therapies; however, recurrence has been reported

after use of both first-line antibiotics (47.2% after treatment with metronidazole and 25.3% after treatment with vancomycin) (Cohen et al., 2010).

The recent changes in CDI incidence and severity have been attributed to the increased use and misuse of antibiotics, the emergence of hypervirulent strains, and an increase in the number of vulnerable and susceptible populations (Khanna & Pardi, 2010). The advent of the new and more virulent strain of CDI (027/BI/NAP1), with its higher mortality rate, has added to the burden of CDI management and control. Although the virulent strains of CDI are mostly detected in healthcare settings, some studies have reported sporadic virulent strains amongst CA-CDI cases (CDC, 2008; Lessa et al., 2015). While there are no reports of resistance to the antibiotics for *C. difficile*, limited treatment options after recurrence and overall efforts to decrease antimicrobial exposure in the population, especially in healthcare settings, mandate informed preventive strategies. The Canadian Nosocomial Infections Surveillance Program (CNISP) reports that although HA-CDI rates have not shown a noticeable variation between 2007 and 2011, the number of deaths attributable to HA-CDI has increased more than two times (Table1). Although no national Canadian data exist to report the rate of and mortality from CA-CDI over the years, a study from Quebec reports the incidence rate of CA-CDI increased from 20/100,000 person years in 1998 to almost 60/100,000 person years in 2004 (Dial, Kezouh, Dascal, Barkun, & Suissa, 2008).

To date, particularly in Canada, limited studies evaluate the community pattern or risk factors associated with CA-CDI. Figure 1.2 presents an estimate of the number of *C. difficile* infections in Canada in 2012 (Levy et al., 2015). While the increase of HA-CDI cases is a source of concern for hospitals and healthcare systems, the sizable numbers of this infection in communities and in individuals without the traditional risk factors, as well as the sparse number

of studies focusing on CA-CDI, warrants further exploration of possible risk factors to inform preventive policies.

Niagara Region's CDI problem, September 2011 through December 2013.

The Niagara Region is located in southern Ontario, Canada. It has a total area of 1852 square kilometres and a population of 427,421. The Niagara Region consists of 12 municipalities: Fort Erie, Grimsby, Lincoln, Niagara-on-the-Lake, Niagara Falls, Pelham, Port Colborne, St. Catharines, Thorold, Wainfleet, Welland, and West Lincoln. Figure 1.3 is a map of the Niagara Region and its municipalities, based on the 2011 census (Niagara Region, 2012; Statistics Canada, 2016). The Niagara Health System (NHS) is the largest multisite hospital amalgamation in Ontario's Niagara Region, providing a comprehensive range of health programs and services to meet the healthcare needs of Niagara Region residents.

Between September 2011 and December 2013, NHS experienced multiple outbreaks of CDI across multiple sites. In addition to a significant number of HA-CDIs, hospitals experienced an unusually high number of CA-CDI cases. In healthcare settings such as the NHS sites, surveillance activities follow a cause and effect pattern, and mainly look for contributory origins or follow up on HA-CDI patients. Even though management and care of CA-CDI cases put a high level of stress on NHS healthcare facilities and communities, no studies or analyses of the CA-CDI cases were conducted. The notable number of CA-CDI cases admitted to NHS hospitals demands further analysis to provide a better understanding of the contributing factors and characteristics of this infection at a population level, with possible applicability elsewhere.

Methodological Considerations

To meet the objectives of the dissertation and to explore the research questions, the following methodological concerns were considered.

Application of a conceptual framework.

In clinical research, theory serves as a guiding framework for the research hypotheses (Cresswell, 2009). Theory explains natural phenomena through a series of organized and dependent constructs, definitions, and suggestions, and presents a methodical view of events by postulating relations between variables (Kerlinger, p. 64). The application of theory-based processes allows researchers to mitigate problems encountered during the research process in a more simplistic quasi-experimental design (Mertens, 2010). This is not to say a theory-based approach is less effective: Mertens argues that linking social sciences theories and evaluations not only guides research questions and data gathering but also increases the effectiveness of a research program (Mertens, 2010). A research process using a theoretical lens can efficiently and purposefully achieve its objectives.

More specifically, theories provide frameworks for conceptual thinking and research designs through which hypothesis formation, observation, analysis, and inference are guided. Small or program-level theories allow clarity about the components of a program and the mechanism of its activities, allowing the evaluation of key outcomes and describing how measurement and evaluation tools and methods function (Davidoff, Dixon-Woods, Leviton, & Michie, 2015). Small theories are intervention-specific and comprise a mix of formal and informal theories that collectively map the descriptors of an intervention's components to the aim of the intervention, using descriptions related to the behavioural process or contextual features of the process (Lipsey, 1993).

Mid-range theories are used to understand problems or to develop interventions, such as the diffusion of innovation theory in healthcare improvement interventions; this has led to innovative interventions, from recruiting opinion leaders to customizing innovations for

individual systems (Rogers, 1995; Rogers, Medina, Rivera, & Wiley, 2005). For academics, clinicians, or researchers, mid-range theories are bounded in their area of application, between a program-level and an all-inclusive abstract grand theory.

The concept of grand theory offers a generalized worldview across multiple domains, at a high level of perception that uncovers assumptions across multiple domains and disciplines. Theories such as the theory of social inequity do not offer a customized way of thinking for specific circumstances, but a universal semantic guide to the logical articulation of situations at an abstract level (Davidoff et al., 2015). Theoreticians have traditionally proposed that a postpositivism metatheoretical paradigm is the dominant worldview guiding our understanding of studies involving human beings (Lincoln & Guba, 1985).

The advent of the patient safety movement in the years following the Institute of Medicine report, *Crossing the Quality Chasm: A New Health System For the 21st Century.* (Institute of Medicine (IOM), 2001), resulted in enforced measurement, reporting, and improvement of infection prevention and control (IPAC) indicators. However, few studies in infection prevention and control offer a theoretical perspective that explains the conceptual thinking behind the process of the hypothesis/research question formation, observation, and analysis. Although healthcare systems and substructures are increasingly adopting a comprehensive approach to patient safety and the improvement of the quality of care, many population safety questions remain unanswered, probably due to the expansive continuum of hospital-based issues that can be rooted beyond hospital boundaries.

A systems-based approach to the complex and multifaceted problems in health care can guide and mitigate these challenging problems. Given the interrelatedness of IPAC programs with internal and external stakeholders, a broad viewpoint must guide the processes of research,

from objectives and question postulation to evaluation and inference. Accordingly, this dissertation is guided by the theoretical background of complex adaptive systems (CAS); this is described in detail in Chapter Two.

Conducting a scoping review.

Scoping reviews are evaluative studies that can bring together literature within disciplines where new evidence is emerging (Peters et al., 2015). Scoping reviews are acknowledged as particularly useful when a body of literature does not have a full and systematic review of a particular intervention or treatment (Peters et al., 2015). While systematic reviews can answer questions on the effectiveness of specific interventions or treatment options, scoping reviews can summarize and disseminate the research findings, identifying research gaps, and making recommendations about future research. In general, scoping reviews enable a broader approach to extensive research questions, as they are able to map the literature and the key concepts underpinning the research area (Arksey & O'Malley, 2005). Scoping reviews can map a body of literature with respect to time, location, or origin. They have the power to identify gaps in the research, clarify concepts, and identify evidence to inform practice from a comprehensive evidence-based examination of the literature.

Our knowledge of CA-CDI is evolving, and new information has been emerging as I have been working on this dissertation. Therefore, to present an overview of the evidence for the questions addressed in Chapters Four and Five, I have conducted a scoping review on the extent of CA-CDI research (Chapter Three).

Use of administrative data.

In Chapters Four and Five, administrative data are used to investigate the epidemiological patterns of CA-CDI in the Niagara Region. Administrative data, such as those data found in

quality improvement and patient safety databases, infection prevention and control databases, or decision support databases, are collected for healthcare administrative purposes. Administrative data enable researchers to access a large repository of information relatively quickly and to combine several databases (Williams & Young, 1996). The risks of recall bias, social desirability bias, or acquiescence bias are also reduced, as the data gathering process does not rely on self-reporting or the memory of the participants (Mertens, 2010).

As the initial purpose of collecting these administrative data was not for research, unfilled data fields may expose the study to the risk of bias because of missing outcome data (Stern et al., 2009). There are three types of missing data: 1) data missing completely at random (MCAR), defined as when there are no systematic differences between the missing values and the observed values; 2) data missing at random (MAR), defined as when a systematic difference between missing values and observed values can be explained by differences in observed values; and 3) data not missing at random. The risk of bias is subject to the reasons why data are missing. There are several statistical methods to compensate for missing data: complete-case analysis, available case analysis, available case estimates, single value imputation and multiple imputation. Many studies recommend multiple imputation to handle missing data. However, this method requires approximation and multiple algorithm runs that may cause difficulties if run in settings different from those in which they were developed and can result in false outcome data and wrong conclusions. Deletion methods, such as complete-case analysis (CCA), have been recommended for their simplicity and comparability across analyses. But CCA can reduce the statistical power (lower n), does not use all the information, and may result in biased outcome estimates if data are not MCAR (Dong & Peng, 2013; Pigott, 2001).

I found no systematic differences between the missing values and the collected data for

CA-CDI and HA-CDI, possibly because a standardized surveillance tool and unified standards of practice were used across NHS sites. Therefore, the dissertation uses a complete-case analysis method for statistical analysis.

Time series and temporal analysis.

To explore the temporal postulations in this research, I applied three different methods. First, as suggested in Benneyan (1998), I used the Statistical Process Control (SPC) approach to show unusual variations and exceptional changes in CDI infection rates between months and seasons (Benneyan, 1998).

Next, in a more specific experiment, I identified non-random temporal clusters amongst CA-CDI and HA-CDI using Scan Statistic, which applies the Bernoulli binominal distribution to search for non-random clusters of high CDI concentrations. A Bernoulli distribution is a 0/1, case-control type of binary data analysis. Scan Statistic uses multiple different window sizes to gradually scan across time and/or space and documents the number of observed and expected observations within the windows. The risk inside the clusters is compared to that outside the clusters, measuring for irregularity, based on a likelihood ratio (Lawson, Banerjee, Haning, & Yugarte, 2016). The cluster that yields the most extreme ratio is least likely to be by chance (Lawson et al., 2016). In this step, the null hypothesis assumes that the temporal clusters of hospitalized CA-CDIs and HA-CDIs occur at the same time. The alternative hypothesis suggests the presence of clusters in hospitalized CA-CDIs does not show up at the same time as clusters in HA-CDIs.

The third temporal experiment was a test of seasonality for small datasets (under 50 data points). To find out whether seasonal properties have a role in the increase of CDIs in certain

periods, the time series data for both CA-CDIs and HA-CDIs were adjusted for seasonal

components (Carlberg, 2015), with seasonally adjusted values for each season of the study.

The methods supplement to the dissertation provides more detailed information on each

method described in this section.

Spatial analysis.

For the three main epidemiologic variables influencing the dynamics of disease

transmission—host, agent, and environment—environmental factors (such as the topographical

distribution of a disease) are frequently the more challenging to explore and visualize (Choi,

2013). Environmental influences on the health of individuals can be a random or non-random

experience that stimulates exposure to the disease. Technological advances offer researchers the

opportunity to differentiate these phenomena and quantify the variations in geographical

patterns, allowing them to make projections for managing, planning, and even preventing public

health interventions (Jacquez, 2007). Spatial clusters of a disease are defined as a geographically

bounded group of occurrences of sufficient size and concentration that are unlikely to have

occurred by chance (Aldstadt, 2009). Exploratory spatial data analysis identifies patterns through

visualization and geo-statistics and recognizes the location and magnitude of the statistically

significant descriptors. The analysis, in turn, leads to the test of a hypothesis that attempts to

interpret the geographical patterns through further epidemiological studies. To explore this

postulation, I used spatial Scan Statistics; this allows researchers to measure the significance and

location of a general or focused cluster (Kulldorff & Nagarwalla, 1995), subsequently leading to

clues about the disease under investigation. Further details about this method appear in a

supplement at the end of the dissertation. More methodological considerations also appear in

each manuscript comprising the dissertation.

Policy and Equity Considerations

  The dissertation will provide a better understanding of the epidemiology of CA-CDI in general and in the Niagara Region specifically. It has the potential to inform policy solutions that will support CDI reduction programs in the community and achieve more equitable health practices. This fits with current policy goals. In 2010, Ontario's *Excellent Care for All Act* stated that high quality health systems must "deliver world-leading effective, patient centered services; efficiently and in a timely manner, resulting in optimal health status for all communities" (Ontario Ministry of Health and Long-Term Care, 2010). In 2016, to complement the Act, Health Quality Ontario stated that creating a safe, effective, patient centred, timely, efficient, and equitable health system requires a systems improvement approach (Health Quality Ontario's System Quality Advisory Committee, 2016).

  Health equity is an essential feature of an equitable healthcare system, with concrete implications for policy decisions (Culyer, 2001). Health inequities have been defined as differences in health experiences that "are not only unnecessary and avoidable but, in addition, are considered unfair and unjust" (Kawachi, Subramanian, & Almeida-Filho, 2002; see also Whitehead, 1992). In her ground-breaking work on defining health inequities, Whitehead (1992) maintained that individuals should have a fair opportunity to attain their full and normative health potential, and, what is more, that all inequitable approaches and disadvantages should be avoided. Inequitable approaches include "irrelevant" characteristics such as race/ethnicity, age, gender, education, and income; these should not affect the way a patient is treated unless there are legitimate grounds for the different handling of the patient (Kawachi et al., 2002). To quantify inequitable approaches empirically and to inform health equity policies objectively, Culyer (2001) indicates that practical implications for policy on health equity are shaped by

"research into the actual distribution of health and sickness: performed in advance of policy initiatives so that the initiatives be informed by the results" (Culyer, 2001; Culyer & Wagstaff, 1993).

A variety of methods have been used to measure and quantify health inequities. The most frequently applied method is to compare a health indicator in a disadvantaged group to a similar indicator in a reference, and advantaged, group (Braveman, 2006). However, in a report published by the World Health Organization in 2000, this method was criticized for its prejudged causation effect, as this can obscure differences between groups (Murray, Gakidou, & Frenk, 1999; World Health Organization, 2000). Therefore, some propose measuring health inequities across individuals by means of social groups' defining criteria, such as community location (Murray et al., 1999). This research looks for inequity indicators without applying the previously established markers of social disadvantages (such as income or race). This allows the comparison of sick and healthy individuals rather than rich and poor.

The concept of health equity has been categorized as vertical equity (the unequal, but equitable, treatment of unequals) and horizontal equity (the equal treatment of those with equal needs) (Mooney & Jan, 1997). Whitehead's remarks (1992) encouraged me to look at healthcare-associated infections through a different lens. Accordingly, I explored explainable but new and different patterns in the epidemiology of a community-acquired infection, in a quest to locate vertical and horizontal equity policy intervention points to create a fair healthcare system for all.

Thesis Overview

The dissertation consists of six chapters, as summarized in Figure 1.4. The first chapter (this chapter) provides a general introduction to the concepts and premises, and the last chapter

provides an overall conclusion. Three of the other four chapters represent manuscripts prepared for submission to a peer-reviewed journal.

Chapter Two introduces the theoretical lens guiding the conceptual framework of the dissertation. The conceptual framework brings the epidemiologic triad of host, agent, and environment together with the complex adaptive system (CAS) view. Chapter Three offers a scoping review of CA-CDI; the chapter represents the literature review of this dissertation.

Chapter Four consists of a manuscript titled: "Epidemiology of patients hospitalized with *Clostridium difficile* infection in the Niagara Region, Ontario, Canada, September 2011 through December 2013: A comparative analysis of community-associated and healthcare-associated *Clostridium difficile* infections." The chapter analyzes the host factors—including characteristics and experiences confirmed by the scoping review. It also includes a univariate comparative analysis of the attributing factors to incidences of CA-CDI and HA-CDI.

Chapter Five is a manuscript titled: "A spatial, temporal, and molecular epidemiology study of hospitalized patients infected with community-acquired or healthcare-associated *Clostridium difficile* in the Niagara Region, Ontario, Canada." The chapter applies a variety of the methods described earlier to address the research questions on temporal and spatial patterns and the genetic relatedness of CA-CDI, and it considers how these compare with those of the HA-CDI cases in the Niagara Region during the study period.

Chapter Six offers an overall conclusion and a summary of the findings. It touches on the study limitations, implications for conducting future research and practice, and potential policy implications. A supplement at the end of Chapter Six provides more detail on the methodologies used for the research.

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Tables

Table 1.1 – A comparison of the rate per 10,000 patient days, the number of deaths, and the mortality rate per 100 cases of HA-CDI in Canada between 2007 and 2011.

Year	Rate per 10,000 patient days	Number of deaths	Mortality rate/100 HA-CDI cases
2007	4.51	33	4.9
2008	5.49	25	5.0
2009	4.75	33	3.1
2010	4.53	88	6.1
2011	5.35	88	5.3

Note. Adapted with permission from Canadian Nosocomial Infection Surveillance Program (CNISP). *Healthcare-associated Clostridium difficile infection (HA-CDI) 2007 – 2011*. Ottawa, ON: Author. Retrieved from http://www.phac-aspc.gc.ca/nois-sinp/projects/cdad-eng.php
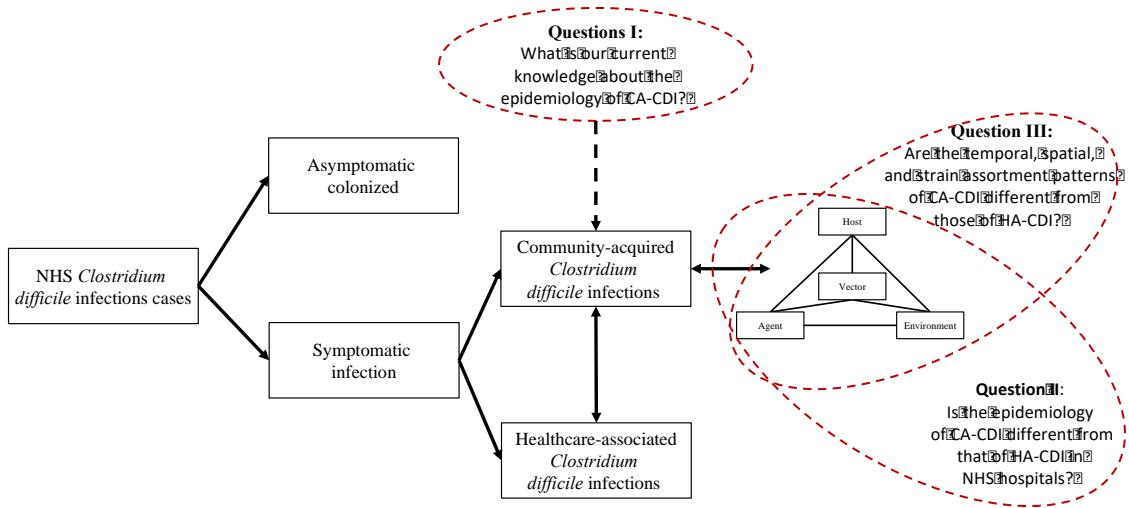
Figures

Figure 1.1 – Framework depicting the formation of research questions explored in this study to better understand the epidemiology of CA-CDI in the Niagara Region between September 2011 and December 2013.

BASE CASE

17,310 — Source: CNSIP and CIHI	Initial Hospital Acquired (HA) CDI cases Canada 2012	17,310 — Source: CNISP and CIHI

SENSITIVITY ANALYSIS

BASE CASE

17,310

Source: CNSIP and CIHI

+

9,737

Source: Lambert 2009; CA CDI represents 36% of all CDI

Initial Hospital Acquired (HA) CDI cases Canada 2012

Initial Community Acquired (CA) CDI cases Canada 2012

SENSITIVITY ANALYSIS

17,310

Source: CNISP and CIHI

9,737

Source: Dumyati 2012: CA CDI represents 18% of all CDI

27,047

Initial CA and HA CDI cases Canada 2012

21,110

+

10,885

Recurrent CDI cases Canada 2012

Source: PHC analyses; 27.1% of all CDI is recurrent

8,677

37,932*

*includes 831 initial and recurrent HA and CA CDI cases from Manitoba

Total CDI cases Canada 2012

29,787*

*includes 831 initial and recurrent HA and CA CDI cases from Manitoba

Figure 1.2 – Estimated number of infections and of *Clostridium difficile* in Canada in 2012, base infection and sensitivity analysis (Levy et al., 2015).
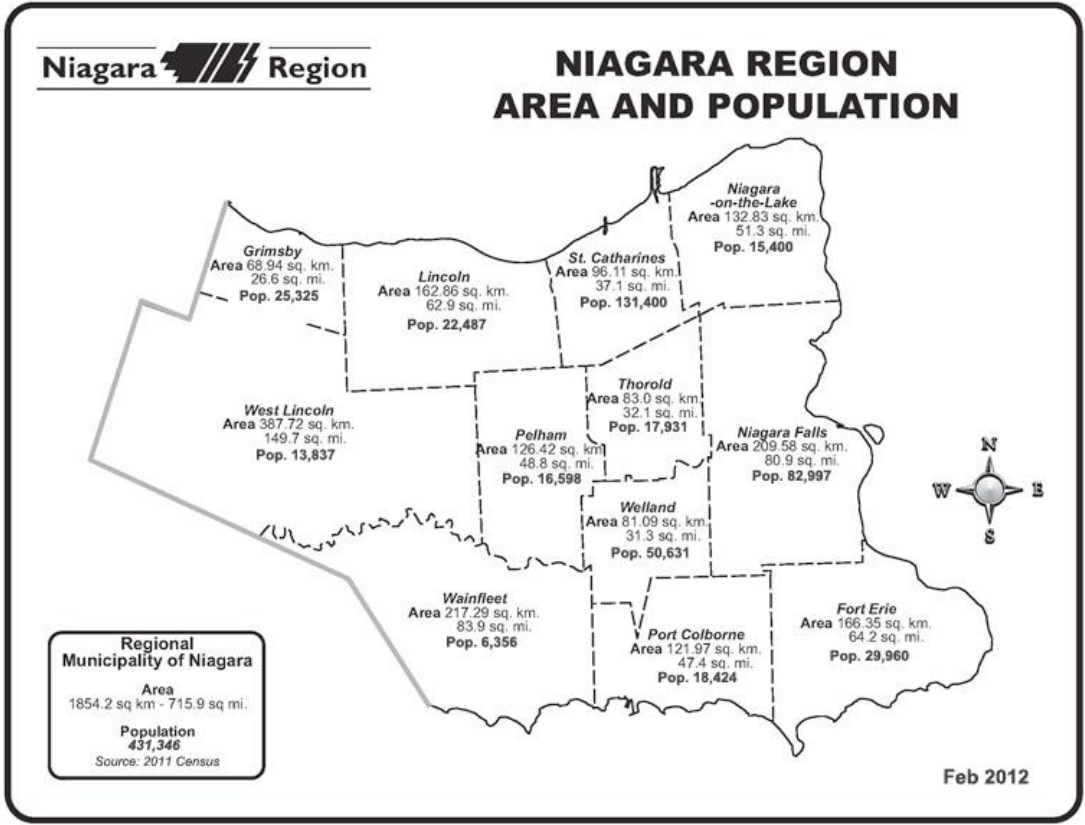
Figure 1.3 – Niagara Region and population of each municipality (Statistics Canada, 2016).
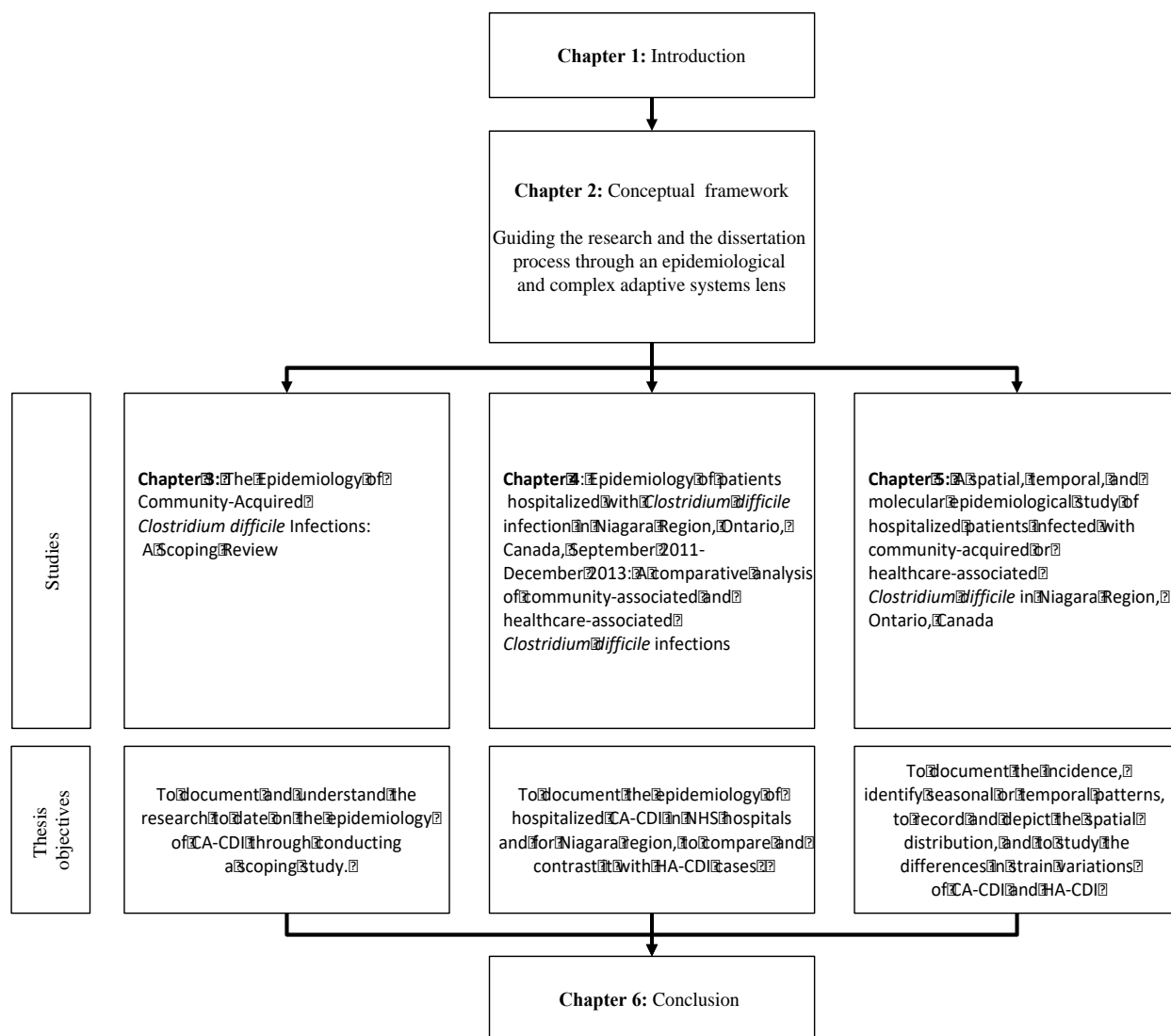
Figure 1.4 – Dissertation structure: A summary of the objectives and studies presented in each chapter.

Chapter Two – Conceptual Framework

The epidemiology of Community-acquired *Clostridium difficile* infections in the Niagara

Region, Ontario, Canada, between September 2011 and December 2013

Introduction

The value of combining population-level epidemiological studies in disease prevention with the biology and pathogenesis of diseases has been acknowledged since the 19th century, when John Snow's spatial study of cholera cases in London revealed water contamination as a source of the outbreak (Gordis, 2000). For this, and numerous other reasons, including the complexities of healthcare practices, as well as the multiple aspects of diagnosis, treatment, and care delivery settings, scholars in the field of healthcare quality improvement and patient safety argue the need for a systems approach. As two leading researchers in healthcare quality improvement and patient safety make clear: "Systems approaches are necessary for sustained improvement because they consider clinical workflows, care processes, and the overall environment clinicians practice in" (Baker & Axler, 2015). Following this line of thinking, the 2016 recommendations for improving healthcare quality in Ontario urge institutional and organizational leaders to connect with other parts of health systems using their relationship management skills and applying systems thinking throughout their practices (Health Quality Ontario's System Quality Advisory Committee, 2016).

Systems thinking also appears in recommendations for a systems-based approach to reporting (Howley & Chuang, 2011; Petula, 2005). A systems-based approach, such as the National Healthcare Safety Networks for reporting healthcare-associated infections (HAI) in the United States, has been proven to promote safe practices through well-crafted policies, prevent

diseases through interdisciplinary efforts, support evidence-based collaborative practices, and improve healthcare quality outcomes.

Given the recent push to apply systems-based approaches to healthcare challenges, in this chapter, I view my dissertation topic through the lens of Complex Adaptive Systems (CAS) theory, a modern and inclusive archetype of systems thinking. In what follows, I explain my choice of a conceptual framework and show how it shaped my research questions and methodologies.

Background

In hospitals, patients with multiple complications are frequently exposed to antimicrobials causing healthcare-associated *Clostridium difficile* infections (HA-CDI), making *Clostridium difficile* infections (CDI) largely a hospital problem. Historically, surveillance and investigation of healthcare-associated infections have been conducted within the scope of practice of hospital-based infection prevention and control (IPAC) programs, with little attention to cases meeting the definition of community-acquired infections. For cases or outbreaks of infectious diseases in hospitals, IPAC programs commonly use a cause-and-effect model of investigation (e.g., a Fishbone diagram), looking for contributing factors, brainstorming, sorting through ideas, and identifying causes of infections from a hospital perspective and within hospital boundaries (Chuang et al., 2015; Wu, Lipshutz, & Pronovost, 2008). The intent of this approach is to identify and eliminate the hospital-based factors that contribute to the problem. However, recent years have seen a surge in cases of community-acquired CDI (CA-CDI), without the traditionally recognized risk factors for HA-CDI (Khanna et al., 2012). In addition, the cause-and-effect approach using hospital surveillance data alone has proven insufficient, even for hospitals, as we repetitively witness outbreaks; simply stated, this type of approach

occasionally lacks the evidence-based support for successful interventions that reduce infection outbreaks.

In order to allocate the right resources to IPAC services or public health programs and to come up with more effective preventive measures in hospital and communities, we must develop a better understanding of the flow and the pathways of CDI infection, both in hospitals and between communities and hospitals. The proposition of this research is that by applying an analytic systems-wide lens, we can transform data on CA-CDI and HA-CDI into epidemiological patterns and actionable knowledge that can objectively inform future preventive practices and equitable health policies to improve the effectiveness of the preventive strategies in hospital settings and extend that knowledge to communities, thus expanding our focus from a solely institutional level to include a population level.

To uncover the epidemiological patterns of diseases, we need a framework that reflects the interrelationships and interdependencies both within and between hospitals and communities. This is not a new idea. For example, when a systems lens was applied to study the epidemiology of other infectious diseases such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), or Ebola virus disease, studies found that despite the high rate of person-to-person transmission and the associated high mortality of these infections in hospitals and healthcare settings, the possibility of single or multiple introduction and reintroduction from the community played an integral role in the spread and outbreak of these infections in hospitals (Assiri et al., 2013; Lloyd-Smith, Galvani, & Getz, 2003; Rico, 2016).

A systems level understanding of the transmission pathways of infections that spread along the continuum of hospitals and communities can prevent emergent infections by making effective interventions. The bottom line is that preventing and reducing transmission in

communities reduces the overall burden on healthcare resources. For instance, tuberculosis (TB) outbreaks are disproportionally prevalent in homeless populations; in the United States, there was a10-fold increase in the TB rate (6%) in this group compared to the non-homeless population between 1994 and 2010 (Bamrah et al., 2013). The prevalence has been associated with equity indicators, including crowding and poor ventilation in shelters for the homeless (Figueroa-Munoz & Ramon-Pardo, 2008; Hripcsak et al., 1999). Consequently, in 2005 the US Center for Disease Control and Prevention (CDC) recommended improved ventilation standards for shelters (CDC, 2005), but providing proper housing and social services is obviously a better solution. It would decrease the number of homeless- and shelter-associated cases of TB and reduce hospital and healthcare utilization.

In 2003, in a World Health Organization (WHO) communication, Pang and colleagues proposed an inclusive agenda for health research systems. In their view, researchers from different disciplines should form an interconnected system of scientific knowledge, accessing research-based information with the ultimate goal of improving and solving health and health equity problems (Pang et al., 2003). Other scholars in the field of quality and health systems have supported this proposal, with cross-disciplinary, theory-driven collaboration between hospitals and public health departments noted as a way to broaden the epidemiological tools used to evaluate and investigate causal factors in population health (Perneger, 2005). However—and despite calls for systems-level safety and quality initiatives—very few studies reflect on the interrelatedness of CA-CDI and HA-CDI infections at a population level using a systems and epidemiological lens (Baker & Axler, 2015; Barbut & Petit, 2001). Discussions of this nature are called for, especially given the trans-connectivity of hospital-based IPAC programs with other

in-house or external programs and with the movement of patients between hospitals and the community, on what I refer to above as the continuum of health care.

To describe the conceptual lenses through which the questions for this research were proposed, the next section explains some fundamental concepts of IPAC programs. It begins with the IPAC mandate and framework, outlined in the most recently published IPAC standards in Ontario. Next, to support the search for a suitable theory for this research, I present examples of the theoretical concepts used in IPAC and health studies. I then discuss the rationale for theory selection and the final choice of theory. Finally, I explain the guiding conceptual framework of this research; I show how it directed the formulation of the research questions and the data collection, evaluation, and interpretation.

The Role of IPAC Programs in Healthcare Organizations

IPAC goal and function.

The goal of IPAC programs is to protect patients, healthcare workers, and others in the healthcare environment (APIC, 2013; PIDAC, 2011). Put more pragmatically, IPAC programs seek to do the following: obtain and manage critical information, develop or recommend policies and procedures, prevent infection, and provide education for patients, caregivers, and others involved in the process of care (APIC, 2013; PIDAC, 2011). By taking these steps, IPAC programs promote patient safety and improve quality of care in healthcare organizations, including hospitals and long-term care facilities, by reducing and preventing mortality, morbidity, complications, and the extra hospital days needed due to healthcare-associated infections. The programs work closely with external organizations, such as public health departments, nursing homes, community care providers, and homecare services, and with services within healthcare organizations, such as laboratories, clinical care services, and

occupational health and support services. Importantly, IPAC programs seek guidance from local or global evidence-based guidelines and standards to carry out their mandate. In Canada, IPAC programs and services are directed by multiple federal or provincial standards or guidelines.

Standard IPAC framework.

In Canada, the IPAC foundational framework is an integral part of the IPAC program standards developed by Infection Prevention and Control–Canada (IPAC–Canada, 2016). Although the standards clarify the role of internal and external stakeholders, such as public health departments, for event or outbreak management purposes or for service-specific consultations, the narrative of the framework focuses mainly on the governance, administration, and performance aspects of IPAC programs (IPAC–Canada, 2016). My review of guidance for IPAC programs and services did not reveal recommendations for a macro-level theory-driven conceptual framework that can guide practices or research within the discipline. In my view, this type of framework would be extremely useful, and in this chapter, I propose one possibility.

Figure 2.1 depicts an approximation of current processes of IPAC practice in healthcare settings in Canada related to CDI surveillance. The cause-and-effect model of surveillance and evaluation shown in the figure classifies patients into one of two categories, HA-CDI or CA-CDI, collects patient demographic and previous medical history, implements isolation requirements, and follows up patients until discharge from the hospital. Since the emphasis of the IPAC practices is on hospital cases, little attention is paid to the CA-CDI cases other than surveillance data collection and isolation precautions and treatment when patients are admitted to hospital. The approach lacks many aspects of the traditional method advocated by the epidemiological triad of host, agent, and environment, the interaction of which produces diseases found both in communities and in hospitals' emergency departments.

As seen in Figure 2.2, disease formation is considered a product of the human host's characteristics, such as genetics or occupation, an infectious agent, and the environment that promotes the exposure (Gordis, 2000). Therefore, to better understand the exposure risks and contributing factors to the disease transmission processes, the dynamics of disease transmission and their interplay must be evaluated from all aspects. The present surveillance practices omit the systems' view that is needed to clearly understand communicable diseases' processes and the factors contributing to infection formation.

Frameworks Guiding IPAC Studies

A literature search reveals that a few IPAC studies have followed conceptual models, particularly when implementation, adoption, and the application of quality improvement or patient safety initiatives are the focus. Table 2.1 lists the IPAC studies using models or conceptual or theoretical frameworks to guide their research or interventions. Researchers and practitioners in IPAC often heuristically select either program theories (small or micro theories) or mid-level theories (meso theories) when a model for understanding a problem or a guide to developing interventions is required (Davidoff, Dixon-Woods, Leviton, & Michie, 2015). Frameworks such as Kotter's change leadership model, Rogers' diffusion of innovation (DOI) theory, or Langley's model for improvement have been used to guide hypothesis postulation or program implementation, such as developing a hand hygiene program (Mitchell & Gardner, 2013; Pittet, Hugonnet, Harbarth, & Mourouga, 2000). As described in Chapter One, program-level theories specific to a program are helpful in providing clarity about the component of a program or the mechanism that leads the input to outcomes. They are useful tools to understand evaluation and methods functions (Davidoff et al., 2015). More specifically, mid-level theories,

such DOI, allow a better understanding of a problem or function as a guiding principle for developing targeted interventions (Davidoff et al., 2015).

However, micro and meso theories lack the scope required to address the complexities of multidimensional preventive strategies at a program and population level. The application of macro theories has been recommended to academics and researchers as a means to uncover assumptions and explain phenomena across multiple different disciplines; this proposed usage fits with the present research. Despite their potential utility, macro-level theories have seldom been applied, however. With the exception of one study applying a macro-level theory or grand theory (systems theory) for management and control of scabies outbreaks, most studies have used mid-level or program-level theories. A review of the studies listed in Table 2.1 shows that the majority used the theory of DOI (n=4) or the theory of continuous quality improvement (n=3) for implementation studies, behaviour change studies, and measurement or education effectiveness measurement studies. Given their popularity, before explaining my own theory selection, in what follows, I discuss the diffusion of information (DOI) theory and the theory of continuous quality improvement (CQI). Although each is clearly useful, neither works within the context of my research.

The theory of DOI has been widely used in many disciplines, including healthcare. Initially, the foundations of this theory were set when researchers observed the communication patterns that influenced the behaviour of hybrid corn farmers. Rogers later formalized the concept of DOI as the "processes through which innovations are communicated, using certain channels and over time and amongst members of certain social systems" (Rogers, 1995).

Although initially presented as an adoption theory at an individual level, emphasis on innovation and the desire to apply a staged model led to its adaptation for use at an organization

level. The staged model covers the span of an innovation, from "initiation" to "decision" and "implementation" over varying lengths of time (Rogers, 1995). Despite the evidence provided by Larson, Quiros, and Lin (2007) or Abbott et al. (2006) of their success adapting evidence-based practices to a DOI model (see Table 2.1), the implementation in both studies was limited to inter-organizational teams or departments. This does not offer a pliable theoretical ethos for comprehensive, trans-organizational programs. In addition, the use of a staged model of DOI has been criticized for its lack of applicability to complex innovations where multiple paths and cycles are involved in inter- and intra-organizational innovation processes (Wolf, 1994). Given these limitations, I rejected DOI and tested other theoretical lenses.

The theory of continuous quality improvement (CQI) has been used widely in healthcare for attaining, implementing, and monitoring quality improvement interventions. The operational and practical effectiveness of CQI theories has been demonstrated in numerous quality improvement initiatives (Scales et al., 2011; Misset et al., 2004; Vollman, 2006), Application of CQI models to the adaptation of quality improvement interventions in healthcare became common after the Institute of Medicine report on healthcare quality in 1999 and the advent of the patient safety movement (Kohn, Corrigan, & Donaldson, 1999). This model has essentially been used as a tool to measure the effectiveness of improvement initiatives (Langley et al., 2009). To reduce medical practice errors and to incorporate and maintain safety science in daily clinical tasks, CQI models have been applied to frameworks supporting a myriad of quality improvement and patient safety bundles (Pronovost, Wu, & Saxon, 2004). Many lives have undoubtedly been saved by applying the CQI theory to infection control safety bundles, such as the ventilator-associated pneumonia reduction bundle, or the bundle for preventing surgical site infections. However, the CQI theory is recommended more as an overarching management philosophy for

operational processes and less as a grand theory (Public Health Ontario, 2018). A CQI model cannot provide the required philosophical context to explain the many phenomena of complex healthcare functions, hence my rejection of it as a theoretical framework.

Reductionist and single cause approaches to disease formation and prevention have long been replaced by methods that consider biological, behavioural, and population-level factors and feature an analytical focus on their interrelatedness. Epidemiological studies increasingly focus on complex social, environmental, and individual factors to explain causes of disease (Galea, Riddle & Kaplan, 2010). In the field of infectious disease, the known dependence between individuals and communities at a local or a population level is an added reason to approach infections through a complex systems lens. The role of genetics in the significance of an individual's risk factors, combined with the interplay of causative agents and the environment, work together to define the dynamics of a disease formation in an individual (Diez Roux, 2011).

Correspondingly, scholars stress the value of unbiased health inequity evaluations by detecting patterns in different subgroups of a population (Braveman, 2006). Frameworks that apply an all-inclusive theoretical lens can conceptualize and capture the open dynamics of complexities at a population level, such as the interdependencies of health indicators and the environment. To understand and explain infectious disease pathways and enrich the research on possible routes of transmission, an all-encompassing and adaptable grand theory that tolerates the complexities of transdisciplinary, multi-organizational functions should guide research and practice processes.

Frameworks Guiding Health Studies

Systems-thinking theories have historically been a dominant ethos guiding health research and practice (Dredger et al., 2007; Green, 2006; Leischow et al., 2008; Likosky, 2014; Perneger, 2005; Peters, 2014; Revere et al., 2007). With the advent of continuous process improvement movements in healthcare settings, systems thinking has increasingly been incorporated into clinical practices (Henriksen et al., 2005). Healthcare quality improvement scholars maintain that systems thinking improves transdisciplinary communication and team building, supports collaboration and trust, enhances conflict management, process orientation, and organizational learning, reduces power differentials, and ultimately promotes health (Petula, 2005). Systems thinking can guide us to improved data collection methods, better data quality, new questions, and different ways of looking at the hypothesis formation processes. There are many theories of systems thinking, each explaining certain phenomena. Table 2.2 summarizes and compares several theories and their application in health studies (Peters, 2014).

The table makes clear that systems theory is a dominant grand theory and a leading viewpoint used repeatedly in healthcare and public health to define biological and social phenomena. Von Bertalanffy says: "The characteristic of life does not lie in a distinctiveness of a single life process, but rather in a certain *order* among all the processes" (von Bertalanffy, 1968). As this comment suggests, systems theory refers to a general science of "wholeness" (Drack, 2008). Through a systems theory lens, the conflict between "mechanisms" and "vitalism" can be solved by metaphysical sciences (i.e., the order among all life processes), rather than by empirical sciences (i.e., the distinctiveness of a single life process) (Cordon, 2013). General systems theory addresses the metaphysical field of science by integrating various sciences. Universal principles apply to the systems in general, such as holism, boundaries, hierarchy,

mutuality, equilibrium, equifinality, and entropy, as listed and explained in Table 2.3 (Drack, 2008). For example, Chuang et al. selected a systems-oriented event analysis model to guide their interventions and to halt the ongoing scabies outbreaks in a hospital ward. They used systems modelling and analysis to prioritize hazards and integrated a set of risk control measures into the traditional root cause analysis and preventative guideline recommendations (Chuang et al., 2015). The challenges of applying systems theory to modern healthcare include the complexity of the problems, the unpredictability of events, and the multiplicity of agents involved in programs, but in the scabies study by Chuang and colleagues, the systems-level analysis was conducted only within a hospital ward, with fewer external interactions or distinguishing individualities of multiple and external agents.

As in many other subunits of healthcare, the dynamic and evolving nature of IPAC programs requires a guiding theory to accommodate the continuous evolution of multiple interconnected stakeholders. A complex systems viewpoint is increasingly used in healthcare and the public health domain, mainly because of the insufficiencies of the traditional reductionist approaches in explaining the dynamic, emergent, and nonlinear behaviour of these systems (Plsek & Greenhalgh, 2001; Diez Roux, 2011). Complexity theory is now being applied to the frameworks guiding healthcare research, such as studies in epidemiology and infectious diseases, healthcare organization, biomedicine, health and social sciences, and health geography (Rickles, Hawe, & Shiell, 2007).

As long ago as 1994, Anderson claimed that the interaction between various components that trigger and cause infections in individual patients and the factors that control the transmission in communities are complex, interrelated, and nonlinear (Anderson, 1994). In his research, Anderson applied mathematical modelling to infections and immunity pathways to

explain and study the role and the interaction of antigenic variation, pathogenic persistence, and vaccination policies to control childhood infections. He noticed themes of dynamic complexity deriving from explainable biological assumptions. Quite early on, Anderson's study emphasized the value of viewing interdisciplinary research in the infectious diseases and immunological fields through a complex theoretical lens, underlining that a reductionist approach to disease prevention cannot be successful.

An extension of complexity theory, the complex adaptive systems (CAS) theory, speaks to the challenges of 21st century health care (Plsek & Greenhalgh, 2001). CAS is a recommended paradigm for research perspectives on public health similar to those of Anderson (1994), where the complexity and co-evolution of the system components are continuously influencing evidence-based feedback (CPHA, 2016).

The theory of complex adaptive systems postulates a dynamic, emergent, and intuitive paradigm within which the inconsistencies, interdependencies, and unpredictabilities associated with the human system and with health systems are explainable (Waldrop, 1992). The evolution of human responses to communicable disease dynamics that have caused pandemics or epidemics, such as the HIV/AIDS epidemic in Brazil or the Toronto-area SARS outbreak in 2003, is typical of complex adaptive systems characteristics. In 1990, a World Bank study ranked Brazil and South Africa as the two countries with the highest number of HIV/AIDS cases, with Brazil having almost twice as many cases as South Africa. Although international organizations suggested an emphasis on preventive approaches, Brazilians at all levels responded to this problem with a cure-for-all mindset (Westley et al., 2007). All levels of society joined forces to manufacture and provide free treatment to everyone affected by HIV/AIDS, and to promote, market, and implement preventative measures at all levels using creative approaches.

Consequently, by 2000, Brazil's HIV/AIDS infection rate had been reduced to 0.6 percent (1 person in 160). South Africa now lagged behind Brazil, with one in four persons infected. Brazil's experience with control and management of the HIV/AIDS epidemic is just one example in which unanticipated resources have been pulled together in response to a complicated health problem, and the response of individuals and group dynamics at various levels has impacted disease outcomes and incidence at a population level.

With the understanding that IPAC services are faced with multiple complex inter-organizational problems influenced by both hospital and community dynamics, the theory choice for this dissertation must include internal and external stakeholders and their collaborative interplay, while maintaining the individuality of each organization.

Theory Guiding the Conceptual Framework: Epidemiology Informing Health Equity Policies

Health systems and their human and environmental adjuvants are complex, unpredictable, and evolving (Plsek & Greenhalgh, 2001). Systems thinking has been used as an umbrella theory underpinning the philosophy of practice and research in health care. But the trans-dependencies, interrelatedness, and unknowns associated with this research context must also be embraced by theory. The general systems theory, which posits that efficient health systems function as well-oiled machines, omits the dynamic living aspect of the practices and the people, or ignores the individuality of the stakeholders or their collective effect on the system's relationships. Hence, the reductionist approach of the traditional systems theory cannot explain the unpredictability of health systems or the greater impact that can be achieved by summing together the systems' various agents (Westley, Zimmermann, & Patton, 2007). According to Diez Roux, questions about population-level health disparities are difficult to answer because there is a lack of clarity

on dynamic processes. Knowledge of these processes could better inform the etiology or policy enquiries (Diez Roux, 2011). Systems methodologies that consider the heterogeneity, adaptation, non-linear dynamics, and stochasticity of these dynamic agents at various levels are able to reveal patterns at various scales (Diez Roux, 2011). In turn, identifying new and emergent patterns can improve our understanding of the factors contributing to infectious diseases incidence, thus reducing health problems at a population level. Given the above considerations, in this dissertation, I opt for a CAS lens.

Complex Adaptive System (CAS) Theory

Complex adaptive system theory is often used as a subset of complexity theory. Complexity science embraces life as it occurs, as an unpredictable, emergent, evolving, and adaptable phenomenon (Westley et al., 2007). The concept of complexity is based on the work of Laplace, an 18th-century philosopher and mathematician whose research led to Neumann's study of dynamic weather system models in the 1950s (Rogers, Medina, Rivera, & Wiley, 2005). It is thought that an interdisciplinary team of experts developed the term "complex adaptive systems" (CAS) in the 1980s. CAS theory has since been used to study weather, ecosystems, immune systems, and organizational and human behaviour. CAS is widely used in recent medical sciences literature as a modern prototype of general systems theory (Plsek & Greenhalgh, 2001; Zimmermann, Lindberg, & Plsek, 1998). More specifically, the feedback mechanisms that are key characteristics of this theory (discussed later) can inform future directions of practice, research and policies in population-level health.

Organizational complexity theorists assert that complexity theory is the right ethos to explain processes that cannot be explained by analyzing their parts, just as human body or disease processes cannot be fully understood by simply itemizing their organs or agents (Westley

et al., 2007). Complexity results from the unpredictable inter-relationship and interconnectivity of the elements within a system and between the system and its environment (Chan, 2001). The relationships emerging from interactions in a complex system may result in new patterns that empower the system to structure new changes. As in Anderson's childhood disease prevention and vaccine development process (mentioned previously), discovering the relationship between biological interactions, diseases processes, and interfaces amongst individuals and groups could yield findings relevant to population health.

CAS has been defined as a range of critical and simultaneous interactions between multiple stakeholders with various goals and purposes, where ambiguous outcomes may be anticipated (Zimmermann et al., 1998). For example, the reaction of multiple stakeholders to natural disasters such as hurricanes can be explained by this theory. The non-linear, spatio-temporal interactions between and within the components, factors, and mechanisms of stakeholders and their environments at different levels comprise a CAS (Glann-Mann, 1995/96). Many inseparable natural and artificial systems involved in healthcare, such as the human body, body organs, and computer systems, are characterized by these CAS behaviours, making CAS theory increasingly applicable to health problems and increasingly popular with population health researchers.

A CAS is equally dependent on relationships, emerging patterns, and iterations of multiple complex subsystems that are constantly adapting to their environment (The Health Foundation, 2010). Operators and stakeholders in a CAS are active participants in a system through connections, relationships, and insights about how the world is changing (Westley et al., 2007). For example, the transformation and/or adjustments of CAS participants in one subsystem can motivate the development and evolution of other subsystems; to give one example, practice

modification in operating rooms can reduce post-surgical site infections and reduce the burdens to the health system and the patient caused by additional hospitalization.

Figure 2.3 gives a simple representation of CAS components. As the figure shows, the experiences and feedback from patterns formed through interactions and relationships inform the agents and the system(s), and shape the emergence of future patterns, causing them to evolve.

Properties of CAS Theory

Unlike mechanical systems with well-defined boundaries, a CAS has undefined and variable boundaries to allow interaction and exchange between the subsystems and between the subsystems and their environment, while maintaining the individuality of each subsystem. The following five principles are the main differentiating and unique characteristics of a CAS (McDaniel, Lanham, & Anderson, 2009; The Health Foundation, 2010).

Connectivity: A CAS is interactive, with interactions leading to reciprocal feedback and the influence of agents or systems on each other. In fact, the relationship of agents and subsystems is critical to the survival of a CAS (The Health Foundation, 2010). CAS behaviour evolves from the interactions between agents and/or systems, and systems are more than just a collection of agents. These interactions are inevitably complex and will change the context for other agents. Many examples in nature (colonies of bacteria), human groups (families or a healthcare team), and organizations show this characteristic of a CAS.

Emergence: A characteristic distinguishing a CAS theory from a reductionist theory is the rise of unexpected and new structures, patterns, properties, or processes. Emergent phenomena have their own rules, laws, and possibilities, but they can be created from a few simple rules or "minimum specifications" (Plsek & Wilson, 2001). Four elements associated with minimum specifications that promote innovative and complex behaviour are: direction pointing,

boundaries, resources, and permissions (Baker, 2001). As an example, the Institute of Medicine in the United States used a minimum specification process, in the form of reflecting on innovations presented by various groups of healthcare teams, to transition to a new design of the healthcare system for the 21st century. While coping with anxiety and stresses related to human systems is considered an influence of minimum specification, the significance of emergent phenomena may be downplayed because the control mechanisms generated by organizational hierarchies may have a limiting effect on emergence.

Adaptation: An essential feature of a CAS is its ability to adapt by changing the rules and patterns of interactions within subsystems or amongst agents. Adaptation has been also interpreted as improved performance over time, with different outcomes based on the timeline of adaptation. These time frames include a single event's adaptation with internal or external systems (resulting in learning) or lifetime adaptation (resulting in evolution). Studies of CAS indicate that adaptation is a result of self-organizing processes related to the internal dynamics of a system. As an example, Lloyd-Smith et al. (2003) found the hospital implications of SARS could be reduced by implementing measures that reduced community–hospital transmission. What appeared to be a hospital infection with a high rate of transmission amongst healthcare workers in initial stages of this outbreak ended up having roots in the community, with a lower potential rate of transmission. In this case, interaction and learning from explorations of different subsystems resulted in adaptation, with the implementation of stronger screening and isolation policies upon hospitalization.

Nonlinearity/Iteration: A CAS is often nonlinear, in that small changes in the initial agents can lead to huge differences within the system. In nonlinear systems, outputs are not proportional to inputs; therefore, tallying the parts of the system does not result in a logical

combination of its separate parts. An ongoing challenge for public health is to find ways to apply

and incorporate the experiences of other academic disciplines to tackle health policies (Clarke et

al., 2007). In public health, the will to use methods used in health services for other purposes—

such as etiological epidemiology—could help develop multidisciplinary methods to evaluative

interventional epidemiology (Clarke et al., 2007). As an example, the HIV/AIDS recovery in

Brazil described earlier was the result of a combined collection of solutions over time, which

magnified the spread and impact of the interventions at a societal level (Westley et al., 2007).

Drawing on experiences in other areas of science could result in improvements in the function of

the healthcare system.

     Self-organization: Patterns, properties, and innovations emerge naturally and universally

throughout CAS, without input from or the influence of a hierarchy of command or external

forces. This constant process is the system's method of reorganizing itself to find the best fit for

a changing environment. A vivid example of this characteristic is Toronto's experience during

the SARS outbreak in 2003. At this time, hospitals and public health departments were dealing

with many unknowns. Multiple groups in healthcare organizations at various levels came

together to respond to an evolving outbreak. Emergent ideas and innovative practices, such as

treatment options or modifying personal protective equipment and isolation requirements, were

continuously changing as a result of changing case definitions and with new information on

transmission routes.

     The ideal condition for self-organization to materialize is called the "edge of chaos," that

is, the zone between too much rigidity and too much lenience (Plsek & Greenhalgh, 2001;

Zimmermann et al., 1998). This is a critical phase of a dynamic complex system, as depicted in

Figure 2.4, when the potential for the emergence of new and more adaptive patterns is at its

maximum (Zimmermann et al., 1998) and where new attractors are formed as a result of a system's dynamics. In natural systems, such as health care, the edge of chaos conditions (also called far-from-equilibrium conditions) lead to critical thresholds for the manifestation of self-organization and emergence. Organizational innovation is likely to happen in an edge of chaos-like condition (Zimmermann et al., 1998). In the SARS example, guidelines for personal protective equipment were changing as exposure to infection and numbers of infected cases were increasing and information about the new cases' exposure revealed new routes of transmission. Bifurcation of various resources and an edge of chaos-like environment led practitioners and researchers to recognize new patterns in this community infection (attractors), despite initial beliefs that SARS infections had their roots in healthcare facilities. The new patterns resulted in practice and policy changes. A limitation of CAS theory has been cited as the lack of firm criteria to gauge a "complex system" or the ambiguity on how to enrich bifurcation or the edge of chaos-like condition in organizations to allow emergence and innovation (Rickles, Hawe, & Shiell, 2007a).

A feature of a CAS is the possibility of multiple interconnected agents and/or systems embedded within each other, where the evolution of one influences others (Rhodes & MacKechnie, 2003). Good examples are healthcare teams, programs, or systems. The initially heterogeneous agents or subsystems become linked through continuous interactions. While this may increase the interdependencies of the systems or agents, the whole system will acquire an increased organism-like structure (Zimmermann et al., 1998), with work being done collaboratively toward achieving crucial goal/s for the subsystems. A CAS positions its functions in continuously determined trajectories toward achieving a fundamental purpose rather than arriving at a point. This can be compared to multiple interconnected micro improvement cycles

in clinical units; each section of the unit has goals, but together they move towards an umbrella goal (i.e. improving quality of health in that unit). The greater the variety of agents and subsystems, the stronger the system will be in achieving new possibilities and co-evolution.

A CAS doesn't have to be perfect (The Health Foundation, 2010). Theorists claim that the energy used to maintain a flawless CAS—a substitute for a system/subsystem that is better than other alternatives—is wasted energy. Overall, the two key distinguishing characteristics of a CAS are self-organization in a non-equilibrium environment and emergence (McDaniel et al., 2009). The flexible adaptability of a CAS is in tune with the random mutation and transformation of its internal models, its environment, and natural selection (Zimmermann et al., 1998). This is partially a result of the continuous learning and evolution in a dynamic CAS and a side effect of the collective experiences and feedback of its components.

Feedback and, more specifically, feedback loops are important to the functioning of complicated and dynamic systems. Feedback loops occur when the output of a practice or development from within a system serves as an input into the same system (Rickles, Hawe, & Shiell, 2007b). In this fashion, feedback loops are able to address the complexity of the delivery, implementation, and usage of multifaceted healthcare preventive measures (Gericke, Kurowski, Ranson, & Mills, 2005). In healthcare, feedback loops can uncover practices inconsistent with evidence-based medicine and lead to positive change. For example, providing cost information feedback to physicians or informing physicians about the cost of diagnostic testing has been reported to influence their ordering behaviour (Busato & Künzi, 2008; Fisher & Wennberg, 2003; Krumholz, 2008). In general, positive feedback can have an amplifying effect, informing and encouraging change in processes or practices, such as access to healthy food to promote a healthier diet, which, in turn, increases the demand for healthy food. Negative feedback often has

an inhibiting effect and a moderating influence on the system's equilibrium, such as the moderating effect of childhood immunization on the prevalence of a disease in communities and on epidemic prevention.

Feedback loops have been successful in identifying variations in quality of care between organizations based on their geographical positioning. For example, in a study of provider behaviour amongst local clinical practices , Fisher and Wennberg (2003) found that uneven care delivery processes throughout the healthcare system in American institutions were based on geographic variations, organizational settings, or payment systems (Fisher & Wennberg, 2003). The feedback loops caused by practice inconsistencies resulted in the delivery of ineffective care and showed differences in providers' practices. Feedback loops have been also used to explain the mechanisms through which social determinants influence health (Paina & Peters, 2012). For example, in the vicious cycle of poverty, malnutrition, and ill health, each factor has an amplifying effect on the others. Poverty reduces access to food, resulting in immune systems that are more vulnerable due to malnutrition, leading to illnesses that prevent the individual from functioning and working. This result has an amplifying influence (positive feedback) in that it leads to more poverty, driven by lack of employment.

To sum up: Table 2.4 lists the main properties and characteristics of a CAS. As the table suggests, CAS theory appreciates healthcare systems as a mix of dynamic environments and agents, where interaction and the relationship of various components simultaneously affect each other. Current IPAC practices, at best, are focused on healthcare-associated cases (HA-CDI), and surveillance activities are aimed at antimicrobial exposure or hospital environment cross-contamination as the main risk factors. However, this traditional approach omits the investigation of contributing factors to a large proportion of CDI cases that are occurring in our communities

but influence the hospital environment. Evaluating half of the problem cannot inform objective and equitable policies.

This research is based on three main research foci that integrate the dynamics of disease spread, based on the epidemiologic triad of disease transmission (see Figure 2.2) through a CAS lens. In the epidemiologic triad, three categories of risk factors are associated with an increased likelihood of human disease: host characteristics, the types of agent that cause disease, and environmental factors (Gordis, 2000). A CAS–IPAC paradigm elucidates the association and considers various disciplines' interrelationship by providing a model for practice and research. A macro-level analysis of these experiences can result in meaningful epidemiological findings that can influence disease prevalence at a population level.

Epidemiology of CA-CDI in the Niagara Region: A Conceptual Framework

The questions postulated to meet the objectives of this research are described in detail in Chapter One. They are repeated here for ease of access:

Question1: What is our current knowledge about the epidemiology of CA-CDI?

Question 2: Is the epidemiology (demographic, patient characteristics) of CA-CDI different from that of HA-CDI in NHS hospitals?

Question 3: Are the temporal, spatial, and strain assortment patterns of CA-CDI different from those of HA-CDI?

The antecedents for the questions are the following specific CAS properties:

Connectivity (many interacting parts): The dynamic interaction of individuals and programs in healthcare settings can lead to productive, novel approaches to tackle the challenging issues faced by IPAC. More specifically, in this research, translating data to actionable epidemiological knowledge is made possible by connecting internal and external

services to elucidate the transmission routes between communities and NHS hospitals. Highlighting connectivity may reveal risk factors beyond the traditional healthcare-associated risk factors or community patterns, such as population proximity to farmland, animals, and animal rearing practices. The identification of patterns will suggest that the research framework has successfully identified the underlying contributing factors. The goal of this research is to promote the interplay of multiple stakeholders, such as NHS hospitals' clinical and nonclinical programs and public health programs in communities, to move towards a systems approach and reduce infections at a population level. These considerations are the antecedents for questions 2 and 3.

Emergence (emergent behaviour): Dynamic relationships and interactions between the agents of a CAS may result in the emergence of novel patterns between groups in the study (CA-CDI and HA-CDI groups), leading to a better understanding of CA-CDI epidemiology or potential health equity factors that explain the increase in community cases and the resulting increase in hospitalized cases. For example, locating unusual CA-CDI activity with irregular spatial distributions or temporal patterns may encourage future research to explore indicators, such as the presence of food/waterborne sources, occupational exposure (from soil, animal farms or animal rearing stations), poor housing structures, or crowding in living accommodations. The research relies on the acquisition of empirical data, such as administrative data, surveillance and laboratory findings, to find answers. The search for unexpected emergent patterns using empirical data is the antecedent of all three questions.

Adaptation (co-evolution): Long-term, transdisciplinary systems'-level adaptations between IPAC and multiple other stakeholders, such as new epidemiological trends, can result from the application of CAS and the knowledge adjustments of subsystems. Although a system

thinking evolution may not be an immediate possibility, the patterns identified in this research will inform future studies. As an example of how this works, during the 2003 SARS outbreak, a high proportion of patients infected with the SARS virus were healthcare workers (51% of cases in Toronto), and hospitals were recognized as the highest-risk settings for SARS (Lloyd-Smith et al., 2003). But the collaborative functions of hospitals, IPAC, and public health, and other community organizations, plus multiple simulation and modeling studies, revealed the initial sources of this infection to be in communities. With this knowledge, successful preventive interventions in hospitals, along with stringent screening and case management upon admission to hospitals, played a critical role in preventing the leakage of this infection back into communities and reduced its reintroduction into the hospitals from communities. The connective progression of IPAC and other stakeholders as a result of the interaction between internal and external departments guided the operationalization of this research and is the antecedent for questions 2 and 3.

Iteration (nonlinearities): Complex adaptive systems are interactive and interrelated; their components provide feedback on the subsystems and on the entire system (Zimmermann et al., 1998). The research looks at interactions between specialized modular and cooperative subsystems (interrelated subsystems) at a functioning level. This increases the research efficiency by accessing, analyzing, and interpreting encapsulated information in multiple subsystems (in a conceptual framework, as in Figure 2.5, they are exemplified as agents). Small outcomes of this study may lead to nonlinear but significant efficiencies in population health quality improvement initiatives through the feedback loops both in hospitals and in communities. Unanticipated large or small outcomes dependent on previous practices may influence future practices. This property of CAS is the antecedent for all three research objectives, with specific

focus on research question 3. Epidemiologic analysis of CA-CDI cases has the potential to identify the community drivers of CA-CDI that are rooted in the environment.

Self-organization (decentralization): This research explores emergent patterns to reveal unique epidemiological properties and actionable knowledge that can point to new directions in research and equitable health policies. Multiple stakeholders are involved. In addition, novel and versatile statistical analysis allows the detection of new and emergent patterns, structures, or information. The diverse range of analysis (patient characteristics, temporal, spatial, and strains identification) is essential to understand emergent patterns at a time when NHS hospitals are experiencing unusually high numbers of cases (far-from-equilibrium condition). Identifying new patterns as a result of bifurcation of the outcome data of this research may lead to long-lasting improvements. Similar to what was seen in 2003 with SARS or during the Brazilian HIV/AIDS epidemic, in a CAS, self-organization and reorganization of the subsystems and the approach to studying and handling a problem results in the identification of novel intervention points, leading to long-lasting changes in behaviours and functioning. Identifying patterns among the CA-CDI partners and decentralizing the hospital study outcomes are antecedents for questions 2 and 3.

Figure 2.5 summarizes the conceptual framework for the research on the epidemiology of CA-CDI in the Niagara Region and shows its grounding in CAS theory. The research is based on the transdisciplinary connectivity of the components, the emergence of new and different patterns, and the respective agents' adaptation by forming nonlinear efficiencies as a result of positive or negative feedback derived from self-organization of the system's (study's) components. In this framework (see Figure 2.5), the role of the CAS in supporting the epidemiological study of CA-CDI is a foundational one, guiding internal and external stakeholders' ongoing feedback and adaptation. Positive feedback can improve the overall

healthcare practices and health policies. In the long term, these changes will impact the infection rates in the community and in hospitals, improving population health. In contrast, negative feedback will have a moderating effect on healthcare practices and results by maintaining the status quo.

In this study, the antecedents for the research questions are the trans-disciplinary connectivity and adaptation of the agents involved, leading to the emergence of new and different patterns. By applying a CAS lens, this research will enhance our understanding of the fundamental variables of CA-CDI epidemiology. Findings will yield useful insights into factors contributing to the increased incidence of CA-CDI by looking at those who sought hospitalization and suggest improvements in the quality and equity of population health. The goal is to use current data and to identify patterns and previously unidentified leverage points in the surveillance and demographic information to inform health equity policies. As Diez Roux states: "The key question is no longer about partitioning groups and individual effects or social and biological effects but rather about understanding how these dynamically relate to generate the macro patterns that we see" (Diez Roux, 2011).

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Tables

Table 2.1 – Theories guiding IPAC studies.

Research/publication, author, year	Theory/model and key reference
Introduction of an isolation policy in paediatric wards (Hall, Roopnarine, & McLean, 2007).	Change leadership (Kotter, 1996)
Achieving zero catheter-related bloodstream infections: 15 months' success in a community-based medical center (Harnage, 2007).	Model for improvement (Langley, 2009) (Langley, Nolan, Nolan, Norman, & Provost, 2009)
Effectiveness of a hospital-wide program to improve compliance with hand hygiene (Pittet et al.)	Behavioural theory (Kretzer & Larson, 1998)
Implementation of an industrial systems engineering approach to reduce the incidence of methicillin-resistant *Staphylococcus aureus* infection (Muder et al., 2008).	Toyota production system (Spear & Bowen, 1999)
A multifaceted intervention for quality improvement in a network of intensive care units; a cluster randomized trial (Scales et al., 2011).	Continuous quality improvement
A continuous quality-improvement program reduces nosocomial infection rates in the ICU (Misset et al., 2004).	Continuous quality improvement
Ventilator-associated pneumonia and pressure ulcer prevention as targets for quality improvement in the ICU (Vollman, 2006).	Continuous quality improvement
Dissemination of the CDC's hand hygiene guideline and its impact on infection rates (Larson, Quiros, & Lin, 2007).	Diffusion of innovations (Rogers, 1995)
The impact of US-style infection control programs in an Asian country (Leu, 1995).	Diffusion of innovations

Research/publication, author, year	Theory/model and key reference
	(Rogers, 1995)
Adoption of a ventilator-associated pneumonia clinical practice guideline (Abbott, Dremsa, Stewart, Mark, & Swift, 2006).	Diffusion of innovations (Rogers, 1995)
Hydration and nosocomial pneumonia; killing two birds with one stone (a toothbrush) (Farrell & Petrik, 2009).	Diffusion of innovations (Rogers, 1995)
Implementing systems thinking for infection prevention; the cessation of repeated scabies outbreaks in a respiratory ward (Chuang et al., 2015).	(von Bertalanffy, 1969)
Patient safety and healthcare-associated infections (Cole, 2011)	Model of safety (Sammer et al., 2010)
Infection control; a psychological approach to changing practice (Elliott, 2009).	Biopsychosocial approach (Elliott, 2009)
Behavioural interventions to improve infection control practices (Kretzer & Larson, 1998).	Multiple models: Health belief model (Janz & Becker, 1984); Theory of reasoned action (Fishbein & Middlestadt,1987); Social cognitive theory (Banduar, 1986)
Conceptual model for reducing infections and antimicrobial resistance in skilled nursing facilities; focusing on residents with indwelling devices (Mody et al., 2011).	PRECEDE – Health education model

Research/publication, author, year	Theory/model and key reference
Infection control in the acute care setting; time for a change of perspectives (Nicol, Watkins, & Plant, 2007).	Theory of planned behaviour (Schifter & Ajzen, 1985); Health belief model (Janz & Becker, 1984)
The power of vivid experience in hand hygiene compliance (Nicol, Watkins, Donovan, Wynadan, & Cadwallader, 2009).	Theory of planned behaviour (Schifter & Ajzen, 1985)
Knowledge systems, healthcare teams and clinical practice; a study of successful change (Olson, Tooman, & Alvarado, 2010).	Soft knowledge system (Engle, 1997)
Knowledge sharing and organizational learning in the context of hospital infection prevention (Rangarachi, 2010).	Positive deviance systems (Sternin, 2003)
For the good of many; an infection control perspective on ethics (Zimmerman, 2001).	Ethical decision-making framework (Soskolne, 1991)
Accommodating patients with a history of colonization or infection with a multi resistant organism; a case study investigation (Zimmerman, Rowe, & Wallis, 2004).	Practice development model (McCormack & Garbett, 2003)

Note. Partly adapted from Zimmerman (2012) and Mitchell & Gardner (2013) and expanded with findings from the literature review.

Table 2.2 – Systems thinking theories and their application in health studies.

Purpose and description of the theory in health studies	Theory and key reference
A theory in mathematics and geometry to study how small changes in parameters of a non-linear system can lead to sudden and large changes in the behaviour of a system.	Catastrophe theory (Poston & Stewart, 2014)
Historically used as a synonym for systems theory, it is a field of study of the communication and control of regulatory feedback in both living and non-living (e.g., organizations, machines) systems.	Cybernetics (Ashby, 1961)
A field of study in mathematics with applications in a number of disciplines, to explain a dynamic system that is highly sensitive to the initial conditions so that small changes in initial conditions produce wildly different results. There are fixed rules about changing relationships, and changes are not random.	Chaos theory (Strogatz, 2014; von Bertalanffy, 1969)
Less a theory than a way of finding a general theory to explain systems in all fields of science. It is not intended to be a single theory of systems, but more a systematic inquiry into different domains of philosophy, science, and technology.	General systems theory (von Bertalanffy, 1969)
Organizations facilitate learning amongst their members and continuously transform themselves. Systems thinking approaches are the conceptual basis for understanding the organization in its environment; they provide a basis for other key characteristics: a process of learning (personal mastery), the building of mental models, and the development of a shared vision and team learning.	Learning organizations theory (Senge, 2006)
Theories used in economics, social sciences, and physics, referring to explanations of why processes can have similar starting points yet lead to different outcomes even if they follow the same rules, and why outcomes are sensitive not only to initial conditions but also to bifurcations and choices made along the way.	Path dependency theories (Arthur, 1994)
Theory inspired by evolutionary biology (Eldredge & Gould, 1985; Eldredge & Gould, 1972) to explain long periods of stasis interrupted by rapid and radical change, particularly as applied to the evolution of policy change or conflict.	Punctuated equilibrium (in social theory) (Baumgartner & Jones, 2010)

Purpose and description of the theory in health studies	Theory and key reference
Complex adaptive systems thinking is an approach that challenges simple cause and effect assumptions and sees healthcare and other systems as a dynamic process—one where the interactions and relationships of different components simultaneously affect and are shaped by the system.	Complexity/complex adaptive system, 1980s (Santa Fe Institute, 1980) (Glann-Mann, 1995/96)

Note. Partly adapted from Peters (2014) and extended to include additional studies reviewed.

Table 2.3 – Principles of the general systems theory.

Principles	Interpretation
Holism	The whole is greater than the sum of its parts.
Boundaries	Systems regulate what happens between them and their environment.
Hierarchy	All parts must obey the rules of the whole to which they belong.
Mutuality	Interdependency prevents the knowledge about the cause/s of events.
Equilibrium	Systems tend to seek a steady state between their components.
Equifinality	There is more than one way to get from one point to another point.
Entropy	Systems tend to fall into disrepair unless maintained.

Note. Source: Drack (2008).

Table 2.4 – Characteristics and properties of a Complex Adaptive System (CAS).

Properties of CAS	Description
Main properties	
Connectivity/many interacting parts	The relationship between agents is critical to the system's survival.
Emergence/emergent behaviour	Patterns emerging because of agents' interaction ultimately inform and change the behaviours of the agents and the system.
Co-evolution/adaptation	Systems and their environment evolve, adapt, and change continuously because of the interactions amongst agents and between agents and their environments.
Iteration/nonlinearities	Small changes in a system can lead to larger changes.
Self-organizing /decentralization	A CAS does not have a hierarchy of command; it reorganizes to find the best fit with the environment.
Additional properties	
Nested systems	Systems are embedded within other systems. Therefore, the evolution of one influences others.
Simple rules	A CAS is governed by simple rules and is not complicated.
Specialization, modularity/cooperation	Differentiation as a result of interactions will result in fast, efficient, and encapsulated knowledge gains. Cooperating increases the chance of accomplishment.
Sub-optimal	A CAS does not have to be perfect.
Mandatory variety/dynamic change	The greater the variety, the stronger the system will be, allowing new possibilities and co-evolution.

Note. From the Health Foundation, UK (2010); Edgeware, Zimmermann et al. (1998); Plesk & Greenhalgh (2001); www.trojanmice.com/articles/complexadaptivesystems.html

Figures
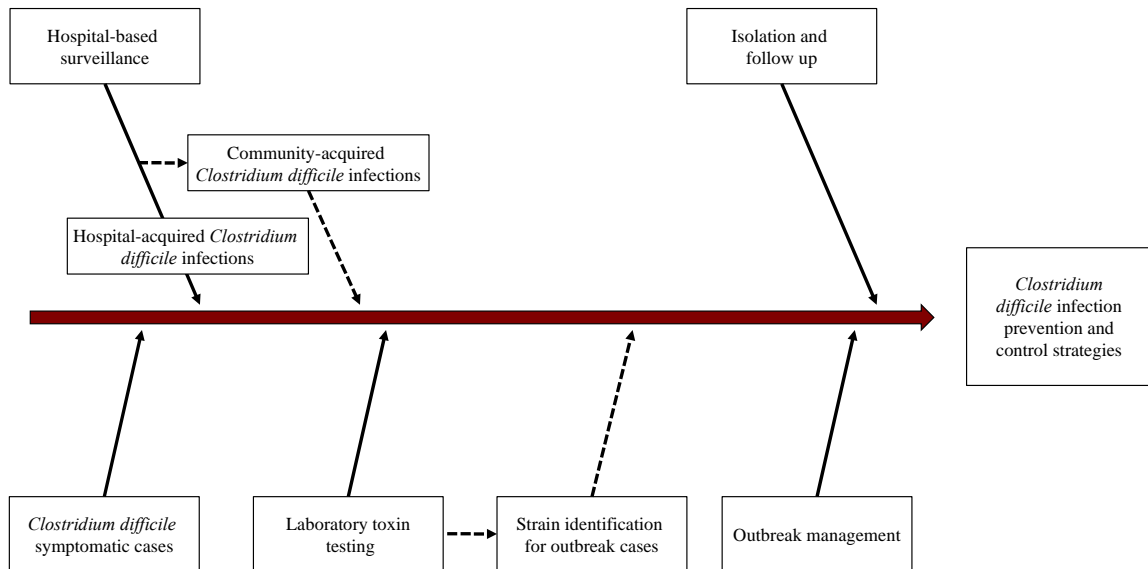
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Figure 2.1 – Approximation of current practices related to control and management of *Clostridium difficile* infections in healthcare settings.
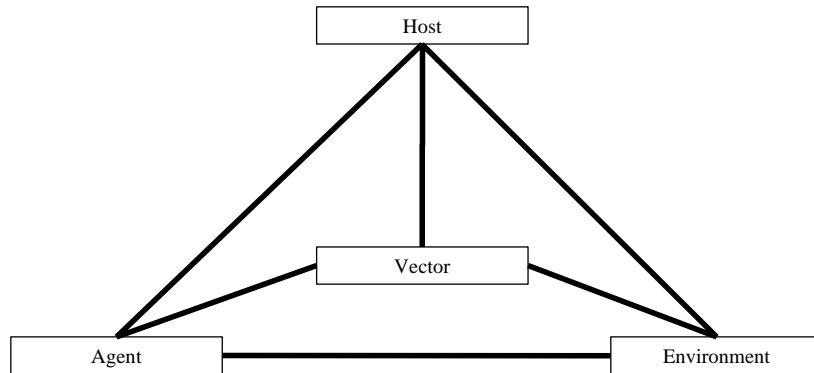
Figure 2.2 – Epidemiological triad of a disease and factors that may be associated with the increased risk of human diseases, adapted and modified from Gordis (2000).
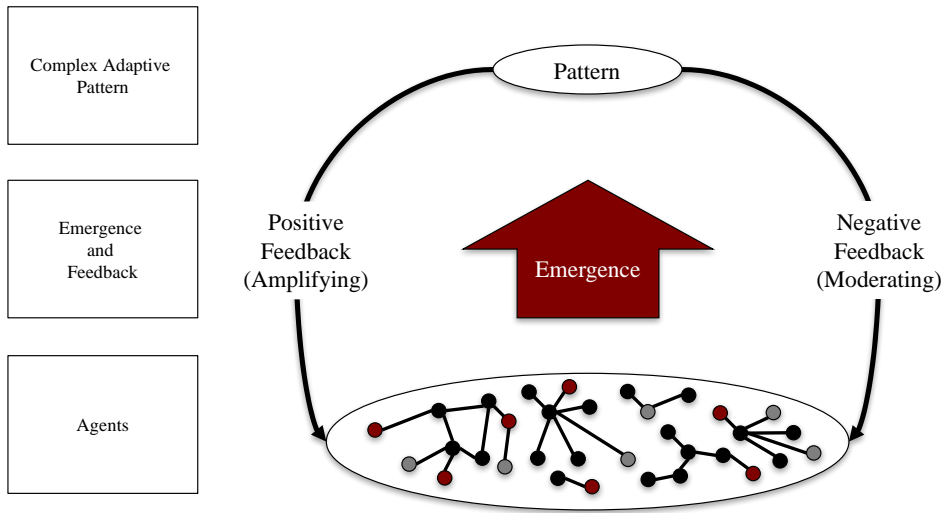
Figure 2.3 – A representation of the components of a complex adaptive system, modified based on The Health Foundation (2010) report and Zimmerman et al. (1998).
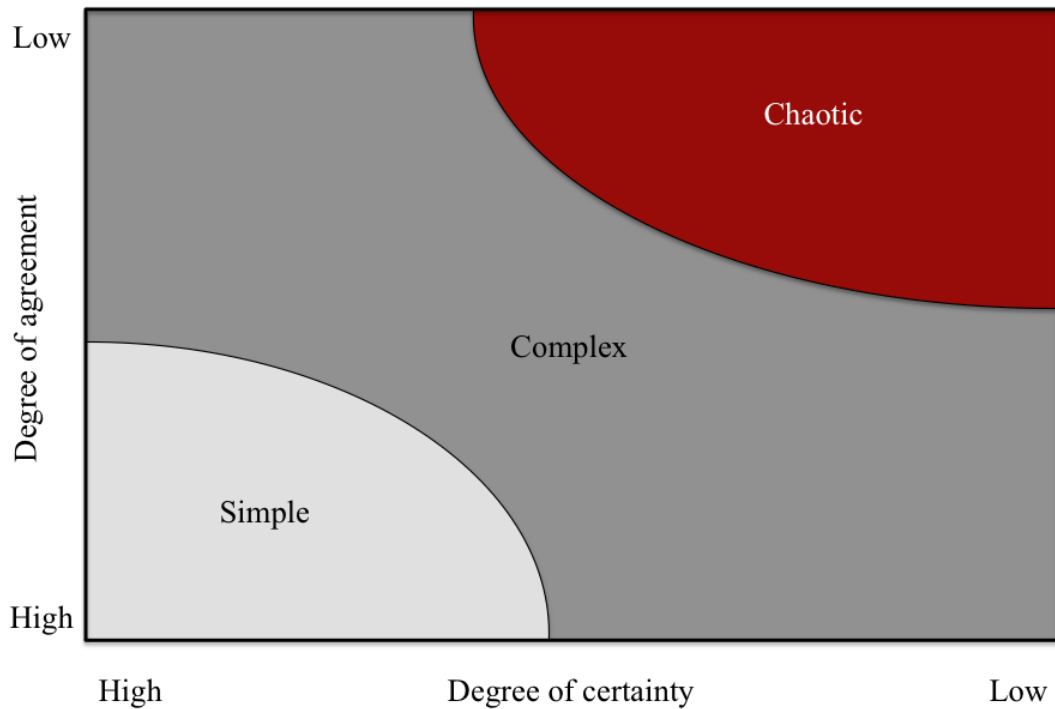
Figure 2.4 – The certainty-agreement diagram: Edge of chaos zone where there is insufficient agreement and uncertainty to choose the next step, but not so much that the system is thrown into chaos, adapted and modified from Plsek & Greenhalgh (2001), based on Stacey (1996).

Improving Population Health

Informing health equity policies and quality improvement practices	**Improving quality of *Clostridium difficile* infection prevention control**
Population level exploration and evaluation	**Patterns / risk factors**

Feedback   **Feedback**

Complex Adaptive System (CAS) lens	**Infection Prevention & Control** Surveillance Case confirmation **Administration data** Temporal data Spatial data **Public Health laboratories** Strain testing

Epidemiological lens	Host	Environment	Agent
Context	Niagara Health Region *Clostridium difficile* infection cases, Sept. 2011 – Dec. 2013		

Figure 2.5 – The conceptual framework for epidemiological evaluation of CDI cases in the Niagara Region.

Chapter Three – The Epidemiology of Community-Acquired *Clostridium difficile* Infections (CA-CDI): A Scoping Review

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Abstract

Objective: The purpose of this scoping study is to review the literature for existing evidence on risk factors for community-acquired *Clostridium difficile* infections.

Methods: Recommended protocols published by the *Joanna Briggs Institute (JBI) Reviewers' Manual 2015, Methodology for JBI Scoping Reviews* were followed. Three life sciences databases were searched for studies on the epidemiological aspects of CA-CD: Cumulative Index to Nursing and Allied Health Literature (CINAHL), Nursing and Allied Health Source (ProQuest), and MEDLINE. After applying the inclusion and exclusion criteria and full article reviews, 22 peer reviewed articles were examined for the study.

Results: Compared to HA-CDI cases, CA-CDI is seen more often in younger, female populations. No seasonal patterns were consistently reported, and one spatial study identified that proximity to animal farms, animal services, and nursing homes was associated with a higher incidence of CA-CDI in the community. Although exposure to antimicrobials and use of PPI were associated CA-CDI, the associations were not as strong as those seen in HA-CDI studies.

Conclusion: CA-CDI was seen more often in younger, female populations, but no significant temporal or spatial patterns were identified in the reviewed studies. Exposure to antimicrobials was still the foremost amongst all other medications, but not as significant as that observed in HA-CDI cases. More epidemiological studies are required to inform the discourse of the community drivers of CA-CDI.

Background

Clostridium difficile, a gram-positive, spore-forming anaerobic bacillus, is one of the most common enteropathogens (Lucado, 2012). While neonates can be asymptomatic carriers of this organism, *C. difficile* can cause a variety of complications in susceptible hosts, especially the elderly, ranging from self-limiting, mild diarrhea to severe diarrhea, with or without pseudomembrane formation, toxic megacolon, perforation, and peritonitis (Barbut & Petit, 2001; Kelly & Lamont, 1998; Poxton, 2013). *Clostridium difficile* infections (CDI) have a significant financial impact on healthcare systems across the world, due to the worsening of health outcomes and increased length of hospitalization (Gupta & Khanna, 2014; Kuijper, Coignard, & Tüll, 2006; Kelly & Lamont, 2008; Lemaire et al., 2015).

Historically, CDIs have been closely associated with exposure to healthcare settings. In recent years, quality improvement initiatives, such as rigorous infection control practices and antimicrobial stewardship programs, have resulted in an overall decline in HA-CDI infections (Furuya-Kanamori et al., 2016). Despite these efforts, the incidence of CA-CDI, including community cases infected with invasive strains previously associated with hospital settings, is increasing (Khanna et al., 2012; Kotila, Mentula, Ollgren, Virolainen-Julkunen, & Lyytikäinen, 2016) and approximately one case out of four requires hospitalization (Kuntz, Chrischilles, Pendergast, Herwaldt, & Polgreen, 2011). For example, in Finland, the rate of CA-CDI increased from 30.8/100,000 to 37.5 /100,000 population between 2008 and 2013. Similarly, in the US, the CA-CDI rate greatly increased from 1/100,000 to 22 /100,000 population between 1994 and 2004 (Kotila, Mentula, Ollgren, Virolainen-Julkunen, & Lyytikäinen, 2016; Dial, Delaney, Barkun, & Suissa, 2005). In Canada, almost 38,000 cases of CDI were reported nationally in 2012, of which nearly 10,000 were community-acquired (Levy et al., 2015).

It is thought that when CA-CDI cases are admitted to hospitals, they can increase the risk of HA-CDI or hospital outbreaks of HA-CDI through increased bioburden and environmental contamination ((Kuntz, Chrischilles, Pendergast, Herwaldt, & Polgreen, 2011). Furthermore, a study in Saskatchewan, Canada, reported that up to one third of HA-CDI cases showed symptom onset in the community (McLeod, 2017). Many years of research and surveillance have established that advanced age, exposure to antimicrobials, and the use of proton pump inhibitors are risk factors associated with HA-CDI (Kotila, Mentula, Ollgren, Virolainen-Julkunen, & Lyytikäinen, 2016; Dubberke et al., 2006; Henrich, Krakower, Bitton, & Yokoe, 2009). However, far less is known about the epidemiology of CA-CDI. To this end, the objective of this scoping review is to evaluate the research to date on epidemiological patterns and the risk profile for CA-CDI. The findings will inform the focus of future systematic reviews and primary research studies.

Methods

This review followed the recommendations of *The Joanna Briggs Institute (JBI) Reviewers' Manual 2015, Methodology for JBI Scoping Reviews* (Levac, Colquhoun, & O'Brien, 2010; The Joanna Briggs Institute, 2015; Peters et al., 2015; Arksey & O'Malley, 2005; Colquhoun et al., 2010). Available literature on CA-CDI was searched in three medical and life sciences databases, with no date restriction. The three databases—Cumulative Index to Nursing and Allied Health (CINAHL), Nursing and Allied Health Source (ProQuest), and MEDLINE— were searched for studies on the epidemiological aspects of CA-CDI and its incidence, risk factors, strain typing, environmental influences, and outcomes.

Epidemiological features were defined as patient-specific characteristics and temporal and spatial patterns. Information on potential associated risk factors was collected for exposure

to antimicrobials, history of gastrointestinal (GI) comorbidities including previous GI surgery, use of proton pump inhibitors (PPI), and use of laxatives or corticosteroids. Strain-testing information was gathered regardless of laboratory testing methods to allow understanding of the variations in ribotype prevalence. During the study period, the invasive North American strain that was more resistant to fluoroquinolones and standard therapies (Lemaire et al., 2015) was referred to as the North American Pulsotype 1 (NAP1), if pulsed-field gel electrophoresis was used. However, if typing methods were used, it was referred to as Polymerase Chain Reaction ribotype 027 (or PCR ribotype 027).

The three databases were searched from the date of database inception to June 7, 2017 (search date), using the following search terms: 1-"community-acquired" OR "community-associated" AND 2-"*Clostridium difficile*" OR "*C. difficile*". Databases were searched for full text studies in the English language. We justified excluding non-English language articles, as no evidence exists of systematic bias caused by language restrictions (Morrison et al., 2012). A uniform, pre-piloted data collection tool was used to extract information from those studies, meeting the criteria for final review.

Inclusion and exclusion criteria.

The inclusion criteria for this scoping review comprised original studies on both genders of hospitalized and non-hospitalized humans with CA-CDIs. All definitions of CA-CDI as indicated in the studies were included.

The exclusion criteria comprised of studies on HA-CDI only, *C. difficile* colonization, precision of *C. difficile* laboratory testing methods, efficacy of therapeutic interventions, and pediatrics studies, as children under two years of age can be asymptomatic carriers. Non-peer-

reviewed publications, conference presentations, and opinion papers without original research findings were excluded.

Bias reducing strategy.

The objectives, inclusion criteria, and methods for this scoping review were specified and documented in a protocol *a priori* (The Joanna Briggs Institute, 2015). Due to the broad objective of scoping reviews, an assessment of risk of bias was not conducted (The Joanna Briggs Institute, 2015). Similarly, methodological quality assessment of the included studies was not required, due to the descriptive nature of scoping reviews in mapping out the body of literature under review.

Results

Three database searches identified a total of 146 articles. Nine studies were added through citation retrieval of a narrative review and a meta-analysis, bringing the total to 155 articles. All citations were first appraised applying the eligibility criteria during title and abstract review. After screening by abstract and title, 66 articles met the criteria for full-text review. Full texts of the citations were accessed based on the inclusion and exclusion criteria; 44 articles did not meet the requirements. In the end, 22 peer-reviewed articles were compiled for the scoping review.

Results for one of the studies were divided into two subgroups: Veterans' Affairs and Durham County (Kutty et al., 2010). One study had a subgroup of children under two years of age (Søes et al., 2014); this subgroup was not included in the data extraction and interpretation. Figure 3.1 depicts the process of the literature search and selection.

Incidence of CA-CDI.

Seven of the 22 studies included the incidence of CA-CDI, three used community-based data, one used hospital-based data, and three used a mix of community and hospitalized CA-CDI cases. In their study, Dial et al. (2008) noticed an increasing trend in the rate of CA-CDI that required hospitalization. They reported the rate of CA-CDI increased from 20/100,000 person years in 1998 to almost 60/100,000 person years in 2004 in Quebec, Canada (Dial, Kezouh, Dascal, Barkun, & Suissa, 2008).

In one study, the active surveillance of a mixed urban and rural population in the US found the incidence of outpatient cases of CA-CDI was 51.9/100,000 population for 10 geographic areas (Lessa et al., 2017), and a matched nested case-control study in Scotland found a rate of 20.3/100,000 population (Marwick et al., 2013). A study of outpatient research databases in the UK found a rate of 22/100,000 person years (Dial, Delaney, Barkun, & Suissa, 2005), and an unmatched case-control study of Veterans' Affairs hospital patients in North Carolina found an incidence for CA-CDI of 21/100,000 population (in the VA catchment area) and 46/100,000 population (in the Durham region) (Kutty et al., 2010). Two prospective studies of mixed hospitalized and community cases in Sweden and the US reported rates of 25/100,000 and 11.6/100,000 population respectively (Norén et al., 2004; Kuntz, Chrischilles, Pendergast, Herwaldt, & Polgreen, 2011) and a prospective study from the UK that included cases from hospitals, long-term care, and community reported a rate of 7.3/100,000 patient years for CA-CDI.

Epidemiology of CA-CDI.

Demographics.

Overall, 15 studies reported on age. In general, CA-CDI cases had a lower median age than those reported for HA-CDI. The median age varied quite widely, from 50 to 81 years (Søes et al., 2014; Miyajima et al., 2011), but only six of the 22 studies reported a median age higher than 65 years. Of these, three were conducted solely in elderly populations (those older than 65 years), one was in the urban arm of the study, and one was in a small population (n=42) (Naggie et al., 2010). Nine of the 22 studies reported a median age lower than 65 years, and the semi-rural arm of a study in the UK reported a median age of 45 years.

The proportion of females with CA-CDI was higher than that of males, ranging from 11% to 75% (Kutty et al., 2010; Lessa et al., 2017). Fifteen studies reported a higher incidence of CA-CDI in the female population as compared to male; this ranged from 75% in Denmark to 56% in the US and 63% in Quebec, Canada (Kutty et al., 2010; Naggie et al., 2010). Only one study reported a lower proportion of females, and it was conducted in a population of veterans in the US (Kutty et al., 2010). One report of active surveillance through the Emerging Infectious Diseases program by the CDC in 10 counties in the US found the CA-CDI incidence was 61/100,000 persons in the female population compared to 42.5/100,000 persons in the male population for the year 2011 (Lessa et al., 2017). More details of demographics are listed in Table 3.1.

Temporal and spatial patterns.

Four studies looked into the seasonal temporality of CA-CDI incidences; of these, two found no seasonal pattern (Fawley et al., 2016; Anderson et al., 2017). One study in Sweden reported an increase in March (Norén et al., 2004) and another reported a peak in winter months

(December, January, and March), where samples were positive for both CDI and norovirus (Taori, Wroe, Hardie, Gibb, & Poxton, 2014).

Six studies considered geographical patterns, and their findings are mixed. One of the studies, a population-based retrospective cohort study in the US, found that proximity to livestock farms (p=0.01), farming raw material services (p=0.02), and nursing homes (p=0.04) was associated with increased incidence of CA-CDI (Anderson et al., 2017). Although one study found a concentration of CA-CDI in a Swedish rural county (Dial, Delaney, Barkun, & Suissa, 2005), another study found no association between CA-CDI and residence in rural areas ($p=$ 0.789) (Norén et al., 2004; Taori, Wroe, Hardie, Gibb, & Poxton, 2014). One study found that one of five CA-CDI cases was associated with community-based residential care (Fawley et al., 2016), but another did not find geographical clustering of CA-CDI cases amongst those who lived in their own homes or in a nursing home care facility (Miyajima et al., 2011). A study in Scotland noticed an increase associated with postal codes indicating more affluent areas, where care-home residences were located (Marwick et al., 2013).

Molecular diversity.

Eight of the 22 studies reported strain testing of the CA-CDI isolates. A UK study of CA-CDI (n=42) found that PCR-ribotype 078 (n=8; 19.0%) was the most common epidemiological type, followed by PCR-ribotype 014/020 (n=7; 16.7%) (Taori, Wroe, Hardie, Gibb, & Poxton, 2014). Another study conducted on CA-CDI cases in Monroe County in the US reported 12 (31.6%) and two (5.3%) NAP1 and NAP1-related cases of CA-CDI (Dumyati et al., 2012). This study also reported 14 (36.8%) unnamed-strain cases. A recent UK study found that in comparison to HA-CDI, CA-CDI cases were more likely to be due to ribotype 002 (p≤0.0001),

020 (p=0.009), and RT056 (p< 0.0001) (Fawley et al., 2016). In general, novel non-typical strains were mainly detected in strain testing of CA-CDI.

In a prospective study from the UK, ribotypes 078 and 027 were the fourth and eighth most frequently identified ribotypes for CA-CDI cases respectively, and these ribotypes were more often noted in cases with healthcare exposure or institutional contact than in cases living at home (10.4% vs. 2.9% and 12.8% vs. 4.5% respectively, both p<0.001) (Fawley et al., 2016). One study from Denmark reported 40 different PCR ribotypes in CA-CDI beef consumers, including types 078, 001, 012, and a series of minor ribotypes (Søes et al., 2014). A US study reported the top three strains in CA-CDI as NAP1 (18.8%), NAP4 (11.4%), and NAP11 (10.7%) (Lessa et al., 2017). In a UK study, four non-toxigenic strains (PCR ribotypes 009, 026 (n=2), and 039) and two toxigenic strains (PCR ribotypes 003 and 039) were identified out of seven samples acquired from the cases. One of the cases presenting with the toxigenic isolate had been working as a volunteer in a hospital where the strain was prevalent (Miyajima et al., 2011).

Risk factors.

Ten of the 22 studies reported antimicrobial exposure for CA-CDI as a risk factor. The analysis showed a strong association between CA-CDI acquisition and antimicrobial exposure ranging from (OR, 3.1; 95% CI, 2.7-3.6) to (OR, 19.6; 95% CI, 7.6-51.0) (Dial, Delaney, Barkun, & Suissa, 2005; Kutty et al., 2010). The association was larger in studies conducted in elderly populations (aRR: 10.6; 95%CI, 8.9-12) (Dial, Kezouh, Dascal, Barkun, & Suissa, 2008). Only one of the studies did not find a significant association between the antimicrobial exposure and CA-CDI occurrence (OR, 1.083; 95%CI, 0.99-1.174) (Furuya-Kanamori et al., 2016).

Nine studies evaluated PPI use as a risk for CA-CDI. The reported association between PPI use and CA-CDI acquisition ranged from (aOR, 0.4; 95%CI, 0.2-1.23) to (aOR, 3.5; 95%CI, 2.3-5.2) (Naggie et al., 2010; Dial, Delaney, Schneider, & Suissa, 2006).

Association of CA-CDI with the use of corticosteroids was evaluated in three studies. One study reported no significant association (OR, 1.043; 95% CI, 0.952-1.133; p=0.34) (Furuya-Kanamori et al., 2016), but two reported association of (OR, 4.4; 95%CI, 0.9-20.5) and (OR, 2.3; 95% CI. 0.41-13) (SØes et al., 2014; Kutty et al., 2010). Three studies evaluated the association with laxatives; two found no significant association (OR: 1.056, 95%CI, 0.963-1.151, *p*=0.235) and (OR: 0.91; 95%CI, 0.2-4.1) (Furuya-Kanamori et al., 2016; SØes et al., 2014) but one reported an association of (OR: 6.6; 95%CI, 1.2-37.8) (Kutty et al., 2010).

Seven studies assessed CA-CDI association with gastrointestinal disorders. Four studies showed associations for inflammatory bowel diseases ranging from (aOR, 46.1; 95% CI, 14.5-146.7) to (OR, 3.6; 95%CI, 2.6-5.1) (Dial, Delaney, Barkun, & Suissa, 2005; Dial, Delaney, Schneider, & Suissa, 2006), but two did not report on an association with gastrointestinal disorders (Naggie et al., 2010; Taori, Wroe, Hardie, Gibb, & Poxton, 2014) (see Table 3.1). One study found that gastroesophageal reflux disease (OR 8.7; 95% CI, 1.9-39.1) was strongly associated with the occurrence of CA-CDI (Kutty et al., 2010).

One study that evaluated the age-adjusted Charlson co-morbidity index (OR:1.12, 95%CI, 0.99-1.04) did not find a significant difference between underlying comorbidities of CA-CDI and HA-CDI (Taori, Wroe, Hardie, Gibb, & Poxton, 2014). More information about risk factors is shown in Table 3.1.

Outcome.

Mortality and morbidity.

Overall, mortality and post-infection morbidities were not well studied. Five studies comprising hospitalized CA-CDI cases or a mix of hospital and community-based CA-CDI cases reported mortality in the 30 days after CA-CDI diagnosis (see Table 3.1). An adjusted US national estimate of deaths associated with CDI reported the death rate associated with CA-CI was 0.7/100,000 persons for 2011(95%CI, 0.4-0.9), which translates to an estimated 2000 deaths (95% CI,1200-2800) (Lessa et al., 2017). A population-based, retrospective, nested case-control study of CA-CDI found 77 of 304 cases of CA-CDI were hospitalized as a result of their infection (Kuntz et al., 2007). A case control study of toxin-positive patients revealed that 13% of the cases (vs. 9% of controls) sought hospitalization as a result of their diarrhea, and 26 % of cases (vs. 14 % of controls) sought out short-term healthcare services (Wilcox, Mooney, Bendall, Settle, & Fawley, 2008). In another study, an active surveillance based on laboratory specimen test results discovered that 45% of the CA-CDI cases required hospitalization (Naggie et al., 2010). A summary of reported results extracted for this review is shown in Table 3.1.

Discussion

Twenty-two studies were reviewed to summarize the research on CA-CDI epidemiological features and risk factors. CA-CDI were seen more often in younger, female populations than were HA-CDI cases and the control arm of the community-based studies. Limited studies reported an increase in winter months for CA-CDI, and one spatial epidemiological study stated that proximity to animal farms, animal services, and nursing homes was associated with a higher incidence of CA-CDI. Although exposure to antimicrobials and use

of PPI were associated with CA-CDI, the associations were not as strong as those seen in HA-CDI studies.

Although CA-CDI was found to cause infection in all age groups, in articles included in this scoping review, it was often reported in a younger population than HA-CDI; this could be explained by the comorbidities that bring older patients to hospitals and increase their risk of HA-CDI. After an eight-year study, Dial et al. (2008) reported almost a three-fold increase of CA-CDI amongst the elderly population in Quebec, Canada.

The gender inclination of CA-CDI in communities has been attributed to healthcare seeking behaviours in the female population that subsequently result in more testing and diagnosis of CDI, or to females' exposure to the *C. difficile* spores as a result of environmental contamination in healthcare settings (Fellmeth, Yarlagadda, & Lyer, 2010). Increased contact with fecal matter as a result of diaper changing practices has also been hypothesised as a potential contributing factor (Gupta & Khanna, 2014). Establishing gender-specific risk factors may help reduce the community spread through interventions such as community awareness educational programs.

Apart from the regional predominance of certain ribotypes in CA-CDI clusters, strain testing of CA-CDI and HA-CDI cohorts found comparable ribotype diversity and relative strain prevalence (Fawley et al., 2016). The ribotypes for CA-CDI cases with healthcare exposure tend to be more diverse (and include a higher proportion of the hypervirulent strain) even as they age, in contrast to what is seen in HA-CDI patients (Fawley et al., 2016). Unlike other community-acquired infections (e.g., community–acquired methicillin-resistant *Staphylococcus aureus*) that are genetically divergent from their healthcare-associated counterparts (David & Daum, 2010; Huang et al., 2006), similarities in genetic relatedness and strain distribution of CA-CDI and

HA-CDI have been demonstrated in multiple studies this could be interpreted as a bi-directional transmission pathway between communities and hospitals (Fawley et al., 2016; Miyajima et al., 2011; Dumyati et al., 2012) .

Temporal studies failed to establish an effect of seasonality. Exposure to antimicrobials was cited as the leading risk factor for CA-CDI, and increase of CA-CDI was not consistently associated with increased use of antimicrobials during the influenza season (Taori, Wroe, Hardie, Gibb, & Poxton, 2014; Center for Disease Control, 2008; Lowe, Mamdani, Kopp, Low, & Juurlink, 2006). Records from community settings in the UK indicated that exposure to antimicrobials may not be a strong risk factor, but of those who used antimicrobials, cases using fluoroquinolones were at greater risk of CA-CDI (Delaney, Dial, Barkun, & Suissa, 2007).

Notwithstanding the reports of association in several studies, the role of PPI as an independent risk factor was not consistently established. However, the strong association between the presence of GERD and incidents of CA-CDI can be interpreted as an increased risk in undocumented use of PPI by over-the-counter community consumers.

Reported attributable mortality to CA-CDI has been lower (1.3%-4%) than the mortality attributable to HA-CDI (16.3%) (Lessa et al., 2017; Norén et al., 2004; Naggie et al., 2010; Gravel et al., 2009). However, a risk-adjusted study in senior Americans identified the likelihood of a three-fold increase in mortality in an elderly compared to a younger population when infected with CA-CDI (Collins et al., 2014).

Implications for Research and Practice

This review of CA-CDI within a traditional epidemiological triad (time, place, and person) evaluated temporal patterns, spatial distribution, and patient characteristics and experiences. Comprehensive epidemiological studies are required to evaluate and translate the

clinical, demographic, temporal, and spatial data into knowledge that may inform the discourse of population-level risks of CA-CDI. Modifying the traditional surveillance tools to include patients' experiences in hospitals and communities may be a first step in hypothesising large-scale studies.

Limitations

Although the JBI guidelines for a scoping review were followed, lack of another reviewer created a risk of screening bias and data extraction (charting) bias. To minimize potential partialities, a standard data extraction protocol was developed and used.

Conclusion

The number of CA-CDI cases with unique demographic patterns is gradually growing in communities with cases that require hospitalization. Studies reviewed indicated antimicrobial exposure could be one of the causes, but old age and use of PPI or other medications were not as strongly associated with CA-CDI. While this review provides insight into research to date on CA-CDI, the diversity of findings related to CA-CDI attributing variables suggests that identifying the unique risk factors and understanding the complex epidemiology and the community transmission pathways of CA-CDI calls for further research-based evidence. Until customized research and surveillance programs identify the community risk factors, epidemiological analysis of existing surveillance data can inform the immediate emphases of preventative measures and future research direction.

Conflict of Interest

All authors report no conflicts of interest relevant to this article.

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Tables

Table 3.1 – Epidemiology and risk factor data extracted from studies included in the scoping review.

| | | Demographics | | | Risk Factors | | | | | | | Temporal | Spatial | Geno-typing | Outcome | |
| Study information | | | | | | | | | | | | | | | | |
Author/ origin/ year	Study design	Me-dian age	Male n (%); Female n (%)	Age ≥65	Antimicro-bial use up to 8 weeks prior to CDI	GI co-morbidi-ties, including surgery	Use of PPI	Cortico-steroids	Laxa-tives	Pre-vious sur-gery	Pre-vious CDI	Seasonal patterns	Geo pattern urban/ rural index	Strains	Incidence per 100,000 pt years	Mortality (attribut-able death in 30 d) or morbidity
Taori et al., UK, 2014,	Prospective laboratory-confirmed from hospital, LTC, & GP N=335 CA=42 (12.5%)	69	12=m 30=f	26 (42%)	21(50%) p=0.005 OR: 8.04 CI,1.85-35.02	17 (42%) p=0.365 OR: 1.55 CI, 0.66-4.3	16 (37%)	2 (4.8%)	nr*	nr	nr	Winter (Dec-Mar) (21/36)	36 non-rural/ 5 rural p=0789	Ribotype 078=8, non-078 =31 p=0.006	7.3/ 100,000 patient years in over-18 pop'n, 6.4 in under-18 pop'n	4 deaths (n=42) Immuno-suppressed, p=0.035
Dumyati et al., US, 2012 6-month surveillance of some lab-positive samples	Active prospective population based surveillance 20% hospitalized N=366 CA= 67 (18%)	53	41 (61%)=f	nr	32 (76%) OR N/A	nr	11 (26%)	nr	nr	nr	nr	nr	nr	Similar distri-bution of various strains 12 (36%) NAP1	N/A due to lack of complete lab catchment of samples	nr
Naggie et al., US, 2010	Active prospective lab surveillance mixed settings, hospital, & LTC	58	Majority male: VA populatio n	21 (68%)	15 (48%) <.001	nr	12 (39%) <.001	nr	nr	3 (10%)	nr	nr	nr	nr	nr	1(3.2%) p=0.06 45% required hospital-ization

Study information		Demographics			Risk Factors							Temporal	Spatial	Geno-typing	Outcome	
Author/ origin/ year	Study design	Me-dian age	Male n (%); Female n (%)	Age ≥65	Antimicro-bial use up to 8 weeks prior to CDI	GI co-morbidi-ties, including surgery	Use of PPI	Cortico-steroids	Laxa-tives	Pre-vious sur-gery	Pre-vious CDI	Seasonal patterns	Geo pattern urban/ rural index	Strains	Incidence per 100,000 pt years	Mortality (attribut-able death in 30 d) or morbidity
Kutty et al., USA, 2010	Case control of hospital cases	62 (VA) 61 (Dur-ham)	4 (11%)=f 57 (58%)=f	nr	24 (66%) cases 10 (9%) controls OR:19.6 CI 7.6-51.0 p<0.05 32 (44%) cases 8 (17%) controls OR:3.9 CI, 1.6-9.5) p<0.05	GERD 20 (27%) cases 2 (4%) controls OR: 8.7 CI,1.9-39.1 p<.05	13 (36%) cases 26 (24%) controls OR:1.7 CI 0.7-4. 9(12%) Cases 2(4) control s OR:3.2 CI,0.7-15.7	4 (11%) cases 3 (3%) controls OR4.4 CI 0.9-20.5	4 (11%) cases 2 (2%) controls OR 6.6 CI, 1.2-37.8 n/a	nr	nr	nr	nr	nr	21/100000 46/100000	nr
Naggie et al., USA, 2011	66 cases 114 controls; 5 hospital cases reported through lab	64	56% =f	49% cases 47% controls p=.74 aOR.99 CI, 0.96-1.01	61% cases 25% controls p<.001 aOR:6.07 CI, 2.62-14	38% cases 45% controls p=.37 aOR:1.008 CI, 0.23-5.12	33% cases 39% controls p=.48 aOR:0.49 CI, 0.2-1.23	20% cases 13% controls p=.24	nr	17% cases 8% con-trols p=.07 aOR: 6.8 CI, 1.74-26.6	nr	nr	nr	nr	162 cases= 15% of all CDI	nr
Fawley et al., UK, 2016	Prospective laboratory surveillance of samples from outside of hospitals	nr	More female 467/701	25% 519/693	58% used 39% not used p<0.0001	nr	nr	nr	nr	nr	nr	Not seen in two years of study	1/5 assoc. with commu-nity-based residen-tial care 125/525	002, 020, RT056 078 and 027 were 4th and 8th ribotypes in CA-CDI	Otherwise ranking and prevalence similar in two group	nr

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Study information		Demographics			Risk Factors								Temporal	Spatial	Geno-typing	Outcome	
Author/ origin/ year	Study design	Me-dian age	Male n (%); Female n (%)	Age ≥65	Antimicro-bial use up to 8 weeks prior to CDI	GI co-morbidi-ties, including surgery	Use of PPI	Cortico-steroids	Laxa-tives	Pre-vious sur-gery	Pre-vious CDI	Seasonal patterns	Geo pattern urban/ rural index	Strains	Incidence per 100,000 pt years	Mortality (attribut-able death in 30 d) or morbidity
Delaney et al., UK, 2007	Population-based case-control from GP research database	nr	nr	nr	37% cases used, 13% controls used aOR: 3.7 CI,3.1-4.4 Increased risk of CA-CDI 2-3-fold with any Abx. use, 6-fold if FQ used	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Norén et al., Sweden, 2004	Prospective in hospital and in community	64	nr	nr	nr	nr	nr	nr	nr	nr	nr	March	In main county and main hospital	SE17 C	25/100000 person	4%
Dial et al., UK, 2005	Case 1233 control 12330 Retrospec-tive from GP research database	71 (mean)	65=f cases 58=f controls aOR1.3; CI,1.1-1.3	75% cases 74% controls	37% cases 13% controls aOR: 3.1 CI, 2.7-3.6	IBD:5% cases 1% controls aOR:3.6 CI;2.6-5.1	23% cases 8% controls aOR: 2.9 CI, 2.4-3.4	nr	nr	nr	nr	nr	nr	nr	22/100000 person	nr
Søes et al., Denmark, 2014	Prospective matched case n=177 control n=242 lab testing of community patients with symptoms	50	75%	nr	48% cases 13% controls OR: 6.7 CI, 3.4-13		17% cases 22% controls OR: 0.68 CI,0.34-1.4	3% cases 1% controls OR: 2.3 CI, 0.41-13	2% cases 2% controls OR: 0.91 CI,0.2-4.1	nr	nr	nr	nr	type 078, 001, 012, 014/020/ 077, 015, 017, 023, 027, 029, 066, 070, 106/117, and 107	nr	nr

Study information		Demographics			Risk Factors							Temporal	Spatial	Geno-typing	Outcome	
Author/ origin/ year	Study design	Me-dian age	Male n (%); Female n (%)	Age ≥65	Antimicro-bial use up to 8 weeks prior to CDI	GI co-morbidi-ties, including surgery	Use of PPI	Cortico-steroids	Laxa-tives	Pre-vious sur-gery	Pre-vious CDI	Seasonal patterns	Geo pattern urban/ rural index	Strains	Incidence per 100,000 pt years	Mortality (attribut-able death in 30 d) or morbidity
Lessa et al., US, 2015	Active surveillance of population and laboratory results, outpatient samples	Na	42.5 /100000 =m 61 /100000 =f	146.2 /100000	nr	nr	nr	nr	nr	nr	nr	nr	nr	18.8% =NAP1 11.4+N AP4 10.7+N AP11	51.9 /100000 incidence, higher in females, rate ratio 1.26; CI, 1.25-1.27	1.3% in 30 days after dx. CA-CDI=0.7 CI (0.4-0.9) HA-CDI= 8.9 CI, 5.0-12.8) /100,000 persons
Anderson et al., US, 2017	Population-based retrospec-tive cohort in and outpatient	54.5 mean	62%=f	47%	nr	nr	nr	nr	nr	nr	nr	No seasonal or temporal linear trend	Proxi-mity to livestock farms (p=0.01), farming, raw material services (p=0.02), nursing homes(p =0.04)	nr	nr	nr
Garg et al., US, 2013	Retrospec-tive CDI positive, randomly chosen from hospital admits with ICD codes	53.8	31.4%=m	21.9%	41.8% p<.05	nr	43% p<0.00 01	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr

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Study information		Demographics			Risk Factors							Temporal	Spatial	Geno-typing	Outcome	
Author/ origin/ year	Study design	Me-dian age	Male n (%); Female n (%)	Age ≥65	Antimicro-bial use up to 8 weeks prior to CDI	GI co-morbidi-ties, including surgery	Use of PPI	Cortico-steroids	Laxa-tives	Pre-vious sur-gery	Pre-vious CDI	Seasonal patterns	Geo pattern urban/ rural index	Strains	Incidence per 100,000 pt years	Mortality (attribut-able death in 30 d) or morbidity
CDC, MMWR, US, 2008,	Surveillance summary of lab reports hospital, LTC, and GP		80=33% m 161=67% f	33%	68%	nr	nr	nr	nr	nr	nr	nr	nr	12 were tested: 3 NAP18 NAP1-like	nr	nr
Furuya-Kanamori et al., Australia, 2016	Cases series-community	n/a	n/a	n/a	Not significant OR 1.083, CI,0.990-1.174 p=0.067	nr	Not sig. OR= 1.052 CI,0.943-1.163 p= 0.348	Not sig. OR=1.043 CI, 0.952-1.133 p=0.348	Not sig. OR=1.056 CI,0.963-1.151 p=0.235	nr	nr	nr	nr		nr	nr
Wilcox et al., UK, 2008	Prospective surveillance of community-derived fecal samples	Urban =73 Semi-rural =45	44%=m 56%=f	nr	52% p=0.001	nr	2% p=1.0	nr	nr	nr	nr	nr	nr	60% =U 13% Sr PCR ribotype 001 urban cases one subtype, semi-rural, different subtypes	nr	Death 10% CA-CDI cases 1% controls p=0.023 hospital-ization 13%; short-term 26%
Suissa et al., UK, 2012	Retrospec-tive population-based C-C of GP research database	NR	NR	NR	50.1% p<.0001	nr	26.2% p<.0001	22% p=0.065	nr	nr	nr	nr	nr	nr	nr	nr

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Study information		Demographics			Risk Factors							Temporal	Spatial	Geno-typing	Outcome	
Author/ origin/ year	Study design	Me-dian age	Male n (%); Female n (%)	Age ≥65	Antimicro-bial use up to 8 weeks prior to CDI	GI co-morbidi-ties, including surgery	Use of PPI	Cortico-steroids	Laxa-tives	Pre-vious sur-gery	Pre-vious CDI	Seasonal patterns	Geo pattern urban/ rural index	Strains	Incidence per 100,000 pt years	Mortality (attribut-able death in 30 d) or morbidity
Lowe et al., Canada, 2006	Population-based, nested, case controlled, linked health database	Mean 78.7 +/- 7.2SD	59.8 =m	All cases over 65	78.1 cases 77.3 controls used one Abx.	IBD 2.8% cases 1.0 controls	In 90 days, prior 22.0 cases 18.3 controls aOR: 0.9 CI, 0.8-1.1	17.4	nr	nr	nr	nr	nr	nr	nr	nr
Dial et al., UK, 2006	Case 317 Control 3167 using UK clinical research database GPRD	65	36.6 =m	NR	54.9 cases 12.8 controls aOR: 8.2 CI, 6.1-11	IBD 5.7%cases 0.2 controls aOR: 46.1CI, 14.5-146.7	19.2% cases 5% controls aOR:3.5 CI, 2.3-5.2	nr	nr	nr	nr	nr	nr	nr	nr	nr
Dial et al., Canada, 2008	Matched nested Case 836 Control 8360 2-database data merge, hospital admits	79.8 cases 77.5 contr ols RR#: 1.45 CL, 1.3-1.5 p<0.0 05	66.3%=f cases 59.1% =f controls RR: 1.3 CI1.0-1.4	All cases over 65	47.1 % cases 7.6 %controls aRR: 10.6 CI,8.9-12.8	IBD 4.9%cases 1.1 controls aRR: 4.1 CI, 2.6-6.6	aRR: 1.6 CI,	nr	nr	nr	nr	nr	nr	nr	nr	nr
Marwick et al., Scotland, 2013	Matched nested c-c of databases	81	72.6%=f	All cases over 65	30.1% <0.001	nr	27.6 p.001	nr	nr	nr	nr	nr	More risk in postal codes of affluent	nr	20.3/100, 000 pop'n	nr

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Study information		Demographics			Risk Factors							Temporal	Spatial	Geno-typing	Outcome	
Author/ origin/ year	Study design	Me-dian age	Male n (%); Female n (%)	Age ≥65	Antimicro-bial use up to 8 weeks prior to CDI	GI co-morbidi-ties, including surgery	Use of PPI	Cortico-steroids	Laxa-tives	Pre-vious sur-gery	Pre-vious CDI	Seasonal patterns	Geo pattern urban/ rural index	Strains	Incidence per 100,000 pt years	Mortality (attribut-able death in 30 d) or morbidity
Kuntz et al., US, 2011	Retrospec-tive nested Case 304 Control 3040	nr	cases 60.53%=f 51.64% controls	Charlson comorbid index cases=0.17 controls=0.05 aOR 1.33 CI,0.98-1.97	73.3%cases 30.26 controls aOR: 6.09 CI, 4.59-8.08	IBD 3.95 %cases 0.13 %controls aOR:41.89 CI, 11.83-148.35	18.9% cases 5.16% controls aOR:2.3 CI, 1.56-3.39	nr	nr	nr	nr	nr	nr	nr	11.6/100,000 pop'n	77 of 304 cases were hospitalized

* nr: not reported

RR: Rate ratio when greater than 1 implies that the rate of hospital admission because of CDI was greater amongst patients with the particular exposure than amongst those without.

Figures
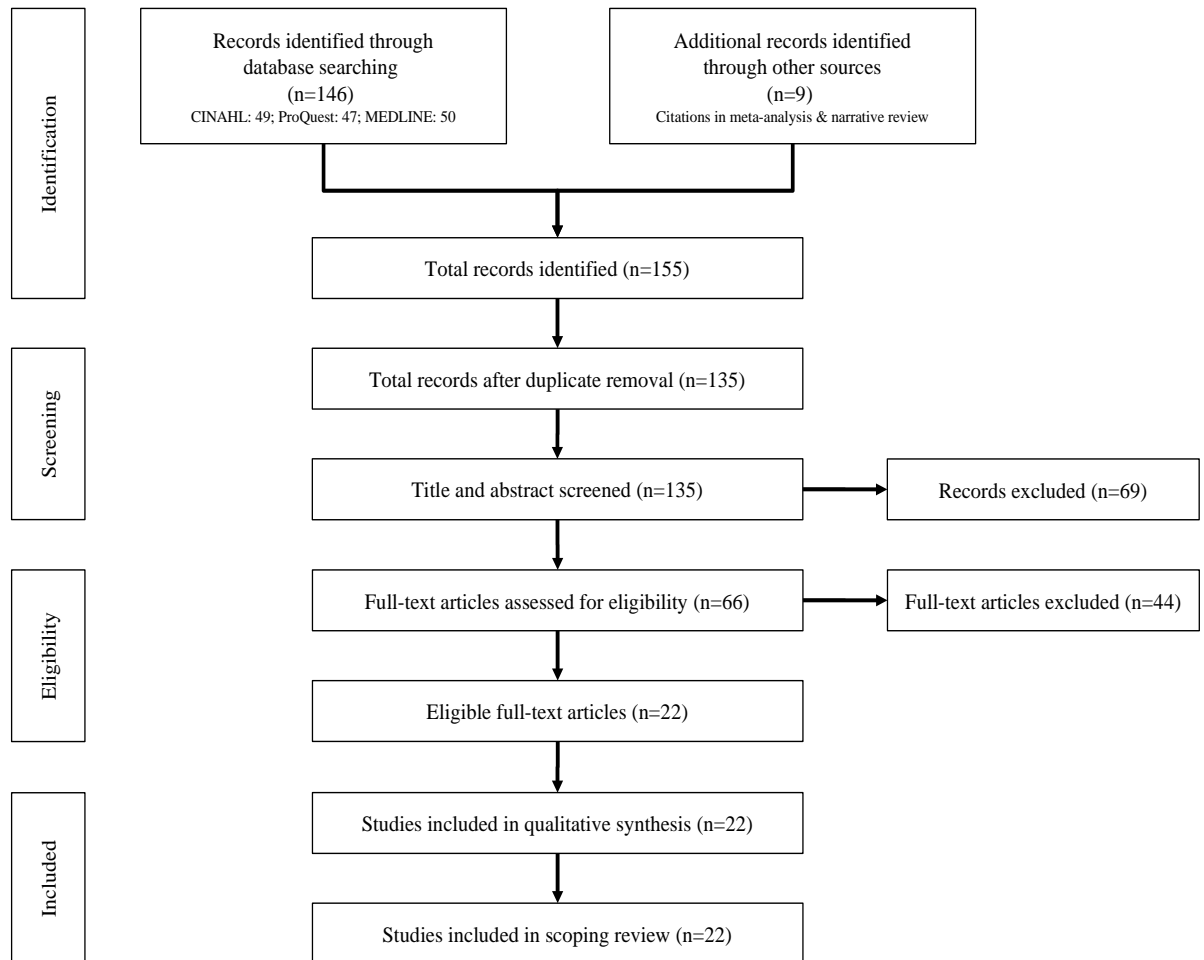
Figure 3.1 – Flow diagram of the literature search conducted for the scoping review of community-acquired *Clostridium difficile,* using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) template.

Chapter Four – Epidemiology of Patients Hospitalized with *Clostridium difficile* Infection in the Niagara Region, Ontario, Canada, Between September 2011 and December 2013: A Comparative Analysis of Community-associated and Healthcare-associated *Clostridium difficile* Infections

Abbreviated Title: Epidemiology of *Clostridium difficile* infections in the Niagara Region

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Counts:
Abstract: 260
Main Text: 2129
References: 45
Tables: 4
Figures: 1

Abstract

Objectives: To compare the epidemiology of hospitalized patients with community-acquired *Clostridium difficile* infections (CA-CDI) and those with healthcare-associated *Clostridium difficile* infections (HA-CDI).

Design: A retrospective case series analysis was conducted.

Setting: Niagara Health System, a multi-site hospital amalgamation in the Niagara Region, Ontario, Canada.

Participants: Hospitalized patients with confirmed CA-CDI and HA-CDI, between September 2011 and December 2013.

Methods: Patients with *Clostridium difficile* infections (CDI) were identified through surveillance and laboratory testing, then stratified in two groups: CA-CDIs and HA-CDIs. Data were obtained from the Infection Prevention and Control (IPAC) surveillance database and the Decision Support database. Nonparametric descriptive statistics were applied to compare the characteristics of patients with CA-CDI and HA-CDI.

Results: Of 628 hospitalized patients identified with CDI, 315 (50.2%) had CA-CDI and 313 (49.8%) had HA-CDI. Compared to patients with HA-CDI, patients with CA-CDI were younger (median age 72 years, interquartile range (IQR) 26, versus 77 years, IQR 18; $p<.001$), had less exposure to antibiotics (52% versus 83%, $p<.001$), and used fewer proton pump inhibitors (PPI) (30% versus 52%, $p<.001$). Gender proportions were similarly distributed between the two groups (58% of CA-CDI and 55% of HA-CDI were female, $p=.38$). There were differences in the proportion of comorbidities between CA-CDI and HA-CDI as follows: presence of an inflammatory bowel disease (18% of CA-CDI versus 40% of HA-CDI, $p<.001$) and surgery in the past three months (13% of CA-CDI versus 23% of HA-CDI; $p<.001$).

Conclusion: CA-CDI must be considered as a potential diagnosis in patients admitted to hospital with diarrhea, even in the absence of conventional CDI risk factors.

Keywords: Epidemiology, *Clostridium difficile*, infections, community-acquired.

Introduction

The incidence and severity of healthcare-associated *Clostridium difficile* infections (HA-CDI) have been increasing since the emergence and the epidemic spread of the invasive strain BI/NAP1/027 (Khanna & Pardi, 2010; Khanna et al., 2013; Barbut & Petit, 2001; Freeman et al., 2010). Concern is also growing that *Clostridium difficile* (*C. difficile*), historically considered a healthcare-associated infection, is increasingly a cause of diarrhea in the community, causing community-associated *Clostridium difficile* infections (CA-CDI) (Khanna & Pardi, 2010; Khanna et al., 2012). Although many studies have explored the increasing burden of HA-CDI, more research is required to fully understand the epidemiology of patients hospitalized with CA-CDI (Levy et al., 2015; Dumyati et al., 2012).

In the summer of 2011, the Niagara Health System (NHS) in Ontario experienced an unusual increase in hospitalized HA-CDI and CA-CDI cases, combined with multiple HA-CDI outbreaks. To this end, this paper describes the clinical characteristics and the epidemiology of patients admitted to NHS hospitals with CA-CDI and compares them to the epidemiology of patients admitted with HA-CDI during the same period.

Methods

Setting.

NHS is a large, multi-site hospital network in the Niagara Region in Ontario, Canada. The region has 12 municipalities and a population of 427,421 (Statistics Canada, 2016). NHS consists of six hospital sites providing a wide range of healthcare services. The subjects of this study were hospitalized patients confirmed to have *Clostridium difficile* infections (CDI). During the study period, NHS hospitals experienced a significantly higher than usual number of cases and clusters of CDI.

Study period and study design.

In a case-series retrospective study of consecutive patients admitted to all NHS hospitals with confirmed CDI between September 2011 and the end of December 2013, we analysed the patients' demographic information, comorbidities, antibiotic history, and presence of conventional risk factors for CDI. Table 4.1 lists the evidence-based covariates evaluated in this study, and their implications.

Case identification, data sources, and privacy.

Case definitions used in this study for CDI, HA-CDI, and CA-CDI are listed in Table 4.2. Hospitalized patients suspected as having CDI were identified by active daily surveillance using a standardized (NHS) surveillance tool based on signs and symptoms manifestation, followed by positive laboratory testing. Final case confirmation was done after positive laboratory toxin testing and case review by an infectious diseases physician and the Infection Prevention and Control (IPAC) personnel at NHS hospitals.

Data for this study were electronically obtained from IPAC surveillance databases and the administrative databases from NHS hospitals. The surveillance, clinical information, and demographics files for the study period from NHS hospitals were combined, creating one large file that was reviewed by a member of the Decision Support Department for completeness of data elements. Deficiencies in demographics and clinical or surveillance information were reviewed on a case-by-case basis. In cases of missing information, the electronic record of the patient was matched with the paper records, using name, admission date, and the site-specific medical records number. Missing information was then retrieved from the paper copies of the surveillance forms and medical records. A de-identified dataset was used for final analysis of this study's objectives.

Laboratory methods and testing for CDI.

From September 2011 to April 2012, NHS sent CDI samples for diagnostic testing to a nearby academic centre that used an in-house developed Polymerase-Chain Reaction (PCR) method using the BD GeneOhm™ Cdiff Assay, with a sensitivity and specificity of 93.8% and 95.5% respectively (BD Diagnostics GSCI: BD GeneOhm™ Cdiff assay, 2010). From April 2012 to December 2013, NHS sent samples to an external commercial laboratory that used BD MAX ™ Cdiff, a Nucleic Acid Amplification Test (NAAT) with a sensitivity of 96.3% and a specificity of 92.4% (Dalpke, Hofko, Zorn, & Zimmerman, 2013).

Statistical analysis.

Descriptive statistics for age are presented using the median value (and interquartile range [IQR]) (Moore & McCabe, 2003). Significance in the difference between the age median for HA-CDI and CA-CDI cases was evaluated using the Mann-Whitney U test (Pagano & Gauvreau, 2000). Categorical covariates, including gender, age $\geqq$ 65, previous CDI (previous is defined as eight weeks before the onset of CDI symptoms), previous surgery (past three months), previous laxative use, proton pump inhibitor (PPI) or antibiotic use, and previous inflammatory bowel disease, were dichotomized and presented as proportions. Differences in proportions of all covariates were tested using Chi-Square. In the event of missing data, complete-case analysis was conducted. Data were analyzed using SPSS software, version 21.0 (IBM Corp., Armonk, NY).

Ethical considerations.

The protocol for this study was approved by York University's Research Ethics Board and the Niagara Health Service's Research Ethics Board. De-identified data were retrospectively accessed from hospital administrative databases; therefore, the requirement for informed consent

was waived.

Results

Surveillance and classification of cases.

During the study period, 1,051 cases of CDI were identified by surveillance and

confirmed by laboratory testing. A breakdown of patient classification and the criteria of the

eligible and ineligible cases is presented in Figure 4.1. Overall, 423 cases did not meet the case

definition (relapse, colonized or transferred cases from other facilities) and were eliminated from

further analysis, leaving 628 cases that fulfilled the criteria for case definitions for CA-CDI and

HA-CDI (see Supplement for detailed information).

Demographics, clinical characteristics, and comorbidities.

Out of the 628 patients, 315 (50.2%) cases were categorized as CA-CDI and 313 (49.8%)

as HA-CDI. The median age of CA-CDI patients (72 years, IQR 26) was lower than that of the

HA-CDI group (77 years, IQR 18, $p<.001$). The proportion of patients aged $\geqq 65$ was 60% for

CA-CDI and 79% for HA-CDI ($p<.001$). There were no significant differences in the gender

proportions of the two groups; 58% of the CA-CDI cases were female and 55% of HA-CDI cases

were female ($p=0.38$).

Report on CDI risk factors.

Approximately half of patients with CA-CDI used antimicrobials prior to the onset of

their CDI; the proportion was higher in patients with HA-CDI (52% of CA-CDIs versus 83% of

HA-CDIs, $p<.001$). Cephalosporins and fluoroquinolones were used more than other

antimicrobials in both groups but were prescribed less often for patients with CA-CDI during the

eight to12 weeks prior to the onset of their CDI infection than for HA-CDI patients (51% and

37% for CA-CDIs and 67% and 56% for HA-CDIs for cephalosporins and fluoroquinolones

respectively, $p<.001$).

Similarly, a smaller proportion of CA-CDI cases compared to HA-CDI cases used PPI (30% of CA-CDI versus 52% of HA-CDI, $p<.001$) and laxatives (8% of CA-CDI versus 31% of HA-CDI, $p<.001$). Patients with a previous inflammatory bowel disease (18% of CA-CDI and 40% of HA-CDI, $p<.001$) and those who had had a previous surgery (13% of CA-CDI versus 23% of HA-CDI, $p<.001$) were proportionally lower amongst patients with CA-CDI than those with HA-CDI. Fewer CA-CDI cases had no history of CDI compared to HA-CDI cases (32% and 45% respectively, $p=.002$). The comparison of patient characteristics and the risk factors for hospitalized patients with CA-CDI and HA-CDI is presented in Table 4.3 in more detail. Table 4.4 lists the proportion of antimicrobials used prior to the onset of CA-CDI and HA-CDI.

CDI treatment.

Of the patients with CA-CDI (n=315), 218 (69%) had a documented record of antibiotic treatment after their CDI infection was confirmed; of these, 54 patients (54/218=24%) were treated with vancomycin and 150 patients (150/218=69%) received metronidazole. Of the patients with HA-CDI (n=313), 251 (80%) had a documented record of antibiotic treatment post-infection; of these, 74 (74/251=29%) were treated with vancomycin and 159 (159/251=63%) received metronidazole. 31% of the CA-CDI and 20% of HA CDI did not have a documented record of their treatment.

Discussion

This retrospective case-series study compared the epidemiology of patients hospitalized with CA-CDI with that of patients hospitalized with HA-CDI. The study found that hospitalized CA-CDI patients accounted for slightly more than half of all hospitalized CDI cases; they were younger than HA-CDI patients and, overall, had a lower proportion of established CDI risk

factors.

In this study, CA-CDI patients comprised a substantially larger proportion of the total hospitalized patients with CDI than has been reported elsewhere. A North Carolina study conducted on laboratory confirmed cases of CDI reported patients with CA-CDI represented 20% of all hospitalized CDI patients, while another American study reported 40% and a Swedish study reported 22%-28% (Kutty et al., 2010; Khanna, Pardi, Aronson, Kammer, & Baddour, 2012; Karlstrom, Fryklun, Tullus, & Burman, 1998; Norén et al., 2004). One potential explanation could be the rural nature of the Niagara Region and the role of the environment in harboring *C. difficile* spores. Natural sources of surface water, which are common in the Niagara Region, have been known to harbour *C. difficile*, as well as dried airborne debris that can carry spores (AL Saif & Brazier, 1996; Lin, Wade, & Hilborn, 2015). *C. difficile,* including the invasive strain PCR Ribotype 027, has also been isolated from dairy calves, beef calves, and adult cattle (Rodriguez-Palacios, Staempfli, Duffield, & Weese, 2007; Weese, Avery, Rousseau, & Reid-Smith, 2009; Weese, Reid-Smith, Avery, & Rousseau, 2010), and the Niagara Region has a large farming community.

The median age of CA-CDI patients was significantly lower than that of patients with HA-CDI, a finding consistent with those of other studies (CDC, 2008; Fellmeth, Yarlagadda, & Lyer, 2010). However, our CA-CDI median age was notably higher than that reported elsewhere (72 versus ~50 years) (Dumyati et al., 2012; Khanna et al., 2012). A study in England conducted in a similar geographical setting on community patients who tested positive for CDI reported that almost all cases of CA-CDI occurred in individuals younger than 65 (Fellmeth et al., 2010). Similarly, studies from rural areas in the US based on laboratory confirmation of a mixed community and hospitalized cohort found that only 30% of CA-CDI cases were older than 65

(CDC, 2008; Khanna et al., 2012; Gupta & Khanna, 2014). These differences might be explained by the relatively higher population-level median age in the Niagara Region (median age 44.4 years in the 2011 census, compared with 39.9 years for the south of England, reported in 2014) (Statistics Canada, 2016).

Our finding of a uniform distribution of CDI in males and females does not follow the pattern reported elsewhere. Almost all studies of CA-CDI regardless of the study settings, report a higher proportion of women with CA-CDI (Khanna et al., 2012; Gupta & Khanna, 2014). Some studies have considered this could be a result of more antibiotic exposure due to more healthcare-seeking behaviour by women, or as a result of exposure while changing diapers Khanna et al., 2012; Gupta & Khanna, 2014; Leffler & Lamont, 2011). The equal proportions of male and female CA-CDI infections could not be explained by differences in the population construct, as a comparison of the population pyramids of the Niagara Region and those in Connecticut and Monroe County in the US reveals similar proportions of men and women (Statistics Canada, 2016; United States Census, 2016). Other environmental factors or sources of exposure, such as occupation, must be explored to understand this difference.

While exposure to antimicrobial agents is known to be a key risk factor for HA-CDI, a recent study reported less of an association with CA-CDI (Kutty et al., 2010). In a case control study of antibiotic utilization, Wilcox et.al. indicated that approximately 50% of the CA-CDI cases in their study used antibiotics prior to the onset of their infection (Wilcox, Mooney, Bendall, Settle, & Fawley, 2008). Similarly, fewer patients with CA-CDI received PPI than did patients with HA-CDI; this echoes finding of a case-control study of antimicrobial-naïve CA-CDIs that found only 50% of patients with CA-CDI had received PPI (Freedberg & Abrams, 2013). Our findings also confirmed previous studies, in that CA-CDI cases in NHS had lower

proportions of previous inflammatory bowel disease and surgery compared to HA-CDI cases (Barbut & Petit, 2001; Pépin, Valiquette, & Cossette, 2005). Our results suggest the risk factors for CA-CDI are different than for HA-CDI and should be explored further.

Although the convenience of a sizable dataset was one of the advantages of this study, our surveillance and demographics reports were missing some data elements. Despite our best efforts to complete missing data, there were still a notable number of missing data elements that could introduce bias (Wood & White, 2004; Stern et al., 2009). In addition, the use of hospital-based administrative data reduced the generalizability and comparability of our findings to non-hospitalized CA-CDI cases.

CA-CDI is emerging as an important cause of diarrhea in patients without healthcare exposure; it accounted for half of all hospitalized cases of CDI in our study. CA-CDI affects a younger, healthier population and can occur even in the absence of the risk factors traditionally associated with this infection. Lack of the conventional risk factors suggests the possibility of novel community reservoirs. More research on CA-CDI is required to understand the scope of this infection, to determine additional or different risk factors in the community, and to devise preventive measures that enable and inform clinical and public health policies and practices.

Acknowledgements

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Tables

Table 4.1 – List of selected independent covariates, supporting rationale and implications based on a review of the literature.

Supporting Literature: Author and Study Year	Predisposing Risk Factor	Justification and Implications
Demographics and patient characteristics		
Pépin & Valiquette et al., 2005 Barbut & Petit, 2001 Southern & Rahmani et al., 2005 Brown et al.,1990	Age $\geqq$ 65 years	Increased incidence explained by old age comorbidities Increased risk: OR[*] 114.1 (CI[**] 95%) 1.4–141
Aronsson & Mollby et al., 1985, CDC 2008, Lessa & Mu et al., 2014	Being female	Increased incidence due to healthcare-seeking behaviour or changing diapers Increased incidence: RR[♣]1.9 (CI 95%) 1.5-2.5
Comorbidities and clinical history		
Thibault et al.,1991 Gupta & Khanna, 2014	Inflammatory bowel Disease	Disease flare ups may lead to colonization Increased risk: OR 4.7 (CI 95%) 1–21
Brown et al.,1990	Gastrointestinal surgery	Intestinal stasis may predispose to CDI Increased risk: OR 23.2 (CI 95%) 2.1–255
Fekety & McFarland et al., 1997 Modena & Gollamoudi et al., 2006	History of CDI	Failure of treatment due to other antibiotics Reported in up to 20% of cases
Medication use		
Aronsson & Mollby et al., 1985 Bauer & Veenendaal et al., 2009 Southern & Rahmani et al., 2010 Baxter & Ray et al., 2008 Deshpande et al., 2013	Use of antimicrobial agents	Increased incidence as a result of imbalance of normal flora of the intestines Increased risk: OR 6.91 (95% CI) 4.17-11.44

Supporting Literature: Author and Study Year	Predisposing Risk Factor	Justification and Implications
Wern & Ahmed et al., 2005		
Batajoo & Weber et al., 2015 McFarland et al.,1990	Use of laxatives or stool softeners	Positive result on CDI testing Increased risk: OR 3.26 (CI 95%) 1.51–7.02
Dial & Alrasadi et al., 2004 Deshpande & Pant et al., 2012	Use of PPI	Increased risk due to reduced gastric acid Increased Risk: OR 2.7 (CI 95%) 1.4–5.2

[*] OR: Odds Ratio

[**] CI: Confidence Interval

[♣] RR: Relative risk

Table 4.2 – NHS definitions of CDI, HA-CDI and CA-CDI used between September 2011 and December 2013 for surveillance and case identification.

CDI definition
• A patient with diarrhea with laboratory confirmation of a positive toxin assay (A/B) for *Clostridium difficile*, or   • Visualization of pseudomembranes on sigmoidoscopy, or   • Colonoscopy, or histological/pathological diagnosis of pseudomembranous colitis.

Definition of HA-CDIs	Definition of CA-CDIs
An HA-CDI case is defined as a patient who has not had CDI in the past eight weeks, but meets one of the following criteria: • He or she does not present with CDI upon admission but shows onset of symptoms >72 hours after admission. • The infection was present at time of admission but was related to a previous admission to the same facility within the last four weeks.	A CA-CDI case matches the case definition for CDI and does *not* match the HA-CDI definitions: In other words: • The symptoms of CDI *were* present upon admission, or symptom onset *was less* than 72 hours after admission. • No exposure to any healthcare facility occurred within the last four weeks, or the source of infection cannot be determined and the patient has not had HA- CDI in the last eight weeks.

Table 4.3 – Patient characteristics and risk factors: A univariate analysis of patients with CA-CDI and HA-CDI for hospitalized patients in NHS hospitals between September 2011and December 2013.

Characteristics and Risk Factors	CA-CDI (n=315) (50.2%)	HA-CDI (n=313) (49.8%)	p-value
Demographics			
Age, median	72 (IQR=26)	77 (IQR=18)	<.001
Age ≧ 65			
	190 (60%)	247 (79%)	<.001
Female	183 (58%)	170 (55%)	.38
Comorbidities and clinical history			
History of an inflammatory bowel disease			
Yes	56 (18%)	125 (40%)	<.001
No	49 (16%)	29 (9%)	
Not documented	210 (66%)	159 (51%)	
Previous surgery			
Yes	41 (13%)	71 (23%)	
No	92 (29%)	100 (32%)	<.001
Not documented	182 (58%)	142 (45%)	
History of previous CDI			
Yes	12 (5%)	15 (5%)	
No	100 (32%)	140 (45%)	.002
Not documented	203 (63%)	158 (50%)	

Medication use			
Characteristics and Risk Factors	**CA-CDI (n=315) (50.2%)**	**HA-CDI (n=313) (49.8%)**	**p-value**
Previous exposure to antimicrobials			
Yes	163 (52%)	259 (83%)	<.001
No	152 (48%)	54 (17%)	
Not documented	N/A	N/A	
Proton Pump Inhibitor (PPI) use			
Yes	93 (30%)	163 (52%)	<.001
No	58 (18%)	45 (14%)	
Not documented	164 (52%)	105 (34%)	
Previous laxative use			
Yes	26 (8%)	98 (31%)	
No	71 (22%)	56 (18%)	<.001
Not documented	217 (70%)	159 (51%)	

Table 4.4 – Proportion of patients receiving antimicrobial agents prior to the onset of CDI, stratified by CA-CDI and HA-CDI.

	Patients who received antimicrobials prior to the onset of CDI		
	CA-CDI (n= 315)	HA-CDI (n=313)	*p* value
Number of patients that used at least one antimicrobial during the past 8 to12 weeks preceding the onset of CDI *	163 (52%)	259 (83%)	<.001
Cephalosporins	83 (83/163) (51%)	174 (174/259) (67%)	<.001
Fluoroquinolones	61 (61/163) (37%)	146 (146/259) (56%)	<.001
Clindamycin	9 (9/163) (6%)	11 (11/259) (4%)	.55
Vancomycin	7 (7/163) (4%)	37 (37/259) (14%)	<.001
Macrolides	14 (14/163) (9%)	23 (23/259) (9%)	.92
Sulfonamides	4 (4/163) (2%)	13 (13/259) (5%)	.20
Others	93 (93/163) (57%)	229 (229/259) (88%)	<.001

*Some patients received more than one antimicrobial prior to onset of their symptoms.
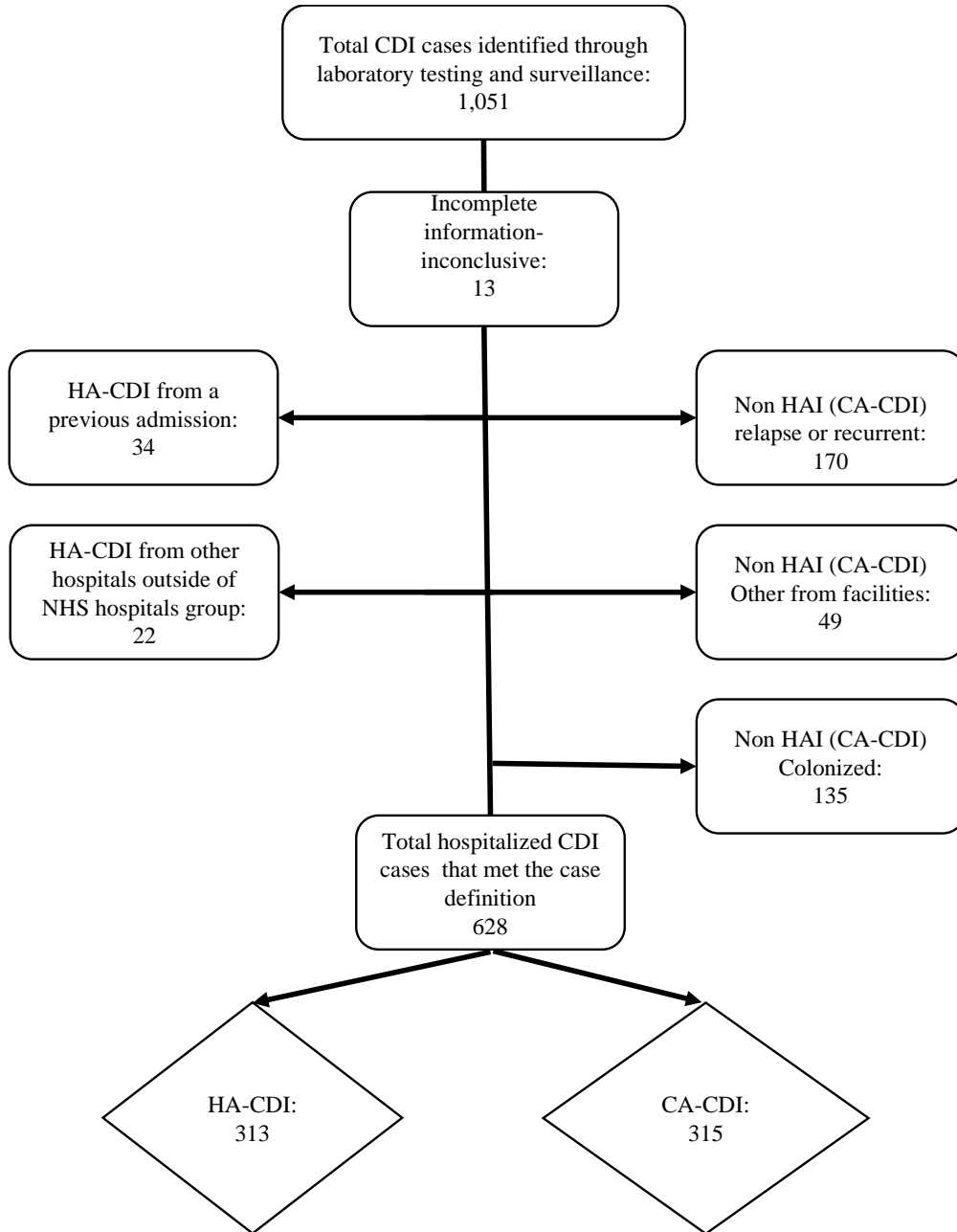
Figures

Figure 4.1 – Decision process flowchart describing the case inclusion and exclusion procedure among 1051 cases with toxin positive *C. difficile* test results.

Chapter Five – A Spatial, Temporal, and Molecular Epidemiological Study of Hospitalized Patients Infected with Community-acquired or Healthcare-associated *Clostridium difficile* in the Niagara Region, Ontario, Canada, Between September 2011 and December 2013

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Abstract: 275
Main Text: 2920
References: 37
Tables: 1
Figures: 5
Appendix: 1

Abstract

Objectives: To investigate and compare the incidence, geographical distribution, temporal patterns, and genetic relatedness of hospitalized patients with community-acquired *Clostridium difficile* infections (CA-CDI) and healthcare-associated *Clostridium difficile* infections (HA-CDI) in the Niagara Region, Ontario, over the time of a large, multi-hospital outbreak.

Method: We conducted a retrospective case series study of the consecutive hospitalized confirmed CDI cases between September 2011 and December 2013, using SaTScan statistics and Statistical Process Control. We used multiple-locus variable-number tandem-repeat analysis to identify the strain of the CDI of patients associated with a registered outbreak.

Results: Using provincial guidelines on classification of *C. difficile* cases, we identified 629 cases of CDI, 318 were CA-CDI and 311 were HA-CDI. The rate per 100,000 population for the hospitalized CA-CDIs was 14.84 in 2011; 33.22 in 2012, and 25.5 in 2013and for HA-CDIs, 3.8 CDIs /1000 patient days for the entire study period. We identified spatial clusters for CA-CDIs using the first three digits of the patients' home postal codes. A temporal cluster of HA-CDI was identified after a period when a high number of CA-CDI cases were hospitalized. Molecular typing related to outbreaks was performed on 6% (59/1051) of the cases, of which 4% (n=13) were CA-CDI and 9% (n=27) were HA-CDI. The majority of the NAP1 strains (12 cases (3.8%) of 311) were seen in patients with HA-CDI.

Conclusion: CA-CDIs and HA-CDIs had geographical clustering, temporal features, and genotypic features that appeared to be unique to CID cases in the community and unlike those in the hospital. Understanding the potentially bi-directional transmission pathways between hospitalized CA-CDI incidence and HA-CDI manifestation, as well as the community drivers of CA-CDIs, can inform clinical and public health patient safety and prevention policies.

Introduction

      Clostridium difficile (*C. difficile*) has been emerging as a significant source of infectious diarrhea beyond hospital settings, with an increasing number of community-acquired *Clostridium difficile* infections (CA-CDI) being reported (Gupta & Khanna, 2014; Khanna & Pardi, 2010). The reservoirs of CA-CDI in the community remain unclear, and many of those infected with CA-CDI do not have the conventionally established risk factors for healthcare-associated *Clostridium difficile* infections (HA-CDI) (Gupta & Khanna, 2014; Khanna et al., 2012). CA-CDI has been linked to various environmental sources, such as floodwater, rivers, lakes, marine sediments, food, farm animals, and household pets (Gupta & Khanna, 2014; Hoover & Rodriguez-Palacios, 2013; Lin, Wade, & Hilborn, 2015). Unlike other gastrointestinal infections, increases in CA-CDI rates in the Northern hemisphere have not been associated with the warmer summer months (Furuyama-Kanamori et al., 2015; Brown, Daneman, Arora, Moineddin, & Fisman, 2013; Burckhardt, Friedrich, Beier, & Eckmanns, 2008). Yet research has pointed to the increased use of antimicrobials in winter and spring months as a contributing risk factor in both CA-CDIs and HA-CDIs (Furuya-Kanamori et al., 2015; Brown et al., 2013). Scholars also debate whether asymptomatic hospitalized patients can be a source of transmission in the community or if hospitalized CA-CDI plays a role in spreading the spores in hospital settings (Walker et al., 2012; Sethi, Al-Nassir, Nerandzic, Bobulsky, & Donskey, 2015).

      In a bid to answer these questions, we investigated and compared the geographical distribution, temporal patterns, and genetic relatedness of CA-CDI and HA-CDI cases admitted to the Niagara Health System (NHS) between the summer of 2011 and the winter of 2013, a period when a series of *C. difficile* outbreaks had occurred in the hospitals of this region.

Method

Study design, study period, and setting.

The design featured a retrospective case-series study of consecutive patients with confirmed CDI infections hospitalized in NHS hospitals between September 2011 and December 2013. NHS hospitals are the service providers for the Niagara Region in Ontario; they offer a wide range of programs and services to a catchment area spanning 12 municipalities with a population of approximately 430,000 (Statistics Canada, 2016).

Case definition, identification, data source, and privacy.

Case definition and eligibility criteria followed the provincial guidelines for CDI prevention in healthcare settings (Public Health Agency of Canada, 2013), as reflected in the policies of the infection prevention and control (IPAC) at NHS (see Appendix A).

Cases of CDI were identified after laboratory testing of stool samples from symptomatic patients. Daily surveillance by IPAC service personnel at NHS sites confirmed the laboratory testing results. Confirmed cases were then approved and finalized in consultation with an external infectious diseases and infection control physician.

Data for this study were aggregated in a central database; data came from all IPAC offices of the various NHS hospitals and from the administrative database and medical records of NHS hospitals. For more accurate data collection, expert personnel in the Decision Support (DS) department of NHS conducted a retrospective query in the databases. Where data were missing, an electronic record review and a paper chart review were conducted using name, date of admission, and site-specific medical records numbered to match the records. A de-identified dataset was used for final analysis.

Clostridium difficile **testing and strain typing methods.**

Between September 2011 and April 2012, all CDI samples were sent to an academic hospital laboratory that used an in-house-developed DNA amplification technique to identify toxin-producing CDI strains. The BD GeneOhm™ Cdiff Assay had a sensitivity of 93.8% and a specificity of 95.5% (Becton, 2008). From April 2012 to December 2013, NHS sent the CDI samples to an external commercial laboratory that used a Nucleic Acid Amplification Test (NAAT), BD MAX™Cdiff, with a sensitivity of 96.3% and a specificity of 92.4% (Dalpke, Hofko, Zorn, & Zimmermann, 2013).

The provincial reference laboratory performed the strain typing of the *C. difficile* isolates, using a pulsed-field gel electrophoresis (PFGE) technique. A fraction of the culture prepared for PFGE was also used to extract DNA using the Bio-Rad Instagene reagent and following the manufacturer's protocol. Extracted DNA was analyzed by modified, multiple-locus, variable-number, tandem-repeat analysis (MMLVA), according to the protocol developed at Public Health Ontario's laboratory (Alfa et al., 2000). PFGE and MMLVA data were processed with the BioNumerics software (v.5, Applied Maths) to identify genetic profiles and relatedness of isolates. A standard set of 12 PFGE profiles from NML was used to classify pulsotypes; those not matching any of the 12 were assigned arbitrary letter designations. MMLVA profiles with a difference of less than 3% were considered to belong to the same strain.

Statistical analysis.

We stratified the CDI cases using the incidence of CA-CDI and HA-CDI. Data included CDI discreet count values, month and year of laboratory testing, the first three digits of the postal codes or forward sortation area (FSA) of the eligible CDI patients, and total patient days for all NHS sites per month for rate calculation. Rate per 1000 patient days was computed for each CDI

category, and rate per 100,000 population was calculated for CA-CDIs. We used information on the Niagara Region's population from Statistics Canada's 2011 census when needed for analysis of data. Monthly incidence measures were calculated and out-of-control ranges searched using Statistical Process Control.

We performed a purely spatial and spatio-temporal scan of the CA-CDI and HA-CDI cases to test for the presence of patterns in their approximate geographical origin and conducted a space-time permutation study to identify clusters independent of time and location. To evaluate the temporal pattern of the CDIs, we used a purely temporal statistics test for the investigation of non-random clustering with hospital cases, considered cases, and community cases, considered controls.

Using the additive seasonal cases, a mean was calculated for each season to allow us to test for seasonality in our relatively small datasets.

Data were combined and stored in SPSS software, version 21.0 (IBM Corp., Armonk, NY) and Microsoft® Excel for Mac, Version 15.27(161010). To determine the spatial and temporal scan statistics, we used SaTScan version 9.4.4 64-bit (Kulldorff and Information Management Services 2009) (Kulldorff, 2005). Information on geocodes for FSAs was accessed from GPSVisualizer (Schneider, 2003).

We categorized the results of molecular testing for each category as discreet counts and as proportions of the total specimens tested.

Ethics statement.

The protocol for this study was approved by York University's Research Ethics Board and Niagara Health Service's Research Ethics Board. This study entirely consisted of secondary

data analysis of de-identified quality improvement patient data; therefore, the requirement for informed consent was waived.

Results

A total of 1,051 CDI cases were identified through laboratory detection of toxins produced by *C. difficile* strains, 629 of which met the eligibility criteria; 318 (50.1%) were CA-CDI, and 311 (49.4%) were HA-CDI.

The rate per 100,000 population for hospitalized CA-CDIs was 14.84 in 2011; 33.22 in 2012, and 25.5 in 2013. The rate per 1000 patient days for HA-CDI was 3.83 for the entire study period. Table 5.1 lists the rate for each study year for the two CDI categories.

Spatial scan statistics

Figures 5.1a, 5.1b, and 5.1c provide the scan statistics of the purely temporal, spatio-temporal, and time-space permutations, respectively, of the hospitalized CA-CDI cases in the Niagara Region. Cluster ($p<0.005$) identification was based on their specimen collection date and their residential FSA information. Figures 5.2a, 5.2b, and 5.2c present the scan statistics of the purely temporal, spatio-temporal, and time-space permutations, respectively, for HA-CDI cases. Clusters ($p<0.005$) identified in each category are listed in the relevant figure. The identified clusters have different geocodes, and the radii of the circular windows were set for 1 kilometre for each cluster. CA-CDI scan statistics identified five very localized, purely spatial clusters ($p<0.05$), with one FSA attributing to each cluster; the analysis found a less contained and a larger number of FSAs for HA-CDI cases.

Time series analyses and statistical process control charts.

Figures 5.3a, 5.3b, and 5.3c explore the time series pattern of CDIs in NHS hospitals. When the control limit is set at ±2 sigma, the control chart for CA-CDIs indicates many months

of higher than average CA-CDI rates, with no out-of-control range. The control charts show an out-of-control period for HA-CDIs starting in January 2013 and lasting until April 2013. To confirm this result, and to understand whether the increase in CA-CDI and HA-CDI cases co-occurred, we turned to purely temporal analysis.

Temporal scan statistics.

The diagram in Figure 5.4 illustrates a cluster identified between December 2012 and April 2013. Identification of a cluster rejects our null hypothesis that the cases in hospitals and the community happened at the same time. Instead, cases acquired in the community occurred at a different time than those acquired in hospitals during the period of the cluster.

Test of seasonality.

The crude grand mean for the study period for all seasons was 35 for CA-CDIs and 36 for HA-CDIs. To better understand the effect of the seasons as an influencing factor on the prevalence of CA- and HA-CDIs, we calculated the additive seasonal indexes and numerically plotted the computed seasonal effects for all seasons in the study period. Graphical evaluation of the crude and seasonally adjusted cases for CA- and HA-CDIs indicated a lower seasonal influence in the former than the latter (see Figures 5.5a and 5.5b).

***C. difficile* strain typing.**

Molecular typing on 6% (59/1051) of CDI patients in the Niagara Region was conducted. Nineteen strain typing results were excluded from our analysis as they did not meet the case definition for our study (relapse or colonized patients). 6% (40/ 629) of the study cases were tested for molecular typing. Four percent (13/318) of CA-CDI specimens were tested, and PFGE identified various strains, including two (0.6%) NAP1 strains; the rest (3.5%) were other unrelated strains (A, B, C, D, I, N, M). Nine percent (26/311) of the HA-CDIs were tested for

strain identification: 12 cases (3.86%) were NAP1strain, two (0.6%) were non-NAP1, and the

rest (3.86%) were other unrelated strains (A, B, D, L, M, N, O, T, V).

Discussion

In our case series study, we found some notable differences between the temporal

patterns and the spatial distribution of the hospitalized CA-CDI and HA-CDI cases. Our study

did not reveal a seasonality pattern for the CA-CDI cases, and we discovered that cases of CA-

CDI and HA-CDI were temporally independent. Although our study was conducted on only

hospitalized patients with CA-CDI, the overall incidence was notably higher for the Niagara

Region (14.84 in 2011; 33.22 in 2012, and 25.5 in 2013) than for the UK in 2004 (22.0 per

100,000 population), Connecticut in 2006 (6.9 per 100,000 population), and Philadelphia in 2005

(7.6 per 100,000 population) (Centers for Disease Control, 2008). Similarly, given the fact that

the region experienced many outbreaks during the study period, HA-CDI rates in the Niagara

Region were markedly higher (3.83/1000 patient days) than the average rates/1000 patient days

for the entire province of Ontario, which were 0.30 and 0.33 in 2011-12 and 2012-13,

respectively (Health Quality Ontario, 2014).

The localized geographical clustering of CA-CDI cases in our study did not copy the

spatial distribution of HA-CDIs. Although most published studies have reported proximity to

livestock as a risk factor, the clustering of CA-CDI cases in the Niagara Region was

predominantly positioned in urban zones. Recent studies have suggested a positive association

between environmental elements, such as flooding (Lin et al., 2015), rainfall, exposure to

agricultural structures (exposure to soil, animals, or raw animal products), bathing in potentially

contaminated watercourses, and an increased risk of CA-CDI (Furuya-Kanamori et al., 2014;

Kistemann, Zimmer, Vagsholm, & Andersson, 2004; Anderson et al., 2017). However, our

discovery of urban clusters of the CA-CDI cases in the Niagara Region (Figures 5.1a, 5.1b, and 5.1c compared with Figures 5.2a, 5.2b and 5.2c) reduced the applicability of previous findings to our study. Upon further exploration and plotting of public dwellings and communal residences (such as nursing homes, shelters, schools, and group homes), we noticed multiple assisted-living supportive housing demarcations within the perimeters of the spatial clusters of CA-CDI. In a spatial study conducted by Anderson et al. in North Carolina, proximity to nursing homes was a risk factor for CA-CDI (Anderson et al., 2017). In Ontario, the *Long-Term Care Homes Act* (S.O.2007, c.8.) and the *Retirement Homes Act* (S.O.2010, c.11) specify the need for infection prevention and control training and practices in these settings, but the legislation does not pertain to other fast-growing communal dwellings, such as assisted living or supportive housing (*Long Term Care Homes Act,* 2007; *Retirement Homes Act*, 2010).

Despite studies suggesting an increase of CA-CDI in the winter months in both the southern and northern hemispheres (Brown et al., 2013; Gilca, Fortin, Frenette, Longtin, & Gourdeau, 2012; Kuntz, Chrischilles, Pendergast, Herwaldt, & Polgreen, 2011), the detection of more CA-CDI cases in the summer months, especially in the southern hemisphere, does not substantiate the role of antibiotic prescribing practices as a reason for the surge of CDIs in the winter months (Furuyama-Kanamori et al., 2015). The seasonal associations found in other CDI studies were not evident in our NHS study; this may be explained by the presence of *C. difficile* in retail meat, farm services, soil, pets, and domestic animals (Borriello, Honour, Turner, & Barclay, 1983; Baumgartner, 2012; Rodriguez-Palacio, Staempfli, Duffield, & Weese, 2007; Weese, Avery, Rousseau, & Reid-Smith, 2009; Stone et al., 2016; Anderson et al., 2014). However, our purely temporal study of the CA-CDI and HA-CDI cases also establishes a hospital-associated cluster spanning from December 2012 to April 2013, where a rise in CA-CDI

cases predated the HA-CDI's temporal cluster (see Figures 5.3 and 5.4). One hypothesis could be that the asymptomatic carriage of HA-CDIs after discharge from NHS hospitals in the weeks or months before our study period may have contributed to an increase of CA-CDI cases in the community. Another possibility is that the admission to hospitals of non-suspected CA-CDI cases due to a lack of established risk factors might have prompted HA-CDI outbreaks.

Our analysis of the *C. difficile* strain results associated with hospital outbreaks did not show homogeneity within the outbreak isolates, but we found similar unrelated strains amongst the CA-CDI and HA-CDI cases tested (including a NAP1 isolate in the CA-CDI samples). Thus, considering the lack of an anticipated genomic uniformity in HA-CDI cases, our study suggests that not all HA-CDI cases were acquired from a healthcare-associated source, and perhaps CA-CDIs had an effect on the increase of CDI cases in NHS hospitals.

The temporal independence of the CA- and HA-CDI cases, the higher than expected number of hospitalized CA-CDI cases, and the multiple reported HA-CDI outbreaks with unrelated molecular patterns all point to a possible association between the appearance of hospitalized CA-CDI cases and the hospital outbreaks. Other studies have hypothesised a positive correlation between increased rates of HA-CDI in hospitals and community prevalence and have suggested that hospital cases could be a driver of CDI in the community (Walker et al., 2012; Furuya-Kanamori et al., 2016; Yakob, Riley, Paterson, & Marquess, 2014). Some studies have postulated a community reservoir as a potential attributing base for the arrival of this infection in hospitals (Lin et al., 2015; Rodriguez-Palacios et al., 2007; Weese et al., 2009). Only comprehensive epidemiological studies can answer these questions.

Limitations

Our study was limited to hospitalized CA-CDI cases; we have no knowledge of the CA-CDI patients who did not need hospitalization, and this limits the generalizability of our findings. Moreover, because we lacked access to the full postal code information, we could not document the precise location of the CA-CDIs. This reduced our ability to pinpoint the location of potential public sources of infection in the community. Our strain typing assessment was limited to the CDI cases that were tested as a result of an outbreak investigation and composed a small proportion of all CDIs.

The risk of misclassification of CDI cases in this study was reduced by using the surveillance database, which was based on case definition, case confirmation, and expert consultation. Epidemiological evaluation by means of administrative and quality improvement databases allowed for a large-scale dataset.

Recommendations for Future Research

Identification of space and time patterns suggests that environmental factors have a role in the causation of CDI (Gordis, 2000) and could yield to better understanding of the epidemiology of these infections. We therefore suggest that when added to the traditional surveillance methods used in hospitals or community health facilities, spatial and temporal monitoring software can offer early identification of disease clusters and facilitate more efficient preventive measures. Using a combination of conventional and novel tools for comprehensive epidemiological evaluation can reveal illustrative and informative details on risk factors and initial causes of CDI in the community. Given the increasing numbers of the elderly and their dependence on supportive housing structures, community level reporting and detailed

surveillance programs identified through spatial heterogeneity should be included on public health agendas (Furuya-Kanamori et al., 2014).

Conclusion

Although the study points to the temporal independence of CA-CDI and HA-CDI, it also finds molecular heterogeneity and an increase in hospitalized CA-CDI activity before HA-CDI cases appear. The concentrated spatial distribution of CA-CDI could suggest undiscovered community sources of CDI that could be a transmission source and a driver of hospital outbreaks. Availability of a complete genotyping, added to a comprehensive epidemiological assessment, can reveal information about the transmission pathways of CA-CDI. Novel research programs that combine hospital and community findings can detect the direction of transmission of CA-CDI. Understanding the epidemiology of the community drivers of CA-CDI will guide hospital and community patient safety policies, inform public health programs, and improve quality of health at a population level.

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Tables

Table 5.1 – Rate of hospitalized CA-CDI and HA-CDI for NHS hospitals, between September 2011 and December 2013.

	CA-CDI	HA-CDI	Ontario hospitals	International literature
Rate/1000 patient days				
Overall rate for study period	3.9	3.83		
2011	5.26	3.7	0.3*	
2012	4.15	3.36	0.35*	
2013	3.2	4.34	0.33*	
Rate /100,000 population				
2011	14.84			11.6 (in Kuntz et al., 2011)
2012	33.22			
2013	25.5			

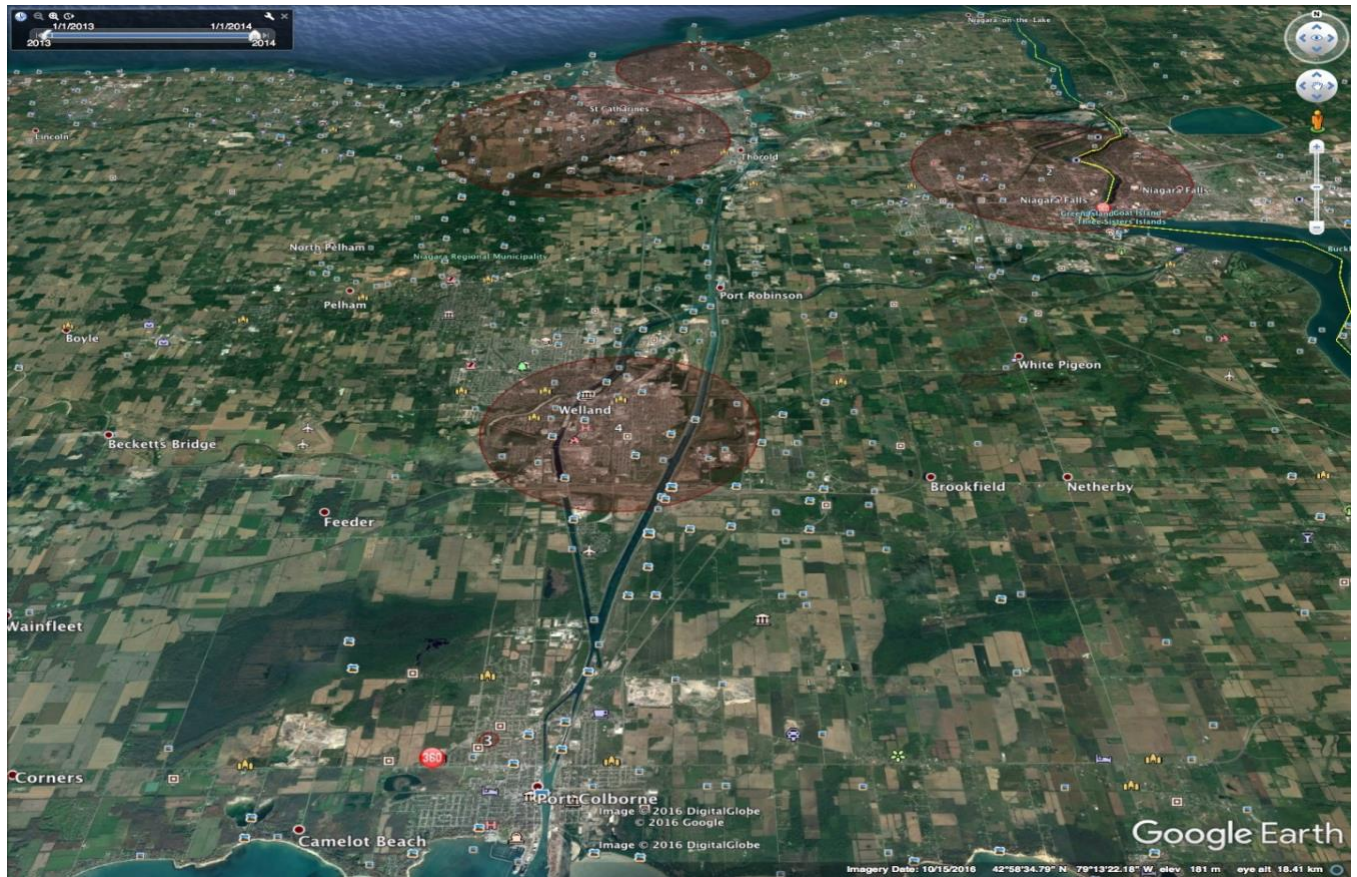*Note*. Data source: Health Quality Ontario, 2014

Figures

Figure 5.1a – Purely spatial scan statistics of CA-CDI cases in the Niagara Region, based on their FSA, between September 1, 2011, and December 31, 2013.

Number of significant clusters (p< 0.05):
5 FSA of the significant clusters: L3K; L2G; L2E; L2N; L3B

Figure 5.1b – Spatio-temporal scan statistics of the CA-CDI cases in the Niagara Region, based on their FSA, between September 1, 2011, and December 31, 2013.

Number of significant clusters (p< 0.05), identified with an arrow on the image:
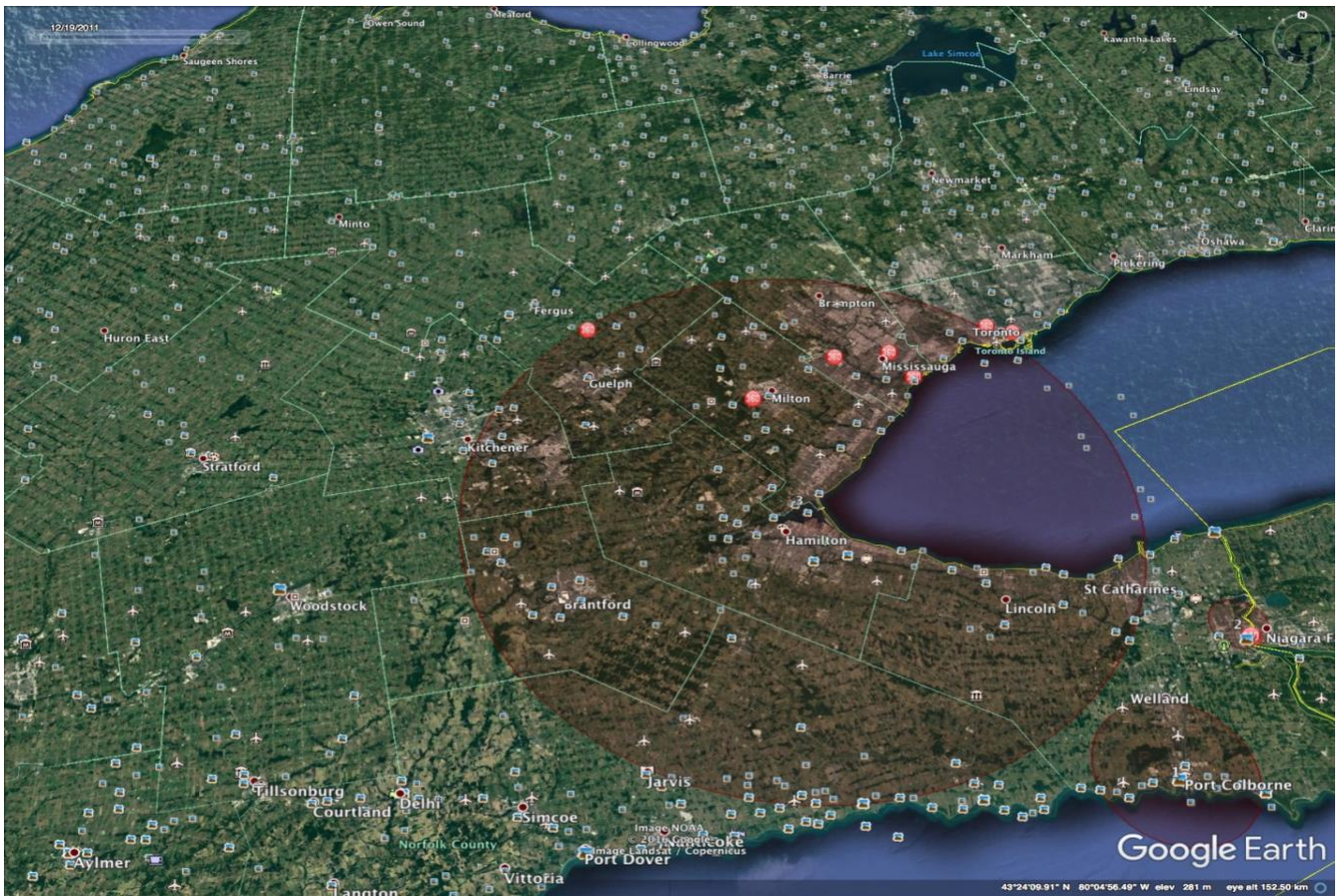9 FSA of the significant clusters: L2M; L3C; L2N; L3K; L2G; L3B; L2E; L2J; L2V

Figure 5.1c – Space-time permutation scan statistics of CA-CDI cases in the Niagara Region, based on their FSA, between September 1, 2011, and December 31, 2013.

Number of significant clusters (p< 0.05):
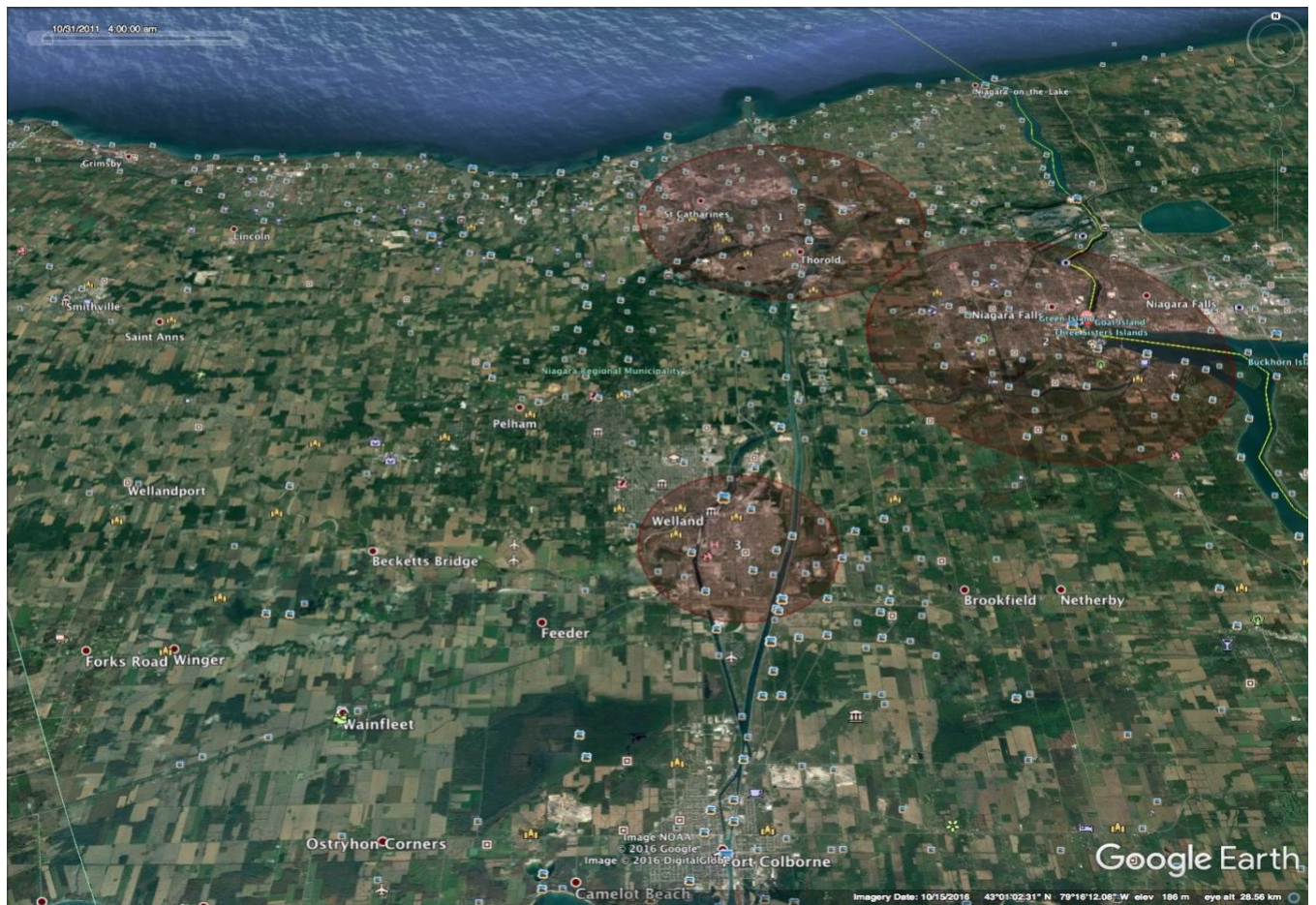3 FSA of the significant clusters: (L3K, L3B, L3C); (L2E, L2J, L2H, L2G); (L7T, L9A, L3M, L0R, L2R, L2N, L2S, L2M)

Figure 5.2a – Purely spatial scan statistics of HA-CDI cases in the Niagara Region, based on their FSA, between September 1, 2011, and December 31, 2013.

Number of significant clusters (p< 0.05):
1 FSA of the significant clusters: L2E, L2J, L2H, L2G, L2V, L2P, L2T, L2M, L2S, L2N, L2R, L3B, L3C

Figure 5.2b – Spatio-temporal scan statistics of the HA-CDI cases in the Niagara Region, based on their FSA, between September 1, 2011, and December 31, 2013.

Number of significant clusters (p< 0.05):
2FSA of the significant clusters: (L2E, L2J, L2H, L2G, L2V, L2P, L2T, L2M, L2S, L2N); (L3K, L3B, L3C, L0S)

Figure 5.2c – Space-time permutation scan statistics of HA-CDI cases in the Niagara Region, based on their FSA, between September 1, 2011, and December 31, 2013.

Number of significant clusters (p< 0.05):
3 FSA of the significant clusters: (L4K, L4A, L7T, L3M, L9A, L2N, L2M, L2R, L0R, L2P, L2S, L2T, L2V); (L3B, L3C, L0S, L3K); (L2G, L2H, L2E)
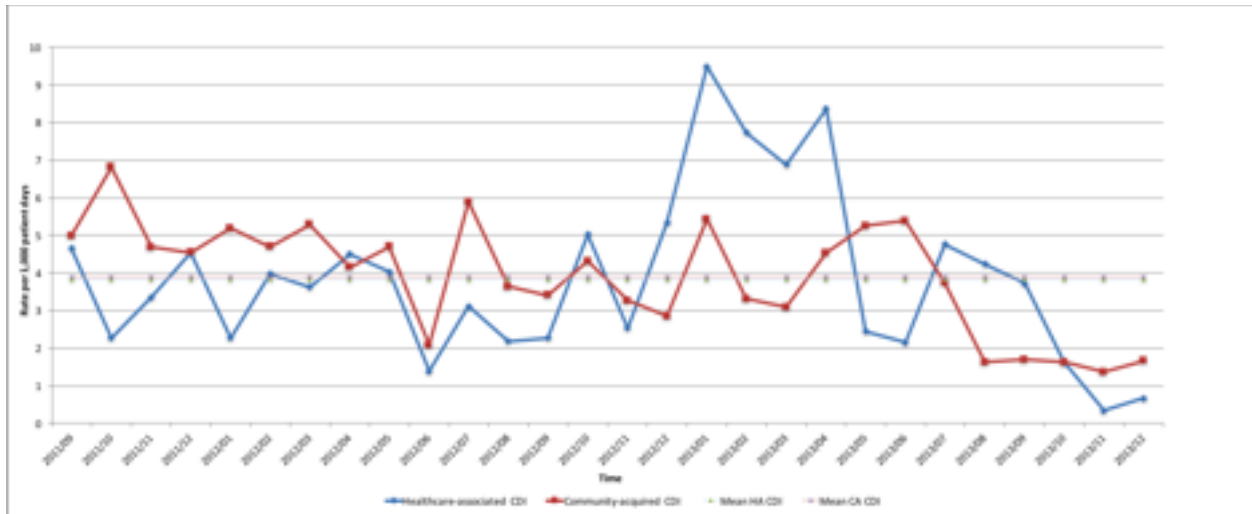
Figure 5.3a – Temporal visualization of CDI cases in the Niagara Region.

Comparison of time series trends of CA-CDI and HA-CDI patients hospitalized in NHS hospitals between September 2011 and December 2013.
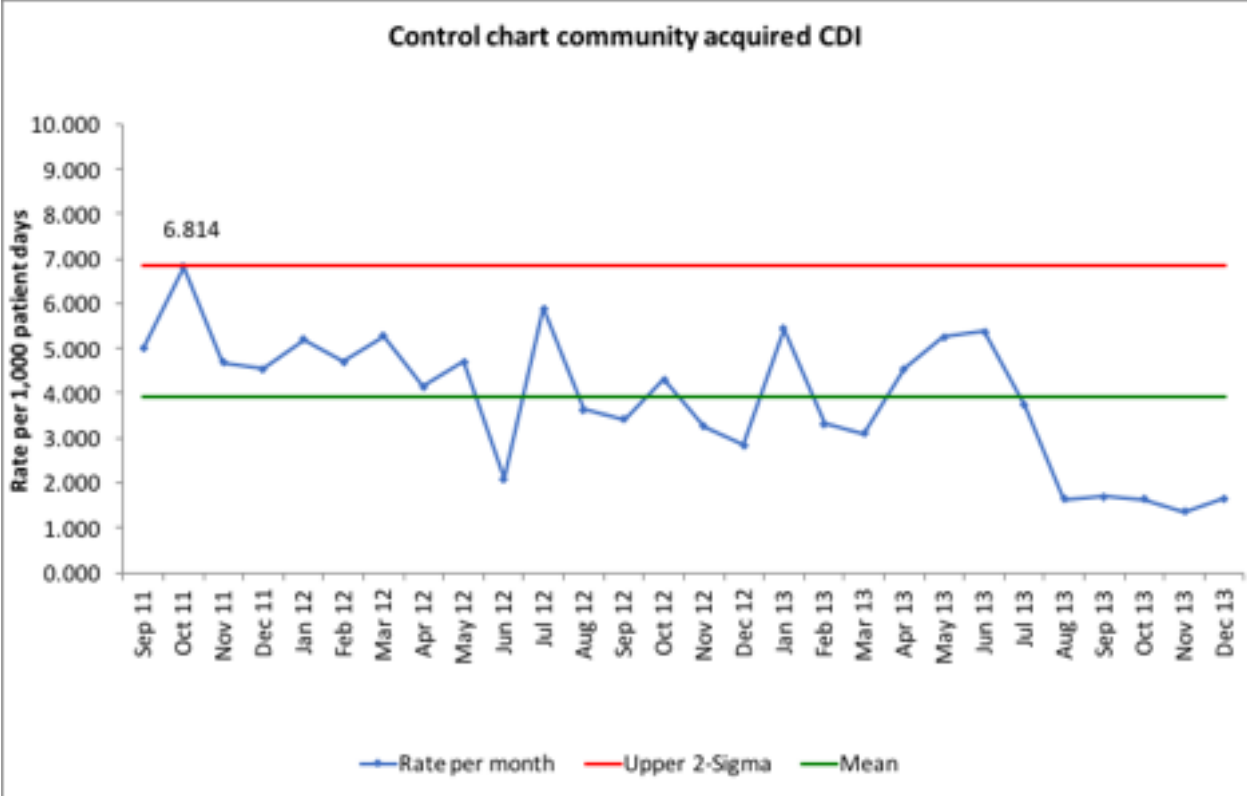
Figure 5.3b – Statistical process control display of hospitalized CA-CDI rates per 1000 admissions hospitalized in NHS hospitals between September 2011 and December 2013.

Figure 5.3c – Statistical process control display of hospitalized HA-CDI rates per 1000 admissions hospitalized in NHS hospitals between September 2011 and December 2013.
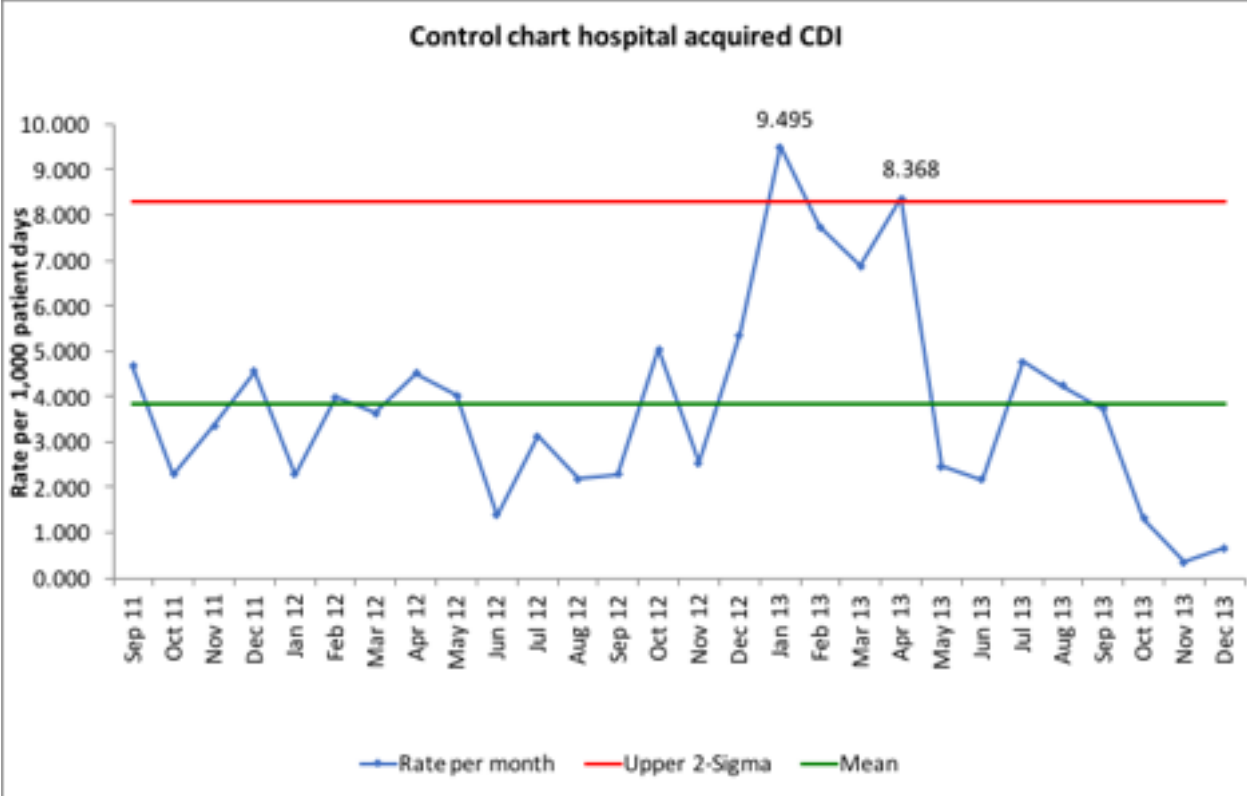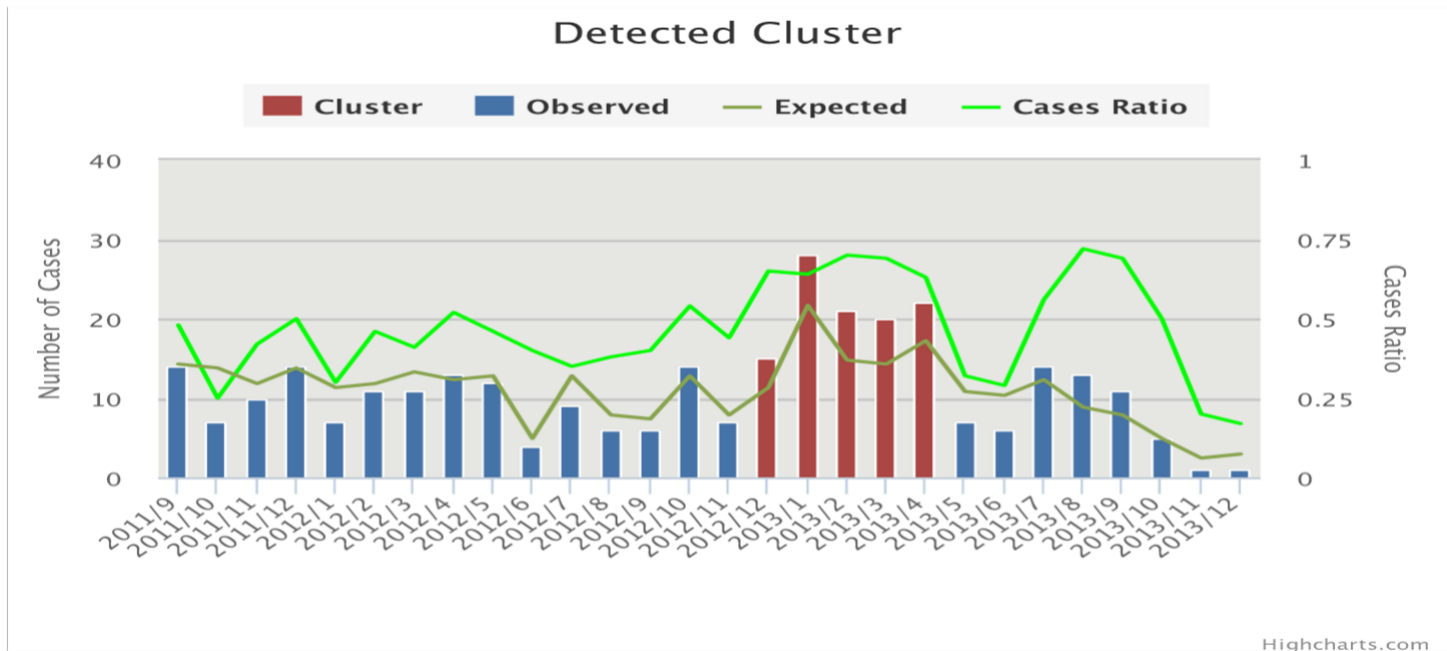
Figure 5.4 – Purely temporal analysis scanning for clusters with high rates: A retrospective study of the CDI cases in NHS hospitals between September 2011 and December 2013, using the Bernoulli model, SaTScan v9.4.4

Information on the detected temporal cluster: Time frame: 2012/12/1 to 2013/4/30;
Log likelihood ratio: 12.027272; Monte Carlo rank: 1/1000; P-value: 0.001

A cluster is statistically significant when its log likelihood ratio is greater than the critical value, which is, for significance level:
Gumbel Critical Values: 0.00001: 13.971596; 0.0001: 11.659499
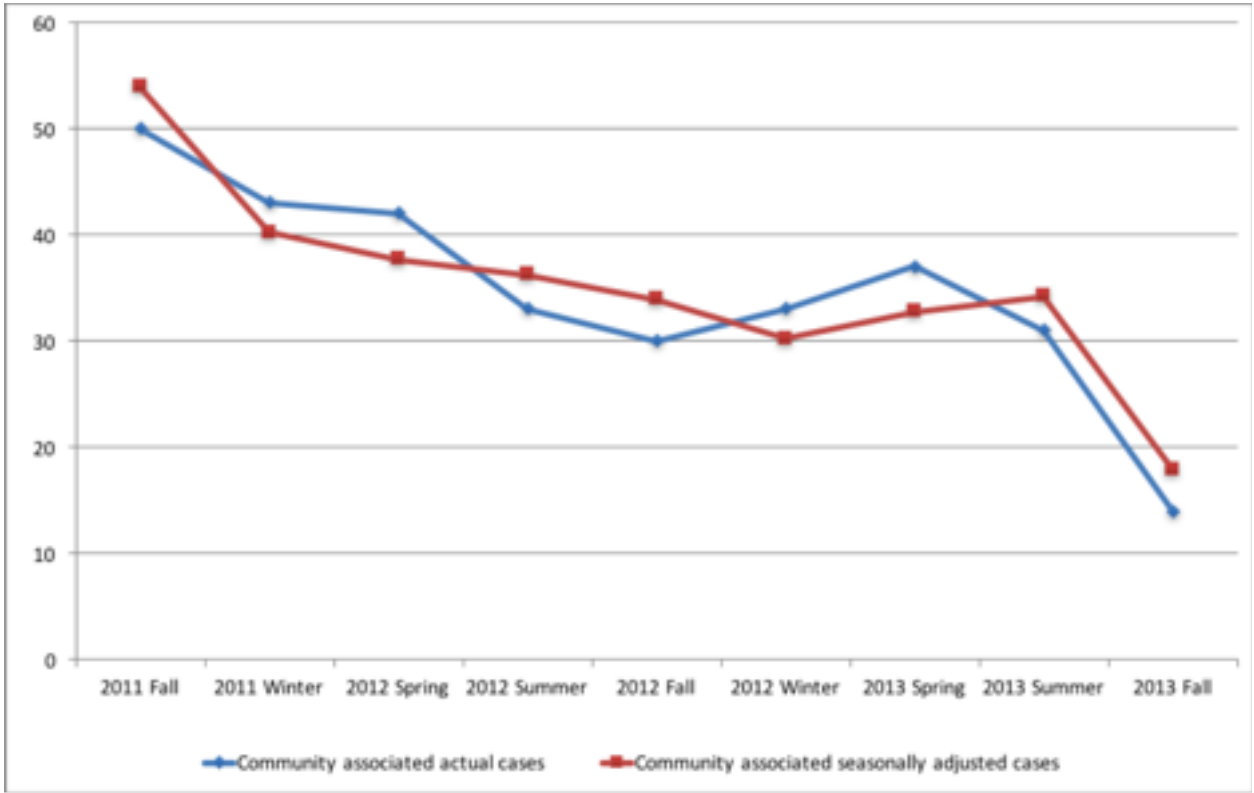Standard Monte Carlo Critical Values: 0.001: 8.060346; 0.01: 7.215835;0.05: 5.575158

Figure 5.5a – Crude and seasonality adjusted values for CA-CDI cases in the Niagara Region between September 2011 and December 2013.
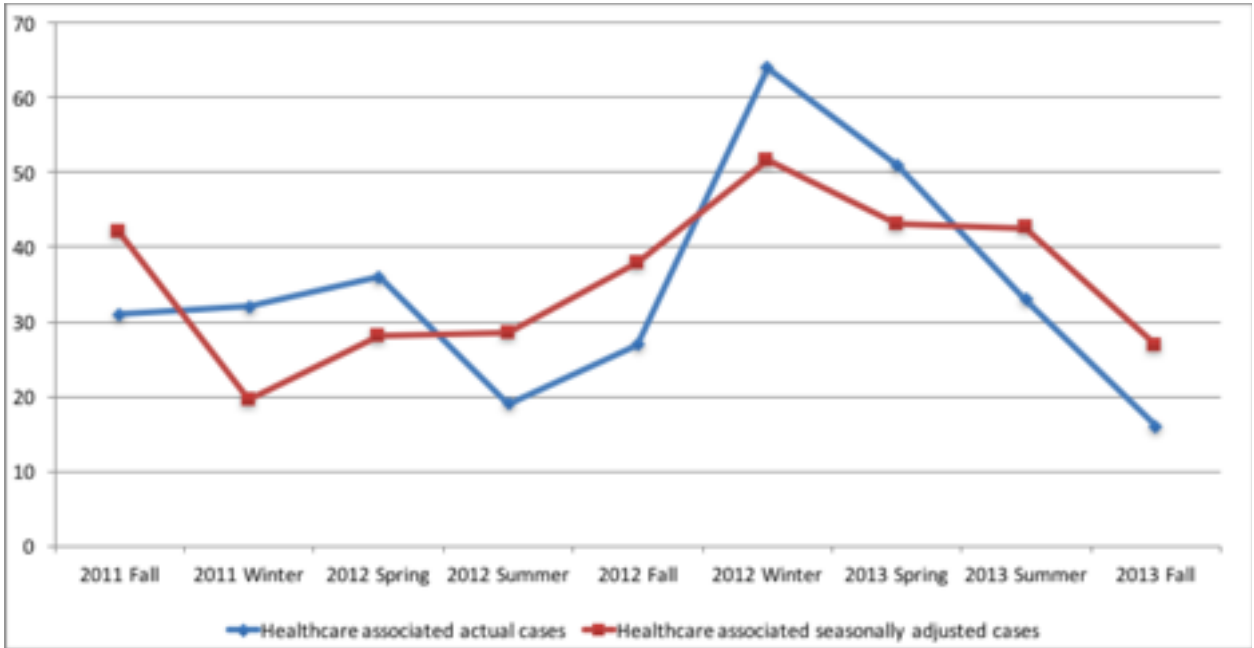
Figure 5.5b – Crude and seasonality adjusted values for HA-CDI cases in the Niagara Region between September 2011 and December 2013.

Appendix

Appendix A – NHS definitions of CDI, HA-CDI, and CA-CDI used between September 2011 and December 2013 for surveillance and case identification.

<table>
<tr>
<td colspan="2" align="center">CDI definition

• A patient with diarrhea with
• Laboratory confirmation of clostridium difficile (e.g. by positive toxin A/B assay, or PCR) or
• Visualization of pseudomembranes on sigmoidoscopy, or
• Colonoscopy, or histological/pathological diagnosis of pseudomembranous colitis.</td>
</tr>
<tr>
<td align="center">Definition of HA-CDI</td>
<td align="center">Definition of CA-CDI</td>
</tr>
<tr>
<td>An HA-CDI case is defined as a patient who has not had CDI in the past eight weeks, but meets one of the following criteria:

• He or she does not present with CDI upon admission, but shows onset of symptoms >72 hours after admission.
• The infection was present at time of admission but was related to a previous admission to the same facility within the last four weeks.</td>
<td>A CA-CDI case matches the case definition for CDI and does *not* match the HA-CDI definitions: in other words:

• The symptoms of CDI *were* present upon admission, or symptom onset *was less* than 72 hours after admission.
• No exposure to any healthcare facility occurred within the last four weeks, or the source of infection cannot be determined and the patient has not had HA-CDI in the last eight weeks.</td>
</tr>
</table>

Chapter Six – Conclusion

Value of a Complex Adaptive Systems View for Exploring Health Problems

A panoramic view of the many agents contributing to health and their interplay is necessary if we are to improve health at an individual and a population level (Westley, Zimmermann, & Patton, 2007). The quality of an individual's health and wellbeing cannot be enriched without considering all physiological processes, nor can it be isolated from biological and environmental interactions. Accordingly, population health researchers working in the area of health disparities have been using approaches that recognize multiple functioning systems, such as the reciprocal relationship between health and income (Diez Roux, 2011). Nonlinear dynamics between multiple, diverse, and interconnected agents resulting in unpredictable patterns, such as in healthcare, are characteristic of complex systems. Therefore, an expanded view of processes, structures, rules, and patterns is necessary to construct, organize, and achieve quality population-level health strategies.

This dissertation proposes the use of Complex Adaptive Systems (CAS) theory as an example of an expanded theoretical viewpoint. CAS-based frameworks offer toolkits to researchers that allow them detect macro-level patterns as an outcome of operational interactions and process multiplicity, at different levels and between various subsystems. The dynamics operating within a CAS framework guide the research process toward the ultimate objective of inquiry by unraveling postulations from multiple perspectives. Mintzberg (1987) denotes this as achieving a balance between crafting "umbrella strategies" and creating "process strategies" that enable the emergence of feedback loops in a complex system. Whereas the umbrella strategy is stationary and does not reflect the needs of the various parts of a complex system, the feedback

loops generated by a strategy based on process permit a system to be flexible and to evolve and change.

The dissertation has explored its research questions using a framework grounded in CAS, with an intent to unveil new and different epidemiological findings and to initiate useful feedback loops by discovering novel health equity leverage points. This final chapter summarizes the findings from the three manuscripts comprising the dissertation (Chapters Three, Four, and Five) and discusses the implications of the theoretical framework to the findings in each case. It concludes by suggesting prospective feedback loops emerging as a result of the adaptability of the subsystems as topics of future study.

Summary of Findings and Contribution to the Literature using a CAS framework

Together, the three manuscripts prepared for this dissertation shape a broad understanding of the scope of available knowledge on CA-CDI, specifically, in the Niagara Region of Ontario, Canada. The study is unique; it is one of the first comprehensive Canadian studies to evaluate CA-CDI through a systems lens, and it combines this focus with an epidemiological disease transmission dynamics framework to formulate policy recommendations that could enhance equity in health. More precisely, Chapter Three applies a scoping review methodology to determine the overall extent of our knowledge of the epidemiology of CA-CDI. Chapters Four and Five comprise an epidemiological analysis of hospitalized CA-CDI patients in the Niagara Region and compare their characteristics with those of HA-CDI patients during the study period, in an attempt to clarify the extent of the CDI problem. The results of these chapters quantify and visualize variables that could lead to health equity policy leverage points.

Epidemiology of Community-acquired *Clostridium difficile* infections (CA-CDI): A scoping review.

Chapter Three constitutes a scoping study of CA-CDI. The purpose was to review the literature on risk factors for CA-CDI. I applied the protocols suggested by *The Joanna Briggs Institute (JBI) Reviewers' Manual 2015, Methodology for JBI Scoping Reviews* (The Joanna Briggs Institute, 2015). I searched three life sciences databases for studies on the epidemiological aspects of CA-CDI: The Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Nursing and Allied Health Source (ProQuest), and MEDLINE. After applying the inclusion and exclusion criteria and full article reviews, I was left with 22 peer reviewed articles. A reading of this work confirms that compared to HA-CDI, CA-CDI is seen more often in younger individuals and in female populations. Seasonal patterns are not consistently noticed in the literature, and only one spatial study finds proximity to animal farms, animal services, or nursing homes was associated with a higher incidence of CA-CDI within the community (Anderson et al., 2017). In terms of medications used, although exposure to antimicrobials and proton pump inhibitor (PPI) use are at the top of the list of medications connected with CA-CDI, the associations are not as strong as those for HA-CDI. Overall, the scoping review indicates that the number of CA-CDI cases with unique demographic patterns is gradually growing in communities, with more cases requiring hospitalization.

While the scoping review provides insight into the research to date on CA-CDI, applying a systems lens highlights the complexity of this infection and its emergent behaviour between communities and healthcare settings. It is clear that CDI is no longer an issue specific to healthcare settings and hospitals. The patterns found in hospitalised cases could inform or influence the patterns in communities, or conversely, the agents or patterns in the community

could influence those in healthcare settings. This is supported by literature finding overlapping genetic strains in CA-CDI and HA-CDI cases. There are knowledge gaps in several areas, such as determining the incidence rate for CA-CDI as an operational baseline benchmark, establishing potential community-driven risk factors for CA-CDI, or explicating CA-CDI concentration within communities. Connectivity and co-evolution of the healthcare-associated and community-associated arms of surveillance using a complex systems approach can inform the discourse on this infection until further targeted research is conducted.

Epidemiology of patients hospitalized with *Clostridium difficile* infection in the Niagara Region, Ontario, Canada, between September 2011 and December 2013: A comparative analysis of community-associated and healthcare-associated *Clostridium difficile* infections.

Chapter Four compares the epidemiology of hospitalized patients with CA-CDI and HA-CDI though a retrospective case series analysis. The results show that patients with CA-CDI are younger, have less exposure to antibiotics, and use fewer PPIs than patients with HA-CDI. Gender proportions are similarly distributed between the two groups. However, my study finds a higher proportion of male CA-CDI patients than other studies. A systems evaluation of the patients' characteristics and established risk factors concludes that CA-CDI is emerging as an important cause of diarrhea in patients with no previous healthcare-related exposure. Therefore, CDI must be considered as a potential diagnosis when patients are admitted to hospitals with diarrhea, even in the absence of conventional CDI risk factors. Changes in policies for isolation initiation on admission could potentially have a large impact on hospital infection rates for CDI; such changes would acknowledge the nonlinearities in an evolving CAS. I also conclude that CA-CDI affects a younger, healthier population and can occur even in the absence of the risk

factors traditionally associated with this infection. The lower proportion of the conventional risk factors in CA-CDI cases suggests the possibility of novel community reservoirs. Therefore, in the next chapter, I conduct a systems analysis of the data on all aspects of the disease transmission dynamics to investigate the epidemiology of this infection in the community.

A spatial, temporal, and molecular epidemiological study of hospitalized patients infected with community-acquired or healthcare-associated *Clostridium difficile* in the Niagara Region, Ontario, Canada.

In Chapter Five, I conduct a systems level evaluation of the incidence, geographical distribution, temporal patterns, and genetic relatedness of hospitalized CA-CDI patients in NHS hospitals and compare the results to those of NHS patients hospitalized with HA-CDI. The systems level evaluation identifies spatial clusters of CA-CDI localized in the urban forward sortation areas (FSAs) of the Niagara Region. This new and emergent pattern is unlike patterns seen in other published data for CA-CDI; most work to date associates this infection in the community with farmlands, animal farms, and rural areas (Anderson et al., 2017). When I look for the effects of communal dwellings such as shelters or group homes, I find that a number of assisted living accommodations present on the spatial map within the circular windows for high CDI concentration. Other interesting emergent findings from the evaluation of the systems connectivity are the presence and temporal independence of various unrelated strains in each category of CDI.

Interpretation and implications of results

      Epidemiological patterns of CA-CDI: The view through a Complex Adaptive Systems (CAS) lens.

      The inter-dependency of individuals is a dominant characteristic of the population-level health problems in the field of infectious and communicable diseases (Diez Roux, 2011). In a CAS, the physical interactions and environmental influences of the subsystems are critical to the success of the preventative measures and the effectiveness of the control processes. Findings from the scoping review in this dissertation establish that research to date has mainly focused on diagnosis, treatment, and preventive interventions in HA-CDI, with a dearth of studies on CA-CDI. The CAS framework used in this research yields valuable information on the epidemiology of CA-CDI, detecting some of the contributing factors that add to the overall burden of this infection.

      Chapters Four and Five establish that hospitalized patients infected with CA-CDI present different characteristics from HA-CDI patients and display independent temporal and spatial patterns but share genetically similar strains. The connectivity of the various CAS elements considered in this study reveals that CDI is not always a problem associated with or originating in healthcare settings. Moreover, the coevolution and adaptation of multiple subsystems in this particular CAS result in the emergence of a positive feedback loop containing evidence that could be constructive for the NHS CAS. More specifically, the positive feedback loops could lead to role clarification and better specification of responsibilities; this, in turn, could lead to closer cooperation, connectivity and, ultimately, the coevolution of a hospital/ public health CAS. For example, modified surveillance processes, research priority setting or funding for CA-CDI research may develop into additional findings able to guide decision-makers toward more

effective preventative processes and novel control strategies. In addition, the cooperation of interdependent subsystems could reveal the ambiguities in the direction of transmission pathways between hospitals and communities. Identifying emergent community patterns of infection transmission within subsystems would lead to planning for interventions and improvements in the overall CAS functions and goals. Ultimately, the self-organization of stakeholders in hospitals and communities, accompanied by their interaction and adaptation, would ensure improvements in the quality of the population health.

Each manuscript of this dissertation presents a leverage point for strengthening health equity policies. The next section interprets each of these in turn, looking at horizontal and vertical equity concepts, as defined in Chapter One.

Inequities in health: Can epidemiology motivate policy-makers?

Comparative trans-population research and responsible analysis of the empirical results represent standards of practice to inform responsible policy decisions that impact population health (Schrecker, 2013). This is particularly effective when supporting evidence is challenged by political powers (Schrecker, 2013). Given the possibility of such challenges, selecting the right research design is essential. Scholars say reductionist approaches that consider a single variable at a time may dampen or cover the realities of health inequity (Murray, Gakidou, & Frenk, 1999; Rydin et al., 2012). The pluralist concept of "epidemiological worlds" has recently been proposed as a methodology to organize the process of research and inquiry in the healthcare field (Rydin et al., 2012). Many scholars argue that health inequities mirror the multi-dimensional influences of the environment, with each influence having an amplifying effect on the others (Braveman, 2006; Kawachi, Subramanian, & Almeida-Filho, 2002). Given that environmental agents, neighbourhoods, and communities are increasingly recognized as factors

impacting health equity, it is very likely they will influence health outcomes at a population level (Braveman, 2006; Kawachi, Subramanian, & Almeida-Filho, 2002).

A significant take-away from the scoping review is the message of under-researched areas of CA-CDI. In Canada, the imperative to improve the quality of population and public health is clear in the Canadian Institute of Health Research's (CIHR) emphasis on strategic research priorities. CIHR defines coherent intersectoral action for population health improvement, scalable population health solutions, and equitable population health impacts as research primacies for Canadian scholars in health (Canadian Institute of Health Research, 2017). From a health policy and equity perspective, the lack of available science to elucidate unique clinical care requirements (such as different treatment options for CA-CDI), along with the shortage of studies to inform preventative practices and policies, suggests the need for better allocation of research resources.

Despite the undeniable impact of CA-CDI on hospital dynamics and on the quality of health and wellbeing within communities, the rate, possible risk factors, and epidemiological patterns of CA-CDI in Canada are under-explored. The dissertation's visualization of communal places in its spatial analyses points to the presence of assisted living accommodations with a high concentration of CA-CDI in urban parts of the Niagara Region. This feedback provides thought-provoking grounds for further exploration and raises the question of safety and environmental hygiene in these facilities. The *Canada Health Act* (CHA) requires provinces to deliver all necessary health services to every insured resident on a non-profit basis. In terms of disease prevention, the Act denotes that Canadians can achieve further improvements in their well-being by "combining individual lifestyles that emphasize fitness*, prevention of disease* and health promotion with collective action against the social, environmental and occupational causes of

disease, and that they desire a system of health services that will promote physical and mental health and protection against disease" (Canada Health Act, 1985). To complement the CHA, the Ontario provincial government protects the health and safety of the elderly in nursing homes and retirement homes through additional provisions related to safety, environmental hygiene, and infection prevention and control within the *Long-Term Care Homes Act* (S.O.2007, c.8.) and the *Retirement Homes Act* (2010, S.O. 2010, c. 11). The province mandates "The right to live in a safe and clean environment where he or she is treated with courtesy and respect and in a way, that fully recognizes the resident's individuality and respects the resident's dignity". In 2017, the *Long-Term Care Homes Act* and *the Retirement Home Act* were amended to include provisions for infection prevention and control. Unfortunately, the legislation does not cover the fast-growing area of assisted living accommodations.

Public health seeks to improve the quality of life of the elderly population through numerous primary, secondary. and tertiary preventive programs, such as cardiovascular disease prevention programs, impairment of vision programs, and hearing or dementia programs (Schneider, 2006). The increase of the median age in Canada (5.7 years in the past 20 years), means that the number of older people with unique and complex medical needs is increasing (Statistics Canada, 2015). This creates a two-fold challenge for public health: to improve the health of people through prevention programs and to manage the cost control issue as a result of these additional programs in an equitable way. A fundamental concern of the dissertation was to reveal findings that can be used as leverage points to inform vertical and horizontal policies in equity, and, in fact, as the findings suggest, taking a complex systems approach to the CA-CDI problem has the potential to inform equitable public health policies supporting new preventative

programs. Responding to increasing infections and preventing their complications in the community will improve population health and control the cost of ill-health.

Dissertation limitations

The studies conducted to answer the questions of this dissertation have undeniable strengths but show some common limitations as well. First, the use of CDI surveillance data provided a sizeable dataset, but retrospective studies are inherently embedded with a data confounding concept that influences dependent and independent variables. This could have affected the analyses of the risk factors. In addition, the surveillance reports were missing some data elements, possibly introducing the risk of missing data bias; to reduce bias, I used complete-case analysis. Second, the research lacked access to information on CA-CDI cases that were not hospitalized. This reduced the generalizability of the outcomes, as hospitalized patients were potentially more ill than those who did not seek hospitalization. However, this would not have influenced the validity of the testing methods and statistical processes. Third, a limitation specific to the genetics evaluation is that the strain typing assessment was limited to the samples from outbreak investigations. A larger comparison of strain typing would have allowed a clearer understanding of the genetic relatedness of CA-CDI and HA-CDI.

Future directions

Several themes emerge from this research as priority recommendations for future research in epidemiology, public health, and hospitals. The outcomes also support advocacy of policy proposals geared toward health equity. Immediate future directions and policy proposals are forecasted and summarized in Figure 6.1. The figure shows how feedback loops that emerge from the recommended public health programs, hospital practices, and health policies will lead to the overall evolution of the system.

Recommendations for policy-makers.

For policy advocates who influence health policies and decision-makers who allocate funding for improvement programs and research, the following two themes emerge from the outcomes of this research:

1. This research demonstrates an urgent need for studies that improve our understanding of CA-CDI. We cannot wait until our communities are hit by multiple outbreaks to begin discussions of funding CA-CDI studies. Fiscal provisions for research and discovery must be enforced through policies that support systems level (community- and hospital-based) studies that inform equitable health policies and evidence-informed recommendations for practices.

2. There is a clear need for a national surveillance system to answer imminent CA-CDI questions and to create hypotheses for empirical research. This recommendation is aligned with the goals of Pan-Canadian Public Health Network (PCPHN) set by the Communicable and Infectious Diseases Steering Committee Antimicrobial Resistance Surveillance Task Group: an understanding of CA-CDI infection rates and identifying the surveillance data elements requirement for CA-CDI is essential for a robust Pan-Canadian antimicrobial resistance surveillance system (Pan-Canadian Public Health Network, 2016). Currently, the only information on CA-CDI is captured by hospital surveillance programs, mostly in acute-care settings.

Recommendations for research in epidemiology for hospitals and public health.

For hospital administrators and federal, provincial, or local public health departments, the results of the research lead to both transdisciplinary and independent recommendations.

1. Hospitals must evaluate the impact of asymptomatic carriers and colonized patients on hospital environments to map out the overall CDI transmission pathways and to evaluate the feasibility of current practices in healthcare settings. Admission screening studies to quantify this question could contribute to our understanding of the bioburden and the role of asymptomatic carriers in hospital outbreaks. Australia, the United States, and several European countries have begun to emphasize systems level surveillance and evaluation of CA-CDI. Canada should follow their lead. Until we gain a better understanding of the CDI continuum, the use of only hospital surveillance and preventive measures cannot be completely successful in reducing the hospital cases or outbreaks.

2. There is a limited understanding of the burden of CA-CDI on health care, as some cases are not captured by traditional hospital surveillance programs. The last published Canadian study to conduct a cost analysis of hospitalized and community-dwelling patients estimated the cost (based on the anticipated projection from HA-CDI) at $281 million, 92% of which ($260 million) was attributed to in-hospital costs, 4% ($12 million) to direct medical costs, and 4% (10 million) to lost productivity costs (Levy et al., 2015). An accurate evaluation of the CA-CDI cost impact can encourage advocacy for policies that recommend and support CA-CDI research and funding.

3. In addition to quantifiable empirical studies to inform the discourse of risk factors, treatment options, and environmental influences, we need community-based research on CA-CDI and its impact on quality of life (QOL). QOL is defined as "the degree to which a person enjoys the important possibilities of his/her life" (Raphael, 2010). CA-CDI is increasing in hospitals, with community cases progressively seeking hospitalization; it mostly targets the elderly, causing morbidities and creating tangible and intangible costs

to the patient, family members, or care providers in the community. Research has established a strong association between health status and QOL in older persons. Considering the growing proportion of the elderly in our communities, measurement of QOL in the affected elderly with CA-CDI can be used to directly evaluate the impact of existing services, programs, treatment options, and additional required health services (Raphael, 2010).

Final statement

Three complementary manuscripts answer the questions formulated in this dissertation; they evaluate the overall scope of our knowledge about CA-CDI and offer an epidemiological comparative analysis of CA-CDI in NHS hospitals. Each manuscript opens up opportunities for future research and suggests themes to inspire policies supporting health equity. The findings confirm that a CAS approach to research and analysis grounded in an epidemiological framework can detect leverage points toward improvement and equity in population health.

In 2010, during a course on the political economy of health, there was an interesting discussion of the effects of living conditions on Canadians' experiences with adult-onset diabetes. Included in the discussion was the fact that the incidence of Type II diabetes is noticed more in lower-income neighbourhoods (Mikkonen & Raphael, 2010). The discussion instigated the question of whether the incidence of community acquired infections that historically used to be hospital problems may be related to an equity element. This research begins to answer that question. Using a combined complex adaptive systems tenet and an epidemiological disease transmission triad, it evaluates the dynamics of one such community acquired infection.

If they are heeded by policy-makers, the results could lead to immediate improvements in equitable health policies at a hospital and population level. Policy-makers could advise hospitals,

community stakeholders, and public health departments to take a multidisciplinary approach, examine the problem from every angle, create an infrastructure to share resources, and facilitate collaboration; this should give them the resources to tackle the CA-CDI issue.

Forrester says: "In the complex system … causes are usually found, not in prior events, but in the structure and policies of the system …" (Forrester, 1969, pp. 9 &10). It is through systems thinking, exploration, and collaboration that evidence advises the structures and policies able to inform innovative ideas.

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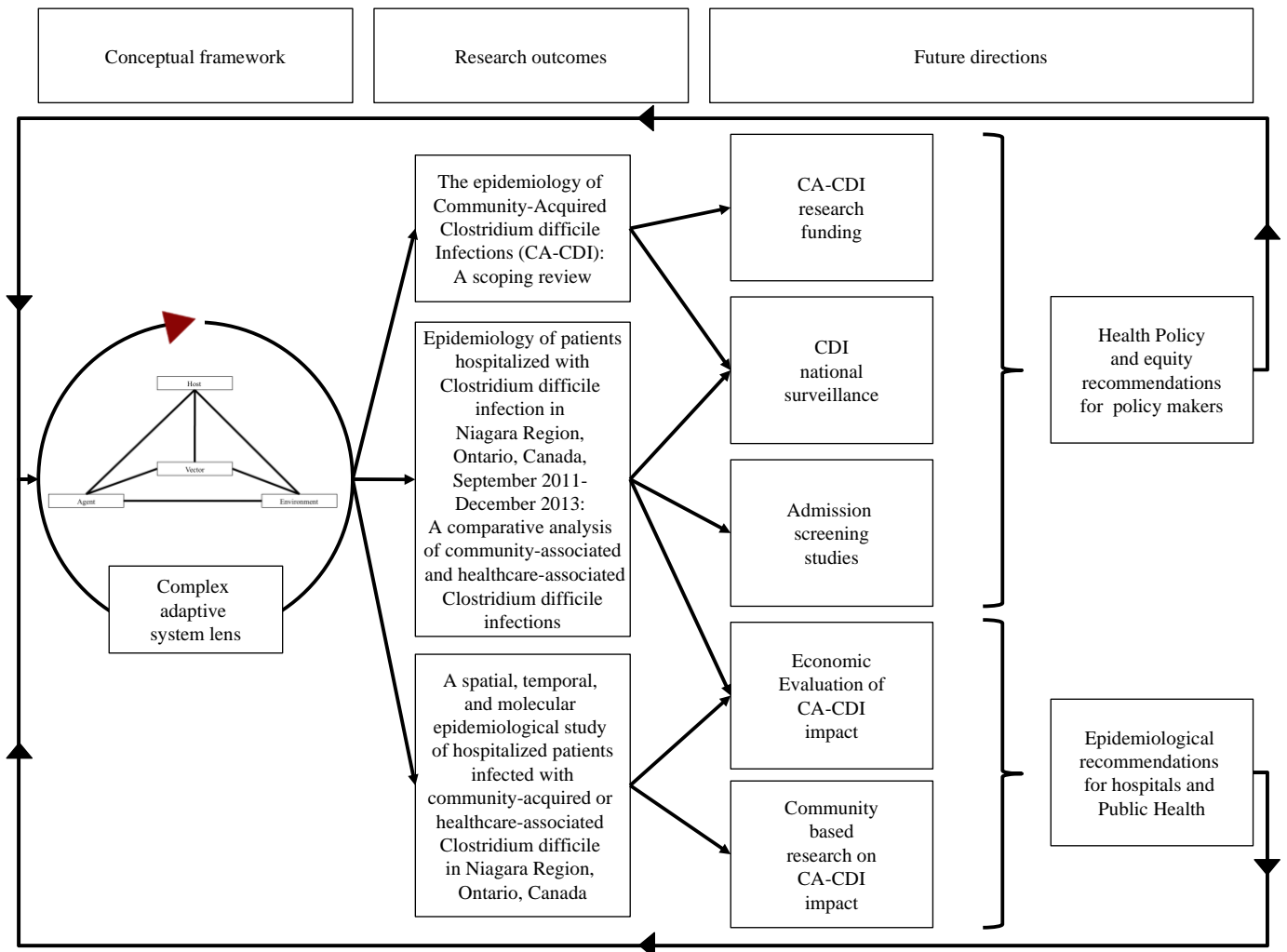   *changed* Toronto, ON: Vintage Canada, Random House of Canada Limited.

Figures

Figure 6.1 – Recommendations for future directions for policy-makers, hospitals, and public health departments.

Supplement – Methodology

Chapter Overview

This supplemental chapter discusses the research methodology, along with the setting, participants, case definition, eligibility criteria, instrumentation, and measures. It explains the use of administrative data, the statistical analyses and software used for analysis, and the temporal and spatial analysis in Chapters Four and Five, and gives the ethical considerations.

Study Design

This study used a case series design to examine community-acquired *Clostridium difficile* infections (CA-CDI) cases identified at Niagara Health System (NHS) hospitals. The epidemiological characteristics of the cases, the molecular relatedness of *Clostridium difficile,* and the temporal and spatial patterns of CA-CDI cases were compared and contrasted with the cases acquired in hospitals, known as healthcare-associated *Clostridium difficile* infections (HA-CDI).

Setting

The Niagara Region is located in southern Ontario, Canada. It has a total area of 1,852 square kilometres and a total population of 427,421. The Niagara Region consists of 12 municipalities: Fort Erie, Grimsby, Lincoln, Niagara-on-the-Lake, Niagara Falls, Pelham, Port Colborne, St. Catharines, Thorold, Wainfleet, Welland, and West Lincoln. Figure Supl.1 is a map of the Niagara Region and its municipalities, based on the 2011 census (Statistics Canada, 2016).

The NHS, which comprises six sites, is the largest multisite hospital amalgamation in Ontario, providing healthcare services to the entire Niagara Region. Approximately 26,000 patients are admitted to NHS hospitals each year, where they have access to a complete range of

health programs and services (see Table Supl.1). Data for this study comprised CDI cases during the study period from all NHS sites.

Participants

Purposive sampling of the Infection Prevention and Control (IPAC) surveillance database identified 1052 cases of CDI in-patients admitted to all NHS hospitals between September 2011 and December 2013. Overall, 425 cases did not meet the eligibility criteria and were eliminated from further analysis. This included recurrent and relapse cases (n=170), cases that were positive in another healthcare facility and were transferred or admitted to NHS with known CDI (n=49). Colonized cases that tested positive but had no clinical sign or symptoms of a typical CDI were also excluded (n=135). Thirteen patients had incomplete records that could not be resolved after a review of electronic and hard copies of their records. In purposive sampling, a non-probable group of samples based on a desired characteristic is selected from a population. The study used this technique because of its reliance on case confirmation for participant selection. The surveillance database was an Excel spreadsheet that compiled the cases of CDI. Data were manually entered in the surveillance spreadsheet (see Table Supl.2 for sample surveillance form), after reviewing patient charts and after case confirmation by laboratory reports of the positive cases of *C. difficile* toxin (see eligibility criteria section for case identification and confirmation). The surveillance database included patient demographics, admission date, specimen collection date, classification of community-acquired or healthcare-associated, and other relevant information to allow IPAC personnel to manage and perform investigation, assessment, and follow up of each case on a daily basis and to allow IPAC personnel to implement or discharge isolation requirements. The surveillance list also provided information to detect, track, and manage CDI outbreaks at NHS sites.

Eligibility Criteria and Case Definition

Cases of CDI were detected through daily surveillance and symptoms exploration of hospitalized patients or by symptoms observation upon admission. A positive laboratory stool toxin test and clinical indications were used to finalize cases. All positive CDI cases were reviewed by an infectious diseases physician and by IPAC staff. Cases had to align with the criteria set out in NHS Policy 170 100 020 and NHS Procedure 170 100 021 (see Appendix B) and had to meet the CDI definition of HA-CDI or CA-CDI (see Table Supl. 3), as well as eligibility criteria based on laboratory findings and other significant clinical manifestations.

CDI cases were defined as patients with diarrhea, with laboratory confirmation of a positive toxin assay (A/B) for *Clostridium difficile*, and/or with visualization of pseudomembranes on sigmoidoscopy, or colonoscopy, or histological/pathological diagnosis. Pending clinical verification, CDI cases were categorized into two groups: CA-CDI or HA-CDI.

The definitions of HA-CDI and CA-CDI cases were based on the NHS policies for CDI infections derived from the provincial guidelines for management of *Clostridium difficile* infections in healthcare settings, summarized in Table Supl. 3 (Provincial Infectious Diseases Advisory Committee (PIDAC), 2011).

A CA-CDI case was a case that matched the clinical case definition for CDI and met the criteria below:

- The symptoms of CDI *were* present on admission, or symptoms onset occurred *less than* 72 hours after admission.

- No exposure to any healthcare facility had occurred within the last four weeks, or the source of infection could not be determined and the patient had not had HA-CDI in the last eight weeks.

An HA-CDI case was a case that met the clinical case definition of CDI and met one of the two criteria listed below:

- The patient did not present with CDI on admission but showed onset of symptoms >72 hours after admission.

- The infection was present at the time of admission but was related to a previous admission to the same facility within the last four weeks.

Testing for CDI

From September 2011 to April 2012, NHS sent their CDI samples for diagnostic testing to St. Joseph's Hospital in Hamilton, Ontario. They used a laboratory-developed Polymerase-Chain Reaction (PCR) method using the BD GeneOhm™ Cdiff Assay, with a sensitivity and specificity of 93.8% and 95.5% respectively. This method used specific primers and a fluorescent-labeled TaqMan probe directed at the *tcd*C gene (toxin A and B regulator), the *cdt*A (binary toxin gene), and the *rrn*B gene (16Sr DNA internal control), documented key indicators of the presence of *C. difficile*. The TaqMan-based quantitative PCR is a highly selective and highly accurate method of detecting targeted strains, testing for as low as 10^3 cells/gram of stool of the specimen. The high sensitivity and specificity increase the accuracy of detection (Hiroyuki et al., 2014). From April 2012 to December 2013, NHS sent the samples for CDI diagnostic testing to Life Labs, which used BD MAX ™ Cdiff, a Nucleic Acid Amplification Test (NAAT), with a sensitivity of 96.3% and a specificity of 92.4% (Dalpke, Hofko, Zorn, & Zimmermann, 2013).

The provincial reference laboratory performed the strain typing of the *C. difficile* isolates, using a pulsed-field gel electrophoresis (PFGE) technique, a standard National Medical Laboratory procedure. A fraction of the culture medium prepared for PFGE was also used to

extract DNA using the Bio-Rad Instagene reagent and following the manufacturer's protocol. Extracted DNA was analyzed by modified, multiple-locus, variable-number, tandem-repeat analysis (MMLVA), according to the protocol developed at Public Health Ontario's laboratory (Alfa et al., 2000). PFGE and MMLVA data were processed with the BioNumerics software (v.5, Applied Maths) to identify genetic profiles and relatedness of isolates. A standard set of 12 PFGE profiles from NML was used to classify pulsotypes; those not matching any of the 12 were assigned arbitrary letter designations. MMLVA profiles with a difference of less than 3% were considered to belong to the same strain. Whenever a specimen was canceled because of poor specimen quality, it was reported to the clinical wards, and repeat samples were sent to the laboratory for confirmation of *C. difficile* toxin.

Data Source

Surveillance data collection and data entry.

The processes of data collection and surveillance for HA-CDI and CA-CDI cases were carried out by certified and trained IPAC professionals on a daily basis as a part of their routine practice. The surveillance tool was an industry standard that was aimed to collect data elements for investigation of CDI cases (see Table Supl.2). Many evidence-based resources were used to develop the CDI surveillance tool (and the policies and procedures for CDI management and control in NHS), such as the guidelines developed by the Provincial Infectious Diseases Advisory Committee (PIDAC) in Ontario (PIDAC, 2011). Each case of CDI had a single surveillance form, and the CDI cases for each NHS hospital site were compiled in a database shared with the Decision Support department on a shared drive with restricted access. The Excel files were combined by matching cases through medical records numbers, creating one large file combining matched/aligned data from all the files in all NHS hospitals over the study period.

Data for postal codes of the CDI cases were added to the combined file for the cases

detected through surveillance. FSA (forward sortation area—using the first three digits of the

postal code) and admission diagnosis information were pulled from Meditech, the NHS database

for demographics, history taking, and data collection upon admission. The strain testing results

were accessed through public health laboratories and added to the data.

The combined file was reviewed by a member of the Decision Support department for

deficiencies in demographic information and surveillance records. In cases of missing

information, the electronic record of the patient was matched with the paper record, using name,

admission date, and a site-specific medical records number. Missing information was then

retrieved from the paper copies of the surveillance forms and medical records. For privacy and

confidentiality of patient information, a sequential number was assigned to the patients, and their

medical records numbers were eliminated from the research file. A de-identified file of complied

information was the final product. A list of the final variables used for data analysis is presented

in Table Sup.4.

Use of administrative data.

Chapters Four and Five use administrative data to investigate the epidemiological

patterns of CA-CDI in the Niagara Region. Administrative data are defined as secondary data,

because they were collected initially by individuals other than the researcher and served another

purpose (Mertens, 2010). Secondary data, such as quality improvement and organizational record

databases, infection prevention and control surveillance databases, or decision support databases

for patients' discharge chart summary, are collected for quality improvement reporting and

evaluation, managerial and organizational purposes. But they are useful for researchers as well.

Secondary data give researchers access to a large repository of information relatively quickly and

efficiently and allow them to combine several databases (Williams & Young, 1996). The risks of recall bias, social desirability bias, or acquiescence bias are reduced, as the data gathering process does not rely on self-reports or the memory of the participants (Mertens, 2010). However, as the initial purpose of collecting the administrative data used in the dissertation was not for research, unfilled data fields may expose the study to the risk of missing outcome data (Stern et al., 2009). Therefore, during analysis, complete-case analysis was conducted when missing data were noted (missing data rates are listed in Chapter Four, Table 4.3).

Structure of Variables

Patient demographics, co-morbidities, exposure to certain medications (antimicrobials, corticosteroids and proton pump inhibitors), strain testing of *C. difficile* isolates, infection date (laboratory test date), and community location (based on the first three digits of the patient's postal code) were variables of interest based on the literature search described in detail in Chapter Three.

Many studies conclude that exposure to antimicrobials and disturbance of intestinal flora are among the main factors that lead to patients' development of CA-CDI. However, some studies challenge this statement, arguing that antimicrobial exposure is not always a contributing factor. Nonetheless, the research must look for these as contributing factors. Similarly, for proton pump inhibitors (PPIs) and corticosteroids, despite contradictory reports on the contributing effects of these medications to an increased risk of CA-CDI, research must still connect exposure with the risk of CA-CDI acquisition. Association with gastrointestinal disorders has also been reported in some studies (see Chapter Four). Accordingly, the dissertation looks for the patterns of antimicrobial, PPI, steroids, and history of GI disorders, comparing the findings to those reported in other studies and/or findings on HA-CDI in NHS hospitals (see Table Supl.5).

The dissertation's comparative evaluation of CA-CDI and HA-CDI patients queried possible differences in the distribution pattern of the disease between the two categories of CDI. It finds that HA-CDI often occurs in the elderly, while the majority of CA-CDI studies report a higher prevalence in younger individuals (aged 50 to 81) and in women (ranging from 11% to 77% ((Kutty et al., 2010).

The dissertation's evaluation of the strain variation between CA-CDI and HA-CDI samples (especially outbreak cases sent for strain testing) spoke to the genetic relatedness of the two categories and determined whether CA-CDI is genetically divergent from HA-CDI. In other words, did the community cases cause the hospital cases? Other studies have reported the presence of unique and different strains, pointing to the possibility of reservoirs in the community (Dumyati et al., 2012).

Studies examining the seasonal variations in HA-CDI often report an increase in winter and spring months, a pattern attributed to the increased antibiotic use during the flu/pneumonia season and winter months. However, studies examining seasonality in CA-CDI mostly find no consistent patterns. This dissertation looked into seasonality, temporality, and spatial distribution to determine whether an increase in the community cases could lead to an increased risk of HA-CDI in hospitals. It evaluated the temporal patterns of each category and assessed pattern dependencies.

Spatial analysis of CA-CDI cases was used in one previous study, as noted in the scoping review in Chapter Three; this study found an association between CA-CDI and animal farms and animal production sites (Anderson et al., 2017). Unusual spatial concentrations of diseases in the community could be attributed to underlying risk factors that may potentially increase infections in certain neighbourhoods.

Overall, the dissertation's selection of variables and their evaluation were determined by the fact that, to date, few Canadian studies have explored the epidemiological patterns of CA-CDI in hospitals and in communities. Table Supl. 5 lists the variables analyzed in this research; it gives the rationale for their selection and some of the main references.

Statistical Analysis

Significant testing and descriptive analysis.

Differences between the median age and gender of HA-CDI and CA-CDI cases were compared using the Mann-Whitney U test for independent samples and the Pearson Chi-Square. For significant testing of binary outcome data, the Mann-Whitney U test is recommended. To determine the significance of the variations of the categorical variables, the Chi-Square test for identifying differences in covariate properties is applicable. Descriptive and inferential analyses used the SPSS version 21 (IBM Corp., Armonk, NY).

Spatial cluster analysis.

Amongst the three main epidemiologic variables—time, person and place—the latter is often the more challenging to explore and visualize (Choi, 2013). Environmental influences on the health of individuals could be a random or non-random experience. However, technological advances offer researchers new opportunities to compare these phenomena and quantify the variations in geographical patterns, allowing them to make projections for managing, planning, and even preventing the need for public health interventions (Jacques, 2008). Spatial clustering has been defined as "a geographically bounded group of occurrences of sufficient size and concentration to be unlikely to have occurred by chance"(Aldstadt, 2009). Exploratory spatial data analysis identifies patterns through visualization and geo-statistics and recognizes the location and magnitude of the statistically significant descriptors. My use of this type of analysis

in the dissertation allowed me to test a hypothesis that attempts to interpret geographical patterns in epidemiological studies.

Application of scan statistics.

Descriptive maps have long been used for geographical investigations of epidemiological studies. Most maps show geographical patterns and areas of high or low outcome concentration that are visually apparent to the observer, regardless of the significance or randomness of the detected clusters. Therefore, complementing geographical distribution maps with spatial randomness statistical tests indicates whether the clustering is an act of chance or the result of an underlying risk factor. Some global clustering tests, such as Mantel-Bailar's Test, evaluate the overall presence of clusters within an area of interest, without an indicative location of the cluster(s). Other global clustering tests, such as Cuzick-Edwards' K-nearest Neighbor Test, are more powerful if used in rural structures because of the designations used to define the analysis. In contrast, statistical processes, such as Tango's Maximized Excess Event Test, are statistically more powerful when used in an urban setting.

The application of spatial scan statistics allows researchers to measure the significance and the location of a general or focused cluster (Kulldorff & Nagarwalla, 1995) that subsequently leads to clues about the disease under investigation. Spatial scan statistics employ a likelihood ratio test to assess clusters of various sizes and adjust for multiple testing (Heffernan et al., 2004). The Monte Carlo simulation of 999 randomization of the dataset ranks the likelihood of the cluster's significance (Kulldorff, 1997). Focused clusters are detected based on multiple circular (or other shaped) windows of variable sizes, scanning the given geographical area for the variable of interest. The null hypothesis of equivalent risk inside and outside the circular scan windows is rejected when the number of cases inside the cluster zone is more than

the expected number of cases, independent of the specific geographical locations and administrative boundaries. Appendix C provides the statistical processes used to calculate the likelihood test and the number of expected cases.

1 – Purely spatial Scan Statistics for investigation of non-random clusters.

Using a circular scan window centred on each possible point throughout the study area, this one-dimensional spatial Scan Statistic process compares the disease risk observed inside the window (cluster) with the risk outside the window (cluster). The most likely cluster has the highest likelihood ratio, with p values of 0.005 or less.

2 – Spatio-temporal Scan Statistics for investigation of non-random clusters.

The space-time Scan Statistics identify clusters throughout the study region by scanning for cases using a cylindrical window, where the base of the cylinder is centred on one of the multiple centroids within the study area. The height of the cylinder defines the time interval as a whole, for the entire study period. The cylindrical window then scans the geographic base while changing the radius of the base as well as scanning for possible time intervals (changing the height of the cylinder).

3 – Space-time permutation Scan Statistics for investigating of independent clusters.

This model identifies the increased risk of a disease or differences in geographical distribution at different times by adjusting for time and space. Therefore, the number of observed cases in a cluster is compared to the expected number of cases if all cases were independent of each other in terms of their temporal and spatial locations.

For computation purposes, a Poisson distribution model was used while operating the SatScan software. The first three digits of individuals' postal codes were used to identify the locations or smaller geographical units within the overall study area. The time precision was set

by the day. Temporal and geographical checks were in place to ensure that all cases, controls, and populations were within the specified temporal period and geographical area of the study. The maximum temporal cluster size was set for 50% of the study time and the maximum spatial cluster size was set for 50% of the study's at-risk population.

Temporal Cluster Analysis

Statistical Process Control charts to investigate out-of-control abnormalities and outbreaks.

As suggested in Benneyan (1998), the Statistical Process Control (SPC) approach was used to provide information on unusual variations and exceptional changes in CDI infection rates between months and seasons (Benneyan, 1998a). In this methodology, endemic or epidemic conditions can be identified based on the location of the plotted values and their relationship to the centre line (almost always the arithmetical mean of the plotted values) and the upper and lower control limits or the natural process limits (Benneyan, 1998b). In industry, a process is considered stable if data fall within 3 sigma limits. Therefore, deviance from 3 sigma limits identifies medium to large shifts in data. Although in an industrial environment, use of control charts with ±3 sigma has been recommended (99.73% of all plot points in a normal distribution and stable process), use of a 3-sigma control limit is questionable for healthcare (Sellick, 1993). If an incidence is plotted above or below three standard deviations of the centre line, an erroneous event or phenomenon has caused the variation. Therefore, for epidemiological investigation of infections, more sensitive and less specific standards should be applied to increase the power and the confidence of the "out of statistical control" state of CDI (Benneyan, 1998b). For this study, the control limits were set at ±2-sigma, covering 95% of the plotted points; smaller variations in data could be identified that, in practice, are signals for thorough

epidemiological investigation (Sellick, 1993). Choosing a tighter control limit increases the rate of false positives or out of control points (type I error) to 5% for each plotted value (compared to 0.27%); this can also be clarified by epidemiological investigation.

Rare events of disease clustering in a given time period are best explained by the Poisson process (Benneyan, 1998b). Therefore, this analysis used *u* control charts for discrete data (numerator) with a varying size of monthly patient days (denominator) to monitor the total number of incidents per month (Benneyan, 1998a; Sellick, 1993). Control limits were set at $\pm$ 2-sigma to allow the detection of out-of-range activities and outbreaks. The statistical process control charts were developed using MS Excel for Mac, Version 15.27(161010).

Temporal Scan Statistics for investigation of non-random clusters.

To further explore the temporal features of CA-CDI and HA-CDI in the Niagara Region, Scan Statistics using the Bernoulli binominal distribution were used to search for non-random temporal clusters of high CDI rates. Scan Statistics identifies and evaluates clusters of cases in a purely spatial, purely temporal, or space-time setting (Kulldorff, 2005). A Bernoulli distribution is a 0/1, case-control type of binary data. Scan Statistics uses multiple different window sizes to gradually scan across time and/or space and documents the number of observed and expected observations inside the windows. The risk inside the clusters compared to outside the clusters, measuring for irregularity of the potential cluster, is based on a likelihood ratio (Lawson, Banerjee, Haning, & Yugarte, 2016). The cluster that yields the most extreme ratio is least likely to be by chance (Lawson et al., 2016).

For computation purposes, HA-CDI cases were assigned as cases and CA-CDI cases as controls. A purely temporal retrospective multivariate Scan Statistics was conducted, scanning for clusters with high rates using the Bernoulli model. The minimum temporal precision was set

at one month, and the maximum temporal cluster size was set at 50% of the study period. A maximum temporal cluster size limits the maximum size of the population at risk within the cluster to no more than 50% of the population at risk in the study (Elliott & Wartenberg, 2004; Kulldorff & Nagarwalla, 1995).

Random replication of the dataset using computer simulation is a feature of Scan Statistics that adds to the power of the test. The number of replications under the null hypothesis for the standard Monte Carlo test was set at 999 to ensure statistical power for the Scan Statistic and the *p*-value calculation (Kulldorff, 2005). Under this setting, a high likelihood ratio rejects the null hypothesis and favours the clustering inside the scanning window(s) (Kulldorff, 2005). In this step of the temporal study, the null hypothesis assumes that the temporal clusters of hospitalized CA-CDI and HA-CDI occur at the same time. The alternative hypothesis suggests the presence of clusters in hospitalized CA-CDI that do not show up at the same time as those in HA-CDI.

Test of seasonality.

To find out whether seasonal properties have a role in the increase of CDI in certain periods, the time series data for both groups, CA-CDI and HA- CDI, were adjusted for a seasonal component (Carlberg, 2015). Given the small number of seasonal points, an analytical approach was used rather than a graphical depiction of the seasonal influences (more common but mainly used for longer study periods). The additive seasonal indexes were calculated by subtracting the grand mean from each seasonal average. Subtracting each seasonal index from the associated seasonal measurement provided the seasonal adjusted values for each season (Carlberg, 2015).

Ethical Considerations

The data used for the statistical analysis for this research were stored in administrative databases in the NHS Decision Support Department and the Infection Prevention and Control Department. The de-identified list of CDI patients was obtained from the central Decision Support department of the NHS only after obtaining REB approval at York University and NHS.

Data were de-identified by the Decision Support staff to protect the private and personal information of the CDI cases in this study. All files were password protected, and the passwords were emailed to the researcher in a separate email.

Use of administrative archival clinical data for quality improvement purposes is very common within the hospital environment. However, for this research and to follow the recommendations of the Canadian Institutes of Health Research (Canadian Institutes of Health Research, 2010) policy for "Ethical Conduct for Research Involving Humans," relevant ethical approval was obtained from York University's Research Ethics Board (see Appendix D) and the Niagara Health Service's Research Ethics Board (see Appendix E).

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Tables

Table Supl.1 – NHS hospital sites and the programs and services offered in each site.

NHS Hospital Site	Programs and services
• Douglas Memorial, in Fort Erie	• Complex Care • Diagnostic Imaging • Laboratory • Ontario Breast Screening Clinic • Outpatient Clinics • Outpatient Mental Health Services • Urgent Care Services
• Greater Niagara General, in Niagara Falls	• Cardiology • Complex Care • Critical Care Services • Diagnostic Imaging • Emergency Department • Laboratory • Medicine • Off-site Niagara Falls dialysis centre • Ontario Breast Screening Clinic • Outpatient Clinics • Outpatient Mental Health Services • Regional Geriatric Assessment • Regional Stroke Services • Surgery • Pharmacy
• Niagara-on-the-Lake	• Diagnostic Imaging • Laboratory

NHS Hospital Site	Programs and services
• Port Colborne	• Addictions Services • Complex Care • Diagnostic Imaging • Laboratory • Ontario Breast Screening Clinic • Outpatient Clinics • Urgent Care Services
• St. Catharines	• Cardiology Services • Children's Health • Critical Care Services • Diagnostic Imaging • Emergency and Urgent Care • Kidney Care Program • Laboratory • Medicine • Mental Health and Addictions • Ontario Breast Screening Clinic • Outpatient Clinics • Pharmacy • Surgery • Walker Family Cancer Centre • Women's and Babies Health
• Welland	• Ambulatory Clinics • Complex Care • Critical Care Services • Diabetes Education Centre • Diagnostic Imaging • Emergency Department • Laboratory • Long-Term Care • Medicine • Ontario Breast Screening Clinic • Ophthalmology Program • Outpatient Mental Health Services

NHS Hospital Site	Programs and services
	- Pharmacy - Satellite dialysis Centre - Surgery

Table Supl.2 – Data elements on NHS surveillance form for CDI investigation.

Surveillance data elements	Comments
Initiated IPAC personnel	
Completed IPAC Personnel	
Patient's name	
Admission diagnosis	
Admission date	
Previous admission within 4 weeks	
Surgeries	
Patient ID#	
Specimen collection date	
Lab specimen #	
CDI attribution	
Unit attributed	
Other location attributed	
Room#	
Temperature (date and result)	
Albumin (date and result)	
Creatinine (date and result)	
White blood cells (date and result)	
Onset of diarrhea	
Recent negative	
Risk factors: Age>65, previous CDI, previous surgery, previous admission, laxative use, PPI use, other GI problems	
Antibiotic history, previous and current	
Current CDI treatment: Flagyl/Vancomycin	
Dialysis: Y/N	
Flag? IPAC measures on admission? Y/N	

Table Supl.3 – NHS definition for CDI, HA-CDI, and CA-CDI based on the NHS policies for CDI infections derived from the provincial guidelines for management of *Clostridium difficile* infections in healthcare settings.

<table>
<tr>
<td colspan="2" align="center">

CDI definition

- A patient with diarrhea with laboratory confirmation of a positive toxin assay (A/B) for *Clostridium difficile*, or
- Visualization of pseudomembranes on sigmoidoscopy, or
- Colonoscopy, or histological/pathological diagnosis of pseudomembranous colitis.

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Definition of HA-CDIs

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Definition of CA-CDIs

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An HA-CDI case is defined as a patient who has not had CDI in the past eight weeks but meets one of the following criteria:

- He or she does not present with CDI upon admission but shows onset of symptoms >72 hours after admission.
- The infection was present at time of admission but was related to a previous admission to the same facility within the last four weeks.

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<td>

A CA-CDI case matches the case definition for CDI and does *not* match the HA-CDI definitions: in other words:

- The symptoms of CDI *were* present upon admission, or symptom onset *was less* than 72 hours after admission.
- No exposure to any healthcare facility occurred within the last four weeks, or the source of infection cannot be determined and the patient has not had HA-CDI in the last eight weeks.

</td>
</tr>
</table>

Note. Eligibility criteria are based on the case definitions for each category (PIDAC, 2011) .

Table Supl.4 – Research file data elements for CA-CDI study in the Niagara Region.

Research data elements collected in a combined Excel file
Coding number
Gender
Age
Admission date
Specimen collection date
HA-CDI or CA-CDI
Admission within four weeks of previous admission
Admission diagnosis
Age >65
Previous CDI
Previous surgery
Laxative use
Another inflammatory GI
PPI use
Previous antibiotics use
Current antibiotics use
Postal code (FSA)
PFGE results: Toxin A, B or Binary?

Table Supl.5 – Variables of interest in study of CA-CDI in the Niagara Region: Rationale for selection and supporting references

Variable	Rationale	Reference
Antimicrobial exposure	Increased incidence as a result of imbalance of normal flora of the intestines Increased risk: OR 6.91, (95% CI) 4.17-11.44	Aronsson & Mollby et al., 1985 Bauer & Veenendaal et al., 2009 Southern & Rahmani et al., 2010 Baxter& Ray et al., 2008 Deshpande et al., 2013 Wern, Ahmed et al., 2005
Use of proton pump inhibitors (PPEs)	Increased risk due to reduced gastric acid Increased Risk: OR 2.7 (CI 95%) 1.4–5.2	Dial & Alrasadi et al., 2004 Deshpande & Pant et al., 2012
Use of laxatives or stool softeners	Positive result on CDI testing Increased risk: OR 3.26 (CI 95%) 1.51–7.02	Batajoo & Weber et al., 2015 McFarland et al.,1990
Inflammatory bowel disease	Disease flare ups may lead to colonization Increased risk: OR 4.7 (CI 95%) 1–21	Thibault et al.,1991 Gupta & Khanna, 2014
Gastrointestinal surgery	Intestinal stasis may predispose to CDI Increased risk: OR 23.2 (CI 95%) 2.1–255	Brown et al.,1990

Variable	Rationale	Reference
History of CDI	Failure of treatment due to other antibiotics Reported in up to 20% of cases	Fekety & McFarland et al. 1997 Modena & Gollamoudi et al., 2006
Demographics (age, gender)	Looking for new and different patterns of disease distribution in demographics, usually higher incidence in old age and in female	Aronsson & Mollby et al., 1985, CDC, 2008 Lessa & Mu et al., 2014 Pépin & Valiquette et al., 2005 Barbut & Petit, 2001 Southern &Rahmani et al., 2005 Brown et al.,1990
Genetic strain variations	To confirm or rule out the genetic relatedness between CA-CDI and HA-CDI cases.	Gupta et al., 2014
Temporal or seasonal variations	To search for temporal and seasonal patterns. Some studies on HA-CDI concluded association with flu season as a result of antimicrobial use	Gilca et al., 2012 Pépin et al., 2005
Spatial variations	To search for unusual and new distribution patterns	Anderson et al., 2017

Figures
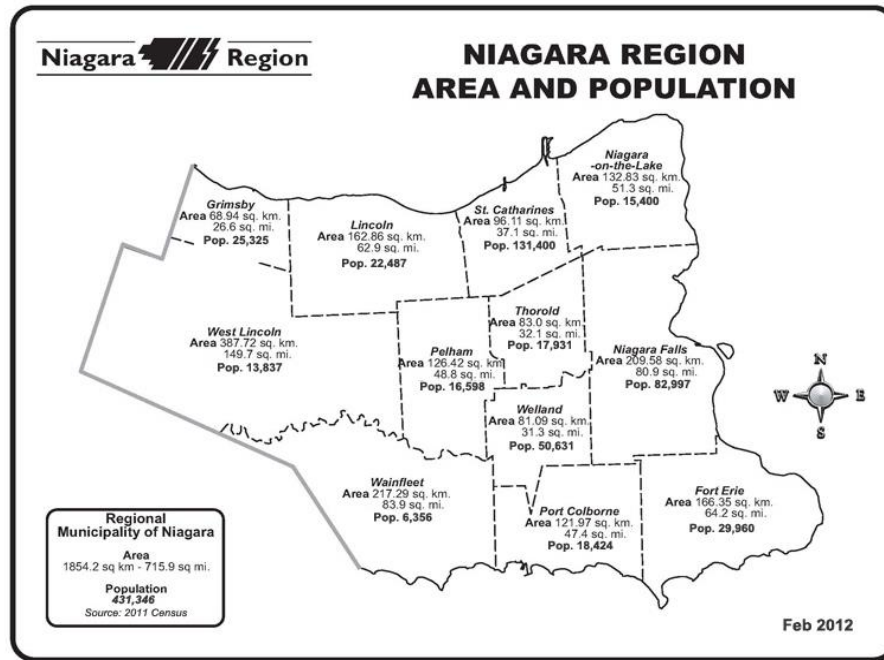
Figure Supl.1 – An illustration of the Niagara Region and its population, based on data from the 2011 Census (Statistics Canada, 2011).

Appendices

Appendix B – Niagara Health System Policy and Procedure Documents.

a) NHS Policy: Document Number 170-100-020.

NIAGARA HEALTH SYSTEM SYSTÈME DE SANTÉ DE NIAGARA	**TITLE:** *Clostridium difficile* Infection (CDI)	**POLICY**
DOCUMENT NUMBER: 170-100-020	PAGE 1 OF 2	
SECTION: Infection Prevention and Control SUBSECTION: Nosocomial Transmissions	EFFECTIVE DATE: (DD/MM/YY)	25/06/08
APPROVED BY: Chair, Infection Control Committee Interim Chair, Medical Advisory Committee VP Clinical Services	REVISION DATE: (DD/MM/YY)	07/04/11

1.0 Purpose
To identify, prevent and control the spread of *Clostridium difficile* Infection (CDI).

2.0 Scope
Applies to all programs and services at all sites of the Niagara Health System (NHS).

3.0 Definitions

3.1 **Diarrhea:** Loose/watery bowel movements (conforms to the shape of the container) the bowel movements are unusual or different for the patient; and there is no other recognized etiology for the diarrhea (for example, laxative use).

3.2 *Clostridium difficile* Infection (CDI) case definition:
Diarrhea (as defined above)
WITH
Laboratory confirmation of a positive toxin assay (A/B) for *Clostridium difficile,*
OR
Visualization of pseudomembranes on sigmoidoscopy or colonoscopy;
OR
Histological/pathological diagnosis of pseudomembranous colitis.

3.3 New nosocomial case: A case that meets the case definition for CDI; AND CDI was not present on admission (i.e. onset of symptoms >72 hours after admission); OR The infection was present at time of admission but was related to a previous admission to the same facility within the last 4 weeks; AND The case has not had CDI in the past 8 weeks.

3.4 Nosocomial case attributed to other Health Care Facilities (HAI-Other) :
a) A case that meets the case definition for CDI; AND CDI was present on admission; OR
b) The case had symptoms onset <72 hours after admission: AND There was exposure to any health care facility within the last 4 weeks; AND The case has not had CDI in the past 8 weeks.

3.5 Indeterminate case: The infection was present on admission or <72 hours after admission and there was no admission to the same facility within the last 4 weeks AND the case has not had CDI in the past 8 weeks.

3.6　　Relapse: The patient has had a recurrence within 8 weeks of the completion of treatment for previous CDI.

3.7　　Cluster: A grouping of cases within a specific time frame and geographic location suggesting a possible association between the cases with respect to transmission.

4.0　　Policy

4.1　　This document provides a guideline for the control of a CDI case within the NHS by early identification, appropriate isolation and timely communication following best practices for the management of CDI.

5.0　　Related Documents

Appendix – NHS Sample Fact Sheets for Patients/Visitors (English Version) – 170-100-021C
Appendix – NHS Sample Fact Sheets for Patients/Visitors (French Version) – 170-100-021D
Appendix – CDI – NHS CDI Patient Data Collection – 170-100-021B
Appendix – Educational Handout for Healthcare Workers – 170-100-021F
Appendix – Diarrhea Algorithm – 170-100-021A
Appendix – Outbreak Management Checklist – 170-100-021E
Procedure – *Clostridium difficile* Infection (CDI) – 170-100-021

6.0　　References

6.1　　Provincial Infectious Diseases Advisory Committee   Annex to Routine Practices and Additional Precautions Annex C: Testing, surveillance and management of *Clostridium difficile* in all health care settings. Available from http://www.health.gov.on.ca/english/providers/program/infectious/diseases/ic_cdiff.html

6.2　　Public Health Division: Public Health Protection and Prevention Branch, Ministry of Health and Long Term Care (December, 2009). Available from http://www.health.gov.on.ca/patient_safety/pro/cdad/pro_resource/guide_cdi_infect_control.pdf

6.3　　Fact sheet – *Clostridium difficile (C. difficile).* Public Health Agency of Canada. http://www.phac-aspc.gc.ca/id-mi/cdiff-eng.php

6.4　　McFarland, L.V., Beneda, H. W., Clarridge, J. E., Raugi, G. J. Implication of the changing face of *Clostridium difficile* disease for health care practitioners. *Am. J. Infect. Control* 2007; 35:237-53.

6.5　　Cohen, S., Gerding, D., Johnson, S., Kelly, C. Loo, V et al. Clinical practice guideline for Clostridium difficile infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infection Control and Hospital Epidemiology 2010; 31 (5): 431-455.

b) NHS Procedure: Document Number 170-100-021.

	TITLE: *Clostridium difficile* Infection (CDI)	**PROCEDURE**
NIAGARA HEALTH SYSTEM SYSTÈME DE SANTÉ DE NIAGARA		

DOCUMENT NUMBER: 170-100-021	PAGE 1 OF 6
SECTION: Infection Prevention and Control SUBSECTION: Nosocomial Transmissions	EFFECTIVE DATE: 25/06/08 (DD/MM/YY)
APPROVED BY: Chair, Infection Control Committee Chair, Medical Advisory Committee VP Clinical Services	REVISION DATE: 05/04/11 (DD/MM/YY)

1.0   Purpose

To identify, prevent and control the spread of *Clostridium difficile* Infection (CDI).

2.0   Scope

Applies to all programs and services at all sites of the Niagara Health System (NHS).

3.0   Definitions

3.1   **Diarrhea:**

Loose/watery bowel movements (conforms to the shape of the container) and the bowel movements that are unusual or different for the patient; and there is no other recognized etiology for the diarrhea (for example, laxative use).

3.2   ***Clostridium difficile* Infection (CDI) Case Definition:**

Diarrhea (as defined above)
    WITH
Laboratory confirmation of *Clostridium difficile* (e.g. by positive toxin A/B assay or PCR);
    OR
Visualization of pseudomembranes on sigmoidoscopy or colonoscopy;
    OR
Histological/pathological diagnosis of pseudomembranous colitis.

3.3   **New nosocomial case:**

A case that meets the case definition for CDI; AND The infection was not present at the time of admission (i.e. onset of symptoms >72 hours after admission); OR The infection is present at time of admission but is related to a previous admission to the same facility within the last 4 weeks; AND The case has not had CDI in the past 8 weeks.

3.4   **Nosocomial Cases Attributed to Other Health Care Facilities:**

A case that meets the case definition for CDI; AND CDI was present on admission; OR the case had symptoms onset <72 hours after admission; AND there was exposure to any health care facility (including long-term care) other than the reporting facility within the last 4 weeks; AND the case has not had CDI in the past 8 weeks.

3.5   **Indeterminate Case:**

The infection was present on admission or <72 hours after admission and there was no admission to the same facility within the last 4 weeks AND the case has not had CDI in the past 8 weeks.

3.6   **Relapse:**

The patient has had a recurrence within 8 weeks of the completion of treatment for previous CDI.

3.7 **Cluster:**
A grouping of cases within a specific time frame and geographic location suggesting a possible association between the cases with respect to transmission.

4.0 Procedure
4.1 **Testing**
a) Nursing staff will watch for the signs and symptoms of diarrhea. Follow the *C difficile* management algorithm. (See Appendix A – Diarrhea Algorithm – 170-100-021A).
b) Send stool specimen for *C. difficile* toxin assay to lab for all patients with suspected *C difficile*, except children under the age of 12 months.
c) Specimen collection: Liquid stool must be collected in a sterile specimen container. Any patient with formed or semi-formed stool should not have stools collected. Label sample and send to lab.
d) For specimens sent for *C. difficile*, a test for VRE should be considered.
e) Lab will notify Infection Control with positive lab results.
f) Do not rely on a single negative result. If the patient continues to have diarrhea, send another specimen.
Note: There is no screening test for *C diff* on patients who do not exhibit symptoms. Testing should be done for symptomatic patients only.

4.2 **Contact precautions**
a) The Nurse caring for the patient is empowered to institute additional precautions (contact precautions) at the onset of diarrhea.

4.3 **Responsibilities**
a) The Charge Nurse/Designate is responsible for notifying Infection Prevention and Control and Admitting departments of the institution of additional precautions for diarrhea/suspect *C. difficile*.
b) The Charge Nurse/Designate is responsible for notifying Environmental Services through the Resource Centre that the room should be cleaned twice daily with sporicidal agent (eg. Rescue® gel).
c) It is the responsibility of the Infection Control Practitioner to investigate all positive cases. An sample worksheet is provided in Appendix B – CDI Patient Data Collection – 170-100-021B.

4.4 *Accommodation*
a) A private room with dedicated toileting facilities is recommended (private bathroom or dedicated commode chair).
b) If not available, priority for accommodation should be cohorting CDI lab confirmed cases only under the direction of Infection Prevention and Control.
c) If the patient has recurrent CDI, consideration may be given to leaving the patient in a private room even after resolution of symptoms to minimize the risk of transmission.

4.5 **Signage**
a) A "CONTACT PRECAUTIONS" sign is placed on the door of patient's room as soon as CDI is suspected.

4.6 **Hand Hygiene and Personal Protective Equipment**
a) Refer to the procedure for Routine Practices and Additional Precautions.

4.7 **Equipment**
a) If a bedpan is used, it must be lined with a Hygie® bag. Following use, the bag must be securely tied and disposed of in patient's room.
b) Commode chairs must remain with the patient. The chair must be lined with a Hygie® bag. Following use, the bag must be securely tied and disposed of in patient's room.

Commodes must be wiped with Virox by the nurse following each use. Commodes must cleaned/disinfected by Housekeeping each time the room is cleaned using a sporicidal agent for the recommended contact time (eg. Rescue® gel, 10 minutes contact time). When precautions are discontinued, commodes and bedpans must be cleaned and disinfected as per department's protocol.

c) Ensure reusable equipment is not used for another patient until it has been cleaned and disinfected.
d) Properly discard single-use items.
e) Temperatures should not be taken rectally as rectal thermometers have been linked with spread of CDI.
f) Dedicated patient care equipment should be provided. Stethoscope, thermometer, BP cuff, wheelchair, lifts, scales, glucometers, walker, commode, flashlight, recreational equipment, basins, bedpan and other personal equipment should be cleaned and disinfected after each use and before removing equipment from patient's room. Follow manufacturer's instructions for cleaning and disinfecting the product.
g) Do not take patient's medical chart into patient's room.
h) Only washable toys (no stuffed animals) are to be used in paediatric settings, waiting rooms, etc., and must be cleaned and disinfected.

4.8 Dietary
a) Routine practices are required for dishes and cutlery. Disposable meal trays are not required.

4.9 Linen
a) Use routine practices and contact precautions when disposing linen in a laundry bag in patient's room. Remove laundry bag when ¾ full and when required and place a clean plastic laundry bag in patient's room. Ensure each new shift has a clean laundry bag available.
b) No special handling of linen is required.

4.10 Garbage
a) Follow routine practices and contact precautions.
b) Hygie bags should be disposed of in the regular garbage in the patient room and the garbage must be removed as necessary and at least once each shift..

4.11 Environmental Cleaning
a) All horizontal surfaces in the room and all items within patient's reach should be cleaned **twice daily.** Include high touch surfaces such as bedside rails, telephone, call bells, light switches, door handles, faucets, commodes, toilets, etc. Twice daily cleaning should be documented on the appropriate hospitality checklists.
b) Apply disinfection solution directly onto all cleaning cloths, fully saturate before cleaning surfaces. Change cleaning cloths and mop heads frequently. Refer to Hospitality Procedures.
c) Use sporicidal agent (eg. STBC® gel on toilets, sinks, commodes) twice daily.
d) Commode is cleaned and disinfected whenever the room/bathroom is cleaned.
e) Disposable toilet brushes should be used in the rooms of patients with CDI and should be left in the patient washroom and should be discarded when contact precautions are discontinued and the room is terminally cleaned or on discharge.
f) After patient discharge/transfer/discontinuation of isolation, terminal cleaning is recommended using hospital approved germicide. This includes all curtains taken down and sent for laundering. Discard disposable items and toilet paper. Follow Hospitality Department's terminal cleaning checklist.

4.12 Discharges/Transfers to other Institutions
a) Charge Nurse is to notify the receiving facility regarding patient status and complete transfer form. Advise transport personnel (eg. ambulance) of the need for additional

precautions when booking the transport prior to transfer. All transport personnel will follow the transport guidelines below.

b) If inpatient transfer necessary, Charge Nurses will notify receiving unit about the need for precautions.

c) Charge Nurses will notify the diagnostic department if patient is *C. difficile* positive prior to testing, procedures, or therapies. This department may schedule these patients at the end of the day for non-urgent cases. Departmental personnel are to follow additional precautions and guidelines as indicated in this protocol.

4.13 **Transport Guidelines**
a) Refer to the Patient Transportation policy and procedure. (See Policy – Patient Transportation on Routine Practices and Additional Precautions – 170-100-030 and Procedure – Patient Transportation on Routine Practices and Additional Precautions – 170-100-031).

4.14 **Other Activities (Day Pass, Physiotherapy)**
a) Patient participation in recreational activities, day pass or physiotherapy will be assessed on an individual basis in consultation with Infection Control.

4.15 **Visitors**
a) Instruct visitors regarding hand hygiene, routine practices and contact precautions. Provide Fact Sheets for patient and visitors on hand hygiene, proper donning and doffing PPE, and CDI information (See Appendix C – NHS Sample Fact Sheets for Patients/Visitors (English Version) – 170-100-021C and Appendix D – NHS Sample Fact Sheets for Patients/Visitors (French Version) – 170-100-021D).

b) Visitors must not use patient's bathroom or go into another patient's bedspace/room.

4.16 **Discontinuation of Isolation Precautions**
a) **Patient with Suspected CDI**
   i) Patients on precautions for suspected CDI may, after consultation with Infection Prevention and Control, have the precautions discontinued when two (2) negative tests have been reported or the etiology has been identified as non-infectious.
   ii) If CDI is still suspected the clinician should evaluate the patient and consider other diagnostic modalities**.**
b) **Patient with confirmed CDI**
   i) Contact precautions may be discontinued when the patient has completed treatment and has had at least 48 hours without diarrhea.
   ii) Contact precautions should only be discontinued in consultation with Infection Prevention and Control.
   iii) Retesting for *C diff* cytotoxin is not necessary to determine the end of isolation and should not be done unless symptoms recur.
   iv) Contact precautions should not be discontinued until the room has been terminally cleaned.

4.17 **Notification Thresholds**
a) The ICP must notify the Public Health Department when notification threshold has been reached.
   i) For units with $\geq$ 20 beds:
      3 cases of nosocomial CDI identified within a 7-day period
      OR
      5 cases within a 4-week period

      OR
   ii) For units with <20 beds:
      2 cases of nosocomial CDI identified within a 7-day period

OR

4 cases within a 4 week period

OR

iii) A site has baseline CDI rate for 2 months that is at or above the 80th percentile for comparator hospitals

OR

iv) A facility rate that is greater than or equal to 2 standard deviations above baseline

4.18 It is the responsibility of the Infection Control Practitioner to provide timely notification that the alert threshold has been reached so that there is heightened vigilance and enhanced precautions can be implemented to avert an outbreak. Notification must be sent to the Manager of Infection Prevention and Control, Director of Infection Prevention and Control, Medical Director of Infection Prevention and Control, clinical manager(s) of the respective unit(s), and the Environmental Services director and Health Program Director for the site.

4.19 **CDI Outbreak Thresholds**
Declaration of an outbreak may be made by either the ICP following consultation with Niagara Regional Public Health or the Medical Officer of Health, following review of the number of cases, historic levels, trends, epidemiologic investigation and control measures.

4.20 **Outbreak Management**
Institute control measures. Follow Outbreak Management Checklist. (See Appendix E – Outbreak Management Checklist – 170-100-021E).

4.21 **Education**
a) Reinforce all infection prevention and control measures for staff, including Routine Practices, Additional Precautions, hand hygiene, and environmental cleaning protocols (See Appendix F – Educational Handout for Healthcare Workers – 170-100-021F);
b) Educate visitors on infection prevention and control measures, including the proper use of appropriate personal protective equipment.
c) Health care workers must not consume food or beverages in patient care areas.
d) Antimicrobial stewardship by Pharmacy – limiting inappropriate use of antimicrobials by optimizing antimicrobial selection, dosing, route of administration and duration of therapy.

4.22 *Evaluation*
Review CDI protocol on a regular basis for improvements based on new research, data and standards. Periodic audits on environmental cleaning protocols should be carried out by both Infection Prevention/Control and Hospitality Departments.

5.0 Related Documents
Appendix – NHS Sample Fact Sheets for Patients/Visitors (English Version) – 170-100-021C
Appendix – NHS Sample Fact Sheets for Patients/Visitors (French Version) – 170-100-021D
Appendix – Outbreak Management Checklist – 170-100-021E
Appendix – Educational Handout for Healthcare Workers – 170-100-021F
Appendix – Diarrhea Algorithm – 170-100-021A
Appendix – NHS CDI Patient Data Collection – 170-100-021B
Policy – Clostridium *difficile* Infection (CDI) – 170-100-020

6.0 References
6.1 Provincial Infectious Diseases Advisory Committee Annex to Routine Practices and Additional Precautions Annex C: Testing, surveillance and management of *Clostridium difficile* in all health care settings. Available at:
http://www.health.gov.on.ca/english/providers/program/infectious/diseases/ic_cdiff.html

6.2   Public Health Division: Public Health Protection and Prevention Branch (December, 2009) Control of *Clostridium difficile* Infection (CDI) outbreaks in hospitals; A guide for hospital and health unit staff. Retrieved Feb. 11, 2010 from: http://www.health.gov.on.ca/patient_safety/pro/cdad/pro_resource/guide_cdi_infect_control.pdf

6.3   Gerding, D. N. (2004). Pseudomembranous colitis (*Clostridium difficile*). In APIC test of Infection Control and Epidemiology. 2nd edition, volume 2, chapter 75.

6.4   Conly, J. (2000). *Clostridium difficile-associated diarrhea-the new scourge of the health care facility.* Canadian Journal of Infectious Diseases, 11(1), 25-26.

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Appendix C – Statistical processes used by Sat Scan to calculate the likelihood ratio and the number of expected cases: Source for formulas a, b, c & d (Kulldorff, 2005).

a) Likelihood ratio for Poisson distribution:

$$\left[\frac{C}{E(c)}\right]^c \left[\frac{C-c}{C-E(c)}\right]^{C-c} I0$$

C: total number of cases
C: observed number of cases within the scan window
E[c]: covariate adjusted number of cases within the window under the null-hypothesis

b) Likelihood ratio for Bernoulli distribution:

$$\left[\frac{c}{n}\right]^c \left[\frac{n-c}{n}\right]^{n-c} \left[\frac{C-c}{N-n}\right]^{C-c} \left[\frac{(N-n)-(C-c)}{N-n}\right]^{(N-n)(C-c)}$$

C: total number of cases
C: observed number of cases within the scan window
N; total number of cases and controls within the scan window
N: The combined total number of cases and controls in the dataset.
Calculating the number of Expected cases:

c) Calculating the expected number of cases:

$$E = T \cdot \frac{S\,fsa}{T\,fsa} \cdot \frac{S\,baseline/Tbaseline}{S\,fsa\frac{baseline}{T}fsa\,baseline}$$

T: total population in the geographic area for the time period under investigation.
S fsa: Number of cases for the specific FSA for the given time
T fsa: Population of the FSA for the given time
S baseline: Cases during the 14-day baseline period
T baseline: Population during the 14-day baseline period
S fsa baseline: Total cases for an FSA
T fsa baseline: Total population of an FSA

d) Calculating the expected ratio:

$$\left(\frac{O_{in}}{E_{in}}\right)^{O_{in}}\left(\frac{O_{out}}{E_{out}}\right)^{O_{out}}$$

O: Number of observed cases inside or outside of the scan window.
E: Number of

Appendix D – York University Research Ethics Board approval letter.

Note: Letter is proportionally reduced in order to fit onto page.

Appendix E – Niagara Health System's Research Ethics Board approval letter.

Note: Letter is proportionally reduced in order to fit onto page.