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Incidence of and risk factors for community-associated Clostridium difficile infection

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INCIDENCE OF AND RISK FACTORS FOR COMMUNITY-ASSOCIATED *CLOSTRIDIUM DIFFICILE* INFECTION

by

Jennifer Lee Kuntz

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the Doctor of
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Thesis Supervisor: Professor Elizabeth Chrischilles

ABSTRACT

Clostridium difficile infection (CDI) is the most common cause of hospital-acquired infectious diarrhea in the United States. Although *C. difficile* is widely-recognized as a pathogen among hospitalized populations, CDI has emerged in the community setting and may be under-diagnosed. This study sought to increase knowledge about the incidence of, risk factors for, and outcomes associated with community-associated CDI (CA-CDI).

A retrospective nested case-control study was conducted using insurance claims data from the Wellmark Data Repository for the time period between January 1, 2003 and December 31, 2007. Persons with CDI were identified and were classified as community-associated CDI and hospital-acquired CDI. During this time, 304 cases of CA-CDI and 338 cases of HA-CDI were identified. Within this population, the incidence rate for CA-CDI was 11.16 cases per 100,000 person-years, whereas the incidence rate for HA-CDI was 12.41 cases per 100,000 person-years.

Conditional logistic regression was utilized to determine the risk for CA-CDI related to pharmacologic exposures, comorbidity, demographic characteristics, and healthcare utilization. Prior to controlling for other risk factors and covariates; being over the age of 50 years, gender, history of hospitalization, number of outpatient physician visits, antimicrobial use, gastric acid suppressant use, underlying comorbidity, and diagnosis of gastrointestinal disease (including IBD, diverticular disease, GERD) were associated with the development of CA-CDI. However, after adjustment for all covariates, increased risk for CA-CDI within this population was consistently associated with antimicrobial use, being between the age of 19 and 74 years, and diagnosis of inflammatory bowel disease. Gastric acid suppressant use was a risk factor in a number of models, although this association was not consistent. Furthermore, persons who last

received antimicrobials in the previous 150 days and persons who received a greater number of different antimicrobial agents were at increased risk for CA-CDI.

Antimicrobial use was the primary risk factor for CA-CDI, although 27% of cases did not have prior exposure to antimicrobials. In fact, 17% of CA-CDI cases did not have any of the traditional risk factors for CDI (i.e., no antimicrobial or gastric acid suppressant exposure, no underlying illness, and no history of hospitalization). Furthermore, none of the CA-CDI cases underwent surgical procedures attributable to CA-CDI, although approximately 25% of CA-CDI cases were hospitalized with a diagnosis of CDI.

This research demonstrates that CDI is occurring in the community setting and in populations that were previously not considered to be at risk. In this study, the risk factors for CA-CDI were similar to those identified in hospitalized populations, although it was not uncommon for persons to develop CA-CDI without any of these risk factors. Furthermore, the characteristics of persons with CA-CDI and the outcomes in this group were different than those previously reported among hospital-acquired CDI cases. Collectively, this study provides valuable knowledge about the epidemiology of CA-CDI and serves as a foundation for future research.

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Graduate College
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CERTIFICATE OF APPROVAL

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PH.D. THESIS

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This is to certify that the Ph.D. thesis of

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To my wonderful family

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Conditional logistic regression was utilized to determine the risk for CA-CDI related to pharmacologic exposures, comorbidity, demographic characteristics, and healthcare utilization. Prior to controlling for other risk factors and covariates; being over the age of 50 years, gender, history of hospitalization, number of outpatient physician visits, antimicrobial use, gastric acid suppressant use, underlying comorbidity, and diagnosis of gastrointestinal disease (including IBD, diverticular disease, GERD) were associated with the development of CA-CDI. However, after adjustment for all covariates, increased risk for CA-CDI within this population was consistently associated with antimicrobial use, being between the age of 19 and 74 years, and diagnosis of inflammatory bowel disease. Gastric acid suppressant use was a risk factor in a number of models, although this association was not consistent. Furthermore, persons who last

received antimicrobials in the previous 150 days and persons who received a greater number of different antimicrobial agents were at increased risk for CA-CDI.

Antimicrobial use was the primary risk factor for CA-CDI, although 27% of cases did not have prior exposure to antimicrobials. In fact, 17% of CA-CDI cases did not have any of the traditional risk factors for CDI (i.e., no antimicrobial or gastric acid suppressant exposure, no underlying illness, and no history of hospitalization). Furthermore, none of the CA-CDI cases underwent surgical procedures attributable to CA-CDI, although approximately 25% of CA-CDI cases were hospitalized with a diagnosis of CDI.

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CHAPTER ONE - INTRODUCTION

Overview

The purpose of this study is to describe *Clostridium difficile* infection (CDI) within an insured population and to examine the epidemiology of community-associated *C. difficile* infection (CA-CDI). This study is one of the first population-based epidemiologic investigations of CA-CDI, thus the information gained serves as a foundation for understanding this infection in the community setting, raising awareness among healthcare providers, and providing the basis for interventions to prevent CA-CDI. This chapter provides a brief review of the epidemiology of CDI, an overview of the clinical and public health significance of CDI, and an introduction to current knowledge about the emergence of CDI in the community setting. This chapter also describes the rationale for this study and the significance of the research and its results. The chapter concludes with the specific aims and hypotheses upon which this research is based.

Clostridium difficile Infection

C. difficile is a gram-positive, spore-forming bacillus that has the potential to infect humans and cause gastrointestinal disease. Persons can be asymptomatically colonized with *C. difficile*, although when infection does occur, disease can range from acute, watery diarrhea to severe, fulminant disease potentially requiring surgical intervention or resulting in death.

C. difficile was first reported as a cause of infectious diarrhea in the late 1970s (1, 2) and has since become the most common cause of hospital-acquired infectious diarrhea in the United States. Subsequently, numerous investigations have studied CDI in the healthcare environment. Nosocomial risk factors are well-established and include prior antimicrobial use, advanced age, and multiple underlying medical conditions. Despite research efforts and the development of infection prevention and control interventions,

researchers and clinicians have reported increases in the incidence and severity of this infection in recent years.

Clinical and Public Health Significance

Hospital-acquired CDI (HA-CDI) is a significant burden on the healthcare system, with over 300,000 hospital discharges listing a primary or secondary diagnosis of *C. difficile* infection in 2005 alone (3). Furthermore, hospitalizations due to CDI in the Nationwide Inpatient Sample (NIS) increased by 109% in the decade from 1993 to 2003 (4). During this time, the colectomy rate also increased from 1.2 to 3.4 colectomies per 1000 discharges, while the case-fatality rate rose from 7.84% to 9.26%, suggesting that CDI became more severe over this time period (4). An additional study reported that, between 2000 to 2005, adult CDI hospitalizations doubled from 5.5 cases per 10,000 population to 11.2 cases per 10,000 population (5).

Increasing numbers of cases, as well as severe outcomes such as surgical intervention or death, are also contributing to increased healthcare costs. Collectively, in the United States, the cost of healthcare associated with CDI has been estimated to range from $1.1 to 3.4 billion dollars per year (6, 7). These healthcare costs are a result of treatment costs, length of stay and healthcare resource utilization, and recurrent or relapsing infection.

Emergence of *Clostridium difficile* Infection in the Community and in Low-risk Populations

Although *C. difficile* is widely-recognized as a pathogen among hospitalized populations, CDI has emerged in the community setting and may be under-diagnosed. Sporadic reports of CA-CDI date back to the late 1970s and early 1980s. However, in recent years, members of the infection prevention and medical communities have reported cases of CA-CDI more frequently than in the past.

These reports have generated interest in CA-CDI, although little research has been conducted to determine the epidemiology of CDI in the community setting. Early estimates of CA-CDI incidence rates in the U.S. ranged from 7 cases to 12 cases per 100,000 person-years. However, these reports were published in the mid-1990s before increases in CA-CDI incidence (8, 9). Recently, the Centers for Disease Control and Prevention (CDC) reported incidence rates of approximately 7 cases per 100,000 population in two separate populations. These studies used voluntary reporting in limited geographic areas over short periods of time (10, 11). In addition, few studies have evaluated the risk factors for or the outcomes of CA-CDI. CDI previously occurred among patients with previous exposures to healthcare and antimicrobials, whereas CDI is now occurring among people in the community who were thought to be at low risk. Thus, community-associated cases of *C. difficile* may have different risk factors than those previously identified in hospitalized populations. Prior research has suggested that patients with CA-CDI may be younger, have fewer comorbid conditions and less exposure to medications and healthcare settings than patients with HA-CDI (12).

Rationale for Study

The incidence of CDI is increasing within the hospital setting, and recent reports suggest that a similar phenomenon may be occurring in the general, non-hospitalized population. Although researchers have recently started to study CA-CDI, many knowledge gaps persist and the available research has substantial limitations. This study aimed to address these gaps and limitations.

The first case of community-acquired CDI in the United States was reported in 1994. However, the incidence of CDI in the general, non-hospitalized population has not been well-documented, with only four publications providing estimates. These estimates vary widely, are primarily based on populations outside of the United States, and were provided before the incidence and severity of CDI increased. Furthermore, these

estimates do not provide enough information to determine whether CA-CDI rates are currently increasing or the extent to which these rates may be increasing in the ambulatory care setting and in the community. Barriers to determining the incidence of CDI in the general, non-hospitalized population include a lack of an active national surveillance system for CDI in the United States and the lack of a widely-accepted case definition. Additionally, the perceived confinement of CDI to hospitalized patients and persons with traditional risk factors has meant that surveillance and clinical practice have primarily focused on these populations and preventive interventions have relied on hospital infrastructure. In contrast, little is known about the risk factor epidemiology of CA-CDI. Therefore, clinicians may be less likely to consider or recognize CDI in populations who may not have traditional risk factors and the public health and medical communities can do little to prevent these infections.

This study aims to increase the information about the incidence of, risk factors for, and outcomes associated with CA-CDI. This study will be one of the first to comprehensively examine the epidemiology of CA-CDI, thus the results will provide knowledge that has the potential to increase clinician, public health, and patient awareness of this infection in the community setting. In addition, the identification of CA-CDI cases may encourage clinicians to consider CDI as a diagnosis in patients presenting with diarrhea who may not have traditional risk factors. The results of this study will also provide knowledge that can be used to design clinical interventions, such as the implementation of appropriate prescribing and infection prevention and control practices, to reduce the potential for spread of CDI in the community. Finally, this study provides a foundation for additional CA-CDI research.

Currently, surveillance systems do not track CA-CDI, thus alternate data sources are vital to determining the burden of this infection and to conducting research. The Wellmark Data Repository (Data Repository) provides a unique opportunity to address the specific aims of this study. The stable, longitudinal enrollment of Iowans and South

Dakotans for up to five years allowed us to examine the incidence of community-associated CDI in this population over time. In addition, medical, institutional, and pharmacy claims data provide the opportunity to examine risk factors (i.e., medication use and comorbidity) for CA-CDI and outcomes (i.e., subsequent hospitalization) of these infections.

Research Specific Aims

Aim 1: To apply case definitions for community-associated and hospital-acquired *C. difficile* infection in an insured population over the period from 2004 to 2007. To provide incidence rate estimates for the study period and descriptive statistics for cases of community-associated and hospital-acquired *C. difficile* infection.

Hypothesis: CA-CDI and HA-CDI have occurred in this study population. Cases can be identified and characterized in this population for the time period from 2004 to 2007.

Aim 2: To identify patient-related risk factors for CA-CDI in an insured population.

Hypotheses: The acquisition of CA-CDI is associated with patient characteristics, underlying health status, and medication use. Increased risk for CA-CDI infection is associated with exposure to antimicrobial agents and gastric acid suppressants. Increased risk for CA-CDI occurs following more recent receipt of antimicrobials and following exposure to multiple antimicrobial agents. Increased risk for CA-CDI is also associated with greater underlying comorbidity, the presence of underlying gastrointestinal disease, and prior hospitalizations. In addition, although this infection usually occurs in younger persons than HA-CDI does, the risk for CA-CDI increases as age increases. Prior observations of

risk related to antimotility agents are a result of reverse causality, thus the use of these medications is not a true risk factor for CA-CDI.

Aim 3: To describe adverse health outcomes of CA-CDI and to explore potential risk factors for these outcomes in persons with CA-CDI.

Hypotheses: CA-CDI causes negative health outcomes such as surgical intervention and subsequent hospitalization. These outcomes are related to older age, comorbidity, and the use of antimotility agents following diagnosis.

CHAPTER TWO - REVIEW OF THE SCIENTIFIC LITERATURE

Overview

This chapter serves as a comprehensive review of the epidemiology of *Clostridium difficile*. The chapter begins with an introduction to *C. difficile* including its history and clinical features of infection, a discussion of existing research, and an overview of the clinical and public health significance of this infection. This chapter also examines the emergence of CDI in populations previously considered low-risk and discusses what is currently known about the epidemiology of CA-CDI. Finally, this chapter presents gaps in knowledge and introduces how this study will address these gaps.

Clostridium difficile

C. difficile is an anaerobic, gram-positive spore-forming bacillus. This bacterium has the potential to produce a spectrum of clinical illness, ranging from asymptomatic colonization to pseudomembranous colitis with severe diarrhea (3).

History of *Clostridium difficile*

C. difficile was first identified in 1935 (13, 14). At that time, *C. difficile* was found to be a part of the normal bacterial colonic flora in newborns and was subsequently shown to produce a toxin that was lethal in mice, although it was not linked to clinical disease in humans (14). In addition, clinicians had observed pseudomembranous changes in the intestinal tract, which are characterized as inflammation of the colon and white or yellow plaques consisting of white blood cells and inflammatory debris. Subsequently called pseudomembranous colitis (PMC), these findings were generally considered to be a complication of colonic, pelvic, or gastric surgeries (14) . Following the introduction of antimicrobials in the 1950s, most felt that pseudomembrane formation and antibiotic use were associated, although most deemed *Staphylococcus aureus* or *Candida albicans* as

the causative organisms. Forty years later, in 1974, Tedesco et al. published a report of high rates of PMC among patients at Barnes Hospital who were receiving clindamycin (14, 15). Stool cultures of these patients were negative for *S. aureus*, suggesting that this 'clindamycin-associated colitis' might be related to other pathogens. Further investigation revealed that *C. difficile* toxin was present within the Barnes Hospital population and in other available stool specimens from patients with diarrheal disease of unknown etiology. A few years later, Bartlett et al. proved that colitis induced by clindamycin in hamsters was indeed caused by *C. difficile*, while Larson et al. showed that *C. difficile* cytotoxin was present in the stools of patients with histologically-confirmed pseudomembranous colitis (1, 2). Since the late 1970s, *C. difficile* has become the most common cause of hospital-acquired infectious diarrhea and has been recognized as a significant cause of morbidity and mortality.

Pathogenesis of *Clostridium difficile* Infection

One to three percent of healthy adults have *C. difficile* as a normal component of their colonic flora, although carriage rates of 15-25% have been reported in persons with recent healthcare exposure (16-19). In contrast, the asymptomatic carriage rate in healthy newborn infants up to 12-18 months of age is 60-70%; this carrier state generally ends between 18 and 24 months of age when adult microflora develops (20-22).

C. difficile spores are transmitted from person to person via the fecal-oral route. Individual persons acquire this bacterium by ingesting either the vegetative form of *C. difficile* or *C. difficile* spores (i.e., the non-vegetative form). The vegetative form of *C. difficile* is killed at normal gastric pH (defined as a pH < 4.0), whereas *C. difficile* spores may survive exposure to acid in the stomach (23). Spores that do pass through the stomach germinate to their vegetative form in the small intestine. Indigenous colonic flora is the first line of defense against colonization by pathogens such as *C. difficile*. This "colonization resistance" can be disrupted by antimicrobial drugs, a few other

medications (i.e., chemotherapy drugs), illness, or surgical procedures. This disruption allows *C. difficile* to colonize the intestinal tract, reproduce, and cause clinical disease (24).

The virulence of the infecting strain and the host's immune response determine whether a person develops clinical disease and also determines the severity of disease. *C. difficile* virulence factors include toxin production, sporulation, surface layer proteins and adherence. The primary virulence factor of *C. difficile* is its ability to produce and release two toxins: Toxin A and Toxin B. Both toxins are cytotoxic and both stimulate production of tumor necrosis factor and pro-inflammatory interleukins that collectively result in inflammation and increased vascular permeability in the colon, the release and accumulation of neutrophils, and pseudomembrane formation (25). The resulting clinical disease is characterized by colitis and watery diarrhea, with the potential for fever, cramping and dehydration, and leukocytosis. Investigators have believed that the toxins work in tandem with each other, although recent research using hamster models suggested that Toxin A may play a more critical role in the pathogenesis of *C. difficile* diarrheal disease than Toxin B, because Toxin A has been shown to be more closely associated with tissue damage and fluid accumulation (26, 27). These models also suggest that Toxin B may contribute to disease only after Toxin A has damaged the gastrointestinal wall. However, researchers have also observed that either one of the two toxins alone can cause disease (26, 28, 29).

Some *C. difficile* strains do not produce toxins and do not cause disease, although many *C. difficile* strains are toxigenic and can cause disease. These toxigenic strains most often produce both Toxin A and Toxin B, although 2-5% produce only Toxin B. Some strains also release a binary toxin (also known as CDT) that is unrelated to either Toxin A or Toxin B. Binary toxin alone does not appear to cause disease; although one study found that patients infected with strains producing binary toxin reported more abdominal

pain and longer duration of diarrhea (30). Further research is needed to determine the effect of binary toxin on human disease.

The rate of *C. difficile* sporulation is an important virulence factor. Some *C. difficile* strains, including the recent BI/NAP1 'epidemic' strain, produce more spores than others (31). This 'hyper-sporulation', in addition to the ability of spores to survive in the environment, propagates the spread of *C. difficile* from person-to-person. Preliminary investigations have suggested that surface layer proteins also contribute to the virulence of *C. difficile*. These proteins allow *C. difficile* to adhere to the gut mucosa and they can induce an immune response in hosts. Different strains of *C. difficile* exhibit different proteins; therefore, differences in these proteins may alter a particular strain's ability to adhere to intestinal epithelial cells (32-35).

Virulence of the infecting strain is being recognized as an increasingly important factor in the development and severity of *C. difficile* infection. Since 2000, a new highly virulent strain has caused outbreaks in healthcare facilities and has spread across the United States, Canada, and Europe. Mortality rates in outbreaks caused by this strain have been 3-times higher than in outbreaks caused by less virulent strains (36-38). Although the strain was initially isolated in the 1980s and named BI, it is currently referred to in North America as North American Pulsed Field type 1 (NAP1) and PCR ribotype 027 (i.e., BI/NAP1/027) or the BI/NAP1 strain. The BI/NAP1 strain is characterized by higher levels of toxin production, fluoroquinolone resistance, and the production of binary toxin. A deletion mutation in a toxin-inhibitory gene allows this strain to produce 10 times more toxin than produced by other strains, which results in increased colonic tissue injury and inflammation (38, 39). Because this strain is resistant to fluoroquinolone drugs, it flourishes in healthcare facilities where fluoroquinolone use is common. This strain also produces binary toxin, which has enterotoxic activity, although its role in disease causation is currently unknown (40, 41).

Finally, host immune response influences the clinical expression of *C. difficile* infection. Human immune response to *C. difficile* seems to develop in infancy; infants who carry *C. difficile* develop antibodies to Toxin A and to Toxin B. In adults, high titers of serum immunoglobulin G (IgG) against Toxin A promote the development of an asymptomatic carrier state rather than infection (42). When infection does occur, persons with high antibody concentrations tend to have shorter durations of illness and less risk of recurrence than persons who lack these antibodies. In fact, individuals without prompt development of these antibodies to Toxin A are more likely to experience more severe symptoms and have an increased risk for recurrence of CDI (43, 44).

Clinical Presentation of *Clostridium difficile* Infection

The clinical presentation of CDI ranges from asymptomatic colonization to pseudomembranous colitis with severe diarrhea (3). Mild *C. difficile* disease typically presents as acute watery diarrhea, occurring up to but most often less than 10 bowel movements per day. These patients usually do not have systemic symptoms, although colonic inflammation can typically be identified by endoscopy or computed tomography (CT) scan. Patients with severe cases of CDI can present with watery diarrhea, occurring up to 15-20 times per day. Severe disease is typically accompanied with lower abdominal pain and cramping, fevers, and marked increases in white blood cell counts. Fulminant *C. difficile* colitis (i.e., sudden and severe colitis) occurs in approximately 3-8% of cases (45-47). Patients with fulminant disease may experience systemic complications such as nausea, vomiting, dehydration, lethargy, or tachycardia (24, 48). Hospitalized patients at increased risk for fulminant colitis include those with leukocytosis, recent prior surgical therapy, a history of inflammatory bowel disease (IBD), immunosuppression, or history of successfully treated CDI (49, 50) .

The most severe cases of CDI may progress to toxic megacolon or paralytic ileus. These conditions may prevent passage of stool; therefore, if clinicians are highly

suspicious of CDI, they must recognize that patients with severe disease may present without diarrhea. Toxic megacolon is diagnosed based on the findings of a dilated colon, accompanied by signs and symptoms of severe toxicity (i.e., fever, chills, dehydration, high white count) (51). Less commonly, cases can proceed to colonic perforation or death. Individuals with colonic perforation may present with signs such as abdominal rigidity, involuntary guarding, rebound tenderness, and reduced bowel sounds (51).

Diagnosis of *Clostridium difficile* Infection

Clinicians diagnose CDI by recognizing clinical symptoms and confirming the diagnosis with microbiological methods. Clinicians should consider CDI in persons with prolonged periods of watery diarrhea, especially in patients who have received antimicrobial therapy. In addition, only watery or loose stools should be tested for *C. difficile* because the rate of asymptomatic colonization is relatively high; therefore, testing in persons who do not have diarrheal symptoms may identify patients who are colonized but not infected (52).

Diagnosis of CDI is generally based on the detection of Toxins A and/or B in stool filtrates. Routine laboratory tests for CDI diagnosis include a cytotoxin assay for Toxin B, a rapid enzyme immunoassay (EIA), a latex agglutination test to detect bacterial antigen, and anaerobic stool culture. Of the potential diagnostic methods, the *C. difficile* cytotoxin assay is considered the “gold standard” (53). This assay detects the cell cytotoxicity of Toxin B in fecal specimens, although it also has the capacity to detect Toxin A if specific methods are used. Following identification of *C. difficile* toxin, *C. difficile* is confirmed as the cause of infection by the neutralization of the cytotoxic effect by antitoxin antibodies. The cytotoxicity assay has a sensitivity and specificity of 98% and 99%, respectively, as compared with diagnosis based on clinical and laboratory criteria (54). Despite its advantages, the cytotoxin assay has a relatively long turnaround time due to the technical demands of the lab procedures.

Rapid enzyme immunoassays involve the immunological detection of *C. difficile* toxins in stool, and a number of commercial toxin detection kits are available. These kits are used in routine laboratory diagnosis, have sensitivities ranging from 80% to 90%, and detect Toxin A, Toxin B, or both toxins. The kits have unacceptably low positive predictive values (PPV), as low as 50% in some cases, despite negative predictive values greater than 95% (55). Low positive predictive value presents a problem in settings where the prevalence of disease is low such as in the community. Since positive predictive value is influenced by prevalence of disease, PPV will be lower and false-positive results will be more likely in low-prevalence settings than in high-prevalence settings. In this case, false-positive results would result in unnecessary treatment for CDI. Additionally, most laboratories currently use kits that test only for Toxin A, which means that they do not detect strains which produce Toxin B but do not produce Toxin A. This practice is beginning to change as manufacturers are increasing the availability of kits which test for both toxins.

Latex agglutination testing can detect the presence of a common clostridial protein, glutamate hydrogenase, in stool samples. This test is rapid although its sensitivity and specificity are not adequate for reliably diagnosing CDI (56). Additionally, molecular methods that detect genes coding for Toxin B are being developed as a detection method that could provide results in a rapid and sensitive manner. However, these methods could identify strains that do not produce toxin, and, hence, are carried asymptomatically.

Anaerobic stool culture is the most sensitive test for *C. difficile,* although the stool culture has low specificity primarily related to the high prevalence of asymptomatic carriage, especially among hospitalized patients. To counteract this problem, stool culture can be supplemented by cytotoxic assay testing to detect *C. difficile* toxins in the stool, as opposed to the stool culture which simply detecting *C. difficile* strains that have the capacity to produce toxin. In practice, stool culture is seldom used for diagnosis because

results are not available for 24-48 hours. However, cultures must be done if molecular typing of *C. difficile* isolates is necessary (57).

Abdominal imaging, such as CT scans, may be utilized to detect the presence of mucosal edema, although these changes are not specific to CDI. Direct visualization of the colonic mucosa with sigmoidoscopy or colonoscopy allows clinicians to identify pseudomembranes which appear as white or yellow plaques which are loosely-adherent to the mucosal surface. These pseudomembranes are made of immune cells, cellular debris, and mucin (58). Clinicians must be aware that the absence of pseudomembranes does not necessarily exclude CDI as a diagnosis; therefore, further diagnostic testing should be considered if CDI is suspected. In addition, endoscopy may be contra-indicated in patients who have fulminant colitis, since the procedure increases risk for colonic perforation.

Treatment of *Clostridium difficile* Infection

A number of effective treatment options for CDI exist, although research is ongoing to increase these options, especially for the most severe cases of CDI. Antimicrobial treatment is typically required for initial CDI episodes; however, clinicians must choose the initial treatment regimen based on disease severity and patient characteristics. Mild infection in younger patients may subside following discontinuation of the offending antimicrobial therapy and supportive care such as the provision of fluids may be effective (15, 24). Moderate to severe infections and infections occurring in older patients or those with comorbid conditions must be treated with antimicrobials. The most severe infections that do not respond to antimicrobial therapy must be treated with surgical interventions, although additional non-surgical treatments are currently being developed and tested for patients with severe CDI.

The current treatment guidelines for an initial case of *C. difficile* infection include the discontinuation of the inciting antimicrobial agents and treatment with either

metronidazole or oral vancomycin for 10 to 14 days (59, 60). Oral vancomycin is the only agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of CDI, although metronidazole is usually prescribed as initial treatment (59). In clinical practice, oral vancomycin therapy has typically been reserved for treatment of pregnant women and for treatment of more severe or recurrent CDI, although clinicians and researchers are debating whether metronidazole or vancomycin should be used initially. A review of controlled trials of CDI therapy conducted prior to 2000 found failure rates for metronidazole and oral vancomycin therapy of 2.5% and 3.5%, respectively (61). Since these trials were conducted, the epidemic strain of *C. difficile* was identified and investigators have observed failure rates as high as 18.2% for metronidazole therapy (62-64). Pepin et al. noted that, after adjustment for risk factors, patients initially given vancomycin were 79% less likely to progress to severe disease than patients initially treated with metronidazole (OR: 0.2; 95% CI: 0.06,0.8) (65). Zar et al. conducted a prospective, randomized controlled trial and found that cure rates for patients with mild infection were 98% for vancomycin and 90% for metronidazole. In contrast, vancomycin was significantly more effective than metronidazole for the treatment of severe CDI (97% versus 76%, p=0.02) (66). At the present time, metronidazole has remained the first-line agent because it is less expensive than oral vancomycin and because oral vancomycin may increase the current burden of antimicrobial-associated infections (i.e., vancomycin-resistant enterococci) in hospitals and the community.

Treatment strategies for multiple recurrences of CDI are not standardized and have not been widely researched. First recurrences (i.e., second occurrence of infection) are typically treated with the agent used to treat an initial infection. Regimens including tapering or pulsed administration of oral vancomycin have been shown to decrease risk for recurrence, as compared with other methods of administering vancomycin or metronidazole (67). Results from studies of probiotics have been inconsistent and these agents should not be used as therapy for active infection (68).

In addition to metronidazole and oral vancomycin, a number of potential therapies have been effective in randomized comparative trials of CDI treatment or are undergoing clinical research to determine their utility in the treatment of CDI. Teicoplanin is similar to vancomycin in mode of action and antibacterial activity although this drug is not approved for use in the United States. Nitazoxanide, a synthetic antiparasitic and antimicrobial, is comparable in efficacy to metronidazole and vancomycin in vitro and clinically, although this drug is not approved by the FDA for the treatment of CDI (69-71). The efficacy of Ramoplanin is similar to that of vancomycin for the treatment of patients with mild-to-moderate CDI, and this antimicrobial is active against *S. aureus* and vancomycin-resistant enterococci (22). Rifaximim is a good candidate therapy for CDI patients requiring prolonged treatment. This antimicrobial appears to be efficacious for initial and recurrent infection, although resistant *C. difficile* strains are already appearing, which may limit its long-term and widespread use (72-75). Rifampin has been studied as both a stand-alone treatment and in combination with metronidazole. However, a recent study suggested that mortality rates may be higher for patients treated with a rifampin-metronidazole combination than for patients treated with metronidazole alone (76).

Patients who do not mount an immune response are at higher risk of acquiring CDI than are patients who do mount an immune response, suggesting that antibody against *C. difficile* toxins may protect persons from CDI. Initially, monoclonal antibodies were shown to induce immunity in mice, and antibodies against Toxin A and Toxin B prevented morbidity and mortality in hamsters (77, 78). Recently, a randomized, double-blind, placebo-controlled study found that monoclonal antibodies administered during antimicrobial therapy significantly decreased recurrence of CDI (7% recurrence rate in monoclonal antibody groups versus 25% in placebo group). Similar reductions in recurrence were observed among persons with the BI/NAP1 ‘epidemic’ strain (79). Intraveneous immunoglobulin (IVIG), which is pooled from human serum and contains antibodies against *C. difficile* toxins, has also been used for the induction of passive

immunity (80). Research studies of IVIG have reported inconsistent results, ranging from no benefit to favorable outcomes (81, 82). Finally, a vaccine containing inactivated Toxins A and B is being tested in healthy volunteers who seem to tolerate the vaccine well. In this trial, three patients with chronic, recurrent infection did not have subsequent relapse following vaccination (83, 84).

Restoration of the normal bacterial colonic flora may also prevent recurrent infection; therefore, healthcare providers have started to recognize bacteriotherapies as an option. Bacteriotherapy treatments include the administration of a non-toxigenic *C. difficile* strain to "fill" the niche in the colonic flora that would otherwise allow toxigenic strains to colonize and grow. This may be accomplished by the administration of a filtrate of feces from a healthy human donor through a nasogastric tube or a colonoscope (i.e., fecal reconstitution) (85, 86). In case series, fecal reconstitution has been effective in preventing recurrence after 90 days (86). This treatment option is thought to be effective because it re-establishes healthy, normal colonic flora. Additionally, it may decrease the use of additional antimicrobials, thus reducing the potential for antimicrobial-resistant *C. difficile* strains and drug-related costs of recurrent infection. Despite these benefits, the use of this procedure has not been widely accepted by patients for aesthetic reasons.

Epidemiology of *Clostridium difficile* Infection

C. difficile infection has historically been considered an infection related to exposures to healthcare settings, although this appears to be changing. The majority of epidemiologic *C. difficile* research has been conducted in the hospital setting and a number of risk factors for HA-CDI have been identified, with evidence being stronger for some than for others. The most common risk factors are: antimicrobial use; advanced age (i.e., 65 years of age or older); underlying comorbidity; use of gastric acid suppressants, particularly proton pump inhibitor use; underlying comorbidity; and duration of hospital stay, especially prolonged length of stay (87-90). Less common risk factors include

laxative use; treatment with antineoplastic chemotherapy; renal insufficiency or failure; gastrointestinal surgical procedures; and, nasogastric intubation. Despite the plethora of potential risk factors, it is generally thought that patients at particular risk for CDI are those who are exposed to antimicrobials, patients of advanced age, and patients with multiple underlying conditions; all of which are characteristics of hospitalized populations (18, 91-94). Few studies have been conducted to identify risk factors for CDI in the community-setting; therefore, it is unknown if or to what extent the risk factor epidemiology of HA-CDI applies to CA-CDI.

Antimicrobial Use

Antimicrobial use is generally considered to be the primary risk factor for CDI. Essentially, antimicrobials kill the normal bacterial colonic flora while treating harmful bacterial infections, thus allowing *C. difficile* to grow without competition and to cause serious disease. More specifically, the normal adult colon contains approximately 10^{12} bacteria per gram of contents, with the majority of these bacteria being obligate anaerobes (95). The amount and diversity of these bacterial microflora in the colon are an important host defense against *C. difficile* and other gastrointestinal pathogens (95, 96). Antimicrobial use reduces both the amount and diversity of colonic microflora, with these changes typically lasting for approximately two weeks after completion of therapy.

All antimicrobials have been associated with CDI; however, the risk is particularly high with certain antimicrobials including clindamycin, cephalosporins, penicillins, and most recently, fluoroquinolones (97, 98). The associations between particular antimicrobials and *C. difficile* seem to have evolved along with antimicrobial prescribing practices, although biologically plausible reasons for these associations include the effect of antimicrobials on the colonic microflora, differences in anaerobic activity among drugs and the emergence of antimicrobial resistance among *C. difficile* strains. First, antimicrobials that are active against *C. difficile* and other anaerobic

organisms may decrease both the risk for *C. difficile* colonization and infection during their use (e.g., piperacillin-tazobactam), whereas agents which lack anaerobic activity against *C. difficile* and disrupt the normal colonic flora may increase the risk for CDI (e.g., trimethoprim-sulfamethoxazole) (99). Second, antimicrobial-resistant *C. difficile* strains have been associated with a number of outbreaks (98). In turn, it has been suggested that some of the lower-risk antimicrobials (e.g., piperacillin-tazobactam and tigecycline) may stimulate less toxin production by *C. difficile* than other higher-risk antimicrobials (100). In addition, beta-lactamase antimicrobials may not be associated as strongly with CDI since they inhibit activity of many *C. difficile* strains during treatment (101).

Clindamycin was the first antimicrobial to be associated with pseudomembranous colitis in the early 1970s, when the disease was referred to as 'clindamycin-induced colitis'. In 1977, researchers discovered that this 'clindamycin-induced colitis' was actually attributable to *C. difficile*. In the 1970s and 1980s, clindamycin was used extensively for treating infections caused by anaerobic organisms and this agent was implicated in outbreaks in which the predominant strain of *C. difficile* was found be highly resistant to clindamycin (102). The relationship between clindamycin and CDI was confirmed in hamster models, which allowed investigators to demonstrate that this antimicrobial disrupts normal colonic flora for a longer duration than other antimicrobials, thus providing greater opportunity for *C. difficile* to colonize and infect patients (103). Clindamycin use in hospitals subsequently decreased, resulting in the reduction of outbreaks and decreased clindamycin resistance among *C. difficile* strains.

Cephalosporins such as cefuroxime, ceftazidime, cefotaxime, and ceftriaxone were introduced and widely-prescribed in the United States in the 1980s and 1990s, at which time a link between CDI and these antimicrobials became apparent. One study showed that CDI occurred 40 times more often following cephalosporin use than following use of narrow-spectrum penicillins (104). In fact, many studies have shown

that cephalosporin use is strongly associated with outbreaks and have suggested that risk for CDI is higher after the use of these drugs than after the use of other antimicrobials. Furthermore, it has been shown that institutional CDI rates decrease following reductions in cephalosporin use (13, 37, 98, 105-108). In recent years, *C. difficile* has become universally resistant to most cephalosporins (108).

Penicillins, including broad-spectrum agents, have been frequently associated with elevated risk for CDI, in both hospitalized populations and in the community (8, 102, 109). For example, aminopenicillins, such as ampicillin and amoxicillin, have been associated with CDI since the first appearance of this infection. One study found that 109 of the 329 CDI cases occurred following use of ampicillin or amoxicillin (110, 111). In addition, aminopenicillins can lead to CDI despite the fact that most strains of *C. difficile* are susceptible to these antimicrobials (112).

When introduced in the 1980s, the fluoroquinolone antimicrobial class was considered to have low-risk for development of CDI. Since then, additional fluoroquinolones including gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, and ofloxacin have been introduced and fluoroquinolones have become the most widely-prescribed antimicrobial class among adults (113). Recently, this antimicrobial class has been associated with outbreaks of CDI and fluoroquinolones have been shown to increase risk for CDI. This increased risk is related to poor in vitro activity against *C. difficile* and differences in their effects on intestinal flora compared with other antimicrobials (37, 114, 115). One of the most influential studies suggesting the association between fluoroquinolones and CDI outlined the response to an outbreak in Quebec, Canada which was notable for the severity of disease and for a high mortality rate. Investigators determined that the BI/NAP1 strain, which is fluoroquinolone-resistant, was responsible for this outbreak. Prior to development of *C. difficile*, case patients received fluoroquinolones at four-time higher rates than control patients. In particular, ciprofloxacin, gatifloxacin and moxifloxacin were significantly associated with CDI (37).

Levofloxacin was not associated with CDI in this outbreak (37), although a number of subsequent studies have reported increased risk related to its use and increased incidence of CDI following formulary changes in which levofloxacin use increased (98, 114).

Researchers have also reported that persons receiving multiple antimicrobials may be more likely to develop CDI, with risk increasing as the number of antimicrobials received increases (109, 116-120) . In fact, among patients at a Veterans' Administration hospital, the risk for CDI increased for each additional antimicrobial which was utilized, even after adjustment for other antimicrobial use and comorbidity (OR: 1.4; 95% CI, 1.1,1.7) (121). Similarly, a study by Changela et al. found that all antimicrobial classes were significantly associated with CDI, although this study was most notable for the fact that multiple antimicrobials were prescribed concurrently; therefore, it was difficult to distinguish independent risk for particular antimicrobials (122).

Extended periods of antimicrobial use have been associated with increased risk of CDI, although CDI has also occurred after short durations, such as after single doses of prophylactic antimicrobials prior to surgical procedures (114, 123-125). Prolonged antimicrobial therapy probably increases risk for CDI by extending the amount of time a patient is susceptible to *C. difficile* acquisition and to development of disease. A study of outpatients with cancer found that risk increased for each additional day of therapy with either clindamycin or third-generation cephalosporins (126).

Researchers have also assessed the at-risk period after antimicrobial therapy. CDI symptom onset has occurred in cases immediately after the initiation of therapy, as well as several weeks after completion of therapy (19, 127, 128). In a small study among outpatients with cancer, 85% of patients with CDI had received antimicrobials within 60 days of diagnosis, with a median of 16.5 days from completion of therapy to CDI diagnosis (126). Among general practice patients, the highest risk for CDI occurred within 30 days after the start of antimicrobial therapy, with significant decreases after 45 days and a return to baseline risk occurring within 80 days (129). Finally, several studies

have reported CDI among persons with no exposure to antimicrobial agents, especially among persons with CA-CDI (129, 130).

Antimicrobial use is considered to be the primary risk factor for CDI, although many questions about their relationship with CDI remain. Little is known about whether specific antimicrobials are related to CDI in both the hospital and community settings, especially since prescribing patterns vary between these environments. In addition, there is not a clear consensus among researchers and clinicians in regard to modifiable factors related to increased risk for CDI, such as the amount and duration of antimicrobial use as prescribed by clinicians. . Moreover, the time period in which persons are at highest risk for CDI following antimicrobial use has not been defined precisely.

Gastric Acid Suppressant Use

Gastric acid suppressants such as proton-pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2-antagonists) are widely-prescribed drugs in the United States. Specifically, proton pump inhibitors include omeprazole (Prilosec), lansoprazole (Prevacid), rabeprazole (Aciphex), pantoprazole (Protonix), esomeprazole (Nexium), and Zegerid (a rapid release form of omeprazole). Histamine-2 receptor antagonists include cimetidine, ranitidine, famotidine, and nizatidine.

The biologic mechanism by which gastric acid suppressants could increase risk for CDI is not completely understood, although it is hypothesized that associations between these drugs and CDI might be related to their impact on gastric acidity. Since *C. difficile* spores are acquired through ingestion, gastric acidity may serve as a non-specific mechanism protecting patients against *C. difficile* and subsequent infection. Gastric acid does not kill spores directly, but it does inhibit germinants, which are factors that initiate spore germination (131). When gastric acid suppressants reduce production and release of gastric acid and allow gastric pH to increase, germinants can then bind to spores more effectively, thus allowing actively-dividing spores to pass into the small intestine and

germinate into the vegetative form (132). If there is a disruption of normal flora, these vegetative cells can then multiply in the intestines, potentially lead to colonization and infection (23).

Gastric acid suppressant use is common among hospitalized populations; therefore, several studies have focused on the relationship between the use of these agents and CDI among hospital patients. Beaulieu et al. did not find a statistically significant association between CDI and gastric acid suppressants among patients in an intensive care unit (134). Jayatilaka et al. found increased risk associated with PPI use before or during an admission in which CDI was diagnosed, after controlling for antimicrobial use. They found a similar increase in risk even among patients who first-received PPIs during that admission (135). A case-control study at a small hospital found that the risk for CDI was elevated for patients receiving PPIs compared to patients not receiving PPIs (OR: 3.6; 95% CI: 1.7, 8.3), even after controlling for antimicrobial use (136). Baxter et al. reported that PPI use increased risk for CDI (OR: 1.23; 95%CI: 1.03, 1.48) among a hospitalized population receiving antibiotics, even after controlling for factors such as age, time in a hospital, and diagnosis of gastrointestinal disease (137). Finally, Dubberke et al. conducted a cohort study and a nested case-control study and found that the use of histamine-2 blockers and proton pump inhibitors consistently increased risk for CDI, after controlling for comorbidity, other medication use, and *C. difficile*-associated disease (CDAD) pressure (90, 138).

Cunningham et al. found that PPI use was independently associated with CDI (OR: 2.5; 95% CI: 1.5, 4.2), although even higher risk was observed among receiving PPIs while also undergoing treatment with antimicrobials and/or cytotoxic chemotherapy (139). In fact, patients undergoing a combination of PPIs and these other therapies had 43 times the odds of acquiring CDI than patients not exposed to these agents (139). Dial et al. have conducted a number of studies assessing risk associated with PPI use among both hospitalized and outpatient populations. In the first of these publications, the researchers

reported increased risk for CDI associated with PPI use, even after controlling for female sex, prior renal failure, hospital admission in the prior three months, cancer, and methicillin-resistant *Staphylococcus aureus* (MRSA) colonization (140). Dial et al. also reported that the use of PPIs increased the risk for community-associated CDI in patients included in the United Kingdom General Practice Research Database (GPRD). Among patients with CDI who had not been hospitalized in the previous year, current PPI use was associated with an adjusted rate ratio for CDI of 2.9 (95% CI: 2.4-3.4), while current H_2-antagonist use was associated with a rate ratio of 2.0 (95% CI: 1.6-2.7). Of note, the incidence of CA-CDI increased in this population during the study time period. During the study time period, antimicrobial prescribing decreased while PPI prescribing increased, leading the authors to suggest that PPI use is related to increases in CA-CDI (130). An additional study by Dial et al. found an increased risk for CA-CDI associated with proton pump inhibitor use or antimicrobial use, whereas no increased risk was associated with the use of H_2- antagonists. In this study, the authors also noted that 45% of cases were not exposed to antimicrobials within the 90 days prior to diagnosis, suggesting that infection in the community setting may be related to exposures other than antimicrobial use, such as PPI use (141). These studies provide ample reason for continued research into this association, although the use of one population precludes the broad application of these results in other populations. In addition, these studies were conducted in a population of individuals receiving care from a national health system, which may affect the patterns of use of these drugs and other medications which increase risk for CDI.

Despite the existence of plausible biologic mechanisms and a number of studies finding associations between gastric acid suppression and CDI, it has been suggested that the association may not be causal. First, many studies exist which did not find an association between gastric acid suppressant use and CDI. Second, the use of gastric acid suppressants may simply serve as a marker for increased comorbidity rather than as an

independent risk factor (142). Third, gastric acid suppressants are so widely-prescribed that they are often used concurrently with other medications such as antimicrobial agents, which makes it difficult to determine whether gastric acid suppressant use is an independent risk factor for *C. difficile*.

Age

Elderly persons are predisposed to CDI and to more severe CDI. In fact, advanced age is one of the most commonly-cited risk factors for CDI (19, 90, 120, 137, 143), with one study showing that patients over 65 years of age had a 10-fold higher risk for CDI during an outbreak than did younger patients (36). McDonald et al. reported that the rate of hospital discharge with CDI as any diagnosis was several-fold higher among patients over 65 years of age than among patients 45-64 years of age, which was in turn, higher than the rates among patients 15-44 years of age and less than 15 years. The trend of increasing CDI-related hospital discharges was significantly more pronounced among persons greater than 65 years of age than among those 45-64 years of age (144). Collectively, higher incidence and severity of infection among older persons are most likely related to the increased likelihood for older persons to have a greater number of comorbid conditions, to have more severe illness, to have suppressed immune systems, and to be hospitalized or reside in long-term-care settings as compared with younger persons. Although persons of advanced age have traditionally experienced the highest incidence rates of CDI, this infection, and most commonly CA-CDI, is now being reported more frequently in all age groups and among children (145).

Exposure to Healthcare

Admission to a healthcare facility or residence in a long-term care facility increases risk for *C. difficile* acquisition due to exposures in the healthcare settings. First, patients may have a higher propensity to come into contact with surfaces contaminated with *C. difficile*, persons who carry or are infected with *C. difficile*, or healthcare workers

who do not perform adequate hand hygiene. Second, a high proportion of hospitalized patients and residents in long-term care facilities receive antimicrobials. Third, hospitalized and long-term care populations are predominantly elderly with worse overall health status.

Transmission of *C. difficile* is common within hospital settings due to the presence of both asymptomatic carriers of *C. difficile* and patients with active infection. Hospitalized patients with *C. difficile* diarrhea contaminate their surrounding environment with spores that can persist on surfaces for several months. *C. difficile* spores are resistant to dessication, chemicals, and extreme temperatures, which permits them to survive in the environment and, subsequently be transmitted to other patients. In fact, McFarland et al. showed that the rooms of patients with *C. difficile* diarrhea are significantly more likely to be contaminated than the rooms of asymptomatic carriers (49 vs. 29%), while the contamination rate of rooms with patients who do not carry *C. difficile* was 8% (146).

Healthcare workers' hands are a major vector for the spread of *C. difficile*, with studies showing that the prevalence of *C. difficile* on healthcare workers' hands increases as levels of environmental contamination increase (147). In addition, although alcohol-based hand rubs are the preferred agents for hand hygiene in healthcare facilities, alcohol does not kill spores. In contrast, the mechanical action of handwashing with soap and water has proven effective in reducing or removing *C. difficile* on the hands of healthcare workers (13). In addition, patients with CDI should be placed in private rooms or rooms with other CDI patients, and healthcare workers caring for these patients should do hand hygiene with soap and water and should wear gowns and gloves (13).

The spread of *C. difficile* within hospitals is well-documented. Clabots et al. observed that risk of *C. difficile* colonization increased proportionately with length of hospital stay. Early studies showed that hospitalized populations exhibit much higher rates of colonization, with one study reporting that hospitalized adults have a 20-40% rate

of colonization compared with a rate of 2-3% among healthy adults (21, 146). A more recent study reported that, after one to two weeks of hospitalization, the rate of *C. difficile* colonization was 13%, and after 4 weeks it was greater than 50% (148). Additionally, the duration and intensity of a patient's exposure to other patients with active CDI on the same unit independently increases the risk for the acquisition of CDI, almost to the same magnitude as antimicrobial use (138).

Although hospitalization is the most common source of exposure to *C. difficile*, exposure may also occur in the ambulatory care setting. For example, outpatient dialysis or chemotherapy patients may be a population at increased risk for CDI due to frequent visits to healthcare facilities and the clinical characteristics of these patients. A recent study conducted within an outpatient dialysis cohort found that greater underlying comorbidity and low serum albumin levels were associated with risk for CDI (149). Previous antimicrobial use was not associated with increased risk, although dialysis patients with and without CDI were treated with antimicrobials frequently (149). Although risk factors among this population have been assessed, investigators have not determined whether outpatient dialysis clinics are actually a source of *C. difficile*.

Acquisition of *C. difficile* in non-hospitalized populations have been reported in long-term care facilities, day care facilities and outpatient clinics (114, 150), although little is known about sources of *C. difficile* in the community setting outside of these facilities. Hypothesized potential sources of *C. difficile* within the community setting include soil, water, pets, vegetables, and animals used for food (151, 152). In addition, *C. difficile* may be transmitted via close personal contact with persons who are colonized or who have symptomatic disease (152). However, available evidence neither proves nor disproves the roles of these sources in the acquisition of CA-CDI.

Comorbidity

Both specific comorbid conditions and the total burden of comorbidity have been cited as risk factors for CDI. For example, the Agency for Healthcare Research and Quality (AHRQ) found that hospitalized patients with CDI had, on average, twice as many concurrent diagnoses as patients without CDI (153). In addition, Dubberke et al. reported that higher severity of illness was also more common among patients hospitalized for CDI (90).

A number of specific comorbid conditions are associated with CDI, although investigators believe that some of these relationships are likely attributable to antimicrobial and chemotherapy use among persons with chronic conditions; an increased likelihood of exposure to healthcare settings among persons with chronic conditions; or, the severity of disease in patients with end-stage chronic conditions (154). Specific comorbid conditions that have been associated with CDI include chronic obstructive pulmonary disease (COPD), cancer, renal disease or failure, diabetes, HIV, and conditions resulting in an immunocompromised state (122, 129, 155). Within a hospital with endemic CDI, Dubberke et al. found that myocardial infarction, COPD, mild liver disease, renal failure, and leukemia and/or lymphoma were associated with increase risk for CDI in univariate analysis, although only leukemia and/or lymphoma were associated with CDI in the multivariate analysis (90). Chronic diseases which result in immunosuppression such as HIV, chronic renal failure, diabetes mellitus, leukemia, and lymphoma are associated with CDI. However, it is unclear whether increased risk for CDI is due to the actual condition or if risk is due to treatment for sequela of their chronic illness. For example, immunosuppression may increase the risk for development of bacterial infections, which are treated with antimicrobials, thus increasing risk for CDI among these persons (156, 157).

In turn, investigators have hypothesized that patients undergoing antineoplastic chemotherapy may be at increased risk for CDI since chemotherapeutic agents can alter

colonic bacterial normal flora and may cause intestinal changes, thus allowing for the growth of *C. difficile* and toxin production (127). However, recent research has suggested that this association may be related to concurrent use of antimicrobials and immunosuppression rather than to the use of chemotherapeutic drugs among these patients (158-160).

Persons with chronic, underlying conditions are also likely to seek medical care in healthcare facilities more often than persons who do not have comorbid conditions. For example, patients with cancer or chronic renal failure who are undergoing chemotherapy or outpatient dialysis receive these treatments within healthcare facilities. These "exposures" to healthcare facilities may increase the likelihood for them to be exposed to surfaces and persons contaminated with *C. difficile*, thus increasing their risk for CDI for a reason other than their specific underlying illness.

Overall, the burden of underlying illness probably increases the risk for CDI more than individual comorbid conditions. Furthermore, the relationships between specific conditions and CDI are most likely due to impaired immune response related to the disease or to medication use related to treatment of the disease and its sequela.

Gastrointestinal Conditions

Persons with gastrointestinal conditions are considered to be at particular risk for CDI. Inflammatory bowel diseases (IBD), which include Crohn's disease and ulcerative colitis, are chronic relapsing conditions that affect the colon and small intestine. Crohn's disease can affect any area of the gastrointestinal tract, although it most often starts in the terminal ileum, whereas ulcerative colitis is restricted to the colon and the rectum (161). Although these diseases are definitively different, both present with any of a number of symptoms such as abdominal pain, vomiting, diarrhea, blood in stool, weight loss and may be accompanied by a number of conditions like arthritis, pyoderma gangrenosum, and primary sclerosing cholangitis.

Several studies have found increasing incidence rates among patients with IBD that exceed those in the general, hospitalized population (162). Furthermore, investigators estimate that *C. difficile* may be the cause of 5-19% IBD flares resulting in hospitalization (163, 164). Between 1998 and 2004, the highest prevalence rate of CDI occurred among patients with ulcerative colitis (37.3 per 1,000) followed by patients with Crohn's disease, patients with non-IBD gastrointestinal conditions, and finally, the general medical population within the NIS. During this 7-year study period, the incidence of CDI in patients with ulcerative colitis nearly doubled, and these patients had significantly increased CDI-related mortality rates, while patients with Crohn's disease did not experience increased mortality. In addition, CDI resulted in significantly increased hospital stays and healthcare expenses for patients with IBD (165). Two studies examining CDI among patients with IBD were conducted using the NIS. In fact, the mortality rate was four times higher among hospitalized patients who had IBD and CDI than among patients hospitalized for IBD alone, and was two times higher among patients hospitalized with CDI alone. In this study, patients with ulcerative colitis were more likely to undergo endoscopy or surgical interventions for CDI than were patients with Crohn's disease (166).

Patients with gastrointestinal conditions may be more vulnerable to CDI for a number of reasons, including antimicrobial treatment of other gastrointestinal pathogens and immunosuppressive therapy. Patients with IBD also require hospitalization frequently, which increases probability of acquiring *C. difficile*. Although potential biological mechanisms for this association exist, the elevated rate of identification of CDI among persons with IBD may be an artifact of differential surveillance. First, persons with IBD may be more likely to experience symptoms of their disease which are similar in nature to those of CDI (i.e., diarrhea). Second, reports in scientific literature have found increased incidence and severity of outcomes among these patients; therefore,

clinicians may test for *C. difficile* more often in this population, leading to the identification of more true cases as well as more false positive results.

Antimotility Agent Use

Antimotility agents may be viewed as a means to provide symptom relief for patients with CDI during treatment and until infection is resolved. Despite this belief, current recommendations state that antimotility agents should not be used to treat patients with symptomatic CDI since these drugs may lead to toxin retention and possibly the development of toxic megacolon (18). This recommendation is consistent with current practice that discourages the use of antimotility agents for the treatment of colitis associated with enteric pathogens such as salmonella, shigella, and campylobacter species (167, 168). However, there is little data supporting the potential association between antimotility and antidiarrheal drugs and negative outcomes of CDI.

One small retrospective study analyzed the clinical course of six patients with CDI who received loperamide (an antimotility agent). These patients experienced a significantly longer duration of diarrhea, a greater maximum number of diarrhea episodes per day, and longer duration of all disease symptoms than patients not receiving loperamide (169). Koo et al. examined unpublished postmarketing surveillance reports of antimotility agent use among patients with CDI. Among the studies in this literature review, fifty-five patients with CDI were treated with antimotility agents. Seventeen of these patients (31%) deteriorated clinically and developed complications of their disease including toxic megacolon or colonic dilation after receiving antimotility agents alone as treatment (i.e., none of these patients were treated with appropriate antimicrobial therapy) (170). These data suggest that patients with unrecognized CDI may be at the highest risk of adverse outcomes, since they are being treated for their symptoms rather than the causative agent. In fact, it has been reported that patients did not experience any

complications of CDI after receiving antimicrobial therapy and antimotility agents concurrently (171).

Dubberke et al. found that the use of antimotility agents increased risk for the development of CDI (OR: 1.3), even after controlling for comorbid conditions and the use of other medications such as PPIs and antimicrobials (90). This association was also noted in a case-control study conducted by the same research group within the same cohort of patients (138). A biological mechanism for this association has not been identified, thus there is the possibility that the results of these two studies may be a result of protopathic bias (also known as reverse causality). This bias occurs when treatment for the first symptoms of a disease appear to cause that disease, and is a concern in this case since there is a potential for lag time between the first symptoms of CDI (i.e., diarrhea), resultant use of antimotility agents, and actual diagnosis. In addition, the studies which found that treatment with antimotility agents increased risk for CDI were conducted in a hospitalized population, in which antimotility agents may be used more often in response to underlying disease or in response to increased intestinal motility following other medication use.

The use of antimotility agents following CDI and the development of adverse outcomes have been researched in small patient populations; prior to emergence of more virulent strains; and in some cases, prior to the implementation of the current treatment guidelines for other pathogens. Researchers have yet to examine a number of issues. First, it is unclear whether these drugs pose any risk of complication among CDI patients once antimicrobial therapy has been initiated. Second, the use of antimotility drugs may simply complicate clinicians' ability to determine if infection is resolving in response to treatment. Third, it is unknown whether severe, adverse outcomes among patients who are given antimotility agents can be directly ascribed to this therapy or whether these outcomes are related to other patient characteristics or risk factors.

Adverse Outcomes of *C. difficile* Infection

C. difficile infection may result in adverse outcomes, especially in cases of very severe disease and in vulnerable populations. The most common adverse event related to CDI is hospitalization. Additional serious complications and adverse outcomes can occur and include relapse or recurrent infection, surgical intervention, or death.

Relapse or Recurrent *Clostridium difficile* Infection

Recurrent or relapsing *C. difficile* infection, a symptomatic infection occurring after the completion of a successful initial therapy, remains one of the biggest challenges in the management of CDI. Recurrence occurs in approximately 19-20% of patients, with similar rates occurring following metronidazole and vancomycin therapy (63, 66). The risk for recurrence is increased in patients who have a history of at least one recurrent infection, such that the recurrence rate of 20% after an initial episode increases to about 40% after a first recurrence and to over 60% after two or more recurrences (67, 172). Recurrence of CDI occurs as a result of either the persistence of the same strain of *C. difficile* in a person (i.e., relapse) or the acquisition of a new strain of *C. difficile* (i.e., reinfection). Little is known about the relative frequency of these two phenomena in patients with CDI, although it has been shown that the mean time from the end of therapy for a prior episode to recurrent infection is much shorter for relapse than for reinfection (14.5 days versus 42.5 days, respectively) (173).

The reasons for recurrent infection are relatively ill-defined, although the most common hypothesis is that recurrence is related to differential immune response. For instance, a patient who has primary immune response evidenced by high serum IgG antitoxin during an initial episode will be 44-times less likely to have a recurrence than patients who have lower antitoxin titers (43). Additional risk factors for recurrent infection include persistent disruption and decreased diversity of the colonic flora,

advanced age, continued antimicrobial therapy (in addition to *C. difficile* treatment), extended hospital stays, and concomitant therapy with antacid medications (174, 175).

Surgical Intervention

Surgical intervention is, at times, necessary for the treatment of fulminant colitis, although these surgical procedures may increase risk of death, healthcare utilization, and cost for both patients and insurers. Subtotal colectomy and ileostomy are the 'gold standard' surgical procedures for patients with fulminant disease and severe ileus, toxic megacolon, or localizing peritoneal signs. Reported colectomy rates in single institutions have ranged from 0.17% to 1.3%, whereas the overall rate of these procedures in the NIS was reported at 0.28% (4, 176, 177). These rates may vary for a number of reasons, including differences in the severity of infection, the health status of the patients, and the potential for patients to refuse surgical intervention

The impact of timing or type of surgical procedure on survival has not been evaluated in randomized trials (47, 178-183). Hermsen et al. found that time from first diagnosis of symptomatic CDI to surgical intervention averaged 23 days (range, 1 to 138 days; median, 5 days), while time from acute diagnosis of either an initial or recurrent infection to surgery averaged 3 days (range, 1-8 days). In this population, 46% of patients (6 of 13) died postoperatively, and no increased trend in survival was noted over the ten-year period in which the study was conducted (176).

Mortality

Death is a rare outcome of CDI, although mortality rates have increased concurrently with increased severity of CDI. Death is most often observed following surgical intervention in CDI patients with the most severe disease and among patients with poor health status. In the U.S., death certificate data suggest that mortality rates due to CDI increased from 5.7 per million population in 1999 to 23.7 per million in 2004 (184). Mortality rates for CDI increased with age, and females had higher mortality rates

than males (185). Finally, the unadjusted case-fatality rate increased from 1.2% in 2000 to 2.3% in 2004 among discharges in the Nationwide Inpatient Sample (5). Furthermore, mortality rates also vary depending on the severity of CDI. Patients with fulminant *C. difficile* colitis whose disease has progressed to toxic megacolon have relatively high mortality rates ranging from 24-38%. In-hospital mortality following surgical intervention for patients with severe CDI ranges between 30% and 80% (49, 176, 177, 182).

Kyne et al. found that patients with CDI were significantly more likely to have higher 3-month and 1-year mortality rates than patients without CDI, although CDI was not an independent predictor of mortality after adjusting for age, comorbidity, and severity of CDI (6). In a small study conducted in a veteran population, half of all patients with CDI died, and one-third of these deaths occurred within 30 days of diagnosis. Despite this high overall mortality rate, the investigators could only attribute five deaths to CDI (122).

Clinical and Public Health Significance

Increases in Morbidity and Mortality

Investigators have typically utilized administrative discharge databases to conduct population-based studies which examine increases in the prevalence and severity of CDI. A number of studies have utilized NIS data to examine trends in the incidence of hospitalizations with CDI as a primary or secondary diagnosis, and to examine case-fatality and adverse outcome rates. Ricciardi et al. noted a statistically significant increase from 261 cases of CDI per 100,000 discharges to 546 cases of CDI per 100,000 discharges ($p<0.001$) between 1993 and 2003, representing a 109% increase (4). The colectomy rate also increased from 1.2 to 3.4 colectomies per 1000 discharges, while the mortality rate increased from 7.84% to 9.26%, suggesting that CDI became more severe over this time period (4). After further examination of patient characteristics, more

women than men were being hospitalized with *C. difficile* and the mean age of patients with CDI increased in the time period from 1993 to 2003. In a similar study, Zilberberg et al. reported that the incidence of CDI hospitalizations among adults doubled from 5.5 cases per 10,000 population in 2000 to 11.2 cases per 10,000 population in 2005; the greatest increase in incidence occurred among patients aged 85 years and older (5). The overall CDI-related mortality rate increased from 1.2% to 2.2% during this time period, even after adjusting for the effect of age (5). Furthermore, Elixhauser et al. noted that, in the NIS, hospitalizations with CDI as a diagnosis increased at a higher rate between 2001 and 2005 than in the 8-year period from 1993 to 2000. In addition, this study confirmed that patients with CDI were primarily elderly and that patients with CDI were considerably sicker and had more complex disease than patients without CDI. In fact, patients with CDI were often admitted through emergency rooms (nearly 65% of the time), and had twice as many comorbities, on average, when compared with all other patients. Hospital stays for patients with CDI were three times longer than the average hospital stay and death rates that were 4.5 times higher than the average rate in the NIS population (153).

McDonald et al. determined that, within the National Hospital Discharge Survey (NHDS) database, hospital discharges with CDI listed as any diagnosis significantly increased from 31 discharges per 100,000 population (82,000 cases) in 1996 to 61 discharges per 100,000 population (178,000 cases) in 2003 ($p=0.01$)(144). Patients over the age of 65 years experienced both the highest overall rate of CDI and the most rapid increases in incidence (144).

Investigators have also estimated the incidence of hospital-acquired CDI in various geographic regions ranging from individual states in the United States to entire countries. From 2000 to 2004, acute care hospitals in the state of New Jersey reported that the mean annual rate of CDI increased from 3.7 cases per 1,000 admissions to 7.7 cases per 1,000 admissions. These hospitals also reported a perceived increase in

recurrent or complicated cases and death (186). Incidence in the state of Oregon increased from 1.4 to 3.3 cases per 1,000 hospital discharges from 1995 to 2002, with the largest increases occurring in hospitals with more than 250 total beds and more than 5 intensive care unit beds (187). In 2006, the state of Ohio instituted active public reporting of healthcare-onset CDI in all Ohio acute care hospitals and nursing homes. Overall, there were 12,600 initial cases of CDI and 5,600 recurrent cases of CDI in Ohio during 2006. The initial (i.e., non-recurrent) CDI case rate in acute care hospitals ranged from 6.4 to 7.9 cases per 10,000 patient-days, while the rate in nursing homes was 1.7 to 2.9 cases per 10,000 patient days. In addition, there were 893 deaths listing CDI as any cause of death, with 528 of these having CDI listed as the primary underlying cause of death (188). Finally, Jarvis et al. conducted a point prevalence survey among a subset of United States acute care facilities, which estimated an overall prevalence rate of 13.1 cases per 1000 inpatients. The majority of these patients were female (55.5%), were over 60 years of age (69.2%), had one or more comorbid conditions (67.6%), or had received antimicrobials (79%). This survey also found that 54.4% of these cases had been diagnosed within 48 hours of admission, but were still considered hospital-acquired because they had either been admitted to a long-term care facility within 30 days (35%) or had been hospitalized within 90 days (47%) (189).

Similar studies have been conducted outside of the United States. Researchers in Quebec conducted a retrospective chart review of cases served by one hospital and extrapolated the results to calculate population-based incidence from 1991 to 2003. The incidence increased from 35.6 cases per 100,000 population in 1991 to 156.3 cases per 100,000 population in 2003, with the greatest increases in persons over 65 years of age (65). In this population, the proportion of cases experiencing complications and death as a result of their infection also increased (65). In the United Kingdom, 360 medical microbiologists reported that the number of cases of CDI increased from 1,572 in 1993 to 8,211 in 1996 (190). These respondents also reported increased ward (i.e., unit) closures

in response to CDI, indicating that CDI was widespread and increasing prior to the emergence of the epidemic strain and the subsequent alarm among public health and medical professionals (191).

Individual institutions have reported similar increases in morbidity, and in severe outcomes and death. The University of Pittsburgh Medical Center reported that both the incidence and the rate of CDI patients requiring additional intervention doubled within a sixteen-month period (98). In fact, disease was so severe in this institution during this outbreak that 44 patients required colectomy and an additional 20 patients died of their infection (98).

Two studies focused on incidence of CDI at Oregon Health Sciences University (OHSU) Medical Center in two different time periods. In the first, Jobe et al. noted a sharp increase in the number of cases of CDI from 1984 to 1994, with a disproportionate number of cases occurring among surgical patients and among those receiving perioperative antibiotics, most notably cephalosporins (192). A follow-up study found that the incidence of CDI was 30.2% higher incidence in CDI in the six years between 1994 and 2000 than in the preceding ten years. The overall mortality rate among CDI patients was 15.3% (193).

Healthcare Costs and Utilization

Healthcare costs due to CDI are related to treatment, length of stay, healthcare resource utilization, and recurrent or relapsing infection. The economic impact of CDI for individual patients is significant. For example, Song et al. found that although CDI did not contribute to excess mortality in infected patients compared with uninfected patients, although it did increase length of stay and direct costs for patients with CDI. Furthermore, direct costs for CDI increased from $306 per case in 2000 to $6,326 per case in 2004 (7). This report is higher than estimates provided by Kyne et al., which estimated that patients incurred an adjusted hospital cost of $3,669 per case (6), although

Kyne conducted this research prior to the emergence of the BI/NAP1 strain. Whereas these investigations examined costs in all *C. difficile* cases, Dubberke et al. assessed the cost of infection for cases who did not undergo surgical intervention. The cost for an episode of CDI was $2,454 when compared to non-CDI admissions, and cases encountered an increase of $5,042 in medical costs attributable to CDI in the 180 days after the initial hospitalization (194). Collectively, in the United States, the estimated cost of healthcare associated with CDI has been estimated to range from $1.1 to 3.4 billion dollars per year (6, 7).

Emergence of *Clostridium difficile* Infection in the Community Setting and in Low-risk Populations

C. difficile has traditionally been linked to disease in hospitalized populations, although *C. difficile* infection has emerged in the community setting but is probably under-diagnosed. Sporadic reports of CA-CDI date back to the late 1970s and early 1980s, although, recently, cases of CA-CDI are being reported more frequently by members of the infection control and medical communities. Until recently, little research has been conducted to describe this phenomenon; therefore, the incidence of, risk factors for, and outcomes of community-associated infection are relatively unknown.

Estimates of the Incidence of Community-associated *Clostridium difficile* Infection

The incidence and prevalence of CDI in the community setting has often been estimated in the general practice setting through surveys and through the collection and microbiological analysis of fecal samples. In Germany, Weil et al. prospectively analyzed stool samples from 704 general practice patients with diarrhea, of which 66 (9.4%) samples were positive for *C. difficile*. Fifty-three percent of these patients (35 of 66) with a positive immunoassay result had documented recent use of cephalosporins or fluoroquinolones (191). A similar study conducted among general practice patients in the

United Kingdom reported that, 2.1% of 2100 randomly selected fecal samples were positive for *C. difficile* cytotoxin, which translated to an annual incidence of 20.2 to 29.5 cases per 100,000 persons (195). A positive result was associated with antimicrobial exposure within the previous 4 weeks and hospital admission in the prior 6 months although one-third of these patients were not exposed to either of these risk factors (195). In a third study, Bauer et al. determined that 1.5% of general practice patients with diarrhea were infected with *C. difficile*. A high percentage of these patients had not been admitted to a healthcare facility in the previous year (65%) and/or had not utilized antimicrobials in the 6 months prior to symptom onset (42%) (196). Finally, researchers reported that the *C. difficile* seroprevalence rates in a Danish general adult population increased from 19% in 1990 to 27% in 1998 ($p<0.0001$). Higher seroprevalence rates were observed in older age groups, although increases in seroprevalence over the study time period were relatively uniform across age groups (197). The results of this study suggest that environmental exposure to *C. difficile* may be increasing in the community setting, although the researchers did not determine whether these IgG antibodies were related to the actual development of CDI and they did not examine potential risk factors for acquisition of *C. difficile* (197).

In the U.S., reports of CA-CDI have been generated from brief periods of voluntary surveillance in limited geographic areas and in targeted populations. The first of these studies was reported by the CDC in the 2005 Morbidity and Mortality Weekly Report (MMWR). A number of severe CDI cases occurring among peripartum women prompted a period of population-wide surveillance in the Philadelphia area. During this voluntary reporting period, public health officials and clinicians identified a total 23 cases of CA-CDI, of which10 cases occurred among peripartum women (10). The mean age for non-peripartum cases was 26 years, with cases ranging in age from 6 months to 72 years. Four of these cases had evidence of transmission between close contacts, and eight cases (25%) had no prior antimicrobial use within the three months before onset of CDI (10).

Roughly 46% of cases required hospitalization or an emergency department visit, and 39% (13 of 23) experienced recurrence and required additional treatment (10). The annual incidence of CA-CDI for this area was estimated at 7.6 cases per 100,000 population, with one case of CDI occurring for every 5,549 outpatient antimicrobial prescriptions (based on national estimates of antimicrobial prescribing applied to this population), although investigators acknowledged that these estimates may be low because of the voluntary nature of reporting (10) .

In 2008, the MMWR published Connecticut surveillance data from 2006, which identified 241 CA-CDI cases and reported an annual incidence of 6.9 cases per 100,000 population (11). During the surveillance period, incidence of CA-CDI increased with age; females had nearly twice the incidence of males; and, rates were highest during the spring and summer months. Among these cases, 46% (110 of 241 cases) required hospitalization, mainly for diagnosis and treatment of dehydration and colitis, although thirteen cases required intensive care unit stays and two cases required colectomy for toxic megacolon. Two patients died of complications related to CDI. Cases requiring hospitalization had a median length of stay of four days, with a range of 1 to 39 days. Of these patients, 68% had taken antimicrobials in the 3 months preceding specimen collection, 67% had an underlying comorbid conditions, and 29% had been discharged from a healthcare facility or long-term care center 3 to 12 months prior to disease onset. However, 25% of cases (59 of 241) had no underlying comorbidities or exposure to a healthcare setting, and 21 cases had no exposure to antimicrobials. Cases without these exposures were younger, were less likely to be hospitalized for their CA-CDI, and were more likely to report bloody diarrhea (11). Together, these observations suggest that CDI is occurring in populations which are not traditionally considered at-risk. Furthermore, CA-CDI may be underascertained among persons who do not have traditional risk factors.

Risk Factors for Community-associated *Clostridium difficile* Infection

Multiple studies have suggested that persons with CA-CDI, in general, may be younger, have less comorbidity, have less history of hospitalization, and less exposure to healthcare settings than individuals with HA-CDI (8, 10, 196). In studies of CA-CDI, the most commonly cited risk factor is antimicrobial use. Additional potential risk factors in the community setting include the use of proton pump inhibitors, contact with a contaminated healthcare environment in the outpatient setting, contact with persons who are infected with and shedding *C. difficile* (i.e., person-to-person transmission), and contact with contaminated food (11).

The first epidemiologic study of CDI in the community setting was published in 1994. Hirschhorn et al. identified 51 patients with CA-CDI over a two-year period, for an overall incidence rate of 7.7 cases per 100,000 person-years within the Harvard Community Health Plan population (8). Patients with CA-CDI had a median age of 37 years; less than half of them (43%) had a concurrent or predisposing condition; and, the majority of cases (82%) were diagnosed and treated in the ambulatory care setting. The researchers also reported that 6.7 cases of CA-CDI occurred per 10^5 antibiotic risk periods. Risk associated with specific antimicrobials ranged from no risk following tetracycline use to significantly increased risk associated with ampicillin, cefuroxime, cephalexin, and nitrofurantoin. Although the median age of these patients was relatively low, increased risk was observed with increasing age (with persons <20 years of age as the reference group). Furthermore, exposure to combinations of antimicrobials, sex, and known human immunodeficiency virus infection were not associated with increased risk (8).

A descriptive study conducted by Riley et al. determined the frequency of *C. difficile* in stool samples submitted to general practitioners in Australia, and surveyed providers who cared for patients with *C. difficile* (198). Sixty-one patients were identified

as having at least one bout of CDI. Of these patients, 85% (45 of 53 patients for whom survey information was available) of cases had received antimicrobials, most commonly beta-lactams, within the previous four weeks. The authors cited this as being consistent with the prescribing practices of general practitioners, which may differ from hospital settings (198).

Prospective surveillance for CDI among the Swedish population determined that 28% of all cases were community-associated (94). These investigators reviewed medical records and found that the median age of cases was 59 years; 88% had received antimicrobials within the previous six weeks; and, 56% were subsequently hospitalized for a mean of 6.6 days. The incidence of CA-CDI ranged from 5-47 cases per 100,000 inhabitants. However, these researchers defined patients as having community-associated infection if they had not been hospitalized during the 4 weeks prior to diagnosis, which, by current standards, is too short of a time span (94).

Beugerie et al. prospectively followed patients who were prescribed antimicrobial therapy in the outpatient setting (199). These patients acquired *C. difficile* at a rate of 2700 cases per 100,000 exposures to antimicrobial drugs. Duration and type of antibiotics, and particularly exposure to amoxicillin-clavulanic acid, were predictors of the development of diarrhea due to *C. difficile* among outpatients, while age and gender were not predictive (199). In one Swedish county, Noren et al. identified 371 total cases of CDI, of which 59 (16%) were classified as community-associated (200). Community-associated cases were younger (median age of 64 years vs. 72 years), had 37-fold lower per capita consumption of antimicrobials (despite the fact that most of overall antimicrobial consumption in this county actually occurred in the community setting), and had significantly lower mortality rates (4% versus 15%) when compared with HA-CDI cases. Finally, seventeen percent of community-associated cases experienced recurrence of their infections (200).

At a Veterans' Administration hospital, Chang et al. found that twenty-seven of 140 patients (19%) with onset of *C. difficile* in the ambulatory care environment were defined as CA-CDI because they had not been hospitalized in the 100 days prior to a positive toxin test (201). Twenty of these 27 patients had received outpatient antimicrobials within the previous 60 days, most commonly clindamycin, broad-spectrum penicillins, and fluoroquinolones. Additionally, of cases identified in the ambulatory setting but not classified as CA-CDI, the majority (90%) had developed symptoms within 30 days of a hospital discharge, while 1 patient experienced symptom onset 30-60 days after discharge and 6 patients developed symptoms more than 60 days after discharge. Although this study focused on CA-CDI, the investigators suggest that symptom onset within 30 days of a prior discharge may be a reasonable time frame for identifying hospital-associated cases diagnosed in the ambulatory care setting (201).

Delaney et al. conducted a case-control study of patients in the General Practice Research Database (GPRD) over a ten-year period (202). A CA-CDI case was defined as a case-patient without a history of hospitalization in the year prior to diagnosis. Use of any antimicrobial within the prior 60 days was associated with increased risk, although o 63% of case-patients had not received any antimicrobials. Specific antimicrobial classes conferred varying degrees of risk, with the greatest risk associated with fluoroquinolones (OR: 6.2) and lesser degrees of risk associated with cephalosporins (OR: 2.21), macrolides (OR: 2.15), penicillins (OR: 1.89), and sulfonamides (OR: 1.88). Furthermore, the risk due to antimicrobial use diminished by one-half over the 3 months after antimicrobials were discontinued and risk was essentially non-existent after 6 months (202).

McFarland et al. identified 20 CA-CDI cases among patients presenting with CDI to a Seattle-area Veterans' Administration hospital (121). Patients with community-associated infection were younger (56.5 years vs. 65.9 years, p=0.05), had fewer and less severe comorbid conditions (5.3 versus 6.8, p=0.02), and were more likely to have lower

intestinal conditions than patients with nosocomial infection. Sixty percent of patients with CA-CDI had no exposure to antimicrobials, compared with 15% of nosocomial cases. Patients with CA-CDI also had shorter mean durations of hospitalization and lower mortality than patients with HA-CDI. Furthermore, none of the patients with CA-CDI underwent a surgical procedure for their infection (121).

Wilcox et al. conducted prospective surveillance in one semi-rural cohort and one urban cohort in the United Kingdom to determine the burden of *C. difficile* cytotoxin positivity in patients seeking medical care from general practitioners. Of 2000 random samples, roughly 2% were cytotoxin positive. The median age of cases occurring in the urban cohort was significantly higher than that of cases in the semi-rural cohort (73 years vs. 45 years, respectively). When compared to a random subset of patients without CDI, cases were found to have received antimicrobials significantly more often in the month prior to onset of diarrhea (52% versus 18%, p=0.0001) and to have been hospitalized in the six months prior to CDI onset. Of note, 35% of all patients with CA-CDI were not exposed to either antibiotics or hospitalization, and the only additional significant risk factor in this study was contact with an infant under 2 years of age (195).

A series of studies conducted by Dial et al. using the GPRD focused primarily on risk associated with the use of gastric acid suppressants, although they also identified a number of other risk factors for CA-CDI. First, over a ten-year period from 1994 to 2004, the incidence of *C. difficile* in patients diagnosed by their general practitioners increased from less than 1 case per 100,000 persons to 22 cases per 100, 000 persons (203). Patients with CA-CDI had a mean age of 71 years and were more likely to be women. Use of antimicrobials (OR: 3.1; 95% CI: 2.7, 3.6), proton pump inhibitors (OR: 2.9; 95% CI: 2.4, 3.4), H_2-receptor antagonists (OR: 2.0; 95% CI: 1.6, 2.7) and non-steroidal anti-inflammatory drugs (OR: 1.3; 95% CI: 1.2, 1.5) in the 90 days before diagnosis were related to an increased risk for CDI. Elevated risk was also related to comorbid conditions including renal failure (adjusted RR: 3.7; 95% CI: 2.4, 5.6), inflammatory

bowel disease (RR: 3.6; 95% CI: 2.6, 5.1); malignancy (RR: 1.9; 95% CI: 1.4, 2.7); and being methicillin-resistant *Staphylococcus aureus* (MRSA)–positive (RR: 4.2; 95% CI: 2.7, 6.4). In this study, only 37% of patients with CA-CDI received antimicrobials. Furthermore, the incidence of CA-CDI was increasing, antimicrobial prescribing rates were decreasing, and proton pump inhibitor prescribing rates were increasing. As a result, these researchers concluded that antimicrobial use may not be an absolute prerequisite for CDI, and proton pump inhibitors may play a larger part in the acquisition of CDI than has been acknowledged in prior research (203).

A second study conducted by Dial et al. approached this research question in a similar manner, except cases of CA-CDI were identified as patients receiving oral vancomycin prescriptions in the outpatient setting (204). Exposure to a proton pump inhibitor (OR: 3.5; 95% CI: 2.3, 5.2) or an antibiotic (OR: 8.2; 95% CI: 6.1, 11.0) was related to increased risk for CA-CDI. Additional results were consistent with the prior study; however, 45% of cases had not received a prescription for an antimicrobial agent within 90 days of their infection. In addition, renal failure, inflammatory bowel disease, malignancies, and prior MRSA infection resulted in increased risk for CA-CDI (204).

A final case-control study conducted by Dial et al. examined patterns of antimicrobial among elderly patients with CA-CDI (129). Eight-hundred thirty-six cases of CA-CDI were identified from 1998 to 2004. Incidence rates in this population remained relatively stable from 1998 to 2002, but increased in 2003 and 2004. Cases were more likely to be female and, on average, had more encounters with their physician within the two years prior to admission for CA-CDI. Of the 836 cases, 442 (52.9%) cases had no antimicrobial use in the 45 days prior to admission to a hospital with CA-CDI, and 382 (45.7%) had no exposure in the 90 days before admission. All antimicrobials except trimethoprim-sulfamethoxazole and those classified as “other” were associated with increased risk, with the highest risk noted after the use of clindamycin, cephalosporins, or gatifloxacin. The researchers also determined that, in this population,

the highest risk for CDI occurred within 30 days after the start of antimicrobial therapy. Risk decreased significantly after 45 days and returned to baseline risk within 80 days. Proton pump inhibitor use was associated with a small increase in risk, while concurrent medical conditions related to increased risk included inflammatory bowel disease, irritable bowel syndrome, and renal failure (129).

Finally, Lambert et al. applied CDC surveillance recommendations to one year of surveillance data in Manitoba and determined that approximately 27% of all *C. difficile* cases were community-associated. HA-CDI and CA-CDI had significantly different age distributions, with HA-CDI cases being older than CA-CDI cases (12).

A number of recent studies have suggested that CA-CDI may be increasing among children and peripartum women. Asymptomatic carriage in infants is common; however, in general, children have not been considered to be at risk for the acquisition of CDI (205, 206). However, at one children's hospital, Benson et al. found that the incidence of CDI increased significantly in the outpatient setting from 2001 to 2006, largely due to the increasing number of community-associated cases in this pediatric population (145). In addition, only 57% of the patients with CDI in this population had any record of recent antibiotic use (145).

Two case series of peripartum women with CDI have been published. In the first, Rouphael et al. conducted passive surveillance of clinical and pathology data for severe cases of CDI in peripartum women, and also conducted a survey among infectious diseases consultants (207). This study identified 10 peripartum women with CDI, only three of whom had a history of hospital admission or antimicrobial therapy in the three months prior to symptom onset. The outcomes of these infections were severe and included three stillbirths and three maternal deaths. This study also found that 37 of 419 infectious disease consultants had provided medical care for 55 cases of CDI in peripartum women in the six months before the survey was conducted. In the second, Garey et al. reported the clinical experiences of four peripartum women with CDI at a

tertiary care center. All of these women were exposed to antimicrobials and all developed severe CDI, although none of the infections resulted in maternal death or stillbirth (208).

Summary of Gaps in Knowledge and Contributions of this Study

The epidemiology of HA-CDI is relatively well-established, although the emergence of CDI in the general, non-hospitalized population has demonstrated that significant gaps in our knowledge about this infection persist. This study aimed to build upon the prior research by estimating the incidence of CA-CDI and HA-CDI in an insured population and by examining the relationships between potential risk factors and the acquisition of CA-CDI.

Although reports of CA-CDI are becoming increasingly common, the incidence of this infection cannot be determined easily because there is no active national surveillance system for CDI in the U.S. and because case definitions for CA-CDI are not standardized. This study applied recent CDC surveillance definitions, identified CA-CDI and HA-CDI cases within an insured population, and determined the incidence of infection from 2004 to 2007. By accomplishing these two goals, this study is one of a few to confirm the presence of CDI in the community setting and to estimate the incidence of CA-CDI and HA-CDI within the same population.

Traditional risk factors for HA-CDI include advanced age, severe underlying illness, and antimicrobial use; therefore, clinicians have historically considered persons to be at 'low-risk' for CDI if these risk factors were not present. Additionally, CDI was not typically considered as a diagnosis among persons who were not currently or recently hospitalized; therefore the epidemiologic research which is available has been conducted primarily within hospitalized populations. The few, available epidemiologic studies of community-associated CDI have focus primarily on the distribution of CDI in populations seeking medical care and the description of how and where patients acquire

C. difficile in the community, rather than risk factors that may be associated with infection (9, 199, 209-212). Thus, little is known about potential differences between the characteristics of CA-CDI and HA-CDI cases, the risk factors for CA-CDI, or how these risk factors for CA-CDI may differ from traditional risk factors. However, anecdotal reports have suggested that persons with CA-CDI, in general, may be younger, have fewer comorbid conditions, and have fewer hospitalizations and less exposure to healthcare settings than persons with HA-CDI (8, 10, 196).

The medications commonly associated with increased risk for CDI are antimicrobials and gastric acid suppressants. Although there is a plethora of research about the general association between CDI and antimicrobials, prior research has not defined a consistent at-risk period for CDI following use of antimicrobials and has not addressed the impact of sequential use of different antimicrobials on the risk for CDI. To examine this relationship in depth, the current study determined the risk for CA-CDI related to the use of specific antimicrobials and antimicrobial classes. This study also examined the risk for CDI related to timing of antimicrobial use and the total number of antimicrobial agents utilized in the previous 180 days. Additionally, this study explored whether CA-CDI occurred among persons who do not have exposure to antimicrobials.

The association between gastric acid suppressants and CDI has been inconsistently cited and questions remain about the true nature of this association. It has been suggested that observed associations between gastric acid suppression and CDI can be explained partially or wholly by exposure to antimicrobials. To examine this relationship, this study assessed the risk for CDI related to any use of gastric acid suppressants after controlling for antimicrobial use and the risk related to the timing of the use of these medications. In addition, this study explored the potential interaction between the use of gastric acid suppressants and antimicrobials.

Finally, two studies found an association between the use of antimotility agents and CDI. However, some feel that this association may be explained by reverse causality,

since it is presumed that exposure to antimotility drugs does not typically precede exposure to *C. difficile* or true development of disease. Rather, patients receive antimotility agents to alleviate symptoms of active infection (213, 214). To explore the nature of this association, this study examined the use of antimotility agents and the timing of their use in relation to CDI.

The association between underlying comorbidity and CDI has been established in research conducted in hospitalized populations, although it is unclear if comorbid conditions are a driving force in the development of CA-CDI. This study hypothesized that underlying comorbidity does increase risk for CA-CDI, although it is anticipated that CA-CDI cases will have less comorbidity than typically observed among hospitalized patients with CDI. Furthermore, gastrointestinal disease is associated with increased incidence and severity of CDI, although it is unclear whether these associations are attributed to the gastrointestinal diseases themselves or to therapies used to treat persons with gastrointestinal diseases. This study hypothesized that gastrointestinal disease increases risk for CA-CDI. Sensitivity analysis was conducted to determine if estimates of risk for CA-CDI varied after exclusion of cases with gastrointestinal disease; variations in risk estimates would suggest that CA-CDI cases with gastrointestinal conditions may have different patient of clinical characteristics than CA-CDI cases without these conditions.

Additional sensitivity analyses explored the influence of measurement error in case definitions and the influence of differential surveillance and confounding by indication on risk estimates. Finally, this study also assessed adverse outcomes within this population to determine whether CA-CDI contributed to healthcare services use and healthcare costs at a magnitude similar to that previously reported for HA-CDI.

CHAPTER THREE - RESEARCH METHODS

Overview

This chapter provides a detailed description of the research methodology used to address the specific aims of this study. The chapter opens with an overview of the Data Repository used and the data elements necessary for this study. This is followed by an explanation of the research study design and study population, as well as the inclusion criteria, exclusion criteria, case definitions, and control selection criteria applied to this population. This chapter also describes the potential risk factors and covariates examined, as well as how these data were ascertained from the Data Repository. Finally, this chapter details the methods of statistical analyses for the specific aims of this study.

Ethical Review

This study was initially reviewed and approved by the University of Iowa Institutional Review Board on December 1, 2008. Modifications to the study and continuing review were approved on June 1, 2009 and November 3, 2009, respectively.

Study Data

A retrospective nested case-control study of persons with *Clostridium difficile* infection was conducted utilizing insurance claims data from the Data Repository for the time period between January 1, 2003 and December 31, 2007. The Data Repository is a limited, longitudinal data set consisting of annual data files of de-identified health care claims information for individual members and their covered family members who are fully-insured through commercial insurance underwritten by Wellmark Blue Cross and Blue Shield of Iowa and South Dakota (Wellmark). Wellmark is the largest provider of health insurance in the states of Iowa and South Dakota. The insurance claims in the Data Repository represent care in inpatient, outpatient, office, home health, pharmacy, and extended care/skilled nursing settings for members with health and/or pharmacy benefits.

Claims are linked across claim type and longitudinally by unique de-identified reference identifier (ID) for each individual. The reference identifier can track the same individual over time, even if he/she changes employers and identifies those covered under the same insurance plan (e.g., family members). Individuals are lost to observation upon leaving their insurance coverage. There are no administrative claims for any self-insured group, persons with Medicare Supplemental Insurance, dental insurance, or federal employees.

The number of individuals with both health care and pharmacy insurance ranges from 783,673 (in 2003) to 853,904 (in 2007). Over the entire study period, the Data Repository includes 1,367,656 cumulative unique people. Of these, 240,000 are children. Over the five-year period between 2003 and 2007, the mean duration of coverage for 854,521 individuals was 47.1 months with a median of 50 months and range of 1 to 60 months. Of the members in 2007, 94.4% were continuously covered in 2006, 62.8% in 2005, 46.6% in 2004, and 33.5% in 2003. The age and gender distribution for persons included in the Data Repository from 2003 to 2007 are given in Table 1.

Available information includes insurance coverage and demographic information; medical claims data including prescription medications, diagnosis codes, procedure codes, and claims paid; and provider information. Data obtained for this study included: (1) inpatient and outpatient data with service dates, diagnostic codes (International Classification of Diseases, Ninth Edition (ICD-9) codes; up to five codes per encounter), procedure codes (coded as Current Procedural Terminology, 4th Edition (CPT-4) codes for outpatient physicians and as ICD-9-CM procedure codes for hospitals and surgical centers), type of service, and place of service; (2) outpatient pharmacy data with National Drug Codes (NDCs) codes, date of prescription fill, and drug-days supplied; (3) membership data including type and extent of insurance coverage (i.e., health coverage, prescription drug coverage), duration of insurance coverage and family indicators; (4) demographic data including birth year (utilized to calculate age in years), gender, and member location.

The Data Repository is held and maintained by the Center for Public Health Statistics (CPHS) in the University of Iowa College of Public Health. The University of Iowa and Wellmark, Inc. maintain an open-ended data use agreement that established the Data Repository, which operates under University of Iowa Institutional Review Board (IRB) approval. Access to this data for the purposes of this study was obtained through the required process approved by both parties.

A proposal for this research was submitted to Wellmark through the CPHS in January 2009, and was subsequently approved on February 3, 2009. Upon approval, the staff at CPHS created a subset of the Data Repository containing necessary data elements for the study population, which was stored on a password-protected and isolated server in the College of Public Health. In addition, control selection was conducted by CPHS staff, in accordance with the study design.

Overview of Research Study Design

This research study and its specific aims were designed to provide a comprehensive examination of CDI among members of an insured population. In order to accomplish the goals of the study, CDI cases were identified, case definitions were applied to categorize CDI in the community and hospital settings, and incidence rates for CA-CDI and HA-CDI were calculated for the years from 2004 to 2007. Furthermore, the demographic and clinical characteristics of community-associated and hospital-acquired cases were reported; and, age, medication use, and underlying illness among these case groups were compared. To examine risk factors for CA-CDI within this population, a retrospective nested case-control study was conducted. A case-control study design was chosen due its ability to compare cases (diseased persons) to controls (non-diseased persons) based on their exposure to risk factors. More specifically, the nested case-control study design makes these comparisons within a well-defined cohort over a specified period of follow-up. Recent research reports have documented that the severity

of CDI is increasing, as are adverse outcomes of infection. Thus, adverse outcomes among CA-CDI cases were identified and the use of antimotility agents and demographic and clinical characteristics of cases with and without adverse outcomes were compared.

Study Population

Study Cohort and Subject Selection

All persons in the Data Repository from January 1, 2003 to December 31, 2007 were included in the study cohort. Within this cohort, cases were identified through the use of ICD-9 codes, were selected according to inclusion/exclusion criteria, and were classified according to case definitions. Controls were selected by applying control selection criteria to the study cohort.

Identification of *Clostridium difficile* Infection

Cases were identified within the study cohort as persons with a primary or secondary diagnosis of ICD-9 code 008.45 for 'Infection due to *Clostridium difficile*' listed on an inpatient or outpatient insurance claim. Previous studies have documented the validity of utilizing this ICD-9 code to identify cases of CDI in hospitalized populations. In fact, Dubberke et al. conducted a retrospective cohort study that found that the correlation between *C. difficile*-toxin assay results and this ICD-9 code was good ($\kappa = 0.72$, $p<0.01$); and, the sensitivity and specificity of this ICD-9 code were 78% and 99.7%, respectively (215, 216). Further research by Scheurer et al. reported that, when using microbiological testing as the gold standard, the sensitivity, specificity, positive, and negative predictive values of ICD-9 coding for CDI were 71%, 99%, 87%, and 96%, respectively. The authors of this study suggested that *C. difficile* ICD-9 codes closely approximates true CDI and can be used as an alternative to microbiological data in the hospital setting (217). More recently, Dubberke et al. determined that, when using *C. difficile* toxin assay results as the 'gold standard', this ICD-9 code is adequate for

measuring overall CDI burden but may not be an appropriate surrogate for surveillance of hospital-onset CDI. In this study, hospital-onset CDI was identified through secondary diagnosis codes, while primary diagnosis codes were utilized to identify community-onset CDI cases. This approach over-reported hospital-onset cases, with most of the misidentified cases being community-onset infection or recurrent infection (218). Although validation of this ICD-9 code has primarily occurred within the hospital setting, it has been utilized frequently in studies conducted in administrative databases (144, 153, 219). This study determined that this ICD-9 code is the most appropriate and only viable method for case detection in this administrative database.

Following identification of cases in the study cohort, study inclusion and exclusion criteria were applied. Once these criteria were applied, cases were further classified as community-associated, indeterminate, or hospital-acquired.

Study Inclusion Criteria

Only subjects with complete and continuous membership information were included because incomplete information would prevent comprehensive ascertainment of demographic information. In addition, only subjects with both health and drug insurance coverage were included in this study to ensure complete ascertainment of healthcare utilization and the use of prescription medications. Subjects were required to have equal to or greater than 12 months of insurance coverage prior to diagnosis date or index date (for controls) to be considered eligible for inclusion in this study. This period of insurance coverage was determined from membership information confirming duration of health and drug insurance coverage. This follow-up time was required to ensure the adequate measurement of prescription drug exposures and patient medical history, including comorbid conditions. Furthermore, CA-CDI cases were required to have observation time of at least 180 days following diagnosis of *C. difficile* in order to identify potential outcomes and to identify the use of antimotility agents.

Study Exclusion Criteria

A case was excluded if he/she was diagnosed with CDI in a nursing home or if he/she had a history of nursing home claims in the six months prior to CDI diagnosis. Potential study subjects were also excluded from control selection if they had a documented history of nursing home claims within six months of the diagnosis for a case. Long-term care exposure was identified as an insurance claim with a service place listed as 'nursing home'. This exclusion criterion acknowledges prior research suggesting that patients who acquire *C. difficile* or develop CDI in nursing home settings may have healthcare experiences or exposure to risk factors which differ from those in hospital or community settings. For example, in nursing home settings, prevalence of antimicrobial usage is high, infection control practices may be less stringent than in hospitals, periods of contact between patients and healthcare workers may be more prolonged than in hospital settings, and nursing home workers may be less aware of indications for *C. difficile* testing (220, 221).

For cases, only the first occurrence of *C. difficile* diagnosis was utilized in this study because patients with a previous diagnosis of CDI may be different than those with a first diagnosis. For example, patients with prior disease may be less likely to receive a prescription for antimicrobials because they may be considered at high risk for CDI. Therefore, the exclusion of second diagnoses of CDI in risk factor assessment over this time period decreases the risk of bias in antibiotic use estimates.

Development and Application of *C. difficile* Infection Case Definitions

Background Information

C. difficile infection is clinically defined as a case of diarrhea or toxic megacolon that meets one of the following criteria: 1) a positive *C. difficile* toxin assay or culture; 2) pseudomembranous colitis seen during endoscopic examination or a surgical procedure;

and/or 3) pseudomembranous colitis seen during autopsy (87). In addition, cases of CDI are categorized according to where the infections were acquired or the location of the patient at the time of symptom onset.

The current practice in hospital epidemiology is to define HA-CDI as a case of CDI with symptoms occurring more than 48 hours after admission to a healthcare facility, or a case presenting in the community or to a hospital with onset of symptoms less than 4 weeks after a prior discharge from a healthcare facility (222). Because the majority of epidemiological studies on this infection have been conducted in hospitalized populations--mainly due to the relatively high incidence in this group, its high importance as an infection control issue, as well as the availability of data for these patients--case definitions for hospital-acquired infection are more widely accepted and more frequently applied. In contrast, the classification of CDI acquired outside of the hospital setting is still in the early stages of application in research.

A consensus on defining CA-CDI does not exist, although The European Centre for Disease Prevention and Control and the United States Centers for Disease Control and Prevention (CDC) have proposed similar definitions (222, 223). These recommended surveillance definitions suggest that a patient with *C. difficile* has community-associated infection if he/she experienced symptom onset either in the community (i.e., outside a healthcare facility) or within the first 48 hours after admission to a healthcare facility, provided that the patient has no hospital admissions within the past 12 weeks. The CDC additionally defines indeterminate cases of CDI as those who do not meet criteria for community-associated or hospital-acquired classification; this group includes patients who were hospitalized between 4 and 12 weeks prior to onset of CDI symptoms and subsequent *C. difficile* diagnosis.

These recommendations have not been applied widely at this time. Kutty et al. reported that a substantial proportion of hospital-acquired cases with onset in the community occurred and resulted in medical care less than 4 weeks after a preceding

hospital discharge. This observation supports the premise that cases occurring within this four-week period should be attributed to exposure in a hospital setting, and suggests that cases occurring outside this window of time are most likely not hospital-acquired, but rather are community-associated or indeterminate in nature. Further research is needed to solidify the merit of classifying community-associated and indeterminate cases beyond this four week period (224).

Study Case Definitions

For this study, CDC-recommended surveillance definitions were adapted for application in the Data Repository and cases were classified into three case groups: community-associated, indeterminate, or hospital-acquired (222). Only community-associated and hospital-acquired CDI cases were utilized to address the specific aims of the study.

A case of CA-CDI was defined as meeting one of the following: (a) a primary or secondary diagnosis of ICD-9 code 008.45 diagnosed in the outpatient setting with no history of being discharged from a hospital in the twelve weeks prior to diagnosis; or, (b) a primary diagnosis of 008.45 at the time of hospitalization with no history of being discharged from a hospital in the twelve weeks prior to diagnosis.

A case of HA-CDI was defined as meeting one of the following: (a) a secondary diagnosis of ICD-9 code 008.45 during hospitalization; (b) a primary diagnosis of 008.45 at the time of hospitalization with a history of being discharged from a hospital in the 4 weeks prior to diagnosis; or, (c) a primary or secondary diagnosis of ICD-9 code 008.45 in the outpatient setting with a history of being discharged from a hospital in the 4 weeks prior to diagnosis.

Finally, a case of indeterminate CDI was defined as meeting one of the following*:* (a) a primary or secondary diagnosis of ICD-9 code 008.45 in the outpatient setting with a history of being discharged from a hospital between four and twelve weeks prior to

diagnosis; or, (b) a primary diagnosis of ICD-9 code 008.45 at the time of hospitalization with a history of being discharged from a hospital between four and twelve weeks prior to diagnosis.

Control Selection

In nested case-control studies, controls are selected using a 'risk set sampling' approach. In this approach, 'risk sets' are defined as a case and all persons in the study cohort who are 'at risk' on the corresponding diagnosis date for that case (i.e., those that have not been diagnosed with *C. difficile* up to that point in time). Once a risk set was established for each case, ten controls who met the control selection criteria were randomly selected for each case. Selection criteria were similar to that for cases, except that controls were required to not have *C. difficile* prior to the diagnosis date for a case. The control selection criteria for this study were: a) no diagnosis of *C. difficile* prior to diagnosis date for cases; b) current and complete health and drug coverage on the date that a case was diagnosed – controls were "matched" to cases based on this "index date"; c) one year (12 months) of continuous health and drug insurance coverage prior to the diagnosis date for a corresponding case; d) complete membership information; and e) no history of nursing home claims in the 6 months prior to index date.

The ratio of 10 controls for each case was chosen because it has been shown that, when 10 controls are selected per case in nested case-control studies, the precision of the parameter estimates will be nearly identical to the parameter estimates obtained from analysis of the entire cohort (225). This study allows future cases to serve as controls, which is consistent with the nested case-control design. The primary advantage of this approach is that it allows us to calculate odds ratios which validly estimate rate ratios, without need for the rare-disease assumption. Finally, this control selection algorithm controls for the effect of calendar time since cases and controls were matched based on diagnosis/index date. The effects of calendar time may be important if there were changes

in clinical recognition and diagnosis of CDI or if there have been changes in antimicrobial prescribing practices during the study period. This method of matching by date also accounts for the possibility that CDI occurrence is seasonal in nature. Prior research has suggested that CDI may follow a seasonal pattern due to seasonal variations in the incidence of infection and resultant antibiotic prescribing (226).

Risk Factors and Outcomes Examined in this Study

Prescription Drugs

This study addressed use of antimicrobial agents and gastric acid suppressants as potential risk factors for CA-CDI. Specific prescription drugs of interest were identified through the review of scientific literature, and data were obtained from outpatient prescription claims data. National Drug Codes (NDCs) were utilized to identify drugs prescribed to study subjects. NDCs are unique, three-segment numbers that serve as the universal product identifier for drugs used for human treatment. The Multum Lexicon®, RxNorm®, and Red Book® databases were utilized to identify prescription drugs and their variations and to classify drugs further (i.e., antimicrobial classes) (227-229). All prescription drug data variables in this study were constructed through a combination of NDCs, the date the prescription was filled, and the number of days for which the prescription was supplied. The date of prescription fill and days supplied for each fill was used to estimate the days on which cases or controls were exposed to prescription medication. Cases or controls were considered to be exposed in the 180 days preceding the diagnosis date for cases or 180 days preceding the assigned index date for controls if they had exposure to a prescription drug for at least one day within the time period. Use of antimotility agents was examined by identifying the use of these drugs in both the 180 days preceding but not including the diagnosis date for cases and index date for controls, and within the 180 days following diagnosis date for CA-CDI cases.

Identification of Prescription Medications

Prescription medications received by study subjects between January 1, 2003 and December 31, 2007 were identified by National Drug Codes on outpatient prescription drug claims. During the study time period, there were 55,662 total paid insurance claims for prescription drugs for CA-CDI cases, while control subjects had 79,499 paid prescription drug claims. Among these claims, there were 4,065 unique NDCs coded within the case population claims and 4,744 unique codes within the control population claims. These NDC codes were matched to three medication classification systems to identify prescription drugs: Multum Lexicon® (227), RxNorm® (228) , Red Book® (229) . After comparing the NDC codes on prescription drug claims for CA-CDI cases to these databases, we were able to identify prescription drugs on 54,679 out of 55,662 claims (98.23%) utilizing the Multum Lexicon; 53,423 out of 55,662 claims (95.98%) codes utilizing RxNorm; and 55,452 out of 55,662 claims (99.62%) utilizing Red Book. For control subjects, we were able to identify prescription drugs for 78,340 out of 79,499 claims (98.54%) utilizing the Multum Lexicon; 76,071 out of 79,499 claims (95.69%) codes utilizing RxNorm; and, 79,303 out of 79,499 claims (99.75%) utilizing Red Book. Although we were not able to identify all prescription drugs, the rate of NDC code identification was extremely high and adequately identified drugs that were specified of interest in this study.

Antimicrobial Medications

This study aimed to assess the associations between the use of specific antimicrobial drugs and/or classes and CA-CDI. This knowledge is important for the development of interventions, such as appropriate prescribing practices, which may prevent CA-CDI. Timing of antimicrobial use prior to CDI diagnosis was assessed to determine the at-risk period for CA-CDI following the use of antimicrobial agents. The total number of different antimicrobial drugs was also examined to determine whether

exposure to a greater number of antimicrobial agents increased risk for CA-CDI. Further analyses were conducted to describe the duration of antimicrobial use among cases and controls.

Antimicrobial use was first examined through the creation of indicator variables representing ever- or never-use for each antimicrobial agent and/or antimicrobial class. The prevalence of use of specific antimicrobial agents among cases and controls was calculated using these indicator variables. Specific antimicrobials or antimicrobial classes included aminoglycosides, beta-lactamase inhibitors, cephalosporins, clindamycin, fluoroquinolones, macrolides, penicillins, sulfonamides, tetracyclines, and intravenous vancomycin. In addition to examining which antimicrobials are more strongly-associated with CA-CDI, this analysis was utilized to assess whether the at-risk antimicrobials identified in this study were different from those most commonly-cited in prior studies (i.e., clindamycin, cephalosporins, penicillins, and fluoroquinolones) (16, 24, 37). Antimicrobial drugs and their corresponding classes are shown in Table 2.

The timing of most recent use of any antimicrobial in relation to CDI diagnosis date (or index date for controls) was categorized as use in the 1 to 30 days prior to diagnosis or index date, in the 31 to 60 days prior to diagnosis/index date, in the 61 to 90 days prior to diagnosis/index date, in the 91 to 120 days prior to diagnosis/index date, in the 121 to 150 days prior to diagnosis/index date, and in the 151 to 180 days prior to diagnosis/index date. To program these measures of antimicrobial use, each person-day of use for any antimicrobial drug was classified according to these categories of timing of use. Subjects were categorized into one of these mutually exclusive groups based on their most recent use of an antimicrobial agent in relation to diagnosis or index date was classified within that timing category.

The total number of different antimicrobial agents prescribed to and filled by each case or control was calculated and compared among study groups. The number of agents was calculated by identifying each individual antimicrobial from prescription drug claims

data and summing the number of different agents used during the 180 days prior to diagnosis date for cases and index date for controls.

The number of days for which antimicrobials were prescribed and filled was utilized as a descriptive statistic. The duration of antimicrobial use was calculated as the sum of antimicrobial drug-days supplied in the 180 days up to but not including the diagnosis date for cases and index date for controls and was analyzed as a continuous variable.

For all analyses of antimicrobial use, the use of topical or ophthalmic antimicrobials was excluded because these antimicrobials do not disrupt normal colonic flora and, therefore, are not related to the acquisition of CDI. In addition, metronidazole and oral vancomycin use were not included in risk factor analysis, since these drugs are both utilized as treatments for CDI.

Gastric Acid Suppressants

The use of gastric acid suppressants has been linked with CDI in some studies, but not in others. This study aimed to determine if gastric acid suppressant use increases the risk for CA-CDI and if this risk varies based on time since last receipt of a gastric acid suppressant. Indicator variables were created to represent ever or never use of proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H_2A) in the 180 days prior to but not including the diagnosis date for cases or index date for controls. The prevalence of use of these medications and the use of any gastric acid suppressant was determined through the use of these indicator variables. Classes of gastric acid suppressants and the medications corresponding to these classes are included in Table 3.

The timing of gastric acid suppressant use in relation to the CDI diagnosis date (or index date for controls) was assessed to determine the at-risk period for CA-CDI following use of these medications. Timing of the most recent use of any gastric acid suppressant was categorized as use in the 1 to 30 days prior to diagnosis or index date,

use in the 31 to 60 days prior to diagnosis/index date, use in the 61 to 90 days prior to diagnosis/index date, use in the 91 to 120 days prior to diagnosis/index date, use in the 121 to 150 days prior to diagnosis/index date, and use in the 151 to 180 days prior to diagnosis/index date. Each person-day of use for any of these drugs was classified according to these categories. Subjects were categorized into each mutually exclusive group based on their most recent use of a gastric acid suppressant in relation to diagnosis or index date was classified within that group.

Antimotility Agents

This study examined outpatient use of antimotility agents in the 180 days prior to diagnosis date for CA-CDI cases and index date for controls and in the 180 days following diagnosis among CA-CDI cases. Use of these agents was determined through NDC codes for the following agents: diphenoxylate (Lomotil) and loperamide (Immodium) (Table 3). Antimotility agent use was coded and analyzed as an indicator variable representing ever/never use of these medications. The prevalence of antimotility agent use was assessed through a series of indicator variables.

This study hypothesized that there is no association between the use of antimotility agents and development of CDI. Rather, previously-reported associations are most likely explained by reverse causality, such that it is presumed that exposure to these drugs does not typically precede exposure to *C. difficile* or CDI symptom onset and patients receive antimotility agents to alleviate symptoms of active infection (213, 214). To determine the true nature of this association, the risk associated with any antimotility agent use was assessed by univariate and multivariate analysis to determine the unadjusted and adjusted risk related to their use.

The timing of antimotility agent use in relation to diagnosis for CA-CDI cases and index date for controls was examined to determine if risk due to antimotility agent use is consistent over time. Consistently elevated risk estimates for timing categories would

suggest a true association. In turn, a sudden decrease in risk over time would suggest that these medications were used for alleviation of symptoms of CDI and were not related to infection. If the latter is true, observed associations between antimotility agents and CA-CDI would be due to reverse causality. The timing of use of antimotility agents was categorized as most recent use in the 1 to 7 days prior to diagnosis or index date, in the 8 to 30 days prior to diagnosis/index date, in the 31 to 60 days prior to diagnosis/index date, in the 61 to 90 days prior to diagnosis/index date, in the 91 to 120 days prior to diagnosis/index date, in the 121 to 150 days prior to diagnosis/index date, and in the 151 to 180 days prior to diagnosis/index date. Finally, use of antimotility agents following diagnosis was assessed descriptively and as a potential predictor of adverse outcomes among CA-CDI cases.

Comorbidity Measures

The presence of comorbid conditions was determined for all cases and controls based on diagnoses codes recorded on inpatient and outpatient claims in the year up to but not including the diagnosis date for cases and the index date for controls.

Charlson Comorbidity Index

Underlying severe illness is associated with CDI, although some investigators have hypothesized that cases in the community setting may be younger and may have less comorbidity than cases in the hospital setting. Comorbidities, in general, are medical conditions that are underlying the primary illness for which a person is seeking medical attention (230). These medical conditions increase a person's total burden of disease, are likely to contribute to risk of complications or death, and may affect physician choice of treatment for other illness (230). When trying to account for these conditions in medical research, it is often difficult to include individual comorbid conditions in one statistical model due to the concern for overfitting (231-233). To address this issue and to account for underlying illness in CDI cases and control, the collective effect of multiple comorbid

conditions was assessed through the use of Deyo-Charlson Comorbidity Index with a modification outlined by Klabunde et al (234, 235).

The Charlson Comorbidity Index was first developed as a weighted index which was shown to predict one-year mortality in a small cohort of hospitalized patients (236, 237). The index assigns a weight to each of 19 conditions based on their potential for increasing the likelihood of death. Each patient's specific conditions are identified, at which point the weights for comorbidities are added to serve as a summary score. This summary score takes into account both the number of conditions and the risk associated with these conditions into account. A higher score represents higher levels of comorbidity (236). Deyo et al. adapted this index for use with ICD-9-CM diagnosis and procedure codes; consequently, the Deyo-Charlson Comorbidity Index is widely used in studies conducted in administrative databases and has been shown to be predictive of adverse outcomes such as substantial increases in length of stay, hospital charges, and mortality.(238). A complete listing of comorbid conditions included in the Deyo-Charlson Comorbidity Index, the associated ICD-9 codes, and weighting of conditions within the index are included in Table 4.

The Deyo-Charlson Comorbidity Index was initially developed and validated for research using inpatient medical claims. To address this limitation, Klabunde et al. developed revised methods based on the Charlson Comorbidity Index but extended its application to outpatient physician claims. In this modification, a comorbid condition is considered "present" if the ICD-9 code corresponding to a comorbid condition is listed as a primary or secondary diagnosis on one inpatient claim or on two outpatient claims occurring 30 or more days apart in the year prior to diagnosis date for cases or index date for controls (234, 235).

Gastrointestinal Comorbid Conditions

Several gastrointestinal comorbidities are of interest as independent risk factors for CDI. Gastrointestinal comorbidities of interest include inflammatory bowel disease (includes Crohn's disease and ulcerative colitis), diverticular disease, and gastroesophageal reflux disease (GERD). A literature review was conducted to identify ICD-9 codes associated with these conditions. Primary or secondary diagnoses of gastrointestinal conditions were identified on inpatient and outpatient claims, and were subsequently coded as dichotomous variables representing the presence or absence of each respective comorbidity. Gastrointestinal conditions were considered "present" if the corresponding ICD-9 code was either listed as a diagnosis on one inpatient claim or a diagnosis on two outpatient claims occurring 30 or more days apart in the year prior to diagnosis date for cases or index date for controls (234). Relevant diagnosis codes for gastrointestinal conditions are listed in Table 5.

History of Hospitalization

Acquisition of *C. difficile* is common within hospitals; therefore, a history of hospitalization may provide insight into the source of this pathogen even in cases with CA-CDI. History of hospitalization was defined as ever or never being discharged from a hospital in the time period from 84 to 365 days (i.e., 12 weeks to one year) prior to diagnosis date for cases or index date for controls, as determined by inpatient insurance claims. This time period was necessary to account for the case definition of CA-CDI, which required that cases not have a history of hospitalization in the 12 weeks (84 days) prior to diagnosis.

Age

Advanced age has been consistently related with HA-CDI, thus this study aimed to determine if this same is true for CA-CDI. Age was ascertained from membership data files. Birth year was present in membership information; therefore, age was calculated as

the difference between birth year and the year in which a case subject was diagnosed with CDI or the year of the index date for a control subject. This study provided descriptive statistics for age and categorized age for risk factor analysis. Age was categorized as 'less than 18 years', '19-49 years', '50-64 years', '65-74 years', and '75 years or greater'.

Covariates

Gender

Gender was obtained from membership information for cases and controls, and was categorized and coded as an indicator variable for 'male' or 'female'.

Healthcare Utilization

Healthcare utilization was measured by the number of outpatient physician visits in the year (365 days) prior to but not including the diagnosis date for cases and the index date for controls. Physician visit data were ascertained from outpatient insurance claims, and the number of outpatient visits was modeled as a continuous variable. This variable was included in the analysis to serve as another measure of underlying health status.

Assessment of Adverse Outcomes

Potential adverse outcomes of CDI include surgical intervention, subsequent hospitalization related to CDI, and additional treatment due to presumed recurrent or relapsing infection. Surgical procedures that are included as adverse outcomes of CDI were identified through literature review and include the following colectomy procedures: partial or subtotal colectomy, cecal colectomy, left colon colectomy, multiple segmental colectomy, right colon colectomy, sigmoid colectomy, subtotal colectomy, and transverse colon colectomy (176). Of note, subtotal colectomy is the surgical standard of care for patients with complicated *C. difficile* colitis (219). Surgical procedures related to CDI were identified through ICD-9 procedure codes on inpatient insurance claims during

the 180 days following CDI diagnosis, and the presence or absence of a procedure was analyzed as an indicator variable.

Subsequent hospitalization related to CDI was defined as an admission to a healthcare facility with a primary diagnosis of ICD-9 code 008.45 occurring on the initial date of diagnosis or within 8 weeks (i.e., 56 or fewer days) of this date. These events were categorized as ever hospitalized due to CDI or never hospitalized due to CDI.

The use of either metronidazole or oral vancomycin after initial therapy in the 180 days following the diagnosis date was assessed to identify prolonged need for treatment and to explore the potential use of these measures as a marker for CDI recurrence or relapse.

Statistical Methods

All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC). Two-tailed tests were used to determine statistical significance, with the Type I error rate (α) set at 0.05. Two-sample statistical comparisons of continuous variables were conducted utilizing the Student's t-test, while statistical comparisons for categorical variables were conducted using the chi-squared test. The Fisher's exact test was used for the statistical comparison of categorical variables with small sample sizes.

Specific Aim I Statistical Analysis

To apply case definitions for community-associated and hospital-acquired C. difficile infection in an insured population over the period from 2004 to 2007. To provide incidence rate estimates for the study period and descriptive statistics for cases of community-associated and hospital-acquired C. difficile infection.

Description of Cohort and Application of Case Definitions

The distributions of age and gender for the entire study cohort were determined from membership information. Cases were identified based on diagnosis information provided on inpatient and outpatient claims. Membership and insurance claims data were accessed for persons with an inpatient or outpatient diagnosis of ICD-9 code 008.45. After identification of persons with CDI, case definitions were applied by examining place of service in which CDI was diagnosed and history of hospitalization prior to diagnosis date. The history of hospitalization was ascertained from inpatient insurance claims and was classified as no hospitalization, discharge from a hospital in the four weeks prior to diagnosis, discharge four to twelve weeks prior to diagnosis, and discharge over twelve weeks prior to diagnosis.

Exploratory analysis was conducted to determine if CDI cases had undergone *C. difficile* diagnostic testing in the 180 days prior to the appearance of ICD-9 code 008.45 on an insurance claim. This analysis was intended to provide further information about the potential for delayed identification and diagnosis of CDI within insurance claims. Diagnostic testing was identified by the following CPT codes: 87230 (toxin or antitoxin assay, tissue culture); 87493 (Infectious agent detection by nucleic acid (DNA or RNA); *Clostridium difficile*, toxin gene(s), amplified probe technique); 87803 (antigen detection by immunoassay; *Clostridium difficile* toxin A); and, 87324 (Infectious agent antigen enzyme immunoassay technique; *Clostridium difficile* toxin). Descriptive statistics were conducted to provide the number of cases who underwent *C. difficile* testing prior to ICD-9 code diagnosis and the duration of time between *C. difficile* testing and the appearance of ICD-9 code 008.45.

Calculation of Incidence Rates

Incidence rates for first occurrence of community-associated and hospital-acquired CDI were calculated for all years from 2004 to 2007. Incidence rates were

calculated as the number of persons meeting the case definitions for CA-CDI or the number of persons meeting the case definition for HA-CDI per 100,000 person-years of observation time. The denominator data for the incidence rates included the entire Data Repository population and were calculated based on observation time for each person for each year. The monthly incidence of CA-CDI and HA-CDI were also calculated; these incidence estimates were utilized to describe potential seasonality in the occurrence of CDI.

Description of Community-associated and Hospital-acquired CDI Cases

Summary statistics were calculated for the demographic characteristics, healthcare utilization, comorbid conditions, and medication use of CA-CDI and HA-CDI cases. The mean, median, range, and standard deviation were calculated for continuous variables (including age, Charlson Comorbidity Index score, number of antimicrobials utilized). Mean values for continuous variables were statistically compared. The frequency and distribution of categorical variables (including age categories, gender, use of specific medications, specific Charlson comorbid conditions, and presence of gastrointestinal conditions) were examined and compared among CA-CDI and HA-CDI cases.

Specific Aim II Statistical Analysis

To identify patient-related risk factors for CA-CDI in an insured population.

Description of Community-associated CDI Cases and Corresponding Controls

Summary statistics were calculated for the demographic characteristics, healthcare utilization, clinical characteristics, and medication use of CA-CDI cases and

controls. The mean, median, range, and standard deviation were calculated for continuous variables (including age, number of primary care visits, Charlson Comorbidity Index score, number of antimicrobials utilized, and duration of antimicrobial use). Mean values for continuous variables were statistically compared. The frequency and distribution of categorical variables (including age categories, gender, use of specific classes of medications, timing of antimicrobial and gastric acid suppressant use, gastrointestinal conditions, and history of hospitalization) were examined and statistically compared among case and control subjects.

Univariate and Multivariate Modeling Procedures

Conditional logistic regression methods were necessary for both univariate and multivariate modeling to account for matching of cases and controls on date. Univariate conditional logistic regression was used to estimate the crude odds ratios and corresponding 95% confidence intervals for the associations between CA-CDI and specific antimicrobial use, the number of antimicrobial agents prescribed, use of any gastric acid suppressant, comorbidity, gastrointestinal disease, history of hospitalization, healthcare utilization, age (in categories), and gender. In univariate analyses, the timing of antimicrobial and gastric acid suppressant use were assessed as a series of indicator variables utilizing 'no use in the prior 180 days' as the reference group. The significance of univariate associations was assessed through the use of 95% confidence intervals; confidence intervals not including one were considered statistically significant. Univariate models for the use of antimotility agents and the timing of use of these medications were also constructed, and were utilized to determine whether a true association exists or whether potential associations may be due to protopathic bias (i.e., reverse causality).

Multivariate conditional logistic regression models were utilized to estimate odds ratios and 95% confidence intervals for all predictor variables after adjustment for all

other covariates. Demographic characteristics, healthcare utilization, comorbid conditions, and medication use were included in these multivariate models based on prior knowledge and prevalence among study groups. Demographic characteristics and healthcare utilization measures assessed in multivariate models included age, gender, history of hospitalization in the prior 365 days, and number of outpatient physician visits within the prior year. Age was assessed as a risk factor for CA-CDI, since advanced age is a risk factor in numerous, prior studies. History of hospitalization was included in the models to assess the effect of exposure to medications and to the pathogen itself in the hospital setting, neither of which could be measured directly in this study. The number of outpatient visits served as a measure of underlying health status and healthcare utilization. The Charlson Comorbidity Index and gastrointestinal comorbid conditions (i.e., IBD, diverticular disease, and GERD) were included in the multivariate models to assess the effect of underlying comorbidity and gastrointestinal disease on the risk of CA-CDI and to control for confounding by indication. Only specific antimicrobial agents and/or classes that were prescribed sufficiently often among the study groups were included in multivariate modeling. Drugs modeled in multivariate analysis included: clindamycin, penicillins, beta-lactamase/beta-lactamase inhibitor combinations, cephalosporins, fluoroquinolones, macrolides, penicillins, sulfonamides, and tetracyclines. Multivariate models were constructed separately to assess the use of specific antimicrobials or antimicrobial classes, timing of antimicrobial use, and the total number of antimicrobial agents. These models were also utilized to determine the effect of any gastric acid suppressant use. Separate models were utilized to determine the effects of the use of antimotility agents and to assess the timing of antimotility agent use.

In all multivariate models, confounding was assessed for variables that were potentially related to the outcome and to other predictor variables. Variables were considered to be potential confounders if they were deemed plausible through a priori knowledge of the association of a confounder with other exposures and with CA-CDI or

if they were significantly correlated with other predictor variables and with CA-CDI at a p-value < 0.20. Confounding variables were controlled for in the analysis by inclusion in multivariate models.

Interaction between antimicrobial use and gastric acid suppressant use was assessed to determine whether the effect of one exposure on acquisition of CA-CDI depends on the presence of the other exposure. Multiplicative interaction was examined by comparing observed and expected joint effects of antimicrobial use and gastric acid suppressants obtained from a logistic regression model including these variables. The expected joint odds ratio is estimated as the multiplication of independent odds ratios. If the expected joint odds ratio is similar to the observed joint odds ratio, interaction is not present or is weak. In addition, the statistical significance of an interaction term for antimicrobial use and gastric acid suppressant use was tested in a logistic regression model including main effects and the interaction term. A p-value of less than 0.05 for the interaction term is considered statistically significant, suggesting that these two terms interact.

The use of multiple multivariate models was considered to be the most effective approach to addressing the specific aims of this study, while controlling for all hypothesized risk factors for CA-CDI, covariates, and potential confounding factors. C-statistics were calculated to determine the predictive ability of all multivariate models.

Sensitivity Analyses

Sensitivity analyses were conducted to determine whether the risk estimates obtained from multivariate models are robust following examination of potential measurement error in the study case definition and examination of the potential role of protopathic bias. First, sensitivity analyses were conducted to determine if variation in the case definition results in different estimates than those provided by the multivariate models in the primary analysis. In this analysis, CA-CDI was defined as a primary or

secondary diagnosis of ICD-9 code 008.45 in the outpatient setting without a history of being discharged from a hospital during the 12 weeks prior to diagnosis (i.e., excluding cases whose CDI diagnosis occurred in the hospital). This alternate case definition provided a more conservative approach to the classification of cases than that used in the primary analysis since it assumes that all community-associated cases were diagnosed in the outpatient setting following a period of 12 or more weeks without hospitalization. Summary statistics were calculated to identify potential differences in the descriptive information for this case group in comparison to all cases included in the main study. Univariate and multivariate analyses were conducted for all study risk factors to determine if the use of an alternate case definition effected risk estimates.

Another sensitivity analysis excluded CA-CDI cases who: (1) had a diagnosis of a gastrointestinal condition in the one year prior to diagnosis of CDI; or, (2) had a history of hospitalization within 6 months prior to diagnosis; or, (3) underwent outpatient dialysis or chemotherapy in the 1 year prior to diagnosis. The cases meeting any of these criteria may not be homogeneous with others in the study population in regard to disease surveillance or exposure to *C. difficile* itself. Cases with gastrointestinal conditions may have pharmacologic exposures for treatment of their disease which are not directly measured in this study but may be related to CDI. In addition, persons with gastrointestinal conditions may present with symptoms of their disease that are similar to those of CDI. Thus, clinicians may have a higher degree of diagnostic suspicion, resulting in differential surveillance for CDI within this population. The exclusion of these cases also acknowledges the potential that exposures during hospitalization may impact risk for CDI longer than suspected, thus leading to misclassification of cases as community-associated when their infection is actually related to exposures in the hospital setting. Finally, the exclusion of persons undergoing outpatient dialysis or chemotherapy acknowledges that, although these persons are not admitted to a healthcare facility, they may have increased opportunity of exposure to *C. difficile* due to frequent visits to

healthcare facilities. Persons undergoing outpatient dialysis were identified by the following Current Procedural Terminology (CPT) codes: 90935, 90936, 90937, and 90999 (239). Persons undergoing outpatient chemotherapy were identified by the following ICD-9 and Healthcare Common Procedure Coding System (HCPCS) codes for administration of chemotherapy: ICD-9 diagnosis code V58.1; ICD-9 procedure code 99.25; and HCPCS codes 964xx, 965xx, and Q0083-Q0085. Controls corresponding to excluded cases were also excluded from analysis. All exposure ascertainment used in the primary analysis remained the same for cases and controls, except, history of hospitalization for controls was redefined as discharge from a hospital occurring in the time period between 180 and 365 days (i.e., 6 months to one year) prior to index date. Summary statistics were calculated to identify potential differences in the descriptive information for this case group in comparison to all cases included in the main study. Univariate and multivariate analyses were conducted for all study risk factors to determine if these exclusions effected risk estimates.

An additional sensitivity analysis was performed to determine whether the redefinition of diagnosis date and the resultant shift in the time window for exposure assessment affected risk estimates obtained from multivariate modeling. This analysis assumed that cases had symptoms of CDI earlier than identified by insurance claims if they had recent history of treatment of CDI infection, use of medication for alleviation of CDI symptoms, or diarrheal disease. These cases had: (1) a prescription drug claim listing an NDC code associated with antimotility agents in the 180 days prior to diagnosis; or, (2) a prescription drug claim listing an NDC code associated with oral vancomycin in the 180 days prior to diagnosis; or, (3) a diagnosis of non-specific diarrheal disease on inpatient or outpatient claims in the 180 days prior to the original diagnosis date. The diagnosis date for cases who met any of these criteria was reassigned as either the date of the first prescription or the date of the diagnosis of nonspecific diarrheal disease. The CA-CDI case definition from the main analysis was again applied

such that cases with a history of discharge from a hospital within 12 weeks of the revised diagnosis date were excluded from this analysis. Assessment of medication exposure was conducted in the 180 days prior to the revised diagnosis dates for cases, while comorbidity and healthcare utilization were measured in the 365 days prior to this date. The index date for controls was not adjusted to account for these revised diagnosis dates, although it is unlikely that this impacted the risk estimates obtained from this analysis. Non-specific diarrheal diseases were identified by the following ICD-9 codes: 008.49, 008.5, 008.69, 008.8, 009.x, 558.x, 787.9, and 787.91 (240). Summary statistics were calculated to identify potential differences in the descriptive information for this case group in comparison to all cases included in the main study. Univariate and multivariate analyses were conducted for cases with and without revised diagnosis dates for all study risk factors to determine if the redefinition of diagnosis date impacted risk estimates. It should be noted that, although metronidazole is also a treatment for CDI, its use was not assessed in this analysis because this drug can be used for other indications in the outpatient setting. The inclusion of metronidazole use in this analysis was considered although it was felt that concurrent diagnosis of diarrheal disease and metronidazole prescription would be required to make valid assumptions about delayed diagnosis, thus the use of diagnosis of diarrheal use accounts for these individuals.

Power Calculation

The statistical power of this study was calculated utilizing the number of CA-CDI cases identified in the study population. Statistical power was calculated by varying the minimum significant risk estimates we were able to detect, using a two-tailed test with an α of 0.05, and a control to case ratio of 10:1. For this study, the expected exposure rate, σ, was set to 0.20, since preliminary results revealed that roughly one-fourth of study participants utilized an antimicrobial drugs during the study period. The power to detect

was 96.2% for an OR of 2.0; 93.1% for an OR of 1.9; 87.9% for an OR of 1.8; 80.1% for an OR of 1.7; 69.4% for an OR of 1.6; and, 56% for an OR of 1.5.

Specific Aim III Statistical Analysis

To describe adverse health outcomes of CA-CDI and to explore potential risk factors for these outcomes in persons with CA-CDI.

Identification and Description of Adverse Health Outcomes in CA-CDI Cases

Adverse outcomes occurring among persons with CA-CDI in the 180 days following diagnosis were identified through ICD-9 codes on inpatient and outpatient insurance claims. Surgical procedures were identified and dichotomized as presence or absence. The following procedures and associated codes were identified: 45.79 (partial/subtotal), 45.72 (cecal), 45.75 (left colon), 45.71 (multiple segmental), 45.73 (right colon), 45.76 (sigmoid), 45.8 (subtotal), and 45.74 (transverse colon) (176).

Subsequent hospitalization related to CDI was defined as an admission to a healthcare facility with a primary diagnosis of ICD-9 code 008.45 on the date of diagnosis or within 8 weeks (i.e., 56 or fewer days) of diagnosis date. These events were determined from inpatient claims and were analyzed as a dichotomous variable representing ‘ever admitted for CDI’ or ‘never admitted for CDI’.

Use of metronidazole or oral vancomycin in the 180 days following diagnosis date was defined as the presence or absence of NDC codes for these medications on outpatient prescription drug claims. The receipt of these prescription medications was categorized as ‘ever received’ or ‘never received’.

Use of Antimotility Agents among CA-CDI Cases Following Diagnosis

Use of antimotility agents among CA-CDI cases in the 180 days following diagnosis date was assessed through the NDC codes for atropine-diphenoxylate and loperamide on outpatient prescription drug claims. Inpatient use of these medications could not be ascertained from prescription drug claims. Receipt of these drugs was coded as an indicator variable for ever or never prescribed antimotility agents in this time period.

Statistical Analysis of Adverse Outcomes Associated with CA-CDI

The absolute number of cases with outcomes was reported and rates for these outcomes were calculated. Descriptive summary statistics of all study variables were calculated for CA-CDI cases who experienced adverse health outcomes. The mean, range, and standard deviation were calculated for continuous variables. The frequency of categorical variables among these cases was also examined.

The time period between diagnosis of CDI and the occurrence of outcomes for cases was calculated and reported as the mean and the median days since the diagnosis date for CA-CDI to the date of the surgical procedure or the admission date for a subsequent hospitalization. The proportion of cases to undergo surgical intervention was calculated and reported as the number of CA-CDI cases undergoing surgical procedures associated with CDI divided by the total number of CA-CDI cases. In turn, the proportion of cases who were subsequently hospitalized was calculated as the number of CA-CDI cases who were admitted due to CDI divided by the total number of first-occurrence cases of CA-CDI in this population.

The absolute number of CA-CDI cases receiving metronidazole and/or oral vancomycin after initial therapy in the 180 days following diagnosis was reported. In

addition, statistics describing the use of these medications by CA-CDI cases included the mean number of prescriptions received per case following initial therapy, the range of time over which these prescriptions were utilized, and the mean time between diagnosis and date of prescription fill.

Demographic characteristics, healthcare resource utilization, clinical characteristics, and medication use for cases with subsequent hospitalization were compared to those of cases without subsequent hospitalization. The prevalence of antimotility agent use among these two groups of CA-CDI cases was also reported and statistically compared.

Table 1. Age and Gender Distribution of Persons Included in the Data Repository, 2003-2007.

Age Category (in years)	Gender	% of Total Population (N)
<18 years	Female	14.4 (122,913)
	Male	13.7 (116,932)
19 to 49 years	Female	23.8 (203,665)
	Male	22.9 (196,039)
50 to 64 years	Female	11.0 (93,724)
	Male	11.4 (97,420)
65 to 74 years	Female	1.1 (9,023)
	Male	1.1 (9,400)
75+ years	Female	0.3 (2,284)
	Male	0.3 (2,968)

Table 2. Antimicrobial Classes and Drugs Prescribed to Persons within the Study Population.

Antimicrobial Class	Antimicrobial Drug
Aminoglycosides	Gentamycin
	Neomycin
	Tobramycin
Beta-lactamase Inhibitors	Amoxicillin-clavulanate
Cephalosporins	
First-generation	Cephalexin
	Cefadroxil
Second-generation	Cefprozil
	Cefuroxime
	Cefoxitin
	Cefaclor
	Loracarbef
Third-generation	Cefdinir
	Cefditoren
	Cefixime
	Cefpodoxime
	Ceftriaxone
Lincomycin Derivatives	Clindamycin
Fluoroquinolones	Gatifloxacin
	Levofloxacin
	Moxifloxacin
	Ciprofloxacin
	Norfloxacin
	Ofloxacin
Macrolides	Azithromycin
	Clarithromycin
	Erythromycin
	Telithromycin
Penicillins	Amoxicillin
	Ampicillin
	Penicillin
	Dicloxacillin

Table 2. continued

Rifamycin derivatives	Rifampin
Sulfonamides	Trimethoprim-sulfamethoxazole
Tetracyclines	Tetracycline
	Minocycline
	Doxycycline
Miscellaneous Antimicrobials	Intravenous Vancomycin

Table 3. Gastric Acid Suppressants and Antimotility Agents.

Drug Class	Medication
Proton Pump Inhibitors	Esomeprazole
	Lansoprazole
	Omeprazole
	Pantoprazole
	Rabeprazole
H_2-Receptor Antagonists	Cimetidine
	Famotidine
	Nizatidine
	Ranitidine
Antimotility/Antidiarrheal Agents	Atropine-diphenoxylate (Lomotil)
	Loperamide

Table 4. Chronic Comorbid Conditions included in the Deyo-Charlson Comorbidity Index and Corresponding ICD-9 Codes.

Comorbid Condition[a,b,c]	ICD-9[a] Codes	Index Weight[b,c]
Acute Myocardial Infarction	410.x	1
Old Myocardial Infarction	412.x	1
Congestive Heart Failure	428.x	1
Peripheral Vascular Disease	443.9, 441.x, 785.4, V43.4 Procedure: 38.13, 38.14, 38.16, 38.18, 38.33, 38.34, 38.36, 38.38, 38.43, 38.44, 38.46, 38.48, 39.22-39.26, 39.28, 39.29	1
Cerebrovascular Disease	430.x-438.x Procedure: 38.12, 38.42	1
Chronic Pulmonary Disease	490.x-496.x, 500.x-505.x, 506.4	1
Dementia	290.x	1
Rheumatic Disease	710.0, 710.1, 710.4, 714.0-714.2, 714.81, 725.x	1
Peptic Ulcer Disease	531.x-534.x	1
Mild Liver Disease	571.2, 571.4-571.6	1
Diabetes without chronic complications	250.0-250.3, 250.7	1
Diabetes with chronic complications	250.4-250.6, 250.8-250.9	2
Hemiplagia or Paraplegia	342.x, 344.1	2
Chronic Renal Failure	582.x, 583-583.7, 585.x, 586.x, 588.x	2
Any Malignancy[d]	140.x-172.x, 174.x-195.8, 200.x-208.x	2
Moderate or Severe Liver Disease	456.0-456.21, 572.2-572.8 Procedure: 39.1, 42.91	3
Metastatic Solid Tumor	196.x-199.1	6
AIDS/HIV	042.x-0.44x	6

[a] ICD-9=International Classification of Disease, Ninth Revision

[b] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[c] Klabunde C.N., et al. J Clin Epidemiol. 2000;53:1258-67.

[d] Including lymphoma and leukemia, except malignant neoplasm of skin

Table 5. Gastrointestinal Conditions and Corresponding ICD-9 Codes.

Gastrointestinal Condition	ICD-9[a] Codes
Inflammatory Bowel Disease (IBD)[b,c]	555.0-555.9, 556-556.9
Diverticular Disease[d]	562.10, 562.11
Gastroesophageal Reflux Disease (GERD)[e]	530.1, 530.10, 530.11, 530.12, 530.19, 530.81, 787.1-787.29, 251-251.9

[a] ICD-9=International Classification of Disease, Ninth Revision

[b] Includes Crohn's disease and ulcerative colitis

[c] Nguyen GC, et al. Am J Gastroenterol. 2008;1:1443-50.

[d] Weber WP, et al. Arch Surg. 2007;142:253-9.

[e] Brook RA, et al. Aliment Pharmacol Ther. 2007 ;26:889-98

CHAPTER FOUR - RESULTS

Overview

This chapter details the results of this study. First, the results of selection of potential CDI cases, classification of these cases according to the study case definitions, and the calculation of incidence rates are presented. This section also includes results of the statistical comparison of the characteristics of CA-CDI and HA-CDI cases. Second, this chapter describes the nested case-control study population, the statistical comparison of cases and controls, and the results of risk factor assessment for CA-CDI. Finally, this chapter describes adverse health outcomes experienced by CA-CDI cases and examines the use of antimotility agents. Characteristics of cases experiencing adverse outcomes and risk factors related to these outcomes are also reported.

Specific Aim I Results

To apply case definitions for community-associated and hospital-acquired C. difficile infection in an insured population over the period from 2004 to 2007. To provide incidence rate estimates for the study period and descriptive statistics for cases of community-associated and hospital-acquired C. difficile infection.

Selection of Cases and Application of Case Definitions

During the study time period, 1,172 diagnoses of ICD-9 code 008.45 were identified. Of these diagnoses, 1,039 represented the first occurrence of CDI for an individual patient. Three-hundred fifty-five potential cases were excluded for the following reasons: less than 12 months of observation time prior to diagnosis date (n=281); lack of complete longitudinal health and drug coverage (n=4); CDI diagnosed in a long-term care facility (n=21); history of long-term care insurance claims in the six months prior to CDI diagnosis (n=49). After the application of inclusion and exclusion criteria, 684 cases of *C. difficile* were eligible for the study (Figure 1). Of these cases, 304

cases met the definition for CA-CDI, 338 cases met the definition for HA-CDI, and 42 cases met the definition for indeterminate infection (Figure 2).

Exploratory analysis was conducted to identify the first occurrence of *C. difficile* diagnostic testing in the 180 days prior to the appearance of ICD-9 code 008.45. Among 304 CA-CDI cases, 73 cases underwent 93 *C. difficile* tests prior to diagnosis on an insurance claim, in comparison to 29 HA-CDI cases undergoing 32 *C. difficile* tests. After limiting these observations to the first occurrence of testing, CA-CDI cases underwent testing, on average, 27.7 days prior to diagnosis (Range: 1 to 178 days). Despite the wide range in days, 25% of CA-CDI cases underwent testing in the 5 days prior to diagnosis, and 75% underwent testing within the previous 35 days. Furthermore, HA-CDI cases underwent initial testing, on average, 28.1 days prior to diagnosis (Range: 1 to 165 days). Although testing occurred over a wide range of time, 25% of HA-CDI cases underwent testing in the 5 days prior to diagnosis, and 75% underwent testing within the previous 33 days.

Incidence of *Clostridium difficile* Infection

Incidence rates were calculated for all years within the study time period. Table 6 outlines the number of incident CA-CDI and HA-CDI cases for each year during the study period, the total number of person-years for each year during the study period, and the annual incidence rates for each respective case definition. Incidence rates are expressed as the number of cases of CA-CDI or HA-CDI per 100,000 person-years. Of the 304 CA-CDI cases, there were 62 cases in 2004; 84 cases in 2004; 74 cases in 2005; and 84 cases in 2007. A total of 338 HA-CDI cases were identified, with 85 cases occurring in 2004; 76 in 2005; 84 in 2006; and 93 in 2007. Within the study period, the overall incidence rate for CA-CDI was 11.16 cases per 100,000 person-years, and the incidence rate for HA-CDI was 12.41 cases per 100,000 person-years. The highest incidence of CA-CDI was observed in 2005 (12.47 cases per 100,000 person-years), and

the incidence of HA-CDI was highest in 2007 (12.98 cases per 100,000 person-years). The lowest incidence rates for CA-CDI and HA-CDI occurred in 2003 and 2004, respectively (Table 6). It has been suggested that the CDI may exhibit seasonality. In this population, no specific months exhibited elevated incidence of CA-CDI and HA-CDI (Tables 7, 8).

Demographic Characteristics and Healthcare Utilization for Community-associated and Hospital-acquired CDI Cases

Summary statistics for the demographic and clinical characteristics of CA-CDI cases and HA-CDI cases are shown in Table 9. CA-CDI cases were, on average, approximately 8 years younger than HA-CDI cases (42.65 vs. 50.31, $p<0.0001$). The majority of CA-CDI and HA-CDI cases were female (60.53% and 54.14%, respectively, $p=0.1026$). HA-CDI cases were seen by a physician in the outpatient setting significantly more often than were CA-CDI cases (mean of 26.67 visits versus 17.08 visits; $p<0.0001$) (Table 9).

HA-CDI cases were significantly more likely than CA-CDI cases to have one or more gastrointestinal or Charlson comorbid conditions, although the prevalence of comorbid conditions was relatively low in both case groups (Tables 9 and 10). In fact, 75.33% of CA-CDI cases and 53.85% of HA-CDI cases did not have a comorbid condition during the one year prior to their CDI diagnosis date (Table 10). The prevalence of any gastrointestinal comorbid condition was16.45% among CA-CDI cases versus a prevalence rate of 17.75% among HA-CDI cases (Table 9).

The mean Charlson Comorbid Index scores were 0.67 for HA-CDI cases and 0.17 for CA-CDI cases, both representing low levels of underlying comorbidity (Table 9). Six comorbid conditions affected at least 1% of CA-CDI cases: gastroesophageal reflux disease (GERD), chronic pulmonary disease, diverticular disease, IBD, diabetes without complications, and rheumatic disease (Table10). Fourteen comorbid conditions were

diagnosed among at least 1% of HA-CDI cases: chronic pulmonary disease, diabetes without complications, GERD, diverticular disease, chronic renal failure, diabetes with chronic complications, congestive heart failure, cerebrovascular disease, IBD, peripheral vascular disease, old myocardial infarction, acute myocardial infarction, and hemiplagia/paraplegia. None of the other conditions affected more than 1% of the HA-CDI cases (Table 10).

Nearly 17% percent of HA-CDI cases and nearly 27% of CA-CDI cases did not receive antimicrobials in the 180 days prior to diagnosis. Among HA-CDI cases, 13.9% and 17.2% received one or two antimicrobial agents, respectively. In turn, roughly 38% of CA-CDI cases received one antimicrobial and 21% received two agents. The prevalence of use of specific antimicrobials and antimicrobial classes among case groups are shown in Table 11.

In the outpatient setting, gastric acid suppressants were prescribed significantly more often to HA-CDI cases (44%) than to CA-CDI cases (18.1%) in the 180 days prior to CDI diagnosis date (Table 12). PPI use was common among both HA-CDI cases (15.8% of cases) and CA-CDI cases (37.3% of cases). Overall, H_2-receptor antagonist use was less common than PPI use among either case group, but these agents were prescribed significantly more often for HA-CDI cases (13%) than for CA-CDI cases (2%) (Table 12).

Specific Aim II Results

To identify patient-related risk factors for CA-CDI in an insured population.

Demographic Characteristics of and Healthcare Utilization among CA-CDI Cases and Controls

The demographic characteristics of CA-CDI cases (n=304) and controls (n=3040) are shown in Table 13. The majority of the case group was comprised of women (60.53%), as was true of the control group (51.24%). The mean age of cases was 42.65

years, while controls were significantly younger at an average of 35.76 years of age ($p<0.0001$) (Table 13). Although the average age of these two groups differed, the majority of all study subjects were between the ages of 19 and 64 years (76% of cases and 69% of controls) (Table 13).

The use of healthcare services was significantly different among CA-CDI cases and controls (Table 13). CA-CDI cases were more likely to be hospitalized than controls between 84 and 365 days prior to diagnosis or index date ($p<0.0001$). Although the difference was significant, only 10.86% (33 of 304) of cases and 3.49% (103 of 3040) of controls were discharged from a hospital during this period of time. CA-CDI cases, on average, visited their physician in the outpatient setting 17.08 times in the year prior to CDI diagnosis, in comparison to 8 visits for controls ($p<0.0001$) (Table 13).

Clinical Characteristics of CA-CDI Cases and Controls

Comorbidity among CA-CDI Cases and Controls

The prevalence of Charlson comorbid conditions and gastrointestinal conditions among CA-CDI cases and controls is shown in Table 13. Approximately 25% of all CA-CDI cases and 7% of controls were diagnosed with a comorbid condition in the year prior to diagnosis or index date (Table 14).

The case group had a higher prevalence for many Charlson comorbid conditions or gastrointestinal conditions than controls, although these conditions actually affected few cases. At a 5% level of significance, the prevalence was significantly higher among cases than controls for the following conditions: congestive heart failure, chronic pulmonary disease, dementia, rheumatic disease, and diabetes without complications. Cases were also significantly more likely than controls to experience IBD, diverticular disease, and GERD (Table 14).

The collective effect of underlying comorbidity was measured through the Charlson Comorbidity Index score. For cases, Charlson scores for cases ranged from 0 to

7, while Charlson scores for controls ranged from 0 to 4. Average Charlson scores for both groups were less than one (Table 13).

Antimicrobial Use among CA-CDI Cases and Controls

Antimicrobial use in the 180 days prior to diagnosis date among CA-CDI cases was significantly more common than use in the same time period prior to index date among controls. Approximately 73% of CA-CDI cases received one or more antimicrobial drugs, whereas roughly 30% of controls received one or more of these drugs. The prevalence of the use of specific antimicrobials and antimicrobial classes are shown in Table 15.

Forty-six percent of cases last utilized one or more antimicrobial agents within the prior 30-day period compared to 10% of controls; 11.84% of cases last utilized an antimicrobial between 31 and 60 days prior compared to 4.87% of controls; 4.93% of cases last utilized an antimicrobial between 61 and 90 days prior compared to 4.97% of controls; 5.59% of cases last utilized an antimicrobial between 91 and 120 days prior compared to 4.74% of controls; 2.96% of cases last utilized an antimicrobial between 121 and 150 days prior compared to 3.19% of controls; and, 1.32% last utilized an antimicrobial between 151 and 180 days prior compared to 2.5% of controls (Table 16).

On average, CA-CDI cases received a greater number of antimicrobial agents than controls (1.26 antimicrobial agents versus 0.39 antimicrobial agents; $p<0.0001$). Moreover, CA-CDI cases received antimicrobials for more days than did control (16.1 days versus 3.70 days) (Cases: 25^{th} percentile: 5 days, 75^{th} percentile: 21.5 days; Controls: 25^{th} percentile: 0 days, 75^{th} percentile: 5 days; $p<0.0001$) (Table 13).

One-hundred thirty-one CA-CDI cases (43.09%) and 27 controls (0.89%) received metronidazole in the 180 days prior to diagnosis or index date, while 11 cases (3.62%) and no controls received oral vancomycin during the same time period. Use of these antimicrobials was not assessed in risk factor analysis since they are utilized as

treatment for CDI, although their use prior to CDI diagnosis was assessed in sensitivity analysis.

Gastric Acid Suppressant Use among CA-CDI Cases and Controls

Gastric acid suppressants were prescribed for 18.09% of cases and 5.16% of controls in the 180 days prior to diagnosis or index date (Table 19). Forty-eight of 304 cases (15.79%), and 157 of 3040 controls (5.16%) received a proton pump inhibitor. Furthermore, 2.30% of cases and 0.82% of controls were prescribed a histamine-2 receptor antagonist (Table 19). A cross-tabulation of antimicrobial agent use and gastric acid suppressant use among cases is shown in Table 18. As can be seen in this table, 84% of CA-CDI who received a gastric acid suppressant in the prior 180 days also received one or more antimicrobials agents.

Thirteen percent of cases last utilized one or more gastric acid suppressants within the prior 30-day period compared to nearly 4% of controls; while roughly 1% of cases and less than one percent of controls last received these drugs in any of the other timing periods of interest (i.e., 31 to 60 days, 61 to 90 days, 91 to 120 days, 121 to 150 days, and 151 to 180 days prior) (Table 19).

Antimotility Agent Use Among CA-CDI Cases and Controls

Antimotility agents were prescribed to 12.5% of cases and 0.1% of controls in the 180 days prior to diagnosis or index date. Atropine-diphenoxylate was used more often among cases than loperamide (11.84% versus 0.66%). Among cases who did use antimotility agents, 47% received these agents within the 7 days prior to diagnosis date with fewer cases receiving these medications in time periods greater than 7 days prior to diagnosis date (Table 20).

Univariate Associations between Demographic Characteristics, Healthcare Utilization, Comorbidity, Medication Use and Community-associated *Clostridium difficile*

Persons under the age of 18 years were at decreased risk for CA-CDI (95% CI: 0.34, 0.66), while increased risk was observed among persons 50 to 64 years of age (OR: 1.49; 95% CI: 1.16, 1.91), persons 65 to 74 years of age (OR: 2.03; 95% CI: 1.21, 3.43), and persons over the age of 75 years (OR: 2.90; 95% CI: 1.43, 5.90). Females had 1.4-times the odds of CA-CDI as compared to males (95% CI: 1.13, 1.83). A history of hospitalization was related to 3.5-times the odds of developing CA-CDI in comparison to no prior hospitalization (95% CI: 2.30, 5.23). The odds for CA-CDI significantly increased with each additional outpatient physician visit (OR: 1.05; 95% CI: 1.04, 1.06). In univariate analysis, a one-point increase in Charlson Comorbid Index score was associated with increased risk for CA-CDI (OR: 2.03; 95% CI: 1.55, 2.64). A diagnosis of IBD within the past year was related to 30-fold greater odds of developing CA-CDI. Furthermore, a diagnosis of diverticular disease increased odds of disease almost 4-fold and a GERD diagnosis was related with 3-fold greater odds of CA-CDI. The unadjusted risk estimates and corresponding confidence intervals are shown in Tables 21, 22, and 23.

Univariate conditional logistic regression was conducted and statistically significant increases in risk for CA-CDI were observed after the use of the following antimicrobials or antimicrobial classes: beta-lactamase inhibitors (OR: 5.58; 95% CI: 3.79, 8.30); cephalosporins (OR: 4.06; 95% CI: 3.02, 5.47); clindamycin (OR:15.65; 95% CI: 9.09, 26.95); fluoroquinolones (OR: 8.33; 95% CI: 5.94, 11.67); macrolides (OR:2.27; 95% CI: 1.68, 3.07); penicillins (OR:1.86; 95% CI: 1.34, 2.58); and, sulfonamides (OR:3.16; 95% CI: 1.79, 5.60) (Table 21). The use of tetracycline antimicrobials (OR: 1.43; 95% CI: 0.75, 2.71) were not significant predictors of CA-CDI in univariate modeling. Aminoglycoside use and intraveneous vancomycin use were not

assessed in univariate analysis because these antimicrobials were not prescribed frequently enough to make meaningful statistical comparisons. Results of univariate conditional logistic regression for antimicrobial use are shown in Table 21.

Increased risk for CA-CDI was observed for persons who last received antimicrobials in the previous 1 to 150 days. The highest odds for CA-CDI were observed after receipt of antimicrobials in the 30-day time period prior to diagnosis (OR: 12.06; 95% CI: 8.88, 16.36) followed by use in the prior 31 to 60-day time period (OR: 6.25; 95% CI: 4.06, 9.63), use in the prior 61 to 90-day period (OR: 2.50; 95% CI: 1.40, 4.47), use in the prior 91 to 120-day period (OR: 2.84; 95% CI: 1.63, 4.93), use in the prior 121 to 150-day period (OR: 2.3; 95% CI: 1.12, 4.73). Risk for CA-CDI was not significantly elevated for persons whose last receipt of antimicrobials was 151 to 180 days ago (OR: 1.39; 95% CI: 0.5, 3.91) (Table 22). Finally, each additional antimicrobial agent prescribed increased the risk for CA-CDI significantly (OR: 2.72; 95% CI: 2.40, 3.09) (Table 23).

Use of any gastric acid suppressant resulted in 4.4-times the odds of CA-CDI compared to not using these medications (95% CI: 2.74, 7.08) (Tables 21, 22, and 23). Increased risk for CA-CDI was observed for persons who last received gastric acid suppressants 1 to 30 days, 61 to 90 days, or 91 to 120 days prior to diagnosis (Table 24). Timing of gastric acid suppressant use was not assessed in a multivariate model, since the numbers of cases and controls were not sufficient among all levels of timing of exposure.

In univariate analysis, use of any antimotility agent was related to almost 127 – times the odds of CA-CDI compared to not using these medications (95% CI: 39.10, 410.33) (Table 25). Univariate analysis of timing of antimotility agent use showed that increased risk was only observed for last use of these drugs within the 7 days prior to diagnosis date (OR: 90.0; 95% CI: 20.88, 387.87) (Table 26). Timing of antimotility use was not assessed in a multivariate model, since numbers of cases and controls were not sufficient among all levels of timing of exposure.

Multivariate Models of Risk Factors for Community-associated *Clostridium difficile* Infection

Separate multivariate models were constructed for use of specific antimicrobials and antimicrobial classes, timing of antimicrobial use, and total number of antimicrobial agents. Gastric acid suppressant use was assessed in each of these multivariate models. All additional predictor variables and covariates included in the multivariate model were significant in univariate analysis; the following variables were included in all multivariate models: age, gender, number of outpatient physician visits, Charlson Comorbidity score, IBD, diverticular disease, and GERD.

The relationship between specific antimicrobial agents or classes and CA-CDI after controlling for demographic and clinical characteristics and healthcare utilization are shown in Table 21. After controlling for other covariates, increased risk for CA- CDI was associated with beta-lactam/beta-lactamase inhibitor use (OR: 3.93; 95% CI: 2.46, 6.28), cephalosporin use (OR: 2.76; 95% CI: 1.91, 3.98), clindamycin use (OR: 13.88; 95% CI: 7.35, 26.18), fluoroquinolone use (OR: 4.53; 95% CI: 2.99, 6.85), macrolide use (OR: 1.99; 95% CI: 1.39, 2.85), and penicillin use (OR: 1.73; 95% CI: 1.17, 2.56). The use of sulfonamides and tetracyclines did not result in increased risk. In this model, being 19 to 74 years of age (in comparison to persons under age of 18 years), number of outpatient visits, a diagnosis of IBD, and gastric acid suppressant use significantly contribute to risk of acquiring CA-CDI (Table 21).

The highest odds for CA-CDI were observed among persons who last used an antimicrobial in the 30-day time period prior to diagnosis (OR: 10.93; 95% CI: 7.78, 15.35) followed by last use in the prior 31 to 60-day time period (OR: 4.91; 95% CI: 3.05, 7.91), last use in the prior 61 to 90-day period (OR: 1.98; 95% CI: 1.05, 3.73), last use in the prior 91 to 120-day period (OR: 2.03; 95% CI: 1.10, 3.75), last use in the prior 121 to 150-day period (OR: 2.43; 95% CI: 1.11, 5.29); and finally, risk among persons with last use 151 to 180 days ago (OR: 1.07; 95% CI: 0.34, 3.34) (Table 22). Even after

controlling for demographic and clinical characteristics, the increased risk for CA-CDI was present for persons who last used antimicrobials up to 150 days ago (Table 22). In this model, being in any age category greater than 18 years of age, the number of outpatient visits, a diagnosis of IBD, and gastric acid suppressant use increased risk for CA-CDI following adjustment for timing of antimicrobial use and all other covariates (Table 22).

Each additional antimicrobial agent increased the risk for CA-CDI, even after controlling for all other demographic and clinical characteristics (OR: 2.49; 95% CI: 2.16, 2.87). In this model, being between the ages of 19 and 74 years, the number of outpatient physician visits, a diagnosis of IBD, a diagnosis of diverticular disease, and gastric acid suppressant use were significantly related to CA-CDI, after controlling for the number of antimicrobial agents and other covariates (Table 23).

Gastric acid suppressant use was significantly associated with CA-CDI in all multivariate models which accounted for antimicrobial use. When controlling for the use of specific antimicrobial agents and all other covariates, gastric acid suppressant use was not a risk factor for CA-CDI (OR: 1.54; 95% CI: 0.96, 2.46) (Table 21). In multivariate modeling accounting for the timing of antimicrobial use, gastric acid suppressant use increased risk for CA-CDI (OR: 1.78; 95% CI: 1.12, 2.82) (Table 22). Finally, when accounting for the number of antimicrobial agents and all other covariates, the use of gastric acid suppressants retained an odds ratio of 1.56 (95% CI: 1.00, 2.45) (Table 23).

The relationships among predictor variables and between predictor variables and CA-CDI were assessed to identify confounding relationships. GERD and diverticular disease were related to both gastric acid suppressant use and CA-CDI. Persons with GERD are likely to receive these medications as treatment. Biological relationship between CA-CDI and these two gastrointestinal diseases are not established. However, examination of risk estimates from univariate and multivariate analysis showed that the effect of gastric acid suppressant use is reduced after controlling for these conditions.

Therefore, these results suggest that these conditions account for a portion of the risk attributed to medication use. In contrast, IBD was associated with increased risk for CA-CDI, although an association was not observed between this condition and gastric acid suppressant use. Confounding was not found to be a factor in any of the other associations identified by this study. Interaction between gastric acid suppressant use and antimicrobial use was assessed to determine whether these two risk factors modify the effects of each other. However, interaction was not present. When using 'no antimicrobial or gastric acid suppressant use' as the reference category in a conditional logistic regression model controlling for only these exposures, antimicrobial use only was associated with an OR of 5.74 (95% CI: 4.32, 7.63); gastric acid suppressant use only was associated with an OR of 3.03 (95% CI: 1.46, 6.28); and, the use of both antimicrobials and gastric acid suppressants was associated with an OR of 18.60 (95% CI: 11.86, 29.18). Thus, the joint effects observed were similar to those expected. Furthermore, an interaction term included in the logistic model was not statistically significant (p= 0.8728).

Results of Sensitivity Analysis

A sensitivity analysis was conducted to examine the effects of an alternate case definition for CA-CDI on risk estimates provided by multivariate models. This analysis utilized an alternate case definition that conservatively defined CA-CDI by excluding persons with a primary diagnosis of CDI at hospital admission who did not have a hospital discharge within the prior 12 weeks. For the main study analysis, 304 CA-CDI cases were identified, whereas 241 CA-CDI cases met the alternate case definition used in this sensitivity analysis (Figure 4). Demographic characteristics, healthcare utilization, and summary information for medication use were similar to those of the main study population (Table 27). The prevalence of comorbid conditions and medication use and timing of antimicrobial use were also similar to that of the main study population (Tables

28-31). The restriction of analysis to this case group did not affect the estimates or confidence intervals obtained from univariate or multivariate analyses, although the risk estimate associated with gastric acid suppressant use was statistically significant and the risk estimate associated with IBD was decreased from that found in the primary analysis. Overall, this analysis did not affect the interpretation of the study results, and did not change the study conclusions based on the original analysis (Tables 32-34).

A sensitivity analysis was conducted to determine whether exclusion of cases with gastrointestinal conditions, a history of hospitalization within six months, or a history of outpatient dialysis or chemotherapy affected the risk estimates from models of CA-CDI in the original study population. Of the 304 CA-CDI cases utilized in the primary analysis, 45 cases were excluded due to diagnosis of a gastrointestinal condition; 8 cases were excluded due to a history of hospitalization in the prior 6 months; and, 5 cases were excluded for meeting both of these criteria. None of the CA-CDI cases underwent outpatient dialysis or chemotherapy within the year prior to diagnosis, thus there were no exclusions for these reasons. Following these exclusions, 246 CA-CDI cases were eligible for inclusion in this analysis (Figure 4). Summary statistics for these cases and corresponding controls are shown in Table 35. Demographic characteristics and healthcare utilization of this case group and corresponding controls did not differ from those of the population used in the primary analysis, although these exclusions resulted in a lower level of comorbidity and a lower level of exposure to gastric acid suppressants among the case group (Tables 35-37). Antimicrobial use among cases and their controls and the timing of use were similar to the main study population (Tables 38, 39). Timing of gastric acid suppressant use was also similar to that among the original study population (Table 40). Restricting the analysis to this case group did not significantly affect the estimates or confidence intervals obtained from univariate or multivariate analyses (Tables 41-43), although there were two notable differences. First, persons who last received antimicrobials in the previous 120-to-150 or 150-to-180 days

did not have an increased risk for CA-CDI (Table 42). Second, gastric acid suppressant use was not a significant predictor of CA-CDI in any of the multivariate models controlling for the use of specific antimicrobials, for timing of antimicrobial use, or for the total number of antimicrobial agents (Tables 41, 42, 43).

A sensitivity analysis was conducted to account for the possibility that medication use and diarrheal disease in the 180 days prior to the appearance of the ICD-9 code 008.45 may indicate true onset of CDI. CA-CDI cases were assessed for exposure to antimotility agents or oral vancomycin or a diagnosis of a nonspecific diarrheal disease. One-hundred eighty-two cases met either of these criteria, and were considered to have symptom onset prior to the original diagnosis date. The diagnosis date for these cases was redefined to be the date on which a prescription was filled or the date on which an unspecified diarrheal disease was diagnosed. For these 182 cases, seven cases had revised diagnosis dates based on first receipt of antimotility agents and/or oral vancomycin; 159 cases had revised diagnosis dates based on first diagnosis of a non-specific diarrheal disease; and, 16 cases had revised diagnosis dates based on concurrent receipt of medications and a diagnosis of diarrheal disease. Five CA-CDI cases were excluded because they had been discharged from a hospital in the 12 weeks prior to this revised diagnosis date. Thus, 299 CA-CDI cases (i.e., 122 cases with original diagnosis date and 177 cases with revised diagnosis date) were included in this sensitivity analysis (Figure 4). On average, the redefined diagnosis date was 37.15 days (Range: 1 day to 179 days) prior to the first appearance of ICD-9 code 008.45 on insurance claims, although 25% of the redefined diagnosis dates were 4 or fewer days prior to diagnosis on insurance claims; 50% of the redefined diagnosis dates were 17 or fewer days prior to diagnosis on insurance claims; and, 75% of the redefined diagnosis dates were 52 or fewer days prior to diagnosis on insurance claims. Demographic characteristics and comorbidity were similar to the original case group, although in this analysis, CA-CDI cases were more likely to be hospitalized within the year prior to their revised diagnosis date (Tables 44,

45). The percentage of CA-CDI cases who utilized antimicrobial agents was slightly less than that in the primary analysis, although timing of this use was relatively unchanged (Tables 46, 47). Gastric acid suppressant use was similar to that among the main study groups (Table 48). In univariate and multivariate analyses, risk estimates were similar, although a history of hospitalization in the previous one year significantly increased risk for CA-CDI, except in the model controlling for the timing of antimicrobial use (Tables 49-51). In addition, the risk associated with a diagnosis of inflammatory bowel disease was lower in this population than that estimated from the original population (Tables 49-51Increased risk for CA-CDI was observed among persons whose last receipt of antimicrobials occurred in the prior 60 days, in contrast to the 150-day time period of increased risk found in the primary analysis (Table 50). Finally, gastric acid suppressant use was a significant predictor of CA-CDI in all multivariate models ((Tables 49-51). Of note, in the main study population, 131 CA-CDI cases (43.09%) received metronidazole prior to diagnosis of CDI. One-hundred thirteen of these 131 cases had revised diagnosis dates based on the criteria applied in this sensitivity analysis, suggesting that this analysis detected individuals who received metronidazole for CDI symptoms.

Specific Aim III Results

To describe adverse health outcomes of CA-CDI and to explore potential risk factors for these outcomes in persons with CA-CDI.

Surgical Procedures Following Diagnosis of CA-CDI

None of the CA-CDI cases met criteria indicating that they had undergone surgical procedures related to CDI. One person with CA-CDI did undergo a colectomy of the transverse colon 132 days after the diagnosis of *C. difficile*, although the ICD-9 code 008.45 was not listed as a diagnosis at the time of the procedure. Three additional cases underwent surgical procedures possibly related to CDI, although the dates of these surgical procedures were more than 180 days after CDI diagnosis date and ICD-9 code

008.45 was not listed as a diagnosis at the time of the procedures. These surgical procedures were presumably not related to their CDI since they did not occur within the 180 days after diagnosis and ICD-9 code 008.45 was not present as a concurrent diagnosis of the procedure on inpatient insurance claims.

Subsequent Hospitalization among CA-CDI Cases

Seventy-seven CA-CDI cases were admitted a total of 79 times with a primary diagnosis of ICD-9 008.45 on the initial CDI diagnosis date or within 8 weeks (i.e., 56 or fewer days) of this date, resulting in a hospitalization rate of 25% (77 out of 304 total CA-CDI cases). Of the 77 first-time admissions, sixty-three (81.82%) occurred on the date of diagnosis; ten admissions (12.7%) occurred one day after the *C. difficile* diagnosis; one admission each occurred 4 days, 20 days, 24 days, and 30 days after diagnosis. The mean length of time between diagnosis of CA-CDI and hospital admission was 1.14 days (25^{th} percentile: 0 days; 75^{th} percentile: 0 days; SD: 4.87). The mean length of stay was 4.01 days (SD: 5.96 days), with a range from 1 day to 52 days.

Two cases were admitted with a primary diagnosis of *C. difficile* on two separate occasions. One of these cases was first admitted on the diagnosis date, was discharged two days later, and was subsequently hospitalized for *C. difficile* again on the 5^{th} day following diagnosis. The other case was admitted on the date of initial diagnosis, was discharged after 3 days, and was re-admitted 34 days after diagnosis date.

CA-CDI cases who were hospitalized for CDI (n=77) were not significantly different from those who were not hospitalized (n=227) with respect to patient demographic and clinical characteristics (Table 52). Of the 77 cases who were hospitalized, 2 cases received antimotility agents, while 5 of 227 cases who were not hospitalized received antimotility agents. Use of antimotility agents among cases who were hospitalized and those that were not was similar (p=1.000) (Table 52). However, the

use of antimotility agents in the hospital setting cannot be assessed adequately using these data.

Use of Metronidazole and Oral Vancomycin Following Initial Therapy for CA-CDI

Outpatient use of metronidazole or oral vancomycin following initial treatment for CDI may serve as an indicator for relapse or reinfection. Of 304 CA-CDI cases, 21 cases (6.9%) received a total of 38 prescriptions for metronidazole or oral vancomycin after completion of initial therapy. Twelve cases received only one prescription for metronidazole or oral vancomycin after initial therapy; 3 cases received 2 prescriptions following initial therapy; 4 cases received 3 prescriptions; and, 2 cases received 4 prescriptions. Of these cases, 76% received these medications for the first time after initial therapy within 30 days of diagnosis with CDI and 90% of these cases received these medications within 60 days of diagnosis.

Use of Antimotility Agents Following Diagnosis of CA-CDI

The outpatient use of antimotility agents upon or following diagnosis of CA-CDI was relatively uncommon. Seven CA-CDI cases received antimotility agents in the outpatient setting during this time period. These seven cases received a total of thirteen prescriptions, all of which were for atropine-diphenoxylate. One case received 7 of these prescriptions, with the first of these occurring 55 days following diagnosis. Three of the seven cases received a prescription for atropine-diphenoxylate on the date of diagnosis; with three cases receiving these agents 2, 8, and 11 days after diagnosis, respectively. Finally, the average duration of use of antimotility agents was 8.7 days (Minimum: 2 days; Maximum: 12 days: SD: 4.3 days). Of the 7 cases who received antimotility agents, 2 cases were subsequently hospitalized and 5 cases were not.

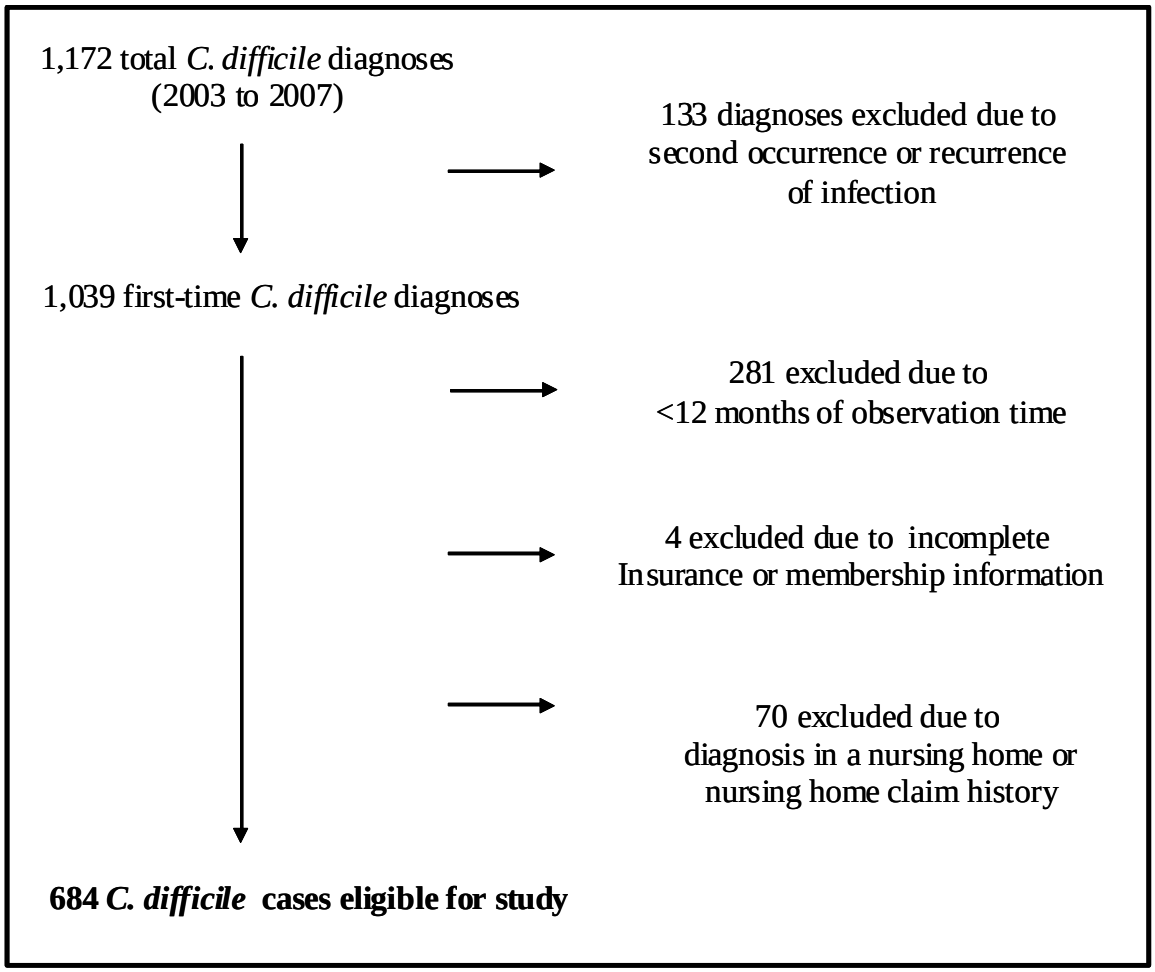

Figure 1. Results of the Application of Inclusion and Exclusion Criteria.

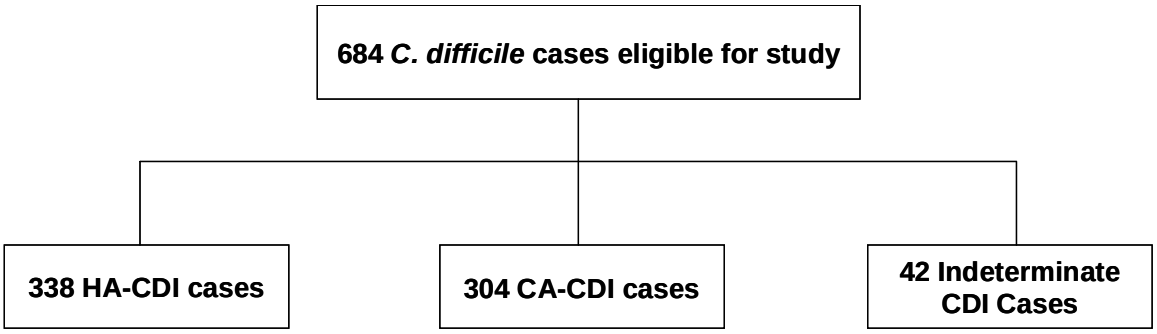

Figure 2. Results of the Application of Case Definitions.

Table 6. Number of Cases and Incidence Rates of Community-associated and Hospital-acquired *C. difficile* Infection, 2004-2007

Year	Total Person-years	Number of CA-CDI Cases	CA-CDI Incidence Rate[a]	Number of HA-CDI Cases	HA-CDI Incidence Rate[a]
2004	667,113	62	9.29	85	12.71
2005	673,630	84	12.47	76	11.28
2006	666,127	74	11.11	84	12.61
2007	716,265	84	11.76	93	12.98

[a] Incidence rates expressed as number of cases per 100,000 person-years

Table 7. Number of CA-CDI Cases by Month and Year.

	Year			
Month	2004	2005	2006	2007
	(N)	(N)	(N)	(N)
January	7	9	5	10
February	1	13	8	8
March	5	12	11	10
April	10	6	6	12
May	9	6	6	9
June	5	8	7	5
July	5	8	7	6
August	2	6	7	6
September	2	5	3	6
October	7	1	1	5
November	9	8	9	5
December	1	3	5	2
Total	62	84	74	84

Table 8. Number of HA-CDI Cases by Month and Year.

	Year			
Month	2004	2005	2006	2007
	(N)	(N)	(N)	(N)
January	5	8	7	11
February	11	5	4	3
March	11	8	7	9
April	7	8	8	4
May	4	7	10	9
June	8	12	6	5
July	6	4	3	8
August	5	10	4	10
September	13	5	13	13
October	11	5	8	12
November	2	3	4	6
December	1	0	9	2
Total	85	76	84	93

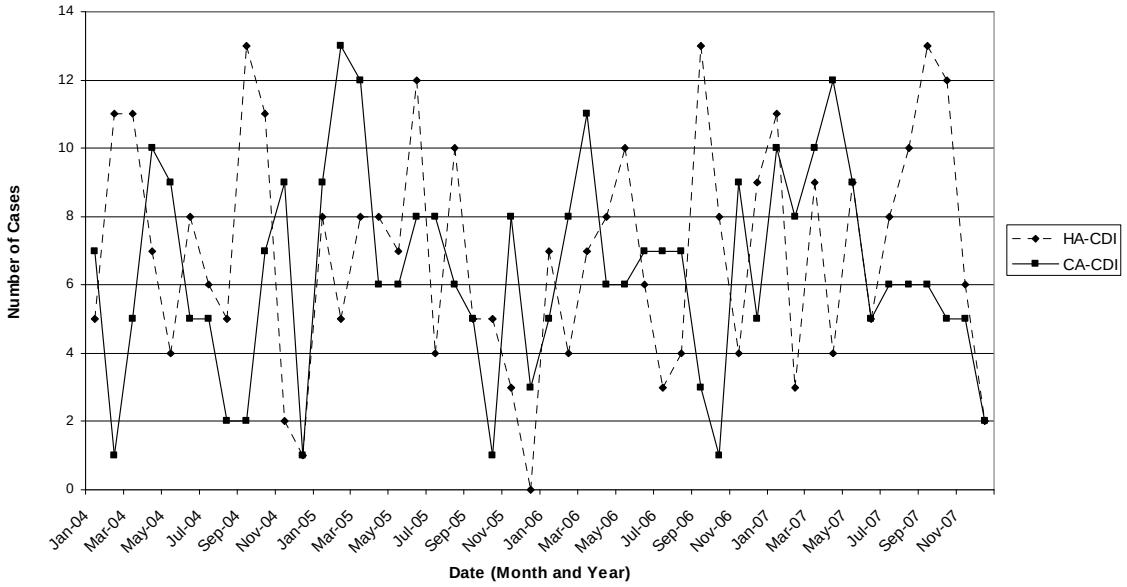

Figure 3. CA-CDI and HA-CDI Cases by Month and Year.

Table 9. Comparison of Demographic and Clinical Characteristics of Community-associated and Hospital-acquired *C. difficile* Infection Cases.

Variable	CA-CDI Cases (N = 304)	HA-CDI Cases (N = 338)	p-value[a]
Mean Age in Years ± SD (Range)	42.65 ± 20 (1 - 91)	50.31 ± 18.59 (1 – 90)	<0.0001
Age in Years (by category)			
<18 years	45 (14.80)	26 (7.69)	
19 to 49 years	125 (41.12)	112 (33.14)	
50 to 64 years	106 (34.87)	143 (42.31)	0.0006
65 to 74 years	18 (5.92)	35 (10.36)	
≥75 years	10 (3.29)	22 (6.51)	
Gender (female)	184 (60.53)	183 (54.14)	0.1026
Mean Number of Outpatient Primary Care Visits in Previous Year ± SD	17.08 ± 15.67	26.67 ± 23.20	<0.0001
Number of Comorbid Conditions[b]			
0	229 (75.33)	182 (53.85)	
1	57 (18.75)	91 (26.92)	<0.0001
2	13 (4.28)	30 (8.88)	
3+	5 (1.64)	35 (10.35)	
Mean Number of Comorbid Conditions[b] ± SD	0.34 ± 0.71	0.79 ± 1.07	<0.0001
Charlson Comorbidity Index Score			
0	269 (88.49)	226 (66.86)	
1	26 (8.55)	54 (15.98)	
2	6 (1.97)	27 (7.99)	<0.0001
3	1 (0.33)	14 (4.14)	
4	1 (0.33)	10 (2.96)	
5+	1 (0.33)	7 (2.08)	
Mean Charlson Comorbidity Index Score[c] ± SD	0.17 ± 0.62	0.67 ± 1.20	<0.0001
Presence of a Gastrointestinal Condition[d]	50 (16.45)	60 (17.75)	0.6615

Table 9. continued

Antimicrobial Use in the Prior 180 Days			
Any	222 (73.03)	281 (83.14)	<0.0001
None	82 (26.97)	56 (16.57)	
Receipt of a Gastric Acid Suppressant in the Prior 180 Days[e]	55 (18.09)	149 (44.08)	<0.0001

NOTE. Data are number (%) of patients, unless otherwise stated.

[a] p-value obtained from Student's t-test for comparing mean values for continuous variables and chi-square test for comparing frequency distributions for categorical variables

[b] Includes Charlson comorbid conditions and gastrointestinal conditions

[c] Charlson ME, et al. J Chronic Dis. 1987;40:373–383

[d] Includes inflammatory bowel disease (Crohn's disease, Ulcerative Colitis), diverticular disease, and gastroesophageal reflux disease (GERD)

[e] Includes proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2As)

Table 10. Prevalence of Charlson Chronic Comorbid Conditions among Community-associated and Hospital-acquired *C. difficile* Cases.

	CA-CDI Cases (N = 304)	HA-CDI Cases (N = 338)
	N (%)	N (%)
Charlson Comorbid Condition[a]		
Acute Myocardial Infarction	0 (0)	4 (1.18)
Old Myocardial Infarction	2 (0.66)	5 (1.48)
Congestive Heart Failure	3 (0.99)	17 (5.03)
Peripheral Vascular Disease	1 (0.33)	10 (2.96)
Cerebrovascular Disease	1 (0.33)	16 (4.73)
Chronic Pulmonary Disease	19 (6.25)	47 (13.91)
Dementia	2 (0.66)	0 (0)
Rheumatic Disease	4 (1.32)	8 (2.37)
Peptic Ulcer Disease, excluding bleeding	0 (0)	0 (0)
Mild Liver Disease	0 (0)	0 (0)
Diabetes without chronic complications	10 (3.29)	44 (13.02)
Diabetes with chronic complications	2 (0.66)	19 (5.62)
Hemiplegia or Paraplegia	1 (0.33)	4 (1.18)
Chronic Renal Failure	3 (0.99)	23 (6.80)

Table 10. continued

Any Malignancy[b]	0 (0)	0 (0)
Moderate or Severe Liver Disease	0 (0)	0 (0)
Metastatic Solid Tumor	0 (0)	0 (0)
AIDS/HIV[c]	0 (0)	0 (0)
Gastrointestinal Conditions		
Inflammatory Bowel Disease (IBD)[d]	12 (3.95)	14 (4.14)
Diverticular Disease	16 (5.26)	24 (7.10)
Gastroesophageal Reflux Disease (GERD)	26 (8.55)	30 (8.88)

[a] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[b] Includes lymphoma and leukemia, except malignant neoplasm of skin

[c] AIDS/HIV = Acquired Immune Deficiency Syndrome/Human Immunodeficiency Virus

[d] Includes Crohn's disease and ulcerative colitis

Table 11. Prevalence of Antimicrobial Use among Community-associated and Hospital-acquired *C. difficile* Cases in the 180 days prior to diagnosis.

Antimicrobial Exposure		CA-CDI Cases (N = 304) N (%)	HA-CDI Cases (N = 338) N (%)
Number of Antimicrobials	No antimicrobial exposure	82 (26.97)	57 (16.86)
	1 antimicrobial	116 (38.16)	47 (13.91)
	2 antimicrobials	64 (21.05)	58 (17.16)
	3 antimicrobials	30 (9.87)	47 (13.91)
	4 antimicrobials	11 (3.62)	59 (17.46)
	5 or more antimicrobials	1 (0.33)	70 (20.69)
Antimicrobial Class	**Antimicrobial Drug**		
Aminoglycosides		1 (0.33)	12 (3.55)
	Gentamycin	0 (0)	2 (0.59)
	Neomycin	1 (0.33)	8 (2.37)
	Tobramycin	0 (0)	1 (0.30)
Beta-lactamase Inhibitors	Amoxicillin-clavulanate	45 (14.80)	87 (25.74)
Cephalosporins (generation)		75 (24.67)	145 (42.90)
First-generation		30 (9.87)	120 (35.50)
	Cephalexin	26 (8.55)	116 (34.32)
	Cefadroxil	4 (1.32)	6 (1.78)
Second-generation		22 (7.24)	29 (8.58)
	Cefprozil	8 (2.63)	11 (3.25)
	Cefuroxime	14 (4.61)	19 (5.62)
	Cefaclor	1 (0.33)	2 (0.59)
Third-generation		27 (8.88)	23 (6.80)
	Cefdinir	22 (7.24)	12 (3.55)
	Cefditoren	1 (0.33)	3 (0.89)
	Cefpodoxime	6 (1.97)	7 (2.07)
	Ceftriaxone	0 (0)	1 (0.30)

Table 11. continued

Lincomycin Derivatives	Clindamycin	35 (11.51)	24 (7.10)
Fluoroquinolones		67 (22.04)	169 (50.00)
	Gatifloxacin	1 (0.33)	5 (1.48)
	Levofloxacin	28 (9.21)	142 (42.01)
	Moxifloxacin	7 (2.30)	24 (7.10)
	Ciprofloxacin	38 (12.50)	71 (21.02)
Macrolides		61 (20.07)	132 (39.05)
	Azithromycin	50 (16.45)	102 (30.18)
	Clarithromycin	8 (2.63)	38 (11.24)
	Erythromycin	3 (0.99)	13 (3.85)
	Telithromycin	3 (0.99)	9 (2.66)
Penicillins		50 (16.45)	110 (32.54)
	Amoxicillin	41 (13.49)	92 (27.22)
	Ampicillin	1 (0.33)	1 (0.30)
	Dicloxacillin	0 (0)	7 (2.07)
	Penicillin	8 (2.63)	26 (7.69)
Rifamycin derivatives	Rifampin	2 (0.66)	4 (1.18)
Sulfonamides	Trimethoprim-sulfamethoxazole	16 (5.26)	87 (25.74)
Tetracyclines		11 (3.62)	38 (11.24)
	Tetracycline	1 (0.33)	5 (1.48)
	Minocycline	1 (0.33)	3 (0.89)
	Doxycycline	9 (2.96)	33 (9.76)
Miscellaneous Antimicrobials	Intravenous Vancomycin	4 (1.32)	1 (0.30)

Table 12. Prevalence of Gastric Acid Suppressant Use in the 180 days prior to diagnosis among Community-associated and Hospital-acquired *C. difficile* Infection Cases.

		CA-CDI Cases (N = 304)	HA-CDI Cases (N = 338)
Drug Class	**Medication**	**N (%)**	**N (%)**
Proton Pump Inhibitor		48 (15.79)	126 (37.28)
	Esomeprazole	15 (4.93)	41 (12.13)
	Lansoprazole	15 (4.93)	58 (17.16)
	Omeprazole	13 (4.28)	26 (7.69)
	Pantoprazole	5 (1.64)	36 (10.65)
	Rabeprazole	3 (0.99)	8 (2.37)
H_2-Receptor Antagonists		7 (2.30)	43 (12.72)
	Cimetidine	1 (0.33)	3 (0.89)
	Famotidine	3 (0.99)	24 (7.10)
	Nizatidine	0 (0)	2 (0.59)
	Ranitidine	3 (0.99)	18 (5.33)

Table 13. Comparison of the Demographic and Clinical Characteristics of Community-associated *C. difficile* Infection Cases and Matched Controls.

Variable	CA-CDI Cases (N = 304)	Controls (N = 3040)	p-value[a]
Mean Age in Years ± SD (Range)	42.65 ± 20 (1 – 91)	35.76 ± 19.9 (1 – 96)	<0.0001
Age in years (by category)			
<18 years	45 (14.80)	814 (26.78)	
19 to 49 years	125 (41.12)	1296 (42.63)	
50 to 64 years	106 (34.87)	803 (26.41)	<0.0001
65 to 74 years	18 (5.92)	92 (3.03)	
≥75 years	10 (3.29)	35 (1.15)	
Gender (female)	184 (60.53)	1570 (51.64)	0.0029
History of Hospitalization in Previous Year	33 (10.86)	103 (3.39)	<0.0001
Mean Number of Outpatient Physician Visits in Previous Year ± SD	17.08 ± 15.67	8.0 ± 10.08	<0.0001
Number of Comorbid Conditions[b]			
0	229 (75.33)	2840 (93.42)	
1	57 (18.75)	163 (5.36)	<0.0001
2	13 (4.28)	31 (1.02)	
3+	5 (1.64)	6 (0.19)	
Mean Number of Comorbid Conditions[b] ± SD	0.34 ± 0.71	0.08 ± 0.33	<0.0001
Presence of a Gastrointestinal Condition[c]	50 (16.45)	95 (3.13)	<0.0001
Mean Charlson Comorbidity Index Score ± SD	0.17 ± 0.62	0.05 ± 0.27	<0.0001
Charlson Comorbidity Index Score			
0	269 (88.49)	2917 (95.95)	
1	26 (8.55)	98 (3.22)	
2	6 (1.97)	20 (0.66)	<0.0001
3	1 (0.33)	4 (0.13)	
4	1 (0.33)	1 (0.03)	
5+	1 (0.33)	0 (0)	

Table 13. continued

Mean Number of Antimicrobial Agents ± SD	1.26 ± 1.10	0.39 ± 0.68	<0.0001
Mean Number of Days of Antimicrobial Use ± SD	16.07 ± 17.23	3.70 ± 7.82	<0.0001
Antimicrobial Use			
Any	222 (73.03)	920 (30.26)	<0.0001
None	82 (26.97)	2120 (69.74)	
Receipt of a Gastric Acid Suppressant[d]	55 (18.09)	157 (5.16)	<0.0001

NOTE. Data are number (%) of patients, unless otherwise stated.

[a] p-value obtained from Student's T-test for comparing mean values for continuous variables and chi-square test for comparing frequency distributions for categorical variables

[b] Includes Charlson comorbid conditions and gastrointestinal conditions

[c] Includes peptic ulcer disease, inflammatory bowel disease (Crohn's disease, Ulcerative Colitis), diverticular disease, and gastroesophageal reflux disease (GERD)

[d] Includes proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2As)

Table 14. Prevalence of Charlson Chronic Comorbid Conditions among Community-associated *C. difficile* Cases and Controls.

	CA-CDI Cases (N = 304)	Controls (N = 3040)
	N (%)	N (%)
Charlson Comorbid Condition[a]		
Acute Myocardial Infarction	0 (0)	2 (0.07)
Old Myocardial Infarction	2 (0.66)	4 (0.13)
Congestive Heart Failure	3 (0.99)	6 (0.20)
Peripheral Vascular Disease	1 (0.33)	6 (0.20)
Cerebrovascular Disease	1 (0.33)	14 (0.46)
Chronic Pulmonary Disease	19 (6.25)	39 (1.28)
Dementia	2 (0.66)	0 (0)
Rheumatic Disease	4 (1.32)	6 (0.20)
Peptic Ulcer Disease, excluding bleeding	0 (0)	0 (0)
Mild Liver Disease	0 (0)	0 (0)
Diabetes without chronic complications	10 (3.29)	50 (1.64)
Diabetes with chronic complications	2 (0.66)	7 (0.23)
Hemiplagia or Paraplegia	1 (0.33)	1 (0.03)
Chronic Renal Failure	3 (0.99)	8 (0.26)

Table 14. continued

Any Malignancy[b]	0 (0)	0 (0)
Moderate or Severe Liver Disease	0 (0)	0 (0)
Metastatic Solid Tumor	0 (0)	0 (0)
AIDS/HIV[c]	0 (0)	0 (0)
Gastrointestinal Conditions		
Inflammatory Bowel Disease (IBD)[d]	12 (3.95)	4 (0.13)
Diverticular Disease	16 (5.26)	33 (1.09)
Gastroesophageal Reflux Disease (GERD)	26 (8.55)	63 (2.07)

[a] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[b] Includes lymphoma and leukemia, except malignant neoplasm of skin

[c] AIDS/HIV = Acquired Immune Deficiency Syndrome/Human Immunodeficiency \Virus

[d] Includes Crohn's disease and ulcerative colitis

Table 15. Antimicrobial Use in the 180 days prior to Diagnosis or Index Date among Community-associated *C. difficile* Infection Cases and Matched Controls.

		CA-CDI Cases (N = 304)	Controls (N = 3040)
Antimicrobial Exposure		**N (%)**	**N (%)**
Number of Antimicrobials			
	No antimicrobial exposure	82 (26.97)	2120 (69.74)
	1 antimicrobial	116 (38.16)	695 (22.86)
	2 antimicrobials	64 (21.05)	182 (5.99)
	3 antimicrobials	30 (9.87)	33 (1.09)
	4 antimicrobials	11 (3.62)	9 (0.30)
	5+ antimicrobials	1 (0.33)	1 (0.03)
Antimicrobial Class	**Antimicrobial Drug**		
Aminoglycosides		1 (0.33)	1 (0.03)
	Gentamycin	0 (0)	1 (0.03)
	Neomycin	1 (0.33)	0 (0)
Beta-lactamase Inhibitors	Amoxicillin-clavulanate	45 (14.80)	94 (3.09)
Cephalosporins		75 (24.67)	230 (7.57)
First-generation		30 (9.87)	162 (5.33)
	Cephalexin	26 (8.55)	152 (5.00)
	Cefadroxil	4 (1.32)	10 (0.33)
Second-generation		22 (7.24)	52 (1.71)
	Cefprozil	8 (2.63)	21 (0.69)
	Cefuroxime	14 (4.61)	16 (0.53)
	Cefaclor	1 (0.33)	15 (0.49)
Third-generation		27 (8.88)	28 (0.92)
	Cefdinir	22 (7.24)	27 (0.89)
	Cefditoren	1 (0.33)	0 (0)
	Cefpodoxime	6 (1.97)	1 (0.03)
Lincomycin Derivatives	Clindamycin	35 (11.51)	26 (0.86)
Fluoroquinolones		67 (22.04)	94 (3.09)
	Gatifloxacin	1 (0.33)	1 (0.03)
	Levofloxacin	28 (9.21)	49 (1.61)
	Moxifloxacin	7 (2.30)	7 (0.23)

Table 15. continued

Macrolides		61 (20.07)	300 (9.87)
	Azithromycin	50 (16.45)	251 (8.26)
	Clarithromycin	8 (2.63)	37 (1.22)
	Erythromycin	3 (0.99)	17 (0.56)
	Telithromycin	3 (0.99)	7 (0.23)
Penicillins		50 (16.45)	291 (9.57)
	Amoxicillin	41 (13.49)	256 (8.42)
	Ampicillin	1 (0.33)	4 (0.13)
	Dicloxacillin	0 (0)	4 (0.13)
	Penicillin	8 (2.63)	32 (1.05)
Rifamycin derivatives	Rifampin	2 (0.66)	0 (0)
Sulfonamides	Trimethoprim-sulfamethoxazole	16 (5.26)	52 (1.71)
Tetracyclines		11 (3.62)	78 (2.57)
	Tetracycline	1 (0.33)	9 (0.30)
	Minocycline	1 (0.33)	25 (0.82)
	Doxycycline	9 (2.96)	46 (1.51)
Miscellaneous Antimicrobials	Intravenous Vancomycin	4 (1.32)	0 (0)

Table 16. Timing of Antimicrobial Use among Community-associated *C. difficile* Cases and Controls within the 180 days prior to diagnosis or index date.

	CA-CDI Cases (N = 304)	Controls (N = 3040)
Timing of Antimicrobial Use	**N (%)**	**N (%)**
No Use	82 (26.97)	2120 (69.74)
Within 1-30 Days	141 (46.38)	304 (10.00)
Within 31-60 Days	36 (11.84)	148 (4.87)
Within 61-90 Days	15 (4.93)	151 (4.97)
Within 91-120 Days	17 (5.59)	144 (4.74)
Within 121-150 Days	9 (2.96)	97 (3.19)
Within 151-180 Days	4 (1.32)	76 (2.50)

Table 17. Prevalence of Gastric Acid Suppressant Use among Community-associated *C. difficile* Infection Cases and Matched Controls in the 180 days prior to diagnosis or index date.

		CA-CDI Cases (N = 304)	Controls (N = 3040)
		N (%)	N (%)
Use of Any Gastric Acid Suppressant[a]		55 (18.09)	157 (5.16)
Drug Class	**Medication**		
Proton Pump Inhibitors		48 (15.79)	157 (5.16)
	Esomeprazole	15 (4.93)	41 (1.35)
	Lansoprazole	15 (4.93)	41 (1.35)
	Omeprazole	13 (4.28)	36 (1.18)
	Pantoprazole	5 (1.64)	15 (0.49)
	Rabeprazole	3 (0.99)	11 (0.36)
H_2-Receptor Antagonists		7 (2.30)	25 (0.82)
	Cimetidine	1 (0.33)	4 (0.13)
	Famotidine	3 (0.99)	5 (0.16)
	Ranitidine	3 (0.99)	16 (0.52)

[a] Includes the use of all medications classified as either a proton pump inhibitor or H_2-receptor antagonist

Table 18. Cross-tabulation of Prevalence Antimicrobial Use and Gastric Acid Suppressant Use among 304 CA-CDI Cases.

	Gastric Acid Suppressant Use		
Antimicrobial Use	Yes	No	**Total**
Yes	46	176	222
No	9	73	92
Total	55	249	304

Table 19. Timing of Gastric Acid Suppressant Use among Community-associated *C. difficile* Cases and Controls within the 180 days prior to diagnosis or index date.

Timing of Gastric Acid Suppressant Use	CA-CDI Cases (N = 304)	Controls (N = 3040)
	N (%)	N (%)
No Use	249 (81.91)	2883 (94.84)
Within 1-30 Days	41 (13.49)	117 (3.85)
Within 31-60 Days	3 (0.99)	13 (0.43)
Within 61-90 Days	4 (1.32)	11 (0.36)
Within 91-120 Days	4 (1.32)	7 (0.23)
Within 121-150 Days	3 (0.99)	9 (0.30)
Within 151-180 Days	0 (0)	0 (0)

Table 20. Use of Antimotility Agents among Community-associated *C. difficile* Cases and Controls within the 180 days prior to diagnosis or index date.

	CA-CDI Cases (N = 304)	Controls (N = 3040)
Variable	**N (%)**	**N (%)**
Use of any Antimotility Agent	38 (12.50)	3 (0.10)
Antimotility Agent		
Atropine-diphenxylate	36 (11.84)	2 (0.07)
Loperamide	2 (0.66)	2 (0.03)
Timing of Antimotility Agent Use		
No Use	266 (87.50)	3037 (99.90)
Within 1-7 Days	18 (5.92)	2 (0.07)
Within 8-30 Days	8 (2.63)	0 (0)
Within 31-60 Days	5 (1.64)	0 (0)
Within 61-90 Days	5 (1.64)	0 (0)
Within 91-120 Days	0 (0)	1 (0.03)
Within 121-150 Days	2 (0.66)	0 (0)
Within 151-180 Days	0 (0)	0 (0)

Table 21. Relationship between Community-associated *C. difficile* Infection and Antimicrobial Use, Demographic Characteristics, Healthcare Utilization, and Gastric Acid Suppressant Use among Cases and Controls.

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Age in yrs. (by category)				
<18 years	0.48	(0.34, 0.66)	reference	--
19 to 49 years	0.94	(0.74, 1.19)	1.77	(1.17, 2.68)
50 to 64 years	1.49	(1.16, 1.91)	1.89	(1.21, 2.94)
65 to 74 years	2.03	(1.21, 3.43)	2.89	(1.41, 5.94)
≥75 years	2.90	(1.43, 5.90)	2.32	(0.85, 6.36)
Gender (female)	1.44	(1.1, 1.83)	1.08	(0.81, 1.44)
History of Hospitalization[b]	3.47	(2.30, 5.23)	0.75	(0.42, 1.33)
Number of Outpatient Physician Visits[c]	1.05	(1.04, 1.06)	1.05	(1.03, 1.06)
Charlson Comorbidity Index[d]	2.03	(1.55, 2.64)	0.95	(0.63, 1.41)
IBD[e]	30.0	(9.68, 93.02)	42.48	(10.32, 174.80)
Diverticular Disease	4.98	(2.72, 9.11)	2.02	(0.96, 4.28)
Gastroesophageal Reflux Disease	4.41	(2.74, 7.08)	1.73	(0.86, 3.46)
Gastric Acid Suppressant Use[f]	4.07	(2.91, 5.69)	1.54	(0.96, 2.46)
Beta-lactamase Inhibitor Use	5.58	(3.79, 8.20)	3.93	(2.46, 6.28)
Cephalosporin Use	4.06	(3.02, 5.47)	2.76	(1.91, 3.98)
Clindamycin Use	15.65	(9.09, 26.95)	13.88	(7.35, 26.18)
Fluoroquinolone Use	8.33	(5.94, 11.67)	4.53	(2.99, 6.85)
Macrolide Use	2.27	(1.68, 3.07)	1.99	(1.39, 2.85)
Penicillin Use	1.86	(1.34, 2.58)	1.73	(1.17, 2.56)
Sulfonamide Use	3.16	(1.79, 5.60)	1.51	(0.74, 3.08)
Tetracycline Use	1.43	(0.75, 2.71)	0.90	(0.41, 1.98)

NOTE: OR=Odds Ratio; CI=Confidence Interval

NOTE: c-statistic = 0.836

[a] Adjusted for all covariates shown

Table 21. continued

[b] History of being discharged from a hospitalization in the 365 days prior to diagnosis date for cases and index date for controls

[c] Number of outpatient visits in the 365 days prior to diagnosis date for cases and index date for controls

[d] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[e] Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis

[f] Includes any use of proton pump inhibitors or H_2-receptor antagonists.

Table 22. Relationship between Timing of Antimicrobial Use and CA-CDI among Cases and Controls.

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Timing of Antimicrobial Use				
No Use	reference	--	reference	--
Within 1-30 Days	12.06	(8.88, 16.36)	10.93	(7.78, 15.35)
Within 31-60 Days	6.25	(4.06, 9.63)	4.91	(3.05, 7.91)
Within 61-90 Days	2.50	(1.40, 4.47)	1.98	(1.05, 3.73)
Within 91-120 Days	2.84	(1.63, 4.93)	2.03	(1.10, 3.75)
Within 121-150 Days	2.30	(1.12, 4.73)	2.43	(1.11, 5.29)
Within 151-180 Days	1.39	(0.50, 3.91)	1.07	(0.34, 3.34)
Age in yrs. (by category)				
<18 years	0.48	(0.34, 0.66)	reference	--
19 to 49 years	0.94	(0.74, 1.19)	1.96	(1.32, 2.92)
50 to 64 years	1.49	(1.16, 1.91)	2.02	(1.32, 3.08)
65 to 74 years	2.03	(1.21, 3.43)	2.85	(1.36, 5.96)
≥75 years	2.90	(1.43, 5.90)	2.68	(1.04, 6.91)
Gender (female)	1.44	(1.13, 1.83)	1.06	(0.80, 1.41)
History of Hospitalization[b]	3.47	(2.30, 5.23)	1.08	(0.62, 1.87)
Number of Physician Visits[c]	1.05	(1.04, 1.06)	1.04	(1.03, 1.06)
Charlson Comorbid Index[d]	2.03	(1.55, 2.64)	0.95	(0.65, 1.40)
IBD[e]	30.0	(9.68, 93.02)	48.97	(12.28, 195.27)
Diverticular Disease	4.98	(2.72, 9.11)	2.24	(1.05, 4.76)
Gastroesophageal Reflux Disease	4.41	(2.74, 7.08)	1.34	(0.60, 2.61)
Gastric Acid Suppressant Use[f]	4.07	(2.91, 5.69)	1.78	(1.12, 2.82)

NOTE: OR=Odds Ratio; CI=Confidence Interval

NOTE: c-statistic = 0.840

Table 22. continued

[a] Adjusted for all covariates shown

[b] History of being discharged from a hospitalization in the 365 days prior to diagnosis date for cases and index date for controls

[c] Number of outpatient visits in the 365 days prior to diagnosis date for cases and index date for controls

[d] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[e] Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis

Table 23. Relationship between Total Number of Different Antimicrobial Agents and CA-CDI among Cases and Controls.

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Number of Antimicrobial Agents[b]	2.72	(2.40, 3.09)	2.49	(2.16, 2.87)
Age in yrs. (by category)				
<18 years	0.48	(0.34, 0.66)	reference	--
19 to 49 years	0.94	(0.74, 1.19)	2.08	(1.39, 3.10)
50 to 64 years	1.49	(1.16, 1.91)	2.18	(1.43, 3.33)
65 to 74 years	2.03	(1.21, 3.43)	3.05	(1.49, 6.24)
≥75 years	2.90	(1.43, 5.90)	2.52	(0.99, 6.43)
Gender (female)	1.44	(1.13, 1.83)	1.08	(0.82, 1.43)
History of Hospitalization[c]	3.47	(2.30, 5.23)	0.86	(0.50, 1.48)
Number of Outpatient Physician Visits[d]	1.05	(1.04, 1.06)	1.04	(1.03, 1.06)
Charlson Comorbid Index[e]	2.03	(1.55, 2.64)	0.98	(0.68, 1.40)
IBD[f]	30.0	(9.68, 93.02)	40.56	(10.32, 159.33)
Diverticular Disease	4.98	(2.72, 9.11)	2.33	(1.13, 4.82)
Gastroesophageal Reflux Disease	4.41	(2.74, 7.08)	1.63	(0.85, 3.12)
Gastric Acid Suppressant Use[g]	4.07	(2.91, 5.69)	1.56	(1.00, 2.45)

NOTE: OR=Odds Ratio; CI=Confidence Interval

NOTE: c-statistic = 0.827

[a] Adjusted for all covariates shown

[b] Total number of antimicrobial agents utilized in the 180 days prior to diagnosis date for cases and index date for controls

[c] History of being discharged from a hospitalization in the 365 days prior to diagnosis date for cases and index date for controls.

[d] Number of outpatient visits in the 365 days prior to diagnosis date for cases and index date for controls

Table 23. continued

[e] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[f] Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis

[g] Includes any use of proton pump inhibitors or H_2-receptor antagonists

Table 24. Relationship between Timing of Gastric Acid Suppressant Use and CA-CDI among Cases and Controls.

Variable	Unadjusted OR	95% CI
Timing of Gastric Acid Suppressant Use[a]		
No Use	reference	--
Within 1-30 Days	4.09	(2.79, 6.00)
Within 31-60 Days	2.75	(0.78, 9.71)
Within 61-90 Days	4.22	(1.34, 13.31)
Within 91-120 Days	6.59	(1.92, 22.65)
Within 121-150 Days	3.48	(0.94, 12.87)

NOTE: OR=Odds Ratio; CI=Confidence Interval

[a] Includes any use of proton pump inhibitors or H_2-receptor antagonists

Table 25. Relationship between Antimotility Agent Use and CA-CDI among Cases and Controls.

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Antimotility Agent Use	126.67	(39.10, 410.33)	91.43	(25.45, 328.44)
Age in yrs. (by category)				
<18 years	0.48	(0.34, 0.66)	reference	--
19 to 49 years	0.94	(0.74, 1.19)	1.67	(1.08, 2.59)
50 to 64 years	1.49	(1.16, 1.91)	1.84	(1.15, 2.93)
65 to 74 years	2.03	(1.21, 3.43)	2.69	(1.25, 5.78)
≥75 years	2.90	(1.43, 5.90)	2.67	(0.89, 8.05)
Gender (female)	1.44	(1.13, 1.83)	1.09	(0.80, 1.48)
History of Hospitalization[b]	3.47	(2.30, 5.23)	0.87	(0.48, 1.60)
Number of Physician Visits[c]	1.05	(1.04, 1.06)	1.04	(1.03, 1.05)
Charlson Comorbid Index[d]	2.03	(1.55, 2.64)	0.83	(0.55, 1.25)
IBD[e]	30.0	(9.68, 93.02)	57.68	(13.90, 239.4)
Diverticular Disease	4.98	(2.72, 9.11)	2.17	(0.97, 4.85)
Gastroesophageal Reflux Disease	4.41	(2.74, 7.08)	1.81	(0.87, 3.79)
Gastric Acid Suppressant Use[f]	4.07	(2.91, 5.69)	1.50	(0.91, 2.46)
Beta-lactamase Inhibitor Use	5.58	(3.79, 8.20)	4.50	(2.75, 7.37)
Cephalosporin Use	4.06	(3.02, 5.47)	2.61	(1.76, 3.88)
Clindamycin Use	15.65	(9.09, 26.95)	12.59	(6.38, 24.85)
Fluoroquinolone Use	8.33	(5.94, 11.67)	4.56	(2.90, 7.17)
Macrolide Use	2.27	(1.68, 3.07)	2.07	(1.42, 3.03)
Penicillin Use	1.86	(1.34, 2.58)	1.71	(1.13, 2.59)
Sulfonamide Use	3.16	(1.79, 5.60)	1.53	(0.74, 3.17)
Tetracycline Use	1.43	(0.75, 2.71)	0.90	(0.39, 2.05)

Table 25. continued

NOTE: OR=Odds Ratio; CI=Confidence Interval

NOTE: c-statistic = 0.852

[a] Adjusted for all covariates shown

[b] History of being discharged from a hospitalization in the 365 days prior to diagnosis date for cases and index date for controls

[c] Number of outpatient visits in the 365 days prior to diagnosis date for cases and index date for controls

[d] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[e] Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis

[f] Includes any use of proton pump inhibitors or H_2-receptor antagonists

Table 26. Relationship between Timing of Antimotility Agent Use and CA-CDI among Cases and Controls.

Variable	Unadjusted OR	95% CI
Timing of Antimotility Agent Use		
No Use	reference	--
Within 1-7 Days	90.00	(20.88, 387.87)

NOTE: OR=Odds Ratio; CI=Confidence Interval

NOTE: Insufficient numbers of CA-CDI cases were available in other timing categories, thus odds ratios and confidence intervals could not be estimated.

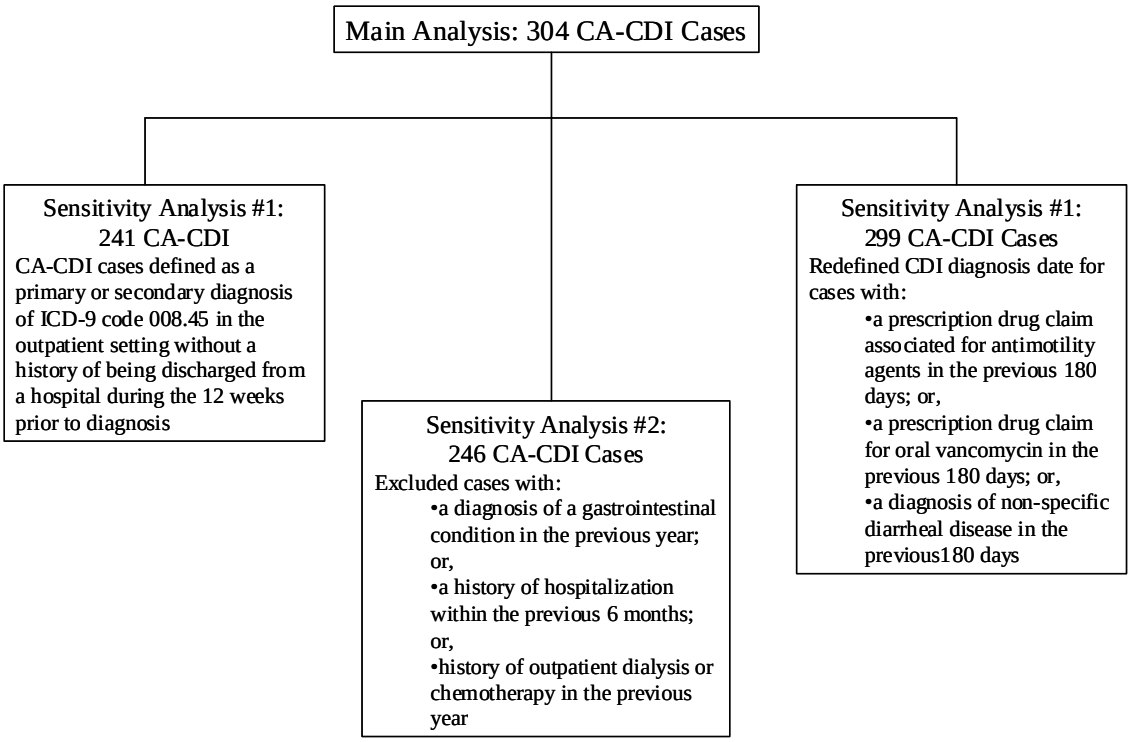

Figure 4. Summary of Sensitivity Analyses.

Table 27. Comparison of the Demographic and Clinical Characteristics of Community-associated C. difficile Infection Cases and Matched Controls following Application of a Secondary Case Definition.

Variable	CA-CDI Cases (N = 241)	Controls (N = 2410)	p-value[a]
Mean Age in Years ± SD (Range)	42.77 ± 19.01 (1 – 83)	35.73 ± 19.9 (1 – 96)	<0.0001
Age in years (by category)			
<18 years	29 (12.03)	651 (27.01)	
19 to 49 years	113 (46.89)	1022 (42.41)	
50 to 64 years	80 (33.20)	640 (26.56)	<0.0001
65 to 74 years	12 (4.98)	68 (2.82)	
≥75 years	7 (2.90)	29 (1.20)	
Gender (female)	141 (58.51)	1250 (51.87)	0.0491
History of Hospitalization in Previous Year	28 (11.62)	78 (3.24)	<0.0001
Mean Number of Outpatient Physician Visits in Previous Year ± SD	17.54 ± 16.59	8.02 ± 10.31	<0.0001
Number of Comorbid Conditions[b]			
0	184 (76.35)	2261 (93.82)	<0.0001
1	41 (17.01)	123 (5.10)	
2	11 (4.56)	20 (0.83)	
3+	5 (2.08)	6 (0.25)	
Mean Number of Comorbid Conditions[b] ± SD	0.34 ± 0.75	0.08 ± 0.32	<0.0001
Presence of a Gastrointestinal Condition[c]	37 (15.35)	73 (3.03)	<0.0001
Mean Charlson Comorbidity Index Score ± SD	0.19 ± 0.67	0.05 ± 0.26	<0.0001
Charlson Comorbidity Index Score			
0	212 (87.97)	2319 (96.22)	
1	21 (8.71)	75 (3.11)	
2	5 (2.07)	12 (0.50)	<0.0001
3	1 (0.41)	3 (0.12)	
4	1 (0.41)	1 (0.04)	
5+	1 (0.41)	0 (0)	

Table 27. continued

Mean Number of Antimicrobial Agents ± SD	1.22 ± 1.06	0.39 ± 0.68	<0.0001
Mean Number of Days of Antimicrobial Use ± SD	16.26 ± 136.23	3.69 ± 7.98	<0.0001
Antimicrobial Use			
Any	179 (74.27)	719 (29.83)	<0.0001
None	62 (25.73)	1691 (70.17)	
Receipt of a Gastric Acid Suppressant[d]	47 (19.50)	122 (5.06)	<0.0001

NOTE. Data are number (%) of patients, unless otherwise stated.

[a] p-value obtained from Student's t-test for comparing mean values for continuous variables and chi-square test for comparing frequency distributions for categorical variables

[b] Includes Charlson comorbid conditions and gastrointestinal conditions

[c] Includes peptic ulcer disease, inflammatory bowel disease (Crohn's disease, Ulcerative Colitis), diverticular disease, and gastroesophageal reflux disease (GERD)

[d] Includes proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2As)

Table 28. Prevalence of Charlson Chronic Comorbid Conditions among Community-associated *C. difficile* Cases and Controls following Application of a Secondary Case Definition.

	CA-CDI Cases (N = 241)	Controls (N = 2410)
	N (%)	N (%)
Charlson Comorbid Condition[a]		
Acute Myocardial Infarction	0 (0)	2 (0.08)
Old Myocardial Infarction	2 (0.83)	4 (0.17)
Congestive Heart Failure	3 (1.24)	5 (0.21)
Peripheral Vascular Disease	0 (0)	2 (0.08)
Cerebrovascular Disease	1 (0.41)	12 (0.50)
Chronic Pulmonary Disease	16 (6.64)	27 (1.12)
Dementia	2 (0.83)	0 (0)
Rheumatic Disease	3 (1.24)	5 (0.21)
Peptic Ulcer Disease, excluding bleeding	0 (0)	0 (0)
Mild Liver Disease	0 (0)	0 (0)
Diabetes without chronic complications	10 (4.15)	35 (1.45)
Diabetes with chronic complications	2 (0.83)	6 (0.25)
Hemiplegia or Paraplegia	0 (0)	1 (0.04)
Chronic Renal Failure	3 (1.24)	5 (0.21)
Any Malignancy[b]	0 (0)	0 (0)

Table 28. continued

Moderate or Severe Liver Disease	0 (0)	0 (0)
Metastatic Solid Tumor	0 (0)	0 (0)
AIDS/HIV[c]	0 (0)	0 (0)
Gastrointestinal Conditions		
Inflammatory Bowel Disease (IBD)[d]	9 (3.73)	4 (0.17)
Diverticular Disease	12 (4.98)	24 (1.00)
Gastroesophageal Reflux Disease (GERD)	19 (7.88)	49 (2.03)

[a] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[b] Includes lymphoma and leukemia, except malignant neoplasm of skin

[c] AIDS/HIV = Acquired Immune Deficiency Syndrome/Human Immunodeficiency Virus

[d] Includes Crohn's disease and ulcerative colitis

Table 29. Antimicrobial Use in the 180 days prior to Diagnosis or Index Date among Community-associated *C. difficile* Infection Cases and Matched Controls following Application of a Secondary Case Definition.

Antimicrobial Exposure		CA-CDI Cases (N = 241) N (%)	Controls (N = 2410) N (%)
Number of Antimicrobials			
	No antimicrobial exposure	62 (25.73)	1691 (70.17)
	1 antimicrobial	103 (42.74)	543 (22.53)
	2 antimicrobials	49 (20.33)	140 (5.81)
	3 antimicrobials	18 (7.47)	28 (1.16)
	4 antimicrobials	8 (3.32)	7 (0.29)
	5+ antimicrobials	1 (0.41)	1 (0.04)
Antimicrobial Class	**Antimicrobial Drug**		
Aminoglycosides		1 (0.41)	1 (0.04)
	Gentamycin	0 (0)	1 (0.04)
	Neomycin	1 (0.41)	0 (0)
Beta-lactamase Inhibitors	Amoxicillin-clavulanate	36 (14.94)	75 (3.11)
Cephalosporins		55 (22.82)	173 (7.18)
First-generation		23 (9.54)	121 (5.02)
	Cephalexin	20 (8.30)	113 (4.69)
	Cefadroxil	3 (1.24)	8 (0.33)
Second-generation		17 (7.05)	35 (1.45)
	Cefprozil	6 (2.49)	15 (0.62)
	Cefuroxime	11 (4.56)	10 (0.41)
	Cefaclor	1 (0.41)	10 (0.41)
Third-generation		18 (7.47)	24 (1.00)
	Cefdinir	14 (5.81)	23 (0.95)
	Cefditoren	1 (0.41)	0 (0)
	Cefpodoxime	5 (2.07)	1 (0.04)

Table 29. continued

Lincomycin Derivatives	Clindamycin	26 (10.79)	21 (0.87)
Fluoroquinolones		52 (21.99)	76 (3.15)
	Gatifloxacin	1 (0.41)	1 (0.04)
	Levofloxacin	22 (9.13)	37 (1.54)
	Moxifloxacin	4 (1.66)	7 (0.29)
	Ciprofloxacin	31 (12.86)	32 (1.33)
Macrolides		50 (20.75)	228 (9.46)
	Azithromycin	41 (17.01)	191 (7.93)
	Clarithromycin	7 (2.90)	28 (1.16)
	Erythromycin	2 (0.83)	13 (0.54)
	Telithromycin	2 (0.83)	6 (0.25)
Penicillins		35 (14.52)	235 (9.75)
	Amoxicillin	30 (12.45)	207 (8.59)
	Ampicillin	0 (0)	4 (0.17)
	Dicloxacillin	0 (0)	4 (0.17)
	Penicillin	5 (2.07)	23 (0.95)
Rifamycin derivatives	Rifampin	1(0.41)	0 (0)
Sulfonamides	Trimethoprim-sulfamethoxazole	10 (4.15)	44 (1.83)
Tetracyclines		10 (4.15)	64 (2.66)
	Tetracycline	1 (0.41)	8 (0.33)
	Minocycline	1 (0.41)	18 (0.75)
	Doxycycline	8 (3.32)	40 (1.66)
Miscellaneous Antimicrobials	Intravenous Vancomycin	3 (1.24)	0 (0)

Table 30. Timing of Antimicrobial Use among Community-associated *C. difficile* Cases and Controls within the 180 days prior to diagnosis or index date following Application of a Secondary Case Definition.

	CA-CDI Cases (N = 241)	Controls (N = 2410)
Timing of Antimicrobial Use	**N (%)**	**N (%)**
No Use	62 (25.73)	1691 (70.17)
Within 1-30 Days	108 (44.81)	236 (9.79)
Within 31-60 Days	30 (12.45)	117 (4.85)
Within 61-90 Days	14 (5.81)	122 (5.06)
Within 91-120 Days	14 (5.81)	118 (4.90)
Within 121-150 Days	9 (3.73)	73 (3.03)
Within 151-180 Days	4 (1.66)	53 (2.20)

Table 31. Prevalence of Gastric Acid Suppressant Use among Community-associated *C. difficile* Infection Cases and Matched Controls in the 180 days prior to Diagnosis or Index Date following Application of a Secondary Case Definition.

		CA-CDI Cases (N = 241)	Controls (N = 2410)
		N (%)	N (%)
Use of Any Gastric Acid Suppressant[a]		47 (19.50)	122 (5.06)
Drug Class	**Medication**		
Proton Pump Inhibitors		42 (17.43)	122 (5.06)
	Esomeprazole	13 (5.39)	31 (1.29)
	Lansoprazole	14 (5.81)	33 (1.37)
	Omeprazole	11 (4.56)	29 (1.20)
	Pantoprazole	4 (1.66)	12 (0.50)
	Rabeprazole	3 (1.24)	9 (0.37)
H_2-Receptor Antagonists		5 (2.07)	16 (0.66)
	Cimetidine	0 (0)	2 (0.08)
	Famotidine	2 (0.83)	4 (0.17)
	Ranitidine	3 (1.24)	10 (0.41)

[a] Includes the use of all medications classified as either a proton pump inhibitor or H_2-receptor antagonist

Table 32. Relationship between Community-associated CDI and Antimicrobial Use, Demographic Characteristics, Healthcare Utilization, and Gastric Acid Suppressant Use among Cases and Controls following Application of a Secondary Case Definition.

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Age in years (by category)				
<18 years	0.37	(0.25, 0.55)	reference	--
19 to 49 years	1.20	(0.92, 1.56)	2.76	(1.69, 4.49)
50 to 64 years	1.37	(1.04, 1.82)	2.50	(1.48, 4.21)
65 to 74 years	1.80	(0.96, 3.38)	3.20	(1.36, 7.53)
≥75 years	2.45	(1.06, 5.64)	1.94	(0.58, 6.50)
Gender (female)	1.31	(1.00, 1.71)	1.09	(0.79, 1.48)
History of Hospitalization[b]	3.96	(2.51, 6.26)	0.94	(0.49, 1.79)
Number of Outpatient Physician Visits[c]	1.05	(1.04, 1.06)	1.02	(1.01, 1.04)
Charlson Comorbid Index[d]	2.16	(1.61, 2.91)	1.14	(0.75, 1.73)
IBD[e]	22.5	(6.93, 73.06)	23.63	(5.19, 107.62)
Diverticular Disease	5.09	(2.53, 10.25)	1.74	(0.73, 4.13)
Gastroesophageal Reflux Disease	4.11	(2.38, 7.10)	1.48	(0.69, 3.17)
Gastric Acid Suppressant Use[f]	4.54	(3.14, 6.57)	2.03	(1.23, 3.36)
Beta-lactamase Inhibitor Use	5.55	(3.61, 8.52)	4.62	(2.76, 7.74)
Cephalosporin Use	3.89	(2.76, 5.49)	2.95	(1.93, 4.51)
Clindamycin Use	14.31	(7.74, 26.46)	11.25	(5.56, 22.76)
Fluoroquinolone Use	8.17	(5.60, 11.93)	4.07	(2.56, 6.46)
Macrolide Use	2.48	(1.77, 3.48)	2.14	(1.44, 3.18)
Penicillin Use	1.58	(1.08, 2.32)	1.58	(1.01, 2.50)
Sulfonamide Use	2.32	(1.16, 4.68)	1.37	(0.60, 3.11)
Tetracycline Use	1.59	(0.80, 3.13)	1.08	(0.48, 2.42)

NOTE: OR=Odds Ratio; CI=Confidence Interval

NOTE: c-statistic = 0.827

[a] Adjusted for all covariates shown

Table 32. continued

[b] History of being discharged from a hospitalization in the 365 days prior to diagnosis date for cases and index date for controls

[c] Number of outpatient visits in the 365 days prior to diagnosis date for cases and index date for controls

[d] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[e] Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis

[f] Includes any use of proton pump inhibitors or H_2-receptor antagonists

Table 33. Relationship between Timing of Antimicrobial Use and CA-CDI among Cases and Controls following Application of a Secondary Case Definition.

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Timing of Antimicrobial Use				
No Antimicrobial Use	reference	--	reference	--
Within 1-30 Days	12.61	(8.89, 17.89)	12.56	(8.52, 18.50)
Within 31-60 Days	6.89	(4.26, 11.14)	5.93	(3.48, 10.09)
Within 61-90 Days	3.02	(1.63, 5.61)	2.78	(1.42, 5.44)
Within 91-120 Days	3.06	(1.65, 5.67)	2.24	(1.14, 5.44)
Within 121-150 Days	3.27	(1.56, 6.85)	3.83	(1.74, 8.44)
Within 151-180 Days	2.09	(0.73, 6.00)	1.77	(0.56, 5.57)
Age in years (by category)				
<18 years	0.37	(0.25, 0.55)	reference	--
19 to 49 years	1.20	(0.92, 1.56)	3.10	(1.95, 4.95)
50 to 64 years	1.37	(1.04, 1.82)	2.60	(1.57, 4.29)
65 to 74 years	1.80	(0.96, 3.38)	3.12	(1.30, 7.48)
≥75 years	2.45	(1.06, 5.64)	2.46	(0.80, 7.57)
Gender (female)	1.31	(1.00, 1.71)	1.03	(0.75, 1.41)
History of Hospitalization[b]	3.96	(2.51, 6.26)	1.32	(0.71, 2.43)
Number of Outpatient Physician Visits[c]	1.05	(1.04, 1.06)	1.02	(1.01, 1.04)
Charlson Comorbid Index[d]	2.16	(1.61, 2.91)	1.20	(0.80, 1.78)
IBD[e]	22.5	(6.93, 73.06)	29.22	(6.61, 129.25)
Diverticular Disease	5.09	(2.53, 10.25)	1.90	(0.80, 4.52)
Gastroesophageal Reflux Disease	4.11	(2.38, 7.10)	1.22	(0.58, 2.56)
Gastric Acid Suppressant Use[f]	4.07	(2.91, 5.69)	2.24	(1.37, 3.65)

NOTE: OR=Odds Ratio; CI=Confidence Interval

Table 33. continued

NOTE: c-statistic = 0.831

[a] Adjusted for all covariates shown

[b] History of being discharged from a hospitalization in the 365 days prior to diagnosis date for cases and index date for controls

[c] Number of outpatient visits in the 365 days prior to diagnosis date for cases and index date for controls

[d] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[e] Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis

[f] Includes any use of proton pump inhibitors or H_2-receptor antagonists

Table 34. Relationship between Total Number of Different Antimicrobial Agents and CA-CDI among Cases and Controls following Application of a Secondary Case Definition.

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Number of Antimicrobial Agents[b]	2.67	(2.31, 3.08)	2.02	(1.25, 3.25)
Age in years (by category)				
<18 years	0.37	(0.25, 0.55)	reference	--
19 to 49 years	1.20	(0.92, 1.56)	3.14	(1.96, 5.04)
50 to 64 years	1.37	(1.04, 1.82)	2.72	(1.65, 4.48)
65 to 74 years	1.80	(0.96, 3.38)	3.54	(1.53, 8.22)
≥75 years	2.45	(1.06, 5.64)	2.06	(0.66, 6.38)
Gender (female)	1.31	(1.00, 1.71)	1.07	(0.79, 1.46)
History of Hospitalization[c]	3.96	(2.51, 6.26)	1.07	(0.58, 1.96)
Number of Outpatient Physician Visits[d]	1.05	(1.04, 1.06)	1.02	(1.01, 1.04)
Charlson Comorbid Index[e]	2.16	(1.61, 2.91)	1.17	(0.81, 1.69)
IBD[f]	22.5	(6.93, 73.06)	22.70	(5.22, 98.80)
Diverticular Disease	5.09	(2.53, 10.25)	1.95	(0.85, 4.46)
Gastroesophageal Reflux Disease	4.11	(2.38, 7.10)	1.50	(0.73, 3.07)
Gastric Acid Suppressant Use[g]	4.07	(2.91, 5.69)	2.02	(1.25, 3.25)

NOTE: OR=Odds Ratio; CI=Confidence Interval

NOTE: c-statistic = 0.821

[a] Adjusted for all covariates shown

[b] Total number of antimicrobial agents utilized in the 180 days prior to diagnosis date for cases and index date for controls

[c] History of being discharged from a hospitalization in the 365 days prior to diagnosis date for cases and index date for controls

[d] Number of outpatient visits in the 365 days prior to diagnosis date for cases and index date for controls

Table 34. continued

[e] Charlson ME, et al. J Chronic Dis. 1987 ;40 :373–383.

[f] Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis

[g] Includes any use of proton pump inhibitors or H_2-receptor antagonists

Table 35. Comparison of the Demographic and Clinical Characteristics of Community-associated *C. difficile* Infection Cases and Matched Controls following Exclusion of Cases with Gastrointestinal Conditions or History of Hospitalization within 6 months of diagnosis.

Variable	CA-CDI Cases (N = 246)	Controls (N = 2460)	p-value[a]
Mean Age in Years ± SD (Range)	41.15 ± 19.98 (1 – 83)	35.33 ± 19.8 (1 – 96)	<0.0001
Age Category			
<18 years	42 (17.07)	672 (27.32)	
19 to 49 years	102 (41.46)	1064 (43.25)	
50 to 64 years	84 (34.15)	628 (25.53)	0.0002
65 to 74 years	12 (4.88)	70 (2.85)	
≥75 years	6 (2.44)	26 (1.06)	
Gender (female)	146 (59.35)	1263 (51.34)	0.0165
History of Hospitalization in Previous Year	17 (6.91)	84 (3.41)	0.0784
Mean Number of Outpatient Physician Visits in Previous Year ± SD	15.05 ± 13.63	7.85 ± 9.40	<0.0001
Number of Comorbid Conditions[b]			
0	223 (90.35)	2305 (93.70)	
1	21 (8.54)	129 (5.24)	0.2017
2	1 (0.41)	21 (0.85)	
3+	1 (0.41)	5 (0.20)	
Mean Number of Comorbid Conditions[b] ± SD	0.11 ± 0.36	0.08 ± 0.32	<0.0001
Mean Deyo-Charlson Comorbid Index Score ± SD	0.12 ± 0.42	0.05 ± 0.25	<0.0001
Charlson Comorbidity Index Score			
0	223 (90.65)	2366 (96.18)	
1	19 (7.72)	77 (3.13)	
2	3(1.220	14 (0.57)	<0.0001
3	0 (0)	3 (0.12)	
4	1 (0.41)	0 (0)	
5+	0 (0)	0 (0)	

Table 35. continued

Mean Number of Antimicrobial Agents ± SD	1.26 ± 1.10	0.40 ± 0.69	<0.0001
Mean Number of Days of Antimicrobial Use ± SD	14.77 ± 14.85	3.76 ± 7.85	<0.0001
Antimicrobial Use			
Any	180 (73.17)	752 (30.57)	<0.0001
None	66 (26.83)	1708 (69.43)	
Receipt of a Gastric Acid Suppressant[c]	29 (11.79)	124 (5.04)	<0.0001

NOTE. Data are number (%) of patients, unless otherwise stated.

[a] p-value obtained from Student's t-test for comparing mean values for continuous variables and chi-square test for comparing frequency distributions for categorical variables

[b] Includes Charlson comorbid conditions and gastrointestinal conditions

[c] Includes proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2As)

Table 36. Prevalence of Charlson Chronic Comorbid Conditions among Community-associated *C. difficile* Cases and Controls following Exclusion of Cases with Gastrointestinal Conditions or History of Hospitalization within 6 months of diagnosis.

	CA-CDI Cases (N = 246)	Controls (N = 2460)
	N (%)	N (%)
Charlson Comorbid Condition[a]		
Acute Myocardial Infarction	0 (0)	2 (0.08)
Old Myocardial Infarction	0 (0)	4 (0.17)
Congestive Heart Failure	0 (0)	5 (0.21)
Peripheral Vascular Disease	1 (0.41)	2 (0.08)
Cerebrovascular Disease	0 (0)	10 (0.41)
Chronic Pulmonary Disease	12 (4.88)	32 (1.30)
Dementia	2 (0.81)	0 (0)
Rheumatic Disease	1 (0.41)	5 (0.20)
Peptic Ulcer Disease, excluding bleeding	0 (0)	0 (0)
Mild Liver Disease	0 (0)	0 (0)
Diabetes without chronic complications	6 (2.44)	35 (1.42)
Diabetes with chronic complications	1 (0.41)	4 (0.16)
Hemiplagia or Paraplegia	1 (0.41)	1 (0.04)
Chronic Renal Failure	2 (0.81)	6 (0.24)

Table 36. continued

Any Malignancy[b]	0 (0)	0 (0)
Moderate or Severe Liver Disease	0 (0)	0 (0)
Metastatic Solid Tumor	0 (0)	0 (0)
AIDS/HIV[c]	0 (0)	0 (0)

[a] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[b] Includes lymphoma and leukemia, except malignant neoplasm of skin

[c] AIDS/HIV = Acquired Immune Deficiency Syndrome/Human Immunodeficiency Virus

Table 37. Prevalence of Gastric Acid Suppressant Use among Community-associated *C. difficile* Infection Cases and Matched Controls in the 180 days prior to diagnosis or index date following Exclusion of Cases with Gastrointestinal Conditions or History of Hospitalization within 6 months of diagnosis.

		CA-CDI Cases (N = 246)	Controls (N = 2460)
		N (%)	N (%)
Use of Any Gastric Acid Suppressant[a]		29 (11.79)	124 (5.04)
Drug Class	**Medication**		
Proton Pump Inhibitors		23 (9.35)	124 (5.04)
	Esomeprazole	10 (4.07)	36 (1.46)
	Lansoprazole	5 (2.03)	31 (1.26)
	Omeprazole	7 (2.85)	24 (0.98)
	Pantoprazole	1 (0.41)	14 (0.57)
	Rabeprazole	1 (0.41)	9 (0.37)
H_2-Receptor Antagonists		6 (2.44)	19 (0.77)
	Cimetidine	1 (0.41)	2 (0.08)
	Famotidine	2 (0.81)	3 (0.12)
	Ranitidine	3 (1.22)	14 (0.57)

[a] Includes the use of all medications classified as either a proton pump inhibitor or H_2-receptor antagonist

Table 38. Antimicrobial Use in the 180 days prior to diagnosis or index date among Community-associated *C. difficile* Infection Cases and Matched Controls Following Exclusion of Cases with Gastrointestinal Conditions or History of Hospitalization within 6 months of diagnosis.

Antimicrobial Exposure		CA-CDI Cases (N = 246) N (%)	Controls (N = 2460) N (%)
Number of Antimicrobials	No antimicrobial exposure	66 (26.83)	1708 (69.43)
	1 antimicrobial	96 (39.02)	568 (23.09)
	2 antimicrobials	51 (20.73)	148 (6.02)
	3 antimicrobials	23 (9.35)	28 (1.14)
	4 antimicrobials	9 (3.66)	7 (0.28)
	5+ antimicrobials	1 (0.41)	1 (0.04)
Antimicrobial Class	**Antimicrobial Drug**		
Aminoglycosides		1 (0.41)	1 (0.04)
	Gentamycin	0 (0)	1 (0.04)
	Neomycin	1 (0.41)	0 (0)
Beta-lactamase Inhibitors	Amoxicillin-clavulanate	33 (13.41)	84 (3.41)
Cephalosporins		61 (24.80)	192 (7.80)
First-generation		20 (8.13)	133 (5.41)
	Cephalexin	18 (7.32)	125 (5.08)
	Cefadroxil	2 (0.81)	8 (0.33)
Second-generation		20 (8.13)	47 (1.91)
	Cefprozil	8 (3.25)	18 (0.73)
	Cefuroxime	12 (4.88)	15 (0.61)
	Cefaclor	1 (0.41)	14 (0.57)
Third-generation		25 (10.16)	23 (0.93)
	Cefdinir	20 (8.31)	23 (0.93)
	Cefditoren	1 (0.41)	0 (0)
	Cefpodoxime	6 (2.44)	0 (0)
Lincomycin Derivatives	Clindamycin	30 (12.20)	22 (0.89)
Fluoroquinolones		50 (20.33)	70 (2.85)

Table 38. continued

	Gatifloxacin	0 (0)	1 (0.04)
	Levofloxacin	20 (8.13)	36 (1.46)
	Moxifloxacin	7 (2.85)	7 (0.28)
	Ciprofloxacin	328 (11.38)	28 (1.14)
Macrolides		50 (20.33)	240 (9.76)
	Azithromycin	41 (16.67)	203 (8.25)
	Clarithromycin	7 (2.85)	29 (1.18)
	Erythromycin	2 (0.81)	12 (0.49)
	Telithromycin	2 (0.81)	7 (0.28)
Penicillins		44 (17.89)	237 (9.63)
	Amoxicillin	36 (14.63)	206 (8.37)
	Ampicillin	1 (0.41)	4 (0.16)
	Dicloxacillin	0 (0)	3 (0.12)
	Penicillin	7 (2.85)	29 (1.18)
Rifamycin derivatives	Rifampin	2 (0.81)	0 (0)
Sulfonamides	Trimethoprim-sulfamethoxazole	13 (5.28)	43 (1.75)
Tetracyclines		8 (3.25)	62 (2.52)
	Tetracycline	1 (0.41)	7 (0.28)
	Minocycline	1 (0.41)	17 (0.69)
	Doxycycline	6 (2.44)	39 (1.59)
Miscellaneous Antimicrobials	Intravenous Vancomycin	3 (1.22)	0 (0)

Table 39. Timing of Antimicrobial Use among Community-associated *C. difficile* Cases and Controls within the 180 days prior to diagnosis or index date following Exclusion of Cases with Gastrointestinal Conditions or History of Hospitalization within 6 months of diagnosis.

	CA-CDI Cases (N = 246)	Controls (N = 2460)
Timing of Antimicrobial Use	**N (%)**	**N (%)**
No Use	66 (26.83)	1708 (69.43)
Within 1-30 Days	117 (47.56)	243 (9.88)
Within 31-60 Days	27 (10.98)	121 (4.92)
Within 61-90 Days	12 (4.88)	130 (5.28)
Within 91-120 Days	14 (5.69)	115 (4.67)
Within 121-150 Days	6 (2.44)	76 (3.09)
Within 151-180 Days	4 (1.63)	67 (2.72)

Table 40. Timing of Gastric Acid Suppressant Use among Community-associated *C. difficile* Cases and Controls within the 180 days prior to diagnosis or index date following Exclusion of Cases with Gastrointestinal Conditions or History of Hospitalization within 6 months of diagnosis.

	CA-CDI Cases (N = 246)	Controls (N = 2460)
Timing of Gastric Acid Suppressant Use	**N (%)**	**N (%)**
No Use	249 (81.91)	2883 (94.84)
Within 1-30 Days	41 (13.49)	117 (3.85)
Within 31-60 Days	3 (0.99)	13 (0.43)
Within 61-90 Days	4 (1.32)	11 (0.36)
Within 91-120 Days	0 (0)	0 (0)
Within 121-150 Days	0 (0)	0 (0)
Within 151-180 Days	0 (0)	0 (0)

Table 41. Relationship between Community-associated *C. difficile* Infection and Antimicrobial Use, Demographic Characteristics, Healthcare Utilization, and Gastric Acid Suppressant Use among Cases and Controls following Exclusion of Cases with Gastrointestinal Conditions or History of Hospitalization within 6 months of diagnosis.

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Age in years (by category)				
<18 years	0.55	(0.39, 0.78)	reference	--
19 to 49 years	0.93	(0.71, 1.21)	1.73	(1.12, 2.66)
50 to 64 years	1.51	(1.14, 2.00)	2.17	(1.37, 3.45)
65 to 74 years	1.75	(0.94, 3.27)	2.82	(1.28, 6.23)
≥75 years	2.33	(0.95, 5.68)	2.49	(0.79, 7.88)
Gender (female)	1.39	(1.01, 1.81)	1.10	(0.81, 1.50)
History of Hospitalization[b]	2.10	(1.23, 3.59)	0.64	(0.32, 1.28)
Number of Outpatient Physician Visits[c]	1.05	(1.04, 1.06)	1.03	(1.02, 1.04)
Charlson Comorbid Index[d]	1.89	(1.35, 2.65)	0.96	(0.60, 1.54)
Gastric Acid Suppressant Use[e]	2.50	(1.63, 3.83)	1.15	(0.68, 1.95)
Beta-lactamase Inhibitor Use	4.48	(2.90, 6.91)	3.64	(2.19, 6.07)
Cephalosporin Use	3.97	(2.85, 5.52)	3.13	(2.11, 4.65)
Clindamycin Use	15.72	(8.74, 28.27)	14.52	(7.44, 28.35)
Fluoroquinolone Use	8.62	(5.79, 12.82)	5.34	(3.36, 8.46)
Macrolide Use	2.35	(1.68, 3.29)	2.17	(1.48, 3.18)
Penicillin Use	2.05	(1.44, 2.91)	1.75	(1.16, 2.65)
Sulfonamide Use	3.12	(1.66, 5.89)	1.43	(0.66, 3.12)
Tetracycline Use	1.30	(0.62, 2.75)	1.15	(0.68, 1.95)

NOTE: OR=Odds Ratio; CI=Confidence Interval

NOTE: c-statistic = 0.803

[a] Adjusted for all covariates shown

[b] History of being discharged from a hospitalization in the 365 days prior to diagnosis date for cases and index date for controls

[c] Number of outpatient visits in the 365 days prior to diagnosis date for cases and index date for controls

Table 41. continued

[d] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[e] Includes any use of proton pump inhibitors or H_2-receptor antagonists

Table 42. Relationship Between Timing of Antimicrobial Use and CA-CDI among Cases and Controls following Exclusion of Cases with Gastrointestinal Conditions or History of Hospitalization within 6 months of Diagnosis.

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Timing of Antimicrobial Use				
No Antimicrobial Use	reference	--	reference	--
Within 1-30 Days	12.78	(9.08, 18.00)	12.69	(8.83, 18.25)
Within 31-60 Days	5.71	(3.49, 9.35)	5.12	(3.05, 8.59)
Within 61-90 Days	2.37	(1.24, 4.52)	2.24	(1.15, 4.35)
Within 91-120 Days	3.03	(1.64, 5.60)	2.49	(1.31, 4.73)
Within 121-150 Days	1.93	(0.81, 4.62)	2.30	(0.96, 5.55)
Within 151-180 Days	1.59	(0.56, 4.52)	1.40	(0.47, 4.17)
Age in years (by category)				
<18 years	0.55	(0.39, 0.78)	reference	--
19 to 49 years	0.93	(0.71, 1.21)	2.00	(1.33, 3.01)
50 to 64 years	1.51	(1.14, 2.00)	2.31	(1.49, 3.58)
65 to 74 years	1.75	(0.94, 3.27)	2.88	(1.30, 6.38)
≥75 years	2.33	(0.95, 5.68)	2.75	(0.95, 7.94)
Gender (female)	1.39	(1.01, 1.81)	1.05	(0.78, 1.43)
History of Hospitalization[b]	2.10	(1.23, 3.59)	0.86	(0.45, 1.67)
Number of Outpatient Physician Visits[c]	1.05	(1.04, 1.06)	1.03	(1.02, 1.04)
Charlson Comorbid Index[d]	1.89	(1.35, 2.65)	1.08	(0.70, 1.68)
Gastric Acid Suppressant Use[e]	1.59	(0.94, 2.70)	1.35	(0.81, 2.26)

NOTE: OR=Odds Ratio; CI=Confidence Interval

NOTE: c-statistic = 0.810

[a] Adjusted for all covariates shown

Table 42. continued

[b] History of being discharged from a hospitalization in the 365 days prior to diagnosis date for cases and index date for controls

[c] Number of outpatient visits in the 365 days prior to diagnosis date for cases and index date for controls

[d] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[e] Includes any use of proton pump inhibitors or H_2-receptor antagonists

Table 43. Relationship between Total Number of Different Antimicrobial Agents and CA-CDI among Cases and Controls following Exclusion of Cases with Gastrointestinal Conditions or History of Hospitalization within 6 months of diagnosis.

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Number of Antimicrobial Agents[b]	2.72	(2.36, 3.14)	2.67	(2.29, 3.12)
Age in years (by category)				
<18 years	0.55	(0.39, 0.78)	reference	--
19 to 49 years	0.93	(0.71, 1.21)	2.14	(1.41, 3.25)
50 to 64 years	1.51	(1.14, 2.00)	2.64	(1.70, 4.11)
65 to 74 years	1.75	(0.94, 3.27)	2.90	(1.33, 6.35)
≥75 years	2.33	(0.95, 5.68)	3.01	(1.04, 8.65)
Gender (female)	1.39	(1.01, 1.81)	1.10	(0.82, 1.48)
History of Hospitalization[c]	2.10	(1.23, 3.59)	0.79	(0.41, 1.50)
Number of Outpatient Physician Visits[d]	1.05	(1.04, 1.06)	1.03	(1.01, 1.04)
Charlson Comorbid Index[e]	1.89	(1.35, 2.65)	0.97	(0.62, 1.53)
Gastric Acid Suppressant Use[f]	1.59	(0.94, 2.70)	1.21	(0.73, 2.02)

NOTE: OR=Odds Ratio; CI=Confidence Interval

NOTE: c-statistic = 0.794

[a] Adjusted for all covariates shown

[b] Total number of antimicrobial agents utilized in the 180 days prior to diagnosis date for cases and index date for controls.

[c] History of being discharged from a hospitalization in the 365 days prior to diagnosis date for cases and index date for controls

[d] Number of outpatient visits in the 365 days prior to diagnosis date for cases and index date for controls

[e] Charlson ME, et al. J Chronic Dis. 1987 ;40 :373–383.

[f] Includes any use of proton pump inhibitors or H_2-receptor antagonists

Table 44. Comparison of the Demographic and Clinical Characteristics of Community-associated *C. difficile* Infection Cases and Matched Controls following Redefinition of Diagnosis Date.

Variable	CA-CDI Cases (N = 299)	Controls (N = 2990)	p-value[a]
Mean Age in Years ± SD (Range)	42.61 ± 20.08 (1 – 91)	35.74 ± 19.8 (1 – 96)	<0.0001
Age Category			
<18 years	45 (15.05)	801 (26.79)	
19 to 49 years	122 (40.80)	1278 (42.74)	
50 to 64 years	104 (34.78)	787 (26.32)	<0.0001
65 to 74 years	18 (6.02)	89 (2.98)	
≥75 years	10 (3.34)	35 (1.17)	
Gender (female)	180 (60.30)	1546 (51.71)	0.0050
History of Hospitalization in Previous Year	50 (16.72)	100 (3.34)	<0.0001
Mean Number of Outpatient Physician Visits in Previous Year ± SD	17.97 ± 17.76	7.96 ± 10.06	<0.0001
Number of Comorbid Conditions[b]			
0	239 (79.93)	2792 (93.70)	
1	47 (15.72)	162 (5.42)	<0.0001
2	8 (2.68)	31 (1.04)	
3+	5 (1.66)	5 (0.16)	
Mean Number of Comorbid Conditions[b] ± SD	0.27 ± 0.67	0.08 ± 0.33	<0.0001
Presence of a Gastrointestinal Condition[c]	38 (12.71)	95 (3.18)	<0.0001
Mean Charlson Comorbidity Index Score ± SD	0.15 ± 0.60	0.05 ± 0.26	<0.0001
Charlson Comorbidity Index Score			
0	270 (90.30)	2869 (95.95)	
1	22 (7.36)	97 (3.24)	
2	4 (1.34)	20 (0.67)	<0.0001
3	1 (0.33)	4 (0.13)	
4	1 (0.33)	0 (0)	
5+	1 (0.33)	0 (0)	

Table 44. continued

Mean Number of Antimicrobial Agents ± SD	1.14 ± 1.07	0.40 ± 0.69	<0.0001
Mean Number of Days of Antimicrobial Use ± SD	12.64 ± 15.18	3.72 ± 7.87	<0.0001
Antimicrobial Use			
Any	203 (67.89)	906 (27.55)	<0.0001
None	96 (32.11)	2084 (69.70)	
Receipt of a Gastric Acid Suppressant[d]	50 (16.72)	152 (5.08)	<0.0001

NOTE. Data are number (%) of patients, unless otherwise stated.

[a] p-value obtained from Student's t-test for comparing mean values for continuous variables and chi-square test for comparing frequency distributions for categorical variables

[b] Includes Charlson comorbid conditions and gastrointestinal conditions

[c] Includes peptic ulcer disease, inflammatory bowel disease (Crohn's disease, Ulcerative Colitis), diverticular disease, and gastroesophageal reflux disease (GERD)

[d] Includes proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2As)

Table 45. Prevalence of Charlson Chronic Comorbid Conditions among Community-associated *C. difficile* Cases and Controls following Redefinition of Diagnosis Date.

	CA-CDI Cases (N = 299)	Controls (N = 2990)
	N (%)	N (%)
Charlson Comorbid Condition[a]		
Acute Myocardial Infarction	0 (0)	2 (0.07)
Old Myocardial Infarction	2 (0.67)	4 (0.13)
Congestive Heart Failure	3 (1.00)	6 (0.20)
Peripheral Vascular Disease	0 (0)	6 (0.20)
Cerebrovascular Disease	0 (0)	13 (0.43)
Chronic Pulmonary Disease	15 (5.02)	39 (1.30)
Dementia	2 (0.67)	0 (0)
Rheumatic Disease	4 (1.34)	6 (0.20)
Peptic Ulcer Disease, excluding bleeding	0 (0)	0 (0)
Mild Liver Disease	0 (0)	0 (0)
Diabetes without chronic complications	10 (23.34)	49 (1.64)
Diabetes with chronic complications	2 (0.67)	6 (0.20)
Hemiplegia or Paraplegia	0 (0)	1 (0.03)
Chronic Renal Failure	3 (1.00)	7 (0.23)
Any Malignancy[b]	0 (0)	0 (0)

Table 45. continued

Moderate or Severe Liver Disease	0 (0)	0 (0)
Metastatic Solid Tumor	0 (0)	0 (0)
AIDS/HIV[c]	0 (0)	0 (0)
Gastrointestinal Conditions		
Inflammatory Bowel Disease (IBD)[d]	8 (2.68)	4 (0.13)
Diverticular Disease	10 (3.34)	33 (1.10)
Gastroesophageal Reflux Disease (GERD)	23 (7.69)	63 (2.11)

[a] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[b] Includes lymphoma and leukemia, except malignant neoplasm of skin

[c] AIDS/HIV = Acquired Immune Deficiency Syndrome/Human Immunodeficiency Virus

[d] Includes Crohn's disease and ulcerative colitis

Table 46. Antimicrobial Use in the 180 days prior to diagnosis or index date among Community-associated *C. difficile* Infection Cases and Matched Controls following Redefinition of Diagnosis Date.

Antimicrobial Exposure		CA-CDI Cases (N = 299) N (%)	Controls (N = 2990) N (%)
Number of Antimicrobials	No antimicrobial exposure	96 (32.11)	2084 (69.70)
	1 antimicrobials	110 (36.79)	682 (22.81)
	2 antimicrobials	58 (19.40)	181 (6.05)
	3 antimicrobials	28 (9.36)	33 (1.10)
	4 antimicrobials	6 (2.01)	9 (0.30)
	5+ antimicrobials	1 (0.33)	1 (0.03)
Antimicrobial Class	**Antimicrobial Drug**		
Aminoglycosides		1 (0.33)	1 (0.03)
	Gentamycin	0 (0)	1 (0.03)
	Neomycin	1 (0.33)	0 (0)
Beta-lactamase Inhibitors	Amoxicillin-clavulanate	47 (15.72)	94 (3.14)
Cephalosporins		68 (22.74)	227 (7.59)
First-generation		26 (8.70)	160 (5.35)
	Cephalexin	25 (8.36)	150 (5.02)
	Cefadroxil	1 (0.33)	10 (0.33)
Second-generation		22 (7.36)	51 (1.71)
	Cefprozil	8 (2.68)	21 (0.70)
	Cefuroxime	13 (4.35)	16 (0.54)
	Cefaclor	1 (0.33)	14 (0.47)
Third-generation		24 (8.03)	28 (0.94)
	Cefdinir	20 (6.69)	27 (0.90)
	Cefditoren	1 (0.33)	0 (0)
	Cefpodoxime	5 (1.67)	1 (0.03)
Lincomycin Derivatives	Clindamycin	37 (12.37)	26 (0.87)

Table 46. continued

Fluoroquinolones		51 (17.06)	92 (3.08)
	Gatifloxacin	0 (0)	1 (0.03)
	Levofloxacin	24 (8.03)	47 (1.57)
	Moxifloxacin	6 (2.01)	7 (0.23)
	Ciprofloxacin	24 (8.03)	39 (1.30)
Macrolides		56 (18.73)	295 (9.87)
	Azithromycin	46 (15.38)	247 (8.26)
	Clarithromycin	9 (3.01)	36 (1.20)
	Erythromycin	1 (0.33)	17 (0.57)
	Telithromycin	2 (0.67)	7 (0.23)
Penicillins		44 (14.72)	286 (9.57)
	Amoxicillin	35 (11.71)	251 (8.39)
	Ampicillin	1 (0.33)	4 (0.13)
	Dicloxacillin	0 (0)	4 (0.13)
	Penicillin	8 (2.68)	32 (1.07)
Rifamycin derivatives	Rifampin	1 (0.33)	0 (0)
Sulfonamides	Trimethoprim-sulfamethoxazole	14 (4.68)	52 (1.74)
Tetracyclines		11 (3.68)	78 (2.61)
	Tetracycline	1 (0.33)	9 (0.30)
	Minocycline	1 (0.33)	25 (0.84)
	Doxycycline	9 (3.01)	46 (1.54)
Miscellaneous Antimicrobials	Intravenous Vancomycin	0 (0)	0 (0)

Table 47. Timing of Antimicrobial Use among Community-associated *C. difficile* Cases and Controls within the 180 days prior to Diagnosis or Index Date following Redefinition of Diagnosis Date.

	CA-CDI Cases (N = 299)	Controls (N = 2990)
Timing of Antimicrobial Use	**N (%)**	**N (%)**
No Use	96 (32.11)	2084 (69.70)
Within 1-30 Days	142 (47.49)	301 (10.07)
Within 31-60 Days	21 (7.02)	145 (4.85)
Within 61-90 Days	12 (4.01)	149 (4.98)
Within 91-120 Days	13 (4.35)	141 (4.72)
Within 121-150 Days	11 (3.68)	96 (3.21)
Within 151-180 Days	4 (1.34)	74 (2.47)

Table 48. Prevalence of Gastric Acid Suppressant Use among Community-associated *C. difficile* Infection Cases and Matched Controls in the 180 days prior to Diagnosis or Index Date following Redefinition of Diagnosis Date.

		CA-CDI Cases (N = 299)	Controls (N = 2990)
		N (%)	N (%)
Use of Any Gastric Acid Suppressant[a]		50 (16.72)	152 (5.08)
Drug Class	**Medication**		
Proton Pump Inhibitors		45 (15.05)	131 (4.38)
	Esomeprazole	15 (5.02)	40 (1.34)
	Lansoprazole	16 (5.35)	37 (1.24)
	Omeprazole	14 (4.68)	35 (1.17)
	Pantoprazole	3 (1.00)	15 (0.50)
	Rabeprazole	3 (1.00)	11 (0.37)
H_2-Receptor Antagonists		6 (2.01)	25 (0.84)
	Cimetidine	1 (0.33)	4 (0.13)
	Famotidine	3 (1.00)	5 (0.17)
	Ranitidine	2 (0.67)	16 (0.54)

[a] Includes the use of all medications classified as either a proton pump inhibitor or H_2-receptor antagonist

Table 49. Relationship between Community-associated *C. difficile* Infection and Antimicrobial Use, Demographic Characteristics, Healthcare Utilization, and Gastric Acid Suppressant Use among Cases and Controls following Redefinition of Diagnosis Date.

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Age in years (by category)				
<18 years	0.49	(0.35, 0.67)	reference	--
19 to 49 years	0.92	(0.73, 1.18)	1.64	(1.09, 2.47)
50 to 64 years	1.49	(1.16, 1.92)	1.86	(1.20, 2.86)
65 to 74 years	2.11	(1.25, 3.56)	3.13	(1.56, 6.28)
≥75 years	2.90	(1.43, 5.90)	2.64	(1.03, 6.71)
Gender (female)	1.42	(1.11, 1.81)	1.11	(0.84, 1.47)
History of Hospitalization[b]	4.31	(3.03, 6.12)	2.63	(1.63, 4.25)
Number of Physician Visits[c]	1.05	(1.04, 1.06)	1.03	(1.02, 1.04)
Charlson Comorbid Index[d]	1.88	(1.42, 2.48)	0.73	(0.50, 1.06)
IBD[e]	20.0	(6.02, 66.42)	15.91	(3.43, 73.79)
Diverticular Disease	3.08	(1.51, 6.30)	0.71	(0.28, 1.79)
Gastroesophageal Reflux Disease	3.87	(2.36, 6.35)	1.34	(0.68, 2.64)
Gastric Acid Suppressant Use[f]	4.11	(2.93, 5.77)	1.62	(1.02, 2.56)
Beta-lactamase Inhibitor Use	6.13	(4.12, 8.93)	4.69	(2.99, 7.35)
Cephalosporin Use	3.99	(2.96, 5.39)	2.41	(1.67, 3.49)
Clindamycin Use	16.59	(9.69, 28.41)	15.38	(8.29, 28.55)
Fluoroquinolone Use	8.63	(6.13, 12.14)	3.42	(2.21, 5.32)
Macrolide Use	2.41	(1.79, 3.26)	1.90	(1.32, 2.72)
Penicillin Use	1.90	(1.37, 2.64)	1.36	(0.91, 2.02)
Sulfonamide Use	3.16	(1.79, 5.60)	1.60	(0.77, 3.31)
Tetracycline Use	1.56	(0.84, 2.89)	0.98	(0.46, 2.08)

NOTE: OR=Odds Ratio; CI=Confidence Interval

NOTE: c-statistic = 0.818

[a] Adjusted for all covariates shown

Table 49. continued

[b] History of being discharged from a hospitalization in the 365 days prior to diagnosis date for cases and index date for controls

[c] Number of outpatient visits in the 365 days prior to diagnosis date for cases and index date for controls

[d] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[e] Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis

[f] Includes any use of proton pump inhibitors or H_2-receptor antagonists

Table 50. Relationship between Timing of Antimicrobial Use and CA-CDI among Cases and Controls following Redefinition of Diagnosis Date.

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Timing of Antimicrobial Use				
No Antimicrobial Use	reference	--	reference	--
Within 1-30 Days	10.38	(7.74, 13.94)	9.83	(7.11, 13.60)
Within 31-60 Days	3.07	(1.85, 5.09)	2.64	(1.53, 4.56)
Within 61-90 Days	1.71	(0.91, 3.20)	1.45	(0.74, 2.84)
Within 91-120 Days	1.91	(1.04, 3.51)	1.30	(0.67, 2.53)
Within 121-150 Days	2.44	(1.26, 4.71)	2.98	(1.50, 5.91)
Within 151-180 Days	1.21	(0.43, 3.39)	0.85	(0.28, 2.62)
Age in years (by category)				
<18 years	0.49	(0.35, 0.67)	reference	--
19 to 49 years	0.92	(0.73, 1.18)	1.87	(1.26, 2.77)
50 to 64 years	1.49	(1.16, 1.92)	2.12	(1.39, 3.22)
65 to 74 years	2.11	(1.25, 3.56)	3.43	(1.66, 7.06)
≥75 years	2.90	(1.43, 5.90)	3.03	(1.19, 7.70)
Gender (female)	1.42	(1.11, 1.81)	1.12	(0.84, 1.48)
History of Hospitalization[b]	4.31	(3.03, 6.12)	2.86	(1.79, 4.58)
Number of Physician Visits[c]	1.05	(1.04, 1.06)	1.03	(1.02, 1.04)
Charlson Comorbid Index[d]	1.88	(1.42, 2.48)	0.81	(0.57, 1.51)
IBD[e]	20.0	(6.02, 66.42)	22.21	(5.30, 93.03)
Diverticular Disease	3.08	(1.51, 6.30)	0.94	(0.39, 2.28)
Gastroesophageal Reflux Disease	3.87	(2.36, 6.35)	1.34	(0.71, 2.55)
Gastric Acid Suppressant Use	4.11	(2.93, 5.77)	1.85	(1.17, 2.93)

NOTE: OR=Odds Ratio; CI=Confidence Interval

NOTE: c-statistic = 0.821

[a] Adjusted for all covariates shown

Table 50. continued

[b] History of being discharged from a hospitalization in the 365 days prior to diagnosis date for cases and index date for controls

[c] Number of outpatient visits in the 365 days prior to diagnosis date for cases and index date for controls

[d] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[e] Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis

[f] Includes any use of proton pump inhibitors or H_2-receptor antagonists

Table 51. Relationship between Total Number of Different Antimicrobial Agents and CA-CDI among Cases and Controls following Redefinition of Diagnosis Date.

Variable	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Number of Antimicrobial Agents[b]	2.46	(2.16, 2.79)	2.28	(1.98, 2.62)
Age in years (by category)				
<18 years	0.49	(0.35, 0.67)	reference	--
19 to 49 years	0.92	(0.73, 1.18)	1.91	(1.29, 2.83)
50 to 64 years	1.49	(1.16, 1.92)	2.14	(1.42, 3.23)
65 to 74 years	2.11	(1.25, 3.56)	3.23	(1.61, 6.46)
≥75 years	2.90	(1.43, 5.90)	2.56	(1.05, 6.22)
Gender (female)	1.42	(1.11, 1.81)	1.12	(0.86, 1.48)
History of Hospitalization[c]	4.31	(3.03, 6.12)	2.51	(1.60, 3.94)
Number of Outpatient Physician Visits[d]	1.05	(1.04, 1.06)	1.03	(1.02, 1.04)
Charlson Comorbid Index[e]	1.88	(1.42, 2.48)	0.80	(0.57, 1.10)
IBD[f]	20.0	(6.02, 66.42)	18.84	(4.28, 82.86)
Diverticular Disease	3.08	(1.51, 6.30)	1.03	(0.45, 2.36)
Gastroesophageal Reflux Disease	3.87	(2.36, 6.35)	1.36	(0.73, 2.55)
Gastric Acid Suppressant Use[g]	4.11	(2.93, 5.77)	1.65	(1.07, 2.56)

NOTE: OR=Odds Ratio; CI=Confidence Interval

NOTE: c-statistic = 0.806

[a] Adjusted for all covariates shown

[b] Total number of antimicrobial agents utilized in the 180 days prior to diagnosis date for cases and index date for controls

[c] History of being discharged from a hospitalization in the 365 days prior to diagnosis date for cases and index date for controls

[d] Number of outpatient visits in the 365 days prior to diagnosis date for cases and index date for controls

Table 51. continued

[e] Charlson ME, et al. J Chronic Dis. 1987;40:373–383.

[f] Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis

[g] Includes any use of proton pump inhibitors or H_2-receptor antagonists

Table 52. Comparison of the Demographic and Clinical Characteristics of Community-associated *C. difficile* Cases Who Were Hospitalized with Those Who Were Not Hospitalized.

Variable	Cases Who Were Subsequently Hospitalized (N = 77)	Cases Who Were Not Subsequently Hospitalized (N = 227)	p-value[a]
Mean Age in Years ± SD	40.77 ± 23	43.30 ± 18.88	0.3384
Gender (female)	52 (67.53)	132 (58.15)	0.1455
History of Hospitalization in Year Prior to Diagnosis	6 (7.79)	27 (11.89)	0.3174
Mean Number of Outpatient Physician Visits in Year Prior to Diagnosis ± SD	16.61 ± 13	17.24 ± 16.5	0.7603
Mean Number of Comorbid Conditions[b] ± SD	0.26 ± 0.50	0.36 ± 0.77	0.2807
Presence of a Gastrointestinal Condition[c]	13 (16.88)	37 (16.30)	0.9050
Mean Charlson Comorbidity Index Score ± SD	0.09 ± 0.33	0.20 ± 0.69	0.1872
Mean Number of Antimicrobial Agents Prior to Diagnosis ± SD	1.10 ± 1.02	0.98 ± 0.95	0.3403
Antimicrobial Use Prior to Diagnosis			
Any	48 (62.34)	141 (62.11)	0.9143
None	29 (37.66)	81 (35.68)	
Gastric Acid Suppressant Use Prior to Diagnosis[d]	8 (10.39)	35 (15.42)	0.2738
Antimotility Agent Use After Diagnosis[e]	2 (2.60)	5 (2.20)	1.000

NOTE. Data are number (%) of patients, unless otherwise stated.

[a] P-value obtained from Student's t-test for continuous variables and chi-square test for categorical variables

[b] Includes Charlson comorbid conditions and gastrointestinal conditions

[c] Includes Inflammatory Bowel Disease (Crohn's disease, ulcerative colitis), diverticular disease, and gastroesophageal reflux disease (GERD)

[d] Includes proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2As)

[e] Includes atropine-diphenoxylate and loperamide use on diagnosis date or in the 180 days following the diagnosis date

CHAPTER FIVE - DISCUSSION

Overview

This study provides a number of meaningful findings about CDI and its emergence in the community setting. In fact, this study's results support the growing belief that the epidemiology of CDI is changing, and more specifically, demonstrate that CDI is occurring in the community setting and in populations that are not traditionally considered 'high-risk'.

Summary of Findings

The incidence rates of CA-CDI were similar to rates of HA-CDI within this population, suggesting that CDI may be affecting the general population more than has been reported in the scientific literature. Further examination of these case groups revealed that CA-CDI cases were younger, had less comorbidity, used few healthcare services, and had less exposure to antimicrobials and gastric acid suppressants than HA-CDI cases had.

CDI has traditionally been associated with hospitalization, advanced age, underlying severe illness, gastric acid suppressant use and, most prominently, exposure to antimicrobials. Antimicrobial use was the primary risk factor for CA-CDI among this study population. In fact, the population attributable risk percent for antimicrobial use was nearly 58%; therefore, the population risk for CA-CDI would be reduced by more than one-half if antimicrobial use were eliminated from this population. However, it must be noted that 27% (82 of 304) of CA-CDI cases did not receive any antimicrobials in the 180 days prior to diagnosis.

In addition to antimicrobial use, many of the risk factors for CA-CDI identified in this study were similar to those commonly associated with HA-CDI, although it was not uncommon for persons to acquire CA-CDI without exposure to any of these risk factors. In fact, seventeen percent (51 of 304) of CA-CDI cases did not have any of the traditional

risk factors for CDI (i.e., no antimicrobial or gastric acid suppressant exposure, no underlying illness, and no history of hospitalization). Furthermore, although reports of severe infection are becoming more common in scientific literature, none of the CA-CDI cases underwent surgical procedures related to their infections and only 25% of these were hospitalized due to CA-CDI.

Collectively, these findings have significant relevance in research and clinical practice. First, this study solidifies prior reports of the movement of CDI into healthy populations and into the community setting. Second, these results reiterate a need for preventive interventions not limited to hospitalized or less healthy populations as has traditionally been the case. In addition, this study proves that there is a need for research to determine the source of *C. difficile* in non-hospitalized populations. Finally, the relative lack of adverse outcomes suggests that CA-CDI may be less severe than HA-CDI, or it may suggest that these severe outcomes occur less frequently among CA-CDI cases because they are younger and have less underlying illness than do HA-CDI cases.

Incidence of CDI

The overall incidence rate for CA-CDI was 11.16 cases per 100,000 person-years, whereas the incidence rate for HA-CDI was 12.41 cases per 100,000 person-years. Although it is difficult to compare among incidence rates from different populations and across studies that utilize different methods of case ascertainment and varied case definitions, the incidence of CA-CDI within this population is relatively consistent with prior reports from studies conducted in the United States (8, 10, 11, 240).

Remarkably, the incidence of CA-CDI was similar to that of HA-CDI. These results suggest that CDI contributes to morbidity in non-hospitalized populations more than expected. The study population primarily consisted of young, healthy individuals, thus, these incidence rates may not be representative of those experienced in populations inclusive of older persons or persons with higher levels of underlying comorbidity.

However, since the analyses were not adjusted for age, the observed rates may actually underestimate the incidence of CA-CDI.

Moreover, this study found that 44.4% of incident CDI cases were community-associated; 49.4% were hospital-acquired; and, 6.2% did not meet either definition. There are few studies which have identified both CA-CDI and HA-CDI cases in the same population. Of those that have, CA-CDI cases have accounted for 15% to 28% of the total burden of CDI (12, 94, 200, 201). The reasons for the difference between the findings of this study and of studies have not been determined.

Numerous studies have reported that the incidence of HA-CDI has increased, whereas similar observations do not exist for CA-CDI. Although the short time span of this study limited our ability to statistically assess trends in incidence over time, it can be noted that the incidence rates for both CA-CDI and HA-CDI were relatively stable over the study period. If the rates observed in this population are truly stable, these results may serve as an early indication that the incidence of CDI may not be changing at the same rate in all populations or geographic areas.

Demographic and Clinical Characteristics of CA-CDI and HA-CDI Cases

Within this population, CA-CDI cases were younger, had less underlying comorbidity, and had fewer pharmacologic exposures than did HA-CDI cases. Although CA-CDI cases were significantly younger than HA-CDI cases, the mean ages of the case groups were 43 years and 50 years, respectively. Collectively, these mean ages are still much younger than those typically reported in the scientific literature. However, the underlying population primarily includes younger persons who are insured through employers and excludes older persons (i.e., those who would primarily be insured through Medicare), thus partially explaining the younger ages of both case groups.

Charlson comorbid conditions were diagnosed more often among HA-CDI cases than among CA-CDI cases. This observation may be expected since HA-CDI cases were hospitalized during this time period and were also more likely to visit their physicians. However, it must be noted that these healthcare visits also result in greater recorded history within insurance claims which increase the potential for identifying comorbid conditions. Although a statistical difference in comorbidity was observed, a substantial proportion of both case groups did not have any comorbid or gastrointestinal conditions diagnosed or recorded on insurance claims within the year prior to diagnosis; therefore, underlying illness may not have as substantial of an impact on risk for CDI among younger and healthier populations such as this.

Any exposure to antimicrobials in the 180 days before diagnosis was more common among HA-CDI cases than among CA-CDI cases. In addition, HA-CDI cases received more different antimicrobials than CA-CDI cases. However, the prevalence of antimicrobial use among both case groups was much higher than that expected among the general population, which is consistent with the observation that these exposures contribute to the risk for CDI in both settings. Gastric acid suppressant use was elevated among both case groups in comparison to control subjects, although the prevalence of use among HA-CDI cases was two-times higher than among CA-CDI cases. The reason for this finding is less clear although it may be related to other characteristics of the HA-CDI population, such as increased likelihood for physician encounters, a history of hospitalization, or the presence of underlying comorbid conditions.

Epidemiology of Community-associated *Clostridium difficile* Infection

Prior to controlling for other risk factors and covariates; age greater than 50 years, gender, history of hospitalization, number of outpatient physician visits, antimicrobial use, gastric acid suppressant use, underlying comorbidity, and diagnosis of

gastrointestinal disease (including IBD, diverticular disease, GERD) were associated with acquiring CA-CDI. However, after adjustment for other risk factors, increased risk for CA-CDI within this population was consistently associated with antimicrobial use, age between 19 and 74 years, and diagnosis of inflammatory bowel disease. Gastric acid suppressant use was a risk factor in a number of models, although this association was not consistent. The number of outpatient physician visits in the previous year was also a predictor of CA-CDI.

Antimicrobial use accounted for the majority of risk for CA-CDI. More specifically, the results showed that use of antimicrobials, in general, increases risk while also demonstrating that persons are at-risk for CA-CDI as long as 150 days after the last receipt of an antimicrobial drug and the risk for CA-CDI increases with the receipt of each additional antimicrobial agent.

All antimicrobial agents have been implicated in acquiring CDI to some degree, although some agents have been associated with risk for CDI more often and at a greater magnitude than others. Traditionally ‘high-risk’ antimicrobials include clindamycin, cephalosporins, penicillins, and, more recently, fluoroquinolones. In this study, the antimicrobials with the strongest associations were clindamycin, fluoroquinolones, and beta-lactamase inhibitors, although risk was also observed following the use of cephalosporins, penicillins, and macrolides. It must be noted that this analysis examined any use of antimicrobial agents, but did not investigate the concurrent use of these drugs. Since it is common to treat infections with multiple antimicrobials, it may be difficult to determine independent risk for specific drugs. Thus, although the concomitant use of antimicrobials may confound the relationship between specific antimicrobials and CA-CDI, these results still demonstrate increased risk due to the use of individual antimicrobial drugs and classes.

Risk due to antimicrobial use is biologically related to the effect of these drugs on the normal bacterial colonic microflora, their activity or lack thereof against *C. difficile*,

and antimicrobial resistance in *C. difficile* strains. What is known about the biological plausibility of the relationships between specific antimicrobials or antimicrobial classes and CDI varies. About 90% of an oral clindamycin dose is absorbed within the gastrointestinal tract, which disrupts normal bacterial microflora, reduces colonization resistance, and increases the opportunity for *C. difficile* to grow. In addition, most, if not all, strains of *C. difficile* are resistant to clindamycin (99). Fluoroquinolones exhibit poor in vitro activity against *C. difficile* (114). In addition, it has been shown that the BI/NAP1 *C. difficile* strain (i.e., epidemic strain) is highly resistant to fluoroquinolones which contributes to higher incidence of infection (98). However, the incidence of CDI reported in this study suggests that this strain is not circulating widely in this population. Finally, *C. difficile* has becoming universally resistant to most cephalosporins (108). In fact, it is thought that some strains of *C. difficile* can still cause disease during cephalosporin administration (108). Beta-lactamase inhibitors and macrolides are less commonly cited in the scientific literature as risk factors for CDI than other antimicrobials. Beta-lactamase inhibitors are highly active against *C. difficile* strains; thus it would be expected that these antimicrobials would result in lesser degrees of risk or no risk (117, 118). Despite this expectation, this study identified risk associated with this antimicrobial class.

The observed associations between the use of certain antimicrobials and CA-CDI are clinically important. Clindamycin is used to treat infections caused by Gram-positive or by anaerobic bacteria, such as infections of the respiratory tract, skin and soft tissue infections, bone and joint infections, and peritonitis. In turn, fluoroquinolone antimicrobials have often been used to treat infections with Gram-negative organisms, although newer drugs in this class have expanded and improved activity against gram-positive and/or anaerobic bacteria. Thus, newer fluoroquinolones are recommended and widely-used in the treatment of infections such as community-acquired pneumonia and

acute exacerbations of chronic bronchitis (226, 241). In turn, antimicrobials within the cephalosporin class are used for a large number of indications.

Macrolides are less commonly used in hospitalized populations, but when they are used, almost all patients will receive them along with other antimicrobials. In fact, macrolides are used concurrently with cephalosporins for empirical treatment of community-acquired pneumonia in the hospital setting. Thus, in hospitalized populations, associations between macrolide use and CDI are highly confounded by the concurrent use of other antimicrobials (99). Although this may still be the case, macrolides are more likely to be used as monotherapy in the outpatient setting, thus this study implies that these antimicrobials may increase risk for CA-CDI independent of the use of other antimicrobials.

Since antimicrobials are widely prescribed in the outpatient setting and are related to acquiring CA-CDI, clinicians must consider the implications of antimicrobial prescribing in the outpatient setting. For example, a number of the antimicrobials cited as risk factors in this study are typically prescribed in the outpatient setting for the treatment of respiratory infections. However, prior research has shown that these drugs may be over-prescribed, especially in settings where it is unknown whether the etiology of infection is viral or bacterial in nature (242, 243). If inappropriate use of antimicrobials in the outpatient setting continues and leads to increased occurrence of CA-CDI, this infection will continue to become a growing public health problem, much like the emergence of antimicrobial resistance in the community setting.

The risk for CA-CDI increased among persons who were last exposed to antimicrobials up to 150 days ago. The highest risk was observed in persons who most recently received antimicrobials in the prior 1 to 30 days, followed by persons last receiving these drugs in the prior 31 to 60 days. There was a rather sharp decrease in risk related to most recent antimicrobial exposure in the prior 61 to 150 days although it was still elevated from baseline. Risk returned to baseline for those whose last antimicrobial

exposure occurred over this 150-day threshold. Even in sensitivity analysis where the diagnosis date was revised to the potential first indication of symptoms, increased risk for CA-CDI was observed among persons last receiving antimicrobials in the previous 60 days or in the previous 121 to 150 days. A few studies have assessed the at-risk period following antimicrobial use, with some studies reporting that CDI can occur directly following receipt of antimicrobial therapy and others reporting that CDI can occur weeks after discontinuation of antimicrobial therapy (19, 127, 129, 202). Delaney et al. reported that the risk due to antimicrobial use diminished significantly after 3 months but only returned to baseline after 6 months (202), although the relative risk at 3 months was still much lower than that reported in the current study. Dial et al. reported that the maximum risk for CA-CDI appeared to be in the 30 days after the start of antimicrobial prescription with a significant decrease occurring after 45 days (129).

The at-risk period for antimicrobial use reported by the current study may differ from that reported by past researchers for a number of reasons. First, different time windows for ascertainment of antimicrobial use were utilized in this study than were utilized in the study conducted by Dial et al. (180 days in this study vs. 90 days in the Dial study) (129). Second, this analysis was inclusive of the use of any antimicrobial agent, whereas Delaney et al. analyzed the at-risk period for fluoroquinolone-users only.

The total number of different antimicrobial agents utilized was also a significant contributor to the acquisition of CA-CDI, with each additional antimicrobial agent increasing the risk for CA-CDI. The most recent study to examine this association reported an odds ratio of 1.4 for each additional antimicrobial agent (95% CI: 1.1, 1.7) among a VA population (121). The current study estimated that the odds for CA-CDI related to the use of each additional antimicrobial is twice that reported in the VA study. Of note, the VA study was conducted in a much smaller population and one which primarily consisted of HA-CDI cases, thus comparisons between the results of these studies may not be appropriate.

Antimicrobial use was associated with increased risk for CA-CDI, although nearly 27% of cases did not have exposure to an antimicrobial agent in the 180 days prior to diagnosis. Previous studies have reported this observation among both CA-CDI and HA-CDI cases; however, antimicrobial non-use is seemingly more common among CA-CDI cases. In fact, studies investigating CA-CDI have reported prevalences of antimicrobial non-use ranging from 12% to 63% of CA-CDI cases (10, 11, 94, 140, 145, 195, 196)(203). The percentage of CA-CDI cases not receiving antimicrobials in this study falls within the range of values previously reported, although time windows for antimicrobial exposure ascertainment vary across studies. For example, if the time window for antimicrobial exposure ascertainment was limited to the 90 days prior to diagnosis, 38% (115 of 304) of CA-CDI cases in this study would have no exposure to an antimicrobial agent. Overall, the lack of antimicrobial exposure among a substantial proportion of CA-CDI cases supports suggestions that CDI is occurring among persons without this traditional risk factor. Furthermore, this observation reiterates that antimicrobial exposure is still a strong risk factor for CDI although it is not a necessary exposure prior to the acquisition of CDI.

Gastric acid suppressant use has been cited as a risk factor rather often in CDI research, although risk estimates have been inconsistent (130, 141, 244). In this population, the risk associated with gastric acid suppressants was inconsistent across multivariate models. Although increased risk due to gastric acid suppressant use was noted in some multivariate models, this association was not apparent in an analysis accounting for the use of specific antimicrobials and in an analysis conducted after the exclusion of cases with gastrointestinal disease and cases hospitalized in the prior 6 months. The first of these findings suggests that gastric acid suppressant use does not account for substantial risk when in the presence of antimicrobial use. Next, the prevalence of gastric acid suppressant use among CA-CDI cases following exclusions was 7% lower than among the original case group, whereas exclusion of corresponding

controls did not reduce the prevalence of use among that group. The change in prevalence of use and lack of association following these exclusions indicate that confounding by indication may account for the association observed in the main analysis.

Prior research studies have noted that gastric acid suppressant use may be the primary risk factor in persons who are not exposed to antimicrobials. In the current study, the majority of cases (84%) exposed to gastric acid suppressants were also exposed to antimicrobials. Although interaction between these two groups of medication was not present, it is likely that some or all of the risk attributed to gastric acid suppression may, in fact, be related to concurrent antimicrobial use. Finally, the interpretation of this association must take into account that a number of gastric acid suppressants are available without a prescription, which most likely resulted in an underestimation of gastric acid suppressant use. However, there is no reason to believe that this underestimation would occur more often among controls, thus this study most likely underestimates the true magnitude of this association.

The analysis of the timing of gastric acid suppressant use showed that risk was elevated following last use within the prior 30 days. However, the risk estimates and confidence intervals did not suggest that there was a distinct increase or decrease in risk for any of the time periods. This finding is consistent with patterns of use of these drugs. Whereas antimicrobials are acutely-used and have nearly immediate physiologic effects, gastric acid suppressant exposure typically occurs at relatively constant levels over long periods of time. Thus, considering our results, it is suggested that, if this association is true, gastric acid suppressants may contribute to a long-term low level of risk as opposed to the acute increase in risk observed following antimicrobial use.

A diagnosis of inflammatory bowel disease was a significant predictor for CA-CDI. In fact, having Crohn’s disease or ulcerative colitis was related to the greatest increase in risk for CA-CDI, after controlling for age, physician visits, antimicrobial use, and gastric acid suppressant use; although, it must be noted that this association is based

on relatively small numbers (i.e., 12 cases and 4 controls) and the confidence intervals for risk estimates are very wide. This finding is consistent with prior research, although the biological mechanism behind this association is not completely understood. Potential reasons for this association include differences in the gut flora of persons with IBD or medication use among persons with IBD. Prior research has shown that greater colonic involvement in IBD is related to the acquisition of CDI. Further research is needed to determine whether this association is potentially related to the extent to which IBD disrupts the mucosal barrier of the colon, the alteration of gut flora due to CDI, or other mechanisms that have yet to be determined. Crohn's disease and ulcerative colitis are chronic, immune-mediated inflammatory diseases, thus a high proportion of persons with either condition are treated with long-term immunosuppressive therapy, which may be the underlying reason for the association observed in this study. Finally, patients with IBD may have chronic diarrhea and may be more likely to visit their physicians or be hospitalized for diarrhea. Therefore, there may be a higher degree of suspicion of CDI within this patient population, resulting in higher rates of testing and higher rates of diagnoses among this group. This study attempted to control for this by including the number of physician visits in the multivariate model, although it did not completely account for the effects of IBD.

The presence of underlying comorbid conditions and their collective impact on health status was measured through the use of the Deyo-Charlson Comorbidity Index Score. Chronic comorbid conditions were relatively rare in among cases and controls. However, this low prevalence of chronic medical conditions would be expected among this study population since it consists of persons under the age of 65 years and those insured through employment and their families. The Deyo-Charlson Comorbidity Index did not reach statistical significance after adjusted for other covariates, suggesting that underlying comorbidity does not impact risk for CA-CDI directly or at the same magnitude as pharmacologic exposures. In spite of this, underlying comorbidity was

deemed necessary in multivariate models to control for health status which could not be directly measured in this study.

In this population, persons between the ages of 19 and 74 years had roughly 2-times the odds of CA-CDI in comparison to persons under the age of 18 years. This finding reiterates that increasing age is related risk for CA-CDI, although it must be noted that persons over the age of 75 years were not at increased risk for CA-CDI. Although this finding contradicts the conclusion that risk increases with age, it is, in part, related to the small number of persons over the age of 75 years in the study population.

The age distributions of cases and controls were statistically different. Controls were more likely to be under the age of 18 years than cases, while cases were slightly more likely to be over the age of 50 years than were controls. Collectively, the majority of both cases and controls were 49 years of age or younger, primarily due to the nature of this insured population (i.e., no persons on Medicare). Differences in the age distribution can be addressed by matching cases and controls. However, this study did not match cases and controls on age because risk factors for CA-CDI are not established and matching on age precludes assessing this variable in risk factor analysis.

The number of outpatient physician visits within the prior year was a significant predictor of CA-CDI. This association is not biological in nature; however, the inclusion of this variable served as a method to control for exposures which could not be measured more effectively within this data source. It is thought that greater need for physician visits serves as a measure of increased comorbidity, increased opportunity for exposure to *C. difficile* in ambulatory care settings, or increased opportunity for the receipt of prescription medications. Furthermore, a greater number of outpatient physician visits and claims for these visits among cases results in a greater recorded medical history within the Data Repository, which may increase the likelihood of a patient being tested for and diagnosed with CDI.

A number of variables were significant in univariate analyses, although they did not retain statistical significance after controlling for all other covariates. Gender was not a significant predictor of CA-CDI. Many studies have noted that females account for a higher percentage of CDI cases, although there is no obvious biologically plausible reason for gender to increase risk for CDI. Although hospitalization would presumably increase risk for CA-CDI due to increased exposure to the pathogen itself, a history of hospitalization did not contribute to risk for CA-CDI. The lack of significance of this measure in this study implies that although some CA-CDI cases may have been exposed to *C. difficile* exposure in the hospital setting, this exposure does not adequately predict later development of infection in the community setting. However, in sensitivity analysis, history of hospitalization was a significant predictor of CDI following revision of diagnosis date based on medication use or diarrheal disease. Since revised diagnosis dates resulted in exposure ascertainment for some cases in time periods prior to that used in the primary analysis, this finding either implies that less recent hospitalization may increase risk for CDI or the methods of identification of symptom onset and exposure assessment in the primary analysis prevented the ascertainment of these exposures.

This study also hypothesized that there is no biologically plausible reason that antimotility agents would be related to the development of CDI. Rather, an exploratory analysis determined that the use of antimotility drugs was most likely in response to symptoms of disease prior to diagnosis and was not a true risk factor for CA-CDI. Despite this, there are a number of reasons for further research focused on determining the prevalence of antimotility use among persons with CDI. First, the use of these drugs simply masks symptoms of infection rather than providing a treatment of the infection itself, thus propagating the spread of infection by persons who are unaware that they have *C. difficile*. Second, by masking symptoms, persons may be prolonging the course of CDI, which may lead to adverse outcomes.

The importance of these findings is reflected in the direction they provide for clinical practice. First, antimicrobial use was strongly associated with increased risk for CA-CDI, thus antimicrobial prescribing in the outpatient setting must be accompanied by understanding of the risks associated with these medications. In turn, underlying comorbid conditions and age may not impact risk for CA-CDI to the extent reported in prior studies of HA-CDI. In general, these findings support clinician awareness for CDI as a potential diagnosis among all patients presenting with diarrhea. Furthermore, this knowledge has the potential to result in earlier and increased identification of CA-CDI, which reduces delays in treatment and which may, ultimately, improve outcomes among these cases.

Adverse Outcomes of Community-associated *C. difficile* Infection

None of the CA-CDI cases in this study underwent a surgical procedure related to CDI. This finding may be expected since surgical intervention is typically expected more often among older and sicker patients. Furthermore, prior research has found that the rate of surgical intervention rates tend to increase along with increases in incidence (176). Since CA-CDI was relatively rare in this population, one would expect that surgical intervention would also be rare. It must be acknowledged that this result may be due to inadequate methods of ascertainment, although the methods of this study are the most valid and appropriate for this data source. First, the ICD-9 codes utilized in this study were validated through prior research and are consistent with prior administrative database research. In addition, inadequate ascertainment of surgical outcomes is unlikely since these procedures would not be easily omitted or miscoded within insurance claims.

Subsequent hospitalization was much more common among CA-CDI cases, occurring in roughly one out of every four within this case group. These admissions occurred most frequently on the date of *C. difficile* diagnosis, and were 4 days in length

on average. The short length of stay is consistent with a low severity of infection, although a 52-day admission was also observed. Hospitalization has a number of implications for these cases, as well as for healthcare facilities and insurers. First, CA-CDI cases who undergo hospitalization serve as a means of transferring *C. difficile* from the community into the healthcare facility. Second, if CA-CDI can be prevented through clinical interventions, these cases represent an unnecessary burden on the healthcare facilities which provide care and on the insurers who pay for that care.

The use of metronidazole and oral vancomycin by CA-CDI cases after completion of initial therapy for CDI was assessed as a measure of recurrence of infection since this outcome could not be directly measured. Although it is likely that this measure does not completely ascertain recurrent cases, it is the only available method to approximate this adverse outcome within this data source. A small percentage of these cases (7%) received additional treatment, suggesting that, if medication use is an appropriate measure, prolonged need for treatment and recurrence of infection were relatively rare among CA-CDI cases. This may be due to less severe infection among these cases or low failure rates for initial therapies.

Very few adverse outcomes were observed and cases with and without adverse outcomes were similar in regard to demographic and clinical characteristics. It is unclear whether adverse outcomes are indeed less common among CA-CDI cases. In addition, when adverse outcomes occur, this analysis was unable to determine what characteristics may predispose CA-CDI cases to adverse outcomes.

Antimotility agents were not widely utilized by CA-CDI cases within the time period 180 days following diagnosis. The use of these drugs is important to this research study because clinical recommendations do not currently support the use of antimotility or antidiarrheal drugs following diagnosis of CDI or other infections related to enteric pathogens. It is thought that antimotility agents prevent clearance of these pathogens from the body, thus allowing disease to worsen. This phenomenon was not confirmed in

this research since this population experienced a low number of adverse outcomes and there was little documented use of antimotility agents. Overall, antimotility agents were not utilized commonly among this population, although the availability of these drugs without the need for a prescription leads me to think that the use of antimotility agents is more common than what was observed from prescription drug claims.

Strengths and Potential Limitations of the Study Design

This study addressed a number of gaps in prior knowledge and shortcomings of previous research regarding the epidemiology of CDI and its emergence in the community setting. Also, since this is the first study to examine CA-CDI and HA-CDI in the same population, we were able to distinguish differences in the characteristics of persons with infection in the community setting and those with infection acquired in the hospital setting.

Data Source

The infrastructure to conduct surveillance for CDI does not exist, thus there are few data sources to conduct research and to determine the burden of this infection. This Data Repository provided a unique opportunity to conduct CDI research within a stable population for which de-identified demographic and clinical data are available. This large study population was necessary since *C. difficile* is a relatively rare infection, especially in the community setting. Additionally, the Data Repository provided diagnoses and drug exposure data coded in a manner that allowed us to identify persons with CDI, control subjects, their exposures more easily than a prospective study design and at a lower cost.

Individuals in this population obtain health insurance through an employer-based plan, thus they are of working age or are the member of a family in which someone is employed. Furthermore, the Data Repository does not include persons who have insurance coverage through Medicare or Medicaid programs. This age distribution may be construed as a weakness and a limit to generalizability. However, this population

actually provided the opportunity to identify CDI in younger persons with less exposure to healthcare--a group in which it was hypothesized that community-associated *C. difficile* was occurring more frequently. This is in contrast to prior research primarily focused on older persons and hospitalized patients. Overall, the demographic characteristics of the study population mean that the research results are best applied to populations of similar demographic, health status, and health insurance coverage. However, the findings also confirm that CA-CDI is occurring in populations traditionally considered low-risk and that persons with CA-CDI are younger and generally healthier persons than HA-CDI, both of which are meaningful contributions to the scientific literature.

Outcome and Exposure Assessment

Case Ascertainment and Classification

Cases were identified through the ICD-9 code, 008.45. This ICD-9 code has been widely-used to identify cases of CDI within administrative claims data. The use of the code could not be validated in the Wellmark population since fecal samples were not available to confirm CDI through microbiological testing and medical record review was not available for identification of symptoms. Although validation would be optimal, widespread collection of fecal samples and medical record review for surveillance of this infection are not feasible in the Wellmark population. In lieu of this fact, the use of this ICD-9 code was the most appropriate, available method for identification of CDI cases in this study since prior research has shown that the ICD-9 code for *C. difficile* infection (008.45) closely approximates true CDI in hospitalized populations.

Despite the appropriateness of using ICD-9 code 008.45 to identify *C. difficile*, there is the possibility that *C. difficile* was suspected or even diagnosed earlier but was not recorded on insurance claims. To explore this possibility, analysis was conducted to identify *C. difficile* testing prior to a recorded diagnosis. Roughly 24% of CA-CDI cases

were tested for *C. difficile* prior to diagnosis, at an average of one month before diagnosis based on insurance claims. In turn, 8.5% of HA-CDI cases were tested, on average, 28 days in advance of the diagnosis date used in this study. These findings suggest that *C. difficile* symptoms were present earlier than could be identified by this study, although this data source did not provide test results to confirm or disprove the presence of CDI. If cases were positive for *C. difficile* prior to appearance of the ICD-9 code 008.45, we may have misclassified persons although sensitivity analysis assessing other markers of symptom development and delayed diagnosis did not show an excess of misclassified cases.

In addition, this study was only able to identify *C. difficile* cases among persons who have insurance claims within the Data Repository; therefore, the study population is limited to persons seeking medical care. Although there may have been persons with CDI who did not seek medical intervention, the debilitating and prolonged nature of this infection when not treated would conceivably result in a low number of cases not seeking medical care.

Cases were classified as community-associated, indeterminate, or hospital-acquired. These definitions were based on the location at which diagnosis occurred, the history of hospitalization, and the dates available on insurance claims at which these events occurred. Although this information can be identified from insurance claims, the accuracy of this study may have benefited from more detailed medical information such as that available on medical records. For instance, studies using medical record review would typically define diagnosis date based on the timing of the development of *C. difficile* symptoms whereas this study defined date of diagnosis for CDI based on the first appearance of the ICD-9 code 008.45 on insurance claims. Exploratory analysis found that prescription drugs for treatment of infection and alleviation of symptoms, and diarrheal disease occurred prior to diagnosis was identified. All of these occurrences on insurance claims may signify development of symptoms predating diagnosis. There is

also the potential for misclassification of cases because of discrepancy between diagnosis date based on ICD-9 coding and onset of symptoms, although sensitivity analysis was conducted to further examine small variations in timing of CDI development through the assessment of prescription drug claims and diagnosis of diarrheal disease. This analysis showed that the majority of cases would be consistently classified as CA-CDI following redefinition of diagnosis date, and exposure assessment would not vary significantly.

Cases who acquired *C. difficile* symptoms in the outpatient setting but who were diagnosed at the time of hospitalization are classified as community-associated rather than hospital-acquired. These cases were identified as a primary diagnosis of *C. difficile* in the inpatient setting in a person who did not have a history of hospitalization during the 12 weeks prior to this diagnosis. Since this case definition may be a liberal approach to classification with the potential for misclassification bias, a sensitivity analysis was conducted to determine whether a conservative definition of CA-CDI resulted in different identified risk factors and odds ratio estimates. Results of this analysis did not reveal differences in relative risk estimates after the exclusion of the potentially misclassified cases; therefore, measurement error in case ascertainment did not impact study results or the interpretation of these results. An additional sensitivity analysis excluded cases with gastrointestinal conditions and cases with a history of hospitalization in the prior 6 months, since these persons may undergo differential surveillance for CDI and may be different in regard to medication use and exposure to *C. difficile* than CA-CDI cases identified by the main study case definition. Relative risk estimates obtained from this analysis did not vary from those obtained from analysis of the original study population, although gastric acid suppressant use was not a significant predictor of CA-CDI following exclusions. Although this may suggest confounding by indication as an alternative explanation for prior findings, underascertainment of use is also a potential bias that could have an opposing influence on the estimate of effects. This topic requires

further investigation in a population with coverage of over-the-counter gastric acid suppressant use.

Exposure Assessment

Identification and Measurement of Medication Use

The measurement of medication use was ascertained from prescription drug insurance claims. Prescription drug insurance claims are only included in the Data Repository if they are submitted and paid, thus this study can only identify medication use for which a patient filled a prescription. Furthermore, these claims allow us to identify prescription drugs received by a patient, but not available are data on patient adherence to prescribed medication. This creates the potential for measurement error in risk factor assessment since persons may be prescribed and fill a drug that they may not use. If this is indeed occurring, persons are defined as users of a medication based on prescription claims although they are not actually ingesting the drug, resulting in overestimation of actual use. If misclassification of medication exposure exists, it would presumably not vary based on case or control status and would result in an underestimation of the effects of medication use. In addition, this study did not distinguish exposure to antimicrobials administered during physician visits or at outpatient clinics (e.g.., during ambulatory surgery) from exposure occurring in the outpatient setting. It is possible that antimicrobials administered in physician offices or ambulatory clinics could account for some of the risk associated with specific antimicrobials, although this use most likely accounted for a small amount of overall exposure.

Inpatient medication use is not available in Wellmark prescription insurance claims; therefore, medication use for persons who were hospitalized may have been underestimated. This was more likely to occur for HA-CDI cases due to the increased likelihood of hospitalization as opposed to CA-CDI cases; therefore, the differences

between the medication use of these two case groups may have also been underestimated. In contrast, it is unlikely that a lack of inpatient prescription drugs claims would impact the results of our nested case-control study since hospitalization within the 180 days prior to diagnosis or index date for which medication use was collected was rare among CA-CDI cases and controls.

Medication exposure data is based on prescription drug claims, which did not allow us to measure the use of over-the-counter medications. Although antimicrobial use requires a prescription, many gastric acid suppressants do not. Therefore, gastric acid suppressant use is probably underestimated, although this misclassification of this use would presumably result in an underestimation of risk. It must be noted that Wellmark did provide prescription drug coverage for over-the-counter omeprazole (Prilosec) from September 2006 through the end of the study time period, although it is unclear whether this practice resulted in increased ascertainment of exposure during that time period. In addition, all antimotility agents included in this study are available over-the-counter. Since these drugs are available without a prescription and since patients are likely to self-treat diarrhea with antimotility drugs, this study may have greatly underestimated their use among CA-CDI cases.

During the study time period, generic drug programs were introduced and became more common. These programs, which are typically offered at large pharmacy chains, provide generic versions of brand-name prescription medications to patients for a low cost. This data source may not capture the use of medication obtained through generic drug programs. However, it is thought that pharmacists tend to access customer's insurance info when they fill these prescriptions regardless of whether or not they are filled through a generic drug program. Since antimicrobials require a prescription, the claims for these medications are still likely to be entered into the prescription drug claims system.

Identification and Measurement of Comorbidity

Comorbid conditions were identified from inpatient and outpatient insurance claims using ICD-9 codes that were validated in prior studies. The methods utilized to identify and statistically program the Deyo-Charlson comorbid conditions and to calculate the associated index were consistent with methods used in other studies. These methods were also applied for the identification of gastrointestinal conditions.

The Deyo-Charlson Comorbidity Index was used to measure health status in lieu of modeling individual comorbid conditions. Indices are widely used in studies with small sample sizes to account for the concern for overfitting a model if a large number of comorbid conditions are included. The sample size of this study suggested that an index would be appropriate. However, gastrointestinal conditions were individually modeled since they may be related to CDI independent of underlying comorbidity. Comorbidity indices were first designed to predict outcomes such as one-year mortality and length of stay and have primarily been validated in the chronic disease research literature, thus very little is known about their predictive value in infectious disease research. A validated method for statistical control of comorbidity does not exist for infectious disease research, although the Deyo-Charlson Comorbidity Index has been utilized in a number of studies of antibiotic-associated infection and other nosocomial infections (233). Additionally, the use of the Klabunde modification to identify Charlson comorbid conditions was appropriate and necessary for this study data. Cases in this study predominantly received medical care in the outpatient setting, so the inclusion of outpatient physician claims greatly increased our ability to identify comorbid conditions.

The validity of the identification of comorbid conditions may also be affected by the inclusion of only five diagnosis or procedure codes on insurance claims included in the Data Repository. It has been shown that inaccuracies in coding can occur when diagnoses are omitted because the data fields for the related codes are exhausted by more important diagnoses. Since administrative claims data originate for billing rather than

research purposes, omitted diagnoses may tend to be those which result in lower charges or less healthcare. In fact, prior studies have shown that the sensitivity to identify specific diagnoses in administrative databases with five diagnosis fields is reduced by an average of 13 percent compared to records with 25 fields (245).

Future Research Directions

This study serves as one of the first to thoroughly examine the incidence of CA-CDI and to explain the risk factors for and adverse outcomes of CA-CDI. There are limitations to this research; thus, there is opportunity to expand these research aims into different populations. This study could not examine trends in the incidence of CDI due to the short period of time over which the study was conducted. The expansion of this research into populations for which data are available for a longer period of time would allow for analysis of trends in incidence. In turn, if incidence of CA-CDI is increasing over time, further investigation into what is driving these increases would be warranted. For example, in hospitalized populations, increases in incidence have been attributed to the introduction of a highly-virulent strain and changes in antimicrobial prescribing practices. Stable incidence of CA-CDI may suggest that these factors are not driving the occurrence of this infection in this population, whereas increases in incidence may indicate a similar phenomenon in the community setting. Furthermore, since the generalizability of this study is limited by the population used, further research should focus on extending this line of research into larger populations which may be more diverse and inclusive of persons from a larger age range. In addition, the use of a data source which can provide detailed clinical information and microbiological results would increase the accuracy of case ascertainment and classification. The quality and accuracy of exposure measurement would also benefit from records of inpatient medication use and from the use of a data source inclusive of over-the-counter medication use.

There is a growing need for the development and implementation of a national CDI surveillance system, in both the hospital and community settings. However, barriers to a national surveillance system include the lack of validated and easily-implemented methods to identify cases of CDI, as well as the lack of methods to determine when and where CDI develops. Although the ICD-9 code for CDI (008.45) represents the most-researched, most cost-effective, and timely method to identify cases, there is value in further validation of the code's use in identifying cases, especially in the community setting. Further validation of the use of ICD-9 codes to identify CDI will become even more pertinent, especially for healthcare facilities, if and when hospital-acquired infection is categorized as a non-reimbursable diagnosis by the Center for Medicare and Medicaid Services. In addition, for the purposes of properly classifying cases and for risk factor assessment utilizing administrative data, future research should focus on validating case ascertainment methods which can more definitively determine the date of onset of CDI symptoms and which can differentiate between symptom onset and clinical diagnosis. Currently, diagnosis codes are assigned upon discharge from a hospital and do not provide detailed information regarding symptom onset in relation to actual diagnosis. In this study, it was noted that cases received medications related to the treatment or alleviation of the symptoms of CDI prior to diagnosis, thus suggesting that the development of CDI symptoms may have occurred earlier than could be determined from insurance claims. Thus, future research would benefit from the development of methods to identify symptom onset.

The association between gastrointestinal disease, especially IBD, and CA-CDI was consistently identified in this study, although it is possible that persons with these conditions may be innately different than the general population in regard to risk for CDI. This possibility was partially verified through sensitivity analysis, although future research within a population of persons with gastrointestinal disease is needed to more fully examine the true nature of CDI among these persons. In addition, future research is

needed to determine if differential surveillance is occurring in this population due to the similarities between the signs and symptoms of gastrointestinal disease and CDI.

The spread of *C. difficile* in the hospital and nursing home settings is well-documented, whereas little is known about the routes of transmission in the community setting. This study was able to determine risk factors for CA-CDI, although the source of this pathogen in the community setting is still unknown. In addition to the development of methods to prevent acquisition of *C. difficile* in the community, additional knowledge would help to determine whether these infections are related to spread of *C. difficile* from the hospital or nursing home setting to the community setting, or if colonization among persons in the community is contributing to the burden within healthcare facilities. In addition, future research efforts should focus on increasing the available knowledge about the natural history of *C. difficile* infection. For example, little is known about the incubation period for *C. difficile* prior to disease development. In addition, in many cases, biological mechanisms by which risk factors cause disease have been hypothesized but not proven. Increased information in these areas have the potential to both solidify the conclusions of prior research and provide direction for future research and the identification of risk factors for CDI which are currently unknown.

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