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Quantitative Study of Clostridium difficile Incidence Related to Influenza and Antimicrobial Use

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Abstract

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by

Eileen M. Yaeger

MPH, Northern Illinois University, 1997

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health Epidemiology

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Abstract

In the United States, influenza causes approximately 36,000 deaths and over 200,000

hospitalizations each year with elderly most often affected. *Clostridium difficile* infection

(CDI) is another major health care challenge and pressing public health issue associated

with 14,000 deaths and over 335,000 hospitalizations annually. The use of antibiotics has

been implicated in the development of CDI. This study's purpose was to test the

relationship of seasonal influenza incidence and antiviral/antibiotic use in CDI

development among hospitalized patients. Grounded in the epidemiologic wheel model

of man-environment interactions, this retrospective observational study described and

analyzed data from a proprietary, laboratory, and pharmacy-based system from a cohort

of hospitals. The association between 147 patients with a diagnosis and/or positive test

for influenza, the independent variables of delivery of antivirals/antibiotics ($n = 130$)

during the patient's hospitalization, and the dependent variable of positive test or

diagnosis of CDI ($n = 17$) was tested using multiple logistic regressions. The study results

did not prove to be significant for the 3 research questions, suggesting no impact of

antiviral use ($R^2 = .05$, $p = .336$), antibiotic use ($R^2 = .05$, $p = .290$), or antiviral and/or

antibiotic use ($R^2 = .04$, $p = .382$) on development of CDI within 60 days of discharge.

However, findings indicated that recommended antiviral medication was inconsistently

administered to influenza positive patients and that inappropriate prescribing patterns for

antimicrobial agents coincided with seasonal influenza. Implications for positive social

change include confirming the importance of antibiotic stewardship as an essential aspect

of quality healthcare.

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Dedication

This is dedicated to my family; my hubby Bill and my son Sabastian, my Mom, and especially my Dad who advised me after completing my Masters degree…to maybe just stop there. My parents have always been my biggest fans by supporting and cheering me on during every degree I obtained. From them I inherited the strength of perseverance and the belief you can do anything you dream of and put your mind to. My hubby and son have shown such patience, and I love them both so much for this gift.

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Chapter 1: Introduction to the Study

Background

The word *influenza* is derived from the Latin "influentia," meaning influence of the stars. This star influence was thought to be the cause of influenza epidemics by ancient populations (Nelson & Williams, 2007). The *Clostridium difficile* organism is difficult to isolate in culture, requiring anaerobic conditions and special culture media, leading to the name *Clostridium difficile* (Isada, Kasten, Goldman, & Aberg, 2003). Individually, the prevalence of influenza and *Clostridium difficile* represent public health issues. Therefore, a study opportunity exists to gather insight and determine the details of the type of relationship between these two organisms.

In Chapter 1, I provide background information and a platform of clinical descriptive facts about influenza and *Clostridium difficile*. For the purpose of this study, I provide evidence of the influenza virus complex structure and epidemiology, the financial, morbidity, and mortality burden this organism has on society, and the impact the influenza vaccine plays in prevention. Additionally, *Clostridium difficile* microbiology, epidemiology, statistics, burden, and role of antimicrobial stewardship will be discussed.

Influenza Microbiology and Clinical Description

Influenza is a highly contagious illness caused by the orthomyxoviruses. The influenza virus is an enveloped, eight-segmented, single-stranded, helical shaped ribonucleic acid (RNA) virus from the orthomyxovirus family (Orthomyxovirus, 2012). This virus is classified into three groups: A, B, and C, which are based on antigenic

differences of internal proteins (Isada et al., 2003). Influenza type A is the most common form of influenza and is found to attack in epidemic proportions in humans and other animals. Type B is not as common as A and generally causes outbreaks every 2 to 4 years. Type C is the least common, causing milder forms of sporadic infection. All three groups of influenza viruses frequently mutate due to the small amount of RNA genetic material within a virus (Influenza, 2003).

Orthomyxoviruses cause illness when they gain entry into host cells and replicate within them (Influenza, 2003). The new viruses explode from the host cell and infect other cells. Orthomyxoviruses are sphere-shaped viruses that contain RNA. The virus's RNA is used like a blue-print plan for replication within host cells. The outer envelope of an orthomyxovirus is studded with protein spikes that aid the virus to invade host cells (Influenza, 2003). There are two different types of spikes on the virus's outer envelope; one type is composed of hemagglutinin (H) protein (Influenza, 2003). The H protein fuses with the host cell membrane and allows the virus particle to enter the cell. The second type of spike is made of the neuraminidase (N) protein (Influenza, 2003). The N protein helps the newly formed virus particles to bud out from the host cell membrane (Influenza, 2003).

In the envelope transmembrane protein spike H, there are three types, and N has two types. This ability to mutate allows the virus to cause frequent outbreaks. The mutations occur from the gradual and continuous antigenic changes in the H and N proteins. Subtle changes, typically in the H protein, are termed "antigenic drift," responsible for most seasonal influenza strain changes (Nelson & Williams, 2007).

Sudden and significant changes in the H and N proteins are termed "antigenic shift" and are responsible for influenza pandemics (Nelson & Williams, 2007). Strains of influenza are labeled according to a standard naming convention of the type of internal protein: A, B, or C; the location where the strain was first identified; strain number from isolating laboratory; year of isolation; and the virus subtype or H/N type (Nelson & Williams, 2007). Some examples include A/California/7/2009/H1N1 and A/Fujian/411/2002/H3N2 (Nelson & Williams, 2007).

Influenza Epidemiology

Influenza is a highly infectious viral illness and the cause of worldwide respiratory disease. It is spread person to person by inhalation of aerosolized droplets that contain the virus and exposure to contaminated fomites (Heymann, 2008). Recurrent episodes of influenza happen every 1 to 3 years due to "antigenic drift" and have been observed for over 400 years (Isada et al., 2003). Worldwide pandemics caused by antigenic shift occur every 10 to 20 years and result in high mortality rates (Isada et al., 2003). The epidemic or pandemic population response varies in the size and impact due to the degree of antigenic variation, virulence of the new virus, and the level of protective immunity of the affected population (Nelson & Williams, 2007). The Centers for Disease Control and Prevention (CDC) reports, in North America seasonal influenza epidemics usually occur between November and March each year with peak months typically being January and February (CDC, 2009). These epidemics are characterized by high attack rates of 10 to 20% of the population (Nelson & Williams, 2007). The results are absenteeism among schools and work place, increased visits to healthcare providers,

increased pneumonia, influenza related hospital admissions, and death from influenza and influenza complications. Common complications from the flu can include coinfections with other viral or bacterial organisms, primary viral pneumonia, exacerbation of underlying medical conditions such as pulmonary and cardiac diseases, secondary bacterial pneumonia, sinusitis, and otitis media (CDC, 2011). Viral spread during North American winter months is a result of the influenza virus's increased survival in lower temperatures and humid environments. Additionally, indoor crowding caused by weather may lead to viral spread (Nelson & Williams, 2007).

Influenza Statistics and Burden

Each year, influenza causes approximately 36,000 deaths in the United States and over 200,000 hospitalizations (CDC, 2007b). Rates of infection are higher in infants and children than adults, which is often attributed to children being immunologically naïve to the virus (CDC, 2009). The rates of hospitalization are highest among infants and elderly (CDC, 2009). The economic impact of the flu is greater than $80 billion annually in the form of hospital costs, outpatient visits, loss of life, and missed days of work (Klepser & Hagerman, 2011). Data released from the CDC indicated that influenza vaccination coverage remains low in adults and children (CDC, 2009). During the 2005 to 2006 flu season, one in five children ages 6 to 23 months were fully vaccinated, and many other children who needed to receive the two dose regimen only received one dose (CDC, 2007). Throughout the United States, no state had more than 40% of children fully vaccinated and significantly fell below the 60% target for high risk people ages 18 to 64 years (CDC, 2007). In age categories for adults in the 2005 to 2006 season, vaccination

coverage was 30.5% for 18 to 49 year olds in high risk categories, 18.3% in nonhigh risk

of this same age group, 36.6% in adults 50 to 64 years old, and 69.3% in adults who were

65 and older (CDC, 2007c). However, Healthy People 2020 objectives outline to increase

the proportion of children and adults who are vaccinated annually against seasonal

influenza, thereby improving vaccination for all ages (U.S. Department of Health and

Family Services, 2012).

Influenza Vaccine Use

The fall and winter months in the United States are when the influenza virus

causes disease, illness, and death. Each flu season, there are hundreds of thousands of

hospitalizations and deaths due to the virus. Many hospitalizations and death could be

avoided because the use of the influenza vaccination can prevent the infection and its

health complications (CDC, 2010). The vaccine is targeted and recommended for use in

individuals at risk of influenza complications and to reduce the transmission of flu to

others. In particular, the attack rate of the seasonal illness from the flu is of concern

among individuals 65 years and older, in which the death rate from influenza is greatest

(CDC, 2009). The CDC's Advisory Committee on Immunization Practice (ACIP)

provides the annual recommendations for flu prevention strategy efforts. The ACIP

examines vaccine effectiveness, coverage, supply, safety, and efficacy. The influenza

vaccine must be given annually because the circulating strains change slightly each year,

and the vaccine must be formulated to match what the predicted strains will be. Despite

efforts to improve the number of people who receive a yearly influenza vaccine, vaccine

receipt coverage still remains low. Furthermore, the antigenic diversity of the influenza

virus complicates efforts to aggressively vaccinate the public, as was seen in the recent years from the H1N1 circulating strain (Klepser & Hagerman, 2011).

Clostridium difficile Microbiology and Clinical Description

Clostridium difficile, another variable that was considered in this study, is a gram-positive, spore forming, anaerobic rod (Isada et al., 2003). It is the most frequent cause of colitis associated with antibiotic use (Nelson & Williams, 2007). This bacterium can live in the gut of infant and adult carriers causing no harm, but it can lead to severe diarrheal disease in susceptible people. *Clostridium difficile* infection (CDI) commonly causes diarrhea but has been linked to the more severe disease of pseudomembraneous colitis and toxic megacolon (Drekonja et al., 2011). *Clostridium difficile* can produce two toxins: A and B; these "exotoxins" cause damage to the colon and result in diarrheal illness (Isada et al., 2003). Certain environmental conditions are required for expression of the toxigenic process within the intestinal lumen. The more common toxin A is described by Isada et al. as an "enterotoxin" and B as a "cytopathic" toxin. Most strains causing diarrheal illness produce both A and B toxin; however, there are cases where only one of the two toxins is expressed. There are a number of nontoxigenic *Clostridium difficile* strains that lack the gene for toxin A and B and do not cause diarrheal illness. *Clostridium difficile* toxin production is of clinical importance and relevance to detect by laboratory methods because the toxins cause inflammation and damage of the intestinal wall in addition to secretion of fluid into the intestinal lumen that can lead to necrosis of the colonic mucosa (Farrow et al., 2013; Isada et al., 2003). Garey (2011) described the hyper-virulent BI/NAP1/027 strain of *Clostridium difficile* as being associated with an

increased toxin production and a higher rate of sporulation, resulting in increased

morbidity and mortality in the United States. Therefore, *Clostridium difficile* can produce

no toxins, low levels of toxins, or be highly toxigenic.

The *Clostridium difficile* organism can be found in two forms: a vegetative form

and spore form. The vegetative form is sensitive to oxygen and is easily killed in the

environment (Isada et al., 2003). The spore form is hardy and heat stable, allowing it to

survive in even the most inhospitable conditions of gastric acids and endure many

commercial disinfectants (Isada et al., 2003).

Clostridium difficile Epidemiology

Risk factors for acquisition of CDI are exposure to antibiotics, hospitalization,

and advanced age with a decreased immune response (APIC, 2008). CDI is most

commonly associated with exposure to antibiotics and the acquisition of *Clostridium*

difficile from fecal-oral transmission. Some people will develop CDI and its associated

clinical diseases while others will only be asymptomatic and colonized. According to

APIC, the "pathogenesis" of *Clostridium difficile* acquisition involves oral ingestion of

spores that resist the acidity of the stomach and germinate into vegetative bacteria in the

small intestines. Exposure to antibiotics alters the normal intestinal flora and provides the

environmental conditions for *Clostridium difficile* to multiply, thrive, and potentially

produce toxins that cause mucosal damage. Garey (2011) described nearly all antibiotics

have been implicated as the causative agent in the development of CDI. In particular,

broad spectrum antibiotics, antibiotics that eliminate anaerobic flora, and certain

antibiotic classes such as cephalosporins, clindamycin, and flouroquinolones are most

highly implicated (APIC, 2008; Gerding, 2004). Antibiotics are the cause of the suppression of normal intestinal flora and this permits the overgrowth of *Clostridium difficile,* which can result in high levels of toxins to be produced (Isada, 2003). In contrast, Isada described when the selective pressure of antibiotics is not present, the acute infection with *Clostridium difficile* is self-limited and the person is asymptomatic afterwards.

"Colonization" with *Clostridium difficile* can be found in people of all ages and not be associated with clinical disease. The organism can be cultured from healthy adult stool 3% to 5%, and among hospitalized adults, 10% to 30% are colonized with this organism (Isada, 2003). Colonization can occur with toxin-producing strains and interpretation of stool tests for *Clostridium difficile* should be correlated with diarrhea and symptoms (APIC, 2008).

Clostridium difficile Statistics and Burden

The CDC (2012) reported between the years 2000 to 2009 an increase in the number of patients with CDI in any discharge diagnosis doubling from 139,000 to 336,600 and the number with a primary diagnosis of CDI tripling from 33,000 to 111,000. Additionally, the CDC described *Clostridium difficile* was associated with 14,000 deaths, with more than 90% in $\geq$ 65 years of age, and over 335,000 annual hospitalizations, Garey (2011) reported the cost of CDI ranges from $433 to $797 million annually. The CDC reported excess healthcare costs of hospital-onset CDI as $5,042 to $7,179 per case with a national annual estimate exceeding $1 billion dollars (CDC, 2012b). Tabak, Zilberberg, Johannes, Sun, and McDonald (2013) mirrored the

attributable cost of hospital-onset CDI at $6,117 per case. Additionally, Tabak et al. discovered patients with hospital-onset CDI lengths of stay were 2.3 days longer and experienced a statistically significant higher mortality rate of 4.5% for in-hospital attributable mortality effect compared to endemic setting attributable mortality of 1 to 2%. The CDC has reported *Clostridium difficile* is no longer just a hospital issue, with almost 94% of CDI occurring in people who recently received medical care in or out of the hospital setting. Furthermore, 75% of infections have an onset in nursing home settings or in people who were recently cared for in an outpatient medical setting (CDC, 2012b).

One aspect of quality health care that can prevent the occurrence of CDI is antimicrobial stewardship (CDC, 2012b). The CDC reports the risk of CDI development increases by seven to 10 fold while a patient is taking antibiotics, and this risk persists for 1 month after discontinuation of antibiotics. Additionally, this risk is three fold for the next 2 months post antibiotics use (CDC, 2012b).

Influenza continues to be unpredictable as new and emerging strains occur, making the reality that influenza related illness and hospitalizations will continue despite best efforts to immunize the population. The rates of CDI continue to increase nationally. Of concern is the impact this disease has on the aging population where the risk factors for acquisition are more pronounced: exposure to antibiotics, hospitalization, and advanced age with a decreased immune response. In summary, both influenza and *Clostridium difficile* represent a significant impact to patients and heath care providers in

terms of hospitalization, morbidity, mortality, and economics related to management of these diseases.

Problem Statement

Annually influenza causes thousands of deaths in the United States and hundreds of thousands hospitalizations (CDC, 2010). CDI has emerged as the most common cause of antibiotic-associated diarrhea and a highly problematic healthcare-associated infection (Garey, 2011). Nearly all antibiotics have been implicated in CDI, with certain antimicrobial classes causing higher risk for disease (APIC, 2008). Use of antibiotic agents can vary by season (Gelband, 2009; Linder, Bates, & Platt, 2005). Seasonal antibiotic use may indicate inappropriate prescribing patterns (Polgreen, Yang, Bohnett, & Cavanaugh, 2010). CDI does follow a seasonal pattern that peaks in mid-March in the United States (Jagai et al., 2007). Incidence of CDI may be related to the incidence of seasonal influenza; however, most of the literature reviewed revealed access limitations to clinical, microbiologic, and dispensed antibiotic data in the same databases, and no readily available national data that aggregate the monthly receipt of antibiotic agents in hospitalized populations (Polgreen et al., 2010). This limitation has made it difficult to draw conclusions about the role antibiotics may have in the development of CDI during flu seasons. Therefore, this study addressed a problem of using a database that includes microbiologic, antibiotic, and antiviral agent use in hospitalized patients. Use of a database rich in these elements in this study helped improve understanding of the development of CDI during influenza seasons. The potential for social change exists, providing additional insight into linking seasonal fluctuations in CDI and influenza

activity, and further implying reasons to prevent influenza through immunization and focus appropriate antibiotic/antiviral use during the influenza season.

Purpose of the Study

The purpose of this quantitative study was to examine the temporal progression of CDI incidence and the possible influence that seasonal variation of influenza and antibiotic and antiviral use has on the incidence of CDI. An enhanced understanding was determined about the relationship of CDI and seasonal influenza and the role/influence of antibiotic use and selection. The study's significance further contributed to the growing body of knowledge of the implications that antibiotic use has on CDI. In this study, I determined if the overuse and/or inappropriate use of antibiotics has an impact on the development of CDI during seasonal disease outbreaks of influenza.

Research Questions and Hypotheses

This study was guided by the following research questions:

Research Question 1: Is there a relationship between use of prescription antivirals and CDI within 60 days of discharge in patients who have been hospitalized for influenza?

$H_0 1$: There is not a statistically significant association between use of prescription antivirals and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

$H_a 1$*:* There is a statistically significant association between use of prescription antivirals and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

Research Question 2: Is there a relationship between use of prescription antibiotics and CDI within 60 days of discharge in patients who have been hospitalized for influenza?

H_02: There is not a statistically significant association between use of prescription antibiotics and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

H_a2: There is a statistically significant association between use of prescription antibiotics and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

Research Question 3: Does the use of prescription antivirals and/or prescription antibiotics predict CDI within 60 days of discharge in patients who have been hospitalized for influenza?

H_03: The use of prescription antivirals and/or prescription antibiotics does not predict CDI within 60 days of discharge in patients who have been hospitalized for influenza.

H_a3: The use of prescription antivirals and/or prescription antibiotics does predict CDI within 60 days of discharge in patients who have been hospitalized for influenza.

Theoretical Foundation

The epidemiologic wheel is a model of disease causation that brings together the outer wheel segments of physical, social, and biological environment factors with two inner circles, with genetics nested in the host circle (Davis, 2000). The wheel of causation illustrates there are multiple etiologic factors that interact to cause human infectious

disease (Peterson, 1995). This model was used as the theoretical foundation for this study and is discussed further in Chapter 2.

Nature of the Study

A retrospective, observational design was used to describe and analyze the relationship between the incidence of CDI and the variables of antiviral/antibiotics among an influenza positive population. The data were abstracted using a convenience sample from a propietary database. This database receives hospital data feeds of admission, transfer, and discharge (ADT), laboratory microbiologic, and pharmacy data. The collected patient data were queried and abstracted for study variables; the independent variables' delivery of antiviral/antibiotics as well as the dependent variable of positive test or diagnosis of CDI among patients with a diagnosis and/or positive test for influenza was analyzed using multiple logistic regression.

Definition of Terms

The following section provides definitions of terms and phrases that were used to describe concepts and variables important to this study.

Antibiotic: "A drug that is used to kill harmful bacteria and cure infections" (Antibiotic, 2013).

Antigenic drift: "The 'evolutionary' changes that take place in the molecular structure of DNA/RNA in microorganisms during their passage from host to another. It may be due to recombination, deletion, or insertion of genes, to point mutations, or to several of these events. It leads to alteration in the antigenic composition and thus in the

immunological responses of individuals and populations to exposure to the microorganisms concerned" (Porta, 2008, p. 7).

Antigenic shift: "A mutation, or sudden change in the molecular structure of DNA/RNA, in microorganisms, especially viruses, that produce new strains of microorganisms. Hosts previously exposed to other strains have little or no acquired immunity. Antigenic shift is believed to be the explanation for the occurrence of strains of influenza associated with large-scale epidemics and pandemic spread" (Porta, 2008, p. 7).

Antimicrobial: "Any drug, medication, or agent that acts to destroy bacteria" (Rothenberg, 1999, p.23).

Antimicrobial stewardship: "Coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen dosing, duration of therapy, and route of administration" (Society for Healthcare Epidemiology of America [SHEA], Infectious Diseases Society of America [IDSA], & Pediatric Infectious Diseases Society [PIDS], 2012, p. 323).

Antiviral: "Opposing a virus, weakening or abolishing its action" ("Antiviral," 1972, p. 86).

Clostridium difficile: "A gram-positive, spore forming, anaerobic rod which causes millions of human infections each year, with an increasing incidence in recent years" (Isada et al., 2003, p. 83).

Colonization: "Presence of organisms in or on the body site, but not causing clinical signs or symptoms of infection" ("Colonization," 2002, p. 69*).*

Cytopathic: "Pertaining to a diseased condition of a cell" ("Cytopathic," 1972, p. 319*).*

Enterotoxin: **"**A toxin that is produced by microorganisms and causes gastrointestinal symptoms" ("Enterotoxin," 2012).

Exotoxin: **"**A protein produced by a bacterium and released into its environment causing damage to the host by destroying other cells or disrupting cellular metabolism" (APIC, 2008, p. 7).

Influenza: "An acute viral disease of the respiratory tract characterized by fever, cough (usually dry), headache, myalgias, prostration, coryza and sore throat" (Heymann, 2008, p. 315)

Influenza antiviral agent: "Four licensed prescription antiviral agents available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir" (CDC, 2011, p. 6).

Influenza diagnostic tests: "Diagnostic tests available for influenza include viral culture, serology, rapid diagnostic (antigen) testing, reverse transcription polymerase chain reaction (RT-PCR), and immunofluorescence assays" (CDC, 2011, p. 4).

Pathogenesis: "The mechanisms by which a cause or etiological agent produces disease" (Porta*,* 2008, p. 181).

RT-PCR: "Reverse transcription polymerase chain reaction is a method to amplify small quantities of the nucleic acid of a microorganism so the microorganism can be detected by other molecular biology means" (Isada et al., 2003, p. 553).

Seasonal variation: "Change in physiologic status or in disease occurrence that conforms to a regular seasonal pattern" (Porta, 2008, p. 225).

Assumptions and Limitations

Assumptions

In this research, I assumed that the established risk factors for exposure to antibiotics and antivirals during the influenza season were not significantly different among the U.S. hospitals in this study. Jarvis et al. (2009) studied hospitalized patients and found 79% of patients received antibiotics prior to *Clostridium difficile* associated disease (CDAD). It is assumed for the purpose of this study that antibiotic/antiviral consumption will be similar across the hospitals used in the study data set.

Another assumption was the diagnosis data received were based on clinical signs and symptoms and interpreted laboratory results from qualified healthcare professionals. Laboratory test results are assumed to be performed using Clinical and Laboratory Standards Institute standards, qualified laboratory professionals, and FDA approved tests. While the data were not directly collected by me, it was assumed the data were accurate.

Limitations

The data used in this study were collected for patient care and not for research. The accuracy for use of these data for the purpose of a research study may have been

questionable. The study's retrospective design may have had limits of interpretability because of the data accuracy.

The study was limited to association of data and would not allow for a cause and effect inference because I did not directly collect the data. An observational, nonexperimental design limits the interpretation of the results (McPherson & Bunker, 1991). I used a proprietary database from a set of hospitals that pay for the electronic surveillance system and pharmacy modules. This willingness to pay for these services made this group of hospitals unique in terms of their commitment to infection prevention, data collection, and antimicrobial monitoring. The collected research cohort increased sampling bias more than that seen in random sampling, while increased internal validity from the surveillance system's organized, consistent methodology for isolate and antimicrobial results data.

Additional limitations include that the patient data were not queried for documentation of underlying medical conditions that can be exacerbated by influenza infection, nor were they queried for secondary infections, coinfections, or complications from influenza. Moreover, documentation or knowledge of influenza vaccine receipt was not queried in the study population, and the patient's immune response to the vaccine, if received, remained unknown.

Scope and Delimitations

Influenza causes thousands of deaths in the United States annually and hundreds of thousands hospitalizations (CDC, 2010), and CDI has emerged as the most common cause of antibiotic-associated diarrhea and a highly problematic healthcare-associated

infection (Garey, 2011). The focus of this study, therefore, was to gather a convenience sample of information across U.S. hospitals. I used sampling from a group of hospitals that pay for an electronic surveillance system.

For this study, long term care, rehabilitation, and children's hospitals were excluded from sampling. Sampling was from acute care hospitals and adult patients. In long term hospital and rehabilitation settings, patients are often treated as residents and have healthcare issues and disease management that are not considered acute. Children's hospitals were also excluded, as seasonal respiratory illnesses seen in the very young during the typical influenza season often manifest as respiratory syncytial virus (RSV) and other respiratory syndromes (Nelson & Williams, 2007). The CDC reports that during the influenza season, there are more outpatient visits in children 7 to 12 years old (CDC, 2010). Furthermore, among children age 5 to 7, there were more antibiotic prescriptions provided per 100 children than age 15 and younger compared to time periods when seasonal influenza is not circulating (CDC, 2010). Additionally, annual hospitalization rates for lab confirmed influenza decrease with increasing age (CDC, 2010). Children are often less exposed to antibiotics in terms of years and the antibiotic choices selected by pediatricians and neonatologists. Therefore, data for lab confirmed influenza with inpatient antibiotic utilization among children would be more difficult to find.

The cohort of hospitals used in the study may not accurately represent all United States hospitals and, therefore, the resulting delimitation may have decreased the ability to generalize.

Significance

Researchers have shown the relationship of risk factors for CDI as exposure to antibiotics, hospitalization, and advanced age (AHRQ, 2012; APIC, 2008; Garey, 2011; Jarvis, Schlosser, Jarvis & Chinn, 2009). Little published literature exists supporting the theoretical aspects of how seasonal variations of influenza incidence and antibiotic use relate to CDI development in hospitalized patients. Influenza and CDI development studies have been limited by data sources, including administrative data versus clinical or microbiologic data (Polgreen, 2010). Furthermore, antibiotic use is an additional factor in this equation that has not been studied due to lack of readily available, nationwide data aggregating receipt of antibiotics in hospitalized patients or access to reliable antibiotic data in individual hospitalized patients (Polgreen, 2010).

There are significant implications for social change. Knowledge from an epidemiologic study of seasonality of disease and antibiotics can have an influence at local and organizational levels. Healthcare providers can benefit from recognizing the affect that antibiotic delivery in hospitals and healthcare settings has through more informed choices for use and pharmacologic recommendations, in other words, through increased "antibiotic stewardship". Jarvis et al. (2009) found the considerable morbidity and mortality associated with CDI calls for implementation of comprehensive evidence-based *Clostridium difficile* measures. Antibiotic resistance and CDI are health care issues that affect the hospitalized patient and can have implications for affecting the general public once the patient is released from a healthcare setting, such as exposing the community population and environment to antibiotic resistance and CDI.

Summary

The epidemiology of CDI has changed over recent years. The attributable economic burden to healthcare providers and the added morbidity and mortality to patients makes this issue a public health concern. Influenza puts the population and public health into a conundrum every year as the virus shifts and drifts causing challenges for vaccine producers to provide a good match to the circulating strain. Vaccine receipt is an important part of reducing the incidence of influenza. The populations most at risk for complications of the flu are often hospitalized and die due to lack of prevention efforts such as annual vaccination.

In Chapter 2, a review of the literature will be as analyzed to further describe the role of influenza, CDI, and antibiotic stewardship. This review is important to provide further understanding for the readers about the study variables and highlight what is known and where inconsistencies and gaps exist. From the analysis, a gap in the literature will be revealed and formulate the need for research. In Chapter 3, methodology, I will describe how the research was carried out, and I will discuss how the study answers the research questions and hypotheses. I will also describe the study variables, ethics, and data handling. Chapters 4 and 5 will outline the study results, discussion of the findings, and implications for social change. References and any appendices are provided in the last pages of the document.

Chapter 2: Literature Review

Introduction

The literature review was performed to gain a thorough understanding of the epidemiologic research related to *Clostridium difficile*, influenza, and the concept of antimicrobial stewardship. In order to comprehend the current models and beliefs of CDI development, the literature review includes a historic and current perspective of CDI epidemiology; searches for this literature were performed without date limitations in multiple databases. This literature search revealed hundreds of articles that were then narrowed to relevance for this study.

The purpose of the literature review is to effectively discuss the problems associated with the development of CDI in the United States and reveal a gap in the literature for the variables of this study. The approach is to organize the literature into a basic historic and epidemiologic perspective of CDI through the history and microbiology of *Clostridium difficile*. The literature review also provides background information and data to support the problem of variability of physician ordering of antiviral/antibiotics use overall and during times of influenza incidence. Furthermore, the literature provides an understanding of the concept of antimicrobial stewardship and provides supporting literature of antimicrobial use related to the development of CDI. In the final portion of this chapter, I will discuss the literature related to the variables used in this study. Also drawn from literature are components of population and setting as a framework that shaped the study design and methods.

Research Strategy

The literature search was conducted through multiple databases including EBSCOhost, MEDLINE, CINAHL Plus, and Cochran Collection Plus (through the Walden University library). In addition, searches were conducted through Google Scholar and the CDC website. Finally, the Michigan eLibrary and Ironwood Carnegie Library were used to search for literature. EBSCOhost MEDLINE full text search for scholarly peer reviewed journals, years 2000 to 2013 revealed the following: 147 results using the terms *influenza* and *antibiotics*, 113 results using the terms *influenza* and *antivirals*, 47 results using the term *antibiotic stewardship*, and 949 results using the term *Clostridium difficile.* ProQuest search of peer reviewed articles, years 2009 to 2013, using terms *influenza* and *antibiotics,* revealed 54 results with one article used. Also searched were the CDC's primary peer-reviewed publication, *Morbidity and Mortality Weekly Report,* and I used my own peer reviewed journal holdings and subscriptions of the American Journal of Infection Control and the American Journal of Public Health to search for articles of relevance. Use of bibliography mining for citation chains was a search strategy used from key articles that were of close relevance to my research questions. Any journals or books pertinent to the research were downloaded, purchased, or procured for use.

A variety of terms were used to search for pertinent literature in the databases listed. The following common terms were searched: *influenza and antibiotics, influenza and antivirals, Clostridium difficile, Clostridium difficile risk factors, Clostridium difficile-associated disease, Clostridium difficile infection, antibiotic stewardship,*

history of Clostridium difficile, seasonal influenza, and *wheel model*. Searches were also

enhanced from article referrals from work colleagues who are pharmacists and have

ready access to pharmacy journals and positions papers on the key subjects of

antimicrobial stewardship, Clostridium difficile, and *antibiotic and antiviral use*. Faculty

suggestions for articles were also incorporated into the literature review. Periodic

searches have been conducted through the current month and year to ensure any newly

published articles or positions statements of relevance are found for use.

Theoretical Foundation

Epidemiologic Wheel

Mausner and Bahn (1974) described overall that models of disease have multiple

causation. In the medical community, the focus is on the patient with forces and factors

within the patient, the environment, and microorganisms contributing to disease. This has

been depicted as the epidemiologic triangle with the corners of host, agent, and

environment as labels. This model illustrates that a change in any of the components will

ultimately alter the equilibrium of the triangle and increase or decrease the disease

frequency (Mausner & Bahn, 1974). Mausner and Bahn first described the wheel model

(see Figure 1). It is an elaboration of the man-environment concept with the host or man

at the center, and the man has a genetic makeup nested at the core of this host hub that is

surrounded by the environment, which is divided into three sections. These three

sections--biological, social, and physical--can differ in size depending on the specific

disease or problem. Diseases that are hereditary would have a large genetic core, while

those diseases such as smallpox would have a smaller genetic core. The immune status of

the host in the biologic environment section and social section may change in size when

considering factors such as exposure to the virus, receipt of a preventative vaccine, or

herd immunity. Mausner and Bahn stated that the wheel model "implies a need to

identify multiple etiologic factors of disease without emphasizing the agent of disease"

(p. 35). In addition, "the wheel model does encourage separate delineation of host and

environmental factors" (Mausner & Bahn, 1974, p. 35).
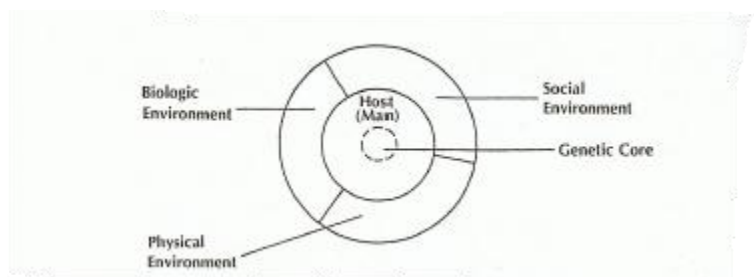
Figure 1. Wheel model of man-environment interactions. From *Epidemiology: An introductory text* (p. 36), by J. S. Mausner and A. K. Bahn, 1974, Philadelphia: Saunders. Copyright 1974 by W. B. Saunders Company. Reprinted with permission.

The use of this theory relates to the study of understanding determinents of CDI,

seasonal influenza, and the role/influence of antibiotic use and selection. The host or man

at the center has the three sections of environment in play at many stages of the disease

development of CDI. The development of influenza can be based on the lack of vaccine

receipt, naïve host, or a vaccine mismatch due to a differing circulating/novel influenza

strain (CDC, 2009). This section weighs heavy in the biological section, as does receipt

of a good strain match of vaccine for influenza prevention. Additionally, there can be

biological factors of a dose-response relationship in the development of influenza with

the occurrence of influenza based exposure to the associated influenza strain and the

proportion of vaccine match for those who received it (CDC, 2009; Glezen, 2006).

Admission to the hospital or the need to seek medical intervention for influenza is in the

social and biological sections. This can have social constructs of individual, family, or

cultural groups influencing the health seeking behavior and decisions to seek treatment.

The physical environment includes exposure to *Clostridium difficile* spores in the

physical hospital environment, and the social aspects include if the physician prescribes

antibiotics that may alter the host gut to develop CDI, as well as the host request and

acceptance of antibiotics. The physican's desire to use antibiotics may be based on the

need to provide comprehensive coverage for all upper and lower respiratory conditons

without a clear etiology, not having or waiting for influenza testing results prior to the

administration of antibiotics for bacterial infections versus antivirals for viral infections

such as influenza, lack of critical thinking, physician's need to do something for the

patient, or maintaining patient satifaction as they request medications (Bonner, Monroe,

Talley, Klasner, & Kimberlin, 2003; Linder et al., 2006). The social aspects of care for

the host by the medical provider can greatly influence this portion of the wheel.

      Peterson (1995) used the wheel model to describe war and disease. The wheel

model was used to detail the complexity of war conditions. This included concentrations

of people and intermixing of populations. Additionally, resources that may be in short

supply, such as basic hygiene and medical care, along with the diversion of food supplies

that lead to conditions of malnutrition and famine. These factors interact to increase the

rate of infectious disease and may lead to social disintegration. Peterson found this model to be more encompassing of multiple etiologic factors, which was necessary to fully explain the relationship between war and disease. Uzoigwe, Khaitsa, and Gibbs (2007) used the wheel model to describe the multiple etiologic factors that influence irritable bowel syndrome. They described the interaction of genetic and environmental factors that can influence the disease process, including infectious agents, diet, drugs, stress, and social status. The use of the wheel model by Peterson and Uzoigwe et al. provided examples of use for research questions that involve a complex set of factors. In this study, the model can also be used to describe the complexity of antivirals and antimicrobials with the influence of physician ordering and patient factors.

Current Trends in Influenza

Morbidity and mortality from influenza is linked to the underlying status of the host, and many factors such as age and comorbidities play a significant role in the acquisition and ultimate presentation of the disease. In the United States, influenza deaths have increased over the past 25 years with the highest attack rates among children under age 5 and individuals aged 65 and older (Klepser & Hagerman, 2011, p. 207). Influenza-related complications and hospitalization are lowest among children (Klepser & Hagerman, 2011, p. 209). Aggressive vaccination for the seasonal flu can minimize the impact of health related influenza illness to populations. Glezen (2006) noted mortality and hospitalization due to influenza has increased despite increasing vaccine coverage to the most vulnerable populations. Furthermore, the most vulnerable populations are the least likely to elicit a full immune response to the vaccine. Glezen found in a review of

the literature on novel strategies for influenza control that indirect effectiveness of the influenza vaccine could be obtained when children received the live attenuated vaccine and herd protection was conferred to adults. Herd immunity or herd protection of a group can occur when a large proportion of individuals from that group are immune or immunized to an infectious agent, thereby reducing exposure of those susceptible to that agent (Porta, 2008). Glezen also noted this same concept for herd protection occurred among Japanese school children where 50% to 85% of the student population was vaccinated using injectable vaccine. Traditional Japanese families live in multigenerational households, the conferred herd protection to the elderly in the household occurred as a result of the school children's immunization. In contrast, Kelly, Kromelis, Jordan, Merryman, and Siegle (2012) used a novel strategy to deliver the influenza vaccine to primarily adult household contacts of infants aged less than 60 months to increase vaccine uptake among household contacts and reduce household influenza transmission. The importance of this strategy illustrated it may be the only means to protect the very young as no influenza vaccine is available for infants aged less than 6 months. The CDC (2009) statistics indicated that serious illness and death are highest among children less than 2 years old and adults aged 65 years and older; adults aged 85 years and older are at the highest risk for death, with approximately 36,000 deaths between 1990 to 1999 and 226,000 hospitalizations from 1979 to 2001.

Symptoms associated with the flu typically emerge abruptly after an incubation period of 1 to 4 days, and symptoms resolve in 3to 7 days in uncomplicated cases, even though cough and malaise may last for a few weeks longer (Heymann, 2008). In adults,

the symptoms are cough, fever, respiratory symptoms, malaise, myalgias, sore throat, and

rhinitis. Children may present with these symptoms and also may exhibit nausea,

vomiting, and otitis media (Heymann, 2008). Because these respiratory symptoms are

often clinically indistinguishable from other respiratory syndromes and viruses, accurate

diagnosis and laboratory confirmation is critical for appropriate treatment choices to

occur. Diagnosis is complicated by the varied and often nonspecific signs and symptoms

of influenza. The primary methods used for diagnosis of influenza infection are viral

culture, rapid diagnostic tests, reverse transcriptase-polymerase chain reactions, or

clinical diagnosis without the laboratory testing based on sign and symptoms and current

statistics of the influenza burden in the population for the time period. Each method has

varied accuracy to predict the presence of the influenza virus; test sensitivity, specificity,

and positive and negative predictive values, therefore, require careful data interpretation

by qualified healthcare professionals. Point-of-care rapid testing can aid in the speed of

diagnosing influenza and can assist clinical decision making for appropriate therapy and

control measures (Heymann, 2008).

Falsey, Murata, and Walsh (2007) studied the impact of rapid diagnosis testing

and the management of adults who were hospitalized with influenza. A review of medical

records over four flu seasons revealed rapid influenza testing leads to reduced antibiotic

use in hospitalized patients. The results of this study found the positive influenza test was

associated with modest withholding or discontinuing antibiotics; however, a significant

portion of the test positive patients at low risk for bacterial infection continued to receive

antibiotics. Physicians were surveyed to assess the beliefs of being comfortable to

discontinue antibiotics in patients with negative chest x-rays and negative bacterial

cultures, and two thirds of the respondents believed they would be (Falsey et al., 2007).

Medical record review, however, found in practice that these physicians did not

discontinue antibiotic use (Falsey et al., 2007). Physicians are concerned about secondary

bacterial infections with an influenza diagnosis and the ability to distinguish concomitant

bacterial or viral infections during peak seasons for respiratory illness (Falsey et al.,

2007). Even with sound medical evidence of no secondary or concomitant respiratory

illness or disease, practitioners justified their choice to continue antibiotic use.

Several studies have shown that diagnosis and treatment of influenza is not

consistent among physicians. Linder et al. (2005) found that physicians prescribed

inappropriate antibiotics to 26% of patients, and physicians prescribed antiviral

medication to 19% of patients with an influenza diagnosis. This was similar to results

from a study by Bonner et al. (2003) on decision making in a pediatric emergency room

based on influenza testing information. This study found emergency room physicians,

when blinded to the rapid influenza testing result, were more likely to perform more

blood counts, blood cultures, urinalysis and cultures, and chest x-rays, prescribe

antibiotics, and have patients stay longer in the emergency room with all the associated

costs to the patient. In contrast, emergency room physicians who were aware of the

positive influenza test result used less laboratory tests, antibiotics, and emergency room

time in addition to prescribing antiviral medications more than those physicians who did

not know the influenza test result. The findings of this study provided evidence that

physicians can alter their clinical decisions and patient management in a pediatric

emergency room setting when they are made aware of influenza rapid testing results prior to seeing the patient for evaluation. This type of clinical management is the focal point of antimicrobial stewardship, which involves improving clinical outcomes while minimizing antibiotic use and its unintended adverse consequences.

Antibiotic/Antiviral Stewardship

Antimicrobial stewardship is defined as "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen dosing, duration of therapy, and route of administration" (SHEA, IDSA, & PIDS, 2012, p. 323).

Bartlett (2011) noted CDI and the crisis of antimicrobial resistance as two major health care challenges and one of the most pressing public health issues. At the heart of both of these two challenges is antimicrobial use and abuse (Bartlett, 2011). The CDC (2012b) noted that "good antibiotic stewardship is an important aspect of quality healthcare that prevents CDI" (p. 3). Inappropriate antimicrobial use can diminish the therapeutic benefit of the drug and facilitate the development of drug resistance (Moody et al., 2012). Antibiotic use is a major contributor to the spread of antimicrobial resistance, and broad-spectrum antibiotics can lead to diarrhea. "*Clostridium difficile* is the most common cause of antibiotic-associated diarrhea" (Olivo & Ranalli, 2013, p32). Hicks, Taylor, and Hunkler (2013) found among United States outpatients in 2010, 258 million antibiotic prescriptions were written, 8.33 per 1,000 Americans or five antibiotic prescriptions for every six people. Abbett et al. (2009) discovered the initiation of

antimicrobial stewardship programs are complex. There are multiple points of care by healthcare workers and often require difficult behavior changes.

An appropriate choice to treat influenza is antiviral medications. They can reduce the duration of influenza symptoms by one to almost three days and reduce complications that require the use of antibiotics (Linder et al., 2005). Additionally, antiviral use may decrease hospitalization and mortality. Linder et al. found the use of antiviral medications for management of influenza important, given influenza vaccine receipt and effectiveness can vary. The CDC states "antiviral medications are an adjunct to influenza vaccination and are effective when administered as treatment and when used for chemoprophylaxis after exposure to the influenza virus" (CDC, 2009, p. 2). The primary goal of antimicrobial stewardship is to improve clinical patient outcomes and minimize unintended adverse consequences due to inappropriate selection, dosing, and duration of these medication therapies.

Antibiotic/Antiviral Stewardship and CDAD

The incidence of CDAD before and after implementing antibiotic stewardship programs has been described by many studies across the United States and other countries, with similar results. The removal or reducing the use of an offending antimicrobial agent can result in decreased CDAD. The stewardship protocol of requiring infectious disease physician or pharmacist approval for prescriptions for most parenteral antibiotics brought about a significant and lasting reduction in CDAD incidence; a 47% decrease in all CDAD and 42% decrease in new cases in a hospital setting (Nuila, Cadle, Logan, & Musher, 2008). Gerding (2004) interpreted epidemiologic evidence that related

attributable risks for CDAD may be due to the antimicrobial selected and overall frequency and of use in the population. This was more specifically found in a study by Gaynes et al. (2004) in a long term care (LTC) setting where two different but similar fluoroquinolones (gatifloxacin and levofloxacin) were used. The findings by Gaynes et al. described the use of gatifloxacin and clindamycin were associated with increased risk of CDAD, and in particular the increased number of days receiving gatifloxacin therapy; 67% of the study patients with CDAD received gatifloxacin compared to 24% who received clindamycin. Increasing the duration of therapy of gatifloxacin significantly increased the attack rate and risk for CDAD. Clindamycin has historically been the second most frequently associated antimicrobial agent associated with CDAD (APIC, 2013; Gerding, 2004). A cost saving measure, formulary change, from levofloxacin to gatifloxacin had indeed coincided with an increase of CDAD among LTC residents, but when the gatifloxacin was substituted back to levofloxacin the rate of CDAD decreased (Gaynes et al., 2004). Similarly, Pear, Williamson, Bettin, Gerding, and Galgiana (1994) found the increased use and duration of clindamycin use was statistically associated with and epidemic strain of clindamycin resistant *Clostridium difficile* and by restricting clindamycin use, the associated epidemic pattern of CDI resolved, and there was a marked decreased in new cases of *Clostridium difficile.* In a contradicting case, Berild, et al. (2003) compared two similar hospitals in Norway for CDI in terms of antibiotic use and infection control practices. The researchers obtained point prevalence data of antibiotic associated diarrhea and antibiotic use from both facilities. Despite the decreased use of antibiotics in the one hospital, a higher reported incidence of CDI was

reported. Interestingly, the study could lead the reader to surmise the decreased antibiotic use did not have an effect on CDI. The study data revealed there was a higher frequency of *Clostridium difficile* testing at this hospital, which consequently resulted in a higher reported incidence of CDI. The results of this study are confounding and may not actually correlate hospital antibiotic use and the reflected incidence of CDI, but an artifact of varied laboratory testing and reporting.

The role of antibiotic induced *Clostridium difficile* diarrhea, infection, and colitis has been well documented, while the discrete use antivirals in the development of CDI has not. Colarian (1988) reported a case of *Clostridium difficile* colitis in a male patient, with a history of acquired immunodeficiency syndrome (AIDS), who had been treated with the antivirals acyclovir and azidothymidine (AZT), and had not received any antibiotics in the prior six months. A group of *Clostridium difficile* studies where the patients' immune systems were compromised revealed use of antivirals, but did not specify antiviral use individually in the data analysis (Gellad et al., 2007; Gorschlüter et al., 200; Pulvirenti et al., 2002). In the study by Pulvirenti et al., antimicrobials-- defined as antivirals, antifungal, and antibacterial agents-- were studied for development of CDI in human immunodeficiency virus (HIV) patients. The study did not provide detailed names of the antivirals included nor did it analyze the use of antivirals as an individual variable. Gellad et al. studied the severity of CDAD in solid organ transplant patients and specified exposure to antivirals as a variable; the study did not find any statistically significant differences in development of severe colitis among the study groups of transplant and non-transplant patients with CDAD. The study did include antivirals as a

characteristic variable, but did not analyze antiviral use individually. This was also noted in a study by Gorschlüter et al., where the specific oral antiviral, acyclovir, was used among study patients. Antiviral class use was an aspect considered in a specific, large outbreak study by Muto et al., (2005), but was not independently associated with CDI.

Antimicrobial-induced diarrhea and development of CDI are serious complications of patient medical management and requires thoughtful antimicrobial selection in the choice to treat any infecting pathogen.

History and Changing CDI Epidemiology

Bartlett (2011) reviewed the 30 year history of CDI and indicated in the late 1970s, antibiotic-associated colitis could occur from almost any antibiotic with an antibacterial spectrum of activity, but primary offenders were clindamycin and broad-spectrum antibiotics. Cephalosporins, clindamycin, and fluoroquinolones have a higher risk for causing disease due to the antibiotic's ability to disrupt lower intestine normal flora (APIC, 2013). Bartlett noted for the first 25of the 30 year time period, CDI was a severe complication of antibiotic use that could be life threatening, but the mortality rates were low. Bartlett, 2011; Elixhauser and Jhung, 2008 reported a surge of CDI cases during the years 2001 to 2005. Not only was there a 102% increase in four years, but also a substantial increase in attributable mortality. Noticing among the increase in CDAD deaths and that 80% of these deaths occur in acute care hospital settings, Zilberberg, Shorr, and Kollef (2008) further found there was an increase in CDAD hospitalizations for the years 2000 to 2005. This surge in the number of cases and increased mortality has retrospectively been associated with the new strain of *Clostridium difficile*, the NAP1

strain (Bartlett, 2011). The emergence of this strain has been thought to be due to the developed resistance of *Clostridium difficile* to fluoroquinolones which had been widely used, as the NAP1 strain was uncommon in historic strains (Bartlett, 2011). The NAP1 strain hallmark is higher toxin production, which may account for the increase in severity of outcomes and mortality. Concurrent with this hyper-virulent epidemic strain, fully identified as BI/NAP1/027, CDI prevalence more than doubled in hospitalized patients (Tabak et al., 2013). The highest rates of CDI occurred among persons 65 years and older, with over two-thirds of the patients with CDI being elderly (APIC, 2013; Elixhauser & Jhung, 2008). Females had higher rates of CDI related hospital stays than males, and new populations previously thought to be low risk have emerged: healthy peripartum women, children and healthy adults with minimal or no recent exposure to healthcare settings (APIC, 2013). An additional change in CDI epidemiology has been noted in the regional incidence from review of U.S. hospital discharge data. Elixhauser and Jhung (2008) found "the Northeastern rate was two times higher than the West, which had the lowest rate. The rates in the Midwest and South were 69 percent and 42 percent higher than the Western rate, respectively" (p. 2). The purpose of this quantitative study was to examine the temporal progression of CDI incidence and take into account meaningful data elements, such as geographic regional differences.

CDI Seasonality

Seasonal patterns for CDI have been noted by Jagai et al. (2007), in the United States a pattern that peaks in mid-March for all age groups. In addition, Polgreen et al. (2010) found seasonal influenza activity peaked in January and February with CDI peaks

occurring in March. In contrast, Bruckhardt, Friedrich, Beier, and Eckmanns (2008) found trends of CDI did not follow obvious seasonal trends like other enteric diseases such as *Salmonella* species, Rotavirus, and Norovirus, rather an overall increase in CDI incidence. In another case, a study conducted by Larang, Repayo, Chan and Murillo (2011) described *Clostridium difficile* testing for the year of 2009 and found a bimodal distribution for ages 71 to 75 and 1 to 5 years, along with a bimodal seasonal distribution of positive tests that peaked in March and November. R. S. Larang clarified that this *Clostridium difficile* study did not consider the influenza season, but indicated it was interesting the age groups in the study are the same as those most affected by influenza (personal communication, July 18, 2011). The significance of this study is the data year used was 2009, this was the year of the novel influenza A (H1N1) that showed very unique activity and distinct bimodal peaks of influenza activity, in contrast to the typical seasonal influenza single peak in late fall/early winter in the United States. The 2008/2009 seasonal influenza peak was January 2008 through March 2009, with the second novel influenza A (H1N1) activity starting and peaking quickly in late April to early May 2009. The influenza A (H1N1) activity continued through June 2009. The A (H1N1) strain co-circulated, and in many U.S. regions it never completely diminished when the seasonal influenza again emerged in September lasting through late December 2009 (CDC, 2012a). Accordingly, Polgreen et al. (2010) found using time-series methodology while reviewing regional and national level data revealed peak CDI incidence occurred during or after monthly influenza peaks. The use of time series

analysis performed for the study implied the seasonal variation was included because the typical influenza season occurs within each year and recurs periodically year after year.

Summary

The literature review I presented in this chapter provided some historic and epidemiologic background information of influenza and CDI. Additionally, the concept of antimicrobial stewardship and the factors driving the need for this strategy where identified. The literature offered evidence of the well known, key risk factor of antibiotic exposure contributing the development of CDAD. Also, the literature revealed the key population characteristics that was used to select my study sample population.

Moreover, the literature provided insight to the dependent and independent variables. The study basis to suspect that seasonal influenza may be linked to an increase in the subsequent development of CDI was revealed in the literature. However, lacking in the literature are studies to analyze aggregate data and support an influenza and CDI link due to monthly receipt of antibiotics/antivirals in hospitalized patients. The literature reviewed does provide justification to test the proposed hypotheses and analyze the association of the independent variables and the one dependent variable using multiple logistic regression. In Chapter 3, I will describe the research method and design. Also, the study variables will be discussed and the context of the intended data elements to be collected will be clarified.

Chapter 3: Research Method

The purpose of this study is to address the use of antiviral/antibiotic usage during the influenza season and the incidence of CDI. In this chapter, I discuss the testing of the hypotheses that explain an association between the use of prescription antivirals or antibiotics to predict CDI within 60 days of discharge in patients who have been hospitalized for influenza. A retrospective, observational design was used to describe and analyze the relationship between the incidence of CDI development and the related variables of antiviral/antibiotics among patients hospitalized for influenza. The chapter is divided into sections of research design, population and setting samples, variable descriptions, data analysis plan, threats to validity, and ethical concerns.

Research Design

In this study, I describe and analyze retrospective observations of data from a proprietary, laboratory, and pharmacy based system from a cohort of hospitals. The retrospective nature of this research was chosen based on the timing of the influenza seasons for the study years. This observational study provides information to explore the cause of CDI incidence and determinants.

A retrospective observational cohort design was chosen due to the novelty of the relationship between the variables that had not previously been documented in the literature reviewed. It seemed reasonable to begin the study inquiry using an observational study approach. The benefits of using this type of observational study include a simpler design with the efficiency and ease of collecting retrospective data

using fewer resources compared to a logistically challenging prospective experimental design (McPherson & Bunker, 1991).

The limitation of using a retrospective cohort study compared to a prospective experimental study is detailed information on exposure and confounders may not be controlled for in the data collection process (Aschengrau & Seage, 2003). Despite this recognized limitation, the observational design was used for the novel hypotheses with the rationale the study may not require the resources for an experimental design.

An observational design was chosen over a cross-sectional design due to cross-sectional observations are based on a single point in time (Babbie, 2007). The influenza and development of *Clostridium difficile* data in this study lends itself to the time-related option of observations over a longer period of time. The best way to study changes over time is to utilize a longitudinal study (Babbie, 2007). Therefore, this retrospective cohort study was based on data collected over the influenza seasons time frame.

Population and Sampling

Study Population

The study population for this research consisted of U.S. hospitals that subscribe to the surveillance and pharmacy system known as MedMined Surveillance Advisor, a division of CareFusion (CareFusion, 2013). There are approximately 400 hospitals that subscribe to the MedMined electronic surveillance module and about 30%, representing approximately 125 hospitals, subscribe to the electronic pharmacy module known as Patient Event Advisor. Hospitals that use MedMined have a business agreement for the

services and pay a monthly fee. The hospital demographic using MedMined services are primarily short-term acute care hospitals across the United States.

For this study, long term care, rehabilitation, and children's hospitals were excluded from sampling. Sampling was from acute care hospitals and adult patients. In long term hospital and rehabilitation settings, patients are often treated as residents and have healthcare issues and disease management that are not considered acute. A convenience sample was used taking into account that the highest rates of CDI occur among persons 65 years and older, with over two-thirds of the patients with CDI being elderly, and females having higher rates of CDI related hospital stays than males (APIC, 2013; Elixhauser & Jhung, 2008). It was noted in Chapter 2 that new populations previously thought to be low risk populations for CDI have emerged: healthy peripartum women, children, and healthy adults with minimal or no recent exposure to healthcare settings (APIC, 2013). Healthy, peripartum women and healthy adults with minimal or no recent exposure to healthcare settings were not excluded. For this study, children were excluded because the respiratory syndromes seen in the very young during the typical seasonal influenza season often manifest as RSV (Nelson & Williams, 2007). The CDC (2010) reported that during the influenza season, there are more outpatient visits in children and annual hospitalization rates for lab confirmed influenza decrease with increasing age. Additionally, children are often less exposed to antibiotics in terms of years and the antibiotic choices selected by pediatricians and neonatologists. Therefore, data for lab confirmed influenza with inpatient antibiotic utilization among children would be more difficult to find in this secondary data source (CDC, 2010).

The changes in CDI epidemiology noted in the regional incidence from a review of U.S. hospital discharge data was taken into account by sampling more in the Northeast, Midwest, and South than the Western portion of the United States (Elixhauser & Jhung, 2008). The United States is divided into four main regions by the U.S. Census Bureau for population survey and registration data. These four regions are designated by the Census Bureau as Northeast, Midwest, South, and West and were used for this study data collection (U.S. Department of Commerce, 2013).

The exact peak and year of seasonality incidence was determined using CDC's FluView tracking system (CDC, 2012a). Additionally, seasonal incidence was viewed in the MedMined graphing feature for each hospital's source specific data. The graphing feature allows for visualization of the epidemiologic curve based on the frequency of positive microbiologic isolates for influenza with the axis' of number of isolates and calendar week. Based on this graph, the peak weeks of the season can easily be identified and further verified with the CDC FluView system of reports geographic incidence density. This provided time series analysis and insight to seasonal variation.

Sample Size

In order to estimate the minimum sample size required to confidently accept the results of the analysis, sample size tables for logistic regression were consulted (Hsieh, 1989). The literature indicated the probability of a CDAD diagnosis within 60 days of hospitalization is approximately 12 (Rodemann, Dubberke, Reske, Seo, & Stone, 2007). To detect an odds ratio of 2.0 for an individual diagnosed with CDI, one standard

deviation above the mean using a one-tailed test with a significance of 0.5 and a power of 80%, a minimum of 146 participants was needed (Hseih, 1989).

Variable Descriptions

For this study, the measures collected from each hospital and analyzed for possible association included the of diagnosis and/or positive test for influenza and the independent variables of delivery of antiviral/antibiotics during the patient's hospitalization as well as the dependent variable of positive test or diagnosis of CDI. In this study, I used all eligible adult and elderly patients with the operational definition of adult, 18 to 64 years old, and elderly defined as age 65 years and older. This definition was consistent for age groups used and defined in the Healthy People 2020 objectives for improving health (U.S. Department of Health and Human Services, 2020).

The dependent variable of a diagnosis of CDI is defined as a positive laboratory test for *Clostridium difficile* using standard laboratory methodology such as, toxin assay, polymerase chain reaction (PCR), or antigen tests. The definition of CDI included the diagnosis field listing terms CDI, *Clostridium difficile* infection, or *Clostridium difficile*.

The study population was pulled from hospitalized patients with influenza. The definition of influenza included the diagnosis field listing terms of influenza, flu, and any flu specific types such as influenza A, B, and H1N1. The diagnosis of influenza is also defined as a positive laboratory test for influenza using standard laboratory methodology such as viral culture, serology, rapid diagnostic (antigen) testing, reverse transcription polymerase chain reaction (RT-PCR), and immunofluorescence assays (CDC, 2011).

For this study, the antimicrobial independent variables were use of antibiotics and antivirals among the patient population. Garey (2011) described that nearly all antibiotics have been implicated as the causative agent in the development of CDI. Broad spectrum antibiotics and certain antibiotic classes such as cephalosporins, clindamycin, and fluoroquinolones are most highly implicated (Bartlett, 2011). Therefore, based on the literature, data extraction to determine if antimicrobials were used was performed, and use of any antimicrobial without categorization was included for this variable definition (Bartlett, 2001; Garey, 2011). Several studies provided insight that physicians often prescribe antibiotics along with antivirals to treat influenza (Bonner et al., 2003; Falsey et al., 2007; Linder et al., 2005). In particular, among adult patients, Linder et al. found 26% of patients diagnosed with flu were prescribed antibiotics not associated with an antibiotic appropriate diagnosis, meaning excluded people whose diagnosis could credibly include a bacterial infection where antibiotic therapy is appropriate treatment. To illustrate the impact, Linder et al. found between 2 and 4 million people seek medical care for the flu every year, and this calculates into 500,000 to 1 million inappropriate antibiotic prescriptions. Bacterial complication rates from the flu among older adults have not been studied fully and there lacks data to support antibiotic use as a method of preventing influenza related complications (Bonner et al., 2003). Additionally, studies have shown that diagnosis and treatment of influenza is not consistent among physicians (Bonner et al., 2003; Linder et al., 2005).

In the United States, there are currently four licensed prescription antiviral agents used to treat influenza: amantadine, rimantadine, zanamivir, and oseltamivir (CDC,

2011). For this study, the use of any antiviral, including the four antiviral agents used to treat influenza, was included for this independent variable.

The study population was hospitalized patients with influenza. The definition of influenza included the diagnosis field listing influenza terminology and/or a positive laboratory test for influenza. Within this population, the dichotomous dependent (CDI) and independent variables (antibiotics use, antiviral use, antiviral and/or antibiotic use) were each coded for value of Yes =1 and No = 0. Table 1 lists the study variables.

Table 1

Study Variables

Variable type	Name	Definition	Coded value Yes	Coded value No
Dependent	*Clostridium difficile* infection	Positive laboratory test for *Clostridium difficile* using standard laboratory methodology such as, toxin assay, polymerase chain reaction (PCR) or antigen tests. Definition of CDI include the diagnosis field listing terms CDI, *Clostridium difficile* infection*,* or *Clostridium difficile*.	1 = Meets definition criteria	0 = Does not meet definition criteria
Independent	Antibiotic	Use of any antibiotic without class categorization	1 = Antibiotic given, meets definition criteria	0 = Antibiotic not given, does not meet definition criteria
Independent	Antiviral	Use of any antiviral, including the four antiviral agents used to treat influenza	1 = Antiviral given, meets definition criteria	0 = Antiviral not given, does not meet definition criteria
Independent	Antiviral and/or Antibiotic	Use of any antibiotic without class categorization and/or use of any antiviral	1 = Either antibiotic, antiviral, or both given, meets definition criteria	0 = Neither antibiotic nor antiviral given, does not meet definition criteria

Data Analysis Plan

The data were from a cohort of hospitals that use CareFusion MedMined services. In this study, I used proprietary surveillance data that includes patient level information such as diagnostic laboratory test results, ADT, and prescribed medications such as antimicrobials and antivirals. Microbiology data for the dependent outcome variable of *Clostridium difficile* or diagnosis of CDI and the independent variables of antibiotics/antivirals use among patients hospitalized with a positive test or diagnosis for influenza was analyzed using SPSS (Version 22.0). The web based tool owned within CareFusion MedMined to perform such a query is the Virtual Surveillance Interface (VSI). The VSI allows the end user to perform specific data extraction by creating customized, specific reports based on search criteria such as influenza and *Clostridium difficile* and inpatient versus outpatient criteria. For this study, a report was written and used to query based on these organisms and inpatient categorization. The patients identified from this inquiry were then be further queried for diagnosis details and medication delivery.

These patient data were queried and abstracted by looking up the indvidual patient level details using the patient name or medical record number (MRN) and searching the patient gender, date of birth, and diagnosis data field for a diagnosis of influenza, and CDI. For the independent variables of delivery of antiviral/antibiotics, a patient level inquiry was performed from the Patient Event Advisor portion of the MedMined surveillance system. This was performed using the patient name or MRN search

functions and running a query for the associated hospitalization admission time frame and the prescribed antiviral/antibiotics given.

After the data were collected, they were exported and populated into a spreadsheet to categorize the data elements and details. To protect the identity of the patient name and identifiable MRN, a new spreadsheet was created and random numbers assigned. This random number assignment allowed from this point forward to represent each study subject. From this spreadsheet, the variables were coded and formatted in preparation for the data analysis.

Before proceeding, a test of the assumptions of the multivariate analysis was performed. Logistic regression was used to answer both the association and prediction hypotheses and research questions. Multivariate analysis was performed using logistic regression to test the hypotheses and determine whether or not the use of antiviral/antibitotics is associated and predictive of CDI among hospitalized influenza positive patients. For the first two hypotheses, each independent variable was tested individually to determine statistical significance.

Research Question 1: Is there a relationship between use of prescription antivirals and CDI within 60 days of discharge in patients who have been hospitalized for influenza?

$H_0 1$: There is not a statistically significant association between use of prescription antivirals and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

H$_a$1: There is a statistically significant association between use of prescription antivirals and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

The first hypothesis of there is not a statistically significant association between use of prescription antivirals and CDI within 60 days of discharge in patients who have been hospitalized for influenza was tested using logistic regression. The dependent outcome variable of *Clostridium difficile* or diagnosis of CDI and the independent variable of antiviral use among patients hospitalized with positive test or diagnosis for influenza. A *p* value of 0.05 was used to determine significance. If the results yeild a *p* value less than 0.05, the null hypothesis was rejected and the alternative hypothesis was accepted.

Research Question 2: Is there a relationship between use of prescription antibiotics and CDI within 60 days of discharge in patients who have been hospitalized for influenza?

H$_0$2: There is not a statistically significant association between use of prescription antibiotics and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

H$_a$2: There is a statistically significant association between use of prescription antibiotics and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

The second hypothesis of there is not a statistically significant association between use of prescription antibiotics and CDI within 60 days of discharge in patients

who have been hospitalized for influenza was tested using logistic regression. The dependent outcome variable of *Clostridium difficile* or diagnosis of CDI and the independent variable of antibiotic use among patients hospitalized with positive test or diagnosis for influenza. A *p* value of 0.05 was used to determine significance. If the results yeild a *p* value less than 0.05, the null hypothesis was rejected and the alternative hypothesis was accepted.

Research Question 3: Does the use of prescription antivirals and/or prescription antibiotics predict CDI within 60 days of discharge in patients who have been hospitalized for influenza?

$H_0$3*:* The use of prescription antivirals and/or prescription antibiotics does not predict CDI within 60 days of discharge in patients who have been hospitalized for influenza.

H_a3*:* The use of prescription antivirals and/or prescription antibiotics does predict CDI within 60 days of discharge in patients who have been hospitalized for influenza.

The third hypothesis was tested using multiple logistic regression analysis. The use of prescription antivirals and/or prescription antibiotics does not predict CDI within 60 days of discharge in patients who have been hospitalized for influenza. The dependent outcome variable of *Clostridium difficile* or diagnosis of CDI and the independent variables are antibiotics and/or antivirals use among patients hospitalized with positive test or diagnosis for influenza. The independent variables of either antibiotics, antivirals, or both were used in the regression analysis for the third hypothesis. Coefficient size and associated *p* values for the independent variables was interpreted. If the interpretation is

not predictive of CDI then the null hypothesis was rejected. The positive or negative

value of each coefficient was analyzed to determine acceptance of the alternative

hypothesis.

Threats to Validity

The potential threat to internal validity that may arise from this study could occur

in the sample selection. Study subjects could have medical or physical characteristics that

may predispose them to certain outcomes or being more susceptible to disease. This type

of detailed data is not in the proprietary data base; therefore, I was unaware of these

details. To account for this threat, use of random selection will increase the probability

that these characteristics will be evenly distributed in the patient study subjects selected

(Creswell, 2009). A potential threat to external validity is the sample population being

only selected from hospitals who subscribe to use of CareFusion MedMined services.

Because this data set only contains a fraction of the all U.S. hospitals, I may not be able

to generalize the results to patient populations in other hospitals. To account for this

threat, research findings will have to restrict claims about other hospitalized patient

populations which the results cannot be generalized.

Ethical Concerns

This study, I did not use human participants directly, but used individual health

information from hospitalized patients with all personal identifiers removed. Data

confidentiality has been described above using a random number system after data

extraction. Protection of the raw data that contains patient names and medical records

with diagnosis and laboratory testing results will be maintained in a locked office during

the research time period. No personal identifiable information will be reported in the

research study, aggregate data will be reported. After the study is complete and the

dissertation does not require further data review the data will be moved to a locked safe

and maintained for five years before being shredded and destroyed. Data access will be

limited to only me and my committee members, if deemed necessary for dissertation

review and guidance. Procedures for data collection and handling were in accordance to

the Walden University Institutional Review Board (IRB). The IRB application for study

approval reference number is 02-10-14-0119262.

The hospital patient level data within the study population has a business

agreement that includes health insurance portability and accountability act (HIPAA)

language for protection of the data that use MedMined services as a computerized

healthcare vendor. The business agreement allows CareFusion MedMined Services to use

de-identified data for publications and marketing purposes both internal and external to

the company. For the purpose of this study and research access to the data related to the

hospitals and individual patients contained therein will require authorization by

CareFusion MedMined Services. (Appendix B)

The study was carried out using secondary data from CareFusion MedMined

Services and therefore access will be from a remote work environment. The office used

for work is the same office used for research, just with different workstations and

computers. This is a locked office with limited access. Working with CareFusion

MedMined Services database involves using detailed confidential data and the work

environment is set up to be conducive for maintaining confidentiality.

Summary

I used a retrospective, observational design to describe and analyze the relationship between the incidence of CDI development and the related variables of antiviral/antibiotics among patients hospitalized for influenza. The purpose of this study was to address the use of antiviral/antibiotic usage during the influenza season and the incidence of CDI using a proprietary laboratory based surveillance system of secondary data from a cohort of U.S. hospitals.

The data collected was used to test the hypotheses that explains a statistically significant association between use of prescription antivirals or antibiotics to predict CDI within 60 days of discharge in patients who have been hospitalized for influenza. The hypotheses were tested and analyzed using multiple logistic regressions. A detailed description of the actual analysis and results is presented in the next chapter.

Chapter 4: Results

The purpose of this study was to examine the use of antiviral/antibiotic usage during the influenza season and the incidence of CDI among hospitalized patients using a proprietary laboratory based surveillance system of secondary data from a cohort of U.S. hospitals. Three research questions with the according hypotheses were explored:

Is there a relationship between use of prescription antivirals and CDI within 60 days of discharge in patients who have been hospitalized for influenza?

$H_0 1$: There is not a statistically significant association between use of prescription antivirals and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

$H_a 1:$ There is a statistically significant association between use of prescription antivirals and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

Is there a relationship between use of prescription antibiotics and CDI within 60 days of discharge in patients who have been hospitalized for influenza?

$H_0 2$: There is not a statistically significant association between use of prescription antibiotics and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

$H_a 2:$ There is a statistically significant association between use of prescription antibiotics and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

Does the use of prescription antivirals and/or prescription antibiotics predict CDI within 60 days of discharge in patients who have been hospitalized for influenza?

$H_0 3$: The use of prescription antivirals and/or prescription antibiotics does not predict CDI within 60 days of discharge in patients who have been hospitalized for influenza.

$H_a 3$: The use of prescription antivirals and/or prescription antibiotics does predict CDI within 60 days of discharge in patients who have been hospitalized for influenza.

In Chapter 4, I examine the data collection details, population sampling, data analysis results with tables, and the research questions' findings summarization.

Data Collection

Data were generated using a proprietary laboratory based surveillance system of secondary data from a cohort of U.S. hospitals. The initial steps to obtain the data set required a query of hospitals using both the CareFusion MedMined Surveillance Advisor module and Patient Event Advisor module from the total number of hospitals that subscribe. From the selected segment of hospitals meeting this criteria, custom, individual VSI reports were written for each site to query search criteria of inpatients with influenza and *Clostridium difficile* across time frames to incorporate the 60 days of discharge. Population data were extracted based on meeting the criteria of adult patient age and hospitalized with a postive test for influenza. Multiple years were queried to obtain data across many flu seasons using years 2005 to 2014. The years selected for each hospital's VSI report was based on each individual site's specific available data for review. This was based on the database findings of how far back in time (years) data had

been stored in the repository. This was also joined to the database utilization of the

Patient Event Advisor module that houses the pharmacy portion of the patient records.

The development of CDI within 60 days of discharge was based on the date listed in the

database for the patient discharge timeframe and a positive laboratory test for *Clostridium*

difficile.

After the reports were generated, the sample population was selected. The

population was randomly chosen without regard for gender. States in which hospitals

were located were randomly dispersed within the census bureau regions. Patients who

were selected into the population data set were then queried using the Patient Event

Advisor module using their specific MRN and time frame of hospital admission. Specific

pharmacy data were retrieved, and the data elements of antiviral and antibiotics

prescribed and dispensed were gathered. The exact names of the antivirals and individual

antibiotics were identified and logged for data analysis. The population selected was

chosen and verified based on positive laboratory test for influenza and *Clostridium*

difficile. Cases were coded according to the dichotomous dependent variable (0 = No

CDI, 1 = Yes CDI). The independent variables of antibiotic use, antiviral use, and either

antiviral use, antibiotic use, or both used were coded No = 0 and Yes = 1. The population

selected was also logged according to the four census regions: Northeast, Midwest,

South, and West. Data were assessed for missingness, reviewed for accuracy, and cleaned

prior to entry into SPSS to perform regression testing.

Although the number of hospitals that subscribe to the MedMined database is

over 400, a query of the potential sample dataset revealed some of the hospitals that

subscribed to use of both MedMined modules did not have complete data variables populated for this study. Hospitals that did not have data in both modules for the time year periods required for the study were not used, resulting in the final study sample frame of 25 hospitals. While this limitation was a factor for not achieving the large sample size, the final study population was 147 patients, which met the minimum sample size requirement to achieve 80% power. After reviewing the diagnosis field in the data set and finding it unreliable and inconsistently documented, it was deemed best to use results of a positive laboratory tests for the criteria of both influenza and *Clostridium difficile* to ensure accuracy and consistency in the data collection.

Results

Data were gathered from 147 participants and entered in to SPSS version 22.0 for Windows. Descriptive statistics were conducted to outline the sample demographics. Frequencies and percentages were calculated for gender and regional representation according to the United States Census Bureau regions. Means (standard deviations) and ranges were used to describe the central tendency and spread of ages within the sample.

Of the 147 study participants, 117 (79.6%) participants received antibiotics, 106 (72.1%) received antivirals, 130 (88.4%) received antibiotics and/or antivirals, and 17 (11.6%) patients developed *Clostridium difficile* within 60 days of discharge. Out of the 17 patients who developed CDI, 11 had received both antibiotics and antivirals, four had received antibiotics only, and two did not receive antibiotics or antivirals.

The overall sample had an average age of 62.9 years (*SD* = 19.7), with a range from 19 to 101 years. The participants who developed *Clostridium difficile* ages ranged

from 36 to 91 years with an average age of 67.6 years (SD = 16.5), compared with the

average age of 62.3 years (SD = 19.9) for participants who did not develop *Clostridium*

difficile. In Table 2 the distribution of samples positive with Clostridium difficile by

region, gender, age and antimicrobial receipt are presented.

Table 2

Clostridium difficile Positive Sample by Region, Gender, Age, and Antimicrobial Receipt (n=17)

Region	Gender	Age	Antibiotic	Antiviral
Midwest	Female	91	No	No
Midwest	Male	86	Yes	Yes
Midwest	Female	83	No	No
Midwest	Male	73	Yes	Yes
Midwest	Male	69	Yes	No
Midwest	Male	36	Yes	Yes
Northeast	Female	64	Yes	No
Northeast	Male	89	Yes	No
Northeast	Male	83	Yes	Yes
Northeast	Male	77	Yes	No
Northeast	Male	59	Yes	Yes
Northeast	Male	47	Yes	Yes
South	Female	56	Yes	Yes
South	Male	58	Yes	Yes
West	Female	68	Yes	Yes
West	Female	37	Yes	Yes
West	Male	74	Yes	Yes

The participant geographic region sample revealed (n = 44, 29.9%) from the

Midwest region, Northeast region (n = 42, 28.6 %), South (n = 33, 22.4%), and the West

(n = 28, 19.0%). Next, each region was examined for frequency of *Clostridium difficile*.

The highest percentages for regions from which multiple participants were gathered were

the Midwest and Northeast. A total of 12 participants, six participants from the Midwest

and six participants from the Northeast developed *Clostridium difficile,* representing a

total of approximately 8% of the 147 participants. In the West region, three participants

of the 147 total developed *Clostridium difficile,* representing 2.0%, and two participants

of the 147 total developed *Clostridium difficile,* representing 1.4% from the South.

Within the regions, six participants of the 44 total participants from the Midwest,

13.6%, and six participants of the 42 from the Northeast, 14.2%, developed *Clostridium*

difficile. Overall, approximately 28% from these regions were diagnosed within 60 days

from discharge with CDI. In the West region, three of the 28 (10.7%), had *Clostridium*

difficile diagnosis, and for participants from the South region, two of the 33 (6.1%) were

diagnosed from this sample with *Clostridium difficile* within 60 days.

The sample was approximately equally divided between males ($n = 72$, 48.9%)

and females ($n = 75$, 51.0%). Males had a slightly higher rate of *Clostridium difficile*

diagnosis than females for the sample (7.5% vs. 4.1%). Within the gender specific

categories, male gender diagnosed with *Clostridium difficile* is 15.3% and female gender

with *Clostridium difficile* is 8.0%. The categorical demographic frequency and

percentages of the study participants for each region and gender are presented in Table 3

along with the region and gender specific percentages with *Clostridium difficile.*

Table 3

Frequency for Sampled Gender and Regions and Percent With Clostridium difficile (N=147)

Demographic	*n*	%
Gender frequency		
Male	72	48.9
Female	75	51.0
Gender percent with *Clostridium difficile*		
Male	11	7.5
Female	6	4.1
Gender specific percent with *Clostridium difficile*		
Male (*n=72*)	11	15.3
Female (*n=75*)	6	8.0
Region frequency		
Midwest	44	29.9
Northeast	42	28.6
South	33	22.4
West	28	19.0
Region percent with *Clostridium difficile*		
Midwest	6	4.1
Northeast	6	4.1
South	2	1.4
West	3	2.0
Region specific percent with *Clostridium difficile*		
Midwest (*n=44*)	6	13.6
Northeast (*n=42*)	6	14.2
South (*n=33*)	2	6.1
West (*n=28*)	3	10.7

Research Question 1

Is there a relationship between use of prescription antivirals and CDI within 60 days of discharge in patients who have been hospitalized for influenza?

$H_0$1: There is not a statistically significant association between use of prescription antivirals and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

H_a1: There is a statistically significant association between use of prescription antivirals and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

To examine Research Question 1, a binary logistic regression was conducted with the use of prescription antivirals predicting instances of *Clostridium difficile* within 60 days of discharge while controlling for age and gender. Results of the binary logistic regression were not statistically significant ($\chi^2(3) = 3.38$, $p = .336$, Negelkerke $R^2 = .05$) indicating that age, gender, and the use of antivirals were not significant predictors of *Clostridium difficile* diagnosis within 60 days from discharge. Thus, the null hypothesis was retained and no further interpretations were made. Results of the binary logistic regression with antiviral use predicting *Clostridium difficile* within 60 days of discharge are presented in Table 4.

Table 4

Binary Logistic Regression With Antiviral use Predicting Clostridium Difficile 60 Days After Discharge

						95% CI	
Predictor	*B*	*SE*	Wald χ^2	*p*	*OR*	Lower	Upper
Antiviral use	0.52	0.81	0.42	0.52	1.69	0.34	8.28
Age	0.02	0.02	1.16	.282	1.02	0.99	1.05
Gender	0.61	0.56	1.21	.271	1.84	0.62	5.48

Note. Female referent group.

To examine the first regression model, the Hosmer Lemeshow test was used in conjunction with the classification table to determine the model's fit. For this model, the Hosmer Lemeshow test did not indicate a significant difference between the final regression model and the observed data ($\chi^2(7) = 6.80$, $p = .450$). The classification table was examined to further detail the model fit that suggested that 88.3% of the participants' placement in the outcome groups was accurately predicted. However, this may be due to the fact that the model consistently classified all participants into the larger group, which contained 88.3% of the sample. The nonsignificant predictors ($p > .05$ for each) indicated that the model could not use the independent variables to accurately classify participants into a group of *Clostridium difficile* within 60 days versus no *Clostridium difficile* within 60 days. Table 5 provides the classification table for this regression model.

Table 5

Classification Table for Antiviral Use as Examined in Research Question 1

Observed	Predicted		% Correct
	No CDI	CDI within 60 days	
No CDI	128	0	100
CDI within 60 days	17	0	0

Note. Overall correct classification of 88.3%.

Research Question 2

Is there a relationship between use of prescription antibiotics and CDI within 60 days of discharge in patients who have been hospitalized for influenza?

$H_0 2$: There is not a statistically significant association between use of prescription antibiotics and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

$H_a 2$: There is a statistically significant association between use of prescription antibiotics and CDI within 60 days of discharge in patients who have been hospitalized for influenza.

To examine Research Question 2, a binary logistic regression was conducted with the use of prescription antibiotics predicting instances of *Clostridium difficile* within 60 days of discharge while controlling for age and gender. Results of the binary logistic regression were not statistically significant ($\chi^2(3) = 3.75$, $p = .290$, Negelkerke $R^2 = .05$) indicating that age, gender, and the use of antibiotics were not significant predictors of *Clostridium difficile* diagnosis within 60 days from discharge. Thus, the null hypothesis was retained and no further interpretations were made. Results of the binary logistic

regression with antibiotic use predicting *Clostridium difficile* within 60 days of discharge are presented in Table 6.

Table 6

Binary Logistic Regression With Antibiotic Use Predicting Clostridium Difficile 60 Days After Discharge

						95% CI	
Predictor	*B*	*SE*	Wald χ^2	*p*	*OR*	Lower	Upper
Antibiotic use	-0.52	0.56	0.85	.357	0.60	0.20	1.79
Age	0.02	0.01	1.10	.295	1.02	0.99	1.04
Gender	0.78	0.55	2.02	.155	2.19	0.74	6.42

Note. Female referent group.

To examine the second regression model, the Hosmer Lemeshow test was used in conjunction with the classification table to determine the model's fit. For this model, the Hosmer Lemeshow test did not indicate a significant difference between the final regression model and the observed data ($\chi^2(7) = 1.97$, $p = .961$). The classification table was examined to further detail the model fit which suggested that 88.3% of the participants' placement in the outcome groups was accurately predicted. However, this may be due to the fact that the model consistently classified all participants into the larger group, which contained 88.3% of the sample. The nonsignificant predictors ($p > .05$ for each) indicated that the model could not use the independent variables to accurately classify participants into a group of *Clostridium difficile* within 60 days versus no *Clostridium difficile* within 60 days. Table 7 provides the classification table for this regression model.

Table 7

Classification Table for Antibiotic Use as Examined in Research Question 2

Observed	Predicted		% Correct
	No CDI	CDI within 60 days	
No CDI	128	0	100
CDI within 60 days	17	0	0

Note. Overall correct classification of 88.3%.

Research Question 3

Do the use of prescription antivirals and/or prescription antibiotics predict CDI within 60 days of discharge in patients who have been hospitalized for influenza?

$H_0$3: The use of prescription antivirals and/or prescription antibiotics does not predict CDI within 60 days of discharge in patients who have been hospitalized for influenza.

H_a3: The use of prescription antivirals and/or prescription antibiotics does predict CDI within 60 days of discharge in patients who have been hospitalized for influenza.

To examine Research Question 3, a binary logistic regression was conducted with the use of prescription antivirals or antibiotics predicting instances of *Clostridium difficile* within 60 days of discharge while controlling for age and gender. For this regression, the variable of antiviral or antibiotic use was coded such that 0 = neither antibiotic nor antivirals used, and 1 = either antibiotics, antivirals, or both used. Results of the binary logistic regression were not statistically significant ($\chi^2(3) = 3.07$, $p = .382$, Negelkerke $R^2 = .04$) indicating that age, gender, and the use of antivirals or antibiotics were not accurate predictors of *Clostridium difficile* diagnosis within 60 days from

discharge. Thus, the null hypothesis was retained and no further interpretations were made. Results of the binary logistic regression with antiviral and antibiotic use predicting *Clostridium difficile* within 60 days of discharge are presented in Table 8.

Table 8

Binary Logistic Regression With Antibiotic and/or Antiviral Use Predicting Clostridium Difficile 60 Days After Discharge

Predictor	B	SE	Wald χ^2	p	OR	95% CI Lower	Upper
Antiviral and/or Antibiotic use	-0.32	0.83	0.15	.701	0.73	0.14	3.72
Age	0.02	0.01	1.13	.287	1.02	0.99	1.04
Gender	0.75	0.55	1.84	.175	2.12	0.72	6.29

Note. Female referent group.

To examine the third regression model, the Hosmer Lemeshow test was used in conjunction with the classification table to determine the model's fit. For this model, the Hosmer Lemeshow test did not indicate a significant difference between the final regression model and the observed data ($\chi^2(8) = 5.49$, $p = .705$). The classification table was examined to further detail the model fit which suggested that 88.3% of the participants' placement in the outcome groups was accurately predicted. However, this may be due to the fact that the model consistently classified all participants into the larger group, which contained 88.3% of the sample. The non-significant predictors ($p > .05$ for each) indicated that the model could not use the independent variables to accurately classify participants into a group of *Clostridium difficile* within 60 days versus no *Clostridium difficile* within 60 days. Table 9 provides the classification table for this regression model.

Table 9

Classification Table for Use of Antivirals and/or Antibiotics as Examined in Research Question 3

	Predicted		
Observed	No CDI	CDI within 60 days	% Correct
No CDI	128	0	100
CDI within 60 days	17	0	0

Note. Overall correct classification of 88.3%.

Summary of Results

Three logistic regressions were conducted to determine a possible relationship between the use of antiviral or antibiotic medication with development of *Clostridium difficile* within 60 days of discharge from the hospital while controlling for the effect of gender and age. Results of the first logistic regression indicated there was no impact of antiviral use on development of *Clostridium difficile* within 60 days of discharge. Results of the second logistic regression indicated there was no impact of antibiotic use on development of *Clostridium difficile* within 60 days of discharge. Results of the final logistic regression examined cases of antiviral and/or antibiotic use and indicated there was no statistically significant impact of either medication on development of *Clostridium difficile* within 60 days of discharge.

In Chapter 5 the study findings will be examined and interpreted further to provide comparisons to the literature review, analyze the findings in the context of the theoretical framework, describe recommendations for future studies based on this study's

findings and limitations, and explore the study's impact for social change and

recommendations for healthcare practice.

Chapter 5: Discussion, Conclusions, and Recommendations

The purpose of the study was to to examine the temporal progression of CDI incidence and the possible influence that the seasonal variation of influenza and antibiotic and antiviral use has on the incidence of CDI. An enhanced understanding could be determined about the relationship of CDI and seasonal influenza as well as the role/influence of antibiotic use and selection. The study's significance may be to further contribute to the growing body of knowledge of the implications that antibiotic use has on CDI. In this study, I examined if the overuse and/or inappropriate use of antibiotics has an impact on the development of CDI during seasonal disease outbreaks of influenza.

Three logistic regressions were conducted to determine the relationship between the use of antiviral or antibiotic medication with development of *Clostridium difficile* within 60 days of discharge from the hospital while controlling for the effect of gender and age. The first logistic regression results indicated there was no impact of antiviral use on development of *Clostridium difficile* within 60 days of discharge. Next, the second logistic regression indicated there was no impact of antibiotic use on development of *Clostridium difficile* within 60 days of discharge. Finally, the third logistic regression results indicated when cases of antiviral and/or antibiotic use were examined, there was no statistically significant impact of either medication on development of *Clostridium difficile* within 60 days of discharge.

Interpretation of the Findings

The data from this study resulted in a representative population based on the literature review. The highest rates of influenza and CDI occur among persons 65 years

and older, with over two-thirds of the patients with CDI being elderly (APIC, 2013; Elixhauser & Jhung, 2008). This study population's average age was 62.9 years old, with an age range of 19 to 101. Among the influenza positive study population who developed *Clostridium difficile,* the average age was 67.6 years old, similar to the results by APIC, 2013 and Elixhauser and Jhung, 2008.

Additionally noted by Elixhauser and Jhung are changes in CDI epidemiology regional incidence based on a review of United States hospital discharge data, finding the Northeastern rate was 2 times higher than the West, which had the lowest rate. The frequencies in the Midwest and South were 69% and 42% higher than the West frequency, respectively (Elixhauser & Jhung ,2008). I found a slight difference in the highest percentage of *Clostridium difficile* coming from the Midwest (4%) and Northeast (4%) equally and the West (2%) was slightly higher than the South (1%), which includes taking into account the study's design of more sampling in the Northeast, Midwest, and South than the West. Although rates of CDI related hospital stays are higher in females than males (APIC, 2013), this study revealed the incidence of CDI within 60 days of discharge among hospitalized patients with the flu nearly double in males (7%) versus females (4%). The study population was nearly equal sample population of males versus females. This difference in gender incidence was in contrast to cited findings (APIC, 2013) and therefore suggests the need for further study.

As described in Chapter 2, using the wheel model of man-environment interactions framework, the study increased understanding determinents of CDI, seasonal influenza, and the role/influence of antibiotic use and selection. The study population of

adults (host) at the center of the three sections of the environment illustrated the role in

disease development of CDI as many medical decisions start with the individual. The

development of influenza is based on the lack of vaccine receipt, naïve host, or a vaccine

mismatch due to a differing circulating/novel influenza strain (CDC, 2009). This section

weighs heavy in the biological section, as does receipt of a good strain match of vaccine

for influenza prevention. Additionally, there can be biological factors of a dose-response

relationship in the development of influenza with the occurrence of influenza based

exposure to the associated influenza strain and the proportion of vaccine match for those

who received it (CDC, 2009; Glezen, 2006). Admission to the hospital or need to seek

medical intervention for influenza is in the social and biological sections. This can have

social constructs of individual, family, or cultural groups influencing the health seeking

behavior and decisions to seek treatment. The study database was not accessible for

determinants of reasons for hospitalization or social constructs to seek care. The physical

environment includes exposure to *Clostridium difficile* spores in the physical hospital

environment and the social aspects include if the physician prescribes antibiotics that may

alter the host gut to develop CDI as well as the host request and acceptance of antibiotics.

Although this is true, the environmental factors that influenced CDI development were

not explored in this study. The physician's desire to use antibiotics may be based on the

need to provide comprehensive coverage for all upper and lower respiratory conditons

without a clear etiology, not having or waiting for influenza testing results prior to

administration of antibiotics for bacterial infections versus antivirals for viral infections

such as influenza, lack of critical thinking, physician's need to do something for the

patient, or maintain patient satifaction as they request medications (Bonner et al., 2003; Linder et al., 2006). Social aspects of care for the study population by the medical providers would greatly influence this portion of the wheel. This area of the physicians' use of antibiotics in the face of a positive influenza result could not be explored fully due to database limitations; it was not a full medical record with access to documentation of coinfection or other signs and symptoms.

There were clear cases of study individuals who did not receive any antibiotics or antivirals and cases who received antibiotics only without antivirals despite the fact they were test positive for influenza. Antivirals are the appropriate choice to treat influenza. They can reduce the duration of influenza symptoms by 1 to almost 3 days and reduce complications that require the use of antibiotics (Linder et al., 2005). Additionally, antiviral use may decrease hospitalization and mortality. Linder et al. found the use of antiviral medications for management of influenza important, given influenza vaccine receipt and effectiveness can vary. The study data demonstrated within this hospital cohort and sample population that the recommended administration of antiviral medication was not consistent among influenza positive patients. Of the 147 study participants, 117 participants received antibiotics, 106 received antivirals, and 130 received antibiotics and/or antivirals. Each of the study participants had laboratory evidence of positive influenza; with this diagnostic certainty, the sample population should have all received antiviral medication according to practice recommendations (ACIP, 2011). The study data confirmed findings in the literature (Falsey et al., 2007; Linder et al., 2005) of the utilization of antibiotics with a lab confirmed influenza

diagnosis and antibiotic use continued during the hospital stay. Although it is true that there were database limitations of no access to indicators of antibiotic use that could be found in the full medical record, documentation of coinfection, or other signs and symptoms, the data could be extrapolated based on the literature that physicians prescribed inappropriate antibiotics about 26% of the time (Linder et al., 2005). Additionally, this study illustrated the evidence that physicians do not alter their clinical decisions for treatment of influenza when positive results are readily available and treated with antibiotics. This confirmed the findings of Falsey et al. that with sound medical evidence, practitioners justify the choice to continue antibiotic use and supported the work by Linder et al. that physicians prescribe inappropriate antibiotics to patients with an influenza diagnosis. The study data contradicted the findings of Bonner et al. (2003) that physicians who have knowledge of influenza test results used less antibiotics and prescribed more antiviral medications. In this study, I found the physicians had evidence of positive influenza test results documented in the microbiology data on each individual patient. The lab tests were ordered, testing was performed in the clinical laboratory, and the results were available for physicians to utilize while making medical decisions for care and treatment. Based on the lab test results, the need to order and dispense medication, such as antivirals and antibiotics, may be indicated. The study population of 147 participants were all positive for influenza, yet 117 (79.6%) participants received antibiotics, 106 (72.1%) received antivirals, 130 (88.4%) received antibiotics and/or antivirals and 17 (11.6%). The 17 patients who developed *Clostridium difficile* within 60 days of discharge, 11 had received both antibiotics and antivirals, four had received

antibiotics only and two did not receive antibiotics or antivirals. Therefore, my study

findings indicate more antibiotics and less antivirals are prescribed when physicians have

knowledge of influenza test results.

Limitations of the Study

The data used in this study were collected for patient care and not for research.

The study was limited to the association of data and did not allow for a cause and effect

inference because I did not directly collect the data used for this research study. An

observational, nonexperimental design limits the interpretation of the results (McPherson

& Bunker, 1991). Use of these data for the purpose of a research study revealed

limitations but did allow for data analysis within the database limitations to answer the

research questions. Additionally, the database did not include signs and symptoms of

patients' medical conditions or chief complaints, detailed documentation of underlying

medical conditions that can be exacerbated by influenza infection, or queried for

secondary infections, coinfections, or complications from influenza, such as pneumonia.

With this in mind, sign and symptom information, along with documentation of

coinfections and complications from influenza, did not allow me to extrapolate definitive

clinical implications for the use of antibiotics in the sample population hospitalized with

positive influenza. Moreover, documentation or knowledge of influenza and

pneumococcal vaccine receipt was limited to only the data recorded in the medication

module; therefore, vaccine receipt from anywhere other than the hospital's dispensing

data could not be queried for the study population. This leads to the patient's receipt of

vaccines given elsewhere to remain unknown. The research study did not use vaccine reciept as a variable. Extraction of the available data set used for the research was limited to the hospital's geographic location, laboratory results, admitting diagnosis, medication orders and dispensing, patient age, and gender.

Another study limitation was the sample size. As indicated by the calculation described in Chapter 3, the study sample collected would be sufficient; however, this depended on the distribution of the outcome and size of the effect. The study revealed few CDI, so the lack of significant findings may have been influenced by two factors. The effect sizes were small and therefore impacted the study power.

I used a proprietary database from a set of hospitals that pay for the electronic surveillance system and pharmacy modules. The database used was taken at face value for data accuracy from the hosted hospital documentation and electronic results. Paid services of electronic surveillance and pharmacy medication modules made this group of hospitals unique in terms of their commitment to infection prevention data collection and antimicrobial monitoring. As a result, increased sampling bias may have been introduced from this database being used as a research cohort than that seen in random sampling, indicating that the sample may not have been representative of the United States population.

Recommendations

Findings from this research revealed the need to further study populations of influenza positive patients. Specifically, future studies should seek access to detailed medical records and determine if the use of antibiotics was clinically indicated in addition

to antiviral use across a large geographic cohort. Pneumococcal vaccine and seasonal influenza vaccine receipt could be comprehensively researched in the influenza positive population as factors that may influence the use of antibiotics and as additional study variables.

Consistent with the literature in Chapter 2, Falsey et al. (2007) studied the impact of rapid diagnosis testing and the management of adults who were hospitalized with influenza; rapid influenza testing leads to reduced antibiotic use in hospitalized patients. Falsey et al. found positive influenza testing was associated with modest withholding or discontinuing antibiotics; however, a significant portion of the test positive patients at low risk for bacterial infection continued to receive antibiotics. Physicians were surveyed to assess the beliefs of being comfortable to discontinue antibiotics in patients with negative chest x-rays and negative bacterial cultures, and two thirds of the respondents believed they would be (Falsey et al., 2007). Medical record review, however, found that in practice these physicians did not discontinue antibiotic use (Falsey et al., 2007). Physicians are concerned about secondary bacterial infections with an influenza diagnosis and the ability to distinguish concomitant bacterial or viral infections during peak seasons for respiratory illness (Falsey et al., 2007). Even with sound medical evidence of no secondary or concomitant respiratory illness or disease, practitioners justified their choice to continue antibiotic use.

Several studies have shown that diagnosis and treatment of influenza is not consistent among physicians. Linder et al. (2005) found that physicians prescribed inappropriate antibiotics to 26% of patients, and physicians prescribed antiviral

medication to 19% of patients with an influenza diagnosis. Similar results from a study

by Bonner et al. (2003) illustrated these same findings. As the literature suggests, there is

clearly a need to further study the effects of antibiotic use during the influenza season

among patient populations positive for influenza and the subsequent development of CDI

outcome.

Research could be expanded to include hospitals not using this proprietary

surveillance and pharmacy module to identify a more representative population across the

United States. A study that would include a larger sample size population has the

potential to identify CDI among a cohort altering the distribution of the outcome and size

of the effect, while increasing the power. Moreover, the effect of age as a variable could

be further studied using categorization of age groups among the study population, such as

distribution categories of ages from 18 to age 65 and older.

The role of antibiotic induced *Clostridium difficile* diarrhea, infection, and colitis

has been well documented (Bartlett, 2011; Gaynes et al., 2004; Gerding, 2004; Nelson &

Williams, 2007) while the discrete use of antivirals in the development of CDI has not

(Colarian, 1988; Gellad et al., 2007; Gorschlüter et al., 2001; Pulvirenti et al., 2002;).

Additional study of influenza positive populations using specific United States licensed

prescription antiviral agents to treat influenza would add to the body of knowledge

identified from this literature gap.

Implications

The results of this study offered an understanding of *Clostridium difficile*

epidemiology in this unique influenza positive population and significant implications for

social change. Better understanding leads to new areas of inquiry and further study. The

primary goal of antimicrobial stewardship is to improve clinical patient outcomes and

minimize unintended adverse consequences due to inappropriate selection, dosing, and

duration of these medication therapies. The incidence of CDAD before and after

implementing antibiotic stewardship programs has been described across the United

States with similar results (AHRQ, 2012). The removal or reducing the use of an

offending antimicrobial agent can result in decreased CDAD (Garey, 2011; Nuila et al.,

2008). Although antimicrobial stewardship has become more common among hospitals,

standardization of protocols and what stewardship details encompass are still being

formulated. This has been fueled by recent governmental attention to improve antibiotic

stewardship according to the metrics outlined within President Obama's Executive Order-

Combating Antibiotic Resistant Bacteria (The White House, 2014). This research study

revealed that there were inconsistencies in antiviral delivery and the need to further study

the overall use of antibiotics in influenza positive populations, which can serve as a

platform for implementing antimicrobial stewardship efforts.

Knowledge from this epidemiologic study of seasonality of disease and antibiotics

may have an influence at local and organizational levels. Healthcare providers may

benefit from recognizing the effect that antibiotic delivery in hospitals has through more

informed choices for use and pharmacologic recommendations. Increasing antibiotic

stewardship may considerably reduce morbidity and mortality associated with CDI.

There is a need for research and studies of this kind to contribute to the literature in order

for there to be implementation of comprehensive evidence-based *Clostridium difficile*

measures.

Antibiotic resistance and CDI are health care issues that affect the hospitalized

patient and may have implications for affecting the general public once the patient is

released from a healthcare setting, such as exposing the community population and

environment to antibiotic resistance and CDI. Individuals need to increase their

awareness of vaccine receipt to reduce the potential to contract influenza and spread to

others. Additionally, individuals need to be an active participant in their own medical

care and seek medical attention quickly to be diagnosed with influenza and receive the

appropriate antivirals to lessen the severity and duration of illness. This action may

reduce hospitalizations and risks for influenza complications. Individuals may also

influence receipt of antibiotics by demanding them from medical care providers when

they are not medically indicated, thereby ultimately affect CDI development. Families

may be affected by the vaccine receipt in households as described in literature through

herd immunity. Herd protection of a family or group may occur when a large proportion

of individuals from that group are immune or immunized to influenza reducing exposure

of those susceptible to the flu. The importance of vaccine receipt among family/groups

and seeking diagnostic medical care and appropriate treatment for influenza has been

recognized as an integral part of reducing household and group setting transmission.

Although this study did not have access to data of vaccine receipt specifically, the study

variables did include antiviral and antibiotic receipt among hospitalized patients with

influenza. As a result, hospital medical staff, families, groups and individuals may benefit from the findings.

Conclusion

The purpose of this quantitative study was to examine the temporal progression of CDI incidence and possible influence of seasonal variation of influenza and antibiotic and antiviral use has on the incidence of CDI. The study aspired to enhance understanding about the relationship of CDI and seasonal influenza and the role/influence of antibimicrobial use and selection. Although the study findings did not prove to be significant for the three research questions with the premise that seasonal influenza leads to increased prescribing of antimicrobial agents which can lead to increased CDI; there was evidence to support recommended administration of antiviral medication was not consistent among influenza positive patients. Furthermore, the study indicated seasonal antimicrobial use that coincided with seasonal influenza did enable the identification of inappropriate prescribing patterns for antimicrobial agents. The future of antimicrobial stewardship is targeted *Clostridium difficile* reduction efforts as a complementary strategy to decrease CDI frequency by adressing inappropriate antibiotic use. Consequently, this study illustrated the need to highlight on the primary goals of antimicrobial stewardship: to focus on reducing inappropriate antimicrobial use and ultimately minimizing the unintended adverse consequences of this practice.

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Appendix A: Figure 1 Usage Permission

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Sent: 17 March 2013 22:06
To: Rights and Permissions (ELS)
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First name:	Eileen
Last name:	Yaeger
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Appendix B: Data Usage Permission

From: Stricklin, David
Sent: Monday, January 13, 2014 12:20 PM
To: Yaeger, Eileen
Subject: RE: Research Authorization

1.13.2014

Dear Eileen Yaeger,

Based on my review of your research proposal, I give permission for you for you to conduct the study entitled "A Quantitative Study of Clostridium difficile Incidence Related to Influenza Seasonality and Antimicrobial Utilization" within CareFusion MedMined services. As part of this study, I authorize you to:

1. Query the MedMined Surveillance Advisor service to collect data of positive microbiologic test results for influenza, Clostridium difficile, and antimicrobial use in a sample of hospitalized patients.
2. Query the MedMined Surveillance Advisor service to collect diagnosis results for *Clostridium difficile* and influenza in a sample of hospitalized patients.
3. Query the MedMined Surveillance Advisor service for admission/readmission designation and inpatient/outpatient status in a sample of hospitalized patients.
4. Collect data from preapproved hospitals based on contractual agreements with these hospitals.

I confirm that I am authorized to approve research in this setting.

I understand that the data collected will remain entirely confidential and may not be provided to anyone outside of the of the research team without permission from the Walden University IRB.

Sincerely,

David R. Stricklin
Director, Customer Operations
MedMined® services
CareFusion