ORIGINAL ARTICLE

Epidemiology of patients hospitalized with *Clostridium difficile* infection: A comparative analysis of community-associated and healthcare-associated *Clostridium difficile* infections

Maryam Salaripour, MSc, MPH, PhD;[1] Jennie Johnstone, MD, PhD, FRCPC;[2,3,5] Michael Gardam, MSc, MD, CM, MSc, FRCPC[1,4,5]

[1]*School of Health Policy and Management, York University, Toronto, ON*
[2]*Public Health Ontario, Toronto, ON*
[3]*St. Joseph's Health Centre, Toronto, ON*
[4]*Humber River Hospital, Toronto, ON*
[5]*Department of Medicine, University of Toronto, ON*

Corresponding author:
Maryam Salaripour, MSC, MPH, PhD, School of Health Policy and Management, York University, Room 409 HNES Building, 4700 Keele Street, Toronto, ON M3J 1P3
Email: msalaripour@hotmail.com; msalarip@yorku.ca

Alternate correspondence to:
Dr. Michael Gardam, MSc, MD, CM, MSc, FRCPC, Chief of Staff, Humber River Hospital, 1235 Wilson Avenue, Toronto, ON M3M 0B2
Email: mgardam@hrh.ca

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 that were reported to the local public health department. 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.

Acknowledgements: We would like to thank the staff of the Decision Support and Infection Prevention and Control departments at Niagara Health System.
Funding: None.
Conflicts of interest: All authors report no conflicts of interest relevant to this article.

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 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 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

TABLE 1: List of selected independent covariates, supporting rational 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≧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 Wren & Ahmed et al., 2005	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
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 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.

then retrieved from the paper copies of the surveillance forms and medical records. Ultimately, a complete-case analysis (CCA) method that is a recommended statistical approach to analyse datasets with data missing completely at random (MCAR) was used (Stern et al., 2009). A de-identified data set 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≧65, previous CDI (previous is defined as eight weeks before the onset of CDI symptoms), previous surgery (past three months), previous (8-12 weeks prior to admission) 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

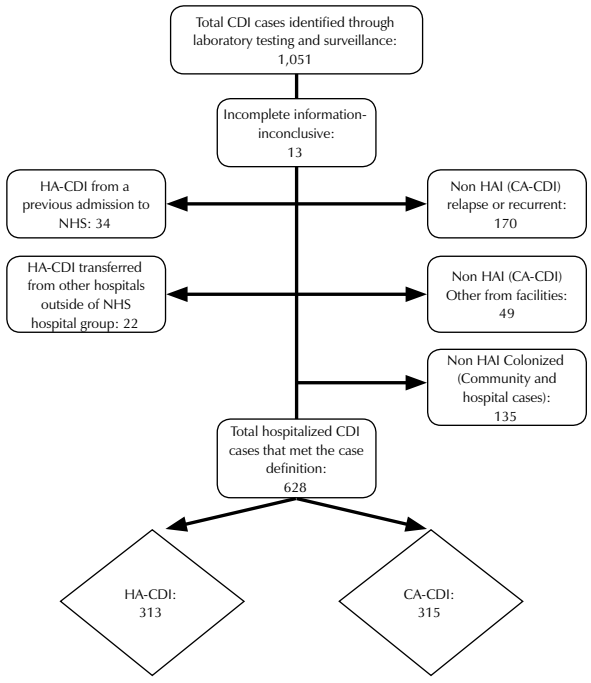
The protocol for this study was approved by York University's Research Ethics Board and the Niagara Health Service's Research Ethics Board. De-identified data were retrospectively accessed from hospital administrative databases; therefore, the requirement for informed consent was waived.

RESULTS

Surveillance and classification of cases

During the study period, 1,051 cases of CDI were identified with laboratory testing and confirmed through surveillance that did not include colonized HA-CDI patients. Overall, 423 cases were eliminated from further analysis (colonized hospital and community cases, transferred and previously positive patients), leaving 628 cases that fulfilled the criteria for case definitions for CA-CDI and HA-CDI. Breakdown of patient classification and the criteria of the eligible and ineligible cases is presented in Figure 1.

FIGURE 1: Decision process flowchart describing the case inclusion and exclusion procedure among 1,051 cases that had toxin positive C. difficile test results



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 ≧65 was 60% for CA-CDI and 79% for HA-CDI ($p<.001$). There were no differences in gender proportions between the two groups, where 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. 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 to 12 weeks prior to the onset of their CDI infection when compared to HA-CDI patients. Similarly, a smaller proportion of CA-CDI compared to HA-CDI cases used PPI and laxatives. Patients with a previous inflammatory bowel disease and those who had had a previous surgery were proportionally lower amongst patients with CA-CDI versus those with HA-CDI. Fewer CA-CDI cases had no history of CDI compared to HA-CDI cases.

The comparison of patient characteristics and the risk factors for hospitalized patients with CA-CDI and HA-CDI is presented in Table 3 in more detail. Table 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 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 record of antibiotic treatment post-infection; of these, 74 (74/251=29%) were treated with vancomycin and 159 (159/251=63%) received metronidazole.

TABLE 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			
Previous exposure to antimicrobials			
Yes	163 (52%)	259 (83%)	<.001
No	152 (48%)	54 (17%)	
Not documented	N/A	N/A	
Protein 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%)	

DISCUSSION

This retrospective case-series study compared the epidemiology of patients hospitalized with CA-CDI with that of those 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 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 harbor *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).

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, 2006; 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 with a similar environmental background in England reported that almost all cases of CA-CDI occurred in individuals younger than 65 (Fellmeth et al., 2010). Similarly, studies from rural areas in

TABLE 4: Types of antimicrobials and the 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.

the US found that only 30% of CA-CDI cases were older than 65 (CDC, 2006; 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). However, other age-related dynamics that could have attributed to a transient epidemic activity should be studied.

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 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 when compared to patients with HA-CDI; this is similar to 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 in NHS had had lower proportions of previous inflammatory bowel disease and surgery compared to HA-CDI (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. Epidemiological studies can lead to root causes of fundamental differences between the risk factors contributing to CA-CDI and HA-CDI.

Although the convenience of a sizable data set 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 (previous medical history or previous medication used) that existed in our data set, there were still a notable number of missing data elements that couldn't be retrieved from electronic databases or patient records that could introduce bias due to the missing outcome data (Wood & White, 2004; Stern et al., 2009). In addition, the use of hospital-based administrative data reduced the generalizability 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 seen in HA-CDI cases. Lack of the conventional risk factors suggests the possibility of novel community reservoirs. Comprehensive surveillance and 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.

REFERENCES

Al Saif N, Brazier JS. The distribution of *Clostridium difficile* in the environment of South Wales. *J Med Microbiol.* 1996;455(2):133-137.

Aronsson B, Mollby R, Nord CE. Antimicrobial agents and *Clostridium difficile* in acute enteric disease: Epidemiological data from Sweden: 1980 to 1982. *J Infec Dis*. 1985;151(3):476-481. doi:10.1093/infdis/151.3.476

Barbut F, Petit JC. Epidemiology of *Clostridium difficile*-associated infections. *Clin Microbiol Infect*. 2001;7(8):405-410. doi:10.1046/j.1198-743x.2001.00289.x

Batajoo S, Weber J, Fried J, Brady K, Baghban A, Schwartz R, . . . Hirsch B. Pseudo-epidemic *Clostridium difficile* and laxative use. *Open Forum Infect Dis*. 2015;2(Supplement 1). doi:10.1093/ofid/ofv133.660

Bauer MP, Veenendaal D, Verhoef L, Bloembergen P, van Dissel JT, Kuijper EJ. Clinical and microbiological characteristics of community-onset *Clostridium difficile* infection in The Netherlands. *Clin Microbiol Infect*. 2009;15(12):1087-1092. doi:http://dx.doi.org/10.1111/j.1469-0691.2009.02853.x

Baxter R, Ray G, Fireman B. Case-control study of antibiotic use and subsequent *Clostridium difficile*-associated diarrhea in hospitalized patients. *Infect Control Hosp Epidemiol*. 2008;29(1):44-50. doi:10.1086/524320

BD Diagnostics GSCI. BD GeneOhm™ Cdiff Assay. https://www.bd.com/resource.aspx?IDX=17953. 2010.

Brown E, Talbot GH, Axelrod P, Provencher M, Hoegg C. Risk factors for *Clostridium difficile* toxin-associated diarrhea. *Infect Control Hosp Epidemiol*. 1990;11(6): 283-290.

Centers for Disease Control and Prevention. Surveillance for community-associated *Clostridium difficile* – Connecticut, 2006. *MMWR Surveill Summ*. 2008;(57):340-343.

Dalpke AH, Hofko M, Zorn M, Zimmermann S. Evaluation of the fully automated BD MAX Cdiff and Xpert *C. difficile* assays for direct detection of *Clostridium difficile* in stool specimens. *J Clin Microbiol*. 2013;*51*(6): 1906-1908. doi:10.1128/JCM.00344-13

Deshpande A, Jury LA, Sitzlar B, Kundrapu S, Cadnum JL, Summers KM, . . . Donskey CJ. Outpatient healthcare settings and transmission of *Clostridium difficile*. *PLOS ONE*. 2013;8(7). doi:10.1371/journal.pone.0070175

Deshpande A, Pant C, Pasupuleti V, Rolston DDK, Jain A, Deshpande N, . . . Hernandez AV. Association between Proton Pump Inhibitor therapy and *Clostridium difficile* infection in a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10(3):225-233. doi:*http://dx.doi.org/10.1016/j.cgh.2011.09.030*

Dial S, Alrasadi K, Manoukian C, Huang A, Menzies D. Risk of *Clostridium difficile* diarrhea among hospital inpatients prescribed proton pump inhibitors: Cohort and case-control studies. *CMAJ*. 2004;171. doi:10.1503/cmaj.1040876

Dumyati G, Stevens V, Hannet GE, Thompson AD, Long C, MacCannell D, et al. Community-associated *Clostridium difficile* infections, Monroe county, New York, USA. *Emerg Infect Dis*. 2012;18(3):14.

Fekety R, McFarland LV, Surawicz CM, Greenberg RN, Elmer GW, Mulligan ME. Recurrent *Clostridium difficile* diarrhea: Characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial. *Clin Infect Dis* 1997;24(3),:324-333. doi:10.1093/clinids/24.3.324

Fellmeth G, Yarlagadda S, Lyer S. Epidemiology of community-onset *Clostridium difficile* infection in a community in the south of England. *J. Infect. Public Health*. 2010;3(3):118-123. doi:10.1016/j.jiph.2010.07.002

Freedberg DE, Abrams JA. *Clostridium difficile* infection in the community: Are proton pump inhibitors to blame? *World J Gastroenterol*. 2013;19(40),:6710-6713. doi:10.3748/wjg.v19.i40.6710. PubMed PMID: PMC3812469

Freeman J, Bauer MP, Baines SD, Corver J, Fawley WN, Goorhuis B, et al. The changing epidemiology of *Clostridium difficile* infections. *Clin Microbiol Rev*. 2010;23(3):529-549.

Gupta A, Khanna S. Community-acquired *Clostridium difficile* infection: An increasing public health threat. *Infect Drug Resist*. 2014;(7):63-72. doi:10.2147/idr.s46780

Karlström O, Fryklun B, Tullus K, Burman L. A prospective nationwide study of *Clostridium difficile*-associated diarrhea in Sweden. The Swedish *C. difficile* study group. *Clin Infect Dis*.1998;26(1):141-145.

Khanna S, Baddour LM, Huskins WC, Kammer PP, Faubion WA, Zinsmeister AR, et al. The epidemiology of *Clostridium difficile* infection in children: A population-based study. *Clin Infect Dis*. 2013;56(10):1401-1406.

Khanna S, Pardi DS. The growing incidence and severity of *Clostridium difficile* infection in inpatient and outpatient settings. *Expert Rev Gastroenterol Hepatol*. 2010;4(4):409-416. doi:10.1586/egh.10.48. PubMed PMID: WOS:000297983200009

Khanna S, Pardi DS, Aronson SL, Kammer PP, Baddour LM. Outcomes in community-acquired *Clostridium difficile* infection. *Aliment Pharmacol Ther*. 2012;35(5):613-618.

Khanna S, Pardi DS, Aronson SL, Kammer PP, Orenstein R, St. Sauver JL, et al. The epidemiology of community-acquired *Clostridium difficile* infection: A population-based study. *Am J Gastroenterol*. 2012;107(1),:89-95.

Kutty PK, Woods CW, Sena AC, Benoit SR, Naggie S, Frederick J, et al. Risk factors for and estimated incidence of community-associated *Clostridium difficile* infection – North Carolina, USA. *Emerg Infect Dis*. 2012;16(2). doi:10.3201/eid1602.090953

Leffler DA, Lamont J. Not so nosocomial anymore: The growing threat of community-acquired *Clostridium difficile*. *Am J Gastroenterol*. 2011;(107):96-98. doi:10.1038/ajg.2011.404

Lessa, FC, Mu Y, Winston LG, Dumyati GK, Farley MM, Beldavs ZG, . . . Fridkin SK. Determinants of *Clostridium difficile* infection incidence across diverse United States geographic locations. *Open Forum Infect Dis* 2014;1(2):ofu048. doi:10.1093/ofid/ofu048

Levy AR, Szabo SM, Lozano-Ortega G, Lloyd-Smith E, Leung V, Lawrence R, Romney MG. Incidence and costs of Clostridium difficile infections in Canada. *Open Forum Infect Dis*. 2015;2(3):ofv076. doi:10.1093/ofid/ofv076.

Lin C, Wade T, Hilborn E. Flooding and *Clostridium difficile* infection: A case-crossover analysis. *Int J Environ Res Public Health*. 2015;12(6):6948. doi:10.3390/ijerph120606948

Lloyd-Smith,E, Leung V, Lawrence R, et al. Incidence and costs of *Clostridium difficile* infections in Canada. *Open Forum Infect Dis*. 2015;2(3):ofv076. doi:10.1093/ofid/ofv076. PubMed PMID: PMC4503917

McFarland L, Surawicz C, Stamm W. Risk factors for *Clostridium difficile* carriage and *C. difficile*-associated diarrhea in a cohort of hospitalized patients. *J Infect Dis*. 1990;162(3):678-684.

Modena S, Gollamoudi S, Friedenberg F. Continuation of antibiotics is associated with failure of metronidazole for *Clostridium difficile*-associated diarrhea. *J Clin Gastroenterol*. 2006;40(1):49-54.

Moore D, McCabe G. *Introduction to the Practice of Statistics*. 4th ed. New York, NY: Freeman; 2003.

Norén T, Åkerlund T, Bäck E, Sjöberg L, Persson I, Alriksson I, et al. Molecular epidemiology of hospital-associated and community-acquired *Clostridium difficile* infection in a Swedish county. *J Clin Microbiol*. 2004;42(8):3635-3643. doi:10.1128/JCM.42.8.3635-3643.2004

Pagano M, Gauvreau K. *Principles of Biostatistics*. 2nd ed. Pacific Grove, CA: Duxbury; 2007.

Pépin J, Valiquette L, Cossette B. Mortality attributable to nosocomial *Clostridium difficile*-associated disease during an epidemic caused by a hypervirulent strain in Quebec. *CMAJ*. 2005;173(9):1037-1042. doi:10.1503/cmaj.050978.

Rodriguez-Palacios A, Staempfli HR, Duffield T, Weese JS. *Clostridium difficile* in retail ground meat, Canada. *Emerg Infect Dis*. 2007;13(3):485-487. doi:10.3201/eid1303.060988

Southern WN, Rahmani R, Aroniadis O, Khorshidi I, Thanjan A, Ibrahim C, Brandt LJ. Post-surgical *Clostridium difficile*-associated diarrhea. *Surgery*. 2010;148(1):24-30. doi:10.1016/j.surg.2009.11.021

Statistics Canada. Focus on geography series: Census metropolitan area of St. Catharines – Niagara 2016. https://www12.statcan.gc.ca/census-recensement/2011/as-sa/fogs-spg/Facts. 2016.

Stern JAC, White I, Carlin J, Spratt M, Royston P, Kenward M, et al. Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. *BMJ*. 2009;(338):b2393. doi:10.1136/bmj.b2393

Thibault A, Miller MA, Gaese C. Risk factors for the development of *Clostridium difficile*-associated diarrhea during a hospital outbreak. *Infect Control HospEpidemiol*. 1991;12(6):345-348.

United States Census. U.S. Department of Commerce. Monroe County, NewYork. http://www.census.gov/research/data. 2016.

Weese JS, Avery BP, Rousseau J, Reid-Smith RJ. Detection and enumeration of *Clostridium difficile* spores in retail beef and pork. *Appl Environ Microbiol*. 2009;75(15):5009-5011. doi:10.1128/AEM.00480-09

Weese, JS, Reid-Smith RJ, Avery BP, Rousseau J. Detection and characterization of *Clostridium difficile* in retail chicken. *Lett Appl Microbiol*. 2010;50(4):362-365. doi:10.1111/j.1472-765X.2010.02802.x

Wren S, Ahmed N, Jamal A, Safadi B. Preoperative oral antibiotics in colorectal surgery increase the rate of *Clostridium difficile* colitis. *Arch Surg*. 2005;140(8):752-756. doi:10.1001/archsurg.140.8.752

Wilcox MH, Mooney L, Bendall R, Settle CD, Fawley WN. A case-control study of community-associated *Clostridium difficile* infection. *J Antimicrob Chemother*. 2008;62(2):388-396. doi:10.1093/jac/dkn163

Wood AM, White IR, Thompson SG. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. *Clin Trials*. 2004;1(4):368-376. doi:10.1191/1740774504cn032oa